Leitlinienprogramm Onkologie

Evidenztabellen der S3-Leitlinie Prostatakarzinom

Version 7.01 – März 2024
AWMF-Registernummer: 043-022OL

Evidenztabellen

DKG Krebsgesellschaft · Deutsche Krebshilfe Helfen. Forschen. Informieren. · AWMF

Inhalt

1 Informationen zu dieser Leitlinie

1.1 Herausgeber

Leitlinienprogramm Onkologie der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V. (AWMF), Deutschen Krebsgesellschaft e. V. (DKG) und der Stiftung Deutsche Krebshilfe (DKH).

1.2 Federführende Fachgesellschaft(en)

Deutsche Gesellschaft für Urologie (DGU)

1.3 Finanzierung der Leitlinie

Diese Leitlinie wurde von der Deutschen Krebshilfe im Rahmen des Leitlinienprogramms Onkologie gefördert.

1.4 Kontakt

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1.5 Zitierweise

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Prostatakarzinom, Langversion 7.01, 2024, AWMF-Registernummer: 043-022OL https://www.leitlinienprogramm-onkologie.de/leitlinien/prostatakarzinom/; Zugriff am [tt.mm.jjj]

1.6 Abkürzungsverzeichnis

Tabelle 1: Abkürzungsverzeichnis

Abkürzung	Erläuterung
ACP	American College of Physicians
AD	Androgendeprivation
AE	Adverse Events
AHB	Anschlussheilbehandlung
AP	Anteroposterior
AR	Androgen Receptor
AS	Active Surveillance (aktive Überwachung)
AS	Androgen Suppression
ASAP	Atypical Small Acinar Proliferation
AUA	American Urological Association
BMV	Bundesmantelverträge
BOO	Bladder outlet (oder: orifice) obstruction
BSC	Best Supportive Care
CCI	Charlson Comorbidity Index
CTCAE	Common Terminology Criteria for Adverse Events
DCE-MRI	Dynamic contrast-enhanced magnetic resonance imaging
DES	Diethylstilbestrol
DRU	Digital-Rektale Untersuchung
DWI	Diffusion-weightend imaging
EAU	European Association of Urology
EBRT	External Beam Radiotherapy = perkutane Strahlentherapie
ECOG	Eastern Cooperative Oncology Group

Abkürzung	Erläuterung
EK	Expertenkonsens
EKG	Elektrokardiogramm
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ePLND	Extended Pelvic Lymph Node Dissection
FDA	Food and Drug Administration
FDG	Fluordesoxyglucose
fPSA	freies Prostata-sprezifsiches-Antigen
G-BA	Gemeinsamer Bundesausschuss
GKV	Gesetzliche Krankenversicherung
GnRH	Gonadotropin-Releasing-Hormone
GS	Gleason-Score
Gy	Kurzbezeichnung für die Maßeinheit der Energiedosis Gray
HDR	high dose rate
HIFU	Hochintensiver Fokussierter Ultraschall
HR	Hazard Ratio
HRR	homologen Rekombinationsreparatur
HT	Hormontherapie
HTA	Health Technology Assessment
ICI	Intrakavernöse Injektionen
ICRU	International Commission in Radiation Units and Measurement
IGeL	individuelle Gesundheitsleistungen
IGF	Insulin-like Growth Facors (insulinähnliche Wachstumsfaktoren)

Abkürzung	Erläuterung
IGRT	Image-guided radiation therapie (bildgesteuerte Strahlentherapie)
IMRT	Intensitätsmodulierte Radiotherapie
IPSS	International Prostate Symptom Score
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KHK	Koronare Herzkrankheit
KI	Konfidenzintervall
KM	Knochenmetastase
LDR	Low-Dose Rate
LH-RH	Luteinisierendes Hormon Releasing Hormon
LK	Lymphknoten
LL	Leitlinie
LND	lymphonodectomy
LoE	Level of Evidence
mCRPC	metastasiertes, kastrationsresistentes Prostatakarzinom
mHSPC	hormonsensitives, metastasierten Prostatakarzinoms
MRS	Magnetresonanzspektoskopie
MRSI	Magnet Resonance Spectroscopy Imaging
MRT	Magnetresonanztomographie
NICE	National Institute for Health and Care Excellence
nmCRPC	nicht-metastasiertes, kastrationsresistentes Prostatakarzinom
NNT	number needed to treat
NW	Nebenwirkungen
OL	Leitlinienprogramm Onkologie

Abkürzung	Erläuterung
OR	Quotenverhältnis (Odds-Ratio)
OS	Gesamtüberleben (Overall Survival)
PCa	Prostatakarzinom
PCTCC	Prostate Cancer Trialists Collaborative Group
PET/CT	Positronen-Emmisions-Tomographie/Computertomographie
PIN	Prostatische Intraepitheliale Neoplasie
PLCO	Prostate, Lung, Colorectal and Ovarian Cancer Screening
PPW	Positive prädikativer Wert
PSA	Prostataspezifisches Antigen
PSADT	PSA-Doubling-Time
PSMA	Prostataspezifisches Membranantigen
QoL	Lebensqualität (Quality of Life)
RCT	Randomized Controlled Trial
RPE	Radikale Prostatektomie
rPFÜ	radiologischen progressionsfreies Überleben
RT	radiotherapy = Radiotherapie
RTOG	Radiation Therapy Oncology Group
SEER	Surveillance, Epidemiology, and End Results (USA)
SGB	Sozialgesetzbuch
SIGN	Scottish Intercollegiate Guidelines Network
SPECT	Single-Photon-Emissionscomputertomographie
SRE	Skeletal related event, Skelett-bezogenes Ereignis
SRT	Salvagestrahlentherapie

Abkürzung	Erläuterung
SUV	Standardized uptake value
TED	Tele-Dialog
TRUS	Transrektale Ultraschalluntersuchung
TTP	Time To Progression
TURP	Transurethrale Resektion der Prostata
UAW	Unerwünschte Arzneimittelwirkungen
UICC	Union Internationale Contre le Cancer (eng.: Union for International Cancer Control)
UTI	Urinary Tract Infections
V.a.	Verdacht auf
VACURG	Veterans Administration Cooperative Urology Research Group
WHO	World Health Organization (Welt-Gesundheitsorganisation)
WW	Watchful Waiting
zVT	zweckmäßige Vergleichstherapie

2 Leitliniensynopse

Evidenzlevel

Leitlinie	Empfehlungsgrad/ LoE	Erläuterung
AUA/ASTRO, 2022 [1]	LoE A	high we are very confident that the true effect lies close to that of the estimate effect
	LoE B	moderate we are moderately confident in the effect estimate the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
	LoE C	low our confidence in the effect 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
	Strong Recommendation	directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is substantial
	Moderate Recommendation	directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is moderate

Leitlinie	Empfehlungsgrad/ LoE	Erläuterung
	Conditional Recommendation	non-directive statements used when the evidence indicates that there is no apparent net benefit or harm or when the balance between benefits and risks/burden is unclear.
EAU/EANM/ ESTRO/ESUR/ ISUP/SIOG 2023 [2]	LoE	based on the 2009 Oxford Centre for Evidence-Based Medicine (CEBM) Levels of Evidence
	Strong Recommendation	These principles follow the well-established GRADE methodology.
	Weak Recommendation	
NCCN 2023 [3]	Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
	Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
	Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
	Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.
NICE 2021 [4]	Evidence profile	These principles follow the well-established GRADE methodology. The evidence profiles were not assigned to the specific recommendations.

2.1 AG Aktive Überwachung

Leitlinie	Empfehlungen	AGREE II- Bewertung
AUA/ASTRO, 2022 [1]	Risk-Based Management For patients with low-risk prostate cancer, clinicians should recommend active surveillance as the preferred management option. (Strong Recommendation; Evidence Level: Grade A) For patients with favorable intermediate-risk prostate cancer, clinicians should discuss active surveillance, radiation therapy, and radical prostatectomy. (Strong Recommendation; Evidence Level: Grade A) *Clinicians should inform patients with intermediate-risk prostate cancer considering whole gland or focal ablation that there are a lack of high-quality data comparing ablation outcomes to radiation therapy, surgery, and active surveillance. (Expert Opinion)* Principles of Active Surveillance *Patients managed with active surveillance should be monitored with serial PSA values and repeat prostate biopsy. (Expert Opinion)* *In patients selecting active surveillance, clinicians should utilize mpMRI to augment risk stratification, but this should not replace periodic surveillance biopsy. (Expert Opinion)*	Scope and Purpose (Domain 1): 17/21 Rigour of Development (Domain 3): 31/56 Editorial Independence (Domain 6): 9/14
EAU/EANM/ ESTRO/ESUR/ ISUP/SIOG 2023 [2]	Summary of evidence and guidelines for follow-up during active surveillance Summary of evidence Serial magnetic resonance imaging can improve the detection of aggressive cancers during follow-up. (LoE 3) A progression on magnet resonance imaging mandates a repeat biopsy before a change in treatment strategy. (LoE 3)	Scope and Purpose (Domain 1): 11/21 Rigour of Development (Domain 3): 38/56

Leitlinie	Empfehlungen	AGREE II- Bewertung
	A stationary magnet resonance imaging does not make repeat biopsy superfluous. (LoE 3) (S. 79) Recommendations Base follow-up during active surveillance on a strict protocol including digital rectal examination (at least once yearly), prostate-specific antigen (at least once every 6 months) and repeated biopsy every 2 to 3 years. (strong) Perform magnetic resonance imaging and repeat biopsy if prostate-specific antigen is rising (prostate-specific antigen doubling time < 3 years). (strong) Re-classify patients with low-volume ISUP grade group 2 disease included in active surveillance protocols, if repeat non-magnetic resonance imaging-based systematic biopsies performed during monitoring reveal > 3 positive cores or maximum core involvement > 50%/core of ISUP 2 disease. Base change in treatment on biopsy progression, not on progression on MRI and/or prostate-specific antigen. (weak) Patients with a PI-RADS 1-2 findings on MRI and a low PSA density (< 0.15) may be excepted from repeat biopsy. (weak) (S. 79) Summary of evidence and guidelines for the management of low-risk disease Summary of evidence Active surveillance or watchful waiting is standard of care, based on life expectancy. (LoE 2a) All active treatments options present a risk of over-treatment. (LoE 1a) (S. 79) Recommendations Manage patients with a life expectancy > 10 years and low-risk disease by active surveillance. (strong) (S. 80)	Editorial Independence (Domain 6): 11/14

Leitlinie	Empfehlungen	AGREE II- Bewertung
	Selection of patients Patients with intraductal histology on biopsy should be excluded from active surveillance. (strong) Perform magnetic resonance imaging before a confirmatory biopsy if no magnetic resonance imaging has been performed before the initial biopsy. (strong) Take both targeted biopsy (of any PI-RADS ≥ 3 lesion) and systematic biopsy if a confirmatory biopsy is performed. (strong) If magnetic resonance imaging is not available, per-protocol confirmatory prostate biopsies should be performed. (weak) If a patient has had upfront magnetic resonance imaging followed by systematic and targeted biopsies there is no need for confirmatory biopsies. (weak) (S. 80) *Follow-up of patients* Repeat biopsies should be performed at least once every 3 years for 10 years. (weak) In case of prostate-specific antigen progression or change in digital-rectal examination or magnetic resonance imaging findings, do not progress to active treatment without a repeat biopsy. (strong) (S. 80/S. 129f.) Guidelines for the treatment of intermediate-risk disease Offer active surveillance to highly selected patients with ISUP grade group 2 disease (i.e. < 10% pattern 4, prostate-specific antigen < 10 ng/mL, ≤ cT2a, low disease extent on imaging and low biopsy extent [defined as ≤ 3 positive cores and cancer involvement ≤ 50% core involvement/per core]), or another single element of intermediate-risk disease with low disease extent on imaging and low biopsy extent, accepting the potential increased risk of metastatic progression. (weak) Patients with ISUP grade group 3 disease should be excluded from active surveillance protocols. (strong)	

Leitlinie	Empfehlungen	AGREE II- Bewertung
	Re-classify patients with low-volume ISUP grade group 2 disease included in active surveillance protocols, if repeat non- magnetic resonance imaging -based systematic biopsies performed during monitoring reveal > 3 positive cores or maximum core involvement > 50%/core of ISUP 2 disease. (weak) (S. 82/S. 130) Guidelines for quality of life in men undergoing local treatments Advise eligible patients for active surveillance that global quality of life is equivalent for up to 5 years compared to radical prostatectomy or external beam radiotherapy. (strong) (S. 145)	
NCCN 2023 [3]	PRINCIPLES OF ACTIVE SURVEILLANCE AND OBSERVATION The NCCN Prostate Cancer Panel and the NCCN Prostate Cancer Early Detection Panel (See NCCN Guidelines for Prostate Cancer Early Detection) remain concerned about overdiagnosis and overtreatment of prostate cancer. The Prostate Cancer Panel recommends that patients and their physicians carefully consider active surveillance based on the patient's prostate cancer risk profile and estimated life expectancy. In settings where the patient's age and comorbidities suggest a shorter life expectancy, observation may be more appropriate. Shared decision-making, after appropriate counseling on the risks and benefits of the various options, is critical. ACTIVE SURVEILLANCE Active surveillance involves actively monitoring the course of disease with the expectation to intervene with curative intent if the cancer progresses. Life Expectancy: Life expectancy is a key determinant for the choice between observation, active surveillance, and definitive treatment. Consider incorporating a validated metric of comorbidity such as the Adult Comorbidity Evaluation-27 Index (ACE-27) to differentiate between recommendations for observation versus active surveillance. Prior studies	Scope and Purpose (Domain 1): 21/21 Rigour of Development (Domain 3): 40/56 Editorial Independence (Domain 6): 13/14

Leitlinie	Empfehlungen	AGREE II- Bewertung
	did not incorporate a validated metric of comorbidity to estimate life expectancy, which is a potential limitation when interpreting the data for a patient who is in excellent health. Life expectancy can be challenging to estimate for individual patients (see Principles of Life Expectancy Estimation, PROS-A). Candidacy for Active Surveillance: Active surveillance is preferred for patients with very-low-risk prostate cancer (See Risk Group Criteria [PROS-2]) and a life expectancy ≥10 years. (Observation is preferred for patients with a life expectancy <10 years and very-low-risk disease.) Active surveillance is preferred for most patients with low-risk prostate cancer (See Risk Group Criteria [PROS-2]) and a life expectancy ≥10 years. The panel recognizes that there is heterogeneity across this risk group, and that some factors may be associated with an increased probability of near-term grade reclassification including high PSA density, a high number of positive cores (eg, ≥3), and high genomic risk (from tissue-based molecular tumor analysis). In some of these cases, upfront treatment with RP or prostate RT may be preferred based on shared decision-making with the patient. Patients with favorable intermediate-risk prostate cancer (See Risk Group Criteria [PROS-2]) and a life expectancy >10 years may also consider active surveillance. Particular consideration for active surveillance may be appropriate for those patients with a low percentage of Gleason pattern 4 cancer, low tumor volume, low PSA density, and/or low genomic risk (from tissue-based molecular tumor analysis). Confirmatory Testing to Establish Appropriateness of Active Surveillance: Goals of confirmatory testing are to help facilitate early identification of those patients who may be at a higher risk of future grade reclassification or cancer progression. Since an initial prostate biopsy may underestimate tumor grade or volume, confirmatory testing is strongly recommended within the first 6 to 12 months of diagnosis for patients who are considering active surveillance.	

Leitlinie	Empfehlungen	AGREE II- Bewertung
	Options for confirmatory testing include prostate biopsy, mpMRI with calculation of PSA density (and repeat biopsy as indicated), and/orp molecular tumor analysis, see Principles of Risk Stratification (PROS-D). Early confirmatory testing may not be necessary in patients who have had an mpMRI prior to diagnostic biopsy. All patients should undergo a confirmatory prostate biopsy within 1–2 years of their diagnostic biopsy. Active Surveillance Program: Patients who choose active surveillance should have regular follow-up, and key principles include: PSA no more often than every 6 months unless clinically indicated. DRE no more often than every 12 months unless clinically indicated. Repeat prostate biopsy no more often than every 12 months unless clinically indicated. While the intensity of surveillance may be tailored on an individual basis, most patients should have prostate biopsies incorporated as part of their monitoring. Consider repeat mpMRI no more often than every 12 months unless clinically indicated. In patients with a suspicious lesion on mpMRI, MRI-ultrasound fusion biopsy improves the detection of higher grade (Grade Group ≥2) cancers. Patients should be transitioned to observation when life expectancy is <10 years. Repeat molecular tumor analysis is discouraged. The intensity of surveillance may be tailored based on patient life expectancy and risk of reclassification. Considerations for Treatment of Patients on Active Surveillance: Grade reclassification on repeat biopsy is the most common factor influencing a change in management from active surveillance to treatment.	

Leitlinie	Empfehlungen	AGREE II- Bewertung
	Other factors affecting decisions to actively treat include: increase in tumor volume, a rise in PSA density, and patient anxiety. Considerations for a change in management strategy should be made in the context of the patient's life expectancy. Advantages of active surveillance: Between 50% and 68% of those eligible for active surveillance may safely avoid treatment for at least 10 years. Patients will avoid possible side effects of definitive therapy that may be unnecessary while on active surveillance. Quality of life/normal activities will be less affected while on active surveillance. Risk of unnecessary treatment of small, indolent cancers will be reduced. Limitations of active surveillance: Between 32% and 50% of patients will undergo treatment by 10 years,4-6 although treatment delays do not seem to impact cure rate. Although the risk is very low (<0.5% in most series), it is possible for a cancer to progress to a regional or metastatic stage. OBSERVATION Observation involves monitoring with a history and physical exam no more often than every 12 months (without surveillance biopsies) until symptoms develop or are thought to be imminent. Observation is recommended for:	

Leitlinie	Empfehlungen	AGREE II- Bewertung
	Asymptomatic patients in very-low-, low-, and intermediate-risk groups with life a expectancy ≤5 years. Asymptomatic patients with very-low- and low-risk prostate cancer with a life expectancy 5–10 years. Observation is preferred for: Asymptomatic patients with favorable and unfavorable intermediate-risk prostate cancer and a life expectancy between 5–10 years. Observation may be considered for: Asymptomatic patients with high-risk, very-high-risk, regional, and metastatic prostate cancer and life expectancy ≤5 years. Life expectancy can be challenging to estimate for individual patients (see Principles of Life Expectancy Estimation, PROS-A). Consider incorporating a validated metric of comorbidity (see Life Expectancy, above). If patients under observation become symptomatic, an assessment of disease burden can be performed, and treatment or palliation can be considered (see PROS-12). Advantages of observation: Patients will avoid possible side effects of unnecessary confirmatory testing and definitive therapy. Limitation of observation: There may be a risk of local or systemic symptoms (eg, urinary retention, pathologic fracture), without prior symptoms or concerning PSA levels. PROS-A: PRINCIPLES OF LIFE EXPECTANCY ESTIMATION	

Leitlinie	Empfehlungen	AGREE II- Bewertung
	Life expectancy estimation is critical to informed decision-making in prostate cancer early detection and treatment. Estimation of life expectancy is possible for groups of patients but challenging for individuals. Life expectancy can be estimated using: The Social Security Administration tables (www.ssa.gov/OACT/STATS/table4c6.html) The WHO's Life Tables by country (http://apps.who.int/gho/data/view.main.60000?lang=en) The Memorial Sloan Kettering Male Life Expectancy tool https://www.mskcc.org/nomograms/prostate If using a life expectancy table, life expectancy should be adjusted using the clinician's assessment of overall health as follows: Best quartile of health - add 50% Worst quartile of health - subtract 50% Middle two quartiles of health - no adjustment Example of upper, middle, and lower quartiles of life expectancy at selected ages are included in the NCCN Guidelines for Older Adult Oncology for life expectancy estimation.	
NICE 2021 [4]	Localised and locally advanced prostate cancer 1.3.8 For people with CPG 1 localised prostate cancer: offer active surveillance consider radical prostatectomy or radical radiotherapy if active surveillance is not suitable or acceptable to the person. 1.3.9 For people with CPG 2 localised prostate cancer, offer a choice between active surveillance, radical prostatectomy or radical radiotherapy if radical treatment is suitable.	Scope and Purpose (Domain 1): 13/14 Rigour of Development (Domain 3): 39/56 Editorial Independence (Domain 6): 8/14

