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: 2021-B-174 ^{177}Lu-PSMA-617

Stand: November 2022

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

^{177}Lu-PSMA-617
[zur Behandlung des metastasierten, kastrationsresistenten 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“*. Nicht berücksichtigt wurden Arzneimittel mit expliziter Zulassung für: - das hormonsensitive Prostatakarzinom
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Strahlentherapie
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:** - Olaparib: Beschluss vom 03.06.2021 - Radium-223-dichlorid: Beschluss vom 17.10.2019 - Enzalutamid: Beschluss vom 18.06.2015 - Sipuleucel-T: Beschluss vom 19.03.2015 - Enzalutamid: Beschluss vom 20.02.2014 - Abirateronacetat: Beschluss vom 04.07.2013 - Abirateronacetat: Beschluss vom 29.03.2012 - Cabazitaxel: Beschluss vom 29.03.2012 **Richtlinie Methoden Krankenhausbehandlung** in Anlage II (Methoden, deren Bewertungsverfahren ausgesetzt sind): Protonentherapie beim Prostatakarzinom: Beschluss vom 19.06.2008
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:	
^{177}Lu-PSMA-617 N.N. Pluvicto	Anwendungsgebiet laut positive Opinion: Lutetium (^{177}Lu)-Vipivotid-Tetraxetan ist in Kombination mit einer Androgendeprivationstherapie (ADT) mit oder ohne Androgenrezeptor (AR)-Hemmung für die Behandlung erwachsener Patienten mit progressivem prostataspezifischem Membranantigen (PSMA)-positivem metastasiertem kastrationsresistentem Prostatakrebs (mCRPC) indiziert, die mit AR-Hemmung und Taxan-basierter Chemotherapie behandelt wurden.
Antiandrogene	
Bicalutamid L02BB03 generisch	<u>Fortgeschrittenes Prostatakarzinom</u> - Behandlung des fortgeschrittenen Prostatakarzinoms in Kombination mit einer LHRH-(Luteinisierendes-Hormon-Releasing-Hormon)-Analogon-Therapie oder einer operativen Kastration.

Cyproteronacetat
G03HA01
generisch
	<u>Beim Mann</u>
	- zur palliativen Therapie des metastasierenden oder lokal fortgeschrittenen, inoperablen Prostatakarzinoms,
	  o wenn sich die Behandlung mit LHRH-Analoga oder der operative Eingriff als unzureichend erwiesen haben, kontraindiziert ind oder der oralen Therapie der Vorzug gegeben wird,
	  o 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

Flutamid L02BB01 generisch	Zur Behandlung von Patienten mit fortgeschrittenem Prostatakarzinom, bei denen eine Suppression der Testosteronwirkungen indiziert ist. - Initialtherapie in Kombination mit einem LH-RH-Analogon oder in Verbindung mit Orchiektomie (komplette Androgenblockade) sowie bei Patienten, die bereits mit einem LH-RH-Analogon behandelt werden bzw. bei denen bereits eine chirurgische Ablatio testis erfolgt ist. - Zur Behandlung von Patienten, die auf andere endokrine Therapieformen nicht ansprachen oder für die eine andere endokrine Therapie nicht verträglich, aber notwendigerweise indiziert ist.

GnRH-Antagonisten	
Degarelix L02BX02 Firmagon	Firmagon ist ein Gonadotropin-Releasing-Hormon-(GnRH)-Antagonist zur Behandlung von erwachsenen männlichen Patienten mit fortgeschrittenem hormonabhängigen Prostatakarzinom.
GnRH-Agonisten	
Buserelin L02AE01 z.B. 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 z.B. Zoladex	Behandlung von Patienten mit fortgeschrittenem Prostatakarzinom, bei denen eine endokrine Behandlung angezeigt ist.
Leuprorelin L02AE02 generisch	- Zur Behandlung des fortgeschrittenen hormonabhängigen Prostatakarzinoms. - Zur Behandlung des lokal fortgeschrittenen, hormonabhängigen Prostatakarzinoms; begleitend zur und nach der Strahlentherapie. - Zur Behandlung des lokalisierten hormonabhängigen Prostatakarzinoms bei Patienten des mittleren und Hoch-Risikoprofils in Kombination mit der Strahlentherapie.
Triptorelin L01AA06 generisch	ist indiziert zur Behandlung des - lokal fortgeschrittenen oder metastasierenden, hormonabhängigen Prostatakarzinoms. - lokal fortgeschrittenen, hormonabhängigen Prostatakarzinoms; begleitend zur und nach der Strahlentherapie.
Zytostatika	
Estramustin L01XX11 generisch	Palliative Behandlung des fortgeschrittenen, hormonrefraktären Prostatakarzinoms
Docetaxel L01CD02 generisch	<u>Prostatakarzinom</u> Docetaxel ist in Kombination mit Prednison oder Prednisolon zur Behandlung von Patienten mit hormonrefraktärem metastasiertem Prostatakarzinom angezeigt.

Cabazitaxel L01CD04 Jevtana	Jevtana ist in Kombination mit Prednison oder Prednisolon zur Behandlung von erwachsenen Patienten mit metastasiertem kastrationsresistentem Prostatakarzinom angezeigt, die mit einem Docetaxel-basierten Therapieschema vorbehandelt sind.
Mitoxantron L01D B07 generisch	- ist in Kombination mit Corticosteroiden indiziert zur Palliation (z. B. Schmerzlinderung) bei fortgeschrittenem kastrationsresistentem Prostatakarzinom.
Neuartige Hormontherapeutika	
Enzalutamid L02BB04 Xtandi	Xtandi ist angezeigt: - zur Behandlung erwachsener Männer mit metastasiertem kastrationsresistentem Prostatakarzinom mit asymptomatischem oder mild symptomatischem Verlauf nach Versagen der Androgenentzugstherapie, bei denen eine Chemotherapie klinisch noch nicht indiziert ist - zur Behandlung erwachsener Männer mit metastasiertem kastrationsresistentem Prostatakarzinom, deren Erkrankung während oder nach einer Chemotherapie mit Docetaxel fortschreitet.
Abirateronacetat L02BX03 Zytiga	Zytiga ist indiziert mit Prednison oder Prednisolon: - zur Behandlung des metastasierten kastrationsresistenten Prostatakarzinoms (mCRPC) bei erwachsenen Männern mit asymptomatischem oder mild symptomatischem Verlauf der Erkrankung nach Versagen der Androgenentzugstherapie, bei denen eine Chemotherapie noch nicht klinisch indiziert - zur Behandlung des mCRPC bei erwachsenen Männern, deren Erkrankung während oder nach einer Docetaxel-haltigen Chemotherapie progredient ist.
Olaparib L01XX46 Lynparza	<u>Prostatakarzinom</u> Lynparza wird angewendet als Monotherapie für die Behandlung von erwachsenen Patienten mit metastasiertem kastrationsresistentem Prostatakarzinom und BRCA1/2-Mutationen (in der Keimbahn und/oder somatisch), deren Erkrankung nach vorheriger Behandlung, die eine neue hormonelle Substanz (new hormonal agent) umfasste, progredient ist.
Sonstige	
Radium-223-dichlorid V10XX03 Xofigo	Xofigo wird als Monotherapie oder in Kombination mit einem LHRH-Analogon (LHRH: Luteinisierendes-Hormon-freisetzendes Hormon) zur Behandlung von erwachsenen Patienten mit metastasiertem kastrationsresistentem Prostatakarzinom (mCRPC) und symptomatischen Knochenmetastasen ohne bekannte viszerale Metastasen angewendet, bei denen die Erkrankung nach Erhalt von mindestens zwei vorausgehenden systemischen Therapielinien zur Behandlung des mCRPC (außer LHRHAnaloga) fortschreitet, oder für die keine andere verfügbare systemische mCRPCTherapie geeignet ist.

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2021-B-174 (177Lu-PSMA-617)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	14. Juli 2021

Inhaltsverzeichnis

Abkürzungsverzeichnis

AAP/ABI	Abiraterone acetate
ADT	Androgen Deprivation Therapy
ADT	Androgen deprivation therapy
AE	Adverse Events
AM-RL	Arzneimittel-Richtlinie
AR	Androgen Rezeptor
ASCO	American Society of Clinical Oncology
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BSC	Best Supportive Care
BRFS	Biochemical recurrence-free survival
CAB	Cabazitaxel
CI	Confidence Interval
cORR	Clinical Overall Response Rate
CRPC	Castration-Resistant Prostate Cancer
DFS	Disease-free survival
DOC	Docetaxel
EBRT	External Beam Radiation Therapy
ECOG	Eastern Co-operative Oncology Group
ECOG PS	ECOG Performance Status
EK	Expertenkonsens
EnZ/ENZA/ENZ	Enzalutamide
EQ-5D	EuropeanQuality of Life 5-Dimensions
ESMO	European Society for Medical Oncology
FACT-P	Functional Assessment of Cancer Therapy-Prostate
G-BA	Gemeinsamer Bundesausschuss
GCP	Good Clinical Practice
GIN	Guidelines International Network
GnRH	Gonadotropin-Releasing-Hormon

GoR	Grade of Recommendations
HR	Hazard Ratio
HRQOL	Health-related Quality of Life
HSPC	Hormone-Sensitive Prostata Cancer
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
KMS	Knowledge Management Specialist
LHRH	Luteinizing Hormone-Releasing Hormone
LoE	Level of Evidence
MINORS	Methodological index for non-randomized studies
NOS	Newcastle-Ottawa Scale
mCRPC	metastatic Castration-Resistant Prostate Cancer
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
ORR	Overall Response rate (c:clinical; s:prsotataspecific antigen)
OS	Overall Survival
PBO	Placebo
PCa	Prostate Cancer
PCO	Provisional Clinical Opinion
PFS	Progression-Free Survival
PSA	Prostate-Specific Antigen
QLQC30	European Orga nization for Research and Treatment of Cancer Quality of Life Questionnaire
QoL/QOL	Quality of Life
RR	Relatives Risiko
SBRT	Stereotacitc Body Radiation Therapy
SEOM	Sociedad Española de Oncología
SIGN	Scottish Intercollegiate Guidelines Network
SSE	Symptomatic Skeletal Event
sORR	prostate-specific Antigen Overall Response Rate

TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Behandlung des metastasierten kastrationsresistenten Prostatakarzinoms.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Prostatakarzinom* durchgeführt. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, SIGN, TRIP, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien.

Die Erstrecherche wurde am 11.09.2020 durchgeführt, die Folgerecherche am 26.04.2021. Die Recherchestrategie der Erstrecherche wurde für die Folgerecherche übernommen und der Suchzeitraum jeweils auf die letzten 5 Jahre eingeschränkt. Die letzte Suchstrategie ist am Ende der Synopse detailliert dargestellt. Nachträglich wurde ein G-BA-Beschluss [5] identifiziert und in die Synopse aufgenommen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 1987 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 27 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA-Beschlüsse/IQWiG-Berichte

G-BA, 2021 [5].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: Olaparib (neues Anwendungsgebiet: Prostatakarzinom, BRCA1/2-Mutationen, Progredienz nach hormoneller Behandlung) vom 3. Juni 2021

Anwendungsgebiet

Lynparza wird angewendet als Monotherapie für die Behandlung von erwachsenen Patienten mit metastasiertem kastrationsresistentem Prostatakarzinom und BRCA1/2-Mutationen (in der Keimbahn und/oder somatisch), deren Erkrankung nach vorheriger Behandlung, die eine neue hormonelle Substanz (new hormonal agent) umfasste, progredient ist.

Erwachsene Patienten mit metastasierten kastrationsresistenten Prostatakarzinom (mCRPC); BRCA1/2- mutiert (in der Keimbahn und/oder somatisch); progrediente Erkrankung nach vorheriger Behandlung mit Abirateron und/ oder Enzalutamid

Zweckmäßige Vergleichstherapie

Patientenindividuelle Therapie unter Auswahl von Abirateron, Enzalutamid, Cabazitaxel und Docetaxel; unter Berücksichtigung der Vortherapien sowie unter Beachtung der Zulassung der jeweiligen Arzneimittel.

Fazit / Ausmaß des Zusatznutzens

Anhaltspunkt für einen beträchtlichen Zusatznutzen.

G-BA, 2020 [12].

Richtlinie zu Untersuchungs- und Behandlungsmethoden im Krankenhaus; Anlage II: Methoden, deren Bewertungsverfahren ausgesetzt sind, 2.1 Protonentherapie beim Prostatakarzinoms; Fassung vom 21. März 2006, veröffentlicht im BAnz. Nr. 111 (S. 4466) 2006, zuletzt geändert am 20. November 2020 in Kraft getreten am 20. Februar 2021.

2.1 Protonentherapie beim Prostatakarzinoms

Beschluss gültig bis 31. Dezember 2021 (verbunden mit Beschluss zur Qualitätssicherung gemäß § 137 SGB V)

G-BA, 2019 [4].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Radium-223-dichlorid (Neubewertung aufgrund neuer wissenschaftlicher Erkenntnisse: Prostatakarzinom) Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die

Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Radium-223-dichlorid

I. Die Anlage XII wird wie folgt geändert:

1. Die Angaben zu Radium-223-dichlorid gemäß Beschluss vom 19. Juni 2014 (BAnz AT 18.07.2014 B4) zuletzt geändert am 1. November 2018 (BAnz AT 16.11.2018 B5) werden aufgehoben.

2. Die Anlage XII wird in alphabetischer Reihenfolge um den Wirkstoff Radium-223-dichlorid wie folgt ergänzt:

Anwendungsgebiet

Xofigo wird als Monotherapie oder in Kombination mit einem LHRH-Analogon (LHRH: Luteinisierendes-Hormon-freisetzendes Hormon) zur Behandlung von erwachsenen Patienten mit metastasiertem kastrationsresistentem Prostatakarzinom (mCRPC) und symptomatischen Knochenmetastasen ohne bekannte viszerale Metastasen angewendet, bei denen die Erkrankung nach Erhalt von mindestens zwei vorausgehenden systemischen Therapielinien zur Behandlung des mCRPC (außer LHRH-Analoga) fortschreitet, oder für die keine andere verfügbare systemische mCRPC Therapie geeignet ist (siehe Abschnitt 4.4).

a) Erwachsene Patienten mit metastasiertem kastrationsresistentem Prostatakarzinom (mCRPC) und symptomatischen Knochenmetastasen ohne bekannte viszerale Metastasen, bei denen die Erkrankung nach Erhalt von mindestens zwei vorausgehenden systemischen Therapielinien zur Behandlung des mCRPC (außer LHRH-Analoga) fortschreitet

Zweckmäßige Vergleichstherapie:

Patientenindividuelle Therapie unter Berücksichtigung der Vortherapien und unter Auswahl von Abirateron, Enzalutamid, Cabazitaxel und Docetaxel

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Radium-223-dichlorid gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt.

b) Erwachsene Patienten mit metastasiertem kastrationsresistentem Prostatakarzinom (mCRPC) und symptomatischen Knochenmetastasen ohne bekannte viszerale Metastasen, für die keine andere verfügbare systemische mCRPC Therapie geeignet ist

Zweckmäßige Vergleichstherapie:

Best-Supportive-Care (insbesondere adäquate Schmerztherapie, Behandlung mit Bisphosphonaten, Denosumab und/oder Radionukliden)

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Radium-223-dichlorid gegenüber der zweckmäßigen Vergleichstherapie:

- Ein Zusatznutzen ist nicht belegt.

G-BA, 2015 [7].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 18. Juni 2015 - Enzalutamid (neues Anwendungsgebiet: Prostatakarzinom, nach Versagen einer Androgenentzugstherapie, vor Chemotherapie)

Anwendungsgebiet

Enzalutamid (Xtandi®) ist angezeigt zur Behandlung erwachsener Männer mit metastasiertem kastrationsresistentem Prostatakarzinom mit asymptomatischem oder mild symptomatischem Verlauf nach Versagen der Androgenentzugstherapie, bei denen eine Chemotherapie klinisch noch nicht indiziert ist.

Zweckmäßige Vergleichstherapie

Für Enzalutamid zur Behandlung des metastasierten kastrationsresistenten Prostatakarzinoms bei erwachsenen Männern mit asymptomatischem oder mild symptomatischem Verlauf der Erkrankung nach Versagen der Androgenentzugstherapie, bei denen eine Chemotherapie noch nicht klinisch indiziert ist, ist die zweckmäßige Vergleichstherapie:

- das abwartende Vorgehen unter Beibehaltung der bestehenden konventionellen Androgendeprivation oder gegebenenfalls
- die kombinierte, maximale Androgenblockade mit einem nichtsteroidalen Antiandrogen (Flutamid, Bicalutamid) oder
- Abirateronacetat unter Beibehaltung der bestehenden Androgendeprivation.

Fazit / Ausmaß des Zusatznutzens

Ausmaß und Wahrscheinlichkeit des Zusatznutzens **gegenüber dem abwartenden Vorgehen** unter Beibehaltung der bestehenden konventionellen Androgendeprivation:

- Hinweis auf einen beträchtlichen Zusatznutzen.

G-BA, 2015 [8].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 19. März 2015 - Sipuleucel-T.

Anwendungsgebiet

Sipuleucel-T (Provenge®) ist angezeigt für die Behandlung von asymptomatischem oder minimal symptomatischem, metastasiertem (nicht viszerale), kastrationsresistentem Prostatakarzinom bei männlichen Erwachsenen, bei denen eine Chemotherapie klinisch noch nicht indiziert ist.

Zweckmäßige Vergleichstherapie

Die zweckmäßige Vergleichstherapie für Provenge® (Sipuleucel-T) zur Behandlung des asymptomatischem oder minimal symptomatischem, metastasiertem (nicht viszerale), kastrationsresistentem Prostatakarzinoms bei männlichen Erwachsenen, bei denen eine Chemotherapie klinisch noch nicht indiziert ist:

- das abwartende Vorgehen unter Beibehaltung der bestehenden konventionellen Androgendeprivation oder gegebenenfalls die kombinierte, maximale Androgenblockade mit einem nichtsteroidalen Antiandrogen (Flutamid, Bicalutamid) oder Abirateronacetat unter Beibehaltung der bestehenden Androgendeprivation.

Fazit / Ausmaß des Zusatznutzens

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber dem abwartenden Vorgehen unter Beibehaltung der bestehenden konventionellen Androgendeprivation:

- Anhaltspunkt für einen nicht quantifizierbaren Zusatznutzen.

G-BA, 2014 [9].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 20. Februar 2014 – Enzalutamid.

Anwendungsgebiet

Enzalutamid (Xtandi®) ist angezeigt zur Behandlung erwachsener Männer mit metastasiertem kastrationsresistentem Prostatakarzinom, deren Erkrankung während oder nach einer Chemotherapie mit Docetaxel fortschreitet.

Zweckmäßige Vergleichstherapie

Die zweckmäßige Vergleichstherapie für Enzalutamid zur Behandlung des metastasierten, kastrationsresistenten Prostatakarzinoms bei erwachsenen Männern, deren Erkrankung während oder nach einer Chemotherapie mit Docetaxel fortschreitet, ist:

- Best-Supportive-Care (z. B. adäquate Schmerztherapie)

Als Best-Supportive-Care wird die Therapie verstanden, die eine bestmögliche, patientenindividuell optimierte, unterstützende Behandlung zur Linderung von Symptomen und Verbesserung der Lebensqualität gewährleistet.

Fazit / Ausmaß des Zusatznutzens

Hinweis für einen beträchtlichen Zusatznutzen.

G-BA, 2013 [6].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 4. Juli 2013 - Abirateronacetat (neues Anwendungsgebiet: Prostatakarzinom, nach Versagen einer Androgenentzugstherapie, vor Chemotherapie).

Anwendungsgebiet

Neu zugelassenes Anwendungsgebiet vom 18. Dezember 2012: Zytiga® ist zugelassen in Kombination mit Prednison oder Prednisolon:

- zur Behandlung des metastasierten kastrationsresistenten Prostatakarzinoms bei erwachsenen Männern mit asymptomatischem oder mild symptomatischem Verlauf der Erkrankung nach Versagen der Androgenentzugstherapie, bei denen eine Chemotherapie noch nicht klinisch indiziert ist.

Zweckmäßige Vergleichstherapie

Die zweckmäßige Vergleichstherapie für Abirateronacetat zur Behandlung des metastasierten, kastrationsresistenten Prostatakarzinoms bei erwachsenen Männern,

deren Erkrankung nach Versagen einer konventionellen Androgenentzugstherapie asymptomatisch oder mild symptomatisch ist, ist das abwartende Vorgehen unter Beibehaltung der bestehenden konventionellen Androgendeprivation oder gegebenenfalls die kombinierte, maximale Androgenblockade mit einem nichtsteroidalen Antiandrogen (Flutamid, Bicalutamid).

- Erläuterungen: Unter konventioneller Androgenentzugstherapie wird im Rahmen des vorliegenden Anwendungsgebietes die operative Kastration oder die medikamentöse Kastration durch Therapie durch LHRH-Analoga oder GnRH-Antagonisten verstanden und unter "Versagen" eine auf der Grundlage von Surrogatparametern (z. B. PSA-Anstieg und radiographischer Progress oder Up-Grading) definierte Krankheitsprogression. Nach Versagen einer konventionellen Androgenentzugstherapie stellt die kombinierte, maximale Androgenblockade mit einem nicht-steroidalen Antiandrogen eine mögliche Therapieoption dar, deren Einsatz jedoch aufgrund der zu erwartenden höheren Nebenwirkungen gegenüber der geringen Überlebensverlängerung sorgfältig mit dem Patienten abzuwägen ist. Bei der Erkrankung des metastasierten, kastrationsresistenten Prostatakarzinoms handelt es sich um eine palliative Therapiesituation. Dem Erhalt der Lebensqualität und der Symptomkontrolle kommen daher besondere Bedeutung zu.

Fazit / Ausmaß des Zusatznutzens

Hinweis für einen beträchtlichen Zusatznutzen.

G-BA, 2012 [10].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 29. März 2012 – Abirateronacetat.

Anwendungsgebiet

Zytiga® ist indiziert mit Prednison oder Prednisolon zur Behandlung des metastasierten kastrationsresistenten Prostatakarzinoms bei erwachsenen Männern, deren Erkrankung während oder nach einer Docetaxel-haltigen Chemotherapie progredient ist.

Zweckmäßige Vergleichstherapie

a) Patienten mit metastasiertem kastrationsresistentem Prostatakarzinom, die während oder nach einer Docetaxel-haltigen Chemotherapie progredient sind und für die eine erneute Behandlung mit Docetaxel nicht mehr infrage kommt:

- Palliative Behandlung mit Dexamethason, Prednison, Prednisolon oder Methylprednisolon sowie "Best Supportive Care" (z.B. adäquate Schmerztherapie).

  Als "Best Supportive Care" (BSC) wird die Therapie verstanden, die eine bestmögliche, patientenindividuell optimierte, unterstützende Behandlung zur Linderung von Symptomen und Verbesserung der Lebensqualität gewährleistet.

Fazit / Ausmaß des Zusatznutzens

Hinweis auf einen beträchtlichen Zusatznutzen.

G-BA, 2012 [11].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 29. März 2012 – Cabazitaxel.

Anwendungsgebiet

Jevtana® ist in Kombination mit Prednison oder Prednisolon zur Behandlung von Patienten mit hormonrefraktärem metastasiertem Prostatakarzinom angezeigt, die mit einem Docetaxel-basierten Therapieschema vorbehandelt sind.

Zweckmäßige Vergleichstherapie

Patienten mit hormonrefraktärem metastasiertem Prostatakarzinom, die während oder nach einer Docetaxel-haltigen Chemotherapie progredient sind und für die eine erneute Behandlung mit Docetaxel nicht mehr infrage kommt:

- Palliative Behandlung mit Dexamethason, Prednison, Prednisolon oder Methylprednisolon sowie "Best Supportive Care" (z.B. adäquate Schmerztherapie).

  Als "Best Supportive Care" (BSC) wird die Therapie verstanden, die eine bestmögliche, patientenindividuell optimierte, unterstützende Behandlung zur Linderung von Symptomen und Verbesserung der Lebensqualität gewährleistet.

Fazit / Ausmaß des Zusatznutzens

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber ,,Best Supportive Care“:

- Hinweis auf einen geringen Zusatznutzen.

3.2 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.3 Systematische Reviews

Cassinello et al.,2021 [2].

Optimal treatment sequencing of abiraterone acetate plus prednisone and enzalutamide in patients with castration-resistant metastatic prostate cancer: A systematic review and meta-analysis

Fragestellung

To evaluate the impact of the hormonal treatment sequencing including abiraterone acetate plus prednisone (AAP) and enzalutamide (ENZ) in mCRPC, and determine which sequence provides more benefits for patients.

Methodik

Population:

- Patients with castration-resistant metastatic prostate cancer

Intervention/Komparator:

- AAP→ENZ and ENZ→AAP

Endpunkte:

- PSA-progession-free-survival (PSA-PFS) and OS

Recherche/Suchzeitraum:

- Studies published in English between 1 January 2013 and 30 September 2017 were identified in PubMed and EMBASE electronic databases

Qualitätsbewertung der Studien:

- The GRADE approach was used to rate the quality of evidence found in the research and strength of recommendation, using a four-level scale: high, moderate, low, very low
- The Rosenthal Index, which indicates the number of unpublished stueides of non-significant results that would be necessary to invalidate the conclusion oft he meta-analysis, was estimated.
- Q Test and I2 index (I2=0% non-heterogeneity; 25% low heterogeneity; 50% moderate heterogeneity; 75% high heterogeneity)

Ergebnisse

Anzahl eingeschlossener Studien:

- Seventeen studies met the inclusion criteria

Charakteristika der Population:

Table 1
Characteristics of the eligible studies.

Author(s) Year	Country	Study Design	Study Period	Study Summary	PFS	PSA-PFS	OS	Treatment Sequence	No. of patients
Mori et al. [26]	Japan	Retrospective	2014–2016	Comparisons of oncologic outcomes between the treatment sequences: AAP → ENZ vs. ENZ → AAP in CRPC patients, chemo-naïve ($N = 37$) and post-chemotherapy ($N = 32$).	Yes	Yes	Yes	AAP → ENZ ENZ → AAP	29 46
Maughan et al. [27]	USA	Retrospective	Since 2011	Comparisons of oncologic outcomes between the treatment sequences: AAP → ENZ vs. ENZ → AAP in mCRPC patients, chemo naïve ($N = 58$) and post chemotherapy ($N = 23$).	Yes	Yes	Yes	AAP → ENZ ENZ → AAP	65 16
Azad et al. [28]	Canada	Retrospective	Until March 2014	Comparison of the efficacy of enzalutamide following abiraterone in docetaxel-experienced ($N = 68$) and docetaxel-naïve ($N = 47$) mCRPC patients.	–	–	Yes	Doc → AAP → ENZ	115
Badrising et al. [29]	Netherlands	Retrospective	2012–2013	Evaluation of the efficacy and tolerability of enzalutamide in mCRPC patients who previously received docetaxel and abiraterone.	Yes	–	Yes	Doc → AAP → ENZ	61
Badrising et al. [30]	Netherlands	Retrospective	Until May 2014	Investigation of prognostic factors for ENZ-responders after Doc and AAP treatment in mCRPC.	Yes	–	Yes	Doc → AAP → ENZ	102
Bianchini et al. [31]	UK	Retrospective	2012–2013	Analysis of antitumor activity and safety of ENZ in CRPC patients previously treated with Doc and AAP.	Yes[1]	–	Yes	Doc → AAP → ENZ	39
Bruno et al. [32]	Denmark, Germany, UK	Retrospective		Analysis of the effect of ENZ in CRPC patients progressing following taxane-based chemotherapy and AAP.	Yes	–	Yes	Doc → AAP → ENZ	137
Cheng et al. [33]	USA, Canada	Retrospective	2009–2014	Evaluation of the response and outcomes of ENZ treated mCRPC patients in the real-world context of prior treatments of AAP and/or Doc.		Yes	Yes (Doc → AAP → ENZ)	AAP → ENZ Doc → AAP → ENZ ENZ (no prior AAP and Doc) Doc → ENZ	79 165 86 30
Davies et al. [34]	UK	Retrospective		Evaluation of the activity of third-line ENZ in men with mCRPC after Doc and AAP.	Yes	–	Yes	Doc → AAP → ENZ	34
Schmid et al. [35]	Germany	Observational prospective	Since 2012	Evaluation of the efficacy and tolerability of ENZ after Doc and AAP in mCRPC patients.	Yes	–	Yes	Doc → AAP → ENZ	35
Schrader et al. [36]	Germany	Observational	Since 2012	Evaluation the effectiveness of ENZ after failure of AAP (all patients had undergone prior docetaxel chemotherapy).	–	–	Yes	Doc → AAP → ENZ	33
Thomsen et al. [37]	Denmark	Observational prospective	Until July 2013	Analysis of PSA response and OS for a group of mCRPC patients treated with ENZ following progression after AAP treatment in the post-chemotherapy setting.	–	–	Yes	Doc → AAP → ENZ	24
Zhang et al. [38]	USA	Retrospective	2013	Exploring the clinical benefit of Doc or ENZ after disease progression during AAP treatment in men with mCRPC.	Yes	–	Yes	AAP → ENZ AAP → Doc Doc → AAP → ENZ	9 13 19
De Bono et al. [39]	Belgium, France, Germany, Spain, UK	Phase IV	2014–2017	Assessment of the efficacy and safety of ENZ in patients with progressing mCRPC previously treated with AAP.	Yes	–	Yes	AAP → ENZ	215
Suzman et al. [40]	USA	Retrospective	March 2014	Assessment of the clinical activity of ENZ versus Doc in men with mCRPC who progressed on AAP.	Yes	Yes	–	AAP → ENZ AAP → Doc	30 31
Loriot et al. [41]	France, UK	Retrospective	2012–2013	Investigation of the antitumor activity of AAP in patients with mCRPC who had progressed following treatment with Doc and ENZ.	Yes	–	Yes	Doc → ENZ → AAP	38
Noonan et al. [42]	Canada, USA	Retrospective	2012–2013	Evaluation of the activity of AAP in patients with mCRPC progressing after enzalutamide.	–	Yes	Yes	Doc → ENZ → AAP	30

AAP = abiraterone acetate plus prednisone; ENZ = enzalutamide; Doc = docetaxel; PFS = Progression Free Survival; PSA-PFS = Prostate-specific antigen progression-free survival; OS = Overall Survival; Dx = age at diagnosis; E = age at the start of ENZ treatment; ST = Soft tissue metastasis.
1: PFS was defined as the interval from initiation of enzalutamide and the date of PSA, radiological or clinical progression.

