Prostate and Bladder Cancers What have we learned over the past year?

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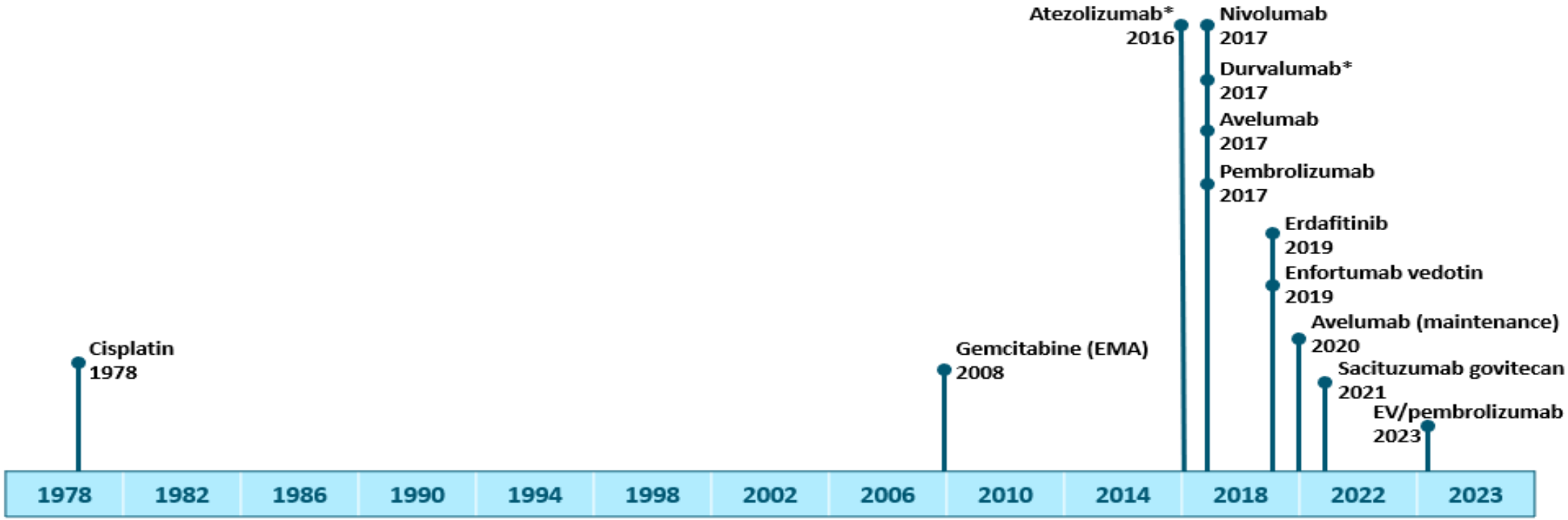
NORTON CANCER INSTITUTE

What we have learned in Bladder Cancer in 2025

1. New Standard of Care coming in localized Bladder Cancer
2. Perioperative immunotherapy becomes new standard of care for bladder cancer patients
3. HER2+ expressing metastatic bladder cancer treatment should be considered (new FDA approval)

The Treatment Landscape for Locally Advanced/ Metastatic Urothelial Carcinoma Has Evolved Rapidly



*Not FDA approved; indication withdrawn.

Cisplatin PI. www.ema.europa.eu/en/medicines/human/referrals/gemzar. Rhea. Clin Med Insights Oncol. 2021;15:11795549211044963. Nivolumab PI. Avelumab PI. Pembrolizumab PI. Erdafitinib PI. Enfortumab vedotin PI. Avelumab PI. Sacituzumab govitecan PI.

National Comprehensive Cancer Network®

NCCN Guidelines Version 6.2024
Non-Muscle Invasive Bladder Cancer

NCCN Guidelines Index
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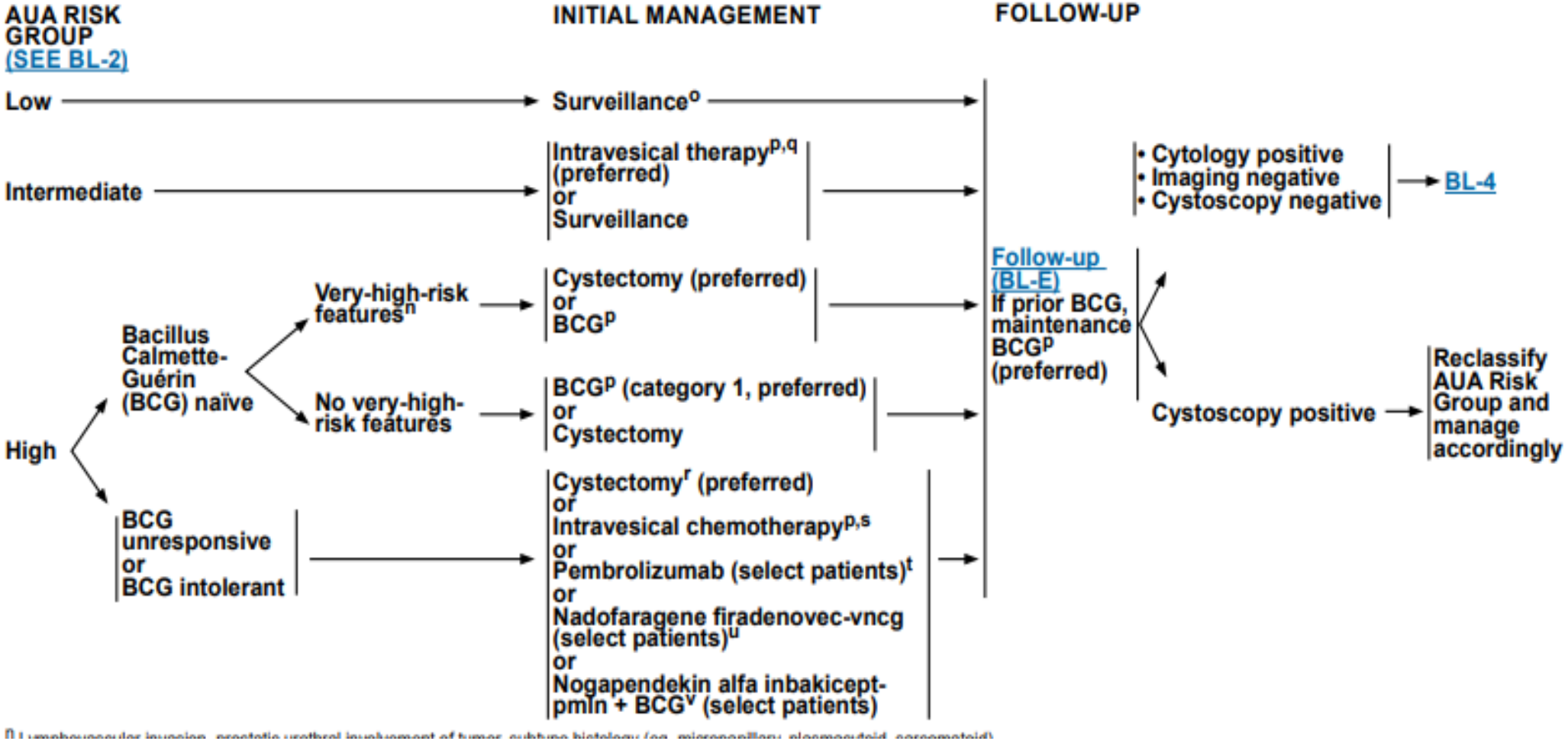
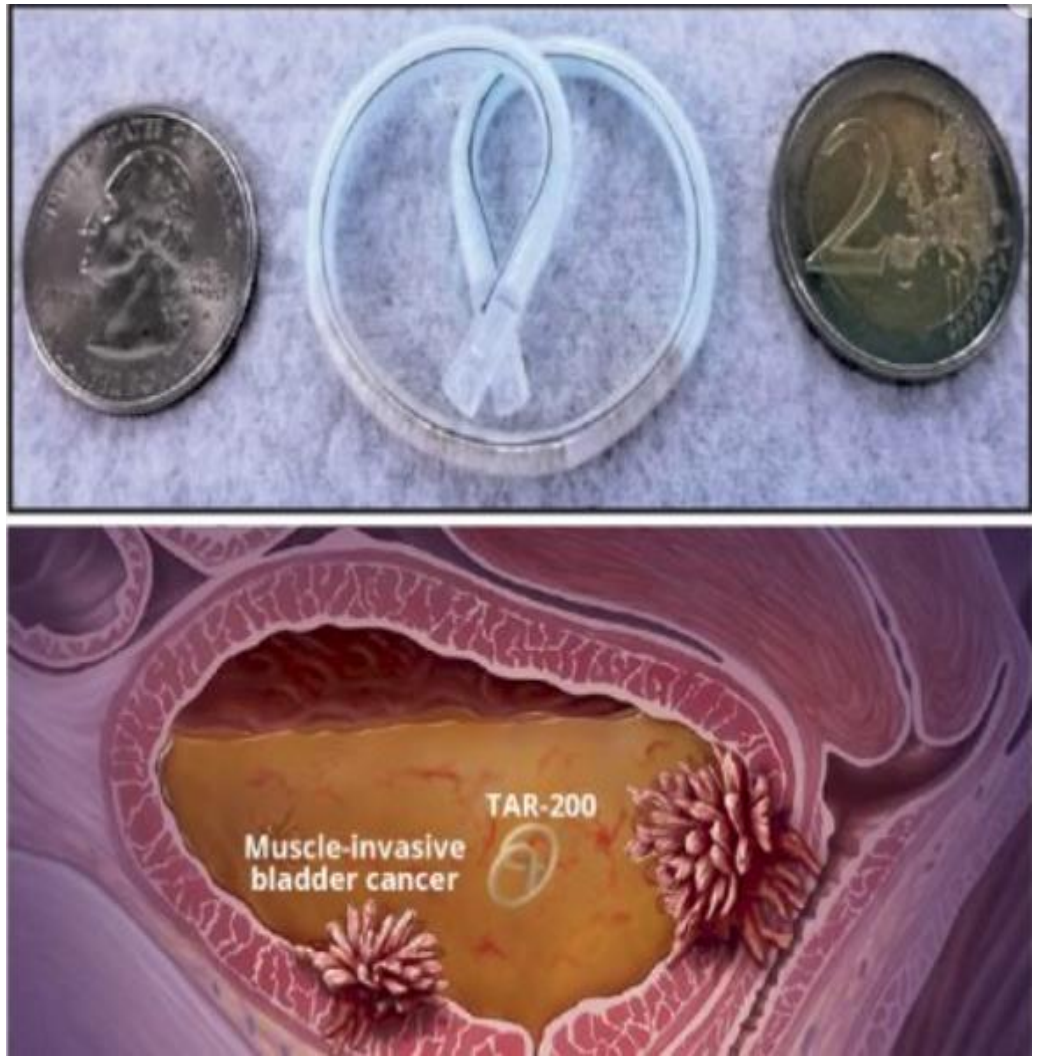
MANAGEMENT PER NMIBC RISK GROUP



[] Lymphovascular invasion, prostatic urethral involvement of tumor, subtype histology (eg, microcapillary, plasmacytoid, sarcomatoid)

TAR 200 delivery device



- "Pretzel" Device
- Placed in the bladder
- Sustained local release of gemcitabine chemotherapy over time
- SunRISE 01 placed every 21 day cycle

Van der Heijden ESMO 2024

TAR-200 +/- Cetrelimab and Cetrelimab Alone in Patients With Bacillus Calmette-Guérin–Unresponsive High-Risk Non–Muscle-Invasive Bladder Cancer: Updated Results From SunRISe-1

Michiel S van der Heijden[1], Giuseppe Simone[2], Martin Bögemann[3], Evanguelos Xylinas[4], Mathieu Roumiguié[5], Felix Guerrero-Ramos[6], Andrea Necchi[7], Siamak Daneshmand[8], Charles Van Praet[9], Philipp Spiegelhalder[10], Karel Decaestecker[11], Harm Arentsen[12], Daniel Zainfeld[13], Shalaka Hampras[14], Christopher J Cutie[15], Hussein Sweiti[16], Katharine Stromberg[14], Jason Martin[17], Abhijit Shukla[15], Joseph M Jacob[18]

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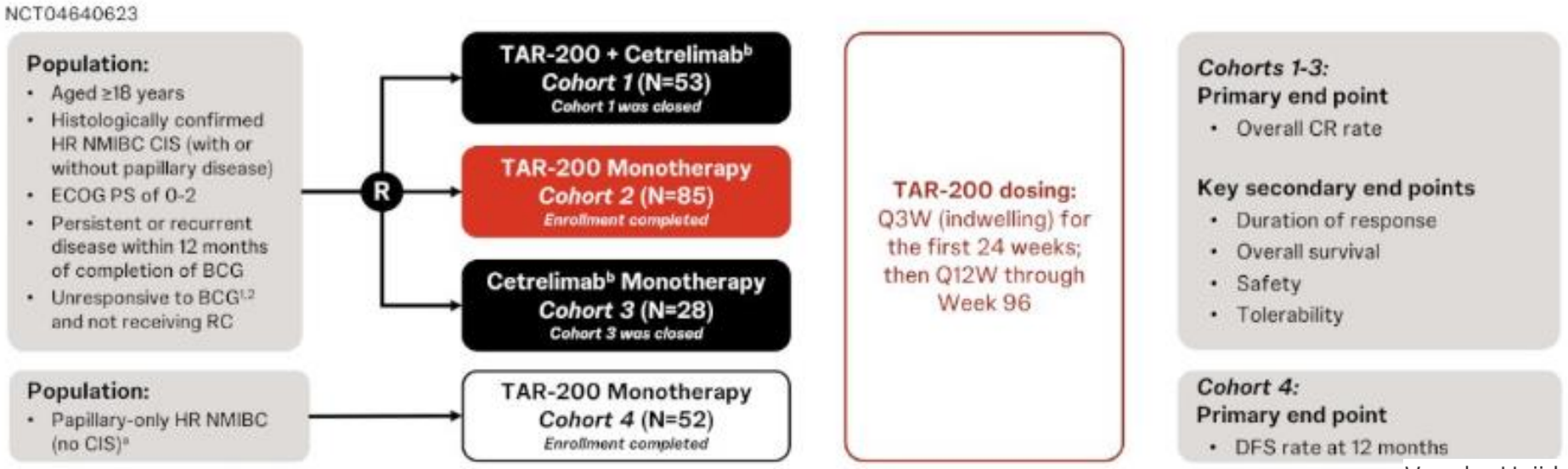
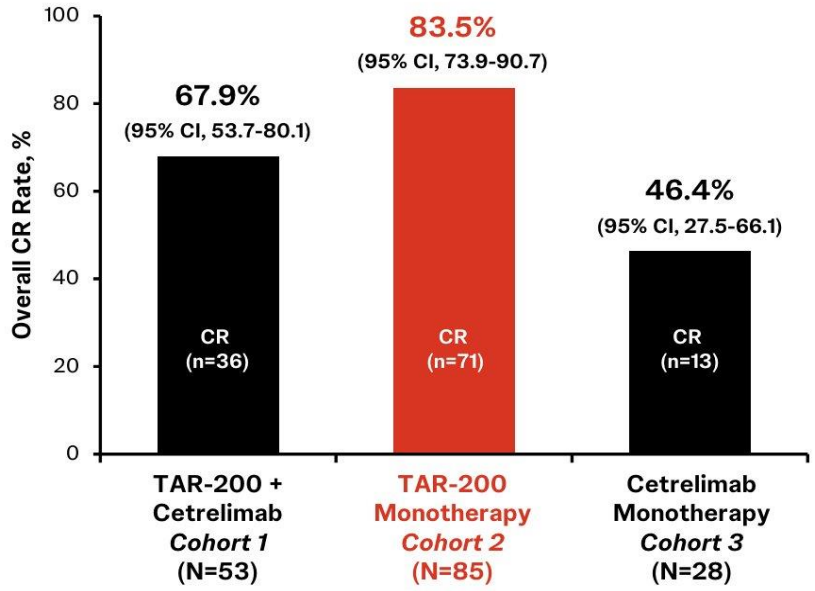


Van der Heijden ESMO 2024

Centrally Assessed CR Rate at Any Time[a,b]



	TAR-200 + Cetrelimab *Cohort 1* (N=53)	TAR-200 Monotherapy *Cohort 2* (N=85)	Cetrelimab Monotherapy *Cohort 3* (N=28)
Estimated 12-month CR rate[c], % (95% CI)	**56.7** (41.2-69.6)	**57.4** (40.6-71.0)	**22.8** (8.6-41.1)
Estimated 12-month DOR rate[c], % (95% CI)	**75.9** (57.5-87.2)	**65.7** (45.2-80.1)	**48.5** (17.9-73.7)
Median follow-up in responders, months (range)	**21.8** (9.2-35.9)	**9.2** (3.7-36.6)	**18.2** (11.3-33.1)
Patients remaining in response, % (n/N)	**75.0** (27/36)	**81.6** (58/71)	**53.8** (7/13)