Leitlinie	Empfehlungen	AGREE II- Bewertung
	1.3.10 For people with CPG 3 localised prostate cancer: offer radical prostatectomy or radical radiotherapy and consider active surveillance (in line with recommendation 1.3.14) for people who choose not to have immediate radical treatment. 1.3.11 Do not offer active surveillance to people with CPG 4 and 5 localised and locally advanced prostate cancer. (S. 20) Multiparametric magnetic resonance imaging and protocol for active surveillance 1.3.13 Offer multiparametric magnetic resonance imaging to people having active surveillance who have not had an magnetic resonance imaging previously. If the magnetic resonance imaging results do not agree with the biopsy findings, offer a new magnetic resonance imaging -influenced biopsy. 1.3.14 Consider using the protocol in table 2 for people who have chosen active surveillance. (S. 21) <u>Table Protocol for active surveillance</u> <u>Year 1 of active surveillance</u> Every 3 to 4 months: measure prostate-specific antigen (could be carried out in primary care if there are agreed shared-care protocols and recall systems) Throughout active surveillance: monitor prostate-specific antigen kinetics (could include prostate-specific antigen density and velocity) At 12 months: digital rectal examination (should be done by a healthcare professional with expertise and confidence in performing digital rectal examination. In a large United Kingdom trial that informed this protocol, digital rectal examinations were carried out by a urologist or a nurse specialist)	

Leitlinie	Empfehlungen	AGREE II- Bewertung
	At 12 to 18 months: multiparametric magnetic resonance imaging <u>Year 2 and every year thereafter until active surveillance ends</u> Every 6 months: measure prostate-specific antigen (could be carried out in primary care if there are agreed shared-care protocols and recall systems) Throughout active surveillance: monitor prostate-specific antigen kinetics (could include PSA density and velocity) Every 12 months: digital rectal examination (should be done by a healthcare professional with expertise and confidence in performing digital rectal examination. In a large United Kingdom trial that informed this protocol, digital rectal examinations were carried out by a urologist or a nurse specialist) (S. 22) 1.3.15 If a person wishes to move from active surveillance to radical treatment at any stage in their care, make a shared decision to do so based on the person's preferences, comorbidities and life expectancy. 1.3.16 Offer radical treatment to people with localised prostate cancer who had chosen an active surveillance regimen and who now have evidence of disease progression. (S. 22)	

2.2 AG Pathologie

Leitlinie	Empfehlungen	AGREE II- Bewertung
AUA/ASTRO, 2022 [1]	**Staging** In patients with prostate cancer at high risk for metastatic disease with negative conventional imaging, clinicians may obtain molecular imaging to evaluate for metastases. (Expert Opinion) (S. 2) **Risk Assessment** Clinicians should use clinical T stage, serum prostate-specific antigen (PSA), Grade Group (Gleason score), and tumor volume on biopsy to risk stratify patients with newly diagnosed prostate cancer. (Strong Recommendation; Evidence Level: Grade A) (S. 1) Clinicians may selectively use tissue-based genomic biomarkers when added risk stratification may alter clinical decision-making. (Expert Opinion) Clinicians should not routinely use tissue-based genomic biomarkers for risk stratification or clinical decision-making. (Moderate Recommendation; Evidence Level: Grade B) (S. 2) Clinicians should perform an assessment of patient and tumor risk factors to guide the decision to offer germline testing that includes mutations known to be associated with aggressive prostate cancer and/or known to have implications for treatment. (Expert Opinion) (S. 3)	Scope and Purpose (Domain 1): 17/21 Rigour of Development (Domain 3): 31/56 Editorial Independence (Domain 6): 9/14
EAU/EANM/ ESTRO/ESUR/ ISUP/SIOG 2023 [2]	**Classification and staging systems** Recommendations Use the Tumour, Node, Metastasis (TNM) classification for staging of prostate cancer. (strong)	Scope and Purpose (Domain 1): 11/21

Leitlinie	Empfehlungen	AGREE II- Bewertung
	Clinical stage should be based on digital rectal examination only; additional staging information based on imaging should be reported separately. (strong) Use the International Society of Urological Pathology 2019 system for grading of prostate cancer. (strong) Use the EAU risk group stratification for prognostic subgrouping of patients. (strong) (S. 24) **Guidelines for germline testing** <u>Recommendations</u> Consider germline testing in men with metastatic prostate cancer. (weak) Consider germline testing in men with high-risk prostate cancer who have a family member diagnosed with PCa at age < 60 years. (weak) Consider germline testing in men with multiple family members diagnosed with PCa at age < 60 years or a family member who died from prostate cancer. (weak) Consider germline testing in men with a family history of high-risk germline mutations or a family history of multiple cancers on the same side of the family. (weak) (S. 27)	Rigour of Development (Domain 3): 38/56 Editorial Independence (Domain 6): 11/14

3 Systematische Recherchen

AG mCRPC/mHSPC

3.1 Welche Bildgebung/Kriterien ist für die Indikationsstellung für Pluvicto notwendig?

Literaturreferenzen: [437], [438], [439], [440]

Refe-renz	Studien-charakteristika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
Systematische Übersichtsarbeiten								
[437]	Systematic review with meta-analysis study protocol: CRD42020206349 2++	We performed a systematic review and meta-analysis to assess the concordance between response evaluation using	n=10 retrospective studies n=247 men with mCRPC Austria, Germany, India, Turkey Seach date: 27 August 2020	PSMA PET, PET/CT or PET/MRI	PSA	**177Lu-PSMA** (n=5 studies) 0.78 (95% CI 0.71-0.85), p=0.69, I²=0%	PSA and PSMA PET response assessments are discordant in nearly a fourth of patients with mCRPC undergoing systemic treatments. Results were consistent across different therapeutic agents and PET response criteria.	sources of funding of the included studies were not reported The authors declare no conflict of interest. This research was funded in part through the NIH/NCI Cancer

Refe-renz	Studien-charakteristika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
		PSMA PET and PSA after systemic treatment and the association between PSMA PET and other robust endpoints of overall and radiologic PFS in patients with mCRPC.						Center Support Grant.
[438]	Systematic review 2-	We present a comprehensive overview	men with mCRPC n=40 studies	Lutetium-177-PSMA-617		**Imaging/Biomarkers** PSMA-PET: has shown	Amongst the studies, there is also inherent variation in measurement/biomarkers of response,	no study protocol, no information if efforts were made to

Refe-renz	Studien-charakteristika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
		of the current literature, covering retrospective studies, prospective studies, and clinical trials that established 177Lu-PSMA-617 for the treatment of mCRPC.	retrospective studies (n=16) phase I/II trials (n=9) phase III trial (n=1) clinical trials (n=11) real-world studies (n=3) Seach date: February 1, 2023			heterogeneity in PSMA expression among metastases suggesting its use as a biomarker of PSA response to 177Lu-PSMA-617 FDG-PET: It provided the measure of tumor glycolysis, and in conjunction with PSMA-PET identified sites of disease that were FDG-positive but PSMA-negative high ALP and LDH have been associated with worse PFS and OS Androgen receptor mutations have	PSMA imaging modalities used, retrospective vs. prospective designs, and small recruitment size.	minimise errors in the data extraction, no summary (e. g. Table 1) of included studies, wrong risk of bias tool for included studies used, sources of funding of the included studies were not reported Detailed list of conflict of interest reported in the paper. This paper received no funding.

Refe-renz	Studien-charakteristika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						been shown to be associated with worse prognosis in mCRPC and may be a way to predict resistance to 177Lu PSMA-617 treatment PSMA expression in circulating tumor cells has been studied as a novel prognostic biomarker SUVmean of PSMA has shown to be a predictive biomarker for response to 177Lu-PSMA-617 Nomograms: it was noted that tumors with high PSMA expression were associated		

Refe-renz	Studien-charakteristika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						with more favorable outcomes while bone disease was less likely to be adequately controlled with Lu-PSMA		
[439]	Systematic Review 2-	To review current data in the literature regarding the impact of antiandrogen therapy on PSMA expression of metastatic sites and the role of serial	n=36 studies (animal experiment/case reports, prospective and retrospective cohort studies) men with metastatic prostate cancer Search period:	antiandrogen therapy		**Role of serial PSMA PET/CT in assessing treatment responses** **in advanced PC** (n=5) 177Lu-PSMA-617 & mCRPC Substudies of the TheraP and VISION trials recently found that SUVmean at baseline PSMA PET was predictive of a	PSMA PET imaging is essential in selecting patients for 177Lu-PSMA RLT. Growing evidence favors its use in assessing treatment responses after RLT. Preliminary evidence indicates the value of PSMA PET for assessment of the treatment response in patients receiving systemic treatment other than RLT for metastatic prostate cancer.	in the tables are 38 studies included, unclear which studies were identified via literature search, reference 15 are not included in the tables, only one database used and no additional hand search reported, only keywords reported, no information if efforts were made to

Refe-renz	Studien-charakteristika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
		(baseline and at least 1 follow-up scan) PSMA PET to assess treatment response in patients with metastatic prostate cancer.	2010- July 2022			favourable response to 177Lu-PSMA-617 RLT Prognostic significance of changes in PSMA PET parameters at followup scan has also been demonstrated Prognostic PET Parameter: PSMA-TV and PSMA-TL decrease had significantly longer OS than those without a decrease Progression according to PPP criteria was a significant prognostic marker for OS		minimise errors in the data extraction, no risk of bias assessment of the included studies, sources of funding of the included studies were not reported Ken Herrmann has received personal fees from Bayer, Sofie Biosciences, SIRTEX, Adacap, Curium, Endocyte, Boston Scientific, Ipsen, Siemens Healthineers, GE Healthcare, Amgen, Novartis, ymabs, Aktis

Refe-renz	Studien-charakteristika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						At early response assessment: OS was significantly higher in complete/partial response/stable disease than in progressive disease according to modified PERCIST/EORTC criteria		Oncology, Pharma15, Theragnostics Ltd., Janssen, Telix, Debiopharm, Bain Capital, and Eco1R, other fees from Sofie Biosciences, nonfinancial support from ABX, and grants from Boston Scientific, all outside the submitted work. Obtaining funding: None.
Health Technology Assessment								
[441]	SR Includes: 3 RCTs	Male patients (≥18 years old)	177Lu-labelled PSMA inhibitor	Best standard of care: Chemotherapy, e.g.:		**OS:** 1 RCT	hinsichtlich des Gesamtüberlebens:	GRADE: sehr niedrige bis moderate

Refe-renz	Studien-charakteristika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
	Literature search: December 2018 to December 2022	with PSMA-positive mCRPC (ICD-10 Code: Z19.2) total 1071 patients (age range: 68-72 yrs) ECOG Status ≤2 Follow up range Range 18.4-20.3 months **Diagnosis, imaging**	therapy administered intravenously The active substance is the radionuclide 177-Lutetium (177Lu) Available agents of the RLT with PSMA: - 177Lu-PSMA-617 (Pluvicto®, Endocyte, a Novartis company, USA) - 177Lu-PSMA-I&T (Scintomics	- Docetaxel (Docefrez/Taxotere®) + prednisone - Cabazitaxel (Jevtana®) +prednisolone +/- carboplatin - Mitoxantrone (Novantrone®) +prednisolone - Estramustine (Emcyt®) + docetaxel + prednisolone Hormonal agents, e.g: - Enzalutamide (Xtandi®) - Abiraterone (Zytiga®) Radiopharmaceuticals, e.g.: - Radium 223 (Xofigo®) PARP inhibitors for HRRm, e.g.: - Olaparib		(n=831): difference 15.3 vs. 11.3 mo, HR 0.62 **PFS:** 1 RCT (n=581) 8.7 vs. 3.4 mo, HR 0.40 2 RCTs (n=280) no difference 177Lu-PSMA-617 Vs Chemo **ORR:** 3 RCTs, nur 1 RCT (n=200) zeigte Unterschied nach 18,4 Mo: 49 % vs. 24 %, RR 2,12 **HRQL:**	bei vorbehandelten mCRPC eine Überlegenheit von 177Lu-PSMA-617 in Kombination mit der Standardbehandlung (ohne zytotoxische Chemotherapie) gegenüber der Standardbehandlung alleine. mögliche Überlegenheit der 177Lu- PSMA-617 Kombinationstherapie hinsichtlich des progressionsfreien Überlebens und der gesundheitsbezogenen Lebensqualität. Für weitere randomisierte	Vertrauenswürdigkeit der Evidenz zur Wirksamkeit; niedrige Vertrauenswürdigkeit der Evidenz zur Sicherheit Begründung: open-label Studiendesigns, fehlenden Daten, etc.

Refe-renz	Studien-charakteristika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
		procedure **Used for initial tumor evaluation:** 1 RCT not reported, 1 RCT CT, MRI, or bone-scan imaging, 1 RCT Ga-PSMA-11 PET/CT, biopsy	GmbH, Germany) - Agents synthesised by radiopharmacists			1 RCT (n=581) berichtete längere Dauer bis HRQoL & Schmerz- Verschlechterung in Pat. mit 177Lu-PSMA-617 + Standardbehandlung keine Evidenz zur allgemeinen Lebensqualität **Unerwünschte Ereignisse:** 1 RCT (n=183) keine Therapie-bedingten Todesfälle,	Evidenz zur klinischen Wirksamkeit und Sicherheit sind die Ergebnisse der längeren Nachbeobachtung der TheraP-Studie und laufende RCTs abzuwarten.	

Refe-renz	Studien-charakteristika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						in 2 RCTs (n=774) starben etwas mehr Pat. in der 177Lu-PSMA-617 (+ Standardbehandlung) Gruppe 2 RCTs (n=223) weniger Grad ≥3 AEs in 177Lu-PSMA-617-vs. Chemotherapie-Gruppen, 1 RCT (n=734) mehr Grad ≥3 AEs in Pat. mit 177Lu-PSMA-617 +		

Refe-renz	Studien-charakteristika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						Standardbehandlung		
Randomisierte kontrollierte Studien								
[440]	RCT NCT03392428 (TheraP) 1+	We aimed to analyse gallium-68 [^{68}Ga]Ga-PSMA-11 PET (PSMA-PET) and 2-[^{18}F]fluoro-2-deoxy-D-glucose PET (FDG-PET) imaging parameters as predictive and prognosti	n=200 men with mCRPC 2018-2019 Australia (11 centres) Median follow-up: 18.4 mo (IQR 12.8-21.8 mo)	[^{177}Lu]Lu-PSMA-617 (intravenously, every 6 weeks for a maximum of six cycles) n=99 Median age: 72.1 y (66.9-76.7 y)	Cabazitaxel (20 mg/m² intravenously, every 3 weeks for a maximum of ten cycles) n=101 Median age: 71.8 y (66.7-77.3 y)	**Cabazitaxel vs. [^{177}Lu]Lu-PSMA-617** **PSA response** PSMA SUVmean <10 OR: 2.22 (95% CI 1.11-4.51) PSMA SUVmean ≥10 OR: 12.19 (95% CI 3.42-58.76) **Radiografic PFS** PSMA SUVmean <10 HR: 0.85 (95% CI 0.59-1.24)	In men with metastatic castration-resistant prostate cancer, PSMA-PET SUVmean was predictive of higher likelihood of favourable response to [^{177}Lu]Lu-PSMA-617 than cabazitaxel, which provides guidance for optimal [^{177}Lu]Lu-PSMA-617 use. High FDG-PET MTV was associated with lower responses regardless of randomly assigned treatment, warranting further research for	Neither participants nor investigators were masked to group assignment, funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report, PET-CT images that were obtained as part of the eligibility assessment were centrally reviewed by three expert

Refe-renz	Studien-charakteristika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
		c biomarkers in this patient population.				PSMA SUVmean ≥10 HR: 0.46 (95% CI 0.25-0.84) **PSA PFS** PSMA SUVmean <10 HR: 0.77 (95% CI 0.53-1.12) PSMA SUVmean ≥10 HR: 0.45 (95% CI 0.25-0.80) **PSA response** FDG MTV <200 mL Reference FDG MTV ≥200 mL OR: 0.44 (0.23-0.84) **Radiografic PFS**	treatment intensification.	nuclear medicine physicians OS is not yet published Detailed list of conflict of interest reported in the paper. Funding Prostate Cancer Foundation of Australia, Endocyte (a Novartis company), Australian Nuclear Science and Technology Organization, Movember, The Distinguished Gentleman's Ride, It's a Bloke Thing, and CAN4CANCER.

Refe-renz	Studien-charakteristika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						FDG MTV <200 mL Reference FDG MTV ≥200 mL HR: 1.79 (1.28-2.52) **PSA PFS** FDG MTV <200 mL Reference FDG MTV ≥200 mL HR: 1.44 (1.03-2.02) There was no evidence that other PET parameters (PSMA-PET SUVmax, PSMA-PET MTV, FDG-PET SUVmax, and FDG-PET		

Refe-renz	Studien-charakteristika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						SUVmean) were more valuable markers of response or prognosis than PSMA-PET SUVmean or FDG-PET MTV.		

3.2 Wann sollte die Indikation für eine Therapie mit Lutetium-177-PSMA beim mCRPC gestellt werden?

Literaturreferenzen: [439], [442], [443], [444], [445], [446], [447], [448], [449], [450], [440], [451]

Referenz	Studiencharakteristika LoE	Studienziel	Patientenmerkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
Systematische Übersichtsarbeiten								
[439]	Systematic Review 2-	To review current data in the literature regarding the impact of antiandrogen therapy on PSMA expression of metastatic sites and the role of serial	n=36 studies men with metastatic prostate cancer Search period: 2010- July 2022	antiandrogen therapy		**Role of serial PSMA PET/CT in assessing treatment responses** **in advanced PC** (n=5) 177Lu-PSMA-617 & mCRPC 177Lu-PSMA-617 RLT prolonged OS and imaging-based PFS	PSMA PET imaging is essential in selecting patients for 177Lu-PSMA RLT. Growing evidence favors its use in assessing treatment responses after RLT. Preliminary evidence indicates the value of PSMA PET for assessment of the treatment response in patients receiving systemic treatment other than RLT for metastatic prostate cancer.	in the tables are 38 studies included, unclear which studies were identified via literature search, reference 15 are not included in the tables, only one database used and no additional hand search reported, only keywords reported, no

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
		(baseline and at least 1 follow-up scan) PSMA PET to assess treatment response in patients with metastatic prostate cancer.				when added to the standard of care (VISION 3) nomograms to predict outcomes after 177Lu-PSMA-617 therapy found that tumor SUVmax was an independent predictor of OS, PSA-PFS, and a PSA decline of ≥50%. Substudies of the TheraP and VISION trials recently		information if efforts were made to minimise errors in the data extraction, no risk of bias assessment of the included studies, sources of funding of the included studies were not reported Ken Herrmann has received personal fees from Bayer, Sofie Biosciences, SIRTEX, Adacap, Curium, Endocyte,

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						found that SUVmean at baseline PSMA PET was predictive of a favourable response to 177Lu-PSMA-617 RLT Prognostic significance of changes in PSMA PET parameters at followup scan has also been demonstrated		Boston Scientific, Ipsen, Siemens Healthineers, GE Healthcare, Amgen, Novartis, ymabs, Aktis Oncology, Pharma15, Theragnostics Ltd., Janssen, Telix, Debiopharm, Bain Capital, and Eco1R, other fees from Sofie Biosciences, nonfinancial support from ABX, and grants from Boston Scientific,

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
								all outside the submitted work. Obtaining funding: None.
[442]	Systematic Review N=17 prospective or retrospective clinical (dosimetry) studies between January 2014 and July 2021 LoE: 2-	To assess the organs at risk and the absorbed dose received by tumor lesions in 177Lu-PSMA therapy: **(1)** assess the organs at risk and maximum tolerance limit in 177Lu-PSMA therapy and	N= 263 patients with mCRPC of any age received 177Lu-PSMA therapy pre- or post-therapeutic dosimetry in a single cycle or multiple cycles	177Lu-PSMA systemic radiation therapy (SRT)		**Median cumulative absorbed dose received** by lacrimal, salivary glands and kidneys were found 9.04 Gy (range: 2.8–28.12 Gy), 4.66 Gy (range: 1.74–9.88 Gy) and 3.08 Gy (range:	177Lu-PSMA systemic radiation therapy (SRT) is a well-tolerated and reliable treatment option against the management of the mCRPC stage of prostate carcinoma. Tumors receive 3–6 times higher absorbed doses compared to organs at risk. BUT:	**Conflicts of interest:** None **Funding**: ? **ROB:** No risk of bias assessment (at all!); no explanation of the selection of the study designs for inclusion in the review; no list of excluded studies or justification of exclusions; no report on the sources of

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
		(2) assess the dose received by tumor lesions.				1.68–5.32 Gy). *maximum tolerance doses*: ~ 40 Gy for lacrimal, ~ 20 Gy for salivary, ~ 23 Gy for kidneys. **Median absorbed dose per unit of administered activity for**: kidneys, salivary, liver, spleen, lacrimal and bone marrow	Lacrimal gland (especially), salivary gland and kidneys are the organs that receive a significant amount of dose in 177Lu-PSMA therapy. àlt is well-tolerated to achieve a number of treatment cycles of 177Lu-PSMA SRT before surpassing the tolerance limit of lacrimal glands, salivary glands and kidneys. Individualized patient dosimetry is required to determine the maximum administered activity and number of treatment cycles	funding; no heterogeneity-discussion;

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						0.55, 0.81, 0.1, 0.1, 2.26 and 0.03 Gy/GBq. **Median absorbed dose per unit of activity for tumor lesions:** in a range of 2.71–10.94 Gy/GBq. **Assumption**: no variation in the tracer uptake during 3-4 treatment cycles with 177Lu-PSMA in normal organsà	before177Lu-PSMA therapy to prevent organ toxicity.	

