UNC | LINEBERGER COMPREHENSIVE CANCER CENTER

NORTH CAROLINA Oncology Association

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NCOA 2022 ANNUAL CONFERENCE

Genitourinary Cancers Update

Matthew Milowsky, MD, FASCO

9/9/22

Disclosure of Conflicts of Interest

Matt Milowsky, MD, FASCO has the following financial relationships to disclose:

- **Stock and Other Ownership Interests** – Pfizer, Merck, Gilead Sciences
- **Consulting or Advisory Role** – Loxo/Lilly
- **Research Funding (institution)**– Merck, Roche/Genentech, Bristol-Myers Squibb, Seagen, G1 Therapeutics, Mirati Therapeutics, Incyte, Alliance Foundation Trials, Alliance for Clinical Trials in Oncology, Clovis Oncology, Arvinas, Regeneron
- **Other Relationship** – Elsevier (Co-Editor CLGC), Medscape

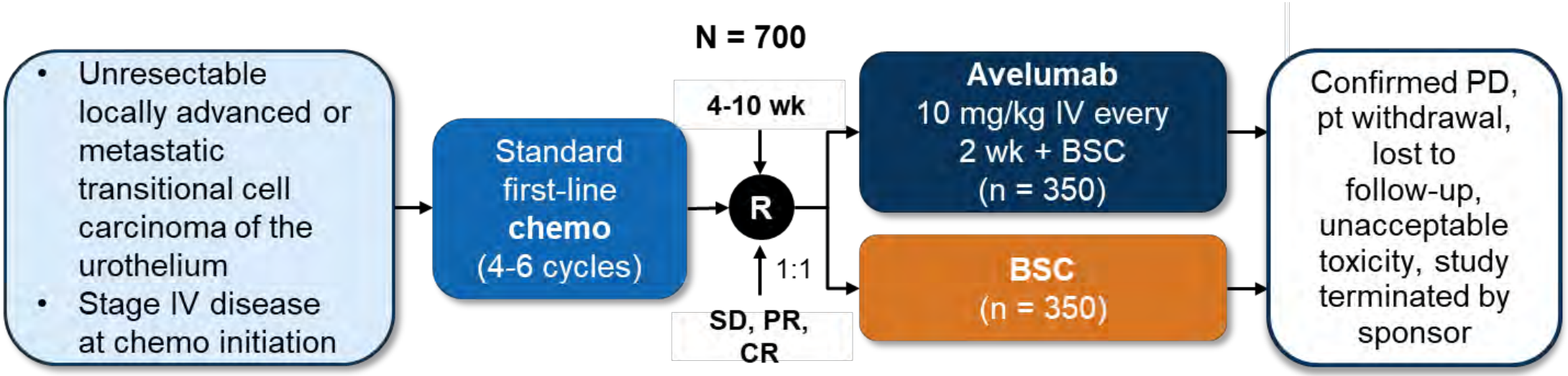
https://coi.asco.org/share/7UQ-6ARQ/Matthew%20Milowsky

Objectives

- **Review recent studies (ASCO Annual Meeting 2022):**
  - New agents and combinations in the treatment of muscle-invasive and metastatic urothelial cancer.
  - Management of patients with high-risk localized kidney cancer including adjuvant therapy and the treatment of metastatic disease.
  - Management of metastatic castration-resistant prostate cancer including radioligand therapy and targeted agents.

Updates in Bladder Cancer

JAVELIN Bladder 100: Switch maintenance after first-line chemotherapy

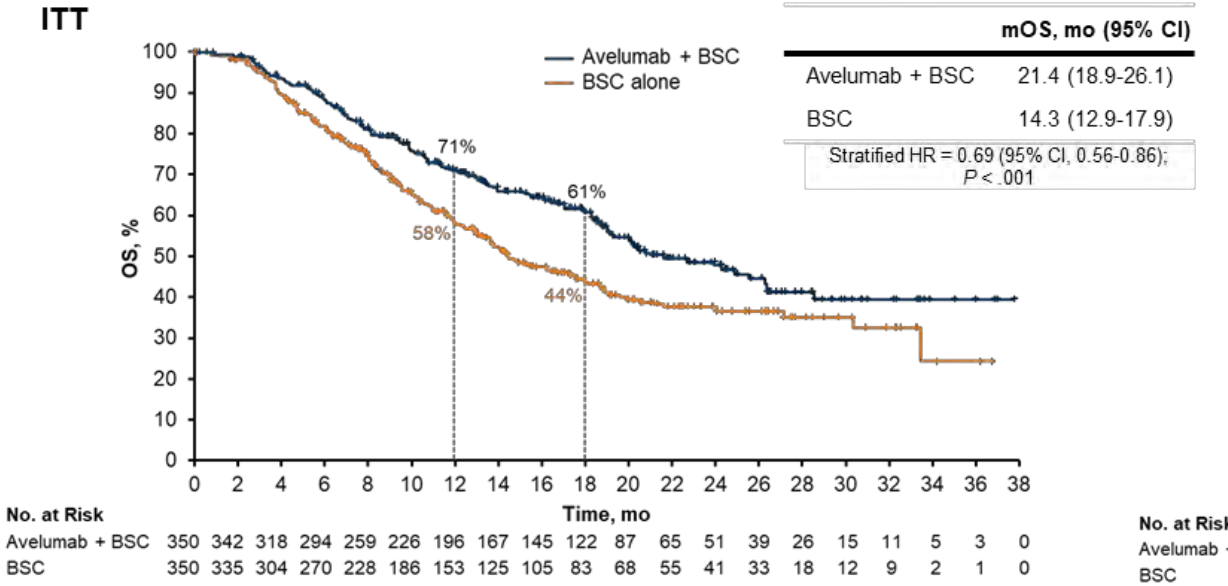


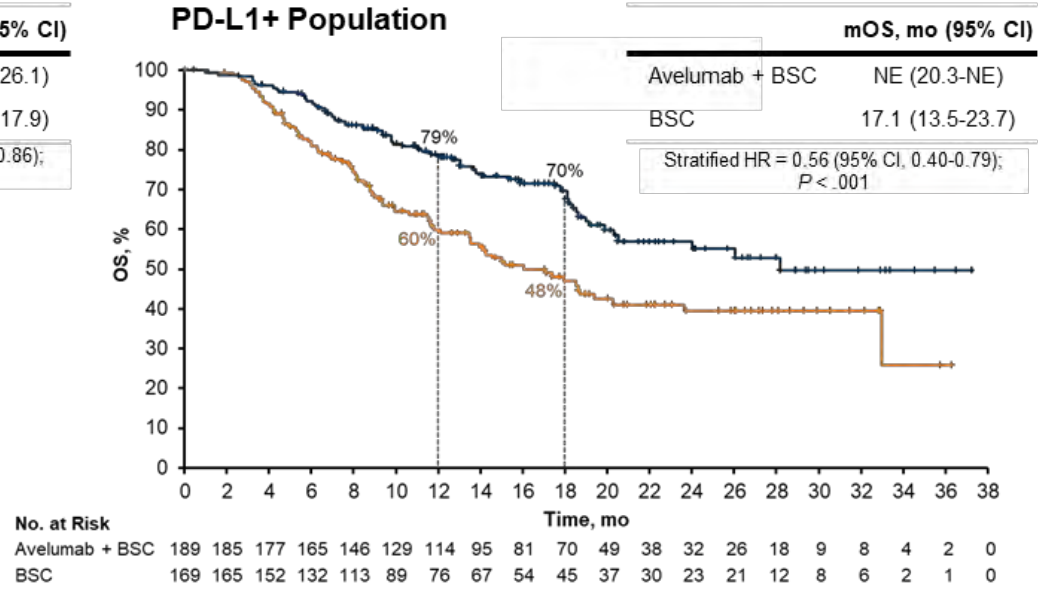
- **Primary endpoint:** OS

- Allowed first-line chemo regimens: gemcitabine + cisplatin or carboplatin
- Randomization at least 4 wk and no more than 10 wk after last dose of first-line chemo, stratified by
  - Best response on first-line therapy (CR or PR vs SD)
  - Metastatic disease site (visceral vs nonvisceral)

1. https://clinicaltrials.gov/ct2/show/NCT02603432. 2. Powles T et al. *N Engl J Med*. 2020;383:1218-1230.

JAVELIN Bladder 100: Overall survival



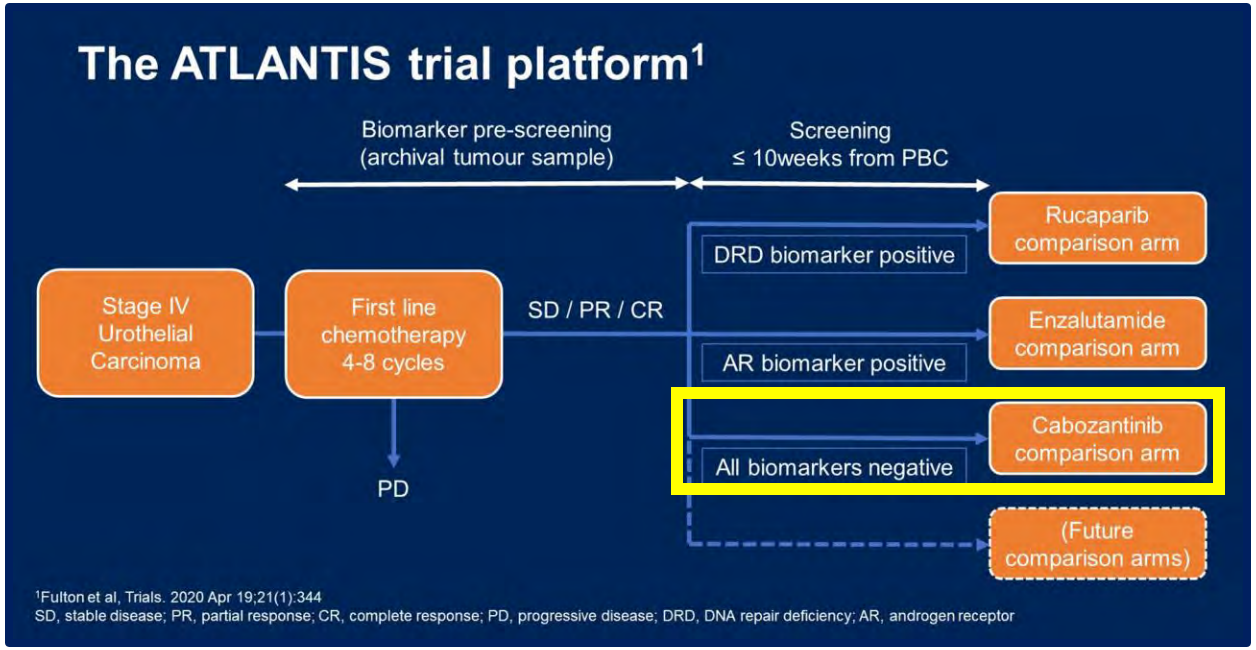


OS and PFS benefits were observed across subgroups, including primary tumor location, disease stage, genomic subtype, and in patients with PD-L1+ tumors who had received 1L gemcitabine + carboplatin[1,2]

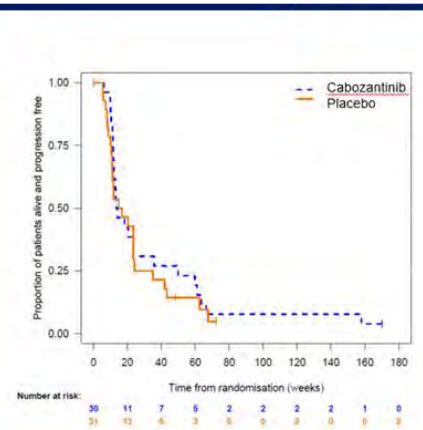
Avelumab was FDA approved for maintenance treatment of locally advanced UC or mUC that has not progressed with first-line platinum therapy[3]

1. Powles T et al. *N Engl J Med*. 2020;383:1218-1230. 2. Powles T et al. ASCO 2021. Abstract 4520.
3. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-avelumab-urothelial-carcinoma-maintenance-treatment.

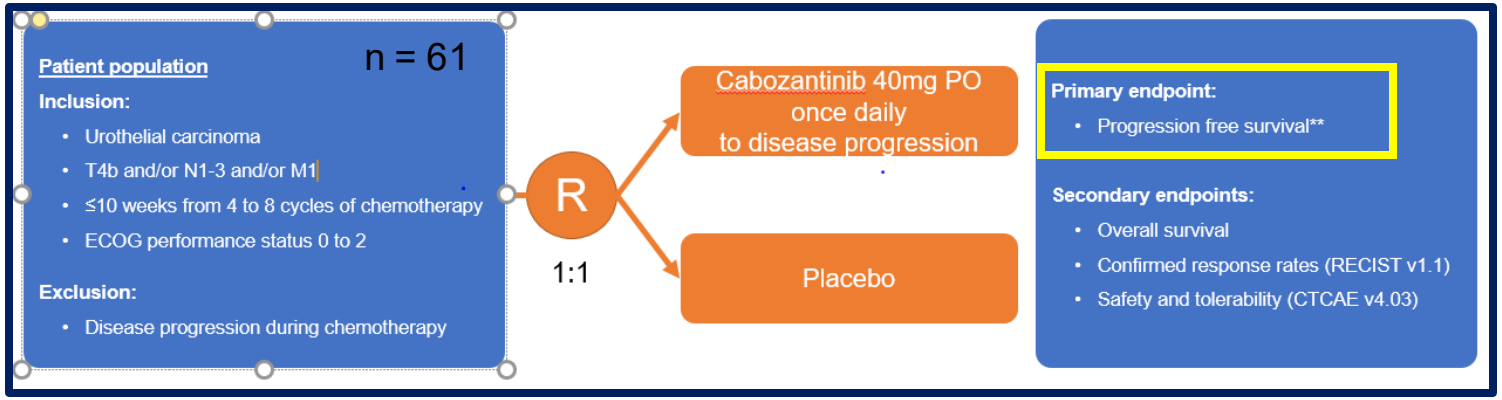
Abstract LBA4505:A randomised, double blind, phase II clinical trial of maintenance cabozantinib following chemotherapy for metastatic urothelial carcinoma (mUC): Final analysis of the ATLANTIS cabozantinib comparison. Robert Jones et al.



PFS- Primary Endpoint



	Cabozantinib	Placebo	p
PFS events	25 (83%)	26 (84%)	
Median PFS, weeks	13.7 (80% CI 12.1, 23.3)	15.8 (80% CI 11.3, 23.6)	
Hazard ratio*	0.89 (80% CI 0.61, 1.30)		0.35



Underpowered study related to COVID and maintenance Avelumab approval.

Jones et al. *J Clin Oncol* 40, 2022 (suppl 17; abstr LBA4505)
Gupta S. Is there a Role for VEGF-TKIs in Bladder Cancer? ASCO Annual Meeting 2022

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Rucaparib comparison in ATLANTIS

Rucaparib comparison arm trial design[1]

n = 61

Patient population

Inclusion:

- DRD biomarker positive*
- Urothelial carcinoma
- T4b and/or N1-3 and/or M1
- ≤10 weeks from 4 to 8 cycles of chemotherapy
- ECOG performance status 0 to 2

Exclusion:

- Disease progression during chemotherapy

R

1:1

Rucaparib 600 mg PO BID to disease progression

Placebo

Primary endpoint:

- Progression free survival**

Secondary endpoints:

- Overall survival
- Confirmed response rates (RECIST v1.1)
- Safety and tolerability (CTCAE v4.03)

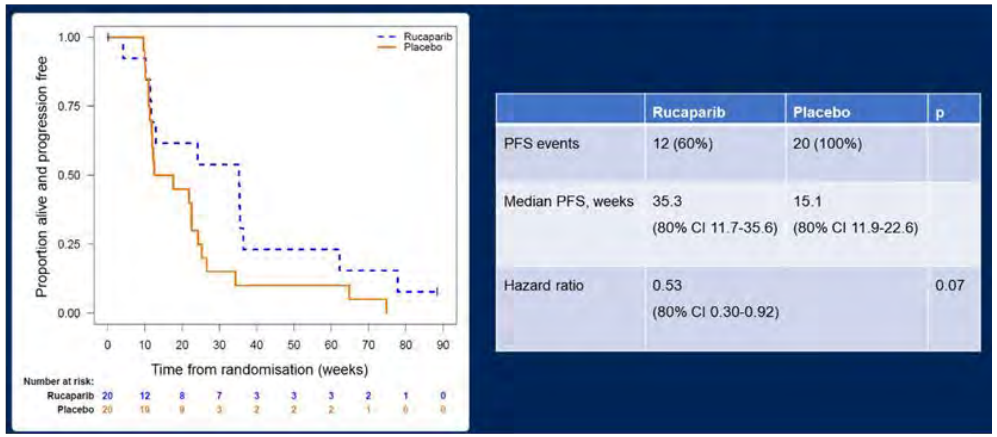
* DRD biomarker 'positive' defined as one, or more, of the following:

- ≥10% genome-wide loss of heterozygosity
- Somatic alteration in any of: *ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD54L*
- Known germline *BRCA1* or *BRCA2* alteration

Somatic tumour testing utilised the FoundationOne next-generation sequencing assay, https://www.foundationmedicine.com/test/foundationone-cdx

	Original parameters	Revised parameters
Target hazard ratio	0.5	0.5
Power	90%	85.4%
Alpha, 1-sided	20%	20%
PFS events required	39	30
n	48	40

PFS- Primary Endpoint



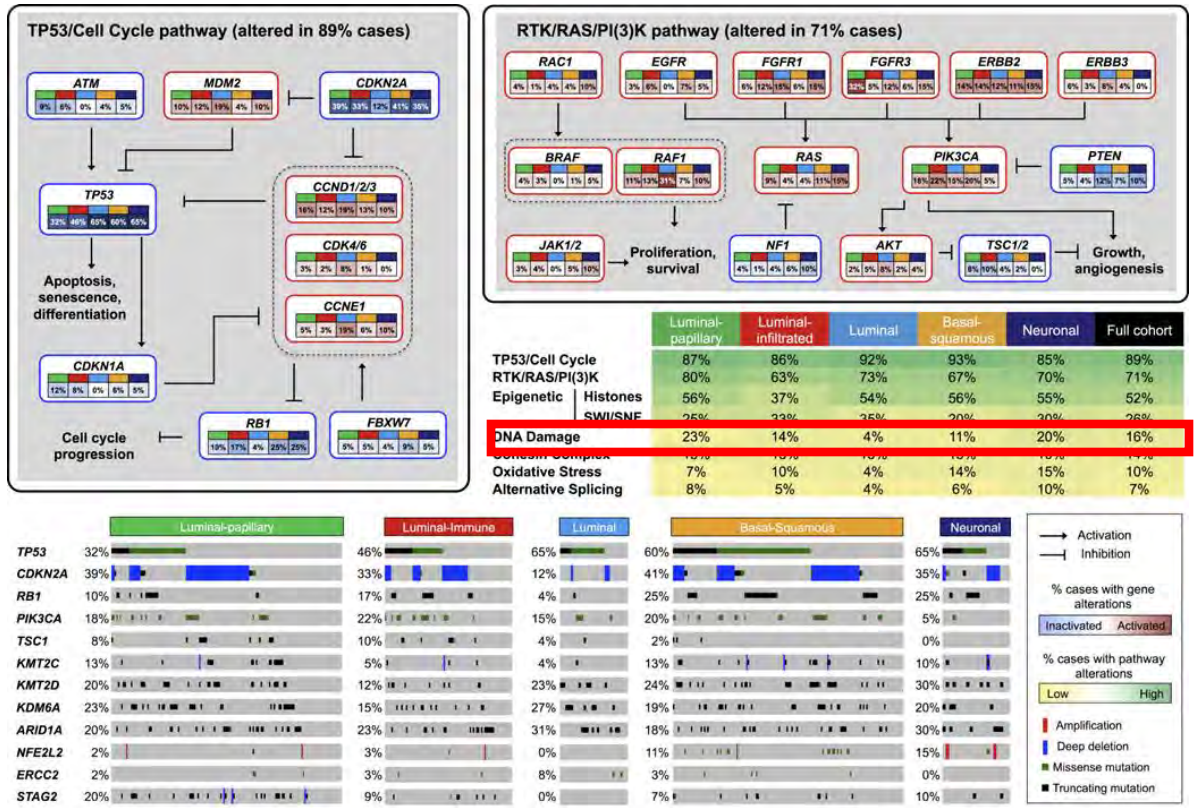
	Rucaparib	Placebo	p
PFS events	12 (60%)	20 (100%)	
Median PFS, weeks	35.3 (80% CI 11.7-35.6)	15.1 (80% CI 11.9-22.6)	
Hazard ratio	0.53 (80% CI 0.30-0.92)		0.07

The statistical change did not affect power much in this biomarker-driven cohort and benefit was seen in molecularly selected patients

Crabb S et al J Clin Oncol 40, 2022 (suppl 6; abstr 436)

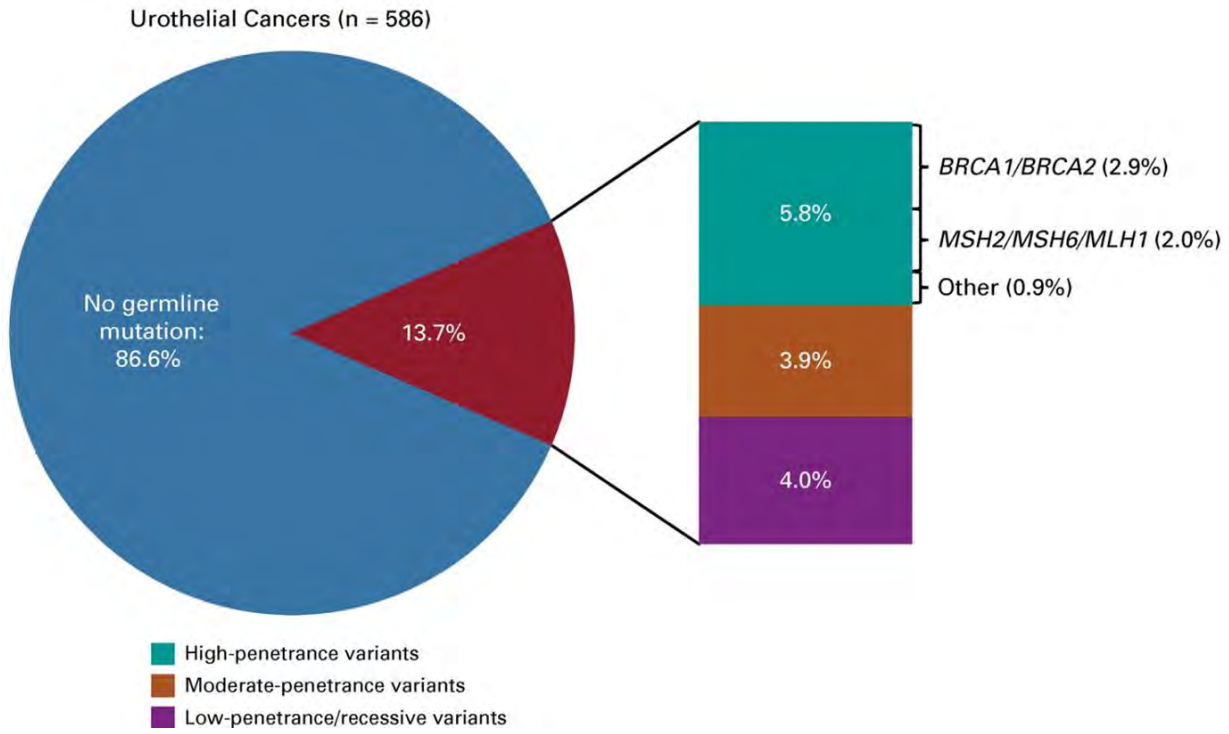
Gupta S. Is there a Role for VEGF-TKIs in Bladder Cancer? ASCO Annual Meeting 2022

DDR alterations in UC



	Luminal-papillary	Luminal-infiltrated	Luminal	Basal-squamous	Neuronal	Full cohort
TP53/Cell Cycle	87%	86%	92%	93%	85%	89%
RTK/RAS/PI(3)K	80%	63%	73%	67%	70%	71%
Epigenetic – Histones	56%	37%	54%	56%	55%	52%
Epigenetic – SWI/SNF	25%	23%	25%	20%	20%	26%
DNA Damage	23%	14%	4%	11%	20%	16%
Cohesin Complex	13%	13%	10%	13%	15%	14%
Oxidative Stress	7%	10%	4%	14%	15%	10%
Alternative Splicing	8%	5%	4%	6%	10%	7%

Germline Variants in Urothelial Cancer: Frequency and Penetrance



Cell 2017 171540-556.e25DOI: (10.1016/j.cell.2017.09.007)
Carlo et al. *J Clin Oncol*. 2020;38:406.

Rationale for combining cabozantinib and IO in UC

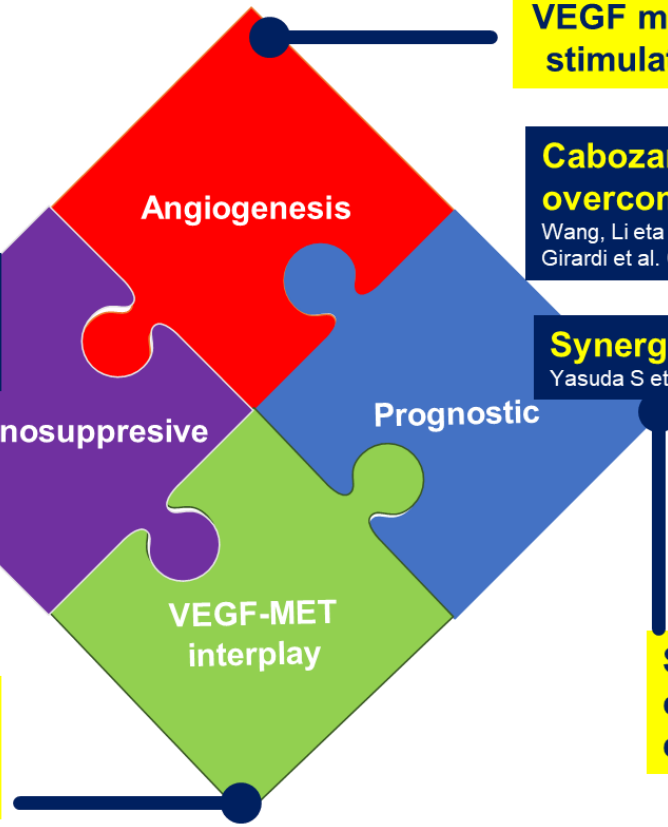
VEGF is a potent immunosuppressive factor in both innate and adaptive anti-tumor immunity

VEGF mediates angiogenesis and stimulation of mitogenic activity

Cabozantinib can potentially overcome resistance to IO
Wang, Li eta al. CCR 2021
Girardi et al. CCR 2022

Cabozantinib is immunomodulatory
Kwilas AR J Transl Med 2014
Apolo et al, JCO 32, no 15_suppl May 20, 2014, 4501
Apolo et al, Lancet Oncology 2020

Synergistic anti-tumor effect in vivo
Yasuda S et al. Clin Exp Immunol. 2013



Cabozantinib inhibits MET, VEGFRs, TAM kinases
Yakes FM et al .Mol Cancer 2011
Lee YI Cancers 2014

Serum and tissue VEGF levels correlate with disease stage, grade, disease recurrence and progression

HGF/c-Met induces epithelial-mesenchymal transition (EMT) and progression in bladder cancer

Wu Wu et al. Oncogene 2003, Bernardini S et al. J Urol 2001, Campbell S et al. Cancer Res 1998, Mori K et al. Eur Urology Focus 2022, Kunze D et al. Int J Oncol 2008, sim E J et al Nature Communications 2019

Abstract 4504: Cabozantinib (C) in combination with atezolizumab (A) in urothelial carcinoma (UC): Results from Cohorts 3, 4, 5 of the COSMIC-021 study. Sumanta K. Pal et al.

COSMIC-021 Study Design for UC Cohorts 3, 4, and 5

Key Eligibility Criteria

Inoperable locally advanced/metastatic UC with transitional cell histology and ECOG PS 0–1

- **Cohort 3:** no prior systemic therapy* and cis-ineligible†‡
- **Cohort 4:** no prior systemic therapy* and cis-eligible‡
- **Cohort 5:** One prior ICI and no prior VEGFR-TKI therapy*; ≤2 lines of therapy

→ **Cabozantinib** 40 mg QD PO
+
Atezolizumab 1200 mg Q3W IV
(N=30 per cohort)

→ Tumor assessment per RECIST v1.1 by investigator every 6 weeks for the first year and every 12 weeks thereafter

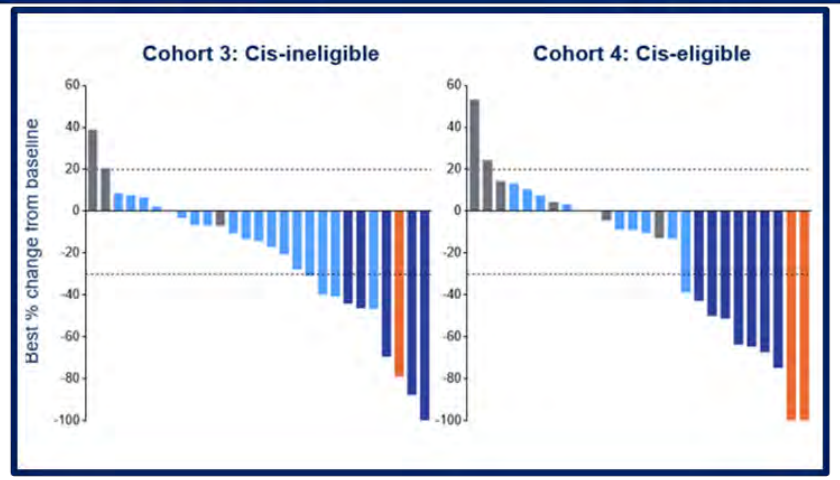
Primary endpoint:	ORR per RECIST v1.1 by investigator
Secondary endpoint:	Safety (AEs, SAEs, AESIs)
Exploratory endpoints:	DOR, PFS per RECIST v1.1 by investigator, OS

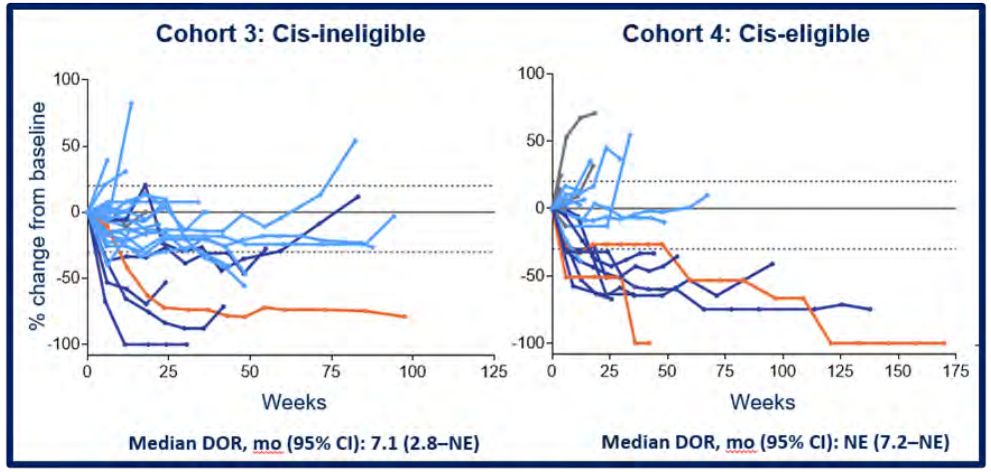
Pal et al. J Clin Oncol 40, 2022 (suppl 16; abstr 4504)
Gupta S. Is there a Role for VEGF-TKIs in Bladder Cancer? ASCO Annual Meeting 2022

Efficacy – Cohort 3 and 4

	Cohort 3 Cis-ineligible (N=30)	Cohort 4 Cis-eligible (N=30)
ORR, % (95% CI)	**20 (8–39)**	**30 (15–49)**
Best overall response, n (%)		
Complete response	1 (3)	2 (7)
Partial response	5 (17)	7 (23)
Stable disease	18 (60)	10 (33)
Progressive disease	3 (10)	7 (23)
Missing / not evaluable	3 (10)	4 (13)
Disease control rate, % (95% CI)	**80 (61–92)**	**63 (44–80)**

- Disease control rate is encouraging
- Low rates of PD
- DOR in cis-ineligible patients lower than historically reported with single-agent atezolizumab (IMvigor 210)

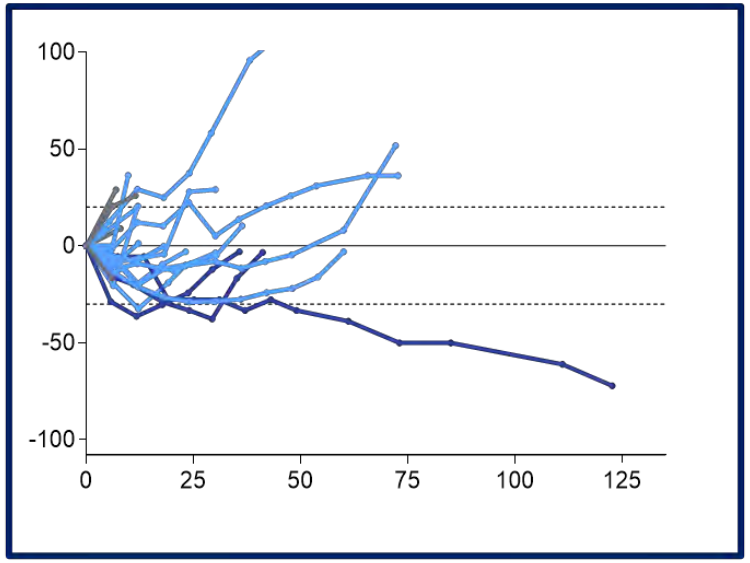


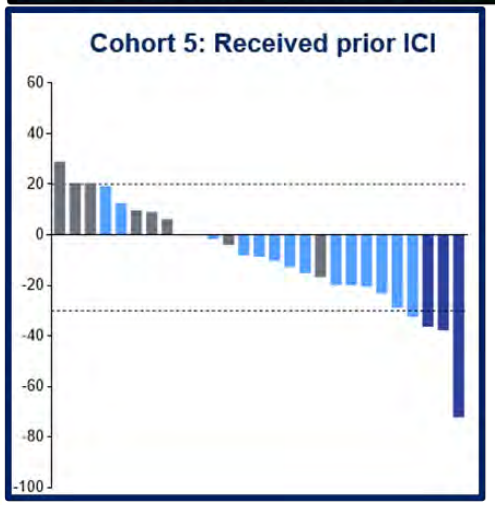


Pal et al. J Clin Oncol 40, 2022 (suppl 16; abstr 4504)
Gupta S. Is there a Role for VEGF-TKIs in Bladder Cancer? ASCO Annual Meeting 2022

