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: 2024-B-187 Darolutamid

Stand: Oktober 2024

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

Darolutamid
[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 • Enzalutamid: Beschluss vom 19.11.2021 • Relugolix: Beschluss vom 06.04.2023 • Darolutamid (Kombination mit Docetaxel und ADT): Beschluss vom 21.09.2023
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:	
Darolutamid L02BB06 Nubeqa	<u>Vorläufig geplantes Anwendungsgebiet laut Beratungsanforderung:</u> Darolutamid zur Behandlung erwachsener Männer mit metastasiertem hormonsensitivem Prostatakarzinom (mHSPC) in Kombination mit einer Androgendeprivationstherapie.
Antiandrogene	
Bicalutamid L02BB03 generisch	• 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 LHRH-Analogon oder in Verbindung mit Orchiektomie (komplette Androgenblockade) sowie bei Patienten, die bereits mit einem LHRH-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 zugelassen: • zur Behandlung von erwachsenen männlichen Patienten mit fortgeschrittenem hormonabhängigen Prostatakarzinom. • […]
Relugolix	Orgovyx ist indiziert zur Behandlung von erwachsenen Patienten mit fortgeschrittenem hormonsensitivem Prostatakarzinom.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
L02BX04 Orgovyx	
Buserelin L02AE01 Profact	Profact® Depot 9,45 mg 3-Monatsimplantat ist angezeigt bei Erwachsenen zur Behandlung des fortgeschrittenen hormonempfindlichen Prostatakarzinoms. Profact® Depot 9,45 mg 3-Monatsimplantat 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. • […]
Triptorelin L01AA06 Pamorelin	ist indiziert zur Behandlung des • lokal fortgeschrittenen oder metastasierenden, hormonabhängigen Prostatakarzinoms. • […]
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). • […]
Enzalutamid L02BB04 Xtandi	Xtandi ist angezeigt: • zur Behandlung erwachsener Männer mit metastasiertem hormonsensitivem Prostatakarzinom (metastatic hormone-sensitive prostate cancer, mHSPC) in Kombination mit einer Androgenentzugstherapie • […]

II. Zugelassene Arzneimittel im Anwendungsgebiet

Darolutamid L02BB06 Nubeqa	NUBEQA wird angewendet zur Behandlung erwachsener Männer mit: • metastasiertem hormonsensitivem Prostatakarzinom (mHSPC) in Kombination mit Docetaxel und einer Androgendeprivationstherapie. • […]
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: AMIce-Datenbank, Fachinformationen

Inhaltsverzeichnis

Abkürzungsverzeichnis

ADT	Androgen Deprivations-Therapie
AE	Adverse Event/Adverse Effect
AR	Androgen Receptor
ARSI	Androgen Receptor Signaling Inhibitor
ARAT	Androgen-Receptoraxis-Targeted
ARTA	Androgen Receptor Targeted Agents
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
CADT	Continuous Androgen-Deprivation Therapy
EBRT	External Beam Radiotherapy
ECOG	Eastern Cooperative Oncology Group
ECRI	Emergency Care Research Institute
FACT-P	Functional Assessment of Cancer Therapy – Prostate
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRH	Growth Hormone Recept
HR	Hazard Ratio
HVD	High-Volume Disease
IADT	Intermittent Androgen-Deprivation Therapy
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LHRH	Luteinizing Hormone-Releasing Hormone
LDH	Lactate Dehydrogenase
LoE	Level of Evidence
LVD	Low-Volume Metastatic Disease
mCSPC	Metastatic Castration-Sensitive Prostate Cancer
mHSPC	Metastasiertes hormonsensitives Prostatakarzinom
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
OS	Overall survival
PBO	Placebo
PFS	Progression-Free Survival
PSA	Prostate-Specific Antigen

RP	Radical Prostatectomy
rPFS	Radiographic Progression-Free Survival
RoB	Risk of Bias
RR	Relatives Risiko
RT	Radiotherapy
SIGN	Scottish Intercollegiate Guidelines Network
SoC	Standard of Care
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Behandlung erwachsener Männer mit metastasiertem hormonsensitivem Prostatakarzinom (mHSPC).

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Prostatakarzinom* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.google.com/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 28.06.2024 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 3213 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. 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 Referenzen 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 17 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Sathianathen NJ et al., 2020 [13].

Abiraterone acetate in combination with androgen deprivation therapy compared to androgen deprivation therapy only for metastatic hormone-sensitive prostate cancer

Fragestellung

To assess the effects of early abiraterone acetate, in combination with systemic ADT, for newly diagnosed metastatic hormone-sensitive prostate cancer.

Methodik

Population:

- Men diagnosed with hormone-sensitive prostate cancer.
- We excluded men with advanced prostate cancer who received chemotherapy without known metastases, and those who received prior chemotherapy of any agent for their prostate cancer.

Intervention:

- Abiraterone acetate and prednisone in combination with androgen deprivation therapy (using methods outlined under 'Comparator interventions' below).

Komparator:

- Androgen deprivation therapy alone (using luteinizing hormone-releasing hormone agonist or antagonist; nonsteroidal antiandrogen monotherapy; combination of antiandrogen plus luteinizing hormone-releasing hormone agonist [maximum androgen blockade], or bilateral orchiectomy).

Endpunkte:

- Primary outcomes: Time to death due to any cause, Quality of life.
- Secondary outcomes: Grades III to V adverse events, Time to death due to prostate cancer, Time to disease progression, Discontinued treatment due to adverse events.

Recherche/Suchzeitraum:

- We searched CENTRAL, MEDLINE, Embase, six other databases, two trials registries, grey literature, and conference proceedings, up to 15 May 2020.

Qualitätsbewertung der Studien:

- Cochrane's 'Risk of bias' assessment tool.
- GRADE.

Ergebnisse

Anzahl eingeschlossener Studien:

- We included two randomized controlled trials (RCT).
- This review included a total of 2201 men with metastatic, hormonesensitive prostate cancer, 1097 of whom received abiraterone acetate and prednisone in addition to androgen deprivation therapy.

Charakteristika der Population/Studien:

Fizazi 2017

Study characteristics	
Participants	Inclusion criteria: • Willing and able to provide written, informed consent • Men aged 18 years and older • Newly diagnosed metastatic prostate cancer within 3 months prior to randomization • Adenocarcinoma of the prostate confirmed by histology or cytology without neuroendocrine differentiation or small cell histology • Distant metastatic disease documented by positive bone scan or metastatic lesions on CT or MRI • Two of the following high-risk prognostic factors: Gleason score ≥ 8, presence of 3 or more lesions on bone scan, presence of measurable visceral (excluding lymph node disease) metastasis (RECIST 1.1) • Eastern Cooperative Oncology Group (ECOG) performance status grade of 0, 1, or 2 • Adequate hematologic, hepatic, and renal function • Ability to swallow study medication tablets • Agrees to use a condom and another effective method of birth control if having sex with a woman of childbearing potential
	Exclusion criteria: • Active infection or other medical condition that would contraindicate use of prednisone • Any chronic medical condition requiring a higher systemic dose of corticosteroid than 5 mg prednisone per day • Pathological finding consistent with small cell carcinoma of the prostate • Known brain metastasis • Any prior pharmacotherapy, radiation therapy, or surgery with curative intent for metastatic prostate cancer. The following exceptions were allowed: up to 3 months of ADT with LHRH agonists or orchiectomy, with or without concurrent anti-androgens, prior to the men's randomization was permitted; men may have one course of palliative radiation or surgical therapy to treat symptoms resulting from metastatic disease (e.g. impending cord compression or obstructive symptoms) if it was administered prior to randomization. Radiation or surgical therapy could not have been initiated 4 weeks after the start of ADT or orchiectomy • Uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg or diastolic BP ≥ 95 mmHg) • Men with a history of hypertension were allowed, provided blood pressure was controlled by anti-hypertensive treatment • Active or symptomatic viral hepatitis or chronic liver disease • History of adrenal dysfunction • Clinically significant heart disease, as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) Class II to IV heart disease, or cardiac ejection fraction measurement of < 50% at baseline • Atrial fibrillation, or other cardiac arrhythmia requiring pharmacotherapy • Other malignancy (within 5 years), except non-melanoma skin cancer • Administration of an investigational therapeutic or invasive surgical procedure (not including surgical castration) within 30 days of cycle 1, day 1, or currently enrolled in an investigational study • Any condition or situation, which in the opinion of the investigator, would put the man at risk, may confound study results, or interfere with the man's participation in this study

James 2017

Study characteristics	
Participants	Inclusion criteria: • High risk newly diagnosed men with one of: (i) stage T3/4 N0 M0 histologically confirmed prostate adenocarcinoma with PSA ≥ 40 ng/mL or Gleason sum score 8 to 10; (ii) stage Tany N+ M0 or Tany Nany M+ histologically confirmed prostate adenocarcinoma; (iii) multiple sclerotic bone metastases with a PSA ≥ 100 ng/mL without histological confirmation; or men with histologically confirmed prostate adenocarcinoma previously treated with radical surgery or radiotherapy who are now relapsing with one of: (i) PSA ≥ 4 ng/mL and rising, with doubling time less than 6 months; (ii) PSA ≥ 20 ng/mL • Intention to treat with long-term androgen suppression • Fit for all protocol treatment and follow-up, WHO performance status 0 to 2 • Have completed the appropriate investigations prior to randomization • Adequate haematological function: neutrophil count > 1.5 x 109/L and platelets > 100 x 109/L • Adequate renal function: serum creatinine < 1.5 ULN • Adequate liver function: ALT or AST < 1.5 ULN, bilirubin < ULN • Normal testosterone level prior to hormone treatment

James 2017 *(Continued)*

Exclusion criteria:

- Prior systemic therapy for locally advanced or metastatic prostate cancer except those listed in inclusion criteria 1
- Metastatic brain disease or leptomeningeal disease
- Any other previous, or current malignant disease, which in the judgement of the responsible physician, is likely to interfere with STAMPEDE treatment or assessment
- Symptomatic peripheral neuropathy grade 2 (NCI CTC)
- Any surgery (e.g. TURP) performed within the past 4 weeks

Qualität der Studien:

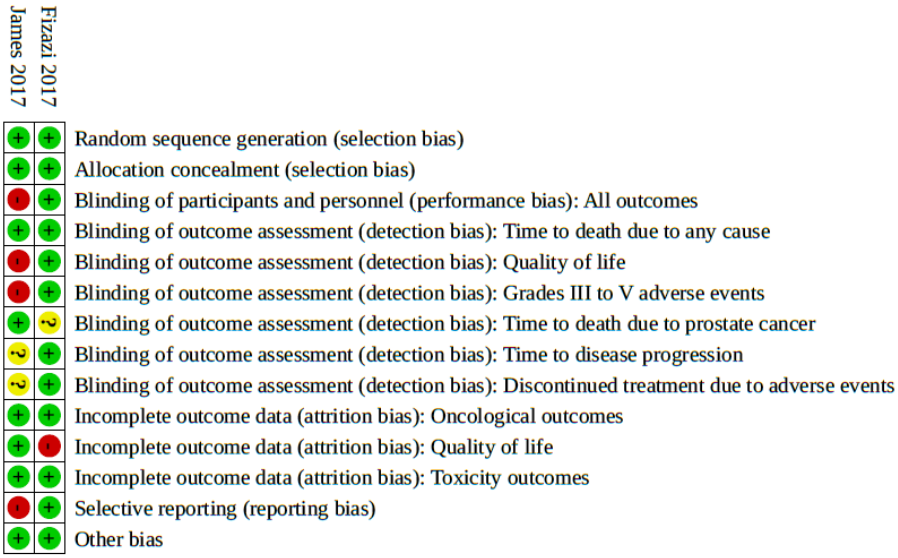
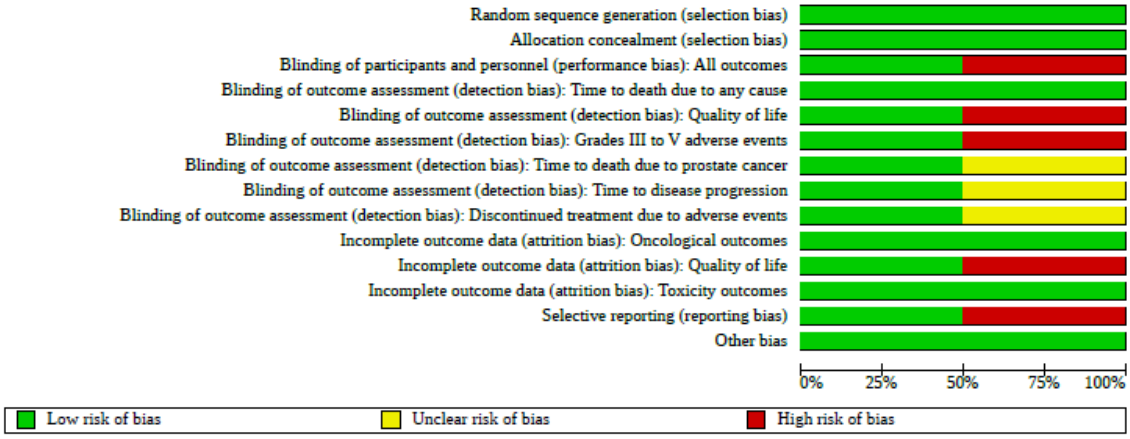


Figure 3. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies.



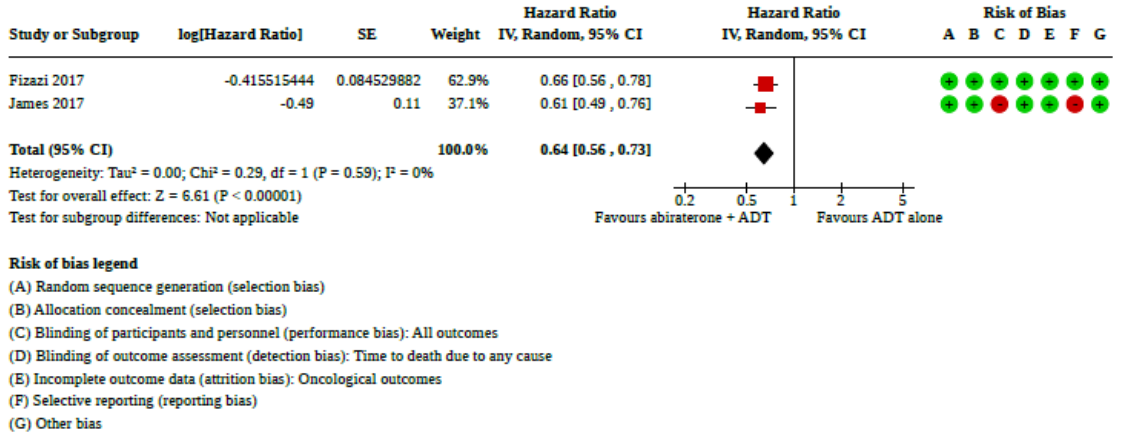
Studienergebnisse:

1. Abiraterone acetate and prednisone in combination with androgen deprivation therapy versus androgen deprivation therapy only

1.1 Time to death due to any cause

- **Abiraterone acetate in addition to androgen deprivation therapy (ADT) reduced the probability of dying from any cause more than ADT alone** (hazard ratio [HR] 0.64, 95% confidence interval [CI] 0.56 to 0.73; two RCTs, 2201 men; Analysis 1.1; Figure 4; high-certainty evidence).
- Compared to the five-year survival for stage IV prostate cancer in the Surveillance, Epidemiology, and End Results (SEER) registry in the pre-docetaxel era (2007 to 2013; Rawla 2019), **the addition of abiraterone acetate resulted in 163 fewer deaths (95% CI -210 to -115) from all causes per 1000 men with hormone-sensitive metastatic prostate cancer.**

Figure 4. Forest plot of comparison: 1 Abiraterone + ADT vs ADT alone, outcome: 1.1 Time to death due to any cause.



1.2 Quality of life

- **Abiraterone acetate in addition to ADT probably results in a small, likely not clinically meaningful improvement in quality of life at 12 months** compared to ADT alone (mean difference [MD] 2.90 points, 95% CI 0.11 to 5.60; one RCT, 838 men; Analysis 1.2; moderate certainty evidence) assuming a minimally clinically important difference of 6 – 10 (Cella 2009).
- We downgraded the certainty of the evidence due to concerns regarding possible attrition bias.

1.3 Grades III to V adverse events

- **Abiraterone acetate in addition to ADT increases the risk of grades III to V adverse events** compared to ADT alone (risk ratio [RR] 1.34, 95% CI 1.22 to 1.47; one RCT, 1199 men; Analysis 1.3; high-certainty evidence). This corresponds to 162 more (95% CI 105 to 224) grades III to IV adverse events per 1000 men treated with abiraterone acetate and ADT compared to ADT alone, at a median follow-up of 30 months.

1.4 Time to death due to prostate cancer

- **Abiraterone acetate in addition to ADT probably reduces the probability of prostate cancer-specific death** compared to ADT alone (HR 0.58, 95% CI 0.50 to 0.68; two RCTs, 2201 men; Analysis 1.4; moderate-certainty evidence). Compared to the event rate in

the control arm of the LATITUDE trial at a median follow-up of 30.4 months, the addition of abiraterone acetate resulted in 120 fewer (95% CI -145 to -90) deaths from prostate cancer per 1000 men with hormone-sensitive metastatic prostate cancer (Fizazi 2017).

- We downgraded the level of the certainty due to concerns regarding possible performance bias.

1.5. Time to disease progression

- **Abiraterone acetate in addition to ADT probably reduces the probability of progression of disease** compared to ADT alone (HR 0.35, 95% CI 0.26 to 0.49; two RCTs, 2201 men; Analysis 1.5; moderate-certainty evidence). Compared to the three-year event rate in the control arm of the STAMPEDE trial, **the addition of abiraterone acetate resulted in 369 fewer (95% CI -456 to -256) incidents of disease progression per 1000 men with hormone-sensitive metastatic prostate cancer** (James 2017).
- We downgraded the certainty of the evidence due to concerns regarding possible detection bias.

1.6 Discontinued treatment due to adverse events

- **Abiraterone acetate in addition to ADT probably increases the risk of discontinuing treatment due to adverse events** compared to ADT alone (RR 1.50, 95% CI 1.17 to 1.92; one RCT, 1199 men; Analysis 1.6; moderate-certainty evidence). This corresponds to 51 more men (95% CI 17 to 93) discontinuing treatment because of adverse events per 1000 men treated with abiraterone acetate and ADT compared to ADT alone, at a median follow-up of 30 months.
- We downgraded the certainty of the evidence due to concerns regarding possible detection bias and imprecision.

<u>2. Subgroup analysis: volume of metastases</u>

2.1 Time to death due to any cause

- The probability of dying from any cause for men with low volume of metastases was HR 0.68 (95% CI 0.50 to 0.91); for men with high volume of metastases it was HR 0.61 (95% CI 0.53 to 0.71; Analysis 2.1).
- **The test for interaction was not significant** (P = 0.56; I^2 = 0%).

2.2 Quality of life

- The mean difference in FACT-P scores for the men with low volume of metastases who received abiraterone acetate was -2.03 (95%CI -10.98 to 6.92); for men with high volume of metastases, the mean difference was 3.68 (95%CI 0.73 to 6.63; Analysis 2.2)
- **The test for interaction was not significant** (P = 0.23; I^2 = 29%).

2.4 Time to death due to prostate cancer

- The probability of dying from prostate cancer for men with low volume disease was HR 0.67 (95%C CI 0.44 to 1.01); for men with high volume disease it was HR 0.57 (95% CI 0.49 to 0.67; Analysis 2.3).
- **The test for interaction was not significant** (P = 0.50; I^2 = 0%).

2.5 Time to progression

- The probability of progression of disease for men with low volume of metastases was HR 0.46 (95% CI 0.33 to 0.63); for men with high volume of metastases, the HR was 0.46 (95% CI 0.31 to 0.69; Analysis 2.4).

- **The test for interaction was not significant** (P = 0.97; I^2 = 0%).

4. Sensitivity analysis

- For the primary outcome of time to death due to any cause, we rated both trials at overall low risk of bias, therefore, the results of the sensitivity analysis are the same as Analysis 1.1.
- For grades III to V adverse events, we only rated Fizazi 2017 at overall low risk of bias, therefore, the results of the sensitivity analysis are the same as Analysis 1.3.
- We were unable to conduct a sensitivity analysis for quality of life.

Anmerkung/Fazit der Autoren

The addition of abiraterone acetate with prednisolone to androgen deprivation therapy improves overall survival, and probably extends disease-specific survival and delays progression, compared to androgen deprivation therapy alone. It also results in a small improvement in quality of life at 12 months, but this is not clinically meaningful. However, grades III to V adverse events are increased, and probably more men discontinue treatment because of them. Therefore, men should be counseled about adverse events before commencing treatment, to help them understand the tradeo Hs of treatment.

Kommentare zum Review

- Die Ergebnisse sollten mit Vorsicht betrachtet werden, da sie lediglich auf zwei randomisierten kontrollierten Studien basieren.

3.2 Systematische Reviews

Matsukawa A et al., 2024 [9].

Impact of disease volume on survival efficacy of triplet therapy for metastatic hormone-sensitive prostate cancer: a systematic review, meta-analysis, and network meta-analysis

➔ Siehe auch folgende SR mit ähnlicher Schlussfolgerung:
- Ciccarese C et al., 2022 [4]
- Yanagisawa T et al., 2022 [17]: Nur direkte Evidenz berücksichtigen, indirekte Evidenz weist methodische Mängel auf.

Fragestellung

We performed a systematic review, meta-analysis, and network meta-analysis to assess the oncologic benefit of triplet therapy in mHSPC patients stratified by disease volume and compare them with doublet treatment regimens.

Methodik

Population:

- Patients with mHSPC.

Intervention/Komparator:

- triplet therapy (Interventions) […] compared to […] other currently available treatment regimens (Comparisons).

Endpunkte:

- OS stratified by disease volume.

Recherche/Suchzeitraum:

- PubMed, Web of Science, and Scopus databases […] in March 2023.

Qualitätsbewertung der Studien:

- using the Cochrane Handbook for Systematic Reviews of Interventions risk-of-bias tool (RoB version 2).

Ergebnisse

Anzahl eingeschlossener Studien:

- we finally identified eight RCTs […] comprising 6969 patients.