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						estimated absorbed dose between: **lacrimal glands**:27.12 and 36.16 Gy, **salivary glands**: 13.98 and 18.64 Gy **kidneys**:9.24 and 12.32 Gy. àabsorbed doses for the kidneys: far below the dose tolerance limits. àlacrimal glands & salivary		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						glands: critical organs for 177Lu-PSMA SRT since the predicted absorbed dose limit after four treatment cycles* are very near to tolerance dose limit and will probably surpass it after five or six therapy cycles. *a cumulative activity of 20–21 GBq of 177Lu-PSMA can be		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						safely administered in 3–4 treatment cycles after considering the tolerance limit of these organs.		
[443]	Systematic Review and Meta-analysis N=24 (n= 3 prospective studies, n= 21 retrospective studies) LoE: 2-	To evaluated the efficacy and toxicity of PRLT.	N= 1192 patients with metastatic CRPC prior to PRLT (expect 1 study)	177Lu-PSMA or/and 177Lu-PSMA-I&T 177Lu-PSMA-617 (N=20 studies; 927 patients), 177Lu-PSMA-I&T (n=3 studies - 133 patients) a mix of 177Lu-PSMA-617 and 177Lu-PSMA- (1 study - 132 patients and reported aggregate data)		**PSA decrease of ≥50%:** **177Lu-PSMA-617 vs. 177Lu-PSMA-I&T:** (after therapy; n=23 studies)	**aggregate data:** ~ 46% of CRPC patients being treated with more than one cycle of PRLT with either 177Lu-PSMA-I&T or 177Lu-PSMA-617 have PSA reductions of ≥50%, indicating that these agents are objectively effective for this patient population.	**Funding/Support:** supported by: the National Institute of Biomedical Imaging and Bioengineering of the National Institutes of Health under award number T32EB006351;

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						0.41(0.36; 0.47); I^2= 67% **PSA response ≥50%** (after more than one cycle of with 177Lu-PSMA-I&T or 177Lu-PSMA-617; n=16 studies): 0.46 (0.41; 0.51); I^2=45% **177Lu-PSMA-617** (after therapy at least an 8-wk interval between therapy and	**Higher proportion of responders with therapy in the ≥8-wk interval group**. PRLT: associated with ≥50% reduction in: prostate-specific antigen level in a large number of patients low rate of toxicity àpotential in treating castration-resistant prostate cancer Extraction of: ≥50% serum prostate-specific antigen any PSA decrease, any PSA increase Ultimate utility of this treatment	the statistical analysis by the National Center for Research Resources and the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health through grant number 1UL1TR001079 ; funding from CA134675, CA183031, CA184228, EB024495, the Prostate Cancer Foundation Young Investigator

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						PSA measurement; n= 17 studies): 0.44 (0.39; 0.50); I^2=52% **177Lu-PSMA-I&T**(after therapy with 177Lu-PSMA-I&Tà ≥50% PSA reduction; n=3 studies) 0.36(0.26; 0.47); I^2=18% **Any <u>decrease</u> in PSA after therapy with:**	modality will become clearer as multiple prospective studies continue to accrue.	Award, and the European Union's Horizon 2020 research and innovation program under Marie Sklodowska-Curie grant agreement 701983. **Conflicts of interest:** None **Limitations**: single-arm designs of the included studies heterogeneity between the studies 15 of the included

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						177Lu-PSMA-I&T or 177Lu-PSMA-617 (after therapy n= 17 studies) 0.71(0.66; 0.75); I^2=42% **177Lu-PSMA-617** (after therapy; n=17 studies) 0.70(0.66; 0.75); I^2=43% **Any <u>increase</u> in PSA after therapy with:**		studies were ongoing trials supplement is incomplete no comprehensive search strategy Numbers of reviewers: unclear Exclusion list: no information Risk of bias: just for publication bias pooled, but no information on the risk of bias

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						177Lu-PSMA-I&T or 177Lu-PSMA-617 (after therapy; n=6 studies) 0.27(0.20; 0.35); I^2= 0% ---------- **<u>≥50% PSA decline</u>** **after radioligand therapy, vs. the time interval between PRLT and PSA measurement (≥8 vs <8 wk interval)** 2.20, p < 0.001, 95%		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						CI [1.30; 3.10] àhigher proportion of responders with therapy in the ≥8-wk interval group **One cycle vs more than one cycle of PRLT**: 0.84, p < 0.001, 95% CI [0.36; 1.32]à more than one cycle: greater proportion of patients with ≥50%		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						PSA reduction **Grade 3 and 4 toxicities** (were uncommon) nausea, fatigue, diarrhea, elevated aspartate transaminase 0.01 (0.00;0.04) anemia 0.08 (0.05; 0.12) **Overall survival (pooled HRs):** for any PSA decline		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						0.29 (0.18; 0.46) for >50% PSA reduction 0.67 (0.43; 1.07) for >50% PSA decline 0.53 (0.32–0.86) for the PFS of >50% PSA decline **Progression-free survival** (pooled HR of >50% PSA reduction): 0.53 (0.32; 0.86)		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
[444]	Systematic review N= 12 (11 retrospective and 1 prospective study) articles up to May 2020, LoE: 2-	To precisely evaluate the impact of visceral metastases on biochemical response and survival outcomes in patients of mCRPC treated with Lu-PSMA RLT.	N= 1504 mCRPC-patients with progressive disease despite prior treatments with antiandrogens and/or chemotherapy and administered 177Lu- PSMA RLT as salvage/compassionate treatment.	177Lu-PSMA-617 or 177Lu-PSMA-I&T		**Visceral metastases and low biochemical response rate:** **(pooled univariate)** OR: 0.38, 95% CI, 0.22–0.66 **Visceral metastases and prognosticator of worse** **progression-free survival** (pooled univariate)	Presence of visceral metastases was associated with poor response and survival outcomes in patients of mCRPC treated with 177Lu-PSMA RLT. The results are clinically significant for pretreatment risk stratification of such patients and to guide optimal treatment strategies.	**Funding**: ? **Conflict of interest**: ? Individual regression estimates for biochemical response, PFS, and OS were not available in all of thes studies, and consequently, pooled analysis of the ORs and HRs was feasible only in a limited number of studies. Most studies were retrospective and single-arm in nature and

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						HR, 1.85; 95% CI, 1.39–2.46 (pooled multivariate) HR, 1.48; 95% CI, 1.15–1.92 **Visceral metastases and OS** **(**pooled univariate) HR, 1.77; 95% CI, 1.29–2.44 (pooled multivariate) HR, 2.22; 95% CI, 1.82–2.70		thus had an inherent high risk of bias. Pooled estimates of univariate ORs and HRs could have been affected by other clinical variables; however, the corresponding multivariate estimates, wherever available, were not markedly different. The impact of liver metastasis vis-à-vis lung metastasis on treatment outcomes was

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
								also not investigated in most of the studies and needs further research.
[445]	Systematic Review with meta-analysis 2++	This study was conducted to precisely evaluate the impact of prior taxane chemotherapy on response and survival outcomes in mCRPC patients after [177Lu]Lu-PSMA-RLT.	n=13 articles (11 single-arm interventional studies, 2 retrospective studies) n=2068 patients with mCRPC Median age: 71.6 y (range 30-92 y) Median follow-up: 9.9 mo	Taxane-Naïve patients n=590	Taxane-Treated Patients n=1477	**Taxane-naïve vs. taxane-treated patients after 177Lu-PSMA-RLT** **PSA Response** (n=6 studies) OR 1.82 (95% CI, 1.21–2.71; p=0.004) I^2=0%	mCRPC patients with no prior taxanes had significantly better outcomes after [177Lu]Lu-PSMA-RLT than did taxane-treated patients.	sources of funding of the included studies were not reported No potential conflict of interest relevant to this article was reported. Funding not reported.

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
			(range 0.5-72 mo) search date: December 19, 2022			**PFS** (n=5 studies) HR 0.6 (95% CI, 0.51–0.69; P<0.001), I^2=0% **OS** (n=8 studies) HR 0.54 (95% CI, 0.43–0.68; P<0.001), I^2=0%		
[446]	systematic review and meta-analysis N= 36 (all types of study design) Search for publications up to 31 September 2020	To evaluate patient and treatment characteristics for patients with metastatic castration-resistant	N= 2346 patients above 18 with multi-resistant mCRPC	PRLT (177Lu PRLT or 225 Act PRLT)	Comparative analyses evaluated whether characteristics differed in impact on	**OS in general:** Patients with PSA decline ≥ 50% vs. with less PSA decline median 20 months vs.	**OS**: 177Lu PSMA I&T and 177Lu PSMA-617 had a similar rates of PSA decline ≥ 50%. More patients treated with an intensive schedule	**Conflicts of Interest:**None **Funding**: None Some publications did not state whether they reported consecutive

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
	LoE: 2-	prostate cancer (mCRPC) treated with PSMA radioligand therapy (PRLT) associated with above-average outcome. associated with an **above-average overall survival (OS)**. proportion of patients with **severe adverse e ects (SAE)**			the outcome	12 months, $p = 1.6 \times 10^{-6}$ Relevant characteristi cs of patients regarding OS: **Metastases / cancer** PSA decline ≥ 50% after PRLT: (patients with lymph node metastases (LNM) vs. patients with bone metastases): 36 of 45 versus 38 of	for 177Lu PRLT in the first series had a PSA decline ≥ 50% than those treated with a conventional schedule Patients treated with an intensified schedule of 177Lu PRLT lived longer than those treated with a conventional* schedule. *Conventional schedule mostly: 6 GBq 177Lu for each cycle of PRLT and ≥8 weeks between cycle. Characteristics regarding the patients, art of cancer/ metastases, restaging and PLRT	patients, other publications reported preliminary results, and a third group of publications did not report on all outcomes our systematic review aimed to address. Only a few patients with favorable patient characteristics were reported, only a few patients treated with intensified 177Lu PRLT, and only two radioligands

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						100, p < 0.0005. Patients with cancer lesions with a high uptake of 177Lu lived longer than patients with a low uptake. **Restaging - PET/CT:** PSA decline ≥ 50% after 1st series of PLRT (PSMA based radioligand therapy) **First series of PRLT**	contribute to an above-average OS after PLRT of patients with mCRPC (= highliy significant findings). Only hepatic metastases caused the negative impact visceral metastases to have an outcome after PTRLT relative to that of bone metastases. PSMA PET/CT resulted in a better staging of patients with PC than conventional imaging such as bone and CT scans **Chemotherapy-naïve patients were treated at an earlier phase** in the	used as monotherapy for patients with mCRPC. No report in the combined effect of all characteristics that determine the response after PRLT and OS. No list of excluded studies; risk of bias only regarding publication bias; heterogeneity between publications but no separate summary

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						Intensive 177 LU N= 2 studies (Rasul, Seifert) 56(46-66); 95% CI **lymph node metastases** N= 1 study (Von Eyben) 80(67-92); 95% CI 255 Act N=2 (Sathekge, Yadav) 75(59-89); 95% CI **Convention al 177LU**	sequence of treatments of mCRPC than patients resistant to chemotherapy.For many cancers in addition to PC, asymptomatic patients with good performance status live longer than patients with symptoms and poor performance status **Severe Adverse Effects (SAE)** Treatment with 177Lu PRLT=safe; none died of SAE; none developed leukemia. In the treatment of mCRPC, PRLT is an optimal candidate	estimates for RCTs and NRSI

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						N=18 studies 44(39-49); 95% CI **TOTAL**: 48(43-54); 95% CI <u>PSA decline ≥ 50% after 2nd series of PRLT</u> **225 Actinium PLRT** N=3 studies 46(19-75) 95% CI **177 LU PLRT** 55(44-66); 95% CI **TOTAL:**	for being combined with established drugs.	

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						50(36-56) 95% CI SUVaverage/ min **SAE:** rare and maily hematologic SAE grade 3* (of the treated patients, a median of 10% had anemia grade 3, median 3% had leucopenia grade 3, median 2%, throbocytopenia grade 3 *similar rates of		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						grade 3 hematologic SAE between 225 Act PRLR or 177Lu PRLT		
Randomisierte kontrollierte Studien								
[447]	RCT NCT03511664, (VISION) 1-	We report additional HRQOL, pain, and symptomatic skeletal event results.	n=831 men with mCRPC 2018-2019 84 sites in nine countries 52 in North America 32 in Europe	177Lu-PSMA-617 (maximum of six cycles every six weeks) plus standard care n=385 Median age: 71 y (range 65-75 y)	standard care n=196 Median age: 72 y (range 66-76 y)	**177Lu-PSMA-617 vs. standard care** **Median time to first symptomatic skeletal event** *Median follow-up: 17 mo* 11.5 vs. 6.8 mo; HR 0.5 (95% CI 0.4-	[^{177}Lu]Lu-PSMA-617 plus standard of care delayed time to worsening in HRQOL and time to skeletal events compared with standard of care alone. These findings support the use of [^{177}Lu]Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer who received previous androgen receptor pathway inhibitor	open-label study The funder of the study had a role in study design, data analysis, data interpretation, and writing of the report, but had no role in data collection. Detailed list of conflict of interest

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						0.62) p<0.001 **Time to worsening (FACT-P score)** *Median follow-up: 4.37 mo (IQR: 1.02-8.08 mo)* 5.7 vs. 2.2 mo; HR 0.54 (95% CI 0.45–0.66) p<0.001 **EQ-5D-5L utility score** 1 vs. 0.5 mo; HR 0.65 (95% CI 0.54–0.78) p<0.001	and taxane treatment.	reported in the paper. Supported by Endocyte, a Novartis company

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						Pain intensity (BPI-SF) *Median follow-up: 4.14 mo (IQR: 1.64-8.77 mo)* 6.9 vs. 2.6 mo; HR 0.52 (95% CI 0.42–0.63) p<0.001 **Treatment-related adverse events** <u>Death</u> 177Lu-PSMA-617: 5 (pancytopenia [n=2], bone marrow failure [n=1],		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						subdural haematoma [n=1], and intracranial haemorrhage [n=1]) standard care: 0		
[448]	RCT CTRI/2019/12/022282 1-	We report the final analysis of OS for a phase 2 RCT.	n=40 men with chemotherapy-naïve patients with mCRPC Mean follow-up: 33.4 mo	[177Lu]Lu-PSMA-617 (6.0–7.4 GBq/cycle intravenously, up to 4 cycles, 8–12 wk apart) n=20	docetaxel (75 mg/m2/cycle intravenously, up to 10 cycles, 3 wk apart) n=20	**Median OS** Lutetium: 15.0mo (95% CI, 9.5–20.5 mo) docetaxel: 15 mo(95% CI, 8.1–21.9 mo)	Long-term outcomes with [177Lu]Lu-PSMA- 617 administered earlier in the prechemotherapy setting are comparable to those with docetaxel.	The study sample size was based on the primary endpoint of prostate-specific antigen response rate and was not adequately powered for other analyses. Randomisation process not clearly described,

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
								open-label study, important patient characteristics not described (e. g. age) No potential conflict of interest relevant to this article was reported. Funding: not reported
[449]	randomized, controlled, phase 2non-inferiority trial CTRI/2019/12/022282 LoE: 1-	To prospectively compare the efficacy and safety of 177 Lu-PSMA-617 and docetaxel in chemothera	N= 40 men with chemotherapy-naïve patients with mCRPC and high PSMA-expressing	N=20 patients 177 Lu- PSMA-617 (6.0–7.4 GBq/cycle, every 8	N=20 patients docetaxel (75 mg/m2 /cycle, every 3 weeks, up	**per-protocol analysis:** best PSA-RR 177 Lu-PSMA-617: (9/15) (60%, 95% CI: 35–85)	**77 Lu-PSMA-617=** safe and non-inferior to docetaxel in the treatment of mCRPC regarding achieving PSA response in chemotherapy-naïve mCRPC with an	**Conflict of interest:** none **Funding**: ? **Limitations**: open-label nature of the study; lack of a baseline ^{18} F-

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
		py-naïve mCRPC patients. Primary outcome: best prostate-specific antigen response rate (PSA-RR)	lesions on 68 Ga-PSMA-11 PET/CT 2019-2021	weeks, up to 4 cycles) high-grade prostate cancer 14 (70%) 15/20 = treatment per protocol **49 cycles - median cumulative activity**: of 15 GBq (range 6–30 GBq) over 1–4 cycles at intervals of 8–16 weeks àIntervals were disturbed by COVID-19	to 10 cycles) high-grade prostate cancer 12 (60%) 20/20= treatment per protocol **5 cycles:** all the patients; **10 cycles:** 11 patients (55%) **discontinued fur-** **ther cycles due to**	docetaxel: (8/20) (40%, 95% CI: 19–61) Difference (PSA-RRs): 177 Lu-PSMA-617 vs. docetaxel 20% (95% CI: − 12–47, P = 0.25) **ITT analysis** Best PSA-RR(defined according to Prostate Cancer Clinical Trials Working Group-3 as proportion	acceptable safety profile. Could be potentially employed earlier in the disease course rather than being solely reserved for advanced end-stage disease. Further large-scale trials are required to validate our observations and determine the specific sequence of treatment options for these patients.	FDG-PET/CT; unavoidable delays in the treatment administration and follow-up in few patients during the COVID-19 pandemic; calculated sample size was adequate for PSA-RR as the primary end-point and not for the other observations.