Efficacy – Cohort 5

	Cohort 5 Received prior ICI (N=31)
ORR, % (95% CI)	**10 (2–26)**
Best overall response, n (%)	
Complete response	0
Partial response	3 (10)
Stable disease	16 (52)
Progressive disease	8 (26)
Missing / not evaluable	4 (13)
Disease control rate, % (95% CI)	**61 (42–78)**





Important to consider shortcomings of traditional imaging and ORR endpoint

Tumor necrosis/lack of tumor progression may be associated with improvement in outcomes with targeted therapy/IO

- Modest ORR with combination BUT low rates of PD (Investigator assessment)
- (ORR 16% with Cabo/Nivo in 30 mUC patients)
- Disease control rate is encouraging

Pal et al. J Clin Oncol 40, 2022 (suppl 16; abstr 4504)
Gupta S. Is there a Role for VEGF-TKIs in Bladder Cancer? ASCO Annual Meeting 2022

Toxicity

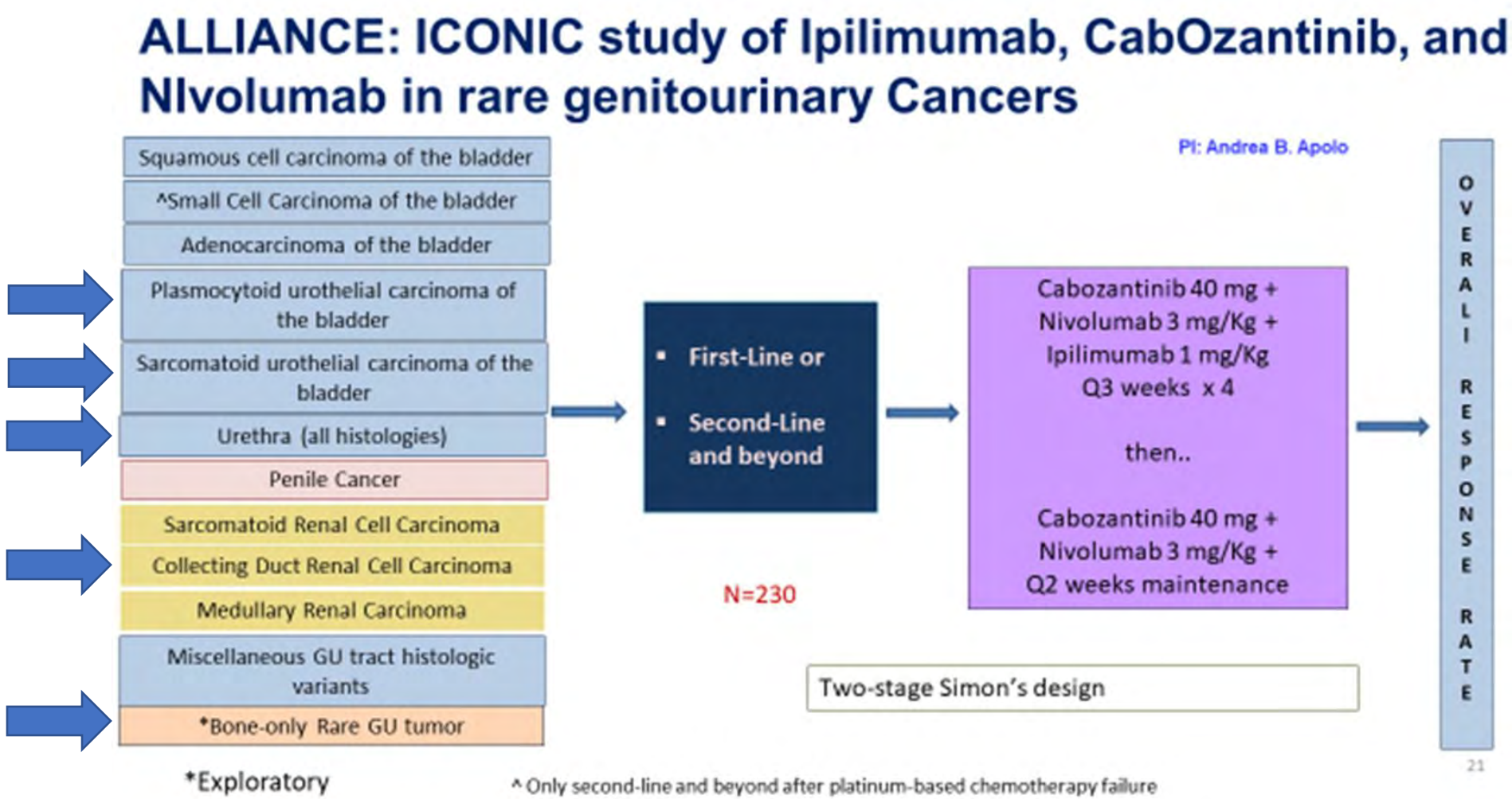
	Cohort 3 Cis-ineligible (N=30)	Cohort 4 Cis-eligible (N=30)	Cohort 5 Received prior ICI (N=31)
Patients on study treatment at data cut-off, n (%)	1 (3)	6 (20)	1 (3)
Duration of exposure, median (range), months			
Cabozantinib + atezolizumab*	5.3 (0.7–26.8)	4.2 (0.5–42.0)	2.8 (0.3–30.3)
Cabozantinib	5.3 (0.5–26.8)	3.4 (0.5–42.0)	2.8 (0.3–30.3)
Atezolizumab	4.4 (0.0–22.6)	3.5 (0–41.4)	2.1 (0–29.7)
AEs leading to cabozantinib dose reductions, n (%)	13 (43)	8 (27)	11 (35)
AEs leading to cabozantinib dose hold, n (%)	23 (77)	21 (70)	23 (74)
AEs leading to atezolizumab dose delay, n (%)	19 (63)	12 (40)	16 (52)
Discontinuation due to TRAEs, n (%)			
Cabozantinib	8 (27)	9 (30)	6 (19)
Atezolizumab	5 (17)	5 (17)	7 (23)
Either	8 (27)	9 (30)	7 (23)
Both	4 (13)	5 (17)	6 (19)

- No new safety signals with combination
- Manageable toxicity, NO treatment-related deaths
- 13% Treatment discontinuation of both drugs due to TRAEs

	Cohort 3 Cis-ineligible (N=30)		Cohort 4 Cis-eligible (N=30)		Cohort 5 Received prior ICI (N=31)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Any TRAE, n (%)	29 (97)	19 (63)	28 (93)	13 (43)	28 (90)	14 (45)
Diarrhea	13 (43)	0	10 (33)	1 (3)	11 (35)	0
AST increased	11 (37)	0	6 (20)	2 (7)	6 (19)	0
Decreased appetite	10 (33)	0	8 (27)	2 (7)	12 (39)	1 (3)
ALT increased	9 (30)	0	5 (17)	3 (10)	5 (16)	1 (3)
Fatigue	8 (27)	1 (3)	8 (27)	1 (3)	15 (48)	2 (6)
Nausea	8 (27)	0	5 (17)	0	8 (26)	0
PPE	6 (20)	0	6 (20)	0	3 (10)	0
Amylase increased	6 (20)	2 (7)	2 (7)	0	2 (6)	2 (6)
Stomatitis	4 (13)	0	6 (20)	0	5 (16)	1 (3)

Pal et al. J Clin Oncol 40, 2022 (suppl 16; abstr 4504)
Gupta S. Is there a Role for VEGF-TKIs in Bladder Cancer? ASCO Annual Meeting 2022

ICONIC – Cabo and IO doublet study



Gupta S. Is there a Role for VEGF-TKIs in Bladder Cancer? ASCO Annual Meeting 2022

MAINCAV- Phase III randomized trial of maintenance cabozantinib and avelumab vs maintenance avelumab after 1L platinum-based chemotherapy in patients with mUC (NCT05092958)

PI – S. Gupta

Patients with locally advanced/mUC, N3 only disease allowed

CR/PR/SD with standard 1st-line platinum-based chemotherapy (4-6 cycles)

Stratification:
- **Best response to 1st-line chemo (CR vs PR vs SD)**
- **Sites of metastases: visceral vs non-visceral**

1:1

N = 654

Avelumab 800 mg IV q2 wk x 2 yrs

Cabozantinib 40 mg PO daily + Avelumab 800 mg IV q2 wk x2yrs

Primary endpoint: OS

Secondary endpoints: PFS, Safety, Tumor response, HRQOL

C2 D1

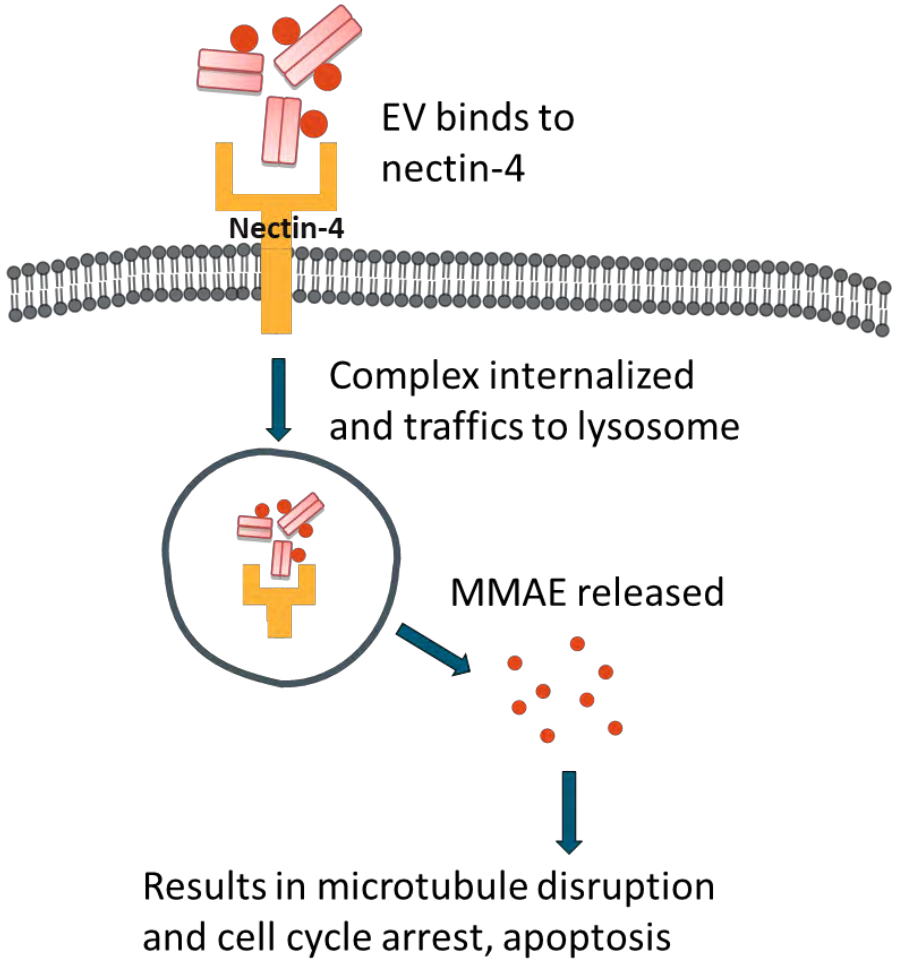
Progression/end of Tx

- RNAseq
- WES
- TCRseq
- IHC multicolor
- PBMC - Flow MDSC, etc

- ctDNA
- PBMC - Flow MDSC, etc
- TCRseq
- Cytokine/Chemokine assay

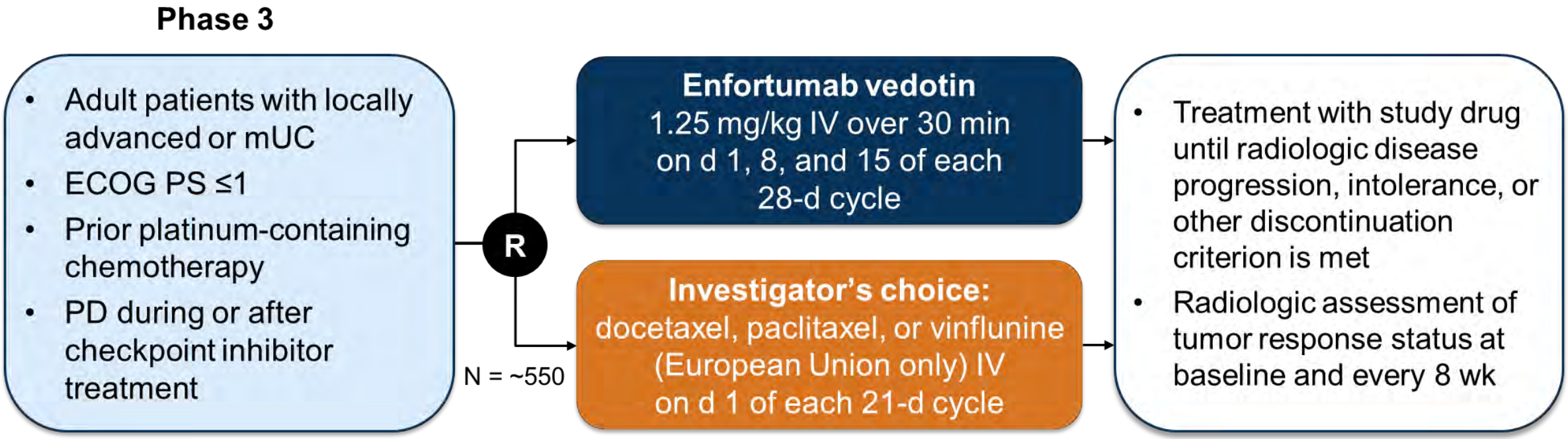
Enfortumab vedotin

- Enfortumab vedotin[1]
  - A fully humanized monoclonal antibody against nectin-4
  - Conjugated with microtubule-disrupting agent, monomethyl auristatin E (MMAE), by a protease-cleavable linker
- Nectin-4 is a transmembrane cell adhesion molecule[2] that is highly expressed in 97% of mUC patient samples[3]



1. Challita-Eid. Cancer Res. 2016;76:3003. 2. Samanta. Cell Mol Life Sci. 2015;72:645. 3. Petrylak. JCO. 2017;35:106.

EV-301

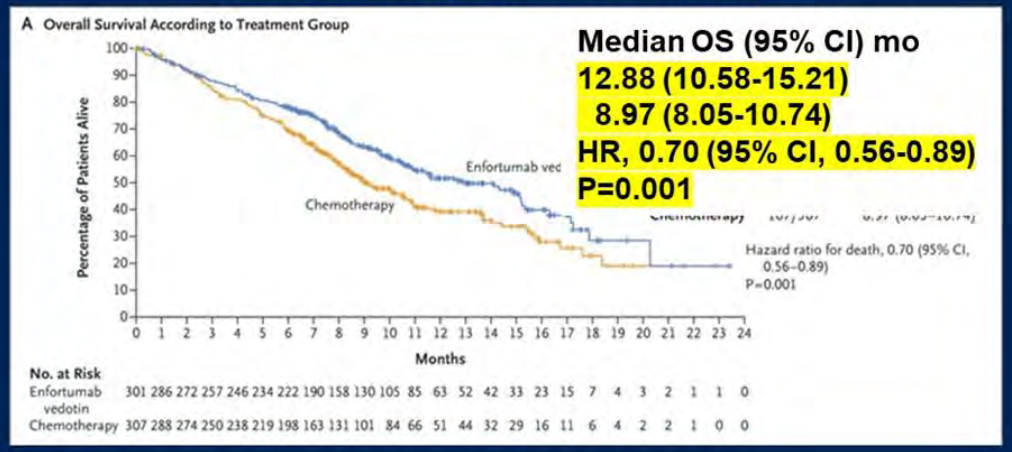


- **Primary endpoint:** OS
- **Secondary endpoints:** PFS, DOR, ORR, safety/tolerability, QOL

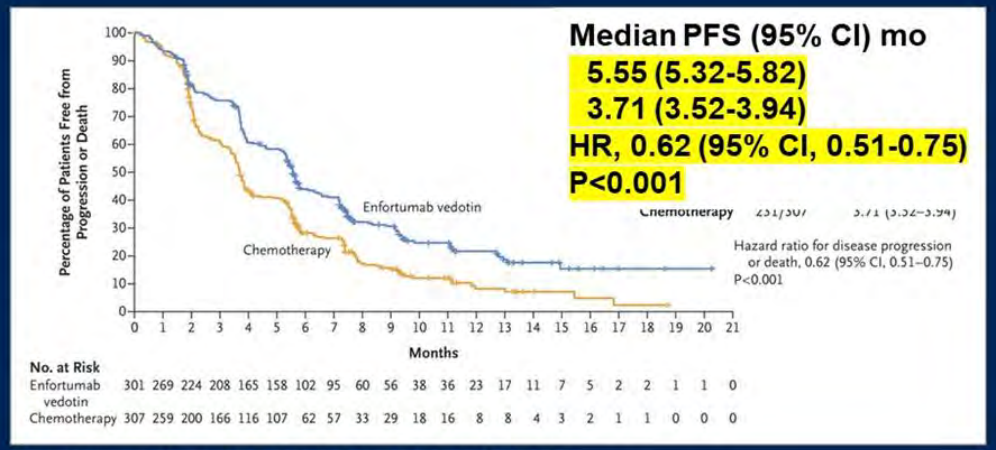
1. https://clinicaltrials.gov/ct2/show/NCT03474107. 2. Powles T et al. *N Eng J Med.* 2021;384:1125-1135.

Long-Term Outcomes in EV-301: 24-Month Findings

Median Follow-Up 11.1 months



Median OS (95% CI) mo
12.88 (10.58-15.21)
8.97 (8.05-10.74)
HR, 0.70 (95% CI, 0.56-0.89)
P=0.001



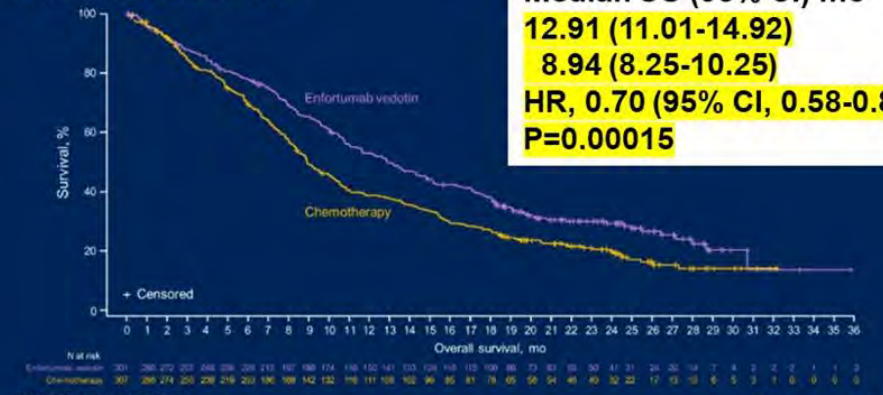
Median PFS (95% CI) mo
5.55 (5.32-5.82)
3.71 (3.52-3.94)
HR, 0.62 (95% CI, 0.51-0.75)
P<0.001

Powles T et al. N Engl J Med 2021;384:1125-1135

Median Follow-Up ~ 24 months

31

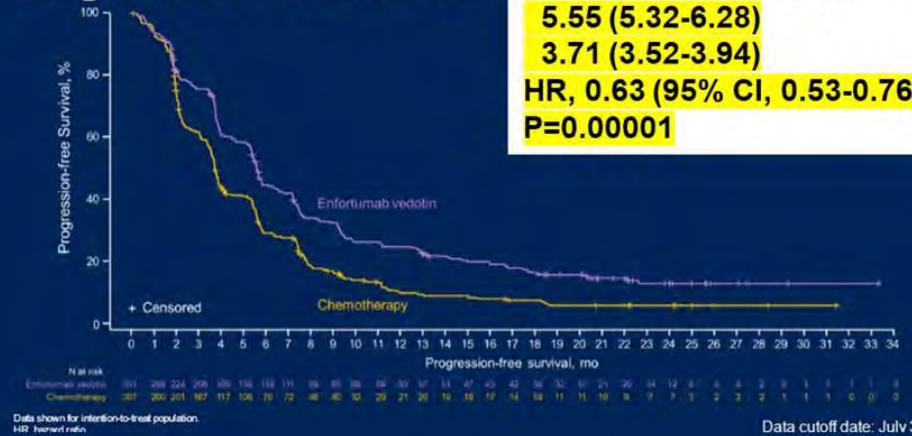
Overall Survival



Median OS (95% CI) mo
12.91 (11.01-14.92)
8.94 (8.25-10.25)
HR, 0.70 (95% CI, 0.58-0.86)
P=0.00015

Data cutoff date: July 30, 2021

Progression-Free Survival



Median PFS (95% CI) mo
5.55 (5.32-6.28)
3.71 (3.52-3.94)
HR, 0.63 (95% CI, 0.53-0.76)
P=0.00001

Data cutoff date: July 30, 2021

Rosenberg J. et al. *J Clin Oncol* 40, 2022 (suppl 16; abstr 4516)
Milowsky M. Improving Ouctomes Across the Stages of Bladder Cancer. ASCO Annual Meeting 2022

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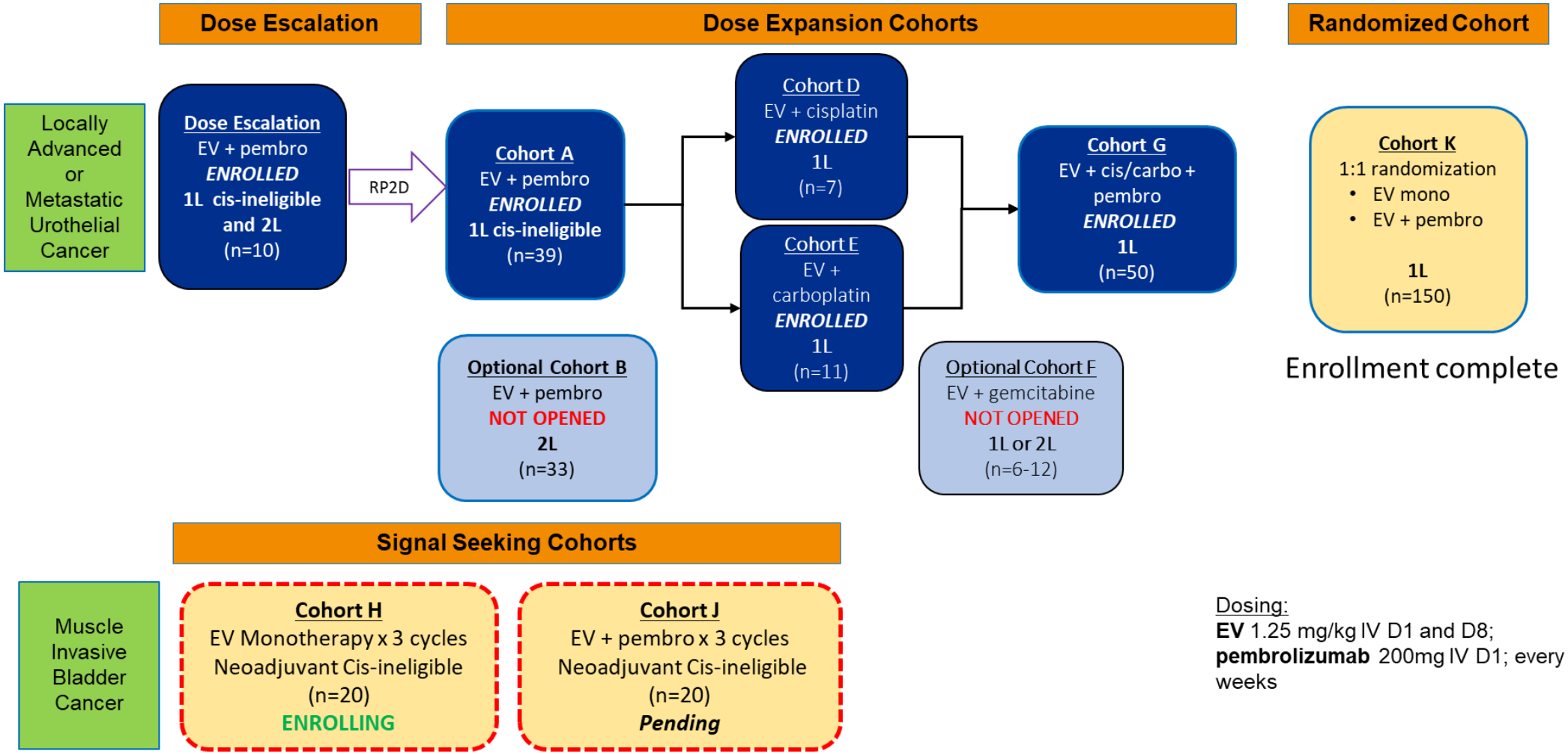
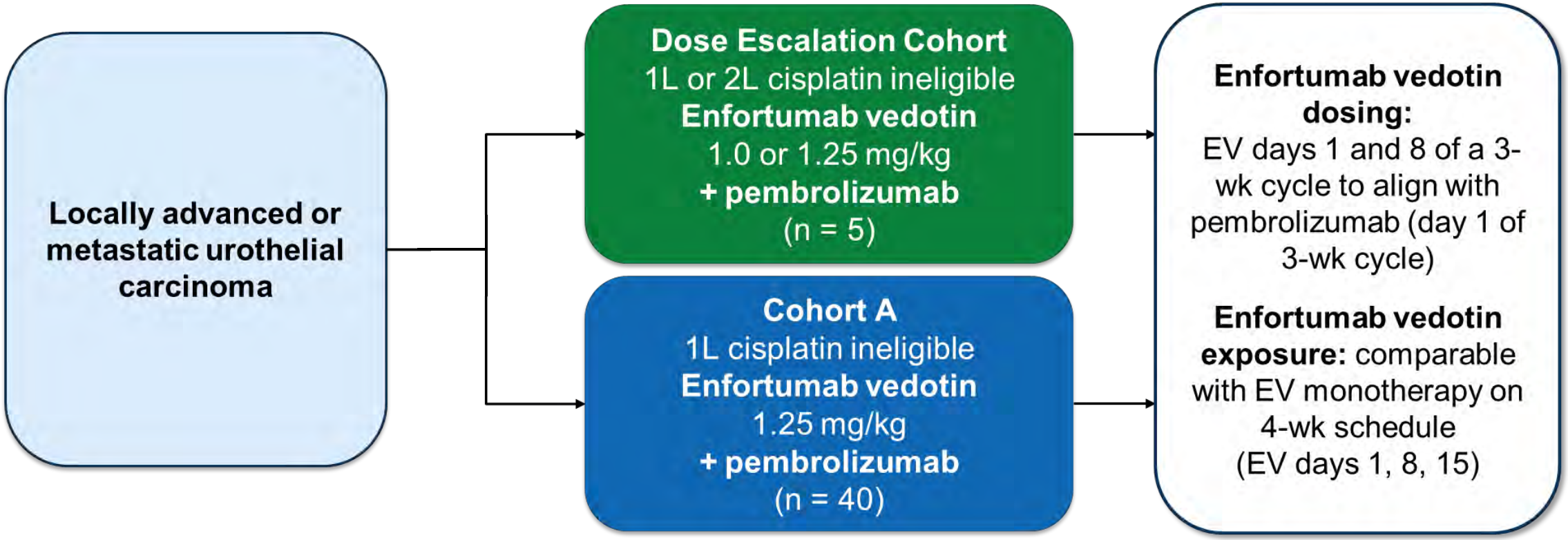
EV-103 study (NCT03288545)



Dosing:
EV 1.25 mg/kg IV D1 and D8;
pembrolizumab 200mg IV D1; every 3 weeks

EV-103: Enfortumab vedotin plus pembrolizumab



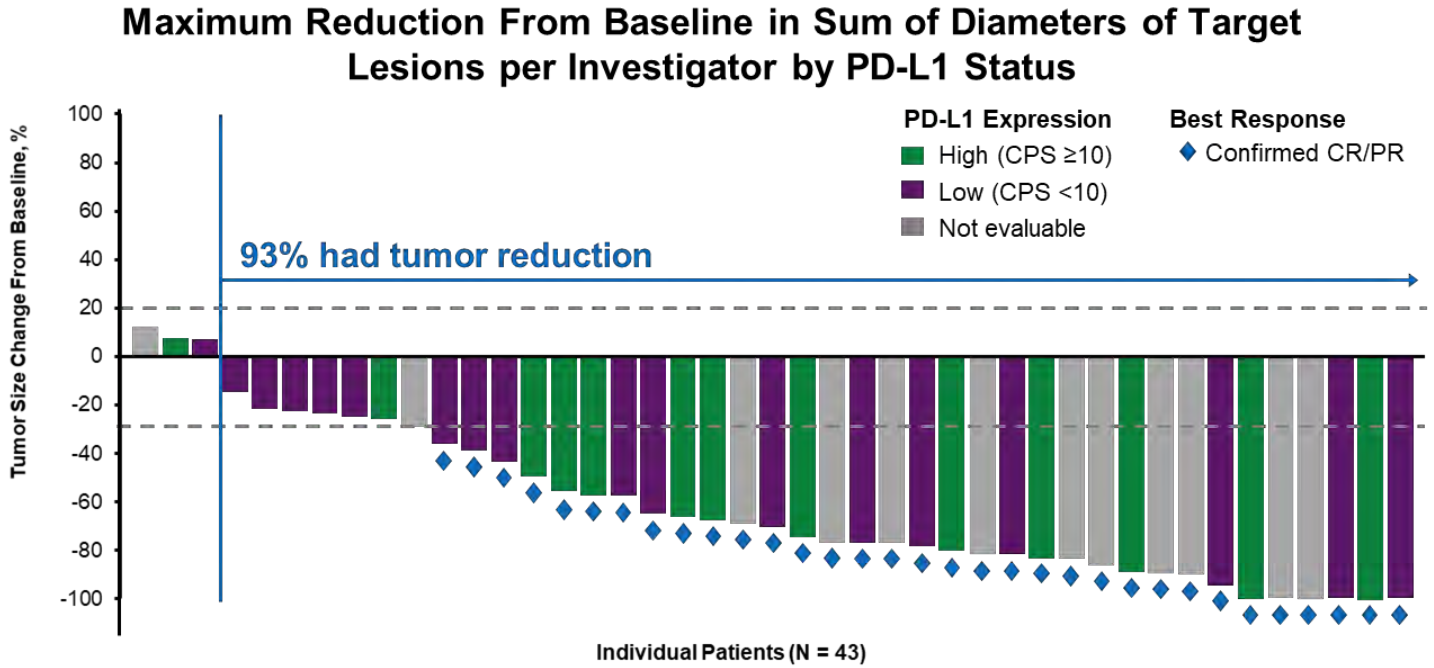
- **Primary endpoints:** AEs and laboratory abnormalities
- **Secondary endpoints:** DLTs, ORR, DCR, DOR, and OS

1. https://clinicaltrials.gov/ct2/show/NCT03288545.

