Overview

Saturday, March 23rd

Module 1: 7:30 AM – 9:10 AM — Hodgkin and Non-Hodgkin Lymphoma

Module 2: 9:30 AM – 10:20 AM — Gynecologic Cancers

Module 3: 10:20 AM – 11:10 AM — Localized Breast Cancer; SABCS 2023 Review

Module 4: 11:10 AM – 12:00 PM — Metastatic HER2-Positive and Triple-Negative Breast Cancer; SABCS 2023 Review

Module 5: 12:30 PM – 1:20 PM — Renal Cell Carcinoma

Module 6: 1:20 PM – 2:10 PM — Urothelial Bladder Cancer

Module 7: 2:10 PM – 3:00 PM — Prostate Cancer

Module 8: 3:20 PM – 4:10 PM — Targeted Therapy for Non-Small Cell Lung Cancer

Module 9: 4:10 PM – 5:00 PM — Nontargeted Treatments for Lung Cancer

Third Annual National General Medical Oncology Summit

Agenda

Module 1: Current Management of Metastatic Clear Cell Renal Cell Carcinoma (RCC) — Dr Rini

Module 2: Treatment Approaches for Nonmetastatic RCC; Optimal Care of Patients with Non-Clear Cell RCC — Dr Jonasch

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Module 1: Current Management of Metastatic Clear Cell Renal Cell Carcinoma (RCC) — Dr Rini

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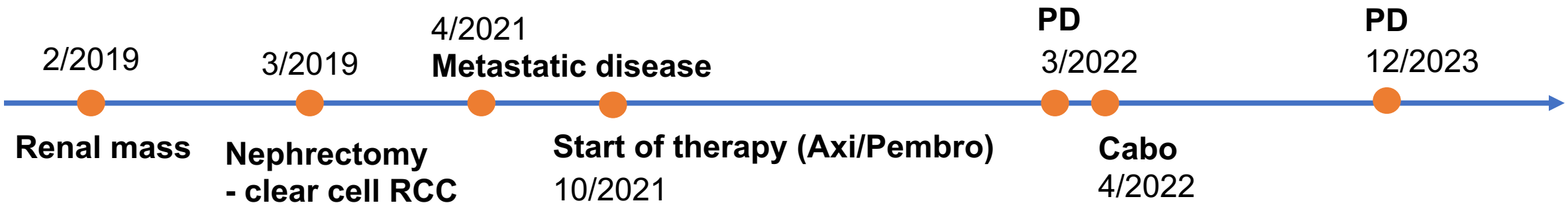
Systemic Therapy for Front-line and Refractory RCC

Brian I. Rini, MD, FASCO
Chief of Clinical Trials
Vanderbilt-Ingram Cancer Center
Ingram Professor of Medicine
Division of Hematology/Oncology
Vanderbilt University Medical Center

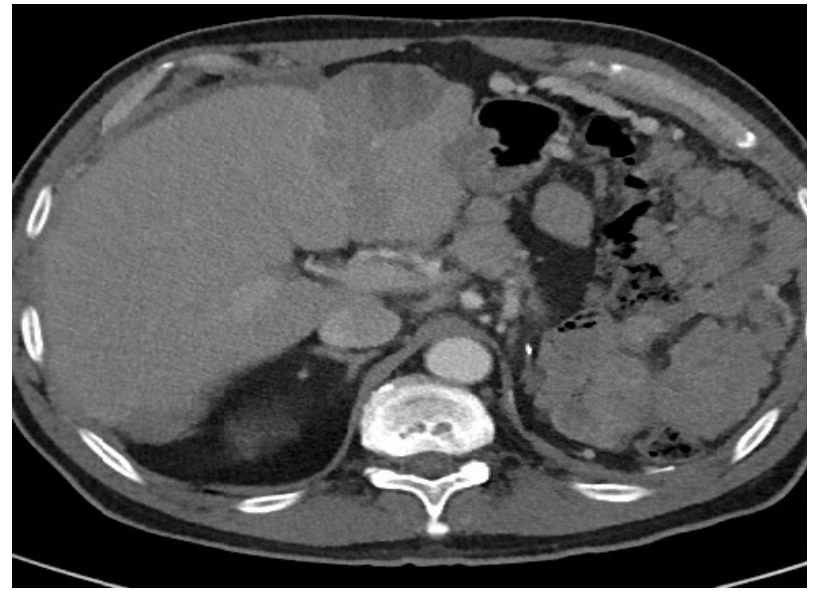
Disclosures

Advisory Committee	AstraZeneca Pharmaceuticals LP
Consulting Agreements	Alkermes, Aravive Inc, Arrowhead Pharmaceuticals, Athenex, Aveo Pharmaceuticals, Bristol Myers Squibb, Corvus Pharmaceuticals, Debiopharm, Eisai Inc, EUSA Pharma, Genentech, a member of the Roche Group, HiberCell, Merck, NiKang Therapeutics Inc, Pfizer Inc, Sanofi, Surface Oncology
Contracted Research	ADC Therapeutics, Adela, Arcus Biosciences, Arrowhead Pharmaceuticals, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bristol Myers Squibb, Daiichi Sankyo Inc, Dracen Pharmaceuticals, Dragonfly Therapeutics, Exelixis Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, HiberCell, Incyte Corporation, Janssen Biotech Inc, Merck, Pfizer Inc, Pionyr Immunotherapeutics, POINT Biopharma, Strata Oncology, Surface Oncology, Tempus, VasGene Therapeutics Inc
Data and Safety Monitoring Board/Committee	AstraZeneca Pharmaceuticals LP

72 yr old male

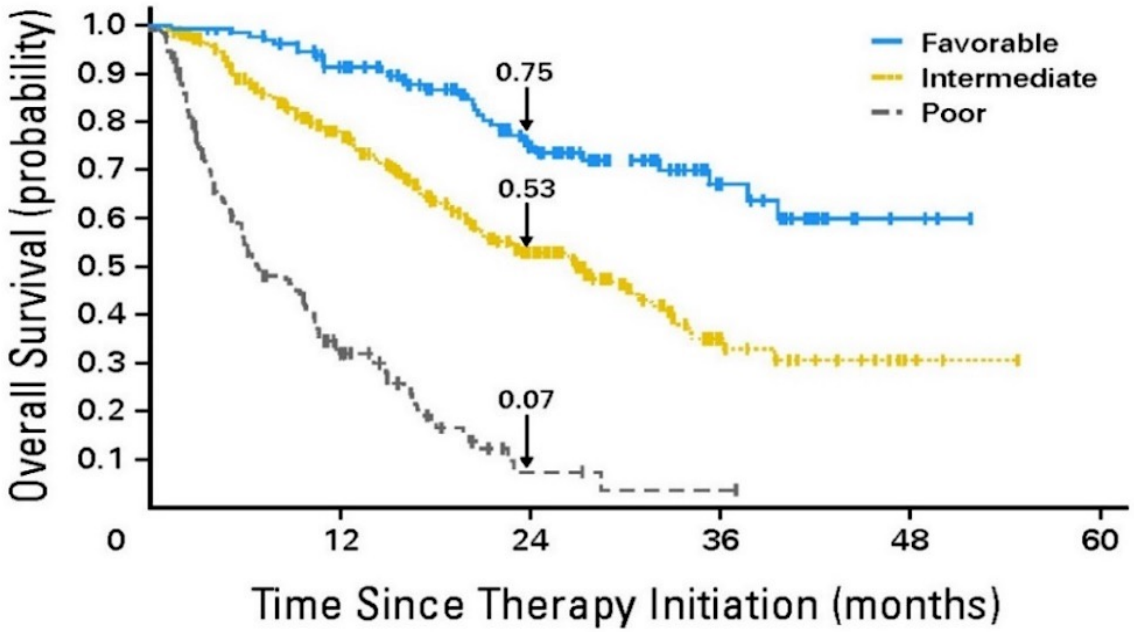


- Front-line Axi/Pembro; well tolerated with PR on CT scans at 3 months
- CT scan 1.5 years after start of therapy reveals new hepatic mets
- Cabozantinib 2nd-line for 8 months, then PD in liver and bone
- ECOG PS 1 (mild bone pain; anorexia); hgb 10.6; other labs wnl



IMDC Prognostic Criteria

- **Clinical**
  - KPS < 80%
  - Time from diagnosis to treatment < 1 year
- **Laboratory**
  - Hemoglobin < LLN
  - Calcium > ULN
  - Neutrophil count > ULN
  - Platelet count > ULN

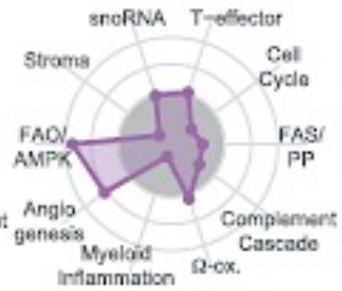
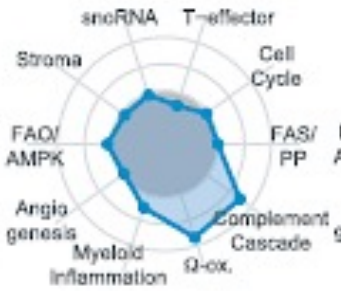
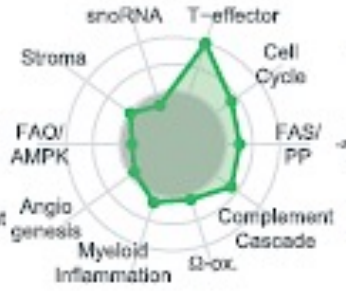
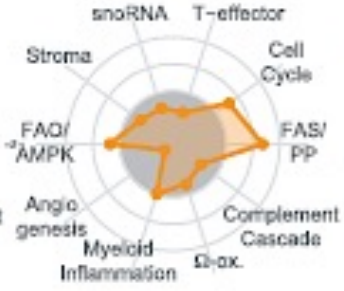
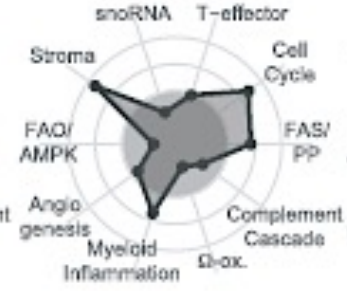


No. of events/No. at risk					
Favorable	11/133	16/110	4/62	2/22	0/3
Intermediate	61/301	50/182	17/82	2/18	0/3
Poor	94/152	19/36	1/3	0/1	0/0

- Favorable: 0 risk factors ⟶ means slow-growing and/or VEGF-responsive
- Intermediate: 1-2 risk factors ⟶ medium growth rate and somewhat VEGF-responsive
- Poor: 3-6 risk factors ⟶ fast-growing and VEGF-unresponsive

Heng DYC, et al. J Clin Oncol. 2009;27:5794-5799

The biology of RCC is driven primarily (although not exclusively) driven by angiogenic and inflammatory pathways

	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6	Cluster 7
	98/823 (12%)	245/823 (30%)	156/823 (19%)	116/823 (14%)	74/823 (9%)	106/823 (13%)	28/823 (3%)
Pathways	Angiogenesis Stroma	Angiogenesis Fatty acid oxidation	Complement cascade Ω-oxidation	T-effector Cell Cycle Fatty acid synthesis	Cell Cycle Fatty acid synthesis	Stroma Cell Cycle	snoRNA
RNA profile							
DNA alts	VHL PBRM1 KDM5C PTEN	VHL PBRM1 KDM5C	VHL PBRM1 KDM5C PTEN BAP1	VHL CDKN2A/B BAP1	CDKN2A/B TP53	VHL CDKN2A/B TP53	VHL SETD2 PTEN

Motzer, Rini et al. *Cancer Cell* 2020

First-line IO Combination Trials in mRCC (ITT)

	CheckMate 214 (Ipi/Nivo)[1] (n=550 vs n=546)	KEYNOTE-426 (Axi/Pembro)[2] (n=432 vs n=429)	CheckMate 9ER (Cabo/Nivo)[3] (n=323 vs n=328)	CLEAR (Len/Pembro)[4] (N=355 vs n=357)
OS HR mOS, months	**0.72** 52.7	**0.84**	**0.77**	**0.79** 53.7 v. 54.3
Landmark OS	**35%** at 7.5 years	**63%** at 3 years **42%** at 5 years	**49%** at 4 years	**66%** at 3 years
PFS HR mPFS, months	**0.88** **12.4** vs 12.3	**0.69**	**0.58**	**0.47**
Landmark PFS	**23%** at 7.5 years (IRC) **16%** at 7.5 years (investigator)	**18%** (5 years)	**17%** (4 years)	**37%** (3 years)
[illegible]	[illegible]	[illegible]	**56** vs 28	**71** vs 37
[illegible]	[illegible]	[illegible]	**14** vs 5	**18** vs 4
Med f/u, months	**96**			
Primary PD, %	**18**	**12**	**7**	**5**

Consistent OS benefit vs VEGF TKI

More tumor shrinkage with TKI-containing regimens

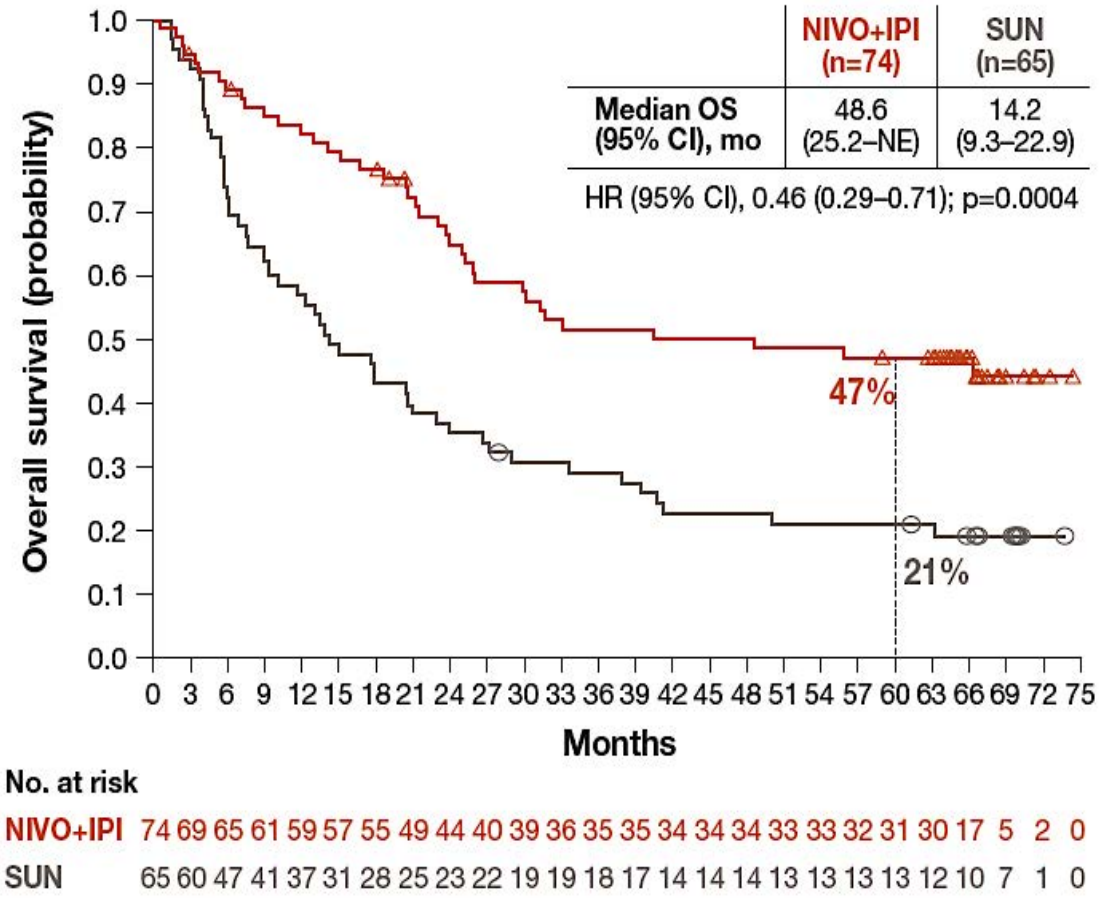
CTLA-4 containing regimen perhaps with higher tail of the curve / more durable responses

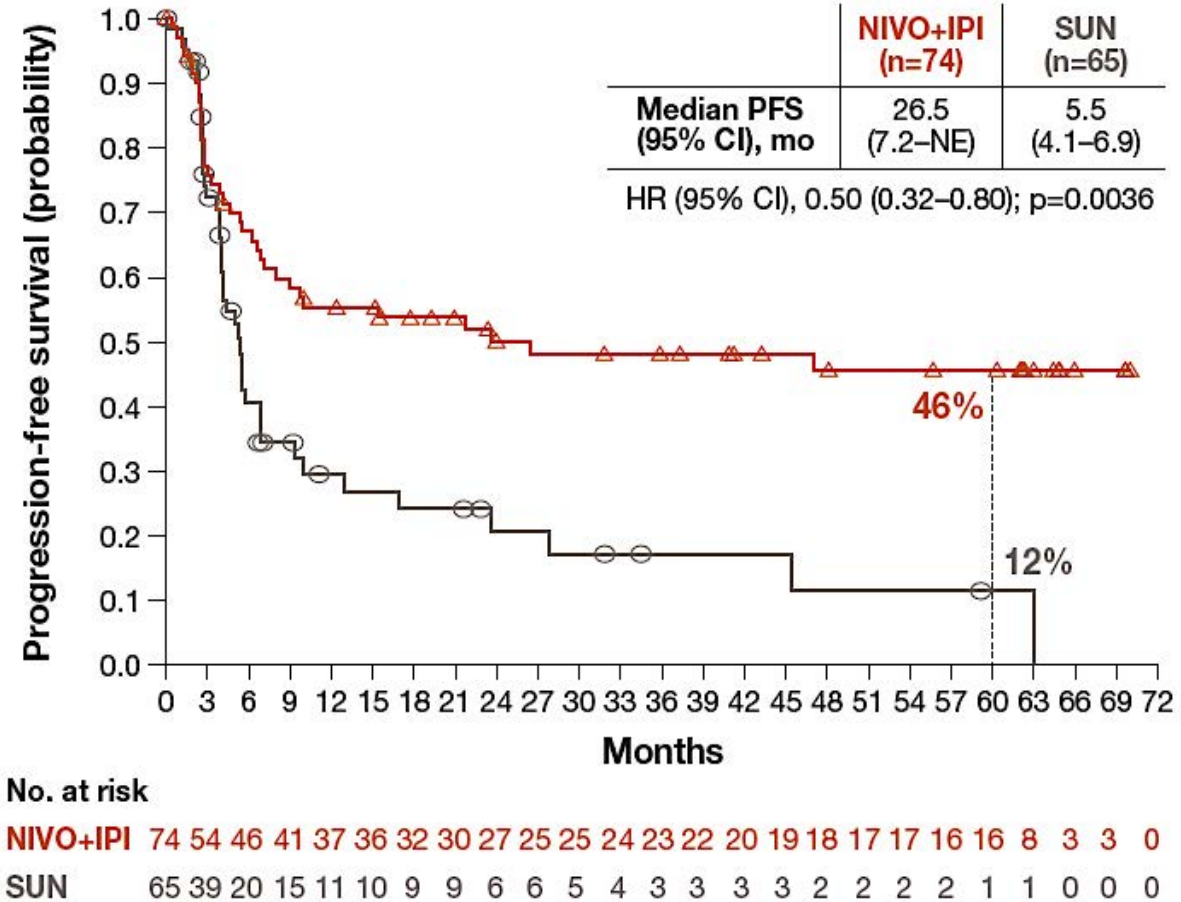
Less early PD with TKI-containing regimens

1. Tannir et al. ASCO GU 2024
2. Rini et al. ASCO 2023
3. Bourlon et al. ASO GU 2024
4. Motzer et al. ASCO 2023

@brian_rini and @Uromigos (podcasts: https://podcasters.spotify.com/pod/show/the-uromigos)

Sarcomatoid histology is the best biomarker for Ipi/Nivo





- ORR 61% / 23% CR

Rini et al. JITC 2023

Subcutaneous nivolumab vs intravenous nivolumab in patients with previously treated advanced or metastatic clear cell renal cell carcinoma: pharmacokinetics, efficacy, and safety results from CheckMate 67T

Key eligibility criteria

- Advanced or metastatic ccRCC that progressed during or after receiving 1-2 prior systemic regimens
- No prior immuno-oncology therapy
- Karnofsky PS ≥ 70

R 1:1

- NIVO SC 1200 mg + rHuPH20 Q4W (n = 248)
- NIVO IV 3 mg/kg Q2W (n = 247)

Treat until disease progression, unacceptable toxicity, withdrawal of consent, completion of 2 years' treatment, or death

Key stratification factors

- IMDC risk group
- Baseline weight

Co-primary PK endpoints for noninferiority testing:

- C_{avgd28} and C_{minss}

Key powered secondary endpoint for noninferiority testing:

- ORR by BICR

- Patients were enrolled across 73 sites in 17 countries[a]
- Minimum follow-up was 8 months

Other secondary endpoints:

- Other efficacy, safety, and PK measures
- Incidence of anti-NIVO antibodies and neutralizing antibodies

[a]Due to closure of Russian sites, data collection was incomplete for Russian patients. All available data from Russian patients were included in the analyses.
BICR, blinded independent central review; C_{avgd28}, average serum concentration at day 28; ccRCC, clear cell renal cell carcinoma; C_{minss}, trough serum concentration at steady-state; IMDC, International Metastatic renal cell carcinoma Database Consortium; IV, intravenous; NIVO, nivolumab; ORR, objective response rate; PK, pharmacokinetics; PS, performance status; QXW, every X weeks; R, randomization; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous.

George S et al. ASCO GU 2024;Abstract LBA360.

Co-primary endpoints: PK noninferiority

- Noninferiority for the co-primary PK endpoints was met

	NIVO SC + rHuPH20 (n = 242)	NIVO IV (n = 245)	Geometric mean ratio[a] (90% CI)
Geometric mean C_{avgd28}, µg/mL (90% CI)	77.373 (74.555–80.297)	36.875 (35.565–38.235)	2.098 (2.001–2.200)
Geometric mean C_{minss}, µg/mL (90% CI)	122.227 (114.552–130.416)	68.901 (64.676–73.402)	1.774 (1.633–1.927)

Geometric mean is a type of average that is useful when log transformed values follow normal distribution, and is frequently used for PK exposures
Geometric means and **geometric mean ratios** are estimated from a linear model with treatment and stratification factors as fixed effects, fitted to the log-transformed C_{avgd28} and C_{minss}

C_{avgd28}, time-averaged serum concentration at day 28; CI, confidence interval; C_{minss}, trough serum concentration at steady state; IV, intravenous; NIVO, nivolumab; PK, pharmacokinetics; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous.

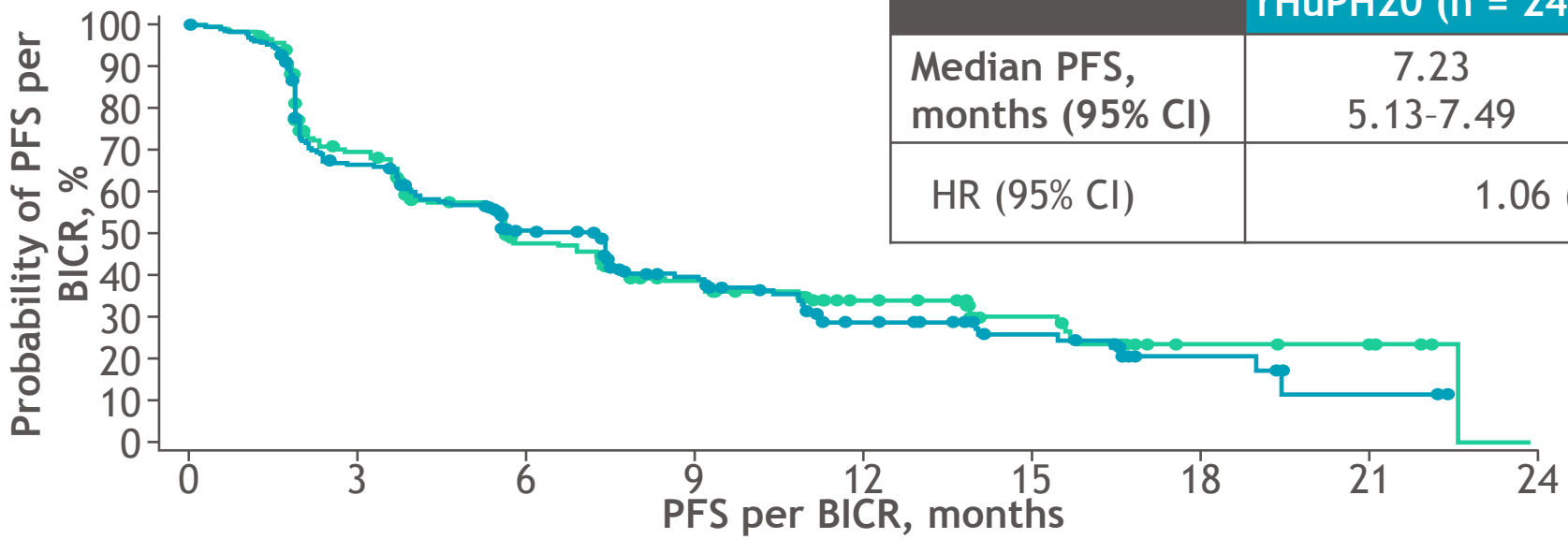
George S et al. ASCO GU 2024;Abstract LBA360.

ORR and PFS

- Noninferiority for the key powered secondary endpoint ORR by BICR was met

	NIVO SC + rHuPH20 (n = 248)	NIVO IV (n = 247)
ORR, n (%) **95% CI**	60 (24.2) 19.0–30.0	45 (18.2) 13.6–23.6
Relative risk[a] (95% CI)	1.33 (0.94–1.87)	

	NIVO SC + rHuPH20 (n = 248)	NIVO IV (n = 247)
Median PFS, months (95% CI)	7.23 5.13–7.49	5.65 5.29–7.39
HR (95% CI)	1.06 (0.84–1.34)	



[a]Relative risk ratio of ORR is stratified Mantel-Haenszel estimate.
BICR, blinded independent central review; CI, confidence interval; IV, intravenous; NIVO, nivolumab; ORR, objective response rate; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous.

George S et al. ASCO GU 2024;Abstract LBA360.

2nd-Line Agents: Post VEGF-TKI

	Axitinib [1,2]	Nivolumab [3]	Cabozantinib [4]	Lenvatinib/Eve (RP2) [5,6]
Patient Population	2nd Line	TKI-refractory (72% 1 prior)	TKI-refractory (71% 1 prior)	TKI-refractory (100% 1 prior)
MSKCC risk: good/int/poor	28/37/33	35/49/16	45/42/12	24/37/39
Comparator	Sorafenib	Everolimus	Everolimus	Everolimus
ORR, % PD, %	19% 22%	22% 35%	17% 12%	35% 4%
PFS, months	4.8	4.6	7.4	12.8
OS, months	20.1	25.0	21.4	25.5
Dose reductions	31% (37% Increase)	n/a	62%	71%
D/C due to AE	4%	8%	12%	24%
Toxicity	Grade 3: 50% Grade 4: 6%	Grade 3 or 4: 19%	Grade 3: 63%* Grade 4: 8%	Grade 3: 57% Grade 4: 14%

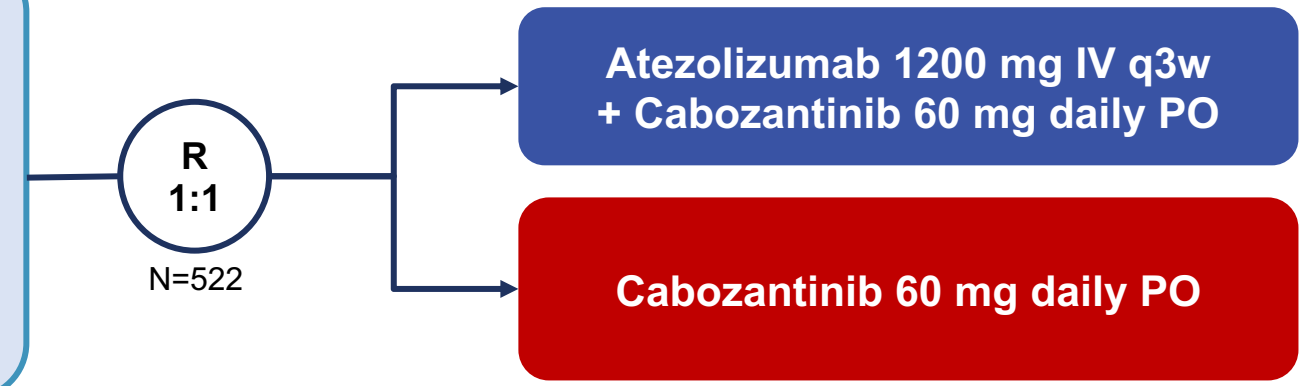
* All AEs regardless of attribution to the drugs

[1] Motzer, et al. *Lancet Oncol*. 2013;14:552. [2] Rini, et al. *Lancet* 2011;378:19312. [3] Motzer, et al. *N Engl J Med*. 2015;373:1803. [4] Choueiri, et al. *Lancet Oncol*. 2016.
[5] Motzer, et al. *Lancet* 2015;16:1473. [6] Motzer, et al. *Lancet* 2016;17:E4-45.

Phase III CONTACT-03 study

Key eligibility criteria

- Advanced/metastatic clear cell or non–clear cell[a] RCC with or without a sarcomatoid component
- Radiographic progression on or after prior ICI treatment
  - ICI as adjuvant, 1L or 2L (single agent or in combination with another permitted agent)
  - ICI in the immediately preceding line of therapy



Stratification factors

- **IMDC risk group**
  0 vs 1-2 vs ≥3
- **Histology**
  Dominant clear cell without sarcomatoid vs dominant non-clear cell without sarcomatoid vs any sarcomatoid[b]
- **Most recent line of ICI**
  Adjuvant vs 1L vs 2L

Primary endpoints

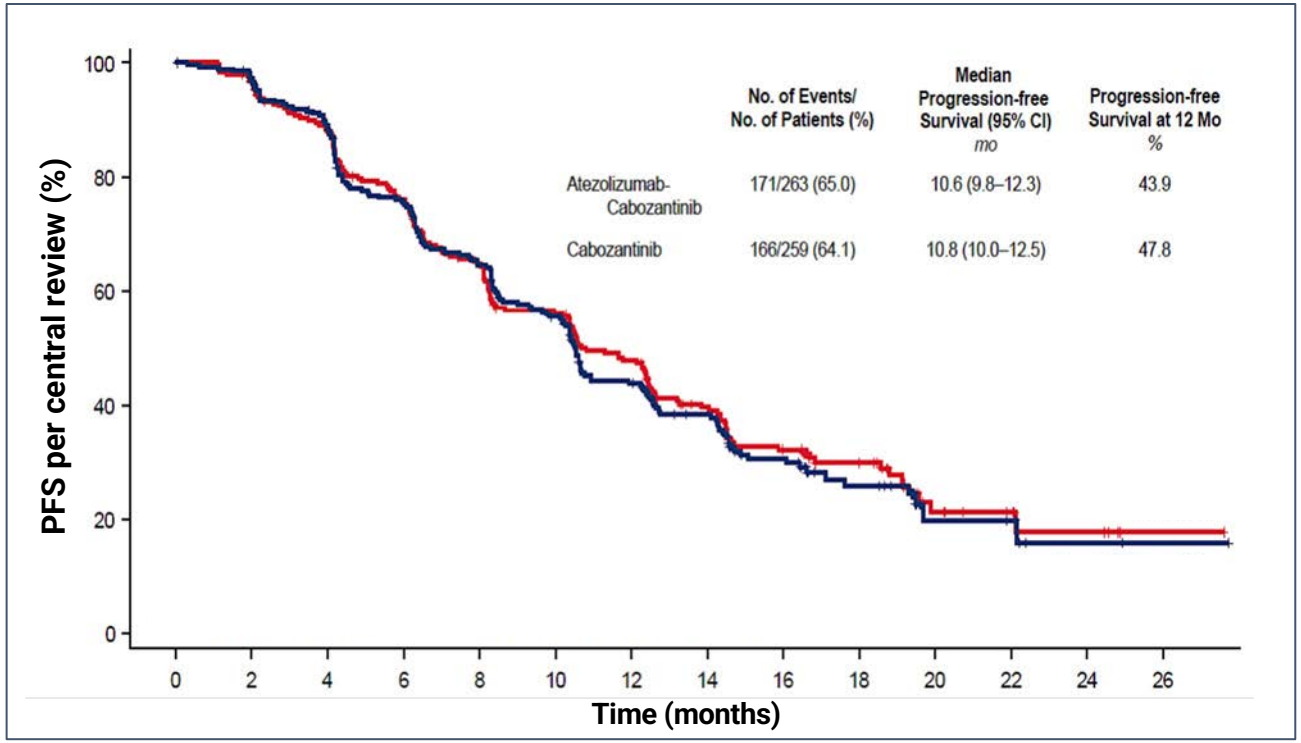
- Independent centrally-assessed PFS[c]
- OS

Key secondary endpoints

- Investigator-assessed PFS[c]
- ORR (per central review and per investigator)[c]
- Duration of response (per central review and per investigator)[c]
- Safety

ClinicalTrials.gov ID, NCT04338269. IMDC, International Metastatic RCC Database Consortium. Patients were enrolled between July 28, 2020 and December 27, 2021.
[a] Papillary, chromophobe or unclassified (chromophobe requires sarcomatoid differentiation). [b] Clear cell or non-clear cell. [c] Assessed according to RECIST 1.1.

CONTACT-03 was completely negative



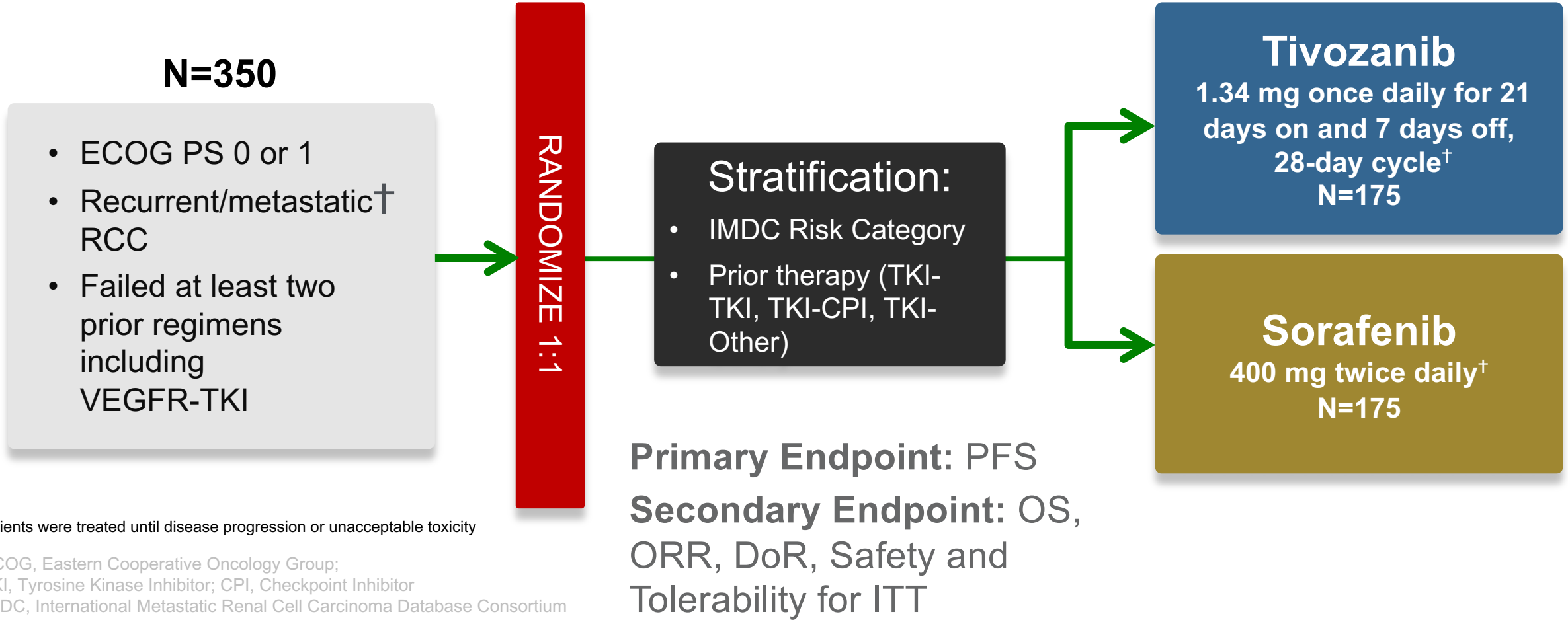
	Atezo + Cabo (n=259)	Cabo (n=254)
ORR	41%	41%
CR	0%	1%
PR	41%	40%
SD	51%	48%
PD	4%	5%
Median DOR (mos)	12.7	14.8

Adverse event	Atezo + Cabo (n=262)	Cabo (n=256)
Grade 3 or 4 treatment-related AE	55%	47%
Death due to treatment-related AE	1%	0%
Serious treatment-related AE	24%	12%

[a] Treatment-related AEs leading to death were immune-mediated enterocolitis and renal failure (both related to atezo) and intestinal perforation (related to cabo).

Adapted from Choueiri, et al. CONTACT-03 (LBA4500).

TIVO-3: Randomized Phase 3 Trial in Refractory Advanced Renal Cell Carcinoma

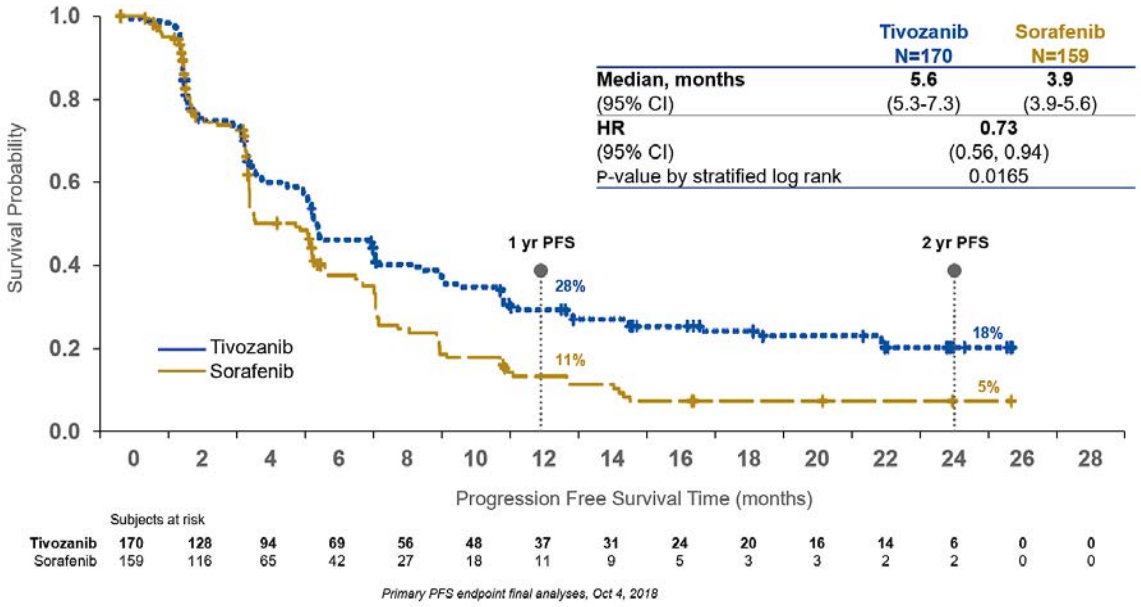


†Patients were treated until disease progression or unacceptable toxicity

ECOG, Eastern Cooperative Oncology Group;
TKI, Tyrosine Kinase Inhibitor; CPI, Checkpoint Inhibitor
IMDC, International Metastatic Renal Cell Carcinoma Database Consortium

Rini BI et al *Lancet Oncol* 2020;21(1):95-104

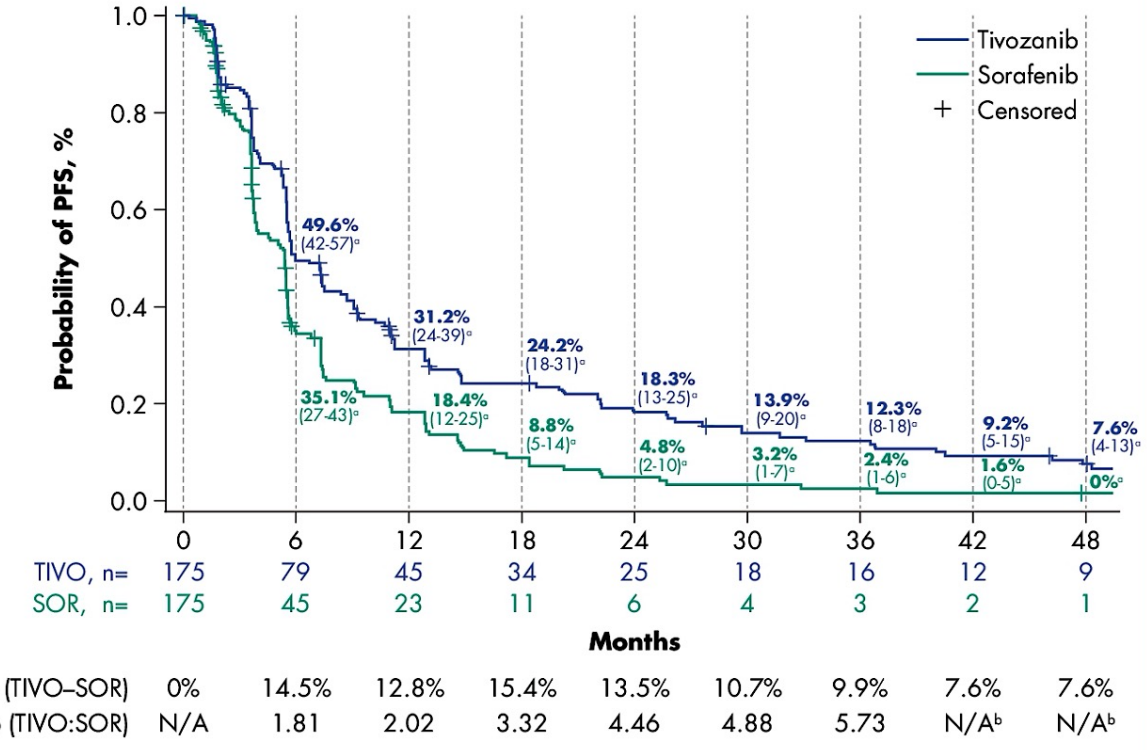
Primary Endpoint: PFS



	Tivozanib N=170	Sorafenib N=159
Median, months	**5.6**	**3.9**
(95% CI)	(5.3-7.3)	(3.9-5.6)
HR	**0.73**	
(95% CI)	(0.56, 0.94)	
P-value by stratified log rank	0.0165	

Primary PFS endpoint final analyses, Oct 4, 2018

Figure 2. Landmark Rates (95% CI) of LT-PFS in TIVO-3: TIVO vs SOR



TIVO, n=	175	79	45	34	25	18	16	12	9
SOR, n=	175	45	23	11	6	4	3	2	1

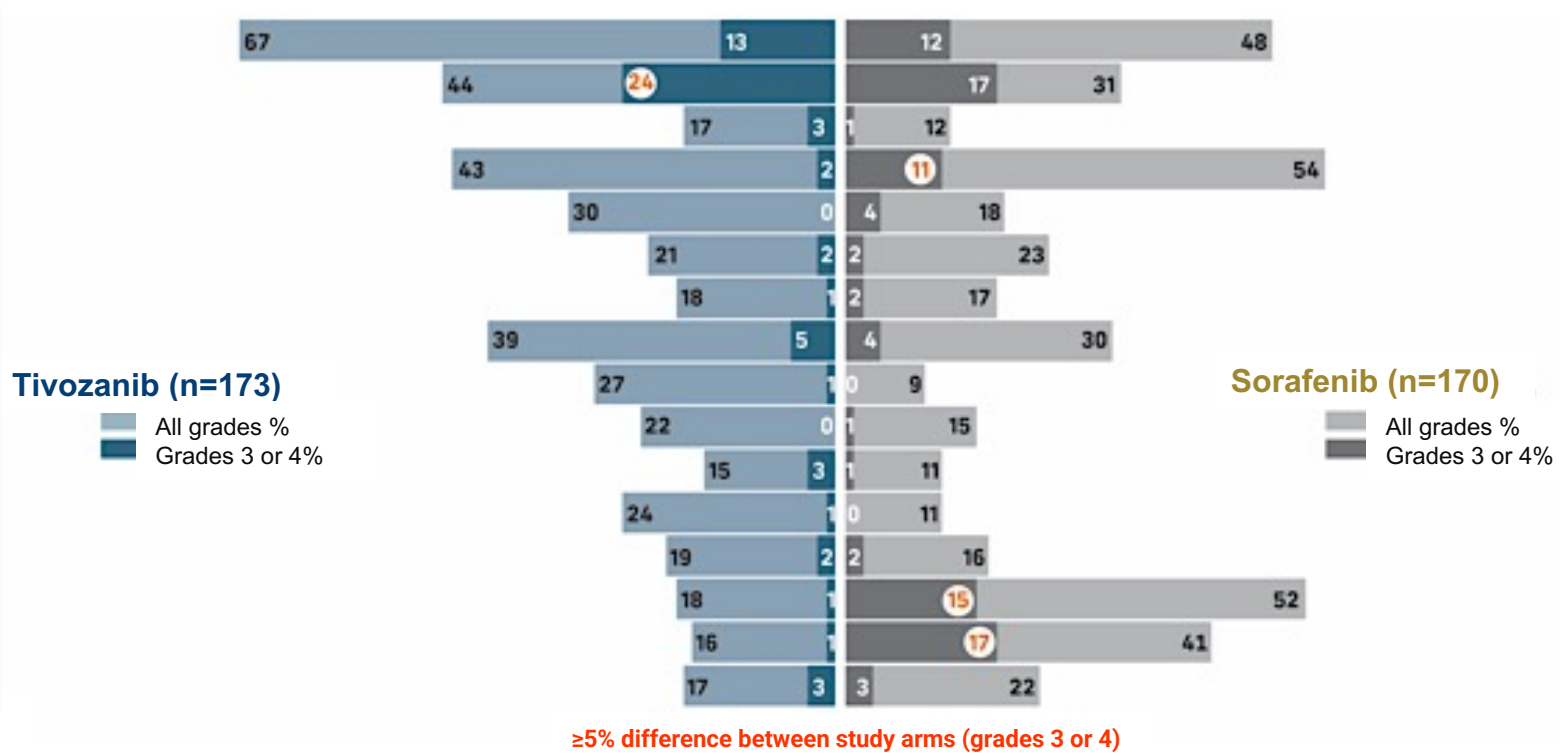
LT-PFS Δ (TIVO–SOR)	0%	14.5%	12.8%	15.4%	13.5%	10.7%	9.9%	7.6%	7.6%
Odds ratio (TIVO:SOR)	N/A	1.81	2.02	3.32	4.46	4.88	5.73	N/Aᵇ	N/Aᵇ

ᵃ% (95% CI). ᵇOR not calculated at months 42 and 48 due to insufficient number at risk.

HR, 0.624 (95% CI, 0.49-0.79); log-rank *P*<.0001

Rini BI et al *Lancet Oncol* 2020;21(1):95-104. Atkins MB et al. ASCO GU 2022;Abstract 362.

Adverse Reactions in ≥ 15% of Patients



Most common Grade 3 and 4 laboratory abnormalities (≥5%) were sodium decreased, lipase increased, phosphate decreased, and lymphocytes decreased

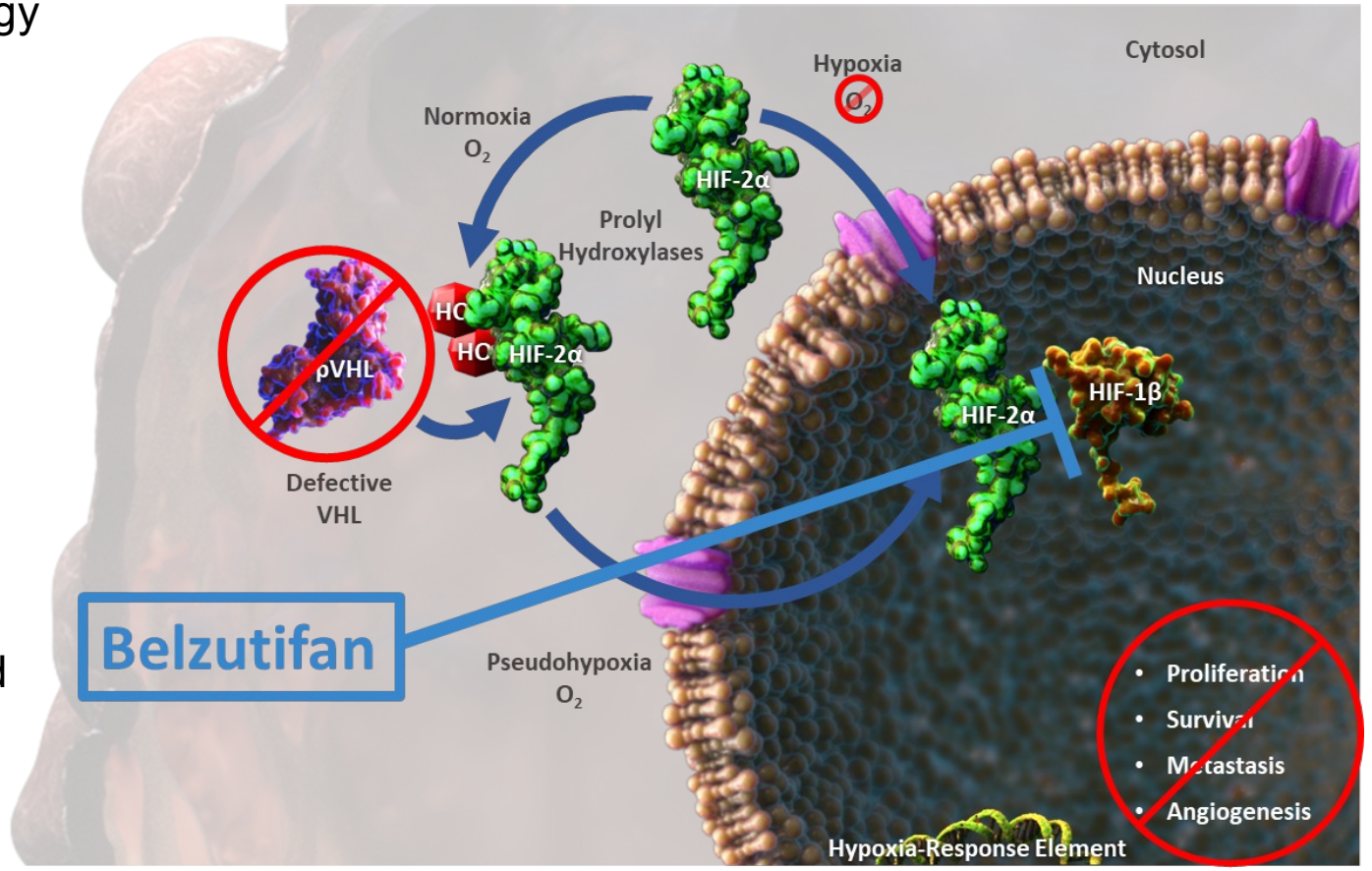
PPE, palmar-plantar erythrodysesthesia

*Includes hypertension, blood pressure increased, hypertensive crisis
†Includes hematuria, epistaxis, hemoptysis, hematoma, rectal hemorrhage, vaginal hemorrhage, confusion, gastrointestinal hemorrhage, hematochezia, intraocular hemorrhage, melena, metrorhaggia, pulmonary hemorrhage, subdural hemorrhage, gingival bleeding, hematemesis, hemorrhage intracranial, hemorrhoidal hemorrhage, splinter hemorrhage,
±Includes diarrhea and frequent bowel movements
§Includes hypothyroidism, blood thyroid stimulating hormone increase, tri-iodothyronine decreased, tri-iodothyronine free decreased
¶Includes dermatitis, dermatitis acneform, dermatitis contact, drug eruption, erythema multiforme, photosensitivity reaction, pruritus, psoriasis, rash, rash erythematous, rash generalized, rash macular, rash maculo-popular, rash morbilliform, rash pruritic, seborrheic, skin exfoliation, skin irritation, skin lesion, swelling face, toxic skin eruption, urticaria

Tivozanib [package insert]. March 2021

HIF-2α Inhibition in Renal Cell Carcinoma

- The HIF pathway is central to the pathophysiology of clear cell renal cell carcinoma (ccRCC) and von Hippel-Lindau (VHL) disease
- Belzutifan, a model of bench to bedside development, is a first-in-class oral HIF-2α inhibitor that blocks heterodimerization with HIF-1β and downstream oncogenic pathways[1,2]
  - Approved in the US for certain VHL disease-associated RCC, pNET and CNS-HB
  - Demonstrated clinical activity in pretreated advanced ccRCC[2-5]

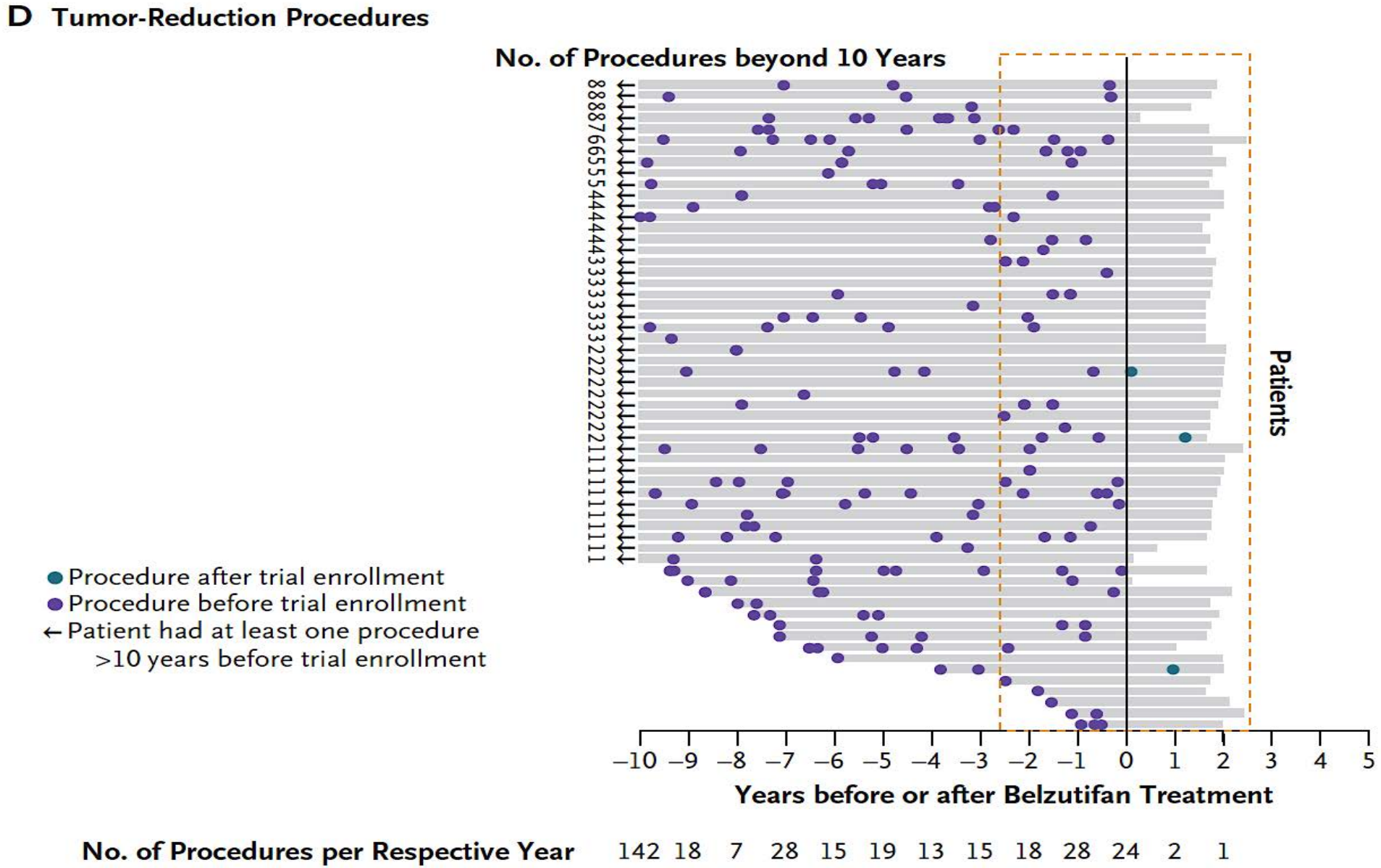


Albiges, et al. ESMO 2023.

CNS-HB, central nervous system hemangioblastoma; pNET, pancreatic neuroendocrine tumor; VEGFR-TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor.

1. Jonasch et al. *New Eng J Med* 2021;385:2036-2046; 2. Choueiri et al. *Nat Med* 2021;27:802-805; 3. Agarwal et al. ESMO 2023; Presentation 1881O; 4. Choueiri et al. *Lancet Oncol* 2023;24:553-562; 5. Choueiri et al. ESMO 2023; Presentation LBA87.

Belzutifan in VHL Syndrome



Jonasch and Srinivasan *NEJM* 2021

LITESPARK-005 Study (NCT04195750)

Key Eligibility Criteria

- Unresectable, locally advanced or metastatic clear cell RCC
- Disease progression after 1-3 prior systemic regimens, including ≥1 anti−PD-(L)1 mAb and ≥1 VEGFR-TKI
- Karnofsky Performance Status score ≥70%

Stratification Factors

- IMDC prognostic score[a]: 0 vs 1-2 vs 3-6
- Prior VEGF/VEGFR-targeted therapies: 1 vs 2-3

Dual Primary Endpoints:

- PFS per RECIST 1.1 by BICR
- OS

Key Secondary Endpoint:

- ORR per RECIST 1.1 by BICR

Other Secondary Endpoints Include:

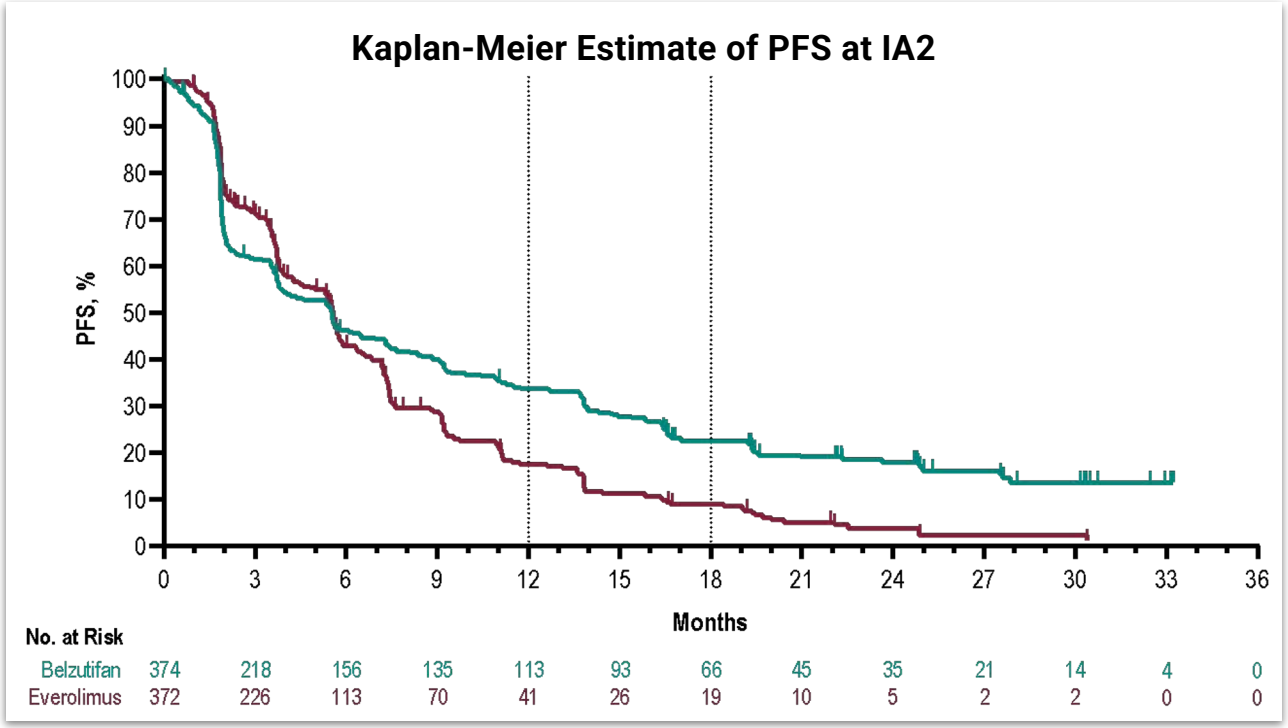
- DOR per RECIST 1.1 by BICR
- Safety
- Time to deterioration in FKSI-DRS and EORTC QLQ-C30 GHS/QoL

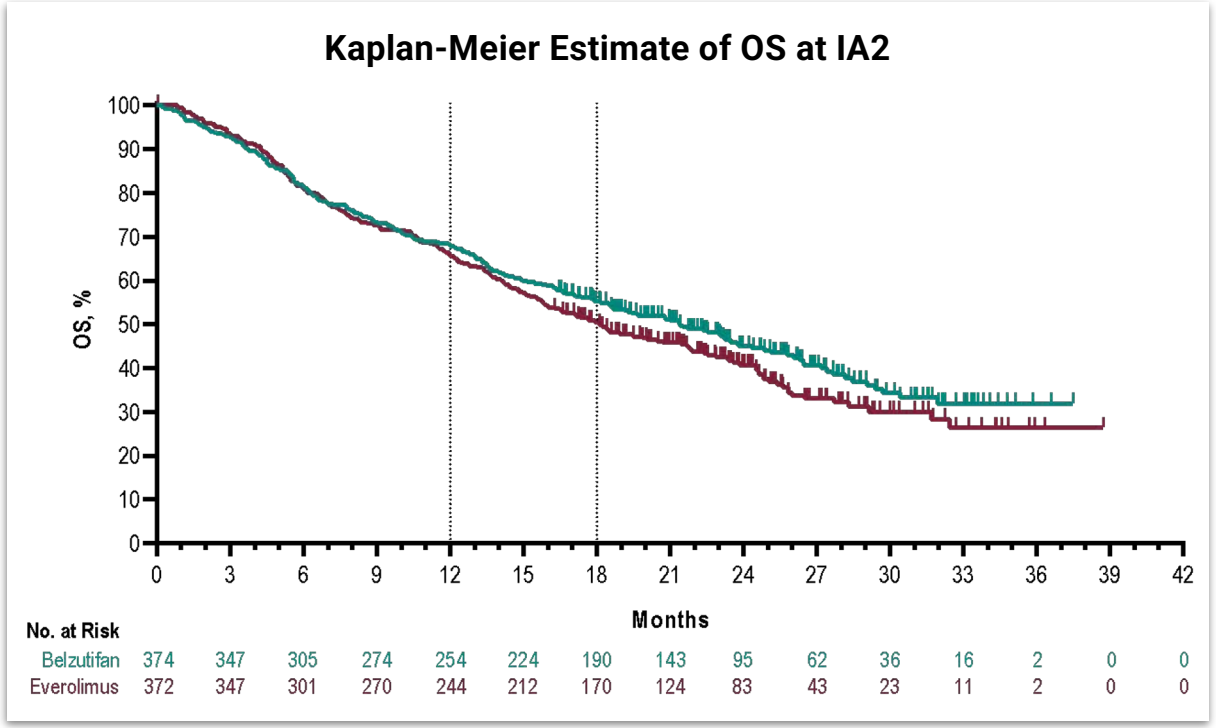
[a] Based on the number of present risk factors according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC).

