mCRPC first-line: Stellenwert von PARP-Inhibitoren & Co

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NATIONALES CENTRUM
FÜR TUMORERKRANKUNGEN
HEIDELBERG

getragen von:
Deutsches Krebsforschungszentrum
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Thoraxklinik-Heidelberg
Deutsche Krebshilfe

Conflicts of Interest

Advisory Board / Honoraria:

Amgen, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, Eisai, EUSA, Gilead, Ipsen, Janssen, Merck, MSD, Novartis, Pfizer, Roche, Sanofi Aventis

Resaech Funding:

Eisai

Travel and conference expenses:

Amgen, Astellas, AstraZeneca, Bayer, Ipsen, Janssen, Merck, MSD, Pfizer

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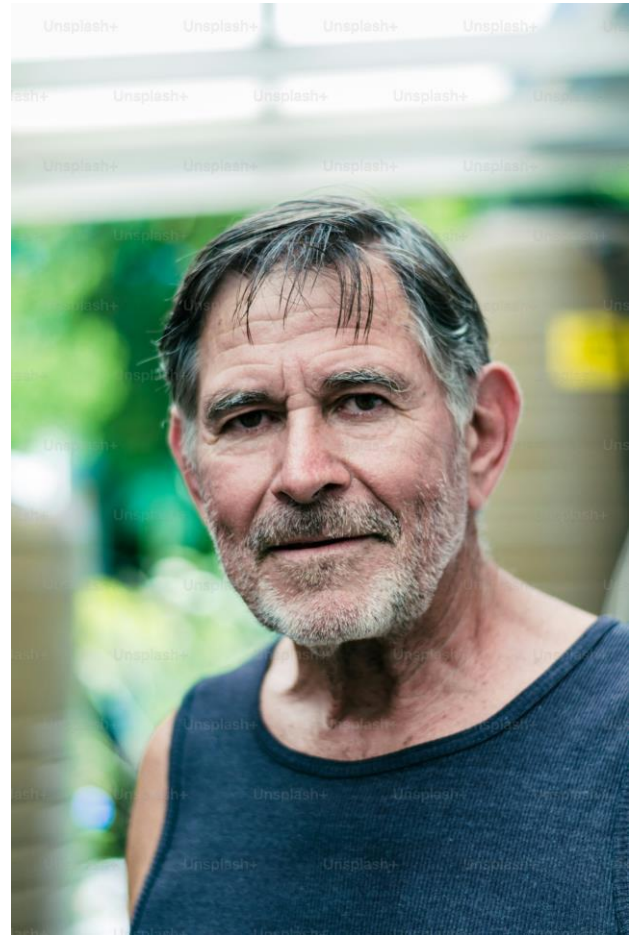
Fallvignette



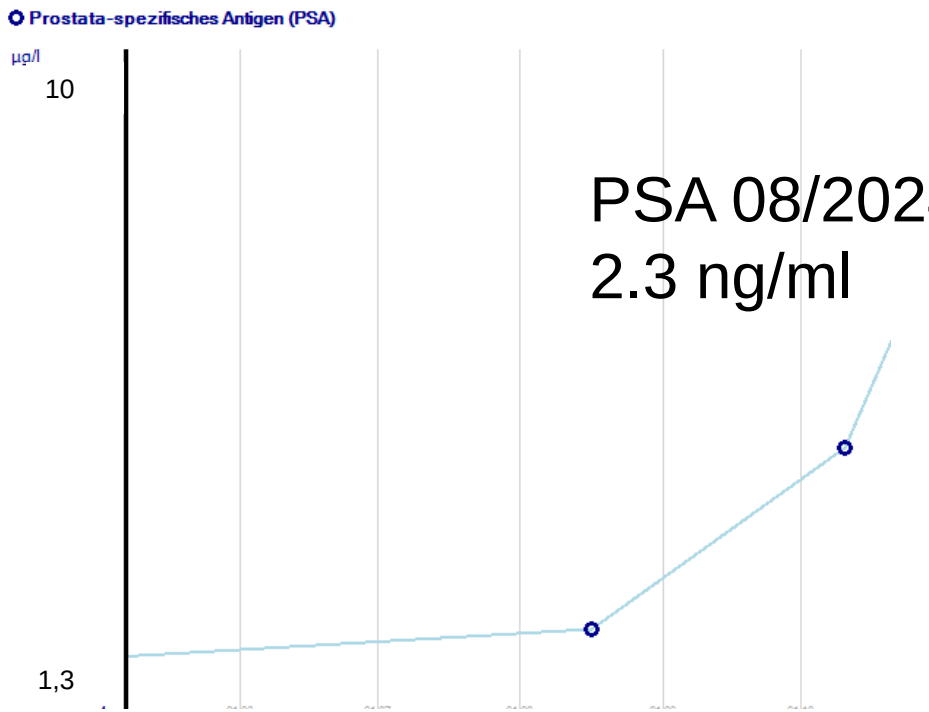
Herr K.

- 64 Jahre
- keine Ko-Morbiditäten, ECOG 0
- Rentner
- 2 x in der Woche Sport (Laufen, Fußball)
- 2021 Erstdiagnose synchron ossär metastasiertes Prostatakarzinom Gleason-Score 4+5=9 (high volume, high risk), initialer PSA-Wert 163 ng/ml
- Familienanamnese: Schwester mit 53 Jahren an Mammakarzinom erkrankt, lebt, keine Angaben zum HRR-Status bekannt

Fallvignette

Vortherapie

- Seit 07/2021 Leuporelin und Abiraterone/Prednison
  Best response: PSA < 0.1ng/ml, bildgebend SD
- PSA-Progress seit 05/2024
- Bildgebend (konventionell): keine Änderung
- Klinik: ECOG 0, keine Symptome



PSA 08/2024
2.3 ng/ml

PSA 05/2024
0.9 ng/ml

Fallvignette

Fragen des Zuweisers:

- Testen (jetzt, wenn ja, was? BRCA1/2? Großes NGS? HRR-Gene? Somatisch und Keimbahn?)
- Welche Therapie
  - Docetaxel?
  - Enzalutamid?
  - Enzalutamid/ Talazoparib?
  - Ggf. Olaparib
  - Studie?

Therapielandschaft des fortgeschrittenen Prostatakarzinoms

nmHSPC non metastatic hormone sensitive Prostate Cancer	nmCRPC non metastatic castration resistant Prostate Cancer	mHSPC metastatic hormone sensitive Prostate Cancer	mCRPC metastatic castration resistant Prostate Cancer
ADT +			
• Enzalutamid#	• Apalutamid* • Darolutamid* • Enzalutamid*	• Abiraterone (high risk+) • Apalutamid • Enzalutamid • Docetaxel • Docetaxel + Abiraterone (PEACE1) • Docetaxel + Darolutamid (ARASENS) • Darolutamid (keine Zulassung, ARANOTE)	• Abiraterone • Abiraterone/ Niraparib## • Abiraterone/ Olaparib## • Cabazitaxel* • Docetaxel • Enzalutamid • Enzalutamid/ Talazoparib## • LuPSMA-617 • Olaparib## • Ra-223** • Ra-223 + Enzalutamid (keine Zulassung) • Rucaparib##

high risk nmHSPC: vgl. EMBARK-Kriterien
*high risk nmCRPC: Verdopplungszeit ≤ 10 Monate
+high risk LATITUDE 2/3 Kriterien (Gleason-Score 8-10, viszerale Metastasen, >/= 4 Knochenläsionen)
**bone only-disease, symptomatisch
different lables durch FDA/ EMA
*nach Docetaxel

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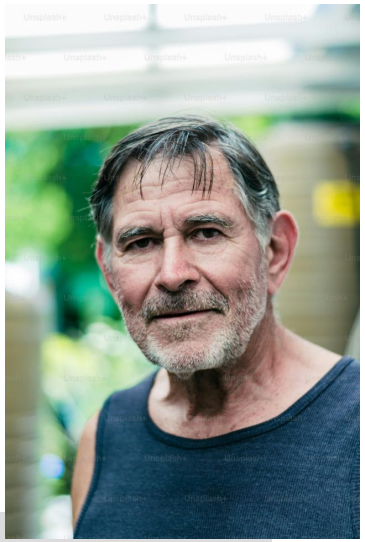
Moving on to mCRPC

1 Patient , >40 Optionen



Therapie im mHSPC

ADT

- + Docetaxel + Prednisone
- + Abiraterone + Prednisone
- + ARPI (Enzalutamide/ Apalutamide)
- + Abiraterone + Docetaxel + Prednisone
- + Darolutamid + Docetaxel + Prednisone
- + „nothing“

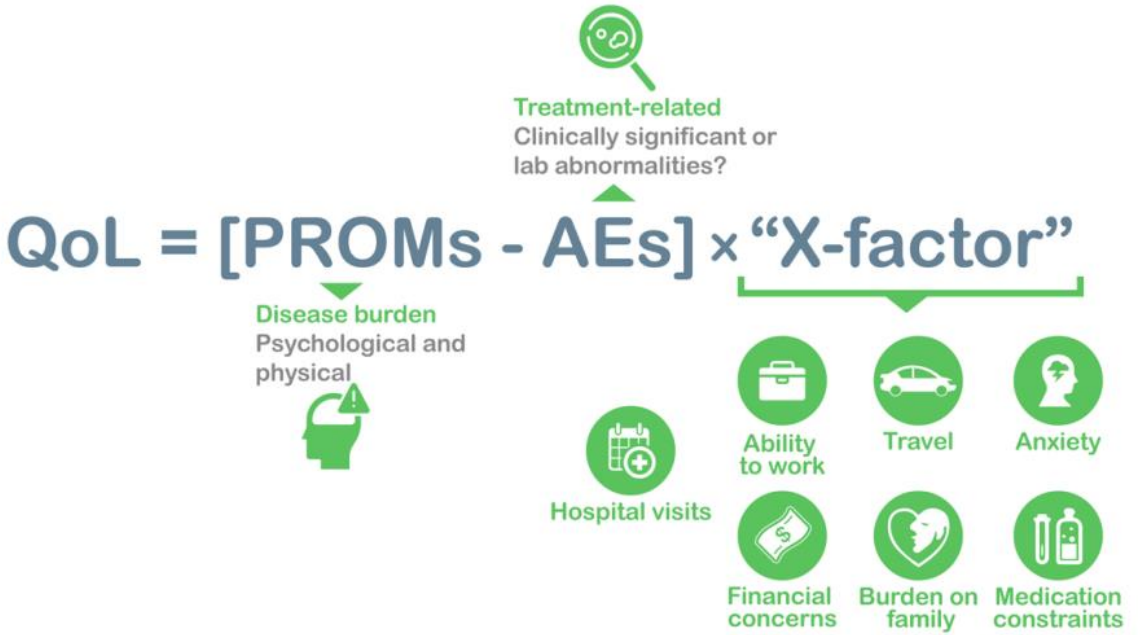
Therapie im mCRPC

ADT

- + Abirateron + Prednisone
- + Enzalutamid
- + Docetaxel + Prednisone
- + Cabazitaxel
- + Olaparib/ Rucaparib
- + Olaparib + Abirateron + Prednisone
- + Niraparib/ Abirateron + Prednisone
- + Talazoparib + Enzalutamid
- + Lutetium-177-PSMA
- + Radium-223

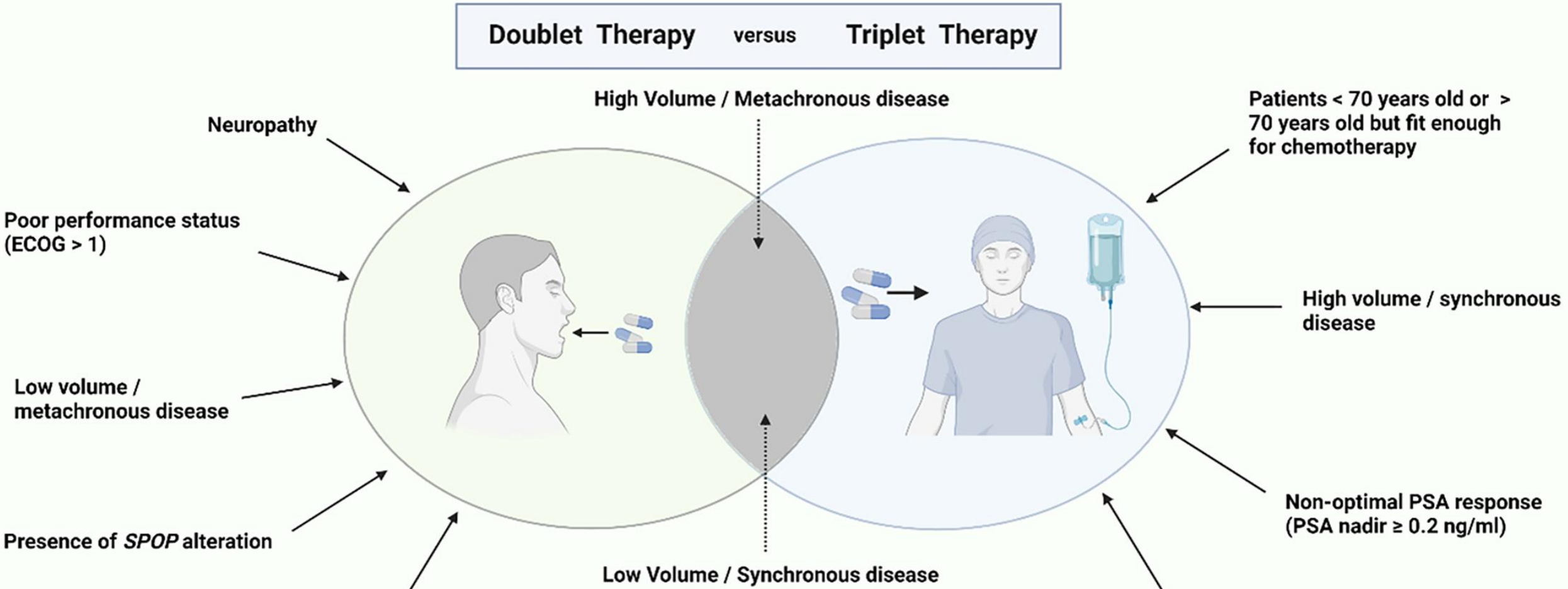
Festlegung der Therapieziele

- Lebenszeitverlängerung (OS)?
- Verbesserung oder Erhalt der Lebensqualität (Schmerzen)
- Verzögerung der Progression (PFS)



Images/Graphics Kidney Cancer - IKCC - International Kidney Cancer Coalition; A. Morgans, GU Connect, 2021
MFS = metastasis free survival, OS = overall survival; PFS= progression free survival

Kriterien für Entscheidungsfindung im mHSPC



- Gleason Score
- PSA-Wert in Korrelation zur Tumorlast
- Lokalisation von Metasasen (Leber, Lunge), kritische Localisation, Bedarf von Lokaltherapie, instable spinale Metastasen
- Zulassungsstatus/ Verfügbarkeit
- Patientenpräferenz
- Studienverfügbarkeit

When Would You Use Doublet Therapy and Not Triplet Therapy for a Patient With Newly Diagnosed mHSPC? (ascopubs.org), abgerufen 29.06.2024

Definition mCRPC – was ist das?

