Can we extrapolate the evidence on synchronous mHSPC to metachronous mHSPC

Prof. Amit Bahl

Consultant Oncologist

Bristol Cancer Institute

Bristol, UK

NHS
University Hospitals Bristol and Weston
NHS Foundation Trust

9th edition
GLOBAL CONGRESS ON PROSTATE CANCER

Congress management by e-HIMS bvba

Mirrors of medicine

Organised by ISSECAM ivzw
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Conflicts of Interest

- Advisory boards and honoraria
  - Amgen, Astellas, Bayer, Ipsen, Janssen, MSD, Novartis, Sanofi Genzyme
- Research grants (To Institution)
  - Ipsen, Sanofi Genzyme, Janssen
- Meeting sponsorship
  - Bayer, Ipsen, Roche, Sanofi Genzyme

Recent Advances in mHSPC

mHNPC, metastatic hormone-naive prostate cancer.

1. Sweeney CJ, et al. N Engl J Med 2015;373:737–746; 2. James ND, et al. *Lancet* 2016;387:116–177; 3. Fizazi K, et al. *N Engl J Med* 2017;377:352–360; 4. Armstrong AJ, et al. *J Clin Oncol* 2019;37:2974-86; 5. Davis ID, et al. *N Engl J Med* 2019;381:121-31; 6. Chi KN, et al. *N Engl J Med* 2019;381:13-24. 7 Fizazi K et al ESMO Sep 2021.

Terminology	Definition
Synchronous metastatic disease (de novo M1 disease)	The presence of metastases in the context of newly diagnosed prostate cancer
Metachronous metastatic disease	The presence of metastases after local treatment, usually radiotherapy and/or surgery to the prostate
High-volume disease	As defined by the CHAARTED trial. This is defined as visceral metastases and/or ≥ 4 bone lesions (with ≥ 1 beyond the vertebral bodies and pelvis)
High-risk disease (LATITUDE trial)	As defined by the LATITUDE trial, in the context of recruiting patients with de novo metastatic disease (M1). This is defined as the presence of ≥ 2 high-risk features, i.e. ≥ 3 bone metastases, visceral metastases and Gleason score ≥ 8
High-risk disease (STAMPEDE trial)	As defined by the STAMPEDE trial, in the context of recruiting patients with locally advanced prostate cancer (M0). This is defined by the presence of ≥ 2 of these features, i.e. T3/4 disease, Gleason score ≥ 8, and PSA > 40 ng/mL

M0 No distant metastases detectable, *M1* metastatic disease, *PSA* prostate specific antigen

Phase III Trials in mHSPC

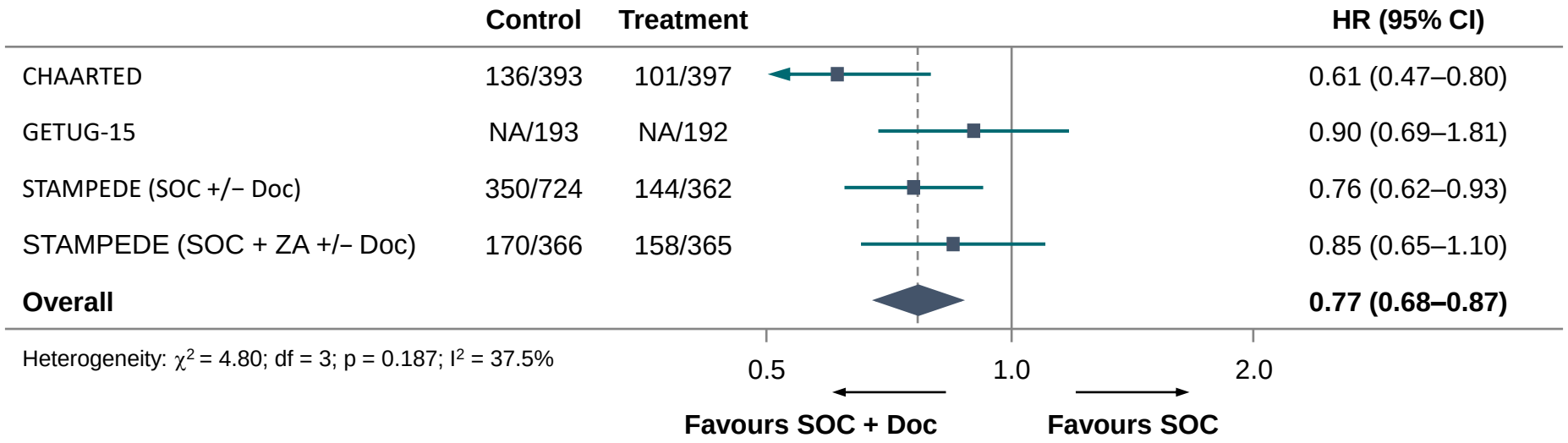
Study	Agents	N	*De novo* M1	Median FU*	HR
CHAARTED[1]	DOC vs ADT	790	76%	**53.7**	0.72
STAMPEDE[2]	DOC/P vs ADT	1,086	95%	**78.2**	0.81
GETUG 15[3]	DOC vs ADT	385	71%	**83.9**	0.88
LATITUDE[4]	ABI/P vs ADT	1,199	100%	51.8	0.66
STAMPEDE[5]	ABI/P vs ADT	1,002	94%	40.0	0.61
TITAN[6]	APA vs ADT	1,052	81%	45.0	0.65
ENZAMET[7]	ENZA vs ADT	1,125	61%	34.0	0.67
ARCHES[8]	ENZA vs ADT	1,150	67%	14.4	0.81
PEACE-1[9]	**ADT+Doc+Abi vs ADT+Doc**	710	100%	44.0	0.75

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. 9. Fizazi K, et al ESMO 2021

Survival with Upfront DOC in mHSPC

- Results based on 2,993 men/2,198 events



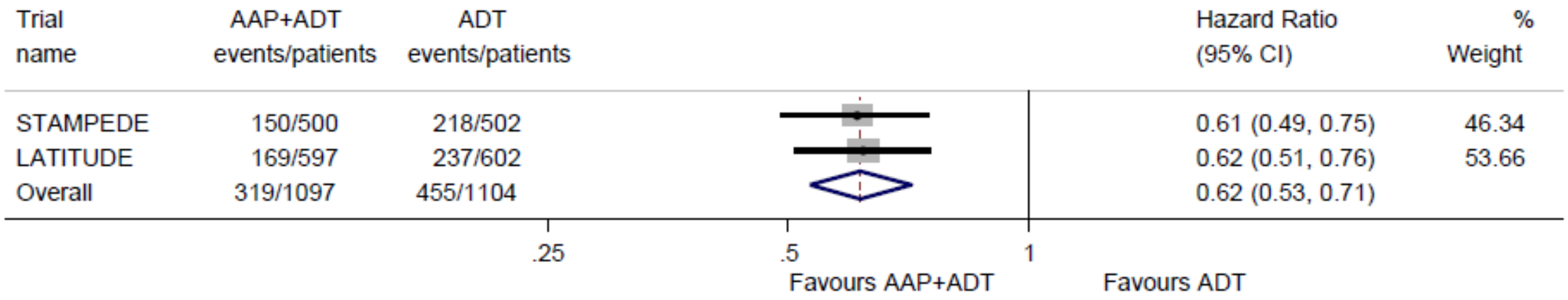
Absolute 9% OS benefit at 4 years

Doc, docetaxel, NA, not available; SOC, standard of care; ZA, zoledronic acid.

