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: 2025-B-154 Niraparib

Stand: Juli 2025

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

**Niraparib/ Abirateron**
**[zur Behandlung des metastasierten hormonsensitiven Prostatakarzinoms und HRR-Mutation]**

| **Kriterien gemäß 5. Kapitel § 6 VerfO** | |
|---|---|
| Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben. | Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“. |
| Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein. | • Orchiektomie |
| Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen | Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V:<br>• Abirateronacetat: Beschluss vom 07.06.2018<br>• Apalutamid: Beschluss vom 20.08.2020<br>• Enzalutamid: Beschluss vom 19.11.2021<br>• Relugolix: Beschluss vom 06.04.2023<br>• Darolutamid (Kombination mit Docetaxel und ADT): Beschluss vom 21.09.2023 |
| Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören. | Siehe systematische Literaturrecherche |

## II. Zugelassene Arzneimittel im Anwendungsgebiet

| **Wirkstoff**<br>**ATC-Code**<br>**Handelsname** | **Anwendungsgebiet**<br>(Text aus Fachinformation) |
|---|---|
| Zu bewertendes Arzneimittel: | |
| Niraparib/<br>Abirateron<br>L01XK52<br>Akeega | <u>Anwendungsgebiet laut Positive Opinion:</u><br>Akeega is indicated with prednisone or prednisolone:<br>in combination with androgen deprivation therapy (ADT) for the treatment of adult patients with metastatic hormone-sensitive prostate cancer (mHSPC) and BRCA 1/2 mutations (germline and/or somatic). |
| **Antiandrogene** | |
| Bicalutamid<br>L02BB03<br>generisch | • zur Behandlung des fortgeschrittenen Prostatakarzinoms in Kombination mit einer LHRH-(Luteinisierendes Hormon-Releasing-Hormon)-Analogon-Therapie oder einer operativen Kastration.<br>• […] |
| Cyproteron-acetat<br>G03HA01<br>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.<br>• 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.<br>• Zur Behandlung von Hitzewallungen, die unter der Behandlung mit LHRH-Agonisten oder nach Hodenentfernung auftreten.<br>• […] |
| Flutamid<br>L02BB01<br>generisch | Zur Behandlung von Patienten mit fortgeschrittenem Prostatakarzinom, bei denen eine Suppression der Testosteronwirkungen indiziert ist<br>• Initialtherapie in Kombination mit einem LHRH-Analogon oder in Verbindung mit Orchiektomie (komplette Androgenblockade) sowie bei Patienten, die bereits mit einem LHRH-Analogon behandelt werden bzw. bei denen bereits eine chirurgische Ablatio testis erfolgt ist<br>• zur Behandlung von Patienten, die auf andere endokrine Therapieformen nicht ansprachen oder für die eine andere endokrine Therapie nicht verträglich, aber notwendigerweise indiziert ist. |
| Apalutamid<br>L02BB05<br>Erleada | Erleada ist indiziert:<br>• zur Behandlung erwachsener Männer mit metastasiertem hormonsensitivem Prostatakarzinom (mHSPC) in Kombination mit Androgendeprivationstherapie (ADT).<br>[…] |

## II. Zugelassene Arzneimittel im Anwendungsgebiet

| | |
|---|---|
| Enzalutamid<br>L02BB04<br>Xtandi | Xtandi ist angezeigt:<br>• zur Behandlung erwachsener Männer mit metastasiertem hormonsensitivem Prostatakarzinom (metastatic hormone-sensitive prostate cancer, mHSPC) in Kombination mit einer Androgenentzugstherapie<br>[…] |
| Darolutamid<br>L02BB06<br>Nubeqa | NUBEQA wird angewendet zur Behandlung erwachsener Männer mit:<br>• metastasiertem hormonsensitivem Prostatakarzinom (mHSPC) in Kombination mit Docetaxel und einer Androgendeprivationstherapie.<br>[…] |
| **GnRH-Analoga** | |
| Degarelix<br>L02BX02<br>Firmagon | FIRMAGON ist ein Gonadotropin-Releasing-Hormon-(GnRH)-Antagonist zugelassen:<br>• zur Behandlung von erwachsenen männlichen Patienten mit fortgeschrittenem hormonabhängigen Prostatakarzinom.<br>• […] |
| Relugolix<br>L02BX04<br>Orgovyx | Orgovyx ist indiziert zur Behandlung von erwachsenen Patienten mit fortgeschrittenem hormonsensitivem Prostatakarzinom. |
| Buserelin<br>L02AE01<br>Profact | Profact® Depot 9,45 mg 3-Monatsimplantat ist angezeigt bei Erwachsenen zur Behandlung des fortgeschrittenen hormonempfindlichen Prostatakarzinoms.<br>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<br>L02AE03<br>Zoladex | Behandlung von Patienten mit fortgeschrittenem Prostatakarzinom, bei denen eine endokrine Behandlung angezeigt ist. |
| Leuprorelin<br>L02AE02<br>Trenantone | • Zur Behandlung des fortgeschrittenen hormonabhängigen Prostatakarzinoms.<br>• […] |
| Triptorelin<br>L01AA06<br>Pamorelin | ist indiziert zur Behandlung des<br>• lokal fortgeschrittenen oder metastasierenden, hormonabhängigen Prostatakarzinoms.<br>• […] |
| **Androgenbiosynthesehemmer** | |

## II. Zugelassene Arzneimittel im Anwendungsgebiet

| | |
|---|---|
| Abirateron-acetat<br>L02BX03<br>Zytiga | ZYTIGA ist indiziert mit Prednison oder Prednisolon:<br>• zur Behandlung des neu diagnostizierten Hochrisiko-metastasierten hormonsensitiven Prostatakarzinoms (mHSPC) bei erwachsenen Männern in Kombination mit Androgenentzugstherapie (androgen deprivation therapy, ADT)<br>• […] |
| **Zytostatika** | |
| Docetaxel<br>L01CD02<br>Taxotere | TAXOTERE ist in Kombination mit einer Androgendeprivationstherapie, mit oder ohne Prednison oder Prednisolon, zur Behandlung von Patienten mit metastasiertem hormonsensitivem Prostatakarzinom angezeigt.<br>[…] |

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

## Abteilung Fachberatung Medizin

# Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie

# Vorgang: 2025-B-154 (Beratung nach § 35a SGB V) Niraparib/Abirateron

| | |
|---|---|
| Auftrag von: | Abt. AM |
| Bearbeitet von: | Abt. FB Med |
| Datum: | 3. Juli 2025 |

# Inhaltsverzeichnis

# Abkürzungsverzeichnis

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

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

# 1 Indikation

Behandlung erwachsener Patienten mit metastasiertem hormonsensitivem Prostatakarzinom (mHSPC) und HRR-Mutationen (Keimbahn- und/oder somatisch)

*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.

Der Suchzeitraum der systematischen Literaturrecherche wurde auf die letzten fünf Jahre eingeschränkt und die Recherchen am 24.02.2025 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Auflistung durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 3400 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. Dabei wurde für systematische Reviews, inkl. Meta-Analysen, ein Publikationszeitraum von 2 Jahren und für Leitlinien von 5 Jahren betrachtet. 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 5 Referenzen eingeschlossen.

Vor Fertigstellung der Synopse wurde am 02.07.2025 die Aktualität eingeschlossener Leitlinien geprüft, es wurde eine aktualisierte Leitlinie [4] identifiziert. Es erfolgt eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

# 3 Ergebnisse

## 3.1 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

## 3.2 Systematische Reviews

Es wurden keine relevanten systematischen Reviews identifiziert.

## 3.3 Leitlinien

*Methodikeranmerkung: Es konnten keine Leitlinien zum mHSPC identifiziert werden, welche spezifische Empfehlungen hinsichtlich einer HRR-Mutation geben. Das Anwendungsgebiet wurde folglich erweitert, sodass die nachfolgend dargestellten Leitlinien Empfehlungen zum mHSPC geben, ohne Berücksichtigung einer HRR-Mutation.*

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**Leitlinienprogramm Onkologie, 2025 [3,4,5,6].**

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

S3-Leitlinie Prostatakarzinom; Langversion 8.0 und Leitlinienreport

**Methodik**

Grundlage der Leitlinie

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

Die S3-Leitlinie ist bis zur nächsten Aktualisierung gültig (maximal 5 Jahre, 31.05.2030).

Recherche/Suchzeitraum:

- Für (die AG) mHSPC und mCRPC wurden drei systematische Recherchen durchgeführt. Eingeschlossen wurden nur randomisierte kontrollierte Studien (RCTs), systematische Übersichtsarbeiten und Metaanalysen in englischer oder deutscher Sprache, die seit 2020 publiziert wurden (Suchdatum für alle Suchen: 15.11.2023). Die Suchen wurden in Medline via Ovid und in der Cochrane Library durchgeführt.

  *Methodikeranmerkung: Informationen zur systematischen Recherche im Kontext des mHSPC wurden aus dem Leitlinienreport 7.0 entnommen.*

- Für die von der AG (Bildgebung) definierten Schlüsselfragen wurde am 30.08.2024 eine Suche nach aggregierter Evidenz in Medline und der Cochrane Library durchgeführt. Eingeschlossen wurden nur Übersichtsarbeiten in englischer oder deutscher Sprache, die seit 2012 publiziert wurden.

  *Methodikeranmerkung: Teilweise Überarbeitungen in Kapitel 7 „Diagnostik und Therapie des rezidivierten oder metastasierten Prostatakarzinoms“ (u. a. modifizierte*

*Empfehlungen 7.30 und 7.31 bezüglich Darolutamid + ADT) basieren auf der systematischen Literaturrecherche zum Thema Bildgung für das Therapiemonitoring.*

LoE/GoR

- Cochrane Risk of Bias Tool.
- für systematische Übersichtsarbeiten/Metaanalysen das AMSTAR II Tool.
- Die Klassifikation der Evidenz erfolgte nach den Kriterien des Scottish Intercollegiate Guidelines Network (SIGN) (siehe Tabelle 4).