Unter laufender Androgensuppression

- **Testosteron** in Serum < 50 ng/ml und
- **PSA-Progress** mit 3 konsekutiven Anstiegen in mind. wöchentl. Abstand, Anstieg ≥ 50% zum Nadir und PSA ≥ 2ng/ml und/oder
- Progress in der **Bildgebung**

- **→ dies entspricht auch in der Regel den Einschlusskriterien in eine Studie**

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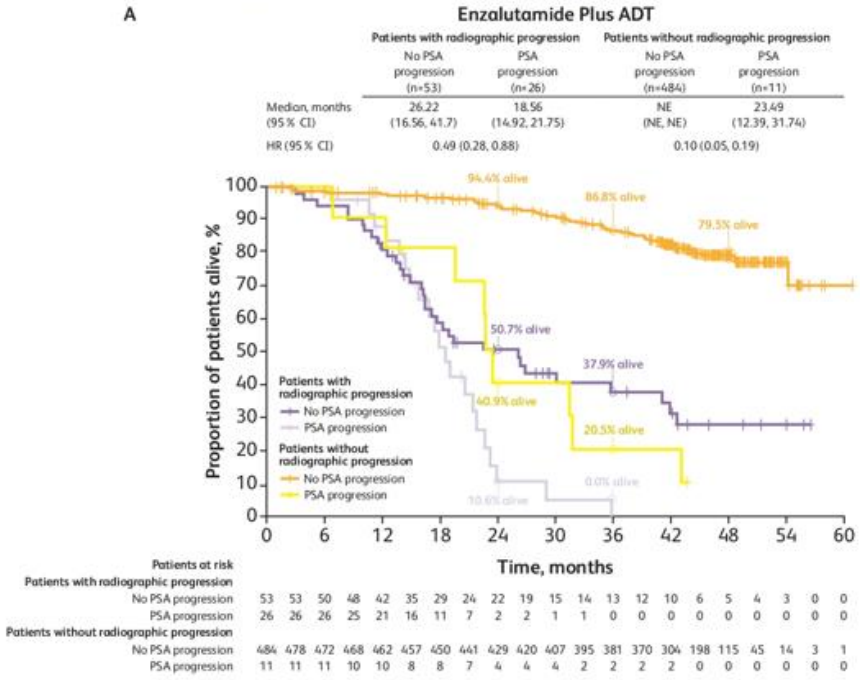
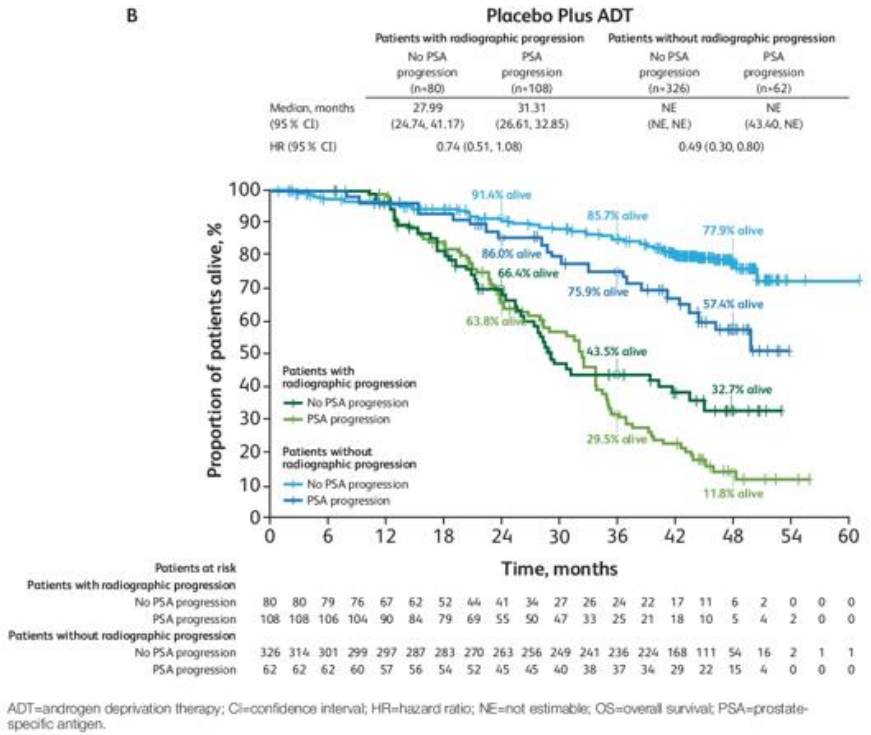
Das mCRPC erkennen – die Prognose einschätzen

67% der Patienten im ARPI/ADT-Arm und 43% der Patienten im Placebo/ADT-Arm in der ARCHES-Studie waren bildgebend progredient ohne PSA-Anstieg!

Figure 2. Kaplan-Meier Curves of OS by Radiographic and PSA Progression in Patients Treated With A) Enzalutamide Plus ADT or B) Placebo Plus ADT

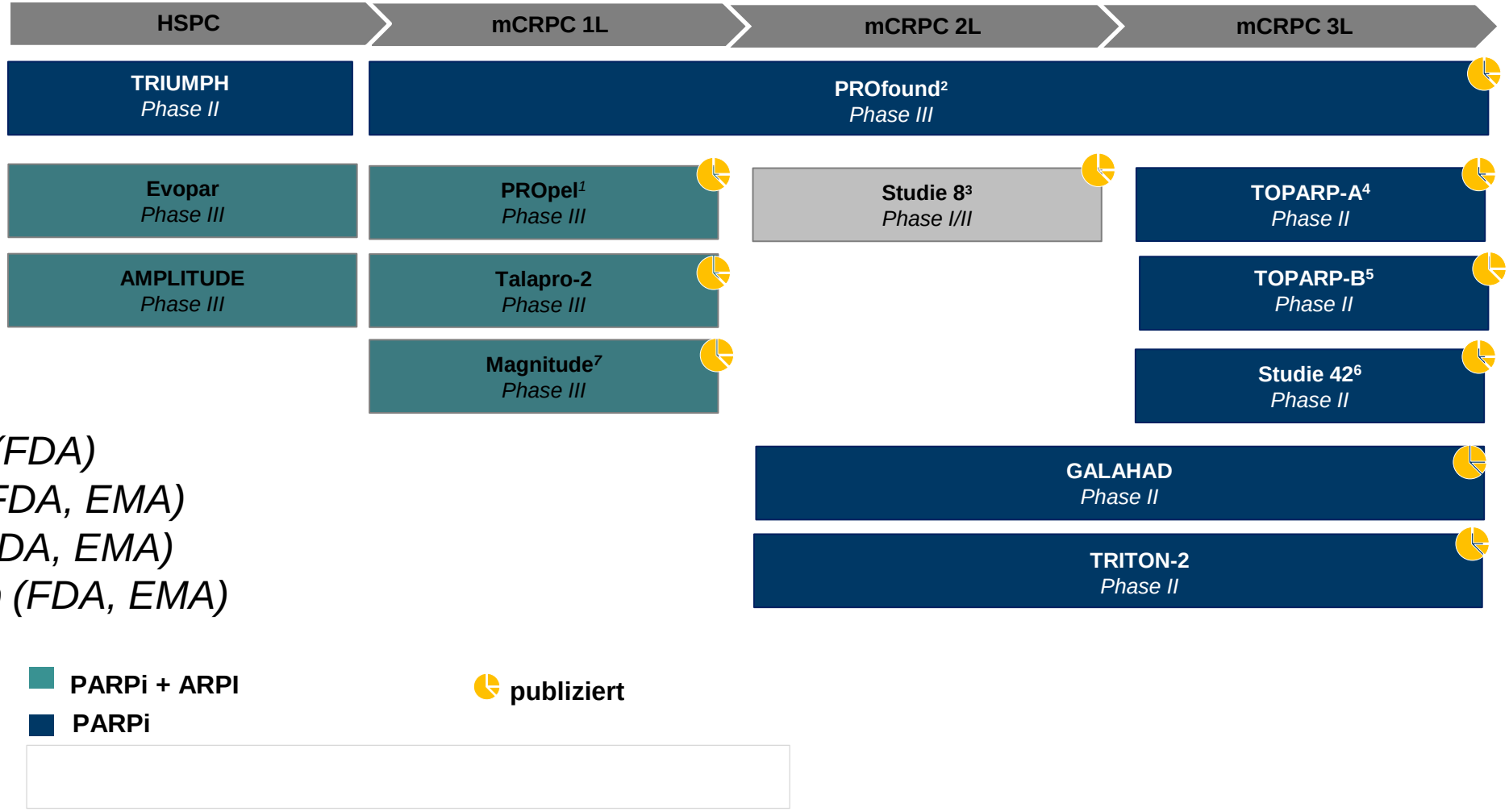




ADT=androgen deprivation therapy; CI=confidence interval; HR=hazard ratio; NE=not estimable; OS=overall survival; PSA=prostate-specific antigen.

Armstrong et al, J Clin Oncol 40, 2022 (suppl 16; abstr 5072)

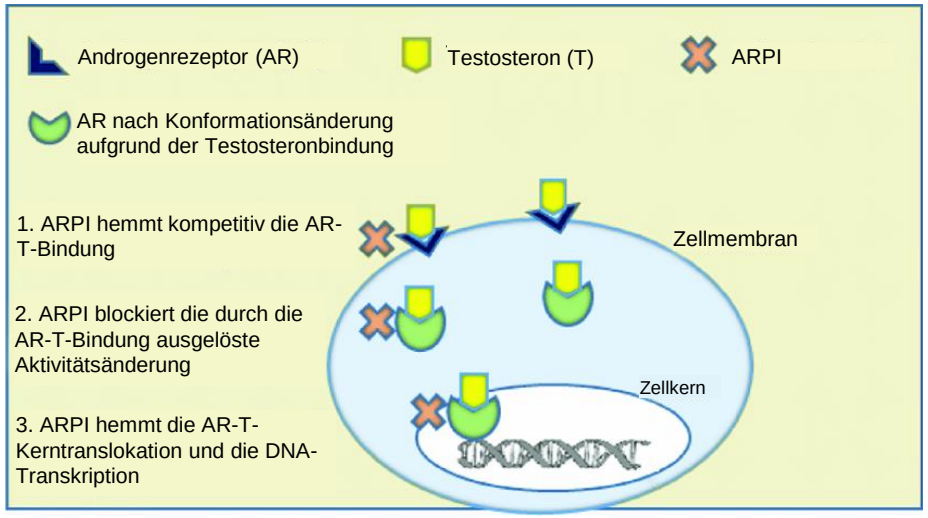
PARPi in der Therapielandschaft des Prostatakarzinoms

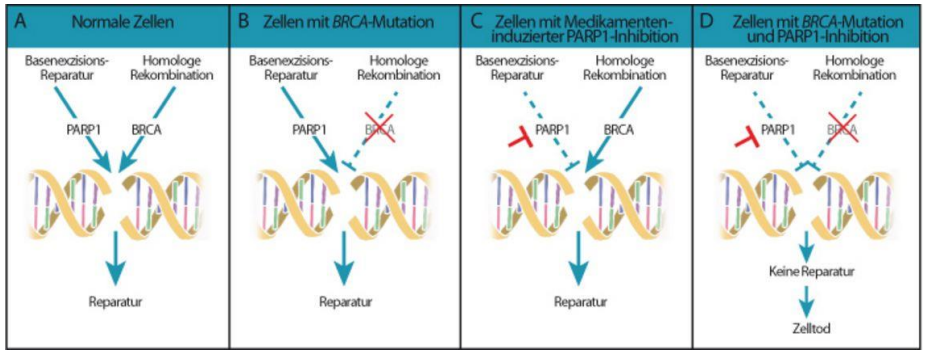


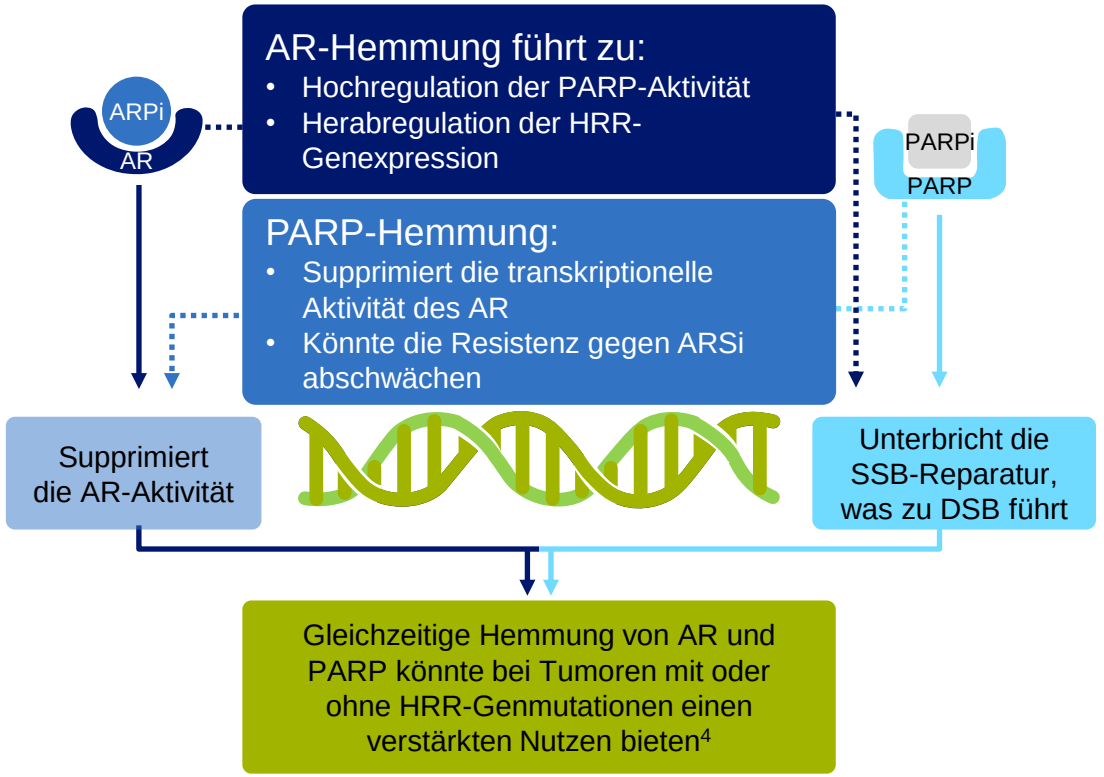
Rucaparib (FDA)
Niraparib (FDA, EMA)
Olaparib (FDA, EMA)
Talazoparib (FDA, EMA)
Veliparib

