Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2019-B-249 Olaparib

Stand: Dezember 2019

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

Olaparib
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:** • 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 29.3.2012
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:	
Olaparib L01XX46 Lynparza®	Geplantes Anwendungsgebiet laut Beratungsanforderung: Lynparza wird angewendet als Monotherapie für die: • *Variante 1:* Behandlung des metastasierten kastrationsresistenten Prostatakarzinoms (mCRPC) mit BRCA- oder ATM-Mutation (in der Keimbahn und/oder somatisch) bei erwachsenen Patienten, deren Erkrankung nach vorheriger Behandlung mit einer neuen antihormonellen Substanz (NHA) progredient ist. • *Variante 2:* Behandlung des metastasierten kastrationsresistenten Prostatakarzinoms (mCRPC) bei erwachsenen Patienten mit Mutationen von in der homologen Rekombinationsreparatur (HRR) involvierten Genen (in der Keimbahn und/oder somatisch), deren Erkrankung nach vorheriger Behandlung mit einer neuen antihormonellen Substanz (NHA) progredient ist.
Antiandrogene	
Bicalutamid L02BB03 generisch	Fortgeschrittenes Prostatakarzinom - Behandlung des fortgeschrittenen Prostatakarzinoms in Kombination mit einer LHRH-(Luteinisierendes-Hormon-Releasing-Hormon)-Analogon-Therapie oder einer operativen Kastration. […]
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.
Cyproteronacetat G03HA01 generisch	Zur palliativen Therapie des metastasierenden oder lokal fortgeschrittenen, inoperablen Prostatakarzinoms, • wenn sich die Behandlung mit LHRH-Analoga oder der operative Eingriff als unzureichend erwiesen haben, kontraindiziert sind oder der oralen Therapie der Vorzug gegeben wird. • Initial zur Verhinderung von unerwünschten Folgeerscheinungen und Komplikationen, die zu Beginn einer Behandlung mit LHRH-Agonisten durch den anfänglichen Anstieg des Serum -Testosteron hervorgerufen werden können. • Zur Behandlung von Hitzewallungen, die unter der Behandlung mit LHRH-Agonisten oder nach Hodenentfernung auftreten. […]

II. Zugelassene Arzneimittel im Anwendungsgebiet

GnRH-Antagonisten	
Abarelix L02BX01 Plenaxis®[1]	Plenaxis® ist angezeigt zur Einleitung einer hormonalen Kastration bei fortgeschrittenem oder metastasierendem hormonabhängigem Prostatakarzinom, wenn eine Androgensuppression erforderlich ist.
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.
Histrelin L02AE05 Vantas®[1]	Palliative Behandlung bei fortgeschrittenem Prostatakrebs.
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. […]

[1] Nicht verkehrsfähig

II. Zugelassene Arzneimittel im Anwendungsgebiet

Zytostatika	
Estramustin L01XX11 generisch	Palliative Behandlung des fortgeschrittenen hormonrefraktären Prostatakarzinoms
Docetaxel L01CD02 generisch	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) beim fortgeschrittenen kastrationsresistenten 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 neu diagnostizierten Hochrisiko-metastasierten hormonsensitiven Prostatakarzinoms (mHSPC) bei erwachsenen Männern in Kombination mit Androgenentzugstherapie (androgen deprivation therapy, ADT) • 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.
Sonstige	

II. Zugelassene Arzneimittel im Anwendungsgebiet

Radium-223-dichlorid ATC: 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: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2019-B-249 (Olaparib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	28. November 2019

Inhaltsverzeichnis

Abkürzungsverzeichnis

ADT	Androgen Deprivation Therapy
AE	Adverse Events
ASCO	American Society of Clinical Oncology
AUA	American Urological Association
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
cORR	clinical Overall Response Rate
CRPC	Castration-Resistant Prostate Cancer
EBRT	External Beam Radiation Therapy
EK	Expertenkonsens
ESMO	European Society for Medical Oncology
G-BA	Gemeinsamer Bundesausschuss
GCP	Good Clinical Practice
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
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
mCRPC	metastatic Castration-Resistant Prostate Cancer
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
OS	Overall Survival
PCa	Prostate Cancer
PCO	Provisional Clinical Opinion
PFS	Progression-Free Survival

PSA	Prostate-Specific Antigen
QoL/QOL	Quality of Life
RR	Relatives Risiko
SBRT	Stereotacitc Body Radiation Therapy
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

Metastasierte kastrationsresistente Prostatakarzinom bei erwachsenen Patienten.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *kastrationsresistentes Prostatakarzinom* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 21.10.2019 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 1025 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 20 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

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 - 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.

G-BA, 2012 [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 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, 2013 [5].

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, 2014 [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 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, 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 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, 2015 [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 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, 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).

Zweckmäßige Vergleichstherapie

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.

3.2 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.3 Systematische Reviews

Leal F et al., 2019 [13].

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.

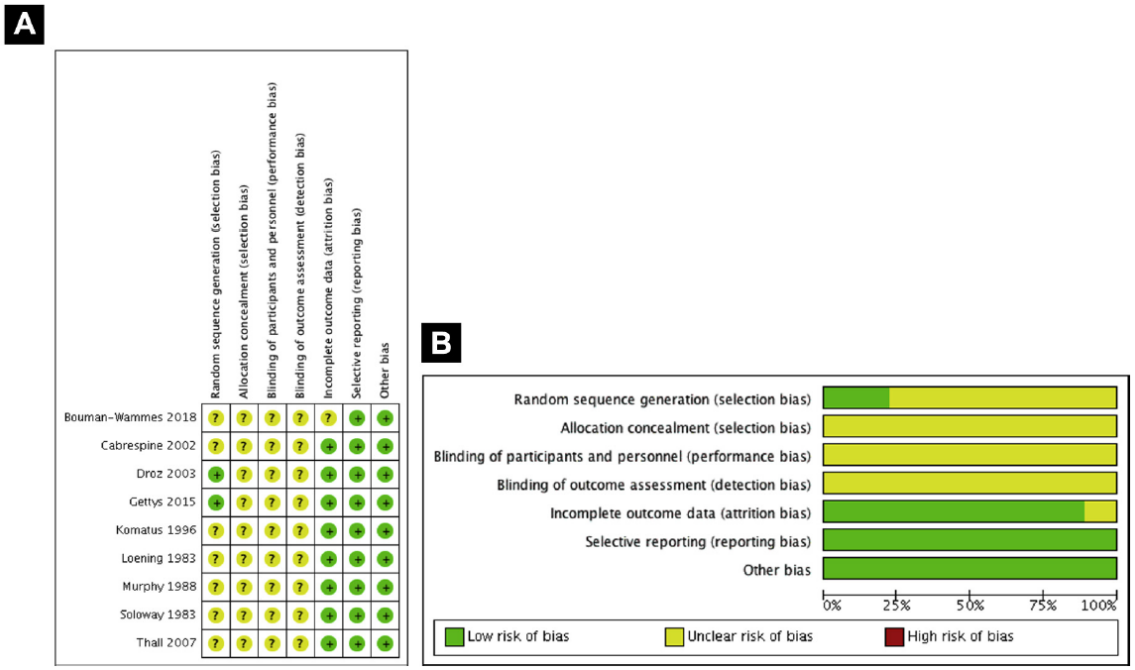

Figure 1: Risk of Bias. Risk of Bias (A) Within Randomized Studies, (B) Across Randomized Studies

<u>Studienergebnisse:</u>

Clinical Overall Response Rate

- 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).

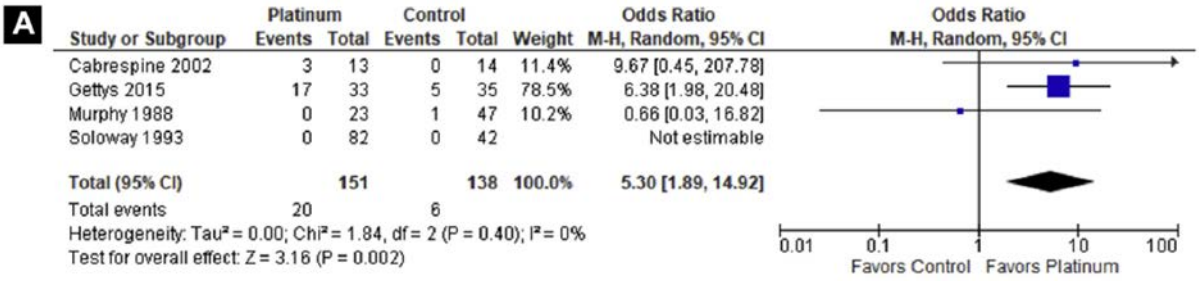

Figure 2A: Random-effect-model Meta-analysis of Platinum-containing Therapy Versus Other Nonplatinum Chemotherapy

Prostate-Specific Antigen Overall Response Rate

- 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)

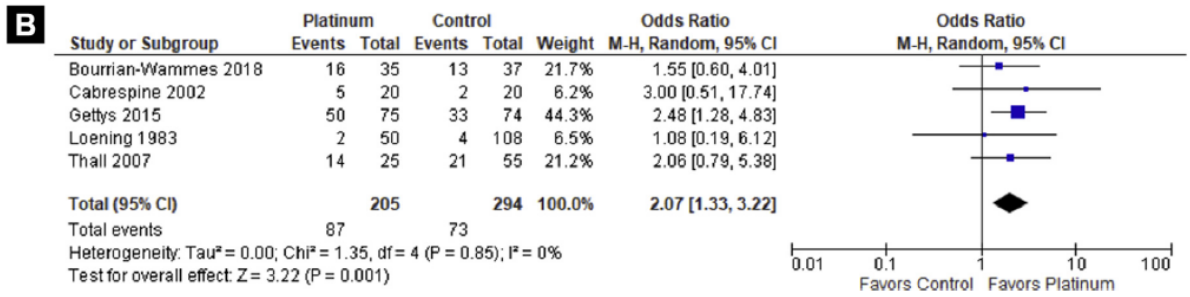

Figure 2B: Random-effect-model Meta-analysis of Platinum-Based Chemotherapy Versus Other Nonplatinum Chemotherapy

Progression-Free Survival

- 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 metaanalysis was not performed.

Overall Survival

- 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 end point.

Toxicity

- 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.

Referenzen:
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Fryzek, J. P. et al., 2018 [3].

Indirect treatment comparison of cabazitaxel for patients with metastatic castrate-resistant prostate cancer who have been previously treated with a docetaxel-containing regimen.

Fragestellung

to conduct an indirect treatment comparison between cabazitaxel, abiraterone and enzalutamide to determine the clinical efficacy and safety of cabazitaxel relative to comparators in the treatment of patients with metastatic castrate-resistant prostate cancer who progress on docetaxel-based therapies.

Methodik

Population:

- adult (age 18 or older) mCRPC patients previously treated with docetaxel-based regimens.

Intervention/Komparator:

- interventions of interest: cabazitaxel, abiraterone, enzalutamide, mitoxantrone, ipilimumab, radium-223, sipuleucel-T, and estramustine

Endpunkte:

- OS rate, PFS rate, and grade 3 or 4 AEs

Recherche/Suchzeitraum:

- MEDLINE, Embase, and Cochrane CENTRAL were conducted from January 1, 2010 to February 26, 2015

Qualitätsbewertung der Studien:

- using guidance adapted from the University of York's Centre for Reviews and Dissemination / Jadad score

Ergebnisse

Anzahl eingeschlossener Studien:

- Three of thirteen trials

Charakteristika der Population:

- The studies are similar in terms of treatment line (pre-treated with docetaxel-based regimen), study years (range: 2007–2010), total patients (range: 755–1199), age (median range: 68–69) and ECOG score (0–1 range: 90%-93%).

Qualität der Studien:

- Based on our assessment of design heterogeneity, we did not identify potential sources of qualitative variability or bias that would preclude the combination of quantitative data across studies. Because only a few studies were deemed relevant for the quantitative meta-analysis, we were able to efficiently compare and contrast the study design and characteristics between studies. Specifically, for OS, important study characteristics, such as age, ECOG score, and length of follow-up were relatively similar between studies. The TROPIC study had an expanded definition for a progression-free endpoint, which may have shortened PFS compared to AFFIRM or COU-AA-301.

Studienergebnisse:

- Individual study results
  - for median OS

Table 2. Hazard ratios (HR) and 95% Confidence Interval (CI) for overall survival (OS) for studies included in the indirect treatment comparison for cabazitaxel, abiraterone acetate and enzalutamide.

Author (Year)	Acronym	Treatment / Comparator	Length of follow-up (median)	Median OS HR (95% CI)	HR p-value
Joulain (2010)	TROPIC	Cabazitaxel + prednisone /	623.96 days	0.72 (0.61–0.84)	<0.0001
		Mitoxantrone + prednisone			
Fizazi (2012)	COU-AA-301	Abiraterone acetate + prednisone /	614.82 days	0.74 (0.64–0.86)	<0.0001
		Placebo + prednisone			
Scher (2012)	AFFIRM	Enzalutamide /	438.29 days	0.63 (0.53–0.75)	<0.001
		Placebo			

  - Median PFS

Table 3. Hazard ratios (HR) and 95% Confidence Interval (CI) for progression-free survival (PFS) for studies included in the indirect treatment comparison for cabazitaxel, abiraterone acetate and enzalutamide.

Study	Treatment	Length of follow-up (median)	Median PFS HR (95% CI; p-value)	Description of PFS Endpoint
TROPIC	Cabazitaxel + prednisone	85 days	0.75 (0.65–0.87; <0.0001)	The earliest progression in tumor, PSA or pain or death
	Mitoxantrone + prednisone	43 days		
COU-AA-301	Abiraterone acetate + prednisone	170.45 days	0.66 (0.58–0.76; <0.0001)	Soft-tissue disease progression by modified Response Evaluation Criteria In Solid Tumors (RECIST) criteria
	Placebo + prednisone	109.57 days		
AFFIRM	Enzalutamide	252.63 days	0.40 (0.35–0.47; <0.001)	Progression of soft-tissue disease according to RECIST, version 1.1, progression of osseous disease according to bone scans showing two or more new lesions per PCWG2, and death from any cause.

- Indirect treatment comparison results
  - Overall survival: No statistically significant difference in median OS for patients treated with abiraterone was observed when compared with patients treated with cabazitaxel. While patients on enzalutamide had a better median OS compared to cabazitaxel, this difference was not statistically significant. For this analysis, statistical heterogeneity was not significant (I2 3.1% (0%-89.9%)) and the DIC was low (DIC = 5.93).
  - Progression-free survival: PFS was modestly lower for abiraterone than cabazitaxel, but the difference was not statistically significant.
  - Adverse events: The results for the AEs must be interpreted with caution as many of these outcomes were based on very few events resulting in unstable risk estimates. Of some of the more frequently reported AEs in the 3 included trials (e.g., fatigue, anaemia, back pain, diarrhoea), only anaemia (OR = 3.71; 95% CI = 1.01–10.44) and diarrhoea (OR = 16.60; 95% CI = 1.41–75.31) were statistically significantly more likely to occur in the cabazitaxel group compared to abiraterone. In addition, the indirect treatment comparison showed haematuria (OR = 3.88; 95% CI = 1.03–10.09) and pyrexia (OR = 36.23; 95% CI = 1.14– 206.40) were higher among those receiving cabazitaxel compared to those receiving abiraterone and enzalutamide, respectively. None of the other AEs were statistically significantly different for the three groups.

Anmerkung/Fazit der Autoren

In this analysis ofpivotal clinical trial data, cabazitaxel, abiraterone and enzalutamide had similar survival outcomes and AE profiles. To the best ofour knowledge, this is the first indirect treatment comparison including these 3 agents evaluating both efficacy and safety outcomes. Data from future trials should be incorporated into this study framework to garner additional information about the relative performance ofthese drugs.

Kommentare zum Review

- Es bestehen Unsicherheiten bezüglich der methodischen Qualität (insbesondere bzgl. der Berücksichtigung weiterer möglicher Effektmodifikatoren (z. B. Gleason Score, PSA, etc.).
- AEs must be interpreted with caution as well since patients treated with mitoxantrone/prednisone may experience different rates of safety outcomes than those treated with prednisone alone.

Ghatalia P et al., 2017 [11].

Effect of Single-agent Daily Prednisone on Outcomes and Toxicities in Metastatic Castration-resistant Prostate Cancer: Pooled Analysis of Prospective Studies

Fragestellung

we performed a meta-analysis comparing the control or placebo arms of trials of patients with mCRPC that had or had not included low-dose oral daily prednisone.

Methodik

Population:

- metastatic castration-resistant prostate cancer (mCRPC)

Intervention/Komparator:

- single-agent placebo (or no anticancer therapy) or single agent prednisone (with or without a placebo) were eligible for analysis.
- Patients receiving prednisone combined with other agents were excluded.

Endpunkte:

- Efficacy outcomes (OS, progression-free survival [PFS], PSA response, pain response, Response Evaluation Criteria In Solid Tumors response) and toxicity outcomes (toxicities of all grades and grade ≥ 3 toxicities) were collected, with special emphasis on hyperglycemia, hypertension, hypokalemia, skeletal-related events, and edema.

Recherche/Suchzeitraum:

- PubMed/Medline from January 1966 to January 2015

Qualitätsbewertung der Studien:

- Jadad score (0-5 Punkte)

Ergebnisse

Anzahl eingeschlossener Studien:

- 18 trials; 9 had control arms that contained prednisone (n = 2831) and 9 did not (n = 2784).

Charakteristika der Population:

- Across the 17 trials that reported patient age, the median age was 71 years (range, 67-75.5 years). Age, pre- and post docetaxel status, ECOG PS, and publication year were similar in both groups. No statistically significant difference was reported for any characteristic between the trials that included prednisone and those that had not.