BICR, blinded independent central review; DOR, duration of response; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index – Disease-Related Symptoms; GHS, global health status; mAb, monoclonal antibody; QoL, quality of life.

Albiges, et al. ESMO 2023.

Belzutifan versus everolimus





	IA2	
	Belzutifan	Everolimus
Events	289 (77.3%)	276 (74.2%)
Median, mo (95% CI)	5.6 (3.8-6.5)	5.6 (4.8-5.8)
HR (95% CI)	**0.74 (0.63-0.88)**	

	IA2	
	Belzutifan	Everolimus
Events	213 (57.0%)	228 (61.3%)
Median, mo (95% CI)	21.4 (18.2-24.3)	18.1 (15.8-21.8)
HR (95% CI)	**0.88 (0.73-1.07); *P*=.099**	

Albiges, et al. ESMO 2023.

All-Cause AEs in ≥15% of Treated Patients in Either Arm[1]

AE, n (%)	Belzutifan n = 372		Everolimus n = 360	
	All Grade	Grade 3-5	All Grade	Grade 3-5
Any AE	369 (99.2)	230 (61.8)	357 (99.2)	225 (62.5)
Anemia	308 (82.8)	121 (32.5)	204 (56.7)	65 (18.1)
Fatigue	117 (31.5)	6 (1.6)	91 (25.3)	13 (3.6)
Nausea	67 (18.0)	2 (0.5)	41 (11.4)	1 (0.3)
Constipation	62 (16.7)	0	29 (8.1)	0
Peripheral edema	60 (16.1)	0	61 (16.9)	1 (0.3)
Dyspnea	56 (15.1)	6 (1.6)	51 (14.2)	10 (2.8)
Asthenia	54 (14.5)	7 (1.9)	61 (16.9)	0
Decreased appetite	54 (14.5)	4 (1.1)	57 (15.8)	0
Diarrhea	44 (11.8)	4 (1.1)	71 (19.7)	4 (1.1)
Cough	31 (8.3)	0	74 (20.6)	0
Pruritus	29 (7.8)	0	60 (16.7)	0
Rash	17 (4.6)	0	68 (18.9)	5 (1.4)
Stomatitis	13 (3.5)	0	136 (37.8)	12 (3.3)
Hyperglycemia	10 (2.7)	2 (0.5)	54 (15.0)	20 (5.6)

1. Albiges L et al. *Ann Oncol*. 2023;34:S1329-S1330. Data cutoff date for IA2: June 13, 2023.

Tivozanib versus belzutifan for refractory RCC

	Tivozanib (n=175)	Belzutifan (n=374)
Population	0% second line 62% third line 38% fourth line	12% second line 42% third line 45% fourth line
IMDC	19%/62%/18%	21%/67%/12%
ORR	18%	23%
PFS	5.6 months	5.6 months
PFS HR	0.73 vs sorafenib	0.74 vs everolimus
Landmark PFS	24% at 18 months	23% at 18 months
Grade 3-5 TRAEs	46%	39%

Conclusions

- IO-based doublets are SOC in front-line metastatic RCC with no reliable biomarker. Various clinical selection strategies have been tested with limited success to date.

- Refractory RCC
  - IO after IO is not active until proven otherwise
  - Several non-curative options exist, and selection is based on several factors including toxicity, bulk/pace of disease, physician familiarity.
  - Tivozanib has activity in 3rd/4th line and was the first positive trial in that setting.
  - Belzutifan has revolutionized VHL-associated RCC management and has activity in refractory, sporadic RCC

Agenda

Module 1: Current Management of Metastatic Clear Cell Renal Cell Carcinoma (RCC) — Dr Rini

Module 2: Treatment Approaches for Nonmetastatic RCC; Optimal Care of Patients with Non-Clear Cell RCC — Dr Jonasch

Treatment Approaches for Nonmetastatic RCC; Optimal Care of Patients with Non-Clear Cell RCC; Latest in the Treatment of VHL Disase

Eric Jonasch, MD
Professor
Department of GU Medical Oncology
UT MD Anderson Cancer Center

Disclosures

Consulting Agreements	Aveo Pharmaceuticals, Eisai Inc, Exelixis Inc, GSK, Ipsen Biopharmaceuticals Inc, Merck, Nikang Therapeutics Inc, Novartis, Takeda Pharmaceuticals USA Inc, Telix Pharmaceuticals Limited
Contracted Research	Arrowhead Pharmaceuticals, Aveo Pharmaceuticals, Corvus Pharmaceuticals, Merck, Nikang Therapeutics Inc, Novartis, Telix Pharmaceuticals Limited
Data and Safety Monitoring Board/Committee	Pfizer Inc

65-year-old female diagnosed with RCC

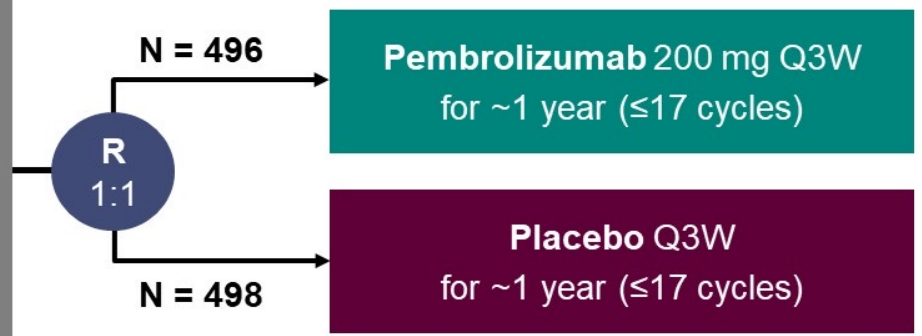
- Incidental finding of a left renal mass during workup for GERD.
- Underwent left nephrectomy revealing a 9.7cm clear cell renal cell carcinoma, Fuhrman grade 4, with extracapsular extension and renal vein invasion.
- Probability of recurrence at two years based on ASSURE nomogram is around 35 percent.
- You discuss adjuvant treatment options with patient, including recent data on KEYNOTE-564, a study testing adjuvant pembrolizumab

Advances in Adjuvant Therapy for RCC

KEYNOTE-564 Study (NCT03142334)

Key Eligibility Criteria

- Histologically confirmed clear cell RCC with no prior systemic therapy
- Surgery ≤12 weeks prior to randomization
- Postnephrectomy intermediate-high risk of recurrence (M0):
  - pT2, grade 4 or sarcomatoid, N0
  - pT3, any grade, N0
- Postnephrectomy high risk of recurrence (M0):
  - pT4, any grade, N0
  - Any pT, any grade, N+
- Postnephrectomy + complete resection of metastasis (M1 NED)
- ECOG PS 0 or 1



Stratification Factors

- M stage (M0 vs. M1 NED)
- M0 group further stratified:
  - ECOG PS 0 vs. 1
  - US vs. non-US

Primary Endpoint

- Disease-free survival by investigator

Key Secondary Endpoint

- Overall survival

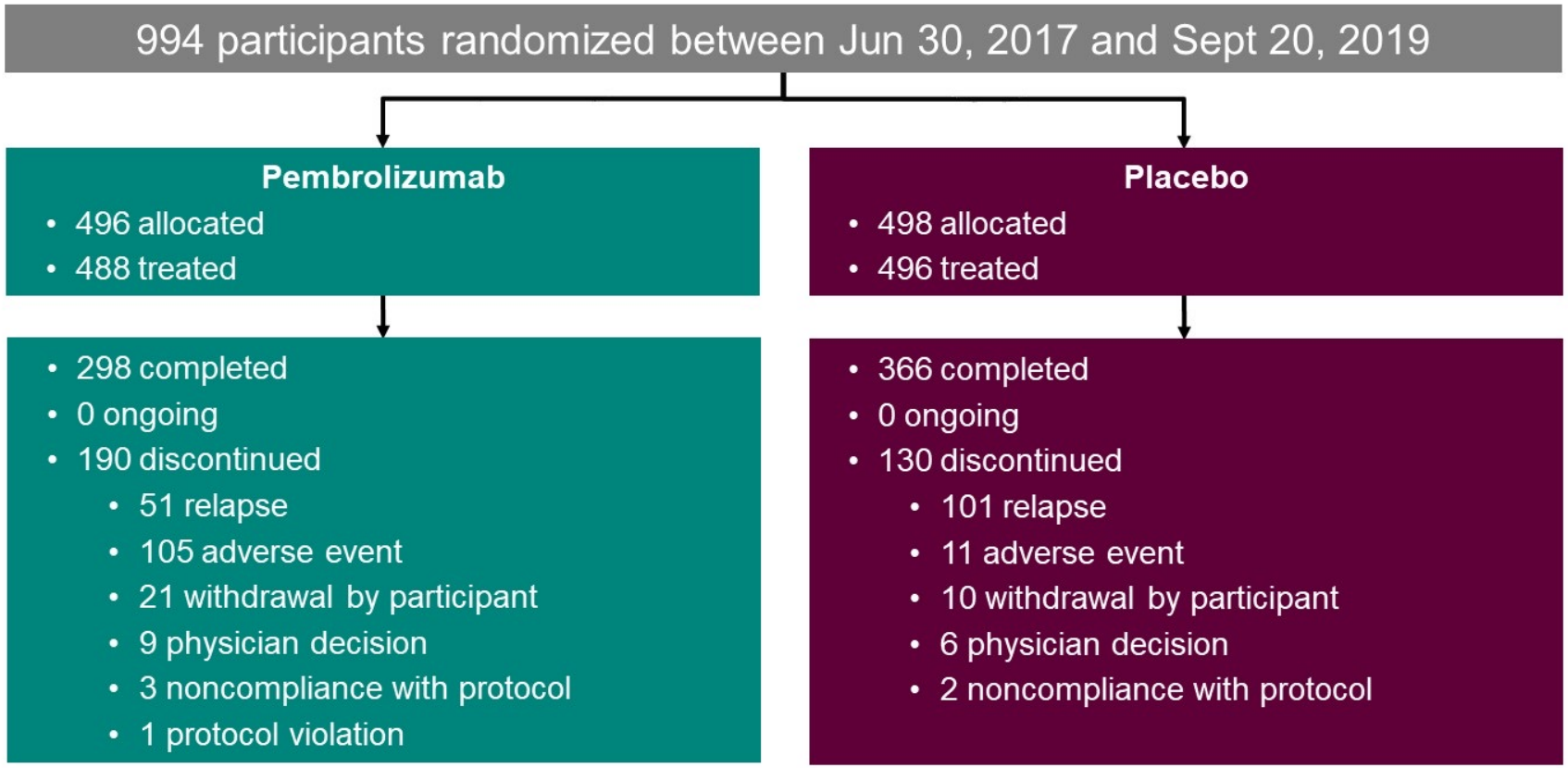
Other Secondary Endpoint

- Safety

NED, no evidence of disease.

Choueiri TK et al. ASCO GU 2024;Abstract LBA359.

Participant Disposition



- Median time from randomization to data cutoff date was 57.2 months (range, 47.9–74.5)
- As of December 2020, all participants had completed or discontinued study therapy

Data cutoff date: September 15, 2023.

Choueiri TK et al. ASCO GU 2024;Abstract LBA359.

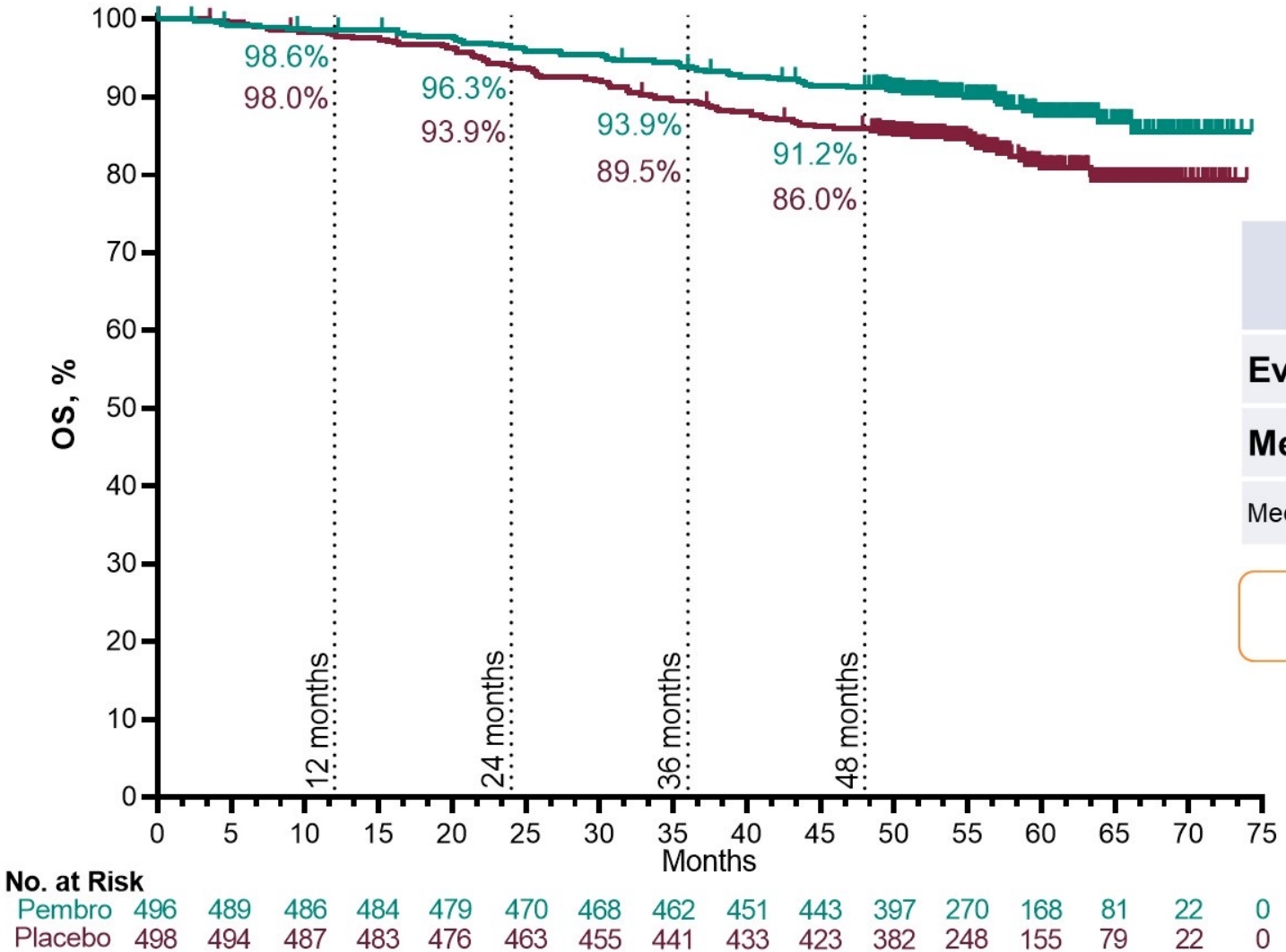
Baseline Characteristics

	Pembrolizumab (N = 496)	Placebo (N = 498)
Age, median (range), yrs	60 (27–81)	60 (25–84)
Male	70.0%	72.1%
ECOG performance status of 0	84.9%	85.5%
Region		
United States (US)	23.0%	23.5%
Outside US	77.0%	76.5%
M stage		
M0	94.2%	94.4%
M1	5.8%	5.6%
Disease risk category[a]		
M0 intermediate-high risk	85.1%	86.9%
M0 high risk	8.1%	7.4%
M1 NED	5.8%	5.6%
Sarcomatoid features		
Present	10.5%	11.8%
Absent	83.5%	83.3%
Unknown	6.0%	4.8%
PD-L1 status[b]		
CPS <1	25.0%	22.7%
CPS ≥1	73.6%	76.9%
Missing	1.4%	0.4%

[a]Another 1.0% of pts in the pembro group and 0% in the placebo group had T2 (grade ≤3) N0 M0 or T1 N0 M0 disease (protocol violations). [b]Assessed with PD-L1 IHC 22C3 pharmDx. PD-L1 combined positive score (CPS) is the # of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total # of viable tumor cells, multiplied by 100. Data cutoff date: September 15, 2023.

Choueiri TK et al. ASCO GU 2024;Abstract LBA359.

Overall Survival, Intention-to-Treat Population



	Pembro (N = 496)	Placebo (N = 498)
Events, n	55	86
Median, mo (95% CI)	NR (NR–NR)	NR (NR–NR)
Median follow-up was 57.2 months (range, 47.9–74.5)		

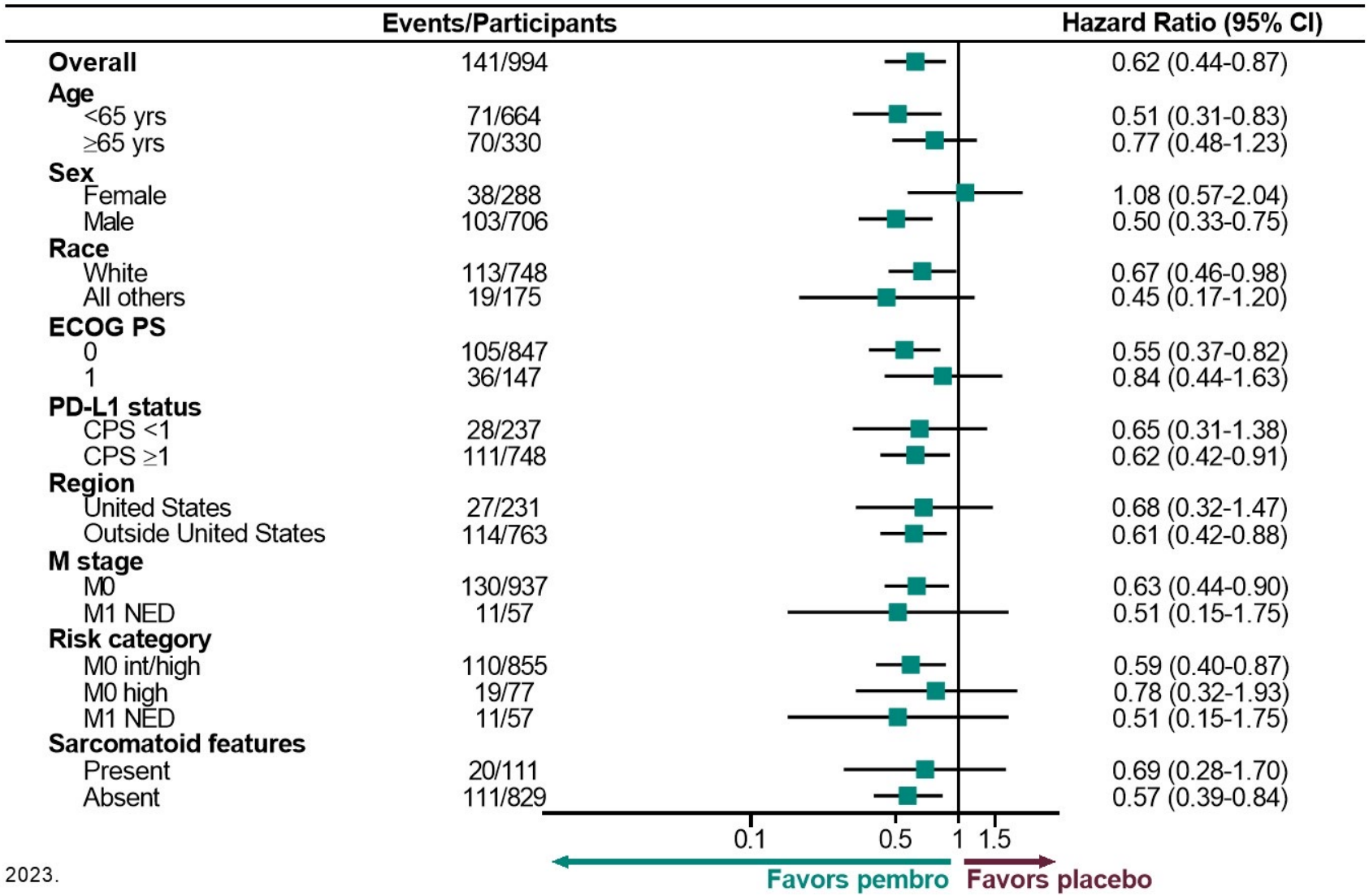
HR 0.62 (95% CI 0.44–0.87); *P* =.002*

* **denotes statistical significance**. P-value boundary for OS at IA3 was 0.0072 (1-sided) per Lan-DeMets O'Brien-Fleming spending approximation α-spending function. As this key secondary endpoint was formally met, any future OS analyses will be descriptive only.

Data cutoff date: September 15, 2023.

Choueiri TK et al. ASCO GU 2024;Abstract LBA359.

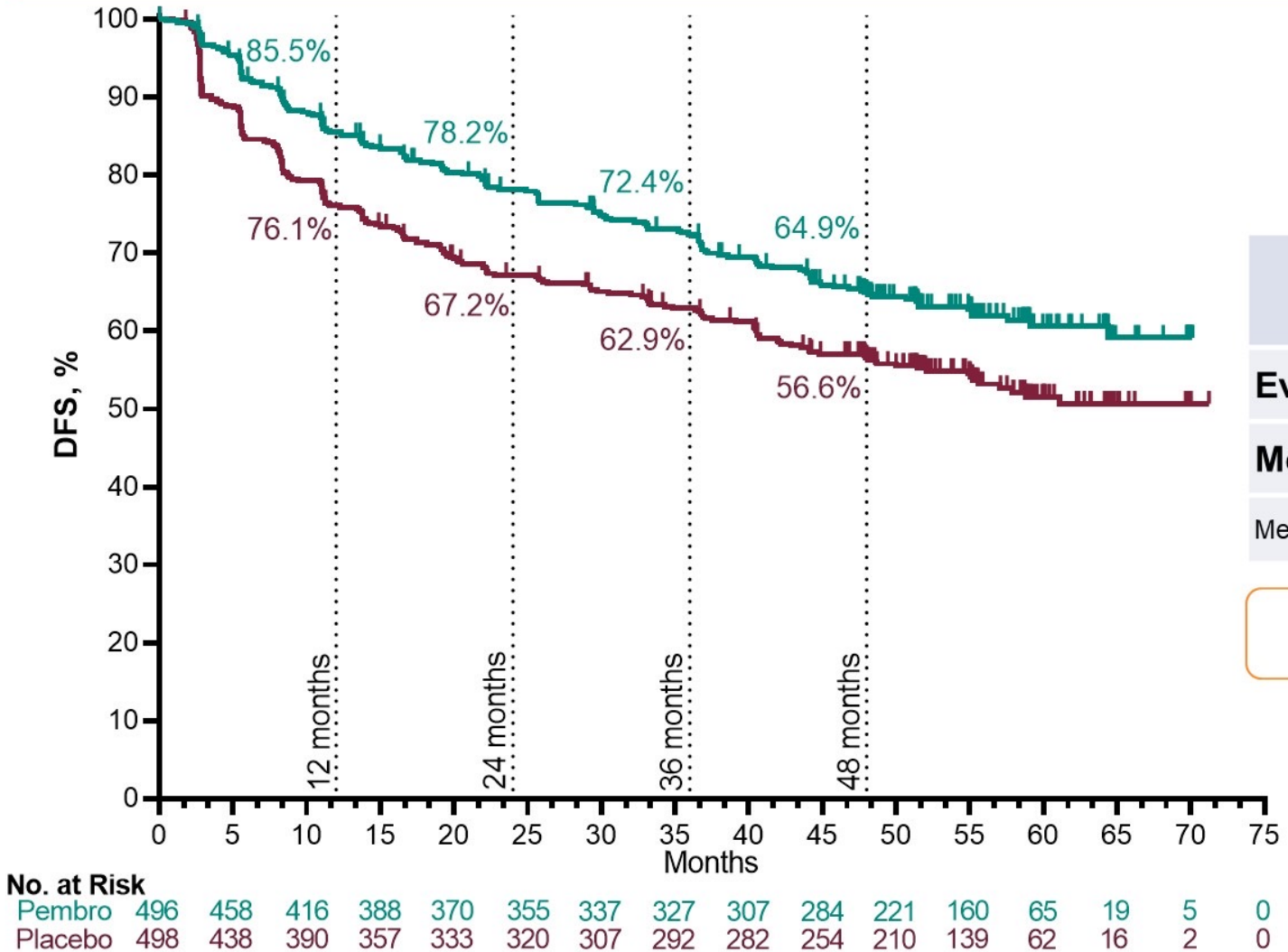
Overall Survival by Subgroups



Data cutoff date: September 15, 2023.

Choueiri TK et al. ASCO GU 2024;Abstract LBA359.

Updated Disease-Free Survival by Investigator, Intention-to-Treat Population



	Pembro (N = 496)	Placebo (N = 498)
Events, n	174	224
Median, mo (95% CI)	NR (NR–NR)	NR (54.9–NR)

Median follow-up was 57.2 months (range, 47.9–74.5)

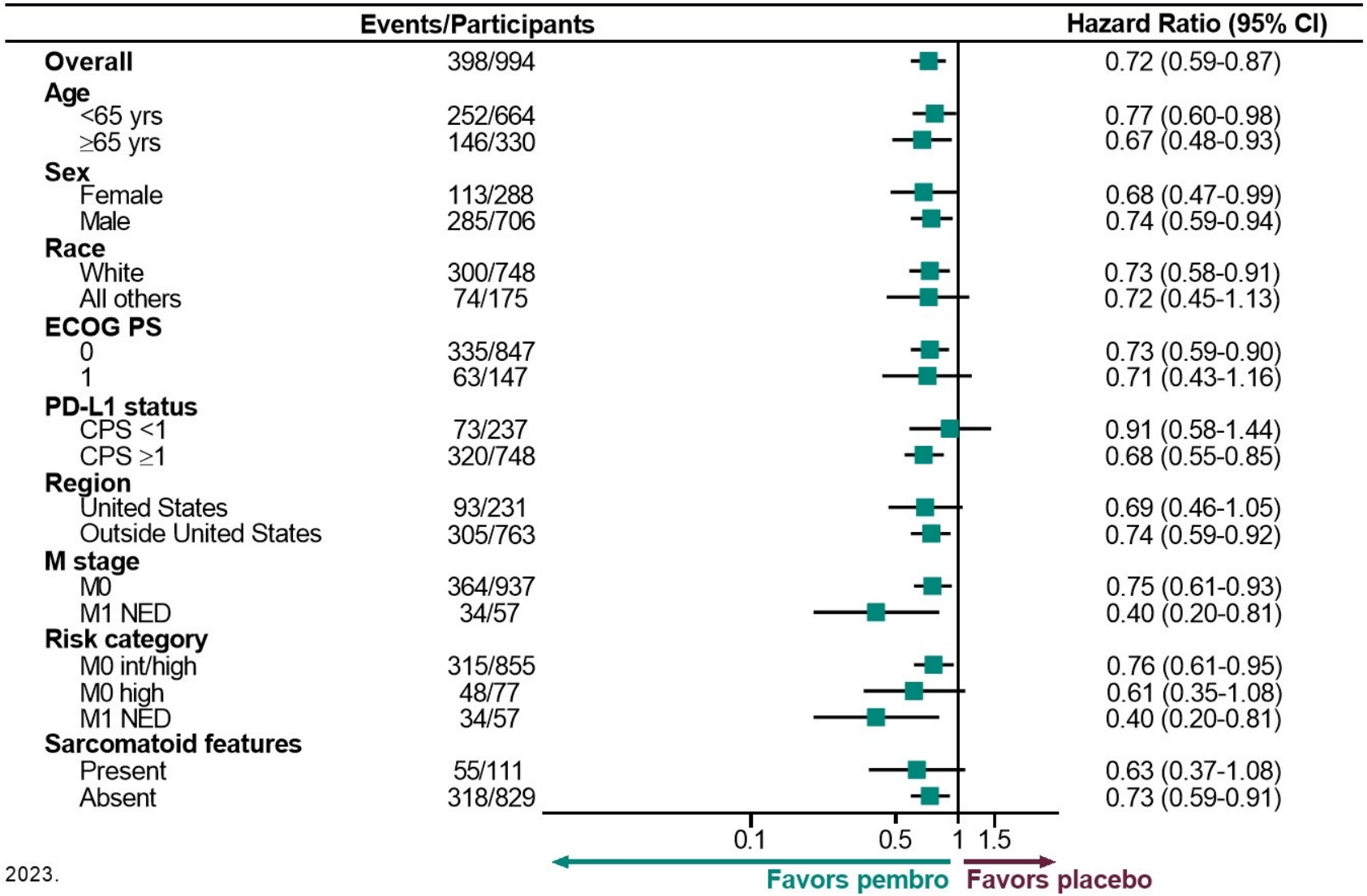
HR 0.72 (95% CI 0.59–0.87)

Primary DFS endpoint was met at IA1 and was not formally statistically tested thereafter.

Data cutoff date: September 15, 2023.

Choueiri TK et al. ASCO GU 2024;Abstract LBA359.

Disease-Free Survival by Subgroups

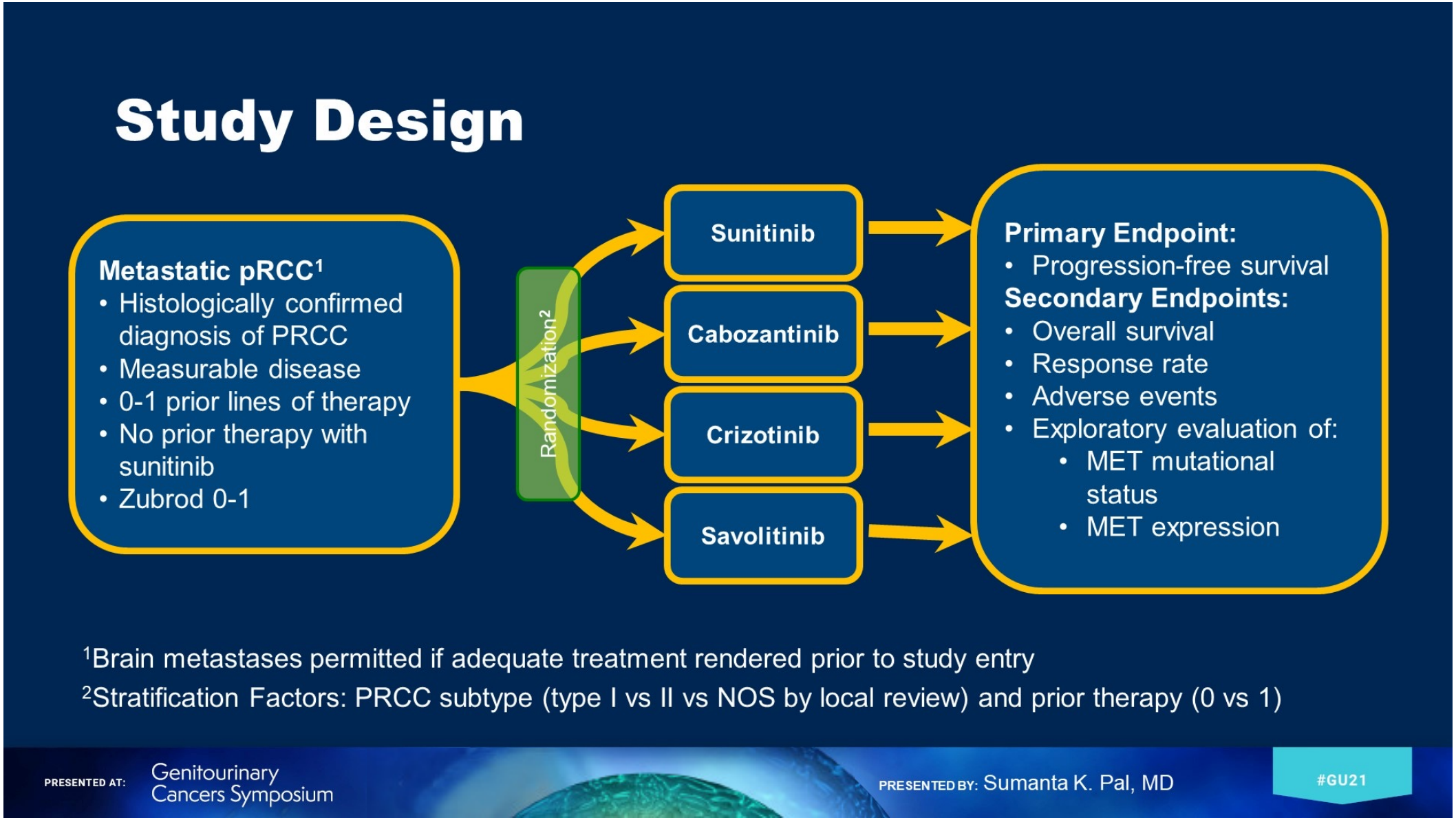


Data cutoff date: September 15, 2023.

Choueiri TK et al. ASCO GU 2024;Abstract LBA359.

Treatment of Non-Clear Cell RCC

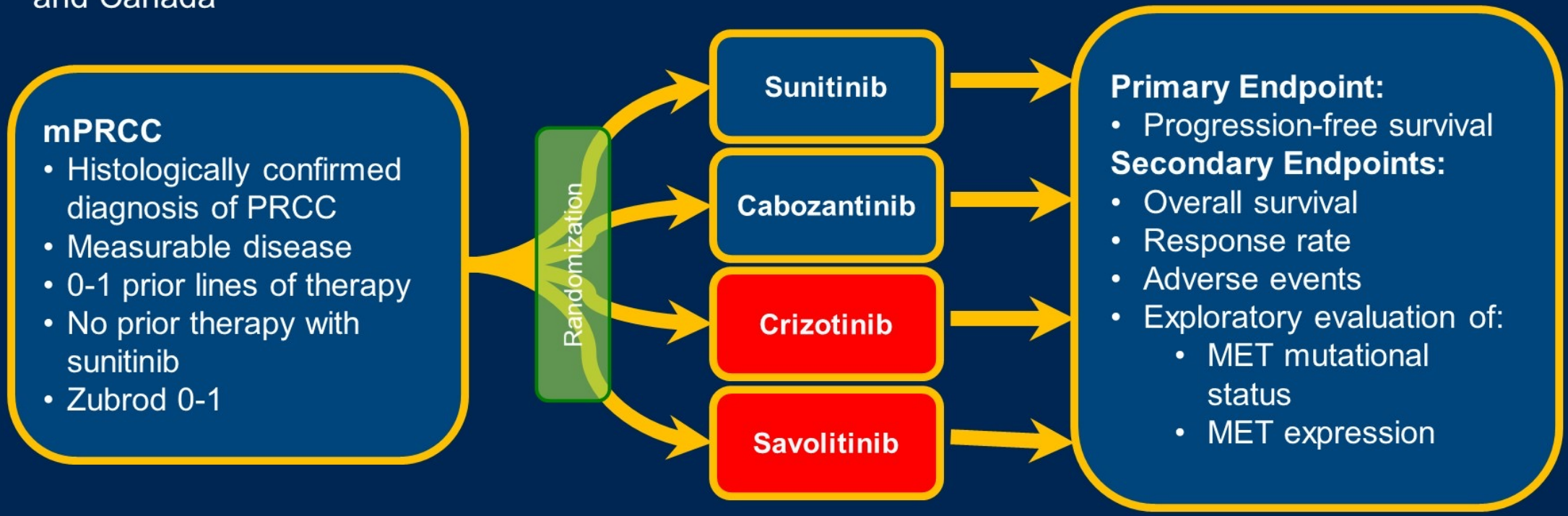
SWOG 1500 Study



Presented By Sumanta Pal at 2021 Genitourinary Cancers Symposium

Results: Accrual and Futility Analysis

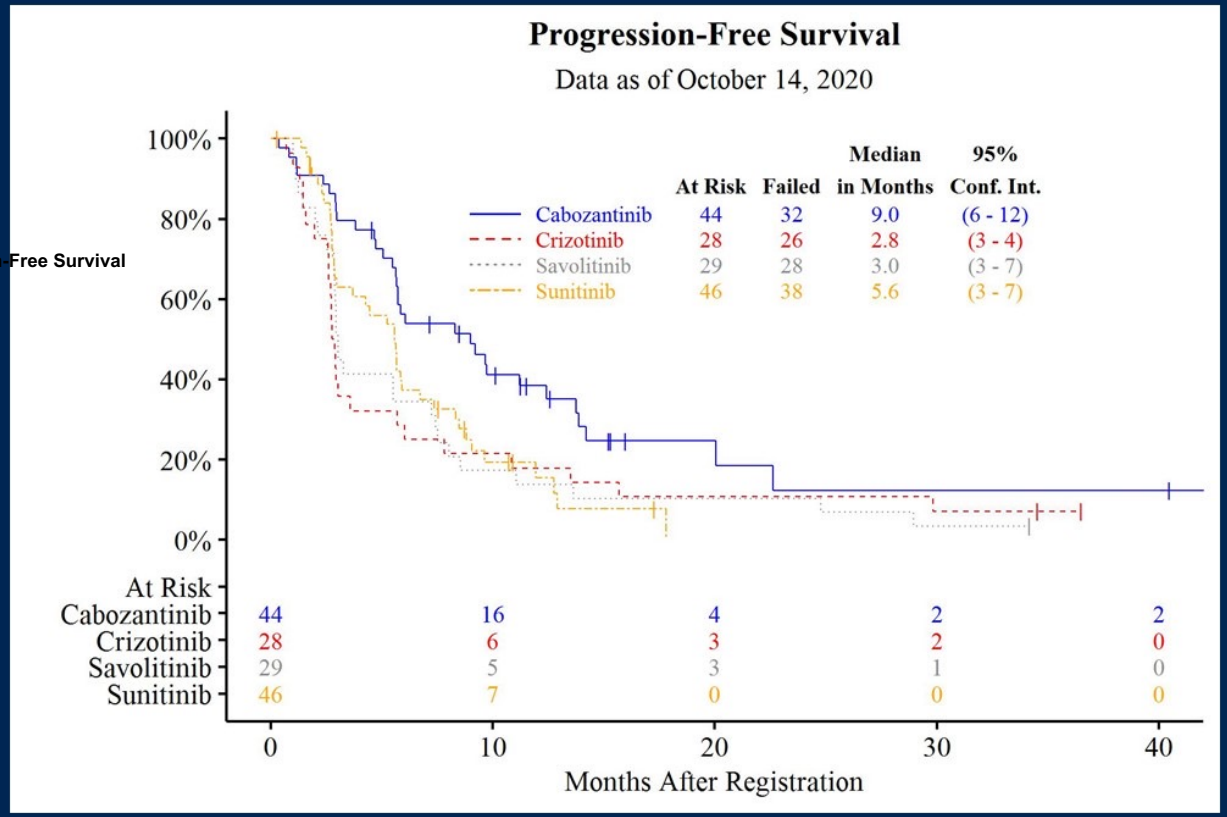
- From April 2016 to December 2019, 152 patients were enrolled at 65 centers throughout the US and Canada



- Savolitinib and crizotinib arms closed for futility in December of 2018

Presented By Sumanta Pal at 2021 Genitourinary Cancers Symposium

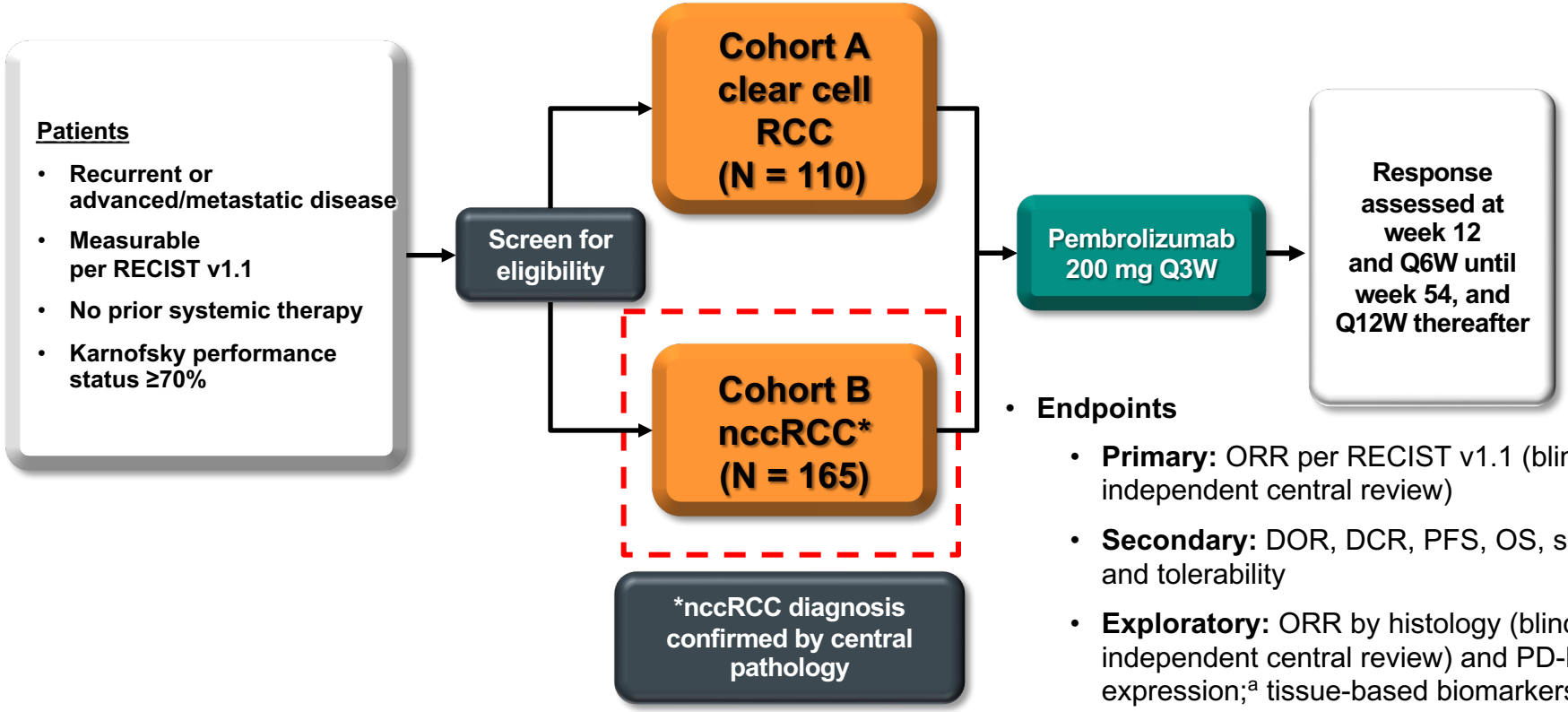
Results: Progression-Free Survival



Results: Progression-Free Survival

- Cabozantinib significantly prolonged PFS relative to sunitinib (HR 0.60 (95%CI 0.37-0.97 [1-sided P-value=0.019])

KEYNOTE-427- Frontline Pembrolizumab Monotherapy



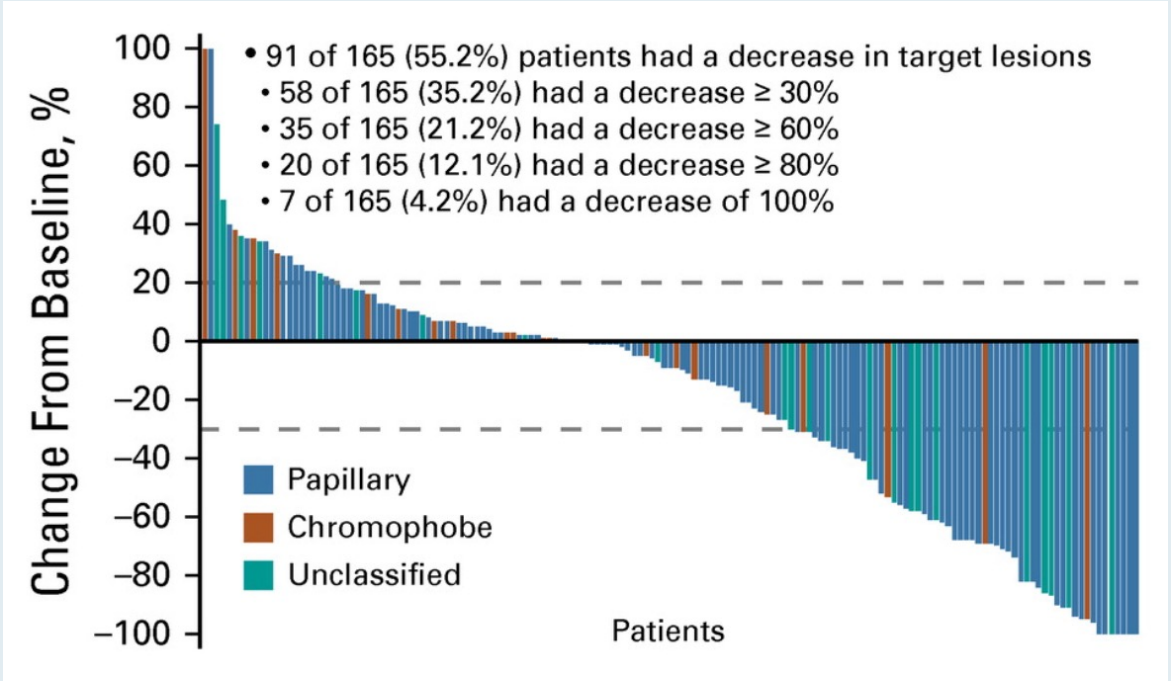
- **Endpoints**
  - **Primary:** ORR per RECIST v1.1 (blinded independent central review)
  - **Secondary:** DOR, DCR, PFS, OS, safety, and tolerability
  - **Exploratory:** ORR by histology (blinded independent central review) and PD-L1 expression;[a] tissue-based biomarkers (eg, IHC, RNA sequencing)

[a]PD-L1 positive defined as combined positive score [CPS] ≥1.

McDermott *et al, Journal of Clinical Oncology* 37, no. 7_suppl (March 1 2019) 546-546

KEYNOTE-427: Frontline Pembrolizumab Monotherapy

Parameter	Overall (N = 165)	RCC Histology		
		Papillary (n = 118)	Chromophobe (n = 21)	Unclassified (n = 26)
ORR, % (95% CI)	26.7 (20.1 to 34.1)	28.8 (20.8 to 37.9)	9.5 (1.2 to 30.4)	30.8 (14.3 to 51.8)
DCR (CR + PR + SD ≥ 6 mo), (95% CI)	43.0 (35.4 to 51.0)	47.5 (38.2 to 56.9)	33.3 (14.6 to 57.0)	30.8 (14.3 to 51.8)
Best response, n (%)				
CR	11 (6.7)	7 (5.9)	1 (4.8)	3 (11.5)
PR	33 (20.0)	27 (22.9)	1 (4.8)	5 (19.2)
SD	51 (30.9)	39 (33.1)	10 (47.6)	2 (7.7)
PD	60 (36.4)	38 (32.2)	9 (42.9)	13 (50.0)
Nonevaluable[a]	2 (1.2)	1 (0.8)	0 (0)	1 (3.8)
No assessment[b]	8 (4.8)	6 (5.1)	0 (0)	2 (7.7)



McDermott DF et al. *J Clin Oncol* 2021;39(9):1029-39.

KEYNOTE-B61 Study: Lenvatinib with Pembrolizumab for nccRCC

Key Eligibility Criteria

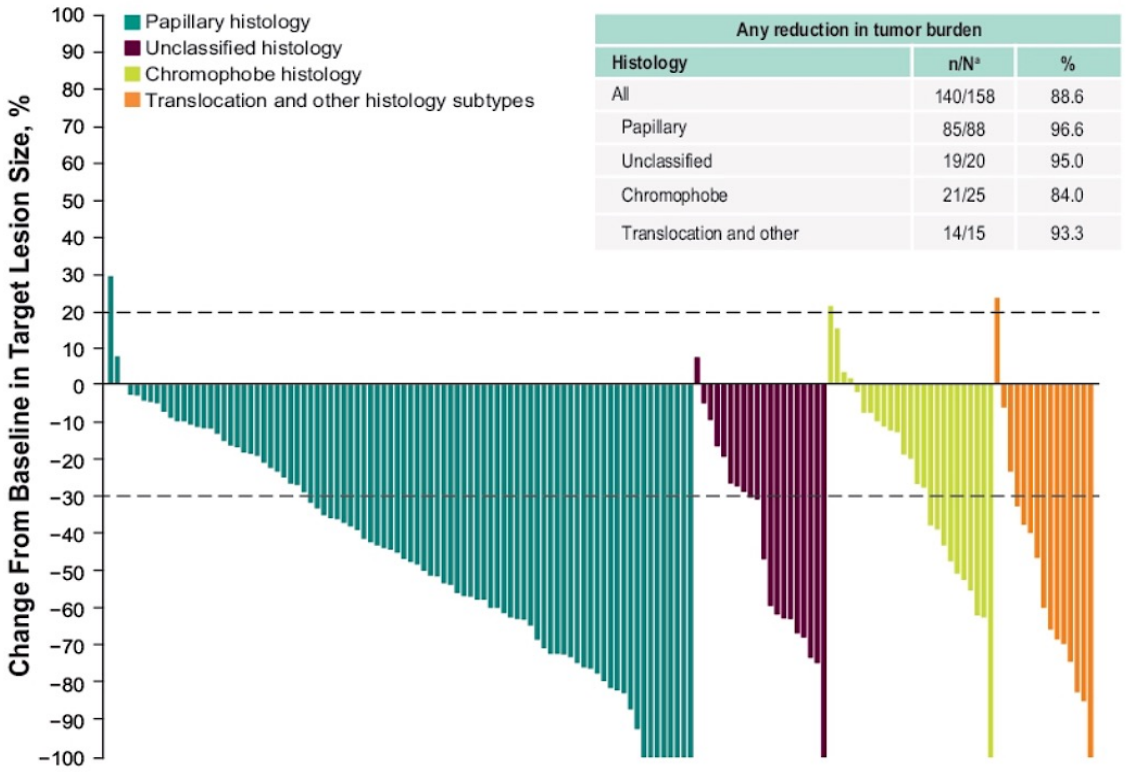
- Histologically confirmed diagnosis of non–clear cell RCC (per investigator)
- Locally advanced/metastatic disease
- No prior systemic therapy
- Measurable disease per RECIST v1.1
- Tumor tissue sample available
- KPS ≥70%

N = 158

Pembrolizumab 400 mg IV Q6W for ≤18 cycles (~2 years) + Lenvatinib 20 mg PO QD

Tumor Assessments

- 12 weeks from allocation then Q6W for 54 weeks then Q12W thereafter



Any reduction in tumor burden		
Histology	n/N[a]	%
All	140/158	88.6
Papillary	85/88	96.6
Unclassified	19/20	95.0
Chromophobe	21/25	84.0
Translocation and other	14/15	93.3

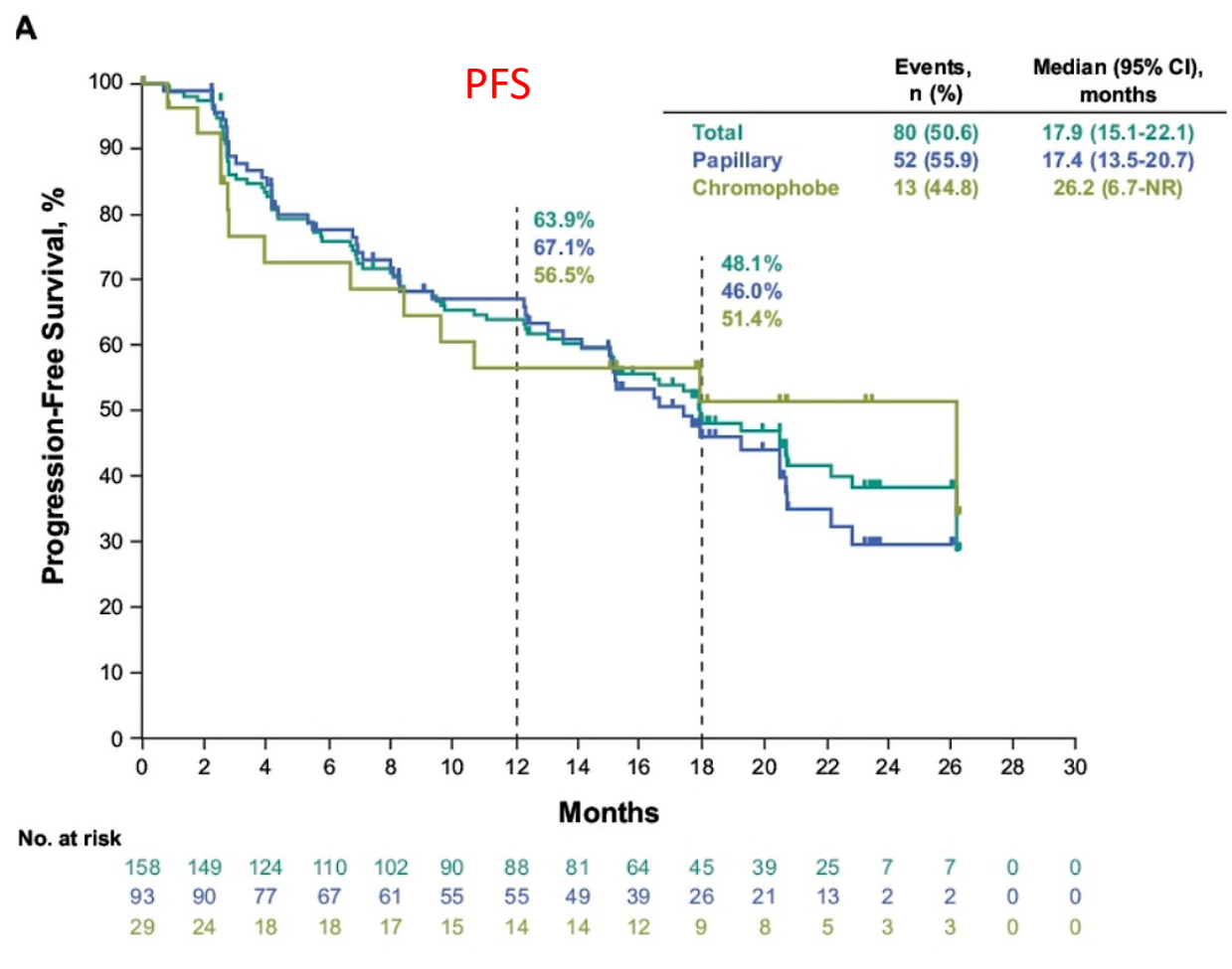
	Pembrolizumab + lenvatinib N = 158
ORR, % (95% CI)	50.6 (42.6-58.7)
DCR,[a] % (95% CI)	82.3 (75.4-87.9)
CBR,[b] % (95% CI)	71.5 (63.8-78.4)
Best overall response, n (%)	
CR	13 (8.2)
PR	67 (42.4)
SD	50 (31.6)
SD ≥6 months	33 (20.9)
PD	17 (10.8)
NE/NA[c]	11 (7.0)

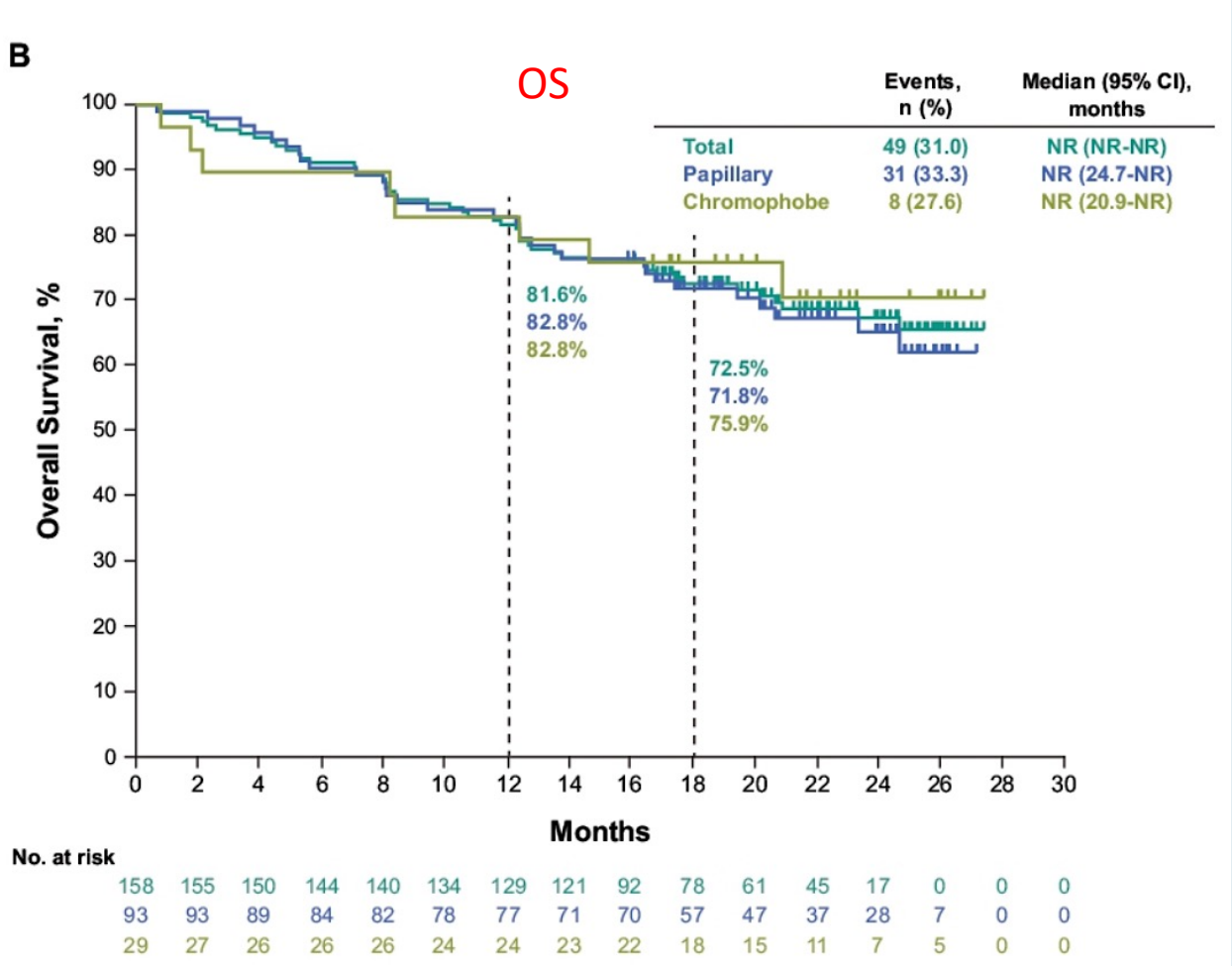
nccRCC = non-clear cell renal cell carcinoma; ORR = objective response rate; DCR = disease control rate; CBR = clinical benefit ratio; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE/NA = not evaluable/not assessed

Voss MH et al. Genitourinary Cancers Symposium 2024;Abstract 2.