EV-103: Potential for a platinum-free regimen

Efficacy[1]

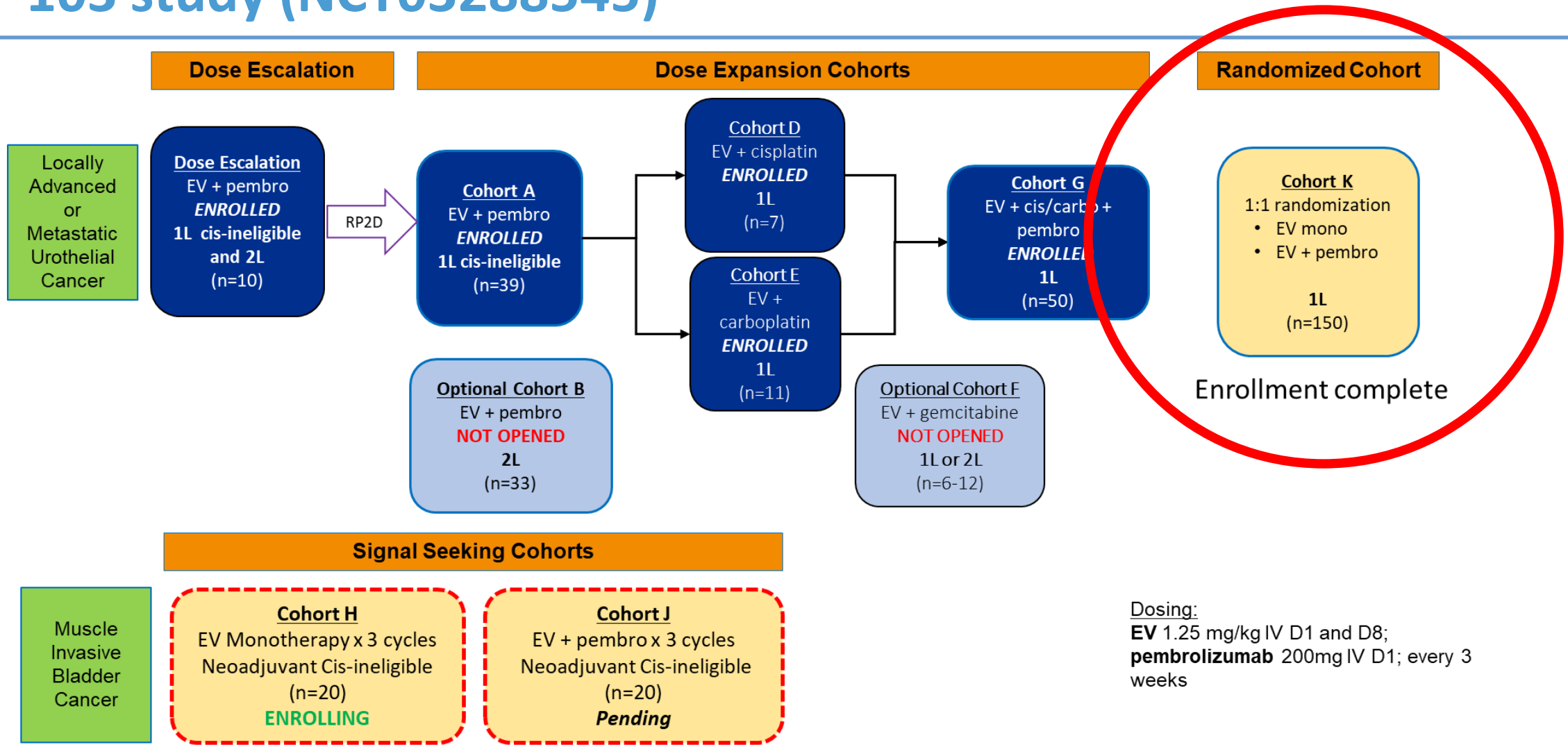
- ORR of 73.3%
- Median PFS of 12.3 mo
- Median OS not reached
- 81.6% OS rate at 12 mo



Safety: Most common TEAEs were fatigue (49%; grade ≥3, 9%), alopecia (49%), and peripheral sensory neuropathy (49%; grade ≥3, 4%)

1. Rosenberg J et al. ASCO 2020. Abstract 5044.

EV-103 study (NCT03288545)



Dosing:
EV 1.25 mg/kg IV D1 and D8;
pembrolizumab 200mg IV D1; every 3 weeks

EV-103 study (NCT03288545) – Cohort K

July 16, 2022 - Astellas and Seagen Announce Positive Topline Results For PADCEV® (enfortumab vedotin-ejfv) with KEYTRUDA® (pembrolizumab) as First-Line Treatment for Advanced Urothelial Cancer

In patients treated with enfortumab vedotin and pembrolizumab, results demonstrated a **64.5% confirmed objective response rate (ORR) (95% CI: 52.7 to 75.1) per blinded independent central review (BICR), the primary endpoint of Cohort K.**

The median duration of response (DOR) per BICR was not reached.

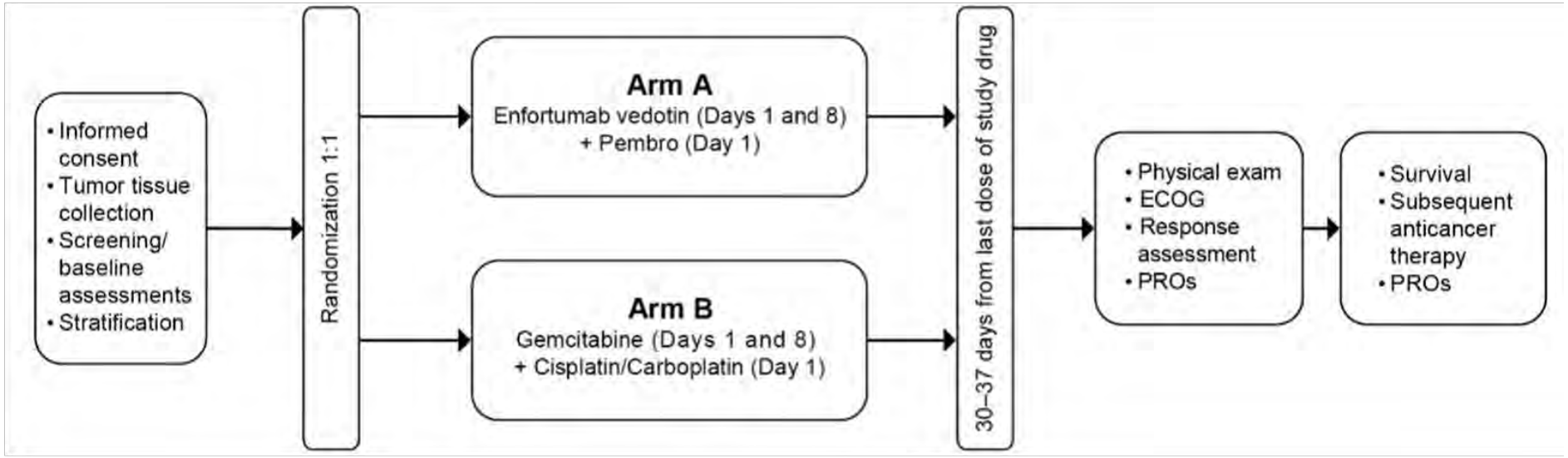
The most frequently reported treatment-emergent adverse events Grade 3 or greater that occurred in more than 5% of patients were rash maculo-papular, anemia, lipase increased, urinary tract infection, hyperglycemia, fatigue, neutropenia, hematuria, diarrhea, acute kidney injury, hyponatremia, chronic kidney disease, weight decreased, syncope, hypophosphatemia, pneumonitis, sepsis, and alanine aminotransferase increased.

https://investor.seagen.com/press-releases/news-details/2022/Seagen-and-Astellas-Announce-Positive-Topline-Results-For-PADCEV-enfortumab-vedotin-ejfv-with-KEYTRUDA-pembrolizumab-as-First-Line-Treatment-for-Advanced-Urothelial-Cancer/default.aspx

EV-302 study (NCT04223856)

Eligibility

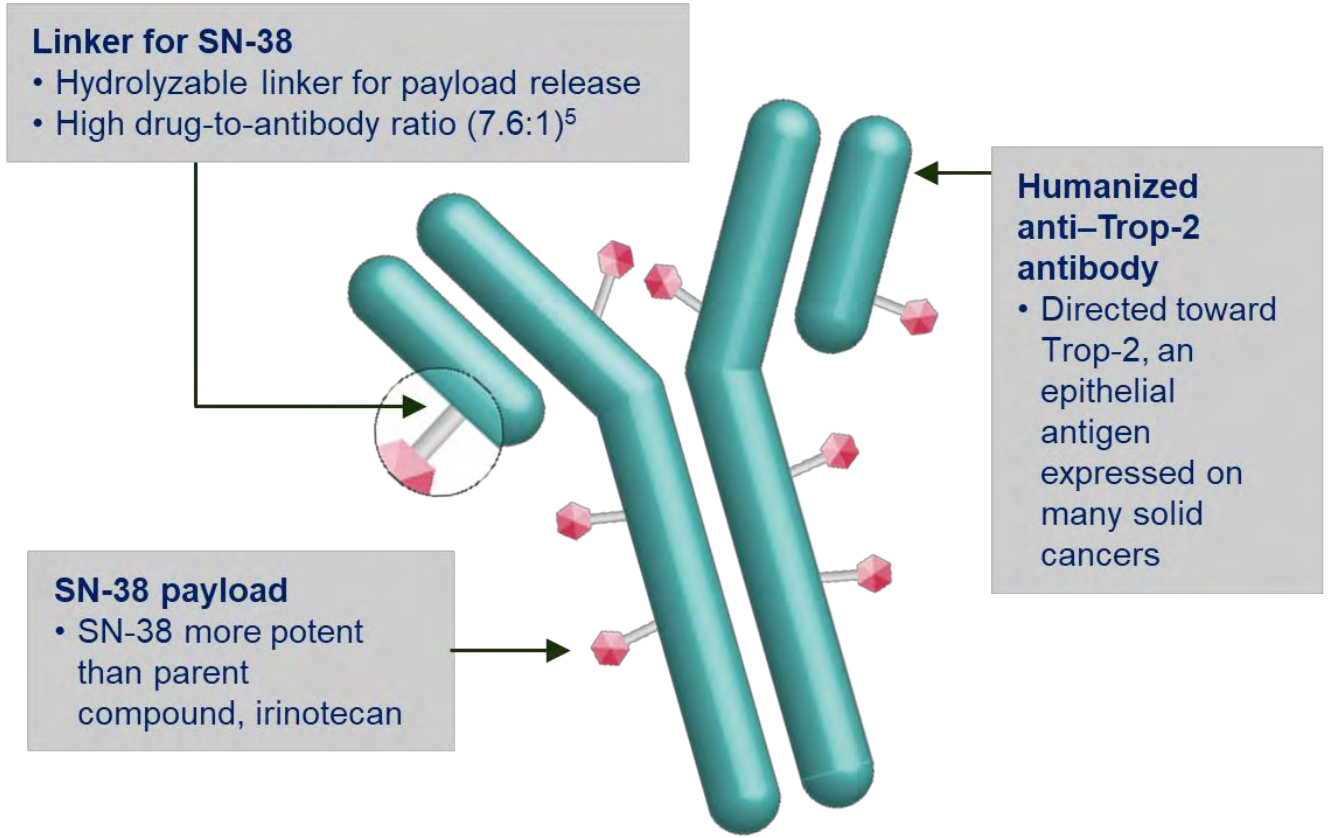
- Locally advanced or metastatic urothelial carcinoma
- 1st line systemic therapy
- Platinum-eligible



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

Sacituzumab govetican

- Trop-2 is an epithelial cell surface antigen highly expressed in UC[1]
- SG is distinct from other ADCs[2-6]:
  - High drug-to-antibody ratio[5]
  - Bystander effect due to hydrolyzable linker hydrolysis[6a]
- Significant activity across tumors[3,7-10]
  - Approved for mTNBC
  - Phase 3 trial in mUC ongoing

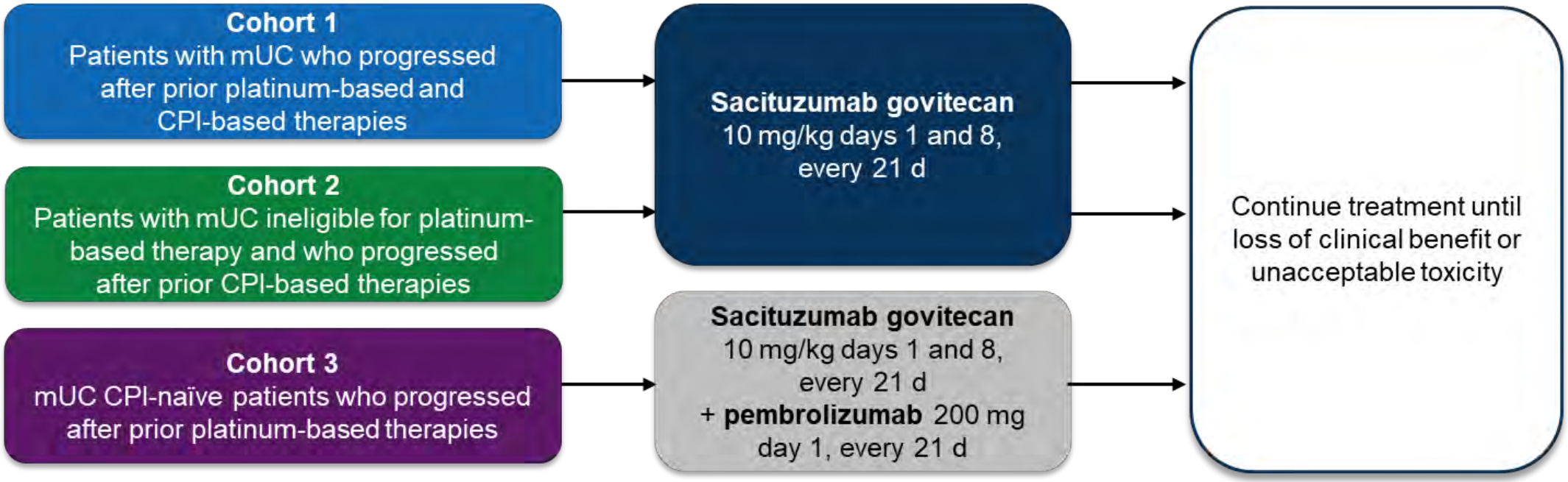


[a]Sacituzumab govitecan–bound tumor cells are killed by intracellular uptake of SN-38, and adjacent tumor cells are killed by SN-38 released extracellularly.

mTNBC, metastatic triple-negative breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Trop-2, trophoblast cell surface antigen 2; UC, urothelial cancer. 1. Avellini et al. *Oncotarget* 2017; 2. Starodub et al. *Clin Cancer Res* 2015; 3. Cardillo et al. *Clin Cancer Res.* 2011; 4. Sharkey et al. *Clin Cancer Res.* 2015; 5. Cardillo et al. *Bioconjugate Chem.* 2015; 6.Govindan et al. *Mol Cancer Ther.* 2013; 7. Faltas et al. *Clin Genitourin Cancer.* 2016; 8. Bardia et al. *J Clin Oncol.* 2017; 9. Bardia et al. *N Engl J Med.* 2019; 10. Tagawa et al. *J Clin Oncol.* 2019.

TROPHY-U-01 study

Sacituzumab Govitecan in Pretreated Locally Advanced Metastatic Urothelial Carcinoma



- **Primary endpoint:** ORR by central review
- **Secondary endpoints:** PFS, DOR, OS, safety/tolerability

1. https://clinicaltrials.gov/ct2/show/NCT03547973. 2. Loriot Y et al. *Ann Oncol*. 2020;31(suppl 4):s1142-s1215.
3. Petrylak DP et al. *J Clin Oncol*. 2020;38(15_suppl):Abstract 5027.

Loriot et al. *Ann Oncol*. 2020;31(suppl 4):s1142-s1215
Petrylak et al. *J Clin Oncol*. 2020;38(15_suppl):Abstract 5027

TROPHY-U-01: Outcomes

Endpoint	Cohort 1 (N = 113)
ORR, n (%) [95% CI]	31 (27) [19-37]
CR, n (%)	6 (5)
PR, n (%)	25 (22)
Median duration of response, mo [95% CI] (range)	5.9 [4.7-8.60] (1.4-11.7)
Median time to onset of response, mo (range)	1.6 (1.2-5.5)

At median follow-up of 6.3 mo

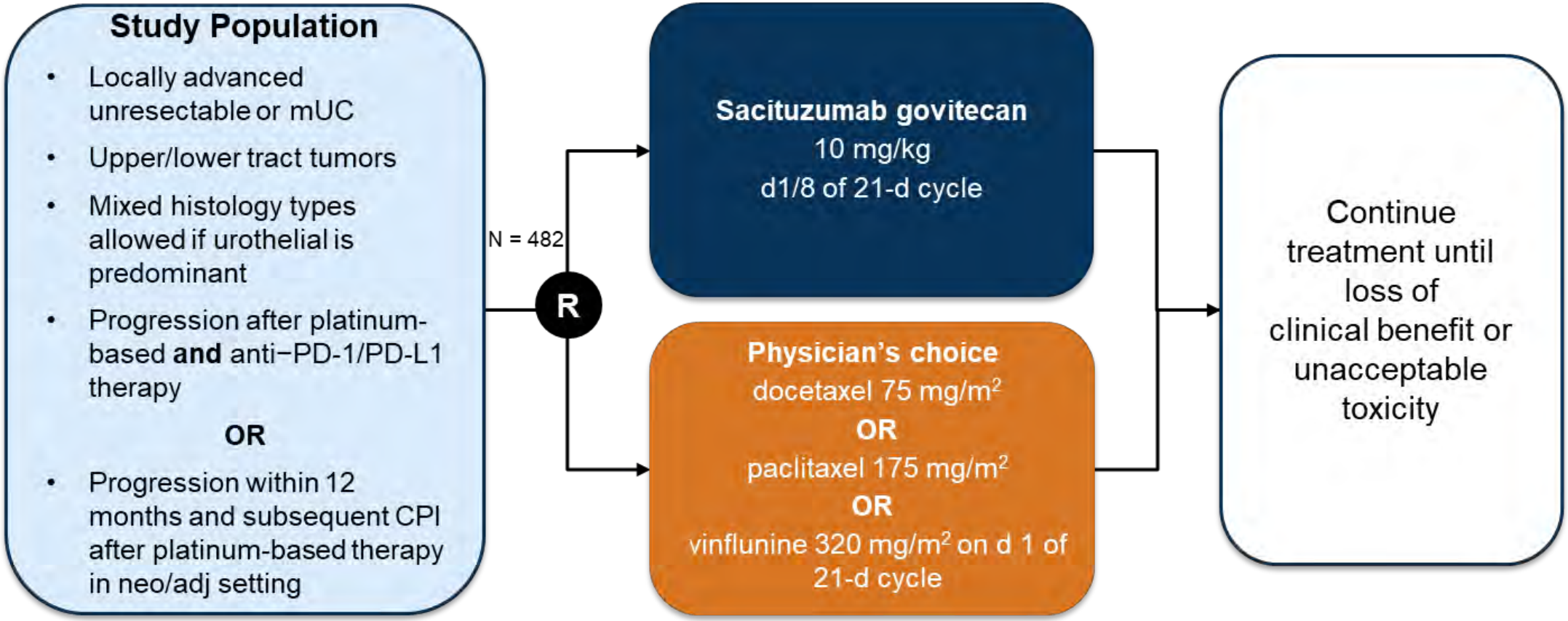
- Median PFS (95% CI): 5.4 (3.5-6.9) mo
- Median OS (95% CI): 10.5 (8.2-12.3) mo

- ORR, median DOR, and median TTR values were consistent with investigator assessments

[a] Assessments were per Blinded Independent Review Assessment, RECIST v1.1.

1. Loriot Y et al. *Ann Oncol*. 2020;31(suppl 4):s1142-s1215.

Phase 3 TROPICS-04 study (NCT04527991)

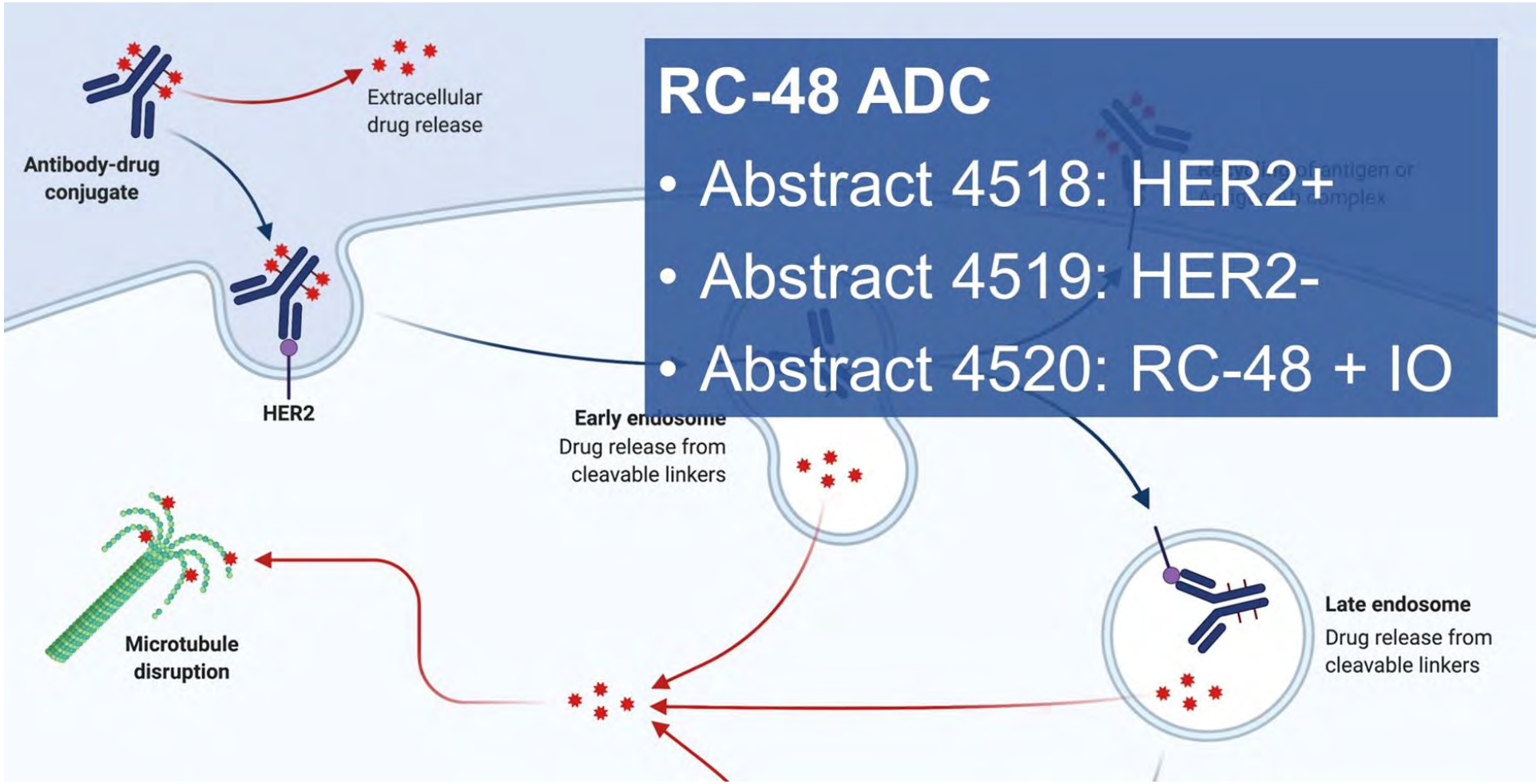


- **Primary endpoint:** OS
- **Secondary endpoints:** PFS by PI assessment using RECIST v1.1; ORR, DOR, and CBR by PI assessment using RECIST v1.1; EORTC QLQ C30 score and EuroQOL EQ-5D-5L QOL score

1. https://clinicaltrials.gov/ct2/show/NCT04527991.

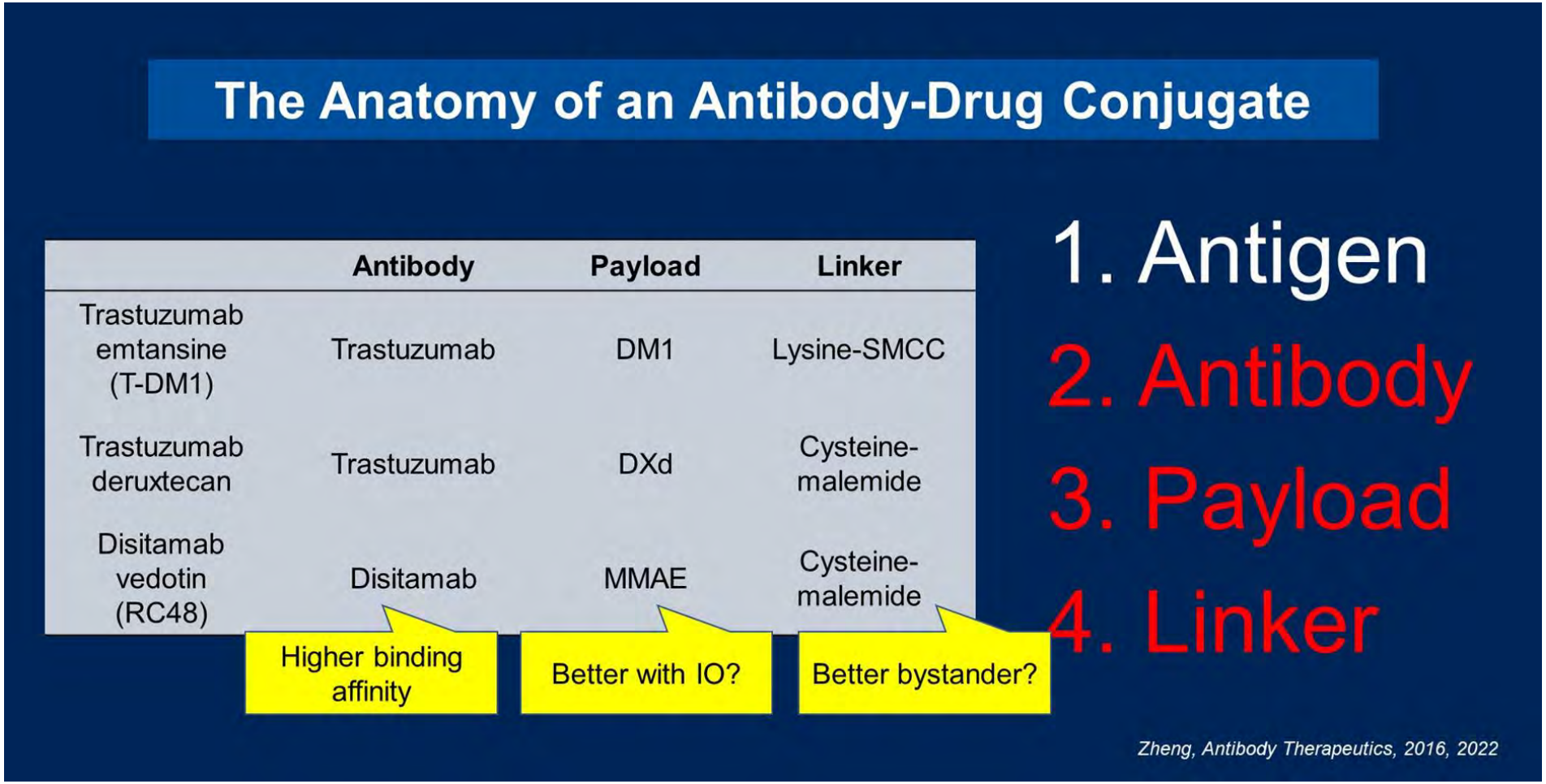
https://clinicaltrials.gov/ct2/show/NCT04527991

RC-48 ADC



Galsky, M. HER2 is New Again in Bladder Cancer. ASCO Annual Meeting 2022

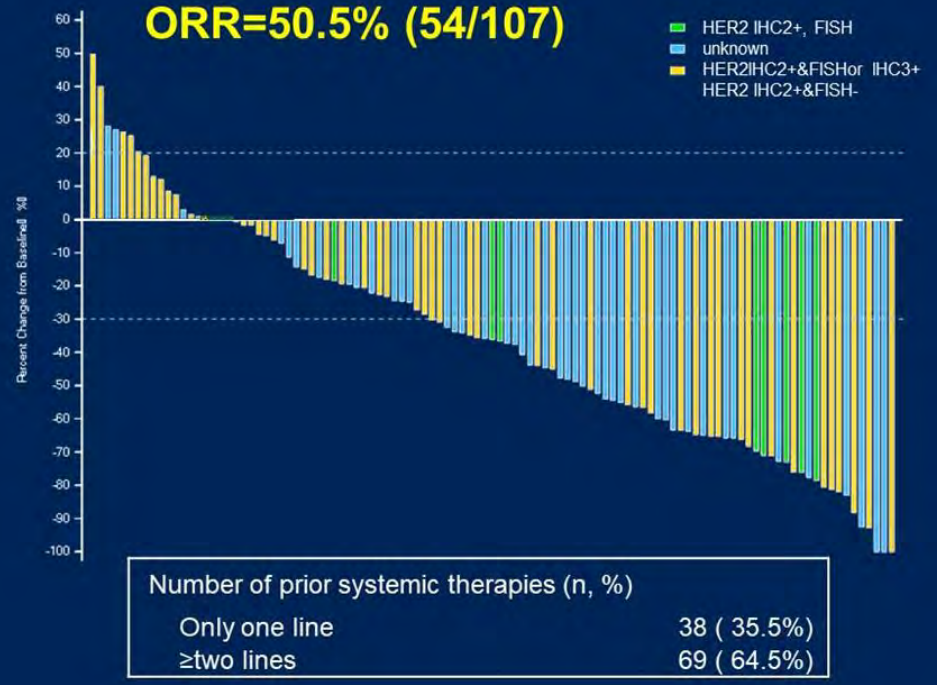
HER2 ADCs


The Anatomy of an Antibody-Drug Conjugate
Antibody
Payload
Linker
Trastuzumab emtansine (T-DM1)
Trastuzumab
DM1
Lysine-SMCC
Trastuzumab deruxtecan
Trastuzumab
DXd
Cysteine-malemide
Disitamab vedotin (RC48)
Disitamab
MMAE
Cysteine-malemide
Higher binding affinity
Better with IO?
Better bystander?
1. Antigen
2. Antibody
3. Payload
4. Linker
Zheng, Antibody Therapeutics, 2016, 2022

RC48 in HER2 2-3+ mUC

RC48 active in HER2 2-3+ mUC (#4518 – Sheng et al)

Target Lesion Change from Baseline



Number of prior systemic therapies (n, %)	
Only one line	38 (35.5%)
≥two lines	69 (64.5%)

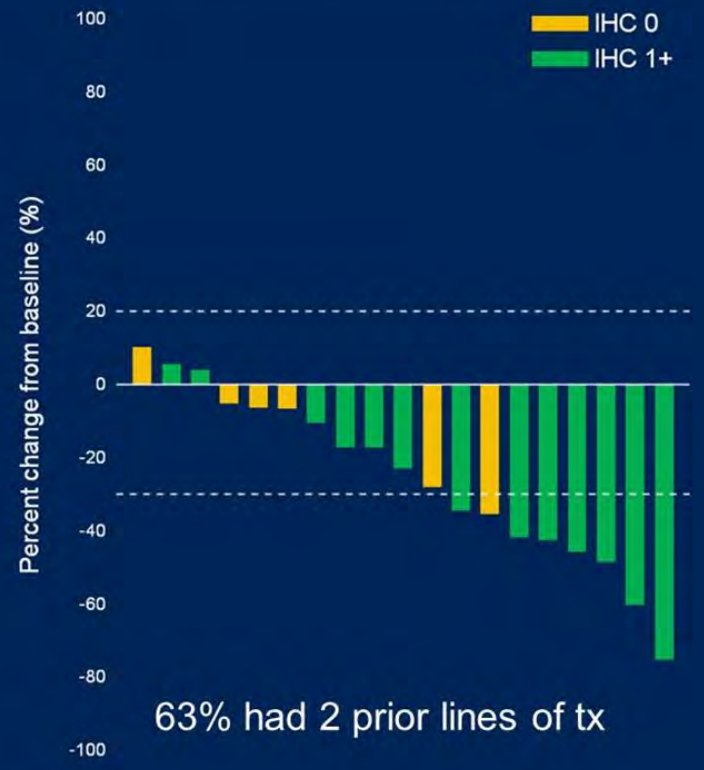
Subgroup Analysis for cORR

Subgroups	cORR (%, 95% CI)
HER2 status	
IHC2+FISH+ or IHC3+ (n=45)	62.2% (46.5%, 76.2%)
IHC2+FISH- (n=53)	39.6% (26.5%, 54.0%)
Metastasis site	
Visceral Metastasis (n=97)	51.5% (41.2%, 61.8%)
Metastasis to Liver (n=48)	52.1% (37.2%, 66.7%)
Prior therapies	
Post PD1/PDL1 Treatments (n=27)	55.6% (35.3%, 74.5%)
Post 1 line of Chemotherapy (n=38)	50.0% (33.4%, 66.6%)
Post ≥2 Lines of Chemotherapy (n=69)	50.7% (38.4%, 63.0%)

Sheng et al. J Clin Oncol 40, 2022 (suppl 16; abstr 4518)
Galsky, M. HER2 is New Again in Bladder Cancer. ASCO Annual Meeting 2022

RC48 in HER2 1+ mUC

RC48 active in HER2 1+ mUC (#4519 – Xu et al)

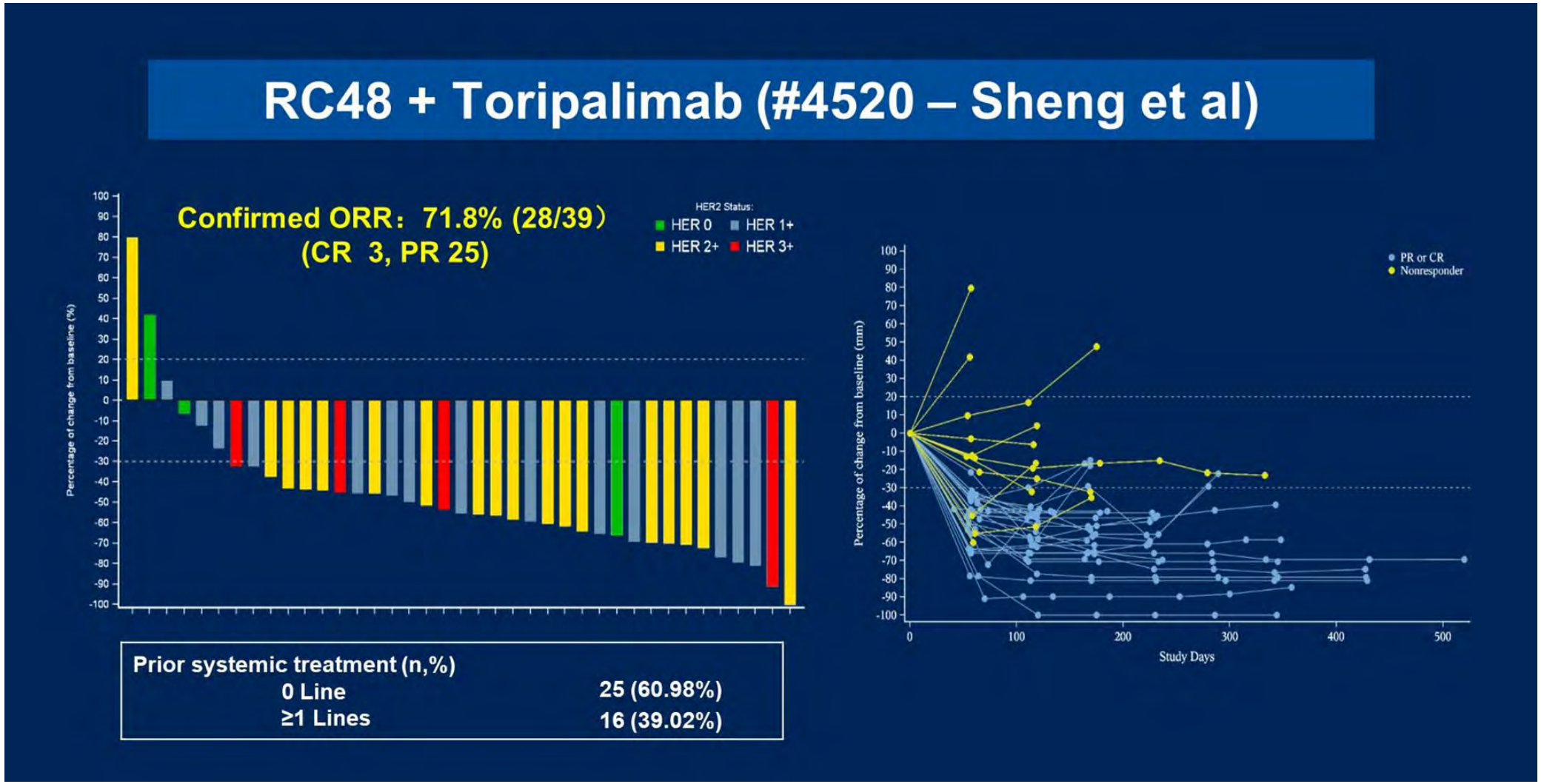


Confirmed ORR	
n (%)	5 (26.3%)
95%CI	9.1%, 51.2%

Subgroups	cORR (%, 95% CI)
IHC 0 (n=6)	0
IHC 1+ (n=13)	38.5 (13.9, 68.4)

Xu et al. J Clin Oncol 40, 2022 (suppl 16; abstr 4519)
Galsky, M. HER2 is New Again in Bladder Cancer. ASCO Annual Meeting 2022

RC48 plus Toripalimab (anti-PD-1)



Sheng et al. J Clin Oncol 40, 2022 (suppl 16; abstr 4520)
Galsky, M. HER2 is New Again in Bladder Cancer. ASCO Annual Meeting 2022

Is there something special about MMAE?

