Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

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

Vorgang: 2023-B-220-z Niraparib/Abirateronacetat

Stand: Oktober 2023

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

Niraparib/Abirateronacetat
[zur Behandlung des metastasierten kastrationsresistenten Prostatakarzinoms (mCRPC)]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Strahlentherapie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	<u>Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V:</u> - Olaparib (Kombinationstherapie), Beschluss vom 06.07.2023 - (177Lu)Lutetiumvipivotidtetraxetan, Beschluss vom 06.07.2023 - Olaparib (Monotherapie), Beschluss vom 03.06.2021 - Radium-223-dichlorid, Beschluss vom 17.10.2019 - Enzalutamid, Beschluss vom 18.06.2015 - Sipuleucel-T, Beschluss vom 19.03.2015 (EU-Zulassung zurückgezogen) - Radium-223-dichlorid, Beschluss vom 19.06.2014 - Enzalutamid, Beschluss vom 20.02.2014 - Abirateronacetat, Beschluss vom 04.07.2013 - Abirateronacetat, Beschluss vom 29.03.2012
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:	
Niraparib/Abirateronacetat L01XK Akeega	<u>Anwendungsgebiet laut Zulassung vom 19.4.2023:</u> Akeega wird angewendet mit Prednison oder Prednisolon zur Behandlung von erwachsenen Patienten mit metastasiertem kastrationsresistentem Prostatakarzinom (mCRPC) und BRCA1/2-Mutationen (in der Keimbahn und/oder somatisch), bei denen eine Chemotherapie nicht klinisch indiziert ist.
Antiandrogene	
Bicalutamid L02BB03 generisch	Behandlung des fortgeschrittenen Prostatakarzinoms in Kombination mit einer LHRH-(Luteinisierendes-Hormon-Releasing-Hormon)-Analogon-Therapie oder einer operativen Kastration.
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.
Flutamid L02BB01 generisch	Zur Behandlung von Patienten mit fortgeschrittenem Prostatakarzinom, bei denen eine Suppression der Testosteronwirkungen indiziert ist. - Initialtherapie in Kombination mit einem LH-RH-Analogon oder in Verbindung mit Orchiektomie (komplette Androgenblockade) sowie bei Patienten, die bereits mit einem LH-RH-Analogon behandelt werden bzw. bei denen bereits eine chirurgische Ablatio testis erfolgt ist. - Zur Behandlung von Patienten, die auf andere endokrine Therapieformen nicht ansprachen oder für die eine andere endokrine Therapie nicht verträglich, aber notwendigerweise indiziert ist.
GnRH-Analoga	

Degarelix L02BX02 Firmagon	Firmagon ist ein Gonadotropin-Releasing-Hormon-(GnRH)-Antagonist zur Behandlung von erwachsenen männlichen Patienten mit fortgeschrittenem hormonabhängigen Prostatakarzinom.
Buserelin L02AE01 z.B. Profact	Profact Depot 9,45 mg 3-Monatsimplantat ist angezeigt bei Erwachsenen zur Behandlung des fortgeschrittenen hormonempfindlichen Prostatakarzinoms. Profact Depot 9,45 mg 3-Monatsimplantat ist jedoch nicht angezeigt nach beidseitiger Orchiektomie, da es in diesem Fall zu keiner weiteren Absenkung des Testosteronspiegels kommt.
Goserelin L02AE03 z.B. Zoladex	Behandlung von Patienten mit fortgeschrittenem Prostatakarzinom, bei denen eine endokrine Behandlung angezeigt ist.
Leuprorelin L02AE02 generisch	- Zur Behandlung des fortgeschrittenen hormonabhängigen Prostatakarzinoms. - Zur Behandlung des lokal fortgeschrittenen, hormonabhängigen Prostatakarzinoms; begleitend zur und nach der Strahlentherapie. - Zur Behandlung des lokalisierten hormonabhängigen Prostatakarzinoms bei Patienten des mittleren und Hoch-Risikoprofils in Kombination mit der Strahlentherapie.
Triptorelin L01AA06 generisch	ist indiziert zur Behandlung des - lokal fortgeschrittenen oder metastasierenden, hormonabhängigen Prostatakarzinoms. - lokal fortgeschrittenen, hormonabhängigen Prostatakarzinoms; begleitend zur und nach der Strahlentherapie.
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 generisch	Zytiga ist indiziert mit Prednison oder Prednisolon: - zur Behandlung des metastasierten kastrationsresistenten Prostatakarzinoms (mCRPC) bei erwachsenen Männern mit asymptomatischem oder mild symptomatischem Verlauf der Erkrankung nach Versagen der Androgenentzugstherapie, bei denen eine Chemotherapie noch nicht klinisch indiziert

	- zur Behandlung des mCRPC bei erwachsenen Männern, deren Erkrankung während oder nach einer Docetaxel-haltigen Chemotherapie progredient ist. - […]
Sonstige	
Radium-223-dichlorid V10XX03 Xofigo	Xofigo wird als Monotherapie oder in Kombination mit einem LHRH-Analogon (LHRH: Luteinisierendes-Hormon-freisetzendes Hormon) zur Behandlung von erwachsenen Patienten mit metastasiertem kastrationsresistentem Prostatakarzinom (mCRPC) und symptomatischen Knochenmetastasen ohne bekannte viszerale Metastasen angewendet, bei denen die Erkrankung nach Erhalt von mindestens zwei vorausgehenden systemischen Therapielinien zur Behandlung des mCRPC (außer LHRH-Analoga) fortschreitet, oder für die keine andere verfügbare systemische mCRPC-Therapie geeignet ist.
Olaparib L01XX46 Lynparza	<u>Prostatakarzinom</u> Lynparza wird angewendet: - als Monotherapie für die Behandlung von erwachsenen Patienten mit metastasiertem kastrationsresistentem Prostatakarzinom (mCRPC) und BRCA1/2-Mutationen (in der Keimbahn und/oder somatisch), deren Erkrankung nach vorheriger Behandlung, die eine neue hormonelle Substanz (new hormonal agent) umfasste, progredient ist. - in Kombination mit Abirateron und Prednison oder Prednisolon für die Behandlung von erwachsenen Patienten mit mCRPC, bei denen eine Chemotherapie nicht klinisch indiziert ist.
(177Lu)Lutetiumvipivotidtetraxetan V10XX05 Pluvicto	Pluvicto wird in Kombination mit Androgendeprivationstherapie (ADT) mit oder ohne Inhibition des Androgenrezeptor-(AR-)Signalwegs angewendet zur Behandlung von erwachsenen Patienten mit progredientem Prostata-spezifischen-Membranantigen-(PSMA-)positiven, metastasierten, kastrationsresistenten Prostatakarzinom (mCRPC), die zuvor mittels Inhibition des AR-Signalwegs und taxanbasierter Chemotherapie behandelt wurden.

Quellen: AMIce-Datenbank, Fachinformationen

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Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Behandlung von erwachsenen Patienten mit metastasiertem kastrationsresistentem Prostatakarzinom (mCRPC).

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

2 Systematische Recherche

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

Die Erstrecherche wurde am 04.08.2022 durchgeführt, die folgende am 17.04.2023. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die letzte Suchstrategie inkl. Angabe verwendeter Suchfilter und durchsuchter Leitlinienorganisationen ist am Ende der Synopse dargestellt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 2354 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf wurden insgesamt 19 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es konnten keine Cochrane Reviews identifiziert werden.

3.2 Systematische Reviews

Ternov K et al., 2021 [15].

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

Fragestellung

The aim was to compare patient-reported health-related quality of life (HRQoL) in men treated with enzalutamide vs. abiraterone acetate plus prednisone (AAP) for metastatic castrationresistant prostate cancer (mCRPC).

Methodik

Population:

- men treated with first-line mCRPC

Intervention/Komparator:

- enzalutamide or AAP

Endpunkte:

- HRQoL, short-term (12 weeks) measured by the Functional Assessment of Cancer Therapy-Prostate total score (FACT-P)

Recherche/Suchzeitraum:

- The literature was systematically searched 10 June 2020

Qualitätsbewertung der Studien:

- Cochrane Handbook for Systematic Reviews of Interventions for randomised clinical trials

Ergebnisse

Anzahl eingeschlossener Studien:

- 17 publications from 8 studies fulfilled the eligibility criteria
- Of the eight studies included in this systematic review, four were RCTs and four were observational studies.
- One of the RCTs directly compared enzalutamide with AAP

Charakteristika der Population:

Table 1 Trial characteristics.

Studies	Study design	Primary endpoint	Used questionnaires for PRO	PRO follow-up time	Patients in each treatment group	Included publications/ trial	Support/funding	Predefined PRO endpoints
COU-AA-302	RCT, phase III trial of AAP vs. PP	Overall and radiographic progression-free survival	HRQoL measured by FACT-P and pain measured by BPI-SF.	52 weeks	**AAP** 546 **PP** 542	4	Sponsor: Janssen	None
PREVAIL	RCT, phase III trial of enzalutamide vs. placebo	Overall and radiographic progression-free survival	HRQoL measured by FACT-P and EQ-5D. Pain measured by BPI-SF.	61 weeks for HRQoL. 25 weeks for pain.	**Enzalutamide** 872 **Placebo** 846	4	Sponsor: Pfizer in collaboration with Astellas	None
TERRAIN	RCT, phase VI trial of enzalutamide vs. bicalutamide	Progression-free survival[a]	HRQoL measured by FACT-P and EQ-5D. Pain measured by BPI-SF.	61 weeks	**Enzalutamide** 184 **Bicalutamide** 191	3	Sponsor: Astellas in collaboration with Pfizer	None
Phase II	RCT, phase II trial of enzalutamide vs. AAP	PSA response rate after PSA progression on first-line therapy when crossed over to second-line therapy with the opposite agent	HRQoL measured by FACT-P. Depression measured by PHQ-9. Cognitive function measured by MoCA test.	24 weeks for HRQoL and depression. 12 weeks for cognitive function.	**Enzalutamide** 101 **AAP** 101	1	Sponsor: British Columbia Cancer Agency Funding: Grant-in-aid from Janssen and Astellas, and grants from Prostate Cancer Canada.	None

Qualität der Studien:

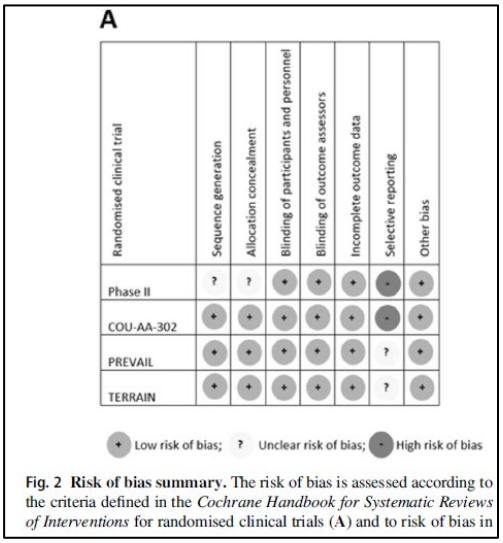


Fig. 2 Risk of bias summary. The risk of bias is assessed according to the criteria defined in the *Cochrane Handbook for Systematic Reviews of Interventions* for randomised clinical trials (A) and to risk of bias in

Studienergebnisse:

- Short-term health-related quality of life and metaanalyses
  - The pooled change in the FACT-P total score was −1.3 points [95% CI −2.7; 0.1] after enzalutamide. The heterogeneity (I^2 = 0%, p value = 0.42) was low in this meta-analysis, as the included results (from PREVAIL, Phase II and TERRAIN) all showed no change or a minor reduction in HRQoL.
  - The pooled change was 4.7 points [−0.1; 9.6] after AAP, with high heterogeneity (I^2 = 85%, p value = 0.01). The results from both COU-AA 302 and Phase II showed improved HRQoL after AAP, but with a large difference in the effect size and no overlap of the 95% CI (Fig. 3A)

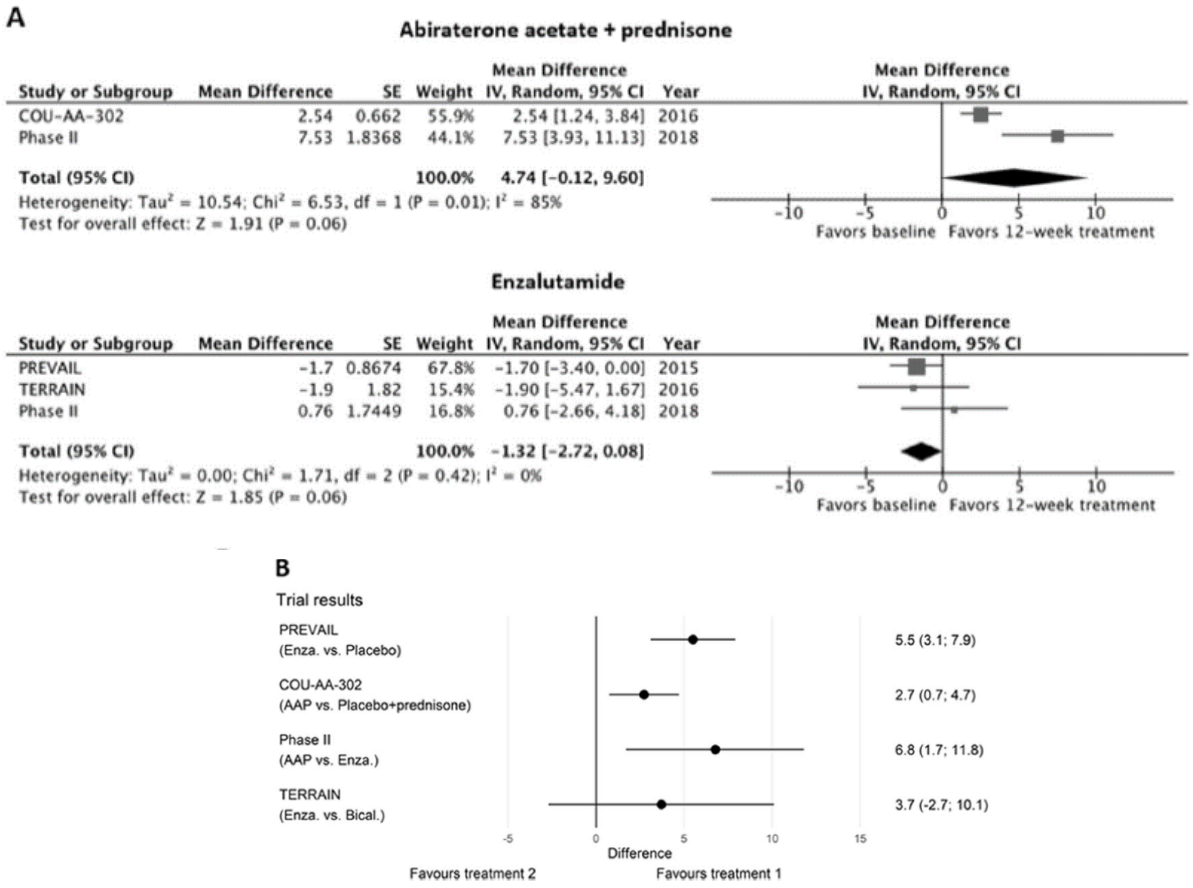


Fig. 3 Changed short-term health-related quality of life. Changed short-term health-related quality of life (HRQoL) is defined as the change in the Functional Assessment of Cancer Therapy-Prostate (FACT-P) total score from baseline to 12-week follow-up. The considered minimal clinical important difference in FACT-P total score is 6 points on a group level. Higher FACT-P total scores indicate better HRQoL. **A** The within-subject change in short-term HRQoL are analysed for AAP and enzalutamide in separate meta-analyses with random effects, comparing the FACT-P total score at baseline with the FACT-P total score at 12 weeks. **B** The difference in changed short-term HRQoL against comparator are shown for each included randomised clinical trial. The mean treatment differences (with 95% confidence intervals in brackets) between active treatment versus placebo groups and head-to-head comparisons are reported. The firstly mentioned treatment group for each trial is "treatment 1" and the secondly mentioned treatment group for each trial is "treatment 2". AAP, abiraterone acetate plus prednisone; Bical. bicalutamide; Enza. enzalutamide.

Table 4 Evidence grading of the meta-analyses.

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

Anmerkung/Fazit der Autoren

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

- The meta-analysis on short-term changes in HRQoL after AAP was limited by the high heterogeneity caused by the differences in small or large improvements in HRQoL.

Kommentare zum Review

Es liegen weitere SRs zu dieser Fragestellung mit derselben Schlussfolgerung vor:

- Kretschmer et al., 2021 [5].; A recent systematic review reported on HRQoL in patients treated with the available androgen axis targeting agents (enzalutamide, AAP, darolutamide and apalutamide) for these earlier stages of the disease. The overall finding was that active treatment was associated increased time to HRQoL decline or preservation of HRQoL compared with placebo. No formal comparison between the active treatments were made.

Wei Z et al., 2021 [18].

Efficacy and Safety of Abiraterone Acetate and Enzalutamide for the Treatment of Metastatic Castration-Resistant Prostate Cancer: A Systematic Review and Meta-Analysis

Fragestellung

A meta-analysis was conducted to compare the efficacy and safety of abiraterone acetate and enzalutamide in patients with mCRPC.

Methodik

Population:

- mCRPC

Intervention:

- abiraterone or enzalutamide

Komparator:

- placebo

Endpunkte:

- The primary outcome was overall survival (OS), and the secondary outcomes were radiographic progression-free survival (rPFS), time to prostatespecific antigen development (TTPP) and serious adverse events (sAEs).

Recherche/Suchzeitraum:

- PubMed, Cochrane Library, EMBASE, and ClinicalTrials.gov from the date of database inception to December 31, 2020.

Qualitätsbewertung der Studien:

- Cochrane risk of bias assessment tool

Ergebnisse

Anzahl eingeschlossener Studien:

- The study included 4 clinical trials, all of which were published in English and administered a placebo to the control group. All were phase III, double-blind, randomized controlled trials.

Charakteristika der Population:

TABLE 1 | Characteristics of the eligible studies.

Study	Years	NCT Number	Pahse	Line	Masking	OS follow-up	Patients	Treatment (N)	Control (N)	Median Age (SD)	region
Karim Fazzi 2012	2008-2014	00638690	3	2	Quadruple	Up to 60 months	1187	abiraterone + prednisone (797)	prednisone + placebo (390)	69 (8.46)	multicenter
Kurtr Miller 2017	2009-2018	00887198	3	1	Quadruple	Up to 61 months	1088	abiraterone + prednisone (546)	prednisone + placebo (542)	70.3 (8.76)	multicenter
Andrew J 2020	2009-2018	00974311	3	2	Triple	up to 101 months	1199	Enzalutamide (800)	placebo (399)	68.7 (8.11)	multicenter
Nancy Devlin 2017	2010-2020	01212991	3	1	Triple	up to 3 years	1717	Enzalutamide (872)	placebo (845	71.3 (8.47)	multicenter

Qualität der Studien:

- All four trials were conducted with blinding of the participants, investigators, and outcome assessors. Data for each of the major outcome indicators were reported. Although random assignment was performed, the methods were not described in detail

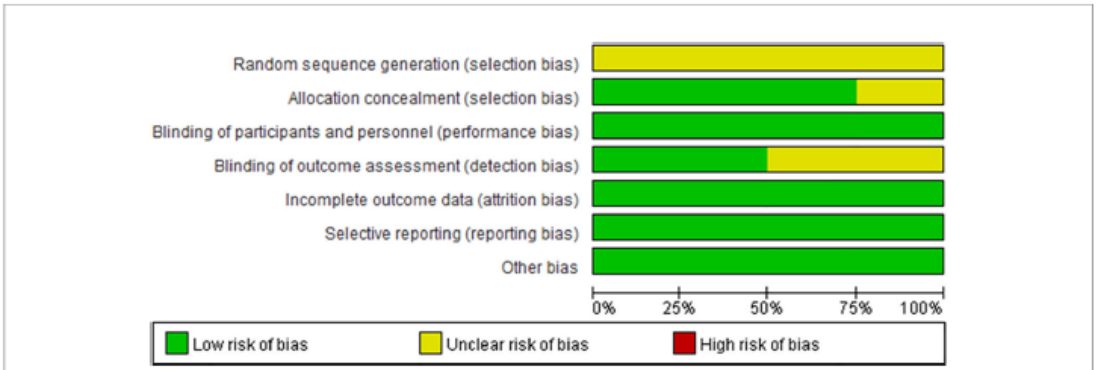
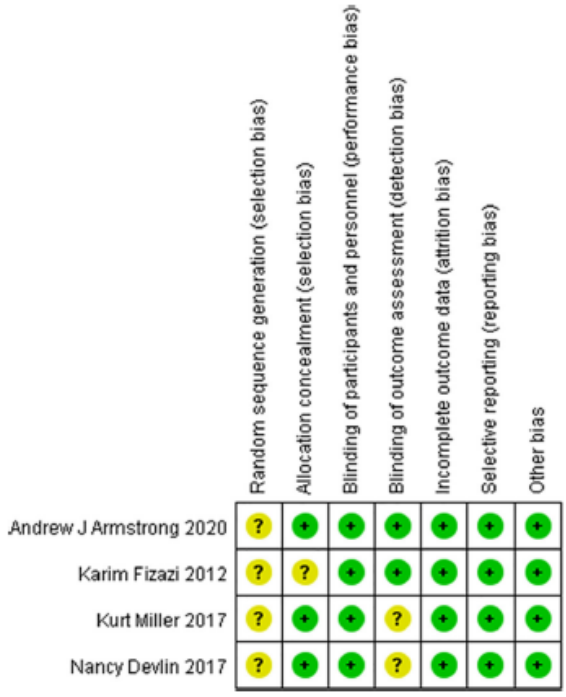
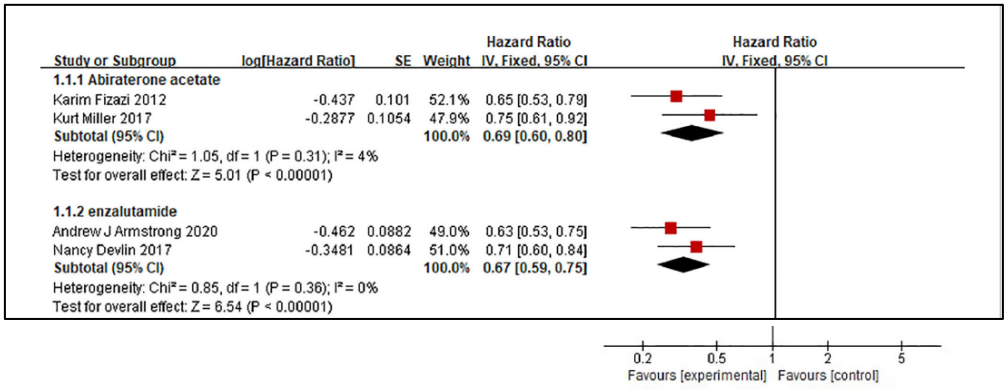


FIGURE 2 | Risk of bias summary. Green circles represent a low risk of bias; red circles represent a high risk of bias; yellow circles represent an unknown risk of bias.

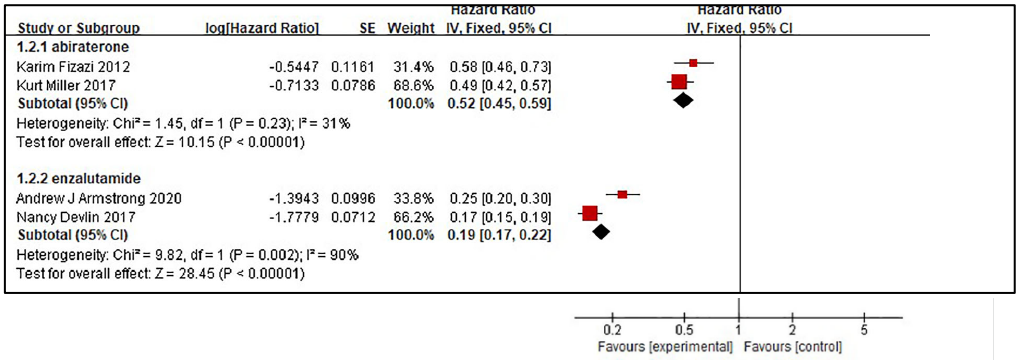


Studienergebnisse:

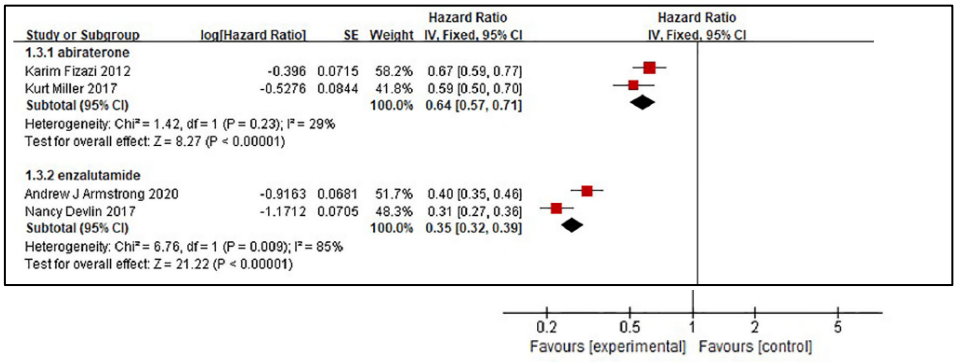
- OS:



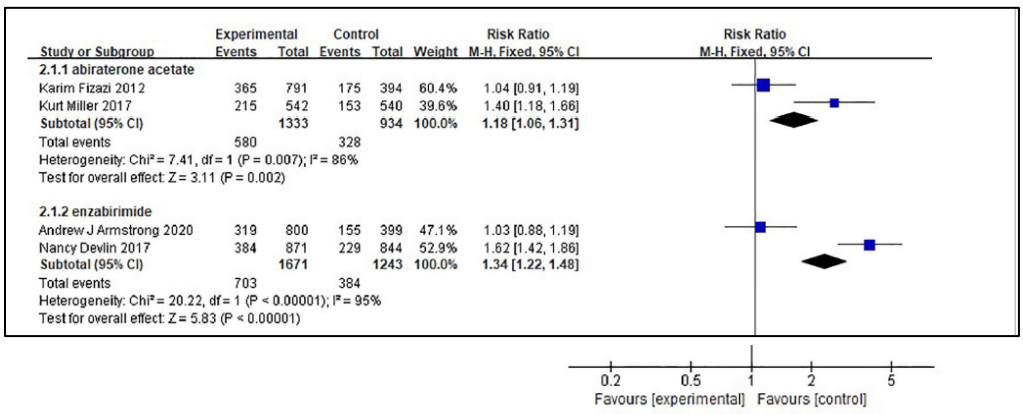
- Time to Prostate-Specific Antigen Progression:



- Radiographic PFS:



- SAE:



Anmerkung/Fazit der Autoren

In summary, the current evidence suggests that enzalutamide is not significantly different from abiraterone with regard to improving the OS of mCRPC patients, but it has a greater effect on TTPP and rPFS. The evidence from this study can be used when selecting a treatment option for mCRPC in clinical practice. Due to the lack of a direct comparison, the conclusions drawn from the results of the indirect comparison performed in this analysis need to be verified in high-quality prospective studies.