Table 1 Randomized Trials Eligible for Meta-analysis

Investigator	CA[a]	TP	CA[b]	DS	Age,[c] y	ECOG PS 0-1 Versus 2, %	Hb,[c] mg/dL	AP,[c] IU/L	Baseline PSA,[c] ng/mL	GS ≥ 8, n (%)	LDH,[c] U/L	Overall With VM or LM, %	mOS, mo[d]	mPFS, mo[d]	Response, %		Toxicity, n (%)		Jadad Score
															PSA	RECIST	All	Grade ≥ 3	
Trials with control arms containing prednisone																			
DeBono et al,[6] 2011	398	III	394	Post	69 (39-90)	89 versus 11	11.8 (7.2-16.5)	NR	137.7 (0.6-1011.4)	189 (54)	237.5 (123-5125)	11 (liver)	10.9	3.6	5.5	2.8	381 (97)	175 (44.2)	5
Dreicer et al,[37] 2014	146[e]	III	365	Post	70 (48-87)	2 versus 7	NR	NR	134 (1-1900.9)	NR	NR	NR	15.2	5.7	10	3	95 (60)	55 (18)	5
Ryan et al,[38] 2013	218[e]	III	540	Pre	70 (44-90)	NR	NR	90 (21-3056)	37.7 (0.7-6606.4)	254 (50)	184 (87-781)	0 (overall)	27.2	8.3	24	16	524 (97)	225 (42)	5
De Wit et al,[39] 2014	685[f]	III	770	Pre	72 (46-90)	2 versus < 1	< 12, 28%	> 175, 24%	55.3 (1.71-3906)	397 (51)	NR	18 (overall)	29.5	8.7	28	NR	731 (95)	377 (49)	3
Michaelson et al,[40] 2014	167[e]	III	285	Post	68 (47-86)	100 versus 0	NR	NR	NR	129 (45)	NR	NR	11.8	4.1	NR	2	256 (90)	86 (30)	5
Boccardo et al,[41] 2008	44[e,f]	II	44	Pre	75.5 (63-89)	0, 84; 1-2, 15.8	13 (9.5-15.4)	321 (104-2756)	52.07 (5.34-3351)	≥7: 23 (60.5)	NR	0 (liver)	20.5[g]	4.5[h]	11.4	0	43.2%	18.2%	4
Small et al,[42] 2000	230[f]	III	230	Pre	68 (39-87)	NR	NR	NR	186 (6-7898)	NR	NR	12 (overall)	9.9	NR	16	NR	NR	NR	4
Tannock et al,[1] 1996	54[f]	NR	80	Pre	67 (64-74)	63 versus 26	NR	NR	NR	NR	NR	4 (overall)	17.4	NR	22	NR	NR	NR	2
Kantoff et al,[2] 1999	116[e]	NR	123	Pre	72 (65-75)	88 versus 12	12.4 (11-13)	163 (104-369)	141 (54-416)	NR	NR	16 (liver)	12.6	NR	21.5	NR	NR	NR	2
Total	2091	NA	2831	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Trials with control arms not containing prednisone																			
Scher et al,[9] 2012	208[e]	3	399	Post	NR	14.2 versus 7.2	NR	NR	19.2[i]; 10.3[j]	NR	19.2[i]; 8.5[j]	NR	13.6 (11.3-15.8)	2.9	2	4	390 (98)	212 (53)	5
Kwon et al,[11] 2014	305[e]	3	400	Post	67.5 (45-86)	98 versus 0	< 11, 28%; ≥ 11, 67%	< 1.5 × ULN, 58%; > 1.5 × ULN, 38%	176.4 (0-1376.8)	> 7, 47%	< 2 × ULN, 81%; > 2 × ULN, 13%	29 (overall)	10 (8.3-11)	2.1 (2.9-3.4)	5.2	NR	364 (92)	162 (41)	5
Beer et al,[10] 2014	845[e]	3	845	Pre	71 (42-93)	100 versus 0	13.1 (7.4-16.7)	86 (27-2350)	44.2 (0.3-3637)	52.5	185 (67-2321)	12.5 (overall)	31	3.9	3	5	218 (25.8)	16 (1.9)	5
Nelson et al,[43] 2012	NA	3	295	Pre	71 (46-90)	100 versus 0	NR	NR	52.9 (0.7-1860)	NR	NR	NR	22.5	6.5	NR	NR	256 (86.8)	120 (40.7)	5

Table 1 Continued

Investigator	CA[a]	TP	CA[b]	DS	Age,[c] y	ECOG PS 0-1 Versus 2, %	Hb,[c] mg/dL	AP,[c] IU/L	Baseline PSA,[c] ng/mL	GS ≥ 8, n (%)	LDH,[c] U/L	Overall With VM or LM, %	mOS, mo[d]	mPFS, mo[d]	Response, %		Toxicity, n (%)		Jadad Score
															PSA	RECIST	All	Grade ≥ 3	
James et al,[44,45] 2009	51[e]	2	205	Pre	72 (49-91)	NR	NR	NR	72 (0.1-3067)	NR	NR	NR	17.3	3.7[h]	NR	0	93 (87)	26 (24.3)	4
Pili et al,[46] 2011	38[f]	2	67	Pre	73.2 (48-89)	100 versus 0	13.2	87	19	>7, 25 (37)	206	15 (overall)	NR	3.3	NR	0	NR	10%	5
Carducci et al,[47] 2007	NA	3	401	Pre	72 (45-92)	97 versus 3	13.2 (9.1-18.1)	24.8 (2-1599)	79.6 (2.2-5424.8)	NR	NR	NR	NR	NR	NR	NR	NR	NR	4
Carducci et al,[48] 2003	NA	2	104	Pre	72	NR	13.2	NR	94.8	NR	177	NR	NR	4.6[h]	NR	NR	NR	NR	4
Iversen et al,[49] 1997	68[f]	NR	68	Pre	73 (51-84)	0-1, 75%; 2-3, 25%	<6, 8.8%; 6-6.9, 20.6%; 7-7.9, 35.3%; >7.9, 35.3%	< 1.25 ULN, 41.2; 1.26-2.5, 20.6%; 2.6-5, 19.1%; 5.1-10, 11.8%	< 1.25, 13.2%; 2.6-5, 5.9%; 5.1-10, 13.2%; > 10, 67.7%	NR	NR	NR	6.1	NR	2	NR	NR	NR	3
Total	2962	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Abbreviations: AP = alkaline phosphatase; CA = control arm; DS = docetaxel status; ECOG = Eastern Cooperative Oncology Group; GS = Gleason score; Hb = hemoglobin; LDH = lactate dehydrogenase; LM = liver metastasis; mOS = median overall survival; mPFS = median progression-free survival; NA = not applicable; NR = not reported; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; Pre = before docetaxel use; Post = after docetaxel use; PS = performance status; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria In Solid Tumors; ULN = upper limit of normal; VM = visceral metastasis.
[a]Number of patients evaluable for efficacy.
[b]Number of patients evaluable for toxicity.
[c]Data presented as median (range).
[d]Data in parentheses are 95% confidence intervals.
[e]For ORR.
[f]For PSA response rate.
[g]Defined as time to death.
[h]Defined as time to progression.
[i]Less than the median.
[j]Greater than the median.

Qualität der Studien:

- Randomized treatment allocation sequences were generated in all trials. The follow-up time was generally adequate for each trial. Four trials were in the low-quality group (Jadad score 2-3). All other trials were high quality (Jadad score 4-5).

Studienergebnisse:

- no significant differences were identified for OS or toxicities of any grade.

- A significantly greater PSA response rate (18.8% vs. 2.5%; P = 0.023) and a trend toward more frequent grade ≥ 3 fluid retention (1.0% vs. 0.4%; P = 0.097) was seen in the prednisone group.
- In bivariate analyses, prednisone was significant as a prognosticator of PSA response rate, adjusted for age, ECOG PS, previous docetaxel status, or year of publication.
- The median PFS was longer among the treatment arms with prednisone, irrespective of whether patients had received previous docetaxel (8.3 vs. 3.9 months for patients who received previous docetaxel and 4.1 vs. 2.5 months in the docetaxel-naive setting).
- Prednisone was significantly associated with PFS after adjusting for docetaxel status. Single-agent prednisone for mCRPC did not improve OS but was associated with a greater PSA response rate and PFS (Table 4).
- Overall and grade ≥ 3 toxicities were not significantly different with prednisone (Table 4).

Table 4 Significance (*P* Values) for Association of Prednisone With Outcomes in Bivariate Analyses

	Outcome					
Adjustment Factor	**OS**	**PFS**	**PSA**	**RECIST**	**Any Toxicity**	**Grade 3 Toxicity**
Age	.91	.13	.023[a]	.66	.22	.13
ECOG PS	.85	.16	.027[a]	.39	.73	.72
Docetaxel status	.90	.013[a]	.008[a]	.42	.52	.40
Year of publication	.71	.11	.010[a]	.57	.58	.34
Baseline PSA	.92	.035[a]	.074	.20	.20	.10
Visceral disease	.37	.21	.062	.84	.12	.016[a]
Study phase	.84	.10	.052	.74	.44	.30

Abbreviations: ECOG = Eastern Cooperative Oncology Group; OS = overall survival; PFS = progression-free survival; PS = performance status; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria In Solid Tumors.
[a]Statistically significant.

Anmerkung/Fazit der Autoren

our meta-analysis provides useful insights regarding the effect of prednisone on efficacy and toxicities. These data could assist in designing trials and also improve clinical practice. A rationale can be made to avoid daily prednisone in routine daily practice (except in combination with abiraterone, for which it is has a proven role to mitigate toxicities) and in the control arms of randomized trials. In contrast, in trial-ineligible and selected patients, investigators should use their discretion to provide low-dose oral corticosteroids for the potential palliative benefits.

Kommentare zum Review

The present study had the limitations of a trial-level meta-analysis. Individual patient level data were unavailable. However, trial-level meta-analyses appear to provide results similar to those from individual-patient level meta-analyses. Moreover, individual patient level data are generally unavailable for all eligible trials for a meta-analysis, and the individual analysis of a subset of trials will lead to selection biases. Differences in reporting did not permit us to compare toxicities of all grades in all 18 trials. Additionally, a multivariable analysis of all the endpoints was not possible. However, we were able to evaluate the most relevant toxicities.

Iacovelli R et al., 2017 [12].

The Cardiovascular Toxicity of Abiraterone and Enzalutamide in Prostate Cancer

Fragestellung

to update our previous findings related to abiraterone and enzalutamide, including the new available evidences both in castration-resistant prostata cancer (CRPC) and in metastatic hormone-sensitive prostata cancer (HSPC) settings.

Methodik

Population:

- patients with PC

Intervention/Komparator:

- abiraterone and enzalutamide ± prednisone group was considered to be the experimental arm and a placebo ± prednisone group the control

Endpunkte:

- Both all-grade (grades 1-4) and high-grade (grades 3-5) events were considered to be the main outcomes

Recherche/Suchzeitraum:

- We searched MEDLINE/PubMed, the Cochrane Library, and the American Society of Clinical Oncology (ASCO) University Meeting abstracts for citations from 2013 to June 15, 2017.
- search criteria were limited to articles published in the English language and phase III or phase II randomized controlled trials in patients with PC

Qualitätsbewertung der Studien:

- Study quality was assessed using the Jadad 5-item scale, taking into account randomization, double blinding and withdrawals. The final score ranged from 0 to 5.

Ergebnisse

Anzahl eingeschlossener Studien:

- 7 articles were included in the qualitative and quantitative syntheses (n=8660 patients).[13-19]
- Four studies compared abiraterone plus prednisone over a placebo plus prednisone, whereas the remaining 3 compared enzalutamide over a placebo in 2 studies and enzalutamide over bicalutamide in the last study.
- Five studies were performed in patients with metastatic CRPC and 2 in patients with metastatic HSPC.

Charakteristika der Population:

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

Qualität der Studien:

- All the studies were randomized, double-blind clinical trials, with the exception of the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial, which was an open label study. This last trial has 3 points in the Jadad score, whereas all other studies have 5 points.

Studienergebnisse:

Table 1 Main Characteristics of the Included Studies

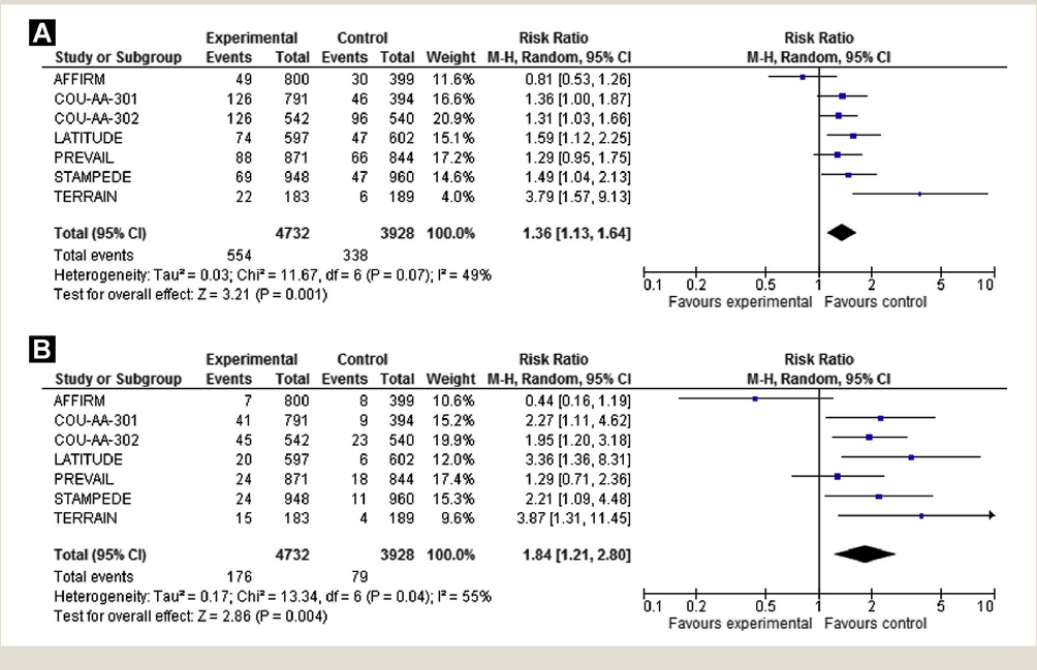
Trial	Year	Previous Docetaxel	Required ADT	Experimental Arm		Control Arm		Median Treatment Duration, mos Exp./Ctr.	Median Follow-up, mos	CTCAE Version	Jadad Score
				No. Pts	Therapy	No. Pts	Therapy				
COU-AA-301	2012	Yes	Yes	791	Abiraterone + P 10 mg	394	Placebo + P 10 mg	8.0/4.0	12.8	3	5
COU-AA-302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

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

Cardiac Toxicity

- In the experimental arm, the incidence of all-grade cardiac events was 11.7%, whereas in the control arm, it was 8.6%.
- Treatment with new hormonal agents increased the risk of all-grade toxicity by 36% and high-grade cardiac toxicity by 84%, both significant heterogeneity (Figure 2A & 2B).

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



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

- abiraterone increased significantly all-grade and high-grade cardiac toxicity compared with placebo, but enzalutamide was not significantly associated (Table 2).

Table 2 Incidence and Relative Risk of Cardiovascular Toxicities by Type of Treatment

Type of Toxicity	Toxicity Grade	Abiraterone				Enzalutamide			
		Exp. Arm, %	Ctr. Arm, %	RR (95% CI); *P* Value	Heterogeneity	Exp. Arm, %	Ctr. Arm, %	RR (95% CI); *P* Value	Heterogeneity
Cardiac	All	13.7	9.5	1.41 (1.21-1.64); <.001	$\chi^2 = 0.96$, $P = .81$; $I^2 = 0\%$	8.6	7.1	1.41 (0.75-2.63); .28	$\chi^2 = 9.82$, $P = .007$; $I^2 = 80\%$
	High	4.5	2.9	2.22 (1.60-3.27); <.001	$\chi^2 = 1.09$, $P = .8$; $I^2 = 0\%$	2.5	2.1	1.32 (0.85–2.06); .2	$\chi^2 = 8.44$, $P = .01$; $I^2 = 76\%$
Hypertension	All	26.2	14.8	1.79 (1.45-2.21); <.001	$\chi^2 = 9.47$, $P = .02$; $I^2 = 68\%$	10.5	4.2	2.74 (2.07–3.63); <.001	$\chi^2 = 2.36$, $P = .31$; $I^2 = 15\%$
	High	6.9	3.6	2.19 (1.73-2.78); <.001	$\chi^2 = 4.52$, $P = .21$; $I^2 = 34\%$	4.8	2.2	2.44 (1.64–3.63); <.001	$\chi^2 = 1.91$, $P = .39$; $I^2 = 0\%$

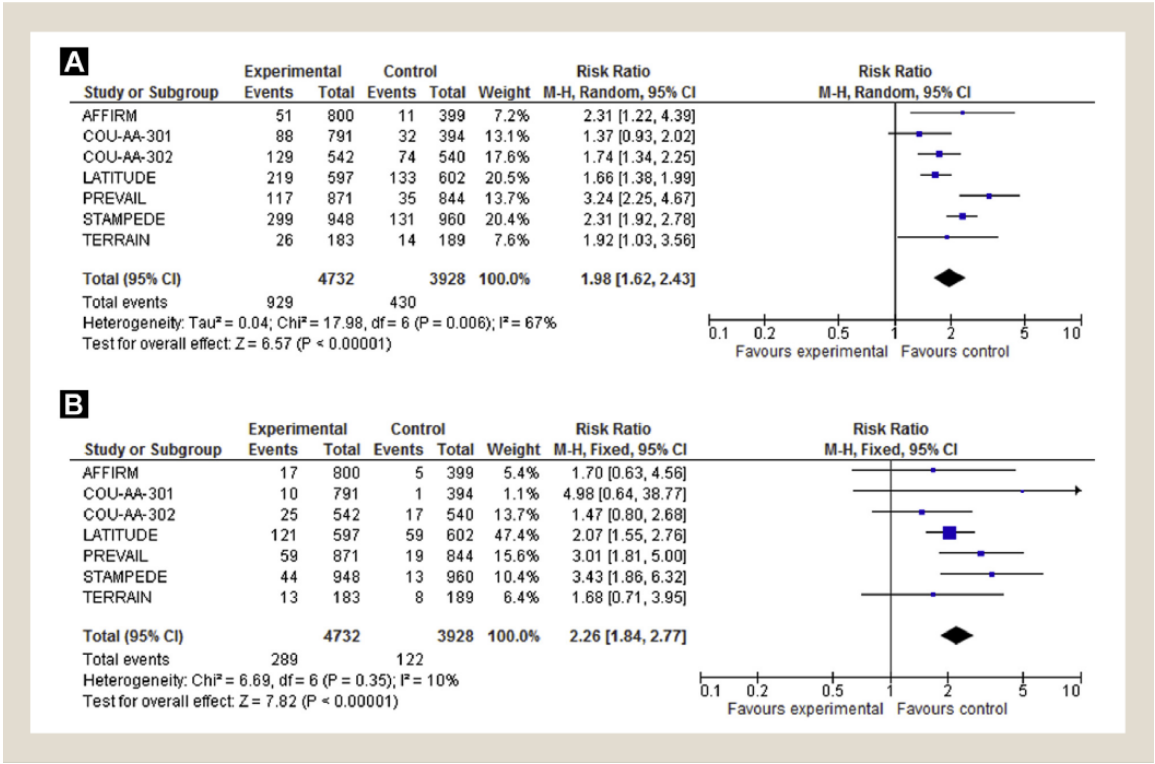
Abbreviations: CI = confidence interval; Ctr. = control; Exp. = experimental; I^2 = inconsistency; RR = risk ratio.

- No differences were found in the RR of both all-grade (P =0.9) and high-grade (P= 0.3) cardiac toxicity between abiraterone and enzalutamide.
- When studies performed in patients with HSPC were compared with those performed in patients with CRPC, patients treated with abiraterone with CRPC have significant major incidence of high-grade cardiac toxicity events compared with patients with HSPC, but no increase of all-grades cardiac toxicity was found. The same evidence was found for patients treated with placebo.

Hypertension

- Treatment with new hormonal agents increased the risk of all-grade toxicity by 98% and more than doubled the risk of high-grade hypertension (Figure 3A & 2B).

