The Clinical Implications of Key Recent Data Sets in Oncology: A Daylong Multitumor Educational Symposium in Partnership with Florida Cancer Specialists

A CME/MOC- and NCPD-Accredited Event

Saturday, October 22, 2022
7:30 AM – 5:30 PM ET

RTP
RESEARCH
TO PRACTICE

Agenda

Module 1 — Lung Cancer: *Drs Langer and Lovly*

Module 2 — Chronic Lymphocytic Leukemia and Lymphomas: *Drs LaCasce and Smith*

Module 3 — Prostate and Bladder Cancers: *Drs Morgans and Yu*

Module 4 — Renal Cell Carcinoma: *Prof Powles*

Module 5 — Multiple Myeloma: *Dr Usmani*

Module 6 — Hepatobiliary Cancers: *Dr Abou-Alfa*

Agenda

Module 7 — Breast Cancer: *Drs Goetz and Krop*

Module 8 — Endometrial Cancer: *Dr Westin*

Module 9 — Ovarian Cancer and PARP Inhibitors: *Dr O'Malley*

Module 10 — Gastrointestinal Cancers: *Drs Messersmith and Strickler*

Module 11 — Melanoma: *Prof Long*

Prostate and Bladder Cancers Faculty

Alicia K Morgans, MD, MPH
Genitourinary Medical Oncologist
Medical Director, Survivorship Program
Dana-Farber Cancer Institute
Boston, Massachusetts

Evan Y Yu, MD
Professor of Medicine
Division of Oncology, Department of Medicine
University of Washington School of Medicine
Member, Clinical Research Division
Fred Hutchinson Cancer Center
Medical Director, Clinical Research Services
Fred Hutchinson Cancer Research Consortium
Seattle, Washington

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The Clinical Implications of Key Recent Data Sets in Oncology: A Daylong Multitumor Educational Symposium in Partnership with Florida Cancer Specialists

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When
Saturday, October 22, 2022
7:30 AM – 5:30 PM

Where
JW Marriott Orlando
Grande Lakes
Orlando, Florida

Moderator Hosting in Person
Neil Love, MD

Faculty Presenting in Person

Breast Cancer
Matthew P Goetz, MD
Ian E Krop, MD, PhD

Chronic Lymphocytic Leukemia and Lymphomas
Ann S LaCasce, MD, MMSc
Mitchell R Smith, MD, PhD

Gastrointestinal Cancers
Wells A Messersmith, MD
John Strickler, MD

Prostate and Bladder Cancers
Alicia K Morgans, MD, MPH
Evan Y Yu, MD

Lung Cancer
Corey J Langer, MD
Christine M Lovly, MD, PhD

Faculty Presenting Virtually

Endometrial Cancer
Shannon N Westin, MD, MPH

Hepatobiliary Cancers
Ghassan Abou-Alfa, MD, MBA

Melanoma
Prof Georgina Long, AO, BSc, PhD, MBBS

CAR T-Cell and Bispecific Therapy for Multiple Myeloma
Saad Zafar Usmani, MD, MBA

Ovarian Cancer and PARP Inhibitors
David M O'Malley, MD

Renal Cell Carcinoma
Thomas Powles, MBBS, MRCP, MD

CME Certified
NCPD Accredited

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ABIM CME MOC ACCREDITED

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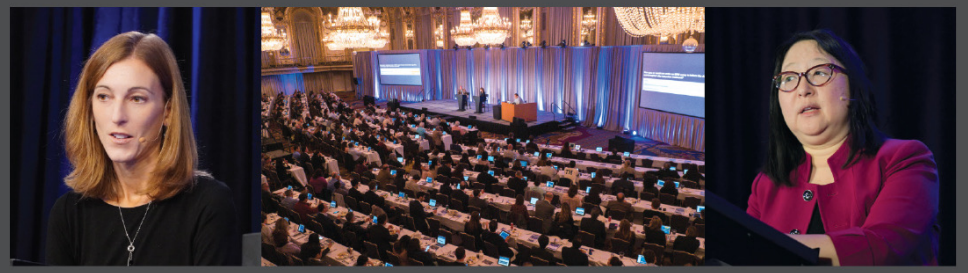
Lunch with the Investigators
Acute Myeloid Leukemia and Myelodysplastic Syndromes



A CME Hybrid Symposium Held in Conjunction with the 2022 ASCO® Annual Meeting

When
Friday, June 3, 2022
11:45 AM – 12:45 PM

Where
Hilton Chicago
Chicago, Illinois

Faculty
Courtney D DiNardo, MD, MSCE
Michael R Savona, MD
Eunice S Wang, MD

Moderator
Neil Love, MD

CME Certified

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RTP RESEARCH TO PRACTICE

Prostate and Bladder Cancers Agenda

MODULE 1: Prostate Cancer

MODULE 2: Urothelial Bladder Cancer

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Prostate and Bladder Cancers Agenda

MODULE 1: Prostate Cancer

MODULE 2: Urothelial Bladder Cancer

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Updates in Advanced Prostate Cancer

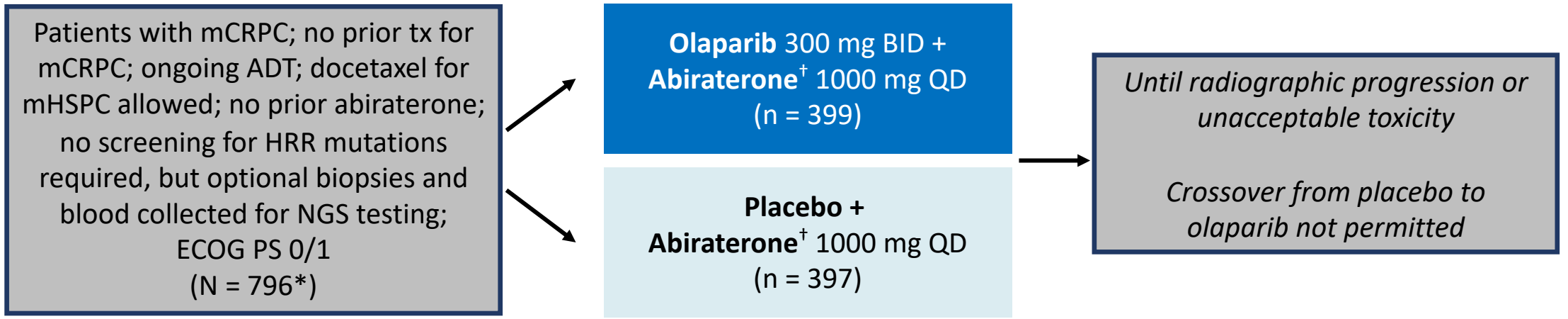
Alicia Morgans, MD, MPH
Dana-Farber Cancer Institute

Dana-Farber
Cancer Institute

PROpel: First-Line Olaparib + Abiraterone vs Placebo + Abiraterone in mCRPC

- Interim analysis of international, randomized, double-blind phase III trial (data cutoff: July 30, 2021)

Stratified by metastatic disease sites (bone only vs visceral vs other), taxane for mHSPC (yes vs no)

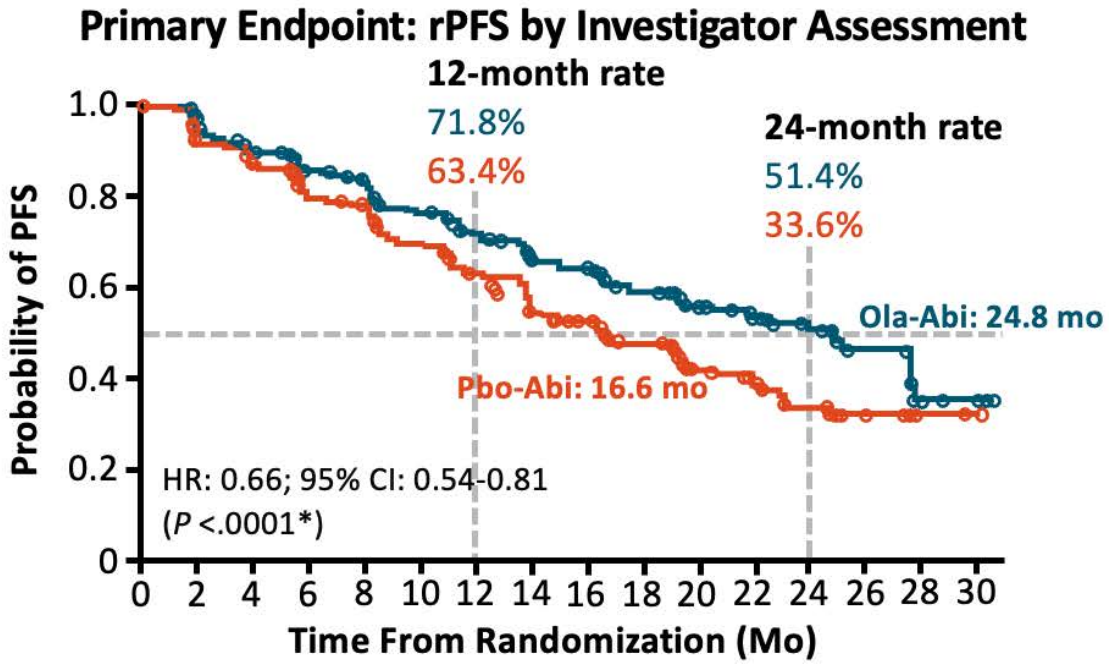


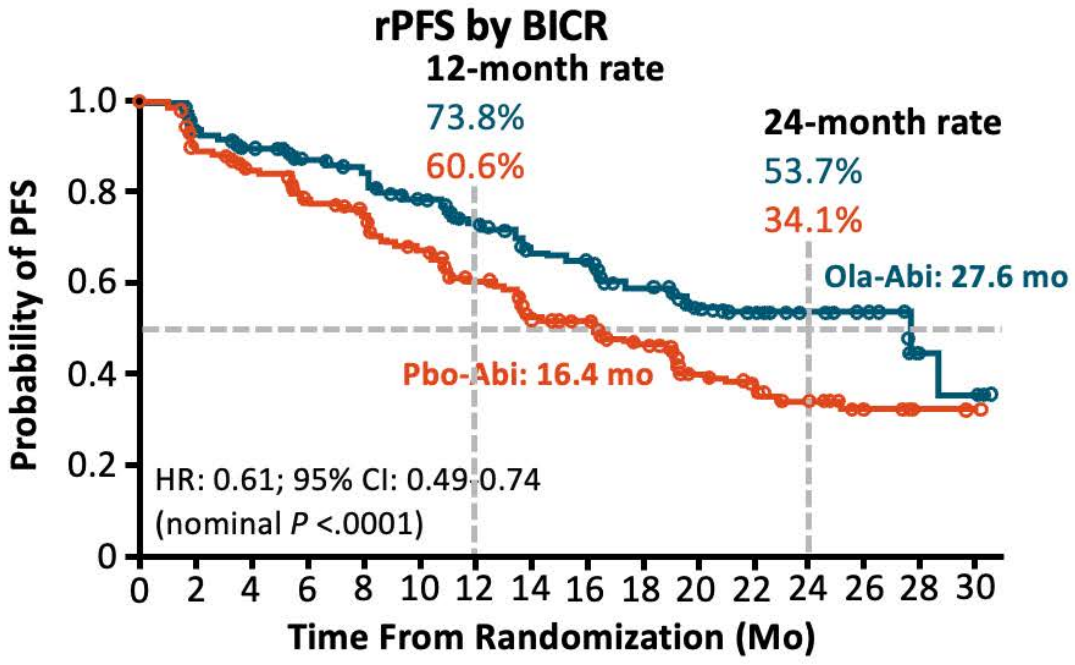
*An additional 108 patients will be randomized 1:1 in China.
†Prednisone/prednisolone (5 mg BID) given with abiraterone.

- **Primary endpoint:** rPFS by investigator
- **Key secondary endpoints:** OS, time to subsequent therapy or death, PFS2, ORR, HRRm prevalence (retrospectively assessed), HRQOL, safety

Saad F, et al. ASCO GU 2022. Abstract 11; Clarke NW, et al. ASCO 2019. Abstract TPS340; ClinicalTrials.gov ID: NCT03732820.

PROpel: Radiologic PFS





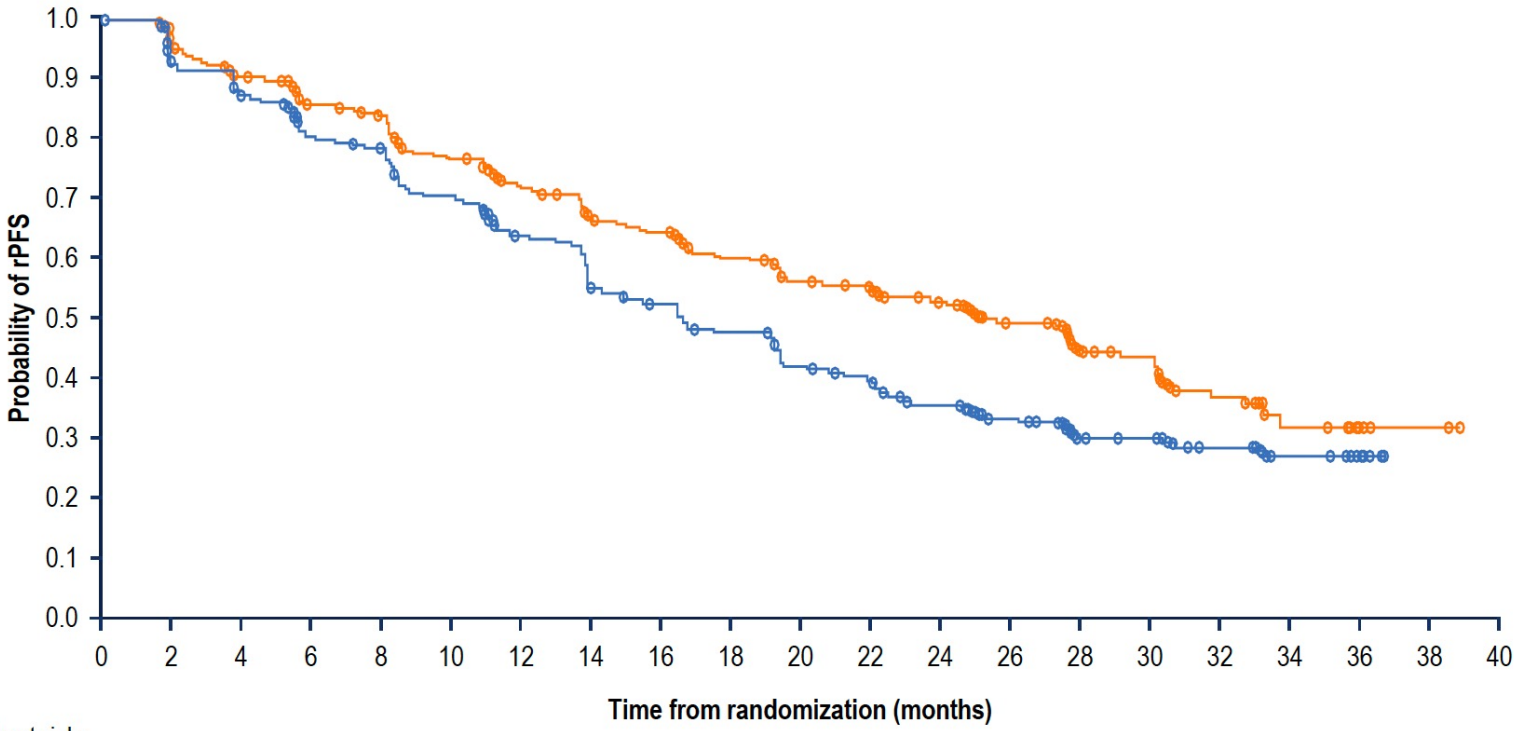
Subgroup	n	Median rPFS		HR (95% CI)
		Olaparib + Abiraterone	Placebo + Abiraterone	
HRRm	226	NR	13.9	0.50 (0.34–0.73)
Non-HRRm	552	24.1	19.0	0.76 (0.60–0.97)

Saad F, et al. ASCO GU 2022. Abstract 11.

*Prespecified 2-sided α = 0.0324.

PROpel: updated rPFS by investigator assessment in the ITT population

At DCO2, rPFS was 8.6 months greater for abiraterone + olaparib versus abiraterone + placebo



Number of patients at risk:

Abiraterone + olaparib	399	367	340	313	301	274	251	228	220	200	184	174	158	110	62	58	33	15	5	3	0
Abiraterone + placebo	397	359	338	306	297	264	232	199	187	169	145	135	117	84	51	48	30	8	3	0	0

	Abiraterone + olaparib (n=399)	Abiraterone + placebo (n=397)
Events, n (%)	199 (49.9)	258 (65.0)
Median rPFS (months)	25.0	16.4
HR (95% CI)	0.67 (0.56–0.81); *P*<0.0001*	

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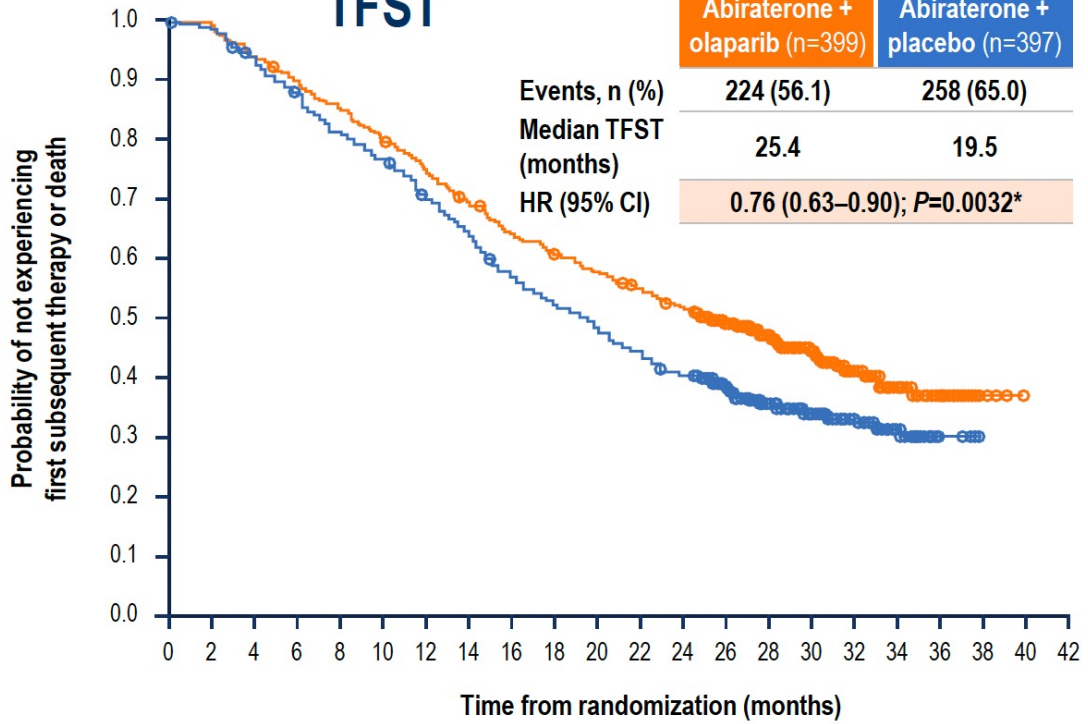
*Nominal

Median duration of follow-up for censored patients was 24.9 months (range 0.03–38.80) in the abiraterone + olaparib arm and 27.4 months (range 0.03–36.76) in the abiraterone + placebo arm

PROpel key secondary endpoints: TFST and PFS2

At DCO2, TFST and PFS2 results supported a trend towards longer-term benefit with abiraterone + olaparib

TFST

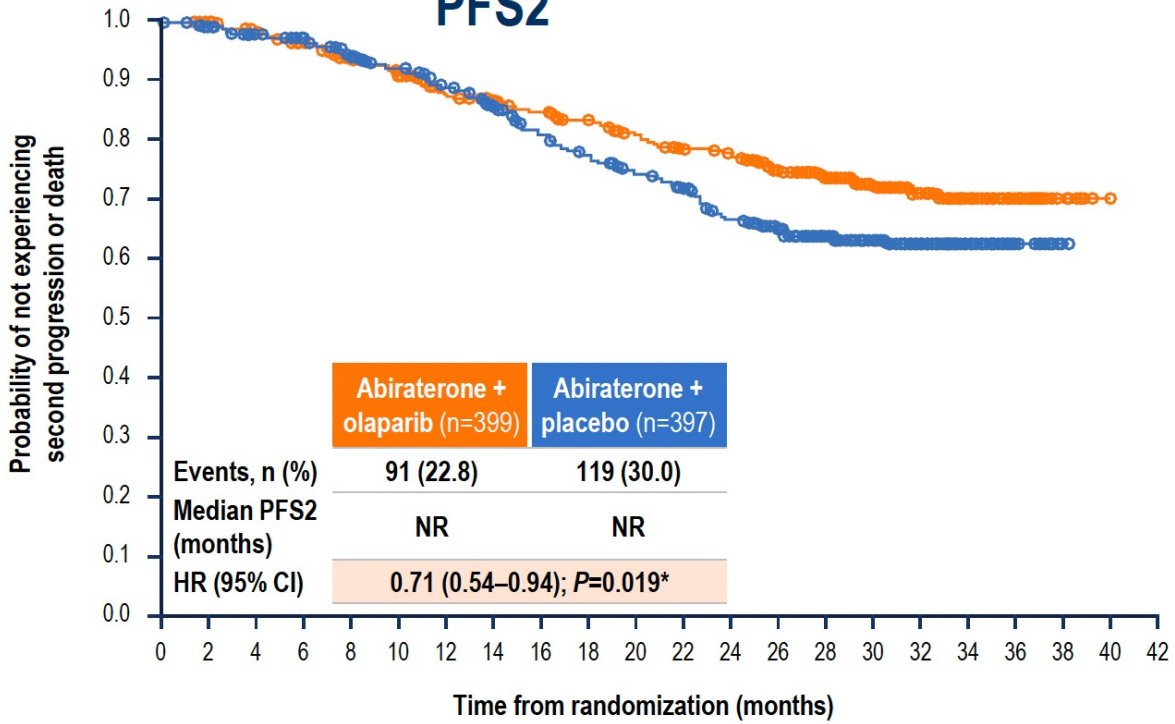


	Abiraterone + olaparib (n=399)	Abiraterone + placebo (n=397)
Events, n (%)	224 (56.1)	258 (65.0)
Median TFST (months)	25.4	19.5
HR (95% CI)	0.76 (0.63–0.90); *P*=0.0032*	

Number of patients at risk:

Abiraterone + olaparib	399	396	374	358	338	317	296	274	252	239	226	213	200	170	132	93	58	36	19	4	1	0
Abiraterone + placebo	397	391	369	345	319	303	273	250	222	203	188	171	156	129	98	66	46	26	6	0	0	0

PFS2



	Abiraterone + olaparib (n=399)	Abiraterone + placebo (n=397)
Events, n (%)	91 (22.8)	119 (30.0)
Median PFS2 (months)	NR	NR
HR (95% CI)	0.71 (0.54–0.94); *P*=0.019*	

Abiraterone + olaparib	399	385	369	349	334	311	289	276	267	259	245	234	230	196	156	113	79	47	22	5	1	0
Abiraterone + placebo	397	380	367	351	338	316	293	271	252	238	225	215	196	162	123	85	62	37	11	1	0	0

First subsequent therapies

- 157 (39.3%) patients in the abiraterone + olaparib arm and 197 (49.6%) in the abiraterone + placebo arm had subsequent therapies
- The most common first subsequent therapies were cytotoxic chemotherapy (n=221) and hormonal therapy (n=103)

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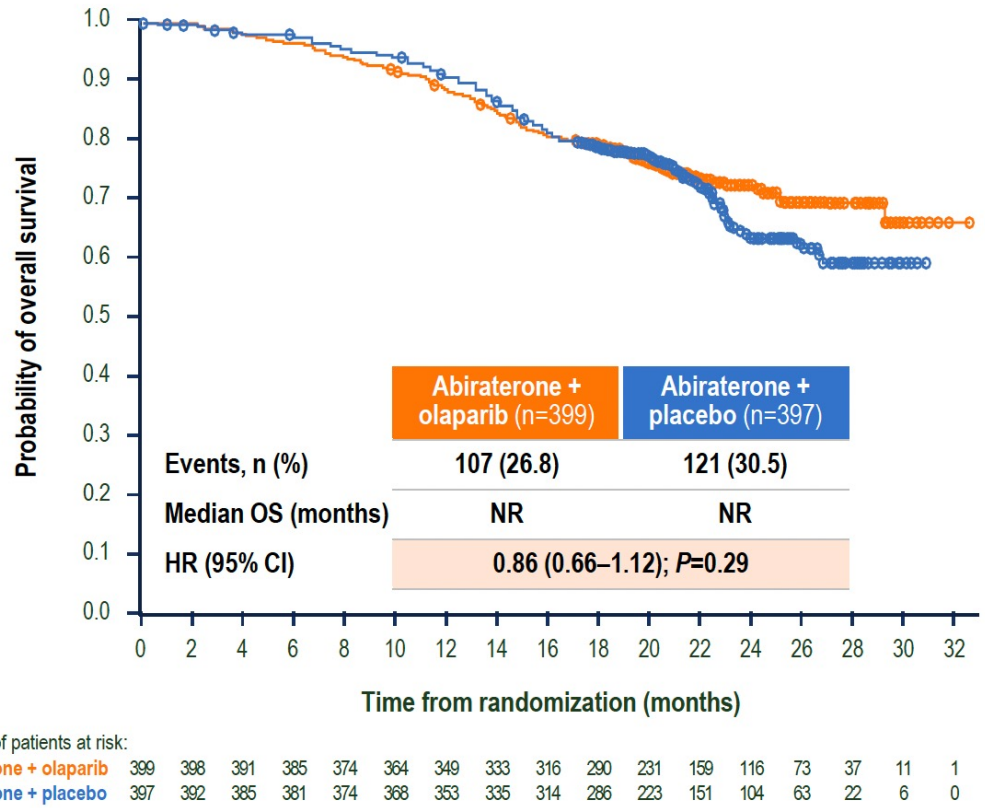
A circle indicates a censored observation
*Nominal
PSF2, time to second progression or death; TSFT, time to first subsequent therapy or death

PROpel key secondary endpoint: OS in the ITT population

At DCO2, there was a continued trend towards improved OS with abiraterone + olaparib, with KM curves showing clear separation between the arms after ~22 months before extensive censoring was observed

Primary analysis (DCO1, 28.6% maturity)

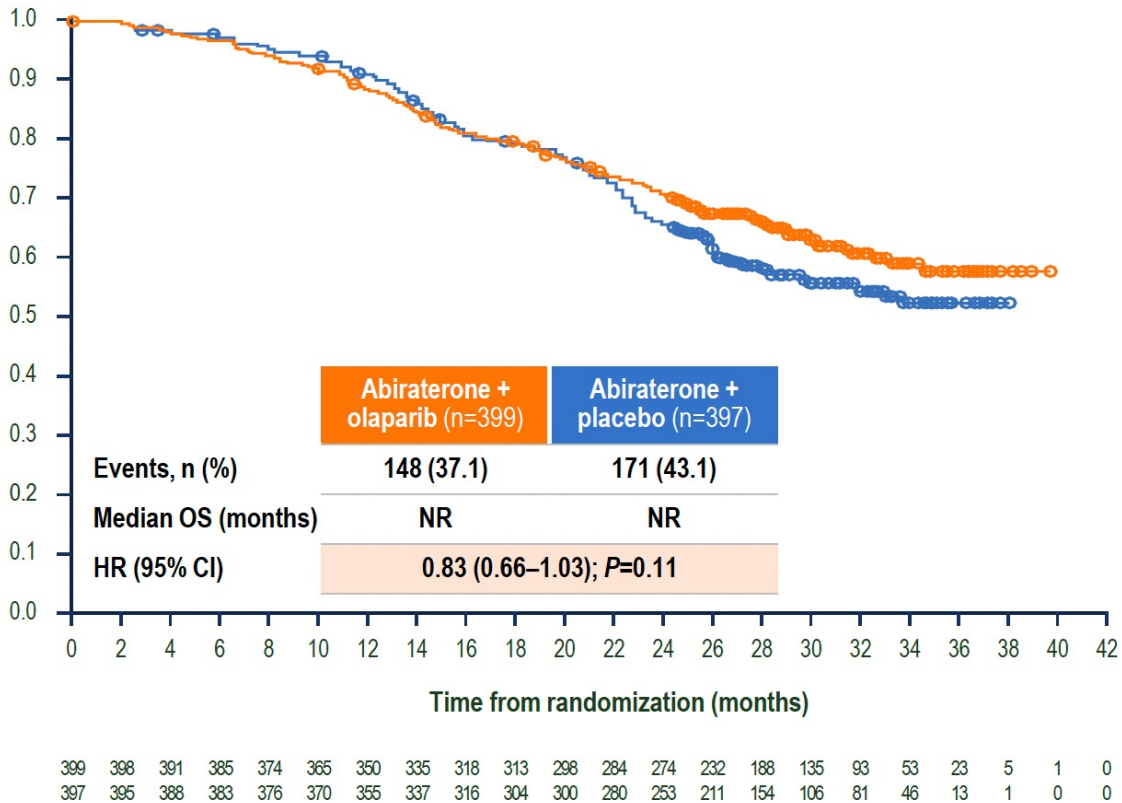


	Abiraterone + olaparib (n=399)	Abiraterone + placebo (n=397)
Events, n (%)	107 (26.8)	121 (30.5)
Median OS (months)	NR	NR
HR (95% CI)	0.86 (0.66–1.12); *P*=0.29	

Number of patients at risk:

Abiraterone + olaparib	399	398	391	385	374	364	349	333	316	290	231	159	116	73	37	11	1
Abiraterone + placebo	397	392	385	381	374	368	353	335	314	286	223	151	104	63	22	6	0

Updated results (DCO2, 40.1% maturity)



	Abiraterone + olaparib (n=399)	Abiraterone + placebo (n=397)
Events, n (%)	148 (37.1)	171 (43.1)
Median OS (months)	NR	NR
HR (95% CI)	0.83 (0.66–1.03); *P*=0.11	

Abiraterone + olaparib	399	398	391	385	374	365	350	335	318	313	298	284	274	232	188	135	93	53	23	5	1	0
Abiraterone + placebo	397	395	388	383	376	370	355	337	316	304	300	280	253	211	154	106	81	46	13	1	0	0

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A circle indicates a censored observation

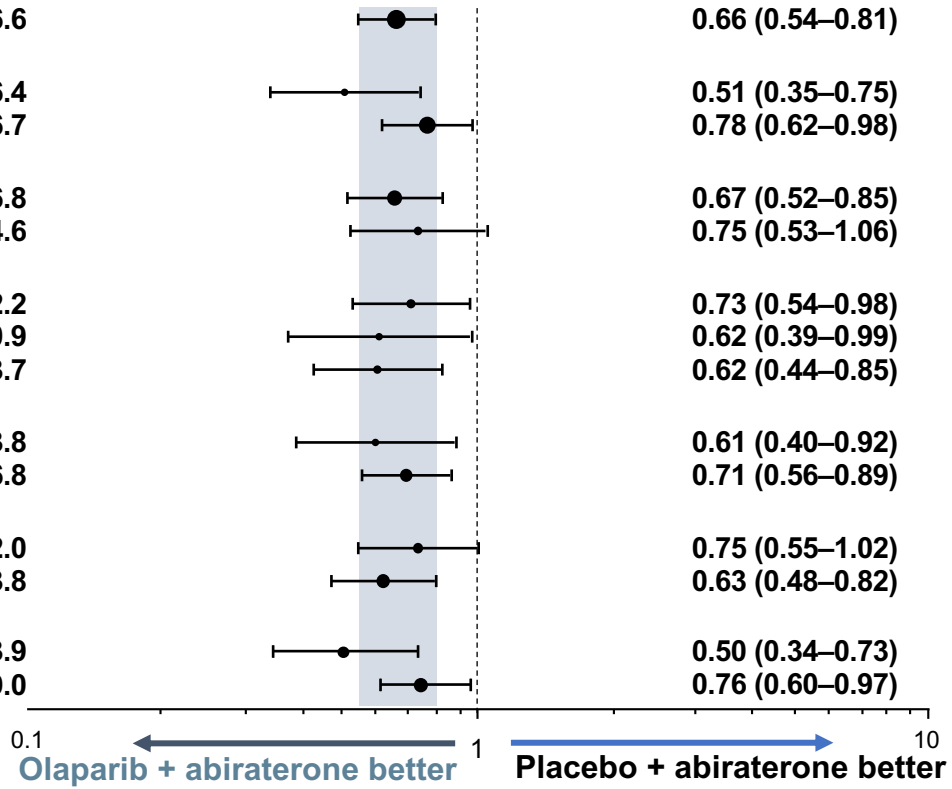
Median duration of follow-up for censored patients at DCO1 was 22.2 months (range 0.03–32.56) in the abiraterone + olaparib arm and 21.8 months (range 0.10–30.88) in the abiraterone + placebo arm.

