Offenlegung Interessenskonflikte

1. Anstellungsverhältnis oder Führungsposition

Programdirektor GU , klin. Abt.f.Onkologie Graz, Koordinator CCC-Outreach

2. Beratungs- bzw. Gutachtertätigkeit

Janssen-Cilag, Astellas, BMS, Merk, MSD, AstraZeneca, Ipsen, Bayer

3. Besitz von Geschäftsanteilen, Aktien oder Fonds

nein

4. Patent, Urheberrecht, Verkaufslizenz

nein

5. Honorare

Janssen,-Cilag Astellas, BMS, MSD, Merk, AstraZeneca, ESAI, Ipsen, Bayer, Novartis

6. Finanzierung wissenschaftlicher Untersuchungen

AstraZeneca, Ipsen

7. Andere finanzielle Beziehungen

nein

8. Immaterielle Interessenkonflikte

nein

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www.jahrestagung-haematologie-onkologie.com

2023
13.–16. Okt.
Hamburg

Oligometastasiertes mHSPC: Abstimmung von Lokaltherapie und Systemtherapie

Thomas Bauernhofer

Med Uni Graz

URO-ONKO ARBEITSGRUPPE

Onkologie Graz

COMPREHENSIVE CANCER CENTER Krebszentrum GRAZ

Fortbildung: Das metastasierte hormonsensitive Prostatakarzinom (mHSPC): 14.10.2023, Hamburg

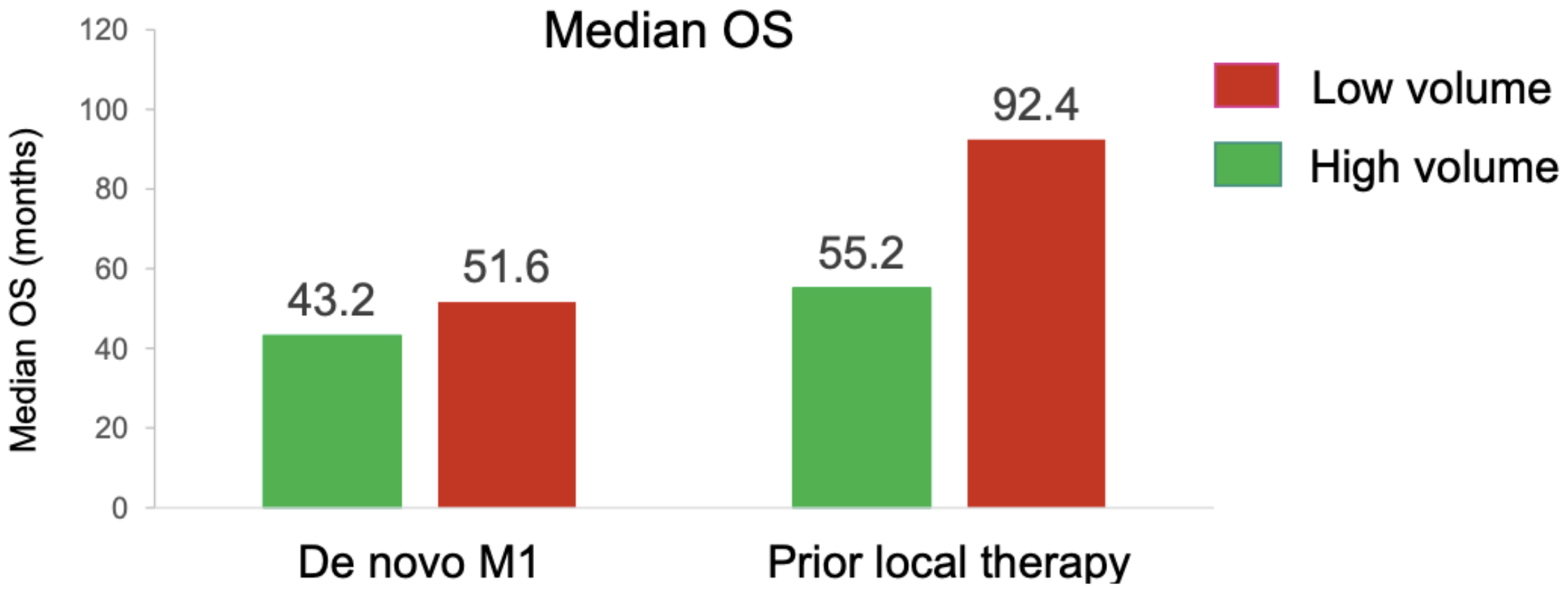
Definitionen

Definitionen für die Kategorisierung des mHSPC

	High	Low
CHAARTED (volume)	≥ 4 Bone metastasis including ≥ 1 outside vertebral column or pelvis **OR/AND** Visceral metastasis	Not high **Sweeney C et al. NEJM 2015**
LATITUDE (risk)	≥ 2 high risk features of • ≥ 3 Bone metastasis • Visceral metastasis • ≥ ISUP grade 4	Not high **Fizazi K et al. NEJM 2017**

- **Oligometastatische Erkrankung** noch nicht ganz klar definiert
- Entweder mit Next Generation- oder konventioneller Bildgebung definiert
- Fällt zumeist in die Kategorie low volume of disease

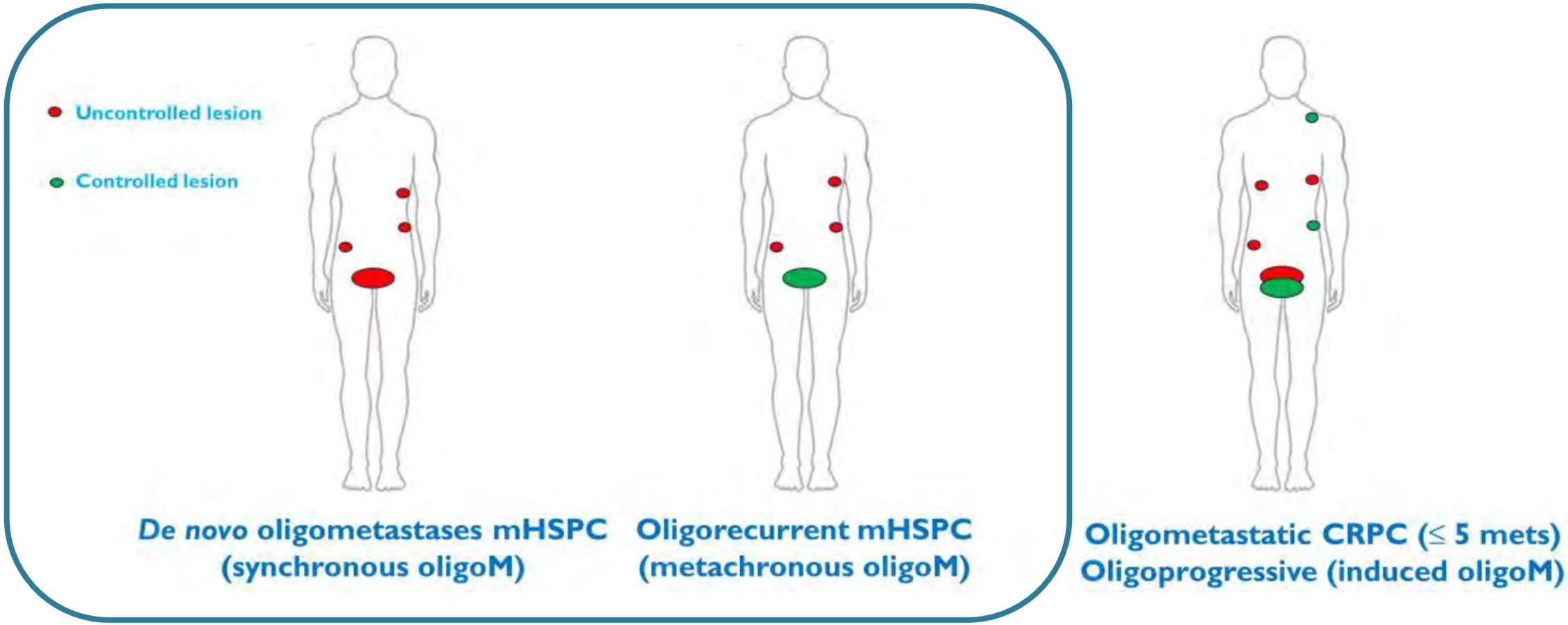
De novo mHNPC hat eine schlechtere Prognose



Retrospective analysis of 436 consecutive patients with M1 HSPC treated with ADT between 1990 and 2013 at the Dana-Farber Institute

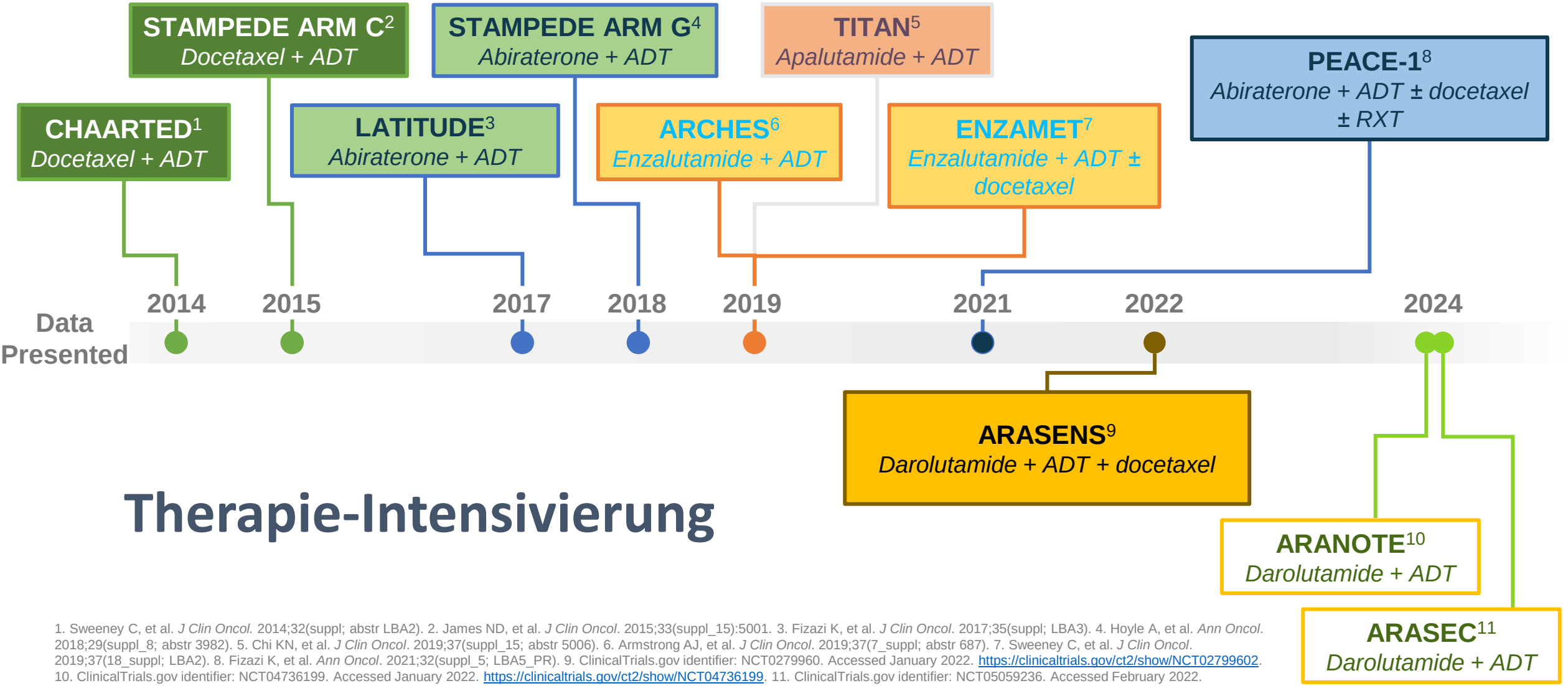
Francini E, et al. The Prostate 2018;78:889-95.

