Fred Hutch Cancer Center

Prostate Cancer Updates

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MLS Updates
September 7, 2024

What's new in prostate cancer?

- EBRT + ADT + Abiraterone/prednisone in high risk or node positive localized prostate cancer (STAMPEDE)
- Talazoparib + Enzalutamide for first line treatment in metastatic castration resistant prostate cancer with HRRm (TALAPRO2)
- Updates in radioligand therapies (PSMA-Fore and SPLASH)

Localized Therapy

STAMPEDE update

Abi/pred for HR non-metastatic prostate cancer

EBRT + ADT + Abi/pred ***preferred*** for any T, N1, M0 and ***recommended*** for very-high-risk as defined per STAMPEDE trial

STAMPEDE: Abi/pred + EBRT + ADT for non-metastatic PC

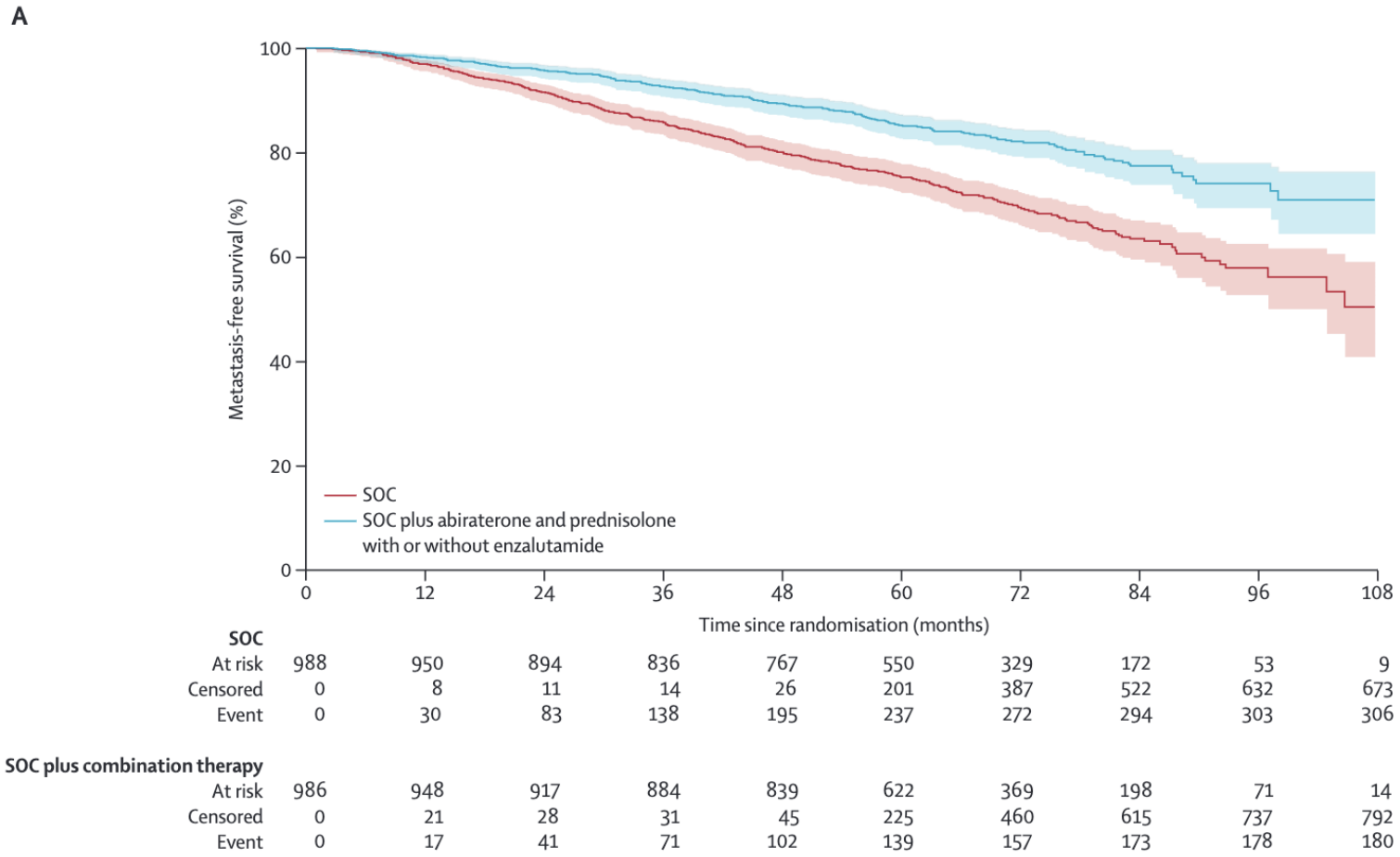
- Two trials:
  - 914 pts, HR, non-metastatic → ADT 3 yrs vs. ADT + AA/pred 2 yrs
  - 1060 pts, HR, non-metastatic → ADT 2 yrs vs. ADT + AA/pred + enza 2 yrs
  - Pooled analysis (contemporary trials in mCRPC pts of combo AA/enza failed to show diff to AA/pred alone)
  - 85% of patients received local radiation therapy in both trials and mandated for those with clinically node-negative disease
  - Primary outcome = MFS