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
				at least one cycle: all patients **at least two cycles:** 15 pat. (75%) **3 cycles** 2 pat. (10%) **4 cycles** 6 pat. (30%) **not complet-** **ing four cycles** (disease progression) 7 pat. (35%) **disease-related deaths:**	**progressive disease:** 7 patients (35%); **did not complete treatment (chemotherapy-related** **interstitial pneumonitis)** 1 patient **8 cycles:** 1 patient died	of patients achieving ≥ 50% decline in PSA from baseline): 177 Lu-PSMA-617: (50%, 95% CI: 28–72) (10/20) Docetaxel: (40%, 95% CI: 19–61) (8/20) Difference - 177 Lu-PSMA-617 vs. docetaxel 10% (95% CI: − 19–37, P = 0.53)		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
				3 pat. (15%) **persistent treatment (myelosuppres-sion) (≥ grade 3)** 2 pat. (10%) **exceptional response** 2 patients (10%)		**Per-protocol analysis** best objective response 177Lu-PSMA-617 (5/11) (46%, 95% CI: 16–75) docetaxel (6/19) (32%, 95% CI: 11–52) difference 14% (95% CI: − 19–45, P = 0.45) best molecular response rates		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						177 Lu-PSMA-617 50% (95% CI: 22–78) docetaxel 32% (95% CI: 11–52) difference 18%, (95% CI: − 14–48, P = 0.31) **ITT analysis:** best objective response 177 Lu-PSMA-617 (5/13) (39%, 95% CI: 12–65) docetaxel		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						(6/19) (32%, 95% CI: 11–52) <u>Difference:</u> (7%, 95% CI: − 24–38, P = 0.69) <u>best molecular responses:</u> 177 Lu-PSMA-617 (6/14) (43%, 95% CI: 17–69) docetaxel (6/19) (32%, 95% CI: 11–52) <u>Difference</u>		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						11%, 95% CI: − 19–41, P = 0.51) **Per-protocol** median PFS durations 177 Lu-PSMA-617 5.0 months (95% CI: 3.3–6.7) docetaxel arms 4.0 months (95% CI: 3.6–4.4) (P = 0.30) Corresp. PFS rate at 6 months		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						177Lu-PSMA-617: 30% Docetaxel: 20% difference 10%, 95% CI: − 18–38, P = 0.50) progression-free survival rates at 6 months: 177 Lu-PSMA-617 and docetaxel arms respectively: 30% and 20% Difference:		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						10% (95% CI: − 18–38, P = 0.50) **ITT analysis** <u>PFS 4.0 months</u> 177 Lu-PSMA-617 (95% CI: 1.8–6.2 months) docetaxel (95% CI: 3.6–4.4 months) (P = 0.98) <u>PFS rate at 6 months</u> 177Lu-PSMA-617 vs. docetaxel 23% vs. 20%		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						difference 3%, 95% CI: − 22–28, P = 0.82 disease progression or death 177 Lu-PSMA-617 versus docetaxel HR:0.90 (95% CI: 0.46–1.77) ---------- **treatment-emergent grade ≥ 3adverse events:** 177 Lu-PSMA-617		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						6/20, (30%, 95% CI: 10–50) docetaxel 10/20, (50%, 95% CI: 28–72) P = 0.20 <u>Difference</u> 20%, (95% CI: − 10–45, P = 0.20) <u>Quality-of-life outcomes</u>: 177 Lu-PSMA-617 compared to docetaxel arm: P < 0.01		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
[450]	RCT NCT0351166 (VISION) 1-	We report the results of VISION, a phase 3 trial investigating the efficacy and safety of 177Lu-PSMA-617 plus protocol- permitted standard care in a specific population of previously treated patients with mCRPC who were selected for PSMA positivity on	n=831 men with mCRPC 2018-2019 84 sites 52 in North America 32 in Europe Median follow-up: 20.9 mo	177Lu-PSMA-617 (maximum of six cycles every six weeks) plus standard care n=551 Median age: 70 y (range 48-94 y)	standard care n=280 Median age: 71.5 y (range 40-89 y)	**177Lu-PSMA-617 vs. standard care** **Median imaging-based PFS** (n=581) 8.7 vs. 3.4 mo; HR 0.40 (99.2% CI 0.29-0.57) p<0.001 **Median OS** (n=831) 15.3 vs. 11.3 mo; HR 0.62 (95% CI, 0.52-0.74) p<0.001 **Median time to first**	Radioligand therapy with 177Lu-PSMA-617 prolonged imaging-based progression-free survival and overall survival when added to standard care in patients with advanced PSMA-positive metastatic castration-resistant prostate cancer.	open-label study, objective response and disease control not reported, conflict of interest not clearly described Standard-care therapy that was permitted by the trial protocol had to be agreed on and assigned by the physician–investigator before randomization,

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
		the basis of PSMA positron-emission tomographic imaging.				**symptomatic skeletal event** (n=581) 11.5 vs. 6.8 mo; HR 0.5 (95% CI 0.4-0.62) p<0.001 **Complete response** (n=248) 9.2% (17/184) vs. 0% (0/64) **Partial response** (n=248) 41.8% (77/184) vs. 3% (2/64) **Incidence of adverse events of**		but it could be modified at the discretion of the treating physician. Standard-care therapies could not include cytotoxic chemotherapy, systemic radioisotopes (e.g. radium-223), immunotherapy, or drugs that were investigational when the trial was designed (e.g. olaparib). Supported by Endocyte, a Novartis company.

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						grade 3 or above (n=831) 52.7% vs. 38.0%		
[440]	RCT NCT03392428 (TheraP) 1+	We aimed to analyse gallium-68 [^{68}Ga]Ga-PSMA-11 PET (PSMA-PET) and 2-[^{18}F]fluoro-2-deoxy-D-glucose PET (FDG-PET) imaging parameters as predictive and prognostic biomarkers in this patient population.	n=200 men with mCRPC 2018-2019 Australia (11 centres) Median follow-up: 18.4 mo (IQR 12.8-21.8 mo)	[^{177}Lu]Lu-PSMA-617 (intravenously, every 6 weeks for a maximum of six cycles) n=99 Median age: 72.1 y (66.9-76.7 y)	Cabazitaxel (20 mg/m² intravenously, every 3 weeks for a maximum of ten cycles) n=101 Median age: 71.8 y (66.7-77.3 y)	**Cabazitaxel vs. [^{177}Lu]Lu-PSMA-617** **PSA response** PSMA SUVmean <10 OR: 2.22 (95% CI 1.11-4.51) PSMA SUVmean ≥10 OR: 12.19 (95% CI 3.42-58.76)	In men with metastatic castration-resistant prostate cancer, PSMA-PET SUVmean was predictive of higher likelihood of favourable response to [^{177}Lu]Lu-PSMA-617 than cabazitaxel, which provides guidance for optimal [^{177}Lu]Lu-PSMA-617 use. High FDG-PET MTV was associated with lower responses regardless of randomly assigned treatment,	Neither participants nor investigators were masked to group assignment, funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report, PET-CT images that were obtained as part of the eligibility assessment

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						Radiografic PFS PSMA SUVmean <10 HR: 0.85 (95% CI 0.59-1.24) PSMA SUVmean ≥10 HR: 0.46 (95% CI 0.25-0.84) **PSA PFS** PSMA SUVmean <10 HR: 0.77 (95% CI 0.53-1.12)	warranting further research for treatment intensification.	were centrally reviewed by three expert nuclear medicine physicians OS is not yet published Detailed list of conflict of interest reported in the paper. Funding Prostate Cancer Foundation of Australia, Endocyte (a Novartis company), Australian Nuclear Science and Technology Organization, Movember, The

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						PSMA SUVmean ≥10 HR: 0.45 (95% CI 0.25-0.80) **PSA response** FDG MTV <200 mL Reference FDG MTV ≥200 mL OR: 0.44 (0.23-0.84) **Radiografic PFS** FDG MTV <200 mL Reference FDG MTV ≥200 mL		Distinguished Gentleman's Ride, It's a Bloke Thing, and CAN4CANCER.

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						HR: 1.79 (1.28-2.52) **PSA PFS** FDG MTV <200 mL Reference FDG MTV ≥200 mL HR: 1.44 (1.03-2.02) There was no evidence that other PET parameters (PSMA-PET SUVmax, PSMA-PET MTV, FDG-PET SUVmax, and FDG-PET SUVmean) were more		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						valuable markers of response or prognosis than PSMA-PET SUVmean or FDG-PET MTV.		
[451]	RCT NCT03392428 (TheraP) 1+	We aimed to compare [¹⁷⁷Lu]Lu-PSMA-617 with cabazitaxel in patients with metastatic castration-resistant prostate cancer.	n=200 men with mCRPC 2018-2019 Australia (11 centres) Median follow-up: 18.4 mo (IQR 12.8-21.8 mo)	[¹⁷⁷Lu]Lu-PSMA-617 (intravenously, every 6 weeks for a maximum of six cycles) n=99 Median age: 72.1 y (66.9-76.7 y)	Cabazitaxel (20 mg/m² intravenously, every 3 weeks for a maximum of ten cycles) n=101 Median age: 71.8 y (66.7-77.3 y)	**[¹⁷⁷Lu]Lu-PSMA-617** **vs. Cabazitaxel** **PSA responses** 65/99 (66%) vs. 37/101 (37%), difference: 29% (16-42%), p<0.001	[¹⁷⁷Lu]Lu-PSMA-617 compared with cabazitaxel in men with metastatic castration-resistant prostate cancer led to a higher PSA response and fewer grade 3 or 4 adverse events. [¹⁷⁷Lu]Lu-PSMA-617 is a new effective class of therapy and a potential alternative to cabazitaxel.	Neither participants nor investigators were masked to group assignment, funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report, PET-CT images that were obtained

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						radiographic Progression HR 0.64 [0.46–0.88]; p=0.0070 **PSA PFS** HR 0.60 [0.44–0.83]; p=0.0017 **PFS at 12 mo** 19% (95% CI 12-27%) vs. 3% (1-9%) **Median PFS** 5.2 mo (3.4-5.7 mo)vs. 5.1 mo (2.8-6 mo) **Pain PFS** HR 0.72 (95% CI		as part of the eligibility assessment were centrally reviewed by three expert nuclear medicine physicians OS is not yet published Detailed list of conflict of interest reported in the paper. Funding Prostate Cancer Foundation of Australia, Endocyte (a Novartis company), Australian Nuclear Science and

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						0.53-0.97) p=0.033 **Patient-reported outcomes***(with clinical meaningful improvement of QoL)* diarrhoea: 9 [95% CI 6–11] vs. 16 [13–19] p<0.0001 fatigue: 34 [31–38] vs. 40 [36–43]; p=0.027 social functioning: 79 [75–82] vs 73 [69–77]; p=0.030)		Technology Organization, Movember, The Distinguished Gentleman's Ride, It's a Bloke Thing, and CAN4CANCER.

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						insomnia: 23 [20–27] vs 29 [25–33]; p=0.023 **Deterioration-free survival for global health status** 29% [95% CI 21–38] vs 13% [95% CI 7–21]; p=0.0002 **Grade 3–4 adverse** 32/98 (33%) vs. 45/85 (53%) No deaths were attributed to		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						[^{177}Lu]Lu-PSMA-617		

3.3 Schlüsselfrage: Welche neu zugelassenen Medikamente/Medikamentenkombinationen sind der Androgendeprivationstherapie oder Docetaxel+Androgendeprivationstherapie in der Therapie des mHSPC überlegen?

Literaturreferenzen: [452], [453], [454], [455], [456], [457], [458], [459], [460], [461], [462], [463], [464], [349], [348], [347]

Referenz	Studiencharakteristika LoE	Studienziel	Studien- und Patientenmerkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
Systematische Reviews								
[452]	Systematic review 1++	We performed a systematic review to evaluate if HRQoL is affected by the combination therapy of ADT and ARSIs in	n = 6 RCTs (ARCHES, ENZAMET, TITAN, LATITUDE, STAMPEDE, ARASENS) n = 6397 patients ≥18 years of age and with a histologically or clinically confirmed	I. ARCHES ENZ +ADT II. ENZAMET ENZ +ADT III. TITAN APA + ADT IV. LATITUDE AAP + ADT	I. ARCHES Placebo + ADT II. ENZAMET Nonsteroideal first generation antiandrogens + ADT III. TITAN Placebo + ADT	Overall HRQoL I. ARCHES TTFD: 11.14 vs 8.38 mo; HR = 0.80 (95% CI: 0.67–0.94; p = 0.007) no significant mean change in HRQoL score over time	**The addition of ARSIs to ADT in mHSPC tends to increase overall HRQoL and prolong time to first deterioration of pain/fatigue compared with ADT alone, ADT with first generation nonsteroideal**	PROSPERO protocol not found (registration number: 334849), sources of funding and potential heterogeneity of the included studies were not reported **We identified a large methodological heterogeneity among studies as different**

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
		mHSPC patients.	mPCa (only the STAMPEDE trial included also patients with high-risk localized or relapsing disease after initial local therapy) Median age 66 - 70 y Search: January 2011-April 2022 Median follow-up: 14 mo - 43.7 mo	V. STAMPEDE AAP + ADT VI. ARASENS DAR + DOC + ADT	IV. LATITUDE Placebo +ADT V. STAMPEDE DOC + ADT VI. ARASENS Placebo + DOC + ADT	II. ENZAMET deterioration-free survival: 31% vs 17%; p < 0.001 no significant mean change in HRQoL score over time III. TITAN No difference in terms of HRQoL outcomes IV. LATITUDE TTFD: HR = 0.85 (95% CI: 0.74–0.99, p = 0.03) V. STAMPEDE MD at 3 mo: 7.0	**anti-androgens, and ADT with docetaxel. ARSIs show a complex interaction with remaining HRQoL domains. We advocate a standardizatio n of HRQoL measurement and reporting to allow further comparisons.**	**questionnaires and time** **points have been used to measure HRQoL and its sub-domains, as well as diversity regarding outcome reporting, which has prevented a direct comparison between different regimens.** **Conflict of interest** RC: Advisory role for Astellas, Janssen, Bayer, Sanofi, MSD, Roche, BMS, Merck, Pfizer, Ipsen; honoraria from Astellas, Janssen, Merck. The remaining authors

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						MD at 6 mo: 8.3 MD at 24 mo:4.8 overall MD: 3.9 p < 0.05 VI. ARASENS No difference in terms of HRQoL outcome		declare no competing interests. **Funding** **no information** **the STAMPEDE trial included also patients with high-risk localized or relapsing disease after initial local therapy**
[453]	Systematic Review and Multivariate Network Meta-analysis PROSPERO: CRD42021272306 1++	To systematically evaluate the literature regarding adverse events (AEs) between the ARSi drugs	mCSPC: n=4 RCTs (LATTITUDE [Fizazi 2019], Chi 2019, ARASENS [Smith 2022], ARCHES ([Armstrong 2019])	I. LATTITUDE ABI + PRED II. Chi (2019) APA III. ARASENS DAR + ADT + DOC	I. LATTITUDE Placebo + ADT II. Chi (2019) Placebo + ADT III. ARASENS Placebo + ADT + DOC	Abiraterone was ranked as the most toxic treatment regarding grade 3 + 4 AEs (RR=1.36, 95% CI 1.22–3.62; SUCRA 3%) and sAEs (RR 1.28, 95% CI 1.15–1.43; SUCRA 6%)	**High-risk mCSPC** **the disease volume or risk in the mCSPC setting may affect AE profiles, particularly for grade 3 + 4 AEs and sAEs, to a greater**	Abiraterone was the only drug studied in a double-blind mCSPC setting (LATITUDE) involving strictly high-risk disease; all other studies for mCSPC had mixed high/low risk/volume disease

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		abiraterone, apalutamide, darolutamide, and enzalutamide in the treatment of metastatic castration-resistant prostate cancer (mCRPC), nonmetastatic CRPC (nmCRPC), and metastatic castration-sensitive prostate cancer (mCSPC).	n= 4703 patients with mCSPC Search: up until September 1, 2022	IV. ARCHES ENZ + ADT	IV. ARCHES Placebo + ADT	(abiraterone was studied strictly in the context of high-risk mCSPC. The other three double-blind RCTs had inclusion criteria that did not differentiate between high/low volume/risk mCSPC.) Enzalutamide was ranked as the most toxic regarding headache (RR 2.10, 95% CI: 1.22–3.62) Subgroup analysis of high-risk mCSPC	**extent than the specific agent used; however, comparisons are difficult to make as no other double-blind RCT evaluating ARSi therapy in this specific setting was included**	Registered protocol did not report the search strategy. It was however reported in the published article. No information on the use of additional literature search methods. No justification on the restriction on English papers and study designs. No information on the source of funding of the included studies. **Conflict of interest** None. **Funding** None.

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						SUCRA curves consistently ranked abiraterone (used for high-risk disease) as the worst treatment with respect to: grade 3 + 4 AEs (RR=1.36, 95% CI: 1.30–1.42) sAEs (RR=1.28, 95% CI: 1.18–1.40) <u>Subgroup analysis of low-risk mCSPC</u> grade 3 + 4 AEs (RR=1.04, 95% CI: 1.00–1.08) sAEs (RR=1.05, 95% CI: 0.98–1.11)		

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
[454]	Systematic review and network meta-analysis 1+	Given the lack of head-to-head randomized trials, we performed this updated meta-analysis to conduct indirect comparison for the efficacy and safety of darolutamide with other new-generation ARTAs.	n = 9 RCTs (ARCHES, TITAN, ENZAMET, PEACE1, LATITUDE, Stampede (arms: C, G), ARASENS, CHAARTED, Getug-AFU) n=11058 patients with mHSPC Search: up until July 2022	Darolutamide combination	other androgen receptor targeted agents	OS (n=9 trials) Compared with Docetaxel Apalutamide: HR 0.84 (95% CI 0.67, 1.1) Darolutamide+DOC: HR 0.68 (95% CI 0.57, 0.81) Abiraterone+DOC: HR 0.75 (95% CI 0.59, 0.95) Abiraterone: HR 0.84 (95% CI 0.7, 1.0) Enzalutamide: HR: 0.86 (95% CI 0.7, 1.1) ADT: HR 1.3 (95% CI 1.1, 1.5)	**Darolutamide appears to be an optional androgen receptor inhibitor for mHSPC patients, especially for patients with Gleason score ≥ 8. Its well-tolerated characteristic may provide a preferred drug option for patients with poor cardiovascular function and bone health.**	**no study protocol, unclear if efforts were made to minimize errors in the data extraction, sources** of funding of the included studies were not reported no **significant heterogeneity in the analysis and no evidence of a significant publication bias** **This study was supported by the National Natural Science Foundation of China, the Tai Shan Scholar Foundation**

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						OS for ARTA+ Docetaxel+ADT (n=5 trials) Compared with DOC+ADT DAR+DOC+ADT: OR 0.63 (95% CI 0.5, 0.78) ABI+DOC+ADT: OR 0.7 (95% CI 0.51; 0.95) ENZ+DOC+ADT: OR 0.84 (95% CI 0.59; 1.2) APA+DOC+ADT: OR 1.3 (95% CI 0.58; 2.8) Progression to CRPC (n=5 trials)		**and Primary Research & Development Plan of Shandong Province.** **Conflicts of interest: The authors declare no conflict of interest.**

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						<u>Compared with Docetaxel</u> Enzalutamide: HR 0.64 (95% CI 0.56, 0.73) Apalutamide: HR 0.56 (95% CI 0.49, 0.63) Darolutamide+DOC: HR 0.36 (95% CI 0.33, 0.39) Abiraterone+DOC: HR 0.38 (95% CI 0.34, 0.42) ADT: HR 1.6 (95% CI 1.5, 1.8) Subgroup analysis Darolutamide showed the lowest mortality risk in all subgroups (ECOG		

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						and Gleason score) Gleason score (≥ 8) were likely to obtain significant survival benefits when treated with darolutamide (HR = 0.71, 95% CrI = 0.59–0.86) Adverse events (≥ Grade 3) abiraterone was significantly associated with a higher incidence Darolutamide, enzalutamide, and apalutamide provided a non-significant likelihood of toxicity		

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						SUCRA: apalutamide had the highest rank associated with the lowest rate of ≥ Grade 3 adverse events, followed by darolutamide and enzalutamide		
[455]	Systematic review and network meta-analysis PROSPERO: CRD42022375347 1++	To conduct a systematic review and network meta-analysis to compare the efficacy of currently available combination therapies in patients	n=12 RCTs (GETUG-AFU 15, CHAARTED, STAMPEDE (arms: B, C, E, G), ENZAMET LATITUDE, TITAN, ARCHES, PEACE1, ARASENS, CHART)	ADT Abiraterone Androgen receptor antagonist drugs used in combination with abiraterone or androgen receptor antagonist		Overall population OS Ranking in comparison with ADT with or without SNA: triplet therapy (HR: 0.57, 95% CrI: 0.48–0.67)	**Overall population**: Triplet therapy was the best treatment. **High-volume mHSPC**: triplet therapy and ADT plus rezvilutamide had the greatest potential to	Due to the trial design, some volume stratification data were not available. Data maturities of the included trials may have affected the results. The protocols for triplet therapies are not uniform and standardized.