Charakteristika der Population/Studien:

Table 1 Study demographics and oncologic outcomes of 8 RCTs included in the analyses

Study name/first author	Year	Treatment arm	Control arm	No. of pts			De novo mets., %		High-volume, %		HR for OS (95%CI)		Median F/U mo
				Total	T	C	T	C	T	C	High-volume	Low-volume	
ARASENS Smith et al Hussain et al	2022	DAR + DOC + ADT	DOC + ADT	1306	c	655	86	87	76	78	0.69 (0.57–0.82)	0.68 (0.41–1.13)	43
PEACE-1 Fizazi et al	2022	ABI + DOC + ADT	DOC + ADT	710	355	355	100	100	63	65	0.72 (0.55–0.95)	0.83 (0.50–1.38)	45.7
ENZAMET Davis et al	2019/2022	*ENZ + DOC + ADT	*DOC + ADT	503	254	249	71	73	71	72	0.87 (0.65–1.17)	0.61 (0.33–1.10)	68
		*ENZ + ADT	*ADT	622	310	312	ND	ND	39	39	0.69 (0.49–0.97)	0.51 (0.35–0.75)	
LATITUDE Fizazi et al	2017/2019	ABI + ADT	ADT	1199	597	602	100	100	82	78	0.62 (0.52–0.74)	0.72 (0.47–1.1)	51.8
STAMPEDE (Arm G) James et al Hoyle et al	2017/2019	ABI + ADT	ADT	990	493	497	94	96	54	51	0.6 (0.46–0.78)	0.64 (0.42–0.97)	40
STAMPEDE (Arm B,C,E) James et al Clarke et al	2016/2019	DOC + ADT	ADT	1086	362	724	96	95	54	57	0.81 (0.64–1.02)	0.76 (0.54–1.07)	78.2
CHAARTED Sweeny et al Kyriakopoulos et al	2015/2018	DOC + ADT	ADT	790	397	393	73	73	66	64	0.63 (0.5–0.79)	1.04 (0.7–1.55)	53.7
GETUG-AFU15 Gravis et al	2013/2016	DOC + ADT	ADT	385	192	193	68	66	48	47	0.78 (0.56–1.09)	0.72 (0.47–1.1)	83.9

RCT Randomized controlled trial, *T* Treatment arm, *C* Control arm, *No* Number, *Pts* Patients, *HR* Hazard ratio, *OS* Overall survival, *CI* Confidence interval, *F/U* Follow-up, *DOC* Docetaxel, *ADT* Androgen deprivation therapy, *ABI* Abiraterone acetate, *APA* Apalutamide, *DAR* Darolutamide, *ENZ* Enzalutamide, *mHSPC* metastatic hormone-sensitive prostate cancer, *ND* No data

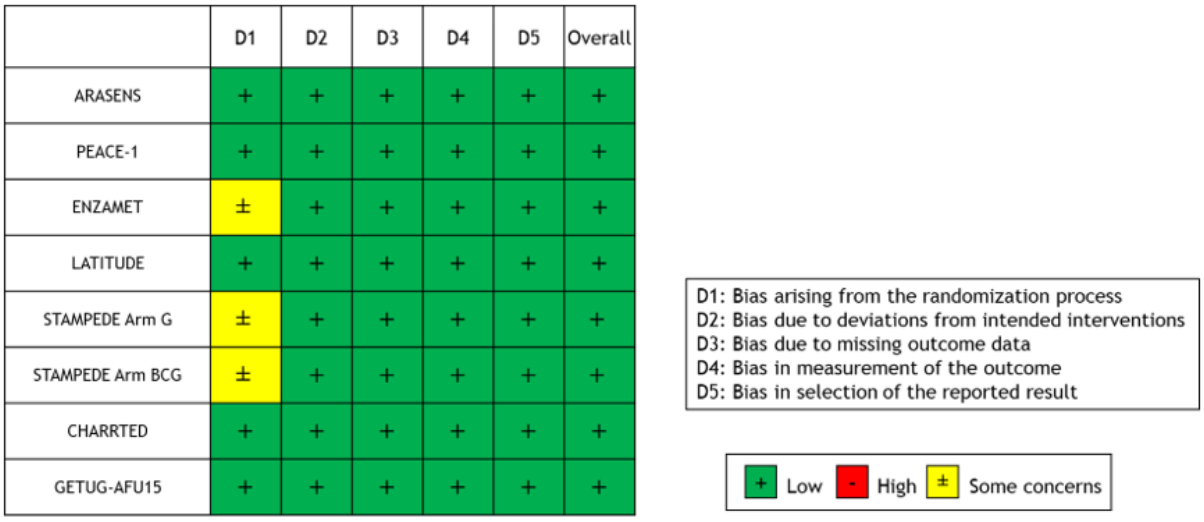
*Data on patients treated with docetaxel was extracted. Control arm contained ADT + nonsteroidal antiandrogen

**Described as rates in overall cohort

Qualität der Studien:

- ll included studies had a low risk of bias owing to the nature of prospective phase 3 RCTs. The quality assessment of this meta-analysis was performed according to the AMSTAR2 checklist; overall confidence in the results of this review was “High”.

Supplementary Figure 1. Risk of bias assessment of the included RCTs



Studienergebnisse:

Meta-analysis of triplet therapy vs. docetaxel plus ADT

- Three studies comprising 2519 patients provided data on OS in mHSPC patients treated with triplet therapy or docetaxel plus ADT separately for high- and low-volume disease.
- As shown in Fig. 2, **adding ARSI to docetaxel plus ADT improved OS in both patients with high- (pooled HR: 0.73, 95%CI 0.64–0.84) and low- (pooled HR: 0.71, 95%CI 0.52–0.97) volume disease**. There was no statistically significant difference between patients

with low- vs. high-volume in terms of OS benefit from adding ARSI to docetaxel plus ADT (p = 0.9).

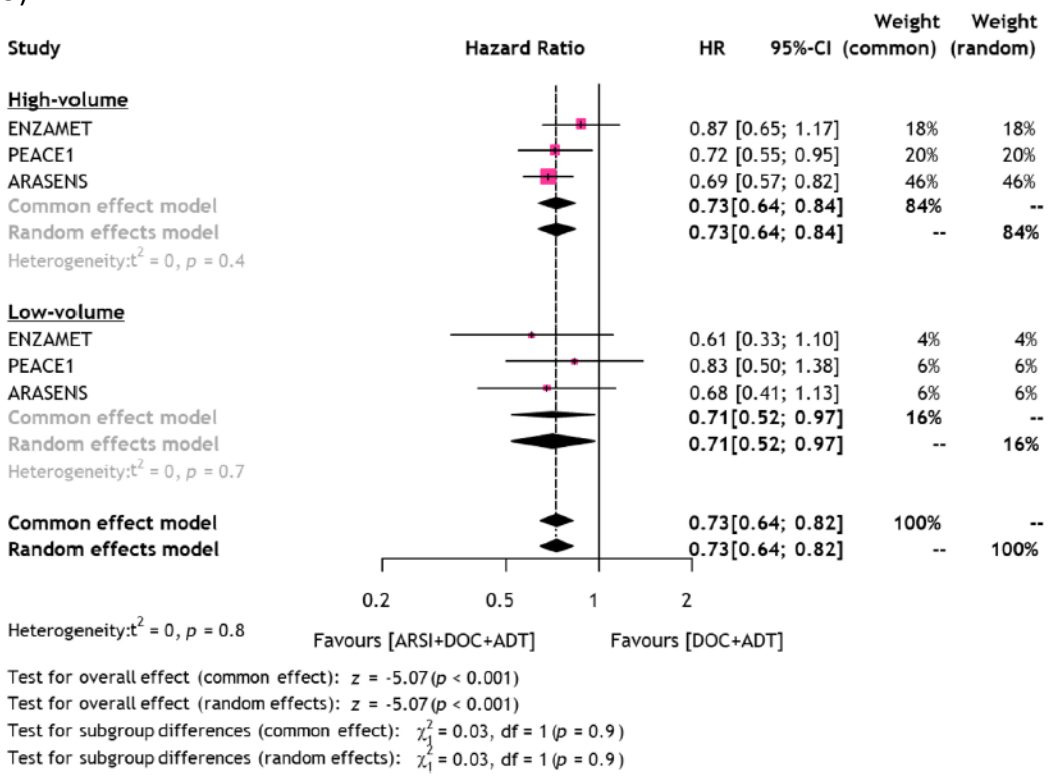
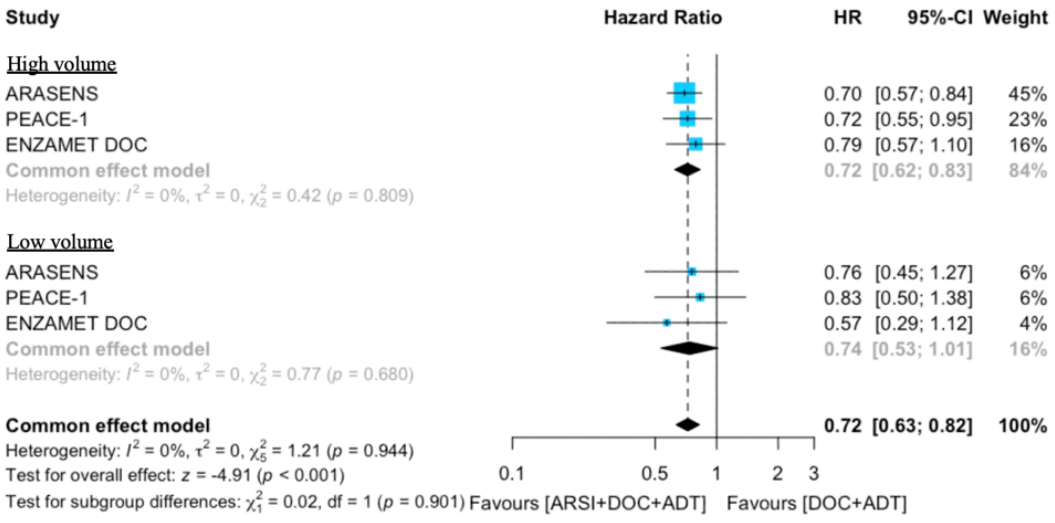


Fig. 2 Forest plots showing the association between OS and triplet or docetaxel-based doublet therapy for mHSPC stratified by disease volume *OS* Overall survival, *mHSPC* metastatic hormone-sensitive prostate cancer, *ARSI* Androgen receptor signaling inhibitors, *DOC* Docetaxel, *ADT* Androgen deprivation therapy

- In an analysis **focusing on patients with de novo mHSPC, adding ARSI to docetaxel plus ADT improved OS in patients with high-volume disease (pooled HR: 0.72, 95%CI 0.62–0.83), but not in those with low-volume disease (pooled HR: 0.74, 95%CI 0.53–1.01)**. There was no significant difference in OS between patients with low- vs. high-volume in terms of OS benefit from adding ARSI to docetaxel plus ADT (p = 0.9; Suppl. Fig. 3).

Supplementary Figure 3. Forest plots showing the association between OS and triplet or docetaxel-based doublet therapy for *de novo* mHSPC stratified by disease volume



- The Cochrane's Q tests revealed no significant heterogeneity in the analysis.

Anmerkung/Fazit der Autoren

We found that compared to docetaxel plus ADT, triplet therapy improves OS in patients with mHSPC, irrespective of disease volume. […] Further investigation with well-designed RCTs is awaited to clarify the comparative oncologic outcomes between triplet and ARSI-based doublet therapies and select the optimal candidates who are most likely to benefit from triplet therapy.

Kommentare zum Review

- Es wurde nur die direkte Evidenz und die sich darauf beziehenden Schlussfolgerungen dargestellt. Die indirekte Evidenz der Netzwerk-Meta-Analyse wurde nicht berücksichtigt, da die Annahmen der Transitivität und der Konsistenz nicht ausreichend überprüft wurden.

Ramos-Esquivel, A et al., 2023 [11].

A systematic review and meta-analysis on overall survival, failure-free survival and safety outcomes in patients with metastatic hormone-sensitive prostate cancer treated with new anti-androgens

➔ Siehe auch:
- Chen X et al., 2023 [3]: Nur direkte Evidenz berücksichtigen, indirekte Evidenz weist methodische Mängel auf.

Fragestellung

[…] the aim of this systematic review and meta-analysis is to assess the overall efficacy and safety of new generation antiandrogens in combination with ADT vs. ADT alone for patients with hormone-sensitive metastatic prostate cancer.

Methodik

Population:

- with hormone-sensitive (i.e., not castrate-resistant) metastatic prostate cancer ('de-novo or recurrent').

Intervention:

- ADT plus either abiraterone, apalutamide, darolutamide or enzalutamide.

Komparator:

- ADT.

Endpunkte:

- OS,
- failure-free survival (time from randomization to castration-resistant prostate cancer, new cancer-related symptoms or radiographic progression-free survival),
- adverse events grade 3 or higher.

Recherche/Suchzeitraum:

- […] four electronic databases (MEDLINE, Embase, LILACS and the Cochrane Central Register of Controlled Trials) from January 2007 to 11 April, 2022.

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool.

Ergebnisse

Anzahl eingeschlossener Studien:

- […] we identified seven trials (n = 7 544; alle RCTs).

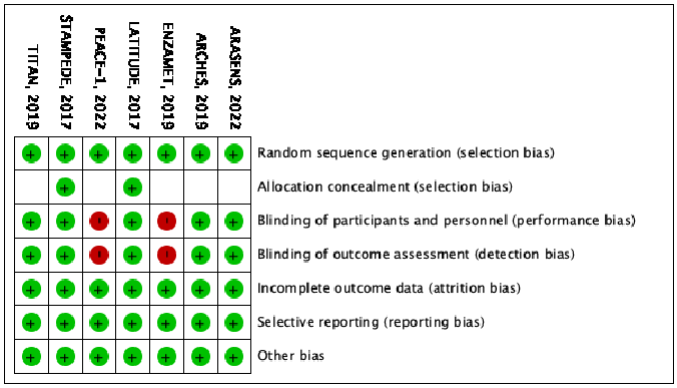
Charakteristika der Population/Studien:

Trial	Arasens trial	Titan trial	Arches trial	Enzamet trial	Stampede trial	Latitude trial	Peace-1 trial
Treatment arms	Experimental: Darolutamide (600 mg/day) + ADT + docetaxel *N*=651 Control: Placebo + ADT + docetaxel *N*=655	Experimental: Apalutamide (240 mg/day) + ADT *N*=525 Control: Placebo + ADT *N*=527	Experimental: Enzalutamide (160 mg/day) + ADT *N*=574 Control: Placebo + ADT *N*=576	Experimental: Enzalutamide (160 mg/day) + ADT *N*=563 Control: Standard of care (Bicalutamide, Nilutamide, Flutamide) + ADT *N*=562	Experimental: Abiraterone (1 g/day) + ADT *N*=500 (with metastatic disease) Control: Placebo + ADT *N*=502(with metastatic disease)	Experimental: Abiraterone (1 g/day) + ADT *N*=597 Control: Placebo *N*=602	Experimental: Abiraterone (1 g/day) + Standard of care (ADT + Docetaxel) ± Radiotherapy *N*=355 Control: Standard of care (ADT + Docetaxel) ± Radiotherapy *N*=355
Enrollment	Nov 2016–June 2018	Dec 2015–July 2017	March 2016–Jan 2018	March 2014–March 2017	Nov 2011–Jan 2014	Feb 2013–Dec 2014	Nov 2013–Dec 2018
Primary endpoint	Overall survival	Radiographic progression-free survival and overall survival	Radiographic progression-free and overall survival	Overall survival	Overall survival	Radiographic progression-free and overall survival	Radiographic progression-free and overall survival
Secondary outcomes	Time to castration-resistant prostate cancer Time to pain progression Symptomatic skeletal event-free survival Time to a first symptomatic skeletal event Time to initiation of subsequent systemic antineoplastic therapy Time to worsening of disease-related physical symptoms Time to initiation of opioid treatment for 7 or more consecutive days Safety	Time to cytotoxic chemotherapy Time to pain progression Time to chronic opioid use Time to skeletal-related event	Time to PSA progression Time to initiation of new antineoplastic therapy PSA undetectable rate Objective response rate Time to deterioration in urinary symptoms Overall survival Time to first symptomatic skeletal event Time to castration resistance Patient-reported outcomes Time to deterioration of QoL Time to pain progression	Progression-free survival by PSA level Clinical progression-free survival (radiographic) Adverse events	Failure-free survival Adverse events Symptomatic skeletal events Progression-free survival Prostate cancer-specific survival Quality of life	Time to the next skeletal-related event Time to progression with respect to PSA level Time to the next therapy for prostate cancer Time to initiation of chemotherapy. Time to pain progression	CRPC-free survival. Serious-genitourinary-event-free survival Prostate-cancer-specific survival Time to next skeletal-related event PSA response rate Prognostic study of serum PSA measured 6–8 monthsafter initiation of systemic therapy Time to pain progression Time to chemotherapy for CRPC Quality of life Changes in bone mineral density Correlation of biomarkers with outcome Event rate per 100 person-years of treatment analysis Toxicity
Key inclusion criteria	Patients with histologically or cytologically confirmed prostate cancer and metastases. Eligible patients had to be candidates for androgen-deprivation therapy and docetaxel, in the investigator's judgment	Eligible patients were required to have documented adenocarcinoma of the prostate and distant metastatic disease documented on the basis of at least one lesion on bone scanning, with or without visceral or lymph-node involvement.	Eligible patients had hormone-sensitive metastatic disease, either de novo or after recurrence after prior local therapy	Patients with prostatic adenocarcinoma with target and non-target metastases according to RECIST 1.1.	Newly diagnosed prostate adenocarcinoma and any of: -Metastatic disease; - Node-positive;and ≥2 of Stage T3-T4/ PSA≥40 ng/ml and Gleason≥8 Or: - Relapsing after previous RP or RT and any of: metastatic disease; node-positive; PSA≥4 ng/ml, rising & PSA doubling time < 6 months, PSA ≥ 20 ng/ml	Patients with M1 disease and at least 2/3 criteria: Gleason score ≥ 8; ≥ 3 bone metastases; visceral metastases	Patients with confirmed prostate adenocarcinoma documented as de novo metastatic. Patients must have received ADT for a maximum of 3 months before randomization and there must be a minimum of 6 weeks between the start of ADT and the start of docetaxel

For the PECE-1 Trial we only included the comparison of abiraterone + docetaxel + ADT therapy vs. placebo + docetaxel + ADT therapy.
ADT, androgen-deprivation therapy; CRPC, castration-resistant prostate cancer; PSA, prostate specific antigen; QoL. quality of life; RECIST. 1.1: Response Evaluation Criteria in Solid Tumors 1.1; RP, radical prostatectomy; RT, radiotherapy.

Qualität der Studien:

- Two of the included trials were unblinded (ENZAMET and PEACE-1), which can raise concerns regarding performance and detection bias.

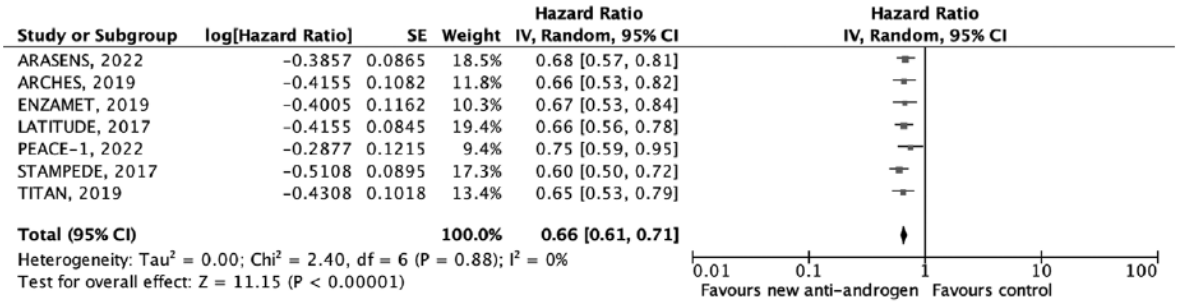


Studienergebnisse:

OS

- adding a new antiandrogen, namely: abiraterone, apalutamide, darolutamide or enzalutamide to ADT resulted in a significant improvement in OS (pooled HR, 0.66; 95%

CI, 0.61–0.71; P < 0.00001), with no evidence of heterogeneity among trials (Tau^2 = 0; I^2 = 0%; P = 0.88).



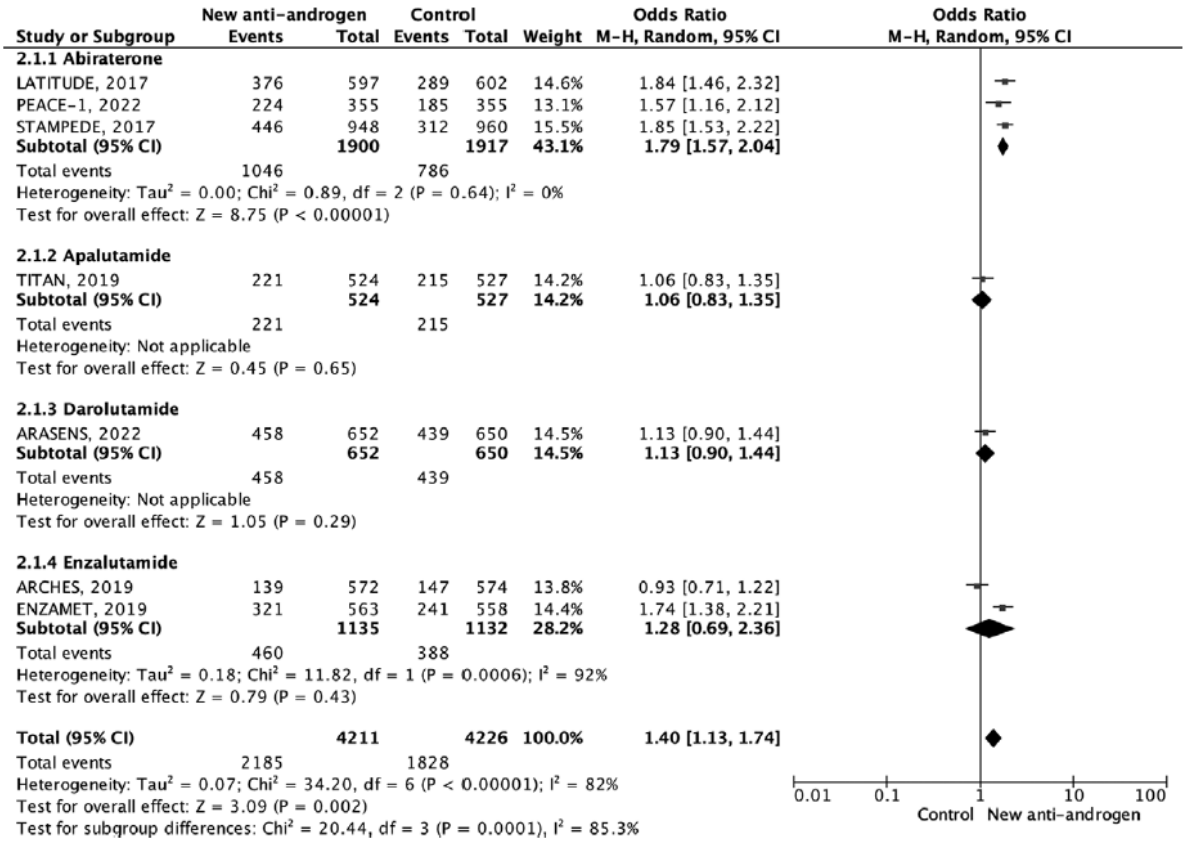
Forest plot for overall survival.

Failure-free survival

- The addition of abiraterone, apalutamide, darolutamide or enzalutamide to ADT conferred a significantly longer failure-free survival in comparison to ADT alone (pooled HR, 0.43; 95% CI, 0.39–0.47; P < 0.00001). There was no statistical heterogeneity among the included trials (Tau^2 = 0; I^2 = 27%; P = 0.22) (Figure 2).