**Tabelle 4: Schema der Evidenzgraduierung nach SIGN**

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

**Tabelle 4: Schema der Empfehlungsgraduierung**

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

Tabelle 6: Schema der Empfehlungsgraduierung

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

## Empfehlungen

### 7.3 Therapie des hormonsensitiven, metastasierten Prostatakarzinoms (mHSPC)

| 7.24 | Konsensbasierte Empfehlung | neu 2024 |
|---|---|---|
| **EK** | Bei Patienten mit metastasiertem, hormonsensitivem Prostatakarzinom soll zeitnah nach Diagnosestellung eine Androgendeprivation zur Reduktion des Risikos typischer Komplikationen (z. B. pathologische Frakturen, Rückenmarkskompression, Harnleiterobstruktion) und ggf. zur palliativen tumorspezifischen Therapie eventueller tumor- bzw. metastasenbedingter Symptome (z. B. Knochenschmerzen) eingeleitet werden. | |
| | Starker Konsens | |

| 7.25 | Evidenzbasierte Empfehlung | neu 2024 |
|---|---|---|
| Empfehlungsgrad **0** | Eine Androgendeprivation kann durch chirurgische Kastration, durch subkutan oder intramuskulär zu verabreichende Gonadotropin-Releasing-Hormon (GnRH)-Agonisten oder durch subkutan oder oral zu verabreichende GnRH-Antagonisten durchgeführt werden. | |
| Evidenzlevel **1++** | [889], [970] | |
| | Starker Konsens | |

| 7.26 | Konsensbasierte Empfehlung | neu 2024 |
|---|---|---|
| **EK** | Bei Patienten mit ausgeprägten tumor- bzw. metastasenbedingten Schmerzen oder drohenden Komplikationen (z. B. Rückenmarkskompression) sollte die Androgendeprivation mit einem Gonadotropin-Releasing-Hormon (GnRH)-Antagonisten und/oder mit einem Androgenrezeptor-Signalweg-Inhibitor (ARPI: Apalutamid, Enzalutamid, Darolutamid) eingeleitet werden. | |
| | Starker Konsens | |

| 7.27 | Konsensbasierte Empfehlung | neu 2024 |
|---|---|---|
| **EK** | Eine Monotherapie mit einem nicht-steroidalen Androgenrezeptor-Antagonisten der ersten Generation (z. B. Bicalutamid, Flutamid) soll bei Patienten mit metastasiertem, hormonsensitivem Prostatakarzinom nicht durchgeführt werden. | |
| | Starker Konsens | |

| 7.28 | Evidenzbasierte Empfehlung | modifiziert 2024 |
|---|---|---|
| Empfehlungsgrad **A** | Bei Patienten mit metastasiertem, hormonsensitivem Prostatakarzinom (mHSPC) soll eine Einteilung nach high- und low-volume, high- und low-risk, sowie de novo und metachron metastasiert erfolgen. | |
| Evidenzlevel **1+, 1-** | [971], [972], [973] | |
| | Starker Konsens | |

| 7.29 | Konsensbasierte Empfehlung | modifiziert 2024 |
|---|---|---|
| **EK** | Patienten mit metastasiertem hormonsensitivem Prostatakarzinom sollen mit Einleitung der Androgendeprivation, spätestens innerhalb von 3 Monaten danach, über eine Kombinationstherapie (gemäß Empfehlung 7.30) aufgeklärt werden, sowie über:<br>• Die zu erwartende Überlebenszeit trotz des nicht-kurativen Charakters der Therapie;<br>• Die unerwünschten Wirkungen;<br>• Den Einfluss auf die Lebensqualität. | |
| | Starker Konsens | |

| 7.30 | Evidenzbasierte Empfehlung | modifiziert 2025 |
|---|---|---|
| Empfehlungsgrad<br>**A/B/0** | a. Patienten in gutem Allgemeinzustand (ECOG 0-1) mit metastasiertem (M1), hormonsensitivem Prostatakarzinom (mHSPC) soll zusätzlich zur Androgendeprivation eine Hormontherapie mit Apalutamid oder Enzalutamid angeboten werden.<br>(Empfehlungsgrad: A)<br>b. Patienten in gutem Allgemeinzustand (ECOG 0-1) mit metastasiertem (M1), hormonsensitivem Prostatakarzinom (mHSPC) sollte zusätzlich zur Androgendeprivation eine Hormontherapie mit Darolutamid angeboten werden.<br>(Empfehlungsgrad: B)<br>*Hinweis: Diese Empfehlung erfolgt unter Vorbehalt, wobei der aktuelle Zulassungsstatus zu beachten ist.*<br>c. Patienten in gutem Allgemeinzustand (ECOG 0-1) mit neu diagnostiziertem (de novo), metastasiertem (M1), hormonsensitivem, high-risk Prostatakarzinom (mHSPC) soll zusätzlich zur Androgendeprivation eine Hormontherapie mit Abirateron (plus Prednison / Prednisolon) angeboten werden.<br>(Empfehlungsgrad: A)<br>d. Patienten in gutem Allgemeinzustand (ECOG 0-1) mit metastasiertem (M1), hormonsensitivem Prostatakarzinom, die für eine Docetaxel-Chemotherapie geeignet sind, soll zusätzlich zur Androgendeprivation eine Hormontherapie mit Darolutamid in Kombination mit 6 Zyklen Docetaxel angeboten werden.<br>(Empfehlungsgrad: A)<br>e. Patienten in gutem Allgemeinzustand (ECOG 0-1) mit neu-diagnostiziertem (de novo), metastasiertem (M1), hormonsensitivem Prostatakarzinom und hohem Tumorvolumen („*high volume disease*"), die für eine Docetaxel-Chemotherapie geeignet sind, kann zusätzlich zur Androgendeprivation eine Hormontherapie mit Abirateron (plus Prednison/Prednisolon) in Kombination mit 6 Zyklen Docetaxel angeboten werden.<br>(Empfehlungsgrad: 0) | |
| Evidenzlevel<br>**1+**<br>**1-**<br>**2+** | [974], [975], [976], [971], [972], [977], [978], [979], [980], [981]<br>1+: Empfehlung a, c & d<br>1-: Empfehlung b<br>2+: Empfehlung e | |
| | Starker Konsens | |

| 7.31 | Evidenzbasierte Empfehlung | modifiziert 2025 |
|---|---|---|
| Empfehlungsgrad<br>**A** | a. Bei Entscheidung für eine kombinierte Behandlung aus Androgendeprivation und Apalutamid, soll die Apalutamid-Gabe innerhalb von 3 Monaten nach Beginn der Androgendeprivation beginnen. Die Therapie soll in einer Dosierung von 240 mg/Tag gegeben werden.<br><br>b. Bei Entscheidung für eine kombinierte Behandlung aus Androgendeprivation und Enzalutamid, soll die Enzalutamid-Gabe innerhalb von 3 Monaten nach Beginn der Androgendeprivation beginnen. Die Therapie soll in einer Dosierung von 160 mg/Tag gegeben werden.<br><br>c. Bei Entscheidung für eine kombinierte Behandlung aus Androgendeprivation und Darolutamid, soll die Darolutamid-Gabe innerhalb von 3 Monaten nach Beginn der Androgendeprivation beginnen. Die Therapie soll in einer Dosierung von 600 mg zweimal täglich gegeben werden.<br><br>*Hinweis: Diese Empfehlung erfolgt unter Vorbehalt, wobei der aktuelle Zulassungsstatus zu beachten ist.*<br><br>d. Bei Entscheidung für eine kombinierte Behandlung aus Androgendeprivation und Abirateron, soll die Abirateron-Gabe innerhalb von 3 Monaten nach Beginn der Androgendeprivation beginnen. Die Therapie soll in einer Dosierung von 1000 mg/Tag in Kombination mit Prednison oder Prednisolon (5 mg/Tag) gegeben werden.<br><br>e. Bei Entscheidung für eine kombinierte Behandlung aus Darolutamid, Docetaxel-Chemotherapie und Androgendeprivation, soll die Darolutamid-Gabe in einer Dosierung von 2 x 600 mg/Tag innerhalb von 3 Monaten nach Einleitung der Androgendeprivation beginnen. Die Chemotherapie soll innerhalb von 6 Wochen nach erster Darolutamid-Gabe beginnen; Docetaxel soll über 6 Zyklen alle 3 Wochen in einer Dosierung von 75 mg/m² Körperoberfläche verabreicht werden.<br><br>f. Bei Entscheidung für eine kombinierte Behandlung aus Abirateron, Docetaxel-Chemotherapie und Androgendeprivation, soll die Abirateron-Gabe in einer Dosierung von 1000 mg/Tag (plus Prednison/Prednisolon) innerhalb von 6 Wochen nach Einleitung der Androgendeprivation beginnen. Die Chemotherapie soll ab 6 Wochen nach Einleitung der Androgendeprivation beginnen; Docetaxel soll über 6 Zyklen alle 3 Wochen in einer Dosierung von 75 mg/m² Körperoberfläche verabreicht werden. | |
| Evidenzlevel<br>**1+**<br>**1-**<br>**2+** | [975], [976], [971], [972], [977], [978], [979], [981]<br><br>1+: Empfehlung a, b, d & e<br><br>1-: Empfehlung c<br><br>2+: Empfehlung f | |
| | Starker Konsens | |

| 7.32 | Konsensbasierte Empfehlung | modifiziert 2024 |
|---|---|---|
| EK | Gründe für einen Therapieabbruch sollen sein: Patientenwunsch, Progress oder intolerable Nebenwirkungen. Wird die Behandlung mit einem Medikament aus der Kombination wegen intolerabler Nebenwirkungen abgebrochen, dann soll die übrige Therapie wie vorgesehen weitergeführt werden. | |
| | Starker Konsens | |

| 7.33 | Evidenzbasierte Empfehlung | modifiziert 2024 |
|---|---|---|
| Empfehlungsgrad A | Patienten, die nicht für eine Kombinationsbehandlung in Frage kommen, soll eine Androgendeprivation angeboten werden. | |
| Evidenzlevel 1++ | [982], [983] | |
| | Starker Konsens | |