Vale CL, et al. *Lancet Oncol.* 2016;17:243-56.

Survival with Upfront ABI in mHNPC

- Overall survival
- Results based on 2,201 men / 774 deaths

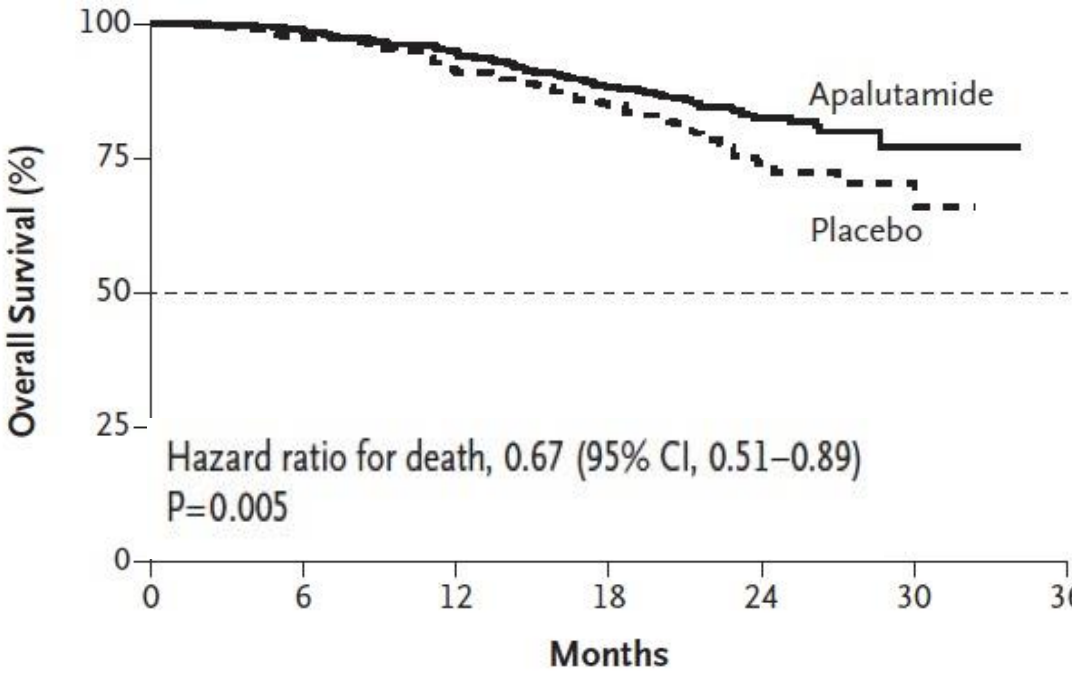


Absolute 14% OS benefit at 3 years

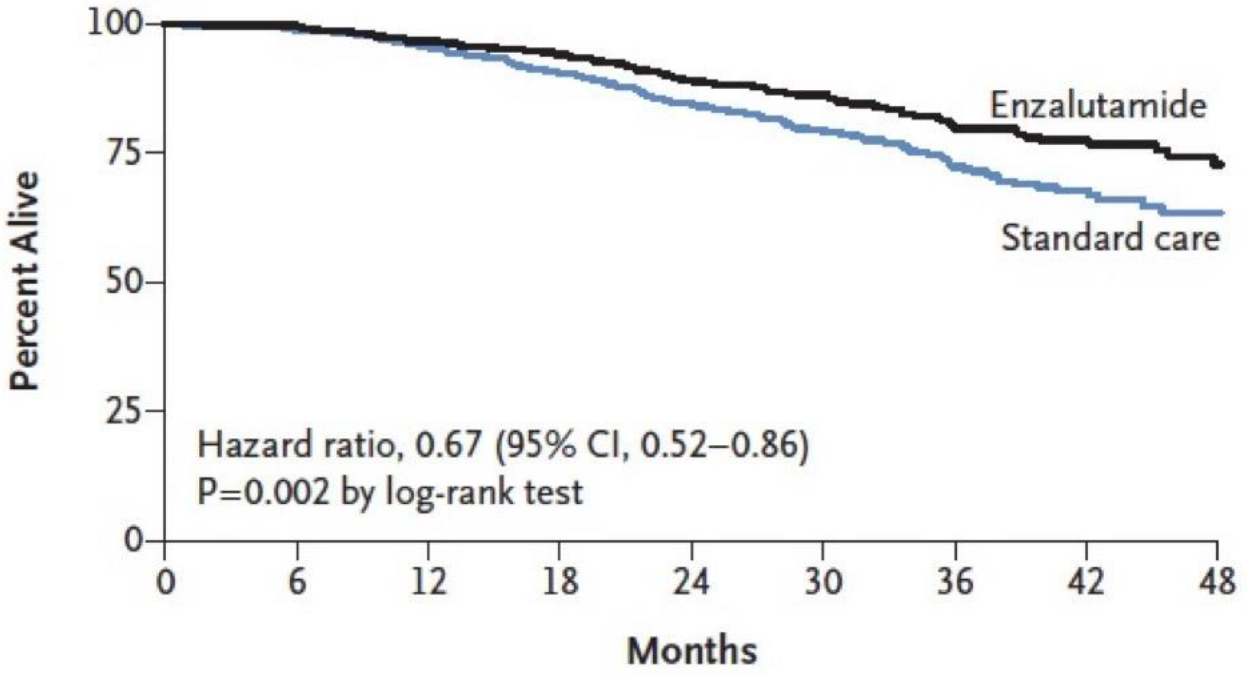
Rydzewska L, et al. *Eur J Cancer.* 2017;84:88-101.