Regimen	Payload	N	Population	HER2	ORR
Enfortumab vedotin + Pembrolizumab	MMAE (tubulin)	43	Cis-ineligible, tx naive	All	73%
Disitimab vedotin + Toripalimab	MMAE (tubulin)	39	60% tx naive	All	72%
Trastuzumab deruxtecan + Nivolumab	Dxd (Topo I)	26	Progressed despite prior platinum	2+ or 3+	36%
Sacitizumab govitecan + Pembrolizumab	SN38 (Topo I)	41	Progressed despite prior platinum	All	34%

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Studies of immunotherapy alone in MIBC

Study	PURE-01	ABACUS	NABUCCO
# patients	50	95	24 (14)
IO agent	Pembrolizumab	Atezolizumab	Ipilimumab + nivolumab
# cycles	3 (9 weeks)	2 (6 weeks)	3 I -> I+N -> N (3, I+N x 2 -> N)
pCR (pT0)	38%	31%	46% (43%)
pRR (<pT2)	54%	Not reported	58% (57%)

Necchi et al, JCO 2018

van Dorp et al, ESMO 2021; abstr 5132

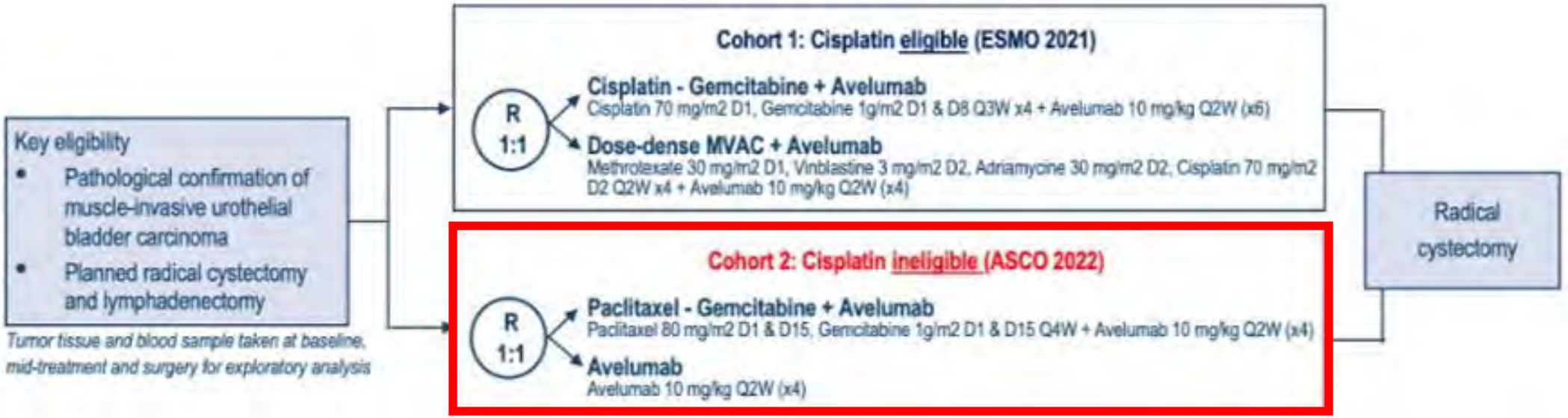
Powles et al, Nat Med 2019

Van Dijk et al, ASCO Annual Mtg 2020;abstr 5020

Kaimakliotis et al, ASCO Annual Mtg 2020;abstr 5019

Avelumab as the basis of neoadjuvant regimen in platinum-eligible and –ineligible patients with non metastatic muscle invasive bladder cancer: AURA (Oncodistinct-004) trial

Nieves Martinez Chanza, Aurélien Carnot, Philippe Barthelemy, Vinciane Casert, Lionel Staudacher, Jan Van den Brande, Brieuc Sautois, Vincent Vanhaudenarde, Emmanuel Seront, Veronique Debien, Thierry Gil, Marianne Paesmans, Nuria Kotecki, Michael Ignatidis, Simone Albisinni, Jean Christophe Fantoni, Thibault Tricard, Romain Diamond, Thierry Roumeguere & Ahmad Awada.



Primary Endpoint:
- Proportion of patients achieving ypT0/is/aN0 (pCR)

Secondary Endpoints:
- Proportion of patients achieving <ypT2N0
- Safety (CTCAE v4)

Statistical considerations (cohort 2):
- Two stage Fleming's design for each treatment arm
- To detect a rate of pCR >5% (90% power reached in case of pCR rate > 25%).
- Planned independent interim analysis after 28 evaluable patients per arm for early efficacy and futility
- Patients who developed metastases while on therapy and those unable to undergo surgery were considered as non -responders

Chanza et al. J Clin Oncol 40, 2022 (suppl 16; abstr 4517)
Milowsky M. Improving Ouctomes Across the Stages of Bladder Cancer. ASCO Annual Meeting 2022

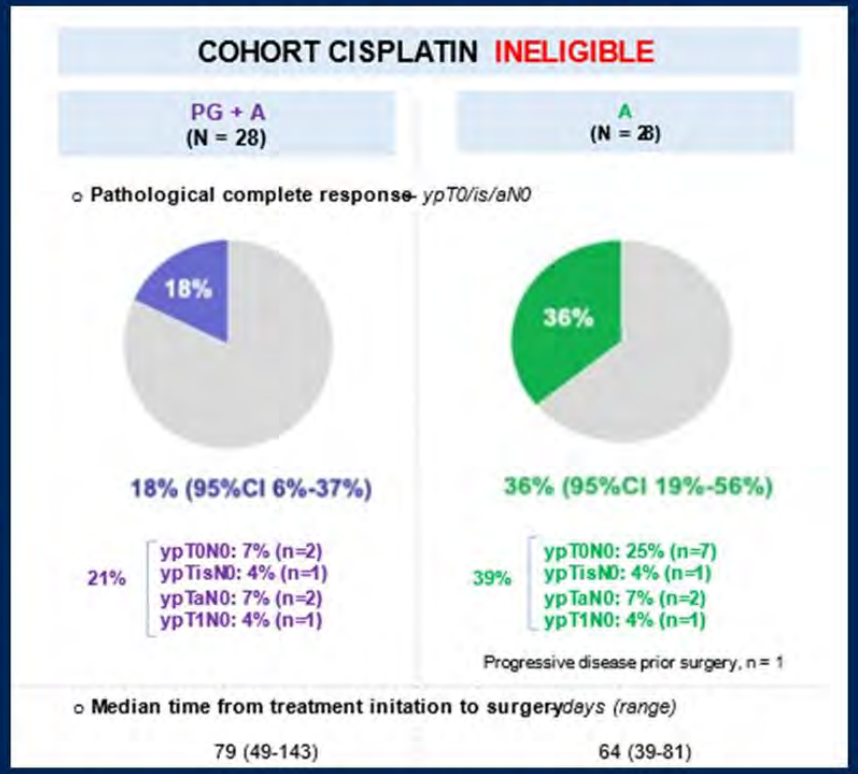
AURA Trial

Population

Variable	PG + A N = 28	A N = 28
Median age at diagnosis, years (range)	72 (41-80)	75 (49-89)
Male gender, n (%)	26 (93%)	26 (93%)
Histology, n (%)		
- Pure UC	22 (79%)	22 (79%)
- UC with mixed histology[1]	6 (21%)	6 (21%)
ECOG PS, n (%)		
- 0	14 (50%)	11 (39%)
- 1	14 (50%)	17 (61%)
Cisplatin inelegibility[2], n(%)		
- Renal impairment	17 (61%)	22 (79%)
- Hearing loss	5 (18%)	8 (29%)
- Peripheral neuropathy	1 (4%)	1 (4%)
- Heart failure	7 (25%)	4 (14%)
Median BMI, kg/m^2 (range)	26,1 (17,9-36,5)	27,4 (22,3-34,3)
Previous intravesical BCG treatment, n (%)	1 (4%)	1 (4%)
Avelumab cycles received, n (%)		
- 4	25 (89%)	26 (93%)
- 3	2 (7%)	1 (4%)
- 1	1 (4%)	1 (4%)

[1]Mixed histology with predominant urothelial component (>50%)
[2] Can have more than one criteria

Pathologic Response



No treatment-related deaths were reported
No patient failed to undergo surgery due to an adverse event
No major surgical complications and morbidity were described

Chanza et al. J Clin Oncol 40, 2022 (suppl 16; abstr 4517)
Milowsky M. Improving Ouctomes Across the Stages of Bladder Cancer. ASCO Annual Meeting 2022

Studies of immunotherapy alone in MIBC

Study	PURE-01	ABACUS	NABUCCO	AURA
# patients	50	95	24 (14)	28
IO agent	Pembrolizumab	Atezolizumab	Ipilimumab + nivolumab	Avelumab
# cycles	3 (9 weeks)	2 (6 weeks)	3 I -> I+N -> N (3, I+N x 2 -> N)	4 (8 weeks)
pCR (pT0)	38%	31%	46% (43%)	36%*
pRR (<pT2)	54%	Not reported	58% (57%)	39%

Necchi et al, JCO 2018

van Dorp et al, ESMO 2021; abstr 5132

Powles et al, Nat Med 2019

Van Dijk et al, ASCO Annual Mtg 2020;abstr 5020

Kaimakliotis et al, ASCO Annual Mtg 2020;abstr 5019

Studies of Chemo-IO in MIBC

Study	UNC LCCC1520	HCRN 14-188	BLASST-1	MSKCC
# Patients	39	43	41	39
Immunotherapy	Pembrolizumab	Pembrolizumab	Nivolumab	Atezolizumab
Chemotherapy	Gem/cis	Gem/cis	Gem/cis	Gem/cis
pCR (pT0)	36%	44%	34%	38%
pRR (<pT2)	56%	61%	66%	69%

Rose et al, JCO 2021.
Hoimes et al, ESMO 2018, abstr 5681.
Gupta et al, JCO 38,6_supp (Feb 2020).
Cathomas et al, ASCO 2022, abstr 4515.
Funt et al, JCO, 2022.

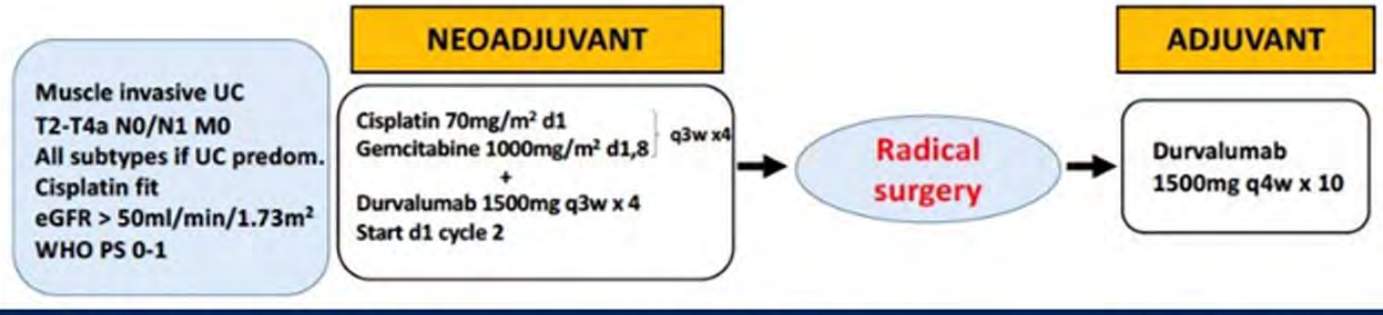
SAKK 06/17

Perioperative chemo-immunotherapy with Durvalumab for operable muscle-invasive urothelial carcinoma (MIUC): primary analysis of the single arm phase II trial SAKK 06/17

Richard Cathomas, Sacha I. Rothschild, Stefanie Hayoz, Martin Spahn, Berna C.Özdemir, Bernhard Kiss, Andreas Erdmann, Stefanie Aeppli, Nicolas Mach, Räto T. Strebel, Boris Hadaschik, Dominik Berthold, Miklos Pless, Deborah Zihler, Mathias Schmid, Martina Schneider, Jana Musilova, Ulf Petrausch

14

SAKK 06/17 is a prospective single arm, open-label multicenter phase II trial



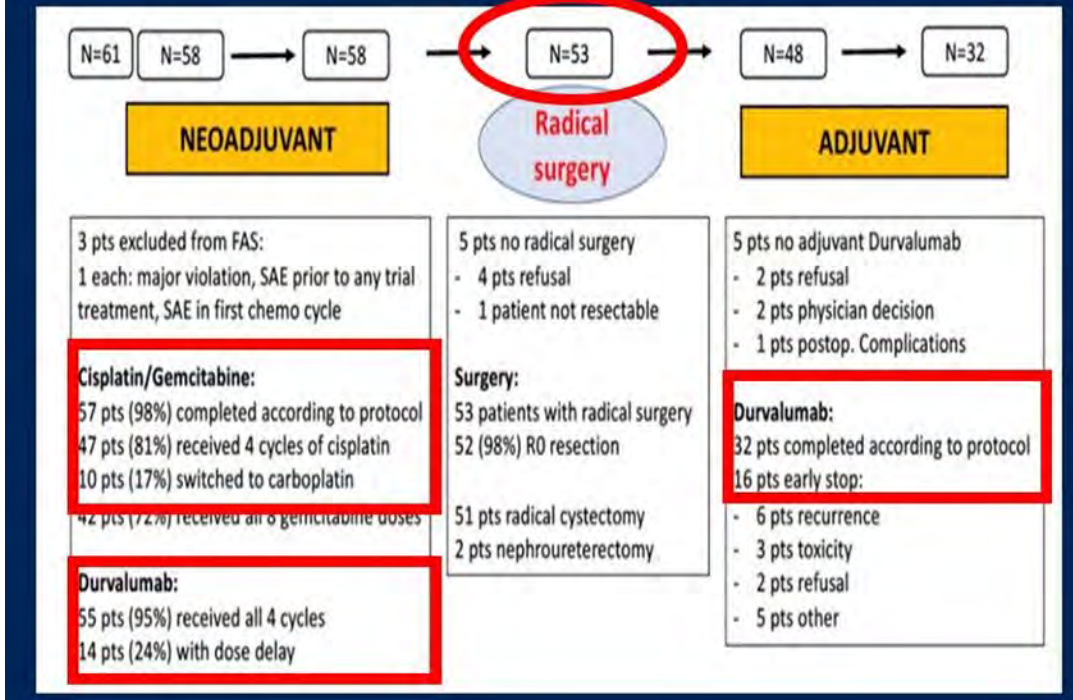
Primary Endpoint: EFS at 2 years (PD during neoadjuvant Rx, locoregional/metastatic recurrence or death

Secondary Endpoints: pCR (ypT0), PaR (≤ypT1N0M0), EFS, RFS, OS, recurrence pattern, AEs, quality resection

Statistical Considerations:
H0: EFS at 2 yrs ≤ 50%; H1: EFS at 2 yrs ≥ 65%; Type 1 error: 10%, Power 80%, Total sample size 61 patients
Full Analysis Set (≥ 1 dose Durvalumab): 58 patients needed

Cathomas et al. J Clin Oncol 40, 2022 (suppl 16; abstr 4515)
Milowsky M. Improving Ouctomes Across the Stages of Bladder Cancer. ASCO Annual Meeting 2022

SAKK 06/17 Results



Overall pathological response (N=53):

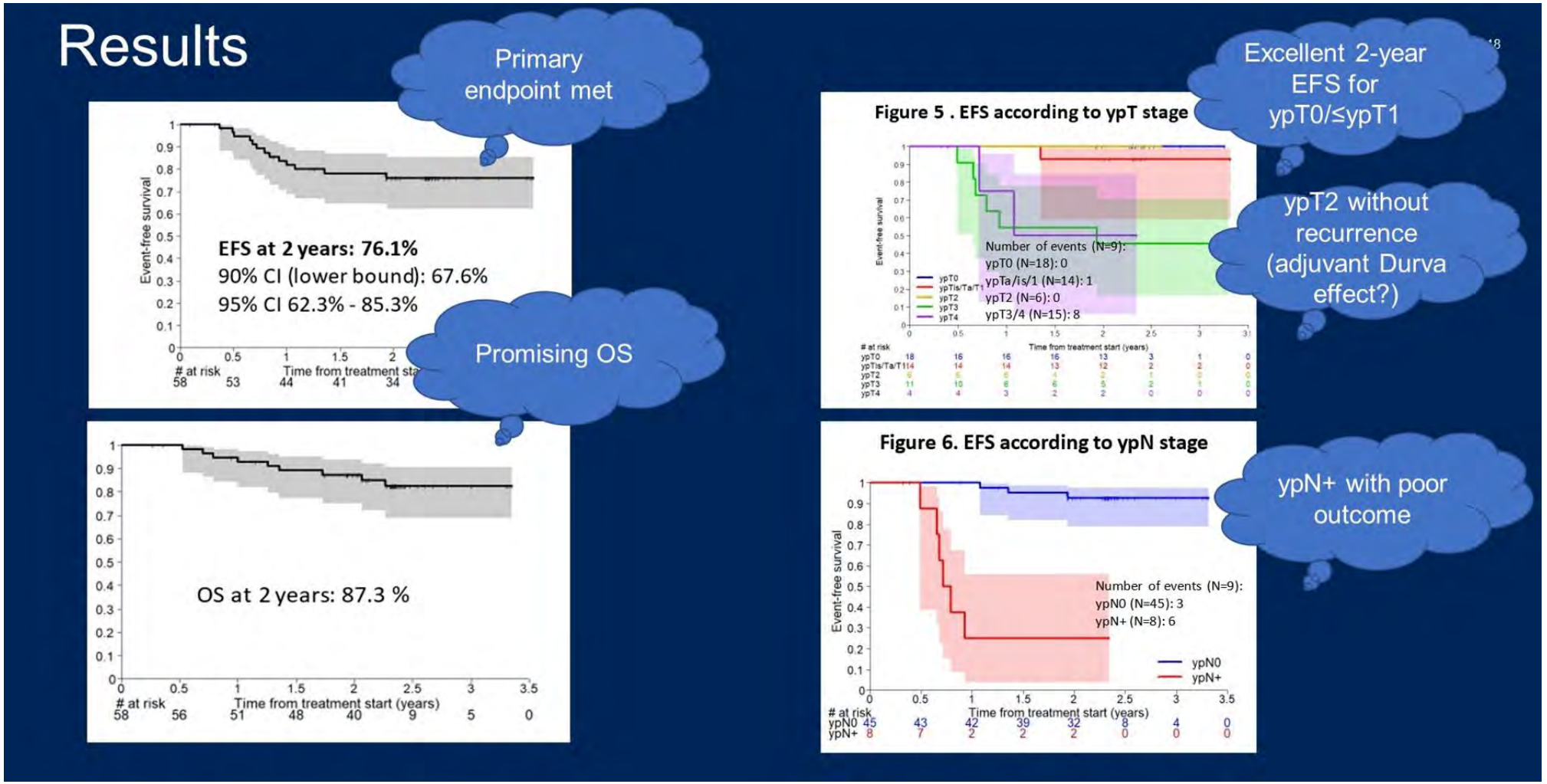
pCR (ypT0): 18 (34.0%; 95% CI: 21.5%,48.3%)

PaR (<ypT2): 32 (60.4%; 95% CI: 46.0%,73.5%)

	cT2 (n=38)	cT3 (n=11)	cT4 (n=4)	cN0 (n=44)	cN1 (n=9)
ypT0	15 (39.5%)	3 (27.3%)	0 (0%)	-	-
ypTa/is/1	10 (26.3%)	4 (36.4%)	0 (0%)	-	-
ypT2	4 (10.5%)	2 (18.2%)	0 (0%)	-	-
ypT3	7 (18.4%)	1 (9.1%)	3 (75%)	-	-
ypT4	2 (5.3%)	1 (9.1%)	1 (25%)	-	
ypN0	-	-	-	39 (88.6%)	6 (66.7%)
ypN1	-	-	-	2 (4.5%)	0 (0%)
ypN2	-	-	-	3 (6.8%)	3 (33.3.%)

Cathomas et al. J Clin Oncol 40, 2022 (suppl 16; abstr 4515)
Milowsky M. Improving Ouctomes Across the Stages of Bladder Cancer. ASCO Annual Meeting 2022

SAKK 06/17 Results



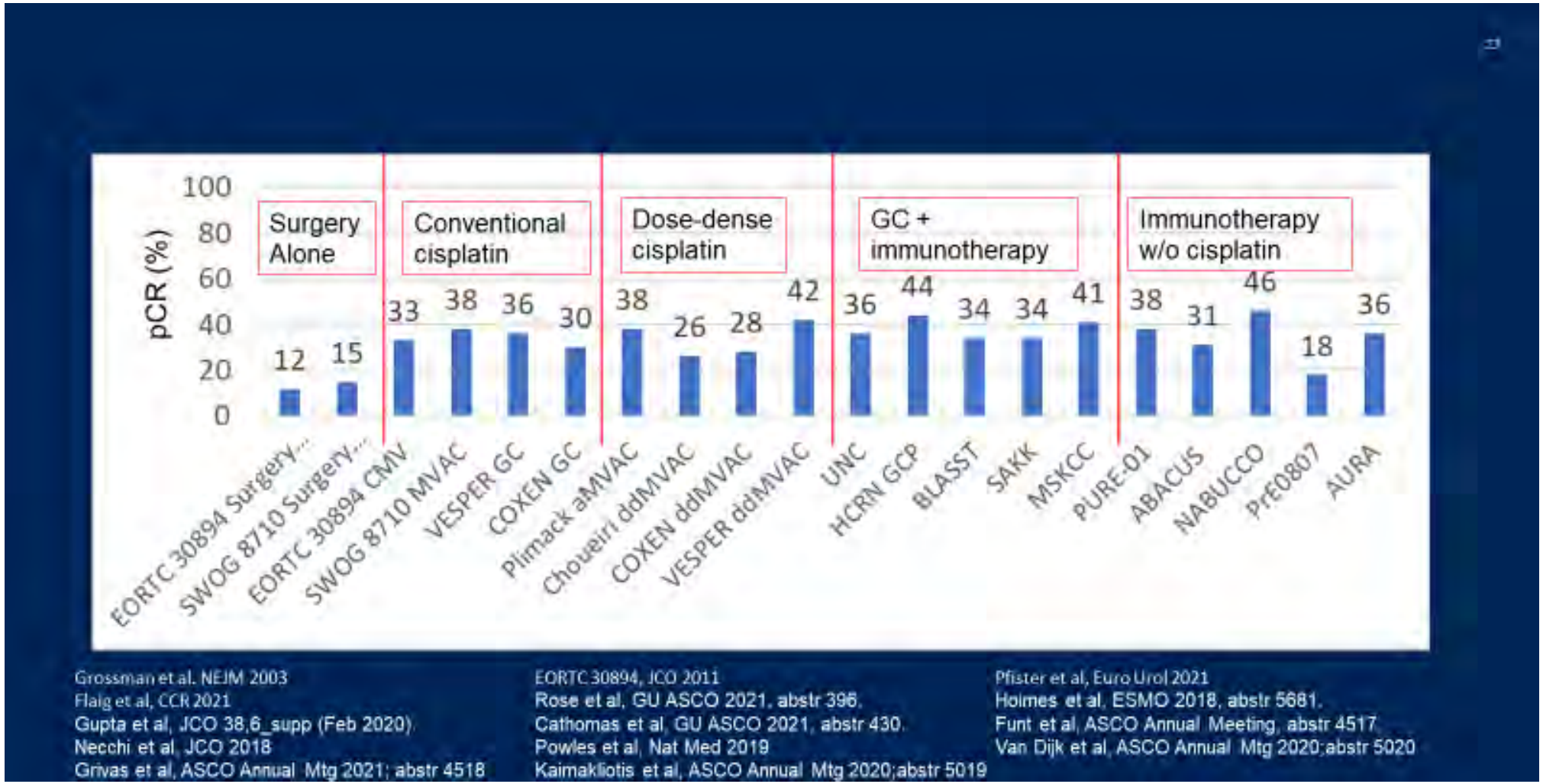
Cathomas et al. J Clin Oncol 40, 2022 (suppl 16; abstr 4515)
Milowsky M. Improving Ouctomes Across the Stages of Bladder Cancer. ASCO Annual Meeting 2022

Studies of Chemo-IO in MIBC

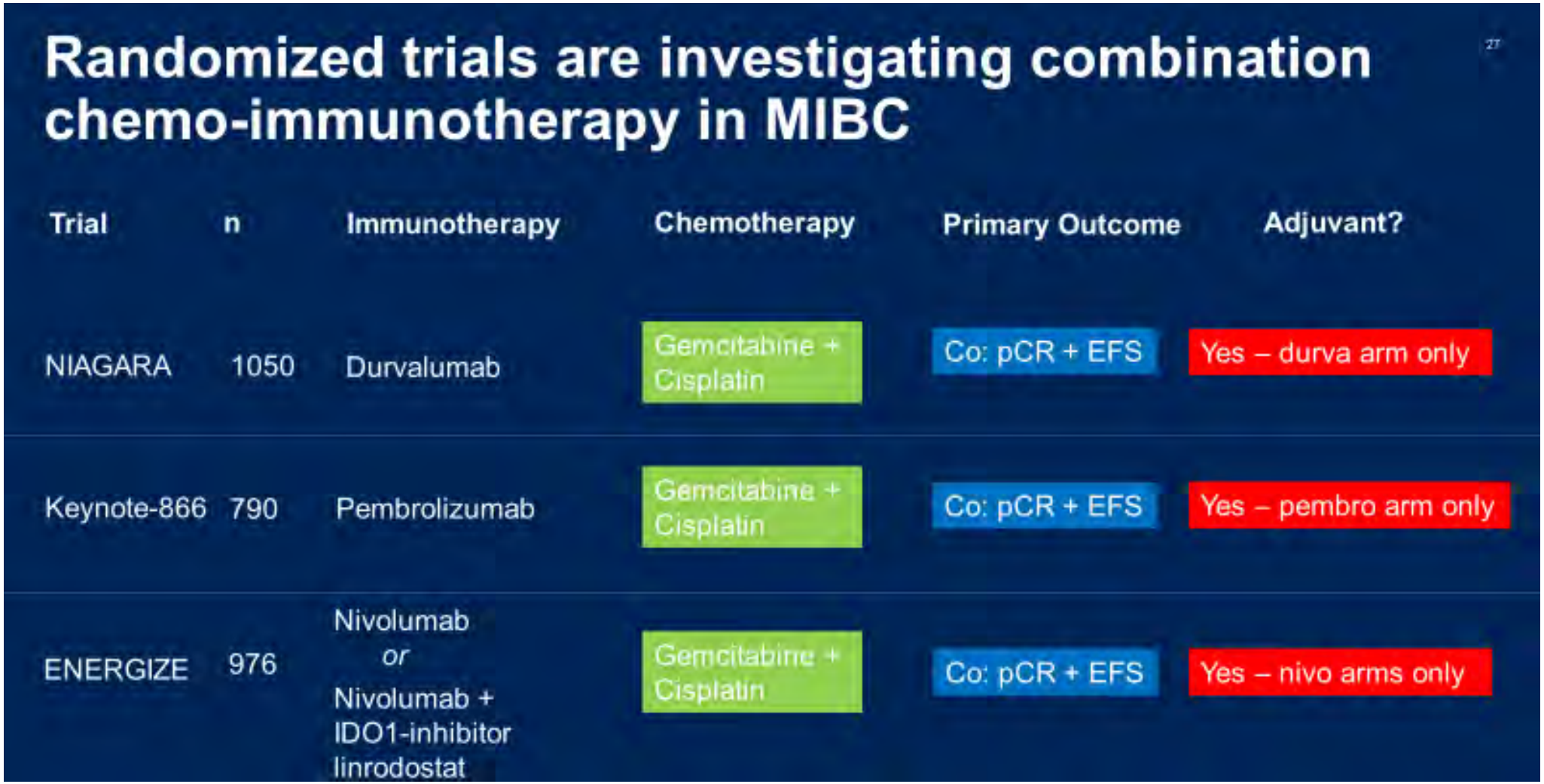
Study	UNC LCCC1520	HCRN 14-188	BLASST-1	MSKCC	SAKK 06/17
# Patients	39	43	41	39	53
Immunotherapy	Pembrolizumab	Pembrolizumab	Nivolumab	Atezolizumab	Durvalumab
Chemotherapy	Gem/cis	Gem/cis	Gem/cis	Gem/cis	Gem/cis
pCR (pT0)	36%	44%	34%	38%	34%
pRR (<pT2)	56%	61%	66%	69%	60%

Rose et al, JCO 2021.
Hoimes et al, ESMO 2018, abstr 5681.
Gupta et al, JCO 38,6_supp (Feb 2020).
Cathomas et al, ASCO 2022, abstr 4515.
Funt et al, JCO, 2022.

Is pathologic response enough?

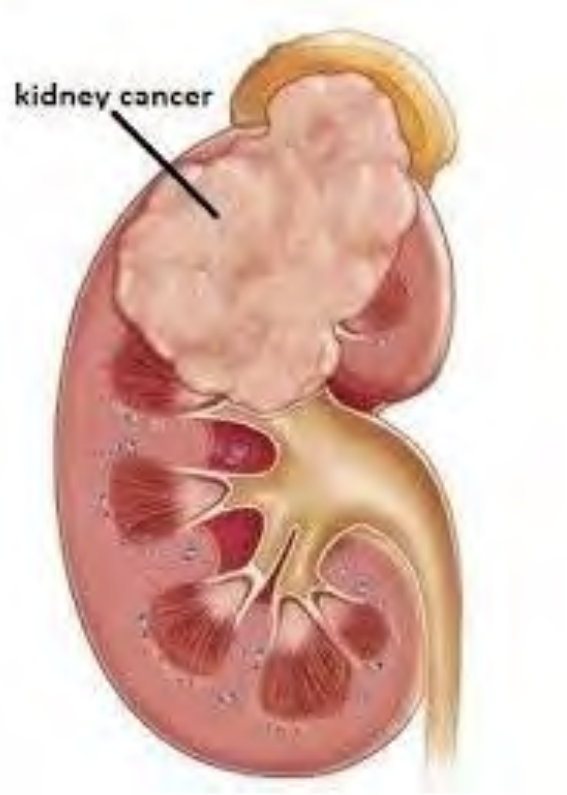


Time to event endpoints are needed



Milowsky M. Improving Ouctomes Across the Stages of Bladder Cancer. ASCO Annual Meeting 2022

Updates in Kidney Cancer



Adjuvant RCC Studies

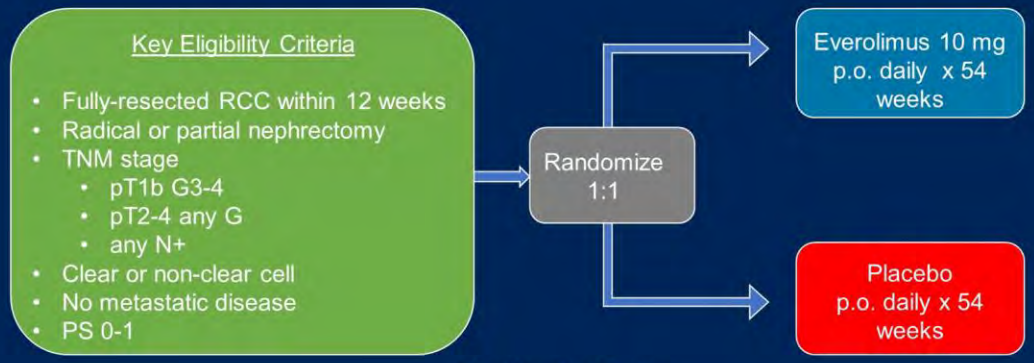
Study	N	Intervention	Primary Endpoint	Outcome
ASSURE	1943	Sorafenib or sunitinib vs placebo for one year	DFS	Non-significant; sunitinib HR 1.02, 97.5% CI 0.85-1.23, P=0.8038; sorafenib HR 0.97, 97.5% CI 0.80-1.17, P=0.718
S-TRAC	615	Sunitinib vs placebo for one year	DFS	Significant; HR 0.76; 95% CI 5.8-NR; P=0.030
PROTECT	1538	Pazopanib (600 mg) vs placebo for one year	DFS	Non-significant; HR 0.86; 95% CI 0.70-1.06; P=0.165
ATLAS	724	Axitinib vs placebo for three years	DFS	Stopped due to futility; non-significant at interim analysis; HR 0.87, 95% CI 0.66-1.15; P=0.321
SORCE	1711	Sorafenib vs placebo for three years	DFS	Non-significant; HR 1.01; 95% CI 0.83-1.23; P=0.950
EVEREST	1218	Everolimus vs placebo (nine courses of six weeks)	DFS	Coming right up!