Kommentare zum Review.

Da die Validität des indirekten Vergleiches nicht anhand der Publikation überprüft werden kann, werden nur die Ergebnisse der Metaanalyse dargestellt. Hierbei ist zu beachten, dass die gepoolten Effektschätzer die Erst- und Zweitlinie umfassen.

Lee HY et al., 2021 [6].

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

Fragestellung

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

Methodik

Population:

- patients with nonmetastatic or metastatic CRPC

Intervention:

- Abiraterone or enzalutamide

Komparator:

- placebo, prednisone, or prednisolone

Endpunkte:

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

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, and Cochrane library (CENTRAL and CDSR) were searched.
- 1990-2020

Qualitätsbewertung der Studien:

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

Ergebnisse

Anzahl eingeschlossener Studien:

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

Charakteristika der Population:

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

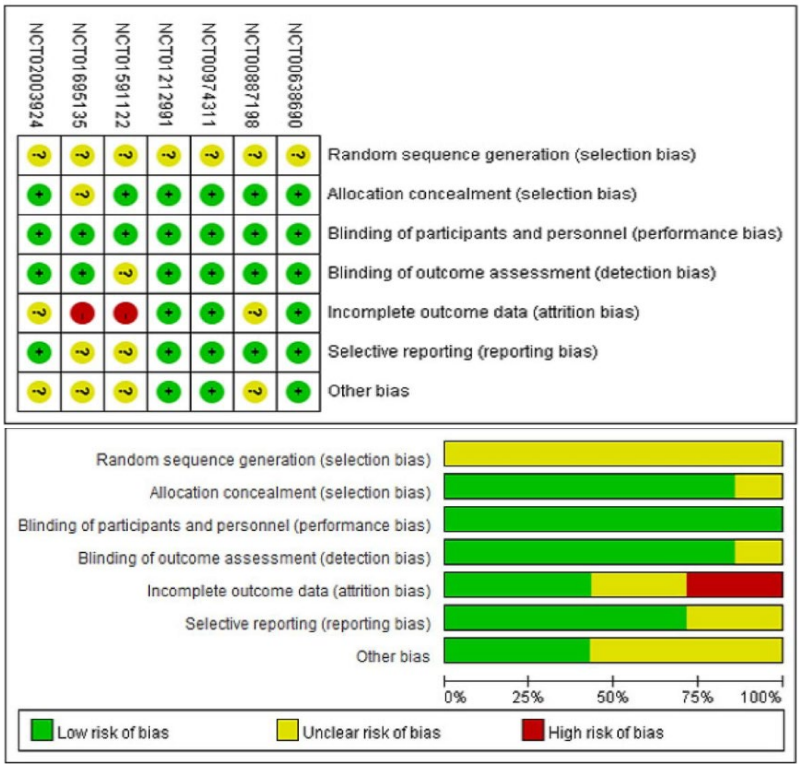
First Author	Inclusion criteria	Experimental arm		Control arm		Median follow-up (months)
		Treatment	No. of patients	Treatment	No. of patients	
Scher et al. (NCT00974311)	mCRPC	Enzalutamide	800	Placebo	399	14.2
Beer et al. (NCT01212991)	mCRPC	Enzalutamide	872	Placebo	845	22
Hussain et al. (NCT 02003924)	nmCRPC	Enzalutamide	933	Placebo	468	Enzalutamide: 18.5 Placebo: 15.1
Fizazi et al. (NCT00638690)	mCRPC	Abiraterone and prednisolone	797	Placebo	398	20.2
Ryan et al. (NCT00887198)	mCRPC	Abiraterone and prednisolone	546	Prednisolone	542	22.2
Sun et al. (NCT01695135)	mCRPC	Abiraterone and prednisolone	143	Prednisolone	71	12.9
Ye et al. (NCT01591122)	mCRPC	Abiraterone and prednisolone	157	Prednisolone	156	3.9

mCRPC: metastatic castration-resistant prostate cancer; nmCRPC: non-metastatic castration-resistant prostate cancer.

Appendix 4. Characteristics of the included studies.

Qualität der Studien:

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



Studienergebnisse:

- Cardiac disorders:

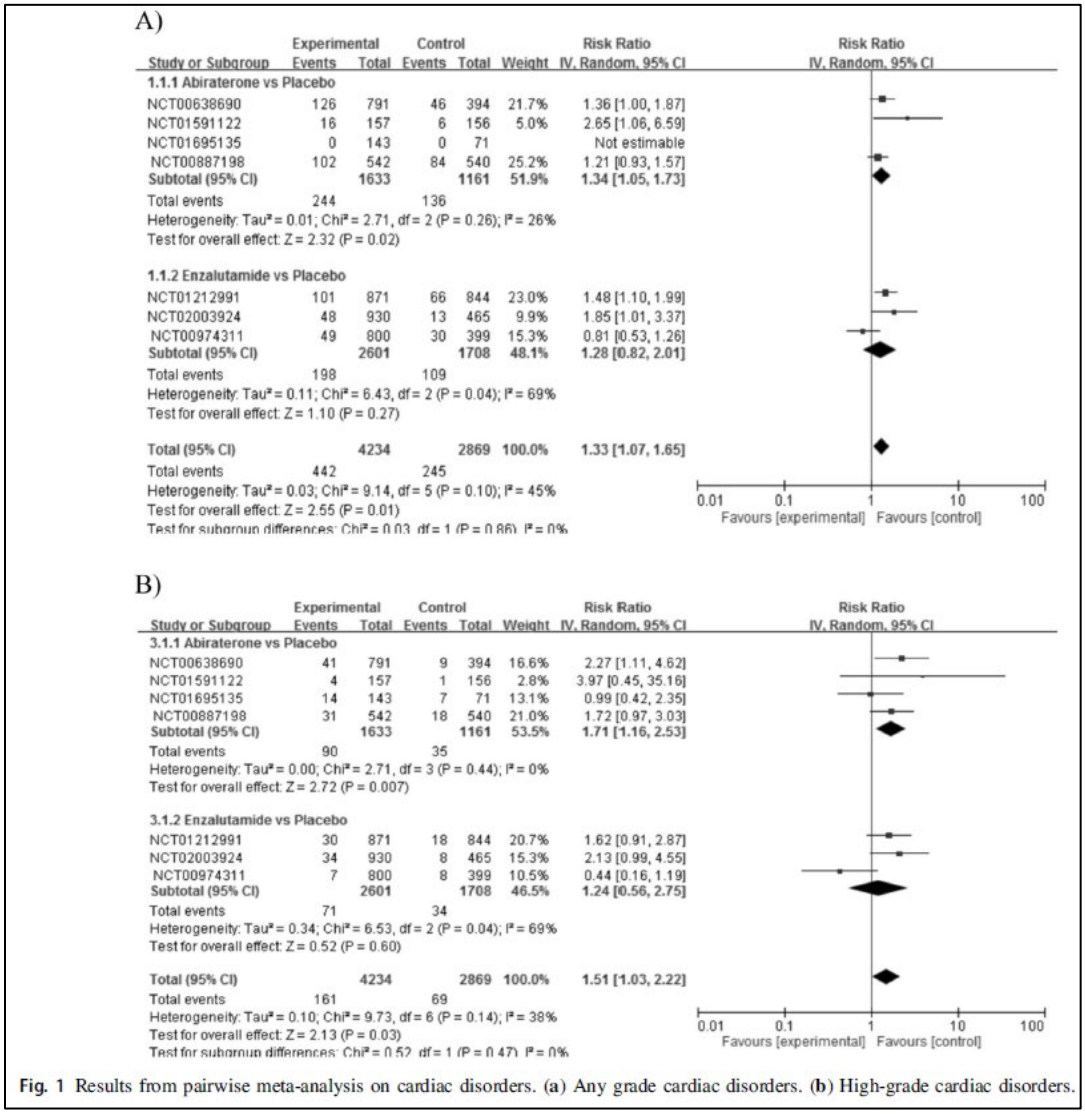


Fig. 1 Results from pairwise meta-analysis on cardiac disorders. (**a**) Any grade cardiac disorders. (**b**) High-grade cardiac disorders.

- Hypertension

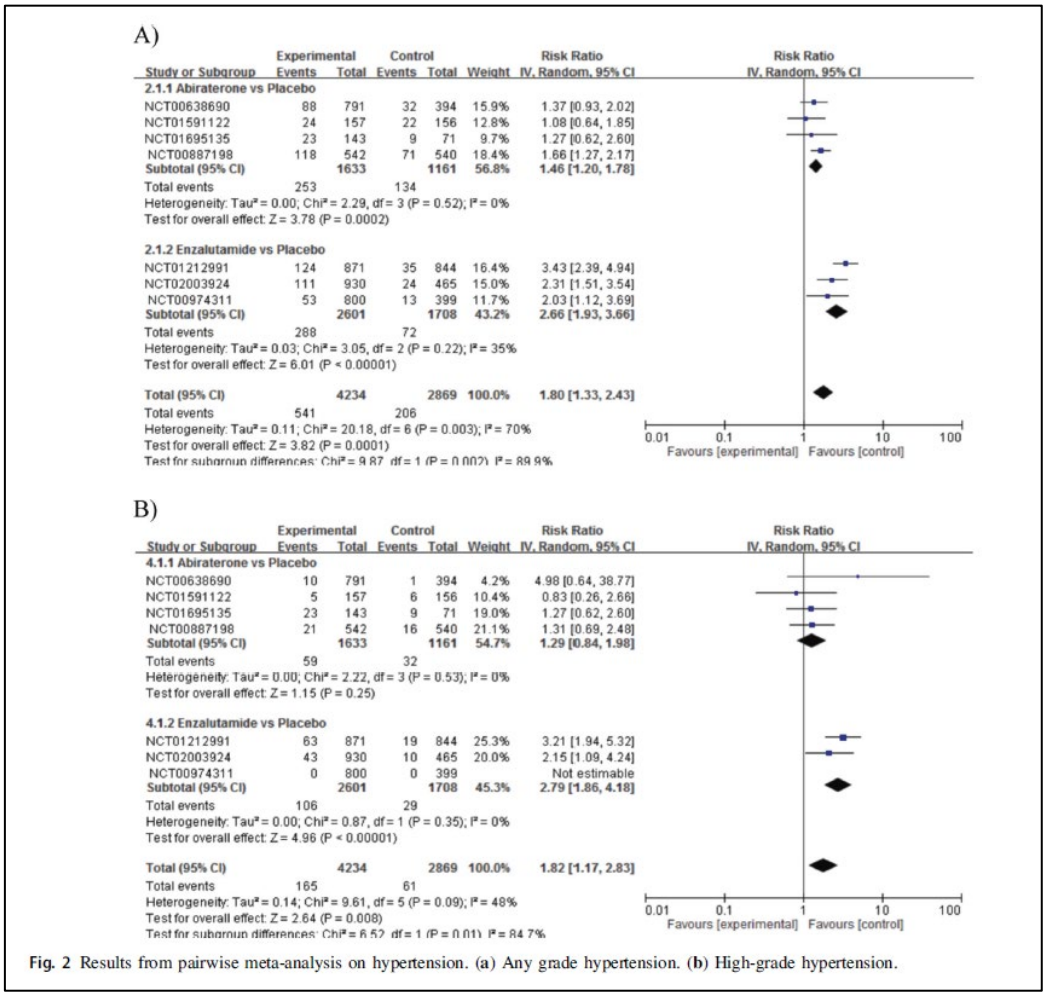


Fig. 2 Results from pairwise meta-analysis on hypertension. (a) Any grade hypertension. (b) High-grade hypertension.

Anmerkung/Fazit der Autoren

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

Kommentare zum Review.

Es wurden nur die Ergebnisse der Metaanalyse dargestellt, da die zentralen Annahmen der Netzwerkmetaanalyse (Transitivität/Ähnlichkeit und Konsistenz) nicht in der Publikation dargestellt sind. Es liegen keine Angaben zur Therapielinie vor.

Tan G et al., 2020 [14].

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

Fragestellung

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

Methodik

Population:

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

Intervention:

- Abiraterone acetate

Komparator:

- Control arm as comparison

Endpunkte:

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

Recherche/Suchzeitraum:

- PubMed, EMBASE, Cochrane library
- To September 2019

Qualitätsbewertung der Studien:

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

Ergebnisse

Anzahl eingeschlossener Studien:

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

Charakteristika der Population:

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

Table 1 Studies characteristic

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

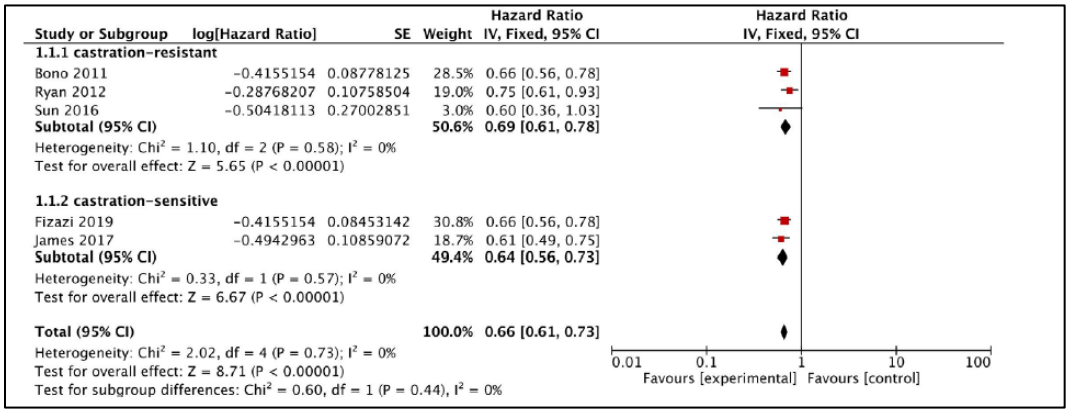
PSA, prostate-specific antigen; ADT, androgen deprivation therapy.

<u>Qualität der Studien:</u>

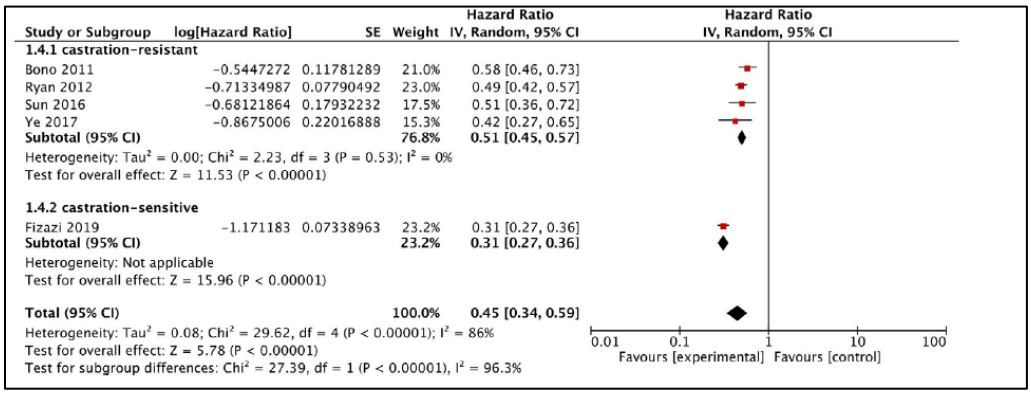
- 2 Studien Jadad Score: 4 und 5 Studien Jadad Score: 5 (siehe Abbildung unter Charakteristika der Population)

<u>Studienergebnisse:</u>

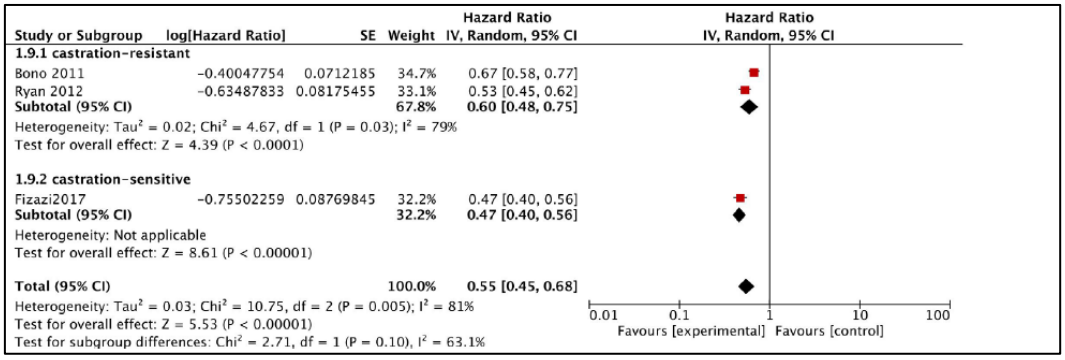
- OS:



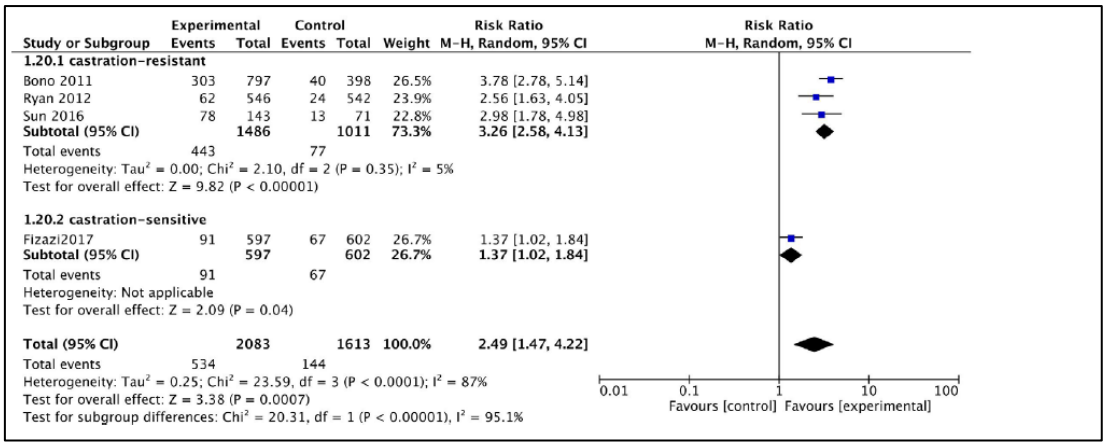
- Time to PSA progression:



PFS according to radiographic evidence:



- PSA response rate:



- Adverse events:
  - adverse events included asthenia, fatigue, back pain, constipation, arthralgia, bone pain, hypokalemia, cardiac disorder, and hypertension.
  - The pooled analysis reported that abiraterone acetate showed a higher incidence of some adverse events in high-risk prostate cancer patients, including hypokalemia (RR 2.47, 95% CI, 1.39–4.39, P=0.002; I2=86%), hypertension (RR 1.57, 95% CI, 1.37–1.79, P<0.00001; I^2=24%), cardiac disorder (RR 1.48, 95% CI, 1.03–2.13, P=0.04; I^2=75%) and arthralgia (RR 1.19, 95% CI, 1.05–1.35, P=0.007; I^2=0%), but not for asthenia, fatigue, constipation, back pain, and bone pain.

Anmerkung/Fazit der Autoren

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

Kommentare zum Review

- In the studies included, the primary endpoints were not entirely consistent. James (2017) enrolled patients with nonmetastatic prostate cancer, while the other studies only permitted metastatic prostate cancer patients.
- Die Qualitätsbewertung der Primärliteratur wurde anhand der Jadad-Skala vorgenommen. Diese Bewertung ermöglicht keine umfassende Einschätzung des Verzerrungspotenzials.

Wang X et al., 2020 [17].

Comparison of effectiveness and safety outcomes of abiraterone versus enzalutamide in patients with metastatic castration-resistant prostate cancer: a systematic review and meta-analysis

Fragestellung

The aim of this systematic review was to conduct a metaanalysis of studies to assess the impact of these two drugs on effectiveness and safety outcomes in patients with mCRPC.

Methodik

Population:

- Patients with mCRPC

Intervention/ Komparator:

- abiraterone and enzalutamide

Endpunkte:

- effectiveness or safety

Recherche/Suchzeitraum:

- PubMed, Cochrane, Embase from their inception through November 4, 2019

Qualitätsbewertung der Studien:

- Observational studies assessed the quality using the NewcastleOttawa Scales (NOS). RCTs were appraised for methodological quality using the criteria developed by the Cochrane risk of bias tool.

Ergebnisse

Anzahl eingeschlossener Studien:

- 15 Kohortenstudien (n=3546); keine RCTs

Charakteristika der Population/Studien:

Table 1. The characteristics of included studies

Source	Study design, years, region	Patients enrolled	Median age, years (range)	Follow up (months)	Abiraterone (n)	Enzalutamide (n)	Treatment stage
Miyake, 2017 [12]	Cohort, 2014.8 - 2015.12, Japan	280	76.9 (47-96)	24	113	167	Pre-chemotherapy
Norris, 2017 [13]	Cohort, 2011.9 - 2015.11, UK	198	NR	NR	98	100	Pre-chemotherapy and post-chemotherapy
Salem, 2017 [14]	Cohort, 2011.9 - 2015.6, Canada	189	76.5	12	76	113	Pre-chemotherapy
Pilon, 2017 [15]	Cohort, 2005.1 - 2014.12, NR	1659	NR	12	1067	592	NR
Al-Ali, 2018 [16]	Cohort, 2013.9 - 2016.8, Austria	334	74.4	30	195	139	Pre-chemotherapy and post-chemotherapy
Antoine, 2018 [17]	Cohort, 2016.3-2018.3, Europe	105	74.5 (53-92)	3	46	59	NR
Richter, 2016 [18]	Cohort, NR, Czech	32	NR	6.5	9	23	Post-chemotherapy
Lista, 2016 [19]	Cohort, 2014.1 - 2015.9, NR	42	74.02	NR	22	20	NR
Heo, 2017 [20]	Cohort, 2013 – 2014, NR	54	70 (45-86)	15	25	29	Post-chemotherapy
Selvi, 2018 [21]	Cohort, 2013.1 - 2017.6, NR	74	76	12	59	15	Pre-chemotherapy and post-chemotherapy
García, 2018 [22]	Cohort, 2015.1 - 2017.7, Spain	48	75.8 (56-92)	NR	26	22	Pre-chemotherapy and post-chemotherapy
Khalaf, 2018 [23]	Cohort, 2009.7 - 2016.9, NR	210	85 (83-88)	NR	106	104	Pre-chemotherapy
Shore, 2018 [24]	Cohort, 2015.12-2017-1, US	92	75	2	46	46	NR
Dearden, 2019 [25]	Cohort, 2011 - 2015, France, Germany and the UK	152	NR	NR	78	74	Pre-chemotherapy and post-chemotherapy
Chang, 2019 [26]	Cohort, 2012.4-2018.1, China	77	68.1	18.2(abiraterone) vs. 14.5(enzalutamide)	64	13	Prior treatment-failure with docetaxel

CRPC, castration resistant prostate cancer; mCRPC' metastatic castration resistant prostate cancer; NR, not report.

Qualität der Studien:

- All included observational studies were high quality, 6 studies (14-17, 22-23) were missed one indicator, 6 studies (13, 18-21, 24) were missed two indicators.

Table 2. Quality of observational studies (indicators from New-Castle-Ottawa scale)

Study	1[a]	2[b]	3[c]	4[d]	5A[e]	5B[f]	6[g]	7[h]	8[i]	Total quality scores
Miyake, 2017 (12)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Norris, 2017 (13)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
Salem, 2017 (14)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8
Pilon, 2017 (15)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8
Al-Ali, 2018 (16)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
Antoine, 2018 (17)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8
Richter, 2016 (18)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
Lista, 2016 (19)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
Heo, 2017 (20)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
Selvi, 2018 (21)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
García, 2018(22)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
Khalaf, 2018 (23)	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Shore, 2018 (24)	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	7
Dearden, 2018 (25)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	9
Chang, 2019 (26)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	9

[a] Indicates exposed cohort truly representative; [b] Non-exposed cohort drawn from the same community; [c] Ascertainment of exposure from the same community; [d] Outcome of interest not present at start of study; [e] Cohorts comparable on basis of site and etiology of infection; [f] Cohorts comparable on others factors; [g] Assessment of outcome of record linkage or independent blind assessment; [h] Follow-up long enough for outcomes to occur; [i] Complete accounting for cohorts

Studienergebnisse:

- Prostate-specific antigen response rate.

○ Six studies enrolling 867 patients evaluated the PSA response rate in mCRPC settings (12, 13, 20, 22-23, 26). Pooled results showed PSA response rate in the enzalutamide group was significantly greater than that in the abiraterone group (RR 0.69, 95% CI 0.610.79, p＜0.00001, I2=29%). T

- Adverse event rate.

○ Four studies evaluated the total rate of AEs and there was no statistical difference in the total incidence of AEs in the enzalutamide group compared to that in the abiraterone group (730 patients, RR 0.42, 95% CI 0.14-1.31, p = 0.14, I2=84%).

- The most common adverse reaction reported for the two drugs was central nervous system (CNS). Fatigue and perceived cognitive impairments were the most common CNS events affecting patients during treatment. Seven articles reported the rate of fatigue (12, 14, 15, 17, 24-26) and three articles reported the rate of perceived cognitive impairments (15, 17, 24). Patients who received enzalutamide had the higher risk to have the feeling of fatigue compared with abiraterone group (2555 patients, RR 0.45, 95% CI 0.24-0.85, p=0.01, I2=92%; Figure 4). And there was no statistical difference between two groups respect to the side effect of perceived cognitive impairments (1856 patients, RR 0.94, 95% CI 0.47-1.88, p=0.85, I2=15%)

  - Overall survival.

- Five articles enrolling 851 patients evaluated the OS between abiraterone group and enzalutamide group, statistical analysis was not applied due to limited available data. Four articles reported that statistical difference was not observed in OS between the groups (13, 18, 23, 26). And another one article reported the median OS but p value was not reported (16.7 ± 0.8 months vs 19.7 ± 1.1 months) (16).

  - Progression-free survival.

- Four articles enrolling 463 patients evaluated the PFS between abiraterone group and enzalutamide group, statistical analysis was not applied due to limited available data. The conclusions of the four articles were not consistent. Three articles reported that there was no statistical difference in PFS between enzalutamide group and abiraterone group (18, 21, 26), but Miyake et al (12) reported that the median PFS was longer in the enzalutamide group than abiraterone group (11.6 months vs 9.0 months, p=0.014).

