Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2020-B-266 Enzalutamid (mHSPC)

Stand: Oktober 2020

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Enzalutamid
zur Behandlung des metastasierten, hormonsensitiven Prostatakarzinoms

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	• Orchiektomie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: • Abirateronacetat: Beschluss vom 07.06.2018 • Apalutamid: Beschluss vom 20.08.2020
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Enzalutamid L02BB04 Xtandi	Geplantes Anwendungsgebiet: Behandlung erwachsener Männer mit metastasiertem hormonsensitivem Prostatakarzinom (metastatic hormone-sensitive prostate cancer, mHSPC) in Kombination mit einer Androgenentzugstherapie.
Antiandrogene	
Bicalutamid L02BB03 generisch	• ist angezeigt entweder als alleinige Therapie oder adjuvant zu radikaler Prostatektomie oder Strahlentherapie bei Patienten mit lokal fortgeschrittenem Prostatakarzinom und hohem Progressionsrisiko • zur Behandlung des fortgeschrittenen Prostatakarzinoms in Kombination mit einer LHRH-(Luteinisierendes Hormon-Releasing-Hormon)-Analogon-Therapie oder einer operativen Kastration.
Cyproteron-acetat G03HA01 generisch	• Zur palliativen Therapie des metastasierenden oder lokal fortgeschrittenen, inoperablen Prostatakarzinoms, wenn sich die Behandlung mit LHRH-Analoga oder der operative Eingriff als unzureichend erwiesen haben, kontraindiziert sind oder der oralen Therapie der Vorzug gegeben wird. • Initial zur Verhinderung von unerwünschten Folgeerscheinungen und Komplikationen, die zu Beginn einer Behandlung mit LHRH-Agonisten durch den anfänglichen Anstieg des Serum -Testosteron hervorgerufen werden können. • Zur Behandlung von Hitzewallungen, die unter der Behandlung mit LHRH-Agonisten oder nach Hodenentfernung auftreten. • […]
Flutamid L02BB01 generisch	Zur Behandlung von Patienten mit fortgeschrittenem Prostatakarzinom, bei denen eine Suppression der Testosteronwirkungen indiziert ist • Initialtherapie in Kombination mit einem LH-RH-Analogon oder in Verbindung mit Orchiektomie (komplette Androgenblockade) sowie bei Patienten, die bereits mit einem LH-RH-Analogon behandelt werden bzw. bei denen bereits eine chirurgische Ablatio testis erfolgt ist • zur Behandlung von Patienten, die auf andere endokrine Therapieformen nicht ansprachen oder für die eine andere endokrine Therapie nicht verträglich, aber notwendigerweise indiziert ist.
GnRH-Analoga	
Degarelix L02BX02 Firmagon	FIRMAGON ist ein Gonadotropin-Releasing-Hormon-(GnRH)-Antagonist zur Behandlung von erwachsenen männlichen Patienten mit fortgeschrittenem hormonabhängigen Prostatakarzinom.

II. Zugelassene Arzneimittel im Anwendungsgebiet

Buserelin L02AE01 Profact	• ist angezeigt bei Erwachsenen zur Behandlung des fortgeschrittenen hormonempfindlichen Prostatakarzinoms. • ist jedoch nicht angezeigt nach beidseitiger Orchiektomie, da es in diesem Fall zu keiner weiteren Absenkung des Testosteronspiegels kommt.
Goserelin L02AE03 Zoladex	Behandlung von Patienten mit fortgeschrittenem Prostatakarzinom, bei denen eine endokrine Behandlung angezeigt ist.
Leuprorelin L02AE02 Trenantone	• Zur Behandlung des fortgeschrittenen hormonabhängigen Prostatakarzinoms. • Zur Behandlung des lokal fortgeschrittenen, hormonabhängigen Prostatakarzinoms; begleitend zur und nach der Strahlentherapie. • Zur Behandlung des lokalisierten hormonabhängigen Prostatakarzinoms bei Patienten des mittleren und Hoch-Risikoprofils in Kombination mit der Strahlentherapie • […]
Triptorelin L01AA06 Pamorelin	ist indiziert zur Behandlung des • lokal fortgeschrittenen oder metastasierenden, hormonabhängigen Prostatakarzinoms. • des lokalisierten Hochrisiko- oder lokal fortgeschrittenen, hormonabhängigen Prostatakarzinoms in Kombination mit Strahlentherapie. • […]
Weitere Hormontherapeutika	
Abirateron-acetat L02BX03 Zytiga	ZYTIGA ist indiziert mit Prednison oder Prednisolon: • zur Behandlung des neu diagnostizierten Hochrisiko-metastasierten hormonsensitiven Prostatakarzinoms (mHSPC) bei erwachsenen Männern in Kombination mit Androgenentzugstherapie (androgen deprivation therapy, ADT) • […]
Apalutamid L02BB05 Erleada	Erleada ist indiziert: • zur Behandlung erwachsener Männer mit metastasiertem hormonsensitivem Prostatakarzinom (mHSPC) in Kombination mit Androgendeprivationstherapie (ADT). • […]
Zytostatika	
Docetaxel L01CD02 Taxotere	TAXOTERE ist in Kombination mit einer Androgendeprivationstherapie, mit oder ohne Prednison oder Prednisolon, zur Behandlung von Patienten mit metastasiertem hormonsensitivem Prostatakarzinom angezeigt. […]

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Inhaltsverzeichnis

Abkürzungsverzeichnis

AAP	abiraterone acetate plus prednisone / prednisolone
ADT	Androgen Deprivation Therapy
AE	Adverse Events
ARAT	androgen receptor axis targeted therapy
ASCO	American Society of Clinical Oncology
AST	Aspartate transaminase
ALT	Alanine transamine
AUA	American Urological Association
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
cORR	clinical Overall Response Rate
CRPC	Castration-Resistant Prostate Cancer
CTIBL	CancerTreatment-Induced Bone Loss
EAU	European Association of Urology
EBRT	External Beam Radiation Therapy
EK	Expertenkonsens
ESMO	European Society for Medical Oncology
ESTRO	European Society for Radiotherapy & Oncology
FAME	framework for adaptive meta-analysis
G-BA	Gemeinsamer Bundesausschuss
GCP	Good Clinical Practice
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
HSPC	Hormone-Sensitive Prostata Cancer
mHSPC	metastatic Hormone-Sensitive Prostata Cancer
HVD	high-volume disease
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall

LHRH	Luteinizing Hormone-Releasing Hormone
LoE	Level of Evidence
LVD	low-volume disease
mHNPC	metastatic hormone-naive prostate cancer
mCRPC	metastatic Castration-Resistant Prostate Cancer
NICE	National Institute for Health and Care Excellence
NMA	Netzwerkmetaanalyse
OR	Odds Ratio
OS	Overall Survival
PCa	Prostate Cancer
PCO	Provisional Clinical Opinion
PFS	Progression-Free Survival
PSA	Prostate-Specific Antigen
QoL/QOL	Quality of Life
RR	Relatives Risiko
RoB	Risk of bias
SBRT	Stereotacitc Body Radiation Therapy
SIGN	Scottish Intercollegiate Guidelines Network
SIOG	International Society of Geriatric Oncology
SSE	Symptomatic Skeletal Event
STAMPEDE	Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy
sORR	prostate-specific Antigen Overall Response Rate
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Behandlung erwachsener Männer mit metastasiertem hormonsensitivem Prostatakarzinom (metastatic hormone-sensitive prostate cancer, mHSPC) in Kombination mit einer Androgenentzugstherapie.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Prostatakarzinom* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 11.09.2020 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 1700 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 29 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

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3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2018 [7].

Abirateronacetat (neues Anwendungsgebiet: metastasiertes hormonsensitives Prostatakarzinom (mHSPC))

Beschluss vom: 7. Juni 2018; gültig bis: unbefristet; BAnz AT 17.07.2018 B1

Anwendungsgebiet

Hochrisiko-Patienten mit neu diagnostiziertem, metastasiertem, hormonsensitivem Prostatakarzinom

Zweckmäßige Vergleichstherapie

– die konventionelle Androgendeprivation, gegebenenfalls in Kombination mit einem nicht-steroidalen Antiandrogen (Flutamid oder Bicalutamid),

oder

– die konventionelle Androgendeprivation in Kombination mit Docetaxel und Prednison oder Prednisolon.

Fazit / Ausmaß des Zusatznutzens

ZYTIGA ist indiziert mit Prednison oder Prednisolon zur Behandlung des neu diagnostizierten Hochrisiko-metastasierten hormonsensitiven Prostatakarzinoms (mHSPC) bei erwachsenen Männern in Kombination mit Androgenentzugstherapie (androgen deprivation therapy, ADT).

- Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der konventionellen Androgendeprivation: Hinweis auf einen beträchtlichen Zusatznutzen.

G-BA, 2020 [6].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Apalutamid neues Anwendungsgebiet: metastasiertes, hormonsensitives Prostata-karzinom (mHSPC)

Beschluss vom: 20. August 2020

Anwendungsgebiet

Zweckmäßige Vergleichstherapie

- die konventionelle Androgendeprivation in Kombination mit Docetaxel mit oder ohne Prednison oder Prednisolon (nur für Patienten mit Fernmetastasen (M1-Stadium) und gutem Allgemeinzustand (nach ECOG / WHO 0 bis 1 bzw. Karnofsky Index ≥ 70 %)

oder

- die konventionelle Androgendeprivation in Kombination mit Abirateronacetat und Prednison oder Prednisolon (nur für Patienten mit neu diagnostiziertem Hochrisiko-metastasiertem hormonsensitivem Prostatakarzinom)

Fazit / Ausmaß des Zusatznutzens

Erleada ist indiziert zur Behandlung erwachsener Männer mit metastasiertem hormonsensitivem Prostatakarzinom (mHSPC) in Kombination mit Androgendeprivationstherapie (ADT).

- Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Apalutamid in Kombination mit Androgendeprivationstherapie (ADT) gegenüber Docetaxel in Kombination mit Prednisolon und ADT (für Patienten mit Fernmetastasen (M1-Stadium) und gutem Allgemeinzustand (nach ECOG / WHO 0 bis 1 bzw. Karnofsky Index ≥ 70 %)): Ein Zusatznutzen ist nicht belegt.

3.2 Cochrane Reviews

Sathianathen NJ et al., 2018 [23].

Taxane-based chemohormonal therapy for metastatic hormone-sensitive prostate cancer

Fragestellung

To assess the effects of early taxane-based chemohormonal therapy for newly diagnosed, metastatic, hormone-sensitive prostate cancer.

Methodik

Population:

- men with a confirmed histological diagnosis of adenocarcinoma of the prostate and radiologic evidence of metastases as determined by cross-sectional imaging (computer tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) with or without bone scans. This included both men who had and had not undergone local therapy.

Intervention:

- taxane-based chemotherapy with systemic androgen deprivation therapy (ADT) within 120 days of beginning ADT

Komparator:

- ADT alone at the time of diagnosis of metastatic disease

Endpunkte:

- Primary outcomes
  - Time to death due to any cause.
  - Grade III to V adverse events.
- Secondary outcomes
  - Time to death due to prostate cancer (analyzed as prostate cancer-
  - specific death, see Differences between protocol and review).
  - Time to progression.
  - Discontinuation due to adverse events.
  - All adverse events.
  - Quality of life.

Recherche/Suchzeitraum:

- comprehensive search using multiple databases (the Cochrane Library, MEDLINE, Embase, Scopus, Google Scholar, and Web of Science), trials registries, other sources of grey literature, and conference proceedings,
- up to 10 August 2018.
- We applied no restrictions on publication language or status.

Qualitätsbewertung der Studien:

- Cochrane's 'Risk of bias' assessment tool

Ergebnisse

Anzahl eingeschlossener Studien:

- three studies in which 2261 participants

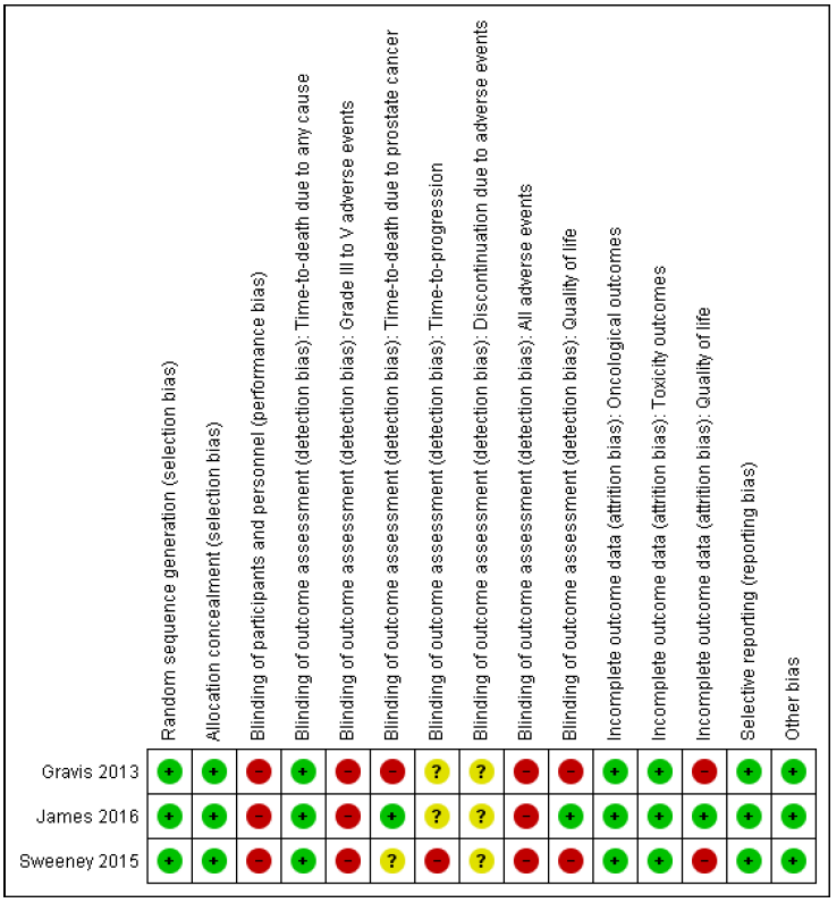
Charakteristika der Population:

This review includes a total of 2,261 randomized participants with metastatic hormone-sensitive prostate cancer, of whom 951 received docetaxel in addition to androgen deprivation therapy (ADT). One trial also enrolled 1,145 participants with non-metastatic disease but we did not include this subgroup in the review (James 2016). The median age and prostate-specific antigen (PSA) level at randomization of participants ranged from 63 to 64 years old and 25.8 nanograms per milliliter (ng/mL) to 50.9 ng/mL, respectivel (Gravis 2013; Sweeney 2015). Separate demographic characteristics for participants with metastatic diease were not reported in James 2016. The proportion of participants with high-volume metastases ranged from 48% to 65% (Gravis 2013; Sweeney 2015); this information was not reported in James 2016. The majority of participants had an initial Gleason score above seven in all trials.

The proportion of participants with prior local treatment before the diagnosis of metastatic disease ranged from 4% to 28% (Gravis 2013; James 2016; Sweeney 2015). Participants over the age of 18 years old were eligible for inclusion in the trials if they had a pathological diagnosis of prostate cancer and radiological evidence of metastatic disease (Gravis 2013; James 2016; Sweeney 2015). One trial also included individuals without a histological diagnosis as long as they had a clinical scenario that was consistent with prostate cancer (Sweeney 2015). Participants were also required to have an adequate functional status, defined as Eastern Cooperative Oncology Group (ECOG) score of zero to two in all trials, and be fit for chemotherapy. Prior neoadjuvant or adjuvant hormone therapy (or both) was allowed in the included studies if it was completed at least 12 months prior to randomization.

The receipt of any previous chemotherapy in the adjuvant or neoadjuvant setting (or both) was an exclusion criterion in two trials (James 2016; Sweeney 2015), but this was permitted in the third trial if the course of chemotherapy had been completed at least 12 months prior to randomization and there had not been any evidence of PSA or disease progression (or both) for at least one year (Gravis 2013).

Qualität der Studien:



Studienergebnisse:

- OS

  Early treatment with taxane-based chemotherapy in addition to ADT probably reduces death from any cause compared to ADT alone (hazard ratio (HR) 0.77, 95% confidence interval (CI) 0.68 to 0.87; moderate-certainty evidence); this would result in 94 fewer deaths per 1,000 men (95% CI 51 to 137 fewer deaths). We downgraded the certainty of evidence due to study limitations related to potential performance bias. Based on the results of one study with 375 participants, the addition of taxane-based chemotherapy to ADT may increase the incidence of Grade III to V adverse events compared to ADT alone (risk ratio (RR) 2.98, 95% CI 2.19 to 4.04; low-certainty evidence); this would result in 405 more Grade III to V adverse events per 1,000 men (95% CI 243 to 621 more events). We downgraded the certainty of evidence due to study limitations and imprecision.

- Secondary outcomes

  Early taxane-based chemotherapy in addition to ADT probably reduces the risk of prostate cancer-specific death (RR 0.79, 95% CI 0.70 to 0.89; moderate-certainty evidence). We downgraded the certainty of evidence due to study limitations related to potential performance and detection bias. The addition of taxane-based chemotherapy also probably reduces disease progression compared to ADT alone (HR 0.63, 95% CI 0.56 to 0.71; moderate-certainty evidence). We downgraded the certainty of evidence because of study limitations related to potential performance bias. The addition of taxane-based chemotherapy to ADT may result in a large increase in the risk of treatment discontinuation due to adverse

events (RR 79.41, 95% CI 4.92 to 1282.78; low-certainty evidence). We downgraded the certainty of evidence due to study limitations and imprecision. This estimate is derived from a single study with no events in the control arm but a discontinuation rate of 20% in the intervention arm. Taxane-based chemotherapy may increase the incidence of adverse events of any grade (RR 1.11, 95% CI 1.06 to 1.17; low-certainty evidence). We downgraded our assessment of the certainty of evidence due to very serious study limitations. There may be a small improvement, which may not be clinically important, in quality of life at 12 months with combination treatment (mean difference (MD) 2.85 on the Functional Assessment of Cancer Therapy—Prostate scale, 95% CI 0.13 higher to 5.57 higher; low-certainty evidence). We downgraded the certainty of evidence for study limitations related to potential performance, detection and attrition bias.

Summary of findings for the main comparison.

Early taxane-based chemotherapy and ADT compared to ADT only for metastatic hormone-sensitive prostate cancer

Participants: men with metastatic hormone-sensitive prostate cancer

Setting: multicenter

Intervention: early docetaxel with androgen deprivation therapy

Control: androgen deprivation therapy only

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with ADT only	Risk difference with taxane-based chemotherapy and ADT
Time to death due to any cause (absolute effect size estimates based on all-cause mortality at 5 years) Follow-up: median 43 to 84 months	2,261 (3 RCTs)	⊕⊕⊕⊖ MODERATE [3]	HR 0.77 (0.68 to 0.87)	Study population[1]	
				610 per 1,000	94 fewer per 1,000 (137 fewer to 51 fewer)
				General Population[2]	
				702 per 1,000	96 fewer per 1,000 (141 fewer to 51 fewer)
Grade III to V adverse events Follow-up: median 50 months	375 (1 RCT)	⊕⊕⊖⊖ LOW [4]	RR 2.98 (2.19 to 4.04)	Study population	
				204 per 1,000	405 more per 1,000 (243 more to 621 more)

Prostate cancer-specific death[5] Follow-up: median 29 to 84 months	2,261 (3 RCTs)	⊕⊕⊕⊖ MODERATE [6]	RR 0.79 (0.70 to 0.89)	Study population[7]	
				512 per 1,000	108 fewer per 1,000 (154 fewer to 56 fewer)
Time to progression (absolute effect size estimates based on progression rate at 5 years) Follow-up: median 43 to 84 months	2,261 (3 RCTs)	⊕⊕⊕⊖ MODERATE [6]	HR 0.63 (0.56 to 0.71)	Study population[8]	
				822 per 1,000	159 fewer per 1,000 (202 fewer to 116 fewer)
Discontinuation due to adverse events Follow-up: median 50 months	385 (1 RCT)	⊕⊕⊖⊖ LOW [9]	RR 79.41 (4.92 to 1282.78)	Study population	
				0 per 1,000	41 more per 1,000 (25 more to 1000 more)
All adverse events Follow-up: median 50 months	375 (1 RCT)	⊕⊕⊖⊖ LOW [4]	RR 1.11 (1.06 to 1.17)	Study population	
				898 per 1,000	99 more per 1,000 (54 more to 153 more)
Quality of life at 12 months (measured with the Functional Assessment of Cancer Therapy-Prostate (FACT-P) scale, higher score is better)	790 (1 RCT)	⊕⊕⊖⊖ LOW [10]	-	The mean quality-of-life (FACT-P) score in the control arm was 116.4	MD 2.85 higher (0.13 higher to 5.57 higher)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **HR:** hazard ratio; **RR:** Risk ratio; **OR:** Odds ratio; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Baseline risk of death for any cause was calculated from the 5-year event rate of control group from CHAARTED trial (Kyriakopoulos 2018).
[2] Population data from SEER registry, prostate cancer stage IV 5-year survival (70.2%) in the pre-docetaxel era (2007 to 2013).
[3] Severe concerns regarding study limitations (high risk of performance bias) contributed to our decision to downgrade by one level overall.
[4] Severe concerns regarding study limitations (high risk of performance and detection bias), imprecision (wide CI consistent with both large and very large increase in grade III to V adverse events), and additional concerns about selective reporting (outcome only adequately reported by one of three trials) contributed to our decision to downgrade by two levels overall.
[5] We planned to assess this as a time-to-event outcome (time to prostate cancer-specific death), but we evaluated this as a dichotomous outcome due to insufficient data.
[6] Severe concerns regarding study limitations (high risk of performance bias and unclear risk of detection bias) contributed to our decision to downgrade by one level overall.
[7] Baseline risk of prostate cancer-specific death was calculated from the 5-year event rate of control group from the GETUG-AFU15 trial.
[8] Baseline risk of progression was calculated from the 5-year event rate of control group from CHAARTED trial (Kyriakopoulos 2018).
[9] Severe concerns regarding study limitations (high risk of performance and detection bias), imprecision (wide confidence intervals suggesting small and very large increase in treatment discontinuation due to adverse events), and additional concerns about selective reporting (outcome only adequately reported by one of three trials) contributed to our decision to downgrade by two levels overall.
[10] Very severe concerns regarding study limitations (high risk of detection, performance and attrition bias) contributed to our decision to downgrade by two levels overall.

Anmerkung/Fazit der Autoren

Compared to ADT alone, the early (within 120 days of beginning ADT) addition of taxane-based chemotherapy to ADT for hormone-sensitive prostate cancer probably prolongs both overall and disease-specific survival and delays disease progression. There may be an increase in toxicity with taxane-based chemotherapy in combination with ADT. There may also be a small, clinically unimportant improvement in quality of life at 12 months with taxane-based chemotherapy and ADT treatment.

3.3 Systematische Reviews

Buonerba C et al., 2020 [3].

Predictors of efficacy of androgen-receptor-axis-targeted therapies in patients with metastatic castration-sensitive prostate cancer: A systematic review and meta-analysis

Fragestellung

Both docetaxel and androgen-receptor-axis-targeted (ARAT) agents are approved in metastatic castration-sensitive prostate cancer (mCSPC) patients. Predictive factors of therapy efficacy are lacking.

In this systematic review and meta-analysis, we aimed to identify baseline clinical characteristics associated with differential benefit from ARATs. We focused on the results obtained with ARAT agents to compute quantitatively their overall efficacy as a pharmaceutical class.

Hence, we adopted a novel statistical approach that we and others have applied elsewhere (Buonerba et al., 2020, 2019; Conforti et al., 2018) to explore potential baseline factors associated with heterogeneity of efficacy outcomes.

Methodik

Population:

- Metastatic castration-sensitive prostate cancer (mCSPC)

Intervention:

- androgenreceptor-axis-targeted (ARAT) agents plus ADT

Komparator:

- ADT

Endpunkte:

- The primary objective of the meta-analysis was to obtain pooled estimates of the hazard ratios for progression or death (PFS-HRs) and the hazard ratios for death (OS-HRs)

Recherche/Suchzeitraum:

- PubMed, Cochrane Library and EMBASE
- published since inception until March, 30th 2020

Qualitätsbewertung der Studien:

- Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- n = 5

Charakteristika der Population:

- Five different open-label RCTs of were included. All RCTs included were two arm phase III trials.

- Two studies, the LATITUDE (Fizazi et al., 2019) and the STAMPEDE trials (James et al., 2017; Hoyle et al., 2019),
- compared abiraterone plus prednisone plus ADT vs. ADT alone. LATITUDE was a placebo-controlled trial that included mCSPC patients showing at least 2 of 3 high-risk features, including a Gleason score of 8 or more (on a scale of 2–10, with higher scores indicating more aggressive disease),>= 3 bone metastases and measurable visceral metastasis. STAMPEDE was an open-label trial enrolling men with both non-metastatic and metastatic castration-sensitive prostate cancer testing multiple additional systemic therapies in addition to standard of care (Sydes et al., 2012). Only data obtained in mCSPC men randomized to abiraterone plus prednisone plus ADT vs. ADT alone were considered for the purposes of this meta-analysis. Both trials did not enroll men pretreated with docetaxel. While the LATITUDE trial had a Jadad score of 5, the STAMPEDE trial had a Jadad score of 3 because of the lack of double blindness. The ARCHES (Armstrong et al., 2019) and ENZAMET trials (Davis et al., 2019) both tested enzalutamide in men with mCSPC and allowed pretreatment or concurrent treatment with docetaxel, respectively. While the ARCHES trial was double-blind and placebo controlled (Jadad Score, 5), the ENZAMET trial was open-label (Jadad score, 3) and a standard nonsteroidal antiandrogen therapy was used in the comparator arm. Finally, the double-blinded TITAN (Chi et al., 2019) trial randomized mCSPC men to apalutamide plus ADT vs. placebo plus ADT, with docetaxel being allowed before enrollment in the trial.

Main characteristics of the trials and trial populations included in the quantitative meta-analysis.

Ref.	Interventions	Primary end point	Secondary end points	Age (median, range)	PFS (median,range)	OS (median, range)	Use of subsequent therapies (%)	Follow-up (median, range)	baseline PSA (median, range)
LATITUDE (Fizazi et al., 2019)	AAPrednisone + ADT	OS - rPFS		67.3	33.0 (29.6-NR)	53.3 (48.2-NR)	30 %	51.8 (47.2–57.0)	
	PLACEBO + ADT			66.8	14.8 (14.7–18.3)	36.5 (33.5–40.0)	57 %		
TITAN (Chi et al., 2019)	APALUTAMIDE + ADT	OS - rPFS		69 (45–94)	NE	NE	37.6 %	22.7	5.97 (0–2682) ug/l
	PLACEBO + ADT			68 (43–90)	22.1 (18.5–32.9)	NE	60.9 %		4.02 (0–2229) ug/l
ENZAMET (Davis et al., 2019)	ENZALUTAMIDE	OS	cPFS	69.2 (63.2–74.5)	80 % at 3 years	0.80 (0.75–0.83)	67 %	34	
	STANDARD CARE			69 (63.6–74.5)	72 % at 3 years	0.72 (0.68–0.76)	85 %		
ARCHES (Armstrong et al., 2019)	ENZALUTAMIDE + ADT	rPFS	OS	70 (46–95)	NR	NR		14.4	5.4 (0–4,823.5) ng/ml.
	PLACEBO + ADT			70 (42–92)	19.0 (16.6–22.2)	NR			5.1 (0–19,000.0) ng/ml.
STAMPEDE (James et al., 2017; Hoyle et al., 2019)	COMBINATION THERAPY	OS	PFS	67 (62.5–71.5)	HR 0.61 CI 95 % (0.49–0.79)	HR 0.45 CI 95 % (0.37–0.54)		42	113.5 (37.5–394.5)
	ADT			67 (62.5–73)					111 (30.5–453.5)

Gemeinsamer Bundesausschuss

Qualität der Studien:

siehe oben (Charakteristika)

Studienergebnisse:

Overall, a total of 5427 mCSPC patients enrolled in five RCTs were evaluable for OS and PFS. Pooled OS-HR was 0.66 (95 % CI: 0.60−0.74), with no significant heterogeneity (p = 0.87, I^2 = 0.0 %) (Fig. 2). Pooled PFS-HR was 0.46 (95 % CI: 0.40−0.53), with significant heterogeneity (p = 0.02, I^2 = 63.5 %) (Fig. 3).

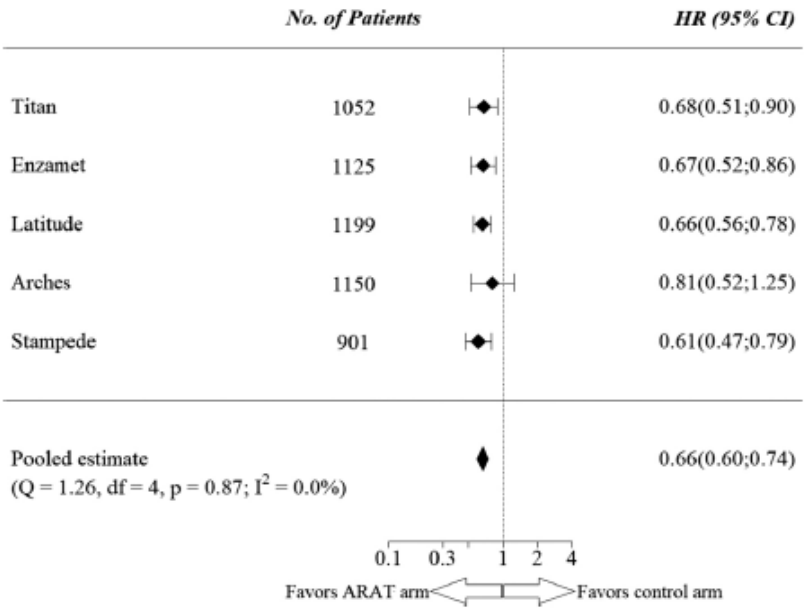


Fig. 2. Pooled HR for death of the trials included.

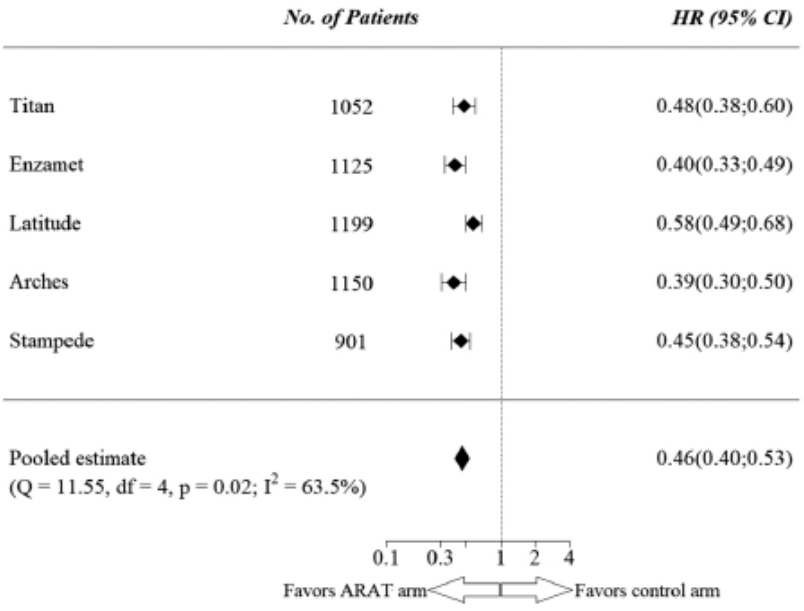


Fig. 3. Pooled HR for progression or death of the trials included.

Among these 8 different dichotomous baseline variables, we found significant heterogeneity for OS-HR in men who had been pretreated or concurrently treated with docetaxel vs. men who were naïve to docetaxel (interaction OS-HR = 1.77; 95 % CI = 1.12–2.77; p = 0.0134) (Fig. 4).

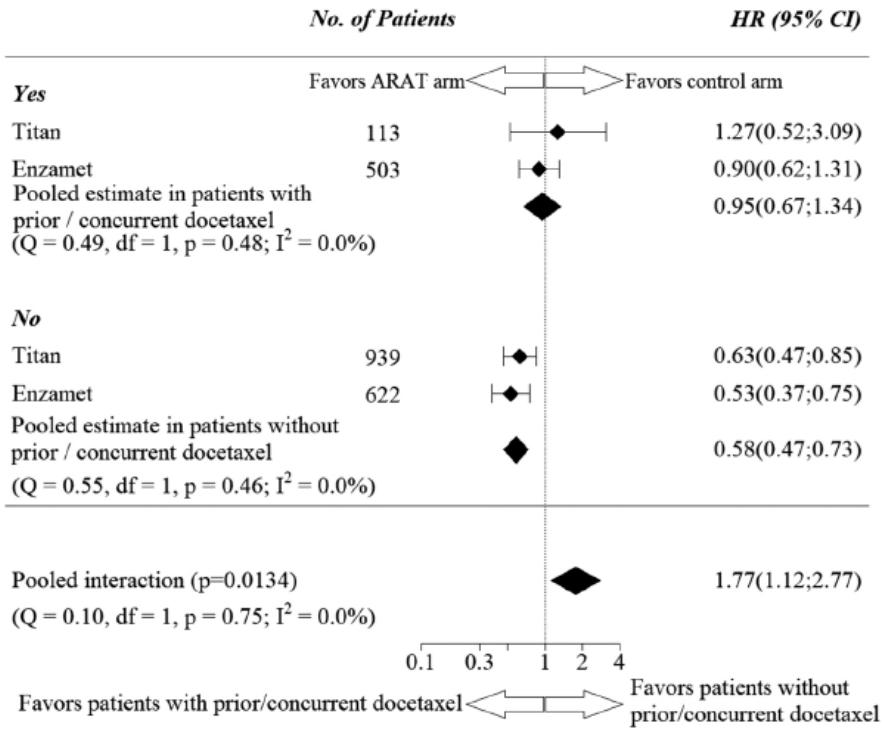


Fig. 4. Interactions between HR for death and previous docetaxel use.

Men who had a high -disease burden vs. men who had a low disease burden had worse PFS benefit associated with ARAT agents (interaction PFS-HR = 1.27; 95 % CI = 1.01–1.59; p = 0.0395) (Fig. 5).

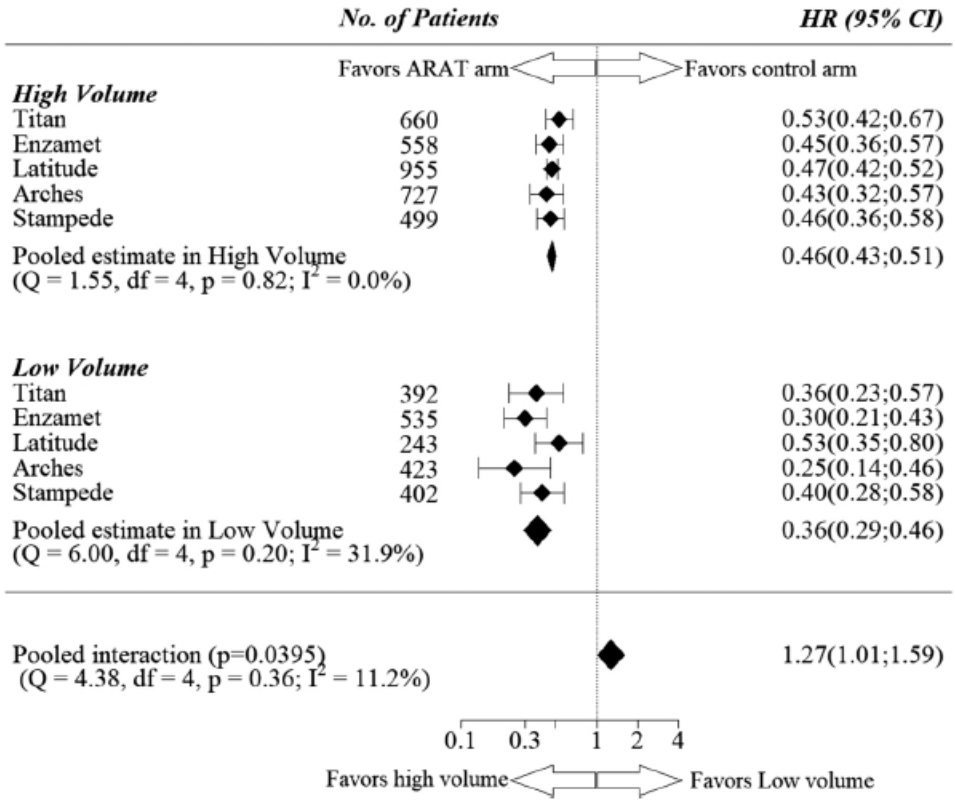


Fig. 5. Interactions between HR for progression or death and tumor volume.

Similarly, men with visceral metastases vs. men without visceral metastasis also showed less benefit from ARAT in terms of PFS (interaction PFS-HR = 1.35; 95 % CI = 1.02–1.79; p = 0.0347) (Fig. 6).

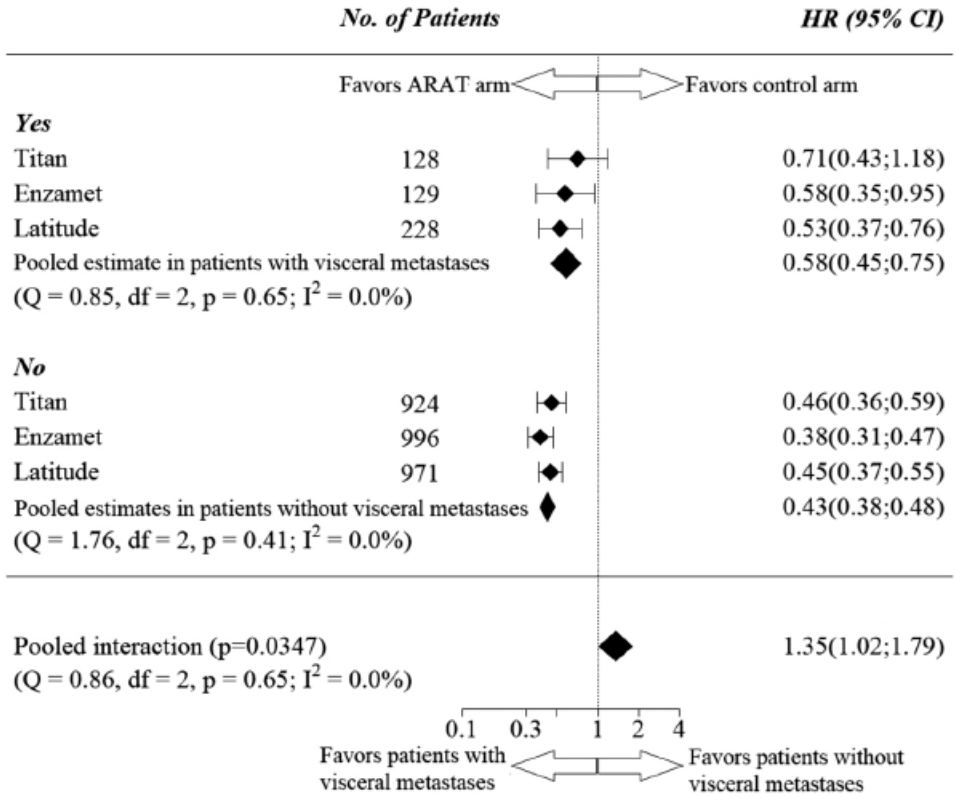


Fig. 6. Interactions between HR for progression or death and presence of visceral metastasis.

No significant interaction was found for OS-HR and ECOG PS, Gleason score, age, LDH, PSA, tumor volume, visceral metastasis (Table 2) and for PFS-HR and ECOG PS, Gleason score, age, LDH, PSA, prior/concurrent docetaxel (Table 3).

Anmerkung/Fazit der Autoren

In conclusion, our results discourage the sequential or concurrent use of both docetaxel and an ARAT agent regardless of tumor volume or other factors. It is also interesting to note that prior docetaxel use and tumor volume/presence of visceral metastasis were the only factors showing a negative influence on ARAT efficacy among the eight considered, which underlines the need for predictive factors in this setting. Further large, randomized clinical trials, such as the ongoing PEACE1 study, are required to define optimal treatment choice in men with mCSPC.

Abufaraj, M et al., 2020 [1].

Differential Impact of Gonadotropin-releasing Hormone Antagonist Versus Agonist on Clinical Safety and Oncologic Outcomes on Patients with Metastatic Prostate Cancer: A Meta-analysis of Randomized Controlled Trials

Fragestellung

Androgen deprivation therapy is the mainstay treatment of metastatic prostate cancer, achieved mainly by gonadotropin-releasing hormone (GnRH) agonists or antagonists. Objective: To

investigate the differential impact of GnRH agonists and antagonists on clinical safety and oncologic outcomes.

Methodik

Population:

- patients with metastatic PCa

Intervention:

- Gonadotropin-releasing hormone (GnRH) antagonists

Komparator:

- agonists

Endpunkte:

- oncologic outcomes and AEs (nicht näher präspäzifiziert)

Recherche/Suchzeitraum:

- This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. A PRISMA 2009 checklist was completed to describe the methodology of our study (Supplementary Table 1). We searched the electronic databases (MEDLINE, Web of Science, Cochrane Library, and Scopus) in May 2019 for trials comparing the clinical safety and oncologic outcomes between GnRH antagonist and agonist. We updated the search in April 2020 and included one phase 2 trial [9] that was identified in the initial search as a meeting abstract.

Qualitätsbewertung der Studien:

- Two reviewers independently assessed the risk of bias (RoB) of each individual study. An evaluation of RoB of the included studies was performed according to the Cochrane handbook.

Ergebnisse

Anzahl eingeschlossener Studien:

eight clinical trials (20 published studies) comparing GnRH agonists with antagonist in patients with metastatic PCa for inclusion in this systematic review and meta-analysis.

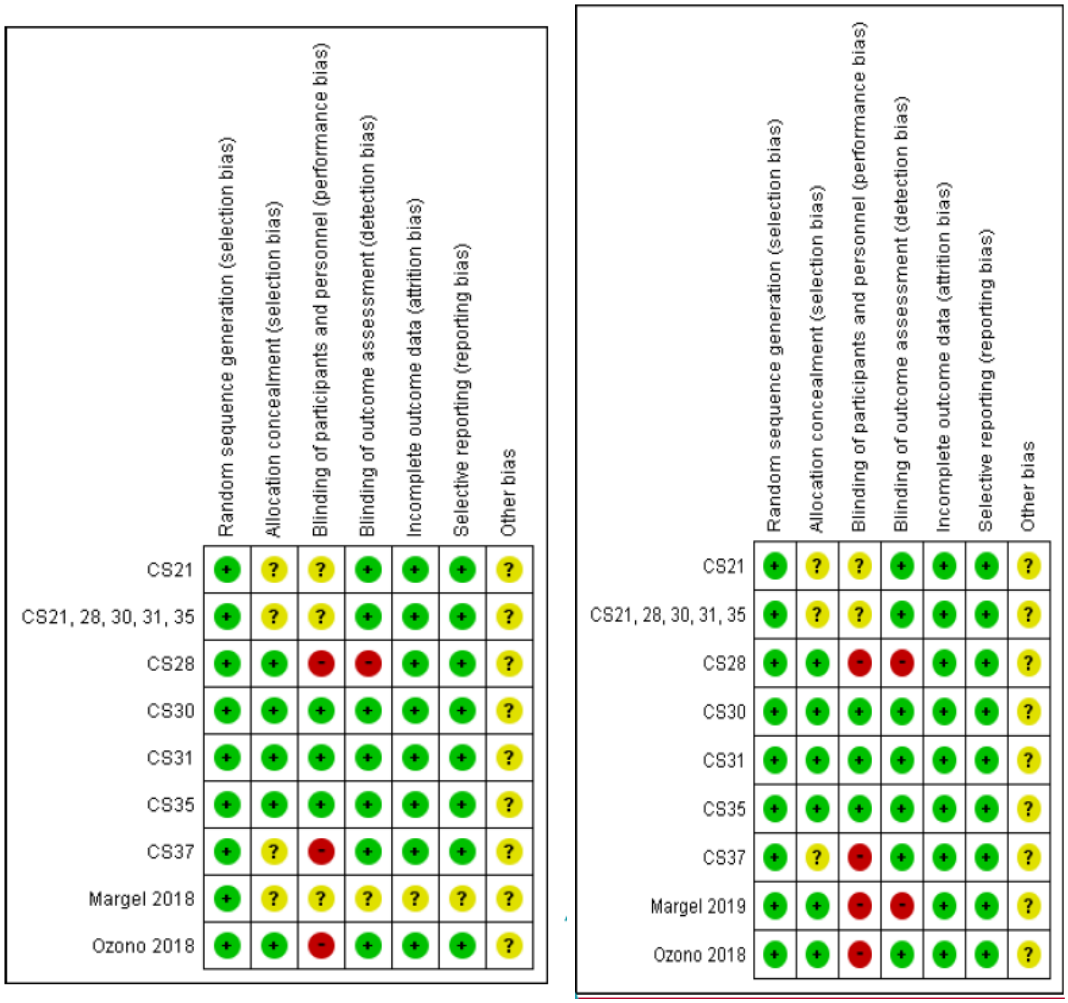
Charakteristika der Population:

Table 1 – Characteristics of randomized controlled trials assessing gonadotropin-releasing hormone agonists versus antagonists included in meta-analysis.

Trial	Year	*n*	Arm	Follow-up (mo)	Inclusion criteria	Primary endpoint
CS21 Klotz et al [4]	2008	610	Degarelix 240/80 mg Or Degarelix 240/160 mg Or Leuprorelin 7.5 mg ± bicalutamide	12	PCa (all stage) except for neoadjuvant hormonal therapy PSA level ≥2 ng/ml	Percentage of patients with testosterone level ≤0.5 ng/ml
CS28 Anderson et al [12]	2013	40	Degarelix 240/80 mg Or Goserelin 3.6 mg + bicalutamide	3	Treatment-naïve PCa (all stage) PSA level ≥10 ng/ml IPSS ≥12 Prostate size >30 ml	Change from baseline in IPSS
CS30 Mason et al [7]	2013	245	Degarelix 240/80 mg Or Goserelin 3.6 mg + bicalutamide	3	Treatment-naïve PCa planned radiotherapy (T2b-4 N0 M0) Gleason score ≥7 PSA level ≥10 ng/ml Prostate size >30 ml	Change from baseline in prostate size
CS31 Axcrona et al [13]	2012	173	Degarelix 240/80 mg Or Goserelin 3.6 mg + bicalutamide	3	Treatment-naïve PCa (all stage) PSA level ≥2 ng/ml Prostate size >30 ml	Change from baseline in prostate size
CS35 Tombal et al [15]	2012	847	Degarelix 240/480 mg Or Goserelin 3.6 mg ± bicalutamide	12	PCa (all stage) except suitable for curative therapy Testosterone >2.2 ng/ml	Percentage of patients with testosterone level ≤0.5 ng/ml
CS37 Higano et al [11]	2015	403	Continuous or intermittent degarelix 240/80 mg Or Leuprorelin 7.5 mg	14	PSA failure after curative treatment without metastasis Testosterone >1.5 ng/ml	Percentage of patients with PSA level ≤4 ng/ml
Ozono et al [14]	2018	234	Degarelix 240/480 mg Or Goserelin 3.6/10.8 mg ± bicalutamide	12	PCa (all stage) except suitable for curative therapy PSA level ≥2 ng/ml Testosterone >2.2 ng/ml	Cumulative castration rate of treatment in terms of testosterone level
Margel et al [9]	2019	80	Degarelix or GnRH agonist	12	High-risk or metastatic PCa	Endothelial function

GnRH = gonadotropin-releasing hormone; IPSS = International Prostate Symptom Score; PCa = prostate cancer; PSA = prostate-specific antigen.

Qualität der Studien:



Studienergebnisse:

- Oncologic outcomes

There was no significant difference in PSA progression between GnRH antagonist and agonist (RR: 1.02, 95% CI: 0.69–1.50, p = 0.92; Fig. 4A). GnRH antagonist was associated with lower overall mortality rates than GnRH agonist (RR: 0.48, 95% CI: 0.26–0.90, p = 0.02; Fig. 4B and Table 3). The Cochrane's Q and I^2 tests did not show any heterogeneity in all pooled analyses (Fig. 4).

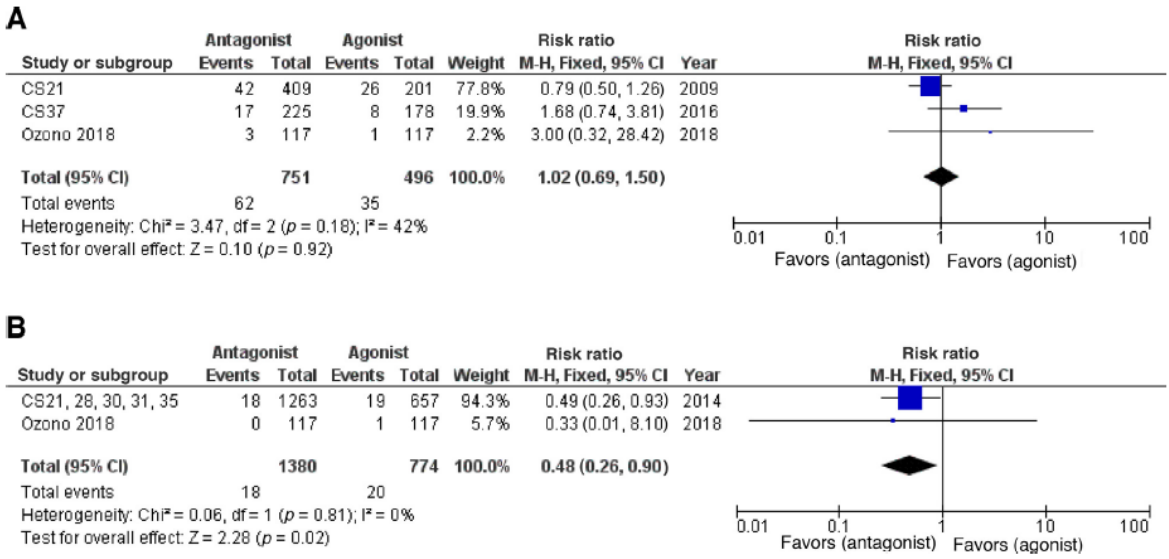


Fig. 4 – (A) PSA progression and (B) overall mortality in patients who received gonadotropin-releasing hormone agonists or antagonists. CI = confidence interval; M-H = Mantel-Haenszel; PSA = prostate-specific antigen.

- Clinical safety outcomes

  Safety outcomes were investigated in seven trials including 2552 patients with metastatic PCa treated with GnRH antagonist and agonists. Treatment-emerging AE rates were 73% for GnRH antagonist and 68% for GnRH agonist (RR: 1.10, 95% CI: 1.04–1.15, p < 0.001; Fig. 2A). Rates of serious adverse effects (SAEs) were 9.8% for GnRH antagonist and 11% for GnRH agonist (RR: 0.92, 95% CI: 0.73–1.17, p = 0.49) (Fig. 2B). Dropout rates due to AEs were 6.5% for GnRH antagonist and 5.9% for GnRH agonist (RR: 1.12, 95% CI: 0.81–1.54, p = 0.49; Fig. 2C). The Cochrane's Q and I2 tests showed significant heterogeneity in pooled analysis in AEs (Fig. 2A), and did not show heterogeneity in pooled analyses of SAEs or dropout (Fig. 2B and 2C). There was no difference in the subgroup analysis including goserelin only (Supplementary Fig. 2A).

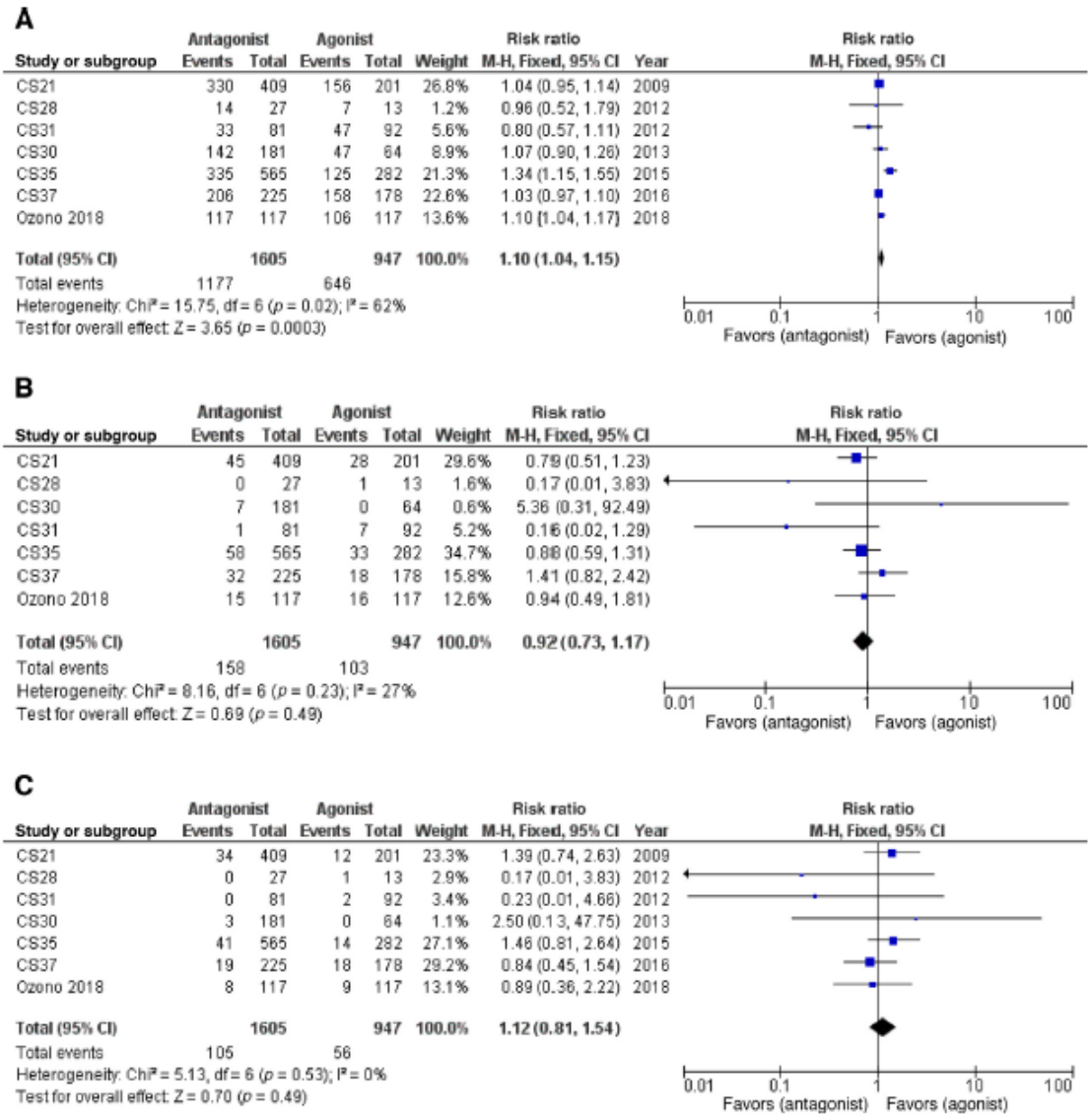


Fig. 2 – (A) Adverse effects (AEs) in patients who received gonadotropin-releasing hormone agonists or antagonists. (B) – Serious adverse effects (SAEs) of gonadotropin-releasing hormone agonists or antagonists. (C). Dropout rates due to adverse effects of gonadotropin-releasing hormone agonists or antagonists.
CI=confidence interval; M-H= Mantel-Haenszel.

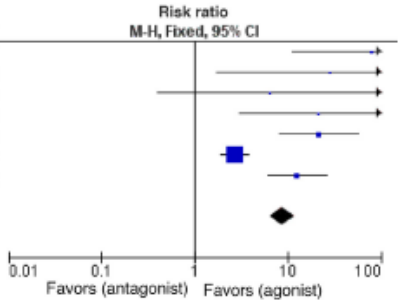
- Adverse effects

  GnRH antagonist was associated with higher injection site reaction rates (38%) compared with GnRH agonists (4.8%; RR: 8.73, 95% CI: 6.48–11.78, p < 0.001; Fig. 3A). There was no significant difference in fatigue (RR: 0.91, 95% CI: 0.69–1.21, p = 0.52) between GnRH antagonist and agonists (Fig. 3B and Table 2). GnRH antagonist was associated with fewer musculoskeletal (RR: 0.76, 95% CI: 0.60–0.95, p = 0.02) and cardiovascular events (RR: 0.52, 95% CI: 0.34–0.80, p = 0.003) compared with GnRH agonist (Fig. 3C and 3D). The Cochrane's Q and I2 tests showed significant heterogeneity in pooled analyses in injection site reaction and musculoskeletal events (Fig. 3A and 3C), and did not show any heterogeneity in pooled analyses of fatigue or cardiovascular events (Fig. 3B and 3D). There was no difference in the subgroup analysis including goserelin only (Supplementary Fig. 2B and 2C).

A

Study or subgroup	Antagonist Events	Antagonist Total	Agonist Events	Agonist Total	Weight	Risk ratio M-H, Fixed, 95% CI	Year
CS21	162	409	1	201	2.6%	79.61 (11.23, 564.49)	2009
CS31	12	81	0	92	0.9%	28.35 (1.71, 471.45)	2012
CS28	6	27	0	13	1.3%	6.50 (0.39, 107.32)	2012
CS30	60	181	1	64	2.8%	21.22 (3.00, 149.95)	2013
CS35	173	565	4	282	10.3%	21.59 (8.09, 57.57)	2015
CS37	108	225	32	178	68.7%	2.67 (1.90, 3.76)	2016
Ozono 2018	88	117	7	117	13.5%	12.57 (6.08, 25.98)	2018
Total (95% CI)		**1605**		**947**	**100.0%**	**8.73 (6.48, 11.78)**	
Total events	609		45				

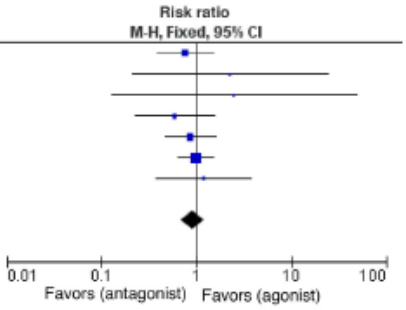
Heterogeneity: Chi² = 56.76, df = 6 (p < 0.00001); I² = 89%
Test for overall effect: Z = 14.21 (p < 0.00001)



B

Study or subgroup	Antagonist Events	Antagonist Total	Agonist Events	Agonist Total	Weight	Risk ratio M-H, Fixed, 95% CI	Year
CS21	20	409	13	201	19.7%	0.76 (0.38, 1.49)	2009
CS31	2	81	1	92	1.1%	2.27 (0.21, 24.59)	2012
CS28	2	27	0	13	0.8%	2.50 (0.13, 48.62)	2012
CS30	10	181	6	64	10.0%	0.59 (0.22, 1.56)	2013
CS35	26	565	15	282	22.6%	0.87 (0.47, 1.61)	2015
CS37	40	225	32	178	40.3%	0.99 (0.65, 1.51)	2016
Ozono 2018	6	117	5	117	5.6%	1.20 (0.38, 3.82)	2018
Total (95% CI)		**1605**		**947**	**100.0%**	**0.91 (0.69, 1.21)**	
Total events	106		72				

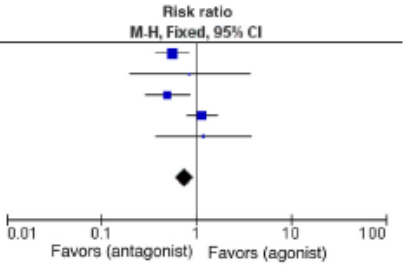
Heterogeneity: Chi² = 2.46, df = 6 (p = 0.87); I² = 0%
Test for overall effect: Z = 0.64 (p = 0.52)



C

Study or subgroup	Antagonist Events	Antagonist Total	Agonist Events	Agonist Total	Weight	Risk ratio M-H, Fixed, 95% CI	Year
CS21	43	409	38	201	37.2%	0.56 (0.37, 0.83)	2009
CS31	3	81	4	92	2.7%	0.85 (0.20, 3.69)	2012
CS35	26	565	26	282	25.4%	0.50 (0.30, 0.84)	2015
CS37	55	225	38	178	31.0%	1.15 (0.80, 1.65)	2016
Ozono 2018	6	117	5	117	3.7%	1.20 (0.38, 3.82)	2018
Total (95% CI)		**1397**		**870**	**100.0%**	**0.76 (0.60, 0.95)**	
Total events	133		111				

Heterogeneity: Chi² = 10.29, df = 4 (p = 0.04); I² = 61%
Test for overall effect: Z = 2.40 (p = 0.02)



D

Study or subgroup	Antagonist Events	Antagonist Total	Agonist Events	Agonist Total	Weight	Risk ratio M-H, Fixed, 95% CI	Year
CS21	7	409	10	201	24.8%	0.34 (0.13, 0.89)	2009
CS31	0	81	1	92	2.6%	0.38 (0.02, 9.15)	2012
CS35	14	565	11	282	27.2%	0.64 (0.29, 1.38)	2015
CS37	13	225	10	178	20.7%	1.03 (0.46, 2.29)	2016
Margel 2019	2	41	13	39	24.7%	0.15 (0.04, 0.61)	2019
Total (95% CI)		**1321**		**792**	**100.0%**	**0.52 (0.34, 0.80)**	
Total events	36		45				

Heterogeneity: Chi² = 6.87, df = 4 (p = 0.14); I² = 42%
Test for overall effect: Z = 3.00 (p = 0.003)

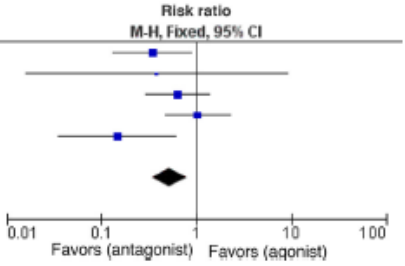


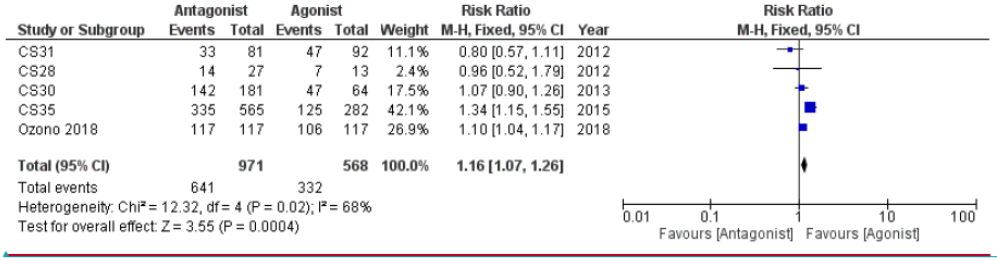
Fig. 3 – (A) Injection site reaction rates, (B) fatigue rates, (C) musculoskeletal events, and (D) cardiovascular events in patients who received gonadotropin-releasing hormone agonists or antagonists.
CI = confidence interval; M-H = Mantel-Haenszel.

Table 2 – Adverse effects of gonadotropin-releasing hormone agonists and antagonist included in meta-analysis.