Adverse Events

Adverse events grade 3 or higher were more frequently reported by participants receiving the combination of a new antiandrogen plus ADT than in patients allocated to ADT alone (OR, 1.40; 95% CI, 1.13–1.74; P = 0.002). For this particular outcome, we detected a considerable heterogeneity among included trials (Tau^2 = 0.07; I^2, 82%). In concrete, the addition of abiraterone to ADT resulted in a significantly increased the OR for severe adverse events [OR, 1.79 (95% CI, 1.57–2.04; P < 0.00001)]. In contrast, the OR for severe adverse events was not significantly different between experimental and control arms in those trials employing apalutamide, darolutamide or enzalutamide (Fig. 3).



Forest plot for treatment-related side effects grade 3 or higher.

Anmerkung/Fazit der Autoren

In conclusion, our analysis shows an OS benefit of adding a new antiandrogens to ADT in patients with newly diagnosed or recurrent metastatic prostate cancer.

Vale CL et al., 2023 [14].

Which patients with metastatic hormone-sensitive prostate cancer benefit from docetaxel: a systematic review and meta-analysis of individual participant data from randomised trials

Fragestellung

Adding docetaxel to androgen deprivation therapy (ADT) improves survival in patients with metastatic, hormone-sensitive prostate cancer, but uncertainty remains about who benefits most. We therefore aimed to obtain up-to-date estimates of the overall effects of docetaxel and to assess whether these effects varied according to prespecified characteristics of the patients or their tumours.

Methodik

Population:

- Patients with metastatic, hormone-sensitive prostate cancer.

Intervention/Komparator:

- Docetaxel plus ADT compared with ADT alone.

Endpunkte:

- The primary outcome was overall survival.
- Secondary outcomes were progression-free survival and failure-free survival.

Recherche/Suchzeitraum:

- In brief, we ran comprehensive search strategies (appendix pp 2–5) for MEDLINE (from database inception to March 31, 2022), Embase (from database inception to March 31, 2022), and the Cochrane Central Register of Controlled Trials (from database inception to March 31, 2022).
- We also regularly searched the clinical trials register ClinicalTrials.gov from database inception to March 28, 2023, and screened the proceedings and abstracts of relevant conferences (from Jan 1, 1990, to Dec 31, 2022) […].

Qualitätsbewertung der Studien:

- Version 2 of the Cochrane Risk of Bias Assessment Tool.

Ergebnisse

Anzahl eingeschlossener Studien:

- We identified five eligible trials;
- The trials […] accrued 385 patients (GETUG-AFU15), 790 patients (CHAARTED), and 1086 metastatic patients (STAMPEDE) to eligible comparison groups (table 1).

Charakteristika der Population/Studien:

	GETUG-AFU15[5]	CHAARTED[2]	STAMPEDE[7]
Accrual period	October, 2004, to December, 2008	July, 2006, to November, 2012	November, 2005, to March, 2013
Number of patients randomly assigned	385	790	1086
Control group treatment	ADT (LHRH agonist or LHRH agonist plus anti-androgen therapy or surgical castration)	ADT (LHRH agonist or LHRH antagonist or surgical castration); oral calcium carbonate 500 mg daily; oral vitamin D 400 IU daily	ADT (GRH agonists or antagonists or orchidectomy)
Intervention group treatment	ADT (LHRH agonist or LHRH agonist plus antiandrogen therapy or surgical castration) plus docetaxel (75 mg/m² intravenously every 3 weeks for a maximum of nine cycles); premedication with an oral corticosteroid (8 mg dexamethasone or equivalent) the evening before, on the day of, and on the day after docetaxel infusion plus subcutaneous injection of G-CSF from day 5 for 5 days	ADT (LHRH agonist or LHRH antagonist or surgical castration) plus docetaxel (75 mg/m² intravenously every 3 weeks for six cycles); oral dexamethasone (8 mg approximately 12 h, 3 h, and 1 h before docetaxel); oral diphenhydramine optional; 500 mg oral calcium carbonate once daily; 400 IU oral vitamin D once daily	ADT (GRH agonists or antagonists or orchidectomy) plus docetaxel (75 mg/m² intravenously every 3 weeks for six cycles) plus oral prednisolone (10 mg once daily)
Median follow-up for all participants (IQR), months*	84 (79–89)	54 (42–67)	78 (63–96)

ADT=androgen deprivation therapy. G-CSF=granulocyte-colony stimulating factor. GRH=gonadotropin-releasing hormone. LHRH=luteinising hormone-releasing hormone.
*Data supplied for inclusion in the meta-analysis, and follow-up duration for each trial is in keeping with the most recent version of reported trial analysis, as cited.

Table 1: **Trial design details and key participant characteristics**

	GETUG-AFU15[4]		CHAARTED[3]		STAMPEDE[1]	
	ADT alone group (n=193)	ADT plus docetaxel group (n=192)	ADT alone group (n=393)	ADT plus docetaxel group (n=397)	ADT alone group (n=724)	ADT plus docetaxel group (n=362)
Age, years	64·3 (58·3–70·1)	63·1 (57·7–68·9)	63·0 (56·0–69·0)	64·0 (57·0–69·0)	65·9 (60·5–71·1)	65·4 (61·0–70·9)
WHO performance status						
0	176 (91%)	181 (94%)	272 (69%)	277 (70%)	521 (72%)	270 (75%)
1–2	7 (4%)	2 (1%)	121 (31%)	120 (30%)	203 (28%)	92 (25%)
Missing	10 (5%)	9 (5%)	0	0	0	0
Alkaline phosphatase, IU/L*	359 (136–570)	280 (155–545)	–	–	110 (75–253)	106 (72–233)
Missing	122 (63%)	113 (59%)	393 (100%)	397 (100%)	10 (1%)	4 (1%)
Prostate-specific antigen, ng/mL	25·9 (4·9–127·0)	26·7 (5·0–109·3)	13·7 (1·8–71·4)	10·8 (2·0–66·0)	102·5 (32·8–354·0)	97·1 (40·5–340·0)
Missing	3 (2%)	1 (1%)	1 (<1%)	0	0	0
Risk group						
High	70 (36%)	72 (38%)	169 (43%)	182 (46%)	257 (36%)	122 (34%)
Low	89 (46%)	88 (46%)	91 (23%)	105 (26%)	237 (33%)	115 (32%)
Missing	34 (18%)	32 (17%)	133 (34%)	110 (28%)	230 (32%)	125 (35%)
Gleason sum score						
<8	78 (40%)	84 (44%)	104 (26%)	117 (29%)	158 (22%)	66 (18%)
≥8	113 (59%)	103 (54%)	243 (62%)	241 (61%)	479 (66%)	253 (70%)
Missing	2 (1%)	5 (3%)	46 (12%)	39 (10%)	87 (12%)	43 (12%)
Nodal involvement						
N0	35 (18%)	31 (16%)	103 (26%)	127 (32%)	242 (33%)	118 (33%)
N+	43 (22%)	29 (15%)	138 (35%)	124 (31%)	416 (57%)	211 (58%)
Missing	115 (60%)	132 (69%)	152 (39%)	146 (37%)	66 (9%)	33 (9%)
Clinical T stage						
T1–2	45 (23%)	32 (17%)	190 (48%)	207 (52%)	90 (12%)†	52 (14%)†
T3	58 (30%)	48 (25%)	68 (17%)	63 (16%)	404 (56%)	197 (54%)
T4	3 (2%)	8 (4%)	38 (10%)	41 (10%)	163 (23%)	82 (23%)
Missing	87 (45%)	104 (54%)	97 (25%)	86 (22%)	67 (9%)	31 (9%)
Timing of metastatic disease diagnosis						
Synchronous	144 (75%)	128 (67%)	286 (73%)	289 (73%)	689 (95%)	347 (96%)
Metachronous	46 (24%)	62 (32%)	106 (27%)	108 (27%)	35 (5%)	15 (4%)
Missing	3 (2%)	2 (1%)	1 (<1%)	0	0	0
Evidence of bone metastases						
Yes	156 (81%)	157 (82%)	236 (60%)	252 (63%)	634 (88%)	307 (85%)
No	35 (18%)	34 (18%)	14 (4%)	11 (3%)	90 (12%)	55 (15%)
Missing	2 (1%)	1 (1%)	143 (36%)‡	134 (34%)‡	0	0
Evidence of visceral metastases§						
Yes	26 (13%)	31 (16%)	72 (18%)	66 (17%)	87 (12%)	40 (11%)
No	167 (87%)	161 (84%)	320 (81%)	331 (83%)	637 (88%)	322 (89%)
Missing	0	0	1 (<1%)	0	0	0
Disease volume						
Low	88 (46%)	87 (45%)	143 (36%)	134 (34%)	238 (33%)	124 (34%)
High	97 (50%)	100 (52%)	250 (64%)	263 (66%)	320 (44%)	148 (41%)
Missing	8 (4%)	5 (3%)	0	0	166 (23%)	90 (25%)

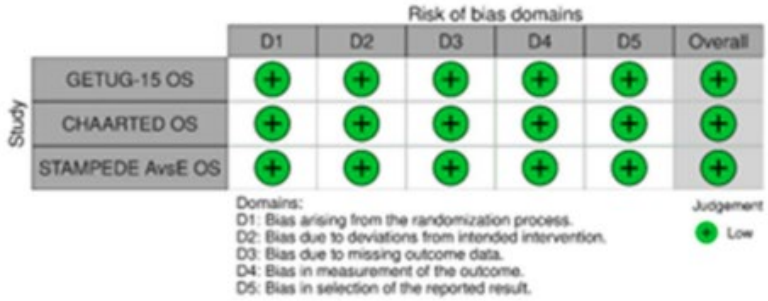
Data are median (IQR) or n (%). Percentages might not sum to 100 as a result of rounding. Data supplied for inclusion in the meta-analysis are in keeping with the most recent version of reported trial analysis, as cited. Comparison of baseline characteristics of patients by availability of clinical T stage data is in the appendix (p 51). *In GETUG-AFU15, specific values were only recorded for patients who were noted as having values outside the normal range at randomisation; 219 participants whose baseline reading was recorded as within the normal range had no specific value noted and are included here as missing. †Four patients randomly assigned in STAMPEDE reported as T stage 0, M stage 1 were included alongside the patients with T stage 1–2 for reporting and analysis purposes. ‡277 patients in CHAARTED were recorded as low volume without specifically characterising presence or absence of bone metastases. §Visceral metastases located in lung, liver, or adrenal gland.

Table 2: **Patient baseline characteristics**

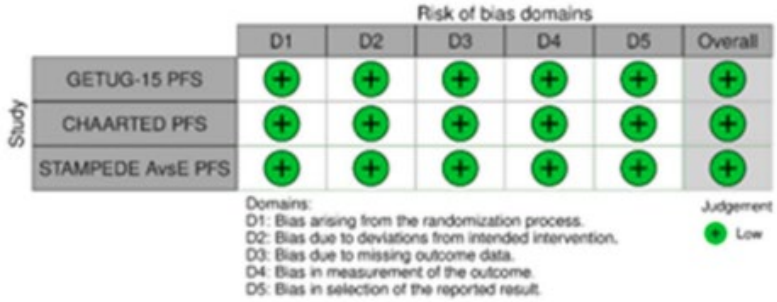
Qualität der Studien:

Figure S2: Risk of Bias summary of assessments (traffic light)

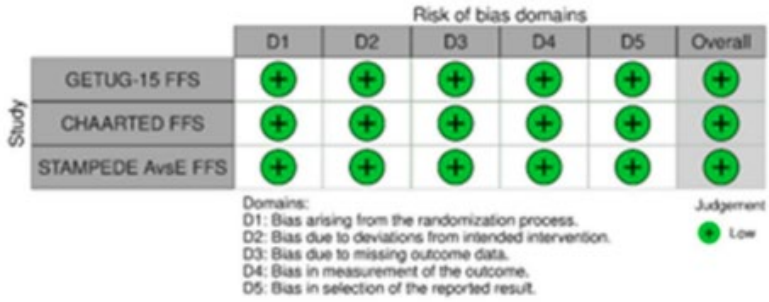
a) Overall survival



b) Progression-free survival



c) Failure-free survival



Studienergebnisse:

- Data on **overall survival** were available for all 2261 participants, and 1355 deaths were reported across the three trials. **The adjusted analysis showed clear evidence of a relative benefit of adding docetaxel to ADT (HR 0·79, 95% CI 0·70–0·88; p<0·0001**), with little evidence of statistical heterogeneity (p=0·32, I^2=13%; appendix p 55). Absolute survival benefit of docetaxel was 11% (95% CI 7–15), increasing 5-year survival from 39% (36–41) with ADT alone to 49% (46–52) with ADT plus docetaxel (appendix p 56). Planned sensitivity analyses gave similar results (appendix p 47).
- Data on **progression-free survival** were available for all 2261 participants, and 1624 events were reported across the three trials. Radiological progression (with or without a clinical progression) was the most common first event reported (1105 [68%] of 1624), followed by similar numbers of clinical progressions (264 [16%]) and deaths without evidence of progression (255 [16%]; appendix p 57). **The adjusted analyses showed**

clear evidence of a benefit of adding docetaxel to ADT (HR 0·70, 95% CI 0·63–0·77; p<0·0001), with little evidence of statistical heterogeneity (p=0·31, I^2=15%; appendix p 55). Absolute benefit of docetaxel was 9% (95% CI 6–13) on 5-year progression free survival, increasing it from 24% (22–27) with ADT alone to 34% (31–37) with ADT plus docetaxel (appendix p 56). Results of sensitivity analyses were similar (appendix p 47).

- Data on **failure-free survival** were available for all 2261 participants, and 1848 events were reported across the three trials. Data on failure-free survival were available for all 2261 participants and 1848 events were reported across the three trials. First events were dominated by biochemical progressions either alone (1296 [70%]) or in combination with another event (52 [3%] of 1848) and deaths without progression (87 [5%]; appendix p 58). **There was evidence of a benefit of adding docetaxel to ADT (HR 0·64, 95% CI 0·58–0·71; p<0·0001),** with little evidence of statistical heterogeneity (p=0·29, I^2=20%; appendix p 55). Absolute benefit of docetaxel was 9% (95% CI 6–12) on 5-year failure-free survival, increasing it from 14% (13–16) with ADT alone to 23% (21–26) with ADT plus docetaxel (appendix p 56). Results of sensitivity analyses were similar (appendix p 47).
- Results of analyses of the sensitivity outcomes of radiological progression-free survival, prostate cancer-specific survival, time to PSA failure, and time to castrate-resistant disease all showed clear relative benefits of adding docetaxel to ADT. The associated absolute differences in benefits were all in the region of 10% at 5 years (appendix p 48). All overall effects remained significant at 5% after post-hoc correction for multiple testing (data not shown).
- **We found no evidence that the effect of docetaxel on progression-free survival was modified by age, BMI, WHO performance status, Gleason sum score, risk, or clinical N stage** (appendix p 49). **There was evidence that the effect of docetaxel on progression-free survival was modified by disease volume ($p_{interaction}$ =0·020), timing of metastatic disease ($p_{interaction}$=0·077), and clinical T stage ($p_{interaction}$ =0·0019**; figure 1).
- Clinical T stage remained significant after correction for multiple testing (Hochberg procedure with alpha 0·1 and nine subgroup interaction tests; post hoc).34 There was evidence that disease volume ($p_{interaction}$ =0·073) and clinical T stage ($p_{interaction}$ =0·0022) independently modified the effect of docetaxel on progression-free survival after mutual adjustment, whereas timing of metastatic disease diagnosis did not ($p_{interaction}$ =0·45; appendix p 50).
- Considering volume and the timing of the diagnosis of metastatic disease together, docetaxel did not appear to improve progression-free survival in the low-volume, metachronous disease subgroup either in relative HR 0·98, 95% CI 0·67 to 1·45; figure 2) or absolute terms at 5 years (–1%, 95% CI –15 to 12; table 3; figure 3). qBased on available data, this group almost entirely comprised patients with clinical T stages 1–3 (161 [98%] of 165).
- By contrast, docetaxel use was associated with a relative improvement in progression-free survival and overall survival in all other volume-by-timing subgroups (figures 2, 3; appendix p 59), with estimated absolute effects at 5 years ranging from 8% to 12% (table 3). As most participants had synchronous metastatic disease, the power to detect an interaction was relatively low.
- We observed a significant interaction between effect of docetaxel and T stage 4 versus other T stage categories; 5-year baseline survival rate was broadly consistent for T stage 1–2 (27%, 95% CI 22–32) and 3 (25%, 22–29) compared with T stage 4 (17%, 12–23); and the T stage 4 category correlated strongly with disease timing (326 [97%] of 335 patients with clinical T stage 4 disease also had synchronous diagnoses, regardless of volume).

- **The clearest evidence and the largest benefit of docetaxel was seen in patients with high-volume disease, who also had clinical T stage 4 disease (HR 0·36, 95% CI 0·26–0·49; figure 2): the group with the poorest prognosis** (figure 4; appendix p 60). For this subgroup, the estimated absolute 5-year benefit of docetaxel on progression-free survival was 27% (95% CI 17–37), increasing it from 9% (5–15) with ADT alone to 35% (27–45) with ADT plus docetaxel (table 3). For overall survival, there was an estimated improvement in absolute survival of 35% (95% CI 24 to 47) at 5 years, improving it from 20% (14–29) with ADT alone to 55% (47–66) with ADT plus docetaxel (table 3).

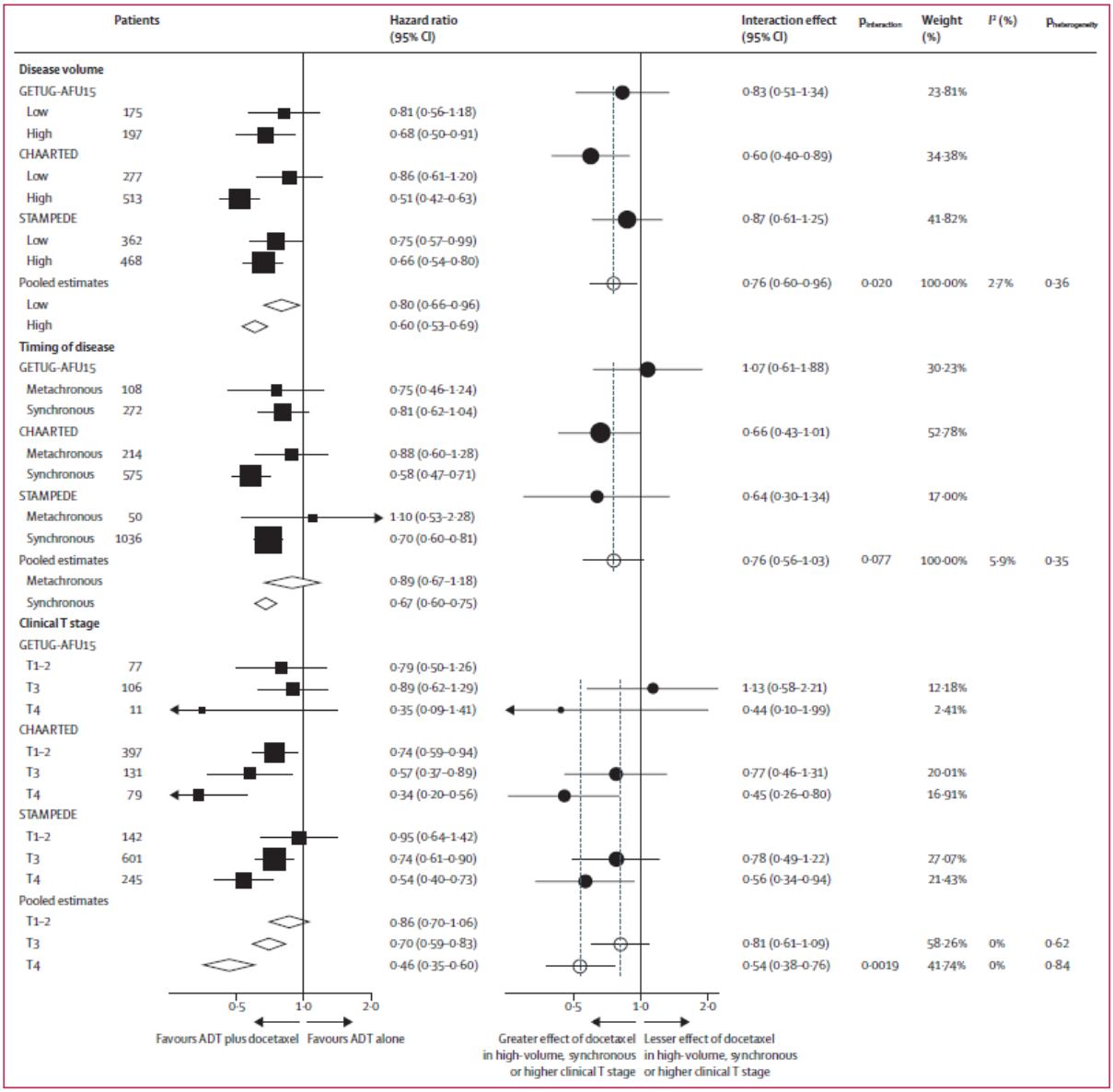


Figure 1: **Effect of docetaxel on progression-free survival by disease volume, timing of metastatic disease diagnosis, and clinical T stage at randomisation**
The left-hand panel shows estimates of treatment effects within subgroups for individual trials, with boxes representing hazard ratios derived from Cox regression models fitted to each trial in turn, adjusted for the core covariate set and with missing covariate values imputed. The size of each square is directly proportional to the amount of information contributed by a trial, and the horizontal lines show the 95% CIs. The diamonds represent pooled estimates for each subgroup, derived using a within-trials framework,[39] with the centre denoting the HR and the extremities the 95% CI. The filled circles on the right-hand panel show the interaction effects (ratio of hazard ratios) within each trial. These are derived from Cox regression models fitted to each trial in turn, including a treatment interaction term, and adjusted for the core covariate set and with missing covariate values imputed. Horizontal lines show the 95% CIs. Open circles show the meta-analysis interaction effect from two-stage, fixed-effect inverse-variance meta-analysis, with the centre denoting the hazard ratio and the extremities the 95% CI. ADT=androgen deprivation therapy.