Attard G. et al. Lancet 2022

STAMPEDE: Abi/pred + EBRT + ADT for non-metastatic PC

6-year MFS =
69% ADT vs. **82%** ADT
+ AA/pred

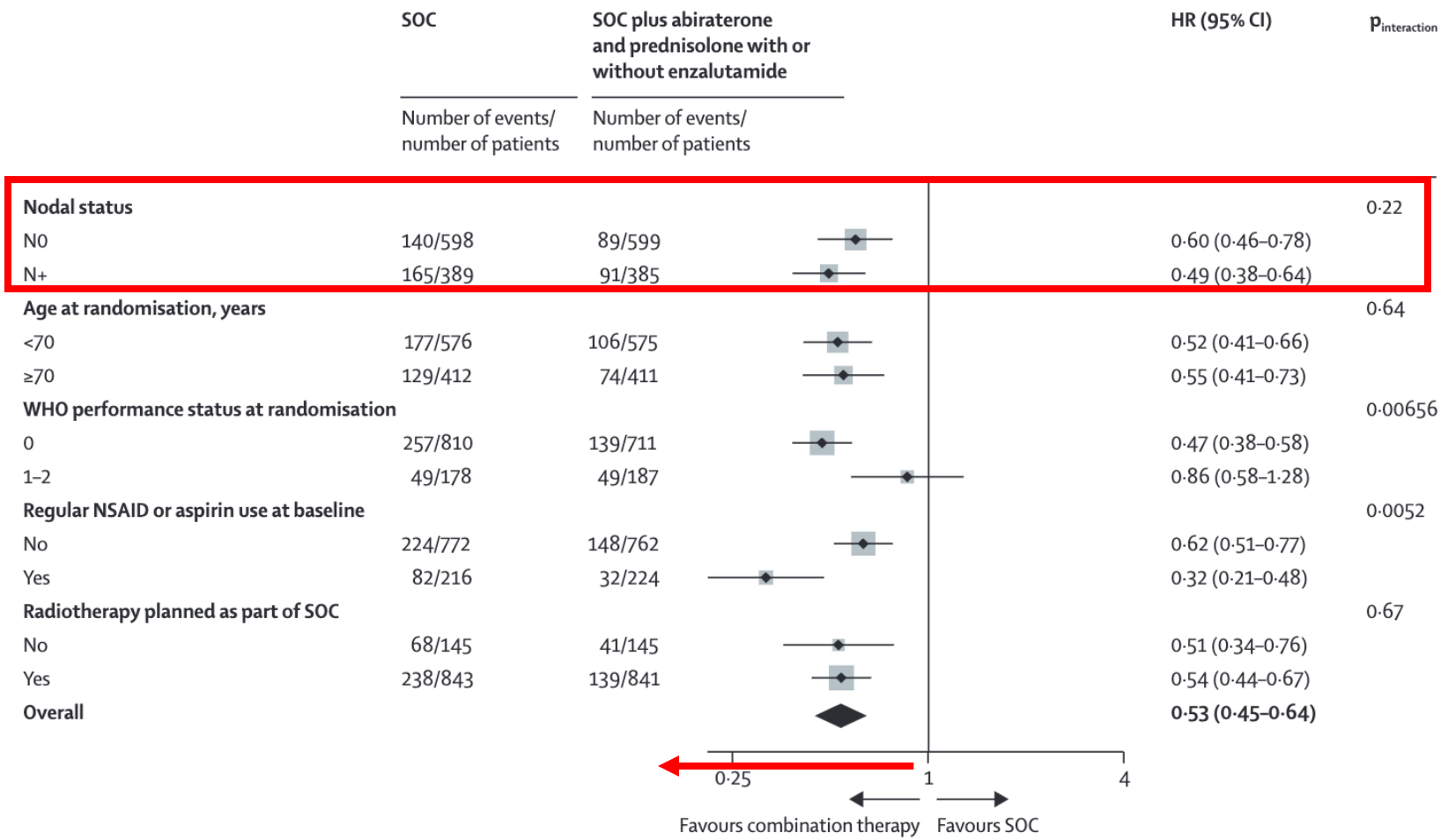
6-year OS =
77% ADT vs. **86%** ADT
+ AA/pred