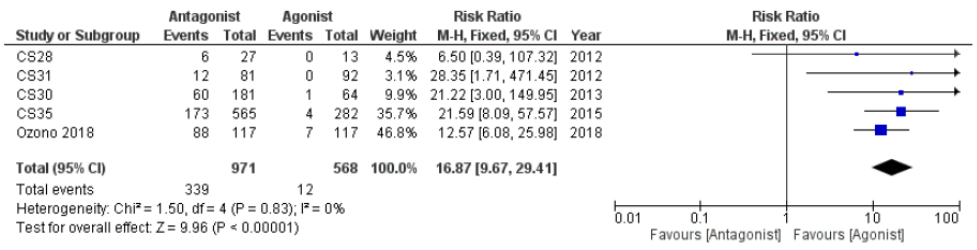
Study	Year	Arm	N	AEs (%)	SAEs (%)	Injection site reaction (%)	Fatigue (%)	Musculoskeletal events (%)	Fracture (%)	Cardiovascular events (%)
CS21	2008	Degarelix	409	81	11	40	4.9	11	0.5	1.7
Klotz et al [4]		Agonist	401	78	14	0.5	6.5	19	1.5	5.0
CS28	2014	Degarelix	27	52	0	22	7.4	0	0	0
Anderson et al [12]		Agonist	13	54	7.7	0	0	0	0	0
CS30	2013	Degarelix	181	79	3.9	33	5.5	0	0	0
Mason et al [7]		Agonist	64	73	0	1.6	9.4	0	0	0
CS31	2012	Degarelix	81	39	1.2	15	-	4.6	0.2	0
Axcrona et al [13]		Agonist	92	48	7.1	0		7.4	0.4	1.1
CS35	2012	Degarelix	565	60	10	31	4.6	4.6	0.2	2.5
Tombal et al [15]		Agonist	282	44	12	1.4	5.3	9.2	0.4	3.9
CS37	2015	Degarelix	225	92	14	48	18	24	0	5.8
Higano et al [11]		Agonist	178	89	10	18	18	21	0.6	5.6
Ozono et al [14]	2018	Degarelix	117	100	13	75	8.5	5.1	-	-
		Agonist	117	91	14	6.0	3.4	4.3		
Margel et al [9]	2019	Degarelix	41	-	-	-	-	-	-	4.8
		Agonist	39							33

AE = adverse effect; SAEs = serious adverse effect.

Supplementary Figure 2A. Adverse effects (AEs) in patients who received gonadotropin-releasing hormone agonists (goserelin only) or antagonists



Supplementary Figure 2B. Injection site reaction rates in patients who received gonadotropin-releasing hormone agonists (goserelin only) or antagonists



Anmerkung/Fazit der Autoren

GnRH antagonist is associated with lower all-cause mortality rates and cardiovascular events as compared with GnRH agonists, based on trials having relatively short follow-ups and assessing cardiovascular events as secondary endpoints. There was no significant difference in dropout rates, fatigue, or musculoskeletal events between these two forms of ADT. On the contrary, injection site reactions were higher in patients treated with GnRH antagonist. While such data provide physicians with useful information for patient counseling about the potential benefits and risks of GnRH antagonist and agonist, such conclusions should be interpreted carefully within the context of the aforementioned limitations.

Di Nunno V et al., 2020 [4].

Systemic Treatment for Metastatic Hormone Sensitive Prostate Cancer: A Comprehensive Meta-Analysis Evaluating Efficacy and Safety in Specific Sub-Groups of Patients

Fragestellung

Several systemic treatments are available for metastatic hormone sensitive prostate cancer (mHSPC) including docetaxel (D), abiraterone and prednisone (A + P) and new anti-androgens (NA). In our study we performed a systematic review and meta-analysis assessing efficacy outcomes (survival and radiological-free survival), safety and survival on specific subgroups of patients.

Methodik

Population:

- metastatic hormone sensitive prostate cancer (mHSPC)

Intervention:

- new hormonal agent or other compounds in addition to ADT

Komparator:

- nicht definiert

Endpunkte:

- Risk of death, biochemical and radiological progression among all patients.
- Risk of death according to different pathological/clinical features.
- Evaluation of the relative risk (RR) and risk difference of serious toxicity defined as adverse events (AEs) with grade ≥ 3 specific AEs.

Hazard ratios (HRs) and RR were measures adopted for endpoints.

Recherche/Suchzeitraum:

- published between 01 January 2012 to 15 September 2019

Qualitätsbewertung der Studien:

- Cochrane tool for risk of bias assessment in randomized trials

Ergebnisse

Anzahl eingeschlossener Studien:

- eight randomized trials were included in meta-analysis for a total of 9987 patients
- all perspective, randomized Phase III clinical trials

Charakteristika der Population:

Overall, 9987 patients were included in this meta-analysis. Of these, 4994 patients received ADT monotherapy, while 4993 received ADT plus experimental compounds. In particular, among 4993 patients included in experimental arms, 1774 received docetaxel (593 also received zoledronic acid), 1557 received abiraterone, 1662 were treated with enzalutamide (n = 1137) and apalutamide (n = 525).

Of note, in the STAMPEDE trials, we considered only patients with metastatic disease for bPFS, rPFS, OS and subgroup analyses (Table 2).

Table 1 Description of studies included in meta-analysis

GETUG-AFU-15 [5, 6]

Randomized, open-label, Phase 3 trial evaluating androgen-deprivation therapy (ADT) ± docetaxel (75 mg/m^2) in patients with radiologically proven mHSPC

Primary endpoint: overall survival (OS)

Secondary endpoints: clinical progression-free survival (cPFS), biochemical progression-free survival (bPFS)

No. of patients

192 in ADT + Docetaxel arm, 193 in ADT alone arm

Median follow-up

83.9 months

Primary endpoint (mOS)

Hazard ratio (HR): 0.88 (95% CI, 0.68–1.14, $p = 0.3$)

Secondary endpoints (bPFS, rPFS)

0.69 (95% CI, 0.55–0.87; $p = 0.002$);

HR: 0.67 (95% CI, 0.54–0.84; $p < 0.001$)

CHAARTED [7, 8]

Randomized, open-label, Phase 3 trial evaluating androgen-deprivation therapy (ADT) ± docetaxel (75 mg/m^2) in patients with radiologically proven mHSPC

Primary endpoint: overall survival (OS)

Secondary endpoints: time to development of castration resistant prostate cancer (TCRPC). Two amendments were made in this study: the first allowed the inclusion of patients with low volume metastatic disease (high volume metastatic disease was defined as: presence of visceral metastases or 4 or more bone lesions with one or more lesions beyond vertebral bodies and pelvis) and the second which expanded the initial overall cohort to 780 patients

No. of patients

397 in ADT + docetaxel arm, 393 in ADT alone arm

Median follow-up

53.7 months

Primary endpoint (mOS)

HR: 0.72 (95% CI, 0.59–0.89; $p = 0.0018$)

Secondary endpoints (TCRPC)

HR: 0.61 (95% CI, 0.52–0.73; $p < 0.001$)

STAMPEDE [9]

STAMPEDE is a multi-arm, multistage trial evaluating multiple distinct strategies in parallel against a single control arm. In this stage, patients with high risk, locally advanced, metastatic or recurrent hormono sensitive prostate cancer were randomized to receive ADT, ADT + zoledronic acid (ZA, 4 mg every 28 days), ADT + ZA + docetaxel (75 mg/mq) or ADT + docetaxel. Primary outcome was OS, secondary outcome failure free survival (FFS)

No. of patients

1184 ADT arm, 593 ADT + ZA, 593 ADT + ZA + docetaxel, 592 ADT + docetaxel

Median follow-up

43 months

Primary endpoint (mOS)

ADT vs ADT + ZA (HR = 0.94, 95% CI 0.79–1.11; $p = 0.45$)

ADT vs ADT + docetaxel (HR = 0.78, 95% CI 0.66–0.93; $p = 0.006$)

ADT vs ZA + docetaxel (HR = 0.82, 95% CI 0.69–0.97; $p = 0.022$)

Secondary endpoints (FFS)

ADT vs ADT + ZA (HR = 0.92, 95% CI 0.81–1.04, $p = 0.198$)

ADT vs ADT + docetaxel (HR = 0.61, 95% CI 0.53–0.70, $p < 0.001$)

ADT vs ZA + docetaxel (HR = 0.62, 95% CI 0.54–0.70; $p < 0.001$)

LATITUDE [10]

Double-blind, placebo-controlled, Phase 3 trial comparing ADT alone to ADT + abiraterone (1000 mg daily) + prednisone (5 mg daily). All patients enrolled in this study had a diagnosis of mHSPC. Moreover only patients with two of these risk factors have been enrolled: (1) Gleason of 8 or more, (2) visceral metastases, (3) three or more bone metastases

Primary endpoints: OS, rPFS

Secondary endpoints: time to the next "skeletal-related event", bPFS, time to next treatment, time to initiation of chemotherapy and time to pain progression

Table 1 (continued)

No. of patients
602 ADT + placebo + placebo arm, 597 ADT + abiraterone + prednisone arm

Median follow-up
30.4 months

Primary endpoints (1. mOS, 2. rPFS)
1. ADT + placebo + placebo vs ADT + abiraterone + prednisone (HR = 0.62, 95% CI, 0.51–0.76, $p < 0.001$)
2. ADT + placebo + placebo vs ADT + abiraterone + prednisone (HR = 0.47, 95% CI, 0.39–0.55, $p < 0.001$)

Secondary endpoints (1. time to the next "skeletal-related event", 2. bPFS, 3. time to next treatment, 4. time to initiation of chemotherapy and 5. time to pain progression)
1. ADT + placebo + placebo vs ADT + abiraterone + prednisone (HR = 0. 70, 95% CI 0.54–0.92, $p = 0.009$)
2. ADT + placebo + placebo vs ADT + abiraterone + prednisone (HR = 0.30, 95% CI 0.26–0.35, $p < 0.001$)
3. ADT + placebo + placebo vs ADT + abiraterone + prednisone (HR = 0.42, 95% CI 0.35–0.5, $p < 0.001$)
4. ADT + placebo + placebo vs ADT + abiraterone + prednisone (HR = 0.44, 95% CI 0.35–0.56, $p < 0.001$)
5. ADT + placebo + placebo vs ADT + abiraterone + prednisone (HR = 0.70, 95% CI 0.58–0.83, $p < 0.001$).

STAMPEDE [11]

STAMPEDE is a multi-arm, multistage trial evaluating multiple distinct strategies in parallel against a single control arm. In this stage, patients with newly diagnosed and metastatic, node-positive, or high-risk locally advanced (defined with the presence of two of these risk factors: T3–4, Gleason 8–10, PSA of 40 ng/mL or more) or patients with high-risk disease relapsing after radiation therapy or surgery (defined as a PSA > 4 ng/mL., with a doubling time < 6 months, PSA level > 20 ng/mL., nodal or metastatic relapse or < 12 months of total ADT with an interval of > 12 months without treatment) were randomized to receive ADT alone or ADT + abiraterone (1000 mg) + prednisone (5 mg). Of note, this was not a placebo-controlled trial. Primary outcome was OS while FFS was the intermediate primary endpoint. Adverse events, symptomatic skeletal events, PFS, prostate cancer specific survival and quality of life were secondary endpoints

No. of patients
957 ADT arm, 960 ADT + abiraterone + prednisone arm

Median follow-up
40 months

Primary endpoints (1. mOS, 2. FFS)
1. ADT vs ADT + abiraterone + prednisone (HR = 0.63, 95% CI 0.52–0.76, $p < 0.001$)
2. ADT vs ADT + abiraterone + prednisone (HR = 0.29, 95% CI 0.25–0.34, $p < 0.001$)

Secondary endpoints (1. adverse events, 2. symptomatic skeletal events, 3. PFS, prostate cancer specific survival and 4. quality of life)
1. ADT vs ADT + Abiraterone + prednisone (Grade 3–5 AEs occurred in 33% and 47% respectively)
2. ADT vs ADT + abiraterone + prednisone (HR = 0.46, 95% CI 0.37–0.58, $p < 0.001$)
3. ADT vs ADT + abiraterone + prednisone (HR = 0.40, 95% CI 0.34–0.47, $p < 0.001$)
4. Not reported

ARCHES [14]

Phase III randomized, placebo-controlled clinical trial comparing ADT + placebo vs ADT + enzalutamide (160 mg) in patients with mHSPC. Primary endpoint was rPFS and OS. Secondary endpoints are: bPFS, time to new anticancer treatment, PSA undetectable rate, objective response rate (ORR), time to deterioration in urinary symptoms. To date only data of rPFS final analysis and interim OS analysis have been published

No. of patients
576 ADT + placebo arm, 574 ADT + enzalutamide arm

Median follow-up
Not reported

Primary endpoints (1. mOS, 2. rPFS)
1. Only result of interim analysis reported (immature follow up)
2. ADT + placebo vs ADT + enzalutamide (HR = 0.39, 95% CI 0.30–0.50, $p < 0.0001$)

Secondary endpoints (1. bPFS, 2. time to new anticancer treatment, 3. PSA undetectable rate, 4. objective response rate, 5. time to deterioration in urinary symptoms):
1. ADT + placebo vs ADT + enzalutamide (HR 0.19, 95% CI 0.13–0.26, $p < 0.0001$)
2. ADT + placebo vs ADT + Enzalutamide (HR 0.28, 95% CI 0.20–0.40, $p < 0.0001$)
3. ADT + placebo vs ADT + enzalutamide (17.6% vs 68.1%, $p < 0.0001$)
4. ADT + placebo vs ADT + enzalutamide (63.7% vs 83.1%, $p < 0.0001$)
5. Not reported

Table 1 (continued)

ENZAMET [13]

Open-label, randomized, Phase 3 trial investigating the combination between enzalutamide (160 mg) and ADT versus ADT alone in patients with mHSPC. Primary endpoint was OS while bPFS, clinical PFS, radiological PFS and safety were secondary outcomes. After the enrollment of 88 patients, the early administration of docetaxel with testosterone suppression was permitted. Up to two cycles of docetaxel were permitted before randomization. Randomization was performed considering also the presence of high or low volume disease (high volume disease defined as defined as the presence of visceral metastases or at least four bone lesions with at least one lesion located beyond the vertebral bodies and pelvis)

No. of patients:
562 ADT, 563 ADT + enzalutamide arm

Median follow-up:
34 months

Primary endpoints (1. mOS, 2. PFS):
1.ADT vs ADT + enzalutamide arm (HR 0.67, 95% CI 0.52–0.86, $p = 0.002$)
2.ADT vs ADT + enzalutamide arm (HR clinical PFS = 0.40, 95% CI 0.33–0.49 $p < 0.0001$)

Secondary endpoints (1. bPFS, 2. clinical PFS, and 3. safety)
1. ADT vs ADT + enzalutamide arm (HR clinical PFS = 0.39, 95% CI 0.33–0.47 $p < 0.0001$)
2. ADT vs ADT + enzalutamide arm (HR clinical PFS = 0.40, 95% CI 0.33–0.49 $p < 0.0001$)
3 ADT vs ADT + enzalutamide arm (34% vs 42%)

TITAN [12]

Double-blind, Phase 3 trial comparing apalutamide (240 mg) to placebo in addition to standard ADT in patients with mHSPC. Previous docetaxel treatment was allowed. Primary endpoints were OS and rPFS. Secondary endpoint were: time to cytotoxic chemotherapy, time to pain progression, time to chronic opioid use, time to skeletal-related event
Randomization was performed considering also the presence of high or low volume disease (high volume disease defined as defined as the presence of visceral metastases or at least four bone lesions with at least one lesion located beyond the vertebral bodies and pelvis)

No. of patients
527 ADT + placebo, 525 ADT + apalutamide

Median follow-up
22.7 months

Primary endpoints (1. mOS, 2. rPFS)
1. ADT + placebo vs ADT + apalutamide (HR 0.67; 95% CI 0.51–0.89, $p = 0.005$)
2. ADT + placebo vs ADT + apalutamide (HR 0.48, 95% CI 0.39–0.60, $p < 0.001$)

Secondary endpoints (*1. time to cytotoxic chemotherapy, 2. time to pain progression, 3. time to chronic opioid use, 4. time to skeletal-related event, 5. bPFS*)
1. ADT + placebo vs ADT + apalutamide (HR 0.39, 95% CI 0.27–0.56, $p < 0.0001$)
2. Not performed
3 Not performed
4. Not performed
5. ADT + placebo vs ADT + apalutamide (HR 0.26, 95% CI 0.21–0.32, $p < 0.0001$)

Qualität der Studien:

Table 2 Risk of bias among trials included: + low risk of bias, – high risk of bias, ? uncertain risk of bias

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome and assessment	Incomplete outcome data	Selective reporting	Other bias
GETUG-AFU-15 [5, 6]	+	+	–	–	+	+	+
CHAARTED [7, 8]	+	+	–	–	+	?	+
STAMPEDE [9]	+	+	–	–	+	+	+
LATITUDE [10]	+	+	+	+	+	+	+
STAMPEDE [11]	+	+	–	–	+	+	+
ARCHES [14]	?	+	+	+	–	–	?
ENZAMET[13]	+	+	–	–	+	+	+
TITAN [12]	+	+	+	+	+	+	+

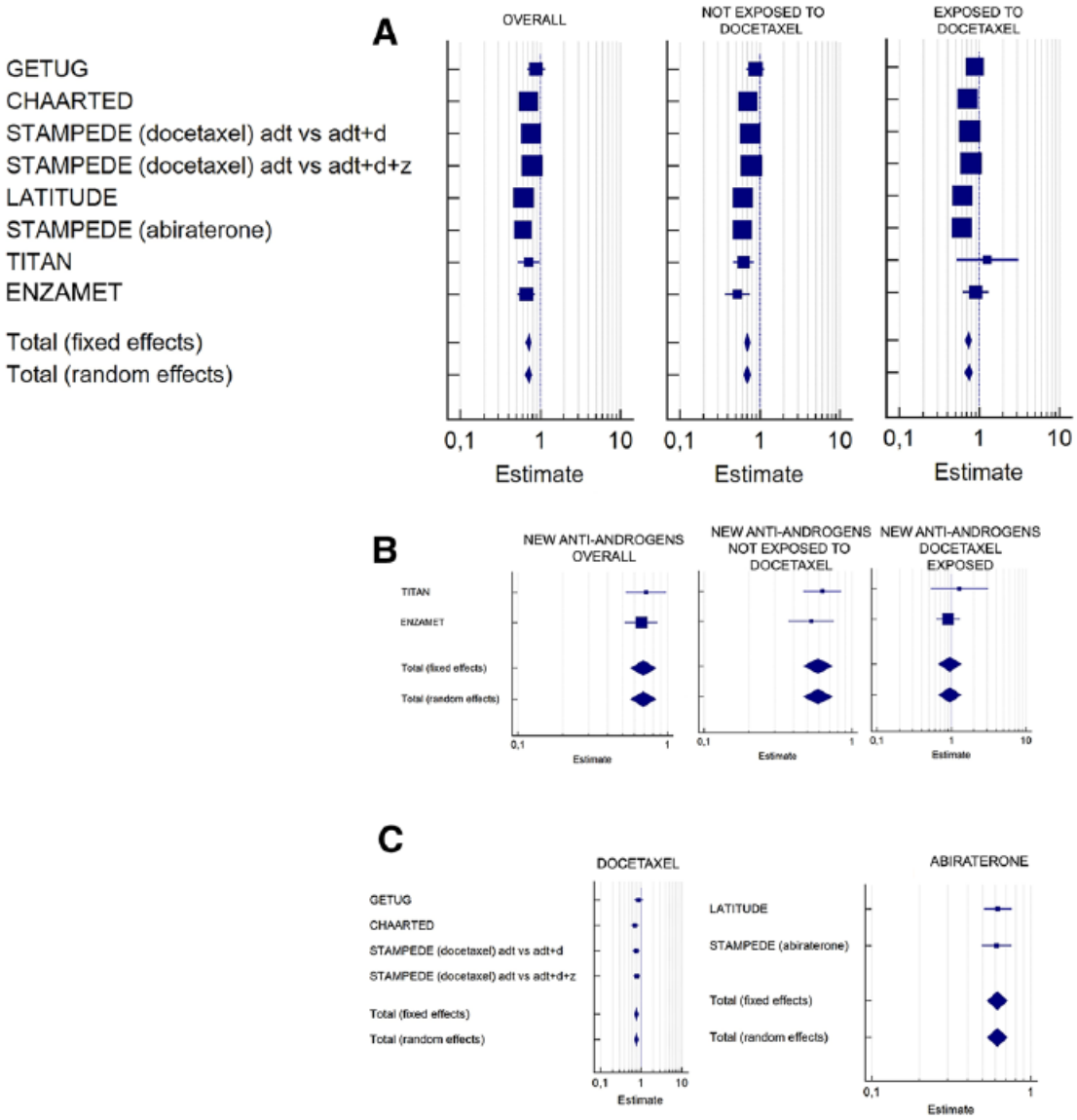
Studienergebnisse:

- Overall survival (OS) analysis among patients with metastatic hormone sensitive prostate cancer.

  a All patients included, including patients not previously exposed to docetaxel, patients previously exposed to docetaxel.

  b New anti-androgens overall, exposed and not previously exposed to docetaxel.

c OS result among metastatic patients receiving docetaxel; OS result among metastatic patients receiving abiraterone

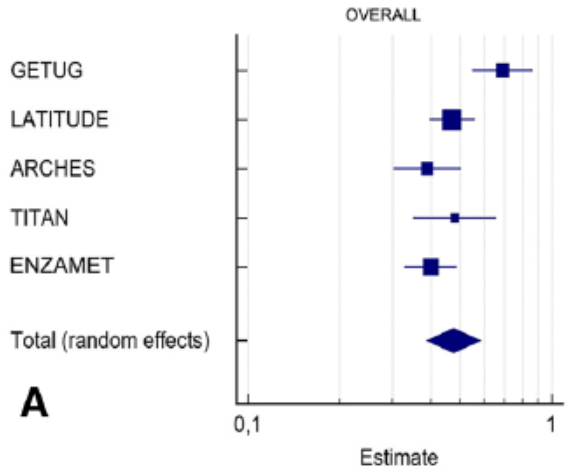


- Radiological progression-free (rPFS) analysis.

  a All studies reporting rPFS.

  b All studies including patients who received docetaxel before experimental treatment, all studies including patients not exposed to docetaxel.

  c New anti-androgen treatment among patients who did not receive docetaxel and among patients previously exposed to docetaxel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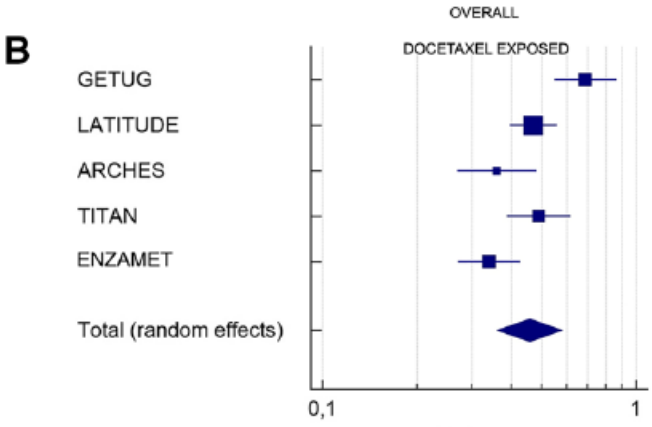
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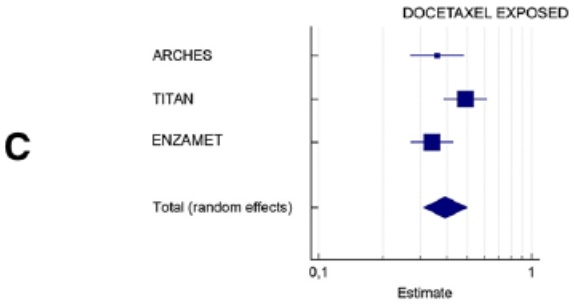
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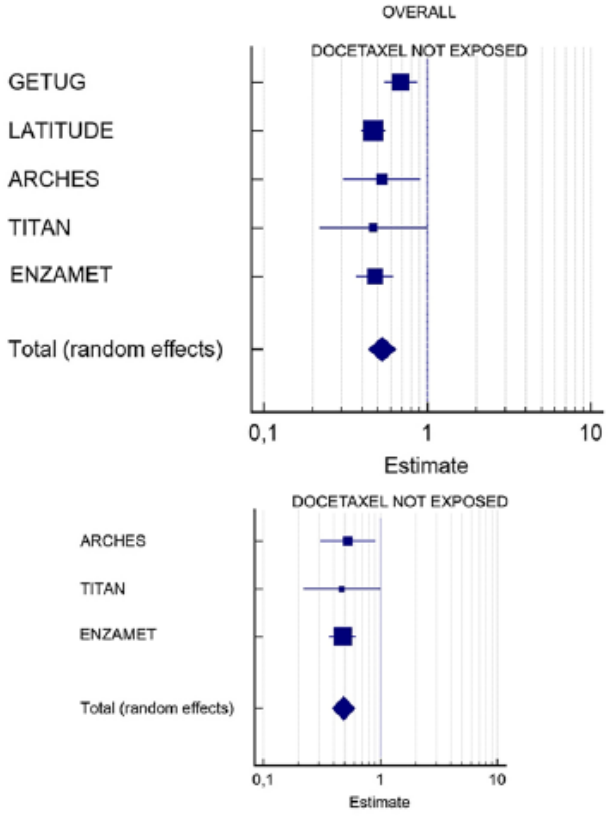


Overall Survival (OS) and Radiological Progression-Free Survival (rPFS) Analysis

Overall, the administration of experimental compounds resulted in a survival advantage (pooled-random HR 0.714; CI 0.656–0.777; p value < 0.001; I2 = 15.66%, p = 0.31; Fig. 2a.1). The survival advantage was confirmed after the inclusion of previously untreated patients (pooled-randommHR 0.697; CI 0.629–0.772; p value < 0.001; I2 = 37.78%, p = 0.13; Fig. 2a.2) and previous docetaxel or concomitant exposed patients (pooled-random HR 0.736; CI 0.662–0.819; p value < 0.001; I2 = 35.59%, p = 0.14; Fig. 2a.3).

Survival benefit was demonstrated in patients treated with docetaxel (pooled-random HR 0.736; CI 0.662–0.819; p value < 0.001; I2 = 0.00%, p = 0.69; Fig. 2c.1), abiraterone (pooled-random HR 0.615, 95% CI 0.532–0.712; p value < 0.001; I2 = 0.00%, p = 0.91; Fig. 2c.2) and new anti-androgens (pooled-random for enzalutamide/apalutamide- treated patients: 0.690, 95% CI 0.568–0.838; pvalue < 0.001; I2 = 0.00%, p = 0.72; Fig. 2b.1).

Among patients treated with apalutamide or enzalutamide, the survival benefit was confirmed in previously untreated patients (pooled random HR 0.587, 95% CI, 0.467–0.736, p < 0.001, I2 = 0.00%, p = 0.46; Fig. 2b.2) but no survival benefit emerged in patients exposed (concomitant or subsequently) with docetaxel (pooled random HR 0.948, 95% CI 0.671–1.338, p = 0.760, I2 = 0%, p = 0.48; Fig. 2b.3).

Regarding rPFS analyses, we considered five of eight studies selected [5, 6, 10, 12–14] (three studies did not report data on rPFS [7–9, 11]). Overall, the administration of experimental compounds resulted in prolonged rPFS in overall cohort (pooled random HR: 0.475, 95% CI 0.390–0.579, p < 0.001). Heterogeneity was statistically significant with an I2 value of 74%, p = 0.004 (Fig. 3a). The radiological progression-free advantage was also achievable including patients previously untreated (Fig. 3b.1) and exposed (concomitant or subsequently) with docetaxel to docetaxel (in this case Heterogeneity was statistically significant. I2 value: 81.62%, p = 0.0002; Fig. 3b.2).

When we consider only the three studies with a cohort of previously treated patients, the rPFS advantage was available in all patients, previously untreated patients (Fig. 3c.2) and previously treated patients (or patients who receivedconcomitant docetaxel) (Fig. 3c.3). An extensive summary of the results achieved for this aim are available in the Supplementary Material.

In bPFS analyses, we collected data provided by four of eight studies [5, 6, 10, 13, 14]. In this analyses, administration of experimental compounds (docetaxel, enzalutamide or abiraterone) resulted in a significant improvement of bPFS, although heterogeneity was statistically significant ($I2 = 93.99\%$, $p < 0.0001$). Similar results have been observed when analysis was restricted to patients who received hormonal experimental compounds ($I2 = 85.9\%$, $p = 0.0008$) or enzalutamide ($I2 = 92.38\%$, $p = 0.0003$)

Anmerkung/Fazit der Autoren

The addition of chemotherapy, abiraterone or new antiandrogens to ADT improves survival of patients with mHSPC. Our finding is not surprising considering results achieved by each drug in randomized studies. The use of a new anti-androgen may not improve survival of patients receiving concomitant docetaxel or previous docetaxel. However, the large heterogeneity among studies evaluating this issue limits the value of this observation. According to our results, patients with visceral metastases did not seem to show a survival benefit with the administration of new anti-androgens. Initial Gleason score may be related to different outcomes among patients receiving docetaxel or abiraterone. Toxicity profiles of these drugs confirmed the known hematological toxicity of docetaxel and cardio-vascular toxicity associated with abiraterone. High-grade AEs typically associated with new anti-androgens rarely occur during or after treatment.

Results of our meta-analysis suggest that:

• Patient selection is essential before treatment planning. Indeed, some patients do not benefit from a specific treatment (such as docetaxel for patients with low tumor volume or enzalutamide/apalutamide in patients previously exposed to chemotherapy)

• Disease assessment may be an important issue to consider before treatment planning. Low Gleason score may be associated with lowest effect of abiraterone on survival. The presence of visceral metastases should discourage the adoption of apalutamide or enzalutamide.

• Toxicity profile of agents should be carefully considered, and administration of enzalutamide/apalutamide may be a treatment of choice in frail patients. The cardiotoxicity of abiraterone should be considered in patients with high number of cardiovascular comorbidities, while patients with hematopoietic dysfunction or higher risk of infective disease should be discouraged from the adoption of docetaxel in this setting.

Iacovelli R et al., 2018 [8].

The Cardiovascular Toxicity of Abiraterone and Enzalutamide in Prostate Cancer

Fragestellung

The cardiovascular toxicity related to abiraterone and enzalutamide has been previously studied by our group. In this analysis, we aim to update our previous findings related to abiraterone and enzalutamide, including the new available evidence, both in castration-resistant and hormone-sensitive prostate cancer.

Methodik

Population:

- castration-resistant and hormone-sensitive prostate cancer

Intervention:

- abiraterone, enzalutamide

Komparator:

- nicht präspezifiziert

Endpunkte:

The cardiovascular toxicity considered included both arterial hypertension and cardiovascular toxicity. The latter was defined as the onset of any adverse cardiac event signs and symptoms.

Recherche/Suchzeitraum:

- MEDLINE/PubMed, the Cochrane Library, and the American Society of Clinical Oncology (ASCO) University Meeting abstracts for citations
- from 2013 to June 15, 2017

Qualitätsbewertung der Studien:

- Jadad 5-item scale

Ergebnisse

Anzahl eingeschlossener Studien:

- N= 7; covered a total of 8660 patients

Charakteristika der Population:

- Among them, 2878 patients were treated with abiraterone and 1854 with enzalutamide in the experimental arms, whereas 3928 received a placebo ± prednisone in the control arms.

Table 1 Main Characteristics of the Included Studies

Trial	Year	Previous Docetaxel	Required ADT	Experimental Arm		Control Arm		Median Treatment Duration, mos Exp./Ctr.	Median Follow-up, mos	CTCAE Version	Jadad Score
				No. Pts	Therapy	No. Pts	Therapy				
COU-AA-301	2012	Yes	Yes	791	Abiraterone + P 10 mg	394	Placebo + P 10 mg	8.0/4.0	12.8	3	5
COU-AA-302	2013	No	Yes	542	Abiraterone + P 10 mg	540	Placebo + P 10 mg	15.0/9.0	22.0	3	5
AFFIRM	2012	Yes	Yes	800	Enzalutamide	399	Placebo	8.3/3.0	14.4	4	5
PREVAIL	2014	No	Yes	872	Enzalutamide	845	Placebo	16.6/4.6	22.0	4	5
TERRAIN	2016	No	Yes	184	Enzalutamide	191	Bicalutamide	11.7/5.8	20.0/16.7	4	5
LATITUDE	2017	No	Yes	597	Abiraterone + P 5 mg	602	Placebo + P 5 mg	24/14	30.4	4	5
STAMPEDE	2017	No	Yes	948	Abiraterone + P 5 mg	960	NA	10.1/8.9	NA	NA	3

Abbreviations: ADT = androgen deprivation therapy; CTCAE = Common Terminology Criteria for Adverse Events; Ctr. = control group; Exp. = experimental group; mos = months; No. = number; NA = not available; P = prednisone; pts = patients.

Qualität der Studien:

- Siehe oben: Charakteristika der Studien

Studienergebnisse:

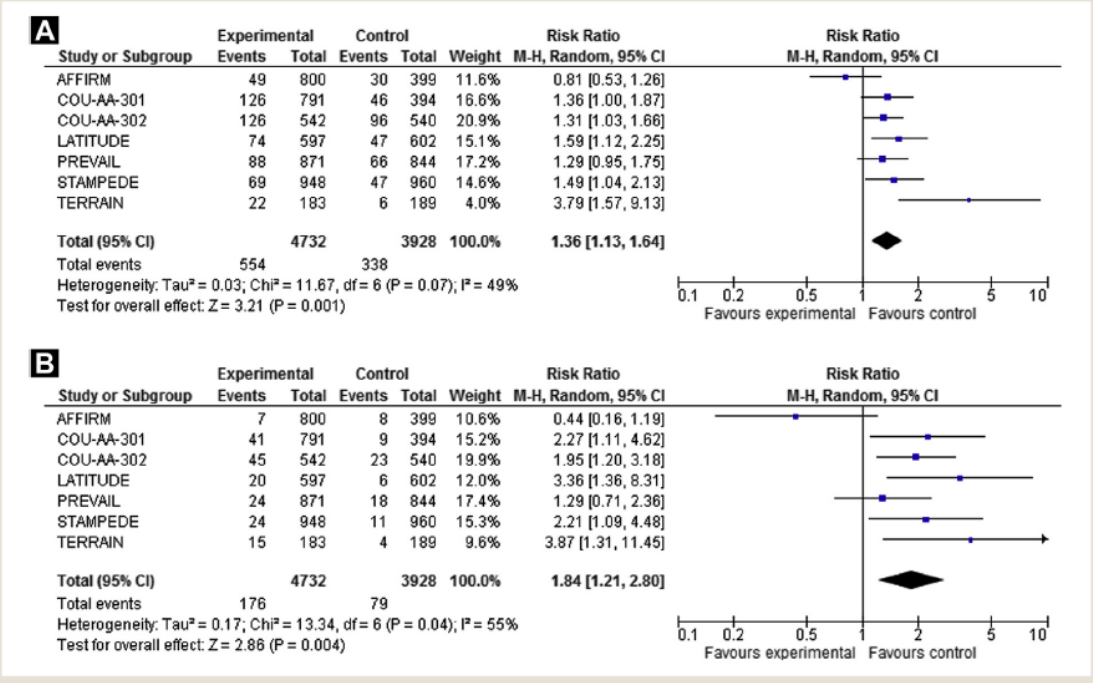
- **Cardiac Toxicity**

In the experimental arm, the incidence of all-grade cardiac events was 11.7%, whereas in the control arm, it was 8.6%. Treatment with new hormonal agents increased the risk of all-grade toxicity by 36% (random effect: RR, 1.36; 95% CI, 1.13-1.64; P = .001). There was significant heterogeneity (chi^2, 11.7; P = .07; I^2, 49%). The incidence of high-grades cardiac events was 3.7% in the experimental arms and 2.0% in the control arms. Treatment with new hormonal agents significantly increased the risk of high-grades cardiac toxicity (random effect, RR, 1.84; 95% CI, 1.21-2.80; P = .004), significant heterogeneity was found (chi^2, 13.3; P = .04; I^2, 56%) (Figure 2).

The incidence of all-grade and high-grade cardiac toxicity by the abiraterone was 13.7% and 4.5%, respectively; these were significantly increased compared with placebo (RR, 1.41; 95% CI, 1.21-1.64; P < .001 and RR, 2.22; 95% CI, 1.60-3.07; P < .001) (Table 2).

The incidence of all-grade and high-grade cardiac toxicity by the enzalutamide was 8.6% and 2.5%, respectively; these were not significantly increased compared with placebo (RR, 1.25; 95% CI, 0.99-1.59; P = .3 and RR, 1.28; 95% CI, 0.45-3.66; P = .7) (Table 2). No differences were found in the RR of both all-grade (P = .9) and high-grade (P = .3) cardiac toxicity between abiraterone and enzalutamide.

Figure 2 Relative Risk for All-grade (A) and High-grade (B) Cardiac Toxicity in Patients Treated With New Hormonal Agents or Control



Abbreviations: CI = confidence interval; df = degrees of freedom.

When studies performed in patients with HSPC were compared with those performed in patients with CRPC, patients treated with abiraterone with CRPC have significant major incidence of highgrade cardiac toxicity events compared with patients with HSPC, but no increase of all-grades cardiac toxicity was found. The same evidence was found for patients treated with placebo (see Supplemental Table 1 in the online version).

Supplemental Table 1	Incidence of Cardiac Toxicity Based on Type of Disease (ie, HSPC vs. CRPC)		
Disease	**Incidence, %**	**χ^2**	***P* Value**
High-grade cardiac toxicity abiraterone			
HSPC	2.85	21.55	<.001
CRPC	6.45		
All-grade cardiac toxicity abiraterone			
HSPC	9.2	56.27	>.05
CRPC	19.9		
High-grade cardiac toxicity placebo			
HSPC	1.09	16.60	<.001
CRPC	3.43		
All-grade cardiac toxicity placebo			
HSPC	6.0	59.10	>.05
CRPC	15.2		

Abbreviations: CPRC = castration-resistant prostate cancer; HSPC = hormone-sensitive prostate cancer.

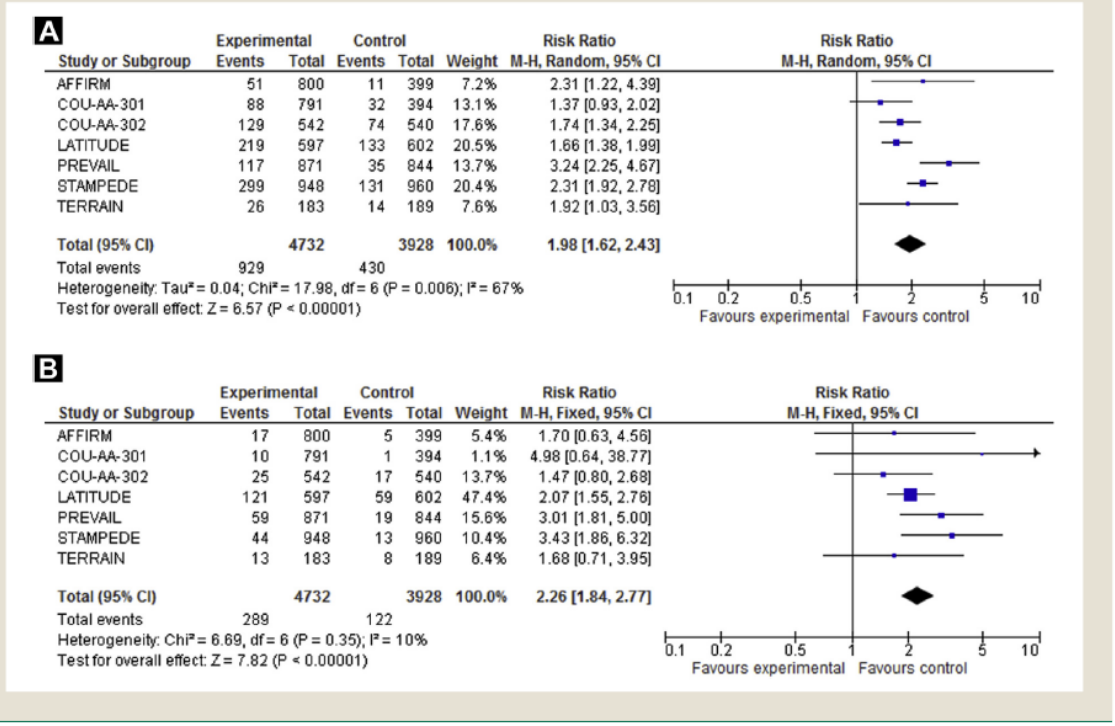
- **Hypertension**

In the experimental arms, the incidence of all-grade hypertension was 19.6%, whereas in the control arms, it was 10.9%. Treatment with new hormonal agents increased the risk of all-grade hypertension by 98% (random effect, RR, 1.98; 95% CI, 1.62-2.43; P = .001). There was significant heterogeneity (chi^2, 12.0; P = .006; I^2, 67%). The incidence of high-grade hypertension was 6.1% in the experimental arms and 3.1% in the control arms. Treatment with new hormonal agents more than doubled the risk of high-grade hypertension (fixed effect, RR, 2.26; 95% CI, 1.84-2.77; P < .001); no significant heterogeneity was found (chi^2, 6.68; P = .35; I^2, 10%) (Figure 3).

The incidence of all-grade and high-grade hypertension by the abiraterone was 26.2% and 6.9%, respectively; these were significantly increased compared with placebo (RR, 1.79; 95% CI, 1.45-2.21; P < .001 and RR, 2.19; 95% CI, 1.73-2.78; P < .001) (Table 2).

The incidence of all-grade and high-grade hypertension by the enzalutamide was 10.5% and 4.8%, respectively; these were significantly increased compared with placebo (RR, 2.66; 95% CI, 1.94-3.66; P < .001 and RR, 2.44; 95% CI, 1.64-3.63; P < .001) (Table 2). A significant difference was found in the RR for all-grade (P = .04) but not for high-grade (P ¼ .7) hypertension between abiraterone and enzalutamide.

Figure 3 Relative Risk for All-grade (A) and High-grade (B) Hypertension in Patients Treated With New Hormonal Agents or Control



Abbreviations: CI = confidence interval; df = degrees of freedom.

When studies performed in patients with HSPC were compared with those performed in patients with CRPC, patients treated with abiraterone for HSPC have major incidence of hypertension, but the difference was not significant. When the incidence of hypertension was compared in patients treated with placebo, patients with HSPC have a significantly increased incidence of adverse events compared with patients with CRPC (see Supplemental Table 2 in the online version).

Supplemental Table 2	Incidence of Hypertension Based on Type of Disease (ie, HSPC vs. CRPC)		
Disease	**Incidence, %**	**χ^2**	***P* Value**
High-grade hypertension abiraterone			
HSPC	10.7	71.78	>.05
CRPC	2.6		
All-grade hypertension abiraterone			
HSPC	33.5	111.95	>.05
CRPC	16.3		
High-grade hypertension placebo			
HSPC	4.6	12.10	<.001
CRPC	1.9		
All-grade hypertension placebo			
HSPC	16.9	14.27	<.001
CRPC	11.3		

Abbreviations: CPRC = Castration-resistant prostate cancer; HSPC = hormone-sensitive prostate cancer.

Anmerkung/Fazit der Autoren

- Abiraterone was found to significantly increase the risk of both cardiac toxicity and hypertension, whereas enzalutamide significantly increases only the risk of hypertension. No differences were found based on the dose of prednisone used with abiraterone. The major limitation of this study is that data are available only as aggregate, and no single-patient information could be analyzed.
- Conclusions: Abiraterone and enzalutamide significantly increase the incidence and RR of cardiovascular toxicity in patients affected by metastatic prostate cancer. Follow-up for the onset of treatment-related cardiovascular events should therefore be considered in these patients.

  Clinical Practice Points:

  - Abiraterone and enzalutamide are standard therapies for treatment of metastatic PC. Cardiovascular toxicity has not been well-addressed for these molecules.
  - In this meta-analysis, we found that these 2 drugs increased the risk of cardiac toxicity by 36% for all-grade and by 84% for high- grade events. In addition, the risk of arterial hypertension was increased by 100% for all-grade events and by 220% for highgrade events.

Gemeinsamer Bundesausschuss

Fragestellung

The assessment of “soft” endpoints such as health-related quality of life (HRQOL) is increasingly relevant when evaluating the optimal treatment sequence of novel therapeutic options in patients with advanced prostate cancer (PCa). Objective: To systematically review contemporary data regarding HRQOL outcomes in patients with advanced PCa.

Methodik

Population:

- advanced PCa, defined as mHNPC, nmCRPC, and mCRPC

Intervention:

- nicht präspezifiert

Komparator:

- nicht präspezfiziert

Endpunkte:

- HRQOL outcomes

Recherche/Suchzeitraum:

- between January 2011 and March 2019
- PubMed/Medline Database

Qualitätsbewertung der Studien:

- Risk of bias assessment following current EAU recommendations. EAU = European Association of Urology.

Ergebnisse

Anzahl eingeschlossener Studien:

- 14 studies evaluating HRQOL in 12 661 patients, darunter n=3 für nicht kastrationsrestistenten PCa (nachfolgend dargestellt)

Charakteristika der Population:

Recently, HRQOL outcomes of three randomized controlled phase III trials have been published. The main features of each study are summarized chronologically in Table 1.

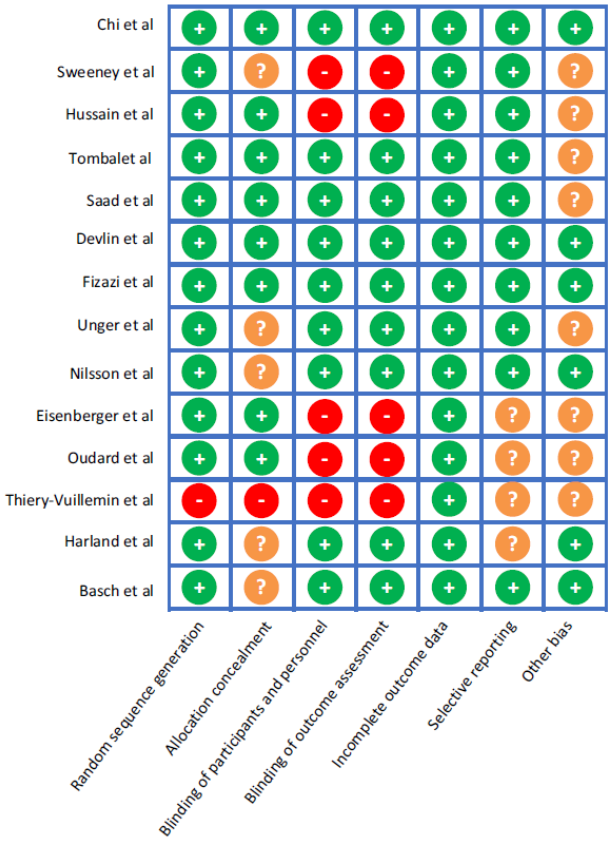
Table 1 – Main features of studies addressing patients with metastatic hormone naive prostate cancer.

Study	Intervention	Phase	n	Follow-up	Tool	HRQOL baseline	Main findings
Hussain et al (2013) [16]	IADT vs CADT	III	1162	Up to 15 mo	SWOG QOL questionnaire	NR	Net differences in primary SWOG QOL outcomes after 15 mo: erectile dysfunction –3% (IADT) vs 2% (CADT), p = 0.12; high libido 13% (IADT) vs 3% (CADT), p = 0.46; vitality –2.02 (IADT) vs –3.02 (CADT), p = 0.45; mental health –0.64 (IADT) vs –1.10 (CADT), p = 0.69; physical functioning –2.68 (IADT) vs –5.72 (CADT), p = 0.04
Chi et al (2018) [18] (LATITUDE)	ABI vs PBO	III	1199	Median 30.9 mo (ABI) vs 29.7 mo (PBO)	FACT-P EQ-5D (–5 L)	FACT-P (total): ABI: 113 PBO: 112 EQ-5D–5 L (VAS): ABI: 74 PBO: 74	Median time to deterioration of FACT-P total score 12.9 mo (ABI) vs 8.3 mo (PBO), HR 0.85, 95% CI 0.74–0.99, p = 0.032; EQ-5D VAS: better general health status for ABI vs PBO, same findings for EQ-5D utility score
Morgans et al (2018) [19] (E3805 CHAARTED)	DOC + ADT vs ADT	III	790	Up to 12 mo	FACT-P (FACT-Taxane)	FACT-P (total): DOC: 119 ADT: 119	Net differences in FACT-P total scores after 3 mo: –2.7 (DOC) vs –1.1 (ADT), p = 0.02; net differences in FACT-P total scores after 12 mo: –0.7 (DOC) vs –4.2 (ADT), p = 0.04; changes not considered clinically meaningful

ABI = abiraterone acetate; ADT = androgen deprivation therapy; CADT = continuous androgen deprivation therapy; CI = confidence interval; DOC = docetaxel; EQ-5D = European Quality of life 5-Dimensions; FACT-P = Functional Assessment of Cancer Therapy-Prostate; HR = hazard ratio; HRQOL = health-related quality of life; IADT = intermittent androgen deprivation therapy; NR = not reported; PBO = placebo; QOL = quality of life; VAS = visual analog scale.

Qualität der Studien:

Risk of bias assessment following current EAU recommendations. EAU = European Association of Urology.



Studienergebnisse:

Metastatic hormone-naive prostate cancer

Hussain et al [16] randomized 1535 patients with newly diagnosed mHNPC to receive either continuous or intermittent ADT. HRQOL outcomes were assessed based on the SWOG HRQOL questionnaire. Net differences in physical functioning favored patients undergoing intermittent ADT (–2.68 vs –5.72, p = 0.04), as did vitality, libido, and mental health, without reaching statistical significance. Since the study was designed as open label, risk of bias assessment showed mixed results with a tendency toward a low risk of bias (Fig. 2).

The randomized controlled phase III LATITUDE trial analyzed oncological [17] as well as HRQOL outcomes [18] in 1199 patients with newly diagnosed high-risk mHNPC. Risk assessment was performed based on Gleason grading as well as PSA doubling time. Patients were randomly assigned to receive standard ADT in combination with placebo or in combination with abiraterone acetate 1000 mg daily (in combination with 5 mg prednisone daily). Regarding HRQOL outcomes, EQ-5D-5L and FACT-P questionnaires were used, and 10% of the data were missing. Regarding general HRQOL, as assessed by the FACT-P total score, the authors found increased time to deterioration of FACT-P total scores for patients who underwent treatment with abiraterone acetate (8.3 vs 12.9 mo, hazard ratio [HR] 0.85, 95% confidence interval [CI] 0.74–0.99, p = 0.032). Similar results were found for remaining subscales [18]. These findings have a low risk of bias (Fig. 2).

The CHAARTED study reported oncological [3] as well as HRQOL outcomes [19] of 790 patients with mHNPC who were randomly assigned to receive either ADT or ADT in combination with docetaxel 75 mg/m2. HRQOL assessment was based on the FACT-P questionnaire. Missing data were up to 23% at the 12-mo assessment. The authors found a significant decline in FACT-P total scores after 3 mo for patients who underwent combination therapy ($p < 0.001$), with a consecutive rise in the longer-term assessment up to 12 mo. Consequently, patients receiving docetaxel showed significantly lower FACT-P total scores than patients with ADT monotherapy after 3 mo (net differences –2.7 vs –1.1, $p = 0.02$), but significantly higher FACT-P total scores after 12 mo (net differences –0.7 vs –4.2, $p = 0.04$). Notably, CHAARTED was an open-label study. Thus, as illustrated in Fig. 2, risk of bias assessment showed mixed results, especially regarding detection as well as performance bias. Notably, baseline FACT-P total scores were slightly higher within the CHAARTED [19] than in the LATITUDE cohort [17].

Anmerkung/Fazit der Autoren

There is strong evidence from several phase III trials supporting a beneficial effect of current systemic treatment options on HRQOL outcomes in patients with advanced PCa compared with standard androgen deprivation therapy.

Feyerabend S et al., 2018 [5].

Survival benefit, disease progression and quality-of-life outcomes of abiraterone acetate plus prednisone versus docetaxel in metastatic hormone-sensitive prostate cancer: A network meta-analysis

Fragestellung

Androgen deprivation therapy (ADT) has long been the gold standard for patients with metastatic hormone-sensitive prostate cancer (mHSPC). Clinical trials have demonstrated significant survival benefits when docetaxel (DOC) or abiraterone acetate (AA) and prednisone (P) are added to ADT, necessitating comparison of these combination treatments. […] A key question is whether AA þ P or DOC holds an advantage over the other when combined with ADT in patients with mHSPC.

Methodik

Population:

- patients with metastatic hormone-sensitive prostate cancer (mHSPC)

Intervention:

ADT + docetaxel (DOC) or abiraterone acetate (AA) and prednisone (P)

Komparator:

- ADT

Endpunkte:

- overall survival (OS),
- radiographic progressionfree survival (rPFS) and
- quality of life (QoL) measured by the Brief Pain Inventory, and the Functional Assessment of Cancer Therapy-Prostate questionnaire

Recherche/Suchzeitraum:

- keine Angabe (Supplements nicht auffindbar)

Qualitätsbewertung der Studien:

- wurde durchgeführt (siehe unten); keine Angabe zum Bewertungsverfahren (Supplements nicht auffindbar)

Ergebnisse

Anzahl eingeschlossener Studien:

- 4

Charakteristika der Population:

Overview of trials included in the NMA.

	GETUG-AFU 15 [8,9]	CHAARTED [5–7,34]	LATITUDE [2]	STAMPEDE [3,10,25,26]
NCT number	NCT00104715	NCT00309985	NCT01715285	NCT00268476
Accrual years	2004–2008	2006–2012	2013–2014	ADT arm: 2006–2017 AA arm: 2012–2013 DOC arm: 2006–2013
Patient population	Patients with mHSPC	Patients with mHSPC	Patients with NDx HRD mCNPC	Patients with NDx metastatic, node-positive or high-risk locally advanced PC
Therapy	• DOC + ADT (75 mg/m^2 every 3 weeks for up to nine cycles) • ADT alone (LHRH receptor agonist alone or combined with non-steroidal antiandrogens or orchiectomy)	• DOC + ADT (75 mg/m^2 every 3 weeks for six cycles) • ADT alone (LHRH receptor agonist or an LHRH receptor antagonist or orchiectomy; antiandrogens were given at the investigators' decision)	• AA + P + ADT • ADT alone (LHRH or surgical castration + placebo)	**DOC vs. ADT comparison** • DOC + SoC (75 mg/m^2 every 3 weeks for six cycles) + P (10 mg daily) • SoC (ADT ± radiotherapy) **AA vs. ADT comparison** • AA + P + SoC • SoC (ADT ± radiotherapy) **AA vs. DOC comparison** • AA + P + SoC • DOC + SoC (75 mg/m^2 every 3 weeks for six cycles) + P (10 mg daily)
Number of patients with mCNPC/mHSPC	385/385 (100%)	790/790 (100%)	1199/1199 (100%)	DOC vs ADT comparison: 1086/1086 (100%) AA vs ADT comparison: 1002/1002 (100%) AA vs. DOC comparison: 342[a]/342 (100%)
Patients with newly diagnosed mCNPC/mHSPC	272/385 (71%)	575/790 (73%)	1199/1199 (100%)	DOC vs. ADT comparison: 1037/1086 (95.5%) AA vs. ADT comparison: 941/1002 (93.9%) AA vs. DOC comparison: 342[a]/342 (100%)
Patients with HVD[b]	183/385 (48%)[c]	513/790 (65%)[b]	955/1199 (79·6%)[c]	NR
Gleason score of 8–10	216/385 (56%) (ITT) NR (HVD subgroup)	484/790 (61.2%) (ITT) 323/513 (63%) (HVD subgroup)	1170/1199 (97.6%) (HRD ITT) 927/955 (97%) (HRD&HVD)	DOC vs. ADT comparison: 1246/1776 (70.2%) (ITT; M1 population NR) AA vs. ADT comparison: 1436/1917 (74.9%) (ITT; M1 population NR) AA vs. DOC comparison: NR
ECOG performance status of 0–1	NR	778/790 (98.5%) (ITT) 503/513 (98%) (HVD subgroup)	1157/1199 (96%) (HRD ITT) 916/955 (96%) (HRD&HVD)	NR
Prior adjuvant hormonal therapy	Permitted if ADT discontinued 12 months before study entry	Permitted if ADT was ≤24 months in duration and progression had occurred >12 months after completion of therapy	Prior pharmacotherapy, radiation therapy or surgery for metastatic PC was not permitted, except for up to 3 months of ADT or one course of palliative radiation or surgical therapy	Permitted if ADT discontinued 12 months before the study entry and ≤12 months in duration
Median follow-up	83.9 months	53.7 months	30.4 months	DOC vs. ADT comparison: 43 months AA vs. ADT comparison: 40 months AA vs. DOC comparison: 48 months

NMA, network meta-analysis; AA, abiraterone acetate; ADT, androgen deprivation therapy; DOC, docetaxel; ECOG, Eastern Cooperative Oncology Group; HVD, high-volume disease; ITT, intention-to-treat; LHRH, luteinising hormone–releasing hormone; mCNPC, metastatic castration-naïve prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; NDx, newly diagnosed; NR, not reported; OS, overall survival; P, prednisone; PC, prostate cancer; PSA, prostate-specific antigen; SoC, standard of care; ZA, zoledronic acid.

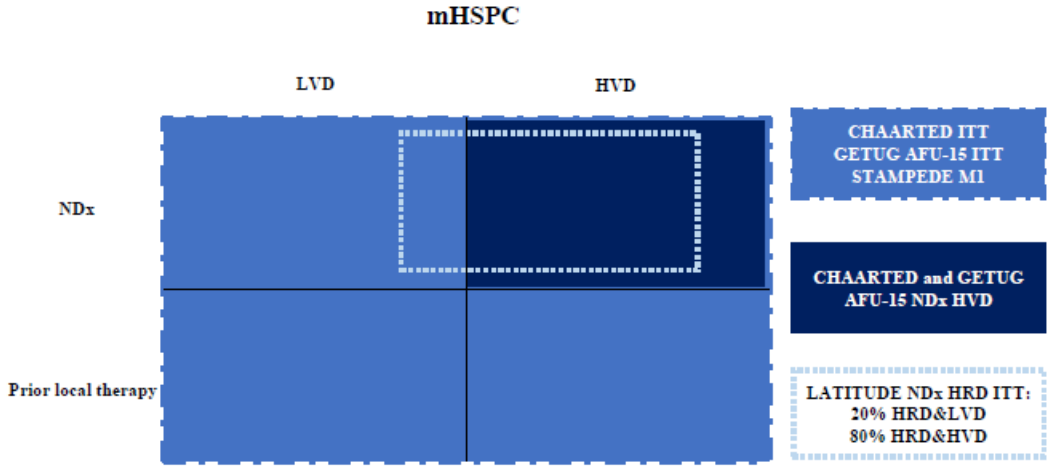
[a] Number of patients with metastatic PC at randomisation, who were randomised contemporaneously to the AA + P + ADT and DOC + P + ADT arms.

[b] High-volume disease defined as visceral metastases and/or ≥4 bone metastases with at least one metastasis beyond the pelvis or vertebral column.

[c] High-volume disease was retrospectively defined in the GETUG-AFU 15 and LATITUDE trials following the CHAARTED definition.

Overview of patient populations from the trials included in the NMA:

Patients with at least two of the following criteria were considered to have HRD: Gleason score >8; presence of three or more lesions on a bone scan and presence of measurable visceral metastasis (excluding lymph node disease). Patients with evident visceral metastases and/or four or more bone metastases of which at least one was outside the vertebral column and pelvis were classified as having HVD in CHAARTED, a definition that was used to identify patients in the GETUG-AFU 15 and LATITUDE trials. NMA, network meta-analysis; HRD, high-risk disease.

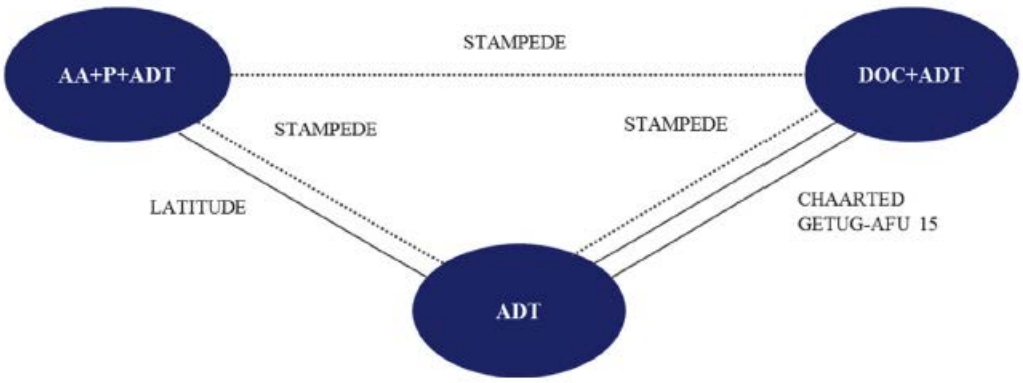


Qualität der Studien:

According to the risk-of-bias assessment, GETUGAFU 15 [8,9] and LATITUDE [2] had low overall risk of bias, whereas CHAARTED [5e7] was found to have a high overall risk (selection and performance bias).

Studienergebnisse:

Network diagram. Continuous lines in this network represent the trials contributing to the main analyses. Dotted lines represent the trials contributing to the exploratory analyses. Of note, the three arms from STAMPEDE trial were treated as three separate trials. AA, abiraterone acetate; ADT, androgen deprivation therapy; DOC, docetaxel; P, prednisone.



Efficacy results: OS

An 8% relative reduction in mortality was observed for the ITT population with NDx HRD treated with AA + P + ADT in LATITUDE [2] compared with patients with NDx HVD treated with DOC þ ADT (HR 0.92 [95% CrI: 0.69, 1.23]), with the Bayesian probability of AA þ P þ ADT being the better treatment found to be 71.8%. Using the LATITUDE NDx HRD&HVD population resulted in an HR of 0.85 (95% CrI: 0.63, 1.14; probability of being better: 86.7%).

Efficacy results: rPFS

Results based on the LATITUDE [2] NDx HRD ITT population showed AA þ P þ ADT to be associated with a 24% reduction in the risk of radiographic progression or death compared with

DOC + ADT (HR 0.76 [95% CrI: 0.53, 1.10]) and the Bayesian probability of AA + P þ ADT being the better treatment was 92.9%. Using the LATITUDE NDx HRD&HVD population, the results were somewhat more in favour of AA + P + ADT (HR 0.71 [95% CrI: 0.49, 1.02]; probability of being better: 96.8%).

QoL results

For the NDx HRD ITT population from LATITUDE [2], there was a significant improvement in BPI scores of AA + P + ADT compared with DOC +ADT at all time points analysed (3, 6, 9 and 12 months), and the Bayesian probability of AA + P + ADT being the better treatment ranged from 88.0% to 100.0%. For analyses involving the NDx HRD ITT population from LATITUDE [2], the mean difference in CFB in FACT-P total score was 4.2 (95% CrI: 1.18, 7.21) for AA+P+ADTcomparedwithDOC+ADTat 3 months, bn with a 99.7% Bayesian probability of AA þ P + ADT being the better treatment. Findings at 6, 9 and 12 months also suggested an improved QoL with AA þ P + ADT compared with DOC + ADT, with the probability for AA + P +ADT being the better treatment ranging from 92.3% to 97.0% across time points.

