Developing Targeted Therapy for GU Malignancies
March 5, 2023

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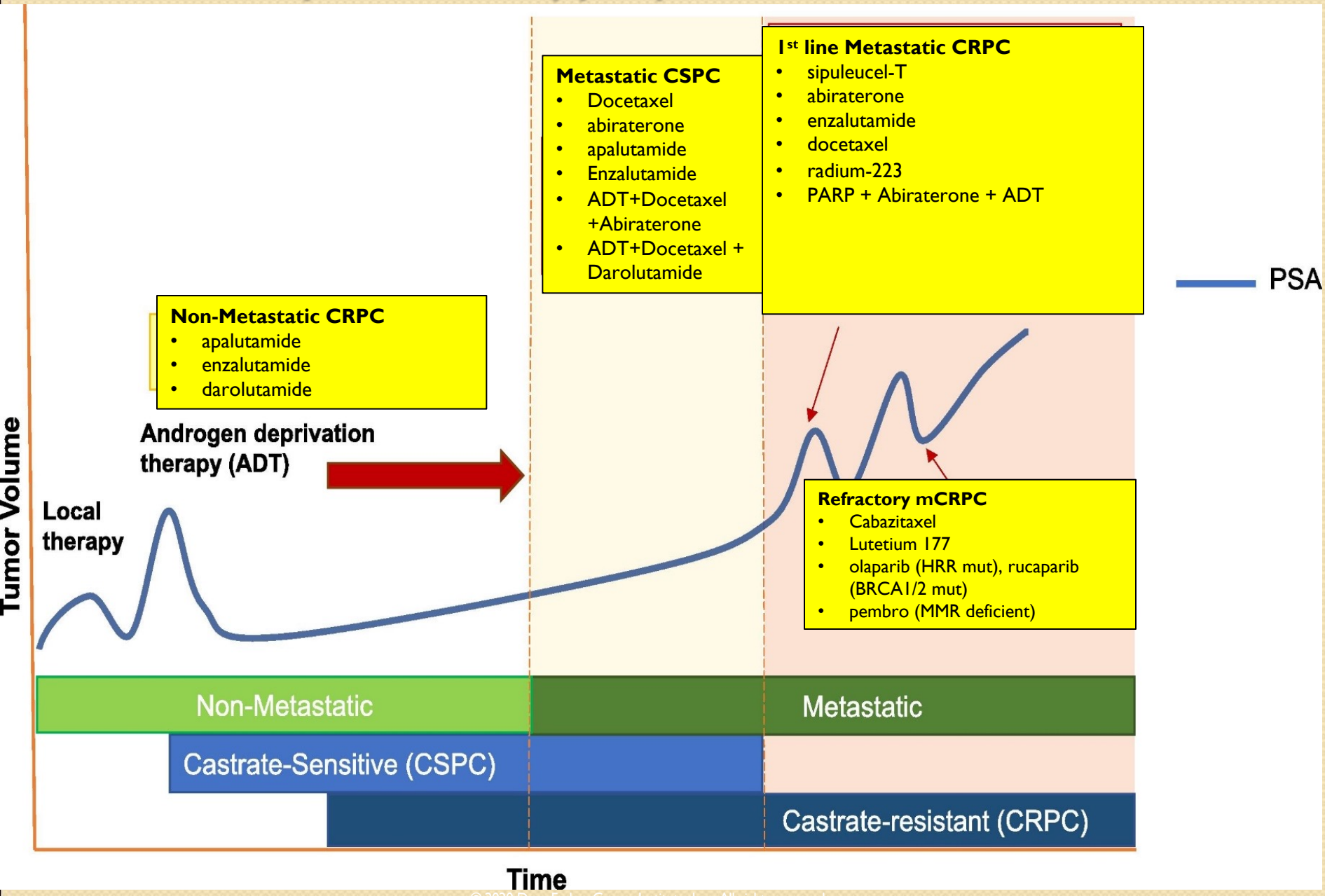
NORTON CANCER INSTITUTE

Agenda

- Targeted Therapy in Prostate Cancer
  - Androgen Pathway Inhibitor
  - Radioligand Therapy
  - PARP inhibitor

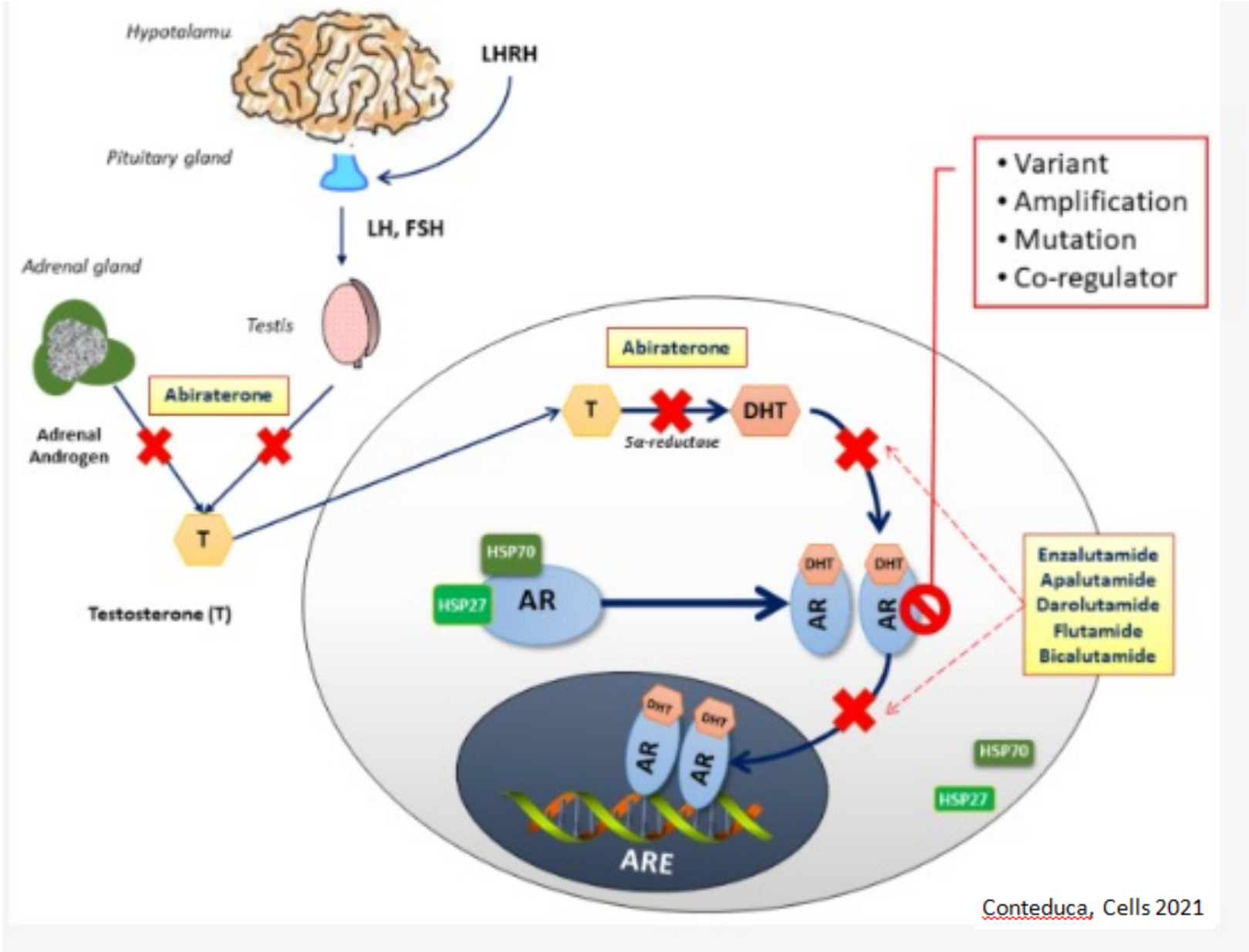
- Targeted Therapy in Urothelial Cancer
  - FGFR 2/FGFR 3 inhibitor
  - Nectin-4 directed therapy
  - TROP 2 directed therapy
  - HER 2 directed therapy

Systemic therapy of prostate cancer 2023



Alkhudair NA. *Saudi Pharm J.* 2019 Mar;27(3):368-372.