Survival with Upfront APA or ENZA in mHNPC

TITAN (apalutamide)[1]
(N=1,052)



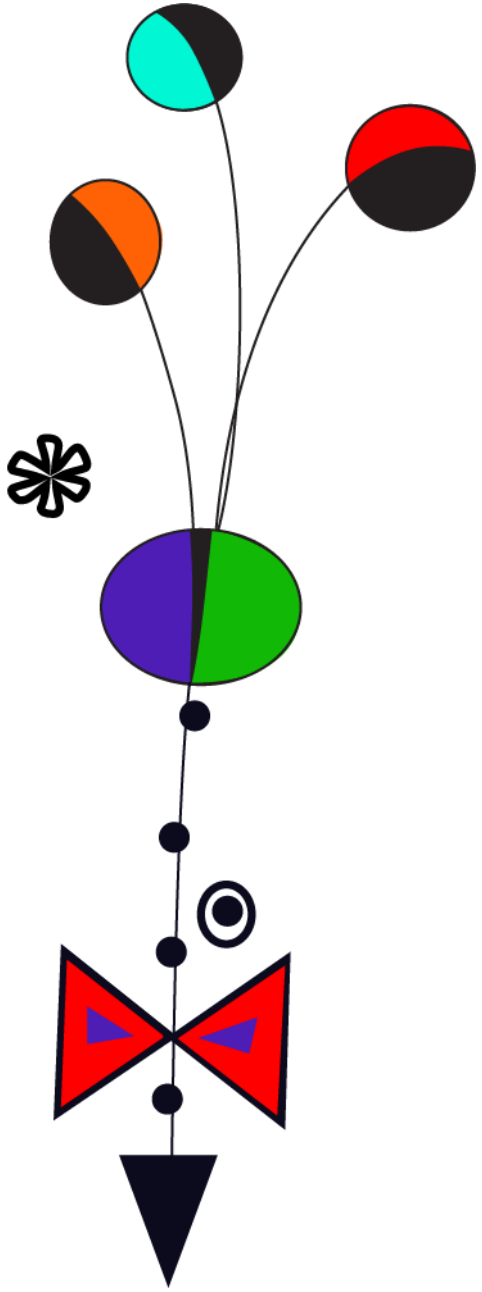
ENZAMET (enzalutamide)[2]
(N=1,125)

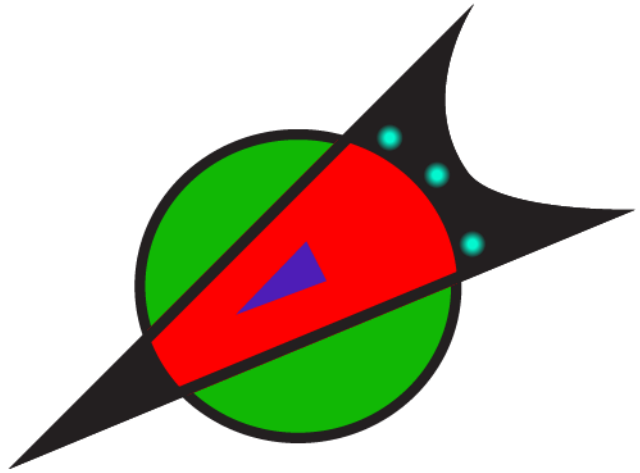


ENZA is licensed by EMA for M0 CRPC and M1 CRPC

APA: apalutamide; ENZA: enzalutamide; EMA: European Medical Agency; M0 CRPC: non-metastatic castration-resistant prostate cancer

Chi KN, et al. *N Engl J Med.* 2019;381:13-24; Davis ID, et al. *N Engl J Med.* 2019;381:121-31.

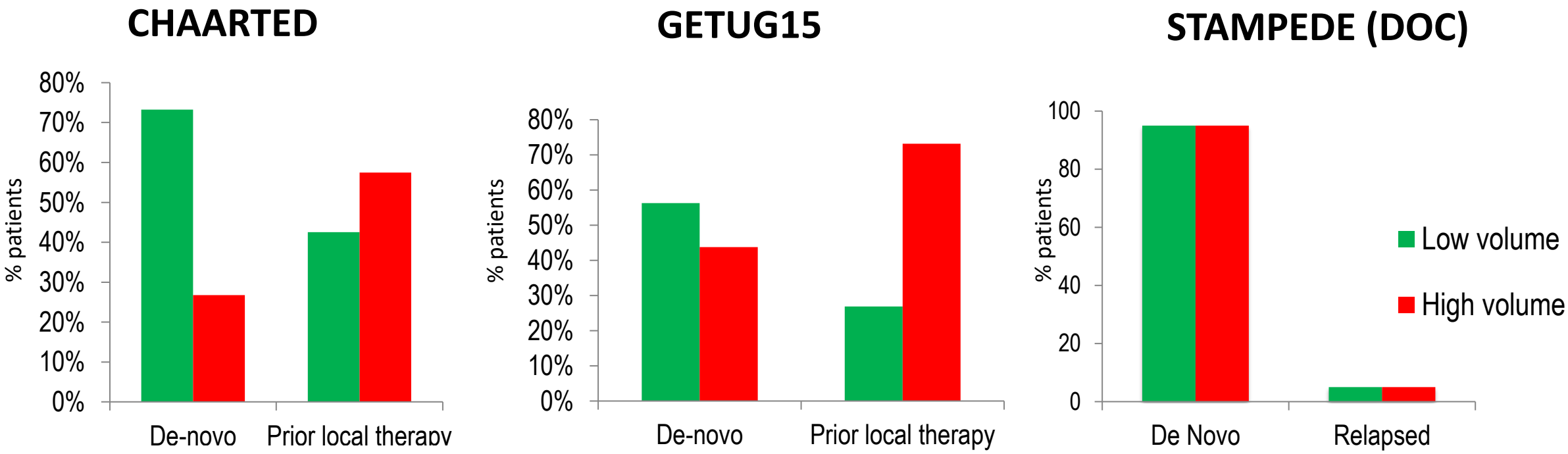




Can We Compare These Trials?