Tacconi et al. OncoTargets and Therapy 2020: Haas et al. Lancet. 2016; Ravaud et al. NEJM 2016; Motzer et al. JCO 2017; Gross-Goupil et al. Ann Oncol. 2018; Eisen et al. Ann Oncol. 2019

SWOG S0931 – EVEREST
EVErolimus for Renal cancer Ensuing Surgical Therapy, a phase III study*

Christopher W. Ryan, Catherine Tangen, Elisabeth I. Heath, Mark N. Stein, Maxwell Meng, Ajjai Shivaram Alva, Sumanta K. Pal, Igor Puzanov, Joseph I Clark, Toni K. Choueiri, Neeraj Agarwal, Robert Uzzo, Naomi B. Haas, Timothy W. Synold, Melissa Plets, Ulka N. Vaishampayan, Brian M. Shuch, Nicholas J. Vogelzang, Ian M Thompson Jr., Primo "Lucky" N. Lara Jr

Study Design



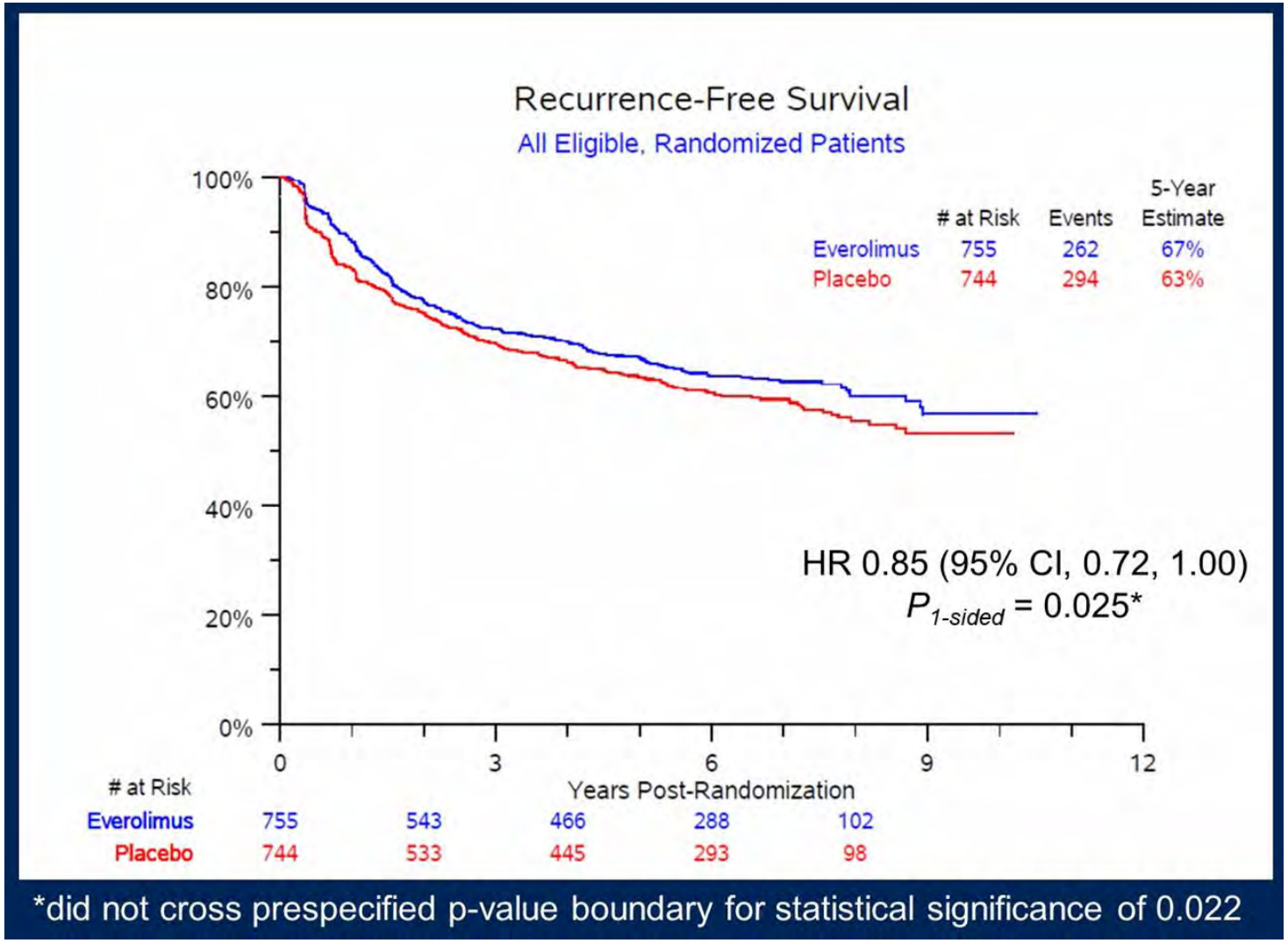
Stratification Factors:
Risk Group (Intermediate-High vs. Very High)
Histology (Clear cell vs. non-Clear Cell)
Performance Status (0 vs. 1)

Intermediate High Risk			Very High Risk		
pT1b	pT2	pT3a	pT3a	pT3b-c, T4	Any pT
Grade 3-4	Any Grade	Grade 1-2	Grade 3-4	Any Grade	Any Grade
N0	N0	N0	N0	N0	N+

* Modified UCLA Integrated Staging System

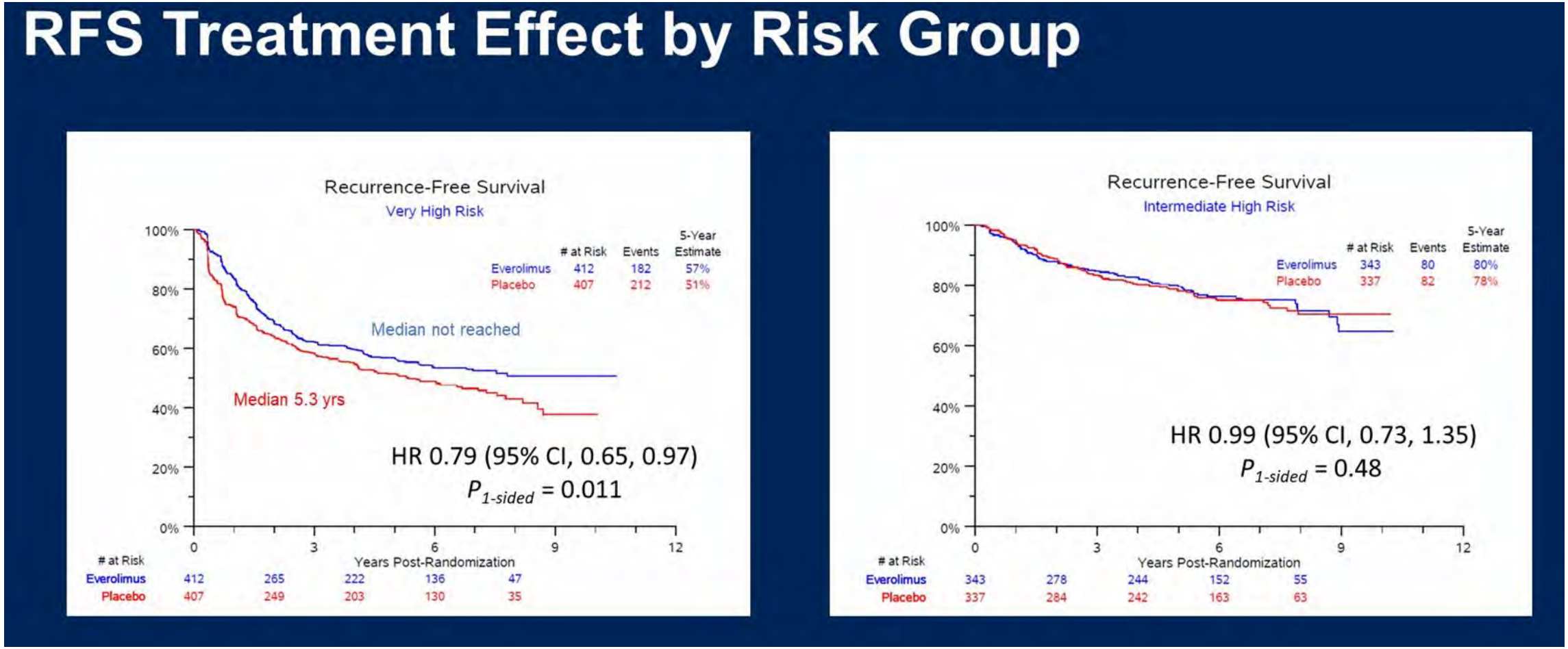
Ryan et al. J Clin Oncol 40, 2022 (suppl 17; abstr LBA4500)

EVEREST RFS



Ryan et al. J Clin Oncol 40, 2022 (suppl 17; abstr LBA4500)

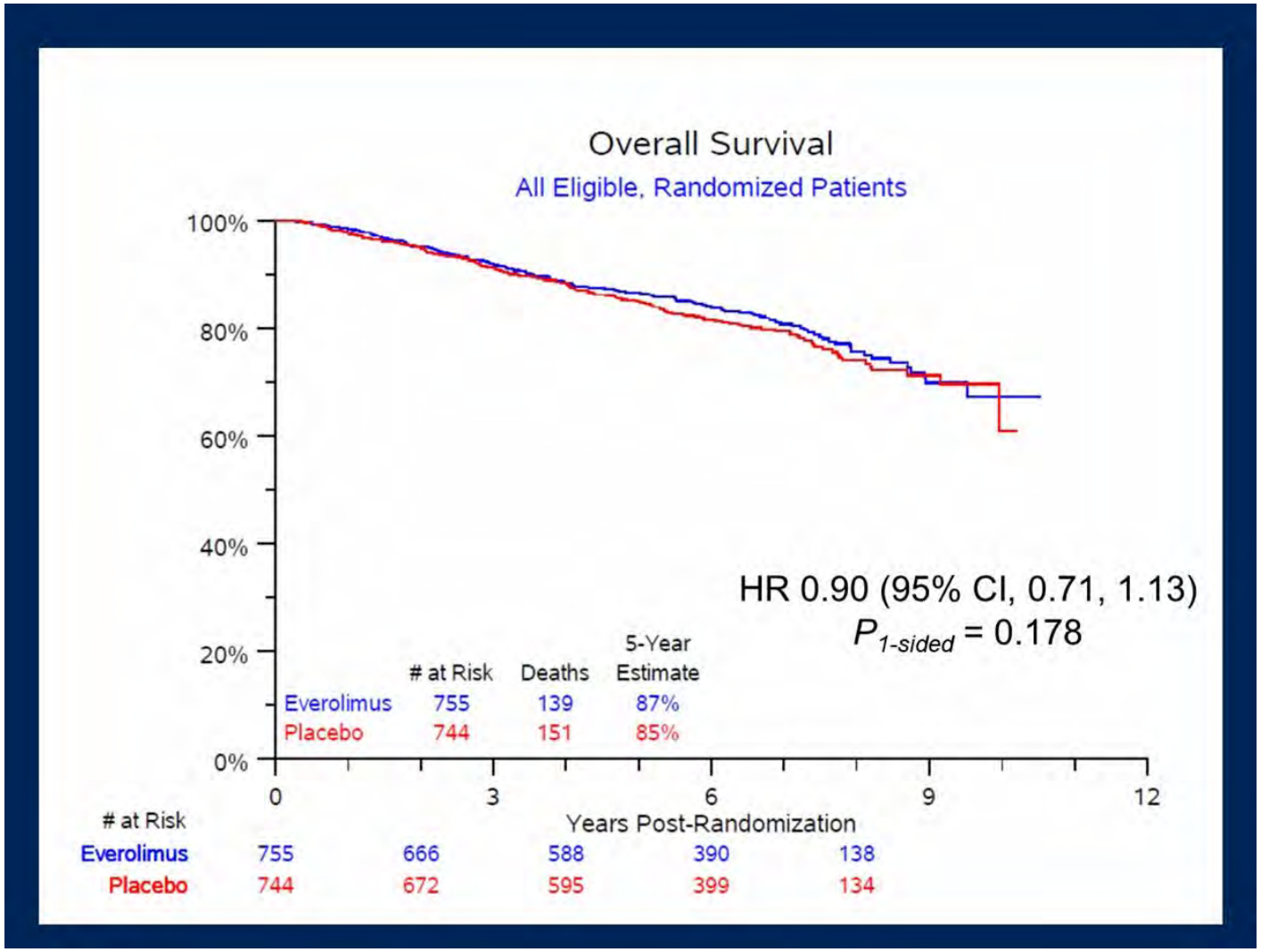
EVEREST RFS by Risk Group



Ryan et al. J Clin Oncol 40, 2022 (suppl 17; abstr LBA4500)

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

EVEREST OS



Ryan et al. J Clin Oncol 40, 2022 (suppl 17; abstr LBA4500)

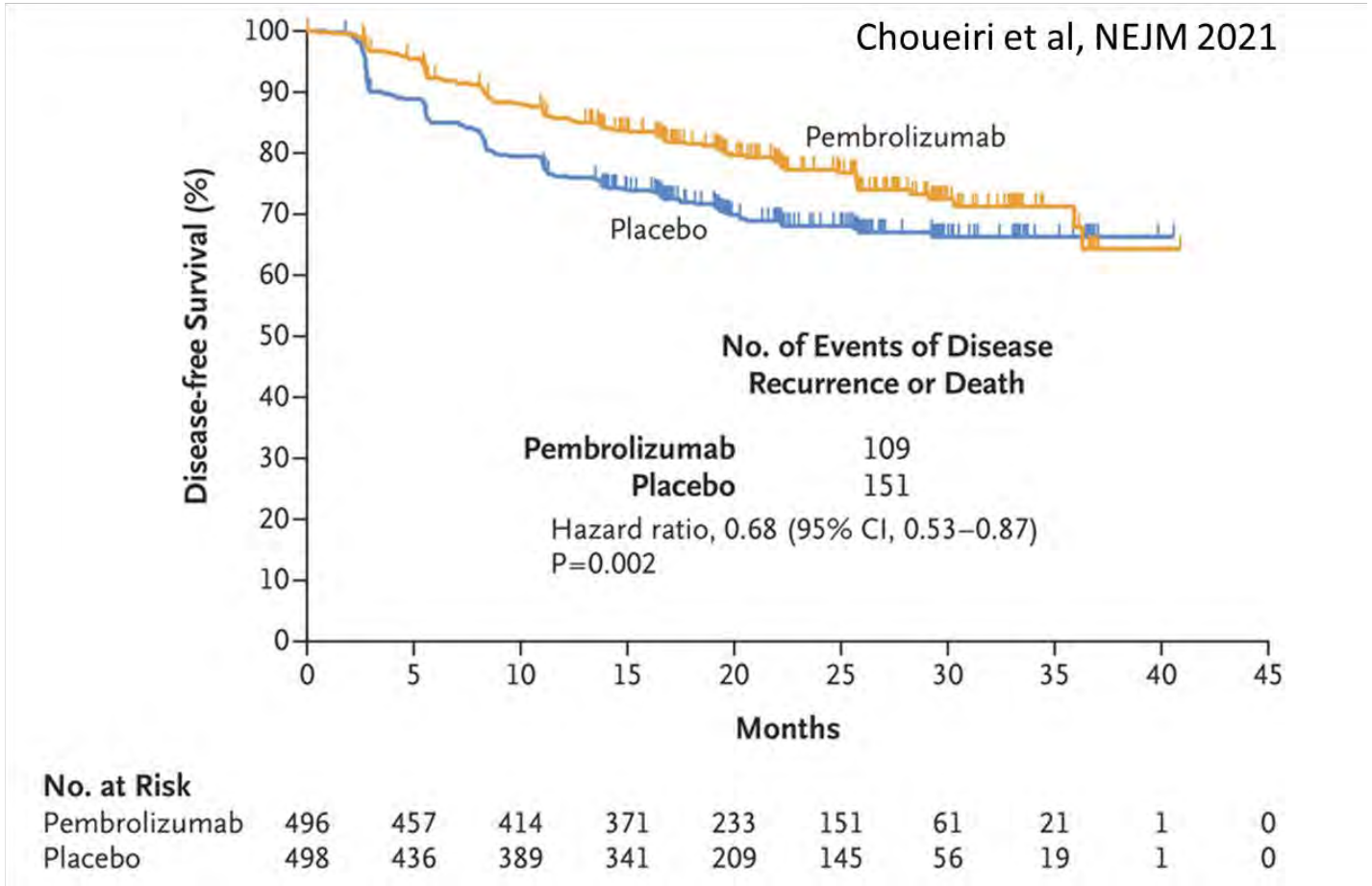
Adjuvant RCC Studies

Study	N	Intervention	Primary Endpoint	Outcome
ASSURE	1943	Sorafenib or sunitinib vs placebo for one year	DFS	Non-significant; sunitinib HR 1.02, 97.5% CI 0.85-1.23, P=0.8038; sorafenib HR 0.97, 97.5% CI 0.80-1.17, P=0.718
S-TRAC	615	Sunitinib vs placebo for one year	DFS	Significant; HR 0.76; 95% CI 5.8-NR; P=0.030
PROTECT	1538	Pazopanib (600 mg) vs placebo for one year	DFS	Non-significant; HR 0.86; 95% CI 0.70-1.06; P=0.165
ATLAS	724	Axitinib vs placebo for three years	DFS	Stopped due to futility; non-significant at interim analysis; HR 0.87, 95% CI 0.66-1.15; P=0.321
SORCE	1711	Sorafenib vs placebo for three years	DFS	Non-significant; HR 1.01; 95% CI 0.83-1.23; P=0.950
EVEREST	1218	Everolimus vs placebo (nine courses of six weeks)	DFS	Non-significant; HR 0.85; 95% CI 0.72-1.00; P=0.025

Tacconi et al. OncoTargets and Therapy 2020: Haas et al. Lancet. 2016; Ravaud et al. NEJM 2016; Motzer et al. JCO 2017; Gross-Goupil et al. Ann Oncol. 2018; Eisen et al. Ann Oncol. 2019; Ryan et al. J Clin Oncol 40, 2022 (suppl 17; abstr LBA4500)

Adjuvant pembrolizumab is associated with a benefit in DFS compared with placebo

Keynote-564 Inclusion Criteria:
- RCC with clear cell component
- Nephrectomy within 12 weeks
- pT2 grade 4 or sarcomatoid *or* pT3-4 *or* N+ *or* M1 with NED



CheckMate-914 and IMmotion 010 do NOT meet primary endpoint

Bristol Myers Squibb Provides Update on CheckMate -914 Trial Evaluating Opdivo (nivolumab) Plus Yervoy (ipilimumab) as Adjuvant Treatment of Localized Renal Cell Carcinoma

07/29/2022

CATEGORY: Corporate/Financial News

PRINCETON, N.J.--(BUSINESS WIRE)-- Bristol Myers Squibb (NYSE: BMY) today announced that Part A of the Phase 3 CheckMate -914 trial, evaluating *Opdivo* (nivolumab) plus *Yervoy* (ipilimumab) as an adjuvant treatment for patients with localized renal cell carcinoma (RCC) who have undergone full or partial removal of the kidney and who are at moderate or high risk of relapse, did not meet the primary endpoint of disease-free survival (DFS) as assessed by Blinded Independent Central Review (BICR).The safety profile was consistent with previously reported studies of the *Opdivo* plus *Yervoy* combination in solid tumors.

https://news.bms.com/news/details/2022/Bristol-Myers-Squibb-Provides-Update-on-CheckMate--914-Trial-Evaluating-Opdivo-nivolumab-Plus-Yervoy-ipilimumab-as-Adjuvant-Treatment-of-Localized-Renal-Cell-Carcinoma/default.aspx

https://www.fiercepharma.com/pharma/roches-tecentriq-flunks-postsurgery-kidney-cancer-early-stage-liver-lung-cancer-readout-draw

First-line Metastatic RCC

	Checkmate 214 Ipilimumab + Nivolumab	Keynote 426 Pembrolizumab + Axitinib	Checkmate 9ER Nivolumab + Cabozantinib	CLEAR Pembrolizumab + Lenvatinib
ORR CR	39% 11%	60% 10%	55% 9%	71% 16%
Median follow-up	67.7 mos	43 mos	23.5 mos	27 mos
Median PFS HR	12.3 mos 0.86 (0.73-1.01)	15.7 mos 0.68 (0.58-0.8)	17 mos 0.52 (0.43-0.64)	24 mos 0.39 (0.32-0.49)
Median OS HR	56 mos 0.72 (0.62-0.85)	46 mos 0.73 (0.6-0.88)	NR 0.66 (0.50-0.87)	NR 0.66 (0.49-0.88)
>= Gr 3 TRAE	46 vs 63	68 vs 64	61 vs 51	72 vs 59

Motzer et al, ESMO 2021
Motzer et al, NEJM 2018

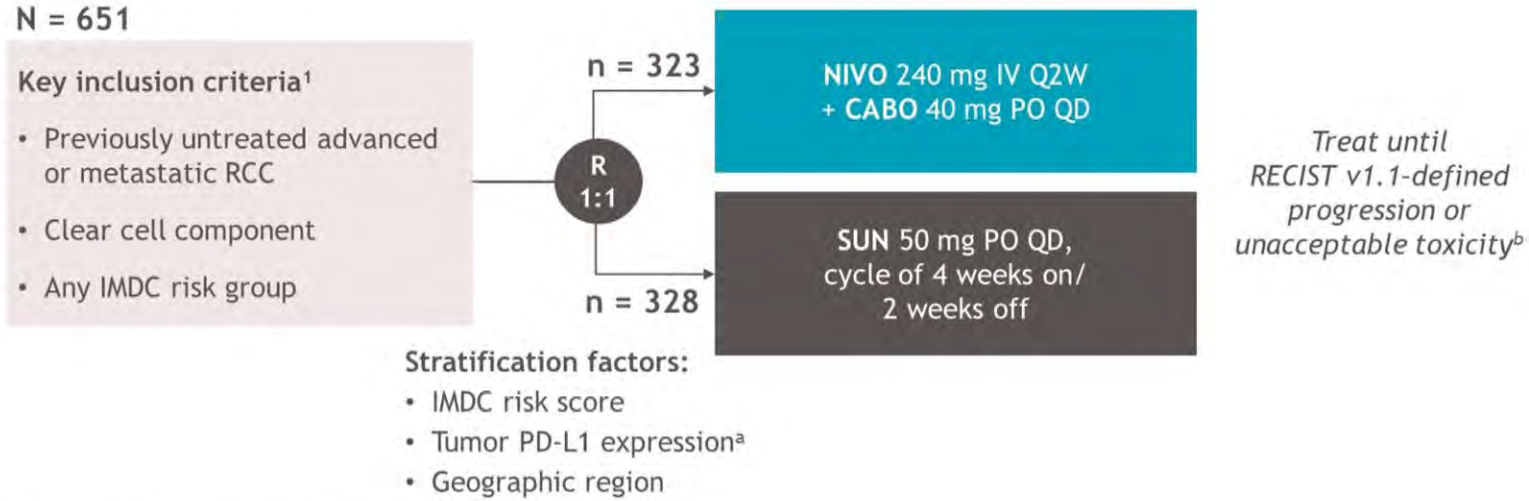
Rini et al, 2020 ASCO meeting

Motzer et al, 2021 GU ASCO Meeting

Motzer et al, NEJM 2021

Association between depth of response and clinical outcomes: exploratory analysis in patients with previously untreated advanced renal cell carcinoma in CheckMate 9ER

Cristina Suárez,[1] Toni K. Choueiri,[2] Mauricio Burotto,[3] Thomas Powles,[4] Maria T. Bourlon,[5] Amishi Y. Shah,[6] Yoshihiko Tomita,[7] Jens Bedke,[8] Joshua Zhang,[9] Burcin Simsek,[9] Christian Scheffold,[10] Bernard Escudier,[11] Robert J. Motzer,[12] Andrea B. Apolo[13]



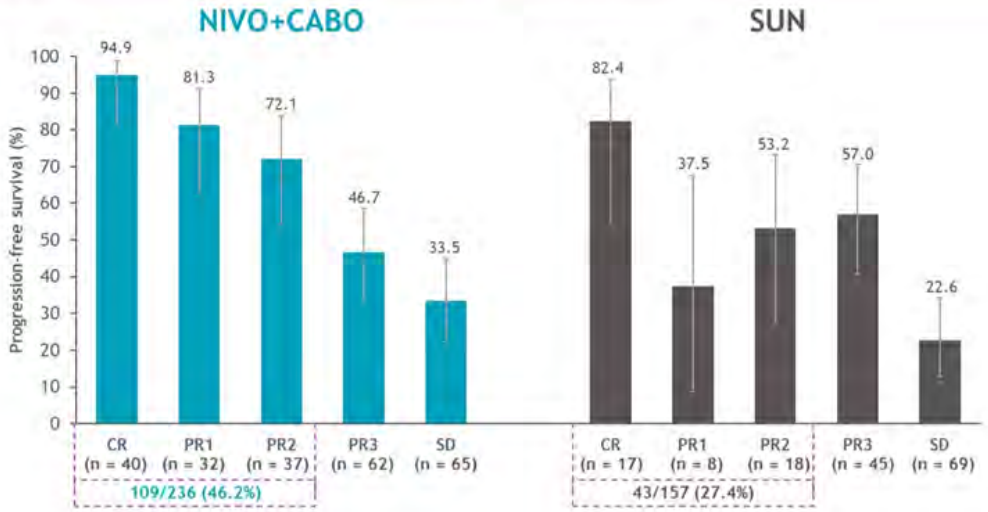
Primary endpoint: PFS per BICR (RECIST v1.1)
Secondary endpoints: OS, ORR per BICR (RECIST v1.1), and safety

DepOR subgroup	Definition
CR	Complete response
PR1	PR with best % reduction in sum of diameters for target lesions by ≥ 80%
PR2	PR with best % reduction in sum of diameters for target lesions by ≥ 60% to < 80%
PR3	PR with best % reduction in sum of diameters for target lesions by < 60%
SD	Stable disease
PD	Progressive disease

Suarez et al. J Clin Oncol 40, 2022 (suppl 16; abstr 4501)

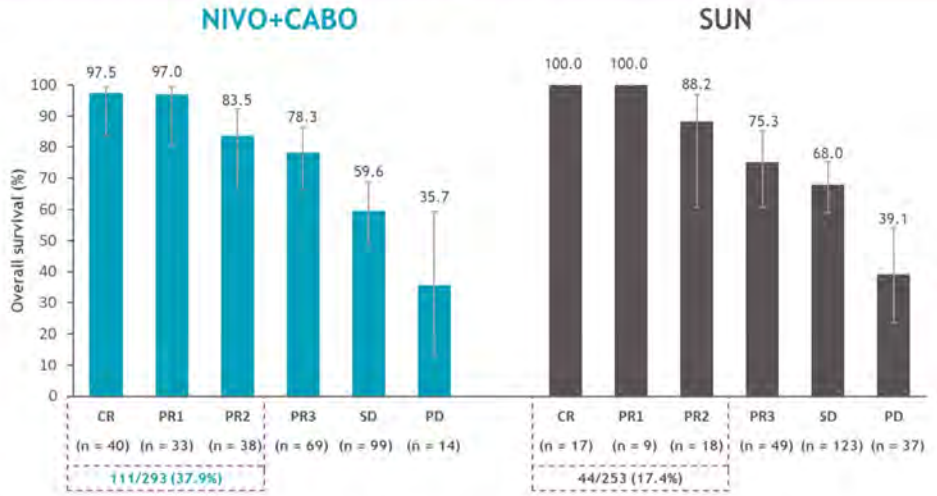
DepOR associated with improvement in PFS/OS

12-month PFS rates by DepOR subgroups[a,b]



- Deeper responses led to improved 12-month PFS rates

8-month OS rates by DepOR subgroups[a]



Increasingly deeper responses led to better OS outcomes

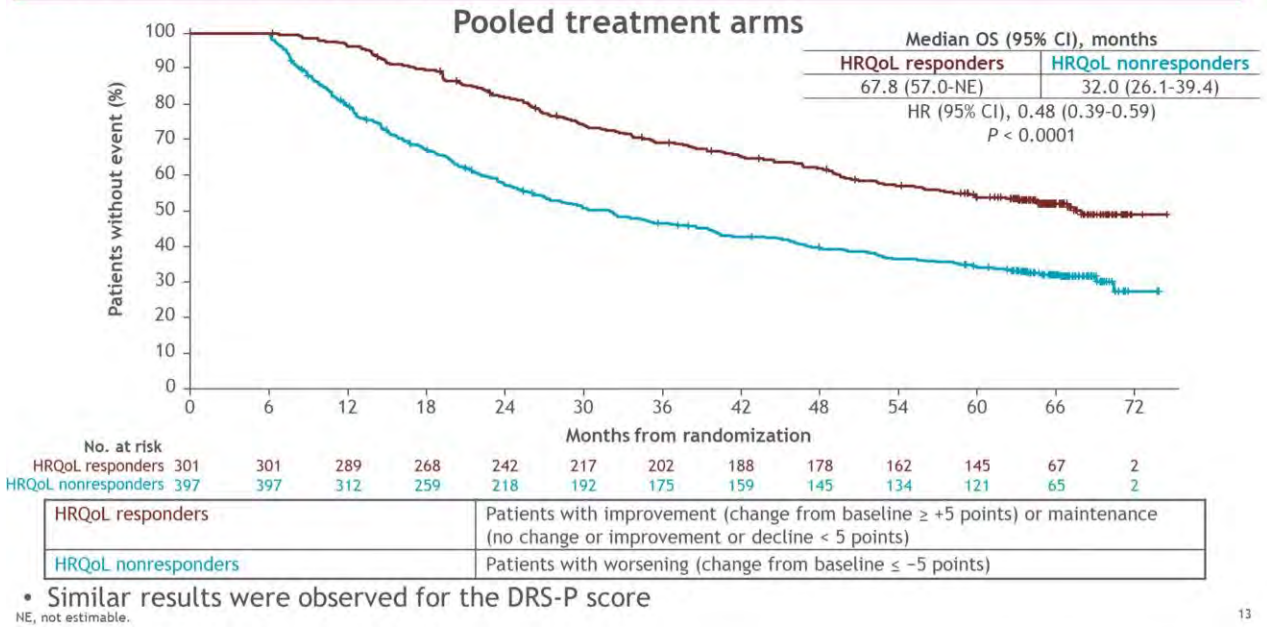
Suarez et al. J Clin Oncol 40, 2022 (suppl 16; abstr 4501)

The relationship between health-related quality of life and clinical outcomes in patients with advanced renal cell carcinoma in CheckMate 214

David Cella,[1] Melissa Hamilton,[2] Steven Blum,[2] Cristina Ivanescu,[3] Abi Williams,[4] Flavia Ejzykowicz,[2] Robert J. Motzer[5]

Landmark analysis: Overall Survival by FKSI-19 total score response at 6 months (threshold = 5)

CheckMate 214



HRQoL responders	Patients with improvement (change from baseline ≥ +5 points) or maintenance (no change or improvement or decline < 5 points)
HRQoL nonresponders	Patients with worsening (change from baseline ≤ −5 points)

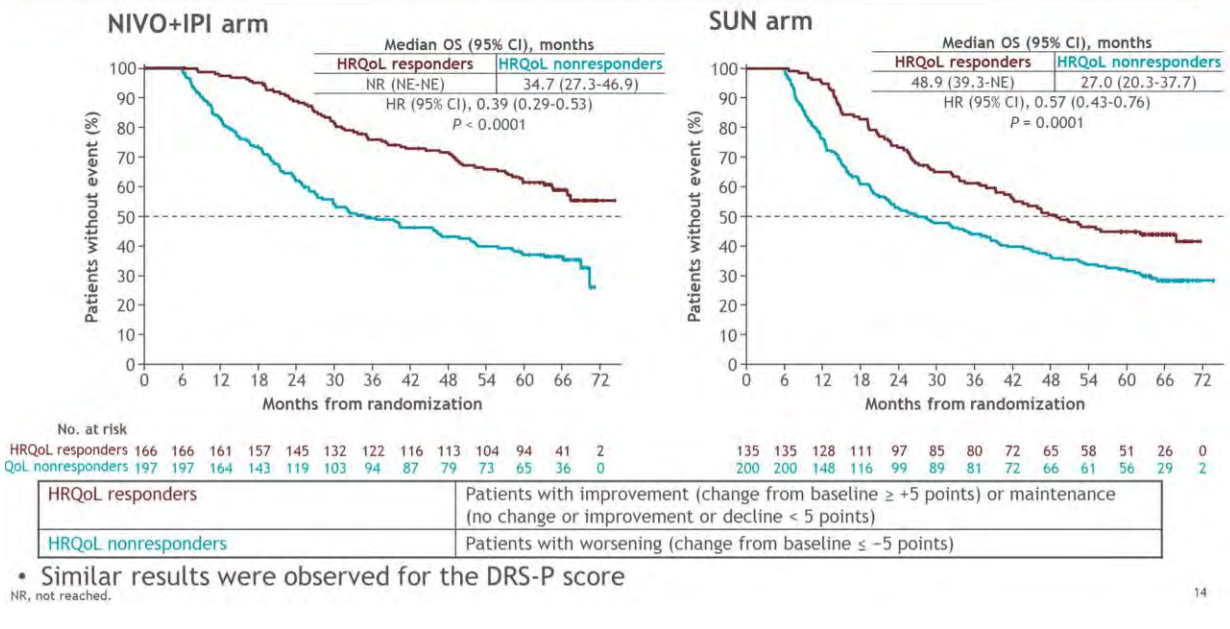
- Similar results were observed for the DRS-P score

NE, not estimable.