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



- Abiraterone and enzalutamide were significantly associated with all-grade and high-grade hypertension (Table 2).
- A significant difference was found in the RR for all-grade (P=0.04) but not for high-grade (P=0.7) hypertension between abiraterone and enzalutamide.
- When studies performed in patients with HSPC were compared with those performed in patients with CRPC, patients treated with abiraterone for HSPC have major incidence of hypertension, but the difference was not significant. When the incidence of hypertension

was compared in patients treated with placebo, patients with HSPC have a significantly increased incidence of adverse events compared with patients with CRPC.

Role of Prednisone Dose

- A total of 2267 patients received prednisone 10 mg daily, and 3107 patients received prednisone 5 mg daily; among these 2 groups, 1333 and 1545 received abiraterone.
  - o No significant difference was found between the RR of all-grade and high-grade cardiac toxicity in patients treated with 10 mg or 5 mg prednisone.
  - o No significant difference was found between the RR of all grades and high-grade hypertension in patients treated with 10 mg or 5 mg prednisone

Anmerkung/Fazit der Autoren

Despite these limitations, our analysis reported a significant increase of cardiac toxicity and hypertension in patients receiving abiraterone or enzalutamide for PC. Considering that, patients should be investigated for pre-existing risk factors in order to optimize those who are modifiable, and there should be careful follow-up for the onset of new treatment-related cardiovascular events.

Kommentare zum Review

The increased incidence of cardiac toxicity in patients treated for CRPC but not for HSPC suggests that the length of therapy with abiraterone, longer in patients with HSPC, is not directly related to the increased risk of cardiac events. These are probably related to the longer duration of Androgen deprivation therapy (ADT) in patients with CRPC. The increased incidence of hypertension in HSPC is probably related to the use of lower dose of prednisone in these trials and to the increased risk of abiraterone-related toxicities.

The evaluation of cardiovascular toxicity in this analysis must also account for several factors. First, not all the patients had previous therapy with ADT, and others could have several years of exposition and continue this treatment during the administration of new hormonal therapies. This analysis was also unable to explore the effect of several other factors such as a patient's medical history, age, and other possible data that may be predictive of cardiovascular toxicity. Moreover, the definition of cardiac toxicity includes several diseases that cannot be standardized over the trials included.

Poorthuis MHF et al., 2017 [17].

First-line non-cytotoxic therapy in chemotherapy naïve patients with metastatic castration-resistant prostate cancer: a systematic review of 10 randomised clinical trials.

Fragestellung

The aim of this study is to systematically evaluate all available treatment options in chemotherapy-naive patients with metastatic castration-resistant prostate cancer (mCRPC).

Methodik

Population:

- chemotherapy-naive patients with mCRPC

Intervention:

- first-line treatment (abiraterone, enzalutamide, 223radium, sipuleucel-T, orteronel, or classic androgen receptor-blocker therapy)

Komparator:

- placebo, prednisone, or each other

Endpunkte:

- PFS, OS, QoL like Prostate cancer (FACT-P) questionnaire or EQ-5D questionnaire, or AE

Recherche/Suchzeitraum:

- PubMed, EMBASE, and the Cochrane library (including CDSR, DARE, and CENTRAL) from 2007 to 1 March 2016 to identify articles reporting original data written in English or Dutch

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- N=10 RCTs, davon 9 mit Placebovergleich und 1 RCT mit Vergleich von Biculatamid 50mg tgl. und Enzalutamide 160mg tgl.

Charakteristika der Population:

Table 1 Overview of baseline demographic and clinical characteristics of the patients in the included randomised clinical trials.

Study	No. of included patients		Experimental agent	Comparison	Median/mean (range) age, years		Patients previously treated with chemotherapy or docetaxel, *n* (%) or %	Median PSA level, ng/mL[a]	Sites of metastases, *n* (%)[a]	Duration of follow-up, months, median	Trial identification number
	Exp.	Comp.			Exp.	Comp.					
COU-AA-302 [16–21]	546	542	Abiraterone acetate 1000 mg daily plus prednisone 5 mg twice a day	Prednisone 5 mg twice daily plus placebo	71.0 (44–95)	70.0 (44–90)	0 (0)	42.0/37.7	Bone only: 274 (51)/267 (49) Soft tissue or node: 267 (49)/271 (50) Visceral 0 (0)/0 (0)	49.2	NCT00887198
PREVAIL [22,23]	872	845	Enzalutamide 160 mg daily	Placebo	72 (43–93)	71 (42–93)	0 (0)	54.1/44.2	Bone: 741 (85.0)/690 (81.7) Lymph node: 437 (50.1)/434 (51.4) Visceral disease (lung or liver): 98 (11.2)/106 (12.5)	~22	NCT01212991
ALSYMPCA [24–28]	614[b]	307[b]	^{223}Radium 50 kBq/kg every 4 weeks; total of 6 injections	Placebo	71 (49–90)[c]	71 (44–94)[c]	Previous docetaxel use: 352 (57)/174 (57)[d]	146/173[e]	≥2 bone: 614 (100)/307 (100) Visceral: 0 (0)	36 (planned)	NCT00699751
^{223}Radium vs placebo trial [29,30]	33	31	^{223}Radium 50 kBq/kg every 4 weeks; total of 4 injections	Placebo	73 (57–88)	72 (60–84)	N/A[f]	167/233[g]	Bone: 64 (100)	≥18 (range 18–24)	NCT00459654
IMPACT [31,32]	341	171	Sipuleucel-T every 2 weeks, total of 3 infusions	Placebo	72 (49–91)	70 (40–89)	Previous chemotherapy use: 19.6% vs 15.2%. Previous docetaxel use: 15.5% vs 12.3%.	51.7/47.2	Bone only: (50.7)/(43.3) Soft tissue only: (7.0)/(8.2) Bone and soft tissue: (41.9)/(48.5) Visceral: (0)/(0)	34.1	NCT00065442
D9901and D9902A [33,34]	147	78	Sipuleucel-T every 2 weeks, total of 3 infusions	Placebo	72 (47–85)	71 (50–87)	6.9% vs 9.0%[h]	50.7/45.8	Bone only: (44.5)/(26.7) Soft tissue only: (8.2)/(13.3) Bone and soft tissue: (47.3)/(60.0) Visceral: (0)/(0)	N/A	NCT00005947 and NCT01133704
ELM-PC4 [35]	781	779	Orteronel 400 mg plus prednisone 5 mg twice daily	Placebo plus predisone 5 mg twice daily	71.0 (65.0–77.0)	72.0 (66.0–77.0)	0 (0)	55.8/55.3	Bone: 730 (93)/705 (91) Liver: 27 (3)/45 (6) Lung: 71 (9)/70 (9) Lymph node: 346 (44)/329 (42)	20.7	NCT01193244
Bicalutamide vs placebo trial [36–39]	102	101	Bicalutamide 80 mg daily	Placebo	<75 years: 53 (52.0%) ≥75 years: 49 (48.0%)	<75 years: 50 (49.5%) ≥75 years: 51 (50.5%)	0 (0)	<60: 40 (39.2%)/37 (36.6%) ≥60: 62 (60.8%)/64 (63.4%)	Bone: 40 (39.2)/40 (39.6) Lymph node: 28 (27.5)/38 (37.6) Other: 2 (2.0)/3 (3.0)	62.4	N/A

TERRAIN [40]	184	191	Bicalutamide 50 mg daily	Enzalutamide 160 mg daily	71 (48–91)	71 (50–96)	0 (0)	22/21	Bone only: 83 (45)/92 (48) Soft tissue only: 36 (20)/29 (15) Bone and soft tissue: 64 (35)/69 (36) Missing: 1 (1)/1 (1)	16.7/20.0	NCT01288911

[a]If possible, data are provided for the experimental group and the control group respectively. [b]The number of included patients without previous docetaxel use was 262 and 113 in the experimental group and the comparison group, respectively. [c]The median age of included patients without previous docetaxel use was 74 (49–90) and 74 (52–94) years in the experimental group and the comparison group, respectively. [d]These patients that had not received docetaxel, declined or were not healthy enough to receive docetaxel. [e]The median PSA level of included patients without previous docetaxel use was 88 (4–5837) and 98 (2–2210) µg/L for the experimental group and the comparison groups, respectively. [f]Patients with chemotherapy during the past 6 weeks were excluded from this study. [g]Two consecutive rising amounts of serum PSA was one of the inclusion criteria. [h]These patients received chemotherapy ≥6 months prior to inclusion. Comp, comparison group; Exp, experimental group; IQR, interquartile range; kBq, kilobecquerel.

<u>Qualität der Studien:</u>

- Siehe Angaben im Ergebnisteil

<u>Studienergebnisse:</u>

- Abiraterone plus prednisone vs placebo plus prednisone

Patient or population: Chemotherapy-naive asymptomatic or mildly symptomatic patients with mCRPC and without visceral metastases
Intervention: Abiraterone plus prednisone
Comparison: Placebo plus prednisone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Placebo plus prednisone	Corresponding risk Abiraterone plus prednisone				
PFS	**649 per 1000**	**420 per 1000** (376–472)	**HR 0.52** (0.45–0.61)	1088 (1 study)	⊕⊕⊕⊕ **high**	
OS Deaths	**714 per 1000**	**637 per 1000** (584–688)	**HR 0.81** (0.70–0.93)	1088 (1 study)	⊕⊕⊕⊕ **high**	
QoL FACT-P deterioration after 1 year	**795 per 1000**	**652 per 1000** (604–700)	**RR 0.82** (0.76–0.88)	1088 (1 study)	⊕⊕⊕⊕ **high**	
Toxicity AE grade ≥3	**437 per 1000**	**533 per 1000** (472–607)	**RR 1.22** (1.08–1.39)	1082 (1 study)	⊕⊕⊕⊕ **high**	

The **corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.*

- Enzalutamide vs placebo

Patient or population: Chemotherapy-naïve asymptomatic or mildly symptomatic patients with mCRPC
Intervention: Enzalutamide
Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Placebo	Corresponding risk Enzalutamide				
PFS at 12 months	**191 per 1000**	**39 per 1000** (31–48)	**HR 0.19** (0.15–0.23)	1633 (1 study)	⊕⊕⊕⊕ **high**	
OS at 12 months Survival	**830 per 1000**	**715 per 1000** (654–774)	**HR 0.71** (0.60–0.84)	1717 (1 study)	⊕⊕⊕⊕ **high**	
QoL FACT-P	**229 per 1000**	**396 per 1000** (339–461)	**RR 1.73** (1.48–2.01)	1616 (1 study)	⊕⊕⊕⊕ **high**	
QoL EQ-5D	**159 per 1000**	**277 per 1000** (222–342)	**RR 1.74** (1.40–2.15)	1435 (1 study)	⊕⊕⊕⊕ **high**	
Toxicity AE grade≥ 3	**371 per 1000**	**430 per 1000** (382–482)	**RR 1.16** (1.03–1.30)	1715 (1 study)	⊕⊕⊕⊕ **high**	

The **corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.*

- 223Radium vs placebo

Patient or population: Patients with mCRPC and ≥2 bone metastases and no known visceral metastases. This RCT included patients with previous docetaxel use and docetaxel-naive patients considered unfit for docetaxel
Intervention: ^{223}Radium
Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Placebo	Corresponding risk 223-Radium				
PFS	–	–	–	–	–	No evidence available
OS (continuous)	**16.1 months**	**11.5 months**	**HR 0.69** (0.52–0.92)	474 (1 study)	⊕⊕⊕⊕ **high**	Not possible to calculate the mean difference since no details on statistical variability were provided.
OS at 24 months	**129 per 1000**	**64 per 1000** (35–114)	**HR 0.48** (0.26–0.88)	64 (1 study)	⊕⊕⊕⊖ **moderate**†	
QoL meaningful improvement at week 24 by FACT-P total score	**83 per 1000**	**182 per 1000** (96–343)	**RR 2.18** (1.15–4.12)	434 (1 study)	⊕⊕⊕⊕ **high**	
QoL meaningful improvement at week 24 by EQ-5D utility score	**153 per 1000**	**218 per 1000** (139–344)	**RR 1.43** (0.91–2.25)	474 (1 study)	⊕⊕⊕⊖ **moderate**‡	
Toxicity	**592 per 1000**	**575 per 1000** (480–687)	**RR 0.97** (0.81–1.16)	383 (1 study)	⊕⊕⊕⊖ **moderate**‡	
Toxicity Haematological AE grade 3–4	**65 per 1000**	**83 per 1000** (15–467)	**RR 1.29** (0.23–7.24)	64 (1 study)	⊕⊕⊖⊖ **low**†,‡	
Serious AEs	**452 per 1000**	**235 per 1000** (113–479)	**RR 0.52** (0.25–1.06)	64 (1 study)	⊕⊕⊖⊖ **low**†,‡	

The **corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. †High risk of bias because of no blinding of patients and personnel after 12 months with 24 months of follow-up. ‡Lower interval of the CI results in different conclusion than the upper limit.*

- Sipuleucel-T vs placebo

Patient or population: Asymptomatic or mildly symptomatic patients with mCRPC and without visceral metastases
Intervention: Sipuleucel-T
Comparison: Placebo

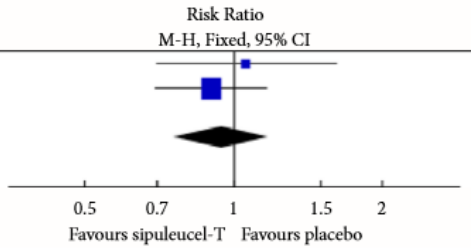
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Placebo	Corresponding risk Sipuleucel-T				
PFS	Unknown	Unknown	**IMPACT**: HR 0.95 (0.77–1.17) **D9901 and D9902A**: HR 1.26 (0.95–1.68)	3 studies	⊕⊕⊖⊖ **low**†,‡	Continuous outcomes are not provided in the studies and HRs of the two studies could not be pooled, because in the IMPACT study, the risk estimate was defined as the risk in patients treated with sipuleucel-T divided by the risk in patients treated with placebo and in the D9901 and D9902A studies, the risk estimate was defined as the risk in patients treated with placebo divided by the risk in patients treated with sipuleucel-T.
OS	Unknown	Unknown	**IMPACT**: HR 0.78 (0.61–0.98) **D9901 and D9902A**: HR 1.50 (1.10–2.05)	3 studies	⊕⊕⊕⊖ **moderate**†	Continuous outcomes are not provided in the studies and HRs of the two studies could not be pooled, because in the IMPACT study, the risk estimate was defined as the risk in patients treated with sipuleucel-T divided by the risk in patients treated with placebo and in the D9901 and D9902A studies, the risk estimate was defined as the risk in patients treated with placebo divided by the risk in patients treated with sipuleucel-T.
QoL	–	–	–	–	–	No evidence available
Toxicity AE grade 3 or 4 AEs	**340 per 1000**	**320 per 1000** (259 to 402)	**RR 0.94** (0.76–1.18)	720 (3 studies)	⊕⊕⊖⊖ **low**†,‡	

The **corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. †IMPACT: unclear risk of bias due to no description of allocation concealment. D9901 and D9902A: unclear risk of bias due to no description of randomisation methods, allocation concealment, blinding methods, and protocol. ‡Lower interval of the CI results in different conclusion than the upper limit.*

- sipuleucel-T vs placebo for the outcome of AEs (grade ≥3)

Study	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
D9901 and D9902A	49	147	21	67	26.8%	1.06 [0.70, 1.62]
IMPACT	107	338	59	168	73.2%	0.90 [0.70, 1.17]
Total patients		485		235	100.0%	0.94 [0.76, 1.18]
Total events	156		80			

Heterogeneity: $Chi^2 = 0.43$, df = 1 (P = 0.51); $I^2 = 0\%$
Test for overall effect Z = 0.50 (P = 0.61)



- Orteronel plus prednisone vs placebo plus prednisone

Patient or population: Chemotherapy-naive patients with mCRPC and radiographic nodal, bone or visceral metastases
Intervention: Orteronel plus prednisone
Comparison: Placebo plus prednisone

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Placebo	Illustrative comparative risks* (95% CI) Corresponding risk Orteronel	Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
PFS	Unknown	Unknown	**HR 0.71** (0.63–0.80)	1554 (1 study)	⊕⊕⊕⊕ **high**	Continuous outcomes are not provided in the studies
OS	Unknown	Unknown	**HR 0.92** (0.79–1.08)	1554 (1 study)	⊕⊕⊕⊖ **moderate**†	Continuous outcomes are not provided in the studies
QoL	–	–	–	–	–	No evidence available
Toxicity AE grade 3–5	**406 per 1000**	**593 per 1000** (537–659)	**RR 1.46** (1.32–1.62)	1554 (1 study)	⊕⊕⊕⊕ **high**	

The **corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). †Lower interval of the CI results in different conclusion than the upper limit. GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.*

- Bicalutamide vs placebo

Patient or population: Chemotherapy-naive patients with mCRPC
Intervention: Bicalutamide
Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Placebo	Illustrative comparative risks* (95% CI) Corresponding risk Bicalutamide	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
PFS	–	–	–	–	–	No evidence available
OS	N/A	N/A	**HR 0.78** (0.60–0.99)	203 (1 study)	⊕⊕⊕⊖ **moderate**†	Continuous outcomes are not provided in the studies
QoL		The mean QoL in the intervention groups was **3.19 higher** (1.82–8.20 higher)		203 (1 study)	⊕⊕⊖⊖ **low**†	
Toxicity	–	–	–	0	–	No evidence available

The **corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. †Unclear risk of bias because of details lacking regarding randomisation, allocation concealment, blinding, and a protocol.*

- Enzalutamide vs bicalutamide

Patient or population: Asymptomatic or mildly symptomatic patients with mCRPC and at least two bone lesions or soft tissue metastases
Intervention: Enzalutamide
Comparison: Bicalutamide

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Bicalutamide	Corresponding risk Enzalutamide				
PFS	Unknown	Unknown	HR 0.44 (0.34–0.57)	203 (1 study)	⊕⊕⊕⊕ high	Continuous outcomes are not provided in the studies
OS	–	–	–	–	–	No evidence available
QoL	–	–	–	0	–	No evidence available
Toxicity AE grade 3–5	381 per 1000	400 per 1000 (309–514)	RR 1.05 (0.81–1.35)	372 (1 study)	⊕⊕⊕⊖ moderate†	

The **corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). CI, confidence interval; RR, risk ratio; HR, hazard ratio. GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. †Lower interval of the CI results in different conclusion than the upper limit.*

Anmerkung/Fazit der Autoren

The best evidence for effective prolongation of OS and PFS in chemotherapy-naive patients with mCRPC was found for abiraterone plus prednisone and enzalutamide. In two RCTs that compared 223radium to placebo a prolonged OS considered of high quality in one and of moderate quality in the other was found in patients treated with 223radium, but the effect of 223radium on PFS is unknown. In three RCTs that compared sipuleucel-T to placebo a prolonged OS considered of moderate quality was found in patients treated with sipuleucel-T, but the PFS considered of low quality was not prolonged. In one RCT that compared orteronel with placebo, a prolonged PFS considered of high quality was found in patients treated with orteronel, but OS considered of moderate quality was not prolonged. In one RCT that compared bicalutamide to placebo, a prolonged OS considered of moderate quality was found in patients treated with bicalutamide, but the effect of bicalutamide on PFS is unknown. In one RCT that compared bicalutamide to enzalutamide, a prolonged PFS considered of high quality was found in patients treated with enzalutamide, but the effect on OS is unknown. Treatment options besides enzalutamide and abiraterone plus prednisone could be considered for individual patients by taking the quality of the studies, selection of patients, and both the QoL and AEs into consideration. The sequence and combination of treatment options in chemotherapy-naive patients with mCRPC remain a clinical challenge.