- Overall, most AEs were grade 1 or 2
- Higher rates of grade ≥3 TRAEs were observed with the combination regimen (35.8%) than with TAR-200 (9.4%) or cetrelimab (7.1%) monotherapy
- Patients with serious TRAEs:
  - ***Cohort 1:*** TAR-200 + cetrelimab, 13.2%
  - ***Cohort 2:*** TAR-200, 5.9%
  - ***Cohort 3:*** Cetrelimab, 3.6%
- Rates of discontinuation due to TRAEs:
  - ***Cohort 1:*** TAR-200, 26.4%; cetrelimab, 22.6%[a]
  - ***Cohort 2:*** TAR-200, 5.9%[b]
  - ***Cohort 3:*** Cetrelimab, 7.1%[c]
- No treatment-related deaths were reported

Patients with events, n (%)	TAR-200 + Cetrelimab *Cohort 1* (N=53)[d]	TAR-200 Monotherapy *Cohort 2* (N=85)[d]	Cetrelimab Monotherapy *Cohort 3* (N=28)[d]
≥1 TRAEs of any grade	49 (92.5)	71 (83.5)	14 (50.0)
Most frequent TRAEs of any grade[e]			
Pollakiuria	16 (30.2)	33 (38.8)	0
Dysuria	16 (30.2)	30 (35.3)	0
Hematuria	11 (20.8)	12 (14.1)	0
UTI	11 (20.8)	17 (20.0)	0
Pruritus	7 (13.2)	1 (1.2)	3 (10.7)
Hypothyroidism	4 (7.5)	0	3 (10.7)

Patients with events, n (%)	TAR-200 + Cetrelimab *Cohort 1* (N=53)[d]	TAR-200 Monotherapy *Cohort 2* (N=85)[d]	Cetrelimab Monotherapy *Cohort 3* (N=28)[d]
≥1 TRAEs of grade ≥3	19 (35.8)	8 (9.4)	2 (7.1)[f]
Most frequent TRAEs grade ≥3[g]			
UTI	2 (3.8)	1 (1.2)	0
AST increased	2 (3.8)	0	0
Urinary tract pain	1 (1.9)	3 (3.5)	0

Van der Heijden ESMO 2024

BARCELONA 2024 ESMO congress

A Randomised Phase 3 Trial of Neoadjuvant Durvalumab Plus Chemotherapy Followed by Radical Cystectomy and Adjuvant Durvalumab in Muscle-invasive Bladder Cancer (NIAGARA)

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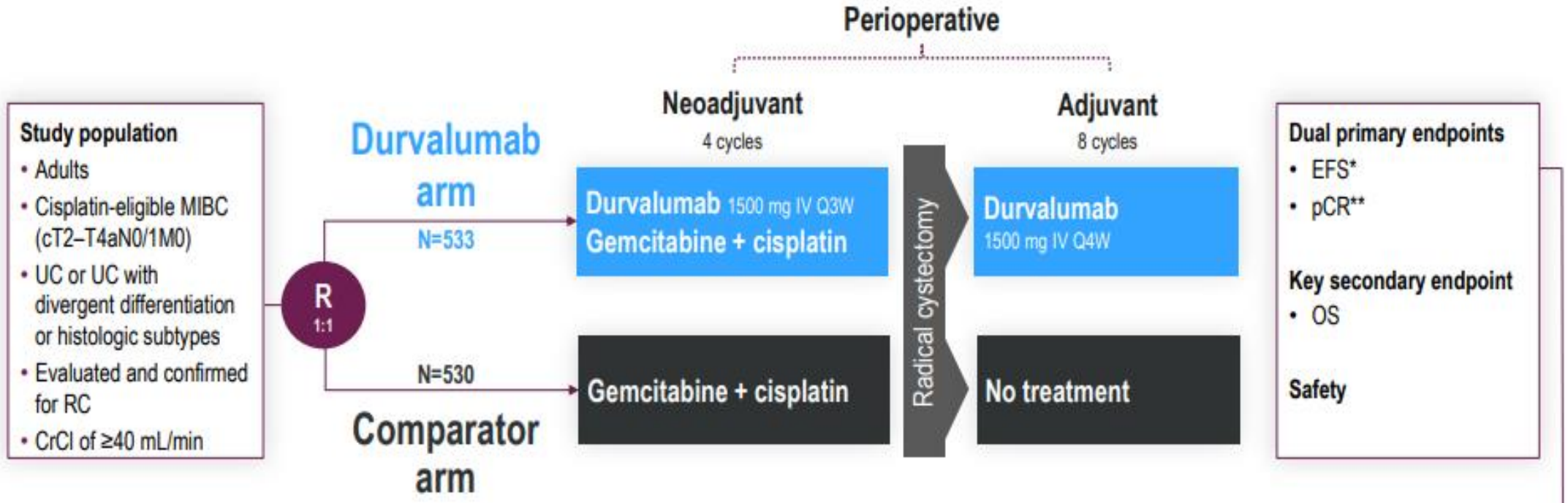
LBA5

Presenter: Thomas Powles, MBBS, MRCP, MD, London, UK

Powles, ESMO 2024

NIAGARA: Study Design



Stratification factors

Clinical tumour stage (T2N0 vs >T2N0)

Renal function (CrCl ≥60 mL/min vs ≥40–<60 mL/min)

PD-L1 status (high vs low/negative expression)

Gemcitabine/cisplatin dosing

CrCl ≥60 mL/min: Cisplatin 70 mg/m^2 + gemcitabine 1000 mg/m^2 Day 1, then gemcitabine 1000 mg/m^2 Day 8, Q3W for 4 cycles

CrCl ≥40–<60 mL/min: Split-dose cisplatin 35 mg/m^2 + gemcitabine 1000 mg/m^2 Days 1 and 8, Q3W for 4 cycles

EFS was defined as:

- Progressive disease that precluded RC
- Recurrence after RC
- Date of expected surgery in patients who did not undergo RC
- Death from any cause

Other endpoints (not reported here): DFS, DSS, MFS, HRQoL, 5-year OS

*Evaluated by blinded independent central review or central pathology review (if a biopsy was required for a suspected new lesion). **Evaluated by blinded central pathology review.

ClinicalTrials.gov, NCT03732677; EudraCT number, 2018-001811-59. CrCl, creatinine clearance; DFS, disease-free survival; DSS, disease-specific survival; EFS, event-free survival; HRQoL, health-related quality of life; IV, intravenous; MFS, metastasis-free survival; MIBC, muscle-invasive bladder cancer; OS, overall survival; pCR, pathologic complete response; PD-L1, programmed cell death ligand-1; Q3W, every 3 weeks; Q4W, every 4 weeks; R, randomised; RC, radical cystectomy; UC, urothelial carcinoma..

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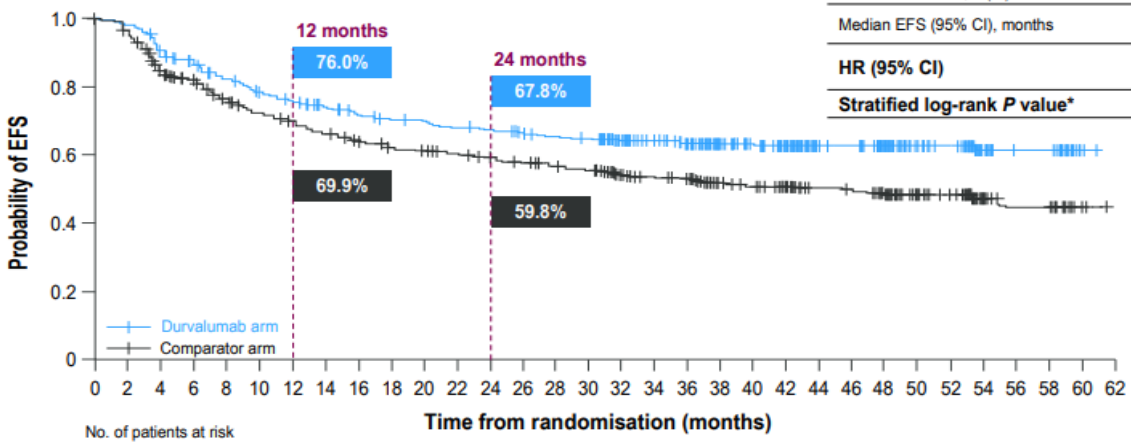
NIAGARA: Event-free Survival by Blinded Independent Central Review (ITT)

	Durvalumab arm N=533	Comparator arm N=530
Number of events, n (%)	187 (35.1)	246 (46.4)
Median EFS (95% CI), months	NR (NR–NR)	46.1 (32.2–NR)
HR (95% CI)	**0.68 (0.56–0.82)**	
Stratified log-rank *P* value*	**<0.0001**	



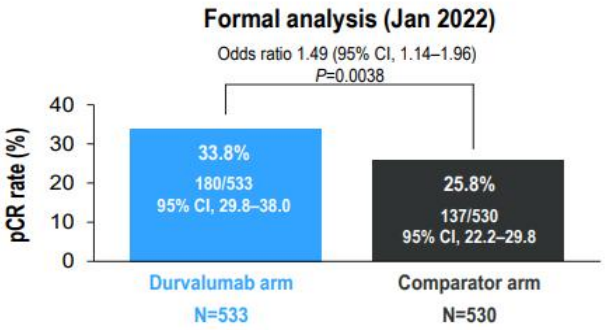
No. of patients at risk

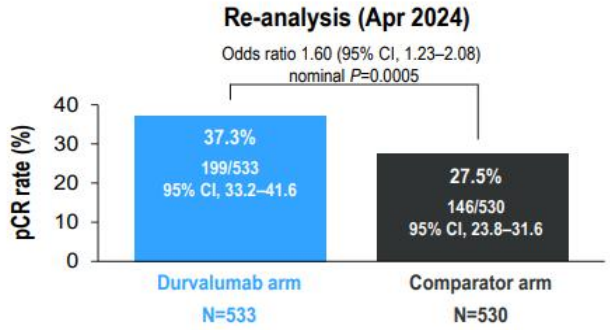
Durvalumab arm	533	519	475	454	424	401	386	370	356	348	344	335	330	321	315	312	282	269	255	214	202	180	141	140	115	86	81	32	20	20	1	0
Comparator arm	530	498	437	416	381	358	343	328	313	300	296	288	281	273	264	259	228	219	214	177	172	159	132	129	94	69	62	24	18	16	2	0

Median follow-up in censored patients: 42.3 months (range, 0.03–61.3)

EFS was assessed using RECIST v1.1. EFS is defined as the time from randomisation to the first: 1) progressive disease that precluded RC; 2) recurrence after RC; 3) date of expected surgery in patients who did not undergo RC; 4) death from any cause.
*The threshold to declare statistical significance was based on a Lan-DeMets alpha spending function with O'Brien-Fleming boundary – with the observed number of events, the boundary for declaring statistical significance was 0.04123 for a 4.9% overall 2-sided alpha.
Data cutoff 29 Apr 2024. CI, confidence interval; EFS, event-free survival; HR, hazard ratio; ITT, intent-to-treat population; NR, not reached; RC, radical cystectomy; RECIST, Response Evaluation Criteria In Solid Tumors.

NIAGARA: Pathologic Complete Response (ITT)





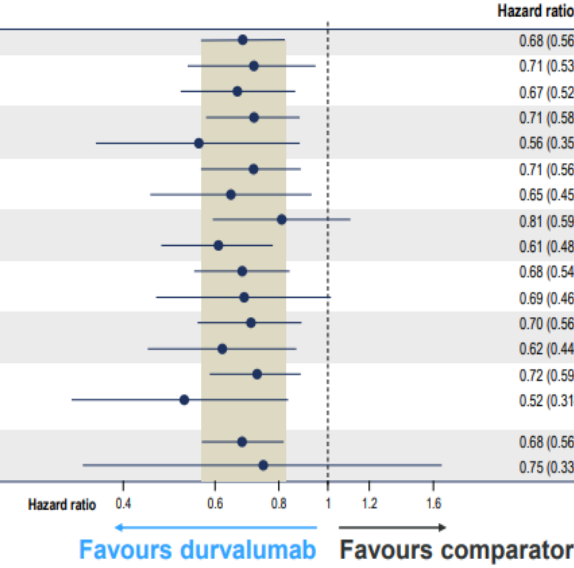
- The planned formal analysis for pCR was not statistically significant (threshold for significance, p-value 0.001)
- 59 evaluable samples were incorrectly considered non-responders rather than their true result*

- The re-analysis showed nominal statistical significance in favour of the durvalumab arm
- This analysis includes the results of the 59 omitted samples (28 additional pCRs)*

*pCR was statistically tested as the final analysis in Jan 2022 (formal analysis). The results of 59 evaluable samples were omitted due to applying the DCO to the date of central review, rather than date of surgery. The re-analysis is a descriptive analysis of pCR rate and associated odds ratios that includes all samples from the formal pCR analysis and applies the DCO to the date of surgery for all samples. Alpha spend for the multiple testing procedure is associated with the formal pCR analysis only. pCR statistical significance was set at a threshold of 0.001.
95% CIs for the pCR rate are calculated using the Clopper-Pearson method. Odds ratio, corresponding CI, and *P* value are obtained using logistic regression adjusted for the stratification factors (renal function, tumour stage, and PD-L1 status). Pathological staging of samples taken during RC was performed centrally; pCR was the proportion of patients with stage T0N0M0 at RC (American Joint Committee on Cancer 8th edition classification). CI, confidence interval; DCO, data cutoff; ITT, intent-to-treat population; pCR, pathologic complete response; RC, radical cystectomy.

NIAGARA: Event-free Survival Subgroup Analyses

Subgroup	Category	N	Hazard ratio (95% CI)
All patients		1063	0.68 (0.56–0.82)
Age at randomisation	<65 years	499	0.71 (0.53–0.94)
	≥65 years	564	0.67 (0.52–0.86)
Sex	Male	870	0.71 (0.58–0.88)
	Female	193	0.56 (0.35–0.88)
Race	White	712	0.71 (0.56–0.89)
	Non-White	315	0.65 (0.45–0.92)
Tumour stage at baseline	T2N0	428	0.81 (0.59–1.10)
	>T2N0	635	0.61 (0.48–0.78)
Renal function at baseline	CrCl ≥60 mL/min	862	0.68 (0.54–0.84)
	CrCl ≥40–<60 mL/min	201	0.69 (0.46–1.01)
PD-L1 expression at baseline*	High	777	0.70 (0.56–0.88)
	Low/negative	286	0.62 (0.44–0.87)
Histology at baseline	UC	898	0.72 (0.59–0.89)
	UC with divergent differentiation or histologic subtypes	165	0.52 (0.31–0.84)
Lymph node positive at baseline	N0	1005	0.68 (0.56–0.83)
	N1	58	0.75 (0.33–1.64)



EFS was assessed by blinded independent central review or by central pathology review, using RECIST v1.1. The plot is of hazard ratio and 95% CI. Tan-coloured band represents the 95% CI for the overall (all patients) hazard ratio. The subgroup analyses were performed using an unstratified Cox proportional hazard model, with treatment as only covariate and ties handled by Efron approach.
*Assessed with the VENTANA PD-L1 (SP263) Assay using the TC/IC25% algorithm; high PD-L1 expression was defined as ≥25% of TCs with any membrane staining or ICs staining for PD-L1 at any intensity. Due to observed inconsistencies between central laboratories in PD-L1 IC prevalence, but not TC prevalence, in the PD-L1 TC/IC25% algorithm, additional analyses of EFS by TC expression levels of 1% and 25% were performed and the results were consistent with those in the intent-to-treat population.
Data cutoff 29 Apr 2024. CI, confidence interval; CrCl, creatinine clearance; EFS, event-free survival; IC, immune cell; PD-L1, programmed cell death ligand-1; RECIST, Response Evaluation Criteria In Solid Tumors; TC, tumour cell; UC, urothelial carcinoma.

