Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2012-B-070 Radium-223

Stand: Januar 2013

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

Radium-223
zur Behandlung des kastrationsresistenten Prostatakarzinoms mit Knochenmetastasen

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*siehe Übersicht "II. Zugelassene Arzneimittel im Anwendungsgebiet"*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	• Strahlentherapie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	• Beschluss vom 29. März 2012 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – **Abirateron**: Patientengruppe Best-Supportive-Care: Hinweis auf einen **beträchtlichen Zusatznutzen** Patientengruppe Docetaxel-Retherapie: Zusatznutzen gilt als nicht belegt. • Beschluss vom 29. März 2012 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – **Cabazitaxel**: Patientengruppe Best-Supportive-Care: Hinweis auf einen **geringen Zusatznutzen** Patientengruppe Docetaxel-Retherapie: Zusatznutzen gilt als nicht belegt. • Beschluss vom 17. Dezember 2009 über eine Änderung der Richtlinie Methoden vertragsärztliche Versorgung in Anlage III (Methoden, deren Bewertung ausgesetzt ist): Interstitielle Brachytherapie beim lokal begrenzten Prostatakarzinom • Beschluss vom 19. Juni 2008 über eine Änderung der Richtlinie Methoden Krankenhausbehandlung in Anlage II (Methoden, deren Bewertungsverfahren ausgesetzt sind): Protonentherapie beim Prostatakarzinom
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*siehe systematische Literaturrecherche*
Bei mehreren Alternativen ist die wirtschaftlichere Therapie zu wählen, vorzugsweise eine Therapie, für die ein Festbetrag gilt.	*nicht angezeigt*
[…] vorzugsweise eine Therapie, […] die sich in der praktischen Anwendung bewährt hat.	*nicht angezeigt*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Radium-223 V10XX03 Xofigo®	Xofigo wird angewendet zur Behandlung von Erwachsenen mit kastrationsresistentem Prostatakarzinom, symptomatischen Knochenmetastasen ohne bekannte viszerale Metastasen.
Radiontherapeutika:	
Strontium-89 V10BX01 Metastron®	Metastron® wird als Ergänzung oder Alternative zur externen Radiotherapie bei der palliativen Behandlung von durch Skelettmetastasen des Prostatakarzinoms hervorgerufenen Knochenschmerzen eingesetzt, wenn eine Hormontherapie nicht erfolgreich verlaufen ist. (GI/FI Metastron®, Österreich, 2011-11)
Samarium-153 V10BX02 Quadramet®	Quadramet® ist zur Linderung von Knochenschmerzen bei Patienten mit multiplen schmerzhaften osteoblastischen Skelettmetastasen indiziert, die in der Knochenszintigraphie Technetium (^{99m}Tc)-markierte Bisphosphonate anreichern. Das Vorliegen von osteoblastische Meta-stasen, die Technetium (^{99m}Tc)-markierte Bisphosphonate anreichern, sollte vor der Behandlung bestätigt worden sein. (SPC 2012-08)
Rhenium-186 V10AX05 Rheniumsulfid (^{186}Re) CIS bio international	Rheniumsulfid (^{186}Re) wird eingesetzt für die Radiosynoviorthese mittelgroßer Gelenke […] zur Behandlung einer chronischen Synovialitis mit rezidivierenden Gelenkergüssen bei rheumatoider Arthritis, seronegativer Spondylarthropathie (z.B. reaktive Arthritis, Psoriasisarthritis), pigmentierter villonodulärer Synovitis (nach erfolgter Operation), Hämophilie mit Arthropathie (zur Blutungsprophylaxe). Rheniumsulfid (^{186}Re) darf bei chronisch-entzündlichen Gelenkerkrankungen nur eingesetzt werden, wenn eine vorausgehende 6-monatige konservative Therapie einschließlich intraartikulärer Kortikoidinjektion nicht zum Erfolg geführt hat. […]. (GI Rheniumsulfid (^{186}Re) CIS bio international 2008-12)
Wirkstoffe mit Einfluss auf die Knochenstruktur und die Mineralisation:	
Zoledronsäure M05BA08 Zometa®	- Prävention skelettbezogener Komplikationen (pathologische Frakturen, Wirbelkompressionen, Bestrahlung oder Operation am Knochen oder tumorinduzierte Hyperkalzämie) bei erwachsenen Patienten mit fortgeschrittenen, auf das Skelett ausgedehnten, Tumorerkrankungen. - Behandlung erwachsener Patienten mit tumorinduzierter Hyperkalzämie (TIH). (FI Zometa® 2012-02)
Risedronsäure M05BA07 generisch	[…]. Behandlung der Osteoporose bei Männern mit hohem Frakturrisiko. (FI Risedronsäure AL 2011-08)
Ibandronsäure M05BA06 generisch	- Prävention skelettbezogener Ereignisse (pathologische Frakturen, Knochenkomplikationen, die eine Radiotherapie oder einen chirurgischen Eingriff erfordern) bei Patienten mit Brustkrebs und Knochenmetastasen - Behandlung von tumorinduzierter Hyperkalzämie mit oder ohne Metastasen. (FI Ibandronsäure AL 2012-05)

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Alendronsäuren M05BA04 generisch	[…]. Zur Therapie der Osteoporose bei Männern. […] (FI Fosamax® 2012-10)
Pamidronsäure M05BA03 generisch	Behandlung von Erkrankungen, die mit einer erhöhten Osteoklastenaktivität einhergehen: - Tumorinduzierte Hyperkalzämie - Osteolytische Läsionen bei Patienten mit Brustkrebs-assoziierten Knochenmetastasen - Multiples Myelom im Stadium III. (FI Novapam® 2012-11)
Clodronsäuren M05BA02 generisch	Osteolyse infolge von Knochenmetastasen solider Tumoren (z.B. Mamma-, Prostata-, Schilddrüsenkarzinom) oder infolge hämatologischer Neoplasien (z.B. Plasmozytom). Hypercalcämie infolge ausgedehnter Knochenmetastasierung oder durch maligne Tumoren induzierte Knochenzerstörung ohne Knochenmetastasen. (FI Bonefos® 2012-11)
Denosumab M05BX04 Xgeva®, Prolia®	Prävention von skelettbezogenen Komplikationen (pathologische Fraktur, Bestrahlung des Knochens, Rückenmarkkompression oder operative Eingriffe am Knochen) bei Erwachsenen mit Knochenmetastasen aufgrund solider Tumoren. (FI Xgeva® 2012-08) […]. Behandlung von Knochenschwund im Zusammenhang mit Hormonablation bei Männern mit Prostatakarzinom mit erhöhtem Frakturrisiko. Prolia® vermindert bei Männern mit Prostatakarzinom unter Hormonablationstherapie signifikant das Risiko für vertebrale Frakturen. (FI Prolia® 2012-11)
Wirkstoffe zur hormonablativen Therapie:	
Abirateronacetat L02BX03 Zytiga®	Zytiga® ist indiziert mit Prednison oder Prednisolon - zur Behandlung des metastasierten kastrationsresistenten Prostatakarzinoms bei erwachsenen Männern, deren Erkrankung während oder nach einer Docetaxel-haltigen Chemotherapie progredient ist. (FI Zytiga® 2011-09)
Degarelix L02BX02 Firmagon®	Firmagon® ist ein Gonadotropin-Releasing-Hormon-(GnRH)-Antagonist zur Behandlung von erwachsenen männlichen Patienten mit fortgeschrittenem hormonabhängigen Prostatakarzinom. (FI Firmagon® 2010-06)
Abarelix L02BX01 Plenaxis®	Plenaxis® ist angezeigt zur Einleitung einer hormonalen Kastration bei fortgeschrittenem oder metastasierendem hormonabhängigem Prostatakarzinom, wenn eine Androgensuppression erforderlich ist. (FI Plenaris® 2009-11)
Histrelin L02AE05 Vantas®	Palliative Behandlung bei fortgeschrittenem Prostatakrebs. (FI Vantas® 2011-02)

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Triptorelin L02AE04 generisch	Pamorelin® ist zur Behandlung des lokal fortgeschrittenen oder metastasierenden, hormonabhängigen Prostatakarzinoms indiziert. (FI Pamorelin® 2011-10)
Goserelin L02AE03 Zoladex®	Behandlung von Patienten mit fortgeschrittenem Prostatakarzinom, bei denen eine endokrine Behandlung angezeigt ist. (FI Zoladex®2012-04)
Leuprorelin L02AE02 generisch	Zur symptomatischen Behandlung des fortgeschrittenen hormonabhängigen Prostatakarzinoms. (FI Enantrone® 2012-06)
Buserelin L02AE01 Profact®	Profact® Depot 6,3 mg 2-Monatsimplantat ist angezeigt zur Behandlung des fortgeschrittenen hormonempfindlichen Prostatakarzinoms. Profact Depot 6,3 mg 2-Monatsimplantat ist jedoch nicht angezeigt nach beidseitiger Orchiektomie, da es in diesem Fall zu keiner weiteren Absenkung des Testosteronspiegels kommt. (FI Profact® 2011-10)
Bicalutamid L02BB03 generisch	Casodex® 50 mg ist angezeigt zur Behandlung von Patienten mit fortgeschrittenem Prostatakarzinom, bei denen in Kombination mit Maßnahmen zur Suppression des Plasmatestosterons auf Kastrationsniveau eine maximale Androgenblockade erreicht werden soll. Casodex® 150 mg ist angezeigt entweder als alleinige Therapie oder adjuvant zu radikaler Prostatektomie oder Strahlentherapie bei Patienten mit lokal fortgeschrittenem Prostatakarzinom und hohem Progressionsrisiko. (FI Casodex® 50 bzw. 150 mg 2011-06 bzw. -11)
Flutamid L02BB01 generisch	Zur Behandlung von Patienten mit fortgeschrittenem Prostatakarzinom, bei denen eine Suppression der Testosteronwirkungen indiziert ist: Initialtherapie in Kombination mit einem LHRH-Analogon oder in Verbindung mit Orchiektomie (komplette Androgenblockade) sowie bei Patienten, die bereits mit einem LH-RH-Analogon behandelt werden bzw. bei denen bereits eine chirurgische Ablatio testis erfolgt ist. Zur Behandlung von Patienten, die auf andere endokrine Therapieformen nicht ansprachen oder für die eine andere endokrine Therapie nicht verträglich, aber notwendigerweise indiziert ist. (FI Flutamid-CT 2012-02)
Cyproteronacetat G03HA01 generisch	Palliative Therapie des metastasierenden oder lokal fort-geschrittenen, inoperablen Prostatakarzinoms, wenn sich die Behandlung mit LHRH-Analoga oder der operative Eingriff als unzureichend erwiesen haben oder kontraindiziert sind. (FI Androcur® 2011-06)
Zytostatika:	
Cabazitaxel L01CD04 Jevtana®	Jevtana® ist in Kombination mit Prednison oder Prednisolon zur Behandlung von Patienten mit hormonrefraktärem metastasiertem Prostatakarzinom angezeigt, die mit einem Docetaxel-basierten Therapieschema vorbehandelt sind. (FI Jevtana® 2011-10)