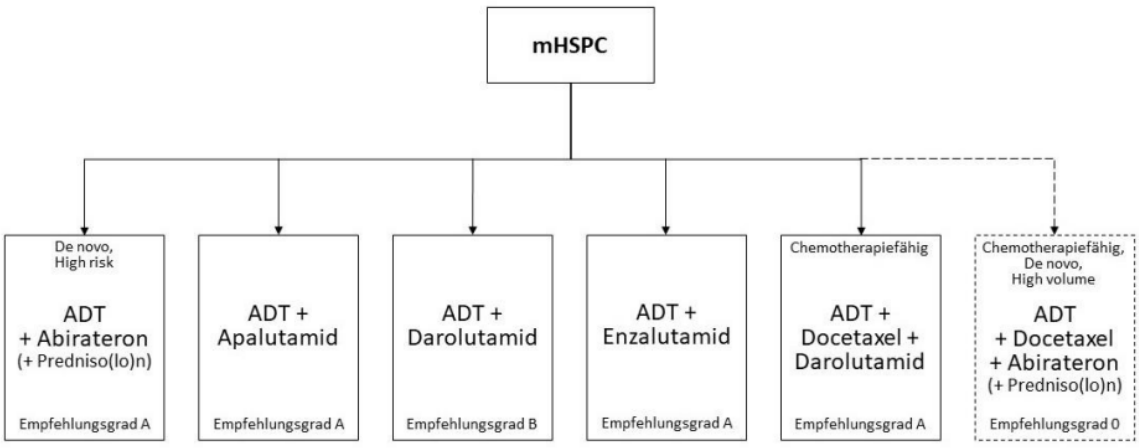


**Abbildung 8: Flussdiagramm zur Darstellung der gemäß 7.30 und 7.31 empfohlenen Therapieoptionen zur systemischen Therapie des mHSPC.**

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**Cornford P et al., 2025 [2].**

*European Association of Urology (EAU)*

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

Update 2025

- 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: trifft zu.

Recherche/Suchzeitraum:

- For the 2025 PCa Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature: Databases searched included Medline, EMBASE and the Cochrane Libraries, covering a time frame between May 1st 2023 and May 1st 2024

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

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

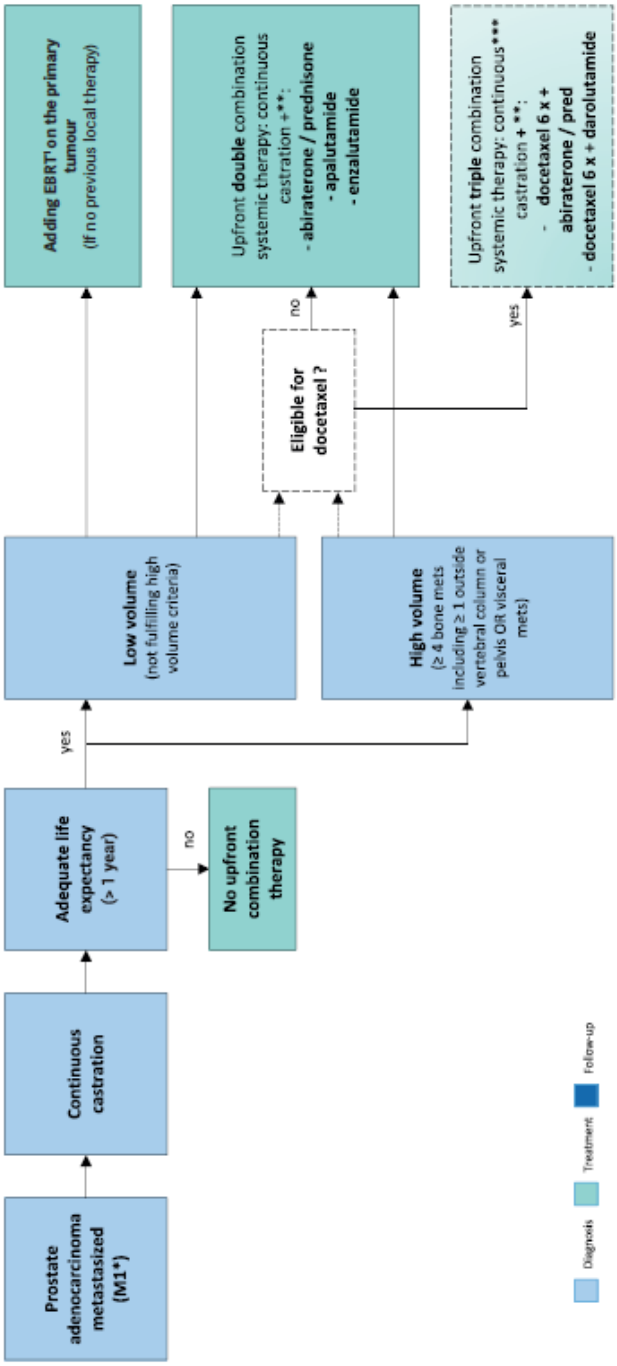
1. The overall quality of the evidence which exists for the recommendation,
2. The magnitude of the effect (individual or combined effects),
3. The certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors),
4. The balance between desirable and undesirable outcomes,
5. The impact of patient values and preferences on the intervention, and
6. The certainty of those patient values and preferences.

## 6.6 Management of Metastatic Prostate Cancer

### 6.6.8 Recommendations for the first-line treatment of hormone-sensitive metastatic disease

| Recommendations | Strength rating |
|---|---|
| ***First-line treatment*** | |
| Discuss all patients with hormone-sensitive metastatic disease in a multidisciplinary team. | Strong |
| Offer immediate systemic treatment with androgen deprivation therapy (ADT) to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction) to M1 symptomatic patients. | Strong |
| Offer short-term administration of an older generation androgen receptor (AR) antagonist to M1 patients starting luteinising hormone-releasing hormone (LHRH) agonist to reduce the risk of the 'flare-up' phenomenon. | Weak |
| At the start of ADT offer LHRH antagonists or orchiectomy to patients with impending clinical complications such as spinal cord compression or bladder outlet obstruction. | Strong |
| Do not offer AR antagonist monotherapy to patients with M1 disease. | Strong |
| Do not offer ADT monotherapy to patients whose first presentation is M1 disease if they have no contra-indications for combination therapy and have a sufficient life expectancy to benefit from combination therapy (≥ 1 year) and are willing to accept the increased risk of side effects. | Strong |
| Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients with M1 disease who are fit for the regimen. | Strong |
| Offer **ADT combined with** darolutamide to patients with M1 disease who are fit for the regimen. | Weak |
| Offer docetaxel only in combination with ADT plus abiraterone or darolutamide to patients with M1 disease who are fit for docetaxel. | Strong |
| Offer ADT combined with prostate radiotherapy (using doses up to the equivalent of 72 Gy in 2 Gy fractions) to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria. | Strong |
| Do not offer ADT combined with surgery to M1 patients outside of clinical trials. | Strong |
| Only offer metastasis-directed therapy to M1 patients within a clinical trial setting or a well-designed prospective cohort study. | Strong |

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




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

**Hintergrundinformationen**

**6.6 Management of Metastatic Prostate Cancer**

**6.6.3 First-line hormonal treatment**

Primary ADT has been the SOC for over 50 years [1158]. There is no high-level evidence in favour of a specific type of ADT for oncological outcomes, neither for orchiectomy nor for a LHRH agonist or antagonist. The level of testosterone is reduced much faster with orchiectomy and LHRH antagonist, therefore patients with impending spinal cord compression or other potential impending complications from the cancer should be treated with either a bilateral orchidectomy or LHRH antagonists as the preferred options.

There is a suggestion in some studies and a SR and meta-analysis that cardiovascular side effects are less frequent in patients treated with LHRH antagonists than patients treated with LHRH agonists [1114, 1159-1161]; therefore, patients with pre-existing cardiovascular disease or other cardio-vascular risk factors might be considered to be treated with antagonists if a chemical castration is chosen.

**6.6.3.1 Non-steroidal anti-androgen monotherapy**

Based on a Cochrane review comparing older generation non-steroidal anti-androgen (NSAA) monotherapy to ADT (either medical or surgical), NSAA was considered to be less effective in terms of OS, clinical progression, treatment failure and treatment discontinuation due to AEs [1162] and is generally not recommended also because ADT-based combination treatments have become SOC.

**6.6.3.2 Intermittent versus continuous androgen deprivation therapy**

Three independent reviews [1163-1165] and two meta-analyses [1166, 1167] looked at the clinical efficacy of intermittent androgen deprivation (IAD) therapy. All of these reviews included 8 RCTs of which only three were conducted in patients with exclusively M1 disease.

So far, the SWOG 9346 is the largest trial addressing IAD in M1b patients [1168]. Of 3,040 screened patients, only 1,535 patients met the inclusion criteria. This highlights that only about 50% of M1b patients can be expected to be candidates for IAD, i.e. the best PSA responders. This was a non-inferiority trial leading to inconclusive results: the actual upper limit was above the pre-specified 90% upper limit of 1.2 (HR: 1.1, CI: 0.99–1.23), the pre-specified non-inferiority limit was not achieved, and the results did not show a significant inferiority for any treatment arm. However, based on this study inferior survival with IAD cannot be completely ruled out even in this highly selected subgroup. The use of intermittent ADT has been superseded as continuous ADT based combination therapy has become SOC.

**6.6.3.3 Early versus deferred androgen deprivation therapy**

Early treatment before the onset of symptoms is recommended in the majority of patients with metastatic hormone-sensitive disease. A Cochrane analysis from 2019 about the topic concluded that early ADT probably extends time to death of any cause and time to death from PCa [1169], but the analysis included only a very limited number of metastatic patients. There is a lack of randomised phase III data in this specific setting and specifically not with the combination therapies that are standard nowadays, however data is accumulating for the use of long-term ADT earlier in the disease pathway.

The addition of RT/ SABR to ADT monotherapy or combination with ARPI as well as the use of SABR to delay ADT is discussed in section 6.6.7.

**6.6.4 Combination therapies**

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

6.6.4.1 'Combined' androgen blockade with older generation NSAA (bicalutamide, flutamide, nilutamide) Systematic reviews have shown that combined androgen blockade using a NSAA appears to provide a small survival advantage (< 5%) vs. monotherapy (surgical castration or LHRH agonists) [1170, 1171]. This minimal survival advantage must be balanced against the increased side effects especially as the newer combination therapies are more effective as shown specifically for enzalutamide which was tested against

NSAA in a phase III trial [1172]. More recently another trial has demonstrated a significant OS benefit for the addition of rezvilutamide vs. addition of bicalutamide to ADT in patients with high-volume mHSPC [1173]. Therefore, combination with NSAAs should only be considered if other combination therapies are not available.