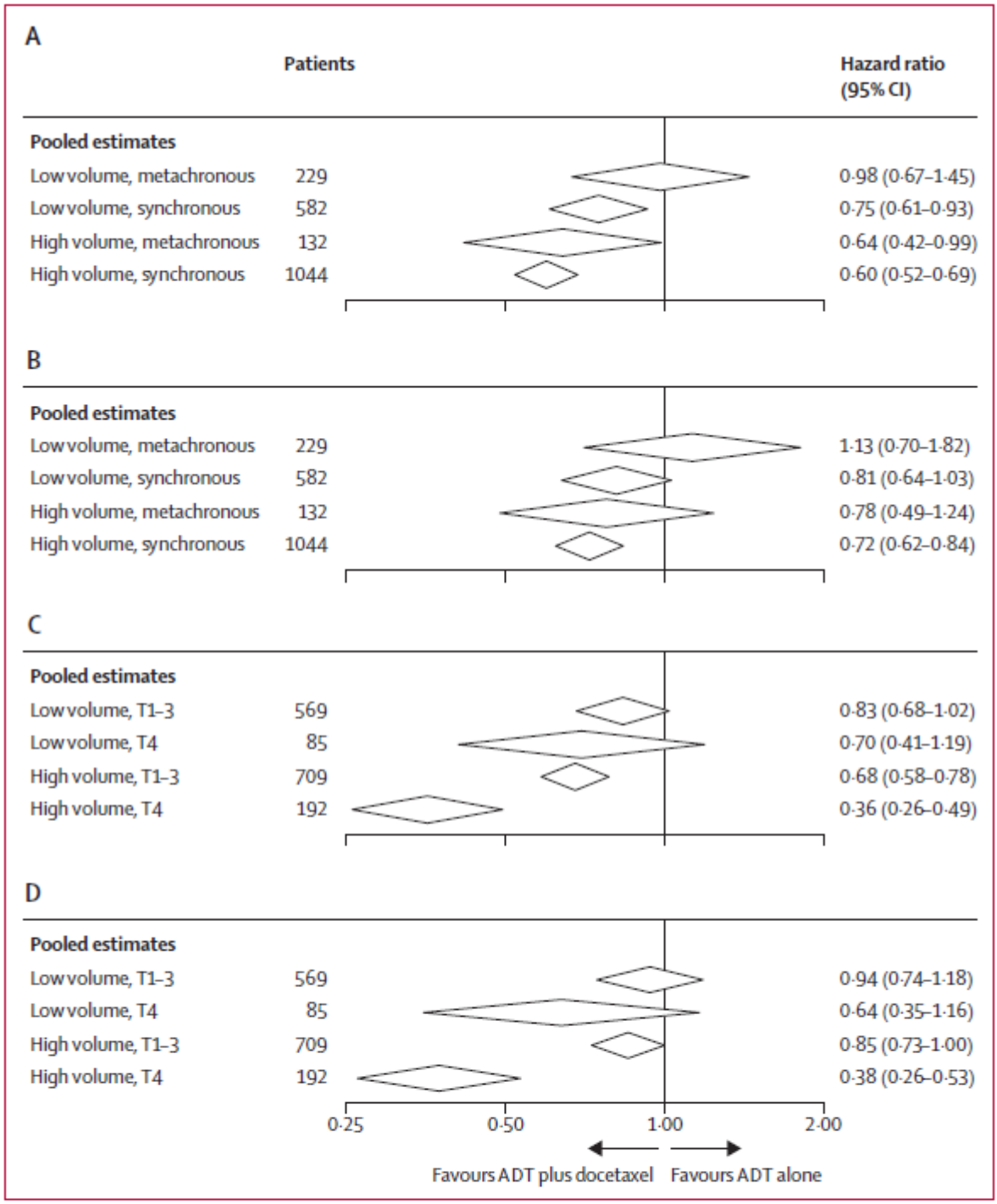


Figure 2: **Effect of docetaxel on progression-free survival and overall survival by volume and timing of metastatic disease diagnosis and by volume and clinical T stage**

Relative effects of ADT plus docetaxel versus ADT alone by disease volume and timing of metastatic disease diagnosis combined on progression-free survival (A); disease volume and timing of metastatic disease diagnosis combined on overall survival (B); disease volume and clinical T stage combined on progression-free survival (C); and disease volume and clinical T stage combined on overall survival (D). Each diamond represents the pooled estimates for each subgroup, derived using a within-trials framework,[36] with the centre denoting the hazard ratio and the extremities the 95% CI. ADT=androgen deprivation therapy.

	Progression-free survival				Overall survival			
	Number of events/ patients*	Difference in survival at 5 years (95% CI)	5-year survival (95% CI), ADT alone	5-year survival (95% CI), ADT plus docetaxel	Number of events/ patients	Absolute effect at 5 years (95% CI)	5-year survival (95% CI), ADT alone	5-year survival (95% CI), ADT plus docetaxel
Disease volume and timing of diagnosis								
Low volume, metachronous†	107/229	−1% (−15 to 12)	48% (39 to 60)	47% (36 to 61)	70/229	0% (−10 to 12)	72% (63 to 82)	73% (63 to 83)
Low volume, synchronous	346/582	8% (1 to 15)	37% (33 to 42)	45% (40 to 52)	267/582	8% (0 to 16)	52% (47 to 57)	60% (54 to 66)
High volume, metachronous	92/132	11% (−2 to 24)	14% (7 to 26)	25% (15 to 41)	78/132	10% (−6 to 26)	28% (18 to 43)	38% (25 to 57)
High volume, synchronous	856/1044	12% (7 to 16)	12% (10 to 14)	23% (20 to 28)	736/1044	12% (7 to 18)	26% (23 to 30)	39% (34 to 43)
Disease volume and clinical T stage								
Low volume, T stage 1–3	302/569	5% (−2 to 12)	42% (37 to 47)	46% (41 to 52)	225/569	4% (−3 to 11)	58% (53 to 63)	62% (57 to 68)
Low volume, T stage 4	61/85	12% (−6 to 29)	25% (15 to 39)	36% (22 to 59)	51/85	16% (−3 to 36)	38% (26 to 54)	54% (39 to 74)
High volume, T stage 1–3	562/709	8% (4 to 13)	14% (12 to 17)	22% (18 to 26)	484/709	6% (0 to 12)	29% (25 to 32)	35% (31 to 37)
High volume, T stage 4‡	157/192	27% (17 to 37)	9% (5 to 15)	35% (27 to 47)	136/192	35% (24 to 47)	20% (14 to 29)	55% (47 to 66)

*Numbers of patients and events per subgroup as defined; however, estimates in the analysis are from a one-stage model with adjustment and imputation including all patients and events, not restricted to those shown within each subgrouping. †161 (70%) of 229 patients had T stage 1–3, four (2%) had T stage 4, and 64 (28%) had missing data. ‡188 (98%) of 192 patients had synchronous and four (2%) had metachronous.

Table 3: **Absolute effects of docetaxel on 5-year progression-free survival and overall survival by volume and timing, and volume and clinical T stage combined**

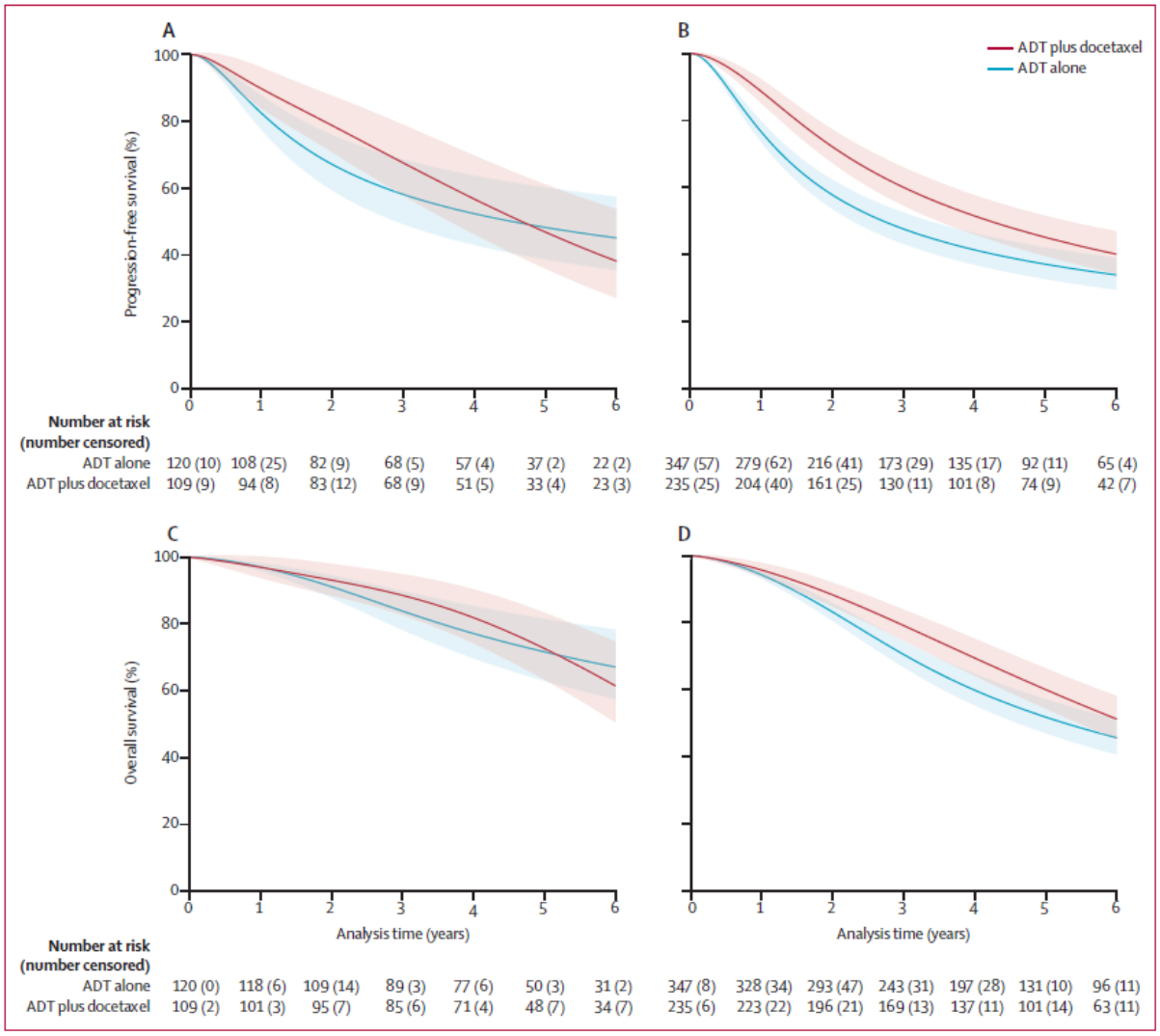


***Figure 3:* Effect of docetaxel on progression-free survival and overall survival for patients with low-volume disease, by timing of metastatic disease diagnosis**
Predicted survival curves for patients with low-volume metastatic disease for the subgroups of patients with synchronous and metachronous diagnosis, based on a one-stage flexible parametric meta-analysis model fitted to the entire participant sample with interaction terms between docetaxel effect and each of the four volume-by-timing subgroups, accounting appropriately for aggregation bias, adjusted for the core covariate set and with missing covariate values imputed, and using regression standardisation to estimate marginal progression-free survival curves for low-volume, metachronous disease (A); progression-free survival curves for low-volume, synchronous disease (B); overall survival curves for low-volume, metachronous disease (C); and overall survival curves for low-volume, synchronous disease (D). Red indicates ADT plus docetaxel and blue indicates ADT alone. Shaded areas denote the 95% CIs. ADT=androgen deprivation therapy.

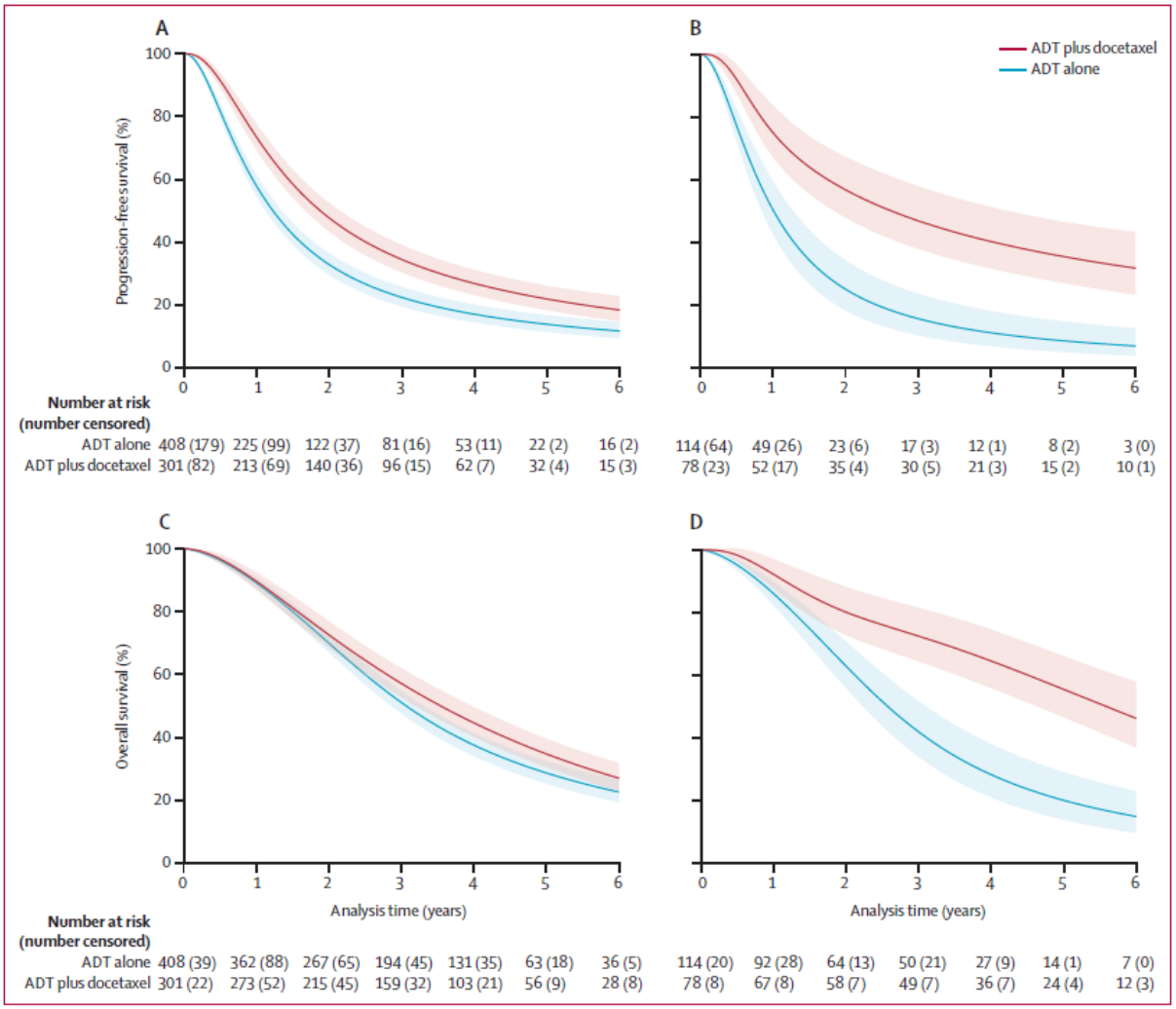


Figure 4: **Effect of docetaxel on progression-free survival and overall survival for patients with high-volume disease, by clinical T stage**
Predicted survival curves for patients with high-volume metastatic disease, for subgroups based on clinical T stage, based on a one-stage flexible parametric meta-analysis model fitted to the entire participant sample with interaction terms between docetaxel effect and each of the four volume-by-stage subgroups, accounting appropriately for aggregation bias, adjusted for the core covariate set and with missing covariate values imputed, and using regression standardisation to estimate marginal progression-free survival curves for high-volume, T stage 1–3 (A); progression-free survival curves for high-volume, T stage 4 (B); overall survival curves for high-volume, T stage 1–3 (C); and overall survival curves for high-volume, T stage 4 (D). Shaded areas denote the 95% CIs. ADT=androgen deprivation therapy.

Anmerkung/Fazit der Autoren

The addition of docetaxel to hormone therapy is best suited to patients with poorer prognosis for metastatic, hormone-sensitive prostate cancer based on a high volume of disease and potentially the bulkiness of the primary tumour. There is no evidence of meaningful benefit for patients with metachronous, low-volume disease who should therefore be managed differently. These results will better characterise patients most and, importantly, least likely to gain benefit from docetaxel, potentially changing international practice, guiding clinical decision making, better informing treatment policy, and improving patient outcomes.

Maiorano BA et al., 2022 [8].

Addition of androgen receptor-targeted agents to androgen-deprivation therapy and docetaxel in metastatic hormone-sensitive prostate cancer: a systematic review and meta-analysis

➔ Siehe auch folgende SR mit ähnlicher Schlussfolgerung:
- Riaz IB et al., 2023 [12]: Nur direkte Evidenz berücksichtigen, indirekte Evidenz weist methodische Mängel auf.

Fragestellung

This study aims to carry out a meta-analysis of RCTs exploring the efficacy of combining a new ARTA plus docetaxel and ADT in patients with mHSPC.

Methodik

Population:

- Participants with mHSPC.

Intervention:

- ARTA (abiraterone, enzalutamide, apalutamide, or darolutamide) in combination with docetaxel and ADT.

Komparator:

- ADT plus docetaxel.

Endpunkte:

- Overall survival (OS), progression-free survival (PFS), both radiographic (rPFS) and clinical (cPFS), major toxicities.

Recherche/Suchzeitraum:

- A literature search with no data restriction using Medline/PubMed, the Cochrane Library, and American Society of Clinical Oncology/European Society for Medical Oncology (ASCO/ESMO) Meeting abstracts to identify relevant studies, including those still unpublished in extenso, was carried out up to 10 April 2022.

Qualitätsbewertung der Studien:

- Considering the nature of evaluated studies (all randomized), we preferred to assess the study quality using the Jadad 5-item scale.

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 Studien

Charakteristika der Population/Studien:

- All selected studies were phase III, double-blind, RCTs. The experimental arm included enzalutamide (n = 2), abiraterone (n = 1), darolutamide (n = 1), apalutamide (n = 1) plus docetaxel and ADT. The control arm was placebo (PBO) + docetaxel + ADT. In the ARASENS, PEACE-1, and ENZAMET trials, the ARTA/PBO was started concomitant to docetaxel and ADT; in the ENZAMET trial, up to two cycles of docetaxel were allowed before ARTA/PBO was started. In the TITAN and ARCHES trials, ARTA/PBO was administered to patients with no evidence of progression after a maximum of six cycles of docetaxel + ADT.

Table 1. Characteristics of the included studies

Trial	First author	Year	Experimental arm	Control arm	Other treatments allowed	Primary endpoint(s)	Age, years (range)	Age (years) median (IQR)	Volume of metastatic disease, *n* (%)		OS HR (95% CI)	rPFS HR (95% CI)	cPFS HR (95% CI)	Median follow-up, months	Jadad score
									Low	High					
TITAN	Chi KN et al.	2019	Apalutamide + ADT	Placebo + ADT	Docetaxel for a maximum of 6 cycles before randomization	rPFS, OS	Exp 69 (45-94) Ctrl 68 (43-90)				0.67 (0.51-0.89)	0.48 (0.39-0.60)		44.0	5
ENZAMET	Davis ID et al.	2019	Enzalutamide + ADT	ADT (NSAA)	Docetaxel for a maximum of 6 cycles, up to 2 cycles were permitted before randomization.	OS		Exp 69.2 (63.2- 74.5) Ctrl 69.0 (63.6-74.5)	Exp 272 (48.3) Ctrl 265 (47.2)	Exp 291 (51.7) Ctrl 297 (52.8)	0.67 (0.52-0.86)		0.40 (0.33-0.49)	34.0	3
ARCHES	Armstrong AJ et al.	2019	Enzalutamide + ADT	Placebo + ADT	Docetaxel for a maximum of 6 cycles before randomization	rPFS	Exp 70 (46-92) Ctrl 70 (42-92)				0.81 (0.53-1.25)	0.39 (0.30-0.50)		44.6	5
PEACE-1	Fizazi K et al.	2021	Abiraterone + docetaxel + ADT	Docetaxel + ADT	Radiotherapy to the primary tumor (for low metastatic burden)	rPFS, OS		Exp 66 (60-70) Ctrl 66 (59-70)	Exp 131 (37) Ctrl 123 (35)	Exp 224 (63) Ctrl 232 (65)	0.75 (0.59-0.95)	0.50 (0.34-0.74)	0.50 (0.40-0.63)	52.0	1
ARASENS	Smith MR et al.	2022	Darolutamide + docetaxel + ADT	Placebo + docetaxel + ADT		OS	Exp 67 (41-89) Ctrl 67 (42-86)				0.68 (0.57-0.80)			Exp 43.7 Ctrl 42.4	5

ADT, androgen deprivation therapy; CI, confidence interval; cPFS, clinical progression-free survival; Ctrl, control arm; Exp, experimental arm; HR, hazard ratio; IQR, interquartile range; NSAA, non-steroidal anti-androgen drug; OS, overall survival; rPFS, radiographic progression-free survival.

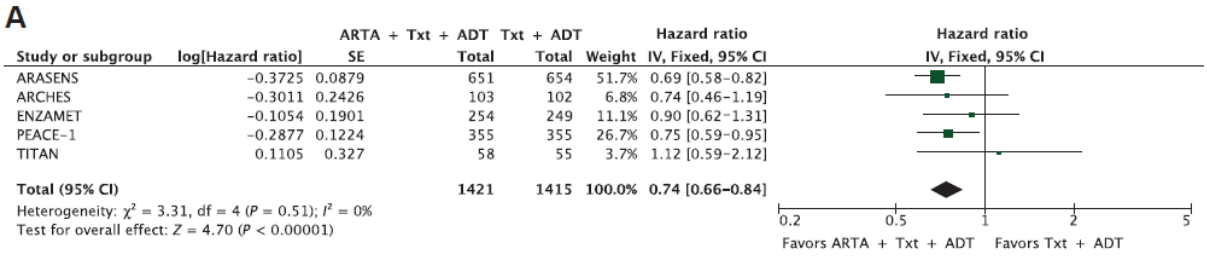
Qualität der Studien:

- Siehe Charakteristika.
- 3 Studien hohe Qualität, eine Studie mittlere Qualität, eine Studie niedrige Qualität.

Studienergebnisse:

OS:

- The pooled HR showed that adding an ARTA to docetaxel and ADT significantly reduced the risk of death compared with PBO plus docetaxel and ADT (HR: 0.74; 95% CI 0.66-0.84; P < 0.00001; I2 = 0%, P = 0.51).



PFS

- The combination of an ARTA, docetaxel and ADT significantly prolonged rPFS compared with docetaxel plus ADT (HR: 0.50; 95% CI 0.42-0.60; P < 0.00001; fixedeffects, 3 studies).
- The combination of an ARTA, docetaxel and ADT significantly prolonged cPFS compared with docetaxel plus ADT (HR: 0.49; 95% CI 0.41-0.58; P < 0.00001; fixed-effects, 2 studies).

UE

- The triplet did not worsen the risk of any grade (P = 0.45) and severe AEs (P = 0.07) compared with the doublet (2 studies).

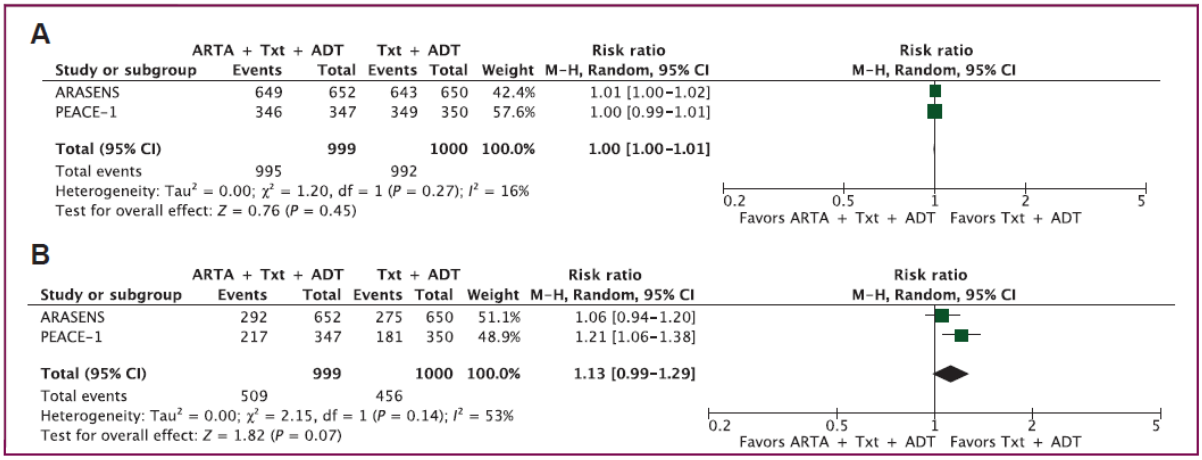


Figure 3. Safety profile ARTA plus docetaxel and ADT versus docetaxel plus ADT for (A) all-grade adverse events (AEs) and (B) severe AEs.
ADT, androgen deprivation therapy; ARTA, androgen receptor targeted agent; CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel; Txt, docetaxel.