Anmerkung/Fazit der Autoren

This was the first study to directly compare the clinical effectiveness and safety of abiraterone and enzalutamide in mCRPC patients. Our results demonstrated that enzalutamide was associated with higher PSA response rate compared to abiraterone in patients with mCRPC, and no significant difference was found between two groups in the overall AE. But enzalutamide use induced higher risk of the AE of fatigue. Prospective or randomized controlled trials compared the clinical outcomes of these agents is needed.

Kommentare zum Review

- Keine RCTs zur Fragestellung identifiziert

Niazi MRK et al., 2021 [10].

Efficacy of PARP Inhibitors as Maintenance Therapy for Metastatic Castration-Resistant Prostate Cancer: A Meta-Analysis of Randomized Controlled Trials

Fragestellung

To identify all the randomized controlled trials (RCTs) in which PARP inhibitors have been assessed in the treatment of mCRPC, and to compare the efficacy of PARP inhibitors in these patients with standard-of-care (SOC)/antihormonal therapies like abiraterone acetate (Zytiga) or enzalutamide (Xtandi) in terms of progression-free survival (PFS) and overall survival (OS).

Methodik

Population:

- Adults with mCRPC

Intervention:

- PARP inhibitors

Komparator:

- standard-of-care (SOC)

Endpunkte:

- PFS and OS

Recherche/Suchzeitraum:

- Cochrane Central Registry of Clinical Trials, Embase, and PubMed

Qualitätsbewertung der Studien:

- Risk of bias tool (Cochrane)

Ergebnisse

Anzahl eingeschlossener Studien:

- N=3 RCTs (n=682)

Charakteristika der Population/Studien:

TABLE. **Characteristics of Randomized Control Trials**

Study name	Treatment drugs	Study characteristic	Inclusion	Exclusion	Primary outcome(s)
Clarke et al (NCT01972217)	Olaparib (300 mg BID) + abiraterone (1000 mg OD) (n = 71) vs abiraterone (1000 mg od) alone (n = 71)	Patients with mCRPC who had previously received docetaxel and were candidates for abiraterone treatment	Male, aged >18, with mCRPC; <2 prior lines of chemotherapy; testosterone <50 ng/dL; no previous exposure to second-generation antihormonal agents; candidate for abiraterone treatment; ECOG performance status of 0-2; life expectancy ≥12 weeks	Any previous treatment with PARPi; previous treatment with DNA-damaging cytotoxic chemotherapy; other malignancies (including MDS and MGUS) within the past 5 years	Percentage of patients experiencing adverse events; number of patients with dose-limiting toxicities; median (rPFS) time; percentage of patients with progression events or death
De Bono et al (PROfound study; NCT02987543)	Olaparib (300 mg BID) vs enzalutamide (160 mg OD) or abiraterone (1000 mg OD) + prednisone (5 mg BID)	Men with mCRPC whose disease had progressed during treatment with enzalutamide or abiraterone. Cohort A = patients with at least 1 alteration in *BRCA1*, *BRCA2*, or ATM. Cohort B = patients with alteration in any of 12 other genes	Men ≥18 years of age with mCRPC; <2 prior lines of chemotherapy; no previous exposure to second-generation antihormonal agents; candidate for abiraterone treatment; ECOG performance status of 0-2; life expectancy ≥12 weeks	Any previous treatment with PARPi; previous treatment with DNA-damaging cytotoxic chemotherapy; other malignancies (including MDS and MGUS) within the past 5 years	PFS via RECIST v1.1 for soft tissue, as 20% increase in the sum of diameters of target lesions
Hussain et al (NCT01576172)	Arm A = abiraterone (1000 mg) + prednisone (5 mg BID). Arm B = veliparib (300 mg BID) + abiraterone (1000 mg) + prednisone (5 mg BID)	Patients stratified by prior ketoconazole and ETS fusion status (positive or negative). Randomly assigned to Arm A or Arm B	Men with mCRPC; ECOG status, 0-2; testosterone < 50 ng/dL; no prior exposure to abiraterone; 2 or fewer prior chemotherapy regimens	Chemotherapy, radiotherapy, or oral antifungal agents (within 3 weeks prior to entering the study); history of active seizures; pituitary or adrenal dysfunction; active or symptomatic viral hepatitis; chronic liver disease; brain metastases	Confirmed PSA response rate time frame: up to 3 years

BID, twice daily; mCRPC, metastatic castration resistant prostate cancer; MDS, myelodysplastic syndrome; MGUS, monoclonal gammopathy of undetermined significance; OD, once daily; PARPi, PARP inhibitors; PFS, progression-free survival; PSA, prostate specific antigen; rPFS, radiologic PFS.

Qualität der Studien:

FIGURE 2. **Risk of Bias Graph: Review Authors' Judgements About Each Risk of Bias Item Presented as Percentages Across All Included Studies**

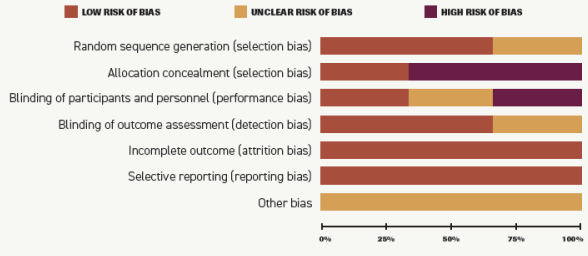
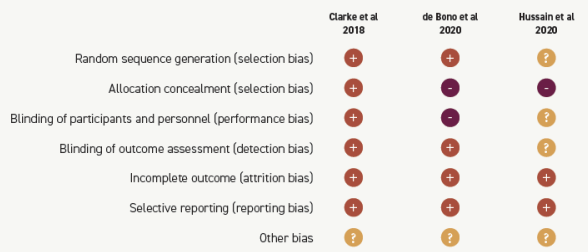


FIGURE 3. **Risk Of Bias Summary: Review Authors' Judgements About Each Risk of Bias Item for Each Included Study**



Studienergebnisse:

- Overall survival
  - Two studies reported OS when patients used PARP inhibitors compared with SOC.[14,15] The difference was statistically significant when calculated using the fixed model (HR, 0.751; 95% CI, 5.82-0.968; P = .027), and I2 = 23.23.
  - When calculated using the random model, there was a strong deviation favouring PARP inhibitors, but it did not reach statistical significance (HR, 0.758; 95% CI, 0.565-1.017; P = .064)
- Progression-free survival
  - Three studies reported PFS when patients used PARP inhibitors compared with SOC.[14-16] The difference was statistically significant when calculated using the fixed model (HR, 0.626; 95% CI, 0.521-0.752; P <.001), and I2 = 80.240.
  - When calculated using the random model, there was a strong deviation favoring_PARP inhibitors, but it did not reach statistical significance (HR, 0.674; 95% CI, 0.437-1.039; P = .074)

Anmerkung/Fazit der Autoren

This meta-analysis shows that PARP inhibitors can prolong PFS or OS compared to SOC treatment in patients with mCRPC irrespective of HRR or other genetic mutation status. Longer PFS and OS were seen when PARP inhibitors were used alone or in combination with AHT therapies like abiraterone or enzalutamide. The effect was more significant when examined with a _xed model analysis. Although there was a signi_cant deviation towards an increase in PFS and OS in the random model analysis, the effect was not statistically signi_cant, and it was likely secondary to a relatively small patient population in the meta-analysis. Although, at baseline, there was heterogeneity among the populations participating in these trials, in terms of genetic alterations, the results of all the trials showed better outcomes in their intervention arms. This heterogeneity can be dealt with by incorporating more RCTs into meta-analyses going forward. More studies can further magnify these results once they are published.

Kommentare zum Review

- Keine Angabe zum Recherchezeitraum

Chen, X et al., 2023 [3].

Comparative efficacy of secondgeneration androgen receptor inhibitors for treating prostate cancer: A systematic review and network meta-analysis

Fragestellung

Therefore, we performed an indirect comparison and network meta-analysis of several SGARIs to assess their efficacy and toxicity in the treatment of patients with mHSPC, non-metastatic CRPC (nmCRPC), and **metastatic CRPC (mCRPC)**, which should in turn inform ARI selection for more effective treatments

Methodik

Population:

- Participants were patients with mHSPC,nmCRPC or **mCRPC**

Intervention:

- Second-generation androgen receptor inhibitors (SGARI)

Komparator:

- Placebo

Endpunkte:

- Nicht näher spezifiziert

Recherche/Suchzeitraum:

- PubMed, EMBASE, and the Cochrane Library (January 2000 to December 2022)

Qualitätsbewertung der Studien:

- Cochrane Collaboration tool to assess the risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- N=7 (n=9488) → nur zwei Studien im vorliegenden AWG relevant
  - Studie AFFIRM (Scher et al., 2014)
  - Studie PREVAIL (Beer et al., 2014)

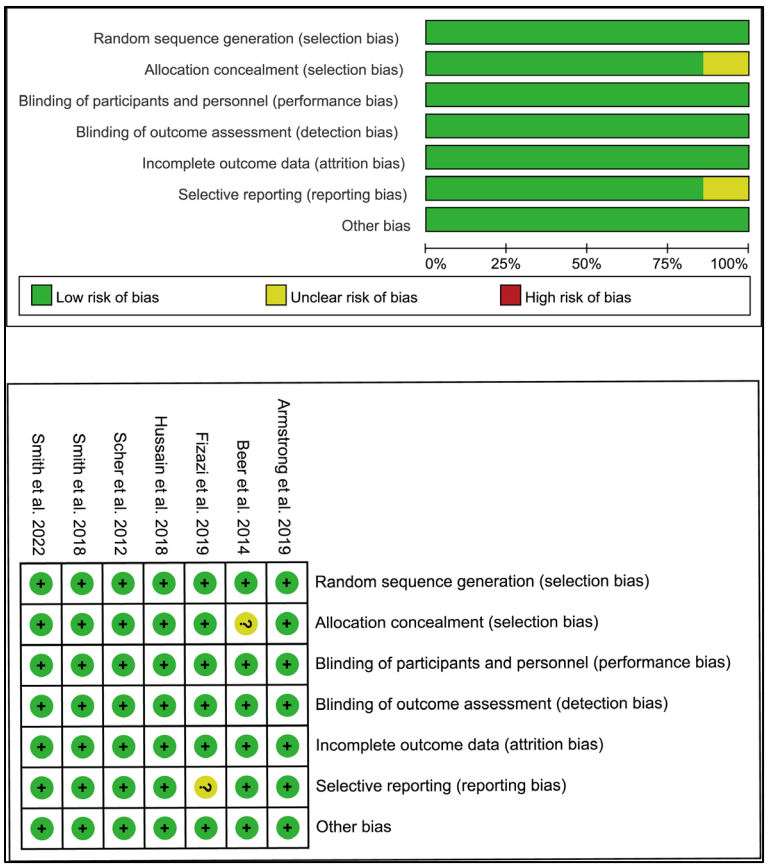
Charakteristika der Population/Studien:

TABLE 1 Characteristics of the trails included in the meta-analysis.

First author	Year	Clinical trial	Cancer characteristics	Median age (yr)	Intervention arm	Control arm	Median PSA (ng/ml)	ECOG performance status score
Armstrong	2019	ARCHES	mHSPC	70	Enzalutamide plus ADT[a]	Placebo plus ADT	5.4	0 (78.0%) 1 (21.8%)
Smith	2022	ARASENS	mHSPC	67	Darolutamide plus ADT	Placebo plus ADT	30.3	0 (71.6%) 1 (28.4%)
Scher	2012	AFFIRM	mCRPC	NA	Enzalutamide plus ADT	Placebo plus ADT	NA	NA
Beer	2014	PREVAIL	mCRPC	NA	Enzalutamide plus ADT	Placebo plus ADT	NA	NA
Smith	2018	SPARTAN	nmCRPC	74	Apalutamide plus ADT	Placebo plus ADT	NA	NA
Hussain	2018	PROSPER	nmCRPC	74	Enzalutamide plus ADT	Placebo plus ADT	11.1	0 (80) 1 (20)
Fizazi	2019	ARAMIS	nmCRPC	74	Darolutamide plus ADT	Placebo plus ADT	9.0	0 (68%) 1 (32%)

NA, Not available.
[a]Androgen deprivation therapy (ADT): Surgical (bilateral orchiectomy) or chemical (pharmaceutical) interventions resulting in the reduction of serum testosterone or blockade of the androgen receptor.

Qualität der Studien:



Studienergebnisse:

mCRPC (2 Studien)

- OS and rPFSs were the primary endpoints of the studies on mCRPC that were included in our analysis. Initial data from the included study showed that both before and after chemotherapy, enzalutamide was beneficial for all included endpoints when compared with placebos
- In random effect direct metaanalysis SGARI improved OS (HR, 0.67; 95% CI, 0.59-0.76), rPFS (HR, 0.28; 95% CI, 0.13-0.57), time to PSA progression (HR, 0.20 95% CI, 0.14-0.30), and time to first skeletal-related event (HR, 0.71; 95% CI, 0.63-0.80)

Anmerkung/Fazit der Autoren

According to our findings, the SGARIs had prolonged OS for mHSPC, OS and rPFS for mCRPC, as well as MFS for nmCRPC.

Further, both pre- and postchemotherapy enzalutamide use improved OS in mCRPC patients, but for improving rPFS pre-chemotherapy use of enzalutamide should be preferred.

Kommentare zum Review

- Nur zwei Studien im vorliegenden AWG relevant
  - Studie AFFIRM (Scher et al., 2014)
  - Studie PREVAIL (Beer et al., 2014)

- Indirekter Vergleich aufgrund methodischer Mängel bzgl. Der Annahmen nicht berichtet

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Rizzo A et al., 2022 [12].

Incidence of grade 3–4 adverse events, dose reduction, and treatment discontinuation in castration-resistant prostate cancer patients receiving PARP inhibitors: a meta-analysis

Fragestellung

The aims of the systematic review and meta-analysis were (1) to evaluate the incidence rate of more frequently reported grade 3–4 adverse events in mCRPC patients treated with PARPi monotherapy and (2) to evaluate the incidence rate of dose reduction and treatment discontinuation in the same patient population.

Methodik

Population:

- Patients with mCRPC,

Intervention:

- PARPi monotherapy

Komparator:

- Nicht näher spezifiziert

Endpunkte:

- grade 3–4 adverse events; available data regarding dose reduction and treatment discontinuation

Recherche/Suchzeitraum:

- PubMed/Medline, Cochrane Library, and EMBASE; 10 June 2000 to 15 November 2021

Qualitätsbewertung der Studien:

- Cochrane Collaboration tool

Ergebnisse

Anzahl eingeschlossener Studien:

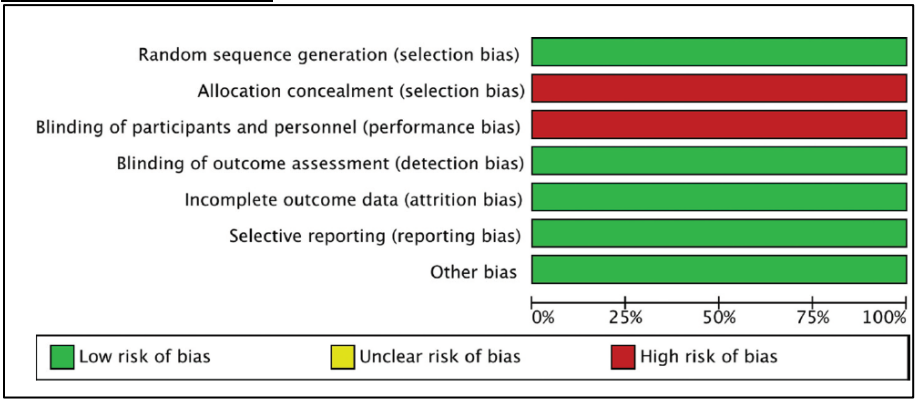
- N=6 phase II and III clinical trials

Charakteristika der Population/Studien:

Table 1. Summary of trials on PARP inhibitor monotherapy in metastatic castration-resistant prostate cancer.

Trial	Phase	Clinical setting	PARP inhibitor
TOPARP-A [21]	II	After 1–2 lines of chemotherapy	Olaparib
TOPARP-B [22]	II	After 1–2 lines of chemotherapy	Olaparib
PROFOUND [23]	III	After enzalutamide or abiraterone; prior taxane-based chemotherapy allowed	Olaparib
TRITON2 [24]	II	After 1–2 lines of novel hormonal therapies and 1 taxane-based chemotherapy	Rucaparib
TALAPRO-1 [25]	II	After 1 or more lines of novel hormonal therapies and 1 or more lines of taxane-based chemotherapy	Talazoparib
GALAHAD [26]	II	After 1 or more lines of novel hormonal therapies and 1 or more lines of taxane-based chemotherapy	Niraparib

Qualität der Studien:



Studienergebnisse:

- The most commonly observed grade 3–4 adverse events were anemia (24.1%; 95% CI, 20.6–27.6), followed by grade 3–4 thrombocytopenia (6.7%; 95% CI, 4.9–8.6)
- Moreover, PARPi treatment was associated with a pooled incidence rate of grade 3–4 neutropenia, fatigue, and leukopenia of 5.2% (95% CI, 4.7–5.7), 4.9% (95% CI, 3.2–6.6), and 3.4% (95% CI, 2.0–4.8), respectively
- The pooled incidence rate of treatment-related dose reduction in mCRPC patients receiving PARPi was 26.9%, with a 95% CI ranging from 22.9% to 30.9% (Table 2). The incidence of treatment discontinuation due to adverse events was 14.1% (95% CI, 11.2–17.0).

Anmerkung/Fazit der Autoren

In this systematic review and meta-analysis, we suggest that mCRPC patients receiving PARPi monotherapy should be carefully monitored for several grade 3–4 toxicities, as well as dose reduction and treatment discontinuation. Results of ongoing studies will probably highlight which PARP inhibitor has the best toxicity profile and clinical efficacy in mCRPC patients.

Chen J et al., 2021 [2].

Comparison of Systemic Treatments for Metastatic Castration-Resistant Prostate Cancer After Docetaxel Failure: A Systematic Review and Network Meta-analysis

Fragestellung

This study aimed to compare the efficacy and safety of systemic treatments for mCRPC after upfront docetaxel failure to assist clinical practice.

Methodik

Population:

- patients who received first-line docetaxel for mCRPC and progressed

Intervention:

- abiraterone, enzalutamide, cabazitaxel and radium-223

Komparator:

- best supportive care (BSC) or active drugs

Endpunkte:

- survival and safety outcomes

Recherche/Suchzeitraum:

- Bibliographic databases including MEDLINE (OVID interface), EMBASE (OVID interface), and the Cochrane Central Register of Controlled Trials (bis June 2021).

Qualitätsbewertung der Studien:

- Cochrane risk of bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- N=5 (n=3862)

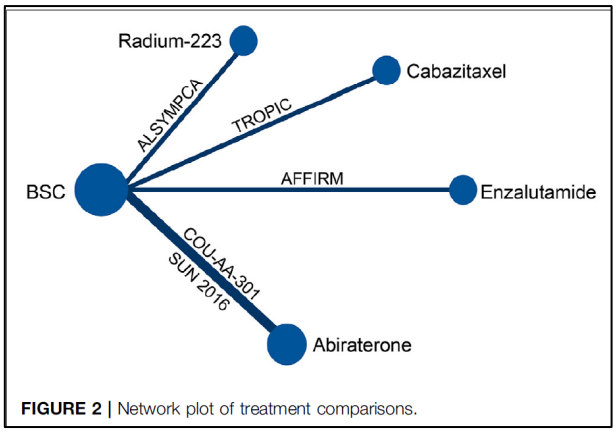


FIGURE 2 | Network plot of treatment comparisons.

Charakteristika der Population/Studien:

TABLE 1 | Characteristics of included trials.

Trial	Study design	Recruitment period	Median follow-up (month)	Interventions	Sample size
COU-AA-301	Phase 3, multicenter, double-blind, RCT	May 2008 to Jul 2009	20.2	Abiraterone + prednisone vs. placebo + prednisone	797 vs. 398
Sun et al. (2016)	Phase 3, multicenter, double-blind, RCT	Aug 2012 to Nov 2013	12.9	Abiraterone + prednisone vs. placebo + prednisone	143 vs. 71
AFFIRM	Phase 3, multicenter, double-blind, RCT	Sep 2009 to Nov 2010	14.4	Enzalutamide vs. placebo	800 vs. 399
TROPIC	Phase 3, multicenter, open-label, RCT	Jan 2007 to Oct 2008	12.8	Cabazitaxel + prednisone vs. mitoxantrone + prednisone	378 vs. 377
ALSYMPCA	Phase 3, multicenter, open-label, RCT	Jun 2008 to Feb 2011	NA	Radium-223 vs. placebo	325[a] vs. 174[a]

Abbreviations: RCT, randomized controlled trial; NA, not available.
[a]Data of patients with previous docetaxel use.

Qualität der Studien:

TABLE 3 | Risk of bias of included trials.

Trial	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall bias
COU-AA-301	Low	Low	Low	Low	Low	Low
Sun et al. (2016)	Low	Low	Low	Low	Low	Low
AFFIRM	Low	Low	Low	Low	Low	Low
TROPIC	Low	Some concerns	Low	Some concerns	Low	Some concerns
ALSYMPCA	Low	Low	Low	Some concerns	Some concerns	Some concerns

Studienergebnisse:

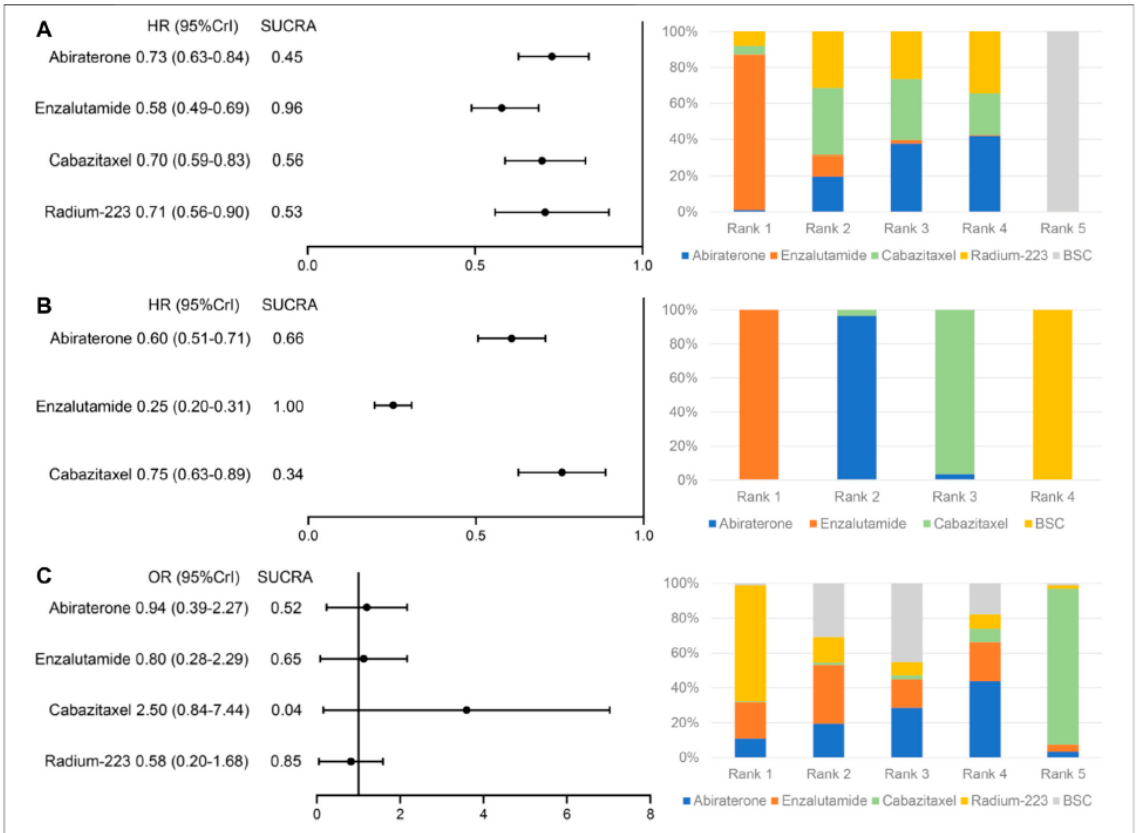


FIGURE 3 | Relative effects of systemic treatments compared to best supportive care and treatment ranking on **(A)** overall survival, **(B)** biochemical progression-free survival, and **(C)** serious adverse events.

TABLE 4 | Relative effect estimates for all pairwise treatment comparisons.

Outcomes	Comparator	Intervention				
OS, HR (95%CrI)		Abiraterone				
	Enzalutamide	1.30 (1.06–1.59)	Enzalutamide			
	Cabazitaxel	1.04 (0.83–1.30)	0.83 (0.65–1.06)	Cabazitaxel		
	Radium-223	1.05 (0.78–1.41)	0.82 (0.61–1.10)	0.99 (0.73–1.34)	Radium-223	
	BSC	0.73 (0.63–0.84)	0.58 (0.49–0.69)	0.70 (0.59–0.83)	0.71 (0.56–0.90)	BSC
bPFS, HR (95%CrI)		Abiraterone				
	Enzalutamide	2.40 (1.80–3.20)	Enzalutamide			
	Cabazitaxel	0.80 (0.63–1.02)	0.33 (0.25–0.44)	Cabazitaxel		
	BSC	0.60 (0.51–0.71)	0.25 (0.20–0.31)	0.75 (0.63–0.89)	BSC	
SAE, OR (95%CrI)		Abiraterone				
	Enzalutamide	1.10 (0.29–4.20)	Enzalutamide			
	Cabazitaxel	0.39 (0.09–1.62)	0.33 (0.07–1.51)	Cabazitaxel		
	Radium-223	1.60 (0.39–6.56)	1.40 (0.31–6.32)	1.72 (0.59–5.01)	Radium-223	
	BSC	0.94 (0.39–2.27)	0.80 (0.28–2.29)	2.50 (0.84–7.44)	0.58 (0.20–1.68)	BSC

Anmerkung/Fazit der Autoren

This interactive network meta-analysis provides the best current evidence on the efficacy and safety profiles of multiple second-line treatments after docetaxel failure in patients with mCRPC. Our findings demonstrate that enzalutamide may provide optimal efficacy and a relatively low risk of SAEs. Cabazitaxel is also effective in post-docetaxel settings but associated with a high risk of SAEs. This study offers important implications for patients and clinicians. However, the results should be used with caution due to the inherent biases across the comparisons. Further head-to-head trials are needed to confirm our findings.

Wu K et al., 2021 [19].

Evaluation of the Efficacy of PARP Inhibitors in Metastatic Castration-Resistant Prostate Cancer: A Systematic Review and Meta-Analysis

Fragestellung

We performed a meta-analysis of current clinical trials to evaluate the efficacy of PARP inhibitors in mCRPC patients based on their genetic status.