Definition: Oligometastatisches mPC



Systemtherapie des mHSPC

Die Standardtherapie von Patienten mit mHSPC hat sich entwickelt! Kombinationen ADT mit ARSIs und/oder Docetaxel



Therapie-Intensivierung

1. Sweeney C, et al. *J Clin Oncol.* 2014;32(suppl; abstr LBA2). 2. James ND, et al. *J Clin Oncol*. 2015;33(suppl_15):5001. 3. Fizazi K, et al. *J Clin Oncol*. 2017;35(suppl; LBA3). 4. Hoyle A, et al. *Ann Oncol*. 2018;29(suppl_8; abstr 3982). 5. Chi KN, et al. *J Clin Oncol*. 2019;37(suppl_15; abstr 5006). 6. Armstrong AJ, et al. *J Clin Oncol*. 2019;37(7_suppl; abstr 687). 7. Sweeney C, et al. *J Clin Oncol*. 2019;37(18_suppl; LBA2). 8. Fizazi K, et al. *Ann Oncol*. 2021;32(suppl_5; LBA5_PR). 9. ClinicalTrials.gov identifier: NCT0279960. Accessed January 2022. https://clinicaltrials.gov/ct2/show/NCT02799602. 10. ClinicalTrials.gov identifier: NCT04736199. Accessed January 2022. https://clinicaltrials.gov/ct2/show/NCT04736199. 11. ClinicalTrials.gov identifier: NCT05059236. Accessed February 2022. https://clinicaltrials.gov/ct2/show/NCT05059236. 12. Sweeney C, et al. *N Engl J Med.* 2015;373(8):737-746. 13. Fizazi K, et al. *N Engl J Med*. 2017;377(4): 352-360. 14. Armstrong A, et al. *J Clin Oncol*. 2019;37(32):2974-2986. 15. Karantanos T, et al. *Oncogene*. 2013;32(49):5501-5511.

Kombination ist wichtig - Phase III Doublet Trials bei mHSPC

Study	Agents	N	*De novo* M1	Median FU*	HR	Median OS*	Δ OS*
CHAARTED[1]	DOC vs ADT	790	**76%**	53.7	**0.72**	57.6 vs 47.2	10.4
STAMPEDE[2]	DOC/P vs ADT	1,086	**95%**	78.2	**0.81**	59.1 vs 43.1	16.0
GETUG 15[3]	DOC vs ADT	385	**71%**	83.9	**0.88**	62.1 vs 48.6	13.5
LATITUDE[4]	ABI/P vs ADT	1,199	**100%**	51.8	**0.66**	53.3 vs 36.5	16.8
STAMPEDE[5]	ABI/P vs ADT	1,002	**94%**	40.0	**0.61**	NR	NR
TITAN[6]	APA vs ADT	1,052	**81%**	22.7	**0.67**	NR	NR
ENZAMET[7]	ENZA vs ADT	1,125	**61%**	34.0	**0.67**	NR	NR
ARCHES[8]	ENZA vs ADT	1,150	**67%**	14.4	**0.81**	NR	NR

ABI: abiraterone; ADT: androgen deprivation therapy; APA: apalutamide; DOC: docetaxel; ENZA: enzalutamide; FU: follow-up; HR: hazard ratio; M1 HSPC: metastatic hormone-sensitive prostate cancer; NR: not reached; OS: overall survival; P: prednisone

1. Kyirakopoulos CE, et al. *J Clin Oncol.* 2018;36:1080-7; 2. Clarke N, et al. *Ann Oncol.* 2019;30:1992-2003; 3. Gravis G, et al. *Eur Urol.* 2016;70:256-62; 4. Fizazi K, et al. *Lancet Oncol.* 2019;20:686-700; 5. James ND, et al. *N Engl J Med*. 2017;377:338-51; 6. Chi KN, et al. *N Engl J Med.* 2019;381:13-24; 7. Davis ID, et al. *N Engl J Med.* 2019;381:121-31; 8. Armstrong A, et al. *J Clin Oncol.* 2019;37:2974-86.

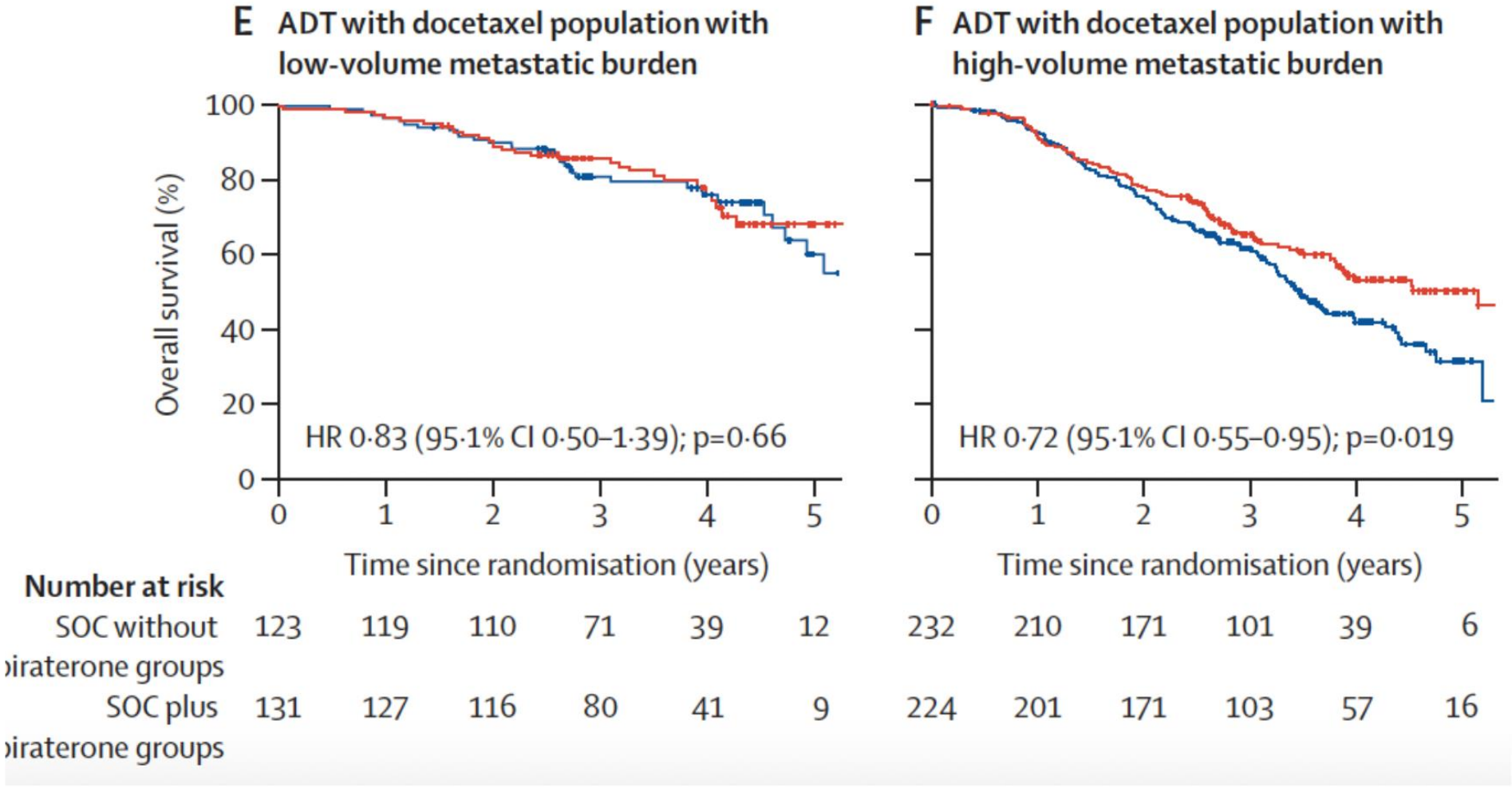
Arches Trial: Post hoc Analyse: Oligo- versus polymetastatische Erkrankung

Endpoint, HR (95% CI)[b]	1 (n = 53[c]; n = 44[d])	≤2 (n = 87[c]; n = 76[d])	≤3 (n = 120[c]; n = 103[d])	≤4 (n = 142[c]; n = 117[d])	≤5 (n = 160[c]; n = 136[d])	≥6 (n = 107[c]; n = 109[d])
rPFS[e]	0.17 (0.02, 1.48)	0.24 (0.07, 0.87)	0.21 (0.08, 0.56)	0.16 (0.06, 0.42)	0.22 (0.10, 0.47)	0.35 (0.22, 0.57)
Time to PSA progression	0.14 (0.03, 0.63)	0.09 (0.02, 0.40)	0.16 (0.06, 0.41)	0.12 (0.05, 0.31)	0.11 (0.04, 0.28)	0.13 (0.06, 0.27)
Time to castration resistance	0.13 (0.03, 0.60)	0.15 (0.05, 0.44)	0.17 (0.07, 0.38)	0.15 (0.07, 0.33)	0.17 (0.09, 0.34)	0.27 (0.17, 0.43)
Time to initiation of new antineoplastic therapy	0.40 (0.10, 1.60)	0.45 (0.16, 1.31)	0.40 (0.17, 0.94)	0.33 (0.14, 0.75)	0.29 (0.13, 0.66)	0.29 (0.16, 0.51)

[a]Oligometastatic mHSPC was defined as 1–≤5 bone metastases; polymetastatic mHSPC was defined as ≥6 bone metastases; [b]HR < 1 favors ENZA + ADT; HR > 1 favors PBO + ADT; [c]Number of patients in subgroup who received ENZA + ADT; [d]Number of patients in subgroup who received PBO + ADT; [e]Assessed by independent central review, or death, within 24 weeks of treatment discontinuation. CI = confidence interval; HR = hazard ratio; PSA = prostate-specific antigen.

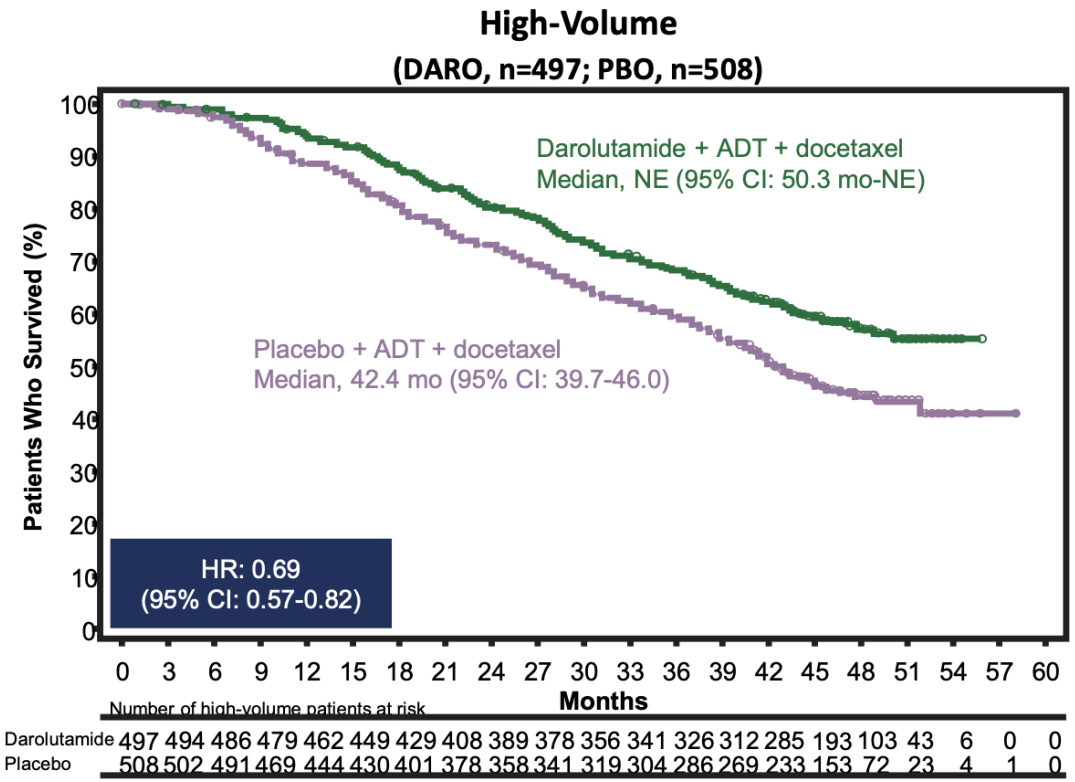
Amstrong AJ. et al. 2021 ASCO Annual Meeting J Clin Oncol 39, 2021 (suppl 15; abstr 5071)