- An increased risk of severe hypertension was associated with the triplet rather than the doublet.
- The risk of other severe AEs such as neutropenia, febrile neutropenia, and hepatotoxicity was not increased.

Anmerkung/Fazit der Autoren

The addition of an ARTA to docetaxel and ADT significantly prolongs survival compared with docetaxel and ADT in patients with mHSPC and should be adopted in daily clinical practice. Given the availability of several strategies in this setting, clinical and biological characteristics, drugs safety profile, and costs may help clinicians select the appropriate therapy for mHSPC patients who are more likely to benefit from treatment intensification.

Kommentare zum Review

- Die Qualitätsbewertung der Primärliteratur wurde anhand der Jadad-Skala vorgenommen. Diese Bewertung ermöglicht keine umfassende Einschätzung des Verzerrungspotenzials.

Buonerba C et al., 2020 [2].

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

Fragestellung

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 […] to explore potential baseline factors associated with heterogeneity of efficacy outcomes.

Methodik

Population:

- mCSPC (metastatic castration-sensitive prostate cancer) patients.

Intervention/Komparator:

- Androgen-receptoraxis-targeted (ARAT) agent plus ADT vs. ADT.

Endpunkte:

- PFS, OS.

Recherche/Suchzeitraum:

- PubMed, Cochrane Library and EMBASE until March, 30th 2020.
- Abstracts and presentations from ASCO, ASCO GU, ESMO, as well as EMUC since 2010 until 2020 were also reviewed.

Qualitätsbewertung der Studien:

- Jadad-Scale.

Ergebnisse

Anzahl eingeschlossener Studien:

- Five different open-label RCTs of were included.

Charakteristika der Population/Studien:

Table 1
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)

Qualität der Studien:

- 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.

Methodische Anmerkung: Der Jadad-Schore für den TITAN-Trial konnte dem SR nicht entnommen werden. In Maiorano BA et al., 2022 [8] wurde der TITAN-Trial mit einem Jadad-Score von 5 (= hohe Qualität) bewertet.

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).

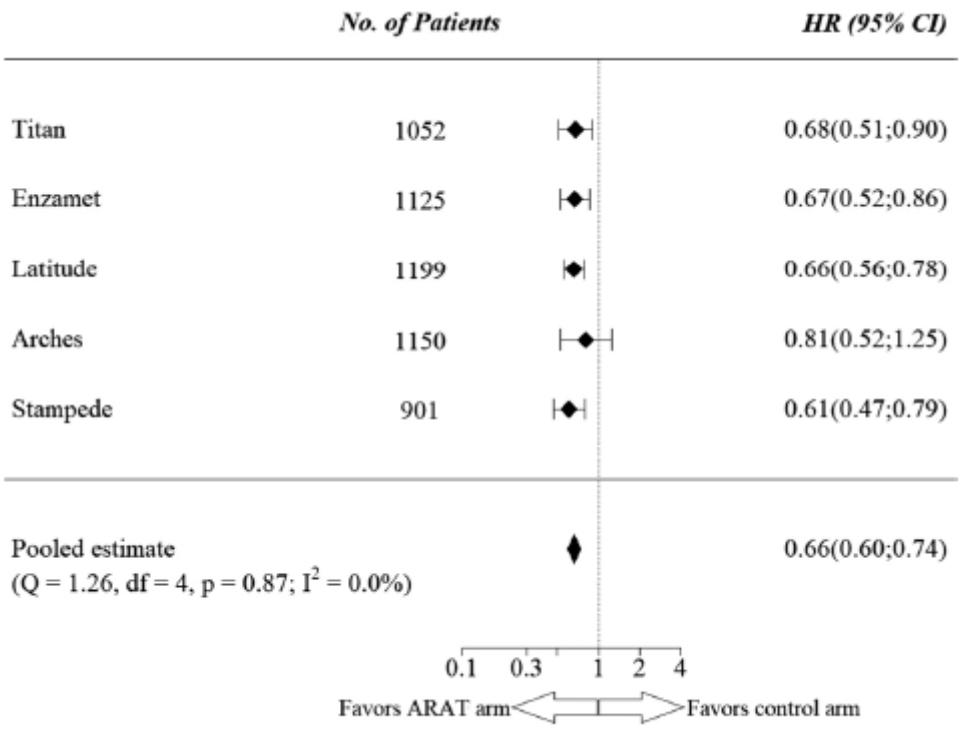


Fig. 2. Pooled HR for death of the trials included.

- Pooled PFS-HR was 0.46 (95 % CI: 0.40–0.53), with significant heterogeneity (p = 0.02, I^2 = 63.5 %) (Fig. 3).

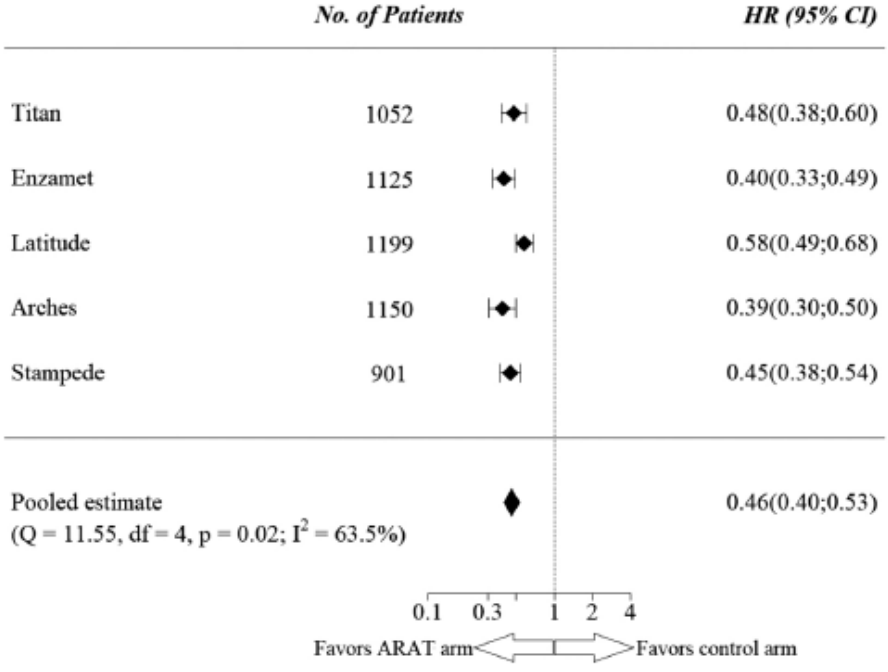


Fig. 3. Pooled HR for progression or death of the trials included.

- 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).

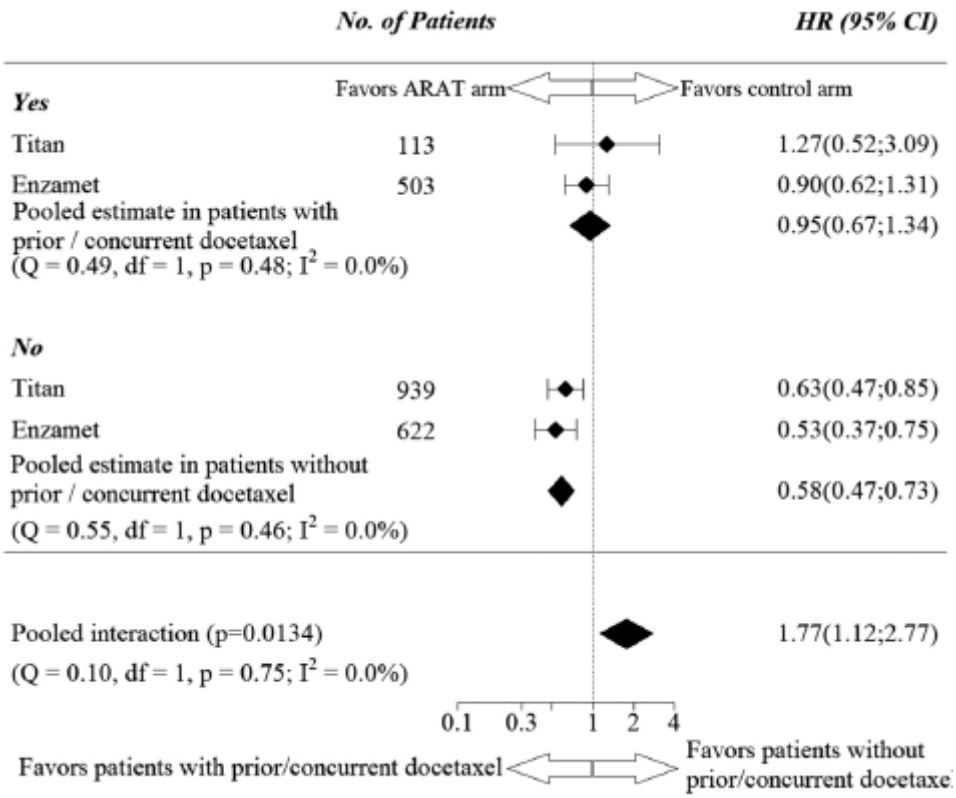


Fig. 4. Interactions between HR for death and previous docetaxel use.

- 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).

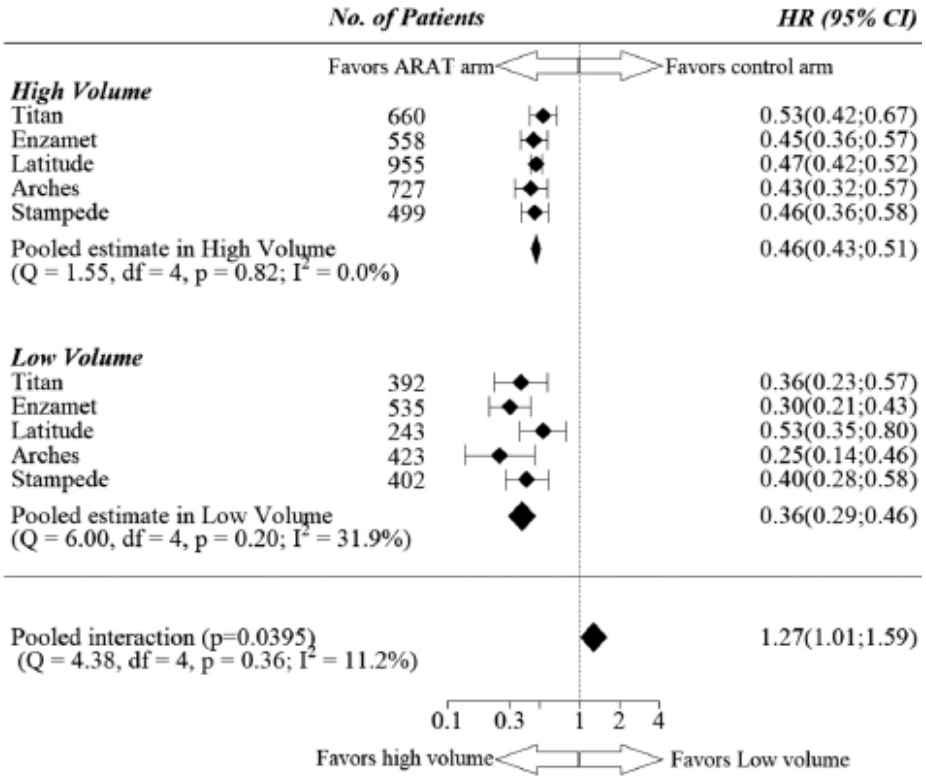


Fig. 5. Interactions between HR for progression or death and tumor volume.

- 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).

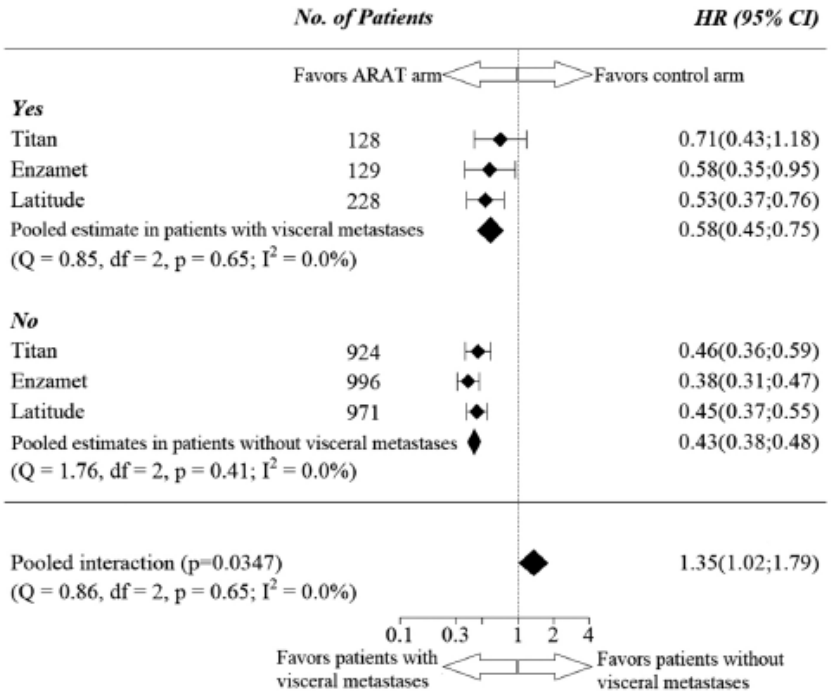


Fig. 6. Interactions between HR for progression or death and presence of visceral metastasis.

- 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).

Table 2
Non-significant sub-group differences in. OS-HR.

Trials with available data	Categorization variable	Sample numerosity	Pooled OS- HR (95 % CI)	Pooled interaction OS-HR (95 % CI)
Titan, Enzamet, Latitude, Arches	Gleason score < = 8	1131	0.63 (0.46 – 0.85)	0.96 (0.68 – 1.35) p = 0.794
	Gleason score > 8	3971	0.66 (0.59 – 0.74)	
Titan, Latitude, Arches	PSA < Median	1124	0.64 (0.52 – 0.79)	0.95 (0.71 – 1.25) p = 0.699
	PSA > Median	1125	0.67 (0.56 – 0.81)	
Titan, Enzamet, Latitude, Stampede	High Volume	2672	0.64 (0.56 – 0.74)	1.05 (0.69 – 1.58) p = 0.826
	Low Volume	1572	0.62 (0.48 – 0.80)	
Titan, Enzamet, Latitude	Visceral metastasis	485	0.79 (0.52 – 1.19)	1.21 (0.75 – 1.98); p = 0.436
	No visceral metastasis	2891	0.66 (0.58 – 0.76)	
Titan, Latitude	< 65 years old	785	0.63 (0.50 – 0.79)	0.86 (0.64 – 1.16); p = 0.323
	> = 65 years old	1709	0.73 (0.61 – 0.88)	
Titan, Enzamet	ECOG = 0	1486	0.68 (0.53 – 0.88)	1.09 (0.74 – 1.59) p = 0.667
	ECOG > 0	690	0.63 (0.47 – 0.83)	
Titan, Latitude	< median LDH levels	1493	0.64 (0.53 – 0.77)	0.90 (0.67 – 1.21); p = 0.475
	> median LDH levels	698	0.71 (0.57 – 0.87)	

Table 3
Non-significant sub-group differences in PFS-HR.

Trials with available data	Categorization variable	Sample numerosity	Pooled HR for progression or death (95 % CI)	Pooled interaction PFS-HR
Titan, Enzamet, Latitude, Arches	Gleason score < = 8	1045	0.45 (0.33–0.60)	1.02 (0.77–1.37) p = 0.8750
	Gleason score > 8	3294	0.44 (0.40–0.49)	
Titan, Latitude, Arches	PSA < Median	1722	0.41 (0.34–0.49)	0.83 (0.66–1.05) p = 0.1273
	PSA > Median	1673	0.49 (0.42–0.58)	
Titan, enzamet, Arches	Prior docetaxel	821	0.49 (0.40–0.61)	1.34 (1.00–1.56) p = 0.051
	No prior docetaxel	2506	0.40 (0.32–0.50)	
Titan, Enzamet, Arches	ECOG PS = 0	2380	0.42 (0.34–0.52)	0.98 (0.76–1.27) p = 0.903
	ECOG PS > 0	948	0.43 (0.35–0.53)	
Titan, Latitude, Arches	< 65 years old	1085	0.41 (0.34–0.50)	0.80 (0.63–1.02) p = 0.074
	> 65 years old	2559	0.52 (0.46–0.57)	
Titan, Latitude	< median LDH	1493	0.45 (0.38–0.54)	0.83 (0.62–1.11); p = 0.217
	> median LDH	698	0.53 (0.42–0.66)	

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.

Kommentare zum Review

- Die Qualitätsbewertung der Primärliteratur wurde anhand der Jadad-Skala vorgenommen. Diese Bewertung ermöglicht keine umfassende Einschätzung des Verzerrungspotenzials.

3.3 Leitlinien

Leitlinienprogramm Onkologie, 2024 [6,7].

S3-Leitlinie Prostatakarzinom / Version 7.0 – Mai 2024 / AWMF-Registernummer: 043-022OL

Zielsetzung/Fragestellung

Die Leitlinie Prostatakarzinom ist ein evidenz- und konsensbasiertes Instrument, um die Früherkennung, Diagnostik und Therapie des Prostatakarzinoms zu verbessern.

Betroffene und Behandelnde sollen durch die Leitlinie bei der Entscheidung über Früherkennungsmaßnahmen unterstützt werden. Die Leitlinie soll dazu beitragen, eine angemessene Gesundheitsversorgung bei der Früherkennung sicherzustellen. Es ist weiterhin die Aufgabe der Leitlinie, dem Mann (mit Verdacht auf Prostatakarzinom oder nachgewiesenem Prostatakarzinom) angemessene, wissenschaftlich begründete und aktuelle Verfahren in der Diagnostik, Therapie und Rehabilitation anzubieten. Dies gilt sowohl für die lokal begrenzte oder lokal fortgeschrittene Erkrankung als auch bei Vorliegen eines Rezidivs oder von Fernmetastasen.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium mit Patientenvertretung;
- 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 explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Suchdatum für alle Suchen: 15.11.2023.
- Die Suchen wurden in Medline via Ovid und in der Cochrane Library durchgeführt.
- Zeitraum für die Suche: 2020-2023.

LoE/GoR

- Cochrane Risk of Bias Tool.
- für systematische Übersichtsarbeiten/Metaanalysen das AMSTAR II Tool.

Tabelle 4: 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

Tabelle 4: Schema der Empfehlungsgraduierung

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	soll/soll nicht
B	Empfehlung	sollte/sollte nicht
0	Empfehlung offen	kann

Tabelle 6: Schema der Empfehlungsgraduierung

Konsensstärke	Prozentuale Zustimmung
Starker Konsens	>95 % der Stimmberechtigten
Konsens	>75–95 % der Stimmberechtigten
Mehrheitliche Zustimmung	50–75 % der Stimmberechtigten
Keine mehrheitliche Zustimmung	<50 % der Stimmberechtigten

Empfehlungen

7.20	**Konsensbasierte Empfehlung**	**neu 2024**
EK	Bei Patienten mit metastasiertem hormonsensitivem Prostatakarzinom soll zeitnah nach Diagnosestellung eine Androgendeprivation zur Reduktion des Risikos typischer Komplikationen (z. B. pathologische Frakturen, Rückenmarkskompression, Harnleiterobstruktion) und ggf. zur palliativen tumorspezifischen Therapie eventueller Tumor- bzw. Metastasen-bedingter Symptome (z. B. Knochenschmerzen) eingeleitet werden.	
	Starker Konsens	

7.21	**Evidenzbasierte Empfehlung**	**neu 2024**
Empfehlungsgrad **0**	Eine Androgendeprivation kann durch chirurgische Kastration, durch subkutan oder intramuskulär zu verabreichende Gonadotropin-Releasing-Hormone (GnRH)-Agonisten oder durch subkutan oder oral zu verabreichende GnRH-Antagonisten durchgeführt werden.	
Level of Evidence **1++**	[1141], [1223]	
	Starker Konsens	

7.22	**Konsensbasierte Empfehlung**	**neu 2024**
EK	Bei Patienten mit ausgeprägten Tumor- bzw. Metastasen-bedingten Schmerzen oder drohenden Komplikationen (z. B. Rückenmarkskompression) sollte die Androgendeprivation mit einem Gonadotropin-Releasing-Hormone (GnRH)-Antagonisten und/oder mit einem Androgenrezeptor-Signalweg Inhibitor (ARPI: Apalutamid, Enzalutamid, Darolutamid) eingeleitet werden.	
	Starker Konsens	

7.23	**Konsensbasierte Empfehlung**	**neu 2024**
EK	Eine Monotherapie mit einem nicht-steroidalen Androgenrezeptorantagonisten der ersten Generation (z. B. Bicalutamid, Flutamid) soll bei Patienten mit metastasiertem hormonsensitivem Prostatakarzinom nicht durchgeführt werden.	
	Starker Konsens	

7.24	Evidenzbasierte Empfehlung	modifiziert 2024
Empfehlungsgrad **A**	Bei Patienten mit metastasiertem hormonsensitivem Prostatakarzinom (mHSPC) soll eine Einteilung nach high- und low-volume, high- und low-risk, sowie de novo und metachron metastasiert erfolgen.	
Level of Evidence **1+, 1-**	[1224], [1225], [1226]	
	Starker Konsens	

7.25	Konsensbasierte Empfehlung	modifiziert 2024
EK	Patienten mit metastasiertem hormonsensitivem Prostatakarzinom sollen mit Einleitung der Androgendeprivation, spätestens innerhalb von drei Monaten danach, über eine Kombinationstherapie (gemäß 7.26) aufgeklärt werden, sowie über: • die zu erwartende Überlebenszeit trotz des nicht-kurativen Charakters der Therapie • die unerwünschten Wirkungen • den Einfluss auf die Lebensqualität.	
	Starker Konsens	