Median duration of follow-up for censored patients at DCO2 was 30.0 months (range 0.03–40.02) in the abiraterone + olaparib arm and 29.4 months (range 2.89–38.34) in the abiraterone + placebo arm

PROpel: subgroup analysis of rPFS

rPFS benefit observed across all pre-specified subgroups

	Number of patients, n	Median rPFS, months		HR (95% CI)
All patients	796	24.8	16.6	0.66 (0.54–0.81)
Age at randomisation				
<65	227	NR	16.4	0.51 (0.35–0.75)
≥65	569	22.0	16.7	0.78 (0.62–0.98)
ECOG performance status at baseline				
0	558	24.9	16.8	0.67 (0.52–0.85)
1	236	17.5	14.6	0.75 (0.53–1.06)
Site of distant metastases				
Bone only	434	27.6	22.2	0.73 (0.54–0.98)
Visceral	105	13.7	10.9	0.62 (0.39–0.99)
Other	257	20.5	13.7	0.62 (0.44–0.85)
Docetaxel treatment at mHSPC stage				
Yes	189	27.6	13.8	0.61 (0.40–0.92)
No	607	24.8	16.8	0.71 (0.56–0.89)
Baseline PSA				
Below median baseline PSA	396	25.2	22.0	0.75 (0.55–1.02)
Above or equal to median baseline PSA	397	18.5	13.8	0.63 (0.48–0.82)
HRRm status[a]				
HRRm	226	NR	13.9	0.50 (0.34–0.73)
Non-HRRm	552	24.1	19.0	0.76 (0.60–0.97)



Global interaction test not significant at 10% level

Global interaction test not significant at 10% level. [a]The HRRm status of patients in PROpel was determined retrospectively using results from tumour tissue and plasma ctDNA HRRm tests. Patients were classified as HRRm if (one or more) HRR gene mutation was detected by either test; patients were classified as non-HRRm patients if no HRR gene mutation was detected by either test; patients were classified as unknown HRRm if no valid HRR test result from either test was achieved. 18 patients did not have a valid HRR testing result from either a tumour tissue or ctDNA test and were excluded from the subgroup analysis. This subgroup analysis is post hoc exploratory analysis.

CI, confidence interval; ctDNA, circulating tumour DNA; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; HRR(m), homologous recombination (mutation); mHSPC, metastatic hormone sensitive prostate cancer; NR, not reached; PSA, prostate specific antigen; rPFS, radiographic progression-free survival

Saad F, et al. ASCO GU 2022. Abstract 11.

Adverse Events and HRQOL

Safety Outcome, n (%)	Olaparib + Abiraterone (n = 399)	Placebo + Abiraterone (n = 397)
Any AE	387 (97.2)	376 (94.9)
Any grade ≥3 AE	188 (47.2)	152 (38.4)
Death due to an AE	16 (4.0)	17 (4.3)
Any AE leading to		
• Dose interruption of olaparib/placebo	178 (44.7)	100 (25.3)
• Dose reduction of olaparib/placebo	80 (20.1)	22 (5.6)
• D/c of olaparib/placebo	55 (13.8)	31 (7.8)
• D/c of abiraterone	34 (8.5)	35 (8.8)

Cardiac and Thromboembolic AE, n (%)	Olaparib + Abiraterone (n = 399)	Placebo + Abiraterone (n = 397)
Cardiac failure*	6 (1.5)	5 (1.3)
Embolic and thromboembolic events, arterial*	8 (2.0)	10 (2.5)
Embolic and thromboembolic events, venous*	29 (7.3)	13 (3.3)
• Pulmonary embolism	26 (6.5)	7 (1.8)

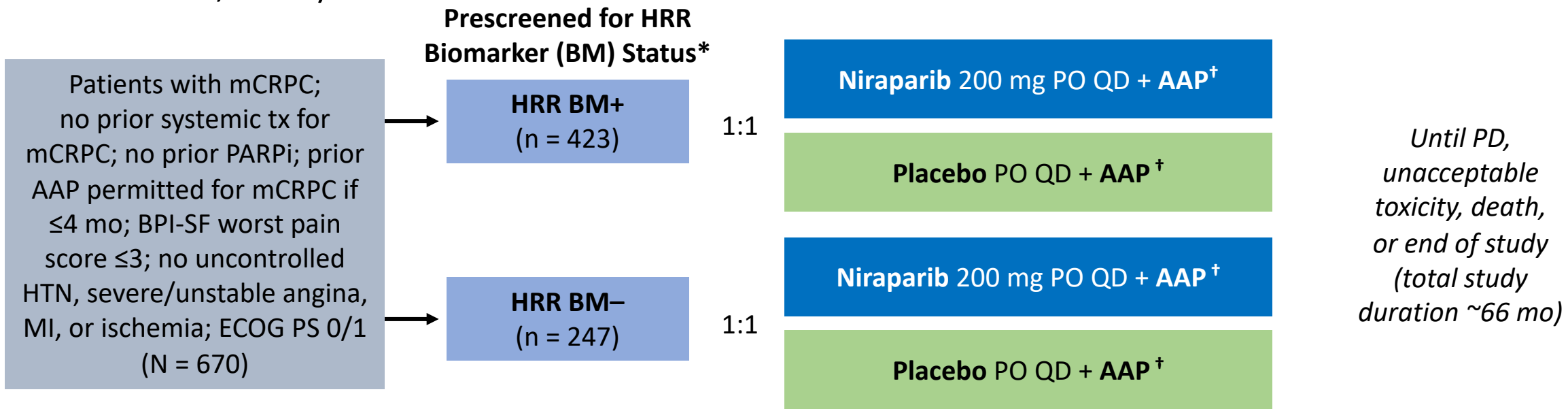
*Standardized MedDRA query (SMQ).

- Incidence of new primary malignancies and pneumonitis balanced between arms
- No cases reported of MDS/AML
- HRQOL per FACT-P was comparable between arms over time

Saad F, et al. ASCO GU 2022. Abstract 11.

MAGNITUDE: First-Line Niraparib + Abiraterone Acetate and Prednisone in mCRPC

- International, randomized, double-blind phase III trial (cutoff for final rPFS analysis: October 8, 2021)

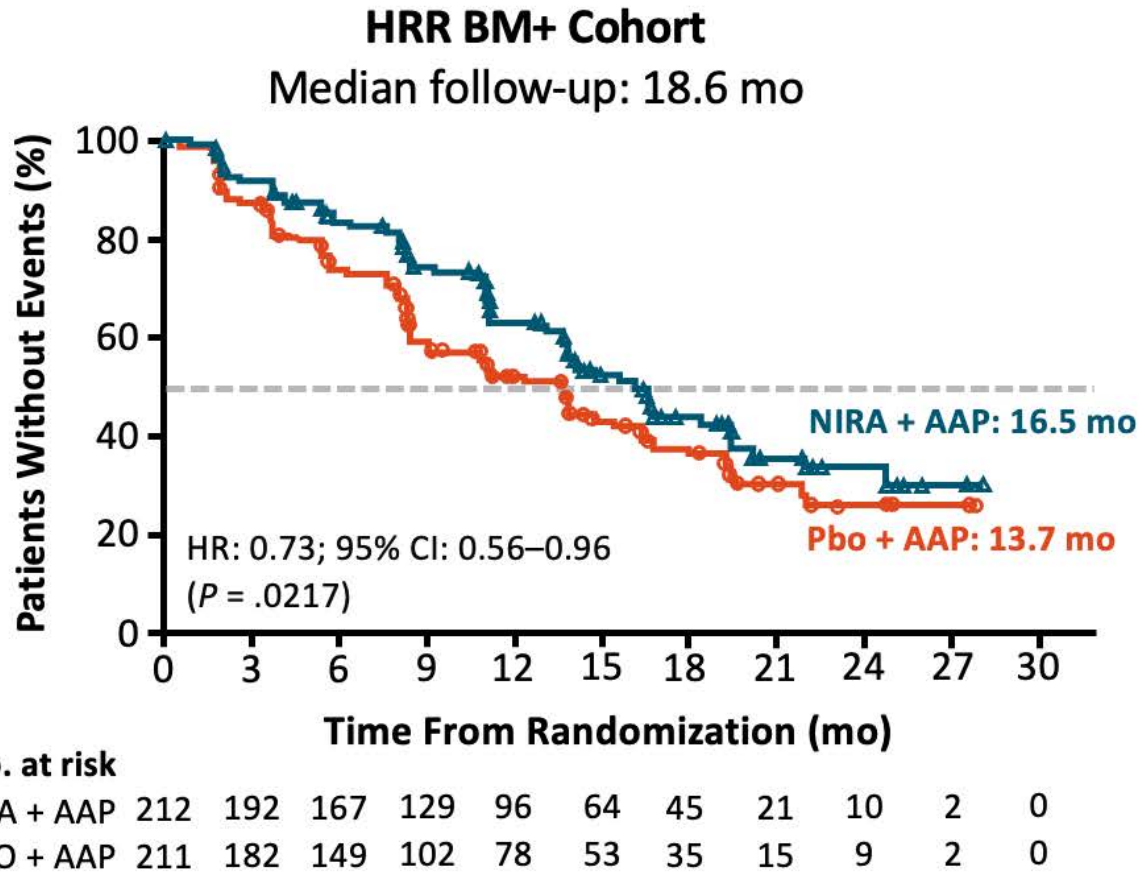


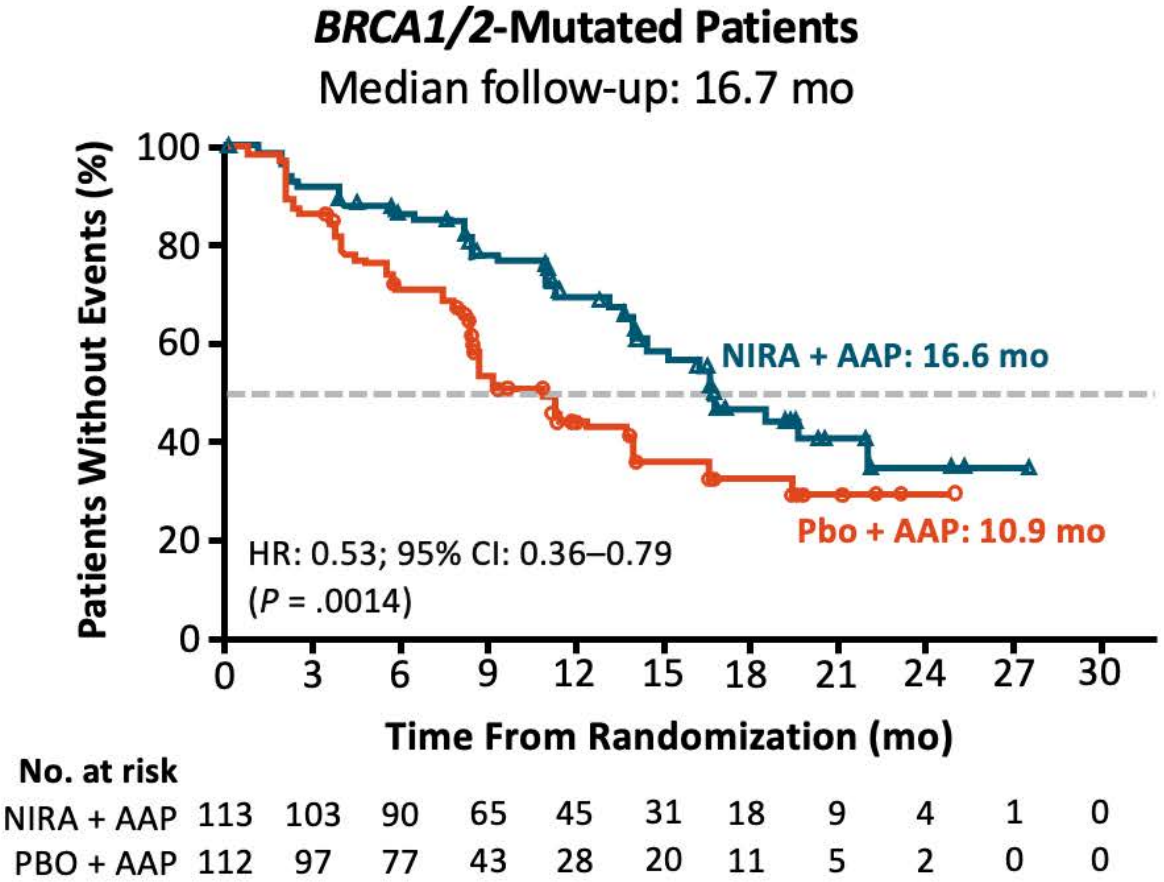
*HRR BM+ per tissue and/or plasma assays for *ATM, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, HDAC2, PALB2*;
†AAP: abiraterone acetate 1000 mg PO QD + prednisone 10 mg PO QD.

- **Primary endpoint:** radiographic PFS by central review
- **Secondary endpoints:** OS, time to symptomatic progression, time to cytotoxic chemotherapy

Chi KN, et al. ASCO GU 2022. Abstract 12; Chi KN, et al. ASCO 2020. Abstract TPS5588. ClinicalTrials.gov ID: NCT03748641.

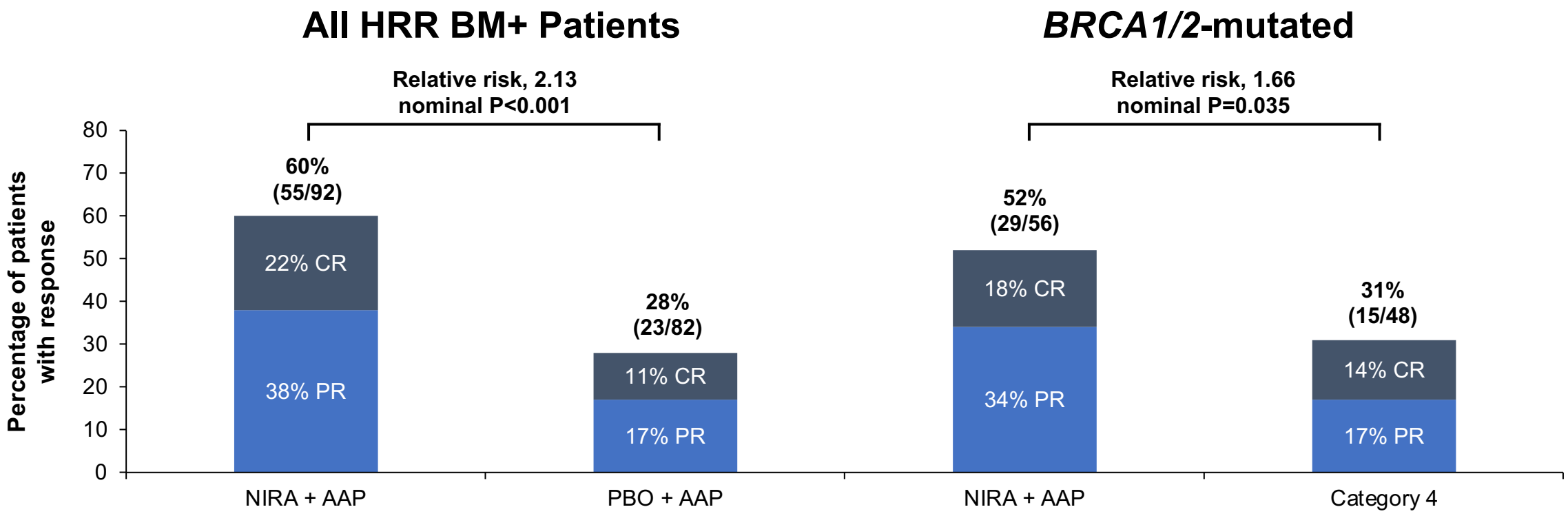
MAGNITUDE: Radiologic PFS by Central Review (primary endpoint)





Chi KN, et al. ASCO GU 2022. Abstract 12.

MAGNITUDE: NIRA + AAP Improves Overall Response Rate Consistently Across Gene Alterations



NIRA + AAP nearly doubles ORR rate and provides deeper response in patients with measurable disease

Note: Relative risk >1 favours niraparib and AAP treatment. Percent of responder is based on the number of subjects with measurable disease at baseline
AAP, abiraterone acetate plus prednisone; CR, complete response; HRR, homologous recombination repair, NIRA, niraparib; PBO, placebo; PR, partial response

Chi K, et al. J Clin Oncol. 2022;40 (suppl 6; abstr 12) (ASCO GU 2022 oral presentation

Treatment-Emergent AEs in HRR BM+ Cohort

Safety Outcome, n (%)	Niraparib + AAP (n = 212)	Placebo + AAP (n = 211)
All TEAEs • Drug related	210 (99.1) 162 (76.4)	199 (94.3) 116 (55.0)
Grade 3/4 TEAEs	142 (67.0)	98 (46.4)
Serious AEs • Drug related	76 (35.8) 24 (11.3)	52 (24.6) 6 (2.8)
Dose reduction due to AE	42 (19.8)	7 (3.3)
Discontinuation of niraparib/placebo due to AE	23 (10.8)	10 (4.7)
All deaths within 30 days of last dose • Death due to prostate cancer • AE	19 (9.0) 8 (3.8) 11 (5.2)	19 (9.0) 12 (5.7) 7 (3.3)

- AEs most frequently leading to dose reduction in niraparib arm
  - Anemia: 13.2%
  - Thrombocytopenia: 2.8%
- Median relative dose intensity in niraparib arm: 99%

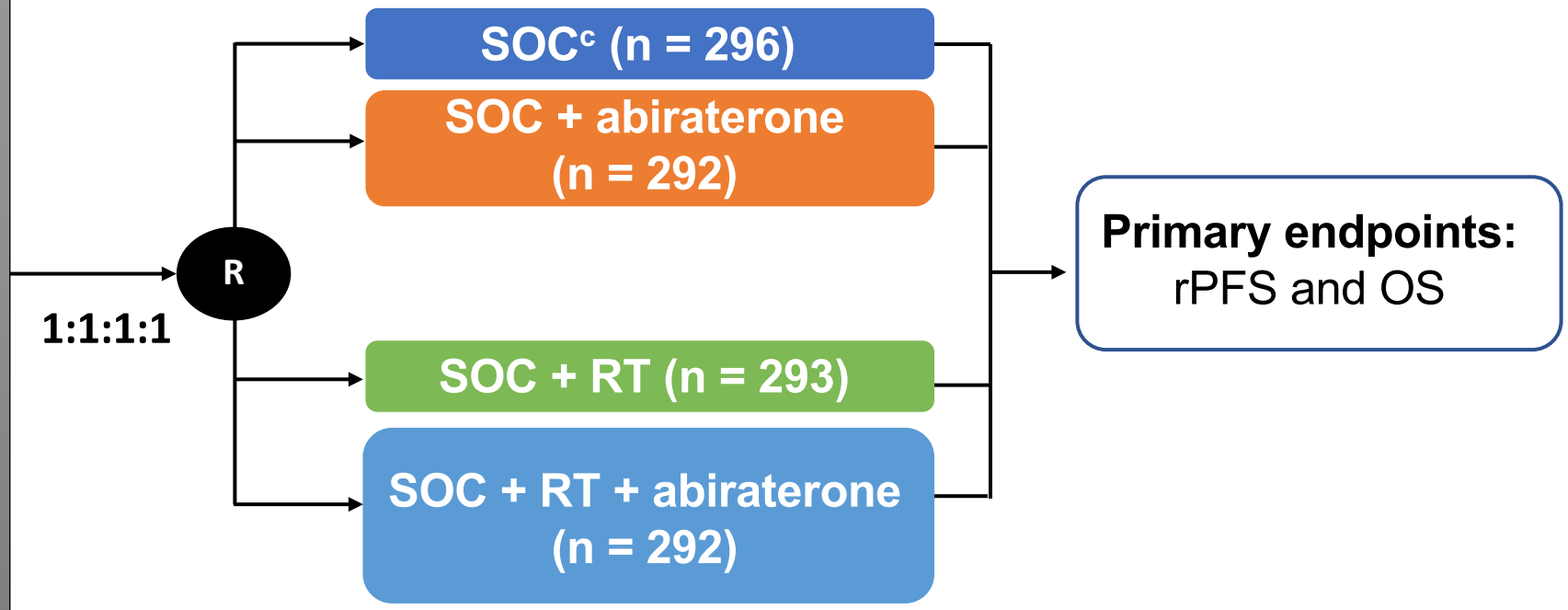
Chi KN, et al. ASCO GU 2022. Abstract 12.

mHSPC: Data on Triplet Therapy

PEACE-1: Abiraterone + Prednisone in Men With De Novo mCSPC

Key Eligibility Criteria
- De novo mCSPC
- Distant metastatic disease
- On-study requirement of continuous ADT
- ADT ≤3 months permitted

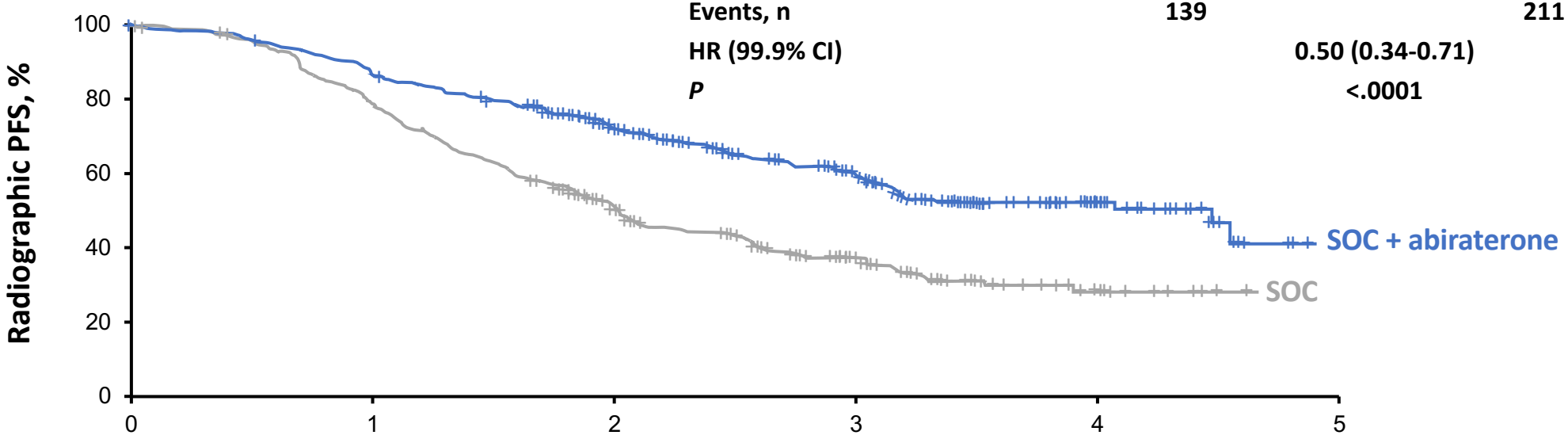
Stratification Factors
- ECOG PS 0 vs 1-2
- Site of metastases (LN vs bone vs viscera)
- Castration type (orchiectomy vs GnRH agonist vs GnRH antagonist)
- Docetaxel (yes vs no)



Fizazi K et al. *J Clin Oncol*. 2021;39(suppl 15):5000. Fizazi K. ESMO 2021. Abstract LBA5_PR.