Methodik

Population:

- patients with mCRPC

Intervention:

- PARP inhibitor as a single agent or in combination with other regimens

Komparator:

- Nicht näher spezifiziert

Endpunkte:

- overall response rate (ORR) (≥50% PSA decline, or response according to Response Evaluation Criteria in Solid Tumors), or progression-free survival (PFS)

Recherche/Suchzeitraum:

- January 2006 to 30 June 2021

Qualitätsbewertung der Studien:

- Cochrane Risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- N=16 Studien

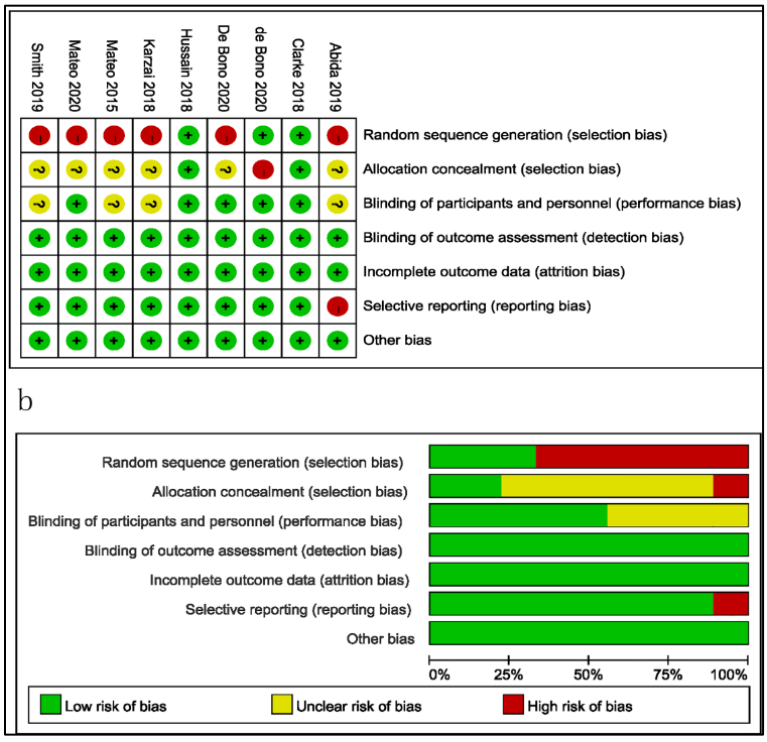
Charakteristika der Population/Studien:

TABLE 1 | Characteristics of the eligible studies.

Study (year)	Study name (NCT number)	Phase	Study design	Study drug	Total no. of patients	No. of HRD patients	No. of *BRCA*m patients	No. of *BRCA*wt patients	No. of non-HRD patients
Mateo et al. (2015)	TOPARP-B (NCT01682772)	II	Single arm	Olaparib	49	16	7	9	33
Clarke et al. (2018)	NCT01972217	II	RCT	Olaparib + abiraterone vs placebo + abiraterone	142	21	6	15	35
Hussain et al. (2018)	NCT01576172	II	RCT	Veliparib + abiraterone vs abiraterone	148	20	7	13	60
Karzai et al. (2018)	NCT02484404	II	Single arm	Olaparib + durvalumab	17	6	3	3	11
Abida et al. (2020a)	TRITON2 (NCT02952534)	II	Single arm	Rucaparib	193	193	115	78	0
Smith et al. (2019)	GALAHAD (NCT02854436)	II	Single arm	Niraparib	81	81	46	35	0
de Bono et al. (2020)	PROfound (NCT02987543)	III	RCT	Olaparib vs. abiraterone or enzalutamide	387	387	141	246	0
de Bono et al. (2020)	TALAPRO-1 (NCT03148795)	II	Single arm	Talazoparib	104	104	61	43	0
Mateo et al. (2020)	TOPARP-B (NCT01682772)	II	Single arm	Olaparib	98	98	32	66	0

Note. NCT, ClinicalTrials.gov identifier; BRCA*m, BRCA mutation;* BRCA*wt, BRCA wild type; HRD, homologous recombination deficiency.*

Qualität der Studien:



Studienergebnisse:

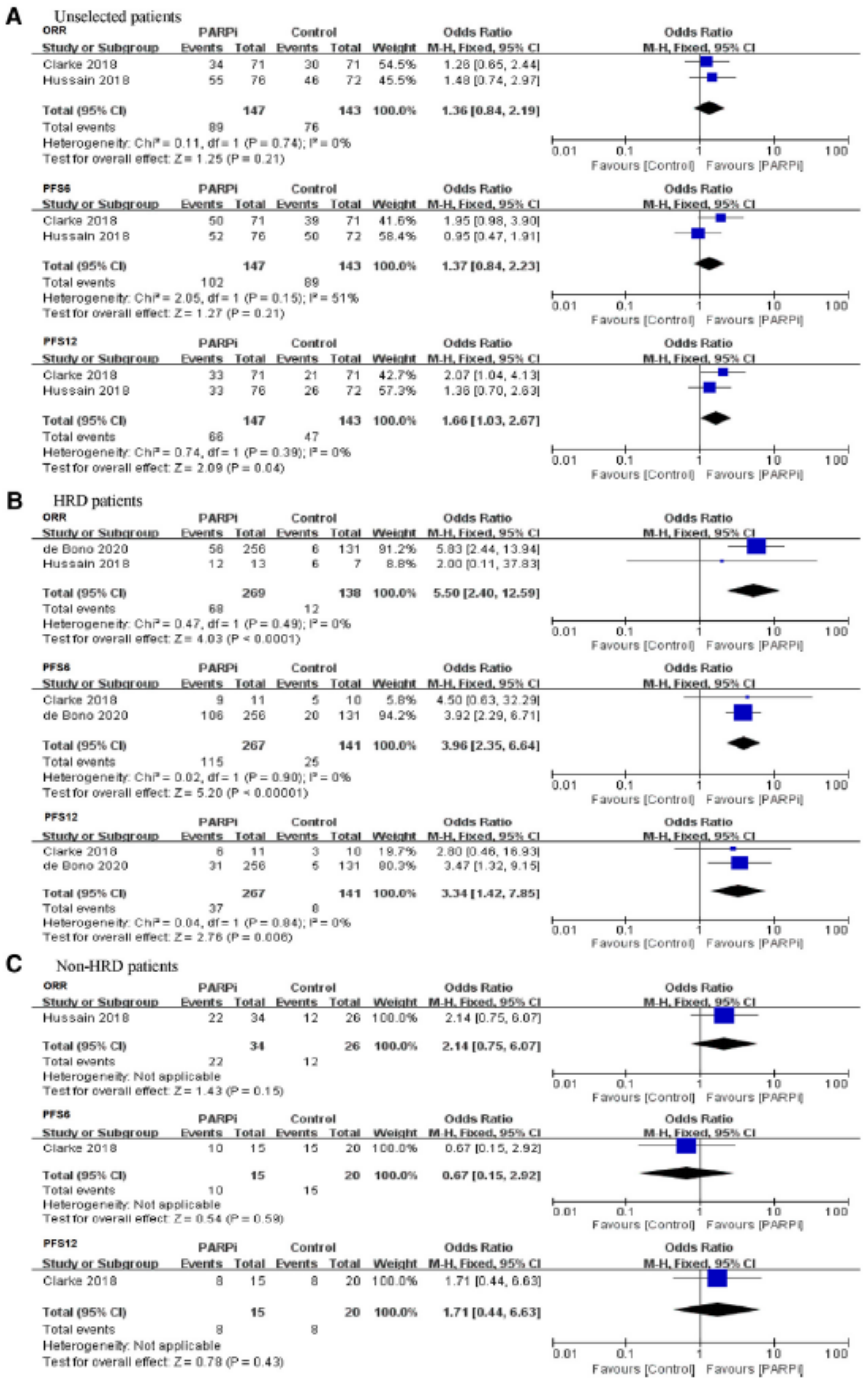


FIGURE 2 | Forest plots of pooled analyses for poly(ADP-ribose) polymerase inhibitors (PARPi) vs. control treatments on overall response rate (ORR) and progression-free survival (PFS) in **(A)** unselected patients, **(B)** homologous recombination deficiency (HRD) patients, and **(C)** non-HRD patients.

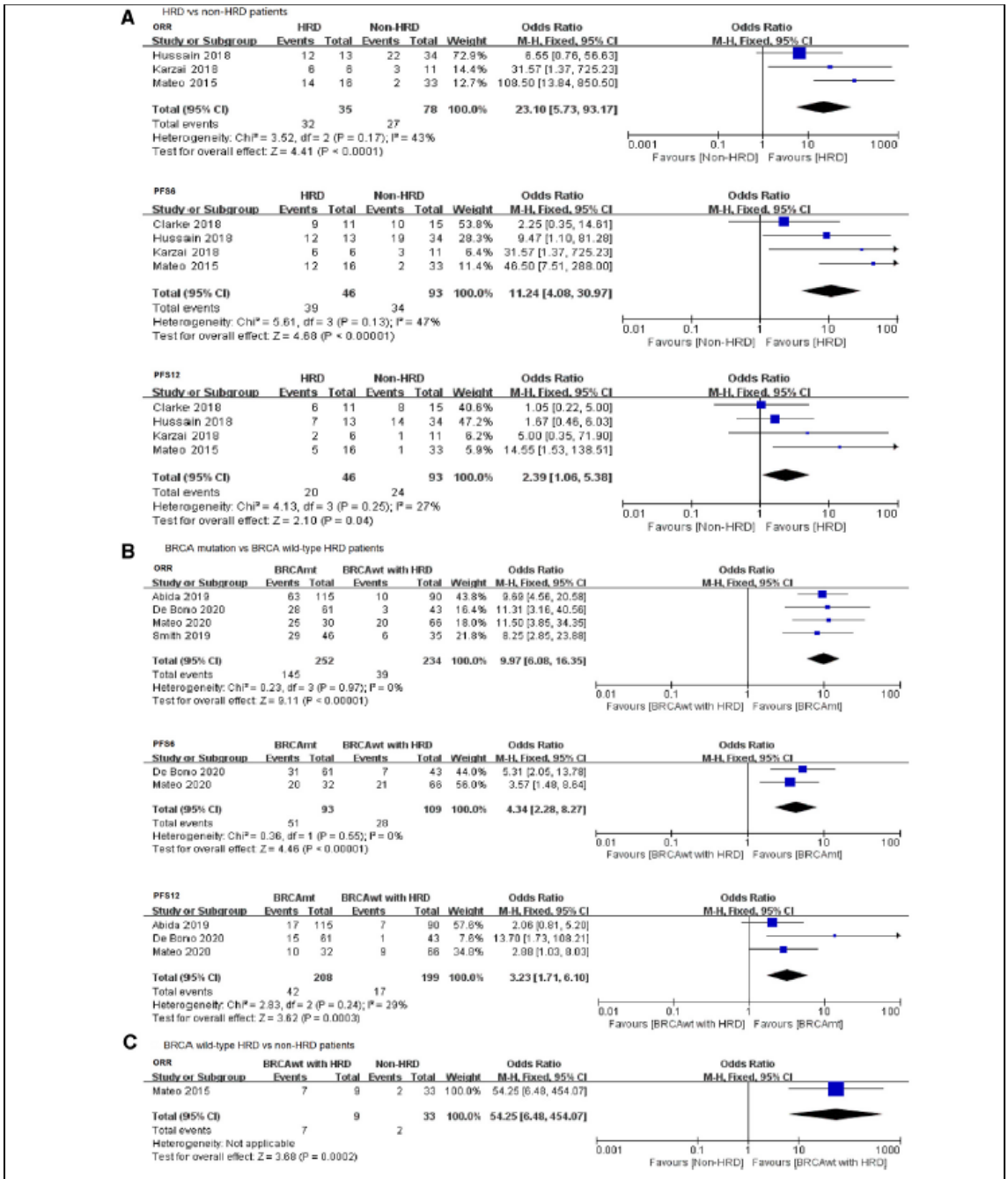


FIGURE 3 | Forest plots of pooled analyses for the effect of PARP inhibitors on ORR and PFS in **(A)** HRD vs. non-HRD patients, **(B)** *BRCA* mutation vs. *BRCA* wild-type HRD patients, and **(C)** *BRCA* wild type with HRD vs. non-HRD patients.

Anmerkung/Fazit der Autoren

Our findings confirmed that mCRPC patients with mutations in genes related to the HR DNA repair pathway are more likely to benefit from PARP inhibitor treatment when compared with non-HRD patients, suggesting that HRD-related gene aberrations can be used as a predictive biomarker to guide clinical decision making. Also, based on the magnitude of benefit of PARP inhibitors and the genetic status of patients, we could rank the subgroups of mCRPC patients in the following order: BRCA-mutant HRD > HRD without BRCA mutation > non-HRD; these results can help identify a suitable subpopulation who may benefit from PARP inhibitors and determine an appropriate control arm for future clinical trials. In addition, more emphasis needs to be placed on the different roles of BRCA1 and BRCA2 mutations.

Kommentare zum Review

- Z.T. nicht zugelassene AM berücksichtigt

3.3 Leitlinien

Leitlinienprogramm Onkologie, 2021 und Leitlinienreport [7,8,16].

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

S3-Leitlinie Prostatakarzinom; Langversion 6.2

Zielsetzung/Fragestellung

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

Methodik

Grundlage der Leitlinie

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

Die Leitlinie (Version 6.2 Oktober 2021) ist bis zur nächsten Aktualisierung gültig (11.05.2024). Vorgesehen sind regelmäßige modulare Aktualisierungen in einem 3-jährlichen Abstand.

Recherche/Suchzeitraum:

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

LoE

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

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

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

GoR

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

Tabelle 3 Einstufung der Empfehlungen

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

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

Empfehlungen

7.4. Therapie des androgenunabhängigen oder kastrationsresistenten Prostatakarzinoms (CRPC)

Nr.	Empfehlungen/Statements	EG	LoE	Quellen
7.26.	Patienten mit kastrationsresistentem Prostatakarzinom sollen über folgende Inhalte aufgeklärt werden: • Eine Heilung kann nicht erreicht werden. • Für die weitere Behandlung stehen verschiedene Optionen zur Verfügung.	A	4	EK
7.27.	Bei Patienten mit symptomatischer progredienter Erkrankung unter medikamentöser Kastration sollten die therapeutischen Optionen und das therapeutische Vorgehen interdisziplinär beraten und festgelegt werden.	B	4	EK
7.28.	Folgende für eine Therapieentscheidung ausschlaggebende Faktoren sollen bedacht werden: • Symptomatik • Nebenwirkungen der Therapieoptionen • Patientenpräferenz • Komorbidität, Lebenserwartung und Lebensqualität • Progressionsdynamik • Lokalisation von Metastasen und generelle Tumorlast.	A	4	EK
7.29.	Behandlungsfähigkeit für Chemotherapie ist keine eindeutig definierte Variable. Es fehlen daher Grenzwerte, ab denen Behandlungsfähigkeit gegeben bzw. nicht gegeben ist.	ST	4	EK
7.30.	Ein Geriatrisches Assessment ist zur Entscheidungsfindung vor Einleitung einer tumorspezifischen Therapie bei multimorbiden Patienten über 70 Jahre hilfreich.	ST	4	EK
7.31.	Bei Patienten mit progredienter Erkrankung unter chirurgischer oder medikamentöser Kastrationstherapie soll der Serumtestosteronspiegel kontrolliert werden.	EK		

Hintergrundinformationen zu den Empfehlungen 7.26 - 7.28

Die Therapie von Patienten mit fortgeschrittenem Prostatakarzinom hat sich in den letzten Jahren grundlegend gewandelt. Vor allem die Einführung neuer Arzneimittel zur systemischen Therapie hat in den verschiedenen Krankheitsstadien zu einer Verlängerung der Überlebenszeit geführt. Die Behandlung des kastrationsresistenten Prostatakarzinoms ist eine palliative Therapie. Dieser Tatsache ist bei der Indikationsstellung zur Therapie Rechnung zu tragen. Die Patienten sind entsprechend aufzuklären. Die therapeutischen Optionen betreffen verschiedene Fachdisziplinen. Zu einer interdisziplinären Tumorkonferenz beim kastrationsresistenten Prostatakarzinom gehören Urologie, internistische Onkologie, Pathologie, Strahlentherapie und Radiologie, in Abhängigkeit von Symptomatik und zu diskutierender Therapieoption auch Nuklearmedizin, Orthopädie, Neurochirurgie oder andere Fachdisziplinen. Ziele der Therapie sind die Verlängerung der Überlebenszeit, die Linderung von Symptomen, die Verbesserung oder der Erhalt der Lebensqualität, sowie die Vermeidung von Komplikationen. Therapieassoziierte Nebenwirkungen sind kritisch gegen die Resultate der Therapie

abzuwägen. Die Entscheidungsfindung bedarf einer umfassenden Aufklärung des Patienten, in die alle für eine Therapieentscheidung abzuwägenden Aspekte einzubeziehen sind.

Zu Statement 7.29

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

Zu Statement 7.30

Da Altern ein sehr heterogen verlaufender Prozess ist und der konventionellen klinischen Anamneseerhebung und körperlichen Untersuchung altersassoziierte Veränderungen häufig entgehen [809,810] und diese Veränderungen mit Outcome-Variablen assoziiert sind [811], wird bei Patienten mit Krebserkrankungen ab einem Alter von 70 Jahren, die Durchführung eines Assessments vor Beginn einer Chemotherapie von nationalen und internationalen Fachgesellschaften empfohlen [812–815]. Spezifische Empfehlungen für Patienten mit Prostatakarzinom sind seitens der Internationalen Gesellschaft für Geriatrische Onkologie (SIOG) ausgesprochen worden [419,816]

In der CRASH (Chemotherapy Risk Assessment for High Aged Patients) Studie analysierten Extermann et al. Variablen, die mit dem Auftreten von Grad 3-4 nichthämatologischen Toxizitäten und Grad 4 hämatologischen Toxizitäten nach CTCAE Kriterien assoziiert waren [817]. Es wurden 518 Patienten im Alter von 70 Jahren und älter eingeschlossen, die mit einer Chemotherapie behandelt wurden [817]. Mit folgenden Variablen ließen sich 4 Risikogruppen (niedrig = 7 %; mittel-niedrig = 23 %; mittel-hoch = 54 % und hoch = 100 %) für das Auftreten von Grad 4 hämatologischen Toxizitäten bilden: Lymphozyten, ASAT, Instrumentelle Aktivitäten des täglichen Lebens (IADL), LDH, diastolischer Blutdruck und MAX-2 Wert der Chemotherapie [817]. Für das Auftreten von Grad 3-4 nicht-hämatologischen Toxizitäten ließen sich 4 Risikogruppen (niedrig = 33 %; mittel-niedrig = 46 %; mittel-hoch = 67 % und hoch = 93 %) mit den Variablen: Hb, Albumin, Kreatinin-Clearance, ECOG-PS, Mini-MentalStatus-Examination (MMSE), Mini-Nutritional-Assessment (MNA) und MAX-2 Wert der Chemotherapie bilden [817]. Docetaxel 75 mg/m2 KOF 3-wöchentlich ist mit einem Punktwert von 2 im CRASH-Score, Docetaxel 35 mg/m2 KOF wöchentlich mit einem Wert von 0 im CRASH-Score zu veranschlagen [817].

In einer prospektiven Kohortenstudie, die 500 Patienten im Alter von 65 Jahren und älter einschloss, median 73 Jahre (Spanne 65–91 Jahre) untersuchten Hurria et al. Prädiktoren einer Chemotherapie assoziierten Toxizität Grad 3-5 [818]. Unter anderem waren Variablen des Geriatrischen Assessments (Mobilitätseinschränkung, Stürze, Hilfsbedürftigkeit in den Instrumentellen Aktivitäten des täglichen Lebens (IADL), Einschränkung der sozialen Aktivitäten) waren Prädiktoren für ein niedriges, intermediäres oder hohes Risiko für das Auftreten von Grad 3-5 Toxizitäten [818].

In einer prospektiven Kohortenstudie, die Patienten im Alter von 70 Jahren und älter einschloss, welche eine Erstlinienchemotherapie erhalten sollten, analysierten Soubeyran et al. Variablen des Geriatrischen Assessment auf ihren Stellenwert zur Prädiktion des Sterbens innerhalb der ersten sechs Monate [819]. Eine fortgeschrittene Erkrankung, eine Einschränkung im Mini-Nutritional-Assessment und Einschränkungen der Mobilität waren mit der 6-Monatsmortalitätsrate assoziiert [819].

Zu Empfehlung 7.31

Hintergrund dieser Empfehlung ist die Tatsache, dass nur bei adäquater kastrationsäquivalenter Testosteronsuppression von einer androgenunabhängigen bzw. kastrationsresistenten Erkrankung ausgegangen werden kann. Daher wird ein Serumtestosteronspiegel unter 20-50 ng/dl angestrebt und dokumentiert (Definition der Kastrationsresistenz in Anlehnung an die EAU-Leitlinie: Serumtestosteron <50 ng/dl bei gleichzeitiger biochemischer [drei aufeinanderfolgende PSA-Anstiege mit einwöchigem Abstand, die zwei Anstiege um 50 % über Nadir ergeben, und ein PSA-Spiegel >2 ng/mL) oder radiologischer Progression [675,820]. Bei progredienter Erkrankung ist der Testosteronspiegel zu

kontrollieren. Die Progredienz der Erkrankung kann sich klinisch, biochemisch (s. Definition oben) oder in der Bildgebung zeigen.

7.4.2. Metastasiertes kastrationsresistentes Prostatakarzinom (mCRPC)

7.4.2.1. Asymptomatische oder gering symptomatische Patienten

Nr.	Empfehlungen/Statements	EG	LoE	Quellen
7.34.	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.	0	4	EK
7.35.	Wenn sich ein Patient mit metastasierter, kastrationsresistenter, asymptomatischer oder gering symptomatischer und progredienter Erkrankung gegen ein abwartendes Verhalten und für die Umstellung der Behandlung entschieden hat, soll eine der folgenden Optionen angeboten werden: (alphabetische Reihenfolge) • Abirateron (in Kombination mit Prednison / Prednisolon) • Docetaxel • Enzalutamid Zur Differenzialtherapie siehe Empfehlungen 7.36. und 7.37..	A	1+	[384-387]
7.36.	Patienten mit metastasierter, kastrationsresistenter, asymptomatischer oder gering symptomatischer und progredienter Erkrankung sollte (alphapetische Reihenfolge) • Abirateron (in Kombination mit Prednison / Prednisolon) oder • Enzalutamid angeboten werden.	B	1+	[386,387]
7.37.	Patienten mit metastasierter, kastrationsresistenter, asymptomatischer oder gering symptomatischer und progredienter Erkrankung kann Docetaxel angeboten werden.	0	1+	[384,385]

Hintergrundinformationen zu Empfehlung 7.34 und 7.35

Die Gruppe der Patienten ohne vorherige Therapie mit einer neuen hormonellen Substanz (new hormonal agent) wird in den kommenden Jahren kleiner werden. Unter dem Begriff einer neuen hormonellen Substanz werden Abirateron, Apalutamid, Darolutamid oder Enzalutamid zusammengefasst. Da diese Patienten derzeit weiterhin eine relevante Population bilden, werden die Empfehlungen aus den vorherigen Fassungen dieser Leitlinie übernommen und ggf. mit aktualisierten Daten ergänzt.

Das Fortschreiten einer metastasierten Erkrankung beim kastrationsresistenten Prostatakarzinom wird als Kontinuum gesehen. Ein Schwellenwert zur Umstellung der Therapie ist durch Studien nicht definiert. Die Entscheidung über den Zeitpunkt der Umstellung einer bisher durchgeführten Androgendeprivation zu weiterführenden Therapiemaßnahmen ist individuell zu treffen. Für Patienten, die sich für ein abwartendes Vorgehen entscheiden, stehen verschiedene Formen der Androgendeprivation zur Verfügung.

Basis der Empfehlungen 7.34 und 7.35 beim metastasierten, kastrationsresistenten Prostatakarzinom sind Studien, die vor Einsatz der erweiterten Therapie beim hormonsensitiven Prostatakarzinom (siehe Kapitel 7.3) bzw. beim nicht-metastasierten kastrationsresistenten Prostatakarzinom (siehe Kapitel 7.4.1) durchgeführt wurden.

Der vorherige Einsatz von Abirateron, Docetaxel oder Androgen-Pathway-Inhibitoren ist bei der Wahl der Folgetherapien im metastasierten Stadium zu berücksichtigen.

Zur Therapie von Patienten mit metastasierter, kastrationsresistenter, asymptomatischer oder gering symptomatischer und progredienter Erkrankung liegen Daten randomisierter Studien zu Formen der Antihormontherapie mit Abirateron oder Enzalutamid, sowie der Chemotherapie mit Docetaxel vor. Die in der Leitlinie ab 2014 gelistete Immuntherapie mit Sipuleucel-T ist seit Mitte 2015 nicht mehr in Europa verfügbar. Abirateron und Enzalutamid wurden gegen Placebo, Docetaxel gegen Mitoxantron getestet. Abirateron wird standardmäßig in Kombination mit Prednison oder Prednisolon gegeben. Die Empfehlungen für diese Patientenpopulation beruhen auf den Einschlusskriterien für Therapie mit Docetaxel [835,837], Abirateron [836] und Enzalutamid [838] bei Patienten ohne Vortherapie in diesem Krankheitsstadium. Progrediente Erkrankung wurde in der Studie zu Abirateron als PSA-Progression gemäß der Kriterien der Prostate Cancer Clinical Trial Working Group (PCWG2) [839] oder bildgebenden Progress definiert, in der Enzalutamid-Studie als PSA- und/oder bildgebenden Progress und in der Docetaxel-Studie als PSA-Progression (steigende Werte in drei aufeinanderfolgenden Messungen) oder bildgebenden Progress. In die Abirateron- ebenso wie in die Enzalutamid-Studie wurden nur Patienten mit einem Brief Pain Inventory-Short Form (BPI-SF)-Score von 0-3 als stärkster Schmerz in den letzten 24 Stunden eingeschlossen. Ob eine Chemotherapie mit Docetaxel schon bei asymptomatischen Patienten mit alleinigem PSA-Anstieg oder bei durch Bildgebung nachgewiesener Progression zu beginnen ist, ist Gegenstand kontroverser Diskussionen. In der Subgruppenanalyse von TAX-327 [837,840] wurde auch bei Patienten ohne Schmerzsymptomatik, bei Patienten ohne viszerale Metastasierung und bei Patienten mit minimal symptomatischer Erkrankung eine Verlängerung der Überlebenszeit im Vergleich zu Mitoxantron erzielt. Eine randomisierte kontrollierte Studie zum Nutzen einer frühen Therapie bei asymptomatischen Patienten versus späterer Therapie bei symptomatischen Patienten gibt es bisher nicht.