RTP RESEARCH TO PRACTICE

KEYNOTE-B61 Study: Lenvatinib with Pembrolizumab — PFS/OS





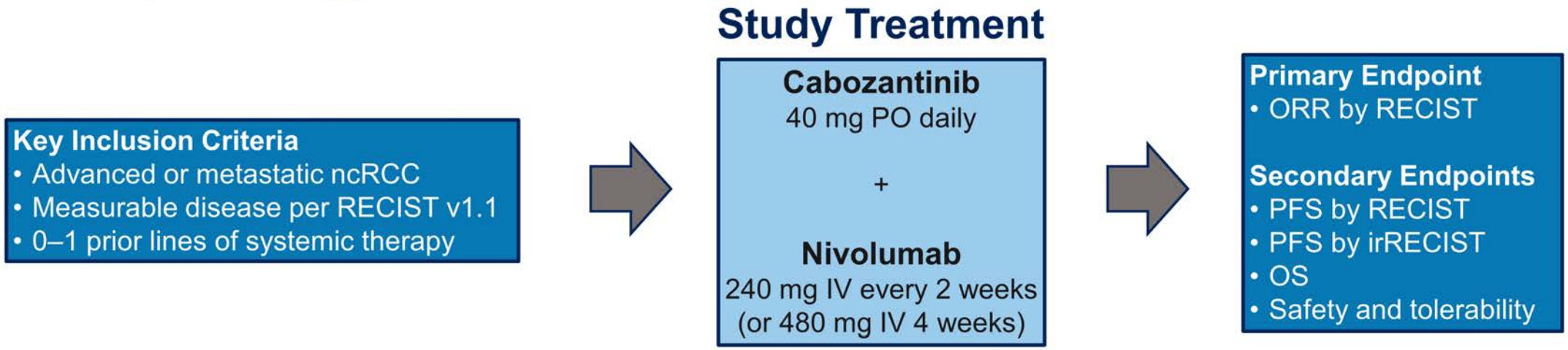
PFS = progression-free survival; OS = overall survival; NR = not reached

Voss MH et al. Genitourinary Cancers Symposium 2024;Abstract 2.

RTP RESEARCH TO PRACTICE

Cabozantinib plus Nivolumab in nccRCC

Study Design



This is a single center, open-label, phase 2 study (NCT03635892) including patients treated with 0 or 1 prior systemic therapies in non-clear cell RCC with select histologies[1]:

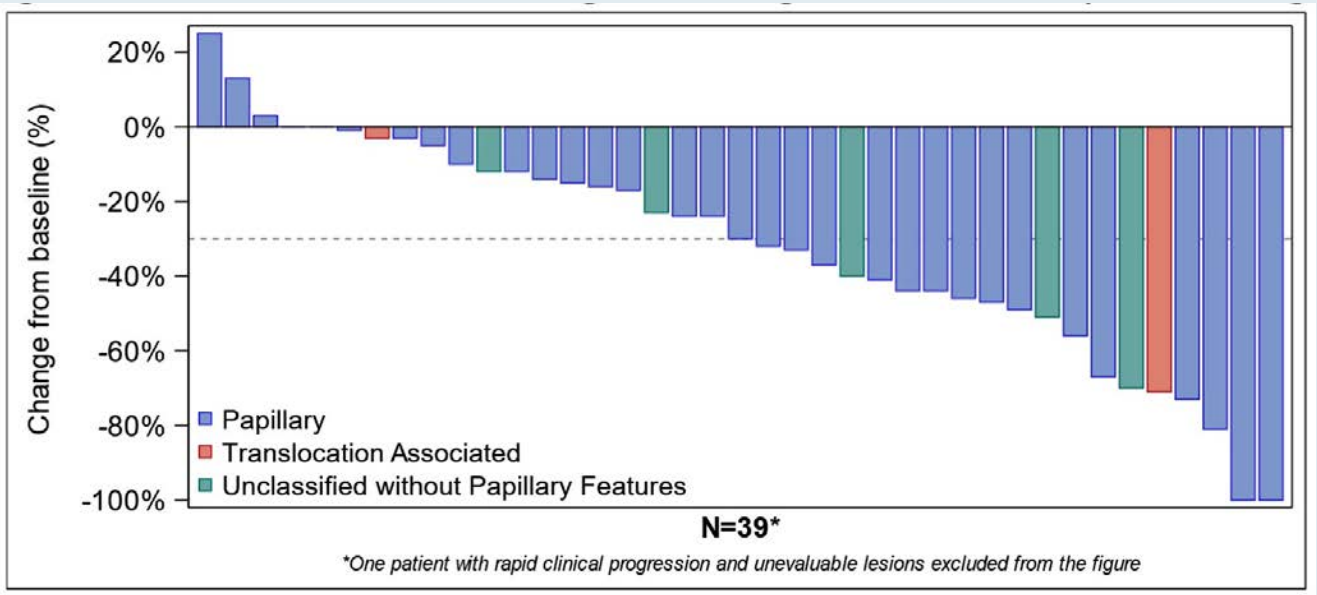
- Cohort 1: papillary[2], unclassified, or translocation-associated RCC (N=40)
- Cohort 2: chromophobe RCC (N=7)

Cohort 1 was a single-stage design that met its primary endpoint (N=20) and was expanded to produce more precise estimates of ORR (total N=40). Cohort 2 was a Simon two-stage design that closed early.

[1]Histopathology was prospectively reviewed at MSKCC and retrospectively reviewed/confirmed by dedicated GU pathologist (YC)
[2]Papillary included unclassified with papillary features, high grade/type 1 papillary, and FH-deficient/type 2 papillary

ncRCC, non-clear cell renal cell carcinoma, ORR, objective response rate; RECIST, Response Evaluation Criteria In Solid Tumors v1.1; irRECIST, immune-related Response Evaluation Criteria In Solid Tumors; PO, orally; IV, intravenously; PFS, progression-free survival; OS, overall survival

Cabozantinib with Nivolumab for nccRCC



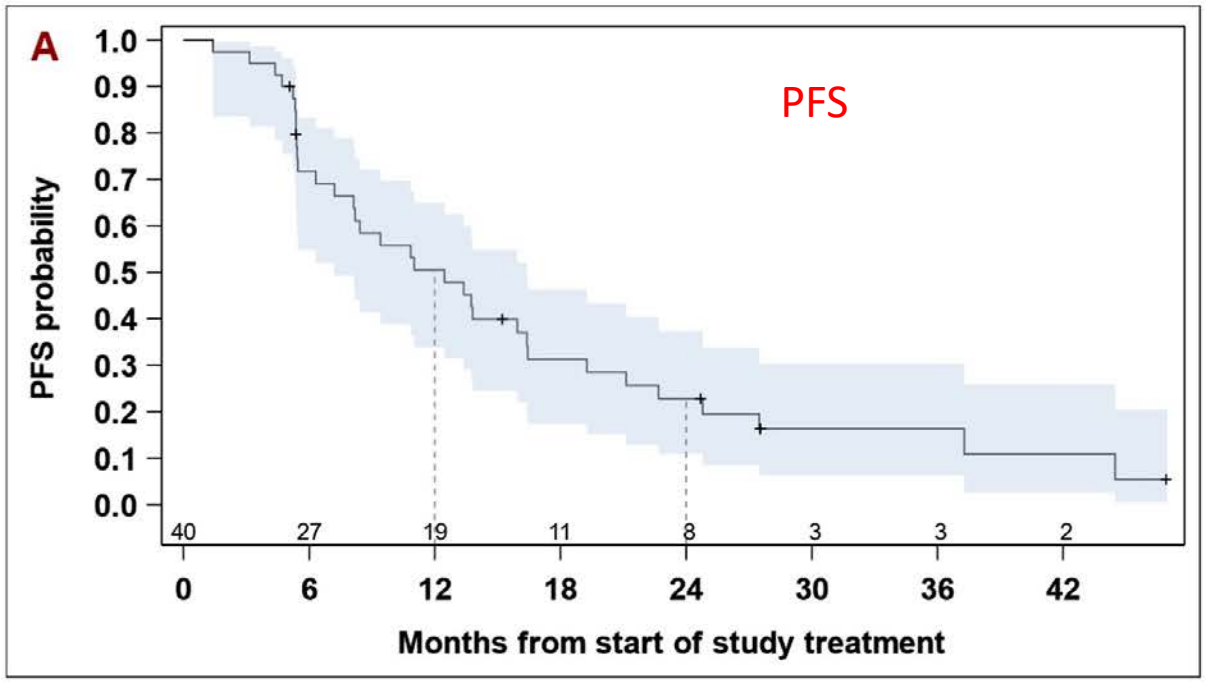
	1st line (any histology, N=26)	2nd line (any histology, N=14)	Papillary* (32)	Unclassified w/o papillary features (6)	Translocation-assoc. (2)
ORR	54% (33, 73)	36% (13, 65)	47% (30, 64)	50% (12, 88)	50% (1, 99)
CR	1 (4%)	0	1 (3%)	0	0
PR	13 (50%)	5 (36%)	14 (44%)	3 (50%)	1 (50%)
SD	12 (46%)	7 (50%)	16 (50%)	2 (33%)	1 (50%)
PD	0	2 (14%)	1 (3%)	1 (17%)	0
Med. PFS, months (95% CI)	11 (7, 19)	13 (5, 16)	13 (7, 16)	8 (1, *NE*)	14 (5, 23)

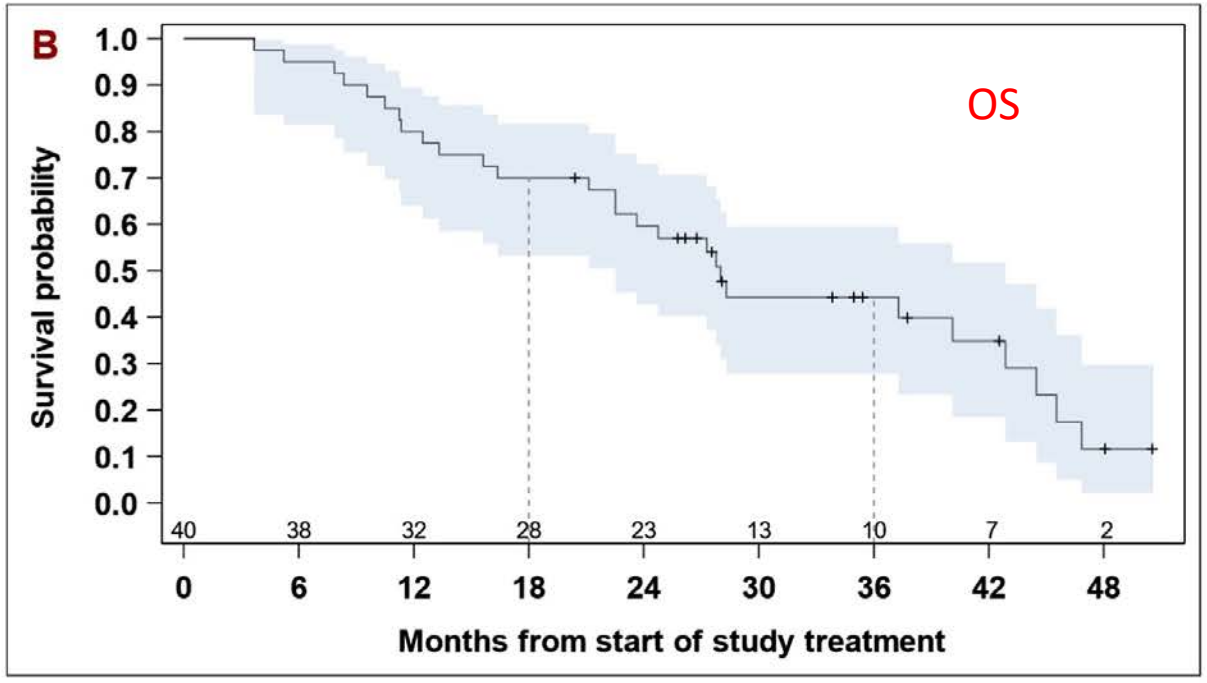
*Includes 16 unclassified with papillary features, 11 high grade papillary and 5 FH-deficient RCC.

Lee C-H et al. ASCO 2023;Abstract 4537.

RTP RESEARCH TO PRACTICE

Cabozantinib with Nivolumab for nccRCC — PFS and OS



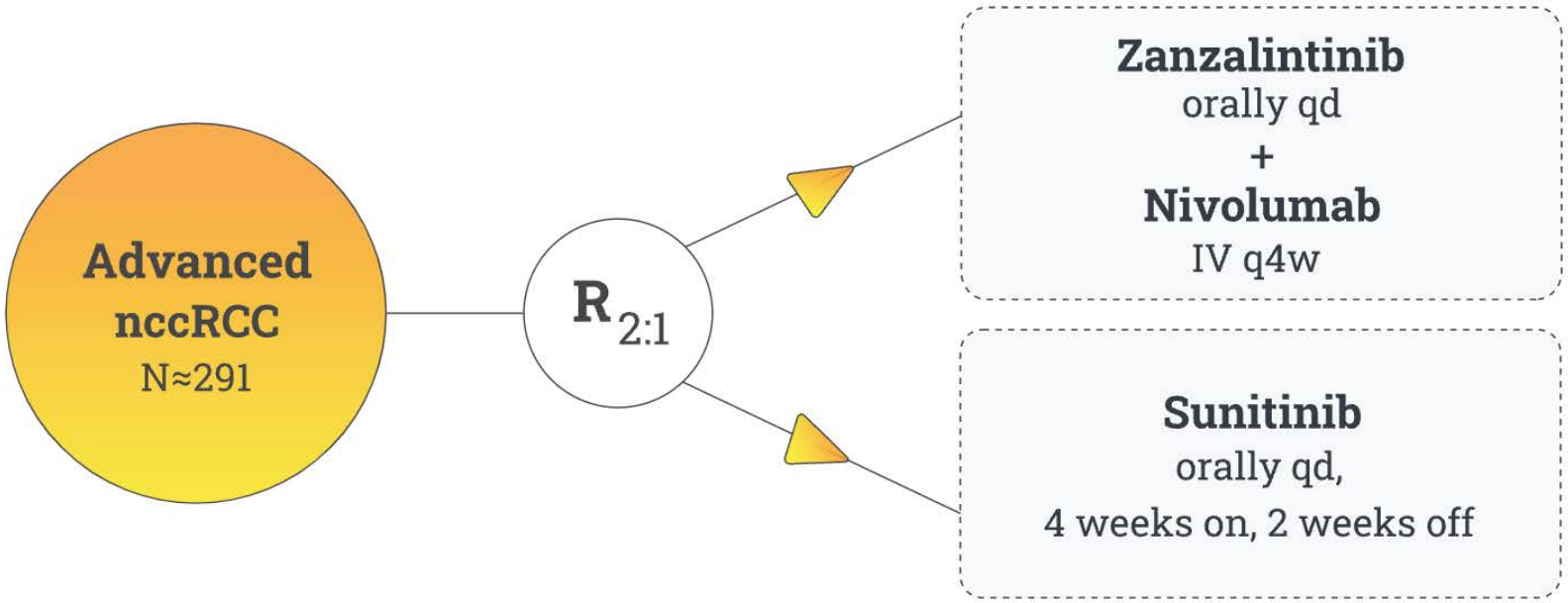


There were 33 PFS events (28 progressions and 5 deaths with no progression). Median PFS is 13 months (95% CI: 7, 16). 51% (95% CI: 34, 65) of patients were alive without progression at 12 months; 23% (95% CI: 11, 37) were alive without progression at 24 months. There were 27 deaths. Median follow-up time for survivors is 34 months (range: 20, 51). Median OS is 28 months (95% CI: 23, 43). 70% (95% CI: 53, 82) of patients were alive at 18 months and 44% (95% CI: 28, 60) were alive at 36 months.

Lee C-H et al. ASCO 2023;Abstract 4537.

RTP RESEARCH TO PRACTICE

STELLAR-304 in nccRCC

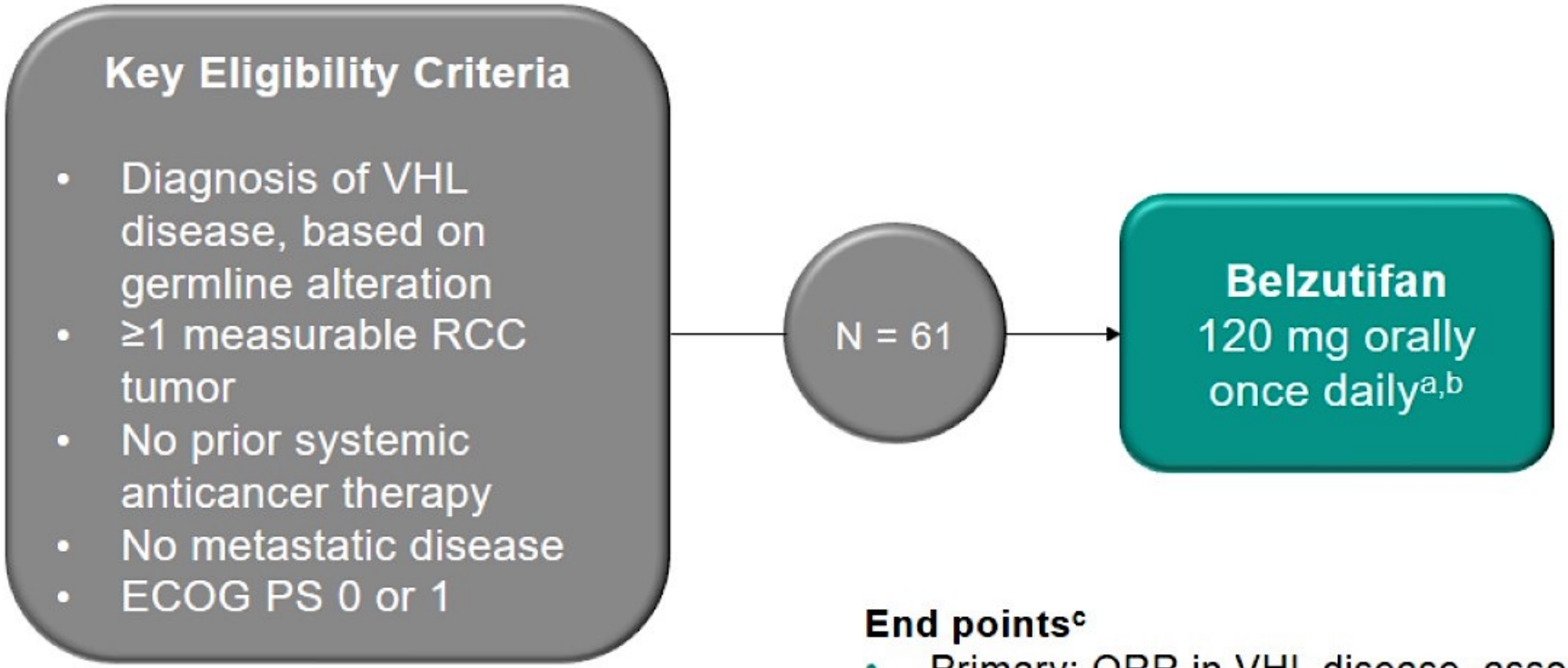


Stratification Factors

- Histology (papillary w/o sarcomatoid features vs other subtypes w/o sarcomatoid features vs any histology with sarcomatoid features)
- IMDC prognostic score (favorable vs intermediate vs poor)

Latest Updates in Treatment of VHL Disease

Study Design of Phase 2 LITESPARK-004 (NCT03401788)



Tumor Assessments

- At screening and every 12 weeks for a minimum of 3 years, then every 24 weeks thereafter

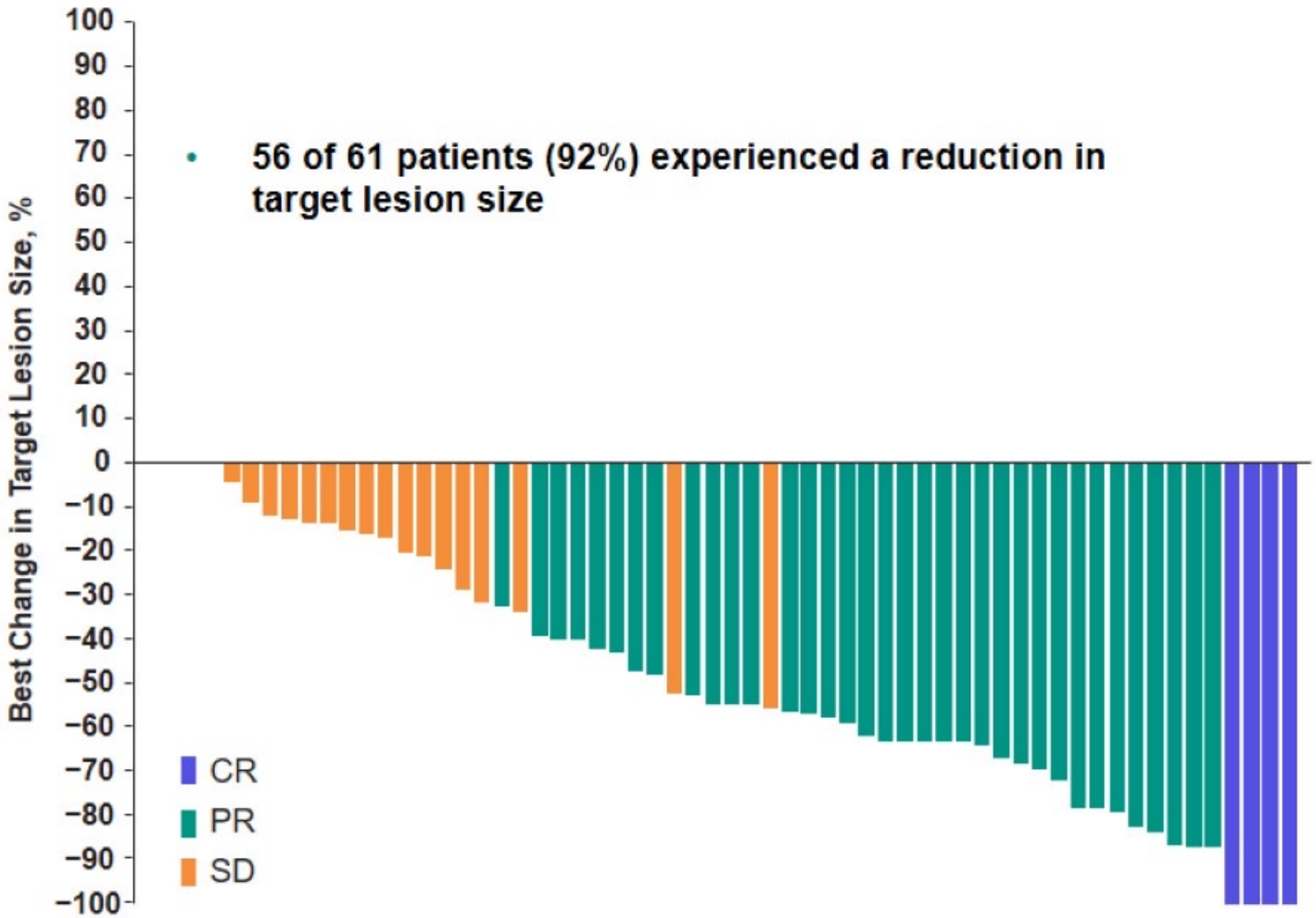
End points[c]

- Primary: ORR in VHL disease–associated RCC tumors per RECIST v1.1 by independent review committee (IRC)
- Secondary: ORR in other VHL disease–associated neoplasms, TTR, and DOR per RECIST v1.1 by IRC; and safety

[a]Until unacceptable toxicity, disease progression, or patient withdrawal. [b]In an event of a mixed response (ie, continuing radiographic response in RCC lesions but progression or surgical requirement for a non-RCC lesion), study treatment may be continued if patient is tolerating the study drug and no alternative treatments are available for patient's progressive VHL-associated non-RCC lesions. [c]95% CIs for ORR in RCC and non-RCC neoplasms were calculated using the 2-sided Clopper-Pearson method; DOR was analyzed using the Kaplan-Meier method, and their 95% CIs were estimated using the generalized Brookmeyer-Crowley method.

Best Objective Response per RECIST v1.1 by IRC in VHL Disease-Associated RCC

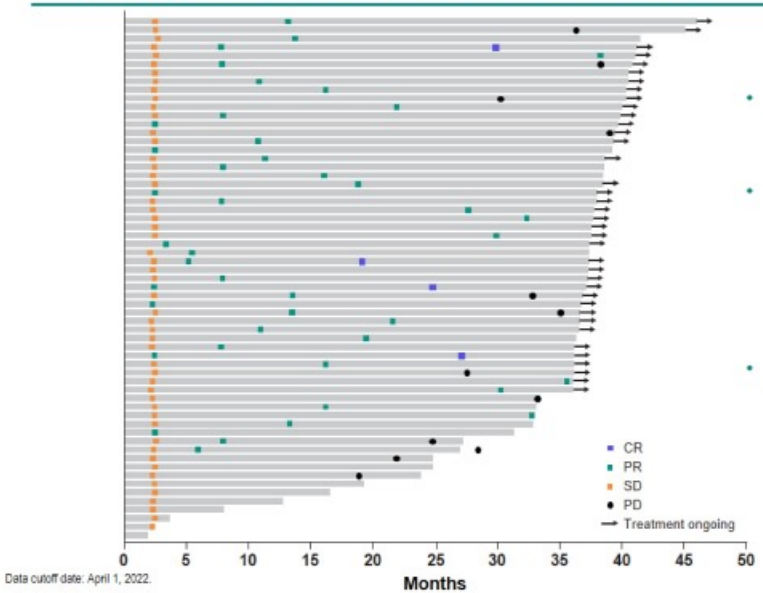
	RCC N = 61
ORR, % (95% CI)	**64 (50.6-75.8)**
Best response n (%)	
CR	4 (7)
PR	35 (57)
SD	21 (34)
PD	0
NE[a]	1 (2)



[a]1 patient discontinued the study before the first postbaseline tumor assessment. Data cutoff date: April 1, 2022.

Srinivasan LITESPARK-004
ESMO 2022

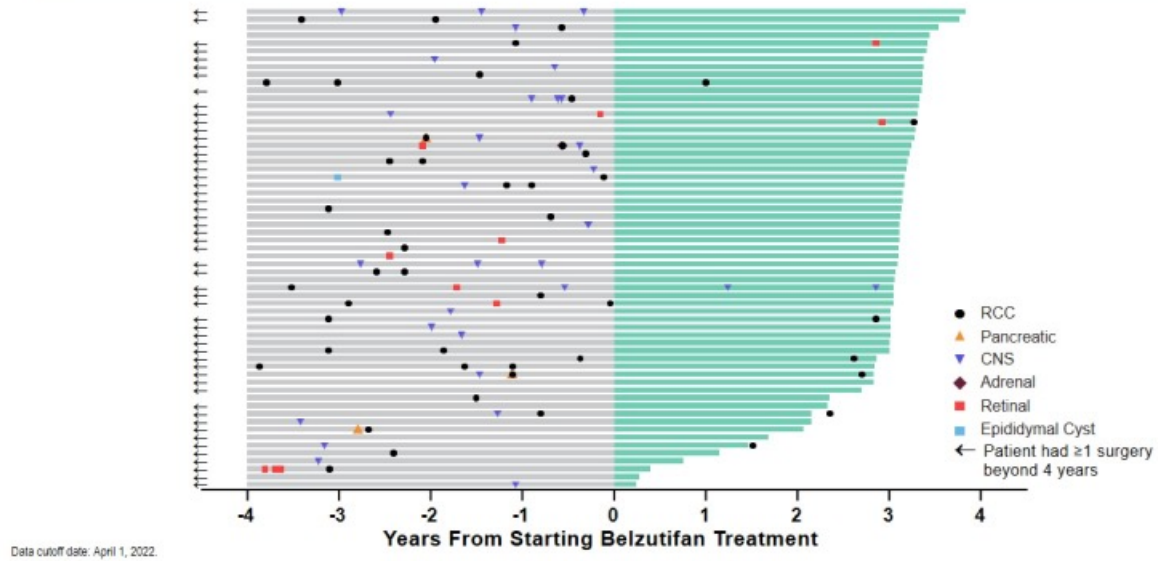
Duration of Treatment for RCC



- Median time to response was 11.1 months (range, 2.7 to 30.5)
- Median DOR per Kaplan-Meier estimate was not reached (range, 5.4+ to 35.8+ months)
  - 34 of 39 patients with a confirmed response (87%) remain in response as of the data cutoff date
- 38 of 61 patients (62%) remain on treatment as of data cutoff date

Srinivasan LITESPARK-004
ESMO 2022

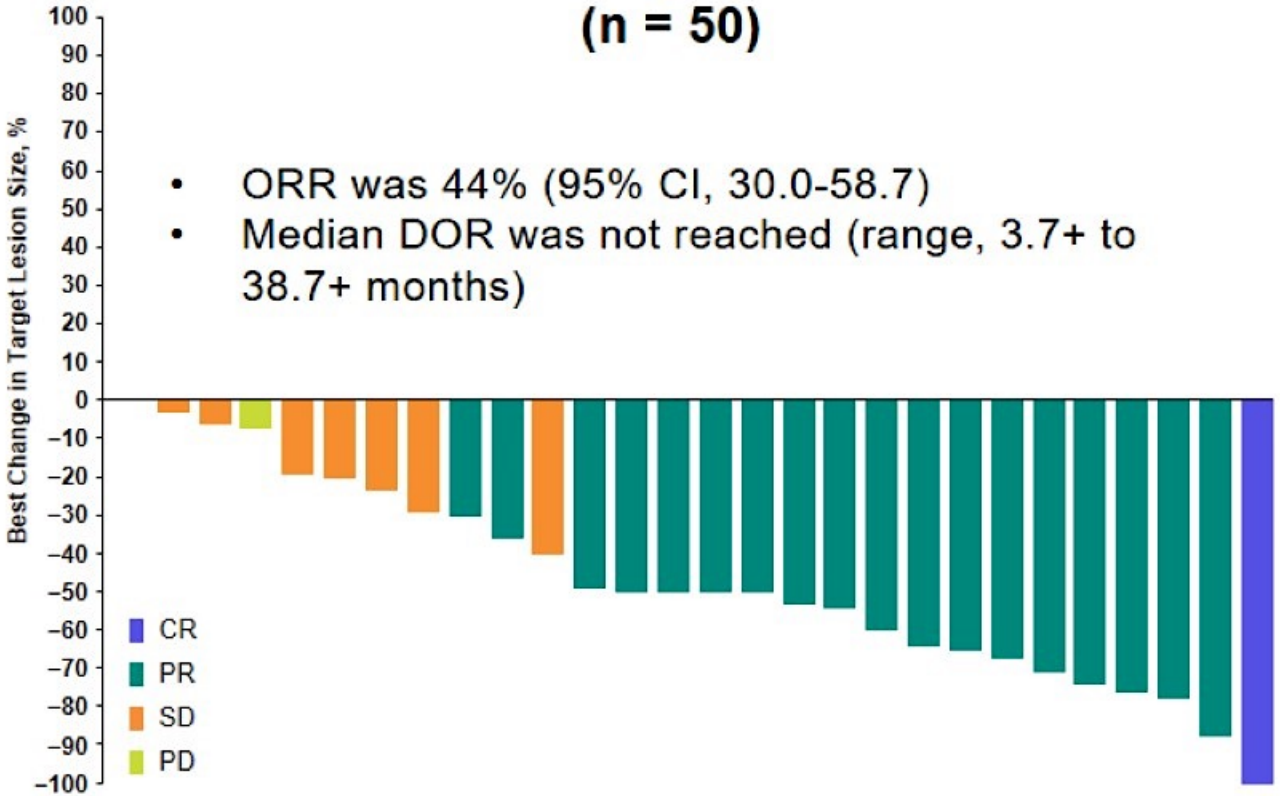
Distribution of VHL Disease–Related Surgeries



Best Response per RECIST v1.1 by IRC in VHL Disease–Associated pNET and CNS and Retinal Hemangioblastomas

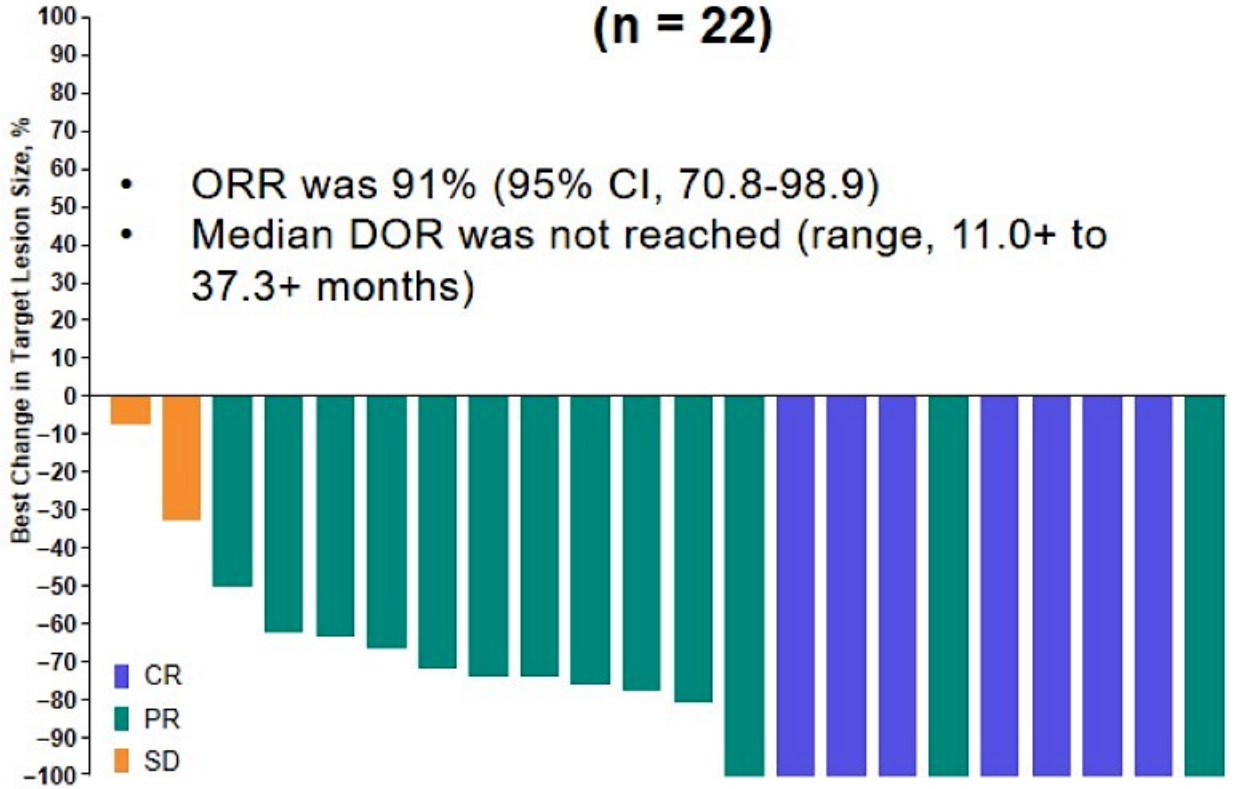
CNS Hemangioblastomas[a] (n = 50)

- ORR was 44% (95% CI, 30.0-58.7)
- Median DOR was not reached (range, 3.7+ to 38.7+ months)



pNET (n = 22)

- ORR was 91% (95% CI, 70.8-98.9)
- Median DOR was not reached (range, 11.0+ to 37.3+ months)



- **Retinal hemangioblastomas**:
  - All 12 patients with retinal hemangioblastomas at baseline showed improvement (100% [95% CI, 73.5-100])
    - All 16 evaluable eyes with retinal hemangioblastomas at baseline showed improvement (100% [95% CI, 74.9-100])
    - Median DOR was not reached (range, 14.3+ to 33.3+ months)

[a]28 patients had evaluable postbaseline data. 4 patients achieved CR, including 3 patients who had only nonmeasurable disease at baseline (not shown on the waterfall plot). Data cutoff date: April 1, 2022.

LS-004

Adverse Event Summary

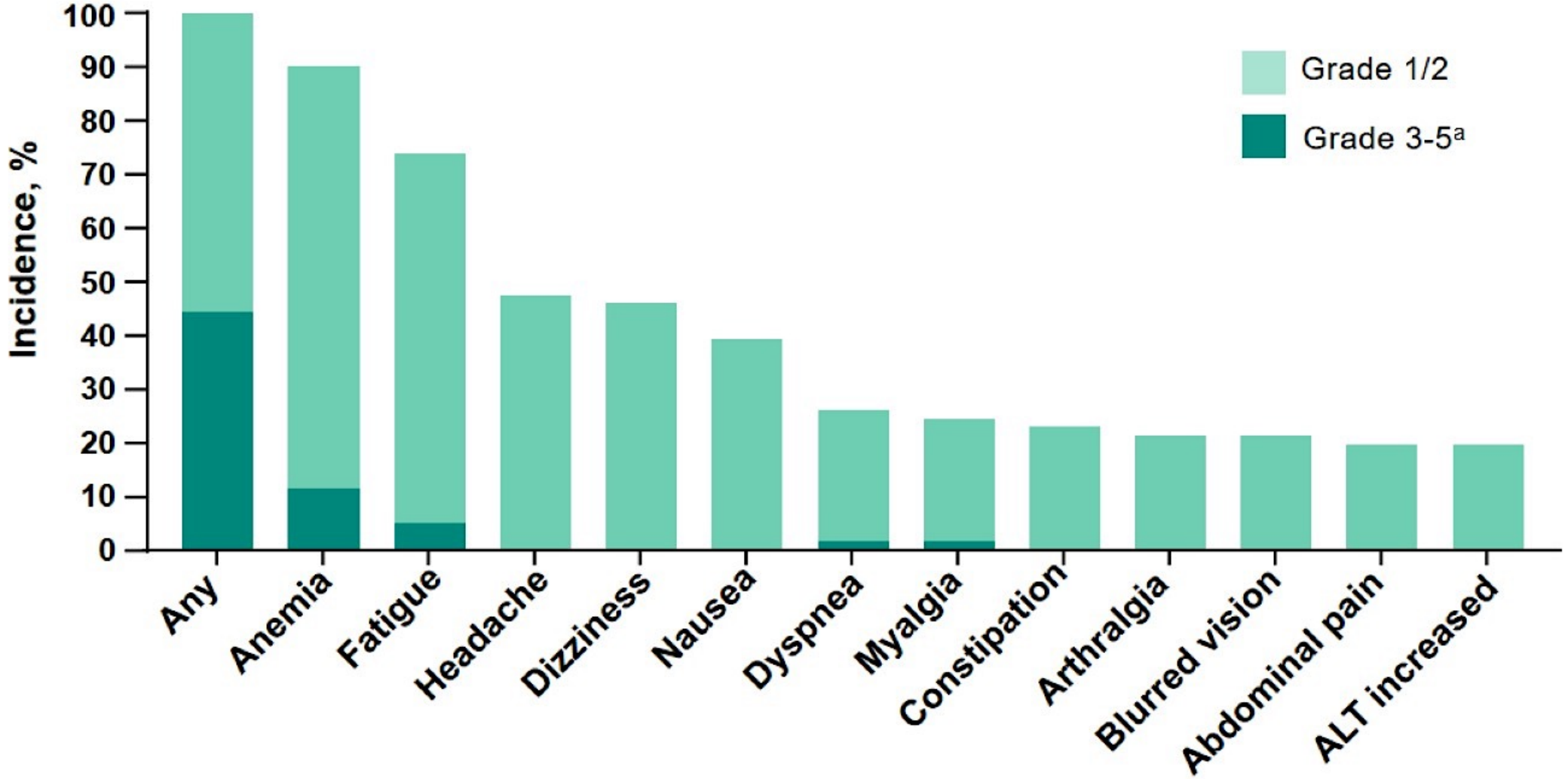
n (%)	All patients N = 61
Any-grade AE	61 (100)
Any-grade treatment-related AE	61 (100)
Grade 3-5 AE	27 (44)
Grade 3 treatment-related AE	11 (18)
Grade 4/5 treatment-related AE	0 (0)
Serious AE	18 (30)
Serious treatment-related AE	4 (7)
Dose interruption because of an AE	26 (43)
Dose interruption because of a treatment-related AE	13 (21)
Dose reduction because of an AE	10 (16)
Dose reduction because of a treatment-related AE	8 (13)
Treatment discontinuation because of an AE	4 (7)
Treatment discontinuation because of a treatment-related AE	2 (3)
Death	2 (3)[a]
Death because of a treatment-related AE	0 (0)

[a]Deaths due to suicide attempt and acute fentanyl toxicity. Data cutoff date: April 1, 2022.

LS-004

Adverse Events with Incidence ≥20%

- **Median duration of treatment was 37 months (range, 1.9 to 46.1)**



[a]Grade 4 embolism (n = 1), retinal detachment (n = 1), and retinal vein occlusion (n = 1) occurred. Grade 5 suicide attempt (n = 1) and acute fentanyl toxicity (n = 1) occurred. Data cutoff date: April 1, 2022.

Overview

Saturday, March 23rd

Module 1: 7:30 AM – 9:10 AM — Hodgkin and Non-Hodgkin Lymphoma

Module 2: 9:30 AM – 10:20 AM — Gynecologic Cancers

Module 3: 10:20 AM – 11:10 AM — Localized Breast Cancer; SABCS 2023 Review

Module 4: 11:10 AM – 12:00 PM — Metastatic HER2-Positive and Triple-Negative Breast Cancer; SABCS 2023 Review

Module 5: 12:30 PM – 1:20 PM — Renal Cell Carcinoma

Module 6: 1:20 PM – 2:10 PM — Urothelial Bladder Cancer

Module 7: 2:10 PM – 3:00 PM — Prostate Cancer

Module 8: 3:20 PM – 4:10 PM — Targeted Therapy for Non-Small Cell Lung Cancer

Module 9: 4:10 PM – 5:00 PM — Nontargeted Treatments for Lung Cancer

Agenda

Module 1: Nonmetastatic Urothelial Bladder Cancer (UBC) — Dr Galsky

Module 2: Metastatic UBC — Dr Rosenberg

Agenda

Module 1: Nonmetastatic Urothelial Bladder Cancer (UBC) — Dr Galsky

Module 2: Metastatic UBC — Dr Rosenberg

Nonmetastatic urothelial bladder cancer

Matthew D. Galsky, MD FASCO

Professor of Medicine

Icahn School of Medicine at Mount Sinai

Director, Genitourinary Medical Oncology

Associate Director, Translational Research

Tisch Cancer Institute

@MattGalsky

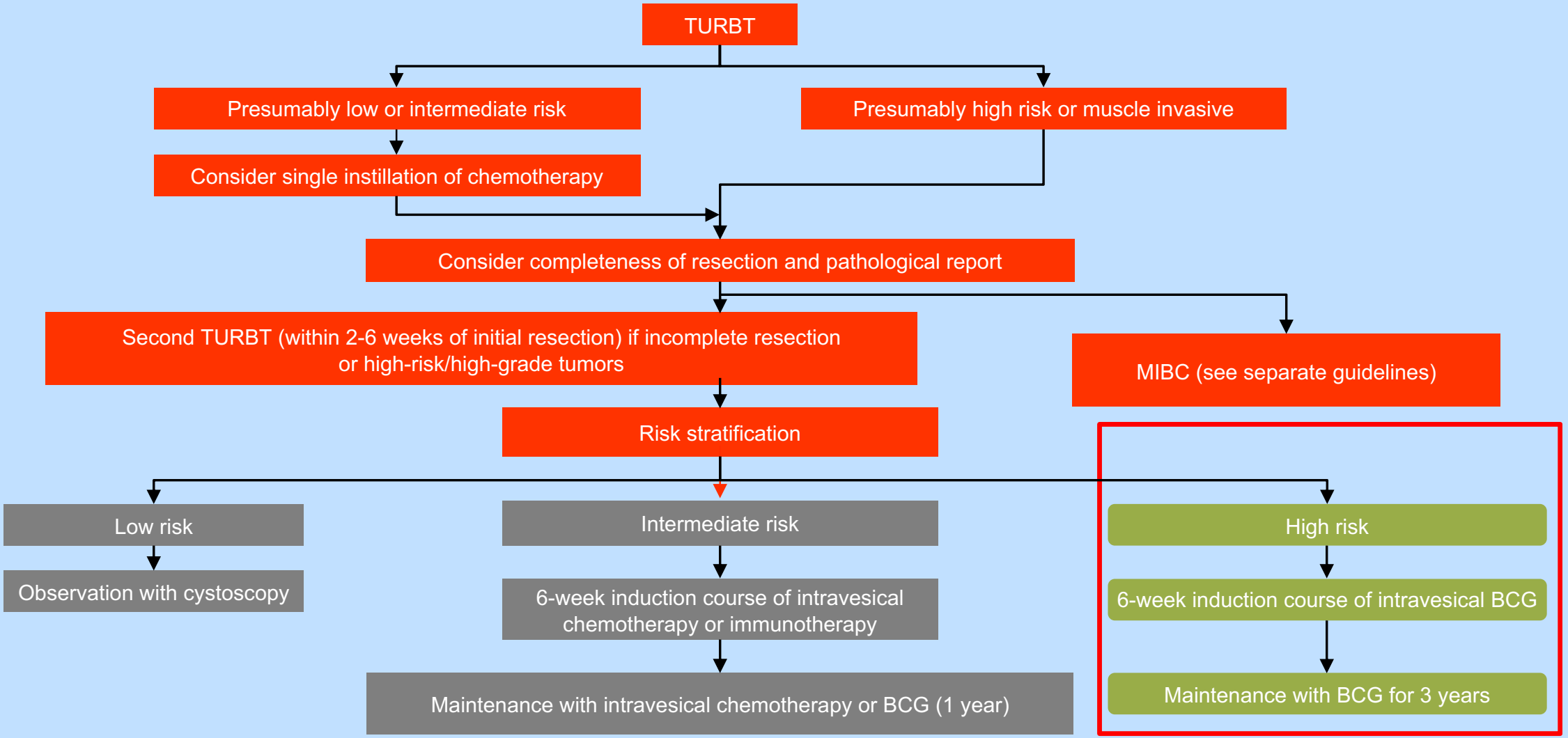
Disclosures

Consulting Agreements	AbbVie Inc, Alligator Bioscience, Analog Devices Inc, Asieris Pharmaceuticals, AstraZeneca Pharmaceuticals LP, Basilea Pharmaceutica Ltd, Bicycle Therapeutics, Bristol Myers Squibb, Curis Inc, Dragonfly Therapeutics, EMD Serono Inc, FUJIFILM Pharmaceuticals USA Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, GSK, Janssen Biotech Inc, Merck, Numab Therapeutics AG, Rappta Therapeutics, Pfizer Inc, Seagen Inc, Silverback Therapeutics, UroGen Pharma
Contracted Research	AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Dendreon Pharmaceuticals Inc, Genentech, a member of the Roche Group, Merck, Novartis

Case

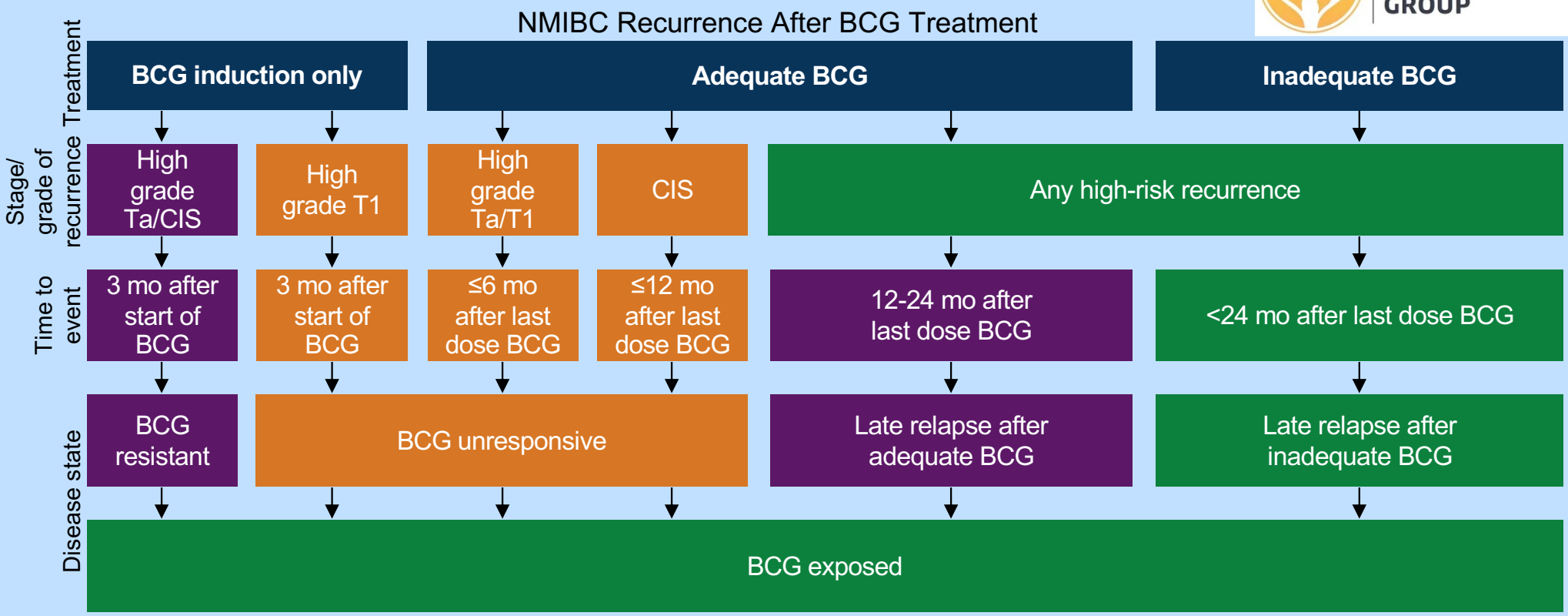
- 78 year old man presents with hematuria.
- A CT scan reveals a bladder mass and TURBT reveals muscle-invasive urothelial cancer of the bladder.
- He proceeds with radical cystectomy and surgical pathology reveals pT3N0 urothelial cancer.
- He is referred for a medical oncology evaluation.
- Labs were notable for WBC 5.5, HGB 10.8, and creatinine 1.*7.*
- Signatera^{TM} is 1.1 mtm/mL.

AUA/SUO Treatment Guidelines for NMIBC



1. Chang SS et al. *J Urol*. 2016;196:1021-1029. 2. Shore ND et al. *Urol Oncol*. 2021;39:642-663.

BCG is standard treatment for high risk NMIBC but a subset of patients will develop disease recurrence



1. Roumiguié M et al. *Eur Urol.* 2022;82(1):34-46.

KEYNOTE-057: Pembrolizumab monotherapy in BCG unresponsive NMIBC

Patients

- HR NMIBC patients unresponsive to BCG who refuse or are ineligible for cystectomy
- Patients with papillary disease must have fully resected disease at study entry
- Two cohorts
  - **Cohort A** (n = 130): CIS ± papillary disease (high-grade Ta or T1)
  - **Cohort B** (n = 130): papillary disease (high-grade Ta or any T1) without CIS

→ **Pembrolizumab** 200 mg Q3W →

Evaluations with cystoscopy, cytology, ± biopsy Q12W × 2 y, then Q24W × 2 y and once yearly thereafter
and
CT urogram Q24W × 2 y or more frequently as clinically indicated

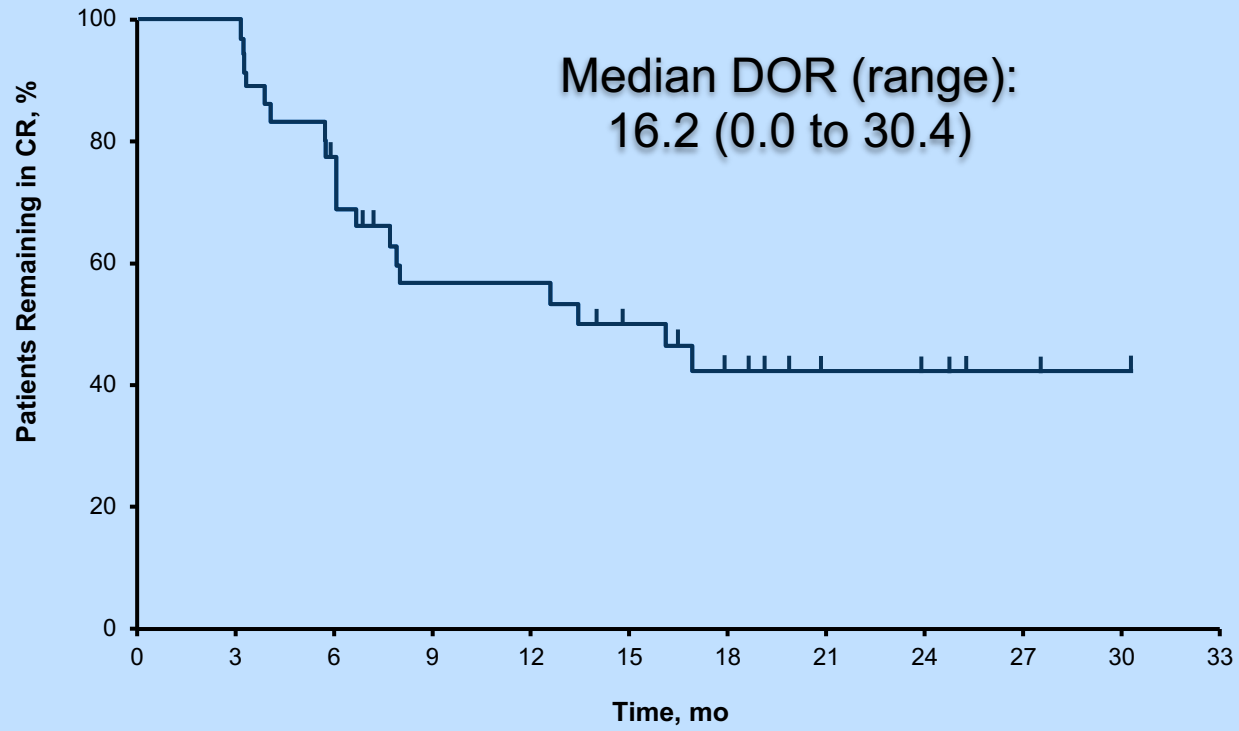
- **Primary endpoints:** CR (absence of HR NMIBC) in cohort A and DFS in cohort B
- **Secondary endpoints:** CR (absence of any disease—high-risk or low-risk NMIBC) in cohort A, DOR in cohort A, and safety/tolerability

If no persistence or recurrence of HR NMIBC at any assessment → Continue assessments and pembrolizumab until recurrence of high-risk NMIBC, PD, or 24 months of treatment complete

If HR NMIBC present at any assessment → Discontinue treatment; enter survival follow-up

Balar AV et al. *Lancet Oncol*. 2021;22:919-930.

KEYNOTE-057: Cohort A - CIS ± papillary disease (high-grade Ta or T1)



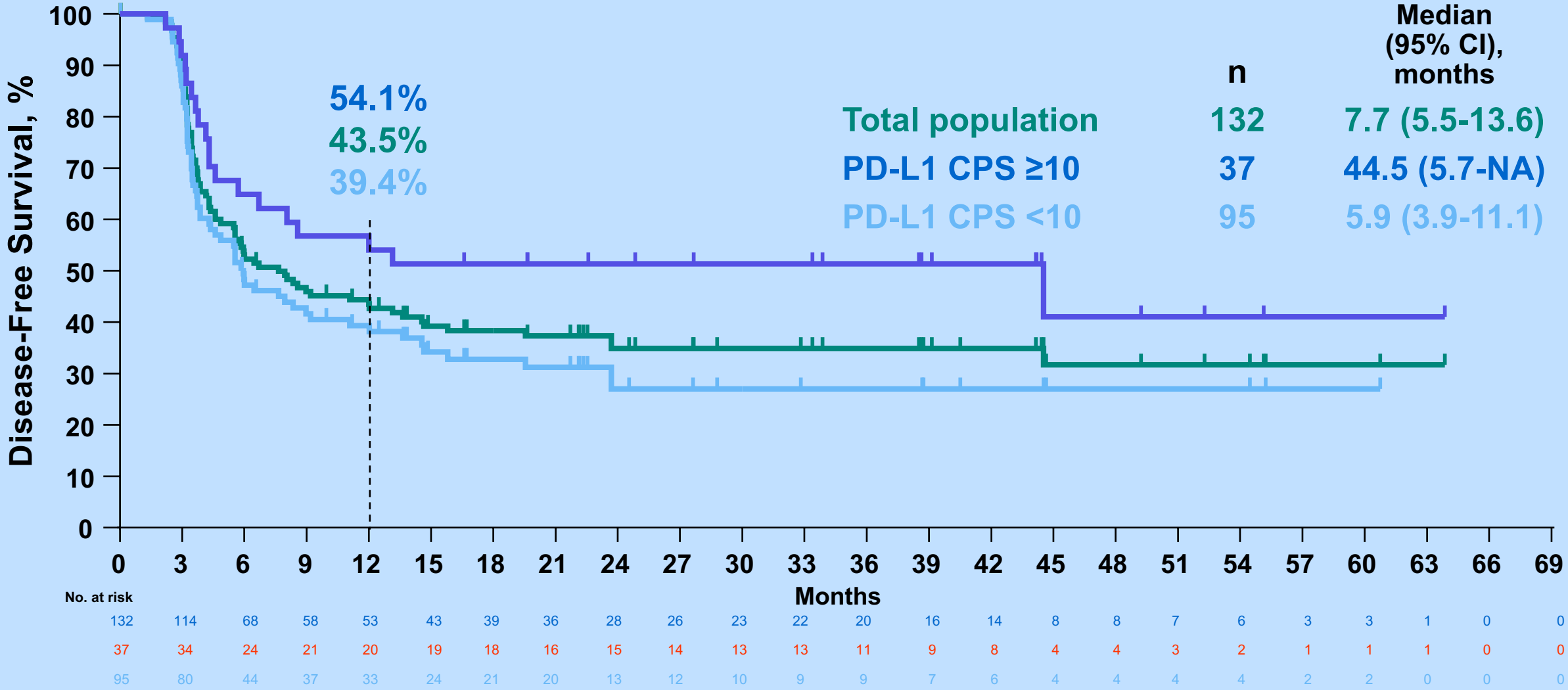
	N = 96	
Best response	**n (%)**	**95% CI**
CR	39 (40.6)	30.7-51.1
Non-CR	56 (58.3)	47.8-68.3
Progression to T2	0	N/A
Non-evaluable	1 (1.0)	0-5.7

- Upstaging to ≥pT2 in 8.3% patients

- Extended minimum follow-up of 26.3 mo
  - Of 39 responders, 13 (33.3%) remained in CR ≥18 mo and 9 (23.1%) remained in CR ≥24 mo as of the data cutoff date
  - No new safety risks were identified

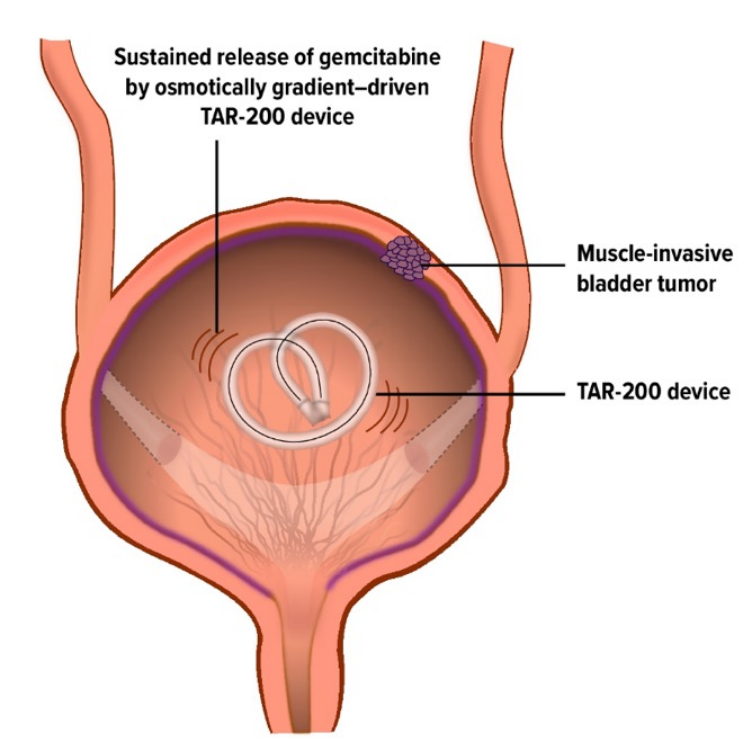
Balar AV et al. *Lancet Oncol*. 2021;22:919-930.