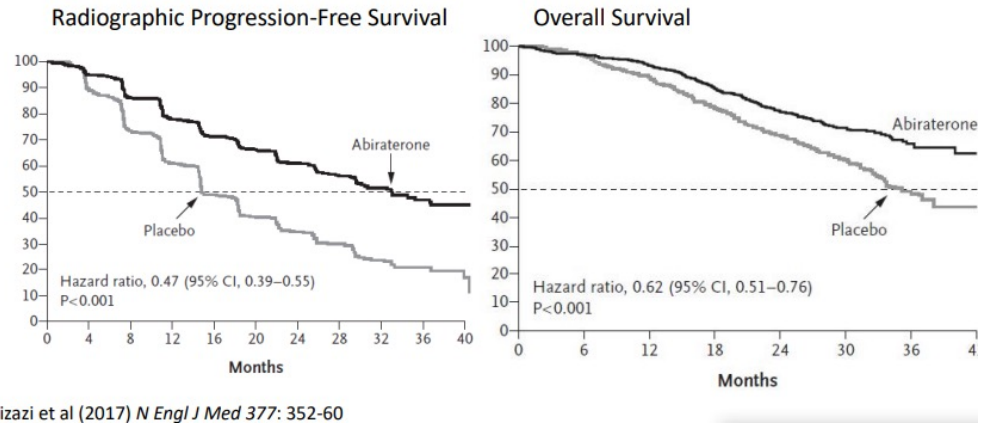
1. Androgen Pathway Inhibitor



Conteduca, Cells 2021

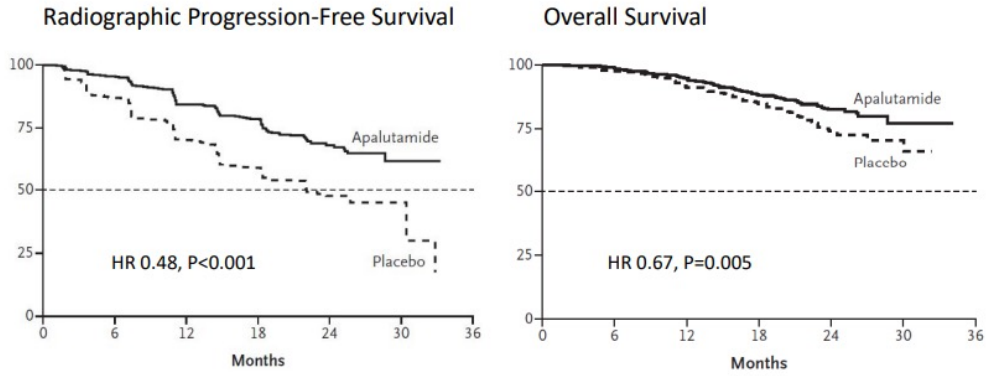
Androgen Pathway Inhibitors

LATITUDE: Abiraterone Acetate for mHSPC



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

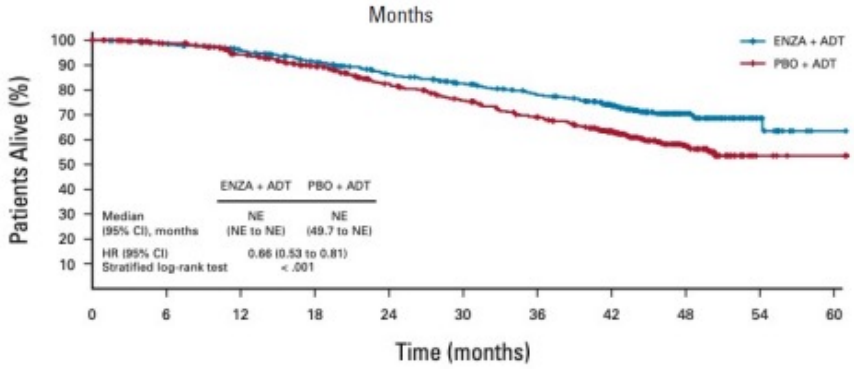
TITAN: Apalutamide for mHSPC



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

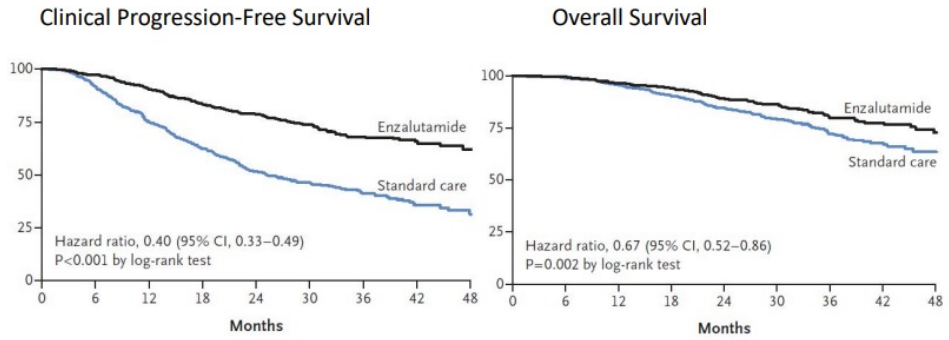
ARCHES and ENZAMET

OS



Armstrong et al (2019) *J Clin Oncol 37:* 2974-2986; Armstrong et al (2022) *J Clin Oncol* DOI: 10.1200/JCO.22.00193

ENZAMET: Enzalutamide for mHSPC



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

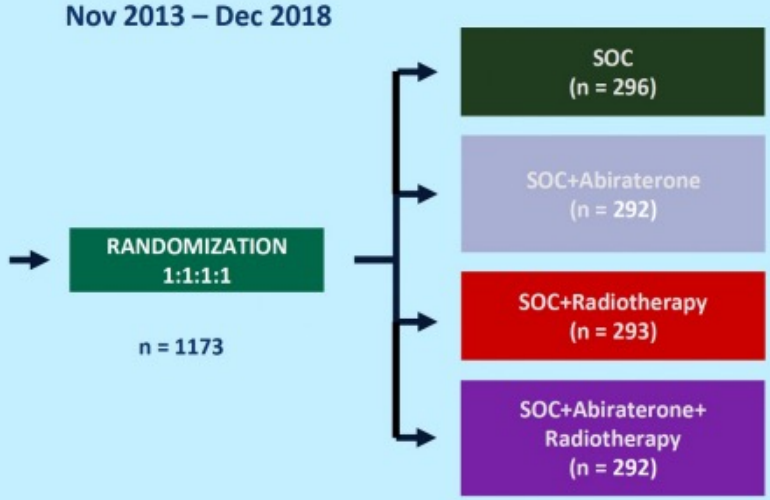
PEACE -1

Key Eligibility Criteria
De novo mCSPC
Distant metastatic disease by ≥ 1 lesion on bone scan and/or CT scan
ECOG PS 0 -2

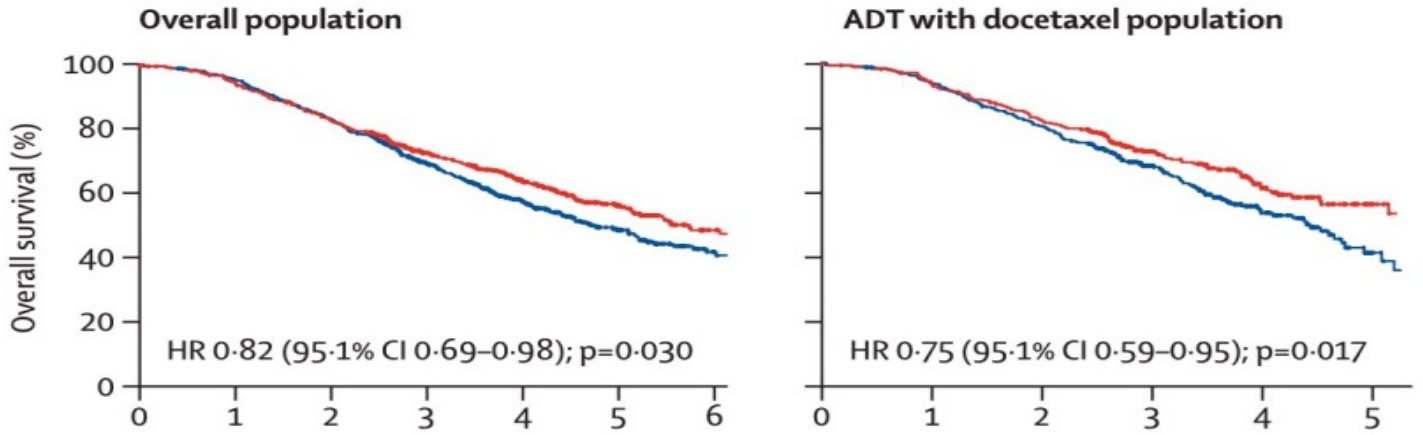
On-Study Requirement
Continuous ADT

Permitted
ADT ≤ 3 months

Stratification
ECOG PS (0 vs 1-2)
Metastatic sites (LN vs bone vs visceral)
Type of castration (orchidectomy vs LHRH agonist vs LHRH antagonist)
Docetaxel (yes vs no)



ECOG PS, Eastern Cooperative Oncology Group performance status



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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer

Matthew R. Smith, M.D., Ph.D., Maha Hussain, M.D., Fred Saad, M.D., Karim Fizazi, M.D., Ph.D., Cora N. Sternberg, M.D., E. David Crawford, M.D., Evgeny Kopyltsov, M.D., Chandler H. Park, M.D., Boris Alekseev, M.D., Álvaro Montesa-Pino, M.D., Dingwei Ye, M.D., Francis Parnis, M.B., B.S., Felipe Cruz, M.D., Teuvo L.J. Tammela, M.D., Ph.D., Hiroyoshi Suzuki, M.D., Ph.D., Tapio Utriainen, M.D., Cheng Fu, M.D., Motohide Uemura, M.D., Ph.D., María J. Méndez-Vidal, M.D., Benjamin L. Maughan, M.D., Pharm.D., Heikki Joensuu, M.D., Silke Thiele, M.D., Rui Li, M.S., Iris Kuss, M.D., and Bertrand Tombal, M.D., Ph.D., for the ARASENS Trial Investigators*

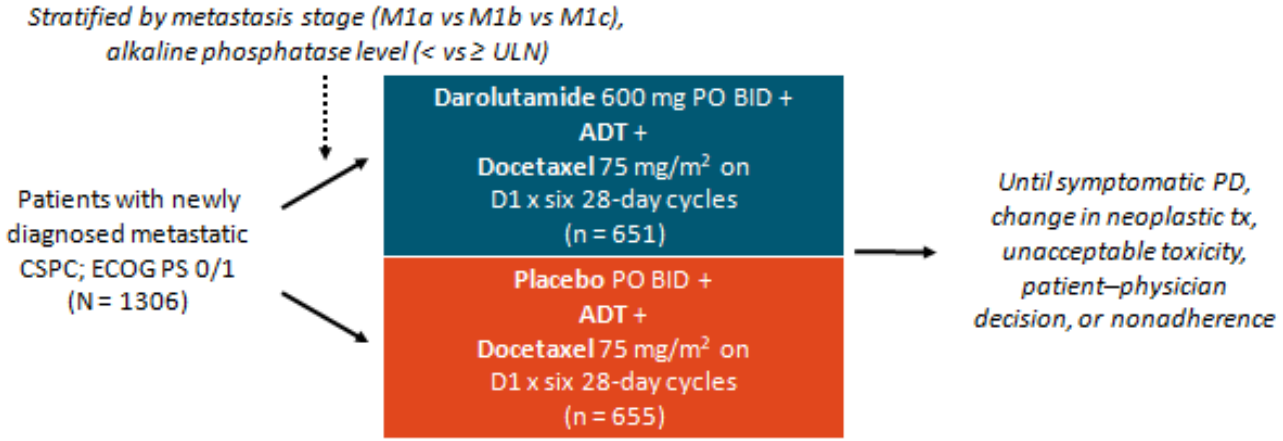
March 24, 2022
N Engl J Med 2022; 386:1132-1142
DOI: 10.1056/NEJMoa2119115