NO

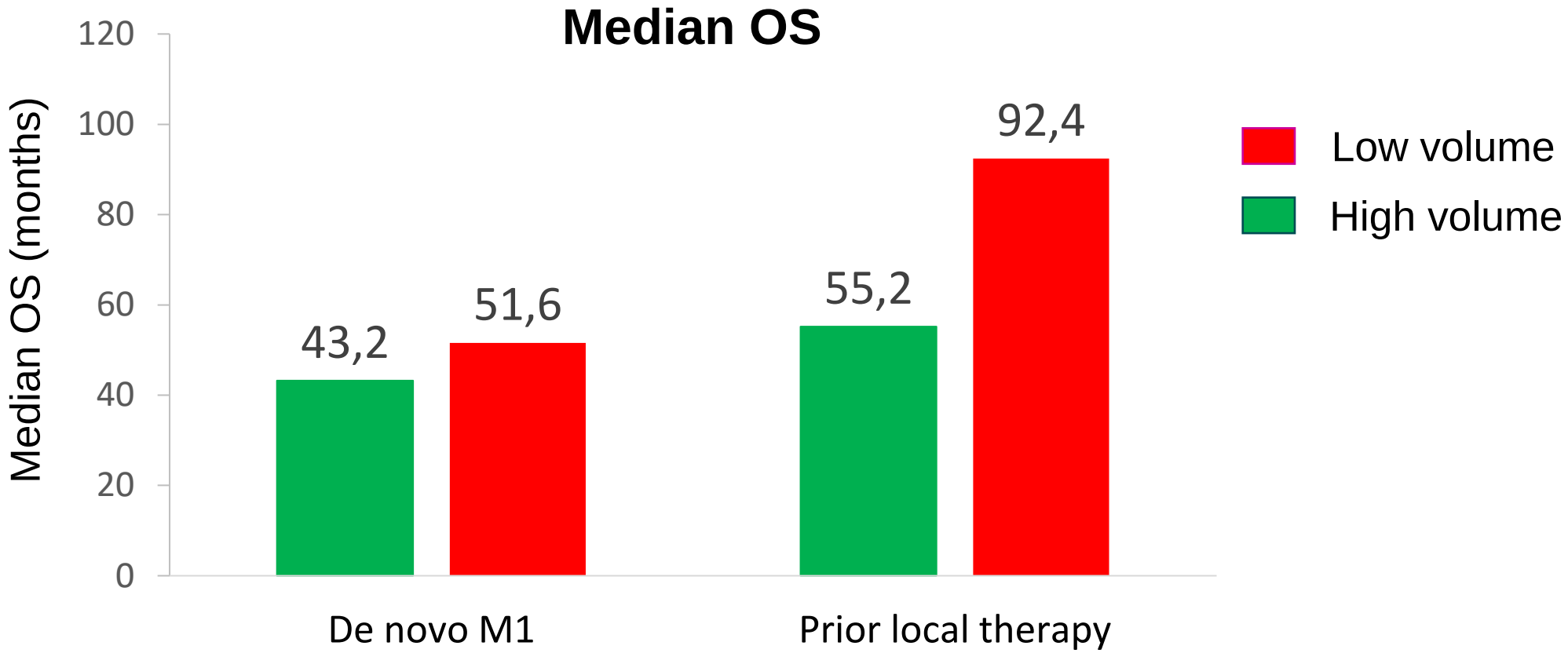
These Trials Enrolled Different Patients



STAMPEDE mainly enrolled *de novo* M1 patients

Clarke N, et al. Ann Oncol 2019;30(suppl 5):844O(podium presentation); Gravis G, et al. *Eur Urol*. 2018;73:847-55.

De novo M1 Disease = Worse Prognosis



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.

Is there a real difference in Metachronous vs Synchronous mHSPC?

- Metachronous metastatic disease (as assessed by conventional imaging), may have cancers that behave differently.
- These patients often have lower burden of disease, and treatment with testosterone suppression alone is associated with longer survival compared to those with de novo/synchronous metastatic prostate cancer at the time of diagnosis.
- Patterns of clinical management may have a role to play in outcome differences.
- Timing of progression and response will likely shift due to lead time bias, particularly if novel imaging technologies used
- Other as-yet-unknown factors must be contributing to the observed biological differences.

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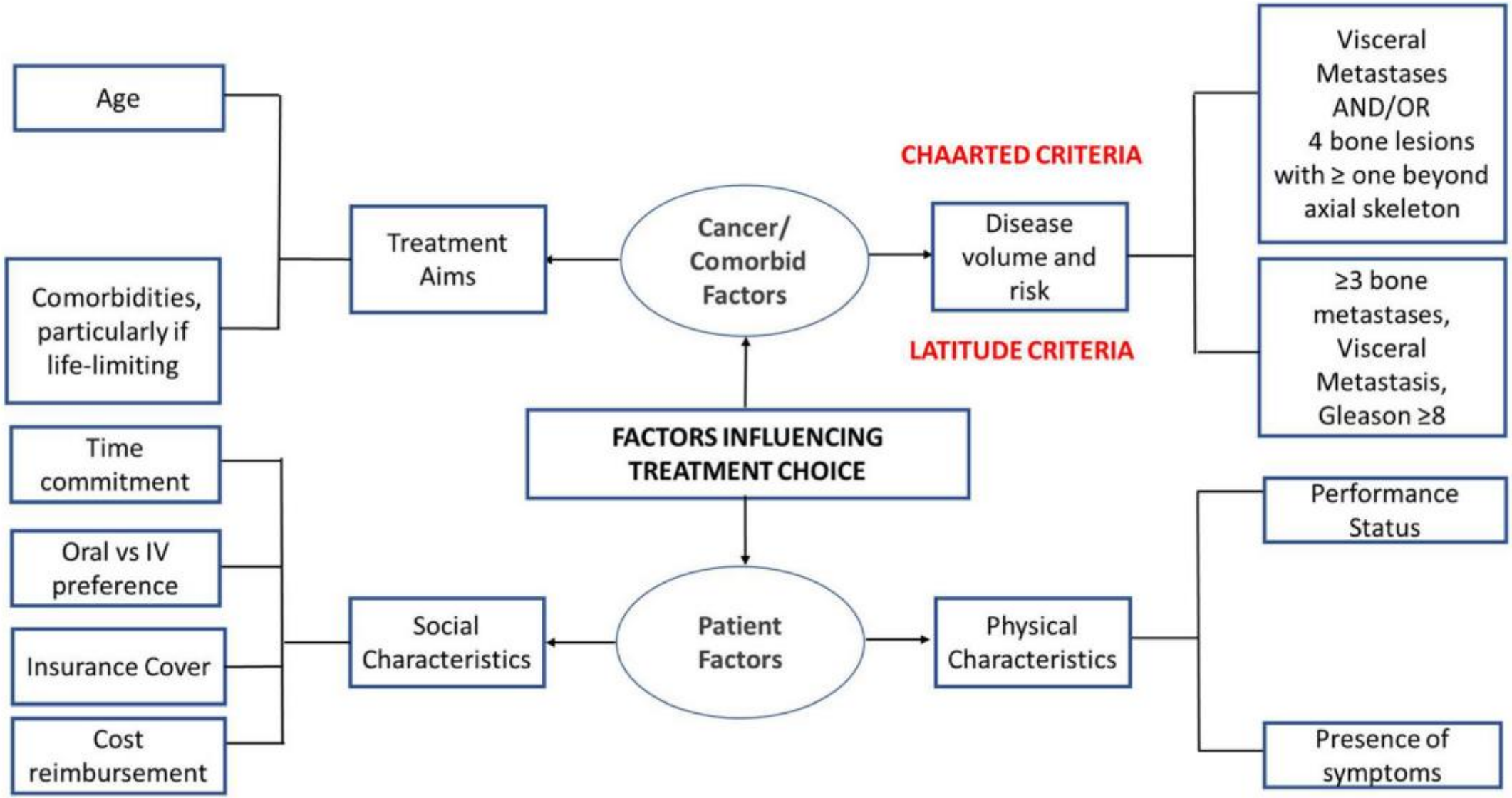
ORIGINAL ARTICLE

The Prostate WILEY

Genomic profiles and clinical outcomes in primary versus secondary metastatic hormone-sensitive prostate cancer

Emily Nizialek MD, PhD[1] | Su Jin Lim ScM[1] | Hao Wang PhD[1] | Pedro Isaacsson Velho MD[2] | Srinivasan Yegnasubramanian MD, PhD[1] | Emmanuel S. Antonarakis MD[1]

Conclusions: *TP53* DN mutations, but not all *TP53* alterations, were the strongest predictor of negative outcomes in men with mHSPC, while *SPOP* mutations were associated with improved outcomes. In subgroup analyses, specific alterations were prognostic of outcomes in secondary, but not primary, mHSPC.