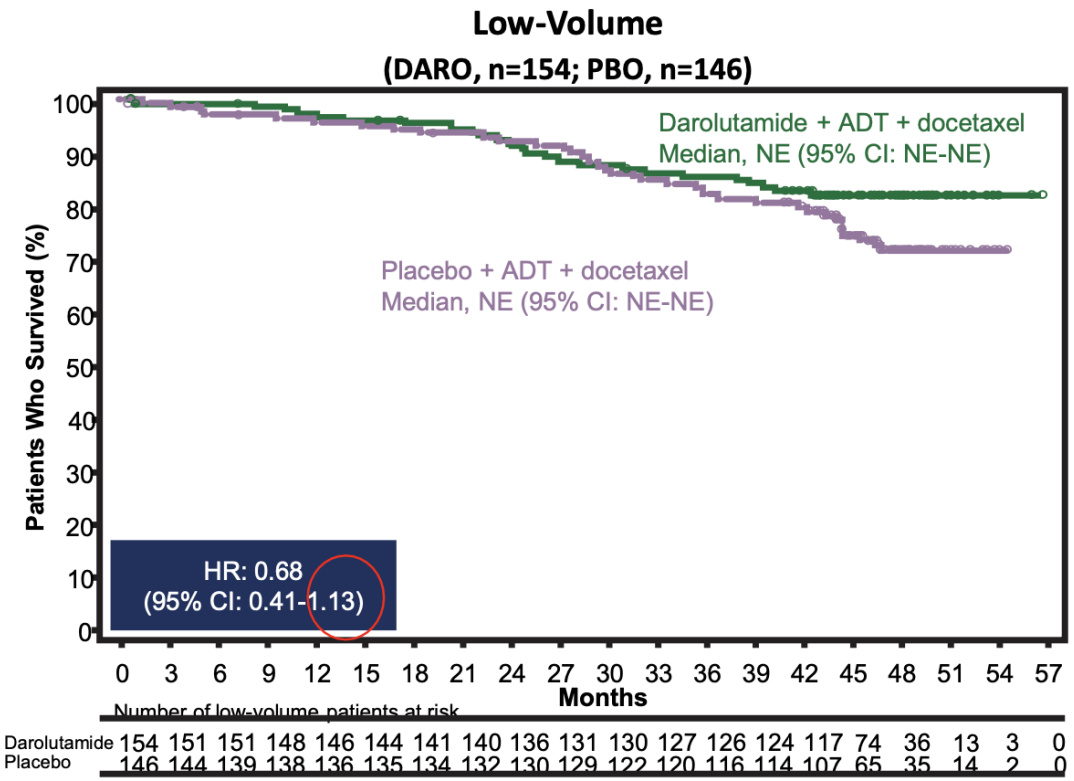
PEACE1: Tripel Therapie ADT+Docetaxel +/-AAP+/-RTX OS in high vs low volume disease



Fizazi K. et al. The Lancet Volume 399, ISSUE 10336, P1695-1707, April 30, 2022

ARASENS: Tripel Therapie ADT +Doce +/- Dara OS in high vs low volume disease





- In the smaller low-volume subgroup, the results were suggestive of a survival benefit

Hussain M, et al. *J Clin Oncol.* 2023. doi:10.1200/JCO.23.00041.

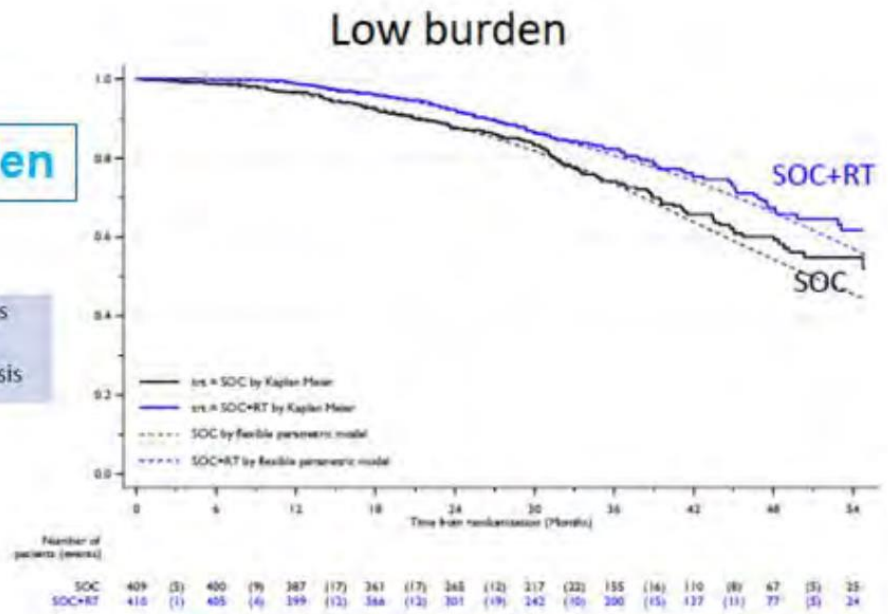
Radiatio der Prostata

bei de-novo mHSPC low volume

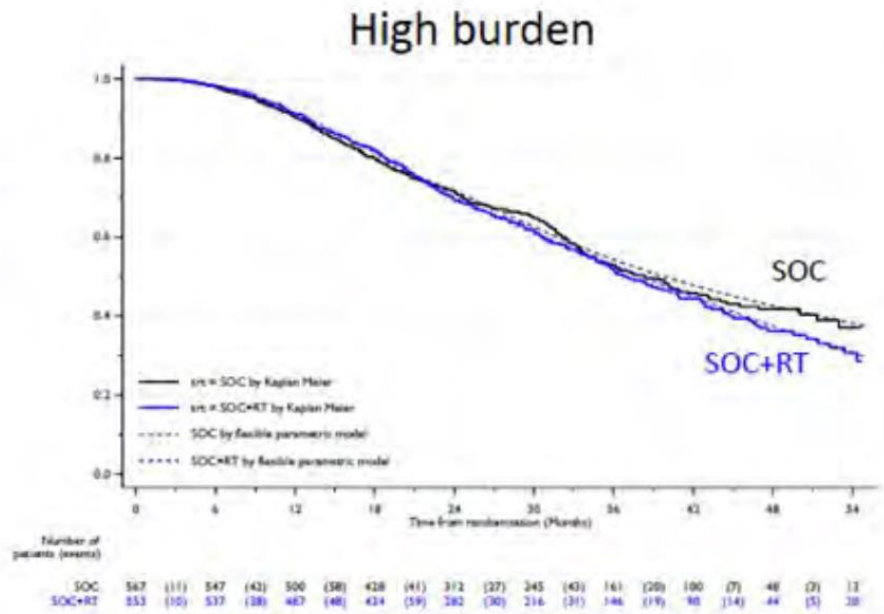
STAMPEDE ARM H: Radiotherapie der Prostata bei Patienten mit mHSPC

Low burden

<4 Bone metastasis
AND
No visceral metastasis



HR: 0.68 (95% CI 0.52-0.90); p=0.007
3 year OS (%): SOC = 73%
SOC+RT = 81%



HR: 1.07 (95% CI 0.90-1.28); p=0.420
3 year OS (%): SOC = 54%
SOC+RT = 53%

High burden

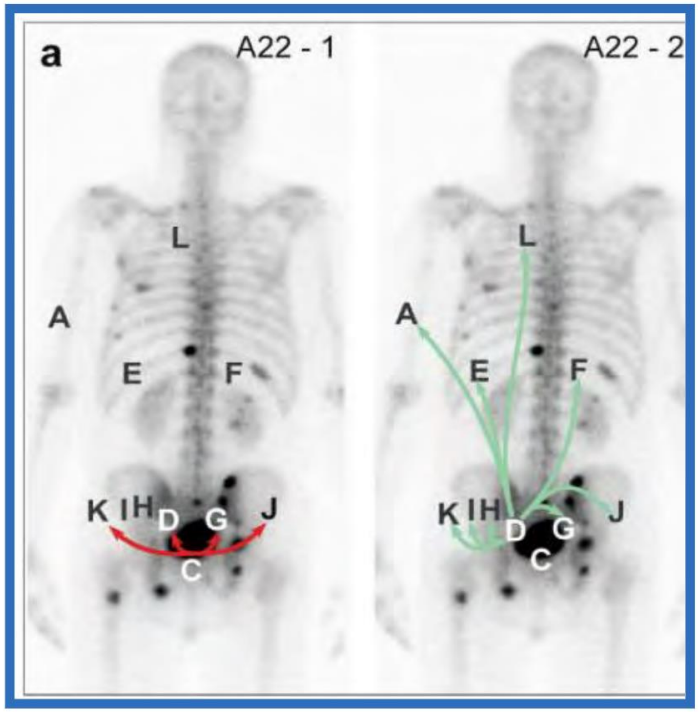
≥4 Bone metastasis
(≥1 outside vertebral column or spine)
OR
Visceral metastasis

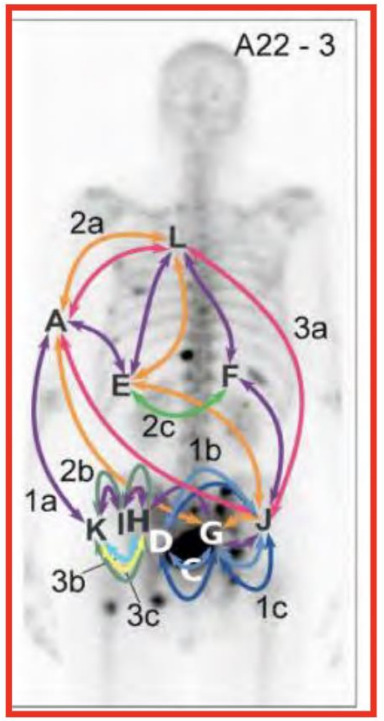
36Gy/6 fractions/6 weeks **or** 55Gy/20 fractions/4 weeks
Schedule nominated before randomisation

Parker CC *et al.* Lancet 2018

Behandeln wir den Primärtumor und die Metastasen?