**6.6.4.2 Androgen deprivation combined with other agents**

**6.6.4.2.1 Combination with an ARPI alone (abiraterone, apalutamide, enzalutamide, rezvilutamide, darolutamide)**

In two large RCTs (STAMPEDE, LATITUDE) the addition of abiraterone acetate (1000 mg daily) plus prednisone (5 mg daily) to ADT in men with mHSPC was studied [1127, 1174, 1175] (Table 6.6.3). The primary objective of both trials was an improvement in OS. Both trials showed a significant OS benefit. In LATITUDE with only de novo high-risk metastatic patients included, the HR reached 0.62 (0.51–0.76) [1127]. The HR in STAMPEDE was very similar with 0.63 (0.52–0.76) in the total patient population (metastatic and non-metastatic) and a HR of 0.61 in the subgroup of metastatic patients [1174]. While only high-risk patients were included in the LATITUDE trial a post-hoc analysis from STAMPEDE showed the same benefit whatever the risk or the volume category was [1176].

All secondary objectives such as PFS, time to radiographic progression, time to pain, or time to chemotherapy were in favour of the combination. No difference in treatment-related deaths was observed with the combination of ADT plus AAP compared to ADT monotherapy (HR: 1.37 [0.82–2.29]). However, twice as many patients discontinued treatment due to toxicity in the combination arms in STAMPEDE (20%) compared to LATITUDE (12%) [1175]. Based on these data upfront AAP combined with ADT should be considered as a standard in men presenting with metastases at first presentation, provided they are fit enough to receive the drug.

In five large RCTs the addition of AR antagonists to ADT in men with mHSPC was tested [1125, 1126, 1172]. In ARCHES the primary endpoint was radiographic PFS (rPFS). In the primary analysis rPFS was significantly improved for the combination of enzalutamide and ADT with a HR of 0.39 (0.3–0.5). Approximately 36% of the patients had low-volume disease; around 25% had prior local therapy and 18% of the patients had received prior docetaxel. In the final prespecified analysis the key secondary enpoint OS was significantly improved with a HR of 0.66 (0.53-0.81) and a significant benefit for rPFS was maintained with a HR of 0.63 (0,52–0.76) [1177].

In ENZAMET the primary endpoint was OS. The addition of enzalutamide to ADT in the first analysis improved OS with a HR of 0.67 (0.52–0.86) compared to ADT plus a non-steroidal antiandrogen. Approximately half of the patients had concomitant docetaxel; about 40% had prior local therapy and about half of the patients had low-volume disease [1126]. In a planned later analysis with a median follow-up of 68 months the OS benefit of adding enzalutamide was maintained with a HR of 0.7 (0.58-0.84) (Table 6.6.4) [1178].

In the TITAN trial, ADT plus apalutamide was used and rPFS and OS were co-primary endpoints. In the primary analysis rPFS was significantly improved by the addition of apalutamide with a HR of 0.48 (0.39–0.6); OS at 24 months was improved for the combination with a HR of 0.67 (0.51–0.89). In the final analysis the HR for OS was 0.65 (0.53–0.79) without adjustment for cross-over. In this trial 16% of patients had prior local therapy, 37% had low-volume disease and 11% received prior docetaxel [1125, 1179] (Table 6.6.4). A secondary analysis of the Titan study found that nearly half of the patients developing subsequent radiographic progression had no concomitant PSA progression, suggesting that heavy reliance on PSA monitoring may be inadequate for assessing disease activity in this context [1180].

In the CHART trial, ADT plus rezvilutamide was tested vs. ADT plus bicalutamide in patients with high-volume de novo metastatic disease. Ninety percent of the patients were recruited in China. Overall survival and rPFS were co-primary endpoints. At the pre-planned interim analysis rezvilutamide significantly improved rPFS compared with bicalutamide with a HR of 0.44 (0.33–0.58) and OS with a HR of 0.58 (0.44–0.77) (Table 6.6.5) [1173].

In ARANOTE, darolutamide plus ADT was randomised 2:1 vs. placebo plus ADT. It showed to significantly improved rPFS which was the primary endpoint (HR 0.54 [95% CI, 0.41 to 0.71]; $p < 0.0001$), with consistent benefits across subgroups, including high- and low-volume disease [1128]. Adverse events were similar in

the two groups. Overall survival was not statistically different, but data are immature (HR, 0.81 [95% CI, 0.59 to 1.12]) (Table 6.6.6).

In summary, the addition of the new AR antagonists significantly improves clinical outcomes with no convincing evidence of differences between subgroups. The majority of patients had de novo metastatic disease but a proportion of patients had metachronous disease; in the subgroup analyses the effect seemed to be consistent and therefore, a combination should also be offered for men progressing after radical local therapy [1178, 1181, 1182].

**6.6.4.2.2. Androgen deprivation therapy combined with chemotherapy**

Three large RCTs were conducted [775, 1088, 1114]. All trials compared ADT alone as the SOC with ADT combined with immediate docetaxel (75 mg/sqm, every three weeks within three months of ADT initiation). The primary objective in all three studies was to assess OS.

In the GETUG 15 trial, all patients had M1 PCa, either de novo or after a primary treatment [1183]. They were stratified based on previous treatment and Glass risk factors [1146]. In the CHAARTED trial the same inclusion criteria applied, and patients were stratified according to disease volume [1149].

STAMPEDE is a multi-arm multi-stage trial in which the reference arm (ADT monotherapy) included 1,184 patients. One of the experimental arms was docetaxel combined with ADT (n = 593), another was docetaxel combined with zoledronic acid (n = 593). Patients were included with either M1 or N1 or having two of the following 3 criteria: T3/4, PSA ≥ 40 ng/mL or ISUP grade group 4–5. Also relapsed patients after local treatment were included if they met one of the following criteria: PSA ≥ 4 ng/mL with a PSA-DT < six months or a PSA ≥ 20 ng/mL, N1 or M1. No stratification was used regarding metastatic disease volume (high/low volume) [839]. In all 3 trials toxicity was mainly haematological with around 12–15% grade 3–4 neutropenia, and 6–12% grade 3–4 febrile neutropenia. The use of granulocyte colony-stimulating factor receptor (GCSF) was shown to be beneficial in reducing febrile neutropenia. Primary or secondary prophylaxis with GCSF should be based on available guidelines [1184, 1185].

Docetaxel in all three trials was used at the standard dose of 75 mg/sqm every three weeks, 6 cycles in CHAARTED and STAMPEDE and up to 9 cycles in GETUG-AFU-15. In subgroup analyses from GETUG-AFU 15 and CHAARTED the beneficial effect of the addition of docetaxel to ADT was most evident in men with de novo metastatic high-volume disease [1150, 1151], while it was in the same range whatever the volume in the posthoc analysis from STAMPEDE [1186]. The effect of adding docetaxel was less apparent in men who had prior local radical treatment although the numbers were small and the event rates low. A SR and meta-analysis which included these 3 trials showed that the addition of docetaxel to SOC improved survival [1185]. The HR of 0.77 (95% CI: 0.68–0.87, p < 0.0001) translates into an absolute improvement in four-year survival of 9% (95% CI: 5–14). In a SR and meta-analysis of individual participant data from the three trials it has been shown that there is no meaningful beneficial effect of addition of docetaxel to ADT for patients with metachronous low volume disease. Interestingly the largest absolute improvement at five years was observed for the patients with high volume and clinical stage 4 disease [1187]. Therefore adding docetaxel alone to ADT should only be considered if no ARPI is available or all available ARPIs are contraindicated.

The addition of abiraterone to ADT and docetaxel has been reported to have a benefit in rPFS and in OS in the PEACE-1 trial [1188, 1189]. The trial has a 2x2 factorial design and participants with de novo (synchronous) metastatic PCa were randomised to SOC; at the beginning of the trial ADT, later ADT plus docetaxel for 6 cycles if chemotherapy-fit) vs. SOC plus radiotherapy vs. SOC plus abiraterone vs. SOC plus radiotherapy plus abiraterone. Co-primary endpoints were rPFS and OS, both were statistically significantly improved in the total population. Also in the group of patients who received ADT plus docetaxel as SOC (n = 710) both rPFS and OS were increased with a HR: 0.5 (0.34–0.71) and 0.75 (0.59–0.95), respectively. Of note; in this population about 35% had low-volume disease. Toxicity was modestly increased, mostly hypertension.

In the ARASENS Phase III trial all patients received ADT and docetaxel for 6 cycles as SOC plus darolutamide or placebo [1190]. 1,306 metastatic patients were included, 14 % of them with relapsed disease after radical local treatment (metachronous). Primary endpoint was OS and this was statistically significantly increased by the addition of darolutamide with a HR of 0.68 (0.57–0.8). Interestingly, in this trial the occurrence of AEs was similar in both arms. In both trials docetaxel and the ARPI have been given concomitantly. Of the included patients 77% had high volume and 70% high-risk disease. In an unplanned

subgroup analysis the beneficial effect of adding darolutamide vs. placebo for OS was seen in the patients with high-volume (HR 0.69; 0.57-0.82), with high-risk (HR 0.71; 0.58-0.86) and in lowrisk disease (HR 0.62; 0.42-0.9), for the small subgroup of patients with low-volume disease the results were suggestive of an OS benefit (HR 0.68; 0.41-1.13) [1191].

Also in ENZAMET, TITAN and ARCHES there were patients who received docetaxel as a part of SOC, thus not all concomitantly, but the percentage of patients receiving docetaxel in these trials was much lower [1125, 1126, 1172, 1177-1179].

There are also SRs and network meta-analysis for systemic triplet therapies and they confirm that the triplets are more effective than ADT and docetaxel alone [1192], in one analysis looking into subgroups statistically significant for patients with high volume disease and de novo disease [1193].