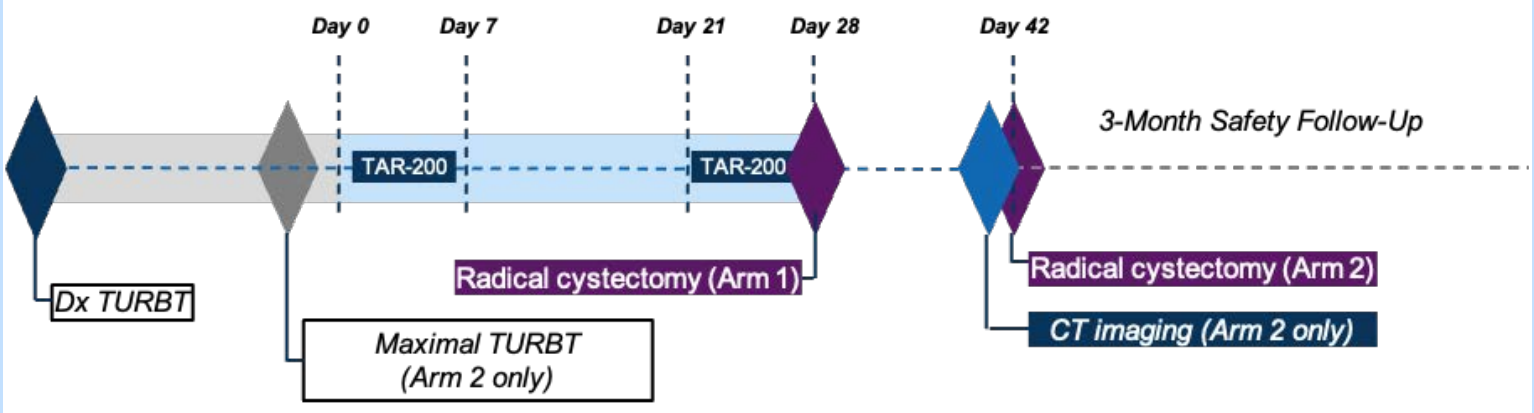
KEYNOTE-057: Cohort B - papillary disease (high-grade Ta or any T1) without CIS



Necchi A et al. ASCO GU 2023 LBA442. 2. Necchi A et al. EAU 2023.

Phase 1 study of a neoadjuvant gemcitabine intravesical drug delivery system (TAR-200)





- In Arm 1, those with residual tumor, 4 of 10 patients exhibited pathologic downstaging; 1 experienced a complete response (CR) and 3 a partial response (PR).
- In Arm 2, those undergoing maximal TURBT, 6 of 10 patients exhibited downstaging; 3 experienced a CR and 3 a PR.

Daneshmand S et al. *Urol Oncol:Semin Orig.* 2022;1-9.

SunRISe-1: TAR-200 + Cetrelimab, TAR-200 Alone, or Cetrelimab Alone in High-Risk NMIBC Unresponsive to BCG

Eligibility criteria

- ECOG PS 0 to 2
- Recurrent or persistent histologically confirmed high-risk NMIBC (CIS) with or without papillary disease (T1, high-grade Ta), who have been diagnosed within 12 mo of last BCG treatment
- Patients ineligible for or who declined RC

N (estimated) = 200

R 2:1:1

Cohort 1:
TAR-200 + cetrelimab
n ≈ 100 (closed)

Cohort 2
TAR-200 alone
n ≈ 80

Cohort 3
Cetrelimab alone
n ≈ 50 (closed)

Primary endpoint: overall CR rate

Secondary endpoints: DoR, OS, safety, and tolerability

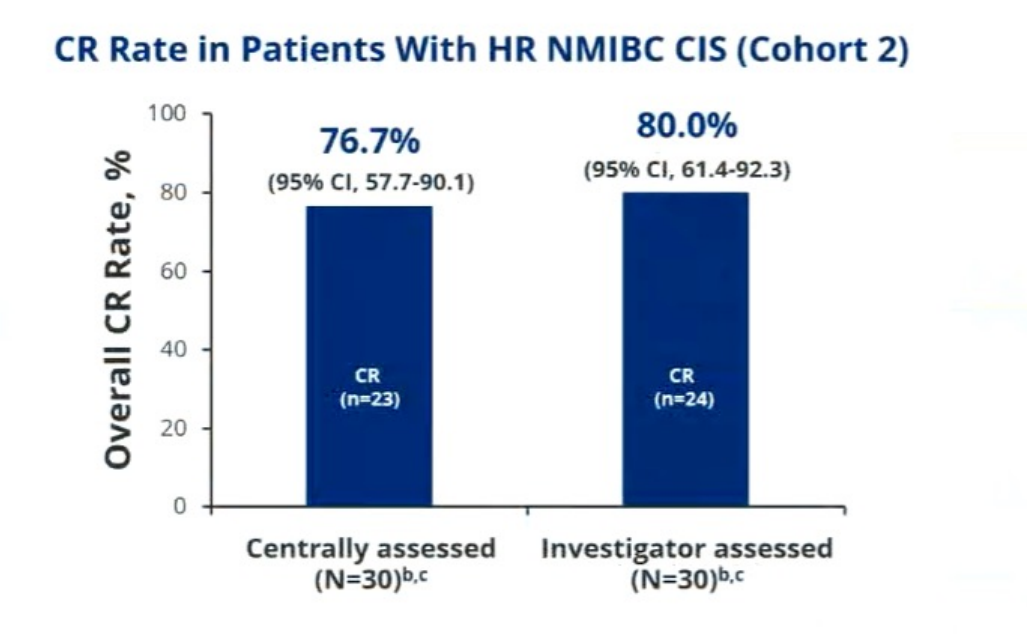
HR NMIBC papillary disease only (no CIS)

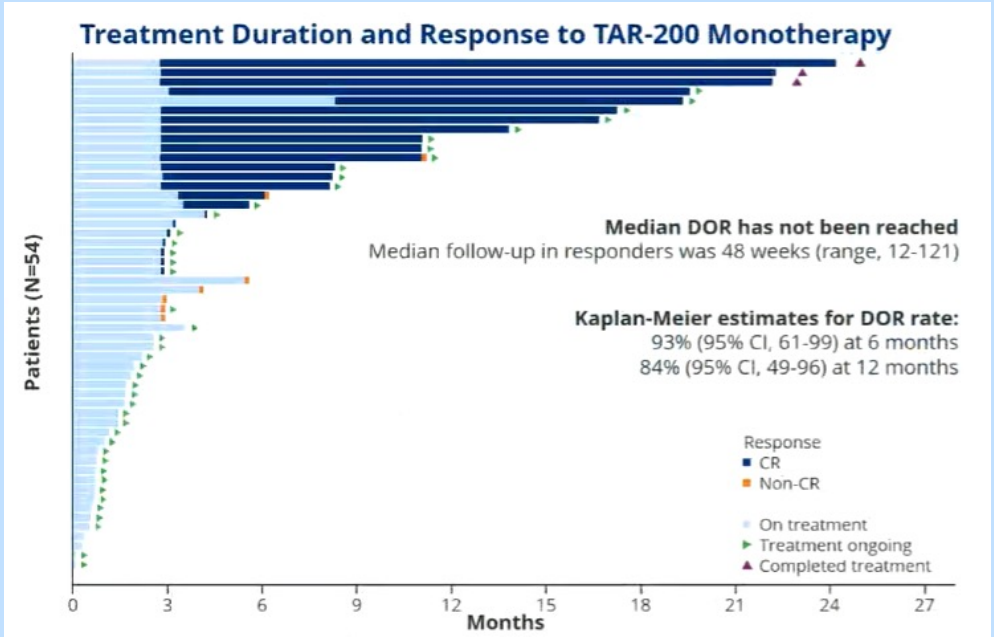
Cohort 4
TAR-200 alone
n ≈ 50

Primary endpoint: DFS rate

Necchi A, et al. Ann Oncol. 2023;34(suppl 2):LBA105.

SunRISe-1: TAR-200 + Cetrelimab, TAR-200 Alone, or Cetrelimab Alone in High-Risk NMIBC Unresponsive to BCG





- 21 of 23 responses are ongoing
  - 11 patients had DoR ≥ 6 mo (10 of 11 ongoing)
  - 6 patients had DoR ≥ 12 mo (all ongoing)
  - None of the patients with CR have undergone RC

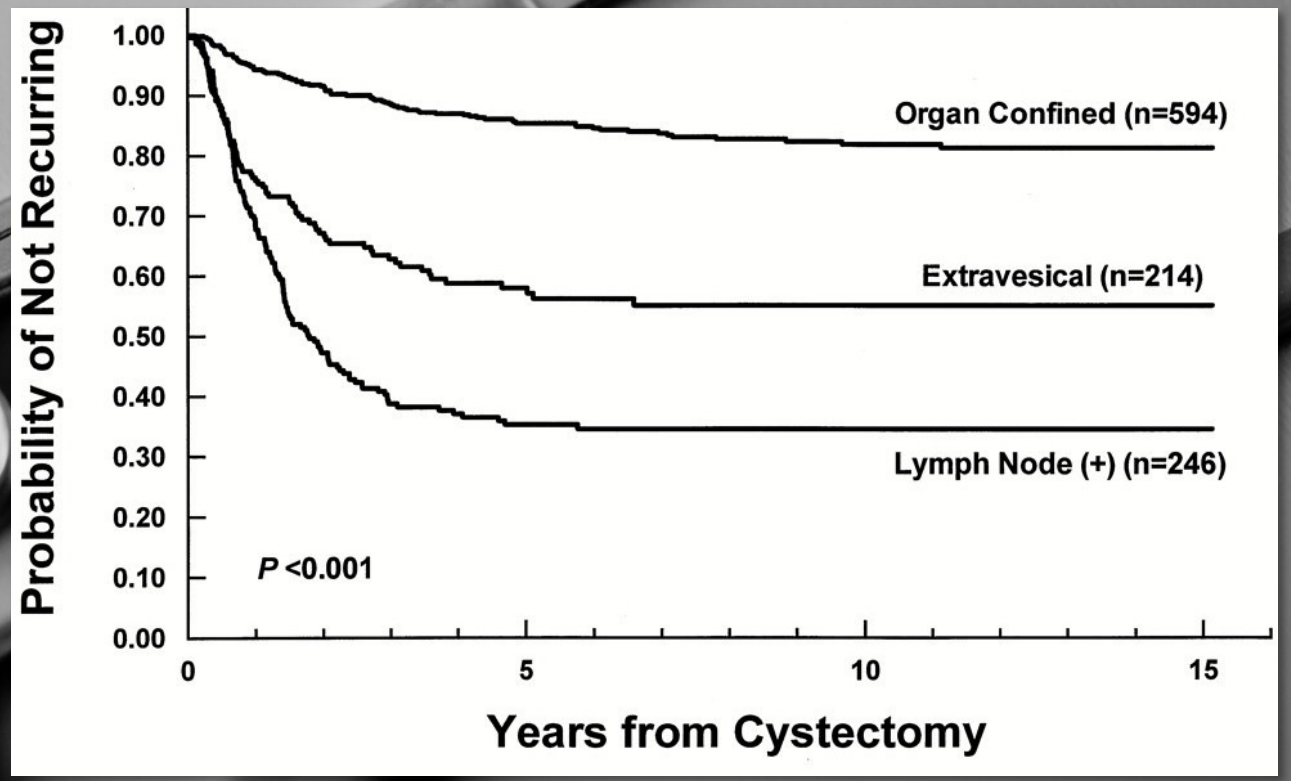
Necchi A, et al. Ann Oncol. 2023;34(suppl 2):LBA105.

SunRISe-1: Safety

Patients With Events, N (%)	TAR-200 (N = 54)	
	Any Grade	Grade ≥ 3
≥ 1 AE	37 (68.5)	9 (16.7)
≥ 1 TRAE	29 (53.7)	4 (7.4)
Pollakiuria	12 (22.2)	1 (1.9)
Dysuria	11 (20.4)	0
Micturition urgency	10 (18.5)	0
Hematuria	6 (11.1)	0
Noninfective cystitis	4 (7.4)	0
Urinary tract pain	3 (5.6)	1 (1.9)
Urinary retention	2 (3.7)	1 (1.9)
Kidney impairment	1 (1.9)	1 (1.9)
Urosepsis	1 (1.9)	1 (1.9)

Necchi A, et al. Ann Oncol. 2023;34(suppl 2):LBA105.

Surgery alone is potentially curative for MIBC



…but the risk of metastatic recurrence remains high

Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1.054 patients. J Clin Oncol. 2001;3(19):666 – 67

A series of practical and scientific challenges have compromised our ability to improve outcomes in MIBC post-cystectomy

1. We don't know who *needs* perioperative systemic therapy or who *benefits* from such therapy

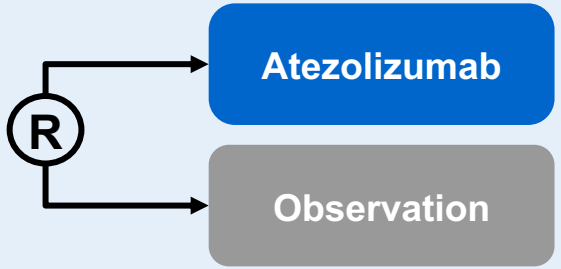
2. Completing perioperative chemotherapy trials has been a major challenge historically

3. Approximately 50% of patients can't receive our "gold standard" treatment (i.e., "cisplatin-ineligible")

4. Residual cancer after NAC associated with poor prognosis and unmet need

Adjuvant PD-1/PD-L1 blockade

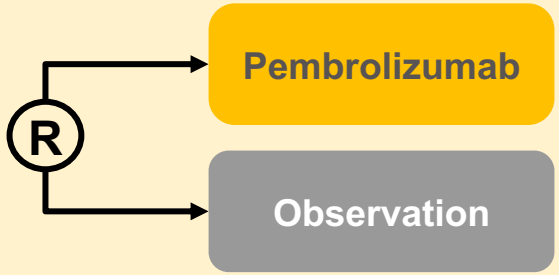
IMvigor010
NCT02450331



Primary endpoint
DFS

Secondary endpoints
OS, DSS, distant metastasis-free survival, AEs and ATAs

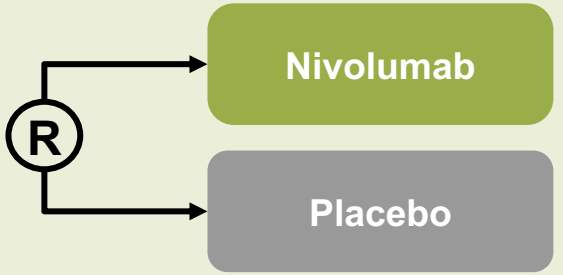
AMBASSADOR
NCT03244384



Co-primary endpoints
DFS and OS

Secondary endpoints
OS and DFS in PD-L1+ and PD-L1– patients

CheckMate 274
NCT02632409



Primary endpoint
DFS in ITT and PD-L1≥1%

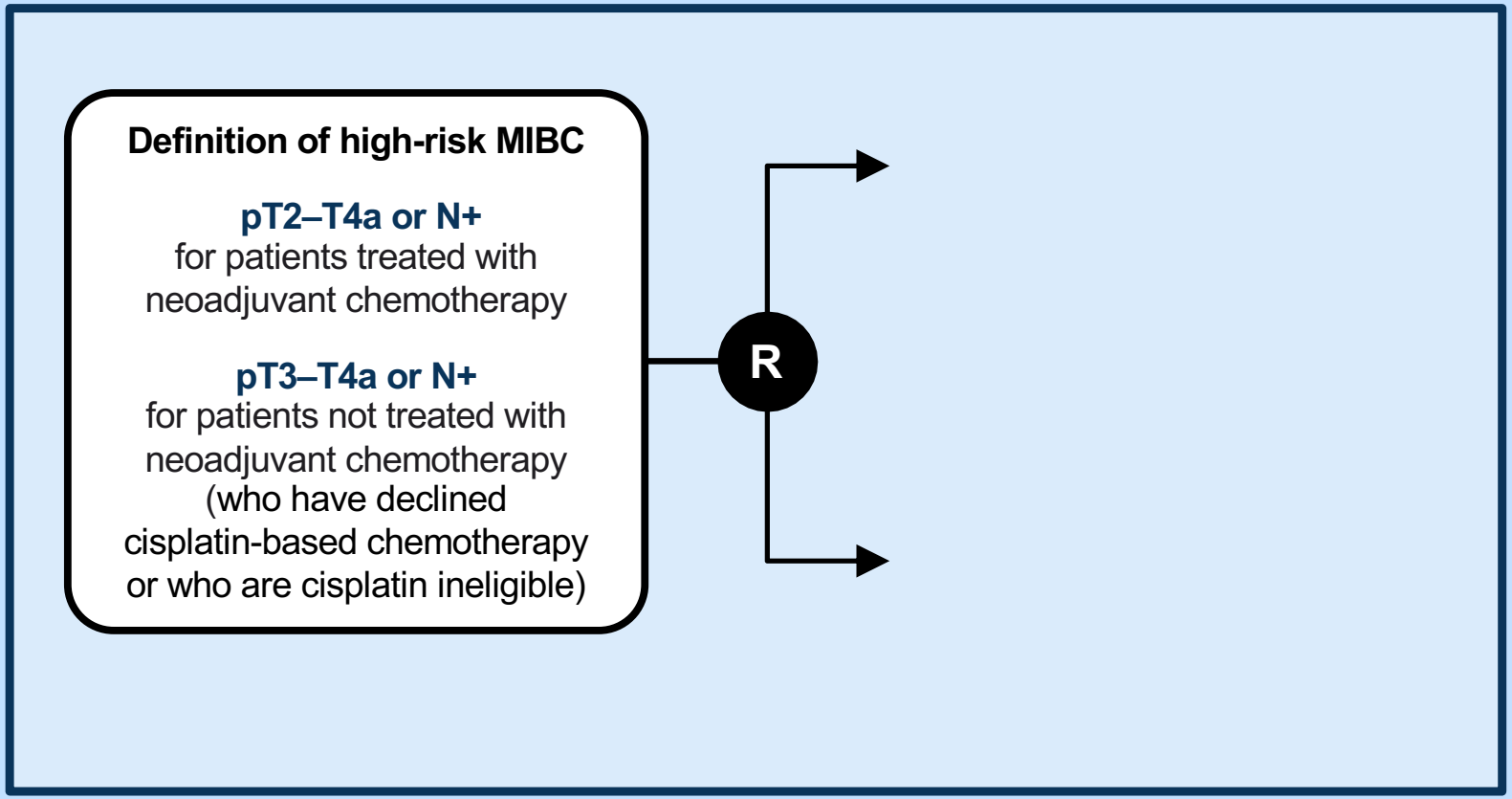
Secondary endpoints
OS,
non-urothelial tract RFS,
disease-specific survival

Standardized definition of “high-risk” MIBC across trials

IMvigor010
NCT02450331

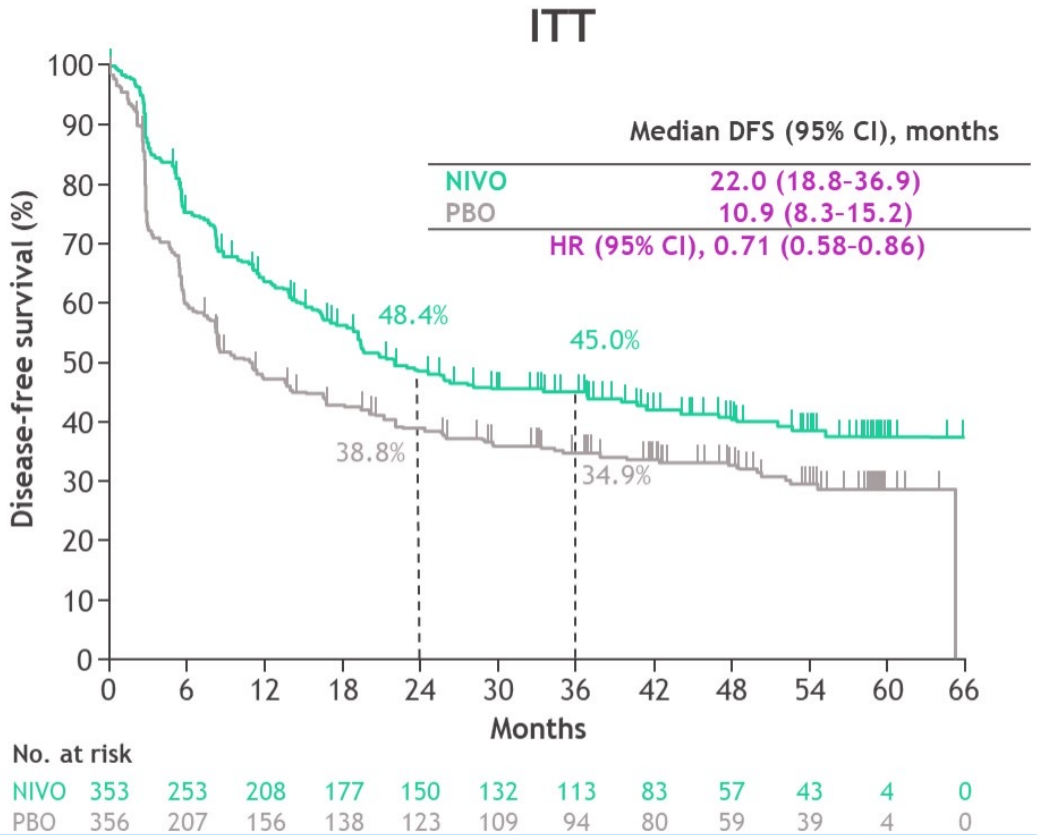
AMBASSADOR
NCT03244384

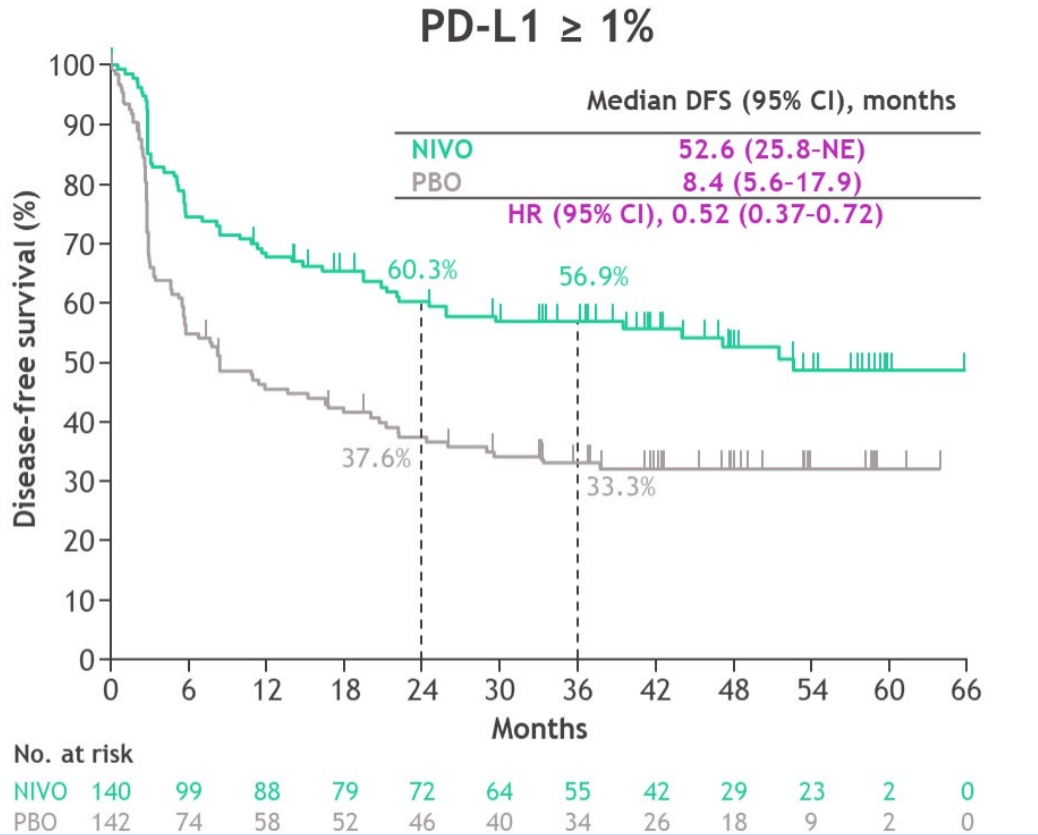
CheckMate 274
NCT02632409



CheckMate 274: Updated DFS

- Continued DFS benefit was observed with NIVO versus PBO both in the ITT and tumor PD-L1 expression ≥ 1% populations





mDFS doubled with nivolumab vs placebo

mDFS >6x with nivolumab vs placebo

Minimum follow-up of 31.6 months; Median follow-up of 36.1 months
Galsky MD et al ASCO GU 2023 LBA443.

CheckMate 274: Summary of Efficacy Outcomes Over Time

ITT

	NIVO (N = 353)	PBO (N = 356)	NIVO (N = 353)	PBO (N = 356)	NIVO (N = 353)	PBO (N = 356)
Minimum follow-up in the ITT population, months	31.6		11.0[1]		5.9[2]	
Median DFS, months	22.0	10.9	22.0	10.9	20.8	10.8
DFS HR (95% CI)	0.71 (0.58-0.86)		0.70 (0.57-0.85)		0.70 (0.55-0.90)[a]	
Median NUTRFS, months	25.9	13.7	26.0	13.7	22.9	13.7
NUTRFS HR (95% CI)	0.72 (0.59-0.88)		0.71 (0.58-0.88)		0.72 (0.59-0.89)	
Median DMFS, months	47.1	28.7	41.1	29.2	40.5	29.5
DMFS HR (95% CI)	0.74 (0.60-0.92)		0.73 (0.58-0.92)		0.75 (0.59-0.94)	

PD-L1 ≥ 1%

	NIVO (N = 140)	PBO (N = 142)	NIVO (N = 140)	PBO (N = 142)	NIVO (N = 140)	PBO (N = 142)
Minimum follow-up in the ITT population, months	31.6		11.0[1]		5.9[2]	
Median DFS, months	52.6	8.4	NR	8.4	NR	8.4
DFS HR (95% CI)	0.52 (0.37-0.72)		0.53 (0.38-0.75)		0.55 (0.35-0.85)[b]	
Median NUTRFS, months	52.6	8.4	NR	10.8	NR	10.8
NUTRFS HR (95% CI)	0.53 (0.38-0.74)		0.54 (0.39-0.77)		0.55 (0.39-0.79)	
Median DMFS, months	NR	20.7	NR	20.7	NR	21.2
DMFS HR (95% CI)	0.58 (0.40-0.84)		0.60 (0.41-0.88)		0.61 (0.42-0.90)	

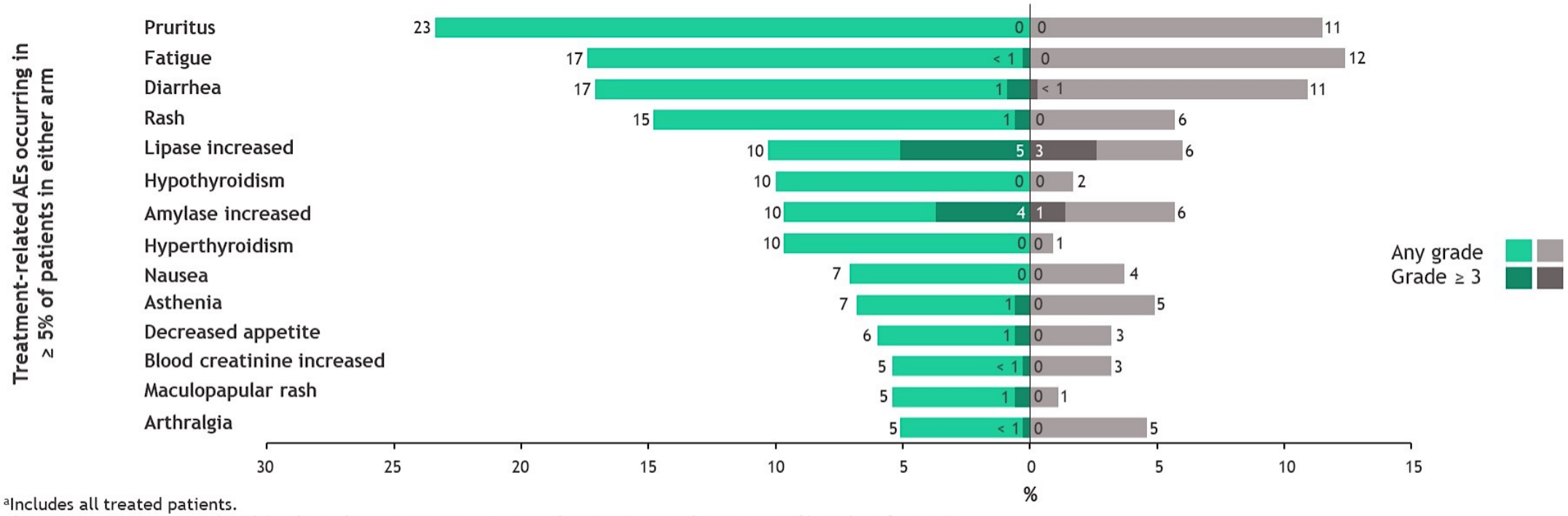
[a]98.22% CI. [b]98.72% CI.

1. Galsky MD, et al. Poster presentation at SUO 2021. 1514. 2. Bajorin DF, et al. *N Engl J Med* 2021;384:2102-2114.

- Adjuvant nivolumab vs placebo is stable over time across primary, secondary and exploratory endpoints
- Fixed duration of treatment (1yr) with sustained effects over time (3yr follow-up)

CheckMate 274: Safety

	NIVO (n = 351)[a]		PBO (n = 348)[a]	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Treatment-related AEs, %	79	18	56	7
Treatment-related AEs leading to discontinuation, %	14	7	2	1

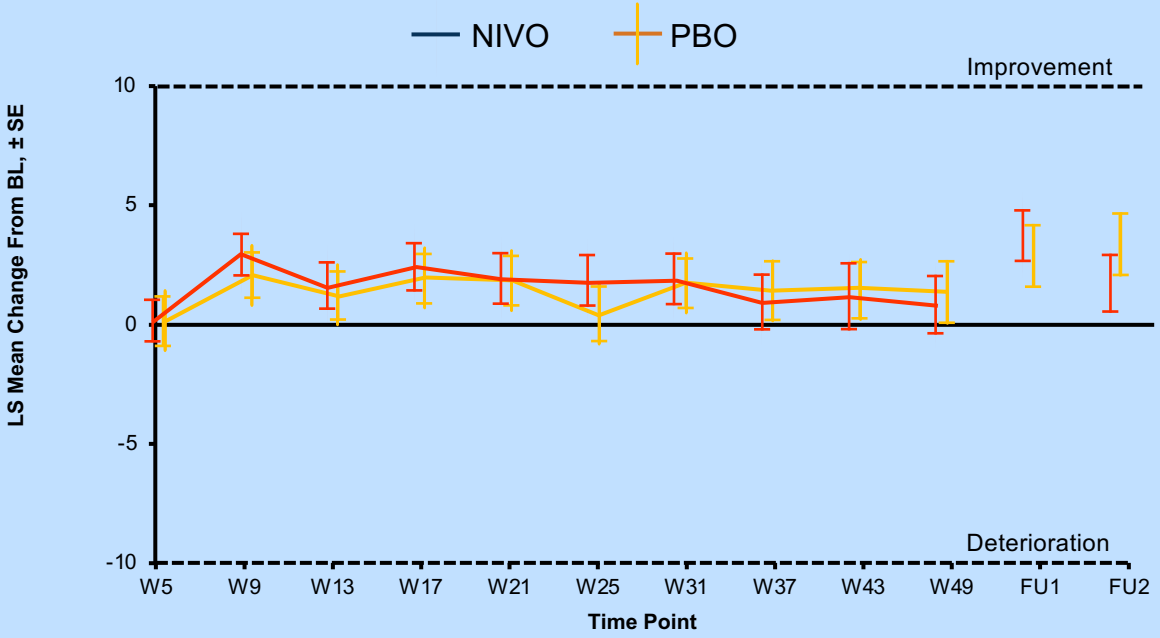


[a]Includes all treated patients.
There were 3 treatment-related deaths in the NIVO arm (2 instances of pneumonitis and 1 instance of bowel perforation).
Includes events reported between the first dose and 30 days after the last dose of study therapy.
Minimum follow-up in the ITT population, 31.6 months.
AE, adverse event.

Galsky MD et al ASCO GU 2023 LBA443.

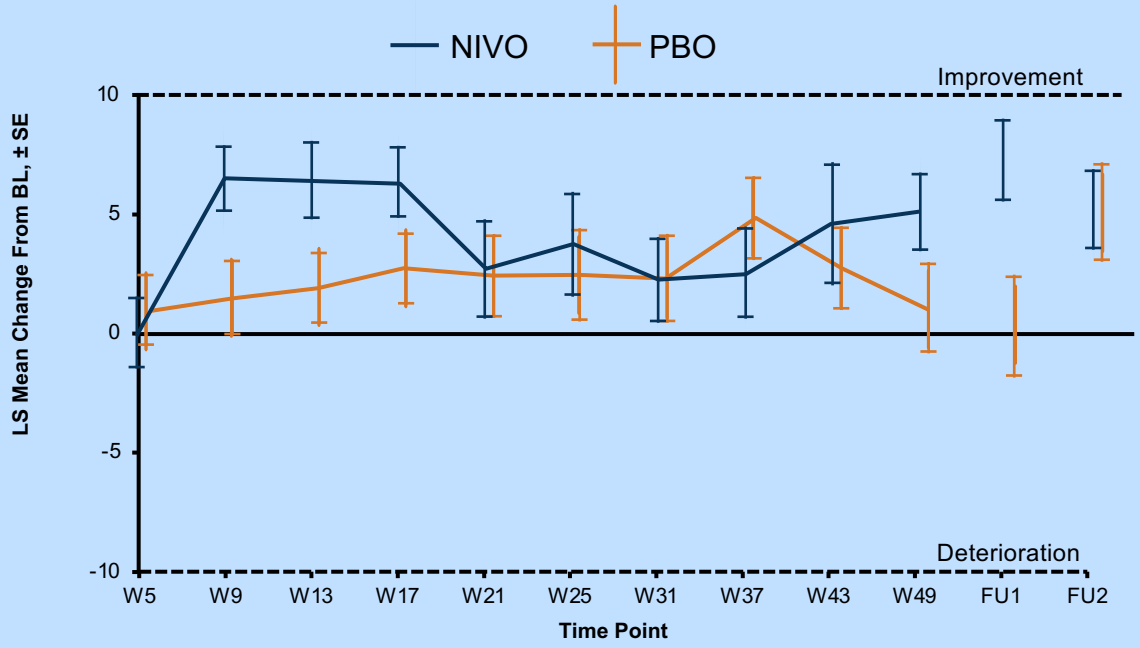
CheckMate 274: HRQOL

ITT



No. at Risk												
NIVO	296	273	250	221	211	192	167	154	139	131	125	112
PBO	291	282	238	212	212	190	162	148	130	124	113	99

PD-L1 ≥1%



No. at Risk												
NIVO	116	106	97	87	80	73	65	61	56	50	50	46
PBO	117	110	87	77	77	68	58	54	47	42	41	36

No deterioration in HRQOL with NIVO versus PBO
was observed in either the ITT or PD-L1 ≥1% populations

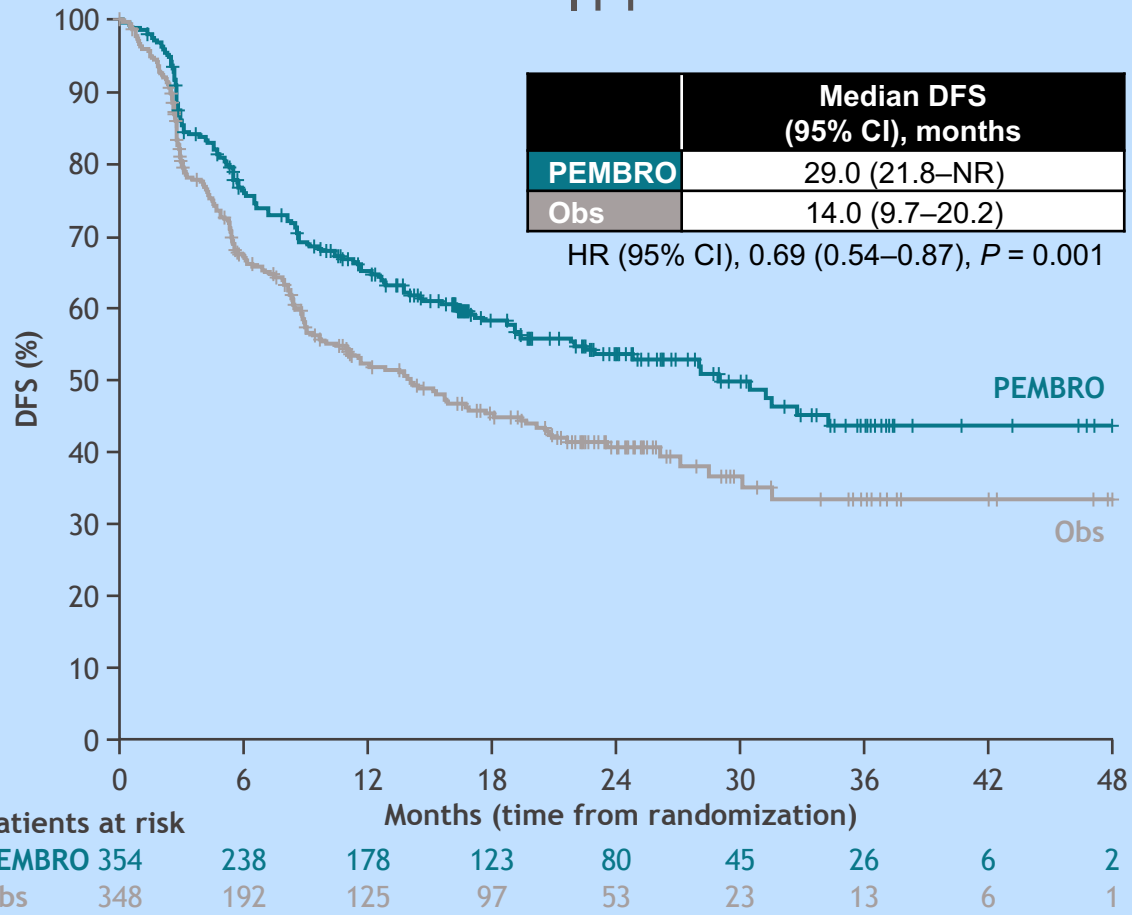
Bajorin DF et al. *N Engl J Med.* 2021;384:2102-2114.

AMBASSADOR

ITT[a,b]

	Median DFS (95% CI), months
PEMBRO	29.0 (21.8–NR)
Obs	14.0 (9.7–20.2)

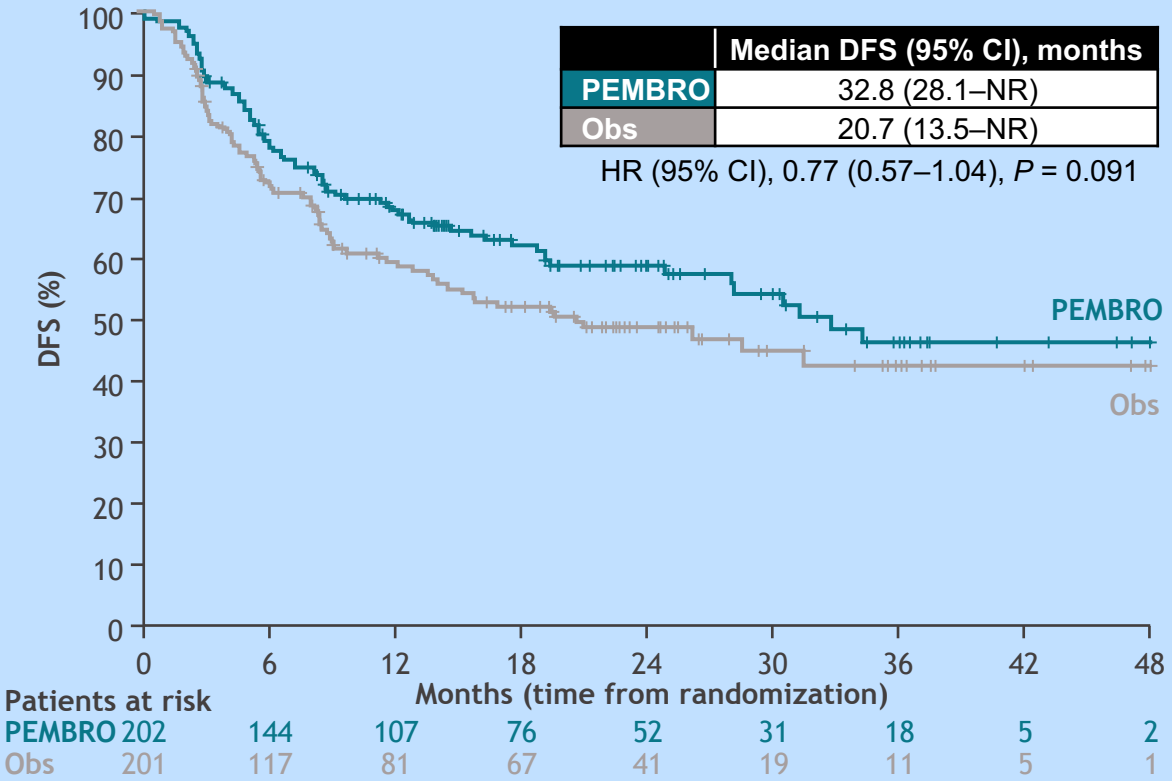
HR (95% CI), 0.69 (0.54–0.87), *P* = 0.001



PD-L1 CPS ≥ 10[c]

	Median DFS (95% CI), months
PEMBRO	32.8 (28.1–NR)
Obs	20.7 (13.5–NR)

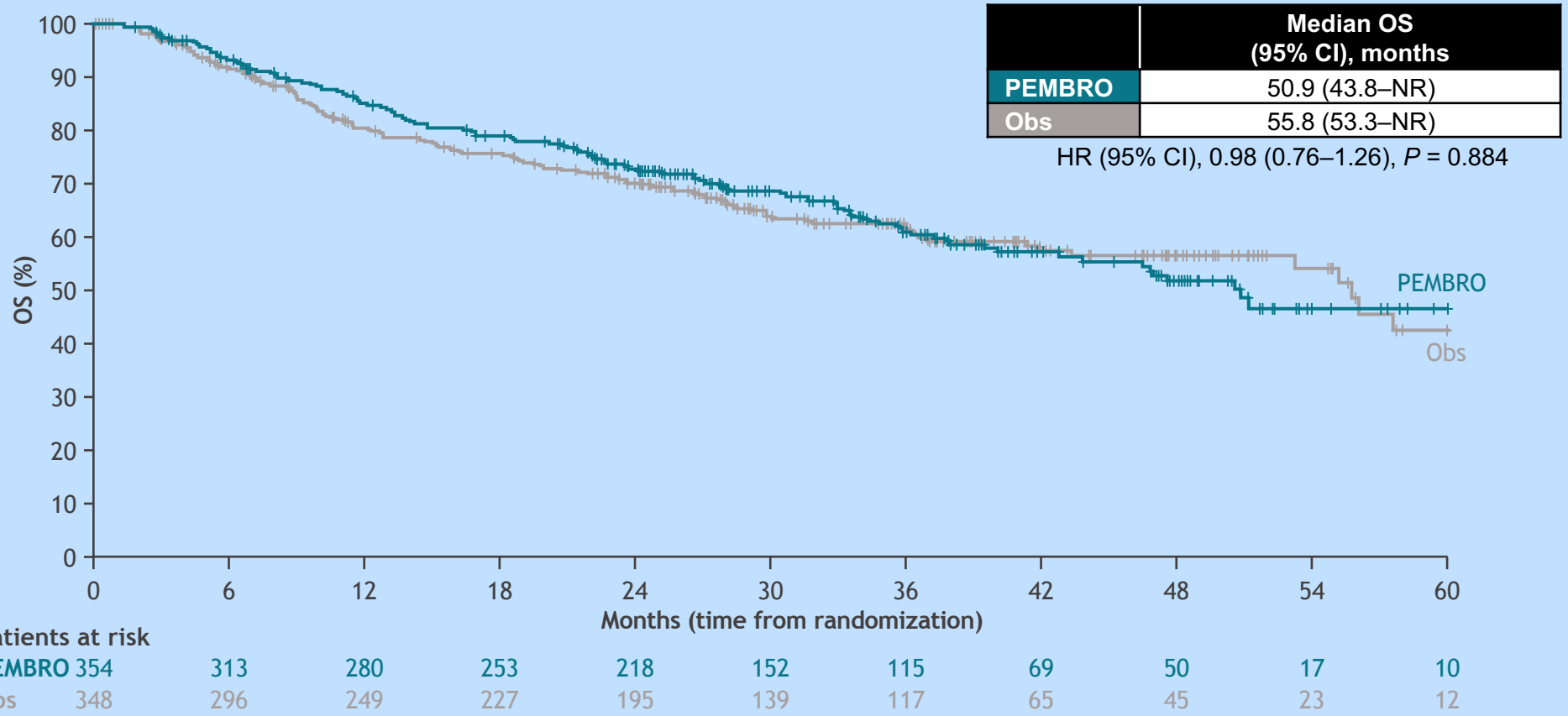
HR (95% CI), 0.77 (0.57–1.04), *P* = 0.091



[a]Median follow-up (range) 22.3 months (0.03–48.9). [b]DFS defined as new MIUC, metastatic disease, or death without recurrence. [c]Dako PD-L1 IHC 22C3 pharmDx assay.
DFS, disease-free survival; MIUC, muscle-invasive urothelial carcinoma; NR, not reached; Obs, observation; PEMBRO, pembrolizumab.
Apolo A et al. Presentation at the American Society for Clinical Oncology Genitourinary Cancers (ASCO GU) Symposium; January 25-27, 2024; San Francisco, California. Abstract LBA531.

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

AMBASSADOR



	Median OS (95% CI), months
PEMBRO	50.9 (43.8–NR)
Obs	55.8 (53.3–NR)

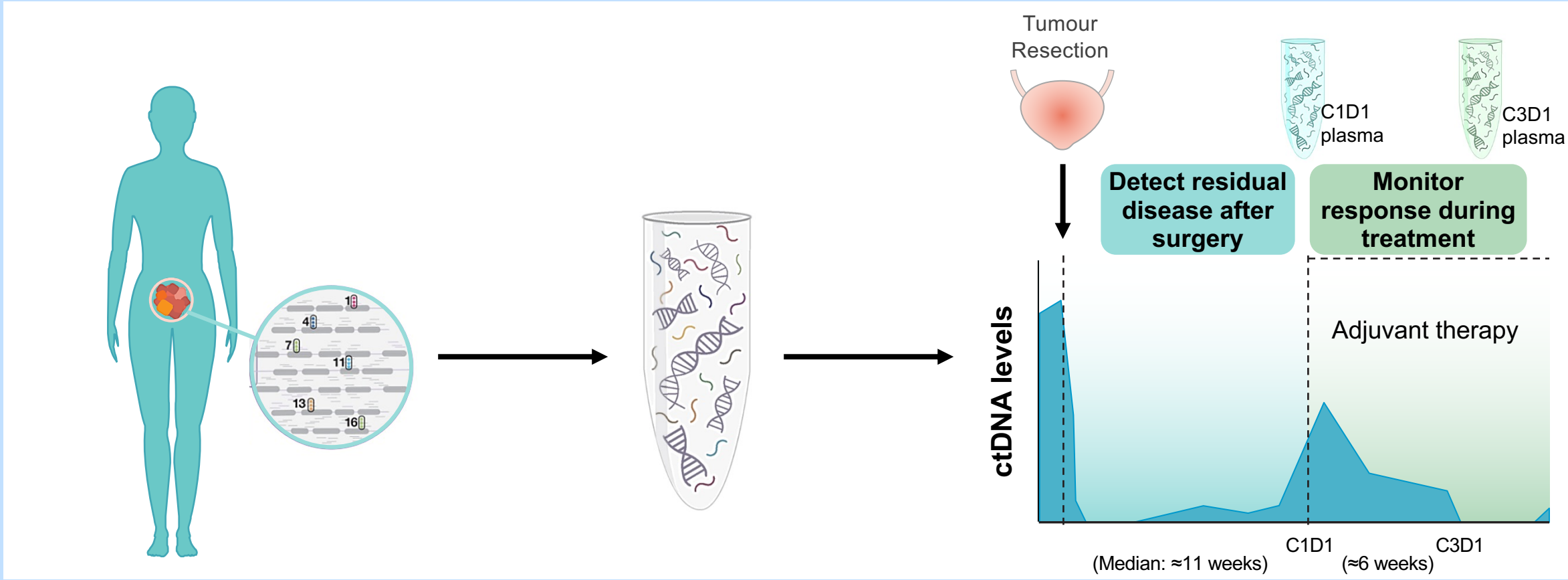
HR (95% CI), 0.98 (0.76–1.26), *P* = 0.884

Median follow-up (range) 36.9 months (0–63.9).

CPI, checkpoint inhibitor; NR, not reached; Obs, observation; OS, overall survival; PEMBRO, pembrolizumab.

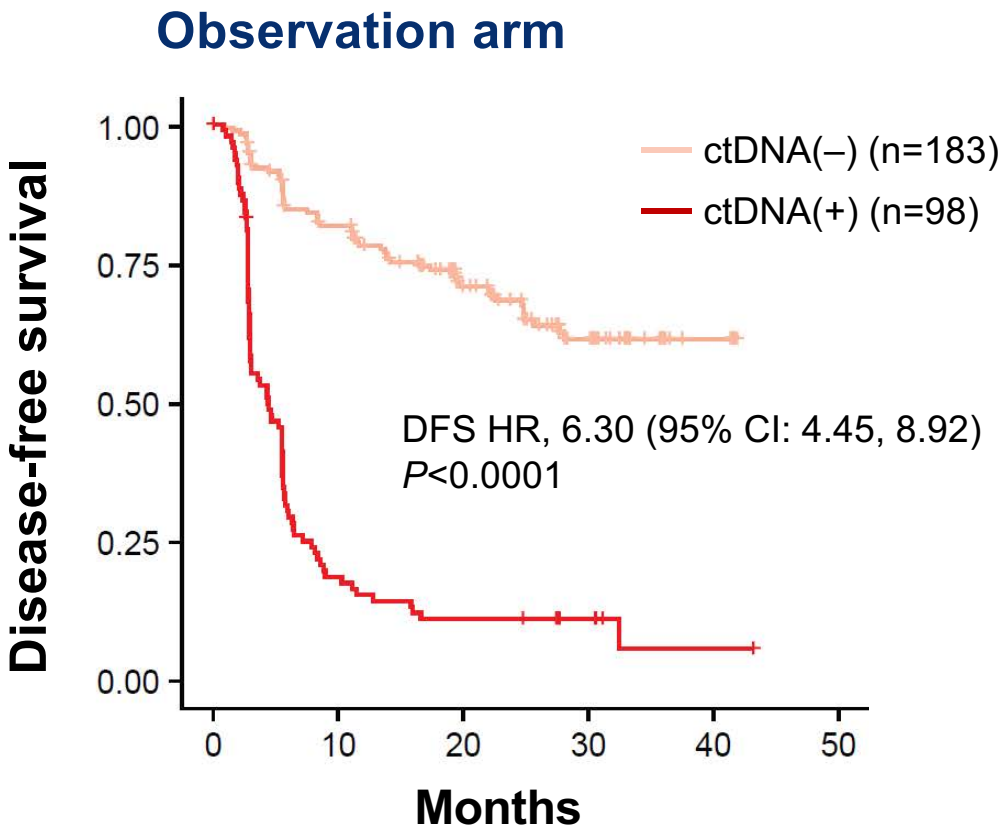
Apolo A et al. Presentation at the American Society for Clinical Oncology Genitourinary Cancers (ASCO GU) Symposium; January 25-27, 2024; San Francisco, California. Abstract LBA531.

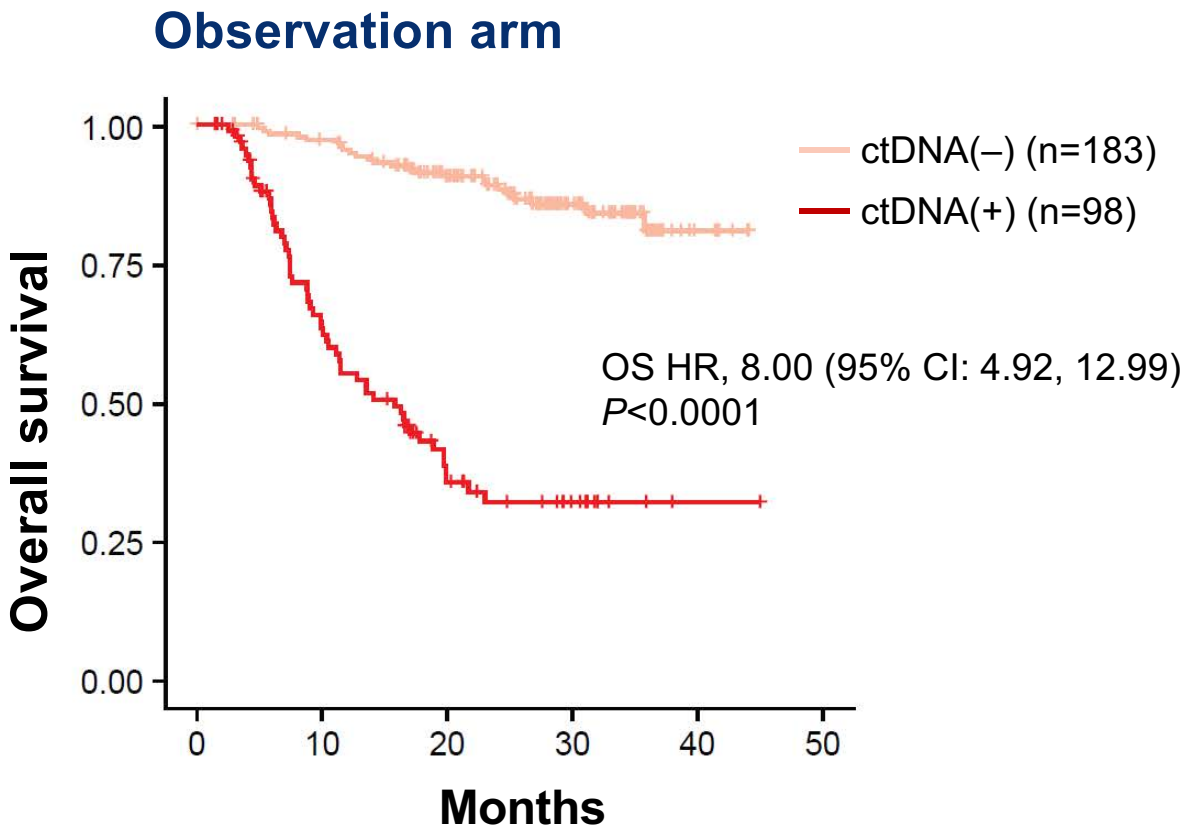
Identifying patients who *need* treatment: Evaluation of ctDNA in IMvigor010



Powles et al, Nature, 2021

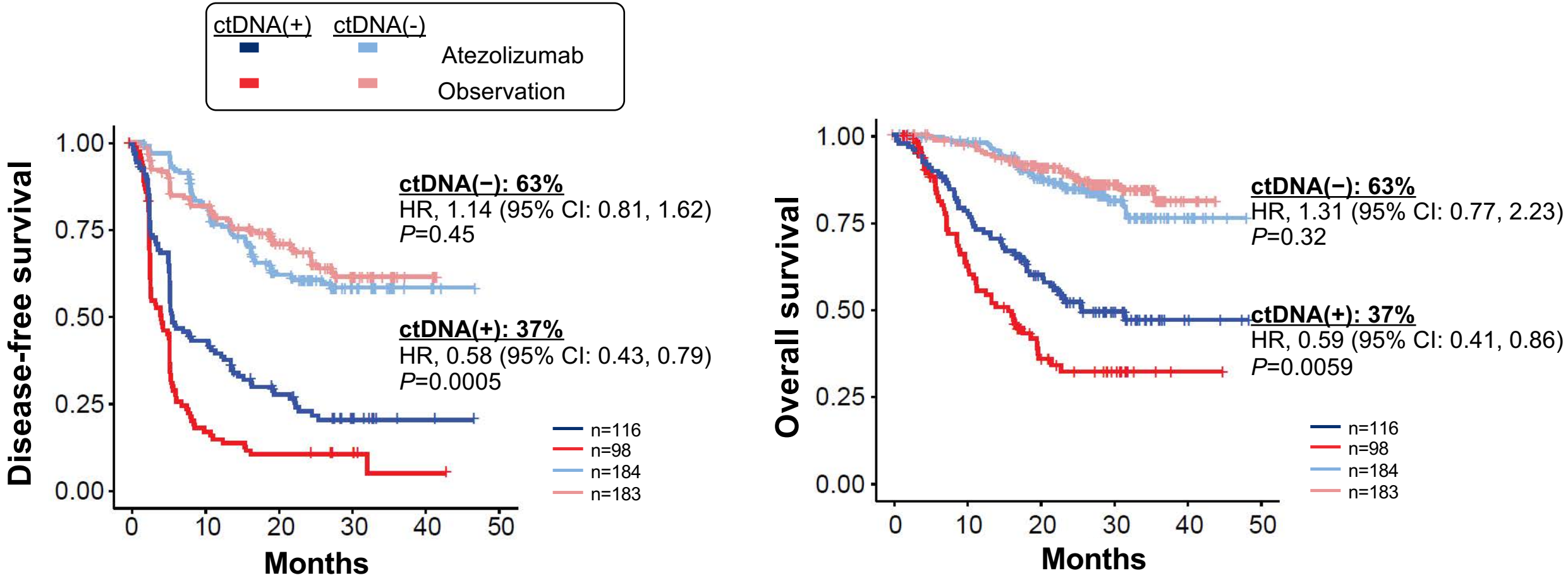
DFS and OS on observation arm of IMvigor010 according to ctDNA at baseline





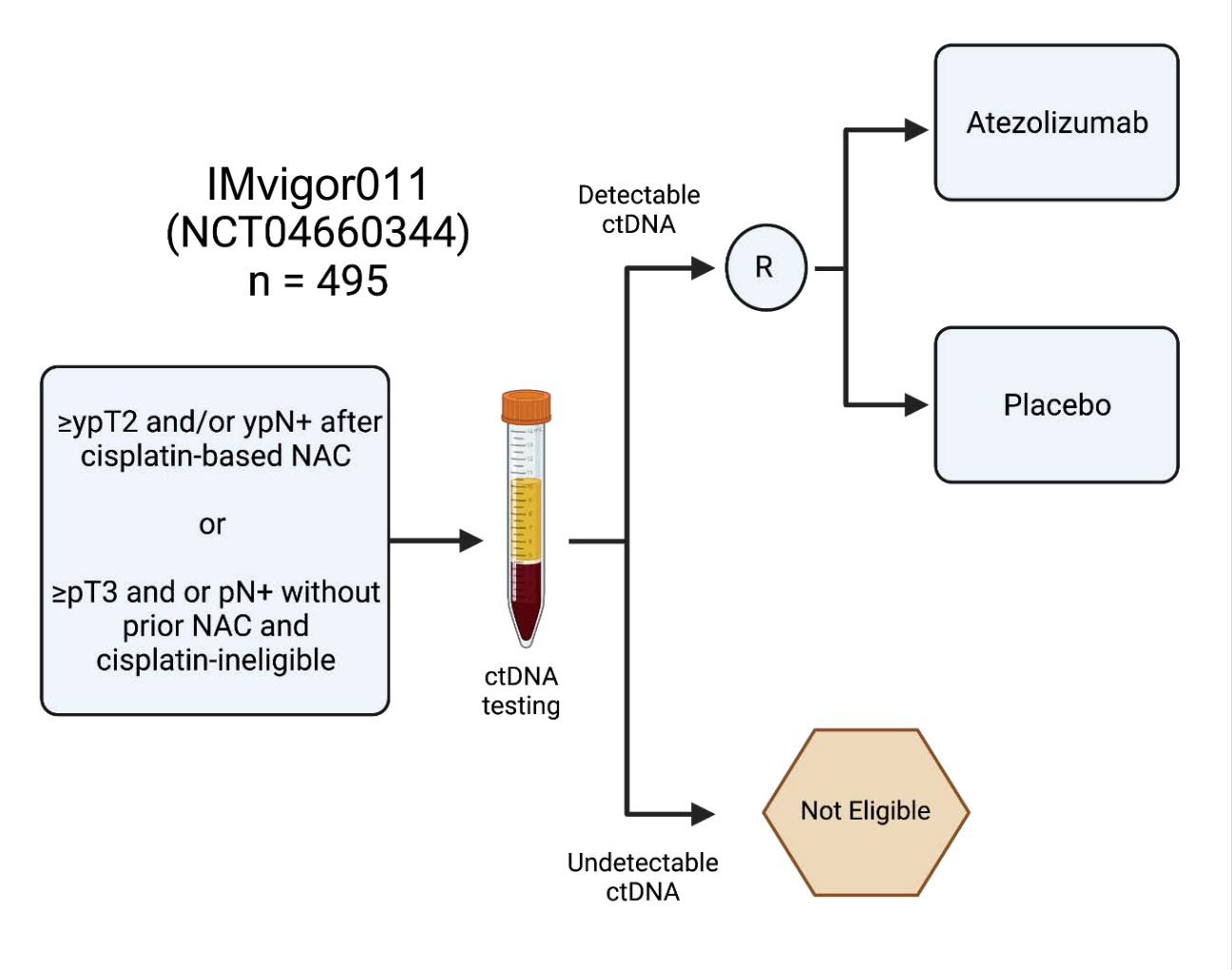
Powles et al, Nature, 2021

Impact of treatment on outcomes according to baseline ctDNA status on IMvigor010

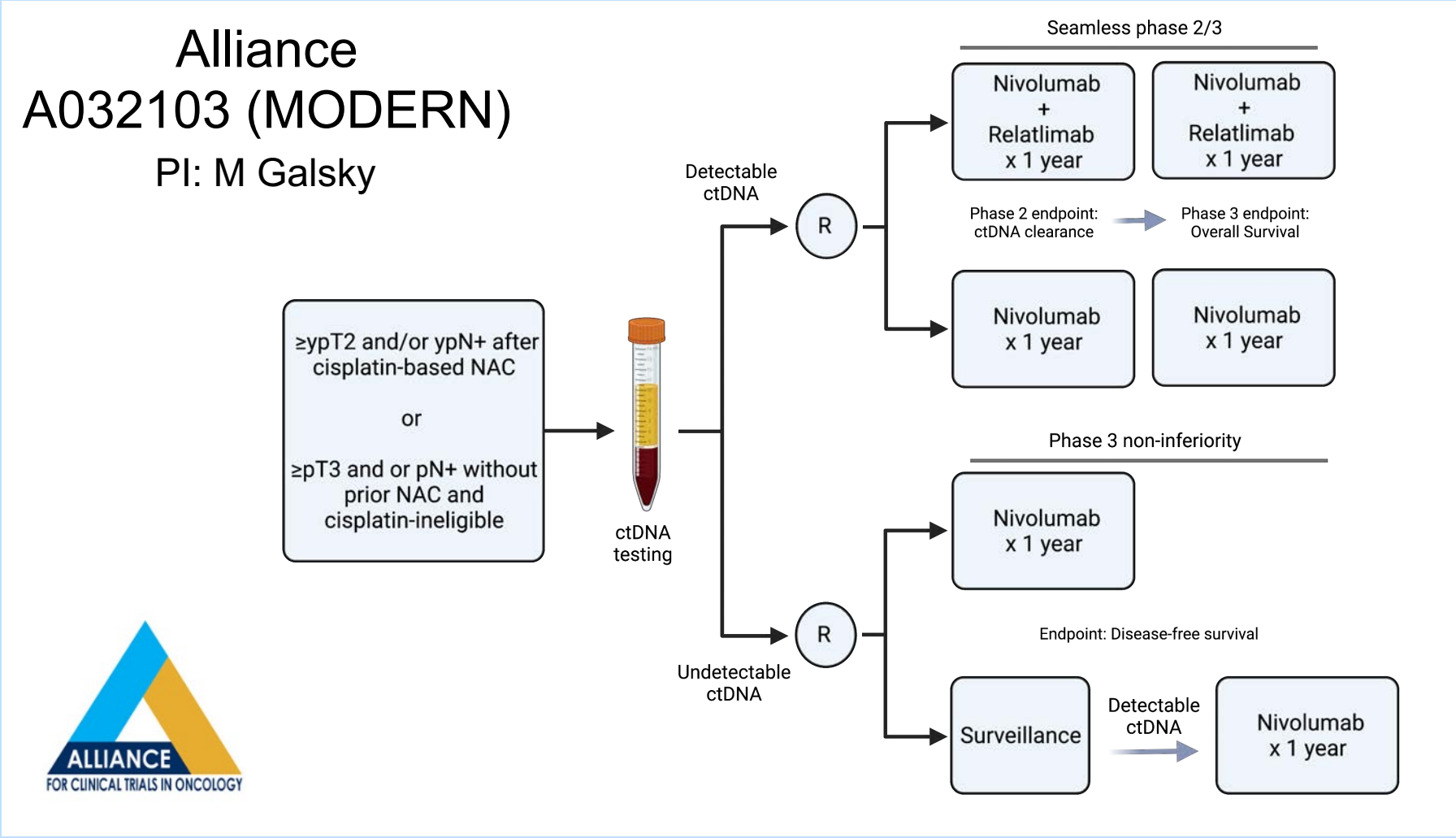


Powles et al, Nature, 2021

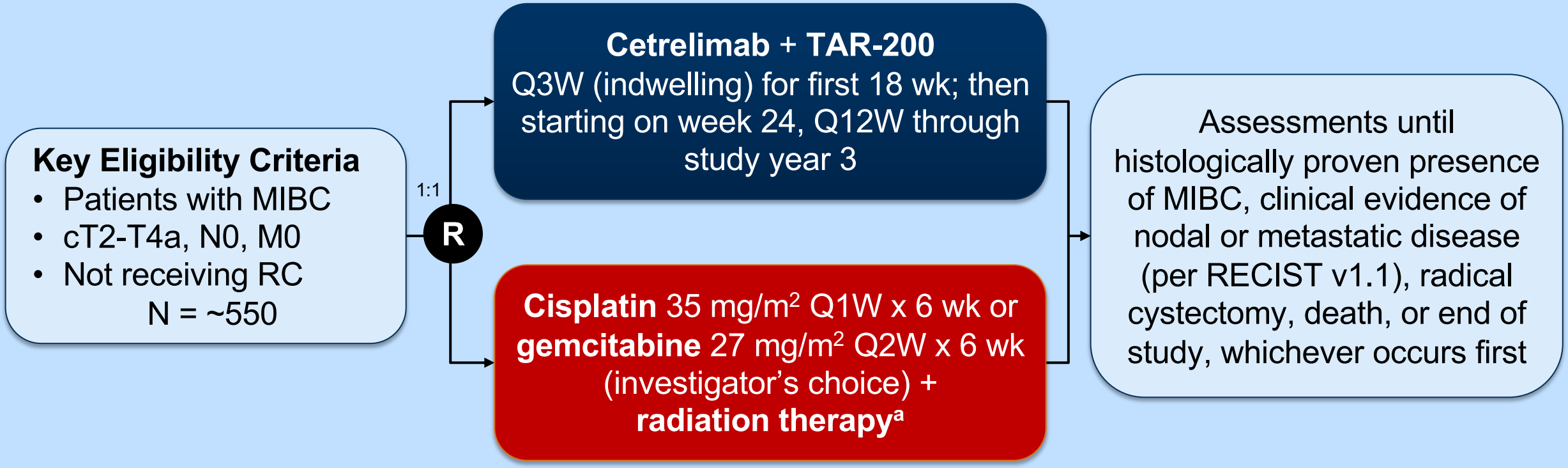
Can ctDNA be used to identify who *needs* treatment?