ARASENS 2023 Update

ARASENS

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

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

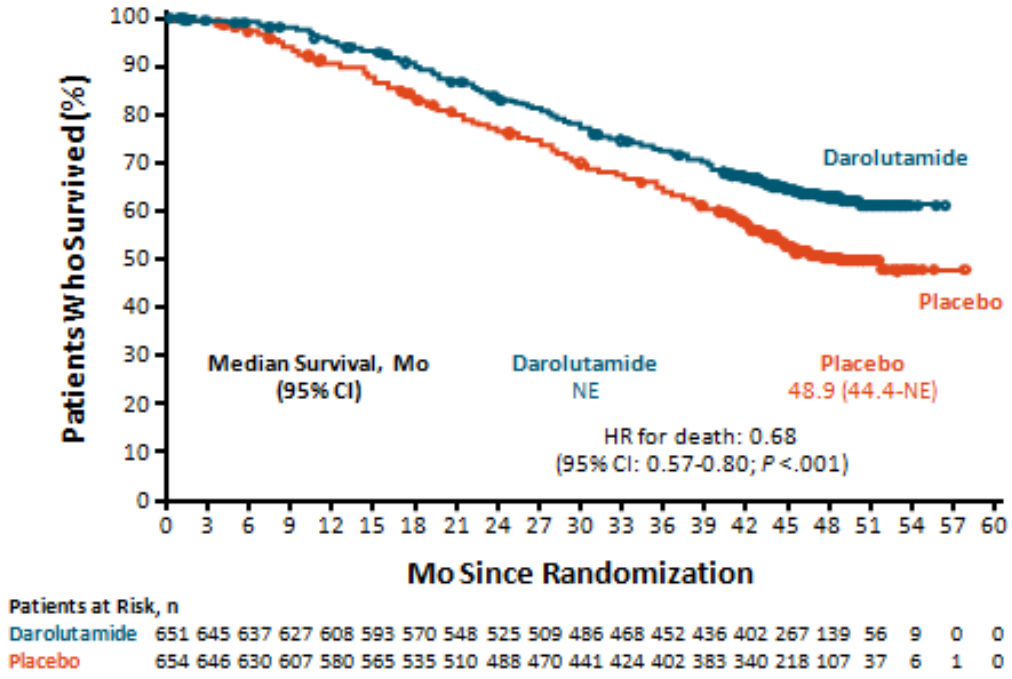


- **Primary endpoint:** OS
- **Secondary endpoints tested hierarchically in this order:** time to CRPC, time to pain progression, SSE-free survival, time to first SSE, time to initiation of subsequent anticancer therapy, time to worsening of physical symptoms, time to first opioid use, safety

Smith. NEJM. 2022;[Epub]. Smith. ASCO GU 2022. Abstr 13. NCT02799602.

Overall Survival

ARASENS: OS (Primary Endpoint)



- Addition of darolutamide to ADT + docetaxel significantly reduced risk of death by 32.5% vs placebo (*P* <.001)
  - 75.6% of patients in placebo arm received subsequent life-prolonging systemic tx
- OS benefit observed across most subgroups
  - HR (95%) for those stratified by metastatic stage at initial dx: M1, 0.707 (0.590-0.848); M0, 0.605 (0.348-1.052)

Smith. NEJM. March 2023

ARASENS Update

Definition of Disease Volume and Risk Subgroups

High-Volume Disease: CHAARTED Criteria[1]	High-Risk Disease: LATITUDE Criteria[2]
• Visceral metastases • ≥4 bone metastases with ≥1 beyond the vertebral column/pelvis[a]	• ≥2 risk factors: ▪ Gleason score ≥8 ▪ ≥3 bone metastases[a] ▪ Visceral metastases

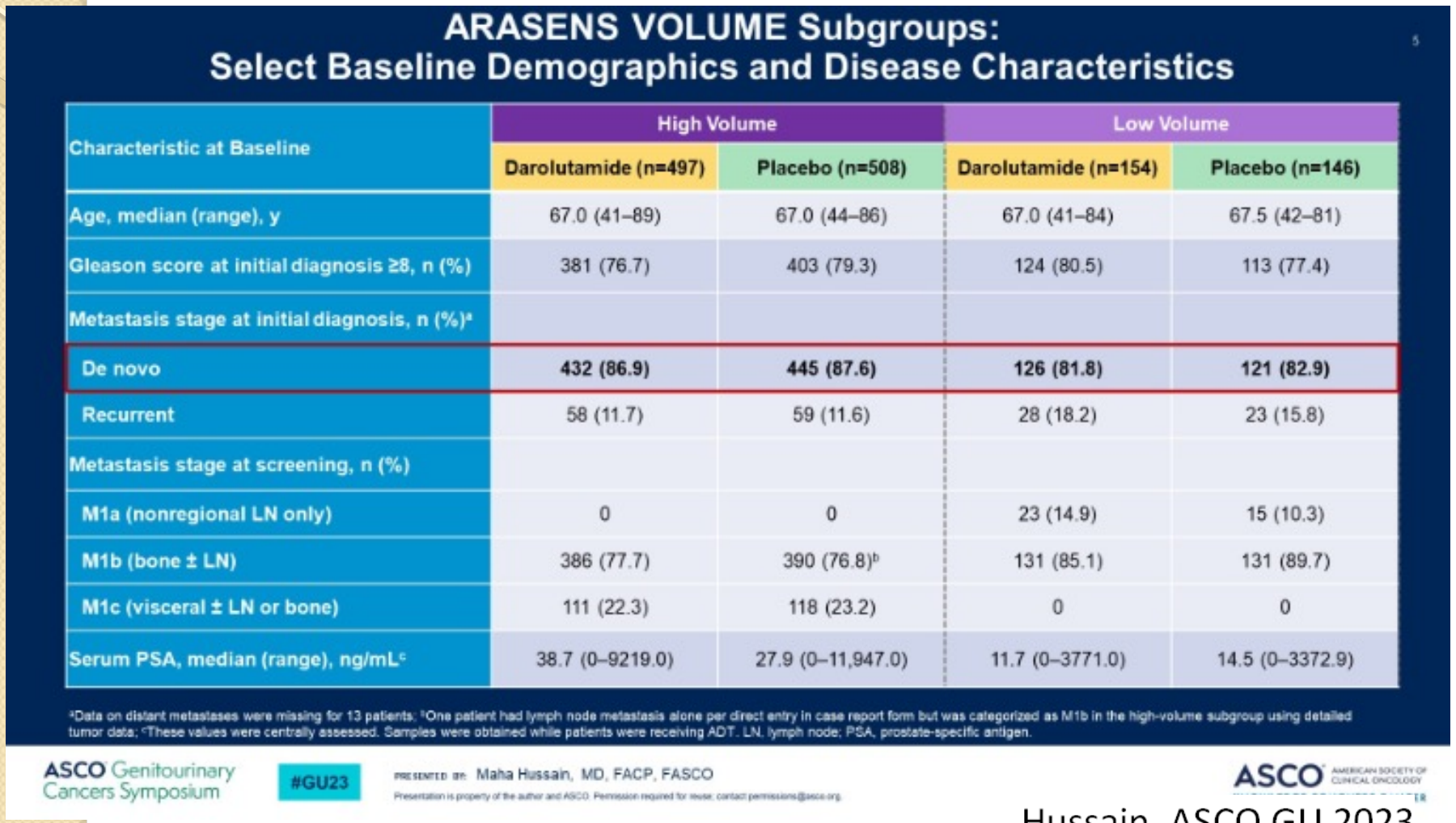
Low-volume and low-risk disease were defined as not meeting the respective high-volume and high-risk criteria
[a]Including those with diffusely increased skeletal metastases with superscan[3]

- Of 1305 patients in the ARASENS full analysis set
  - **1005 (77%) had high-volume disease and 300 (23%) had low-volume disease**
  - **912 (70%) had high-risk disease and 393 (30%) had low-risk disease**

1. Sweeney CJ, et al. *N Engl J Med.* 2015; 373:737-746; 2. Fizazi K, et al. *N Engl J Med.* 2017;377:352-360; 3. Manohar PR, et al. *World J Nucl Med.* 2017;16:39-44.

Hussain, ASCO GU 2023

ARASENS Update



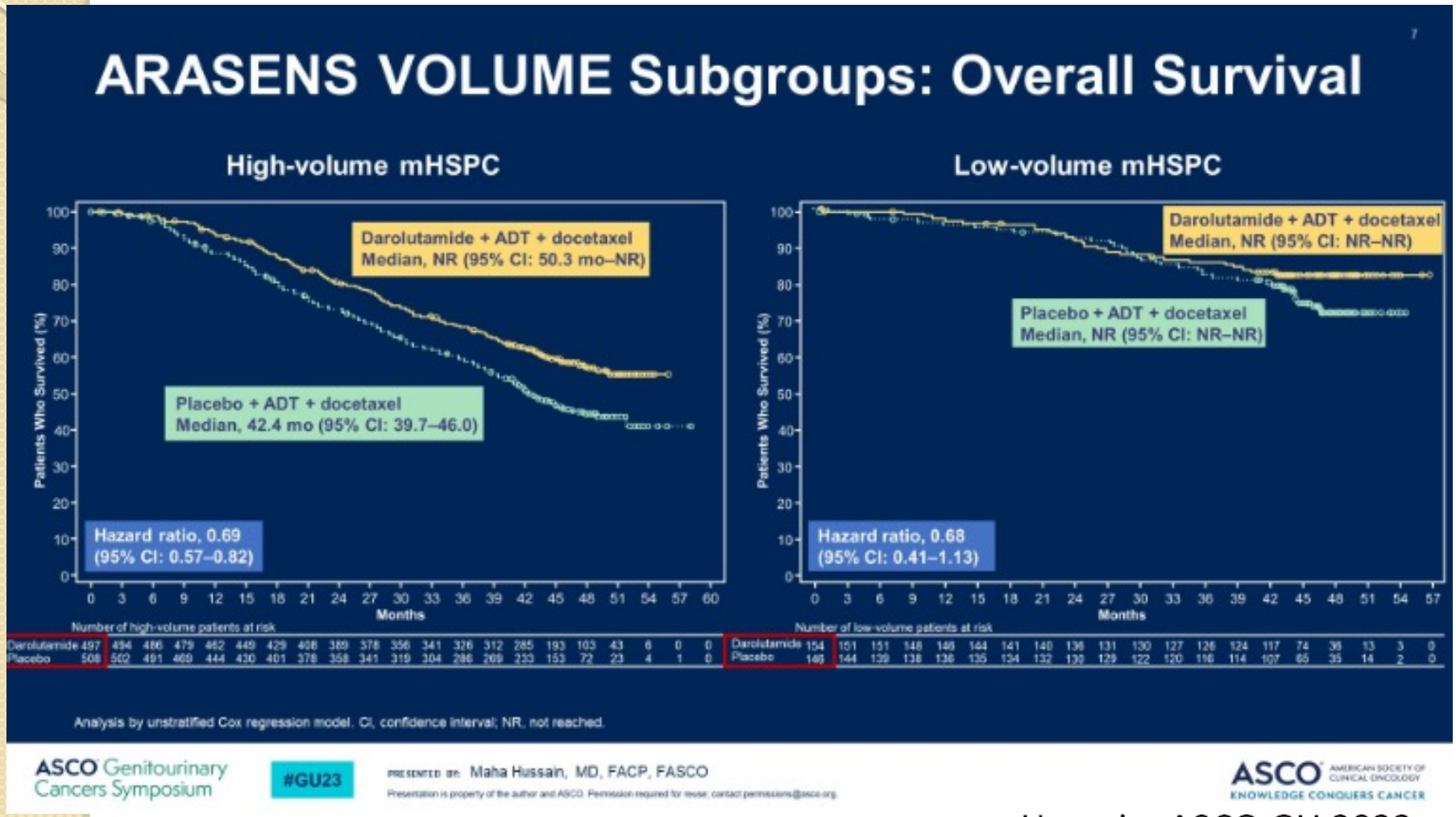
ARASENS VOLUME Subgroups: Select Baseline Demographics and Disease Characteristics