Zu Empfehlung 7.36

Der selektive 7α-Hydroxylase/C17,20-lyase (CYP17)-Hemmer Abirateron bewirkt eine extragonadale Hormonsuppression. Die COU-AA-302 Studie (n = 1088) zeigte einen Überlebensvorteil für Abirateron in Kombination mit Prednison im Vergleich zu Placebo mit Prednison (medianes Gesamtüberleben: 34,7 vs. 30,3 Monate, HR: 0,81, 95 % KI: 0,70-0,93, p = 0,0033) [841]. Das vordefinierte Signifikanzniveau (0,001) wurde in dieser Studie nicht erreicht. Da bei Progredienz der Erkrankung ein Crossover vom Placebo- zum Abirateron-Arm erlaubt war, ist die Aussagefähigkeit des Endpunktes Überlebenszeit eingeschränkt. Darüber hinaus war die weiterführende Therapie bei Progredienz nach Abirateron nicht definiert. In der Zulassungsstudie [836] 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 Analyse werden dagegen keine Angaben zum progressionsfreien Überleben und den weiteren o.g. Endpunkten gemacht. Eingeschlossen wurden nur Patienten mit gutem Allgemeinzustand (ECOG 0-1). Patienten mit viszeralen Metastasen wurden nicht in die Studie eingeschlossen. In der Zulassungsstudie [836] hatten 33 % (n = 178) der Patienten mit Abirateron plus Prednison und 26 % (n = 142) der Patienten mit Placebo plus Prednison mindestens eine schwerwiegende Nebenwirkung. In der finalen Publikation [841] werden als häufigste schwerwiegende Nebenwirkungen Herzerkrankungen (8 vs. 4 %), erhöhte ALT-Werte (6 vs. <1 %) und Bluthochdruck (5 vs. 3 %) genannt [841]. Sehr häufige Nebenwirkungen (> 10 %) unter Abirateron sind laut EMA-Dokument Harnwegsinfektionen, Hypokaliämie, Hypertonie und periphere Ödeme; Herzerkrankungen, Hepatotoxizität und Frakturen sind weitere wichtige Nebenwirkungen [842]. Abirateron ist in Kombination mit Prednison/Prednisolon zugelassen zur Behandlung des metastasierten kastrationsresistenten Prostatakarzinoms bei erwachsenen Männern mit asymptomatischem oder mild symptomatischem Verlauf der Erkrankung nach Versagen der Androgenentzugstherapie, bei denen eine Chemotherapie noch nicht klinisch indiziert ist [842].

Enzalutamid hemmt den Androgenrezeptor-Signalweg auf unterschiedlichen Ebenen. Neben der Hemmung des Androgenrezeptors verhindert Enzalutamid dessen Translokation in den Zellkern, die DNA-Bindung sowie die Aktivierung von Kofaktoren. Die Zulassungsstudie PREVAIL umfasste 1.717 Chemotherapie-naive Patienten mit kastrationsresistentem Prostatakarzinom. Es wurden nur Patienten in

gutem Allgemeinzustand (ECOG 0-1) eingeschlossen. Im Gegensatz zur COU-AA302-Studie mit Abirateron war der Einschluss von Patienten mit einer viszeralen Metastasierung in der PREVAIL-Studie erlaubt. Bei Studienbeginn wiesen 11,2 % der Patienten im Enzalutamid- und 12,5% der Patienten im Placebo-Arm eine viszerale Metastasierung mit pulmonalen und/oder hepatischen Metastasen auf [843]. Sowohl in der Interimanalyse [838] als auch in der Langzeitanalyse zeigte sich ein Überlebensvorteil für Enzalutamid gegenüber Placebo [844] (medianes Gesamtüberleben: 35,3 vs. 31,3 Monate, HR: 0,77, 95 % KI: 0,67-0,87, p=0,0002). Das als koprimärer Endpunkt definierte radiologisch progressionsfreie Überleben wurde lag unter Enzalutamid bei 20 Monaten vs. 5,4 Monaten im Kontrollarm (HR 0,32; p<0,00001) [844]. Unter den sekundären Endpunkten wurden patientenrelevante signifikante Unterschiede zwischen Enzalutamid- und Placebo-Arm gefunden (Zeit bis zum ersten SRE, Dauer bis zu einer Verschlechterung der Lebensqualität oder Beginn einer Opiat-Therapie als Surrogat-Parameter für Schmerz). Sehr häufige Nebenwirkungen unter Enzalutamid sind Hitzewallungen (HR = 2,29) und Kopfschmerzen [844]. Zu den häufigen Nebenwirkungen zählen Neutropenie, visuelle Halluzinationen, Angst, kognitive Störung, Gedächtnisstörung, Hypertonie, trockene Haut, Juckreiz, Frakturen, Stürze. In der Arzneimittel-Information [845] wird außerdem auf Interaktionen mit CYP2C8- und CYP3A4-Inhibitoren und -Induktoren hingewiesen. Ein möglicher Einfluss von Enzalutamid auf andere Arzneimittel wird für 14 Arzneimittelgruppen gelistet. Enzalutamid ist zugelassen 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 [846].

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

Zu Empfehlung 7.37

Die TAX-327 Studie (n =1.006, Karnofsky-performance status ≥ 60 %) zeigte einen Überlebensvorteil von 2,9 Monaten (Spanne null bis sieben Monate) bei dreiwöchentlicher Gabe von Docetaxel im Vergleich zu den beiden anderen Armen (wöchentlich Docetaxel niedriger dosiert, dreiwöchentlich Mitoxantron; Randomisierung 1:1:1) für die Gesamtgruppe [835,837]. 45 % der Patienten waren zu Beginn der Studie symptomatisch (Schmerzen definiert als ein Wert ≥ 2 auf der Present Pain Intensity (PPI) Skala oder ein Wert ≥ 10 auf dem Analgesic Score). 13 % der Patienten hatten einen Karnofsky performance status ≤ 70 %. Schwere Nebenwirkungen (Grad 3/4), die bei mehr als 20 % der Patienten in den Zulassungsstudien auftraten, waren: Alopezie (65 %), Fatigue (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 medianen Veränderungen waren aber gering [835]. In der TAX-327 Studie war neben der dreiwöchigen Gabe auch die wöchentliche Gabe mit einer medianen Verlängerung des Gesamtüberlebens (0,9 Monate, n. s.) im Vergleich zu Mitoxantron verbunden [835]. Eine weitere Studie zeigte einen Überlebensvorteil einer zweiwöchigen im Vergleich zu einer dreiwöchigen Gabe von Docetaxel und eine niedrigere Rate schwerwiegender Nebenwirkungen, insbesondere von Neutropenien [849]. Da die Studie im Vergleich zu anderen Studien mit Docetaxel eine relativ kurze Überlebenszeit für die dreiwöchentliche Gabe von Docetaxel gezeigt hat und zudem methodische Schwächen hat (z. B. Per Protocol Analyse), werden zweiwöchige und dreiwöchige Gabe gleichermaßen empfohlen. Docetaxel ist in Kombination mit Prednison / Prednisolon zur Behandlung des metastasierten, kastrationsresistenten Prostatakarzinoms zugelassen [850].

Die zurückhaltende Empfehlung für den Einsatz von Docetaxel berücksichtigt die höhere Rate schwerer Nebenwirkungen unter Docetaxel.

Literatur:

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7.4.2.2. Symptomatische Patienten

Nr.	Empfehlungen/Statements	EG	LoE	Quellen
7.38.	Patienten mit metastasierter, kastrationsresistenter, symptomatischer progredienter Erkrankung und gutem Allgemeinzustand soll eine systemische Therapie, bei Bedarf in Kombination mit symptombezogener und supportiver Therapie, angeboten werden. Zur Differenzialtherapie siehe Empfehlungen 7.39., 7.40., 7.41..	A	1+	[384-386,388].
7.39.	Patienten mit metastasierter, kastrationsresistenter, symptomatischer und progredienter Erkrankung kann Docetaxel in zwei- oder drei-wöchigen Dosierungsschemata angeboten werden.	0	1+	[384,385]
7.40.	Patienten mit metastasierter, kastrationsresistenter, symptomatischer und progredienter Erkrankung kann (alphabetische Reihenfolge) • Abirateron (in Kombination mit Prednison / Prednisolon) oder • Enzalutamid angeboten werden. Patienten sollen darüber aufgeklärt werden, dass in der Zulassungsstudie nur Patienten mit gering symptomatischer Erkrankung behandelt wurden.	0 A	1+	[386,387]
7.41.	Patienten mit kastrationsresistenter, symptomatischer, progredienter Erkrankung und reduziertem Allgemeinzustand (ECOG ≥ 2, Karnofsky-Index < 70) soll eine symptombezogene Therapie angeboten werden.	A	4	EK
7.42.	Patienten mit kastrationsresistenter, progredienter Erkrankung und reduziertem Allgemeinzustand (ECOG ≥ 2, Karnofsky-Index < 70) kann zusätzlich eine der folgenden Therapieoptionen angeboten werden: (alphabetische Reihenfolge) • Abirateron (in Kombination mit Prednison / Prednisolon) • Chemotherapie, wenn der reduzierte Allgemeinzustand vor allem auf das metastasierte Prostatakarzinom zurückzuführen ist • Enzalutamid • Steroide (Dexamethason, Prednisolon, Prednison)	0	4	EK auf der Grundlage von: [384-387]

Hintergrundinformationen Zu Empfehlung 7.38

Auch bei symptomatischen Patienten wird die Gruppe der Erkrankten ohne vorherige Therapie mit einer neuen hormonellen Substanz (new hormonal agent) in den kommenden Jahren kleiner werden. Unter dem Begriff einer neuen hormonellen Substanz werden Abirateron, Apalutamid, Darolutamid oder Enzalutamid zusammengefasst. Da diese Patienten derzeit weiterhin eine relevante Population bilden, werden die Empfehlungen aus den vorherigen Fassungen dieser Leitlinie übernommen und mit aktualisierten Daten ergänzt.

Die Therapieoptionen für Patienten mit symptomatischer Erkrankung und gutem Allgemeinzustand werden in den Empfehlungen 7.38 – 7.39 behandelt. Ein guter Allgemeinzustand wird von der Leitliniengruppe definiert als ECOG < 2 oder Karnofsky-Index ≥ 70 %. Die Beschreibung der lokalen Therapieverfahren bei Knochenmetastasen finden sich im Kapitel 7.6 „Therapie von Knochenmetastasen“. In den Studien, die die weiteren Therapieoptionen untersuchen, wurden unterschiedliche Einschlusskriterien verwendet, daher sind die Ergebnisse nur schwer vergleichbar. Vergleichende Studien oder Studien zu Kombinationen der Therapieoptionen liegen bisher nicht vor.

Patienten mit Z. n. initialer Hormon-Chemotherapie oder intensivierter Hormontherapie mit Abirateron (+ Prednison oder Prednisolon) oder Apalutamid (ggf. noch Enza in Abhängigkeit des Zulassungsstatus) stellen in diesem Zusammenhang eine Gruppe dar, für die formal keine Datenlage im Rahmen von Studien existiert, da dieser Therapieansatz zum Zeitpunkt der Rekrutierung dieser Studien noch nicht existierte. Dennoch wird hier ein Analogieschluss von der Leitliniengruppe favorisiert.

Zu Empfehlung 7.39

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

Zu Empfehlung 7.40

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

Zu Empfehlung 7.41 und 7.42

Patienten mit schlechtem Allgemeinzustand (ECOG ≥ 2, Karnofsky-Index < 70 %) und Patienten mit Einschränkungen im Geriatrischen Assessment weisen eine eingeschränkte Behandlungsfähigkeit auf. Es gibt keine randomisierten Studien für die Therapie von Patienten mit progredienter Erkrankung und einem reduzierten Allgemeinzustand (ECOG ≥ 2). In den Studien zu Abirateron (ECOG: 0-1), Docetaxel (Karnofsky-Index ≥ 60 %), Enzalutamid (ECOG: 0-1) waren keine oder nur wenige Patienten mit reduziertem Allgemeinzustand eingeschlossen. Daher wird für diese Patienten eine symptombezogene Therapie empfohlen. Des Weiteren können zusätzlich verschiedene Therapieoptionen angeboten werden. Hinweise bzw. Einschränkungen bei den Therapieoptionen werden in den Hintergrundtexten zu den Empfehlungen 7.38-7.40.

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

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

Nr.	Empfehlungen/Statements	EG	LoE	Quellen
7.43.	Patienten mit Progress unter einer neuen hormonellen Substanz (new hormonal agent) sollte ein Wechsel der Therapiestrategie angeboten werden.	B	4	EK auf der Grundlage von [389]
7.44.	Patienten mit Progress nach einer Vortherapie, die eine neue hormonelle Substanz (new hormonal agent) umfasste, soll eine Testung auf BRCA 1/2 -Mutationen angeboten werden.	A	1-	[390,391]
7.45.	Bei Nachweis einer *BRCA1/2* Mutation soll eine Therapie mit Olaparib angeboten werden.	A	1-	[390,391]

Hintergrundinformationen Zu Empfehlung 7.43

Der Nachweis der Wirksamkeit neuer hormoneller Substanzen beim hormonsensitiven, metastasierten Prostatakarzinom sowie beim hoch Risiko nmCRPC (M0CRPC) beeinflusst - ebenso wie der Einsatz von Docetaxel beim metastasierten hormonsensitiven Prostatakarzinom - die gesamte Sequenz der Folgetherapien. Unter dem Begriff einer neuen hormonellen Substanz werden Abirateron, Apalutamid, Darolutamid oder Enzalutamid zusammengefasst.

Die Wahl der jeweiligen Therapieoption richtet sich nach dem patientenindividuellen Therapieziel auf der Basis des Shared-Decision-Making von Patient und Arzt unter Berücksichtigung der Vortherapie und sorgfältiger Abwägung von Nutzen und potenziellem Schaden.

Hierbei sind insbesondere auch die Ergebnisse der Studien zum Wechsel des Wirkprinzips (Mode of Action) mit Einsatz von Cabazitaxel [852] oder von Olaparib [853,854] nach Vortherapie mit einem der neueren Androgenrezeptor-gerichteten Therapien zu berücksichtigen. Ein Wechsel des Therapieprinzips wird auch durch molekularbiologische Untersuchungen zu Resistenzmechanismen gegen eine gegen den Androgen-Rezeptor gerichtete Therapie gestützt [855,856], so dass Empfehlung 7.45 allgemein als Expertenkonsens formuliert wurde. Weitere Ausführungen zur Sequenztherapie finden sich in Empfehlung 7.52.

Die Empfehlungen beruhen auf den Einschlusskriterien der jeweiligen Zulassungsstudien sowie ggf. nachfolgender Daten.

Zu Empfehlung 7.44

Bisher richtet sich die Indikation zur systemischen antineoplastischen Therapie beim fortgeschrittenen Prostatakarzinom nach laborchemischen, radiologischen und klinischen Kriterien. Das ändert sich aktuell. In bis zu 30 % der Patienten mit Prostatakarzinom werden in den Tumorzellen genetische Aberrationen gefunden, die den physiologischen Mechanismus der DNS-Reparatur beeinflussen [857]. Am häufigsten sind dabei Alterationen im BRCA2- (BReast CAncer 2) Gen, aber auch das BRCA1-Gen ist betroffen. Dabei können die Genveränderungen sowohl hereditär bei Trägern von Keimbahnmutationen sein als auch einen somatischen Ursprung aufweisen mit einer erworbenen auf das Tumorgewebe beschränkten Alteration. Patienten mit BRCA1- oder BRCA2-Mutationen weisen ein erhöhtes Risiko für eine Prostatakarzinom-Erkrankung auf; die Prognose der Patienten wird als ungünstiger eingestuft [858,859]. Gleichzeitig bietet die Biologie der BRCA-mutierten Tumorzelle einen Ansatz für gezielte Therapie mit der Poly(ADP-ribose) Polymerasen (PARP) Inhibitoren. PARP-Inhibitoren wurden zuerst beim fortgeschrittenen Ovarialkarzinom, dann auch beim fortgeschrittenen Mamma- oder Pankreaskarzinom mit Nachweis von BRCA1/2-Mutationen zugelassen.

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

Die Empfehlung zur BRCA1/2-Testung richtet sich an Patienten mit metastasiertem, kastrationsresistentem Prostatakarzinom, bei denen bereits eine Therapie mit neuen hormonellen Substanzen (new hormonal agents) durchgeführt wurde. Unter dem Begriff einer neuen hormonellen Therapie werden Abirateron, Apalutamid, Darolutamid oder Enzalutamid zusammengefasst. Falls eine solche Therapie zuvor nicht eingesetzt wurde, ist diese aufgrund der Einschlusskriterien der PROFOUND-Studie und dem darauf beruhenden Zulassungstext vor einem möglichen Einsatz von Olaparib und damit auch vor einer BRCA1/2-Testung indiziert [860].

Zu Empfehlung 7.45

Olaparib ist ein PARP-Inhibitor. Es wurde im November 2020 in der EU als Monotherapie für Patienten mit einem metastasiertem kastrationsresistenten Prostatakarzinom und BRCA1/2-Mutation (in der Keimbahn und/ oder somatisch) zugelassen, deren Erkrankung nach vorheriger Behandlung, die eine neue hormonelle Substanz (new hormonal agent) umfasste, progredient ist. Olaparib wird oral eingenommen.

Basis der Zulassung war die PROfound-Studie. In PROfound wurden 387 Patienten mit metastasiertem Prostatakarzinom, nach Progress unter Abirateron oder Enzalutamid, und mit Nachweis von Mutationen in BRCA1, BRCA2 oder ATM (Kohorte A) oder in 12 selteneren HRR-Mutationen (Kohorte B) eingeschlossen [853,854]. Dabei hatten ca. 60 % der Patienten bei Studieneinschluss bereits eine Taxan-haltige Chemotherapie erhalten, ca. 20 % der Patienten waren mit beiden Androgen-Rezeptor gerichteten Medikamenten vorbehandelt. Randomisiert wurde zwischen Olaparib oder Abirateron/Enzalutamid im Verhältnis 2:1 zugunsten des Olaparib-Arms [854,853]. Die Wahl zwischen Abirateron oder Enzalutamid erfolgte durch den behandelnden Arzt. Olaparib führte gegenüber Abirateron/Enzalutamid in der Kohorte A (BRCA1/2; ATM) zur Steigerung der Ansprechrate (33 vs. 2 %; Odds Ratio (OR) 20,86; p<0,001)), zur signifikanten Verlängerung des progressionsfreien Überlebens (7,4 vs. 3,6 Monate; Hazard Ratio (HR) 0,34; p< 0,001) und zur Verlängerung der medianen Gesamtüberlebenszeit (19,1 vs. 14,7 Monate; HR 0,69; p=0,02) [853,854]. Ebenfalls verlängert wurde die Zeit bis zum Progress von Schmerzen (HR 0,44; p=0,02).

Eine Subgruppenanalyse zu den einzelnen Genalterationen zeigte einen Vorteil von Olaparib v.a. für Patienten mit BRCA1/2-Mutationen. Entsprechend beschränkt sich die Zulassung von Olaparib auf diese Gruppe.

Nebenwirkungen im Schweregrad CTCAE 3/4 traten unter Olaparib bei 51 vs. 38 % im Kontrollarm auf [853,854]. Häufigste Nebenwirkungen aller Schweregrade mit stärkerer Ausprägung als im Kontrollarm waren Anämie (46 %), Übelkeit (41 %), Fatigue (41 %), Appetitverlust (30 %), Diarrhoe (21 %), Erbrechen (18 %), Obstipation (18 %), Husten (11 %) und Dyspnoe (10 %) [853,854]. Bei 22 % der Patienten wurde die Dosierung von Olaparib aufgrund von Nebenwirkungen reduziert, bei 18 % der Patienten wurde die Therapie abgebrochen [853,854].

7.4.2.4. Therapiesequenzen nach Docetaxel

Nr.	Empfehlungen/Statements	EG	LoE	Quellen
7.46.	Patienten mit kastrationsresistenter, progredienter Erkrankung und gutem Allgemeinzustand nach Chemotherapie mit Docetaxel soll eine der folgenden Therapieoptionen, bei Bedarf in Kombination mit symptombezogener und supportiver Therapie, angeboten werden: (alphabetische Reihenfolge) • Abirateron (in Kombination mit Prednison / Prednisolon) • Cabazitaxel • Enzalutamid Zur Differenzialtherapie siehe Empfehlungen 7.47. - 7.49..	A	1+	[392-399]
7.47.	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.	0	1+	Abirateron: [392,393] Enzalutamid [395]
7.48.	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.	0	1+	[396]

Nr.	Empfehlungen/Statements	EG	LoE	Quellen
7.49.	a. Radium-223 kann Patienten angeboten werden, die ein kastrationsresistentes, progredientes Prostatakarzinom mit symptomatischen ossären Metastasen (ohne bekannte viszerale Metastasen) sowie einen guten Allgemeinzustand aufweisen und die mindestens zwei vorausgehende systemische Therapieoptionen in dieser Indikation erhielten oder für die keine andere verfügbare systemische mCRPC-Therapie geeignet ist. b. Radium-223 soll nicht in Kombination mit Abirateron und Prednison/ Prednisolon angewandt werden.	0 A	1+	a. [388,400,401] b. [402]
7.50.	Patienten mit kastrationsresistenter, progredienter Erkrankung nach Chemotherapie mit Docetaxel und reduziertem Allgemeinzustand (ECOG ≥ 2, Karnofsky < 70) kann zusätzlich zur symptombezogenen Therapie eine der folgenden Therapieoptionen angeboten werden: (alphabetische Reihenfolge) • Abirateron (in Kombination mit Prednison / Prednisolon) • Chemotherapie, wenn der reduzierte Allgemeinzustand vor allem auf das metastasierte Prostatakarzinom zurückzuführen ist • Enzalutamid • Steroide (Dexamethason, Prednisolon, Prednison)	0	4	EK auf der Grundlage von Literatur zu 7.49. und [40,106,403].
7.51.	Für Patienten mit kastrationsresistenter, progredienter Erkrankung in gutem Allgemeinzustand kann nach Ausschöpfen der empfohlenen Therapieoptionen (siehe Empfehlung 7.46.) ein Therapieversuch mit Lutetium-177-PSMA auf Basis der Empfehlung einer interdisziplinären Tumorkonferenz angeboten werden.	0	3	[404-411]

Hintergrundinformationen Zu Empfehlung 7.46

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

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

Empfehlung 7.47

Unter Therapie mit Abirateron wurde nach einem medianen Follow-up von ca. zwölf Monaten in einer Interimsanalyse eine Verlängerung des Gesamtüberlebens um im Median 3,9 Monate im Vergleich zu Placebo gezeigt [861]. In die randomisierte kontrollierte Studie (1.195 Patienten, 2:1-Randomisierung) waren asymptomatische und symptomatische Patienten mit sehr gutem Allgemeinzustand einbezogen (90 % ECOG 0-1), die vorher mindestens eine Chemotherapie erhalten hatten. Die Raten an Nebenwirkungen sind im Vergleich zu einer Chemotherapie geringer. Die Nebenwirkungen gründen vor allem auf der mineralokortikoiden Wirkung des Medikaments, zu nennen sind insbesondere Hypokaliämie, Hypertonie

und Flüssigkeitsretention/Ödeme. In der Folgeauswertung [862] verstärkte sich der Vorteil bei einer Verlängerung der Gesamtüberlebenszeit von im Median 4,8 Monaten (15,8 Monate versus 11,2 Monate; HR: 0,74, 95 % KI: 0,64–0,86; p < 0,001). Im Vergleich zu Placebo zeigte Abirateron einen signifikanten Effekt auf verschiedene Endpunkte (progressionsfreies Überleben, biochemische und bildgebende Remission und Symptomatik) [863]. Bei Patienten mit niedrigen Lebensqualitätswerten zu Beginn der Studie verbesserte sich die Lebensqualität bei mehr Patienten, die Abirateron erhielten im Vergleich zu Placebo (definiert als eine Verbesserung des FACT-P um 10 Punkte). Abirateron ist in Kombination mit Prednison / Prednisolon zur Behandlung des metastasierten kastrationsresistenten Prostatakarzinoms bei erwachsenen Männern, deren Erkrankung während oder nach einer Docetaxel-haltigen Chemotherapie progredient ist, zugelassen [842].

Zur erneuten Therapie mit Abirateron, falls dieses bereits vor der Therapie mit Docetaxel eingesetzt wurde, sind derzeit keine Daten verfügbar.

Der Androgenrezeptorblocker Enzalutamid zeigte in einer randomisiert kontrollierten Studie mit 1.199 Patienten (2:1 Randomisierung) in gutem Allgemeinzustand (EGOG 0-2) mit progredienter Erkrankung nach Therapie mit Docetaxel einen signifikanten Vorteil im Gesamtüberleben von im Median 4,8 Monaten (18,4 Monaten versus 13,6 Monaten unter Placebo; HR: 0,63, 95 % KI: 0,53-0,75; P < 0,001) [864]. Unter anderem waren Patienten mit einem erhöhten Risiko für einen Krampfanfall von der Studie ausgeschlossen. Im Vergleich zu Placebo verlängerte Enzalutamid das progressionsfreie Überleben (8,3 Monate vs. 2,9 Monate; HR: 0.40, 95 % KI: 0,35-0,47, p < 0,001) und die Zeit bis zur PSA-Progression (8,3 Monate vs. 3,0 Monate; HR: 0,25, 95 % KI: 0,20-0,30, p < 0,001) und verbesserte die Lebensqualität (definiert als eine Verbesserung des FACT-P um 10 Punkte). Sehr häufige Nebenwirkungen in der klinischen Phase III Studie waren Kopfschmerzen und Hitzewallungen. Krampfanfälle traten nur bei Patienten im Enzalutamid-Arm (n = 6, 0,8 %) auf. Enzalutamid ist seit Juni 2013 zur Behandlung erwachsener Männer mit metastasiertem kastrationsresistentem Prostatakarzinom zugelassen, deren Erkrankung während oder nach einer Chemotherapie mit Docetaxel fortschreitet [846].