Can ctDNA testing define new perioperative treatment paradigms?



Phase 3 SunRISe-2: TAR-200 + PD-1 Inhibitor Cetrelimab vs Concurrent Chemoradiotherapy



- **Stratification**
  - Completeness (visibly completed vs incomplete [residual tumor <3])
  - Tumor stage (t0 vs Ta/T1/Tis vs T2-T4a)
- **Primary endpoint:** bladder-intact EFS

Williams SB et al. ASCO 2021;Abstract TPS4586.

Agenda

Module 1: Nonmetastatic Urothelial Bladder Cancer (UBC) — Dr Galsky

Module 2: Metastatic UBC — Dr Rosenberg

Memorial Sloan Kettering Cancer Center

Treatment of metastatic urothelial bladder cancer

Jonathan Rosenberg, MD
Chief, Genitourinary Oncology Service
Enno Ercklentz Chair
Department of Medicine
Memorial Sloan Kettering Cancer Center
Professor of Medicine
Weill Cornell Medical College

Disclosures

Advisory Committees	Astellas, Seagen Inc, Tyra Biosciences
Consulting Agreements	Aadi Bioscience, Alligator Bioscience, Astellas, AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, EMD Serono Inc, Emergence Therapeutics, Genentech, a member of the Roche Group, Gilead Sciences Inc, Imvax Inc, Infinity Pharmaceuticals Inc, Jiangsu Hengrui Medicine Co Ltd, Lilly, Merck, Mirati Therapeutics Inc, Pfizer Inc, QED Therapeutics, Seagen Inc, Tyra Biosciences
Contracted Research	Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Seagen Inc
Speakers Bureaus	EMD Serono Inc, Pfizer Inc
Nonrelevant Financial Relationships	Clinical Care Options, Medscape, MJH Life Sciences

Case

- 58 yo man with h/o intermediate favorable risk prostate cancer s/p HIFU in 2020, presented with gross hematuria 9/2023.
- Imaging with ill-defined low density liver lesions measuring up to 1.9cm, R>L hydronephrosis, and enhancing thickened bladder wall.
- TURBT with high grade poorly differentiated muscle invasive bladder cancer, and core needle biopsy of liver demonstrated metastatic carcinoma c/w poorly differentiated urothelial carcinoma.
- R PCN was placed and the patient was started on pembrolizumab and enfortumab vedotin
- After 3 cycles, tumors in the liver had resolved, and bladder wall thickening had decreased
- On cycle 4, pt noted increasing neuropathy in fingertips not affecting ADLs

EV-302/KEYNOTE-A39 (NCT04223856)

Patient population

- Previously untreated la/mUC
- Eligible for platinum, EV, and P
- PD-(L)1 inhibitor naive
- GFR ≥30 mL/min[a]
- ECOG PS ≤2[b]

N=886

R 1:1

EV + Pembrolizumab
No maximum treatment cycles for EV, maximum 35 cycles for P

Treatment until disease progression per BICR, clinical progression, unacceptable toxicity, or completion of maximum cycles

Chemotherapy[c]
(Cisplatin or carboplatin + gemcitabine)
Maximum 6 cycles

Dual primary endpoints:

- **PFS by BICR**
- **OS**

Select secondary endpoints:

- ORR per RECIST v1.1 by BICR and investigator assessment
- Safety

Stratification factors: cisplatin eligibility (eligible/ineligible), PD-L1 expression (high/low), liver metastases (present/absent)

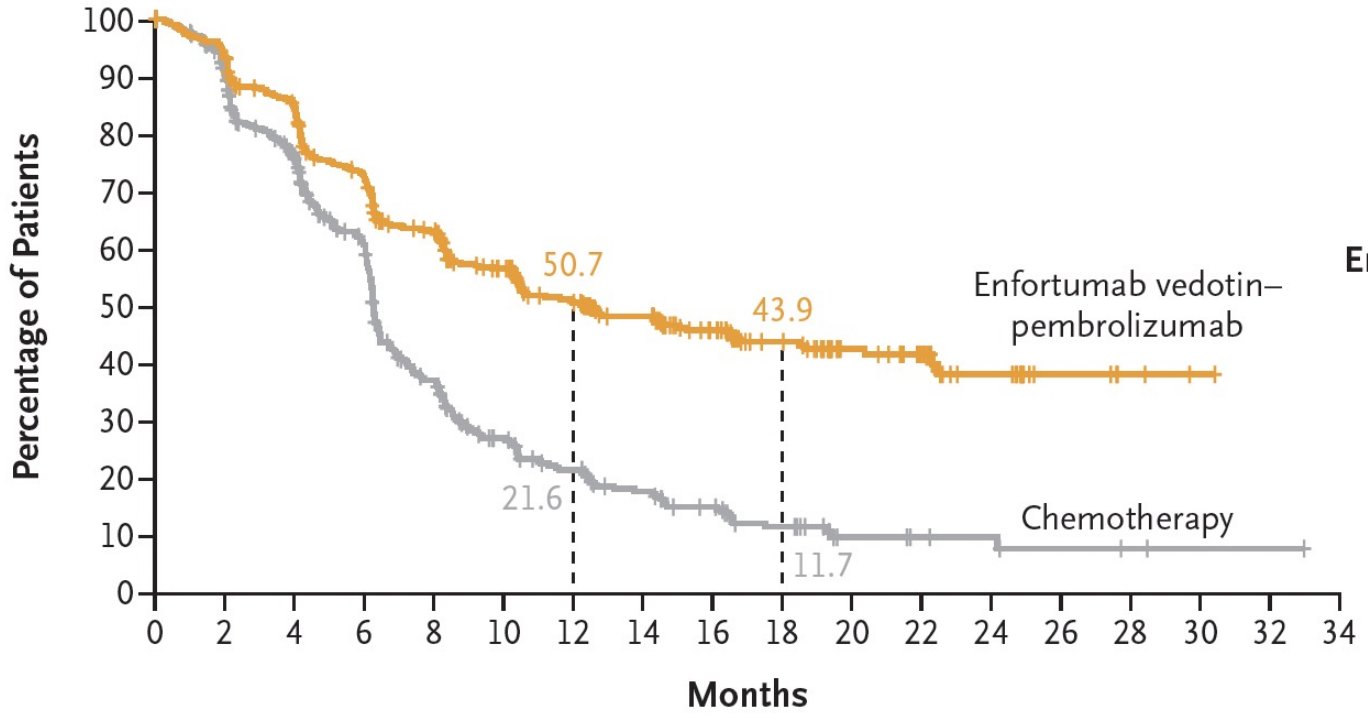
•Cisplatin eligibility and assignment/dosing of cisplatin vs carboplatin were protocol-defined; patients received 3-week cycles of EV (1.25 mg/kg; IV) on Days 1 and 8 and P (200 mg; IV) on Day 1

Statistical plan for analysis: the first planned analysis was performed after approximately 526 PFS (final) and 356 OS events (interim); if OS was positive at interim, the OS interim analysis was considered final

Adapted from Powles et al. ESMO 2023 LBA6

EV-302: Progression-Free Survival per BICR

Risk of progression or death was reduced by 55% in patients who received EV+P



	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)
		mo
Enfortumab Vedotin–Pembrolizumab	223/442	12.5 (10.4–16.6)
Chemotherapy	307/444	6.3 (6.2–6.5)

Hazard ratio, 0.45 (95% CI, 0.38–0.54)
Two-sided P<0.001

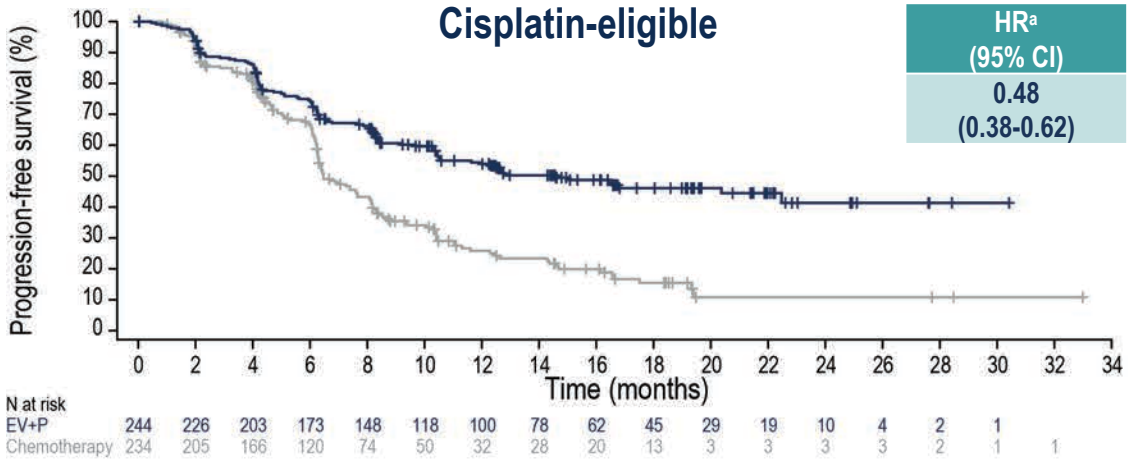
No. at Risk																	
Enfortumab vedotin–pembrolizumab	442	409	361	303	253	204	167	132	102	73	45	33	17	6	3	1	
Chemotherapy	444	380	297	213	124	78	56	41	30	19	8	6	5	3	2	1	1

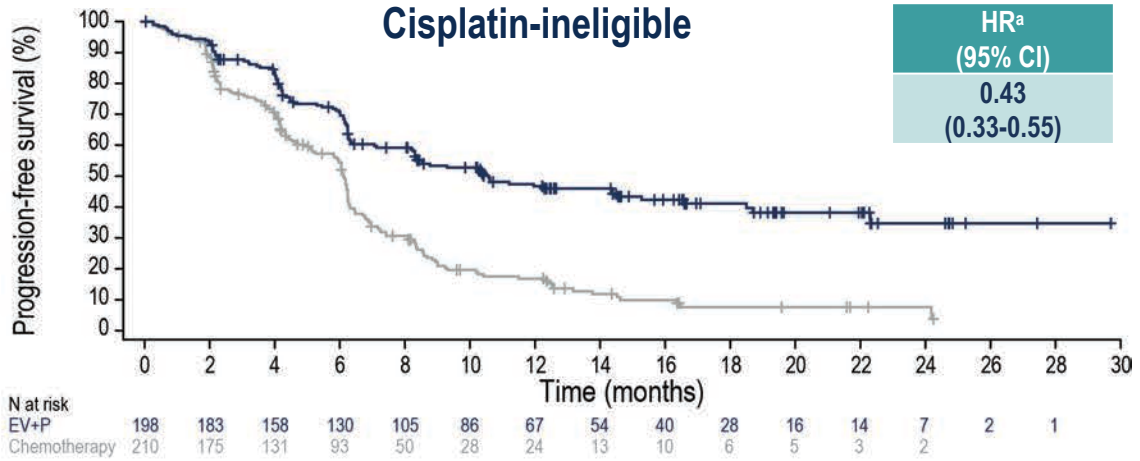
T Powles et al. N Engl J Med 2024;390:875-888.

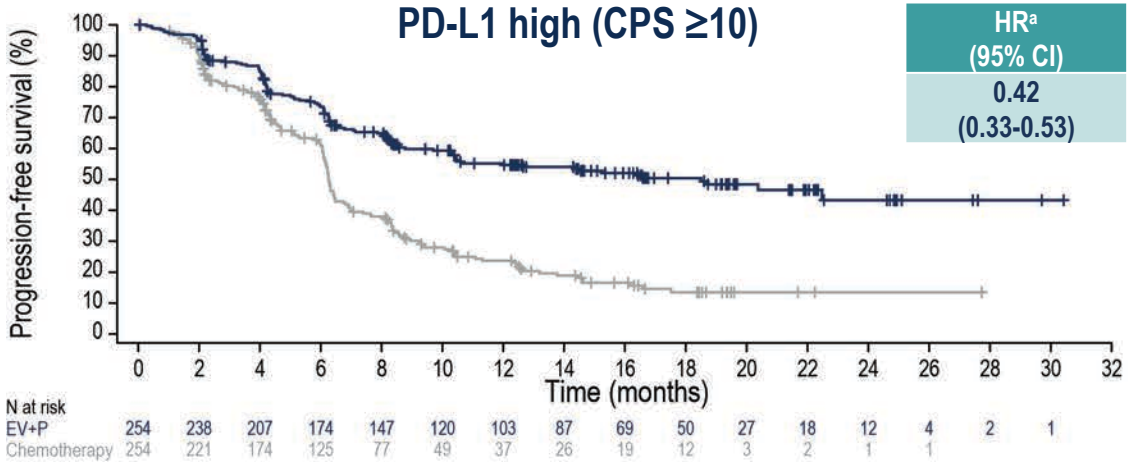
Memorial Sloan Kettering Cancer Center

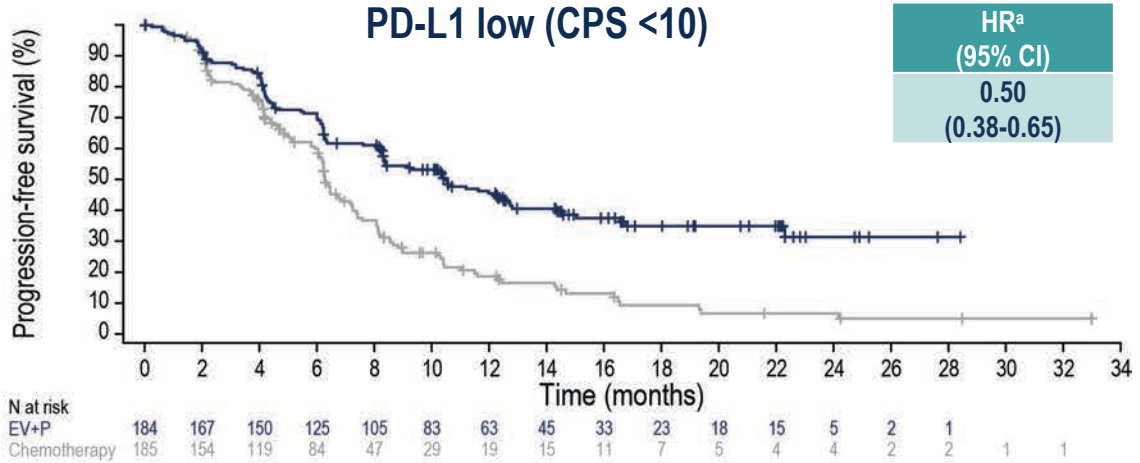
EV302 PFS by BICR Subgroup Analysis: Cisplatin Eligibility and PD-L1 Expression

PFS benefit was consistent with the overall population regardless of cisplatin eligibility or PD-L1 expression status









CPS, combined positive score

[a]Calculated using stratified Cox proportional hazards model; a hazard ratio <1 favors the EV+P arm

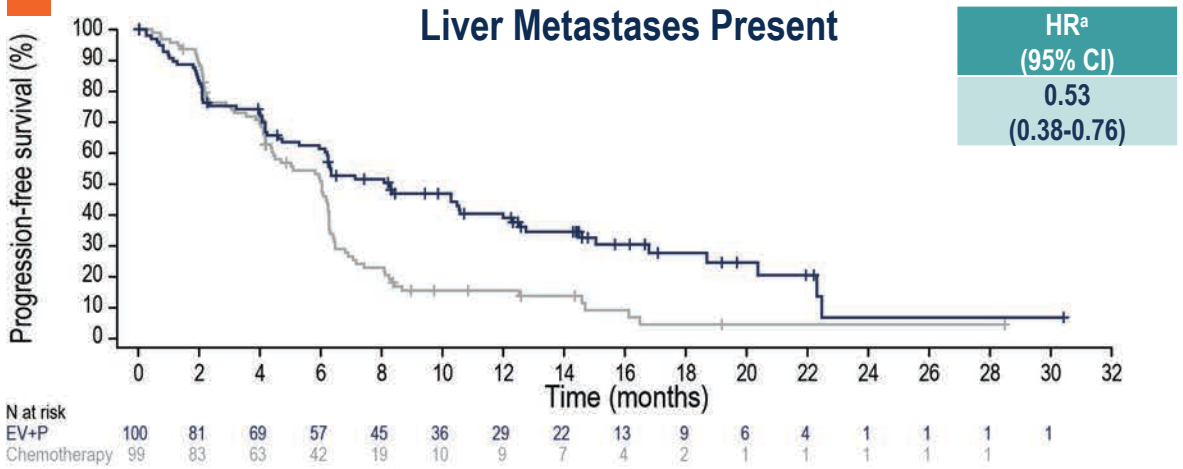
Data cutoff: 08 August 2023

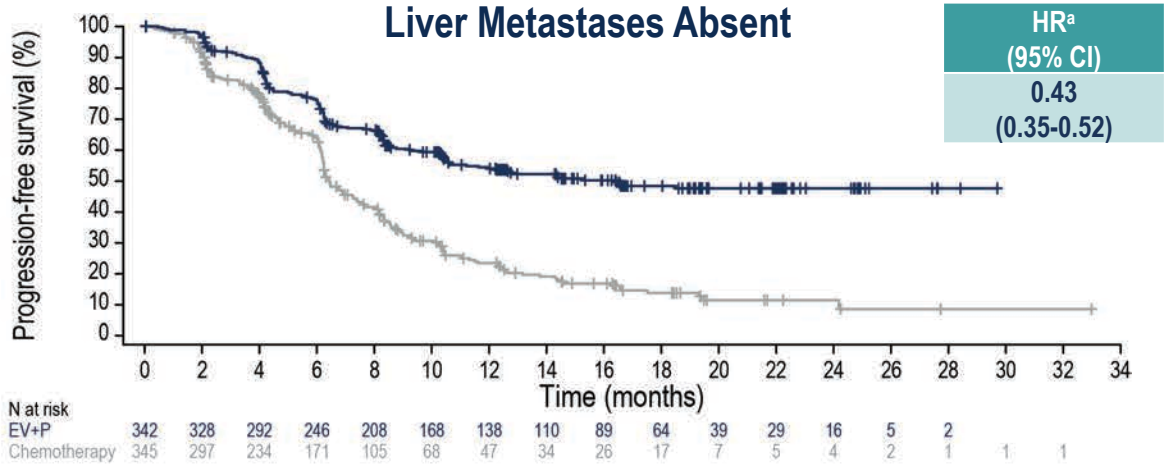
Van Der Heijden MS, et al. *J Clin Oncol* 42, 2024 (suppl 4; abstr LBA530)

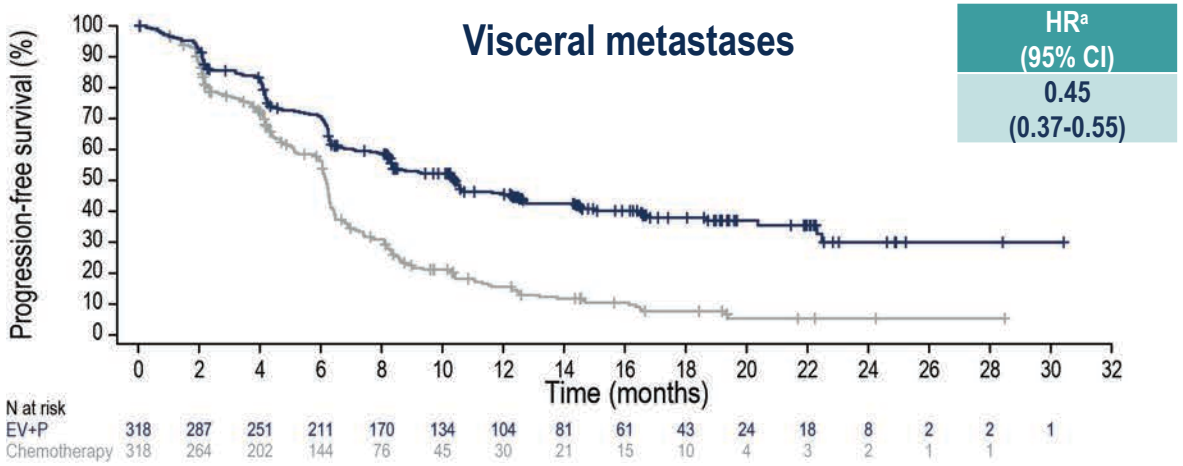
Memorial Sloan Kettering Cancer Center

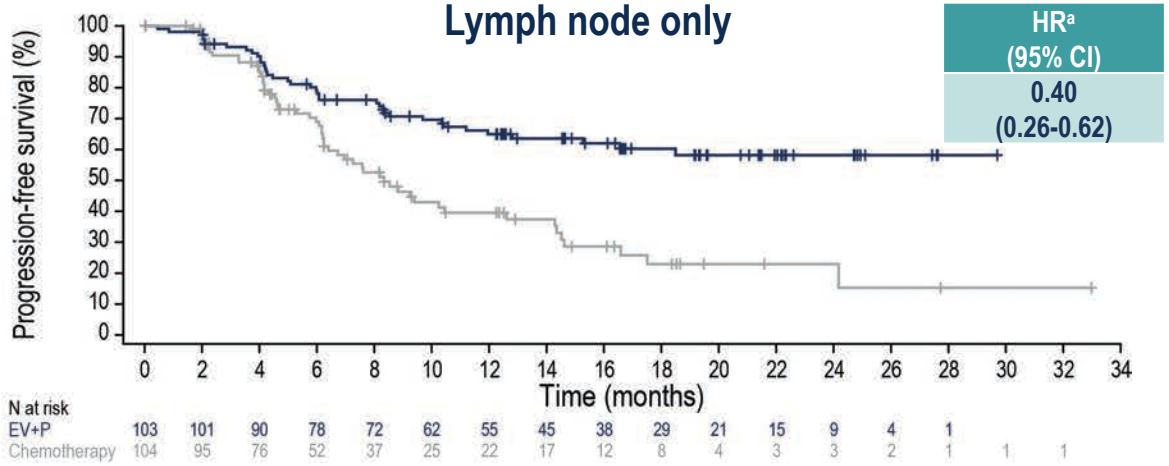
EV302 PFS by BICR Subgroup Analysis: Liver Metastases and Metastatic Disease Site

PFS benefit was consistent with the overall population regardless of the presence or absence of liver or visceral metastases









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Van Der Heijden MS, et al. *J Clin Oncol* 42, 2024 (suppl 4; abstr LBA530)

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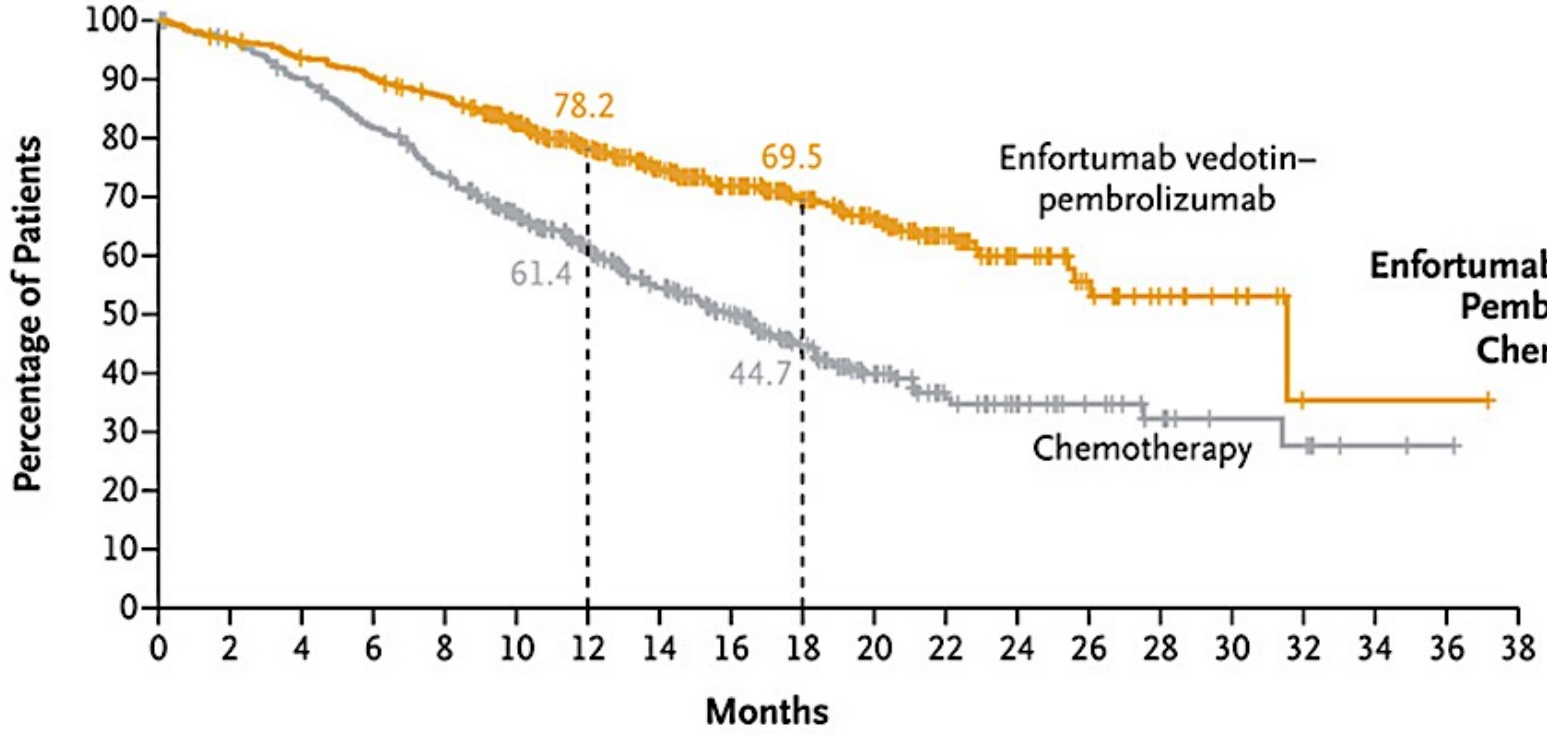
EV-302: Overall Survival

Risk of death was reduced by 53% in patients who received EV+P



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Chemotherapy	226/444	16.1 (13.9–18.3)

Hazard ratio, 0.47 (95% CI, 0.38–0.58)
Two-sided P<0.001

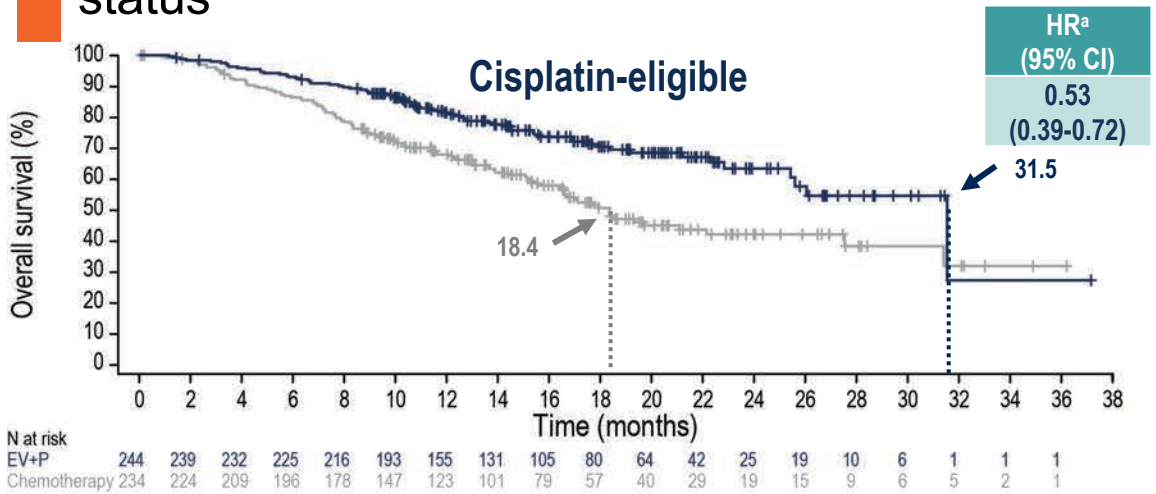
No. at Risk																			
Enfortumab vedotin–pembrolizumab	442	426	409	394	376	331	270	222	182	141	108	67	36	22	12	8	1	1	1
Chemotherapy	444	423	393	356	317	263	209	164	125	90	60	37	25	18	12	7	6	2	1

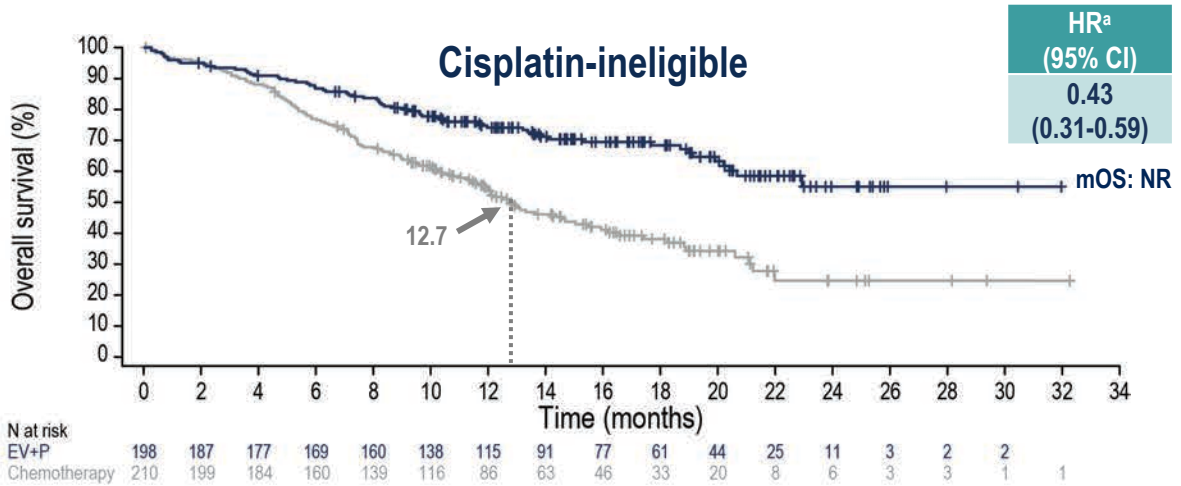
T Powles et al. N Engl J Med 2024;390:875-888.

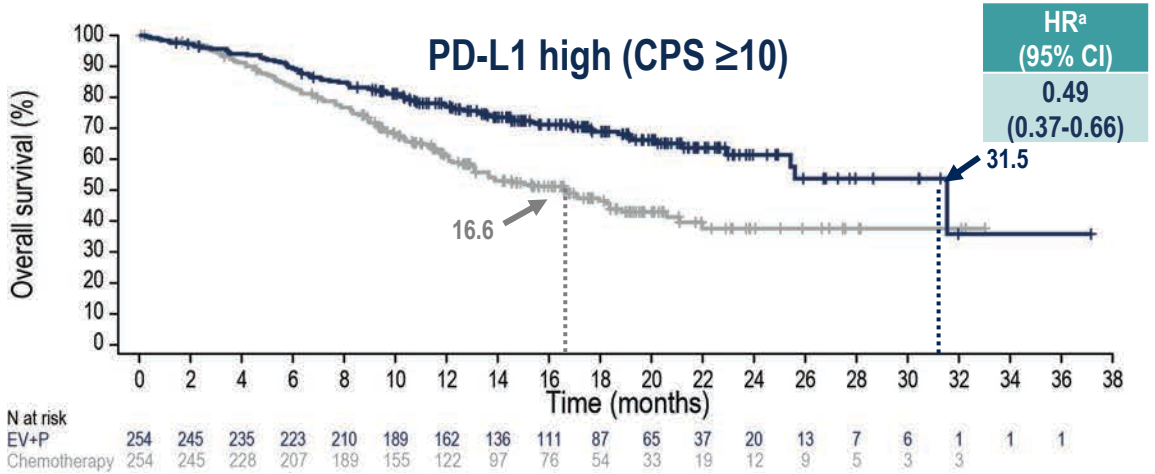
Memorial Sloan Kettering Cancer Center

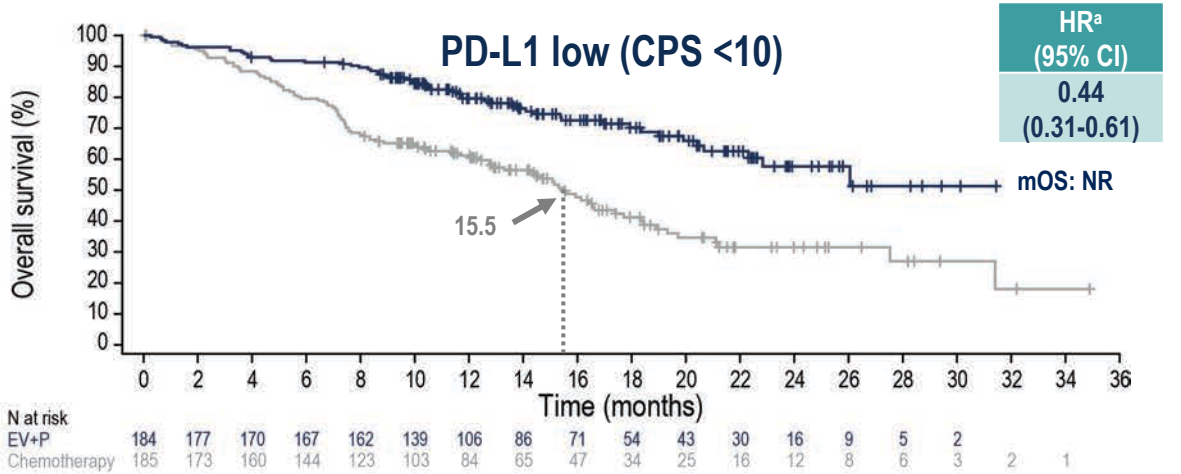
OS Subgroup Analysis: Cisplatin Eligibility and PD-L1 Expression

OS benefit was consistent with the overall population regardless of cisplatin eligibility or PD-L1 expression status









Data cutoff: 08 August 2023

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Van Der Heijden MS, et al. *J Clin Oncol* 42, 2024 (suppl 4; abstr LBA530)

Memorial Sloan Kettering Cancer Center

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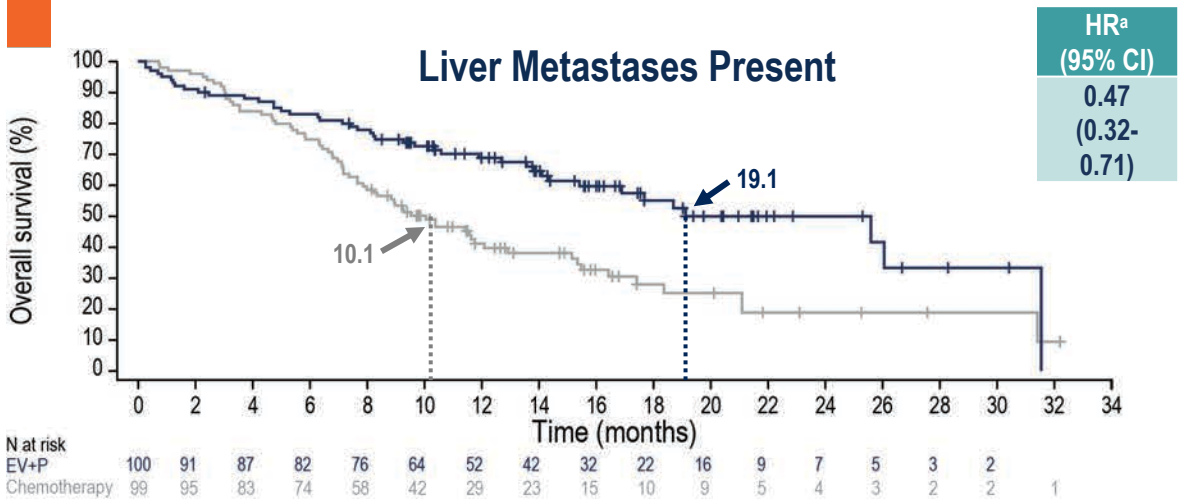
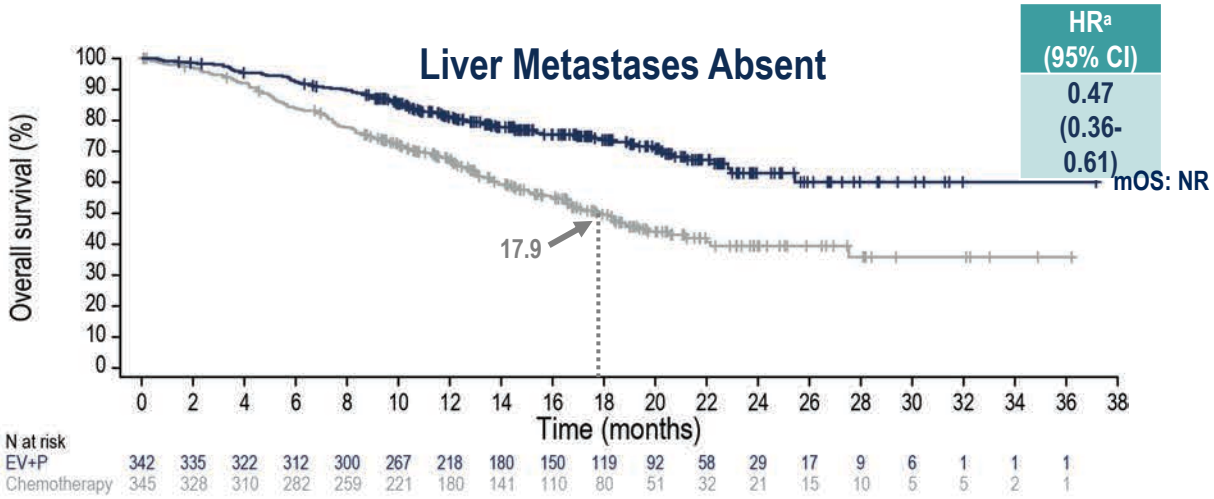
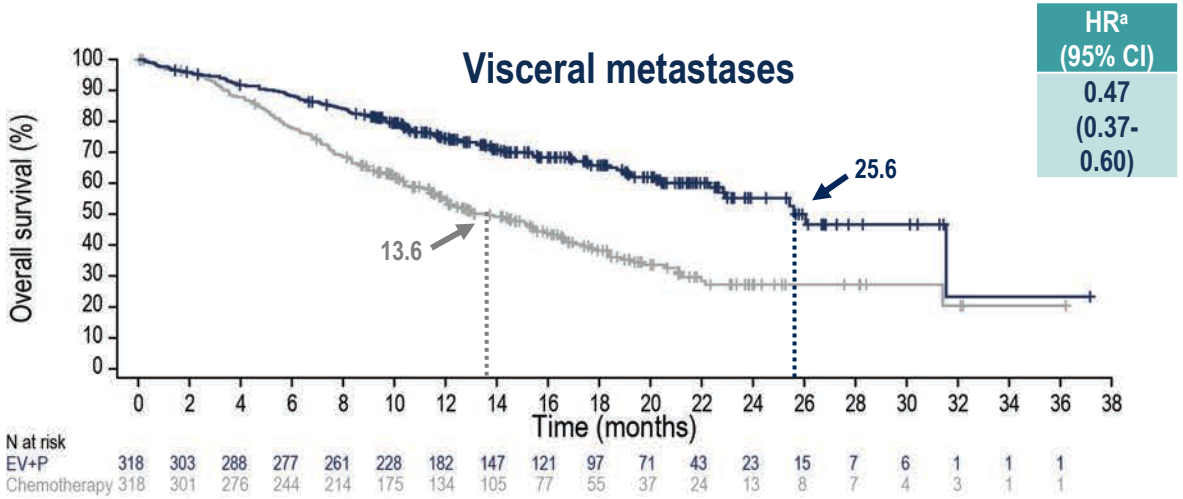
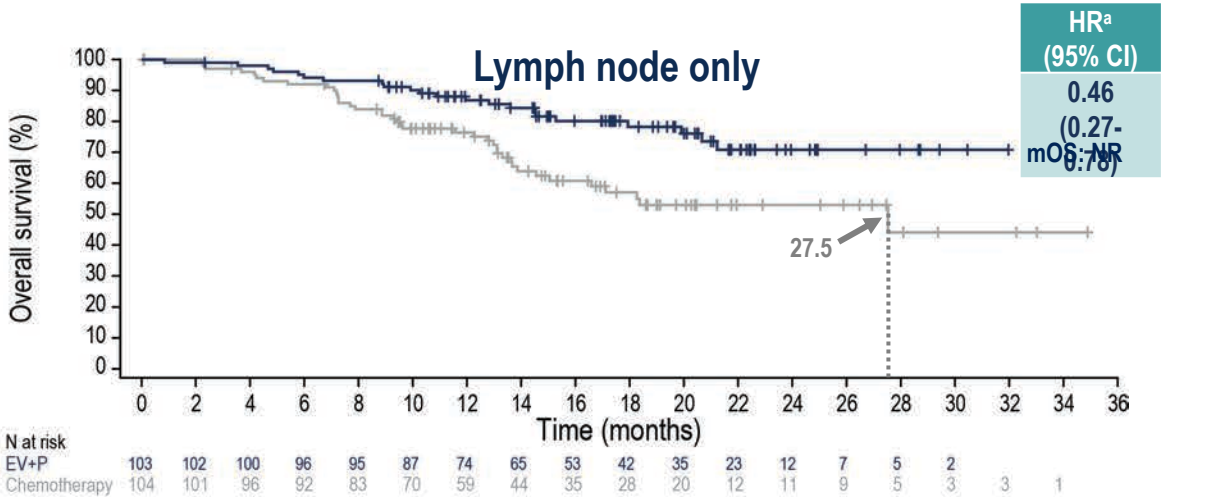






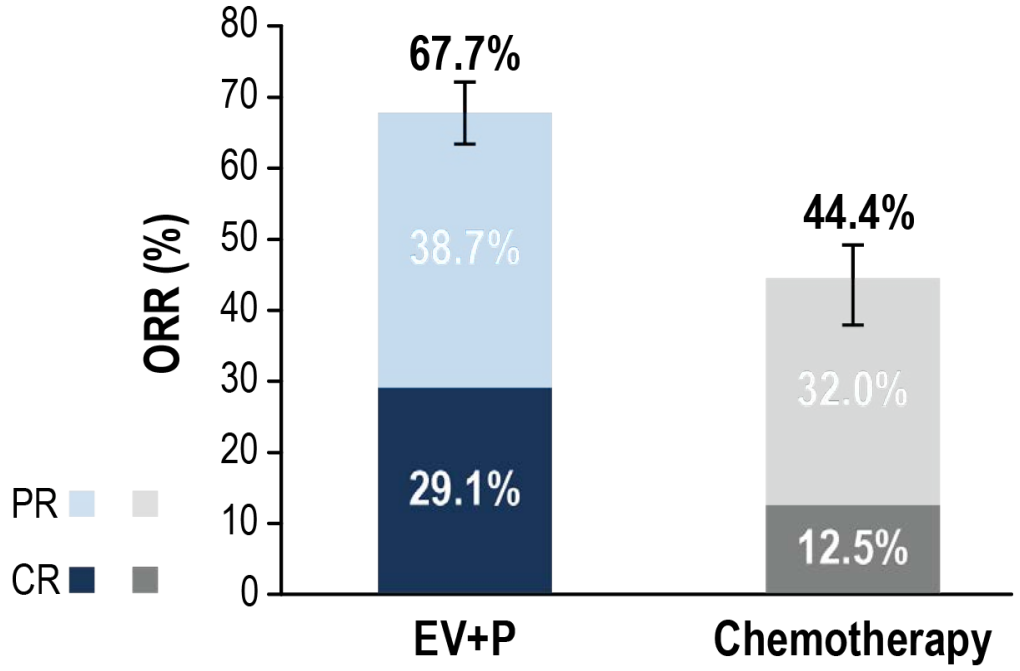


Data cutoff: 08 August 2023

[a]Calculated using stratified Cox proportional hazards model; a hazard ratio <1 favors the EV+P arm

EV-302: Confirmed Overall Response per BICR

Significant improvement in objective response rate was observed with EV+P



	EV+P (N=437)	Chemotherapy (N=441)
Confirmed ORR, n (%) (95% CI)	**296 (67.7) (63.1-72.1)**	**196 (44.4) (39.7-49.2)**
2-sided P value	<0.00001	
Best overall response[a], n (%)		
Complete response	127 (29.1)	55 (12.5)
Partial response	169 (38.7)	141 (32.0)
Stable disease	82 (18.8)	149 (33.8)
Progressive disease	38 (8.7)	60 (13.6)
Not evaluable/No assessment[b]	21 (4.8)	36 (8.2)
Median DOR (95% CI)	NR (20.2, NR)	7.0 (6.2, 10.2)

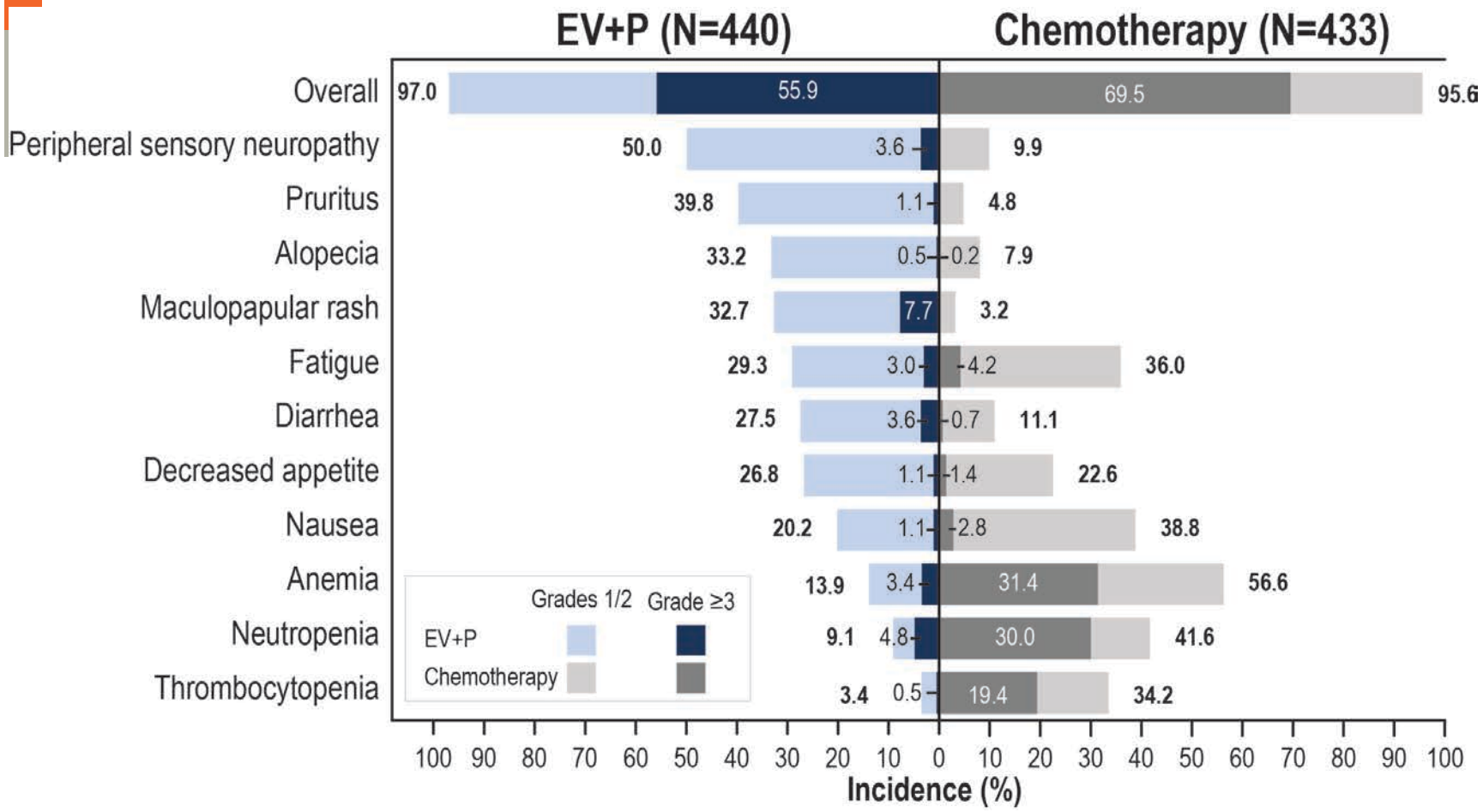
EV+P ORR is remarkably consistent across studies

Adapted from Powles et al. ESMO 2023 LBA6

Memorial Sloan Kettering Cancer Center

EV-302: Treatment-Related Adverse Events

Grade ≥3 events were 56% in EV+P and 70% in chemotherapy



Serious TRAEs:

- 122 (27.7%) EV+P
- 85 (19.6%) chemotherapy

TRAEs leading to death (per investigator):

EV+P: 4 (0.9%)

- Asthenia
- Diarrhea
- Immune-mediated lung disease
- Multiple organ dysfunction syndrome

Chemotherapy: 4 (0.9%)

- Febrile neutropenia
- Myocardial infarction
- Neutropenic sepsis
- Sepsis

Median number of cycles (range): 12.0 (1,46) for EV+P; 6.0 (1,6) for chemotherapy

Adapted from Powles et al. ESMO 2023 LBA6

EV-302: EV Treatment-Related Adverse Events of Special Interest

Majority of treatment-related AESIs were low grade

	EV+P (N=440) n (%)		Chemotherapy (N=433) n (%)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Skin reactions	294 (66.8)	68 (15.5)	60 (13.9)	1 (0.2)
Peripheral neuropathy	278 (63.2)	30 (6.8)	53 (12.2)	0 (0.0)
Sensory events	260 (59.1)	19 (4.3)	51 (11.8)	0 (0.0)
Motor events	44 (10.0)	12 (2.7)	5 (1.2)	0 (0.0)
Ocular disorders	94 (21.4)	0 (0.0)	12 (2.8)	0 (0.0)
Dry eye	82 (18.6)	0 (0.0)	8 (1.8)	0 (0.0)
Hyperglycemia	57 (13.0)	27 (6.1)	3 (0.7)	0 (0.0)
Infusion-related reactions	9 (2.0)	0 (0.0)	9 (2.1)	0 (0.0)

Adapted from Powles et al. ESMO 2023 LBA6

Careful monitoring of skin toxicity is critical to EV management

Prevention[a]	Monitoring[24]	Warning signs and symptoms of severe cutaneous adverse events, including SJS/TEN[32]

Barrier-protecting agents (eg., zinc-containing moisturizers), and sunscreen, regardless of the causative mechanism of the dermatologic event	• Routine skin assessments and follow-up starting with the first cycle of treatment
	• Patient/caretaker education on possible dermatologic events and the need for immediate notification of new or worsening dermatologic events and signs of severe cutaneous adverse events
		• Malaise
		• Fever ≥100.4°F
		• Mucosal involvement
		  • Ocular (conjunctivitis)
		  • Oral
		  • Genital
		• Dermatodynia (skin pain, burning, numbness, or tingling)

Management of dermatologic event by severity

Grade 1 → Supportive care as clinically indicated (eg., topical corticosteroids/antibiotics[a,b] and antihistamines)[24]

Grade 2 → • Supportive care as clinically indicated (eg., topical corticosteroids/antibiotics and antihistamines)[a,b]
• Consider anti-infectives for the treatment of suspected or confirmed concurrent infections[a]

Grade 3 → • Interrupt enfortumab vedotin until grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level[24]
• Oral corticosteroids (eg., prednisone 0.5 mg/kg/day or equivalent for 14 days)[a]
• Consider dermatologic consultation[a]

Recommended dose reduction schedule[24]

	Dose level
Starting dose	1.25 mg/kg up to 125 mg
First dose reduction	1.0 mg/kg up to 100 mg
Second dose reduction	0.75 mg/kg up to 75 mg
Third dose reduction	0.5 mg/kg up to 50 mg

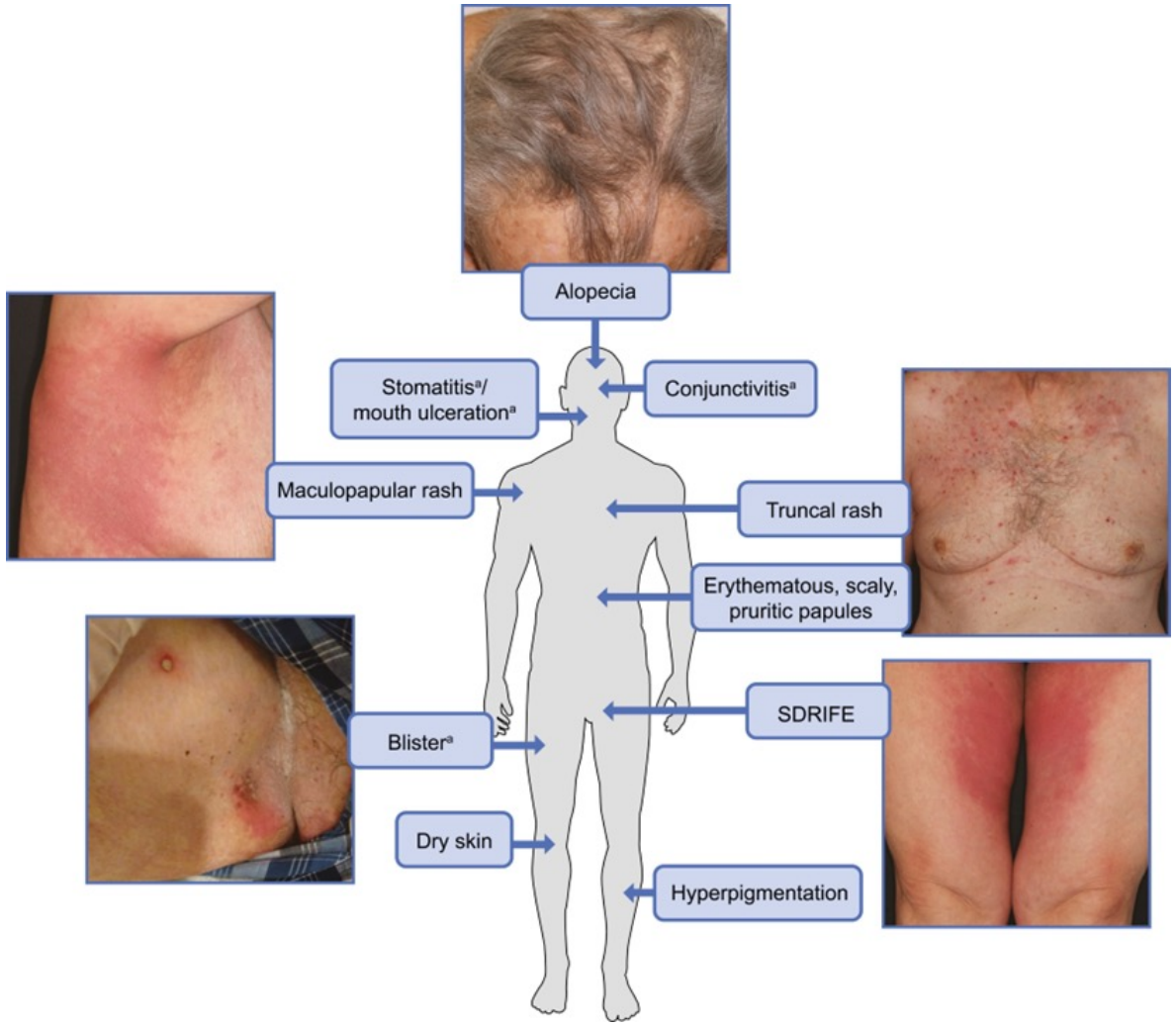
No

Suspected SJS/TEN → • Immediately withhold enfortumab vedotin[24]
• Consider dermatologic consultation[a]
• Biopsy of multiple sites[a]