HSPC = hormonsensitives Prostatakarzinom, mCRPC = metastasiertes kastrationsrefraktäres Prostatakarzinom, PARPi = Poly(ADP-Ribose)-Polymerase Inhibitor
NCT03732820 ClinicalTrials.gov website. Accessed June 02, 2020; de Bono J, et al. *N Engl J Med* 2020;382:2091-2102; Clarke N, et al. *Lancet Oncol* 2018;19:975-986; Mateo J, et al. *N Engl J Med* 2015;373:1697–1708; Mateo J, et al. *Lancet Oncol* 2020;21:162-174. Kaufman B, et al. *J Clin Oncol* 2015;33:244–250.

Kombination Poly-(ADP-Ribose)-Polymerase-Inhibitor (PARPi) und Androgen-Rezeptor-Pathway-Inhibitor (ARPI)





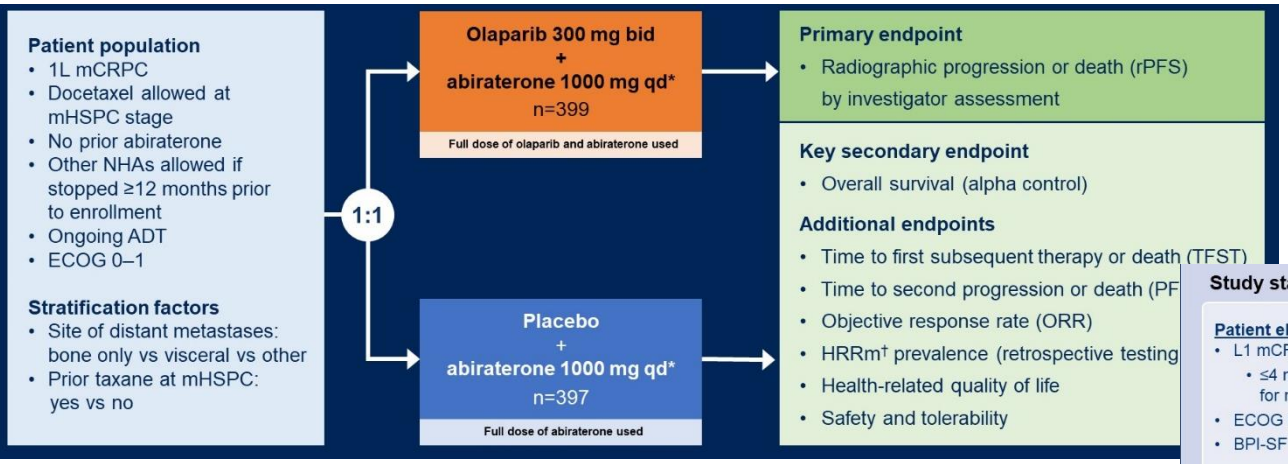


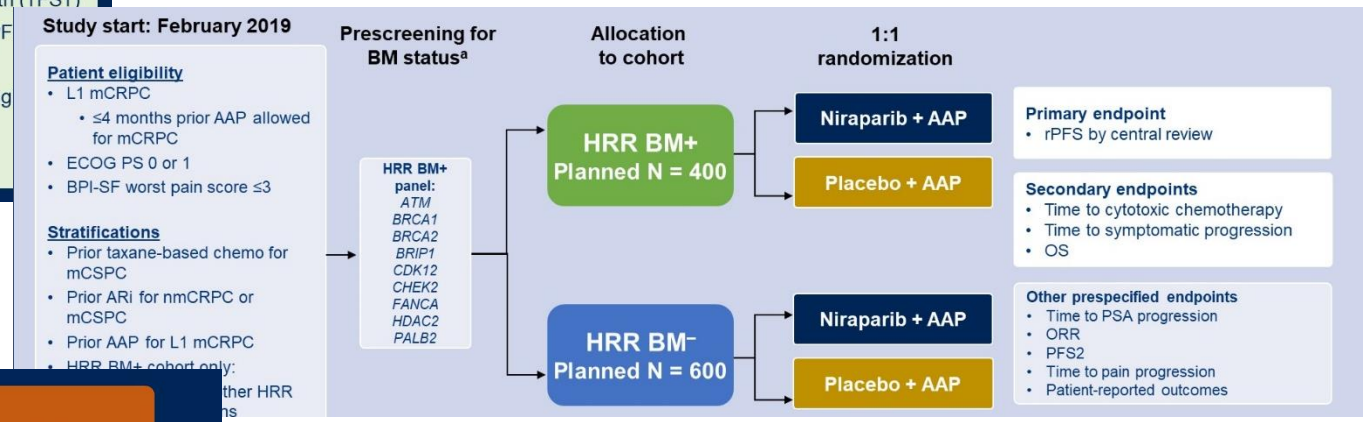
AR(Pi): (Inhibitor des) Androgenrezeptor(-Signalwegs); **DSB:** Doppelstrangbruch; **HRR:** homologe Rekombinationsreparatur; **mCRPC:** metastasiertes kastrationsresistentes Prostatakarzinom; **PARPi:** Poly (ADP-Ribose) Polymerase-Inhibitor; SSB: Einzelstrangbruch.

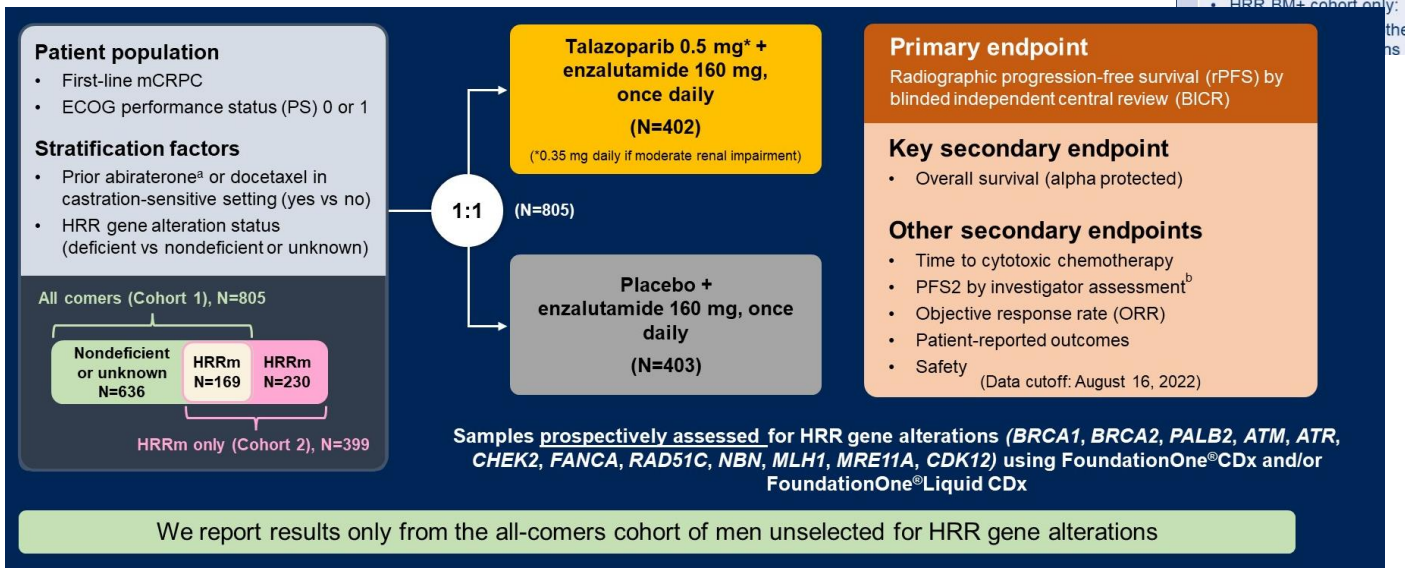
1. Asim, M et al., Nature Comm.; 2017: 8(1): 374; **2.** de Bono JS, et al. Lancet Oncol. 2021; 22:1250-1264; **3.** Agarwal N, et al. Eur J Cancer. 2023; 192:113249. Patel, NK et al, Therapeutics and Clinical Risk Management et al; 2014; 10; 651-664; Kolben, Martin, Trillium Krebsmagazin, Ausgabe 04/2015

Litton, JK, et al., NEJM 2018; 379:753–763.

PARPi + ARPI (PROpel, Magnitude, Talapro-2)







F. Saad bzw. Kim Chi auf dem ASCO – GU 2022; N. Agarwal auf dem ASCO GU 2023

Effektivität von PARPi und ARPI

	PROPEL Ola+Abi	MAGNITUDE Nira+Abi	TALAPRO-2 Tala+Enza
rPFS all comers	24.8 vs. 16.6 Monate HR 0.66 (95% CI 0.54-0.81), p<0.001	-	NR vs. 21.9 months HR 0.63 (95% CI 0.51-0.78), p<0.001
rPFS BRCA	NR vs 8.4 Monate HR 0.23 (95% CI 0.12-0.43)	19.5 vs. 10.9 months HR 0.55 (95% CI 0.39-0.78), p=0.0007	NR vs. 11.0 months HR 0.20 (95% CI 0.11-0.36), p<0.0001
rPFS HRRm	NR vs 13.9 Monate HR 0.50 (95% CI 0.34-0.73)	16.7 vs. 13.7 months HR 0.76 (95% CI 0.60-0.97), p=0.028	NR vs. 13.8 months HR 0.45 (95% CI 0.33-0.61), p<0.001
rPFS non-HRR/unknown	24.1 vs. 19.0 Monate HR 0.76 (95% CI 0.60-0.97)	HR 1.09 (95% CI 0.75-1.57), p=0.66	NR vs. 21.9 months HR 0.70 (95% CI 0.54-0.89), p=0.0039

Disclaimer: Studien können nicht direkt verglichen warden!

rPFS benefit: BRCA > HRRm > all comers > non-HRRm

Abi = Abiraterone, Enza = Enzalutamid, Nira = Niraparib, Ola = Olaparib, Tala = Talazoparibm rPFS = radiographisches progressionsfreies Überleben

Saad F, et al. *Lancet Oncol* 2023;24:1094-108; Clarke NW, et al. *N Engl J Med Evidence* 2022;1:EVIDoa2200043; Agarwal N, et al. *Lancet* 2023;402:291-303. Fizazi K, et al. *Nature Medicine* 2024;30:257-64; Chi KN, et al. *J Clin Oncol* 2023;41:3339-51. Chi KN, et al. *Ann Oncol* 2023;34:772-782.

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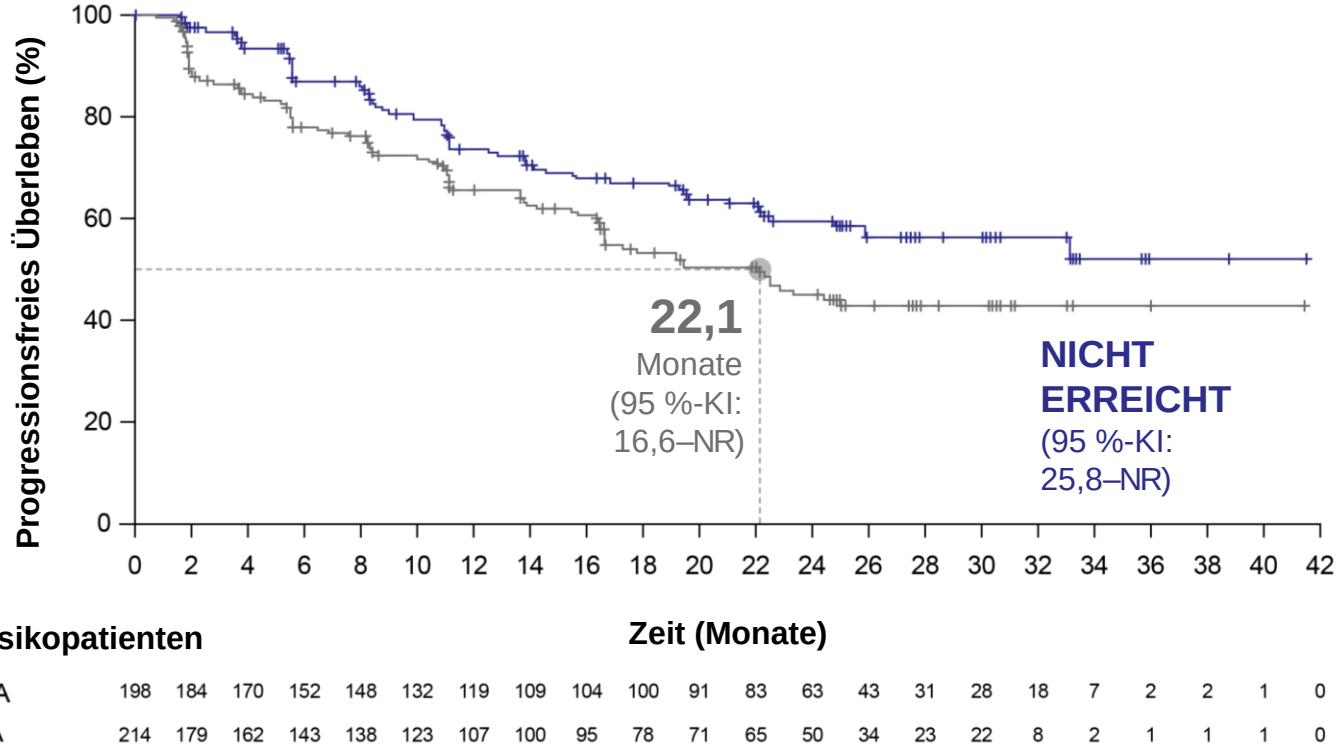
TALAPRO-2 primärer Endpunkt - rPFS laut BICR bei HRR-Status nicht-defizient durch prospektive Untersuchung von Tumorgewebe

34 % Risikoreduktion bei Patienten ohne HRR-Genveränderungen, die durch prospektive Tumorgewebetests nachgewiesen wurden.