Zu Empfehlung 7.48

Zum Einsatz von Cabazitaxel liegen Daten von drei randomisierten Studien vor. In der Zulassungsstudie wurde Cabazitaxel im Unterschied zu Abirateron und Enzalutamid (jeweils gegen Placebo) versus Mitoxantron (jeweils in Kombination mit Prednison) getestet. Die Randomisierung erfolgte 1:1. Das mittlere Alter der Patienten lag bei 67,5 Jahren und es wurden überwiegend (ca. 92 %) Patienten mit ECOG 0-1 eingeschlossen. Die eingeschlossenen Patienten wiesen alle eine ausgeprägte Metastasierung auf. Im Vergleich zu Mitoxantron wurde unter Cabazitaxel eine mittlere Lebensverlängerung um 2,4 Monate (15,1 Monate vs. 12,7 Monate, HR: 0,70; 95 % KI: 0,59-0,83, p < 0.0001) und eine Verlängerung des progressionsfreien Überlebens um 1,4 Monate (2,8 Monate vs. 1,4 Monate, HR: 0,74; 95 % KI: 0,64-0,86, p < 0,0001) erreicht [865]. 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 behandlungsbedingte Todesfälle ein. In der deutschen Behandlungsrealität ist die Therapie-assoziierte Mortalität niedriger als in der Zulassungsstudie [874].

In der PROSELICA-Studie mit 1.200 Patienten wurde eine niedrigere Dosierung von 20mg/m2 mit der bislang empfohlenen Cabazitaxel-Dosierung von 25mg/ m2 randomisiert verglichen. Die Studie erreichte ihren primären Endpunkt und konnte zeigen, dass die niedrigere Dosierung weder bezüglich des Gesamtüberlebens noch bezüglich des progressionsfreien Überlebens unterlegen ist. Gleichzeitig wies die reduzierte Dosierung von 20mg/ m2 ein deutlich günstigeres Nebenwirkungsprofil als die bislang eingesetzte Standarddosierung auf. So konnte insbesondere die Rate febriler Neutropenien deutlich gesenkt werden (2,1 % vs. 9,2 %). Ebenso wurden deutlich weniger Hämaturie, Diarrhoe und Fatigue beobachtet [875]. Beim Einsatz von Cabazitaxel ist ein sorgfältiges Monitoring und Erfahrung im Umgang mit Chemotherapien unerlässlich. Eine Verabreichung von Cabazitaxel erfolgt nur durch erfahrene Ärzte, wobei ein sorgfältiges Monitoring unerlässlich ist. Cabazitaxel ist zugelassen in Kombination mit Prednison oder Prednisolon zur Behandlung von Patienten mit hormonrefraktärem metastasiertem Prostatakarzinom, die mit einem Docetaxel-basierten Therapieschema vorbehandelt sind [876].

In der CARD-Studie wurden insgesamt 255 Patienten randomisiert mit Cabazitaxel 25mg/m2 alle drei Wochen oder Abirateron (+ Prednion/ Prednisolon) bzw. Enzalutamid behandelt [852]. Voraussetzung für den Einschluss in die Studie war eine Vortherapie mit Docetaxel und dem jeweils anderen AR-gerichteten Medikament mit einer Ansprechdauer von weniger als 12 Monaten [852]. Die Cabazitaxel-Therapie führte

zu einer Verlängerung der medianen Gesamtüberlebenszeit mit 13,6 Monaten versus 11 Monaten unter dem zweiten AR-gerichteten Medikament (HR 0.64; p=0,008) [852]. Auch die mediane Zeit bis zum radiologischen Progress (8,8 vs. 4,4 Monate; HR 0,54; p<0,001) und das progressionsfreie Überleben (4,4 vs. 2,7 Monate; HR 0,52; p<0,001) wurde durch Cabazitaxel signifikant verlängert [852]. In einer zusätzlich durchgeführten posthoc Analyse wurde der Einfluss des jeweils eingesetzten AR-Medikaments auf die Studienergebnisse untersucht. Der Vorteil von Cabazitaxel blieb jedoch unabhängig davon bestehen, ob die Patienten als zweites orales Therapeutikum Abirateron (HR 0,44) oder Enzalutamid (HR 0,57) erhielten.

Zu Empfehlung 7.49

Das radioaktive Nuklid Radium-223 ist ein Alpha-Strahler mit einer sehr kurzen Reichweite. Radium-223 war in der europäischen Union im November 2013 für die Therapie von Patienten mit kastrationsresistentem, ossär metastasiertem Prostatakarzinom ohne Hinweis auf bekannte viszerale Metastasierung zugelassen worden. Aufgrund von Sicherheitsbedenken wurde die Zulassung im Juli 2018 begrenzt auf Patienten mit metastasiertem Prostatakarzinom (Metastasen im Knochen ohne bekannte viszerale Metastasen), die bereits zwei andere vorherige Therapieoptionen erhielten sowie Patienten, die keine anderen systemischen Therapieoptionen erhalten können. Aufgrund von Hinweisen auf ein erhöhtes Frakturrisikos in der Kombinationstherapie wurde empfohlen, Radium-223 nicht in Kombination mit Abirateron plus Prednison/Prednisolon einzusetzen [877,878].

Diese Einschränkung der Zulassung ist aufgrund der Sicherheitsbedenken nachvollziehbar. Sie definiert jetzt aber Indikationen für den Einsatz, für die es keine explizite Zulassungsstudie gibt. Basis der Zulassung von 2013 war ALSYMPCA, eine internationale, multizentrische, randomisierte, Placebo-kontrollierte Phase-III-Studie mit 921 Patienten [851]. Die Patienten waren 2:1 zugunsten des Verum-Arms randomisiert worden. Die Verlängerung der Gesamtüberlebenszeit war primärer Studienpunkt von ALSYMPCA. Radium-223 führte zu einer signifikanten Verlängerung der medianen Überlebenszeit von 14,9 vs. 11,3 Monaten (HR 0,70; p<0,001) [851]. Bei Gabe von Radium-223 ab der Drittlinientherapie war der Median der Überlebenszeit in Registeranalysen sehr ähnlich und lag zwischen 10,9 – 11,1 Monaten [879].

Radium-223 führte in ALSYMPCA auch zur Verlängerung der Zeit bis zum Auftreten belastender Komplikationen. Die Rate schwerer Nebenwirkungen im CTCAE Grad 3/4 lag unter Radium-223 bei 58 % vs. 65 % im Placebo-Arm. Nur Thrombozytopenien traten mit 7% häufiger unter Radium-223 als in der Kontrolle auf [870].

Einer der Gründe der Zulassungseinschränkung durch die EMA waren Daten von ERA-223, einer randomisierten, doppelblinden, Placebo-kontrollierten Studie bei 806 Chemotherapie-naiven Patienten mit progredientem, kastrationsresistentem, asymptomatischem oder gering symptomatischem Prostatakarzinom. Verglichen wurde Abirateron (plus Prednison/Prednisolon) + Radium-223 versus Abirateron (plus Prednison/Prednisolon). Primärer Endpunkt war „symptomatic skeletal event-free survival“, definiert als ossäre Ereignisse oder Tod. Das Studienziel wurde nicht erreicht. Frakturen traten bei 29% der Patienten im Radium-223- und bei 11 % im Kontrollarm auf [877,878].

Radium-223 ist weiterhin eine Therapieoption bei Patienten mit symptomatischen ossären Metastasen ohne Nachweis viszeraler Metastasen. Ausdrücklich wird auf die weiteren Optionen der supportiven Therapie bei ossären Metastasen einschließlich lokaler Maßnahmen wie der Strahlentherapie und der systemischen Gabe von Bisphosphonaten oder Denosumab hingewiesen [866–868]. Die Publikation weiterer Daten zur Kombination von Radium-223 mit neuen Formen der Hormontherapie stehen aus [880].

Zu Empfehlung 7.50

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

Patienten mit kastrationsresistentem Prostatakarzinom befinden sich in einem fortgeschrittenen Stadium ihrer Erkrankung. Sie sind oft von Symptomen und psychosozialen Belastungen betroffen, die durch eine niedrigschwellige palliativmedizinische Mitbetreuung positiv beeinflusst werden können [881] (siehe auch Empfehlung 7.71 sowie https://www.leitlinienprogramm-onkologie.de/leitlinien/palliativmedizin/).

Zu Empfehlung 7.51

Mit 177Lu-PSMA-Liganden findet sich ein neuer Ansatz zur Radionuklid-Therapie in der klinischen Erprobung [882]. In einer Übersichtsarbeit von 2019 wurden Ergebnisse von 671 Patienten aus 16 Studien zusammengefasst. Dabei zeigte sich bei 75 % der Patienten unter 177Lu-PSMA ein Rückgang des PSA-Wertes [873]. Diese wurde auch in der offenen, randomisierten Phase-II-Studie TheraP zum Vergleich von 177Lu-PSMA versus Cabazitaxel bestätigt. In die Studie eingeschlossen werden konnten dabei nur Patienten mit einem PSA-Wert > 20ng/ml und einer PSMA-positiven Erkrankung im PSMA-PET-CT. Nicht eingeschlossen werden konnten dagegen Patienten, die in einem zusätzlich durchgeführten FDG-PET-CT FDG-positive Metastasen ohne PSMA-Positivität aufwiesen. In dieser selektionierten Patientengruppe war die Rate von Patienten mit einem Rückgang des PSA-Wertes um >50 % signifikant höher unter 177Lu-PSMA mit 65 vs. 37 % signifikant höher als unter Cabazitaxel. Ergebnisse zu patientenrelevanten Endpunkten stehen aus [883].

Nebenwirkungen von 177Lu-PSMA-Liganden sind hämatologisch (Anämie, Thrombozytopenie, Leukozytopenie), renal und betreffen die Speicheldrüsen. 177Lu-PSMA ist bisher nicht als Arzneimittel zugelassen.

Patienten mit kastrationsresistentem Prostatakarzinom befinden sich in einem fortgeschrittenen Stadium ihrer Erkrankung. Insbesondere Patienten mit reduziertem ECOG-Status aufgrund der Grundkrankheit, aber auch aufgrund von Komorbidität leiden oft unter Symptomen und psychosozialen Belastungen, die durch eine niedrigschwellige palliativmedizinische Mitbetreuung positiv beeinflusst werden können [881] (siehe auch Empfehlung 7.71 sowie https://www.leitlinienprogramm-onkologie.de/leitlinien/palliativmedizin/).

7.4.2.5. Therapiesequenz nach Androgenrezeptor-gerichteter Behandlung

Nr.	Empfehlungen/Statements	EG	LoE	Quellen
7.52.	Patienten mit kastrationsresistenter, progredienter Erkrankung und gutem Allgemeinzustand nach Androgenrezeptor-gerichteter Therapie kann eine Sequenztherapie unter Verwendung eines der anderen wirksamen Arzneimittel (siehe Empfehlung 7.46.) angeboten werden.	0	4	EK

Hintergrundinformationen Zu Empfehlung 7.52

Die Sequenztherapie nach Androgenrezeptor-gerichteter Behandlung ist in kurzer Zeit zur täglichen Praxis geworden. Inzwischen liegen erste Daten zum Einfluss des sequenziellen Einsatzes von Abirateron, Enzalutamid, Cabazitaxel und u. a. vor [853,854,852]. Derzeit kann nicht abschließend beurteilt werden, ob eine zweite Androgenrezeptor-gerichtete Behandlung nach Progress unter der Erstlinienbehandlung mit dem jeweils anderen Wirkstoff möglicherweise weniger effektiv ist als eine Chemotherapie in der Zweitlinie. Festzuhalten ist allerdings, dass in den bislang vorliegenden retrospektiven Studien mit Enzalutamid nach Abirateron ein geringeres PSA-Ansprechen erzielt wird als in einer früheren Therapielinie [884]. Ähnliches scheint für Abirateron nach Enzalutamid zu gelten. Ursachen für diese mögliche Kreuzresistenz sind Gegenstand aktueller Untersuchungen (Vgl. Empfehlung 7.43).

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

Von den verschiedenen medikamentösen Optionen für die androgenunabhängige bzw. kastrationsresistente klinische Situation ist für Prednisolon nicht nur ein Ansprechen des PSA-Verlaufs und damit möglicherweise der klinischen Progression, sondern auch eine positive Beeinflussung der patientenrelevanten Endpunkte Schmerz, Appetitlosigkeit, Müdigkeit und allgemeine Lebensqualität nachgewiesen, die in der palliativen Therapiesituation von herausragender Bedeutung sind [885]. Deshalb wurde Prednisolon bei symptomatischen Patienten im Rahmen dieser Leitlinie eine prominente Stellung

zuerkannt. Dies deckt sich mit der Einschätzung der niederländischen Leitlinie. Auch für die niedrig dosierte Gabe von Dexamethason (0,5 mg/Tag) wurde ein Absinken des PSA-Wertes bei ca. 50 % (49/102) der untersuchten Patienten beschrieben [886]. Da eine vergleichende Studie für die Wirksamkeit der verschiedenen Steroide nicht vorliegt, sind in der Empfehlung alle drei derzeit eingesetzten Substanzen genannt.

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EAU - EANM -ESTRO - ESUR -ISUP - SIOG guidelines on prostate cancer

Zielsetzung/Fragestellung

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

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft zu;

- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- For the 2023 PCa Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A number of comprehensive searches were performd, covering all sections of the PCa Guidelines. The search was limited to English language publications. Databases searched included Medline, EMBASE and the Cochrane Libraries, covering a time frame between May 1st 2021 and April 1st 2022.

LoE

Table 4. EAU Guideline's levels of evidence

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

GoR

- GRADE

Empfehlungen

6.5.16 Guidelines for systematic treatments of castrate-resistant disease

6.5.13 ***Guidelines for systematic treatments of castrate-resistant disease***

Recommendations	Strength rating
Base the choice of treatment on the performance status (PS), symptoms, co-morbidities, location and extent of disease, genomic profile, patient preference, and on previous treatment for hormone-sensitive metastatic PCa (mHSPC) (alphabetical order: abiraterone, cabazitaxel, docetaxel, enzalutamide, olaparib, radium-223, sipuleucel-T).	Strong
Offer patients with mCRPC who are candidates for cytotoxic therapy and are chemotherapy naiive docetaxel with 75 mg/m^2 every 3 weeks.	Strong
Offer patients with mCRPC and progression following docetaxel chemotherapy further life-prolonging treatment options, which include abiraterone, cabazitaxel, enzalutamide, radium-223 and olaparib in case of DNA homologous recombination repair (HRR) alterations.	Strong
Base further treatment decisions of mCRPC on PS, previous treatments, symptoms, co-morbidities, genomic profile, extent of disease and patient preference.	Strong
Offer abiraterone or enzalutamide to patients previously treated with one or two lines of chemotherapy.	Strong
Avoid sequencing of androgen receptor targeted agents.	Weak
Offer chemotherapy to patients previously treated with abiraterone or enzalutamide.	Strong
Offer cabazitaxel to patients previously treated with docetaxel.	Strong
Offer cabazitaxel to patients previously treated with docetaxel and progressing within 12 months of treatment with abiraterone or enzalutamide.	Strong
Novel agents	
Offer poly(ADP-ribose) polymerase (PARP) inhibitors to pre-treated mCRPC patients with relevant DNA repair gene mutations.	Strong
Offer ^{177}Lu-PSMA-617 to pre-treated mCRPC patients with one or more metastatic lesions, highly expressing PSMA (exceeding the uptake in the liver) on the diagnostic radiolabelled PSMA PET/CT scan.	Strong

6.5.17 Guidelines for supportive care of castrate-resistant disease

These recommendations are in addition to appropriate systemic therapy.

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

Hintergrund zu 6.5 Treatment: Castration-resistant PCa (CRPC)

6.5.3 Treatment decisions and sequence of available options

Approved agents for the treatment of mCRPC in Europe are docetaxel, abiraterone/prednisolone, enzalutamide, cabazitaxel, olaparib and radium-223. In general, sequencing of ARPIs like abiraterone and enzalutamide is not recommended particularly if the time of response to ADT and to the first ARPI was short (< 12 months) and high-risk features of rapid progression are present (see detailed discussion in Section 6.5.7) [1169, 1170].

6.5.6 First-line treatment of metastatic CRPC

- 6.5.6.1 Abiraterone

  - Abiraterone was evaluated in 1,088 chemo-naive, asymptomatic or mildly symptomatic mCRPC patients in the phase III COU-AA-302 trial. Patients were randomised to abiraterone acetate or placebo, both combined with prednisone [1182]. Patients with visceral metastases were excluded. The main stratification factors were ECOG PS 0 or 1 and asymptomatic or mildly symptomatic disease. Overall survival and rPFS were the co-primary endpoints. After a median follow-up of 22.2 months there was significant improvement of rPFS (median 16.5 vs. 8.2 months, HR: 0.52, $p < 0.001$) and the trial was unblinded. At the final analysis with a median follow-up of 49.2 months, the OS endpoint was significantly positive (34.7 vs. 30.3 months, HR: 0.81, 95% CI: 0.70–0.93, $p = 0.0033$) [1183]. Adverse events related to mineralocorticoid excess and liver function abnormalities were more frequent with abiraterone, but mostly grade 1–2. Subset analysis of this trial showed the drug to be equally effective in an elderly population (> 75 years) [1184].

- 6.5.6.2 Enzalutamide

  - A randomised phase III trial (PREVAIL) included a similar patient population and compared enzalutamide and placebo [1185]. Men with visceral metastases were eligible but the numbers included were small. Corticosteroids were allowed but not mandatory. PREVAIL was conducted in a chemo-naive mCRPC population of 1,717 men and showed a significant improvement in both co-primary endpoints, rPFS (HR: 0.186, CI: 0.15–0.23, $p < 0.0001$), and OS (HR: 0.706, CI: 0.6–0.84, $p < 0.001$). A > 50% decrease in PSA was seen in 78% of patients. The most common clinically relevant AEs were fatigue and hypertension. Enzalutamide was equally effective and well tolerated in men > 75 years [1186] as well as in those with or without visceral metastases [1187]. However, for men with liver metastases, there seemed to be no discernible benefit [1187, 1188].
  - Enzalutamide has also been compared with bicalutamide 50 mg/day in a randomised double-blind phase II study (TERRAIN) showing a significant improvement in PFS (15.7 months vs. 5.8 months, HR: 0.44, $p < 0.0001$) in favour of enzalutamide [1188]. With extended follow-up and final analysis the benefit in OS and rPFS were confirmed [1189].

- 6.5.6.3 Docetaxel

  - A statistically significant improvement in median survival of 2.0–2.9 months has been shown with docetaxelbased chemotherapy compared to mitoxantrone plus prednisone [1190, 1191]. The standard first-line chemotherapy is docetaxel 75 mg/m2, 3-weekly doses combined with prednisone 5 mg twice a day (BID), up to 10 cycles. Prednisone can be omitted if there are contra-indications or no major symptoms. The following independent prognostic factors: visceral metastases, pain, anaemia (Hb < 13 g/dL), bone scan progression, and prior estramustine may help stratify the response to docetaxel. Patients can be categorised into three risk groups: low risk (0 or 1 factor), intermediate (2 factors) and high risk (3 or 4 factors), and show three significantly different median OS estimates of 25.7, 18.7 and 12.8 months, respectively [1192].
  - Age by itself is not a contra-indication to docetaxel [1193] but attention must be paid to careful monitoring and co-morbidities as discussed in Section 5.4 - Estimating life expectancy and health status [1194]. In men with mCRPC who are thought to be unable to tolerate the standard dose and schedule, docetaxel 50 mg/m2 every two weeks seems to be well tolerated with less grade 3–4 AEs and a prolonged time to treatment failure [1195].

- 6.5.6.4 Sipuleucel-T

  - In 2010 a phase III trial of sipuleucel-T showed a survival benefit in 512 asymptomatic or minimally symptomatic mCRPC patients [1196]. After a median follow-up of 34 months, the median survival was 25.8 months in the sipuleucel-T group compared to 21.7 months in the placebo group, with a HR of 0.78 ($p = 0.03$). No PSA decline was observed and PFS was similar in both arms. The overall tolerance was very good, with more cytokine-related AEs grade 1–2 in the sipuleucel-T group, but the same grade 3–4 AEs in both arms. Sipuleucel-T is not available in Europe.

- 6.5.6.5 Ipatasertib

  - The AKT inhibitor ipatasertib in combination with AAP was studied in asymptomatic or mildly symptomatic patients with and without PTEN loss by IHC and previously untreated for mCRPC. The randomised phase III trial (IPAtential) showed a significant benefit for the first endpoint rPFS in the PTEN loss (IHC) 18.5 vs. 16.5 mo; $p = 0.0335$, HR: 0.77, 95% CI: 0.61–0,98) but not in the intention to treat (ITT) population. The OS results are still pending. Side effects of the AKT inhibitor ipatasertib include rash and diarrhoea [771]. Grade 3 or higher AEs occurred nearly double as often in the combination group and the discontinuation rate due to AEs was 4 times higher. This combination is still investigational [1197].

- 6.5.6.6 Combinations

- Based on the suggestion that there is a synergistic antitumour effect when combining abiraterone with a PARP inhibitor, several such combination trials were conducted with conflicting results.

- Abiraterone/prednisone plus olaparib

- A randomised double-blind, phase 3 trial (PROpel) of abiraterone (1000 mg once daily) plus prednisone 5 mg/ twice daily (AAP) and olaparib (300 mg twice/daily) or placebo in patients with mCRPC in the first-line setting was conducted [1198]. Of note, 796 patients met the eligibility criteria and were randomly assigned 1:1 to study treatment regardless of homologous recombination repair gene mutation (HRRm) status which was retrospectively evaluated and determined by tumour tissue and circulating tumour DNA tests. The primary end point was imaging-based PFS (ibPFS) by investigator assessment. The result was significantly positive in favour of the combination with ibPFS of 24.8 vs. 16.6 mo (HR 0.66; 95% CI: 0.54 to 0.81; p = 0.001). The subgroup of patients with positive HRRm status showed a HR of 0.50 (CI: 0.34 to 0.73) which seems to be a major driver of the overall result. Survival data are still immature. The most common side effects with the combination were anaemia, fatigue/asthenia, and nausea.

- Abiraterone/prednisone plus niraparib

- At ASCO 2022, a randomised, double-blind, phase 3 trial (MAGNITUDE) evaluating abiraterone (1,000 mg once daily) plus prednisone 5 mg twice/daily plus niraparib 200 mg once/daily or placebo, was presented [1199]. The final paper has not yet been published.

Table 6.5.2: Randomised phase III controlled trials - first-line treatment of mCRPC

Study	Intervention	Comparison	Selection criteria	Main outcomes
DOCETAXEL				
SWOG 99-16 2004 [1200]	docetaxel/EMP, every 3 weeks, 60 mg/m², EMP 3 x 280 mg/day	mitoxantrone, every 3 weeks, 12 mg/m² prednisone 5 mg BID		**OS: 17.52 vs. 15.6 mo.** (p = 0.02, HR: 0.80; 95% CI: 0.67-0.97) **PFS: 6.3 vs. 3.2 mo.** (p < 0.001)
TAX 327 2004, 2008 [1190,1201]	docetaxel, every 3 weeks, 75 mg/m² prednisone 5 mg BID or docetaxel, weekly, 30 mg/m² prednisone 5 mg BID	mitoxantrone, every 3 weeks, 12 mg/m², Prednisone 5 mg BID		**OS: 19.2 for 3 weekly vs. 17.8 mo. 4-weekly and 16.3 in the control group.** (p = 0.004, HR: 0.79, 95% CI: 0.67-0.93)
ABIRATERONE				
COU-AA-302 2013, 2014, 2015 [1182, 1183, 1202]	abiraterone + prednisone	placebo + prednisone	- No previous docetaxel. - ECOG 0-1. - PSA or radiographic progression. - No or mild symptoms. - No visceral metastases.	**OS: 34.7 vs. 30.3 mo.** (HR: 0.81, p = 0.0033). **FU: 49.2 mo. rPFS: 16.5 vs. 8.3 mo.** (p < 0.0001)
ENZALUTAMIDE				
PREVAIL 2014 [1185]	enzalutamide	placebo	- No previous docetaxel. - ECOG 0-1. - PSA or radiographic progression. - No or mild symptoms. - 10% had visceral mets.	**OS: 32.4 vs. 30.2 mo.** (p < 0.001). FU: 22 mo. (p < 0.001 HR: 0.71, 95% CI: 0.60-0.84) **rPFS: 20.0 mo. vs. 5.4 mo.** HR: 0.186 (95% CI: 0.15-0.23) p < 0.0001)

SIPULEUCEL-T				
IMPACT2010 [1196]	sipuleucel-T	placebo	- Some with previous docetaxel. - ECOG 0-1. - Asymptomatic or minimally symptomatic.	**OS: 25.8 vs. 21.7 mo.** (p = 0.03 HR: 0.78, 95% CI: 0.61-0.98). **FU: 34.1 mo. PFS: 3.7 vs. 3.6 mo.** (no difference)
2006 [1203]	sipuleucel-T	placebo	- ECOG 0-1. - No visceral met. - No corticosteroids.	**OS: 25.9 vs. 21.4 mo.** (p = 0.1). FU: 36 mo. **PFS: 11.7 vs. 10.0 wk.**
IPATASERTIB				
IPAtential150 2021 [1197]	ipatasertib (400 mg/d) + abiraterone (1000 mg/d) + prednisone (5 mg bid)	abiraterone + prednisolone + placebo	Previously untreated for mCRPC, asymptomatic/ mildly symptomatic, with and without PTEN loss by IHC	**rPFS in PTEN loss (IHC) population: 18.5 vs. 16.5 mo.** (p = 0.0335, HR: 0.77 95% CI: 0.61-0.98)
PROpel [1198]	olaparib (300mg BID) + abiraterone (1000 mg/d) + prednisone (5 mg BID)	placebo + abiraterone + prednisone	- ECOG 0-1. - regardless of HRRm (retrospective testing). - prior taxane for mHSPC allowed.	HR: 0.66; 95% CI: 0.54–0.81; (p = 0.001)

BID = twice a day; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; EMP = estramustine; FU = follow-up; HR = hazard ratio; mets. = metastases; mo = month; ib (imaging based); (r)PFS = (radiographic) progression-free survival; OS = overall survival; IHC = immunohistochemistry ; HRRm = homologour recombination repair genes mutation; ITT = intention to treat; BICR = blinded independent central review.

6.5.7 Second-line treatment for mCRPC and sequence

All patients who receive treatment for mCRPC will eventually progress. All treatment options in this setting are presented in Table 6.5.3. High-level evidence exists for second-line treatments after first-line treatment with docetaxel and for third-line therapy.