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NIAGARA: Overall Survival (ITT)

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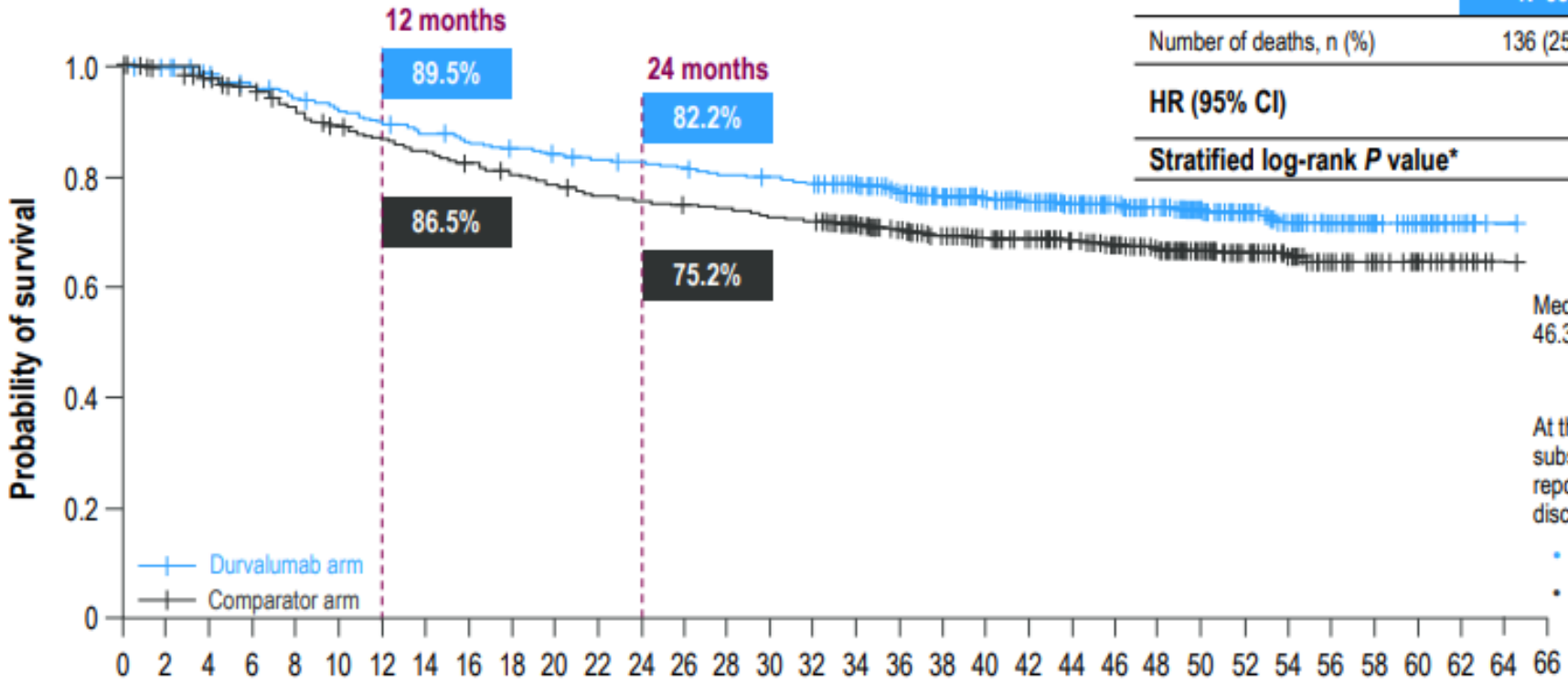


	Durvalumab arm N=533	Comparator arm N=530
Number of deaths, n (%)	136 (25.5)	169 (31.9)
HR (95% CI)	**0.75 (0.59–0.93)**	
Stratified log-rank *P* value*	**0.0106**	

Median follow-up in censored patients: 46.3 months (range, 0.03–64.7)

At the time of this analysis, at least 1 subsequent anti-cancer therapy was reported after treatment discontinuation for:

- 53 patients in the durvalumab arm
- 93 patients in the comparator arm

No. of patients at risk

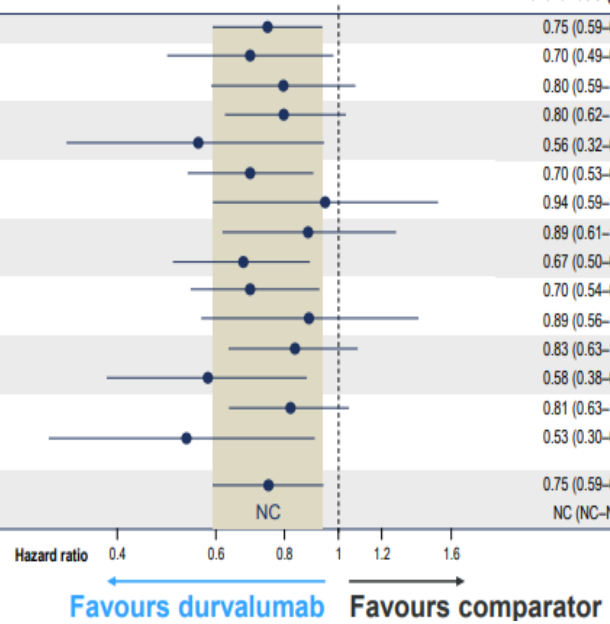
Durvalumab arm	533	528	517	505	492	478	468	457	446	440	434	428	423	418	410	408	400	375	349	321	295	271	238	207	182	152	125	96	68	34	21	7	1	0
Comparator arm	530	516	507	490	467	450	438	425	413	402	392	383	378	373	368	363	358	334	311	281	259	239	215	194	174	141	113	90	60	38	21	10	2	0

OS is the time from the date of randomisation until death due to any cause regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy. *The threshold for statistical significance was based on a Lan-DeMets alpha spending function with O'Brien-Fleming boundary – with the observed number of events, the boundary for declaring statistical significance was 0.01543 for a 4.9% overall 2-sided alpha.
Data cutoff 29 Apr 2024. CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat population; OS, overall survival.

Powles, ESMO 2024

NIAGARA: Overall Survival Subgroup Analyses

Subgroup	Category	N	Hazard ratio (95% CI)
All patients		1063	0.75 (0.59–0.93)
Age at randomisation	<65 years	499	0.70 (0.49–0.98)
	≥65 years	564	0.80 (0.59–1.07)
Sex	Male	870	0.80 (0.62–1.02)
	Female	193	0.56 (0.32–0.94)
Race	White	712	0.70 (0.53–0.90)
	Non-White	315	0.94 (0.59–1.51)
Tumour stage at baseline	T2N0	428	0.89 (0.61–1.28)
	>T2N0	635	0.67 (0.50–0.89)
Renal function at baseline	CrCl ≥60 mL/min	862	0.70 (0.54–0.91)
	CrCl ≥40–<60 mL/min	201	0.89 (0.56–1.40)
PD-L1 expression at baseline*	High	777	0.83 (0.63–1.09)
	Low/negative	286	0.58 (0.38–0.88)
Histology at baseline	UC	898	0.81 (0.63–1.04)
	UC with divergent differentiation or histologic subtypes	165	0.53 (0.30–0.91)
Lymph node positive at baseline	N0	1005	0.75 (0.59–0.94)
	N1	58	NC (NC–NC)



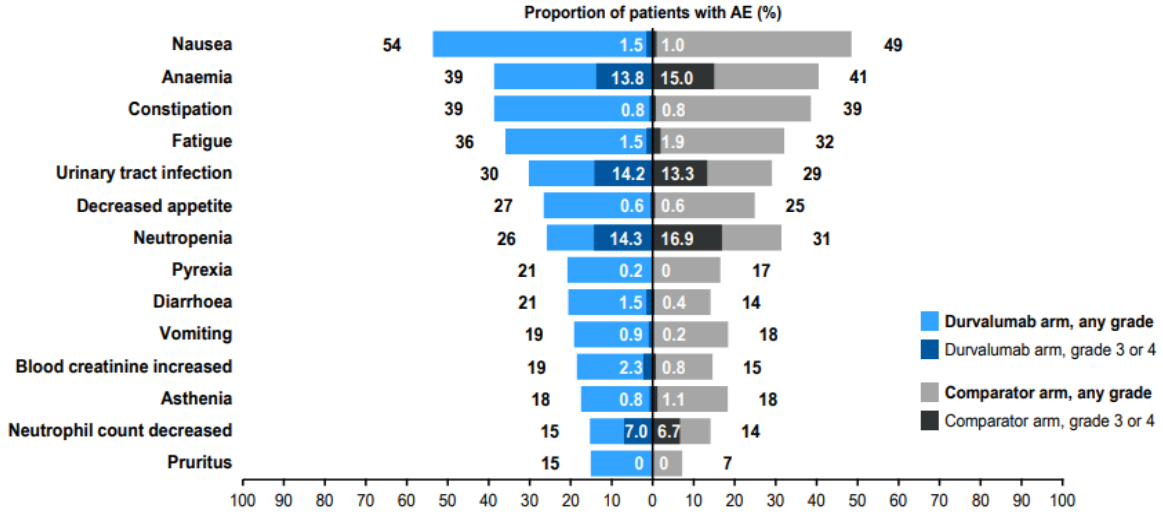
The plot is of hazard ratio and 95% CI. Tan-coloured band represents the 95% CI for the overall (all patients) hazard ratio. The subgroup a
*Assessed with the VENTANA PD-L1 (SP263) Assay using the TC/IC25% algorithm; high PD-L1 expression was defined as ≥25% of TCs
Data cutoff 29 Apr 2024. CI, confidence interval; CrCl, creatinine clearance; IC, immune cell; NC, not calculated; PD-L1, programmed cell

NIAGARA: AE Summary (Safety Population)

Overall study period (unless otherwise stated)	Durvalumab arm N=530	Comparator arm N=526
AEs of any cause, n (%)	527 (99)	525 (100)
Grade 3 or 4	368 (69)	355 (68)
Serious AEs	326 (62)	287 (55)
Outcome of death	27 (5)	29 (6)
Leading to discontinuation of study treatment	112 (21)	80 (15)
Leading to discontinuation of neoadjuvant durvalumab	50 (9)	---
Leading to discontinuation of NAC	72 (14)	80 (15)
Leading to patient not undergoing RC	6 (1)	7 (1)
Leading to delay in surgery*	9 (2)	6 (1)
Leading to discontinuation of adjuvant durvalumab	30/383† (8)	---
AEs possibly related to any treatment, n (%)‡	502 (95)	487 (93)
Grade 3 or 4 (treatment related)	215 (41)	215 (41)
Outcome of death (treatment related)	3 (0.6)	3 (0.6)
Any-grade immune-mediated AEs	111 (21)	16 (3)

The safety population includes all patients who received treatment. *Recommended timeframe for RC was within 56 days after the last dose of NAC. †In patients who started adjuvant durvalumab. ‡Investigator-assessed causality.
lose of treatment, surgery, or last adjuvant visit; 2) date of first dose of subsequent anti-cancer therapy; or 3) data cutoff date.

NIAGARA: Most Frequently Reported AEs (Overall)



All-causality AEs reported for ≥15% of patients in the safety population from either arm in the overall study period are shown. The overall period includes AEs that occurred between the first dose of study treatment, and whichever occurred first: 1) 90 days after the last dose of treatment

Powles, ESMO 2024

What about HER targeted treatment in Bladder Cancer?

Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial

Authors: Funda Meric-Bernstam, MD, Vicky Makker, MD, Ana Oaknin, MD, Do-Youn Oh, MD, Susana Banerjee, PhD, Antonio González-Martín, MD, Kyung Hae Jung, MD, ... SHOW ALL ..., and Jung-Yun Lee, MD | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 42, Number 1 • https://doi.org/10.1200/JCO.23.02005

FDA grants accelerated approval to fam-trastuzumab deruxtecan-nxki for unresectable or metastatic HER2-positive solid tumors

Bernstam JCO 2023

On April 5, 2024, the Food and Drug Administration granted accelerated approval to fam-

Abstract 3000: DESTINY-PanTumor02

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by Herceptest if local test not feasible (ASCO/CAP gastric cancer guidelines)
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1

T-DXd 5.4 mg/kg q3w

n≈40 per cohort planned

(Cohorts with no objective responses in the first 15 patients were to be closed)

- Cervical cancer
- Endometrial cancer
- Ovarian cancer
- Biliary tract cancer
- Pancreatic cancer
- Bladder cancer
- Other tumors[b]

		All patients (N=267)
HER2 testing for eligibility, n (%)[a]	Local	205 (76.8)
	Central	61 (22.8)
	Unknown[b]	1 (0.4)
HER2-expression for eligibility, n (%)[a]	IHC 3+	108 (40.4)
	IHC 2+	153 (57.3)
	IHC 1+[c]	5 (1.9)
	Unknown[b]	1 (0.4)
Centrally confirmed HER2 status for efficacy evaluation, n (%)	IHC 3+	75 (28.1)
	IHC 2+	125 (46.8)
	IHC 1+	25 (9.4)
	IHC 0	30 (11.2)
	Unknown[d]	12 (4.5)

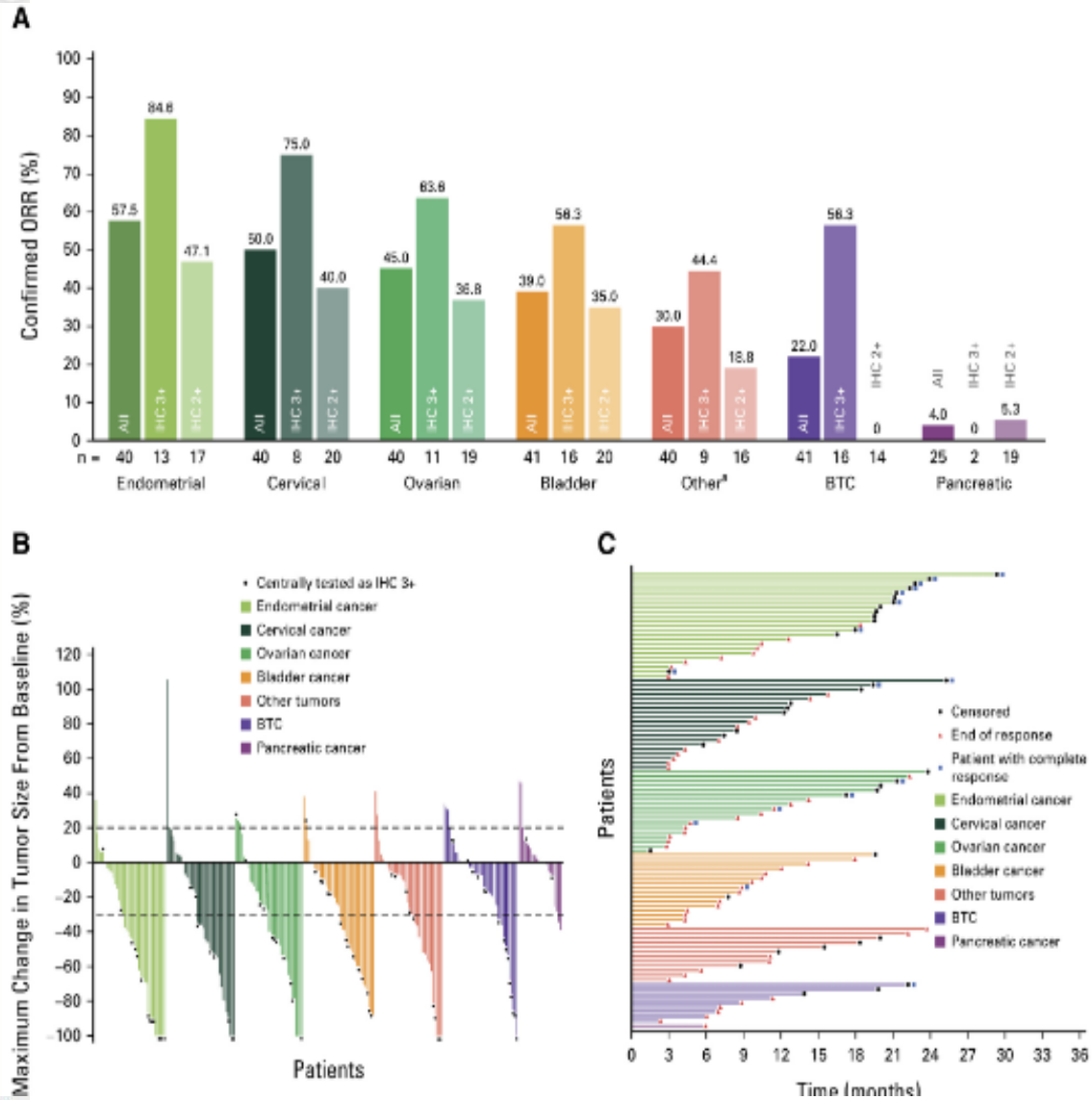
- 77% enrollment by local assessment
- Central conformation: IHC 1+ or 0= 20% (N=55)