SOC										
At risk	988	950	894	836	767	550	329	172	53	9
Censored	0	8	11	14	26	201	387	522	632	673
Event	0	30	83	138	195	237	272	294	303	306
SOC plus combination therapy										
At risk	986	948	917	884	839	622	369	198	71	14
Censored	0	21	28	31	45	225	460	615	737	792
Event	0	17	41	71	102	139	157	173	178	180

Attard G. et al. Lancet 2022

STAMPEDE: Abi/pred + EBRT + ADT for non-metastatic PC



Attard G. et al. Lancet 2022

STAMPEDE: Abi/pred + EBRT + ADT for non-metastatic PC

Safety

~30% grade 3 or worse in ADT alone vs. 37% and 57% in combo studies

- HTN and increase in aminotransferases

Attard G. et al. Lancet 2022

Abi/pred + EBRT + ADT for non-metastatic PC

- Thus, for patients managed with radiation therapy and have high-risk disease (either involved **lymph nodes** or at least **2 of the following**):
  - Tumor stage T3 or T4
  - Grade group 4 or 5
  - PSA ≥ 40 ng/ml

- → DISCUSS adding abiraterone acetate plus prednisone to ADT for extended (2 year) course.

PARP inhibitor combination trials in mCRPC

TALAPRO2

PARP inhibitor combination trials

Trial	Arms	Population (First line mCRPC)	Primary Endpoint	Results
MAGNITUDE	niraparib + AA/P vs AA/P	Biomarker Selected Cohorts (HRR+ & HRR-)	rPFS (by central review)	HRR-: stopped for futility; HRRm: 16.5 v 13.7 months (p=0.02); BRCA 1/2m: 16.6 v 10.9 months (p=0.001) Non-BRCA HPPm: HR 0.99 (95%CI: 0.68-1.44) FDA approved 08/23: BRCAm met CRPC
PROpel	olaparib + AA/P vs AA/P	All comers	rPFS (by investigator assessment)	Overall: 24.8 v 16.6 months (p<0.0001); trend towards OS benefit; most significant benefit in BRCAm FDA approval 05/23: BRCAm metCRPC
TALAPRO-2	talazoparib + enza vs enza	HRR alteration status used to stratify randomization	rPFS (by central review) in all comers and HRR+ group	Median NR v 21.9 months (p<0.001); HRR-: HR 0.7 (95%CI: 0.54-0.89) HRRm: HR 0.46 (95%CI: 0.3-0.7) BRCAm: 27.9 v 16.4 months FDA approval 06/23: HRRm metCRPC

Chi K et al. Ann Oncol 2023, Saad F et al. Lancet 2023, Agarwal N. et al Lancet 2023

Talazoparib plus enzalutamide in HRR mCRPC

“Talazoparib plus enzalutamide is a treatment option for patients with metastatic CRPC and a pathogenic mutation (germline and/or somatic) in a homologous recombination repair gene (BRCA1, BRCA2, ATM, ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, or RAD51C) who have not yet had treatment in the setting of CRPC, depending on prior treatment in other disease settings. There may be heterogeneity of response based on the specific gene mutation.”