Results remained consistent for both the BPI and FACT-P when the NDx HRD ITT population from LATITUDE [2] was replaced with the NDx HRD&HVD population from LATITUDE.

Anmerkung/Fazit der Autoren

In conclusion, our analyses showed that AA + P + ADT is at least as effective as DOC + ADT in reducing the risk of death in men with mHSPC, while it is associated with a reduced risk of disease progression and an improved QoL compared with DOC + ADT. Various supplementary analyses including the different populations from LATITUDE [2] resulted in largely consistent findings.

Lei JH et al., 2016 [10].

Androgen-deprivation therapy alone versus combined with radiation therapy or chemotherapy for nonlocalized prostate cancer: a systematic review and meta-analysis

Fragestellung

a systematic review of the published RCTs to compare the long-term survival outcomes, safety, and QoL of ADT alone versus in combination with other approaches (e.g., RT or chemotherapy), in patients with locally advanced and metastatic PCa

Methodik

Population:

- study population or subpopulation included locally advanced or metastatic PCa patients
- Locally advanced PCa was defined as clinical stage T3/4 N0/X M0 disease or clinical T2 tumors with either PSA >40 ng ml−1, or T2 and PSA >20 ng ml−1 with a Gleason score >8. Studies were excluded if patients suffered metastatic hormone refractory PCa or had been prior treated for PCa, with the exception of ADT

Intervention / Komparator:

- comparison between ADT alone and ADT plus other approaches (e.g., RP, RT, or chemotherapy)

Abkürzungen: androgen-deprivation therapy (ADT), except for radical prostatectomy (RP) and radiation therapy (RT);

Endpunkte:

- reported quantitative data of disease control or
- survival outcomes, e.g., overall survival (OS),
- progression-free survival (PFS),
- cancer-specific mortality (CSM),
- and so on.

Recherche/Suchzeitraum:

- We simultaneously used three databases of OvidSP to search (date: August 4, 2014) relevant studies: Ovid MEDLINE® (1946 to present), EMBASE® (1974 to August 1, 2014), and the Cochrane Central Register of Controlled Trials® (June 2014) at West China Hospital.

Qualitätsbewertung der Studien:

- According to the recommendations of the Cochrane collaboration, the quality of the included studies was assessed based on the study design, conduct, and analysis, and each study was evaluated using a three-point scale: yes (low risk of bias), no (high risk of bias) and unclear

Ergebnisse

Anzahl eingeschlossener Studien:

- n= 7, darunter n= 4 für metastasiertes PCa

Charakteristika der Population (nur metastasiertes PCa):

Table 1: Characteristics of included studies (*n*=8)

Study ID	*Study design/ comparison of treatment*	*Sites*	*Population[a] of PCa*	*ADT/RT/chemotherapy regimen*	*Median follow-up*	*End-points of survival or tumor control*
Studies included metastatic PCa						
Gravis *et al.*[14]	RCT/ADT versus ADT+D	29 centers in France and one in Belgium	Patients with noncastrate metastatic PCa	ADT: Orchiectomy or LHRH-agonists, alone or combined with nonsteroidal anti-androgens Chemotherapy: 9 cycles of D 75 mg m^{-2} on the first day of each 21 days cycle	50 months	OS, PFS
Sweeney *et al.*[15]	RCT/ADT versus ADT+D	US (called ECOG-3805 trial)	Patients with noncastrate metastatic PCa	ADT: Not mentioned Chemotherapy: D dosed 75 mg m^{-2} every 3 weeks for 6 cycles within 4 months of starting ADT	29 months	OS
Noguchi *et al.*[16]	RCT/ADT versus ADT+E	Kurume, Kumamoto and Mie in Japan	Newly diagnosed metastatic PCa	Chemotherapy: E 560 mg day^{-1} ADT: Goserelin 3.60 mg or leuprolide acetate 3.75 mg. Flutamide 125 mg	26 months	OS, CSS, ORR
Hoshi *et al.*[17]	RCT/ADT versus ADT+E	The affiliated hospitals of the Tohoku	Untreated stage D1 or D2 PCa	ADT: Not strictly defined Chemotherapy: E 560 mg day^{-1} treatment was continued until deterioration	ADT versus ADT+E 76.3 versus 92.3 weeks	OS, ORR

[a]Based on the TNM-classification 1992. PSA recurrence: Defined as an increase of PSA of 2 ng ml^{-1} or more above nadir. PSA response: Defined as serum PSA ≤0.2 ng ml^{-1} after 3 months of treatment. PSA progression: Defined by a rising PSA concentration of >5 ng ml^{-1} or reaching on-study value (minimum 1 ng ml^{-1}). ORR: overall response rates: (Complete response [normalization of the PSA level and in patients with measurable disease, disappearance of all lesions without the occurrence of new ones]+partial remission [a decrease of ≥50% in the sum of the products of the longest diameters of all measurable lesions persisting for ≥4 weeks, improvement in bone scan findings, and reossification of lytic lesions, in addition to no increase in the size of any existing lesions and no appearance of new lesions]). PCa: prostate cancer; RCT: randomized controlled trial; EBRT: external beam radiotherapy; ADT: androgen-deprivation therapy; D: docetaxel; DE: docetaxel-estramustine; E: estramustine; ECOG: Eastern Cooperative Oncology Group; GnRH: gonadotropin-releasing hormone; LHRH: luteinizing hormone-releasing hormone; OS: overall survival; OM: overall mortality; PFS: progression-free survival; CSS: cancer-specific survival; CSM: cancer-specific mortality; LR: locoregional recurrence; DM: distant metastases; PSA: prostate-specific antigen; RT: radiation therapy

Qualität der Studien:

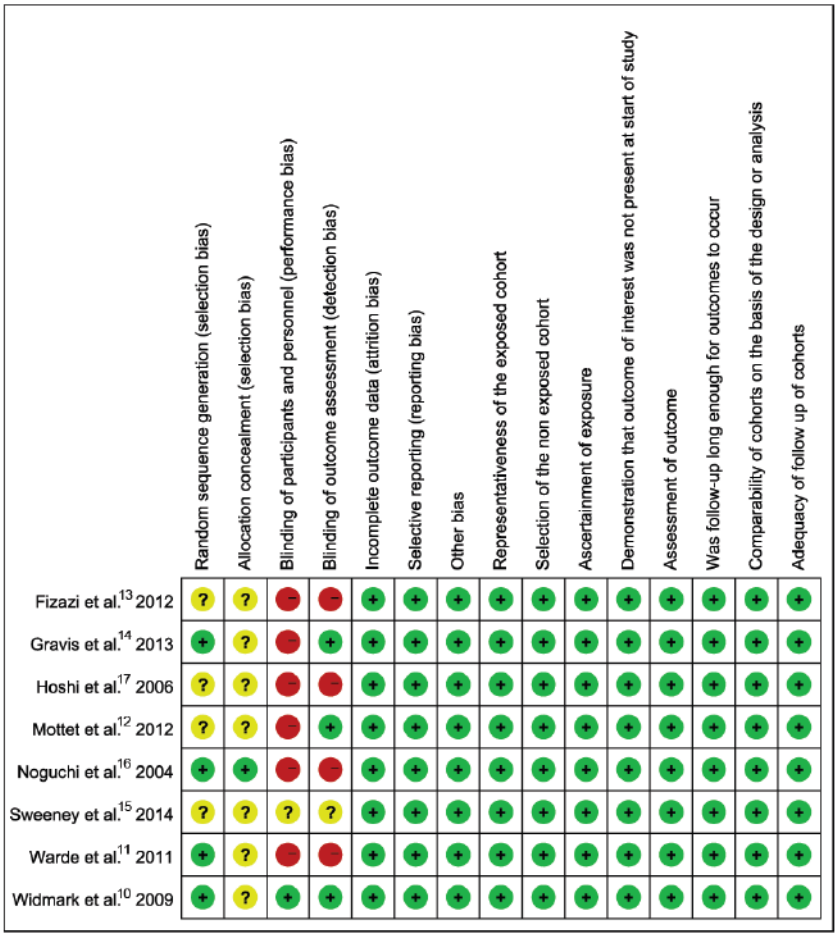


Figure 2: Quality evaluation for each included studies.

Studienergebnisse:

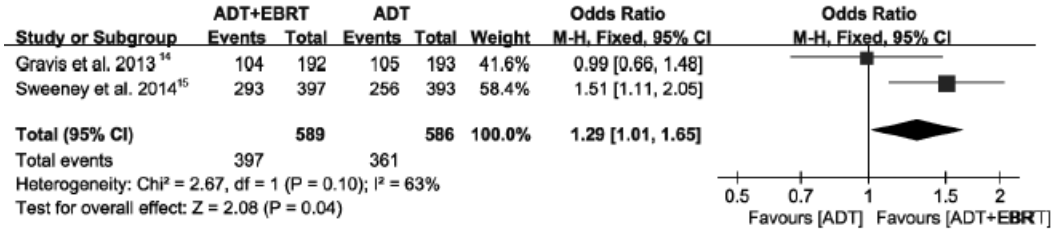
Studies included metastatic prostate cancer (n = 4)

- Androgen-deprivation therapy versus androgen-deprivation therapy plus docetaxel (n = 2)

  The RCT by Gravis et al.14 enrolled 385 patients with metastatic noncastrate PCa. They were randomized to receive ADT alone (n = 193) or ADT plus docetaxel (n = 192). Median OS had no differences (P = 0.955), but median PFS was longer for combined group (P = 0.015). All the 72 serious adverse events reported were in the combined group, of which the most frequent were neutropenia (40 [21%]), febrile neutropenia (6 [3%]), and abnormal liver function tests (three [2%]). All the four treatment-related deaths occurred in the combined group. Another RCT by Sweeney et al.15 included the same population but with a large scale, 393 in ADT arm and 397 in the combined group. The median OS was longer for combined group (P = 0.0006). Particularly for the “high volume” subgroup (visceral metastases and/or 4 or more bone metastases), a prolonged median OS of 17 months was achieved when docetaxel was added (P = 0.0012). All the toxic reaction occurred in the combined group:

  2% for Grade (G) 3/4 Neutropenic fever, 2% for G3 neuropathy, and only one case for treat-related death. The pooled OR of OS for the two trials was 1.29 (95%CI 1.01–1.65) with a moderate heterogeneity (I2 = 63%) when compared ADT plus RT with ADT (P = 0.04) (Figure 4).

Figure 4: Forest plot of pooled odds ratio when compared androgen-deprivation therapy alone versus combined with docetaxel for metastatic prostate cancer.



- Androgen-deprivation therapy versus androgen-deprivation therapy plus estramustine (n= 2)

  Noguchi et al.16 randomly divided 57 patients with newly diagnosed metastatic PCa into two groups, receiving ADT alone and ADT plus estramustine. They found that ADT plus estramustine showed longer clinical CSS than ADT alone (P = 0.03), although there was no difference in the OS and response rate of tumor (P = 0.796 and P > 0.05). Serious side effects only occurred two in the combination group and one in ADT alone group for cardiovascular disorders and one in the ADT alone group for diarrhea. A similar study by Hoshi et al.17 found that OS was significantly prolonged in the combination group (P = 0.0394). However, the response rate of tumor had no differences between groups (P = 0.6723). Both treatment groups tolerated treatment well. Side effects were 7/26 (26.9%) in the ADT group and 14/31 (45.2%) in the combination group, with no significant difference (P = 0.2517) observed between the groups. Serious side effects (grade 3 or higher) were rather low, only one in each group for cardiovascular disorders and two in the combination group for GI toxicity. The detailed results of long-term survival for all studies were summarized at Table 2.

Table 2: Results of long-term survival of included studies (*n*=8)

Study ID	*Comparison of therapy/ simple size*	*Death counts (ADT alone vs combination)*	*End-points (95% CI) (ADT alone vs combination)*					
			OS	*PFS*	*CSS*	*LR/DM/PSA recurrence or progression or response*	*Other end-points*	*Report[§] of toxicity or QoL*
Studies included								
Studies included metastatic PCa								
Gravis *et al.*[14]	ADT versus ADT+D 193 versus 192	88 *vs.* 88	Median OS: 54.2 *vs.* 58.9 months, *P*=0.955	15.4 *vs.* 23.5 months, *P*=0.015	NA	NA	NA	Toxicity
Sweeney *et al.*[15]	ADT versus ADT+D 393 versus 397	137 *vs.* 104	Median OS: 42.3 *vs.* 52.7, *P*=0.0006	NA	NA	NA	NA	Toxicity
Noguchi *et al.*[16]	ADT versus ADT+E 28 versus 29	11 *vs.* 14	OS: 11/28 *vs.* 14/29, 27.8 versus 35.9 months, *P*=0.796	12/28 *vs.* 17/29; 14.6 *vs.* 25.4 months, *P*=0.03	NA	NA	ORR: 55 (12/28) *vs.* 76% (22/29), *P*>0.05	Toxicity
Hoshi *et al.*[17]	ADT versus ADT+E 31 versus 26	NA	5 years OS: 45.8% *vs.* 64.1%, *P*=0.039	NA	NA	NA	ORR: 65.2% (15/23) *vs.* 69.2% (18/26) *P*=0.6723	Toxicity

[§]Data were calculated according to the phoenix definition-the event of biochemical progression was established when an increase of 2 ng ml^{-1} above the PSA nadir occurred; [¶]Dates in details were shown in result section of manuscript. NA: not applicable; CI: confidence interval; QoL: quality-of-life; ADT: androgen-deprivation therapy; OS: overall survival; PFS: progression-free survival; CSS: cancer-specific survival; LR: locoregional recurrence; DM: distant metastases; PSA: prostate specific antigen; D: docetaxel; DE: docetaxel-estramustine; E: estramustine; EBRT: external beam radiotherapy; HR: hazard ratio; PCa: prostate cancer; CSM: cancer-specific mortality; ORR: overall response rates

Anmerkung/Fazit der Autoren

In summary, for locally advanced PCa, the addition of RT to long-term ADT can improve the outcomes of survival and tumor control with fully acceptable adverse effects and QoL than ADT alone; however, added DE to ADT lacks data related to the long-term outcomes on relapse and survival. For newly diagnosed metastatic hormonally sensitive PCa, particularly for cases with visceral metastases and/or 4 or more bone metastases, the concurrent use of docetaxel plus ADT was necessary. It is too soon to say that ADT plus estramustine is better than ADT alone for metastatic PCa.

Liu M et al., 2019 [13].

Comparative clinical effects and cost-effectiveness of maximum androgen blockade, docetaxel with androgen deprivation therapy and ADT alone for the treatment of mHSPC in China

Fragestellung

the objective of this study is to compare the clinical effects of Doc-ADT, MAB and ADT alone based on a network meta-analysis (NMA) for the treatment of patients with mHSPC and to conduct a cost–effectiveness analysis (CEA) to identify the most cost-effective treatment strategy from the perspective of the Chinese healthcare system.

Methodik

<u>Population:</u>

- patients with metastatic hormone-sensitive prostate cancer

<u>Intervention/ Kontrolle:</u>

- maximum androgen blockade (MAB),
- docetaxel to androgen deprivation therapy (Doc-ADT) and
- ADT alone

Endpunkte:

- nicht präspezifiziert

Recherche/Suchzeitraum:

- PubMed and Cochrane Library were searched for trials published in English; the Chinese databases CNKI and WanFang were searched for trials published in Chinese
- up to 30 January 2018

Qualitätsbewertung der Studien:

- Cochrane Collaboration's Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- We identified nine trials [10,16–23] involving a total of 5168 patients: 951 (18%) patients receiving Doc-ADT, 1462 (28%) patients receiving MAB and 2755 (53%) patients receiving ADT alone.

Charakteristika der Population:

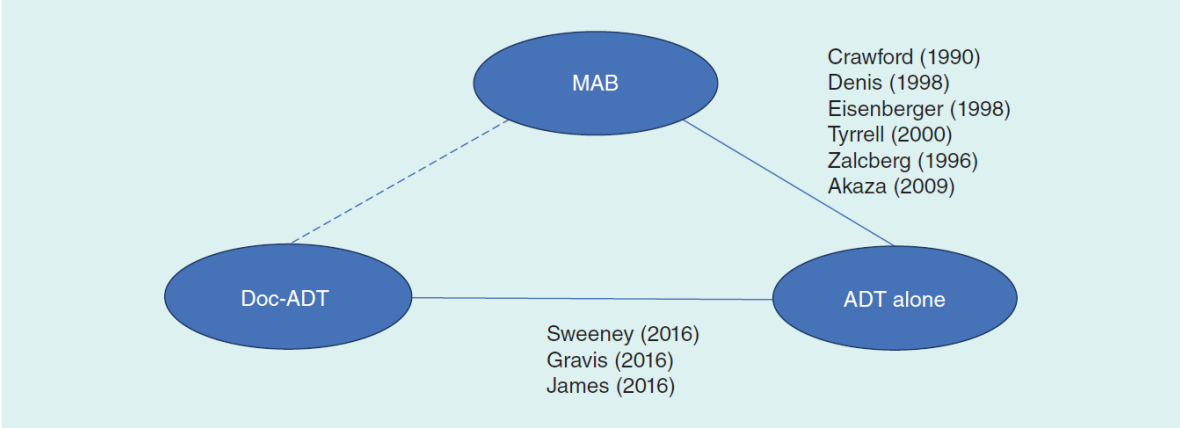


Figure 1. Network of evidence and included studies.
Doc-ADT: Docetaxel to androgen deprivation therapy; MAB: Maximum androgen blockade.

Noted that the STAMPEDE trial [23] includes about 30% patients with M0 disease, thus we only used the subgroup of patient in mHSPC in the analysis. An NMA flowchart and details of the included studies are provided in the Supplementary Material.

[weitere Daten im Supplementary Material nicht hinterlegt]

Qualität der Studien:

- Keine Angabe

Studienergebnisse:

NMA is a meta-analysis in which multiple treatments (three or more) are compared using both direct comparisons of interventions within RCTs and indirect comparisons across trials based on a common comparator. The reported adjusted hazard ratios (HRs) of the clinical outcomes were our preferred outcome measures because they account for censoring, incorporate time-to-event information, and may be adjusted for covariables [15]. If HRs were not reported in a study, we used Wood's method [15] to incorporate the count statistics with HR statistics in a

single analysis. The method avoids potential selection bias and misleading results caused by the selective inclusion of studies and accounts for the correlation among relative treatment effects in trials with more than two treatment groups [16]. Correlations among relative treatment effects in multi-arm trials are preserved by converting the relative treatment effect estimates (the HRs) to arm-specific outcomes (hazards). The deviance information criteria (DIC) was used to compare fit between the fixed- and random-effects models, with lower DIC values being preferred. In addition, sensitivity analyses were performed to determine the probability that each treatment will receive each possible ranking (first best, second best, etc.). The NMA was performed withWinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, UK). We provide the WinBUGS codes for the NMA in the Supplementary Material.

Overall survival & progression-free survival

All nine studies reported the count of deaths, and six studies [10,17,19,20,22,23] also reported HRs of death. Overall, there were a total of 3232 deaths: 1466 in the intervention arms (447 for patients receiving Doc-ADT; 1019 for patients receiving MAB) and 1767 in the ADT-alone arms. Six trials, involving 4556 enrolled patients, contributed to the PFS analysis [10,17,19,20,22,23]. Four of these trials [10,20,22,23] reported both HRs and the counts of progression, and the other two trials [17,19] reported only the counts of progression. We selected the fixed-effects model as the best model because it yielded a lower DIC value than the random-effects model for both OS (DIC: 15.077 for fixed-effects model, 16.106 for random-effects model) and PFS (DIC: 8.819 for fixed-effects model, 10.357 for random-effects model). The results are presented in Figure 2.

The pooled HR assessing OS was 0.782 (95% CI: 0.696–0.877) for Doc-ADT versus ADT alone, 0.897 (95% CI: 0.816–0.981) for MAB versus ADT alone, and 0.873 (95% CI: 0.743–1.002) for Doc-ADT versus MAB. The pooled HR assessing PFS was 0.628 (95% CI: 0.566–0.695) for Doc-ADT versus ADT alone, 0.824 (95% CI: 0.701–0.962) for MAB versus ADT alone and 0.762 (95% CI: 0.616–0.907) for Doc-ADT versus MAB.

Sensitivity analysis of NMA results

We then conducted a sensitivity analysis of the NMA results. Figure 3 represents the uncertainty in the analysis, showing the probability that each treatment will receive each possible ranking (1st best, 2nd best, etc.). For OS, there was a very high probability (96%) thatDoc-ADT is themost efficacious treatment; there was a 4% probability that it is the second-best treatment. For PFS, the probability of Doc-ADT being the most effective treatment was 100%.

Treatment-related toxicity

We originally sought to examine the odds of treatment-related toxicity as measured by Grade 3–5 adverse events (AEs) in a post hoc analysis. However, we found substantial differences in definitions and ratings among studies and thus considered it inappropriate to perform an NMA on AEs.

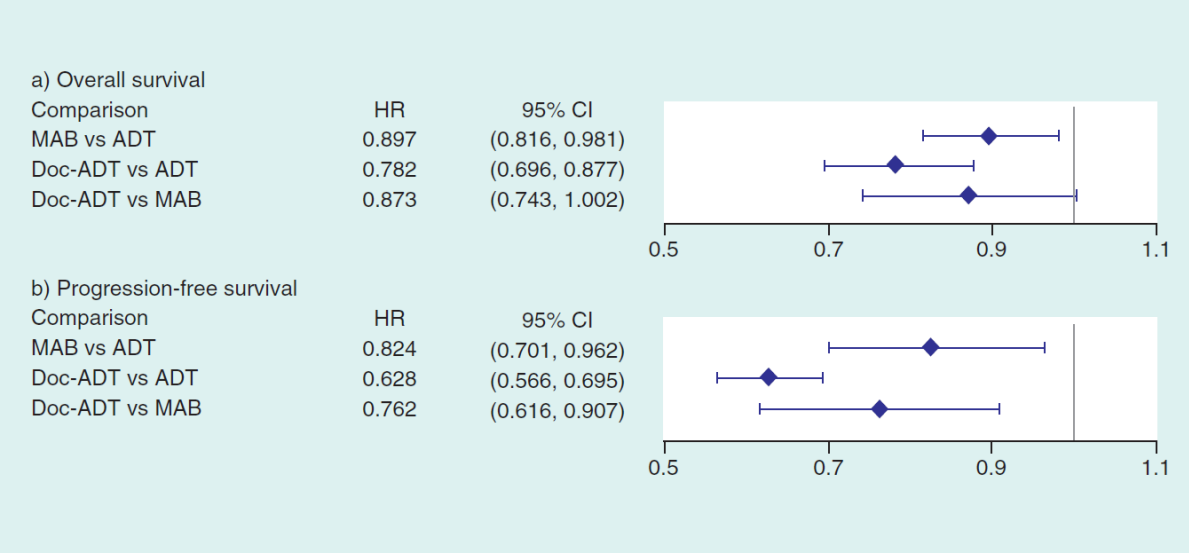


Figure 2. Forest plot of NMA results for OS and PFS.
Doc-ADT: Docetaxel to androgen deprivation therapy; HR: Hazard ratio; MAB: Maximum androgen blockade; OS: Overall survival; PFS: Progression-free survival.

Anmerkung/Fazit der Autoren

Among the three investigated therapies, Doc-ADT was associated with the best OS and PFS outcomes in mHSPC patients.

Hinweis:

Der Bezug auf China ergibt sich allein aus einer im Review enthalten gesundheitsökonomischen Analyse, deren Ergebnisse hier nicht dargestellt sind. Für die Nutzen-/Risiko-Bewertung wurde keine Einschränkung auf in China durchgeführte Studien vorgenommen.

Ramos-Esquivel A et al., 2016 [20].

Androgen-deprivation therapy plus chemotherapy in metastatic hormone-sensitive prostate cancer. A systematic review and meta-analysis of randomized clinica ltrials

Fragestellung

To assess the efficacy and toxicity of androgen-deprivation therapy (ADT) plus chemotherapy in patients with hormone-sensitive metastatic prostate cancer.

Methodik

Population:

- patients newly diagnosed metastatic prostate cancer

Intervention:

- chemotherapy plus ADT

Komparator:

- ADT alone

Endpunkte:

- The primary outcome was OS, calculated from the date of randomization to the date of death.
- Secondary outcomes include the following: (1) biochemical progression-free survival (PFS) defined as an increase in the prostate-specific antigen (PSA) level of more than 50% above the nadir reached after the initiation of ADT or a PSA increase of 25% above the nadir incase of patients without a previous PSA decrease of 50%(with a minimum increase of 5ng/ml); (2) clinical PFS, in general, was considered as an increase of symptoms of bone metastases, progression according oRECIST criteriaversion 1.0, clinical deterioration due to cancer according tothe investigator's opinion or the occurrence of new bone lesions, which ever happen first, or one or more new bonelesions on bone scan or occurrence of anewsoft-tissuelesion.The aforementioned definitions varied among trials.
- We also evaluated the toxicity profile, defined as the number of patients experiencing any adverse drug reaction (ADR) according to the Common Toxicity Criteria of the National Cancer Institute or the World Health Organization Criteria (the criteria used varied among trials).

Recherche/Suchzeitraum:

- electronic databases (MEDLINE, EMBASE, and The Cochrane Central Register of Controlled Trials)
- from January 2000 to October 1, 2015

Qualitätsbewertung der Studien:

- Cochrane CollaborationTool

Ergebnisse

Anzahl eingeschlossener Studien:

- 6 trials (n = 2 675)

Charakteristika der Population:

Table 1
Main characteristics of the included trials

First author	Noguchi [19]	Hoshi [20]	Millikan [21]	GETUG-AFU 15 Gravis [13]	E3805 Sweeney [14]	STAMPEDE James [15]
Patients' characteristics and definition of treatment						
Age	Not specified	<80 y	Not specified	>18 y	>18 y	No age restriction
Performance status	ECOG ≤ 2	ECOG ≤ 3	ECOG ≤ 2	Karnofsky ≥ 70%	ECOG 0–2	WHO 0–2
Stage	Metastatic prostate cancer (Stage D1 or D2 according to the 1983 American Cancer Society criteria)	Metastatic prostate cancer (Stage D1 or D2 according to the 1983 American Cancer Society criteria)	Nonlocalized prostate cancer. If increasing PSA after definitive treatment was the only evidence of metastatic prostate cancer, the PSA doubling time had to be at least 9 mo.	Metastatic prostate cancer	Metastasic prostate cancer	Any of: metastatic prostate cancer (M1); node-positive (N1) cancer; or at least 2 of the following criteria: (1) Stage T3/T4 (2) PSA ≥ 40 ng/ml (3) Gleason 8–10; or relapsing disease after radiotherapy o radical prostatectomy with at least one of the following criteria: (1) PSA ≥ 4 ng/ml and rising with doubling time less than 6 mo; (2) PSA ≥ 20 ng/ml (3) N positive or (4) M1
Tumor differentiation	ADT alone: Gleason 2–4: 9% Gleason 5–6: 55% Gleason 7–10: 36% Chemotherapy + ADT: Gleason 2–4: 3% Gleason 5–6: 59% Gleason 7–10: 38%	ADT alone: Well diff.: 13% Moderately diff.: 58% Poorly diff.: 29% Chemotherapy+ ADT: Well diff.: 6% Moderately diff.: 61% Poorly diff.: 32%	Not reported	ADT alone: Gleason 2–6: 7% Gleason 7: 34% Gleason 8–10: 59% Chemotherapy + ADT Gleason 2–6: 10 % Gleason 7: 35% Gleason 8–10: 55 %	ADT alone: Gleason 4–6: 6% Gleason 7: 24% Gleason 8–10: 70% Chemotherapy + ADT Gleason 2–6: 6 % Gleason 7: 27 % Gleason 8–10: 67 %	ADT alone[a]: Gleason ≤ 7: 24% Gleason 8–10: 68% Unknown: 8% Chemotherapy + ADT[a]: Gleason ≤ 7: 19% Gleason 8–10: 74% Unknown: 8%
PSA at randomization (ng/ml)	ADT alone: <40: 9% 40–200: 32% >200: 59% Chemotherapy + ADT: < 40: 18% 40–200: 31% >200: 51%	ADT alone: 230 (range: 1.8–5,930) Chemotherapy: 171.6 (range: 2.3–4,800)	ADT alone: <10: 24 10–20:18 20–100: 32 > 100: 25 Chemotherapy+ ADT: <10: 25% 10–20: 19% 20–100: 31% > 100: 24%	Median: ADT alone: 26 (IQR: 5–127) Chemotherapy + ADT: 27 (IQR: 5–106)	Median: ADT alone: 56.1 (range: 0.1–8,056) Chemotherapy + ADT: 50.9 (range: 0.2–8,540)	Median: ADT alone[a]: 65 (IQR: 60–70) Chemotherapy + ADT[a]: 70 (IQR: 27–181)

Previous treatment	Prior treatment was not allowed	Prior treatment was not allowed	Prior hormone therapy was allowed as adjuvant after definitive local therapy and it was given for 6 mo or less. The treatment must be completed at least 12 mo before initiating therapy for metastatic disease.	Prior chemotherapy for metastatic disease was not allowed. Prior chemotherapy or ADT, or both, were allowed in the neoadjuvant or adjuvant setting or in case of isolated PSA increase, but the treatment must be discontinued at least 12 mo before inclusion.	Prior docetaxel was not allowed. Adjuvant ADT was allowed if the duration was 24. mo or less, but must be completed at least 12 mo before entering the trial.	Prior chemotherapy and long-term ADT were not allowed. Antiandrogens were allowed to cover tumor flare. Adjuvant treatment was allowed but must be completed at least 12 mo before entering the trial (with a duration no longer than 12 mo).
Other exclusion criteria	Brain metastases, life expectancy less than 3 mo, another neoplasm or severe concomitant illness (renal, hepatic, cardiovascular, or neuropsychiatric disorders).	Another neoplasm and severe dysfunction in heart, liver, kidney, or bone marrow.	Patients with a history of vagotomy or who required continuous therapy with antacids, histamine receptor blockers, proton-pump inhibitors, terfenadine, astemizole, or cisapride. History of transient ischemic attack within the previous 6 mo, a requirement for regular antianginal therapy, or any history of deep venous thrombosis or pulmonary embolism.	Severe cardiac disease, surgical castration before metastatic disease occurred, brain metastases, peripheral neuropathy, history of another cancer in the past 5 y or another serious condition.	Patients with inadequate organ function (e.g., active cardiac disease, creatinine clearance less than 30 ml/min). Any surgery in the preceding 4 wk before randomization.	Metastatic brain disease or leptomeningeal disease; abnormal liver function; any contraindication to prednisolone, inflammatory bowel disease, symptomatic neuropathy grade II, any surgery in the past 4 wk, significant cardiovascular disease, prior exposure to abiraterone, enzalutamide, zolendronic acid, or other biphosphonate, history of seizures, loss of consciousness, transient ischemic attack, or previous stroke.
ADT (it was employed in both arms) (control group)	LHRH agonists + flutamide 125 mg t.i.d.	Endocrine therapy (not specified but included LHRH agonist or surgical castration ± antiandrogen therapy).	LHRH agonists or surgical castration. Use of antiandrogen was left to the discretion of the treating physician but it was not allowed if the patient received ketoconazole.	Orchiectomy or LHRH agonists, alone or combined with nonsteroidal antiandrogens.	Medical or surgical castration; use of nonsteroidal antiandrogens was allowed according to the discretion of the treating physician.	LHRH agonist or antagonist, or surgical castration. (use of antiandrogen drugs were permitted in the first versions of the protocol).
Chemotherapy (experimental group)	Estramustine 280 mg b.i.d. (duration not specified)	Estramustine 560 mg/d. Treatment was continued until patient desired discontinuation, serious side effects or progression.	3 Cycles (repeated every 8 wk) of: Ketoconazole 400 mg orally t.i.d. 7 d/wk in weeks 1,3, and 5; Doxorubicin 20 mg/m^2 administrated IV on days 1, 15 and 29; vinblastine 4 mg/m^2 administrated IV on days 8, 22, and 35; Estramustine 140 mg	Docetaxel (75 mg/m^2 IV day 1 every 3 weeks); up to 9 cycles + standard corticosteroids (no daily prednisone allowed).	Docetaxel (75 mg/m^2 IV day 1 every 3 weeks); up to 6 cycles plus standard dexametasone (no daily prednisone allowed).	Docetaxel (75 mg/m^2 IV day 1 every 3 weeks); up to 6 cycles plus standard dexametasone and prednisone 10 mg/d.

Table 1
Continued

First author	Noguchi [19]	Hoshi [20]	Millikan [21]	GETUG-AFU 15 Gravis [13]	E3805 Sweeney [14]	STAMPEDE James [15]
			PO t.i.d. 7 d/wk in weeks 2, 4, and 6 and hydrocortisone 20 mg PO AM and 10 mg PM.			
Enrollment	From June 1995–March 1998 n = 51	From July 1995–March 1998 n = 57	From September 1996–April 2003 n = 306	From October 2004–December 2008 n = 385	From July 2006–November 2012 n = 790	From October 2005–March 2013 n = 2,962 (n = 1,086 M+)
Timing of chemotherapy initiation	Not specified	Not specified	Up to 3 mo from hormonal therapy to randomization	Docetaxel within 2 mo of ADT start	Docetaxel within 4 mo of ADT start	Docetaxel within 12 wek of ADT start
Endpoints						
Objective	To investigate whether chemohormonal therapy with estramustine phosphate plus LHRH agonist has a more beneficial effect than the hormonal therapy with flutamide plus LHRH agonist for newly diagnosed patients with metastatic prostate cancer.	To investigate the clinical efficacy and the prolongation of survival with combination therapy of estramustine phosphate and endocrine therapy in untreated patients with progressive prostate cancer.	To test the hypothesis that three 8-wk cycles of ketoconazole and doxorubicin alternating with vinblastine and estramustine, given in addition to standard androgen deprivation, would delay the appearance of castrate-resistant disease.	To investigate the effects of the addition of docetaxel to androgen-deprivation therapy for patients with metastatic noncastrate prostate cancer.	To determine whether docetaxel therapy at the beginning of the ADT for metastatic hormone-sensitive prostate cancer would result in longer overall survival than that with ADT alone.	To assess if early use of active therapies may give a larger absolute benefit in overall survival.
Primary end point	Overall survival, objective response to treatment, and time to progression	Overall survival	Time to castrate-resistant progression	Overall survival	Overall survival	Overall survival
Secondary end points	Toxicity	Progression-free survival (defined by PSA increase) and toxicity	Overall survival and toxicity	Clinical progression-free survival, biochemical progression-free survival	PSA response, change of PSA over time, time to hormone refractory disease, time to clinical progression, and time to PSA progression	Quality of life, cost effectiveness, failure-free survival, toxicity, and skeletal-related events

diff. = differentiated; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; LHRH = human luteinizing hormone–releasing hormone; WHO = World Health Organization.
[a]Data include M0 and M1 patients.

Qualität der Studien:

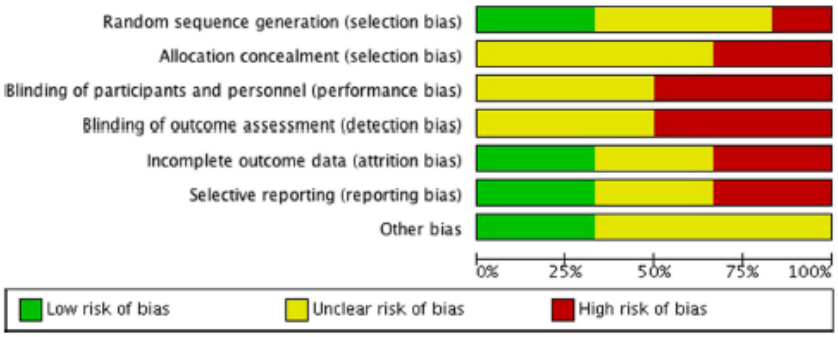


Fig. 5. Risk of bias (review author's judgments about each risk of bias item presented as percentages across all the included studies).

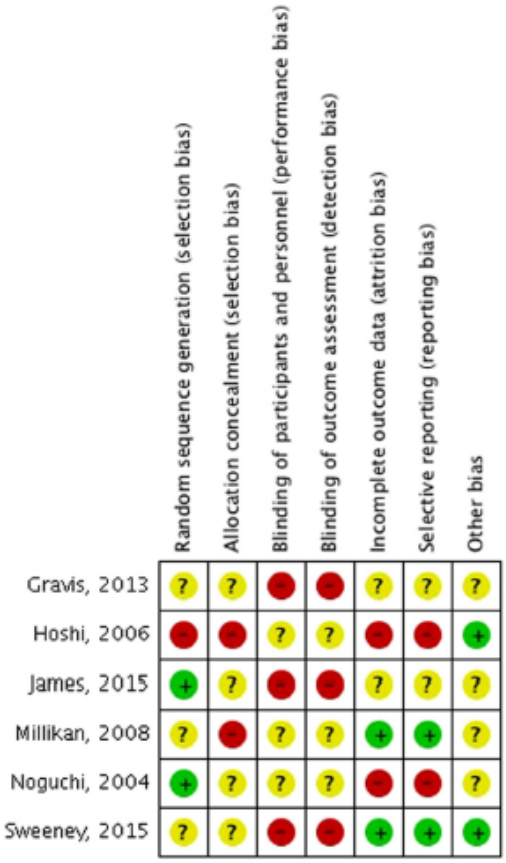


Fig. 6. Risk of bias summary (review author's judgments about each risk of bias item for each included study).

Studienergebnisse:

Overall results of the included trials

First author	Noguchi [19]	Hoshi [20]	Millikan [20]	GETUG-AFU 15 Gravis [9,13]	E3805 Sweeney [14]	STAMPEDE James [15]
Number of patients on ADT (control group)	22	26	149	193	393	1,184 (n = 724 M1)
Number of patients on ADT plus chemotherapy (experimental group)	29	31	137	192	397	592 (n = 362 M1)
Median follow-up	26 mo	Not reported	76.8 mo	82.9 mo[a]	28.9 mo	43 mo
Median number of chemotherapy cycles	Not reported	Not reported	3	8	6	6
Proportion of patients completing the planned chemotherapy scheme	75.8%	83.9%	80%	48%	86%	77%
Overall survival (OS) for metastatic patients	Events: Experimental group: 14 deaths Control group: 11 deaths Median OS: 35.9 mo (experimental) vs. 27.8 mo (control) HR = 1.15 (95% CI: 0.40–3.31) P = 0.796 (Estimated from data)	Events: 18 Deaths (both arms) Median OS: not reached (experimental) vs. 166 wk (control) HR = 0.38 (95% CI: 0.15–0.95) P = 0.0394 (Estimated from data)	Events: 156 Deaths (both arms) Median OS: 6.1 y (experimental) vs. 5.4 y (control) HR = 1.14 (95% CI: 0.83–1.56) P = 0.41 (Estimated from data)	Events[a]: 212 deaths (both arms) Median OS: 60.9 mo (experimental) vs. 46.5 mo (control) HR = 0.90 (95% CI: 0.70–1.20) P = 0.44	Events: Experimental group: 85 Deaths Control group: 144 deaths Median OS: 57.6 mo (experimental) vs. 44.0 mo (control) HR = 0.61 (95% CI: 0.47–0.80) P < 0.001	Events: Experimental group: 144 deaths Control group: 350 deaths Median OS: 60 mo (experimental) vs. 45 mo (control) HR = 0.76 (95% CI: 0.62–0.92), P = 0.005
Clinical progression-free survival	Median: 25.4 mo (experimental) vs. 14.6 mo (control) HR = 2.29 (95% CI: 1.08–4.83) P = 0.03 (Estimated from data)	Not reported	Median: 35 mo (experimental) vs. 24 mo (control) HR = 1.13 (95% CI: 0.85–1.50) P = 0.39 (Estimated from data)	Median: 23.5 mo (experimental) vs. 15.4 mo (control) HR = 0.75 (95% CI: 0.59–0.94) P = 0.015	Median: 33.0 mo (experimental) vs. 19.8 mo (control) HR = 0.61 (95% CI: 0.50–0.75) P < 0.001	Median not reported for the M1 subgroup HR = 0.61 (95% CI: 0.53–0.71) P < 0.001
Biochemical progression-free survival	Not reported	Median: 107 wk (experimental) vs. 48 wk (control) P = 0.3599	Not reported	Median: 22.9 mo (experimental) vs. 12.9 mo (control) HR = 0.70 (95% CI: 0.60–0.90) P = 0.005	Not reported	Not reported
Frequent adverse drug reactions	Chemotherapy plus ADT: Diarrhea grade 3 and 4: n = 1 (3.4%)	Chemotherapy plus ADT: Gastrointestinal toxicity grade 3 and 4: n = 2 (6.5%)	Chemotherapy plus ADT: Febrile neutropenia grade 3 and 4: n = 2 (1.5%); occurrence of any	Docetaxel plus ADT: Febrile neutropenia grade 3 and 4: n = 14 (7%)	Only reported for patients allocated to docetaxel plus ADT:	Docetaxel + ADT[b]: Febrile neutropenia grade 3 to 5: 15% Neutropenia: 12%

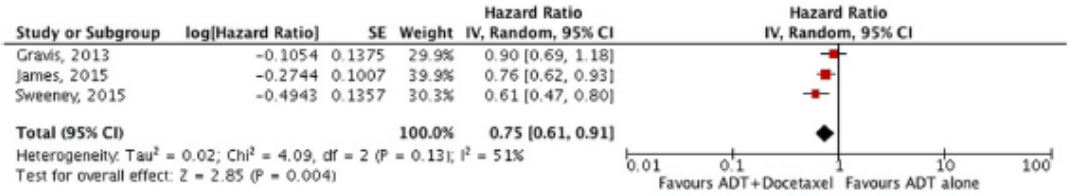


Fig. 2. Forest plot of hazard ratios for overall survival from the selected RCT comparing docetaxel plus ADT vs. ADT alone in patients with hormone-sensitive prostate cancer.

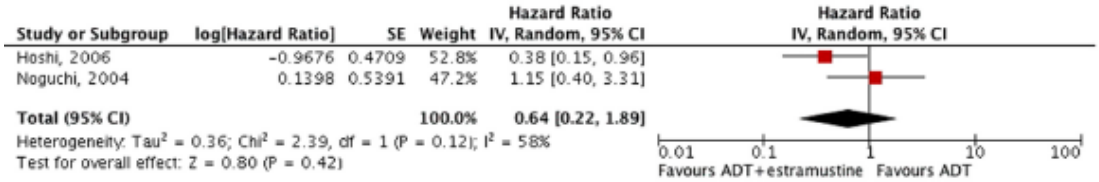


Fig. 3. Forest plot of hazard ratios for overall survival from the selected RCT comparing estramustine plus ADT vs. ADT alone in patients with hormone-sensitive prostate cancer.

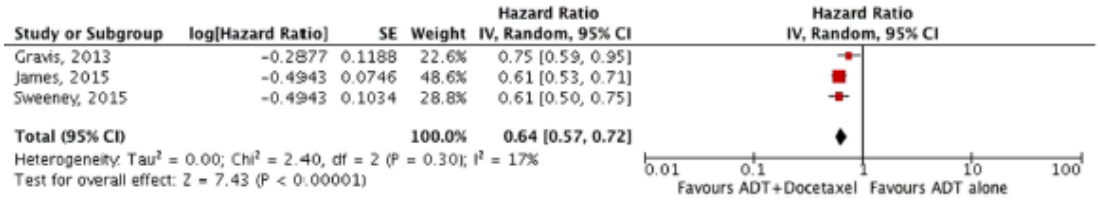


Fig. 4. Forest plot of hazard ratios for clinical progression-free survival from the selected RCT comparing chemotherapy plus ADT vs. ADT alone in patients with hormone-sensitive prostate cancer.

Anmerkung/Fazit der Autoren

Our analysis shows an OS benefit of combining docetaxel- based chemotherapy with ADT inpatients with newly diagnosed metastatic prostate cancer. Thisb benefit was not detected with other cytotoxic agents. A longer follow-up of the current trials would clarify which patients benefit the most from this approach.

Rydzewska LHM et al., 2017 [21].

Adding abiraterone to androgen deprivation therapy in men with metastatic hormone-sensitive prostate cancer: A systematic review and meta-analysis

Fragestellung

There is a need to synthesise the results of numerous randomised controlled trials evaluating the addition of therapies to androgen deprivation therapy (ADT) for men with metastatic hormone-sensitive prostate cancer (mHSPC). This systematic review aims to assess the effects of adding abiraterone acetate plus prednisone/prednisolone (AAP) to ADT.

Methodik

Population:

- men with mHSPC

Intervention:

- ADT plus AAP

Komparator:

- ADT

Endpunkte:

- The primary outcome was OS, defined as the time from randomisation to death from any cause.
- The secondary outcomes were progression-free survival (PFS), defined as the time from randomisation to first evidence of symptomatic clinical progression or radiological progression or death (excluding biochemical (prostatespecific antigen [PSA]) progression) and failure-free survival (FFS), defined as time to first biochemical (PSA), clinical or radiological progression.
- Further secondary outcomes were grade IIIeIV and grade V toxicity (as defined in each trial).

Recherche/Suchzeitraum:

- With no restriction on language, LHMR, SB and CLV searched MEDLINE, Embase, clinicaltrials.gov and the Cochrane Central Register of Controlled Trials
- to May 2017

Qualitätsbewertung der Studien:

- To assess the risk of bias of included trials, based on the outcome of OS, we also sought information on the method of randomisation sequence generation, allocation concealment, blinding of participants, personnel and outcome assessment, completeness of outcome data and whether all key outcomes were reported/available.

Ergebnisse

Anzahl eingeschlossener Studien:

- three eligible trials, one of which was still recruiting (PEACE-1 (NCT01957436)

Gemeinsamer Bundesausschuss

Charakteristika der Population:

Table 1
Characteristics of studies eligible trials.

Trial	Accrual dates	Number of M1 patients	*De novo* or relapsed M1?	Control	Treatment	Median age (range)	Gleason score of 8–10 (%)	Performance status 0–1 (%)	Median follow-up (survival)
STAMPEDE [12] (Arm A versus arm G) M1 patients only	11/2011–01/2014	1002	*De novo* (95%) or relapsed after local therapy (5%)	ADT (LHRH agonist or antagonist or orchiectomy)	ADT + abiraterone (1000 mg/d) + prednisone (5 mg/d)	67 (62 –72)	737 (74%)	988 (97%)	41 months
LATITUDE [11]	02/2013–12/2014	1199	*De novo*	ADT (LHRH agonists or orchiectomy)	ADT + abiraterone (1000 mg/d) + prednisone (5 mg/d)	67 (33 –92)	1170 (98%)	1157 (96%)	30.4 months
PEACE-1[a] (NCT01957436) (patients not receiving docetaxel in addition to ADT)	11/2013–to date	≈476 expected	*De novo*	ADT (LHRH agonist or antagonist or orchiectomy)	ADT + abiraterone (1000 mg/d) + prednisone (10 mg/d)	Not yet available	Not yet available	Not yet available	Not yet available
				ADT (LHRH agonist or antagonist or orchiectomy) + radiotherapy (74 Gy, 37 fractions)	ADT + abiraterone (1000 mg/d) + prednisone (10 mg/d) + radiotherapy (74 Gy, 37 fractions)				
PEACE-1[b] (NCT01957436) (patients receiving docetaxel in addition to ADT)	11/2015–ongoing	Target ≈650 (≈300+ accrued to date)		ADT (LHRH agonist or antagonist or orchiectomy) + docetaxel[c] (75 mg/m^2 q 21 days; 6 cycles)	ADT + docetaxel[c] + abiraterone (1000 mg/d) + prednisone (10 mg/d)	Not yet available	Not yet available	Not yet available	Not yet available
				ADT (LHRH agonist or antagonist or orchiectomy) + docetaxel[c] (75 mg/m^2 q 21 days; 6 cycles) + radiotherapy (74 Gy, 37 fractions)	ADT + docetaxel[c] + abiraterone (1000 mg/d) + prednisone (10 mg/d) + radiotherapy (74 Gy, 37 fractions)				

ADT, androgen deprivation therapy; LHRH, luteinising hormone–releasing hormone.
[a] Patients randomised to PEACE-1, who have not received docetaxel in addition to ADT are eligible for this comparison.
[b] Patients randomised to PEACE-1, who have received docetaxel in addition to ADT will be eligible for a subsequent comparison of the systematic review (PROSPERO CRD42017058300).
[c] Docetaxel use is left to the investigator's discretion (stratification factor).

Table 3
Characteristics of included patients.

	STAMPEDE		LATITUDE	
	ADT	ADT + AAP	ADT	ADT + AAP
Number of patients	502	500	602	597
Age				
Median (IQR)	67 (62–72)	67 (62–71)	67 (61–73)	68 (61–73)
Range	39–84	42–85	33–92	38–89
PSA [ng/ml]				
Median (IQR)	97 (26–358)	96 (29–371)	23.05 (4.96–112.66)	25.43 (4.62, 117.58)
Range	0–10530	0–21460	(0.1–8889.6)	(0–87775.9)
Time from initial diagnosis[a]				
Median	2.3	2.5	2.0	1.8
Range	0–160	0–177	(0–4)	(0–3)
Missing	1	3	0	0
WHO PS (ECOG PS)				
0	370 (73.7%)	374 (74.8%)	331 (55.0%)	326 (54.6%)
1	125 (24.9%)	119 (23.8%)	255 (42.4%)	245 (41.0%)
2	7 (1.4%)	7 (1.4%)	16 (2.7%)	26 (4.4%)
T category[b]				
T0	1 (0.2%)	2 (0.4%)	1 (0.2%)	0
T1	10 (2.0%)	5 (1%)	25 (4.2%)	29 (4.9%)
T2	45 (9.0%)	44 (8.8%)	113 (18.8%)	94 (15.8%)
T3	270 (53.8%)	288 (57.6%)	254 (42.3%)	246 (41.3%)
T4	137 (27.3%)	118 (23.6%)	128 (21.3%)	159 (26.7%)
Tx	39 (7.8%)	43 (9.2%)	80 (13.3%)	68 (11.4%)
N category[c]				
N0	175 (34.9%)	167 (33.4%)	151 (25.2%)	152 (25.5%)
N+	291 (58.0%)	292 (58.4%)	280 (46.7%)	280 (47.0%)
Nx	36 (7.2%)	41 (8.2%)	169 (28.2%)	164 (27.5%)
Location of metastases				
Bone	448 (89.2%)	434 (86.8%)	585 (97.5%)	580 (97.3%)
Liver	8 (1.6%)	7 (1.4%)	30 (5.0%)	32 (5.4%)
Lung	21 (4.2%)	21 (4.2%)	72 (12.0%)	73 (12.2%)
Nodal	150 (29.9%)	142 (28.4%)	287 (47.8%)	283 (47.5%)
Other	26 (5.2%)	23 (4.6%)	182 (30.4%)	180 (30.1%)
Disease history (newly diagnosed/relapsed)				
Newly diagnosed M1	476 (94.8%)	465 (93%)	602 (100%)	597 (100%)
Previously treated M1	26 (5.2%)	35 (7.0%)	0	0
Gleason sum				
≤7	119 (23.7%)	115 (23%)	16 (2.7%)	13 (2.2%)
8–10	373 (74.3%)	364 (72.8%)	586 (97.3%)	584 (97.8%)
Unknown	10 (2.0%)	21 (4.2%)	0	0
Type of ADT[d]				
Orchiectomy	3 (0.6%)	3 (0.6%)	71 (11.8%)	73 (12.2%)
Bicalutamide/anti-androgen alone	1 (0.2%)	0	84 (14.0%)	46 (7.7%)
Dual androgen blockade	3 (0.6%)	1 (0.2%)	NA	NA
LHRH based	495 (98.6%)	496 (99.2%)	450 (74.8%)	449 (75.2%)

AAP, abiraterone acetate plus prednisone/prednisolone; ADT, androgen deprivation therapy; ECOG, Eastern Cooperative Oncology Group; LHRH, luteinising hormone–releasing hormone; PS, performance score; WHO, World Health Organisation.

[a] For STAMPEDE, this also includes men who have relapsed after previous radical treatment.

[b] In LATITUDE, T category unaccounted for in one patient from each arm.

[c] In LATITUDE, N category unaccounted for in two patients in ADT arm and one patient in ADT + AAP.

[d] In LATITUDE, in ADT arm, some patients may have received anti-androgen in addition to LHRHa-based treatment; the patients unaccounted for in ADT + AAP may not yet have been started on ADT as diagnosed only very recently.

Qualität der Studien:

Table 2
Assessment of risk of bias (based on overall survival).

Trial ID	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting
STAMPEDE [12]	Central randomisation using a computerised algorithm. A minimisation method with a random element of 80% was used to stratify for a number of clinically important factors	Central telephone randomisation	Open label; blinding to treatment allocation considered impractical and of limited value, given the primary outcome of death from any cause	All randomised patients included in analyses	All outcomes of interest reported
LATITUDE [11]	A computer-generated randomisation schedule was used. Country by country randomisation was performed using permuted block randomisation.	Centralised interactive Web response system (IWRS)	Double blind, placebo controlled. Participants, care-givers and investigators unaware of treatment allocation	All randomised patients included in analyses	All outcomes of interest reported

Studienergebnisse:

- **OS**

  Results from the two remaining trials (LATITUDE (NCT01715285) and STAMPEDE (NCT00268476)), representing 82% of all men randomised to AAP plus ADT versus ADT (without docetaxel in either arm), showed a highly significant 38% reduction in the risk of death with AAP plus ADT (HR Z 0.62, 95% confidence interval [CI] = 0.53 – 0.71 , p = 0.55 X 10^{-10}), that translates into a 14% absolute improvement in 3-year OS.

  There was no evidence of a difference in the OS benefit by Gleason sum score, performance status or nodal status, but the size of the benefit may vary by age.

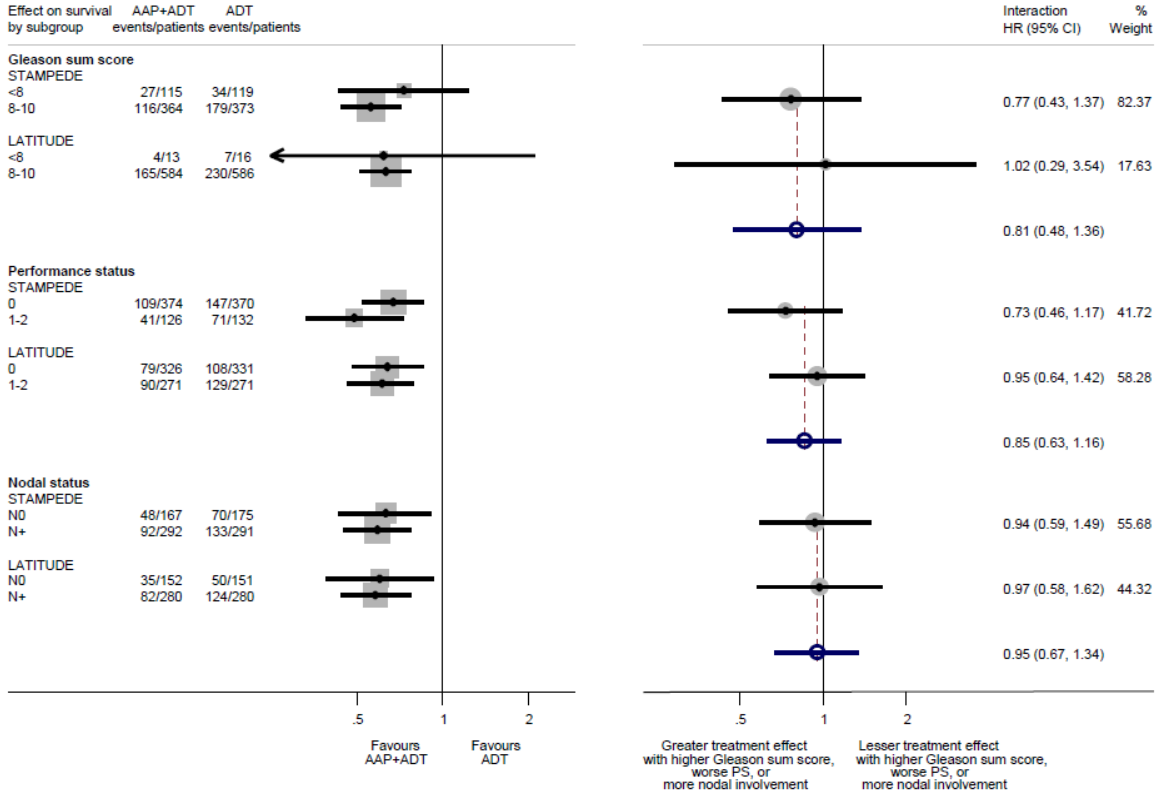


Fig. 3. **Effect of adding AAP to ADT on overall survival by nodal status, Gleason sum score and performance status.** Each filled square denotes the HR for each subgroup of men defined by, Gleason sum score, nodal status and PS within each trial, with the horizontal lines showing the 95% CI. The size of the square is directly proportional to the amount of information contributed by a subgroup. Each filled circle denotes the HR for the interaction between the effect of chemotherapy and these subgroups for each trial, with the horizontal lines showing the 95% CI. The size of each circle is directly proportional to the amount of information contributed by a trial. The open circle represents a (fixed-effect) meta-analysis of the interaction HRs, with the horizontal line showing the 95% CI. AAP, abiraterone acetate plus prednisone/prednisolone; ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; PS, performance status.

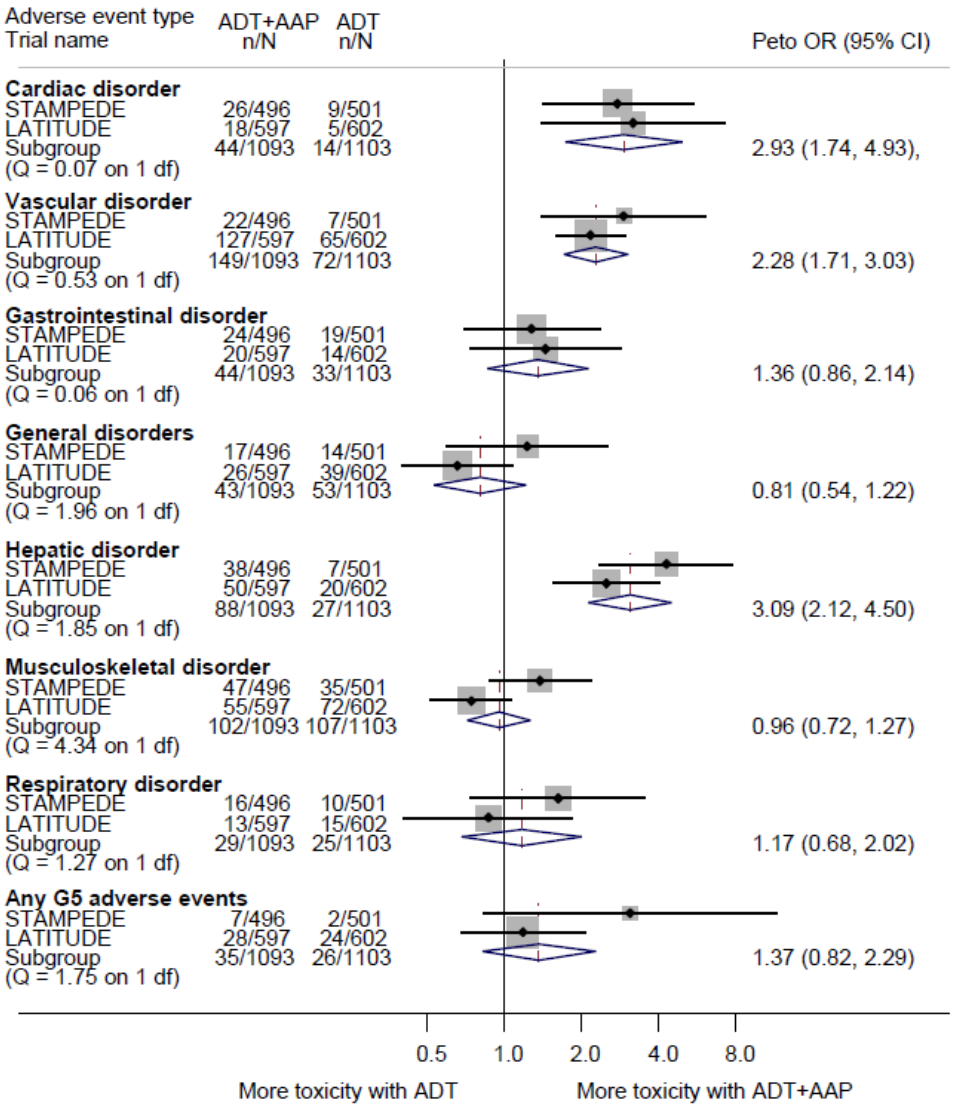
- **PFS**

  Despite differences in PFS definitions across trials, we also observed a consistent and highly significant 55% reduction in the risk of clinical/radiological PFS (HR = 0.45, 95% CI = 0.40-0.51, p = 0.66 X 10^{-36}) with the addition of AAP, that translates to a 28% absolute improvement at 3 years.

- **AE**

  There were more grade IIIeIV acute cardiac, vascular and hepatic toxicities with AAP plus ADT but no excess of other toxicities or death.

  Effect of adding AAP to ADT on grade III-V and grade V adverse events. A part from a Peto OR (rather than hazard ratio) measure of effect, labelling and conventions are as in Fig. 2. AAP, abiraterone acetate plus prednisone/prednisolone; ADT, androgen deprivation therapy; CI, confidence interval; OR, odds ratio.



Anmerkung/Fazit der Autoren

Adding AAP to ADT is a clinically effective treatment option for men with mHSPC, offering an alternative to docetaxel for men who are starting treatment for the first time. Future research will need to address which of these two agents or whether their combination is most effective, and for whom.

Sathianathen NJ et al., 2020 [22].

Indirect Comparisons of Efficacy between Combination Approaches in Metastatic Hormone-sensitive Prostate Cancer: A Systematic Review and Network Meta-analysis

Fragestellung

There have been substantial changes in the management of men with metastatic hormone-sensitive prostate cancer (mHSPC) over the past 5 yr, with upfront combination therapies replacing androgen-deprivation therapy (ADT) alone. A range of therapies have entered the space with no clear answer regarding their comparative efficacy. Objective: To perform a systematic review and network meta-analysis to characterise the comparative efficacy of combination approaches in men with mHSPC.

Methodik

Population:

- patients with mHSPC who were receiving first-line therapy for metastatic disease

Intervention/ Komparator:

- combining ADT with one (or more) of the additional agents (docetaxel, abiraterone acetate, enzalutamide, and apalutamide)

Endpunkte:

- Our primary outcome was overall survival (OS) measured as time from randomisation to death from any cause.
- We also evaluated progression-free survival defined as the time from randomisation to prostate-specific antigen (PSA) progression, and radiographic and/or clinical progression as a secondary endpoint.

Recherche/Suchzeitraum:

- Extensive search of multiple databases (MEDLINE, Embase, Science-Direct, Cochrane Libraries, HTA database, and Web of Science)
- papers published from January 2014 up to June 2019

Qualitätsbewertung der Studien:

- keine speuifischen Angaben; risk of bias assessment were performed by two independent reviewers; vgl. Tabelle *summary of findings* (siehe unten)

Ergebnisse

Anzahl eingeschlossener Studien:

- seven trials that met our eligibility criteria using either docetaxel, abiraterone acetate, enzalutamide, or apalutamide in combination with ADT

Charakteristika der Population:

Table 1 – Details and baseline of included studies.