Anzahl Risikopatienten

TALA + ENZA	198	184	170	152	148	132	119	109	104	100	91	83	63	43	31	28	18	7	2	2	1	0
PBO + ENZA	214	179	162	143	138	123	107	100	95	78	71	65	50	34	23	22	8	2	1	1	1	0

	TALA + ENZA (N = 198)	PBO + ENZA (N = 214)
Ereignisse, n	70	96
Median (95%-KI), Monate	NR (25,8–NR)	22,1 (16,6–NR)
HR (95%-KI)	**0,66 (0,49–0,91); *P* = 0,009**	

Explorative Endpunktanalyse auf der Grundlage des HRR-Genveränderungsstatus aus der klinischen Datenbank (unstratifizierte Analyse).
BICR: Verblindete unabhängige zentrale Überprüfung; **ENZA:** Enzalutamid; **HR:** Hazard Ratio; **HRR:** Homologe Rekombinationsreparatur; **KI:** Konfidenzintervall; **NR:** nicht erreicht; **PBO:** Placebo; **rPFS:** Radiografisch progressionsfreies Überleben; **TALA:** Talazoparib.

Präsentiert von Dr Neeraj Agarwal auf dem ASCO Genitourinary Cancers Symposium 2023; LBA #17.

Basisinformation Talzenna®: http://bit.ly/366uebc

OS in den 1L mCRPC PARPi/ARPI-Studien

OS	PROpel	MAGNITUDE	TALAPRO-2
BRCA	NR vs. 23.0 Mon HR 0.29 (95% CI 0·14–0.56) ✓	29.3 vs. 28.6 Mon HR 0.88 (95% CI, 0.58-1.34) p=0.55 ✗	NR vs. 11.0 Mon HR 0·20 (95% CI 0·11–0·36) ✓ p<0·0001
HRR-defizient	NR vs. 28.5 Mon HR 0.66 (95% CI 0·45–0.95) ✓	29.3 v 32.2 Mon HR 1.01 (95% CI, 0.75-1.36) p=0.95 ✗	NR vs. 33.7 Mon HR 0·69 (95% CI 0·46–1.03) P=0.07 ✓
HRR-nicht-defizient oder unbekannt	42.1 vs. 38.9 Mon HR 0.89 (95% CI 0·70–1.14) ✗		NR
All-comers	42.7 vs. 34.7 Mon HR 0·81 (95% CI 0·67–1.00) P=0.054 ✗		36.2 Mon vs. NR HR 0·89 (95% CI 0·69–1.14) P-0.35 ✗
			-

HRR = homologe Rekombinationsreparatur; HR = Hazard Ratio, Mon = Monate, NR = Nicht erreicht

1. Saad F, Clarke NW, Oya M, Shore N, Procopio G, Guedes JD, et al. Lancet Oncol. 2023;24(10):1094-108.
2. Clarke NW, Armstrong AJ, Thiery-Vuillemin A, Oya M, Shore N, Loredo E, et al. NEJM Evidence. 2022;1(9):EVIDoa2200043.
3. Agarwal N, Azad AA, Carles J, Fay AP, Matsubara N, Heinrich D, et al. Lancet. 2023;402(10398):291-303.
4. Fizazi K, Azad AA, Matsubara N, Carles J, Fay AP, De Giorgi U, et al. Nature Medicine. 2024;30(1):257-64.
5. Chi KN, Rathkopf D, Smith MR, Efstathiou E, Attard G, Olmos D, et al. J Clin Oncol. 2023;41(18):3339-51.
6.. Chi KN, Sandhu S, Smith MR, Attard G, Saad M, Olmos D, et al. Ann Oncol. 2023 Sep;34(9):772-782.

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Blick in die Leitlinien PARPi

Guideline der EAU ProstataCa

Therapienaiv für mCRPC und HRR oder BRCA-Mutation: Abiraterone + Olaparib	Strong
Therapienaiv für mCRPC und BRCA-Mutation: Abiraterone + Niraparib	Strong
Therapienaiv für mCRPC und HRR-Mutation: Enzalutamid +Talazoparib	Strong
Vorbehandelt für mCRPC und relevante DNA-Reparaturgen-Mutation: PARPi	Strong

Guideline der S3 ProstataCa

nach Vortherapie mit einem ARPI und BRCA1/2-Mutation: Olaparib	A
keine Chemotherapie indiziert und BRCA1/2-Mutation: • Niraparib + Abirateron • Olaparib + Abirateron • Talazoparib + Enzalutamid	A
HRR-Defekt außer BRCA1/2, die in der Vortherapie keinen ARPI oder Abirateron erhalten haben: • Abirateron • Abirateron + Olaparib (falls eine Chemotherapie klinisch nicht indiziert ist) • Docetaxel • Enzalutamid • Talazoparib + Enzalutamid	EK
ohne Nachweis einer BRCA1/2-Mutation oder eines anderen HRR-Defektes, die in der Vortherapie keinen ARPI oder Abirateron erhalten haben, falls eine Chemotherapie klinisch nicht indiziert ist,kann eine Kombinationstherapie mit einer dieser Optionen angeboten werden • Abirateron + Olaparib • Enzalutamid + Talazoparib	0

EAU-Leitlinie Prostatakarzinom 2024; S3-Leitlinie Prostatakarzinom 2024

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Sicherheit von ARPI und PARPi – There are Differences….

	PROpel	MAGNITUDE	TALAPRO-2
Grad ≥ 3 AE	47% (Abi + Ola) 38% (Abo + Pbo)	67% (Abi + Nira) 46% (Abo + Pbo) 72%	(Enza + Tala) 41% (Enza + Pbo)
Grad ≥ 3 AE (Experimental arm)	Anämie 15% HT 4% VTE 7%	Anämie 30% HT 16%	Anämie 43% (49% der Patienten hatten Gr 1-2 bei Studieneinschluss)
Dosisreduktion	20% (Abi + Ola) 6% (Abo + Pbo)	20% (Abi + Nira) 3% (Abo + Pbo)	56% (Enza + Tala) 7% (Enza + Pbo)
Therapieabbruch	14% / 9% (Abi + Ola) 8% / 9% (Pbo + Ola)	11% (Abi + Nira) 5% (Abo + Pbo)	19% (Enza + Tala) - 8% wegen Anämie 12% (Enza + Pbo)

Sicherheit von ARPI und PARPi – There are Differences….

	PROPEL Ola+Abi	PROPEL Abi	MAGNITUDE Nira+Abi	MAGNITUDE Abi	TALAPRO-2 Tala+Enza	TALAPRO-2 Enza
Anämie						
jeder Grad	50%	18%	50%	22.7%	66%	17%
Grad >/=3	16%	3%	30.2%	8.5%	46%	4%
Thrombozytopenie						
jeder Grad	<10%	<10%	23.1%	9.5%	25%	3%
Grad >/=3			7.6%	2.4%	7%	1%
Neutropenie						
jeder Grad	<10%	<10%	15.1%	7.1%	36%	7%
Grad >/=3			6.6%	2.4%	18%	1%
Fatigue/ Asthenie						
jeder Grad	39%	30%	46.2%	29%	48%	38%
Grad >/=3	3%	2%	4.7%	5.7%	7%	3%
Nausea						
jeder Grad	31%	14%	25%	15.2%	21%	12%
Grad >/=3	<1%	<1%	0.5%	0.5%	<1%	1%

Abi = Abiraterone, ARPI) Androgenrezeptor-Pathway-Inhibitor, Enza = Enzalutamid, Nira = Niraparib, Ola = Olaparib, PARPi = PARP-Inhibitor, Tala = Talazoparib

Saad F, et al. *Lancet Oncol* 2023;24:1094-108; Clarke NW, et al. *N Engl J Med Evidence* 2022;1:EVIDoa2200043; Agarwal N, et al. *Lancet* 2023;402:291-303. Fizazi K, et al. *Nature Medicine* 2024;30:257-64; Chi KN, et al. *J Clin Oncol* 2023;41:3339-51. Chi KN, et al. *Ann Oncol* 2023;34:772-782.

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PARPi monotherapy

PROFOUND

mCRPC and progression on prior NHA* (could receive previous taxanes) harboring gene alterations† with a role in HRR (N = 387)

Cohort A
BRCA1, *BRCA2*, or *ATM*
(n = 245)

2:1

Olaparib 300 mg BID (n = 162)

Physician's Choice** (n = 83)

Cohort B
Other alterations
(n = 142)

2:1

Olaparib 300 mg BID (n = 94)

Physician's Choice** (n = 48)

TRITON2

TRIAL OF RUCAPARIB IN PROSTATE INDICATIONS

DDR genes

BRCA1	*ATM*	*CHEK2*	*RAD51*
BRCA2	*BARD1*	*FANCA*	*RAD51B*
	BRIP1	*NBN*	*RAD51C*
	CDK12	*PALB2*	*RAD51D*
			RAD54L

Key eligibility criteria

- mCRPC
- Deleterious somatic or germline alteration in DDR gene
- Disease progression on AR-directed therapy (eg, abiraterone, enzalutamide, or apalutamide) for PC ***and*** 1 prior taxane-based chemotherapy for CRPC
- ECOG PS 0 or 1
- No prior PARP inhibitor, mitoxantrone, cyclophosphamide, or platinum-based chemotherapy

Treatment
28-day cycles

Rucaparib 600 mg BID

- Tumour assessments every 8 weeks for 24 weeks, then every 12 weeks
- PSA assessments every 4 weeks

Treatment until radiographic progression or discontinuation for other reason

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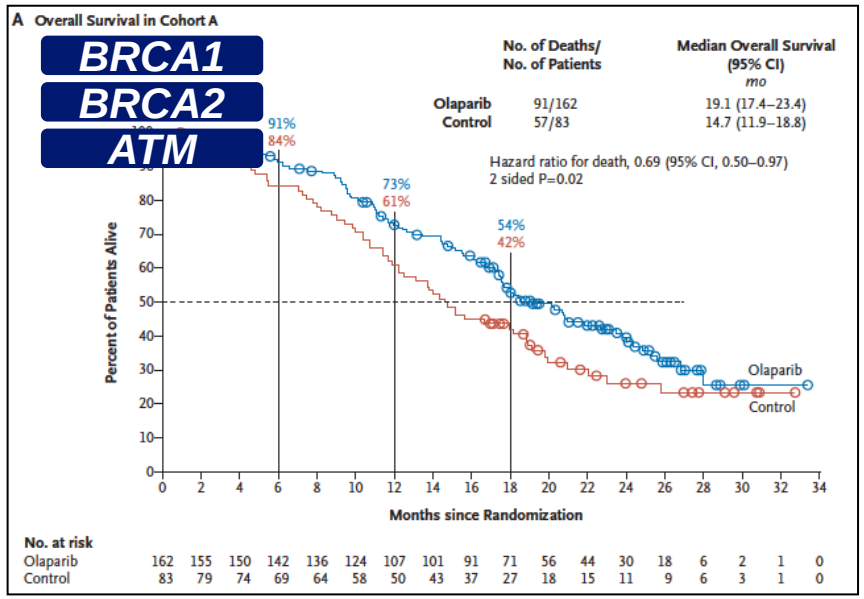
Hussain et al., NEJM 2020: 383:2345; Abida et al, European Urology, 2023, 321-330; Abida et al, ESMO 2019

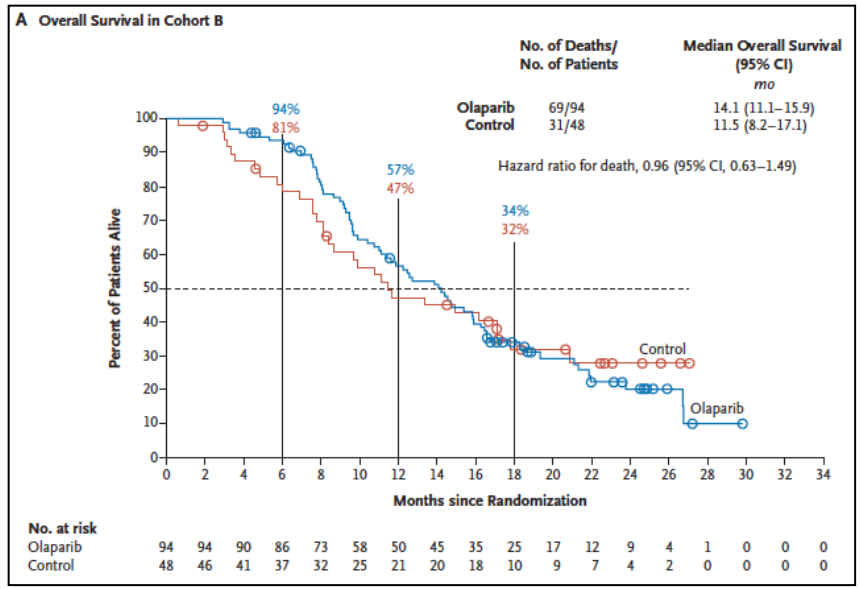
PARPi monotherapy

Olaparib
- BRCA1/2 (EMA, post ARPI)
- HRR (FDA, post ARPI)