PRIMARY TO METASTASES SEEDING





METASTASES TO METASTASES SEEDING

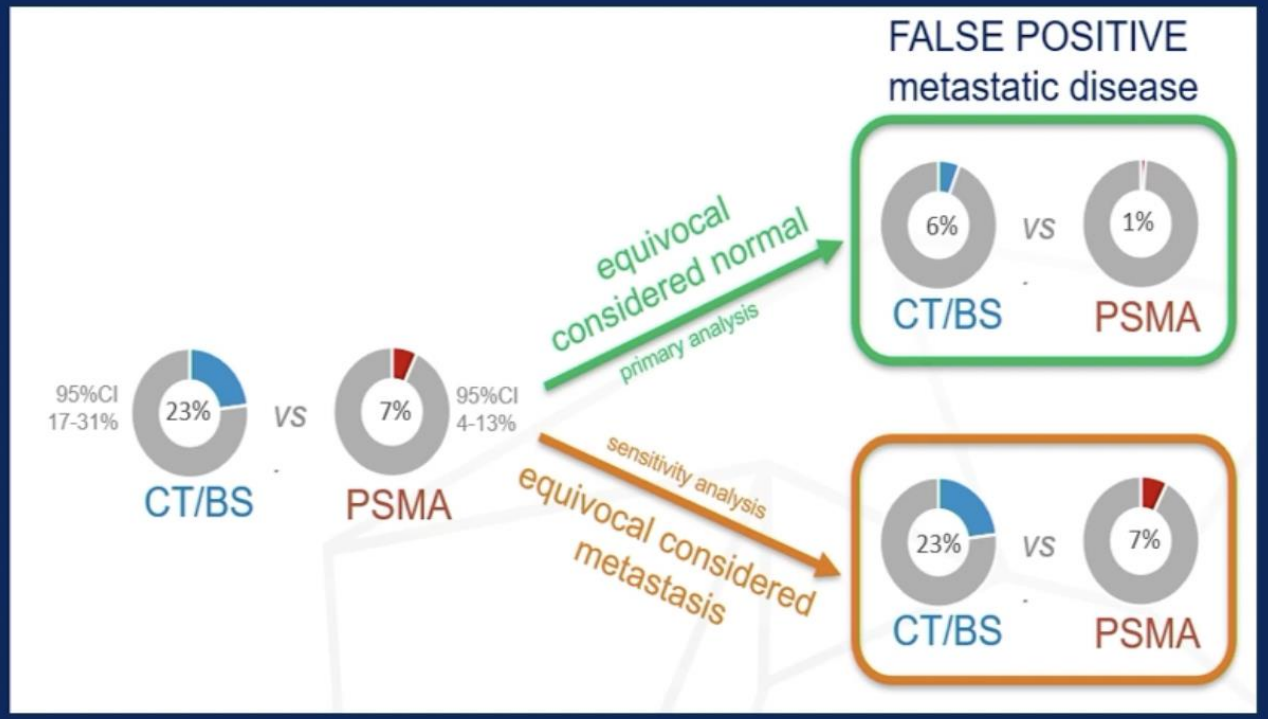
Gundem G *et al. Nature*. 2015

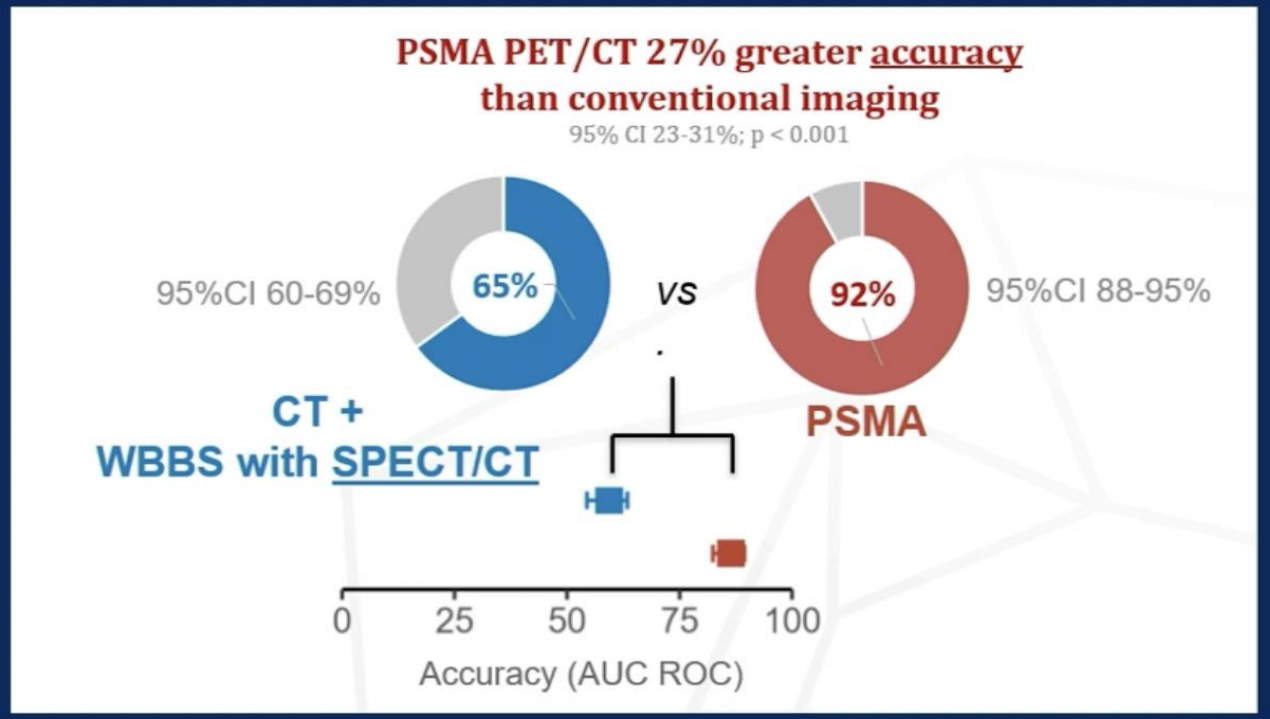
"Good news! The exploratory surgery turned up negative!"

Herausforderung: Bildgebung

Konventionelle Bildgebung versus PSMA-PET-CT

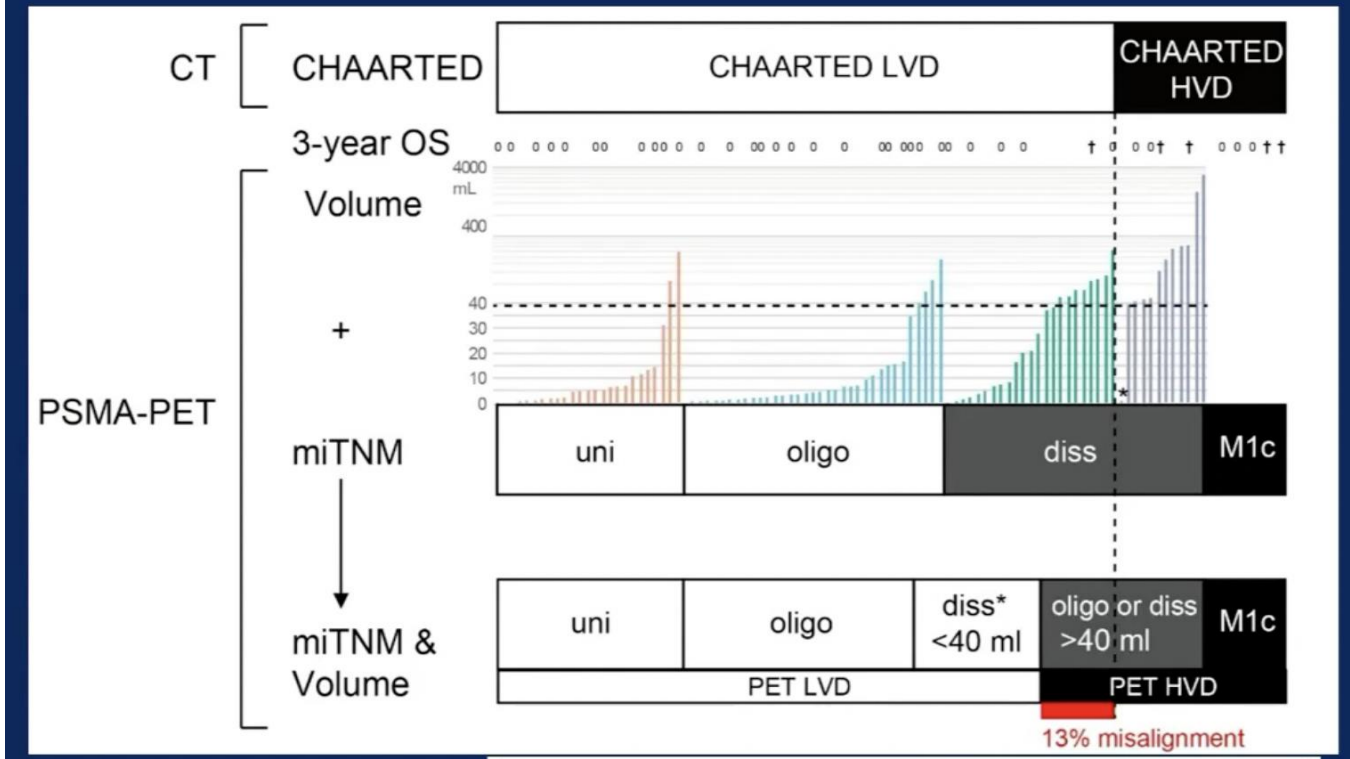
ProPSMA Studie – Randomisertes Staging Showdown



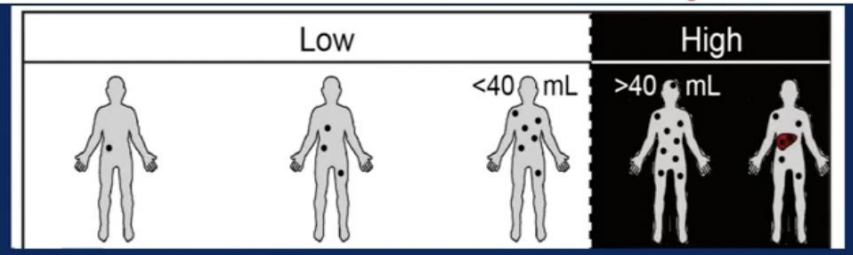


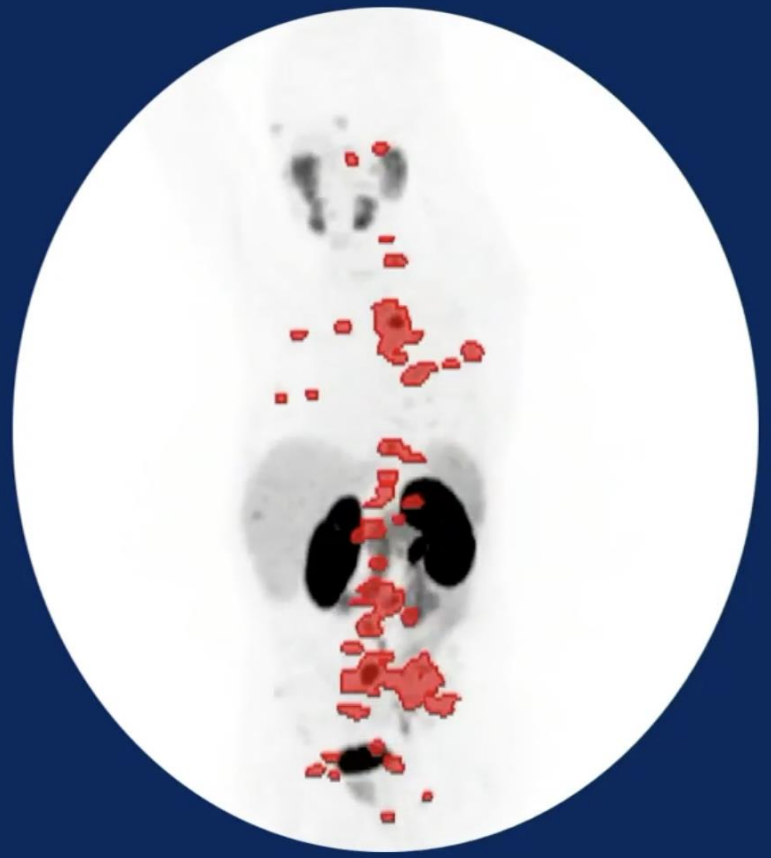
Hofman MS et al, Lancet 2020, Apr 11;395(10231)

mHSPC Volumen bestimmt mit PSMA-PET-CT



40mL the optimal cut-off between CT-based CHAARTED low vs. high burden disease



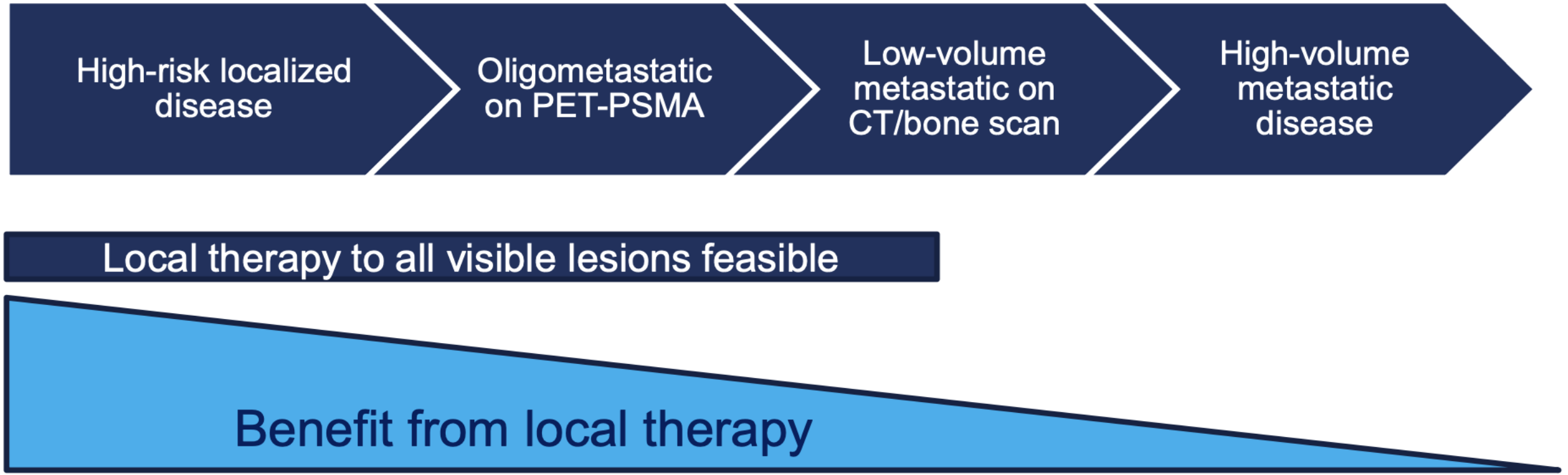


Barbato F et al JNM 2021 62(12))