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Docetaxel L01CD02 Taxotere®	Taxotere® ist in Kombination mit Prednison oder Prednisolon zur Behandlung von Patienten mit hormonrefraktärem metastasiertem Prostatakarzinom angezeigt. (FI Taxotere® 2011-12)
Mitoxantron L01DB07 Onkotrone®	Fortgeschrittenes und hormonresistentes Prostata-Karzinom in Kombination mit niedrig dosierten oralen Glucocorticoiden, einschließlich Prednison und Hydrocortison, zur Schmerzlinderung bei Patienten, die auf Analgetika nicht mehr ansprechen und bei denen eine Strahlentherapie nicht indiziert ist. (FI Onkotrone® 2010-08)
Estramustin L01XX11 Estracyt®	Palliative Behandlung des fortgeschrittenen, hormonrefraktären Prostatakarzinoms. (FI Estracyt® 2012-02)
Cisplatin L01XA01 Cisplatin HEXAL® PI	Palliative Polychemotherapie bei hormonrefraktären Prostatakarzinomen. (FI Cisplatin HEXAL® PI 2008-11)
Glucocorticoide:	
Prednison H02AB07 generisch	Palliativtherapie maligner Erkrankungen Hinweis: Prednison kann zur Symptomlinderung, z.B. bei Inappetenz, Anorexie und allgemeiner Schwäche bei fortgeschrittenenmalignen Erkrankungen nach Ausschöpfung spezifischer Therapiemöglichkeiten angewendet werden. Einzelheiten sind der aktuellen Fachliteratur zu entnehmen. (FI Decortin® 2012-02)
Prednisolon H02AB06 generisch	Palliativtherapie maligner Erkrankungen Hinweis: Prednisolon kann zur Symptomlinderung, z.B. bei Inappetenz, Anorexie und allge-meiner Schwäche bei fortgeschrittenen malignen Erkrankungen nach Ausschöpfung spezifischer Therapiemöglichkeiten angewendet werden. Einzelheiten sind der aktuellen Fachliteratur zu entnehmen. (FI Decortin® H 2012-04)
Methylprednisolon H02AB04 generisch	als ergänzende Maßnahme bei einer Zytostatika- oder Strahlentherapie im Rahmen bestehender Schemata zur Kombinationstherapie, palliativen Therapie bzw. antiemetischen Therapie. (FI Urbason® 2012-01)
Dexamethason H02AB02 generisch	Palliativtherapie maligner Tumoren. (FI Fortecortin® 2011-12)

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

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

Vorgang: 2012-B-070 Radium-223

Stand: Januar 2013

Synoptische Evidenzübersicht zur Ermittlung der zVT:

Inhalt

Indikation für die Recherche

Zur Behandlung von Patienten mit kastrationsresistentem Prostatakarzinom mit Knochenmetastasen.

The target population is patients with progressive symptomatic HRPC, with at least two skeletal metastases on bone scan and no known visceral metastases.

Specifically the target population is

- *Patients who have received docetaxel*
- *Patients who are not fit enough to receive docetaxel*
- *Patients not willing to receive docetaxel,*
- *Patients for whom docetaxel is not available for other reasons*

Berücksichtigte Wirkstoffe/Therapien

Radionuklide: Strontium-89, Samarium-153, Rhenium-186

Bisphosphonate: Zoledronsäure, Risedronsäure, Ibandronsäure, Alendronsäuren, Pamidronsäure, Clodronsäuren

Wirkstoffe zur hormonablativen Therapie: Abirateronacetat, Degarelix, Abarelix, Histrelin, Triptorelin, Goserelin, Leuprorelin, Buserelin, Bicalutamid, Flutamid, Cyproteronacetat

Zytostatika: Cabazitaxel, Docetaxel, Mitoxantron, Estramustin, Cisplatin,

Glucocorticoide: Prednison, Prednisolon, Methylprednisolon, Dexamethason

Weitere: Denosumab

Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation ***„kastrationsresistentes Prostatakarzinom mit Knochenmetastasen“*** durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am ***14.01.2013*** abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (einschl. NHS CRD-Datenbanken), MEDLINE (PubMed), Leitlinien.de (ÄZQ), AWMF, GIN, NGC, TRIP, DAHTA, NIHR HSC. Aufgrund der onkologischen Indikation wurde zusätzlich in folgenden Datenbanken bzw. Internetseiten folgende Organisationen gesucht: DGHO-Onkopedia, NCCN, ESMO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Es wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab ***781*** Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Davon wurden **17** Quellen eingeschlossen.

Abkürzungen

AIPC: Androgen-independent prostate cancer, **BSC**: Best supportive care, **CRPC**: castration-refractory prostate cancer, **ERT**: External beam radiotherapy, **HRPC**: hormone-refractory prostate cancer, **LHRH**: luteinizing hormonereleasing hormone, **RT**: Radiotherapy, **Sm-153**: Samarium-153, **SMR**: skeletal morbidity rate, **Sr-89**: Strontium-89, **SRE**: skeletal related event

Cochrane Reviews	
Yuen et al. Bisphosphonates for advanced prostate cancer. Stand: 2010. Cochrane Database of Systematic Reviews **2006**; (4):	**STUDIENMERKMALE**
	Fragestellung: effectiveness of bisphosphonates in relieving pain in patients with bone metastases from prostate cancer. **Methodik:** systematic review and meta-analysis of RCTs. **Suchzeitraum**: 1966 to May/June 2005 **Intervention**: bisphosphonate. **Komparatoren**: placebo, no bisphosphonate treatment (open control) or another bisphosphonate treatment (active control). **Endpunkte**: pain (all types of pain measurement are accepted, including analgesic consumption). **Anzahl der eingeschlossenen Studien**: 10. **Anzahl der eingeschlossenen Patienten**: 1955.
	ERGEBNISSE
	• **Pain response rates** (515 patients, 5 studies): The OR for was 1.54 (95% CI 0.97 to 2.44, P = 0.07), showing a trend of improved pain relief in the bisphosphonate group compared to placebo, although this was not statistically significant. • **Skeletal events rates** (1332 patients, 3 studies): The OR was 0.79 (95%CI 0.62 to 1.00, P = 0.05). This indicates a marginal statistically significant difference favouring bisphosphonates compared to placebo. • **Prostate cancer death**, **disease progression**, **radiological response, PSA response, reduction in analgesic consumption:** No statistically significant difference between the bisphosphonate group and placebo. • **Adverse events:** o **Nausea** (1021 patients, 2 studies): OR 1.35 (95%CI of 1.02 to 1.77, P = 0.03), indicating significant increase in patients who received bisphosphonates compared to placebo. o No increase in other adverse events. • **Authors' Conclusion:** Bisphosphonates should be considered for patients with metastatic prostate cancer for the treatment of refractory bone pain and prevention of skeletal events.

Weitere Systematische Reviews	
Ford JA et al. Denosumab for treatment of bone metastases secondary to solid tumours: Systematic review and network meta-analysis. Eur J Cancer **2013**; 49 (2): 416-30. Siehe auch: Sun et al. 2012, Peddi et al. 2013, Lipton et al. 2012	**STUDIENMERKMALE**
	Fragestellung: evidence for denosumab for the treatment of bone metastases secondary to solid tumours. **Patienten**: patients with bone metastases from any solid tumour. **Methodik:** systematic review of RCTs. **Suchzeitraum**: 1948 to April 2011. **Intervention**: Denosumab. **Komparatoren**: bisphosphonates, BSC (including radiotherapy, radionuclides, hormone therapy, strontium or samarium). **Endpunkte**: Primary: time to first SRE, time to first subsequent SRE, Secondary: skeletal morbidity rate (defined as ratio of the number of SRE per patient divided by the patient's time at risk), pain, quality of life and overall survival **Anzahl der eingeschlossenen Studien**: Gesamt: 8, Prostata: 2 (1 RCT Denosumab vs. Zoledronic acid bei kastrationsresistenten Patienten, 1 RCT Zoledronic acid vs. Placebo). **Anzahl der eingeschlossenen Patienten**: Denosumab vs. Zoledronic acid: 1901, Zoledronic acid vs. Placebo: 422
	ERGEBNISSE
	Zoledronic acid vs. Placebo (1 RCT, 422 Patienten): • **Time to first SRE**: no statistically significant difference. • **Time to first and subsequent SRE**: RR 0.64 (95% CI k.A., p=0.002). **Denosumab vs. Zoledronic acid** (1 RCT, 1901 Patienten): • **Time to first SRE:** HR 0.82 (95%CI 0.71 to 0.95, p= 0.0002) favouring Denosumab. • **Time to first and subsequent SRE**: RR 0.77 (0.66 to 0.89) favouring Denosumab. • **Pain**: no statistically significant difference in the time to moderate/severe pain (HR 0.89, 95%CI 0.77 to 1.04). • **Overall Survival**: no statistically significant difference. • **Adverse events:** lower renal impairment (16% versus 15%) and acute phase reaction (8% versus 18%). Denosumab was associated with higher incidence of hypocalcaemia (13% versus 6%) and osteonecrosis of the jaw (2 vs. 1%).
Machado et al. Efficacy of clodronate, pamidronate, and zoledronate in reducing morbidity and mortality in cancer patients with bone metastasis: a meta-analysis of randomized clinical trials. Clin Ther **2009**; 31	**STUDIENMERKMALE**
	Fragestellung: efficacy of clodronate, pamidronate, and zoledronate compared to placebo in reducing morbidity and overall mortality in cancer patients with metastatic bone disease. **Methodik:** systematic review and meta-analysis of RCTs. **Suchzeitraum**: from inception to January 2009. **Intervention**: clodronate, pamidronate, zoledronate. **Komparatoren**: placebo. **Endpunkte**: SREs (pathologic fractures, radiation to bone or bone surgery, hypercalthiscemia, overall mortality. **Anzahl der eingeschlossenen Studien**: Gesamt: 18, Prostata: 2. **Anzahl der eingeschlossenen Patienten**: k.A.