TALAPRO2: Talazoparib + enzalutamide in first-line mCRPC

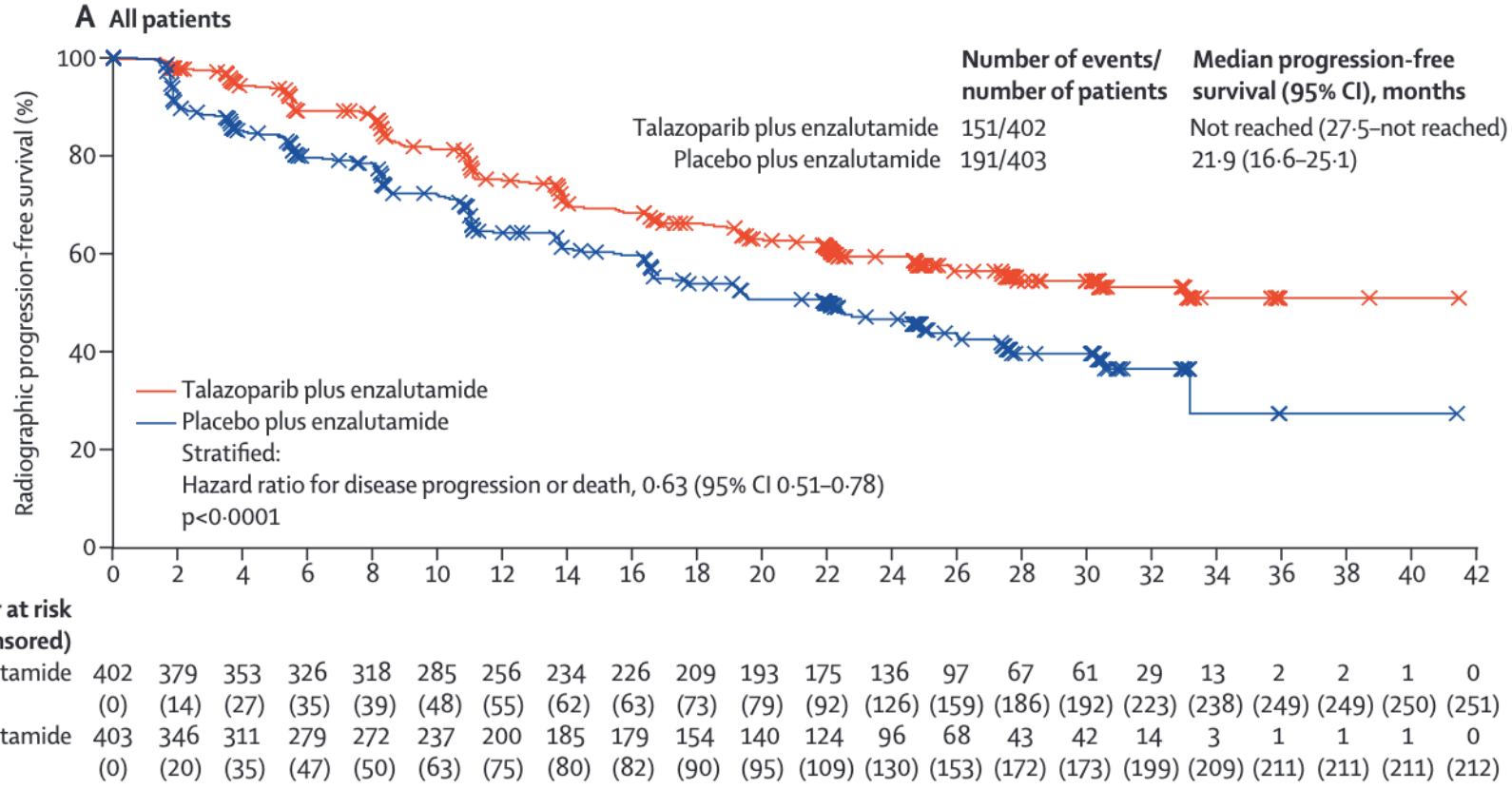
- Randomized, double-blind, Phase 3
- Asymptomatic or mildly symptomatic mCRPC
- Pts prospectively assessed for HRR gene alteration in tumor tissue
- 805 patients randomized → enza/talazoparib vs. enza/placebo
- Randomization was stratified by HRR gene alteration (deficient *vs.* non-deficient or unknown) and by prior NHT or docetaxel (yes *vs.* no)
- Primary outcome = radiographic PFS in ITT