7.26	Evidenzbasierte Empfehlung	modifiziert 2024
Empfehlungsgrad **A/0**	a. Patienten in gutem Allgemeinzustand (ECOG 0-1) mit metastasiertem (M1) hormonsensitivem, Prostatakarzinom (mHSPC) soll zusätzlich zur Androgendeprivation eine Hormontherapie mit Apalutamid oder Enzalutamid angeboten werden. (Empfehlungsgrad: A) b. Patienten in gutem Allgemeinzustand (ECOG 0-1) mit neu-diagnostiziertem (de novo), metastasierten (M1), hormonsensitiven, high-risk Prostatakarzinom (mHSPC) soll zusätzlich zur Androgendeprivation eine Hormontherapie mit Abirateron (plus Prednison / Prednisolon) angeboten werden. (Empfehlungsgrad: A) c. Patienten in gutem Allgemeinzustand (ECOG 0-1) mit metastasiertem (M1) hormonsensitivem Prostatakarzinom, die für eine Docetaxel Chemotherapie geeignet sind, soll zusätzlich zur Androgendeprivation eine Hormontherapie mit Darolutamid in Kombination mit 6 Zyklen Docetaxel angeboten werden. (Empfehlungsgrad: A) d. Patienten in gutem Allgemeinzustand (ECOG 0-1) mit neu-diagnostiziertem (de novo), metastasiertem (M1) hormonsensitivem Prostatakarzinom und hohem Tumorvolumen („*high volume disease*"), die für eine Docetaxel Chemotherapie geeignet sind, kann zusätzlich zur Androgendeprivation eine Hormontherapie mit Abirateron (plus Prednison/Prednisolon) in Kombination mit 6 Zyklen Docetaxel angeboten werden. (Empfehlungsgrad: 0)	

Level of Evidence 1+, 1++, 2+	[1227], [1228], [1229], [1224], [1225], [1230], [1231], [1232], [1233] 1+: Empfehlung a & b 1++: Empfehlung c 2+: Empfehlung d
	Starker Konsens

7.27	Evidenzbasierte Empfehlung	modifiziert 2024
Empfehlungsgrad A	a. Bei Entscheidung für eine kombinierte Behandlung aus Androgendeprivation und Apalutamid, soll die Apalutamidgabe innerhalb von 3 Monaten nach Beginn der Androgendeprivation beginnen. Die Therapie soll in einer Dosierung von 240 mg/Tag gegeben werden. b. Bei Entscheidung für eine kombinierte Behandlung aus Androgendeprivation und Enzalutamid, soll die Enzalutamidgabe innerhalb von 3 Monaten nach Beginn der Androgendeprivation beginnen. Die Therapie soll in einer Dosierung von 160 mg/Tag gegeben werden. c. Bei Entscheidung 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. d. Bei Entscheidung für eine kombinierte Behandlung aus Darolutamid, Docetaxel-Chemotherapie und Androgendeprivation, soll die Darolutamid-Gabe in einer Dosierung von 2 x 600 mg/Tag innerhalb von 3 Monaten nach Einleitung der Androgendeprivation beginnen. Die Chemotherapie soll innerhalb von 6 Wochen nach erster Darolutamid-Gabe beginnen; Docetaxel soll über 6 Zyklen alle 3 Wochen in einer Dosierung von 75 mg/m2 Körperoberfläche verabreicht werden. e. Bei Entscheidung für eine kombinierte Behandlung aus Abirateron, Docetaxel-Chemotherapie und Androgendeprivation, soll die Abirateron-Gabe in einer Dosierung von 1000 mg/Tag (plus Prednison/Prednisolon) innerhalb von 6 Wochen nach Einleitung der Androgendeprivation beginnen. Die Chemotherapie soll ab 6 Wochen nach Einleitung der Androgendeprivation beginnen; Docetaxel soll über 6 Zyklen alle 3 Wochen in einer Dosierung von 75 mg/m2 Körperoberfläche verabreicht werden.	
Level of Evidence 1+ 1++ 2+	[1228], [1229], [1224], [1225], [1230], [1231], [1232] 1+: Empfehlung a, b & c 1++: Empfehlung d 2+: Empfehlung e	
	Starker Konsens	

7.28	Konsensbasierte Empfehlung	modifiziert 2024
EK	Gründe für einen Therapieabbruch sollen sein: Patientenwunsch, Progress oder intolerable Nebenwirkungen. Wird die Behandlung mit einem Medikament aus der Kombination wegen intolerabler Nebenwirkungen abgebrochen, dann soll die übrige Therapie wie vorgesehen weitergeführt werden.	
	Starker Konsens	

7.29	Evidenzbasierte Empfehlung	modifiziert 2024
Empfehlungsgrad A	Patienten, die nicht für eine Kombinationsbehandlung in Frage kommen, soll eine Androgendeprivation angeboten werden.	
Level of Evidence 1++	[1234], [1146]	
	Starker Konsens	

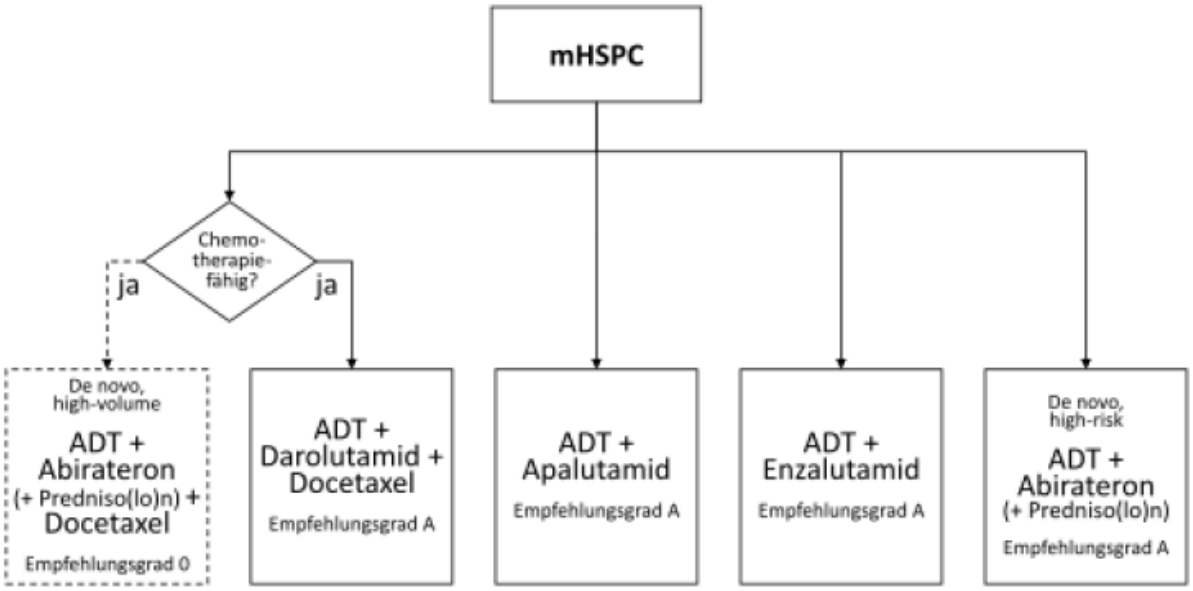


Abbildung 3: Flussdiagramm zur Darstellung der gemäß 7.26 und 7.27 empfohlenen Therapie-optionen zur systemischen Therapie des mHSPC.

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Cornford P et al., 2024 [5].

EAU, EANM, ESTRO, ESUR, ISUP, 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.

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium mit Patientenvertretung;

- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse nicht im Detail beschrieben, externes Begutachtungsverfahren über Peer-Review;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist über den Hintergrundtext dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Databases searched included Medline, EMBASE and the Cochrane Libraries, covering a time frame between April 1st 2022 and May 1st 2023.

LoE/GoR

- Modified GRADE approach, RoB tool.

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

- **Each recommendation should be graded as either "strong" or "weak" and justified by using the strongest, clinically relevant data**. It is important to point out any flaws in the evidence used to support any given recommendation. The panel can also make a recommendation AGAINST performing a certain action.

Empfehlungen: 6.6.8 Guidelines for the first-line treatment of hormone-sensitive 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 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
At the start of ADT offer luteinising hormone-releasing hormone (LHRH) antagonists or orchiectomy to patients with impending clinical complications such as spinal cord compression or bladder outlet obstruction.	Strong
Do not offer AR antagonist monotherapy to patients with M1 disease.	Strong
Do not offer ADT monotherapy to patients whose first presentation is M1 disease if they have no contra-indications for combination therapy and have a sufficient life expectancy to benefit from combination therapy (≥ 1 year) and are willing to accept the increased risk of side effects.	Strong
Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients with M1 disease who are fit for the regimen.	Strong

Offer docetaxel only in combination with ADT plus abiraterone or darolutamide to patients with M1 disease who are fit for docetaxel.	Strong
Offer ADT combined with prostate radiotherapy (using doses up to the equivalent of 72 Gy in 2 Gy fractions) 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 surgery to M1 patients outside of clinical trials.	Strong
Only offer metastasis-directed therapy to M1 patients within a clinical trial setting or a well-designed prospective cohort study.	Strong

**All the following statements are based on metastatic disease defined by bone scintigraphy and CT scan/MRI.*

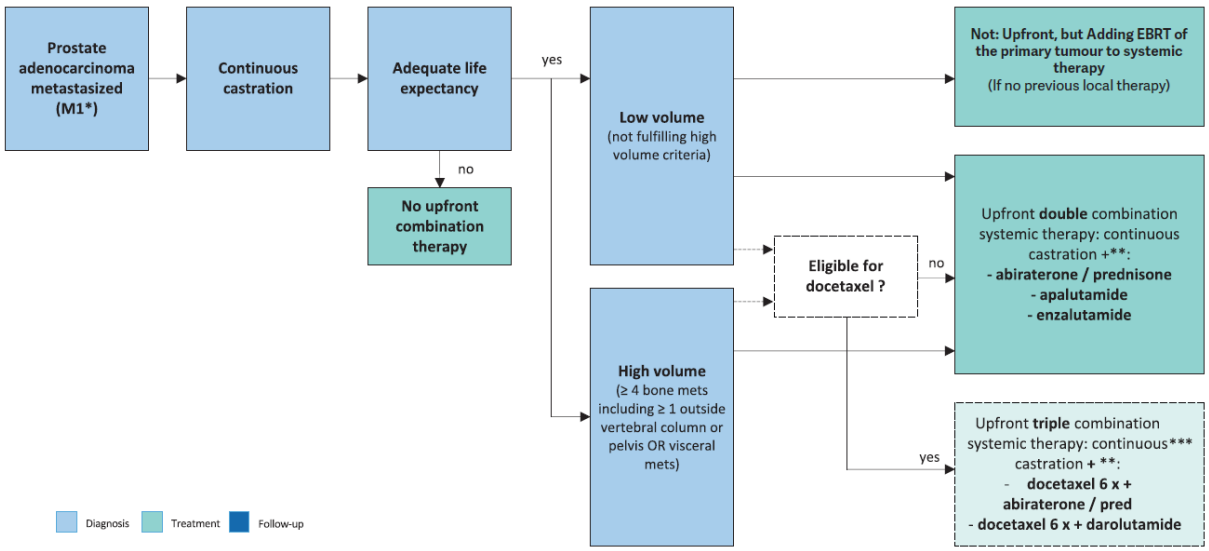

Figure 6.5: Treatment of metastasized (M1) – disease, M+HSPC*

* Based on staging using combination of bone scan and CT.
** Alphabetical order.
***not for low volume, metachronous disease.
1EBRT: IMRT/VMAT + IGRT of the prostate (equivalent of up to 72 Gy in 2 Gy fractions).
☐ = weak recommendation.
EBRT = external beam radiotherapy; IGRT = image-guided radiotherapy; IMRT = intensity-modulated radiotherapy.
#Note: Please be aware that the various options in the following flowcharts present a generalised approach only, and cannot take the management of individual patients into account, nor the availability of resources.

Hintergrundinformation:

6.6 Management of Metastatic prostate cancer

6.6.3 First-line hormonal treatment

Primary ADT has been the SOC for over 50 years [1034]. There is no high-level evidence in favour of a specific type of ADT for oncological outcomes, neither for orchiectomy nor for a LHRH agonist or antagonist. The level of testosterone is reduced much faster with orchiectomy and LHRH antagonist, therefore patients with impending spinal cord compression or other potential impending complications from the cancer should be treated with either a bilateral orchidectomy or LHRH antagonists as the preferred options. There is a suggestion in some studies and a SR and meta-analysis that cardiovascular side effects are less frequent in patients treated with LHRH antagonists than patients treated with LHRH agonists [1053, 1097- 1099]; therefore, patients with pre-existing cardiovascular disease or other cardiovascular risk factors might be considered to be treated with antagonists if a chemical castration is chosen.

6.6.3.1 Non-steroidal anti-androgen monotherapy

Based on a Cochrane review comparing older generation non-steroidal anti-androgen (NSAA) monotherapy to ADT (either medical or surgical), NSAA was considered to be less effective in terms of OS,

clinical progression, treatment failure and treatment discontinuation due to AEs [1100] and is generally not recommended also because ADT-based combination treatments have become SOC.

6.6.3.2 Intermittent versus continuous androgen deprivation therapy

Three independent reviews [1101-1103] and two meta-analyses [1104, 1105] looked at the clinical efficacy of intermittent androgen deprivation (IAD) therapy. All of these reviews included eight RCTs of which only three were conducted in patients with exclusively M1 disease. So far, the SWOG 9346 is the largest trial addressing IAD in M1b patients [1106]. Of 3,040 screened patients, only 1,535 patients met the inclusion criteria. This highlights that only about 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 even in this highly selected subgroup. The use of intermittent ADT has been superseeded as continuous ADT based combination therapy has become SOC.

6.6.3.3 Early versus deferred androgen deprivation therapy

Early treatment before the onset of symptoms is recommended in the majority of patients with metastatic hormone-sensitive disease despite lack of randomised phase III data in this specific setting and specifically not with the combination therapies that are standard nowadays.

A Cochrane analysis from 2019 about the topic concluded that early ADT probably extends time to death of any cause and time to death from PCa [1107]. Since the analysis included only a very limited number of metastatic patients, the benefit of early ADT in this setting remains unproven. All of the trials testing the combination therapies in the metastatic hormone-sensitive setting also included asymptomatic patients.The only candidates with metastatic disease who may possibly be considered for deferred treatment are asymptomatic patients with a strong wish to avoid treatment-related side effects. The risk of developing symptoms, and even dying from PCa, without receiving the benefit from ADT with deferred treatment has been highlighted [1108, 1109], but in the era before next generation imaging was used. Patients with deferred treatment for advanced PCa must be amenable to close follow-up. Another potential exception are patients with recurrent oligometastatic disease who have a strong wish to postpone the start of ADT (see Section 6.4.7).

6.6.4 Combination therapies

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

6.6.4.1 'Combined' androgen blockade with older generation NSAA (bicalutamide, flutamide, nilutamide)

Systematic reviews have shown that CAB using a NSAA appears to provide a small survival advantage (< 5%) vs. monotherapy (surgical castration or LHRH agonists) [1110, 1111] but this minimal survival advantage must be balanced against the increased side effects. In addition, the newer combination therapies (see Tables 6.4.3, 6.4.4, 6.4.5) are more effective as shown specifically for enzalutamide which was tested against NSAA in a phase III trial [1112]. More recently another trial has demonstrated a significant OS benefit for the addition of rezvilutamide vs. addition of bicalutamide to ADT in patients with high-volume mHSPC [1113]. Therefore combination with NSAAs should only be considered if other combination therapies are not available.

6.6.4.2 Androgen deprivation combined with other agents

6.6.4.2.1 Androgen deprivation therapy combined with chemotherapy

Three large RCTs were conducted [775, 1088, 1114]. All trials compared ADT alone as the SOC with ADT combined with immediate docetaxel (75 mg/sqm, every three weeks within three months of ADT initiation). The primary objective in all three studies was to assess OS. The key findings are summarised in Table 6.4.3. In the GETUG 15 trial, all patients had M1 PCa, either de novo or after a primary treatment [1114]. They were stratified based on previous treatment and Glass risk factors [1085]. In the CHAARTED trial the same inclusion criteria applied, and patients were stratified according to disease volume (see Table 6.4.1) [1088].

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 three criteria: T3/4, PSA ≥ 40 ng/mL or ISUP grade group 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

< six months or a PSA ≥ 20 ng/mL, N1 or M1. No stratification was used regarding metastatic disease volume (high/low volume) [775]. In all three 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 [1116, 1117].

Docetaxel in all three trials was used at the standard dose of 75 mg/sqm every three weeks, six cycles in CHAARTED and STAMPEDE and up to nine cycles in GETUG-AFU-15. In subgroup analyses from GETUG-AFU 15 and CHAARTED the beneficial effect of the addition of docetaxel to ADT was most evident in men with de novo metastatic high-volume disease [1089, 1090], while it was in the same range whatever the volume in the post-hoc analysis from STAMPEDE [1115]. The effect of adding docetaxel was less apparent in men who had prior local radical treatment although the numbers were small and the event rates lower. A SR and meta-analysis which included these three trials showed that the addition of docetaxel to SOC improved survival [1117]. The HR of 0.77 (95% CI: 0.68–0.87, p < 0.0001) translates into an absolute improvement in 4-year survival of 9% (95% CI: 5–14). In a SR and meta-analysis of individual participant data from the the three trials it has been shown that there is no meaningful beneficial effect of addition of docetaxel to ADT for patients with metachronous low volume disease. Interestingly the largest absolute improvement at five years was observed for the patients with high volume and clinical stage four disease [1118].

Based on these data, upfront docetaxel combined with ADT was considered as a standard in men presenting with metastases at first presentation, provided they are fit enough to receive docetaxel [1117]. More recently two large Phase III studies have now shown an OS benefit by adding an ARPI to ADT and docetaxel. Therefore adding docetaxel alone to ADT should only be considered if no ARPI is available or all available ones are contraindicated (see Section 6.4.4.2.3).

6.6.4.2.2 Combination with an ARPI alone (abiraterone, apalutamide, 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 mHSPC was studied [814, 1070, 1119] (see table 6.4.4). The primary objective of both trials was an improvement in OS. Both trials showed a significant OS benefit. In LATITUDE with only *de novo* high-risk metastatic patients included, the HR reached 0.62 (0.51–0.76) [1070]. 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 [814]. 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 category was [1120].
All secondary objectives such as PFS, time to radiographic progression, time to pain, or time to chemotherapy were in favour of the combination. No difference in treatment-related deaths was observed with the combination of ADT plus AAP 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%) [1119]. Based on these data upfront AAP 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.

In three large RCTs (TITAN, ARCHES and ENZAMET) the addition of AR antagonists to ADT in men with mHSPC was tested [1068, 1069, 1112]. In ARCHES the primary endpoint was radiographic PFS (rPFS). In the primary analysis rPFS 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 the final prespecified analysis the key secondary enpoint OS was significantly improved with a HR of 0.66 (0.53-0.81) and a significant benefit for rPFS was maintained with a HR of 0.63 (0,52–0.76) [1121]. In ENZAMET the primary endpoint was OS. The addition of enzalutamide to ADT in the first analysis improved OS with a HR of 0.67 (0.52–0.86) compared to ADT plus a non-steroidal antiandrogen. Approximately half of the patients had concomitant docetaxel; about 40% had prior local therapy and about half of the patients had low-volume disease [1069]. In a planned later analysis with a median followup of 68 months the OS benefit of adding enzalutamide was maintained with a HR of 0.7 (0.58-0.84) [1122] In the TITAN trial, ADT plus apalutamide was used and rPFS and OS were co-primary endpoints. In the primary analysis rPFS 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 of 0.67 (0.51–0.89). In the final analysis the HR for OS was 0.65 (0.53–0.79) without adjustment for cross-over. In this trial 16% of patients had prior local therapy, 37% had low-volume disease and 11% received prior docetaxel [1068, 1123]. In the more recently published CHART trial, ADT plus rezvilutamide was tested vs. ADT plus bicalutamide in patients with high-volume de novo metastatic disease. Ninety percent of the patients were recruited in China. Overall survival and rPFS were co-primary endpoints. At

the pre-planned interim analysis rezvilutamide significantly improved rPFS compared with bicalutamide with a HR of 0.44 (0.33–0.58) and OS with a HR of 0.58 (0.44–0.77) [1113].

In summary, the addition of the new AR antagonists significantly improves clinical outcomes with no convincing evidence of differences between subgroups. The majority of patients had de novo metastatic disease and the evidence is most compelling in this situation. In the trials with the new AR antagonists, a proportion of patients had metachronous disease (see Table 6.4.5); in the subgroup analyses the effect seemed to be consistent and therefore, a combination should also be offered for men progressing after radical local therapy [1122, 1124, 1125].

6.6.5 Treatment selection and patient selection

There have been several network meta-analyses of the published data concluding that combination therapy is more efficient than ADT alone, but none of the doublet combination therapies has been convincingly proven to be superior over another [1132-1137]. In a SR and meta-analysis looking at association between age and efficacy of combination therapy patients seemed to profit from combination therapy irrespective of age [1138]. As a consequence, patients should be offered combination treatment unless there are clear contraindications or they present with asymptomatic disease and a very short life expectancy (based on non-cancer comorbidities).

Since the data of the abovementioned Phase III trials of the triplet therapies have been reported, docetaxel as sole addition to ADT is not longer a valid option in the majority of patients if an androgen receptor pathway inhibitor (ARPI) is available and there are no contra-indications to use one. From subgroup analysis of all the above-mentioned RCTs we know that probably all subgroups (high vs. low volume/risk and synchronous vs. metachronous) can profit from the addition of an ARPI to ADT. Therefore, in view of the current data the recommendation is using ADT plus ARPI as the sole additional therapy or the triplet with an ARPI plus docetaxel. Formally the question what the added value of adding docetaxel to ADT plus an ARPI has not been evaluated, but since triplet therapy seems not to add a lot of unexpected overlapping toxicities, the data should be discussed with patients who are fit for chemotherapy and an ARPI, realising that most of the toxicity is caused by adding the chemotherapy. There is more evidence for using the triplet in synchronous disease and the OS benefit in PEACE-1 seemed to be driven mostly by the high volume patients at the time point of the analysis for the publication, in ARASENS only few patients had low volume disease.

Of interest in some SRs and meta-analysis the authors found no significant difference for OS and/or PFS using the systemic triplet therapy compared to adding an ARPI alone to ADT [1135, 1139-1141]. In contrast one meta-analysis suggested a benefit of systemic triplet therapy versus ADT and ARPI and another meta-analysis showed a benefit in patients with high volume disease [1136, 1142]. In summary, the choice will most likely be driven by fitness for docetaxel, the nature of the disease (low/high volume; synchronous/ metachronous), patient preference, the specific side effects, availability, logistics and cost.

6.6.6 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. Four hundred and thirty-two patients were randomised to ADT alone or ADT plus IMRT with IGRT to the prostate. Overall survival was not significantly different (HR: 0.9 [0.7–1.14]), median time to PSA ADT plus RT to the prostate. This trial confirmed that RT to the primary tumour did not improve OS in unselected patients [1091]. 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. This was confirmed by the latest analysis of long-term follow-up (median follow-up of 61 months [HR: 0.64 for OS benefit in the low-volume group]) [1144].

A secondary, not pre-planned analysis of the STAMPEDE trial confirmed the benefit of prostate RT in patients with ≤ 3 bone metastases, but also showed a benefit in patients with M1a disease [1145]. No evidence of difference in time to symptomatic local events was found with median follow-up of over five years [1144]. The dose used in these indications should be equivalent of up to 72 Gy in 2 Gy fractions. Therefore, RT of the prostate only 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 AAP, 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 as results of ongoing trials are awaited.
In a SR 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) [1146]. However, there was a clear difference in the effect of metastatic

burden on survival with an absolute improvement of 7% in three-year survival in men who had four or fewer bone metastases.