Age
Comorbidities, particularly if life-limiting
Time commitment
Oral vs IV preference
Insurance Cover
Cost reimbursement
Treatment Aims
Social Characteristics
Cancer/ Comorbid Factors
Patient Factors
FACTORS INFLUENCING TREATMENT CHOICE
CHAARTED CRITERIA
LATITUDE CRITERIA
Disease volume and risk
Physical Characteristics
Visceral Metastases AND/OR 4 bone lesions with ≥ one beyond axial skeleton
≥3 bone metastases, Visceral Metastasis, Gleason ≥8
Performance Status
Presence of symptoms

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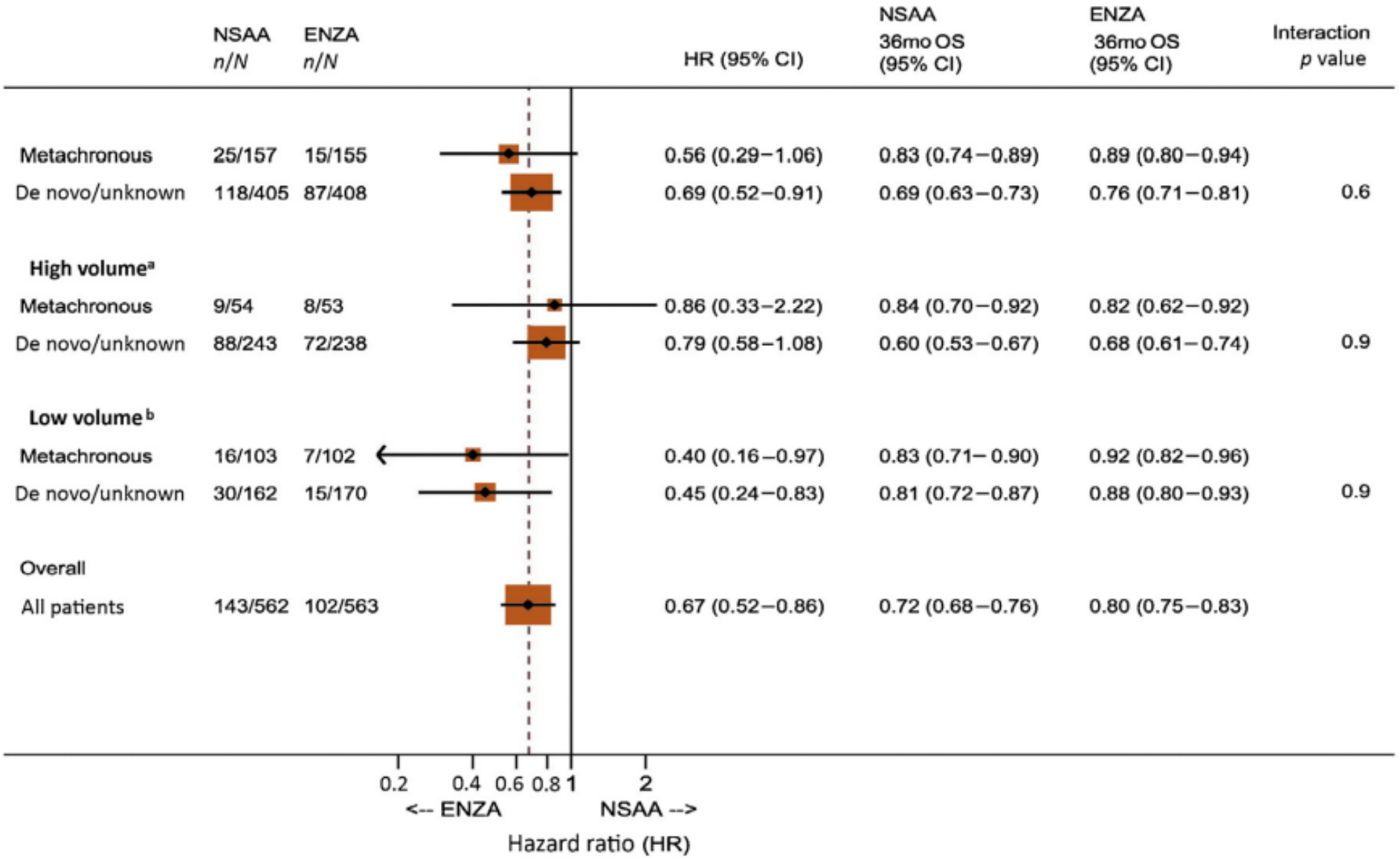
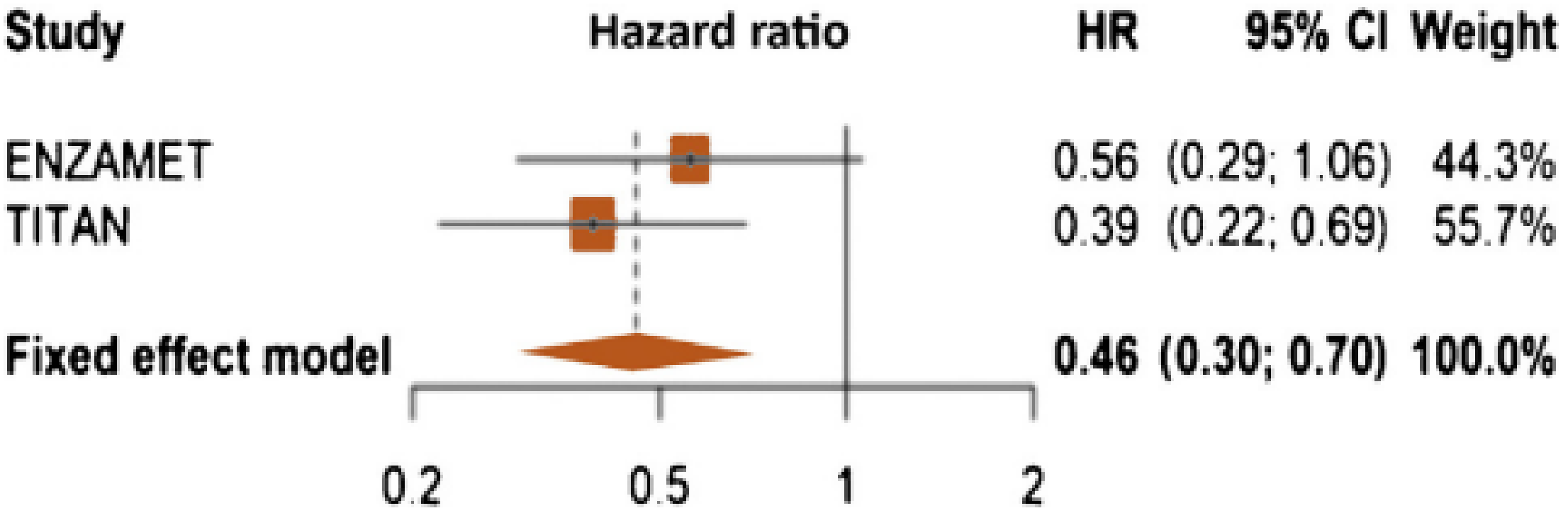
available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Brief Correspondence