Histological evidence of SJS/TEN[32]
- Biopsy demonstrating widespread full thickness epidermal necrosis and detachment is suggestive of SJS/TEN
- Negative direct immunofluorescence test

Yes

Confirmed SJS/TEN → **Grade 4; recurrent Grade 3** → • Discontinue enfortumab vedotin[24]
• Inpatient management for specialized care with dermatologic consultation as appropriate[a]



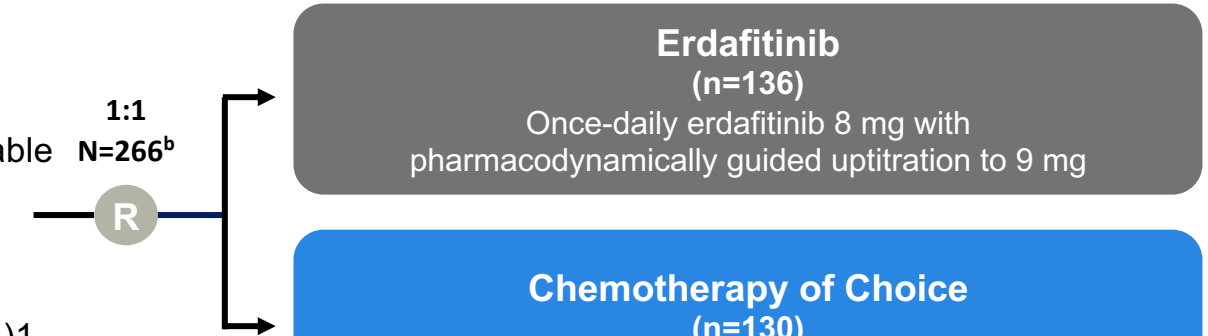
Lacouture M et al. *Oncologist.* 7(3) 2022 e223–e232

Memorial Sloan Kettering Cancer Center

Phase 3 THOR Study Cohort 1: Erdafitinib Versus Chemotherapy of Choice in Patients With Advanced Urothelial Cancer and Select *FGFR* Aberrations

Key eligibility criteria

- Age ≥18 years
- Metastatic or unresectable UC
- Confirmed disease progression
- Prior tx with anti–PD-(L)1
- 1-2 lines of systemic tx
- Select *FGFR3/2alt* (mutation/fusion)
- ECOG PS 0-2



Stratification factors: region (North America vs European Union vs rest of world), ECOG PS (0 or 1 vs 2), and disease distribution (presence vs absence of visceral [lung, liver, or bone] metastases)

Primary end point:

- OS

Key secondary end points:

- PFS
- ORR
- Safety

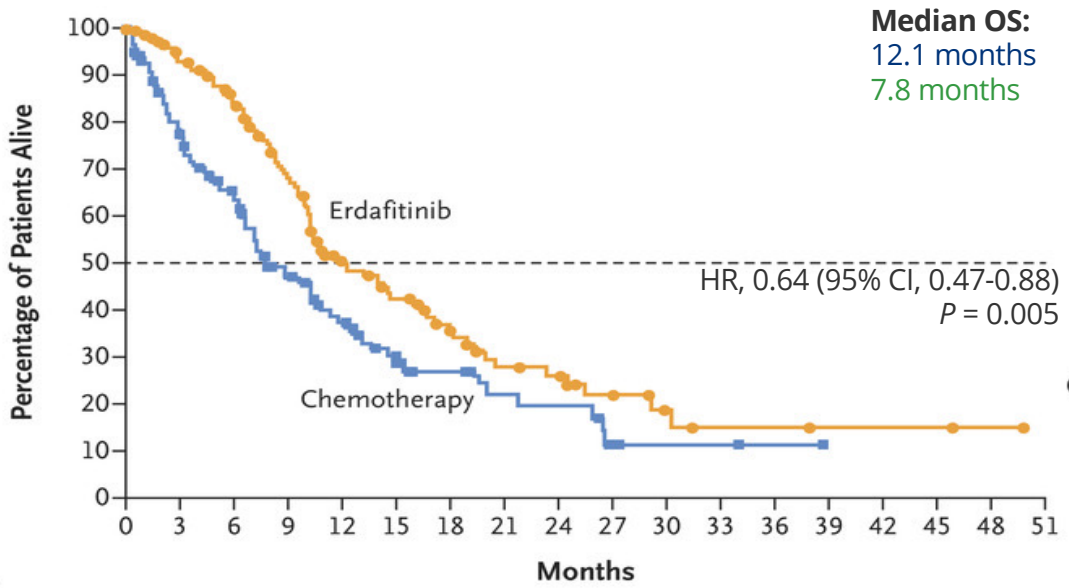
All Patients Received Anti–PD-(L)1 in the First- or Second-Line Setting

NCT03390504

Loriot Y et al. N Engl J Med 2023; 389:1961-1971

THOR: Erdafitinib in refractory mUC

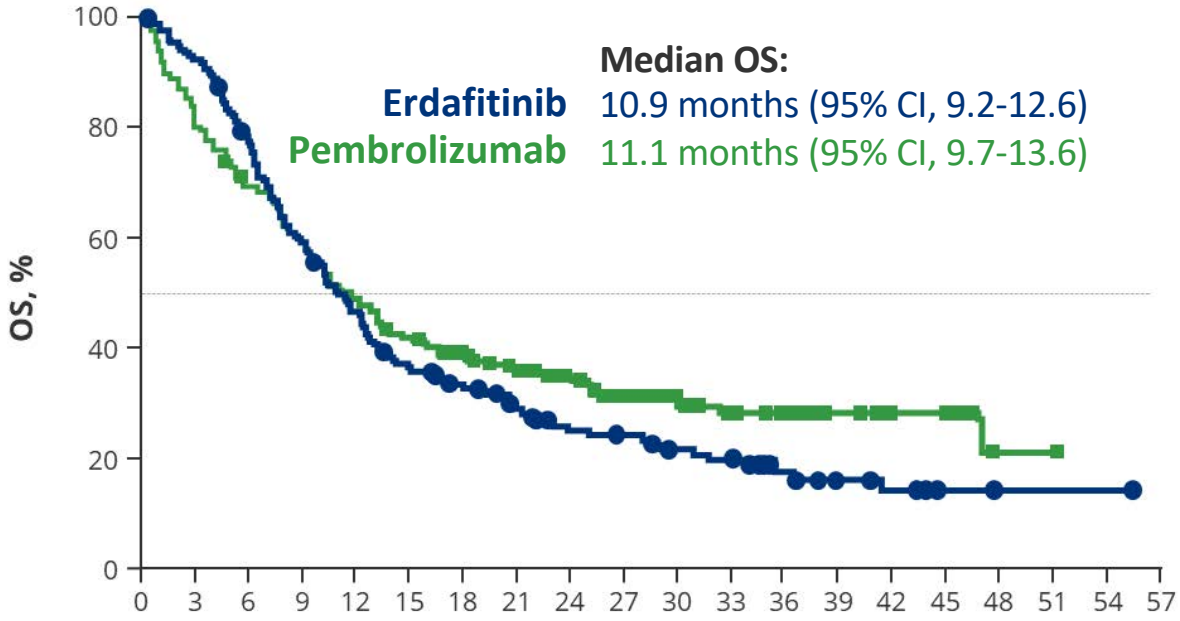
Cohort 1: Erdafitinib improves survival compared to taxane or vinflunine in IO-experienced patients



No. at Risk (no. with censored data)																		
Erdafitinib	136	117	97	74	46	35	25	17	15	9	5	3	3	2	2	2	1	0
	(0)	(10)	(20)	(25)	(35)	(39)	(44)	(47)	(48)	(52)	(55)	(56)	(56)	(57)	(57)	(57)	(58)	(59)
Chemotherapy	130	87	66	43	30	18	13	9	8	3	2	2	1	0	0	0	0	0
	(0)	(17)	(25)	(30)	(35)	(41)	(45)	(47)	(47)	(49)	(50)	(50)	(51)	(52)	(52)	(52)	(52)	(52)

Loriot Y et al. N Engl J Med 2023; 389:1961-1971

Cohort 2: Erdafitinib does not improve survival compared to pembrolizumab in IO-naïve patients



No. at risk																			
Erdafitinib	175	160	131	100	78	60	52	41	30	28	23	21	13	9	7	2	1	1	1	0
Pembrolizumab	176	148	119	103	84	72	60	52	43	34	29	23	19	11	8	8	1	1	0	0

Siefker-Radtke et al. ESMO 2023.

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THOR: Adverse events associated with erdafitinib treatment

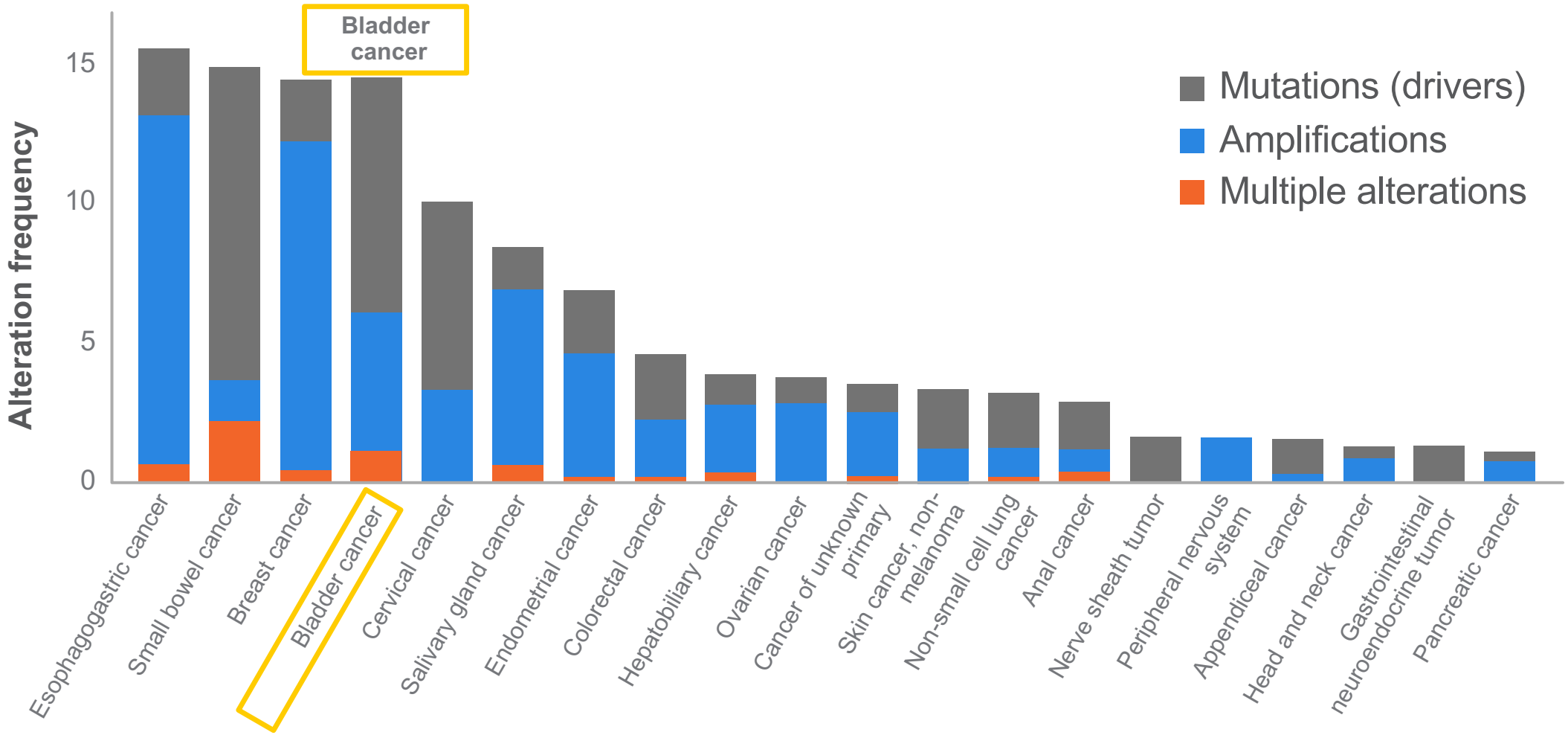
- Hyperphosphatemia is on-target effect and requires monitoring for dose up-titration at 14-21 days
- Gastrointestinal toxicity is common including stomatitis, dry mouth, and dysgeusia
- Skin and nail toxicity are frequent
- Grade 3 central serous retinopathy (in 2.2%) and other eye disorders (in 2.2%) were uncommon but require monitoring per package insert

Table 2. Adverse Events in the Safety Population.*

Event	Erdafitinib (N=135)				Chemotherapy (N=112)			
	Any Grade	Grade 1	Grade 2	Grade ≥3	Any Grade	Grade 1	Grade 2	Grade ≥3
	number (percent)							
Hyperphosphatemia	108 (80.0)	70 (51.9)	31 (23.0)	7 (5.2)	0	0	0	0
Diarrhea	84 (62.2)	49 (36.3)	31 (23.0)	4 (3.0)	19 (17.0)	7 (6.2)	9 (8.0)	3 (2.7)
Stomatitis	65 (48.1)	22 (16.3)	32 (23.7)	11 (8.1)	14 (12.5)	4 (3.6)	8 (7.1)	2 (1.8)
Dry mouth	53 (39.3)	45 (33.3)	8 (5.9)	0	4 (3.6)	4 (3.6)	0	0
Palmar–plantar erythrodysesthesia syndrome	41 (30.4)	6 (4.4)	22 (16.3)	13 (9.6)	1 (0.9)	0	1 (0.9)	0
Dysgeusia	37 (27.4)	28 (20.7)	8 (5.9)	1 (0.7)	8 (7.1)	5 (4.5)	3 (2.7)	0
Alanine aminotransferase increased	37 (27.4)	24 (17.8)	9 (6.7)	4 (3.0)	4 (3.6)	2 (1.8)	1 (0.9)	1 (0.9)
Constipation	36 (26.7)	24 (17.8)	12 (8.9)	0	31 (27.7)	13 (11.6)	16 (14.3)	2 (1.8)
Decreased appetite	36 (26.7)	18 (13.3)	14 (10.4)	4 (3.0)	23 (20.5)	10 (8.9)	10 (8.9)	3 (2.7)
Anemia	35 (25.9)	10 (7.4)	15 (11.1)	10 (7.4)	36 (32.1)	8 (7.1)	19 (17.0)	9 (8.0)
Alopecia	34 (25.2)	29 (21.5)	4 (3.0)	1 (0.7)	27 (24.1)	16 (14.3)	11 (9.8)	0
Dry skin	31 (23.0)	23 (17.0)	6 (4.4)	2 (1.5)	5 (4.5)	4 (3.6)	1 (0.9)	0
Onycholysis	31 (23.0)	9 (6.7)	14 (10.4)	8 (5.9)	1 (0.9)	0	1 (0.9)	0
Weight decreased	30 (22.2)	12 (8.9)	15 (11.1)	3 (2.2)	3 (2.7)	3 (2.7)	0	0
Aspartate aminotransferase increased	29 (21.5)	21 (15.6)	5 (3.7)	3 (2.2)	3 (2.7)	2 (1.8)	1 (0.9)	0
Onychomadesis	28 (20.7)	9 (6.7)	17 (12.6)	2 (1.5)	2 (1.8)	1 (0.9)	1 (0.9)	0
Nail discoloration	24 (17.8)	16 (11.9)	7 (5.2)	1 (0.7)	2 (1.8)	1 (0.9)	1 (0.9)	0
Dry eye	23 (17.0)	20 (14.8)	3 (2.2)	0	2 (1.8)	1 (0.9)	1 (0.9)	0
Asthenia	20 (14.8)	6 (4.4)	12 (8.9)	2 (1.5)	28 (25.0)	9 (8.0)	15 (13.4)	4 (3.6)
Nausea	20 (14.8)	10 (7.4)	8 (5.9)	2 (1.5)	27 (24.1)	15 (13.4)	10 (8.9)	2 (1.8)
Neutropenia	0	0	0	0	22 (19.6)	1 (0.9)	5 (4.5)	16 (14.3)
Fatigue	20 (14.8)	12 (8.9)	8 (5.9)	0	21 (18.8)	13 (11.6)	4 (3.6)	4 (3.6)

* Listed are adverse events (of any cause) that emerged or worsened during treatment, according to preferred term and highest grade, and that were reported in more than 15% of the patients in either treatment group.

HER2 alterations feature at varying frequencies across tumor types

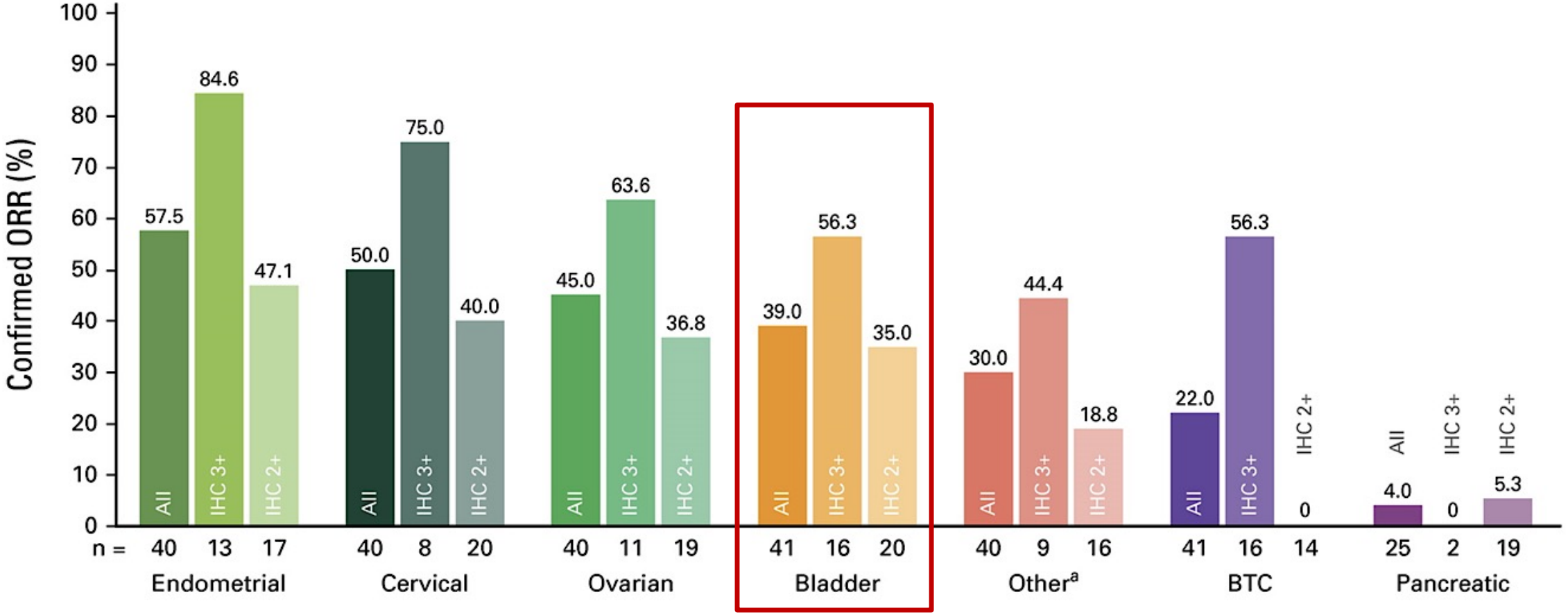


Data source AACR GENIE Cohort v12.0-public, accessed 2022-08-04 via cBioPortal. Exclude alterations (mutations and copy number) of unknown significance, germline, and unprofiled samples. Analysis on 20,500 cases with mutation and CNA data. Filtered for minimal number of cases 200 per indication, and alteration frequency > 1%. Data on file.
AACR, American Association for Cancer Research; CNA, copy number aberrations.

HER2 alterations in UC

- Mutations
  - 5-11% (higher frequency than breast and other cancer types)
- Amplifications
  - 6-9%
  - Can co-exist with mutations in a subset of tumors
  - Amplification, mRNA levels, and protein expression were observed in clusters I and II (luminal tumors) in urothelial TCGA
  - May be enriched in nodal metastases compared to matched primary tumors

DESTINY-PanTumor02: Trastuzumab Deruxtecan leads to high response rates in HER2+ urothelial cancer



ORR 39%

Meric-Bernstam F. et al. *J Clin Oncol*. 2024 Jan 1;42(1):47-58.

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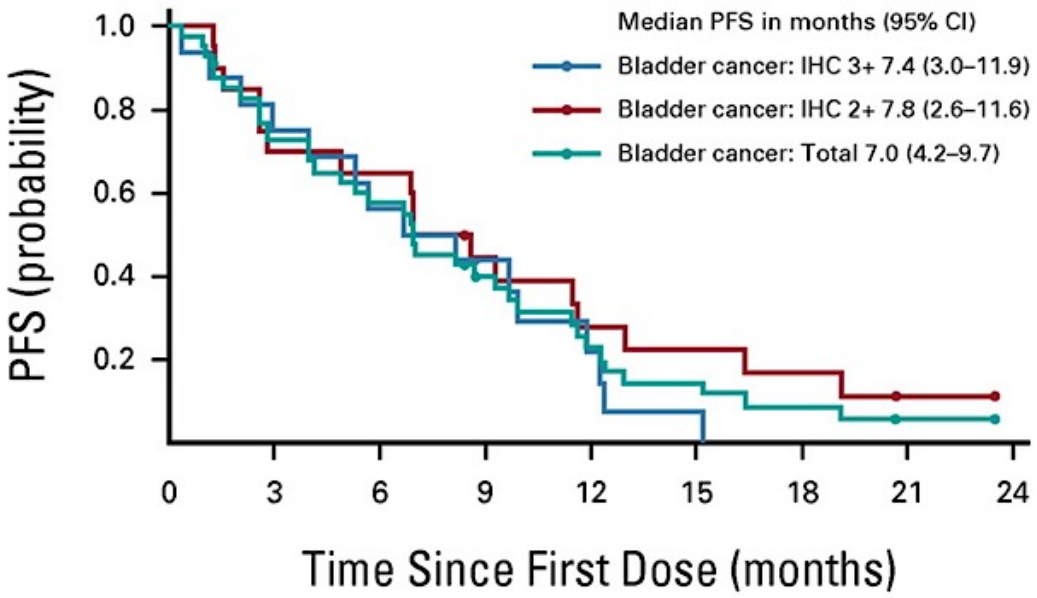
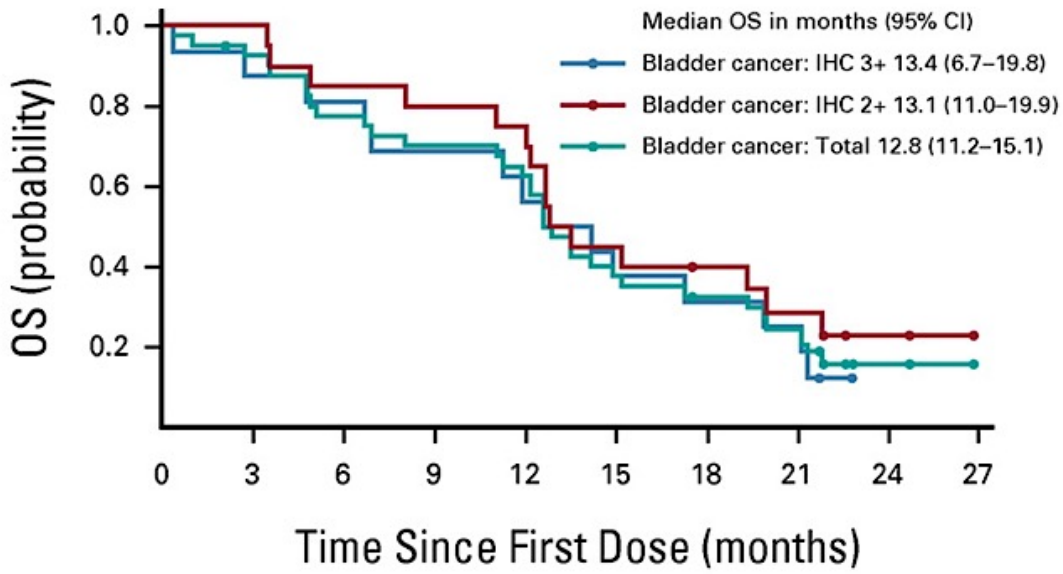
DESTINY-PanTumor02: T-DXd outcomes by HER2 status



No. at risk:									
Bladder cancer: IHC 3+	16	12	9	6	3	1	0		
Bladder cancer: IHC 2+	20	14	13	8	5	4	3	1	0
Bladder cancer: Total	41	29	23	14	8	5	3	1	0

PFS



No. at risk:										
Bladder cancer: IHC 3+	16	14	13	11	9	6	5	4	0	
Bladder cancer: IHC 2+	20	20	17	16	15	9	7	5	2	0
Bladder cancer: Total	41	37	31	28	25	15	12	9	2	0

OS

Meric-Bernstam F. et al. *J Clin Oncol*. 2024 Jan 1;42(1):47-58.

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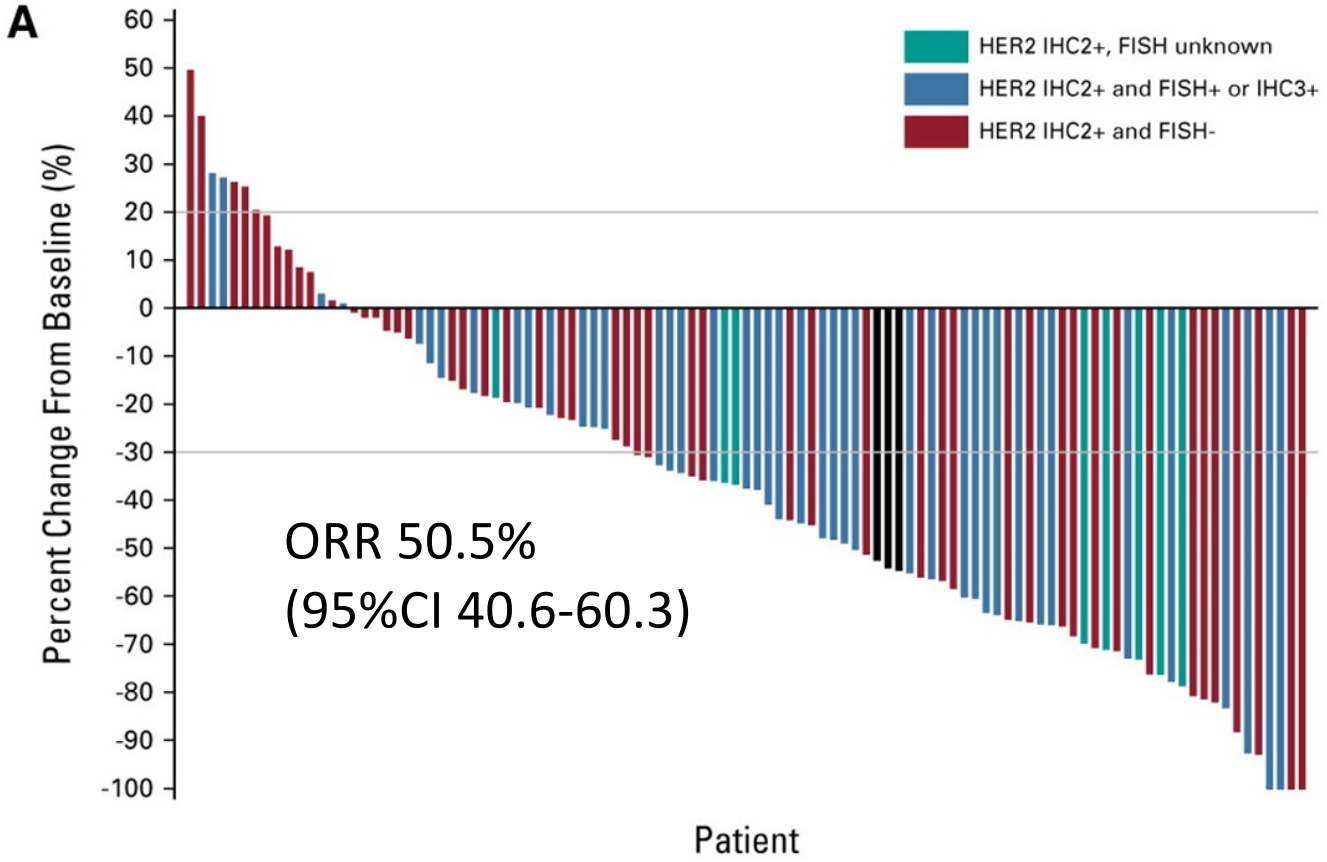
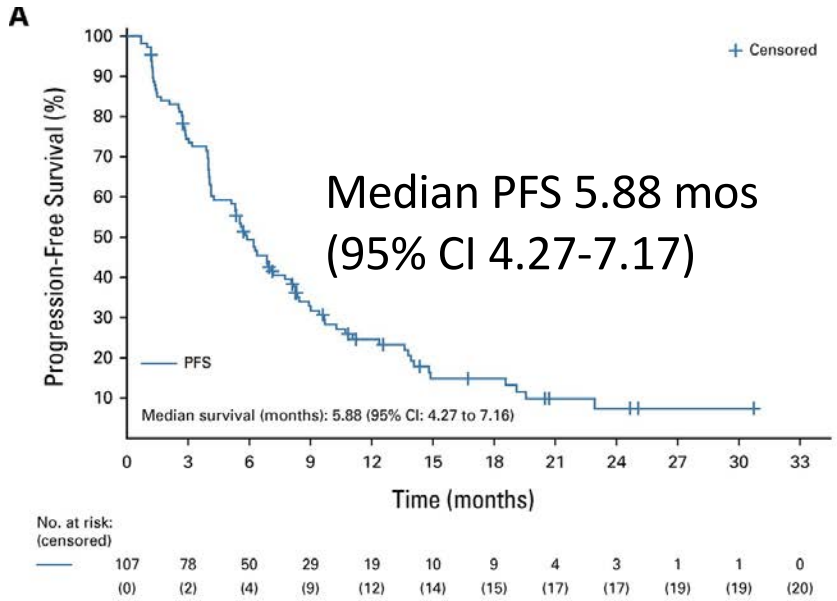
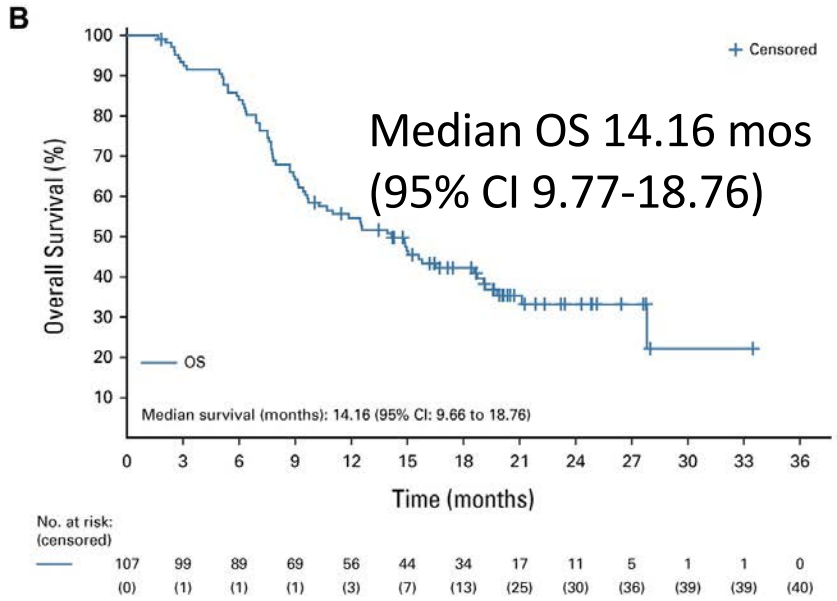
Disitamab vedotin: Combined analysis of two Phase 2 studies in refractory advanced UC

Study population:
- Locally advanced or metastatic UC
- PD after at least 1 prior line of therapy
- ECOG 0-1
- HER2 2/3+





Median PFS 5.88 mos
(95% CI 4.27-7.17)



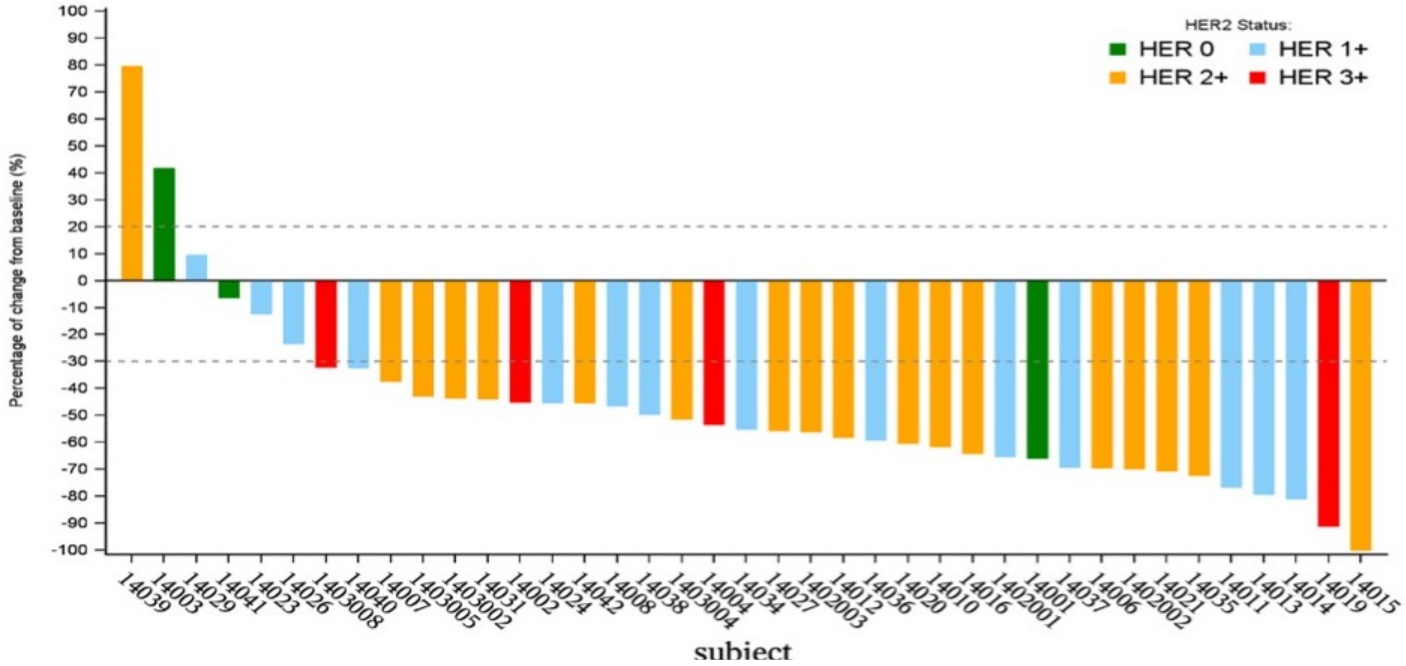
Median OS 14.16 mos
(95% CI 9.77-18.76)

Memorial Sloan Kettering Cancer Center

Sheng et al. *JCO*, epub ahead of print 2023

Disitamab vedotin + Toripalimab
(IgG4 anti-PD1 monoclonal antibody)

- Ph I/II study in patients with LA/mUC (n=41)
- HER2 2-3+ in 59% and PD-L1 positive in 32%
- Disitamab vedotin at 1.5 or 2 mg/kg in combination with toripalimab 3 mg/kg every 2 weeks in dose escalation and expansion cohort
- TRAEs: Transaminitis, peripheral sensory neuropathy, asthenia, hypertriglyceridemia, decreased appetite
- No DLT observed and recommended dose of disitimab vedotin was 2 mg/kg



- Confirmed ORR 73.2% (95% CI 57.1, 85.8) including 9.8% CR
  - HER2 2-3+: 86.3%
  - HER2 1+: 57.1%
  - HER2 0: 33.3%
- Confirmed ORR PD-L1 positive: 66.6% ORR; PD-L1 negative: 74.1%
- Median PFS: 9.2 months; 2-year OS rate 63.2%

Sheng et al, *J Clin Oncol* 41, 2023 (suppl 16; abstr 4566)

Overview

Saturday, March 23rd

Module 1: 7:30 AM – 9:10 AM — Hodgkin and Non-Hodgkin Lymphoma

Module 2: 9:30 AM – 10:20 AM — Gynecologic Cancers

Module 3: 10:20 AM – 11:10 AM — Localized Breast Cancer; SABCS 2023 Review

Module 4: 11:10 AM – 12:00 PM — Metastatic HER2-Positive and Triple-Negative Breast Cancer; SABCS 2023 Review

Module 5: 12:30 PM – 1:20 PM — Renal Cell Carcinoma

Module 6: 1:20 PM – 2:10 PM — Urothelial Bladder Cancer

Module 7: 2:10 PM – 3:00 PM — Prostate Cancer

Module 8: 3:20 PM – 4:10 PM — Targeted Therapy for Non-Small Cell Lung Cancer

Module 9: 4:10 PM – 5:00 PM — Nontargeted Treatments for Lung Cancer

Agenda

Module 1: **Role of Hormonal Therapy in Prostate Cancer (PC) Management** — Dr McKay

Module 2: Evidence-Based Use of Other Therapeutic Approaches — Dr Antonarakis

Agenda

Module 1: Role of Hormonal Therapy in Prostate Cancer (PC) Management — Dr McKay

Module 2: Evidence-Based Use of Other Therapeutic Approaches — Dr Antonarakis

UC San Diego Health

The Role of Hormone Therapy in Prostate Cancer Management

Rana R. McKay

Associate Professor of Medicine and Urology

Co-Lead, Genitourinary Oncology Program

Associate Director, Translational Sciences

@DrRanaMcKay

Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Blue Earth Diagnostics, Bristol Myers Squibb, Calithera Biosciences, Caris Life Sciences, Dendreon Pharmaceuticals Inc, Eisai Inc, Exelixis Inc, Johnson & Johnson Pharmaceuticals, Lilly, Merck, Myovant Sciences, Novartis, Pfizer Inc, Sanofi, Seagen Inc, Sorrento Therapeutics, Telix Pharmaceuticals Limited, Tempus
Contracted Research	AstraZeneca Pharmaceuticals LP, ArteraAI, Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, Exelixis Inc, Oncternal Therapeutics

Clinical Case – 70 year old male

- Elevated PSA on routine screening
  - PSA 7
  - MRI PIRADS 4 lesion with capsule abutment
  - TRUS prostate – Gleason 3+4
- Radical prostatectomy
  - Gleason 3+4
  - Negative margins
  - pT3bN0
- Biochemical recurrence
  - Rising PSA 0.2
  - 3/13/2019: ^{68}Ga-PSMA-11 PET – avid external iliac node
  - MRI prostate – right external iliac node 9 x 5 mm
- Salvage treatment
  - FORMULA-509 trial
    - Abiraterone, apalutamide, leuprolide + salvage EBRT x 6 months
- Biochemical recurrence
  - 2 years later PSA elevated to 0.89 (PSADT 6 months)
  - ^{18}F-DCFPyL – negative
- Initiated treatment with enzalutamide + leuprolide x 9 months

GENOMIC VARIANTS

Somatic - Biologically Relevant

CDKN1B — Copy number loss

ETV6 — Copy number loss

Germline - Pathogenic / Likely Pathogenic

No pathogenic variants were found in the limited set of genes on which we report.

IMMUNOTHERAPY MARKERS

Tumor Mutational Burden		Microsatellite Instability Status		
0.0 m/MB	1st percentile	Stable	Equivocal	High

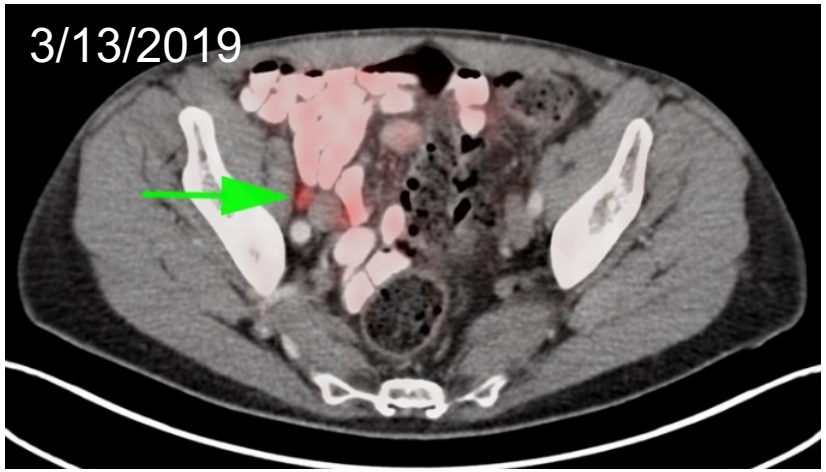
RESULT: UNCERTAIN

Variant(s) of Uncertain Significance identified.

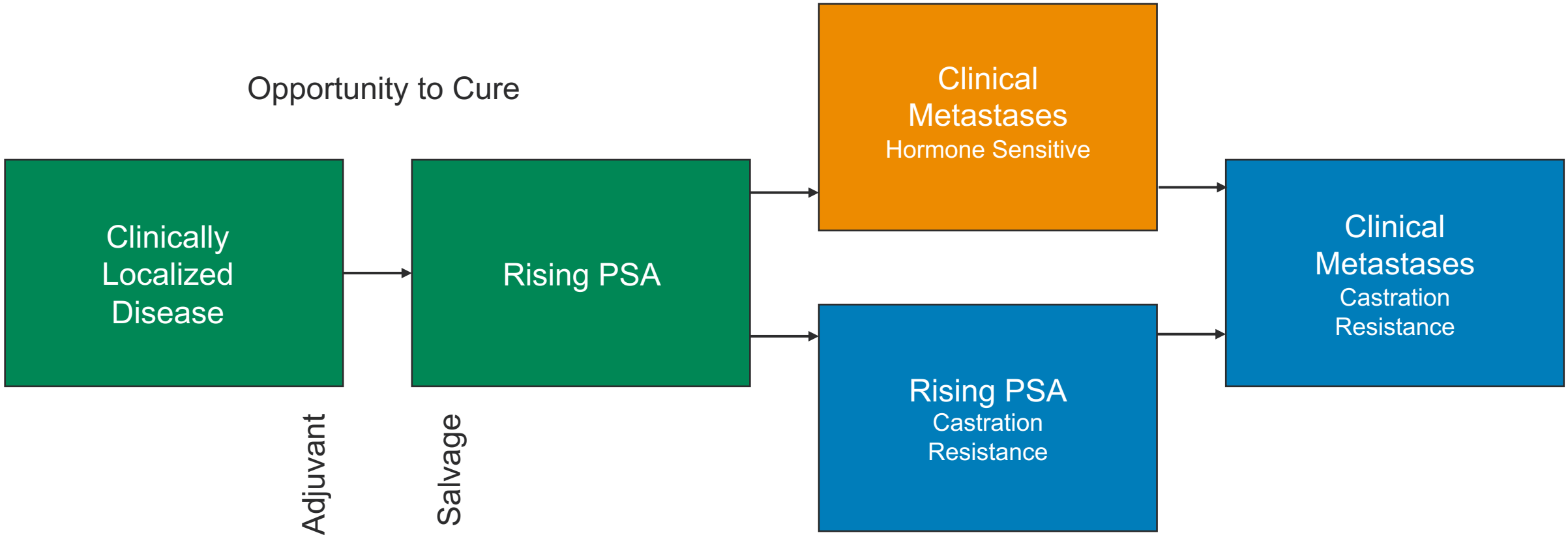
GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
NTHL1	c.176G>T (p.Arg59Leu)	heterozygous	Uncertain Significance

About this test

This diagnostic test evaluates 156 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.



Clinical States of Prostate Cancer



- mHSPC/mCSPC – Metastatic hormone sensitive disease or metastatic castration sensitive disease – Disease responding to castrate levels of testosterone (<50 ng/dL).
- mCRPC – Metastatic castration resistant prostate cancer – Disease that is progressing to castrate levels to testosterone (<50 ng/dL).

ADT is the Backbone of Therapy in mHSPC

Studies on Prostatic Cancer

I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate*

Charles Huggins, M.D., and Clarence V. Hodges, M.D.

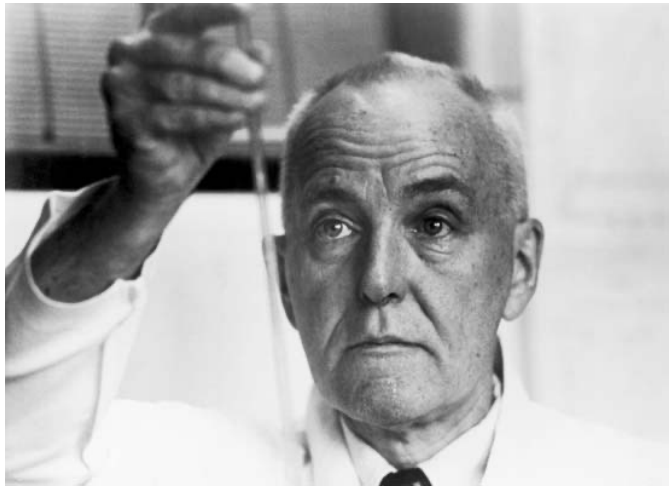
(From the Department of Surgery, the University of Chicago, Chicago, Illinois)

(Received for publication March 22, 1941)

Carcinoma of the prostate gland is peculiarly favorable for endocrine investigation since frequent serial observations of the activity of phosphatases in serum were found to provide objective indices of activity of the neoplasm when the enzymes were increased in amount above normal. In the present paper data are given for the values of serum phosphatases in car-

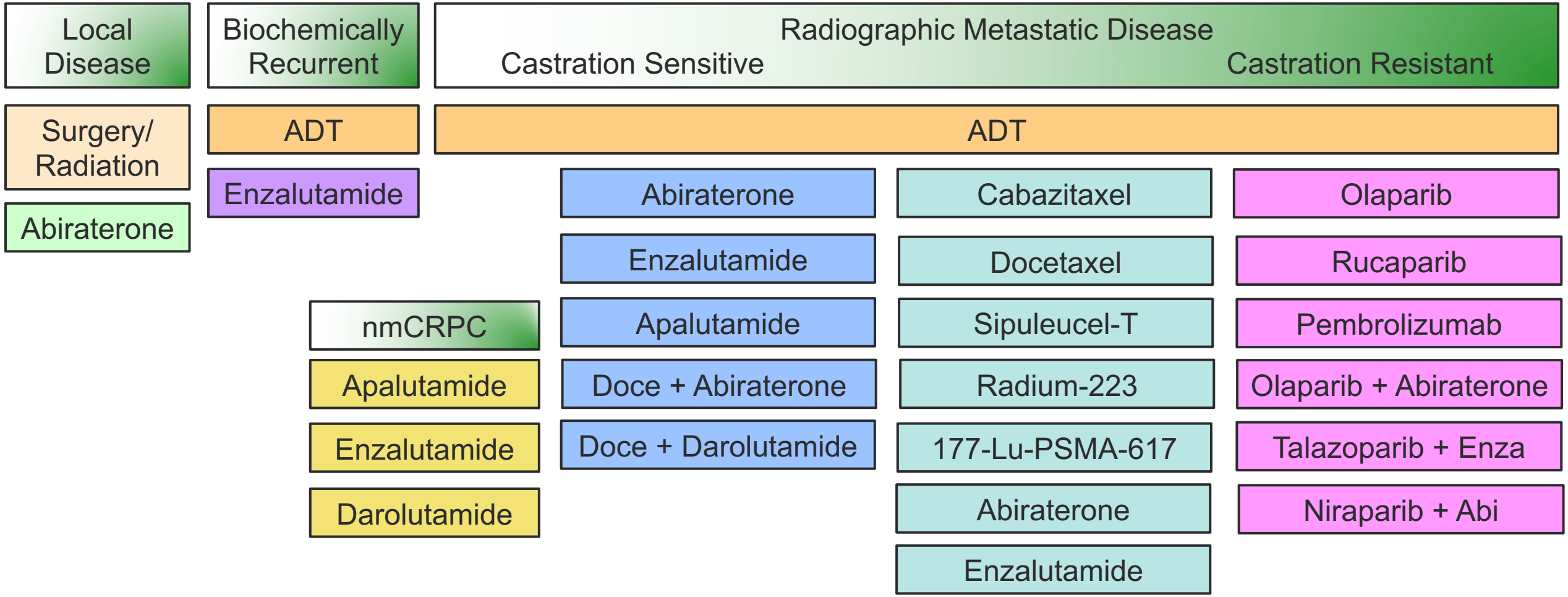
METHODS AND MATERIALS

The phosphatase activity of serum was determined by the method of King and Armstrong (10) using 0.005 M disodium monophenylphosphate as substrate. The buffers used were 0.05 M barbital-sodium at pH 9.3, and 0.1 M Sörensen's citrate-HCl or Walpole's



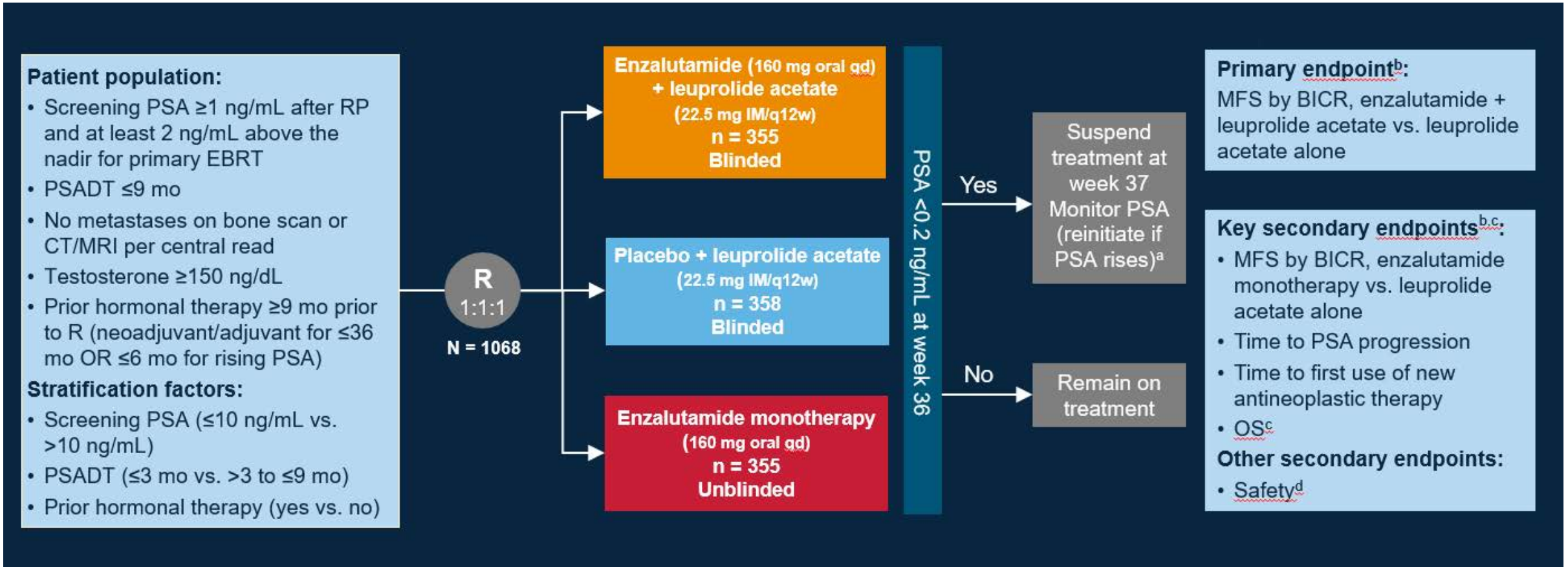
Huggins awarded the 1966
Nobel Prize for Physiology or Medicine

> 80 Years Later



ADT is still the mainstay of therapy…but treatments have evolved for different disease states

EMBARK Trial



Shore et al, AUA, 2023

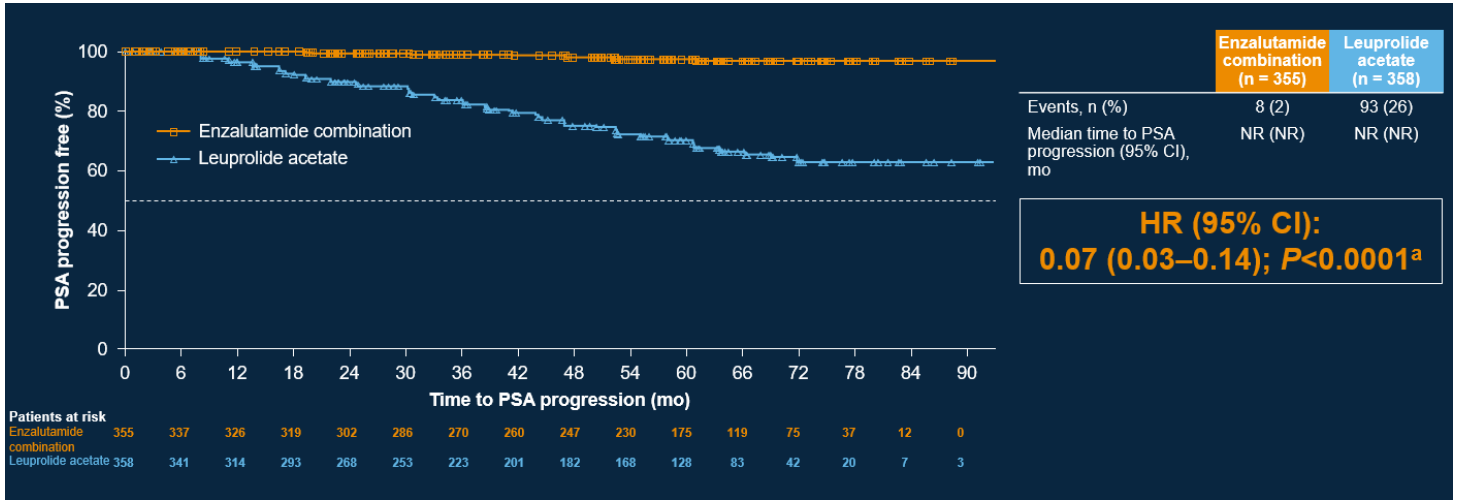
EMBARK Trial – Enzalutamide + ADT vs. ADT

MFS

	Enzalutamide combination (n = 355)	Leuprolide acetate (n = 358)
Median follow-up, mo	60.7	60.6
Events, n (%)	45 (13)	92 (26)
Per BICR, median MFS (95% CI), mo	NR (NR)	NR (85.1–NR)

HR (95% CI): 0.42 (0.31–0.61); *P*<0.0001[a]

PSA Progression

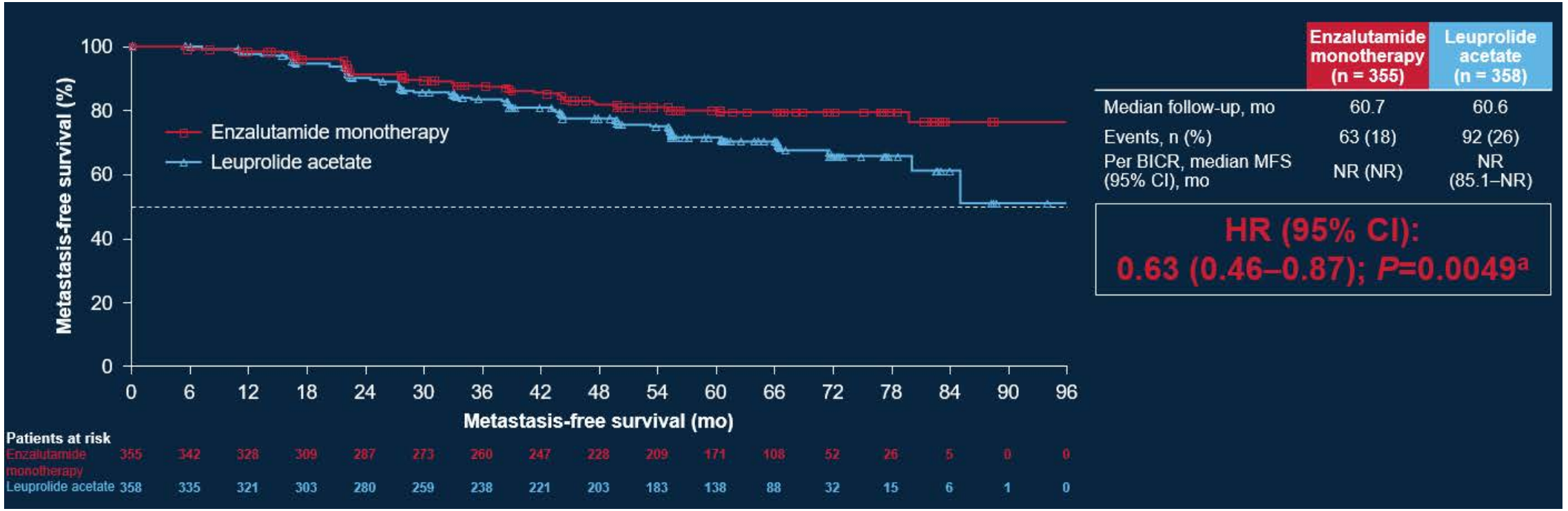


	Enzalutamide combination (n = 355)	Leuprolide acetate (n = 358)
Events, n (%)	8 (2)	93 (26)
Median time to PSA progression (95% CI), mo	NR (NR)	NR (NR)

HR (95% CI): 0.07 (0.03–0.14); *P*<0.0001[a]

Shore et al, AUA, 2023

EMBARK Trial – Enzalutamide vs. ADT

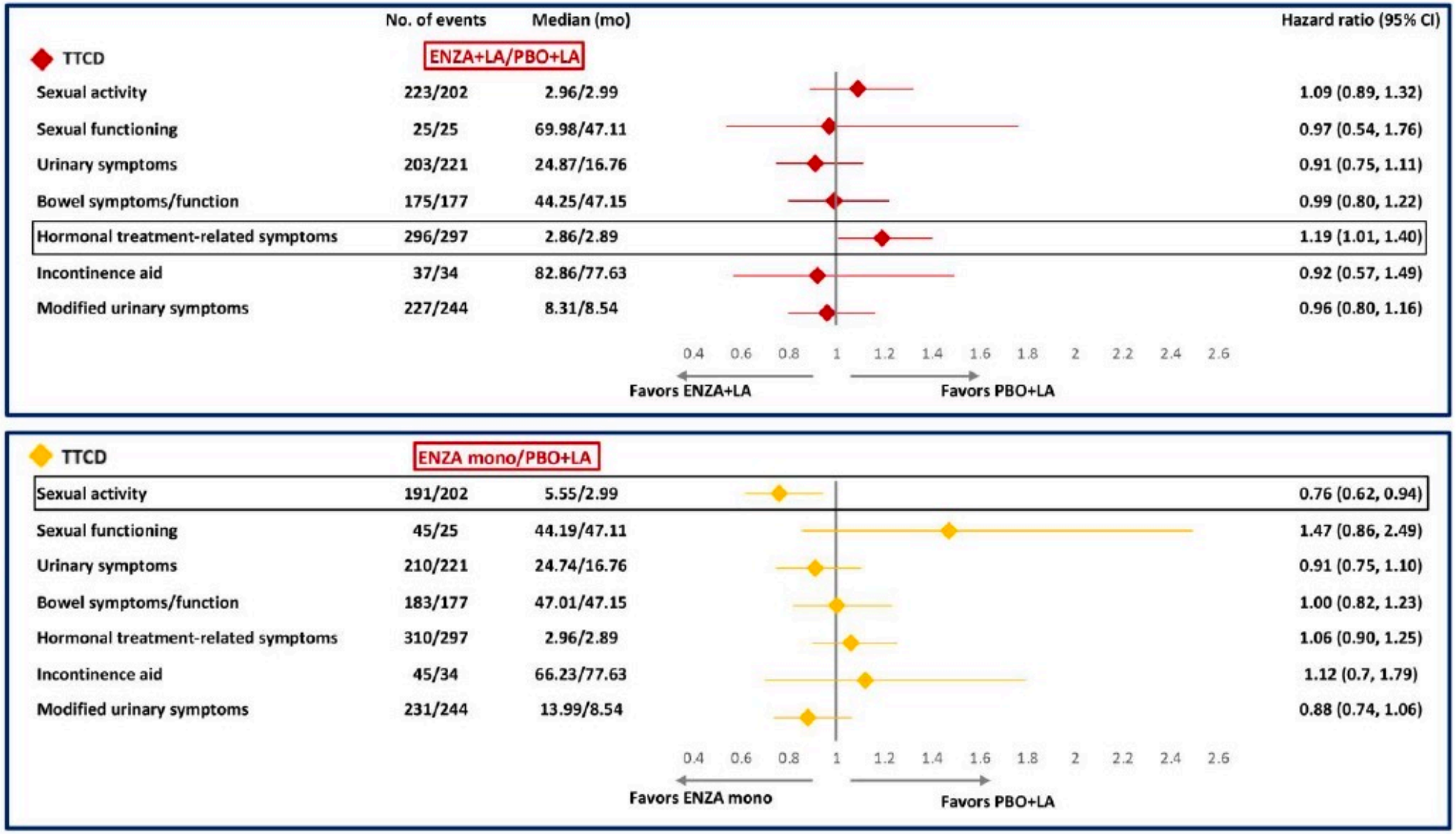


	Enzalutamide monotherapy (n = 355)	Leuprolide acetate (n = 358)
Median follow-up, mo	60.7	60.6
Events, n (%)	63 (18)	92 (26)
Per BICR, median MFS (95% CI), mo	NR (NR)	NR (85.1–NR)

HR (95% CI): 0.63 (0.46–0.87); *P*=0.0049[a]

Shore et al, AUA, 2023

EMBARK Trial – Quality of Life



Freedland et al, ESMO, 2023

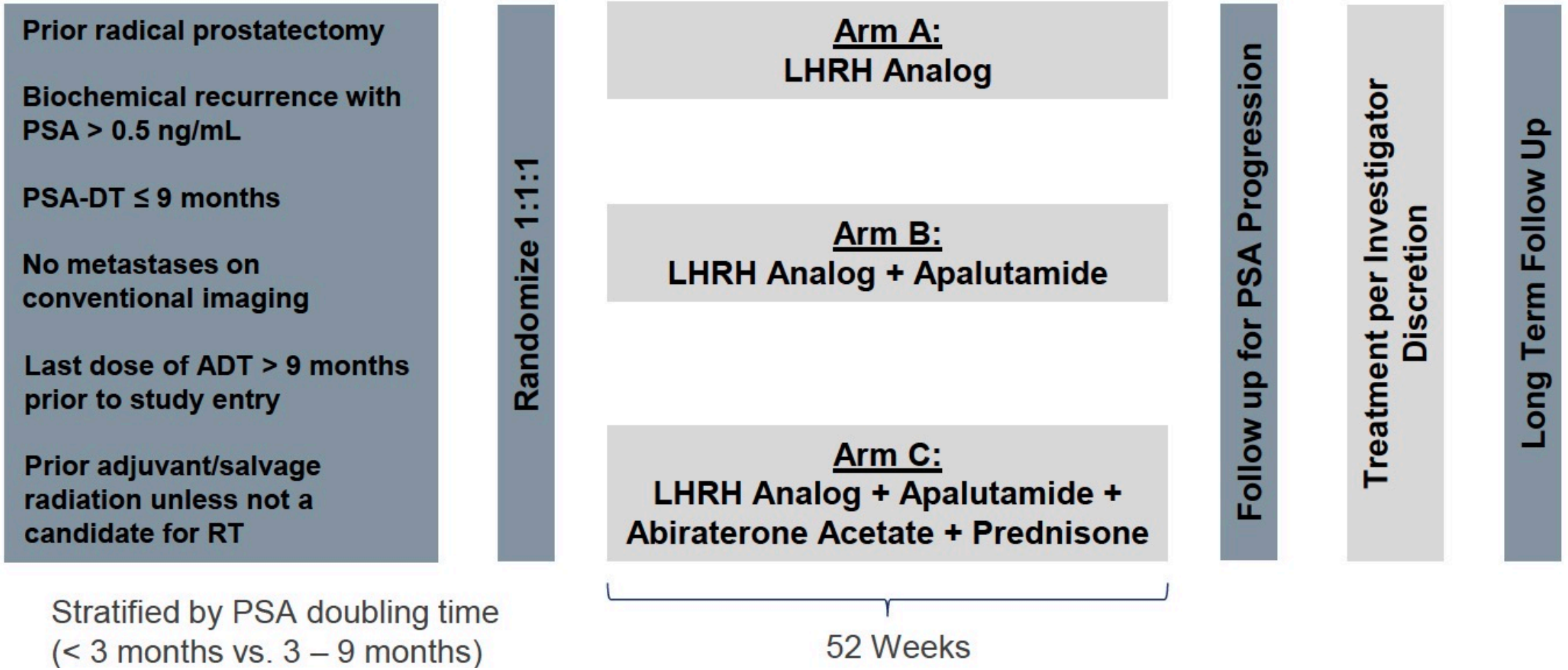
EMBARK Trial – Quality of Life

Clustered TEAEs of special interest, n (%)[a]	Enzalutamide combination (n = 353)		Leuprolide acetate (n = 354)		Enzalutamide monotherapy (n = 354)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Fatigue[b]	178 (50.4)[c]	14 (4.0)	134 (37.9)[c]	6 (1.7)	191 (54.0)[c]	17 (4.8)
Musculoskeletal events[d]	163 (46.2)[c]	13 (3.7)	148 (41.8)[c]	4 (1.1)	158 (44.6)[c]	6 (1.7)
Hypertension	89 (25.2)[c]	27 (7.6)	74 (20.9)	21 (5.9)	77 (21.8)[c]	20 (5.6)
Fall	74 (21.0)	4 (1.1)	51 (14.4)	4 (1.1)	56 (15.8)	7 (2.0)
Fracture[e]	65 (18.4)	14 (4.0)	48 (13.6)	9 (2.5)	39 (11.0)	7 (2.0)
Cognitive and memory impairment	53 (15.0)[c]	2 (0.6)	23 (6.5)	2 (0.6)	50 (14.1)[c]	0
Loss of consciousness[f]	20 (5.7)	17 (4.8)	12 (3.4)	6 (1.7)	12 (3.4)	8 (2.3)
Ischemic heart disease	19 (5.4)	14 (4.0)	20 (5.6)	11 (3.1)	32 (9.0)	21 (5.9)
Other selected CV events[g]	18 (5.1)	13 (3.7)	17 (4.8)	10 (2.8)	13 (3.7)	8 (2.3)
Convulsion (seizure)	4 (1.1)	2 (0.6)	0	0	3 (0.8)	2 (0.6)

- The most common AEs of special interest for all treatment cohorts (≥10% of patients) were fatigue, fall, fracture, hypertension, and musculoskeletal events.