Roviello G et al., 2016 [18].

Targeting the androgenic pathway in elderly patients with castration-resistant prostate cancer

A meta-analysis of randomized trials

Fragestellung

The aim of this study is to evaluate and analyze the clinical data from randomized controlled clinical trials on the efficacy and safety of new antiandrogenic drugs in elderly patients (over 75 years old) with CRPC.

Methodik

Population:

- elderly human participants with CRPC

Intervention:

- new antiandrogenic drug interventions (Abiraterone, Enzaltuamide, Orteronel)

Komparator:

- placebo or active comparator

Endpunkte:

- survival expressed as the hazard ratio (HR) and secondary outcomes of progression-free survival (PFS) expressed as HR, time to prostatic antigen specific (PSA) progression expressed as HR, PSA response rate expressed as relative risk (RR), and major adverse effects (any grade 3–4 adverse event) expressed as RR

Recherche/Suchzeitraum:

- PubMed/ MEDLINE, the Cochrane Library, and American Society of Clinical Oncology (ASCO) University Meeting till April 1, 2016.

Qualitätsbewertung der Studien:

- Jadad score

Ergebnisse

Anzahl eingeschlossener Studien:

- N=9 RCTS including 4 pre-chemotherapy studies (n=2025)

Charakteristika der Population:

- 4 prechemotherapy studies that included 2025 cases (1053 in the experimental arm and 972 as control arm).
- In 4 studies (COU-AA-301, COU-AA-302, ELM-PC 4, ELM-PC 5, Sun et al) the comparator was placebo plus prednisone, while AFFIRM and PREVAIL compared enzalutamide over placebo, finally in TERRAIN and STRIVE the comparator was bicalutamide.
- 5 postchemotherapy studies that included 1487 cases (917 in the experimental arm and 570 as control arm)

Characteristics of the included studies.

Trials	Treatment arms	Cases ≥75 years	Primary endpoints	Jadad score
AFFIRM	Enzalutamide vs placebo	199; 104	Overall survival	5
COU-AA-301	Abiraterone+prednisone vs placebo+prednisone	220; 111	Overall survival	5
COU-AA-302	Abiraterone+prednisone vs placebo+prednisone	185; 165	Radiographic progression-free survival and overall survival	5
ELM-PC 4	Orteronel+prednisone vs placebo+prednisone	453*; 470*	Radiographic progression-free survival and overall survival	5
ELM-PC 5	Orteronel+prednisone vs placebo+prednisone	367*; 194*	Overall survival	5
PREVAIL	Enzalutamide vs placebo	317; 292	Radiographic progression-free survival and overall survival	5
TERRAIN	Enzalutamide vs bicalutamide	54; 64	Progression-free survival	4
STRIVE	Enzalutamide vs bicalutamide	77; 97	Progression-free survival	4
Sun et al	Abiraterone+prednisone vs placebo	98†; 45†	Time to PSA progression	5

PSA=prostatic antigen specific.
* Patients over 70 years old.
† Patients over 65 years old.

Pre-chemotherapy studies + active comparator: TERRAIN, STRIVE

Qualität der Studien:

- Median Jadad Score was 5.

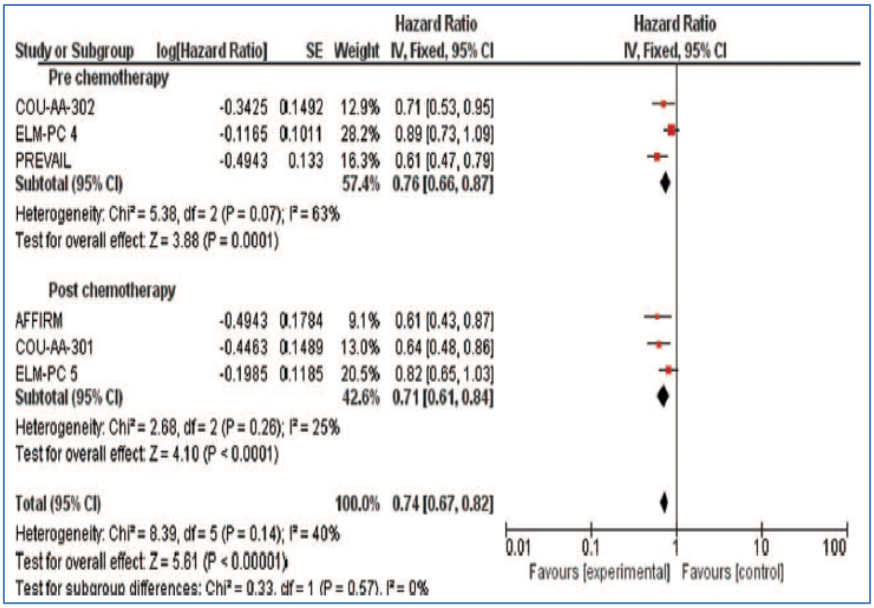
Studienergebnisse:

Data on overall survival, median treatment duration, and median follow-up of the included studies.

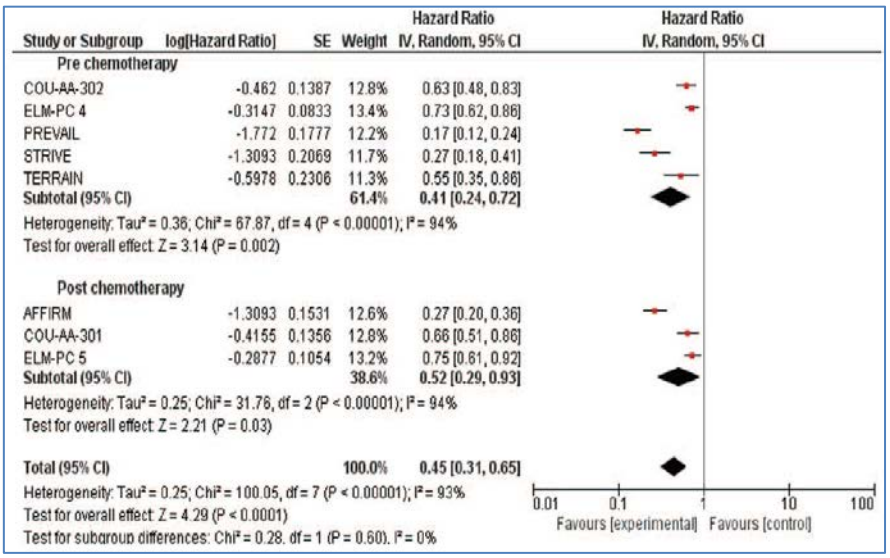
Study	Median OS, mo	Median PFS, mo	Median treatment duration, mo	Median follow-up, mo
AFFIRM				
E vs PL	18.2 vs 13.3; HR: 0.61	9.9 vs 2.8; HR: 0.45	NR	14.4
COU-AA-301				
AA+P vs PL+P	15.6 vs 9.3; HR: 0.64	6.6 vs 5.4; HR: 0.66	AA: 8; PL: 4	20.2
COU-AA-302				
AA+P vs PL+PR	28.6 vs 25.6; HR: 0.71	14.9 vs 8.3	AA: 13.8; PL: 8.3	49.2
ELM-PC 4				
O+P vs PL+P	29.4 vs 27.8; HR: 0.89	HR: 0.63; 13.8 vs 8.7; HR: 0.73	O: 10.1; PL:8.9	20.7
ELM-PC 5				
O+P vs PL+P	15.4 vs 13.1; HR: 0.82	8.3 vs 6.2; HR: 0.75	O: 6.2; PL: 5	10.7
PREVAIL				
E vs PL	32.4 vs 25.1; HR: 0.61	Not reached vs 3.7; HR: 0.17	E: 16.6; PL: 5	31
TERRAIN				
E vs BIC	NR	11.8 vs 5.1; HR: 0.55	E: 11.7; BIC: 5.8	E: 20; BIC: 16.7
STRIVE				
E vs BIC	NR	16.7 vs 5.6; HR: 0.27	E: 14.7; BIC: 8.4	NR
Sun et al				
AA+P vs PL+P	NR	NR	NR	12.9

A=abiraterone, BIC=bicalutamide, E=enzalutamide, HR=hazard ratio, mo=months, NR=not reported, OS=overall survival, P=prednisone, PFS=progression-free survival, PL=placebo.

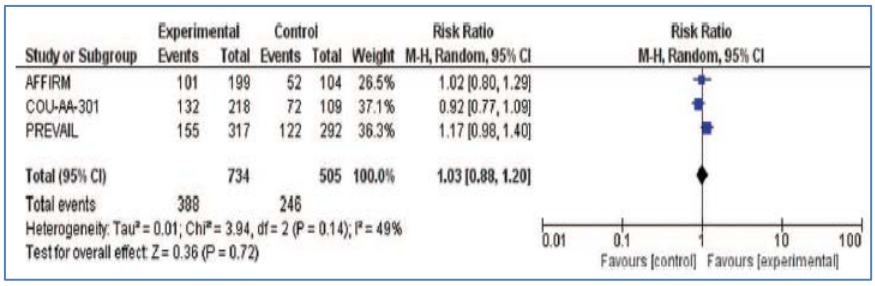
Overall survival (hazard ratios)



Progression-free survival (hazard ratios)



Any grade ≥3 adverse effect (relative risk)



Limitations

- Data were collected from 4 post hoc analyses; and 4 subgroup analyses of only 7 studies, and these studies exhibited very high levels of heterogeneity for some of the end-points.
- the studies involved patients who were asymptomatic or mildly symptomatic (COUAA- 302) and only exhibited bone metastases and patients with visceral disease (PREVAIL, ELM-PC 4, and TERRAIN), while the STRIVE trial included also patients without metastatic disease.
- the abiraterone and orteronel trials has been comparator to prednisone, whereas placebo were used in the enzalutamide trials except for bicalutamide in TERRAIN and STRIVE;
- the investigation of the adverse events was limited to number of patients with at least one grade 3–4 event; different versions of CTCAE has been adopted in the trial; specific toxicity data such falls, cognitive impairment, fatigue are lacking

Referenzen

[11] Graff JN, Baciarello G, Armstrong AJ, et al. Efficacy and safety of enzalutamide in patients 75 years or older with chemotherapy-naïve metastatic castration-resistant prostate cancer: results from PREVAIL. Ann Oncol 2015;27:286–94.
[18] Smith MR, Rathkopf DE, Mulders PF, et al. Efficacy and safety of abiraterone acetate in elderly (75 years or older) chemotherapy naïve patients with metastatic castration resistant prostate. J Urol 2015;194: 1277–84. doi: 10.1016/j.juro.2015.07.004.
[19] Shore ND, Chowdhury S, Villers A, et al. Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomised, double-blind, phase 2 study. Lancet Oncol 2016;17:153–63.
[20] Penson DF, Armstrong AJ, Concepcion R, et al. Enzalutamide versus bicalutamide in castration-resistant prostate cancer: the STRIVE trial. J Clin Oncol 2016;34:2098–3106.

Anmerkung/Fazit der Autoren

In conclusion, our meta-analysis supports the evidence in favor of targeting the androgenic pathway with these novel agents in elderly men with a relative safety profile. In this contest, our analysis which involved patients aged >70 years old and aged >75 years in 4 studies support the use of new hormonal therapies in over 70 years old men.

Roviello G et al., 2016 [19].

Role of the novel generation of androgen receptor pathway targeted agents in the management of castration-resistant prostate cancer.

Fragestellung

In this meta-analysis, the efficacy and safety from randomized controlled trials (RCTs) of these new AR pathway targeted agents in patients with metastatic CRPC have been analysed and reported.

Methodik

Population:

- Patienten mit mCRPC

Intervention:

- Androgen-Rezeptor Medikament

Komparator:

- Placebo oder andere Intervention

Endpunkte:

OS expressed as the hazard ratio (HR) and secondary outcomes of progression-free survival (PFS) expressed as the HR, time to prostatic antigen specific (PSA) progression expressed as the HR, time to the first symptomatic skeletal event (SSE) expressed as the HR, PSA response rate expressed as relative risk (RR) and major adverse effects (grade 3e4 adverse events) expressed as RR

Recherche/Suchzeitraum:

- PubMed, the Cochrane Library, and the American Society of Clinical Oncology (ASCO) Meeting

Qualitätsbewertung der Studien:

- Jadad Score

Ergebnisse

Anzahl eingeschlossener Studien:

- N=8 (n=8598) with 5 pre-chemotherapy studies (n=3479)

Charakteristika der Population:

- 5 Studien mit Chemotherapie-naiven Patienten → Relevante Interventionen: Enzalutamid, Abirateron + Prednison)

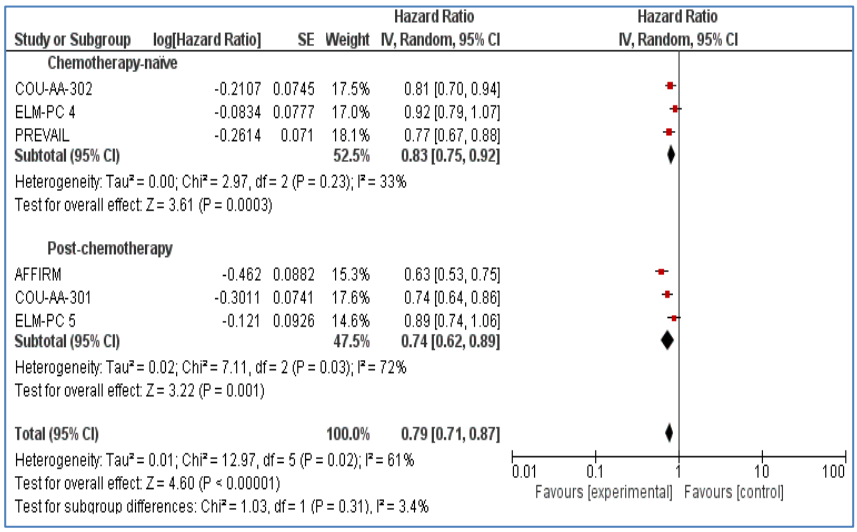
- Relevante Studien mit aktivem Vergleich: TERRAIN, STRIVE (Vergleich Enzalutamid versus Bicalutamid)
- 3 Studien mit Patienten nach Chemotherapie (Interventionen: Enzalutamid, Abirateron + Prednison)

Qualität der Studien:

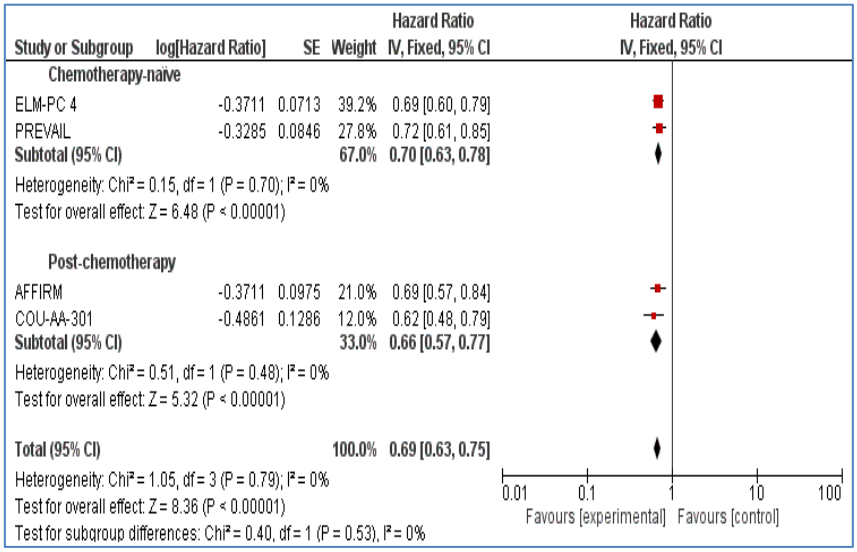
- Median Jadad score: 5

Studienergebnisse

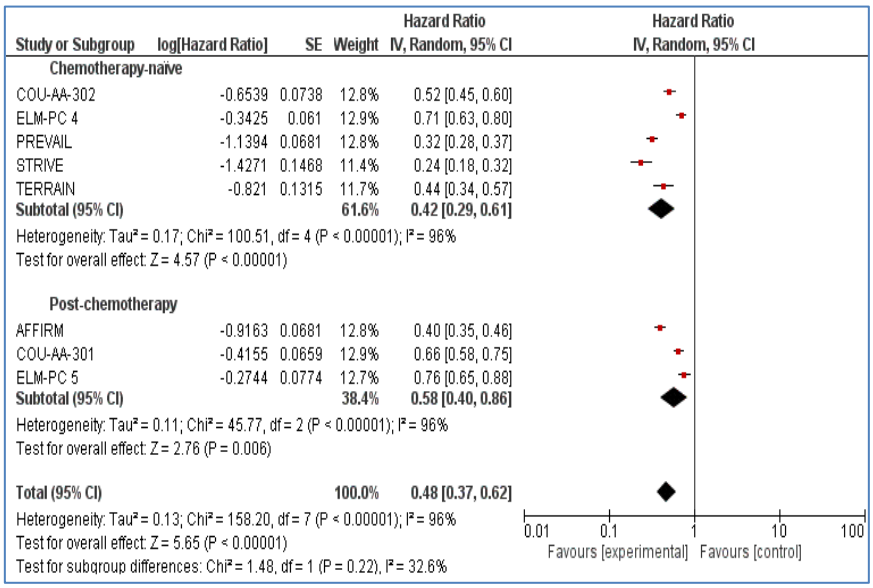
- Overall survival



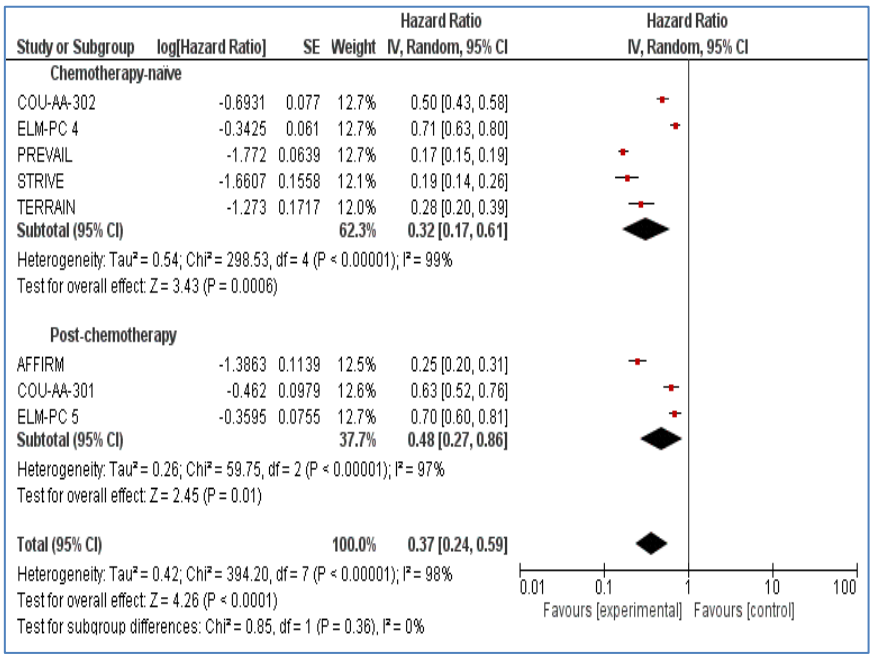
- First symptomatic skeletal event



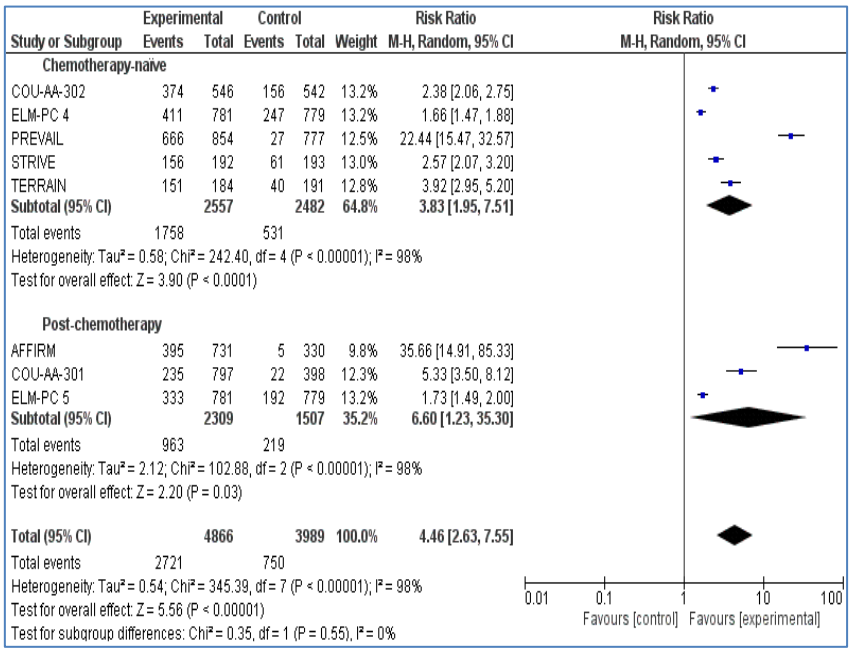
- Progression-free survival



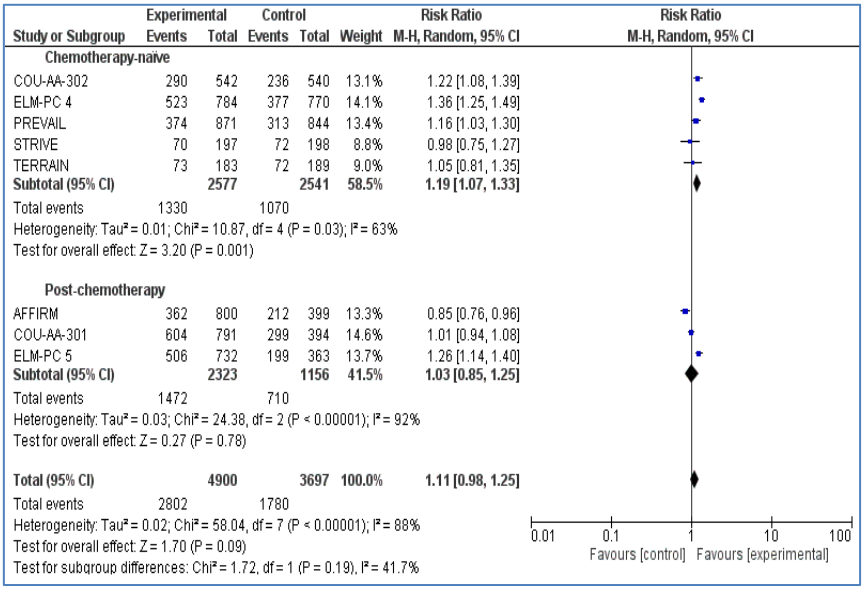
- PSA progression



- PSA response



- Grade ≥3 adverse effect



Referenzen
[17] Shore ND, Chowdhury S, Villers A, Klotz L, Siemens DR, Phung, et al. Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomised, double-blind, phase 2 study. Lancet Oncol 2016 Jan 13. pii: S1470-2045(15) 00518e5.
[18] Penson DF, Armstrong AJ, Concepcion R, Agarwal N, Olsson C, Karsh L, et al. Enzalutamide versus bicalutamide in castrationresistant prostate cancer: the STRIVE trial. J Clin Oncol 2016 Jan 25.Anmerkung/Fazit der Autoren

Anmerkung/Fazit der Autoren

[…] This study confirmed the efficacy and safety of the novel androgen receptor pathway targeted agents.

[…] Currently, abiraterone and enzalutamide are approved for metastatic CRPC in the chemotherapy-naive and postchemotherapy settings. Our literature-based meta-analysis

supports the existing evidence for targeting the androgenic pathway as CRPC still remains a hormone-driven disease.

Perletti, G. et al., 2015 [16].

Efficacy and safety of second-line agents for treatment of metastatic castration-resistant prostate cancer progressing after docetaxel. A systematic review and meta-analysis.

Fragestellung

to assess the efficacy and the safety of second-line agents targeting metastatic castration-resistant prostate cancer (mCRPC) that has progressed after docetaxel.

Methodik

Population:

- patients with mCRPC progressing during or after first-line docetaxel treatment

Intervention:

- systemic intervention: Siehe Ergebnisteil

Komparator:

- Placebo or an active treatment, combined or not with a corticosteroid.

Endpunkte:

- Primärer Endpunkt: overall survival
- Sekundäre Endpunkte: radiographic progression-free survival (rPFS), adverse effects of grade 3 or higher.

Recherche/Suchzeitraum:

- ubMed, MEDLINE, EMBASE, The Cochrane Library, Web of Science, BIOSIS, LILACS, other databases between January 2004 (the year docetaxel was first approved as first-line therapy for CRPC) and January 2015.

Qualitätsbewertung der Studien:

- Cochrane Collaboration’s tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 10 articles met the inclusion criteria for the present review / total of 5047 patients were randomized to experimental (n = 3108) or control interventions (placebo/active drug; n = 1939).
- The experimental interventions tested in these studies were enzalutamide, ipilimumab, abiraterone acetate, orteronel and cabazitaxel.

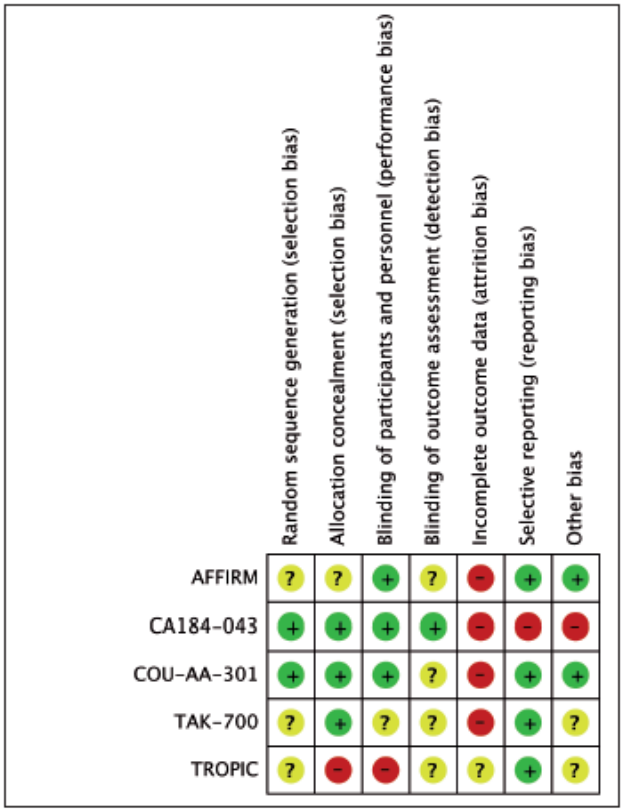
Charakteristika der Population:

Table 1. *Characteristics of included studies and baseline participant data.*

Study name[ref]	AFFIRM (10)	CA184-043 (11)	COU-AA-301 (12)	TAK-700 (16)	TROPIC (17)
Design	Phase-III, randomized, parallel group, double-blind, placebo-controlled trial.	Phase-III, randomized, parallel group, double-blind, placebo-controlled trial.	Phase-III, randomized, parallel group, double-blind, placebo-controlled trial.	Phase-III, randomized, parallel group, double-blind, placebo-controlled trial.	Phase-III, randomized, parallel group, open-label, active drug-controlled trial.
Total randomized patients (n)	1199	799	1195	1099	755
Group 1, experimental intervention (n. patients randomized)	Enzalutamide, oral, 4 x 40 mg once-daily (n=800)	Single dose of 8Gy radiotherapy for at least 1 and up to 5 bone fields, followed by intravenous ipilimumab, 10 mg/kg, every 3 weeks for up to 4 doses (n=399)	Abiraterone acetate, oral, 4 x 250 mg/day, for multiple 28-day cycles, plus prednisone, oral, 10 mg once-daily (n=797)	Orteronel, oral, 2x400 mg/day (Japanese patients: 2x300 mg/day), for multiple 28-day cycles, plus prednisone, oral, 5 mg twice-daily (n=734).	Cabazitaxel, intravenous, 25 mg/m^2 (1 hour infusion) every 21 days, plus prednisone, oral, 10 mg once-daily (n=378)
Group 2, comparator (control) intervention (n. patients randomized)	Placebo, oral, 4 tablets once-daily (n= 399)	Single dose of 8Gy radiotherapy for at least 1 and up to 5 bone fields, followed by intravenous placebo (0.9% sodium chloride), every 3 weeks for up to 4 doses (n=400)	Placebo tablets, oral, 4/day, for multiple 28-day cycles, plus prednisone, oral, 10 mg once-daily (n=398)	Placebo tablets, oral, 2/day, for multiple 28-day cycles, plus prednisone, oral, 5 mg twice-daily (n=365)	Mitoxantrone, intravenous, 12 mg/m^2 (15-30 min. infusion) every 21 days, plus prednisone, oral, 10 mg once-daily (n=377)
Dropouts	189 (Group 1, 111; Group 2, 78)	767 (Group 1, 379; Group 2, 388)	287 (Group 1, 184; Group 2, 103)	889 (Group 1, 583; Group 2, 306)	144 (Group 1, 86; Group 2, 58)
Median age (Group 1/Group 2)	69/69	69/67.5	69/69	69.5/70	68/67
ECOG = 0-1 (Group 1/Group 2)	91%/92%	96%/98%	90%/89%	92%/93%	93%/91%
ECOG = 2 (Group 1/Group 2)	9%/8%	Exclusion criterion	10%/11%	9%/7%	7%/9%
Presence of baseline visceral disease (Group 1/Group 2)	25%21%	28%29%	30%/24%	27%/27%	25%/25%
BPI pain score > 4 (Group 1/Group 2)	28%/29%	49%47%	45%/45%	3.0/3.0 (median value)	46%/45%
Disease progression within 3 months post-docetaxel (Group 1/Group 2)	ND	ND	66%/70%	ND	42%/48%
Previous hormone therapy (Group 1/ Group 2)	ND	17%/16%	100%/100%	96%/95%	99%/99%
Total Docetaxel dose (Group 1/Group 2)	600/600 mg/m^2	ND	906/895 mg/m^2	ND	576.6/529.2 mg/m^2
Corticosteroid use during trial (Group 1/Group 2)	48 %/45%	ND	100%/100%	100%/100%	100%/100%

ECOG = Eastern Cooperative Oncology Group Performance Status; BPI = Brief Pain Inventory Score; ND = Not Determined.

Qualität der Studien:



- Für eine detaillierte Angabe zum Verzerrungspotenzial siehe **Anhang**.

Studienergebnisse:

- Compared to control cohorts (active drug-treated or placebotreated), the significant overall survival advantages achieved were 4.8 months for enzalutamide (hazard ratio for death vs. placebo: 0.63; 95% CI 0.53 to 0.75, P < 0.0001), 4.6 months for abiraterone (hazard ratio for death vs. placebo: 0.66, 95% CI 0.58 to 0.75, P < 0.0001) and 2.4 months for cabazitaxel (hazard ratio for death vs. mitoxantrone-prednisone: 0.70, 95% CI 0.59 to 0.83, p < 0.0001).
- Pooled analysis of androgen synthesis inhibitors orteronel and abiraterone resulted in significantly increased overall and progression-free survival for anti-androgen agents, compared to placebo (hazard ratio for death: 0.76, 95% CI 0.67 to 0.87, P < 0.0001; hazard ratio for radiographic progression: 0.7, 95% CI 0.63 to 0.77, P< 0.00001).
- Androgen synthesis inhibitors induced significant increases in risk ratios for adverse effects linked to elevated mineralocorticoid secretion, compared to placebo (risk ratio for hypokalemia: 5.75, 95% CI 2.08 to 15.90; P= 0.0008; risk-ratio for hypertension: 2.29, 95% CI 1.02 to 5.17; P = 0.05).

Anmerkung/Fazit der Autoren

In conclusion, several new agents have shown to be effective in prolonging survival in men with metastatic castration-resistant prostate cancer in the post-docetaxel setting. It may be hypothesized that survival may be further prolonged by combining these agents or by administering them sequentially. Randomized studies are warranted to demonstrate this hypothesis, but also to exclude reciprocal detrimental effects of these agents (22-26).

3.4 Leitlinien

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften), 2019 [15].

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

Siehe auch: Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft,, Deutsche Krebshilfe, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften), 2018 [14].

Leitlinienorganisation/Fragestellung

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

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: Interdisziplinäre LL-Entwicklergruppe, Beteiligung von Patientenvertreterinnen;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt. Es wurde ein durch die AWMF moderierter, mehrteiliger Nominaler Gruppenprozess durchgeführt.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert: Stand: 01.04.2018, gültig bis 30.04.2021
- In den Kopfzeilen der Empfehlungen und Statements wurde vermerkt, wann diese erstellt bzw. aktualisiert wurden und ob sie modifiziert oder neu erstellt wurden. Folgende Kategorien der Kennzeichnung werden verwendet:
  - geprüft 2018 = Die Empfehlung bzw. das Statement wurde bei der Erstellung der Leitlinie oder bei einer der anschließenden Aktualisierungen (2011, 2014, 2016) erstellt oder modifiziert. Die Gültigkeit der Empfehlung bzw. des Statements wurde während der Aktualisierung 2018 geprüft und mittels Abstimmung erneut konsentiert.
  - spezifiziert 2018 = Die Empfehlung bzw. das Statement wurde während der Aktualisierung 2018 in Detailaspekten angepasst, die Aussage jedoch nicht verändert.
  - modifiziert 2018 = Die Empfehlung bzw. das Statement wurde während der Aktualisierung 2018 in Teilen oder gänzlich aufgrund neuer Evidenz geändert.

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

Recherche/Suchzeitraum:

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

LoE/GoR

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

Tabelle 2: Schema der Evidenzgraduierung nach SIGN

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

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

Schema der Empfehlungsgraduierung

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

- Als Expertenkonsens (EK) werden Empfehlungen bezeichnet, zu denen keine Recherche nach Literatur durchgeführt wurde. In der Regel adressieren diese Empfehlungen

Vorgehensweisen der guten klinischen Praxis, zu denen keine wissenschaftlichen Studien notwendig sind bzw. erwartet werden können. Der Begriff „Expertenkonses“ ersetzt den in den bisherigen Versionen der Leitlinie genutzten Begriff „Good Clinical Practice“ (GCP).

Empfehlungen Therapie des androgenunabhängigen oder kastrationsresistenten Prostatakarzinoms

7.41 Erstlinientherapie asymptomatische oder gering symptomatische Patienten

7.29	Evidenzbasierte Empfehlung	geprüft 2018
Empfehlungsgrad A	Patienten mit kastrationsresistenter, asymptomatischer oder gering symptomatischer, progredienter Erkrankung ohne bildgebenden Nachweis von Metastasen soll ein abwartendes Vorgehen unter Beibehaltung der Androgendeprivation angeboten werden.	
Level of Evidence 4	Expertenkonsens basierend auf [763-767].	
	Gesamtabstimmung: 100 %	

7.30	Evidenzbasierte Empfehlung	geprüft 2018
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 %	

7.31	Evidenzbasierte Empfehlung	modifiziert 2018
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 7.32und 7.33.	
Level of Evidence 1+	Literatur: [764-766, 768]	
	Gesamtabstimmung: 100 %	

Hintergrundinformationen:

(..) 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. Abirateron und Enzalutamid wurden gegen Placebo, Docetaxel gegen Mitoxantron getestet. Es liegen weder Daten zum direkten Vergleich der drei Arzneimittel, noch zu Kombinationen dieser Arzneimittel vor. Es sei darauf hingewiesen, dass Abirateron standardmäßig in Kombination mit Prednison oder Prednisolon gegeben wird. Die Empfehlungen für diese Patientenpopulation beruhen auf den Einschlusskriterien für Studien zur Erstlinientherapie mit Docetaxel [764, 765], Abirateron [766] und Enzalutamid [768].

7.32	Evidenzbasierte Empfehlung	modifiziert 2018
Empfehlungsgrad B	Patienten mit metastasierter, kastrationsresistenter, asymptomatischer oder gering symptomatischer und progredienter Erkrankung sollte (alphapetische Reihenfolge) • Abirateron (in Kombination mit Prednison / Prednisolon) oder • Enzalutamid als Erstlinientherapie angeboten werden.	
Level of Evidence 1+	Literatur:[766, 768]	
	Gesamtabstimmung: 100 %	

Hintergrundinformationen:

Der Cyproteronacetat-17-Hemmer Abirateron bewirkt eine extragonadale Hormonsupp-ression. 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) [784]. 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.

(…) In der Zulassungsstudie [766] wird zum Zeitpunkt der zweiten Interimanalyse eine Verlängerung der progressionsfreien Überlebenszeit von etwa acht Monaten berichtet. Im Vergleich zu Placebo zeigte Abirateron (in Kombination mit Prednison / Prednisolon) in der Interimanalyse einen signifikanten Effekt auf verschiedene Endpunkte (progressionsfreies Überleben, biochemische und bildgebende Remission, Symptomatik und Lebensqualität). (…) In der finalen Publikation [784] werden als häufigste schwerwiegende Nebenwirkungen Herzerkrankungen (8 vs. 4%), erhöhte ALT-Werte (6 vs. <1%) und Bluthochdruck (5 vs. 3%) genannt.(…)

(…) In der Zulassungsstudie zur Erstlinientherapie [768] zeigte sich ein Überlebensvorteil für En-zalutamid gegenüber Placebo (Ergebnisse der geplanten Interimanalyse – medianes Gesamtüberleben: 32,4 vs. 30,2 Monate, HR: 0,71, 95% KI: 0,60-0,84, p<0,001). Das als co-primärer Endpunkt definierte radiografisch progressionsfreie Überleben wurde nicht in die Nutzenbewertung für die Zulassung einbezogen. Unter den sekundären Endpunkten wurden patientenrelevante signifikante Unterschiede zwischen Enzalutamid- und Placebo-Arm gefunden (Zeit bis zum ersten SRE, Dauer bis zu einer Ver-schlechterung der Lebensqualität oder Beginn einer Opiat-Therapie als Surrogat-Para-meter für Schmerz).