(5): 962-79.	**ERGEBNISSE**
	• **Reduction in all SRE**: statistically significant difference in favour of all bisphosphonates. Zoledronate: relative risk 0.70 (95% CI, 0.61 to 0.81; N = 1211); pamidronate: RR 0.81 (95% CI, 0.73 to 0.91; N = 2251); clodronate: RR 0.87 (95% CI, 0.75 to 1.00; N = 681). • **Mortality**: no statistically significant difference. • **Reduction in pathologic fractures**: statistically significant difference in favour of clodronate and zoledronate. clodronate: RR 0.76 (95% CI, 0.64 to 0.90; N = 1096); zoledronate: 0.60 (95% CI, 0.47 to 0.76; N = 1165). Pamidronate: No significant reduction: RR, 0.90 (95% CI, 0.75– 1.07; N = 2127). • **Reduction in Hypercalcemia**: zoledronate: RR 0.27 (95% CI, 0.10 to 0.72; N = 743); pamidronate: 0.60 (95% CI, 0.41 to 0.86; N = 2127); clodronate: 0.73 (95% CI, 0.56 to 0.97; N = 1079) • **Conclusions of the author:** no clear advantage of one drug over the others was observed (CIs overlapped substantially).
Zhu M et al. Zoledronate for Metastatic Bone Disease and Pain: A Meta-Analysis of Randomized Clinical Trials. Pain Med **2012**	**STUDIENMERKMALE**
	Fragestellung: short- and long-term effects of zoledronate for treating patients with metastatic bone disease. **Methodik:** systematic review and meta-analysis of RCTs. **Suchzeitraum**: up to october 2011. **Intervention**: zoledronate. **Komparatoren**: placebo. **Endpunkte**: SREs, bone pain, adverse events. **Anzahl der eingeschlossenen Studien**: Gesamt: 12, Prostata: 5. **Anzahl der eingeschlossenen Patienten**: Gesamt: 4.450.
	ERGEBNISSE

	• **Developing SREs:** statistically significant difference in favour of zoledronate. RR 0.75 (95% CI 0.69 to 0.81, p < 0.001).
	• **Pain:** The likelihood of experiencing a bone pain event was significantly lower in the zoledronate group than in the placebo group (RR 0.83, 95% CI 0.76 to 0.89, p < 0.001).
	• **Adverse events:**
	  ○ **Nausea, emesis, adverse renal events:** no statistically significant difference.
	  ○ **Pyrexia**: significantly higher relative risk in zoledronate group (RR 1.43, 95% CI 1.20 to 1.70, p < 0.001).
	  ○ **Fatigue:** significantly higher relative risk in zoledronate group (RR 1.26, 95% CI 1.10 to 1.43, p < 0.001),
	  ○ **Anemia**: significantly higher relative risk in zoledronate group (RR 1.33, 95% CI 1.14 to 1.55, p < 0.001).

G-BA	
Gemeinsamer Bundesausschuss (G-BA). Zusammenfassende Dokumentation über die Änderung der Arzneimittel - Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: Cabazitaxel. Vom 29. März **2012**.	**CABACITAXEL VS. ZWECKMÄßIGE VERGLEICHSTHERAPIE** • **Zweckmäßige Vergleichstherapie**: Die zweckmäßige Vergleichstherapie "Docetaxel in Kombination mit Prednison oder Prednisolon" gilt für Patienten, die nach einer Docetaxel-haltigen Chemotherapie progredient sind, grundsätzlich aber noch für eine adäquate Docetaxel-haltige Chemotherapie infrage kommen ("Rechallenge") und somit abweichend von der Festlegung der zweckmäßigen Vergleichstherapie durch den Unterausschuss Arzneimittel am 13. September 2011 nicht für Patienten, die während einer Docetaxel-haltigen Chemotherapie progredient sind. Für alle anderen Patienten wird Docetaxel nicht mehr als geeignete Therapieoption angesehen. Hier ist "Best Supportive Care" die zweckmäßige Vergleichstherapie. • **Zusatznutzen von Cabazitaxel:** o Für Patienten, die während oder nach einer Docetaxel-haltigen Chemotherapie progredient sind und für die eine erneute Behandlung mit **Docetaxel nicht mehr infrage kommt**, liegt ein Hinweis für einen geringen Zusatznutzen gegenüber der zweckmäßigen Vergleichstherapie vor. o Für Patienten, die nach einer Docetaxel-haltigen Chemotherapie progredient sind und für die eine erneute Behandlung mit **Docetaxel infrage kommt**, gilt ein Zusatznutzen als nicht belegt, da die erforderlichen Nachweise zum maßgeblichen Zeitpunkt durch den pharmazeutischen Unternehmer nicht vollständig vorgelegt wurden (§ 35a Abs. 1 Satz 5 SGB V).
Gemeinsamer Bundesausschuss (G-BA). Zusammenfassende Dokumentation über die Änderung der Arzneimittel - Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: Abirateronacetat. Vom 29. März **2012**.	**ABIRATERONACETAT VS. ZWECKMÄßIGE VERGLEICHSTHERAPIE** • **Zweckmäßige Vergleichstherapie:** Die zweckmäßige Vergleichstherapie "Docetaxel in Kombination mit Prednison oder Prednisolon" gilt für Patienten, die nach einer Docetaxel-haltigen Chemotherapie progredient sind, grundsätzlich aber noch für eine adäquate Docetaxel-haltige Chemotherapie infrage kommen ("Rechallenge") und somit abweichend von der Festlegung der zweckmäßigen Vergleichstherapie durch den Unterausschuss Arzneimittel am 13. September 2011 nicht für Patienten, die während einer Docetaxel-haltigen Chemotherapie progredient sind. Für alle anderen Patienten wird Docetaxel nicht mehr als geeignete Therapieoption angesehen. Hier ist "Best Supportive Care" die zweckmäßige Vergleichstherapie. • **Zusatznutzen von Abirateronacetat:** o Für Patienten, die während oder nach einer Docetaxel-haltigen Chemotherapie progredient sind und für die eine erneute Behandlung mit **Docetaxel nicht mehr infrage kommt**, liegt ein Hinweis für einen beträchtlichen Zusatznutzen gegenüber der zweckmäßigen Vergleichstherapie vor. o Für Patienten, die nach einer Docetaxel-haltigen Chemotherapie progredient sind und für die eine erneute Behandlung mit **Docetaxel infrage kommt**, gilt ein Zusatznutzen als nicht belegt, da die erforderlichen Nachweise zum maßgeblichen Zeitpunkt durch den pharmazeutischen Unternehmer nicht vollständig vorgelegt wurden (§ 35a Abs. 1 Satz 5 SGB V).

Leitlinien	

Deutsche Gesellschaft für Urologie (DGU). Interdisziplinäre Leitlinie der Qualität S3 zur Früherkennung, Diagnose und Therapie der verschiedenen Stadien des Prostatakarzinoms. Version 2.0-1.Aktualisierung 2011. Stand: September, **2011**.	**THERAPIE DES ANDROGENUNABHÄNGIGEN ODER KASTRATIONSRESISTENTEN PROSTATAKARZINOMS**
	
	Erstlinientherapie, symptomatische Patienten
	
	• Patienten mit symptomatischer progredienter Erkrankung unter medikamentöser Kastration und in gutem Allgemeinzustand soll als Erstlinientherapie die Gabe einer zytostatischen Therapie mit Docetaxel 75 mg/m2 Körperoberfläche alle drei Wochen in Kombination mit Prednisolon 5 mg zweimal täglich angeboten werden (LoE 1+, GoR B).
	• Weitere empfohlene Therapieoptionen: wöchentliche Gabe von Docetaxel, Mitoxantron und Estramustin (LoE 1++, GoR 0).
	
	Zweitlinientherapie
	
	• **Abirateron:** Patienten mit progredienter Erkrankung nach oder unter Chemotherapie und ECOG Status 0-2 sollen über die Möglichkeit einer Zweitlinientherapie mit Abirateron informiert werden (LoE: 1+ / GoR: A).
	• **Cabazitaxel:** Patienten mit progredienter Erkrankung nach/unter Chemotherapie und ECOG Status 0-1 sollen über die Möglichkeit einer Zweitlinientherapie mit Cabazitaxel informiert werden (LoE: 1+ / GoR: A). Unter Therapie mit Cabazitaxel zusätzlich zu Prednison wurde im Vergleich zu einer Therapie mit Mitoxantron eine Verlängerung des Gesamtüberlebens um 2,4 Monate im Median gezeigt. Informiert werden soll auch über die zu erwartenden Nebenwirkungen, insbesondere über die erhöhte Rate v. a. an hämatologischen Nebenwirkungen Grad 3-5, die auch behandlungsbedingten Tod einschließen (LoE: 1+ / GoR: A).
	• **Weitere zytostatische Therapie:** (Docetaxel in wöchentlicher oder dreiwöchentlicher Dosierung, Mitoxantron oder Estramustin) kann Symptome lindern. Ein positiver Einfluss auf die Überlebenszeit ist nicht gesichert (LoE: 1+ / GoR: 0).
	