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
		with mHSPC. We indirectly compared the efficacy of specific therapies in patients with mHSPC with the high- and low-volume disease.	n= 11.386 mHSPC-patients high-volume disease (n=6043) low-volume disease (n=3471) Median follow-up: 29-84 mo Search date: published before November 2022			doublet therapy of ADT plus ARTA doublet therapy ADT plus docetaxel Radiographic PFS Ranking in comparison with ADT with or without SNA: triplet therapy (HR: 0.33, 95% CrI: 0.26–0.41) doublet therapy of ADT plus ARTA doublet therapy ADT plus docetaxel High-volume mHSPC	benefit patients. **Low-volume mHSPC**: most likely to benefit from ADT plus androgen receptor-targeted agents. Triplet therapy was associated with a higher risk of adverse events than the other therapies.	The proportion of different races in trials may limit comparability between studies. Trials with high heterogeneity were excluded to ensure that I2 values were <50%. **Funding** supported by Jilin Scientific and Technological Development Program, and Bethune Urological Oncology Special Grant, Beijing Bethune Charitable Foundation. **Conflict of interest**

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						OS Ranking in comparison with ADT with or without SNA: triplet therapy (HR: 0.57; 95% CrI: 0.44–0.75) ADT plus ARTA ADT plus docetaxel Best combinations: abiraterone triplet therapy (HR, 0.52; 95% CrI: 0.38–0.72) ADT plus rezvilutamide (HR, 0.58; 95% CrI: 0.44–0.77)		The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						Radiographic PFS Ranking in comparison with ADT with or without SNA: triplet therapy (HR: 0.29; 95% CrI: 0.23–0.37) ADT plus ARTA ADT plus docetaxel Best combination: abiraterone triplet therapy (HR, 0.28; 95% CrI: 0.21–0.38) ADT plus rezvilutamide (HR, 0.44; 95% CrI: 0.33–0.58)		

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						Low-volume mHSPC OS Ranking in comparison with ADT with or without SNA: doublet and triplet therapies (HR: 0.68, 95% CrI:0.58–0.80) Best combination: ADT plus apalutamide (0.53, 95% CrI:0.35–0.79) Radiographic PFS Ranking in comparison		

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						with ADT with or without SNA: doublet and triplet therapies (HR: 0.37, 95% CrI: 0.25–0.55) Best combination: enzalutamide triplet therapy (HR: 0.27, 95% CrI:0.15–0.51) Adverse Events: Comparison with ADT with or without SNA: none of the doublet therapies with ADT and ARTA had an increased risk docetaxel-based doublet or triplet		

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						therapies significantly increased the risk ADT plus rezvilutamide lowest incidence (OR: 1.00, 95% CrI: 0.31–3.15) All combination therapies increased the risk of grade ≥3 adverse events.		
[456]	Systematic review and network meta-analysis 1++	We aimed to determine which oral chemotherapeutic agents with ADT combination therapy could most	n= 18 RCTs (ARASENS, ARCHES, ENZAMET, LATITUDE, PEACE-1, CHART, TITAN, MANSMED, STAMPEDE)	treatment group n=6753	control group n=6756	total mHPSC OS comparison more effective than SOC: ADT+abiraterone ADT+abiraterone +docetaxel	Novel oral chemotherapeutic agent combination therapies must replace current ADT monotherapy and	additional hand search, PROSPERO number and sources of funding of the included studies were not reported The funnel plot does not suggest a publication bias in eligible

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
		benefit mHSPC patients.	n=13509 patients search date: November 12, 2022			ADT+apalutamide ADT+bicalutamide ADT+darolutamide+docetaxel ADT+enzalutamide ADT+orteronel ADT+rezvilutamide ADT+abiraterone was more effective than ADT+abiraterone +docetaxel ADT+bicalutamide ADT+bicalutamide nilutamide	ADT+docetaxel SOC. ADT+docetaxel with ARTA triplet therapy still is not the best mHSPC treatment and requires further study.	studies. The authors declare no conflicts of interest. supported by the Korean Urological Association in 2022 and the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning.

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						flutamide ADT+flutamide SOC high-volume mHSPC OS comparison more effective than SOC: ADT+abiraterone ADT+abiraterone +docetaxel ADT+apalutamide ADT+enzalutamide low-volume mHSPC OS comparison ADT+apalutamide was more		

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						effective than SOC Total mHSPC OS SUCRA value ranking ADT+rezvilutamide (98%) ADT+enzalutamide (77%) ADT+abiraterone (76%) High-volume mHSPC OS SUCRA value ranking ADT+abiraterone (84%) ADT+enzalutamide (70%) ADT+apalutamide (58%)		

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						Low-volume mHSPC OS SUCRA value ranking ADT+apalutamide (91%) ADT+enzalutamide (70%) ADT+abiraterone (62%) total mHPSC PFS comparison most treatments were more effective than SOC, except: ADT+bicalutamide nilutamide flutamide, ADT+bicalutamide+palbociclib		

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						ADT+nilutamide more effective than ADT+abiraterone: ADT+apalutamide ADT+darolutamide+docetaxel ADT+orteronel ADT+rezvilutamide Total mHSPC PFS SUCRA value ranking ADT+rezvilutamide (95%) ADT+metformin+bicalutamide (88%) ADT+orteronel (81%)		

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
[457]	Systematic review with network meta-analysis PROSPERO: CRD42022332079 1++	To compare directly and indirectly combination therapies among older and younger patients for mHSPC.	n= 9 RCTs (ARASENS, ARCHES, ENZAMET, TITAN, LATITUDE, STAMPEDE (arms: B, C, E, G) CHAARTED, GETUG-AFU15) n= 9183 patients with mHSPC The cut-off for age stratification was 70 years (±5 years, depending on the threshold	doublet combination therapies (docetaxel plus ADT) (n=3 RCTs) ARSI plus ADT (n=3 RCTs) Triplet combination therapy with ARSI plus docetaxel plus ADT (n=1 RCT)		OS Docetaxel plus ADT significantly improved OS with no differences according to age. <u>Younger patients</u> (n=3 RCTs) HR 0.79, 95% CI 0.69–0.90, p < 0.001 <u>Older patients</u> (n=3 RCTs) HR 0.79, 95% CI 0.63–0.99, p = 0.04 ARSI-based combination systemic therapies	Patients with mHSPC benefit from combination systemic therapies irrespective of age; the effect is, however, more evident in younger patients. Chronological age alone seems not to be a selection criteria for the administration of combination systemic therapies.	sources of funding of the included studies were not reported, no information to publication bias Authors have (strong) relation to pharmaceutical industries. Funding: EUSP Scholarship of the European Association of Urology

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
			provided in the RCTs) Date literature search: May 2022 Median follow-up: 22.9 to 83.9 mo			significantly improved OS, younger patients did benefit more (p = 0.02) <u>Younger patients</u> (n=5 RCTs) HR 0.58, 95% CI 0.51–0.66, p < 0.001 <u>Older patients</u> (n=5 RCTs) HR 0.72, 95% CI 0.64–0.80, p < 0.001 Network treatment ranking showed that triplet therapy had the highest probability of OS benefit irrespective of		

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						age group; in older patients, the benefit of triplet therapy compared to doublet was less expressed (Fig 4).		
[458]	Living Systematic Review and Network Meta-analysis registered at OSF (https://osf.io/e2q3w) 1+	To assess the comparative effectiveness of contemporary systemic treatment options for patients with mCSPC across clinically relevant subgroups.	n=10 RCTs (GETUG-AFU1, CHAARTED, STAMPEDE, LATITUDE, ENZAMET, ARCHES, TITAN, SWOG, PEACE-1, ARASENS) n=11043 patients with mCSPC (except STAMPEDE,	contemporary treatment options (taxane-based chemotherapy, androgen pathway inhibitors)		Direct Comparisons Doublet therapy (either API or DOC as add-on treatments to ADT) vs. ADT alone (It was assumed that the relative efficacy of ADT to be similar to ADT+nonsteroidal antiandrogen which was the comparator in ENZAMET trial for	The findings of this systematic review and meta-analysis indicate that the decision of treatment intensification with triplet therapy for patients with mCSPC must be considered carefully by accounting for the volume of	The relative efficacy of the control group—nonsteroidal antiandrogen (including bicalutamide, flutamide, or nilutamide) and ADT—in 2 trials was considered equivalent to ADT for the purpose of pooling studies. Registered protocol did not report the

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
			which included a small subset of patients with high-risk localized prostate cancer) Median age Range: 63-70 y Search date: July 10, 2022			the purpose of pooling studies together for direct comparisons.) OS overall population (n=8 RCTs; n=9069) HR=0.72 (95 % CI: 0.66-0.78) *Subanalysis* API doublet vs. ADT (n= 6808): HR=0.69 (95 % CI: 0.62-0.76) DOC doublet vs. ADT: HR=0.79 (95 % CI: 0.71-0.89)	disease, the timing of metastatic presentation, and API doublet options with significant survival benefit and fitness for chemotherapy. In summary, triplet therapy may be preferred for fit patients with synchronous (de novo) high-volume disease. The API doublet combinations may be preferred for patients with metachronous (recurrent) low-volume disease.	search strategy. It was however reported in the published article. No justification on the restriction on English papers and study designs. No information on the source of funding of the included studies. According to the authors the study is limited by an open network that did not allow to assess incoherence for most comparisons and precluded formal assessment of publication bias. Conflict of interest

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						<u>High volume</u> (n=7 RCTs; n=3793) HR=0.68 (95 % CI: 0.63-0.74) <u>Low volume</u> (n=7 RCTs; n=2280) HR=0.69 (95 % CI: 0.57-0.84) <u>Synchronous</u> (n=7 RCTs; n=4579) HR=0.68 (95 % CI: 0.62-0.74) <u>*Subanalysis*</u> API doublet vs. ADT: HR=0.65 (95 % CI: 0.60-0.72)	The choice of treatment with metachronous (recurrent) high-volume disease and synchronous (de novo) low-volume disease requires an individualized risk-based approach, including consideration of patient comorbidities. Evidence in this regard is rapidly increasing, and the results of this living meta-analysis will be updated as new	A comprehensive list is stated in the publication. <u>Funding</u> No detailed information stated.

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						DOC doublet vs. ADT: HR=0.78 (95 % CI: 0.58-1.06) <u>Metachronous</u> (n=5 RCTs, n=1077) HR=0.70 (95 % CI: 0.54-0.91) <u>*Subanalysis*</u> API doublet vs. ADT: HR=0.61 (95 % CI: 0.43-0.87) DOC doublet vs. ADT: HR=0.90 (95 % CI: 0.62-1.32) PFS	data are published.	

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						<u>overall population</u> (n=8 RCTs; n=9069) HR=0.55 (95 % CI: 0.49-0.62) <u>High volume</u> (n=7 RCTs; n=4772) HR=0.51 (95 % CI:0.46-0.57) <u>Low volume</u> (n=7 RCTs; n=3103) HR=0.49 (95 % CI: 0.36-0.67) <u>Synchronous</u> (n=5 RCTs; n=4422)		

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						HR: 0.48 (95 % CI: 0.40-0.58) <u>Metachronous</u> (n=3 RCTs, n=863) HR=0.42 (95 % CI: 0.33-0.54) Grade ≥3 adverse events <u>overall population</u> (n=6 RCTs; n=9480) RR=1.42 (95 % CI: 1.19-1.69) Mixed treatment comparisons OS <u>overall population</u> rank 1: DARO + DOC + ADT		

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						[DARO + DOC + ADT vs. DOC + ADT: HR=0.68 (95 % CI: 0.57-0.81] rank 2: abiraterone + DOC + ADT [abiraterone + DOC + ADT vs. DOC + ADT: HR=0.75 (95 % CI: 0.59-0.95) No statistically significant improvement in OS was observed with triplet regimes vs.: rank 3: APA + ADT rank 4: ENZ + ADT		

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						rank 5: abiraterone + ADT rank 6: DOC + ADT rank 7:orteronel + ADT rank 8: non-steroidal antiandrogen + ADT rank 9: ADT PFS <u>overall population</u> rank 1: abiraterone + DOC + ADT [abiraterone + DOC + ADT vs. abiraterone + ADT: HR=0.61		

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						(95 % CI:0.41-0.91)]; rank 2: ENZ +ADT; rank 3: APA +ADT; rank 4: abiraterone + ADT rank 5: orteronel + ADT rank 6: DOC + ADT rank 7: non-steroidal antiandrogen + ADT rank 8: ADT Adverse Events (Grade 3 or higher)		

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						rank 1: non-steroidal antiandrogen + ADT rank 2: ENZ +ADT rank 3: ADT rank 4: APA + ADT rank 5: abiraterone + ADT rank 6: DOC + ADT rank 7: DARO + DOC + ADT rank 8: abiraterone + DOC + ADT rank 9: orteronel + ADT		

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
[459]	Systematic review with network meta-analysis PROSPERO: CRD420223 39754 1++	We conducted this systematic review, meta-analysis, and network meta-analysis to assess the impact of performenc e status on the efficacy of combinatio n systemic therapies in patients with prostate cancer.	n=18 RCTs mHSPC: PEACE1, ARASENS, ARCHES, ENZAMET, LATITUDE, ENZAMET, CHAARTED, STAMPEDE (arm: G, B, C) Search date: June 2022	Triplet therapy Doublet therapy with ARSI + ADT Doublet therapy with DOC + ADT		mHSPC OS <u>DOC + ADT vs ADT alone</u> (n=3 studies, 2261 patients) Reduce the risk of patients with ECOG PS ≥ 1 (HR 0.70, 95% CI 0.56–0.87) vs. ECOG PS 0 (HR 0.81, 95% CI 0.71–0.93) p=0.3 <u>ARSI + SOC vs SOC</u> (n=5 studies, 6443 patients) Reduce the risk of patients with ECOG PS ≥ 1 (HR 0.61, 95% CI	Among RCTs, novel systemic therapies seem to benefit the OS of patients with prostate cancer irrespective of performance status. Our findings suggest that worse performance status should not discourage treatment intensification across all disease stages.	sources of funding of the included studies were not reported, no information to publication bias no significant heterogeneity among all analyses Conflict of interest: Takahiro Kimura is a paid consultant/advisor of Astellas, Bayer, Janssen and Sanofi. Shahrokh F. Shariat received follows: Honoraria: Astellas, AstraZeneca, BMS, Ferring,

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						0.53–0.70) vs. ECOG PS 0 (HR HR 0.68, 95% CI 0.60–0.76) p=0.24 ARSI + DOC + ADT vs DOC + ADT (n=2 studies, 2015 patients) Reduce the risk of patients with ECOG PS ≥ 1 (HR 0.63, 95% CI 0.50–0.79) vs. ECOG PS 0 (HR HR 0.75, 95% CI 0.63–0.90) p=0.2 Network meta-analyses of the effect of combination therapies		Ipsen, Janssen, MSD, Olympus, Pfizer, Roche, Takeda. Consulting or Advisory Role: Astellas, AstraZeneca, BMS, Ferring, Ipsen, Janssen, MSD, Olympus, Pfizer, Pierre Fabre, Roche, Takeda. Speakers Bureau: Astellas, Astra Zeneca, Bayer, BMS, Ferring, Ipsen, Janssen, MSD, Olympus, Pfizer, Richard Wolf, Roche, Takeda. No external funding provided. EUSP Scholarship of the

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						<u>stratified by performance status</u> Compared to DOC + ADT, only the DAR + DOC +ADT combination resulted in significantly improved OS regardless of ECOG PS ECOG PS ≥ 1: DAR + DOC + ADT had the highest likelihood of providing the maximal OS benefit (94%) ECOG PS 0, ABI + DOC + ADT had the highest likelihood of		European Association of Urology (PR).

Referenz	Studien-charakteristika LoE	Studienziel	Studien- und Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						providing the maximal OS benefit (79%), followed by DAR + DOC + ADT (73%)		
[460]	Systematic review with network meta-analysis PROSPERO: CRD42022352440 1++	We aimed to analyze and compare the efficacy of combination systemic therapies in metastatic hormone-sensitive prostate cancer and metastatic castration-resistant	n=12 RCTs mHSPC: ARASENS, ARCHES, ENZAMET, TITAN, LATITUDE, CHAARTED Search date: July 2022	combination systemic therapy (androgen receptor signaling inhibitor and/or docetaxel	standard of care	mHSPC Metaanalysis results for fixed effect model are reported OS for ARSI-based systemic combination therapy incl. triplet therapy (n=5) <u>Overall</u> HR 0.68 (CI 95% 0.63-0.74) <u>Visceral metastasis</u>	The effectiveness of novel systemic therapies is similar in both mHSPC and mCRPC patients with and without visceral metastasis.	sources of funding of the included studies were not reported No external funding was provided. Detailed list of conflict of interest reported in the paper. We did not find any heterogeneity in all analyses.

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
		prostate cancer with or without visceral metastasis.		plus androgen deprivation therapy)		HR 0.77 (95% CI 0.64-0.94) <u>without visceral metastasis</u> HR 0.66 (95% CI 0.60-0.72) OS for ARSI-based doublet therapy (n=4) <u>Overall</u> HR 0.67 (95% CI 0.62-0.74) <u>Visceral metastasis</u> HR 0.77 (95% CI 0.61-0.96) <u>without visceral metastasis</u> HR 0.66 (95% CI 0.59-0.73)		

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						PFSfor ARSI-based doublet therapy (n=3) Overall HR 0.45 (95% CI 0.41-0.51) Visceral metastasis HR 0.58 (95% CI 0.45-0.75) without visceral metastasis HR 0.43 (95% CI 0.38-0.48) SUCRA analysis OS Visceral metastasis DAR+DOC+ADT (90%)		

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						DOC+ADT (76%) ABI+ADT (63%) without visceral metastasis DAR+DOC+ADT (98%) all combination regimens significantly reduced the risk of death inwhen compared to ADT alone PFS for mHSPC SUCRA analysis: Visceral metastasis ABI+ADT (82%) without visceral metastasis		

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						ENZ+ADT (91%) all combination regimens significantly reduced the risk of disease progression in patients without visceral metastasis compared to ADT alone		
[461]	Systematic review with network meta-analysis PROSPERO: CRD42022359472 1++	To analyze current data from RCTs that investigated first-line treatment of high-volume mHSPC to compare the	n = 11 RCTs (ENZAMET, ARCHES, TITAN, CHART, LATITUDE, STAMPEDE (arms: C, G), CHAARTED, GETUF AFU	ADT (±SOC: bicalutamide, nilutamide, or flutamide) alone doublet therapies (including DOC, ABI, APA, REZ, and ENZ on the basis of ADT) triplet therapies (including DAR+DOC, ENZ+DOC and		OS ADT compared with: ABI: HR 0.61 (95% CI 0.53, 0.71) DOC+ABI: HR 0.52 (95% CI 0.38, 0.71)	We did not find significant differences in OS and PFS between REZ+ADT and available doublet or triplet therapies in patients with high-volume	sources of funding and potential heterogeneity of the included studies were not reported, no information to publication bias No potential conflict of interest was reported by the author(s).