Systemtherapie der Oligometastatischer Erkrankung

- **Synchron Oligometastasiertes mHSPC das auf Basis einer PSMA-PET** CT Untersuchung diagnostiziert wird, ist **möglicherweise in der konventionellen Bildgebung nicht detektierbar**
- **Up-Staging** von manchen Patienten mit **hoch-Risiko lokalisierter** Erkrankung **zu metastasierter** Erkrankung durch PSMA-PET-CT

Systemtherapie der Oligometastatischer Erkrankung



Systemtherapie von Oligometastatischer Erkrankung

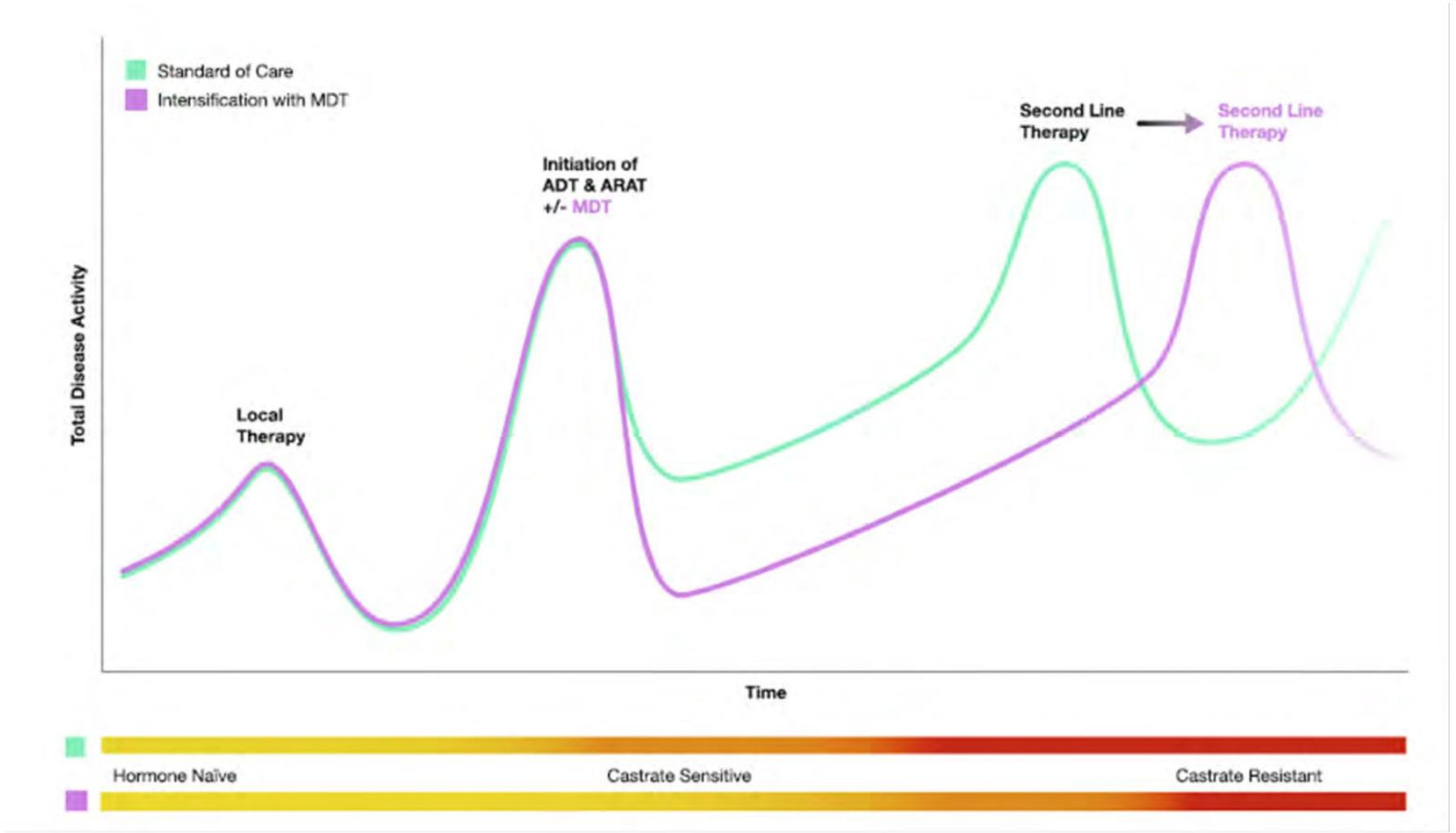
Indolente Biologie

- Männer, die ein sehr kleines Risiko haben, an mPC zu sterben
- Männer, die hohe Wahrscheinlichkeit haben, von einer lokalen Therapie zu profitieren
- Bei denen die Systemtherapie hinausgezögert oder de-eskaliert werden kann

Aggressive Biologie

- Früh im Krankheitsverlauf mit Next Generation Bildgebung entdeckt
- Männer, die eher von einer intensivierten Systemtherapie profitieren

Metastasen-zielgerichtete Therapie MDT



Kucharczyk MJ *et al. Radiother Oncol* 2020

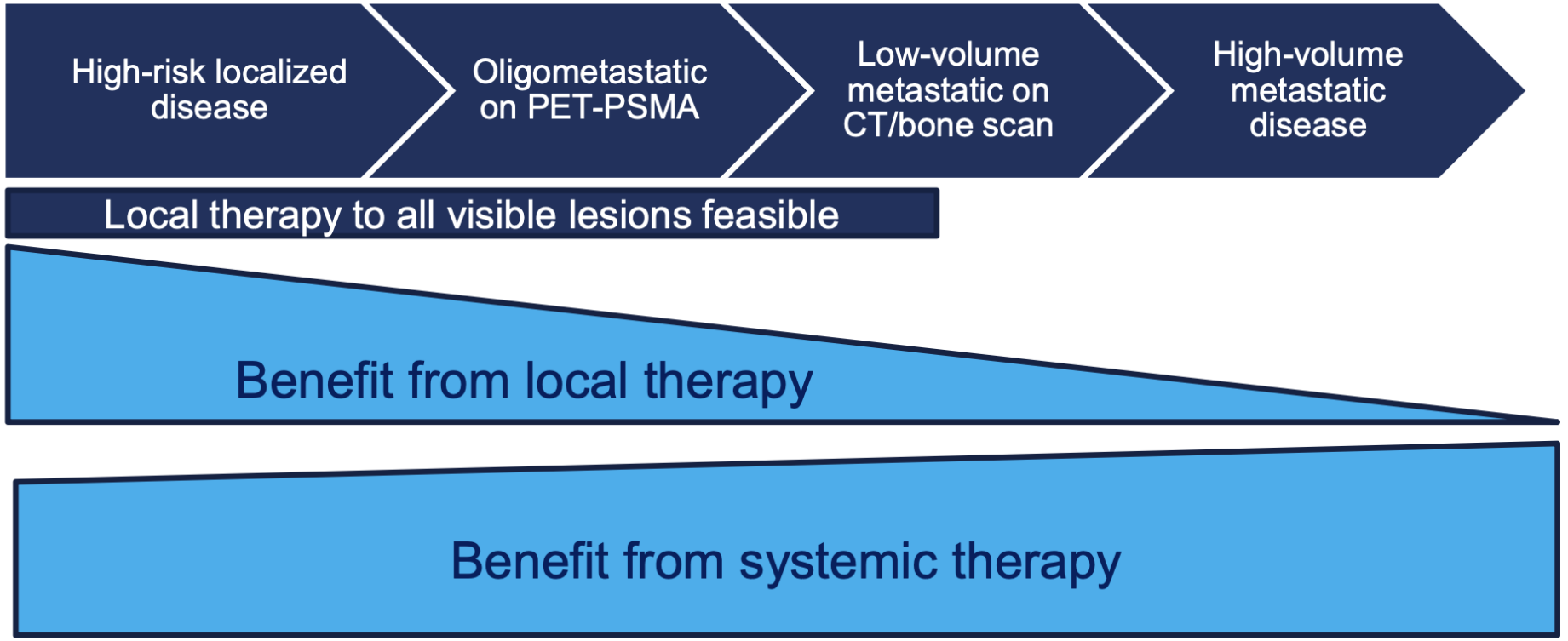
Fallpräsentation

- Patient, 77a
- ECOG 0
- DV assistierte RPE (17.08.2015)
  - Histo: Adenoca d. Prostata, pT3a, pN0 (0/13), L-0, V-0, Pn-1, R1, GS 7(4+3)
- Salvage RTX der Prostataloge bei biochem Rezidiv (3-4/2019)
- SBRT eines PSMA pos. Pelvinen Lymphknoten (03/2020)
- PSA Anstieg von (03/20) 3,7 auf (7/20) 5,43
- PSMA-PET 07/2020 zwei neue PSMA positive Lymphknoten pelvin Höhe L/3-4 SUV max 8,5 außerhalb des SBRT Bereichs , Knochenherd HWK3 unklar
- Bisher hormonnaive

Fallpräsentation

- mHSPC low volume, low risk (Gleason 7, M1a)
- Pat will keine neuerliche SBRT der neuen pelvinen Lymphknoten, wegen Verstärkung der Inkontinenz nach SBRT 3/20
- Einleitung **ADT mit Trenatone plus Apalutamid** 60mg 0-0-4 (8/20)
- **PSA-Abfall auf <0,01 10/20** im Sinne kompl. PSA-Response 6 Wochen nach Einleitung von ADT plus Apalutamid
- **PSMA PET CT 17.05.21 PSMA negativ** und radiologische CR
- Seither **anhaltende PSA-Response** <0,01 (zuletzt 9/23)

Systemtherapie von Oligometastatischer Erkrankung



Therapieoptionen bei de-novo Oligometastatischen mHSPC

STAMPEDE M0 (bone scan/CT): ADT 3a+24mo AAP +/- Enza

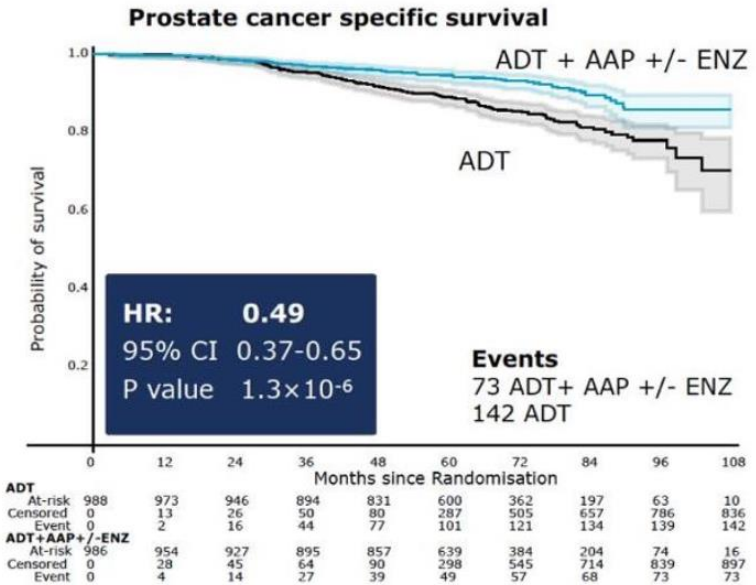
M0
No evidence of metastases on bone and CT scan of pelvis, abdo, chest
(pre-defined stratification criterion)