Overall Survival of Men with Metachronous Metastatic Hormone-sensitive Prostate Cancer Treated with Enzalutamide and Androgen Deprivation Therapy


NSAA n/N
ENZA n/N
HR (95% CI)
NSAA 36mo OS (95% CI)
ENZA 36mo OS (95% CI)
Interaction p value
Metachronous 25/157 15/155 0.56 (0.29–1.06) 0.83 (0.74–0.89) 0.89 (0.80–0.94)
De novo/unknown 118/405 87/408 0.69 (0.52–0.91) 0.69 (0.63–0.73) 0.76 (0.71–0.81) 0.6
High volume[a]
Metachronous 9/54 8/53 0.86 (0.33–2.22) 0.84 (0.70–0.92) 0.82 (0.62–0.92)
De novo/unknown 88/243 72/238 0.79 (0.58–1.08) 0.60 (0.53–0.67) 0.68 (0.61–0.74) 0.9
Low volume[b]
Metachronous 16/103 7/102 0.40 (0.16–0.97) 0.83 (0.71–0.90) 0.92 (0.82–0.96)
De novo/unknown 30/162 15/170 0.45 (0.24–0.83) 0.81 (0.72–0.87) 0.88 (0.80–0.93) 0.9
Overall
All patients 143/562 102/563 0.67 (0.52–0.86) 0.72 (0.68–0.76) 0.80 (0.75–0.83)
0.2 0.4 0.6 0.8 1 2
<-- ENZA NSAA -->
Hazard ratio (HR)


Study
Hazard ratio
HR
95% CI
Weight
ENZAMET
0.56
(0.29; 1.06)
44.3%
TITAN
0.39
(0.22; 0.69)
55.7%
Fixed effect model
0.46
(0.30; 0.70)
100.0%
0.2
0.5
1
2

Can We Combine DOC and ARTA in Metachronous mHSPC?

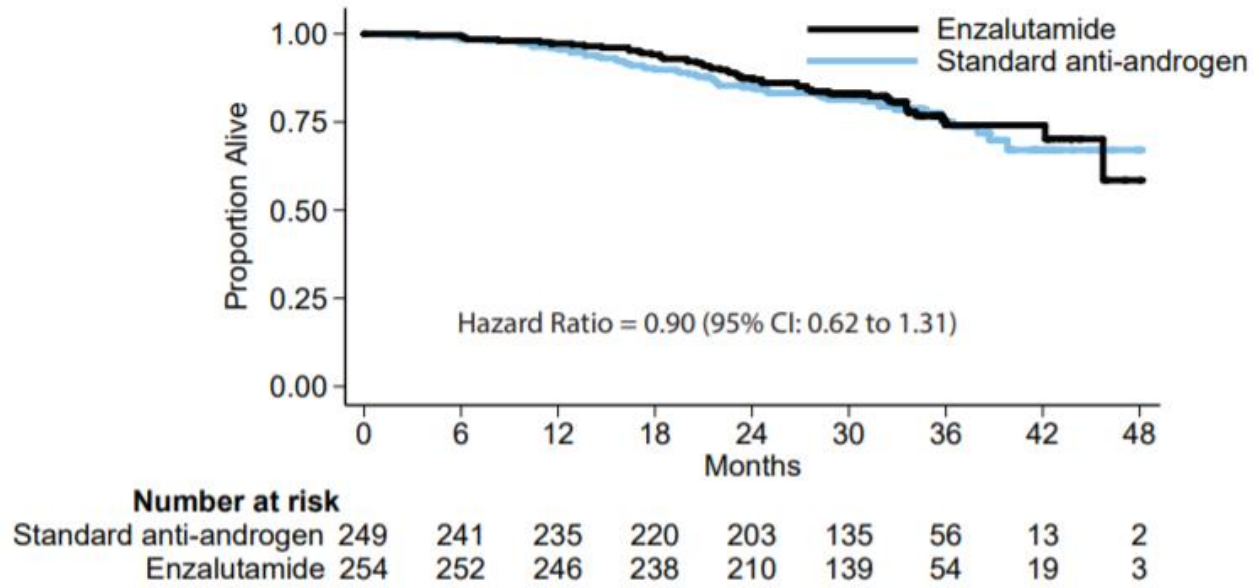
NO

…

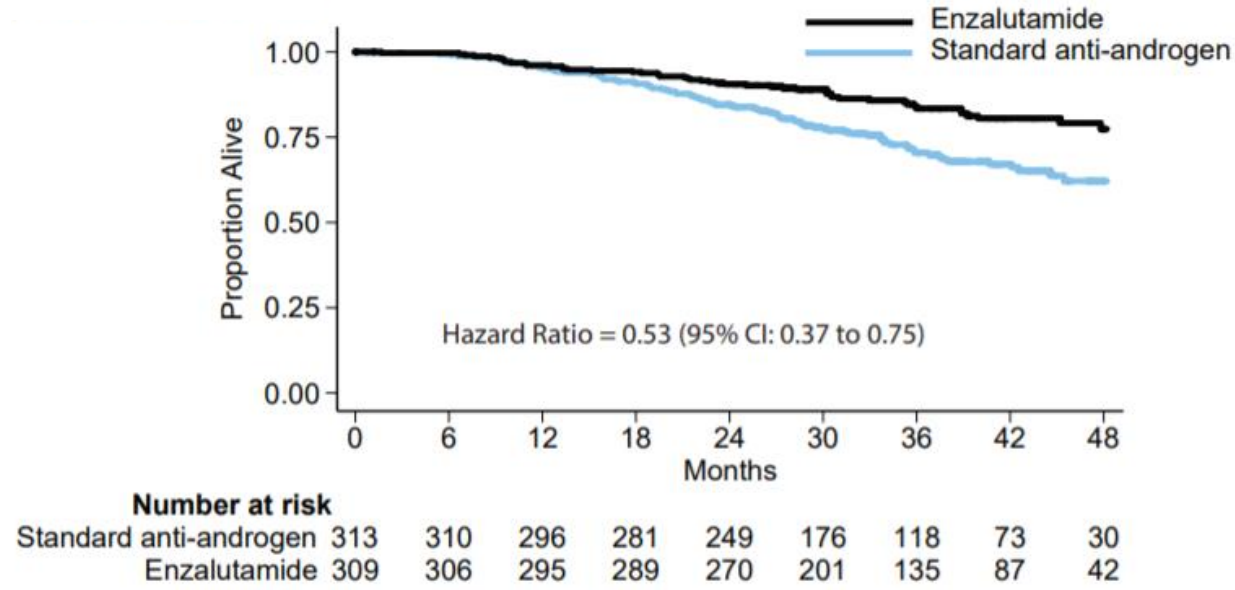
NOT YET

ENZAMET (ADT ± ENZA ± DOC) in mHSPC

OS
(DOC subgroup*; n=503)