Combination agent	Trial name	Performance status	Disease stage	Definition of high volume disease	Previous treatment	Pre-treatment with docetaxel	Control arm treatment	Patients i control arm (*n*)
Docetaxel	GETUG-AFU15	Karnofsky ≥70	Metastatic	NR CHAARTED definition used retrospectively	Chemotherapy or ADT only if discontinued >12 mo prior	Nil	Medical or surgical castration ± nonsteroidal antiandrogen	193
	CHAARTED	ECOG ≤2	Metastatic	Visceral metastases or ≥4 bone lesions with ≥1 beyond spine/pelvis	ADT only if duration <24 mo and discontinued >12 mo prior	Nil	Medical or surgical castration ± nonsteroidal antiandrogen	393
	STAMPEDE	WHO ≤2	Metastatic or node-positive or ≥2 of T3/4, Gleason 8–10, PSA ≥ 40 ng/ml	NR Multiple definitions used retrospectively	ADT only if duration <12 mo and discontinued >12 mo prior	Nil	Medical or surgical castration	1184
Abiraterone	LATITUDE	ECOG ≤2	Metastatic with ≥2 of Gleason ≥8, ≥3 bone lesions, visceral metastasis	NR (see inclusion criteria)	ADT only if duration ≤3 mo; or orchidectomy ± first-generation AR antagonist; or one course palliative radiation/surgery for metastatic symptoms	Nil	Medical or surgical castration	602
	STAMPEDE	WHO ≤2	Metastatic or node positive or ≥2 of T3/4, Gleason 8–10, PSA ≥ 40 ng/ml or previous surgery/ radiotherapy now relapsing with of PSA > 4 ng/ml, doubling time <6 mo, PSA > 20 ng/ml, nodal or metastatic recurrence	NR	ADT only if short term	Nil	Medical or surgical castration	957
Enzalutamide	ENZAMET	ECOG ≤2	Metastatic	Visceral metastases or ≥4 bone lesions with ≥1 beyond spine/pelvis	ADT only if duration <24 mo and discontinued >12 mo prior	15% in the control arm 17% in the experimental arm (within 3 mo prior to randomisation)	ADT + nonsteroidal antiandrogen + early docetaxel up to six cycles ± prednisone in 76%	562
Apalutamide	TITAN	ECOG ≤1	Metastatic	Visceral metastases with at least one bone lesion or ≥4 bone lesions with ≥1 beyond spine/pelvis	Docetaxel up to six cycles prior to randomisation; or ADT only if duration <6 mo for mHSPC; or ADT only if duration <36 mo for localised prostate cancer; or one course palliative radiation/surgery for metastatic symptoms; or local surgery/ radiation at least 12 mo prior	10% in the control arm 11% in the experimental arm	ADT + placebo	527

Age (yr)	PSA (ng/mL)	Gleason grade group 4 and 5, n (%)	Experimental arm treatment (added to the control arm treatment)	Patients in the experimental arm (n)	Age (yr)	PSA (ng/mL)	Gleason grade groups 4 and 5	Primary endpoint	Secondary endpoint	Median follow-up
Median 64 (IQR 58–70)	Median 25.8 (IQR 5.0–126.9)	113 (59)	Docetaxel up to nine cycles without prednisone	192	Median 63 (IQR 57–68)	Median 26.7 (IQR 5.0–106.2)	103 (55)	OS	rPFS and bPFS	82.9 mo
Median 63 (range 39–91)	Median 50.9 (range 0.2–8450.1)	243 (62)	Docetaxel up to six cycles without prednisone	397	Median 64 (range 36–88)	Median 52.1 (range 0.1–8056.0)	241 (61)	OS	PSA < 0.2 ng/ml at 6 mo; PSA < 0.2 ng/ml at 12 mo; time to CRPC; time to clinical progression	28.9 mo
NR separately for the metastatic subgroup	NR separately for the metastatic subgroup	NR separately for the metastatic subgroup	Docetaxel up to 6 cycles with daily prednisone 10 mg ± zoledronic acid	1185	NR separately for the metastatic subgroup	NR separately for the metastatic subgroup	NR separately for the metastatic subgroup	OS	Failure-free survival; time to any treatment after progression including docetaxel or abiraterone	43 mo
Median 67 (range 33–92)	NR	586 (97)	Abiraterone acetate plus prednisone 5 mg daily	597	Median 68 (range 38–89)	NR	584 (98)	OS and rPFS	Time to PSA progression; time to symptomatic SRE; time to any new treatment including chemotherapy	30.4 mo
Median 67 (62–72)	Median 56 (19–165)	721 (75)	Abiraterone acetate plus prednisone 5 mg daily	960	Median 67 (63–72)	Median 51 (19–158)	715 (74)	OS	PFS; DSS; symptomatic SRE; adverse events; QOL	40 mo
Median 69.0 (range 63.2–74.5)	NR	321 (57)	Enzalutamide daily + early docetaxel up to six cycles ± prednisone in 65%	563	Median 69.2 (range 63.2–74.5)	NR	335 (60)	OS	PFS; adverse events	34 mo
Median 68 (range 43–90)	NR	358 (68)	Apalutamide daily	525	Median 68 (range 43–90)	NR	351 (67)	OS and rPFS	Time to chemotherapy; time to pain progression; time to chronic opioid use; time to SRE	22.7 mo

Qualität der Studien:

- Overall, the trials were of moderate quality with downgrading primarily occurring for a lack of blinding.

  [Daten sollen laut Publikation im Supplement zu finden sein. Supplement ist nicht auffindbar.]

Studienergebnisse:

Table 1 Summary of findings table.

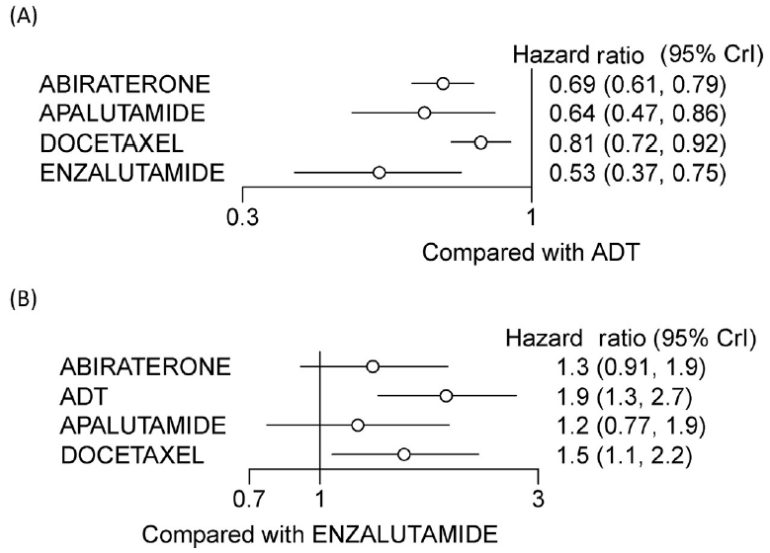
Outcomes and follow-up	No. of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with ADT only	Risk difference with taxane-based chemotherapy and ADT
Time to death due to any cause (absolute effect size estimates based on all-cause mortality at 5 years) Follow-up: median 43–84 months	2261 (3 RCTs)	⊕⊕⊕⊖ Moderate[3]	HR 0.77 (0.68–0.87)	Study population[1] 610 per 1000 General population[2] 702 per 1000	94 fewer per 1000 (137 fewer to 51 fewer) 96 fewer per 1000 (141 fewer to 51 fewer)
Grade III–V adverse events Follow-up: median 50 months	375 (1 RCT)	⊕⊕⊖⊖ Low[4]	RR 2.98 (2.19–4.04)	Study population 204 per 1000	405 more per 1000 (243 more to 621 more)
Prostate cancer-specific death[5] Follow-up: median 29–84 months	2261 (3 RCTs)	⊕⊕⊕⊖ Moderate[6]	RR 0.79 (0.70–0.89)	Study population[7] 512 per 1000	108 fewer per 1000 (154 fewer to 56 fewer)
Time to progression (absolute effect size estimates based on progression rate at 5 years) Follow-up: median 43–84 months	2261 (3 RCTs)	⊕⊕⊕⊖ Moderate[6]	HR 0.63 (0.56–0.71)	Study population[8] 822 per 1000	159 fewer per 1000 (202 fewer to 116 fewer)
Discontinuation due to adverse events Follow-up: median 50 months	385 (1 RCT)	⊕⊕⊖⊖ Low[9]	RR 79.41 (4.92–1282.78)	Study population 0 per 1000	41 more per 1000 (25 more to 1000 more)
All adverse events Follow-up: median 50 months	375 (1 RCT)	⊕⊕⊖⊖ Low[4]	RR 1.11 (1.06–1.17)	Study population 898 per 1000	99 more per 1000 (54 more to 153 more)
Quality of life at 12 months (measured with the FACT-P scale, higher score is better)	790 (1 RCT)	⊕⊕⊖⊖ LOW[10]	–	The mean quality-of-life (FACT-P) score in the control arm was 116.4	MD 2.85 higher (0.13 higher to 5.57 higher)

*RCT, randomised controlled trial. GRADE Working Group grades of evidence: High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. *The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). [1]Baseline risk of death for any cause was calculated from the 5-year event rate of the control group from the ChemoHormonal therapy versus Androgen Ablation Randomized Trial for Extensive Disease in prostate cancer (CHAARTED) trial [8]. [2]Population data from Surveillance, Epidemiology and End Results (SEER) registry, prostate cancer stage IV 5-year survival (70.2%) in the pre-docetaxel era (2007–2013); taxane-based chemohormonal therapy for metastatic hormone-sensitive prostate cancer (Review), The Cochrane Collaboration© 2018 [2]. [3]Severe concerns regarding study limitations (high risk of performance bias) contributed to our decision to downgrade by one level overall. [4]Severe concerns regarding study limitations (high risk of performance and detection bias), imprecision (wide CI consistent with both large and very large increase in grade III–V adverse events), and additional concerns about selective reporting (outcome only adequately reported by one of three trials) contributed to our decision to downgrade by two levels overall. [5]We planned to assess this as a time-to-event outcome (time to prostate cancer-specific death), but we evaluated this as a dichotomous outcome due to insufficient data. [6]Severe concerns regarding study limitations (high risk of performance bias and unclear risk of detection bias) contributed to our decision to downgrade by one level overall. [7]Baseline risk of prostate cancer-specific death was calculated from the 5-year event rate of the control group from the androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15) trial [5]. [8]Baseline risk of progression was calculated from the 5-year event rate of control group from the CHAARTED trial [8]. [9]Severe concerns regarding study limitations (high risk of performance and detection bias), imprecision (wide CIs suggesting small and very large increase in treatment discontinuation due to adverse events), and additional concerns about selective reporting (outcome only adequately reported by one of three trials) contributed to our decision to downgrade by two levels overall. [10]Very severe concerns about study limitations (high risk of detection, performance and attrition bias) contributed to our decision to downgrade by two levels overall.*

- OS

  All agents in combination with ADT were shown to be superior to ADT alone; enzalutamide + ADT had the lowest absolute hazard ratio compared with ADT only (hazards ratio 0.53, 95% confidence interval 0.37–0.75), and an estimated 76.9% probability that it is the preferred treatment to prolong OS compared with other combination treatments, or with ADT alone. Enzalutamide appeared to have better OS compared with docetaxel in men with low-volume disease, but there was no difference in other comparisons.

Overall survival for each intervention compared with (A) ADT and (B) enzalutamide. (ADT = androgen-deprivation therapy; CrI = credible interval.)



Rank probabilities graph for overall survival: primary analysis.

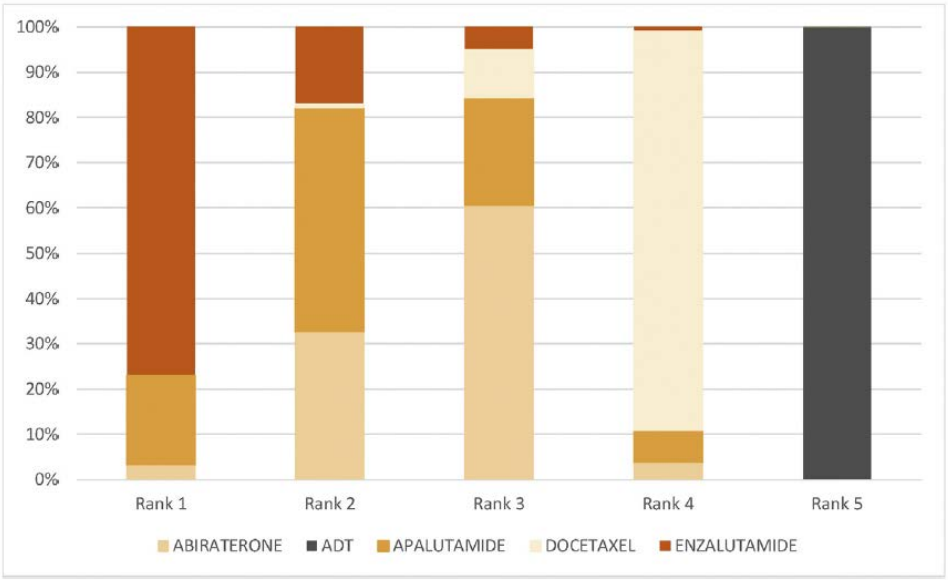
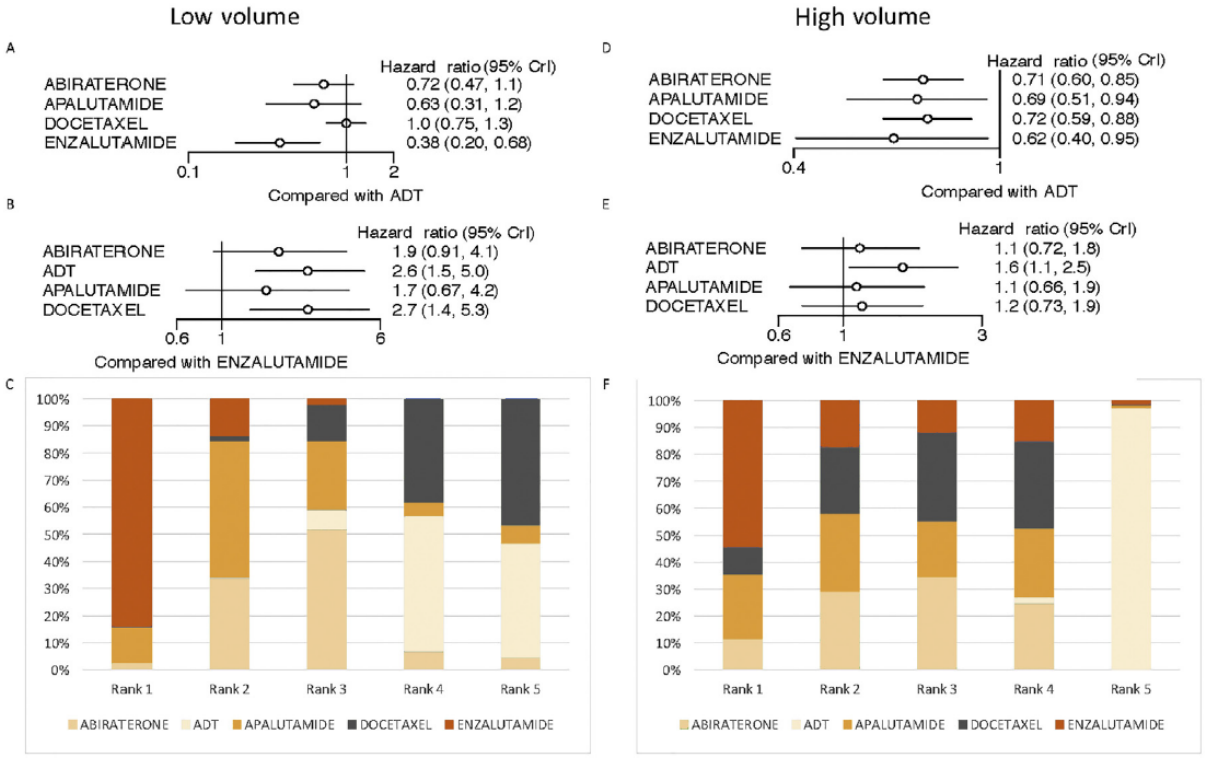


Fig. 3 – Subgroup analysis for volume of disease: low-volume disease forest plot with (A) ADT as reference, (B) enzalutamide as reference, and (C) SUCRA; high-volume disease forest plot with (D) ADT as reference, (E) enzalutamide as reference, and (F) SUCRA.

(ADT = androgen-deprivation therapy; CrI = credible interval; SUCRA = surface under the cumulative ranking.)



- PFS

  The GETUG-AFU15, CHAARTED, STAMPEDE, ENZAMET, and TITAN trials were included in this secondary endpoint. All four interventions delayed progression compared with ADT only (Supplementary Fig. 3). Abiraterone and enzalutamide were comparable to each other and preferred over both docetaxel and apalutamide. All treatment comparisons are outlined in Supplementary Table 3 (see data for “Progression-free survival”). There was no significant heterogeneity (I2 = 4%). There was no difference between the fixed and random effects models with the former demonstrating a better fit (DIC 21.4 vs 22.8). The result of the random effects model is reported in Supplementary Table 4 (see data for “Progression-free survival”). The former two had a 42.7% and 57.3% probability of being the preferred agent, respectively.

  [Supplement sind nicht auffindbar.]

  Anmerkung/Fazit der Autoren

  Our findings demonstrate that combination therapy with any of docetaxel, abiraterone acetate, enzalutamide, or apalutamide provides a significant OS benefit when compared with ADT alone. Subtle differences between these options allow clinicians considerable flexibility when selecting options for individual patients. We await the results of ongoing randomised studies directly comparing upfront combination interventions to provide further guidance for clinicians. In the meantime, it is reasonable to conclude that upfront combination approaches are the new standard of care for men with mHSPC, and ADT alone will likely only be used in limited circumstances or when economic factors constrain options.

Sun G et al., 2018 [25].

What kind of patients with castration-naïve prostate cancer can benefit from upfront docetaxel and abiraterone: A systematic review and a network meta-analysis

Fragestellung

to assess the role of combination therapy in patients with CNPC, com-pare the efficacy and safety of Abi and Doc, further inves-tigate the greatest benefited subgroups, and, finally, attempt to help clinicians and patients choose optimal sys-tematic treatment.

Methodik

Population:

- patients with non-mCNPC or mCNPC

Intervention/ Komparator:

- comparing either addition of docetaxel plus ADT and ADT alone or addition of abiraterone plus ADT and ADT alone

Endpunkte:

- OS, defined as the time from randomization until death from any cause; and
- failure-free survival (FFS), defined as the time from ran-domization to the following forms of treatment failure: PSA progression, onset of metastases on imaging, proven local relapse, or death from any cause.

Recherche/Suchzeitraum:

- Databases of PubMed (1950−2017.7), Medline (1966−2017.7), and Embase (1947−2017.7) were electron-ically searched at PubMed.com and OVIDSP.
- Further searches were conducted through the World Health Organization (WHO) International Clinical Trial Registration Platform (2004−2013), ClinicalTrial.gov (1999−2017.7), and Cochrane Central Register of Controlled Trials (1948−2017.7)

Qualitätsbewertung der Studien:

- RevMan 5.3 software according to the Cochrane Handbook

Ergebnisse

Anzahl eingeschlossener Studien:

- n = 6

Gemeinsamer Bundesausschuss

Charakteristika der Population:

Table 1
Characteristics of studies included in meta-analysis.

	GETUG-12	GETUG-15	CHAARTED	STAMPEDE-doc	STAMPEDE-abi	LATITUDE
Accrual period	Nov 14, 2002–Dec 21 2006	Oct 18, 2004–Dec 31, 2008	Jul 2006–Dec 2012	Oct 5, 2005–Mar 31, 2013	Nov 15, 2011–Jan 17, 2014	Feb 12, 2013–Dec 11, 2014
Stage	High-risk localized PCa (M0)	mCNPC (M1)	mCNPC	High-risk localized PCa; mCNPC	High-risk localized PCa; mCNPC	mCNPC
Sample size	M0: 413	M1: 385	M1: 790	M0: 690 M1: 1086	M0: 915 M1: 1002	M1: 1199
Median follow-up	8.8 years	58.9 months	28.9 months	43 months	9.2 years	8.8 years
Treatment	ADT plus Doc (70 mg/m^2 for four cycles) plus estramustine	ADT plus Doc (75 mg/m^2 nine 3-weekly cycles)	ADT plus Doc (75 mg/m^2 six 3-weekly cycles) plus predisone;	Soc plus Doc (75 mg/m^2 six 3-weekly cycles) plus predisone or Soc plus Doc (75 mg/m^2 every 3 weeks for six cycles) plus ZA (4 mg, six 3-weekly cycles, then 4-weekly until 2 years) plus predisone	ADT plus Abi (1000 mg once daily) plus predisone	ADT plus Abi (1000 mg once daily) plus predisone, for months patients treatment was continued to continue for 2 years until disease progression, for M1 patients treatment continued until disease progression
Time of initiating combination therapy	NA	Doc initiated with 2 months of ADT start	Doc initiated with 4 months of ADT start	Doc initiated with median 8.6 weeks of ADT start	Abi initiated with 8 weeks of ADT start	Abi initiated with 1 month of ADT start
Duration of treatment (Doc or Abi)	95 (94%) patients received the four planned cycles of Doc	96 (48%) patients received nine planned cycles of Doc; 21 (11%) patients receive reduce dosage of Doc	335 (86.1%) patients received six planned cycles of Doc, of which 74% without dose modification	456 (77%) patients received six planned cycles of Doc	Median time of Abi administration: 23.3 months for patients stop intervention at 2 years and for patients continue to disease progression	Median time of Abi administration: 24 months

Abi = Abiraterone; ADT = Androgen deprivation therapy; Doc = Docetaxel; Soc = Standard of care; mCNPC = Metastatic castration naïve prostate cancer; PCa = Prostate cancer; ZA = Zoledronic acid.

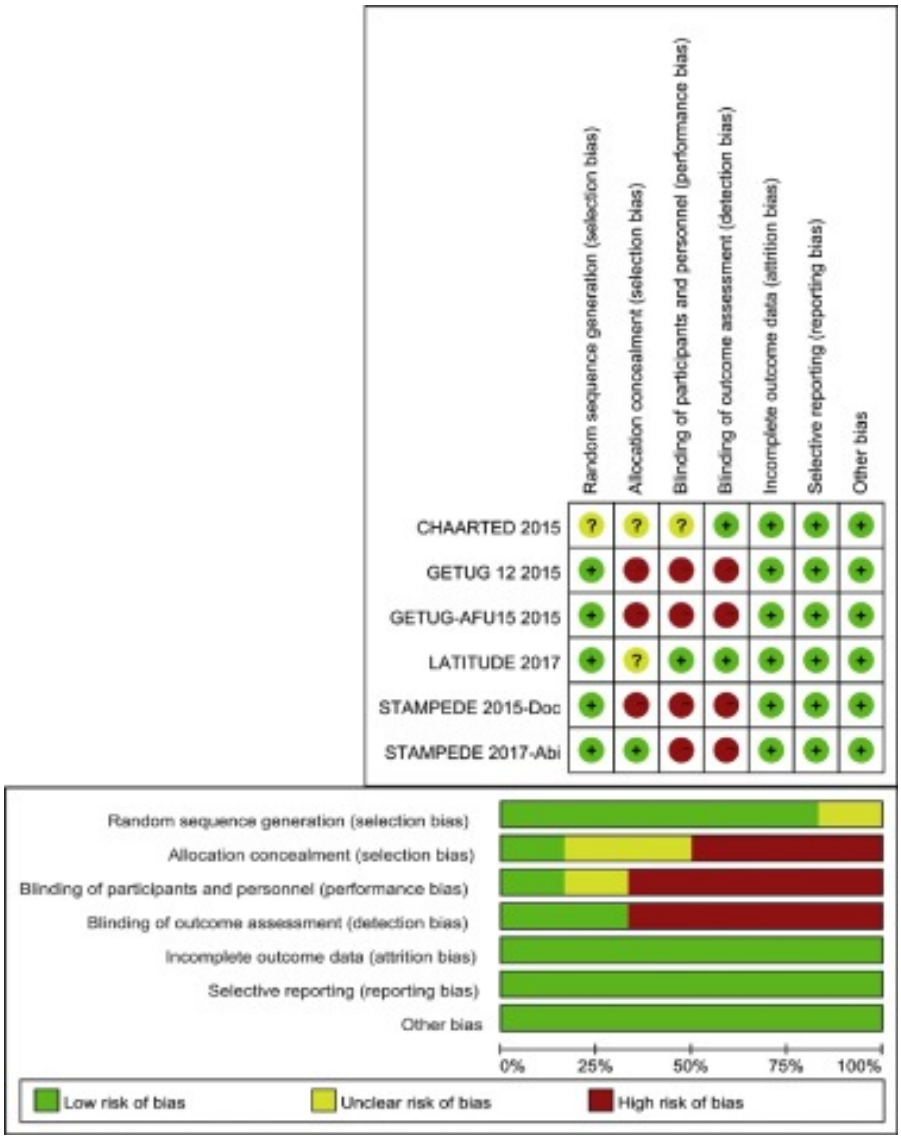
Table 2
Patient characteristics of studies included in meta-analysis.

	GETUG-12		GETUG-15		CHAARTED		STAMPEDE-Doc		STAMPEDE-Abi		LATITUDE	
	SOC+Doc	SOC only	SOC+Doc	SOC only	SOC+Doc	SOC only	SOC+Doc	SOC only	SOC+Abi	SOC only	SOC+Abi	SOC only
Sample size	207	206	192	193	397	393	592	1184	960	957	597	602
PSA level before ADT (ng/ml)	NA	NA	26.7 (5.0–106.2)	25.8 (5.0–126.9)	50.9 (0.2–8540.1)	52.1 (0.1–8056.0)	70 (27–181)	65 (60–70)	51 (19–158)	56 (19–165)	NA	NA
Median age (years)	62 (46–77)	64 (46–77)	63 (57–68)	64 (58–70)	64 (36–88)	63 (39–91)	65 (61–71)	65 (60–70)	67 (63–72)	67 (62–72)	68 (38–89)	67 (33–92)
Age < 70	NA	NA	293 (both arms)		612 (both arms)		419 (71%)	833 (70%)	603 (63%)	596 (62%)	333 (56%)	367 (61%)
Age ≥ 70	NA	NA	92 (both arms)		178 (both arms)		173 (29%)	351 (30%)	357 (37%)	361 (38%)	264 (44%)	235 (39%)
GS < 8	120 (58%)	118 (57%)	84 (45%)	78 (41%)	117 (29.5%)	104 (26.4%)	110 (19%)	282 (24%)	221 (23%)	223 (23%)	13 (2%)	16 (3%)
GS ≥ 8	87 (42%)	88 (43%)	103 (55%)	113 (59%)	241 (60.7%)	243 (61.8%)	436 (74%)	810 (68%)	715 (74%)	721 (75%)	584 (98%)	586 (97%)
ECOG = 0	NA	NA	357 (both arms)		277 (69.8%)	272 (69.2%)	461 (78%)	992 (84%)	745 (78%)	744 (78%)	NA	NA
ECOG ≥ 1	NA	NA	9 (both arms)		120 (30.2%)	121 (30.8%)	131 (23%)	262 (26%)	215 (22%)	213 (22%)	NA	NA
Metastasis	NA	NA	192 (100%)	193 (100%)	397 (100%)	393 (100%)	362 (61%)	724 (61%)	500 (52%)	502 (52%)	597 (100%)	602 (100%)
Bone	NA	NA	155 (81%)	156 (81%)	High volume: 262(66%);	High volume: 251(64%);	307 (52%)	634 (54%)	434 (45%)	448 (47%)	580 (97%)	585 (98%)
Visceral metastases	NA	NA	NA	NA	57 (14.4%)	66 (16.8%)	NA	NA	NA	NA	NA	NA
Liver	NA	NA	9 (5%)	3 (2%)	NA	NA	6 (1%)	15 (1%)	7 (1%)	8 (1%)	32 (5%)	30 (5%)
Lung	NA	NA	22 (11%)	22 (11%)	NA	NA	13 (2%)	33 (3%)	21 (2%)	21 (2%)	73 (12%)	72 (12%)
Nodes	NA	NA	100 (52%)	108 (56%)	NA	NA	102 (17%)	220 (19%)	142 (15%)	150 (16%)	283 (47%)	287 (48%)
Radiotherapy planned	NA	NA	NA	NA	NA	NA	168 (28%)	340 (29%)	396 (41%)	396 (41%)	NA	NA
Deaths	42	49	88	88	101	139	175	415	184	262	169	237
OS (mos)	NA	NA	54.2	58.9	55.7	44	60	45	NA	NA	NA	NA
Progression	88	111	68	75	238	287	315	761	248	535	239	354
FFS (mos)	NA	NA	NA	NA	20.2	11.7	37	20	43.9	30	33	14.8
bPFS (mos)	NA	NA	22.9	12.9	NA	NA	NA	NA	NA	NA	33.2	7.4
rPFS (mos)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	33	14.8
cPFS (mos)	NA	NA	23.5	15.4	33	19.8	NA	NA	NA	NA	NA	NA
Time to subsequent therapy	NA	NA	20	15.4	NA	NA	NA	NA	NA	NA	Not reach	21.6
Life-prolonging treatment	NA	NA	87(45%)	151(78%)	221 (55%)	270 (68%)	139(44%)	385(50%)	131 (53%)	310 (58%)	125 (21%)	246 (41%)
Docetaxel	NA	NA	54 (28%)	120 (62%)	54 (23%)	137 (48%)	44 (14%)	313 (41%)	115 (46%)	200 (37%)	106 (34%)	187 (40%)
Cabazitaxel	NA	NA	3 (2%)	2 (1%)	57 (24%)	37 (13%)	22 (7%)	26 (3%)	15 (6%)	28 (5%)	11 (4%)	30 (6%)
Abiraterone	NA	NA	19 (10%)	21 (11%)	105 (26%)	104 (26%)	89 (28%)	177 (23%)	8 (3%)	120 (22%)	10 (3%)	53 (11%)
Enzalutamide	NA	NA	9 (5%)	7 (4%)	(Abi + Enz)	(Abi + Enz)	25 (8%)	66 (9%)	25 (10%)	138 (26%)	30 (10%)	76 (16%)
Radium-223	NA	NA	NA	NA	69 (29%)	79 (28%)	6 (2%)	6 (1%)	19 (8%)	24 (4%)	11 (4%)	27 (6%)
Sipuleucel T	NA	NA	NA	NA	22 (5%)	19 (5)	NA	NA	NA	NA	NA	NA

Abi = Abiraterone; bPFS = Biochemical progression-free survival; cPFS = Clinical progression-free survival; Doc = Docetaxel; Enz = Enzalutamide; FFS = Failure-free survival; NA = Not available; OS = Overall survival; Soc = Standard of care.

Gemeinsamer Bundesausschuss

Qualität der Studien:



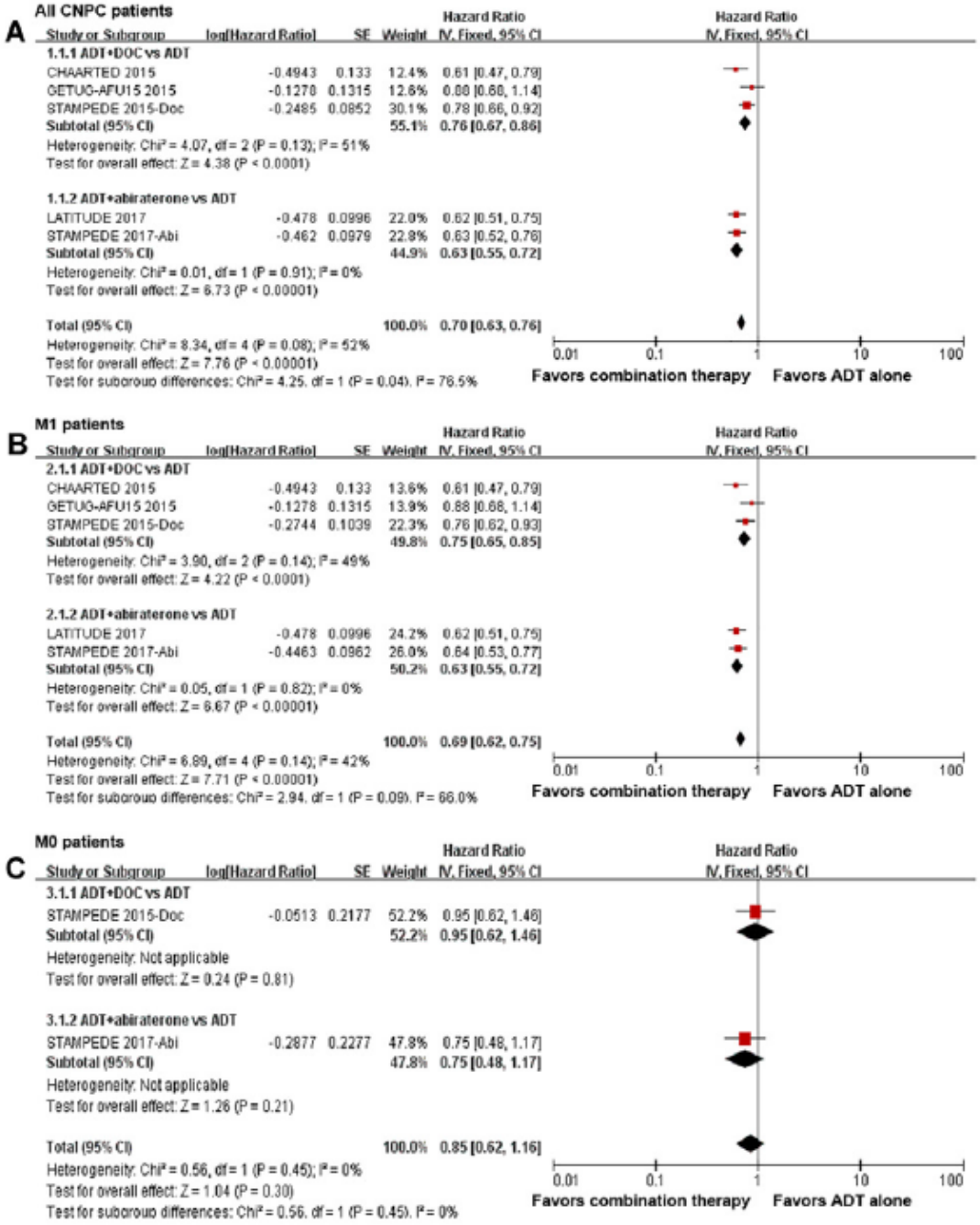
Studienergebnisse:

- Six studies, involving 6480 patients, were included in this meta-analysis, consisting of over 60% (4462/ 6480) of patients with metastatic CNPC (mCNPC, M1), and 31.1% (2018/6480) of patients with non-metastatic CNPC (M0). In total, com-bination therapies (ADT plus Doc or Abi) significantly improved overall survival (OS) and failure-free survival (FFS) for all CNPC patients.
- For M1 patients, combination therapies were dramatically associated with improved OS and FFS, but for M0 patients, only with moderate improvement in FFS. M1 patients < 70 years old, Eastern Cooperative Oncology Group (ECOG) performance status (ECOG PS) 0-1, Gleason score (< 8), or visceral metastases could realize better survival benefit from either combination therapy.
- In indirect comparisons among M1 patients with younger age (< 70 years), ECOG PS 0-1 or aggressive Gleason score (GS ≥ 8), upfront Abi showed superior-ity to Doc in prolonging

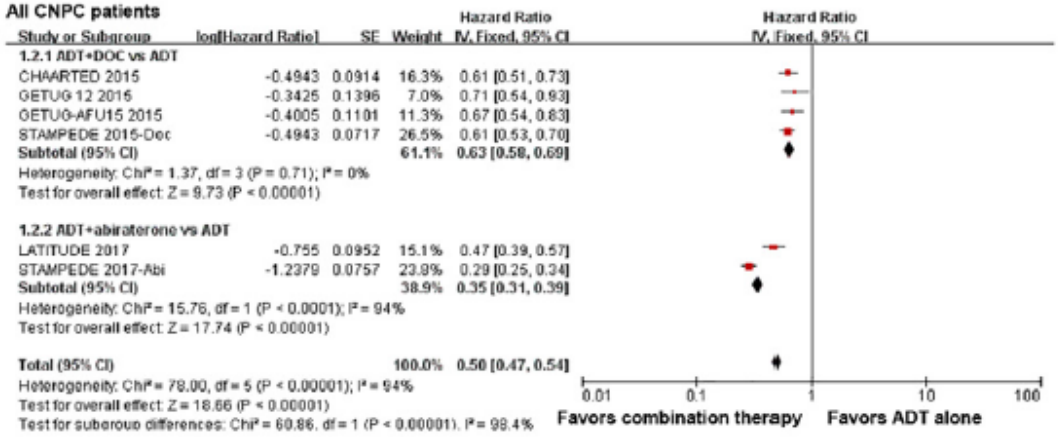
FFS. The incidence of severe adverse events (AEs ≥ 3) was comparable between these two therapeutic regimens.

Fig. 2. Forest plots of hazard ratios of combination therapy (docetaxel or abiraterone plus ADT) on OS and FFS. (A) Effect of combination therapy on OS in all CNPC patients; (B) effect of combination therapy on OS in M1 patients; (C) effect of combination therapy on OS in M0 patients; (D) effect of combination therapy on FFS in all CNPC patients; (E) effect of combination therapy on FFS in M1 patients; (F) effect of combination therapy on FFS in M0 patients.

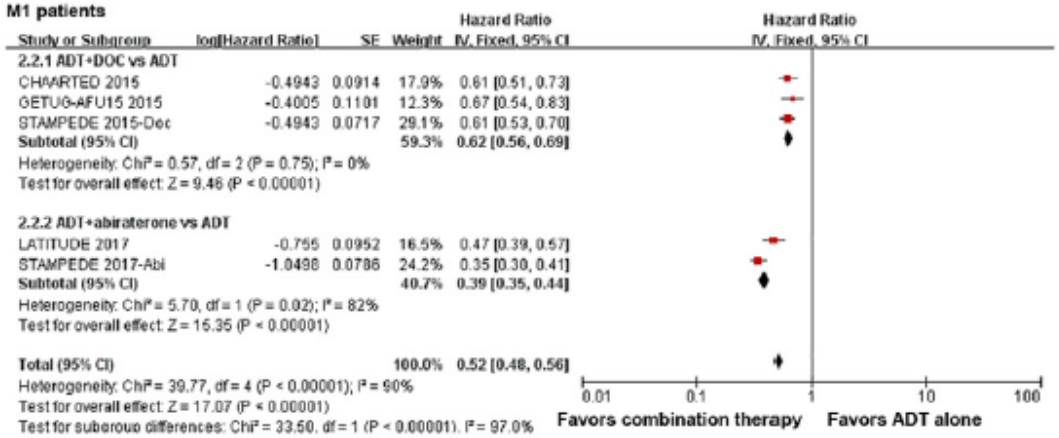
Abi = abiraterone; ADT = androgen deprivation therapy; CI = confidence interval; CNPC = castration-naive prostate cancer; Doc = docetaxel; FFS = failure-free survival; GS = Gleason score; IV = inverse variance; M1 = metastatic castration-naive prostate cancer; M0 = non-metastatic castration-naive prostate cancer; OS = overall survival; SE = standard error.



D All CNPC patients



E M1 patients



F M0 patients

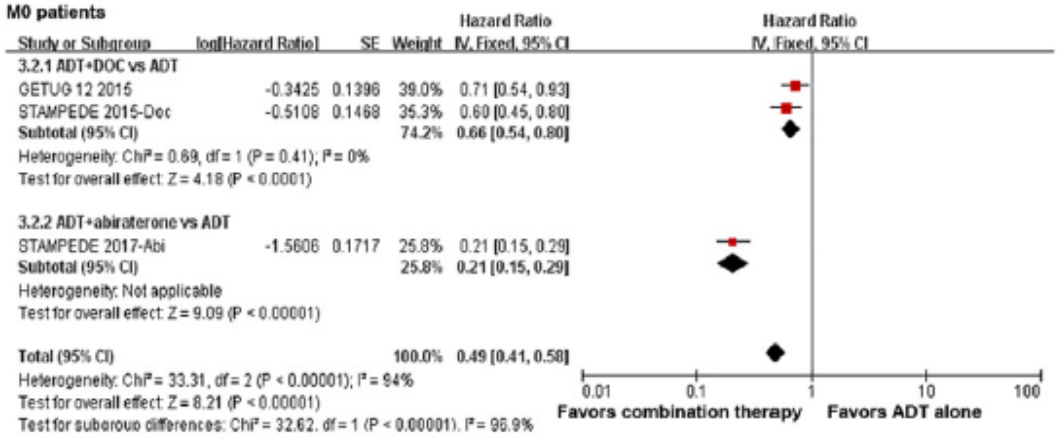
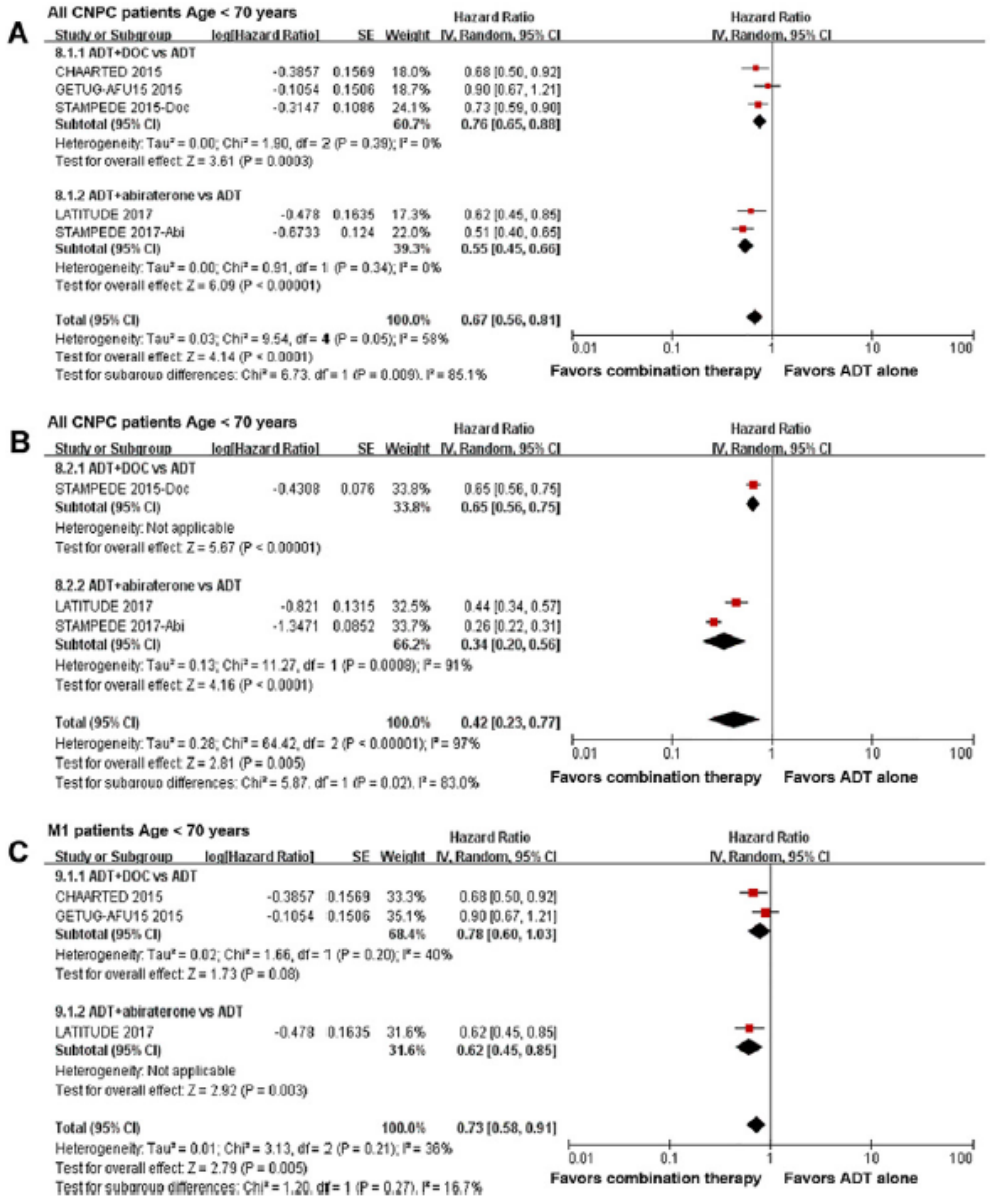
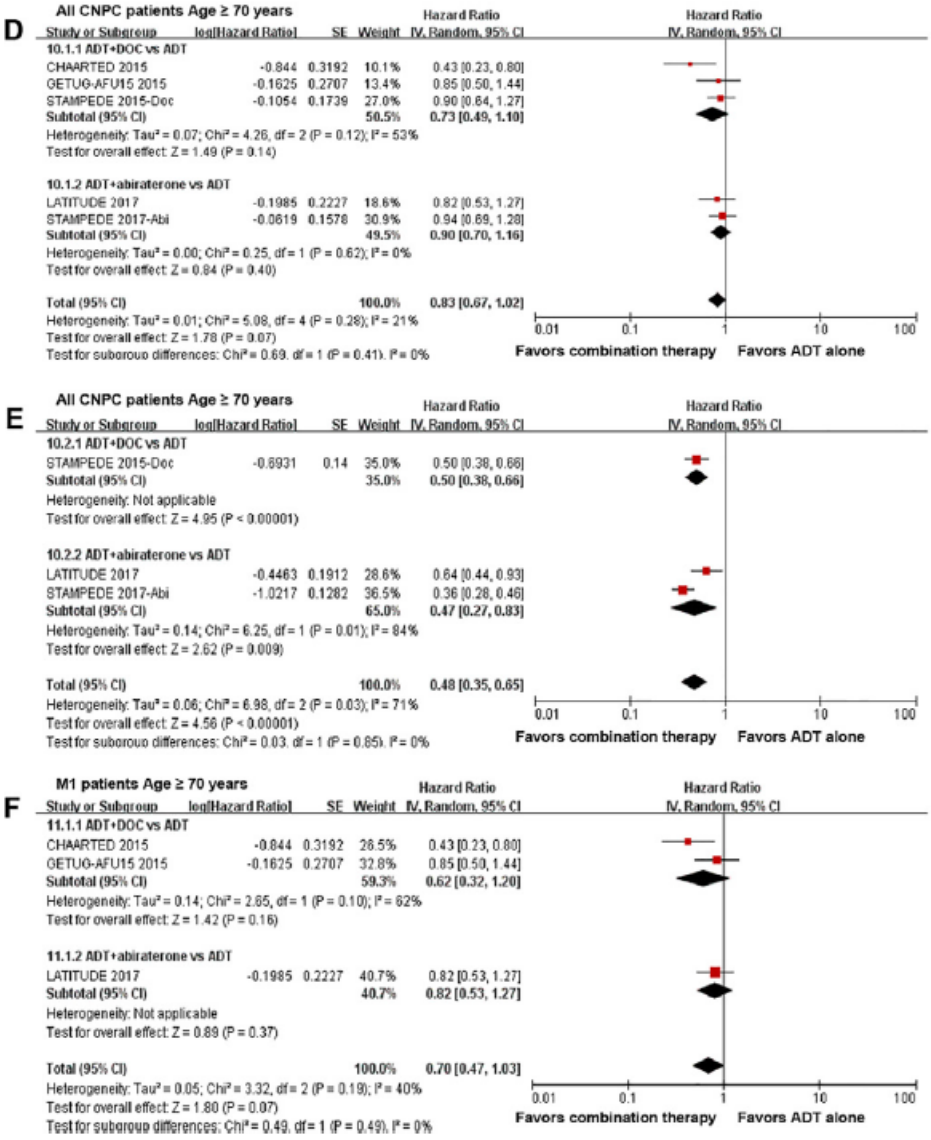


Fig. 3. Forest plots of hazard ratios of combination therapy (docetaxel or abiraterone plus ADT) on OS and FFS in different age subgroups. (A) Effect of combination therapy on OS in all CNPC patients with age < 70; (B) effect of combination therapy on FFS in all CNPC patients with age < 70; (C) effect of combination therapy on OS in M1 patients with age < 70; (D) effect of combination therapy on OS in all CNPC patients with age ≥ 70; (E) effect of combi-nation therapy on FFS in all CNPC patients with age ≥ 70; (F) effect of combination therapy on OS in M1 patients with age ≥ 70.

Abi = abiraterone; ADT = androgen deprivation therapy; CI = confidence interval; CNPC = castration-na€ıve prostate cancer; Doc = docetaxel; FFS = failure-free survival; IV = inverse variance; M0 = nonmetastatic castration-na€ıve prostate cancer; M1 = metastatic castration-na€ıve prostate cancer; OS = overall survival; SE = standard error.





Anmerkung/Fazit der Autoren

For patients with mCNPC, upfront Doc or Abi plus ADT should be considered as a standard of care, especially for those with younger age, favorable performance status, lower Gleason score, or visceral metastasis. For men with non-mCNPC, whether combination therapy could improve survival still needs to be verified. Abi could be the initial management for those who start treatment for the first time. In the future, it is important to determine how to select the best treatment and optimal sequence based on patient and tumor biology for men with mCNPC. Additional studies are urgently needed to identify accurate biomarkers and deeply understand the exact mechanism of combination therapy to obtain the maximum benefit and least toxicity for the mCNPC population.

Tucci M et al., 2016 [26].

Addition of Docetaxel to Androgen Deprivation Therapy for Patients with Hormone-sensitive Metastatic Prostate Cancer: A Systematic Review and Meta-analysis

Fragestellung

To perform a systematic review and meta-analysis of RCTs evaluating the combination of docetaxel and ADT in hormone-sensitive metastatic PCa. […] Exploratory subgroup analysis according to high-volume versus low-volume disease was performed.

Methodik

Population:

- hormone-sensitive metastatic PCa

Intervention:

- docetaxel with ADT

Komparator:

- ADT alone

Endpunkte:

- The primary end point was overall survival (OS).
- Secondary end point was progression-free survival.

Recherche/Suchzeitraum:

- PubMed/Medline, Embase, and the proceedings of major international meetings
- performed in June 2015 and updated in August 2015

Qualitätsbewertung der Studien:

- For each study, the quality of randomization was evaluated based on the information available in the publication or in the study protocol.

Ergebnisse

Anzahl eingeschlossener Studien:

- Overall, 2951 patients were included in the three trials.

Charakteristika der Population:

Table 1 – Characteristics of the three trials included in the meta-analysis

	GETUG-AFU 15 [22,27]	CHAARTED-E3805 [23]	STAMPEDE [24]
Main inclusion criteria			
Age	>18 yr No upper limit declared in the methods	Both <70 and >70 yr were eligible (stratification criteria)	Not specified
Performance status	Karnofsky ≥70	ECOG 0–2 (2 only if due to PCa) (Stratification: 0–1 vs two)	WHO 0–2
Stage	Metastatic prostate cancer (high volume vs low volume assessed retrospectively)	Metastatic prostate cancer (Stratification: high-volume vs low-volume)*	PCa if metastatic, node-positive, or ≥2 among: • Stage T3/T4 • PSA ≥40 ng/ml • Gleason 8–10
Previous treatment	Previous chemotherapy for metastatic disease was not allowed. In the neoadjuvant and adjuvant settings or in the context of isolated PSA increase, previous chemotherapy or ADT, or both, were allowed, with the condition that the treatment had been discontinued at least 12 mo before inclusion in the study	No prior docetaxel was allowed. Adjuvant ADT was allowed, but <24 mo (Stratification: ≤12 vs >12 mo) and interval between end of adjuvant treatment and progression >12 mo	Prior chemotherapy was not allowed. Long-term antiandrogen therapy was not allowed. Short periods of prior antiandrogens to cover tumor flare were allowed. Adjuvant or neoadjuvant hormone therapy had to be completed at least 12 mo before the trial, and duration of therapy had to be no longer than 12 mo
Treatment			
ADT (both arms)	Orchiectomy or LHRH agonists, alone or combined with nonsteroidal antiandrogens	Medical or surgical castration. Use of a nonsteroidal antiandrogen at the time of initiation of therapy was at the discretion of the investigator	LHRH analogs or LHRH antagonists, or bilateral orchidectomy according to local practice
Docetaxel (experimental arm)	Docetaxel (75 mg/m^2 IV day 1 every 3 wk); up to 9 cycles. Standard corticosteroids premedication, no daily prednisone	Docetaxel (75 mg/m^2 IV day 1 every 3 wk); up to 6 cycles. Standard dexamethasone premedication, no daily prednisone	Docetaxel (75 mg/m^2 IV day 1 every 3 wk); up to 6 cycles. Standard dexamethasone premedication, daily prednisolone 10 mg
Timing of treatment	Docetaxel within 2 mo of ADT start	Docetaxel within 4 mo of ADT start	Randomization within 12 wk of ADT start
Study design			
Primary end point	OS	OS	OS
Hypothesis	Increase in 3-yr OS from 50% to 65%	33% increase in median OS (from 33 to 44 mo in high volume patients; from 67 to 89 mo in low volume patients)	25% increase in overall survival
Patient enrollment and follow-up			
Accrual start	October 2004	July 2006	October 2005
Accrual stop	December 2008	November 2012	March 2013
No. of patients			
ADT alone	193	393	1184
ADT plus docetaxel	192	397	592
ADT plus docetaxel and zoledronic acid	–	–	593
Median follow-up	82.9 mo	28.9 mo	NA

ADT = androgen deprivation therapy; ECOG = Eastern Cooperative Oncology Group; IV = intravenous; LHRH = luteinizing hormone-releasing hormone; NA = not available; OS = overall survival; PCa = prostate cancer; PSA = prostate-specific antigen; WHO = World Health Organization.
* After amendment. In the initial protocol version, only high-volume patients were eligible.

Table 2 – Main characteristics of enrolled patients

	GETUG-AFU 15 [22,27]	CHAARTED-E3805 [23]	STAMPEDE [24] (whole trial*)
Age	ADT alone: Median 64 yr (IQR: 58–70)	ADT alone: Median 63 yr (range: 39–91)	Median 65 yr (range: 40–84)
	ADT and docetaxel: Median 63 yr (IQR: 57–68)	ADT and docetaxel: Median 64 yr (range: 36–88)	
Performance status	ADT alone: Median Karnofsky 100% (IQR range: 90–100%)	ADT alone: ECOG 0: 69% ECOG 1: 29% ECOG 2: 1.5%	WHO PS0: 76% WHO PS1: 21% WHO PS2: 1%
	ADT and docetaxel: Median Karnofsky 100% (IQR 90–100%)	ADT and docetaxel: ECOG 0: 70% ECOG 1: 29% ECOG 2: 1.5%	
Gleason score	ADT alone (unknown: 2/193): Gleason 2–6: 7% Gleason 7: 34% Gleason 8–10: 59%	ADT alone (unknown: 46/393): Gleason 4–6: 6% Gleason 7: 24% Gleason 8–10: 70%	NA
	ADT and docetaxel (unknown 5/192): Gleason 2–6: 10% Gleason 7: 35% Gleason 8–10: 55%	ADT and docetaxel (unknown 39/393): Gleason 4–6: 6% Gleason 7: 27% Gleason 8–10: 67%	
PSA at randomization	ADT alone: Median 26 (IQR: 5–127)	ADT alone: Median 52.1 (range: 0.1–8056.0)	NA
	ADT and docetaxel: Median: 27 (IQR: 5–106)	ADT and docetaxel: Median: 50.9 (range: 0.2–8540.1)	
Stage	ADT alone: 100% metastatic	ADT alone: 100% metastatic	61% Metastatic 15% Node-positive M0 24% N0 M0
	ADT and docetaxel: 100% metastatic	ADT and docetaxel: 100% metastatic	
Metastatic at diagnosis	ADT alone: 67%	ADT alone: 73% had not received prior local therapy	94% of randomized patients had not received previous local therapy
	ADT and docetaxel: 76%	ADT and docetaxel: 73% had not received prior local therapy	
Presence of visceral metastases	ADT alone: 11% lung 2% liver	ADT alone: 17%	NA
	ADT and docetaxel: 11% lung 5% liver	ADT and docetaxel: 14%	
Volume of metastatic disease	ADT alone: 52% low volume 48% high volume	ADT alone: 36% low volume 64% high volume	NA
	ADT and docetaxel: 53% low volume 47% high volume	ADT and docetaxel: 34% low volume 66% high volume	

ADT = androgen deprivation therapy; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; M0 = absence of distant metastases; NA = not applicable; N0 = absence of nodal metastases; PS = performance status; PSA = prostate specific antigen; WHO = World Health Organization.
* Details by arm are not provided.

Qualität der Studien:

- im Hauptdokument und in den Anlagen nicht auffindbar

Studienergebnisse:

- OS

  Table 3 summarizes the number of events and OS data reported in each trial. Overall, 916 deaths were recorded for the main comparison (docetaxel and ADT vs ADT alone) in metastatic patients. As shown in Figure 1A, the addition of docetaxel to ADT in metastatic patients was associated with a statistically significant OS benefit (HR: 0.73; 95% CI, 0.60–0.90; p = 0.002). There was no evidence of statistically significant heterogeneity among the three trials (p = 0.15; I2 = 48%). In the whole study population, including also the minority of nonmetastatic patients (Fig. 1B), the addition of docetaxel to ADT was associated with a similar, statistically significant OS benefit (HR: 0.74; 95% CI, 0.61–0.91; p = 0.003). Very

similar results were obtained in the exploratory analysis also including the docetaxel and zoledronic acid arm of the STAMPEDE trial: HR 0.74 (95% CI, 0.63–0.88; p < 0.001) considering only metastatic patients (Fig. 1C), HR 0.76 (95% CI, 0.64–0.89; p = 0.001) in all patients (Fig. 1D). Subgroup analysis was performed for metastatic patients with high-volume and low-volume disease enrolled in the GETUG-AFU 15 and in the CHAARTED-[9TD$DIF]E3805 trial (Fig. 2).

The test for difference of efficacy among the two subgroups did not demonstrate a statistically significant interaction (p = 0.5). The HR for the addition of docetaxel to ADT was 0.67 (95% CI, 0.51–0.88) in patients with high-volume disease and 0.80 (95% CI, 0.49–1.32) in patients with lowvolume disease.

Table 3 – Overall survival data reported in each single trial

	GETUG-AFU 15 [22,27]	CHAARTED-E3805 [23]	STAMPEDE [24]	
			All patients	Metastatic patients
No. of patients				
ADT alone	193	393	1184	725
ADT and docetaxel	192	397	592	362
ADT and docetaxel and zoledronic acid	–	–	593	365
No. of events				
ADT alone	212 (both arms)	136	405	343
ADT plus docetaxel		101	165	134
ADT plus docetaxel and zoledronic acid	–	–	181	152
Median OS, mo				
ADT alone	46.5	44.0	67	43
ADT plus docetaxel	60.9	57.6	77	65
ADT plus docetaxel and zoledronic acid	–	–	72	NA
HR (95% CI)				
ADT plus docetaxel vs ADT alone	0.9 (0.7–1.2) $p = 0.4$	0.61 (0.47–0.80) $p < 0.001$	0.76 (0.63–0.91) $p = 0.003$	0.73 (0.59–0.89) $p = 0.002$
ADT plus docetaxel and zoledronic acid vs ADT alone	–	–	0.81 (0.68–0.97) $p = 0.02$	0.78 (0.65–0.95) p = NA

ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; NA = not available; OS = overall survival.

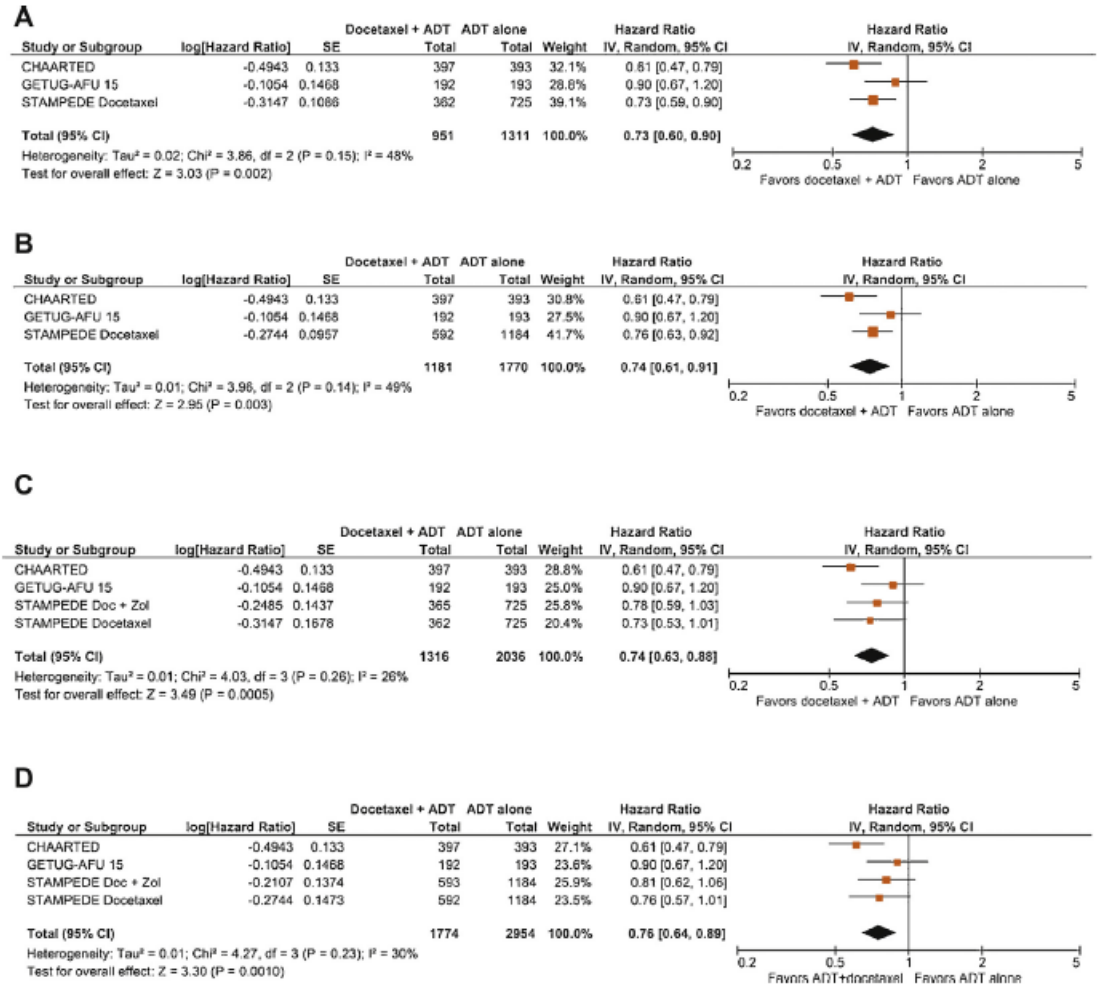


Fig. 1 – Forest plots of hazard ratios (HRs) for overall survival from three randomized trials of docetaxel plus androgen deprivation therapy (ADT) compared with ADT alone in patients with advanced hormone-sensitive prostate cancer. Pooled HRs were computed using random-effect models. The bars indicate 95% confidence intervals. (A, B) Comparisons between docetaxel plus ADT and ADT alone: (A) only metastatic patients and (B) all randomized patients. (C, D) A sensitivity analysis including the comparison of docetaxel and zoledronic acid plus ADT versus ADT alone in the STAMPEDE trial: (C) only metastatic patients and (D) all randomized patients.
ADT = androgen deprivation therapy; CI = confidence interval; IV = inverse variance; SE = standard error; Doc + Zol = docetaxel plus zoledronic acid.