Qualität der Studien:

- Also retrospective studies were included
- Qualitätsbewertung nicht im Dokument (Appendix B)

Studienergebnisse:

- PSA-PFS: Two assessed both treatment sequences AAP → ENZ and ENZ → AAP; it was found that sequence of AAP → ENZ showed a statistically significantly longer PSA-PFS than the observed in ENZ → AAP (pooled HR: 0,54; 95% CI; 0,36–0,82; p < 0,05); in both, chemotherapy-naive and post-chemotherapy mCRPC patients. I2=0%.

- OS data was in favour of the sequence AAP→ENZ. Although a statistically significant fifference was not reached (pooled HR: 0,75(95CI:0,45-1,26); I2= 0%
- Univariate meta-analysis of PFS: the pooled median PFS from these studies for Doc→AAP→ENZ sequence, assuming fixed effects, was 2,78 month (2,59-2,96). I2=0%

Anmerkung/Fazit der Autoren

Significant clinical efficacy of AAP administered as the first-line treatment in mCRPC patients followed by enzalutamide, delaying disease progression, compared with the ENZ → AAP sequence. However, more studies and randomized trials are needed, to validate the best treatment sequencing.

Kommentare zum Review

- This work was supported by Johnson & Johnson

Wang X et al., 2021 [26].

Comparing the clinical efficacy and safety of abiraterone and enzalutamide in metastatic castration-resistant prostate cancer: a systematic review and meta-analysis.

Fragestellung

Systematically reviewed the efficacy and safety of abiraterone and enzalutamide in metastatic castration-resistant prostate cancer in real-world practice.

Methodik

Population:

- men with histologically or cytologically proven mCRPC
- both post chemotherapy and naïve (siehe Charakteristika der Population)

Intervention:

- AA (abiraterone)

Komparator:

- EnZ (enzalutamide)

Endpunkte:

- PSA response, OS, progression-free survival (PFS), number of patients with any adverse event (AE))

Recherche/Suchzeitraum:

- PubMed, Web of Science, Cochrane, Embase was conducted up to 6 March 2019

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool / NOS

Ergebnisse

Anzahl eingeschlossener Studien:

- Fourteen cohort studies involving 3469 participants were included.

Charakteristika der Population:

Table 1. The characteristics of included studies.

Author, year, reference	Study design, years, country	Patients enrolled	Median age, years (range)	Follow-up (months)	AA (N)	EnZ (N)	Treatment setting
Miyake et al.[12]	Cohort, August 2014–December 2015, Japanese	280	76.9 (47–96)	24	113	167	Pre-chemotherapy
Norris et al.[13]	Cohort, September 2011–November 2015, UK	198	NR	NR	98	100	Pre-chemotherapy and post-chemotherapy
Salem et al.[14]	Cohort, September 2011–June 2015, Canada	189	76.5	12	76	113	Pre-chemotherapy
Pilon et al.[15]	Cohort, January 2005–December 2014, US	1659	NR	12	1067	592	NR
Al-Ali et al.[16]	Cohort, September 2013–August 2016, Austria	334	74.4	30	195	139	Pre-chemotherapy and post-chemotherapy
Thiery-Vuillemin et al.[17]	Cohort, March 2016–March 2018, European	105	74.5 (53–92)	3	46	59	NR
Richter et al.[18]	Cohort, NR, Czech	32	NR	6.5	9	23	Post-chemotherapy
Lista et al.[19]	Cohort, January 2014–September 2015, NR	42	74.02	NR	22	20	NR
Heo et a l.[20]	Cohort, 2013–2014, NR	54	70 (45–86)	15	25	29	Post-chemotherapy
Selvi et al.[21]	Cohort, January 2013–June 2017, NR	74	76	12[a]	59	15	Pre-chemotherapy and post-chemotherapy
Sanchez Garcia et al.[22]	Cohort, January 2015–July 2017, Spain	48	75.8 (56–92)	NR	26	22	Pre-chemotherapy and post-chemotherapy
Khalaf et al.[23]	Cohort, July 2009–September 2016, UK	210	85 (83–88)	NR	106	104	Pre-chemotherapy
Shore et al.[24]	Cohort, December 2015–January 2017, US	92	75	2	46	46	NR
Dearden et al.[25]	Cohort, 2011–2015, France, Germany, and the UK	152	NR	NR	78	74	Pre-chemotherapy and post-chemotherapy

AA: abiraterone; EnZ: enzalutamide; CRPC: castration-resistant prostate cancer; mCRPC: metastatic castration-resistant prostate cancer; NR: not reported.[a]The study covered the period from January 2013 to June 2017 of mCRPC patients starting treatment with AA or EnZ between January 2013 and June 2016 being performed.

Qualität der Studien:

- Since there was no RCT comparing the two regimens, risk of bias was assessed using the NOS in all studies. Eight factors were used to assess study quality accord-ing to NOS. Included observational studies were of high quality, six studies missed one indicator, six studies missed two indicators. The results showed that all observational studies were of high quality.

Studienergebnisse:

- Pooled result showed that prostate-specific antigen response was higher for patients receiving enzalutamide than abiraterone (790 patients, odds ratio (OR) 0.47, 95% confidence interval (CI) 0.29-0.77, P = 0.003, 12==59%).
- Enzalutamide was significantly associated with increased adverse events rate in comparison with abiraterone (730 patients, OR 0.35, 95% CI 0.13-0.92, P= 0.03, I^2=65%).Methodikeranmerkung: siehe *Kommentare* mit Diskrepanz zu anderer Auswertung gleicher Autoren.
- There was no statistical difference between abiraterone and enzalutamide with respect to perceived cognitive impairments (1856 patients, OR 0.90, 95%CI 0.29-2.76, P -0.85, I^2=5%).
- Enzalutamide was significantly associated with increased fatigue risk in comparison with abiraterone (2477 patients, OR 0.46, 95%CI 0.34-0.63. P < 0.0000, I^2=0%).

Anmerkung/Fazit der Autoren

This was the first study to directly compare the clinical efficacy and safety of AA and Enz in mCRPC patients in real-world practice. Our results demonstrated that EnZ was more efficacious than AA for patients with mCRPC, but was associated with a significantly increased risk of side effects, particularly fatigue. A prospective or RCT compared the efficacies of these agents is needed.

Kommentare zum Review

- Eine weitere Studie von Wang et al. 2020 [25] (alteres Publikationsalter) aber mit aktuellerem Suchzeitraum (bis November 2019) schließt zusätzlich eine Studie ein (Chang et al. 2019).
- Wurde in Analyse zu PSA Response und Fatigue eingeschlossen nicht aber bei AE und Cognitive Impairment.
  - Einschluss Chang Studie mit n=77 Teilnehmern
    - Für PSA Response: PSA response rate in the enzalutamide group was significantly greater than that in the abiraterone group (867 patients, risk ratio (RR) 0.69, 95% confidence interval (CI) 0.61-0.79, p＜0.00001, I2=29%)
    - And there was no statistical difference between two groups respect to the side effect of perceived cognitive impairments (1856 patients, RR 0.94, 95% CI 0.47-1.88, p=0.85, I2=15%)
  - Unstimmigkeiten:
    - Patients who received enzalutamide had the higher risk to have the feeling of fatigue compared with abiraterone group (2555 patients, RR 0.45, 95% CI 0.24-0.85, p=0.01, I2=92%). Methodikeranmerkung: es dürften mit der zusätzlicher Studie eigentlich nur 2554 patients sein.
    - Die AE rate zeigte trotz gleicher Studienlage (Chang et al. wurde in Analyse nicht berücksichtigt) in dieser Studie keinen Unterschied zwischen AA und E: There was no significant difference in the total incidence of AEs between two groups (730 patients, RR 0.42, 95% CI 0.14-1.31, p = 0.14, I2=84%). Hier RR und nicht OR

Zhang et al., 2021 [27].

Adjuvant Chemotherapy in High-Risk Prostate Cancer Patients after Primary Local Therapy: Recurrence, Metastasis, and Survival – A Meta-Analysis

Fragestellung

The aim of the study was to perform a systematic review and meta-analysis of RCTs evaluating the adjuvant chemotherapy in high-risk prostate cancer patients after primary local therapy.

Methodik

Population:

- Prostate cancer population

Intervention:

- Adjuvant chemotherapy or docetaxel

Komparator:

- Standard of treatment

Endpunkte:

- Primary endpoint was overall survival (OS).
- Secondary endpoint was disease-free survival (DFS) and biochemical recurrence-free survival (BRFS).

Recherche/Suchzeitraum:

- PubMed/Medline, Embase, and Cochrane databases was performed to identify relevant studies published in English up to March 01, 2020.

Qualitätsbewertung der Studien:

- The RCT mainly used Cochrane Collaboration Network bias risk assessment criteria
- Heterogeneity was assessed using Cochran Q statistic and quantified using the I2 statistic. The heterogeneity was classified as low (I2 ≤ 50%) and high (I2 > 50%). Subgroup analysis and sensitivity analysis are used to find the reason of high heterogeneity.

Ergebnisse

Anzahl eingeschlossener Studien:

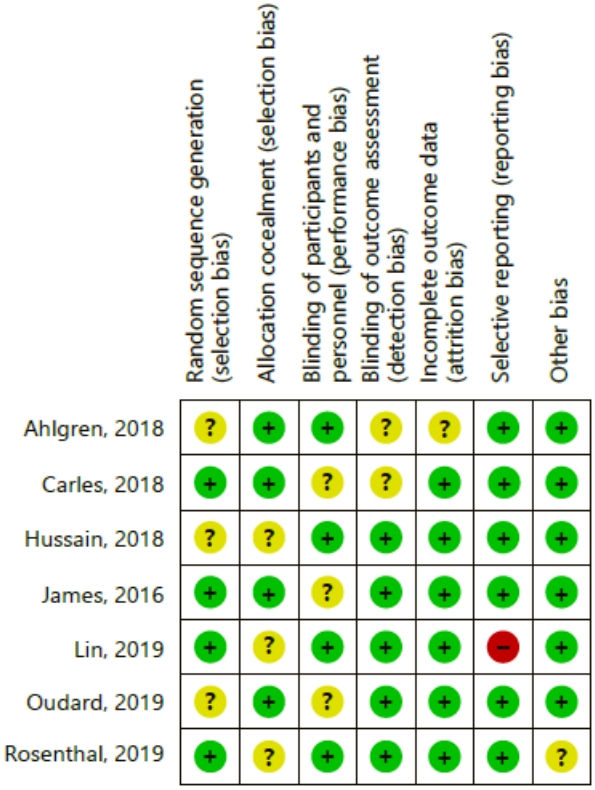
- 7 documents were finally included in this meta-analysis.

Charakteristika der Population:

Author	Study	Publishing time	Country	Study type	Follow-up time	Control	Treatment	Primary endpoints (HR, 95% CI)	OS, number of events		PFS/DFS, number of events	
									Inter-vention	Control	Inter-vention	Control
Hussain et al. [11]	SWOG S9921	2018	America	RCT	1999–2007	RP + ATD	SOC + mitoxantrone	OS (1.06, 0.79–1.43)	91/480	85/481	*150/480	148/481
James et al. [10]	STAMPEDE	2016	America	RCT	2005–2013	RT + ATD	SOC + docetaxel	OS (1.11, 0.67–1.85)	24/168	44/130	–	–
Lin et al. [18]	#553	2019	America	RCT	2006–2011	RP + observation	SOC + docetaxel	PFS (0.80, 0.58–1.11)	11/140	17/157	#66/140	84/157
Ahlgren et al. [19]	SPCG-12	2018	Northern Europe	RCT	2005–2010	RP + observation	SOC + docetaxel	PSA PFSl	–	–	–	–
Oudard et al. [12]	–	2019	France	RCT	2003–2007	RP/RT + ATD	SOC + docetaxel	PSA PFS (0.85, 0.62–1.16)	40/125	46/125	#79/125	81/125
Rosenthal et al. [15]	RTOG 0521	2019	America	RCT	2005–2009	RT + ATD	SOC + docetaxel	OS (0.69, 0.49–0.97)	43/282	59/281	*99/282	123/281
Carles et al. [16]	–	2018	Spanish	RCT	2008–2012	RT + ATD	SOC + docetaxel	OS (0.80, 0.21–2.96)	–	–	*12/65	7/64

RCT, randomized controlled trial; OS, overall survival; PFS, progression-free survival; SOC, standard of care; RP, radical prostatectomy; RT, radiotherapy; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval. * Endpoint was DFS. # Endpoint was PFS.

Qualität der Studien:



Studienergebnisse:

Overall Survival:

- Six trials (RCTs) were selected for inclusion overall survival
- The meta-analysis did not show a significant OS benefit from adjuvant chemotherapy in patients with high-risk prostate cancer after primary local therapy (HR: 0.87; 95% CI, 0.72–1.05; p = 0.15). There was no significant heterogeneity between studies (I2 = 12%)
- But docetaxel in patients with high-risk prostate cancer after primary local therapy was associated with a slightly OS improvement (HR: 0.79; 95% CI, 0.63–0.98; p = 0.03).
- For the initial treatment of chemotherapy and surgery, no significant OS benefit was observed (HR: 0.80, 95% CI, 0.61–1.06, p = 0.11; HR: 0.95; 95% CI, 0.73–1.24, p = 0.72).

DFS and Biochemical Recurrence-Free Survival:

- A total of 3 documents reported on the DFS indicator in detail.
- Adjuvant chemotherapy to high-risk prostate cancer patients after primary local therapy cannot extend the time of DFS (HR: 0.89; 95% CI, 0.75–1.06; p = 0.18). There was no significant heterogeneity between studies (I2 = 22%).
- Adjuvant chemotherapy to high-risk prostate cancer patients after primary local therapy extend the time of biochemical recurrence-free survival (BRFS; HR: 0.85; 95% CI, 0.68–1.06; p = 0.16)

Anmerkung/Fazit der Autoren

This meta-analysis shows a slightly OS benefit from docetaxel in patients with high-risk prostate cancer after primary local therapy. It did not show a significant benefit in DFS and BRFS in patients with high-risk prostate cancer. Due to the limitation of original literature,

the results of meta-analysis in this study need to be further verified and improved by large sample and high-quality RCTs.

Kvorning Ternov K et al., 2021 [23].

Quality of life in men with metastatic castration-resistant prostate cancer treated with enzalutamide or abiraterone: a systematic review and meta-analysis

Fragestellung

The aim was to compare patient-reported healthrelated quality of life (HRQoL) in men treated with enzalutamide vs AAP for mCRPC.

Methodik

Population:

- Men with metastatic castration-resistant prostate cancer treated with enzalutamide or abiraterone.

Intervention/Komparator:

- One RCTs directly compared enzalutamide with AAP (henceforth referred to as the PhaseII trial) [27].
- The other RCTs compared AAP vs. Placebo plus prednisone (COU-AA-302) [1, 20, 25, 28],
- Enzalutamide vs. placebo (PREVAIL) [2, 14, 19, 21] or
- Enzalutamide vs. bicalutamide (TERRAIN) [22, 23, 26].
- Three observational studies compared enzalutamide with AAP (the Vancouver, AQUARiUS and REAAcT studies) [15, 16, 18, 24],
- One evaluated treatment with AAP only (COSMiC) →nicht in Analyse

Endpunkte:

- Patient-reported healthrelated quality of life (HRQoL) measured by the Functional Assessment of Cancer Therapy-Prostate total score (FACT-P).

Recherche/Suchzeitraum:

- The literature was systematically
- searched 10 June 2020.

Qualitätsbewertung der Studien:

- Risk of bias: Cochrane Handbook for Systematic Reviews of Interventions for randomised clinical trials and to risk of bias in non-randomised studies of interventions criteria for non-randomised clinical trials.
- Statistical heterogeneity and inconsistency were assessed using the GRADE guidelines and the Cochrane Handbook for systematic reviews.

Ergebnisse

Anzahl eingeschlossener Studien:

- 17 publications from 8 studies fulfilled the eligibility criteria.
- four were RCTs and four were observational studies

- 4 RCTs eligible for meta-analysis

Charakteristika der Population:

- Keine Details in Tabelle 1.
- Subgruppenanalysen nach Alter

Qualität der Studien:

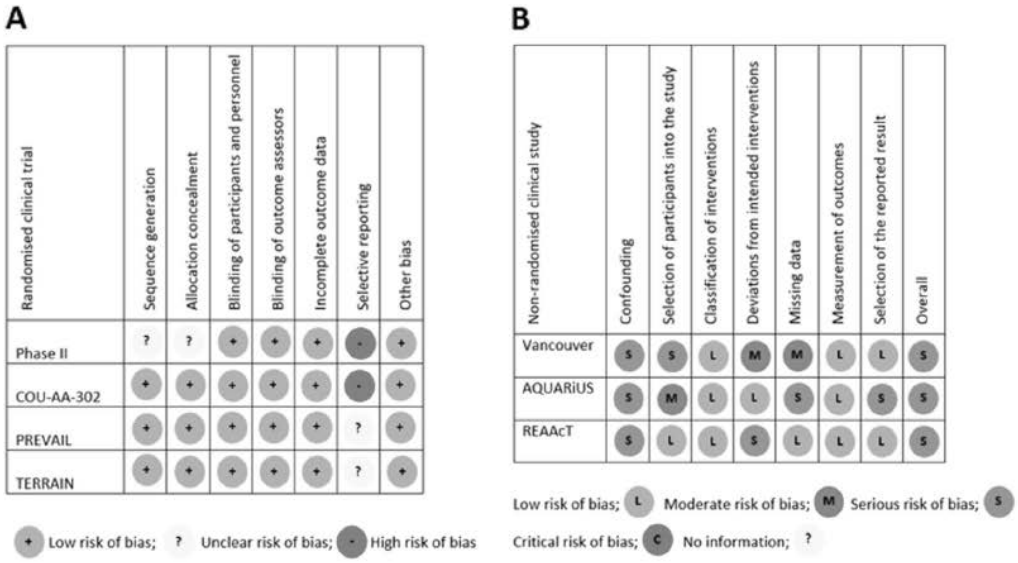


Fig. 2 Risk of bias summary. The risk of bias is assessed according to the criteria defined in the *Cochrane Handbook for Systematic Reviews of Interventions* for randomised clinical trials (**A**) and to risk of bias in non-randomised studies of interventions criteria for non-randomised clinical trials (**B**).

- The non-randomised studies had all a serious risk of bias.

Studienergebnisse:

Direct comparison of enzalutamide and AAP

- One RCT and three non-randomised studies directly compared enzalutamide with AAP. The RCT showed better shortterm HRQoL for AAP (6.8 FACT-P-points, 95% CI 1.7; 11.8) and better long-term HRQoL for AAP in men ≥75 years (7.35 FACT-P-points, 95% CI 2.59; 12.11). Non-randomised clinical studies: No overall treatment difference was found in most of the HRQoL outcomes or pain outcomes.
- The results of patient-reported cognitive function and fatigue favoured AAP in REAAcT and AQUARiUS. Nonetheless, the evidence of a treatment difference in fatigue is limited. First, 12% of the patients in the enzalutamide group and 0% in the AAP group received additional sipuleucel-T after study drug initiation in the REAAcT study, which is associated with fatigue [31]. Second, the treatment differences in fatigue were minor at all time points (<1 point using the Brief Fatigue Inventory-Short Form fatigue interference) in the AQUARiUS study.

Indirect comparison

- The groups that received active treatment with enzalutamide or AAP had better HRQoL and less pain than the placebo groups, and the HRQoL change from baseline to week 25–28 showed improved HRQoL after AAP and unchanged or minimally worse HRQoL after enzalutamide

Short-term health-related quality of life and metaanalyses

- The meta-analyses showed mean within-subject FACT-P changes from baseline to week 12 of −1.3 points (95% confidence interval [CI] −2.7; 0.1) for enzalutamide and 4.7 points (95% CI −0.1; 9.6) for AAP.
- Heterogeneity:
  - Enzalutamide. The heterogeneity (I2 = 0%, p value = 0.42) was low in this meta-analysis, as the included results (from PREVAIL, Phase II and TERRAIN) all showed no change or a minor reduction in HRQoL.
  - AAP, The heterogeneity was high (I2 = 85%, p value = 0.01).

Table 4 Evidence grading of the meta-analyses.

Certainty assessment									
Meta-analysis HRQoL	No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty	Importance
12-week change after treatment with AAP	2	Randomised trial	Serious	Serious	Not serious	Serious	None	+ Very low	6 – important
12-week change after treatment with enzalutamide	3	Randomised trial	Not serious	Not serious	Not serious	Not serious	None	++++ High	6 – important

Anmerkung/Fazit der Autoren

In conclusion, AAP seems to be associated with better short-term HRQoL than enzalutamide. This difference is not apparent at longer follow-up, but the long-term studies had serious risks of bias. Despite the limited evidence, AAP could also be associated with better HRQoL in men older than 75 years and with less symptoms of patientreported depression, cognitive decline and fatigue than enzalutamide.

Kommentare zum Review

- Six studies were sponsored by pharmaceutical companies.
- Conflict of interest: MF is an advisor and speaker for Ferring and Astellas. PBO has been a speaker for Astellas, Ipsen and Ferring. HL is an advisor for Roche, Janssen, Astellas, Bayer and Sanofi-Aventis. OB has been speaker and moderator at non-product specific meetings arranged by AstraZeneca, Janssen, Amgen, Astellas, Ipsen and Bayer.

Lee HY et al., 2021 [16].

Abiraterone and enzalutamide had different adverse effects on the cardiovascular system: a systematic review with pairwise and network meta-analyses

Fragestellung

Abiraterone and enzalutamide may increase the risk of cardiovascular events in patients with castrationresistant prostate cancer (CRPC).

Methodik

Population:

- patients with nonmetastatic or metastatic CRPC

Intervention:

- Abiraterone or enzalutamide

Komparator:

- placebo, prednisone, or prednisolone

Endpunkte:

- The outcome measures included the incidence of (1) any grade cardiac disorders, (2) severe grade cardiac disorders, (3) any grade hypertension, and (4) severe grade hypertension. “Cardiac disorder” and “hypertension” were defined by the Common Terminology Criteria for Adverse Events

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, and Cochrane library (CENTRAL and CDSR) were searched.
- 1990-

Qualitätsbewertung der Studien:

- Quality assessment was performed using the risk of bias (ROB) assessment tool as recommended by the Cochrane Handbook for Systematic Reviews of Interventions.

Ergebnisse

Anzahl eingeschlossener Studien:

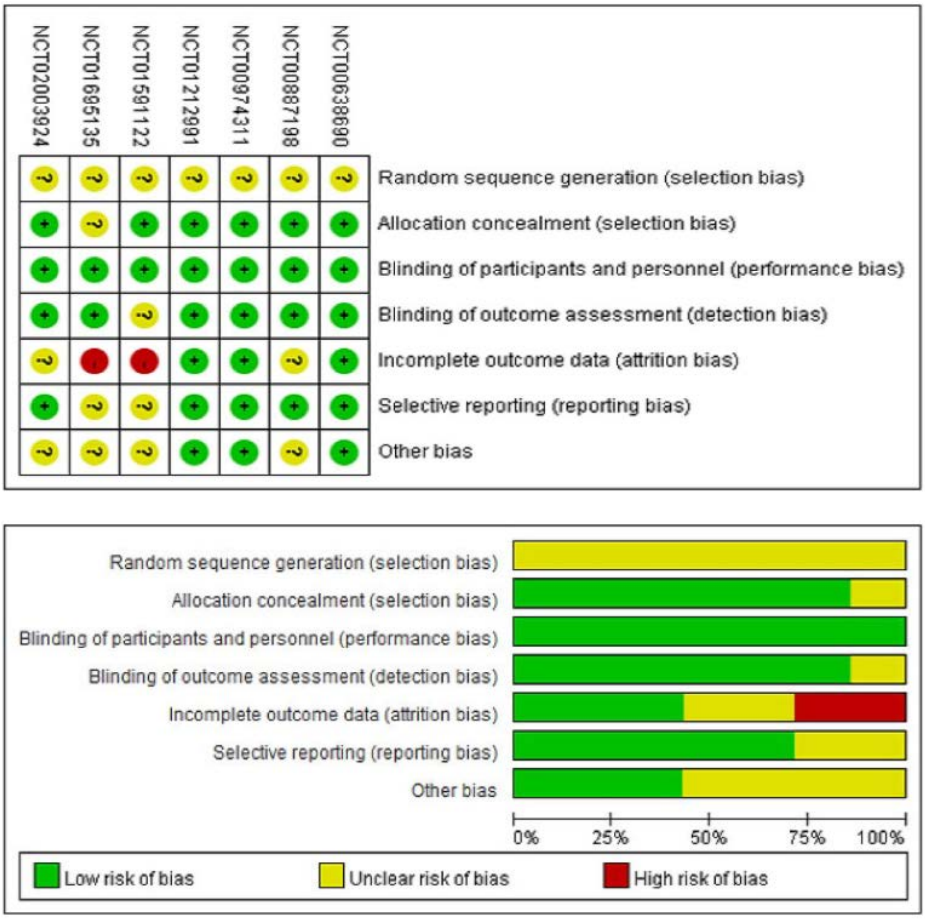
- All seven included studies were phase II or III trials that were completed between 2012 and 2015.

Charakteristika der Population:

- Six RCTs recruited patients with metastatic CRPC, but one RCT comparing between enzalutamide and placebo involved patients without metastatic disease.
- A total of 7103 patients from seven RCTs were included. Among them, 1633 were treated with abiraterone and 2601 were treated with enzalutamide; 2869 patients were treated with placebo, prednisone, or prednisolone in the control arms.

Qualität der Studien:

- Most RCTs are considered high-quality studies with low ROB.



Appendix 5. Risk of bias assessment

<u>Studienergebnisse:</u>

Pairwise meta-analysis:

- Cardiac disorders
  - Abiraterone: there were increased risks of any grade cardiac disorder (RR=1.34, 95% CI=1.05–1.73, I2=26%, p=0.02) and severe grade cardiac order (RR= 1.71, 95% CI=1.16–2.53, I2=0%, p=0.007).
  - Enzalutamide: there was no increased risk of any grade cardiac disorder (RR=1.28, 95% CI=0.82–2.01, I2=69%, p=0.27) and severe grade cardiac disorder (RR for severe events= 1.24, 95% CI=0.56–2.75, I2=69%, p=0.60).
- Hypertension
  - Abiraterone: there were increased risks of any grade hypertension (RR = 1.46, 95% CI = 1.20–1.78, I2 = 70%, p < 0.001), but not severe grade hypertension (RR = 1.29, 95% CI = 0.84–1.98, I2 = 0%, p = 0.25).
  - Enzalutamide: was associated with increased risk of both any grade hypertension (RR = 2.66, 95% CI = 1.93–3.66, I2 = 35%, p < 0.001) and severe grade hypertension (RR = 2.79, 95% CI = 1.86–4.18, I2 = 0%, p < 0.001).

Network meta-analysis

- Cardiac disorders
  - When compared to the placebo group, the RR of any grade cardiac disorders was significantly higher among those who received abiraterone (RR = 1.32, 95% CrI =

1.08–1.62), but not among those who received enzalutamide (RR for any grade = 1.22, 95% CrI = 0.97–1.54)

- Hypertension
  - When compared to the placebo group, the RR of any grade hypertension was significantly higher among those who received enzalutamide (RR = 2.72, 95% CrI = 1.85–3.84), but not among those who received abiraterone (RR = 1.44, 95% CrI = 0.97–1.98). The RRs of severe grade cardiac disorders were 2.79 for enzalutamide and 1.47 for enzalutamide, but they did not reach statistical significance. Interestingly, enzalutamide had a higher risk of any grade hypertension than abiraterone (RR = 1.88, 95% CrI = 1.16–3.13); the RR of severe grade hypertension was 1.89 for enzalutamide but it did not reach statistical significance.

Anmerkung/Fazit der Autoren

Our pairwise and network meta-analyses showed that abiraterone and enzalutamide had different adverse effects on the cardiovascular system. Abiraterone increased the risk of cardiac disorders and enzalutamide increased the risk of hypertension. We should take this into consideration when we are managing patients with CRPC.

Motlagh et al., 2021 [21].

The Risk of New Onset Dementia and/or Alzheimer Disease among Patients with Prostate Cancer Treated with Androgen Deprivation Therapy: A Systematic Review and Meta-AnalysisTitel des Reviews

Fragestellung

“Are prostate cancer patients who receive ADT at a higher risk of dementia and/ or Alzheimer disease compared to those who do not receive ADT?”

Methodik

Population:

- prostate cancer patients who receive ADT

Intervention:

- GnRH agonist or antagonist

Komparator:

- No GnRH agonist or antagonist

Endpunkte:

- Dementia and/or AD (Alzheimer Disease) with reported estimated risk effect (hazard ratio, odds ratio, relative risk) for both patient and control groups

Recherche/Suchzeitraum:

- We searched PubMed and Web of Science for studies published before January 1, 2020.

Qualitätsbewertung der Studien:

- Modified Newcastle-Ottawa scale criteria were used to assess the quality of the included studies

- The group recommends the reporting of quality scoring and also subgroup or sensitivity analysis rather than quality scores as weights in the analysis.
- Heterogeneity across the studies was appraised using p values, and Q and I2 statistics.
- A sensitivity analysis was performed by excluding some studies that reported very different results than other studies to explore the heterogeneity.

Ergebnisse

Anzahl eingeschlossener Studien:

- 14 studies were available for the systematic review and meta-analysis.

Charakteristika der Population:

- Nicht aufgeführt

Qualität der Studien:

- In general, there was not a poor quality study, and of 14 studies 10 had good quality, while the others had fair quality.