	THERAPIE VON KNOCHENMETASTASEN
	
	• **Generell:**
	  ○ Zur palliativen Therapie von Knochenmetastasen stehen neben der analgetischen Behandlung die antihormonelle Therapie, Chemotherapie, lokale Bestrahlung (ggf. in Kombination mit chirurgischer Intervention bei spinaler Kompression), Gabe von Bisphosphonat und von Denosumab sowie die Applikation von Radionukliden zur Verfügung (LoE: 1++).
	  ○ **Bestrahlung:** Die lokale perkutane Bestrahlung soll bei Knochenmetastasen bei folgenden Situationen eingesetzt werden: drohender spinaler Kompression, erhöhtem Frakturrisiko (LoE: 1+ / GoR: A). Bei Persistenz lokalisierter Knochenschmerzen unter systemischer Therapie soll die perkutane Bestrahlung eingesetzt werden (LoE: 1++ / GoR: A).
	  ○ **Radionuklide:** Radionuklide können bei multiplen Knochenmetastasen im hormonrefraktären Stadium mit unzureichender Schmerzkontrolle eingesetzt werden (LoE: 1++ / GoR: 0).
	
	• **Prävention von Komplikationen bei Knochenmetastasen im kastrationsresistenten Stadium:**
	  ○ Prävention von Komplikationen bei Knochenmetastasen im kastrationsresistenten Stadium soll als Bisphosphonat **Zoledronsäure** oder der monoklonale Antikörper **Denosumab** unter Aufklärung von Nutzen und Schaden angeboten werden (LoE: 1+).

	ANMERKUNGEN
	• S3 Leitlinie. • Suchzeitraum der Literaturrecherche: k.A.
Working group of the Clinical Practice Guideline on Prostate Cancer Treatment. Clinical practice guideline for prostate cancer treatment. Madrid: National Plan for the NHS of the MSC Aragon Institute of Health Sciences(I+CS), **2008** Clinical Practice Guidelines in the NHS I+CS No 2006/02	**BONE METASTASES IN PATIENTS WITH AIPC**
	Bisphosphonates

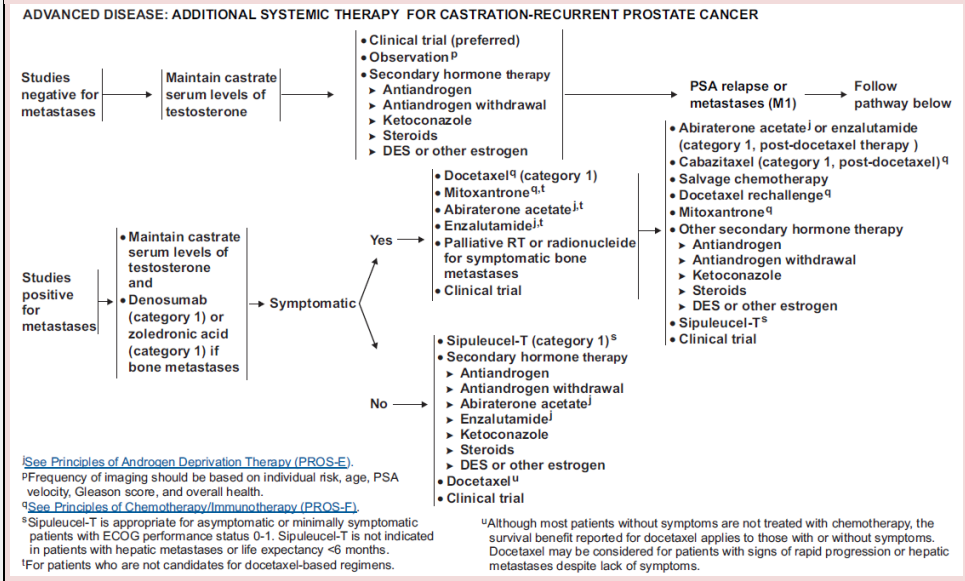
	• **Skeletal events:**
	  ○ In patients with AIPC, zoledronic acid at a dose of 4 mg produced a statistically significant decline in skeletal events when compared with placebo (RR = 0.640; p = 0.002). This decrease was highest in patients without pain. When an 8 mg dose of zoledronic acid was compared with placebo, the difference was not significant (LoE 1-) (basiert auf 1 RCT).
	  ○ Zoledronic acid statistically delayed the first skeletal episode by more than 5 months compared to placebo (p = 0.009) (LoE 1-) (basiert auf 1 RCT).
	  ○ In patients with AIPC treated with zoledronate, the RR for the proportion of patients with a skeletal episode was significant compared with placebo: RR = 0.71 (95% CI: 0.50 to 0.99 (LoE 1-) (basiert auf 1 RCT).
	  ○ In patients with AIPC, there was a modest reduction of skeletal events in those treated with bisphosphonates vs. placebo: 37.8% vs 43.0%; an absolute risk reduction of 5.2% (LoE 1++) (basiert auf 1 RCT).
	• **Fractures**: significant difference in favour of zoledronic acid compared to placebo: RR = 0.57 (95% CI: 0.38 to 0.88 (LoE 1-) (basiert auf 1 RCT).
	• **Pain relief**:
	  ○ In patients with AIPC, there was a non-significant trend towards better results for bone metastasis pain relief with bisphosphonates than with placebo (LoE 1++) (basiert auf 1 RCT).
	  ○ In patients with AIPC, zoledronic acid at a dose of 8 mg produced an improvement in pain rating after 15 months of treatment when compared with placebo (p = 0.026). No significant differences were found when comparing a 4 mg dose of bisphosphonate with placebo (p = 0.134). No significant differences in analgesia levels when comparing each of these doses with placebo (LoE 1-) (basiert auf 1 RCT).
	• **Mortality**: In patients with AIPC, the median survival time was 464 days for those treated with placebo, 546 days for the group receiving a 4 mg dose of zoledronate (p = 0.091) and 407 days for those who received a dose of 8 mg (p = 0.386) (LoE 1-) (basiert auf 1 RCT).
	• **Adverse events**: In patients with AIPC, the use of zoledronic acid produced a deterioration in renal function: 15.2% of patients treated at a dose of 4 mg, 20.7% of those who received a dose of 8 mg and 11.5% of patients treated with placebo (LoE 1-) (basiert auf 1 RCT).
	• **Quality of life**: In patients with AIPC, the quality of life did not differ significantly when comparing bisphosphonate and placebo (LoE 1++) (basiert auf 1 RCT).

	Radiopharmaceuticals

	• **Pain relief:**
	  ○ For patients treated with Sr-89 vs. placebo, no significant differences between the two treatments were found in the long term (1-3 years), but there were differences in the short term (5 weeks) (LoE 1++) (basiert auf 2 RCTs).
	  ○ When Sr-89 was compared with local external beam radiotherapy (RT), some studies found less pain in the group treated with Sr-89 + radiotherapy (RT), although in others there were no differences (LoE 1++) (basiert auf 2 RCTs).

	○ When Sr-89 + local RT was compared with local RT, the reported pain was similar in both groups, but the appearance of new painful locations was significantly higher in the group receiving external radiotherapy (LoE 1++) (basiert auf 2 RCTs). ○ The use of Sm-153 has positive effects on pain 1-4 weeks after starting treatment, when compared with placebo (correlation coefficient r = 0.78; p <0.0001). In addition, it decreased the use of opioids 3-4 weeks after starting treatment, when compared with placebo (p <0.0284) (LoE 1++) (basiert auf 1 RCT). • **Mortality:** ○ When comparing Sr-89 vs. local external beam RT, biochemical progression-free survival was comparable between the two groups, while overall survival was significantly higher in the group receiving external beam RT. A different test carrying out the same comparison, overall survival was similar in both groups (LoE 1++) (basiert auf 2 RCTs). ○ When comparing Sr-89 with placebo, the group treated with Sr-89 showed better overall survival at 2 years (LoE 1++) (basiert auf 1 RCT). ○ When comparing Sr-89 + chemotherapy (CT) with CT, overall survival in the Sr-89 group was better (LoE 1++) (basiert auf einer Phase 2 Studie). • **Adverse events:** ○ Sr-89 was associated with haematological toxicity (thrombocytopenia, neutropenia) in approximately 30-50% of patients who received it (usually to a moderate degree (LoE 1++) (basiert auf NICE Guideline). ○ In randomised trials comparing Sr-89 with local RT, the rate of adverse effects (haematological toxicity and nausea or vomiting) was similar in both groups (LoE 1++) (basiert auf 2 RCTs). ○ The only statistically significant side effect associated with Sm-153 was temporary and slight myelosuppression (LoE 1++) (basiert auf 1 RCT). • **Quality of life:** ○ When comparing Sr-89 + local RT with local RT, no significant differences were found between the two groups regarding the quality of life (LoE 1++) (basiert auf 1 RCT).
	Recommendations
	• Routine use of bisphosphonates (zoledronic acid) as a preventive treatment for bone complications is not recommended. Zoledronic acid (4 mg every 3 weeks) can be offered in selected patients, and those who are hormone-independent or with demonstrated metastasis (GoR B). • Treatment with Sr-89 or Sm-153 can be proposed in men with androgen-independent prostate cancer (AIPC) when third level analgesics are required to adequately control bone pain. A correct haematological formula (> 3,500 leukocytes and > 150,000 platelets) and a bone scan showing bone metastasis are essential before administration (GoR A).
	ANMERKUNGEN
	• Suchzeitraum der Literaturrecherche: k.A. • Vergleichbar mit S3-Vorgehen.
National Comprehensive Cancer Network. NCCN Clinical Practice Guide-lines in Oncology: Prostate Cancer. Version 1.**2013.**	**CHEMOTHERAPY**
	• Every 3-week **docetaxel and prednisone** is the preferred first-line chemotherapy treatment based upon phase 3 clinical trial data for men with symptomatic castration-recurrent prostate cancer. Symptomatic patients who are not candidates for docetaxel-based regimens could be treated with **mitoxantrone and prednisone** (GoR 2A). • Men who have failed docetaxel-based chemotherapy should be encouraged