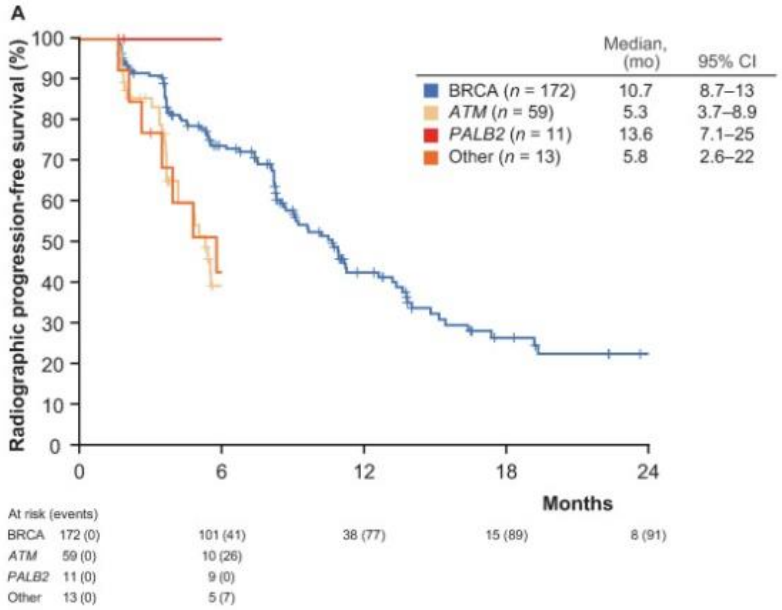
Rucaparib
- BRCA1/2 (FDA, post ARPI and post chemo)



Olaparib (Profound)



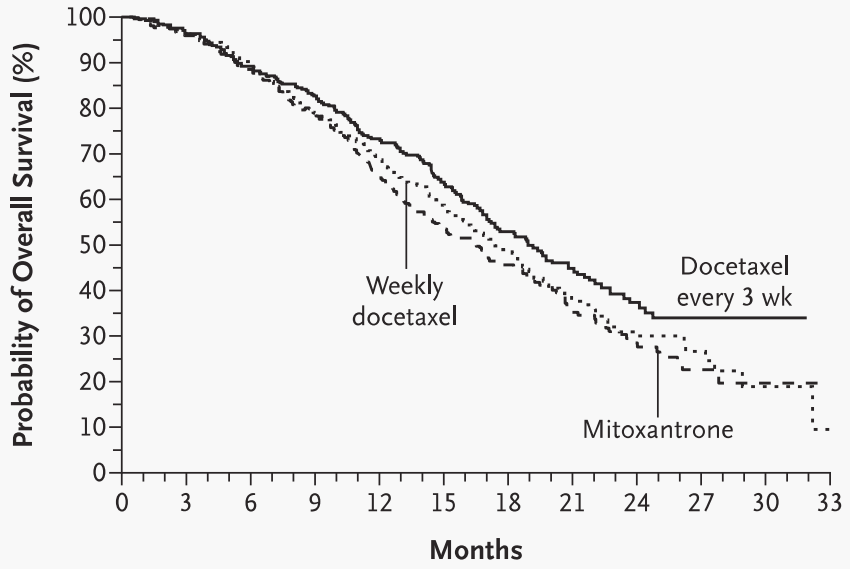
BARD1
BRIP1
CDK12
CHEK1
CHEK2
FANCL
PALB2
PPP2R2A
RAD51B
RAD51C
RAD51D
RAD54L



Rucaparib (Triton-2)

Hussain et al., NEJM 2020: 383:2345; Abida et al, European Urology, 2023, 321-330

Docetaxel im mCRPC



No. at Risk						
Docetaxel every 3 wk	335	296	217	104	37	5
Weekly docetaxel	334	297	200	105	29	4
Mitoxantrone	337	297	192	95	29	3

Medianes Überleben:
Docetaxel 75 mg/m2 q3w: **18,9 Monate**
Mitoxantron: **16,5 Monate**
HR 0,76 (95%-KI 0,62-0,92; p=0,009)

32% Grad 3-4 Neutropenie
30% all grade PNP
53% all grade Fatigue

Tannock et al. N Engl J Med 2004

NCT

Docetaxel Re-Challenge

ELSEVIER

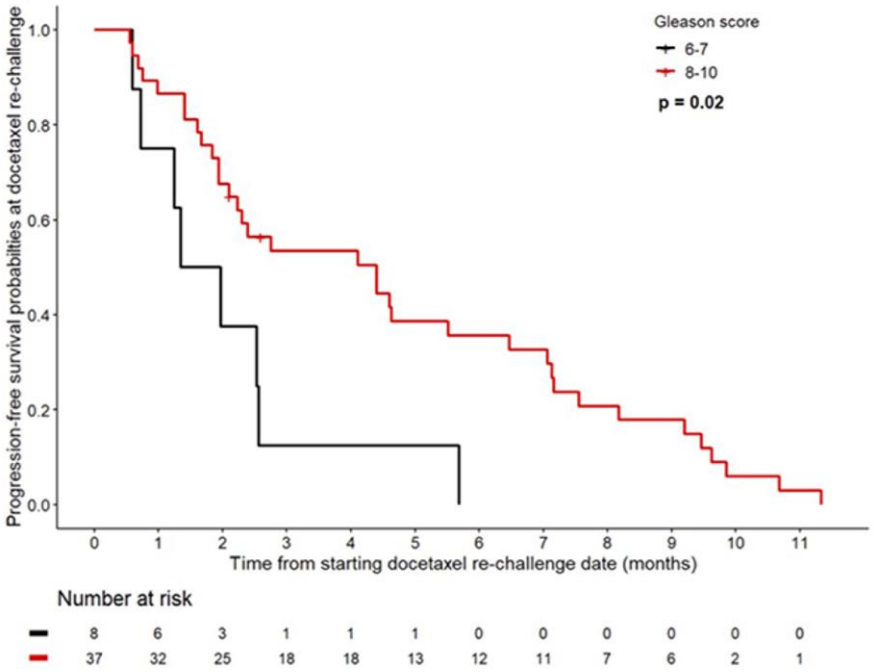
Urologic Oncology: Seminars and Original Investigations

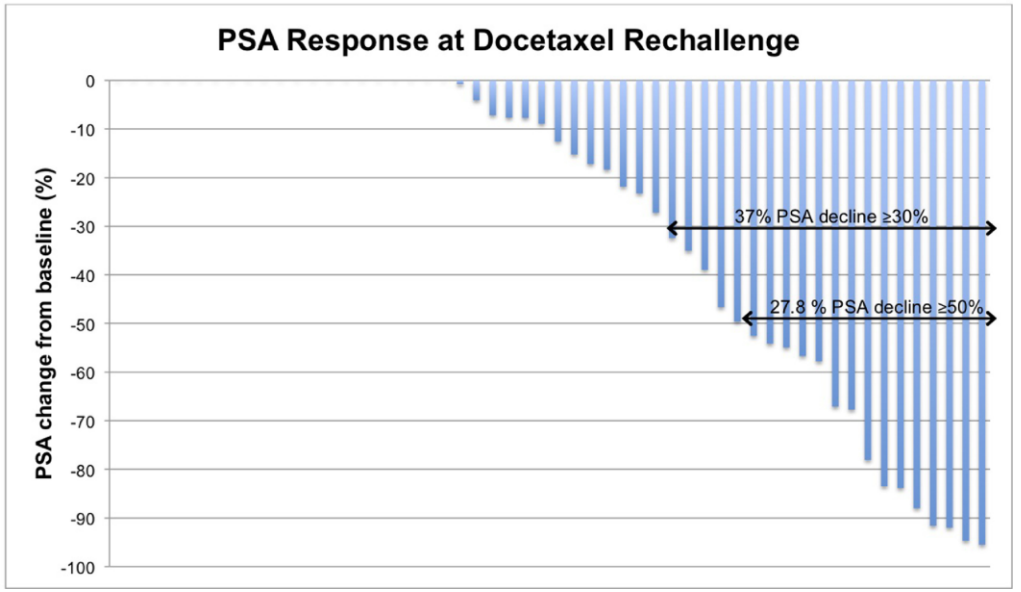
Volume 40, Issue 12, December 2022, Pages 539.e17-539.e22

Clinical-Prostate cancer

UnCHAARTED territory: The role of docetaxel rechallenge following chemohormonal therapy for metastatic castration-sensitive prostate cancer

Mary Mahler M.D. [a, b], Esmail Al-Ezzi M.D. [b], Noa Shani Shrem M.D. [c], Liying Zhang Ph.D. [d], Eric Winquist M.D. [e], Christina Canil [c], Michael Ong M.D. [c], Aaron R. Hansen M.D. [a, b, f], Urban Emmenegger M.D. [a, b, g]





Re-Challenge (post Docetaxel in mHSPC)

- PSA decline ≥30% 37%
- PSA decline ≥50% 28%.
- PFS 4.1 months (95% CI 2.1−4.8)
- "These results suggest a limited role of reexposure to docetaxel for mCRPC after initial docetaxel use for mCSPC. Further prospective studies are needed to better assess the optimal sequencing of therapies following chemohormonal treatment of mCSPC."

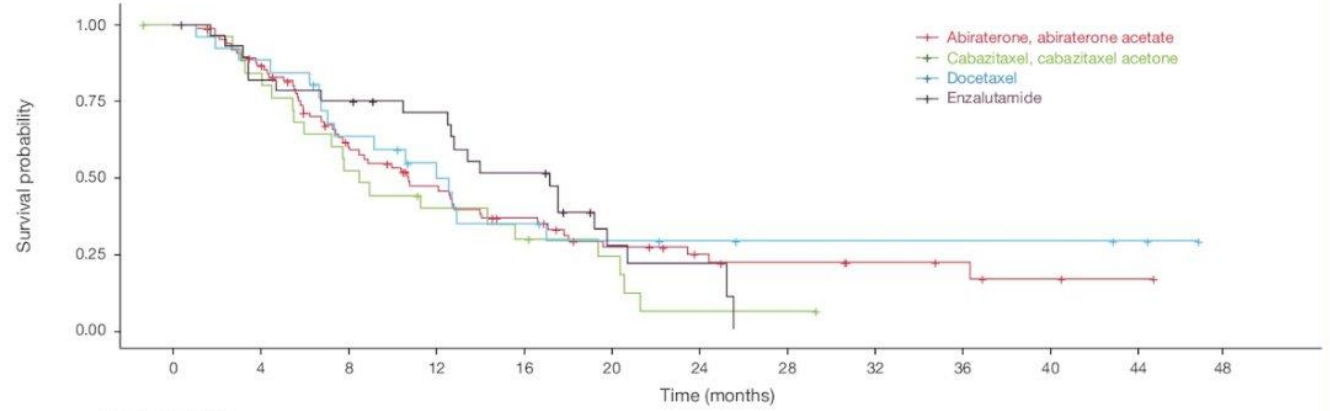
NCT

Was kommt nach der Triplette?

		Darolutamide + ADT + docetaxel (N=315*)	Placebo + ADT + docetaxel (N=495*)
Patients with subsequent life-prolonging systemic antineoplastic therapy,† n (%)		**179 (56.8)**	**374 (75.6)**
First subsequent therapy, n (%)	Abiraterone acetate	83 (46.4)	193 (51.6)
	Enzalutamide	29 (16.2)	97 (25.9)
	Abiraterone acetate/enzalutamide	**112 (62.6)**	**290 (77.5)**
	Cabazitaxel	26 (14.5)	26 (7.0)
	Docetaxel	26 (14.5)	45 (12.0)
	Cabazitaxel/docetaxel	**52 (29.1)**	**71 (19.0)**
	Radium-223	10 (5.6)	8 (2.3)

Was kommt nach der Triplette?

Figure 1. Darolutamide + ADT + docetaxel: Post-progression overall survival based on first subsequent anticancer therapy

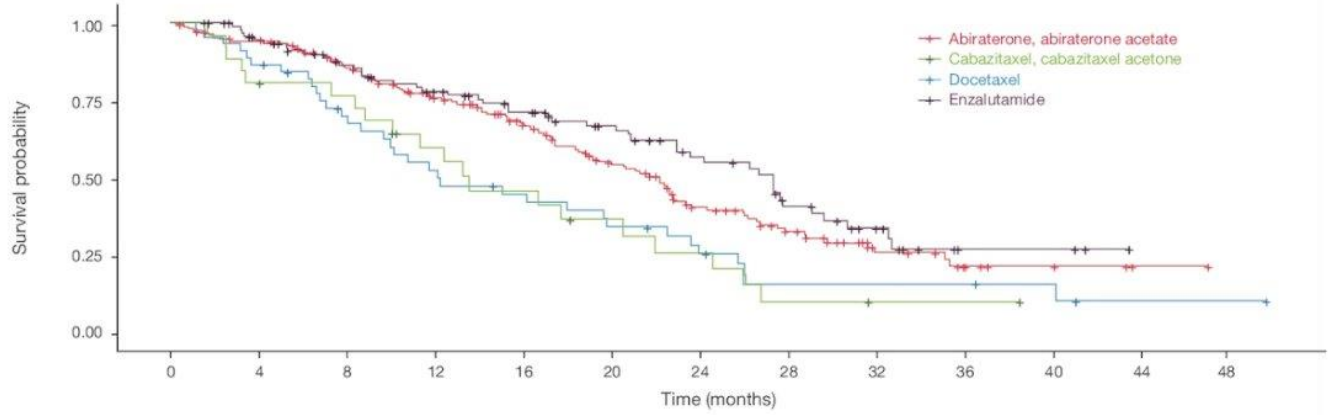


Numbers at risk

Abiraterone, abiraterone acetate	83	70	43	31	22	13	9	7	5	4	2	1	0
Cabazitaxel, cabazitaxel acetone	25	21	13	9	6	4	1	1	0	0	0	0	0
Docetaxel	26	22	15	11	7	5							
Enzalutamide	29	23	21	18	13	5							

Radium-223 was excluded from survival curves due to the small number of patients who received it as

Figure 2. Placebo + ADT + docetaxel: Post-progression overall survival based on first subsequent anticancer therapy