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
		therapeutic effects of these drugs indirectly, to help clinicians and patients select the optimal individualized treatment.	15, PEACE1, ARASENS) n = 6708 high-volume mHSPC patients Search date: May 2023	ABI+DOC on the basis of ADT)		APA: HR 0.70 (95% CI 0.56, 0.88) DOC: HR 0.72 (95% CI 0.63, 0.84) ENZ: HR 0.65 (95% CI 0.53, 0.80) DOC+ENZ: HR 0.70 (95% CI 0.45, 1.10) REZ: HR 0.58 (95% CI 0.44, 0.77) DOC+DAR: HR 0.49 (95% CI 0.39, 0.62) <u>DOC compared with:</u> ABI: HR 0.85 (95% CI 0.69, 1.00)	mHSPC, except for superiority to DOC+ADT and inferiority to DAR+DOC+ADT in terms of PFS benefit. REZ+ADT were the highest ranked doublet therapy for improvement in OS of patients with high-volume mHSPC, second only to triplet therapy (DAR+DOC+ADT and ABI+DOC+ADT).	This study was partly funded by the Natural Science Foundation of Shandong Province Medical and health research program of Qingdao. The funders had no roles in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						DOC+ABI: HR 0.72 (95% CI 0.55, 0.95) ADT: HR 1.4 (95% CI 1.2, 1.6) APA: HR 0.97 (95% CI 0.74, 1.3) ENZ: HR 0.9 (95% CI 0.7, 1.2) DOC+ENZ: HR 0.97 (95% CI 0.64, 1.5) REZ: HR 0.81 (95% CI 0.58, 1.1) DOC+DAR: HR 0.68 (95% CI 0.57, 0.82) PFS ABI: HR 0.46 (95% CI 0.36, 0.58)		

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						DOC+ABI: HR 0.28 (95% CI 0.18, 0.44) APA: HR 0.53 (95% CI 0.41, 0.67) DOC: HR 0.60 (95% CI 0.52, 0.70) ENZ: HR 0.42 (95% CI 0.33, 0.52) DOC+ENZ: HR 0.31 (95% CI 0.22, 0.43) REZ: HR 0.44 (95% CI 0.33, 0.58) DOC+DAR: HR 0.25 (95% CI 0.19, 0.31)		

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						<u>DOC compared with:</u> ABI: HR 0.76 (95% CI 0.57, 1.00) DOC+ABI: HR 0.46 (95% CI 0.30, 0.72) ADT: HR 1.70 (95% CI 1.40, 1.9) APA: HR 0.87 (95% CI 0.66, 1.2) ENZ: HR 0.69 (95% CI 0.53, 0.89) DOC+ENZ: HR 0.51 (95% CI 0.38, 0.69) REZ: HR 0.73 (95% CI 0.53, 0.99)		

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						DOC+DAR: HR 0.41 (95% CI 0.34, 0.49)		
[462]	**Meta-analysis** **1+**	To evaluate whether the addition of an ARSi to ADT improves outcomes of mCSPC patients treated with docetaxel.	n=5 RCTs (ARCHES; ENZAMET; TITAN; PEACE-1; ARASENS) n=2837 mCSPC patients Search: up until February 21, 2022	ARSI + ADT + DOC (n=1421 patients)	ADT + DOC (n=1416 patients)	OS (n=5 RCTs, n=2837 patients) Triplet vs. ADT + DOC *Fixed effect model* HR=0.73 (95% CI: 0.65-0.83; p < 0.00001) Stratified by schedule of ARSi administration with respect to chemotherapy (concomitant to DOC vs. sequential DOC)	In conclusion, our results support the survival advantage of adding an ARSi to ADT in patients with mCSPC treated with docetaxel; the OS benefit of this intensified strategy is particularly evident when the ARSi was administered concomitantly to chemotherapy, especially in the	No study protocol. No information on additional search methods and the study selection process. No justification on the restriction on English papers and study designs. No information on the source of funding of the included studies. No investigation concerning a potential publication bias. Conflict of interest CC: occasional consultant of IPSEN,

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						Triplet (sequential) vs. ADT + DOC (n=2 RCT, ARCHES and TITAN, n=318 patients) *Fixed effect model* HR=0.86 (95% CI: 0.59-1.26; p=0.44) Triplet (concomitant) vs. ADT + DOC (n=3 RCTs) *Fixed effect model* HR=0.72 (95% CI: 0.63-0.82; p < 0.00001)	subgroup of metastatic de novo mCSPC patients.	Jannssen, MSD, Merck, Pfizer, Astellas. RI: advisory board member for Astellas, BMS, EISAI, IPSEN, Janssen, MSD, Novartis, Pfizer, Sanofi. Consultant for Astellas, EISAI, MSD, Pfizer. CS: Served as a consultant for Astellas, Pharma, Sanofi Genzyme, Roche-Genentech, Novartis, Bayer, Pfizer, Merck, MSD, AstraZeneca, Immunomedics (now Gilead), Janssen, Foundation Medicine, Impact

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						Subgroup of men with de novo mCSPC (Triplet vs. ADT + DOC) n=2 RCTs *Fixed effect model* HR=0.72 (95% CI: 0.63-0.84; p < 0.0001)		Pharma, UroToday and Medscape. SG: received (last 3 y) personal honoraria for participation in advisory boards from Amgen, MSD, Orion; other honoraria from Radio-televisione Svizzera Italiana (RSI), German-speaking European School of Oncology (DESO), Patent royalties and other intellectual property for a research method for biomarker WO2009138392. [further declarations in the

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
								corresponding paper]. GT: advisory board member for BMS and Novartis. KF: Participation to advisory boards and talks for: Amgen, Astellas, Astrazeneca, Bayer, Clovis, Janssen, MSD, Novartis/AAA, Pfizer, Sanofi Honoraria go to Gustave Roussy, my institution. Participation to advisory boards with personal honorarium for CureVac and Orion. Funding

Referenz	Studien-charakteristika LoE	Studienziel	Studien- und Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
								None declared. .
[463]	Systematic review with network meta-analysis PROSPERO: CRD42022324980 1+	Performed a systematic review of all docetaxel-based triplet therapies and indirectly compared the efficacy and safety of these therapies through network meta-analysis.	n=5 RCTs (TITAN, ENZAMET, ARCHES, PEACE1, ARASENS) n=2836 patients with mHSPC Search date: April 2022	systemic therapy containing ADT plus docetaxel with or without another agent		OS Compared with ADT+Docetaxel ADT+Docetaxel+ DarolutamideHR 0.68 (95% CrI 0.57, 0.8) ADT+Docetaxel+ EnzalutamideHR 0.74 (95% CrI 0.46, 1.2) ADT+Docetaxel+ Abiraterone HR 0.75 (95% CrI 0.59, 0.95) ADT+Docetaxel+ SNA HR 0.83 (95% CrI 0.45, 1.51)	Systemic triplet therapy was more effective than ADT plus docetaxel for mHSPC. Of the triplet therapy regimens, darolutamide ranked first in terms of improved OS. Abiraterone and enzalutamide triplet ranked first in terms of radiographic FPS, however, it did not confer a statistically difference among all	sources of funding of the included studies were not reported, high risk of bias studies (ENZAMET, PEACE1) were not excluded from the analysis supported by Jilin Scientific and Technological Development Program, Natural Science Foundation of Jilin Province and Bethune Urological Oncology Special Grant, Beijing Bethune Charity Foundation.

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						ADT+Docetaxel+ Apalutamide HR 1.12 (95% Crl 0.59, 2.12) radiographic PFS <u>Compared with ADT+Docetaxel</u> ADT+Docetaxel+ Apalutamide HR 0.47 (95% Crl 0.22, 1) ADT+Docetaxel+ Abiraterone HR 0.49 (95% Crl 0.39, 0.61) ADT+Docetaxel+ Enzalutamide HR 0.52 (95% Crl 0.3, 0.89) ADT+Docetaxel+ SNA HR 1.08	triplet regimens. The overall risk of adverse effects was comparable. More studies are required for current and potential combinations of systemic triplet therapy.	The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. *same studies included in the Maiorano, 2022 paper*

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						(95% CrI 0.59, 1.98) Time to PSA Progression Compared with ADT+Docetaxel ADT+Docetaxel+ EnzalutamideHR 0.22 (95% CrI 0.11, 0.45) ADT+Docetaxel+ SNA HR 0.48 (95% CrI 0.23, 1.01) Time to first skeletal event Compared with ADT+Docetaxel ADT+Docetaxel+ DarolutamideHR 0.71 (95% CrI 0.54, 0.94)		

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						ADT+Docetaxel+ EnzalutamideHR 0.85 (95% CrI 0.39, 1.86) Any adverse events <u>Compared with ADT+Docetaxel</u> ADT+Docetaxel+ DarolutamideOR 2.53 (95% CrI 0.68, 12.63) ADT+Docetaxel+ Abiraterone OR 1.07 (95% CrI 0.03, 36.25) Grade ≥3 adverse events <u>Compared with ADT+Docetaxel</u> ADT+Docetaxel+ DarolutamideOR		

Referenz	Studien-charakteristika LoE	Studienziel	Studien- und Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						1.13 (95% CrI 0.89, 1.43) ADT+Docetaxel+ Abiraterone OR 1.56 (95% CrI 1.15, 2.11)		
[464]	Systematic review with meta-analysis 1+	We carried out a meta-analysis of RCTs to better define the benefit achieved with the use of the triplet in mHSPC.	n=5 RCTs (TITAN, ENZAMET, ARCHES, PEACE1, ARASENS) n=2836 patients with mHSPC search date: 10 April 2022	enzalutamide (n=2 studies) abiraterone (n=1 study) darolutamide (n=1 study) apalutamide+ docetaxel+ ADT (n=1 study) n=1415	placebo+ docetaxel+ ADT n=1421	ARTA + docetaxel + ADT vs. docetaxel + ADT OS (n=5) HR 0.74 (95% CI 0.66-0.84) p<0.00001 OS: high volume (n=2) HR 0.79 (95% CI 0.63-0.99) p=0.04 OS: low volume (n=2)	The addition of an ARTA to docetaxel and ADT significantly prolongs survival compared with docetaxel and ADT in patients with mHSPC and should be adopted in daily clinical practice.	PEACE1 was rated with Jadad Score 1, bias was not discussed and the study not excluded from the analysis, sources of funding of the included studies were not reported, no study protocol no significant heterogeneity among all analyses The review was not registered.

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						HR 0.79 (95% CI 0.50-1.23) p=0.29 OS: *de novo*(n=2) HR 0.77 (95% CI 0.67-0.88) p=0.0002 OS: metachronous (n=1) HR 0.61 (95% CI 0.35-1.06) p=0.08 OS: concomitant ARTA+ docetaxel+ADT (n=3) HR 0.73 (95% CI 0.64-0.83) p<0.00001		The publication bias or sensitivity analysis has not been carried out because of the low number of included trials. No conflict of interest. No funding received. *same studies included in the Jian, 2022 paper*

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						OS: ARTA after docetaxel+ADT (n=2) HR 0.86 (95% CI 0.59-1.26) p=0.43 radiographic PFS (n=3) HR 0.50 (95% CI 0.42-0.60) p<0.00001 clinical PFS (n=3) HR 0.49 (95% CI 0.41- 0.58) p<0.00001 All-grade adverseevents (n=2) RR 1 (95% CI 1-		

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						1.01) p=0.45 All-grade adverseevents (n=2) RR 1.13 (95% CI 0.99- 1.29) p=0.07		
Randomisierte kontrollierte Studien								
[349]	RCT NCT019574 36 (PEACE-1) Overall population: 1- Docetaxel population: 2+	We aimed to evaluate the efficacy and safety of abiraterone plus prednisone, with or without radiotherap	n=1173 patients with mHSPC Belgium, France, Ireland, Italy, Romania, Spain, and Switzerland	SOC (androgen deprivation therapy alone or with intravenou s docetaxel 75 mg/m²	SOC+ radiotherapy n=293 SOC+ abiraterone (oral 1000 mg abiraterone once daily plus oral 5	SOC+abiraterone with/without radiotherapy (n=583) vs. SOC with/without radiotherapy (n=589) radiographic PFS	Combining androgen deprivation therapy, docetaxel, and abiraterone in de novo metastatic castration-sensitive prostate cancer	Neither the investigators nor the patients were masked to treatment allocation, no randomization process for docetaxel, no separate results for all randomized

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
		y, in addition to standard of care.	(n=77 hospitals) 2013-2018 Median follow-up radiographic PFS: 3.5 y (IQR 2.8–4.6 y) OS: 4.4 y (IQR 3.5–5.4 y)	once every 3 weeks) n=296	mg prednisone twice daily) n=292 SOC+ radiotherapy + abiraterone n=291	HR: 0.54 (99.9% CI 0.41-0.71) p<0.001 OS HR: 0.82 (95.1% CI 0.69-0.98) p=0.03 ADT with docetaxel population SOC+abiraterone with/without radiotherapy (n=355) vs. SOC with/without radiotherapy (n=355) radiographic PFS HR: 0.5 (99.9% CI 0.34-0.71) p<0.001 OS	improved overall survival and radiographic progression-free survival with a modest increase in toxicity, mostly hypertension. This triplet therapy could become a standard of care for these patients.	groups, no results of adverse events for the overall population, the influence of radiotherapy remains unclear Funding Janssen-Cilag, Ipsen, Sanofi, and the French Government. Detailed list of conflict of interest reported in the paper.

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						HR: 0.75 (95.1% CI 0.59-0.95) p=0.017 Grade 3 or worse adverse events abiraterone: 217/347 (63%) no abiraterone: 181/350 (52%)		
[348]	post hoc analysis Smith 2022 NCT02799602 (ARASENS)	We present efficacy and safety outcomes from ARASENS in patients with mHSPC by disease volume and disease risk.	Patient subgroups on the basis of disease volume and disease risk were assessed: **high-volume** *(= visceral metastases and/or ≥ 4*	darolutamide (dose of 600 mg [two 300-mg tablets] twice daily) with ADT (Investigator's choice) and docetaxel (75 mg/m2	placebo with ADT (Investigator's choice) and docetaxel (75 mg/m2 Day 1 as 1 hour IV infusion every 21 days)	**Darolutamide vs. placebo** **OS** high-volume HR: 0.69; 95% CI, 0.57 to 0.82 low-volume HR, 0.68; 95% CI, 0.41 to 1.13 high-risk	Patients with high-volume and high-risk/low-risk mHSPC, treatment intensification with darolutamide, androgen-deprivation therapy, and docetaxel increased OS	**Support** Supported by Bayer AG and Orion Pharma **Conflict of interests:** The following represents disclosure information provided by authors of this manuscript. All relationships are

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
			bone metastases with ≥ 1 beyond the vertebral column/pelvis): N=1005 patients (77%) **low-volume** N=300 patients (23%) **high-risk***(=≥ 2 risk factors: Gleason score ≥ 8, ≥ 3 bone lesions, and* *presence of measurable visceral metastases)*:	Day 1 as 1 hour IV infusion every 21 days) **high-volume** (n=497) Median: 67 y (41-89 y) **low-volume** (n=154) Median: 67 y (41-89 y) **high-risk** (n=452) Median: 67 y (41-86 y) **low-risk**	**high-volume** (n=508) Median: 67 y (44-86 y) **low-volume** (n=146) Median: 67.5 y (42-81 y) **high-risk** (n=460) Median: 67 y (44-86 y) **low-risk** (n=194) Median: 67 y (42-85 y)	HR, 0.71; 95% CI, 0.58 to 0.86 low-risk HR, 0.62; 95% CI, 0.42 to 0.90 **Prolonged time to castration resistance** high-volume HR: 0.41; 95% CI, 0.34 to 0.49 low-volume 0.21; 95% CI, 0.14 to 0.33 high-risk HR: 0.38; 95% CI, 0.32 to 0.46 low-risk HR: 0.32; 95% CI, 0.23 to 0.45	with a similar adverse event profile in the subgroups, consistent with the overall population.	considered compensated unless otherwise noted. Relationships are self-held unless noted. I5Immediate Family Member, Inst5My Institution. Relationships may not relate to the subject matter of this manuscript. More information about ASCO's conflict of interest policy: www.asco.org/rwcor ascopubs.org/jco/authors/author-center.

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
			N= 912 patients (70%) **low-risk** N= 393 patients (30%)	(n=199) Median: 67 y (41-89 y)		**Incidences of serious adverse events** high-volume 45.4% vs 43.5% low-volume 42.9% vs. 38.2% high-risk 45.3% vs 42.9% low-risk 43.7% versus 40.9% **Adverse events**: Similar between treatment groups across subgroups by disease volume and risk. **Grade 3 or 4 Adverse events**		

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						high-volume 64.9% vs. 64.2% low-volume 70.1% versus 61.1% high-risk 67.5 % vs 64.3 % low-risk 62.8% versus 61.7%		
[347]	RCT NCT02799602 (ARASENS) 1++	**Primary end point**: OS **Secondary end points:** time to castration-resistant prostate cancer, time to	n= 1306 patients <65 y with mHSPC 286 centers in 23 countries 2016-2018 Median follow-up:	darolutamide (dose of 600 mg [two 300-mg tablets] twice daily) with ADT (Investigator's choice) and	placebo with ADT (Investigator's choice) and docetaxel (75 mg/m2 Day 1 as 1 hour IV infusion	**OS at 4 y** darolutamide: 62.7% (95% CI, 58.7 to 66.7) placebo: 50.4% (95% CI, 46.3 to 54.6) **Darolutamide vs. Placebo**	OS was significantly longer with the combination of darolutamide, androgen-deprivation therapy, and docetaxel than with placebo plus	international, phase 3 trial Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) 1 patient was randomly assigned to the placebo group but received

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
		pain progression, symptomatic skeletal event-free survival, time to a first symptomatic skeletal event, time to initiation of subsequent systemic antineoplastic therapy, time to worsening of disease-related physical symptoms, time to	Darolutamide: 43.7 mo placebo group: 42.4 mo	docetaxel (75 mg/m2 Day 1 as 1 hour IV infusion every 21 days) n=651 Median: 67 y (41-89 y)	every 21 days) n=655 Median: 67 y (42-86 y)	Time to castration-resistant prostate cancer HR: 0.36 (0.30–0.42) p<0.001 Pain progression HR: 0.79 (0.66–0.95) p=0.01 Symptomatic skeletal event HR: 0.71 (0.54–0.94) p=0.02 Worsening of disease-related physical symptoms HR: 1.04 (0.89–1.22) p=0.59 Symptomatic skeletal event-free survival	androgendeprivation therapy and docetaxel, and the addition of darolutamide led to improvement in key secondary end points. The frequency of adverse events was similar in the two groups.	darolutamide was included in the placebo group in the full analysis set. The trial was designed by Bayer and the first and last authors, with support from the protocol steering committee. Funding: Bayer and Orion Pharma. Conflict of interests: unknown

Refe-renz	Studien-charakteris-tika LoE	Studienziel	Studien- und Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
		initiation of opioid treatment for 7 or more consecutive days, and safety.				HR: 0.61 (0.52–0.72) p<0.001 **Adverse events**: Similar in the two groups <u>Grade 3 or 4 adverse events</u>: darolutamide: 66.1% placebo: 63.5%		

3.4 Schlüsselfrage: Welchen Stellenwert hat Relugolix im Vergleich zu anderen Androgendeprivationstherapien?

Referenz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
[465]	RCT (phase III) NCT03085095 (HERO) 155 centers (worldwide) 2017-2018 1-	The goals of the phase 3 HERO trial were to evaluate the efficacy and safety of oral relugolix as compared with leuprolide in men with advanced prostate cancer.	n=930 men with advanced prostate cancer presence of metastatic disease: 295/930 (31.7%) Median age: 71 y (47-97 y)	relugolix (120 mg once daily after a single oral loading dose of 360 mg) for 48 weeks n=622	leuprolide 22.5 mg* (injections every 3 months) for 48 weeks n=308 *11.25 mg in Japan/Taiwan	**Testosterone suppression to castrate levels** *(<50 ng/dl) through 48 wk* Relugolix: 96.7% (95% CI 94.9-97.9%) Leuprolide: 88.8% (95% CI 84.6-91.8%) relugolix was determined to be noninferior to leuprolide (between group difference, 7.9 percentage	In this trial involving men with advanced prostate cancer, relugolix achieved rapid, sustained suppression of testosterone levels that was superior to that with leuprolide, with a 54% lower risk of major adverse cardiovascular events.	open label, randomisation process and allocation concealment not clearly described testosterone values for the primary end-point analysis were measured at a blinded central laboratory Supported by Myovant Sciences. Disclosure forms provided by

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						points; 95% CI, 4.1 to 11.8) **Cumulative probability of testosterone suppression to (<50 ng/dl)** on day 4 Relugolix: 56% Leuprolide: 0 p<0.001 on day 15 Relugolix: 98.7% Leuprolide: 12% p<0.001		the authors are available.