- 3.5. Progression-free survival

  As shown in Figure 3A, the addition of docetaxel to ADT in metastatic patients was associated with a statistically significant benefit in PFS (HR: 0.63; 95% CI, 0.57–0.70; p < 0.001) without significant heterogeneity among the three trials (p = 0.7; I2 = 0%). The same benefit was shown considering the whole study population including the minority of patients without metastases (HR: 0.63; 95% CI, 0.57–0.70; p < 0.001) (Fig. 3B). Very similar results were obtained in the exploratory analysis including also the docetaxel and zoledronic acid arm of the STAMPEDE trial: HR: 0.63 (95% CI, 0.56–0.70; p < 0.001) in metastatic patients (Fig. 3C), HR 0.63 (95% CI, 0.57–0.70; p < 0.001) in all patients (Fig. 3D).

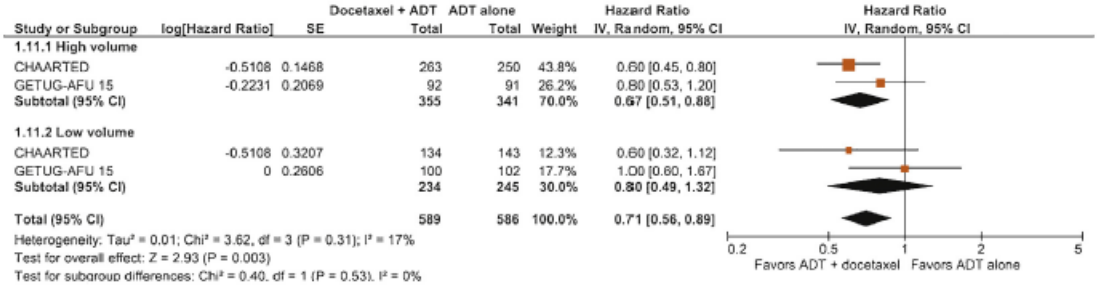


Fig. 2 – Forest plot of hazard ratios (HRs) for overall survival (subgroup analysis according to disease volume: patients with high- and low-volume disease) in two randomized trials of docetaxel plus androgen deprivation therapy (ADT) compared with ADT alone in patients with metastatic hormone-sensitive prostate cancer. Pooled HRs were computed using random-effect models. The bars indicate 95% confidence intervals. Definitions of high- and low-volume disease are provided in text.
ADT = androgen deprivation therapy; CI = confidence interval; IV = inverse variance; SE = standard error.

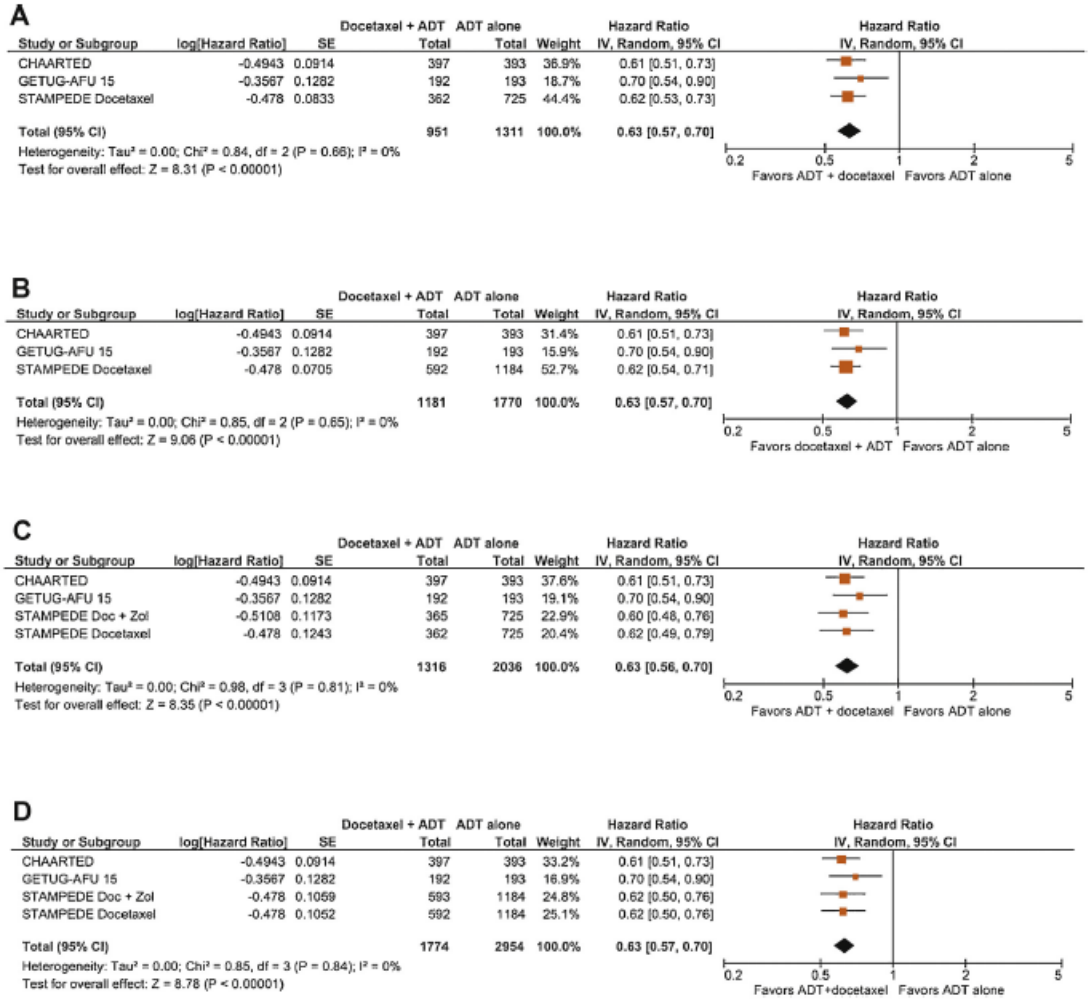


Fig. 3 – Forest plots of hazard ratios (HRs) for biochemical progression-free survival from three randomized trials of docetaxel added to androgen deprivation therapy (ADT) compared with ADT alone in patients with advanced hormone-sensitive prostate cancer. Pooled HRs were computed using random-effect models. The bars indicate 95% confidence intervals. (A,B) Comparisons between docetaxel plus ADT and ADT alone: (A) only metastatic patients and (B) all randomized patients. (C,D) A sensitivity analysis including comparison of docetaxel and zoledronic acid plus ADT versus ADT alone in the STAMPEDE trial: (C) only metastatic patients and (D) all randomized patients.
ADT = androgen deprivation therapy; CI = confidence interval; IV = inverse variance; SE = standard error; Doc + Zol = docetaxel plus zoledronic acid.

Anmerkung/Fazit der Autoren

In conclusion, our meta-analysis clearly shows a significant impact on OS with the concomitant administration of docetaxel and ADT in patients with metastatic hormonesensitive PCa.

Considering the absence of heterogeneity among the available trials, and the balance between magnitude of efficacy and risk of toxicity, the combination of chemotherapy and hormonal treatment should be reasonably offered to patients with metastatic disease, if judged eligible for chemotherapy. Higher statistical power would be needed to better understand the interaction, if any, between the efficacy of docetaxel and the volume of disease.

Vale CL et al., 2016 [27].

Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data

Fragestellung

Results from large randomised controlled trials combining docetaxel or bisphosphonates with standard of care in hormone-sensitive prostate cancer have emerged. In order to investigate the eff ects of these therapies and to respond to emerging evidence, we aimed to systematically review all relevant trials using a framework for adaptive meta-analysis.

Methodik

Population:

- men with high-risk localised or metastatic, hormonesensitive (ie, not castrate-resistant) prostate cancer

Intervention / Komparator:

- either standard of care versus standard of care plus docetaxel or standard of care versus standard of care plus bisphosphonate (at a therapeutic dose)

Endpunkte:

- The primary outcome, survival, was defi ned as the time from randomisation until death from any cause.
- The secondary outcome was failure-free survival. Although there is no widely accepted definition of failure-free survival, for the purpose of this systematic review and meta-analysis, we defined it as the time from randomisation to biochemical failure, clinical failure (local relapse or metastases), or death from any cause.

Recherche/Suchzeitraum:

- MEDLINE, Embase, LILACS, and the Cochrane Central Register of Controlled Trials, trial registers, conference proceedings, review articles, and reference lists of trial publications for all relevant randomised controlled trials (published, unpublished, and ongoing)
- From inception to Sept 30, 2015

Qualitätsbewertung der Studien:

- Keine Angabe zum Bewertungsverfahren, aber durchgeführt (siehe unten)

Ergebnisse

Anzahl eingeschlossener Studien:

- five eligible randomised controlled trials of docetaxel

Charakteristika der Population:

	Accrual dates	Number of patients	Metastatic status	Primary outcome	Secondary outcomes	Reason not included
ADT vs ADT + docetaxel						
ARTIC AOM-03108[31]	June, 2003–November, 2009	254	M0	PSA progression-free survival	PSA response; duration of PSA response; time to clinical progression; overall survival; tolerability; quality of life	Reported results could not be used (safety 2010, progression-free survival* 2011, quality of life 2013)
GENTAX[32]	October, 2005–December, 2009	30	M0 and M1	Progression-free survival	Overall survival; toxicity; quality of life	Reported results could not be used (progression-free survival*)
SPCG-13[33]	May, 2007–November, 2004	378	M0	PSA progression	PSA doubling time; quality of life; safety; metastasis-free survival; overall survival	Reported results could not be used (safety)
TAX 3503[34]	July, 2007–September, 2012	400	M0	Progression-free survival	Overall survival; cancer-specific survival; adverse events	Reported results could not be used (safety)
CAN-NCIC-PR12 (NCT00651326)	March, 2008–January, 2011	48	M0	Disease-free survival	Overall survival; time to biochemical disease progression; time to local or distant disease progression; time to next anti-cancer therapy; progression-free survival; degree of PSA suppression before radiotherapy; quality of life; adverse events	No results reported yet
QRT-SOGUG[35]	December, 2008–September, 2012	134	M0	PSA relapse	Unclear	Reported results could not be used (toxicity)
05-043 (NCT00116142)	June, 2005–August, 2015	350	M0	Overall survival	PSA doubling time; PSA failure; cancer-specific survival	No results reported yet
GOUP-01/04 (NCT00796458)	April, 2005–ongoing	200	M1	2-year progression-free survival	Overall survival; time to treatment failure; toxicity; PSA response rate; disease response rate; PSA normalisation; quality of life; control of bone pain; change in chromogranin A concentration; cost analysis	Ongoing

	Accrual dates	Number of patients	Metastatic status	Primary outcome	Secondary outcomes	Reason not included
(Continued from previous page)						
ADT *vs* ADT + bisphosphonates						
Smith 2005[36]	September, 1999–March, 2003	544	M0	Bone metastasis-free survival and overall survival	Time to first skeletal-related events; quality of life; pain	Reported results could not be used (overall survival*, time to first bone metastasis)
Ryan 2007[37]	January, 2000–December, 2002	42	M0 + M1	BMD	Urinary NTX concentration and serum BAP concentration	Reported results could not be used (bone mineral density, urinary NTX, serum BAP)
Smith 2003[38]	February, 2000–November, 2000	106	M0	LS BMD	Other bone mineral density	Reported results could not be used (bone mineral density)
Israeli[39]	February, 2003–May, 2005	222	M0	LS BMD	TH bone mineral density; serum NTX; serum BSAP	Reported results could not be used (LS bone mineral density, TH bone mineral density, serum NTX)
Ryan 2006[40]	April, 2003–March, 2004	120	M0	FN/LS BMD	Serum BSAP; urine NTX; TH BMD	Reported results could not be used (bone mineral density, urinary NTX, serum BSAP)
Zenith (NCT00063609)	April, 2003–April, 2005	200	M0	LS BMD	TH BMD; markers of bone turnover	No results reported yet
Rao[41]	June, 2003–May, 2004	50	M0	BMD	Urinary DPD	Reported results could not be used (BMD)
HOG GU02-41[42]	December, 2003–August, 2005	63	M1	Skeletal-related events	Time to castrate-resistant prostate cancer; markers of bone turnover	Reported results could not be used (skeletal-related events, castrate-resistant prostate cancer, serological progression, prostate-specific antigen nadir, adverse events, urine DPD, urine NTX, serum BAP)
Bhoopalam[43]	December, 2003–May, 2006	93	M0	LS bone mineral density	NA	Reported results could not be used (bone mineral density)
Casey[44]	Unclear	200	M0	LS bone mineral density	FN/TH BMD; change in height; safety	Reported results could not be used (bone mineral density)
Yedavelli[45]	Unclear	42	M0	Skeletal-related events	Bone mineral density	Reported results could not be used (bone mineral density)
Rodrigues[46]	Unclear	94	M0	Bone mineral density	NA	Reported results could not be used (bone mineral density)
CEGOG (NCT00294437)	December, 2003–November, 2007	376	M0	Time to bone metastasis	Pain; time to first bone pain; skeletal-related events; serum PSA; safety	No results reported yet
Ueno[47]	July, 2006–June, 2011	60	M1	PSA progression-free survival	Skeletal-related events; bone pain; markers of bone turnover	Reported results could not be used (PSA and progression-free survival,* skeletal-related events, bone pain)
KYUHTRIGU0705 (NCT00685646)	May, 2008–December, 2013	227	M1	Time to treatment failure	Time to first skeletal-related event; overall survival; extent of disease; pain	No results reported yet
NU-02U1 (NCT00058188)	March, 2003–September, 2015	70	M0	Bone mineral density	LS bone mineral density	No results reported yet

ADT=androgen deprivation therapy. NA=non-applicable. PSA=prostate-specific antigen. NTX=N-terminal telopeptide. BAP=bone alkaline phosphatase. LS BMD=lumbar spine bone mineral density. FN/LS BMD=femoral neck/lumbar spine bone mineral density. TH BMD=total hip bone mineral density. BSAP=bone-specific alkaline phosphatase. CRPC=castrate-resistant prostate cancer. DPD=deoxypridinoline. *Data reported not usable.

Table 2: Characteristics of studies included in the systematic review that could not be included in the meta-analyses

Qualität der Studien:

	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting
TAX 3501[17]	Randomisation with stratification factors reported	Randomised	NA	All randomised patients included in the analyses	Yes, although survival not reported, data not mature
CHAARTED[7]	Randomisation with stratification factors reported	Centrally randomised	NA	All randomised patients included in the analyses	Yes, all outcomes of interest are reported
GETUG-12[25,26]	Randomisation with stratification factors reported	Centrally randomised	NA	All randomised patients included in the analyses	Yes, outcomes of interest are reported, although survival data reported are not yet mature
STAMPEDE[8]	Used a method of minimisation over a number of clinically important stratification factors with an additional random element	Central telephone randomisation	NA	All randomised patients included in the analyses	Yes, outcomes of interest are reported
RTOG 0521[28]	Randomisation with stratification factors reported	Centrally randomised	NA	45 ineligible patients (3% of the total) were excluded from analyses; not clear if balanced by treatment group	Yes, outcomes of interest are reported
GETUG-15[30]	Minimisation method with stratification factors reported	Centrally randomised	NA	All randomised patients included in the analyses	Yes, outcomes of interest are reported
CALGB 90202[29]	Randomised block design with stratification factors	Central online registration and randomisations	Double-blind or placebo-controlled	All randomised patients are included in the efficacy analyses	Reports survival, but not failure-free survival as defined in the meta-analysis
RADAR[21]	Minimisation with a random element and stratification factors	Central trials office computer based randomisation	Open label; the endpoints committee were unaware of patient identity or treatment assignment; treatment was not masked to the investigators, patients, or trial statistician	All randomised patients are included in the efficacy analyses	Reports survival, but not failure-free survival as defined in the meta-analysis
ZEUS[19]	Minimisation method described by Pocock[23] with stratification factors	Central randomisation by fax	Open label	40 patients (3% of total randomised) excluded from analyses; seven patients were ineligible; 27 patients withdrew consent; six patients were lost to follow-up; exclusions are balanced by group	Reports survival, but not failure-free survival as defined in the meta-analysis
PR04[32]	Minimisation method over five stratification factors	Central randomisation	Double blind; placebo-controlled; clinicians assessing cause of death were blinded to treatment allocation	In the primary analysis, no randomised patients were excluded from the analyses; in the analysis with long-term follow-up, 37 patients were excluded as they had not been flagged with the NHS Information Centre	Reports survival, but not failure-free survival as defined in the meta-analysis
PR05[32]	Minimisation method over four stratification factors	Central randomisation	Double blind; placebo controlled	In the primary analysis, no randomised patients were excluded from the analyses; in the analysis with long-term follow-up, 33 patients were excluded as they had not been flagged with the NHS Information Centre	Reports survival, but not failure-free survival as defined in the meta-analysis
STAMPEDE[8]	Used a method of minimisation over a number of clinically important stratification factors with an additional random element	Central telephone randomisation	Open label	All randomised patients included in the analyses	Yes, outcomes of interest are reported, including survival and failure-free survival

NA=non-applicable. NHS=National Health Service.

Table 3: **Assessment of risk of bias**

Studienergebnisse:

- Results from three (CHAARTED, GETUG-15, STAMPEDE) of these trials (2992 [93%] of 3206 men randomised) showed that the addition of docetaxel to standard of care improved survival. The HR of 0·77 (95% CI 0·68–0·87;p<0·0001) translates to an absolute improvement in 4-year survival of 9% (95% CI 5–14). Docetaxel in addition to standard of care also improved failure-free survival, with the HR of 0·64 (0·58–0·70; p<0·0001) translating into a reduction in absolute 4-year failure rates of 16% (95% CI 12–19).
- We identified 11 trials of docetaxel for men with locally advanced disease (M0). Survival results from three (GETUG-12, RTOG 0521, STAMPEDE) of these trials (2121 [53%] of 3978 men) showed no evidence of a benefi t from the addition of docetaxel (HR 0·87 [95% CI 0·69–1·09]; p=0·218), whereas failure-free survival data from four (GETUG-12, RTOG 0521, STAMPEDE, TAX 3501) of these trials (2348 [59%] of 3978 men) showed that docetaxel improved failure-free survival (0·70 [0·61–0·81]; p<0·0001), which translates into a reduced absolute 4-year failure rate of 8% (5–10).

- We identified seven eligible randomised controlled trials of bisphosphonates for men with M1 disease. Survival results from three of these trials (2740 [88%] of 3109 men) showed that addition of bisphosphonates improved survival (0·88 [0·79–0·98]; p=0·025), which translates to 5% (1–8) absolute improvement, but this result was infl uenced by the positive result of one trial of sodium clodronate, and we found no evidence of a benefi t from the addition of zoledronic acid (0·94 [0·83–1·07]; p=0·323), which translates to an absolute improvement in survival of 2% (–3 to7). Of 17 trials of bisphosphonates for men with M0 disease, survival results from four trials (4079 [66%] of 6220 men) showed no evidence of benefit from the addition of bisphosphonates (1·03 [0·89–1·18]; p=0·724) or zoledronic acid (0·98 [0·82–1·16]; p=0·782). Failure-free survival defi nitions were too inconsistent for formal meta-analyses for the bisphosphonate trials.

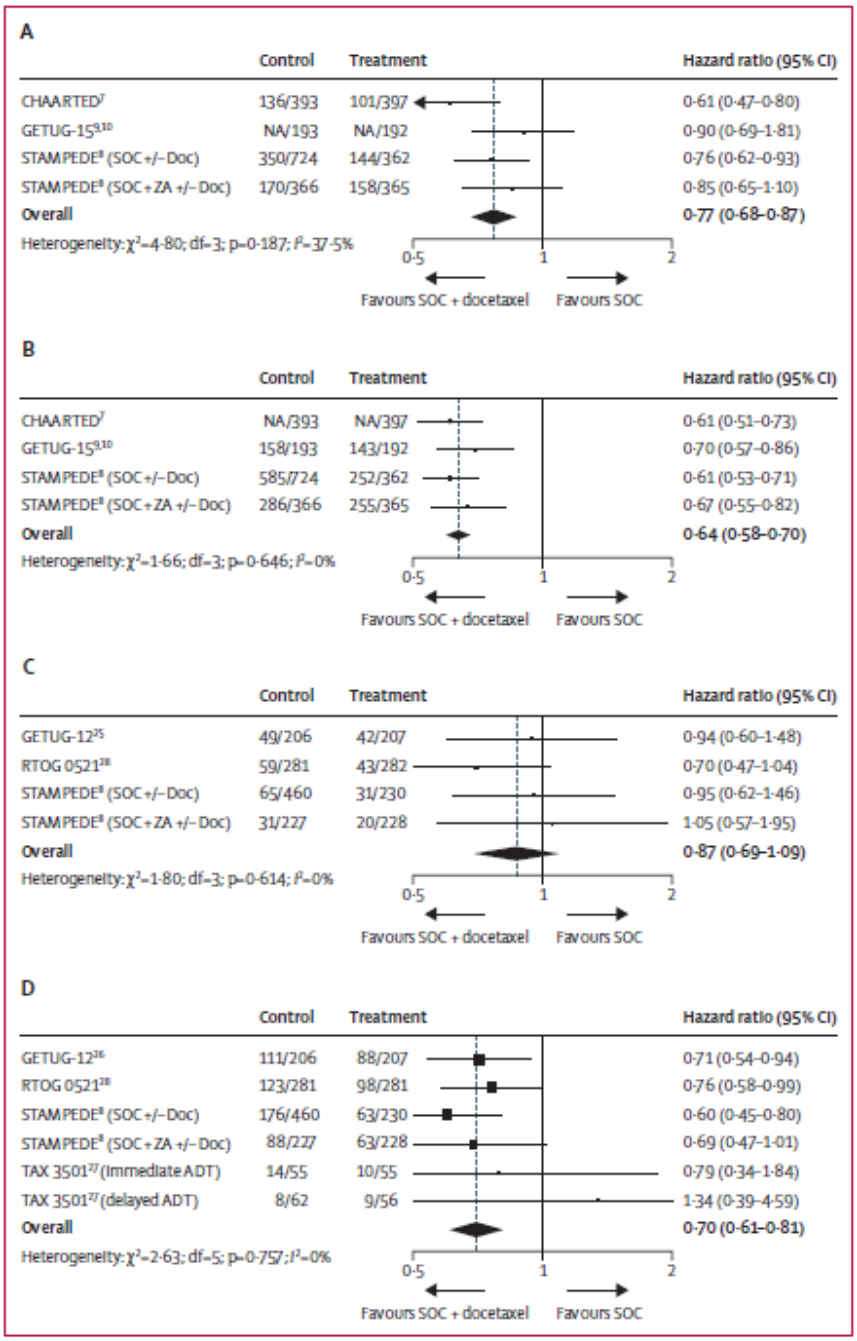


Figure 2: **Effect of addition of docetaxel to standard of care on survival and failure-free survival**
(A) Effect of the addition of docetaxel on survival in men with M1 disease. (B) Effect of the addition of docetaxel on failure-free survival in men with M1 disease. (C) Effect of the addition of docetaxel on survival in men with M0 disease. (D) Effect of the addition of docetaxel on failure-free survival in men with M0 disease. NA=event numbers by group not available. SOC=standard of care.

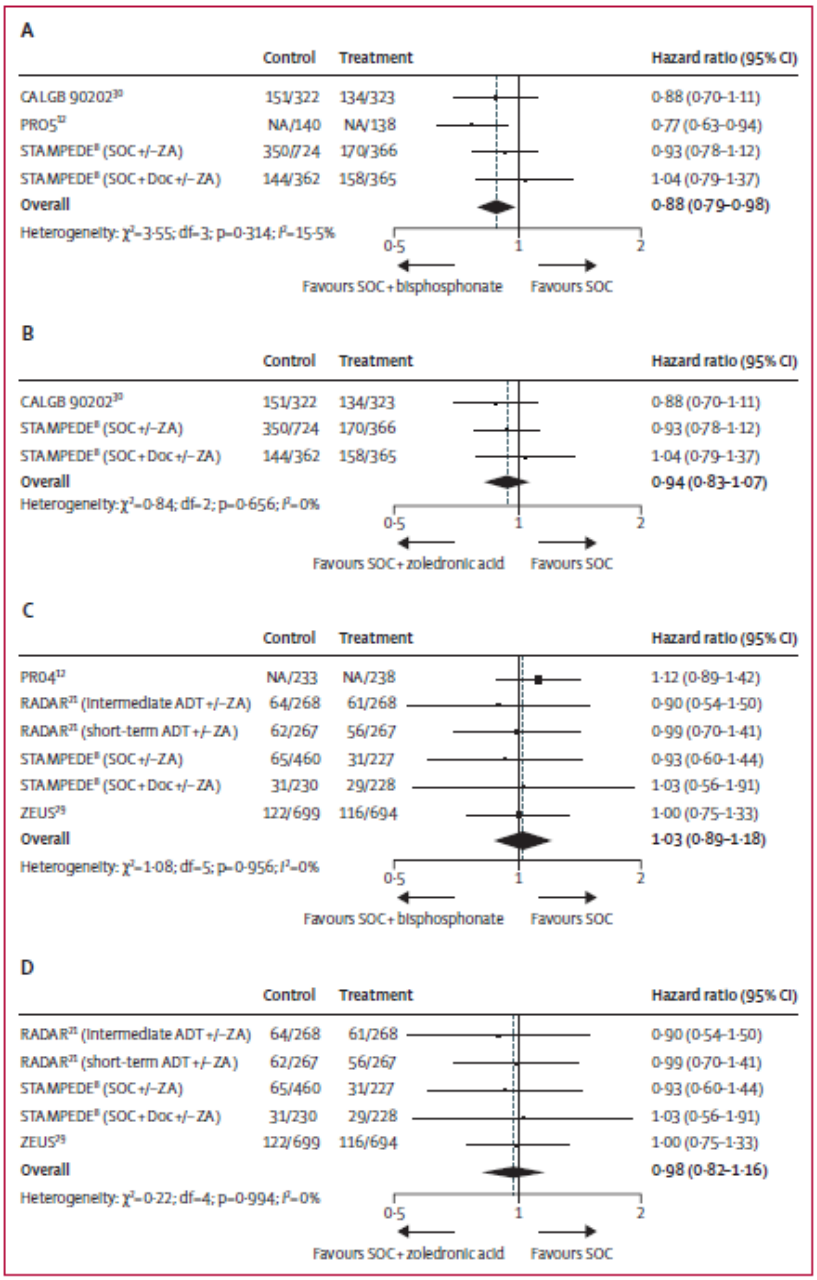


***Figure 3*: Effect of addition of bisphosphonates to standard of care on survival**
(A) Effect of the addition of bisphosphonates on survival in men with M1 disease. (B) Effect of the addition of zoledronic acid on survival in men with M1 disease. (C) Effect of the addition of bisphosphonates on survival in men with M0 disease. (D) Effect of the addition of zoledronic acid on survival in men with M0 disease. NA=event numbers by group not available. SOC=standard of care.

Anmerkung/Fazit der Autoren

The addition of docetaxel to standard of care should be considered standard care for men with M1 hormone-sensitive prostate cancer who are starting treatment for the first time. More evidence on the eff ects of docetaxel on survival is needed in the M0 disease setting. No evidence exists to suggest that zoledronic acid improves survival in men with M1 or M0 disease, and any potential benefi t is probably small.

Vale CL et al., 2018 [28].

What is the optimal systemic treatment of men with metastatic, hormone-naive prostate cancer? A STOPCAP systematic review and network meta-analysis

Fragestellung

Our prior Systemic Treatment Options for Cancer of the Prostate systematic reviews showed improved survival for men with metastatic hormone-naive prostate cancer when abiraterone acetate plus prednisolone/prednisone (AAP) or docetaxel (Doc), but not zoledronic acid (ZA), were added to androgen-deprivation therapy (ADT). Trial evidence also suggests a benefit of combining celecoxib (Cel) with ZA and ADT. To establish the optimal treatments, a network meta-analysis (NMA) was carried out based on aggregate data (AD) from all available studies.

Methodik

Population:

- Men randomised were diagnosed withmHNPC, and either starting or responding to the first-line ADT for metastatic disease (they may have received prior treatments for early, localised disease).
- Trials were also eligible if they met the above criteria but additionally co-administered supportive treatments on the experimental armonly.

Intervention(Komparator:

- ADT alone with ADT in combination with any of the agents (or combinations of agents) under consideration, namely celecoxib (Cel), zoledronic acid (ZA), celecoxib and zoledronic acid (ZA+Cel), docetaxel (Doc), zoledronic acid+docetaxel (ZA+Doc) or abiraterone acetate plus prednisolone (AAP).

Endpunkte:

- The primary outcome was overall survival (OS),
- with failure-free survival (FFS) the secondary outcome.

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, clinicaltrials.gov and the Cochrane Central Register of Controlled Trials (CENTRAL),
- Suchzeitraum: keine Angabe

Qualitätsbewertung der Studien:

- Assessment of study quality for all trials included in the prior STOPCAP reviews was previously carried out in the individual reviews, using the Cochrane risk of bias tool [7] Ergebnisse]. Risk of bias assessments for additional eligible studies identified for inclusion in the network meta-analysis was also carried out using the Cochrane tool.

Ergebnisse

Anzahl eingeschlossener Studien:

- 10 completed trials which had closed to recruitment, and one trial in which recruitment was ongoing, as eligible for inclusion.

- Results are based on six trials including 6204 men (97% of men randomised in all completed trials).

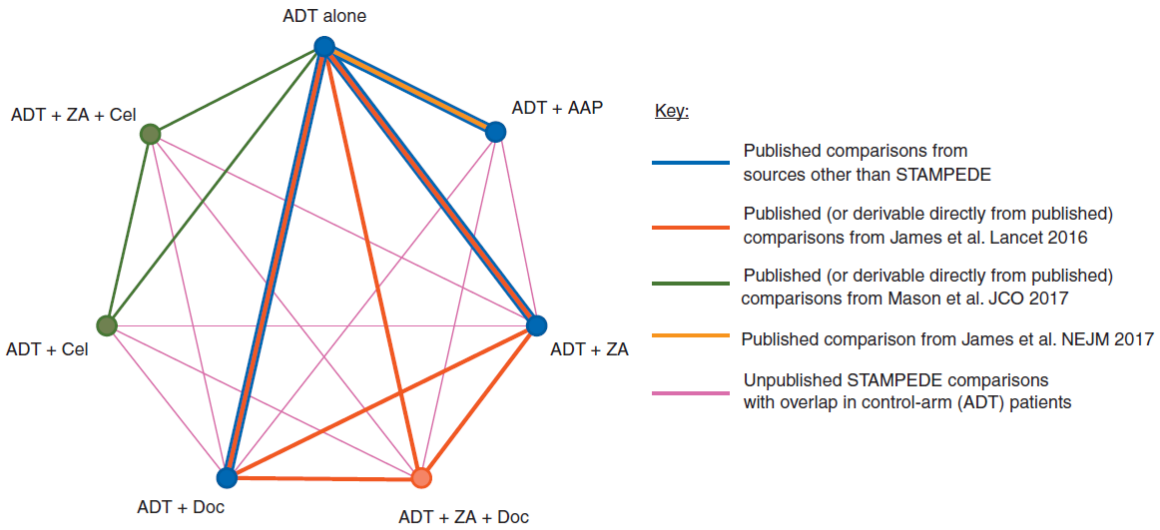


Figure 1. Network meta-analysis structure. AAP, abiraterone acetate plus prednisolone/prednisone; ADT, androgen-deprivation therapy; Cel, celecoxib; Doc, docetaxel; ZA, zoledronic acid.

Charakteristika der Population:

Table 1. Description of included trials (or treatment comparisons from the STAMPEDE trial) and FFS definition used in the trial. All trials had a control arm of ADT

Trial	Recruitment period	Median follow-up (months)	Treatment	Treatment (*N*)	Control (*N*)	Definition of FFS
CALGB 90202 [21]	June 2004 to April 2012	Unknown	ADT + ZA	323	322	Time to first bone progression, PSA progression, or death
GETUG 15 [22]	Oct 2004 to Dec 2008	84	ADT + Doc	192	193	Time to PSA progression, clinical progression or death
STAMPEDE (Arms A versus D) [3]	Oct 2005 to April 2011	69	ADT + Cel	188	377	Time to PSA failure, progression of local, lymph-node, or distant metastases; or death from prostate cancer
STAMPEDE (Arms A versus F) [3]	Oct 2005 to April 2011	69	ADT + ZA + Cel	190	377	Time to PSA failure, progression of local, lymph-node, or distant metastases; or death from prostate cancer
STAMPEDE (Arms A versus B) [13]	Oct 2005 to March 2013	43	ADT +ZA	366	724	Time to PSA failure, progression of local, lymph-node, or distant metastases; or death from prostate cancer
STAMPEDE (Arms A versus C) [13]	Oct 2005 to March 2013	43	ADT + Doc	362	724	Time to PSA failure, progression of local, lymph-node, or distant metastases; or death from prostate cancer
STAMPEDE (Arms A versus E) [13]	Oct 2005 to March 2013	43	ADT + ZA + Doc	365	724	Time to PSA failure, progression of local, lymph-node, or distant metastases; or death from prostate cancer
CHAARTED [23]	July 2006 to Dec 2012	54	ADT + Doc	397	393	Time to PSA rise or clinical progression
ZAPCA (KYUH TRIG0705) [24]	May 2008 to Dec 2010	42	ADT +ZA	109	110	Time to earliest date of PSA progression, clinical progression, first SRE, death for any reason, or cessation of protocol treatment for any reason
STAMPEDE (Arms A versus G) [12]	Nov 2011- Jan 2014	40	ADT + AAP	500	502	Time to PSA failure, progression of local, lymph-node, or distant metastases; or death from prostate cancer
LATITUDE [14]	Feb 2013 to Dec 2014	30	ADT + AAP	597	602	Time to radiographic progression or death from any cause

AAP, abiraterone acetate plus prednisolone/prednisone; ADT, androgen-deprivation therapy; Cel, celecoxib; Doc, docetaxel; FFS, failure-free survival; SRE, skeletal related events; ZA, zoledronic acid.

Qualität der Studien:

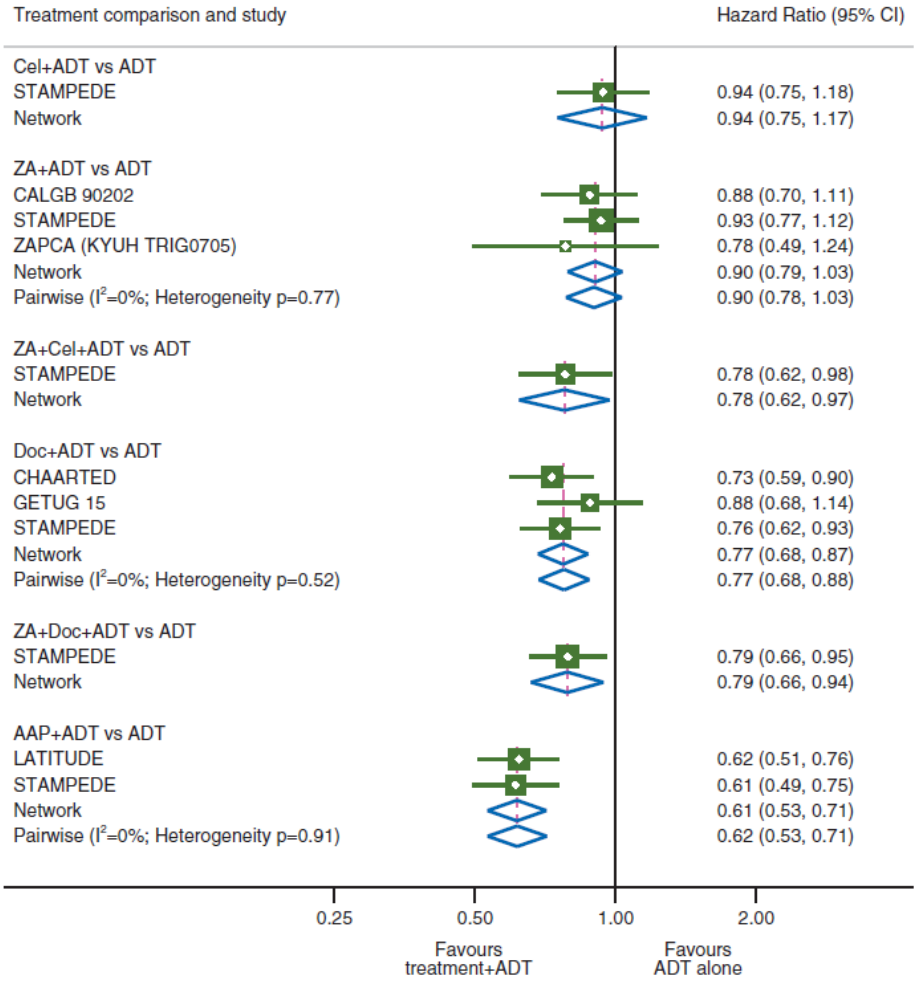
- and all included studies were assessed as having low risk of bias based on reported information and study protocols

Studienergebnisse:

- Overall survival

  The network meta-analysis HR estimates suggested that compared with ADT alone each of AAP (HR 0.61, 95% CI 0.53–0.71), Doc (HR 0.77, 95% CI 0.68–0.87), ZA+Doc (HR 0.79, 95% CI 0.66–0.94) and ZA+Cel (HR 0.78, 95% CI 0.62–0.97) in combination with ADT improved survival. There was no survival advantage observed with ADT in combination with either ZA (HR 0.90, 95% CI 0.79–1.03) or Cel (0.94, 95% CI 0.75–1.17) over ADT alone. For the comparisons of ADT versus ADTþCel, ADT+ZA+Cel and ADT+ZA+Doc, the only data available were from single comparisons within the STAMPEDE trial [3, 13]. There was no evidence of heterogeneity between the effects of treatment within any of the individual treatment comparisons and all of the estimates from the network analysis were in keeping with those obtained in the previously reported pairwise meta-analyses where available (Figure 2).

Figure 2. Overall survival. Forest plot of network and pairwise estimates of treatment effects [all treatments compared with androgen-deprivation therapy (ADT) alone]. AAP, abiraterone acetate plus prednisolone/prednisone; CI, confidence interval; Cel, celecoxib; Doc, docetaxel; ZA, zoledronic acid.



Treatment rankings When used in combination with ADT, AAP has the highest probability (94%) of being the most effective treatment, Doc has a 35% probability of being the second-best treatment and ADT alone has the highest probability of being the least effective treatment (67%, Table 3).

Table 3. Treatment ranking (% probability) and SUCRA values based on overall survival results

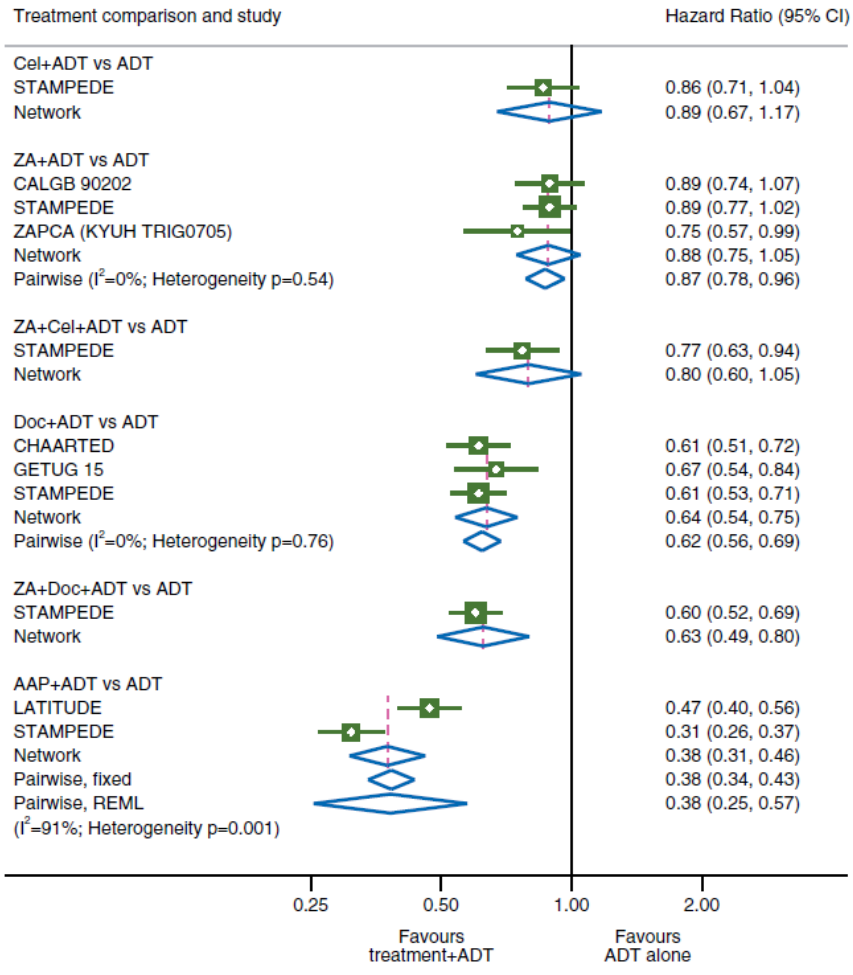
	AAP	Doc	ZA + Doc	ZA + Cel	ZA	Cel	ADT alone
Best	94.2	0.7	1.3	3.8	0.0	0.0	0.0
Second best	5.3	34.9	25.5	33.0	0.3	1.0	0.0
Third best	0.4	36.8	30.3	27.0	2.4	3.1	0.0
Fourth best	0.1	23.6	30.8	23.9	12.2	9.3	0.1
Fifth best	0.0	3.8	9.3	9.3	48.7	26.0	2.9
Sixth best	0.0	0.2	2.6	2.5	31.3	33.6	29.8
Worst	0.0	0.0	0.2	0.5	5.1	27.0	67.2
SUCRA	1.0	0.7	0.6	0.6	0.3	0.2	0.1

AAP, abiraterone acetate plus prednisolone/prednisone; ADT, androgen-deprivation therapy; Cel, celecoxib; Doc, docetaxel; SUCRA, surface under the cumulative rank; ZA, zoledronic acid.

- Failure-free survival

There was an FFS benefit associated with adding ADT to each of AAP (HR 0.38 95% CI 0.31–0.46), Doc (HR 0.64 95% CI 0.54–0.75) and ZAþDoc (HR 0.63 95% CI 0.49–0.80) compared with ADT alone. No statistically significant benefit was seen with the addition of Cel (HR 0.89 95% CI 0.67–1.17); ZAþCel (HR 0.80 95% CI 0.60–1.05) or ZA alone (HR 0.88 95% CI 0.75–1.05). In all cases, the HR estimates obtained through the network were very similar to those obtained using a standard pairwise meta-analysis, providing confirmation that the network model is behaving as expected. There was evidence of variation or inconsistency between the effects of treatment within the individual treatment comparisons of ADT versus ADT plus AAP (I^2=91%, heterogeneity P=0.001) where there was a large variation between the size of the relative effects (but not the direction of the effect) observed between the two included trial comparisons. However, there was no evidence of variation or inconsistency between the effects of treatment within the remaining treatment comparisons, and all of the estimates from the network analysis were in keeping with those obtained in the previously reported pairwise meta-analyses where available (Figure 3).

Figure 3. Failure-free survival. Forest plot of network and pairwise estimates of treatment effects [all treatments compared with androgendeprivation therapy (ADT) alone]. AAP, abiraterone acetate plus prednisolone/prednisone; CI, confidence interval; Cel, celecoxib; Doc, docetaxel; ZA, zoledronic acid.



Therefore, we carried out a sensitivity analysis using the outcome of time to PSA failure as reported in LATITUDE to assess the robustness of our primary analysis. This analysis, whilst not changing our interpretation, did result in an HR estimate from the network analysis was

slightly more in favour of treatment (HR 0.30, 95% CI 0.27–0.34) with no evidence of variation of inconsistency (I^2=0, heterogeneity P=0.78). Based on the treatment rankings, when combined with ADT, AAP has the highest probability (100%) of being the most effective treatment in terms of FFS, whilst either Doc alone (45% probability) or in combination with ZA (52% probability) is most likely to be the second-best treatment. ADT alone has the highest probability of being the least effective treatment (73%, Table 4).

Table 4. Treatment ranking (% probability) and SUCRA values based on failure-free survival results

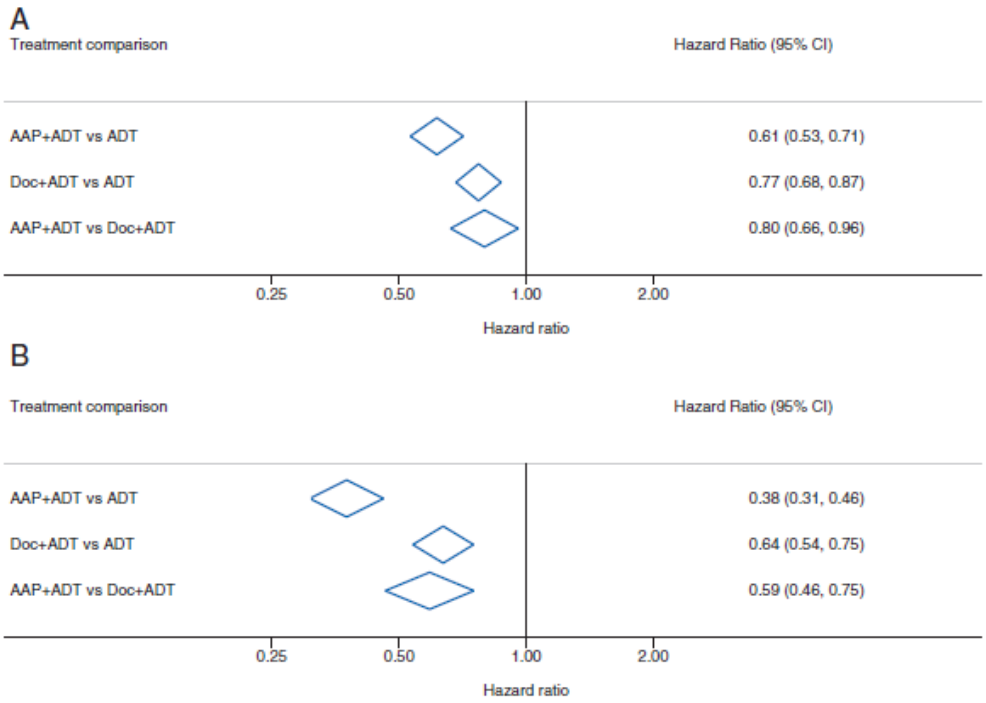
	AAP	ZA + Doc	Doc	ZA + Cel	ZA	Cel	ADT alone
Best	100.0	0.0	0.0	0.0	0.0	0.0	0.0
Second best	0.0	52.0	45.1	2.6	0.0	0.3	0.0
Third best	0.0	41.3	47.9	9.5	0.1	1.2	0.0
Fourth best	0.0	5.7	6.7	53.3	14.7	19.1	0.5
Fifth best	0.0	1.0	0.3	21.5	42.0	31.4	3.8
Sixth best	0.0	0.0	0.0	10.4	37.6	29.1	22.9
Worst	0.0	0.0	0.0	2.7	5.6	18.9	72.8
SUCRA	1.0	0.7	0.7	0.4	0.3	0.3	0.1

AAP, abiraterone acetate plus prednisolone/prednisone; ADT, androgen-deprivation therapy; Cel, celecoxib; Doc, docetaxel; SUCRA, surface under the cumulative rank; ZA, zoledronic acid.

- Indirect comparison of the two most effective treatments

When used in combination with ADT, two treatments, AAP and Doc, emerged as being effective in terms of improving both OS and FFS relative to ADT alone, and with the greatest probabilities of being the top two most effective treatments; therefore, they were compared indirectly in a pairwise comparison. The HR estimate for the effect of ADTþAAP relative to the effect of ADT+Doc on OS is 0.80 (95% CI 0.66–0.96). Assuming a baseline OS of 60% at 3 years with ADTþDoc, this translates to an absolute survival benefit associated with AAP of 6% (95% CI 1% to 11%), that is, to 66% at 3 years (95% CI 61% to 71%). For FFS, the HR for the effect of ADT+AAP relative to ADT+Doc is 0.59 (95% CI 0.46–0.75) (Figure 4).

Figure 4. Indirect comparison of the two most effective treatment combinations (A) overall survival and (B) failure-free survival. AAP, abiraterone acetate plus prednisolone/prednisone; ADT, androgen-deprivation therapy; CI, confidence interval; Cel, celecoxib; Doc, docetaxel; ZA, zoledronic acid.



Anmerkung/Fazit der Autoren

Our results support the use of either AAP or Doc alongside ADT in men with mHNPC. AAP appears to be themost effective treatment, but it is not clear to what extent and whether this is due to a true increased benefit with AAP or to the variable features of the individual trials. To fully account for patient variability across trials, changes in prognosis or treatment effects over time, and the potential impact of treatment on progression, a network meta-analysis based on individual participant data is currently in development.

Marchioni M et al., 2020 [15].

New Antiandrogen Compounds Compared to Docetaxel for Metastatic Hormone Sensitive Prostate Cancer: Results from a Network Meta-Analysis

Fragestellung

Docetaxel represent the standard of care in patients with metastatic, hormone sensitive prostate cancer. However, androgen receptor axis targeted therapies have also been shown to be effective. We aimed to analyze findings in randomized controlled trials investigating first-line treatment for hormone sensitive prostate cancer.

Methodik

Population:

- patients with mHSPC

Intervention/ Komparator:

- novel systemic compounds compared to ADT only or in association with any systemic treatment

Endpunkte:

- The primary outcome of interest was OS and secondary outcomes of interest were PFS and high grade (grades 3 to 5) AEs.
- OS followup was defined as the time from treatment initiation to death from any cause or to the last followup available.
- PFS followup was defined as the time from treatment initiation to radiological or clinical progression, death or the last followup.

Recherche/Suchzeitraum:

- In July 2019 we performed a computerized, systematic literature search of studies published up to June 2019 using PubMed, Web of Science, Scopus and ScienceDirect.

Qualitätsbewertung der Studien:

- The RoBs of each study and outcomewere evaluated and then graphically depicted as RoB summaries and graphs using RevMan, version 5.3.

Ergebnisse

Anzahl eingeschlossener Studien:

- n= 13

Charakteristika der Population:

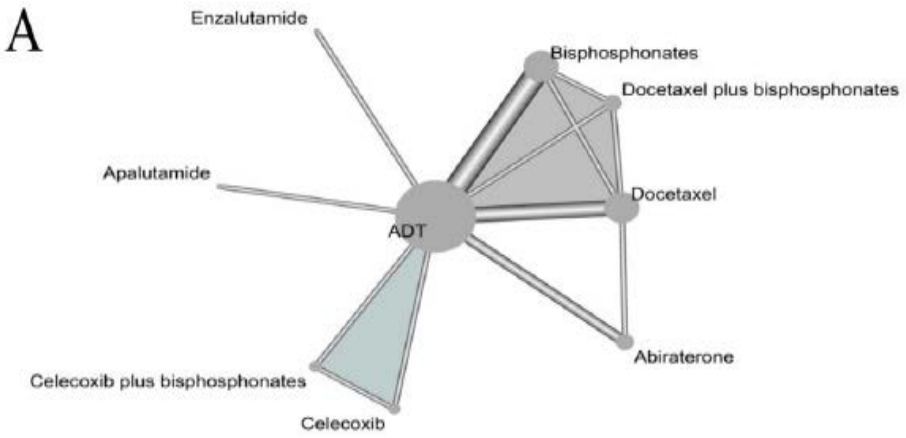
Supplementary Table 1 – Main characteristics of included studies

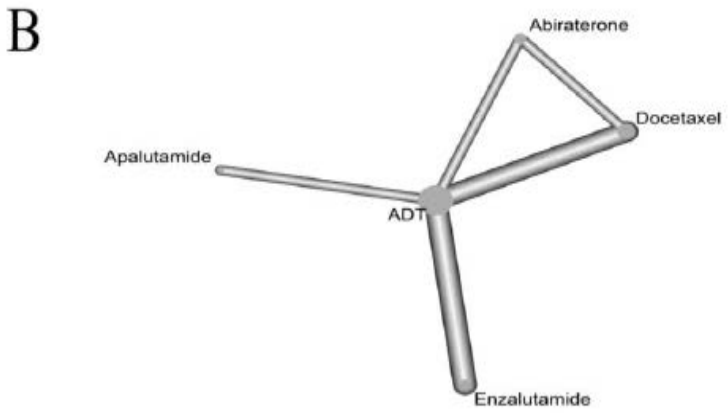
Study	First author (publication year)	Years enrollment	Type of study	Treatment comparison	Primary endpoint	Number of patients
STAMPEDE (Arm G)	James et al. (2017)	2011 - 2014	Open label	ADT+ AA vs. ADT	OS	502 vs. 500
STAMPEDE (Arm B) (Arm C) (Arm E)	James et al (2016)	2005 - 2013	Open label	ADT + ZA vs. ADT ADT + DOC vs. ADT ADT + ZA + DOC vs. ADT	OS	366 vs. 724 362 vs. 724 365 vs. 724
CHAARTED	Kyriakopoulos (2018)	2006 - 2012	Open label	ADT + DOC vs. ADT	OS	393 vs. 397
ARCHES	Armstrong et al. (2019)	2016 - 2018	Double blind	ADT + ENZA vs. ADT	rPFS	576 vs. 574
GETUG AFU 15	Gravis et al. (2016)	2004 - 2008	Open label	ADT + DOC vs. ADT	OS	192 vs. 193
LATITUDE	Fizazi et al. (2019)	2013 - 2014	Double blind	ADT + AA vs. ADT	OS	597 vs. 602
ENZAMET	Davis et al. (2019)	2014 - 2017	Open label	ADT + ENZA vs. ADT	OS	563 vs. 562
TITAN	Chi et al. (2019)	2015 - 2017	Double blind	ADT + APA vs. ADT	rPFS	525 vs. 527
ZAPCA	Kamba et al. (2017)	2008 - 2010	Open label	ADT + ZA vs. ADT	FFS	115 vs. 112
CALGB	Smith et al. (2014)	2004 - 2012	Double blind	ADT + ZA vs. ADT	SREFS	323 vs. 322
MRC-PRO5	Dearnaley et al. (2003)	1994 - 1998	Double blind	ADT + SC vs. ADT	BPFS	155 vs. 156
STAMPEDE (Arm D) (Arm F)	Mason et al. (2017)	2005 - 2011	Open label	ADT + Celecoxib vs. ADT ADT + ZA + Celecoxib vs. ADT	OS	188 vs. 377 190 vs. 377
STAMPEDE (Arm C) (Arm G)	Sydes et al. (2018)	2011 - 2013	Open label	ADT + AA vs. ADT + DOC	OS	227 vs. 115

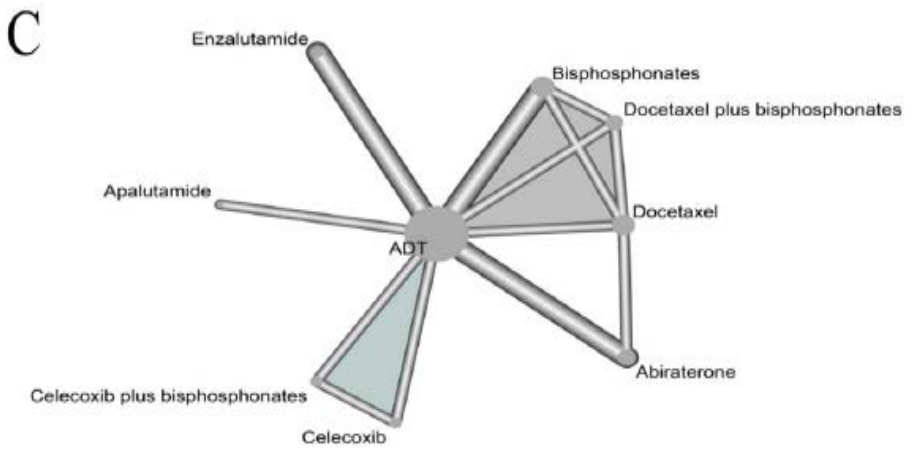
ADT: Androgen deprivation therapy; AA: Abiraterone Acetate; ZA: Zoledronic Acid; DOC: Docetaxel; ENZA: Enzalutamide; APA: Apalutamide; SC: Sodium Clodronate; OS: Overall Survival; FFS: Failure free survival; rPFS: radiographic progression-free survival; SREFS: Skeletal related events-free survival; BPFS: Bone progression-free survival

Figure 1. Evidence networks. A, overall mortality. B, progression. C, high grade adverse events.

Thickness of each arm is proportional to number of studies participating in network. Diameter of each junction point is proportional to number of studies including respective treatment. Shadowed areas indicate multi-arm studies.

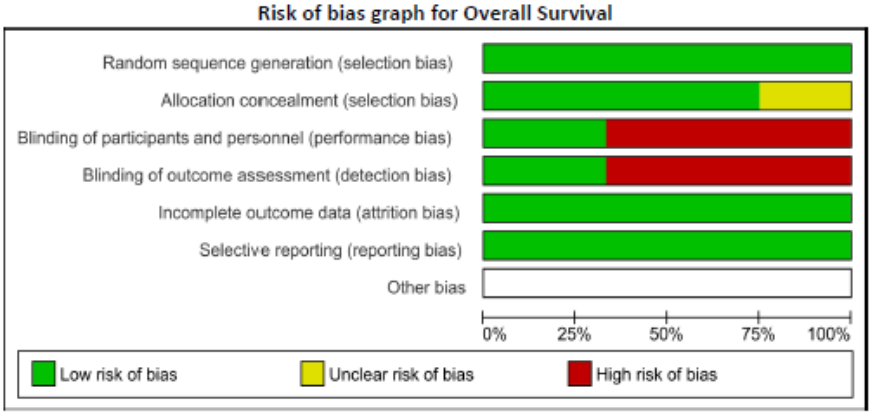




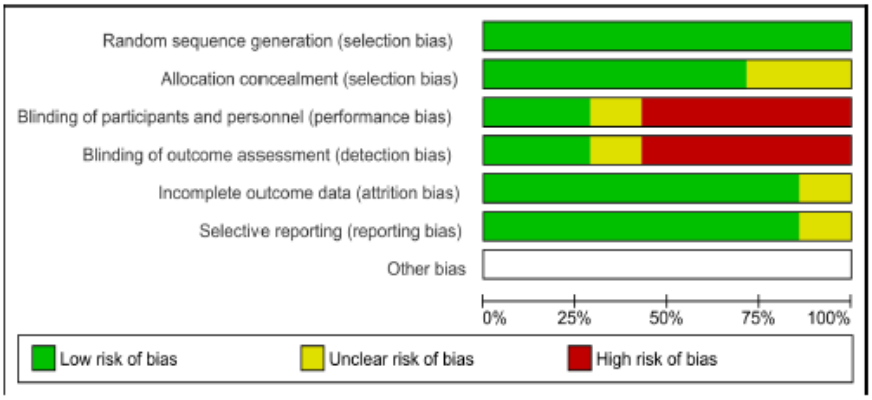


Qualität der Studien:

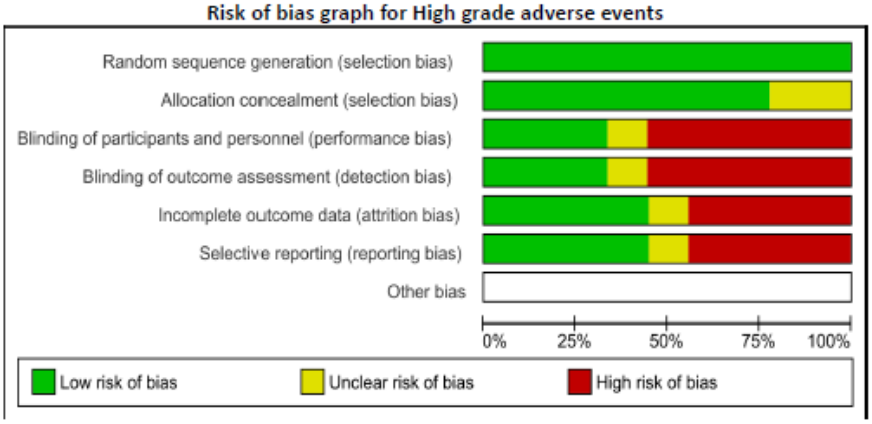
Risk of bias graph for Overall Survival

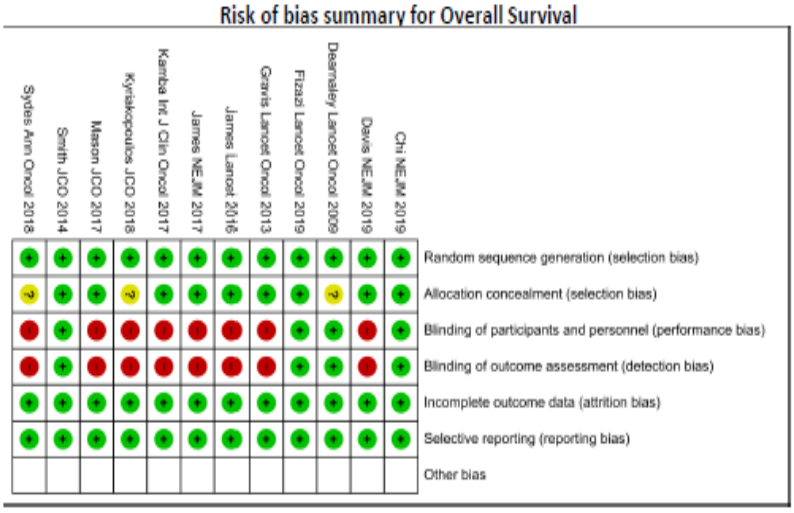


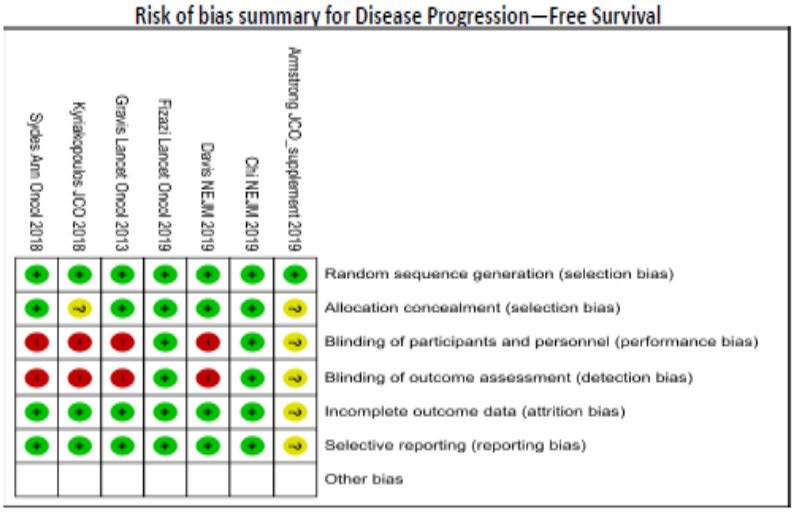
Risk of bias graph for Progression—Free Survival

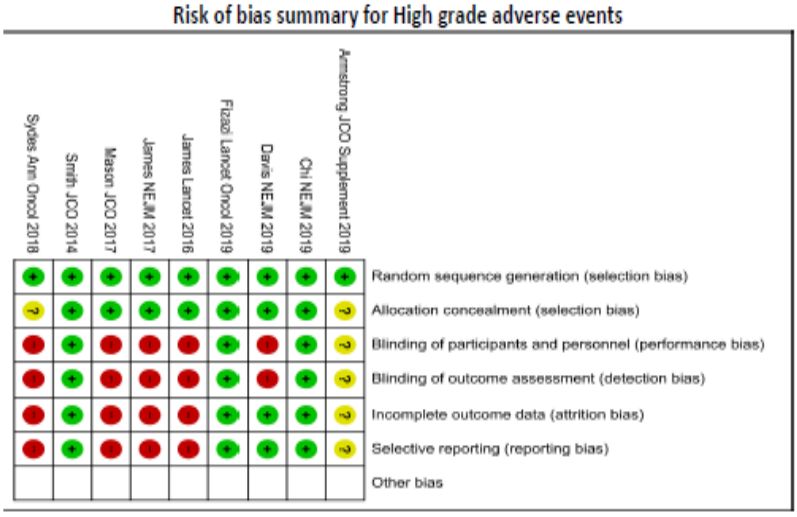


Risk of bias graph for High grade adverse events









The overall quality of included studies was high with a low selection and reporting RoB for the main investigated outcomes but with a high performance and detection RoB. Conversely, there was high attrition and reporting RoB for AEs outcome due to incomplete information on AEs and no stratification by metastatic status.