- 6.5.7.1 Cabazitaxel

  - Cabazitaxel is a novel taxane with activity in docetaxel-resistant cancers. It was studied in a large prospective, randomised, phase III trial (TROPIC) comparing cabazitaxel plus prednisone vs. mitoxantrone plus prednisone in 755 patients with mCRPC, who had progressed after or during docetaxel-based chemotherapy [1204].
  - Patients received a maximum of ten cycles of cabazitaxel (25 mg/m2) or mitoxantrone (12 mg/m2) plus prednisone (10 mg/day). Overall survival was the primary endpoint which was significantly longer with cabazitaxel (median: 15.1 vs. 12.7 months, p < 0.0001). There was also a significant improvement in PFS (median: 2.8 vs. 1.4 months, p < 0.0001), objective RECIST response (14.4% vs. 4.4%, p < 0.005), and PSA response rate (39.2% vs. 17.8%, p < 0.0002). Treatment-associated WHO grade 3‑4 AEs developed significantly more often in the cabazitaxel arm, particularly haematological (68.2% vs. 47.3%, p < 0.0002) but also non-haematological (57.4 vs. 39.8%, p < 0.0002) toxicity. In two post-marketing randomised phase III trials, cabazitaxel was shown not to be superior to docetaxel in the first-line setting; in the second-line setting in terms of OS, 20 mg/m2 cabazitaxel was not inferior to 25 mg/m2, but less toxic. Therefore, the lower dose should be preferred [1205, 1206]. Cabazitaxel should preferably be given with prophylactic granulocyte colonystimulating factor (G-CSF) and should be administered by physicians with expertise in handling neutropenia and sepsis [1207].

- 6.5.7.2 Abiraterone acetate after docetaxel

  - Positive results of the large phase III trial (COU-AA-301) were reported after a median follow-up of 12.8 months [1208] and confirmed by the final analysis [1209]. A total of 1,195 patients with mCRPC were randomised 2:1 to AAP or placebo plus prednisone. All patients had progressive disease based on the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria after docetaxel therapy (with a maximum of two previous chemotherapeutic regimens). The primary endpoint was OS, with a planned HR of 0.8 in favour of AAP. After a median follow-up of 20.2 months, the median survival in the AAP group was 15.8 months compared to 11.2 months in the placebo arm (HR: 0.74, p < 0.0001). The benefit was observed in all subgroups and all the secondary objectives were in favour of AAP (PSA, radiologic tissue response, time to PSA or objective progression). The incidence of the most common grade 3‑4 AEs did not differ significantly between arms, but mineralocorticoid-related side effects were more frequent in the AAP group, mainly grade 1‑2 (fluid retention, oedema and hypokalaemia).

- 6.5.7.3 Enzalutamide after docetaxel

- The planned interim analysis of the AFFIRM study was published in 2012 [1210]. This trial randomised 1,199 patients with mCRPC in a 2:1 fashion to enzalutamide or placebo. The patients had progressed after docetaxel treatment, according to the PCWG2 criteria. Corticosteroids were not mandatory, but could be prescribed, and were received by about 30% of the patients. The primary endpoint was OS, with an expected HR benefit of 0.76 in favour of enzalutamide. After a median follow-up of 14.4 months, the median survival in the enzalutamide group was 18.4 months compared to 13.6 months in the placebo arm (HR: 0.63, $p < 0.001$).
- This led to the recommendation to halt and unblind the study. The benefit was observed irrespective of age, baseline pain intensity, and type of progression. In the final analysis with longer follow-up the OS results were confirmed despite crossover and extensive post-progression therapies [1189]. Enzalutamide was active also in patients with visceral metastases.
- All the secondary objectives were in favour of enzalutamide (PSA, soft tissue response, QoL, time to PSA, or objective progression). No difference in terms of side effects was observed in the two groups, with a lower incidence of grade 3‑4 AEs in the enzalutamide arm. There was a 0.6% incidence of seizures in the enzalutamide group compared to none in the placebo arm.

- 6.5.7.4 Radium-223

- The only bone-specific drug that is associated with a survival benefit is the α-emitter radium-223. In a large phase III trial (ALSYMPCA) 921 patients with symptomatic mCRPC, who failed or were unfit for docetaxel, were randomised to six injections of 50 kBq/kg radium-223 or placebo plus SOC. The primary endpoint was OS. Radium-223 significantly improved median OS by 3.6 months (HR: 0.70, $p < 0.001$) and was also associated with prolonged time to first skeletal event, improvement in pain scores and improvement in QoL [1211]. The associated toxicity was mild and, apart from slightly more haematologic toxicity and diarrhoea with radium-223, which did not differ significantly from that in the placebo arm [1211]. Radium-223 was effective and safe whether or not patients were docetaxel pre-treated [1212]. Due to safety concerns, use of radium-223 was recently restricted to after docetaxel and at least one AR targeted agent [1213]. In particular, the use of radium-223 in combination with AAP showed significant safety risks related to fractures and more deaths. This was most striking in patients without the concurrent use of bone health agents [1214].

6.5.8 Treatment after docetaxel and one line of hormonal treatment for mCRPC

- 6.5.8.1 Hormonal treatment

- For men progressing quickly on AR targeted therapy (< 12 months) it is now clear that cabazitaxel is the treatment supported by the best data. The CARD trial, an open label randomised phase III trial, evaluated cabazitaxel after docetaxel and one line of ARPI (either AAP or enzalutamide) [1169]. It included patients progressing in less than 12 months on previous abiraterone or enzalutamide for mCRPC. Cabazitaxel more than doubled rPFS vs. another ARPI and reduced the risk of death by 36% vs. ARPI. The rPFS with cabazitaxel remained superior regardless of the ARPI sequence and if docetaxel was given before, or after, the first ARPI.
- The choice of further treatment after docetaxel and one line of HT for mCRPC is open for patients who have a > 12 months response to first-line abiraterone or enzalutamide for mCRPC [1215]. Either radium-223 or second-line chemotherapy (cabazitaxel) are reasonable options. In general, subsequent treatments in unselected patients are expected to have less benefit than with earlier use [1216, 1217] and there is evidence of cross-resistance between enzalutamide and abiraterone [1218, 1219].
- In this context, radioligand therapy has been discussed for many years. In pre-treated and highly selected patients, based on PSMA- and FDG PET scan results, 117Lu-PSMA-617 was compared with cabazitaxel in a randomised phase II trial. The primary endpoint PSA reduction > 50% was in favour of the radioligand therapy [1220]. Pivotal phase III data for 117Lu-PSMA-617 are discussed in Section 6.5.8.2.2.
- Poly (ADP-ribose) polymerase inhibitors have shown high rates of response in men with somatic homologous recombination repair (HRR) deficiency in initial studies. Men previously treated with both docetaxel and at least one ARPI and whose tumours demonstrated homozygous deletions or deleterious mutations in DNA-repair genes showed an 88% response rate to olaparib [1221] and in another confirmatory trial a confirmed composite response of 54.3% (95% CI: 39.0‑69.1) in the 400 mg cohort and in 18 of 46 (39.1%; 25.1‑54.6) evaluable patients in the 300 mg cohort [1222]. See also section ‘Second-line management’).

- **6.5.8.2 Radiopharmaceuticals**

- 6.5.8.2.1 Introduction

- Historically, several radiopharmaceuticals including phosphorous-32, strontium-89, yttrium-90, samarium-153, and rhenium-186 were developed for the treatment of bone pain secondary to metastasis from PCa [1223]. They proved effective in a palliation setting, by relieving pain and improving QoL, especially in the setting of diffuse bone metastases. However, they never gained widespread adoption. The first radioisotope to demonstrate a survival benefit was radium-223 (see Section 6.5.7.4).
- 6.5.8.2.2 PSMA-based therapy
- The increasing use of PSMA PET as a diagnostic tracer and the realisation that this allowed identification of a greater number of metastatic deposits led to attempts to treat cancer by replacing the imaging isotope with a therapeutic isotope which accumulates where the tumour is demonstrated (theranostics) [1224]. Therefore, after identification of the target, usually with diagnostic 68Gallium-labelled PSMA, therapeutic radiopharmaceuticals labelled with β(lutetium-177 or yttrium-90) or α(actinium-225)-emitting isotopes could be used to treat metastatic PCa.

The PSMA therapeutic radiopharmaceutical supported by the most robust data is 177Lu-PSMA-617. The first patient was treated in 2014 and early clinical studies evaluating the safety and efficacy of 177Lu-PSMA therapy have demonstrated promising results, despite the fact that a significant proportion of men had already progressed on multiple therapies [1225]. The early data were based on single-centre experience [1226]. Data from uncontrolled prospective phase II trials reported high response rates with low toxic effects [1227, 1228]. Positive signals are also coming from a randomised trial (TheraP) [1220]. In TheraP, a randomised phase II trial, patients for whom cabazitaxel was considered the next appropriate standard treatment after docetaxel and who were highly selected by 68Ga-PSMA-11 and 18FDG PET-CT scans, were randomised to receive 177Lu-PSMA-617 (6.0‑8.5 GBq intravenously every 6 weeks for up to 6 cycles) or cabazitaxel (20 mg/m2 for up to ten cycles). The primary endpoint was a reduction of at least 50% in PSA. The first endpoint was met (66% vs. 37% for 177Lu‑PSMA-617 vs. cabazitaxel, respectively, by ITT; difference 29% (95% CI: 16‑42; p < 0.0001; and 66% vs. 44% by treatment received; difference 23% [9‑37]; p = 0.0016) [1220].

- An open-label phase III trial (VISION) compared 177Lu‑PSMA-617 radioligand therapy with protocol-permitted SOC (i.e., excluded chemotherapy, immunotherapy, radium-223 and investigational drugs) in mCRPC patients, with PSMA expressing metastases on PET/CT, previously treated with at least one ARPI and one (around 53%) or two taxanes. Imaging-based PFS and OS were the alternate primary endpoints. More than 800 patients were randomised. 177Lu-PSMA-617 plus SOC significantly prolonged both imaging-based PFS and OS, as compared with SOC alone (see Table 6.5.3). Grade 3 or above AEs were higher with 177Lu-PSMA-617 than without (52.7% vs. 38.0%), but QoL was not adversely affected. 177Lu‑PSMA-617 has shown to be a valuable additional treatment option in this mCRPC population [1229].
- Recently, a systematic review and meta-analysis was updated, investigating the proportion of patients with any or more than 50% PSA decrease, and OS. The review, including 69 articles and a total of 4,157 patients, showed that patients treated with 177Lu‑PSMA 617 had a significantly higher response to therapy compared to controls, based on > 50% PSA decrease (OR = 5.33, 95% CI: 1.24‑22.90, p < 0.05). Meta-analysis revealed an OS of 0.26 according to pooled HRs for any PSA decline, which was significant after 177Lu‑PSMA-617 therapy (95% CI: 0.18‑0.37, p < 0.00001) and an OS of 0.52 for > 50% PSA decrease, also significant after radioligand (RLT) (95% CI: 0.40‑0.67, p < 0.00001) [1230].
- Currently, an increased interest for PSMA-targeted alpha therapy (225Ac-PSMA) is observed, due to the ability to deliver potent higher local radiation more selectively to cancer cells than PSMA-targeted beta therapy, while minimising unwanted damage to the surrounding normal tissues. Additionally, the intensive radiation to cancer cells results in more effective DNA strand breakage and reduces the development of treatment resistance. A meta-analysis, including 9 studies with 263 patients, investigated the therapeutic effects of 225Ac-PSMA RLT in patients with metastatic CRPC, pre-treated with chemotherapy, 177Lu-PSMA and/or radium-223. The pooled proportions of patients with more than 50% PSA decline and any PSA decline were 60.99% (95% CI: 54.92%‑ 66.83%) and 83.57% (95% CI: 78.62%‑87.77%), respectively. The estimated mean PFS and mean OS were 9.15 months (95% CI: 6.69‑11.03 months) and 11.77 months (95% CI: 9.51‑13.49 months), respectively. These findings suggests that 225Ac-PSMA RLT may be an effective treatment option for patients with mCRPC [1231]. Despite the encouraging therapeutic response and survival of patients who received 225Ac-PSMA RLT, major AEs like xerostomia and severe haematotoxicity have to be considered as possible reasons for dose reduction or discontinuation of the therapy.

- **6.5.8.3 PARP inhibitors for mCRPC**

- So far, two PARP inhibitors, olaparib and rucaparib, are licenced by the FDA (EMA only approved olaparib) and several other PARP inhibitors are under investigation (e.g., talazoparib, niraparib). A

randomised phase III trial (PROfound) compared the PARP inhibitor olaparib to an alternative ARPI in mCRPC with alterations in > 1 of any qualifying gene with a role in HRR and progression on an ARPI. Most patients were heavily pre-treated with 1‑2 chemotherapies and up to 2 ARPIs [1166, 1167]. Radiographic PFS by blinded independent central review in the BRCA1/2 or ATM mutated population (Cohort A) was the first endpoint and significantly favoured olaparib (HR: 0.49, 95% CI: 0.38‑0.63). The final results for OS demonstrated a significant improvement among men with BRCA1/2 or ATM mutations (Cohort A) (p = 0.0175; HR: 0.69, 95% CI: 0.50‑ 0.97). This was not significant in men with any (other) HRR alteration (Cohort B) (HR: 0.96, 95% CI: 0.63‑1.49). Of note, patients in the physician ' s choice of enzalutamide/abiraterone-arm who progressed, 66% (n = 86/131) crossed over to olaparib.

- The most common AEs were anaemia (46.1% vs. 15.4%), nausea (41.4% vs. 19.2%), decreased appetite (30.1% vs. 17.7%) and fatigue (26.2% vs. 20.8%) for olaparib vs. enzalutamide/abiraterone. Among patients receiving olaparib 16.4% discontinued treatment secondary to an AEs, compared to 8.5% of patients receiving enzalutamide/abiraterone. Interestingly, 4.3% of patients receiving olaparib had a pulmonary embolism, compared to 0.8% among those receiving enzalutamide/abiraterone, none of which were fatal. There were no reports of myelodysplastic syndrome or acute myeloid leukaemia. This is the first trial to show a benefit for genetic testing and precision medicine in mCRPC.
- The olaparib approval by the FDA is for patients with deleterious or suspected deleterious germline- or somatic HRR gene-mutated mCRPC, who have progressed following prior treatment with enzalutamide or abiraterone. The EMA approved olaparib for patients with BRCA1 and BRCA2 alterations [1232]. The recommended olaparib dose is 600 mg daily (300 mg taken orally twice daily), with or without food.
- Rucaparib has been approved by the FDA for patients with deleterious BRCA mutations (germline and/ or somatic) who have been treated with ARPI and a taxane-based chemotherapy [1233]. Approval was not based on OS data but on the results of the single-arm TRITON2 trial (NCT02952534). The confirmed ORR per independent radiology review in 62 patients with deleterious BRCA mutations was 43.5% (95% CI: 31‑57) [1234].

- **6.5.8.4 Sequencing treatment**

- 6.5.8.4.1 ARPI -> ARPI (chemotherapy-naive patients)
- The use of sequential ARPIs in mCRPC showed limited benefit in retrospective series as well as in one prospective trial [1235-1242]. In particular in patients who had a short response to the first ARPI for mCRPC (< 12 months), this sequence should be avoided because of known cross resistance and the availability of chemotherapy and PARP inhibitors (if a relevant mutation is present).
- In highly selected patients treated for more than 24 weeks with AAP, the sequence with enzalutamide showed some activity with a median rPFS of 8.1 months (95% CI: 6.1‑8.3) and an unconfirmed PSA response rate of 27% [1243]. In case the patient is unfit for chemotherapy and a PARP inhibitor, best supportive care should be considered in case no other appropriate treatment option is available (clinical trial or immunotherapy if MSI-high). An ARPI-ARPI sequence should never be the preferred option but might be considered in such patients if the PS still allows for active treatment and the potential side effects seem manageable.
- First prospective cross-over data on an ARPI-ARPI sequence [1235] and a systematic review and meta-analysis suggest that for the endpoints PFS and PSA PFS, but not for OS, abiraterone followed by enzalutamide is the preferred choice [1244].
- 6.5.8.4.2 ARPI -> PARP inhibitor/olaparib
- This sequence in patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC is supported by data from the randomised phase III PROfound trial [1167]. A subgroup of patients in this trial was pre-treated with one or two ARPIs and no chemotherapy (35%). The ARPI ‑ docetaxel – PARP inhibitor vs. ARPI ‑ PARP inhibitor - docetaxel sequences are still under investigation.
- 6.5.8.4.3 Docetaxel for mHSPC -> docetaxel rechallenge
- There is limited evidence for second- or third-line use of docetaxel after treatment with docetaxel for mHSPC. Docetaxel seems to be less active than ARPI at progression to mCRPC following docetaxel for mHSPC [1245].
- 6.5.8.4.4 ARPI -> docetaxel or docetaxel -> ARPI followed by PARP inhibitor
- Both olaparib and rucaparib are active in biomarker-selected mCRPC patients after ARPI and docetaxel in
- either sequence [1167, 1233].

- 6.5.8.4.5 ARPI before or after docetaxel
- There is level 1 evidence for both sequences (see Table 6.5.3).
- 6.5.8.4.6 ARPI -> docetaxel -> cabazitaxel or docetaxel -> ARPI -> cabazitaxel
- Both third-line treatment sequences are supported by level 1 evidence. Of note, there is high-level evidence favouring cabazitaxel vs. a second ARPI after docetaxel and one ARPI. CARD is the first prospective randomised phase III trial addressing this question (see Table 6.5.3) [1169].

Table 6.5.3: Randomised controlled phase II/III - second-line/third-line trials in mCRPC

Study	Intervention	Comparison	Selection criteria	Main outcomes
ABIRATERONE				
COU-AA-301 2012 [1209]	abiraterone + prednisone HR	placebo + prednisone	Previous docetaxel. ECOG 0-2. PSA or radiographic progression.	**OS: 15.8 vs. 11.2 mo.** (p < 0.0001, HR: 0.74, 95% CI: 0.64–0.86; p < 0.0001). FU: 20.2 mo. **rPFS: no change**
COU-AA-301 2011 [1208]				**OS: 14.8 vs. 10.9 mo.** (p < 0.001 HR: 0.65; 95% CI: 0.54–0.77). FU: 12.8 mo. **rPFS: 5.6 vs. 3.6 mo.**
Radium-223				
ALSYMPCA 2013 [1211]	radium-223	placebo	Previous or no previous docetaxel. ECOG 0-2. Two or more symptomatic bone metastases. No visceral metastases.	**OS: 14.9 vs. 11.3 mo.** (p = 0.002, HR: 0.61; 95% CI: 0.46–0.81). All secondary endpoints show a benefit over best SOC.
CABAZITAXEL				
TROPIC 2013 [1246]	cabazitaxel + prednisone	mitoxantrone + prednisone	Previous docetaxel. ECOG 0-2.	**OS: 318/378 vs. 346/377 events** (OR: 2.11; 95% CI: 1.33–3.33). FU: 25.5 months OS ≥ 2 yr 27% vs. 16% PFS: -
TROPIC 2010 [1204]				**OS: 15.1 vs. 12.7 mo.** (p < 0.0001, HR: 0.70; 95% CI: 0.59–0.83). FU: 12.8 mo. PFS: 2.8 vs. 1.4 mo. (p < 0.0001, HR: 0.74, 95% CI: 0.64-0.86)
CARD 2019 [1169]	cabazitaxel (25 mg/m^2 Q3W) + prednisone + G-CSF	ARTA: abiraterone + prednisone OR enzalutamide	Previous docetaxel. Progression ≤ 12 mo. on prior alternative ARTA (either before or after docetaxel)	**Med OS 13.6 vs. 11.0 mo.** (p = 0.008, HR: 0.64, 95% CI: 0.46–0.89). **rPFS 8.0 vs. 3.7 mo.** (p < 0.001, HR: 0.54, 95% CI: 0.40–0.73). FU: 9.2 mo.
ENZALUTAMIDE				
AFFIRM 2012 [1210]	enzalutamide	placebo	Previous docetaxel. ECOG 0-2.	**OS: 18.4 vs. 13.6 mo.** (p < 0.001, HR: 0.63; 95% CI: 0.53–0.75). FU: 14.4 mo. **rPFS: 8.3 vs. 2.9 mo.** (HR: 0.40; 95% CI: 0.35–0.47, p < 0.0001).

PARP inhibitor				
PROfound 2020 [1166, 1167, 1247]	olaparib	abiraterone + prednisolone or enzalutamide; cross-over allowed at progression	Previous ARPI, alterations in HRR mutated genes	**rPFS: 7.39 vs. 3.55 mo.** ($p < 0.0001$, HR: 0.34; 95% CI: 0.25–0.47), conf. ORR 33.3% vs. 2.3% (OR 20.86, 95% CI: 4.18–379.18). **OS: 19.1 mo vs. 14.7 mo.** (in pts with *BRCA1/2, ATM* alterations) ($p = 0.0175$; HR 0.69, 95% CI: 0.5–0.97).
Radioligand therapy				
VISION 2021 [1229]	^{177}Lu-PSMA-617 SOC	SOC alone	Previous at least 1 ARPI and one or two taxane regimens; Mandatory: PSMA-positive gallium-68 (^{68}Ga)–labeled PSMA-PET scan	**Imaging-based PFS: 8.7 vs. 3.4 mo.** ($p < 0.001$; HR 0.40; 99.2% CI: 0.29–0.57) **OS: 15.3 vs. 11.3 mo.** ($p < 0.001$; HR 0.62; 95% CI: 0.5–0.74)
TheraP 2021 [1220, 1248]	^{177}Lu-PSMA-617 (8.5 GBq i.v.q 6-weekly, decreasing 0.5 GBq/cycle; up to 6 cycles)	^{177}Lu-PSMA-617 1:1 randomisation cabazitaxel (20 mg/m^2 i.v.q 3-weekly, up to 10 cycles)	mCRPC post docetaxel, suitable for cabaziaxel	**PSA reduction of > 50%:** 66 vs. 37 PSA responses; 66% vs. 37% by ITT; difference 29% (95% CI: 16–42; $p < 0.0001$; and 66% vs. 44% by treatment received; difference 23% [9–37]; $p = 0.0016$).

**Only studies reporting survival outcomes as primary endpoints have been included.*
ARPI = androgen receptor pathway inhibitor; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; FU = follow-up; GBq = gigabecquerel; HR = hazard ratio; Lu = lutetium; mo = months OS = overall survival; OR = odds ratio; ORR = objective response rate; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; (r)PFS = (radiographic) progression-free survival; SOC = standard of care; yr = year; HRR= homologous recombination repair.

- **6.5.8.5 Platinum chemotherapy**
  - Cisplatin or carboplatin as monotherapy or combinations have shown limited activity in unselected patients in the pre-docetaxel era [1249]. More recently, the combination of cabazitaxel and carboplatin was evaluated in pre-treated mCRPC patients in a randomised phase I/II trial. The combination improved the median PFS from 4.5 months (95% CI: 3.5‑5.7) to 7.3 months (95% CI: 5.5‑8.2; HR: 0.69, 95% CI: 0.50‑0.95, p = 0.018) and the combination was well tolerated [1250]. On a histopathological and molecular level, there is preliminary evidence that platinum adds efficacy in patients with aggressive variant PCa molecular signatures including TP53, RB1, and PTEN [1251].
  - Patients with mCRPC and alterations in DDR genes are more sensitive to platinum chemotherapy than unselected patients [1252], also after progression on PARP inhibitors. Interestingly, in contemporary retrospective series, unselected patients as well as patients without DDR gene alterations also showed a 50% PSA decline in up to 36% of patients [1253]. In view of the excellent tolerability of e.g., carboplatin monotherapy, platinum could be offered to patients with far advanced mCRPC harbouring DDR gene aberrations after having progressed on standard treatment options. Prospective controlled trials are ongoing.

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Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline PART II

Zielsetzung/Fragestellung

The summary presented herein represents Part II of the two-part series dedicated to Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline discussing prognostic and treatment recommendations for patients with castration-resistant disease.

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- The systematic review utilized to inform this guideline was conducted by an independent methodological consultant
- Ovid MEDLINE (1998 to January Week 5 2019), Cochrane Central Register of Controlled Trials (through December 2018), and Cochrane Database of Systematic Reviews (2005 through February 6, 2019). An updated search was conducted prior to publication through January 20, 2020

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Table 1: Strength of Evidence Definitions

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

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

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

Sonstige methodische Hinweise

- Formale Konsensusprozesse und externes Begutachtungsverfahren angegeben, können aber nicht überprüft werden

Empfehlungen

Metastatic Castration-Resistant Prostate Cancer

Treatment

27. In newly diagnosed mCRPC patients, clinicians should offer continued ADT with abiraterone acetate plus prednisone, docetaxel, or enzalutamide. (Strong Recommendation; Evidence Level: Grade A [abiraterone acetate plus prednisone and enzalutamide]/B [docetaxel])

Hintergrundinformation:
Abiraterone acetate plus prednisone, enzalutamide, and docetaxel chemotherapy all have an FDA indication for use in men with mCRPC. For each agent, there is a randomized clinical trial that shows a survival benefit for men with mCRPC. […]
Abiraterone Acetate
COU-AA-302 study, Ryan et al.[116]

COU-AA-301 trial, de Bono et al. [22]
Enzalutamide
PREVAIL study, Beer et al.[118]
AFFIRM study, Scher et al.[21]
Docetaxel
TAX-327 trial, Tannock et al.[19,119,20]
[…] The choice of initial treatment in this disease state should be driven by side effect profile and prior treatment. […] A second issue is prior treatment. All of the trials above were performed prior to studies demonstrating the efficacy of apalutamide, darolutamide, enzalutamide, abiraterone acetate, and docetaxel in mHSPC and nmCRPC disease states. As such, the choice of subsequent therapy should be influenced by prior therapy, and clinicians should favor treatments that have a different mechanism of action than what was used previously.

28. In mCRPC patients who are asymptomatic or minimally symptomatic, clinicians may offer sipuleucel-T. (Conditional Recommendation; Evidence Level: Grade B)

Sipuleucel-T is an 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,[23] published in 2010. […] Enrollment was restricted to patients with ECOG performance status scores of 0 or 1 who were asymptomatic or minimally symptomatic; patients with visceral metastases were excluded. As such, sipuleucel-T should only be considered for patients with asymptomatic or minimally symptomatic mCRPC. Sipuleucel-T is not associated with objective anti-tumor activity; its use is not appropriate for patients with large tumor burdens, those with visceral disease or with rapidly progressive disease. The use of sipuleucel-T immunotherapy is not recommended in symptomatic disease that necessitates opioid use, consistent with the FDA indication for this approach.