	to participate in clinical trials. However, **cabazitaxel with prednisone** has been shown in a randomized phase 3 study to prolong overall survival, progression-free survival, and PSA and radiologic responses when compared with mitoxantrone and prednisone and is FDA approved in the post-docetaxel second line setting (GoR 1). • **Mitoxantrone** has not demonstrated a survival improvement in the post-docetaxel setting but remains a palliative therapeutic option, particularly in men who are not candidates for cabazitaxel therapy. No chemotherapy regimen to date has demonstrated improved survival or quality of life following cabazitaxel, and trial participation should be strongly encouraged. Outside of a clinical trial, several systemic agents have shown palliative benefits in single arm studies. Treatment decisions should be individualized based on comorbidities and functional status. Finally, for patients who have not demonstrated definitive evidence of progression on prior docetaxel therapy, retreatment with this agent can be attempted (GoR 2A).
	ANDROGEN DEPRIVIATION THERAPIES
	• **Abiraterone acetate with low-dose prednisone** prolongs overall survival among men with metastatic CRPC who have been treated previously with docetaxel, as demonstrated in a randomized, placebo-controlled phase III trial. Statistically significant improvements in time to progression, tumor response and PSA also were observed. Thus, the administration of abiraterone acetate (1000 mg per day without food) with prednisone (5 mg twice daily) is a reasonable treatment option after docetaxel has failed. Side effects of abiraterone acetate that require ongoing monitoring include hyper-tension, hypokalemia, peripheral edema, liver injury, and fatigue, as well as the known side effects of ADT and long-term corticosteroid use (GoR 1).
	BONE METASTASES
	• In men with CRPC who have bone metastases, **denosumab and zoledronic acid** have been shown to prevent disease related skeletal complication, which include fracture, spinal cord compression, or the need for surgery or RT to bone (GoR 1). When compared to zoledronic acid, denosumab was shown to be superior in prevention of skeletal related events. • Systemic therapy for metastatic CRPC: For symptomatic patients who cannot tolerate docetaxel, **mitoxantrone** may provide palliative benefit. The traditional option of glucocorticoids and external beam radiotherapy (EBRT) for symptomatic bone metastases remains available for patients with focal pain or impending pathologic fractures. • Widespread bone metastases can be palliated using strontium 89 or samarium 153 with or without focal external bean radiation if the patient is not responding to palliative chemotherapy or systematic analgesia and if he is not candidate for localized EBRT (GoR 2A).
	DOCETAXEL FAILURE IN METASTATIC CRPC PATIENTS
	• Currently, no consensus exists for the best additional therapy following docetaxel failure in metastatic CRPC patients. Options include abitaterone acetate (GoR 1), cabazitaxel (GoR 1), salvage chemotherapy, docetaxel rechallenge, mitroxantrone, secondary ADT, sipuleucel-T, and participation in clinical trials (GoR 2A). • **Abirateron acetate** has demonstrated clinical benefit and thus represents a new standard of care after failure of docetaxel chemotherapy for metastatic CRPC (GoR 1). It should be given with Prednison. • The NCCN panel included **cabazitaxel** as an option for second-line therapy after docetaxel failure for patients with symptomatic metastatic CRPC. This

	recommendation is category 1 based on randomized phase III study data, however, extension of survival is relatively short and side effects are relatively high. In addition, **supportive care** should include anti-emetics and symptom directed anti-diarrheal agents. Cabazitaxel should be stopped upon clinical disease progression or intolerance (GoR 2A). • The decision to initiate therapy with abiteraterone acetate with prednisone or cabazitaxel with prednisone in the post-docetaxel CRPC setting should be based on the available high-level evidence of safety, efficacy, and tolerability of these agents and the application of this evidence to an individual patient. There are no randomized trials comparing these two agents, and there are currently no predictive models or biomarkers that are able to identify patients who are likely to benefit from either approach (GoR 2A). • NCCN panelists agreed that **docetaxel rechallenge** may be useful in some patients (GoR 2A). • **Mitoxantrone** remains a palliative treatment option for men who are not candidates for taxane-based therapy (GoR 2A). • While limited evidence suggests potential palliative benefits with mitoxantrone and a variety of chemotherapeutic or hormonal agents, no randomized studies have demonstrated improved survival with these agents after docetaxel failure (GoR 2A).
	
	ANMERKUNGEN
	• Suchzeitraum der Literaturrecherche: k.A. • Vergleichbar mit S3-Vorgehen.
	METASTATIC PROSTATE CANCER
Horwich et al. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol **2010**; 21 Suppl 5 v129-v133.	• **Mitoxantrone** can be considered if there is a contraindication to docetaxel, but is inferior in palliation and does not prolong survival (LoE 1, GoR B). ○ In a large international multicentre stage III trial, two different schedules of docetaxel were compared with a combination of mitoxantrone and prednisolone. 1006 patients were recruited and randomized between weekly docetaxel at 30 mg/m2 for 5 weeks out of every 6, 75 mg/m2 with docetaxel every 3 weeks and mitoxantrone 12 mg/m2 every 3 weeks. Patients in all arms of the trial received prednisone. Median survival was 19.2 months in the 3-weekly docetaxel arm, 17.8 months in the weekly docetaxel arm and 16.3 months after mitoxantrone. Just under one quarter treated with docetaxel had a significant improvement in quality of life. The conclusion was that 3-weekly docetaxel was superior to the other treatments in its palliative effects and in prolongation of survival.

	• **Radioisotope** therapy with strontium-89 or samarium-153 should be considered for patients with painful bone metastases from castration-refractory disease (LoE 1, GoR B). • Intravenous **bisphosphonates** should be considered for patients with bone pain resistant to palliative radiotherapy and conventional analgesics (LoE 1, GoR B).
	ANMERKUNGEN
	• Suchzeitraum der Literaturrecherche: k.A.
Heidenreich et al. EAU Guidelines on Prostate cancer. Stand: Juni **2010**.	**CASTRATION-REFRACTORY PCA (CRPC)**
	Androgen deprivation in castration-independent PCa
	• Continued testicular androgen suppression has a minimal overall effect in CRPC. The recommendation to continue androgen deprivation therapy with LHRH analogues, despite PSA progression, is based on 1 RCT. This study demonstrated significantly lower survival rates in patients without complete androgen blockade. However, these data have been challenged by two recent trials that showed only a marginal survival benefit for patients remaining on LHRH analogues during second- and third-line therapies *(abgeleitet aus einer Phase II Studie und einer retrospektiven Studie).* • However, in the absence of prospective data, the modest potential benefits of a continuing castration outweigh the minimal risk of treatment. Androgen suppression should therefore be continued indefinitely in CRPC patients.
	Cytotoxische Therapie
	• **Docetaxel-based chemotherapy compared to mitoxantrone + prednisone therapy:** A significant improvement in median survival of about 2 months occurred with docetaxel-based chemotherapy compared to mitoxantrone + prednisone therapy. Pain relief was similar in both groups, though side-effects occurred significantly more often with docetaxel than with mitoxantrone. *(Basiert auf 2 RCTs).* • **Mitoxantrone combined with corticosteroids vs. hydrocortisone:** No differences were observed with regard to survival, PSA response, and median time to progression. However, the QoL was significantly improved in the combination arm compared to hydrocortisone. *(Basiert auf 1 RCT).* • **Mitoxantrone + prednisone versus prednisone:** significant benefit in pain reduction in the combination group (29%) versus prednisone alone (12%, $p = 0.01$). duration of palliation was longer in patients who received mitoxantrone (43 weeks vs 18 weeks, $p < 0.0001$) *(Basiert auf 1 RCT).* • **Cabazitaxel, + prednisone versus mitoxantrone + prednisone:** *(1 RCT, 755 CRPC Patienten)*: ○ **Survival**: Patients in the cabazitaxel arm experienced a significantly increased overall survival of 15.1 versus 12.7 months ($p < 0.0001$) in the mitoxantrone arm. The cabazitaxel treatment arm also showed significant improvement in progression-free survival (2.8 vs 1.4 months, $p < 0.0001$). ○ **Response rate**: Patients in the cabazitaxel arm experienced a significantly increased objective response rate (14.4% vs 4.4%, $p < 0.005$), and PSA response rate (39.2% vs 17.8%, $p < 0.0002$). ○ **Adverse events:** Treatment-associated WHO grade 3-4 side-effects developed significantly more often in the cabazitaxel arm, particularly hematological (68.2% vs 47.3%, $p < 0.0002$) and non-haematological toxicities (57.4% vs 39.8%, $p < 0.0002$).

	Knochenmetasen
	• **Radiotherapy:** External beam radiotherapy is highly effective, even as single fraction. *(Basiert auf 1 RCT).* • **Radioisotopes:** strontium-89 and samarium-153 can partially or completely decrease bone pain in up to 70% of patients, but should not be given too late when pain is intractable. • **Bisphosphonates:** Currently, bisphosphonates can be proposed to patients with HRPC bone metastases to prevent skeletal complications, even if the best dosing interval is unclear. At present, it is every 3 weeks or less. The toxicity, e.g. jaw necrosis, of these drugs, especially aminobisphosphonate, must always be kept in mind. *(Basiert auf 1 RCT).*
	RECOMMENDATIONS
	• In patients with symptomatic osseous metastases due to CRPC, **either docetaxel or mitoxantrone with prednisone or hydrocortisone** are viable therapeutic options (GoR A). • Second-line **docetaxel** should be considered in previously responding patients to docetaxel. Otherwise, treatment is tailored to the individual patient (GoR B). • According to the positive results of a prospective randomised clinical phase III trial (LoE 1), **cabazitaxel** should be considered in the management of progressive CRPCA following docetaxel therapy (GoR A). • **Bisphosphonates** may be offered to patients with skeletal masses (mainly zoledronic acid has been studied) to prevent osseous complications. However, the benefits must be balanced against the toxicity of these agents, in particular jaw necrosis must be avoided (GoR A). • Palliative treatments such as **radionuclides, external beam radiotherapy**, adequate use of analgesics should be considered early in the management of painful osseous metastases (GoR B).
	ANMERKUNGEN
	• Suchzeitraum der Literaturrecherche: bis Januar 2010. • Mit S3-Vorgehen vergleichbar.
Climent et al. Recommendations from the Spanish Oncology Genitourinary Group for the treatment of patients with metastatic castration-resistant prostate cancer. Crit Rev Oncol Hematol **2012**; 83 (3): 341-52.	**METASTATIC DOCETAXEL-REFRACTORY CRPC PATIENTS**
	Continuing treatment with LHRH
	• Reports of clinical experiences in men who have progressed on endocrine therapy, and have been treated with chemotherapy, have shown an increase in PSA levels, with a subsequent decrease when androgen deprivation was reinstituted, suggesting that a persistent population of hormone-sensitive tumor cells persists despite overall progressive disease. • In the absence of prospective data, the current recommendation is to maintain androgen deprivation therapy with LHRH analogs indefinitely in patients with CRPC. ➢ **Recommendation:** LHRH analogs should be continued in patients with CRPC (LoE: 3, GoR C).
	Secondary hormonal therapy
	• After failure of complete androgen blockade in metastatic prostate cancer, there are several treatment options that can be offered to patients before moving on to chemotherapy. However, their impact has not been established in randomized clinical trials, and the reported responses have not shown to