Studienergebnisse:

- Survival

  Overall. A total of 4,006 deaths were recorded. The pooled effect favored each combination treatment compared to ADT alone except for celecoxib (HR 0.94, 95% CI 0.75-1.18, fig. 2, A). Our analyses failed to demonstrate the superiority of any included treatment compared to docetaxel (fig. 2, B). However, abiraterone, enzalutamide and apalutamide were associated with lower overall mortality rates. On P-score analysis there was a higher probability of being the preferred treatment for abiraterone (85%), enzalutamide (78%) and apalutamide (78%) compared to docetaxel (60%). NMA estimated effects favored docetaxel, abiraterone, enzalutamide and apalutamide over other treatments (supplementary table 2, https://www.jurology.com).

Supplementary Table 2– Head to head comparison of each treatment showing hazard ratios and 95% confidence interval for risk of overall mortality. The lower-left of the table show the results from the network meta-analysis (direct and indirect evidences), the upper-right of the table (gray background) show the results deriving from direct comparisons only. Statistically significant comparisons are reported in bold.

Comparisons should be read from the left to the right in both the lower-left and upper-right of the table. For instance the comparison Abiraterone vs. androgen deprivation therapy (ADT) derived from the meta-analysis of direct comparisons within randomized clinical trials showed an hazard ratio [95% confidence interval]: 0.64 [0.56-0.73] in favor to Abiraterone. Similarly, the comparison of Abiraterone vs. ADT derived from the network meta-analysis, taking into account both direct and indirect comparisons, showed an hazard ratio [95% confidence interval]: 0.66 [0.58-0.75] in favor to Abiraterone.

	Hazard ratios [95%CI] derived from meta-analysis of direct evidences							
Abiraterone	.	.	1.13 [0.77; 1.66]	.	.	.	.	**0.64 [0.56; 0.73]**
0.98 [0.72; 1.33]	**Apalutamide**	.	.	.	.	.	.	**0.67 [0.51; 0.89]**
0.98 [0.74; 1.30]	1.00 [0.69; 1.46]	**Enzalutamide**	.	.	.	.	.	**0.67 [0.52; 0.86]**
0.89 [0.76; 1.05]	0.90 [0.67; 1.22]	0.90 [0.69; 1.19]	**Docetaxel**	0.82 [0.67; 1.00]	0.96 [0.78; 1.18]	.	.	**0.77 [0.68; 0.87]**
0.76 [0.64; 0.90]	0.77 [0.57; 1.04]	0.77 [0.59; 1.02]	**0.85 [0.74; 0.99]**	**Bisphosphonates**	1.18 [0.97; 1.43]	.	.	**0.87 [0.77; 0.98]**
0.86 [0.70; 1.06]	0.87 [0.63; 1.21]	0.87 [0.65; 1.18]	0.97 [0.81; 1.16]	1.13 [0.95; 1.35]	**Docetaxel plus bisphosphonates**	.	.	**0.79 [0.66; 0.95]**
0.70 [0.54; 0.91]	0.71 [0.50; 1.02]	0.71 [0.51; 1.00]	0.79 [0.61; 1.02]	0.92 [0.72; 1.19]	0.82 [0.62; 1.08]	**Celecoxib**	1.21 [0.93; 1.57]	0.94 [0.75; 1.18]
0.84 [0.65; 1.10]	0.86 [0.60; 1.23]	0.86 [0.61; 1.21]	0.95 [0.73; 1.23]	1.11 [0.86; 1.44]	0.98 [0.74; 1.31]	1.21 [0.93; 1.57]	**Celecoxib plus bisphosphonates**	**0.78 [0.62; 0.98]**
0.66 [0.58; 0.75]	**0.67 [0.51; 0.89]**	**0.67 [0.52; 0.86]**	**0.74 [0.66; 0.83]**	**0.87 [0.77; 0.97]**	**0.77 [0.65; 0.91]**	0.94 [0.75; 1.18]	**0.78 [0.62; 0.98]**	**ADT**
Hazard ratios [95%CI] derived from network meta-analysis (direct and indirect evidences)								

Comparisons should be read from the left to the right in both the lower-left and upper-right of the table. For instance the comparison Abiraterone vs. androgen deprivation therapy (ADT) derived from the meta-analysis of direct comparisons within randomized clinical trials showed an hazard ratio [95% confidence interval]: 0.64 [0.56-0.73] in favor to Abiraterone. Similarly, the comparison of Abiraterone vs. ADT derived from the network meta-analysis, taking into account both direct and indirect comparisons, showed an hazard ratio [95% confidence interval]: 0.66 [0.58-0.75] in favor to Abiraterone.

The model failed to show heterogeneity (within design I^2=0%, t2=0, p= 0.664) and inconsistency (between design p= 0.380). The GRADE quality of all direct comparisons was high but it was downgraded to intermediate and low in most cases for the NMA evidence. No statistically significant difference was found between estimates (all p >0.05, supplementary material 4, https://www.jurology.com)

Supplementary material 4 – Quality of evidences comparing treatment on respect to the overall mortality according to the GRADE working Group approach.

	Direct evidence			Indirect evidence			Network Meta-analysis evidence			
comparison	logHR ± SE	p-value	Quality	logHR ± SE	p-value	Quality	logHR ± SE	p-value	p-value for disagreement	Quality
Abiraterone vs ADT	-0.45 ± 0.07	<0.001	⊕⊕⊕⊕	-0.15 ± 0.21	0.456	⊕⊕⊕	-0.42 ± 0.06	<0.001	0.177	⊕⊕⊕
Abiraterone vs Apalutamide	-	-		-0.02 ± 0.16	0.913	⊕⊕	-0.02 ± 0.16	0.913	-	⊕⊕
Abiraterone vs Biphosfonate	-	-		-0.28 ± 0.09	0.001	⊕⊕⊕	-0.28 ± 0.09	0.001	-	⊕⊕⊕
Abiraterone vs Celecoxib	-	-		-0.36 ± 0.13	0.007	⊕⊕⊕	-0.36 ± 0.13	0.007	-	⊕⊕⊕
Abiraterone vs Celecoxib plus bisph	-	-		-0.17 ± 0.13	0.204	⊕⊕	-0.17 ± 0.13	0.204	-	⊕⊕
Abiraterone vs Docetaxel	0.12 ± 0.2	0.533	⊕⊕⊕	-0.17 ± 0.09	0.063	⊕⊕⊕	-0.12 ± 0.08	0.154	0.177	⊕⊕⊕
Abiraterone vs Docetaxel plus bisph	-	-		-0.15 ± 0.11	0.150	⊕⊕⊕	-0.15 ± 0.11	0.15	-	⊕⊕⊕
Abiraterone vs Enzalutamide	-	-		-0.02 ± 0.14	0.906	⊕⊕⊕	-0.02 ± 0.14	0.906	-	⊕⊕⊕
Apalutamide vs ADT	-0.4 ± 0.14	0.005	⊕⊕⊕⊕	-	-		-0.4 ± 0.14	0.005	-	⊕⊕⊕⊕
Biphosfonate vs ADT	-0.14 ± 0.06	0.019	⊕⊕⊕	-0.11 ± 0.25	0.648	⊕⊕	-0.14 ± 0.06	0.017	0.902	⊕⊕⊕
Celecoxib vs ADT	-0.06 ± 0.12	0.593	⊕⊕⊕	-	-		-0.06 ± 0.12	0.593	-	⊕⊕⊕
Celecoxib plus bisph vs ADT	-0.25 ± 0.12	0.033	⊕⊕⊕	-	-		-0.25 ± 0.12	0.033	-	⊕⊕⊕
Docetaxel vs ADT	-0.26 ± 0.06	<0.001	⊕⊕⊕⊕	-0.57 ± 0.17	0.001	⊕⊕⊕	-0.3 ± 0.06	<0.001	0.081	⊕⊕⊕
Docetaxel plus bisph vs ADT	-0.24 ± 0.1	0.014	⊕⊕⊕⊕	-0.39 ± 0.2	0.049	⊕⊕	-0.27 ± 0.09	0.002	0.478	⊕⊕⊕
Enzalutamide vs ADT	-0.4 ± 0.13	0.002	⊕⊕⊕⊕	-	-		-0.4 ± 0.13	0.002	-	⊕⊕⊕⊕
Apalutamide vs bisph	-	-		-0.26 ± 0.15	0.094	⊕	-0.26 ± 0.15	0.094	-	⊕
Apalutamide vs Celecoxib	-	-		-0.34 ± 0.18	0.064	⊕	-0.34 ± 0.18	0.064	-	⊕
Apalutamide vs Celecoxib plus bisph	-	-		-0.15 ± 0.18	0.408	⊕	-0.15 ± 0.18	0.408	-	⊕
Apalutamide vs Docetaxel	-	-		-0.1 ± 0.15	0.512	⊕⊕⊕	-0.1 ± 0.15	0.512	-	⊕⊕⊕
Apalutamide vs Docetaxel plus bisph	-	-		-0.14 ± 0.17	0.415	⊕⊕⊕	-0.14 ± 0.17	0.415	-	⊕⊕⊕
Apalutamide vs Enzalutamide	-	-		0.00 ± 0.19	0.999	⊕⊕⊕	0 ± 0.19	0.999	-	⊕⊕⊕
Biphosfonate vs Celecoxib	-	-		-0.08 ± 0.13	0.536	⊕⊕⊕	-0.08 ± 0.13	0.536	-	⊕⊕⊕
Biphosfonate vs Celecoxib plus bisph	-	-		0.11 ± 0.13	0.418	⊕⊕⊕	0.11 ± 0.13	0.418	-	⊕⊕⊕
Biphosfonate vs Docetaxel	0.20 ± 0.1	0.049	⊕⊕⊕⊕	0.11 ± 0.11	0.343	⊕	0.16 ± 0.08	0.037	0.522	⊕⊕⊕
Biphosfonate vs Docetaxel plus bisph	0.16 ± 0.1	0.102	⊕⊕⊕⊕	-0.09 ± 0.23	0.700	⊕	0.12 ± 0.09	0.179	0.312	⊕⊕⊕
Biphosfonate vs Enzalutamide	-	-		0.26 ± 0.14	0.068	⊕	0.26 ± 0.14	0.068	-	⊕
Celecoxib vs Celecoxib plus bisph	0.19 ± 0.13	0.164	⊕⊕⊕	-	-		0.19 ± 0.13	0.164	-	⊕⊕
Celecoxib vs Docetaxel	-	-		0.24 ± 0.13	0.067	⊕⊕⊕	0.24 ± 0.13	0.067	-	⊕⊕
Celecoxib vs Docetaxel plus bisph	-	-		0.20 ± 0.14	0.159	⊕	0.2 ± 0.14	0.159	-	⊕

- Progression-Free.

  Overall progression was noted in 1,265 cases. The pooled effect was in favor of each treatment included in analysis compared to ADT (fig. 3, A). The largest magnitude in terms of the effect on PFS was an advantage of enzalutamide (HR 0.40, 95% CI 0.34-0.46). This effect was also reflected in the indirect comparison of enzalutamide to docetaxel (HR 0.61, 95% CI 0.49-0.75). However, abiraterone (HR 0.71, 95% CI 0.59-0.86) and apalutamide (HR 0.74, 95% CI 0.57-0.95) also showed an advantage over docetaxel (fig. 3, B). On P-score analysis enzalutamide (96%), followed by abiraterone (67%) and apalutamide (62%) had the highest probability of being the preferred treatment.

  The NMA failed to show a statistically significant difference when comparing abiraterone, apalutamide and enzalutamide to each other (fig. 4).

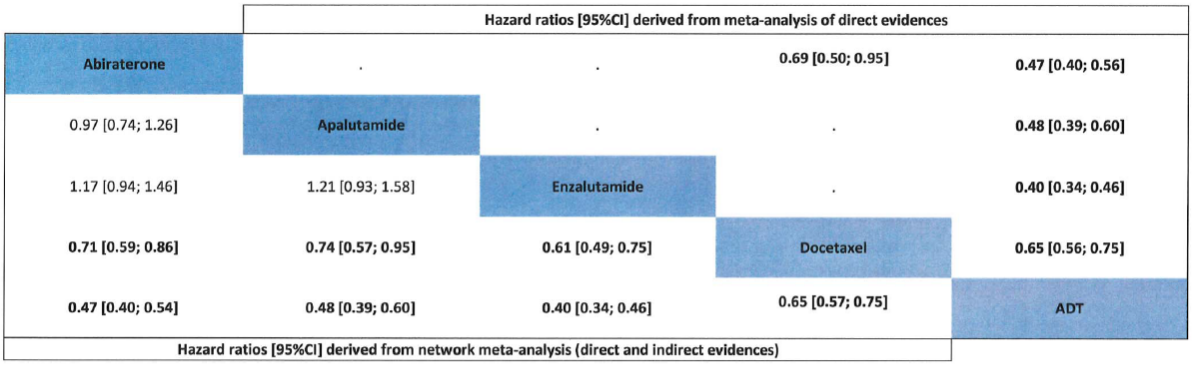


Figure 4. Head-to-head comparison of each treatment shows HR and 95% CI of disease progression risk. Read comparisons from left to right, ie abiraterone vs ADT comparison from direct comparison meta-analysis in RCTs shows HR 0.47 (95% CI 0.40–0.56) in favor of abiraterone. Lower left, network meta-analysis results (direct and indirect evidence). Gray upper right, direct comparison results. Bold indicates statistically significant comparison.

The model also failed to show heterogeneity (within design I^2=0%, t2=0 and p=0.774) and inconsistency (between design p= 0.804). The GRADE quality of all direct comparisons was high but it was downgraded to intermediate and low in most cases for the NMA evidence. No

statistically significant difference was found between estimates (all p >0.05, supplementary material 5, https://www.jurology.com).

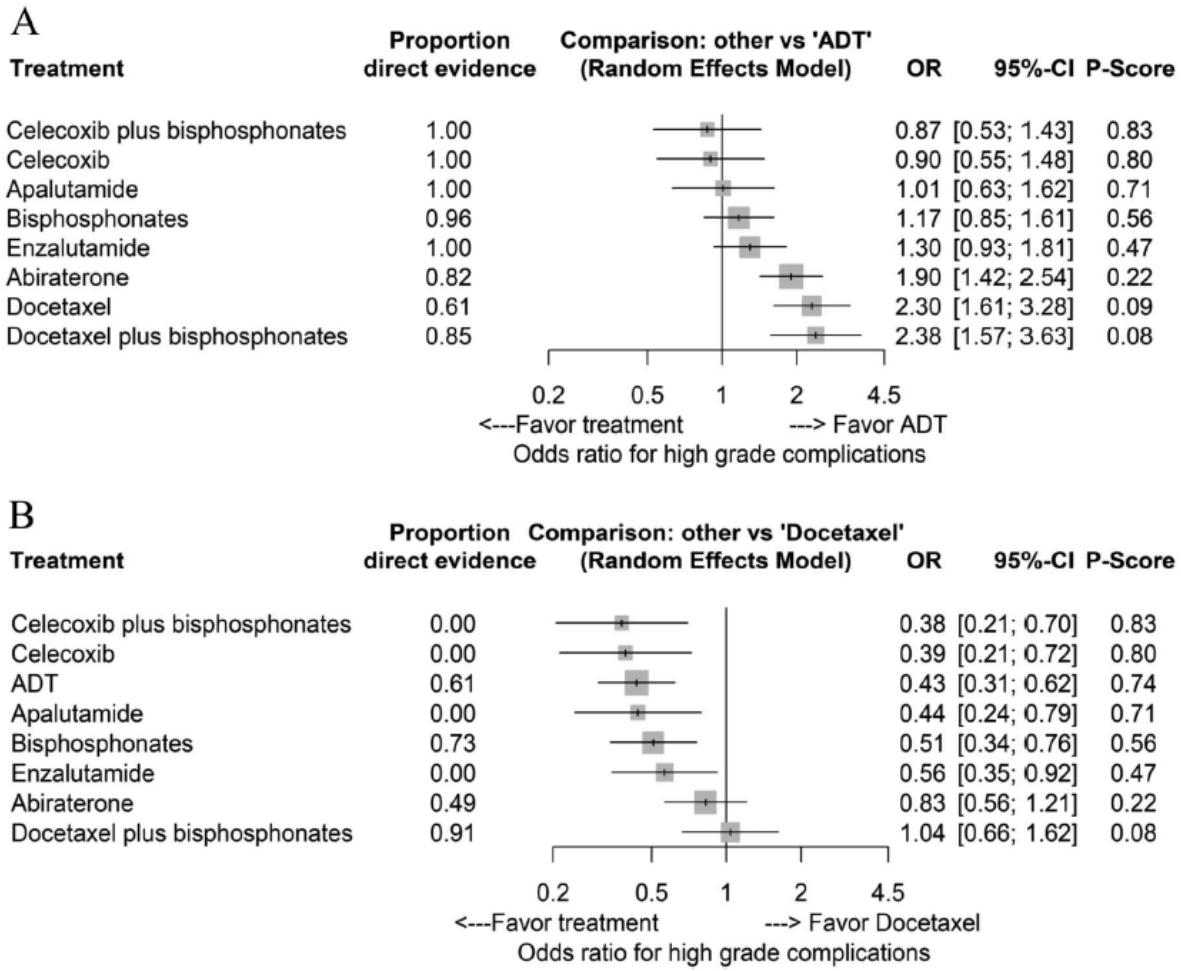
Supplementary material 5 – Quality of evidences comparing treatment on respect to the disease progression according to the GRADE working Group approach.

	Direct evidence			Indirect evidence			Network Meta-analysis evidence			
comparison	logHR ± SE	p-value	Quality	logHR ± SE	p-value	Quality	logHR ± SE	p-value	p-value for disagreement	Quality
Abiraterone vs ADT	-0.76 ± 0.09	<0.001	⊕⊕⊕⊕	-0.80 ± 0.18	<0.001	⊕⊕⊕	-0.77 ± 0.08	<0.001	0.804	⊕⊕⊕
Abiraterone vs Apalutamide	-	-		-0.03 ± 0.13	0.821	⊕⊕⊕	-0.03 ± 0.14	0.821		⊕⊕⊕
Abiraterone vs Docetaxel	-0.37 ± 0.16	0.023	⊕⊕⊕⊕	-0.32 ± 0.12	0.005	⊕⊕⊕	-0.34 ± 0.09	<0.001	0.804	⊕⊕⊕
Abiraterone vs Enzalutamide	-	-		0.16 ± 0.11	0.151	⊕⊕⊕	0.16 ± 0.11	0.151		⊕⊕⊕
Apalutamide vs ADT	-0.71 ± 0.11	<0.001	⊕⊕⊕⊕	-	-		-0.73 ± 0.11	<0.001		⊕⊕⊕
Docetaxel vs ADT	-0.43 ± 0.07	<0.001	⊕⊕⊕⊕	-0.38 ± 0.19	0.039	⊕⊕⊕	-0.43 ± 0.07	<0.001	0.804	⊕⊕⊕
Enzalutamide vs ADT	-0.93 ± 0.08	<0.001	⊕⊕⊕⊕	-	-		-0.93 ± 0.08	<0.001		⊕⊕⊕
Apalutamide vs Docetaxel	-	-		-0.31 ± 0.13	0.018	⊕⊕⊕	-0.31 ± 0.13	0.018		⊕⊕⊕
Apalutamide vs Enzalutamide	-	-		0.19 ± 0.14	0.158	⊕⊕⊕	0.19 ± 0.14	0.158		⊕⊕⊕
Docetaxel vs Enzalutamide	-	-		0.50 ± 0.11	<0.001	⊕⊕⊕	0.50 ± 0.11	<0.001		⊕⊕⊕

- Adverse Events

  The pooled effect revealed a higher AE rate in patients treated with abiraterone (OR 1.90, 95% CI 1.42-2.54), docetaxel alone (OR 2.30, 95% CI 1.61-3.28) or in combination with bisphosphonates (OR 2.38, 95% CI 1.57-3.63, fig. 5, A). The NMA head-to-head comparison showed a higher AE rate for abiraterone and docetaxel compared to apalutamide or enzalutamide (fig. 5, B, and fig 6). However, the model showed high within design heterogeneity (I^2=66.9%, t2=0.042 and p=0.009).

Figure 5. Forest plot of OR(95%CI) of high grade adverse events of each compound vs ADTalone (A) orADTcombined with docetaxel (B). Within design heterogeneity I2=66.9%, t2=0.042 and p=0.009. Between design test for inconsistency showed low risk of inconsistency (p=0.161).



	Hazard ratios [95%CI] derived from meta-analysis of direct evidences							
Abiraterone	.	.	0.93 [0.54; 1.60]	.	.	.	.	**1.82 [1.32; 2.50]**
1.88 [1.08; 3.27]	**Apalutamide**	.	.	.	.	.	.	1.01 [0.63; 1.62]
1.46 [0.94; 2.28]	0.78 [0.44; 1.39]	**Enzalutamide**	.	.	.	.	.	1.30 [0.93; 1.81]
0.83 [0.56; 1.21]	**0.44 [0.24; 0.79]**	**0.56 [0.35; 0.92]**	**Docetaxel**	**2.29 [1.44; 3.66]**	1.01 [0.63; 1.61]	.	.	**2.28 [1.45; 3.59]**
1.63 [1.08; 2.46]	0.87 [0.49; 1.53]	1.11 [0.70; 1.77]	**1.97 [1.32; 2.94]**	**Bisphosphonates**	0.44 [0.28; 0.70]	.	.	1.19 [0.86; 1.66]
0.80 [0.49; 1.29]	**0.42 [0.23; 0.80]**	**0.54 [0.32; 0.93]**	0.96 [0.62; 1.51]	**0.49 [0.32; 0.76]**	**Docetaxel plus bisphosphonates**	.	.	**2.26 [1.44; 3.56]**
2.11 [1.19; 3.76]	1.12 [0.57; 2.23]	1.44 [0.79; 2.63]	**2.56 [1.39; 4.71]**	1.30 [0.72; 2.35]	**2.65 [1.38; 5.09]**	**Celecoxib**	1.03 [0.61; 1.75]	0.90 [0.55; 1.48]
2.18 [1.22; 3.88]	1.16 [0.58; 2.30]	1.49 [0.82; 2.71]	**2.64 [1.43; 4.87]**	1.34 [0.74; 2.43]	**2.74 [1.43; 5.25]**	1.03 [0.61; 1.75]	**Celecoxib plus bisphosphonates**	0.87 [0.53; 1.43]
1.90 [1.42; 2.54]	1.01 [0.63; 1.62]	1.30 [0.93; 1.81]	**2.30 [1.61; 3.28]**	1.17 [0.85; 1.61]	**2.38 [1.57; 3.63]**	0.90 [0.55; 1.48]	0.87 [0.53; 1.43]	**ADT**
Hazard ratios [95%CI] derived from network meta-analysis (direct and indirect evidences)								

Figure 6. Head-to-head comparison of each treatment shows HR and 95% CI of high grade adverse event risk. Read comparisons from left to right, ie abiraterone vs ADT comparison from direct comparison meta-analysis in RCTs shows HR 1.82 (95% CI 1.32–2.50) in favor of abiraterone. Lower left, network meta-analysis results (direct and indirect evidence). Gray upper right, direct comparison results. Bold indicates statistically significant comparison.

Conversely, tests for between design inconsistency showed a low risk of inconsistency (p= 0.161). The GRADE quality of all direct comparisons was intermediate, although it was downgraded to low in most cases for the NMA evidence. No statistically significant difference was found between estimates (all p >0.05, supplementary material 6, Moreover, sensitivity analysis was performed after excluding the STAMPEDE trial due to the limited information on AEs reported only in patients with metastasis. Our results showed no statistically

significant differences in AE rates when comparing ADT to apalutamide (OR 1.01, 95% CI 0.48-2.13), enzalutamide (OR 1.29, 95% CI 0.76-2.19) and bisphosphonates (OR 1.46, 95% CI 0.77-2.74). Similarly on sensitivity analysis abiraterone demonstrated no statistically significant higher AE rate compared to ADT (OR 1.84, 95% CI 0.87-3.87).

Supplementary material 6 - Quality of evidences comparing treatment on respect to the high grade adverse events according to the GRADE working Group approach.

	Direct evidence			Indirect evidence			Network Meta-analysis evidence			
comparison	logHR ± SE	p-value	Quality	logHR ± SE	p-value	Quality	logHR ± SE	p-value	p-value for disagreement	Quality
Abiraterone vs ADT	0.6 ± 0.16	<0.001	⊕⊕⊕	0.84 ± 0.35	0.017	⊕⊕	0.64 ± 0.15	<0.001	0.593	⊕⊕
Abiraterone vs Apalutamide	-	-		0.63 ± 0.28	0.030	⊕⊕	0.63 ± 0.28	0.026		⊕⊕
Abiraterone vs Bisphosphonates	-	-		0.49 ± 0.21	0.021	⊕⊕	0.49 ± 0.21	0.021		⊕⊕
Abiraterone vs Celecoxib	-	-		0.75 ± 0.29	0.011	⊕⊕	0.75 ± 0.29	0.011		⊕⊕
Abiraterone vs Celecoxib plus bisphosphonates	-	-		0.78 ± 0.29	0.008	⊕⊕	0.78 ± 0.29	0.008		⊕⊕
Abiraterone vs Docetaxel	-0.07 ± 0.28	0.801	⊕⊕⊕	-0.31 ± 0.27	0.253	⊕⊕	-0.19 ± 0.19	0.322	0.533	⊕⊕
Abiraterone vs Docetaxel plus bisphosphonates	-	-		-0.23 ± 0.25	0.354	⊕⊕	-0.23 ± 0.25	0.354		⊕⊕
Abiraterone vs Enzalutamide	-	-		0.38 ± 0.23	0.093	⊕⊕	0.38 ± 0.23	0.093		⊕⊕
ADT vs Apalutamide	-0.01 ± 0.24	0.966	⊕⊕⊕	-	-		-0.01 ± 0.24	0.966		⊕⊕
ADT vs Bisphosphonates	-0.18 ± 0.17	0.296	⊕⊕⊕	0.35 ± 0.82	0.673	⊕⊕	-0.15 ± 0.16	0.347	0.533	⊕⊕
ADT vs Celecoxib	0.11 ± 0.25	0.673	⊕⊕⊕	-	-		0.11 ± 0.25	0.673		⊕⊕
ADT vs Celecoxib plus bisphosphonates	0.14 ± 0.25	0.587	⊕⊕⊕	-	-		0.14 ± 0.25	0.587		⊕⊕
ADT vs Docetaxel	-0.83 ± 0.23	<0.001	⊕⊕⊕	-0.84 ± 0.29	0.004	⊕⊕	-0.83 ± 0.18	<0.001	0.963	⊕⊕
ADT vs Docetaxel plus bisphosphonates	-0.82 ± 0.23	<0.001	⊕⊕⊕	-1.17 ± 0.56	0.035	⊕⊕	-0.87 ± 0.21	<0.001	0.556	⊕⊕
ADT vs Enzalutamide	-0.26 ± 0.17	0.131	⊕⊕⊕	-	-		-0.26 ± 0.17	0.131		⊕⊕
Apalutamide vs Bisphosphonates	-	-		-0.14 ± 0.29	0.620	⊕⊕	-0.14 ± 0.29	0.620		⊕⊕
Apalutamide vs Celecoxib	-	-		0.12 ± 0.35	0.737	⊕⊕	0.12 ± 0.35	0.737		⊕⊕
Apalutamide vs Celecoxib plus bisphosphonates	-	-		0.15 ± 0.35	0.672	⊕⊕	0.15 ± 0.35	0.672		⊕⊕
Apalutamide vs Docetaxel	-	-		-0.82 ± 0.3	0.006	⊕⊕	-0.82 ± 0.3	0.006		⊕⊕
Apalutamide vs Docetaxel plus bisphosphonates	-	-		-0.86 ± 0.32	0.008	⊕⊕	-0.86 ± 0.32	0.008		⊕⊕
Apalutamide vs Enzalutamide	-	-		-0.25 ± 0.3	0.399	⊕⊕	-0.25 ± 0.3	0.399		⊕⊕
Bisphosphonates vs Celecoxib	-	-		0.26 ± 0.3	0.387		0.26 ± 0.3	0.387		⊕⊕
Bisphosphonates vs Celecoxib plus	-	-		0.29 ± 0.3	0.334	⊕⊕	0.29 ± 0.3	0.334		⊕⊕

Anmerkung/Fazit der Autoren

Treatment with ARATs combined with ADT in patients with mHSPC does not provide a statistically significant OS advantage compared to the standard, docetaxel. However, it is associated with a lower disease progression rate. Moreover, apalutamide and enzalutamide offer a better safety profile.

Zhu J & Wu S, 2019 [29].

Risk of hypertension in Cancer patients treated with Abiraterone: a meta-analysis

Fragestellung

Hypertension is one of the major side effects associated with abiraterone in the treatment of advanced prostate cancer. The specific contribution of abiraterone to hypertension has not been defined. We performed a systematic review and meta-analysis of randomized clinical trials to determine its overall risk.

Methodik

Population:

- patients with advanced prostate cancer

Intervention/ Komparator:

- combination of abiraterone with prednisone

Endpunkte:

- Hypertension was recorded according to versions III of the Common Terminology Criteria for Adverse Events (CTCAE) of National Cancer Institute
- We have included the incidence of hypertension of grade I and above for our analysis.

Recherche/Suchzeitraum:

- Databases including Pubmed (up to July 2018) and Google scholar (up to July 2018)

Qualitätsbewertung der Studien:

- 5-item Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- five studies including 5445 patients

Charakteristika der Population:

Table 1 Characteristics of clinical trials and patients included in the meta-analysis

Trial name	Design	Total enrollment number	Intervention	Control	Study quality
James et al., 2017 [7]	Open label-phase III	1917	Abiraterone prednisone 5 mg qd ADT	ADT alone	4
Fizazi et al., 2017[13]	Double-blind phase III	1199	Abiraterone Prednisone 5 mg qd ADT	ADT + placebo	5
Ryan et al., 2015 [9]	Double-blind phase III	1088	Abiraterone Prednisone 5 mg bid	Placebo Prednisone 5 mg bid	5
Taplin et al., 2014 [14]	Open label phase II	56	Abiraterone Prednisone 5 mg qd ADT	ADT alone	3
Fizazi et al., 2012 [6]	Double-blind phase III	1185	Abiraterone Prednisone 5 mg bid	Placebo Prednisone 5 mg bid	5

Abbreviations: ADT androgen deprivation therapy. qd, once a day; bid, twice a day

Qualität der Studien:

Siehe oben

Studienergebnisse:

Among patients receiving abiraterone, the overall incidences of all grade and high grade (grade 3 and 4) were 21.9% (95% CI: 13.6–33.2%) and 10.2% % (95% CI: 6.9–11.6%). Abiraterone was associated with a significantly increased risk of hypertension of all grade with a relative risk of 1.80 (95% CI: 1.47–2.19%, $p < 0.001$) and high grade with a relative risk of 2.11 (95%CI: 1.66–2.68%, $p < 0.001$) in comparison with controls.

The risk of hypertension may be affected by concurrent use of prednisone with 5mg daily is associated with higher incidence than that of prednisone 5 mg twice daily (32.4% vs 16.5%).

Fig. 2 Annotated forest plot for meta-analysis of the incidence of hypertension in cancer patients who received abiraterone. The summary incidences of all-grade (a) and high-grade (b) hypertension are calculated using a random-effects model. The incidences and 95% confidence intervals for each study and the final combined result are displayed numerically on the left and graphically as a forest plot on the right.

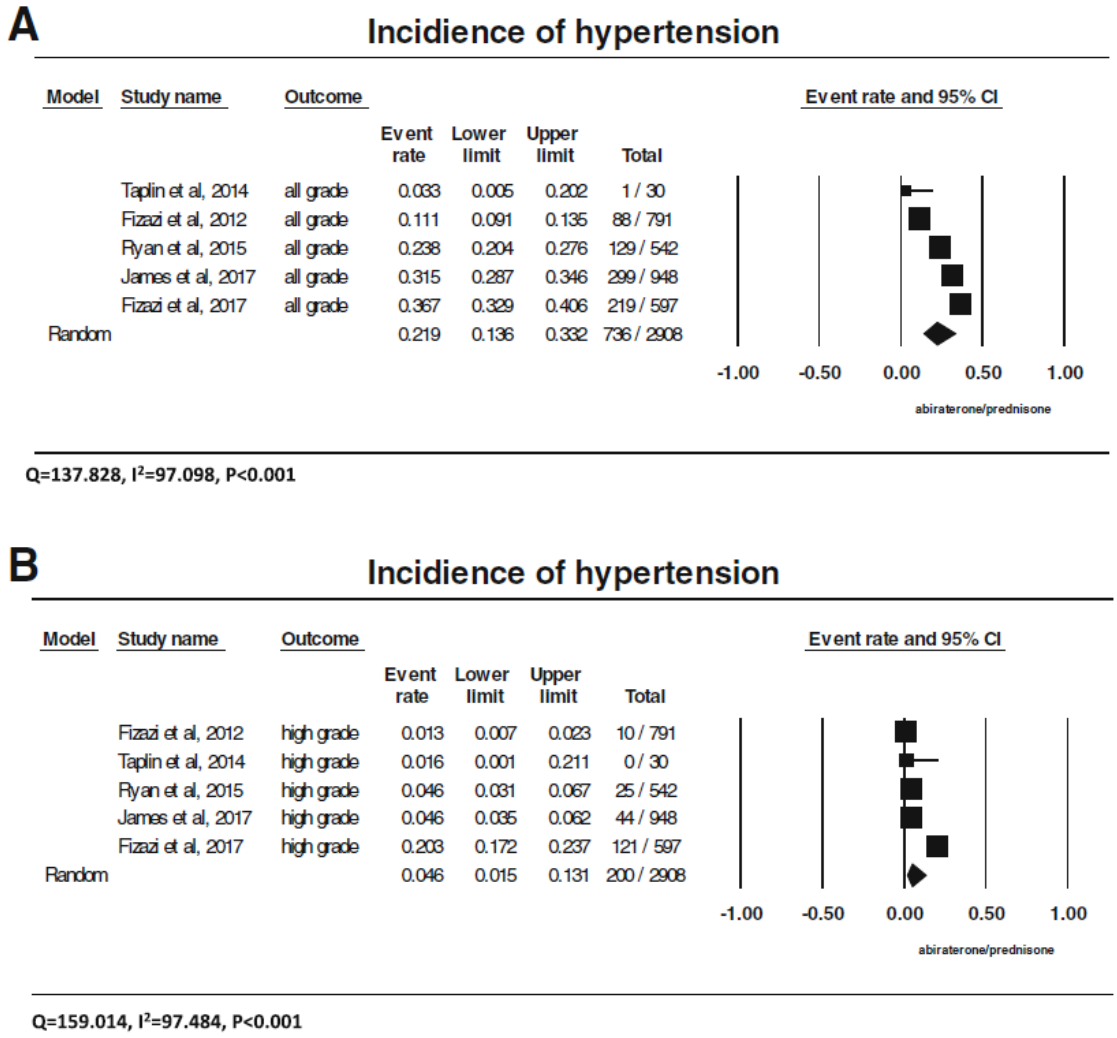
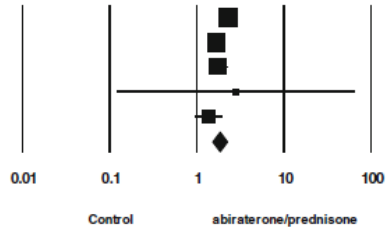


Fig. 3 Relative risk of hypertension associated with abiraterone versus control. The summary relative risks (RR) of all-grade (a) and high-grade (b) hypertension were calculated using the random-effects model.

A

Risk of hypertension

Model	Studyname	Outcome	Risk ratio	Lower limit	Upper limit	p-Value	Intervention	Control
	James et al, 2017	all grade	2.311	1.922	2.780	0.000	299 / 948	131 / 960
	Fizazi et al, 2017	all grade	1.660	1.382	1.994	0.000	219 / 597	133 / 602
	Ryan et al, 2015	all grade	1.737	1.339	2.252	0.000	129 / 542	74 / 540
	Taplin et al, 2014	all grade	2.806	0.119	66.170	0.522	1 / 30	0 / 28
	Fizazi et al, 2012	all grade	1.370	0.931	2.015	0.110	88 / 791	32 / 394
Random			1.800	1.475	2.197	0.000	736 / 2908	370 / 2524

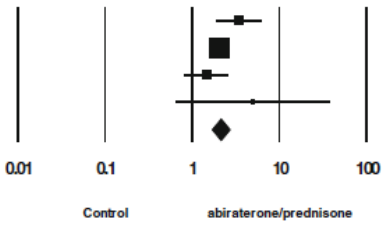


heterogeneity test: $Q=9.531$, $I^2=58.03$, $P=0.049$

B

Risk of hypertension

Model	Studyname	Outcome	Risk ratio	Lower limit	Upper limit	p-Value	Intervention	Control
	James et al, 2017	high grade	3.427	1.858	6.322	0.000	44 / 948	13 / 960
	Fizazi et al, 2017	high grade	2.034	1.525	2.712	0.000	121 / 597	60 / 602
	Ryan et al, 2015	high grade	1.465	0.800	2.682	0.216	25 / 542	17 / 540
	Fizazi et al, 2012	high grade	4.981	0.640	38.772	0.125	10 / 791	1 / 394
Fixed			2.117	1.669	2.685	0.000	200 / 2878	91 / 2496



heterogeneity test: $Q=4.546$, $I^2=34.013$, $P=0.208$

Anmerkung/Fazit der Autoren

This study has demonstrated that the combination of abiraterone with prednisone is associated with significantly increased risk of all-grade and high-grade hypertension in prostate cancer patients. The risk may vary with the dose of prednisone. It is important for physicians and patients to recognize the risk of all-grade hypertension, but also to appreciate the risk of serious hypertension. Early detection and effective management may allow safe use of abiraterone, reducing cardiovascular risk and treatment interruption/discontinuation and improving the overall outcome of these patients.

3.4 Leitlinien

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften), 2019 [12].

Interdisziplinäre Leitlinie der Qualität S3 zur Früherkennung, Diagnose und Therapie der verschiedenen Stadien des Prostatakarzinoms; Langversion 5.1 2019, (18.10.2019): AWMF Registernummer: 043/022OL

Siehe auch: Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften), 2018 [11].

Leitlinienorganisation/Fragestellung

Die interdisziplinäre Leitlinie der Qualität S3 zur Früherkennung, Diagnose und Therapie der verschiedenen Stadien des Prostatakarzinoms ist ein evidenz- und konsensbasiertes Instrument, um Früherkennung, Diagnostik und Therapie des Prostatakarzinoms zu verbessern.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: Interdisziplinäre LL-Entwicklergruppe, Beteiligung von Patientenvertreterinnen;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt. Es wurde ein durch die AWMF moderierter, mehrteiliger Nominaler Gruppenprozess durchgeführt.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert: Stand: 01.04.2018, gültig bis 30.04.2021
- In den Kopfzeilen der Empfehlungen und Statements wurde vermerkt, wann diese erstellt bzw. aktualisiert wurden und ob sie modifiziert oder neu erstellt wurden. Folgende Kategorien der Kennzeichnung werden verwendet:

geprüft 2018 = Die Empfehlung bzw. das Statement wurde bei der Erstellung der Leitlinie oder bei einer der anschließenden Aktualisierungen (2011, 2014, 2016) erstellt oder modifiziert. Die Gültigkeit der Empfehlung bzw. des Statements wurde während der Aktualisierung 2018 geprüft und mittels Abstimmung erneut konsentiert.

spezifiziert 2018 = Die Empfehlung bzw. das Statement wurde während der Aktualisierung 2018 in Detailaspekten angepasst, die Aussage jedoch nicht verändert.

modifiziert 2018 = Die Empfehlung bzw. das Statement wurde während der Aktualisierung 2018 in Teilen oder gänzlich aufgrund neuer Evidenz geändert.

neu 2018 = Die Empfehlung bzw. das Statement wurde während der Aktualisierung 2018 neu erstellt.

Recherche/Suchzeitraum:

- Recherche zur 4. Aktualisierung 2018: Zu allen Fragestellungen erfolgte eine spezifische systematische Literaturrecherche in den Datenbanken Medline (Pubmed) und den Datenbanken der Cochrane Library (Methodikeranmerkung: unterschiedliche Suchzeiträume jeweils angegeben). Es wurden außerdem Studien berücksichtigt, die in Referenzlisten bekannter Studien oder durch Hinweise aus der Leitliniengruppe identifiziert wurden.

LoE/GoR

- Zur Klassifikation des Verzerrungsrisikos der identifizierten Studien wurde das in Tabelle 2 aufgeführte System des Scottish Intercollegiate Guidelines Network (SIGN) verwendet.

Tabelle 2: Schema der Evidenzgraduierung nach SIGN

Grad	Beschreibung
1++	Qualitativ hochwertige Metaanalysen, systematische Übersichten von RCTs, oder RCTs mit sehr geringem Risiko systematischer Fehler (Bias)
1+	Gut durchgeführte Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit geringem Risiko systematischer Fehler (Bias)
1-	Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit hohem Risiko systematischer Fehler (Bias)
2++	Qualitativ hochwertige systematische Übersichten von Fall-Kontroll- oder Kohortenstudien oder qualitativ hochwertige Fall-Kontroll- oder Kohortenstudien mit sehr niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und hoher Wahrscheinlichkeit, dass die Beziehung ursächlich ist
2+	Gut durchgeführte Fall-Kontroll-Studien oder Kohortenstudien mit niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und moderater Wahrscheinlichkeit, dass die Beziehung ursächlich ist
2-	Fall-Kontroll-Studien oder Kohortenstudien mit einem hohen Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und signifikantem Risiko, dass die Beziehung nicht ursächlich ist
3	Nicht-analytische Studien, z. B. Fallberichte, Fallserien
4	Expertenmeinung

- In der Leitlinie werden zu allen evidenzbasierten Statements und Empfehlungen das Evidenzlevel der zugrundeliegenden Studien sowie bei Empfehlungen zusätzlich die Stärke der Empfehlung (Empfehlungsgrad) ausgewiesen. Hinsichtlich der Stärke der Empfehlung werden in dieser Leitlinie drei Empfehlungsgrade unterschieden, die sich auch in der Formulierung der Empfehlungen jeweils widerspiegeln.

Schema der Empfehlungsgraduierung

Empfehlungsgrad	Beschreibung	Syntax
A	Starke Empfehlung	soll
B	Empfehlung	sollte
0	Empfehlung offen	kann

- Als Expertenkonsens (EK) werden Empfehlungen bezeichnet, zu denen keine Recherche nach Literatur durchgeführt wurde. In der Regel adressieren diese Empfehlungen Vorgehensweisen der guten klinischen Praxis, zu denen keine wissenschaftlichen Studien notwendig sind bzw. erwartet werden können. Der Begriff „Expertenkonses“ ersetzt den in den bisherigen Versionen der Leitlinie genutzten Begriff „Good Clinical Practice“ (GCP).

Empfehlungen zur Therapie des hormonsensitiven, metastasierten Prostatakarzinoms

Hintergrundinformationen:

Zum Thema Androgendeprivation beim metastasierten, rezidivierten und progredienten Prostatakarzinom liegt eine evidenzbasierte Leitlinie der ASCO vor, die auf einer systematischen Literaturrecherche beruht und eine explizite Verknüpfung von Evidenz und Empfehlung herstellt [36]. Diese Publikation bildet teilweise die Evidenzgrundlage dieses Kapitels. Die Literaturrecherche für die ASCO-Leitlinien endete im März 2006. Für den Zeitraum von März 2006 bis Oktober 2008 wurde eine Updaterecherche durchgeführt und es wurden relevante Publikationen in einer Evidenztabelle (siehe Evidenzta-bellen zur Leitlinie) hinzugefügt.

Sowohl bezüglich der Indikationsstellung als auch bezüglich anderer Aspekte der Androgendeprivation (AD) lässt sich auf dem Boden der publizierten Analysen die Situation von Patienten mit lokalisiertem PCa nicht sicher von der bei Patienten mit metastasiertem PCa differenzieren. Außerdem existiert kein Nachweis dafür, dass sich hormonnaive Patienten in lokalisierten Tumorstadien bezüglich des Ansprechens auf eine AD an-ders verhalten als solche mit metastasiertem PCa. Demzufolge wurden sowohl in der methodisch guten Metaanalyse von Wilt 2001 als auch in den ASCO-Leitlinien von 2004 bzw. 2007 [36, 695] sowie in der vorliegenden Leitlinie Studienergebnisse von Patienten mit lokalisierten und fortgeschrittenen Stadien für die Empfehlungen herangezogen.

7.17	Evidenzbasiertes Statement	modifiziert 2018
Level of Evidence 1+	Die Möglichkeiten der kombinierten Hormon-Therapie mit Docetaxel oder mit Abira-teron (plus Prednison / Prednisolon) haben die Erstlinienbehandlung des meta-sta-sierten (M1), hormonsensitiven Prostatakarzinoms bei Erstdiagnose grundlegend verändert.	
	Literatur: [736-740]	
	Gesamtabstimmung: 88 %	

7.18	Evidenzbasierte Empfehlung	spezifiziert 2018
Empfehlungsgrad A	Bestandteil der Aufklärung über eine alleinige Androgendeprivation oder eine Kombinationstherapie sollen insbesondere folgende Punkte sein: · der palliative Charakter der Therapie; · Einfluss auf die Lebensqualität; · die unerwünschten Wirkungen.	
Level of Evidence 4	Expertenkonsens basierend auf [686-688, 691, 692]	
	Gesamtabstimmung: 98 %	

7.19	Evidenzbasierte Empfehlung	modifiziert 2018
Empfehlungsgrad B	Patienten in gutem Allgemeinzustand (ECOG 0-1) mit metastasiertem (M1), hormon-sensitiven Prostatakarzinom sollte zusätzlich zur Androgendeprivation eine Chemo-therapie mit Docetaxel oder eine ergänzende antihormonelle Therapie mit Abirate-ron (plus Prednison / Prednisolon) empfohlen werden.	
Level of Evidence 1+	Literatur: [736-740]	
	Gesamtabstimmung: 100 %	

Hintergrundinformationen:

Zu Statement 7.17 Zur Behandlung des hormonsensitiven, metastasierten Prostatakarzinoms wurde bis-lang eine Androgendeprivation empfohlen, und erst im kastrationsresistenten Stadium. eine Chemotherapie. Docetaxel, das in der Kastrationsresistenz verbesserte Überle-bensraten zeigt, wurde nun erstmals auch als Kombinationstherapie mit gleichzeitiger Androgendeprivation im hormonsensitiven Stadium geprüft. Zwei neue Studien, CHAARTED [737] und STAMPEDE [738], zeigten einen bedeutsamen Überlebensvorteil (siehe Tabelle 14) bei früher Chemotherapie ab Beginn der Androgendeprivation bei Patienten mit metastasiertem, hormonsensitivem Prostatakrebs. Diese Ergebnisse le-gen nahe, die Indikation zur Chemotherapie bei Männern in gutem Allgemeinzustand (ECOG 0-1), anders als bislang Standard, bereits in der hormonsensitiven Situation be-gleitend zur Androgendeprivation zu stellen (Docetaxel ist zugelassen für hormonre-fraktäres metastasiertes Prostatakarzinom). Eine alternative Option stellt die Kombina-tionstherapie mit Abirateron (plus Prednison / Prednisolon) dar. In zwei Studien, LATITUDE [739] und STAMPEDE [740] wurde ebenfalls ein Überlebensvorteil im Vergleich zur alleinigen Androgendeprivation bei Patienten mit metastasiertem, hormon-sensitivem Prostatakarzinom gezeigt. Es wird darauf hingewiesen, dass es sich derzeit (Stand: Juni 2017) um eine Off-Label-Therapie handelt.

Zu Empfehlung 7.18 Die Empfehlung zur Aufklärung steht vor dem Hintergrund der informierten Entschei-dung, wie sie guter klinischer Praxis sowie den Anforderungen des Patientenrechte-Gesetzes entspricht. Patienten sollen gemeinsam mit dem aufklärenden Arzt die schwierige Frage der Risikoabwägung entscheiden. Die in Tabelle 14 und Tabelle 16 (siehe Kapitel 7.6) aufgeführten typischen und häufigen Nebenwirkungen von Hor-montherapie und ggf. kombinierter Chemotherapie sollen dem Patienten vermittelt werden.

Zu Empfehlung 7.19 Zur Einschätzung der Effektivität einer Kombinationstherapie von Docetaxel und And-rogendeprivation wurden drei methodisch hochwertige randomisierte klinische Studien sowie eine methodisch hochwertige Metaanalyse [745] identifiziert. In zwei von drei Studien, die eine Kombinationstherapie von Docetaxel mit gleichzeitiger Androgende-privation untersuchten, zeigte sich eine signifikante Verlängerung des Gesamtüberle-bens um 15 bzw. 13,6 Monate (60 vs. 45 bzw. 57,6 vs. 44 Monate; 2.962 bzw. 790 Patienten) [737, 738], die Unterschiede der Ergebnisse einer dritten Studie (62,1 vs. 48,6 Monate; 385 Patienten) waren statistisch nicht signifikant [736]. Das progressionsfreie Überleben bzw. Überleben ohne Therapieversagen war in allen drei Studien durch die Kombinationstherapie signifikant verlängert (Progression: um 10 bzw. 8,5 Monate, Therapieversagen: um 17 Monate). Zwei von drei Studien (CHAARTED und GETUG) führten eine Subgruppenanalyse für Patienten mit hoher Tumorlast durch (in beiden Stu-dien definiert als ‘visceral metastases or ≥4 bone lesions with ≥ 1 beyond vertebral bo-dies and pelvis‘, bei GETUG nur als post-hoc Analyse) und finden deutlich bessere Er-gebnisse für diese Subgruppe. Die Studie mit der größten Population (STAMPEDE) nimmt diese Subgruppenauswertung nicht vor und kommt dennoch zu einem signifikanten Ergebnis für die Gesamtgruppe. Die Leitliniengruppe adressiert diese Sub-gruppe in der Empfehlung daher nicht explizit, spricht aber eine abgeschwächte Empfehlung (sollte) aus. In keiner der drei Studien wurden Subgruppenanalysen hinsichtlich symptomatischen gegenüber asymptomatischen Patienten durchgeführt. Aufgrund der restriktiven Einschlusskriterien der Studien und prognostisch günstigen Faktoren wie einem medianen Alter von 63,5-65 Jahren und den in allen Studien beobachteten ver-mehrten Grad 3-5 Toxizitäten im jeweiligen Docetaxel-Arm wird die Empfehlung für Patienten in gutem Allgemeinzustand mit ECOG-Werten von 0 oder 1 ausgesprochen.

Tabelle 14: Ergebnisse der RCT zur kombinierten Hormon-Chemotherapie

		ADT + Docetaxel	ADT (Studie)	Differenz, Signifikanz
Nutzen:	Gesamtüberleben [Monate]	62,1 57,6 60	48,6 (GETUG) 44 (CHAARTED) 45 (STAMPEDE)	13,5 M., n.s. 13,6 M., p<0,001 15 M., p=0,005
	Subgruppe mit hoher Tumorlast	39,8 49,2	35,1 (GETUG) 32,2 (CHAARTED)	4,7 M., n.s. 17 M., p<0,001
	progressionsfreies Überleben/ failure-free survival	22,9 20,2 37	12,9 (GETUG) 11,7 (CHAARTED) 20 (STAMPEDE)	10 M., p=0,005 8,5 M., p<0,001 17 M., p<0,001
Schaden:	Nebenwirkungen (exemplarisch aus STAMPEDE-Studie, da größtes Patienten-Kollektiv und gute Dokumentation)	52% 15% 12% 10% 8% 7% 6% 5% 4% 3% 3% 1%	32% 1% 0% 12% 3% 4% 6% 2% 6% 3% 2% 0%	Grad 3-5 Ereignisse febrile Neutropenie Neutropenie endokrine Erkrankungen gastrointestinale Erkrankungen Allgemeinerkrankungen muskuloskeletale Erkrankungen respiratorische Erkrankungen renale Erkrankungen kardiale Störungen Erkrankungen des ZNS Nagelveränderungen
	Behandlungs-bedingte Todesfälle	4 1 1	0 (GETUG) 0 (CHAARTED) 0 (STAMPEDE)	

Zur Kombinationstherapie von Abirateron und Androgendeprivation liegen Daten aus zwei methodisch hochwertigen randomisierten klinischen Studien vor [739, 740]. Wäh-rend in der STAMPEDE-Studie – ähnlich wie bereits im Docetaxel-Arm –auch im Abirate-ron-Arm kein Unterschied in der Gruppe der metastasierten Patienten bezüglich der Metastasenlast gemacht wurde, durften in die LATITUDE-Studie ausschließlich Patienten mit hohem Risikoprofil bei neu diagnostizierter Erkrankung eingeschlossen werden (mindestens zwei von drei Risikofaktoren: Gleason Score von 8 oder höher, mindestens drei Knochenmetastasen, viszerale Metastasen). Zum Gesamtüberleben werden sehr ähnliche, statistisch signifikante hazard ratios von 0,62 (95% KI 0,51-0,76) und 0,63 (95% KI 0,52-0,76), jeweils für die gesamte Studienpopulation, berichtet. Stärker ausge-prägt waren die Unterschiede zwischen den Therapie- und Placebo-Gruppen hinsichtlich der Endpunkte progressionsfreies Überleben bzw. failure-free survival mit Differenzen von 13,9 bzw. 18,2 Monaten. Die Raten an Nebenwirkungen waren dagegen zumeist höher in den Kombinationstherapie-Gruppen verglichen mit alleiniger Androgendeprivation (siehe Tabelle 15). Während die STAMPEDE-Studie nur Patienten in gutem Allgemeinzustand (ECOG 0-1) umfasst, durften in die LATITUDE-Studie auch Patienten mit ECOG 2 eingeschlossen werden (Anteil an der Studienpopulation unklar). Da die Nachbeobachtungszeit jedoch kürzer war als in der STAMPEDE-Studie, die Therapie aber wiederum über mehrere Jahre gegeben wird und die kumulative Toxizität nicht abzuschätzen ist, spricht die Leitliniengruppe auch für die Kombinationstherapie mit Abirateron nur für Patienten in gutem Allgemeinzustand eine „sollte“-Empfehlung aus.

Tabelle 15: Ergebnisse der RCT zur Kombinationstherapie mit Abirateron

		ADT + Abirateron	ADT (Studie)	HR/Differenz; Signifikanz
Nutzen:	Gesamtüberleben nach 3 Jahren *	66% 83%	49% (LATITUDE) 76% (STAMPEDE)	0,62; p<0,001 0,63; p<0,001
	progressionsfreies Überleben [Monate]/ failure-free survival	33,0 43,9	14,8 (LATITUDE) 30,0 (STAMPEDE)	18,2 Mo.; HR 0,47; p<0,001 13,9 Mo.; HR 0,29; p<0,001
Schaden:	Nebenwirkungen (exemplarisch aus STAMPEDE-Studie, da größeres Patienten-Kollektiv und längeres Follow-up)	47% 14% 10% 7% 5% 7% 5% 5% 4%	33% 14% 4% 5% 4% 1% 3% 2% 2%	Grad 3-5 Ereignisse endokrine Erkrankungen kardiovask.Erkankungen muskuloskeletale Erkrankungen gastrointestinale Erkrankungen hepatische Erkrankungen Allgemeinerkrankungen respiratorische Erkrankungen abnormale Laborwerte
	Todesfälle im Verlauf der Behandlung	5 9	4 (LATITUDE) 3 (STAMPEDE)	
		* jeweils für die gesamte Studienpopulation; LATITUDE und STAMPEDE unterschieden sich in den Einschlusskriterien		

Da die Therapie mit Abirateron in den vorliegenden Studien langfristig (bis zum Progress) gegeben wurde und es sich im Vergleich zu Docetaxel um ein patentgeschütztes Medikament handelt, sind die wirtschaftlichen Folgen eines breiten Einsatzes in dieser Indikation bislang noch nicht abzusehen.

Für beide Varianten der Kombinationstherapie herrscht Unsicherheit in der Frage, welche Wirksamkeit eine spätere Sequenztherapie im kastrationsresistenten Stadium hat.

7.20	Konsensbasiertes Statement / Empfehlung	neu 2018
EK	Derzeit ist unklar, welche Patientengruppen von welcher Kombinationstherapie den größeren Nutzen haben.	
EK	Die Therapieentscheidung soll abhängig von Patientenpräferenzen, Nebenwirkungen und Begleiterkrankungen getroffen werden.	
	Gesamtabstimmung: 100 %	

7.21	Evidenzbasierte Empfehlung	modifiziert 2018
Empfehlungsgrad A	a. Entscheidet sich der Patient für eine kombinierte Behandlung aus Chemotherapie und Androgendeprivation, soll die Docetaxelgabe innerhalb von 4 Monaten nach Beginn der Androgendeprivation beginnen. Es sollen 6 Zyklen alle drei Wochen in einer Dosierung von 75mg/m² gegeben werden.	
A	b. Entscheidet sich der Patient für eine kombinierte Behandlung aus Androgendeprivation und Abirateron, soll die Abiraterongabe innerhalb von 3 Monaten nach Beginn der Androgendeprivation beginnen. Die Therapie soll in einer Dosierung von 1000 mg/Tag in Kombination mit Prednison oder Prednisolon (5 mg/Tag) gegeben werden.	
A	c. Gründe für einen Abbruch sollen sein: Patientenwunsch, Progress oder intolerable Nebenwirkungen.	
Level of Evidence 1+	Literatur: a: [36, 686, 687, 692] b: [739, 740]	
	Gesamtabstimmung: 98 %	

Hintergrundinformationen:

Zu Empfehlung 7.20. Zu den Vorteilen der einen oder der anderen Variante der Kombinationstherapie für spezifische Patientengruppen kann derzeit noch keine Aussage getroffen werden. In der mehrarmigen STAMPEDE-Studie gab es zwar einen Docetaxel- und einen Abirate-ron-Arm, und es wurde ein stärkerer Effekt hinsichtlich der Zeit bis zum Therapieversagen unter Abirateron als unter Docetaxel berichtet, jedoch nicht im direkten Vergleich. Einerseits wurde in den Studien ein günstigeres Nebenwirkungsprofil von Abirateron beobachtet, andererseits ist die Therapiedauer länger und für Risikopatienten ist die ebenfalls langfristige Gabe von Glucocorticoiden zu bedenken. Daher soll die Wahl der Therapie bei entsprechender Indikation unter Berücksichtigung der Patientenpräferenzen, möglicher Nebenwirkungen sowie dem bestehenden individuellen Komorbiditäts-profil getroffen werden.

Zu Empfehlung 7.21. Die Dosierungsempfehlung 75 mg/m2 alle drei Wochen in sechs Zyklen für die Docetaxelgabe als Kombinationstherapie entspricht der Dosierung und vorranging eingesetzten Frequenz in den RCT zu dieser Fragestellung [737, 738]. Eine Medikation mit 50 mg/m2 alle zwei Wochen wurde in den prospektiven Studien nicht untersucht und wird deshalb nicht empfohlen. Dem längsten Zeitraum in den Evidenz-liefernden Studien entsprechend wird der Beginn der Chemotherapie spätestens 4 Monate nach Beginn der Androgendeprivation empfohlen.

Dem Behandlungsschema der Studien [739, 740] entsprechend soll die Gabe von Abirateron (plus Prednison / Prednisolon) innerhalb der ersten 3 Monate ab Beginn der Androgendeprivation in der entsprechenden Dosierung von 1000 mg/Tag (plus Prednison oder Prednisolon 5 mg/Tag, entsprechend der Dosierung in den RCT) beginnen. Die Therapiedauer ist langfristig angesetzt, jedoch gemäß guter klinischer Praxis bei Krankheitsprogress oder dem Auftreten intolerabler Nebenwirkungen abzubrechen o-der zu modifizieren.

7.22	Evidenzbasierte Empfehlung	geprüft 2018
Empfehlungsgrad A	a. Patienten, die nicht für eine Kombinationsbehandlung in Frage kommen, soll eine Androgendeprivation empfohlen werden.	
0	b. Die Androgendeprivation kann medikamentös oder operativ erfolgen.	
0	c. Die medikamentöse Androgendeprivation kann als Monotherapie oder als maximale Androgenblockade erfolgen.	
B	d. Die Androgendeprivation sollte kontinuierlich durchgeführt werden, wenn der PSA-Wert nach spätestens 7 Monaten nicht unter 4 ng/mL abfällt.	
0	e. Bei Abfall des PSA-Wertes unter 4 ng/mL kann nach ausführlicher Aufklärung alternativ eine intermittierende Hormontherapie angeboten werden.	
Level of Evidence a-c: 1++ d-e: 1(+)	Literatur: [686-688, 691, 692] Literatur: [36, 686, 687, 692] Literatur: [94, 99, 173, 741] d.und e. Literatur: [742-744]	
	Gesamtabstimmung:100 %	

Hintergrundinformationen:

Zu Empfehlung 7.22

a) Eine sofortige hormonablative Therapie ist mit einer Verlängerung des progressi-onsfreien Überlebens verbunden [692]. Wie im Kapitel 6.7 „Primäre hormonablative Therapie und Watchful Waiting“ beim nichtmetastasierten Prostatakarzinom ausgeführt, sind die Ergebnisse jedoch im nichtmetastasierten und ebenso im metasta-sierten Stadium für das Gesamtüberleben nicht eindeutig. Aufgrund der guten An-sprechraten und der Verlängerung des progressionsfreien Überlebens im symptomatischen metastasierten Stadium wird jedoch eine starke Empfehlung zur soforti-gen hormonablativen Therapie ausgesprochen. Die kausale Therapie ist einer symptomatischen Behandlung eindeutig vorzuziehen. Neben einer Verlängerung des progressionsfreien Überlebens gibt es Hinweise darauf, dass eine frühzeitig eingeleitete Androgendeprivation Komplikationen infolge einer Progression der Grunderkrankung (z. B. durch eine pathologische Fraktur) reduziert [695].