Numbers at risk

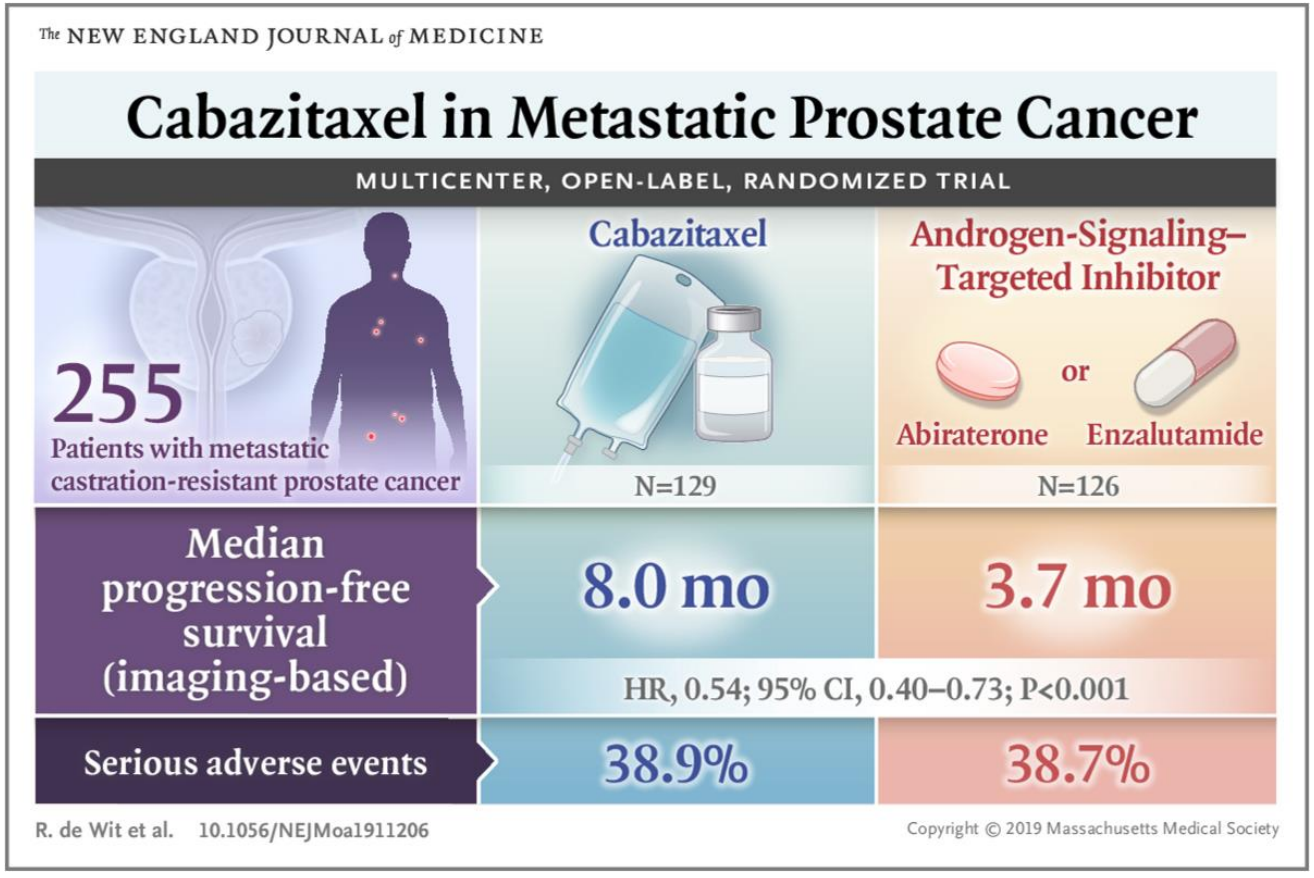
Abiraterone, abiraterone acetate	193	177	152	124	98	74	45	31	14	9	4	1	0
Cabazitaxel, cabazitaxel acetone	26	21	19	13	10	7	5	2	1	1	0	0	0
Docetaxel	45	39	28	21	17	13	9	4	4	4	3	1	1
Enzalutamide	97	86	73	62	53	43	31	19	12	3	3	0	0

Radium-223 was excluded from survival curves due to the small number of patients who received it as first subsequent therapy.

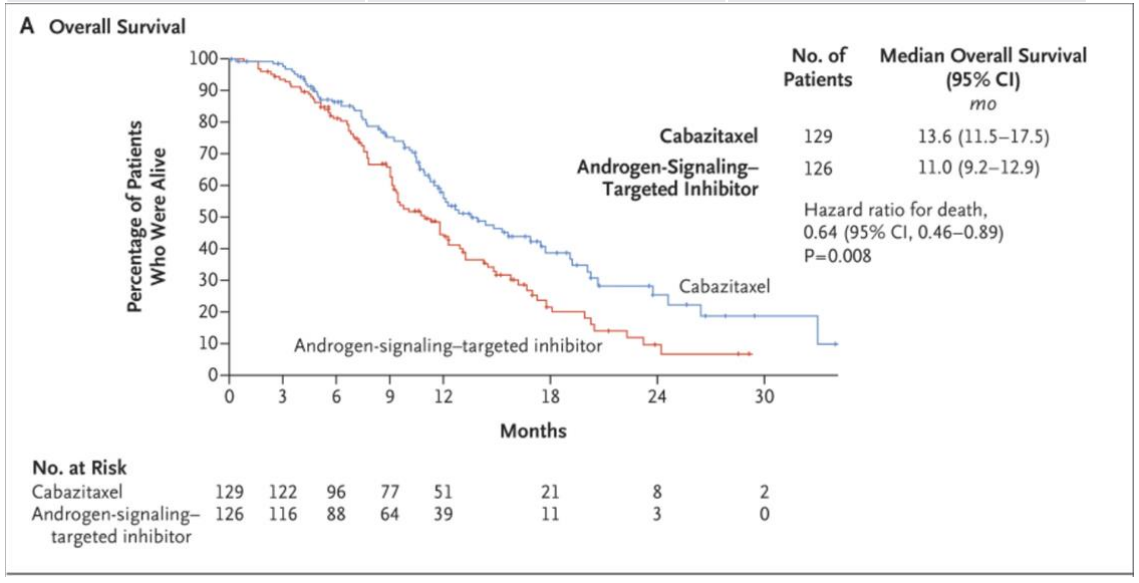
Marc-Oliver Grimm, ASCO 2024

NCT

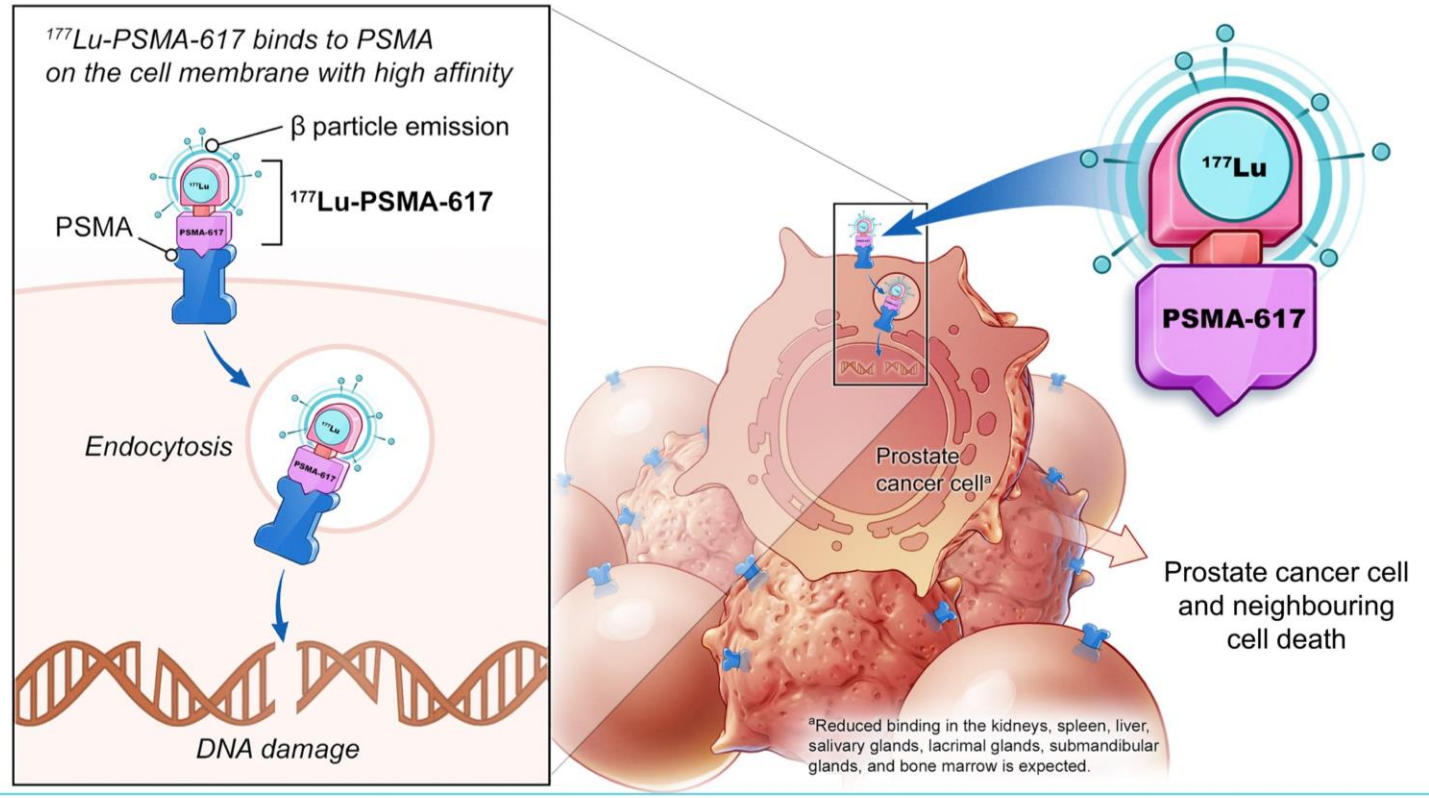
Therapie nach der Triplette? Cabazitaxel



Toxicities >/= Grade 3	Cabazitaxel	Abiraterone or Enzalutamide
All	71 (56.3)	65 (52.4)
Infection, n (%)	10 (7.9)	9 (7.3)
Febrile Neutropenia	4 (3.2)	0
Anemia	10 (8.0)	6 (4.8)
Neutropenia	55 (44.7)	4 (3.2)
Periphere Neuropathy, all grades	25 (19.8)	4 (3.2)

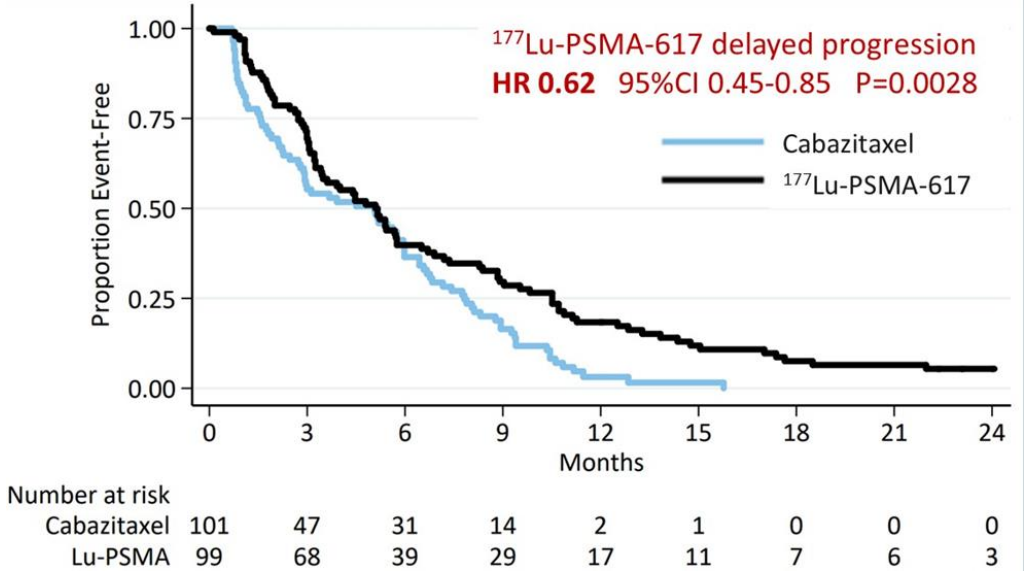


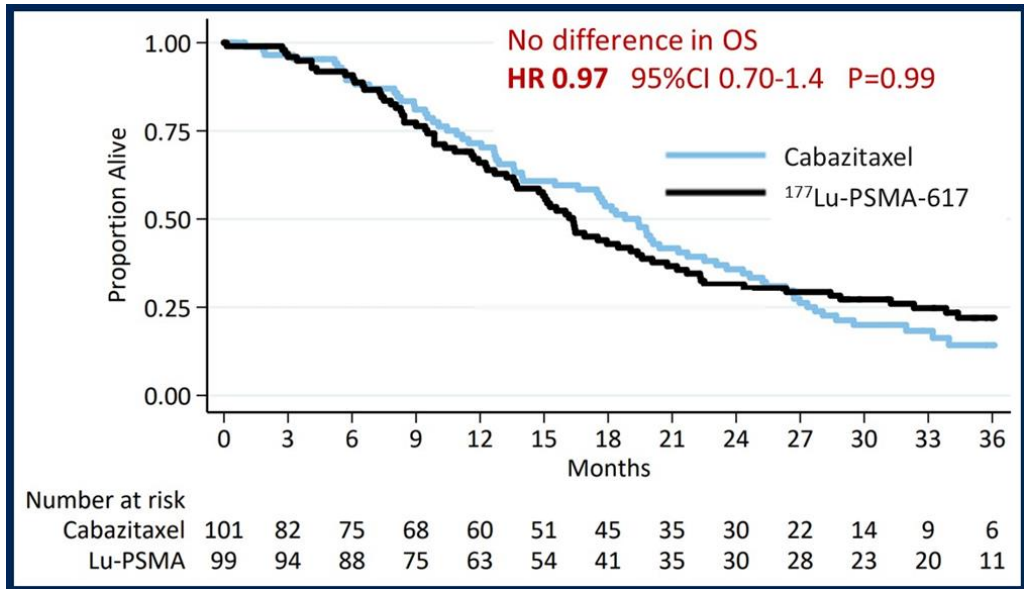
Therapie nach der Triplette?
^{177}Lu-PSMA-617 gerichtete Radioligandentherapie