13

Landmark analysis: Overall Survival by FKSI-19 total score response at 6 months (threshold = 5)

CheckMate 214



HRQoL responders	Patients with improvement (change from baseline ≥ +5 points) or maintenance (no change or improvement or decline < 5 points)
HRQoL nonresponders	Patients with worsening (change from baseline ≤ −5 points)

- Similar results were observed for the DRS-P score

NR, not reached.

14

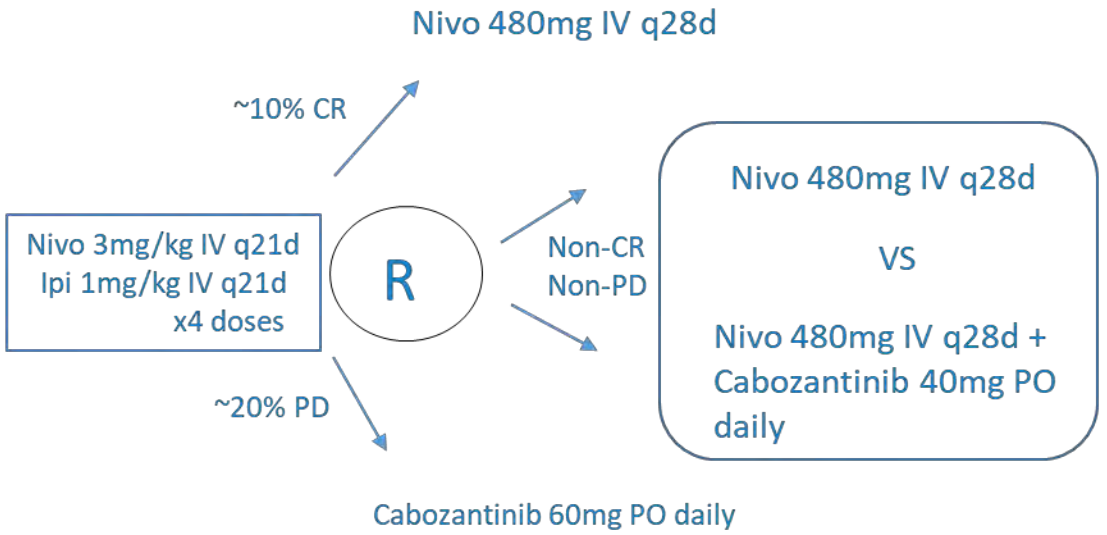
Cella et al. J Clin Oncol 40, 2022 (suppl 16; abstr 4502)

PDIGREE Trial

Metastatic RCC

Key Inclusion:

1. Metastatic clear cell RCC without prior systemic therapy
2. IMDC intermediate or poor risk
3. Archival tissue available or fresh biopsy



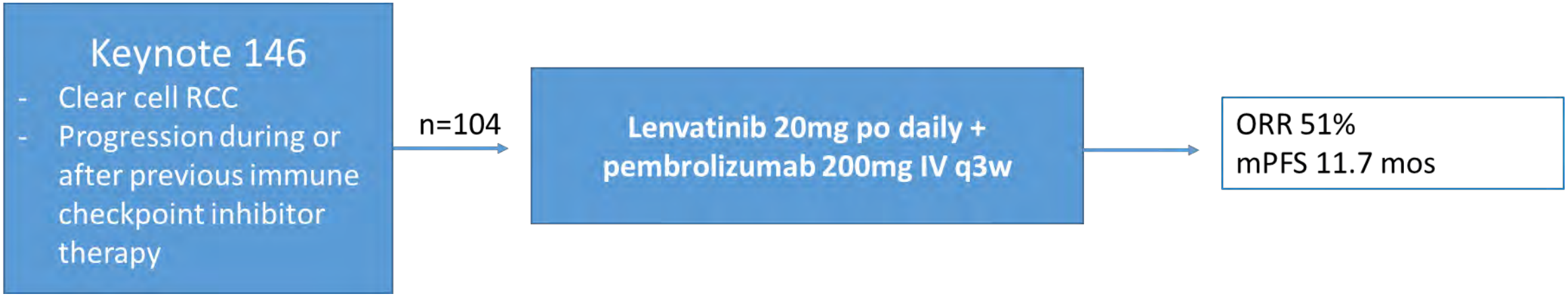
Discontinue:
Progression of disease
OR
Unacceptable toxicity
OR
CR at 1 year

PDIGREE: Alliance trial A031704
NCT03793166

Subsequent therapy for metastatic RCC

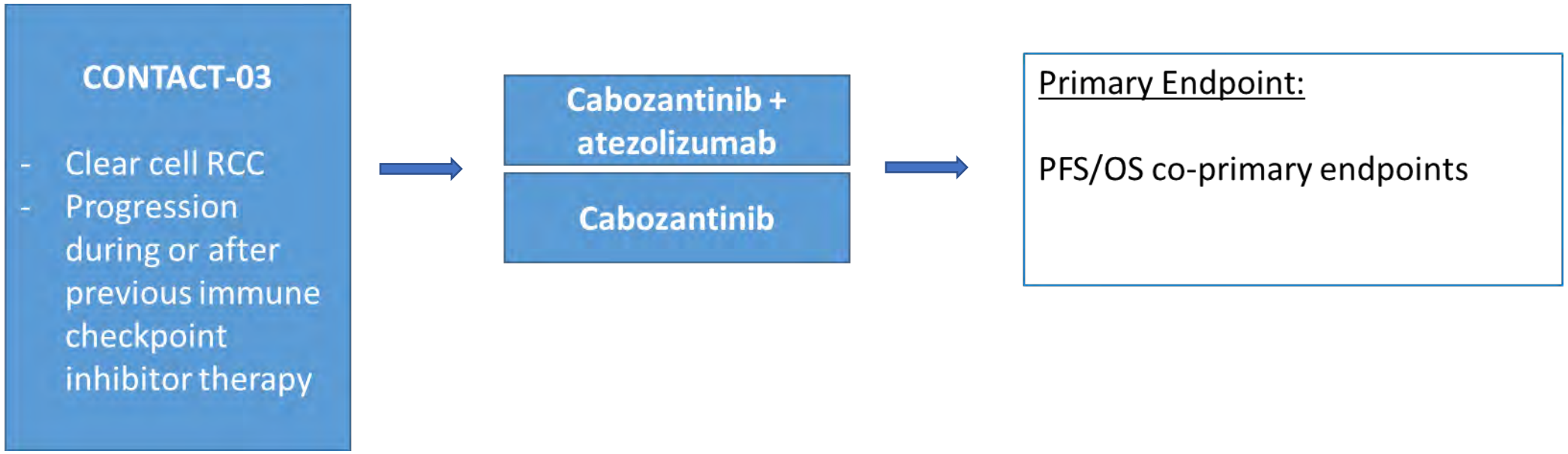
SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• Cabozantinib (category 1) • Lenvatinib + everolimus • Nivolumab[b] (category 1)	• Axitinib (category 1) • Axitinib + pembrolizumab[b] • Cabozantinib + nivolumab[b] • Ipilimumab + nivolumab[b] • Lenvatinib + pembrolizumab[b] • Pazopanib • Sunitinib • Tivozanib[g] (category 1) • Axitinib + avelumab[b] (category 3)	• Everolimus • Bevacizumab[f] (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Sorafenib (category 3) • Temsirolimus[e] (category 2B) • Belzutifan (category 2B)

What is the role for ICI combinations after prior exposure?



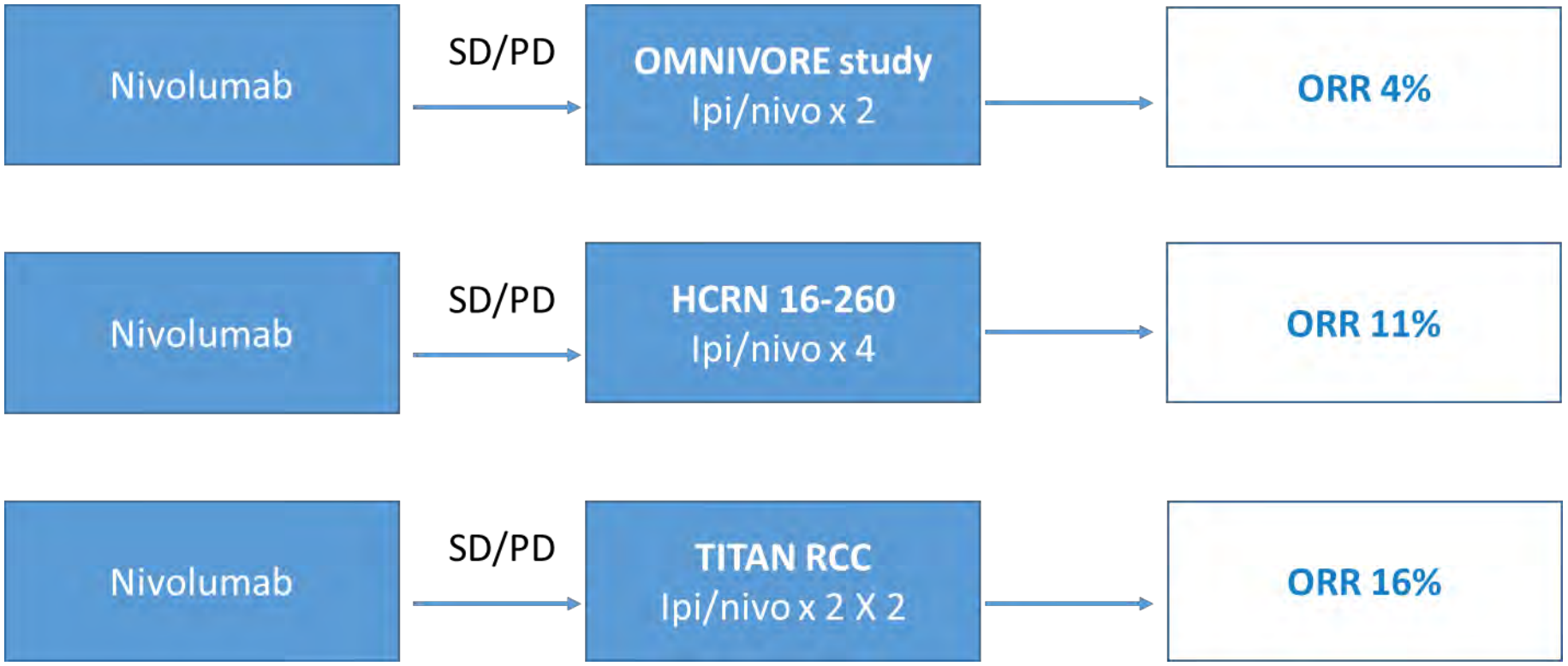
Lee et al. J Clin Oncol 38: 2020 (suppl; abstr 5008).

CONTACT-03



NCT04338269
Rose T. Immunotherapy for Kidney Cancer. SITC 2021

Any role for salvage Ipilimumab?



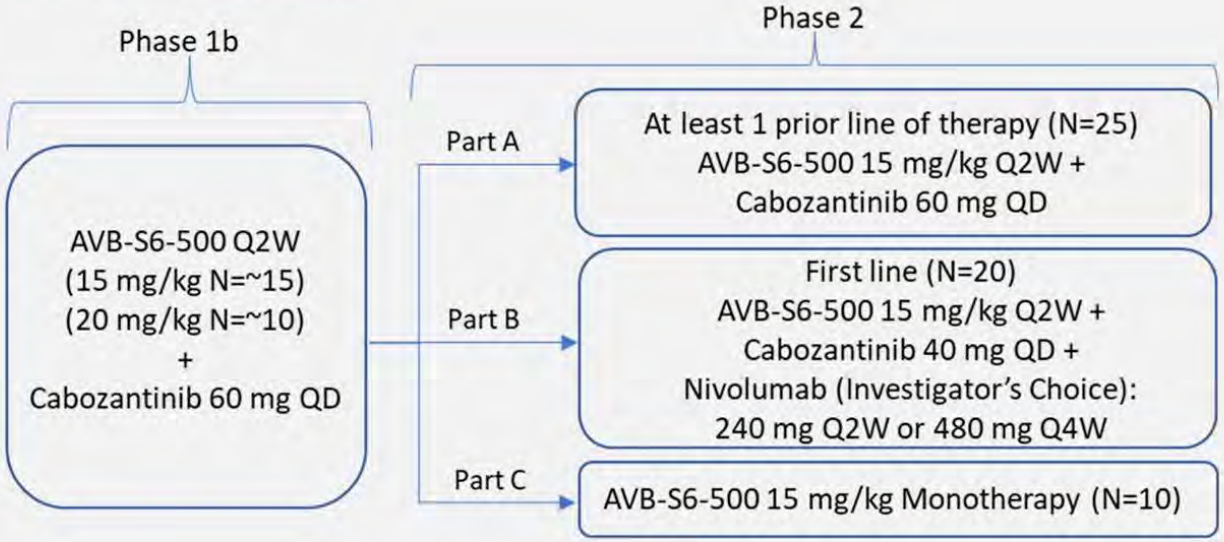
McKay et al. *J Clin Oncol*. 2020:20;38:4240-48.
Atkins et al. J Clin Oncol 38: 2020 (suppl; abstr 5006)
Oliver-Grim et al. J Clin Oncol 39, 2021 (suppl 15; abstr 4576)
Rose T. Immunotherapy for Kidney Cancer. SITC 2021

Phase 1b/2 Study of Batiraxcept (AVB-S6-500) in combination with cabozantinib ccRCC who received front-line treatment

Batiraxcept + Cabozantinib Phase 1b Trial Design

Patient Population

- Advanced or metastatic ccRCC
- Progressed on/after front-line treatment
- Prior cabozantinib treatment was excluded

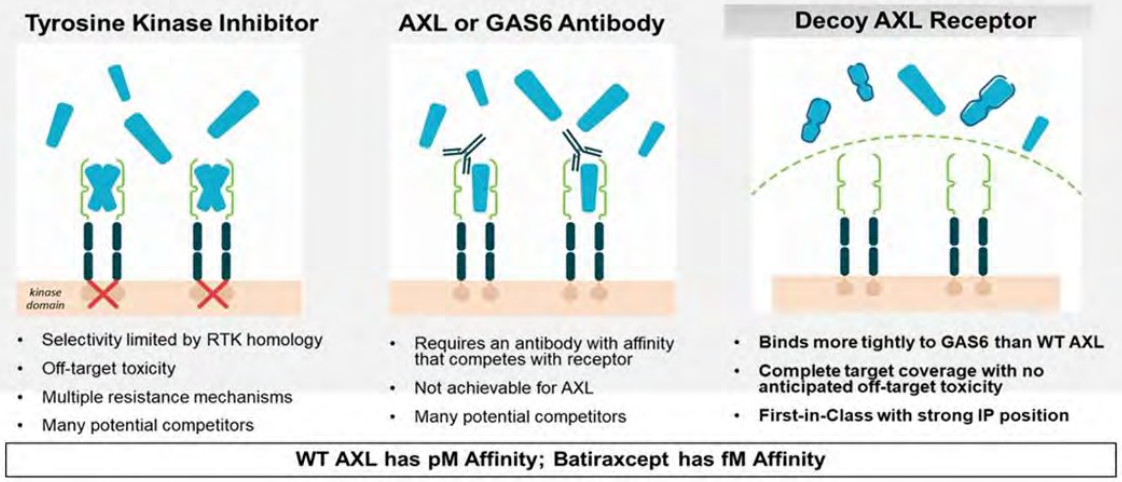


Shah et al. J Clin Oncol 40, 2022 (suppl 16; abstr 4511)
Kapoor A. Moving Beyond TKI and Immuno-Oncology in RCC. ASCO Annual Meeting 2022

Rationale for targeting AXL

Role of AXL Inhibition in ccRCC

- AXL receptor and its activating ligand, GAS6, drive metastasis and therapeutic resistance in cancer
  - AXL is up-regulated by HIF-1 signaling in VHL-deficient and hypoxic tumor cells
  - AXL overexpression is strongly correlated with ccRCC patient prognosis and survival
- Batiraxcept (AVB-S6-500) is a recombinant fusion protein containing an extracellular region of human AXL combined with the human immunoglobulin G1 heavy chain (Fc)
  - Highly potent and specific AXL inhibition
  - Batiraxcept binds GAS6, thus inhibiting interaction with AXL and reducing invasion and migration of human cancers
  - Well tolerated in prior trials, with infusion related reaction and fatigue being the most common AEs



Shah et al. J Clin Oncol 40, 2022 (suppl 16; abstr 4511)
Kapoor A. Moving Beyond TKI and Immuno-Oncology in RCC. ASCO Annual Meeting 2022

Results

Phase 1b Efficacy Results

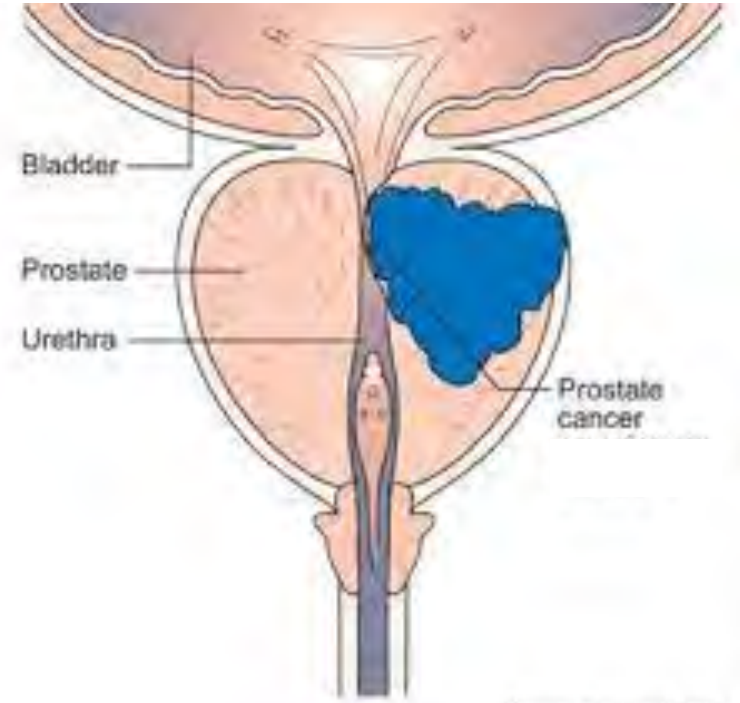
- 42% confirmed ORR for batiraxcept + cabozantinib exceeds historical cabozantinib monotherapy ORR of 17-27.8%

Table 5	Efficacy Overall		
Best Overall Response assessed by Investigator per RECIST v1.1	All Patients N = 26 (%)	15 mg/kg N = 16 (%)	20 mg/kg N = 10 (%)
Confirmed Partial Response (PR)	11 (42)	8 (50)	3 (30)
Unconfirmed PR	1 (4)	0	1 (10)
Stable Disease (SD)	11 (42)	6 (38)	5 (50)
Progressive Disease (PD)[2]	3 (12)	2 (12)	1 (10)
PR for Patients in Biomarker Low (sAXL/GAS6)	0/5 (0)	0/4 (0)	0/1 (0)
PR for Patients in Biomarker High (sAXL/GAS6)	12/20 (60)	8/12 (67)	4/8 (50)

Data cutoff April 30, 2022

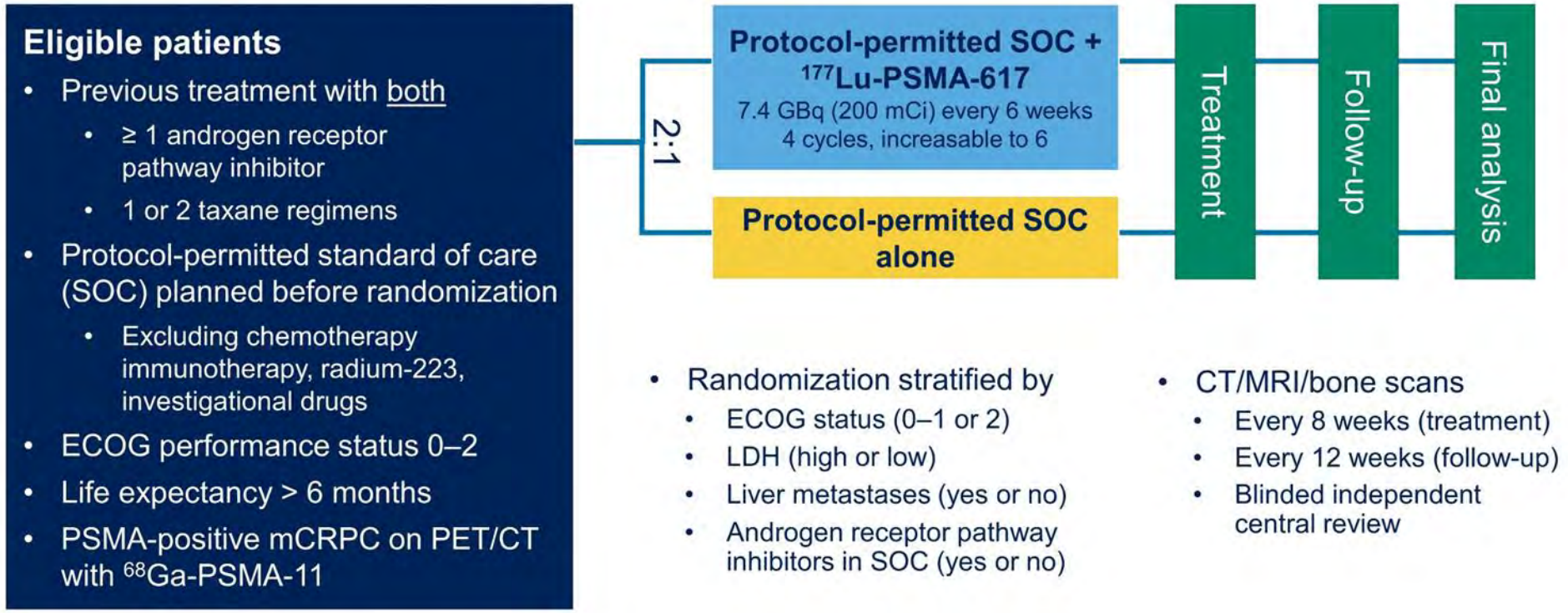
Shah et al. J Clin Oncol 40, 2022 (suppl 16; abstr 4511)
Kapoor A. Moving Beyond TKI and Immuno-Oncology in RCC. ASCO Annual Meeting 2022

Updates in Prostate Cancer



VISION Study

Open-label study of protocol-permitted standard of care ± ^{177}Lu-PSMA-617 in adults with PSMA-positive mCRPC



Morris M. J Clin Oncol 39, 2021 (suppl 15; abstr LBA4);
Sartor et al. *N Engl J Med*. 2021;385:1091-1103.

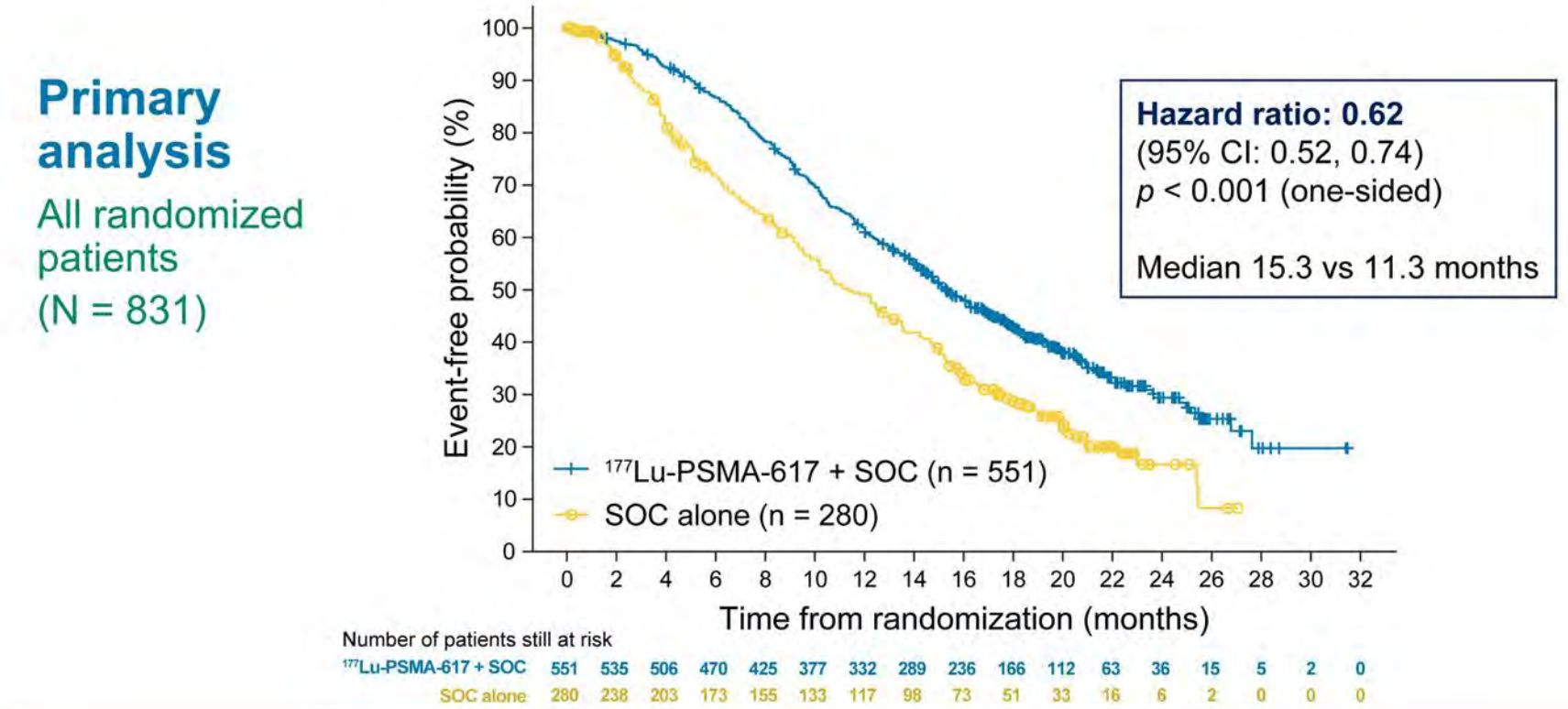
VISION Study

16

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

Primary analysis

All randomized patients (N = 831)

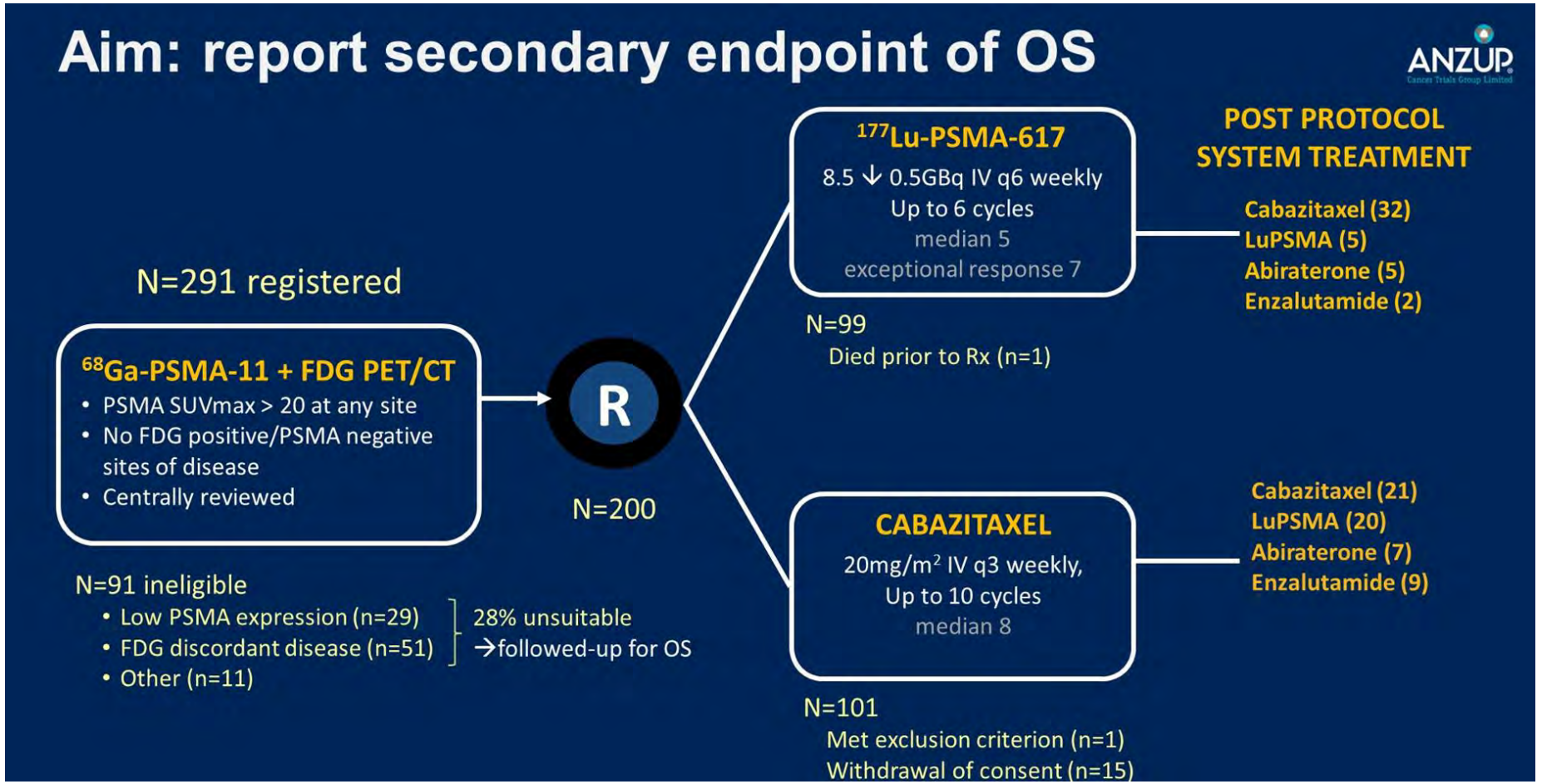


Morris M. J Clin Oncol 39, 2021 (suppl 15; abstr LBA4);
Sartor et al. *N Engl J Med*. 2021;385:1091-1103.