Characteristic at Baseline	High Volume		Low Volume	
	Darolutamide (n=497)	Placebo (n=508)	Darolutamide (n=154)	Placebo (n=146)
Age, median (range), y	67.0 (41–89)	67.0 (44–86)	67.0 (41–84)	67.5 (42–81)
Gleason score at initial diagnosis ≥8, n (%)	381 (76.7)	403 (79.3)	124 (80.5)	113 (77.4)
Metastasis stage at initial diagnosis, n (%)[a]				
De novo	**432 (86.9)**	**445 (87.6)**	**126 (81.8)**	**121 (82.9)**
Recurrent	58 (11.7)	59 (11.6)	28 (18.2)	23 (15.8)
Metastasis stage at screening, n (%)				
M1a (nonregional LN only)	0	0	23 (14.9)	15 (10.3)
M1b (bone ± LN)	386 (77.7)	390 (76.8)[b]	131 (85.1)	131 (89.7)
M1c (visceral ± LN or bone)	111 (22.3)	118 (23.2)	0	0
Serum PSA, median (range), ng/mL[c]	38.7 (0–9219.0)	27.9 (0–11,947.0)	11.7 (0–3771.0)	14.5 (0–3372.9)

[a]Data on distant metastases were missing for 13 patients; [b]One patient had lymph node metastasis alone per direct entry in case report form but was categorized as M1b in the high-volume subgroup using detailed tumor data; [c]These values were centrally assessed. Samples were obtained while patients were receiving ADT. LN, lymph node; PSA, prostate-specific antigen.

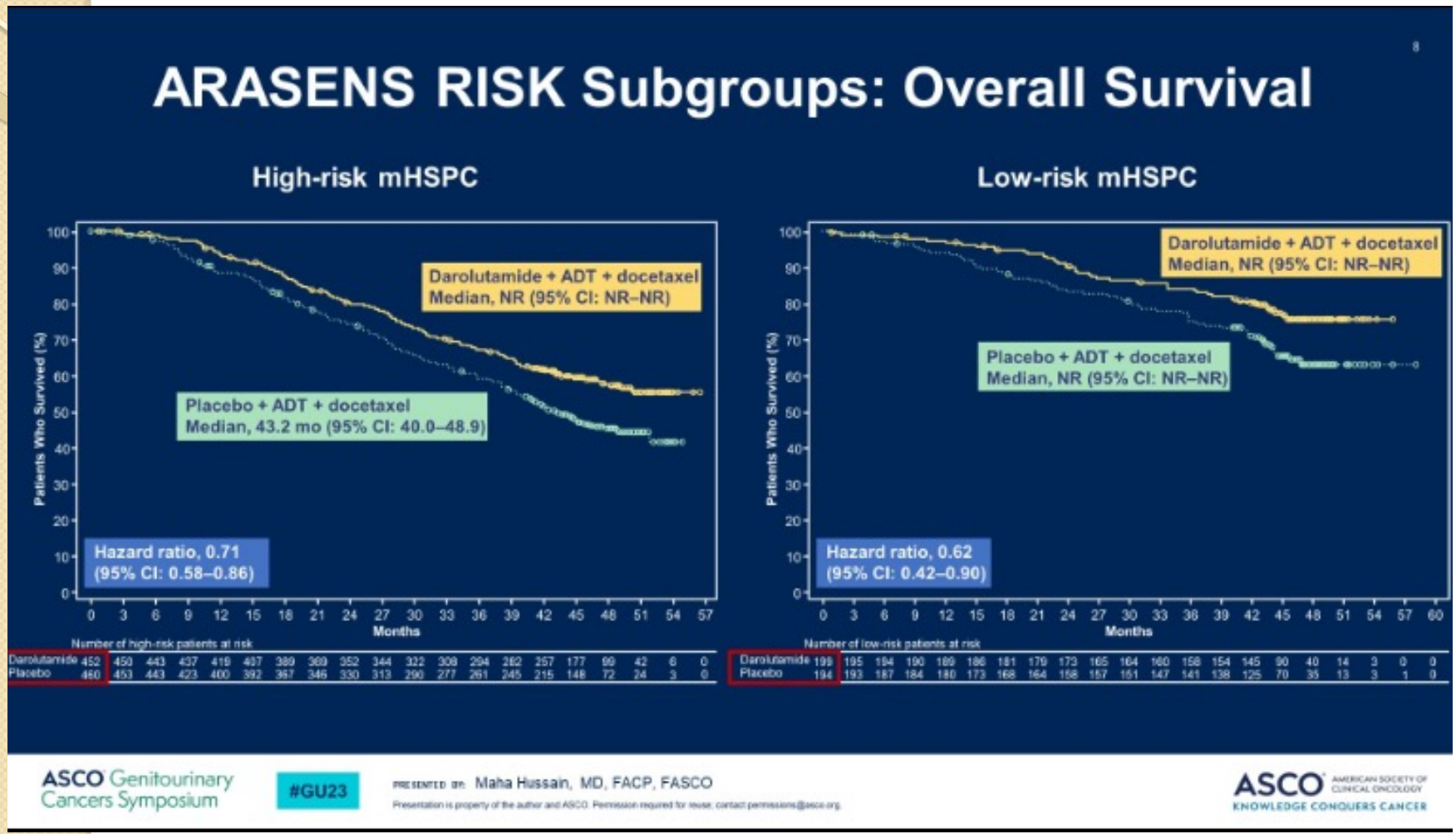
Hussain, ASCO GU 2023

ARASENS Update



Hussain, ASCO GU 2023

ARASENS Update



Hussain, ASCO GU 2023

Adverse Events

Selected Grade 3/4 AE, n (%)	Darolutamide + ADT + Docetaxel (n = 652)	Placebo + ADT + Docetaxel (n = 650)
Neutropenia	220 (33.7)	222 (34.2)
Febrile neutropenia	51 (7.8)	48 (7.4)
Hypertension	42 (6.4)	21 (3.2)
Anemia	31 (4.8)	33 (5.1)
Pneumonia	21 (3.2)	20 (3.1)
Hyperglycemia	18 (2.8)	24 (3.7)
Increased ALT	18 (2.8)	11 (1.7)
Increased AST	17 (2.6)	7 (1.1)
Increased weight	14 (2.1)	8 (1.2)
UTI	13 (2.0)	12 (1.8)

Safety Outcome, n (%)	Darolutamide + ADT + Docetaxel (n = 652)	Placebo + ADT + Docetaxel (n = 650)
Any AE	649 (99.5)	643 (98.9)
Serious AE	292 (44.8)	275 (42.3)
AE leading to permanent d/c of trial agent		
▪ Darolutamide or placebo	88 (13.5)	69 (10.6)
▪ Docetaxel	52 (8.0)	67 (10.3)

Smith. NEJM. March 2023

ARASENS Conclusion

- Darolutamide, Docetaxel, and ADT significantly increased OS vs placebo + ADT + docetaxel in high risk and low risk with metastatic castrate sensitive prostate cancer
- Median OS: NE vs 48.9 mo (HR: 0.68; 95% CI: 0.57-0.80; *P* <.001)
- Adverse events comparable between arms,
- Every patient with metastatic hormone sensitive prostate adenocarcinoma should receive androgen pathway inhibitor with ADT at a bare minimum.
- Consider Darolutamide, Docetaxel, and ADT as new standard of care for mHSPC

Synchronous vs Metachronous Prostate Cancer

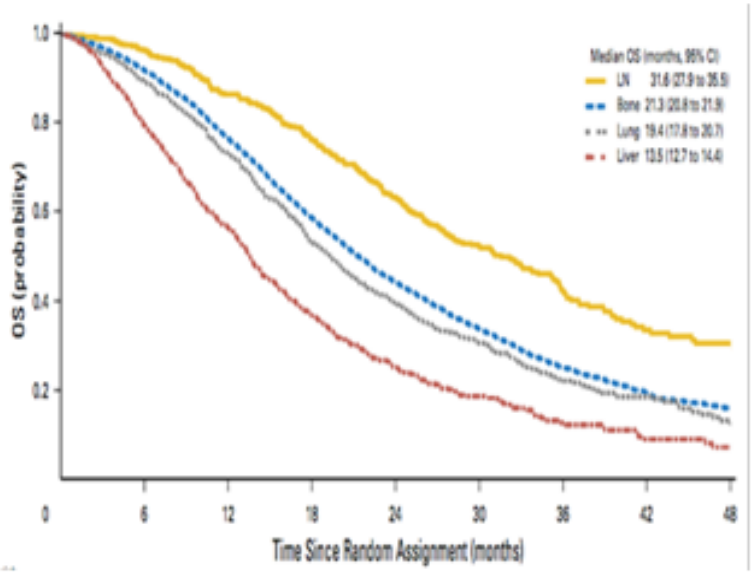
Synchronous

- Patients diagnosed with a primary prostate cancer and metastases simultaneously