	be long lasting. Therefore, these therapies should be reserved for asymptomatic or oligosymptomatic patients, or for those with major contraindications for chemotherapy. ➢ **Recommendation:** Antiandrogen withdrawal should be considered in most patients with CRPC, except in symptomatic patients or in those who show a quick and aggressive progression (LoE 2b, GoR B).
	Treatment options after docetaxel
	• **Abiraterone + prednisone vs placebo + prednisone in metastatic docetaxel-refractory CRPC patients** *(1 RCT, 1195)*: Treatment with abiraterone resulted in a significant improvement in overall survival from 10.4 to 14.8 months ($p < 0.0001$). Abiraterone therapy also yielded superior outcomes with respect to time to PSA progression (10.2 versus 6.6 months; $p < 0.0001$), radiographic progression-free survival (5.6 versus 3.6 months; $p < 0.0001$) and PSA response rate (29.1% versus 5.5%; $p < 0.0001$). Several grade 3–4 toxicities were more frequent in abiraterone treated patients, including fluid retention (2.3% versus 1.0%), hypokalemia (3.8% versus 0.8%), hypertension (1.3% versus 0.3%) and cardiac disorders (4.1% versus 2.3%). ➢ **Recommendation**: Treatment with abiraterone should be considered for patients with metastatic CRPC following progression with docetaxel (LoE 1b, GoR A). • **Cabazitaxel + prednisone vs. mitoxantrone + prednisone in metastatic docetaxel-refractory CRPC patients** *(RCT, 750 patients)*: Median overall survival was 15.1 months in the cabazitaxel group versus 12.7 months in the mitoxantrone group. This result corresponds to a 30% reduction in the relative risk of death (HR: 0.70; 95% CI: 0.59–0.83; $p < 0.0001$). Median progression-free survival was 2.8 months in the cabazitaxel group and 1.4 months in the mitoxantrone group (HR: 0.74; 95% CI: 0.64–0.86; $p < 0.001$). Patients treated with cabazitaxel had significantly higher rates of tumor response (14.4% versus 4.4%) and PSA response (39.2% versus 17.8%). ➢ **Recommendation:** Cabazitaxel should be considered for the treatment of patients with metastatic CRPC with progressive disease after docetaxel-based treatment (LoE 1b, GoR A).
	Docetaxel rechallenge und mitoxantrone
	• **Docetaxel rechallenge**: In a prospective phase II study, patients who initially responded and then progressed after a period of biochemical remission of at least 5 months (range: 5–10 months), and who were not receiving corticosteroids before the rechallenge, were retreated with docetaxel 75 mg/m2 every 3 weeks plus oral prednisone 10 mg daily. The results were worse than previously reported in retrospective studies: a decrease of 50% in PSA levels was observed in 24.5% of patients, median progression-free survival was 5 months and the median overall survival since enrollment was 13 months. Despite these results, docetaxel rechallenge is considered an active treatment. The observed rate of severe neutropenia is lower than that described for cabazitaxel. Thus, rechallenge with docetaxel can be considered an option for patients who require chemotherapy but show significant cabazitaxel related toxicity. • **Mitoxantrone plus prednisone vs. cabazitaxel plus prednisone** *(1 RCT).* mitoxantrone plus prednisone was better tolerated but inferior to cabazitaxel plus prednisone in terms of overall survival. In this heavily pretreated population, mitoxantrone plus prednisone produced a PSA response rate in18% of patients, and pain response in 8% of patients; median progression-free survival was 1.4 months and median overall survival was 12.7 months. ➢ **Recommendation:** Alternative treatments after docetaxel and/or cabazitaxel and/or abiraterone include docetaxel rechallenge, mitoxantrone, oral cyclophosphamide or vinorelbine chemotherapy (LoE 2b, GoR B).

Knochenmetastasen

- **zoledronic acid vs. placebo** *(1 RCT, 643 patients)*: more patients who received placebo suffered from skeletal-related events compared to those who received zoledronic acid at 4mg (44.2% versus 33.2%; difference: −11.0%; 95% CI: −20.3% to −1.8%; p = 0.021). Also, significantly fewer patients who received zoledronic acid at 4mg experienced a fracture (22.1% versus 13.1%, p = 0.015). Median time to the first skeletal-related event was longer in patients treated with zoledronic acid than in patients who received placebo (488 versus 321 days; p = 0.01).
- **Denosumab vs. zoledronic acid** *(1 RCT, 1904 patients)*: The median time to first on-study skeletal-related event was 20.7 months for denosumab compared with 17.1 months for zoledronic acid (HR: 0.82; 95% CI: 0.71–0.95; p = 0.0002 for non-inferiority; p = 0.008 for superiority). Serious adverse events were recorded in a similar proportion in both arms (63% in the denosumab arm versus 60% in the zoledronic acid arm). More events of hypocalcemia occurred in the denosumab group (121 [13%]) than in the zoledronic acid group (55 [6%]; p < 0.0001). Osteonecrosis of the jaw occurred infrequently but more frequently in denosumab treated patients (22 [2%] versus 12 [1%]; p = 0.09).

➢ **Recommendation:** For bone targeted treatments zoledronic acid (4 mg intravenously every 3–4 weeks) or denosumab (120 mg subcutaneously every 4 weeks; if approved by regulatory authorities) are recommended for the treatment of bone metastases in patients with CRPC to prevent bone complications (LoE 1b, GoR A).

Radionuclides and palliative treatments

- When used after radiotherapy palliative treatment, strontium-89 has demonstrated a significant improvement of time to pain recurrence (LoE 1b, GoR A).
- In patients with castration-resistant disease and painful bone metastases, samarium SM 153 lexidronam offers pain relief and decreases analgesic consumption (LoE 1b, GoR A).

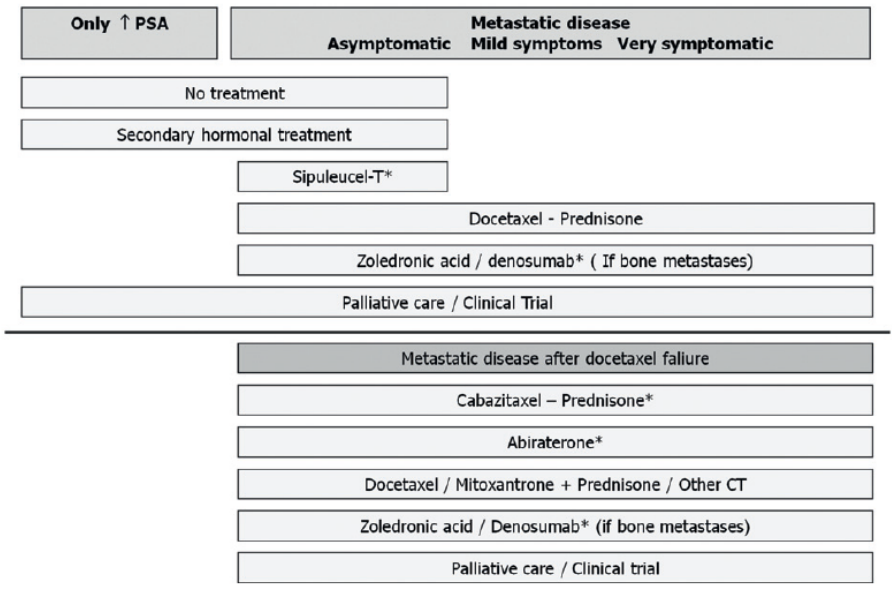


Fig. 1. Treatment algorithm for patients with metastatic castration-resistant prostate cancer.
CT: chemotherapy; PSA: prostate-specific antigen. *Not approved for use by the European Medicines Agency.