Local vs central discordant N=50 (19%)

2023 ASCO ANNUAL MEETING #ASCO23

PRESENTED BY: Kohei Shitara, MD

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER



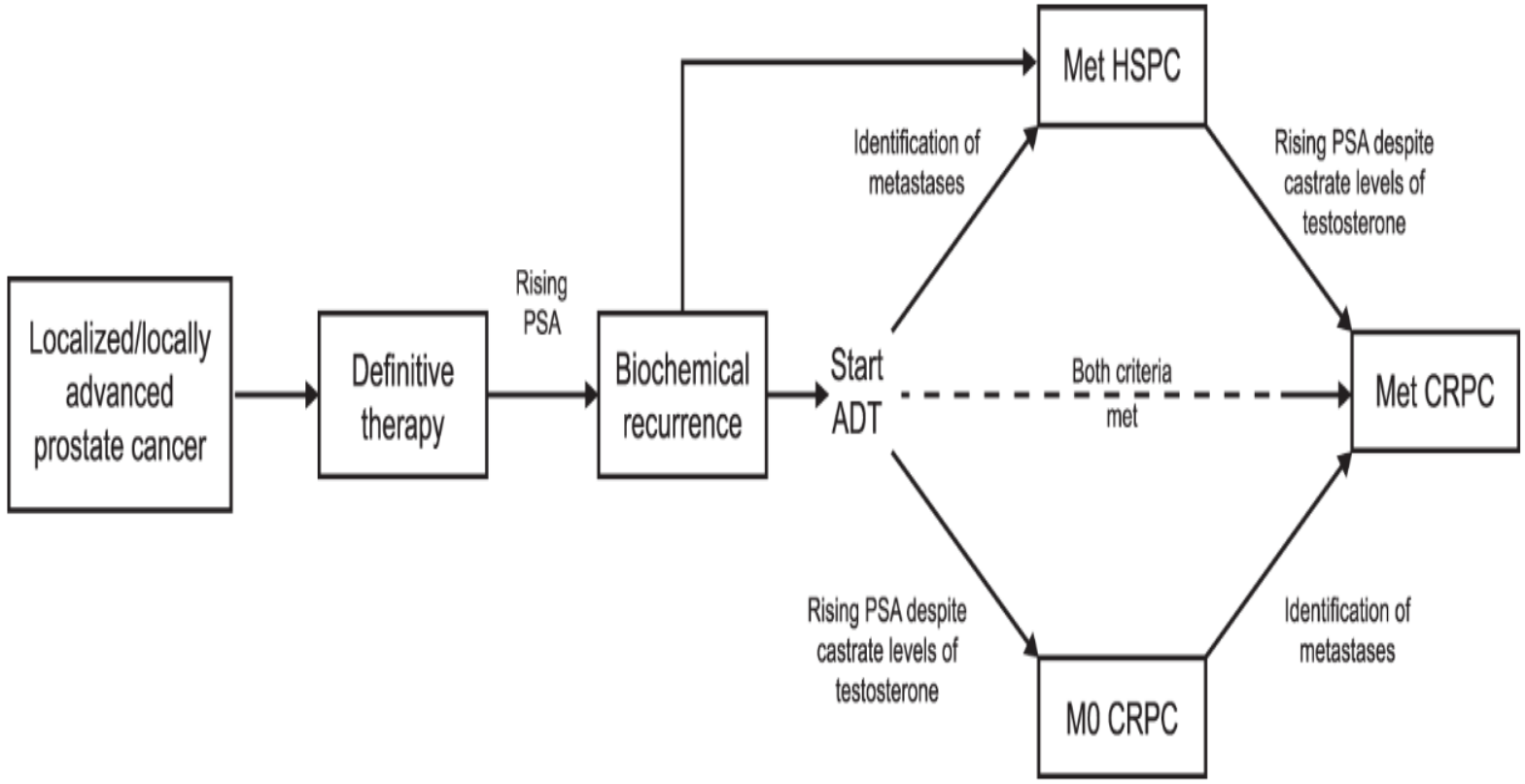
Bernstam JCO 2023

What I do in bladder cancer in February 2025

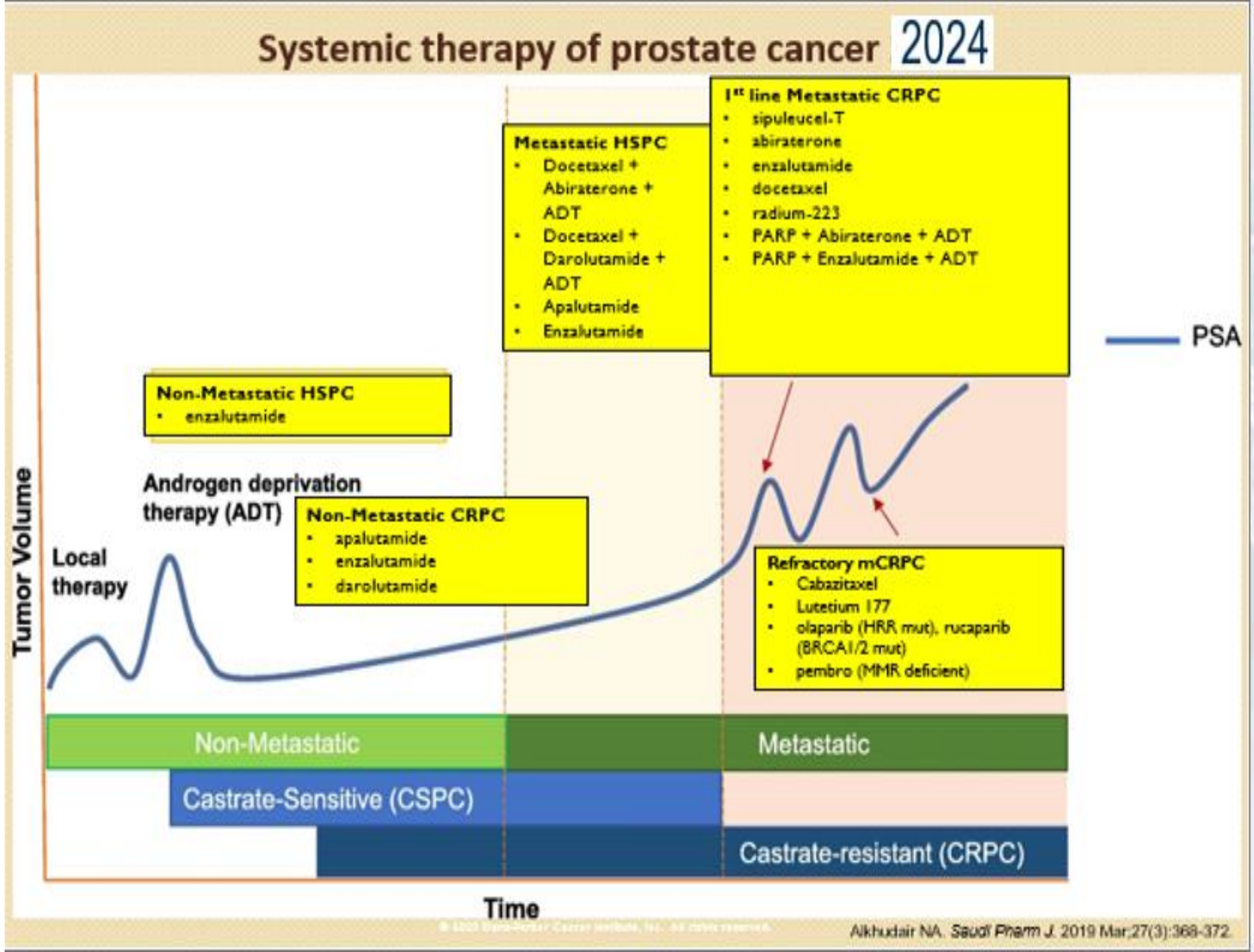
1. Offer perioperative chemoimmunotherapy for all patients that have muscle invasive bladder cancer that are considered candidates cystectomy. Consider dose dense MVAC for some patients based on Niagra study
2. Consider Enfortumab Vedotin and Pembrolizumab for most patients with metastatic urothelial cancer. Cisplatin Gemcitabine Nivolumab for and Platinum Gemcitabine with maintenance Avelumab for some patients
3. Next generation tissue testing for all metastatic urothelial caner patients. Look for HER2 IHC 3+, FGFR3 alteration, NTRK etc

What we have learned in Prostate Cancer in 2024

1. Prostate Cancer Doublet vs Triplet treatment
2. Combination vs Sequential treatment of PARP inhibitors?
3. Lutetium 177 before chemotherapy?



Small, *Expert Rev Anticancer Ther*. 2017


Systemic therapy of prostate cancer 2024
Metastatic HSPC
Docetaxel + Abiraterone + ADT
Docetaxel + Darolutamide + ADT
Apalutamide
Enzalutamide
1st line Metastatic CRPC
sipuleucel-T
abiraterone
enzalutamide
docetaxel
radium-223
PARP + Abiraterone + ADT
PARP + Enzalutamide + ADT
PSA
Non-Metastatic HSPC
enzalutamide
Androgen deprivation therapy (ADT)
Non-Metastatic CRPC
apalutamide
enzalutamide
darolutamide
Local therapy
Refractory mCRPC
Cabazitaxel
Lutetium 177
olaparib (HRR mut), rucaparib (BRCA1/2 mut)
pembro (MMR deficient)
Tumor Volume
Non-Metastatic
Metastatic
Castrate-Sensitive (CSPC)
Castrate-resistant (CRPC)
Time
Alkhudair NA. Saudi Pharm J. 2019 Mar;27(3):368-372

Metastatic Hormone Sensitive Prostate Cancer

Synchronous

Patients diagnosed with a primary prostate cancer and metastases simultaneously

Metachronous

Patients diagnosed with nonmetastatic disease at initial diagnosis and develop metastases during follow up

Prostate Cancer Classification

High Volume
- Visceral
- Greater than 3 bone lesions with 1 extra-axial

Newly-diagnosed
Any of:
- Metastatic
- Node-Positive
- ≥2 of: Stage T3/4, PSA≥40ng/ml, Gleason 8-10

Relapsing after previous RP or RT with ≥1 of:
- PSA ≥4ng/ml and rising with doubling time <6m
- PSA ≥20ng/ml
- Node-positive
- Metastatic

High Risk
Gleason 8-10

At least 3 bone lesion

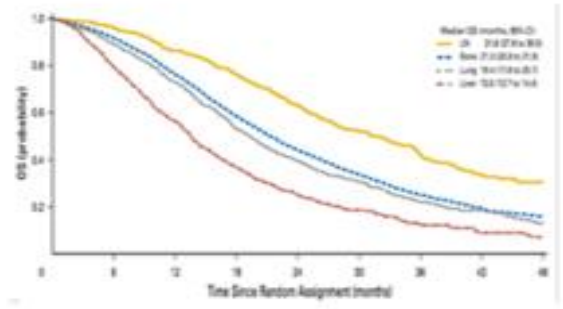
Measurable visceral lesions

All patients
- Fit for all protocol treatment
- Fit for follow-up
- WHO performance status 0-2
- Written informed consent

Full criteria

www.stampedetrial.org

Staging in prognostication



ADT Alone (using CHAARTED and GETUG)	Median OS
Relapsed Low Volume	~8 y
Relapsed High Volume	4.5
De Novo Low Volume	4.5
De Novo High Volume	3

Halabi JCO 2014; Gravis Eur Urol 2018; Kyriakopoulos JCO 2018

Doublet vs Triplet Therapy for mHSPC?

The NEW ENGLAND JOURNAL of MEDICINE

Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer

Authors: Matthew R. Smith, M.D., Ph.D., Maha Hussain, M.D., Fred Saad, M.D., Karim Fizazi, M.D., Ph.D., Cora N. Sternberg, M.D., E. David Crawford, M.D., Evgeny Kopyltsov, M.D., Chandler H. Park, M.D., Boris Alekseev, M.D., Álvaro

Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer

Authors: Kim N. Chi, M.D., Neeraj Agarwal, M.D., Anders Bjartell, M.D., Byung Ha Chung, M.D., Andrea J. Pereira de Santana Gomes, M.D., Robert Given, M.D., Álvaro Juárez Soto, M.D., Axel S. Merseburger, M.D., Mustafa Özgüroğlu,

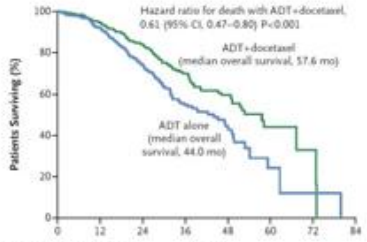
Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer

Authors: Karim Fizazi, M.D., Ph.D., NamPhuong Tran, M.D., Luis Fein, M.D., Nobuaki Matsubara, M.D., Alfredo Rodriguez-Antolin, M.D., Ph.D., Boris Y. Alekseev, M.D., Mustafa Özgüroğlu, M.D., Dingwei Ye, M.D., Susan Feyerabend,

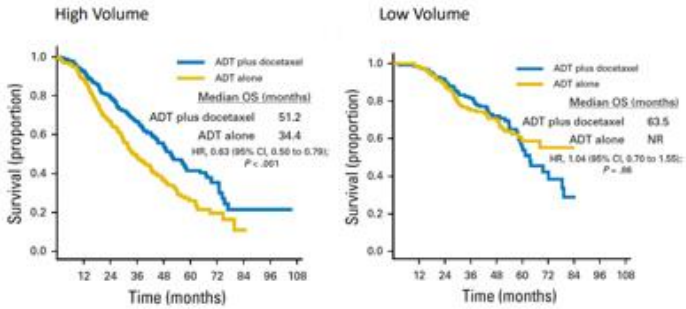
Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer

Authors: Ian D. Davis, M.B., B.S., Ph.D., Andrew J. Martin, Ph.D., Martin R. Stockler, M.B., B.S., Stephen Begbie, M.B., B.S., Kim N. Chi, M.D., Simon Chowdhury, M.B., B.S., Ph.D., Xanthi Coskinas, M.Med.Sc., Mark Frydenberg, M.B., B.S.,

Historical Data: CHAARTED Study

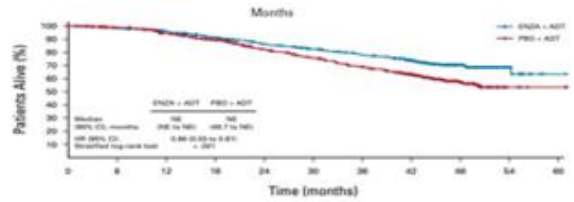


Sweeney et al (2015) *N Engl J Med 373*: 737-46

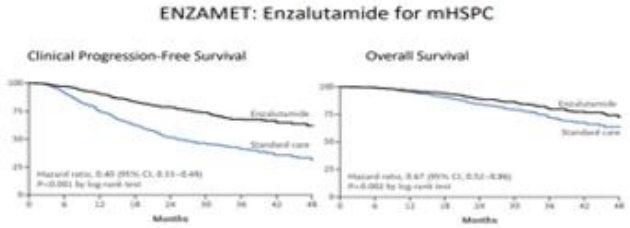


Kyriakopoulos et al (2018) *J Clin Oncol 36*: 1080-0187

ARCHES and ENZAMET

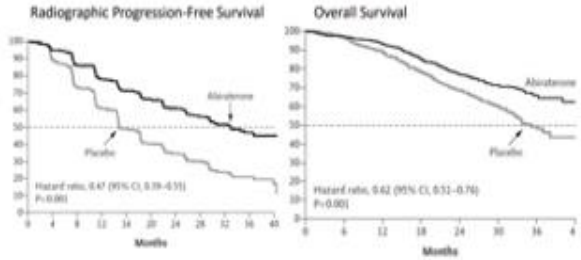


Armstrong et al (2019) *J Clin Oncol 37*: 2974-2986; Armstrong et al (2022) *J Clin Oncol* DOI: 10.1200/JC



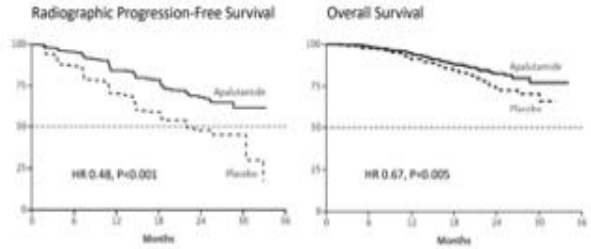
Davis et al (2019) *N Engl J Med 381*: 121-131