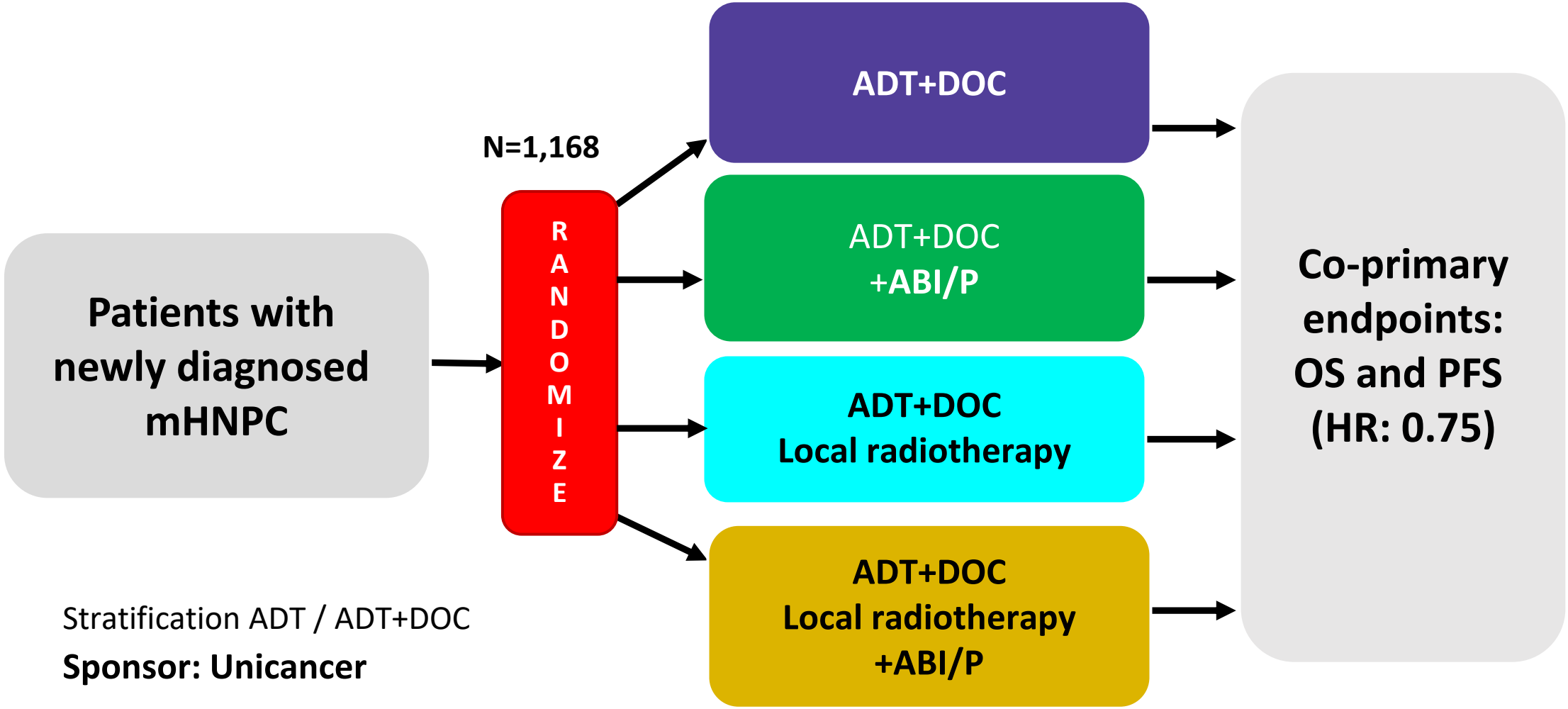
OS
(No DOC subgroup; n=622)



**6 cycles DOC (2 allowed before randomization)*

Davis ID, et al. *N Engl J Med.* 2019;381:121-31. Supplementary Material. Available at https://www.nejm.org/doi/suppl/10.1056/NEJMoa1903835/suppl_file/nejmoa1903835_appendix.pdf. Accessed Jul 14, 2020.

PEACE-1 Phase III Trial in Newly Diagnosed mHSPC (revised design)



Stratification ADT / ADT+DOC

Sponsor: Unicancer

NCT01957436 Clinicaltrials.gov

Management of mHSPC in Practice

Several questions as yet unanswered BUT….

ADT alone in M1 disease in a fit and eligible patient is not an appropriate option