Metachronous

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

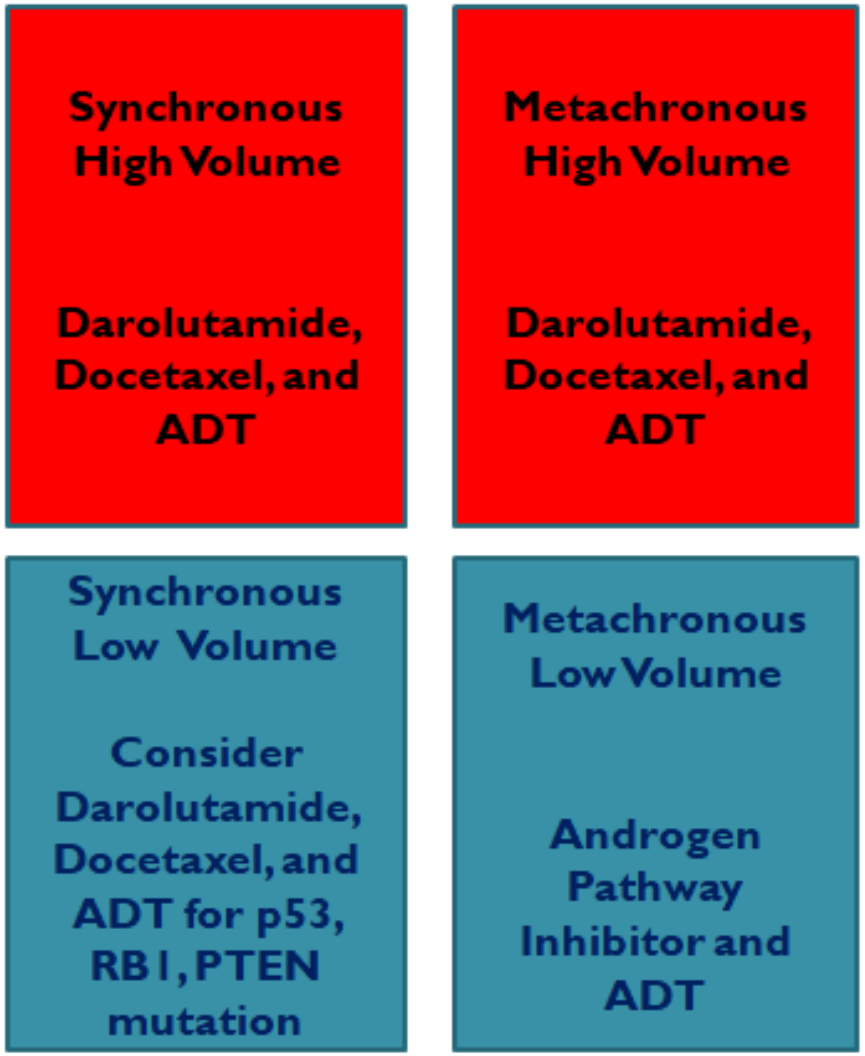
Staging in prognostication



Halabi, JCO, 2016; Gravis Eur Urol 2018; Kyriakopoulos JCO 2018

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

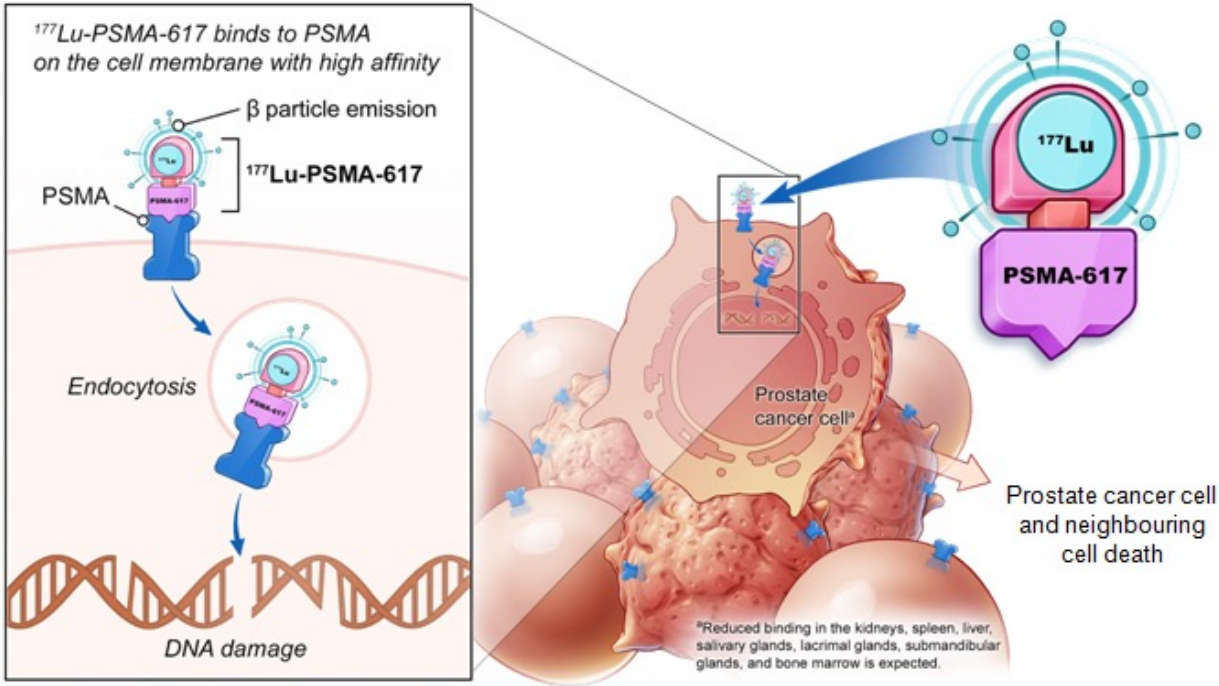
My Practice


Synchronous High Volume
Darolutamide, Docetaxel, and ADT
Metachronous High Volume
Darolutamide, Docetaxel, and ADT
Synchronous Low Volume
Consider Darolutamide, Docetaxel, and ADT for p53, RB1, PTEN mutation
Metachronous Low Volume
Androgen Pathway Inhibitor and ADT

2. Radioligand Therapy

Radioligand Therapy

^{177}Lu-PSMA-617 targeted radioligand therapy



VISION Study

ORIGINAL ARTICLE

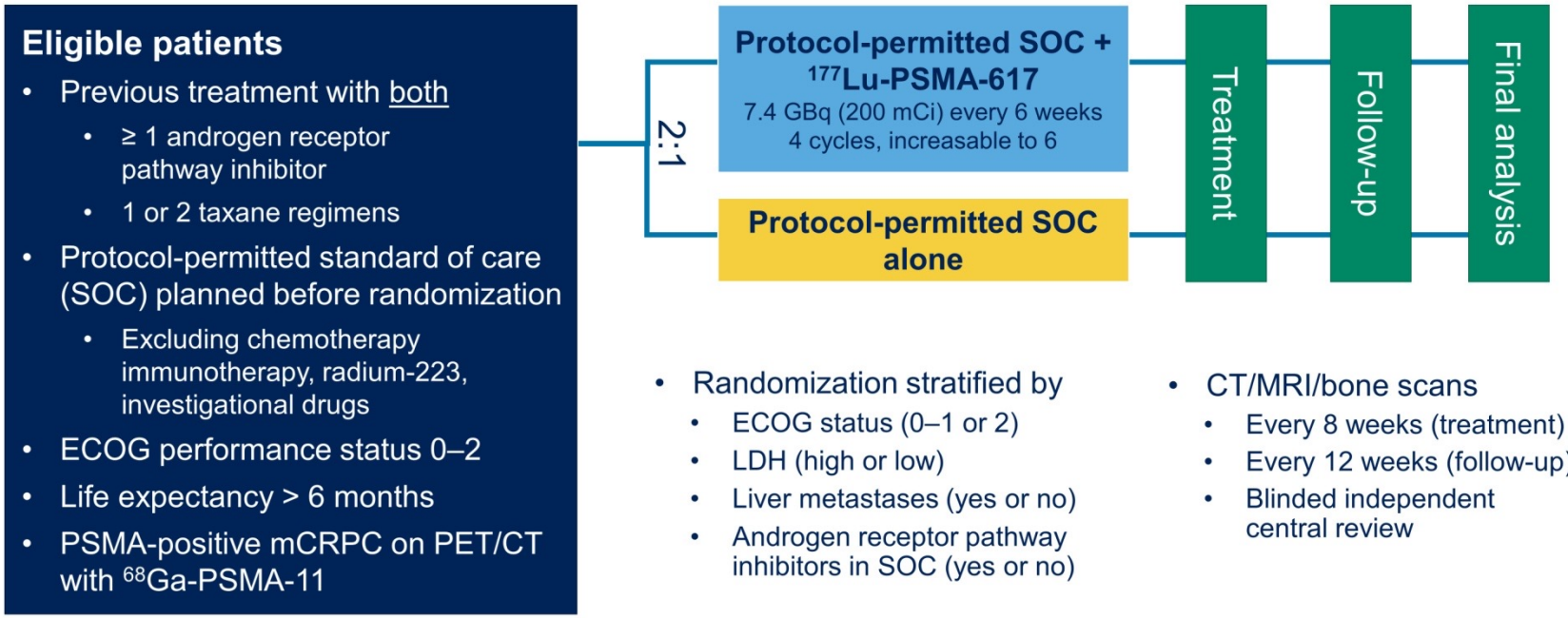
Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

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

September 16, 2021
N Engl J Med 2021; 385:1091-1103
DOI: 10.1056/NEJMoa2107322
Chinese Translation 中文翻译