Agarwal N. et al. Lancet 2023

TALAPRO2: Talazoparib + enzalutamide in first-line mCRPC

Median rPFS= NR enza/talaz vs. 21.9m enza/placebo

HR: 0.63; 95% CI, 0.51-0.78; P < 0.0001



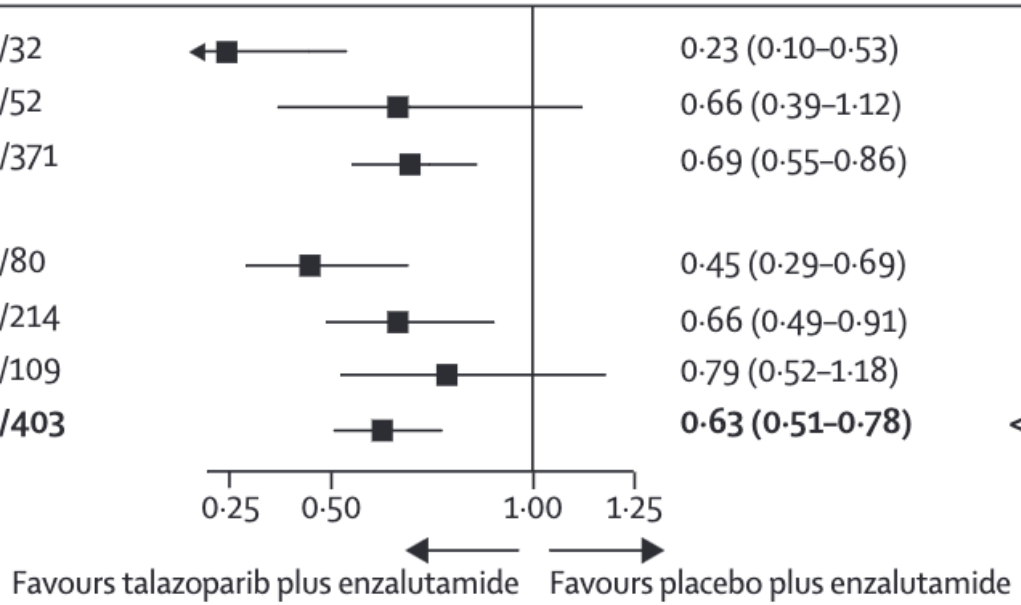
Agarwal N. et al. Lancet 2023

TALAPRO2: Talazoparib + enzalutamide in first-line mCRPC

HRR mutation were present in 169 pts (21%), BRCA most common

B **By *BRCA1/2* status, HRR gene alteration status, and prospective tumour tissue testing**

BRCA1/2-altered, HRR-deficient	8/27	22/32	0·23 (0·10–0·53)	0·0002
Non-*BRCA1/2*-altered, HRR-deficient	29/58	27/52	0·66 (0·39–1·12)	0·12
Non-*BRCA1/2*-altered or unknown, intention-to-treat	143/375	169/371	0·69 (0·55–0·86)	0·0011
By prospective tumour tissue testing				
HRR-deficient	36/83	47/80	0·45 (0·29–0·69)	0·0002
HRR-non-deficient	70/198	96/214	0·66 (0·49–0·91)	0·0092
HRR-unknown	45/121	48/109	0·79 (0·52–1·18)	0·25
Overall	**151/402**	**191/403**	**0·63 (0·51–0·78)**	**<0·0001**



Agarwal N. et al. Lancet 2023

TALAPRO2: Talazoparib + enzalutamide in first-line mCRPC

Effect of prior therapy on radiographic PFS

- In pts that received prior docetaxel (N=179) the HR for rPFS was significant 0.51 (95% CI 0.32-0.81; P=0.0034)
- In pts that received prior NHT (N=50) HR for rPFS was NOT significant 0.57 (95% CI 0.28-1.16; P=0.12)

Agarwal N. et al. Lancet 2023

TALAPRO2: Talazoparib + enzalutamide in first-line mCRPC

Safety

- Consistent with known safety profiles of individual drugs (anemia, neutropenia, fatigue for talazoparib) though hematologic adverse events were higher grade and more frequent than expected with talazoparib alone.

	Talazoparib plus enzalutamide (n=398)		Placebo plus enzalutamide (n=401)	
	All grades	Grade ≥3	All grades	Grade ≥3
Any adverse event	392 (98%)	299 (75%)	379 (95%)	181 (45%)
Treatment-related adverse event	357 (90%)	234 (59%)	279 (70%)	71 (18%)
Serious adverse event	157 (39%)	145 (36%)	107 (27%)	94 (23%)
Serious and treatment-related adverse event	78 (20%)	68 (17%)	12 (3%)	11 (3%)
Adverse event resulting in dose interruption of:				
Talazoparib or placebo*	247 (62%)	..	84 (21%)	..
Enzalutamide†	156 (39%)	..	78 (19%)	..
Adverse event resulting in dose reduction of:				
Talazoparib or placebo*	210 (53%)	..	27 (7%)	..
Enzalutamide†	58 (15%)	..	32 (8%)	..