PEACE-1: Improved rPFS With Abiraterone in the ADT + Docetaxel (+/- RT) Population

	SOC + Abiraterone (n = 355)	SOC (n = 355)
Median, y (IQR)	4.46 (1.9-NR)	2.03 (1.09-NR)
Events, n	139	211
HR (99.9% CI)	0.50 (0.34-0.71)	
P	<.0001	

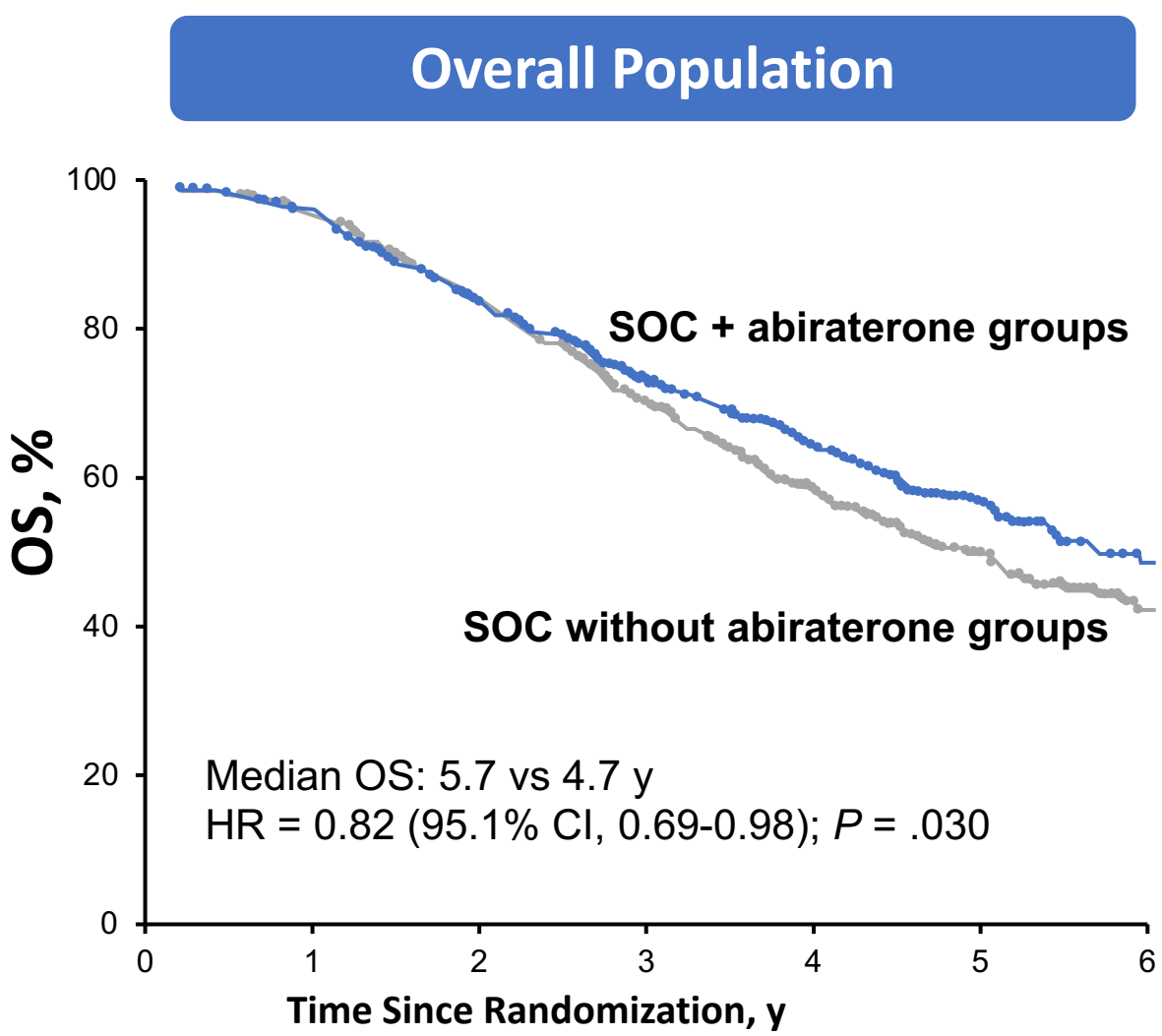


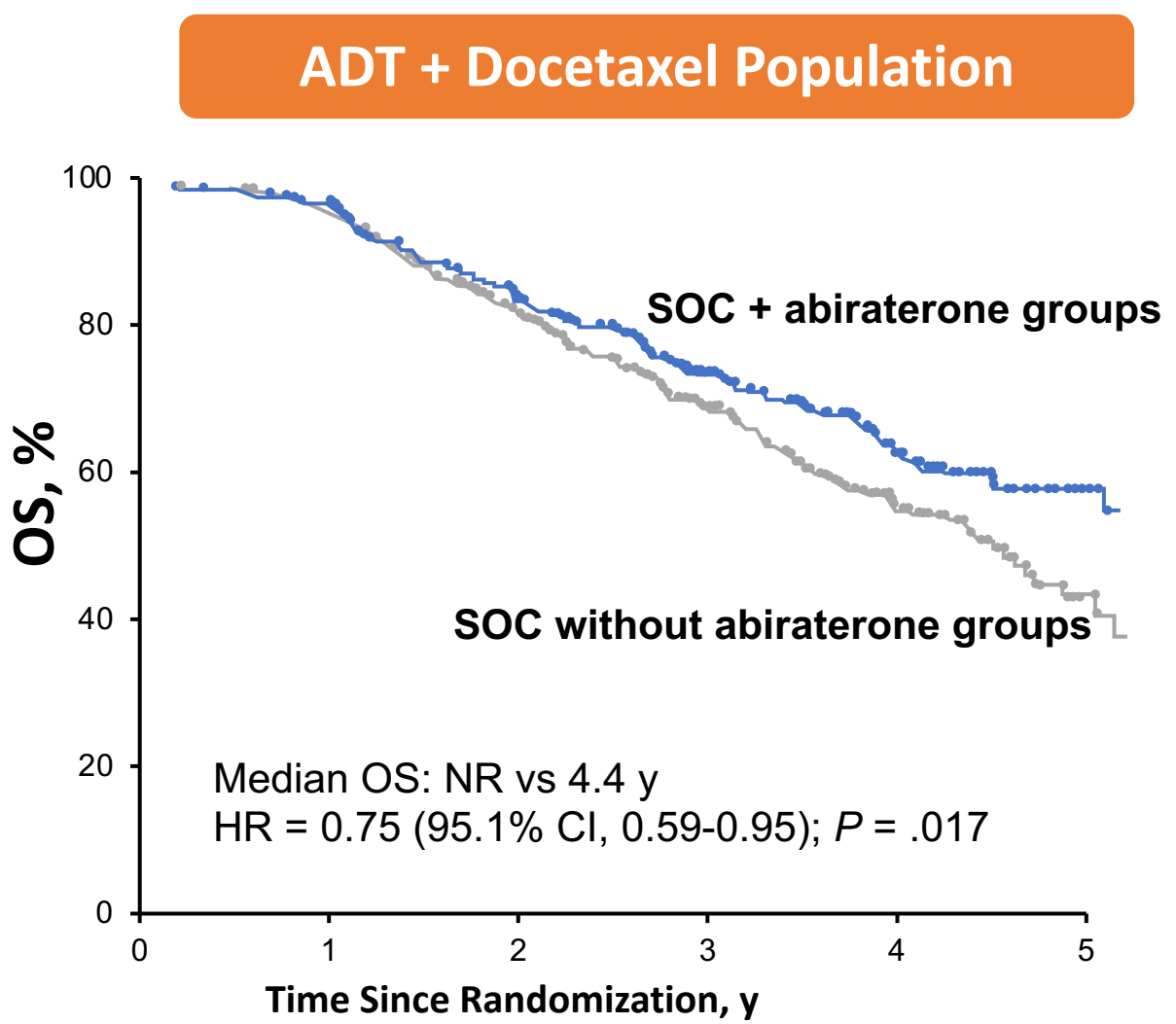
No	355	274	137	61	16	0
Yes	355	303	200	105	35	0

Adding abiraterone to ADT + docetaxel significantly improved rPFS

Fizazi K et al. *Lancet*. 2022;399:1695-1707.

Phase 3 PEACE-1: Improved OS in Men With De Novo mCSPC

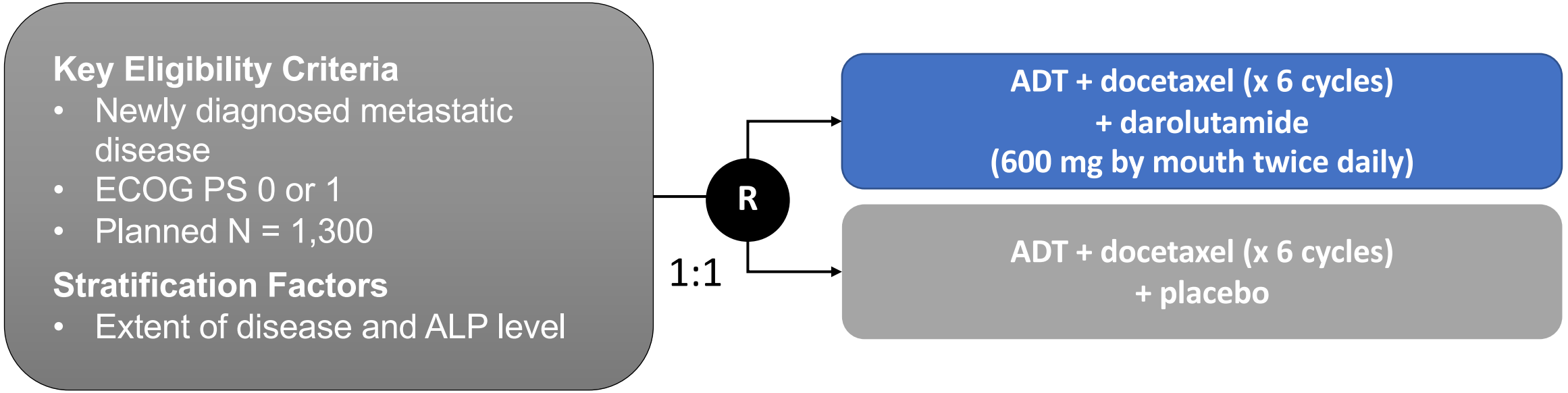




Fizazi K et al. *Lancet*. 2022;399:1695-1707.

ARASENS: Phase 3 Trial

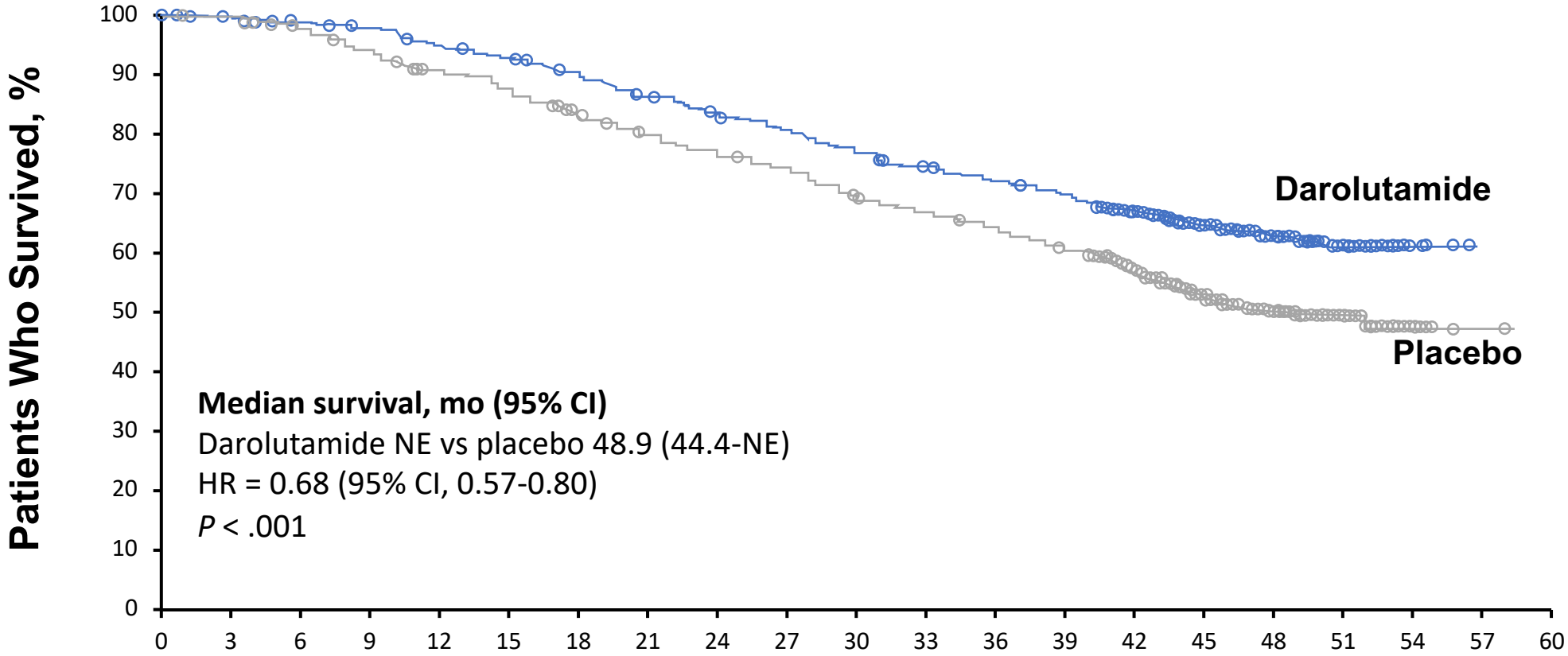
International trial conducted at >300 sites in 23 countries



- **Primary endpoint:** OS
- **Key Secondary endpoints:** time to mCRPC, time to initiation of subsequent anticancer therapy, time to SSE-free survival, time to first SSE, time to pain progression

https://clinicaltrials.gov/ct2/show/NCT02799602. Smith MR et al. ASCO GU 2022. Abstract 13. Smith MR et al. *N Engl J Med*. 2022;386:1132-1142.

ARASENS: Overall Survival



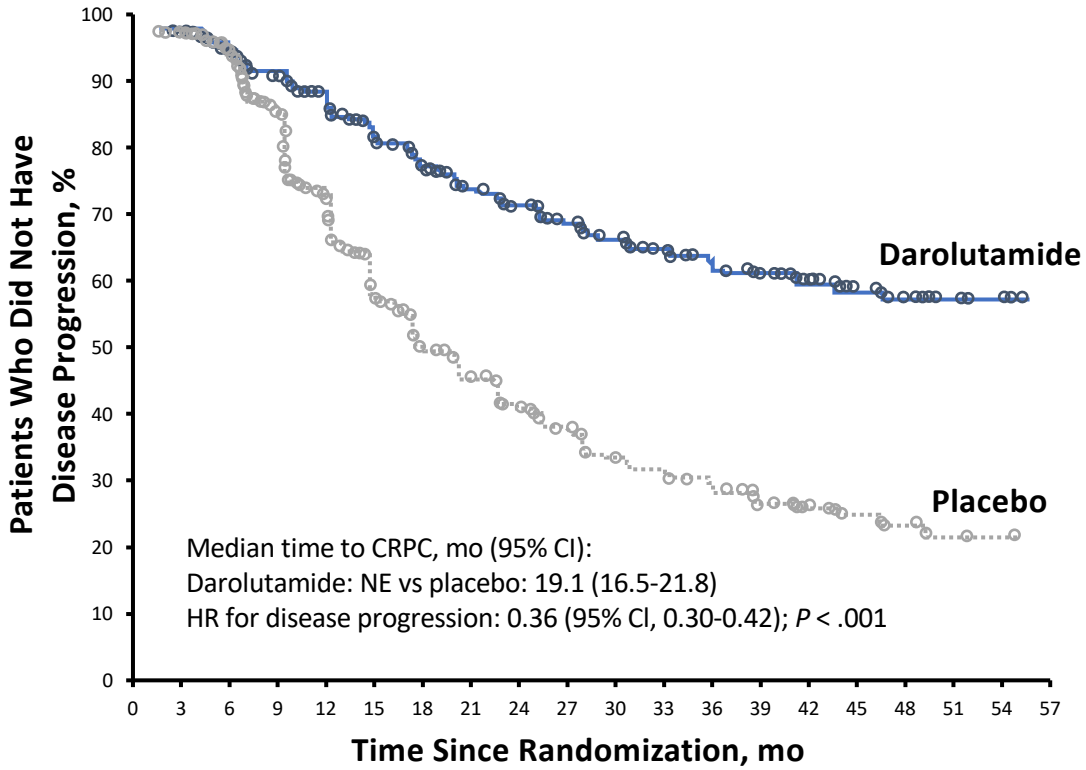
No. at Risk

Darolutamide	651	645	637	627	608	593	570	548	525	509	486	468	452	436	402	267	139	56	9	0	0
Placebo	654	646	630	607	580	565	535	510	488	470	441	424	402	383	340	218	107	37	6	1	0

Smith MR et al. *N Engl J Med*. 2022;386:1132-1142.

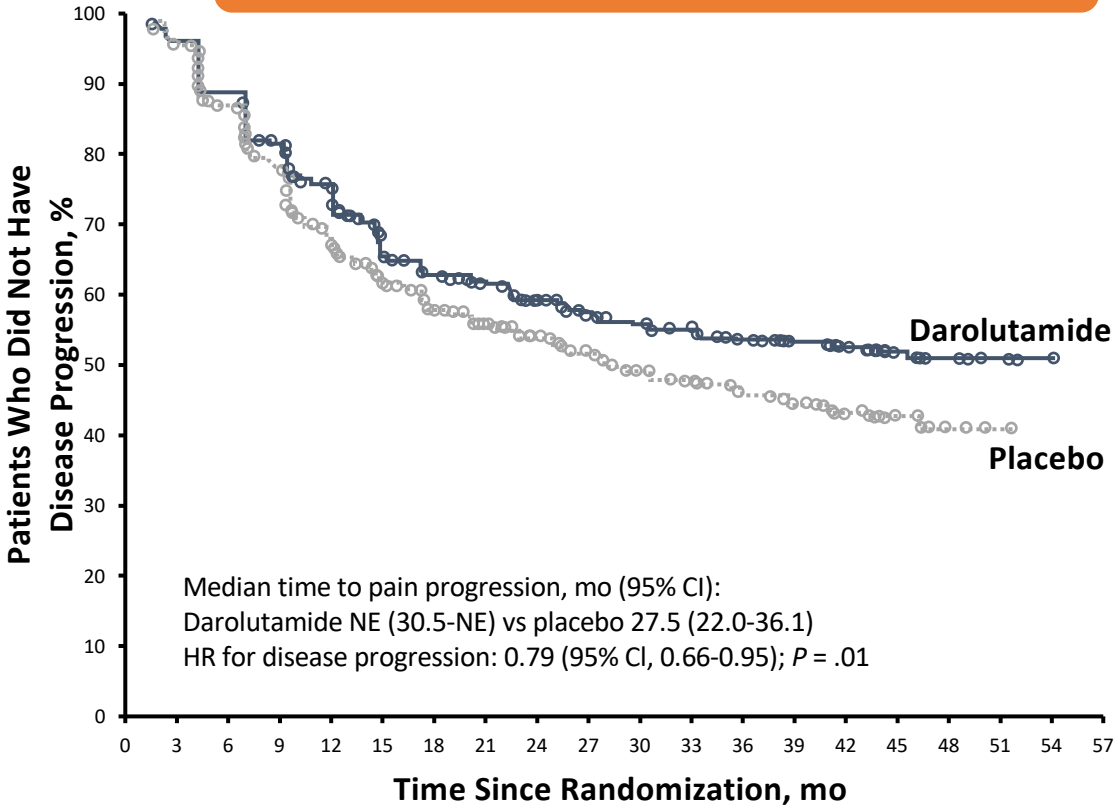
ARASENS: Key Secondary Endpoints

Time to CRPC



No. at Risk																				
Darolutamide	651	616	567	537	496	465	433	401	380	358	340	325	308	292	211	132	54	18	5	0
Placebo	654	613	533	425	348	289	242	215	185	165	143	134	120	105	79	38	14	4	1	0

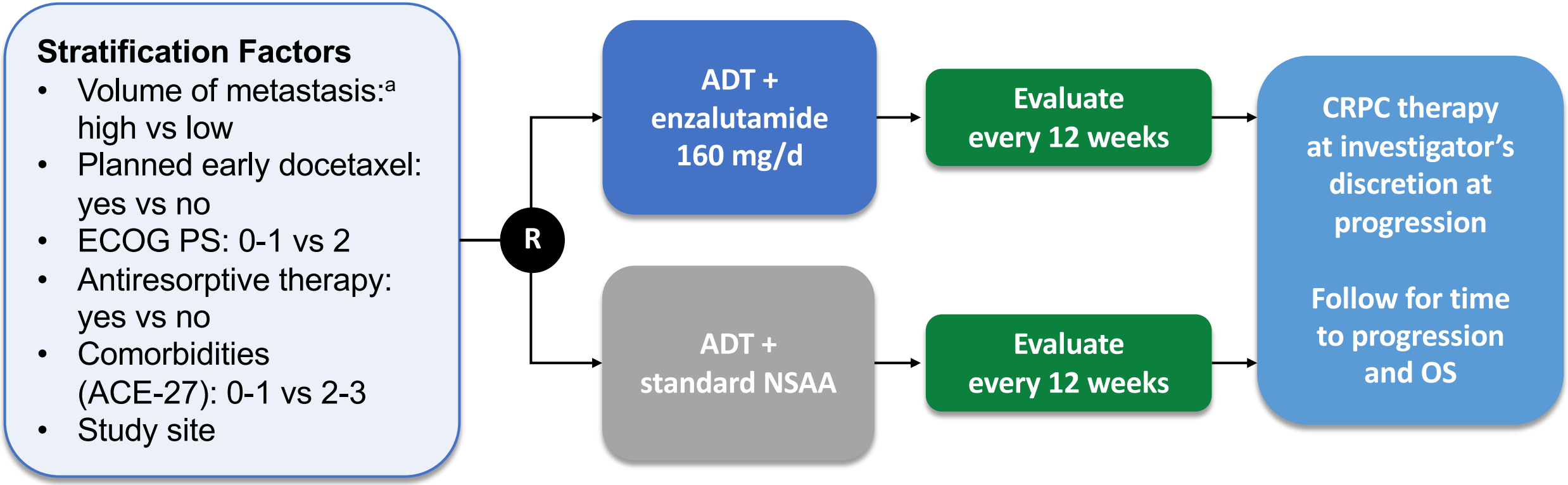
Time to Pain Progression



No. at Risk																				
Darolutamide	651	447	401	363	327	284	265	249	228	211	202	189	175	159	106	67	31	6	1	0
Placebo	654	442	395	332	288	255	221	188	160	134	119	107	93	86	62	35	8	1	0	0

Smith MR et al. *N Engl J Med.* 2022;386:1132-1142.

ENZAMET: SOC ± Enzalutamide in mHSPC



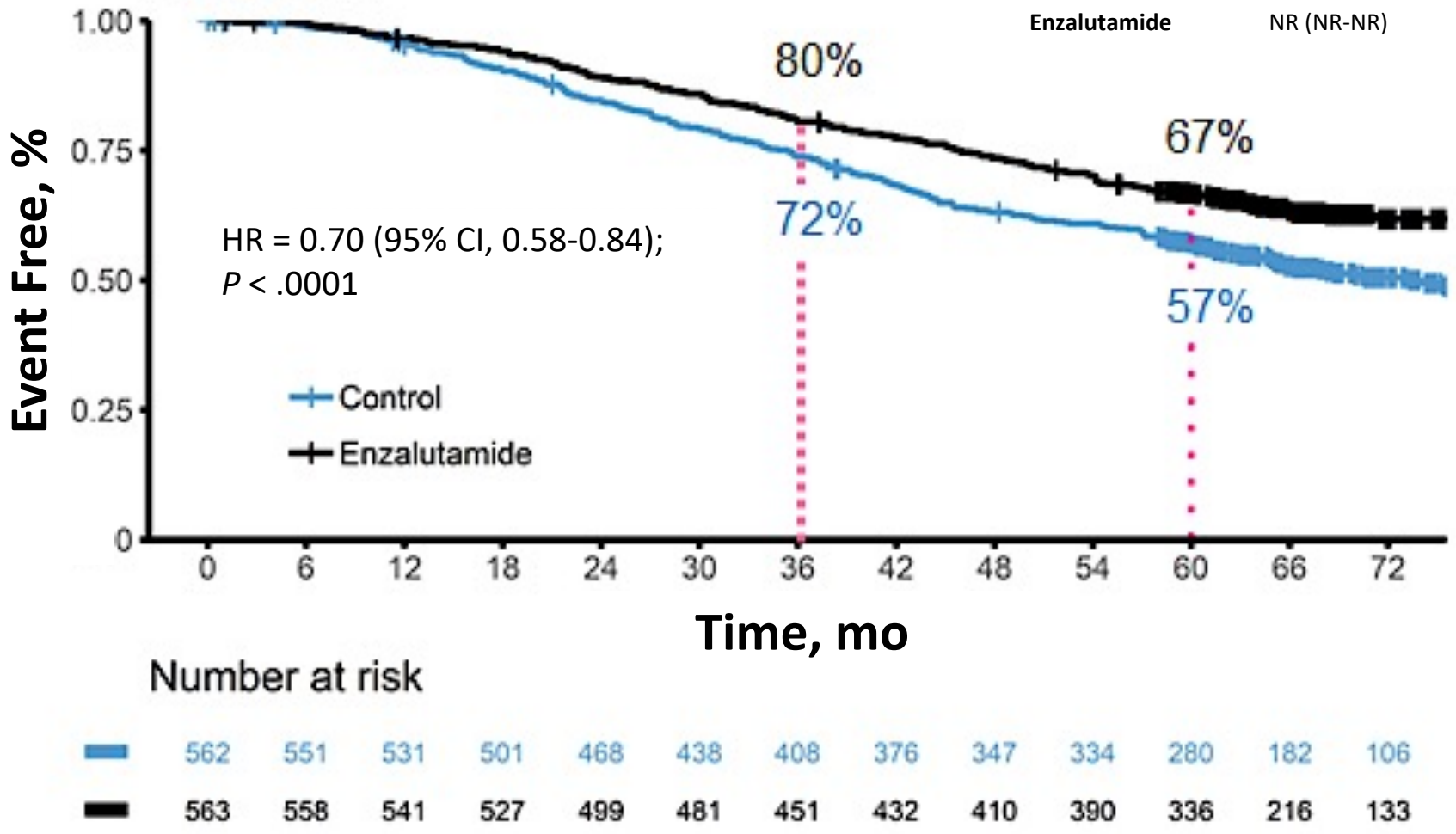
Primary endpoint: OS

- Prior to randomization, testosterone suppression up to 12 weeks and two cycles of docetaxel were allowed
- Intermittent ADT and cyproterone were not allowed
- NSAA: bicalutamide, nilutamide, flutamide

Davis ID et al. New Engl J Medicine. 2019.

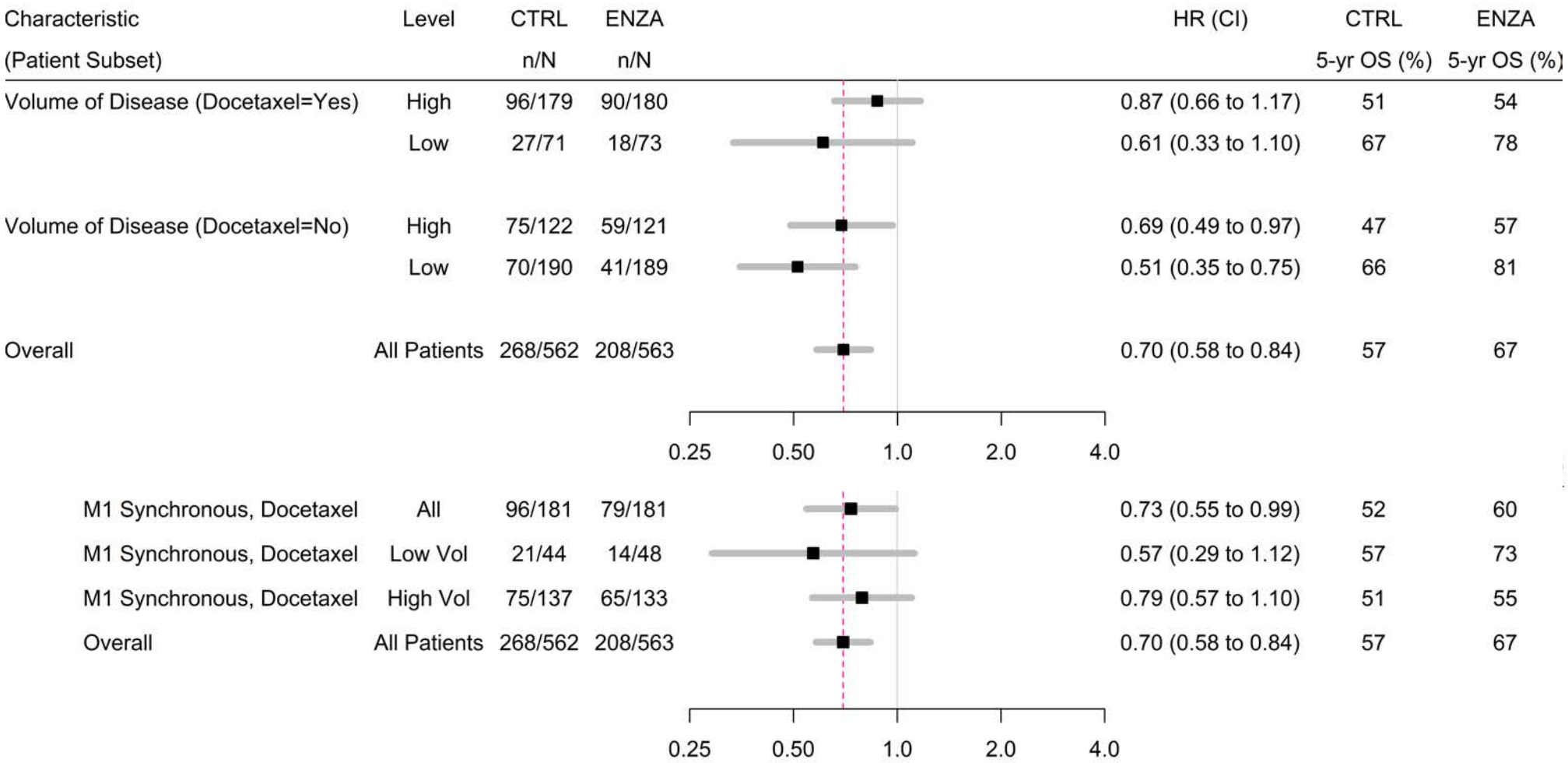
ENZAMET: OS Update

	Median OS, mo (95% CI)	5-Year Survival, %	Median Follow-Up, mo
Control (NSAA)	73.2 (64.7-NR)	57	68
Enzalutamide	NR (NR-NR)	67	



Davis ID et al. ASCO 2022, Abstract LBA5004

ENZAMET: Overall survival



Davis ID et al. ASCO 2022, Abstract LBA5004

Conclusions

- PARPi combinations suggest potential synergy between PARPi and AR targeted treatment
  - Overall survival data not yet mature
  - Ongoing studies will demonstrate whether benefit is confined to patients with HRR mutations or extends to others

- Triplet therapy studies suggest that the addition of darolutamide or abiraterone to ADT and docetaxel is associated with improved overall survival

PARP Inhibitors for mCRPC

Discussion Questions

- Regulatory and reimbursement issues aside, in which situations would you like to use a PARP inhibitor as first-line treatment for mCRPC and combined with what? Which genomic findings would prompt you to do so (eg, germline BRCA, somatic BRCA, LOH)?
- Do you use preemptive gastrointestinal medication with PARP inhibitors?