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						PSA response at day 15 followed by confirmation at day 29 Relugolix: 79.4% Leuprolide: 19.8% p<0.001 **Cumulative probability of profound testosterone suppression to 50 ng/dl) on day 15** Relugolix: 78.4% Leuprolide: 1% p<0.001		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						Mean FSH level at end of wk 24 Relugolix: 1.72 IU/liter Leuprolide: 5.95 IU/liter p<0.001 **Adverse events** <u>Grade 3 or 4</u> any adverse event: Relugolix: 112/622 (18%) Leuprolide: 63/308 (20.5%) serious adverse event:		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen
						Relugolix: 61/622 (9.8%) Leuprolide: 35/308 (11.4%) <u>Incidence of major adverse cardiovascular events</u> Relugolix: 2.9% Leuprolide: 6.2% HR: 0.46 (95% CI 0.24-0.88)		

3.5 Welchen Stellenwert hat die molekulare Diagnostik auf HRR- Mutationen auf das Ergebnis der Therapie mit diesen neu zugelassenen Medikamenten/Medikamentenkombinationen für Patienten mit mCRPC?

Referenz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
Systematische Reviews								
[466]	Systematic review with meta-analysis 1+	We aim to better characterize the PFS and OS in mCRPC patients treated with PARPis and determine the subgroup of patients with this disease who can benefit from these medications at maximum.	n=7 RCTs patients with mCRPC Seach date: 30 May 2023	PARP with or without ARPI (abiraterone acetate or enzalutamide)	standard care (ARPI or docetaxel)	**PARPi vs. Standard care** **PFS in patients without HRR gene mutation** (n=4) HR: 0.747 (95% CI 0.637-0.877) p=0.00 I^2=0%	Our meta-analysis of clinical trials found that PARPis in combination with novel hormonal agents may improve PFS and OS in patients with mCRPC, regardless of their HRR gene mutation status.	The study protocol was not registered. No reported sources of funding for the studies included in the review. Results are reported from fixed-effect models, although random-effect models were planned. The authors declare no

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
								conflict of interest. This research received no external funding.
Randomisierte kontrollierte Studien								
[467]	RCT NCT03395197 (TALAPRO-2) 1+	We aimed to compare the efficacy and safety of talazoparib plus enzalutamide versus enzalutamide alone in patients with mCRPC.	n= 805 patients with mCRPC HRR-deficient: n= 169 (21%) HRR-non-eficient: n= 636 (79%) BRCA alterations: Talazoparib: n= 27 (7%) Placebo:	n= 402 patients (0.5mg Talazoparib plus 160mg enzalutamide orally once daily) Mean age: 71 y (66–76 y) **Median duration of treatment**: Talazoparib:	n= 403 patients (placebo plus 160mg enzalutamide orally once daily) Mean age: 71 y (65–76 y) **Median duration of treatment**:	**Patients with HRR gene alteration status of deficient - median rPFS:** talazoparib plus enzalutamide (95% CI 27.9 (16.6–not reached)	Talazoparib plus enzalutamide resulted in clinically meaningful and statistically significant improvement in rPFS versus standard of care enzalutamide as first-line treatment for	Sponsor, patients, and investigators were masked to talazoparib or placebo, while enzalutamide was open-label. Conflicts of interest and funding: NA has received an honorarium for consultancy since May, 2020, from diverse

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
			n= 32 (8%) 2019- 2020 223 hospitals, cancer centres, medical centres in 26 countries. Median follow-up: rPFS: Talazoparib:24.9 months (IQR 21.9–30.2) Placebo: 24.6 months (14.4–30.2)	19.8 mo (IQR 8.8–26.9 mo) Enzalutamide in the talazoparib group: 22.2 mo (9.9–28.1 mo)	Placebo: 16.1 mo (6.5–25.0 mo) Enzalutamide in the placebo group: 16.6 mo (6.7–25.1 mo)	placebo plus enzalutamide 16.4 (10.9–24.6) Stratified - HR: 0.46 (95% CI 0.30–0.70); p=0·0003 **Patients with HRR gene alteration status of non-deficient or unknown - median rPFS:** talazoparib plus	patients with mCRPC. Final overall survival data and additional long-term safety follow-up will further clarify the clinical benefit of the treatment combination in patients with and without tumour HRR gene alterations.	pharmaceutical companies (detailed list in the paper). Study was sponsored by Pfizer. Astellas Pharma provided enzalutamide. Editorial and medical writing support was provided by Emily Messina and Annette Smith, on behalf of CMC AFFINITY, a division of IPG Health Medical Communications, and was funded by Pfizer.

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						enzalutamide (95% CI Not reached (27.5–not reached) placebo plus enzalutamide 22.5 (19.1–30.5) Stratified - HR: 0.70 (95% CI 0.54–0.89); p=0.0039 **Patients with HRR gene alteration status of non-deficient by**		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						prospective tumour tissue testing – median rPES: talazoparib plus enzalutamide (95% CI Not reached (25.8–not reached) placebo plus enzalutamide 22.1 (16.6–not reached) Unstratified – HR: 0.66		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						(95% CI 0.49–0.91); p=0.0092 **BRCA gene alterations vs. placebo**: Talazoparib: HR 0.23; 95% CI 0.10–0.53; p=0.0002 **Non-BRCA gene alterations vs. placebo:** HR 0.66; 0.39–1.12; p=0.12 Talazoparib (n= 398):		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						most common treatment-emergent adverse events (grade >3): anaemia [46%], neutropenia [18%], fatigue [4%]. Treatment-related deaths: Talazoparib : n= 0 pat. Placebo: n= 2 pat. (<1%)		
[468]	RCT NCT03748641 (MAGNITUDE)	The phase III MAGNITUDE study	n=423 patients with mCRPC HRR+ (n=423)	Niraparib (200 mg once daily with abiraterone acetate 1,000	Abiraterone acetate 1,000 mg once daily	**Niraparib vs. AAP** **HRR+ cohort**	Combination treatment with niraparib+AAP significantly	Randomisation process not clearly described, double-blind

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
	1+	prospectively enrolled patients into two cohorts on the basis of HRR biomarker status and compared the efficacy and safety of niraparib and abiraterone acetate plus prednisone (niraparib+AAP) versus placebo+AAP as first-line treatment for patients with mCRPC.	HRR- (n=247) Age: HRR+: 69.0 y (43-100 y) 2019-2021 worldwide (26 countries) Median follow-up: HRR+: 18.6 mo (range 0.3-29 mo)	mg once daily plus prednisone 5 mg twice daily) n=212 patients with HRR+ n=123 patients with HRR-	plus prednisone 5 mg twice daily n=211 patients with HRR+ n=124 patients with HRR-	<u>radiographic PFS</u> 16.5 vs. 13.7 mo; HR 0.73 (95% CI, 0.56-0.96) p=0.022 <u>Time to PSA progression</u> 18.5 vs. 9.3 mo; HR 0.57 (95% CI 0.43-0.76) p<0.001 <u>OS</u> not estimable; HR 0.94 (95% CI 0.66-1.36) p=0.73 <u>ORR</u>	lengthened radiographic PFS in patients with HRR+ mCRPC compared with standard-of-care AAP.	study, radiographic progression assessed by blinded independent central review. On the basis of the prespecified criteria, futility was declared for the HRR- cohort in August 2020, which was closed to further enrollment on the basis of Independent Data Monitoring Committee recommendations. supported by Janssen

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						RR: 2.13, p<0.001 FACT-P total score changes over time between treatment arms were similar as determined by FACT-P total score **Any TEAEs** **Grade 3** Niraparib: 119/212 (56.1%) AAP: 90/211 (42.7%) **Grade 4**		Research & Development, LLC. Disclosures provided by the authors are available with this article at DOI

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						Niraparib: 23/212 (10.8%) AAP: 8/211 (3.8%) **HRR-cohort** radiographic PFS 12 vs. not estimable; HR 1.03 (95% CI, 0.63-1.76) Time to PSA progression not estimable; HR 1.03 (95% CI 0.67-1.59)		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
[469]	RCT NCT02975934 (TRITON3) 1-	We report the primary results of the trial.	n=405 patients who had mCRPC with a BRCA1, BRCA2, or ATM alteration and who had disease progression after treatment with a second-generation ARPI 2017-2022 143 sites in 12 countries	Rucaparib (600 mg oral twice daily) n=270 BRCA (n=201) ARM (n=69) Median age: 70 y (45–90 y)	physician's choice of: docetaxel (administered intravenously at a dose of 75 mg/m2 every 3 weeks, up to a maximum of 10 cycles + prednisone or prednisolone 5 mg twice daily abiraterone acetate (administered orally at a starting dose of	**Rucaparid vs. control** **Imaging-based median PFS** Intention-to-treat 10.2 mo vs 6.4 mo; HR 0.61 (95% CI 0.47-0.80), p<0.001 BRCA subgroup 11.2 mo vs 6.4 mo; HR 0.5 (95% CI 0.36-0.36) p<0.001 ATM subgroup	The duration of imaging-based progression-free survival was significantly longer with rucaparib than with a control medication among patients who had metastatic, castration-resistant prostate cancer with a BRCA alteration.	open label, allocation concealment not clearly described conflict of interest and median follow-up not reported Funded by Clovis Oncology. Dr. Abida's work is supported by a grant from the National Cancer Institute.

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
					1000 mg once daily + prednisone 10 mg once daily enzalutamide (administered orally at a starting dose of 160 mg once daily) n=135 BRCA (n=101) ARM (n=34) Median age: 71 y (47–92 y)	8.1 mo vs 6.8 mo; HR 0.95 (95% CI 0.59-1.52) **Time to PSA progression** <u>Intention-to-treat</u> 5.7 mo vs 3.6 mo; HR 0.63 (95% CI 0.49-0.81) <u>BRCA subgroup</u> 6.6 mo vs 3.8 mo; HR 0.52 (95% CI 0.38-0.70)		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						ATM subgroup not reported **Objective response rate** Intention-to-treat 35% vs. 16% BRCA subgroup 45% vs. 17% ATM subgroup 0% vs. 14% **Median duration of response** Intention-to-treat		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						7.4 mo vs 7.4 mo; HR 0.86 (95% CI 0.36-2.04) BRCA subgroup Intention-to-treat 7.5 mo vs 7.4 mo; HR 0.75 (95% CI 0.27-2.1) ATM subgroup 4.8 mo vs 11 mo; HR 5.9 (95% CI 0.07-535.35) **OS (interim analysis at 62 mo)**		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						Intention-to-treat 23.6 mo vs 20.9 mo; HR 0.94 (95% CI 0.72-1.32) BRCA subgroup 24.3 mo vs 20.8 mo; HR 0.81 (95% CI 0.58-1.12) p=0.21 ATM subgroup 21.1 mo vs 21.7 mo; HR 1.2 (95% CI 0.74-1.95)		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						Any adverse event **Grade ≥3** Rucaparid: 161/270 (60%) Docetaxel: 43/71 (61%) Second-Generation ARPI: 26/59 (44%) **Most common adverse events** Rucaparid: fatigue, nausea, anemia, decreased hemoglobin		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						Control group: fatigue, diarrhea, and neuropathy		
[470]	RCT NCT01682772(TOPARP-B) 1-	The TOPARP-B trial aims to prospectively validate the association between DDR gene aberrations and response to olaparib in mCRPC.	n=98 men with mCRPC previously treated with one or two taxane chemotherapy regimens and with an Eastern Cooperative Oncology Group performance status of 2 or less 2015-2018	olaparib (300 mg twice daily) n=49 Age: 67.3 y (61.2-72.1 y)	olaparib (400 mg twice daily) n=49 Age: 67.6 y (63.2-72.7 y)	**Composite overall response** 300 mg: 18/46 (39.1%; 95% CI 25.1–54.6) 400 mg: 25/46 (54.3%; 95% CI 39-69.1) **Radiological response** 300 mg: 6/37	Olaparib has antitumour activity against mCRPC with DDR gene aberrations, supporting the implementation of genomic stratification of metastatic castration-resistant prostate	multicentre, open-label, investigator-initiated, randomised phase 2 trial, blinding of outcome assessment unclear, Detailed list of conflict of interest reported in the paper. Funding: Cancer Research UK, AstraZeneca, Prostate Cancer

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
			United Kingdom (17 hospitals) Median follow-up: 24.8 mo (IQR 16.7–35.9)			(16.2%; 95% CI 6.2–32) 400 mg: 8/33 (24.2%; 95% CI 11.1-42.3) **Median PFS** 300 mg: 5.4 mo (95% CI 3-5.6) 400 mg: 5.5 (95% CI 3.6-6.5) **Median OS** 300 mg: 10.1 mo (95% CI 9-17.7) 400 mg: 14.3 (95% CI 9.7-18.9)	cancer in clinical practice.	UK, the Prostate Cancer Foundation, the Experimental Cancer Medicine Centres Network, and the National Institute for Health Research Biomedical Research Centres.

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						Serious adverse events 300 mg: 49 events in 22 patients 400 mg: 58 events in 24 patients most common grade 3–4 adverse event: in both cohorts was anaemia death possibly related to treatment: 1 in the 300 mg group		

Refe-renz	Studien-charakteristika LoE	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						(myocardial infarction)		

3.6 Welche neu zugelassenen Medikamente/Medikamentenkombinationen sind den Standardtherapien in der Therapie des mCRPC überlegen?

Literaturreferenzen: [466], [471], [472], [473], [474], [475], [450], [476], [477], [478], [479], [467]

Referenz	Studien-charakteristika LoE	Studienziel	Studien-/Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
Systematische Reviews								
[466]	Systematic review with meta-analysis 1+	We aim to better characterize the PFS and OS in mCRPC patients treated with PARPis and determine the subgroup of patients with this disease who can benefit from these medications	n=7 RCTs patients with mCRPC Seach date: 30 May 2023	PARP with or without ARPI (abiraterone acetate or enzalutamide)	standard care (ARPI or docetaxel)	**PARPi vs. Standard care** **OS** (n=5) HR: 0.855 (95% CI 0.752-0.974) p=0.018 I^2=0% **PFS** (n=7) HR: 0.626 (95% CI 0.566-0.692) p=0.00 I^2=45% **PFS in patients without HRR gene**	Our meta-analysis of seven RCTs showed that PARPis significantly increased PFS and OS when used with or without antihormonal agents like abiraterone or enzalutamide.	The study protocol was not registered. No reported sources of funding for the studies included in the review. Results are reported from fixed-effect models, although random-effect

Refe-renz	Studien-charakteristika LoE	Studienziel	Studien-/Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
		at maximum.				**mutation** (n=4) HR: 0.747 (95% CI 0.637-0.877) p=0.00 I^2=0%		models were planned. The authors declare no conflict of interest. This research received no external funding.
Randomisierte kontrollierte Studien								
Apalutamide/Abiraterone+Prednisone vs. Abiraterone+Prednisone								
[471]	RCT NCT02257736 (ACIS) 1++	The current phase 3 trial evaluated clinical benefit of apalutamide plus abiraterone-prednisone	n=982 chemotherapy-naive men with mCRPC 2014-2016 17 countries in North America Europe	apalutamide (240 mg once daily) plus abiraterone (1000 mg once daily) + prednisone	placebo plus abiraterone (1000 mg once daily) + prednisone (5 mg twice daily)	**Apalutamid vs. placebo** **Median OS** 54.8 mo (IQR 51.5-58.4 mo) **radiographic PFS**	Despite comparison against an active therapy and the use as first-line treatment, the apalutamide plus	double-blind multicenter study Detailed list of conflict of interest reported in the paper.

Refe-renz	Studien-charakteristika LoE	Studienziel	Studien-/Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
		versus placebo and abiraterone-prednisone (hereafter abiraterone-prednisone) in patients with chemotherapy-naive mCRPC.	the Asia-Pacific region, Africa South America Median follow-up: 54.8 mo (IQR 51.5-58.4 mo)	(5 mg twice daily) n=492 Median age: 71 y (66-78 y)	n=490 Median age: 71 y (65-77 y)	Median follow-up: 25.7 mo apalutamide: 22,6 (95% CI 19,5–27,4) placebo: 16,6 (95% CI 13,9–19,3) HR 0.69 (95% CI 0.58-0.83) p<0.0001 Median follow-up: 54.8 mo apalutamide: 24 (95% CI 19,7–27,5) placebo: 16,6 (95% CI 13,9–19,3)	abiraterone-prednisone combination consistently improved rPFS in chemotherapy-naive mCRPC patients versus abiraterone-prednisone while maintaining quality of life. As survival benefit is limited with non-targeted therapies in mCRPC, we aimed to identify subgroups of patients who might benefit from therapy,	Funded by Janssen Research & Development.

Refe-renz	Studien-charakteristika LoE	Studienziel	Studien-/Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						HR 0.70 (95% CI 0.60-0.83) p<0.0001 **Grade 3 or 4 TEAE** apalutamide: 60% (294/490) placebo: 51% (250/489) **TEAE associated with dead** apalutamide: 3% (17/490) placebo: 37% (37/489)	such as those at an older age.	
Cabazitaxel vs. Abiraterone/Enzalutamide								
[472]	RCT NCT02254785	We report final study results for the primary	n=95 ARPI-naive men with poor prognosis mCRPC	cabazitaxel (25 mg/m2	enzalutamide (160 mg p.o. daily) or	**Cabazitaxel vs. ARPI** **First-line**	Cabazitaxel was associated with a higher clinical benefit	Investigators

Refe-renz	Studien-charakteristika LoE	Studienziel	Studien-/Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
	1-	endpoint of first-line clinical benefit rate, as well as other endpoints including overall survival and time to progression on first- and second-line therapy.	2014-2017 15 sites in Canada Australia Median follow-up: 21.9 mo	intravenously every 3 weeks) plus prednisone (5 mg orally) n=45 Median age: 68.0 y (IQR 59.0-73.0 y)	abiraterone (1000 mg p.o. daily) plus prednisone (5 mg twice daily) (physician's choice) n=50 (27 abiraterone, 23 enzalutamide) Median age: 67.5 y (IQR 60.3-71.0 y)	radiographic response rate 22% vs. 21% (p=1.00) PSA response ≥50% 57% vs. 54% (p=0.84) PFS 5.3 mo vs. 2.8 mo; HR: 0.87 (0.56-1.35) p=0.52 Time to PSA progression 6.6 mo vs. 5.0 mo; HR: 1.01 (0.61-1.66) p=0.98 Stable disease ≥12 wks	rate in patients with ARPI-naive poor prognosis mCRPC.	and participants were not masked to treatment allocation, median PSA level at baseline significantly different in both groups Detailed list of conflict of interest reported in the paper. This work was supported by Sanofi, Laval, Quebec, Canada. Data

Refe-renz	Studien-charakteristika LoE	Studienziel	Studien-/Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						75% vs. 56% p=0.083 Clinical benefit 80% vs. 62% p=0.039 **Second-line** radiographic response rate 38% vs. 34% PSA response ≥50% 0% vs. 25% Stable disease ≥12 wks 42% vs. 63% Clinical benefit 54% vs. 63% p=0.58		analysis and correlative studies were funded through research grants from Prostate Cancer Canada, CIHR, Movember Foundation, Prostate Cancer Foundation, Terry Fox New Frontiers Program Project Grant [TFF116129], Jane and Aatos Erkko

Refe-renz	Studien-charakteristika LoE	Studienziel	Studien-/Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						<u>Time to progression</u> 2.7 mo vs. 3.7 mo; HR: 1.11 (0.60-2.03) p=0.74 <u>Time to PSA progression</u> 3.5 mo vs. 4.3 mo; HR: 0.87 (0.42-1.81) p=0.72 **most common first-line treatment-related grade ≥3 adverse events** neutropenia (32 vs. 0%) diarrhoea (9 vs. 0%)		Foundation, and the Academy of Finland.