A SR and network MA for the different systemic treatments of mHSPC confirms triplets to be more effective than a doublet of ADT and docetaxel but not necessarily better than ADT plus ARPI. For patients with metachronous low-volume PCa, ARPI doublet therapies were ranked as the potentially most efficacious treatment options and the expected outcomes were not significantly different from those achieved by triplet regimens [1194]. In addition, in a MA of individual patient trial data of patients with metachronous low volume prostate cancer did not benefit from receiving docetaxel [1187].

**6.6.5 Treatment selection and patient selection**

There have been several network meta-analyses of the published data concluding that combination therapy is more efficient than ADT alone, but none of the doublet combination therapies has been convincingly proven to be superior over another [1194-1199]. In a SR and meta-analysis looking at association between age and efficacy of combination therapy patients seemed to profit from combination therapy irrespective of age [1199]. As a consequence, patients should be offered combination treatment unless there are clear contra-indications or they present with asymptomatic disease and a very short life expectancy (based on frailty assessment or non-cancer co-morbidities).

Since the data of the above mentioned phase III triplet therapy trials have been reported, docetaxel as sole addition to ADT is no longer a valid option in the majority of patients if an androgen receptor pathway inhibitor (ARPI) is available and there are no contra-indications to use one. From subgroup analysis of all the above-mentioned RCTs we know that probably all subgroups (high vs. low volume/risk and synchronous vs. metachronous) can profit from the addition of an ARPI to ADT. Therefore, in view of the current data the recommendation is using ADT plus ARPI as the sole additional therapy or the triplet with an ARPI plus docetaxel.

Formally the question what the added value of adding docetaxel to ADT plus an ARPI has not been evaluated. The data should be discussed with patients who are fit for chemotherapy and an ARPI, realising that most of the toxicity is caused by adding the chemotherapy. There is more evidence for using the triplet in synchronous disease and the OS benefit in PEACE-1 seemed to be driven mostly by the high volume patients at the time point of the analysis for the publication, in ARASENS only few patients had low volume disease. A living SR and MA, providing continuously automated updates is recommended for review [1194].

The choice of treatment will most likely be driven by fitness for docetaxel, the nature of the disease (low/high volume; synchronous/metachronous), patient preference, the specific side effects, availability, logistics and cost. The lack of high-level evidence for the benefit of triplet (ADT+ARPI+docetaxel) vs. doublet (ADT+ARPI) makes it difficult to make a strong recommendation for one option over the other including for patients with synchronous high-volume mHSPC.

**6.6.6 Treatment of the primary tumour in newly diagnosed metastatic disease**

The first reported trial evaluating prostate RT in men with metastatic castration-sensitive disease was the HORRAD trial. Four hundred and thirty-two patients were randomised to ADT alone or ADT plus IMRT with IGRT to the prostate. Overall survival was not significantly different (HR: 0.9 [0.7–1.14]), median time to PSA progression was significantly improved in the RT arm (HR: 0.78 [0.63–0.97]) [1200]. The STAMPEDE trial evaluated 2,061 men with metastatic castration-sensitive PCa (mCSPC) who were randomised to ADT alone vs. ADT plus RT to the prostate. This trial confirmed that RT to the primary tumour did not improve OS in unselected patients [1152]. However, following the results from CHAARTED and prior to analysing the data, the original screening investigations were retrieved, and patients categorised as low- or high

volume. In the low-volume subgroup (n = 819) there was a significant OS benefit by the addition of prostate RT. This was confirmed by the latest analysis of long-term follow-up (median follow-up of 61 months [HR: 0.64 for OS benefit in the low-volume group]) [1201].

A secondary, not pre-planned analysis of the STAMPEDE trial confirmed the benefit of prostate RT in patients with ≤ 3 bone metastases, but also showed a benefit in patients with M1a disease [1202]. No evidence of difference in time to symptomatic local events was found with median follow-up of over five years [1201]. The dose used in these indications should be equivalent of up to 72 Gy in 2 Gy fractions. Therefore, RT of the prostate only in patients with low-volume metastatic disease should be considered.

A network meta-analysis demonstrates that adding prostate RT to ADT alone results in 27% reduction in the hazard for death (pooled HR: 0.73; 95% credible interval [CrI]: 0.62–0.87), while ADT plus ARPI was associated with a 32% reduction (pooled HR: 0.68; 95% CrI: 0.60–0.78) and ADT plus ARPI plus RT was associated with a 47% reduction (pooled HR: 0.53; 95% CrI: 0.34–0.81) in the hazard for death (in risk of death) [1203]. It is not clear if these data can be extrapolated to RP as local treatment as results of ongoing trials are awaited.

In a SR and meta-analysis including the above two RCTs, the authors found that, overall, there was no evidence that the addition of prostate RT to ADT improved survival in unselected patients (HR: 0.92, 95% CI: 0.81–1.04, p = 0.195) [1204]. However, there was a clear difference in the effect of metastatic burden on survival with an absolute improvement of 7% in three-year survival in men who had four or fewer bone metastases.

The randomised phase-III trial with a 2 × 2 factorial design PEACE-1 (SOC, SOC+Abiraterone, SOC+RT and SOC+Abiraterone+RT) including 1,172 patients demonstrated that adding prostate radiotherapy (total dose 74 Gy in 37 fractions) significantly prolonged the co-primary endpoint of PFS from 4.4 years to 7.5 years in the low-volume metastatic burden group treated with SOC+ARPI. Additionally, a significant delay in the time to castration resistance was observed, although there was no improvement in OS in this group [1205].

PEACE-1 also reported a significant reduction in the incidence of serious genitourinary events such as obstruction, bleeding, insertion of double-J stent and TURP for patients treated with local RT to the prostate. This was an important secondary endpoint in the PEACE-1 study where the preventive effect of radiotherapy was observed both in the cohort of patients with low-volume metastatic disease (26% vs. 11%; delay in the time to first serious genitourinary event p = 0·0002;) and the overall cohort (22.3% vs 12.2%; p = 0·0001) [1205].

**6.6.7 Metastasis-directed therapy in M1-patients**

In patients relapsing after a local treatment, a metastases-targeting therapy has been proposed, with the aim to delay systemic treatment. In a retrospective analysis on 211 patients treated with MDT, Milenkovic et al. aimed at defining prognostic factors for MFS, palliative ADT-free (pADT) survival and cause-specific survival (CSS). With a median follow-up of 42 months after MDT, patients with cN1 only had significantly superior five-years MFS, pADT and CSS when compared to patients with M1 disease (p<0.02). Of interest, 23% of patients were free of biochemical recurrence at five years [1206]. There are two randomised phase II trials testing metastasisdirected therapy (MDT) using surgery ± SABR vs. surveillance [1207] or SABR vs. surveillance in men with oligorecurrent PCa [1208]. Oligo-recurrence was defined as < 3 lesions on choline-PET/CT only [1207] or conventional imaging with MRI/CT and/or bone scan [1208]. The sample size was small with 62 and 54 patients, respectively, and a substantial proportion of them had nodal disease only [1207]. Androgen deprivation therapy-free survival was the primary endpoint in one study which was longer with MDT than with surveillance [1207]. The primary endpoint in the ORIOLE trial was progression after six months which was significantly lower with SBRT than with surveillance (19% vs. 61%, p = 0.005) [1208].

Recently the combined results of STOMP and ORIOLE confirmed the significant improvement in PFS in favour of MDT (HR: 0.44, p < 0.001) [1209].

A phase II trial assessed the biochemical response after 18F-DCFPyL PET/MRI and subsequent MDT. Overall biochemical response rate, defined as ≥ 50% PSA decline, was 60%, including 22% of patients with complete biochemical response [1210].

The phase II randomised EXTEND trial investigated whether MDT when added to standard-of-care systemic treatment improved PFS when compared to standard-of-care systemic treatment alone in oligometastatic prostate cancer patients, with oligometastatic being defined as maximally 5 lesions. In total, 87 patients were randomized and the vast majority presented with 1 or 2 metastatic lesions. In total, 51 patients received ADT alone, while 36 patients also received ARPI. The addition of MDT significantly improved both PFS (15.8 months vs. not reached; HR: 0.25; p<0.001) and eugonadal PFS (6.1 months vs. not reached; HR: 0.32; p = 0.03). This significant benefit was observed both in the patient group receiving ADT alone or ADT + ARPI [1211]. In analogy, the SATURN trial, which included 28 oligo-recurrent metastatic prostate cancer patients, looked at the PFS of adding dual ARPI and MDT to existing ADT. The median PFS in SATURN was 19.3 months and 50% of the patients still had an undetectable PSA six months after testosterone recovery. While MDT-induced toxicity was very low, adding dual ARPI induced grade 3 toxicity in 20% of the patients [1212].

Currently there are no data to suggest an improvement in OS. Two comprehensive reviews highlighted MDT (SABR) as a promising therapeutic approach that must still be considered as investigational until the results of the ongoing RCT are available [1213, 1214]. The toxicity of MDT is low, with nearly no grade ≥ 3 toxicity [1215-1217].