Agarwal N. et al. Lancet 2023

TALAPRO2: Talazoparib + enzalutamide in first-line mCRPC

- Thus, NCCN panel recommends talazaparib with enzalutamide as treatment option for patients with HRRm, metastatic CRPC, if:
  - No prior docetaxel or no prior NHT (category 1)
  - Prior docetaxel but no prior NHT (category 2A)
  - Prior NHT without prior docetaxel (category 2B, controversial, because benefit over PARPi alone has not been shown, but responses are likely)

Radioligand Therapies

PSMA-Fore and SPLASH

Pluvicto (Lu-177-PSMA-617)

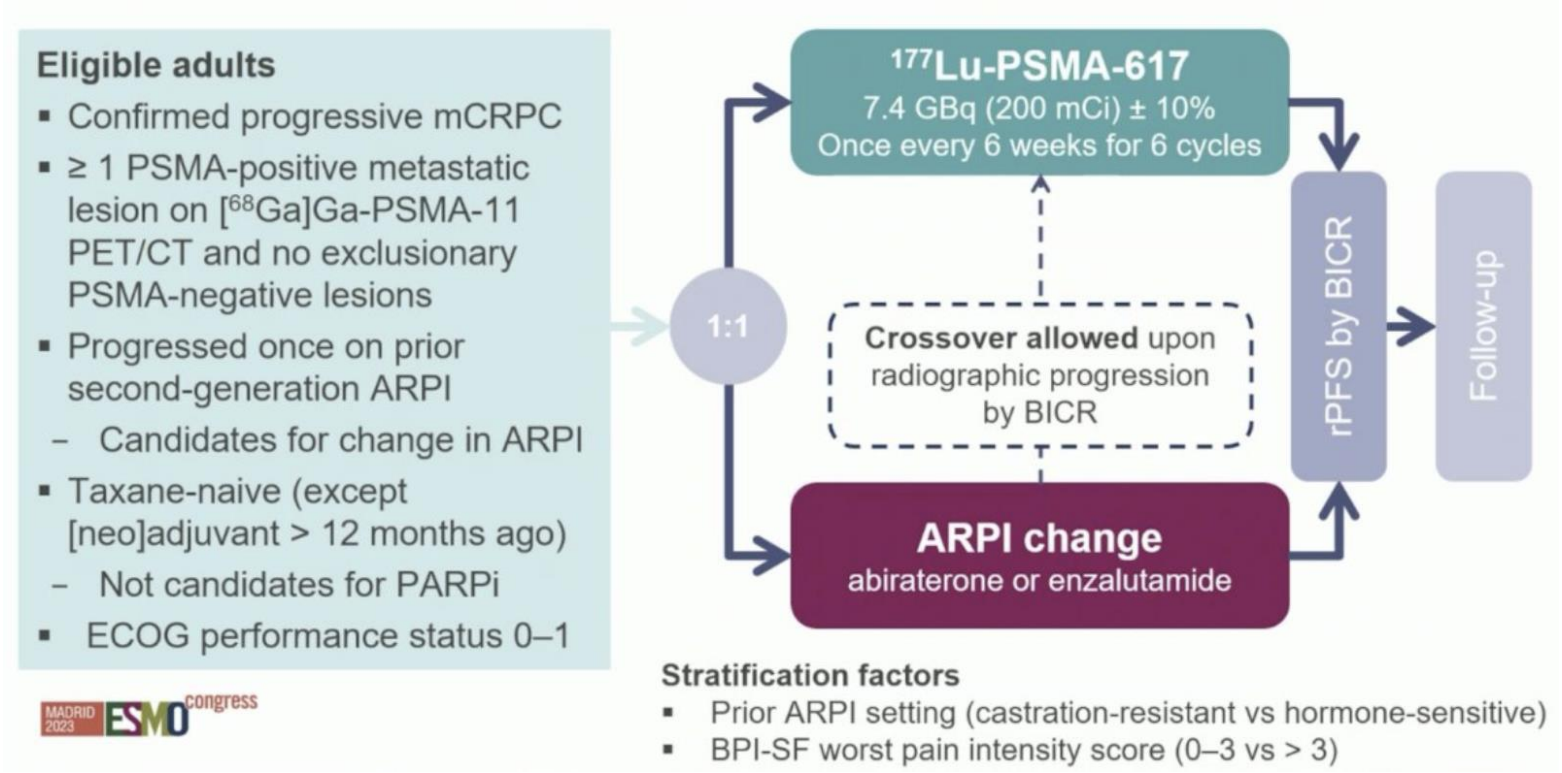
- “NCCN Panel recommends Lu-177-PSMA-617 as a category 1, … For patients with one or more PSMA-positive lesion and no dominant PSMA-negative metastatic lesions who have been previously treated with NHT AND taxane chemotherapy.” (Ph 3 VISION trial)