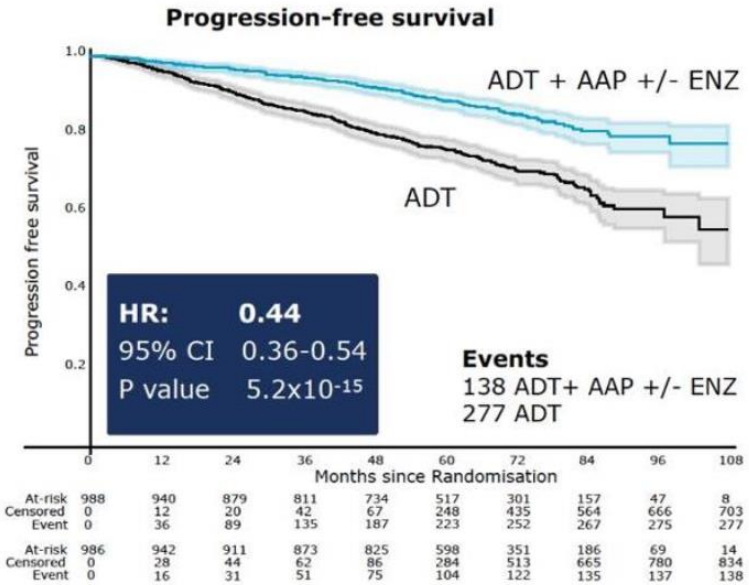
Newly-diagnosed
Any of:
- Node-Positive
- ≥2 of: Stage T3 or T4
  PSA≥40ng/ml
  Gleason 8, 9 or 10

Relapsing after previous RP or RT
Any of:
- Node-positive
- PSA≥4ng/ml, rising & doubling time <6m
- PSA≥20ng/ml

All patients
Written informed consent
Fit for all protocol treatment
Fit for follow-up

Full criteria: www.stampedetrial.org





6-year prostate cancer specific survival improved from 85% to 93%

6-year OS improved from 77% to 86%

Attard CC *et al.* Lancet 2021

Therapieoptionen bei de-novo Oligometastatischen mHSPC

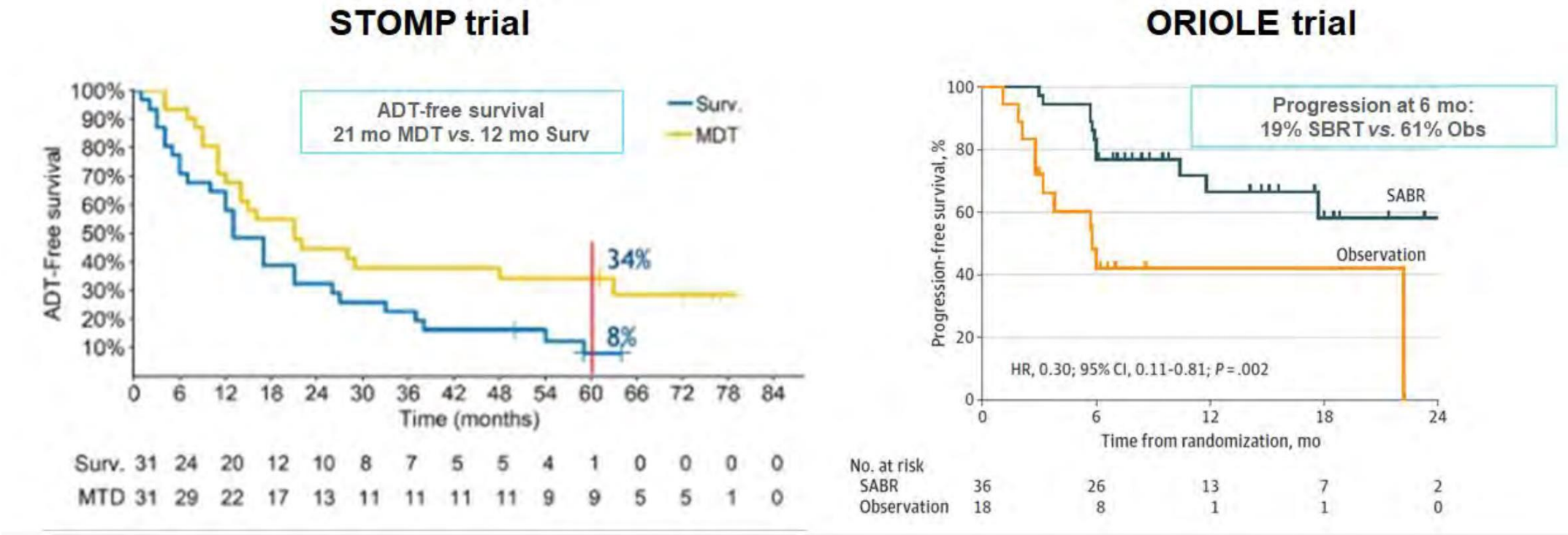
STAMPEDE M0: ADT + AAP

STAMPEDE M1: AAP/docetaxel
LATTITUDE: AAP
CHAARTED: docetaxel
ENZAMET/ARCHES: ENZA
TITAN: APA
PEACE-1: docetaxel + AAP
ARASENS: docetaxel +DARO

Metachrones Oligometastatisches mHSPC

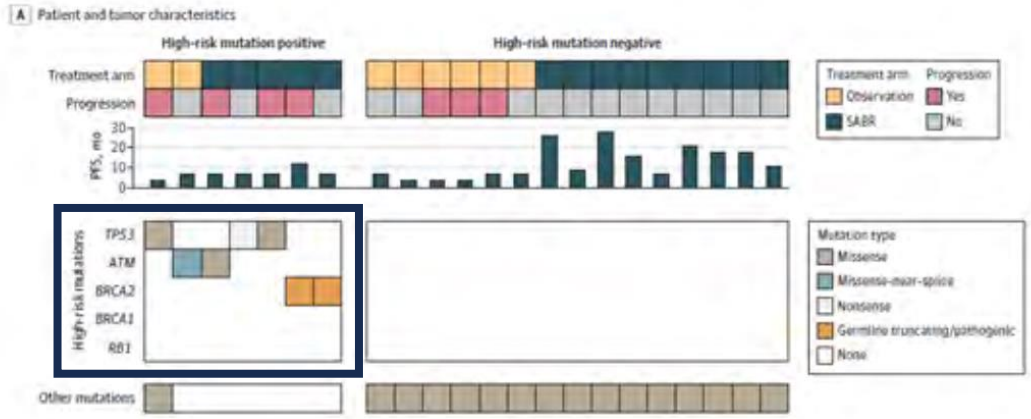
Metastasen-zielgerichtete Therapie mit SBRT

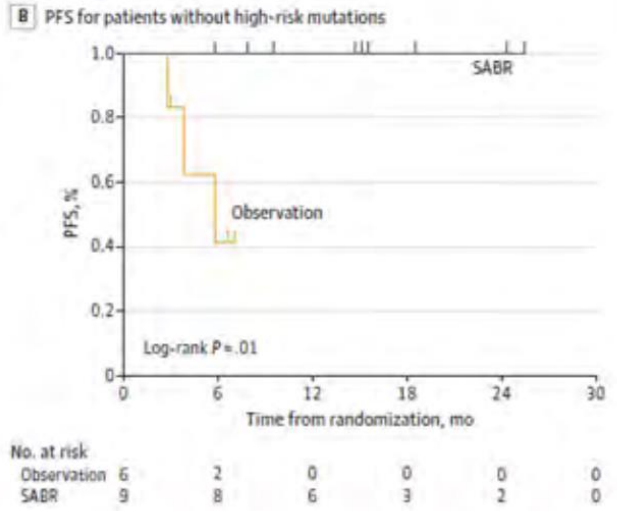
Metachrones oligometastatisches Rezidiv: MDT vs. Observation

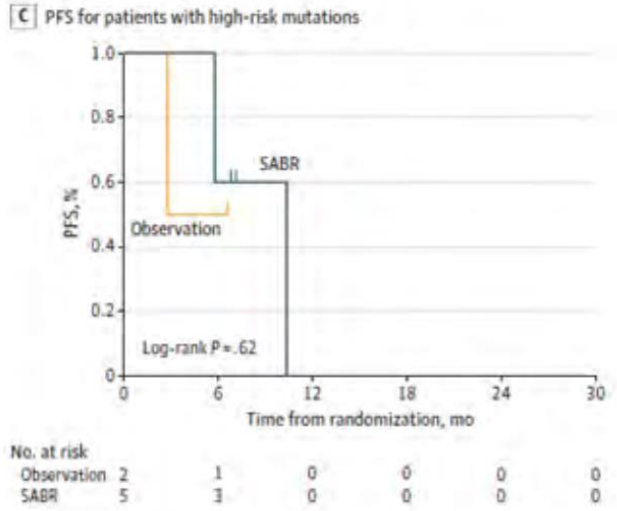


Ost *et al.* JCO 2018 – ASCO GU 2020; Philips R *et al*. JAMA Oncol 2020

ORIOL: Einfluss des Mutationsstatus auf PFS- Benefit der SBRT





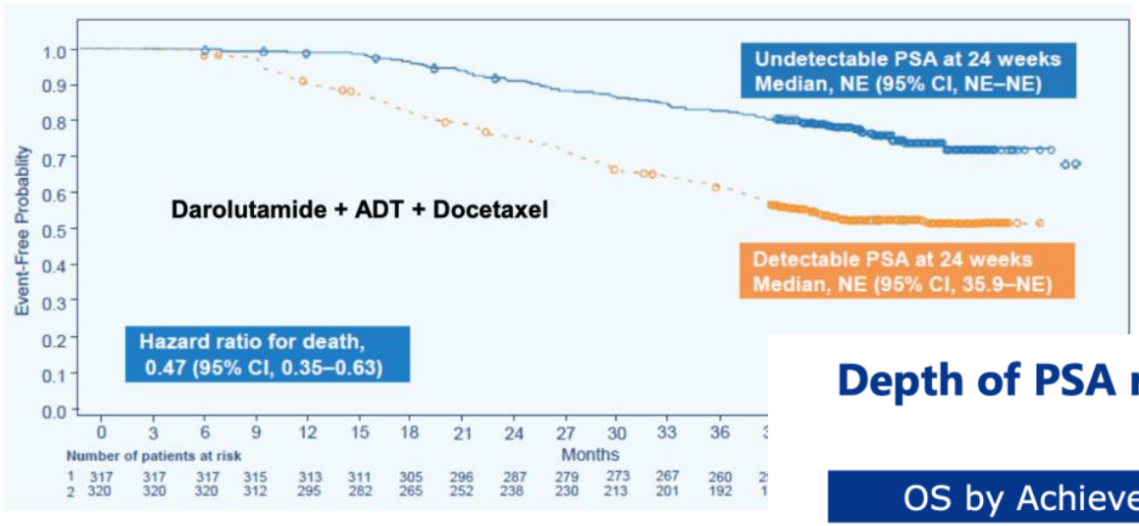


PFS benefit from SBRT mainly in patients without high-risk mutations
Role for systemic therapies in case of high-risk mutations?