LATITUDE: Abiraterone Acetate for mHSPC



Fizazi et al (2017) *N Engl J Med 377*: 352-60

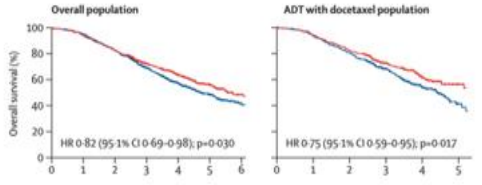
TITAN: Apalutamide for mHSPC



Chi et al (2019) *N Engl J Med 381*: 13-24

Triplet Therapy

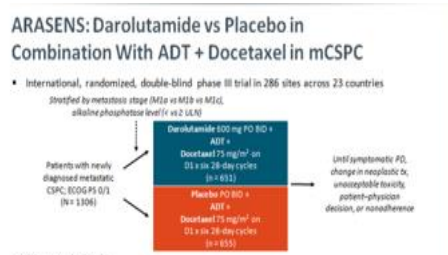
PEACE -1



Fizazi et al (2022) *Lancet* https://doi.org/10.1016/ S0140-6736(22)00367-1

ARASENS: Darolutamide vs Placebo in Combination With ADT + Docetaxel in mCSPC

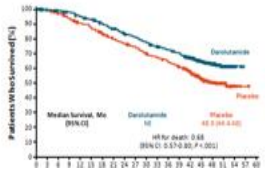
- International, randomized, double-blind phase III trial in 286 sites across 23 countries



- **Primary endpoint:** OS
- **Secondary endpoints tested hierarchically in this order:** time to CRPC, time to pain progression, SSE-free survival, time to first SSE, time to initiation of subsequent anticancer therapy, time to worsening of physical symptoms, time to first opioid use, safety

Overall Survival

ARASENS: OS (Primary Endpoint)



- Addition of darolutamide to ADT + docetaxel significantly reduced risk of death by 32.5% vs placebo (*P* <.001)
  - 75.6% of patients in placebo arm received subsequent life-prolonging systemic tx
- OS benefit observed across most subgroups
  - HR (95%) for those stratified

ESMO 2024 Update

BARCELONA 2024 ESMO congress

Efficacy and safety of darolutamide plus androgen-deprivation therapy in patients with metastatic hormone-sensitive prostate cancer from the phase 3 ARANOTE trial

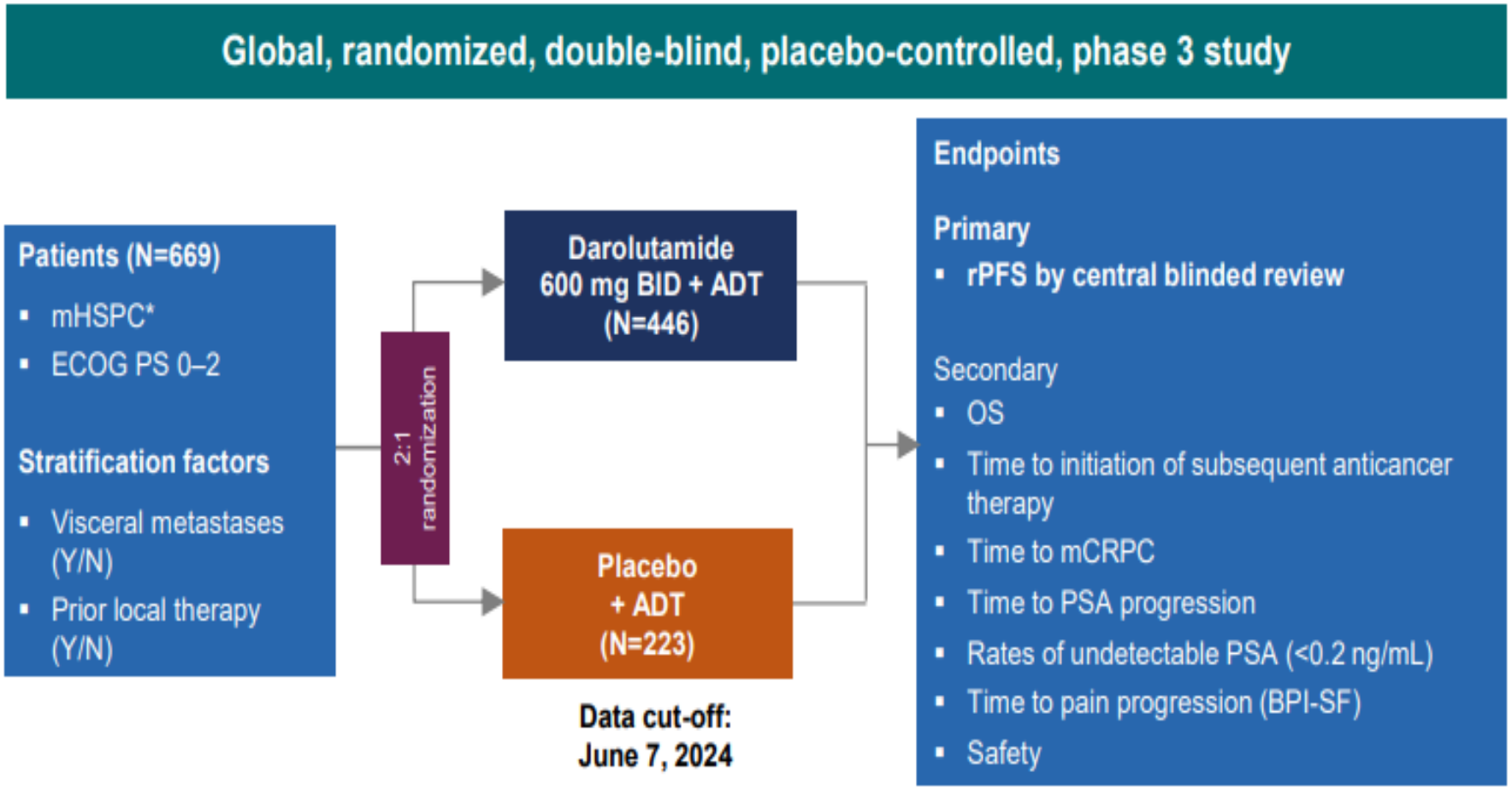
Fred Saad, CQ, MD, FRCS, FCAHS*

Centre Hospitalier de l'Université de Montréal, University of Montreal, Montreal, Quebec, Canada

*On behalf of Egils Vjaters, Neal Shore, David Olmos, Nianzeng Xing, Andrea Juliana P. de Santana Gomes, Augusto Cesar de Andrade Mota, Pamela Salman, Mindaugas Jievaltas, Albertas Ulys, Maris Jakubovskis, Evgeny Kopyltsov, Weiqing Han, Liina Nevalaita, Isabella Testa, Marie-Aude Le Berre, Iris Kuss, and Kunhi Parambath Haresh

Saad, ESMO 2024

ARANOTE Study Design



ClinicalTrials.gov: NCT04736199

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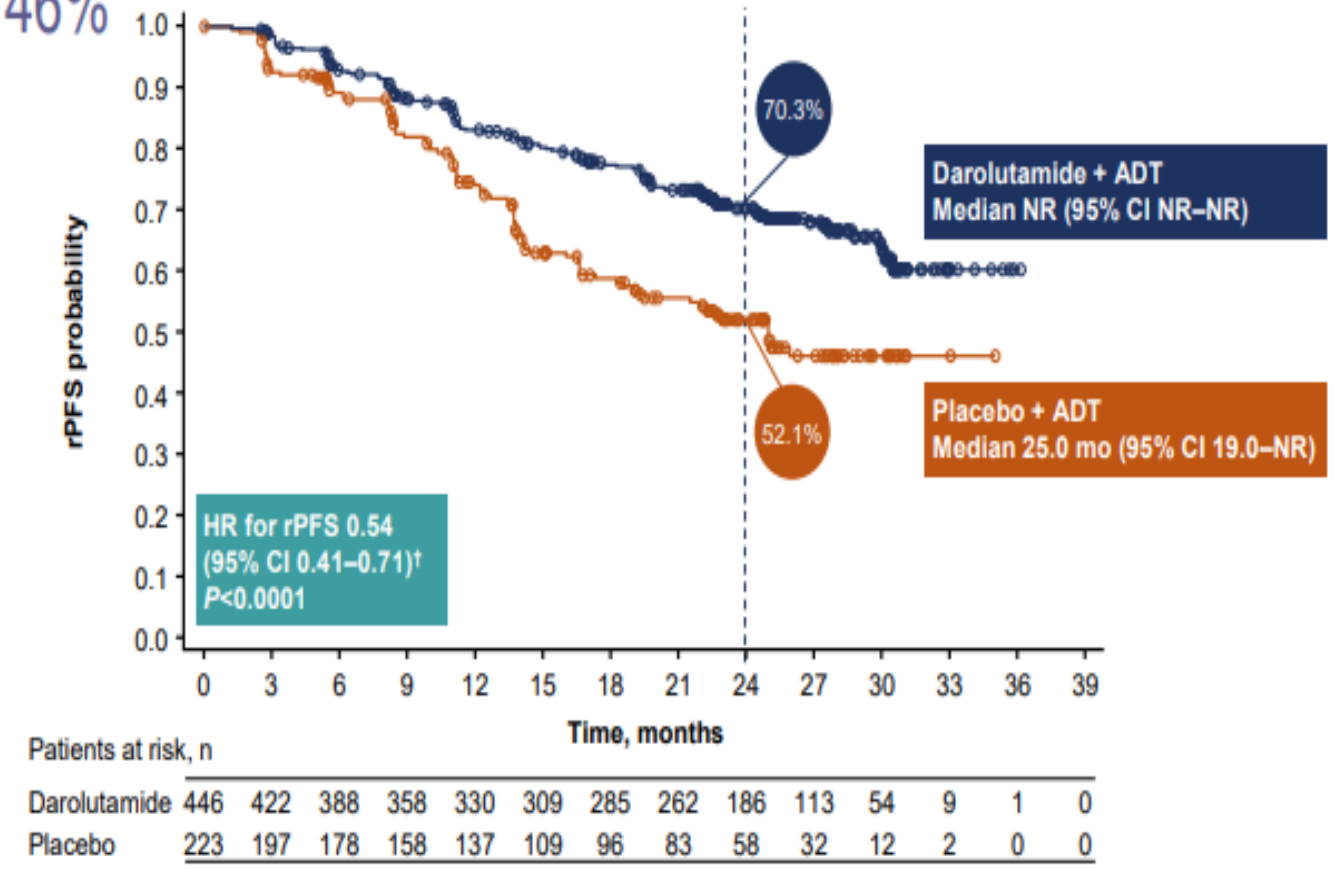
*Metastatic disease confirmed by conventional imaging method as a positive ^{99m}Tc-phosphonate bone scan or soft tissue/visceral metastases on contrast-enhanced abdominal/pelvic/chest CT or MRI scan, assessed by central review.
BPI-SF, Brief Pain Inventory-Short Form.

Saad, ESMO 2024

ARANOTE Primary Endpoint: rPFS*

Darolutamide significantly reduced the risk of radiological progression or death by 46%



Patients at risk, n

Darolutamide	446	422	388	358	330	309	285	262	186	113	54	9	1	0
Placebo	223	197	178	158	137	109	96	83	58	32	12	2	0	0

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Median follow-up: darolutamide group 25.3 months; placebo group 25.0 months

*Primary analysis occurred after 222 events (darolutamide 128; placebo 94).

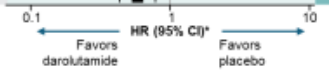
†HR and 95% CI were calculated using the Cox model stratified on visceral metastases (Y/N) and prior therapy (Y/N).

Saad, ESMO 2024

ARANOTE rPFS: Subgroup Analyses

Consistent benefit of darolutamide across all subgroups

rPFS		Darolutamide (n=446) Events/Patients, n/N	Darolutamide (n=446) Median, months	Placebo (n=223) Events/Patients, n/N	Placebo (n=223) Median, months	HR (95% CI)*
Overall population		128/446	NR	94/223	25.0	0.54 (0.41–0.71)
Age subgroups, years	<65	37/118	NR	32/65	14.2	0.44 (0.27–0.71)
	65–74	53/193	NR	35/96	NR	0.64 (0.41–0.98)
	75–84	29/117	NR	22/52	NR	0.48 (0.27–0.83)
	≥85	9/18	27.4	5/10	19.2	0.51 (0.16–1.66)
Baseline PSA values	< median	58/216	NR	44/111	26.0	0.55 (0.37–0.81)
	≥ median	67/220	NR	47/108	22.9	0.55 (0.38–0.80)
ECOG PS at baseline	0	61/235	NR	37/98	NR	0.55 (0.37–0.83)
	≥1	67/211	NR	57/125	22.6	0.56 (0.39–0.79)
Gleason score at initial diagnosis	Missing/not assessed	5/13	NR	4/10	13.8	
	<8	32/122	NR	30/67	22.9	0.46 (0.28–0.75)
	≥8	91/311	NR	60/146	25.1	0.58 (0.42–0.81)
Disease volume	High volume	113/315	30.2	75/157	19.2	0.60 (0.44–0.80)
	Low volume	15/131	NR	19/66	NR	0.30 (0.15–0.60)
Race	White	76/251	NR	55/125	22.2	0.52 (0.36–0.73)
	Asian	38/144	NR	24/65	25.0	0.59 (0.35–0.98)
	Black	10/41	NR	10/24	NR	0.51 (0.21–1.23)
	Other	4/10	NR	5/9	13.7	
Geographic region	Europe and RoW	56/186	NR	39/88	22.6	0.50 (0.33–0.75)
	Asia	37/141	NR	23/63	25.0	0.60 (0.35–1.01)
	Latin America	35/119	NR	32/72	25.1	0.56 (0.35–0.90)
Visceral metastases	Yes	21/53	NR	13/27	25.0	0.71 (0.35–1.41)
	No	107/393	NR	81/196	25.0	0.52 (0.39–0.69)
Prior local therapy	Yes	19/80	NR	18/40	19.5	0.34 (0.17–0.66)
	No	109/366	NR	76/183	25.0	0.59 (0.44–0.79)



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*HR and 95% CI were calculated from univariate analysis usir

TEAEs associated with ARPIs were generally similar between treatment groups

TEAEs	Darolutamide + ADT (n=445) Incidence, %	Darolutamide + ADT (n=445) EAIR/100 PY	Placebo + ADT (n=221) Incidence, %	Placebo + ADT (n=221) EAIR/100 PY
Fatigue	5.6	3.2	8.1	5.7
Mental impairment disorder	1.6	0.9	0.5	0.3
Hypertension	9.4	5.5	9.5	6.7
Cardiac arrhythmias	8.8	5.1	6.8	4.7
Coronary artery disorders	3.6	2.0	1.4	0.9
Heart failure	0.9	0.5	0.9	0.6
Falls, including accident	1.3	0.8	0.9	0.6
Bone fracture	4.0	2.3	2.3	1.5
Vasodilatation and flushing	9.2	5.6	7.2	5.0
Diabetes mellitus and hyperglycemia	9.0	5.3	9.5	6.7
Rash	4.3	2.4	3.6	2.4

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EAIR, exposure-adjusted incidence rate; PY, patient years.

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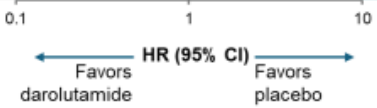
Darolutamide showed a benefit across all secondary endpoints

Endpoint	Darolutamide (n=446)		Placebo (n=223)		Stratified HR (95% CI)
	n (%)	Median, months	n (%)	Median, months	
OS*	103 (23.1)	NR	60 (26.9)	NR	0.81 (0.59–1.12)
Time to mCRPC	154 (34.5)	NR	143 (64.1)	13.8	0.40 (0.32–0.51)
Time to PSA progression	93 (20.9)	NR	108 (48.4)	16.8	0.31 (0.23–0.41)
Time to initiation of subsequent systemic therapy for prostate cancer	68 (15.2)	NR	74 (33.2)	NR	0.40 (0.29–0.56)
Time to pain progression	124 (27.8)	NR	79 (35.4)	29.9	0.72 (0.54–0.96)



*At the time of primary analysis, OS data are immature.