- Potential NCCN updates coming soon:
- PSMAfore ESMO Oct 2023 (Lu-177-PSMA-617 **taxane-naïve**)
- SPLASH press release Dec 2023 (Lu-177-PSMA I&T **taxane-naïve**)

Sartor O et al. NEJM 2021

Pluvicto (Lu-177-PSMA-617)

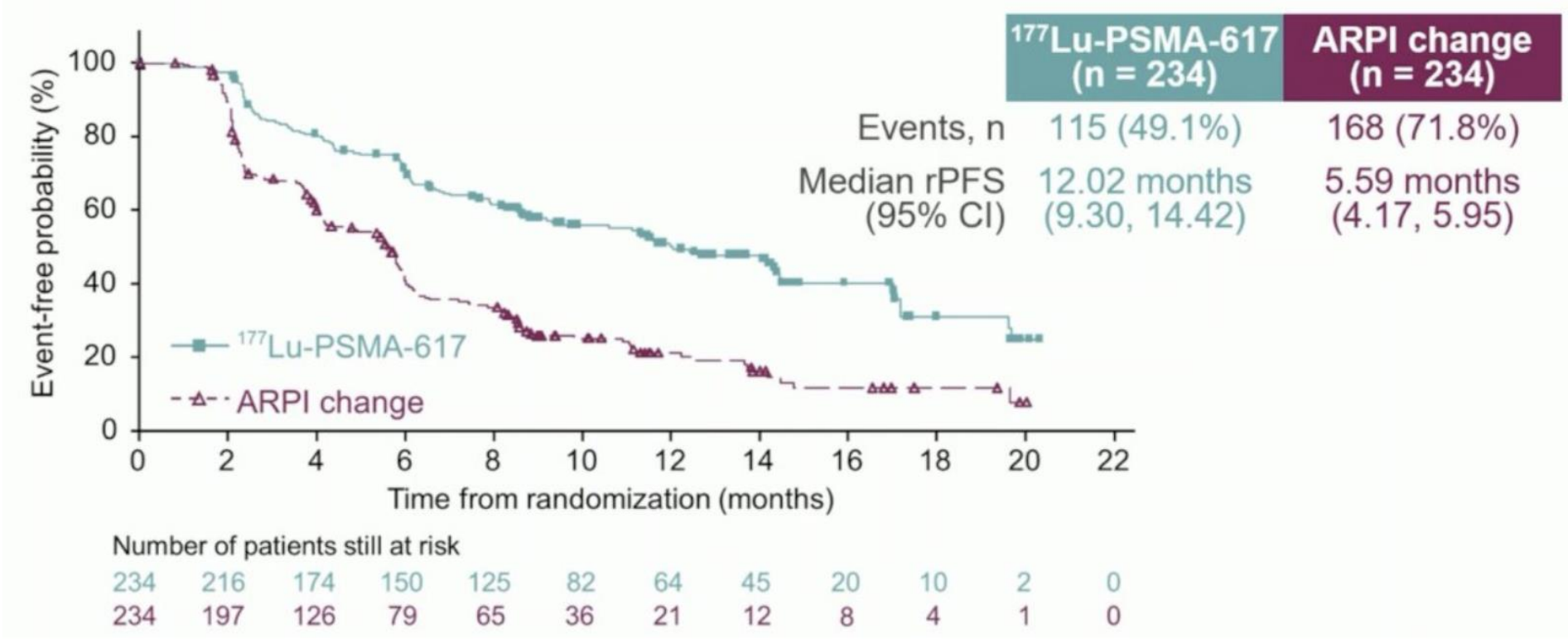
Phase 3: PSMAforeTrial (taxane-naïve CRPC)