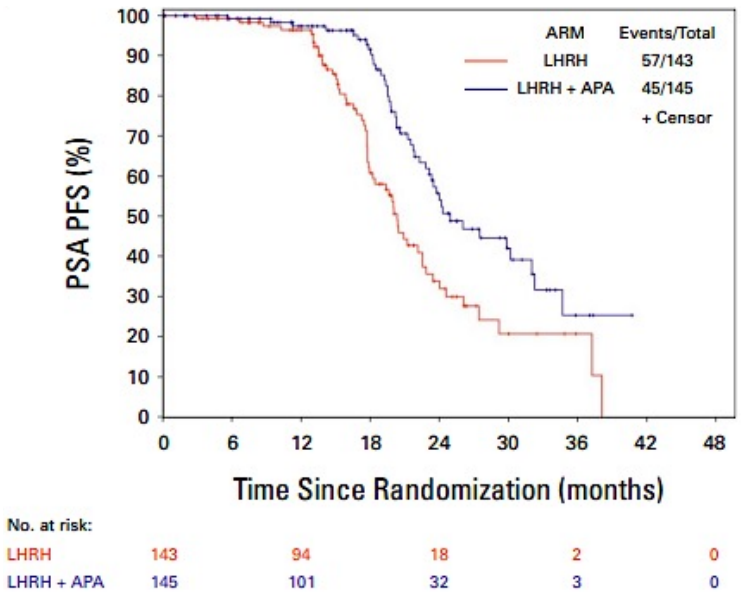
Shore et al, AUA, 2023

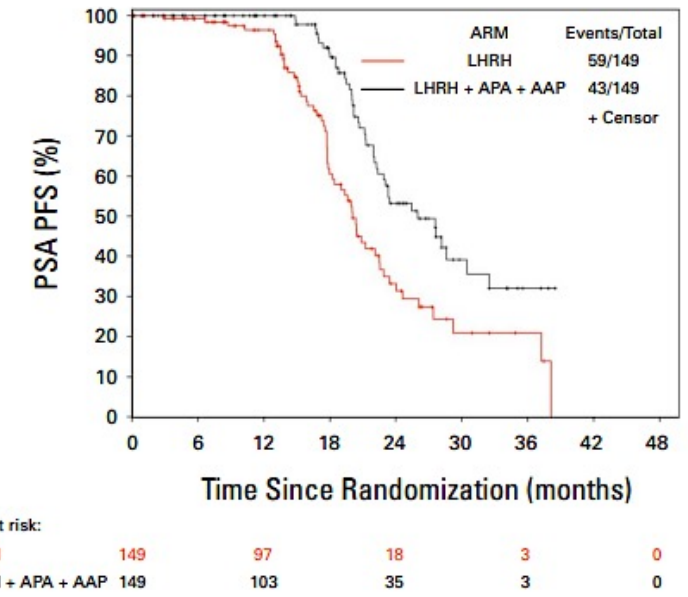
PRESTO

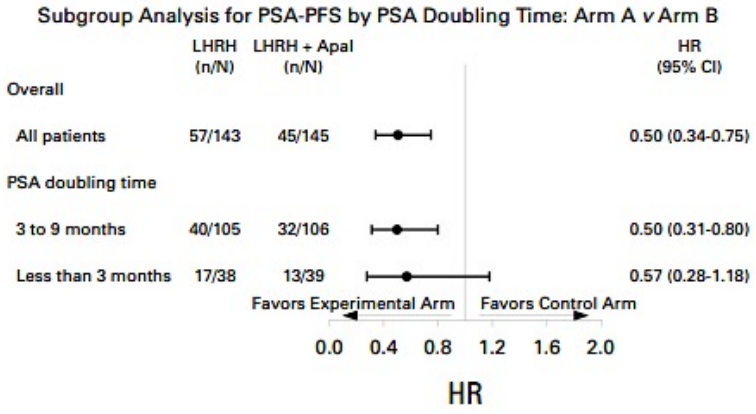


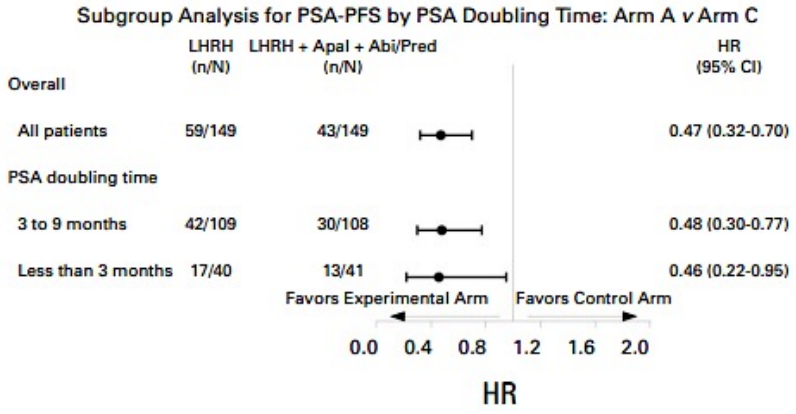
Aggarwal et al, ESMO, 2022

PRESTO





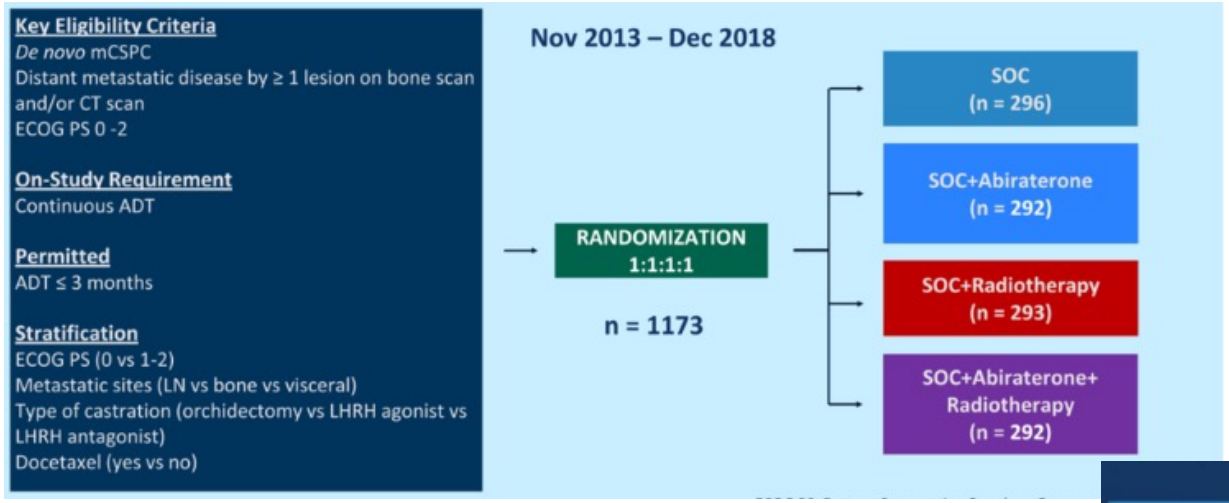




Aggarwal et al, JCO, 2024

Triple Therapy Strategies

PEACE-1 – ADT + Docetaxel + Abiraterone

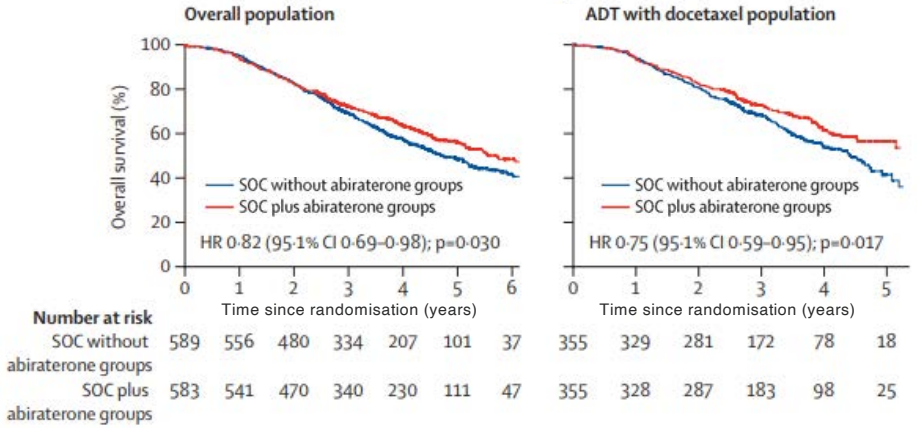


ARASENS – ADT + Docetaxel + Darolutamide

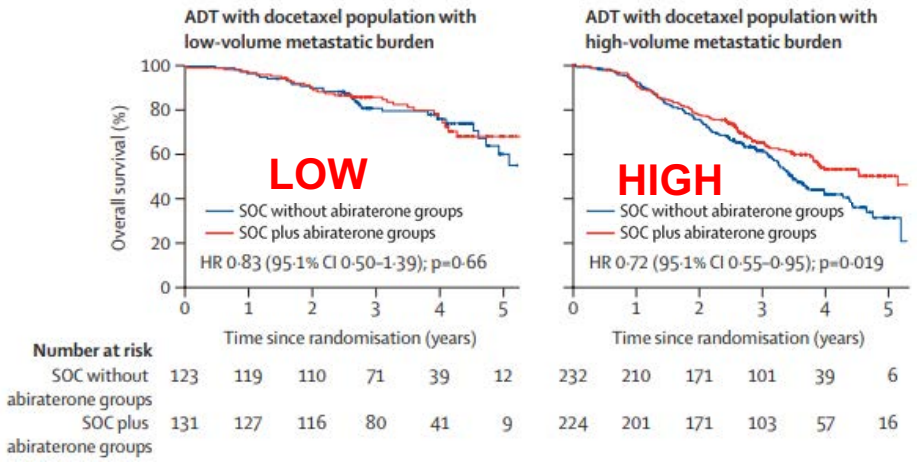
Improved OS with Triple Therapy – High and Low

PEACE-1

Overall

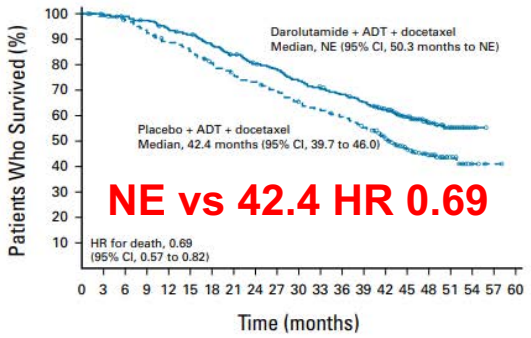


ADT + DOCETAXEL

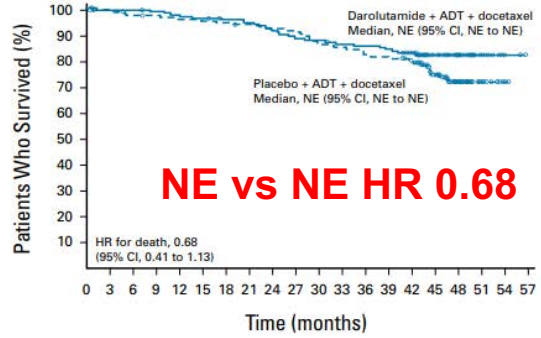


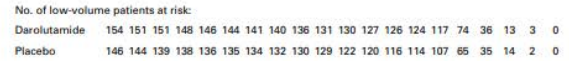
ARASENS

HIGH VOLUME

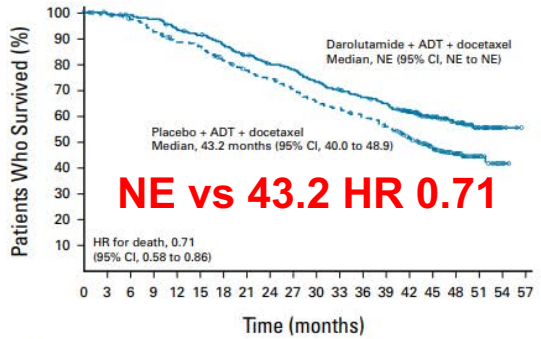


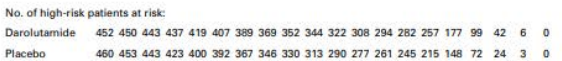
LOW VOLUME



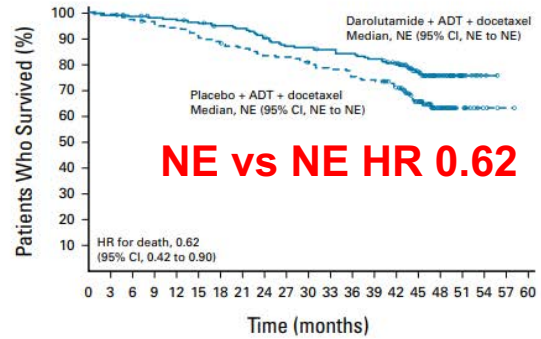


HIGH RISK





LOW RISK



Fizazi et al, Lancet, 2022; Smith et al, NEJM, 2022; Hussain et al, JCO, 2023

Factors that Impact Treatment Decision

Disease Factors

- Volume/Risk of disease
- Recurrent/De Novo
- Sites of Metastasis
- Gleason score
- Genomic features

Clinical Factors

- Symptoms
- Performance status
- Comorbidities
- Concurrent Medications

Drug Factors

- Mechanism of action
- Mode of administration
- Cost

Doublet Treatments – High Volume/Risk

	Treatment Arm	Control Arm	N	Median FU (mo)	OS (mo)	HR (CI)
Docetaxel						
CHAARTED	Doce + ADT	ADT	513	54	51	0.63 (0.50-0.79)
STAMPEDE-C	Doce + ADT	ADT	183	78	40	0.81 (0.64-1.02)
GETUG-15	Doce + ADT	ADT	148	84	40	0.78 (0.56-1.09)
ARSI						
LATITUDE	Abi + ADT	ADT	955	52	50	0.62 (0.52-0.74)
STAMPEDE-G	Abi + ADT	ADT	473	42	-	0.54 (0.41-0.40)
ARCHES	Enza + ADT*	ADT*	727	45	-	0.66 (0.52-0.83)
ENZAMET	Enza + ADT (+/- Doce)	ADT + NSAA (+/- Doce)	588	34	-	0.79 (0.63-0.98)
TITAN	Apa + ADT*	ADT*	660	44	-	0.70 (0.56-0.88)
Radiotherapy						
STAMPEDE-H	RT Prostate + ADT	ADT (+/- Doce)	1120	37	-	1.07 (0.90-1.28)
HORRAD	RT Prostate + ADT	ADT	272	47	-	1.06 (0.80-1.39)

*Prior docetaxel allowed.

Doublet Therapy – Low Volume/Risk

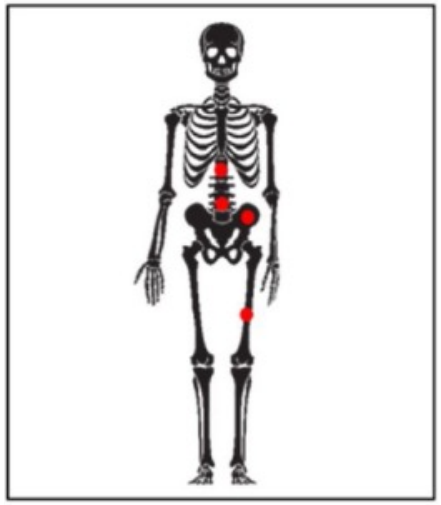
	Treatment Arm	Control Arm	N	Median FU (mo)	OS (mo)	HR (CI)
Docetaxel						
CHAARTED	Doce + ADT	ADT	277	54	64	1.04 (0.70-2.55)
STAMPEDE-C	Doce + ADT	ADT	124	78	-	0.76 (0.54-1.07)
GETUG-15	Doce + ADT	ADT	202	84	NR	1.02 (0.67-1.55)
ARSI						
LATITUDE	Abi + ADT	ADT	243	52	NR	0.72 (0.47-1.10)
STAMPEDE-G	Abi + ADT	ADT	4428	42	-	0.66 (0.44-0.98)
ARCHES	Enza + ADT*	ADT*	423	45	-	0.66 (0.43-1.03)
ENZAMET	Enza + ADT (+/- Doce)	ADT + NSAA (+/- Doce)	537	34	-	0.54 (0.39-0.74)
TITAN	Apa + ADT*	ADT*	390	44	-	0.52 (0.35-0.79)
Radiotherapy						
STAMPEDE-H	RT Prostate + ADT	ADT (+/- Doce)	819	37	-	0.68 (0.52-0.90)
HORRAD	RT Prostate + ADT	ADT	160	47	-	0.68 (0.42-1.10)

*Prior docetaxel allowed.

Defining High and Low Volume/Risk Disease

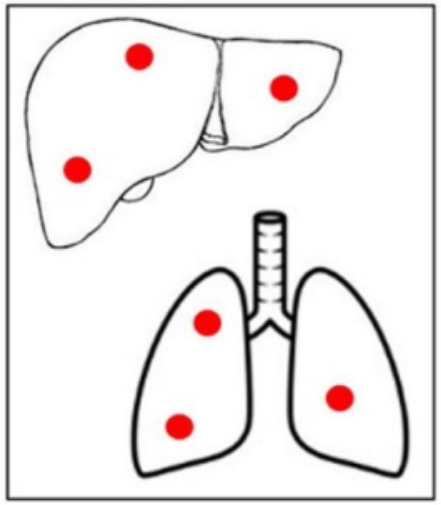
High Volume Disease

According to CHAARTED Study



4 or more bone mets
(with at least one outside the pelvis/column)

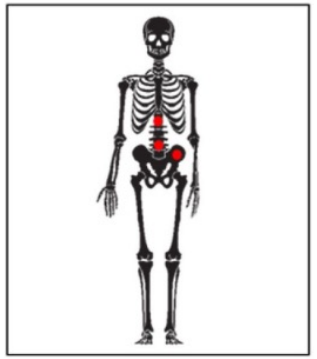
and/or



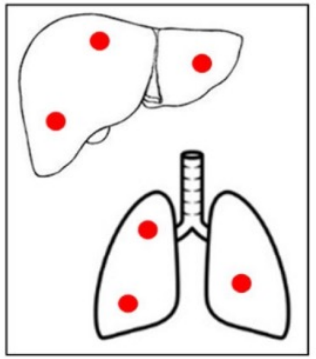
Visceral mets

High Risk Disease

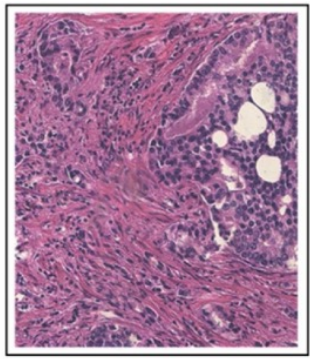
According to Latitude Study



3 or more bone mets



Visceral mets



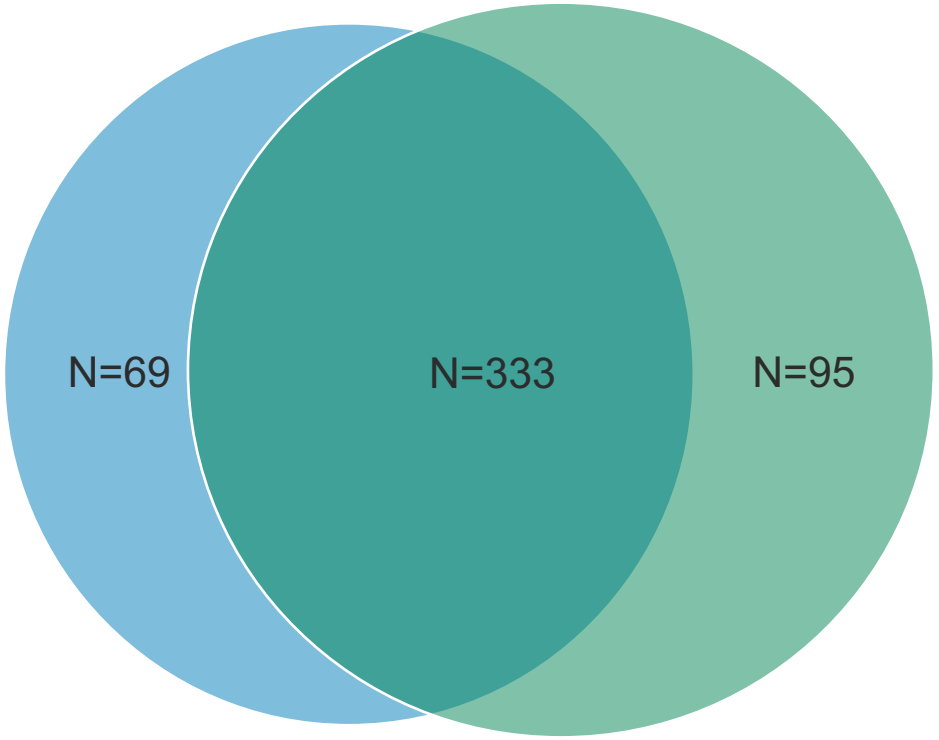
Gleason score ≥ 8

2 or more of the following features

Iacovelli et al, Critical reviews in Oncology/Hematology, 2019

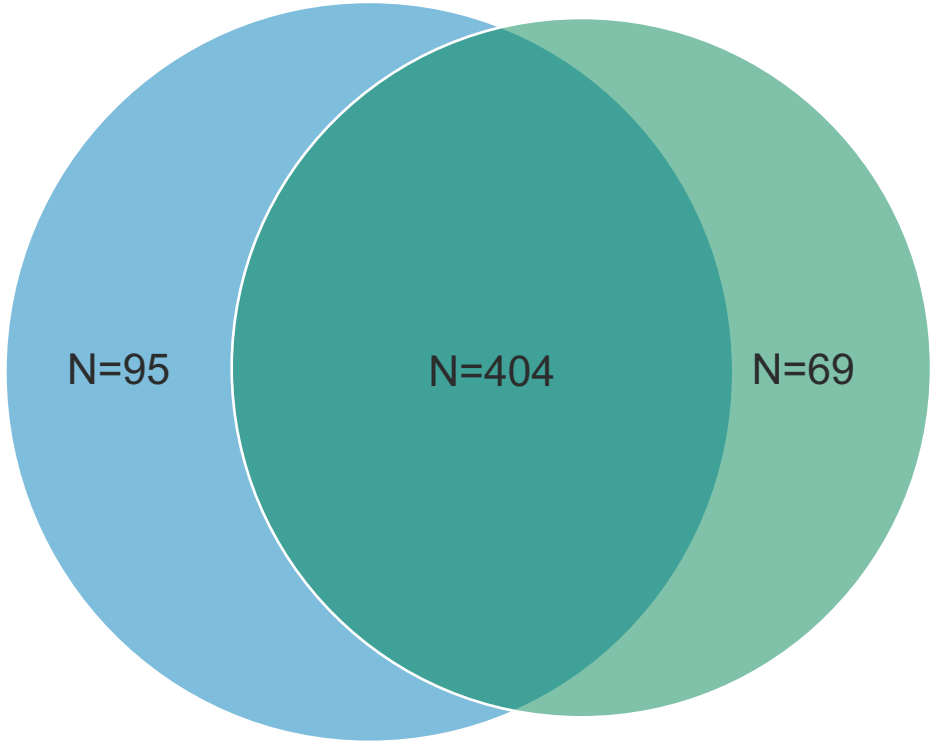
Concordance Between CHAARTED and LATITUDE

Low Volume/Low Risk



CHAARTED = 333/402 (83%) LATITUDE = 333/428 (78%)

High Volume/High Risk



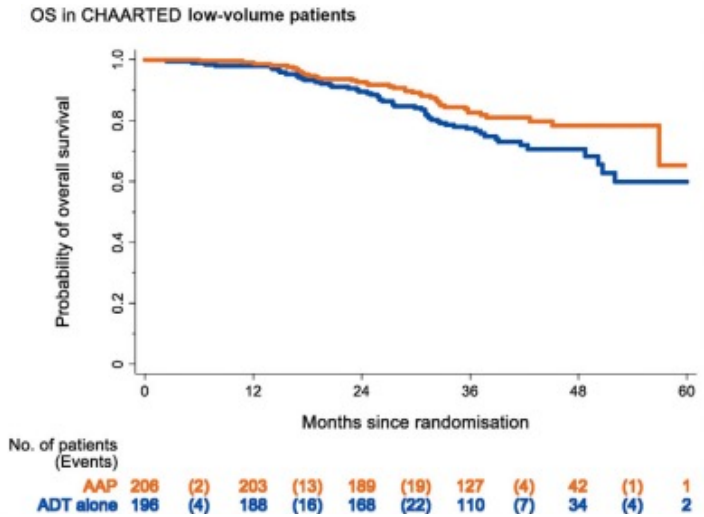
CHAARTED = 404/499 (81%) LATITUDE = 404/473 (85%)

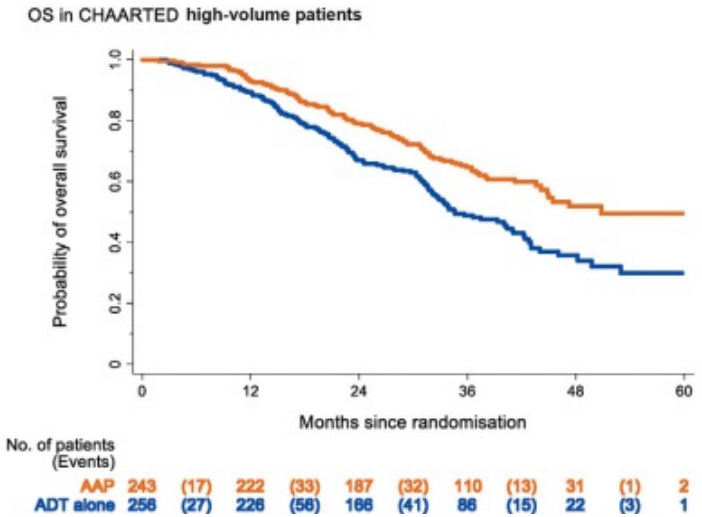
Hoyle et al, European Urology, 2019

Concordance of CHAARTED and LATITUDE Definitions

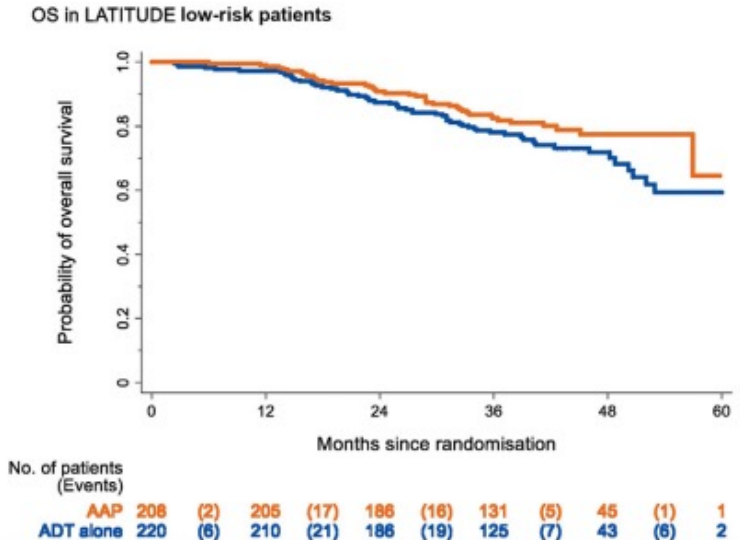
LOW | **HIGH**

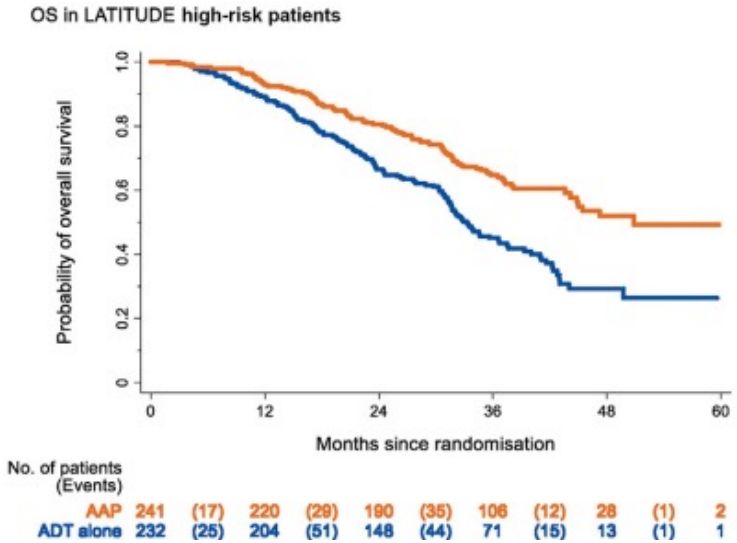
CHAARTED





LATITUDE





Hoyle et al, European Urology, 2019

Clinical Factors to Consider

Abiraterone

- [ ] Hypertension
- [ ] Edema
- [ ] Hypokalemia
- [ ] Liver dysfunction
- [ ] Concurrent prednisone

AR Antagonists

- [ ] Fatigue/falls
- [ ] Rash
- [ ] Hypothyroidism
- [ ] Drug-drug interactions

GNRH Antagonists

- [ ] Obstructive urination
- [ ] Cord compression
- [ ] Mitigate CV risk

Conclusions

- ADT remains the backbone of therapy for patients with prostate cancer across the spectrum of different clinical states in prostate cancer
- Escalated therapy with an ARSI to the backbone of ADT has improved outcomes in high-risk settings for patients with prostate cancer
- Additional studies tested escalated ARSI in the localized, BCR, and PSMA PET positive setting are currently underway and novel hormone therapies are being tested

Agenda

Module 1: **Role of Hormonal Therapy in Prostate Cancer (PC) Management** — Dr McKay

Module 2: Evidence-Based Use of Other Therapeutic Approaches — Dr Antonarakis

Research To Practice
March 23, 2024

Evidence-Based Use of Other Therapeutic Approaches (PARPi, ^{177}Lu-PSMA)

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Clark Endowed Professor of Medicine
Division of Hematology/Oncology & Transplantation, University of Minnesota
Associate Director of Translation, Masonic Cancer Center

Disclosures

Advisory Committees	Aadi Bioscience, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Blue Earth Diagnostics, Curium, Janssen Biotech Inc, Merck, Pfizer Inc, Sanofi, Tango Therapeutics, Tempus
Consulting Agreements	EcoR1 Capital LLC, Hookipa Pharma Inc, Lilly, Menarini Silicon Biosystems, Z-Alpha
Contracted Research	Astellas, Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, Clovis Oncology, MacroGenics Inc, Merck, Novartis, Orion Corporation, Seagen Inc
Patent Holder	QIAGEN

Patient Case #1

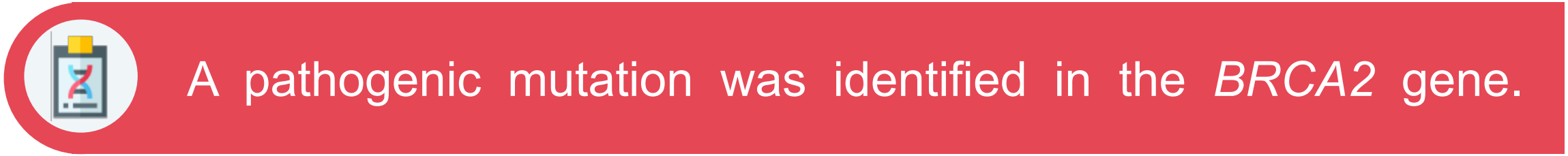
- ❑ African American man
- ❑ Diagnosed with prostate cancer at 58 y
- ❑ PSA 6.9 ng/mL, Gleason 4+4=8, T3b N0 M0
- ❑ Family history: mother, GM, and sister had breast Ca
- ❑ Underwent prostatectomy and adjuvant RT
- ❑ Developed lung mets; started on ADT + docetaxel
- ❑ Developed mCRPC after approximately 20 months (PSA increased to 15 ng/mL)
- ❑ Imaging: growing pulmonary mets; no bone mets

Treatment options:

- ❑ Abiraterone or enzalutamide
- ❑ A second taxane, such as cabazitaxel
- ❑ PARP inhibitor-based treatment

Germline Genetic Testing

Hereditary Cancer Risk Test ***(Color Genomics)***

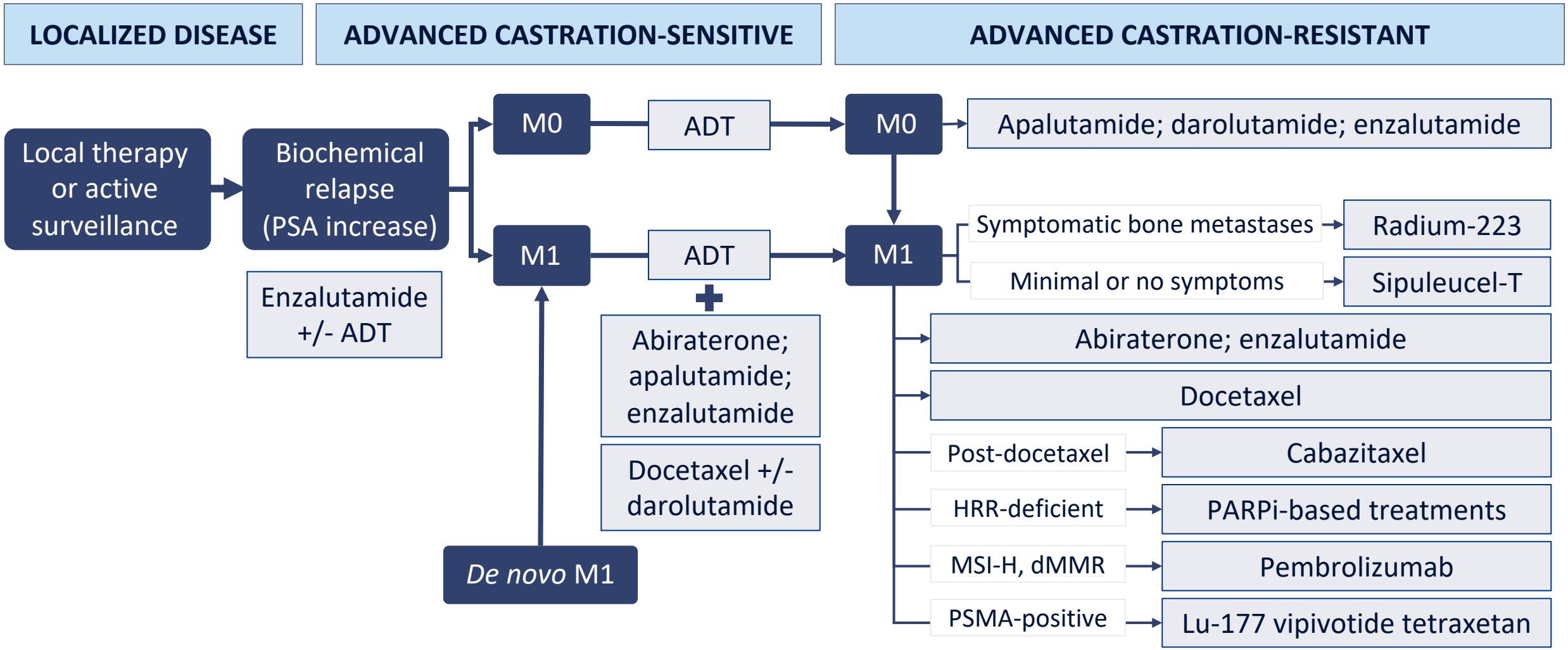


DETAILS

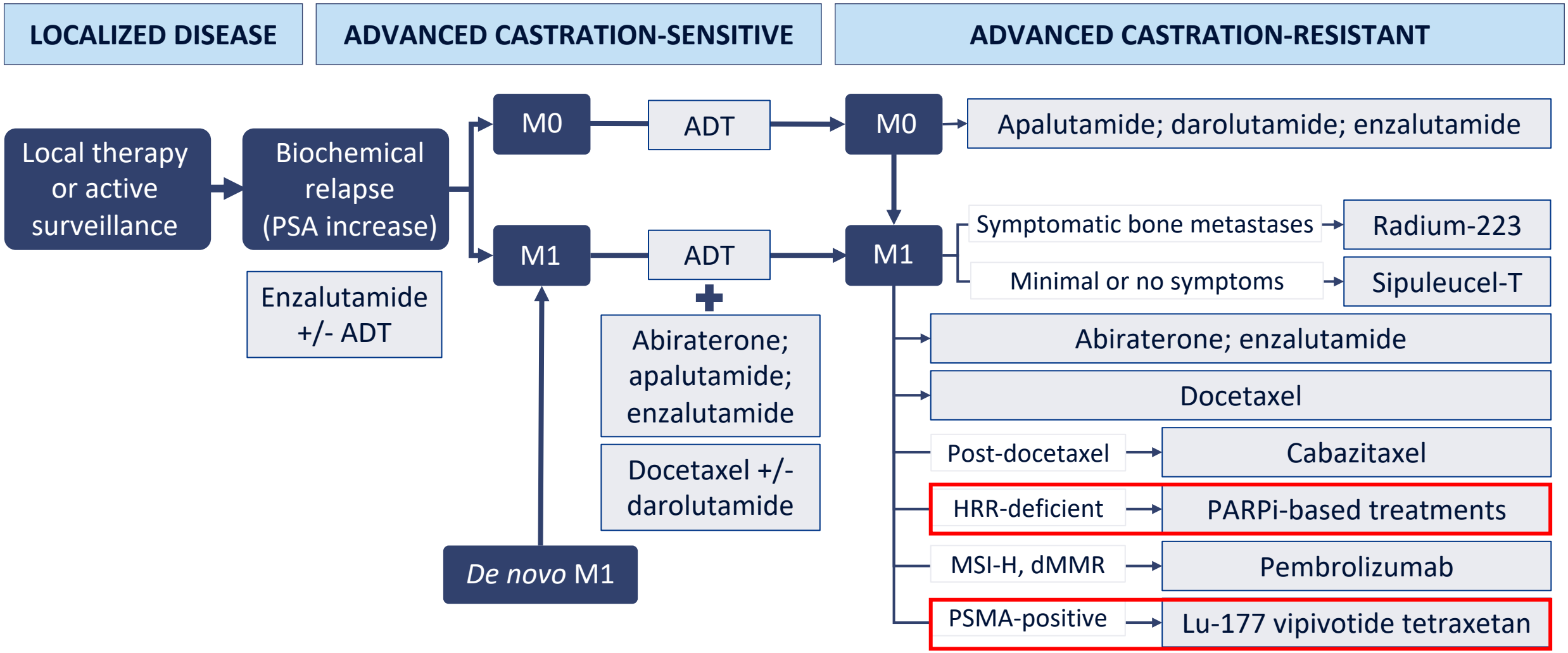
A pathogenic mutation is a variant in the DNA sequence of a gene that affects its ability to function and is also referred to as a mutation in this report

GENE	MUTATION	CLASSIFICATION
BRCA2	**c.1813delA (p.Ile605Tyrfs*9)** *Alternate name(s): chr13.GRCH37:g.32907428delA* *Transcript: ENST00000544455* *Zygosity: Heterozygous*	**Pathogenic**

Treatment Landscape for Prostate Cancer



Treatment Landscape for Prostate Cancer

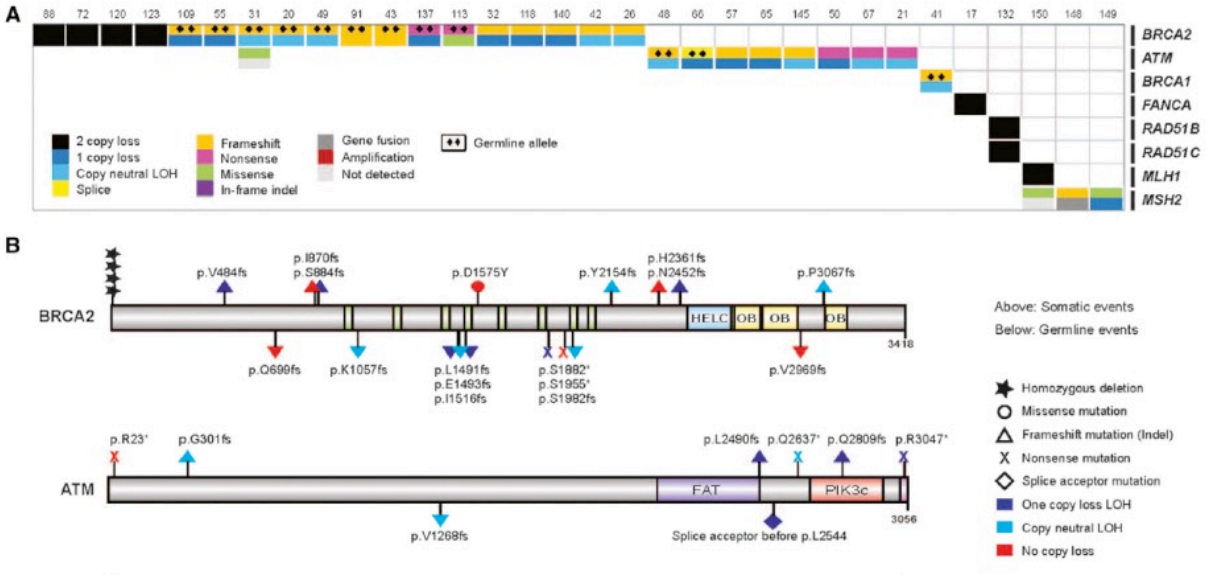


Incidence of HRR mutations in PCa, and Indications for testing

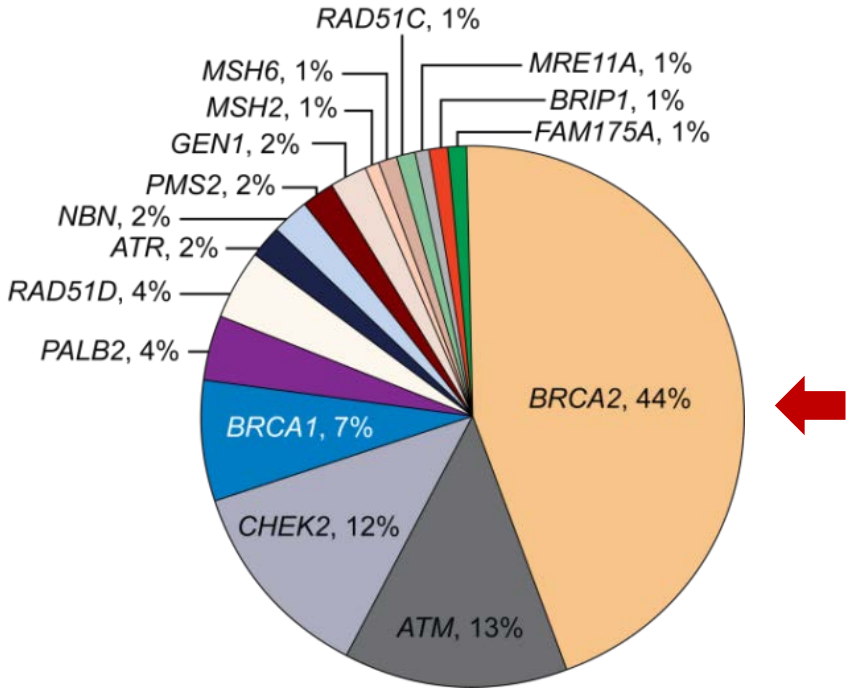
HRR Genes and Metastatic Prostate Cancer

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.

What are the relevant HRR Genes?

"First Tier"	"Second Tier"	"Third Tier"
BRCA2 (6–8%)	***CDK12*** (5–7%)	***ATM*** (5–7%)
BRCA1 (1–2%)	***BARD1*** (1%)	***CHEK2*** (2–3%)
PALB2 (1–2%)	***BRIP1*** (1–2%)	***CHEK1*** (1%)
RAD51B (1%)	***RAD51C*** (1%)	***FANCL*** (1–2%)
RAD54L (1%)	***RAD51D*** (1%)	

Prostate NCCN Guidelines v 1.2024

Germline Testing

Germline testing is recommended in patients with a personal history of prostate cancer who:

- Have metastatic, regional (N+), very-high-risk localized, or high-risk localized prostate cancer
- Have family history and/or ancestry with:
  - ≥1 first, second, or third degree relative with
    - Breast cancer at age ≤50 years
    - Colorectal or endometrial cancer at age ≤50 years
    - Male breast cancer at any age
    - Ovarian cancer at any age
    - Pancreatic cancer at any age
    - Metastatic, regional, very-high-risk, or high-risk prostate cancer at any age
  - ≥1 first degree relative with prostate cancer at age ≤60 years
  - ≥2 first, second, or third degree relatives with:
    - Breast cancer at any age
    - Prostate cancer at any age
  - ≥3 first or second degree relatives with:
    - Lynch syndrome-related cancers, especially if diagnosed at age <50 years
    - A known family history of a familial cancer risk mutation
    - Ashkenazi Jewish ancestry
  - Personal history of male breast cancer

Germline testing may be considered in patients with a personal history of PCa who:

- Have intermediate-risk prostate cancer with intraductal/cribriform histology
- Have a personal history of pancreatic, colorectal, gastric, melanoma, upper tract urothelial, glioblastoma, biliary tract, or small intestinal cancer

Germline multigene testing that includes at least BRCA1, BRCA2, ATM, PALB2, CHEK2, HOXB13, MLH1, MSH2, MSH6, and PMS2 is recommended; additional genes may be appropriate based on clinical context

Somatic Tumor Testing

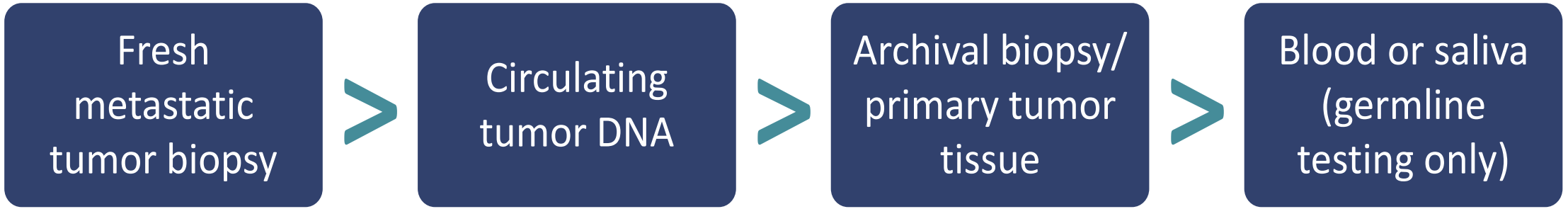
Tumor testing for alterations in HRR DNA repair genes such as ***BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2,*** and ***CDK12*** is recommended in patients with metastatic prostate cancer, and may be considered for patients with regional (N+) prostate cancer

Tumor testing for MSI-H or dMMR is recommended in patients with mCRPC, and may be considered for patients with mCSPC

TMB testing may be considered in patients with mCRPC

NCCN Practice Guidelines: Prostate Cancer. Version 1.2024. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.

How to identify HRR alterations?



Order of preference

Germline-only testing

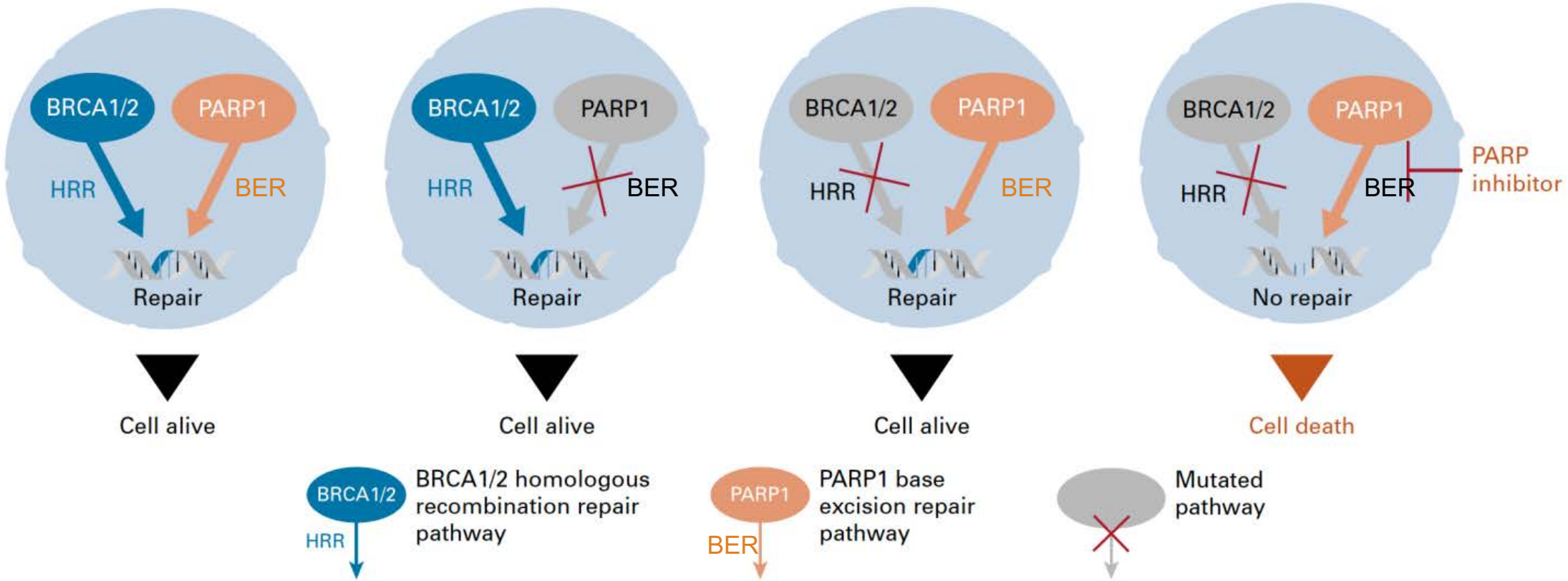
May underestimate important somatic HRR mutations

Unable to discern monoallelic from biallelic HRR mutations

Antonarakis ES, et al. *Eur Urol Oncol* 2020;3:594-611.

PARP inhibitors for HRR-deficient mCRPC

PARP Inhibition: "Synthetic Lethality"



PARP is required for single-strand break repair (e.g. via BER)

MOA – inhibiting SSB/BER is synthetic lethal with HRD

Different PARP inhibitors tested in PCa

Properties of PARP Inhibitors

	Olaparib	Talazoparib	Niraparib	Rucaparib
Mol. Weight	434.5	380.8	320.4	323.4
PARP1 IC_{50}	5 nM	0.56 nM	3.8 nM	0.65 nM
PARP2 IC_{50}	1 nM	0.15 nM	2.1 nM	0.08 nM
Trapping	++	++++	+++	++

Carney B, et al. *Nat Commun* 2018; 9: 176.

PARP inhibitors for HRR-mutated mCRPC

OLAPARIB: In **May 2020,** based on data from the **PROfound study,** the FDA granted **full approval olaparib** for the treatment of patients with deleterious or suspected **germline or somatic HRR[a] gene-mutated mCRPC, who have progressed following prior treatment with enzalutamide or abiraterone[1,b]**

[a]***BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L***.
[b]Select patients for therapy based on two FDA-approved companion diagnostic tests: BRACAnalysis CDx and FoundationOne CDx.

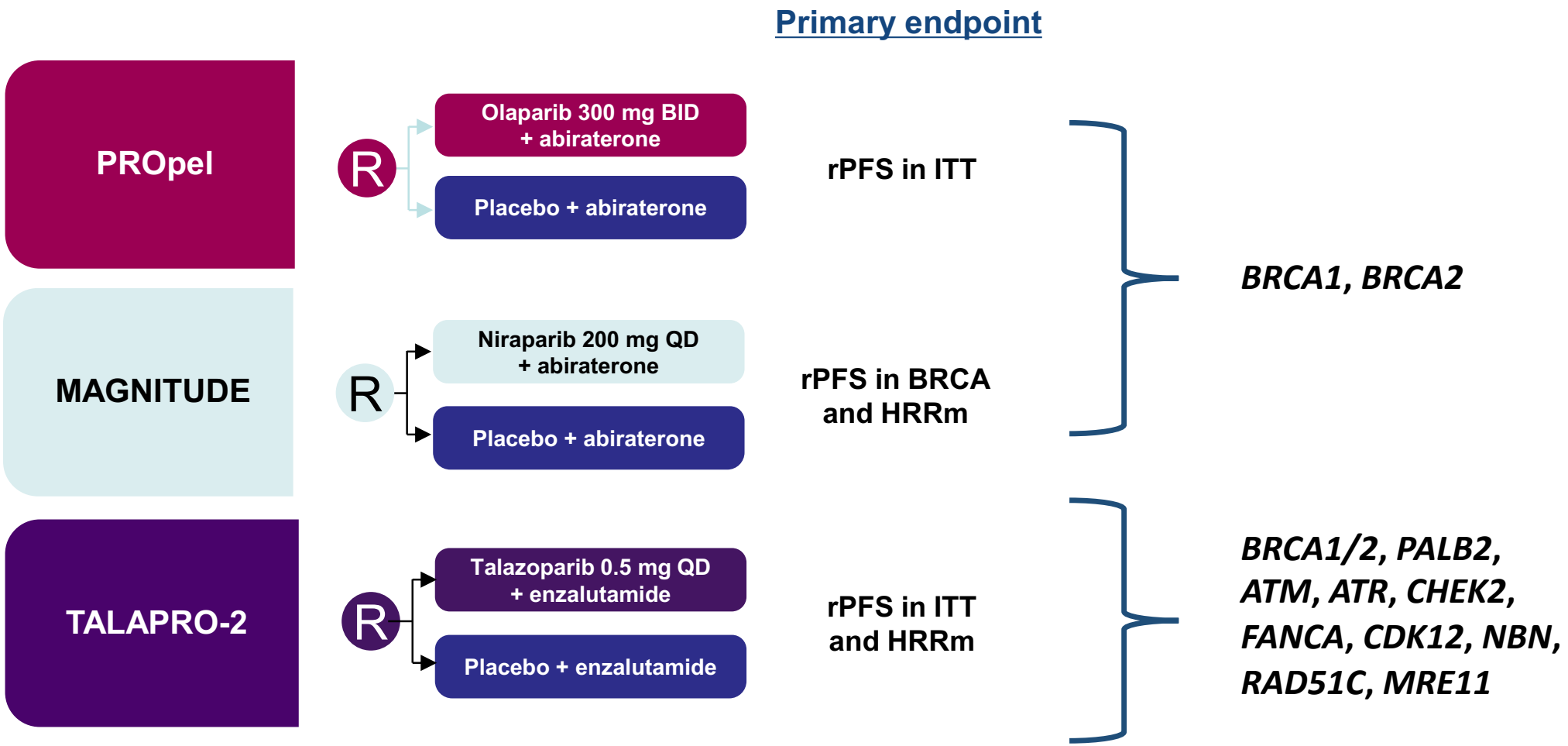
1. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-olaparib-hrr-gene-mutated-metastatic-castration-resistant-prostate-cancer.