6.6.7 Metastasis-directed therapy in M1-patients

In patients relapsing after a local treatment, a metastases-targeting therapy has been proposed, with the aim to delay systemic treatment. In a retrospective analysis on 211 patients treated with MDT, Milenkovic et al. aimed at defining prognostic factors for MFS, palliative ADT-free (pADT) survival and cause-specific survival (CSS). With a median follow-up of 42 months after MDT, patients with cN1 only had significantly superior 5-years MFS, pADT and CSS when compared to patients with M1 disease (p<0.02). Of interest, 23% of patients were free of biochemical recurrence at five years [1147]. There are two randomised phase II trials testing metastasisdirected therapy (MDT) using surgery ± SABR vs. surveillance [1148] or SABR vs. surveillance in men with oligorecurrent PCa [1149]. Oligo-recurrence was defined as < 3 lesions on choline-PET/CT only [1148] or conventional imaging with MRI/CT and/or bone scan [1149]. The sample size was small with 62 and 54 patients, respectively,and a substantial proportion of them had nodal disease only [1148]. Androgen deprivation therapy-free survival was the primary endpoint in one study which was longer with MDT than with surveillance [1148]. The primary endpoint in the ORIOLE trial was progression after six months which was significantly lower with SBRT than with surveillance (19% vs. 61%, p = 0.005) [1149].

Recently the combined results of STOMP and ORIOLE confirmed the significant improvement in PFS in favour of MDT (HR: 0.44, p < 0.001) [1150].

A phase II trial assessed the biochemical response after 18F-DCFPyL PET/MRI and subsequent MDT. Overall biochemical response rate, defined as ≥ 50% PSA decline, was 60%, including 22% of patients with complete biochemical response [1151].

Currently there are no data to suggest an improvement in OS. Two comprehensive reviews highlighted MDT (SABR) as a promising therapeutic approach that must still be considered as investigational until the results of the ongoing RCT are available [1152, 1153]. Thus far, the toxicity of MDT appears to be low, but this also needs to be confirmed [1154, 1155].

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American Urological Association (AUA); Society of Urologic Oncology (SUO), 2023 [1].

Advanced Prostate cancer: AUA/SUO Guideline / (Published 2020; Amended 2023)

Zielsetzung/Fragestellung

The management of advanced prostate cancer is rapidly evolving. 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

- Repräsentatives Gremium mit Patientenvertretung;
- 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 über den Hintergrundtext dargestellt;

- Regelmäßige Überprüfung der Aktualität nicht näher beschrieben.

Recherche/Suchzeitraum:

- The methodology team searched Ovid MEDLINE(R) ALL and the Cochrane Libraries for studies published between 2018 and March 16, 2022.

LoE/GoR

- For randomized trials and cohort studies, methodologists adapted criteria for assessing risk of bias from the U.S. Preventive Services Task Force.
- The methodology team assessed systematic reviews using Assessing the Methodological Quality of Systematic Reviews (AMSTAR 2) criteria.

Table 2: Strength of Evidence Definitions

AUA Strength of Evidence Category	GRADE Certainty Rating	Definition
A	High	• Very confident that the true effect lies close to that of the estimate of the effect
B	Moderate	• 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	• Confidence in the effect estimate is limited • The true effect may be substantially different from the estimate of the effect
	Very Low	• Very little confidence in the effect estimate • The true effect is likely to be substantially different from the estimate of effect

Table 3: 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

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

Hintergrundinformation:
The use of primary ADT for the management of mHSPC has been the SOC since its discovery by Huggins et al. in the 1940's.[83] 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.
At the time of initial publication of this guideline, the methods for achieving castrate levels of testosterone were either surgical or injectable. On December 18, 2020, the FDA approved relugolix as the first oral GnRH receptor antagonist for adult patients with advanced prostate cancer.[84] Approval was based on the phase III HERO study that showed favorable testosterone suppression and adverse effects of oral relugolix (120mg/day) compared to leuprolide.[85]

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

Hintergrundinformation:
mHSPC remains an incurable manifestation of the disease. While ADT, with or without non-steroidal 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, 2 clinical trials demonstrated the benefits of adding docetaxel chemotherapy to ADT for mHSPC patients. In the phase III CHAARTED study,[72] 790 patients with mHSPC were equally randomly assigned to receive either ADT in combination with docetaxel (75mg/m2) for up to 6 cycles or ADT alone. In an updated reporting on the trials, 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,[6] 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 (75mg/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. The durability of these results was supported in an update of this trial. At a median follow-up of 78.2 months, there were 494 deaths on SOC.
There was good evidence of benefit in docetaxel over SOC on OS (HR=0.81; 95% CI: 0.69 to 0.95; P=0.009). Analysis of other outcomes found evidence of benefit for docetaxel over SOC in failure-free survival (HR=0.66; 95% CI: 0.57 to 0.76; P<0.001) and PFS (HR=0.69; 95% CI: 0.59 to 0.81; P<0.001).[86]

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%).[6]

ABIRATERONE ACETATE
Abiraterone acetate is a non-steroidal irreversible inhibitor of CYP17A1, which catalyzes the conversion of C21 progesterone precursors to C19 adrenal androgens, DHEA, and androstenedione.[87] 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 III LATITUDE trial,[24] 1,199 patients were randomly assigned to receive either ADT plus abiraterone acetate (1,000mg 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). Updated results continue to confirm benefit in this trial. The final analysis of this trial, at a median follow-up of 51.8 months, OS was significantly longer in the abiraterone acetate plus prednisone group (median 53.3 months [95% CI: 48.2 to not reached]) compared to the placebo group (36.5 months [33.5 to 40.0]), with an HR of 0.66 (95% CI: 0.56 to 0.78; p<0.0001).[88]

In the STAMPEDE trial, [89] 1,917 patients were randomized in a 1:1 ratio to receive ADT alone or ADT plus abiraterone acetate (1,000mg daily) and prednisolone (5mg 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 trial[24] 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 novel androgen receptor signaling inhibitor (ARSI). 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.[90] In the double-blind, phase III TITAN study,[91] 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). At the time of final analysis (44.0 months median follow-up), a total of 405 deaths had occurred (170 in the apalutamide arm, 235 in the placebo arm). An improvement in median OS was observed: not reached in the apalutamide group versus 52.2 months in the placebo group (HR=0.65; 95% CI: 0.53 to 0.79; P<0.0001), with a 35% reduction in risk of death.[92] 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 ARSI. It is a competitive inhibitor of androgen binding and also inhibits nuclear translocation of the AR, DNA-binding and coactivator recruitment. [93] In the open-label, randomized, phase III ENZAMET trial,[94] 1,125 men were randomized to receive testosterone suppression plus either open-label enzalutamide (160mg daily) or a standard non-steroidal 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 and 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 this study did not impact the observed benefit of enzalutamide. This trial did not address the role of early intensification by adding docetaxel to enzalutamide.

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 (160mg 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. In an update on this trial, the final prespecified analysis of OS, which was a key secondary end point, and an update on radiographic PFS was reported. Following unblinding, 180 (31.3%) progression-free patients randomly assigned to placebo plus ADT crossed over to open-label enzalutamide plus ADT. At a median follow-up of 44.6 months, 154 of 574 patients randomly assigned to enzalutamide plus ADT and 202 of 576 patients randomly assigned to placebo plus ADT had died. Enzalutamide plus ADT reduced risk of death by 34% versus placebo plus ADT (median not reached in either group; HR=0.66; 95% CI: 0.53 to 0.81; P<0.001).[95]

Enzalutamide, apalutamide, and darolutamide 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.

THERAPEUTIC DECISION-MAKING IN MHSPC

Unfortunately, no comparative data on efficacy exist between the previously discussed 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. Duration of treatment may also influence choice. Some patients might prefer a limited 18-week course of docetaxel to daily oral therapy for years. Further, in select patients with metastatic presentations, particularly de novo metastatic patients, triplet therapy is recommended (see following statement).

In terms of intermittent ADT, SWOG 9346[96] 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 patients with de novo mHSPC, clinicians should offer ADT in combination with docetaxel and either abiraterone acetate plus prednisone or darolutamide. *(Strong Recommendation; Evidence Level: [Abiraterone] Grade A/[Darolutamide] Grade B)*

Hintergrundinformation:

The optimal patient for consideration of “dual intensification” or “triplet therapy” are best represented by the patients enrolled in the following two completed trials who are patients with de novo disease and are free of major comorbidities.

Two recent phase III randomized trials have demonstrated improvement in OS of patients receiving either abiraterone acetate (with prednisone) or darolutamide in addition to ADT and docetaxel in selected patients with de novo metastatic prostate cancer.

The PEACE-1 trial enrolled 1,173 patients with de novo metastatic prostate cancer who were randomized to receive ADT plus docetaxel (considered the SOC) plus radiotherapy, SOC plus abiraterone/prednisone or SOC plus abiraterone/prednisone and radiotherapy. In the initial analysis of the study, patients treated with SOC plus abiraterone/prednisone had an improvement in both OS (HR=0.82; 95.1% CI: 0.69 to 0.98; p=0.030) and radiographic PFS (HR=0.54; 99.9% CI: 0.41 to 0.71; p<0.0001) with some increase in toxicity in the abiraterone group, primarily being more hypertension. Data from the radiotherapy arms are anticipated in the near future.[97]

The ARASENS phase III study enrolled 1,306 patients with mHSPC (86.1% of enrolled patients had de novo metastatic disease) and randomized them to receive either darolutamide or placebo in combination with ADT and docetaxel. The trial demonstrated that the combination of darolutamide plus ADT/docetaxel resulted in improved OS, with the risk of death reduced by 32.5% (HR=0.68; 95% CI: 0.57 to 0.80; P<0.001). The frequency of grade 3/4 events was similar between the treatment arms.[98]

As the majority of patients treated in both PEACE-1 and ARASENS had de novo metastatic disease, the role of "dual intensification" or "triplet therapy" in patients with mHSPC with progression following curative-intent local therapy remains undefined.

17. 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)*

Hintergrundinformation:
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.[69] 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.[99] 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).[69] 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 prespecified 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,[69] 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.

18. 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)*

Hintergrundinformation:
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 (e.g., 4 weeks or less) of a first-generation antiandrogen, although there is limited evidence of significant clinical utility.[100]

19. 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)*

Hintergrundinformation:
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.[101]

Bicalutamide, flutamide and nilutamide are first generation antiandrogens extensively studied in combination with either bilateral orchiectomy or LHRH agonists in mHSPC.[102-106] There is insufficient evidence to support the use of first generation antiandrogens as monotherapy.[102, 107-109]

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.[24,89,91,94,110,111] For now, however, these next generation antiandrogens should not be considered without ADT in mHSPC.

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Virgo KS et al., 2023 [15,16].

American Society of Clinical Oncology (ASCO)

Initial Management of Noncastrate Advanced, Recurrent, or Metastatic Prostate Cancer: ASCO Guideline Update

Zielsetzung/Fragestellung

In 2021, ASCO updated a guideline on the initial management of noncastrate recurrent, advanced, or metastatic prostate cancer.1 Several recent developments prompted this focused update.

Methodik

Aktuelles Update der Version von 2021.

Grundlage der Leitlinie

- Repräsentatives Gremium mit Patientenvertretung;
- 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 über den Hintergrundtext dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- A targeted electronic literature search was conducted in September 2022 (June 2020 to the end of August 2022).
- Via PubMed.

LoE/GoR

Table 1. Definitions for Quality of Evidence Grades[7]

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
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
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

- **Strength of recommendations.** The Expert Panel provides a rating of the strength of each recommendation. This assessment reflects the extent to which a guideline panel is confident that desirable effects of an intervention outweigh undesirable effects, or vice versa, across the range of patients for whom the recommendation is intended. Recommendations may fall into two categories; strong and weak. Factors determining the strength of a recommendation include balance between benefits and harms, certainty of evidence, confidence in values & preferences, and resource use. Recommendations may be made for or against the use of an intervention.

Sonstige methodische Hinweise

- Die Literaturrecherche wurde ausschließlich in PubMed durchgeführt. Diese Beschränkung auf eine einzelne Datenbank könnte die Vollständigkeit der erfassten Evidenz einschränken und möglicherweise zu einer unvollständigen Darstellung des aktuellen Forschungsstandes führen.

Empfehlungen

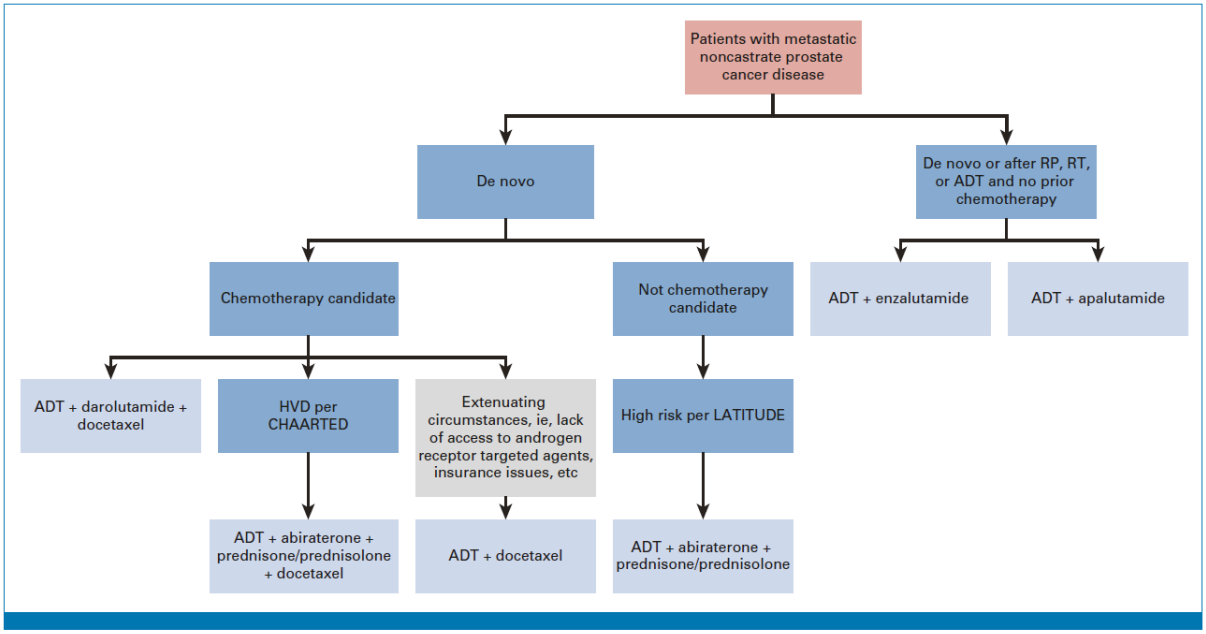

FIG 1. Initial management of noncastrate metastatic prostate cancer algorithm. ADT, androgen-deprivation therapy; HVD, high-volume disease; RP, radical prostatectomy; RT, radiotherapy.

Recommendation	Type, Evidence Quality, Strength of Recommendation
Recommendation 1.0 (updated): Docetaxel, abiraterone, enzalutamide, apalutamide, or darolutamide each when administered with ADT, represent five separate SoCs for noncastrate metastatic prostate cancer. With the exception of the triplet therapies of docetaxel plus abiraterone plus ADT and docetaxel plus darolutamide plus ADT, the use of any of these agents in any other particular combination or in any particular series cannot yet be recommended.	Type: Evidence-based, benefits-harms ratio unknown; Evidence quality: No evidence available; Strength of recommendation: Strong
ADT plus docetaxel[10] *Recommendation 1.1 (updated):* For patients with metastatic noncastrate prostate cancer with HVD as defined per CHAARTED[8] (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 candidates for treatment with chemotherapy but are unwilling or unable to receive triplet therapy (eg, due to insurance constraints), docetaxel plus ADT should be offered.	Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong for patients with HVD
Practical information for Recommendation 1.1 (updated): Patients should be made aware that doublet therapy (docetaxel plus ADT) has proven inferior OS compared to triplet therapy, such as abiraterone and prednisone plus docetaxel plus ADT.	
Recommendation 1.11 (updated): For patients with de novo metastatic noncastrate prostate cancer with HVD as defined per CHAARTED[8] who are being offered ADT plus docetaxel chemotherapy, triplet therapy (abiraterone and prednisone plus ADT and docetaxel) should be offered per PEACE-1.[3] Abiraterone and prednisone plus ADT and docetaxel demonstrated significant OS and rPFS benefits compared to ADT and docetaxel alone for patients with HVD.	Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong for patients with HVD as defined per CHAARTED[8]
Practical information for Recommendation 1.11 (updated): OS data for patients with low-volume de novo metastatic noncastrate prostate cancer from PEACE-1[3] are still too immature to justify recommending abiraterone-based triplet therapy (abiraterone and prednisone plus ADT and docetaxel).	
Recommendation 1.15 (updated): For patients with de novo metastatic noncastrate prostate cancer who are being offered ADT plus docetaxel chemotherapy, triplet therapy (darolutamide plus ADT and docetaxel) should be offered per ARASENS.[2] Compared to placebo plus ADT and docetaxel, darolutamide plus ADT and docetaxel demonstrated significant OS benefits, in addition to significantly longer times to castration-resistant prostate cancer, pain progression, first skeletal event, and initiation of subsequent systemic antineoplastic therapy.	Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong
Recommendation 1.16 (updated): The recommended regimen for patients with metastatic noncastrate prostate cancer treated with darolutamide, docetaxel, and ADT is darolutamide (600 mg as two 300 mg tablets orally with food) twice daily (to a total daily dose of 1200 mg) with ADT. Docetaxel administration (75 mg/m^2) should begin within 6 weeks of the first dose of darolutamide. Docetaxel should be administered intravenously once every 3 weeks for up to six cycles.	Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong
Practical information for Recommendations 1.15 and 1.16 (updated): Discussions with patients should include the cost of darolutamide treatment compared with other options such as abiraterone.	

Recommendation 1.2 (updated): For patients with LVD as defined per CHAARTED[8] who are candidates for chemotherapy, docetaxel plus ADT should not be offered due to lack of sufficient evidence.	Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong for patients with LVD
Recommendation 1.3 (updated): For patients with metastatic noncastrate prostate cancer treated with docetaxel, the recommended regimen is six doses administered once at 3-week intervals at 75 mg/m^2 either alone (per CHAARTED[8]) or with prednisolone (per STAMPEDE).[9]	Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong
Practical information for Recommendation 1.3 (updated) The strongest evidence of benefit for docetaxel is for those patients who were diagnosed with de novo metastatic disease or HVD (defined per CHAARTED[8] 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 apply independent of the presence or absence of nodal disease.[10] Patients with metastatic disease who do not fit into these categories should not be offered docetaxel. The strength of the evidence to support an OS benefit is not compelling for patients who do not have de novo metastatic disease and/or who do not meet the HVD criteria.[10] Long-term survival data from CHAARTED[8] and a post hoc aggregated analysis of CHAARTED and GETUG-AFU-15 data only showed an OS benefit for patients with HVD and de novo metastases. There was no OS benefit for LVD, irrespective of whether the patients had metastases at diagnosis or after failure of prior local therapy.[11] Clarke et al[12] re-examined OS by disease burden using STAMPEDE data with longer follow-up, but the analysis had inadequate statistical power (< 80%) to detect an OS difference by disease burden if in fact one existed. As a chemotherapy agent, docetaxel is associated with somewhat greater toxicity than androgen-targeted therapies (novel hormone therapies), but the treatment course is relatively short (limited to six cycles), much less costly, and generally covered by insurance, hence reducing the financial toxicity.	
ADT plus abiraterone[10] *Recommendation 1.4:* For patients with high-risk de novo metastatic noncastrate prostate cancer, the addition of abiraterone to ADT should be offered per LATITUDE.[14]	Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong for patients with high-risk disease as defined per LATITUDE
Recommendation 1.5: For patients with low-risk de novo metastatic noncastrate prostate cancer, ADT plus abiraterone may be offered per STAMPEDE.[15]	Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Moderate for patients with low-risk disease per STAMPEDE

(continued on following page)

Recommendation	Type, Evidence Quality, Strength of Recommendation
Recommendation 1.6: The recommended regimen for patients with metastatic noncastrate prostate cancer is abiraterone 1,000 mg once per day with either prednisolone or prednisone 5 mg once daily until progressive disease is documented.	Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong
ADT plus enzalutamide *Recommendation 1.7 (updated):* ADT plus enzalutamide should be offered to patients with metastatic noncastrate prostate cancer including both those with de novo metastatic disease and those who have received prior therapies, such as RP or RT for localized disease. Enzalutamide plus ADT has demonstrated short-term survival benefits (PSA progression-free, clinical progression-free, and overall) when compared with ADT alone for patients with metastatic noncastrate prostate cancer as a group per ENZAMET.[13] Enzalutamide also has long-term survival benefits overall, for those with LVD or HVD, and those with LVD or HVD and no docetaxel use.[4] Per ARCHES,[5] enzalutamide significantly improved time to first subsequent antineoplastic therapy in addition to survival benefits overall and among those with high-volume disease, no prior docetaxel and previous use of ADT or orchiectomy.[5]	Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong
Recommendation 1.8 (updated): The recommended regimen for patients with metastatic noncastrate prostate cancer is enzalutamide (160 mg once per day) with ADT.	Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong
Practical information for Recommendation 1.8 (updated): Discussions with patients should include the cost of enzalutamide treatment compared with other options, such as abiraterone.	
ADT plus apalutamide *Recommendation 1.9:* ADT plus apalutamide should also be offered to patients with metastatic noncastrate prostate cancer, including those with de novo metastatic disease or those who have received prior therapy, such as RP or radiation therapy for localized disease per TITAN.[16]	Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong
Recommendation 1.95: The recommended regimen for patients with metastatic noncastrate prostate cancer is apalutamide (240 mg once per day) with ADT.	Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong
Practical information for Recommendations 1.9 and 1.95 (updated): Discussions with patients should include the cost of apalutamide treatment compared with other options, such as abiraterone.	

<u>Methodische Anmerkung:</u> Die Nummerierung der Empfehlungen erscheint teilweise lückenhaft (1.1, 1.11, 1.15, …). In der Leitlinie sowie dem "Data Supplement" sind jedoch weder für die Vorgängerversion (2021) noch für das aktuelle Update (2023) weitere Empfehlungen zwischen Empfehlung 1.11 und 1.15 ersichtlich.

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National Institute for Health and Care Excellence, 2021 [10].

Prostate cancer: diagnosis and management

Zielsetzung/Fragestellung

This guideline covers the diagnosis and management of prostate cancer in secondary care, including information on the best way to diagnose and identify different stages of the disease, and how to manage adverse effects of treatment. It also includes recommendations on follow up in primary care for people diagnosed with prostate cancer.

Methodik

Ursprüngliche Veröffentlichung in 2008, letztes umfassenden Update in 2019, danach fokussierte Updates zwischen 2020 und 2023. Für die Empfehlungen, die für das vorliegende AWG relevant sind, ergaben sich die letzten Änderungen im Jahr 2019.

<u>Grundlage der Leitlinie</u>

- Repräsentatives Gremium mit Patientenvertretung;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;

- Formale Konsensusprozesse nicht näher beschrieben, externes Begutachtungsverfahren über registrierte Stakeholder;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist über das Zusatzdokument „Evidence Review“ dargestellt;
- 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.

Methodische Anmerkung: Da die letzten Änderungen der für das AWG relevanten Empfehlungen in 2019 erfolgten, wird die Recherche-Strategie für das Update aus 2019 dargestellt.