7.33	Evidenzbasierte Empfehlung	spezifiziert 2018
Empfehlungsgrad 0	Patienten mit metastasierter, kastrationsresistenter, asymptomatischer oder gering symptomatischer und progredienter Erkrankung kann Docetaxel als Erstlinienthera-pie angeboten werden.	
Level of Evidence 1+	Literatur: [764, 765]	
	Gesamtabstimmung: 96 %	

Hintergrundinformationen:

(…) Die TAX-327 Studie (n =1.006, Karnofsky-performance status ≥ 60 %) zeigte einen Überlebensvorteil von 2,9 Monaten (Spanne null bis sieben Monate) bei drei wöchentlicher Gabe von Docetaxel im Vergleich zu den beiden anderen Armen (wöchentlich Docetaxel niedriger dosiert, dreiwöchentlich Mitoxantron; Randomisierung 1:1:1) für die Gesamtgruppe [764, 765]. Schwere Nebenwirkungen (Grad 3/4), die bei mehr als 20 % der Patienten in den Zulassungsstudien auftraten, waren: Alopezie (65 %), Fati-gue (53 %), Übelkeit/Erbrechen (42 %), Neutropenie (32 %), Diarrhoe (32 %), sensorische Neuropathie (30 %), Onychodystrophie (30 %). Der Anteil Therapie-assoziierter Todesfälle lag bei 0,3 %. Signifikant mehr Patienten, die Docetaxel erhalten haben, berichteten von einer Verbesserung der Lebensqualität im Vergleich zu Mitoxantron, die media-nen Veränderungen waren aber gering [764]. (…)

Docetaxel ist in Kombination mit Prednison / Prednisolon zur Behandlung des metastasierten, kastrationsresistenten Prostatakarzinoms zugelassen [791].

7.4.2. Erstlinientherapie symptomatische Patienten

7.35	Evidenzbasierte Empfehlung	spezifiziert 2018
Empfehlungsgrad 0	Patienten mit metastasierter, kastrationsresistenter, symptomatischer und progredienter Erkrankung kann Docetaxel als Erstlinientherapie in zwei- oder drei-wöchigen Dosierungsschemata angeboten werden.	
Level of Evidence 1+	Literatur: [764, 765]	
	Gesamtabstimmung: 95 %	

7.36	Evidenzbasierte Empfehlung	modifiziert 2018
Empfehlungsgrad 0	Patienten mit metastasierter, kastrationsresistenter, symptomatischer und progredienter Erkrankung kann (alphabetische Reihenfolge) · Abirateron (in Kombination mit Prednison / Prednisolon) oder · Enzalutamid als Erstlinientherapie 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: [766, 768]	
	Gesamtabstimmung: 95 %	

7.37	Evidenzbasierte Empfehlung	spezifiziert 2018
Empfehlungsgrad 0	Patienten mit kastrationsresistenter, symptomatischer, progredienter Erkrankung mit ossären Metastasen ohne Nachweis extra-ossärer, distanter Metastasen kann Radium-223 als Erstlinientherapie angeboten werden.	
Level of Evidence 1+	Literatur: [792]	
	Gesamtabstimmung: 82 %	

Hintergrundinformationen:

In einer kontrolliert randomisierten Studie (2:1 Randomisierung) von Parker et al. (ALSYMPCA) verlängerte das Radionuklid Radium-223 das Gesamtüberleben im Vergleich zu Placebo signifikant [792]. Die Daten zeigten eine Verlängerung für den primären Endpunkt des Gesamtüberlebens mit einem Median von 14,9 Monaten versus 11,3 Monaten zugunsten von Radium-223 (HR: 0,70; 95 % KI: 0,58-0,83; p < 0,001).

7.38	Evidenzbasierte Empfehlung	geprüft 2018
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 %	

Hintergrundinformationen:

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) und Radium-223 (ECOG: 0-2) waren keine oder nur wenige Patienten mit reduziertem Allgemeinzustand eingeschlossen. Daher wird für diese Patienten eine symptombezogene Therapie empfohlen. Des Weiteren können als Erstlinientherapie zusätzlich verschiedene Therapieoptionen angeboten werden.

7.39	Evidenzbasierte Empfehlung	modifiziert 2018
Empfehlungsgrad 0	Patienten mit kastrationsresistenter, progredienter Erkrankung und reduziertem Allgemeinzustand (ECOG ≥ 2, Karnofsky-Index < 70) kann als Erstlinientherapie 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 • Radium-223 bei ossärer Metastasierung • Steroide (Dexamethason, Prednisolon, Prednison)	
Level of Evidence 4	Expertenkonsens basierend auf [764-766, 768, 792]	
	Gesamtabstimmung: 95 %	

Hintergrundinformationen:

Nur wenn der reduzierte Allgemeinzustand vor allem auf das metastasierte Prostatakarzinom zurückzuführen ist, kann eine Chemotherapie mit Docetaxel angeboten werden. Mitoxantron kann in begründeten Einzelfällen in Erwägung gezogen werden. So zeigt eine systematische Übersichtsarbeit von Winquist [794], dass die Kombination aus Mitoxantron und Prednisolon zu einer Verbesserung in mehreren klinisch relevanten Endpunkten (Lebensqualität, Zeit bis zum Progress, Schmerzen) führen kann und eine wirksame Therapie darstellt. Eine Verlängerung des Gesamtüberlebens gegenüber einer alleinigen Steroidtherapie kann durch die Kombination aus Mitoxantron und Prednisolon jedoch nicht erreicht werden.

Zweitlinientherapie

In den Empfehlungen zur Zweitlinientherapie wird nicht zwischen asymptomatischen und symptomatischen Patienten unterschieden. Aktuelle Studien schließen beide Patientengruppen ein.

7.40	Evidenzbasierte Empfehlung	spezifiziert 2018
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 Radionuklidtherapie mit Radium-223 bei ossärer Metastasierung Zur Differenzialtherapie siehe Empfehlungen 7.41 - 7.43.	
Level of Evidence 1+	Literatur: [792, 795-802]	
	Gesamtabstimmung: 100 %	

7.41	Evidenzbasierte Empfehlung	spezifiziert 2018
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: [795, 796] Enzalutamid [798]	
	Gesamtabstimmung: 100 %	

Hintergrundinformationen:

Unter Therapie mit Abirateron wurde nach einem medianen Follow-up von ca. zwölf Monaten in einer Interimsanalyse eine Verlängerung des Gesamtüberlebens um im Me-dian 3,9 Monate im Vergleich zu Placebo gezeigt [795]. In die randomisierte kontrol-lierte 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.

(…) Zur erneuten Therapie mit Abirateron, falls dieses bereits vor Erstlinientherapie mit Docetaxel eingesetzt wurde, sind derzeit keine Daten verfügbar.

7.42	Evidenzbasierte Empfehlung	spezifiziert 2018
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: [799]	
	Gesamtabstimmung: 100 %	

7.43	Evidenzbasierte Empfehlung	geprüft 2018
Empfehlungsgrad 0	Patienten mit kastrationsresistenter, progredienter Erkrankung und gutem Allgemeinzustand nach Chemotherapie mit Docetaxel kann Radium-223 bei ossären Metastasen angeboten werden. In der Zulassungsstudie wurde eine Verlängerung der Überlebenszeit gezeigt.	
Level of Evidence 1+	Literatur: [792]	
	Gesamtabstimmung: 93 %	

7.44	Evidenzbasierte Empfehlung	spezifiziert 2018
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 • Radionuklidtherapie mit Radium-223 bei ossärer Metastasierung • Steroide (Dexamethason, Prednisolon, Prednison)	
Level of Evidence 4	Expertenkonsens basierend auf Referenzen zu 7.43 und [99, 173, 803].	
	Gesamtabstimmung: 98 %	

Hintergrundinformationen:

Im Unterschied zu Abirateron und Enzalutamid (jeweils gegen Placebo) wurde Cabazitaxel versus Mitoxantron (jeweils in Kombination mit Prednison) getestet. Zu Cabazitaxel liegt eine randomisierte kontrollierte Studie vor (1:1-Randomisierung, open label, d. h. die Anwendung der Medikamente erfolgte nicht verblindet). Die eingeschlossenen Patienten wiesen alle eine ausgeprägte Metastasierung auf. Im Vergleich zu Mitoxantron als Chemotherapeutikum 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 Überleben um 1,4 Monate (2,8 Monate vs. 1,4 Monate, HR: 0,74; 95 % KI: 0,64-0,86, p < 0,0001) erreicht. Signifikante Effekte auf weitere Endpunkte (Tumor Response und PSA-Response) konnten gezeigt werden, wohingegen die Unterschiede in der Symptomatik nicht signifikant waren. Daten zur Lebensqualität liegen nicht vor. Die Leitliniengruppe will besonders auf die potentiellen Nebenwirkungen des Medikaments hinweisen, v. a. febrile Neutropenie. Dies schließt auch behandlungs-bedingte Todesfälle ein. In der deutschen Behandlungsrealität ist die Therapie-assoziierte Mortalität niedriger als in der Zulassungsstudie [812].

Cabazitaxel ist zugelassen in Kombination mit Prednison oder Prednisolon zur Behandlung von Patienten mit hormonrefraktärem me-tastasiertem Prostatakarzinom, die mit einem Docetaxel-basierten Therapieschema vor-behandelt sind [814].

7.45	Evidenzbasierte Empfehlung	neu 2018
Empfehlungsgrad 0	Für Patienten mit kastrationsresistenter, progredienter Erkrankung in gutem Allgemeinzustand kann nach Ausschöpfen der empfohlenen Therapieoptionen (siehe Empfehlung 7.40) ein Therapieversuch mit Lutetium-177-PSMA auf Basis der Empfehlung einer interdisziplinären Tumorkonferenz angeboten werden.	
Level of Evidence 3	Literatur: [804-811]	
	Gesamtabstimmung: 93 %	

Hintergrundinformationen:

Mit 177Lu-PSMA-Liganden findet sich ein neuer Ansatz zur Radionuklid-Therapie in der klinischen Erprobung. In zehn kleinen retrospektiven Fallserien [804-811, 815, 816] (drei davon mit überlappenden Populationen) wird die experimentelle Behandlung ohne Vergleichstherapie beschrieben. In einigen Studien traten Grad 3-4 Toxizitäten auf, in anderen nur mildere Nebenwirkungen. Als Wirksamkeit-Endpunkt wird zumeist eine Abnahme des PSA-Spiegels genannt; der Anteil der Patienten, die mindestens eine Reduktion von 50% erreichte, variiert recht stark zwischen den Fallserien. Die Überlebensdauer wird selten berichtet. Aufgrund der sehr schwachen Datenlage lässt sich keine zuverlässige Aussage zum Stellenwert dieser Therapie treffen. Daher handelt es sich bis auf weiteres bei einer 177Lu-PSMA-Behandlung nach dem Ausschöpfen der anderen, empfohlenen Therapie-optionen um einen Therapieversuch, der nur nach Empfehlung einer interdisziplinären Tumorkonferenz angeboten werden kann.

7.4.3.2. Zweitlinientherapie nach Androgenrezeptor-gerichteter Behandlung

7.46	Evidenzbasierte Empfehlung	spezifiziert 2018
Empfehlungsgrad 0	Patienten mit kastrationsresistenter, progredienter Erkrankung und gutem Allgemeinzustand nach Androgenrezeptor-gerichteter Erstlinientherapie kann eine Sequenztherapie unter Verwendung eines der anderen wirksamen Arzneimittel (siehe Empfehlung 7.40) angeboten werden.	
Level of Evidence 4	Expertenkonsens	
	Gesamtabstimmung: 100 %	

Zur Sequenztherapie nach Androgenrezeptor-gerichteter Behandlung liegen keine Daten aus prospektiv randomisierten Studien vor. Sie ist aber zunehmend häufige Praxis, wenn zugelassene Medikamente konsekutiv eingesetzt werden. Daten zum Einfluss des sequenziellen Einsatzes von Abirateron, Enzalutamid, Cabazitaxel und Radium-223 beschränken sich auf Fallserien. Entsprechend gibt es keine belastbaren Aussagen über zusätzliche Nebenwirkungen oder den Einfluss auf progressionsfreies Überleben oder die Gesamtüberlebenszeit. Somit kann derzeit nicht abschließend beurteilt werden, ob eine zweite Androgenrezeptor-gerichtete Behandlung nach Progress unter der Erstlini-enbehandlung mit dem jeweils anderen Wirkstoff möglicherweise weniger effektiv ist als eine Chemotherapie (Docetaxel) in der Zweitlinie. Festzuhalten ist allerdings, dass in den bislang vorliegenden restrospektiven Studien mit Enzalutamid nach Abirateron ein geringeres PSA-Ansprechen erzielt wird als in der Erstlinientherapie (18 bis 34% vs. 78%) [818-821]. Ähnliches scheint für Abirateron nach Enzalutamid zu gelten (9% vs. 62%) [821].

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CLINICAL PRACTICE GUIDELINE GU-010 Version 1

Advanced/ Metastatic Prostate Cancer

Leitlinienorganisation/Fragestellung

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

Methodik

Grundlage der Leitlinie

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

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

Recherche/Suchzeitraum:

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

LoE/GoR

- Critical Appraisal of the Evidence: The Knowledge Management Specialist (KMS) synthesizes the relevant details of the studies included from the literature search into evidence tables. The quality of the included primary studies is rated by the KMS and reviewed with the Guideline Working Group members according to the following criteria:
  - Level I – evidence from at least one large randomized controlled trial (RCT) of good methodological quality with low potential for bias or meta-analyses of RCTs without heterogeneity
  - Level II – small RCTs, large RCTs with potential bias, meta-analyses including such trials, or RCTs with heterogeneity
  - Level III – prospective cohort studies
  - Level IV – retrospective cohort studies or case-control studies
  - Level V – studies without a control group, case reports, or expert opinions
- The strength of the recommendations will be rated by the GWG members according to the following criteria originally developed by the Infectious Diseases Society of America and adapted for use by the European Society for Medical Oncology (ESMO):
  - Grade A – strongly recommended; strong evidence for efficacy with a substantial clinical benefit
  - Grade B – generally recommended; strong or moderate evidence for efficacy but with a limited clinical benefit
  - Grade C – optional; insufficient evidence for efficacy or benefit does not outweigh the risks/disadvantages
  - Grade D – generally not recommended; moderate evidence against efficacy or for adverse outcomes

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

Empfehlungen

Castrate Resistant Metastatic Disease (Stage M0, M+)

Management

The benefits of treatment are primarily palliative and related to quality of life, although some systemic therapies confer a small survival advantage.

Management of M0 Disease

1. The standard of care is monitoring PSA. In patients with a rapid doubling time (<6 months), more frequent imaging and closer clinical follow-up should be undertaken.

2. Clinical trial options should be considered.

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.[14,15]

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).[16] Funding is currently being sought.

B. 2nd line options:

i. Post progression on docetaxel chemotherapy:

a. Abiraterone acetate17 or enzalutamide (AFFIRM)[17]

b. Cabazitaxel 25mg/m2 IV every 3 weeks in combination with prednisone 10 mg oral daily.[56]

c. Radium 223 can be given to patients with symptomatic bony metastatic CRPC without visceral metastases (ALSYMPCA).[18,19] 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 in Alberta.

• Patient selection is important. These patients should be discussed in multidisciplinary tumor board rounds.

ii. Post progression on Abiraterone or Enzalutamide

a. Docetaxel chemotherapy

C. Subsequent lines:

i. Sequencing with another agent listed above not previously used. For example, abiraterone → docetaxel → enzalutamide → cabazitaxel is a reasonable sequence. There are many others. There is no data to suggest the preferred sequence.

ii. Docetaxel rechallenge or Mitoxantrone 12mg/m2 every 3 weeks in combination with prednisone 5 mg oral twice a day may provide palliation.

iii. Sipuleucel-T is not Health Canada approved.

D. Mitoxantrone 12mg/m2 every 3 weeks in combination with prednisone 5 mg oral twice a day can provide adequate palliation in 2nd or subsequent line.

E. 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).

F. It is important to note that chemotherapy is NOT indicated in patients without evidence of metastatic disease on imaging whose only have manifestation of hormone insensitive disease is a rising PSA.

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). In brief:

A. EBRT to symptomatic sites

B. Strontium 89 (Metastron®) can be considered for appropriate indications, including:

i. Multiple painful sites of bone metastases on both sides of diaphragm

ii. Patient and/or tumor factors contraindicating the use of multiple fields of EBRT for palliation

iii. Adequate bone marrow reserve (NB: Platelet count > 100)

iv. No evidence of impending spinal cord compression

v. No plans for systemic chemotherapy

Management of Oligometastatic Disease

1. The role of local therapy to the prostate (i.e. RT or prostatectomy) and the role of SBRT to sites of metastatic disease remains investigational and should be considered in the context of a clinical trial or based on review in multidisciplinary rounds.

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.

• Patients who have responded well to docetaxel chemotherapy can be re-challenged in the case of subsequent progressive disease.

• 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[17,21]	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[14,15]	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[16]	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[22,23]	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[24-26]	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[27,28]	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)[29]	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)[18,19]	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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ASCO, 2017 [20].

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 (eg, 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-na¨ıve 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 exists54; 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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AUA

Castration-Resistant Prostate Cancer: AUA Guideline

Leitlinienorganisation/Fragestellung

To assist in clinical decision-making, six index patients were developed representing the most common clinical scenarios that are encountered in clinical practice.

Methodik

Grundlage der Leitlinie

- Überwiegend Repräsentatives Gremium (Patientenvertreter nicht explizit aufgeführt);
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz nur limitiert dargelegt;
- 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 postuliert, jedoch nicht spezifiziert.

Recherche/Suchzeitraum:

- Initial literature search: Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Database of Systematic Reviews, Ovid Cochrane Central Register of Controlled Trials and Scopus. The evidence report was limited to English-language, peer-reviewed literature published between January 1996 and February 2013.
- The amendments allowed for the incorporation of additional literature released since the initial publication of this guideline in 2013. Comprehensive searches of several databases from February 2013 to February 2014 (2014 amendment), February 2014 to February 2015 (2015 amendment), and February 2015 to April 2018 (2018 amendment, specific to non-metastatic CRPC patients), English language, were conducted.