RUCAPARIB: In **May 2020,** based on data from the **TRITON2 study,** the FDA granted **accelerated approval to rucaparib** for the treatment of patients with **deleterious *BRCA1/2* (germline and/or somatic)-associated mCRPC, who have been treated with an androgen receptor-directed therapy and a taxane-based chemotherapy.[1]**

1. https://www.fda.gov/drugs/fda-grants-accelerated-approval-rucaparib-brca-mutated-metastatic-castration-resistant-prostate.

Key findings from PROpel, MAGNITUDE, TALAPRO-2

PARPi + NHA in First Line mCRPC



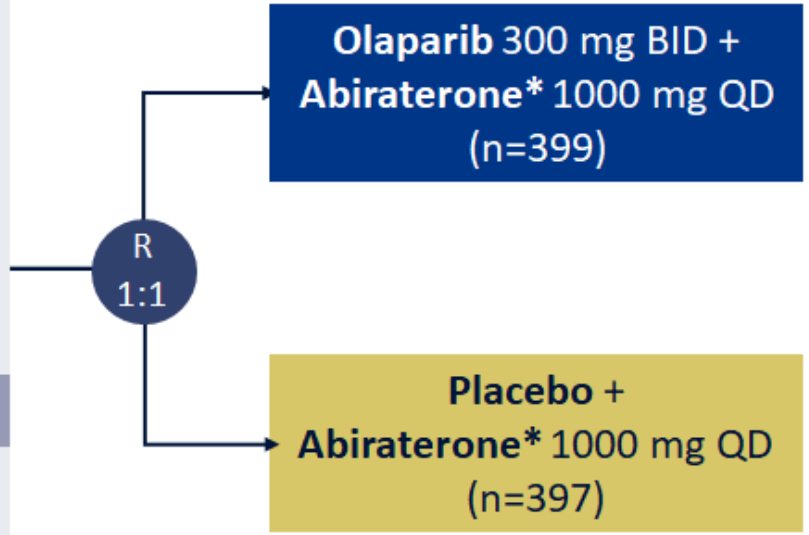
PROpel: Phase III Trial of Abiraterone +/– Olaparib

Patient population

- mCRPC
- Docetaxel for mCSPC allowed
- No prior abiraterone
- Other NHT allowed if stopped ≥12 months prior to enrollment
- Ongoing ADT
- ECOG PS 0–1

Stratification factors

- Site of distant metastases (bone only vs visceral vs other)
- Prior taxane for mCSPC



Primary endpoint

rPFS or death by investigator assessment

Key secondary endpoint

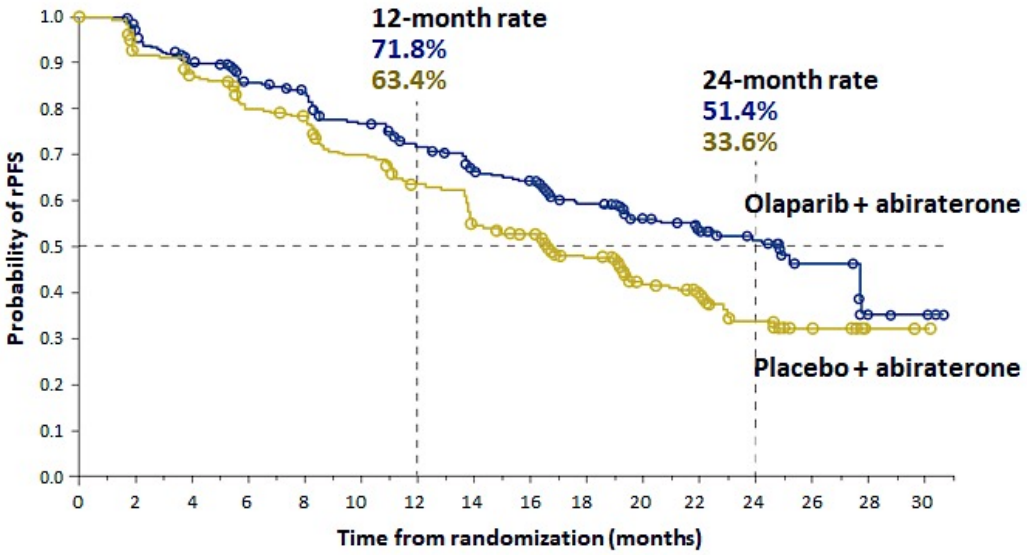
- OS

Additional endpoints

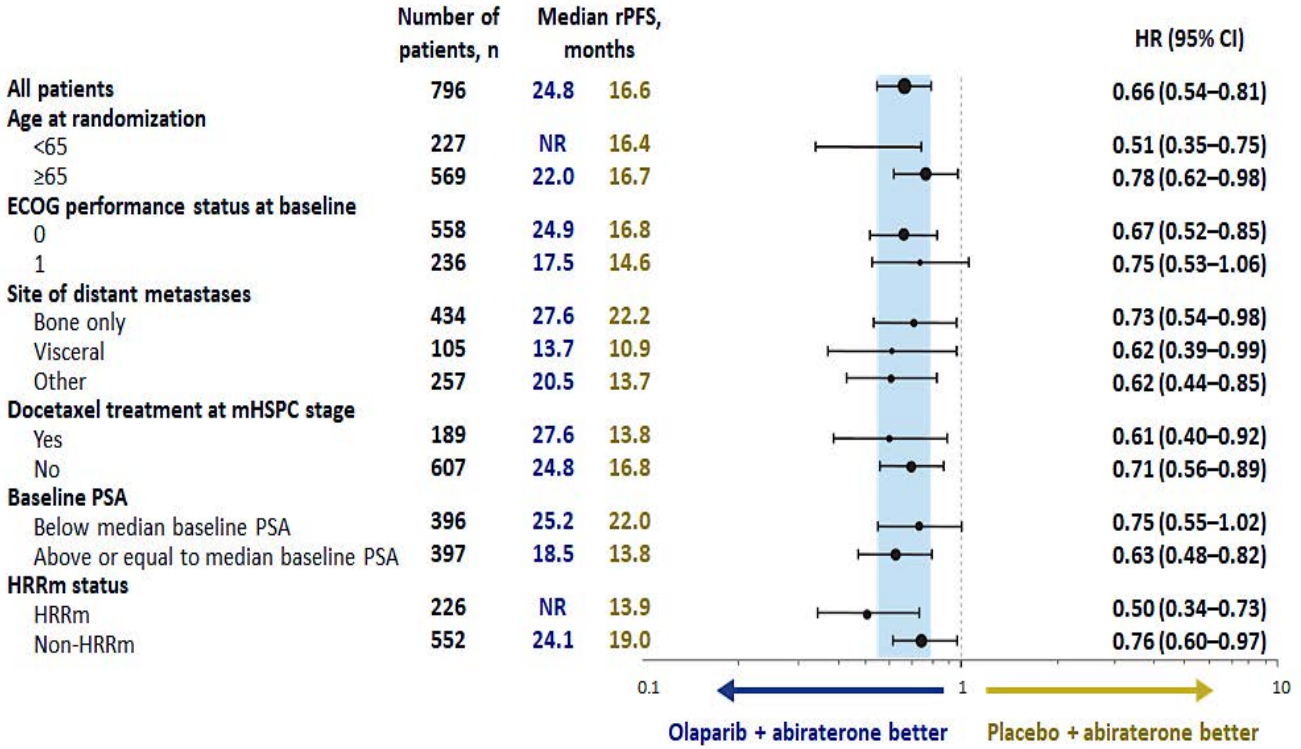
- TFST
- PFS2
- ORR
- HRR mutation prevalence (tested retrospectively)
- HRQOL
- Safety and tolerability

Saad F et al. *ASCO GU 2022*; abstr 11; NCT03732820.

PROpel: Radiographic progression-free survival

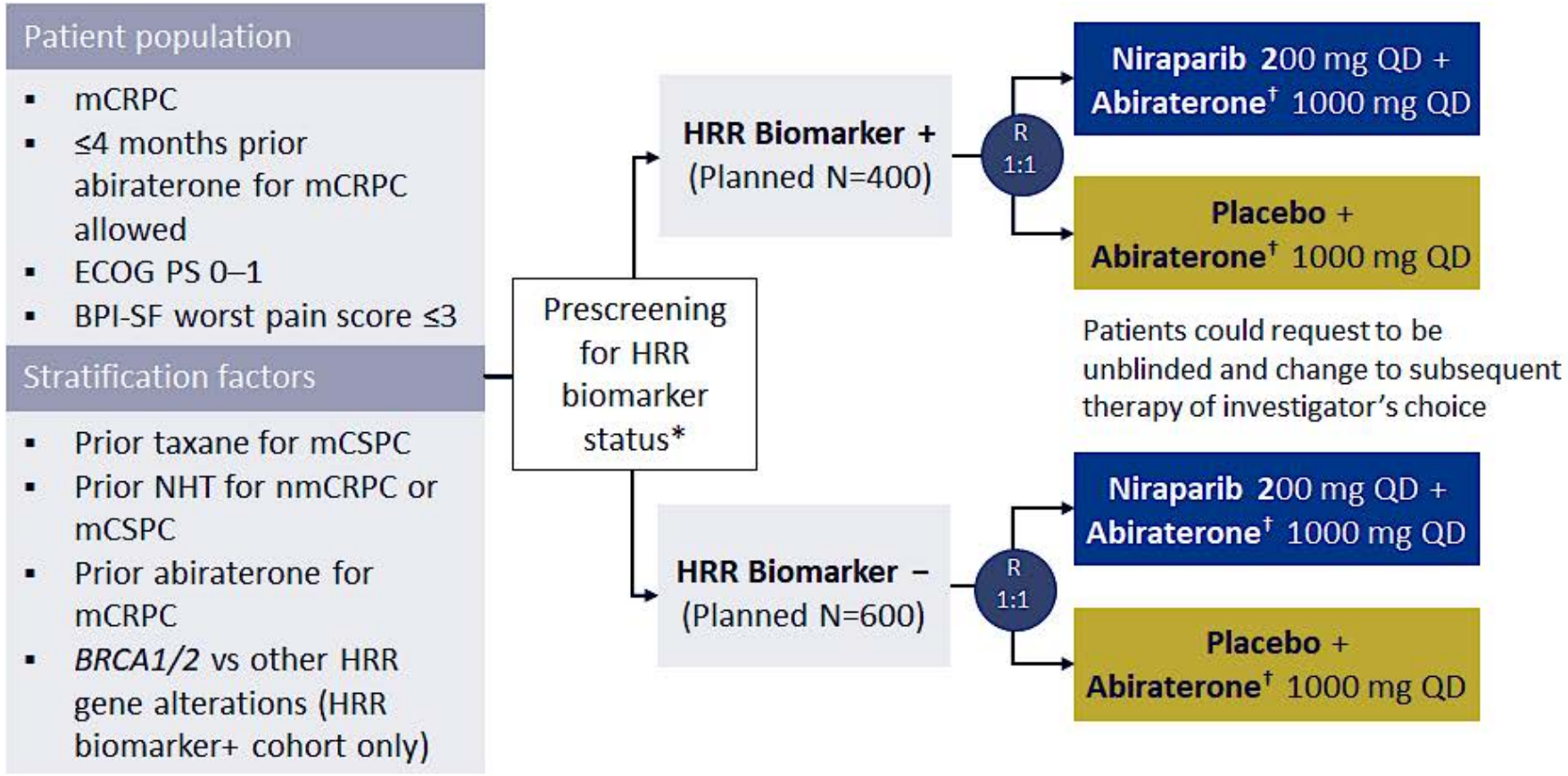


	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
rPFS by investigator assessment		
Events, n (%)	168 (42.1)	226 (56.9)
Median rPFS, months	24.8	16.6
HR (95% CI)	0.66 (0.54–0.81); *P*<0.0001	
rPFS by blinded independent central review		
HR (95% CI)	0.61 (0.49–0.74); *P*<0.0001	



Saad F et al. *NEJM Evidence*; 2022.

MAGNITUDE: Phase III Trial of Abi +/– Niraparib



Primary endpoint

rPFS by central review

Key secondary endpoints

- Time to cytotoxic chemotherapy
- Time to symptomatic progression
- OS

Other prespecified endpoints

- Time to PSA progression
- ORR
- PFS2
- Time to pain progression
- Patient-reported outcomes

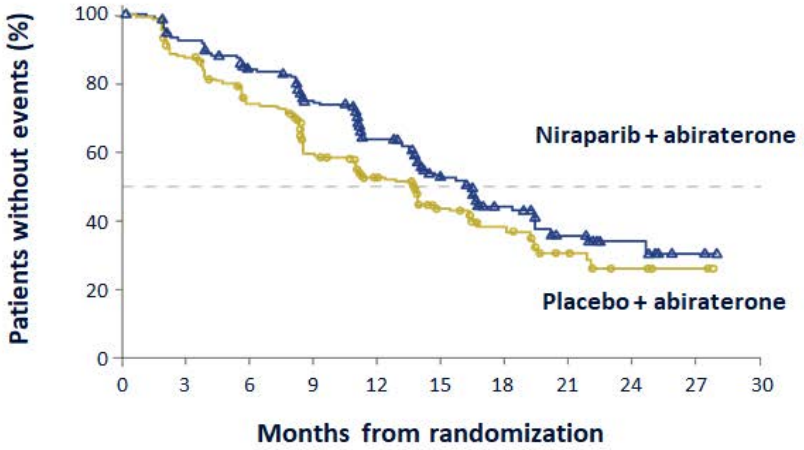
*HRR gene panel: ***ATM, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, HDAC2, PALB2***

†Plus prednisone 10 mg daily

Chi KN et al. *ASCO GU 2022*; abstr 12; NCT03748641.

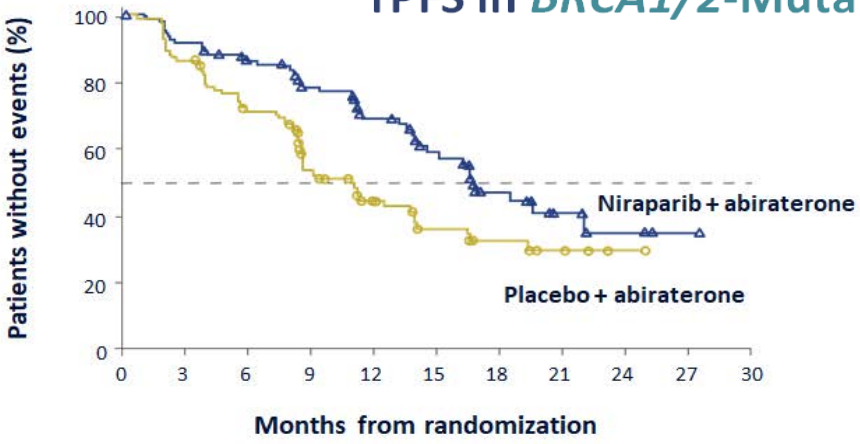
MAGNITUDE: Radiographic progression-free survival

rPFS in All HRR BM+ Cohort



	Niraparib + abiraterone (n=212)	Placebo + abiraterone (n=211)
rPFS by central review		
Median rPFS, months	16.5	13.7
HR (95% CI)	0.73 (0.56–0.96); *P*=0.0217	
rPFS assessed by investigator		
Median rPFS, months	19.0	13.9
HR (95% CI)	0.64 (0.49–0.86); *P*=0.0022	

rPFS in *BRCA1/2*-Mutated Group



	Niraparib + abiraterone (n=113)	Placebo + abiraterone (n=112)
rPFS by central review		
Median rPFS, months	16.6	10.9
HR (95% CI)	0.53 (0.36–0.79); *P*=0.0014	
rPFS assessed by investigator		
Median rPFS, months	19.3	12.4
HR (95% CI)	0.50 (0.33–0.75); *P*=0.0006	

Chi KN et al. *J Clin Oncol 2023*.

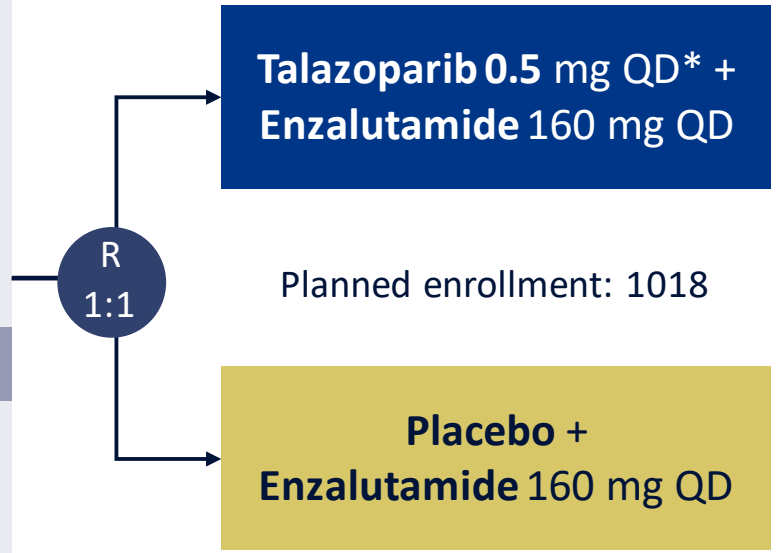
TALAPRO-2: Phase III Trial of Enza +/– Talazoparib

Patient population

- mCRPC with progression (PSA, bone, and/or soft tissue)
- Prior docetaxel and/or abiraterone in CSPC setting allowed
- Ongoing ADT or bilateral orchiectomy
- ECOG PS 0–1

Stratification factors

- Previous treatment with abiraterone or taxane-based chemotherapy for CSPC
- DDR# alteration status (deficient vs nondeficient/unknown)



Co-primary endpoints

- rPFS by BICR per RECIST 1.1 and PCWG3 in **All-comers (Cohort 1), n=804**
- rPFS by BICR in patients with **DDR# alterations (Cohort 2), n=214**

Key secondary endpoints (analyzed for both cohorts separately)

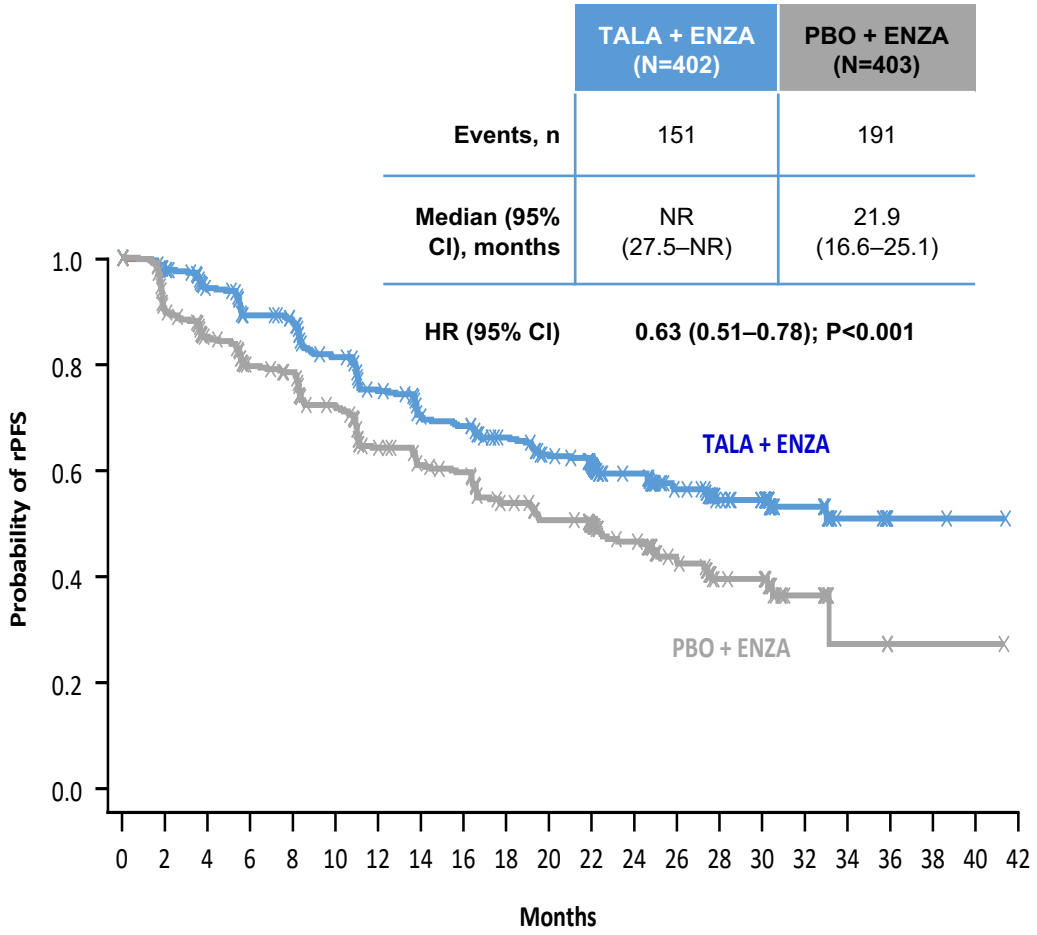
- OS
- OR per RESIST 1.1 (measurable disease)
- PSA response ≥50%
- Time to PSA progression
- Time to initiation of cytotoxic CT or antineoplastic therapy
- Time to first symptomatic skeletal event
- PFS2
- Safety
- Patient-reported outcomes

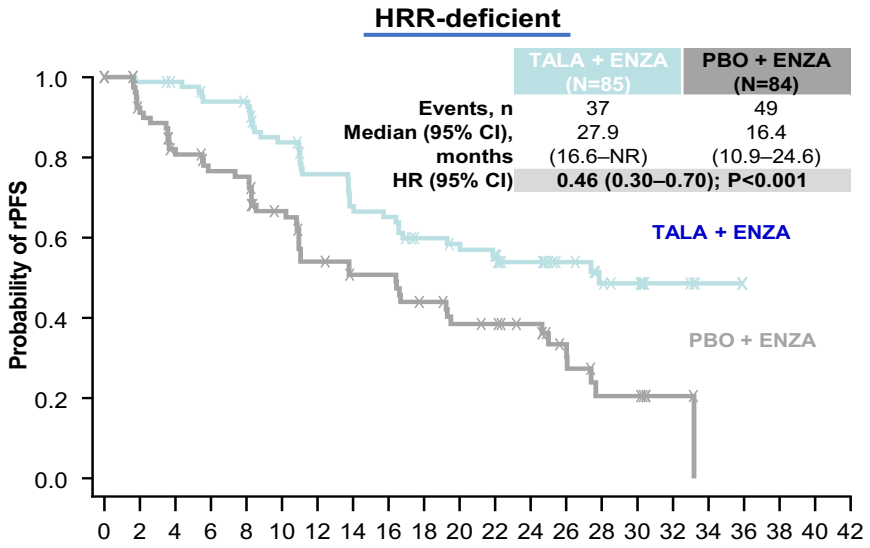
*0.35 mg QD if moderate renal impairment

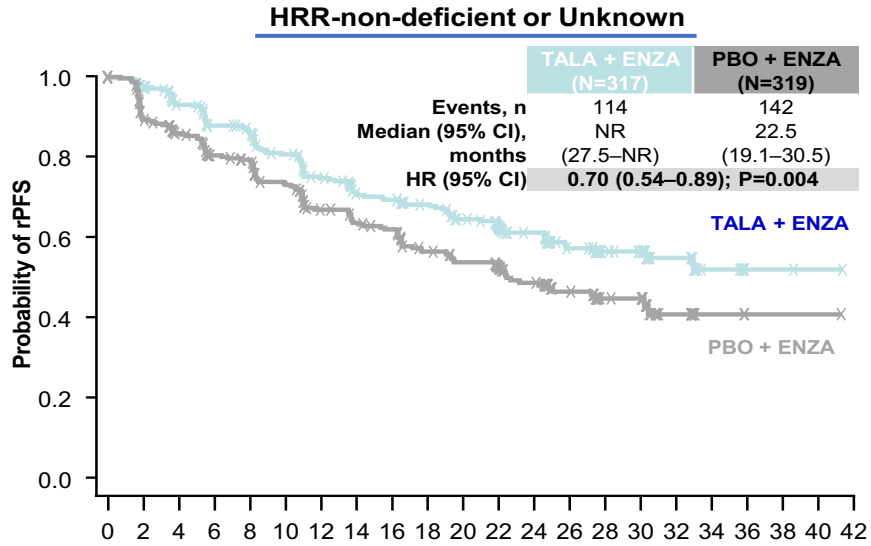
DDR alterations (*BRCA1/2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MLH1, MRE11A, CDK12*).

Agarwal N et al. *Future Oncol.* 2022;18:425-436; NCT03395197.

TALAPRO-2: Phase III Trial of Enza +/– Talazoparib







Agarwal N et al. *Lancet 2023*; 402: 291-303.

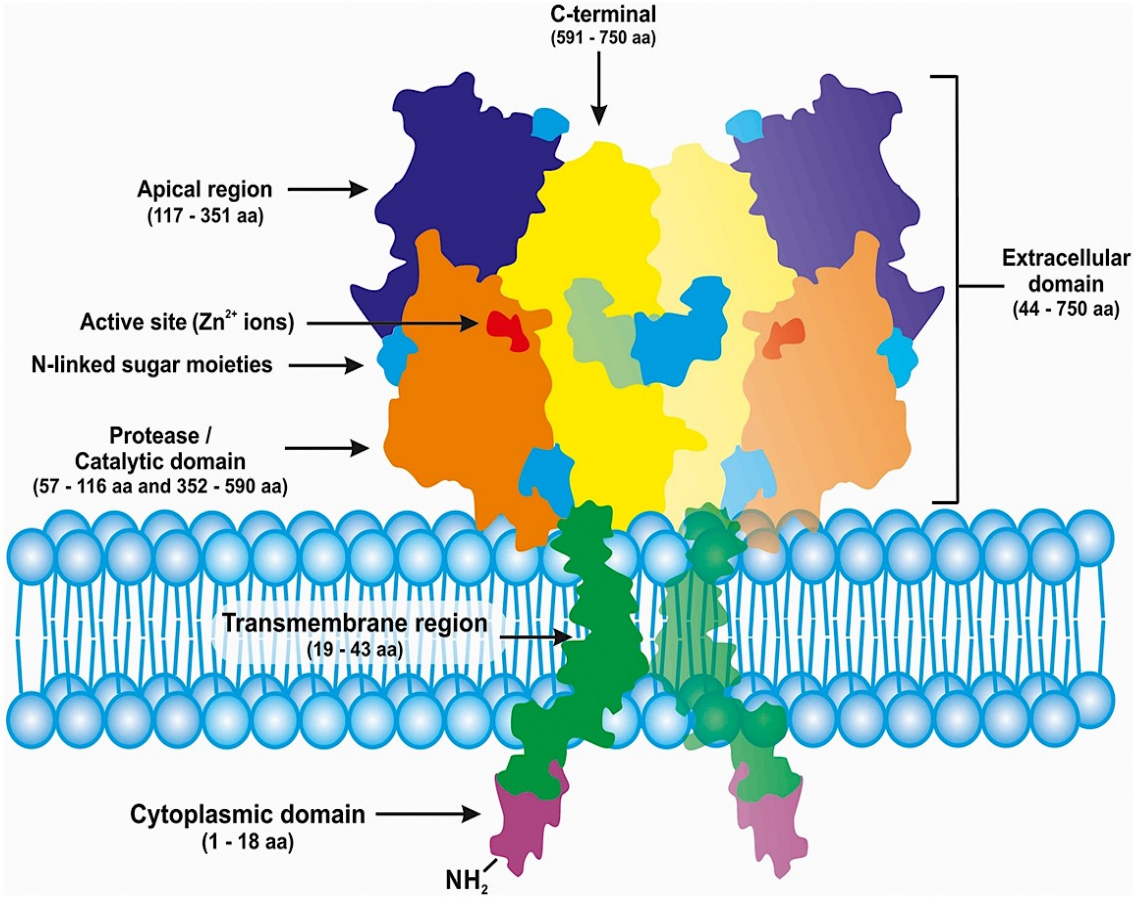
Adverse Events across the 3 studies

	MAGNITUDE N = 212 (HHRm Cohort)		PROpel N = 398 (All Comers)		TALAPRO-2 N = 198 (HHRm Cohort)	
	All Grades (%)	Grade 3-4 (%)	All Grades	Grade 3-4	All Grades	Grade 3-4
Anemia	52	31	50	16	65	41
Fatigue	30	4	38	3	33	2
Nausea	24	1	30	1	21	2
Thrombocytopenia	24	8	7	1	25	7
Neutropenia	16	7	10	5	36	18
Pulmonary embolism	2		7		2	
Transfusion	27		18		36	
AML/MDS	N = 0		N = 2		N = 2	

Lutetium Lu^{177} vipivotide tetraxetan (VISION, PSMAfore)

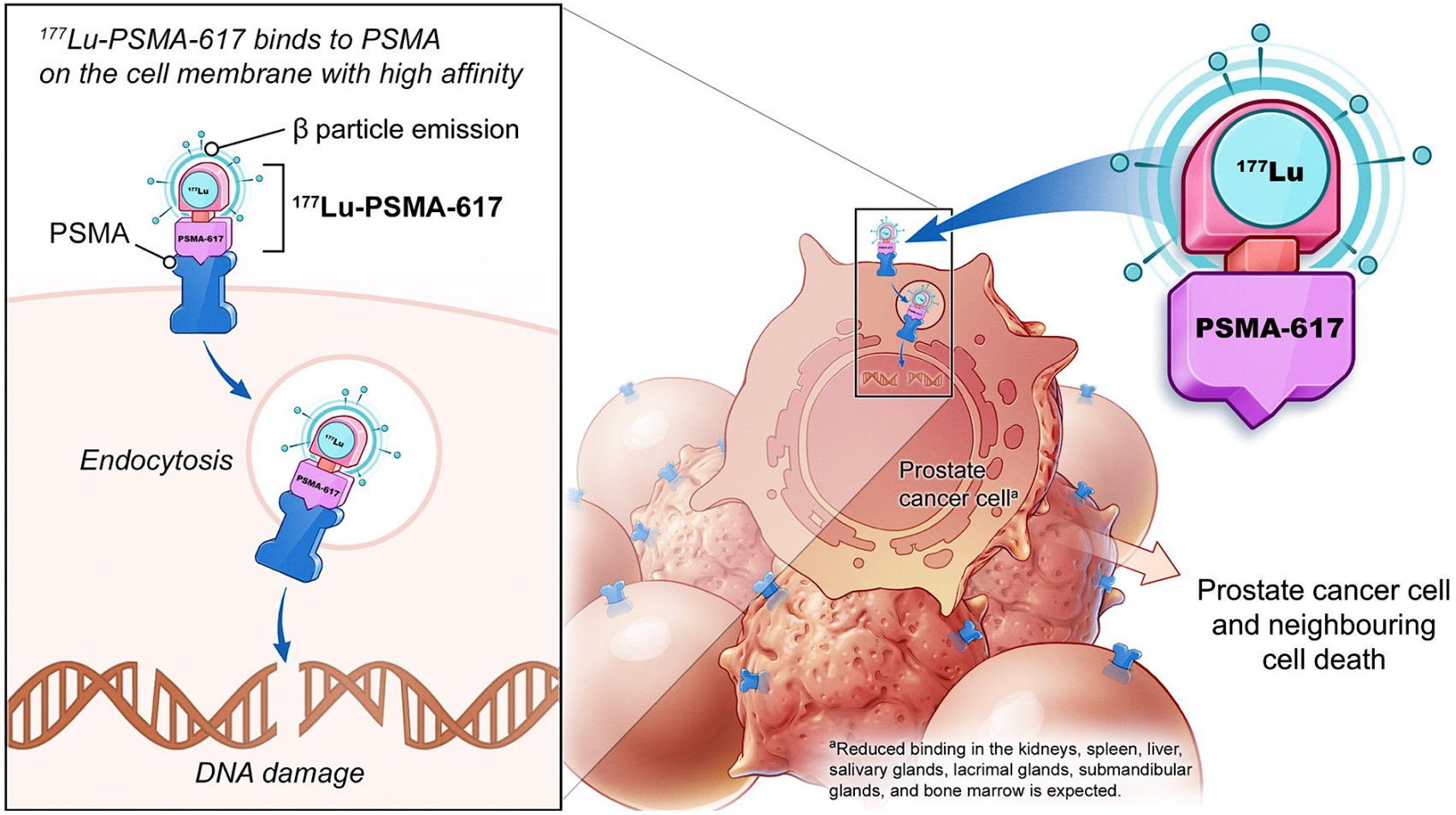
PSMA: Target for imaging and therapy

- Transmembrane carboxypeptidase
- Highly expressed in prostate cancer including metastatic lesions
- Relatively restricted normal expression
  - E.g. salivary and lacrimal glands
- Excellent target for PET imaging



Evans JC, *et al. Br J Pharmacol* 2016; 173: 3041-79.

^{177}Lu-PSMA-617 Radioligand therapy



Morris MJ, *et al.* J Clin Oncol 39; 2021 (ASCO abstract LBA4).

VISION trial for patients with PSMA+ mCRPC

Eligible patients

- Previous treatment with <u>both</u>
  - ≥ 1 androgen receptor pathway inhibitor
  - 1 or 2 taxane regimens
- Protocol-permitted standard of care (SOC) planned before randomization
  - Excluding chemotherapy immunotherapy, radium-223, investigational drugs
- ECOG performance status 0–2
- Life expectancy > 6 months
- PSMA-positive mCRPC on PET/CT with ^{68}Ga-PSMA-11

2:1

Protocol-permitted SOC + ^{177}Lu-PSMA-617
7.4 GBq (200 mCi) every 6 weeks
4 cycles, increasable to 6

Protocol-permitted SOC alone

Treatment → Follow-up → Final analysis

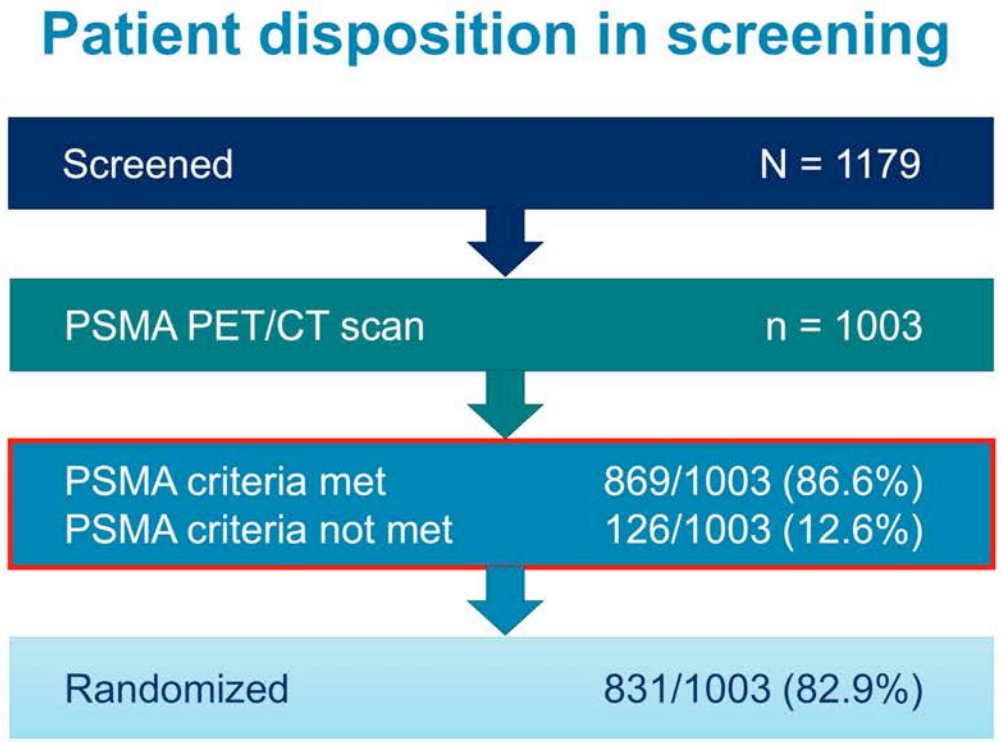
- Randomization stratified by
  - ECOG status (0–1 or 2)
  - LDH (high or low)
  - Liver metastases (yes or no)
  - Androgen receptor pathway inhibitors in SOC (yes or no)

- CT/MRI/bone scans
  - Every 8 weeks (treatment)
  - Every 12 weeks (follow-up)
  - Blinded independent central review

Morris MJ, *et al.* J Clin Oncol 39; 2021 (ASCO abstract LBA4). Sartor O, et al. *NEJM* 2021.

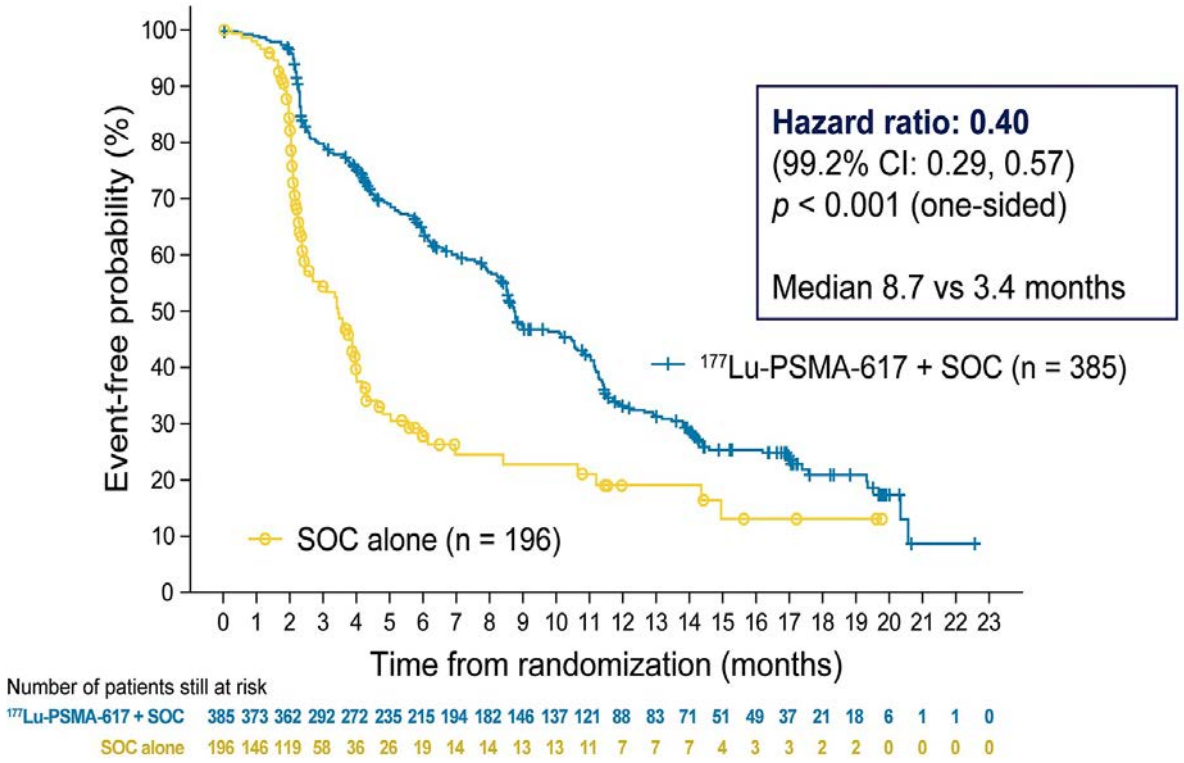
VISION trial: Patient Disposition

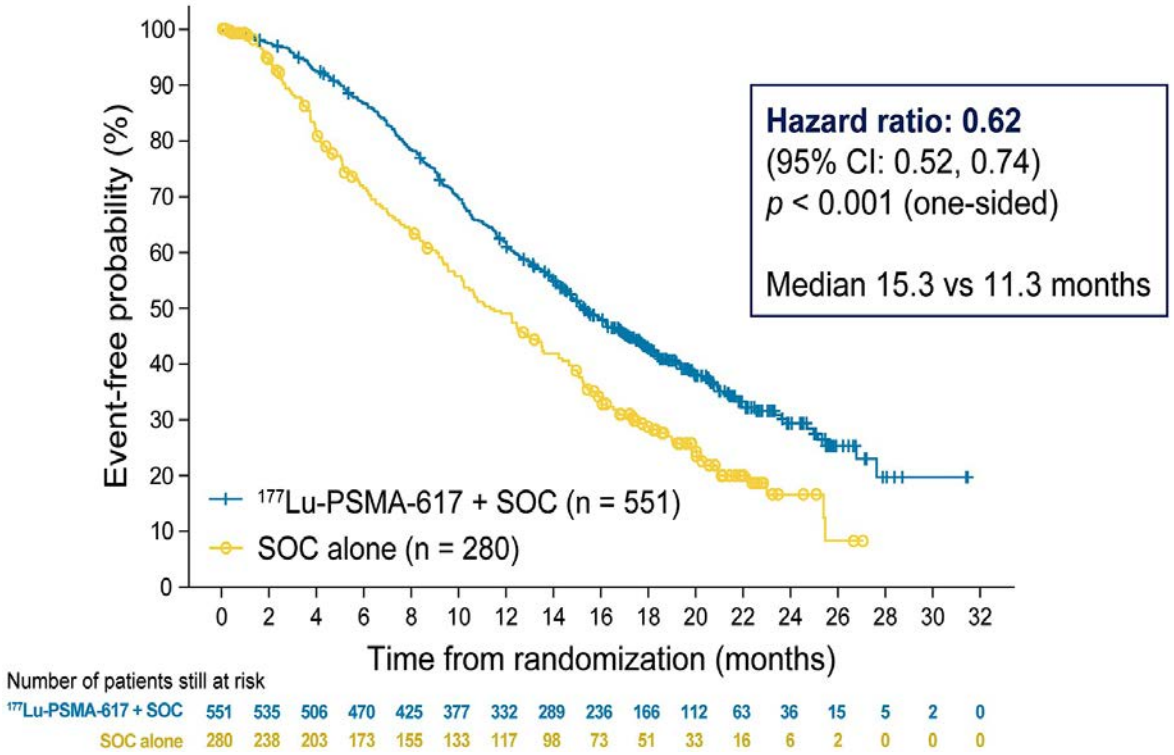
^{68}Ga-PSMA-11 PET/CT: ~87% of patients scanned met the VISION imaging criteria for PSMA-positive mCRPC



Morris MJ, *et al.* J Clin Oncol 39; 2021 (ASCO abstract LBA4). Sartor O, et al. *NEJM* 2021.

VISION trial: rPFS and OS





Morris MJ, *et al.* J Clin Oncol 39; 2021 (ASCO abstract LBA4) . Sartor O, et al. *NEJM* 2021.

VISION trial: Adverse Events

Table 2. Adverse Events.*

Event	^{177}Lu-PSMA-617 plus Standard Care (N=529)		Standard Care Alone (N=205)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Any adverse event	519 (98.1)	279 (52.7)	170 (82.9)	78 (38.0)
Adverse event that occurred in >12% of patients				
Fatigue	228 (43.1)	31 (5.9)	47 (22.9)	3 (1.5)
Dry mouth	205 (38.8)	0	1 (0.5)	0
Nausea	187 (35.3)	7 (1.3)	34 (16.6)	1 (0.5)
Anemia	168 (31.8)	68 (12.9)	27 (13.2)	10 (4.9)
Back pain	124 (23.4)	17 (3.2)	30 (14.6)	7 (3.4)
Arthralgia	118 (22.3)	6 (1.1)	26 (12.7)	1 (0.5)
Decreased appetite	112 (21.2)	10 (1.9)	30 (14.6)	1 (0.5)
Constipation	107 (20.2)	6 (1.1)	23 (11.2)	1 (0.5)
Diarrhea	100 (18.9)	4 (0.8)	6 (2.9)	1 (0.5)
Vomiting	100 (18.9)	5 (0.9)	13 (6.3)	1 (0.5)
Thrombocytopenia	91 (17.2)	42 (7.9)	9 (4.4)	2 (1.0)
Lymphopenia	75 (14.2)	41 (7.8)	8 (3.9)	1 (0.5)
Leukopenia	66 (12.5)	13 (2.5)	4 (2.0)	1 (0.5)

Sartor O, et al. *NEJM* 2021.

^{177}Lutetium–PSMA–617: FDA Approved!

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

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.

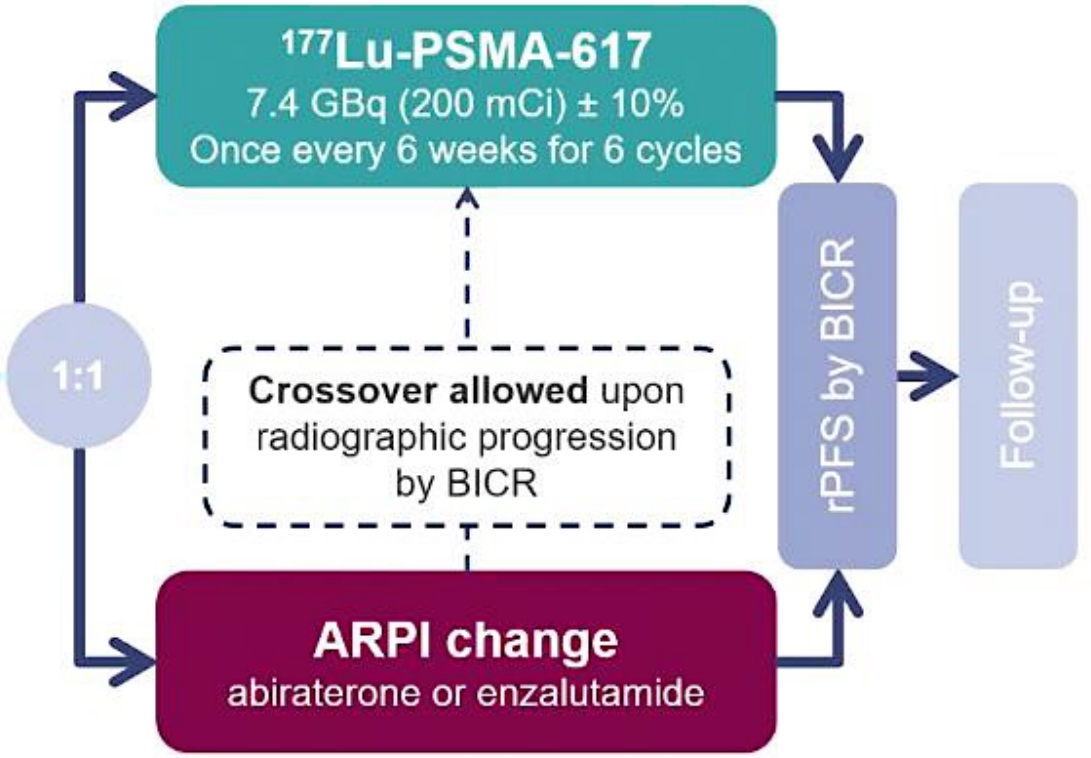
On the same day, the FDA approved gallium Ga 68 gozetotide, a radioactive diagnostic agent for positron emission tomography (PET) of PSMA-positive lesions, including selection of patients with metastatic prostate cancer for whom lutetium Lu 177 vipivotide tetraxetan PSMA-directed therapy is indicated. Gallium Ga 68 gozetotide is the first radioactive diagnostic agent approved for patient selection in the use of a radioligand therapeutic agent. "

PSMAfore: Trial Design

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

Eligible adults

- Confirmed progressive mCRPC
- ≥ 1 PSMA-positive metastatic lesion on [^{68}Ga]Ga-PSMA-11 PET/CT and no exclusionary PSMA-negative lesions
- Progressed once on prior second-generation ARPI
  - Candidates for change in ARPI
- Taxane-naive (except [neo]adjuvant > 12 months ago)
  - Not candidates for PARPi
- ECOG performance status 0–1



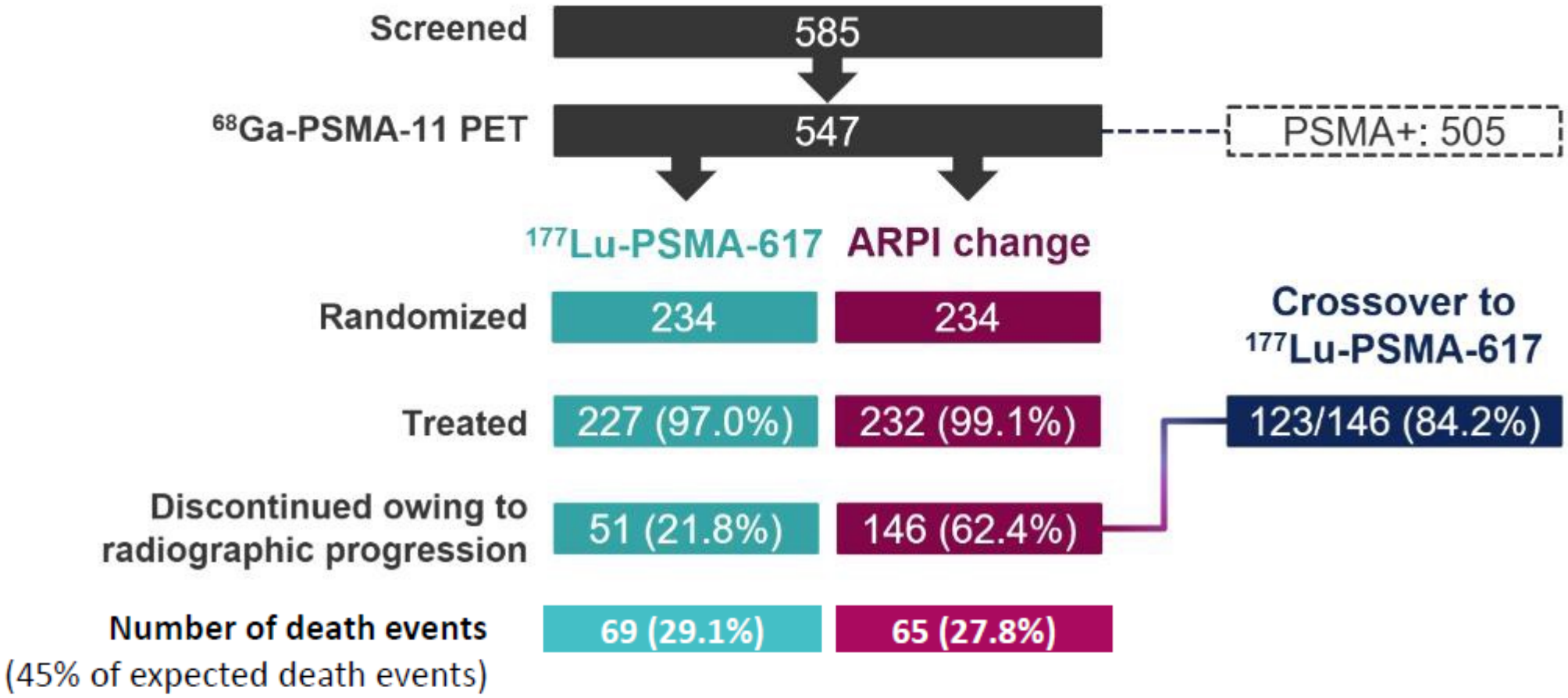
Stratification factors

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

MADRID 2023 ESMO congress

Sartor O, et al. *ESMO* 2023.

PSMAfore: Patient Disposition

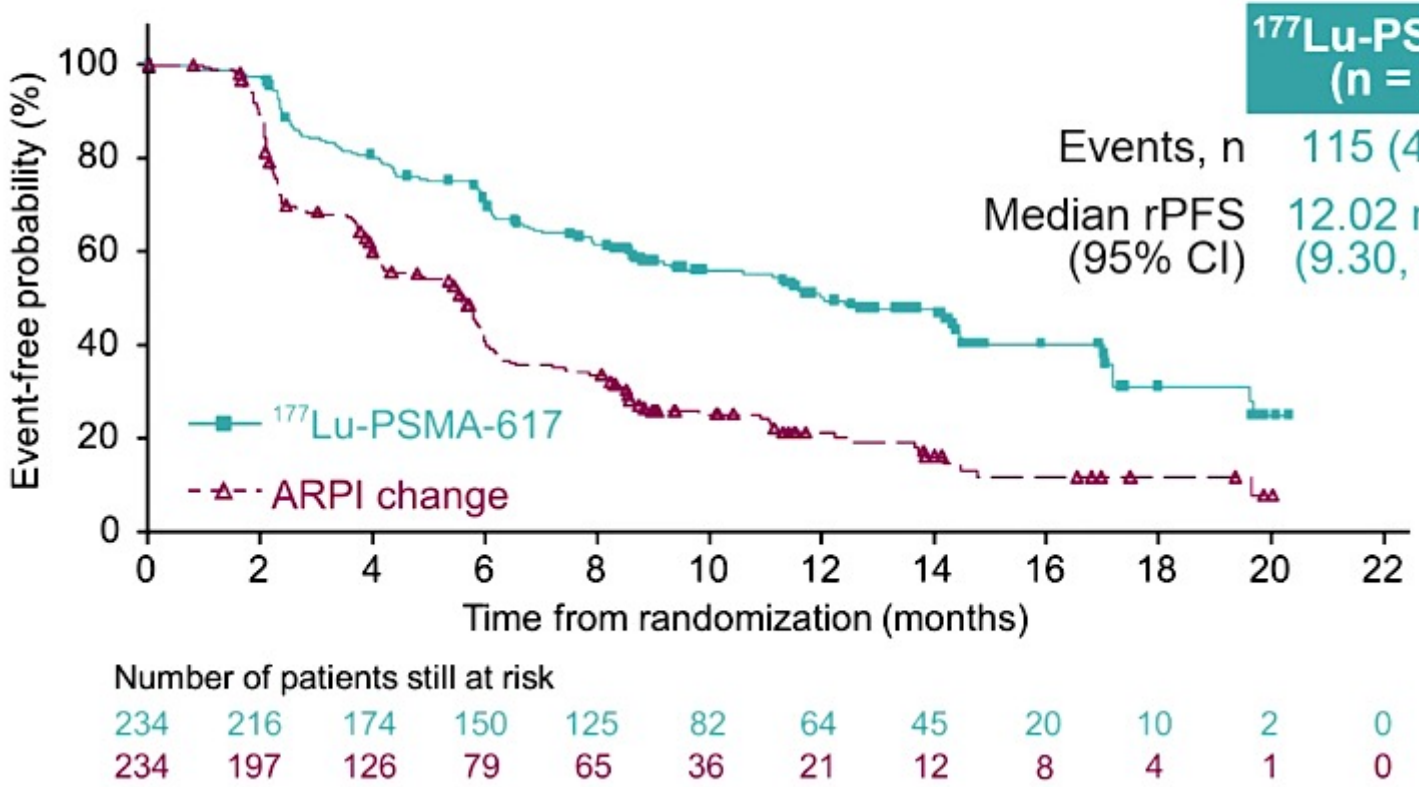


Sartor O, et al. *ESMO* 2023.

PSMAfore: rPFS (primary endpoint)

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

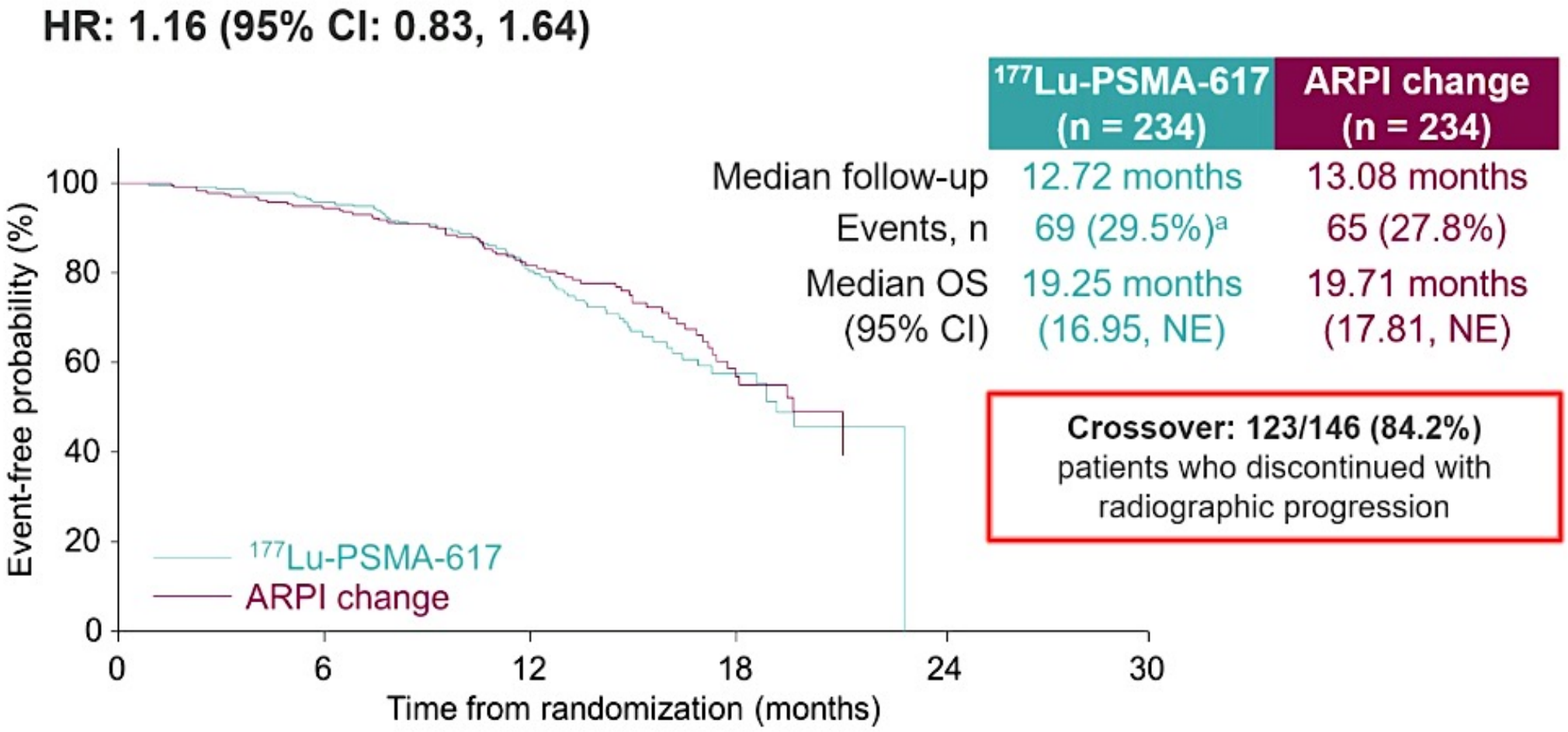
Updated HR: 0.43 (95% CI: 0.33, 0.54)



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

Sartor O, et al. *ESMO* 2023.

PSMAfore: Interim OS (intention to treat)



Sartor O, et al. *ESMO* 2023.

Conclusions

- Germline and somatic DNA-repair mutations are common in mCRPC patients: *ALL PATIENTS SHOULD BE TESTED*
- HRR mutations (esp. *BRCA1/2*) sensitize to PARP inhibitors
- Olaparib and Rucaparib are FDA-approved as *mono*therapies
- Olaparib and Niraparib are approved in *combination* with Abi
- Talazoparib is approved in *combination* with Enza
- PSMA is expressed in >80% of mCRPC patients
- Lu^{177}-PSMA-617 is approved for mCRPC post-NHA and -taxane.

We are taking a short break!

The program will resume at 3:20 PM ET

Up Next…

Drs Ibiayi Dagogo-Jack and Helena Yu discuss the management of targeted therapy for non-small cell lung cancer

RTP
RESEARCH
TO PRACTICE