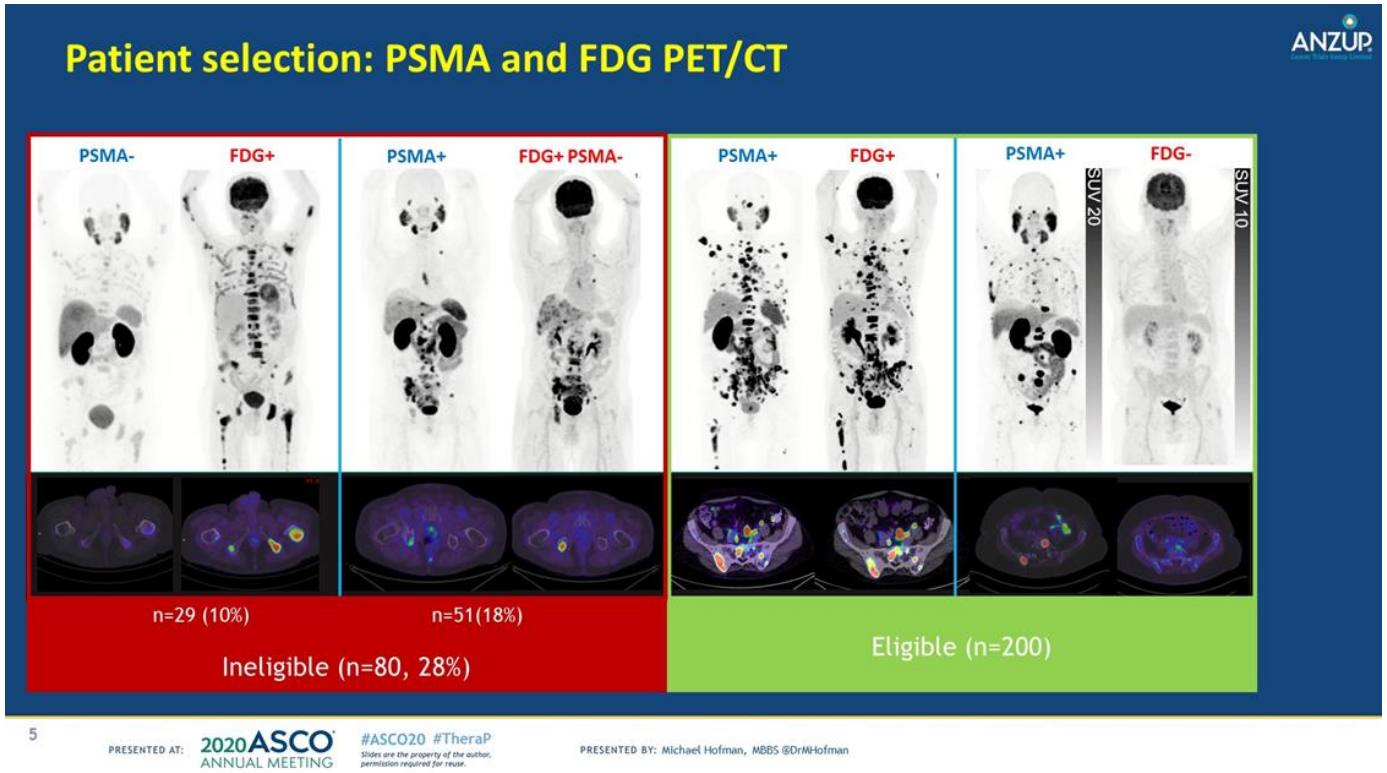


Michael Morris, ASCO 2021

Therapie nach der Triplette?





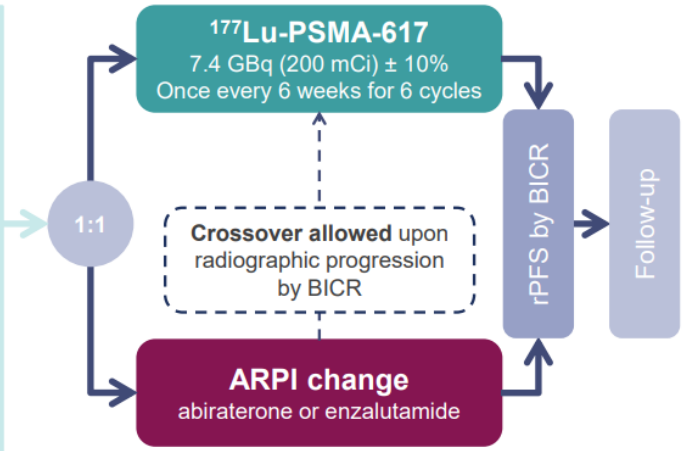


Hofman et al, ASCO 2022, Hofman et al, ASCO 2020, Sartor et al, NEJM, 2021

Ausblick: Lutetium-177-PSMA: PSMAfore

PSMAfore: a phase 3, randomized, open-label study

Eligible adults
- Confirmed progressive mCRPC
- ≥ 1 PSMA-positive metastatic lesion on [^{68}Ga]Ga-PSMA-11 PET/CT and no exclusionary PSMA-negative lesions
- Progressed once on prior second-generation ARPI
  - Candidates for change in ARPI
- Taxane-naive (except [neo]adjuvant > 12 months ago)
  - Not candidates for PARPi
- ECOG performance status 0–1



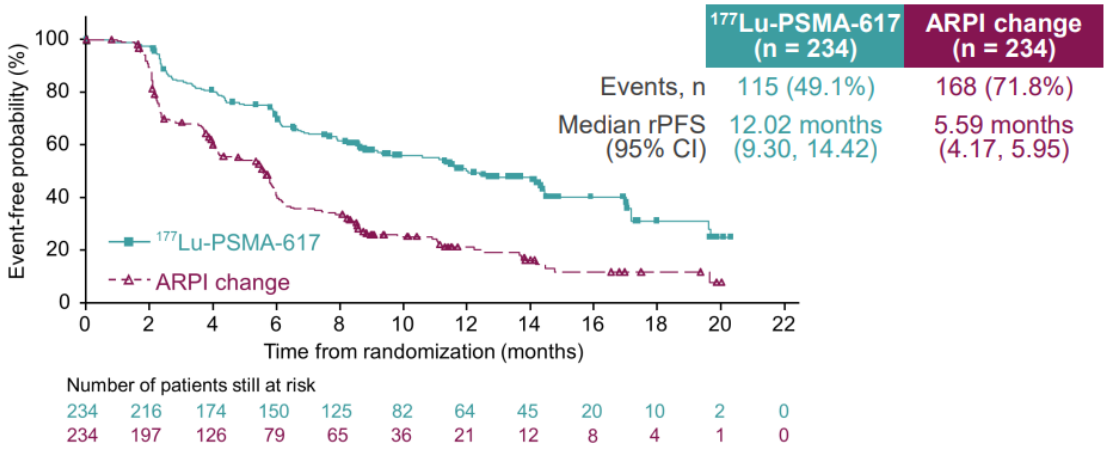
Stratification factors
- Prior ARPI setting (castration-resistant vs hormone-sensitive)
- BPI-SF worst pain intensity score (0–3 vs > 3)

MADRID 2023 ESMO congress

rPFS

Primary HR: 0.41 (95% CI: 0.29, 0.56); $p < 0.0001$

Updated HR: 0.43 (95% CI: 0.33, 0.54)



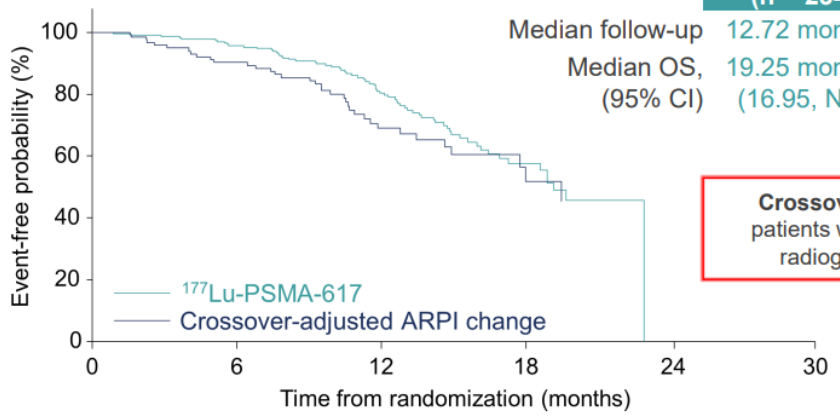
	^{177}Lu-PSMA-617 (n = 234)	ARPI change (n = 234)
Events, n	115 (49.1%)	168 (71.8%)
Median rPFS (95% CI)	12.02 months (9.30, 14.42)	5.59 months (4.17, 5.95)

Treatment-emergent adverse events

AEs, n (%)	^{177}Lu-PSMA-617 (n = 227)	ARPI change (n = 232)
Any	223 (98.2)	223 (96.1)
Grade 3–4	77 (33.9)	100 (43.1)
Serious	46 (20.3)	65 (28.0)
Treatment-related	7 (3.1)	5 (2.2)
Fatal (grade 5)	4 (1.8)	5 (2.2)
Treatment-related	0	1 (0.4)
Leading to dose adjustment	8 (3.5)	35 (15.1)
Leading to discontinuation	13 (5.7)	12 (5.2)

2nd interim OS: prespecified crossover-adjusted analysis

HR: 0.80 (95% CI: 0.48, 1.33)

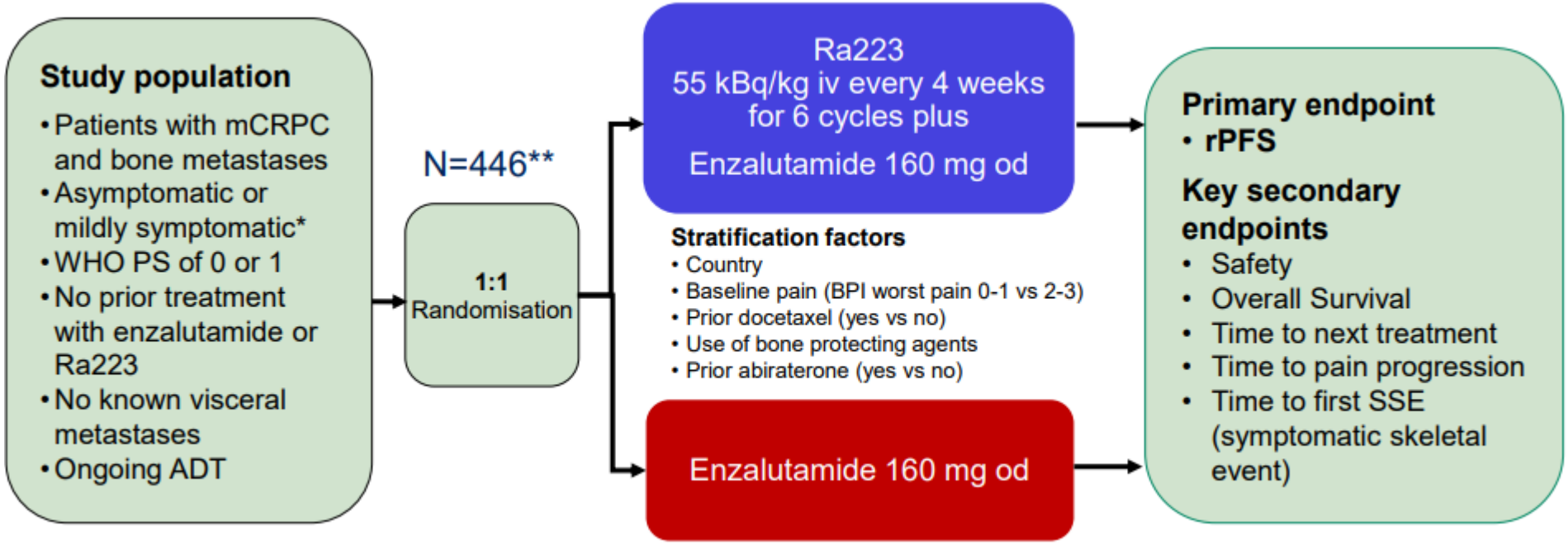


	^{177}Lu-PSMA-617 (n = 234)	ARPI change (n = 234)
Median follow-up	12.72 months	13.08 months
Median OS, (95% CI)	19.25 months (16.95, NE)	19.55 months (14.95, NE)

Crossover: 123/146 (84.2%) patients who discontinued with radiographic progression

Oliver Sartor, ESMO 2023

Ausblick Radium-223 (PEACE3) - Studiendesign



*defined as brief pain inventory WP24 score < 4
** original target accrual N=560, adapted for slow accrual

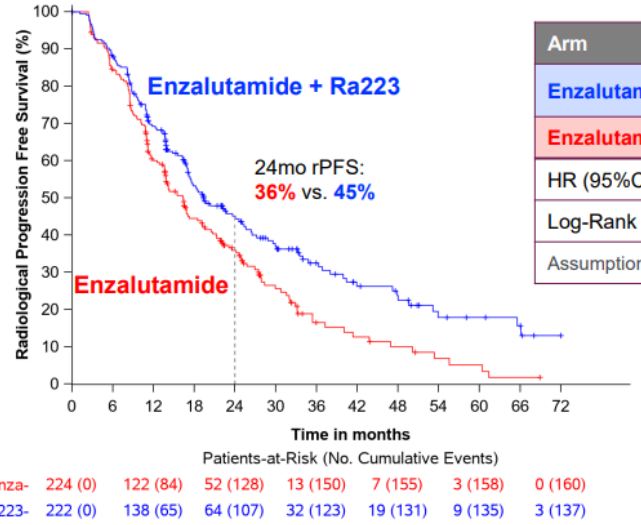
Radium-223 dichloride (Ra223)