Table 1. *Newcastle-Ottawa scale for all studies in quantitative synthesis*

References	Sample Size	Selection Score	Comparability Score	Outcome Score	Total Score	Agency for Healthcare Research and Quality Standards
Krasnova et al[26]	100,414	****	**	**	8	Good
Tully et al[27]	9,117	****	**	**	8	Good
Jayadevappa et al[35]	154,089	****	**	**	8	Good
Tae et al[28]	37,549	****	**	**	8	Good
Nguyen et al[29]	201,797	****	**	**	8	Good
Deka et al[30]	45,218	***	*	**	6	Fair
Baik et al[36]	1,238,879	****	**	**	8	Good
Khosrow-Khavar et al[31]	30,903	****	*	**	7	Good
Jhan et al[37]	24,360	****	**	**	8	Good
Kao et al[32]	1,314	***	*	**	6	Fair
Nead et al[33]	9,272	****	**	**	8	Good
Chung et al[25]	1,335,5,340	***	*	**	6	Fair
Nead et al[38]	16,888	****	**	**	8	Good
Capitanio et al[34]	7,081	***	*	**	6	Fair

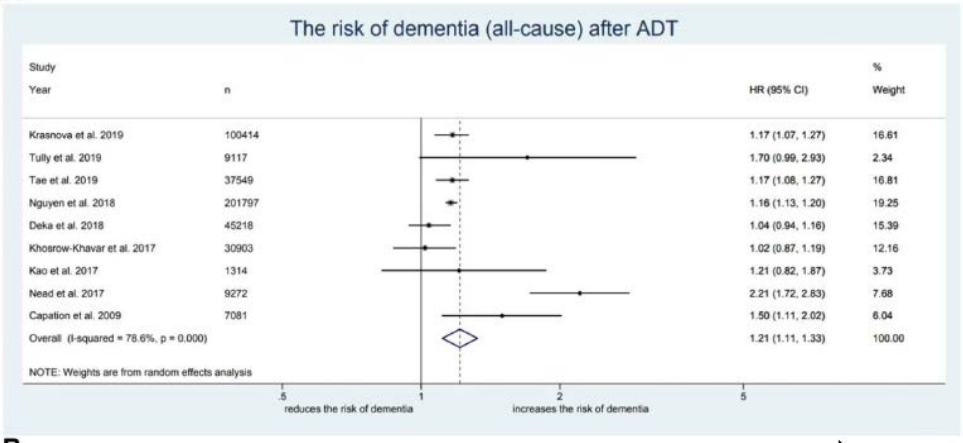
According to Newcastle-Ottawa scale, stars were awarded for each quality item such that highest quality studies were awarded up to 9 stars.

o

Studienergebnisse:

- The risk of new onset dementia (all cause) and Alzheimer disease was higher in patients with prostate cancer who received androgen deprivation therapy compared to those who did not (HR 1.21, 95% CI 1.11-1.33 and HR 1.16, 95% CI 1.09-1.24). The risk of dementia (all cause) was higher in patients with prostate cancer who received androgen deprivation therapy for more than 12 months (HR 1.36, 95% CI 1.07-1.72); however, for those who had less than 12 months of androgen deprivation therapy exposure the difference was not statistically significant 1.06 (95% CI 0.77-1.28).

A



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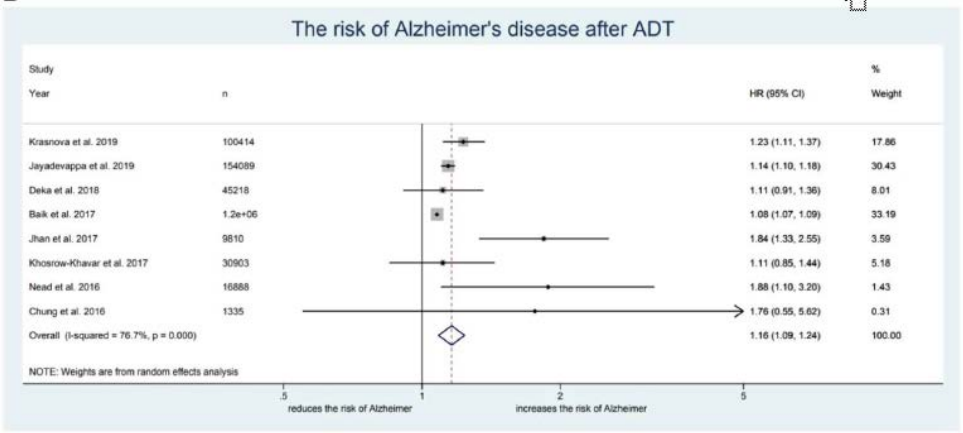


Anmerkung/Fazit der Autoren

Men who receive androgen deprivation therapy for prostate cancer have an increased risk of dementia and/or Alzheimer disease compared to men who do not receive androgen deprivation therapy; this was more pronounced when androgen deprivation therapy was given longer than 12 months.

Kommentare zum Review

- Keine weitere Information über die Population
- Quslitätsanalyse führte nicht zu Gewichtung der Studien in der Analyse
- Kein Conflict of Interest statement

Tan G et al., 2020 [22].

The efficacy and safety of abiraterone acetate in patients with high-risk prostate cancer: a meta-analysis based on six randomized control trials

Fragestellung

The purpose of this study was to investigate the efficacy and safety of abiraterone acetate in high-risk prostate cancer patients, including metastatic castration-resistant prostate cancer (mCRPC) and metastatic castration-sensitive prostate cancer (mCSPC).

Methodik

Population:

- High-risk prostate cancer patients (including castrationresistant and castration-sensitive)

Intervention:

- Abiraterone acetate

Komparator:

- Control arm as comparison

Endpunkte:

- overall survival (OS), the time to prostate-specific antigen (PSA) progression, and progression-free survival (PFS) (according to radiographic evidence) was expressed as a hazard ratio (HR), while PSA response rate and relative adverse events were expressed as risk ratios (RR)

Recherche/Suchzeitraum:

- PubMed, EMBASE, Cochrane library
- To September 2019

Qualitätsbewertung der Studien:

- To assess the quality of included studies, we used the Jadad 5-item scale, the score of which ranged from 0 to 5, taking into account randomization, double-blinding, withdrawals, and dropouts.

Ergebnisse

Anzahl eingeschlossener Studien:

- A total of seven studies were included in the metaanalysis. Fizazi (2017) and Fizazi (2019) belonged to the same RCT. However, they had different endpoints.
- Of the 7 studies, all except James (2017), were randomized, double-blind clinical trials.

Charakteristika der Population:

- 3,190 cases were treated with AAP or AAP combined with ADT, and 2,711 controls were treated with placebo plus prednisone or ADT alone.
- Four studies (11,15-17) enrolled 2,810 patients with mCRPC, while the other 3 studies (12-14) enrolled 3,116 patients with mCSPC.

Table 1 Studies characteristic

Trials	Treatment arms	Cases	Endpoints (eligible for this meta-analysis)	Setting	Jadad Score
de Bono (2011)	Abiraterone plus prednisone	797	Primary: overall survival Secondary: time to PSA progression, progression-free survival according to radiographic evidence, PSA response rate (≥50% decline in PSA level from baseline)	Pre-chemotherapy	5
	Placebo plus prednisone	398			
Ryan (2012)	Abiraterone plus prednisone	546	Primary: progression-free survival according to radiographic evidence, and overall survival Secondary: time to PSA progression, PSA response rate (≥50% decline in PSA level from baseline)	Non-pre-chemotherapy	5
	Placebo plus prednisone	542			
Sun (2016)	Abiraterone plus prednisone	143	Primary: time to PSA progression Secondary: overall survival, PSA response rate (≥50% decline in PSA level from baseline)	Pre-chemotherapy	5
	Placebo plus prednisone	71			
Ye (2017)	Abiraterone plus prednisone	157	Primary: time to PSA progression Secondary: PSA response rate (calculated for RR, which is not available for this meta-analysis)	Non-pre-chemotherapy	4
	Placebo plus prednisone	156			
James (2017)	Abiraterone plus prednisone with ADT	960	Primary: overall survival (extracted from metastatic subgroup)	Non-pre-chemotherapy	4
	ADT alone	957			
Fizazi (2017)	Abiraterone acetate and prednisone plus ADT	597	Exploratory endpoint: PSA response rate (≥50% decline in PSA level from baseline), progression-free survival according to radiographic evidence	Non-pre-chemotherapy	5
	Placebos plus ADT	602			
Fizazi (2019)	Abiraterone acetate and prednisone plus ADT	597	Primary: overall survival Secondary: time to PSA progression	Non-pre-chemotherapy	5
	Placebos plus ADT	602			

PSA, prostate-specific antigen; ADT, androgen deprivation therapy.

Qualität der Studien:

- 2 Studien Jadad Score: 4 und 5 Studien Jadad Score: 5 (siehe Abbildung unter Charakteristika der Population)

Studienergebnisse:

- OS: abiraterone acetate showed significant improvement of OS in high-risk prostate cancer patients (HR 0.66, 95% CI, 0.61–0.73, P<0.001; I2=0%), but no significant heterogeneity was found between mCRPC and mCSPC (I2=0%, P=0.44) by the subgroup analysis.
- The time to PSA progression: abiraterone acetate showed significant improvement in the time to PSA progression in high-risk prostate cancer patients (HR 0.45, 95% CI, 0.34–0.59, P<0.00001; I2=86%), while a significant heterogeneity was found between mCRPC and mCSPC (I2=96.3%, P<0.001) by the subgroup analysis.
- PFS according to radiographic evidence: abiraterone acetate showed significant improvement of PFS in high-risk prostate cancer patients (HR 0.55, 95% CI, 0.45–0.68, P<0.00001; I2=81%), whilea significant heterogeneity was found between mCRPC and mCSPC (I2=63.1%, P=0.10, Figure 4) by the subgroup analysis.
- PSA response rate: abiraterone acetate showed significant improvement of PSA response rate in high-risk prostate cancer patients (RR 2.49, 95% CI, 1.47–4.22, P=0.0007; I2=87%), while a significant heterogeneity had been found between mCRPC and mCSPC (I2=95.1%, P<0.00001) in subgroup analysis.
- Adverse events:
  - adverse events included asthenia, fatigue, back pain, constipation, arthralgia, bone pain, hypokalemia, cardiac disorder, and hypertension.

- The pooled analysis reported that abiraterone acetate showed a higher incidence of some adverse events in high-risk prostate cancer patients, including hypokalemia (RR 2.47, 95% CI, 1.39–4.39, P=0.002; I2=86%), hypertension (RR 1.57, 95% CI, 1.37–1.79, P<0.00001; I2=24%), cardiac disorder (RR 1.48, 95% CI, 1.03–2.13, P=0.04; I2=75%) and arthralgia (RR 1.19, 95% CI, 1.05–1.35, P=0.007; I2=0%), but not for asthenia, fatigue, constipation, back pain, and bone pain.

Anmerkung/Fazit der Autoren

In our study, we observed the potential increase in the incidence of adverse events with the use of abiraterone acetate, mainly grade 1–2 adverse events. However, these adverse events have limited impact on the drug withdrawal rate and dose reduction rate. The mechanism of these adverse events may be related to the blockade of CYP17. The pooled analysis revealed that the incidence of arthralgia (RR 1.19), hypokalemia (RR 2.47), cardiac disorder (RR 1.48), and hypertension (RR 1.57) in the abiraterone acetate group was moderately higher than the control group. At the same time, no statistical difference was found for the other adverse events. Hypokalemia was found to be more likely to occur than the other adverse events. In line with previously published studies (19,24), our study showed that cardiac disorders and hypertension should be paid more attention to follow-up.

Kommentare zum Review

- In the studies included, the primary endpoints were not entirely consistent. James (2017) enrolled patients with nonmetastatic prostate cancer, while the other studies only permitted metastatic prostate cancer patients.

Kretschmer A et al., 2020 [14].

Health-related Quality of Life in Patients with Advanced Prostate Cancer: A Systematic Review

Fragestellung

To systematically review contemporary data regarding HRQOL outcomes in patients with advanced PCa.

Methodik

<u>Population:</u>

- Patients with advanced PCa, defined as mHNPC, nmCRPC, and mCRPC.
- Nine studies focused on patients with metastatic castration-resistant PCa. Hereby, beneficial HRQOL outcomes were described for enzalutamide, abiraterone acetate, and radium-223.

Intervention/Komparator:

Study	Intervention
Harland et al (2013) [24] (COU-AA-301)	ABI + ADT vs PBO + ADT
Basch et al (2013) [25] (COU-AA-302)	ABI + ADT vs PBO + ADT
Fizazi et al (2014) [26] (AFFIRM)	ENZA vs PBO
Nilsson (2015) [29] (ALSYMPCA)	RA223 vs PBO
Devlin et al (2017) [28] (PREVAIL)	ENZA vs PBO
Unger et al (2017) [30] (SWOG S0421)	DOC + ATR vs DOC + PBO
Eisenberger et al (2017) [32] (PROSELICA)	CAB20 vs CAB25
Oudard et al (2017) [33] FIRSTANA	CAB20 vs CAB25 vs DOC
Thiery-Vuillemin et al (2019) [34] (AQUARiUS)	ABI + ADT vs ENZA + ADT

Endpunkte:

- Health-related Quality of Life (HRQOL)
- Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire was used, the EuropeanQuality of Life 5-Dimensions (EQ-5D) questionnaire, the European Orga nization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQC30).

Study	Tool
Harland et al (2013) [24] (COU-AA-301)	FACT-P
Basch et al (2013) [25] (COU-AA-302)	FACT-P
Fizazi et al (2014) [26] (AFFIRM)	FACT-P
Nilsson (2015) [29] (ALSYMPCA)	FACT-P EQ-5D (−5 L)
Devlin et al (2017) [28] (PREVAIL)	EQ-5D (−3 L)
Unger et al (2017) [30] (SWOG S0421)	FACT-P QLQ-C30 (GLH)
Eisenberger et al (2017) [32] (PROSELICA)	FACT-P
Oudard et al (2017) [33] FIRSTANA	FACT-P
Thiery-Vuillemin et al (2019) [34] (AQUARiUS)	QLQ-C30

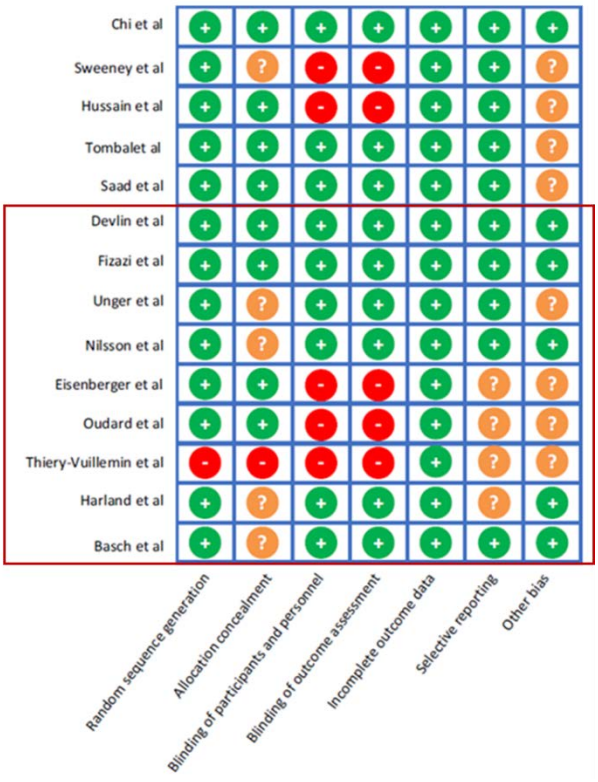
Recherche/Suchzeitraum:

- We performed a systematic review of the literature up to March 2019, starting from January 2011, using the PubMed, Web of Sciences, and Embase databases according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.

Qualitätsbewertung der Studien:

- Studies had to be at least phase II, enroll a minimum of 100 patients, and focus on advanced PCa only.
- Identified articles were assessed for the risk of bias following current European Association of Urology instructions [10]. A summary of risk of bias assessments is provided in Fig 2
- Mostly phase III trials with a low risk of bias
- Keine Metaanalyse und keine Angaben zur Heterogenität der Studien.

Fig. 2 – Risk of bias assessment following current EAU recommendations. EAU = European Association of Urology.



Ergebnisse

Anzahl eingeschlossener Studien:

- 14 studies evaluating HRQOL in 12.661 patients were included in the evidence synthesis
- 9 studies focused on patients with metastatic castration-resistant PCa
- 5 Studies prechemotherapy setting mit Metastasen und AM, die im AWG zugelassen sind

Charakteristika der Population:

- patients with metastatic castration-resistant PCa.

Studienergebnisse:

3.5. Metastatic castration-resistant prostate cancer

- Several studies have reported HRQOL outcomes in mCRPC patients. The main features of each study included in the systematic review are summarized chronologically in Table 3.

Table 3-Main features of studies adressing patients with metastatic castration-resistant cancer.

Table 3 – Main features of studies addressing patients with metastatic castration-resistant prostate cancer.

Study	Intervention	Phase	*n*	Follow-up	Tool	HRQOL baseline	Main findings
Harland et al (2013) [24] (COU-AA-301)	ABI + ADT vs PBO + ADT	III	1395	Median 20.2 mo	FACT-P	NR	Significant improvements in FACT-P total scores in 48% (ABI) vs 32% (PBO), $p < 0.0001$; median time to deterioration in Fact-P total score 59.9 wk (ABI) vs 36.1 wk (PBO), $p < 0.0001$
Basch et al (2013) [25] (COU-AA-302)	ABI + ADT vs PBO + ADT	III	1088	Median 22.2 mo	FACT-P	FACT-P (total): ABI: 122 PBO: 123	Median time to deterioration in FACT-P total scores: 12.7 mo (ABI) vs 8.3 mo (PBO), $p = 0.003$; median time to deterioration in FACT prostate cancer subscale: 11.1 mo (ABI) vs 5.8 (PBO), $p < 0.0001$
Fizazi et al (2014) [26] (AFFIRM)	ENZA vs PBO	III	938	Up to 25 wk	FACT-P	FACT-P (total): ENZA: 109 PBO: 111	Net differences in FACT-P total scores: +1.5 (ENZA) vs −13.7 (PBO), $p < 0.001$; ENZA favored in all subscales at week 25
Nilsson (2015) [29] (ALSYMPCA)	RA223 vs PBO	III	921	Up to 44 wk	FACT-P EQ-5D (−5 L)	FACT-P (total): RA223: 104 PBO: 104 EQ-5D (utility): RA223: 0.66 PBO: 0.66	Net differences in FACT-P total scores: −4.8 (RA223) vs −8.7 (PBO), $p = 0.004$; 24.6% (RA223) vs 16.1% (PBO) with meaningful improvement in FACT-P total score, $p = 0.020$; net differences in EQ-5D utility scores: −0.10 (RA223) vs −0.16 (PBO), $p = 0.002$; 29.2% (RA223) vs 18.5% (PBO) with meaningful improvement in EQ-5D utility score, $p = 0.004$
Devlin et al (2017) [28] (PREVAIL)	ENZA vs PBO	III	1717	Up to 61 wk	EQ-5D (−3 L)	EQ-5D (VAS): ENZA: 77 PBO: 76	Net differences in EQ-5D VAS scores: −1.3 (ENZA) vs −4.4 (PBO), $p < 0.0001$; ENZA favored in pain/discomfort subscale up to week 37
Unger et al (2017) [30] (SWOG S0421)	DOC + ATR vs DOC + PBO	III	978	Up to 37 wk	FACT-P QLQ-C30 (GLH)	FACT-P (total): DOC + ATR: 107 DOC + PBO: 107 QLQ-C30 GLH: DOC + ATR: 64 DOC + PBO: 64	No statistically significant differences in QLQ-C30 and FACT-P total score; improved functional status for DOC + ATR ($p = 0.02$)
Eisenberger et al (2017) [32] (PROSELICA)	CAB20 vs CAB25	III	1200	NR	FACT-P	NR	No significant differences in time to deterioration for all FACT-P subscales
Oudard et al (2017) [33] FIRSTANA	CAB20 vs CAB25 vs DOC	III	1168	NR	FACT-P	NR	Longer median time to deterioration in physical well-being for CAB20 vs DOC (14.9 vs 11.3 mo, HR 0.76, 95% CI 0.61–0.94, $p = 0.013$); no differences in remaining subscales
Thiery-Vuillemin et al (2019) [34] (AQUARIUS)	ABI + ADT vs ENZA + ADT	IV	105	12 wk	QLQ-C30	NR	Net differences in QLQ-C30 GLH scores between ABI and ENZA after 3 mo: 7.05, $p = 0.224$, favors ABI over ENZA; clinically meaningful deterioration of cognitive functioning in 8.0% (ABI) vs ENZA (37.8%), $p = 0.022$

ABI = abiraterone acetate; ADT = androgen deprivation therapy; ATR = atrasentan; CAB20 = cabazitaxel 20 mg/m^2; CAB25 = cabazitaxel 25 mg/m^2; CI = confidence interval; DOC = docetaxel; ENZA = enzalutamide; FACT-P = Functional Assessment of Cancer Therapy-Prostate; GLH = global health status; HR = hazard ratio; HRQOL = health-related quality of life; NR = not reported; PBO = placebo; QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; RA223 = radium-223; VAS = visual analog scale.

- Harland et al [24] analyzed HRQOL outcomes of 1395 patients using the FACT-P questionnaire. The authors found significant improvements in FACT-P total scores in 48% of patients receiving abiraterone acetate in combination with 10 mg prednisone daily versus 32% receiving placebo ($p < 0.0001$). In addition, the median time to deterioration in Fact-P total score was 59.9 wk for the abiraterone subgroup compared with 36.1 wk for the placebo subgroup ($p < 0.0001$). No baseline values of FACT-P total scores were reported. As shown in Fig. 2, the risk of bias was generally low
- […]. Regarding the effect of abiraterone acetate in chemo-therapy-naïve patients, Basch et al [25] reported HRQOL outcomes of 1088 patients. General HRQOL was assessed using the FACT-P questionnaire, and baseline FACT-P total scores were reported. The median time to deterioration in FACT-P total scores was 12.7 mo for the abiraterone sub-group versus 8.3 mo for the placebo subgroup ($p = 0.003$). The median time to deterioration in FACT PCa subscale was 11.1 versus 5.8 mo ($p < 0.0001$) [25]. The risk of bias was mostly low (Fig. 2)[…]
- The PREVAIL trial included 1717 patients with chemo-therapy-naïve mCRPC who were randomized to receive either enzalutamide 160 mg/d or placebo. HRQOL was assessed with the EQ-5D (-3L) questionnaire, and completion rates exceeded 90% at all time points. The authors found a significantly smaller decline in general HRQOL based on the EQ-5D visual analog scale (–1.3 [enzalutamide] vs –4.4 [placebo], $p < 0.0001$) in favor of enzalutamide. Similarly, numerous subscales at various time points favored enzalutamide [28]. As shown in Fig. 2, both AFFIRM and PREVAIL have a low risk of bias.
- In the FIRSTANA trial, 1168 patients with chemotherapy- naïve mCRPC were randomized into one of the three following arms: cabazitaxel 20 mg/m2, cabazitaxel 25 mg/m2, or docetaxel 75 mg/m2 [33]. Using the FACT-P questionnaire, the authors found a longer median time to deterioration in physical well-being for cabazitaxel 20 mg/m2 vs docetaxel 75 mg/m2 (14.9 vs 11.3 mo, HR 0.76, 95% CI 0.61–0.94, $p = 0.013$) with no meaningful differences in the remaining subscales [33]. Analogous to PROSELICA, no baseline FACT-P values were reported and risk of bias assessment showed mixed results (Fig. 2).
- In the observational phase IV AQUARiUS study, HRQOL outcomes of 105 patients with mCRPC receiving either enzalutamide 160 mg/d or abiraterone acetate 1000 mg/d (in combination with 5 mg prednisone daily) in routine clinical practice were recently reported [34]. General HRQOL was assessed using the QLQ-C30 questionnaire. With

respect to the QLQ-C30 global health status, the authors found a net difference of 7.05 points favoring the abiraterone over the enzalutamide subgroup. Notably, a clinically meaningful deterioration of cognitive functioning was seen in 8.0% in the abiraterone subgroup compared with 37.8% in the enzalutamide subgroup (p = 0.022). No baseline global health status scores were reported and, due to the open-label nonrandomized observational study design, risk of bias assessment showed mostly a high risk of bias (Fig. 2).

Anmerkung/Fazit der Autoren

- In the current systematic review, over 800 articles were screened and 14 articles were included in the quantitative analysis. Based on mostly phase III trials with a low risk of bias, beneficial effects on HRQOL outcomes have been described for abiraterone acetate, enzalutamide, and radium-223 in the mCRPC setting. Efforts should be undertaken to optimize comparability between HRQOL outcomes based on different validated questionnaires as well as integration of supportive care regimens.
- Limitations include hampered comparability between different validated question-naires, lack of baseline values, and unclear impact of supportive care on HRQOL outcomes.

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Leal F et al., 2019 [15]

Effectiveness of Platinum-Based Chemotherapy in Patients with Metastatic Prostate Cancer: Systematic Review and Meta-analysis

Fragestellung

to summarize the existing evidence for platinum-based chemotherapy for PCa and to evaluate its role in treating the treatment of this disease.

Methodik

Population:

- patients with castration-resistant prostate cancer (CRPC)

Intervention/Komparator:

- Regimens could be composed of platinum chemotherapy alone or platinum compounds plus any other combination of cytotoxic agents. Control arms could be no chemotherapy or any chemotherapy other than platinum-containing regimens.

Endpunkte:

- overall survival (OS), progression-free survival (PFS), clinical overall response rate (cORR), prostatespecific antigen overall response rate (sORR), and toxicity

Recherche/Suchzeitraum:

- We searched Medline (Ovid), Embase, Lilacs, and the Cochrane Central Register of Controlled Trials from inception to January 2019.
- There were no setting or language restrictions.

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool for RCTs;
- for nonrandomized studies, we used the MINORS tool.

Ergebnisse

Anzahl eingeschlossener Studien:

- 53 studies were included for qualitative synthesis
- 9 RCTs were included for quantitative synthesis.
- Of the 9 randomized trials, 6 were multicenter studies.

Charakteristika der Population:

Table 1: Chemotherapy regimens in RCTs

Study	Year	Platinum Arm	Control Arm (If Any)	Platinum Dose and Schedule	Taxane Dose and Schedule (If Any)
Bouman-Wammes[77]	2017	Docetaxel + carboplatin	Docetaxel + prednisone	AUC 4 q21d	75 mg/m^2 q21d alone; 60 mg/m^2 q21d combined with carboplatin
Droz[61]	2003	Treatment 1: Oxaliplatin Treatment 2: Oxaliplatin + 5-FU	None	130 mg/m^2 q21d	NA
Komatus[68]	1996	Cisplatin + methotrexate	Endocrine therapy alone	70 mg/m^2 q21d	NA
Thall[49]	2007	Carboplatin + paclitaxel + estramustine	Control1: cyclophosphamide + vincristine + dexamethasone; Control 2: paclitaxel + estramustine + etoposide Control 3:doxorubicin + ketoconazole + vinblastine + estramustine	AUC 2 weekly	80 mg/m^2 weekly
Corn[16]	2015	Cabazitaxel + carboplatin	cabazitaxel	AUC 4 q21d	25 mg/m^2 q21d

Soloway[35]	1983	Treatment 1: Cisplatin + estramustine Treatment 2: Cisplatin	Estramustine	Not clear	NA
Loening[34]	1983	Cisplatin	Control 1: Estramustine Control 2: Methotrexate	60 mg/m^2 D1, D4, D21, D24 ther q28d	NA
Murphy[37]	1988	Cisplatin + 5-FU + cyclophosphamide	Control 1: methotrexate Control 2: doxorubicin + cyclophosphamide	50 mg/m^2 q21d	NA
Cabrespine[54]	2006	Carboplatin + paclitaxel	Mitoxantrone	AUC 5 q21d	175 mg/m^2 q21d

Qualität der Studien:

We found that all the randomized studies had unclear risk of bias for allocation concealment and blinding because there was no description related to these issues. Droz et al and Corn 2015 had low risk of bias for random sequence generation. Additionally, all 9 studies had low risk of bias for selective reporting and other bias. Regarding the incomplete outcome data issue, only the study of Bouman-Wammes et al had insufficient recruitment.

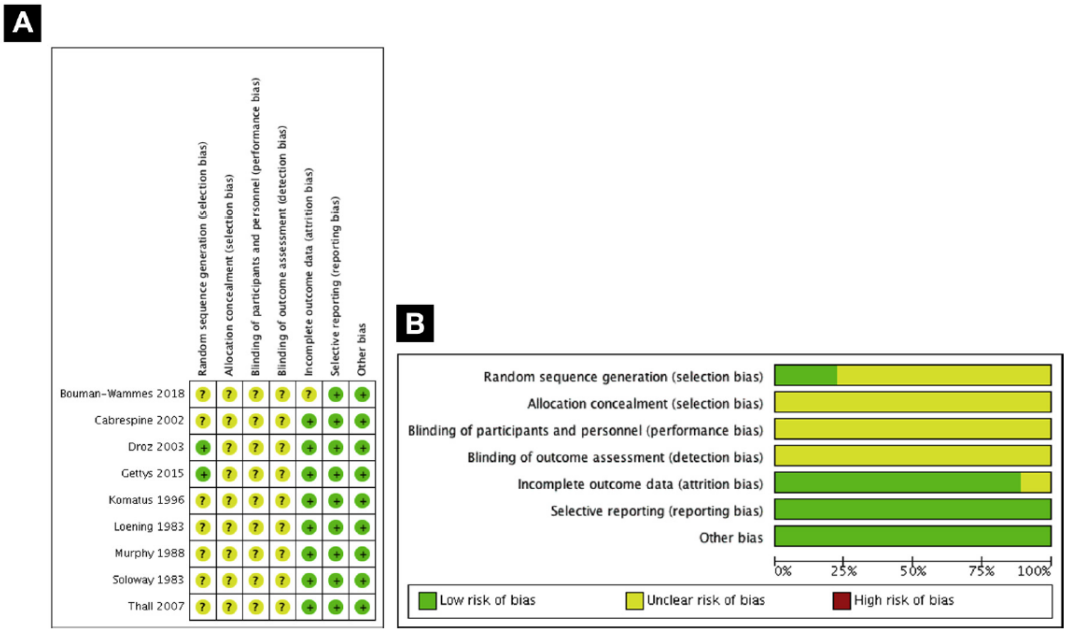

Figure 1: Risk of Bias. Risk of Bias (A) Within Randomized Studies, (B) Across Randomized Studies

Studienergebnisse:

Clinical Overall Response Rate (cORR)

- Four randomized trials tested at least one platinum-containing arm against other none-platinum-containing chemotherapy. However, the study by Soloway et al had to be excluded from this analysis because it reported zero response for either the platinum or control arm. Pooled data from these trials showed a statistically significant benefit for platinum chemotherapy (Figure 2A).