TRITON3 Meets Primary Endpoint for Patients with mCRPC with BRCA or ATM Mutations

Press Release: October 3, 2022

"[The manufacturer] today announced positive top-line data from the Phase 3, open-label, multicenter, randomized TRITON3 trial demonstrating that rucaparib monotherapy treatment achieved the primary endpoint of significantly improved radiographic progression-free survival (rPFS) by independent radiology review (IRR) compared with the control group, which consisted of physician's choice of docetaxel, abiraterone acetate, or enzalutamide.

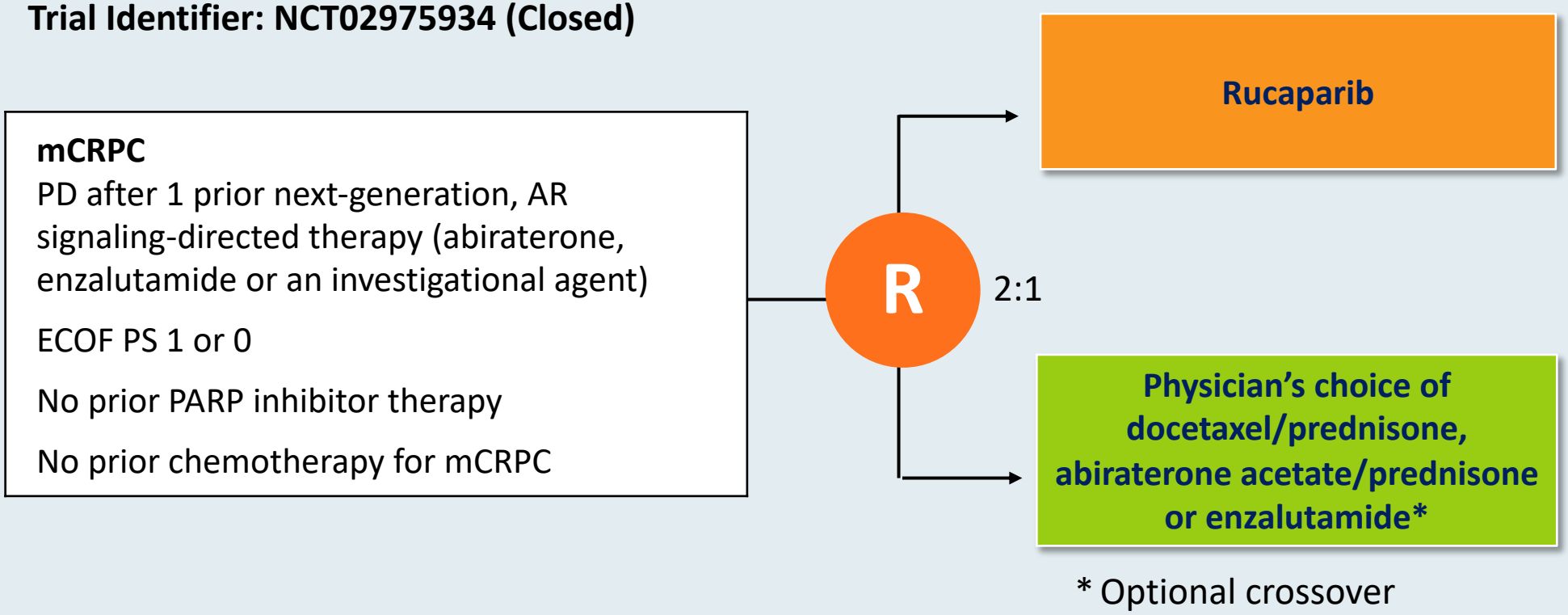
Benefit was observed in both primary efficacy analyses of patients with chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC): first, those who had mutations in BRCA, as well as all patients randomized in the trial, inclusive of mutations in BRCA or ATM (the overall intent-to-treat population (ITT)). The safety profile of rucaparib observed in the TRITON3 study was consistent with rucaparib labelling."

https://www.businesswire.com/news/home/20221003005303/en

RTP RESEARCH TO PRACTICE

TRITON3: Phase III Study of Rucaparib versus Physician's Choice of Therapy for Patients with mCRPC and Homologous Recombination Gene Deficiency

Trial Identifier: NCT02975934 (Closed)



Primary endpoint: Radiographic PFS by independent radiology review
Key secondary endpoints include objective response rate and DoR by modified RECIST, OS and clinical benefit rate

Ryan CJ et al. Genitourinary Cancers Symposium 2018;Abstract TPS389; www.clinicaltrials.gov. NCT02975934. Accessed October 2022.

Phase III TALAPRO-2 Trial Meets Primary Endpoint for Patients with mCRPC with or without HRR Gene Mutations

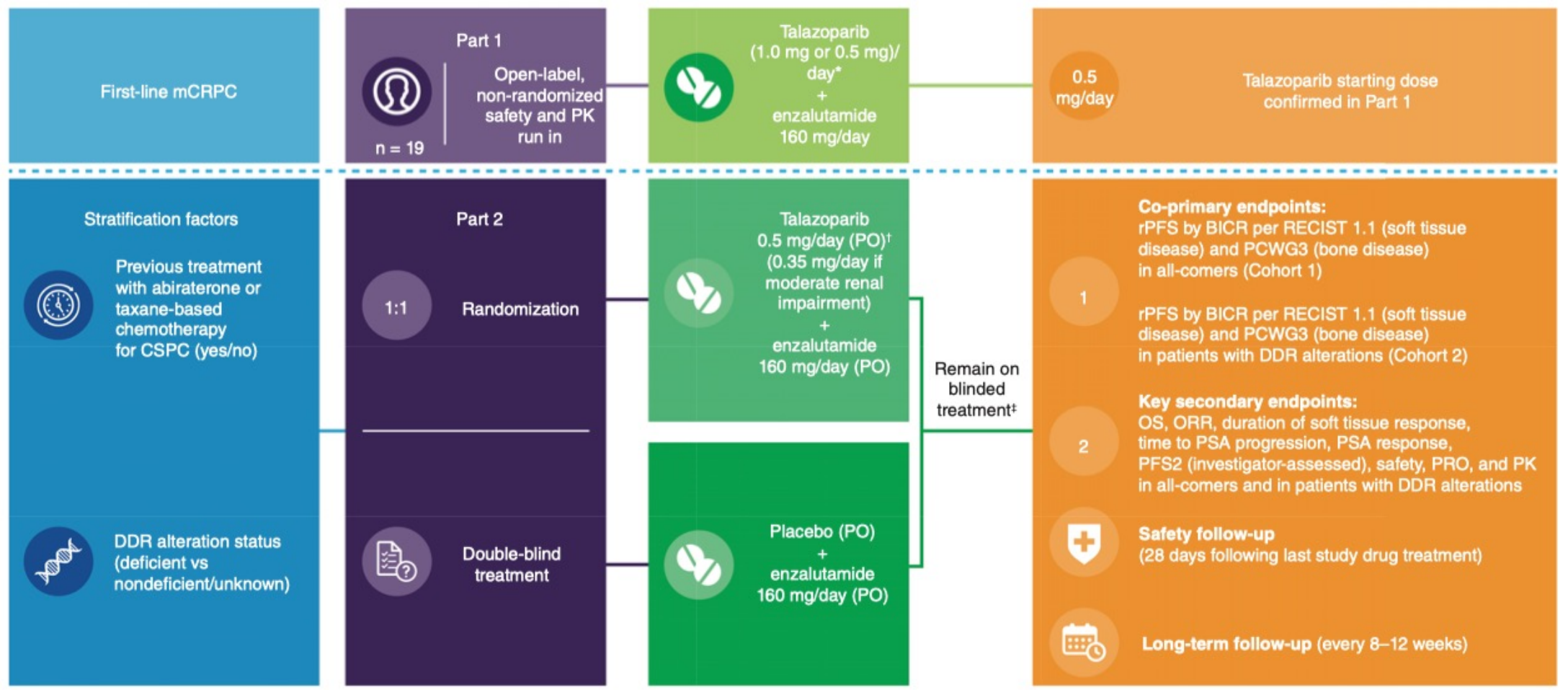
Press Release: October 4, 2022

"[The manufacturer] today announced positive topline results from the Phase 3 TALAPRO-2 study of talazoparib, an oral poly ADP-ribose polymerase (PARP) inhibitor, in combination with enzalutamide compared to placebo plus enzalutamide in men with metastatic castration-resistant prostate cancer (mCRPC), with or without homologous recombination repair (HRR) gene mutations. The study met its primary endpoint with a statistically significant and clinically meaningful improvement in radiographic progression-free survival (rPFS) compared with placebo plus enzalutamide. The results of the primary endpoint exceeded the pre-specified hazard ratio of 0.696.

Results showed a trend toward improved overall survival, a key secondary endpoint, at the time of the analysis, but these data are not yet mature. Benefits were also observed in other secondary endpoints, including investigator assessed rPFS, prostate specific antigen (PSA) response, time to PSA progression, and overall response rate. Other secondary endpoints are being analyzed. At the time of topline analysis, the safety of talazoparib plus enzalutamide were generally consistent with the known safety profile of each medicine."

https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-positive-topline-results-phase-3-talapro-2

TALAPRO-2: Phase III Trial of Talazoparib/Enzalutamide vs Placebo/Enzalutamide for 1L mHRPC ± DNA Damage Repair Mutations



Agarwal N et al. *Future Oncol* 2022;18:425.

Hormone-Sensitive Prostate Cancer

Discussion Questions

- Do you believe there is a clinically meaningful difference in tolerability of antiandrogens, particularly related to “fatigue”?
- Do you believe abiraterone is an acceptable treatment option for M0 disease?
- In which situations, if any, do you use docetaxel, either with an LHRH agonist alone or with additional endocrine therapy?

FDA Approves Darolutamide for Metastatic Hormone-Sensitive Prostate Cancer

Press Release: August 5, 2022

"The FDA approved darolutamide in combination with docetaxel chemotherapy for patients with metastatic hormone-sensitive prostate cancer (mHSPC).

The approval is based on the results of a large Phase 3 clinical trial called ARASENS. This trial compared outcomes among 1300 patients who received docetaxel + standard ADT + darolutamide vs patients who received docetaxel + standard ADT + placebo. 86% of the patients were newly diagnosed with prostate cancer that had metastasized to the bones or other organs.

Patients treated with the addition of darolutamide were 32% less likely to die during the study follow-up period compared to patients treated with docetaxel + ADT alone. These patients also had improved time to castration resistance (when the PSA increases and disease worsens, despite hormone therapy), time to pain progression, time to symptomatic skeletal related events (ie, bone fractures, needing radiation to the bones, etc), and time to next cancer therapy. Importantly, these improved outcomes of triplet therapy intensification were associated with only a modest increase in adverse events."

https://www.pcf.org/c/breaking-news-fda-approves-darolutamide-for-metastatic-hormone-sensitive-prostate-cancer/

RTP RESEARCH TO PRACTICE

^{177}Lu-PSMA-617 for mCRPC

Discussion Questions

- Do you believe there is a clinically meaningful difference in tolerability of antiandrogens, particularly related to “fatigue”?
- Do you believe abiraterone is an acceptable treatment option for M0 disease?
- In which situations, if any, do you use docetaxel, either with an LHRH agonist alone or with additional endocrine therapy?

FDA Approves ^{177}Lu-PSMA-617 for the Treatment of mHRPC

Press Release: March 23, 2022

- "On March 23, 2022, the Food and Drug Administration approved the radio-ligand therapy, ^{177}Lu-PSMA-617, for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.
- On the same day, the FDA approved Locametz (gallium Ga 68 gozetotide), a radioactive diagnostic agent for positron emission tomography (PET) of PSMA-positive lesions, including selection of patients with metastatic prostate cancer for whom lutetium Lu 177 vipivotide tetraxetan PSMA-directed therapy is indicated. Locametz is the first radioactive diagnostic agent approved for patient selection in the use of a radioligand therapeutic agent.
- Efficacy was evaluated in the phase 3 VISION trial which demonstrated a statistically significant improvement in the primary endpoints OS and rPFS. Hazard ratio (HR) for OS was 0.62 (95% CI: 0.52, 0.74; $p<0.001$) for the comparison of 177Lu-PSMA-617 plus BSoC versus BSoC. Median OS was 15.3 months (95% CI: 14.2, 16.9) in the ^{177}Lu-PSMA-617 plus BSoC arm and 11.3 months (95% CI: 9.8, 13.5) in the BSoC arm, respectively."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pluvicto-metastatic-castration-resistant-prostate-cancer

RTP RESEARCH TO PRACTICE

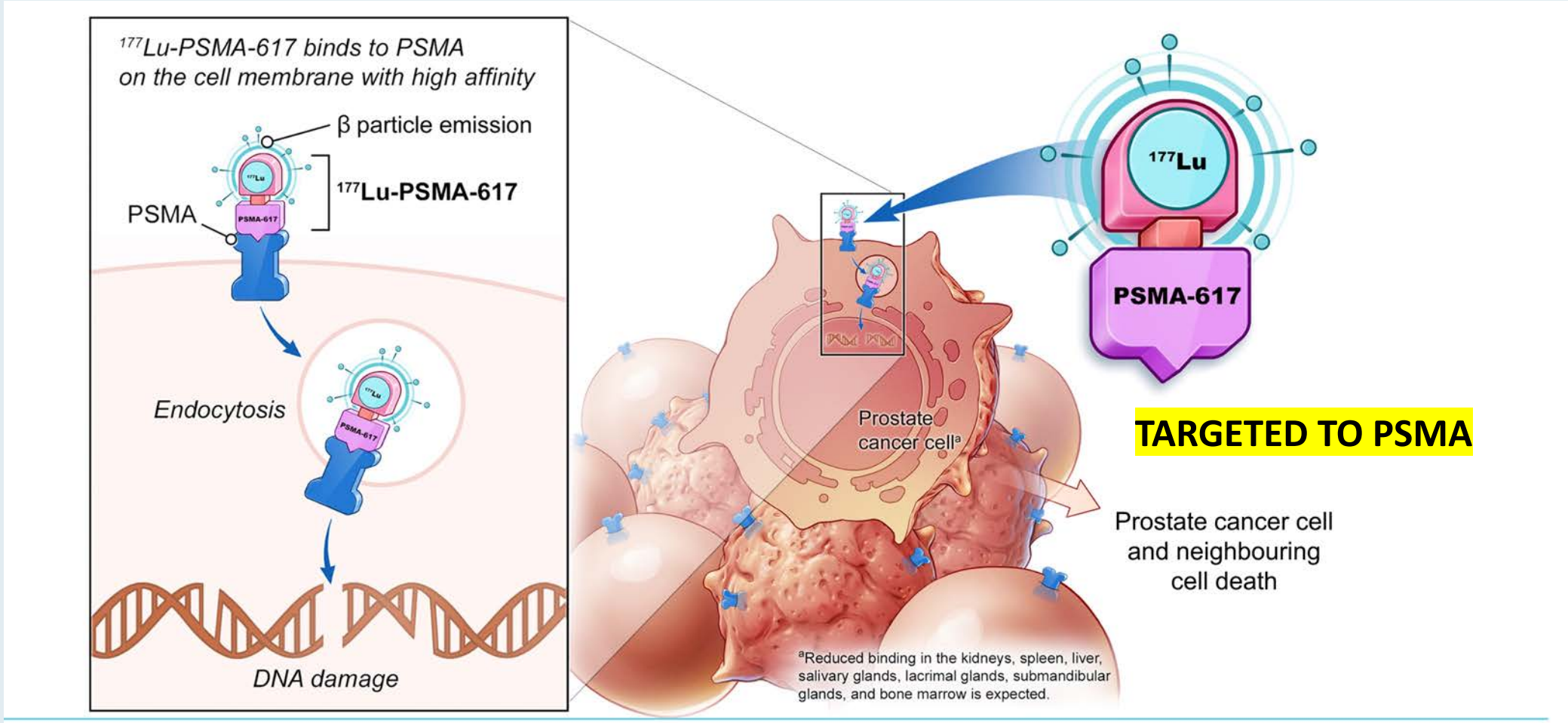
N Engl J Med 2021;385(12):1091-103
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

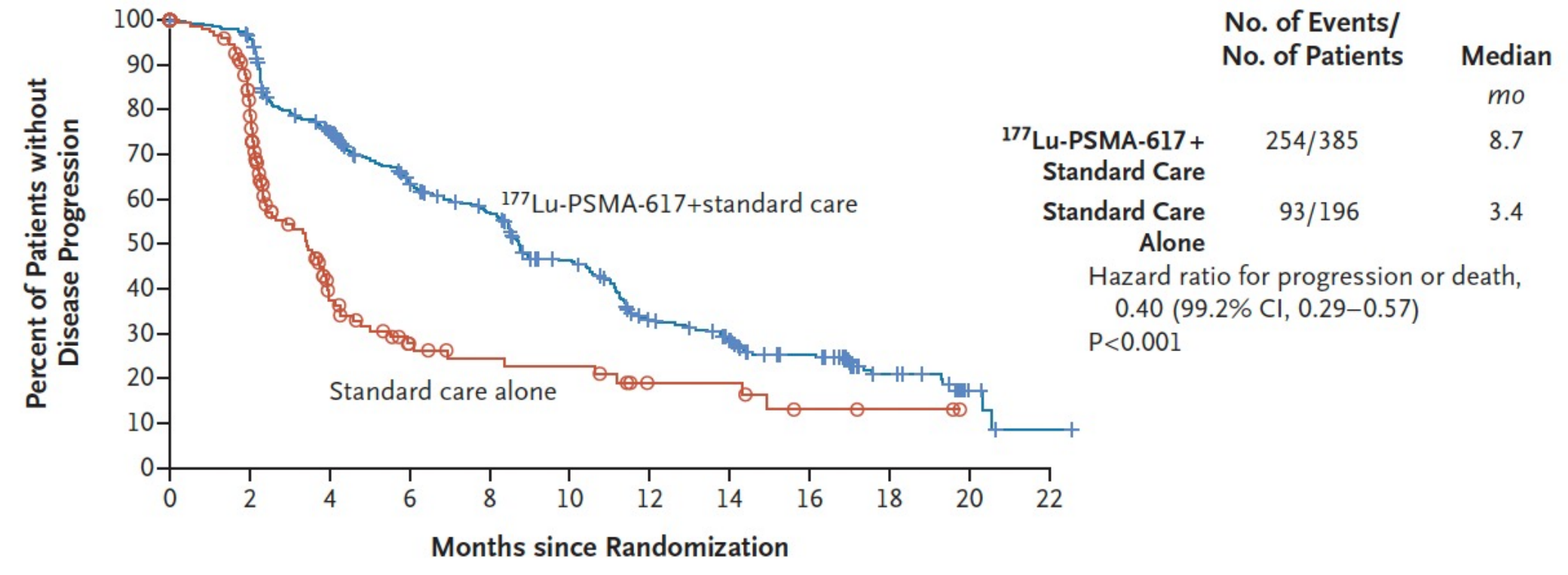
O. Sartor, J. de Bono, K.N. Chi, K. Fizazi, K. Herrmann, K. Rahbar, S.T. Tagawa, L.T. Nordquist, N. Vaishampayan, G. El-Haddad, C.H. Park, T.M. Beer, A. Armour, W.J. Pérez-Contreras, M. DeSilvio, E. Kpamegan, G. Gericke, R.A. Messmann, M.J. Morris, and B.J. Krause, for the VISION Investigators*

^{177}Lu-PSMA-617: Mechanism of Action



Morris MJ et al. ASCO 2021;Abstract LBA4.

VISION: Imaging-Based Progression-Free Survival by Independent Central Review

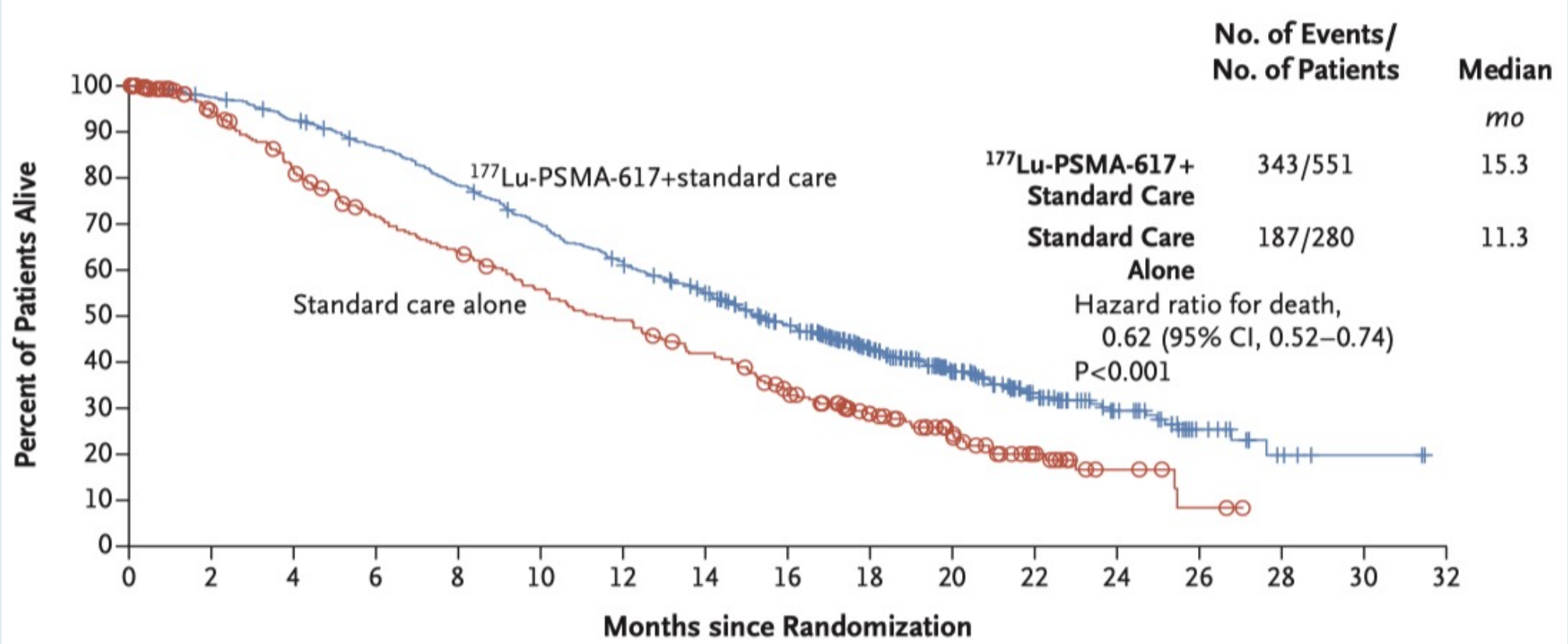


- Median OS (^{177}Lu-PSMA-617 vs standard therapy): 15.3 months vs 11.3 months (HR 0.62, $p < 0.001$)
- Time to first symptomatic skeletal event OS (^{177}Lu-PSMA-617 vs standard therapy): 11.5 months vs 6.8 months (HR 0.50, $p < 0.001$)

Sartor O et al. *N Engl J Med* 2021;385(12):1091-103.

RTP RESEARCH TO PRACTICE

VISION: Overall Survival



Sartor O et al. *N Engl J Med* 2021;385(12):1091-103.

RTP RESEARCH TO PRACTICE

Poster 1372P

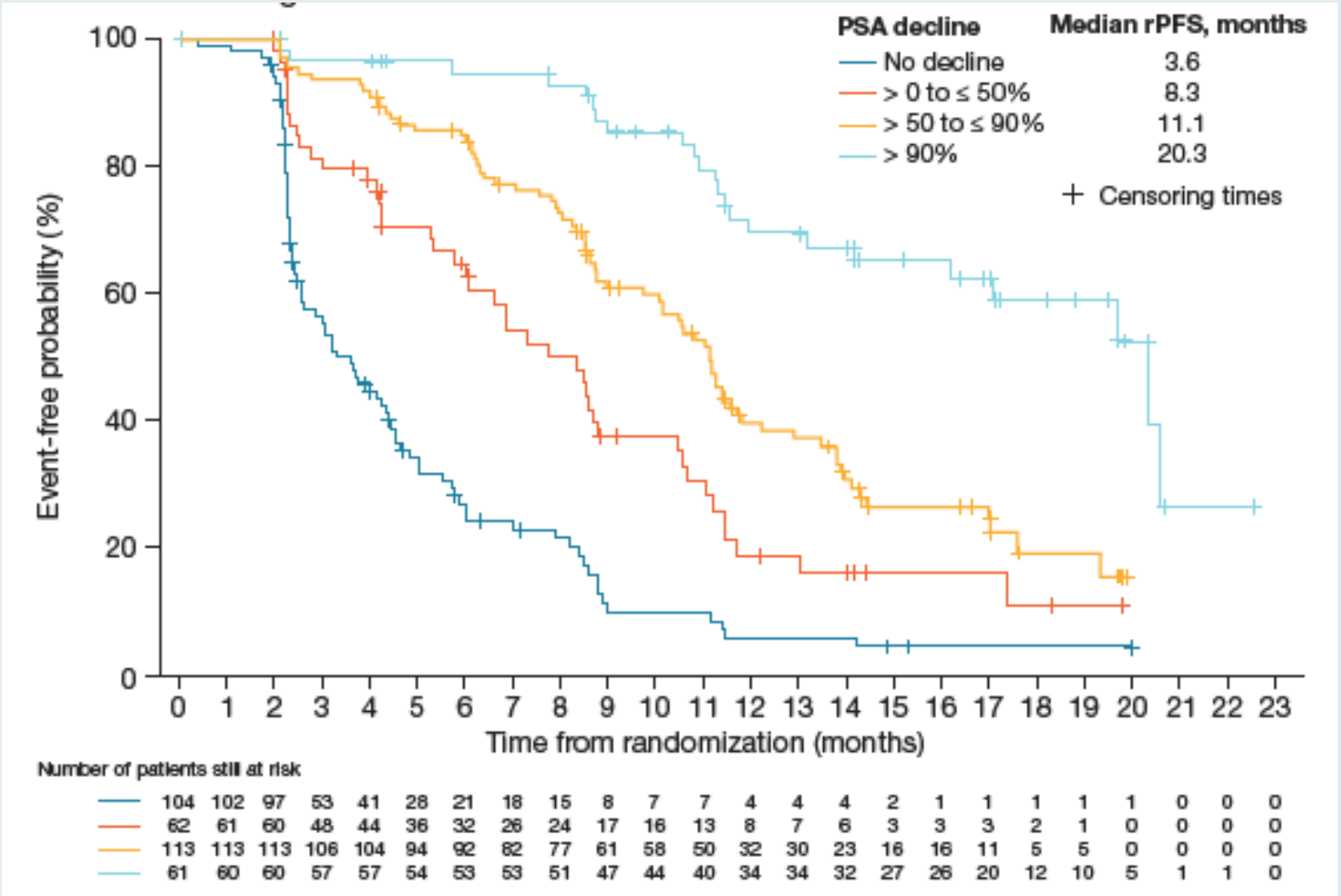
Presenting author: Andrew J Armstrong
Email: andrew.armstrong@duke.edu

Association between prostate-specific antigen decline and clinical outcomes in patients with metastatic castration-resistant prostate cancer in the VISION trial

Andrew J Armstrong,[1] Oliver Sartor,[2] Fred Saad,[3] Johannes Czernin,[4] Neal D Shore,[5] Ayse T Kendi,[6] Tomasz M Beer,[7] Nitin Vaishampayan,[8] Ghassan El Haddad,[9] Jiwen Wu,[10] Osvaldo Mirante,[11] Michael J Morris[12]

ESMO 2022;Abstract 1372P.