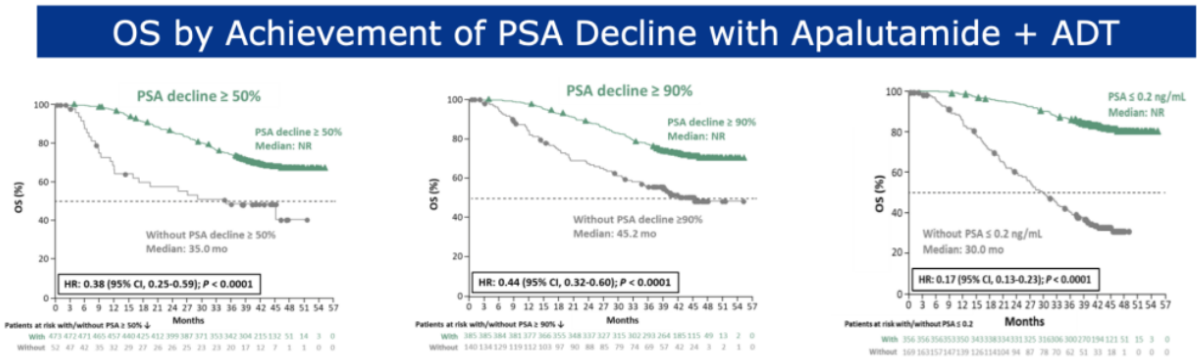
Philips R *et al.* JAMA Oncol 2020

Tiefer PSA Response

Konsistente Daten zum prognostischen Wert der tiefen PSA-Response bei mHSPC



Depth of PSA response in TITAN correlates with OS

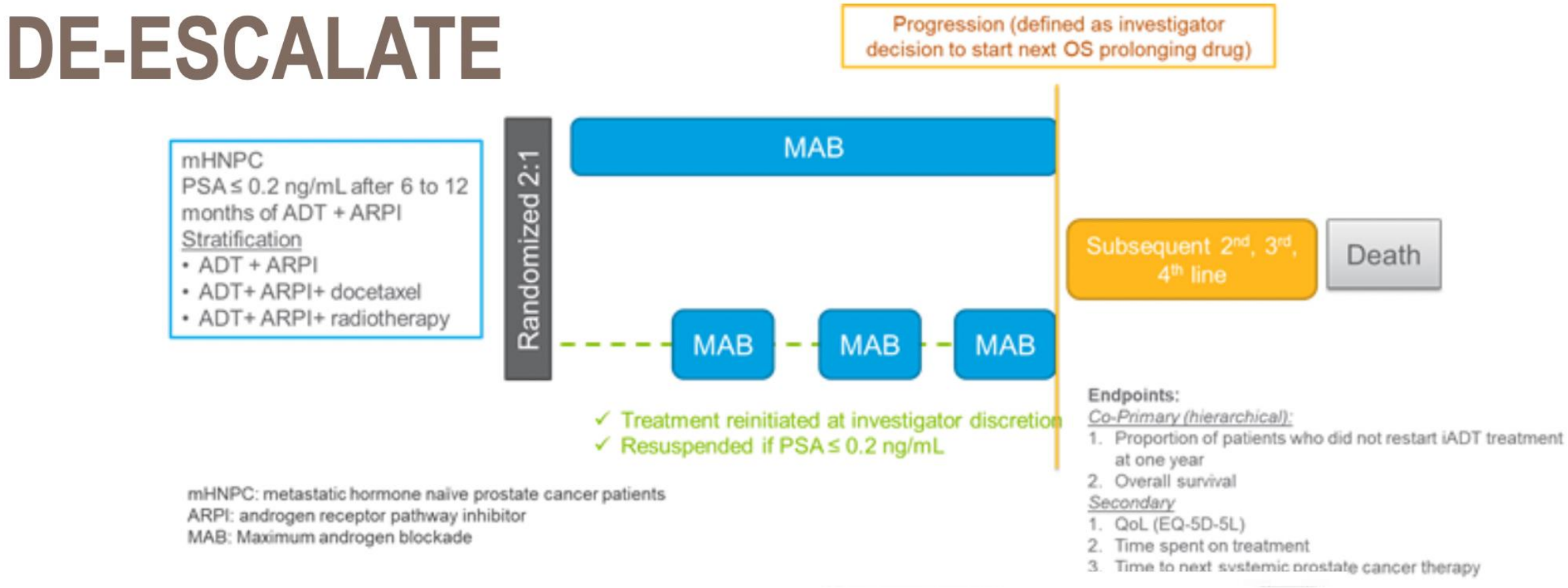


Chi KN, et al. AUA 2021. Presentation PD34. Prostate-Specific Antigen Kinetics in Patients With Advanced Prostate Cancer Treated With Apalutamide: Results From the TITAN and SPARTAN Studies

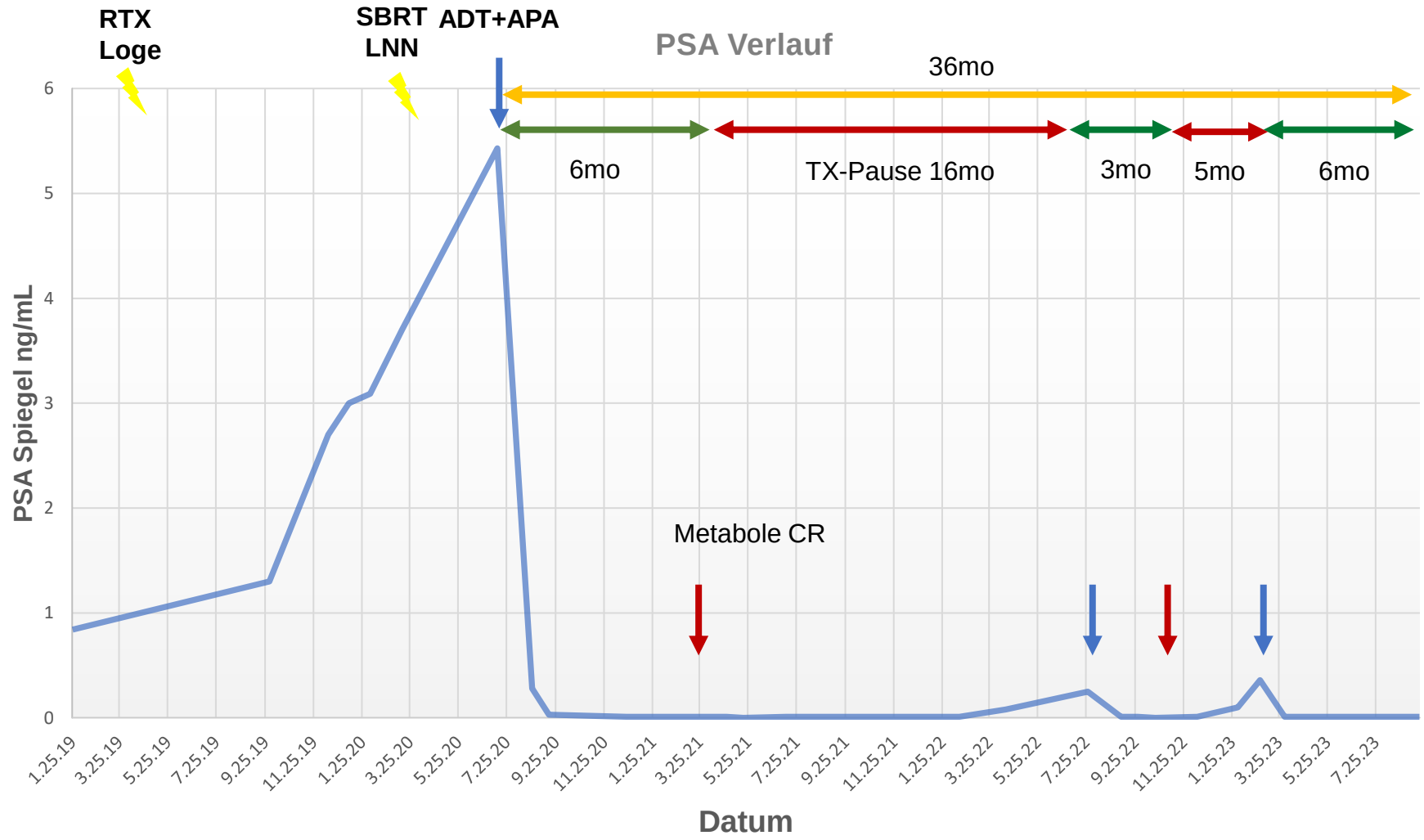
Prognostischer Wert der tiefen PSA-Response

Sollen wir PSA-Response für die De-Eskalation der Behandlung verwenden?

Studie: DE-ESCALATE



Fallpräsentation: Intermittierende ARSI



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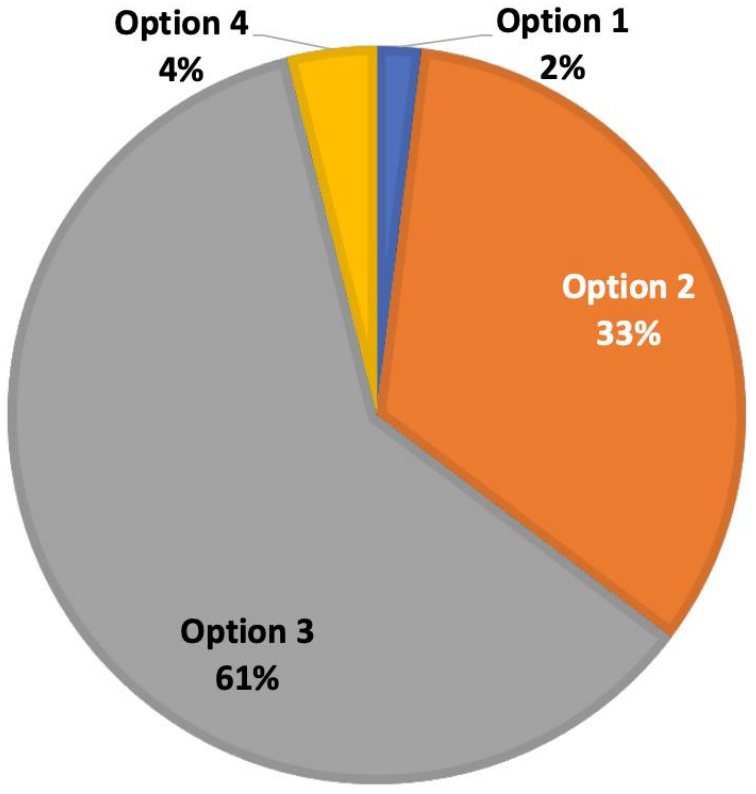
168. For the majority of patients with low-volume/oligometastatic synchronous mHSPC and 1-3 bone lesions on next-generation imaging what is your treatment recommendation?

1. Systemic therapy alone
2. Systemic therapy plus local treatment of the primary
3. Systemic therapy plus local treatment of the primary and MDT
4. Local treatment of the primary and MDT without systemic therapy
5. Abstain/unqualified to answer



Option	Votes
Option 1	2
Option 2	34
Option 3	63
Option 4	4
Option 5	1
Total votes	104

Preliminary results. For interpretation of results please refer to publication, which will follow shortly after APCCC 2022

APCCC
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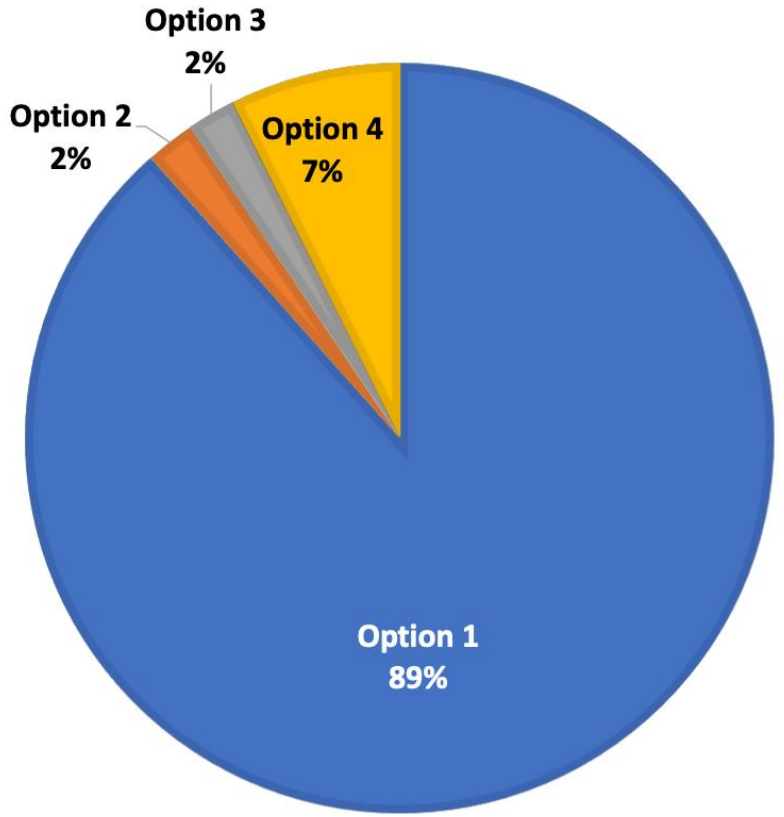
169. If you voted for systemic therapy plus local treatment for the majority of patients with low-volume/oligometastatic synchronous mHSPC e.g. 1-3 bone lesions on next-generation imaging what is your treatment recommendation?