Sowohl bezüglich der Indikationsstellung als auch bezüglich anderer Aspekte der Androgendeprivation (AD) lässt sich auf dem Boden der publizierten Analysen die Situation von Patienten mit lokalisiertem Prostatakarzinom nicht sicher von der bei Patienten mit metastasiertem PCa differenzieren. Außerdem existiert kein Nachweis dafür, dass sich hormonnaive Patienten in lokalisierten Tumorstadien bezüg-lich des Ansprechens auf eine AD anders verhalten als solche mit metastasiertem PCa. Demzufolge wurden sowohl in der methodisch guten Metaanalyse von Wilt 2001[692] als auch in den ASCO-Leitlinien von 2004 bzw. 2007 [36, 695] sowie in der vorliegenden Leitlinie Studienergebnisse von Patienten mit lokalisierten und fortgeschrittenen Stadien für die Empfehlungen herangezogen.

b) Eine ähnliche Empfehlung findet sich im Kapitel Watchful Waiting und alleinige hor-monablative Therapie beim nichtmetastasierten Prostatakarzinom. Die Empfehlung zitiert die Substanzen, die in randomisierten kontrollierten Studien wirksam zur AD eingesetzt wurden. Der systematische Review von Wilt 2001 [692] beinhaltet Studien zu Orchiektomie und LHRH-Agonisten. Zusätzlich sind in den Studien der VACURG [697] noch Östrogene bzw. DES eingesetzt worden. Iversen 2006 [686] setzt Bicalutamid ein, Studer 2006 [687] ebenfalls LHRH-Agonisten oder Orchiekto-mie. Der Einsatz von GnRH-Blockern wird aus der ebenso guten Absenkung des Testosteronspiegels wie durch LHRH-Agonisten abgeleitet. Von den GnRH-Antago-nisten sind die Substanzen Abarelix seit 2005 und Degarelix seit Februar 2007 für die Indikation der hormonablativen Therapie des fortgeschrittenen Prostatakarzi-nom zugelassen. Eine Monotherapie mit steroidalen Antiandrogenen ist im Vergleich zu einer LHRH-Analogatherapie mit einem kürzeren progressionsfreien Überleben assoziiert und sollte nicht empfohlen werden [36].

c) Die PCTCG-Metaanalyse [741] mit überwiegend metastasierten Patienten weist ei-nen nicht signifikanten etwa zweiprozentigen Vorteil im Fünf-Jahres-Überleben für Patienten mit maximaler Androgenblockade nach. Eine Subgruppenanalyse der ma-ximalen Androgenblockade mit Nilutamid oder Flutamid ergibt einen signifikanten Fünf-Jahres-Überlebensvorteil zu Gunsten der maximalen Blockade von 3 %. Demgegenüber ist die kombinierte Gabe mit Cyproteronacetat signifikant schlechter als die einfache AD. Insgesamt fiel ein nichtsignifikanter Trend zu mehr Nebenwirkungen in der Gruppe der maximalen AD auf. Aufgrund des geringen Überlebensvor-teils durch die kombinierte AD bei gleichzeitigen Hinweisen auf eine gesteigerte Toxizität und erheblichen Mehrkosten kommen alle drei Quell-Leitlinien [94, 99, 173] zu dem Schluss, dass die maximale AD nicht als Therapie erster Wahl eingesetzt werden soll. Die ASCO-

Leitlinie [36] empfiehlt dagegen eine Berücksichtigung der kombinierten AD (‚should be considered') und begründet dies durch einen me-thodisch von den Autoren dieser Leitlinie als kritisch zu betrachtenden indirekten Analogieschluss aus mehreren Studien [746]. Weiter verweisen die ASCO-Autoren zur Begründung auf eine methodisch schwache Studie von Akaza 2004 (Update in [747]). Die zusätzliche Toxizität von Bicalutamid in der Kombinationstherapie wird von den ASCO-Autoren als minimal bzw. vernachlässigbar klein eingeschätzt. Daraus resultiert die von den übrigen o. g. Leitlinien abweichende Formulierung.

d) Grundlage dieser Empfehlung sind zwei Metaanalysen [742, 743], die jeweils Pri-märstudien zum Vergleich von kontinuierlicher und intermittierender Androgende-privation zusammenfassen. Die Mehrheit der eingeschlossenen Studien, inklusive der größten Studie mit mehr als eintausend Patienten [744], hatte als Einschlusskri-terium für eine Randomisierung zwischen kontinuierlicher oder intermittierender Therapie das Absinken des PSA-Wertes nach einer mehrmonatigen Induktionsphase (bis zu 7 Monate) unter 4 ng/ml. Für Patienten mit höheren Werten nach der ADT-Induktionsphase liegen nach Ansicht der Leitliniengruppe ungenügende Daten zur Wirksamkeit und Sicherheit einer intermittierenden ADT vor, sodass sie für diese Indikation nicht empfohlen wird.

e) In den vorliegenden, zusammengefassten Studien überwiegend moderater Qualität wurden Patienten unterschiedlicher Stadien eingeschlossen und keine entsprechenden Subgruppenanalysen durchgeführt. Die Metaanalysen, ebenso wie die größte Studie, welche ausschließlich metastasierte Stadien einschloss, können keine eindeutige Unter- oder Überlegenheit einer der Therapieoptionen hinsichtlich Gesamt- oder Krebs-spezifischem Überleben sowie der Zeitdauer bis zum Fortschreiten der Krankheit belegen. Allerdings zeigt die Hussain-Studie einen nicht signifikanten Überlebensvorteil von median 5,8 vs. 5,1 Jahren für die kontinuierliche ADT bei deutlichen Limitationen. Auch bezüglich des Schadenspotentials durch Nebenwirkungen sowie Auswirkungen auf die Lebensqualität ist die Datenlage unklar oder nicht ausreichend vorhanden, deshalb sollen die individuellen Voraussetzungen des Patienten besonders berücksichtigt werden. Die 2016 aktualisierte EAU-Leitlinie [748] spricht ebenfalls eine kann-Empfehlung zur intermittierenden Therapie nach entsprechender Induktionsphase bei metastasierten Patienten aus.

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CLINICAL PRACTICE GUIDELINE GU-010 Version 1

Advanced/ Metastatic Prostate Cancer

Leitlinienorganisation/Fragestellung

- How should advanced/ metastatic prostate cancer be treated?
- How should advanced/ metastatic prostate cancer patients be followed after treatment?

Methodik

Grundlage der Leitlinie

This guideline was originally developed to include early stage prostate cancer in 2005 (updated in January 2009, January 2011, September 2013, October 2014, March 2015) and subsequently split into an advanced/ metastatic only guideline in June 2018.

- Repräsentatives Gremium unklar, keine Patientenvertreter*innen;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse (Delphi Prozess) und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- For the 2018 guideline updates, PubMed was searched; Inclusion criteria: phase III clinical trials, published between January 1, 2010 and June 1, 2018, English language.

LoE/GoR

- Critical Appraisal of the Evidence: The Knowledge Management Specialist (KMS) synthesizes the relevant details of the studies included from the literature search into evidence tables. The quality of the included primary studies is rated by the KMS and reviewed with the Guideline Working Group members according to the following criteria:

Level I – evidence from at least one large randomized controlled trial (RCT) of good methodological quality with low potential for bias or meta-analyses of RCTs without heterogeneity

Level II – small RCTs, large RCTs with potential bias, meta-analyses including such trials, or RCTs with heterogeneity

Level III – prospective cohort studies

Level IV – retrospective cohort studies or case-control studies

Level V – studies without a control group, case reports, or expert opinions

- The strength of the recommendations will be rated by the GWG members according to the following criteria originally developed by the Infectious Diseases Society of America and adapted for use by the European Society for Medical Oncology (ESMO):

Grade A – strongly recommended; strong evidence for efficacy with a substantial clinical benefit

Grade B – generally recommended; strong or moderate evidence for efficacy but with a limited clinical benefit

Grade C – optional; insufficient evidence for efficacy or benefit does not outweigh the risks/disadvantages

Grade D – generally not recommended; moderate evidence against efficacy or for adverse outcomes

Grade E – never recommended; strong evidence against efficacy or for adverse outcomes

Empfehlungen

Castrate Sensitive Metastatic Disease (Stage T1-4, N0-1, M+)

Indications include symptomatic disease or asymptomatic disease.

Staging

• Physical Exam.

• PSA, testosterone, CBC and differential, Aspartate transaminase (AST), Alanine transamine (ALT), creatinine, Blood urea nitrogen (BUN) within the last 1 month.

• Bone scan (within the last 3 months).

• CT scan, (abdomen and pelvis, +/- chest) (within the last 3 months).

Management

1. Androgen Deprivation Therapy is the backbone of therapy. Medical and surgical castration are equivalent in terms of efficacy and both are viable options. Lower rates of fracture, peripheral arterial disease, and cardiac-related complications have been reported in surgical castration patients when compared to medical castration patients in a large retrospective cohort study.4

A. Castrate level serum testosterone can cause a number of undesirable side effects. For this reason intermittent ADT has theoretical advantages, however, in patients with metastatic

prostate cancer continuous ADT is recommended unless survival is considered secondary to quality of life. The phase III intergroup trial reported that intermittent ADT cannot be considered non-inferior compared to continuous ADT in terms of overall survival.5,6

B. Medical castration

i. Treatment with an LHRH analogue (agonist ex: Leuprolide or antagonist ex: Degarelix)

a. When first introduced, a non-steroidal antiandrogen (e.g. bicalutamide 50 mg daily, flutamide 250 mg three times a day or nilutamide 300mg daily) should be given concurrently with the first administration of LHRH for 2 weeks to 1 month in order to block the potential initial testosterone flare.

b. The non-steroidal antiandrogen should be administered concurrently with the first LHRH analogue injection and continue for a minimum of 14 days afterward.

c. Medical and surgical castration is equally effective and the risks, benefits, and economic implications should be discussed with the patient.

ii. Treatment with gonadotropin-releasing hormone (GnRH)

a. The GnRH antagonist Degarelix is as effective at suppressing testosterone and may achieve testosterone suppression faster7 than GnRH Agonists. Treatment with a GnRH antagonist (Degarelix) avoids the risk of testosterone ‘flare” that occurs with GnRH agonists.7,8 Treatment

with a GnRH antagonist eliminates the need for concomitant administration of a non-steroidal anti androgen.

b. PSA reduction occurred significantly faster with Degarelix when compared to GnRH agonists without increases in treatment related side effects.7

c. No survival benefit has been demonstrated with Degarelix compared to traditional LHRH agonists and injections are administered monthly.

d. Degarelix is not presently funded in Alberta.

C. Single agent antiandrogens

i. Monotherapy with non-steroidal AA is inferior to medical castration with LHRH or GnRH agents. However, it may be considered for rare circumstances. To date there is insufficient data to recommend bicalutamide at 150 mg/day (not Health Canada approved). Options include:

ii. Biclutamide 50 mg orally once a day.

iii. Flutamide 250 mg orally three times daily.

iv. Nilutamide 300 mg orally once a day for one month, then decrease to 150 mg daily.

D. Patients undergoing androgen deprivation therapy for prostate cancer have an improved quality of life if they continue to be physically active. Patients should be counseled on the role of maintaining physical fitness and activity while on hormonal therapy.9

NOTE: Ongoing total androgen blockade (e.g. castration with LHRH agonist/antagonist plus a nonsteroidal antiandrogen) is not recommended.

2. Systemic Therapy

A. Chemotherapy

i. All patients presenting with metastatic castrate sensitive prostate cancer who are starting ADT should be considered for docetaxel chemotherapy

ii. Data from the CHAARTED trial10 demonstrated significant overall survival benefit of 13 months when docetaxel was administered to patients with castrate sensitive metastatic prostate cancer who are about to start or just have recently (within 4 months) started hormonal therapy. The greatest benefit was seen in patients with high volume disease (defined as the presence of visceral metastases or >4 bony lesions with 1 beyond the vertebral bodies and pelvis),

iii. Data from the STAMPEDE trial11 demonstrated a significant overall survival benefit of 14 months in all patients with metastatic CSPC.

iv. Patients with high volume disease castrate sensitive metastatic prostate cancer who are about to or just recently started hormonal therapy should be offered 6 cycles of docetaxel chemotherapy at 75 mg/m2 every 3 weeks (given with or without prednisone). Hormone therapy as above is carried throughout and after docetaxel completion.

B. Abiraterone Acetate (Currently not publicly funded in Alberta as of June 2018)

i. The phase 3 LATUTUDE trial (N=1199) demonstrated that ADT plus 1000mg abiraterone acetate (plus 5 mg prednisone) daily resulted in superior median overall survival (not reached

vs. 34.7m; HR 0.62, 95%CI 0.51-0.76, p<0.001) and improved pain progression, time to subsequent therapy for prostate cancer, time to initiation of chemotherapy, and PSA progression (all p<0.001) versus ADT plus placebo in newly diagnosed, metastatic, castration-sensitive prostate cancer patients. Rates of grade 3 hypertension and hypokalemia were higher in the abiraterone group compared to placebo.12

ii. The phase 3 STAMPEDE trial (N=1917) randomized patients with metastatic disease (52%), node-positive or node-indeterminate M0 disease (20%) or node-negative M0 disease (28%) of which 95% were newly diagnosed to received ADT alone or in combination with abiraterone acetate (1000 mg daily with 5mg daily prednisolone). The ADT plus abiraterone group showed superior survival (HR: 0.63, 95%CI: 0.52-0.76, p<0.001). HR was 0.75 in patients with M0 disease vs 0.61 in patients with M1 disease. Grade 3 to 5 adverse events were higher in the combination group (47% vs. 33%).13

C. – There is insufficient evidence to recommend one strategy over another (Docetaxel vs Abiraterone). Clinical decision making should be based on patient factors and access.

3. Consideration of clinical trials is recommended.

Follow-up

Frequency:

• If on chemotherapy or abiraterone acetate, patients should be evaluated as per standard protocol.

• If on ADT alone: q3–6 months following the initiation of therapy to evaluate and then as clinically indicated

• Duration: age-dependent.

Biochemical Recurrence3

Following prostatectomy

• Any rise in PSA.

Following radiotherapy with or without hormonal therapy

• Rise by 2 ng/mL (mcg/L) or more above the nadir PSA (defined as the lowest PSA achieved).

• Date of failure should be determined “at call” and not backdated.

• Patients not meeting these PSA criteria for failure who undergo salvage therapies should also be declared as failures at the time a positive biopsy is obtained or salvage therapy is administered.

Patients with Rising PSA after Curative Intent Treatment without Metastases

It is recommended that patients be referred to a cancer clinic or re-referred to their treating urologist. Please refer to definition of biochemical recurrence above.

Staging

• Bone scan

• CT scan

• MRI

• Consideration for prostate re-biopsy

Post-radical prostatectomy recurrence

• Radiotherapy with or without concurrent or adjuvant ADT is recommended

• Observation is also an option, depending on the findings during staging

Post- radiotherapy recurrence

Recommended options include:

• Active surveillance within a cancer clinic

• Cryosurgery

• Brachytherapy

• ADT

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American Society of Clinical Oncology (ASCO)

Optimizing Anticancer Therapy in Metastatic Non-Castrate Prostate Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Leitlinienorganisation/Fragestellung

This clinical practice guideline addresses abiraterone or docetaxel with androgen-deprivation therapy (ADT) for metastatic prostate cancer that has not been treated (or has been minimally treated) with testosterone-lowering agents.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Fully published English-language reports of phase III RCTs published from 2015 through October 2017, rigorously conducted systematic reviews, or meta-analyses

LoE

Guide for Rating Quality of Evidence

Rating for Strength of Evidence	Definition
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (i.e., balance of benefits *v* harms) and that further research is very unlikely to change either the magnitude or direction of this net effect.
Intermediate	Moderate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect.
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change either the magnitude and/or direction this net effect.
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. The use of the consensus opinion of experts is reasonable to inform outcomes related to the topic.

GoR

Guide for Strength of Recommendations

Rating for Strength of Recommendation	Definition
Strong	There is high confidence that the recommendation reflects best practice. This is based on (1) strong evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, with no or minor exceptions; (3) minor or no concerns about study quality; and/or (4) the extent of Expert Panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on (1) good evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, with minor and/or few exceptions; (3) minor and/or few concerns about study quality; and/or (4) the extent of Expert Panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on (1) limited evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, but with important exceptions; (3) concerns about study quality; and/or (4) the extent of Expert Panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

Empfehlungen

For subsets of men with newly diagnosed metastatic noncastrate disease, treatment with abiraterone or docetaxel in combination with ADT should be offered on the basis of prolonging life relative to ADTalone. For docetaxel, the data are most compelling for men with de novo high-volume metastatic noncastrate prostate cancer (defined as four or more bone metastases, one or more of which is outside of the spine or pelvis, and/or the presence of any visceral disease) who are chemotherapy candidates. The appropriate regimen of docetaxel is six doses of docetaxel administered every 3 weeks at 75 mg/m2 either alone (per CHAARTED) or with prednisolone (per STAMPEDE) (Type: evidence based, benefits outweigh harms; Evidence quality: strong; Strength of recommendation: high).

ADT Plus Docetaxel

- For men with metastatic non-castrate prostate cancer with high-volume disease (HVD) per CHAARTED who are candidates for treatment with chemotherapy, the addition of docetaxel to ADT should be offered (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong for patients with HVD as per CHAARTED).
- For patients with low-volume disease (LVD) per CHAARTED who are candidates for chemotherapy, docetaxel plus ADT may be offered (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: moderate for patients with LVD as per CHAARTED).
- The appropriate regimen of docetaxel is six doses of docetaxel administered every 3 weeks at 75 mg/m2 either alone (per CHAARTED) or with prednisolone (per STAMPEDE) (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

ADT Plus Abiraterone

- For men with high-risk de novo metastatic non-castrate prostate cancer, the addition of abiraterone to ADT should be offered per LATITUDE (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong for patients with high-risk disease per LATITUDE).
- For men with lower-risk de novo metastatic non-castrate prostate cancer, abiraterone may be offered per STAMPEDE (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: moderate for patients with lower-risk disease per STAMPEDE).
- The appropriate regimen is abiraterone 1,000 mg with either prednisolone or prednisone 5 mg once daily until treatment(s) for mCRPC are initiated (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Qualifying Statements

- The strongest evidence of benefit for docetaxel is for those men who were diagnosed with de novometastatic disease or HVD per CHAARTED (defined as four or more bone metastases, one or more of which is outside of the spine or pelvis, and/or the presence of any visceral disease). The criteria are agnostic to the presence or absence of nodal disease.
- Men who do not fit into these categories may be offered docetaxel; however, the strength of the evidence to support an OS benefit is less compelling for men who do not have de novo metastatic disease and/or who do not meet the HVD criteria. A subset analysis of CHAARTED did not demonstrate a survival benefit for low-volume disease, and the GETUG-15 trial was negative.
- LATITUDE examined the benefits of abiraterone acetate in newly diagnosed men with metastatic non-castrate disease defined by high-risk factors associated with a poor prognosis including at least two of the following high-risk factors: a Gleason score ≥ 8, at least three bone lesions, and presence ofmeasurable visceral disease. STAMPEDE did not include a high risk definition.
- The addition of either docetaxel or abiraterone to ADT in men with newly diagnosed metastatic prostate cancer offers a survival benefit as compared with the use of ADTalone. The strongest evidence of benefit with docetaxel is in men with de novo metastatic HVD, whereas the data in other patients with metastatic disease are less clear. LATITUDE and STAMPEDE are mutually supportive for treating high-risk disease with ADTand abiraterone, with only STAMPEDE furnishing evidence that includes men with lower-risk disease.

- In the absence of randomized data comparing the addition of docetaxel versus abiraterone to ADT in men with metastatic non-castrate disease, additional variables including patient comorbidities, toxicity, QOL considerations, drug availability, and cost will ultimately need to be taken into consideration.

Hintergrundinformationen:

Three prospective randomized studies (GETUG-AFU 15, STAMPEDE, and CHAARTED) examined overall survival (OS) with adding docetaxel to ADT. STAMPEDE and CHAARTED favored docetaxel (hazard ratio [HR], 0.78; 95% CI, 0.66 to 0.93; n = 2,962 and HR, 0.73; 95% CI, 0.59 to 0.89; n = 790, respectively). GETUG-AFU 15 was negative. LATITUDE and STAMPEDE examined the impact on OS of adding abiraterone (with prednisone or prednisolone) to ADT. LATITUDE and STAMPEDE favored abiraterone (HR, 0.62; 95% CI, 0.51 to 0.76; n = 1,199 and HR, 0.63; 95% CI, 0.52 to 0.76; n = 1,917, respectively).

Table 3. Quality Assessment

Source	Adequate Randomization	Concealed Allocation	Sufficient Sample Size	Similar Groups	Blinded	Validated and Reliable Measures	Adequate Follow-Up	Intention-to-Treat Analysis	Insignificant COIs	Overall Potential Risk of Bias
ADT ± abiraterone										
Fizazi et al, 2017[13]; LATITUDE 2013-2014	+	+	+	+	+	+	+	NR	—	Moderate
James et al, 2017[12]; STAMPEDE 2011-2014	+	—	+	+	—	+	+	+	+	Low
ADT ± docetaxel										
James et al, 2016[11]; STAMPEDE	+	—	+	+	—	+	+	+	+	Low
Sweeney et al, 2015,[10] 2016[9]; CHAARTED	+	—	+	+	—	+	+	+	+	Low
Gravis et al, 2013,[6] 2016[5]; GETUG-15	+	—	+	+	—	+	+	+	+	Low

NOTE. +, criterion met; —, criterion not met.
Abbreviations: CHAARTED, Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer; COI, conflict of interest; GETUG-15, Groupe d'Etude des Tumeurs Uro-Genital–Association Française d'Urologie; LATITUDE, A Randomized, Double-blind, Comparative Study of Abiraterone Acetate Plus Low-Dose Prednisone Plus Androgen Deprivation Therapy (ADT) Versus ADT Alone in Newly Diagnosed Subjects With High-Risk, Metastatic Hormone-naive Prostate Cancer (mHNPC); NR, not reported; STAMPEDE, Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy.

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Lowrance W et al, 2020 [14].

American Urological Association (AUA), American Society for Radiation Oncology (ASTRO), Society of Urologic Oncology (SUO)

Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline

Leitlinienorganisation/Fragestellung

The management of advanced prostate cancer is rapidly evolving. Clinicians are challenged to remain up-to-date and informed with respect to a multitude of treatment options for patients with advanced prostate cancer. To assist in clinical decision-making, evidence-based guideline statements were developed to provide a rational basis for evidence-based treatment. This guideline covers advanced prostate cancer, including disease stages that range from prostate-specific antigen (PSA) recurrence after exhaustion of local treatment options to widespread metastatic disease.

Methodik

Grundlage der Leitlinie

The systematic review utilized to inform this guideline was conducted by an independent methodological consultant. Determination of the guideline scope and review of the final systematic review to inform guideline statements was conducted in conjunction with the Advanced Prostate Cancer Panel.

Recherche/Suchzeitraum:

A research librarian conducted searches in Ovid MEDLINE (1998 to January Week 5 2019), Cochrane Central Register of Controlled Trials (through December 2018), and Cochrane Database of Systematic Reviews (2005 through February 6, 2019). An updated search was conducted prior to publication through January 20, 2020. The methodology team supplemented rearches of electronic databases with the studies included in the prior AUA review and by reviewing reference lists of relevant articles.

LoE & GoR

Table 1: Strength of Evidence Definitions

AUA Strength of Evidence Category	GRADE Certainty Rating	Definition
A	High	• We are very confident that the true effect lies close to that of the estimate of the effect
B	Moderate	• We are moderately confident in the effect estimate • The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
C	Low Very Low	• Our confidence in the effect estimate is limited • The true effect may be substantially different from the estimate of the effect • We have very little confidence in the effect estimate • The true effect is likely to be substantially different from the estimate of effect

Table 2: AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/ Burden, and Body of Evidence Strength

Evidence Grade	Evidence Strength A (High Certainty)	Evidence Strength B (Moderate Certainty)	Evidence Strength C (Low Certainty)
Strong Recommendation (Net benefit or harm substantial)	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is substantial -Applies to most patients in most circumstances and future research is unlikely to change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is substantial -Applies to most patients in most circumstances but better evidence could change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) appears substantial -Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation)
Moderate Recommendation (Net benefit or harm moderate)	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is moderate -Applies to most patients in most circumstances and future research is unlikely to change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is moderate -Applies to most patients in most circumstances but better evidence could change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) appears moderate -Applies to most patients in most circumstances but better evidence is likely to change confidence
Conditional Recommendation (Net benefit or harm comparable to other options)	-Benefits=Risks/Burdens -Best action depends on individual patient circumstances -Future Research is unlikely to change confidence	-Benefits= Risks/Burdens -Best action appears to depend on individual patient circumstances -Better evidence could change confidence	-Balance between Benefits & Risks/Burdens unclear -Net benefit (or net harm) comparable to other options -Alternative strategies may be equally reasonable -Better evidence likely to change confidence
Clinical Principle	a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature		
Expert Opinion	a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there may or may not be evidence in the medical literature		

Empfehlungen

Metastatic Hormone-Sensitive Prostate Cancer

Treatment

14. Clinicians should offer ADT with either LHRH agonists or antagonists or surgical castration in patients with mHSPC. (Strong Recommendation; Evidence Level: Grade B)

Erläuterung:

The use of primary ADT for the management of mHSPC has been the SOC since its discovery by Huggins and colleagues in the 1940's.78 Castrate levels of testosterone (<50ng/dL) may be achieved with LHRH analogues, gonadotropin-releasing hormone (GnRH) antagonists or orchiectomy. These treatments are considered equivalent in cancer control, although they have never been compared in large RCTs. GnRH antagonists and orchiectomy as monotherapy have a rapid onset of action and avoid the 'testosterone flare' seen with LHRH analogues alone making them useful in situations needing rapid hormone ablation such as impending spinal cord compression.

15. In patients with mHSPC, clinicians should offer continued ADT in combination with either androgen pathway directed therapy (abiraterone acetate plus prednisone, apalutamide, enzalutamide) or chemotherapy (docetaxel). (Strong Recommendation; Evidence Level: Grade A)

Erläuterung:

mHSPC remains an incurable manifestation of the disease. While ADT, with or without nonsteroidal antiandrogens, has been the backbone of mHSPC treatment for many decades, ADT alone is no longer considered sufficient treatment for mHSPC. In just the past five years, multiple studies have shown that additional therapy significantly extends OS and PFS in mHSPC patients.

Docetaxel

Docetaxel is a potent inhibitor of microtubule assembly and disassembly. Since 2015, two clinical trials demonstrated the benefits of adding docetaxel chemotherapy to ADT for mHSPC patients. In the phase III CHAARTED study,67 790 patients with mHSPC were equally randomly assigned to receive either ADT in combination with docetaxel (75 mg/m2) for up to 6 cycles or ADT alone. At a median follow-up of 53.7 months, the median OS was 57.6 months for the chemohormonal therapy arm versus 47.2 months for ADT alone (HR=0.72; 95%CI 0.59 to 0.89; P= .0018. The median time to clinical progression was 33.0 months for the combination arm versus 19.8 months in the ADT alone arm (HR in the combination arm= 0.62; 95%CI 0.51 to 0.75; P < .001).

Similarly, in the STAMPEDE trial,[10] ADT plus docetaxel significantly improved median OS compared with ADT alone. The study randomly assigned 2,962 men 2:1:1:1 to receive SOC defined as hormone therapy for at least 2 years, SOC plus zoledronic acid, SOC plus docetaxel, or SOC with zoledronic acid and docetaxel. Docetaxel (75 mg/m2) was given for six 3-week cycles with prednisolone (10mg) daily. Patients were followed up 6-weekly to 6 months, 12-weekly to 2 years, 6-monthly to 5 years, then annually. At a median follow up of 43 months, median OS was 71 months for SOC compared to 81 months for SOC plus docetaxel (HR=0.78; 95%CI 0.66 to 0.93; p=0.006). SOC plus docetaxel also improved median failure-free survival at 37 months compared 20 months with SOC alone.

Like many chemotherapy agents, docetaxel has a significant toxicity profile that needs consideration. In the STAMPEDE trial, the most frequently reported adverse events in the SOC plus docetaxel group included febrile neutropenia (15%), general disorder (including lethargy, fever, asthenia—7%), and gastrointestinal disorder (including diarrhea, abdominal pain, constipation, vomiting—8%).10

Abiraterone Acetate

Abiraterone acetate is a nonsteroidal irreversible inhibitor of CYP17A1, which catalyzes the conversion of C21 progesterone precursors to C19 adrenal androgens, DHEA and androstenedione.79 In essence, abiraterone acetate is similar to ADT, but it is more potent, inhibiting gonadal and extragonadal androgen synthesis.

In the double-blind, placebo-controlled, phase 3 LATITUDE trial,[28] 1,199 patients were randomly assigned to receive either ADT plus abiraterone acetate (1,000mg daily, given once daily as four 250mg tablets) plus prednisone (5mg daily) or ADT plus placebo. The primary endpoints were OS and radiographic PFS. After a median follow-up of 30.4 months at a planned interim analysis, the median OS was significantly longer in the abiraterone acetate group than in the placebo group (not reached versus 34.7 months) (HR= 0.62; 95%CI 0.51 to 0.76; P<0.001). The median length of radiographic PFS was 33.0 months in the abiraterone acetate group and 14.8 months in the placebo group (HR= 0.47; 95%CI 0.39 to 0.55; P<0.001).

In the STAMPEDE trial,80 1,917 patients were randomized in a 1:1 ratio to receive ADT alone or ADT plus abiraterone acetate (1,000mg daily) and prednisolone (5 mg daily). A total of 52% of patients had metastatic disease. The primary outcome was OS. The median follow-up was 40 months. There were 184 deaths in the abiraterone acetate group compared with 262 in the ADT group (HR= 0.63; 95%CI 0.52 to 0.76; P<0.001); the HR was 0.61 in those with metastatic disease.

Abiraterone acetate can elevate liver enzyme levels, and should be avoided in patients where liver toxicity is a concern. As such, clinicians should monitor liver enzymes as well as potassium levels. Adverse events in the LATITUDE trial28 included mineralocorticoid-related hypertension (20%) and hypokalemia (10%). Further, the use of a steroid in combination with

treatments for metastatic disease may require additional considerations for patients with comorbid conditions, such as diabetes or significant osteoporosis.

Apalutamide

Apalutamide is a nonsteroidal anti-androgen. This oral agent acts as an AR inhibitor that binds directly to the ligand-binding domain of the AR. Apalutamide inhibits AR nuclear translocation, inhibits DNA binding, and impedes AR-mediated transcription.[81] In the double-blind, phase 3 TITAN study,[82] 525 patients were assigned to receive apalutamide (240mg daily) with ADT compared to 527 patients receiving placebo plus ADT. Primary endpoints included radiographic PFS and OS. At a median of 22.7 months follow up, the percentage of patients with radiographic PFS at 24 months was 68.2% in the apalutamide group compared to 47.5% in the placebo group (HR= 0.48; 95%CI 0.39 to 0.60; P<0.001). OS at 24 months was greater with apalutamide compared to placebo (82.4% versus 73.5%; HR= 0.67; 95%CI 0.51 to 0.89; P=0.005). Rash of any grade was more common among patients who received apalutamide compared to those who received placebo (27.1% versus 8.5%).

Enzalutamide

Enzalutamide is a novel AR signaling inhibitor. It is a competitive inhibitor of androgen binding and also inhibits nuclear translocation of the AR, DNA binding and coactivator recruitment.83 In the open-label, randomized, phase 3 ENZAMET trial,[84] 1,125 men were randomized to receive testosterone suppression plus either open-label enzalutamide (160mg daily) or a standard nonsteroidal antiandrogen therapy (bicalutamide, nilutamide, or flutamide—standard care). The primary end point was OS. With a median follow up of 34 months, there were 102 deaths in the enzalutamide group compared to 143 deaths in the standard care group (HR= 0.67; 95%CI 0.52 to 0.86; P= 0.002). Kaplan-Meier estimates of OS at 3 years were 80% in the enzalutamide group an 72% in the standard care group.

Discontinuation of treatment due to adverse events was more frequent in the enzalutamide group (33 events versus 14 events, respectively). Fatigue was more common in the enzalutamide group, and seizures occurred in 7 patients in the enzalutamide group (1%) compared to 0 patients in the standard care group. In this trial, approximately 16% of patients also received docetaxel and in this study did not impact on the observed benefit of enzalutamide. This trial did not address the role of early intensification by adding docetaxel to enzalutamide. Several ongoing studies including ARASENS (NCT02799602 docetaxel with/without darolutamide) will prospectively address this question, until data are available, combination therapy in this setting is not indicated.

In the double-blind, phase III ARCHES trial, Armstrong et al. randomly assigned 1,150 men with mHSPC in a 1:1 ratio to receive either enzalutamide (160 mg per day) or placebo. All patients also received ADT. The primary endpoint was radiographic PFS. As of October 2018, the risk of radiographic PFS or death was significantly reduced with enzalutamide plus ADT versus placebo plus ADT (median not reached versus 19.0 months; HR= 0.39; 95%CI 0.30 to 0.50; P<.001. Similar improvements were also seen in risk of PSA progression, initiation of new antineoplastic therapy, first symptomatic skeletal event, castration-resistance, and reduced risk of pain progression.

Both enzalutamide and apalutamide do present a small risk of seizures, so patients with a seizure disorder should instead choose a drug like abiraterone acetate plus prednisone or docetaxel.

Unfortunately, no comparative data on efficacy exist between these four options. The clinician should consider factors like age and comorbidities when choosing chemotherapy, where toxicity might be more difficult for older patients than fit younger patients. Cost can sometimes be a factor as well when patients are selecting treatment as some options are costly and not always routinely covered for some patients. Finally, duration of treatment may influence choice. Some patients might prefer a limited 18-week course of docetaxel to daily oral therapy for years. Further, no trials have found a benefit for using both docetaxel and enzalutamide/apalutamide as of yet, though ongoing trials will more directly address this. For now such combinations are not recommended.

In terms of intermittent ADT, SWOG 9346 [85] evaluated intermittent ADT compared with continuous ADT and did not demonstrate non-inferiority in mHSPC. In fact, there was a non-significant benefit in OS with continuous ADT. Given all of the recent data suggesting that additional therapy (chemotherapy or androgen receptor-targeted therapy [ART]) added to continuous ADT significantly improves OS, the Panel generally advises against intermittent ADT in otherwise healthy patients with mHSPC.

16. In selected mHSPC patients with low-volume metastatic disease, clinicians may offer primary radiotherapy to the prostate in combination with ADT. (Conditional Recommendation; Evidence Level: Grade C)

Erläuterung:

Two recent Phase III randomized trials examining ADT and prostate radiotherapy versus ADT alone in men with metastatic prostate cancer demonstrated no difference in OS. However, the subgroup analysis for the low-volume group in STAMPEDE Arm H revealed a survival benefit in patients with low-volume metastatic cancer.64 Given this was a secondary analysis, and that few of the patients had received optimized systemic therapy, the Panel provides a conditional recommendation for ADT plus radiation as an option for patients with minimal metastatic disease willing to undergo the risks associated with local therapy.

The HORRAD trial reported on 432 patients randomized either to ADT alone or ADT with EBRT to the prostate.[86] Median PSA was 142ng/mL, and 67% of patients had more than 5 osseous metastases by conventional imaging. OS was not different

(HR= 0.9; 95%; CI 0.7 to 1.14; p=0.4), but median time to PSA progression was improved in the EBRT arm (HR= 0.78; 95%; CI 0.63 to 0.97; p=0.02). A hypothesis was generated that survival might be improved in a subgroup of patients with low metastatic burden (HR= 0.68; 95%; CI 0.42 to 1.10). In the STAMPEDE trial, 2,061 men with metastatic HSPC were randomized to ADT alone versus ADT plus prostate radiation given at moderate doses and with unconventional fractionation (36Gy in 6 fractions over 6 weeks, or 55Gy in 20 daily fractions).[64] Radiotherapy improved failure-free survival (HR=0.76; 95%CI 0.68 to 0.84; p<0.0001), but not OS (HR=0.92; 95%CI 0.80 to 1.06; p=0.266) similar to HORRAD. An additional pre-specified analysis utilizing the CHAARTED definition of low-volume cancer encompassing 40% of the population was performed. Low-volume metastatic disease demonstrated a benefit to ADT plus radiation (HR= 0.68; 95% CI 0.52 to 0.90; p= 0,007) with 3-year survival 73% with ADT alone versus 81% with ADT and radiotherapy. Toxicity is important to minimize in patients who will not be cured of their metastatic disease. There was no significant difference in grade ≥3 toxicity with the addition of radiotherapy (HR= 1.01; 95%CI 0.87 to 1.16; p= .94).

Physicians have suggested these results point to the benefits of local therapy raising the question whether radical prostatectomy might have the same results. These trials are ongoing, and at present the use of surgery should be considered investigational and only conducted within the context of a trial. In the STAMPEDE trial,64 no patients had concurrent abiraterone acetate, and only 18% had early docetaxel so no clear recommendation can be made about other drug combinations combined with prostate radiation in the metastatic setting.

17. Clinicians should not offer first generation antiandrogens (bicalutamide, flutamide, nilutamide) in combination with LHRH agonists in patients with mHSPC, except to block testosterone flare. (Strong Recommendation; Evidence Level: Grade A)

Erläuterung:

With compelling level A evidence supporting the use of docetaxel, abiraterone acetate plus prednisone, apalutamide, or enzalutamide in combination with ADT in men with newly diagnosed mHSPC, the Panel believes that long-term use of first generation antiandrogens bicalutamide, flutamide, nilutamide in lieu of the above noted agents cannot be supported.

In the first week after LHRH agonists are administered, there is typically a surge in luteinizing hormone resulting in an increase in circulating testosterone. This may cause clinical “flares,” which may be associated with worsening of disease symptoms (e.g., bone pain, urinary tract obstruction) in approximately 10% of patients. This surge can be “blocked” by short term (i.e., 4 weeks or less) of a first-generation antiandrogen, although there is limited evidence of significant clinical utility.[87]

18. Clinicians should not offer oral androgen pathway directed therapy (e.g., abiraterone acetate plus prednisone, apalutamide, bicalutamide, darolutomide, enzalutamide, flutamide, nilutamide) without ADT for patients with mHSPC. (Expert Opinion)

Erläuterung:

Non-steroidal antiandrogen therapy without ADT in advanced prostate cancer is not recommended. Evidence based on 11 studies encompassing 3,060 patients suggests that use of non-steroidal antiandrogens without ADT compared with medical or surgical castration monotherapy for advanced prostate cancer is less effective in terms of OS, clinical progression, treatment failure, and treatment discontinuation due to adverse events.[88]

Bicalutamide, flutamide and nilutamide are first generation antiandrogens extensively studied in combination with either bilateral orchiectomy or LHRH agonists in mHSPC.89-93 There is insufficient evidence to support the use of first generation antiandrogens as monotherapy.[89,94-96]

Abiraterone acetate is an inhibitor of CYP17, and apalutamide, darolutamide and enzalutamide are second generation antiandrogens. None of these agents have been studied without ADT for mHSPC, while compelling evidence of survival has been demonstrated with testosterone suppression in combination with either abiraterone acetate plus prednisone, enzalutamide, or apalutamide.[28,80,82,84,97,98] For now, however, these next generation antiandrogens should not be considered without ADT in mHSPC.

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Mottet N et al., 2019 [17].

EAU, EANM, ESTRO, ESUR, SIOG:

Guidelines on Prostate Cancer

Zielsetzung/Fragestellung

The Prostate Cancer (PCa) Guidelines Panel have prepared this guidelines document to assist medical professionals in the evidence-based management of PCa.

The EAU PCa Guidelines were first published in 2001. This 2020 document presents a limited update of the 2019 PCa Guidelines publication.

Methodik

Grundlage der Leitlinie

- The PCa Guidelines Panel consists of an international multidisciplinary group of urologists, radiation oncologists, medical oncologists, radiologists, a pathologist and a patient representative.
- All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website Uroweb: http://uroweb.org/guideline/ prostatecancer/?type=panel.
- For the 2020 PCa Guidelines, new and relevant evidence has been identified, collated and appraised through a comprehensive review of the GRADE forms [see definition below) and

associated recommendation. Changes in recommendations were only considered on the basis of high level evidence (i.e. systematic reviews [SRs] with meta-analysis, randomised controlled trials [RCTs], and prospective comparative studies) published in the English language. A total of 223 additional references were added to the 2020 PCa Guidelines.

- For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology;
- Formale Konsensusprozesse und externes Begutachtungsverfahren nicht dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Keine Angabe

LoE

Table 4. EAU Guideline's levels of evidence

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

GoR

Table 5. EAU Guideline's grades of recommendation

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial
B	Based on well-conducted clinical studies, but without randomised clinical trials
C	Made despite the absence of directly applicable clinical studies of good quality

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Empfehlungen

6.4.9 Guidelines for the first-line treatment of metastatic disease

Recommendations	Strength rating
Offer immediate systemic treatment with androgen deprivation therapy (ADT) to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction) to M1 symptomatic patients.	Strong
Offer luteinising hormone-releasing hormone (LHRH) antagonists, especially to patients with an impending spinal cord compression or bladder outlet obstruction.	Weak
Offer surgery and/or local radiotherapy to any patient with M1 disease and evidence of impending complications such as spinal cord compression or pathological fracture.	Strong
Offer immediate systemic treatment also to M1 patients asymptomatic from their tumour.	Weak
Discuss deferred ADT with well-informed M1 patients asymptomatic from their tumour since it lowers the treatment-related side-effects, provided the patient is closely monitored.	Weak
Offer short-term administration of an older generation androgen receptor (AR) antagonist to M1 patients starting LHRH agonist to reduce the risk of the 'flare-up' phenomenon.	Weak
Do not offer AR antagonists monotherapy to patients with M1 disease.	Strong
Offer ADT combined with chemotherapy (docetaxel) to patients whose first presentation is M1 disease and who are fit for docetaxel.	Strong
Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients whose first presentation is M1 disease and who are fit enough for the regimen.	Strong
Offer ADT combined with prostate radiotherapy to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria.	Strong
Do not offer ADT combined with any local treatment (radiotherapy/surgery) to patients with high volume (CHAARTED criteria) M1 disease outside of clinical trials (except for symptom control).	Strong

Hintergrundinformationen:

6.4.3 First-line hormonal treatment

Primary ADT has been the standard of care for over 50 years [606]. There is no high level evidence in favour of a specific type of ADT, neither for orchiectomy or for an LHRH analogue or antagonist, with the exception of patients with impending spinal cord compression for whom either a bilateral orchidectomy or LHRH antagonists are the preferred options.

6.4.3.1 Non-steroidal anti-androgen monotherapy

Based on a Cochrane review comparing non-steroidal anti-androgen (NSAA) monotherapy to castration (either medical or surgical), NSAA was considered to be less effective in terms of OS, clinical progression, treatment failure and treatment discontinuation due to adverse events [922]. The evidence quality of the studies included

in this review was rated as moderate.

6.4.3.2 Intermittent versus continuous androgen deprivation therapy

Three independent reviews [923-925] and two meta-analyses [926, 927], looked at the clinical efficacy of intermittent androgen deprivation (IAD) therapy. All of these reviews included 8 RCTs of which only 3 were conducted in patients with exclusively M1 disease. The 5 remaining trials included different patient groups, mainly locally advanced and metastatic patients relapsing.

So far, the SWOG 9346 is the largest trial addressing IAD in M1b patients [928]. Out of 3,040 screened patients, only 1,535 patients met the inclusion criteria. This highlights that, at best, only 50% of M1b patients can be

expected to be candidates for IAD, i.e. the best PSA responders. This was a non-inferiority trial leading to inconclusive results: the actual upper limit was above the pre-specified 90% upper limit of 1.2 (HR: 1.1; CI: 0.99-1.23), the pre-specified non-inferiority limit was not achieved, and the results did not show a significant

inferiority for any treatment arm. However, based on this study inferior survival with IAD cannot be completely ruled out.

Other trials did not show any survival difference with an overall HR for OS of 1.02 (0.94-1.11) [923].

These reviews and the meta-analyses came to the conclusion that a difference in OS or CSS between IAD and continuous ADT is unlikely. A recent review of the available phase III trials highlighted the limitations of most trials and suggested a cautious interpretation of the non-inferiority results [929]. None of the trials that addressed IAD vs. continuous ADT in M1

patients showed a survival benefit, but there was a constant trend towards improved OS and PFS with continuous ADT. However, most of these trials were non-inferiority trials. In some cohorts the negative impact on sexual function was less pronounced with IAD. There is a trend favouring IAD in terms of QoL, especially regarding treatment-related side-effects, such as hot flushes [930, 931].

6.4.3.3 Immediate versus deferred androgen deprivation therapy

In symptomatic patients immediate treatment is mandatory, however, controversy still exists for asymptomatic metastatic patients due to the lack of quality studies. A first Cochrane review extracted four RCTs: the VACURG I and II trials, the MRC trial, and the ECOG 7887 study [920, 922]. These studies were conducted in the pre-PSA era and included patients with advanced metastatic or non-metastatic PCa who received immediate vs. deferred ADT [932]. No improvement in PCa CSS was observed, although immediate ADT significantly reduced disease progression. The Cochrane analysis was updated in 2019 and concluded that early ADT probably extends time to death of any cause and time to death from PCa [933]. Since the analysis

included only a very limited number of M1 patients who were not evaluated separately, the benefit of immediate ADT in this setting remains unclear.

6.4.4 Combination therapies

All of the following combination therapies have been studied with continuous ADT, not intermittent ADT.

6.4.4.1 Complete androgen blockade

The largest RCT in 1,286 M1b patients found no difference between surgical castration with or without flutamide [934]. However, results with other anti-androgens or castration modalities have differed and systematic reviews have shown that CAB using a NSAA appears to provide a small survival advantage (< 5%) vs. monotherapy (surgical castration or LHRH agonists) [935, 936] beyond 5 years of survival [937] but this minimal advantage in a small subset of patients must be balanced against the increased side-effects associated with long-term use of NSAAs.

6.4.4.2 Androgen deprivation combined with other agents

6.4.4.2.1 Androgen deprivation therapy combined with chemotherapy

Three large RCTs were conducted [679, 915, 938]. All trials compared ADT alone as the standard of care with ADT combined with immediate docetaxel (75 mg/sqm, every 3 weeks within 3 months of ADT initiation). The primary objective in all three studies was OS. The key findings are summarised in Table 6.4.3.

Table 6.4.3: Key findings - Hormonal treatment combined with chemotherapy

	STAMPEDE James [679]		GETUG Gravis [938]		CHAARTED Sweeney [915]	
	ADT	ADT + Docetaxel + P	ADT	ADT + Docetaxel	ADT	ADT + Docetaxel
n	1,184	592	193	192	393	397
Newly diagnosed M+	58%	59%	75%	67%	73%	73%
Key inclusion criteria	Patients scheduled for long-term ADT - newly diagnosed M1 or N+ situations - locally advanced (at least two of cT3 cT4, ISUP grade ≥ 4, PSA ≥ 40 ng/mL) - relapsing locally treated disease with a PSA > 4 ng/mL and a PSA-DT < 6 mo. or PSA > 20 ng/mL or nodal or metastatic relapse		Metastatic disease Karnofsky score ≥ 70%		Metastatic disease ECOG PS 0, 1 or 2	
Primary objective	OS		OS		OS	
Median follow up (mo)	43		50		29	
HR (95% CI)	0.78 (0.66-0.93)		1.01 (0.75-1.36)		0.61 (0.47-0.80)	
M1 only						
n	1,086		-		-	
HR (95% CI)	0.76 (0.62-0.92)		-		-	

ADT = androgen deprivation therapy; ECOG = Eastern Cooperative Oncology Group; FU = follow-up; HR = hazard ratio; ISUP = ISUP = International Society for Urological Pathology; mo = month; n = number of patients; OS = overall survival; P = prednisone; PSA-DT = prostate-specific antigen-doubling time.

In the GETUG 15 trial, all patients had newly diagnosed M1 PCa, either de novo or after a primary treatment [938]. They were stratified based on previous treatment, and Glass risk factors [912]. In the CHAARTED trial, the same inclusion criteria applied and patients were stratified according to disease volume; high volume being defined as either presence of visceral metastases or four, or more, bone metastases, with at least one outside the spine and pelvis [915].

STAMPEDE is a multi-arm multi-stage trial in which the reference arm (ADT monotherapy) included 1,184 patients. One of the experimental arms was docetaxel combined with ADT (n = 593), another was docetaxel combined with zoledronic acid (n = 593). Patients were included with either M1, or N1, or having two of the following 3 criteria: T3/4, PSA > 40 ng/mL or ISUP grade 4-5. Also relapsed patients after local treatment were included if they met one of the following criteria: PSA > 4 ng/mL with a PSA-DT < 6 months or a PSA > 20 ng/mL, N1 or M1. No stratification was used regarding metastatic disease volume (high/low volume) [679].

In all 3 trials toxicity was mainly haematological with around 12-15% grade 3-4 neutropenia, and 6-12% grade 3-4 febrile neutropenia. The use of granulocyte colony-stimulating factor receptor (GCSF) was shown to be beneficial in reducing febrile neutropenia. Primary or secondary prophylaxis with GCSF should be based on available guidelines [939, 940].

Based on these data, upfront docetaxel combined with ADT should be considered as a standard in men presenting with metastases at first presentation, provided they are fit enough to receive the drug [940].

Docetaxel is used at the standard dose of 75 mg/sqm combined with steroids as pre-medication. Continuous oral corticosteroid therapy is not mandatory.

In subgroup analyses from GETUG-AFU 15 and CHAARTED the beneficial effect of the addition of docetaxel to ADT is most evident in men with de novo metastatic high-volume disease [916, 917], while it was in the same range whatever the volume in the post-hoc analysis from STAMPEDE [941]. The effects were less apparent in men who had prior local treatment although the numbers were small and the event rates lower.

A recent systematic review and meta-analysis which included these 3 trials showed that the addition of docetaxel to standard of care improved survival [940]. The HR of 0.77 (95% CI: 0.68-0.87; p < 0.0001) translates to an absolute improvement in 4-year survival of 9% (95% CI: 5-14). Docetaxel in addition to standard of care also improves failure-free survival, with a HR of 0.64 (0.58-0.70; p < 0.0001) translating into a reduction in absolute 4-year failure rates of 16% (95% CI: 12-19). 6.4.4.2.2 Combination with the new hormonal treatments (abiraterone, enzalutamide)

In two large RCTs (STAMPEDE, LATITUDE) the addition of abiraterone acetate (1000 mg daily) plus prednisone (5 mg daily) to ADT in men with hormone-sensitive PCa (mHSPC) was studied [35, 921, 942]. The primary objective of both trials

was an improvement in OS. Both trials showed a significant OS benefit, but in LATITUDE in high-risk metastatic patients only with a HR of 0.62 (0.51-0.76) [921]. The HR in STAMPEDE was very similar with 0.63 (0.52-0.76) in the total patient population (metastatic and non-metastatic) and a HR of 0.61 in the subgroup of metastatic patients [35]. The inclusion criteria in the two trials differed, but both trials were positive for OS. While only high-risk patients were included in the LATITUDE trial, a post-hoc analysis from STAMPEDE showed the same benefit whatever the risk or the volume stratification [943].

All secondary objectives such as PFS, time to radiographic progression, time to pain, or time to chemotherapy were positive and in favour of the combination. The key findings are summarised in Table 6.4.4. No difference in treatment-related deaths was observed with the combination of ADT plus abiraterone acetate and prednisone compared to ADT monotherapy [HR: 1.37 (0.82-2.29]. However, twice as many patients discontinued treatment due to toxicity in the combination arms in STAMPEDE (20%) compared to LATITUDE (12%). Based on these data, upfront abiraterone acetate plus prednisone combined with ADT should be considered as a standard in men presenting with metastases at first presentation, provided they are fit enough to receive the drug (see Table 6.4.4) [942].

In three large RCTs (ENZAMET, ARCHES and TITAN) the addition of AR antagonists to ADT in men with hormone-sensitive PCa (mHSPC) was tested [944-946]. In ARCHES the primary endpoint was radiographic progression-free survival (rPFS). Radiographic PFS was significantly improved for the combination of enzalutamide and ADT with a HR of 0.39 (0.3-0.5). Approximately 36% of the patients had low-volume disease; around 25% had prior local therapy and 18% of the patients had received prior docetaxel. In ENZAMET the primary endpoint was OS. The addition of enzalutamide to ADT improved OS with a HR of 0.67 (0.52-0.86).

Approximately half of the patients had concomitant docetaxel; about 40% had prior local therapy and about half of the patients had low-volume disease [946]. In the TITAN trial, apalutamide was used as AR antagonist with rPFS and OS as co-primary endpoints. Radiographic PFS was significantly improved by the addition of apalutamide with a HR of 0.48 (0.39-0.6); OS at 24 months was improved for the combination with a HR of0.67 (0.51-0.89). In this trial 16% of patients had prior local therapy, 37% had low-volume disease and 11% received prior docetaxel [944].

In summary, the addition of AR antagonists significantly improves clinical outcomes with no

convincing evidence of differences between subgroups. Again the majority of patients treated had de novo metastatic disease and the evidence is most compelling in this situation. It may still be considered for men progressing after local therapy but this men make up a smaller fraction of the included patients. Lastly, whether the addition of an AR antagonist plus docetaxel adds further benefit is currently not clear as longer follow-up is needed. At the moment, since toxicity clearly increases, AR antagonists plus docetaxel should not be given outside of clinical trials.

Table 6.4.4: Results from the STAMPEDE arm G and LATITUDE studies

	STAMPEDE [James] [35]		**LATITUDE [Fizazi]** [921]	
	ADT	ADT + AA + P	ADT + placebo	ADT + AA + P
n	957	960	597	602
Newly diagnosed N+	20%	19%	0	0
Newly diagnosed M+	50%	48%	100%	100%
Key inclusion criteria	Patients scheduled for long-term ADT - newly diagnosed M1 or N+ situations - locally advanced (at least two of cT3 cT4, ISUP grade ≥ 4, PSA ≥ 40 ng/mL) - relapsing locally treated disease with a PSA > 4 ng/mL and a PSA-DT < 6 mo. or PSA > 20 ng/mL or nodal or metastatic relapse		Newly diagnosed M1 disease and 2 out of the 3 risk factors: ISUP grade ≥ 4, ≥ 3 bone lesions, measurable visceral metastasis	
Primary objective	OS		OS Radiographic PFS	
Median follow up (mo)	40		30.4	
3-yr. OS	83% (ADT + AA + P) 76% (ADT)		66% (ADT + AA + P) 49% (ADT + placebo)	
HR (95% CI)	0.63 (0.52 - 0.76)		0.62 (0.51-0.76)	
M1 only				
n	1,002		1,199	
3-yr. OS	NA		66% (ADT + AA + P) 49% (ADT + placebo)	
HR (95% CI)	0.61 (0.49-0.75)		0.62 (0.51-0.76)	
HR	Failure-free survival (biological, radiological, clinical or death): 0.29 (0.25-0.34)		Radiographic PFS: 0.49 (0.39-0.53)	

AA = abiraterone acetate; ADT = androgen deprivation therapy; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; mo = month; n = number of patients; NA = not available; OS = overall survival; P = prednisone; PFS = progression-free survival; PSA = prostate-specific antigen; yr. = year.

Table 6.4.5 Results from the ENZAMET and TITAN studies

	ENZAMET [945]		**TITAN** [944]	
	ADT+ older antagonist +/-docetaxel (SOC)	ADT + enzalutamide +/-docetaxel	ADT + placebo	ADT + apalutamide
n	562	563	527	525
Newly diagnosed M+	48%	48%	100%	100%
Low volume	47%	48%	36%	38%
Primary objective	OS		OS Radiographic PFS	
Median follow up (mo)	34		30.4	
3-yr. OS	3-yr survival: 80% (ADT + enzalutamide) 72% (SOC)		2-yr survival: 84% (ADT + apalutamide) 74% (ADT + placebo)	
HR (95% CI) for OS	0.67 (0.52-0.86)		0.67 (0.51-0.89)	

ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; mo = month; n = number of patients; NA = not available; OS = overall survival; SOC = standard of care; PFS = progression-free survival; yr = year.

6.4.5 Treatment selection and patient selection

There are no head-to-head data comparing 6 cycles of docetaxel and the long-term use of abiraterone acetate plus prednisone in newly diagnosed mHSPC. However, for a period, patients in STAMPEDE were randomised to either the addition of abiraterone or docetaxel to standard of care. Data from the two experimental arms has been extracted although this was not pre-specified in the protocol and therefore the data were not powered for this comparison. The survival advantage for both drugs appeared similar [947]. A recent meta-analysis also found no significant OK benefit for either drug [948]. In the STOPCAP systematic review and meta-analysis, abiraterone acetate plus prednisone was found to have the highest probability of being the most effective treatment [949]. Both modalities have different and agent-specific side-effects

and require strict monitoring of side-effects during treatment. Therefore, the choice will most likely be driven by patient preference, the specific side-effects, availability and cost.

6.4.6 Deferred treatment for metastatic PCa (stage M1)

The only candidates with metastasised disease who may possibly be considered for deferred treatment are asymptomatic patients with a strong wish to avoid treatment-related side-effects. However, since the median survival is only 42 months, the time without treatment (before symptoms) is short in most cases. The risk of developing symptoms, and even dying from PCa, without receiving any benefit from hormone treatment has been highlighted [674, 683]. Patients with deferred treatment for advanced PCa must be amenable to close follow-up.

6.4.7 Treatment of the primary tumour in newly diagnosed metastatic disease

The first reported trial evaluating prostate RT in men with metastatic castration-sensitive disease was the HORRAD trial. 432 patients were randomised to ADT alone or ADT plus EBRT to the prostate. Overall survival was not significantly different (HR: 0.9 [0.7-1.14]), median time to PSA progression was significantly improved in the RT arm (HR: 0.78 [0.63-0.97]) [950]. The STAMPEDE trial evaluated 2,061 men with mCSPC who were randomised to ADT alone vs. ADT plus RT to the prostate. This trial confirmed radiotherapy to the primary tumour did not improve OS in unselected patients [918]. However, following the results from CHAARTED, and prior to analysing the data, the original screening investigations were retrieved and patients categorised as low- or high volume. In the low-volume subgroup (n = 819) there was a significant OS benefit by the addition of prostate RT. Therefore RT of the prostate in patients with low-volume metastatic disease should be considered.

Of note, only 18% of these patients had additional docetaxel, and no patients had additional abiraterone acetate plus prednisone so no clear recommendation can be made about triple combinations. In addition, it is not clear if these data can be extrapolated to RP as local treatment, results of ongoing trials are awaited.

In a recent systematic review and meta-analysis including the above two RCTs, the authors found that, overall, there was no evidence that the addition of prostate RT to ADT improved survival in unselected patients (HR: 0.92, 95% CI: 0.81-1.04, p = 0.195; heterogeneity chi-square = 0.08, degree of freedom = 1, p = 0.78) [951]. However, there was a clear difference in the effect of metastatic burden on survival, with an absolute improvement of 7% in 3-year survival in men who had four or fewer bone metastases.

6.4.8 Metastasis-directed therapy

In patients relapsing after a local treatment, a metastases-targeting therapy has been proposed, with the aim to delay systemic treatment. There is one randomised phase II trial testing metastasis-directed therapy (MDT) vs. surveillance in men with oligo-recurrent PCa. Oligo-recurrence was defined as < 3 lesions on pet-choline only. The sample size was small with 62 patients and only about half of them had nodal disease. Androgen deprivation therapy-free survival was the primary end-point which was longer with MDT than with surveillance [952]. Currently there is no data to suggest an improvement in OS. A systematic review highlighted that at this time this approach must, as yet, be considered as experimental [902].

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National Institute for Health and Care Excellence (NICE), 2019 [18].

NICE

Prostate cancer: diagnosis and management.

[B] Evidence review for docetaxel in people with hormone sensitive prostate cancer.

NICE guideline NG131. Evidence review

Zielsetzung/Fragestellung

- What is the most clinically- and cost-effective scheduling of docetaxel added to standard treatment for the treatment of hormone-sensitive locally-advanced prostate cancer?
- What is the most clinically- and cost-effective scheduling of docetaxel added to standard treatment for the treatment of hormone-sensitive metastatic prostate cancer?

This review was conducted as part of a larger update of the NICE Prostate Cancer guideline (CG175).

Methodik

Grundlage der Leitlinie

- transparentes Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Source searched for this review question: Cochrane Database of Systematic Reviews – CDSR (Wiley), Cochrane Central Register of Controlled Trials – CENTRAL (Wiley), Database of Abstracts of Reviews of Effects – DARE (Wiley), Health Technology Assessment Database – HTA (Wiley), EMBASE (Ovid), MEDLINE (Ovid), MEDLINE In-Process (Ovid), PubMed (NLM)
- The clinical searches were conducted in October 2017

LoE/ GoR

- Keine Angaben

Sonstige methodische Hinweise

- Die nachfolgend dargestellten Empfehlungen zur Behandlung der metastasierten Prostatakarzinoms entstammen der Online-Publikation der NICE-Leitlinie. Die Hintergrundinformationen (Review) adressieren ausschließlich das metastatisierte hormonsensitive Prostatakarzinom und gehören zur Empfehlung 1.5.6.
- Es ist unklar, weshalb die NICE-Leitlinie keine GoR/LoE für die einzelnen Empfehlungen aufführt. Die Informationen zur Methdodik beziehen sich ausschließlich auf das Review zum metastatisierten hormonsensitiven Prostatakarzinom.