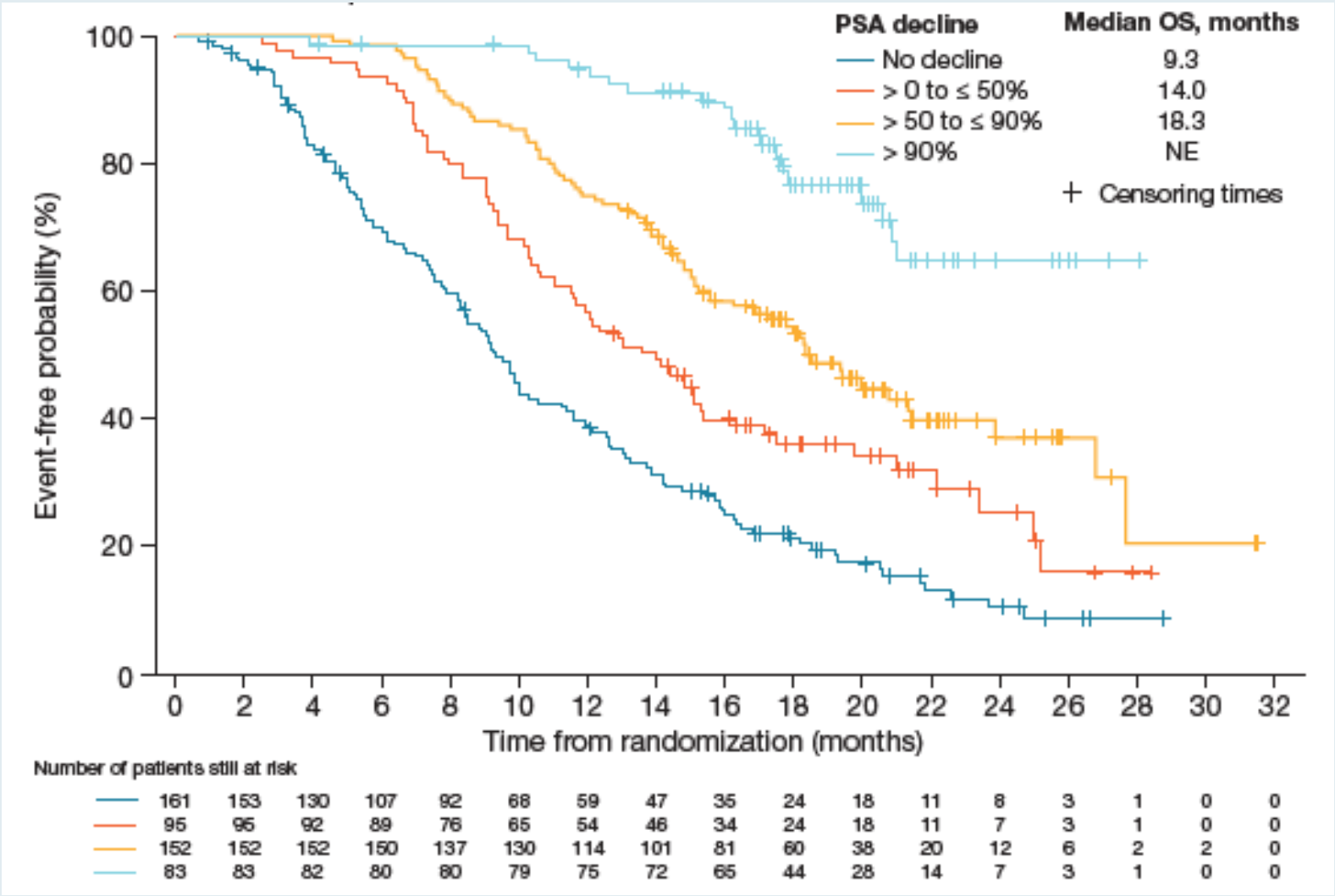
VISION: Post hoc Exploratory Analysis of rPFS and Magnitude of PSA Decline up to 12 Weeks from Baseline in the ^{177}Lu-PSMA-617 Group



Armstrong AJ et al. ESMO 2022;Abstract 1372P.

RTP RESEARCH TO PRACTICE

VISION: Post hoc Exploratory Analysis of OS and Magnitude of PSA Decline up to 12 Weeks from Baseline in the ^{177}Lu-PSMA-617 Group



Armstrong AJ et al. ESMO 2022;Abstract 1372P.

2022 ASCO® ANNUAL MEETING

Abstract 5000

ANZUP® Cancer Trials Group Limited

^{177}Lu-PSMA-617 (LuPSMA) versus cabazitaxel in metastatic castration resistant prostate cancer (mCRPC) progressing after docetaxel: overall survival after median follow-up of 3 years

(TheraP ANZUP 1603)

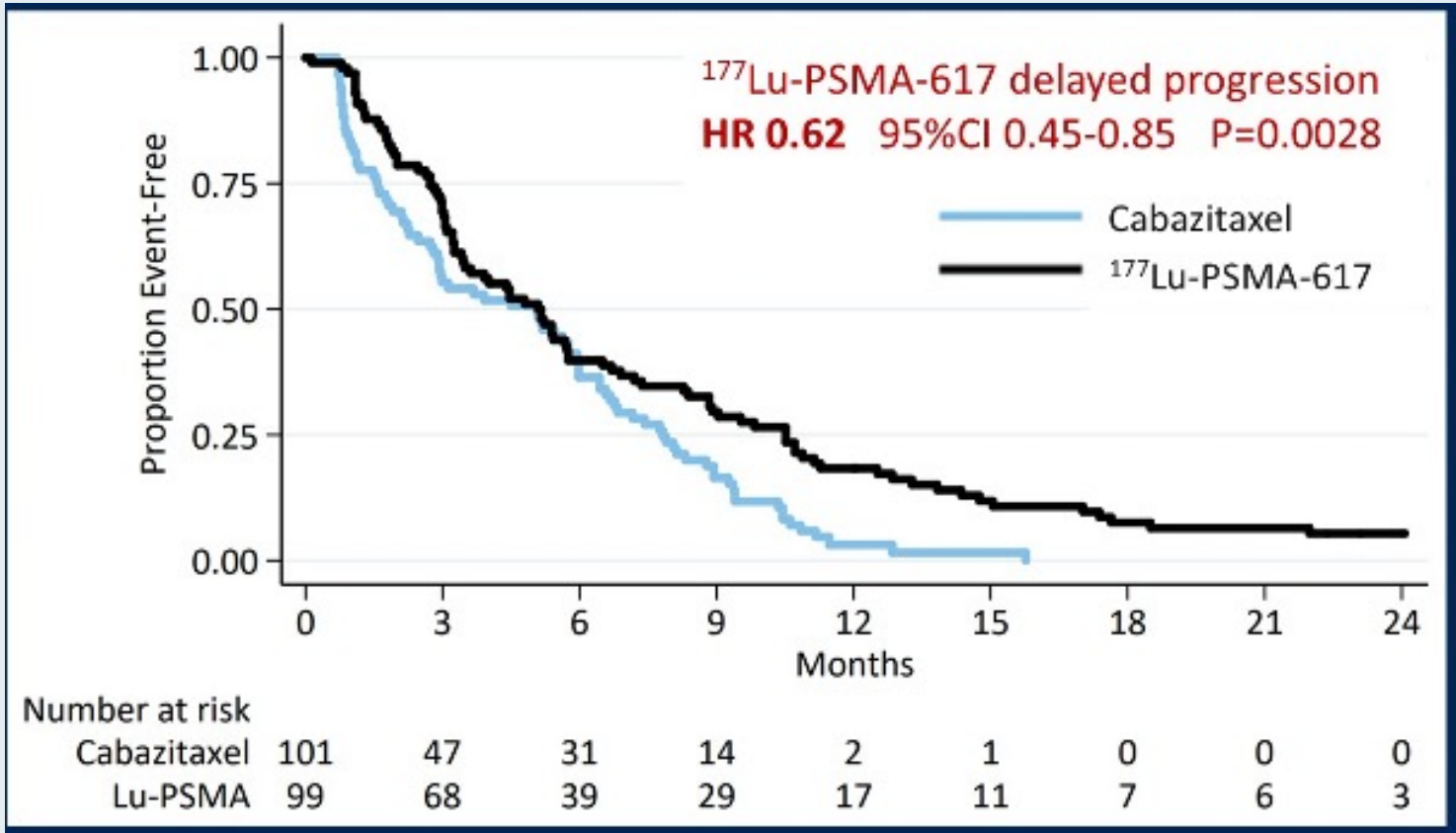
Michael Hofman, Louise Emmett, Shahneen Sandhu, Amir Iravani, Anthony Joshua, Jeffrey Goh, David Pattison, Hsiang Tan, Ian Kirkwood, Siobhan Ng, Roslyn Francis, Craig Gedye, Natalie Rutherford, Andrew Scott, Alison Zhang, Margaret McJannett, Martin Stockler, Scott Williams, Andrew Martin, Ian D. Davis, on behalf of the **TheraP Investigators**

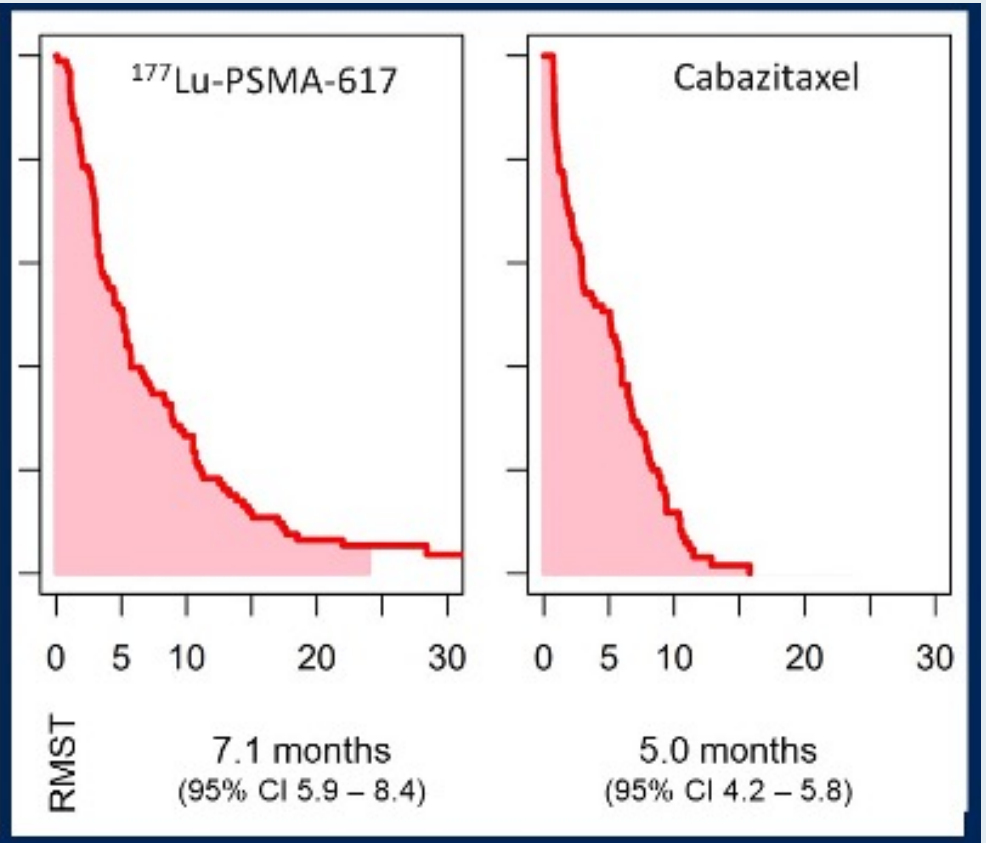
TheraP is a partnership between ANZUP Cancer Trials Group and the Prostate Cancer Foundation of Australia (PCFA) in collaboration with the NHMRC Clinical Trials Centre (CTC) and the Australasian Radiopharmaceutical Trials Network (ARTnet) with support from the Australian Nuclear Science and Technology Organisation (ANSTO) and Endocyte Inc., a Novartis company

Clinicaltrials.gov NCT03392428

RTP RESEARCH TO PRACTICE

TheraP: PFS (PSA and Radiographic)



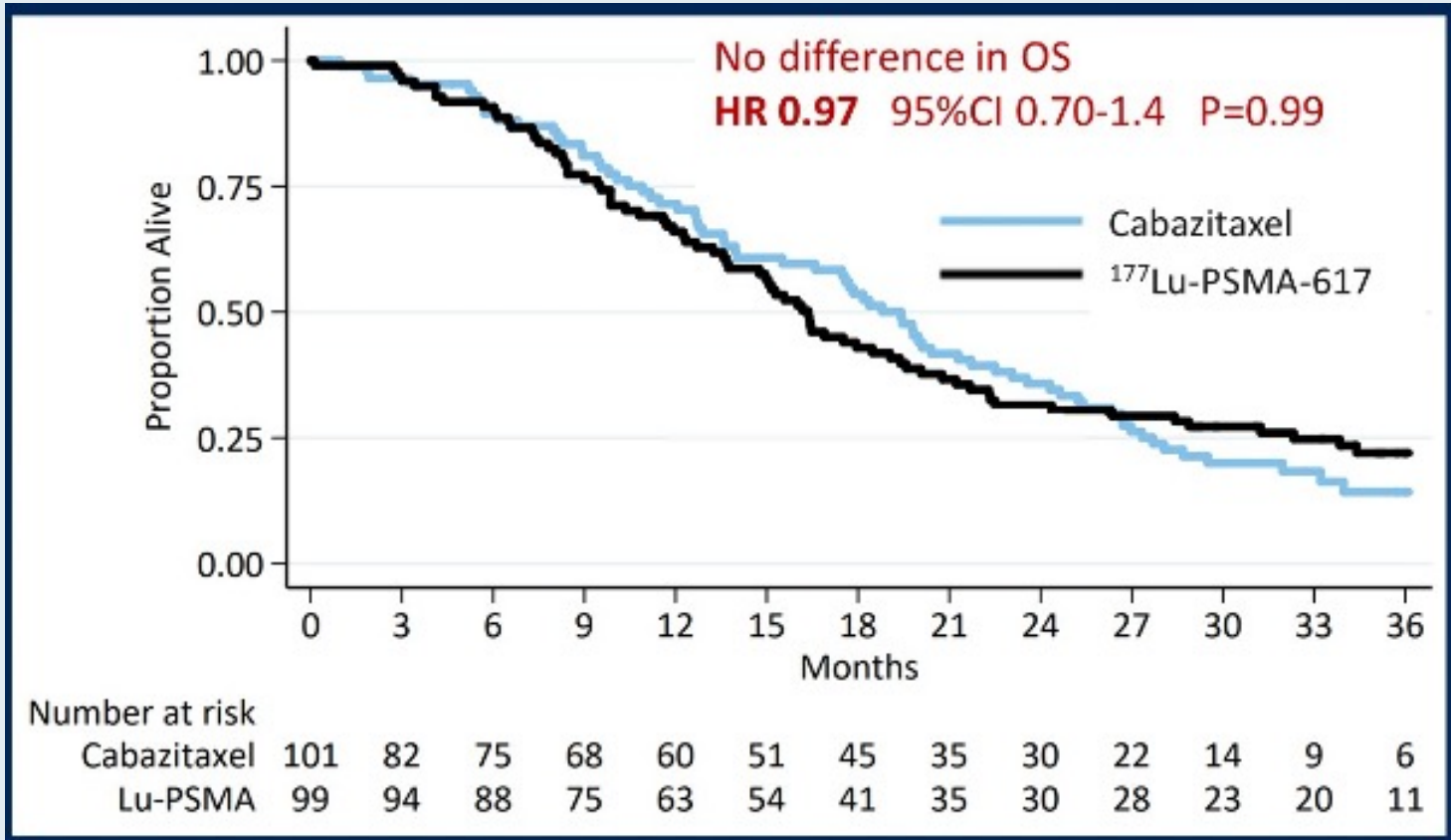


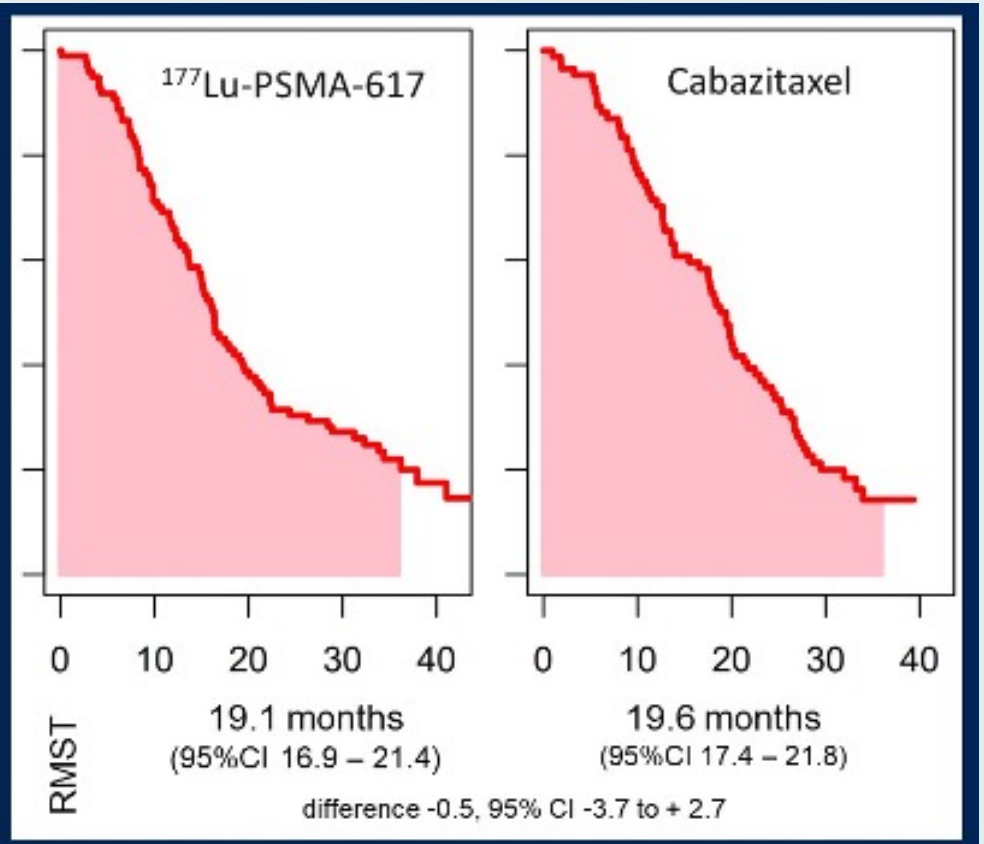
- Treatment effect not constant with respect to time → restricted mean survival time (RMST)
- 177 progression events. Cut-off 31 DEC 2020 for non-OS endpoints.
- Similar HR for rPFS (0.65) and PSA-PFS (0.60), and in per-protocol sensitivity analyses

Hofman MS et al. ASCO 2022;Abstract 5000.

RTP RESEARCH TO PRACTICE

TheraP: OS in the ITT Population





- Cut-off 31 DEC 2021 for OS
- At 36 months follow-up, death reported in 147/200; 70/101 assigned cabazitaxel vs. 77/99 assigned LuPSMA
- Per-protocol analysis: no difference in OS
- No additional safety signals with longer follow-up.

Hofman MS et al. ASCO 2022;Abstract 5000.

RTP RESEARCH TO PRACTICE

Prostate and Bladder Cancers Agenda

MODULE 1: Prostate Cancer

MODULE 2: Urothelial Bladder Cancer

RTP
RESEARCH
TO PRACTICE

Optimal Integration of Antibody Drug Conjugates and Targeted Treatment in Metastatic Urothelial Bladder Cancer

Evan Y. Yu, M.D

Florida Cancer Specialists Retreat
Orlando, FL

October 22, 2022

BLC2001: Phase 2 Trial of Erdafitinib[1]

- Fifteen percent of patients with MIBC have *FGFR* alterations[2]

Patients

- Unresectable Ia/mUC with prespecified *FGFR3/2* alterations
- ECOG PS 0-2
- History of disease progression during or after ≥1 line of prior systemic chemotherapy, or within 12 months after receiving (neo)adjuvant chemotherapy in the metastatic setting (chemo-refractory patients)
- Were cisplatin ineligible (for impaired renal function or peripheral neuropathy)
- Chemotherapy naïve

Screening for *FGFR* fusions/mutations

Randomized 1:1

Regimen 1

Erdafitinib 10 mg/d
7 days on/7 days off
Locally advanced UC

Regimen 2

Erdafitinib 6 mg/d

Regimen 3

Erdafitinib 8 mg/d with potential for uptitration to 9 mg/d

(n=99)

Primary endpoint

- Confirmed ORR

Secondary endpoints

- PFS, DOR, OS, safety, predictive biomarker evaluation, and PK

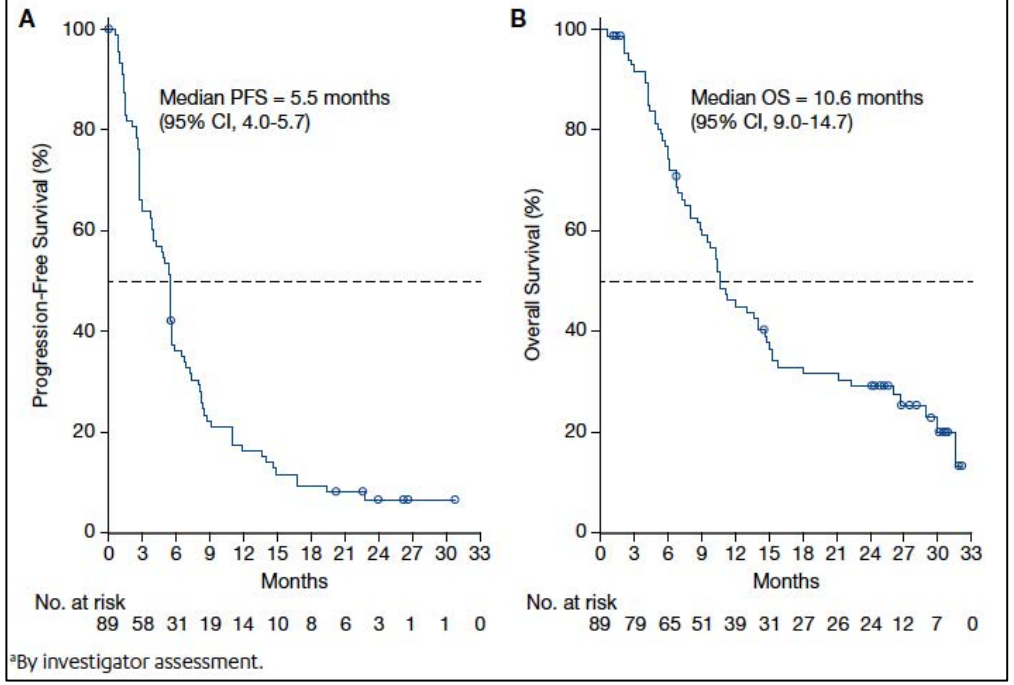
***FGFR* Alterations (n=99)**	
FGFR2 or *FGFR3* fusion, No. (%)	25 (25)
FGFR3 mutation, No. (%)	74 (75)
FGFR2/3 fusions and mutations	0

1. Loriot Y, et al. *N Engl J Med.* 2019;381(4):338-348.
2. Helsten T, et al. *Clin Cancer Res.* 2016;22(1):259-267.

BLC2001: Efficacy

	All Patients (N=99)	*FGFR3* Mutation (n=74)	*FGFR2/3* Fusion (n=25)
ORR, n (%) (95% CI)	40 (**40**) (31-50)	36 (**49**) (37-60)	4 (**16**) (2-30)

Figure 3. A) PFS[a] and B) OS in Patients Who Had Prior Chemotherapy



[a]By investigator assessment.

- **Confirmed response rate 40% (3% CR; 37% PR)**
- **Among 22 pts with prior ICI, confirmed response rate 59%**

Table 2. Efficacy Outcomes by Subgroup

	n	Median DoR[a], mo	n[b]	Median PFS[a], mo	Median OS, mo
FGFR alteration					
FGFRm+f-	33	6.0	70	5.6	12.0
FGFRm-f+	4	6.2	25	2.8	10.3
FGFRm+f+	3	5.6	6	6.9	15.0
Primary tumor location					
Upper tract	11	6.7	25	4.2	10.3
Lower tract	29	6.0	76	5.6	13.8
Presence of visceral metastases					
Yes	30	6.0	78	5.5	10.3
No	10	5.3	23	5.8	14.1
Prior systemic therapy					
None	4	10.9	10	9.8	18.1
1 line	17	6.0	48	5.5	11.3
2 lines	10	6.1	28	5.5	8.0
3 lines	7	4.4	11	5.7	11.2
> 3 lines	2	4.8	4	3.4	12.4
Use of prior chemotherapy					
Yes	35	5.6	89	5.5	10.6
No	5	14.3	12	14.9	20.8
Use of prior IO					
Prior IO	14	6.5	24	5.7	10.9
No prior IO	26	5.6	77	5.5	12.0

[a]By investigator assessment. [b]For PFS and OS.