Sartor O et al. NEJM 2021

Pluvicto (Lu-177-PSMA-617)

Phase 3: PSMAforeTrial (taxane-naïve CRPC)



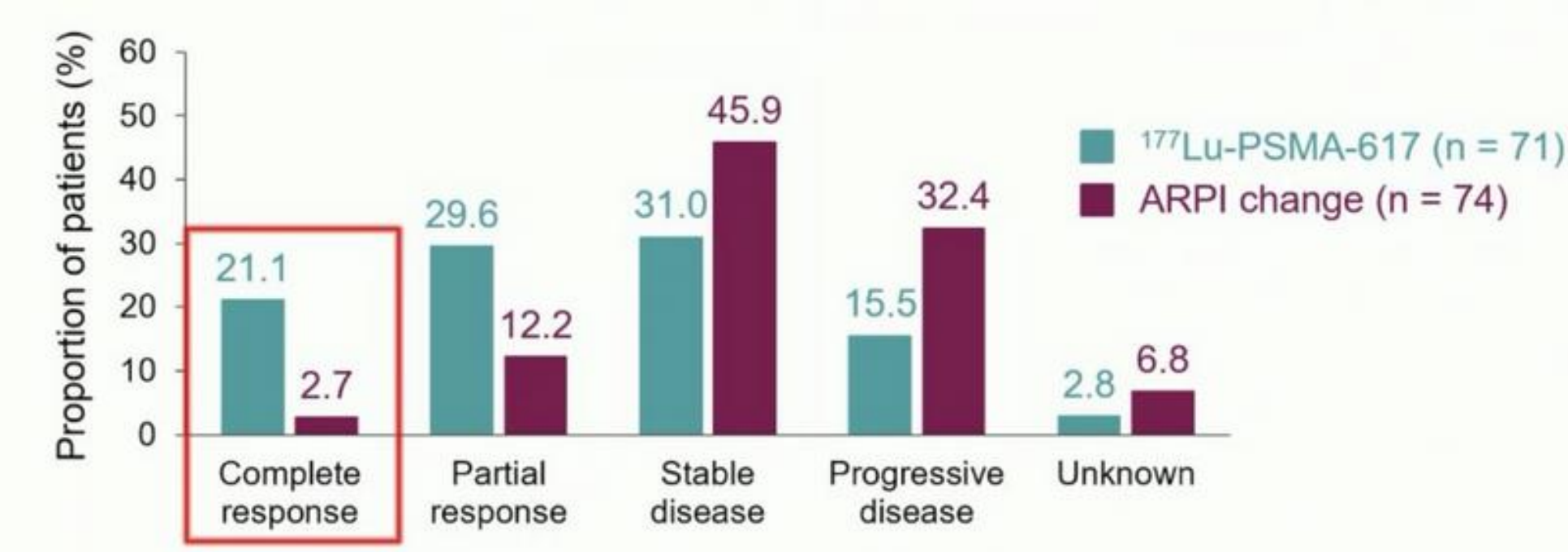
	177Lu-PSMA-617 (n = 234)	ARPI change (n = 234)
Events, n	115 (49.1%)	168 (71.8%)
Median rPFS (95% CI)	12.02 months (9.30, 14.42)	5.59 months (4.17, 5.95)

NOT FDA approved in this setting, awaiting results of the regulators review.

Sartor O et al. ESMO 2023

Pluvicto (Lu-177-PSMA-617)

Phase 3: PSMAforeTrial (taxane-naïve CRPC)



Sartor O et al. ESMO 2023.

Conclusions/Take-Away

- **Effective therapies are moving earlier and in combination!**
- Abiraterone acetate / prednisone now recommended in HR localized settings with EBRT.
- Talazaparib + enzalutamide is recommended in treatment-naïve CRPC setting for patients with HRRm, although may be heterogeneity of response based on the specific gene mutation.
- Targeted Radioligand Therapies show effectiveness in earlier disease stages, i.e., taxane-naïve CRPC (not yet FDA approved or in current NCCN update).

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Thank you