VISION Study

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

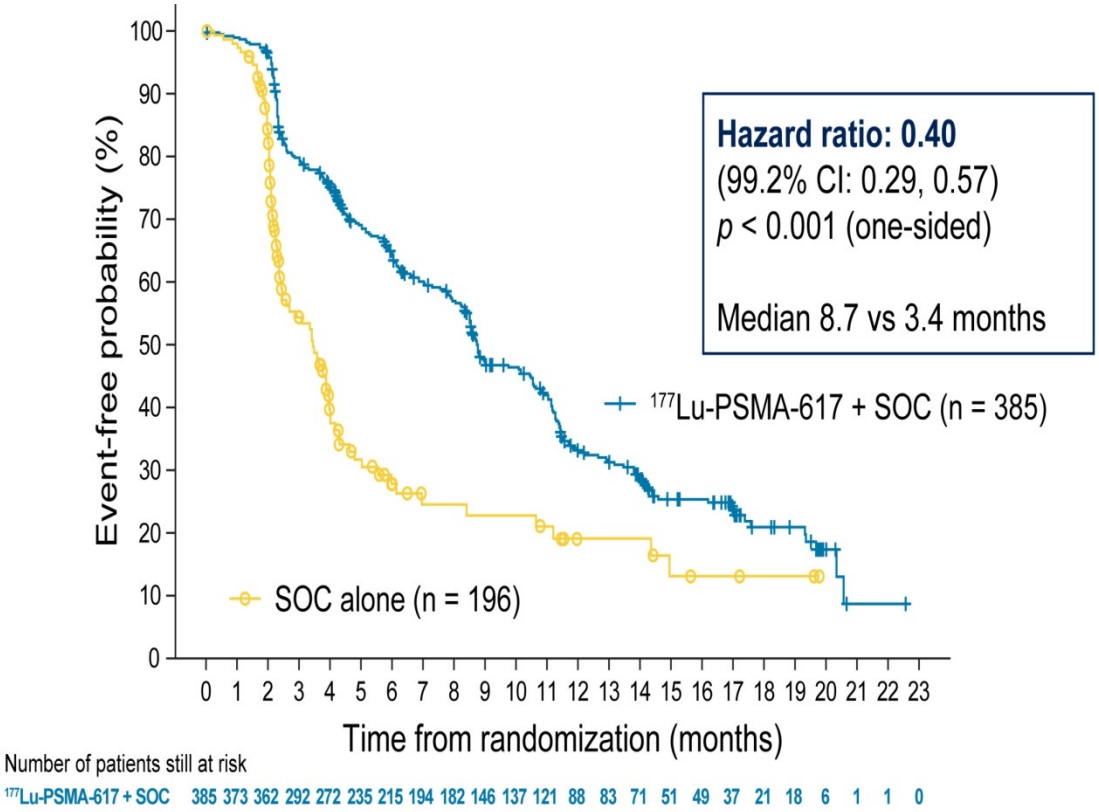


Morris, ASCO 2022

Primary endpoints: ^{177}Lu-PSMA-617 improved rPFS

Primary analysis

rPFS analysis set (n = 581)

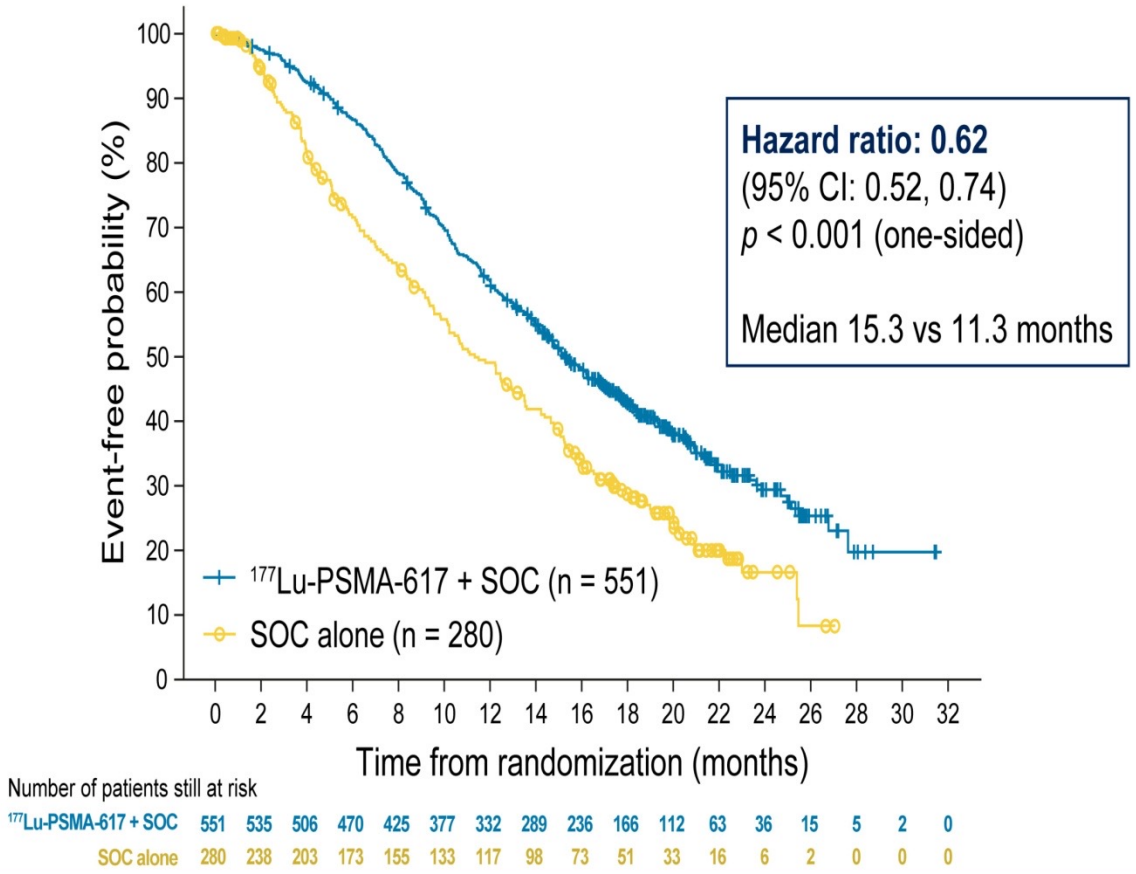


Morris MJ, ASCO 2021

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

Primary analysis

All randomized patients (N = 831)



Morris MJ, ASCO 2021

Treatment-emergent adverse events grouped as topics of interest: no unexpected or concerning safety signals

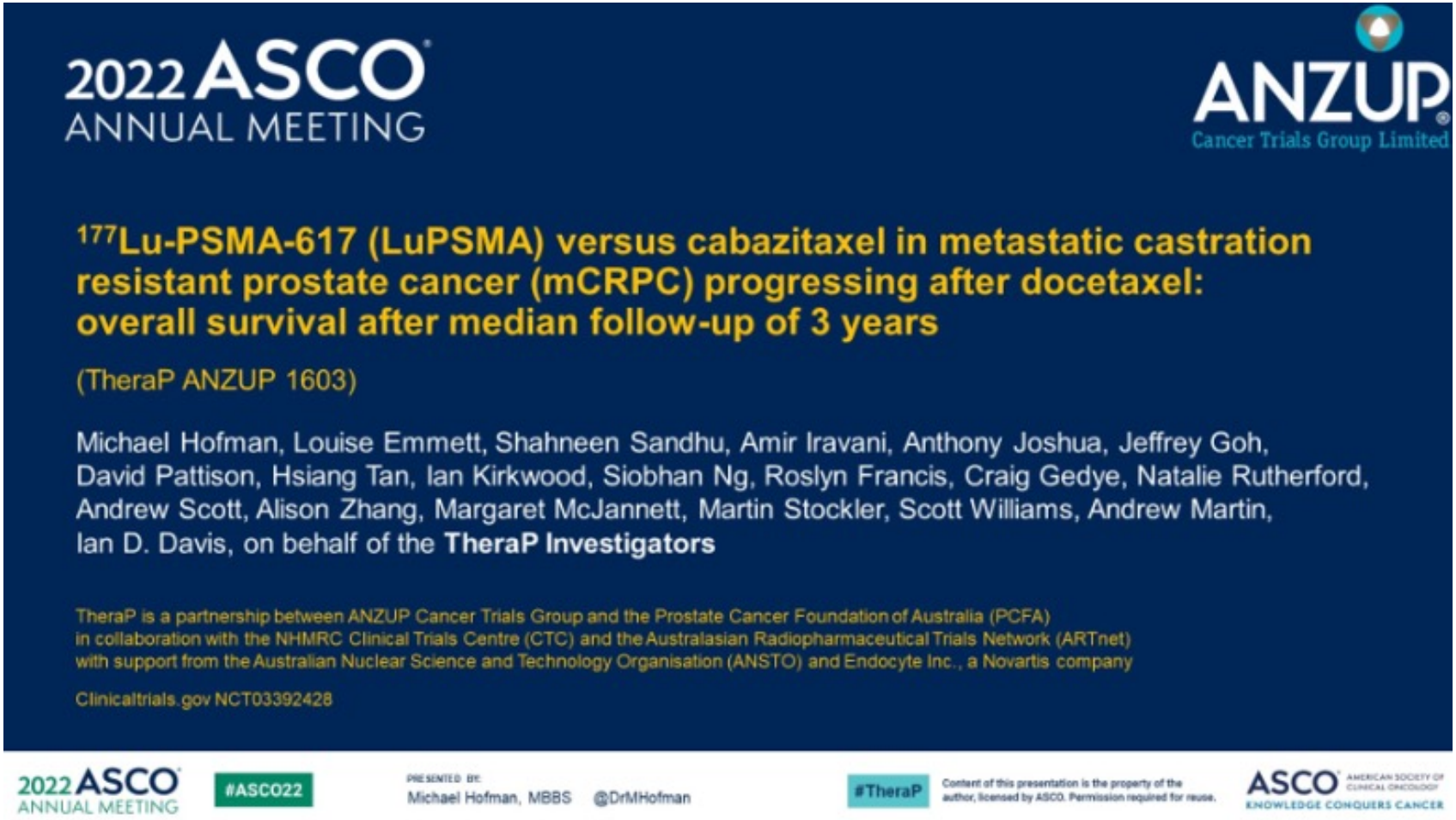
Patients, n (%)	All grades		Grade 3–5	
	^{177}Lu-PSMA-617 + SOC (n = 529)	SOC alone (n = 205)	^{177}Lu-PSMA-617 + SOC (n = 529)	SOC alone (n = 205)
Fatigue	260 (49.1)	60 (29.3)	37 (7.0)	5 (2.4)
Bone marrow suppression	251 (47.4)	36 (17.6)	124 (23.4)	14 (6.8)
Leukopenia	66 (12.5)	4 (2.0)	13 (2.5)	1 (0.5)
Lymphopenia	75 (14.2)	8 (3.9)	41 (7.8)	1 (0.5)
Anemia	168 (31.8)	27 (13.2)	68 (12.9)	10 (4.9)
Thrombocytopenia	91 (17.2)	9 (4.4)	42 (7.9)	2 (1.0)
Dry mouth	208 (39.3)	2 (1.0)	0 (0.0)	0 (0.0)
Nausea and vomiting	208 (39.3)	35 (17.1)	8 (1.5)	1 (0.5)
Renal effects	46 (8.7)	12 (5.9)	18 (3.4)	6 (2.9)
Second primary malignancies	11 (2.1)	2 (1.0)	4 (0.8)	1 (0.5)
Intracranial hemorrhage	7 (1.3)	3 (1.5)	5 (0.9)	2 (1.0)