1. Loriot Y, et al. *N Engl J Med.* 2019;381(4):338-348.

2. Necchi A, et al. ESMO 2020. Presentation 750P.

BLC2001: Safety

Grade ≥3 AEs Occurring in ≥5% of Patients, No. (%)	(N=99)
Stomatitis	10 (10)
Hyponatremia	11 (11)
Asthenia	7 (7)
Nail dystrophy	6 (6)
Hand-foot syndrome	5 (5)
Urinary tract infection	5 (5)

Final Analysis (n=101)

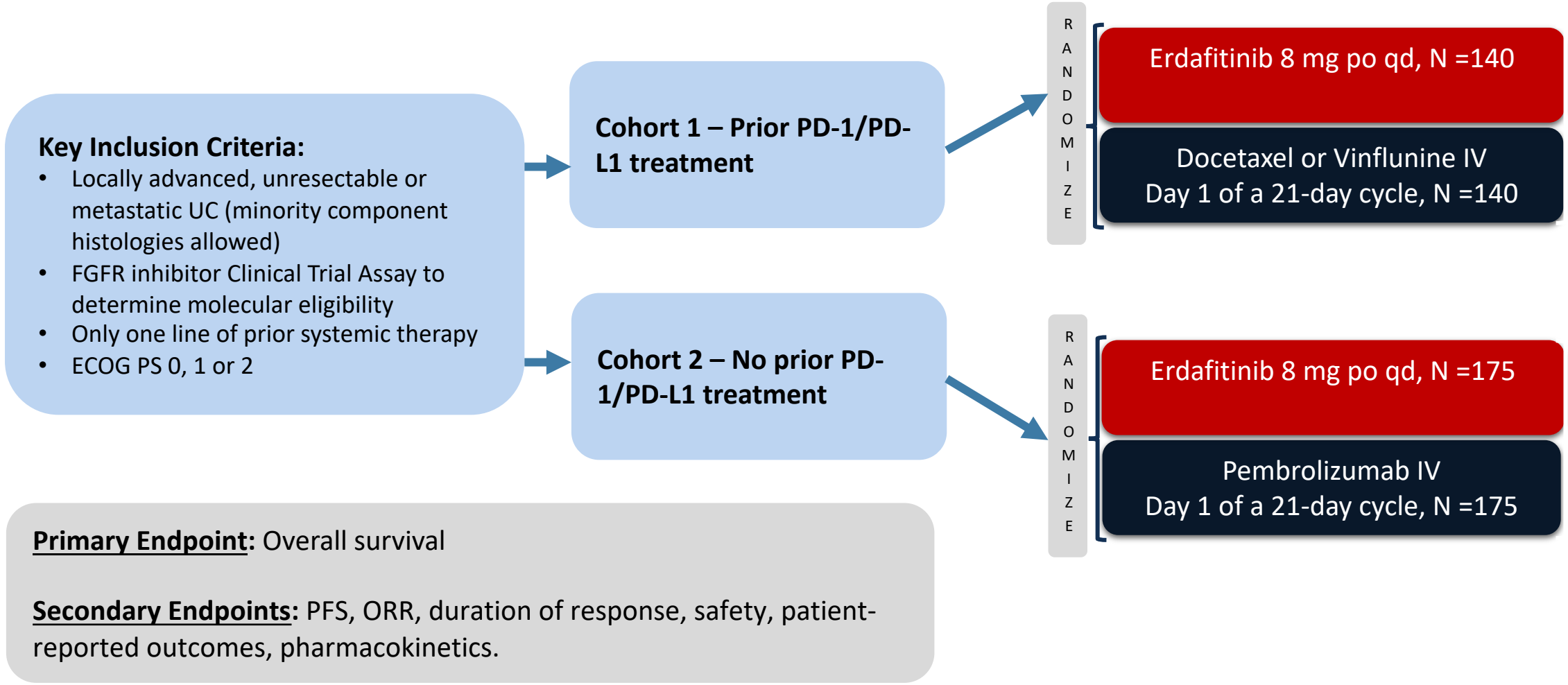
TEAE of Interest	Overall Incidence n (%)
Hyperphosphatemia[a]	**79 (78%)**
Stomatitis	**60 (59%)**
Nail disorders	**60 (59%)**
Skin disorders	**55 (55%)**
Central serous retinopathy	**27 (27%)**

1. Loriot Y, et al. *N Engl J Med.* 2019;381(4):338-348.

2. Necchi A, et al. ESMO 2020. Presentation 750P.

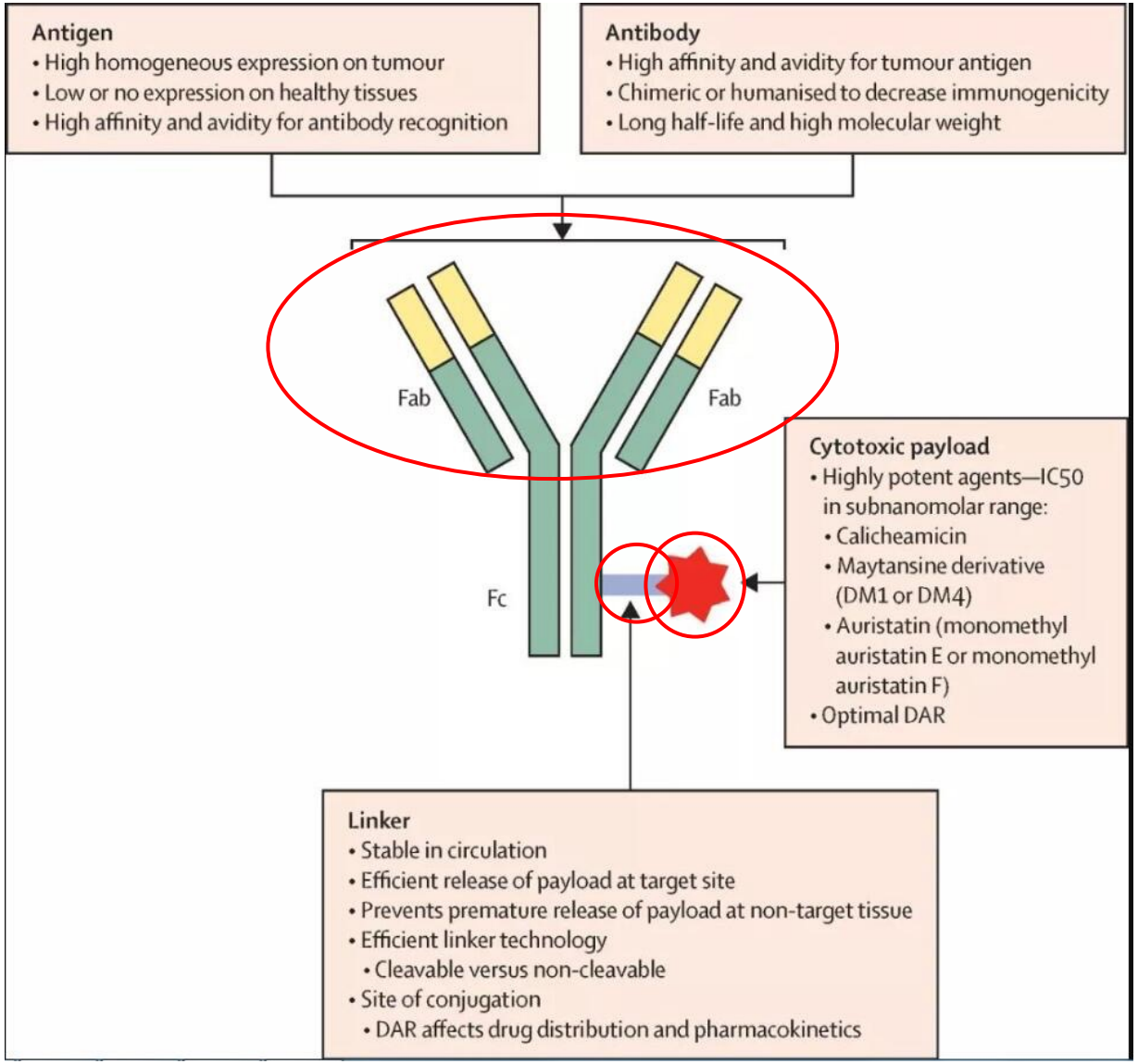
3. Siefker-Radtke *Lancet Oncol*. 2022;23(2):248-258.

Randomized Phase 3 Erdafitinib THOR Trial Schema



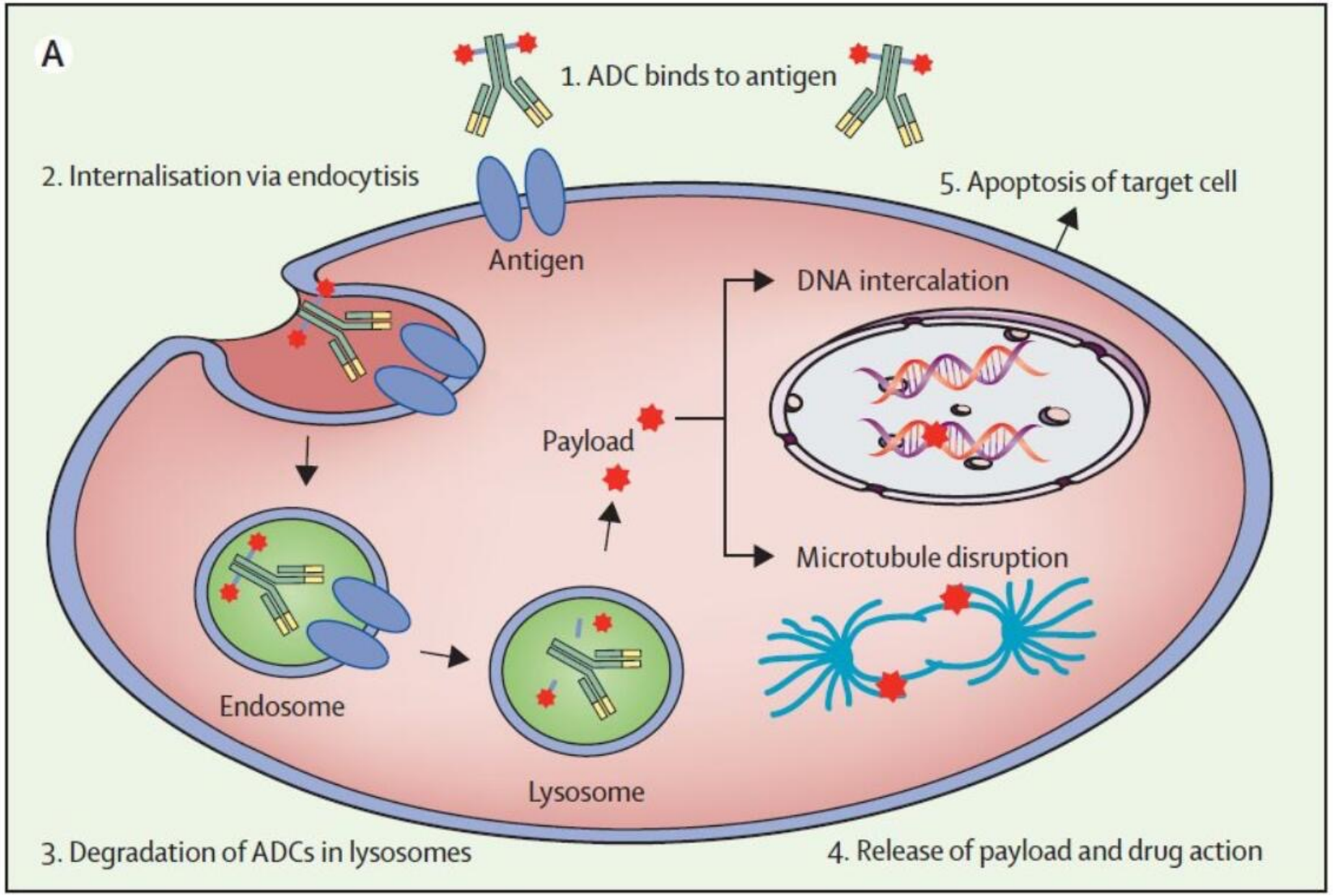
https://clinicaltrials.gov/ct2/show/NCT03390504

General Design Elements for an Antibody Drug Conjugate (ADC)



Chau CH, et al. Lancet 2019; 394:793-804

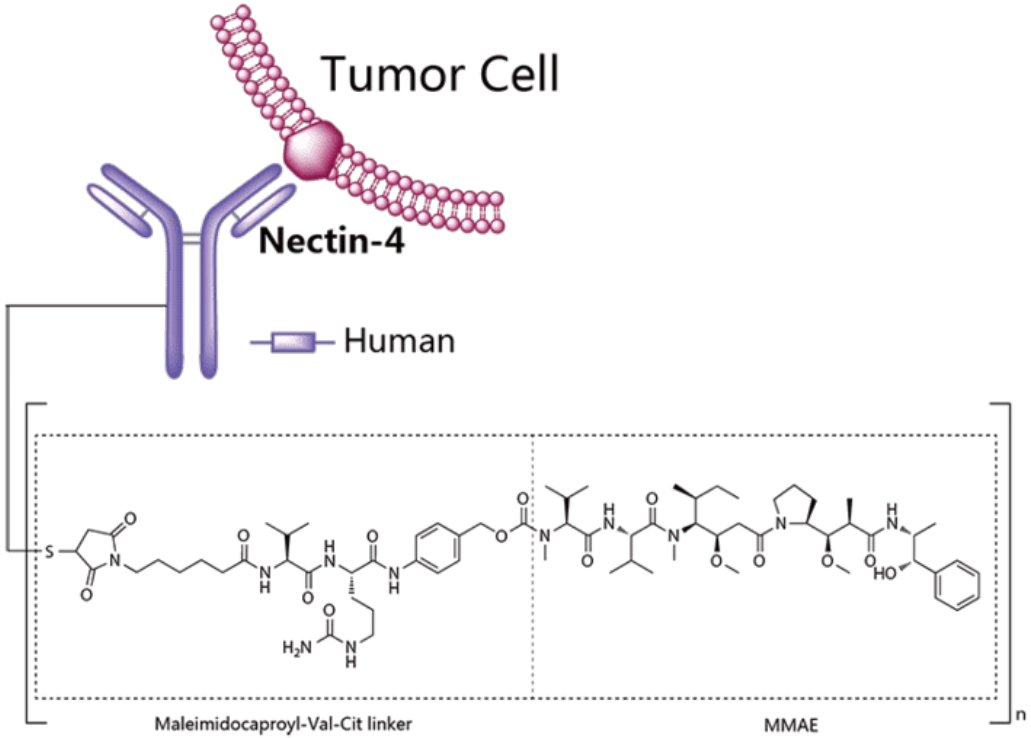
ADC Mechanism of Action



Chau CH, et al. Lancet 2019; 394:793-804

Nectin-4 and ASG-22E (Enfortumab Vedotin)

- Nectin-4 is a transmembrane protein that regulates cell-cell adhesions and mechanisms that underlie contact inhibition of cell movement and proliferation[1]
- Moderate to strong IHC staining was observed in 60% of bladder tumor specimens, whereas normal tissue had very limited staining[2]
  - Clinical data have shown very high H-scores in Enfortumab Vedotin trials
- Initial preclinical work with ASG-22E (eventually enfortumab vedotin) showed inhibition of growth in human breast, bladder, pancreatic and lung cancer xenografts, but breast and bladder showed dramatic tumor regression[2]



1. Takai Y, et al. Nat Rev Mol Cell Biol 2008; 9:603-15
2. Challita-Eid PM, et al. Cancer Res 2016; 76:3003-13

EV-301 Randomized Phase 3 Data

Key Inclusion Criteria:

- Locally advanced, unresectable or metastatic UC (squamous differentiation and mixed histologies allowed)
- Progression or relapse after PD-1/PD-L1 therapy
- Receipt of prior platinum chemotherapy (if perioperative receipt must have progressed within 12 months)
- ECOG PS 0 or 1

→ **1:1** RANDOMIZE

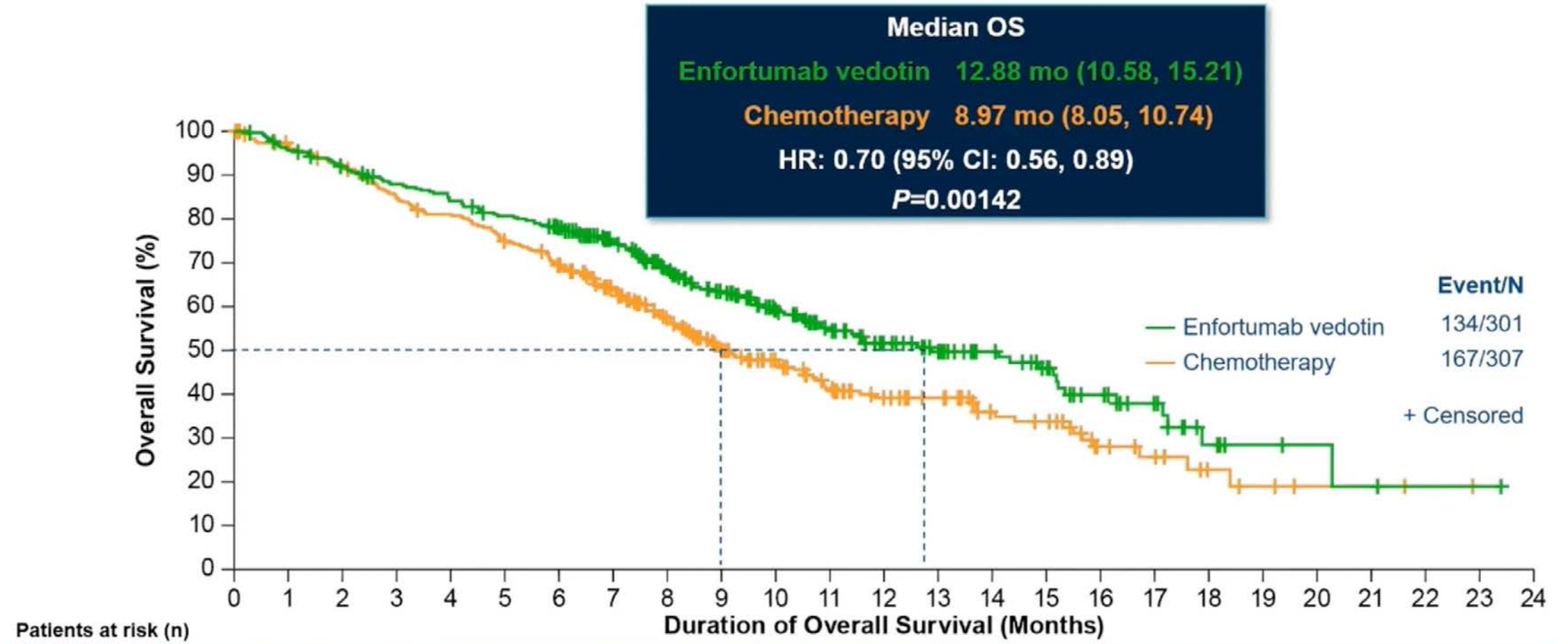
- Enfortumab vedotin 1.25 mg/kg IV on day 1, 8 and 15 of each 28 day cycle, N =301
- Docetaxel, Vinflunine, or Paclitaxel IV Day 1 of a 21-day cycle, N =307

Disease progression or other withdrawal criteria met

Primary Endpoint: Overall survival

Secondary Endpoints: PFS, ORR, disease control rate, duration of response, safety, patient-reported outcomes.

EV-301 Overall Survival



Evaluated in the intent-to-treat population.
Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.

Data cut-off: July 15, 2020

Powles T, et al. N Engl J Med 2021; Epub February 12, 2021.

EV-301 Treatment Related Adverse Events

	Enfortumab Vedotin (N=296)		Chemotherapy (N=291)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any AE	278 (94%)	152 (51%)	267 (92%)	145 (50%)
Alopecia	134 (45%)	0	106 (36%)	0
Peripheral sensory neuropathy[a]	100 (34%)	9 (3%)	62 (21%)	6 (2%)
Pruritus	95 (32%)	4 (1%)	13 (4%)	0
Fatigue	92 (31%)	19 (6%)	66 (23%)	13 (4%)
Decreased appetite	91 (31%)	9 (3%)	68 (23%)	5 (2%)
Diarrhea	72 (24%)	10 (3%)	48 (16%)	5 (2%)
Dysgeusia	72 (24%)	0	21 (7%)	0
Nausea	67 (23%)	3 (1%)	63 (22%)	4 (1%)
Maculopapular rash	48 (16%)	22 (7%)	5 (2%)	0
Anemia	34 (11%)	8 (3%)	59 (20%)	22 (8%)
Decreased neutrophil count	30 (10%)	18 (6%)	49 (17%)	39 (13%)
Neutropenia	20 (7%)	14 (5%)	24 (8%)	18 (6%)
Decreased white cell count	16 (5%)	4 (1%)	31 (11%)	20 (7%)
Febrile neutropenia	2 (<1%)	2 (<1%)	16 (5%)	16 (5%)

[a] A total of 113 patients (55 in the EV group and 58 in the chemotherapy group) had preexisting peripheral neuropathy.

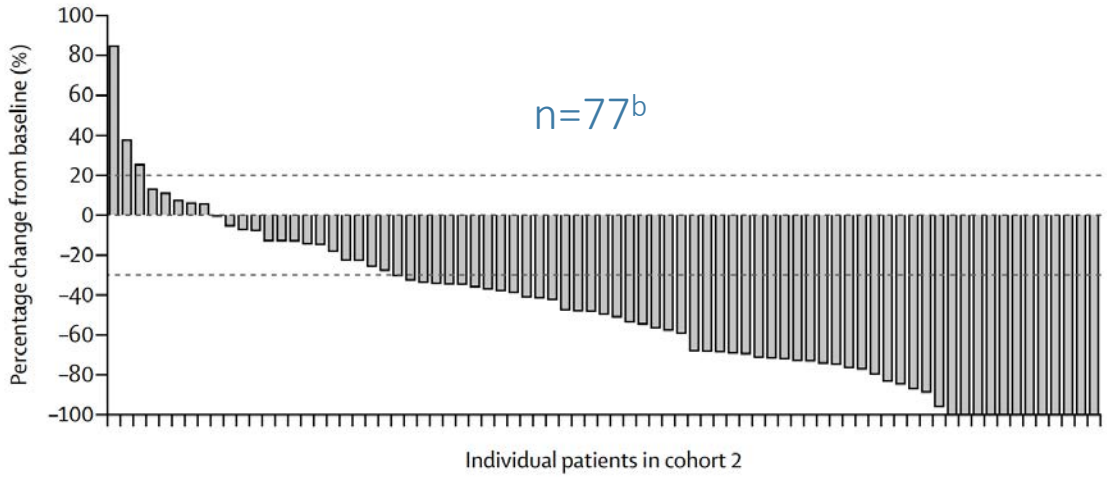
Powles T, et al. *N Engl J Med.* 2021;384(12):1125-1135.

EV-201 Cohort 2 Supports FDA Approval for Cisplatin-Ineligible Patients

Confirmed Best Overall Response per BICR

	Cohort 2 (n=89)
Objective response rate	46 (52%)
95% CI	41-62
Best overall response	
Complete response	18 (20%)
Partial response	28 (31%)
Stable disease	27 (30%)
Progressive disease	8 (9%)
Not evaluable[a]	8 (9%)

Change in Target Lesions From Baseline



Median duration of treatment: 6 months

[a] Includes 5 patients who did not have a response assessment postbaseline, 2 patients whose postbaseline assessment did not meet the minimum interval requirement for stable disease, and 1 patient whose response cannot be assessed due to incomplete anatomy.

[b] Data are not available for 12 patients due to no response assessment of response postbaseline (n=5), incomplete assessment of target lesions postbaseline (n=1), or no measurable disease at baseline per BICR (n=6).

Yu EY, et al. *Lancet Oncol.* 2021;22(6):872-882.

EV-103: Phase 1b/2 Trial of Enfortumab + Pembrolizumab

Patients With 1L Cisplatin-Ineligible la/mUC (N=45)

Dose escalation	Dose expansion cohort A
EV + Pembro (n=5)	EV + Pembro (n=40)

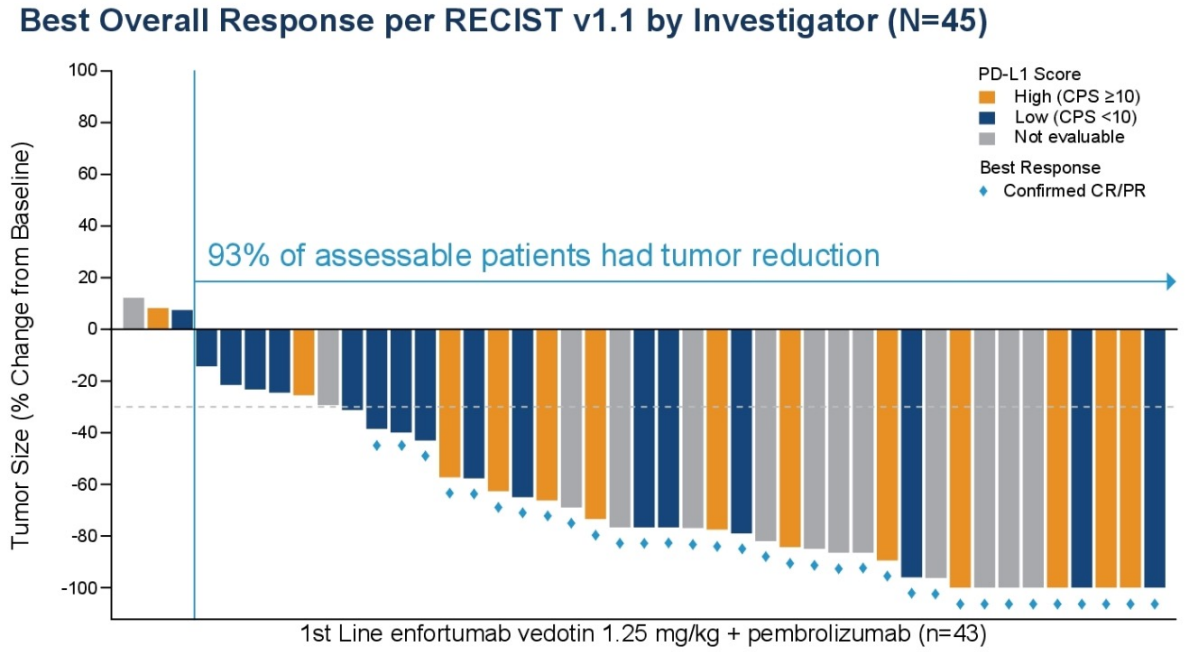
EV 1.25 mg/kg days 1 and 8 of a 3-week cycle
+
Pembrolizumab 200 mg on day 1 of a 3-week cycle

- 84% of patients had visceral disease and 31% had liver metastasis
- 31% of patients had PD-L1 CPS ≥10

Confirmed ORR 95% CI	**73%** (33/45) (58.1, 85.4)
Complete response	16% (7/45)
Partial response	58% (26/45)

- 57% confirmed ORR in patients with liver metastases

Maximum Target Lesion Reduction From Baseline by PD-L1 Status



Friedlander TW, et al. ASCO 2021. Abstract 4528.

EV-103 Cohort K: Phase 1b/2 Trial

Cohort K

- Unresectable la/mUC
- Cisplatin ineligible
- No prior treatment for la/mUC

N=149

R
1:1

n=76
EV 1.25 mg/kg days 1 and 8 of a 3-week cycle
+
Pembrolizumab 200 mg on day 1 of a 3-week cycle

n=73
EV 1.25 mg/kg days 1 and 8 of a 3-week cycle

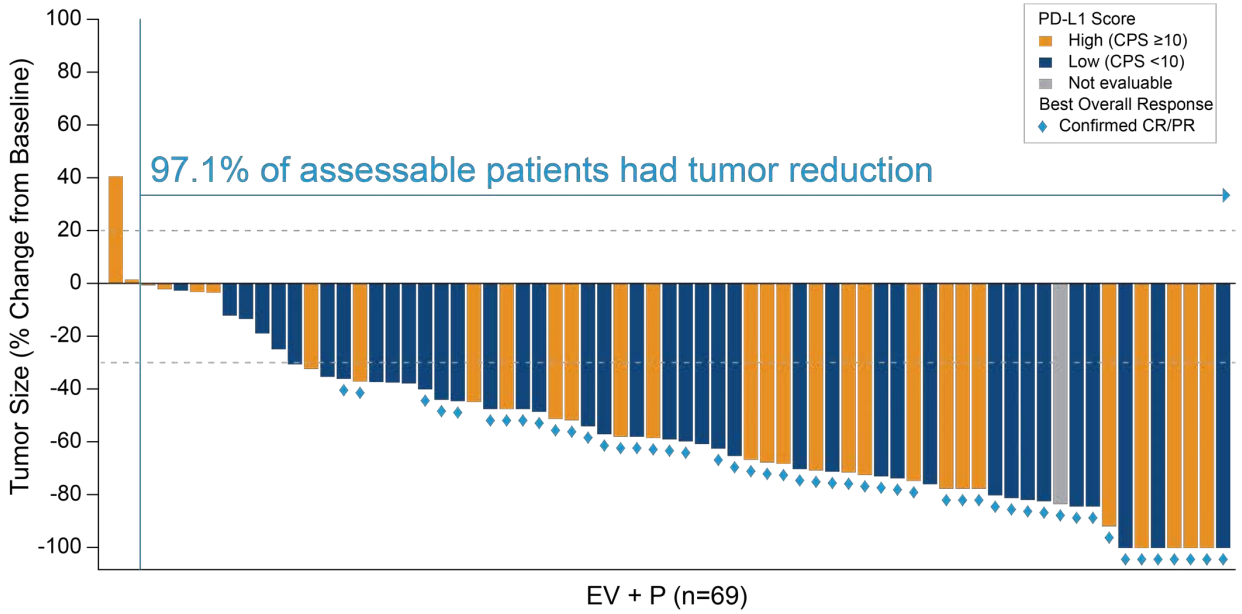
Primary Endpoint

- ORR per BICR

Secondary Endpoints

- ORR per investigator assessment
- DOR
- Disease control rate
- PFS
- OS
- Safety

	EV+P (N=76)	EV Mono (N=73)
Confirmed ORR, n (%) (95% CI)	49 (64.5) (52.7, 75.1)	33 (45.2) (33.5, 57.3)
Best overall response, n (%)		
Complete Response	8 (10.5)	3 (4.1)
Partial Response	41 (53.9)	30 (41.1)
Stable Disease	17 (22.4)	25 (34.2)
Progressive Disease	6 (7.9)	7 (9.6)
Not Evaluable	3 (3.9)	5 (6.8)
No Assessment	1 (1.3)	3 (4.1)
Median time to objective response (range), mos	2.07 (1.1, 6.6)	2.07 (1.9, 15.4)
Median number of treatment cycles (range)	11.0 (1, 29)	8.0 (1, 33)



Data cutoff: 10Jun2022
BICR: Blinded Independent Central Review; cORR: Confirmed Objective Response Rate; NR: Not Reached

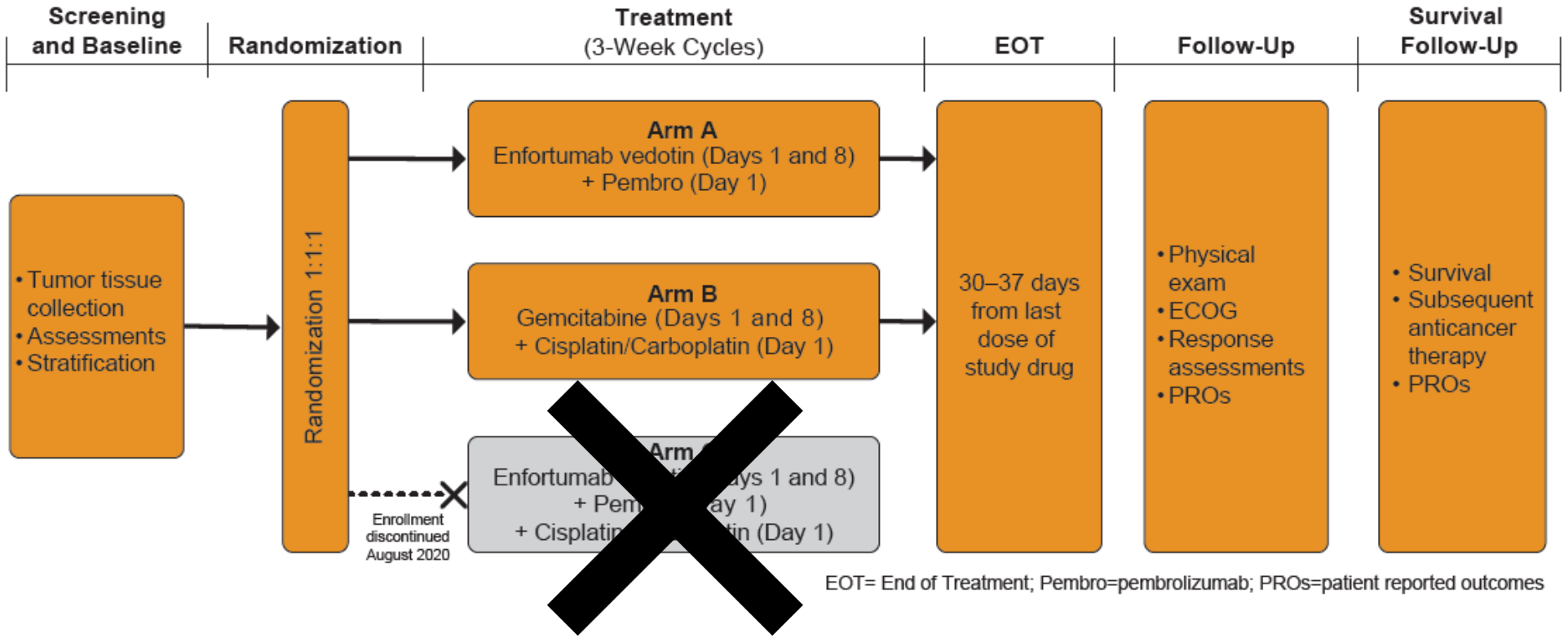
BICR: Blinded Independent Central Review; CPS: Combined Positive Score; CR: Complete Response; PD-L1: Programmed Death-Ligand 1 PR: Partial Response

Rosenberg JE, et al. ESMO 2022. Abstract 2895/LBA73.