And in Metachronous MHSPC evidence accumulating regarding ADT+ARTA

EAU Guidelines 2021 M1 Disease

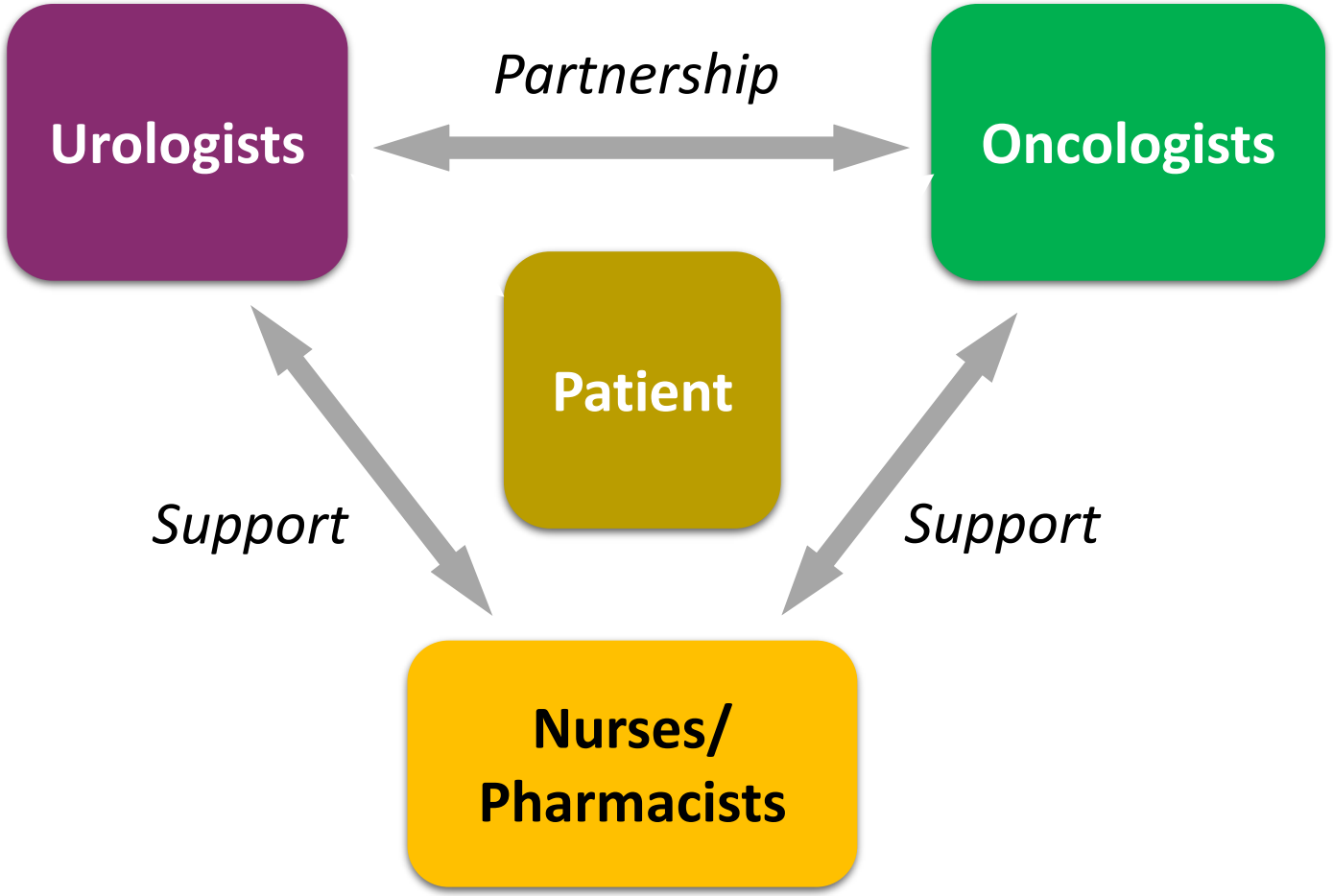
Do not offer AR antagonist monotherapy to patients with M1 disease.	Strong
Discuss combination therapy including ADT plus systemic therapy with all M1 patients.	Strong
Do not offer ADT monotherapy to patients whose first presentation is M1 disease if they have no contraindications for combination therapy and have a sufficient life expectancy to benefit from combination therapy and are willing to accept the increased risk of side effects.	Strong
Offer ADT combined with chemotherapy (docetaxel) to patients whose first presentation is M1 disease and who are fit for docetaxel.	Strong
Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients whose first presentation is M1 disease and who are fit enough for the regimen.	Strong
Offer ADT combined with prostate radiotherapy (using the doses from the STAMPEDE study) to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria.	Strong
Do not offer ADT combined with any local treatment (radiotherapy/surgery) to patients with high volume (CHAARTED criteria) M1 disease outside of clinical trials (except for symptom control).	Strong
Do not offer ADT combined with surgery to M1 patients outside of clinical trials.	Strong
Only offer metastasis-directed therapy to M1 patients within a clinical trial setting or well-designed prospective cohort study.	Strong

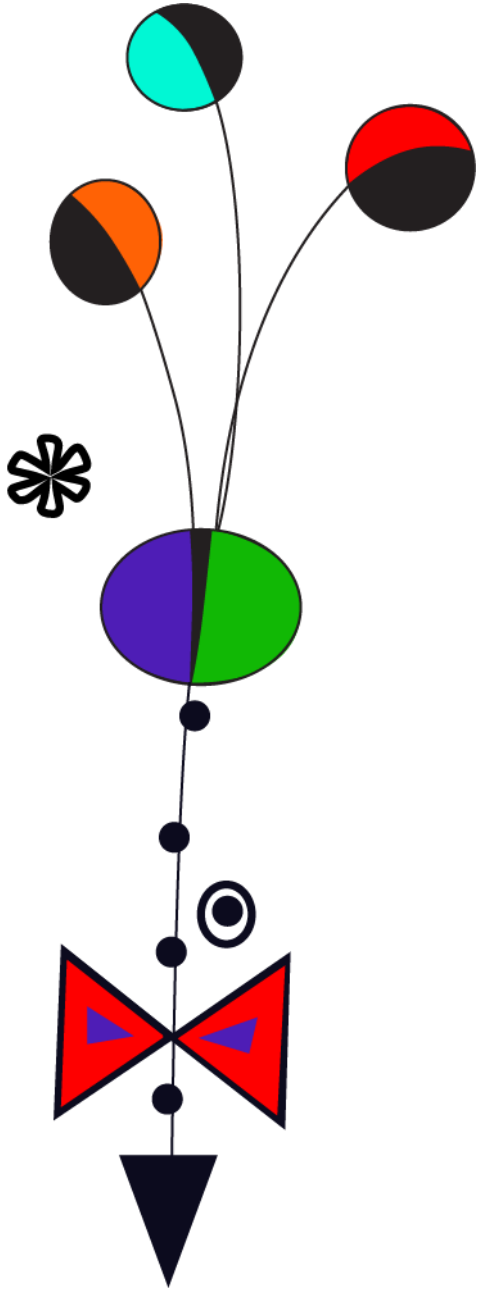
- EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guidelines 2021(uroweb.org)

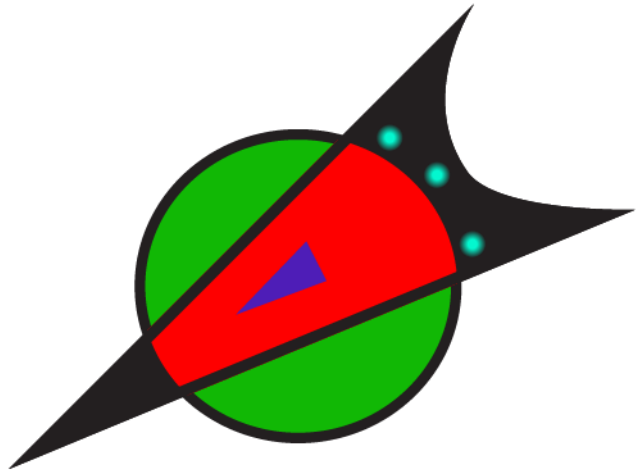
The Challenge for the Uro-oncologist in mHSPC

- To **tailor treatment** for mHSPC
  - Counsel patients on all available treatment options
  - ADT alone should not be considered standard of care in fit and eligible patients
- To **proactively manage adverse events** of new treatment options
  … to optimize treatment outcomes (quality of life, survival)
- **Multidisciplinary care a key to success!!**

Patient Management: a Patient-Centered Partnership







Thank you!