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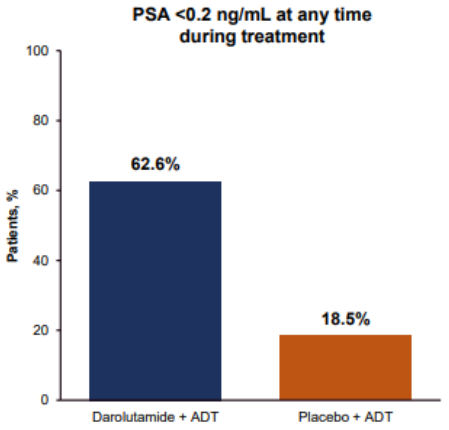
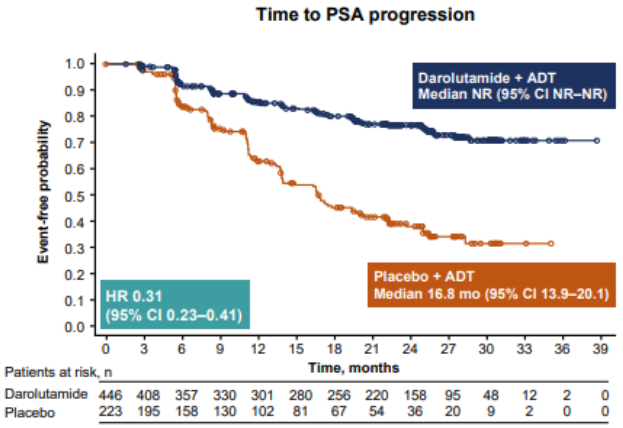
Darolutamide showed a higher rate of PSA <0.2 ng/mL and delayed time to PSA progression





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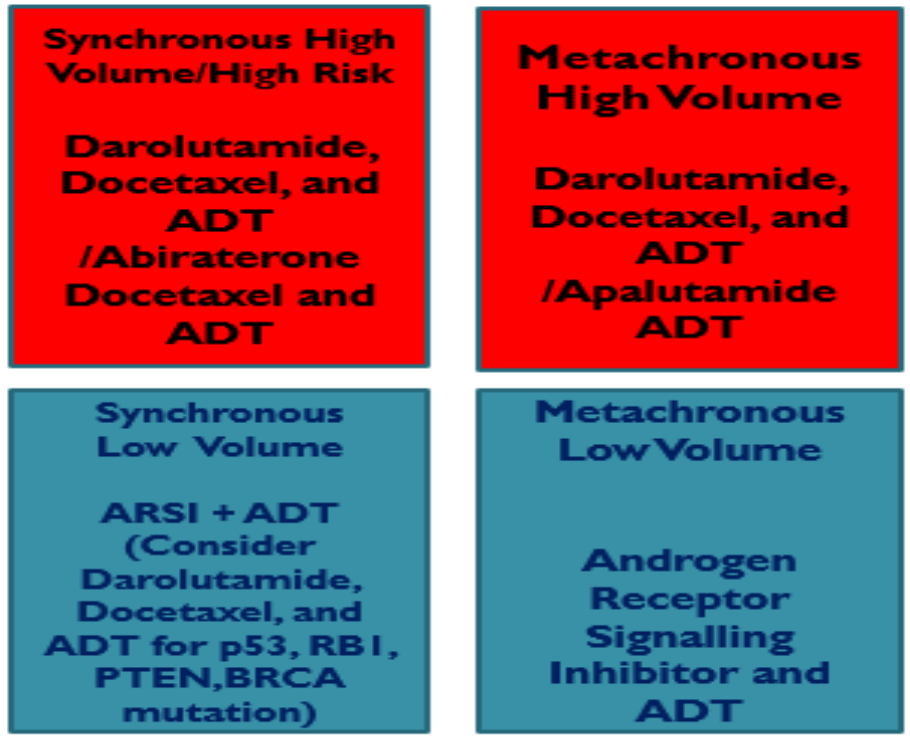
What do I do in my practice?

- Doublet therapy
  - 1. Older patients (Will consider monotherapy Firmagon/Relugolix for over 80)
  - 2. Patients with metastatic lung disease
  - 3. Somatic mutations with SPOP mutation
  - 4. Don't forget about Abiraterone/ADT. Can add Taxotere later.

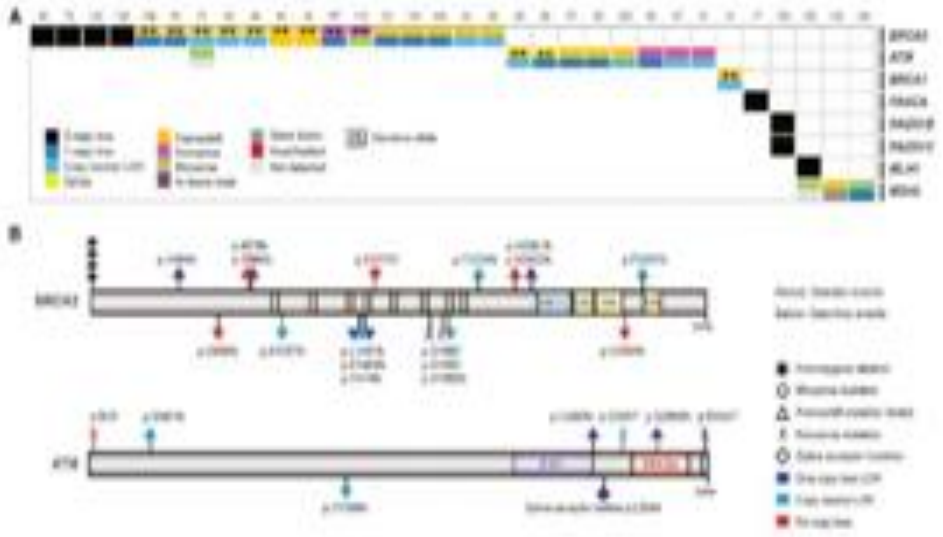
- Triplet therapy
  - 1. Younger patients with High risk and High Volume disease
  - 2. Patients with metastatic liver disease (liver biopsy to rule out small cell)
  - 3. Somatic mutations with p53, pTEN, RB1, and BRCA2 mutations.
  - 4. Germline BRCA2 mutations with High volume.



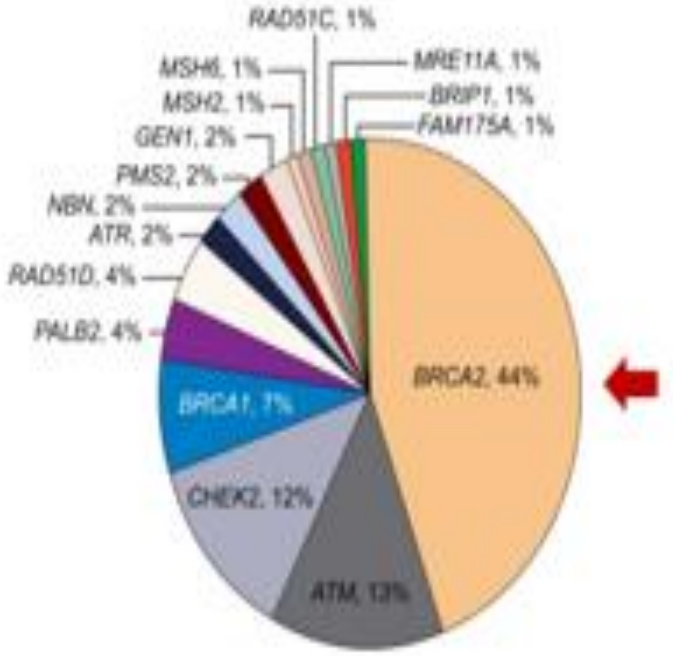
Combination vs Sequential PARP inhibitors

Somatic

- **23%** of metastatic castration-resistant prostate cancers harbor DNA repair alterations
- The frequency of DNA repair alterations **increases in metastatic disease vs. localized disease**

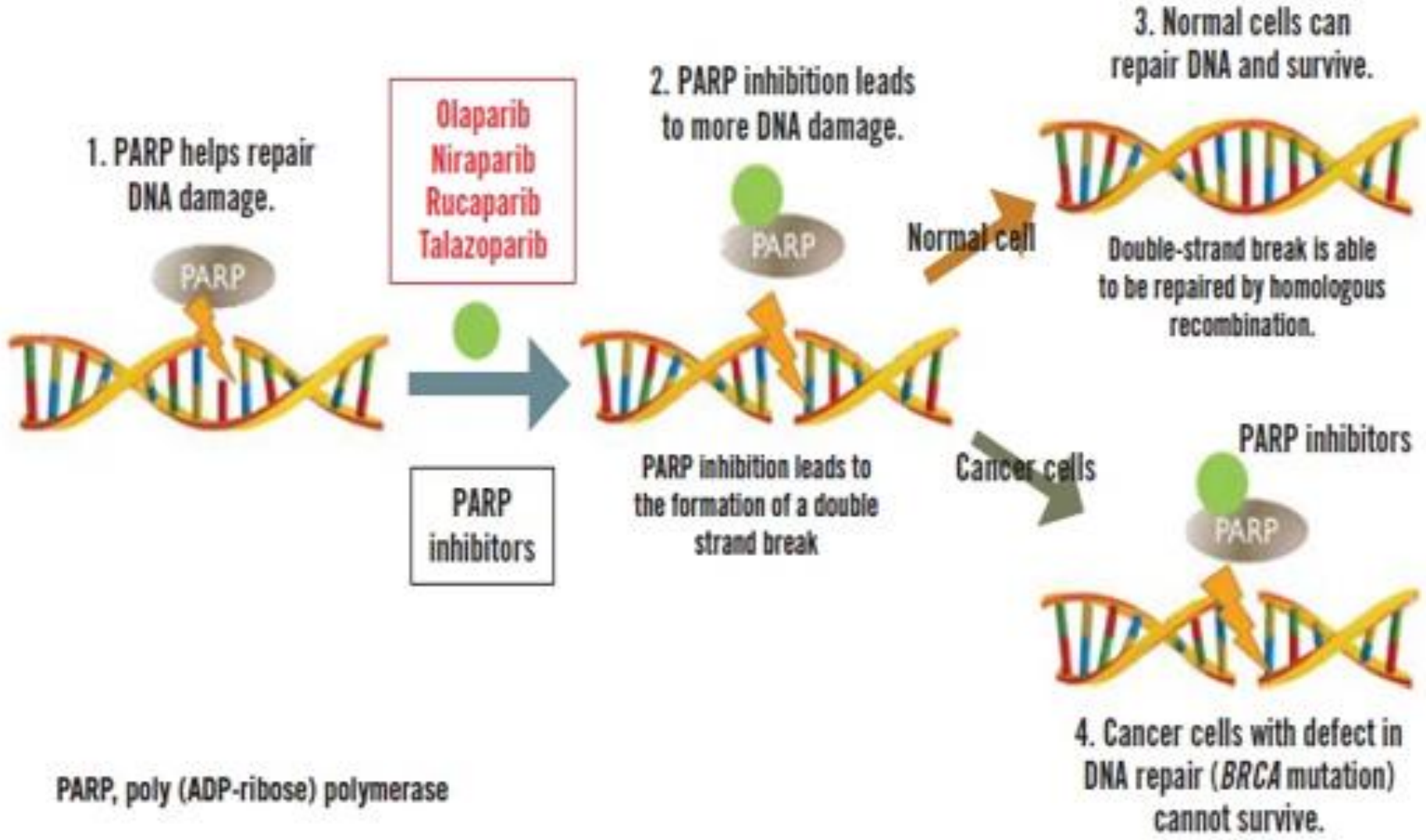


Germline



- **12%** of men with metastatic prostate cancer have a germline DNA repair defect

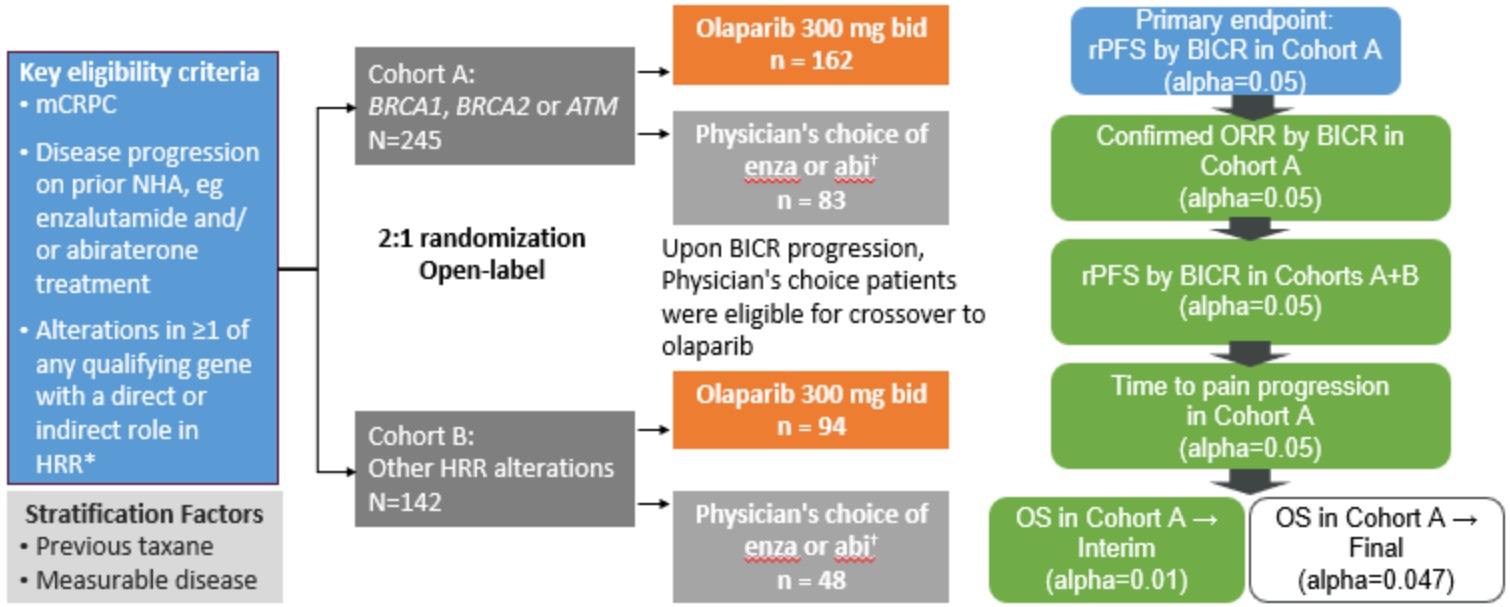
1. Robinson D, et al. Cell. 2015;161:1215-28. 2. Pritchard CC, et al. N Engl J Med. 2016;375:443-53.



PARP, poly (ADP-ribose) polymerase

Jacob et al. UCC December 2020,Volume 09, Issue 04

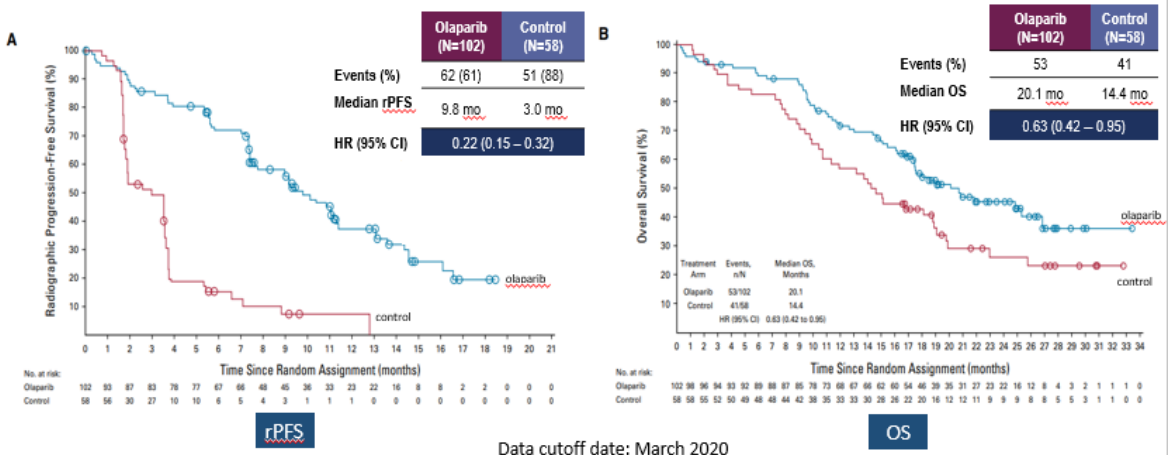
PROfound Trial: Phase 3 Trial Design



Statistical assumption for primary endpoint: Target hazard ratio = 0.53 (assumed 9.5 vs 5 months), 95% power, 2-sided 5% alpha (60% maturity, 143 events)

*BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANC, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D RAD54L; †Physician choice of either enzalutamide (160 mg qd) or abiraterone (1000 mg qd plus prednisone [5 mg bid]); BICR, blinded independent central review; bid, twice daily; ORR, objective response rate; OS, overall survival; rPFS, radiographic progression free survival.