EV-302 Randomized Phase 3 Trial Schema

Eligibility

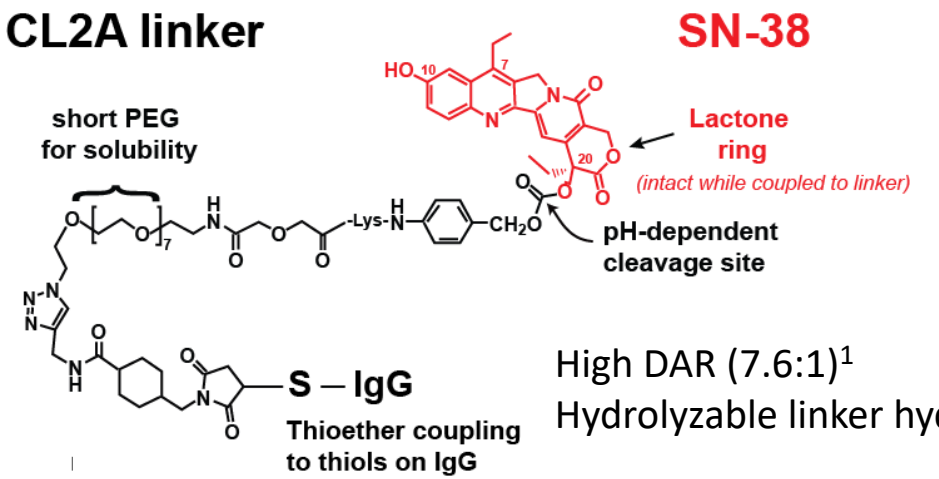
- Locally advanced or metastatic urothelial carcinoma
- 1st line systemic therapy
- Platinum-eligible



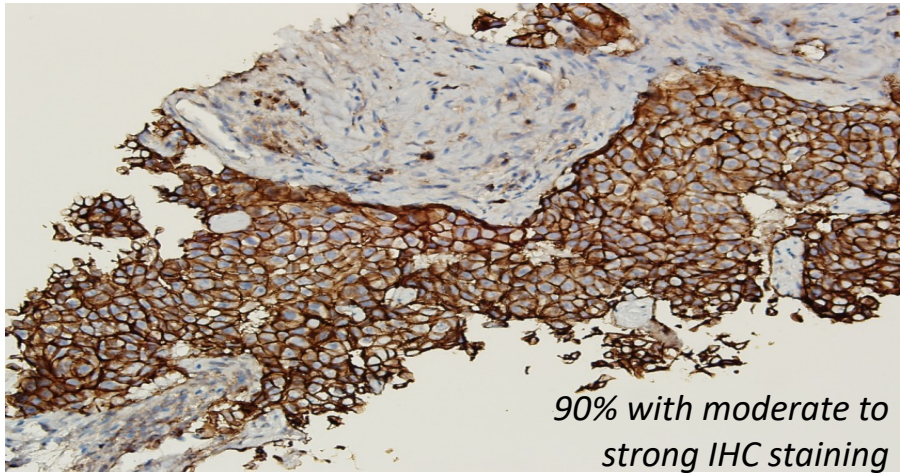
- Stratification Factors for Randomization: cisplatin eligibility (eligible/ineligible), liver metastases (present/absent), PD-L1 expression (high/low)
- Follow-up until disease progression, death, consent withdrawal, or study closure

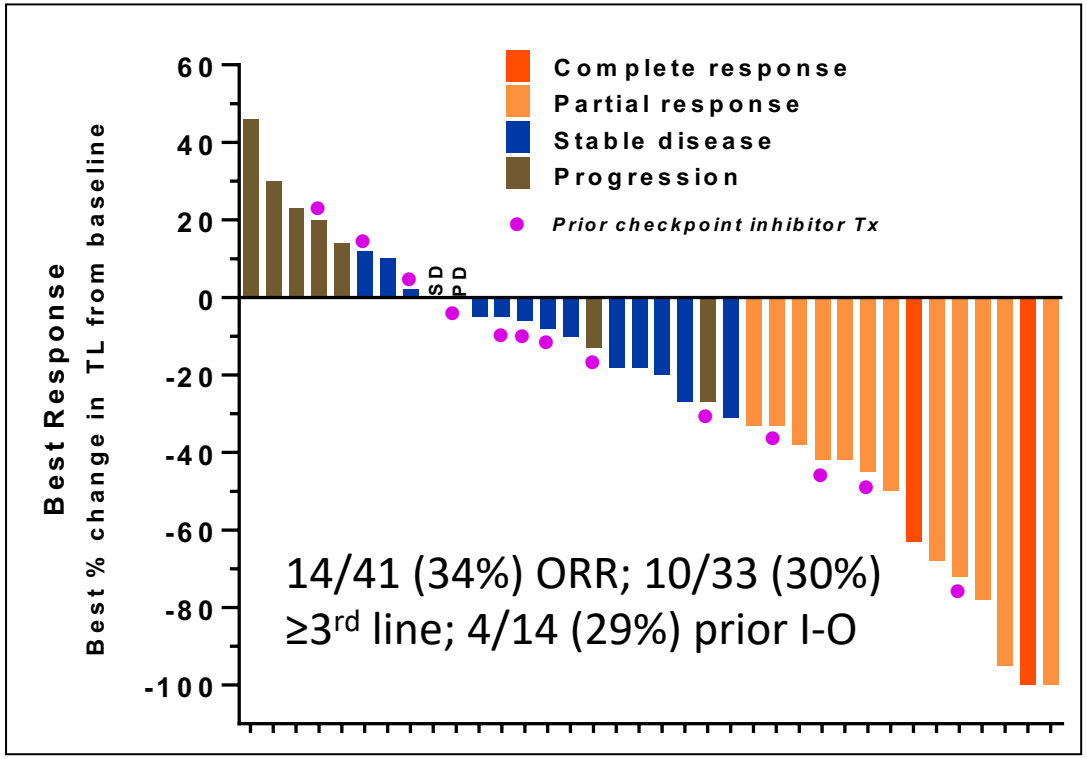
Primary Endpoints: PFS, OS
Secondary Endpoints: ORR, DOR, DCR, QOL, PRO, Safety

Sacituzumab govitecan



High DAR (7.6:1)[1]
Hydrolyzable linker hydrolysis[2]





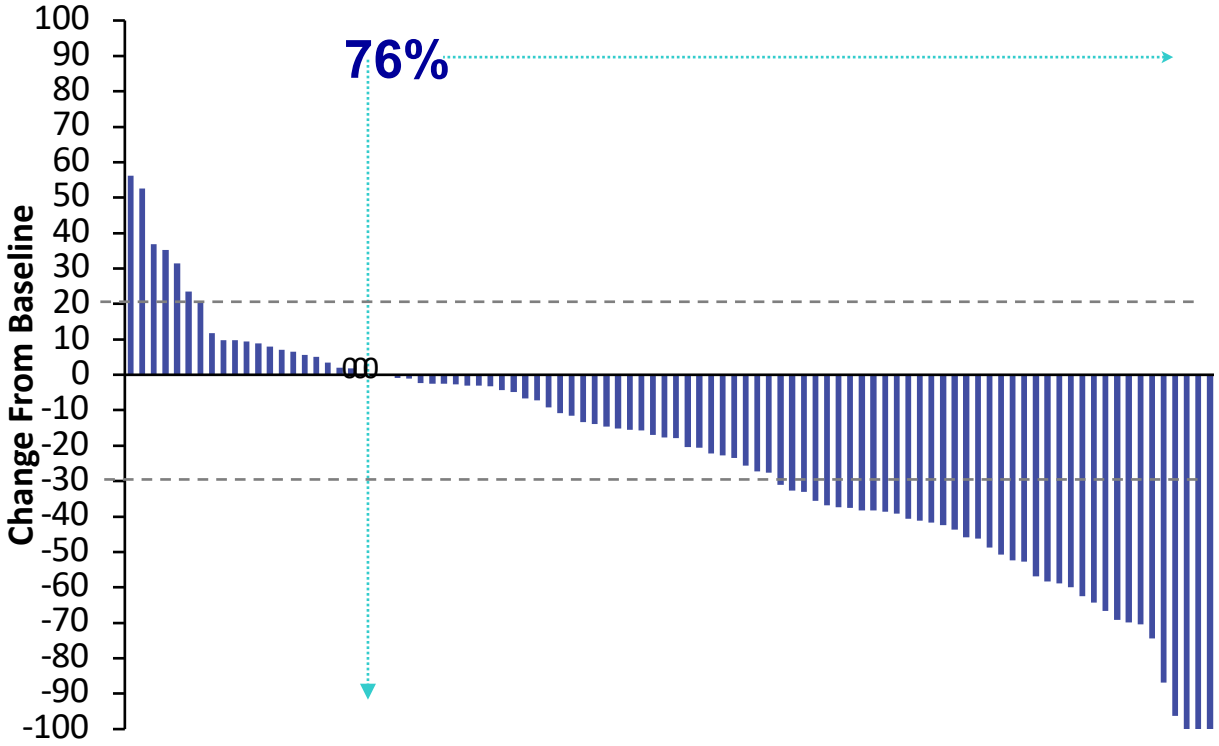
- Final 14/45 (31%) ORR
- Median PFS 7.3 months
- Median OS 18.9 months

1. Cardillo TM, et al. Bioconjug Chem 2015; 26:919-31
2. Govindan SV, et al. Mol Cancer Ther 2013; 12:968-78

Tagawa S, et al. Ann Oncol (2017) 28 (suppl_5):v295-v329
Tagawa S, et al. J Clin Oncol 37, no. 7_suppl (March 1, 2019) 354-354

TROPHY-U-01 Cohort 1 (Prior Platinum and CPI) Response and Reduction in Tumor Size

Endpoint	Cohort 1 (N=113)
ORR, n (%) [95% CI]	**31 (27) [19, 37]**
CR, n (%)	6 (5)
PR, n (%)	25 (22)
Median duration of response, mos [95% CI] (Range)	**5.9** [4.70, 8.60] (1.4–11.7)
Median time to onset of response, mos (Range)	1.6 (1.2–5.5)



[a]Assessments were per Blinded Independent Review Assessment, RECIST 1.1.
CI, confidence interval; CR, complete response; ORR, objective response rate; PR, partial response; TTR, time to response.

[a]71/94 patients with at least one post-baseline target lesion measurement and accepted for central review. Fourteen patients had no post-treatment imaging, 1 patient lacked measurable lesions by central review, and 4 patients had poor image quality.

Loriot Y, et al. Annal Oncol (2020) 31 (suppl_4):S1142-S1215; LBA24

TROPHY-U-01 Cohort 1 Treatment-Related Adverse Events ≥20% any grade or ≥5% Grade ≥3 (n=113)

Category	Event	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Hematologic[a]	**Neutropenia**	**46**	**22**	**12**
	Leukopenia	26	12	5
	Anemia	34	14	0
	Lymphopenia	12	5	2
	Febrile neutropenia	**10**	**7**	**3**
Gastrointestinal	**Diarrhea[b]**	**65**	**9**	**1**
	Nausea	**58**	**4**	**0**
	Vomiting	28	1	0
General disorders & administrative site conditions	**Fatigue**	**50**	**4**	**0**
Skin & subcutaneous tissue	**Alopecia**	**47**	**0**	**0**
Metabolism & nutrition	Decreased appetite	36	3	0
Infections & infestations	Urinary tract infection	8	6	0

Median treatment cycles: 6 (range: 1–22); worst grade CTCAE reported

- 7 (6%) pts discontinued due to TRAEs
  - 3 discontinued due to neutropenia or its complications
- 30% GCSF usage
- One treatment-related death (sepsis due to febrile neutropenia)

Loriot Y, et al. Annal Oncol (2020) 31 (suppl_4):S1142-S1215; LBA24

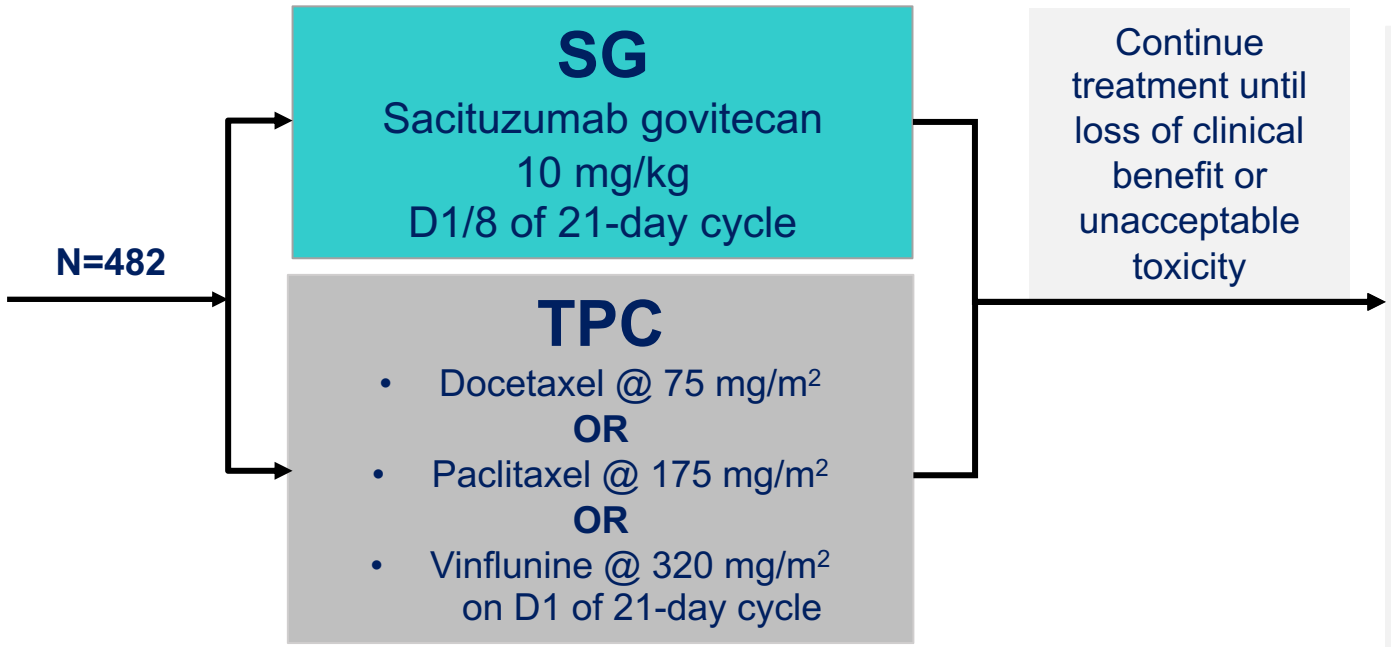
TROPiCS-04 Study Design

Study Population

- Locally advanced unresectable or mUC
- Upper/lower tract tumors
- Mixed histologic types are allowed if urothelial is predominant
- Progression after platinum-based **and** anti–PD-1/PD-L1 therapy

OR

- Platinum in neo/adj setting if progression within 12 months and subsequent CPI



Endpoint (EP)

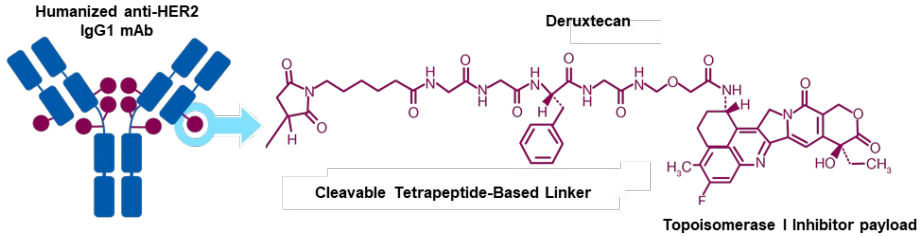
Primary EP:

- OS

Secondary EPs:

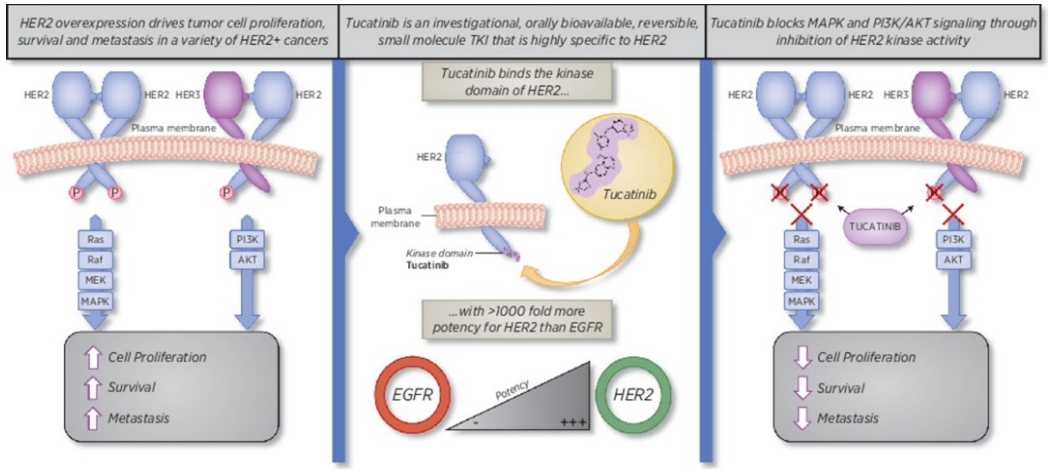
- PFS by PI assessment using RECIST 1.1
- ORR, DOR, and CBR by PI assessment using RECIST 1.1
- EORTC QLQ C30 score and EuroQOL EQ-5D-5L QOL score

HER2 as a Bladder Cancer Target



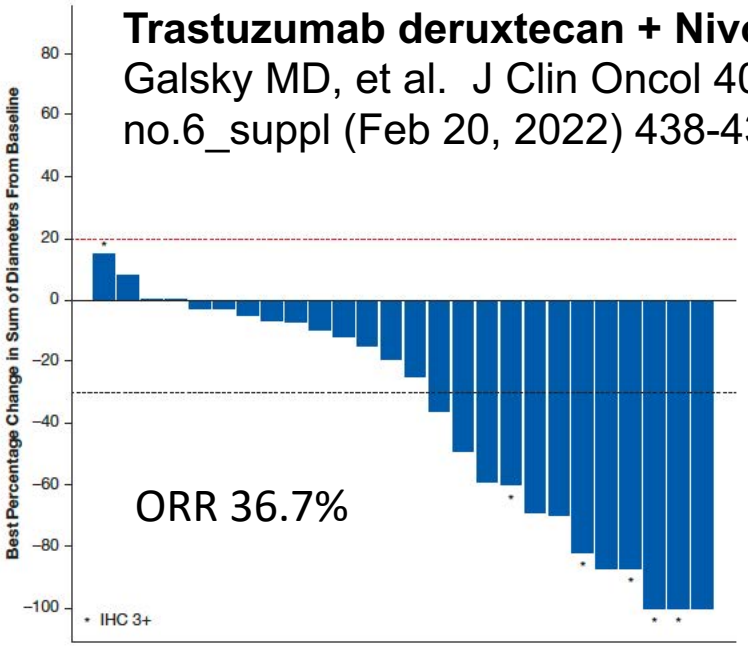
Conjugation chemistry
The tetrapeptide-based cleavable linker is connected to the humanized anti-HER2 IgG1 monoclonal antibody, with the same amino acid sequence as trastuzumab

Tucatinib basket trial with enough responses to go on to Stage 2 of design.



Tucatinib is an investigational agent and its efficacy and safety have not been established

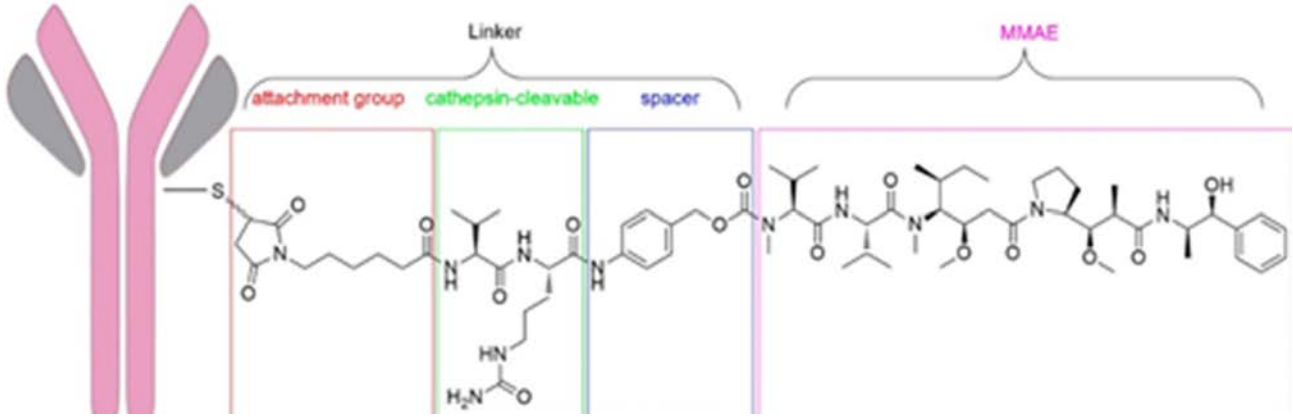
Trastuzumab deruxtecan + Nivolumab
Galsky MD, et al. J Clin Oncol 40, no.6_suppl (Feb 20, 2022) 438-438.



Cohort 3 IHC 3+/2+ (n = 30) (part 2: T-DXd 5.4 mg/kg and nivolumab 360 mg) Best (minimum) percentage change					
n	Mean	SD	Median	Min	Max
26	−37.8	38.52	−22.0	−100	15

*In cohort 3, 4 patients did not have best percentage change available, of whom 2 were IHC 3+.
The line at 20% indicates progressive disease, and the line at −30% indicates a partial response.

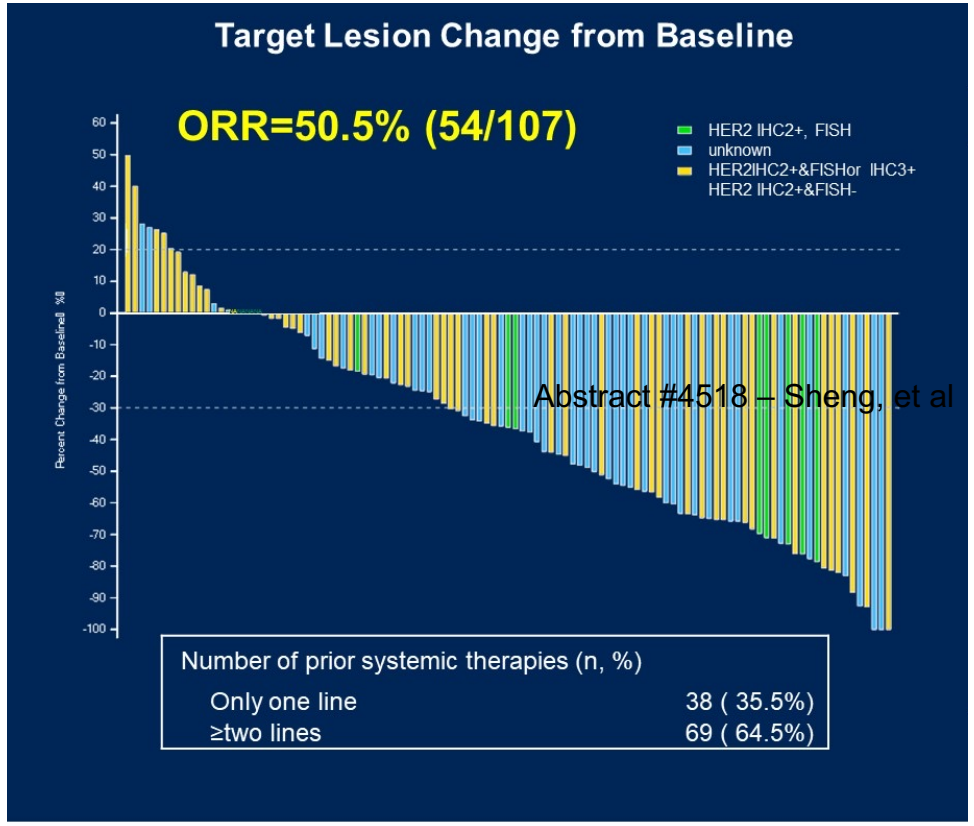
Disitamab vedotin



Hertuzumab

Disitamab Vedotin (RC48) at ASCO 2022

Activity in HER2 2-3+



Abstract #4518 – Sheng, et al

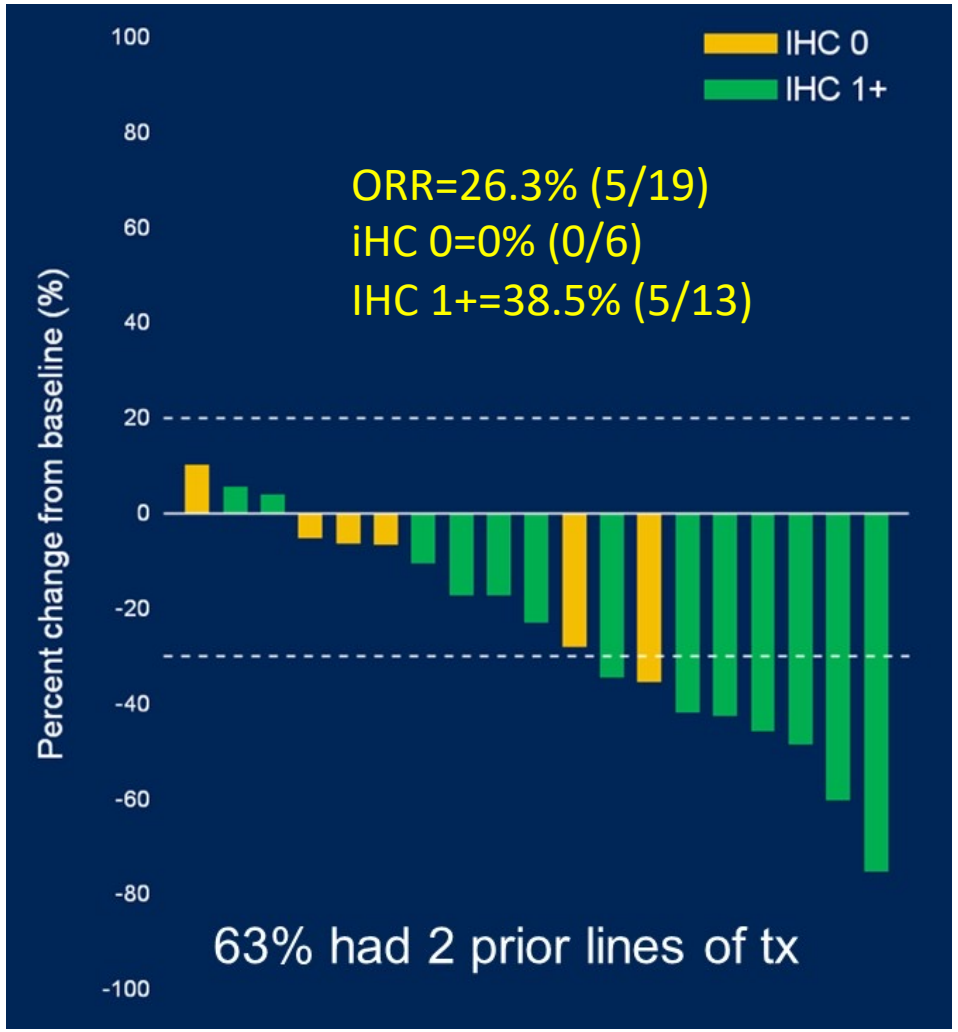
ORR

IHC2+FISH+ or IHC3+ (n=45) = 62.2%

IHC2+FISH- (n=53) = 39.6%

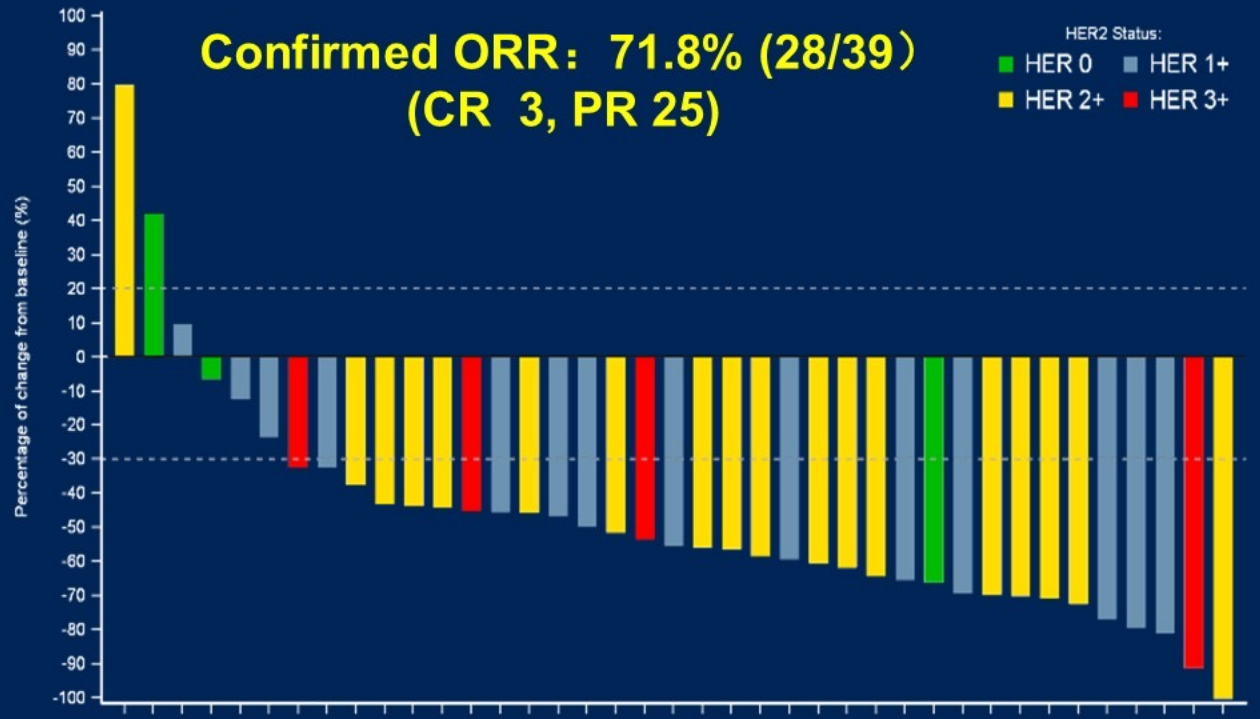
Sheng X, et al. J Clin Oncol 40, no. 16_suppl (June 1, 2022) 4518-4518.