LoE & GoR

Guidelines Statement Classification			
	Evidence Strength A (High Certainty)	**Evidence Strength B (Moderate Certainty)**	**Evidence Strength C (Low Certainty)**
Strong Recommendation (Net benefit or harm substantial)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears substantial Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation)
Moderate Recommendation (Net benefit or harm moderate)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears moderate Applies to most patients in most circumstances but better evidence is likely to change confidence
Conditional Recommendation (No apparent net benefit or harm)	Benefits = Risks/Burdens Best action depends on individual patient circumstances Future research unlikely to change confidence	Benefits = Risks/Burdens Best action appears to depend on individual patient circumstances Better evidence could change confidence	Balance between Benefits & Risks/Burdens unclear Alternative strategies may be equally reasonable Better evidence likely to change confidence

Table 1: AUA Nomenclature Linking Statement Type to Evidence Strength
Standard: Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade A or B evidence
Recommendation: Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade C evidence
Option: Non-directive statement that leaves the decision regarding an action up to the individual clinician and patient because the balance between benefits and risks/burdens appears equal or appears uncertain based on Grade A, B, or C evidence
Clinical Principle: a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature
Expert Opinion: a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence

AUA Nomenclature: Linking Statement Type to Evidence Strength

The AUA nomenclature system explicitly links statement type to body of evidence strength and the Panel's judgment regarding the balance between benefits and risks/burdens (see Table 1).[12] The framework of rating the quality of evidence is an adaptation and modification[12] of the GRADE framework (Grading of Recommendations, Assessment, Development and Evaluation).[13,14] In this adaptation, the AUA rates the quality of evidence as high, moderate or low (A, B or C). Standards are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be

undertaken based on Grade A or Grade B evidence. Recommendations are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken based on Grade C evidence. Options are non-directive statements that leave the decision to take an action up to the individual clinician and patient because the balance between benefits and risks/burdens appears relatively equal or appears unclear; Options may be supported by Grade A, B or C evidence. It is important to note that grading (A, B or C) does not reflect the magnitude of a potential benefit or harm, but is instead related to the methodological review of the study. For some clinical issues, there was little or no evidence from which to construct evidence-based statements. Where gaps in the evidence existed, the Panel provides guidance in the form of Clinical Principles or Expert Opinions with consensus achieved using a modified Delphi technique if differences of opinion existed among Panel members.[15] A Clinical Principle is a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature. Expert Opinion refers to a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge and judgment and for which there is no evidence. The completed evidence report may be requested through AUA.

Empfehlungen

Index Patient 2: Asymptomatic or minimally symptomatic, mCRPC without prior docetaxel chemotherapy

This patient represents a common clinical presentation seen in the CRPC setting today. These patients are characterized as having a rising PSA in the setting of castrate levels of testosterone, documented metastatic disease on radiographic imaging and no prior treatment with docetaxel chemotherapy for CRPC. The key distinction between this patient and Index Patients 3 and 4 is symptom status. Specifically, this patient is defined as having no symptoms or mild symptoms attributable to his prostate cancer. However, one must then consider whether the patient requires regular opioid pain medications for symptoms thought to be attributable to documented metastases to achieve this level of pain control. In general, if patients require regular narcotic medications for pain relief, they are not included in this category. Acknowledging these important definitions, the panel makes the following guidelines statements:

Guideline statement 5: Clinicians should offer abiraterone plus prednisone, enzalutamide, docetaxel, or sipuleucel-T to patients with asymptomatic or minimally symptomatic mCRPC with good performance status and no prior docetaxel chemotherapy. (Standard; Evidence Level Grade A [abiraterone plus prednisone and enzalutamide] / B [docetaxel and sipuleucel-T])

Abiraterone plus prednisone, enzalutamide, docetaxel chemotherapy and sipuleucel-T immunotherapy are currently the only agents that have an FDA indication for use in men with mCRPC who have not yet received docetaxel chemotherapy. For each agent, there is a randomized clinical trial that shows a survival benefit for the drug.

Abiraterone: Prior to docetaxel chemotherapy, abiraterone plus prednisone has demonstrated an improvement in radiographic PFS and OS. In the COU-AA-302 study, Ryan et al.[23,24] randomized 1,088 men with mCRPC who had not received prior chemotherapy to receive

either abiraterone 1,000mg daily plus prednisone 5mg twice a day or placebo plus prednisone 5 mg twice daily. The primary outcomes of the study were radiographic-progression free and OS. Participants randomized to receive abiraterone plus prednisone had statistically significant improvement in radiographic progression-free survival (HR=0.53 p<0.001), as previously reported during interim analyses.[23] The final analysis of OS showed a statistically significant increase in patients treated with abiraterone plus prednisone (HR=0.81; 95% CI, 0.70 to 0.93; P=0.0033).[24]

Although grade 3-4 mineralocorticoid related adverse events and liver function abnormalities were more common in the abiraterone group, the agent was generally well-tolerated.

Enzalutamide: In the double-blind, phase 3 PREVAIL study, Beer et al. randomized 1,717 patients to receive either enzalutamide (at a dose of 160 mg) or placebo once daily.[25] Eligible patients were asymptomatic or mildly symptomatic and had not received cytotoxic chemotherapy, ketoconazole, or abiraterone. The results showed that enzalutamide significantly decreased the risk of radiographic progression (HR=0.19; 95% CI, 0.15 to 0.23; P<0.001) and death (29% reduction in the risk of death; HR=0.71; 95% CI 0.60 to 0.84; P<0.001) and delayed the initiation of chemotherapy (HR=0.35; 95% CI, 0.30 to 0.40; P<0.001) in a group of men with mCRPC and a median follow-up duration for survival of approximately 22 months. Overall, the most common adverse events associated with enzalutamide treatment included fatigue and hypertension.

Docetaxel: Docetaxel is a potent inhibitor of microtubule assembly and disassembly. In the TAX-327 trial, Tannock et al.[4] randomized 1,006 men with mCRPC and good performance status to receive 5mg prednisone twice daily and either docetaxel 75mg/M2 every three weeks; docetaxel 30mg/M2 weekly or; mitoxantrone 12mg/M2 weekly. As the primary outcome of this trial was survival, mitoxantrone effectively served as a “placebo” arm, as a prior RCT showed symptom improvement but failed to show a survival advantage associated with mitoxantrone when compared to placebo.[26] Patients who received docetaxel plus prednisone every three weeks in TAX-327 had significantly better survival than those receiving mitoxantrone (HR for death: 0.75; p=0.009). Median survival in the docetaxel plus prednisone every three weeks group was 18.9 months compared to 16.5 months in the mitoxantrone group. No significant survival differences were noted between the weekly docetaxel plus prednisone group and the mitoxantrone group. While this study provides strong evidence to support the use of docetaxel plus prednisone in men with mCRPC, there are two important caveats to bear in mind, particularly when comparing it to later studies on newer agents. First, this study did include many patients with symptomatic mCRPC (Index Patient 3). Second, 26% of patients in the docetaxel plus prednisone every three weeks arm had one or more serious adverse events, and roughly 11% of patients in this group discontinued treatment due to adverse events. In a second study, SWOG 9916 tested docetaxel and estramustine v. mitoxantrone and prednisone for 12 cycles in 674 men with mCRPC.[5] Patients in the docetaxel plus prednisone arm had improvements in median survival (17.5 v. 15.6 months, p=0.02) and time to progression (TTP) (6.3 v. 3.2 months, p <0.001) and a 20% reduction in risk of death. The side effect profile associated with docetaxel may lead patients to delay docetaxel treatment until symptomatic or to elect not to receive this treatment at all. A thorough discussion of the risks and benefits of this treatment is warranted with all patients who are considering this therapy.

Sipuleucel-T: Sipuleucel-T is an approved immunotherapy for the management of mCRPC. Sipuleucel-T immunotherapy is an FDA-approved agent in this setting based upon the results

of the IMPACT trial, published in 2010.9 In this randomized double-blind placebo controlled clinical trial, 512 men with asymptomatic or minimally-symptomatic mCRPC and good functional status were randomized to receive either sipuleucel-T or placebo on a 2:1 basis. Compared to placebo, sipuleucel-T was associated with a relative reduction of 22% in the risk of death (HR=0.78; p=0.03). Median survival in the sipuleucel-T arm was 25.8 months compared to 21.7 months in the placebo arm. It is worth noting that patients receiving sipuleucel-T therapy rarely (<10%) exhibit a clinical, serologic or radiographic response, and, as such, should be counseled appropriately not to expect to see a decline in PSA or reduction in radiologic volume of disease when undergoing this treatment.
In summary, abiraterone plus prednisone, enzalutamide, docetaxel and sipuleucel-T are considered standard therapies in this index patient. Unfortunately, there are no direct studies comparing the agents that can be used to inform optimal sequencing. As a general principle, it is preferable to give the least toxic agent first, particularly given the lack of head-to-head data, but this must be deliberated in light of other considerations, including convenience of administration. As such, patients should be informed of all options and be allowed to make an informed decision based upon their own preferences and goals related to therapy.

Guideline Statement 6: Clinicians may offer first- generation anti-androgen therapy, ketoconazole plus steroid or observation to patients with asymptomatic or minimally symptomatic mCRPC with good performance status and no prior docetaxel chemotherapy who do not want or cannot have one of the standard therapies. (Option; Evidence Level Grade C)

Manipulation with existing anti-androgen agents, such as bicalutamide, nilutamide or flutamide, or ketoconazole plus steroid can only be considered an option in this setting, if only because they offer patients who do not want or cannot have one of the standard therapies a relatively less toxic therapeutic option.
In patients who elect not to receive the standard therapies, there are a number of other options available. Data to support the use of these options in the setting of asymptomatic or minimally-symptomatic prostate cancer is limited and generally of lesser strength than the standard treatments. Some have suggested that the removal of anti-androgen therapy may have a beneficial effect on mCRPC. The majority of these studies supporting this approach are observational.[27-29] The single RCT addressing this issue failed to show any survival benefit associated with anti-androgen withdrawal.[30]

Anti-androgens: Though anti-androgens (flutamide, bicalutamide and nilutamide) are commonly used, these agents can be associated with side effects including gastrointestinal upset and liver toxicity.

Ketoconazole: The oral androgen synthesis inhibitor ketoconazole is a weak inhibitor of CYP11A and CYP17A and suppresses the synthesis of adrenal and tumor tissue androgens. Ketoconazole can be associated with nausea and hepatotoxicity and must be given with replacement steroids.
Finally, some patients may not wish to pursue any therapy, waiting for the onset of symptoms to pursue treatment (if they were to ever elect treatment at all). Given current data in this patient population, this approach is a reasonable option. In all cases, the patient's preferences and personal goals should be considered when choosing therapy for asymptomatic or minimally symptomatic CRPC.

Index Patient 3: Symptomatic, mCRPC with good performance status and no prior docetaxel chemotherapy

These patients have a rising PSA in the setting of castrate levels of testosterone, documented symptomatic metastatic disease on radiographic imaging and no prior history of docetaxel chemotherapy for prostate cancer. The definition of symptomatic disease warrants additional explanation to contrast with Index Patient 2. First, the patient must have symptoms that are clearly attributable to the metastatic disease burden, not any other medical condition. Second, if having pain, the patient should require regular opiate pain medications for symptoms attributable to documented metastases in order to achieve an acceptable level of pain control. If patients require regular narcotic medications for pain relief, then they are symptomatic from their prostate cancer and should be included in this category.

Guideline Statement 7: Clinicians should offer abiraterone plus prednisone, enzalutamide or docetaxel to patients with symptomatic, mCRPC with good performance status and no prior docetaxel chemotherapy. (Standard; Evidence Level Grade A [abiraterone plus prednisone and enzalutamide] / B [docetaxel])

Abiraterone: In the previously discussed COU-AA-302 study, treatment with abiraterone prolonged OS compared to prednisone alone in both a clinically and statistically significant manner after a median follow-up of over four years. The results support the favorable safety profile of abiraterone in chemotherapy-naïve mCRPC patients.[24] While the randomized phase-III trial was only conducted in asymptomatic and minimally symptomatic men, the mechanism of action of abiraterone is similar to that of ketoconazole and has shown marked palliative and skeletal related benefits. Abiraterone is FDA approved for treatment of a symptomatic patient population, and the label specifies only that it is for the treatment of mCRPC; therefore, it is appropriate for Index Patient 3.

Enzalutamide: As previously noted, the PREVAIL study showed that enzalutamide significantly decreased the risk of both radiographic progression and death in chemotherapy-naïve men in whom the disease progressed despite androgen deprivation therapy. The study was stopped after a planned interim analysis that showed the benefit of the drug with respect to all secondary endpoints, including time until the initiation of chemotherapy, the time until the first skeletal-related event, a complete or partial soft-tissue response, the time until PSA progression and a rate of decline of at least 50% in PSA.25

Docetaxel: As previously noted, the TAX-327 and SWOG-9916 studies support the use of first-line docetaxel every three weeks with daily prednisone in symptomatic mCRPC.[4,5] Bone pain responses were more significant in docetaxel patients (35% v. 22%; p=0.08), as were improvements in QOL compared to the mitoxantrone group. Updated results showed a similar median survival benefit for docetaxel every three weeks v. mitoxantrone, with three-year survival rates of 18.6% and 13.5%, respectively (p=0.005).[31] The magnitude of benefit associated with docetaxel plus prednisone treatment for CRPC was independent of age, performance status or baseline PSA.

Guideline Statement 8: Clinicians may offer ketoconazole plus steroid, mitoxantrone or radionuclide therapy to patients with symptomatic, mCRPC with good performance status and no prior docetaxel chemotherapy who do not want or cannot have one of the standard therapies. (Option; Evidence Level Grade C [ketoconazole] / B [mitoxantrone] / C [radionuclide therapy])

Ketoconazole: Ketoconazole has not shown significant OS improvements in patients with symptomatic, chemotherapy-naive mCPRC. Ketoconazole has substantial treatment-related side effects that have prompted the development of more potent CYP17A inhibitors, such as abiraterone.

Mitoxantrone: Mitoxantrone, a topoisomerase inhibitor, has not shown a survival benefit compared to docetaxel-based chemotherapy regimens in mCRPC, as previously discussed.[4] Mitoxantrone is primarily utilized in symptomatic mCRPC patients with poor performance status (i.e. not candidates for docetaxel-based chemotherapy). In support of its use, mitoxantrone has been shown to provide a palliative response in symptomatic patients. In one study by Tannock et al. mitoxantrone was observed to provide significant palliative care in 29% of patients who received mitoxantrone plus prednisone, as compared to 12% who received prednisone alone (P = 0.01).[26]

Radionuclide Therapy: The use of systemic radiotherapy with samarium-153 or strontium-89 occasionally benefits patients with widely metastatic, symptomatic bone involvement; however, this therapy is usually reserved for candidates who are not responding to palliative chemotherapy and who are not candidates for localized external beam radiotherapy (EBRT).32,33 The risk of bone marrow suppression, which might influence the ability to administer systemic chemotherapy agents, should be considered before initiation of radionuclide therapy. The use of samarium-153 is further discussed for use in Index Patient 6.

Guideline Statement 9: Clinicians should offer radium-223 to patients with symptoms from bony metastases from mCRPC with good performance status and no prior docetaxel chemotherapy and without known visceral disease. (Standard; Evidence Level Grade B)

Radium-223: Radium-223 is an α-emitting radiopharmaceutical capable of inducing double strand DNA breaks in cancer cells while minimizing exposure to surrounding marrow. The use of radium-223 for the treatment on bone metastases relies on the chemical similarity to calcium and the ability of the α-radiation and the short-lived decay products of radium-223 to kill cancer cells. The short range of α -radiation reduces the damage to surrounding healthy tissue creating a more localized effect compared to other radionuclide therapies, such as strontium-89.This is an appropriate treatment for patients with symptomatic bone pain and non-visceral metastases. A phase III trial with radium-223 in symptomatic men with progressive mCRPC with or without prior docetaxel exposure and no evidence of visceral metastasis reported improvement in median survival; 14.9 months v. 11.3 months (HR=0.695, 95% CI 0.581 to 0.832; P=0.00007) in favor of radium-223 over placebo. Time to first SRE improved from 9.8 month with placebo to 15.6 months with radium-223 (HR=0.658, 95% CI 0.522 to 0.830; P=0.00037). Significant improvements in QOL measurements were reported in the patients treated with radium-223. Of the 921 patients of this trial, those receiving treatment were given six intravenous injections with a dose of 50 kBq per kilogram of body weight every four weeks.11 Rates of grade 3 or 4 neutropenia and thrombocytopenia were low at 2.2% and 6.3%, respectively.[34]

Guideline Statement 10: Clinicians should not offer treatment with either estramustine or sipuleucel-T to patients with symptomatic, mCRPC with good performance status and no prior docetaxel chemotherapy. (Recommendation; Evidence Level Grade C)

Estramustine: Estramustine has both cytotoxic and hormonal effects, although the major mechanism of action is as an alkylating agent, which has not shown significant OS advantages. Petrylak et al. showed an OS of 17.5 months for docetaxel plus estramustine compared to 15.6 months for mitoxantrone plus prednisone (P=0.02).[5] However, the survival advantage was similar to Tannock et al for docetaxel without estramustine. Therefore the advantage has been attributed to docetaxel. Given the significant toxicity with estramustine, its use cannot be encouraged.4 A variety of secondary hormonal deprivation strategies have been studied after failure of initial ADT in mCRPC, such as anti-androgen withdrawal, administration of alternative anti-androgens and use of estrogen derivatives, such as diethylstilbesterol (DES) and estramustine; however, none of these strategies have demonstrated significantly improved OS in the symptomatic, pre-chemotherapy mCRPC setting.

Sipuleucel-T: The use of sipuleucel-T immunotherapy is not recommended in symptomatic disease that necessitates narcotic use, consistent with the FDA indication for this compound. Thus, sipuleucel-T currently may be considered only for patients with asymptomatic or minimally symptomatic mCRPC and is most appropriate for Index Patient 2, as previously discussed.9 Patients with large tumor burdens, those with visceral disease and those with more aggressive disease (predicted survival < 12 months) are less likely to respond to immunotherapy.

Index Patient 4: Symptomatic, mCRPC with poor performance status and no prior docetaxel chemotherapy

Clinical trials have generally excluded patients with a poor performance status (ECOG 3-4) from participation. Thus, most data regarding management of such patients is extrapolated from randomized trials of eligible patients who had a better performance status, as well as from some smaller trials and registries. Even a Phase 3 clinical trial that was presumptively designed for a population considered “unfit” for docetaxel (ALSYMPCA to evaluate radium-223) still only allowed a performance status of ECOG 0-1. However, treatments with acceptable safety profiles do exist and should be considered, even in poor performance status patients. This is especially true in those patients in whom the poor performance status may be considered to be directly related to the cancer itself and thus whose status might improve with effective treatment. Treatments must be individually tailored in these patients after a careful discussion of risks and benefits with particular attention to patient QOL.

Guideline Statement 11: Clinicians may offer treatment with abiraterone plus prednisone or enzalutamide to patients with symptomatic, mCRPC with poor performance status and no prior docetaxel chemotherapy. (Option; Evidence Level Grade C)

The FDA approved the label for use of abiraterone plus prednisone in mCRPC independent of docetaxel treatment following interim analysis of data from the previously discussed COU-AA-302 study.[23] Follow up analysis did show significant improvements in OS.[24] Notably, COU-AA-302 was administered only in good performance status patients, but it is the panel’s opinion that abiraterone plus prednisone would be a reasonable alternative to chemotherapy for patients even with a poor performance status.
Please refer to Index Patients 1, 2, and 3 for further discussion of enzalutamide.