ANMERKUNGEN

- Suchzeitraum der Literaturrecherche: from 1980 to February 2011

Australian Cancer Network Management of Metatastic Prostate Cancer Working Party. Clinical Practice Guidelines for the management of locally advanced and metastatic prostate cancer. Cancer Council Australia and Australian Cancer Network(**2010**)	**CASTRATION-RESISTANT PROSTATE CANCER**
	Hormone manipulations
	• Data from large randomised studies are limited. No second-line hormone manipulation in an RCT has been clearly shown to lead to an improvement in overall survival. A minority of patients have prolonged disease control with further hormone manipulations such as an anti-androgen or adrenal androgen suppression with ketoconazole and hydrocortisone In one RCT, overall quality of life scores, pain scores and gastrointestinal symptom scores were significantly better with prednisone compared with flutamide (LoE 2). • There is a sequence of actions that should be followed when a patient is shown to have progressive cancer on androgen deprivation therapy. First, confirm that the patient has a castrate level of testosterone if on an LHRH agonist therapy. If the patient is also on a nonsteroidal anti-androgen, this agent could be withdrawn and observed for the possibility of an anti-androgen withdrawal phenomenon. It is reasonable to trial further hormone manipulations if the patient is asymptomatic or minimally symptomatic prior to use of chemotherapy (e.g. docetaxel) (GoR C).
	Continuing LHRH agonists after the patient has become hormone refractory
	• There is insufficient evidence to make a recommendation as to whether a patient should continue LHRH agonist therapy once his disease has progressed while on androgen deprivation (GoR D).
	Bisphosphonates
	• **Skeletal-related events**: Zoledronic acid (iv) 4mg three-weekly for 15 months significantly reduced skeletal-related events in men with asymptomatic or mildly symptomatic hormone refractory prostate cancer (LoE 2). ➢ **Recommendation**: Zoledronic acid may be considered for the prevention of skeletal-related events in men with asymptomatic or mildly symptomatic hormone-resistant or castrate-resistant metastatic prostate cancer. Men, as part of the informed consent process, should be made aware that nine men will need to be treated for one to achieve a benefit, and that there is a risk of osteonecrosis of the jaw occurring during treatment. Dental review is advised and be sought before commencing treatment (GoR B). • **Bone Pain**: o **Zoledronic acid:** For men with initially asymptomatic or mildly symptomatic bone metastases, zoledronic acid has been shown to be associated with less bone pain at 21 and 24 months (LoE 2). o **Clodronate**: Three underpowered randomised controlled trials have failed to show a significant improvement in the control of metastatic bone pain over placebo either with clodronate alone or in combination with estramustine sulphate. A fourth study found a significant improvement with the addition of clodronate to mitoxantrone/prednisone only in a subgroup of men with moderate rather than mild baseline pain (LoE 2). o **Pamidronate disodium** has not been shown to be effective in controlling bone pain in metastatic prostate cancer, except in a subgroup of men with stable or falling analgesia in which a significant but modest benefit was observed in worst pain (LoE 2). ➢ **Recommendation:** On the basis of the available evidence, bisphosphonates are not recommended for routine palliation of symptomatic bone disease in men, with hormone-resistant prostate cancer with a possible exception of zoledronic acid, where there is some evidence of a benefit in castrate-resistant men (GoR C).

	Radiotherapy
	External beam radiotherapy: **Pain Control** • **strontium 89**. Limited evidence suggests that strontium 89 is effective as a treatment for pain relief (LoE 2). • **samarium 153**. A small volume of low- to moderate-quality grade II consistent evidence suggests that samarium 153 is an effective treatment for relief of bone metastases pain (LoE 2). ➢ **Recommendation:** Unsealed radioisotopes may be considered for the management of multifocal bone pain alongside other options of treatment in patients with hormone refractory prostate cancer (GoR C). **Overall survival** ➢ **Recommendation:** The impact of unsealed radioisotopes on overall survival in men with castrate-resistant metastatic prostate cancer is undefined. The relative roles of unsealed radioisotopes and the newer chemotherapeutic agents (e.g. taxanes) and bisphosphonates have also not been defined (Gor D). **Quality of life** • There are few studies examining the effect of strontium 89 on quality-of-life endpoints and these are generally dissimilar in design and the examined endpoint. The design of these studies is not high quality. In studies that show some beneficial effect, the effects are modest at best, with many patients also exhibiting a worsening of quality-of-life endpoints (LoE 2). ➢ **Recommendation:** It is not known what effect unsealed radioisotopes have on quality of life for men with metastatic prostate cancer (GoR C). **Side effects (toxicity)** • **strontium 89.** At the doses administered, and in a population of patients who were not pre-treated with chemotherapy, strontium 89 appears associated with mild haematological toxicity. The possibility of significant serious adverse events cannot be excluded by the published trials, compared with the use of best supportive care or localised radiation (LoE 2). • **samarium 153.** The limited evidence demonstrates that samarium 153 results in falls in white cell counts and platelets. However, in patients with adequate marrow reserve, the development of grade III or IV neutropaenia or thrombocytopaenia is uncommon (<15%) and clinically significant toxicity is rare. There is no randomised evidence comparing samarium with other radioisotopes such as strontium (LoE 2). ➢ **Recommendation:** Unsealed radioisotopes alone may be associated with higher haematological adverse events compared with supportive care or localised radiation, although overall these rates are low. Unsealed radioisotopes in combination with other treatments such as radiotherapy have higher rates of serious toxicity than radiotherapy alone. The toxicity of unsealed radioisotopes in combination with modern chemotherapy (taxanes) has not yet been defined and caution should be exercised if such combinations are considered (GoR C).
	Chemotherapy
	➢ **Recommendation:** Docetaxel in combination with prednisone is appropriate in the first line setting to improve survival, pain and quality of life in good performance patients with castrate-resistant metastatic prostate cancer (GoR B). ➢ **Recommendation:** The combination of mitoxantrone and prednisolone also offers palliative benefit but no survival benefit compared to docetaxel (Gor C).

	ANMERKUNGEN
	• Suchzeitraum der Literaturrecherche: Bis **April 2006** • Mit S3-Vorgehen vergleichbar
National Institute for Health and Clinical Excellence (NICE). Prostate cancer: diagnosis and treatment. London: NICE, **2009**	**CHEMOTHERAPIE**
	• Docetaxel is recommended, within its licensed indications, as a treatment option for men with hormone-refractory metastatic prostate cancer only if their Karnofsky performance- status score is 60% or more. • It is recommended that treatment with docetaxel should be stopped: - at the completion of planned treatment of up to 10 cycles, or - if severe adverse events occur, or - in the presence of progression of disease as evidenced by clinical or laboratory criteria, or by imaging studies. • Repeat cycles of treatment with docetaxel are not recommended if the disease recurs after completion of the planned course of chemotherapy.
	ÖSTROGENE UND STEROIDE
	• A corticosteroid such as dexamethasone (0.5 mg daily) daily is recommended as thirdline hormonal therapy after androgen withdrawal and anti-androgen therapy for men with hormone-refractory prostate cancer (Evidenz aus Fallserien).
	BISPHOSPHONATE
	• The use of bisphosphonates to prevent or reduce the complications of bone metastases in men with hormone-refractory prostate cancer is not recommended. • Bisphosphonates for pain relief may be considered for men with hormone-refractory prostate cancer when other treatments (including analgesics and palliative radiotherapy) have failed. The oral or intravenous route of administration should be chosen according to convenience, tolerability and cost (Aussage basiert auf einem RCT). • Strontium-89 should be considered for men with hormone-refractory prostate cancer and painful bone metastases, especially those men who are unlikely to receive myelosuppressive chemotherapy(Aussage basiert auf einem RCT).
	ANMERKUNGEN
	• Suchzeitraum der Literaturrecherche: Bis Juni 2007 • Mit S3-Vorgehen vergleichbar

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library am 08.01.2013

Suchschritt	Suchfrage	Treffer
#1	MeSH descriptor Prostatic Neoplasms explode all trees	2830
#2	(prostate OR prostatic):ti,ab,kw and (cancer OR tumor* OR tumour* OR carcinoma OR neoplasm* OR adenocarcinoma):ti,ab,kw	4182
#3	(#1 OR #2), from 2008 to 2013	1013
#4	MeSH descriptor: [Bone Neoplasms] explode all trees and with qualifiers: [Secondary - SC]	565
#5	MeSH descriptor: [Spinal Neoplasms] explode all trees and with qualifiers: [Secondary - SC]	22
#6	MeSH descriptor: [Neoplasm Metastasis] explode all trees	3326
#7	skeletal or osseous or bone*:ti and metastat* or metastas* or event* or complication* or tumor* or tumour* or mass*:ti (Word variations have been searched)	1031
#8	#4 or #5 or #6 or #7, from 2008 to 2013	917
#9	#3 or #8	1850

Cochrane Reviews [44]

14 Cochrane Reviews in Datenbank aufgenommen

Cochrane Library am 14.01.2013

Suchschritt	Suchfrage	Treffer
#1	MeSH descriptor Prostatic Neoplasms explode all trees	2830
#2	MeSH descriptor: [Bone Neoplasms] explode all trees and with qualifiers: [Secondary - SC]	565
#3	MeSH descriptor: [Neoplasm Metastasis] explode all trees	3326
#4	MeSH descriptor: [Spinal Neoplasms] explode all trees	52
#5	MeSH descriptor: [Spinal Cord Compression] explode all trees	86
#6	prostate:ti,ab,kw or prostatic:ti,ab,kw (Word variations have been searched)	6451
#7	cancer*:ti,ab,kw or neoplasm*:ti,ab,kw or carcinoma*:ti,ab,kw or adenocarcinoma*:ti,ab,kw or tumor* or tumour*:ti,ab,kw (Word variations have been searched)	69485
#8	#6 and #7	4184
#9	#1 or #8	4184
#10	independent:ti,ab,kw or independence:ti,ab,kw or resistant:ti,ab,kw or resistance:ti,ab,kw or refractory:ti,ab,kw (Word variations have been searched)	45307
#11	hormone:ti,ab,kw or androgen:ti,ab,kw or castrate:ti,ab,kw or castration:ti,ab,kw (Word variations have been searched)	23658
#12	#10 and #11	2597
#13	#9 and #12	499
#14	#2 or #3 or #4 or #5	3919
#15	skeletal:ti,ab,kw or osseous:ti,ab,kw or bone*:ti,ab,kw or spine:ti,ab,kw or spinal:ti,ab,kw (Word variations have been searched)	33547
#16	metastat*:ti,ab,kw or metastas*:ti,ab,kw or mass* or tumor* or tumour*:ti,ab,kw or event*:ti,ab,kw or complication*:ti,ab,kw (Word variations have been searched)	126722

Suchschritt	Suchfrage	Treffer
#17	#15 and #16	9592
#18	#17 or #14	12762
#19	#18 and #9	604
#20	#19 or #13: from 2008 to 2013	187
#21	metastat*:ti,ab,kw or metastas*:ti,ab,kw (Word variations have been searched)	11226
#22	skeletal-related*:ti,ab,kw (Word variations have been searched)	92
#23	skeletal event*:ti,ab,kw (Word variations have been searched)	289
#24	spinal cord compression:ti,ab,kw (Word variations have been searched)	196
#25	bony metastas*:ti,ab,kw (Word variations have been searched)	32
#26	#15 and #21	1542
#27	#22 or #23 or #24 or #25 or #26 or #14: from 2008 to 2013	1016
#28	#20 or #27	1107