Activity in HER2 1+

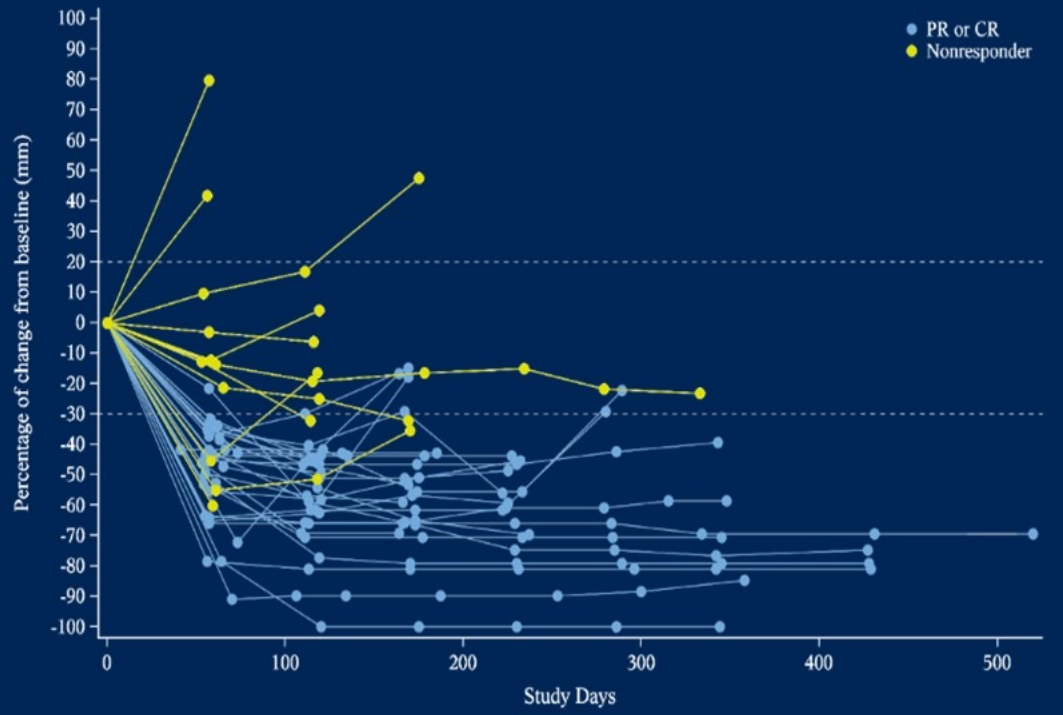


Xu H, et al. J Clin Oncol 40, no. 16_suppl (June 1, 2022) 4519-4519.

Disitamab Vedotin + Toripalimab at ASCO 2022

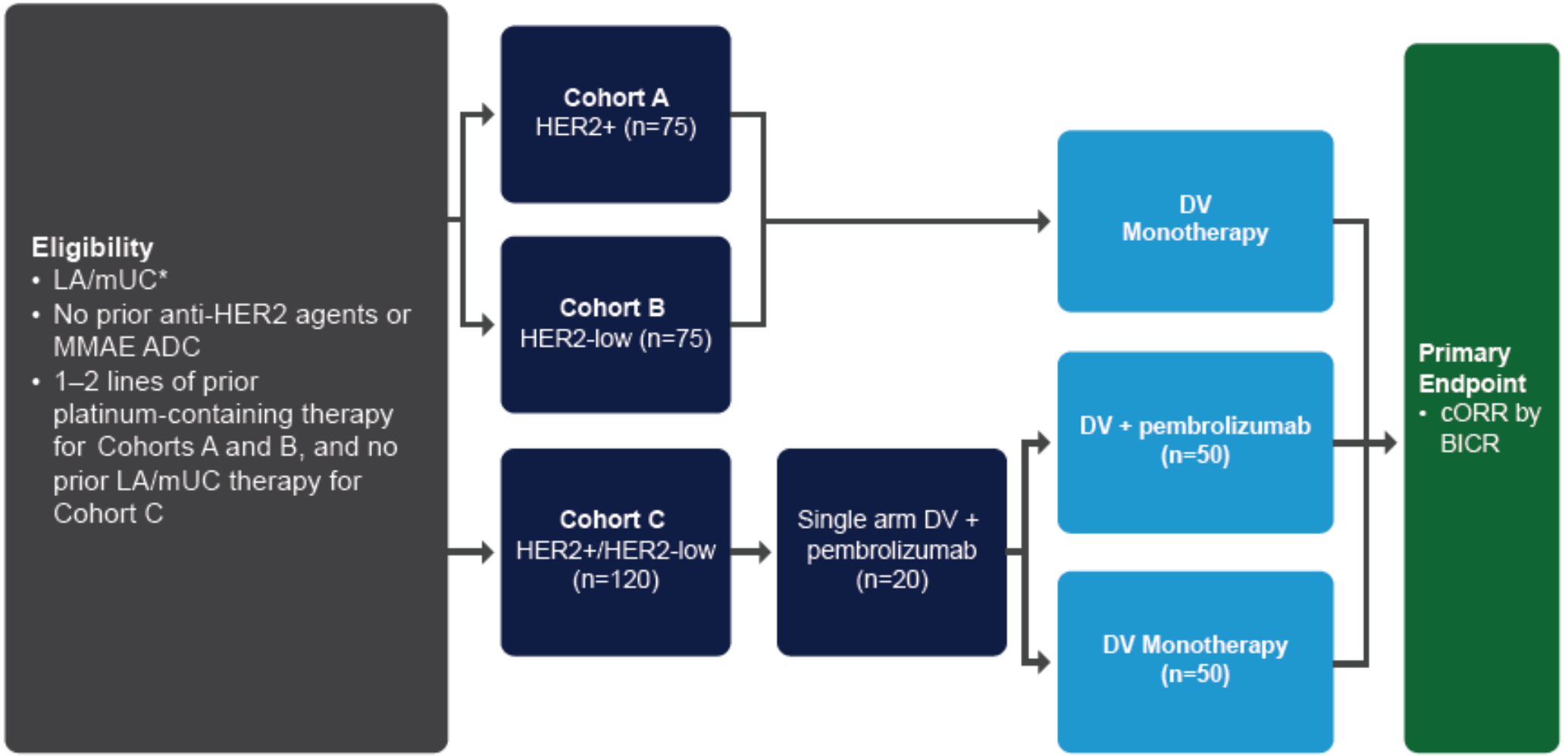


Prior systemic treatment (n,%)	
0 Line	25 (60.98%)
≥1 Lines	16 (39.02%)



Sheng X, et al. J Clin Oncol 40, no. 16_suppl (June 1, 2022) 4520-4520.

Disitamab Phase 2 Trial Schema



ADC: antibody-drug conjugate; **BICR:** blinded independent central review; **cORR:** confirmed objective response rate; **DV: disitamab vedotin; HER2: human epidermal growth factor receptor 2; LA/mUC:** locally advanced unresectable or metastatic urothelial carcinoma; **MMAE:** monomethyl auristatin E

*Histologically-confirmed, including UC originating from the renal pelvis, ureters, bladder, or urethra

Take Home Points

- Fibroblast growth factor 2/3 alterations are the only biomarker proven target with an FDA approved therapy in Erdafitinib
- Antibody drug conjugates offer an exciting technology that recently has shown clinical efficacy in many cancers, including bladder cancer
- Enfortumab vedotin is FDA approved for metastatic urothelial carcinoma patients who have received prior platinum chemotherapy and immune-oncology antibody therapy and now offers an overall survival benefit
- Enfortumab vedotin is also FDA approved in the cisplatin-ineligible disease state post therapy, as this is a significant unmet need
- Enfortumab vedotin has promise in combination with pembrolizumab for first-line metastatic disease with unprecedented ORR
- Other promising ADCs for bladder cancer include Sacituzumab govitecan (has FDA accelerated approval), trastuzumab deruxtecan and disitamab vedotin
- Her2 is being revisited as a promising drug target for patients with urothelial bladder cancer

Non-Muscle-Invasive Bladder Cancer; Neoadjuvant and Adjuvant Treatment for UBC

RTP
RESEARCH
TO PRACTICE

Discussion Questions

- Regulatory and reimbursement issues aside, what is the optimal point to integrate enfortumab vedotin into the treatment of mUBC?
- For practical purposes, how do you prevent and manage the side effects/toxicity of enfortumab vedotin?
- What is your view of the future of enfortumab vedotin/pembrolizumab combination treatment?
- Regulatory and reimbursement issues aside, what is the optimal point to integrate erdafitinib into the treatment of mUBC?

Discussion Questions

- What is your experience with TAR-200, and where do you see it headed?
- Have you or would you use erdafitinib for non-muscle-invasive UBC?
- For which patients with muscle-invasive UBC would you use adjuvant nivolumab?

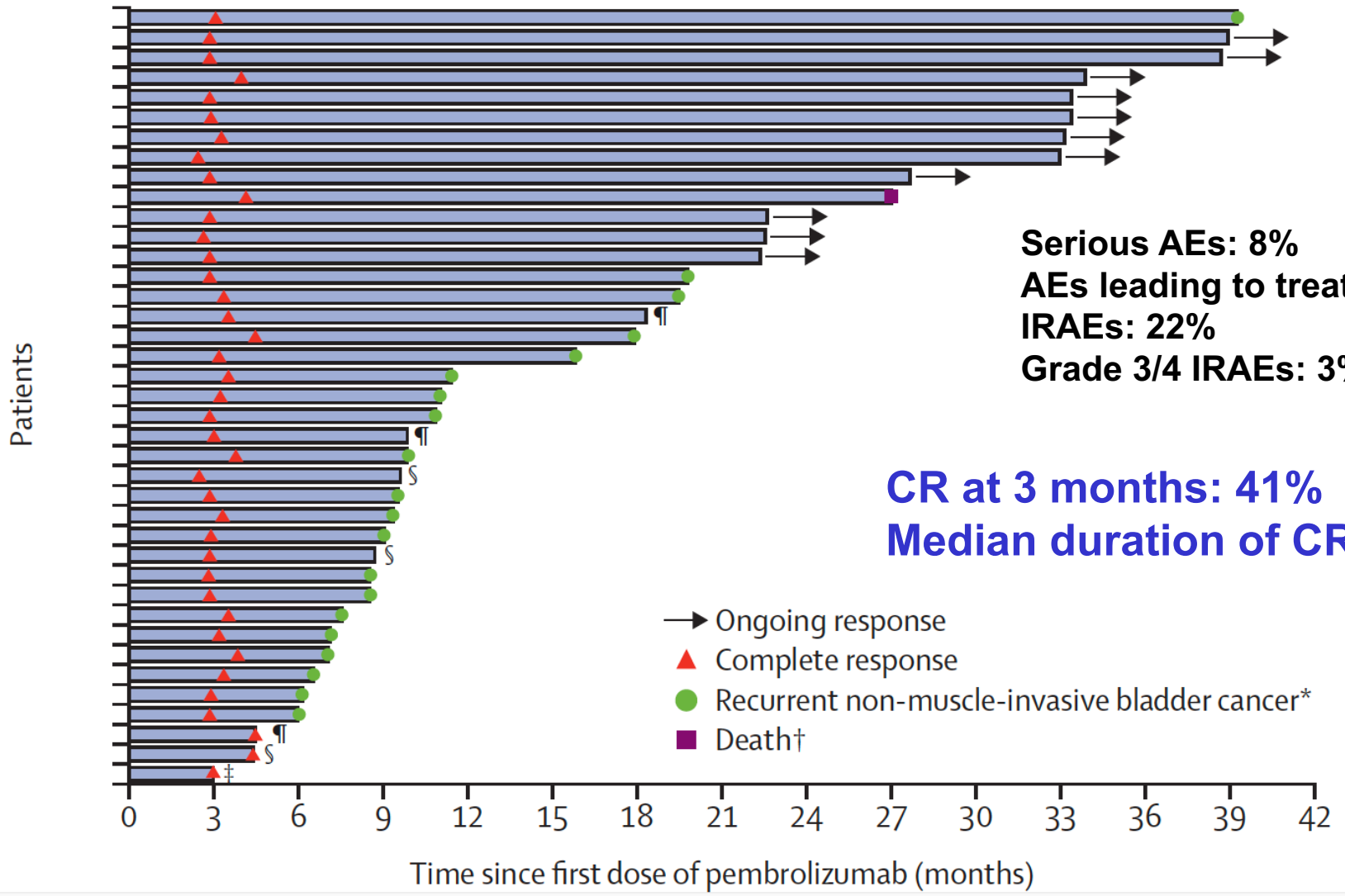
Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study

Arjun V Balar, Ashish M Kamat, Girish S Kulkarni, Edward M Uchio, Joost L Boormans, Mathieu Roumiguié, Laurence E M Krieger, Eric A Singer, Dean F Bajorin, Petros Grivas, Ho Kyung Seo, Hiroyuki Nishiyama, Badrinath R Konety, Haojie Li, Kijoeng Nam, Ekta Kapadia, Tara Frenkl, Ronald de Wit

***Lancet Oncol* 2021 July;22:919-30.**

RTP RESEARCH TO PRACTICE

KEYNOTE-057: Response, Duration of Response and Summary of Adverse Events (AEs)



Serious AEs: 8%
AEs leading to treatment interruption: 13%
IRAEs: 22%
Grade 3/4 IRAEs: 3%

CR at 3 months: 41%
Median duration of CR: 16.2 mo

Balar AV et al. *Lancet Oncol* 2021;22:919-30.

IRAEs = immune-related adverse events

RTP RESEARCH TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

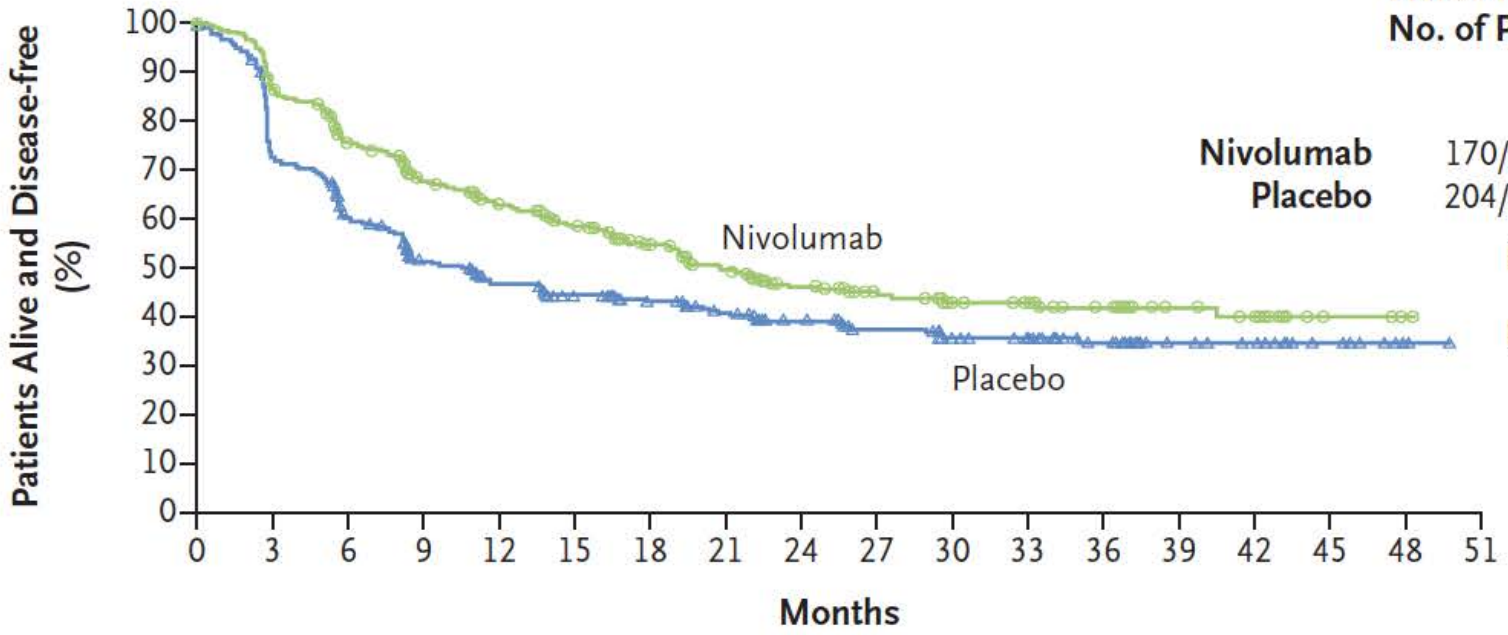
ORIGINAL ARTICLE

Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma

D.F. Bajorin, J.A. Witjes, J.E. Gschwend, M. Schenker, B.P. Valderrama, Y. Tomita, A. Bamias, T. Lebret, S.F. Shariat, S.H. Park, D. Ye, M. Agerbaek, D. Enting, R. McDermott, P. Gajate, A. Peer, M.I. Milowsky, A. Nosov, J. Neif Antonio, Jr., K. Tupikowski, L. Toms, B.S. Fischer, A. Qureshi, S. Collette, K. Unsal-Kacmaz, E. Broughton, D. Zardavas, H.B. Koon, and M.D. Galsky

***N Engl J Med* 2021 June 3;384:2102-14.**

CheckMate 274: Disease-Free Survival in the ITT Population



	No. of Events/ No. of Patients	Disease-free Survival at 6 Mo (95% CI)	Disease-free Survival at 12 Mo (95% CI)
		%	
Nivolumab	170/353	74.9 (69.9–79.2)	62.8 (57.3–67.8)
Placebo	204/356	60.3 (54.9–65.3)	46.6 (41.1–51.9)

Hazard ratio for disease recurrence or death, 0.70 (98.22% CI, 0.55–0.90)
P<0.001

Bajorin DF et al. *N Engl J Med* 2021;384:2102-14.

ELSEVIER

Urologic Oncology: Seminars and Original Investigations 000 (2022) 1–9

UROLOGIC ONCOLOGY

Clinical-Bladder cancer

The safety, tolerability, and efficacy of a neoadjuvant gemcitabine intravesical drug delivery system (TAR-200) in muscle-invasive bladder cancer patients: a phase I trial

Siamak Daneshmand, M.D.[a,*], Iris S.G. Brummelhuis, M.D.[b], Kamal S. Pohar, M.D.[c], Gary D. Steinberg, M.D.[d], Manju Aron, M.D.[e], Christopher J. Cutie, M.D.[f], Kirk A. Keegan, M.D.[f], John C. Maffeo, M.S.H.S.[f], Donald L. Reynolds, Ph.D.[f], Bradley Raybold, M.S.[g], Albert Chau, M.Sc.[h], J. Alfred Witjes, M.D., Ph.D.[b]

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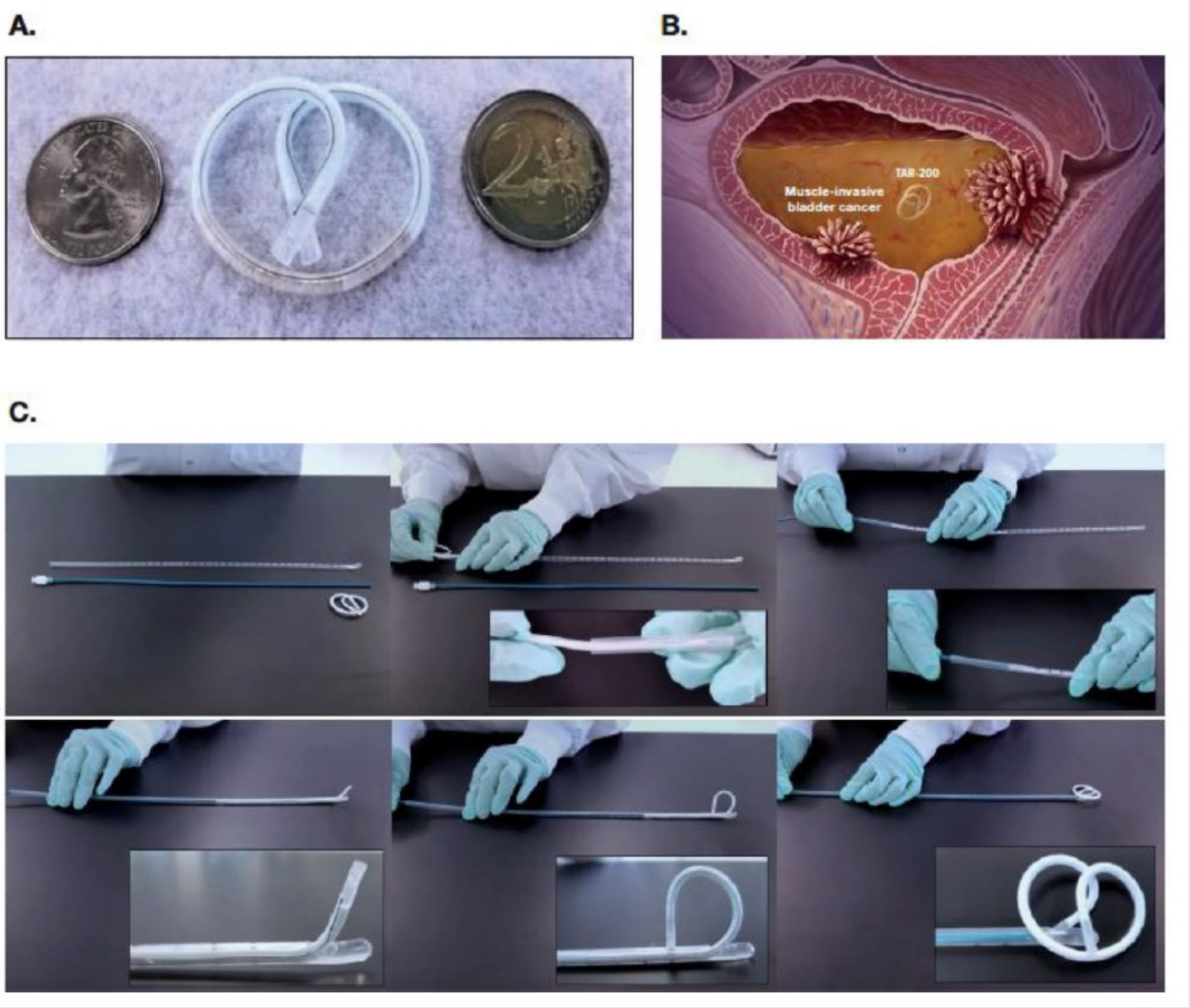
Components of TAR-200



TAR-200, a gemcitabine-releasing intravesical system, is formed into a pretzel-like configuration within the bladder.

TAR-200

- Consists of a small, flexible silicone tube filled with gemcitabine (A)
- Is designed to release drug directly inside the bladder over the indwelling period (B)
- Is inserted using a TARIS urinary placement catheter (C)

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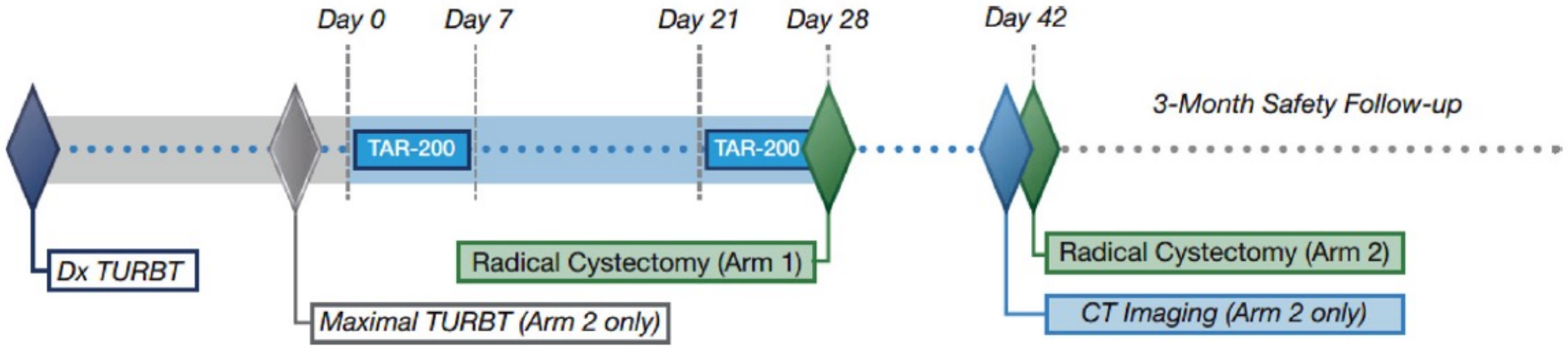
TAR-200-101: Study Design and Outcomes



Response	Arm 1 (>3 cm)	Arm 2 (max TURBT)
Underwent pathology at RC, *n/N* (%)	10/11 (90.9)	10/12 (83.3)
Pathologic response, *n/N* (%)	4/10 (40.0)	6/10 (60.0)
Complete response, *n/N* (%)	1/10 (10.0)	3/10 (30.0)
Partial response, *n/N* (%)	3/10 (30.0)	3/10 (30.0)

Treatment-emergent adverse event, *n* (%)	TAR-200 related[a]	Procedure related[b]
Pollakiuria	3 (13)	2 (9)
Urinary incontinence	2 (9)	2 (9)
Micturation urgency	2 (9)	0
Urinary tract infection	1 (4)	2 (9)
Gross hematuria	0	1 (4)
Hematoma[c]	0	0

RC = radical cystectomy

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CME/MOC and NCPD credit information will be emailed to each participant within 5 business days.

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