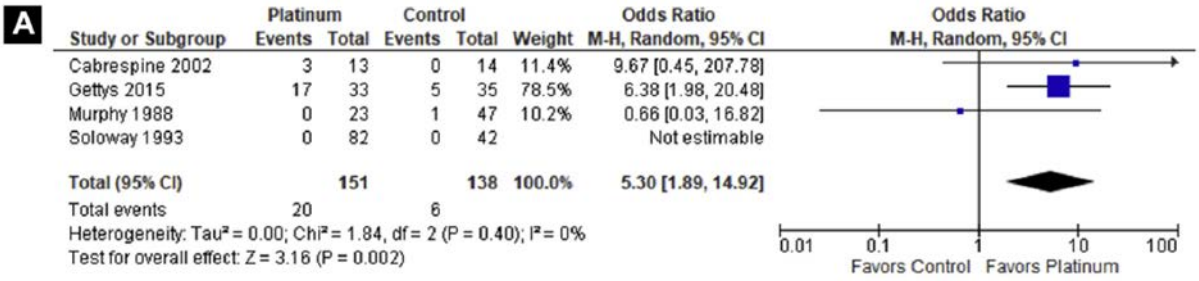

Figure 2A: Random-effect-model Meta-analysis of Platinum-containing Therapy Versus Other Nonplatinum Chemotherapy

Prostate-Specific Antigen Overall Response Rate (sORR):

- Five randomized studies compared platinum-based chemotherapy against treatment with a nonplatinum-based chemotherapy. Pooled data from these trials showed a statistically significant benefit for platinum chemotherapy (Figure 2 B)

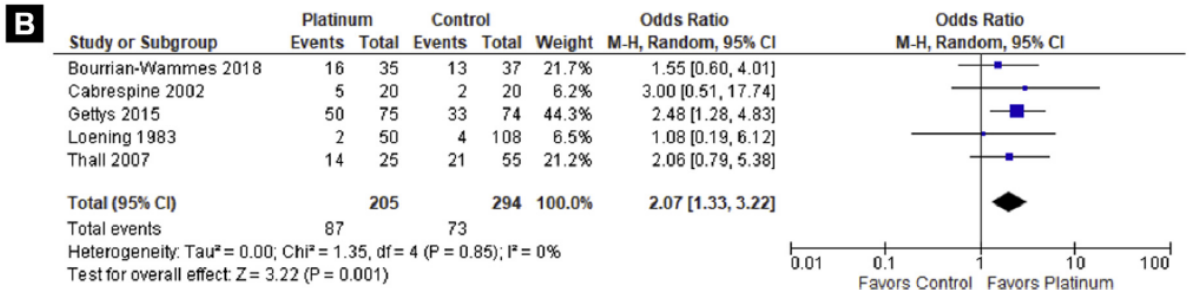

Figure 2B: Random-effect-model Meta-analysis of Platinum-Based Chemotherapy Versus Other Nonplatinum Chemotherapy

<u>Progression-Free Survival (PFS):</u>

- Four randomized controlled trials compared a platinum arm with non-platinum chemotherapy and reported PFS. Both platinum and control arms were heterogeneous in these trials. Two of these reported better PFS with platinum; the two others did not. Because no study expressed its comparison using a hazard ratio, a meta-analysis was not performed.

<u>Overall Survival (OS):</u>

- Five randomized trials compared OS between platinum and nonplatinum chemotherapy regimens. None of these reported a statistically significant difference in OS between the two arms. Because no trial reported hazard ratio for OS, meta-analysis of the extracted data was not performed for this endpoint.

<u>Toxicity:</u>

- All 53 studies reported some information on toxicity, but which toxicities were assessed was highly variable. Use of the World Health Organization grading system was not consistent for some trials. In general, toxicities were within expected parameters.
- In studies testing cisplatin-containing regimens, nausea and vomiting were the most frequently reported toxicities. Grade ¾ nausea and vomiting occurred in 2% to 20% of

patients treated with cisplatin. Older trials tended to report higher rates. Nephrotoxicity and ototoxicity were reported but infrequent.

- Anemia and thrombocytopenia were the most commonly reported toxicities for studies that used carboplatin. Grade 3/4 hematologic toxicity occurred in up to 36% of patients treated with combination chemotherapy including carboplatin. Severe nephrotoxicity, nausea, and vomiting were rare.

Anmerkung/Fazit der Autoren

Platinum chemotherapy is safe and active against CRPC, and can be delivered after failure of other treatments; it may also be provided to patients with contraindications or no access to these treatments. Further research on platinum chemotherapy for CRPC is warranted to demonstrate a survival benefit and to establish predictive markers of response.

Kommentare zum Review

- Fehler bei Autorenangabe in den Abbildungen 1 und 2A & B: Anstelle von Gettys et al 2015 müsste Corn et al 2015 stehen.
- However, most of studies we found were nonrandomized, and eligibility criteria and treatment delivered were highly variable among studies. Our results therefore must be interpreted with care.

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3.4 Leitlinien

Leitlinienprogramm Onkologie , 2021 [18] und Leitlinienreport [17].

Federführende Fachgesellschaft: Deutsche Gesellschaft für Urologie e. V. (DGU)

Interdisziplinäre Leitlinie der Qualität S3 zur Früherkennung, Diagnose und Therapie der verschiedenen Stadien des Prostatakarzinoms; Langversion 6.0 Mai 2021: AWMF Registernummer: 043/022OL

Zielsetzung/Fragestellung

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

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- 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.

  Die Leitlinie (Version 6.0 Mai 2021) ist bis zur nächsten Aktualisierung gültig (11.05.2024). Vorgesehen sind regelmäßige modulare Aktualisierungen in einem 3-jährlichen Abstand.

Recherche/Suchzeitraum:

- Für die Version 6.0 der Leitlinie erfolgten systematische Literaturrecherchen zu insgesamt 16 Fragestellungen nach aggregierter Evidenz sowie randomisierten, kontrollierten Studien, teilweise in Form von Update-Recherchen. Die Recherchen wurden in Medline via Pubmed und der Cochrane-Datenbank durchgeführt. Ergänzend erfolgte eine systematische freie Suche in den Referenzlisten der ermittelten Studien. (Methodikeranmerkung: unterschiedliche Suchzeiträume jeweils angegeben; häufig: 18.09.2020)
- Recherche zur 4. Aktualisierung 2018: Zu allen Fragestellungen erfolgte eine spezifische systematische Literaturrecherche in den Datenbanken Medline (Pubmed) und den Datenbanken der Cochrane Library (Methodikeranmerkung: unterschiedliche Suchzeiträume jeweils angegeben). Es wurden außerdem Studien berücksichtigt, die in Referenzlisten bekannter Studien oder durch Hinweise aus der Leitliniengruppe identifiziert wurden.

LoE

- Die Klassifikation der Evidenz erfolgte nach den Kriterien des Scottish Intercollegiate Guidelines Network (SIGN) (siehe Tabelle 2).

Tabelle 2: Schema der Evidenzklassifikation des Scottish Intercollegiate Guidelines Network (SIGN)

Klasse	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

GoR

- Die Empfehlungsstärken drücken aus, wie sicher sich die Leitliniengruppe ist, dass der größte Teil der beschriebenen Patienten von einer Intervention profitiert. Dies richtet sich nach:
  - der Aussagekraft der Evidenz, beurteilt an Hand von: Studienqualität bzw. Verzerrungsrisiko, Konsistenz der Studienergebnisse, Übertragbarkeit, ggf. Kenntnis/Wahrscheinlichkeit von nicht veröffentlichten Studien zum selben Thema;
  - dem Nutzen-Schaden-Verhältnis;
  - alternativen Handlungsoptionen;
  - den Behandlungszielen und Präferenzen;
  - der Umsetzbarkeit im klinischen Alltag, in verschiedenen Versorgungssettings/Sektoren;
  - ethische, rechtliche sowie sonstigen Erwägungen

Tabelle 3 Einstufung der Empfehlungen

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	Soll
B	Empfehlung	Sollte
0	Empfehlung offen	kann

- Als Expertenkonsens (EK) werden Empfehlungen bezeichnet, zu denen keine Recherche nach Literatur durchgeführt wurde. In der Regel adressieren diese Empfehlungen Vorgehensweisen der guten klinischen Praxis, zu denen keine wissenschaftlichen Studien notwendig sind bzw. erwartet werden können.

Empfehlungen

Kapitel 7: Diagnostik und Therapie des rezidivierten oder metastasierten Prostatakarzinoms

7.4. Therapie des androgenunabhängigen oder kastrationsresistenten Prostatakarzinoms (CRPC)

7.26	Evidenzbasierte Empfehlung	geprüft 2021
Empfehlungsgrad **A**	Patienten mit kastrationsresistentem Prostatakarzinom sollen über folgende Inhalte aufgeklärt werden: • Eine Heilung kann nicht erreicht werden. • Für die weitere Behandlung stehen verschiedene Optionen zur Verfügung.	
Level of Evidence **4**	Expertenkonsens	
	Gesamtabstimmung: 100 %	

7.27	Evidenzbasierte Empfehlung	geprüft 2021
Empfehlungsgrad **B**	Bei Patienten mit symptomatischer progredienter Erkrankung unter medikamentöser Kastration sollten die therapeutischen Optionen und das therapeutische Vorgehen interdisziplinär beraten und festgelegt werden.	
Level of Evidence **4**	Expertenkonsens	
	Gesamtabstimmung: 97 %	

7.28	Evidenzbasierte Empfehlung	geprüft 2021
Empfehlungsgrad A	Folgende für eine Therapieentscheidung ausschlaggebende Faktoren sollen bedacht werden: • Symptomatik • Nebenwirkungen der Therapieoptionen • Patientenpräferenz • Komorbidität, Lebenserwartung und Lebensqualität • Progressionsdynamik • Lokalisation von Metastasen und generelle Tumorlast.	
Level of Evidence 4	Expertenkonsens	
	Gesamtabstimmung: 100 %	

7.29	Evidenzbasiertes Statement	geprüft 2021
Level of Evidence 4	Behandlungsfähigkeit für Chemotherapie ist keine eindeutig definierte Variable. Es fehlen daher Grenzwerte, ab denen Behandlungsfähigkeit gegeben bzw. nicht gegeben ist.	
	Expertenkonsens	
	Gesamtabstimmung: 97 %	

Zu Statement 7.29:

Chemotherapie ist eine Therapie mit relativ geringer therapeutischer Breite. Das Auftreten unerwünschter Arzneimittelwirkungen (UAW) ist auch bei standarddosierter Therapie die Regel und nicht die Ausnahme. Die Toxizität systemischer Therapie wird mittels Common Terminology Criteria for Adverse Event (CTCAE) klassifiziert [http://evs.nci.nih.gov/ftp1/CTCAE/About.html]. Neben dieser objektiven Toxizität spielt die subjektive Belastung des Patienten eine wesentliche Rolle. Beide sind im Rahmen von Therapieentscheidungen (Fortsetzung der Therapie, Dosismodifikation und Therapieabbruch) strukturiert zu erfassen und zu gewichten. Therapeutische Belastungen werden eher in Kauf genommen, wenn die (vermeintlichen) Vorteile durch eine Therapie groß sind. Der Abbruch einer Therapie, eine hohe Rate an Toxizität und Dosismodifikationen sind daher Hinweise auf geringe Behandlungsfähigkeit.

7.4.2. Metastasiertes kastrationsresistentes Prostatakarzinom (mCRPC)

7.4.2.1. Asymptomatische oder gering symptomatische Patienten

7.34	Evidenzbasierte Empfehlung	geprüft 2021
Empfehlungsgrad 0	Patienten mit metastasierter, kastrationsresistenter, asymptomatischer oder gering symptomatischer und progredienter Erkrankung unter Androgendeprivation kann unter Aufklärung über Nutzen und Nebenwirkungen eine Umstellung der Behandlung angeboten werden. Die spezifischen Voraussetzungen und Nebenwirkungen der Therapien sollen dabei berücksichtigt werden.	
Level of Evidence 4	Expertenkonsens	
	Gesamtabstimmung: 97 %	

7.35	Evidenzbasierte Empfehlung	geprüft 2021
Empfehlungsgrad A	Wenn sich ein Patient mit metastasierter, kastrationsresistenter, asymptomatischer oder gering symptomatischer und progredienter Erkrankung gegen ein abwartendes Verhalten und für die Umstellung der Behandlung entschieden hat, soll eine der folgenden Optionen angeboten werden: (alphabetische Reihenfolge) • Abirateron (in Kombination mit Prednison / Prednisolon) • Docetaxel • Enzalutamid Zur Differenzialtherapie siehe Empfehlungen 7.36 und 7.37.	
Level of Evidence 1+	Literatur: [835-838]	
	Gesamtabstimmung: 100 %	

Zu Empfehlung 7.34 und 7.35:

Zur Therapie von Patienten mit metastasierter, kastrationsresistenter, asymptomatischer oder gering symptomatischer und progredienter Erkrankung liegen Daten randomisierter Studien zu Formen der Antihormontherapie mit Abirateron oder Enzalutamid, sowie der Chemotherapie mit Docetaxel vor. Die in der Leitlinie ab 2014 gelistete Immuntherapie mit Sipuleucel-T ist seit Mitte 2015 nicht mehr in Europa verfügbar. Abirateron und Enzalutamid wurden gegen Placebo, Docetaxel gegen Mitoxantron getestet. Abirateron wird standardmäßig in Kombination mit Prednison oder Prednisolon gegeben. Die Empfehlungen für diese Patientenpopulation beruhen auf den Einschlusskriterien für Therapie mit Docetaxel [835,837], Abirateron [836] und Enzalutamid [838] bei Patienten ohne Vortherapie in diesem Krankheitsstadium. […] Ob eine Chemotherapie mit Docetaxel schon bei asymptomatischen Patienten mit alleinigem PSA-Anstieg oder bei durch Bildgebung nachgewiesener Progression zu beginnen ist, ist Gegenstand kontroverser Diskussionen. In der Subgruppenanalyse von TAX-327 [837,840] wurde auch bei Patienten ohne Schmerzsymptomatik, bei Patienten ohne viszerale Metastasierung und bei Patienten mit minimal symptomatischer Erkrankung eine Verlängerung der Überlebenszeit im Vergleich zu Mitoxantron erzielt. Eine randomisierte kontrollierte Studie zum Nutzen einer frühen Therapie bei asymptomatischen Patienten versus späterer Therapie bei symptomatischen Patienten gibt es bisher nicht.

7.36	Evidenzbasierte Empfehlung	geprüft 2021
Empfehlungsgrad B	Patienten mit metastasierter, kastrationsresistenter, asymptomatischer oder gering symptomatischer und progredienter Erkrankung sollte (alphapetische Reihenfolge) • Abirateron (in Kombination mit Prednison / Prednisolon) oder • Enzalutamid angeboten werden.	
Level of Evidence 1+	Literatur: [836,838]	
	Gesamtabstimmung: 100 %	

7.37	Evidenzbasierte Empfehlung	geprüft 2021
Empfehlungsgrad 0	Patienten mit metastasierter, kastrationsresistenter, asymptomatischer oder gering symptomatischer und progredienter Erkrankung kann Docetaxel angeboten werden.	
Level of Evidence 1+	Literatur: [835,837]	
	Gesamtabstimmung: 96 %	

Zu Empfehlung 7.36:

Abirateron: […] Die COU-AA-302 Studie (n = 1088) zeigte einen Überlebensvorteil für Abirateron in Kombination mit Prednison im Vergleich zu Placebo mit Prednison (medianes Gesamtüberleben: 34,7 vs. 30,3 Monate, HR: 0,81, 95 % KI: 0,70-0,93, p = 0,0033) [841]. Das vordefinierte Signifikanzniveau (0,001) wurde in dieser Studie nicht erreicht. Da bei Progredienz der Erkrankung ein Crossover vom Placebo- zum Abirateron-Arm erlaubt war, ist die Aussagefähigkeit des Endpunktes Überlebenszeit eingeschränkt. […] Eingeschlossen wurden nur Patienten mit gutem Allgemeinzustand (ECOG 0-1). Patienten mit viszeralen Metastasen wurden nicht in die Studie eingeschlossen.[…] Abirateron ist in Kombination mit Prednison/Prednisolon zugelassen zur Behandlung des metastasierten kastrationsresistenten Prostatakarzinoms bei erwachsenen Männern mit asymptomatischem oder mild symptomatischem Verlauf der Erkrankung nach Versagen der Androgenentzugstherapie, bei denen eine Chemotherapie noch nicht klinisch indiziert ist [842].

Enzalutamid: […] Die Zulassungsstudie PREVAIL umfasste 1.717 Chemotherapie-naive Patienten mit kastrationsresistentem Prostatakarzinom. Es wurden nur Patienten in gutem Allgemeinzustand (ECOG 0-1) eingeschlossen. Im Gegensatz zur COU-AA302-Studie mit Abirateron war der Einschluss von Patienten mit einer viszeralen Metastasierung in der PREVAIL-Studie erlaubt. Bei Studienbeginn wiesen 11,2 % der Patienten im Enzalutamid- und 12,5% der Patienten im Placebo-Arm eine viszerale Metastasierung mit pulmonalen und/oder hepatischen Metastasen auf [843]. Sowohl in der Interimanalyse [838] als auch in der Langzeitanalyse zeigte sich ein Überlebensvorteil für Enzalutamid gegenüber Placebo

[844] (medianes Gesamtüberleben: 35,3 vs. 31,3 Monate, HR: 0,77, 95 % KI: 0,67-0,87, p=0,0002). Das als koprimärer Endpunkt definierte radiologisch progressionsfreie Überleben wurde lag unter Enzalutamid bei 20 Monaten vs. 5,4 Monaten im Kontrollarm (HR 0,32; p<0,00001) [844].[…]

Unsicherheit herrscht derzeit noch zur Sequenztherapie [847,848]. Überlegungen und Empfehlungen sind in Kapitel 7.4.2.3 zusammengefasst.

Zu Empfehlung 7.37:

Die TAX-327 Studie (n =1.006, Karnofsky-performance status ≥ 60 %) zeigte einen Überlebensvorteil von 2,9 Monaten (Spanne null bis sieben Monate) bei dreiwöchentlicher Gabe von Docetaxel im Vergleich zu den beiden anderen Armen (wöchentlich Docetaxel niedriger dosiert, dreiwöchentlich Mitoxantron; Randomisierung 1:1:1) für die Gesamtgruppe [835,837].[…] Die zurückhaltende Empfehlung für den Einsatz von Docetaxel berücksichtigt die höhere Rate schwerer Nebenwirkungen unter Docetaxel.

7.4.2.2. Symptomatische Patienten

7.38	Evidenzbasierte Empfehlung	geprüft 2021
Empfehlungsgrad A	Patienten mit metastasierter, kastrationsresistenter, symptomatischer progredienter Erkrankung und gutem Allgemeinzustand soll eine systemische Therapie, bei Bedarf in Kombination mit symptombezogener und supportiver Therapie, angeboten werden. Zur Differenzialtherapie siehe Empfehlungen 7.39, 7.40, 7.41.	
Level of Evidence 1+	Literatur: [837,836,835,851].	
	Gesamtabstimmung: 98 %	

7.39	Evidenzbasierte Empfehlung	geprüft 2021
Empfehlungsgrad 0	Patienten mit metastasierter, kastrationsresistenter, symptomatischer und progredienter Erkrankung kann Docetaxel in zwei- oder dreiwöchigen Dosierungsschemata angeboten werden.	
Level of Evidence 1+	Literatur: [837,835]	
	Gesamtabstimmung: 95 %	

Zu Empfehlung 7.38:

[…] Ein guter Allgemeinzustand wird von der Leitliniengruppe definiert als ECOG < 2 oder Karnofsky-Index ≥ 70 %. Die Beschreibung der lokalen Therapieverfahren bei Knochenmetastasen finden sich im Kapitel 7.6 „Therapie von Knochenmetastasen“. In den Studien, die die weiteren Therapieoptionen untersuchen, wurden unterschiedliche Einschlusskriterien verwendet, daher sind die Ergebnisse nur schwer vergleichbar. Vergleichende Studien oder Studien zu Kombinationen der Therapieoptionen liegen bisher nicht vor.

Patienten mit Z. n. initialer Hormon-Chemotherapie oder intensivierter Hormontherapie mit Abirateron (+ Prednison oder Prednisolon) oder Apalutamid (ggf. noch Enza in

Abhängigkeit des Zulassungsstatus) stellen in diesem Zusammenhang eine Gruppe dar, für die formal keine Datenlage im Rahmen von Studien existiert, da dieser Therapieansatz zum Zeitpunkt der Rekrutierung dieser Studien noch nicht existierte. Dennoch wird hier ein Analogieschluss von der Leitliniengruppe favorisiert.

Zu Empfehlung 7.39:

Die Studienlage zu Docetaxel bei Patienten ohne Vortherapie in diesem Krankheitsstadium ist im Hintergrundtext zu Empfehlung 7.37 dargestellt.

7.40	Evidenzbasierte Empfehlung	geprüft 2021
Empfehlungsgrad 0	Patienten mit metastasierter, kastrationsresistenter, symptomatischer und progredienter Erkrankung kann (alphabetische Reihenfolge) · Abirateron (in Kombination mit Prednison / Prednisolon) oder · Enzalutamid angeboten werden.	
A	Patienten sollen darüber aufgeklärt werden, dass in der Zulassungsstudie nur Patienten mit gering symptomatischer Erkrankung behandelt wurden.	
Level of Evidence 1+	Literatur: [836,838]	
	Gesamtabstimmung: 95 %	

Zu Empfehlung 7.40:

Die Studienlage zu Abirateron (in Kombination mit Prednison / Prednisolon) und Enzalutamid bei Patienten ohne Vortherapie in diesem Krankheitsstadium ist im Hintergrundtext zur Empfehlung 7.36 dargestellt. Beide Wirkstoffe sind nur für die Anwendung bei asymptomatischen oder mild symptomatischen Patienten zugelassen [842,846]. Mild symptomatisch bzw. asymptomatisch wurde in den Zulassungsstudien definiert als ein BPI-SF von < 3 als stärkster Schmerz in den letzten 24 Stunden.

7.41	Evidenzbasierte Empfehlung	geprüft 2021
Empfehlungsgrad A	Patienten mit kastrationsresistenter, symptomatischer, progredienter Erkrankung und reduziertem Allgemeinzustand (ECOG ≥ 2, Karnofsky-Index < 70) soll eine symptombezogene Therapie angeboten werden.	
Level of Evidence 4	Expertenkonsens	
	Gesamtabstimmung: 95 %	

7.42	Evidenzbasierte Empfehlung	modifiziert 2021
Empfehlungsgrad 0	Patienten mit kastrationsresistenter, progredienter Erkrankung und reduziertem Allgemeinzustand (ECOG ≥ 2, Karnofsky-Index < 70) kann zusätzlich eine der folgenden Therapieoptionen angeboten werden: (alphabetische Reihenfolge) • Abirateron (in Kombination mit Prednison / Prednisolon) • Chemotherapie, wenn der reduzierte Allgemeinzustand vor allem auf das metastasierte Prostatakarzinom zurückzuführen ist • Enzalutamid • Steroide (Dexamethason, Prednisolon, Prednison)	
Level of Evidence 4	Expertenkonsens basierend auf [835,837,836,838]	
	Gesamtabstimmung: 95 %	

Zu Empfehlung 7.41 und 7.42:

Patienten mit schlechtem Allgemeinzustand (ECOG ≥ 2, Karnofsky-Index < 70 %) und Patienten mit Einschränkungen im Geriatrischen Assessment weisen eine eingeschränkte Behandlungsfähigkeit auf. Es gibt keine randomisierten Studien für die Therapie von Patienten mit progredienter Erkrankung und einem reduzierten Allgemeinzustand (ECOG ≥ 2). In den Studien zu Abirateron (ECOG: 0-1), Docetaxel (Karnofsky-Index ≥ 60 %), Enzalutamid (ECOG: 0-1) waren keine oder nur wenige Patienten mit reduziertem Allgemeinzustand eingeschlossen. Daher wird für diese Patienten eine symptombezogene Therapie empfohlen. […]

Nur wenn der reduzierte Allgemeinzustand vor allem auf das metastasierte Prostatakarzinom zurückzuführen ist, kann eine Chemotherapie mit Docetaxel angeboten werden. Die Studienlage zu Docetaxel als Erstlinientherapie ist im Hintergrundtext zu Empfehlung 7.37 dargestellt.

7.4.2.3. Therapiesequenz nach Vortherapie mit mindestens einer neuen hormonellen Substanz (new hormonal agent)

7.43	Evidenzbasierte Empfehlung	neu 2021
Empfehlungsgrad B	Patienten mit Progress unter einer neuen hormonellen Substanz (new hormonal agent) sollte ein Wechsel der Therapiestrategie angeboten werden.	
Level of Evidence 4	Expertenkonsens basierend auf [852]	
	Gesamtabstimmung: 95 %	

Zu Empfehlung 7.43:

Hierbei sind insbesondere auch die Ergebnisse der Studien zum Wechsel des Wirkprinzips (Mode of Action) mit Einsatz von Cabazitaxel [852] oder von Olaparib [853,854] nach Vortherapie mit einem der neueren Androgenrezeptor-gerichteten Therapien zu berücksichtigen. Ein Wechsel des Therapieprinzips wird auch durch molekularbiologische Untersuchungen zu Resistenzmechanismen gegen eine gegen den Androgen-Rezeptor

gerichtete Therapie gestützt [855,856], so dass Empfehlung 7.45 allgemein als Expertenkonsens formuliert wurde.

7.44	Evidenzbasierte Empfehlung	neu 2021
Empfehlungsgrad A	Patienten mit Progress nach einer Vortherapie, die eine neue hormonelle Substanz (new hormonal agent) umfasste, soll eine Testung auf BRCA 1/2 -Mutationen angeboten werden.	
Level of Evidence 1-	Literatur: [853,854]	
	Gesamtabstimmung: 97 %	

Zu Empfehlung 7.44:

Grundlage für die Empfehlung einer Testung auf BRCA1/2-Mutationen ist PROfound, eine internationale, multizentrische, randomisierte Studie zum Vergleich der Wirksamkeit von Olaparib versus Placebo bei Patienten mit Nachweis eines DNA-Reparaturmechanismusdefekts in den homologen Rekombinations-Reparaturgenen [853,853]. Da eine klinisch bedeutsame Wirksamkeit von Olaparib in der PROFOUND-Studie nur bei Patienten mit BRCA1/2 Mutationen nachgewiesen wurde, wurde eine Testung auf die anderen genetischen Alterationen nicht in diese Empfehlung aufgenommen.

7.45	Evidenzbasierte Empfehlung	neu 2021
Empfehlungsgrad A	Bei Nachweis einer *BRCA1/2* Mutation soll eine Therapie mit Olaparib angeboten werden.	
Level of Evidence 1-	Literatur: [853,854]	
	Gesamtabstimmung: 98 %	

Zu Empfehlung 7.45:

Olaparib führte gegenüber Abirateron/Enzalutamid in der Kohorte A (BRCA1/2; ATM) zur Steigerung der Ansprechrate (33 vs. 2 %; Odds Ratio (OR) 20,86; p<0,001)), zur signifikanten Verlängerung des progressionsfreien Überlebens (7,4 vs. 3,6 Monate; Hazard Ratio (HR) 0,34; p< 0,001) und zur Verlängerung der medianen Gesamtüberlebenszeit (19,1 vs. 14,7 Monate; HR 0,69; p=0,02) [853,854]. Ebenfalls verlängert wurde die Zeit bis zum Progress von Schmerzen (HR 0,44; p=0,02). Eine Subgruppenanalyse zu den einzelnen Genalterationen zeigte einen Vorteil von Olaparib v.a. für Patienten mit BRCA1/2-Mutationen. Entsprechend beschränkt sich die Zulassung von Olaparib auf diese Gruppe

7.4.2.4. Therapiesequenzen nach Docetaxel

7.46	Evidenzbasierte Empfehlung	modifiziert 2021
Empfehlungsgrad A	Patienten mit kastrationsresistenter, progredienter Erkrankung und gutem Allgemeinzustand nach Chemotherapie mit Docetaxel soll eine der folgenden Therapieoptionen, bei Bedarf in Kombination mit symptombezogener und supportiver Therapie, angeboten werden: (alphabetische Reihenfolge) • Abirateron (in Kombination mit Prednison / Prednisolon) • Cabazitaxel • Enzalutamid Zur Differenzialtherapie siehe Empfehlungen 7.47 - 7.49.	
Level of Evidence 1+	Literatur: [861-868]	
	Gesamtabstimmung: 97 %	

Zu Empfehlung 7.46:

Die Empfehlung beruht auf den Einschlusskriterien der Zulassungsstudien zu Abirateron, Cabazitaxel und Enzalutamid und Radium-223. Die Zulassungsstudien werden in den Empfehlungen 7.47 und 7.49 diskutiert. Ein guter Allgemeinzustand wurde von der Leitliniengruppe definiert als ECOG 0-1 oder Karnofsky ≥ 70.

Zur Abwägung einer Chemotherapie mit Cabazitaxel versus Abirateron/Enzalutamid verweisen wir auf die Daten der CARD-Studie, siehe Hintergrundtext zu Empfehlung 7.48 [852]. Eine Docetaxel-Retherapie ist möglich bei Patienten, die auf eine Vorbehandlung gut und mit wenigen Nebenwirkungen angesprochen haben. Eine Docetaxel-Retherapie erfolgt individualisiert. Daten randomisierter Studien mit Festlegung von Selektionskriterien liegen nicht vor.