- Alpha particle-emittierendes Calciummimetikum
- Wirkt an Knochenmetastasen
- Induziert Doppelstrangbrüche der DNA

NCT

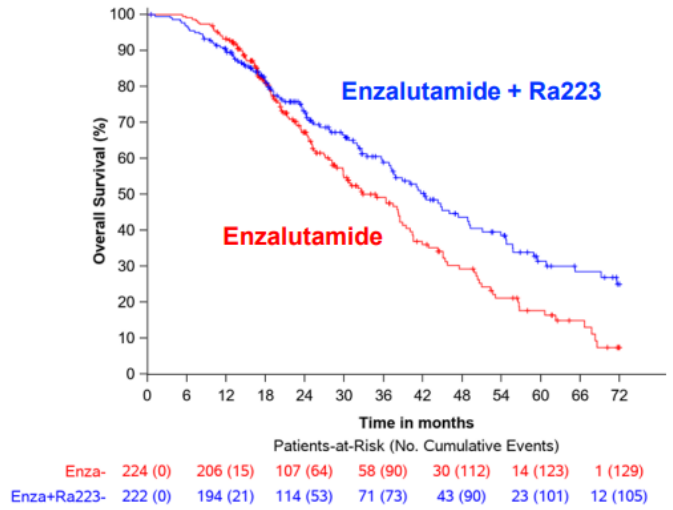
Ausblick Radium-223 (PEACE3) - Überleben

Primary endpoint: rPFS



Arm	n/N	Median (95%CI)
Enzalutamide + Ra223	139/222	**19.4** (17.1-25.3) mo
Enzalutamide	160/224	**16.4** (13.8-19.2) mo
HR (95%CI)	**0.69** (0.54-0.87)	
Log-Rank p-value	**0.0009**	
Assumption of proportional hazard achieved		

Overall Survival at interim analysis (80% of OS events)



Arm	n/N	Median (95%CI)
Enzalutamide + Ra223	110/222	**42.3** (36.8-49.1) mo
Enzalutamide	129/224	**35.0** (28.8-38.9) mo
HR (95%CI)	**0.69** (0.52-0.90)	
Log-Rank p-value	**0.0031**	<0.0034

- Pre-set level of significance for interim analysis was ≤ 0.0034
- Due to non-proportional hazards plus lack of unequivocal significance for RMST (restricted mean survival time) sensitivity analysis, study will continue to final OS analysis

Ausblick Radium 3 (PEACE3) - Toxizität

Patients	Enza+Ra223 (N=218)	Enza (N=224)
	N (%)	N (%)
Adverse events (AEs)	218 (100)	216 (96)
Drug-related AEs	183 (84)	158 (71)
Serious AEs	93 (43)	66 (30)
Serious drug-related AEs	18 (8)	3 (1)
Grade 3-5 AEs	143 (66)	125 (56)
Grade 3-5 drug-related AEs	61 (28)	42 (19)
Death due to AE	7 (3)	4 (2)
Death due to a drug-related AE	0	0
Treatment discontinuation due to toxicity		
Enzalutamide	13 (8)	12 (7)
RA223	7 (3)	

… but actually this is at least a Quadruplet !

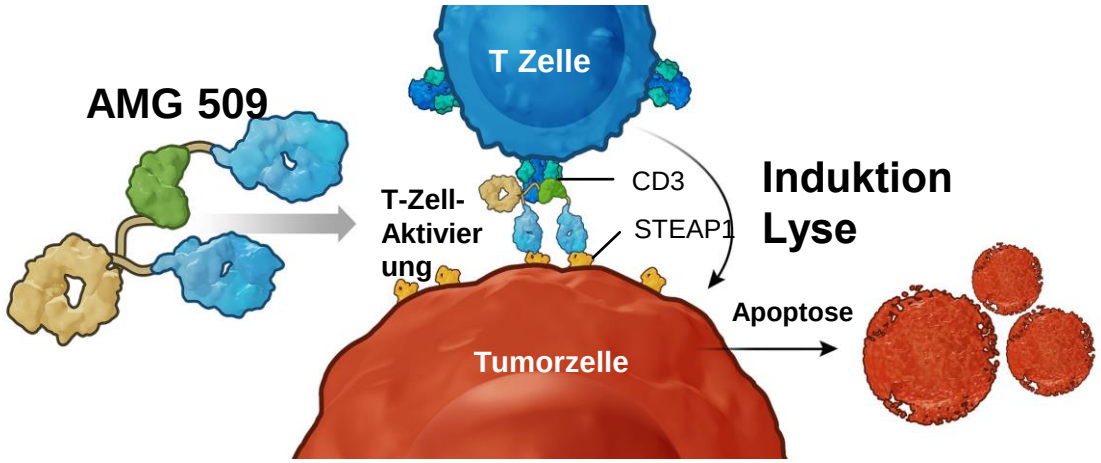
- Enzalutamide
- Radium-223
- Denosumab (or ZA)
- Androgen Deprivation Therapy
- +/- an anti-HTA treatment

Mehr Hämatotoxizität, Fatigue, Frakturen im experimentellen Arm

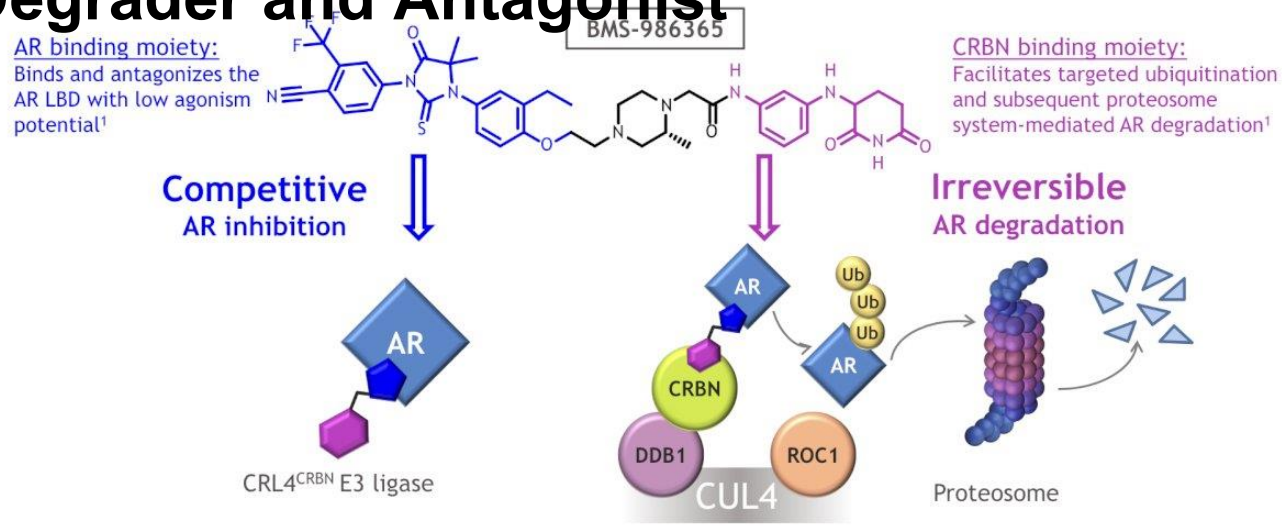
Silke Gillessen, 2024; Karim Fizazi 2024

NCT

Xaluritamig: STEAP1-gerichteter T-cell Engager

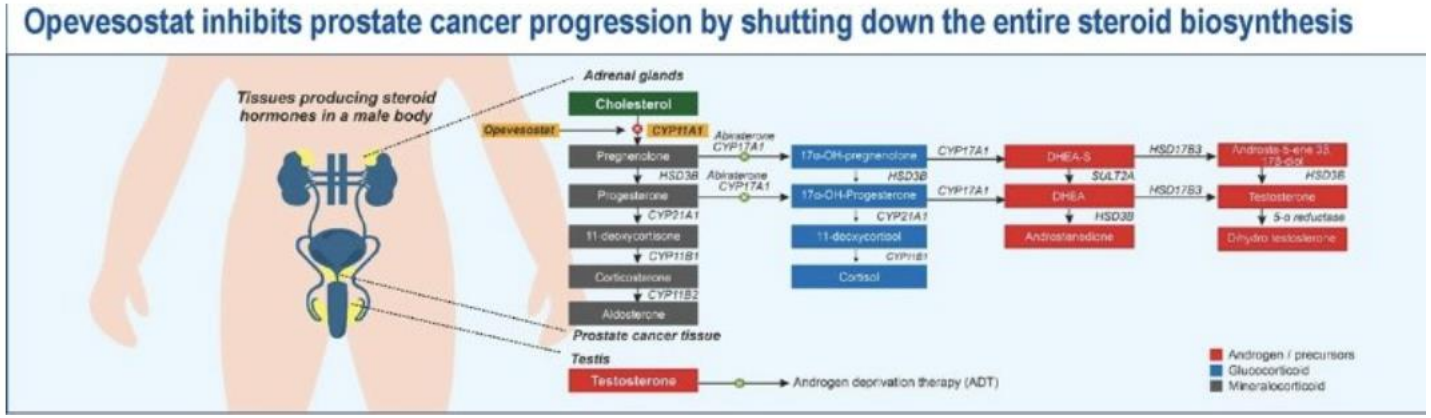


BMS-986365: Dual AR-Ligand-Directed Degrader and Antagonist



Was kommt sonst noch? (Auswahl)

Opevesostat: Cyp11A1-inhibitor



Nolan-Stevaux, American Association for Cancer Research Virtual Annual Meeting I; April 27-28, 2020.; Karim Fizazi ESMO 2024, Dana Rathkopf, ESMO 2024

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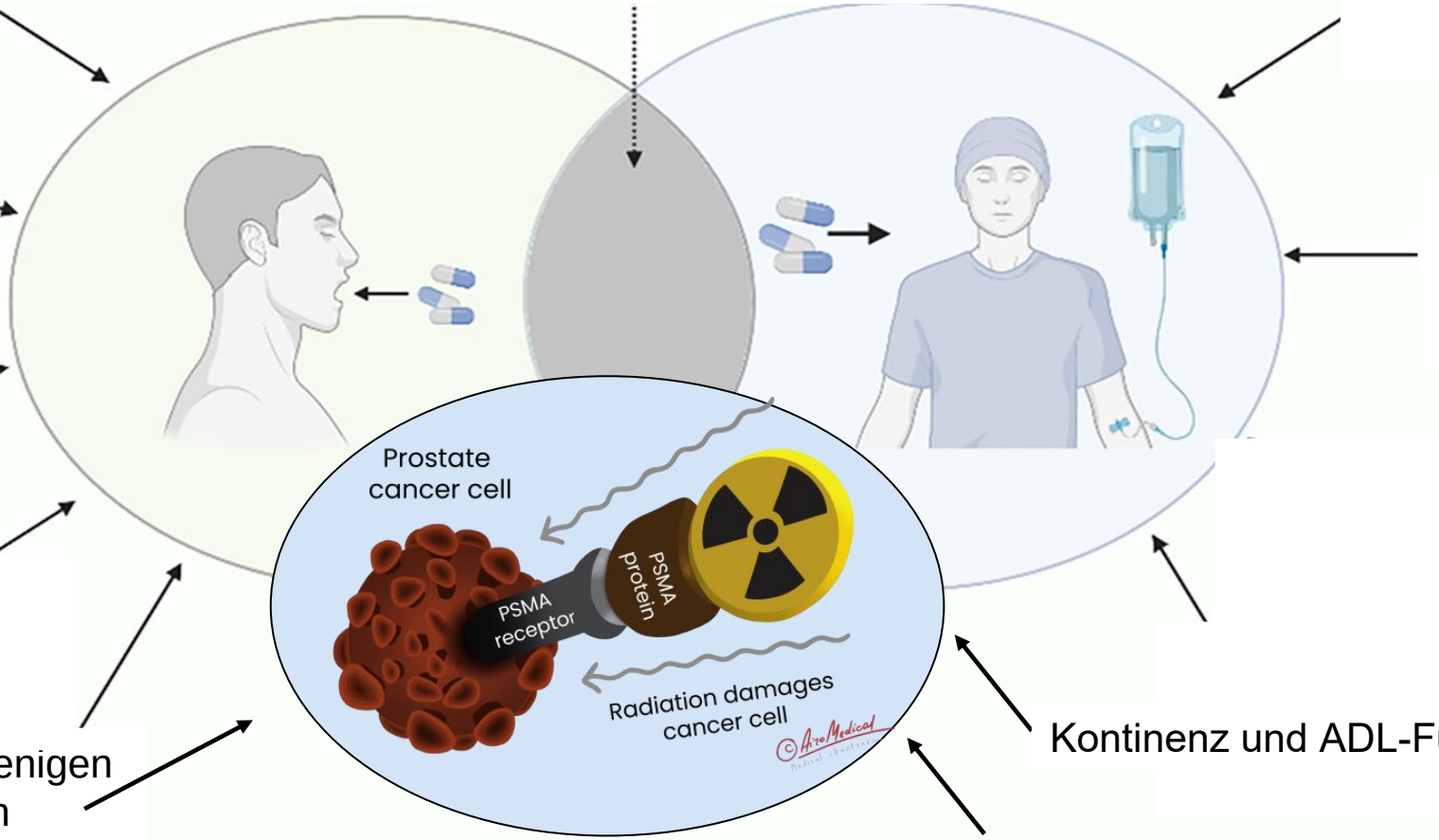
Zusammenfassung

Vorbehandlung im mHSPC

- Undifferenziertes Karzinom
- Transdifferenziertes Karzinom
- Gleason Score
- Low PSA bei hoher Tumorlast

Neuropathy

Poor performance status (ECOG > 1)



Patientenpräferenz

BRCA1/2-Mutation, HRR-Mutation

Wunsch nach wenigen vor Ort-Terminen

Kontinenz und ADL-Funktion

PSMA-Expression

- Zulassungsstatus und Verfügbarkeit
- Studienoption

When Would You Use Doublet Therapy and Not Triplet Therapy for a Patient With Newly Diagnosed mHSPC? (ascopubs.org), abgerufen 29.06.2024

Vielen Dank für die Aufmerksamkeit!

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NATIONAL CENTER FOR TUMOR DISEASES HEIDELBERG

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