29. Clinicians should offer radium-223 to patients with symptoms from bony metastases from mCRPC and without known visceral disease or lymphadenopathy >3cm. (Strong Recommendation; Evidence Level: Grade B)

Radium-223 is an α-emitting radiopharmaceutical capable of inducing double strand DNA breaks in cancer cells while minimizing exposure to surrounding marrow […]. This is an appropriate treatment for patients with symptomatic bone pain and non-visceral metastases. A phase III trial[25] 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. […] As radium-223 targets bone only and is not associated with a PSA decline in a majority of patients, it is imperative for the clinician to carefully assess the patient on a monthly basis. Progression in non-bone sites is not infrequent during this six-month period of treatment. Given the lack of utility of PSA measurement in this space, the Panel recommends consideration to obtain abdomen/pelvis CT imaging and chest x-ray even in the absence of symptoms prior to cycle 4 (of planned 6 monthly cycles) to assess for occult disease progression. Clinicians should also be advised against concurrent use of abiraterone acetate plus prednisone in combination with radium-223 given the association with a higher risk of skeletal related events.[120]

30. In sequencing agents, clinicians should consider prior treatment and consider recommending therapy with an alternative mechanism of action. (Moderate Recommendation; Evidence Level: Grade B)

Optimal sequencing of agents in mCRPC remains an understudied area of research. As most of the agents approved for mCRPC were studied contemporaneously, the control arms typically were inactive agents such as prednisone or mitoxantrone. Furthermore, the only approved agent with a demonstrated survival benefit was docetaxel, so studies of abiraterone acetate and enzalutamide were done in patients either after or before exposure to docetaxel (e.g., COU-AA-301 and COU-AA-302, AFFIRM and PREVAIL, respectively).[21,22,116-118] One conclusion of these trials was that at least the next generation ART therapies abiraterone acetate and enzalutamide clearly have activity both before and after docetaxel chemotherapy. The largest trial evaluating the sequencing of two ART therapies was performed in Canada and was a randomized phase II trial evaluating the sequence of abiraterone acetate plus prednisone followed by enzalutamide (group A) versus the opposite sequence (group B).[121] […] This study suggests that abiraterone acetate plus prednisone followed by enzalutamide would be the favored sequence in mCRPC if both agents were used. In the Prophecy trial,[122] 118 men with mCRPC were enrolled who were starting abiraterone acetate or enzalutamide treatment. […] Men with AR-V7–positive mCRPC had fewer confirmed PSA responses (0% to 11%) or soft tissue responses (0% to 6%).

31. In mCRPC patients who received prior docetaxel chemotherapy with or without prior abiraterone acetate plus prednisone or enzalutamide for the treatment of CRPC, clinicians may offer cabazitaxel. (Conditional Recommendation; Evidence Level: Grade B)

32. In mCRPC patients who received prior docetaxel chemotherapy and abiraterone acetate plus prednisone or enzalutamide, clinicians should recommend cabazitaxel rather than an alternative androgen pathway directed therapy. (Strong Recommendation; Evidence Level: Grade B)

Cabazitaxel was approved as second-line chemotherapy in 2010 based on the results of the TROPIC trial.[14] TROPIC randomized 755 men with mCRPC who had previously received docetaxel chemotherapy and demonstrated median survival of 15.1 months in the cabazitaxel group and 12.7 months in the mitoxantrone group. The HR for death of men treated with cabazitaxel compared with those taking mitoxantrone was 0.70 (95% CI 0.59-0.83; p <0.0001).

Abiraterone acetate and enzalutamide were not available at the time of the TROPIC trial, so it is unknown if this would have influenced the positive outcomes seen in TROPIC.

Optimal third line therapy for mCRPC is unknown. The majority of patients will receive one ART with abiraterone acetate plus prednisone or enzalutamide and docetaxel chemotherapy. The CARD trial[32] tested the efficacy and safety of cabazitaxel versus the alternative ART therapy in patients with mCRPC who progressed after two prior therapies. A total of 255 patients were randomized, and progression or death was reported in 73.6% in the cabazitaxel group compared with 80.2% in the group that received a second ART (HR[0.54; 95% CI 0.40-0.73; p <0.001). The median OS was 13.6 months with cabazitaxel and 11.0 months with the androgen-signaling-targeted inhibitor (HR for death [0.64; 95% CI 0.46-0.89; p[0.008).

33. Clinicians should offer a PARP inhibitor to patients with deleterious or suspected deleterious germline or somatic homologous recombination repair gene-mutated mCRPC following prior treatment with enzalutamide or abiraterone acetate, and/or a taxane-based chemotherapy. Platinum based chemotherapy may be offered as an alternative for patients who cannot use or obtain a PARP inhibitor. (Moderate Recommendation; Evidence Level: Grade C)

In the randomized, open-label, phase 3 PROfound trial,[33] de Bono et al. randomly assigned 387 patients with progression on enzalutamide or abiraterone acetate (2:1) to receive olaparib or the physician's choice of enzalutamide or abiraterone acetate (control). All patients had a qualifying alteration in prespecified genes with a direct or indirect role in homologous recombination repair. Cohort A had at least one alteration in BRCA1, BRCA2, or ATM; cohort B had alterations in any of 12 other prespecified genes. Median OS in cohort A was 18.5 months with olaparib compared to 15.1 months in the control group. Investigators noted that anemia and nausea were the main toxic effects seen in patients on olaparib.

34. In patients with mismatch repair deficient or microsatellite instability high mCRPC, clinicians should offer pembrolizumab. (Moderate Recommendation; Evidence Level: Grade C)

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Canadian Urological Association (CUA)-Canadian Uro Oncology Group (CUOG) guideline

Management of castration-resistant prostate cancer (CRPC)

Zielsetzung/Fragestellung

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

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

LoE/GoR

- Wherever Level 1 evidence is lacking, the guideline attempts to provide expert opinion to aid in the management of patients.
- Levels of evidence and grades of recommendation employ the International Consultation on Urologic Disease (ICUD)/WHO modified Oxford Center for

Evidence-Based Medicine grading system. Based on a modified GRADE methodology,

- The strength of each recommendation is represented by the words STRONG or WEAK.
- Grading: ICUD https://onlinelibrary.wiley.com/doi/epdf/10.1002/nau.20845

  - Level 1 evidence (incorporates Oxford 1a, 1b) usually involves meta-analysis of trials (RCTs) or a good quality randomized controlled trial, or ‘‘all or none’’ studies in which no treatment is not an option, for example, in vesicovaginal fistula.
  - Level 2 evidence (incorporates Oxford 2a, 2b, and 2c) includes‘‘low’’ quality RCT (e.g., <80% follow-up) or meta-analysis (with homogeneity) of good quality prospective ‘‘cohort studies.’’ These may include a single group when individuals who develop the condition are compared with others from within the original cohort group. There can be parallel cohorts, where those with the condition in the first group are compared with those in the second group.
  - Level 3 evidence (incorporates Oxford 3a, 3b, and 4) includes:
    - Good quality retrospective ‘‘case–control studies’’ where a group of patients who have a condition are matched appropriately (e.g., for age, sex, etc.) with control individuals who do not have the condition.
    - Good quality ‘‘case series’’ where a complete group of patients all, with the same condition/disease/therapeutic intervention, are described, without a comparison control group.
  - Level 4 evidence (incorporates Oxford 4) includes expert opinion where the opinion is based not on evidence but on ‘‘first principles’’ (e.g., physiological or anatomical) or bench esearch. The Delphi process can be used to give ‘‘expert opinion’’ greater authority. In the Delphi process a series of questions are posed to a panel; the answers are collected into a series of ‘‘options’’; the options are serially ranked; if a 75% agreement is reached then a Delphi consensus statement can be made

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

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

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

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

Sonstige methodische Hinweise

- Rückfrage an Leitlinienansprechpartner ohne Antwort:
  - Keine Hinweise zu Gremium,
  - Keine Hinweise auf Suchzeitraum

Empfehlungen

Treatment of mCRPC

I. AR signaling therapeutic options

Abiraterone acetate

In the chemo-naive setting:

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

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

In the post-docetaxel setting:

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

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

Enzalutamide

In the chemo-naive setting:

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

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

In the post-docetaxel setting:

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

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

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

II. Chemotherapy

First-line systemic chemotherapy

Docetaxel

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

Hintergrund: The TAX-327 study randomized 1006 patients to one of three treatment arms: 1) docetaxel 75 mg/m2 IV every three weeks; 2) docetaxel 30 mg/m2 weekly for five of six weeks; or 3) control therapy with mitoxantrone.[19] The study report-ed improved survival with docetaxel (every three weeks) compared with mitoxantrone-prednisone (median survival 18.9 vs. 16.5 months; HR 0.76; 95% CI 0.62–0.94; two-sided p=0.009). No OS benefit was observed with docetaxel given on a weekly schedule (HR 0.91; 95% CI 0.75–1.11; two-sided p=0.36). Significantly, more patients treated with docetaxel (every three weeks) achieved a pain response compared with patients receiving mitoxantrone (35% vs. 22%; p=0.01). Quality of life response, defined as a sus-tained 16-point or greater improvement from baseline on two consecutive measurements, was higher with docetaxel given every three weeks (22% vs. 13%; p=0.009) or weekly (23% vs. 13%; p=0.005) compared with mitoxantrone. PSA response rates were also statistically significantly higher with docetaxel compared to mitoxantrone.[19] Although patients received up to 10 cycles of treatment if no progression and no prohibitive toxicities were noted, the duration of therapy should be based on the assessment of benefit and toxicities. Rising PSA alone should not be used as the sole criteria for progression; assessment of response should incorporate clinical and radiographic criteria.

- Recommendation: Alternative therapies that have not demonstrated improvement in OS but can provide disease control, palliation, and improve quality of life include weekly docetaxel plus prednisone, and mitoxantrone plus prednisone **(Level 2, Weak recommendation**).
- Recommendation: The timing of docetaxel therapy in men with evidence of metastases but without symptoms should be discussed with patients, and therapy should be individualized based on patients' clinical status and preferences (**Level 3, Weak recommendation**).
- Recommendation: Patients who do not respond to first-line ADT or who progress clinically or radiologically without significant PSA elevations may have neuroendocrine differentiation. Biopsy of accessible lesions should be considered to identify these patients; these patients should then be treated with combination chemotherapy, such as cisplatin/etoposide or carbo-platin/etoposide (**Level 3, Weak recommendation**).

III. Bone-targeted therapy

Life-prolonging therapy

Radium-223

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

Hintergrund: Radium-223 (previously known as alpharadin) is an intravenous alpha-emitting agent that mimics calcium, preferentially targeting bone metastases. In a random-ized, phase 3 study, radium-223 given every four weeks for six cycles was compared to placebo.20 Radium-223 demonstrated a significant improvement in OS and symp-tomatic SREs. OS was improved by 3.6 months (HR 0.7; p<0.0001) and symptomatic SREs were delayed by 5.8 months (p<0.0001). The study included patients with symptomatic bone metastases who were post-docetaxel or ineligible for docetaxel.[24] The study excluded patients with visceral metastases or lymph node metastases greater than 3 cm. PSA measurements while receiving

radium-223 cannot provide evidence of whether patients are benefitting or not. Given the mechanism of action of the drug, alka-line phosphatase appears to be better marker of activity. A phase 3 study in the first-line mCRPC setting compared radium-223 in combination with abiraterone/prednisone vs. abiraterone/prednisone alone and demonstrated no advantage and an increased risk of fractures.[25]

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

Zusammenfassung:

2021 CUA-CUOG CRPC guideline summary

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

Androgen deprivation therapy

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

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

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

III. mCRPC with moderate or severe symptoms

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

IV. mCRPC who progress after docetaxel-based chemotherapy

Options with survival benefit

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

Options with unknown survival benefit

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

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

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

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

1. **Olaparib 300 mg BID**

Referenzen aus Leitlinien

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Alberta Health Services, 2022 [1].

Advanced/ Metastatic Prostate Cancer. *CLINICAL PRACTICE GUIDELINE GU-010 Version 3*

Leitlinienorganisation/Fragestellung

- 2. How should advanced/ metastatic prostate cancer be treated?
- 3. 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, aber keine Patientenvertreter*innen; This guideline was reviewed and endorsed by the Alberta GUTumour Team. Members include surgical oncologists, radiation oncologists, medical oncologists, nurses, pathologists, and pharmacists.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse (Delphi Prozess) und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- For the 2021 guideline update, selected phase III trials were reviewed by the Alberta GU Tumour group (summarized in Appendix A).
- For the 2020 guideline update, selected phase III trials were reviewed by the Alberta GU Tumour group (summarized in table 3 and 4)
- 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.

Table 3. Resources for Search of Published Guidelines

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

Table 4. Resources for Search of Primary Literature

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

LoE/GoR

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

Table 5. Levels of Evidence

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

- Formulating and Rating the Recommendations: The Working Group members formulate the guideline recommendations based on existing published guidelines and the evidence synthesized by the KMS blended with expert clinical experience and local context. They may decide to adopt the recommendations of another institution without any revisions, adapt the recommendations of another institution with revisions, or develop their ownrecommendations; this decision may be based on the guideline questions, as well as the volume, quality, relevance, and novelty of existing guidelines. Beginning in late 2019, ratings of the strength of the recommendations will be included in all newly developed or updated CPGs, to better align with the standards outlined by the Institute

of Medicine.2 These ratings take into consideration the description of known benefits and possible harms, the available evidence and confidence in the quality and consistency of this evidence, and a discussion of the role of clinical experience, values and opinions of the Working Group members. The strength of the recommendations is rated by the Working Group members according to the criteria in Table 6

Table 6. Strength of Recommendations

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

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

Empfehlungen

Management of M+ Castrate Resistant Prostate Cancer (mCRPC)

1. All patients with mCRPC should be considered for novel anti-androgen therapy (abiraterone/prednisone or 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. Following an androgen receptor axis targeted therapy (ARAT) (eg: , ARAT in the mCSPC setting) subsequent ARAT is discouraged, and taxane based chemotherapy should be strongly considered. Genetic testing for BRCA1/2 or ATM alterations following AR targeted therapy may also be considered, although testing is not yet standard of care and only available via patient pay programs. Genetic testing may have prognostic, therapeutic and familial screening implications, and special access to Poly ADP ribose Polymerase (PARP) inhibitor after treatment with an ARAT at any point of advanced prostate cancer management may be obtained if BRCA1/2 or ATM gene alteration is identified. Discussion at multi-disciplinary rounds is encouraged.

A. 1st line options:

i. Abiraterone acetate 1000 mg oral daily in combination with prednisone 5 mg oral twice daily (COUGAR 302) can be used prior to docetaxel.[23, 24]

ii. Docetaxel 75mg/m$_2$ IV every 3 weeks in combination with prednisone at a dose of 5 mg twice daily.

iii. Enzalutamide 160mg oral daily can be used prior to docetaxel (PREVAIL).[25]

B. 2nd line options:

i. Post progression on docetaxel chemotherapy:

a. Abiraterone acetate26 or enzalutamide.[27]

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

• 20 mg or 25 mg can be considered, as the PROSELICA trial.[28] demonstrated that 20 mg dose was non-inferior to the 25 mg dose and was associated with decreased toxicity.

c. Radium 223 is not funded or available in Alberta. Radium 223 can be given to patients with symptomatic bony metastatic CRPC without visceral metastases (ALSYMPCA).[29, 30] 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.

ii. Post progression on Abiraterone, apalutamide, darolutamide or Enzalutamide.

a. Docetaxel chemotherapy.

b. Olaparib - for patients with BRCA1/2 or ATM alterations. (Not publicly funded, special access program required).[31]

C. Subsequent lines:

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

ii. Optimal sequencing of these agents is unknown.

a. If a patient has already received docetaxel and one ARAT, the CARD trial would suggest that cabazitaxel would be the preferred subsequent agent provided the patient is medically fit for therapy.[32]

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

D. Bone targeted therapy:

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

3. Palliative Radiotherapy

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

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[26, 36]	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[23, 24]	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[25]	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[27, 37]	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[38-40]	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)

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Puente J et al., 2020 [11].

Expert recommendations on the management of patients with metastatic castration-resistant prostate cancer who progress after CHAARTED or LATITUDE

Zielsetzung/Fragestellung

In 2018, there was no robust evidence to define the best next step for patients progressing to the castration-resistant state after ADT plus DOC (CHAARTED) or ABI (LATITUTE). Therefore, the aim of this document is to provide practical recommendations for the management of patients in this setting. These recommendations are based on the available evidence and experience of a panel of prostate cancer experts, covering common clinical scenarios and the characteristics of patients attended in daily practice.

Methodik

Grundlage der Leitlinie

- Repräsentativität des Gremiums wahrscheinlich nicht gegeben (am Delphi-Prozess nahmen 24 Onkologen mit Erfahrung in der Behandlung von Patienten mit

Prostatakrebs teil, eine Beteiligung weitere Fachrichtungen sowie Patientenvertreter ist nicht ersichtlich);

- Interessenkonflikte dargelegt, LL gesponsert von Sanofi;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse dargelegt; kein externes Begutachtungsverfahren;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt; aufgrund fehlender Evidenz wurden viele Empfehlungen auf Basis von Exptertenkonsens getroffen
- Keine Angaben zur regelmäßigen Überprüfung der Aktualität.

Recherche/Suchzeitraum:

- Studies were identified by sensitive search strategies in the main bibliographic. The following bibliographic databases were screened: Medline and Embase from 1961 to 11 January 2018, and Cochrane Central register of Controlled Trials (CENTRAL) up to 11 January 2018.
- The abstracts of the scientific meetings of the American Society of Oncology (ASCO/ASCOGU; 2017, 2018) and European Society for Medical Oncology (ESMO; 2016, 2017) were similarly examined through simple keywords in the organizations' websites.

LoE / GoR

- For each recommendation, the level of evidence (LE) and grade of recommendations (GR) were applied according to the Oxford Centre for Evidence Based Medicine Guidelines.

Empfehlungen

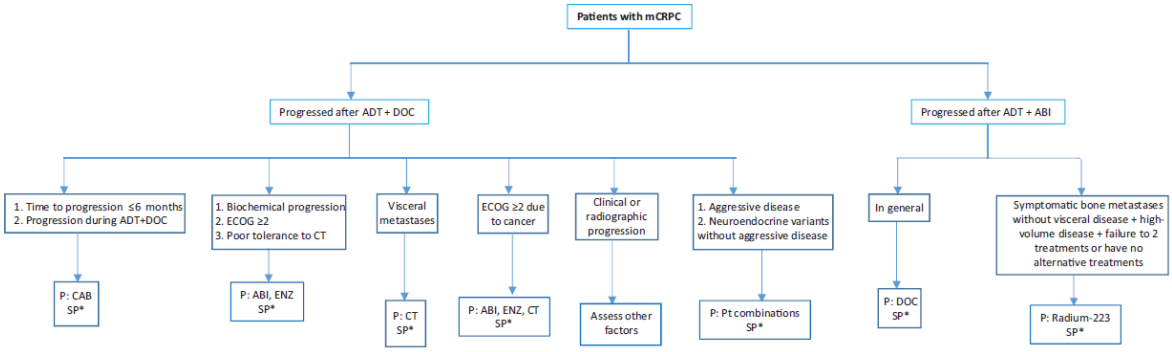

Figure 1. Treatment algorithm for patients with mCRPC upon DOC or ABI plus ADT (1st line) in metastatic prostate cancer.
ABI, abiraterone acetate; ADT, androgen-deprivation therapy; CAB, cabazitaxel; CT, Chemotherapy; DOC, docetaxel; ECOG, Eastern Cooperative Oncology Group performance status; mCRPC, metastatic castration-resistant prostate cancer; P, preferable; PT, platinum; SP, special profiles.
*Check within the main test the treatment options according to other patients or disease particular characteristics.

Recommendation 1. In patients with mCRPC who have progressed after ADT+DOC treatment (1st line) and present a time-to-progression up to 6 months from the last cycle of DOC, the panel considers CAB to be preferable (LE 4; GR D; LA 90%).

The panel considers it important to highlight that time-to-progression is an essential factor to consider. Although it is not possible to establish what this time should be, 6 months seem to be an acceptable cut-off. A small case series supports the use of CAB if the time-to-progression is less than 6 months following upfront DOC.[17] In any case, close monitoring is highly recommended.
There are factors that must similarly be considered, such as previous toxicity of chemotherapy and the patient's health status. For example, for patients with poor chemotherapy tolerance, ABI or ENZ should be considered. These drugs have shown benefits in a small-sized case series of patients who progressed after ADT+DOC treatment.[18]

Similarly, for patients who develop asymptomatic or PSA-only progression, ABI or ENZ are alternative options, …

Recommendation 2. In patients with mCRPC who have progressed during treatment withADT+DOC (1st line), the panel considers CAB to be preferable (LE 5; GR D; LA 90%).

Considering the rapid progression during ADT, it could be assumed or should be borne in mind that these patients will not respond as expected to second-generation antihormonal drugs. Although more studies are required to confirm this, CAB can be beneficial in patients with rapid progression during DOC.[17,19]

Recommendation 3. In patients with mCRPC who have progressed after ADT+DOC treatment (1st line) yet only present biochemical progression, the panel considers ABI or ENZ (LE 5; GR D; LA 75%) to be preferable.

The COU-AA-3013,[20] and AFFIRM trials[21] evaluated the efficacy and safety of ABI and ENZ versus placebo in patients with mCRPC progressing after DOC. Both trials depicted a dramatic PSA response. Given that there is no direct comparison between ABI and ENZ and because of apparent similar efficacy and acceptable safety profiles, treatment selection must be individualized.

Recommendation 4. In patients with mCRPC who have progressed after ADT+DOC treatment (1st line) and present clinical or radiographic progression, the panel considers it appropriate to analyze other factors before making a final treatment decision (LE 5; GR D; LA 85%).

Given this clinical scenario, due to the lack of direct or indirect evidence in favor of a specific drug, the panel proposes to base treatment decisions on other variables and outcomes, (such as time-to-progression, the presence of symptoms and symptom intensity, previous therapeutic response and treatment toxicity, location of metastases, comorbidities, etc.)

Recommendation 5. In patients with mCRPC who have progressed after ADT+DOC treatment (1st line) and present hepatic metastases, the panel considers chemotherapy to be preferable (LE 5; GR D; LA 90%).

Owing to the poor cancer prognosis when associated with many visceral metastases (in general), but especially hepatic metastases, the panel agreed on recommending chemotherapy. Yet, there may be patients, such as those with elevated PSA levels or poor health status, in whom ENZ administration could be assessed. If ENZ turns out to be the final treatment decision, close monitoring of ENZ efficacy must be performed. In other cases, such as small number/size of metastases, certain metastasis localizations, or longer time-to-progression, a different treatment to chemotherapy could be considered as well.

Recommendation 6. In patients with mCRPC who have progressed after ADT+DOC treatment (1st line) and present an ECOG score $\geqslant$2, the panel considers ABI or ENZ to be preferable (LE 5; GR D; LA 70%).

Recommendation 7. In patients with mCRPC who have progressed after ADT+DOC treatment (1st line) and present an ECOG score $\geqslant$2, deemed to be cancer-related, the panel considers chemotherapy to be a potential treatment option (LE 5; GR D; LA 85%).

A patient with an impaired performance status may, in general, be ruled out for chemotherapy, as this setting is associated with both poor prognosis and reduced drug tolerance.[22] However, if the performance status is deemed to be related to disease progression and when the clinician considers it to be possibly reversible, chemotherapy could be discussed with the patient and, if agreed upon, delivered following appropriate dose and schedule adjustments.

Recommendation 8. In patients with mCRPC who have progressed after ADT+DOC treatment (1st line) and present aggressive disease, the panel considers platinum-based combinations as treatment option (LE 5; GR D; LA 95%).

The sequence of first-line carboplatin plus DOC followed by second-line etoposide plus cisplatin was evaluated in a phase II trial that involved 120 mCRPC patients with at least one anaplastic clinical criterion.[23] It was found that, of the seven “anaplastic” criteria, bulky tumor mass was significantly associated with poor outcome, lactic acid dehydrogenase strongly predicted OS (and rapid progression),

and serum carcinoembryonic antigen concentration strongly predicted OS (but not rapid progression), whereas neuroendocrine markers were unable to predict outcome or response to therapy. The authors conclude that patients with "anaplastic" prostate cancer are a recognizable subset, characterized by a high response rate of short duration to platinum-containing chemotherapies. More recently, a phase I–II RCT has shown promising activity with carboplatin added to CAB in metastatic castrationresistant prostate cancers.[24] Although the results require further confirmation, these findings may support decision-making in patients with mCRPC and aggressive disease.

Recommendation 9. In patients with mCRPC who have progressed after ADT+DOC treatment (1st line) and present neuroendocrine variants without other "anaplastic" disease criteria, the panel considers platinum-based combinations as treatment option (LE 5; GR D; LA 95%).

Different non-randomized, retrospective studies have demonstrated platinum-based chemotherapies to be active in men with neuroendocrine prostate cancer.[25–27] Therefore, platinum-based chemotherapy is a treatment option for these patients with poor prognosis.

Recommendation 10. In patients with mCRPC who have progressed after ADT+DOC treatment (1st line) and exhibit poor tolerance to chemotherapy, the panel considers ABI or ENZ to be preferable (LE 5; GR D; LA 70%).

Poor tolerance to previous chemotherapy generally guides the selection of a different drug class for subsequent treatment lines.[28,29] Nevertheless, as ABI and ENZ are also associated with undesirable effects, clinicians must be familiar with the diagnosis and management of these undesirable effects.[29]

Recommendation 11. In patients with mCRPC who have progressed after ADT+ABI treatment (1st line), the panel considers DOC to be generally preferable (LE 5; GR D; LA 90%).

Recommendation 12. Considering the new EMA restrictions with respect to radium-223, for patients with mCRPC who have progressed after ADT+DOC treatment (1st line), the panel considers the possibility of using radium-223 in patients with symptomatic bone- and high-volume disease, yet only in those who have failed in two previous treatments for mCRPC or for whom no alternative treatments are available (LE 5; GR D; LA 71%).

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 04 of 12, April 2023) am 17.04.2023

#	Suchfrage
1	[mh "Prostatic Neoplasms"]
2	(prostate OR prostatic):ti,ab,kw
3	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesion* OR malignan*):ti,ab,kw
4	#1 OR (#2 AND #3)
5	#4 with Cochrane Library publication date from Apr 2018 to present

Systematic Reviews in PubMed am 17.04.2023

verwendete Suchfilter ohne Änderung:

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

#	Suchfrage
1	prostatic neoplasms[mh] AND neoplasm metastasis[mh]
2	prostate[tiab] OR prostatic[tiab]
3	(((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesion*[tiab]) OR malignan*[tiab]
4	(#2 AND #3) AND (advanced[tiab] OR metastat*[tiab] OR metastas*[tiab] OR recurren*[tiab] OR oligometastatic[tiab])
5	#1 OR #4
6	(#5) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR

#	Suchfrage
	reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
7	((#6) AND ("2018/04/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in PubMed am 17.04.2023 [1]

verwendete Suchfilter ohne Änderung:

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

#	Suchfrage
1	prostatic neoplasms[mh]
2	prostate[tiab] OR prostatic[tiab]
3	(((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesion*[tiab]) OR malignan*[tiab]
4	#1 OR (#2 AND #3)
5	(#4) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
6	(((#5) AND ("2018/04/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 17.04.2023

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)
- National Institute for Health and Care Excellence (NICE)

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

- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

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

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

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

Vorliegend erfolgten keine schriftlichen Äußerungen von den wissenschaftlich-medizinischen Fachgesellschaften bzw. der AkdÄ.