7.47	Evidenzbasierte Empfehlung	geprüft 2021
Empfehlungsgrad 0	Patienten mit kastrationsresistenter, progredienter Erkrankung und gutem Allgemeinzustand nach Chemotherapie mit Docetaxel kann (alphabetische Reihenfolge) · Abirateron (in Kombination mit Prednison / Prednisolon) oder · Enzalutamid angeboten werden. In der jeweiligen Zulassungsstudie wurde eine Verlängerung der Überlebenszeit gezeigt.	
Level of Evidence 1+	Literatur: Abirateron: [861,862] Enzalutamid [864]	
	Gesamtabstimmung: 100 %	

Zu Empfehlung 7.47:

Unter Therapie mit Abirateron wurde nach einem medianen Follow-up von ca. zwölf Monaten in einer Interimsanalyse eine Verlängerung des Gesamtüberlebens um im Median 3,9 Monate im Vergleich zu Placebo gezeigt [861]. In die randomisierte kontrollierte Studie (1.195 Patienten, 2:1-Randomisierung) waren asymptomatische und symptomatische Patienten mit sehr gutem Allgemeinzustand einbezogen (90 % ECOG 0-1), die vorher

mindestens eine Chemotherapie erhalten hatten. Die Raten an Nebenwirkungen sind im Vergleich zu einer Chemotherapie geringer.[…] Im Vergleich zu Placebo zeigte Abirateron einen signifikanten Effekt auf verschiedene Endpunkte (progressionsfreies Überleben, biochemische und bildgebende Remission und Symptomatik) [863]. Bei Patienten mit niedrigen Lebensqualitätswerten zu Beginn der Studie verbesserte sich die Lebensqualität bei mehr Patienten, die Abirateron erhielten im Vergleich zu Placebo (definiert als eine Verbesserung des FACT-P um 10 Punkte).

Enzalutamid zeigte in einer randomisiert kontrollierten Studie mit 1.199 Patienten (2:1 Randomisierung) in gutem Allgemeinzustand (EGOG 0-2) mit progredienter Erkrankung nach Therapie mit Docetaxel einen signifikanten Vorteil im Gesamtüberleben von im Median 4,8 Monaten (18,4 Monaten versus 13,6 Monaten unter Placebo; HR: 0,63, 95 % KI: 0,53-0,75; P < 0,001) [864]. […] Im Vergleich zu Placebo verlängerte Enzalutamid das progressionsfreie Überleben (8,3 Monate vs. 2,9 Monate; HR: 0.40, 95 % KI: 0,35-0,47, p < 0,001) und die Zeit bis zur PSA-Progression (8,3 Monate vs. 3,0 Monate; HR: 0,25, 95 % KI: 0,20-0,30, p < 0,001) und verbesserte die Lebensqualität (definiert als eine Verbesserung des FACT-P um 10 Punkte).[…]

7.48	Evidenzbasierte Empfehlung	geprüft 2021
Empfehlungsgrad 0	Patienten mit kastrationsresistenter, progredienter Erkrankung und gutem Allgemeinzustand nach Chemotherapie mit Docetaxel kann Cabazitaxel angeboten werden. In der Zulassungsstudie wurde eine Verlängerung der Überlebenszeit gezeigt.	
Level of Evidence 1+	Literatur: [865]	
	Gesamtabstimmung: 100 %	

Zu Empfehlung 7.48:

Zum Einsatz von Cabazitaxel liegen Daten von drei randomisierten Studien vor. In der Zulassungsstudie wurde Cabazitaxel im Unterschied zu Abirateron und Enzalutamid (jeweils gegen Placebo) versus Mitoxantron (jeweils in Kombination mit Prednison) getestet. […] Die eingeschlossenen Patienten wiesen alle eine ausgeprägte Metastasierung auf. Im Vergleich zu Mitoxantron wurde unter Cabazitaxel eine mittlere Lebensverlängerung um 2,4 Monate (15,1 Monate vs. 12,7 Monate, HR: 0,70; 95 % KI: 0,59-0,83, p < 0.0001) und eine Verlängerung des progressionsfreien Überlebens um 1,4 Monate (2,8 Monate vs. 1,4 Monate, HR: 0,74; 95 % KI: 0,64-0,86, p < 0,0001) erreicht [865].[…] In der CARD-Studie wurden insgesamt 255 Patienten randomisiert mit Cabazitaxel 25mg/m2 alle drei Wochen oder Abirateron (+ Prednion/ Prednisolon) bzw. Enzalutamid behandelt [852]. Voraussetzung für den Einschluss in die Studie war eine Vortherapie mit Docetaxel und dem jeweils anderen AR-gerichteten Medikament […] [852]. Die Cabazitaxel-Therapie führte zu einer Verlängerung der medianen Gesamtüberlebenszeit mit 13,6 Monaten versus 11 Monaten unter dem zweiten AR-gerichteten Medikament (HR 0.64; p=0,008) [852]. Auch die mediane Zeit bis zum radiologischen Progress (8,8 vs. 4,4 Monate; HR 0,54; p<0,001) und das progressionsfreie Überleben (4,4 vs. 2,7 Monate; HR 0,52; p<0,001) wurde durch Cabazitaxel signifikant verlängert [852]. […]

7.49	Evidenzbasierte Empfehlung	modifiziert 2021
Empfehlungsgrad 0	a. Radium-223 kann Patienten angeboten werden, die ein kastrationsresistentes, progredientes Prostatakarzinom mit symptomatischen ossären Metastasen (ohne bekannte viszerale Metastasen) sowie einen guten Allgemeinzustand aufweisen und die mindestens zwei vorausgehende systemische Therapieoptionen in dieser Indikation erhielten oder für die keine andere verfügbare systemische mCRPC-Therapie geeignet ist.	
Empfehlungsgrad A	b. Radium-223 soll nicht in Kombination mit Abirateron und Prednison/ Prednisolon angewandt werden.	
Level of Evidence 1+	Literatur: a. [851,869,870] b. [871]	
	Gesamtabstimmung: a. 100 %, b. 100 %	

Zu Empfehlung 7.49:

Aufgrund von Sicherheitsbedenken wurde die Zulassung im Juli 2018 begrenzt auf Patienten mit metastasiertem Prostatakarzinom (Metastasen im Knochen ohne bekannte viszerale Metastasen), die bereits zwei andere vorherige Therapieoptionen erhielten sowie Patienten, die keine anderen systemischen Therapieoptionen erhalten können. Aufgrund von Hinweisen auf ein erhöhtes Frakturrisikos in der Kombinationstherapie wurde empfohlen, Radium-223 nicht in Kombination mit Abirateron plus Prednison/Prednisolon einzusetzen [877,878].

7.50	Evidenzbasierte Empfehlung	modifiziert 2021
Empfehlungsgrad 0	Patienten mit kastrationsresistenter, progredienter Erkrankung nach Chemotherapie mit Docetaxel und reduziertem Allgemeinzustand (ECOG ≥ 2, Karnofsky < 70) kann zusätzlich zur symptombezogenen Therapie eine der folgenden Therapieoptionen angeboten werden: (alphabetische Reihenfolge) • Abirateron (in Kombination mit Prednison / Prednisolon) • Chemotherapie, wenn der reduzierte Allgemeinzustand vor allem auf das metastasierte Prostatakarzinom zurückzuführen ist • Enzalutamid • Steroide (Dexamethason, Prednisolon, Prednison)	
Level of Evidence 4	Expertenkonsens basierend auf Referenzen zu 7.49 und [103,191,872].	
	Gesamtabstimmung: 97 %	

Zu Empfehlung 7.50:

Zur Behandlung von Patienten mit einem schlechten Allgemeinzustand (ECOG ≥ 2, Karnofsky < 70) liegen kaum Daten vor. In den Zulassungsstudien (siehe Empfehlungen 7.47 - 7.49) wurden jeweils Patienten mit ECOG 0-2 eingeschlossen, allerdings lag die Anzahl eingeschlossener Patienten mit ECOG = 2 nur bei etwa 10 %. Für Patienten mit ECOG > 2 liegen keine Daten vor.

7.51	Evidenzbasierte Empfehlung	geprüft 2021
Empfehlungsgrad 0	Für Patienten mit kastrationsresistenter, progredienter Erkrankung in gutem Allgemeinzustand kann nach Ausschöpfen der empfohlenen Therapieoptionen (siehe Empfehlung 7.46) ein Therapieversuch mit Lutetium-177-PSMA auf Basis der Empfehlung einer interdisziplinären Tumorkonferenz angeboten werden.	
Level of Evidence 3	Literatur: [873]	
	Gesamtabstimmung: 93 %	

Zu Empfehlung 7.51:

Mit 177Lu-PSMA-Liganden findet sich ein neuer Ansatz zur Radionuklid-Therapie in der klinischen Erprobung [882]. In einer Übersichtsarbeit von 2019 […] zeigte sich bei 75 % der Patienten unter 177Lu-PSMA ein Rückgang des PSA-Wertes [873]. Diese wurde auch in der offenen, randomisierten Phase-II-Studie TheraP zum Vergleich von 177Lu-PSMA versus Cabazitaxel bestätigt. In die Studie eingeschlossen werden konnten dabei nur Patienten mit einem PSA-Wert > 20ng/ml und einer PSMA-positiven Erkrankung im PSMA-PET-CT. Nicht eingeschlossen werden konnten dagegen Patienten, die in einem zusätzlich durchgeführten FDG-PET-CT FDG-positive Metastasen ohne PSMA-Positivität aufwiesen. In dieser selektionierten Patientengruppe war die Rate von Patienten mit einem Rückgang des PSA-Wertes um >50 % signifikant höher unter 177Lu-PSMA mit 65 vs. 37 % signifikant höher als unter Cabazitaxel. Ergebnisse zu patientenrelevanten Endpunkten stehen aus [883].

7.4.2.5. Therapiesequenz nach Androgenrezeptor-gerichteter Behandlung

7.52	Evidenzbasierte Empfehlung	geprüft 2021
Empfehlungsgrad 0	Patienten mit kastrationsresistenter, progredienter Erkrankung und gutem Allgemeinzustand nach Androgenrezeptor-gerichteter Therapie kann eine Sequenztherapie unter Verwendung eines der anderen wirksamen Arzneimittel (siehe Empfehlung 7.46) angeboten werden.	
Level of Evidence 4	Expertenkonsens	
	Gesamtabstimmung: 100 %	

Zu Empfehlung 7.52:

Die Sequenztherapie nach Androgenrezeptor-gerichteter Behandlung […] von Abirateron, Enzalutamid, Cabazitaxel und u. a. vor [853,854,852]. Derzeit kann nicht abschließend beurteilt werden, ob eine zweite Androgenrezeptor-gerichtete Behandlung nach Progress unter der Erstlinienbehandlung mit dem jeweils anderen Wirkstoff möglicherweise weniger effektiv ist als eine Chemotherapie in der Zweitlinie. Festzuhalten ist allerdings, dass in den bislang vorliegenden retrospektiven Studien mit Enzalutamid nach Abirateron ein geringeres PSA-Ansprechen erzielt wird als in einer früheren Therapielinie [884]. Ähnliches

scheint für Abirateron nach Enzalutamid zu gelten. Ursachen für diese mögliche Kreuzresistenz sind Gegenstand aktueller Untersuchungen (Vgl. Empfehlung 7.43).

In einer Crossover-Studie mit Abirateron gefolgt von Enzalutamid versus vice versa zeigte die Sequenz Abirateron gefolgt von Enzalutamid eine signifikant bessere Wirksamkeit in Bezug auf den PSA Progress (HR 0,66), während Enzalutamid gefolgt von Abirateron wenig Aktivität zeigte [848]. Auch eine Kombination von Enzalutamid plus Abirateron nach Enzalutamid ist nicht wirksam [847]. Diese Daten könnten laut EAU Leitlinie darauf hindeuten, dass eine Sequenz Abiraterone gefolgt von Enzalutamid zu bevorzugen wäre, sofern ausschließlich eine Therapie mit gegen den Androgenrezeptor gerichteten Substanzen möglich ist.

7.5. Lokale Therapie bei metastasiertem Prostatakarzinom

7.5.2. Perkutane Strahlentherapie und radikale Prostatektomie

7.54	Evidenzbasierte Empfehlung	neu 2021
Empfehlungsgrad **B**	a. Patienten mit einem neu diagnostizierten, oligometastasierten Prostatakarzinom sollten zusätzlich zur systemischen Therapie eine perkutane Strahlentherapie der Prostata erhalten.	
Empfehlungsgrad **B**	b. Die externe Strahlentherapie (EBRT) sollte hypofraktioniert verabreicht werden, die Strahlendosis sollte eine Äquivalenzdosis von 72 Gy in 2 Gy-Standardfraktionierung nicht überschreiten.	
Level of Evidence **1-**	Literatur: [888,887]	
	Gesamtabstimmung: 100 %	

Hintergrundinformation: Durch eine zusätzlich zur Androgendeprivation (+/- Docetaxel) durchgeführte perkutane Strahlentherapie der Prostata wird bei Patienten mit einem neudiagnostizierten oligometastasierten Prostatakarzinom die mediane Zeit bis zur PSA-Progression signifikant verlängert. Patienten mit einer „low-volume“-Erkrankung nach CHAARTED-Kriterien (oder bis zu 3 Knochenmetastasen [887]) können darüber hinaus hinsichtlich des Gesamtüberlebens profitieren [887,888]

7.55	Evidenzbasierte Empfehlung	neu 2021
Empfehlungsgrad **0**	Die perkutane Strahlentherapie der Prostata kann beim oligometastasierten Prostatakarzinom mit einer erweiterten systemischen Therapie kombiniert werden (Androgendeprivation (ADT) simultan, Docetaxel sequentiell).	
Level of Evidence **1-**	Literatur: [887]	
	Gesamtabstimmung: 95 %	

Hintergrundinformationen: In der STAMPEDE-Studie wurde eine Minderheit (18 % der Patienten) frühzeitig zusätzlich zur Strahlentherapie des Primärtumors auch systemisch mit Docetaxel behandelt [887]. Wenn eine Docetaxel-Behandlung erfolgt, so wird eine

sequentielle Therapie empfohlen; die Androgendeprivation erfolgte dagegen in STAMPEDE „lifelong“, also auch simultan zur Strahlenbehandlung [887].

7.6. Therapie von Knochenmetastasen

7.58	Evidenzbasierte Empfehlung	modifiziert 2018
Empfehlungsgrad A	Die Therapie symptomatischer ossärer Metastasen ist Bestandteil des onkologischen Gesamtkonzeptes (siehe Empfehlungen 7.42, 7.46, 7.49, 7.50). Patienten mit ossären Metastasen soll zusätzlich eine oder mehrere der folgenden Therapieoptionen angeboten werden: · medikamentöse Schmerztherapie · lokale Bestrahlung, siehe Empfehlung 7.59 · operative Intervention (in der Regel in Kombination mit Bestrahlung).	
Level of Evidence bei den jeweiligen Empfehlungen	Literatur: [851,895,896]	
	Gesamtabstimmung: 86 %	

Zu Empfehlung 7.58:

Aufgrund der vorliegenden Daten muss derzeit geschlossen werden, dass eine Lebensverlängerung bei der spezifischen Therapie von Knochenmetastasen auch bei Therapie singulärer Metastasen in der Regel nicht erreicht wird. Einzelnen Studien zum Nutzen der perkutanen Bestrahlung oder zur Gabe von Radionukliden, in denen positive Überlebenszeiteffekte erzielt wurden, stehen andere Studien gegenüber, in denen solche Effekte nicht nachweisbar waren [896].

7.59	Evidenzbasierte Empfehlung	geprüft 2018
Empfehlungsgrad A	Die lokale perkutane Bestrahlung soll bei Knochenmetastasen in folgenden Situationen eingesetzt werden: • persistierende lokalisierte Knochenschmerzen • drohende spinale Kompression (ggf. nach operativer Intervention) • nach operativer Stabilisierung • erhöhtes Frakturrisiko	
Level of Evidence 1++	Literatur: [895]	
	Gesamtabstimmung: 97 %	

7.60	Evidenzbasierte Empfehlung	modifiziert 2021
Empfehlungsgrad 0	Radionuklide können bei multiplen Knochenmetastasen im kastrationsresistenten Stadium zur Schmerztherapie eingesetzt werden. Für die Indikation zu Radium-223 wird auf die Empfehlung 7.49 verwiesen.	
Level of Evidence 1+	Literatur: [896]	
	Gesamtabstimmung: 100 %	

Zu Empfehlung 7.60:

Für die Indikation zugelassene Radionuklide sind die genannten Substanzen Strontium-89 (St-89), Samarium-153 (Sm-153) und Rhenium-186 (Re-186). Die Radionuklide Sr-89 in einer Dosierung von 150-200 MBq und Sm-153 in einer Dosierung von 1,0 mCi/kg sind für die Intervention am besten untersucht (jeweils Vorliegen mehrerer Phase-III-RCTs). Bei der Applikation von Sr-89 setzt die Schmerzentlastung mit zwei bis drei Wochen nach Therapiebeginn etwas später ein als bei der Applikation von Sm-153 [895] mit ein bis zwei Wochen. […] Die in 60-80 % erzielte Schmerzlinderung hält bei dem überwiegenden Teil der Patienten im Median zwei bis vier Monate an. Darüber hinaus werden im Vergleich zu Placebo weniger neue schmerzhafte Herde angegeben [896,895]. […] Die Datenlage zu Radium-223 wird bei der Empfehlung 7.49 diskutiert [851].

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Prostate Cancer Version 2.2021-Februar 17, 2021

Zielsetzung/Fragestellung

The NCCN Guidelines for Prostate Cancer address staging and risk assessment after a prostate cancer diagnosis and include management options for localized, regional, and metastatic disease. Recommendations for disease monitoring and treatment of recurrent disease are also included.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;

- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert; All active NCCN Guidelines are reviewed and updated at least annually

Recherche/Suchzeitraum:

- Prior to the update of the NCCN Guidelines for Prostate Cancer, an electronic searchof the PubMed database was performed to obtain key literature in prostate cancerpublished since the previous Guidelines update, usingthe search term “prostate cancer.”

LoE/GoR

- For the ‘uniform NCCN consensus’ defined in Category 1 and Category 2A, a majority Panel vote of at least 85% is required. For the ‘NCCN consensus’ defined in Category 2B, a Panel vote of at least 50% (but less than 85%) is required. Lastly, for recommendations where there is strong Panel disagreement regardless of the quality of the evidence, NCCN requires a Panel vote of at least 25% to include and designate a recommendation as Category 3.
- The large majority of the recommendations put forth in the Guidelines are Category 2A. Where categories are not specified within the Guidelines, the default designation for the recommendation is Category 2A.

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

Empfehlungen

SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA[zz,ccc,ddd,eee]

No prior docetaxel/no prior novel hormone therapy[fff]	Prior novel hormone therapy/No prior docetaxel[fff,lll]
• Preferred regimens ‣ Abiraterone[t,ggg] (category 1[hhh]) ‣ Docetaxel[aaa,iii] (category 1) ‣ Enzalutamide[t] (category 1) •Useful in certain circumstances ‣ Sipuleucel-T[aaa,jjj] (category 1) ‣ Radium-223[kkk] for symptomatic bone metastases (category 1) •Other recommended regimens ‣ Other secondary hormone therapy[t]	• Preferred regimens ‣ Docetaxel (category 1)[aaa] ‣ Sipuleucel-T[aaa,jjj] • Useful in certain circumstances ‣ Olaparib for HRRm (category 1)[mmm] ‣ Cabazitaxel/carboplatin[aaa,nnn] ‣ Pembrolizumab for MSI-H or dMMR[aaa] ‣ Radium-223[kkk] for symptomatic bone metastases (category 1) ‣ Rucaparib for BRCAm[ooo] • Other recommended regimens ‣ Abiraterone[t,ggg] ‣ Abiraterone + dexamethasone[ggg,ppp] ‣ Enzalutamide[t] ‣ Other secondary hormone therapy[t]
Prior docetaxel/no prior novel hormone therapy[fff] • Preferred regimens ‣ Abiraterone[t, ggg] (category 1) ‣ Cabazitaxel[aaa] ‣ Enzalutamide[t] (category 1) • Useful in certain circumstances ‣ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[aaa] ‣ Cabazitaxel/carboplatin[aaa,nnn] ‣ Pembrolizumab for MSI-H or dMMR[aaa] ‣ Radium-223[kkk] for symptomatic bone metastases (category 1) • Other recommended regimens ‣ Sipuleucel-T[aaa,jjj] ‣ Other secondary hormone therapy[t]	Prior docetaxel and prior novel hormone therapy[fff,lll] (All systemic therapies are category 2B if visceral metastases are present) • Preferred regimens ‣ Cabazitaxel[aaa] (category 1[hhh]) ‣ Docetaxel rechallenge[aaa,eee] • Useful in certain circumstances ‣ Olaparib for HRRm (category 1)[hhh,mmm] ‣ Cabazitaxel/carboplatin[aaa,nnn] ‣ Pembrolizumab for MSI-H or dMMR[aaa] ‣ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[aaa] ‣ Radium-223[kkk] for symptomatic bone metastases (category 1[hhh]) ‣ Rucaparib for BRCAm[ooo] • Other recommended regimens ‣ Abiraterone[t,ggg] ‣ Enzalutamide[t] ‣ Other secondary hormone therapy[t]

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

FOOTNOTES t See Principles of Androgen Deprivation Therapy (PROS-G).zz Document castrate levels of testosterone if progression occurs on ADT. Workup for progression should include chest CT, bone imaging, and abdominal/pelvic CT with contrast or abdominal/pelvic MRI with and without contrast. Consider metastatic lesion biopsy. If small cell neuroendocrine is found, see PROS-15. See Principles of Imaging (PROS-C) and Discussion.aaa See Principles of Immunotherapy and Chemotherapy (PROS-H).ccc Visceral metastases refers to liver, lung, adrenal, peritoneal, and brain metastases. Soft tissue/lymph node sites are not considered visceral metastases. ddd Patients can continue through all treatment options listed. Best supportive care is always an appropriate option.eee Patients with disease progression on a given therapy should not repeat that therapy, with the exception of docetaxel, which can be given as a rechallengeafter progression on a novel hormone therapy in the metastatic CRPC setting in men who have not demonstrated definitive evidence of progression on prior docetaxel therapy in the castration-naïve setting.fff Novel hormone therapies include abiraterone, enzalutamide, darolutamide, or apalutamide received for metastatic castration-naïve disease, M0 CRPC, or previous lines of therapy for M1 CRPC.ggg The fine-particle formulation of abiraterone can be used instead of the standard form (other recommended option).hhh The noted category applies only if no visceral metastases.iii Although most patients without symptoms are not treated with chemotherapy, the survival benefit reported for docetaxel applies to those with or without symptoms. Docetaxel may be considered for patients with signs of rapid progression or visceral metastases despite lack of symptoms.jjj Sipuleucel-T is recommended only for asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, and ECOG performance status 0–1.Benefit with sipuleucel-T has not been reported in patients with visceral metastases and is not recommended if visceral metastases are present. Sipuleucel-T also is not recommended for patients with small cell/neuroendocrine prostate cancer.kkk Radium-223 is not recommended for use in combination with docetaxel or any other systemic therapy except ADT and should not be used in patients with visceral metastases. Concomitant use of denosumab or zoledronic acid is recommended. See Principles of Radiation Therapy (PROS-E).lll Consider AR-V7 testing to help guide selection of therapy (See Discussion).mmm Olaparib is a treatment option for patients with mCRPC and a pathogenic mutation (germline and/or somatic) in a homologous recombination repair gene (BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, or RAD54L) who have been treated with androgen receptor-directed therapy. Patients with PPP2R2A mutations in the PROfound trial experienced an unfavorable risk-benefit profile. Therefore, olaparib is not recommended in patients with a PPP2R2A mutation. There may be heterogeneity of response to olaparib for non-BRCA mutations based on which gene has a mutation. (See Discussion).nnn Cabazitaxel 20 mg/m² plus carboplatin AUC 4 mg/mL per min with growth factor support can be considered for fit patients with aggressive variant prostate cancer (visceral metastases, low PSA and bulky disease, high LDH, high CEA, lytic bone metastases, NEPC histology) or unfavorable genomics (defects in at least 2 of PTEN, TP53, and RB1). Corn PG, et al. Lancet Oncol 2019;20:1432-1443.ooo Rucaparib is a treatment option for patients with mCRPC and a pathogenic BRCA1 or BRCA2 mutation (germline and/or somatic) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy. If the patient is not fit for chemotherapy, rucaparib can be considered even if taxane-based therapy has not been given.ppp Switching from prednisone to dexamethasone 1 mg/day can be considered for patients with disease progression on either

formulation of abiraterone. Trials show improved PSA responses and PFS and acceptable safety using this strategy. Romero-Laorden N, et al. Br J Cancer 2018;119:1052-1059 and Fenioux C, et al. BJU Int 2019;123:300-306.

Hintergrund

PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

Secondary Hormone Therapy for M0 or M1 CRPC

- Androgen receptor activation and autocrine/paracrine androgen synthesis are potential mechanisms of recurrence of prostate cancer during ADT (CRPC). Thus, castrate levels of testosterone (<50 ng/dL) should be maintained by continuing LHRH agonist or degarelix while additional therapies are applied.
- Once the tumor becomes resistant to initial ADT, there are a variety of options that may afford clinical benefit. The available options are based on whether the patient has evidence of metastases by conventional imaging, M0 CRPC vs. M1 CRPC, and whether or not the patient is symptomatic.
- Administration of secondary hormonal therapy can include:
  - Second-generation antiandrogen
    - Apalutamide (for M0 and PSADT ≤10 months)
    - Darolutamide (for M0 and PSADT ≤10 months)
    - Enzalutamide (for M0 and PSADT ≤10 months or M1)
  - Androgen metabolism inhibitor
    - Abiraterone + prednisone (for M1 only)
    - Fine-particle abiraterone + methylprednisolone (for M1 only)
  - Other secondary hormone therapy (for M0 or M1)
    - Ketoconazole
    - Ketoconazole plus hydrocortisone
    - First-generation antiandrogen (nilutamide, flutamide, or bicalutamide)
    - Corticosteroids (hydrocortisone, prednisone, ordexamethasone)
    - Estrogens including diethylstilbestrol (DES)
    - Antiandrogen withdrawal
- Abiraterone should be given with concurrent steroid, either prednisone 5 mg orally twice daily for the standard formulation or methylprednisolone 4 mg orally twice daily for the fine-particle formulation. Neither formulation of abiraterone should be given following progression on the other formulation.
- Ketoconazole ± hydrocortisone should not be used if the disease progressed on abiraterone.
- DES has cardiovascular and thromboembolic side effects at any dose, but frequency is dose and agent dependent. DES should be initiated at 1 mg/day and increased, if necessary, to achieve castrate levels of serum testosterone (<50 ng/dL). Other estrogens delivered topically or parenterally may have less frequent side effects but data are limited.
- In a randomized controlled trial in the setting of M1 CRPC prior to docetaxel chemotherapy, abiraterone, and low-dose prednisone (5 mg BID) compared to prednisone alone improved radiographic progression-free survival (rPFS), time to initiation of chemotherapy, time to onset or worsening of pain, and time to deterioration of performance status. An improvement in overall survival was demonstrated. Use of abiraterone and prednisone in this setting is a category 1

recommendation. The side effects of abiraterone that require ongoing monitoring include hypertension, hypokalemia, peripheral edema, atrial fibrillation, congestive heart failure, liver injury, and fatigue, as well as the known side effects of ADT and long-term corticosteroid use.

- A phase 3 study of docetaxel-naïve men with M1 CRPC showed that enzalutamide (160 mg daily) resulted in significant improvement in rPFS and overall survival. The use of enzalutamide in this setting is category 1. The side effects of enzalutamide that require long-term monitoring include fatigue, diarrhea, hot flashes, headache, and seizures (reported in 0.9% of men on enzalutamide).
- For symptomatic patients with M1 CRPC, all secondary hormone options listed above are allowed, but initial use of docetaxel may be preferred. Both randomized trials of abiraterone and enzalutamide in the pre-docetaxel setting were conducted in men who had no or minimal symptoms due to M1 CRPC. How these agents compare to docetaxel for pain palliation in this population of patients is not clear. Both drugs have palliative effects in the post-docetaxel setting. Both abiraterone and enzalutamide are approved in this pre-docetaxel setting and have category 1 recommendations. Both drugs are suitable options for men who are not good candidates to receive docetaxel.
- In the post-docetaxel M1 CRPC population, enzalutamide and abiraterone plus prednisone have been shown to extend survival in randomized controlled trials. Therefore, each agent has a category 1 recommendation.
- Two randomized clinical trials (STRIVE and TERRAIN) showed that 160 mg/day enzalutamide improved PFS compared to 50 mg/day bicalutamide in men with treatment-naïve M1 CRPC and, therefore, enzalutamide may be the preferred option in this setting. However, bicalutamide can still be considered in some patients, given the different side effect profiles of the agents and the increased cost of enzalutamide.
- Evidence-based guidance on the sequencing of agents in either pre- or post-docetaxel remains unavailable.

<u>ADT for Patients on Observation Who Require Treatment and Those with Life Expectancy ≤5 Years</u>

- Treatment for patients who progressed on observation of localized disease is LHRH agonist or antagonist or orchiectomy.

PRINCIPLES OF IMMUNOTHERAPY AND CHEMOTHERAPY

<u>Systemic Therapy for M1 CRPC</u>

<u>Chemotherapy</u>

- Docetaxel with concurrent steroid
  - Concurrent steroids may include: dexamethasone on the day of chemotherapy or daily prednisone.
- Cabazitaxel/carboplatin with concurrent prednisone twice daily
  - Concurrent steroids may include: dexamethasone on the day of chemotherapy or daily prednisone.
- Mitoxantrone with prednisone
- Every-3-week docetaxel with concurrent steroid is the preferred first-line chemotherapy treatment based on phase 3 clinical trial data for men with symptomatic mCRPC. Radium-223 has been studied in symptomatic patients who are not candidates for docetaxel-based regimens and resulted in improved overall survival. Abiraterone and enzalutamide have been shown to extend survival in patients who progressed on

docetaxel. (See PROS-G). Mitoxantrone with prednisone may provide palliation but have not been shown to extend survival.