Other Reviews [131] | Technology Assessments [66] |

MEDLINE (PubMed) am 14.01.2013

Suchschritt	Suchfrage	Treffer
#3	Search prostatic neoplasms[MeSH Terms]	83164
#4	Search (prostate[Title/Abstract]) OR prostatic[Title/Abstract]	129127
#5	Search (((((cancer*[Title/Abstract]) OR neoplasm*[Title/Abstract]) OR carcinoma*[Title/Abstract]) OR adenocarcinoma*[Title/Abstract]) OR tumor*[Title/Abstract]) OR tumour*[Title/Abstract]	1826530
#6	Search (#4) AND #5	93816
#7	Search (#3) OR #6	108673
#8	Search ((((independent[Title/Abstract]) OR independence[Title/Abstract]) OR resistant[Title/Abstract]) OR resistance[Title/Abstract]) OR refractory[Title/Abstract]	1178892
#9	Search (((hormone[Title/Abstract]) OR androgen[Title/Abstract]) OR castrate[Title/Abstract]) OR castration[Title/Abstract]	327623
#10	Search (#8) AND #9	36597
#11	Search (#10) AND #7	8578
#12	Search ((("Bone Neoplasms/secondary"[Majr]) OR "Neoplasm Metastasis"[Majr]) OR "Spinal Neoplasms"[Majr]) OR "Spinal Cord Compression"[Majr]	51958
#13	Search ((((skeletal[Title/Abstract]) OR osseous[Title/Abstract]) OR bone*[Title/Abstract]) OR spine[Title/Abstract]) OR spinal[Title/Abstract]	807557
#14	Search ((((((metastat*[Title/Abstract]) OR metastas*[Title/Abstract]) OR mass*[Title/Abstract]) OR tumor*[Title/Abstract]) OR tumour*[Title/Abstract]) OR event*[Title/Abstract]) OR complication*[Title/Abstract]	2510778
#15	Search (#13) AND #14	171317
#16	Search (#12) OR #15	210701
#17	Search (#7) AND #16	8249
#18	Search (metastat*[Title/Abstract]) OR metastas*[Title/Abstract]	286112
#19	Search (#13) AND #18	33549
#20	Search skeletal-related*[Title/Abstract]	585

#21	Search skeletal event*[Title/Abstract]	150
#22	Search spinal cord compression[Title/Abstract]	3906
#23	Search bony metastas*[Title/Abstract]	713
#24	Search (((((#19) OR #20) OR #21) OR #22) OR #23) OR #12	77438
#25	Search (#11) OR #17	15640
#26	Search ((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))	139764
#27	Search (#25) AND #26	184
#30	Search (#11) OR #17 Filters: Systematic Reviews; Meta-Analysis; Technical Report	275
#31	Search (#27) OR #30	351
#32	Search (#27) OR #30 Filters: published in the last 5 years	188
#33	Search (#24) AND #26	540
#35	Search (((((#19) OR #20) OR #21) OR #22) OR #23) OR #12 Filters: Meta-Analysis; Technical Report	163
#36	Search (#33) OR #35	608
#37	Search (#33) OR #35 Filters: published in the last 5 years	340
#38	Search (#37) NOT #32	297

#32 und #38 in Datenbank aufgenommen

MEDLINE (PubMed) nach Leitlinien am 08.01.2013

Suchschritt	Suchfrage	Treffer
#2	Search "Prostatic Neoplasms"[Mesh]	83026
#3	Search (prostate OR prostatic) AND (cancer OR neoplasm OR tumor OR tumour OR carcinoma OR adenocarcinoma)	111074
#4	Search (#2) OR #3	111074
#5	Search guideline*[Title]	44428
#6	Search (#4) AND #5	306
#8	Search (#2) OR #3 Filters: Practice Guideline; Guideline	193
#9	Search (#6) OR #8	416
#10	Search (#6) OR #8 Filters: Publication date from 2008/01/01 to 2013/12/31	179

#10 20 Treffer in Datenbank aufgenommen

Suchschritt	Suchfrage	Treffer
#5	Search (("Bone Neoplasms"[Majr]) OR "Neoplasm Metastasis"[Majr])	105120

	OR "Spinal Neoplasms"[Majr]	
#6	Search ((skeletal[Title]) OR osseous[Title]) OR bone*[Title]	251456
#7	Search ((((((metastat*[Title]) OR metastas*[Title]) OR mass*[Title]) OR tumor*[Title]) OR tumour*[Title]) OR event*[Title]) OR complication*[Title]	723538
#8	Search (#6) AND #7	20736
#9	Search (#5) OR #8	114778
#10	Search guideline*[Title]	44438
#11	Search (#9) AND #10	91
#12	Search (#5) OR #8 Filters: Practice Guideline	81
#13	Search (#5) OR #8 Filters: Practice Guideline; Guideline	87
#14	Search (#11) OR #13	146
#15	Search (#11) OR #13 Filters: Publication date from 2008/01/01 to 2013/12/31	52

#15 2 Treffer in Datenbank aufgenommen

Darüber hinaus wurde in den HTA- und Leitliniendatenbanken AWMF, GIN, NGC, Trip, ÄZQ, DAHTA und Onkopedia, sowie auf den Internetseiten des GBA, IQWiG, NICE, ESMO, NCCN und HSC-NHSC per Handsuche nach aktuellen Publikationen mit den Suchbegriffen „prostate cancer“ und „bone metastases“ in verschiedenen Variationen gesucht.

Nach Dublettenkontrolle ergab die Recherche insgesamt 781 Quellen.

Literatur:

Australian Cancer Network Management of Metatastic Prostate Cancer Working Party. Clinical Practice Guidelines for the management of locally advanced and metastatic prostate cancer. Sydney: Cancer Council Australia and Australian Cancer Network, 2010.

Climent MA, Piulats JM, Sanchez-Hernandez A, Arranz JA, Cassinello J, Garcia-Donas J, Gonzalez del AA, Leon-Mateos L, Mellado B, Mendez-Vidal MJ, Perez-Valderrama B. Recommendations from the Spanish Oncology Genitourinary Group for the treatment of patients with metastatic castration-resistant prostate cancer. Crit Rev Oncol Hematol 2012; 83 (3): 341-52.

Deutsche Gesellschaft für Urologie (DGU). Interdisziplinäre Leitlinie der Qualität S3 zur Früherkennung, Diagnose und Therapie der verschiedenen Stadien des Prostatakarzinoms. Version 2.0- 1.Aktualisierung 2011. Stand: September, 2011. AWMF Leitlinien-Register Nr 043-022OL http://www.awmf.org/uploads/tx_szleitlinien/043-022OLl_S3_Prostatakarzinom_2011.pdf, Zugriff am 09.07.2012.

Ford JA, Jones R, Elders A, Mulatero C, Royle P, Sharma P, Stewart F, Todd R, Mowatt G. Denosumab for treatment of bone metastases secondary to solid tumours: Systematic review and network meta-analysis. Eur J Cancer 2013; 49 (2): 416-30.

Gemeinsamer Bundesausschuss (G-BA). Zusammenfassende Dokumentation über die Änderung der Arzneimittel -Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: Abirateronacetat. Vom 29. März 2012. Berlin: Gemeinsamer Bundesausschuss (G-BA), 2012.

Gemeinsamer Bundesausschuss (G-BA). Zusammenfassende Dokumentation über die Änderung der Arzneimittel -Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von

Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: Cabazitaxel. Vom 29. März 2012. Berlin: Gemeinsamer Bundesausschuss (G-BA), 2012.

Heidenreich A, Bolla M, Joniau S, van der Kwast T, Matveev V, Mason M, Mottet N, Schmidt H, Wiegel T, Zattoni F. EAU Guidelines on Prostate cancer. Stand: Juni 2010. http://www.uroweb.org/gls/pdf/Prostate%20Cancer%202010%20June%2017th.pdf, Zugriff am 21.04.2011.

Horwich A, Parker C, Bangma C, Kataja V. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010; 21 (Suppl 5): v129-v133.

Lipton A, Fizazi K, Stopeck AT, Henry DH, Brown JE, Yardley DA, Richardson GE, Siena S, Maroto P, Clemens M, Bilynskyy B, Charu V, Beuzeboc P, Rader M, Viniegra M, Saad F, Ke C, Braun A, Jun S. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. Eur J Cancer 2012; 48 (16): 3082-92.

Machado M, Cruz LS, Tannus G, Fonseca M. Efficacy of clodronate, pamidronate, and zoledronate in reducing morbidity and mortality in cancer patients with bone metastasis: a meta-analysis of randomized clinical trials. Clin Ther 2009; 31 (5): 962-79.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer. Version 1.2013. http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf, Zugriff am 07.01.2012.

National Institute for Health and Clinical Excellence (NICE). Prostate cancer: diagnosis and treatment. London: NICE, 2009.

Peddi P, Lopez-Olivo MA, Pratt GF, Suarez-Almazor ME. Denosumab in patients with cancer and skeletal metastases: a systematic review and meta-analysis. Cancer Treat Rev 2013; 39 (1): 97-104.

Sun L, Yu S. Efficacy and Safety of Denosumab Versus Zoledronic Acid in Patients With Bone Metastases: A Systematic Review and Meta-analysis. Am J Clin Oncol 2012. Oct 8 [Epub ahead of print].

Working group of the Clinical Practice Guideline on Prostate Cancer Treatment. Clinical practice guideline for prostate cancer treatment. Madrid: National Plan for the NHS of the MSC Aragon Institute of Health Sciences(I+CS), 2008 Clinical Practice Guidelines in the NHS I+CS No 2006/02.

Yuen KK, Shelley M, Sze WM, Wilt TJ, Mason M. Bisphosphonates for advanced prostate cancer. Stand: 2010. Cochrane Database of Systematic Reviews 2006; (4): CD006250.

Zhu M, Liang R, Pan LH, Huang B, Qian W, Zhong JH, Zheng WW, Li CL. Zoledronate for Metastatic Bone Disease and Pain: A Meta-Analysis of Randomized Clinical Trials. Pain Med 2012. Dec 28 [Epub ahead of print].