Post-hoc Analysis of PROfound Trial: Olaparib Efficacy in Patients with *BRCA* Alterations



Data cutoff date: March 2020
Median follow-up 21.9 mo (olaparib group) and 21.0 mo (control group)

Mateo *et al.*, JCO, 2023

Androgen Receptor Pathway inhibitors w/ PARP inhibitors

ARPIs induce a phenotype resembling HRR deficiency

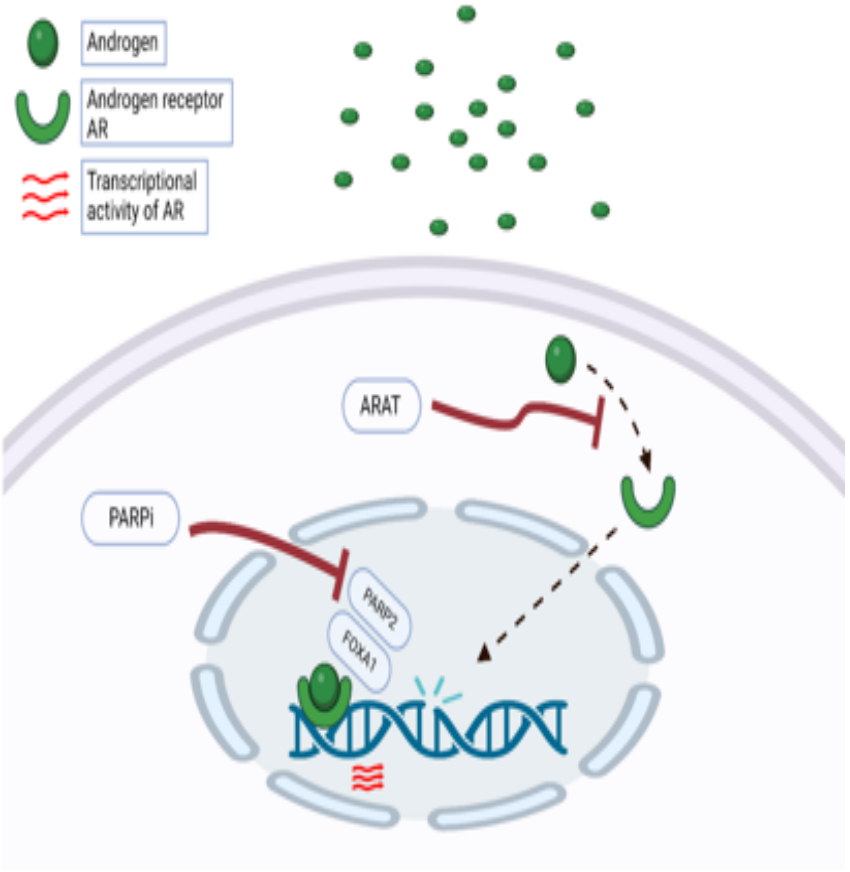
Suppressed AR function causes an upregulation of PARP

ARPIs prime tumor cells for PARP inhibition

PARP augments AR activity

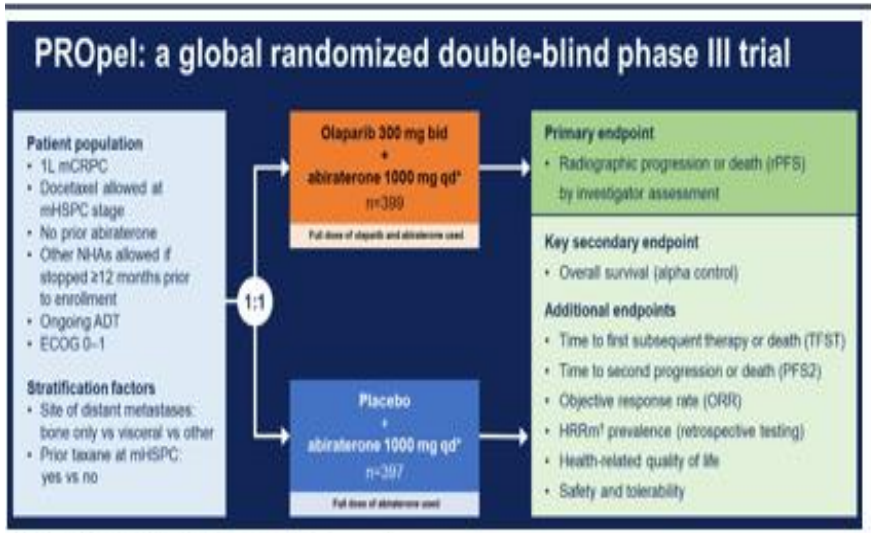
PARP inhibitors may attenuate resistance to ARPIs

PARP inhibitors extend the benefits of ARPIs

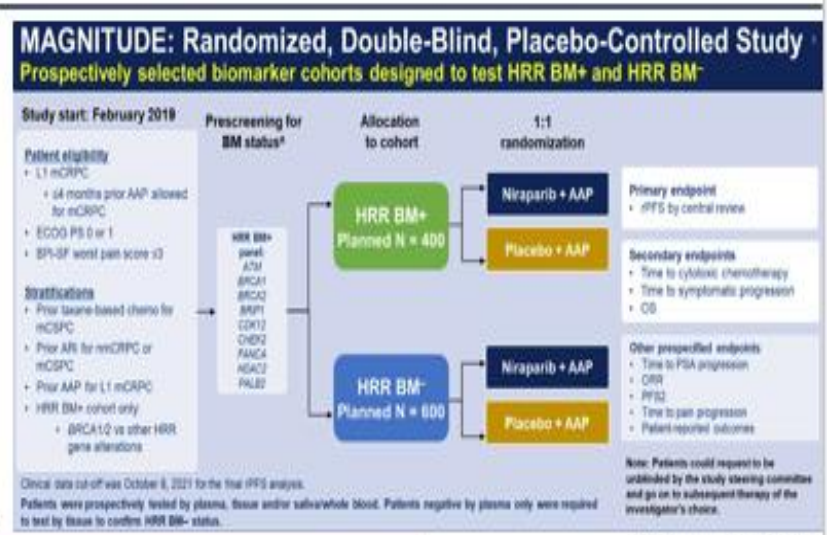


1. Adapted from Bin Gui et al. *PNAS* 2019 June, DOI https://doi.org/10.1073/pnas.1908547116
2. Agarwal N et al. *European Journal of Cancer* 2023.

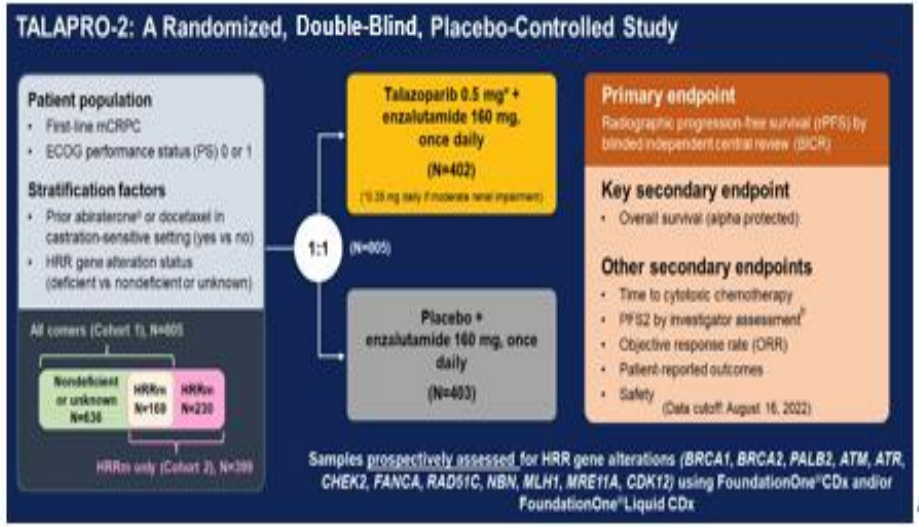
Phase 3 PARPi + ARPI Trials Design



Clarke, NW. *et al.* ***NEJM Evidence***, 2022



Chi, KN. *et al.* ***JCO***, 2022



Agarwal, N. *et al.* ***Lancet***, 2023

Phase 3 combination trials of PARP inhibitors with an ARPI

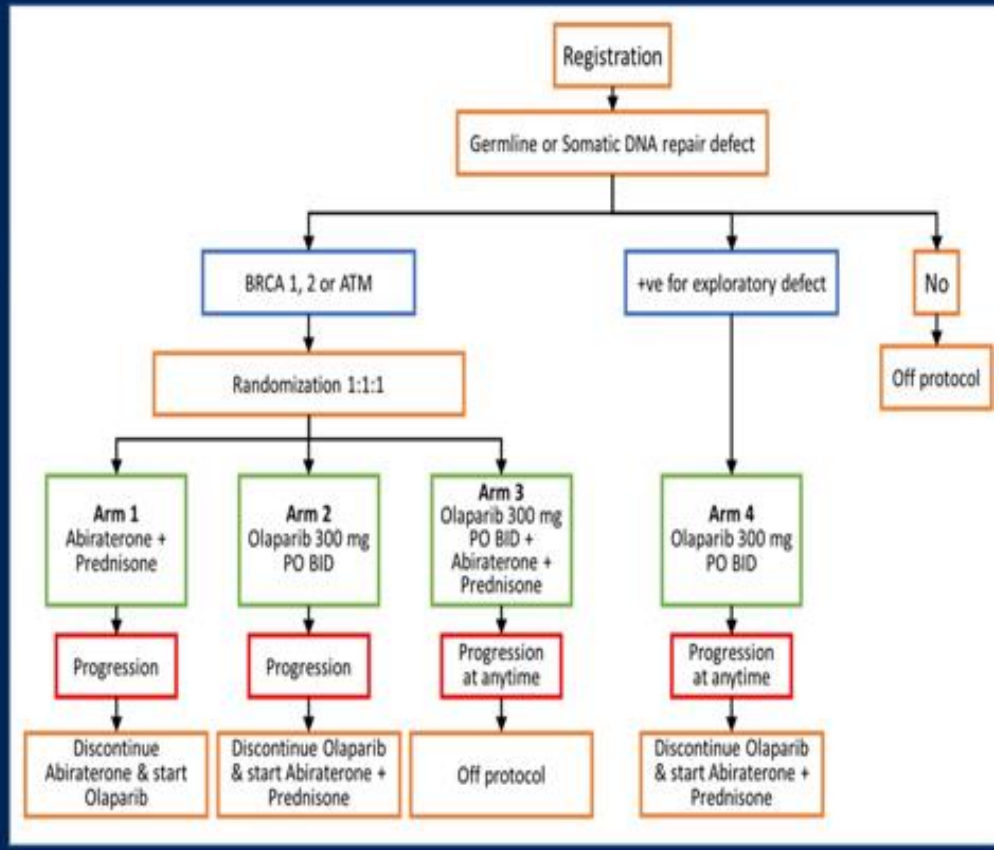
	PROpel (N = 796)	MAGNITUDE (N = 423)	TALAPRO-2 (Cohort 1: N = 805)	TALAPRO-2 (Cohort 2: N = 399)
Trial population mCRPC 1st line	Docetaxel / ARSI in mCSPC setting allowed (ARSI without progression and > 12 months ago)	Docetaxel / ARSI in mCSPC setting allowed ; Abiraterone in mCRPC allowed if given < 4 months	Docetaxel / Abiraterone in mCSPC setting allowed	
Design and randomization	1 : 1 randomization Abiraterone + olaparib (n = 399) vs abiraterone + placebo (n = 397)	Cohort 1: HRR cohort 1 : 1 randomization abiraterone + niraparib (n = 212) vs abiraterone + placebo (n = 211) Cohort 2: non-HRR cohort (closed prematurely because of futility)	All-comer population 1 : 1 randomization Enzalutamide + talazoparib (n = 402) vs enzalutamide + placebo (n = 403)	HRR cohort 1 : 1 randomization Enzalutamide + talazoparib (n = 200) vs enzalutamide + placebo (n = 199)
HRR analysis	Tissue or ctDNA / retrospective	100% tissue / prospective	100% tissue / prospective	99.5% tissue / prospective 0.5% ctDNA or unspecified tissue source / prospective
Primary endpoint	rPFS (investigator review)	rPFS (central review)	rPFS (central review)	rPFS (central review)
rPFS, HR (95% CI)				
All comers	HR 0.66 (0.54-0.81)	NR	HR 0.63 (0.51-0.78)	Not included
HRR -ve	HR 0.76 (0.6-0.97)	HR 1.09 (0.75-1.57)	HR 0.70 (0.54-0.89)	Not included
HRR +ve	**HR 0.50 (0.34-0.73)**	**HR 0.76 (0.60-0.97)**	**HR 0.46 (0.30-0.70)**	**HR 0.45 (0.33-0.61)**
BRCA+	**HR 0.23 (0.12-0.43)**	**HR 0.55 (0.39-0.78)**	**HR 0.23 (0.10-0.53)**	**HR 0.20 (0.11-0.36)**
ORR (all comers)	58% vs 48%	60% vs 28% (only HRR+ pts)	61.7% vs 43.9%	67% vs 40%
OS (all comers)	HR 0.81 (0.67-1)	HR 0.82 (0.60-1.10) (only for HRR+ pts)	Immature HR 0.89 (0.69-1.14)	Immature HR 0.69 (0.46-1.03)
FDA approval; EMA approval	**mCRPC with BRCA1/2 mutations; mCRPC when chemotherapy is not indicated**	**mCRPC with BRCA1/2 mutations**	**mCRPC with any HRR mutations; mCRPC when chemotherapy is not clinically indicated**	
Publication	Clarke N....Saad F. *NEJM Evidence*, 2022	Chi K....Sandhu S. *JCO*, 2023....Chi K Annals Oncol, 2023	Agarwal N....Fizazi K. *Lancet*, 2023	Fizazi K....Agarwal N. ***Nature Medicine***, 2023

1. Adapted from Bin Gui et al. *PNAS* 2019 June, DOI https://doi.org/10.1073/pnas.1908547116
2. Agarwal N et al. *European Journal of Cancer* 2023.

Combination vs Sequential PARP inhibitors?

Methods & Study Design

- **Eligibility:** mCRPC, no prior exposure to PARP-I, AR-I, or chemotherapy for mCRPC, washout of antiandrogen (for mHSPC), radiation, and other investigational agents.
- Eligible pts underwent tumor next-generation sequencing (NGS) & germline testing; pts with inactivating BRCA1/2 and/or ATM alterations were randomized 1:1:1 to:
  - Arm I: abiraterone (1000 mg qd) + prednisone (5mg bid),
  - Arm II: olaparib (300 mg bid)
  - Arm III: olaparib + abiraterone/prednisone
- Arm I and II pts could cross over at progression.



Study Endpoints

Primary Endpoint

- Radiographic progression free survival (PFS) per RECIST 1.1, PCWG3, clinical assessment, or death.

Secondary Endpoints

- Measurable disease response rate (RR), PSA RR, and toxicity.

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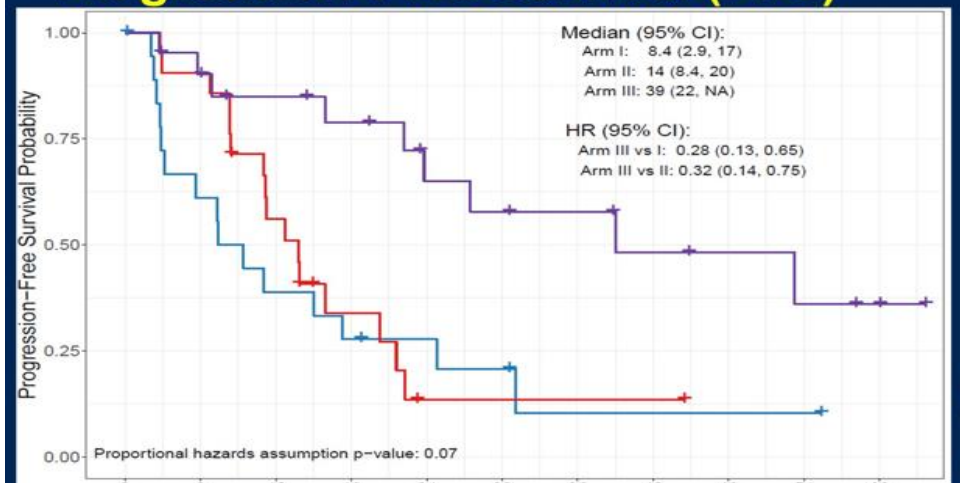
Hussain, ASCO GU 2024

Progression-Free Survival (PFS)



PFS: time from randomization until first progression or death.

Proportional hazards assumption was not met for Arm I versus II comparison.