- Only regimens utilizing docetaxel on an every-3-week schedule demonstrated beneficial impact on survival. The duration of therapy should be based on the assessment of benefit and toxicities. In the pivotal trials establishing survival advantage of docetaxel-based chemotherapy, patients received up to 10 cycles of treatment if no progression and no prohibitive toxicities were noted.
- Patients who are not candidates for docetaxel or who are intolerant of docetaxel should be considered for cabazitaxel with concurrent steroid, based on recent results that suggest clinical activity of cabazitaxel in mCRPC. Cabazitaxel was associated with lower rates of peripheral neuropathy than docetaxel, particularly at 20 mg/m2 (12% vs. 25%) and may be appropriate in patients with pre-existing mild peripheral neuropathy. Current data do not support greater efficacy of cabazitaxel over docetaxel.
- Increasing PSA should not be used as the sole criteria for progression. Assessment of response should incorporate clinical and radiographic criteria.
- Cabazitaxel at 25 mg/m² with concurrent steroid has been shown in a randomized phase 3 study (TROPIC) to prolong overall survival, PFS, and PSA and radiologic responses when compared with mitoxantrone with prednisone and is FDA approved in the post-docetaxel second-line setting. Toxicity at this dose was significant and included febrile neutropenia, severe diarrhea, fatigue, nausea/vomiting, anemia, thrombocytopenia, sepsis, and renal failure. A recent trial, PROSELICA, compared cabazitaxel 25 mg/m² every 3 weeks to 20 mg/m² every 3 weeks. Cabazitaxel 20 mg/m² had less toxicity; febrile neutropenia, diarrhea, and fatigue were less frequent. Cabazitaxel at 20 mg/m² had a significantly lower PSAresponse rate but nonsignificantly lower radiographic response rate and non-significantly shorter PFS and overall survival (13.4 months vs. 14.5 months) compared to 25 mg/m². Cabazitaxel starting dose can be either 20 mg/m² or 25 mg/m² for men with mCRPC who have progressed despite prior docetaxel chemotherapy. Cabazitaxel 25 mg/m² with concurrent steroid may be considered for healthy men who wish to be more aggressive. Growth factor support may be needed with either dose.
- Cabazitaxel at 25 mg/m2 with concurrent steroid improved radiographic PFS and reduced the risk of death compared with abiraterone or enzalutamide in patients with prior docetaxel treatment for mCRPC in the CARD study.
- Cabazitaxel 20 mg/m² plus carboplatin AUC 4 mg/mL per minute with growth factor support can be considered for fit patients with aggressive variant prostate cancer (ie, visceral metastases, low PSA and bulky disease, high LDH, high CEA, lytic bone metastases, NEPC histology) or unfavorable genomics (defects in at least 2 of PTEN, TP53, and RB1). Corn PG, et al. Lancet Oncol 2019;20:1432-1443.
- Docetaxel retreatment can be attempted after progression on a novel hormone therapy in men with metastatic CRPC who have not demonstrated definitive evidence of progression on prior docetaxel therapy in the castration-naïve setting.
- No chemotherapy regimen to date has demonstrated improved survival or quality of life after cabazitaxel, and trial participation should be encouraged.
- Treatment decisions around off-label chemotherapy use in the treatment-refractory CRPC should be individualized based on comorbidities and functional status and after informed consent.
- No benefits of combination approaches over sequential single-agent therapies have been demonstrated, and toxicity is higher with combination regimens.

Targeted Therapy

- Consider inclusion of olaparib in men who have anHHR mutation and have progressed on prior treatment with androgen receptor-directedtherapy regardless of prior docetaxel therapy.
- Consider inclusion of rucaparib for patients with mCRPC and a pathogenic BRCA1or BRCA2mutation (germline and/or somatic) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy. If the patient is not fit for chemotherapy, rucaparib can be considered even if taxane-based therapy has not been given.

Immunotherapy

- Men with asymptomatic or minimally symptomatic mCRPC may consider immunotherapy.
- Pembrolizumab (for MSI-H or dMMR)
  - Only as subsequent systemic therapy for patients with metastatic CRPC who have progressed through prior docetaxel and/or a novel hormone therapy.

Progression to and Management of CRPC

- ADT is continued in patients with metastatic CRPCwhile additional therapies, including secondary hormone therapies, chemotherapies, immunotherapies, radiopharmaceuticals, and/or targeted therapies, are sequentially applied, as discussed in the sections that follow, and should receive best supportive care. Patients with disease progression on a given therapy should not repeat that therapy, with the exception of docetaxel, which can be given as a rechallenge in the second-or subsequent-line metastatic CRPC setting if given in the castration-naive setting in patients who have not demonstrated definitive evidence of progression on prior docetaxel therapy.The decision to initiate therapy in the second and subsequent lines CRPC setting should be based on the available high-levelevidence of safety, efficacy, and tolerability of these agents and the application of this evidence to an individual patient. Prior exposures to therapeuticagents should be considered. There are not much data to informtheoptimalsequence for deliveryof these agents in men with metastatic CRPC (see Sequencing of Therapy in CRPC, below). Choice of therapy is based largely on clinical considerations, which include patient preferences, prior treatment, presence or absence of visceral disease, symptoms, andpotential side effects.

Secondary Hormone Therapy for CRPC

Research has shown enhancement of autocrine and/or paracrine androgen synthesis in the tumor microenvironment of menreceiving ADT.[674,675]Androgen signaling consequent to non-gonadal sources of androgen in CRPC refutes earlier beliefs that CRPC was resistant to further hormone therapies. The development of novel hormonal agents demonstrating efficacy in the non-metastatic and metastatic CRPC setting dramatically changed the paradigm of CRPC treatment.

- Abiraterone Acetate in M1 CRPC
  - Based on the studies described here, abiraterone is a category 1, preferred option in first-line therapy for metastatic CRPC, regardless of previous docetaxel therapy, in the second-line setting following docetaxel, and in subsequent line therapy in the absence of visceral metastases.

    Hintergrund: Based on the results of a phase 3, randomized, placebo-controlledtrial (COU-AA-301) in menwith metastatic CRPC previously treated with docetaxel-

containing regimens.676,677Patients were randomized to receive either abiraterone 1000 mg orally once daily (n = 797) or placebo once daily (n =398), and botharms received daily prednisone. In the final analysis, median survival was 15.8 versus 11.2 months in the abiraterone and placebo arm, respectively (HR, 0.74; 95% CI, 0.64–0.86; P<.0001).[677] Time to radiographicprogression, PSA decline, and pain palliationalso were improved by abiraterone.[677,678] FDA approval in the pre-docetaxel setting occurred on December 10, 2012,and was based on therandomized phase 3 COU-AA-302 trial of abiraterone and prednisone (n = 546) versusprednisone alone(n = 542) in men with asymptomatic or minimally symptomatic, metastatic CRPC.[679] Most men in this trial were not taking narcotics for cancer pain and none had visceral metastatic disease or prior ketoconazole exposure. The coprimary endpoint of radiographic PFSwas improved by treatment from 8.3 to 16.5 months (HR,0.53; P< .001). OS was improved at final analysis with a median follow-up of 49.2 months (34.7 months vs.30.3 months; HR, 0.81; 95% CI, 0.70–0.93; P= .003).[680]

- Enzalutamidein M0 and M1 CRPC
  - Thus, enzalutamide represents a category 1, preferred treatment option for men in both the pre-docetaxel and post-docetaxel metastatic CRPC setting.

    Hintergrund: Based on the results of the randomized, phase 3, placebo-controlled trial (AFFIRM).[686,687] AFFIRMrandomized 1199 men to enzalutamide or placebo in a 2:1 ratio and the primary endpoint was OS. Median survival was improved with enzalutamide from 13.6 to 18.4 months (HR, 0.63;P<.001). […] Another phase 3trial studied enzalutamide in the pre-chemotherapy setting. The PREVAIL study randomly assigned 1717 patients with chemotherapy-naïvemetastatic prostate cancer to daily enzalutamide or placebo.[689,690] The study was stopped early due to benefits shown in the treatment arm.
- Other Secondary Hormone Therapies
  - Other options for secondary hormone therapy include a first-generation antiandrogen, antiandrogen withdrawal, ketoconazole (adrenal enzyme inhibitor) with or without hydrocortisone, corticosteroid, or estrogens including diethylstilbestrol (DES).[703,704] However, none of these strategies has yet been shown to prolong survival in randomized clinical trials.

Chemotherapy, Immunotherapy, and Targeted Therapy

- Docetaxel
  - Thus, docetaxel is a category 1 preferred option for first-line treatment of metastatic CRPC and in second-line post abiraterone or enzalutamide. The panel believes that docetaxel can be given as a rechallenge in the second-or subsequent-line metastatic CRPC setting if given in the castration-naive setting.

    Hintergrund: Men with low-volume metastatic diseasecan be offered early treatment with docetaxel combined with ADT; however, they have less certain benefit fromtreatment than men with higher-volume disease, as this subgroup did nothavedefinitivelyimproved survival outcomes in the ECOG CHAARTED study or a similar European trial (GETUG-AFU 15).[717,719,720]Meta-analyses of randomized controlled trials also concluded that docetaxel provides a significant OS benefit in this setting, with no evidence that the benefit was dependent on the volume of disease.[721-723] […]
- Cabazitaxel
  - The NCCN Guidelines Panel included cabazitaxel as an option for second-line therapy after progression on docetaxel for patients with symptomatic metastatic CRPC. This

recommendationis category 1 based on randomized phase 3 study data (see Cabazitaxel, above).[727,731]NCCN panelists agreed that docetaxel rechallenge may be useful in some patients (category 2A instead of category 1 in this setting), especially in those who have not shown definitive evidence of progression on prior docetaxel therapy.

Hintergrund: An international randomized phase 3trial (TROPIC) randomized 755 men with progressive metastatic CRPC to receive cabazitaxel 25 mg/m2or mitoxantrone 12 mg/m2, each with daily prednisone.[727]A 2.4-month improvement in OSwas demonstrated with cabazitaxelcompared tomitoxantrone (HR, 0.72; P< .0001).Theimprovement in survivalwas balanced against a higher toxic death rate with cabazitaxel(4.9% vs. 1.9%), which wasdue, in large part,to differences in rates of sepsis and renal failure. Recent results from the phase 3 FIRSTANAstudysuggested that cabazitaxel has clinical activity in patients with chemotherapy-naïve mCRPC.731Median OS, the primary endpoint, was similar between 20 mg/m2cabazitaxel, 25 mg/m2cabazitaxel, and 75 mg/m2docetaxel (24.5 months, 25.2 months, and 24.3 months, respectively). Cabazitaxel was associated with lower rates of peripheral sensory neuropathy thandocetaxel, particularly at 20 mg/m2(12% vs. 25%). Therefore, patients who are not candidates for docetaxel, who are intolerant of docetaxel, or who have pre-existing mild peripheral neuropathy should be considered for cabazitaxel.[731]

- Pembrolizumab
  - Based on the available data, the panel supports the use of pembrolizumab in patients with MSI-H or dMMR metastatic CRPC whose disease has progressed through at least one line of systemic therapy for M1 CRPC (category 2B).

    Hintergrund: A growing number of additional patientswithmetastatic CRPC treated with pembrolizumab have been reported.[79,739-743]In an early study, 10 patients with CRPC and non-visceral metastases (bone = 7; lymph nodes = 2; bone and liver =1) who had disease progression on enzalutamide were treated with pembrolizumab and enzalutamide.[739][…] Three of the 10 patients showed a near complete PSA response. Two of these three patients had radiographically measurable disease andachieved a partial radiographic response(including a response in liver metastases).[…] KEYNOTE-199 was a multi-cohort, open-label phase II studyin 258 patients with metastaticCRPC and prior treatment with docetaxel and at least one novel hormonal therapy that assessed pembrolizumab in patients regardless of MSI status.[744]Cohorts 1 and 2 included patients with PD-L1-positive (n = 133) and PD-L1-negative (n = 66) prostate cancer, respectively. Cohort 3 included those with bone-predominant disease with positive or negative PD-L1 expression (n = 59). The primary endpoint of ORR in cohorts 1 and 2 was 5% (95% CI, 2%–11%) in cohort 1 and 3% (95% CI, <1%–11%) in cohort 2.Responses were durable (range, 1.9 –≥ 21.8 months).[…]
- Mitoxantrone
  - Mitoxantrone can be used for palliation in symptomaticpatients with metastatic CRPC who cannot tolerate other therapies.

    Hintergrund: Two randomized trials assessed the role of mitoxantrone in patients with metastatic CRPC.[745,746] Although there was no improvement in OS, palliative responses and improvements in quality of life were seen withmitoxantrone.

Treatment Options for Patients with DNA Repair Gene Mutations

- Olaparib

- The panel recommends olaparib as an option for men with metastatic CRPC, previous abiraterone or enzalutamide, and a HRRm in:
    - 1)second-line after first-line abiraterone or enzalutamide regardless of prior docetaxel therapy[category 1];
    - 2) in second-line after docetaxel [category 2B];and
    - 3) in subsequent lines of therapy [category 1].

The HRR genes to be considered for use of olaparib are BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D andRAD54L. Patients with PPP2R2A mutations in the PROfound trial experienced an unfavorable risk-benefit profile; therefore, olaparib is not recommended in patients with a PPP2R2A mutations.

Hintergrund: Preliminary clinical data using olaparibsuggested favorable activity of this agent in patients with HRR gene mutations, but not in those without HRR mutations.[748,749,760]

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2021 Canadian Urological Association (CUA)-Canadian Uro Oncology Group (CUOG) guideline [20].

Management of castration-resistant prostate cancer (CRPC)

Zielsetzung/Fragestellung

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- This is an update of CUA guideline previously published online June 25, 2019
- MEDLINE search of the English language and conference proceedings were used to produce the present document.
- Methodikeranmerkung: kein Hinweis auf den Suchzeitraum

LoE/GoR

- Wherever Level 1 evidence is lacking, the guideline attempts to provide expert opinion to aid in the management of patients.
- Levels of evidence and grades of recommendation employ the International Consultation on Urologic Disease (ICUD)/WHO modified Oxford Center for Evidence-Based Medicine grading system. Based on a modified GRADE methodology,
- The strength of each recommendation is represented by the words STRONG or WEAK.
- Grading: ICUD https://onlinelibrary.wiley.com/doi/epdf/10.1002/nau.20845
  - Level 1 evidence (incorporates Oxford 1a, 1b) usually involves meta-analysis of trials (RCTs) or a good quality randomized controlled trial, or ‘‘all or none’’ studies in which no treatment is not an option, for example, in vesicovaginal fistula.
  - Level 2 evidence (incorporates Oxford 2a, 2b, and 2c) includes‘‘low’’ quality RCT (e.g., <80% follow-up) or meta-analysis (with homogeneity) of good quality prospective ‘‘cohort studies.’’ These may include a single group when individuals who develop the condition are compared with others from within the original cohort group. There can be parallel cohorts, where those with the condition in the first group are compared with those in the second group.
  - Level 3 evidence (incorporates Oxford 3a, 3b, and 4) includes:
    - Good quality retrospective ‘‘case–control studies’’ where a group of patients who have a condition are matched appropriately (e.g., for age, sex, etc.) with control individuals who do not have the condition.

- Good quality ‘‘case series’’ where a complete group of patients all, with the same condition/disease/therapeutic intervention, are described, without a comparison control group.

- Level 4 evidence (incorporates Oxford 4) includes expert opinion where the opinion is based not on evidence but on ‘‘first principles’’ (e.g., physiological or anatomical) or bench esearch. The Delphi process can be used to give ‘‘expert opinion’’ greater authority. In the Delphi process a series of questions are posed to a panel; the answers are collected into a series of ‘‘options’’; the options are serially ranked; if a 75% agreement is reached then a Delphi consensus statement can be made

Grade A recommendation usually depends on consistent Level 1 evidence and often means that the recommendation is effectively mandatory and placed within a clinical care pathway. However, there will be occasions where excellent evidence (Level 1) does not lead to a Grade A recommendation, for example, if the therapy is prohibitively expensive, dangerous, or unethical. Grade A recommendation can follow from Level 2 evidence. However, a Grade A recom- mendation needs a greater body of evidence if based on anything except Level 1 evidence.

Grade B recommendation usually depends on consistent Level 2 and/or 3 studies, or ‘‘majority evidence’’ from RCTs.

Grade C recommendation usually depends on Level 4 studies or ‘‘majority evidence’’ from Level 2/3 studies or Delphi processed expert opinion.

Grade D ‘‘No recommendation possible’’ would be used where the evidence is inadequate or conflicting and when expert opinion is delivered without a formal analytical process, such as by Delphi.

Sonstige methodische Hinweise

- Rückfrage an Leitlinienansprechpartner ohne Antwort:
  - Keine Hinweise zu Gremium,
  - Keine Hinweise auf Suchzeitraum
- PROfound Studie zu Olaparib nicht zitiert (Studienabschluss)

Empfehlungen

Treatment of mCRPC

I. AR signaling therapeutic options

Abiraterone acetate

In the chemo-naive setting:

- Recommendation: Abiraterone acetate 1000 mg/day plus prednisone 5 mg twice daily is recommended for first-line therapy for asymptomatic or minimally symptomatic mCRPC (**Level 1, Strong recommendation**).

  Hintergrund: In asymptomatic or minimally symptomatic patients (defined as pain that is relieved by acetaminophen or a non-steroidal anti-inflammatory) without visceral metastases, abiraterone acetate significantly improved radiographic PFS (16.5 vs. 8.3 months) (HR 0.53; 95% CI 0.45–0.62; p<0.001) and had a statistically significant 4.4-month improvement in OS (HR 0.81; p=0.0033).[13,14] Abiraterone also significantly delayed time to pain progression, time to chemotherapy initia-tion, time to opiate initiation, and deterioration of the Eastern Cooperative Oncology Group (ECOG) performance status.

In the post-docetaxel setting:

- Recommendation: Abiraterone acetate 1000 mg per day plus prednisone 5 mg twice daily is recom-mended in patients progressing on or after docetaxel-based chemotherapy (**Level 1, Strong recommendation**).

  Hintergrund: In the post-docetaxel setting, abiraterone-prednisone compared to placebo-prednisone significantly prolonged median OS by 4.6 months (15.8 vs. 11.2 months; HR 0.74; p=0.0001) in patients with mCRPC who had progressed after docetaxel treatment. Moreover, all secondary endpoints pro-vided support for the superiority of abiraterone over pla-cebo: median time to PSA progression (8.5 vs.6.6 months; HR 0.63; p<0.0001), radiographic PFS (5.6 vs.3.6 months; HR 0.66; p<0.0001), confirmed PSA response rate defined as ≥50% reduction in PSA from the pretreatment baseline PSA (29% vs. 5.5%; p<0.0001), and objective response by Response Evaluation Criteria in Solid Tumors (RECIST) (14.8% vs. 3.3%; p<0.0001).[15]

Enzalutamide

In the chemo-naive setting:

- Recommendation: Enzalutamide 160 mg per day is recommended as first-line therapy for asymptom-atic or minimally symptomatic mCRPC (**Level 1, Strong recommendation**).

  Hintergrund: In asymptomatic or minimally symptomatic patients (defined as pain that is relieved by acetaminophen or a non-steroidal anti-inflammatory), enzalutamide decreased the risk of radiographic progression or death by 81% (HR 0.19; 95% CI 0.15–0.23; p<0.001) and the risk of death by 29% (HR 0.71; 95% CI 0.60–0.84; p<0.001) as compared to placebo. The benefit of enzalutamide was demonstrated for all secondary endpoints, including time to initiation of cytotoxic chemotherapy, time to first skeletal-related event (SRE), best overall soft tissue response (59% vs. 5%; p<0.001), time to PSA progression (HR 0.17; p<0.001), and ≥50% PSA decline rate (78% vs. 4%; p<0.001). Enzalutamide also significantly delayed time to pain progression, time to opiate initiation, and deterioration of the ECOG performance status.[16,17]

In the post-docetaxel setting:

- Recommendation: Enzalutamide 160 mg per day is recommended in patients progressing on or after docetaxel-based chemotherapy (**Level 1, Strong recommendation**).

  Hintergrund: In patients previously treated with docetaxel, the trial compared enzalutamide and placebo. The study demon-strated a significant advantage in OS of 4.8 months (18.4 vs. 13.6 months; HR 0.62; p<0.0001) and in all secondary endpoints, including confirmed PSA response rate (54% vs. 2%; p<0.001), soft-tissue response rate (29% vs. 4%; p<0.001), time to PSA progression (8.3 vs. 3.0 months; HR 0.25; p<0.001), radiographic PFS (8.3 vs. 2.9 months; HR 0.40; p<0.001), and the time to the first SRE (16.7 vs. 13.3 months; HR 0.69; p<0.001).[18]

- NOTE: The studies in the chemo-naive setting did not include patients with moderate or severe symptoms; how-ever, abiraterone and enzalutamide may be potential thera-peutic options in patients who are deemed chemotherapy-ineligible or refuse chemotherapy (Expert opinion).

II. Chemotherapy

First-line systemic chemotherapy

Docetaxel

- Recommendation: Docetaxel 75 mg/m2 intravenous (IV) every three weeks with 5 mg oral prednisone twice daily is recommended for patients with mCRPC (**Level 1, Strong recommendation**).

  Hintergrund: The TAX-327 study randomized 1006 patients to one of three treatment arms: 1) docetaxel 75 mg/m2 IV every three weeks; 2) docetaxel 30 mg/m2 weekly for five of six weeks; or 3) control therapy with mitoxantrone.[19] The study report-ed improved survival with docetaxel (every three weeks) compared with mitoxantrone-prednisone (median survival 18.9 vs. 16.5 months; HR 0.76; 95% CI 0.62–0.94; two-sided p=0.009). No OS benefit was observed with docetaxel given on a weekly schedule (HR 0.91; 95% CI 0.75–1.11; two-sided p=0.36). Significantly, more patients treated with docetaxel (every three weeks) achieved a pain response compared with patients receiving mitoxantrone (35% vs. 22%; p=0.01). Quality of life response, defined as a sus-tained 16-point or greater improvement from baseline on two consecutive measurements, was higher with docetaxel given every three weeks (22% vs. 13%; p=0.009) or weekly (23% vs. 13%; p=0.005) compared with mitoxantrone. PSA response rates were also statistically significantly higher with docetaxel compared to mitoxantrone.[19] Although patients received up to 10 cycles of treatment if no progression and no prohibitive toxicities were noted, the duration of therapy should be based on the assessment of benefit and toxicities. Rising PSA alone should not be used as the sole criteria for progression; assessment of response should incorporate clinical and radiographic criteria.
- Recommendation: Alternative therapies that have not demonstrated improvement in OS but can provide disease control, palliation, and improve quality of life include weekly docetaxel plus prednisone, and mitoxantrone plus prednisone **(Level 2, Weak recommendation**).
- Recommendation: The timing of docetaxel therapy in men with evidence of metastases but without symptoms should be discussed with patients, and therapy should be individualized based on patients' clinical status and preferences (**Level 3, Weak recommendation**).
- Recommendation: Patients who do not respond to first-line ADT or who progress clinically or radiologically without significant PSA elevations may have neuroendocrine differentiation. Biopsy of accessible lesions should be considered to identify these patients; these patients should then be treated with combination chemotherapy, such as cisplatin/etoposide or carbo-platin/etoposide (**Level 3, Weak recommendation**).

Second-line systemic chemotherapy

Cabazitaxel

- Recommendation: Cabazitaxel is recommended for mCRPC patients pro-gressing on or following docetaxel **(Level 1, Strong recommendation**).

  Hintergrund: A phase 3 study comparing cabazitaxel to mitoxantrone in patients previously treated with docetaxel has shown a statistically significant survival advantage.[20] This randomized, placebo-controlled trial recruited 755 docetaxel-pretreated CRPC patients. OS was the primary endpoint of the study. Patients were randomized to receive prednisone 10 mg/day with three times weekly mitoxantrone 12 mg/m2 or cabazi-taxel 25 mg/m2. An advantage in survival emerged in favor of the cabazitaxel group, with a median survival of 15.1 months compared with 12.7 months in the mitoxantrone group (HR 0.70; 95% CI 0.59, 0.83; p<0.0001).20A recent phase 3 study comparing cabazitaxel 25 mg/m2vs. 20 mg/m2 resulted in non-inferiority for

cabazitaxel 20 mg/m2 with less adverse events. Of note, in the subgroup analysis of patients who had received both docetaxel and abiraterone/enzalutamide, results appeared to favor a higher dose of cabazitaxel.[21]

Other options

- Recommendation: For patients who have had a good response to first-line docetaxel, re-treatment with docetaxel can be considered (**Expert opinion, Weak recommendation**).[22,23]

  Hintergrund: Mitoxantrone has not shown any survival advantage but may provide symptomatic relief. Mitoxantrone may be considered a therapeutic option in symptomatic patients with mCRPC in the first- or second-line setting (Expert opinion, Weak recommendation).

III. Bone-targeted therapy

Life-prolonging therapy

Radium-223

- Recommendation: Radium-223 every four weeks for six cycles is recommended in patients with pain due to bone metastases and who do not have visceral metastases (**Level 1, Strong recommendation**).

  Hintergrund: Radium-223 (previously known as alpharadin) is an intravenous alpha-emitting agent that mimics calcium, preferentially targeting bone metastases. In a random-ized, phase 3 study, radium-223 given every four weeks for six cycles was compared to placebo.20 Radium-223 demonstrated a significant improvement in OS and symp-tomatic SREs. OS was improved by 3.6 months (HR 0.7; p<0.0001) and symptomatic SREs were delayed by 5.8 months (p<0.0001). The study included patients with symptomatic bone metastases who were post-docetaxel or ineligible for docetaxel.[24] The study excluded patients with visceral metastases or lymph node metastases greater than 3 cm. PSA measurements while receiving radium-223 cannot provide evidence of whether patients are benefitting or not. Given the mechanism of action of the drug, alka-line phosphatase appears to be better marker of activity. A phase 3 study in the first-line mCRPC setting compared radium-223 in combination with abiraterone/prednisone vs. abiraterone/prednisone alone and demonstrated no advantage and an increased risk of fractures.[25]

  Recommendation Radium-223 should not be combined with abiraterone. A bone-supportive agent (denosumab or zoledronic acid) should always be used when using radium-223 (**Level 1, Strong recommendation**).

Patients with homologous recombination repair (HRR) mutations

Olaparib

- Recommendation Olaparib 300 mg twice daily is recommended for patients with mCPRC and HRR mutation who have progressed on a previous androgen receptor-axis-targeted therapy (ARAT) (**Level 1, Strong recommendation**).

  Hintergrund: HRR gene mutations occur in approximately 20–30% of prostate cancers from patients with metastatic disease, with the most common altered gene being BRCA2. Defective HRR renders a cancer susceptible to poly (ADP-ribose) polymerase (PARP) inhibition in a form of synthetic lethal-ity. A randomized, phase 3 trial (PROfound) compared the PARP inhibitor, olaparib 300 mg BID, with physician's choice enzalutamide/abiraterone in patients with mCRPC with HRR mutations. Patients with HRR mutations and progression on prior enzalutamide and/or abiraterone with or

without prior exposure to a taxane (docetaxel, cabazitaxel) were eligible. The primary endpoint of the study was radiographic PFS in patients with BRCA1/2 or ATM mutations. Results favored olaparib (7.39 vs. 3.44 months [HR 0.34, 95% CI (0.25, 0.47 p<0.001). The final results for OS also demonstrated a signifi-cant improvement among men with BRCA1/2 or ATM mutations, with a median OS of 19.1 vs. 14.7 months (HR 0.69, 95% CI 0.50, 0.97, p=0.02). Of note, from patients in the physician's choice of enzalutamide/abiraterone arm who progressed, 67% crossed over to receive olaparib. Adjusting for crossover results in a HR 0.42 (95% CI 0.19, 0.91). Other key secondary endpoints include significant improvements in overall measur-able response rates of 33.3% vs. 2.3% (odds ratio [OR] 20.86, 95% CI 4.18, 379.18, p<0.001) and delay in pain progression (HR 0.44, 95% CI 0.22, 0.91, p=0.0192). Adverse events were more common in the olaparib arm (anemia, fatigue, nausea, diarrhea), however, patients reported health-related quality of life was improved in the olaparib arm of the study.(Methodikeranmerkung: PROfound Studie nicht in LL zitiert)

Zusammenfassung:

2021 CUA-CUOG CRPC guideline summary

Castration-resistant prostate cancer (CRPC) includes a wide range of disease types: from patients without metastases or symptoms with rising prostate-specific antigen (PSA) levels despite androgen deprivation therapy (ADT) to patients with metastases and significant debilitation due to cancer symptoms.

Androgen deprivation therapy

Because androgen receptor remains active in most patients who have developed castration-resistant disease, it is recommended that ADT be continued for the remainder of a patient's life *(Strong recommendation).*

II. Chemotherapy-naive metastatic CRPC (mCRPC) without symptoms or minimally symptomatic

1. **Abiraterone acetate 1000 mg/day plus prednisone 5 mg/twice daily is recommended as first-line therapy** *(Level 1, Strong recommendation).*
2. **Enzalutamide 160 mg/day is recommended as first-line therapy** *(Level 1, Strong recommendation).*
3. **Docetaxel 75 mg/m² every three weeks plus 5 mg oral prednisone twice daily can be offered** *(Level 1, Strong recommendation).* The timing of docetaxel therapy in men with evidence of metastases but without symptoms should be discussed with the patient and therapy should be individualized based on the patient's clinical status and preference.