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

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

**Zielsetzung/Fragestellung**

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

**Methodik**

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

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

LoE/GoR

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

Table 2: Strength of Evidence Definitions

| AUA Strength of Evidence Category | GRADE Certainty Rating | Definition |
|---|---|---|
| A | High | • Very confident that the true effect lies close to that of the estimate of the effect |
| B | Moderate | • Moderately confident in the effect estimate<br>• The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different |
| C | Low | • Confidence in the effect estimate is limited<br>• The true effect may be substantially different from the estimate of the effect |
| | Very Low | • Very little confidence in the effect estimate<br>• The true effect is likely to be substantially different from the estimate of effect |

Table 3: AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/Burden, and Body of Evidence Strength

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

## Empfehlungen

## METASTATIC HORMONE-SENSITIVE PROSTATE CANCER

### Treatment

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

**Hintergrundinformation:**
The use of primary ADT for the management of mHSPC has been the SOC since its discovery by Huggins et al. in the 1940's.[83] Castrate levels of testosterone (<50ng/dL) may be achieved with LHRH analogues, gonadotropin-releasing hormone (GnRH) antagonists, or orchiectomy. These treatments are considered equivalent in cancer control, although they have never been compared in large RCTs. GnRH antagonists and orchiectomy as monotherapy have a rapid onset of action and avoid the 'testosterone flare' seen with

LHRH analogues alone making them useful in situations needing rapid hormone ablation such as impending spinal cord compression.
At the time of initial publication of this guideline, the methods for achieving castrate levels of testosterone were either surgical or injectable. On December 18, 2020, the FDA approved relugolix as the first oral GnRH receptor antagonist for adult patients with advanced prostate cancer.[84] Approval was based on the phase III HERO study that showed favorable testosterone suppression and adverse effects of oral relugolix (120mg/day) compared to leuprolide.[85]

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

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

**DOCETAXEL**
Docetaxel is a potent inhibitor of microtubule assembly and disassembly. Since 2015, 2 clinical trials demonstrated the benefits of adding docetaxel chemotherapy to ADT for mHSPC patients. In the phase III CHAARTED study,[72] 790 patients with mHSPC were equally randomly assigned to receive either ADT in combination with docetaxel (75mg/m2) for up to 6 cycles or ADT alone. In an updated reporting on the trials, at a median follow-up of 53.7 months, the median OS was 57.6 months for the chemohormonal therapy arm versus 47.2 months for ADT alone (HR=0.72; 95% CI: 0.59 to 0.89; P=.0018). The median time to clinical progression was 33.0 months for the combination arm versus 19.8 months in the ADT alone arm (HR in the combination arm=0.62; 95% CI: 0.51 to 0.75; P<.001).

Similarly, in the STAMPEDE trial,[6] ADT plus docetaxel significantly improved median OS compared with ADT alone. The study randomly assigned 2,962 men 2:1:1:1 to receive SOC defined as hormone therapy for at least 2 years, SOC plus zoledronic acid, SOC plus docetaxel, or SOC with zoledronic acid and docetaxel. Docetaxel (75mg/m2) was given for six 3-week cycles with prednisolone (10mg) daily. Patients were followed up 6-weekly to 6 months, 12-weekly to 2 years, 6-monthly to 5 years, then annually. At a median follow up of 43 months, median OS was 71 months for SOC compared to 81 months for SOC plus docetaxel (HR=0.78; 95% CI: 0.66 to 0.93; p=0.006). SOC plus docetaxel also improved median failure-free survival at 37 months compared 20 months with SOC alone. The durability of these results was supported in an update of this trial. At a median follow-up of 78.2 months, there were 494 deaths on SOC.
There was good evidence of benefit in docetaxel over SOC on OS (HR=0.81; 95% CI: 0.69 to 0.95; P=0.009). Analysis of other outcomes found evidence of benefit for docetaxel over SOC in failure-free survival (HR=0.66; 95% CI: 0.57 to 0.76; P<0.001) and PFS (HR=0.69; 95% CI: 0.59 to 0.81; P<0.001).[86]

Like many chemotherapy agents, docetaxel has a significant toxicity profile that needs consideration. In the STAMPEDE trial, the most frequently reported adverse events in the SOC plus docetaxel group included febrile neutropenia (15%), general disorder (including lethargy fever, asthenia—7%), and gastrointestinal disorder (including diarrhea, abdominal pain, constipation, vomiting—8%).[6]

**ABIRATERONE ACETATE**
Abiraterone acetate is a non-steroidal irreversible inhibitor of CYP17A1, which catalyzes the conversion of C21 progesterone precursors to C19 adrenal androgens, DHEA, and androstenedione.[87] In essence, abiraterone acetate is similar to ADT, but it is more potent, inhibiting gonadal and extragonadal androgen synthesis.

In the double-blind, placebo-controlled, phase III LATITUDE trial,[24] 1,199 patients were randomly assigned to receive either ADT plus abiraterone acetate (1,000mg given once daily as four 250mg tablets) plus prednisone (5mg daily) or ADT plus placebo. The primary endpoints were OS and radiographic PFS. After a median follow-up of 30.4 months at a planned interim analysis, the median OS was significantly longer in the abiraterone acetate group than in the placebo group (not reached versus 34.7 months) (HR=0.62; 95% CI: 0.51 to 0.76; P<0.001). The median length of radiographic PFS was 33.0 months in the abiraterone acetate group and 14.8 months in the placebo group (HR=0.47; 95% CI: 0.39 to 0.55; P<0.001). Updated

results continue to confirm benefit in this trial. The final analysis of this trial, at a median follow-up of 51.8 months, OS was significantly longer in the abiraterone acetate plus prednisone group (median 53.3 months [95% CI: 48.2 to not reached]) compared to the placebo group (36.5 months [33.5 to 40.0]), with an HR of 0.66 (95% CI: 0.56 to 0.78; p<0.0001).[88]

In the STAMPEDE trial, [89] 1,917 patients were randomized in a 1:1 ratio to receive ADT alone or ADT plus abiraterone acetate (1,000mg daily) and prednisolone (5mg daily). A total of 52% of patients had metastatic disease. The primary outcome was OS. The median follow-up was 40 months. There were 184 deaths in the abiraterone acetate group compared with 262 in the ADT group (HR=0.63; 95% CI: 0.52 to 0.76; P<0.001); the HR was 0.61 in those with metastatic disease.

Abiraterone acetate can elevate liver enzyme levels and should be avoided in patients where liver toxicity is a concern. As such, clinicians should monitor liver enzymes as well as potassium levels. Adverse events in the LATITUDE trial[24] included mineralocorticoid-related hypertension (20%) and hypokalemia (10%). Further, the use of a steroid in combination with treatments for metastatic disease may require additional considerations for patients with comorbid conditions, such as diabetes or significant osteoporosis.

**APALUTAMIDE**

Apalutamide is a novel androgen receptor signaling inhibitor (ARSI). This oral agent acts as an AR inhibitor that binds directly to the ligand-binding domain of the AR. Apalutamide inhibits AR nuclear translocation, inhibits DNA binding, and impedes AR-mediated transcription.[90] In the double-blind, phase III TITAN study,[91] 525 patients were assigned to receive apalutamide (240mg daily) with ADT compared to 527 patients receiving placebo plus ADT. Primary endpoints included radiographic PFS and OS. At a median of 22.7 months follow-up, the percentage of patients with radiographic PFS at 24 months was 68.2% in the apalutamide group compared to 47.5% in the placebo group (HR=0.48; 95% CI: 0.39 to 0.60; P<0.001). OS at 24 months was greater with apalutamide compared to placebo (82.4% versus 73.5%; HR=0.67; 95% CI: 0.51 to 0.89; P=0.005). At the time of final analysis (44.0 months median follow-up), a total of 405 deaths had occurred (170 in the apalutamide arm, 235 in the placebo arm). An improvement in median OS was observed: not reached in the apalutamide group versus 52.2 months in the placebo group (HR=0.65; 95% CI: 0.53 to 0.79; P<0.0001), with a 35% reduction in risk of death.[92] Rash of any grade was more common among patients who received apalutamide compared to those who received placebo (27.1% versus 8.5%).

**ENZALUTAMIDE**

Enzalutamide is a novel ARSI. It is a competitive inhibitor of androgen binding and also inhibits nuclear translocation of the AR, DNA-binding and coactivator recruitment. [93] In the open-label, randomized, phase III ENZAMET trial,[94] 1,125 men were randomized to receive testosterone suppression plus either open-label enzalutamide (160mg daily) or a standard non-steroidal antiandrogen therapy (bicalutamide, nilutamide, or flutamide—standard care). The primary end point was OS. With a median follow-up of 34 months, there were 102 deaths in the enzalutamide group compared to 143 deaths in the standard care group (HR=0.67; 95% CI: 0.52 to 0.86; P=0.002). Kaplan-Meier estimates of OS at 3 years were 80% in the enzalutamide group and 72% in the standard care group.

Discontinuation of treatment due to adverse events was more frequent in the enzalutamide group (33 events versus 14 events, respectively). Fatigue was more common in the enzalutamide group, and seizures occurred in 7 patients in the enzalutamide group (1%) compared to 0 patients in the standard care group. In this trial, approximately 16% of patients also received docetaxel and this study did not impact the observed benefit of enzalutamide. This trial did not address the role of early intensification by adding docetaxel to enzalutamide.

In the double-blind, phase III ARCHES trial, Armstrong et al. randomly assigned 1,150 men with mHSPC in a 1:1 ratio to receive either enzalutamide (160mg per day) or placebo. All patients also received ADT. The primary endpoint was radiographic PFS. As of October 2018, the risk of radiographic PFS or death was significantly reduced with enzalutamide plus ADT versus placebo plus ADT (median not reached versus 19.0 months; HR=0.39; 95% CI: 0.30 to 0.50; P<.001). Similar improvements were also seen in risk of PSA progression, initiation of new antineoplastic therapy, first symptomatic skeletal event, castration-resistance, and reduced risk of pain progression. In an update on this trial, the final prespecified analysis of OS, which was a key secondary end point, and an update on radiographic PFS was reported. Following unblinding, 180 (31.3%) progression-free patients randomly assigned to placebo plus ADT crossed over to open-label enzalutamide plus ADT. At a median follow-up of 44.6 months, 154 of 574 patients randomly assigned to enzalutamide plus ADT and 202 of 576 patients randomly assigned to placebo plus ADT had died. Enzalutamide plus ADT reduced risk of death by 34% versus placebo plus ADT (median not reached in either group; HR=0.66; 95% CI: 0.53 to 0.81; P<0.001).[95]

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

**THERAPEUTIC DECISION-MAKING IN MHSPC**
Unfortunately, no comparative data on efficacy exist between the previously discussed options. The clinician should consider factors like age and comorbidities when choosing chemotherapy, where toxicity might be more difficult for older patients than fit younger patients. Duration of treatment may also influence choice. Some patients might prefer a limited 18-week course of docetaxel to daily oral therapy for years. Further, in select patients with metastatic presentations, particularly de novo metastatic patients, triplet therapy is recommended (see following statement).

In terms of intermittent ADT, SWOG 9346[96] evaluated intermittent ADT compared with continuous ADT and did not demonstrate non-inferiority in mHSPC. In fact, there was a non-significant benefit in OS with continuous ADT. Given all of the recent data suggesting that additional therapy (chemotherapy or androgen receptor-targeted therapy [ART]) added to continuous ADT significantly improves OS, the Panel generally advises against intermittent ADT in otherwise healthy patients with mHSPC.