1. ADT plus AR pathway inhibitor (Abi/Apa/Enza)
2. ADT plus Docetaxel
3. ADT plus Docetaxel plus an AR pathway inhibitor (Abi/Apa/Daro/Enza)
4. ADT alone
5. Abstain/unqualified to answer (including I don't recommend the combination of systemic plus local therapy in this situation)



Option	Votes
Option 1	85
Option 2	2
Option 3	2
Option 4	7
Option 5	8
Total votes	104

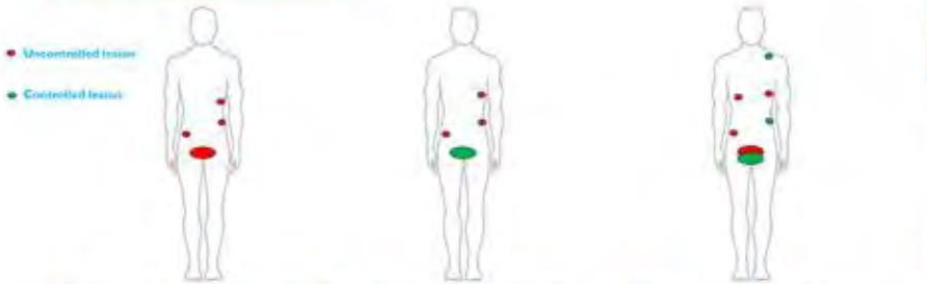
Preliminary results. For interpretation of results please refer to publication, which will follow shortly after APCCC 2022

Systemische Therapie von Patienten mit oligometastastischem mHSPC

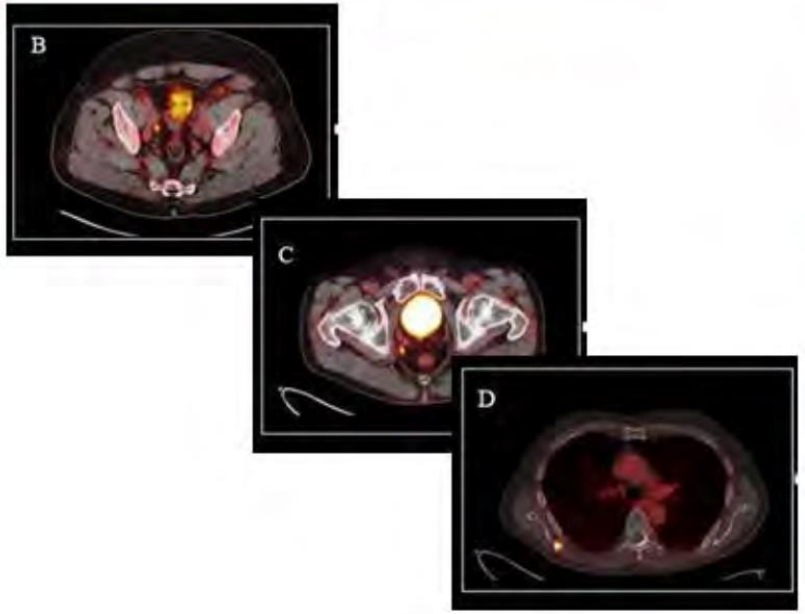
- Die interdisziplinäre Behandlung ist entscheidend
- Der Standard für M-1 Patienten bleibt die ADT plus ARSI
- Patienten mit indolentem mHSPC low volume haben möglicherweise eine Heilungschance mit intensivierter interdisziplinärer Behandlung`entsprechend einer RTX des Primarius und SBRT der Metastasen in Kombination mit dualer Antihormontherapie
- PSMA-PET ist sensitiver und spezifischer als konventionelle Bildgebung und sollte vor der Indikationsstellung lokaler Therapiemaßnahmen eingesetzt werden
- Wir sollen Patienten weder unter- noch überbehandeln

Die Zukunft der Behandlung des Oligometastastischen mHSPC

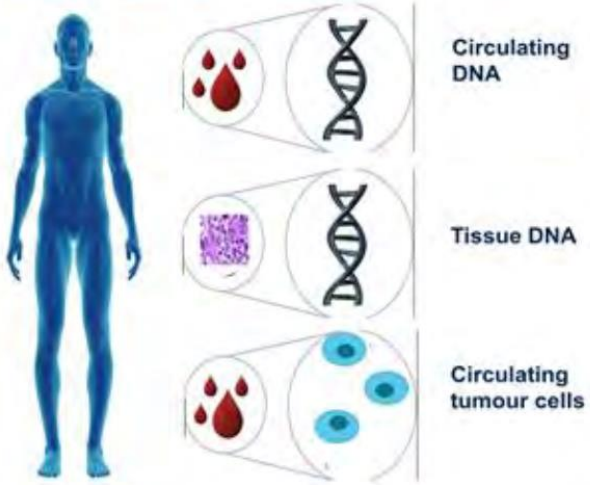
CLINIC



MOLECULAR IMAGING



TUMOR BIOLOGY



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DANKE

Backup slides

Do Bone Scans Over Stage Disease Compared to PSMA PET? An international multicenter retrospective study with blinded independent readers

Wolfgang P. Fendler[5], Thomas A. Hope,[1,2] Fei Jiang ,[4] Daniel Thompson,[1] Francesco Barbato,[5] Roxanna Juarez,[1] Miguel Hernandez Pampaloni ,[1] Martin Allen-Auerbach ,[3] Pawan Gupta,[3] Matthias Benz,[3] Jeremie Calais[3]

- 17% patients M1b on PSMA 30% M1b on Bone scan.
- 57% of positive bone scan findings at staging bone scan false positive.
- Insufficient numbers to evaluate findings in mCSPC.

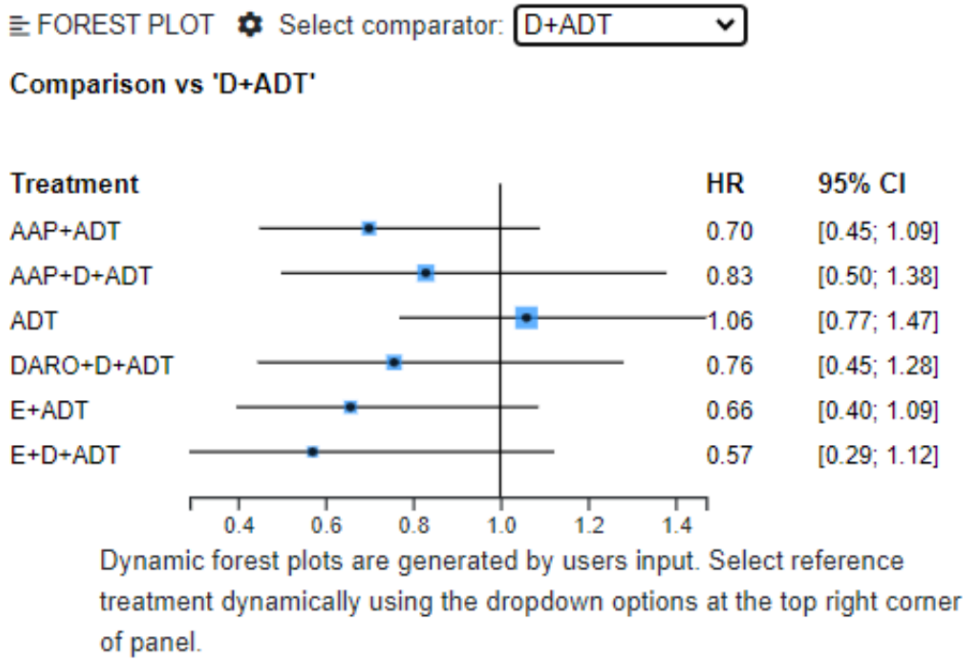
Imaging Results in 167 Patients

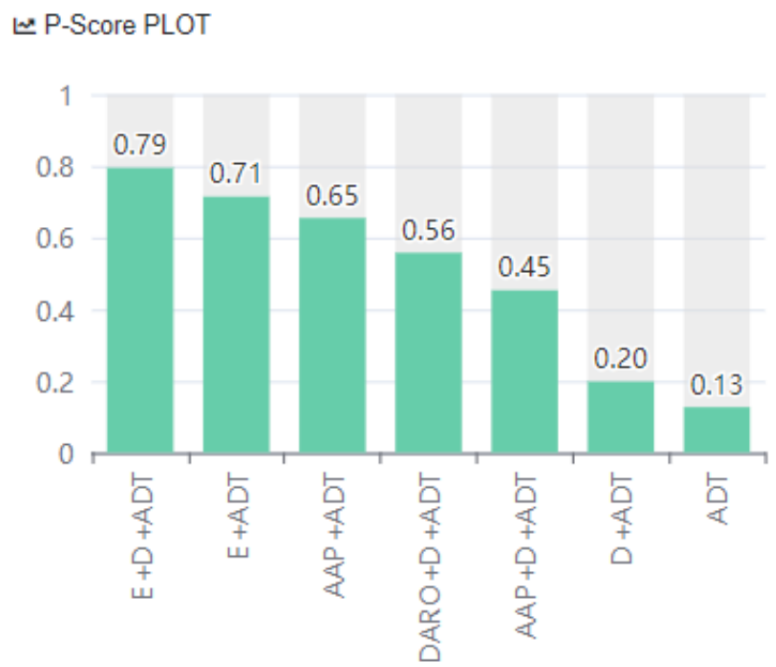
	Initial staging	BCR/CSPC	CRPC	Overall
Bone scan vs PSMA PET comparison				
Both + (TP)	10 (13)	17 (28)	21 (70)	48 (29)
Both – (TN)	51 (66)	28 (47)	5 (17)	84 (50)
BS+/PSMA- (FP)	13 (17)	5 (8)	0 (0)	18 (11)
PSMA+/BS- (FN)	3 (4)	10 (17)	4 (13)	17 (10)

Bone Scan	All Patients (167)	Initial Staging (77)
PPV	73%	43%
NPV	82%	94%
Specificity	82%	80%

De Novo mHSPC: Low Volume

Living NMA: Kein Hinweis für konsistenten Benefit durch Zugabe von Docetaxel zu ADT+ARSI



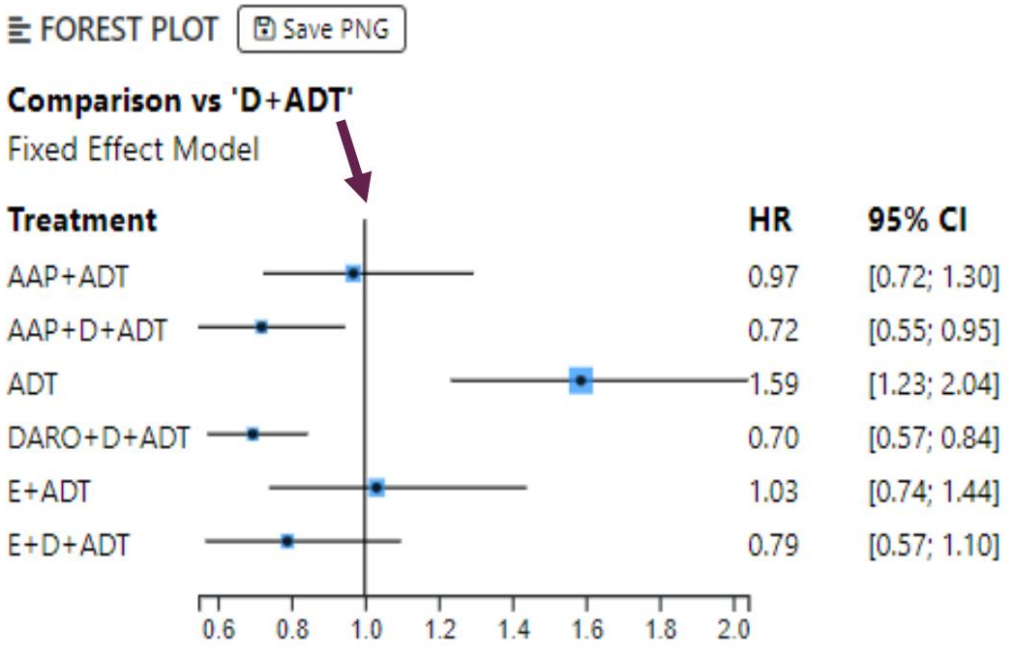


Caveats: APA + ADT shorter follow-up than Enza + ADT + Doc with ENZAMET
APA and Enza (ARCHES) only includes patients not progressing after ADT + docetaxel run-in; ? Selection for better pts

Riaz et al.. 2023;9(5):635-645. https://mcspc.living-evidence.com/
Data presented to be updated on the website; Bossie et al ASCO 2023

De Novo mHSPC: High Volume

Living NMA: Konsistenter Benefit durch Zugabe von Docetaxel zu ADT+ARSI



Note: Does not include apalutamide due to no concurrent ADT + docetaxel in TITAN

"Triplet" ADT + Doc +ARSI

"Doublet" ADT + Doc or ADT + ARSI

Riaz et al. Supplement, JAMA Oncol. 2023;9(5):635-645.
https://mcspc.living-evidence.com/

Courtesy of Chris Sweeney

Konsistent Daten zum prognostischen Wert der tiefen PSA Response bei mHSPC