Hussain, ASCO GU 2024

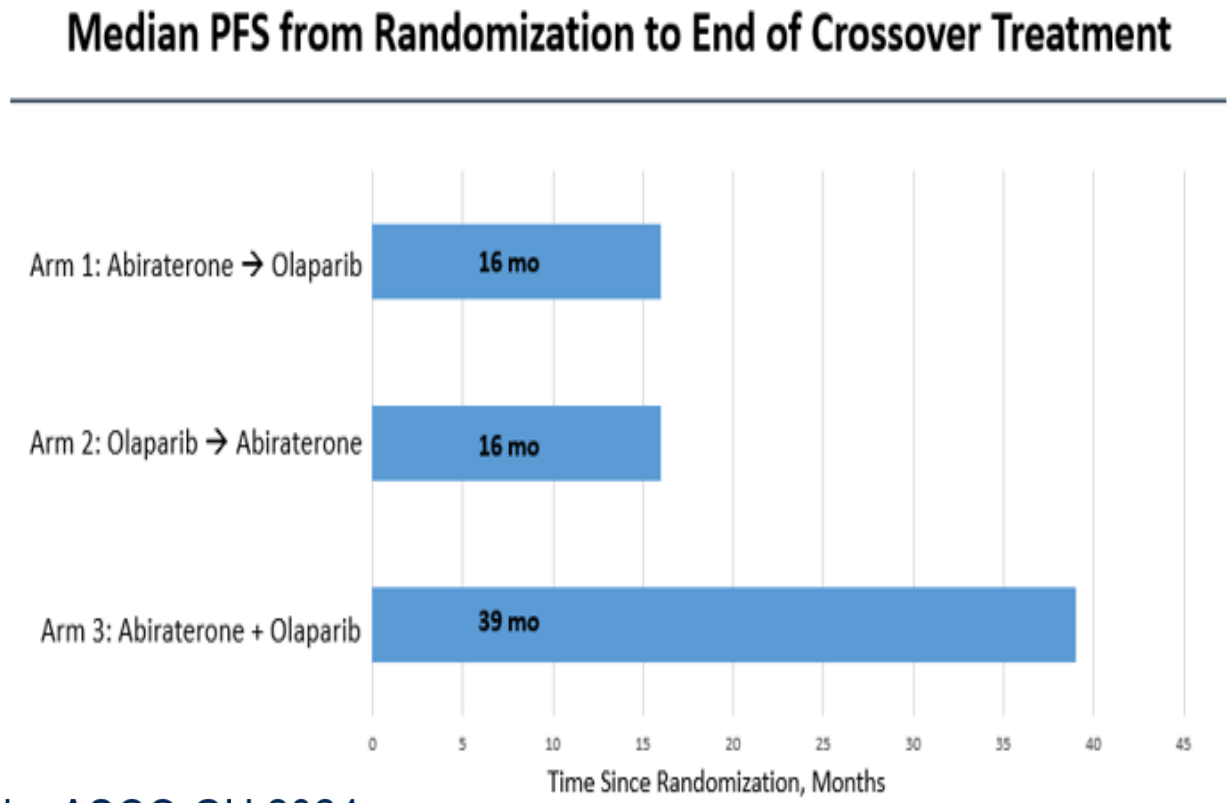
Efficacy Summary

- Arm I: abiraterone (1000 mg qd) + prednisone (5mg bid),
- Arm II: olaparib (300 mg bid)
- Arm III: olaparib + abiraterone/prednisone

	Arm I (n = 19)	Arm II (n = 21)	Arm III (n = 21)
Median PFS, months (95% CI)	**8.4 (2.9, 17)**	**14 (8.4, 20)**	**39 (22, NR)**
Objective RR, % (95% CI)	**22** (6.4, 48)	**14** (3, 36)	**33** (15, 57)
PSA RR, % (95% CI)	**61** (36, 83)	**67** (43, 85)	**95** (76, 100)
Undetectable PSA RR, % (95% CI)	**17** (3.6, 41)	**14** (3, 36)	**33** (15, 57)

NR, Not Reached

My Practice
Combination therapy preferred based on this practice changing study



Hussain, ASCO GU 2024

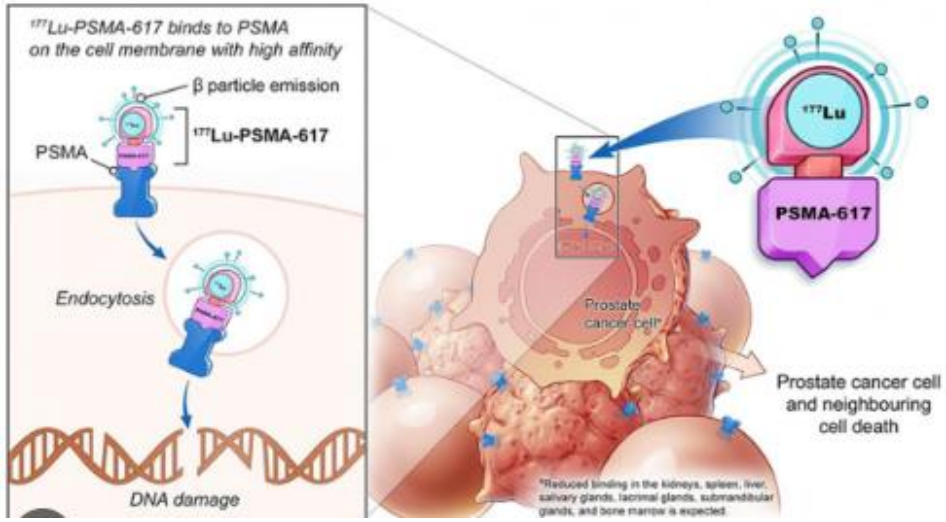
2024 Lutetium 177 Update

VISION Study

ORIGINAL ARTICLE

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

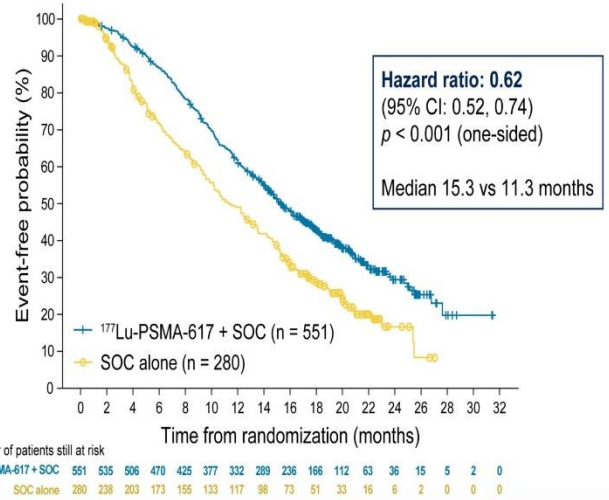
Oliver Sartor, M.D., Johann de Bono, M.B., Ch.B., Ph.D., Kim N. Chi, M.D., Karim Fizazi, M.D., Ph.D., Ken Herrmann, M.D., Kambiz Rahbar, M.D., Scott T. Tagawa, M.D., Luke T. Nordquist, M.D., Nitin Vaishampayan, M.D., Ghassan El-Haddad, M.D., Chandler H. Park, M.D., Tomasz M. Beer, M.D., et al., for the VISION Investigators*



Primary endpoints: ^{177}Lu-PSMA-617 prolonged OS

Primary analysis

All randomized patients (N = 831)



2024 ASCO ANNUAL MEETING

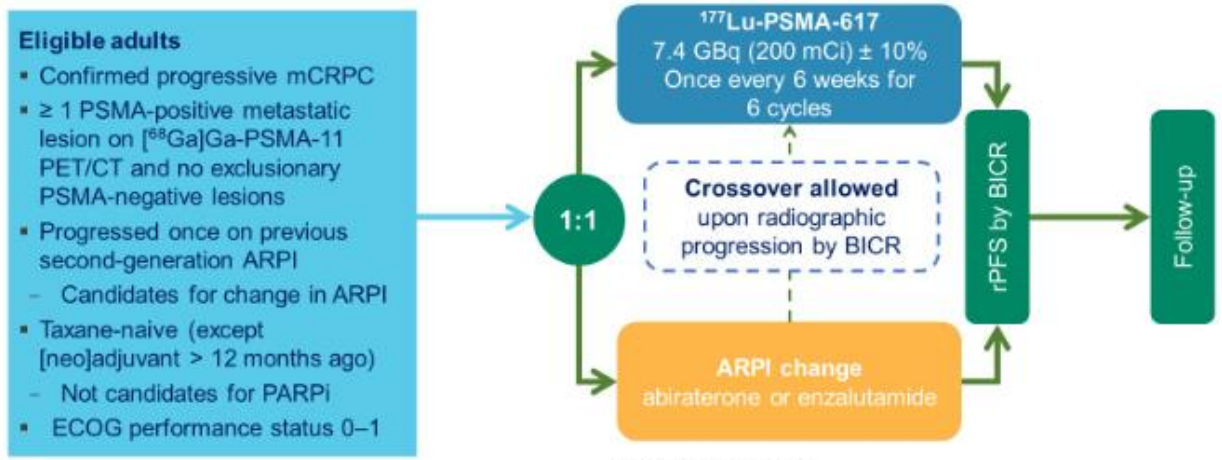
Health-related quality of life and pain in a phase 3 study of [^{177}Lu]Lu-PSMA-617 in taxane-naive patients with metastatic castration-resistant prostate cancer (PSMAfore)

Presenter: Karim Fizazi

Gustave Roussy Institute, Paris-Saclay University, Villejuif, France

Co-authors: MJ Morris, N Shore, K Chi, M Crosby, J de Bono, K Herrmann, G Roubaud, J Nagarajah, M Fleming, B Lewis, L Nordquist, D Castellano, N Carnahan, S Ghebremariam, M Hertelendi, O Sartor,
on behalf of the PSMAfore Investigators

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



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

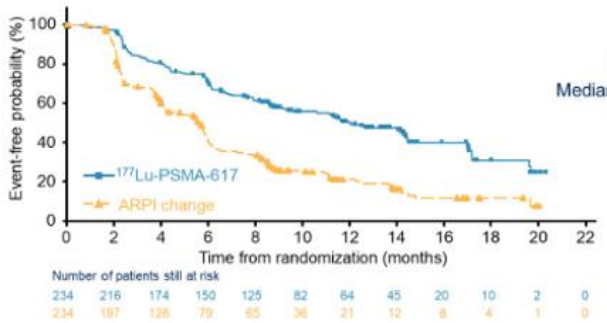
ARPI, androgen receptor pathway inhibitor; BICR, blinded independent central review; BPI-SF, brief pain inventory – short form; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; mCRPC, metastatic castration-resistant prostate cancer; PARPi, Poly (ADP-ribose) polymerase (PARP) inhibitor; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; rPFS, radiographic progression-free survival

Primary and second interim OS analysis

rPFS: the primary endpoint was met

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

Second interim analysis[b] HR: 0.43 (95% CI: 0.33, 0.54)



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

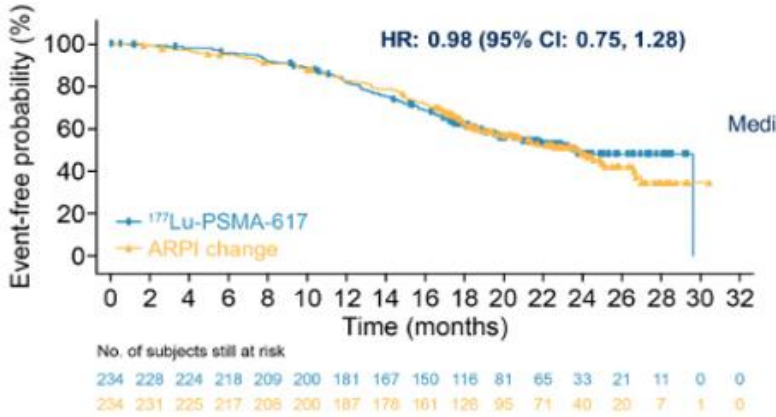
[a]Data cutoff October 2, 2022
[b]Data cutoff June 21, 2023
Previously presented at ESMO23
ARPI, androgen receptor pathway inhibitor; CI, confidence interval; HR, hazard ratio; PSMA, prostate-specific membrane antigen; rPFS, radiographic progression-free survival

Fizazi, ASCO 2024

OS: HR < 1 at third interim analysis with 73% information fraction

Intent-to-treat analysis

Third interim OS analysis



	177Lu-PSMA-617 (n = 234)	ARPI change (n = 234)
Events, n	104 (44.4%)	112 (47.9%)
Median, months (95% CI)	23.66 (19.75, NE)	23.85 (20.6, 26.55)

Crossover:
134/234 (57.3%) in ARPI change group
134/173 (77.5%) eligible patients

RPSFT crossover-adjusted OS analysis

- HR: 0.98 (95% CI: 0.76, 1.27)
- No difference versus the ITT analysis because RPSFT cannot adjust for crossover confounding in the context of overlapping ITT curves

ARPI, androgen receptor pathway inhibitor; CI, confidence interval; HR, hazard ratio; IF, information fraction; ITT, intent-to-treat ; NE, not evaluable; OS, overall survival; PSMA, prostate-specific membrane antigen; RPFST, rank-preserving structural failure time

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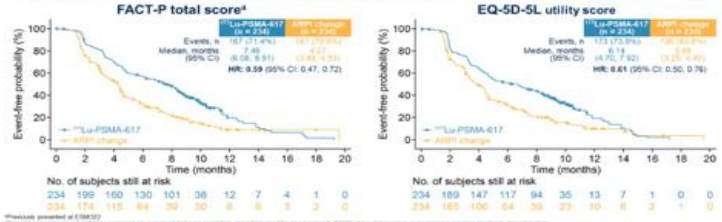
Second interim OS analysis

Time to HRQoL worsening at second interim analysis

Prespecified analysis:
Composite time to worsening in FACT-P, EQ-5D-5L and BPI-SF including clinical progression and death



[a]Previously presented at ESMO20

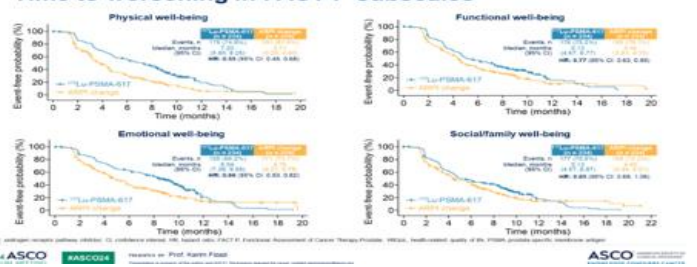
Clinical progression was investigator-assessed as: cancer-related pain escalation, immediate need for new treatment, ECOG status deterioration or progression requiring treatment discontinuation

ARPI, androgen receptor pathway inhibitor; BPI-SF, Brief Pain Inventory – Short Form; CI, confidence interval; EQ-5D-5L, EuroQol-5 Dimensions-5 Level; HR, hazard ratio; FACT-P, Functional Assessment of Cancer Therapy-Prostate; HRQoL, health-related quality of life; PSMA, prostate-specific membrane antigen

2024 ASCO ANNUAL MEETING #ASCO24 PRESENTED BY: Prof. Karim Fizazi

Second interim OS analysis

Time to worsening in FACT-P subscales



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Fizazi, ASCO 2024

What do I do in my practice for mCRPC after ESMO/ASCO 2024

- 1. After Taxane and ARP inhibitor. You have to choose between PARP inhibitor, Cabazitaxel (+/- Carboplatin) , and Lutetium 177. Get Germline and Somatic studies at metastatic disease)

- 2. If BRCA2/BRCA1 mutation. Preference is PARP inhibitor (+ ARPi if possible due to BRCAAWAY study) before Lutetium 177 and Cabazitaxel. For example if patient receives Abiraterone in hormone sensitive, would give Enzalutamide + Talazoparib). Consider PALB2, CDK 12, RAD51 (TALAPRO-2)

- 3. If PSMA PET scan shows mean SUV above 10 with many lesions, give Lutetium 177 before Cabizitaxel.

- 4. If patient progresses fast on ARP inhibitor (less than 12 months) and have mean SUV less than 10. Give Cabazitaxel. (PTEN, RB1, p53)

- 5. Get a 2nd liquid or tissue biopsy post Lutetium 177 when they progress. 15% of the time another somatic mutation develops .

- 6. Give Pembrolizumab for MSI High and TMB above 10. Have patients in my practice that developed BRCA2 somatic mutations and high TMB after "running" out of treatments. They are in stable condition now.

- 7. Consider clinical trials. Bispecific T cell engagers are very promising