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

(TheraP ANZUP 1603)

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



Hofman et al. J Clin Oncol 40, 2022 (suppl 16; abstr 5000)

TheraP: First randomized trial of LuPSMA vs. cabazitaxel[1]

50% MEN TREATED WITH
CABAZITAXEL
20mg/m2 IV q3 weekly
Up to 10 cycles

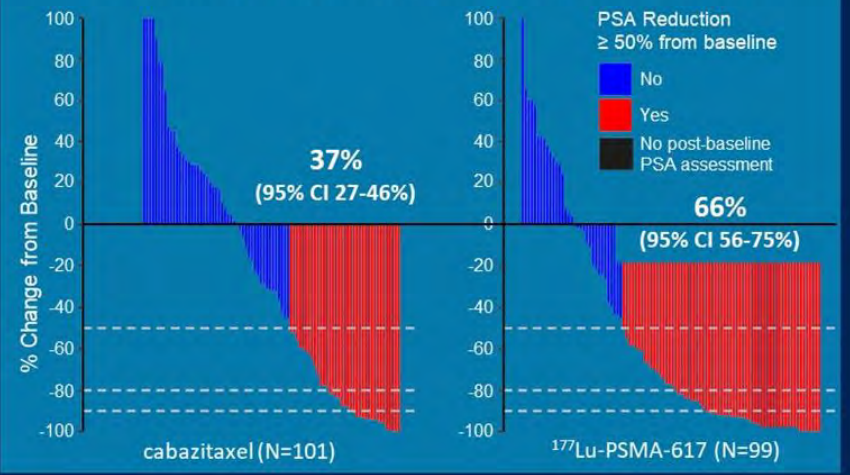
50% MEN TREATED WITH
^{177}Lu-PSMA-617
8.5 GBq IV q6 weekly
↓ 0.5 GBq each cycle
Up to 6 cycles

1° endpoint

PSA Reduction
≥ 50% from baseline

37%
66%

^{177}Lu-PSMA-617: 29% (95% CI 16%-42%; p<0.0001) greater PSA50-RR



2° endpoints

Progression Free Survival
at 12 months

3%
19%

Objective Response Rate
on CT Scan (RECIST)

24%
49%

Troublesome Adverse Events
Grade 3-4

53%
33%

Patient Reported Outcomes

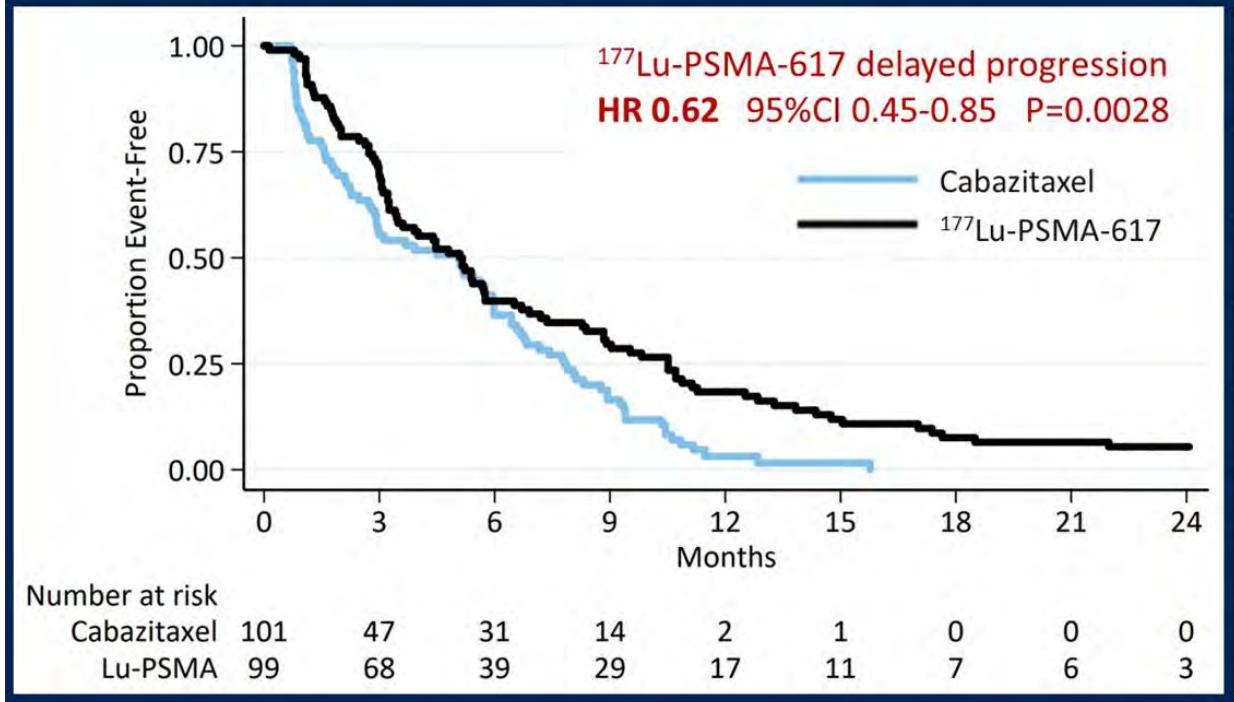
Diarrhea
Fatigue
Hair loss
Urinary symptoms
Dizziness
skin rash
Painful hands/feet
Insomnia

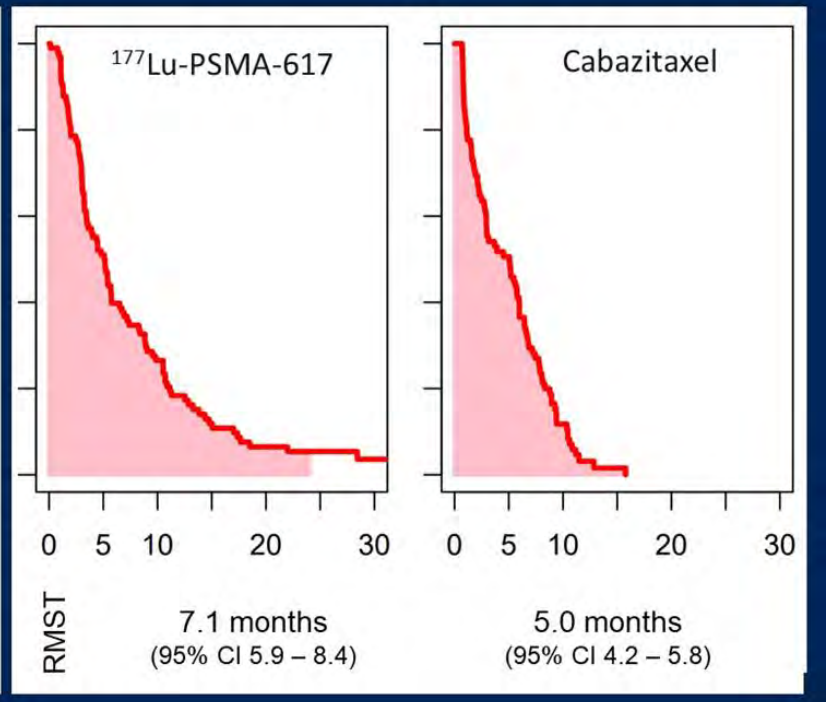
[1] Hofman MS et al, Lancet 2021; 397(10276)

Hofman et al. J Clin Oncol 40, 2022 (suppl 16; abstr 5000)

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

Progression Free Survival (PSA and radiographic)

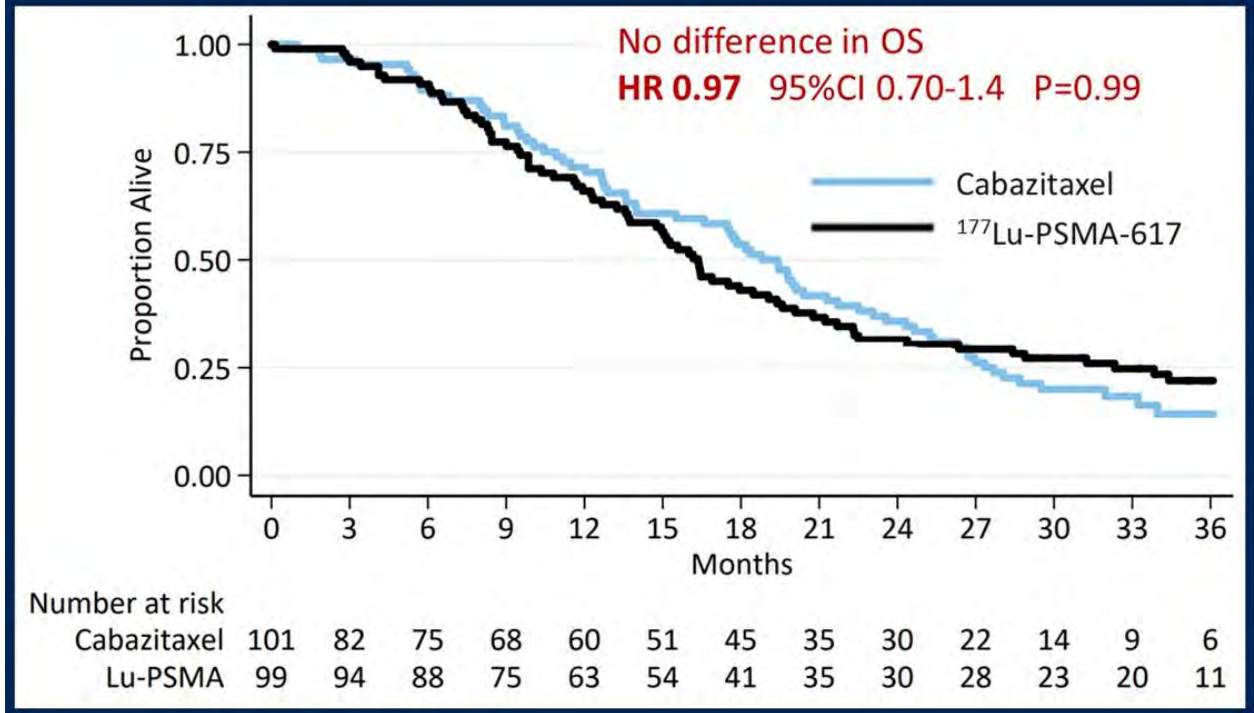


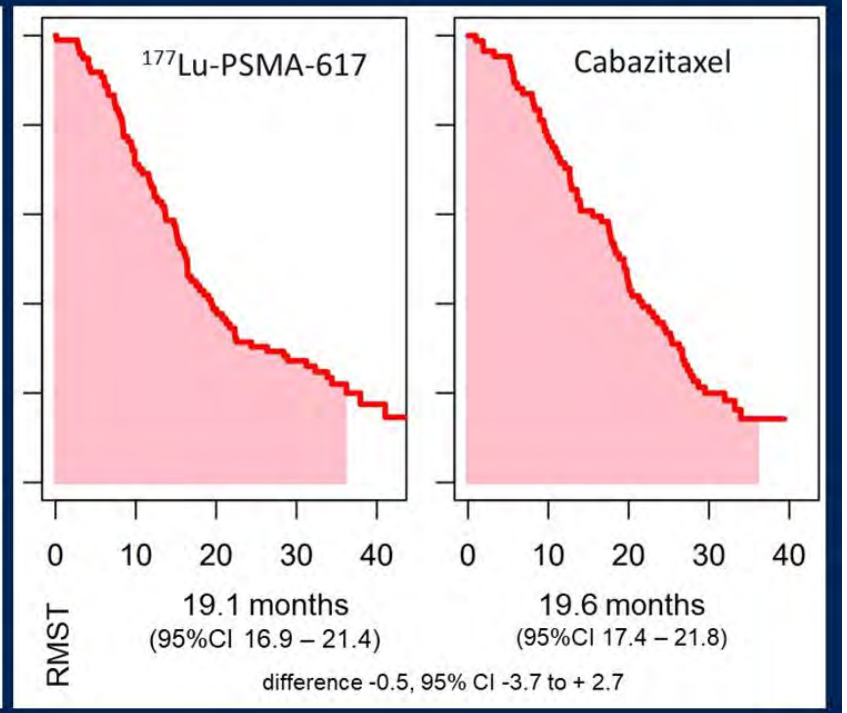


- Treatment effect not constant with respect to time → restricted mean survival time (RMST)
- 177 progression events. Cut-off 31 DEC 2020 for non-OS endpoints.
- Similar HR for rPFS (0.65) and PSA-PFS (0.60), and in per-protocol sensitivity analyses

Hofman et al. J Clin Oncol 40, 2022 (suppl 16; abstr 5000)

Overall survival (ITT)





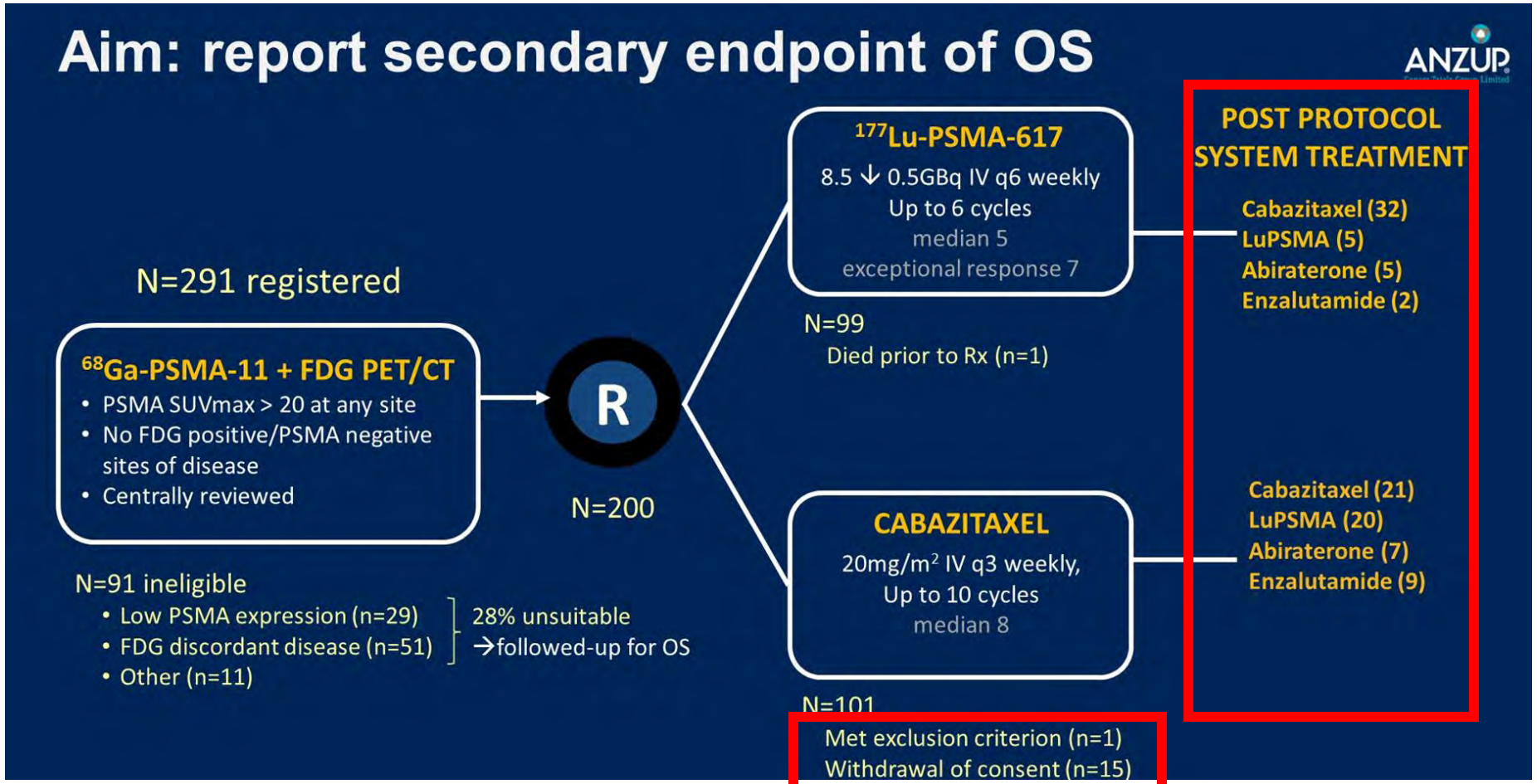
- Cut-off 31 DEC 2021 for OS
- At 36 months follow-up, death reported in 147/200; 70/101 assigned cabazitaxel vs. 77/99 assigned LuPSMA
- Per-protocol analysis: no difference in OS
- No additional safety signals with longer follow-up.

Hofman et al. J Clin Oncol 40, 2022 (suppl 16; abstr 5000)

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

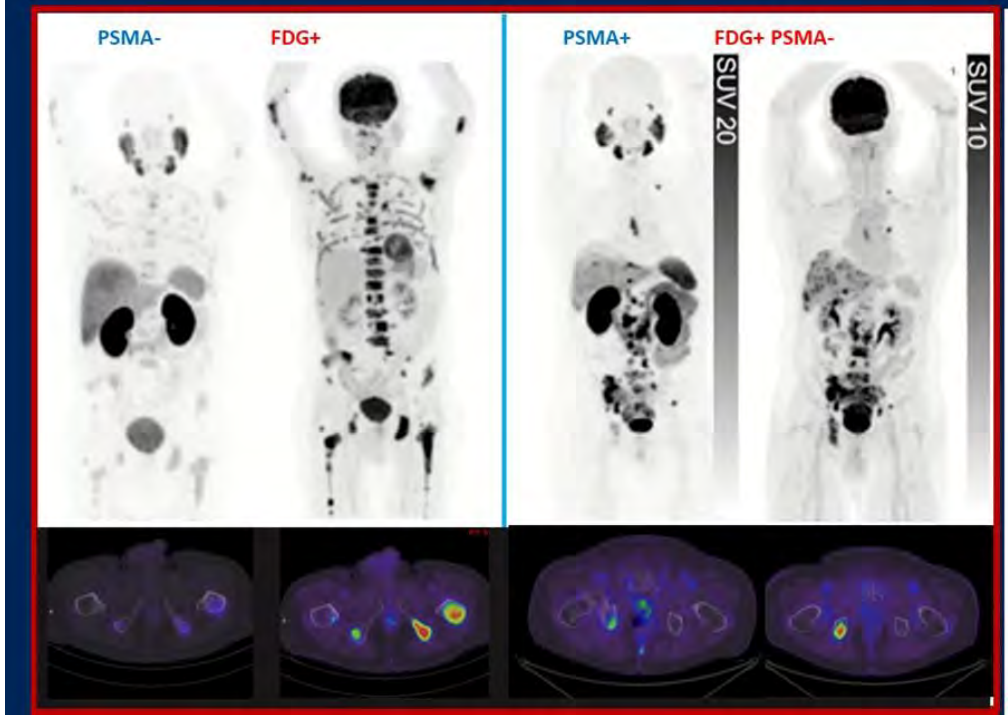
(TheraP ANZUP 1603)

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



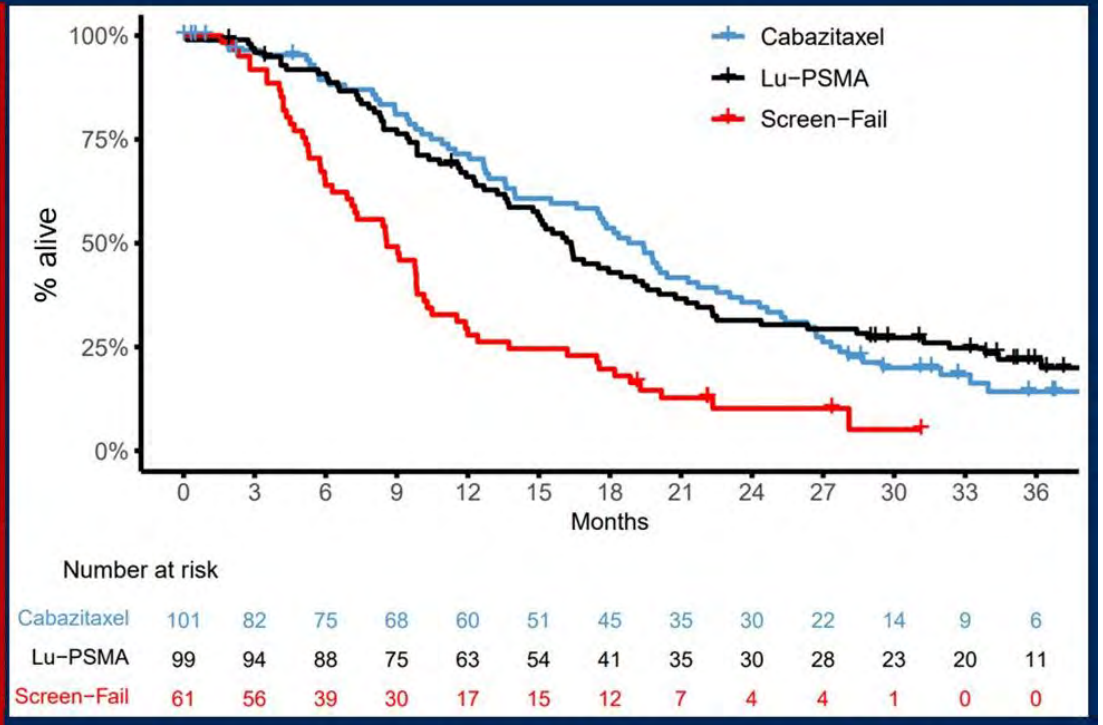
Hofman et al. J Clin Oncol 40, 2022 (suppl 16; abstr 5000)

OS of PSMA/FDG PET Screen Failures



n=51(18%) n=29 (10%)

Ineligible (n=80, 28%)



Number at risk

Cabazitaxel	101	82	75	68	60	51	45	35	30	22	14	9	6
Lu−PSMA	99	94	88	75	63	54	41	35	30	28	23	20	11
Screen−Fail	61	56	39	30	17	15	12	7	4	4	1	0	0

Next line of treatment: cabazitaxel 29 (48%), enzalutamide 4 (7%), LuPSMA 3 (5%), carboplatin 3 (5%), other 3 (5%), mitoxantrone 1 (2%)

Patients met other TheraP trial eligibility criteria.
61 of 80 consented for follow-up

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Conclusion

The TheraP data support the choice of ^{177}Lu-PSMA-617 over cabazitaxel for patients with PSMA-positive, progressive mCRPC after docetaxel and androgen-receptor pathway inhibitor, on the basis of its higher PSA response rate, greater PFS benefit, QoL benefits, favorable safety profile and dosing schedule, and similar survival outcomes.

Survival was considerably shorter for patients excluded on PSMA/FDG-PET with either low PSMA-expression, or discordant disease.

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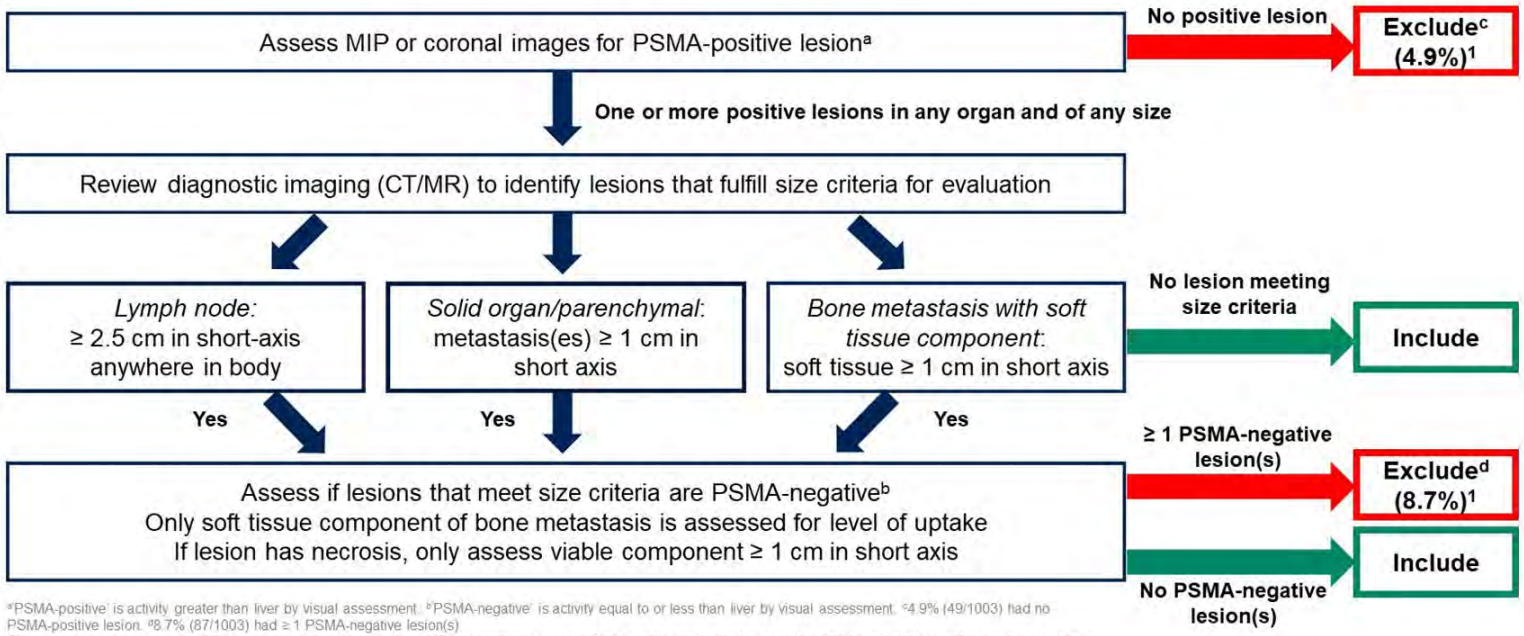
[^{68}Ga]Ga-PSMA-11 PET baseline imaging as a prognostic tool for clinical outcomes to [^{177}Lu]Lu-PSMA-617 in patients with mCRPC

A VISION sub-study

Andrew J Armstrong, Duke University, Durham, NC, USA

Co-authors: PH Kuo, J Hesterman, K Rahbar, AT Kendi, XX Wei, B Fang, N Adra, R Garje, JM Michalski, S Ghebremariam, M Brackman, C Wong, T Benson, NJ Vogelzang

^{68}Ga-PSMA-11 PET/CT for patient selection



[a]'PSMA-positive' is activity greater than liver by visual assessment. [b]'PSMA-negative' is activity equal to or less than liver by visual assessment. [c]4.9% (49/1003) had no PSMA-positive lesion. [d]8.7% (87/1003) had ≥ 1 PSMA-negative lesion(s)
CT, computerized tomography; MIP, maximum intensity projection; MR, magnetic resonance; PET, positron emission tomography; PSMA, prostate-specific membrane antigen
1. Sartor O *et al. N Engl J Med* 2021;385:1091–103. Figure adapted from: Kuo PH *et al. J Nucl Med* 2022;10.2967/jnumed.121.263638

VISION sub-study: quantitative imaging analysis in the ^{177}Lu-PSMA-617 + SoC group

Objective: to assess the association between quantitative parameters from pre-treatment ^{68}Ga-PSMA-11 PET/CT scans and outcomes (rPFS, OS, ORR and PSA response[a]) with ^{177}Lu-PSMA-617 therapy

Whole-body PSMA PET parameters

- SUV_{mean}

Definition

- **SUV:** the ratio of activity per unit volume of a region of interest to the activity per unit whole-body volume (segmented PSMA-positive disease within the whole body for this analysis)
- **SUV_{mean}:** the mean number of counts from all voxels within the whole body, including all lesions pooled together
  - A voxel is a component of an array of imaging elements of volume that represent 3D space

[a]PSA response defined as ≥ 50% decrease from baseline

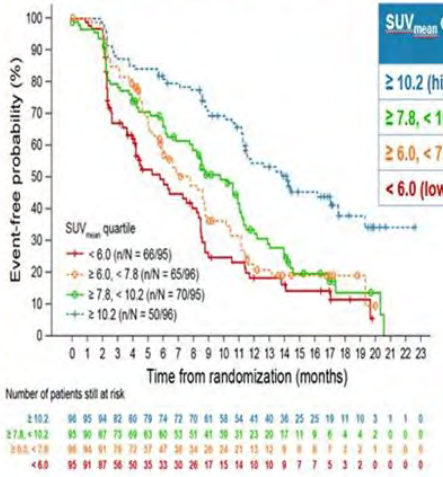
CT, computerized tomography; ORR, objective response rate; OS, overall survival; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; rPFS, radiographic progression-free survival; SoC, protocol-permitted standard of care; SUV, standardized uptake value

Armstrong et al. J Clin Oncol 40, 2022 (suppl 16; abstr 5002)

Associations between whole-body quantitative imaging parameters and clinical outcome

rPFS by whole-body SUV_{mean} quartiles (PFS-FAS)

- Higher whole-body SUV_{mean} was associated with prolonged rPFS



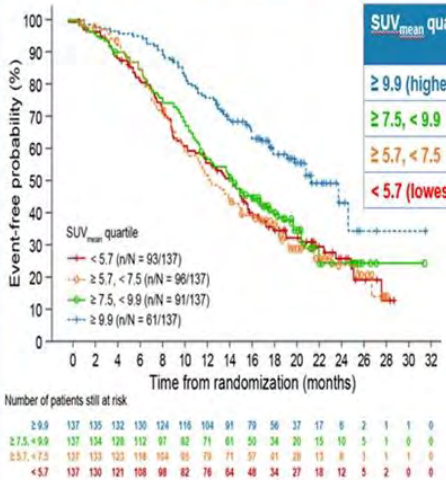
SUV_{mean} quartile	Median rPFS (months)
≥ 10.2 (highest)	14.1
≥ 7.8, < 10.2	9.8
≥ 6.0, < 7.8	7.8
< 6.0 (lowest)	5.8

SUV_{mean}	rPFS HR [95% CI], *p* value
Univariate analysis	**0.88** [0.84, 0.91], < 0.001
Multivariate analysis	**0.86** [0.82, 0.90], < 0.001

CI, confidence interval; HR, hazard ratio; PFS-FAS, progression-free survival-full analysis set; rPFS, radiographic progression-free survival; SUV, standardized uptake value

OS by whole-body SUV_{mean} quartiles (FAS)

- Higher whole-body SUV_{mean} was associated with improved OS



SUV_{mean} quartile	Median OS (months)
≥ 9.9 (highest)	21.4
≥ 7.5, < 9.9	14.6
≥ 5.7, < 7.5	12.6
< 5.7 (lowest)	14.5

SUV_{mean}	OS HR [95% CI], *p* value
Univariate analysis	**0.92** [0.89, 0.95], < 0.001
Multivariate analysis	**0.88** [0.84, 0.91], < 0.001

CI, confidence interval; HR, hazard ratio; FAS, full-analysis set; OS, overall survival; SUV, standardized uptake value

Armstrong et al. J Clin Oncol 40, 2022 (suppl 16; abstr 5002)

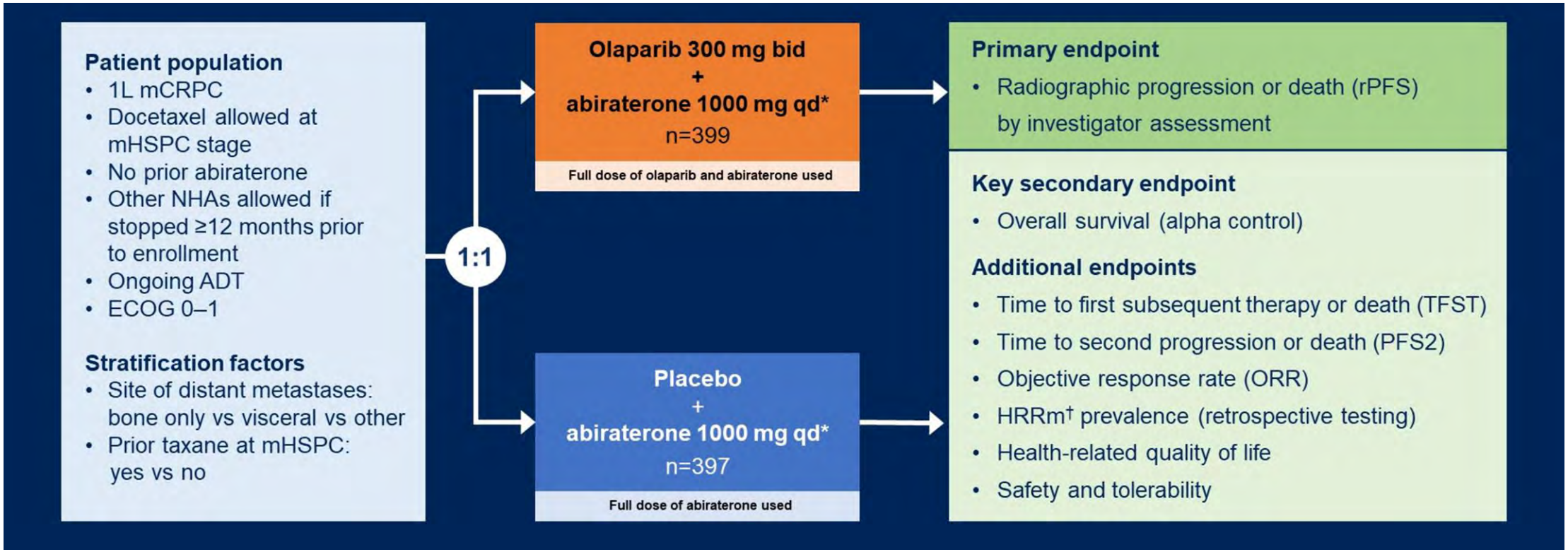
Takeaways…

- Among men treated with 177-Lu-PSMA-617 with PSMA-positive mCRPC on PET/CT, a higher whole-body SUV_{mean} was strongly associated with improved long-term clinical outcomes
  - Patients in the highest SUV_{mean} quartile had rPFS of 14.1 months and OS of 21.4 months,
    vs 5.8 and 14.5 months for those in the lowest quartile, along with improved objective and PSA responses
- The absence of PSMA+ metastatic lesions in liver or bone was associated with improved rPFS and overall survival

Armstrong et al. J Clin Oncol 40, 2022 (suppl 16; abstr 5002)

PROpel: phase III trial of olaparib and abiraterone versus placebo and abiraterone as first-line therapy for patients with metastatic castration-resistant prostate cancer

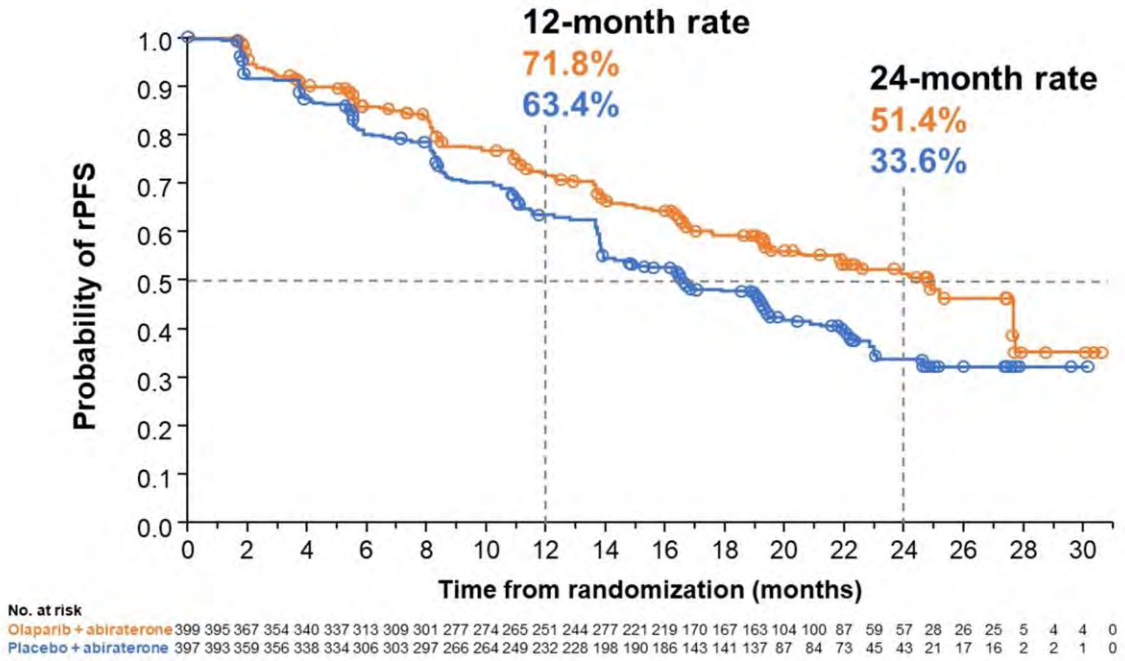
Fred Saad, Andrew J. Armstrong, Antoine Thiery-Vuillemin, Mototsugu Oya, Eugenia Loredo, Giuseppe Procopio, Juliana de Menezes, Gustavo Girotto, Cagatay Arslan, Niven Mehra, Francis Parnis, Emma Brown, Friederike Schlürmann, Jae Young Joung, Mikio Sugimoto, Christian Poehlein, Elizabeth A. Harrington, Chintu Desai, Jinyu Kang, and Noel Clarke



Saad et al. J Clin Oncol 40, 2022 (suppl 6; abstr 11)

PROpel primary endpoint: rPFS by investigator-assessment

34% risk reduction of progression or death with olaparib + abiraterone



	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
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	