Morris MJ, ASCO 2021

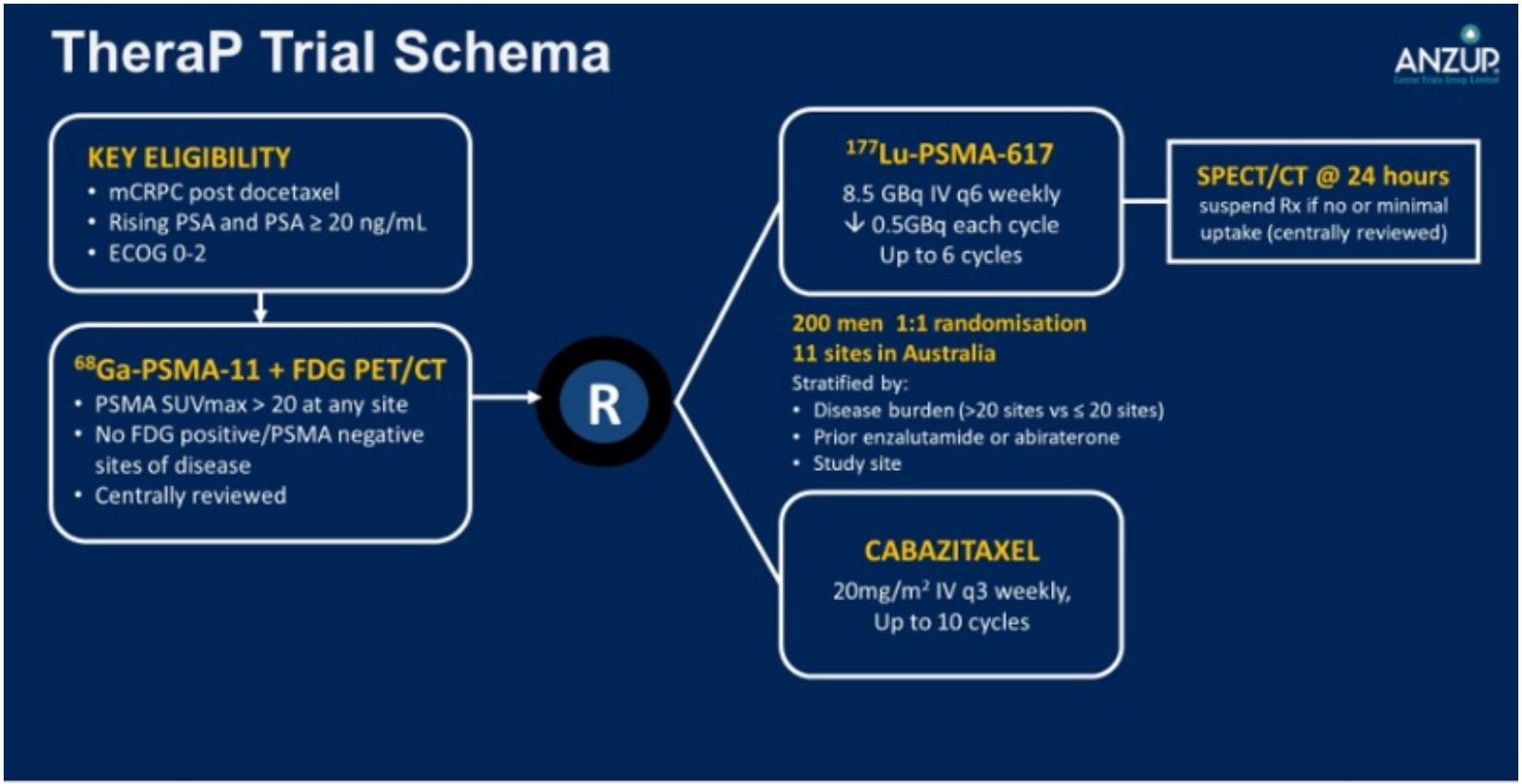
VISION study

- ^{177}Lu-PSMA-617 significantly prolonged vs standard care treatment
- Imaging-based progression-free survival (median, 8.7 vs. 3.4 months; hazard ratio for progression or death, 0.40;)
- Overall survival (median, 15.3 vs. 11.3 months; hazard ratio for death, 0.62;)

ASCO 2022 TheraP

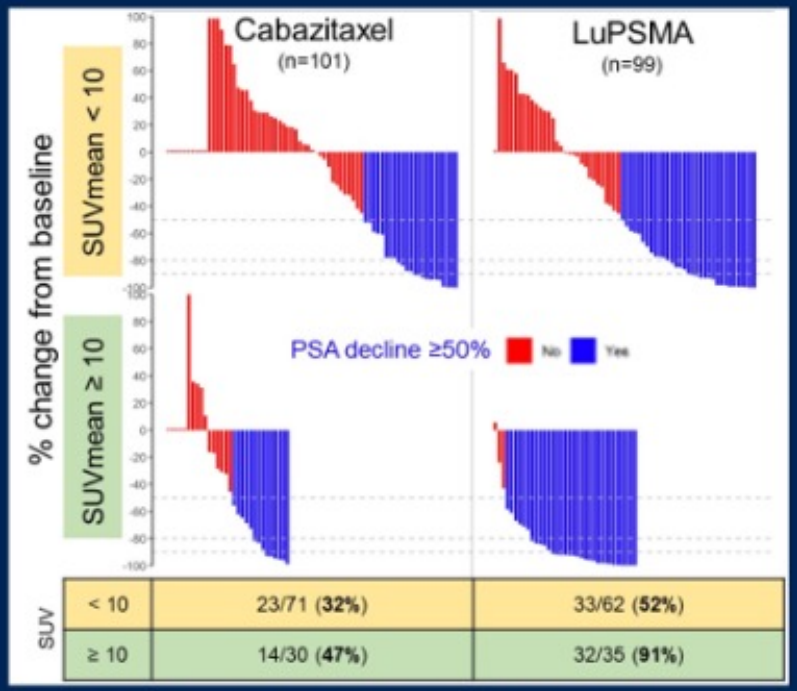


TheraP Trial Study Design

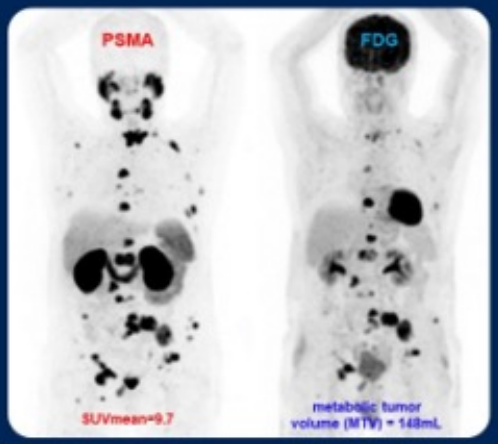


ASCO 2022: TheraP Study

Discussion: PSMA as predictive biomarker[1] (PSA50-RR)[11]



SUV	Cabazitaxel (n=101)	LuPSMA (n=99)
< 10	23/71 (**32%**)	33/62 (**52%**)
≥ 10	14/30 (**47%**)	32/35 (**91%**)



Odds of PSA50-RR to LuPSMA *vs* cabazitaxel

	OR (95% CI)	
PSMA SUVmean < 10	2.2 (1.1 – 4.5)	P=0.03
PSMA SUVmean ≥ 10	12.2 (3.4 - 59)	