III. mCRPC with moderate or severe symptoms

1. **Docetaxel 75 mg/m² every three weeks plus 5 mg oral prednisone twice daily is recommended** *(Level 1, Strong recommendation).*
2. **Radium-223 every four weeks for six cycles is recommended in patients with pain due to bone metastases and who do not have visceral metastases** *(Level 1, Strong recommendation).* Radium-223 significantly improved overall survival and reduced symptomatic skeletal-related events in patients with symptomatic mCRPC who had previously received docetaxel chemotherapy or were deemed unfit for docetaxel.
3. **Abiraterone acetate 1000 mg/day plus prednisone 5 mg twice daily or enzalutamide 160 mg/day may be considered as first-line therapy in patients who cannot receive or refuse docetaxel** *(Expert opinion).*

IV. mCRPC who progress after docetaxel-based chemotherapy

Options with survival benefit

1. **Cabazitaxel (25 mg/m²) plus prednisone (5 mg/day)** *(Level 1, Strong recommendation).*
2. **Radium-223 every four weeks for six cycles** *(Level 1, Strong recommendation).*
3. **If not received prior to docetaxel:**
   i. **Abiraterone acetate (1000 mg per day) plus prednisone (5 mg twice daily)** *(Level 1, Strong recommendation)*
   ii. **Enzalutamide (160 mg/day)** *(Level 1, Strong recommendation)*

Options with unknown survival benefit

1. **Docetaxel plus prednisone re-exposure in patients who have had a previous favorable response to docetaxel may be reasonable** *(Expert opinion).*
2. **Mitoxantrone plus prednisone may be offered for palliative pain relief** *(Expert opinion, Weak recommendation).*

V. Patients with CRPC and bone metastases (includes the pre- or post-chemotherapy settings)

1. **Denosumab (120 mg subcutaneous) or zoledronic acid (4 mg intravenous) every four weeks, along with daily calcium and vitamin D supplementation is recommended to prevent disease-related skeletal complications** *(Level 1, Strong recommendation).*

VI. Patients with mCPRC and HRR mutation who have progressed on a previous ARAT with or without taxane exposure

1. **Olaparib 300 mg BID**

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González del Alba A et al., 2020 [13].

SEOM clinical guidelines for the treatment of advanced prostate cancer (2020)

Zielsetzung/Fragestellung

This guideline is focused on the systemic treatment of advanced prostate cancer

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium; nein (nur 10 Onkologen und keine PatV)
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz; keine Informationen
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt; nein
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Kein Suchzeitraum und keine db angegeben

LoE/GoR

Table 1 Levels of evidence and grades of recommendation

Category, grade	Criteria
Quality of evidence	
I	Evidence from at least 1 properly randomized, controlled trial *
II	Evidence from at least 1 well-designed clinical trial without randomization, from cohort or case-controlled analytical studies (Preferably from more than 1 centre), or from multiple time-series or dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities based on clinical Experience, descriptive studies, or reports of expert committees
Strength of recommendation	
A	Both strong evidence of efficacy and substantial clinical benefit Support recommendation for use. Should always be offered
B	Moderate evidence of efficacy—or strong evidence of efficacy but only limited clinical benefit—supports recommendation for use Should generally be offered
C	Evidence of efficacy is insufficient to support a recommendation For or against use, or evidence for efficacy might not outweigh adverse consequences (e.g., drug toxicity, drug interactions) or Cost of the chemoprophylaxis or alternative approaches Optional
D	Moderate evidence of lack of efficacy or of adverse outcome supports a recommendation against use Should generally not be offered
E	Good evidence of lack of efficacy or of adverse outcome supports a recommendation against use Should never be offered

Sonstige methodische Hinweise

- Developed based on the consensus of 10 genitourinary medical oncologists, designed by the Spanish Society of Medical Oncology (SEOM) and the Spanish Oncology Genitourinary Group (SOGUG)
- Es lässt sich keine Evidenztabelle finden

Empfehlungen:

Definition of castration-resistant prostate cancer (CPRC).

Therapeutic options for nmCRPC

Criteria for selecting the therapeutic sequence in mCPRC

Recommendations:

- Docetaxel—prednisone should be the first option for symptomatic patients who have received ADT alone. For asymptomatic or mildly symptomatic patients, docetaxel, abiraterone–prednisone or enzalutamide are recommended (**I, A**)
- In mCRPC patients who have progressed to docetaxel, abiraterone–prednisone, enzalutamide or cabazitaxel are recommended (**I, A**).
- In mCRPC patients who have progressed to a new generation anti-androgen therapy docetaxel-prednisone are recommended (**I, B**).
- Cabazitaxel is indicated as third line after a sequence of docetaxel and an androgen-signaling-targeted inhibitor (**I, A**).
- In mCRPC patients with symptomatic bone metastases and contraindication or progression to docetaxel, radium-223 may be considered (**I, B**).

Hintergrund: First-line treatment for mCRPC should be decided considering previous treatments and the population of patients that were included in the available trials. According to the TAX327 study [56], docetaxel improves symptoms and OS of patients who progressed to ADT. Symptomatic patients should receive docetaxel as first line, except in

case of contraindication (i.e., hypersensitivity or high risk for toxicity). An increase in OS and symptoms relief has also been demonstrated by adding abiraterone–prednisone or enzalutamide to ADT in asymptomatic or mildly symptomatic patients [57, 58]. No direct comparison between docetaxel, abiraterone, and enzalutamide has been performed to date. Patients with visceral metastases were only included in the pivotal trials of docetaxel and enzalutamide.

Abiraterone–prednisone [59], enzalutamide [60] and cabazitaxel (CBZ) [61] have shown OS benefit in randomized trials after docetaxel. For mCRPC patients who have previously received any new generation AR targeted therapy, the sequence of a different hormone drug failed in demonstrating a survival benefit [62, 63]. Based on the results of TAX327, it seems reasonable to indicate docetaxel in this scenario. The strongest evidence for a third line after docetaxel and a new generation AR targeted therapy comes from the CARD trial that compared cabazitaxel versus the new generation anti-androgen not previously administered [64]. Significant benefit was demonstrated both in PFS (HR: 0.54; 95% CI 0.40–0.73; p < 0.001) and OS (HR 0.64; 95% CI 0.46–0.89; p = 0.008]. According to these results, in absence of contraindication, cabazitaxel should be the third line of choice. In case of contraindication for chemotherapy, exclusive bone metastases and symptomatic disease, radium-223 may be considered, since OS benefit has been demonstrated in mCRPC [65]. The role of new targeted therapies in the sequence is discussed below.

Aggressive variants

Recommendation:

- Platinum-based chemotherapy should be considered the first option in mCRPC with clinicopathological characteristics of AVPC (**II, B**).

Hintergrund: AVPC is sensitive to platinum-based chemotherapies. In a single-arm sequential phase 2 trial, 120 patients with mCRPC and at least one of the seven prior criteria (including neuroendocrine markers on histology or serum) were treated with first-line carboplatin—docetaxel (CD) followed by second-line etoposide—cisplatin (EP). PFS after four courses of CD and EP were 65.4% and 33.8%, respectively. The median OS was 16 months (95% CI 13.6–19.0 m). Neuroendocrine markers did not predict outcome or response to therapy [69]. The same group recently published a phase 1–2 randomized trial of cabazitaxel vs the combination of carboplatin and cabazitaxel in 169 patients with progressive mCRPC, 56% of which met at least one of the prior criteria for AVPC [70]. A maximum tolerated dose of cabazitaxel at 25 mg/ m2 and carboplatin of AUC 4 was selected for phase 2. Prespecified subgroup analysis of PFS showed that the combination favored only patients with AVPC criteria (HR 0.58, 95% CI 0.37–0.89, *p* = 0.013).

New strategies in metastatic prostate cancer (MPC)

Recommendations:

- Olaparib is recommended in *BRCA1/BRCA2* mutated mCRPC patients after progression on at least one new generation AR targeted therapy [**I, A**]
- Immune checkpoint inhibitors may be considered in patients with microsatellite instability or mismatch repair deficiency [**II, B**]
- Currently, insufficient evidence is available in mCRPC to recommend Akt inhibitors [**I, C**] or radioligand therapy [**II, B**].

Hintergrund:

The randomized phase III double blind PROfound trial compared the PARP inhibitor olaparib versus abiraterone or enzalutamide in mCRPC patients with deleterious alterations in at least one of 15 genes involved in DDR, and previous treatment with one of these two AR signaling

inhibitor. In this study, 28% of the 2792 samples analyzed harbored an alteration in the HHR pathway. *BRCA2* was the gene most frequently altered (8.7%) followed by *CDK12* (6.3%), *ATM* (5.9%), *CHEK2* (1.2%), and *BRCA1* (1%). In cohort A (patients with *BRCA1, BRCA2* or *ATM* alterations), a significant benefit was observed for olaparib in rPFS (7.4 vs 3.6 months; HR 0.34; 95% CI 0.25–0.47). A longer OS was also observed (median OS 18.5 vs 15.1 months; HR: 0.64, 95% CI 0.43–0.97), despite crossover to olaparib in 66% of patients [73, 74] In the single-arm, phase II TRITON2 trial, Rucaparib showed a 43.5% ORR and 54.8% PSA response rate in *BRCA1/BRCA2* mutated mCRPC patients progressing after AR inhibitors and docetaxel [75].[…]

Loss of *PTEN* results in activation of the AKT pathway. In the phase III IPATential 150 trial, the combination of abiraterone and the AKT inhibitor ipatasertib showed a benefit in rPFS compared to abiraterone (HR 0.77, 95% CI 0.61–0.98; $p = 0.033$) in patients with PTEN loss as defined by IHC. Further follow-up and data on the impact on OS will be necessary to elucidate the role of Akt inhibitors in mCRPC.

[…] Pembrolizumab achieves ORR of 5–10% [78]. This drug has been approved for tumors MMR deficiency or MSI independent of the tumor type, accounting for 3–8% of MPC. Theragnostics, defined as the combination of a predictive biomarker with a therapeutic agent [79] is another still investigational promising strategy. Some trials with radioligands and PSMA a type II transmembrane overexpressed on prostatic cancer cells [80] are ongoing to clarify the role of RLT in the treatment algorithm of mCRPC [81].

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EAU, 2020 [3].

European Association of Urology (EAU)

Prostate cancer.

Zielsetzung/Fragestellung

To assist medical professionals in the evidence-based management of PCa.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert; This 2021 document presents an update of the 2020 PCa Guidelines publication.

Recherche/Suchzeitraum:

- Medline, EMBASE and the Cochrane library April 22, 2020

LoE/GoR

- GRADE

Table 4. EAU Guideline's levels of evidence

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

Table 5. EAU Guideline's grades of recommendation

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

Recommendations

6.5.15 Guidelines for systematic treatments of castrate-resistant disease

Recommendations	Strength rating
Base the choice of treatment on the performance status, symptoms, co-morbidities, location and extent of disease, genomic profile, patient preference, and on the previous treatment for hormone-sensitive metastatic PCa (mHSPC) (alphabetical order: abiraterone, cabazitaxel, docetaxel, enzalutamide, olaparib, radium-223, sipuleucel-T).	Strong
Offer patients with mCRPC who are candidates for cytotoxic therapy and are chemotherapy naïve docetaxel with 75 mg/m^2 every 3 weeks.	Strong
Offer patients with mCRPC and progression following docetaxel chemotherapy further life-prolonging treatment options, which include abiraterone, cabazitaxel, enzalutamide, radium-223 and olaparib in case of DNA homologous recombination repair (HRR) alterations.	Strong
Base further treatment decisions of mCRPC on performance status, previous treatments, symptoms, co-morbidities, genomic profile, extent of disease and patient preference.	Strong
Offer abiraterone or enzalutamide to patients previously treated with one or two lines of chemotherapy.	Strong
Avoid sequencing of androgen receptor targeted agents.	Weak
Offer chemotherapy to patients previously treated with abiraterone or enzalutamide.	Strong
Offer cabazitaxel to patients previously treated with docetaxel.	Strong
Offer cabazitaxel to patients previously treated with docetaxel and progressing within 12 months of treatment with abiraterone or enzalutamide.	Strong
Novel agents	
Offer poly(ADP-ribose) polymerase (PARP) inhibitors to pre-treated mCRPC patients with relevant DNA repair gene mutations.	Strong

6.5.16 Guidelines for supportive care of castrate-resistant disease

These recommendations are in addition to appropriate systemic therapy.

Recommendations	Strength rating
Offer bone protective agents to patients with mCRPC and skeletal metastases to prevent osseous complications.	Strong
Monitor serum calcium and offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates.	Strong
Treat painful bone metastases early on with palliative measures such as intensity-modulated radiation therapy plus image-guided radiation therapy and adequate use of analgesics.	Strong
In patients with spinal cord compression start immediate high-dose corticosteroids and assess for spinal surgery followed by irradiation. Offer radiation therapy alone if surgery is not appropriate.	Strong

6.6. Summary of guidelines for the treatment of prostate cancer

6.6.3 Guidelines for metastatic disease, second-line and palliative treatments

Recommendations		Strength rating
Metastatic disease in a first-line setting		
M1 patients	Offer immediate systemic treatment with ADT to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction) to M1 symptomatic patients.	Strong
	Offer luteinising hormone-releasing hormone (LHRH) antagonists, especially to patients with an impending spinal cord compression or bladder outlet obstruction.	Weak
	Offer surgery and/or local radiotherapy to any patient with M1 disease and evidence of impending complications such as spinal cord compression or pathological fracture.	Strong
	Offer immediate systemic treatment to M1 patients asymptomatic from their tumour.	Weak
	Discuss deferred ADT with well-informed M1 patients asymptomatic from their tumour since it lowers the treatment-related side effects, provided the patient is closely monitored.	Weak
	Offer short-term administration of an older generation androgen receptor (AR) antagonist to M1 patients starting LHRH agonist to reduce the risk of the 'flare-up' phenomenon.	Weak
	Do not offer AR antagonists monotherapy to patients with M1 disease.	Strong
	Discuss combination therapy including ADT plus systemic therapy with all M1 patients.	Strong
	Do not offer ADT monotherapy to patients whose first presentation is M1 disease if they have no contraindications for combination therapy and have a sufficient life expectancy to benefit from combination therapy and are willing to accept the increased risk of side effects.	Strong
	Offer ADT combined with chemotherapy (docetaxel) to patients whose first presentation is M1 disease and who are fit for docetaxel.	Strong
	Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients whose first presentation is M1 disease and who are fit for the regimen.	Strong
	Offer ADT combined with prostate radiotherapy (using the doses from the STAMPEDE study) to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria.	Strong
	Do not offer ADT combined with any local treatment (radiotherapy/ surgery) to patients with high-volume M1 disease (CHAARTED criteria) outside of clinical trials (except for symptom control).	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 well-designed prospective cohort study.	Strong

Life-prolonging treatments of castration-resistant disease		
	Ensure that testosterone levels are confirmed to be < 50 ng/dL, before diagnosing castration-resistant PCa (CRPC).	Strong
	Counsel, manage and treat patients with metastatic CRPC (mCRPC) in a multidisciplinary team.	Strong
	Treat patients with mCRPC with life-prolonging agents.	Strong
	Offer mCRPC patients somatic and/or germline molecular testing as well as testing for mismatch repair deficiencies or microsatellite instability.	Strong

Systemic treatments of castrate-resistant disease		
	Base the choice of treatment on the performance status (PS), symptoms, co-morbidities, location and extent of disease, genomic profile, patient preference, and on the previous treatment for hormone-sensitive metastatic PCa (mHSPC) (alphabetical order: abiraterone, cabazitaxel, docetaxel, enzalutamide, olaparib, radium-223, sipuleucel-T).	
	Offer patients with mCRPC who are candidates for cytotoxic therapy and are chemotherapy naïve docetaxel with 75 mg/m^2 every 3 weeks.	Strong
	Offer patients with mCRPC and progression following docetaxel chemotherapy further life-prolonging treatment options, which include abiraterone, cabazitaxel, enzalutamide, radium-223 and olaparib in case of DNA homologous recombination repair (HRR).	Strong
	Base further treatment decisions of mCRPC on pre-treatment PS status, previous treatments, symptoms, co-morbidities, genomic profile, extent of disease and patient preference.	Strong
	Offer abiraterone or enzalutamide to patients previously treated with one or two lines of chemotherapy.	Strong
	Avoid sequencing of androgen receptor targeted agents.	Weak
	Offer chemotherapy to patients previously treated with abiraterone or enzalutamide.	Strong
	Offer cabazitaxel to patients previously treated with docetaxel.	Strong
	Offer cabazitaxel to patients previously treated with docetaxel and progressing within 12 months of treatment with abiraterone or enzalutamide.	Strong
Novel agents		
	Offer poly(ADP-ribose) polymerase (PARP) inhibitors to pre-treated mCRPC patients with relevant DNA repair gene mutations.	Strong
Supportive care of castration-resistant disease		
	Offer bone protective agents to patients with mCRPC and skeletal metastases to prevent osseous complications.	Strong
	Monitor serum calcium and offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates.	Strong
	Treat painful bone metastases early on with palliative measures such as IMRT plus IGRT and adequate use of analgesics.	Strong
	In patients with spinal cord compression start immediate high-dose corticosteroids and assess for spinal surgery followed by irradiation. Offer radiation therapy alone if surgery is not appropriate.	Strong

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Advanced/ Metastatic Prostate Cancer. *CLINICAL PRACTICE GUIDELINE GU-010 Version 2*

Leitlinienorganisation/Fragestellung

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

Methodik

<u>Grundlage der Leitlinie</u>

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

- Repräsentatives Gremium, aber keine Patientenvertreter*innen; This guideline was reviewed and endorsed by the Alberta GUTumour Team. Members include surgical

oncologists, radiation oncologists, medical oncologists, nurses, pathologists, and pharmacists.

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

Recherche/Suchzeitraum:

- For the 2018 guideline updates, PubMed was searched; Inclusion criteria: phase III clinical trials, published between January 1, 2010 and June 1, 2018, English language.
- For the 2020 guideline update, selected phase III trials were reviewed by the Alberta GU Tumour group (summarized in table 3 and 4)

Table 3. Resources for Search of Published Guidelines

Guideline Internet Sites
American Society of Clinical Oncology (ASCO)
BC Cancer
Canadian Agency for Drugs and Technology in Health (CADTH)
Ontario Health/Cancer Care Ontario (CCO)
European Society of Medical Oncology (ESMO)
National Comprehensive Cancer Network (NCCN)
National Institute for Health and Care Excellence (NICE)
Guideline Clearinghouses
Cancer Guidelines Database
CPG Infobase: Clinical Practice Guidelines
ECRI Guidelines Trust
Guideline International Network (G-I-N)

Table 4. Resources for Search of Primary Literature

Databases
CINAHL - Nursing and allied health literature
Cochrane Library of Systematic Reviews
DynaMed Plus
Embase - Includes more European articles than Medline or PubMed
Medline
PubMed - 6 weeks ahead of Medline; includes citations to articles not yet assigned MESH headings
TripPro - Clinical search engine
UptoDate - Requires subscription
Other Resources
Conference Abstracts • ASH Annual Meeting Abstracts • San Antonio Breast Cancer Symposium Abstracts
Drug Information • AHS Provincial Drug Formulary (available on internal intranet only) • Alberta Blue Cross Drug Benefit List • Lexicomp® (requires subscription) • CADTH pan-Canadian Oncology Drug Review (pCODR)
Society Websites • Canadian Cancer Society • Canadian Partnership Against Cancer • American Cancer Society
Grey Literature • Google and Google Scholar • Grey Matters

LoE/GoR

- Critical Appraisal of the Evidence: The Knowledge Management Specialist (KMS) synthesizes the relevant details of the studies included from the literature search into evidence tables. The quality of the evidence is rated by the KMS and reviewed with the Working Group members according to the criteria in Table 5.

Table 5. Levels of Evidence

Level	Description of Evidence
I	• evidence from at least one large randomized controlled trial (RCT) of good methodological quality with low potential for bias • meta-analyses of RCTs without heterogeneity
II	• small RCTs • phase II RCTs • large RCTs with potential bias or meta-analyses including such trials RCTs with heterogeneity
III	• prospective cohort studies • post-hoc and ad-hoc analyses of RCTs
IV	• retrospective cohort studies • case-control studies • instrument validation studies (*note:* could be level III, based on size of population, methods)
V	• studies without a control group • case reports • expert opinions • review articles or narrative reviews • Delphi studies • cross-sectional studies (interviews, focus groups, surveys)

- Formulating and Rating the Recommendations: The Working Group members formulate the guideline recommendations based on existing published guidelines and the evidence synthesized by the KMS blended with expert clinical experience and local context. They may decide to adopt the recommendations of another institution without any revisions, adapt the recommendations of another institution with revisions, or develop their ownrecommendations; this decision may be based on the guideline questions, as well as the volume, quality, relevance, and novelty of existing guidelines. Beginning in late 2019, ratings of the strength of the recommendations will be included in all newly developed or updated CPGs, to better align with the standards outlined by the Institute of Medicine.2 These ratings take into consideration the description of known benefits and possible harms, the available evidence and confidence in the quality and consistency of this evidence, and a discussion of the role of clinical experience, values and opinions of the Working Group members. The strength of the recommendations is rated by the Working Group members according to the criteria in Table 6

Table 6. Strength of Recommendations

Grade	Description of Recommendation Strength
A	Strongly recommended; strong evidence for efficacy with a substantial clinical benefit.
B	Generally recommended; strong or moderate evidence for efficacy but with a limited clinical benefit.
C	Optional; insufficient evidence for efficacy or benefit does not outweigh the risks/disadvantages.
D	Generally not recommended; moderate evidence against efficacy or for adverse outcomes.
E	Never recommended; strong evidence against efficacy or for adverse outcomes.

The criteria in Tables 5 and 6 were adapted from the Infectious Diseases Society of America3 and the European Society for Medical Oncology (ESMO).

Sonstige methodische Hinweise

- Die Literaturstellen 54,55 sind nicht im Inhaltsverzeichnis der LL 2020 gelistet und könnnen nicht überprüft warden.

Empfehlungen

Castrate Resistant Metastatic Disease (Stage M0, M+)

Castrate resistant disease is defined as either clinical, biochemical, or radiographic disease progression in the presence of castrate level (<1.7nmol/L) testosterone levels.

Management of M+ Disease

1. All patients with mCRPC should be considered for novel anti-androgen therapy (abiraterone, enzalutamide) or clinical trial options PRIOR to initiation of previously used agents (such as NSAA's)

2. Systemic Therapy

Clinical trials should be given first consideration where appropriate. Currently, there is no data to support one of these agents/sequences over the other.

A. 1st line options:

i Abiraterone acetate 1g oral daily in combination with prednisone 5 mg oral twice daily (COUGAR 302) can be used prior to docetaxel.[16,17]

ii Docetaxel 75mg/m2 IV every 3 weeks in combination with prednisone at a dose of 5 mg twice daily.[54]

iii Enzalutimide 160mg oral daily can be used prior to docetaxel (PREVAIL).[18]

B. 2nd line options:

i. Post progression on docetaxel chemotherapy:

a. Abiraterone acetate19 or enzalutamide [20]

b. Cabazitaxel IV every 3 weeks in combination with prednisone 10 mg oral daily.[56]

- 20 mg or 25 mg can be considered, as the PROSELICA trial [21] demonstrated that 20 mg dose was non-inferior to the 25 mg dose and was associated with decreased toxicity.

c. Radium 223 can be given to patients with symptomatic bony metastatic CRPC without visceral metastases (ALSYMPCA).[22,23] Ra 223 is administered upon referral to nuclear medicine and given at a dose of 50 kBq (1.35 microcurie) per kg body weight at 4 week intervals for a total of 6 injections. Radium 223 is not funded or available in Alberta.

ii. Post progression on Abiraterone or Enzalutamide

a. Docetaxel chemotherapy

C. Subsequent lines:

i. Sequencing with another agent listed above not previously used.

ii. Optimal sequencing of these agents is unknown.

a. If a patient has already received docetaxel and one ARAT, the CARD trial [24] would suggest that cabazitaxel would be the preferred subsequent agent provided the patient is medically fit for therapy.

iii. Docetaxel re-challenge or Mitoxantrone 12mg/m2 every 3 weeks in combination with prednisone 5 mg oral twice a day may provide palliation.

D. Bone targeted therapy: treatment with bisphosphonates bone targeted agents should be considered for some patients with metastatic castrate resistant prostate cancer. See the bone health guideline (available: https://www.albertahealthservices.ca/info/cancerguidelines.aspx).

3. Palliative Radiotherapy

For a complete list of recommendations, see the Alberta Palliative Radiotherapy guidelines located (http://www.albertahealthservices.ca/info/cancerguidelines.aspx in the Radiotherapy Special Topics section).

Management of Oligometastatic Disease

1. Radiotherapy to the prostate

A. The STAMPEDE trial [25] failed to demonstrate improvement in overall survival after radiotherapy in newly diagnosed metastatic prostate cancer.

i. However, pre-specified subgroup analysis of patients with low metastatic burden (by CHAARTED clinical trial criteria) demonstrated an improvement in overall survival with radiotherapy to the prostate compared to standard of care (81% vs. 73% OS at 3 years; HR:0.68, 95%CI: 0.52-0.90).

ii. Discussion in multidisciplinary tumour group meetings is advised if radiotherapy is being considered.

Follow-up

- Patients on docetaxel, abiraterone, enzalutamide, or cabazitaxel should be monitored as per standard protocols. At a minimum, PSA response should be evaluated 12 weeks after starting treatment.
- Once therapy with one of these agents has been discontinued, patients should be assessed for further therapy.
- Repeat staging investigations are recommended at the time of progression.
- Duration: as clinically indicated

Table 1: Systemic Therapy Trials for the Treatment of Metastatic Castration Resistant Prostate Cancer

Drug	Trial Name	Indication	Arms of Study	PFS	p-value	Median OS	p-value
Abiraterone[19,27]	COU-AA-301 (NCT00638690)	Post Docetaxel	5 mg of prednisone twice daily with 1000mg (4x 250mg) of abiraterone acetate (797 patients) or placebo (4x 250mg) daily	Abiraterone group: 5.6mo Placebo: 3.6 mo	p <0.001	Abiraterone group: 14.8mo Placebo: 10.9mo Median follow-up: 12.8mo	p<0.001, HR: 0.65, 95%CI: 0.54-0.77
Abiraterone[16,17]	COU-AA-302 (NCT00887198)	Pre Docetaxel	Abiraterone acetate 1000mg (4 x 250mg) plus prednisone (5mg twice daily) (544 patients) vs placebo plus prednisone (544 patients)	Radiographic PFS Abiraterone group: 16.5mo vs placebo: 8.2mo median follow-up 22.2mo	p<0.0001, HR: 0.52, 95%CI: 0.45-0.61	Abiraterone: 35.3mo Placebo: 30.1 mo	p=0.0037 HR: 0.80; 95%CI: 0.69-0.93
Enzalutamide[18]	PREVAIL (NCT01212991)	Pre Docetaxel	872 in the enzalutamide group, 845 in the placebo group	Radiographic PFS at 12 months was 65% in the enzalutamide group compared to 14% in the placebo group	p<0.001, HR: 0.19, 95%CI: 0.15-0.23	OS was 72% (626 patients) in the enzalutamide group vs 63% (532 patients) in the placebo group	p<0.001, HR: 0.71, 95%CI: 0.60-0.84
Enzalutamide[20,28]	AFFIRM (NCT00974311)	Post Docetaxel	Enzalutamide 160mg once daily (four capsules) (800 patients) vs placebo (399 patients).	Radiographic PFS Enzalutamide group: 8.3mo Placebo: 2.9mo	p<0.001, HR: 0.40	Enzalutamide group: 18.4mo Placebo: 13.6mo	p=0.0151, HR: 0.79, 95%CI: 0.66-0.95
Docetaxel[29-32]	TAX 327	Metastatic CRPC	Docetaxel 75 mg/m^2 q3 weekly + prednisone 5 mg bid vs. Mitoxantrone 12 mg/m^2 + prednisone 5 mg bid (3rd arm of weekly docetaxel demonstrated no benefit)	N/A	N/A	Docetaxel 18.9 vs Mitoxantrone 16.5 months	p=0.009, HR: 0.76, 95%CI: 0.62-0.94)
Cabazitaxel[33,34]	TROPIC (NCT00417079)	Post Docetaxel	10mg oral prednisone daily and 12mg/m^2 mitoxantrone intravenously over 15-30min (377 patients) or 25 mg/m^2 cabazitaxel intravenously over 1h (378 patients) every 3 weeks	cabazitaxel group:2.8mo mitoxantrone group:1.4mo	p<0.0001, HR:0.74 95%CI: 0.64-0.86	Cabazitaxel group: 15.1mo Mitoxantrone group: 12.7mo	p<0.001, HR: 0.63, 95%CI: 0.53-0.75
Sipuleucel-T (Not Health Canada Approved)[35]	IMPACT (NCT000065442)	Asymptomatic or minimally symptomatic CRPC	Sipuleucel-T (341 patients) vs placebo (171 patients).	Similar	p=0.40, HR: 0.92, 95%CI: 0.75-1.12	Sipulencel-T group: 25.8mo Placebo: 21.7mo	p=0.03, HR 0.78, 95%CI: 0.61-0.98
Radium-233 (Xofigo)[22,23]	ALSYMPCA (NCT00699751)	Post docetaxel or non-docetaxel candidates	Radium-233- six injections (1 every 4 weeks), 50kBq/kg of body weight, intravenously vs matching placebo	Time to First Symptomatic Skeletal Event (median): Radium-223: 15.6mo Placebo: 9.8mo	p<0.001, HR: 0.66, 95%CI: 0.52-0.83	Radium-233: 14.9mo Placebo: 11.3mo	p=0.03, HR: 0.78, 95%CI: 0.61-0.98

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Second-Line Hormonal Therapy for Men With Chemotherapy-Naive, Castration-Resistant Prostate Cancer: American Society of Clinical Oncology Provisional Clinical Opinion

Leitlinienorganisation/Fragestellung

Do second-line hormonal therapies play a role in the treatment of chemotherapy-naive men with castration-resistant prostate cancer (CRPC)?

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- The search included the MEDLINE (PubMed: 1985 through June 2015), and Cochrane Library databases (www.cochranelibrary.com to May 31, 2014). Conference proceedings from the 2010-2015 ASCO Annual and Genitourinary meetings were also searched for randomized controlled trials reporting on outcomes of interest

LoE

Guide for Rating Quality of Evidence

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

GoR

Guide for Strength of Recommendations

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

Fragestellungen und Empfehlungen

1. Should a castrate state be maintained in patients who develop CRPC?

PCO 1. For men who develop CRPC despite castrate levels of testosterone:

- Patients should be maintained in a castrate state indefinitely. This PCO is based on indirect scientific evidence and current understandings of disease progression mechanisms in prostate cancer. A discussion with patients about the limited nature of available scientific evidence and the balance among potential harms, benefits, costs, and patient preferences is essential when planning treatment.
- A castrate state should be maintained through orchiectomy or pharmacologic castration (e.g., luteinizing hormone–releasing hormone [LHRH] agonists/antagonists, antiandrogens).