Pre-specified 2-sided alpha: 0.0324

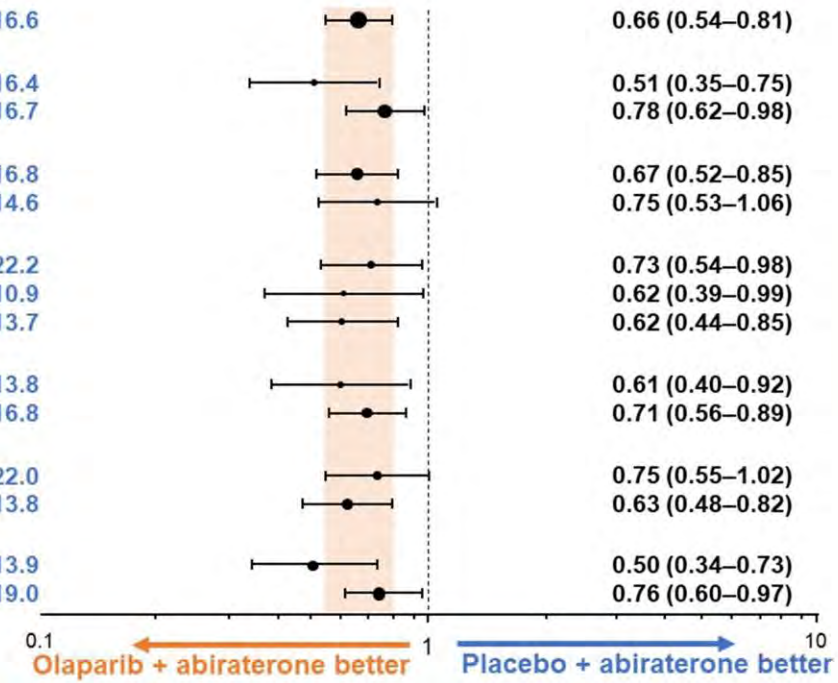
Median rPFS improvement of 8.2 months favors olaparib + abiraterone*

Saad et al. J Clin Oncol 40, 2022 (suppl 6; abstr 11)

PROpel: subgroup analysis of rPFS

rPFS benefit observed across all pre-specified subgroups

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



Global interaction test not significant

Saad et al. J Clin Oncol 40, 2022 (suppl 6; abstr 11)

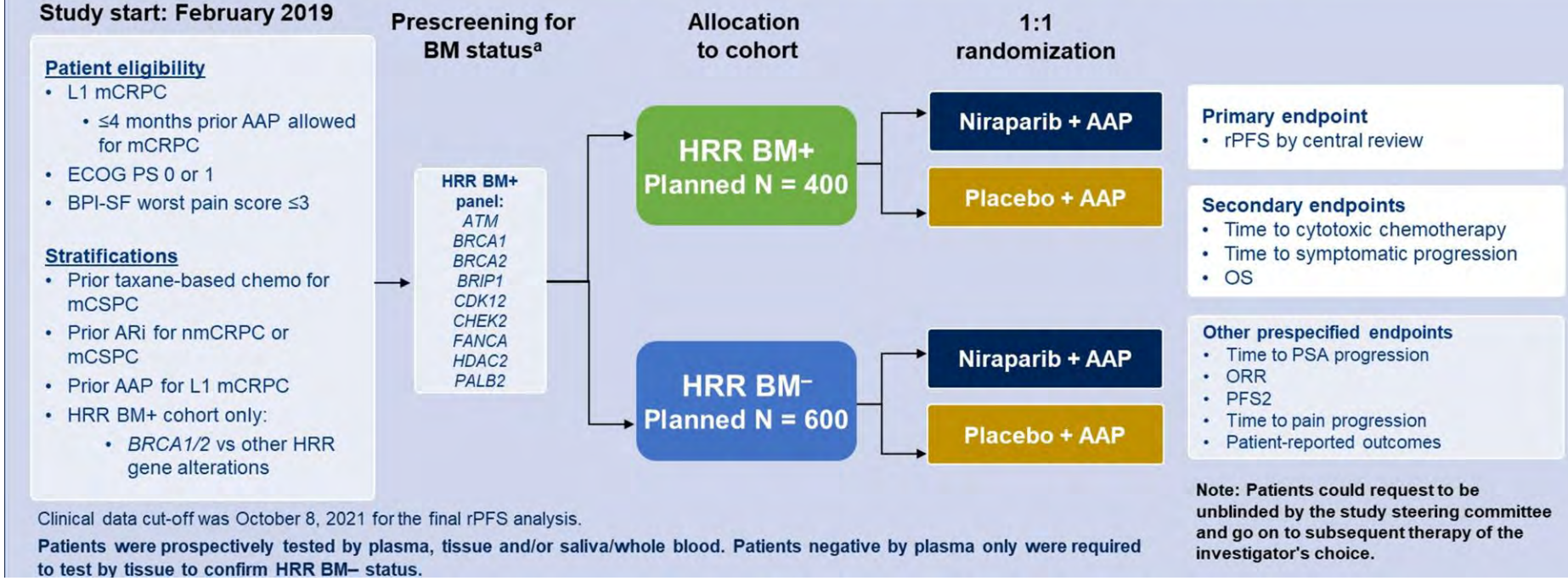
UNC LINEBERGER COMPREHENSIVE CANCER CENTER

Phase 3 MAGNITUDE study: First results of niraparib (NIRA) with abiraterone acetate and prednisone (AAP) as first-line therapy in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) with and without homologous recombination repair (HRR) gene alterations

Kim N. Chi,[1] Dana E. Rathkopf,[2] Matthew R. Smith,[3] Eleni Efstathiou,[4] Gerhardt Attard,[5] David Olmos,[6] Ji Youl Lee,[7] Eric J. Small,[8] Andrea J. Pereira de Santana Gomes,[9] Guilhem Roubaud,[10] Marniza Saad,[11] Bogdan Zurawski,[12] Valerii Sakalo,[13] Gary E. Mason,[14] Adam del Corral,[15] George Wang,[14] Daphne Wu,[16] Brooke Diorio,[17] Angela Lopez-Gitlitz,[16] Shahneen Sandhu[18]

MAGNITUDE: Randomized, Double-Blind, Placebo-Controlled Study [3]

Prospectively selected biomarker cohorts designed to test HRR BM+ and HRR BM–



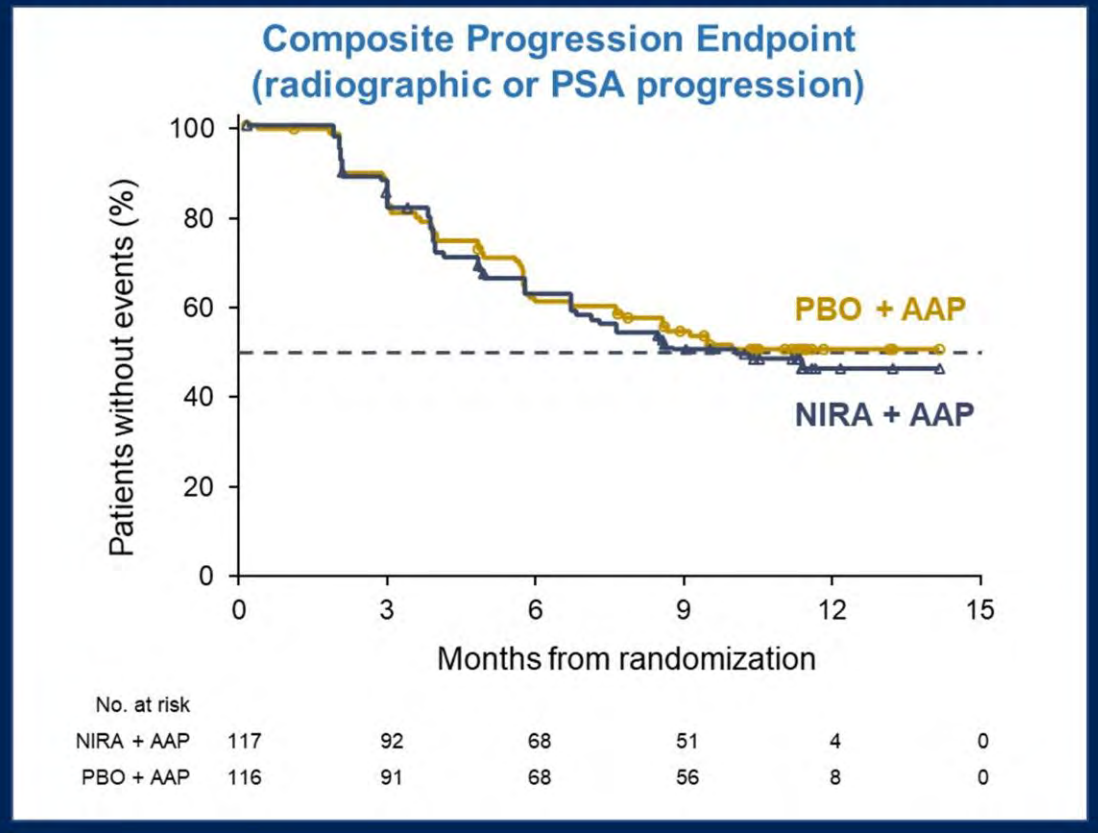
Clinical data cut-off was October 8, 2021 for the final rPFS analysis.

Patients were prospectively tested by plasma, tissue and/or saliva/whole blood. Patients negative by plasma only were required to test by tissue to confirm HRR BM– status.

Chi et al. J Clin Oncol 40, 2022 (suppl 6; abstr 12)

MAGNITUDE HRR BM⁻: Prespecified Early Futility Analysis

No Benefit of NIRA + AAP in HRR BM⁻ Patients



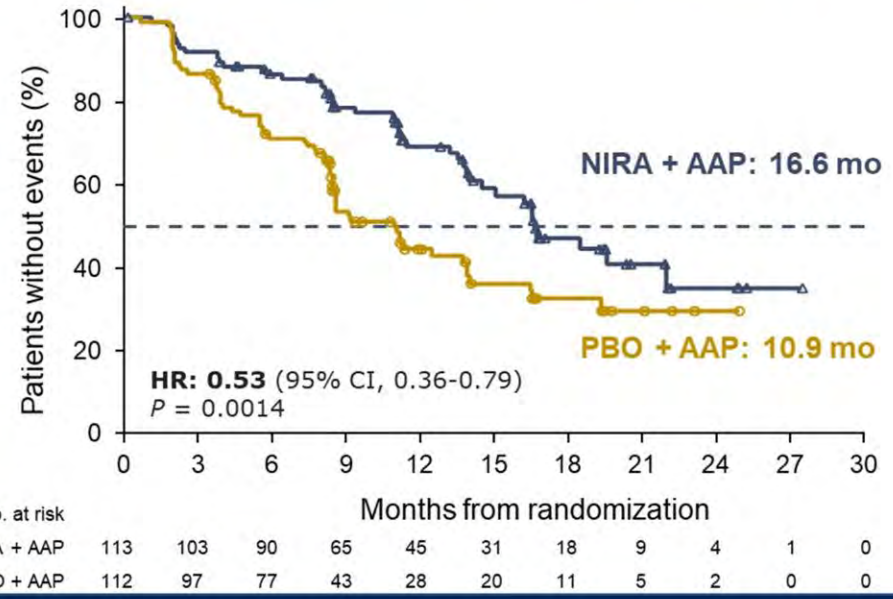
- Composite endpoint[a] (N = 233)
  HR = 1.09[b] (95% CI 0.75-1.59)
  [futility was defined as ≥1]
- Additional grade 3/4 toxicity was observed using NIRA + AAP vs PBO + AAP
- With added toxicity and no added efficacy in patients with HRR BM⁻ mCRPC, the IDMC recommend stopping enrollment in this cohort

[b]Breakdown of composite endpoint events
83 PSA events (HR = 1.03, 95% CI 0.67-1.59)
65 rPFS events (HR = 1.03, 95% CI 0.63-1.67)

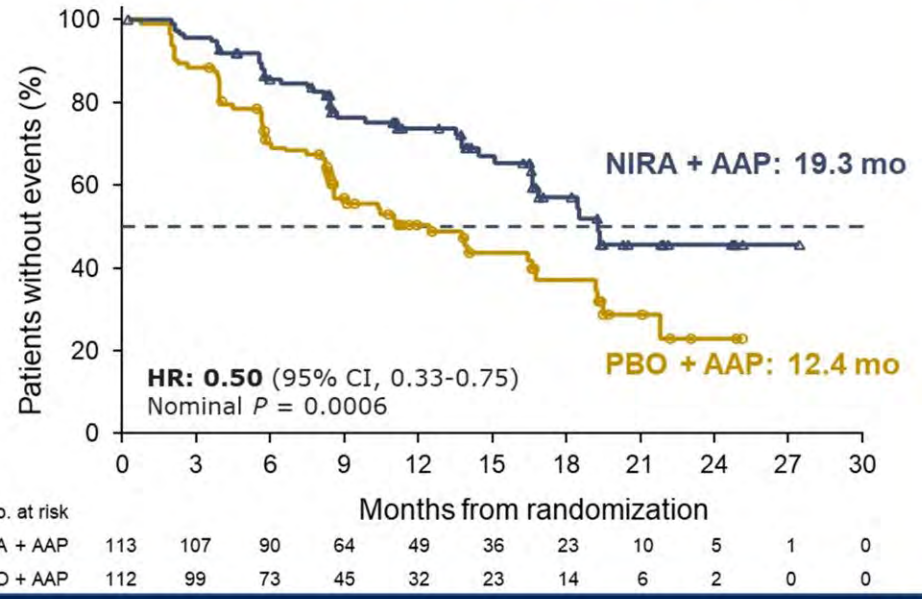
MAGNITUDE *BRCA1/2-mutated*: Primary Endpoint

NIRA + AAP Significantly Reduced the Risk of Progression or Death by 47%

rPFS assessed by central review



rPFS assessed by investigator



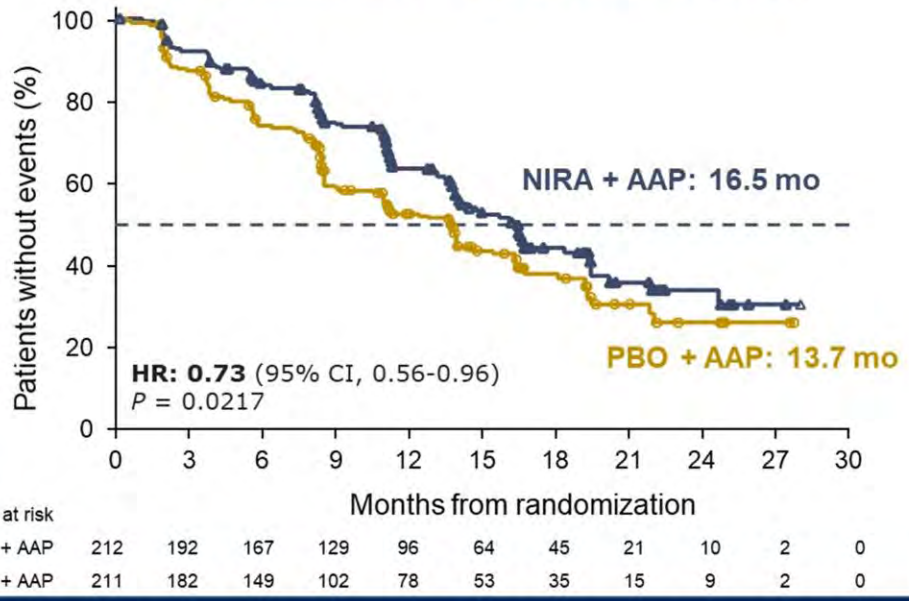
Median follow-up 16.7 months

Chi et al. J Clin Oncol 40, 2022 (suppl 6; abstr 12)

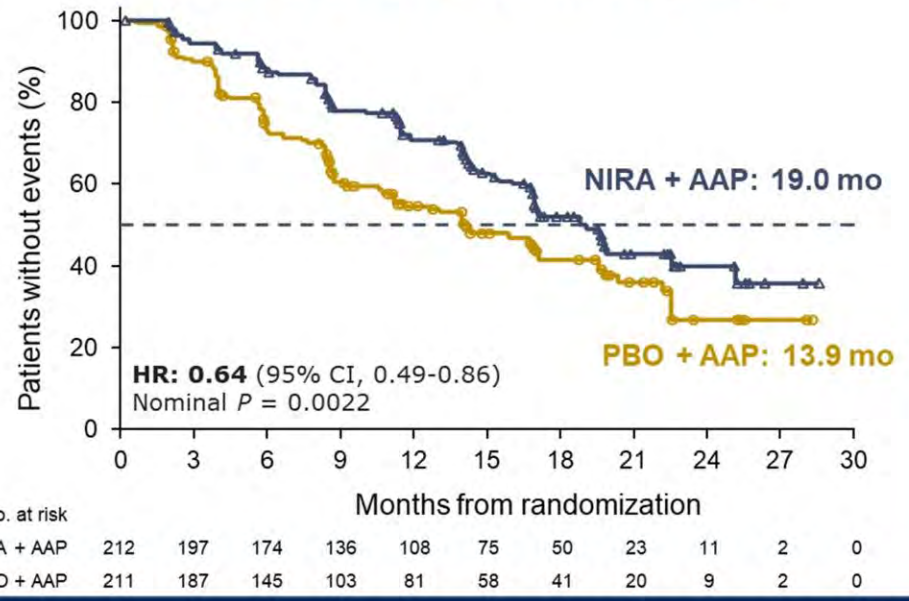
MAGNITUDE All HRR BM+: Primary Endpoint

NIRA + AAP Significantly Reduced the Risk of Progression or Death by 27%

rPFS assessed by central review



rPFS assessed by investigator



Median follow-up 18.6 months

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Gene-by-gene analysis of MAGNITUDE

#5020 Gene-by-gene analysis in the MAGNITUDE study of niraparib with abiraterone acetate and prednisone in patients with mCRPC and homologous recombination repair gene alterations (S.Sandhu, et al.)

Single-gene alteration, HR (95% CI)	NIRA + AAP (N)	PBO + AAP (N)	rPFS, HR (95% CI)	TCC, HR (95% CI)	TSP, HR (95% CI)	OS, HR (95% CI)	TPSA progression, HR (95% CI)	ORR (risk ratio) NIRA vs PBO
BRCA1/2	113	112	0.53 (0.36, 0.79)	0.58 (0.33, 1.01)	0.68 (0.42, 1.11)	0.96 (0.57, 1.63)	0.46 (0.30, 0.69)	1.65 (1.02, 2.71); 29/56 (52%) vs 15/48 (31%)
HRR-Fanconi group	17	14	0.59 (0.23-1.45)	0.68 (0.17-2.74)	0.90 (0.24-3.37)	0.43 (0.12-1.50)	0.65 (0.27-1.59)	1.5 (0.38-6.00); 3/6 (50%) vs 2/6 (33%)
BRIP1	4	4	0.23 (0.02-2.26)	NE	1.14 (0.10-13.27)	NE	0.98 (0.14-7.00)	0.5 (0.13-2.00); 1/2 (50%) vs 1/1 (100%)
FANCA	5	6	1.07 (0.18-6.44)	0.51 (0.05-5.16)	1.23 (0.17-8.74)	NE	0.66 (0.13-3.47)	NE; 0/1 (0%) vs 0/2 (0%)
PALB2	8	4	0.59 (0.15-2.22)	0.39 (0.02-6.19)	0.41 (0.03-6.62)	0.27 (0.05-1.66)	0.59 (0.16-2.20)	2 (0.33-11.97); 2/3 (67%) vs 1/3 (33%)
HRR-associated group	20	23	0.64 (0.26-1.58)	0.72 (0.19-2.69)	0.58 (0.17-2.00)	0.43 (0.13-1.38)	0.43 (0.17-1.10)	6.4 (0.96-43.25); 5/7 (71%) vs 1/9 (11%)
CHEK2	18	20	0.66 (0.25-1.75)	0.36 (0.07-1.88)	0.54 (0.14-2.25)	0.44 (0.12-1.71)	0.37 (0.14-0.99)	NE; 5/7 (71%) vs 0/6 (0%)
HDAC2	2	3	0.71 (0.06-8.02)	NE	0.71 (0.04-11.79)	0.44 (0.04-5.13)	NE	NE; 0/0 (0%) vs 1/3 (33%)
ATM	43	42	1.11 (0.63-1.99)	0.26 (0.08-0.80)	0.75 (0.28-2.00)	1.07 (0.44-2.65)	0.73 (0.39-1.36)	3 (1.12-8.13); 14/17 (82%) vs 3/11 (27%)
CDK12	11	16	1.32 (0.43-3.92)	1.13 (0.27-5.70)	1.05 (0.28-3.94)	1.61 (0.49-5.33)	0.66 (0.24-1.80)	2.25 (0.64-7.97); 3/4 (75%) vs 2/6 (33%)

1. ***PALB2 (12), CHEK2 (38)*** and ***HDAC2 (5)*** each showed benefit across all endpoints
2. ***CDK12 (27),*** no benefit in primary endpoint or >1 secondary endpoint. ***ATM (43),*** mixed bag
3. ***BRIP1 (8), FANCA (11)*** were clustered with HRR-Fanconi group, **but carried by *PALB2*?**

➢ **Let's keep going…**

Sandhu et al. J Clin Oncol 40, 2022 (suppl 16; abstr 5020)

Thank you for your attention

Androgen Receptor Signaling Inhibitors in Addition to Docetaxel with Androgen Deprivation Therapy for Metastatic Hormone-sensitive Prostate Cancer: A Systematic Review and Meta-analysis

Takafumi Yanagisawa [a,b], *Pawel Rajwa* [a,c], *Constance Thibault* [d], *Giorgio Gandaglia* [e], *Keiichiro Mori* [b], *Tatsushi Kawada* [a,f], *Wataru Fukuokaya* [b], *Sung Ryul Shim* [g], *Hadi Mostafaei* [a,h], *Reza Sari Motlagh* [a,i], *Fahad Quhal* [a,j], *Ekaterina Laukhtina* [a,k], *Maximilian Pallauf* [a,l], *Benjamin Pradere* [a,m], *Takahiro Kimura* [b], *Shin Egawa* [b], *Shahrokh F. Shariat* [a,k,n,o,p,q,r,*]

Eur Urol. 2022 Aug 19:S0302-2838(22)02551-9. doi: 10.1016/j.eururo.2022.08.002. Online ahead of print.

	PEACE-1	ARASENS	ARCHES	ENZAMET	TITAN	LATITUDE	STAMPEDE (arm G)	STAMPEDE (arms C, G)	STAMPEDE (arm B, C, E)	CHAARTED	GETUG-AFU15
Author	Fizazi [15]	Smith [16]	Armstrong [1]/Azad [28]	Davis [3]	Chi [14]]	Fizazi [4]	James [19]/ Hoyle [6]	Sydes [12]	Clarke [18]	Kyriakopoulos [7]	Gravis [29]/ Gravis [5]
Year	2022	2022	2019/2022	2019	2021	2019	2017/2019	2018	2019	2018	2013/2016
Treatment arm	Abiraterone + SOC (±RT)	Darolutamide + docetaxel + ADT	Enzalutamide + ADT	Enzalutamide + ADT	Apalutamide + ADT	Abiraterone + ADT	Abiraterone + ADT	Abiraterone + ADT	Docetaxel + ADT	Docetaxel + ADT	Docetaxel + ADT
Dosage	1000 mg	Darolutamide: 600 mg Docetaxel: 75 mg/m^2	160 mg	160 mg	240 mg	1000 mg	1000 mg	1000 mg	75 mg/m^2	75 mg/m^2	75 mg/m^2
Control arm	SOC (±RT)	Placebo + docetaxel + ADT	Placebo + ADT	NSAA + ADT	Placebo + ADT	Placebo + ADT	ADT	Docetaxel + ADT	ADT	ADT	ADT
Inclusion criteria	De novo mHSPC	mHSPC	mHSPC	mHSPC	mHSPC	High-risk de novo mHSPC [a]	mHSPC [b]	mHSPC [b]	mHSPC	mHSPC	mHSPC
Number of patients	1172	1306	1150	1125	1152	1199	1917 (990 [b])	566 (392 [b])	1086	790	385
Treatment	583	651	574	563	525	597	960 (493 [b])	377 (277 [b])	362	397	192
Control	589	655	576	562	527	602	957 (497 [b])	189 (115 [b])	724	393	193
Age (yr), median											
Treatment	66 (IQR: 60–70)	67 (range: 41–89)	70 (range: 46–92)	69.2 (IQR: 63.2–74.5)	69 (range: 45–94)	67.3 ± 8.5 (mean ± SD)	67 (IQR: 63–72)	66 (IQR: 61–70)	65 (IQR: 60–70)	64 (range: 36–88)	63 (IQR: 57–68)
Control	66 (IQR: 59–70)	67 (range: 42–86)	70 (range: 42–92)	69 (IQR: 63.6–74.5)	68 (range: 43–90)	66.8 ± 8.7 (mean ± SD)	67 (IQR: 63–72)	66 (IQR: 62–71)	65 (IQR: 60–71)	63 (range: 39–91)	64 (IQR: 58–70)
De novo disease (%)											
Treatment	100	86	73	58	82	100	94	93	96	73	68
Control	100	87	72	58	85	100	96	97	95	73	66
Disease volume (high/low [c]; %)											
Treatment	63/37	NA	62/38	52/48	62/38	82/18	54/46	NA	54/46	66/34	48/52
Control	65/35	NA	65/35	53/47	64/36	78/22	51/49	NA	57/43	64/36	47/53
No. of docetaxel patients											
Treatment	355	All	103	254	58	No use	No use	NA	NA	NA	NA
Control	355		102	249	55						
HR for OS (95% CI)											
All	0.82 (0.69–0.98)	0.68 (0.57–0.80)	0.66 (0.53–0.81)	0.6 (0.52–0.86)	0.67 (0.51–0.89)	0.66 (0.56–0.78)	0.61 (0.49–0.75)	1.13 (0.77–1.66)	0.81 (0.69–0.95)	0.72 (0.59–0.89)	0.88 (0.68–1.14)
De novo metastasis		0.71 (0.59–0.85)	NA	0.65 (0.47–0.89)	0.68 (0.55–0.85)		0.59 (0.47–0.74)	NA	NA	0.68 (0.54–0.85)	0.93 (0.69–1.25)
Prior local treatment	NA	0.65 (0.35–1.05)	NA	0.7 (0.47–1.09)	0.39 (0.22–0.69)	NA	NA	NA	NA	0.97 (0.58–1.62)	0.83 (0.47–1.47)
Docetaxel cohort	0.75 (0.59–0.95)	0.68 (0.57–0.80)	0.74 (0.46–1.2)	0.9 (0.62–1.31)	1.12 (0.59–2.12)	NA	NA	NA	NA	NA	NA
HR for PFS (95% CI)	rPFS	Time to CRPC	rPFS	cPFS	rPFS	rPFS	PFS	rPFS	rPFS	cPFS	rPFS
All	0.54 (0.44–0.67)	0.36 (0.30–0.42)	0.39 (0.3–0.5)	0.40 (0.33–0.49)	0.48 (0.39–0.60)	0.47 (0.39–0.55)	0.45 (0.37–0.54)	0.69 (0.50–0.95)	0.69 (0.59–0.81)	0.62 (0.51–0.75)	0.69 (0.55–0.87)
Docetaxel cohort	0.5 (0.4–0.62)	0.36 (0.30–0.42)	0.52 (0.3–0.89)	0.48 (0.37–0.62)	0.47 (0.22–1.01)	NA	NA	NA	NA	NA	NA
Follow-up (mo), median (treatment/control arm)	45.7 (46.2/45.0)	43 (43.7/42.4)	44.6	34	44	51.8	40	48	78.2	53.7	83.9

ADT = androgen deprivation therapy, APA = apalutamide; CI = confidential interval; cPFS = clinical PFS; CRPC = castration-resistant prostate cancer; DOC = docetaxel; HR = hazard ratio; IQR = interquartile range;

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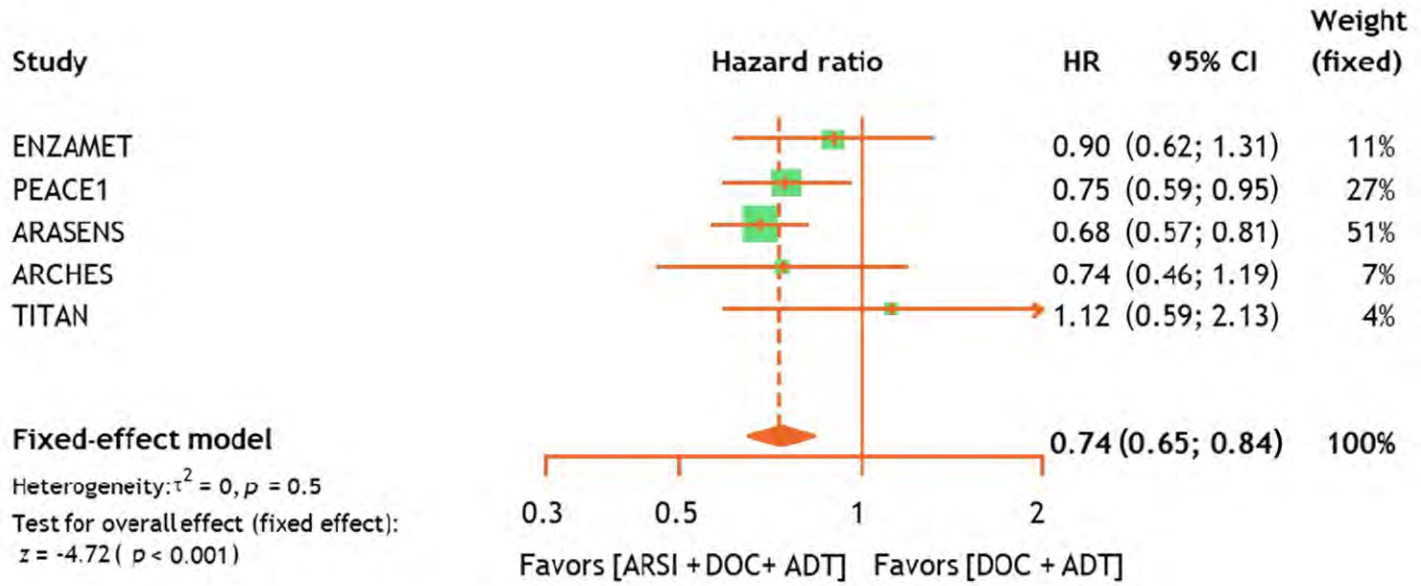
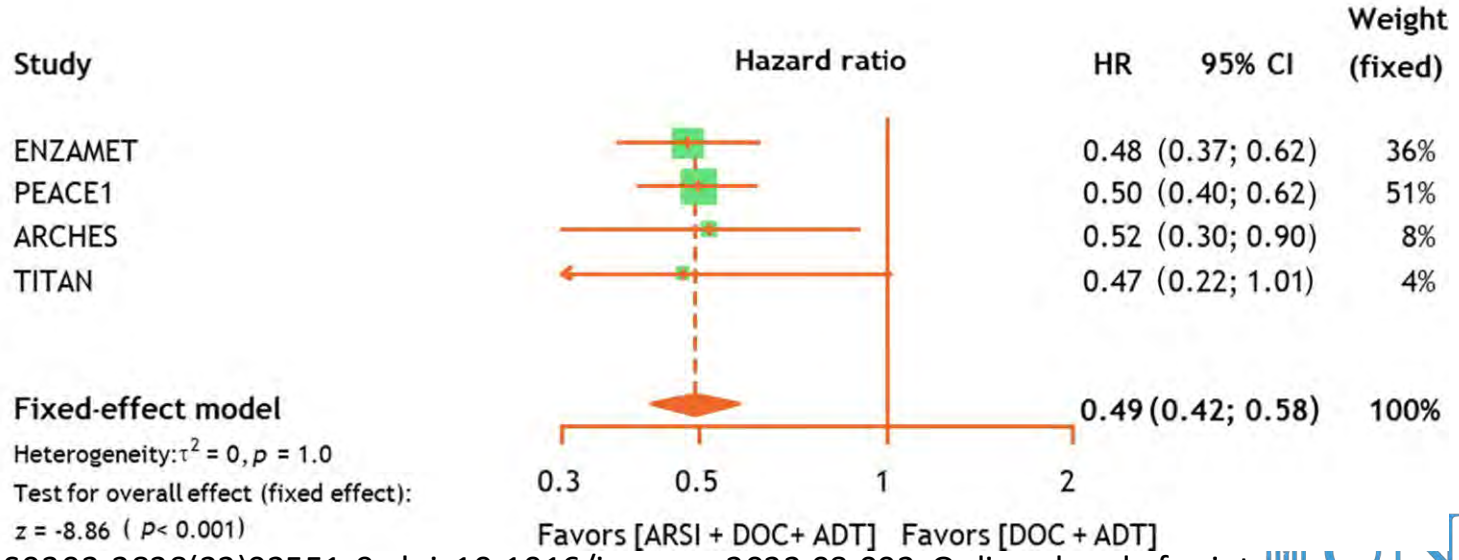
(A) OS



(B) PFS



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Evidence synthesis: Overall, 11 RCTs were included for meta-analyses and network meta-analyses (NMAs). We found that the triplet combinations outperformed DOC + ADT in terms of OS (pooled hazard ratio [HR]: 0.74, 95% confidence interval [CI]: 0.65–0.84) and PFS (pooled HR: 0.49, 95% CI: 0.42–0.58). There was no statistically significant difference between patients with low- and high-volume disease in terms of an OS benefit from adding an ARSI to DOC +ADT (both HR: 0.79; $p = 1$). Based on NMAs, triplet therapy also outperformed ARSI + ADT in terms of OS (DAR + DOC + ADT: pooled HR: 0.74, 95% CI: 0.55–0.99) and PFS (ABI + DOC + ADT: HR: 0.68, 95% CI: 0.51–0.91, and ENZ + DOC + ADT: HR: 0.70, 95% CI: 0.53–0.93). An analysis of treatment ranking among de novo mHSPC patients showed that triplet therapy had the highest likelihood of improved OS in patients with high-volume disease; however, doublet therapy using ARSI + ADT had the highest likelihood of improved OS in patients with low-volume disease.

Conclusions: We found that the triplet combination therapy improves survival endpoints in mHSPC patients compared with currently available doublet treatment regimens. Our findings need to be confirmed in further head-to-head trials with longer follow-up and among various patient populations.

Patient summary: Our study suggests that triplet therapy with androgen receptor signaling inhibitor, docetaxel, androgen deprivation therapy prolongs survival in patients with metastatic hormone-sensitive prostate cancer compared with the current standard doublet therapy.

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