Empfehlungen

1.5 Metastatic prostate cancer

Treatment

1.5.6 Offer docetaxel chemotherapy to people with newly diagnosed metastatic prostate cancer[1] who do not have significant comorbidities as follows:

- start treatment within 12 weeks of starting androgen deprivation therapy and
- use six 3-weekly cycles at a dose of 75 mg/m2 (with or without daily prednisolone). [2019]

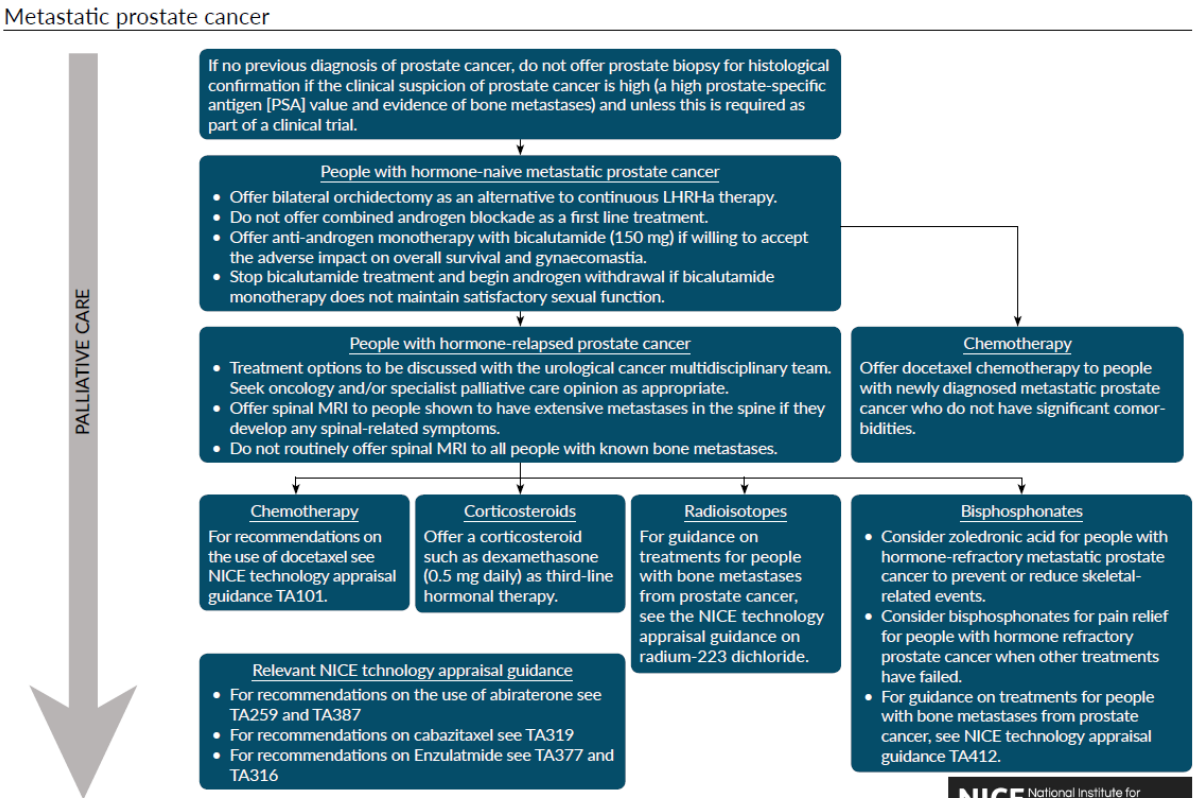
To find out why the committee made the 2019 recommendation on docetaxel chemotherapy and how they might affect practice, see rationale and impact.

1.5.7 Offer bilateral orchidectomy to all people with metastatic prostate cancer as an alternative to continuous luteinising hormone-releasing hormone agonist therapy. [2008]

1.5.8 Do not offer combined androgen blockade as a first-line treatment for people with metastatic prostate cancer. [2008]

1.5.9 For people with metastatic prostate cancer who are willing to accept the adverse impact on overall survival and gynaecomastia with the aim of retaining sexual function, offer anti-androgen monotherapy with bicalutamide[6] (150 mg). [2008]

1.5.10 Begin androgen deprivation therapy and stop bicalutamide treatment in people with metastatic prostate cancer who are taking bicalutamide monotherapy and who do not maintain satisfactory sexual function. [2008]



Hintergrundinformation:

Hormone-sensitive metastatic prostate cancer

Three randomised controlled trials where included in this review. All three unique studies where directly applicable as they adhered to the protocol.

Table 3: Docetaxel doses used in the studies

Study (location)	Study arms (total sample size)	Doses
STAMPEDE James 2016 (United Kingdom)	ADT (plus radiotherapy) versus ADT plus docetaxel	75mg/m2 every 3 weeks for 6 cycles with 10mg of prednisolone daily and standard premedication before each injection
STAMPEDE James 2016 (United Kingdom)	ADT plus zoledronic acid versus ADT plus zoledronic acid plus docetaxel	75mg/m2 of docetaxel every 3 weeks for 6 cycles with 10mg of prednisolone daily and standard premedication before each injection 4mg of zoledronic acid every 3-4 weeks for 2 years
GETUG-15 Gravis 2013 (France)	ADT alone versus ADT plus docetaxel	75mg/m^2 of intravenous docetaxel in a 250cm^3 5% glucose solution in the course of 1h on the first of each 21 day cycle for up to 9 cycles. Premedication with corticosteroid (8mg dexamethasone or equivalent) given orally in the evening before the infusion of docetaxel on the day of docetaxel infusion and on the next day.
CHAARTED Sweeney 2015 (USA)	ADT (luteinizing hormone-releasing hormone agonist or luteinizing hormone-releasing hormone antagonist or surgical castration) versus ADT plus docetaxel	75mg/m2 of docetaxel every 3 weeks for 6 cycles, with 8mg of oral dexamethasone at 12 hours, 3 hours and 1 hour before docetaxel infusion. Daily prednisolone was not required.

Outcomes and sample sizes

The reported outcomes where data was extractable were

• Overall survival

• Clinical progression-free survival defined as failure-free survival expressed as time from randomisation to first evidence of at least one of-: biochemical failure (defined as a rise of 50% above the within-24-week nadir and above 4ng/ml confirmed by rest or treatment), progression either locally, in lymph nodes, or in distant metastases or death from cancer (STAMPEDE James et al. 2016)

• Biochemical progression free survival.

• Prostate cancer-specific survival

• Quality of life

The sample sizes ranged from 385 to 1,776 participants across the studies

Adverse outcomes were only reported for the treatment arm, therefore analysis could not be carried out. An adverse outcome table is included in appendix E.

Hormone-sensitive metastatic prostate cancer

Short Title	Title	New column	New column
Gravis (2013)	Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial	**Study type** Randomised controlled trial **Associated studies** Gravis G, Boher J M, Joly F, Soulie M, Albiges L, Priou F, Latorzeff I, Delva R, Krakowski I, Laguerre B, Rolland F, Theodore C, Deplanque G, Ferrero J M, Culine S, Mourey L, Beuzeboc P, Habibian M, Oudard S, and Fizazi K (2016) Androgen Deprivation Therapy (ADT) Plus Docetaxel Versus ADT Alone in Metastatic Non castrate Prostate Cancer: Impact of Metastatic Burden and Long-term Survival Analysis of the Randomized Phase 3 GETUG-AFU15 Trial. European Urology 70(2), 256-262 **Study details** Study location 29 Centres in France and 1 centre in Belgium Study setting Hospital Study dates	**Random sequence generation** Low risk of bias Randomisation was done by a clinical research organisation and was centralised nationally. **Allocation concealment** High risk of bias Patients, physicians, and data analysts were not masked to treatment allocation **Blinding of participants and personnel** High risk of bias Open label study **Blinding of outcome assessment** High risk of bias Open label study **Incomplete outcome data** Low risk of bias

Short Title	Title	New column	New column
		Oct 18, 2004, and Dec 31, 2008 Duration of follow-up Median follow-up 6 years, 11 months **Sources of funding** French Health Ministry and Institut National du Cancer (PHRC), Sanofi -Aventis, AstraZeneca, and Amgen **Inclusion criteria** Aged more than 18 years Histologically confirmed adenocarcinoma and radiologically proved metastases Karnofsky score of at least 70%; A life expectancy of at least 3 months Adequate hepatic, haematological and renal function **Exclusion criteria** Previous chemotherapy for metastatic disease severe cardiac disease Had surgical castration before metastatic disease occurred had peripheral neuropathy (at least grade 2) A history of another cancer in the past 5 years **Sample characteristics** Sample size 385 patients Split between study groups %female all male - prostate cancer Mean age (SD) ADT plus docetaxel - 63(57-68) ADT alone - 64(58-70) **Interventions** ADT and Docetaxel patients received 75 mg/m² intravenous docetaxel in a 250 cm³ 5% glucose solution in the course of 1 h on the	none identified **Selective reporting** Low risk of bias none identified **Overall risk of bias** Moderate Patients, physicians, and data analysts were not masked to treatment allocation. the study was an open label study, however as the primary outcomes are subjective the study was rated as moderate risk of bias **Directness** Directly applicable

Short Title	Title	New column	New column
		first day of each 21-day cycle. Treatment with docetaxel continued for up to nine cycles on the basis of the median exposure reported in the TAX 327 trial, ADT alone **Outcome measure(s)** Overall survival Clinical progression-free survival; cPFS biochemical progression-free survival; bPFS	
James (2016)	Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial	**Study type** Randomised controlled trial **Study details** Study setting Hospital **Study dates** October 2005 and March 2013 Duration of follow-up 6 weekly to 6 months, 12 weekly to 2 years, 6 monthly to 5 years then annually (Median follow up – 3 years, 6 months) **Sources of funding** Cancer Research Uk, MedicalResearch Council, Novartis, Sanofi-Aventis, Pfizer, Janssen, Astellas, NIHR Clinical Research Network, Swiss Group for Clinical Cancer Research **Inclusion criteria** Newly diagnosed with prostate cancer- as metastatic, node positive or high-risk locally advanced (with at least two of T3/4, Gleason score of 8-10, and prostate-specific >/= 40ng/ml) Or previously treated with radical surgery, radiotherapy or both and relapsing with high-risk features	**Random sequence generation** Low risk of bias Patients were randomised centrally using a computerised algorithm, developed and maintained by the trials unit. **Allocation concealment** High risk of bias Authors state "..Masking to treatment allocation was considered impracticable and of limited value given the primary outcome measure" **Blinding of participants and personnel** High risk of bias As above **Blinding of outcome assessment** Low risk of bias Authors state "Cause of death was determined by masked central review..." **Incomplete outcome data** Low risk of bias None identified

Short Title	Title	New column	New column
		No age restrictions **Exclusion criteria** severe cardiac disease **Sample characteristics** Sample size 1776 patients Split between study groups Mean age (SD) Median age (range) = 65 years (40-84) **Interventions** Docetaxel and standard of care 75mg/m2 was given for six 3-weekly cycles with 10mg of prednisolone daily and standard premedication before each injection. Standard of care Hormone therapy for at least 2 years with gonadotropin-releasing hormone agonists or antagonists or only between 2006 and 2011 for patients with non-metastatic disease, oral anti-androgens alone. Radiotherapy was encouraged for patients with N0M0 disease until November 2011. Outcome measure(s) Overall survival Failure-free survival Time from randomisation to 1st evidence of at least one of the following - biochemical failure, progression either locally, in lymph nodes or in distant metastases or death from prostate cancer	**Selective reporting** Low risk of bias None identified **Other sources of bias** Unclear risk of bias the exclusion criteria mentioned that participants had to be newly diagnosed with prostate cancer, 6% of participants had recurrent Prostate cancer **Overall risk of bias** Moderate No details were provided on sequence generation and blinding, however as the primary outcomes are subjective the study was rated as moderate risk of bias **Directness** Directly applicable
Sweeney (2015)	Chemohormonal therapy in metastatic	**Study type** Randomised controlled trial	**Random sequence generation** High risk of bias The study was randomised however no details

Short Title	Title	New column	New column
	hormone-sensitive prostate cancer	**Study details** Study location Study setting Hospitals **Study dates** July, 2006– November, 2012 Duration of follow up Median follow-up 2 years, 5 months Sources of funding National cancer institut, National Institutes of Health, Department of Health and Human Services and by grants from the Public health services, Sanofi provided the docetaxel and grant to ECOG-ACRIN **Inclusion criteria** Pathological disease of prostate cancer or dora clinical scenario consistent with prostate cancer elevated PSA Radiologic evidence of metastatic disease ECOG performance score of 0, 1, 2 Planned use of combined androgen blockade for more than 30 days or agents approved for prevention of skeletal related events in castration disease (zoledronic acid or denosumab) **Exclusion criteria** None reported **Sample characteristics** Sample size 790 patients Split between study groups Mean age (SD) Not provided - median (range) =64years (36-91)	provided on random sequence generation **Allocation concealment** Unclear risk of bias no details provided **Blinding of participants and personnel** Unclear risk of bias No details provided **Blinding of outcome assessment** Unclear risk of bias no details provided **Incomplete outcome data** Low risk of bias none identified **Selective reporting** Low risk of bias none identified **Other sources of bias** Low risk of bias none identified **Overall risk of bias** Moderate No details were provided on sequence generation and blinding, however as the primary outcomes are subjective the study was rated as moderate risk of bias **Directness** Directly applicable

Short Title	Title	New column	New column
		Interventions ADT and Docetaxel 75mg/m2 every 3 weeks for 6 cycles ADT alone **Outcome measure(s)** Overall survival Clinical progression-free survival; cPFS Time to castration-resistant prostate cancer	

Table 9: Adverse events - Metastatic prostate cancer

Study	Authors description of adverse events	Number (%)
CHAARTED Sweeney 2016	Only docetaxel group was reported - 1 patient had a grade 5 adverse event. 111 patients had grade 3-4 adverse events. The most frequent adverse events were neutropenia (12.1%), febrile neutropenia (6.1%) and fatigue 4.1%	111/390 (28%)
GETUG-15 Gravis 2013	2 patients had grade 5 adverse events. It is unclear how many patients had at least one grade 3-4 adverse event. The most frequent adverse events at grade 3-5 were neutropenia (32%, febrile neutropenia (7%), erectile dysfunction (8%) and decreased lobido (6%)	
STAMPEDE James 2016 (also applies to the locally advanced prostate cancer)	5 patients had grade 5 adverse events and 298 patients had grade 3-5 adverse events in the group that received docetaxel treatment. The most frequent adverse events were endocrine disorder (10% of the intervention group), febrenile neutropenia (15% of the intervention group) and neutropenia (12% of the intervention group)	

Quality assessment of clinical studies included in the evidence review

full GRADE tables

Hormone-sensitive metastatic prostate cancer

Docetaxel (combined with ADT) versus Standard of Care (hormone therapy or ADT)

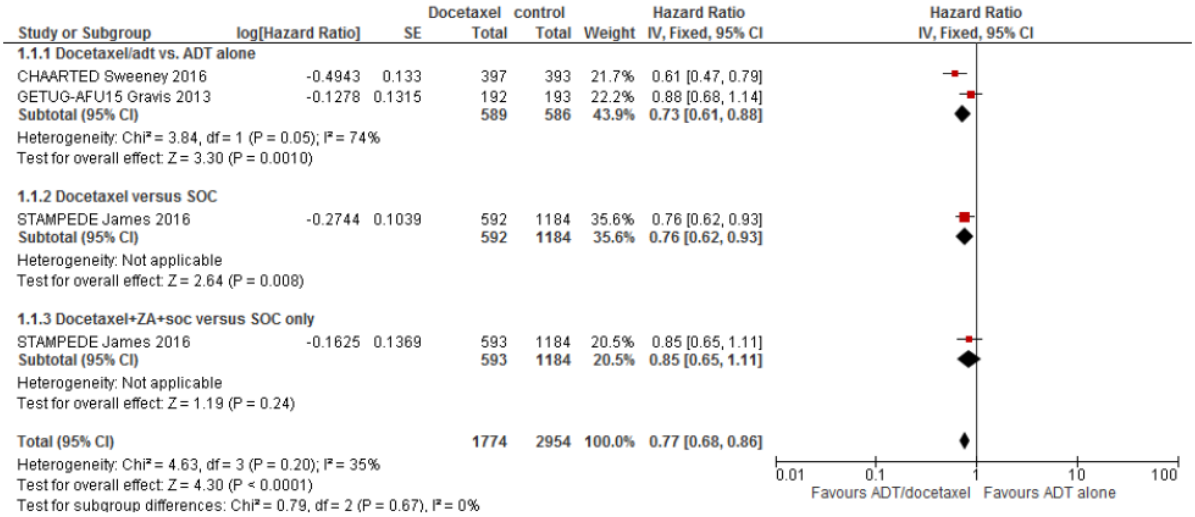
No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Overall survival – HR <1 favours docetaxel group										
3 studies GETUG-AFU15 Gravis 2013, CHAARTED Sweeney 2015, STAMPEDE James 2016	RCTs	2617	HR 0.77 (0.68, 0.86)	-	-	Not serious	Not Serious	Not serious	Not serious	High
Subgroup Analysis - • **Overall survival by dose 75mg/m2 of Docetaxel delivered every 3 weeks for 6 cycles– HR <1 favours docetaxel group**										
2 Studies STAMPEDE James 2016, CHAARTED Sweeney 2015	RCTs	2233	HR 0.74 (0.64, 0.84)	-	-	Not serious	Not serious	Not serious	Not serious	High
• **Overall survival by dose 75mg/m2 of Docetaxel delivered every 3 weeks for 9 cycles – HR <1 favours docetaxel group**										
1 Study GETUG-AFU15 Gravis 2013	RCT	385	HR 0.88 (0.68, 1.14)	-	-	Not serious	N/A	Not serious	Serious[1]	Moderate
• **Overall survival – high volume disease - HR <1 favours docetaxel group**										
2 Studies	RCTs	183	HR 0.67 (0.54, 0.83)	-	-	Not serious	Not serious	Not serious	Not serious	High

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
GETUG-AFU15 Gravis 2013, CHAARTED Sweeney 2015										
Overall survival – low volume disease - HR <1 favours docetaxel group										
2 Studies GETUG-AFU15 Gravis 2013, CHAARTED Sweeney 2015	RCTs	202	HR 0.87 (0.61, 1.23)	-	-	Not serious	Not serious	Not serious	Not serious	High
Clinical progression-free survival/ Failure-free survival/Relapse-free survival– HR <1 favours docetaxel group										
3 Studies GETUG-AFU15 Gravis 2013, STAMPEDE James 2016, CHAARTED Sweeney 2015,	RCTs	2617	HR 0.62 (0.57, 0.77)	-	-	Not serious	Not serious	Not serious	Not serious	High
Biochemical progression free survival – HR <1 favours docetaxel group										
1 Study GETUG-AFU15 Gravis 2013	RCT	385	HR 0.67 (0.54, 0.83)	-	-	Not Serious	N/A	Not serious	Not serious	High
Prostate cancer specific survival – HR <1 favours docetaxel group										

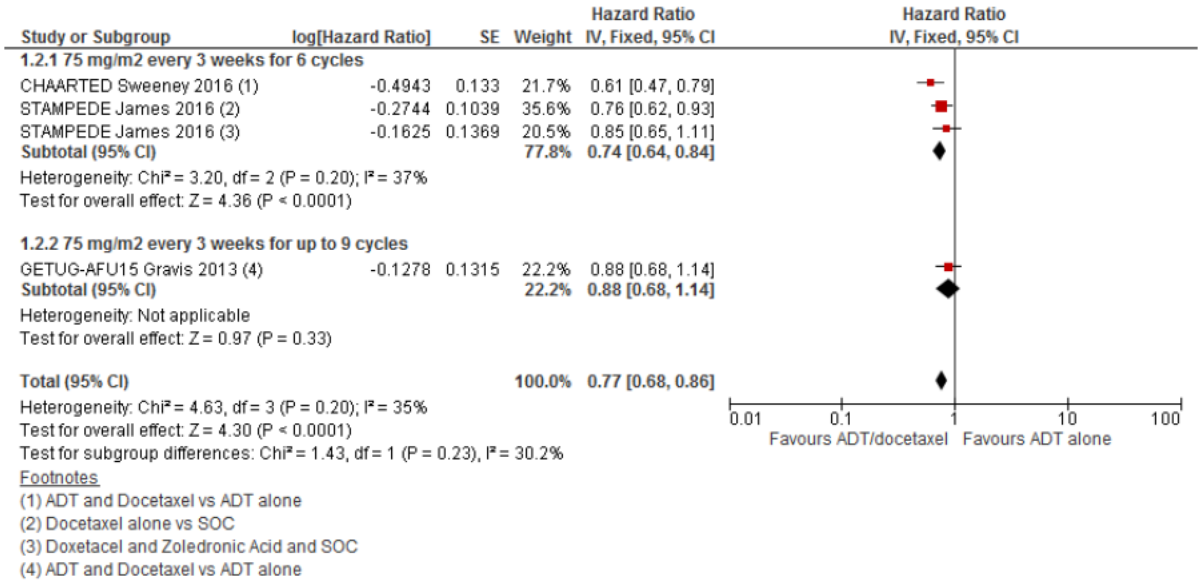
No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 study STAMPEDE James 2016	RCT	1442	HR 0.81 (0.66, 0.98)	-	-	Not serious	N/A	Not serious	Not serious	High
Quality of life scores during treatment phase (@ 6months) – EORTC – MD >1 favours docetaxel group										
1 Study GETUG-AFU15 Gravis 2013	RCT	385	MD -9.08 (-12.79, -5.37)	-	-	Serious[2]	N/A	Not serious	Not serious	Moderate

1. 95% confidence intervals crosses the line of no effect – downgraded once
2. Moderate risk of bias – due to self-completed questionnaires , downgraded once

Overall survival



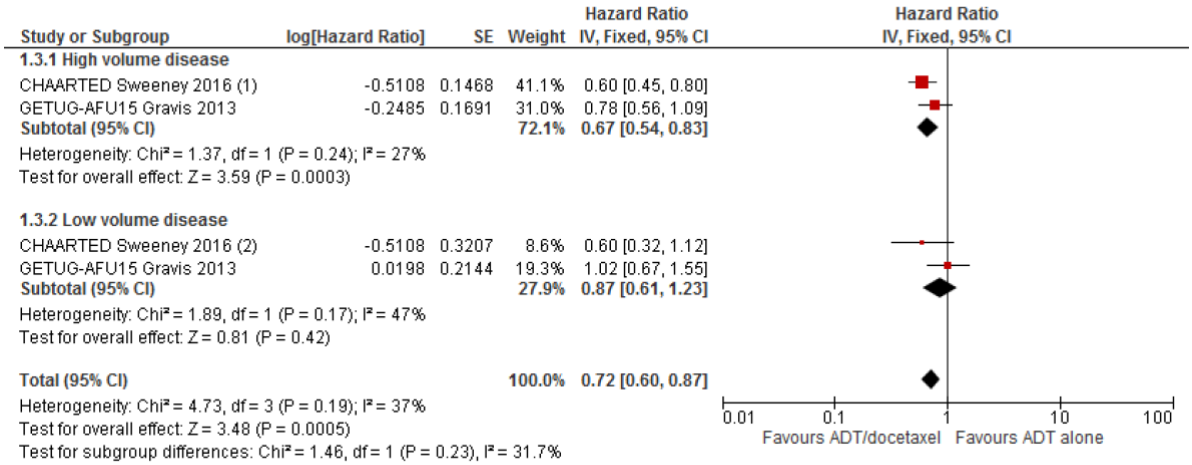
Overall survival stratified by dose



Footnotes

(1) ADT and Docetaxel vs ADT alone
(2) Docetacel alone vs SOC
(3) Doxetacel and Zoledronic Acid and SOC
(4) ADT and Docetaxel vs ADT alone

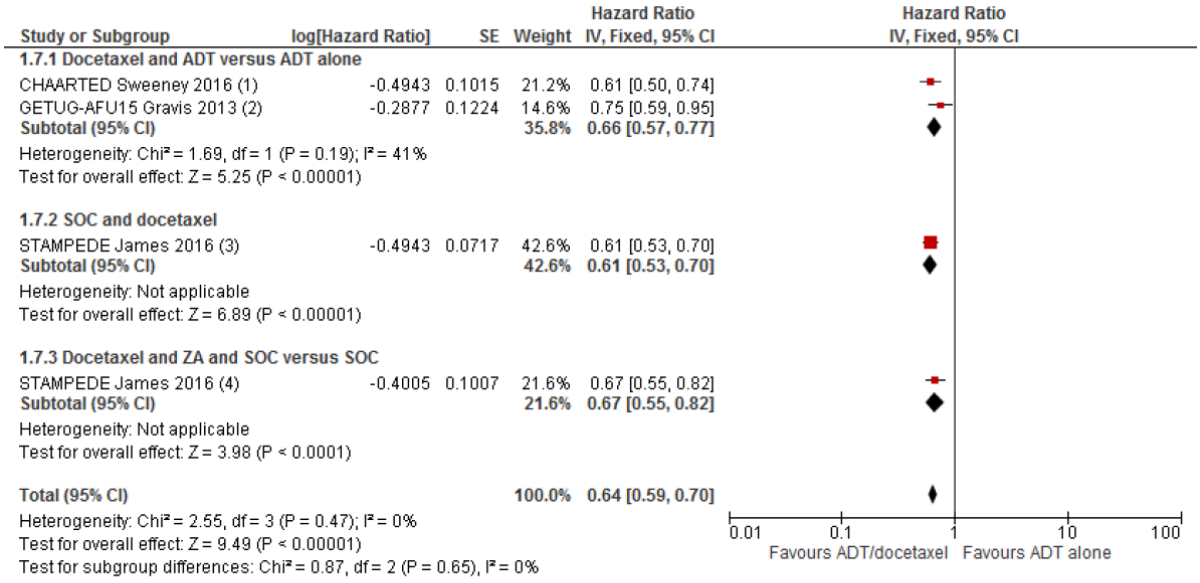
Overall survival by high volume or low volume disease



Footnotes

(1) high volume disease defined as the presence of visceral metastases or at least 4 bone lesions
(2) not meeting the HVD criteria

Clinical progression free survival



Footnotes

(1) defined by increasing symptoms of bone metastases; according to the Response Evaluation Criteria in Solid tumours, clinical deterioration due to...

(2) defined as time to clinical progression or death

(3) Failure-free survival - Biochemical failure, progression either locally, in lymph nodes or in distant mets, or death

(4) Failure-free survival - Biochemical failure, progression either locally, in lymph nodes or in distant mets, or death

High-quality evidence from up to 2 RCTs reporting data on up to 1,442 people with hormone-sensitive metastatic prostate cancer found that quality of life scores during the treatment phase worsened in those receiving docetaxel compared to those receiving standard care alone (defined as either hormone therapy or androgen deprivation therapy).

Moderate-quality to high-quality evidence from up to 3 RCTs reporting data on up to 2,617 people with hormone-sensitive metastatic prostate cancer found overall survival, prostate cancer-specific survival, clinical progression-free survival and biochemical progression-free survival was prolonged in those receiving docetaxel compared to those receiving standard care alone (defined as androgen deprivation therapy). Subgroup analysis of the evidence showed there was improved overall survival in those receiving a dose of 75mg/m2 of docetaxel delivered every 3 weeks for up to 6 cycles and those with high volume disease and could not differentiate overall survival in those receiving the same dose of docetaxel delivered every 3 weeks for up to 9 cycles and those with low volume disease.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that the critical outcomes were overall survival, clinical progression-free survival and adverse events as these had the most impact on the patients. The committee noted that the definition of clinical progression-free survival differed across the studies; however all the studies included biochemical progression (as measured by an increase in prostate-specific antigen [PSA]). The committee raised concerns that this was a laboratory marker, but agreed this was a sufficient marker as an increase in PSA has an impact on the treatment of the patient in practice.

The quality of the evidence

All 6 included studies were at moderate or high risk of bias owing to the lack of blinding of participants and investigators as the studies were open label. The largest study was from the United Kingdom (STAMPEDE (James et al. 2016)). The committee agreed that the evidence presented was representative of current practice and acknowledged that the evidence (especially for high-risk non-metastatic prostate cancer) was likely to become more definitive as more study data becomes available.

The committee was interested in reviewing the evidence for populations with high-risk non-metastatic prostate cancer and those with metastatic prostate cancer. The review question specified high-risk prostate cancer as locally advanced; the committee felt that there was no universal definition of locally advanced or localised prostate cancer. As a result they referred to non-metastatic cancer as just high-risk prostate cancer. The committee agreed to apply the inclusion criteria from studies in non-metastatic disease as the working definition of high-risk prostate cancer for this evidence review.

Three studies (STAMPEDE (James et al. 2016), GETUG-15 (Gravis et al. 2013) and CHAARTED (Sweeney et al.2015)) contributed evidence for the metastatic prostate cancer population group and 3 studies contributed evidence for the

high-risk prostate cancer population group (STAMPEDE (James et al. 2016), TAX 3501 (Schweizer et al. 2014) and Getug-12 (Fizazi et al. 2015). The STAMPEDE trial contributed evidence to both populations.

Despite the relatively small number of studies, the committee appreciated that the studies had large sample sizes ranging from 228 to 1,776 participants.

The GETUG-15 study included the estramustine in the same arm as docetaxel. The committee agreed to not downgrade or exclude this study because it that docetaxel given with estramustine was equivalent to docetaxel given with prednisolone in the other studies. This is reflected by the fact that the results from GETUG study was consistent with the results from the other studies in the meta-analysis.

The committee was also interested in the dose and frequency of docetaxel and whether or not daily prednisolone was used in conjunction with docetaxel. Two of the 3 studies (GETUG-12 (Fizazi et al. 2015) and STAMPEDE (James et al, 2016)) whose population had high-risk prostate cancer included prednisolone as part of their treatment. Only one (STAMPEDE (James et al. 2016)) of the metastatic prostate cancer studies included it.

The doses of docetaxel were similar at 75 mg/m2 in all 3 metastatic prostate cancer studies. However the GETUG-AFU15 (Gravis et al. 2013) study delivered docetaxel for up to 9 cycles every week unlike the STAMPEDE (James et al. 2016) and CHAARTED (Sweeney et al. 2016) studies which delivered for up to 6 cycles.

The committee acknowledged that, though the studies termed clinical progression-free survival as either failure-free survival (STAMPEDE (James et al. 2016)), relapse-free survival (GETUG-12 (Fizazi 2015)), progression-free survival (TAX 3501 (Schweizer et al. 2013)) and clinical progression (CHAARTED (Sweeney et al. 2016) and GETUG-AFU15 (Gravis et al. 2013)), they all included change in prostate-specific antigen in their definitions, among other elements such as death from cancer, distant metastases and proven local relapse.

Overall, when the evidence was assessed using GRADE, the majority of the of it was of moderate to high quality, this was due to precise 95% confidence intervals mean that the studies were not downgraded for imprecision and the objective nature of the outcomes meant that potential sources of bias such as the open-label status of the studies were unlikely to have an impact on the results.

Benefits and harms

Based on the evidence, the benefit of docetaxel for hormone-sensitive metastatic cancer outweighs the harms. The evidence shows that docetaxel can prolong overall survival and clinical progression-free survival in people with newly diagnosed metastatic prostate cancer who are starting long-term hormone therapy (GETUG AFU15 (Gravis et al. 2013), CHAARTED (Sweeney et al. 2016) and STAMPEDE (James et al.2016)). All 3 studies included androgen deprivation therapy and participants were either hormone naïve or hormone sensitive. The committee interpreted this to mean participants were newly diagnosed with metastatic prostate cancer.

The STAMPEDE (James et al. 2016) trial reported that docetaxel chemotherapy is associated with a number of adverse events including infections, febrile neutropenia, gastrointestinal and respiratory symptoms in people with either metastatic or high risk prostate cancer. Because the evidence showed survival benefit in those with hormone-sensitive metastatic cancer, the committee agreed that the benefits of docetaxel chemotherapy outweighed the harm. As a result the committee made a strong recommendation for clinicians to offer docetaxel to those people with hormone-sensitive metastatic prostate cancer.

In addition, the committee was able to specify dose and frequency of treatment because the evidence showed an improvement in survival in studies which considered 75mg/m2 of docetaxel every 3 weeks for 6 cycles (CHAARTED (Sweeney et al. 2016) and STAMPEDE (James et al. 2016)). One study (GETUG-AFU15) which considered a dose of 75mg/m2 of docetaxel delivered every 3 weeks for 9 cycles could not detect a difference in survival between the intervention and control group. The committee explained that docetaxel is a highly toxic chemotherapy treatment therefore it is not unexpected that prolonged use is not beneficial.

The committee considered the definition of ‘high-risk’ non-metastatic prostate cancer and agreed that (based on the inclusion criteria of the Stampede and GETUG-12 studies) for the purposes of these recommendations, high-risk disease meant one or more of the following:

• Stage T3/T4 or

• Gleason score 8-–10 or

• PSA greater than 40ng/ml

The committee also noted that this definition will be different from the one mentioned in the table on risk stratification for people with localised prostate cancer where high risk localised prostate cancer is defined as

• clinical stage ≥T2c or

• PSA >20ng/ml or

• Gleason score 8-10

This is because, the recommendation made here reflects the exact population included in the studies

When considering docetaxel in people with newly diagnosed high-risk non-metastatic prostate cancer, the benefits were not as clear as in those diagnosed with metastatic cancer. The evidence could not detect a difference in overall survival and prostate-specific survival between the intervention and control group. However, the evidence showed that clinical

progression-free survival improved in those who received docetaxel compared with those who were on hormone therapy alone. As a result, the committee made a recommendation for clinicians to discuss the benefits and harms of docetaxel chemotherapy with those people who have been diagnosed with high-risk prostate cancer to arrive at a shared decision about docetaxel chemotherapy. The committee emphasised that this should be a joint decision taking into account the person's values and preferences.

Based on the evidence from 2 out of the 3 studies (STAMPEDE (James 2016), and TAX 3501 (Schweizer 2014)), the committee recommended that clinicians should use six 3-weekly cycles at a dose of 75mg/m2. This dose was shown to prolong clinical progression free-survival in men with high-risk non-metastatic prostate cancer. Similar to the regimen in those with hormone-sensitive metastatic cancer this can be with or without daily prednisolone. Only 1 out of the 3 studies (STAMPEDE (James 2016) used daily prednisolone. Docetaxel chemotherapy was shown to be effective in improving clinical progression-free survival with or without daily prednisolone use.

Parker C et al., 2020 [19].

European Society for Medical Oncology (ESMO)

Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

Zielsetzung/Fragestellung

Keine Angabe

Methodik

Grundlage der Leitlinie

- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz; ESMO-MCBS v1.179 was used to calculate scores for new therapies/indications approved by the EMA since 1 January 2016 (https://www.esmo.org/Guidelines/ESMOMCBS). The scores have been calculated by the ESMOMCBS Working Group and validated by the ESMO Guidelines Committee.
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

Keine Angaben

LoE

Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System)

Levels of evidence

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions

GoR

Grades of recommendation

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

Empfehlungen

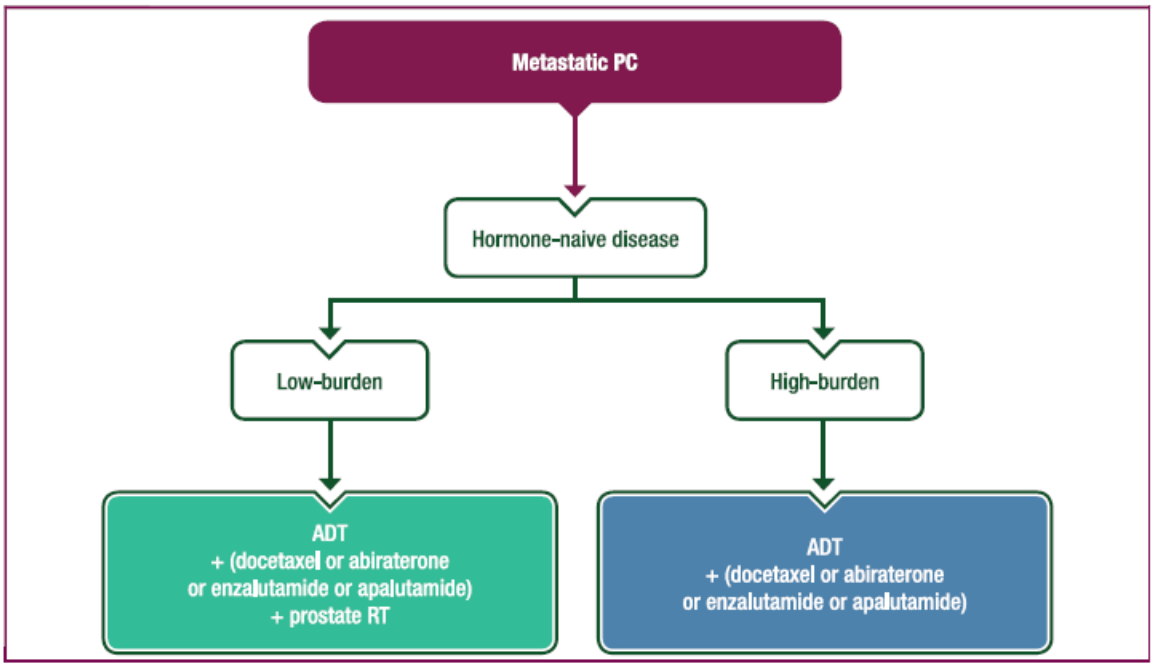


Figure 4. **Metastatic prostate cancer treatment algorithm.**
ADT, androgen deprivation therapy, PC, prostate cancer; RT, radiotherapy.

Empfehlungen

- ADT is recommended as first-line treatment of mHNPC in combination with abiraterone/prednisone [ESMOMagnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: 4] or apalutamide [ESMO-MCBS v1.1 score: 4] or docetaxel [ESMO-MCBS v1.1 score: 4] or enzalutamide [ESMO-MCBS v1.1 score: 4] [I, A].
- RT to the primary tumour combined with the systemic treatment is recommended for patients with lowvolume mHNPC [I, A].
- ADT alone is recommended as first-line systemic treatment of mHNPC in men who are unfit for abiraterone, apalutamide, enzalutamide and docetaxel [III, A].
- For men starting on ADT, management to prevent CTIBL is recommended.[66]

Hintergrundinformationen:

METASTATIC HORMONE-NAIVE PROSTATE CANCER

Treatment recommendations for metastatic hormone-naive prostate cancer (mHNPC) are shown in Figure 4. Addition of abiraterone, apalutamide, enzalutamide or docetaxel to ADT improves OS in mHNPC. Most of the relevant trials, discussed below, largely included men with de novo metastatic disease, and caution should be used when extrapolating the results to men who relapsed with metastases after previous local treatment.

The benefit of docetaxel for mHNPC was established by two phase III trials, CHAARTED52 and STAMPEDE.[32] The CHAARTED study randomised 790 patients to receive ADT alone or in combination with docetaxel 75 mg/m2 every 21 days for 6 cycles. Docetaxel improved OS (HR 0.72; 95% CI 0.59-0.89). The STAMPEDE study is a multi-arm, multistage phase III study designed to test whether the addition of various treatments to ADT improves OS. It includes patients with both M0 and M1 disease. Patients were randomised to ADT alone (n ¼ 1184) or in combination with docetaxel 75 mg/m2 every 21 days with prednisone 10 mg daily for 6 cycles (n = 592). The addition of docetaxel in M1 patients significantly improved OS compared with ADT alone (HR 0.76; 95% CI 0.62-0.92). The OS benefit for docetaxel was similar when combined with zoledronic acid (HR 0.79; 95% CI 0.66-0.96). A third study, GETUG-AFU 1553 randomised 385 mHNPC patients to receive ADT or ADT plus docetaxel 75 mg/m2 every 21 days for 9 cycles. Patients in the ChT arm had improved PSA PFS and radiographic PFS (rPFS), but these did not translate into a benefit in OS

(HR 1.01; 95% CI 0.75-1.36). Subgroup analysis of the CHAARTED study showed more pronounced benefit in patients with high-volume disease (HR 0.63; 95% CI 0.50- 0.79),54 defined as the presence of four or more bone metastases with one or more beyond vertebral bodies and pelvis, visceral metastasis or both. However, meta-analysis of CHAARTED, STAMPEDE and GETUG-AFU 15 have confirmed the improvement in OS with the addition of docetaxel to ADT regardless of disease volume (HR 0.77; 95% CI 0.6-0.87).33,55 The addition of abiraterone to ADT has demonstrated improved OS compared with ADT alone in two phase III trials, LATITUDE56 and STAMPEDE.57 Both studies randomised participants to ADT alone or in combination with abiraterone 1000 mg plus prednisone 5 mg daily until disease progression. LATITUDE randomised 1199 patients with high-risk metastatic prostate cancer, defined as the presence of at least two of the following: GS ≥8, three or more bone metastases or visceral metastases. The addition of abiraterone to ADT resulted in a significant improvement in OS (HR 0.62; 95% CI 0.51-0.76).56 Updated data after crossover and 2-year additional follow-up confirmed this (HR 0.66; 95% CI 0.56e0.78).58 A similar benefit in survival was observed in the STAMPEDE trial for the M1 subgroup (HR 0.63; 95% CI 0.52e0.76).57 LATITUDE enrolled only patients with de novo metastatic prostate cancer, and only 5% of patients included in STAMPEDE were relapsing M1. Therefore, the benefit of adding abiraterone to ADT in the latter group of patients is uncertain.

The phase III trial TITAN demonstrated that addition of apalutamide to ADT improves OS in mHNPC.59 The study randomised 1052 participants to ADT alone or in combination with apalutamide 240 mg per day. A total of 16% of patients had received treatment of localised disease and were enrolled at M1 relapse. Only 11% of patients had received early docetaxel. Most patients had high-volume disease (63%). The addition of apalutamide improved OS (HR 0.67; 95% CI 0.51e0.89; P ¼ 0.005) with no significant differences according to disease volume. Given the limited number of patients that received apalutamide after docetaxel, the benefit of this strategy remains unclear.

The benefit of adding enzalutamide to ADT for the treatment of mHNPC patients has been established by two phase III studies, ARCHES60 and ENZAMET.61 ARCHES randomised 1150 mHNPC patients to ADT plus enzalutamide 160 mg daily or ADT plus placebo. Participants were stratified by disease volume and prior docetaxel therapy. At the interim analysis, the primary end point was met, as enzalutamide significantly improved rPFS (HR 0.39; 95% CI 0.30-0.50; P < 0.001). The rPFS benefit was consistent across all prespecified subgroups, including disease volume and prior docetaxel ChT. At the time of this interim analysis, data on OS were immature.

The second phase III study,ENZAMET,61 randomised 1125 men with mHNPC to either ADT plus other non-steroidal anti-androgens, including bicalutamide, nilutamide or flutamide, versus ADT plus enzalutamide. Enzalutamide resulted in a significant improvement in OS (HR 0.67; 95% CI 0.52-0.86). This is the first study to examine the use of an androgen receptor (AR) signalling inhibitor with or without concurrent docetaxel; 45% of patients were planned to receive docetaxel. The HR for OS was 0.53 (95% CI 0.37-0.75) for those who were not planned to receive docetaxel, and 0.90 (95% CI 0.62-1.31) for those who were planned to receive docetaxel.

Docetaxel plus ADT and abiraterone plus ADT have been compared in an opportunistic randomised analysis from theSTAMPEDE trial, suggesting similar outcomes in the M1 subgroup.62 On the other hand, indirect Bayesian comparisons have suggested that the survival and QoL benefit provided by abiraterone may be greater than that seen with docetaxel.63 Since no biomarkers have been identified to select one therapy over another, the decision to use abiraterone, apalutamide, enzalutamide or docetaxel should be individualised taking into consideration the cost, access to treatment, toxicity profiles, duration of treatment, comorbidities and patient preferences.

Two randomised trials, HORRAD64 and STAMPEDE,65 have compared lifelong ADT alone or in combination with RT to the primary tumour for mHNPC. The HORRAD trial randomised 446 patients to receive ADT alone or in combination with RT to the primary (70 Gy in 35 fractions for 7 weeks or 57.76 Gy in 19 fractions for 6 weeks). RT improved time to PSA progression (HR 0.78; 95% CI 0.63-0.97), but not OS (HR 0.90; 95% CI 0.70-1.14).64 The STAMPEDE trial allowed docetaxel in both arms in addition to ADT. RT to the primary was then commenced within 3e4 weeks after the last docetaxel dose (55 Gy in 20 fractions over 4 weeks or 36 Gy in six fractions over 6 weeks). RT improved failure-free survival (HR 0.76; 95% CI 0.68-0.84; P < 0.0001) but not OS (HR 0.92; 95% CI 0.80-1.06). The prespecified lowvolume subgroup, defined according to the CHAARTED criteria, had a significant benefit in both failure-free survival (HR 0.59; 95% CI 0.49e0.72) and OS (HR 0.68; 95% CI 0.52- 0.90).

Management of bone health and prevention of cancer treatment-induced bone loss (CTIBL) is an important part of the treatment of men with prostate cancer under hormonal treatment. Prevention of CTIBL is covered by separate ESMO guidelines.[66]

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Canadian Urological Association (CUA)

Canadian Urological Association-Canadian Urologic Oncology Group guideline on metastatic castration-naive and castration-sensitive prostate cancer

Zielsetzung/Fragestellung

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: expert panel comprised of urologists, medical oncologists, and radiation oncologists with significant experience managing mCNPC/mCSPC;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren nicht dargelegt, nur genannt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert: unklar.

Recherche/Suchzeitraum:

- EmBASE and Medline databases

- between January 2000 and August 2019

LoE/ GoR

- WHO modified Oxford Center for Evidence-Based Medicine grading system.

Sonstige methodische Hinweise

- Diese Leitlinie entspricht überwiegend, aber nicht vollständig den Grundanforderungen für eine methodisch hochwertige Leitlinie. Insbesondere aufgrund der Aktualität der verarbeiteten Informationen aus Studien wurde sie in diese Synopse aufgenommen.

Empfehlungen

Local therapy: Treatment of the primary cancer in mCNPC

- Patients with low-volume metastatic disease burden should be considered for external beam radiation to the prostate (Level of evidence 2, Strong recommendation).

  Hintergrundinformationen:

  Treatment of the primary PC has theoretical benefits, including reducing local side effects that may occur due to disease progression during mCRPC, as well as removing the cancer that could be source of cytokines and growth factors that may induce disease progression. Two recent, randomized trials assessed the impact of external beam radiation therapy (EBRT) in mCNPC.

  The HORRAD trial randomized 432 men with mCNPC and PSA >20 ng/mL to receive EBRT of the prostate with ADT or ADT alone. The initial prescribed dose was 70 Gy in 35 fractions of 2 Gy, during an overall treatment time of seven weeks. During the study period, an optional schedule was added that was considered biologically equivalent and consisted of a dose schedule of 57.76 Gy in 19 fractions of 3.04 Gy three times a week for six weeks. The median PSA was 142 ng/ml and 67% of patients had more than five bone metastases. No significant difference was found in OS (hazard ratio [HR], 0.90; 95% confidence interval [CI] 0.70–1.14; p=0.4), but there was a benefit to median time to PSA progression in the radiotherapy group (15 vs. 12 m, crude HR 0.78; 95% CI 0.63–0.97; p=0.02). Subgroup analysis showed that mCNPC with <5 metastases (HR 0.90; 95% CI 0.70-–1.14; p=NS) and no bony pain (HR 0.83; 95% CI 0.69–1.14; p=NS) appeared to have the most impact of EBRT.

  The STAMPEDE trial, also known as MRC PR08, is a multi-arm, multi-stage (MAMS), randomized trial recruiting in the U.K. and Switzerland. It aims to evaluate multiple therapeutic strategies in the management of high-risk, locally advanced and mCNPC compared to standard of care (androgen deprivation only). In the EBRT component of the study, the trial randomized 2061 men with mCNPC to either EBRT and ADT or ADT alone.[15] The median PSA was 97 ng/ mL; 819 (40%) men had low metastatic burden based on CHAARTED criteria and 1664 (81%) had no pain.8,15 EBRT was given as one of two schedules: either 36 Gy in six consecutive weekly fractions of 6 Gy, or 55 Gy in 20 daily fractions of 2.75 Gy over four weeks. Subgroup analyses were prespecified for baseline metastatic burden (low vs. high).

  Similar to the HORRAD trial, EBRT improved failure-free survival (FFS) (HR 0.76; 95% CI 0.68–0.84; p<0.0001) but not OS (HR 0.92; 95% CI 0.80–1.06; p=0.266). Subgroup analysis by metastatic burden showed FFS was improved in both low and high metastatic burden (low metastatic burden HR 0.59; 95% CI 0.49–0.72; p<0·0001and metastatic burden, interaction p=0.002; high metastatic burden HR 0.88; 95% CI 0·77–1.01; p=0·059). OS was improved in patients with low metastatic burden at baseline who were allocated EBRT (HR 0.68; 95% CI 0.52–0.90; p=0.007), whereas in patients with a high metastatic burden, there was no impact on OS (HR 1.07; 95% CI 0.90–1.28; p=0.420). Although both trials showed negative impact of EBRT in unselected men in mCNPC, both HORRAD and STAMPEDE reveal the benefits of local therapy in those with low-burden disease. A recent STOPCAP meta-analysis combining data from the trials confirm the benefits of EBRT in men with fewer than five bone metastases.[16] This meta-analysis showed that there was 7% improvement in three-year survival in men with fewer than four bone metastases.

- Radical prostatectomy in mCNPC should only be performed in a clinical trial setting (Expert opinion, Strong recommendation).

  Hintergrundinformationen:

  Currently, there is limited evidence showing the benefit of radical prostatectomy in mCNPC. However, the results from HORRAD and STAMPEDE imply that there may also be certain men with mCNPC that may benefit from surgical extirpation. There are many clinical trials currently assessing this question, including TRoMBONE (Testing radical prostatectomy in men with PC and oligometastases to the bone: a randomized, controlled, feasibility trial),[17] SWOG1802 (Standard systemic therapy with or without definitive treatment in treating participants with metastatic PC; https://www.swog.org/clinical-trials/s1802), and G-RAMPP/AUO–AP-75/13 (Impact of radical prostatectomy as primary treatment in patients with PC with limited bone metastases).[18] Until the results of these trials clarify the impact of radical

prostatectomy in mCNPC and, more importantly, which patients would benefit the most, surgery of the primary is not recommended in patients with metastatic PC.

Systemic therapies: Chemotherapy, abiraterone acetate, enzalutamide, and apalutamide

- Docetaxel (75 mg/m2 every three weeks for six cycles) plus ADT is an option for men with mCNPC/mCSPC with good performance status and high-volume metastatic disease, defined as: presence of visceral metastases, or four or more bone lesions with at least one beyond the vertebral bodies and pelvis (Level 1, Strong recommendation).
- Docetaxel plus ADT may also be an option in patients with mCNPC/mCSPC with good performance status with low-volume disease (Level 2, Weak recommendation).
- "High risk" mCNPC/mCSPC patients (defined as at least two of: Gleason score of 8–10, visceral metastases, and three or more bone metastases) with good performance status can also be considered for docetaxel chemotherapy (Level 1, Strong recommendation).

Hintergrundinformationen:

Docetaxel, a taxane derivative that binds to tubulin that inhibits mitosis and tumor proliferation, was the initial chemotherapeutic agent that improved survival in men with mCRPC.[19] Three different, large, randomized trials assessed the impact of introducing docetaxel in mCNPC/mCSPC: CHAARTED, STAMPEDE, and GETUG-AFU [15,8,20,21]

The CHAARTED trial randomized 790 with mCNPC/mCSPC patients to ADT plus docetaxel (75 mg/m2 every three weeks for six cycles) or ADT alone.[8] Within this trial, 35% (277 patients) had lowvolume metastases and 65% (513 patients) had high-volume metastases (high-volume of metastases was defined by the presence of visceral metastases or four or more bone lesions with at least one beyond the vertebral bodies and pelvis). Overall, the median OS was 13.6 months longer with ADT plus docetaxel than with ADT alone (57.6 vs. 44.0 months; HR 0.61; 95% CI 0.47–0.80; p<0.001). Subgroup analysis showed that OS benefits of combination were maintained in the highvolume mCNPC/mCSPC (n=513; HR 0.63; 95% CI 0.50–0.79; p<0.001), whereas survival benefits were lost in low-volume disease (n=277; HR 1.04; 95% CI 0.70–1.55; p=0.86).[22]

The GETUG-AFU15 trial randomized 385 mCNPC/ mCSPC patients to receive ADT plus docetaxel or ADT alone.[21] Although the dosage of docetaxel was the same as in CHAARTED, patients were allowed to receive up to nine cycles compared to the six cycles in CHAARTED. There was no survival difference between the groups (58.9 months in the combined group vs. 54.2 months in the ADT alone group; HR 1.01; 95% CI 0.75–1.36). The differences in the outcomes of the two studies is likely due to the differences in the burden of disease in the two studies. Although 65% of patients in CHAARTED had high-volume metastases, less than 25% of the patients had low-volume disease. An unplanned posthoc analysis of the high-volume cohort of GETUG-AFU [15] showed a non-significant trend toward improved OS in this cohort (39.8 vs. 35.1 months; HR 0.78; 95% CI 0.56–1.09).[23] A recent pooled analysis of both studies confirm the benefit of combined docetaxel and ADT in high-volume disease and lack of benefit on low-volume metastatic burden.[24] The third trial to assess the impact of docetaxel in mCNPC/ mCSPC was the docetaxel component of the STAMPEDE trial.[20] Unlike the CHAARTED and GETUG-AFU[15] trials, patients with high-risk, non-metastatic PC were included. Eligible patients included: newly diagnosed metastatic, node-positive, or high-risk locally advanced (with highrisk features defined as at least two of: T3/4, Gleason score of 8–10, and PSA ≥40 ng/mL); or previously treated with radical surgery and/or radiotherapy with high-risk features. Of the 2962 patients randomized, 1817 (61%) men had bony metastases and 592 patients received only ADT and six cycles of docetaxel (75 mg/m2 every three weeks for six cycles). The combination of ADT and docetaxel had a survival advantage compared to ADT alone (HR 0.78; 95% CI 0.66–0.93; p=0.006). Although patients were not classified having high- or low-volume metastases, only patients with metastatic disease had evidence of benefit with ADT and docetaxel (HR 0.76; 95% CI 0.62–0.92; p=0.005). A recent post-hoc, non-prespecified analysis of STAMPEDE was published.[25] Metastatic burden was assessable in only 76% of patients for the analysis (830 of 1086 patients) and 362 (44%) had low and 468 (56%) high metastatic burden. Although OS was neither statistically significant in low-burden nor in high-burden disease (HR 0.76; 95% CI 0.54–1.07; p=0.107 vs. HR 0.81; 95% CI 0.64–1.02; p=0.064), the authors found no evidence of heterogeneity of docetaxel effect between metastatic burden subgroups (interaction p=0.827). The authors concluded that upfront docetaxel is considered for mCNPC/mCSPC patients regardless of metastatic burden. This retrospective analysis contradicts the results of CHAARTED, but the authors point out that this may be due to the larger number of de novo mCNPC/mCSPC (n=362) in the low-burden group compared to the low-burden group in the CHAARTED trial (n<160). A recent meta-analysis of CHAARTED, GETUG-AFU[15], and STAMPEDE confirms the benefit of addition of docetaxel to ADT in mCNPC/mCSPC (HR 0.77; 95% CI 0.68–0.87; p<0.0001). The authors of the meta-analysis show that this translates to an absolute improvement in four-year survival of 9%.

- Abiraterone acetate (1000 mg daily) with prednisone (5 mg daily) plus ADT is an option for mCNPC patients with at least two of the three: Gleason score of ≥8, presence of three or

more lesions on bone scan, or presence of measurable visceral metastasis (Level of evidence 1, Strong recommendation).

- Abiraterone acetate (1000 mg daily) with prednisone (5 mg daily) plus ADT may be considered for patients with lowvolume mCNPC (Level of evidence 3, Weak recommendation).

Hintergrundinformationen:

Abiraterone acetate is a prodrug of abiraterone, which is a CYP17A1 inhibitor; CYP17A1 is expressed in and is required for androgen biosynthesis. Abiraterone acetate, when combined with prednisone, was initially shown to improve survival in mCRPC, both prior to and after docetaxel treatment.[26,27] Two trials, LATITUDE and STAMPEDE, assessed the impact of abiraterone in mCNPC/mCSPC.[9,28,29]

In the LATITUDE trial, 1199 patients were randomly assigned to either the abiraterone acetate (1000 mg) plus prednisone (5 mg) once daily orally. Eligible patients included mCNPC with at least two of three high-risk features (Gleason score of ≥8, presence of three or more lesions on bone scan, or presence of measurable visceral metastasis except lymph node metastasis). Updated OS data with median followup of 51.8 months showed that OS was significantly longer in the abiraterone acetate plus prednisone group (median 53.3 months [95% CI 48.2–not reached]) than in the placebo group (median 36.5 months [95% CI 33.5–40.0]), with a HR of 0.66 (95% CI 0.56−0.78; p<0·0001). A post-hoc, exploratory analysis of the impact of disease burden showed that OS was improved only in high-volume disease (n=487 in the abiraterone acetate plus prednisone and ADT, and 468 in the ADT only group; HR 0.62; 95% CI 0.52−0.74; p<0·0001); however, only few patients had low-volume disease in this study (n=110 in the abiraterone acetate plus prednisone and ADT, and n=133 in the ADT only group; HR 0.72; 95% CI 0.47−1.10; p=0.1242).

In the abiraterone component of the STAMPEDE trial, the efficacy of abiraterone acetate and prednisolone was assessed in men with mCNPC.[28] In this study, 1917 mCNPC patients were enrolled with: newly diagnosed and metastatic, node-positive, or high-risk, locally advanced (with at least two of following: cT3 or cT4, a Gleason score of 8–10, or PSA level ≥40 ng/mL), or disease that was previously treated with radical surgery or radiotherapy and was now relapsing with high-risk features (PSA >4 ng/mL with a doubling time of <6 months, a PSA level >20 ng/mL, nodal or metastatic relapse). Men were randomized to receive abiraterone acetate (1000 mg daily) plus prednisolone (5 mg) plus ADT or ADT alone; 52% of the patients had metastatic disease, 20% had node-positive or node-indeterminate non-metastatic disease, and 28% had node-negative, nonmetastatic disease; 95% had newly diagnosed disease. In a subgroup analysis, the OS benefit was seen in PC patients with metastatic disease (HR 0.61; 95% CI 0.49–0.75) but not those with non-metastatic, high-risk patients (HR 0.75; 95% CI 0.48–1.18).28 The impact of volume tumor burden was not reported.

In a recent, unplanned, post-hoc analysis of 759 evaluable patients with bone metastases in the above STAMPEDE trial, patients were reclassified using CHAARTED “high- or low-volume” criterion or LATITUDE “high- or low-risk” criterion.[30] Men with mCNPC had OS benefit with the addition of abiraterone acetate and prednisone to ADT irrespective of risk stratification for “risk” or “volume.” Using CHAARTED criteria, low-volume HR was 0.66 (95% CI 0.44–0.98) and high-volume HR was 0.54 (95% CI 0.41–0.70); using the LATITUDE criteria, low-risk HR was 0.64 (95% CI 0.42–0.97) and high-risk HR was 0.60 (95% CI 0.46–0.78). Although these results are intriguing, the retrospective nature of the reclassification of risk and tumor volume is a significant limitation and, thus, the results can only be considered hypothesis-generating.

- Enzalutamide (160 mg/day) is a treatment option for mCNPC/mCSPC regardless of volume of disease (Level of evidence 1, Strong recommendation).
- Enzalutamide should not be used in combination (concurrent use) with docetaxel to treat mCNPC/mCSPC (Level of evidence 2, Strong recommendation).
- Enzalutamide may be considered in mCSPC patients previously treated with docetaxel chemotherapy (sequential use) (Level of evidence 1, Weak recommendation).

Hintergrundinformationen:

Enzalutamide binds to the androgen receptor (AR) and inhibits the AR nuclear translocation and interaction with DNA. Suppression of the AR with enzalutamide was initially shown to improve survival in docetaxel-naive or treated mCRPC.31,32 Two recent studies assessed the role of enzalutamide in mCNPC: ARCHES and ENZAMET.[33,34] The ARCHES trial randomized 1150 mCNPC/mCSPC patients to either enzalutamide (160 mg/day) plus ADT or placebo plus ADT. The primary endpoint was radiological progression-free survival (rPFS), defined as the time from randomization to the first objective evidence of radiographic disease progression or death. The combination of enzalutamide plus ADT improved rPFS compared to placebo-ADT (HR 0.39; 95% CI 0.30–0.50; p= 0.001; median not reached vs. 19.0 months). Due to the immaturity of the study and the median duration of OS, median OS was not reached in either arm and no survival differences were observed between the two arms. Prior docetaxel of up to six cycles was allowed, and 18% (205) men received at least one dose of docetaxel prior to randomization; subgroup analysis showed that rPFS benefit was seen in both chemotherapy-treated and chemotherapy-naive patients. As well, although 35% (405 patients) of men were

low-volume based on CHAARTED criteria, benefit in rPFS with enzalutamide-treated patients was seen regardless of volume of disease.

ENZAMET was an open-label clinical trial that randomized 1125men with mCNPC/mCSPC to receive ADT and enzalutamide daily (160 mg) or a non-steroidal antiandrogen (NSAA: bicalutamide, nilutamide, or flutamide), with a primary endpoint of OS. There was an OS benefit in the enzalutamide plus ADT arm compared to NSAA (HR 0.67; 95% CI 0.52–0.86; p=0.002). Kaplan-Meier estimates of OS at three years were 80% in the enzalutamide group and 72% in the NSAA arm. Unlike ARCHES, concurrent use of docetaxel was allowed and the decision to treat with chemotherapy was at the discretion of the investigator. Use of chemotherapy was well-balanced between the two arms (45% of those receiving enzalutamide and 44% of those receiving a NSAA planned for early docetaxel use). In a subgroup analysis, the benefits of enzalutamide on OS appeared only in the group without planned early docetaxel use (concurrent docetaxel: HR 0.9; 95% CI 0.62–1.31; no concurrent docetaxel: HR 0.8; 95% CI 0.59–1.07). Although the authors state that the study is underpowered and data is too immature to specifically answer whether combination docetaxel and enzalutamide is beneficial in mCNPC/mCSPC, these results demonstrate that this combination should not be used until further evidence is shown for its benefits.

- Apalutamide (240 mg) is a treatment option for men with mCNPC/mCSPC regardless of volume of disease (Level ofevidence 1, Strong recommendation).

Hintergrundinformationen:

Apalutamide inhibits the AR by preventing its nuclear translocation and DNA binding. The first large, randomized clinical trial assessing apalutamide in mCNPC/mCSPC was the TITAN trial, which randomized 1052 men with mCNPC/ mCSPC (any) to receive apalutamide (240 mg once daily) plus ADT or ADT alone. As well, 10.7% received previous docetaxel therapy and 37.3% had low-volume disease. With a median of 22.7 months of followup, rPFS at 24 months was 68.2% in the apalutamide group and 47.5% in the placebo group (HR 0.48; 95% CI 0.39–0.60; p<0.001). Benefit with apalutamide in rPFS was seen regardless of prior chemotherapy use or disease burden. OS at 24 months was also greater with apalutamide than with placebo (82.4% in the apalutamide group vs. 73.5% in the placebo group; HR 0.67; 95% CI 0.51–0.89; p=0.005).35 Benefit with apalutamide in OS was seen regardless of disease burden.

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 9 of 12, September 2020) am 11.09.2020

#	Suchfrage
1	[mh “Prostatic Neoplasms”]
2	(prostate OR prostatic):ti,ab,kw
3	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesion* OR malignan*):ti,ab,kw
4	mHSPC:ti,ab,kw
5	{AND #2-#3}
6	{OR #1, #4-#5}
7	#6 with Cochrane Library publication date from Sep 2015 to present

Systematic Reviews in Medline (PubMed) am 11.09.2020

#	Suchfrage
1	prostatic neoplasms[mh] AND neoplasm metastasis[mh]
2	prostate[tiab] OR prostatic[tiab]
3	(((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesion*[tiab]) OR malignan*[tiab]
4	(#2 AND #3) AND (advanced[tiab] OR metastat*[tiab] OR metastas*[tiab] OR recurren*[tiab] OR hormone-sensitive[tiab] OR oligometastatic[tiab])
5	mHSPC[tiab]
6	#1 OR #4 OR #5
7	(#6) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR

	Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
8	((#7) AND ("2015/09/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 11.09.2020

#	**Suchfrage**
1	prostatic neoplasms[mh]
2	prostate[tiab] OR prostatic[tiab]
3	(((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesion*[tiab]) OR malignan*[tiab]
4	mHSPC[tiab]
5	#1 OR (#2 AND #3) OR #4
6	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
7	(((#6) AND ("2015/01/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt])

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