Literature review and analysis

No randomized controlled trials (RCTs) met the sample size inclusion criteria. Within the supplementary literature, one small RCT suggested a cost and potential cause-specific survival advantage for intermittent versus continuous androgen blockade in men who develop CRPC (who have not had an orchiectomy), but the study was not adequately powered.[30] However, retrospective post hoc analyses of a prospective series reported that eugonadal or superphysiologic levels of testosterone are associated with a risk of progression and death in men with CRPC.[29] Multiple adverse effects and harms were reported with ADT, including hot flushes, fatigue, impotence, gynecomastia, loss of libido, osteoporosis, and a risk for metabolic syndrome.[31-33]

Clinical interpretation

Maintenance of a castrate state through orchiectomy or pharmacologic castration in patients who develop CRPC despite castrate levels of testosterone is suggested, which is supported by current understandings of disease progression mechanisms[34] and agrees with published guidelines.[35-37] RCTs are needed, such as the ongoing German SPARE trial of abiraterone acetate plus LHRH therapy versus abiraterone acetate–

sparing LHRH therapy in chemotherapy-naive patients with progressive CRPC, to measure the clinical benefit of continued ADT (LHRH therapy) during second-line hormonal therapy (ClinicalTrial.gov identifier NCT02077634).

Table 2. Results of Phase III Randomized Trials

First Author	No. of Patients	Treatment Arms (active agents)	Patient Outcomes: PSA Decline ≥ 50%, %	Objective Response, % CR	PR	SD	Median Survival, Months PFS	OS
Ryan[21,22]	542	Prednisone/placebo	24	16		69	8.3	30.3
	546	Prednisone/abiraterone acetate	62	36		61	16.5	34.7
			$P < .001$	$P < .001$			$P < .001$	$P < .01$
Beer[23]	845	Placebo	3	1	4	NR	3.9	30.2*
	872	Enzalutamide 160 mg/d PO	78	20	39	NR	Not reached (but at 12 months, 81% risk reduction)	32.4*
			$P < .001$	$P < .001$			$P < .001$	$P < .001$
Shamash[24]†	136	Dex/DES—immediate	68	NR	NR	NR	8.1	19.4
	133	Dex/DES—delayed	64	NR	NR	NR	8.1	18.8
Small[25]†	132	AAWD	11	2		NR	NR	16.7
	128	AAWD/ketoconazole	27	20		NR	NR	15.3
			$P = .002$	$P = .02$				
Fossa[26]†	101	Prednisone	9	NR	NR	NR	3.4	10.6
	100	Flutamide	10	NR	NR	NR	2.3	11.2
Dawson[27]†	73	Megestrol acetate—low dose	14	NR	3	30	3.8	11.2
	76	Megestrol acetate—high dose	9	NR	1	37	4.3	12.1

Abbreviations: AAWD, antiandrogen withdrawal; CR, complete response; DES, diethylstilbestrol; Dex, dexamethasone; LHRH, luteinizing hormone–releasing hormone; NR, not reported; OS, overall survival; PFS, progression-free survival; PO, orally; PR, partial response; PSA, prostate-specific antigen; SD, stable disease.
*Including the 116 additional deaths after enzalutamide was offered to eligible patients receiving placebo, at 18 months, estimated median overall survival was 31 months (placebo) versus not yet reached (enzalutamide) (hazard ratio = 0.73; 95% CI, 0.63 to 0.85; $P < .001$), a 27% risk reduction following crossover.
†Patients were enrolled before AAWD; only 15 such patients were enrolled before protocol change.

<u>In chemotherapy-naive patients who develop CRPC and have radiographic evidence of metastases but minimal symptoms (M1a/ M1s CRPC), should second-line hormonal therapies be used? If so, what agents are recommended?</u>

PCO 3. After first-line hormonal treatment failure and a discussion with chemotherapy-naive patients about potential harms, benefits, costs, and patient preferences,

- Abiraterone acetate plus prednisone should be offered because they significantly improved rPFS and OS as well as secondary end points, including median time to opiate use, chemotherapy initiation, performance status deterioration, and PSA progression (v prednisone alone). The drugs are also well tolerated.
- Enzalutamide should be offered because it significantly improves rPFS and OS. Secondary end points are also improved, including time to initiation of cytotoxic chemotherapy, risk of a first skeletal-related event, complete or partial soft tissue response, time to PSA progression, time to deterioration in quality of life, and decline in PSA of ≥ 50% from baseline (v placebo). The drug is also well tolerated.
- Alternative treatment options include immunotherapy (sipuleucel-T),[11] chemotherapy (docetaxel and prednisone),9 and radium-223.
- If none of these therapies can be obtained or tolerated by the patient, other antiandrogens, prednisone, and ketoconazole/ hydrocortisone may be offered because they provide modest clinical benefits in this population, but no survival benefits have been established.
- Other alternative treatment options include enrollment in a clinical trial and observation.
- No evidence provides guidance about the optimal order of hormonal therapies after second-line hormonal therapy for patients with M1 CRPC. The panel was unable to come to a consensus about sequencing.

- Other second-line hormonal therapy options where results from phase III trials are pending are not suggested. • Palliative care should be offered to all chemotherapy-naive men with M1 CRPC, particularly to those who exhibit symptoms or decreased quality of life.[20]

Literature review and analysis

Three phase III RCTs identified in the systematic review provide the evidence base to inform this PCO.[21,23,25] An RCT (COU-AA-302) of abiraterone acetate plus prednisone administered in chemotherapy-naive men with primarily asymptomatic metastatic CRPC resulted in a statistically significant rPFS benefit compared with placebo and prednisone (median rPFS, 16.5 v 8.3 months; HR, 0.53; 95% CI, 0.45 to 0.62; P < .001). Time to opiate use, chemotherapy initiation, performance status deterioration, and PSA progression also were significantly longer in the abiraterone acetate arm (P < .01).[21] After a median follow-up of 49.2 months, abiraterone acetate plus prednisone significantly prolonged OS (median, 34.7 v 30.3 months; HR, 0.81; 95% CI, 0.70 to 0.93; P = .0033) with an acceptable toxicity profile.[41] Similar OS and rPFS benefits for abiraterone acetate plus prednisone versus prednisone alone were seen among men age ≥ 75 years.[42]

An RCT23 (PREVAIL) compared enzalutamide (160 mg oral) versus placebo administered in chemotherapy-naive men with cytologically confirmed adenocarcinoma of the prostate with documented asymptomatic or mildly symptomatic metastases who had PSA progression, radiographic progression, or both in soft tissue or bone, despite receipt of LHRH analog therapy or orchiectomy. The trial was stopped early as a result of significantly improved survival results for patients administered enzalutamide, with an 81% reduction in the risk of radiographic progression or death at 12 months (HR, 0.19; 95% CI, 0.15 to 0.23; P < .001) and a 29% reduction in the risk of death at 18 months (HR, 0.71; 95% CI, 0.60 to 0.84; P < .001) as well as significantly improved time to initiation of chemotherapy, reduction in risk of first skeletal event, time to PSA progression, and response rate combined with an acceptable toxicity profile. Similar OS and rPFS benefits for enzalutamide were seen among men age ≥ 75 years.43 With respect to patient-reported outcomes,[44] median time to deterioration in Functional Assessment of Cancer Therapy–Prostate total score was significantly longer for patients administered enzalutamide (11.3 months; 95% CI, 11.1 to 13.9 months) than placebo (5.6 months; 95% CI, 5.5 to 5.6 months; HR, 0.62; 95% CI, 0.54 to 0.72; P < .001). A significantly greater proportion of patients administered enzalutamide (v placebo) reported clinically meaningful improvements in the Functional Assessment of Cancer Therapy–Prostate total score (40% v 23%), the EuroQual Group Health Questionnaire utility index (28% v 16%), and the visual analog scale (27% v 18%; all P < .001).

In an open-label extended analysis of 787 of the 1,717 patients enrolled in the PREVAIL study, rPFS (as a post hoc analysis only) and OS were revisited after the prespecified number of deaths for the final analysis (n = 784) was reached.[45] With the inclusion of data from 5 months postcrossover for the placebo group, the median follow-up was 31 months. By this point, 52% of the original 872 patients in the enzalutamide arm and 81% of the original 845 in the placebo arm had received subsequent antineoplastic therapies (chemotherapy, abiraterone acetate, sipuleucel-T, or radium-223 dichloride) known to affect survival. Similar statistics were not provided for patients in the open-label extended analysis only. Nevertheless, patients who had been treated with enzalutamide had a 23% reduced risk of death compared with those treated with placebo (35.3 v 31.3 months; HR, 0.77; 95% CI, 0.67 to 0.88; P < .001). In the post hoc analysis, enzalutamide reduced the risk of radiographic progression or death by 68% compared with placebo (20.0 v 5.4 months; HR, 0.32; 95% CI, 0.28 to 0.37; P < .001).

In the supplemental literature, two related phase II trials (TERRAIN and STRIVE) compared enzalutamide (160 mg/day) to the antiandrogen bicalutamide (50 mg/day) for safety and efficacy among chemotherapy-naive men with asymptomatic or mildly symptomatic progressive disease during treatment with ADT.[38,46] As mentioned under Research Question 2, **STRIVE** included patients with either M0N0/1 (n = 139) or M1N1 (n = 257) disease.[38] For the asymptomatic or mildly symptomatic M1 population, median PFS was significantly longer for enzalutamide (16.5 months) versus bicalutamide (5.5 months; HR, 0.24; 95% CI, 0.17 to 0.34). Patients with M1 disease treated with enzalutamide also had significantly greater PSA response (P < .001) irrespective of the definition of complete response (PSA decline ≥ 50% [or 90%] from baseline). Unlike STRIVE, **TERRAIN** randomly assigned only patients with M1 disease and radiographically confirmed metastases (n = 184 enzalutamide; n = 191 bicalutamide) but found similar results for the M1 population. Median PFS was significantly longer for enzalutamide (15.7 months) than for bicalutamide (5.8 months; HR, 0.44; 95% CI, 0.34 to 0.57; P < .001).

Although both are important phase II studies, neither STRIVE nor TERRAIN was designed to compare OS among patients with clinically defined CRPC. Thus, the question of whether earlier treatment with enzalutamide improves survival compared with the current practice of later treatment cannot be answered, but the similarity in results for PFS between the two studies is encouraging.

The remaining phase III randomized trials included a mix of asymptomatic and symptomatic patients[24,25,27] or all symptomatic patients.[26] No significant differences in survival outcomes were reported between treatment groups. However, Small et al[25] found that patients randomly assigned to AAWD and ketoconazole (AAWD/K) experienced higher rates of PSA decline ≥ 50% (27% v 11%; P < .001) and objective response (20% v 2%; P = .02) compared with those who underwent AAWD alone.[25] Of patients randomly assigned to AAWD who later had ketoconazole, the total PSA response rate was similar to those who received immediate AAWD/K, whereas the objective response rate was lower in those who received sequential therapy compared with immediate AAWD/K. The 11% PSA response results with AAWD alone varied from prior phase I and II studies that reported it as high as 40%. This lower rate may reflect shorter patient exposure to antiandrogens than in earlier reports.[47] In contrast, the 20% PSA response rate detected in the ketoconazole intervention arm is in line with a study by Trump et al[48] of 38 patients with CRPC and radiographic metastases treated with high-dose ketoconazole (400 mg three times a day) plus hydrocortisone wherein an objective response was observed in 17% of evaluable patients.

One additional phase III trial was identified in the systematic review of orteronel plus prednisone versus placebo among chemotherapy-naive men with metastatic CRPC. The study does not inform our recommendations because of a lack of improvement in OS and a high adverse event rate (46%). Orteronel is no longer under development for treatment of metastatic CRPC.[49] In the trials of prednisone versus flutamide,26 high- versus low-dose megestrol acetate,[27] and diethylstilbestrol versus bicalutamide (single-facility phase II trial),[29] no meaningful objective differences in outcomes were detected between treatment groups. Three members of the Consensus Panel reported the use of highdose bicalutamide in this setting, but data suggest possible excess mortality associated with this dose in a related context.[50]

No evidence provides guidance about the optimal order of second-line hormonal therapies for patients with M1 CRPC. In the trial by Ryan et al,[21] significant PFS and OS advantages and delay in clinical decline were detected in favor of abiraterone/prednisone compared with prednisone alone. A PSA response was seen in 62% of patients in the abiraterone treatment arm. The Beer et al[23] trial of enzalutamide versus placebo, which reported early significant rPFS and OS advantages, found a PSA decline of > 50% in 78% of men in the

enzalutamide arm. A similar PSA response also has been reported in the phase III randomized trial that compared dexamethasone and aspirin with either immediate or delayed diethylstilbestrol.[24] (AAWD/K produced greater PSA and objective responses than AAWD alone but no differences in OS, and 21% of patients experienced a grade 3 and 4 adverse event.[25] Because ketoconazole usually is given with low-dose corticosteroids, this may influence PSA response. In the control arm of Ryan et al,[21] PSA response was seen in 24% of patients who received prednisone alone. In the Nakabayashi et al[51] retrospective review of 138 patients started on low-dose ketoconazole (200 mg three times a day), 28% had a PSA response. Fifty-five patients (40%) subsequently received highdose ketoconazole (400 mg three times a day); 13% had an additional PSA response (P value not reported). In general, high-dose ketoconazole was associated with a greater risk of adverse effects, and six patients (11%) discontinued therapy as a result of worsening or new adverse effects from high-dose therapy. For patients who could not tolerate high-dose ketoconazole therapy, low-dose ketoconazole had similar efficacy.[51])
ASCO issued a systemic therapy guideline in 2014[9] that supports the use of immunotherapy (sipuleucel-T)[11] or chemotherapy (docetaxel and prednisone) in men with metastatic CRPC. The use of radium-223 was recommended for men with bone metastases.[52] Consult that guideline for the full recommendations.

Clinical interpretation:
For chemotherapy-naive patients who develop CRPC and have radiographic evidence of metastases, two second-line hormonal therapy options are supported by strong clinical trial evidence and are well tolerated. Abiraterone acetate plus prednisone extends rPFS and OS in addition to a variety of secondary end points, such as median time to opiate use, chemotherapy initiation, performance status deterioration, and PSA progression.
According to the manufacturer's warnings and precautions,[53] abiraterone acetate should be used with caution in patients with a history of cardiovascular disease. Drug safety was not established in patients with a left-ventricular ejection fraction < 50% or with New York Heart Association class II to IV disease. Abiraterone acetate can cause hypertension, hypokalemia, and fluid retention. Low risks of adrenocortical insufficiency or hepatotoxicity also are associated with abiraterone acetate use. A low risk of seizure associated with enzalutamide use exists[54]; however, among chemotherapy- naive patients, the risk (0.1%) was similar between those who received enzalutamide and those who received placebo. Posterior reversible encephalopathy syndrome also has been associated with enzalutamide use, which required discontinuation of the drug.

According to the 2014 ASCO systemic therapy guideline for men with metastatic CRPC,[9] other treatment options include immunotherapy (sipuleucel-T) or chemotherapy (docetaxel and prednisone). The systemic therapy guideline specifically recommends radium-223 for men with bone metastases.[52] If none of the aforementioned hormonal therapy, immunotherapy, or chemotherapy options can be tolerated and/or accessed, other antiandrogens, prednisone, and ketoconazole/hydrocortisone may be offered. Enrollment in a clinical trial is always an option. The goal of treatment is symptom relief with extension and quality of life and deferral of chemotherapy for as long as possible. Palliative care should not be overlooked, particularly for patients who exhibit symptoms or decreased quality of life.[20]

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 04 of 12, April 2021) am 23.04.2021

#	Suchfrage
1	[mh "Prostatic Neoplasms"]
2	(prostate OR prostatic):ti,ab,kw
3	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesions* OR malignan*):ti,ab,kw
4	#1 OR (#2 AND #3)
5	#4 with Cochrane Library publication date from Apr 2016 to present

Systematic Reviews in Medline (PubMed) am 23.04.2021

#	Suchfrage
1	prostatic neoplasms[mh] AND neoplasm metastasis[mh]
2	prostate[tiab] OR prostatic[tiab]
3	(((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesion*[tiab]) OR malignan*[tiab]
4	(#2 AND #3) AND (advanced[tiab] OR metastat*[tiab] OR metastas*[tiab] OR recurren*[tiab] OR oligometastatic[tiab])
5	#1 OR #4
6	(#5) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR

#	Suchfrage
	scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
7	((#6) AND ("2016/04/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt]) -- https://pubmed.ncbi.nlm.nih.gov/31610875/

Leitlinien in Medline (PubMed) am 23.04.2021 [1]

#	Suchfrage
1	prostatic neoplasms[mh]
2	prostate[tiab] OR prostatic[tiab]
3	(((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesion*[tiab]) OR malignan*[tiab]
4	#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 ("2016/04/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt])

[1] Das Enddatum der Recherche in Pubmed/Medline wird seit 01/2018 auf „3000“ durch TIM festgelegt. Begründung: das Aufnahme bzw. Erscheinungsdatum neuerer Publikationen sind in der Datenbank (PM/ML) des Öfteren vordatiert, so dass sie durch die Einschränkung des Suchzeitraums nicht miterfasst werden. Zur Abhilfe wird das Enddatum des Suchzeitraums heraufgesetzt.

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

2021-B-174

Kontaktdaten

DGHO Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie

DGU Deutsche Gesellschaft für Urologie

Indikation gemäß Beratungsantrag

Erwachsene Patienten mit PSMA positivem, metastasiertem, kastrationsresistentem Prostatakarzinom (mCRPC), welche bereits mit mindestens einem ARDT und einer taxan-basierten Chemotherapie behandelt worden sind

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, kastrationsresistenten Prostatakarzinoms (mCRPC) hat sich in den letzten Jahren grundlegend geändert. Nach Vortherapie mit einer neuen hormonellen Substanz (new hormonal agent) und einer Taxan-basierten Chemotherapie hängt das Vorgehen wesentlich vom Leidensdruck, der Dynamik der Erkrankung, der Biologie einschließlich molekularpathologischer Veränderungen, der Komorbidität und der Vortherapie ab. Daraus ergibt sich ein patientenindividuelles Vorgehen auf der Basis von Best Supportive Care einschl. osteoprotektiver Therapie unter Berücksichtigung von:

- Chemotherapie, an erster Stelle Cabazitaxel
- Androgen Receptor Targeted Agent (AbiA, ARDT, new hormonal agent); Wechsel auf eine andere, bisher nicht eingesetzte Substanz
- ^{223}Radium
- Olaparib bei gBRCA1/2 Mutationen.

Der therapeutische Standard PSMA-positiver Patienten orientiert sich am allgemeinen Behandlungsstandard. Dabei ist der Nachweis PSMA-speichernder Metastasen im PSMA-PET/CT oder MRT allerdings eine Voraussetzung für eine PSMA-gerichtete Behandlung (z.B. Lutetium oder Aktinium PSMA-Liganden-Therapie).

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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 auf etwa 61.200 geschätzt. Das Prostatakarzinom macht etwa ein Viertel aller Krebserkrankungen bei Männern mit einem mittleren Erkrankungsalter von 72 Jahren aus. Die Inzidenz stieg seit 1980 kontinuierlich aufgrund der Einführung der PSA-gestützten Früherkennung und zuletzt vor allem wegen der demographischen Entwicklung an. Die altersstandardisierte Erkrankungsrate ist seit etwa 10 Jahren konstant. 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.

Die Therapie von Patienten mit fortgeschrittenem Prostatakarzinom hat sich in den letzten Jahren grundlegend gewandelt. Vor allem die Einführung neuer Arzneimittel zur systemischen Therapie hat in den verschiedenen Krankheitsstadien zu einer Verlängerung der Überlebenszeit geführt.

Die Empfehlungen der aktuellen S3-Leitlinie zur Therapie von Patienten mit mCRPC, Progress nach Therapie mit einer neuen hormonellen Substanz (ARTA) und einem Taxan sind [2]:

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7.43	Evidenzbasierte Empfehlung	neu 2021
Empfehlungsgrad **B**	Patienten mit Progress unter einer neuen hormonellen Substanz (new hormonal agent) sollte ein Wechsel der Therapiestrategie angeboten werden.	
Level of Evidence **4**	Expertenkonsens basierend auf [852]	
	Gesamtabstimmung: 95 %	

7.44	Evidenzbasierte Empfehlung	neu 2021
Empfehlungsgrad **A**	Patienten mit Progress nach einer Vortherapie, die eine neue hormonelle Substanz (new hormonal agent) umfasste, soll eine Testung auf BRCA 1/2 -Mutationen angeboten werden.	
Level of Evidence **1-**	Literatur: [853,854]	
	Gesamtabstimmung: 97 %	

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Indikation gemäß Beratungsantrag

Erwachsene Patienten mit PSMA positivem, metastasiertem, kastrationsresistentem Prostatakarzinom (mCRPC), welche bereits mit mindestens einem ARDT und einer taxan-basierten Chemotherapie behandelt worden sind

7.45	Evidenzbasierte Empfehlung	neu 2021
Empfehlungsgrad **A**	Bei Nachweis einer *BRCA1/2* Mutation soll eine Therapie mit Olaparib angeboten werden.	
Level of Evidence **1-**	Literatur: [853,854]	
	Gesamtabstimmung: 98 %	

7.46	Evidenzbasierte Empfehlung	modifiziert 2021
Empfehlungsgrad **A**	Patienten mit kastrationsresistenter, progredienter Erkrankung und gutem Allgemeinzustand nach Chemotherapie mit Docetaxel soll eine der folgenden Therapieoptionen, bei Bedarf in Kombination mit symptombezogener und supportiver Therapie, angeboten werden: (alphabetische Reihenfolge) • Abirateron (in Kombination mit Prednison / Prednisolon) • Cabazitaxel • Enzalutamid Zur Differenzialtherapie siehe Empfehlungen 7.47 - 7.49.	
Level of Evidence **1+**	Literatur: [861-868]	
	Gesamtabstimmung: 97 %	

Kontaktdaten

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Indikation gemäß Beratungsantrag

Erwachsene Patienten mit PSMA positivem, metastasiertem, kastrationsresistentem Prostatakarzinom (mCRPC), welche bereits mit mindestens einem ARDT und einer taxan-basierten Chemotherapie behandelt worden sind

7.47	Evidenzbasierte Empfehlung	geprüft 2021
Empfehlungsgrad **0**	Patienten mit kastrationsresistenter, progredienter Erkrankung und gutem Allgemeinzustand nach Chemotherapie mit Docetaxel kann (alphabetische Reihenfolge) · Abirateron (in Kombination mit Prednison / Prednisolon) oder · Enzalutamid angeboten werden. In der jeweiligen Zulassungsstudie wurde eine Verlängerung der Überlebenszeit gezeigt.	
Level of Evidence **1+**	Literatur: Abirateron: [861,862] Enzalutamid [864]	
	Gesamtabstimmung: 100 %	

Kontaktdaten

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DGU Deutsche Gesellschaft für Urologie

Indikation gemäß Beratungsantrag

Erwachsene Patienten mit PSMA positivem, metastasiertem, kastrationsresistentem Prostatakarzinom (mCRPC), welche bereits mit mindestens einem ARDT und einer taxan-basierten Chemotherapie behandelt worden sind

7.48	Evidenzbasierte Empfehlung	geprüft 2021
Empfehlungsgrad **0**	Patienten mit kastrationsresistenter, progredienter Erkrankung und gutem Allgemeinzustand nach Chemotherapie mit Docetaxel kann Cabazitaxel angeboten werden. In der Zulassungsstudie wurde eine Verlängerung der Überlebenszeit gezeigt.	
Level of Evidence **1+**	Literatur: [865]	
	Gesamtabstimmung: 100 %	

Kontaktdaten

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DGU Deutsche Gesellschaft für Urologie

Indikation gemäß Beratungsantrag

Erwachsene Patienten mit PSMA positivem, metastasiertem, kastrationsresistentem Prostatakarzinom (mCRPC), welche bereits mit mindestens einem ARDT und einer taxan-basierten Chemotherapie behandelt worden sind

7.49	Evidenzbasierte Empfehlung	modifiziert 2021
Empfehlungsgrad **0**	a. Radium-223 kann Patienten angeboten werden, die ein kastrationsresistentes, progredientes Prostatakarzinom mit symptomatischen ossären Metastasen (ohne bekannte viszerale Metastasen) sowie einen guten Allgemeinzustand aufweisen und die mindestens zwei vorausgehende systemische Therapieoptionen in dieser Indikation erhielten oder für die keine andere verfügbare systemische mCRPC-Therapie geeignet ist.	
Empfehlungsgrad **A**	b. Radium-223 soll nicht in Kombination mit Abirateron und Prednison/ Prednisolon angewandt werden.	
Level of Evidence **1+**	Literatur: a. [851,869,870] b. [871]	
	Gesamtabstimmung: a. 100 %, b. 100 %	

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Indikation gemäß Beratungsantrag

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7.51	Evidenzbasierte Empfehlung	geprüft 2021
Empfehlungsgrad **0**	Für Patienten mit kastrationsresistenter, progredienter Erkrankung in gutem Allgemeinzustand kann nach Ausschöpfen der empfohlenen Therapieoptionen (siehe Empfehlung 7.46) ein Therapieversuch mit Lutetium-177-PSMA auf Basis der Empfehlung einer interdisziplinären Tumorkonferenz angeboten werden.	
Level of Evidence **3**	Literatur: [873]	
	Gesamtabstimmung: 93 %	

Die diesen Empfehlungen zugrundeliegende Evidenz kann folgendermaßen zusammengefasst werden (alphabetische Reihenfolge):

- Abirateron führte gegenüber Placebo zu einer Verlängerung der radiologischen, progressionsfreien Überlebenszeit (HR 0,67; Median 2,0 Monate) und der Gesamtüberlebenszeit (HR 0,74; Median 4,6 Monate), der Zeit bis zum ersten skelettalen Ereignis und der Zeit bis zur Schmerzprogression [3]. Unklar ist das Ausmaß der Effektivität, wenn ARTA schon in einer früheren Therapiephase eingesetzt wurde.
- Cabazitaxel 25 mg/m^2 führte gegenüber Mitoxantron zu einer Verlängerung der progressionsfreien Überlebenszeit (HR 0,74; Median 1,4 Monate) und der Gesamtüberlebenszeit (HR 0,70; Median 2,4 Monate) sowie zu einer Steigerung der Remissionsrate [4]. Hauptnebenwirkung ist eine erhöhte Rate an Neutropenien mit Erhöhung der Rate Therapie-assoziierter Todesfälle. Die Reduktion der Cabazitaxel-Dosis von 25 auf 20 mg/m^2 führt zu einer Reduktion schwerer Nebenwirkungen, nicht zu einer Verkürzung der Gesamtüberlebenszeit, aber zu einer niedrigeren Rate von PSA-Remissionen und zu einer Verkürzung der Zeit bis zum PSA-Progress [5].
- Cabazitaxel führte bei Patienten, die mit Docetaxel und ARTA (Abirateron, Enzalutamid) vorbehandelt sind, gegenüber Abirateron oder Enzalutamid zur Steigerung der Remissionsrate, zur

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Verlängerung der progressionsfreien Überlebenszeit (HR 0,52; Median 1,7 Monate) und zur Verlängerung der Gesamtüberlebenszeit (HR 0,64; Median 2,6 Monate). Die Rate schwerer unerwünschter Ereignisse war in den beiden Studienarmen nicht signifikant unterschiedlich [6].

- Enzalutamid führte gegenüber Placebo zur Verlängerung der progressionsfreien Überlebenszeit (HR 0,40; Median 5,4 Monate) und der Gesamtüberlebenszeit (HR 0,63; Median 4,8 Monate), zur Linderung von Symptomen und zur Verlängerung bis zur Schmerzprogression [7]. Unklar ist das Ausmaß der Wirksamkeit, wenn ARTA schon in einer früheren Therapiephase eingesetzt wurde.
- Olaparib führte bei Patienten mit metastasiertem kastrationsresistentem Prostatakarzinom, Nachweis einer BRCA1/2-Mutation (in der Keimbahn und/oder somatisch) und Progress nach Behandlung mit einer neuen hormonellen Substanz (new hormonal agent) zur Steigerung der radiologischen Ansprechrate (44 vs 0%), der PSA-Ansprechrate, zur Verlängerung des progressionsfreien Überlebens (HR 0,19; Median 6,8 Monate) und der Gesamtüberlebenszeit (HR 0,60; Median 5,7 Monate) im Vergleich zu einer erneuten Androgenrezeptor-gerichteten Behandlung [8]. Der Einfluss auf die Gesamtüberlebenszeit wird durch eine hohe Crossover-Rate möglicherweise unterschätzt.
- ^{223}Radium führte bei Patienten mit ausschließlich ossären Metastasen und Lymphknotenmetastasen <3 cm gegenüber Placebo zu einer Verlängerung der Gesamtüberlebenszeit (Hazard Ratio 0,71; Median 3,6 Monate) und zur Verlängerung der Zeit bis zum Auftreten ossärer Komplikationen [9, 10]. Entsprechend der von der EMA im Juni 2018 verordneten Einschränkung der Zulassung ist der Einsatz von ^{223}Radium weiterhin begrenzt auf Patienten ohne viszerale Metastasen. ^{223}Radium soll nicht zusammen mit Abirateron und Prednison/Prednisolon gegeben werden. Bei Einsatz in Kombination mit Enzalutamid sollte eine osteoprotektive Therapie mit Denosumab erfolgen.
- Best Supportive Care einschl. osteoprotektiver Maßnahmen.

Darüber hinaus gibt es eine Reihe weiterer Arzneimittel, für die eine Wirksamkeit beim mCRPC gezeigt, aber keine Verlängerung der Gesamtüberlebenszeit belegt wurde. Dazu gehören Estramustin, Mitoxantron und Platinderivate.

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Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von *„Erwachsene Patienten mit PSMA positivem, metastasiertem, kastrationsresistentem Prostatakarzinom (mCRPC), welche bereits mit mindestens einem ARDT und einer taxan-basierten Chemotherapie behandelt worden sind“* **die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?**

Ja, siehe oben

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