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

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

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

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

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

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

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

**Hintergrundinformation:**
Two recent phase III randomized trials examining ADT and prostate radiotherapy versus ADT alone in men with metastatic prostate cancer demonstrated no difference in OS. However, the subgroup analysis for the low-volume group in STAMPEDE Arm H revealed a survival benefit in patients with low-volume metastatic cancer.[69] Given this was a secondary analysis, and that few of the patients had received optimized systemic therapy, the Panel provides a conditional recommendation for ADT plus radiation as an option for patients with minimal metastatic disease willing to undergo the risks associated with local therapy.

The HORRAD trial reported on 432 patients randomized either to ADT alone or ADT with EBRT to the prostate.[99] Median PSA was 142ng/mL, and 67% of patients had more than 5 osseous metastases by conventional imaging. OS was not different (HR=0.9; 95% CI: 0.7 to 1.14; p=0.4), but median time to PSA progression was improved in the EBRT arm (HR=0.78; 95% CI: 0.63 to 0.97; p=0.02). A hypothesis was generated that survival might be improved in a subgroup of patients with low metastatic burden (HR=0.68; 95% CI: 0.42 to 1.10). In the STAMPEDE trial, 2,061 men with metastatic HSPC were randomized to ADT alone versus ADT plus prostate radiation given at moderate doses and with unconventional fractionation (36Gy in 6 fractions over 6 weeks, or 55Gy in 20 daily fractions).[69] Radiotherapy improved failure-free survival (HR=0.76; 95% CI: 0.68 to 0.84; p<0.0001), but not OS (HR=0.92; 95% CI: 0.80 to 1.06; p=0.266) similar to HORRAD. An additional prespecified analysis utilizing the CHAARTED definition of low-volume cancer encompassing 40% of the population was performed. Low-volume metastatic disease demonstrated a benefit to ADT plus radiation (HR=0.68; 95% CI: 0.52 to 0.90; p=0.007) with 3-year survival 73% with ADT alone versus 81% with ADT and radiotherapy. Toxicity is important to minimize in patients who will not be cured of their metastatic disease. There was no significant difference in grade ≥3 toxicity with the addition of radiotherapy (HR=1.01; 95% CI: 0.87 to 1.16; p=.94).

Physicians have suggested these results point to the benefits of local therapy raising the question whether radical prostatectomy might have the same results. These trials are ongoing, and at present the use of surgery should be considered investigational and only conducted within the context of a trial. In the STAMPEDE trial,[69] no patients had concurrent abiraterone acetate, and only 18% had early docetaxel so no clear recommendation can be made about other drug combinations combined with prostate radiation in the metastatic setting.

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

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

In the first week after LHRH agonists are administered, there is typically a surge in luteinizing hormone resulting in an increase in circulating testosterone. This may cause clinical “flares,” which may be associated with worsening of disease symptoms (e.g., bone pain, urinary tract obstruction) in approximately 10% of patients. This surge can be “blocked” by short term (e.g., 4 weeks or less) of a first-generation antiandrogen, although there is limited evidence of significant clinical utility.[100]

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

**Hintergrundinformation:**
Non-steroidal antiandrogen therapy without ADT in advanced prostate cancer is not recommended. Evidence based on 11 studies encompassing 3,060 patients suggests that use of non-steroidal antiandrogens without ADT compared with medical or surgical castration monotherapy for advanced prostate cancer is less effective in terms of OS, clinical progression, treatment failure, and treatment discontinuation due to adverse events.[101]

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

Abiraterone acetate is an inhibitor of CYP17, and apalutamide, darolutamide, and enzalutamide are second

generation antiandrogens. None of these agents have been studied without ADT for mHSPC, while compelling evidence of survival has been demonstrated with testosterone suppression in combination with either abiraterone acetate plus prednisone, enzalutamide, or apalutamide.[24,89,91,94,110,111] For now, however, these next generation antiandrogens should not be considered without ADT in mHSPC.

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**Virgo KS et al., 2023 [7].**

*American Society of Clinical Oncology (ASCO)*

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

**Zielsetzung/Fragestellung**

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

**Methodik**

Aktuelles Update der Version von 2021.

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

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

LoE/GoR

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

| Grade | Definition |
|---|---|
| High | We are very confident that the true effect lies close to that of the estimate of the effect. |
| Moderate | We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different |
| Low | Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. |
| Very Low | We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect |

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

Sonstige methodische Hinweise

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

## Empfehlungen

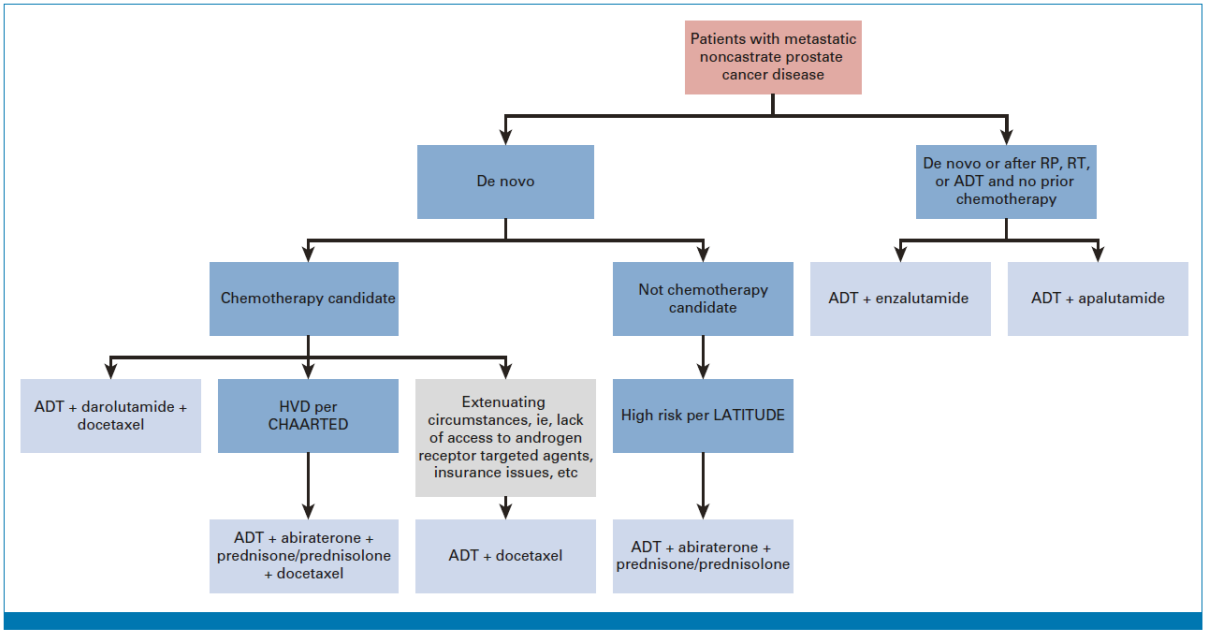


**FIG 1.** Initial management of noncastrate metastatic prostate cancer algorithm. ADT, androgen-deprivation therapy; HVD, high-volume disease; RP, radical prostatectomy; RT, radiotherapy.

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

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

(continued on following page)

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

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

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# 4 Detaillierte Darstellung der Recherchestrategie

**Cochrane Library - Cochrane Database of Systematic Reviews (Issue 02 of 12, February 2025) am 20.02.2025**

| # | Suchschritt |
|---|---|
| 1 | [mh "Prostatic Neoplasms"] |
| 2 | ((prostate OR prostatic) NEAR/3 (cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesion* OR malignan*)):ti,ab,kw |
| 3 | #1 OR #2 |
| 4 | #3 with Cochrane Library publication date from Feb 2020 to present, in Cochrane Reviews |
| 5 | #3 with Cochrane Library publication date from Feb 2023 to present, in Cochrane Reviews |
| 6 | #4 NOT #5 |

**Leitlinien und systematische Reviews in PubMed am 20.02.2025**

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

verwendete Suchfilter für systematische Reviews:
*Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 15.01.2025.*

| # | Suchschritt |
|---|---|
| | **Leitlinien** |
| 1 | prostatic neoplasms[majr] |
| 2 | prostate[tiab] OR prostatic[tiab] |
| 3 | tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR neoplas*[tiab] OR sarcoma*[tiab] OR cancer*[tiab] OR lesion*[tiab] OR malignan*[tiab] |
| 4 | #1 OR (#2 AND #3) |
| 5 | (#4) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti]) |
| 6 | (#5) AND ("2020/02/01"[PDAT] : "3000"[PDAT]) |
| 7 | (#6) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt]) |
| | **systematische Reviews** |
| 8 | "Prostatic Neoplasms/therapy"[Majr] |
| 9 | (#2 AND #3) AND (treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab]) |
| 10 | #8 OR #9 |

| # | Suchschritt |
|---|---|
| 11 | (#10) AND ("systematic review"[pt] OR "meta-analysis"[pt] OR "network meta-analysis"[mh] OR "network meta-analysis"[pt] 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 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"[pt] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab]) |
| 12 | (#11) AND ("2020/02/01"[PDAT] : "3000"[PDAT]) |
| 13 | (#12) NOT "The Cochrane database of systematic reviews"[Journal] |
| 14 | (#13) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt]) |
| | systematische Reviews ohne Leitlinien |
| 15 | (#14) NOT (#7) |
| 16 | (#15) AND ("2023/02/01"[PDAT] : "3000"[PDAT]) |
| 17 | #15 NOT #16 |

**Iterative Handsuche nach grauer Literatur, abgeschlossen am 24.02.2025**

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- National Institute for Health and Care Excellence (NICE)
- 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)
- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO

- Guidelines International Network (GIN)
- Trip Medical Database

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[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.021

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

Verfahrens-Nr.: 2025-B-154

| **Verfasser** | |
|---|---|
| Institution | Deutsche Gesellschaft für Urologie (DGU)<br>Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO) |
| Sachverständige | |
| Datum | TT.MM.JJJJ |

| **Indikation** |
|---|
| Behandlung erwachsener Patienten mit mHSPC und HRR-Mutationen (Keimbahn- und/oder somatisch) |
| **Fragen zur Vergleichstherapie** |
| Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? |

**Zusammenfassung**

Die Therapie des metastasierten, hormonsensitiven Prostatakarzinoms (mHSPC) hat sich in den letzten Jahren grundlegend geändert. Eine umfassende Darstellung deraktuellen Empfehlungen und des Hintergrunds findet sich in der S3 Leitlinie vom Juli 2024 [1]. Beim mHSPC wird eine Einteilung nach High- und Low-Volume, High- und Low-risk, sowie de novo und metachron metastasiert vorgenommen.