Refe-renz	Studien-charakteristika LoE	Studienziel	Studien-/Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						infection (9 vs. 0%) fatigue (7 vs. 5%) **OS** 37 mo vs. 15.5 mo; HR: 0.58 (0.32-1.05) p=0.073		
[473]	RCT NCT02485691 (CARD) 1-	To assess cabazitaxel versus abiraterone/ enzalutamide in older (≥70 y) and younger (<70 y) patients in CARD.	n=135 men (≥70 y) with mCRPC 2015-2018 62 clinical sites across 13 European countries Median follow-up: 9.2 mo (IQR 5.6-13.1 mo)	cabazitaxel (25 mg/m² intravenously over 1 h every 3 weeks) and prednisone (10 mg daily) n=66 (≥70 y) n=63 (<70 y) Median age	Abiraterone (1000 mg orally once daily) with prednisone (5 mg twice daily) or enzalutamide (160 mg given orally once daily)	**Cabazitaxel vs. Abiraterone/ Enzalutamide** **≥70 y** Median radiographic PFS 8.2 vs 4.5 mo; HR 0.58; (95% CI 0.38–0.89) p=0.012) Median PFS	Cabazitaxel improved efficacy outcomes vs. abiraterone/ enzalutamide in patients with mCRPC after prior docetaxel and abiraterone/ enzalutamide, regardless of age. TEAEs were more	The study was open label and participants and investigators were not masked to treatment allocation. Analyses of radiographic PFS (primary endpoint) and safety

Refe-renz	Studien-charakteristika LoE	Studienziel	Studien-/Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
				≥70 y: 76 y (range 70-85 y) <70 y: 65 y (range 46–69 y)	n=69 (≥70 y) n=57 (<70 y) <u>Median age</u> ≥70 y: 74 y (range 70-88 y) <70 y: 63 y (range 45–69 y)	4.5 vs 2.8 mo; HR 0.57; (95% CI 0.39–0.84) p=0.003) <u>Median OS</u> 13.9 vs. 9.4 mo; HR 0.66 (95% CI = 0.41–1.06) p=0.084 <u>Pain response</u> 55 vs. 17% p<0.001 <u>Any TEAE (Grade ≥3)</u> 58 vs. 49 % <u>Any serious TEAE (Grade ≥3)</u> 38 vs. 45 % **<70 y**	frequent among older patients. The cabazitaxel safety profile was manageable across age groups.	by age were prespecified ; others were post hoc. Detailed list of conflict of interest reported in the paper. Funding Sanofi

Refe-renz	Studien-charakteristika LoE	Studienziel	Studien-/Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						Median radiographic PFS 7.4 vs 3.2 mo; HR 0.47; (95% CI 0.3–0.74) p<0.001) Median PFS 4.4 vs 2.5 mo; HR 0.45; (95% CI 0.3–0.68) p=0.001) Median OS 13.6 vs. 11.8 mo; HR 0.66 (95% CI = 0.41–1.08) p=0.093 Pain response 61 vs. 35% p=0.041 Any TEAE (Grade ≥3)		

Refe-renz	Studien-charakteristika LoE	Studienziel	Studien-/Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						48 vs. 42 % Any serious TEAE (Grade ≥3) 26 vs. 30 %		
[474]	RCT NCT02485691 (CARD) 1-	Here, we report the quality-of-life outcomes from the CARD study.	n=255 men with mCRPC 2015-2018 62 clinical sites across 13 European countries Median follow-up: 9.2 mo (IQR 5.6-13.1 mo)	cabazitaxel (25 mg/m² intravenously over 1 h every 3 weeks) and prednisone (10 mg daily) n=129 Median age: 70 y (65-76 y)	Abiraterone (1000 mg orally once daily) with prednisone (5 mg twice daily) or enzalutamide (160 mg given orally once daily) n=126 (58 abiraterone, 66 enzalutamide, 2 loss	**Cabazitaxel vs. Abiraterone/ Enzalutamide** **Median OS** 13.6 vs. 11 mo HR 0.64 (95% CI, 0.46-0.89) p= 0.008 **Median time to pain progression** not estimable vs. 8.5 mo (95% CI 4.9-not estimable)	Since cabazitaxel improved pain response, time to pain progression, time to symptomatic skeletal events, and EQ-5D-5L utility index, clinicians and patients with metastatic castration-resistant prostate cancer can be reassured that cabazitaxel will	The study was open label and participants and investigators were not masked to treatment allocation. Detailed list of conflict of interest reported in the paper. Funding Sanofi

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					to follow-up) Median age: 71 y (64-75 y)	HR 0.55 (95% CI, 0.32-0.97) p= 0.035 **Median time to symptomatic skeletal events** not estimable vs. 16.7 mo (95% CI 10.8-not estimable) HR 0.59 (95% CI, 0.35-1.01) p= 0.05 **Median time to FACT-P total score deterioration** 14.8 mo (95% CI 6.3-not estimable) vs. 8.9 mo (95%	not reduce quality of life when compared with treatment with a second androgen signalling-targeted inhibitor.	

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						CI 0.63-not estimable) HR 0.72 (95% CI, 0.44-1.20) p= 0.21 **Physical wellbeing** 14.8 mo (95% CI 4.9-not estimable) vs. 8.9 mo (95% CI 4.3-not estimable) HR 0.282 (95% CI, 0.51-1.30) **Social or family wellbeing** 14.8 mo (95% CI 7.9-14.8) vs. 8.9 mo (95% CI 6.3-not estimable)		

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						HR 1.03 (95% CI, 0.61-1.73) **Emotional wellbeing** not estimable vs. 13.7 mo (95% CI 6.3-not estimable) HR 0.46 (95% CI, 0.25-0.87) **Functional wellbeing** not estimable vs. 8.9 mo (95% CI 4.8-not estimable) HR 0.81 (95% CI, 0.51-1.28) **Prostate-specific concerns** 14.8 (95% CI 9.8-not		

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						estimable) vs. 8.9 mo (95% CI 4.8-not estimable) HR 0.68 (95% CI, 0.42-1.08) **EQ-5D-5L** significant treatment effect seen in changes from baseline favour of cabazitaxel over abiraterone or enzalutamide (p=0.030) no difference between treatment groups for change from baseline in EQ-5D-5L		

Refe-renz	Studien-charakteristika LoE	Studienziel	Studien-/Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						visual analogue scale (p=0.060).		
Enzalutamide, Docetaxel + Prednisolone vs. Docetaxel plus Prednisolone								
[475]	RCT NCT02288247 (PRESIDE) 1++	We aimed to evaluate the efficacy of continuing enzalutamide after progression in controlling mCRPC treated with docetaxel and prednisolone.	n=271 patient with mCRPC with enzalutamide after progression 2014-2016 123 sites in Europe: Austria Belgium Czech Republic France Germany Greece Italy Netherlands, Norway	enzalutamide (160 mg: oral four 40 mg capsules per day) plus docetaxel (intravenous 75 mg/m² every 3 weeks) + prednisolone (oral 10 mg/day as two 5 mg tablets) n=136	placebo (oral four 40 mg capsules per day) plus intravenous docetaxel (75 mg/m² every 3 weeks) + prednisolone (oral 10 mg/day as two 5 mg tablets) n=135	**Enzalutamide vs. placebo** **Median PFS** 9.5 mo (95% CI 8.3-10.9 mo) vs. 8.3 mo (6.3-8.7 mo); HR 0.72 (95% CI 0.53-0.96) p=0.027 **Median time to PSA progression** 8.4 mo (95% CI 8.2–9.0) vs. 6.2 m (95% CI 5.4–8.3)	The combination of enzalutamide plus docetaxel and prednisolone in men with mCRPC who progressed on enzalutamide therapy alone significantly reduced the risk of disease progression and could serve as an effective treatment option for this	All patients, investigators, clinical staff, and the sponsor's management team were masked to treatment assignment. Detailed list of conflict of interest reported in the paper. This study was funded by Astellas

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			Poland Russia Spain Sweden Switzerland Turkey United Kingdom The median follow-up: enzaklutamide: 8.1 mo (IQR 3.2-11.1) placebo: 6.3 mo (IQR 3.1-10.5 mo)	Age: 71.5 y (65-75 y)	Age: 69 y (65-74 y)	risk of PSA progression: HR 0.58 (95% CI 0.41–0.82) p=0.0021 **ORR** 21/51 (41%) vs. 23/59 (39%) p=0.74 **TEAE** 133 (98%) vs. 131 (97%) **Drug-related treatment-emergent adverse events** 63 (46%) vs. 56 (41%) **Serious treatment-emergent**	subset of patients.	Pharma and Pfizer, the co-developers of enzalutamide.

Refe-renz	Studien-charakteristika LoE	Studienziel	Studien-/Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						adverse events 67 (49%) vs. 52 (39%) **Deaths** 13 (10%) vs. 7 (5%)		
177Lu-PSMA-617+Standard Care vs. Standard Care								
[450]	RCT NCT0351166 (VISION) 1-	We report the results of VISION, a phase 3 trial investigating the efficacy and safety of 177Lu-PSMA-617 plus protocol- permitted standard care in a specific	n=831 men with mCRPC 2018-2019 84 sites 52 in North America 32 in Europe Median follow-up: 20.9 mo	177Lu-PSMA-617 (maximum of six cycles every six weeks) plus standard care n=551 Median age: 70 y (range 48-94 y)	standard care n=280 Median age: 71.5 y (range 40-89 y)	**177Lu-PSMA-617 vs. standard care** **Median imaging-based PFS** (n=581) 8.7 vs. 3.4 mo; HR 0.40 (99.2% CI 0.29-0.57) p<0.001	Radioligand therapy with 177Lu-PSMA-617 prolonged imaging-based progression-free survival and overall survival when added to standard care in patients with advanced	open-label study, objective response and disease control not reported, conflict of interest not clearly described Standard-care therapy that was

Refe-renz	Studien-charakteristika LoE	Studienziel	Studien-/Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
		population of previously treated patients with mCRPC who were selected for PSMA positivity on the basis of PSMA positron-emission tomographic imaging.				**Median OS** (n=831) 15.3 vs. 11.3 mo; HR 0.62 (95% CI, 0.52-0.74) p<0.001 **Median time to first symptomatic skeletal event** (n=581) 11.5 vs. 6.8 mo; HR 0.5 (95% CI 0.4-0.62) p<0.001 **Complete response** (n=248) 9.2% (17/184) vs. 0% (0/64) **Partial response** (n=248)	PSMA-positive metastatic castration-resistant prostate cancer.	permitted by the trial protocol had to be agreed on and assigned by the physician–investigator before randomization, but it could be modified at the discretion of the treating physician. Standard-care therapies could not

Refe-renz	Studien-charakteristika LoE	Studienziel	Studien-/Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						41.8% (77/184) vs. 3% (2/64) **Incidence of adverse events of grade 3 or above** (n=831) 52.7% vs. 38.0%		include cytotoxic chemotherapy, systemic radioisotopes (e.g. radium-223), immunotherapy, or drugs that were investigational when the trial was designed (e.g. olaparib). Supported by Endocyte, a Novartis company.
Radium-223+Enzalutamide vs. Enzalutamide								

Refe-renz	Studien-charakteristika LoE	Studienziel	Studien-/Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
[476]	RCT NCT02199197 1-<![if !supportAnnotations]>[LJ1]<![endif]>	Final Safety and Efficacy Results	n=47 men with mCRPC Median follow-up: 22 mo	Radium-223 (intravenous 55 kBq/kg IV every 4 weeks for six doses) + Enzalutamide (160 mg p.o. daily) n=35 Median age: 71 y	Enzalutamide (160 mg p. o. daily) n=12 Median age: 71 y	**Radium-223+Enzalutamide vs. Enzalutamide** **Median OS** 30.8 vs. 20.6 mo, p=0.73 **PSA-PFS** 8.9 vs. 3.38 mo, p=0.97 **radiographic PFS** 11.5 vs. 7.35 mo, p=0.96 **Adverse events** There was no difference in any adverse events	Long-term safety of radium-223 with enzalutamide was confirmed in this clinical trial.	small sample size (phase II trial), open-label design, randomization and allocation process not clearly described, econdary endpoints were not included in this paper CAVE: patient flow chart shows 41 randomized patients, text described 47 patients

Refe-renz	Studien-charakteristika LoE	Studienziel	Studien-/Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						or any incidence of bone marrow disorders.		Detailed list of conflict of interest reported in the paper. Sponsor: University of Utah
Enzalutamide vs. Enzalutamide and Abiraterone + Prednisone								
[477]	RCT NCT01949337 (Alliance A031201) 1-	We sought to determine whether the addition of AAP to enzalutamide prolongs OS in patients with mCRPC in the first-line setting.	n=1311 men with mCRPC 2014-2016 324 sites participating in the National Cancer Institute-funded National Clinical Trials Network Median follow-up: 60.6 mo (IQR 38.9-63 mo)	enzalutamide (160 mg once daily by mouth) n=657 Age: <65 y: 141 (21%) 65-75 y: 281 (43%)	enzalutamide (160 mg once daily by mouth) plus AAP (abiraterone 1,000 mg once daily and prednisone 5 mg twice daily by mouth)	**Enzalutamide vs. Enzalutamide, Abiraterone+ prednisone** **Median OS** 32.7 mo (95% CI 30.5-35.4 mo) vs. 34.2 mo (95% CI 31.4-37.3 mo)	The addition of AAP to enzalutamide for first-line treatment of mCRPC was not associated with a statistically significant benefit in OS. Drug-drug interactions between the two agents	Trial register describes further outcomes (e. g. ORR) that are not reported in this paper, open label, different withdrawal before treatment start

Refe-renz	Studien-charakteristika LoE	Studienziel	Studien-/Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
				≥75 y: 235 (36)	n=654 Age: <65 y: 153 (23%) 65-75 y: 266 (41%) ≥75 y: 235 (36%)	HR 0.89 (95% CI 0.78-1.01) p=0.03 **Median radiographic PFS** 21.3 mo (95% CI 19.4-22.9 mo) vs. 24.3 mo (95% CI 22.3-26.7 mo) HR 0.86 (95% CI 0.76-0.97) p=0.02 **Adverse events** higher in the combination arm: high-grade nonhematologic toxicity: 55% vs. 69%	resulting in increased abiraterone clearance may partly account for this result, although these interactions did not prevent the combination regimen from having more nonhematologic toxicity.	(enzalutamide: 6; combination: 22) Detailed list of conflict of interest reported in the paper. Supported by the National Cancer Institute of the National Institutes of Health. Also supported in part by funds from Astellas.

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						fatigue: 6% vs. 11% hypertension: 22% vs. 31% all-grade atrial fibrillation: 1% vs. 2% transaminitis: 19% vs. 43% higher in the enzalutamide arm: arthralgia: 45% vs. 36%		
Olaparib + Abiraterone vs. Abiraterone								
[478]	RCT NCT03732820 (PROpel) 1++	We report the final prespecified overall survival analysis.	n=796 men with mCRPC 2018-2020 126 centres in 17 countries worldwide	olaparib (300 mg twice daily taken approximately 12 h apart) +	placebo (twice daily) plus abiraterone (once daily 1000 mg taken	**Olaparib vs. Placebo** **Median OS** 42.1 mo (95% CI 38.4–not reached) vs.	Overall survival was not significantly different between treatment groups at this	The patients, the investigator, and study centre staff were masked to

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			Median follow-up: 36.6 mo (IQR 34.1-40.3 mo)	abiraterone (once daily 1000 mg taken on an empty stomach) n=399 Age: 69 y (63-74 y)	on an empty stomach) n=397 Age: 70 y (65-76 y)	34.7 mo (95% CI 31-39.3 mo) HR 0.81 (95% CI 0.67-1) p=0.054 **Most common grade 3–4 adverse event** anaemia: 64/398 (16%) vs. 13/396 (3%) **Serious adverse events** 161/398 (40%) vs. 126/396 (32%) **Death**	final prespecified analysis.	drug allocation. Detailed list of conflict of interest reported in the paper. Funding AstraZeneca and Merck Sharp & Dohme.

Refe-renz	Studien-charakteristika LoE	Studienziel	Studien-/Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
						One treatment-related death in the placebo group (interstitial lung disease)		
Olaparib vs. Enzalutamide/Abiraterone+Prednisone								
[479]	RCT NCT02987543(PROfound) 1-	We aimed to assess pain and patient-centric HRQOL measures in patients in the trial.	n=245 men with with mCRPC who have failed prior treatment with a new hormonal agent and have homologous recombination repair gene mutations 2017-2019 206 medical centres and hospitals in 20 different countries	olaparib (300 mg orally twice daily) n=162	enzalutamide (160 mg orally once daily) or abiraterone tablets (1000 mg orally once daily) + prednisone tablets (5 mg orally twice daily) n=83	**Olaparib vs. Control group** **OS** HR 0.69 (95% CI 0.50–0.97) p=0.02 **Median time to pain progression** HR 0.44 (95% CI 0.22–0.91) p=0.02	Olaparib was associated with reduced pain burden and better-preserved HRQOL compared with the two control drugs in men with metastatic castration-resistant prostate cancer and homologous recombination	The study was open label; thus, patients and participating health-care professionals were not masked to treatment allocation. AstraZeneca, as part of an alliance between AstraZeneca

Refe-renz	Studien-charakteristika LoE	Studienziel	Studien-/Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
			Median follow-up: Olaparib: 6.2 m (IQR 2.2-10.4 mo) Control: 3.5 mo (1.7-4.9 mo)			**Time to deterioration in health-related quality of life** FACT-P total score HR 0.85 (95% CI 0.54–1.4) p=0.49 Functional wellbeing HR 0.88 (95% CI 0.56–1.42) p=0.54 Physical wellbeing HR 0.95 (95% CI 0.59–1.59) p=0.78 **First symptomatic**	repair gene alterations who had disease progression after a previous next-generation hormonal drug. Our findings support the clinical benefit of improved radiographical PFS and OS identified in PROfound.	and Merck Sharp & Dohme, a subsidiary of Merck, designed the trial and was responsible for overseeing the collection, analysis, and interpretation of the data. The manuscript was written by the authors with medical writing support, funded by AstraZeneca

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						skeletal-related event HR 0.37 (95% CI 0.2–0.7) p=0.0013 **FACT-P total score during treatment** OR 8.32 (95% CU 1.64-151.84) p=0.0065		and Merck Sharp & Dohme. OS results are included in the meta-analysis above (Alameddine, 2023) Detailed list of conflict of interest reported in the paper. Funding AstraZeneca and Merck Sharp & Dohme.
Talazoparib plus Enzalutamide vs. Enzalutamide<![if !supportAnnotations]>[LJ2]<![endif]>								

Refe-renz	Studien-charakteristika LoE	Studienziel	Studien-/Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen des Autors	Methodische Bemerkungen
[467]	RCT NCT03395197 (TALAPRO-2) 1+	We aimed to compare the efficacy and safety of talazoparib plus enzalutamide versus enzalutamide alone in patients with mCRPC.	n= 805 patients with mCRPC HRR-deficient: n= 169 (21%) HRR-non-eficient: n= 636 (79%) BRCA alterations: Talazoparib: n= 27 (7%) Placebo: n= 32 (8%) 2019- 2020 223 hospitals, cancer centres, medical centres in 26 countries. Median follow-up: rPFS:	n= 402 patients (0.5mg Talazoparib plus 160mg enzalutamide orally once daily) Mean age: 71 y (66–76 y) **Median duration of treatment**: Talazoparib: 19.8 mo (IQR 8.8–26.9 mo) Enzalutamide in the talazoparib group: 22.2	n= 403 patients (placebo plus 160mg enzalutamide orally once daily) Mean age: 71 y (65–76 y) **Median duration of treatment**: Placebo: 16.1 mo (6.5–25.0 mo) Enzalutamide in the placebo group: 16.6 mo	**All patients** **Median rPFS**: talazoparib plus enzalutamide (95% CI 27.5 months–not reached) placebo plus enzalutamide 21.9 months (16.6–25·1) Stratified - HR: 0.63; 95% CI 0.51–0.78; p<0.0001.	Talazoparib plus enzalutamide resulted in clinically meaningful and statistically significant improvement in rPFS versus standard of care enzalutamide as first-line treatment for patients with mCRPC. Final overall survival data and additional long-term safety follow-up will further clarify the clinical	Sponsor, patients, and investigators were masked to talazoparib or placebo, while enzalutamide was open-label. Conflicts of interest and funding: NA has received an honorarium for consultancy since May, 2020, from diverse pharmaceutical companies

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			Talazoparib:24.9 months (IQR 21.9–30.2) Placebo: 24.6 months (14.4–30.2)	mo (9.9–28.1 mo)	(6.7–25.1 mo)		benefit of the treatment combination in patients with and without tumour HRR gene alterations.	(detailed list in the paper). Study was sponsored by Pfizer. Astellas Pharma provided enzalutamide. Editorial and medical writing support was provided by Emily Messina and Annette Smith, on behalf of CMC AFFINITY, a division of IPG Health Medical Communications, and

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								was funded by Pfizer.

4 Literaturverzeichnis

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