LoE/GoR

- Quality assessment: RoB und CASP.
- GRADE was used to assess the quality of evidence for the selected outcomes as specified in „Developing NICE guidelines: the manual (2014)“.
- *Anmerkung FBMed:* NICE verzichtet in der Regel auf die Auszeichnung der Stärke der Empfehlung, sondern realisiert das über die Formulierung (Wording):
  - must/must not,
  - should/should not,
  - could/could not.
- For reccomendations on interventions that should be used (strong) use direct instructions rather than using the word „should“. Use verbs such as „offer“, „refer“, „advise“, and „discuss“.

Sonstige methodische Hinweise

- In eckigen Klammern nach den Empfehlungen ist erkenntlich, wann die Empfehlungen das letzte Mal angepasst wurde, z.B. [2019] bedeutet, dass die Empfehlung 2019 überarbeitet wurde.
- Die Informationen zur Methdodik beziehen sich ausschließlich auf das Review zum metastatisierten hormonsensitiven Prostatakarzinom von 2019 (siehe https://www.nice.org.uk/guidance/ng131/evidence/evidence-reviews-may-2019-6779081773?tab=evidence).

Empfehlungen

1.5 Metastatic prostate cancer

Initial treatment

1.5.6 Offer docetaxel chemotherapy to people with newly diagnosed metastatic prostate cancer 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]

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 (150 mg). [2008] In May 2019, this was an off-label use of bicalutamide. See NICE's information on prescribing medicines for further information.

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:

Docetaxel chemotherapy

(Recommendations 1.3.26 and 1.3.27 and recommendation 1.5.6)

Why the committee made the recommendations:

There was good evidence that showed docetaxel improves overall survival, prostate cancer-specific survival and clinical progression-free survival in people with newly diagnosed metastatic prostate cancer who are starting long-term hormone therapy. The committee agreed these benefits outweighed the potential harms of the treatment.

The evidence also showed docetaxel slows clinical progression in people with newly diagnosed high-risk, non-metastatic cancer starting long-term hormone therapy. However, the evidence did not show any extension of overall survival. Because of the known toxicities associated with docetaxel treatment, the benefits and harms are more finely balanced in this population. As a result, the committee identified this decision as being preference sensitive, and the person's values and preferences are likely to be particularly important in their decision about the best course of action for them.

The committee also made a recommendation for research as it identified a gap in the evidence related to there being no universal definition of locally advanced prostate cancer. A risk stratification study will help identify patients at various levels of risks, and help tailor treatment according to need.

Hormone-sensitive metastatic prostate cancer

(siehe https://www.nice.org.uk/guidance/ng131/evidence/evidence-reviews-may-2019-6779081773?tab=evidence)

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.

Appendix E – Clinical evidence tables

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

Appendix G – GRADE tables

Hormone-sensitive metastatic prostate cancer

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

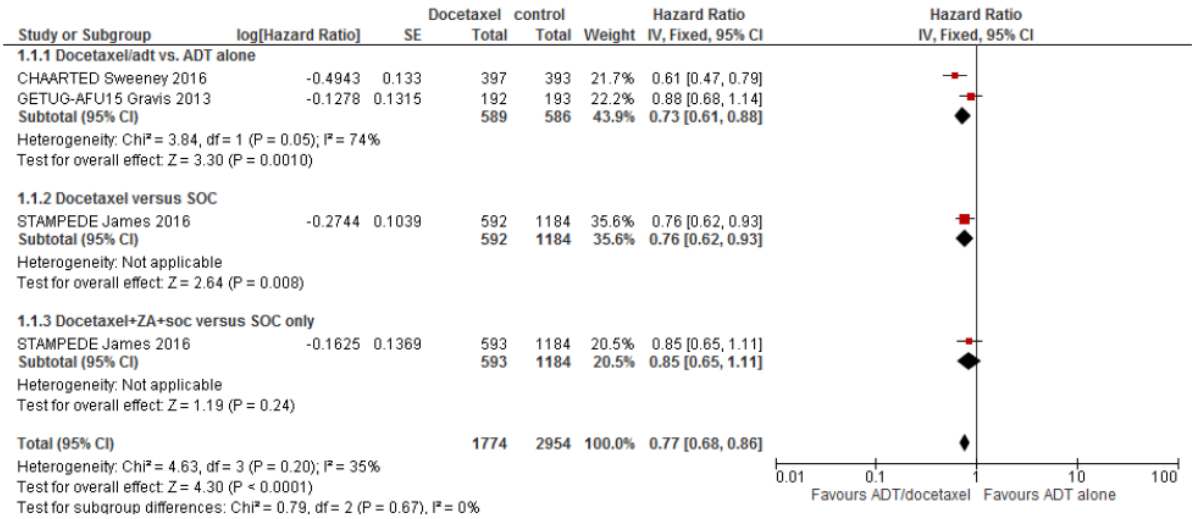
No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Overall survival – HR <1 favours docetaxel group										
3 studies GETUG-AFU15 Gravis 2013, CHAARTED Sweeney 2015, STAMPEDE 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										

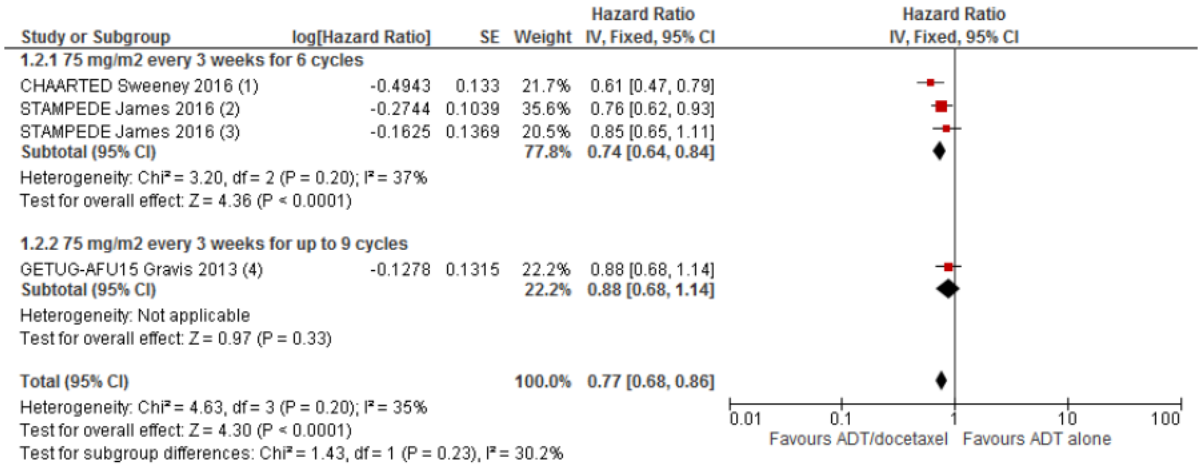
No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 study STAMPEDE James 2016	RCT	1442	HR 0.81 (0.66, 0.98)	-	-	Not serious	N/A	Not serious	Not serious	High
Quality of life 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

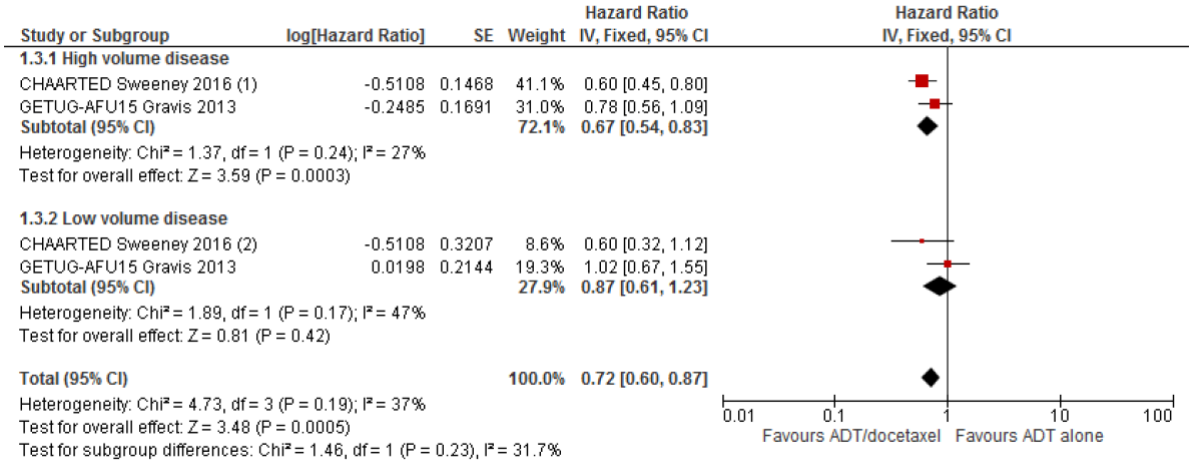


Overall survival stratified by dose



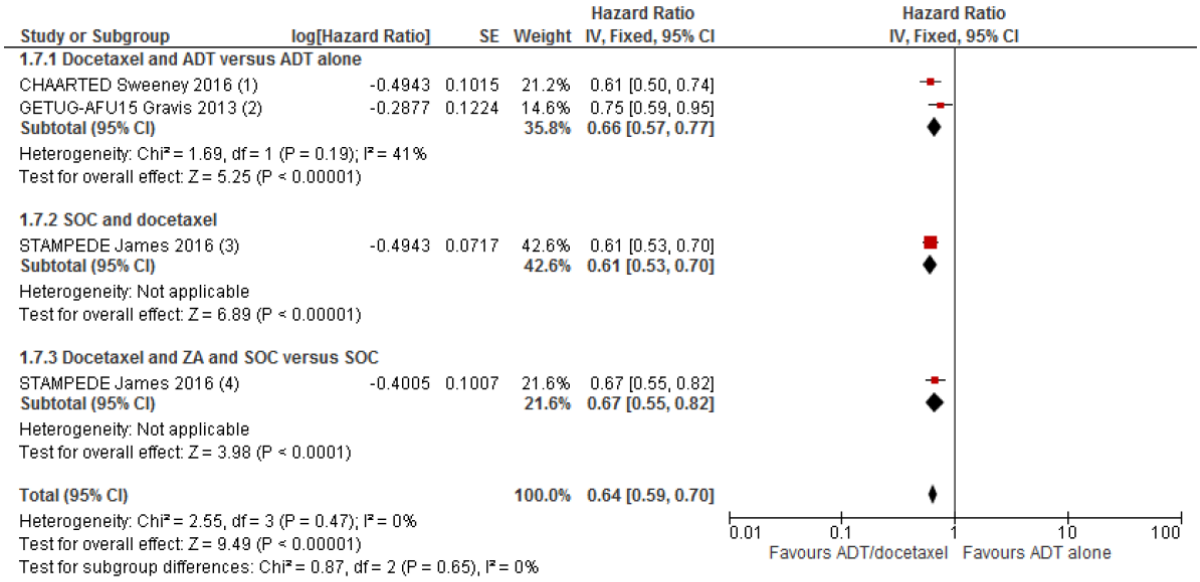
Footnotes
(1) ADT and Docetaxel vs ADT alone
(2) Docetacel alone vs SOC
(3) Doxetacel and Zoledronic Acid and SOC
(4) ADT and Docetaxel vs ADT alone

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



- 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

Referenzen

Siehe die dazugehörige „Evidence Review“: https://www.nice.org.uk/guidance/ng131/evidence/evidence-reviews-may-2019-6779081773?tab=evidence.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 06 of 12, June 2024) am 25.06.2024

#	Suchfrage
1	MeSH descriptor: [Prostatic Neoplasms] explode all trees
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	#1 OR (#2 AND #3)
5	#4 with Cochrane Library publication date from Jun 2019 to present

Systematic Reviews in PubMed am 25.06.2024

verwendete Suchfilter ohne Änderung:

Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchfrage
1	"Prostatic Neoplasms/drug therapy"[Majr] OR "Prostatic Neoplasms/radiotherapy"[Majr] OR "Prostatic Neoplasms/surgery"[Majr] OR "Prostatic Neoplasms/therapy"[Majr]
2	prostate[tiab] OR prostatic[tiab]
3	(#2) AND (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	(#3) AND (treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab])
5	#1 OR #4
6	(#5) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR

#	Suchfrage
	stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
7	(#6) AND ("2019/06/01"[PDAT] : "3000"[PDAT])
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in PubMed am 25.06.2024

verwendete Suchfilter ohne Änderung:

Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	prostatic neoplasms[majr]
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	#1 OR (#2 AND #3)
5	(#4) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
6	(#5) AND ("2019/06/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 28.06.2024

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft (DKG), Deutsche Krebshilfe (DKH), AWMF (AWMF)
- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- National Cancer Institute (NCI)

- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2024-B-187

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Sachverständige	
Datum	28. September 2024

Indikation
Behandlung erwachsener Männer mit metastasiertem hormonsensitivem Prostatakarzinom (mHSPC)
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?*)*

Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Zusammenfassung

Die Therapie des metastasierten, hormonsensitiven Prostatakarzinoms (mHSPC) hat sich in den letzten Jahren grundlegend geändert. Eine umfassende Darstellung der aktuellen Empfehlungen und des Hintergrunds findet sich in der S3 Leitlinie vom Juli 2024 [2].

Die Androgendeprivationstherapie (ADT) wurde durch unterschiedliche Kombinationen erweitert. Empfohlen werden. Folgende Differenzierung ist bei der Indikation klinisch relevant:

- Für Chemotherapie geeignet
  - Docetaxel oder
  - Docetaxel + Abirateron oder
  - Docetaxel + Darolutamid
- Für Chemotherapie nicht geeignet
  - Abirateron oder
  - Apalutamid oder
  - Enzalutamid

Die Auswahl innerhalb der ‚oder'-Optionen wird aktuell vor allem durch die etwas unterschiedlichen Zulassungsbedingungen (High Risk, High Volume, u. a.) und durch das zu erwartende Nebenwirkungsspektrum gesteuert.

Die jeweils neuen Arzneimittel wurden gegen ADT verglichen. Daten zum direkten Vergleich der neuen Kombinationen untereinander liegen bisher nicht vor.

Fragestellung

Die Fragestellung ist sehr weit gefasst. Sinnvoll ist die Integration von Vortherapien in die Fragestellung. Die aktuelle Stellungnahme basiert auf den 2023/2024 überarbeiteten Empfehlungen der S3 Leitlinie.

Stand des Wissens

Das Prostatakarzinom ist der mit Abstand häufigste maligne Tumor des Mannes [1]. Die Zahl der Neuerkrankungen in Deutschland wird für das Jahr 2020 mit etwa 66.000 angegeben. Die Zahl der Todesfälle nach einer Prostatakrebsdiagnose hingegen steigt – trotz sinkender bzw. seit 2007 konstanter Sterberate – jährlich um durchschnittlich 2,3% an. Dafür ist neben steigenden Überlebensraten (relative 5-Jahres-Überlebensrate 2003: 85,9%, 2012: 93,3%) auch eine Zunahme von Personen im höheren Alter verantwortlich [1].

Prostatakarzinomzellen exprimieren Androgenrezeptoren und sind regelhaft hormonempfindlich. Standard bei Fernmetastasen ist die ADT [2, 3]. Sie wird als systemische Therapie mit dem Effekt einer Kastration (Orchiektomie, LHRH-Analoga, GnRH-Blocker) durchgeführt werden. Grundsätzlich ist bei Patienten mit lokal fortgeschrittenem, hormonsensitivem Prostatakarzinom der Nutzen einer Lokaltherapie (Operation, Strahlentherapie) zu prüfen. Dies betrifft auch die oligometastatische Situation.

In den letzten Jahren hat sich die Überlebenszeit der Patienten durch die Möglichkeiten der kombinierten, hormonablativen Erstlinientherapie mit Docetaxel, Abirateron und Inhibitoren des Androgenrezeptorsignalwegs (APRI) deutlich verbessert. Die Empfehlungen der aktuellen S3 Leitlinie zum metastasierten, hormonsensitiven Prostatakarzinom sind [1]:

7.20	**Konsensbasierte Empfehlung neu 2024**
EK	Bei Patienten mit metastasiertem hormonsensitivem Prostatakarzinom soll zeitnah nach Diagnosestellung eine Androgendeprivation zur Reduktion des Risikos typischer Komplikationen (z. B. pathologische Frakturen, Rückenmarkskompression, Harnleiterobstruktion) und ggf. zur palliativen tumorspezifischen Therapie eventueller Tumor- bzw. Metastasen-bedingter Symptome (z. B. Knochenschmerzen) eingeleitet werden.
Starker Konsens	

7.21	**Evidenzbasierte Empfehlung neu 2024**
Empfehlungsgrad **0**	Eine Androgendeprivation kann durch chirurgische Kastration, durch subkutan oder intramuskulär zu verabreichende Gonadotropin-Releasing-Hormone (GnRH)-Agonisten oder durch subkutan oder oral zu verabreichende GnRH-Antagonisten durchgeführt werden.
Level of Evidence **1++**	
Starker Konsens	

7.22	**Konsensbasierte Empfehlung neu 2024**
EK	Bei Patienten mit ausgeprägten Tumor- bzw. Metastasen-bedingten Schmerzen oder drohenden Komplikationen (z. B. Rückenmarkskompression) sollte die Androgendeprivation mit einem Gonadotropin-Releasing-Hormon (GnRH)-Antagonisten und/oder mit

einem Androgenrezeptor-Signalweg Inhibitor (ARPI: Apalutamid, Enzalutamid, Darolutamid) eingeleitet werden.

Starker Konsens

7.23 **Konsensbasierte Empfehlung** **neu 2024**

EK Eine Monotherapie mit einem nicht-steroidalen Androgenrezeptorantagonisten der ersten Generation (z. B. Bicalutamid, Flutamid) soll bei Patienten mit metastasiertem hormonsensitivem Prostatakarzinom nicht durchgeführt werden.

Starker Konsens

7.24 **Evidenzbasierte Empfehlung** **modifiziert 2024**

Empfehlungsgrad **A**

Bei Patienten mit metastasiertem hormonsensitivem Prostatakarzinom (mHSPC) soll eine Einteilung nach high- und low-volume, high- und low-risk, sowie de novo und metachron metastasiert erfolgen.

Level of Evidence **1+, 1-**

Starker Konsens

7.25 **Konsensbasierte Empfehlung** **modifiziert 2024**

EK Patienten mit metastasiertem hormonsensitivem Prostatakarzinom sollen mit Einleitung der Androgendeprivation, spätestens innerhalb von drei Monaten danach, über eine Kombinationstherapie (gemäß 7.26) aufgeklärt werden, sowie über:

- • die zu erwartende Überlebenszeit
- • die unerwünschten Wirkungen
- • den Einfluss auf die Lebensqualität.

Starker Konsens

7.26 **Evidenzbasierte Empfehlung** **modifiziert 2024**

Empfehlungsgrad **A/0**

a. Patienten in gutem Allgemeinzustand (ECOG 0-1) mit metastasiertem (M1) hormonsensitivem, Prostatakarzinom (mHSPC) soll zusätzlich zur Androgendeprivation eine Hormontherapie mit Apalutamid oder Enzalutamid angeboten werden. (Empfehlungsgrad: A)

b. Patienten in gutem Allgemeinzustand (ECOG 0-1) mit neu-diagnostiziertem (de novo), metastasierten (M1), hormonsensitiven, high-risk Prostatakarzinom (mHSPC) soll zusätzlich zur Androgendeprivation eine Hormontherapie mit Abirateron (plus Prednison / Prednisolon) angeboten werden. (Empfehlungsgrad: A)

c. Patienten in gutem Allgemeinzustand (ECOG 0-1) mit metastasiertem (M1) hormonsensitivem Prostatakarzinom, die für eine Docetaxel Chemotherapie geeignet sind, soll zusätzlich zur Androgendeprivation eine Hormontherapie mit Darolutamid in Kombination mit 6 Zyklen Docetaxel angeboten werden. (Empfehlungsgrad: A)

d. Patienten in gutem Allgemeinzustand (ECOG 0-1) mit neu-diagnostiziertem (de novo), metastasiertem (M1) hormonsensitivem Prostatakarzinom und hohem Tumorvolumen („*high volume disease*“), die für eine Docetaxel Chemotherapie geeignet sind, kann zusätzlich zur Androgendeprivation eine Hormontherapie mit Abirateron (plus

Prednison/Prednisolon) in Kombination mit 6 Zyklen Docetaxel angeboten werden. (Empfehlungsgrad: 0)

Level of Evidence
1+, 1++, 2+

Starker Konsens

7.27 **Evidenzbasierte Empfehlung** **modifiziert 2024**

Empfehlungsgrad **A**

a. Bei Entscheidung für eine kombinierte Behandlung aus Androgendeprivation und Apalutamid, soll die Apalutamidgabe innerhalb von 3 Monaten nach Beginn der Androgendeprivation beginnen. Die Therapie soll in einer Dosierung von 240 mg/Tag gegeben werden.
b. Bei Entscheidung für eine kombinierte Behandlung aus Androgendeprivation und Enzalutamid, soll die Enzalutamidgabe innerhalb von 3 Monaten nach Beginn der Androgendeprivation beginnen. Die Therapie soll in einer Dosierung von 160 mg/Tag gegeben werden.
c. Bei Entscheidung 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.
d. Bei Entscheidung für eine kombinierte Behandlung aus Darolutamid, Docetaxel-Chemotherapie und Androgendeprivation, soll die Darolutamid-Gabe in einer Dosierung von 2 x 600 mg/Tag innerhalb von 3 Monaten nach Einleitung der Androgendeprivation beginnen. Die Chemotherapie soll innerhalb von 6 Wochen nach erster Darolutamid-Gabe beginnen; Docetaxel soll über 6 Zyklen alle 3 Wochen in einer Dosierung von 75 mg/m2 Körperoberfläche verabreicht werden.
e. Bei Entscheidung für eine kombinierte Behandlung aus Abirateron, Docetaxel-Chemotherapie und Androgendeprivation, soll die Abirateron-Gabe in einer Dosierung von 1000 mg/Tag (plus Prednison/Prednisolon) innerhalb von 6 Wochen nach Einleitung der Androgendeprivation beginnen. Die Chemotherapie soll ab 6 Wochen nach Einleitung der Androgendeprivation beginnen; Docetaxel soll über 6 Zyklen alle 3 Wochen in einer Dosierung von 75 mg/m2 Körperoberfläche verabreicht werden.

Level of Evidence **1+** **1++ 2+** Starker Konsens	
7.28 **EK** Starker Konsens	**Konsensbasierte Empfehlung** **modifiziert 2024** Gründe für einen Therapieabbruch sollen sein: Patientenwunsch, Progress oder intolerable Nebenwirkungen. Wird die Behandlung mit einem Medikament aus der Kombination wegen intolerabler Nebenwirkungen abgebrochen, dann soll die übrige Therapie wie vorgesehen weitergeführt werden.
7.29 Empfehlungsgrad **A** Level of Evidence **1++** Starker Konsens	**Evidenzbasierte Empfehlung** **modifiziert 2024** Patienten, die nicht für eine Kombinationsbehandlung in Frage kommen, soll eine Androgendeprivation angeboten werden.
Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?	
Ja, diese sind oben dargestellt. Zu den entscheidenden Kriterien gehören die Eignung für eine Chemotherapie mit Docetaxel und ggf. Vortherapien in früheren Krankheitsstadien.	

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