Standard in der Therapie von Patienten mit hormonsensitivem Prostatakarzinom (mHSPC) ist die Fortsetzung der ADT in Kombination mit (alphabetische Reihenfolge):

- Abirateron (für High-Risk Patienten) oder
- Apalutamid oder
- Darolutamid oder
- Enzalutamid oder
- Docetaxel + Abirateron (für Chemotherapie geeignete High-Risk Patienten)
- Docetaxel + Darolutamid (für Chemotherapie geeignete Patienten)

Die Auswahl innerhalb der ‚oder'-Optionen wird aktuell vor allem durch die etwas unterschiedlichen Zulassungsbedingungen, das Ausmaß der Tumorerkrankung und das zu erwartende Nebenwirkungsspektrum gesteuert [1, 2].

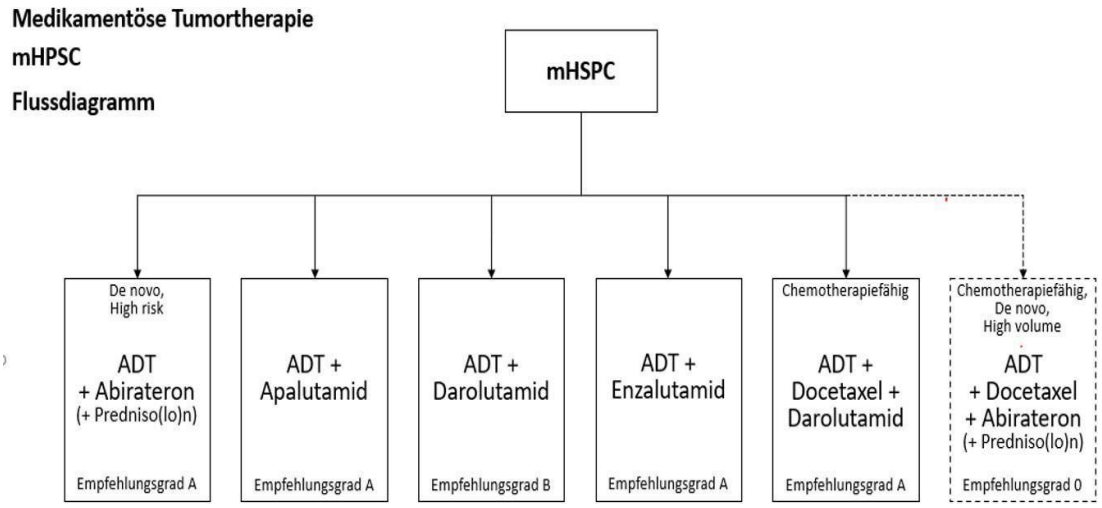
Patienten mit mHSPC und einem Defekt der homologen Rekombination (HRD+) haben eine ungünstige Prognose [2]. Im Stadium des metastasierten, kastrationsresistenten Prostatakarzinoms (mCRPC) verbessert die Therapie mit PARP -Inhibitoren (PARPi) die Prognose, insbesondere bei Nachweis von BRCA1/2-Mutationen. Bisher ist kein PARPi beim mHSPC zugelassen.

**Fragestellung**

Der Therapiestandard hat sich seit unserer letzten gutachterlichen Expertise zu dieser Indikation nicht grundlegend geändert, siehe Verfahren

**Stand des Wissens**

Die aktuellen Empfehlungen sind in der Graphik aus der aktuellen S3 Leitlinie dargestellt [1]:




Die den Empfehlungen zugrunde liegende Evidenz ist wie folgt [1, 2]:

Abirateron: Zur Kombinationstherapie von Abirateron und ADT liegen Daten aus den beiden zwei randomisierten klinischen Studien STAMPEDE und LATITUDE vor [8, 9]. In beiden Studien führte die Kombination zum Zeitpunkt der Zulassung zu einer signifikanten Verlängerung des radiologischen progressionsfreien Überlebens (HR 0,43 in STAMPEDE; 0,47 in LATITUDE) und der Gesamtüberlebenszeit(HR 0,61 in STAMPEDE; 0,62 in LATITUDE). Die finalen Analysen bestätigen die Ergebnisse mit geringen Änderungen der HR.

Apalutamid: Die Kombination aus Apalutamid in Ergänzung zu einer ADT wurde in TITAN, einer randomisierten, doppelt -verblindeten, Placebo -kontrollierten Phase -III-Studie untersucht. Hier führte Apalutamid in Kombination mit ADT gegenüber ADT zur signifikanten Verlängerung des

radiologischen progressionsfreien Überlebens (HR 0,48) und der Gesamtüberlebenszeit (HR 0,67). Der Unterschied war bei Patienten mit hoher und mit niedriger Tumorlast signifikant [10].

Enzalutamid:

Die Kombination aus Enzalutamid in Ergänzung zu einer ADT gegenüber einer alleinigen ADT wurde in ARCHES untersucht. Hier führte Enzalutamid gegenüber Placebo zur signifikanten Verlängerung des radiologischen progressionsfreien Überlebens (HR 0,39) und in einer späteren Analyse auch der Gesamtüberlebenszeit (HR 0,66) [11]. Die Ergebnisse wurden durch die Studie ENZAMET bestätigt. Auch führte Enzalutamid + ADT gegenüber ADT zur signifikanten Verlängerung des progressionsfreien Überlebens (HR 0,40) und der Gesamtüberlebenszeit (HR 0,70) [12, 13].

Darolutamid:

Inzwischen liegen mit ARANOTE auch Daten einer randomisierten Phase-III-Studie zur Wirksamkeit von Darolutamid vor. Hier führte auch Darolutamid zur Verlängerung des radiologischen progressionsfreien Überlebens (HR 0,54). Die Verlängerung der Gesamtüberlebenszeit war statistisch nicht signifikant (HR 0,81; KI 0,59-1,12) [14]. Darolutamid hat in dieser Indikation keine Zulassung.

PARP Inhibitoren:

Kürzlich wurden die Daten der randomisierten Phase-3-Studie AMPLITUDE zur Wirksamkeit von Niraparib + Abirateron bei Patienten mit mCSPC und $\geq$1 Alteration in einem HRR-relevanten Gen (*BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, PALB2, RAD51B, RAD54L*) publiziert [15]. Im Vergleich zu Abirateron führt die Kombination zur signifikanten Verlängerung des radiologischen, progressionsfreien Überlebens und der Zeit bis zum symptomatischen Progress. Die Unterschiede zugunsten von Niraparib waren besonders deutlich bei Patienten mit BRCA1/2-Mutationen (HR 0,52; p<0,001), aber auch signifikant bei mit anderen Alterationen (HR 0,63; p=0,001).

Für Chemotherapie geeignet

Docetaxel: Die Wirksamkeit von Docetaxel wurde in mehreren Studien getestet. Bei Patienten in gutem Allgemeinzustand führte die Kombination von Docetaxel mit ADT gegenüber ADT in der Metaanalyse der randomisierten Studien zur Verlängerung des progressionsfreien Überlebens (HR 0,64) und zu einer Verlängerung der Gesamtüberlebenszeit (HR 0,77) [3, 4]. Von der Therapie mit Docetaxel profitierten in den ersten Studienauswertungen vorallem Patienten mit hoher Tumorlast. Diese warin den prospektiven Studien und den Post-Hoc-Analysen definiert als viszerale Metastasen oder >4 Knochenmetastasen mit $\geq$1 Knochenmetastase außerhalb von Becken und Wirbelsäule. Die vorliegenden Daten hatten zur Aufnahme von Docetaxel beim hormonsensitiven, metastasierten Prostatakarzinom in die Arzneimittelrichtlinie zur Off-Label-Anwendung nicht zugelassener Arzneimittel durch den G-BA geführt. Aufgrund der Ergebnisse der ARASENS-Studie und der PEACE-1 Studie wird die alleinige Hormonchemotherapie mit ADT und Docetaxel nicht mehr empfohlen [1, 2].

Docetaxel + Abirateron: In der PEACE-1-Studie führte die Addition von Abirateron zur Kombination von Docetaxel mit ADT gegenüber Docetaxel/ADT bei Patienten mit de novo metastasiertem, hormonsensitiven Prostatakarzinom zur signifikanten Verlängerung des radiologischen progressionsfreien Überlebens und Gesamtüberlebens (HR 0.75; 0.59-0.95). Dieser Vorteil scheint vor allem durch die Subgruppe der Patienten mit hoch volumiger Erkrankung bedingt (PFS HR 0,47, Gesamtüberlebenszeit HR 0,72) [5]. Diese Kombination ist in der EU nicht zugelassen, wird aber in den Leitlinien als Option („kann“) empfohlen [1, 2].

Docetaxel + Darolutamid: In der Placebo-kontrollierten Phase-III-Studie ARASENS führte die Dreifachtherapie mit ADT + Docetaxel + Darolutamid gegenüber ADT + Docetaxel zur statistisch signifikanten Verlängerung der Gesamtüberlebenszeit (HR 0,675) und der Zeit bis zum Auftreten bzw. der Verschlechterung von krankheitsassoziierten Parametern der Morbidität wie symptomatischen Knochenmetastasen (EFÜHR 0,609) [6, 7].

Es gibt keine Daten für die Kombination aus ein ARPI+ADT bzw. ARPI+ADT+Docetaxel speziell für Patienten mit HRR-Mutation. Insofern spielt auch das Vorliegen einer bzw. einzelner HRR-Mutationen bisher kein Entscheidungskriterium für einer der Standardtherapien beim mHSPC dar.

| |
|---|
| Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen? |
| Die Kriterien sind oben dargestellt. |

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