Guideline Statement 12: Clinicians may offer treatment with ketoconazole plus steroid or radionuclide therapy to patients with symptomatic, mCRPC with poor performance status and no prior docetaxel chemotherapy who are unable or unwilling to receive abiraterone plus prednisone or enzalutamide. (Option; Evidence Level Grade C)

Ketoconazole: Ketoconazole has been demonstrated to have anti-cancer effects[30] in the setting of mCRPC and could be a viable alternative, in particular if abiraterone plus prednisone is unavailable. It is important to recognize that ketoconazole has a worse side effect profile, as previously stated in the discussion of Index Patient 1.

Radionuclide Therapy: Samarium-153 and strontium-89 have not shown a survival benefit but may offer palliative benefit in patients symptomatic with bone pain. These are further discussed under Index Patient 6. The use of radium-223 in this Index Patient is addressed below.

Guideline Statement 13: Clinicians may offer docetaxel or mitoxantrone chemotherapy to patients with symptomatic mCRPC with poor performance status and no prior docetaxel chemotherapy in select cases, specifically when the performance status is directly related to the cancer. (Expert Opinion)

Patients with mCRPC may have a poor performance status for multiple reasons, but the two major possibilities are related to the cancer itself or because of non-prostate cancer related causes. For instance, a patient who was previously active and healthy whose cancer progresses rapidly in bone and liver may develop severe pain, weakness, weight loss and other symptoms thought to be directly related to the progression of cancer. This patient may benefit from treatment. An alternative patient may be one in whom a long history of chronic disorders, such as diabetes, heart disease, arthritis, cirrhosis and other conditions may be underlying the new diagnosis of prostate cancer. In this case, effective treatment of his cancer would not improve any of his underlying conditions.

Docetaxel: Docetaxel is considered the standard first-line therapy in mCRPC and has demonstrated both a survival benefit as well as a palliative benefit in symptomatic disease. Most patients with a poor performance status are not considered qualified candidates for chemotherapy, but it is possible that some patients whose cancers are mostly contributing to their disability may benefit from anti-cancer treatment. Such an approach must be undertaken cautiously by a qualified physician experienced in the administration of chemotherapy. Dosage and schedule modifications might be considered for individual patients to make this more tolerable.

Mitoxantrone: Mitoxantrone was approved in 1996 based on two randomized trials that demonstrated a palliative benefit in symptomatic mCRPC.[26,35] No survival benefit has been seen with mitoxantrone. However, it could be considered as an alternative option to docetaxel or potentially as a second-line therapy in men with symptomatic disease and a poor performance status. Like all of the trials mentioned, no clinical trials allowed patients with poor performance status, so caution must be taken. If the poor performance status is not related to cancer progression, then systemic chemotherapy of any kind is not recommended.

Guideline Statement 14: Clinicians may offer radium-223 to patients with symptoms from bony metastases from mCRPC with poor performance status and no prior docetaxel chemotherapy and without known visceral disease in select cases, specifically when the performance status is directly related to symptoms related to bone metastases. (Expert Opinion)

Radium-223 may be offered for patients with symptomatic bone pain and non-visceral metastases. Radium-223 has showed survival benefit in patients with good performance status. If it is believed that the poor performance status of Index Patient 4 is due to symptomatic bone pain, radium-223 may also be beneficial to these patients.

Guideline Statement 15: Clinicians should not offer sipuleucel-T to patients with symptomatic, mCRPC with poor performance status and no prior docetaxel chemotherapy. (Recommendation; Evidence Level Grade C)

In subsequent analyses of the IMPACT trial, it appears that the survival benefit associated with its use does not appear until six months after therapy.[9] Sipuleucel-T appears to benefit patients with a lower disease burden and better performance status. Most patients in IMPACT had not received prior chemotherapy (18.2% of patients had received prior docetaxel chemotherapy). All patients in the IMPACT trial were either ECOG 0 or 1, and over 80% of patients were ECOG 0.[9]
Thus, the benefit of using sipuleucel-T in men with mCRPC and a shorter life expectancy appears to be limited. Patients with very symptomatic disease and a poor performance status would be unlikely to gain a significant survival benefit from the use of sipuleucel-T and should be directed towards alternative options.

Index Patient 5: Symptomatic, mCRPC with good performance status and prior docetaxel chemotherapy

As patients with prostate cancer receive hormonal therapy earlier in the course of the disease (frequently for non-metastatic disease), they may actually develop castration-resistant disease (based on serologic progression) with non-metastatic or asymptomatic metastatic disease. Thus, additional agents, including docetaxel chemotherapy may be administered earlier in the course of metastatic disease. These trends have resulted in a population of mCRPC patients who have completed docetaxel and may continue to be asymptomatic or minimally-symptomatic with an excellent performance status. While such patients may be healthy enough to receive a number of subsequent therapies, a focus of therapy should also be to maintain their excellent performance status without significant toxicity from additional therapy. It is in this context that providers should choose from a number of additional therapies to offer to this patient population.

Guideline Statement 16: Clinicians should offer treatment with abiraterone plus prednisone, cabazitaxel or enzalutamide to patients with mCRPC with good performance status who received prior docetaxel chemotherapy. If the patient received abiraterone plus prednisone prior to docetaxel chemotherapy, they should be offered cabazitaxel or enzalutamide. (Standard; Evidence Level Grade A [abiraterone] / B [cabazitaxel] / A [enzalutamide])

The trend over the past six to seven years has been to use docetaxel earlier in the course of treatment for a patient with castration-resistant disease, perhaps in those with minimal symptoms or even the asymptomatic patient with evidence of serologic or radiographic

progression. The result is that many patients who have received and failed docetaxel have an excellent performance status and some may remain asymptomatic from their disease. Thus, the risk/benefit ratio of subsequent therapy and the desire to maintain an excellent QOL should certainly be of primary concern when selecting additional therapies post-docetaxel. In this light, abiraterone plus prednisone and enzalutamide appear to provide clinical benefit equivalent to (if not superior to) additional intravenous chemotherapy with an agent such as cabazitaxel. Abiraterone plus prednisone and enzalutamide have significantly less acute toxicity and no apparent cumulative toxicity in patients receiving these agents for prolonged periods. This is in contradistinction to cabazitaxel, which may show cumulative bone marrow toxicity (manifested by pancytopenia) and also cumulative neurotoxicity, particularly in patients with some underlying peripheral neuropathy from their prior docetaxel. Both abiraterone plus prednisone and enzalutamide represent excellent treatment options for such a patient. While there have been no randomized trials comparing these agents and little information exists regarding appropriate sequencing of these drugs, patients may have prolonged responses to either or both of these agents. With the FDA's expansion of the label indication for abiraterone plus prednisone to the pre-chemotherapy setting based on the results of a phase III clinical trial,23 patients will have increasingly already been exposed to and progressed on abiraterone plus prednisone by the time they reach the postdocetaxel setting, making enzalutamide a preferable option compared to cabazitaxel.

Abiraterone: In a phase III trial (COU-AA-301), 1,195 patients who had failed docetaxel received 1,000 mg abiraterone plus prednisone or placebo. At a median of 12.8 months, OS and PFS favored the abiraterone plus prednisone cohort (14.8 months v.10.9 months; hazard ratio, 0.65; P<0.001 and 5.6 months v. 3.6 months; P<0.001, respectively).7 As previously noted, abiraterone plus prednisone was well tolerated during clinical trial but did show an increase in adverse events and specifically those side effects related to mineralocorticoid excess.

Cabazitaxel: Cabazitaxel is another tubulin-binding taxane chosen for clinical development because of preclinical activity in tumor models resistant to other taxanes. An open-label, randomized phase III trial compared cabazitaxel at 25 mg/M2 intravenously with oral prednisone versus mitoxantrone at 12 mg/M2 intravenously with the same dose of prednisone, both administered on an every three week basis.10 In this trial 755 patients who had received prior docetaxel were randomized, and the group receiving cabazitaxel demonstrated improved OS (15.1 months v 12.7 months) and improved PFS (2.8 months v 1.4 months). Cabazitaxel resulted in more-clinically-significant diarrhea, but its primary toxicity is hematologic with 82% of patients developing grade 3 or 4 neutropenia, 8% developing febrile neutropenia and 5% resulting in death. The FDA label indication for this drug recommends prophylactic neutrophil growth factor support in those patients most susceptible to neutropenia, including older individuals and those with significant prior radiotherapy. Because of the need for intravenous administration, the more modest clinical benefit and the higher rates of significant toxicity, cabazitaxel is ranked below abiraterone plus prednisone and enzalutamide for this group of patients.

Enzalutamide: Phase I/II data showed serologic and radiographic responses in both chemo-naïve patients as well as those who had received prior chemotherapy.36 The subsequent double-blind, placebo-controlled AFFIRM phase III trial was performed in 1,199 patients who had received prior docetaxel therapy.6 Patients received either enzalutamide 160 mg/day

orally or placebo, and OS, the primary endpoint, favored enzalutamide (18.4 months v 13.6 months). There was also statistical superiority of enzalutamide for all secondary endpoints, including percentage of patients with 50% PSA reduction, soft-tissue response rate, QOL response rate, time to PSA progression, radiographic PFS and time to first SRE. Toxicity from enzalutamide was related primarily to fatigue, diarrhea and hot flashes, although 5 of 800 patients receiving the drug developed seizure activity. This drug was approved by the FDA in August of 2012 and represents another highly active oral agent with minimal toxicity available to these patients.

Guideline Statement 17: Clinicians may offer ketoconazole plus steroid to patients with mCRPC with good performance status who received prior docetaxel if abiraterone plus prednisone, cabazitaxel or enzalutamide is unavailable. (Option; Evidence Level Grade C)

A number of clinical trials have established the efficacy and toxicity of high-dose ketoconazole in this setting,30, 37-42 with as many as 50% of patients showing a > 50% drop in PSA, fewer bidimensionally measurable disease responses and a median time to progression of five to eight months. One study has suggested that 1) prior response to an antiandrogen; 2) pre-treatment PSA doubling time; and 3) extent of disease may be associated with the likelihood of clinical response to this therapy.39 Although ketoconazole likely has a lower response rate, a shorter time to progression and higher incidence of significant toxicity than abiraterone plus prednisone, it remains a viable alternative for patients unable to obtain abiraterone plus prednisone.

Guideline Statement 18: Clinicians may offer retreatment with docetaxel to patients with mCRPC with good performance status who were benefitting at the time of discontinuation (due to reversible side effects) of docetaxel chemotherapy. (Option; Evidence Level Grade C)

Much of the benefit of docetaxel in the mCRPC patient is seen in improvement of survival and QOL. However, prolonged, continuous therapy with docetaxel can result in cumulative, progressive, non-hematologic toxicity (e.g. neuropathy) that may more than counterbalance any potential serologic, radiographic or symptomatic benefit the patient may be receiving from the drug. In an effort to prolong the overall period of disease control with docetaxel, to allow reversible side effects to improve and to maximize overall QOL by spending as much time off chemotherapy as possible, the use of intermittent therapy with built-in drug holidays has become a common practice. Non-randomized data43-46 as well as one randomized trial47 suggests that a minority of patients may retain sensitivity to the drug with multiple discontinuous periods of administration. It is apparent that those drug holidays may last, on average, four to five months and that subsequent nontreatment periods might also last a number of months. It is logical to assume that patients with the most dramatic clinical benefit from prior docetaxel and with a more prolonged period off therapy prior to reinstitution are more likely to benefit from additional treatment with the same drug. Patients with these characteristics and who have recovered from prior toxicity may be considered for a re-trial of docetaxel before this drug is discarded from the armamentarium.

Guideline Statement 19: Clinicians should offer radium-223 to patients with symptoms from bony metastases from mCRPC with good performance status who received prior docetaxel chemotherapy and without known visceral disease. (Standard; Evidence Level Grade B)

During the course of cancer treatment, bone marrow can become infiltrated by the cancer. Chemotherapeutic agents, such as docetaxel, can suppress bone marrow function while being used to extend survival and improve quality of life. Radium-223 was shown to be an effective therapy in the previously discussed Parker et al. study11 in which 57% of patients had previously received chemotherapy. As with other treatments, such as EBRT, side effects can include anemia and thrombocytopenia. Those patients who have previously received chemotherapy are at greater risk for such side effects compared to chemotherapy-naive patients.

Index Patient 6: Symptomatic, mCRPC with poor performance status and prior docetaxel chemotherapy

The American Society of Clinical Oncology (ASCO) has posted recommendations regarding treatment for patients with advanced solid tumors; particularly in the last months of life. ASCO advocates for an increasing emphasis on a patient's QOL and concentrates on symptom management. Treatment given in the last months of life may delay access to end of life care, increase costs and add unnecessary symptom management. Patients with poor performance status (ECOG 3 or 4) should not be offered further treatment.

Guideline Statement 20: Clinicians should offer palliative care to patients with mCRPC with poor performance status who received prior docetaxel chemotherapy. Alternatively, for selected patients, clinicians may offer treatment with abiraterone plus prednisone, enzalutamide, ketoconazole plus steroid or radionuclide therapy. (Expert Opinion)

Palliative care is an interdisciplinary, holistic approach to managing an advanced disease such as prostate cancer with a guarded prognosis. It can include controlling symptoms that are physical, psychological, spiritual and social. The goal of palliation is to prevent and relieve suffering and to support the best possible QOL for the patient and family. Advanced prostate cancer can be debilitating with bone pain, fatigue and weight loss. Palliative radiotherapy can be an option for controlling bone pain in some patients. An increasing dependence upon others and a feeling of losing control can contribute to anxiety and depression. Other symptoms include urinary outflow obstruction, weakness secondary to spinal cord compression, lymphedema and anemia. Evaluation and treatment should be comprehensive and patient centered, focusing on the goals of the individual patient as well as the patient's family. Comprehensive palliative care often requires a multidisciplinary approach where various providers of differing expertise assess and treat the complex needs of the advanced disease prostate cancer patient.48,49

Abiraterone: Abiraterone is for patients who have CRPC that is resistant to medical or surgical treatments and who have received prior docetaxel chemotherapy. Method of action and dosing information are previously referenced.

Enzalutamide: Enzalutamide is indicated for the treatment of patients with mCRPC who have previously received docetaxel. The previously discussed AFFIRM study found that enzalutamide significantly prolonged the survival of men with mCRPC after chemotherapy. Method of action and dosing information are previously referenced.

Ketoconazole: Ketoconazole provides an available but fairly toxic treatment plan for patients with mCRPC who have received prior docetaxel chemotherapy with poor performance status. Method of action and dosing information are previously referenced.

Radionuclide Therapy: One example of a Phase III randomized clinical trial of radioactive samarium-153 (153Sm) lexidronam versus nonradioactive lexidronam for palliation of bone pain in patients with CRPC is by Sartor (2004).49 A total of 152 men with painful bone metastases were enrolled in this prospective, randomized, double-blind trial. Patients were randomized (2:1) to the radioactive 153Sm153Smlexidronam agent. Inclusion criteria were advanced prostate cancer progressing despite medical or surgical orchiectomy, a positive bone scan, pain scores of greater than 30mm on a 100mm visual analog scale or the use of opioid analgesics in daily doses equivalent to 60mg oral morphine, a Karnofsky performance status of less than 50% and life expectancy of greater than four months. Exclusion criteria were hormonal treatment initiated within eight weeks of dosing or radiotherapy administered within six weeks, pathologic fractures, spinal cord compression, prior hemibody irradiation, inadequate hematological, renal or liver function, allergies to phosphate compounds and prior exposure to radiopharmaceutical agents or bisphosphonates within six months of dosing. Patients completed pain and analgesic diaries twice daily. Blinded medications were given intravenously; the study was unblinded after four weeks when 28 of 52 placebo patients had not achieved satisfactory pain relief by week four; 22 of 28 chose to receive open label treatment with radioactive 153Sm-lexidronam. The authors concluded that 1 mCi/kg 153Sm-lexidronam is safe and effective for palliation of painful bone metastases in patients with hormone-refractory prostate cancer. Side effects included mild bone marrow suppression. The mean nadir white blood cell and platelet count (three to four weeks after treatment) was 3,800/µL and 127,000/µL, respectively. Counts recovered to baseline after approximately eight weeks. No grade 4 decreases in either platelets or white bloods cells were documented.

Multiple non-randomized trials have been done with Samarium-153 alone50,51 with unclear adverse events and outcomes. Other studies included Samarium-153 with docetaxel;52,53 these studies were also unclear in outcomes or adverse events. Studies looking at radium223 have focused on those patients with good performance status, and there is no data indicating an advantage over standard radiopharmaceuticals in this patient population.

Guideline Statement 21: Clinicians should not offer systemic chemotherapy or immunotherapy to patients with mCRPC with poor performance status who received prior docetaxel chemotherapy. (Expert Opinion)

There is insufficient evidence demonstrating a benefit in this patient population. The potential for harm greatly outweighs the potential benefit, so these treatments should not be offered.

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 10 of 12, October 2019) am 17.10.2019

#	Suchfrage
1	(CRPC OR mCRPC):ti,ab,kw
2	MeSH descriptor: [Prostatic Neoplasms] explode all trees
3	(prostate OR prostatic):ti
4	(cancer* OR tumo*r* OR carcinoma* OR neoplasm* OR adenocarcinoma*):ti
5	#3 AND #4
6	#1 OR #2 OR #5
7	#6 with Cochrane Library publication date from Oct 2014 to present, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 17.10.2019

#	Suchfrage
1	Prostatic Neoplasms, Castration-Resistant[mh]
2	CRPC[tiab] OR mCRPC[tiab]
3	Prostatic Neoplasms[mh]
4	(prostate[tiab] OR prostatic[tiab])
5	(cancer*[tiab] OR tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR neoplasm*[tiab] OR adenocarcinoma*[tiab])
6	#4 AND #5
7	#3 OR #6
8	neoplasm metastasis[mh]
9	metastat*[ti] OR metastas*[ti] OR advanced[ti]
10	#8 OR #9
11	independent[tiab] OR independence[tiab] OR insensitive[tiab] OR resistant[tiab] OR resistance[tiab] OR refractory[tiab]
12	hormone[tiab] OR androgen[tiab] OR castrate[tiab] OR castration[tiab]
13	#11 AND #12
14	#10 OR #13
15	#7 AND #14
16	#1 OR #2 OR #15
17	(#16) 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 studies[pt] OR validation studies[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
18	(#17) AND ("2014/10/01"[PDAT] : "3000"[PDAT])
19	(#18) NOT "The Cochrane database of systematic reviews"[Journal]
20	(#19) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
21	(#20) NOT retracted publication[ptyp]

Leitlinien in Medline (PubMed) am 17.10.2019

#	**Suchfrage**
1	CRPC[tiab] OR mCRPC[tiab]
2	Prostatic Neoplasms[majr]
3	(prostate[ti] OR prostatic[ti])
4	(cancer*[ti] OR tumor*[ti] OR tumour*[ti] OR carcinoma*[ti] OR neoplasm*[ti] OR adenocarcinoma*[ti])
5	#3 AND #4
6	#1 OR #2 OR #5
7	(#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
8	(#7) AND ("2014/10/01"[PDAT] : "3000"[PDAT])
9	(#8) NOT retracted publication[ptyp]

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