[1]Buteau J et al, ASCO GU 2022. doi:10.1200/JCO.2022.40.6_suppl.010

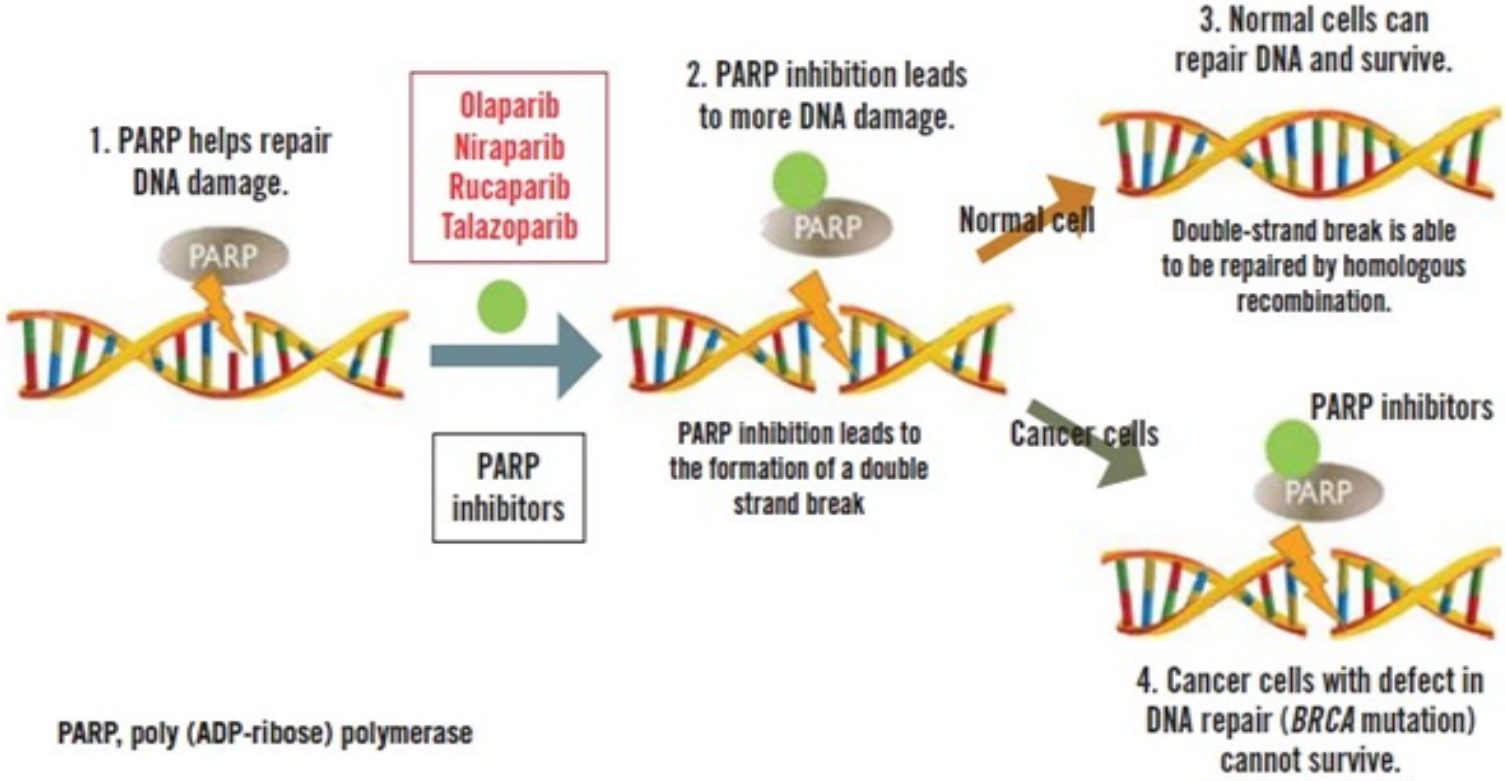
Further analysis to be performed including OS

^{177}Lu-PSMA-617 vs Cabizitaxel.

- PSMA PET scan is a biomaker. If SUV >10 I favor Lu-PSMA 617
- If patient progresses in less than 12 months on androgen pathway inhibitor I favor Cabizitaxel based on CARD Trial
- Phase III PSMAfore trial met primary endpoint. (pre-taxane indication)

3. PARP inhibitor

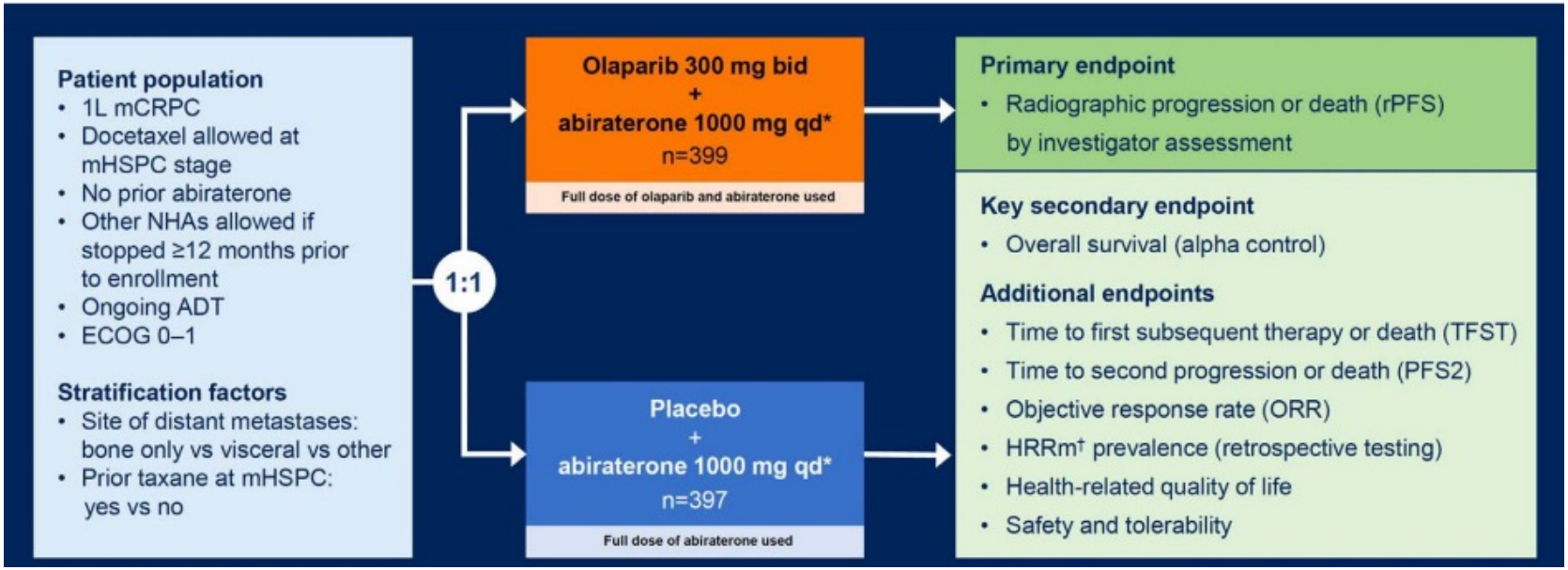
Mechanism of Action



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

PROpel Study

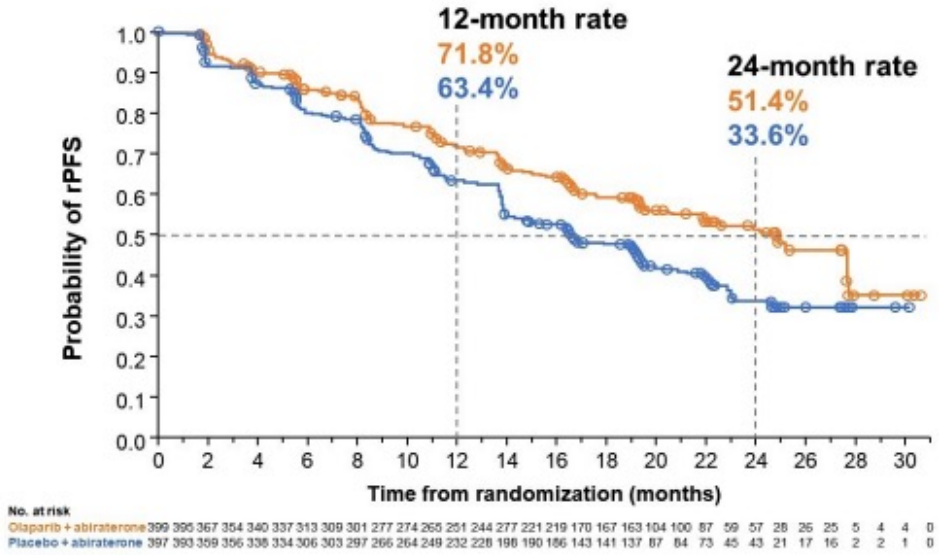
PROpel Study



Saad F et al. Genitourinary Cancers Symposium 2022;Abstract 11.

PROpel study

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	

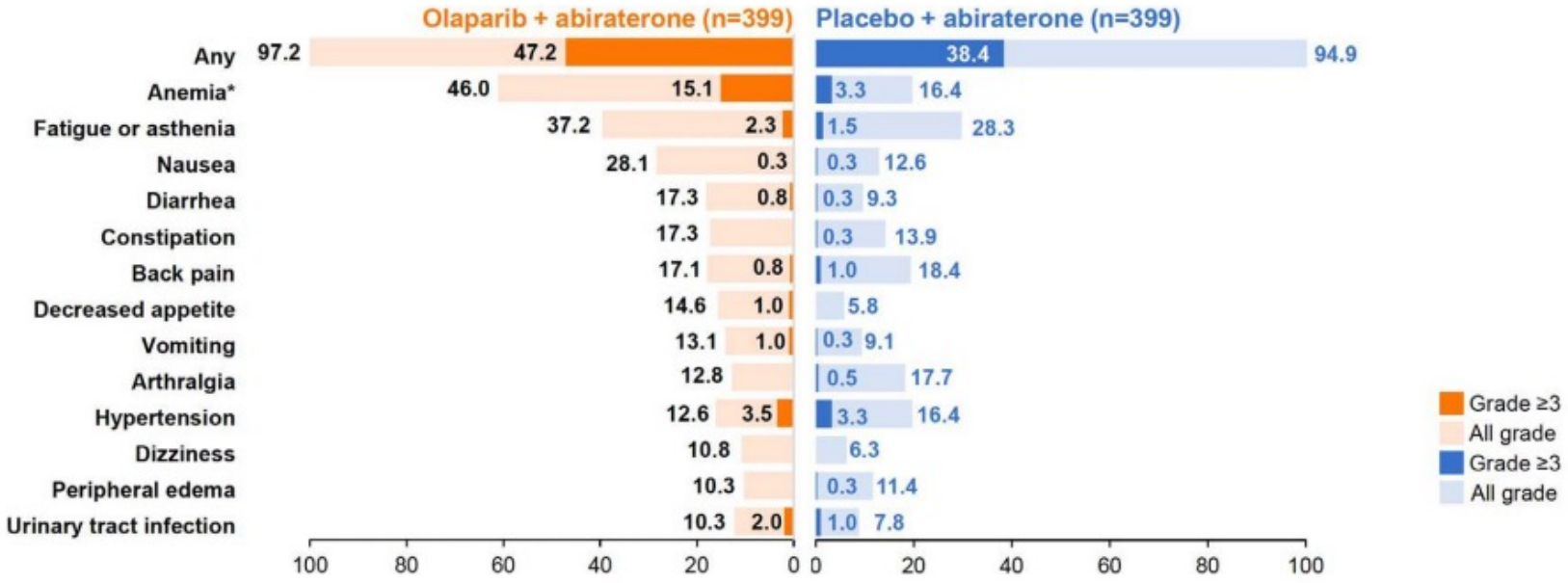
Pre-specified 2-sided alpha: 0.0324

Median rPFS improvement of 8.2 months favors olaparib + abiraterone*

Events: 394; Maturity 49.5%
*In combination with prednisone or prednisolone
CI, confidence interval; HR, hazard ratio.

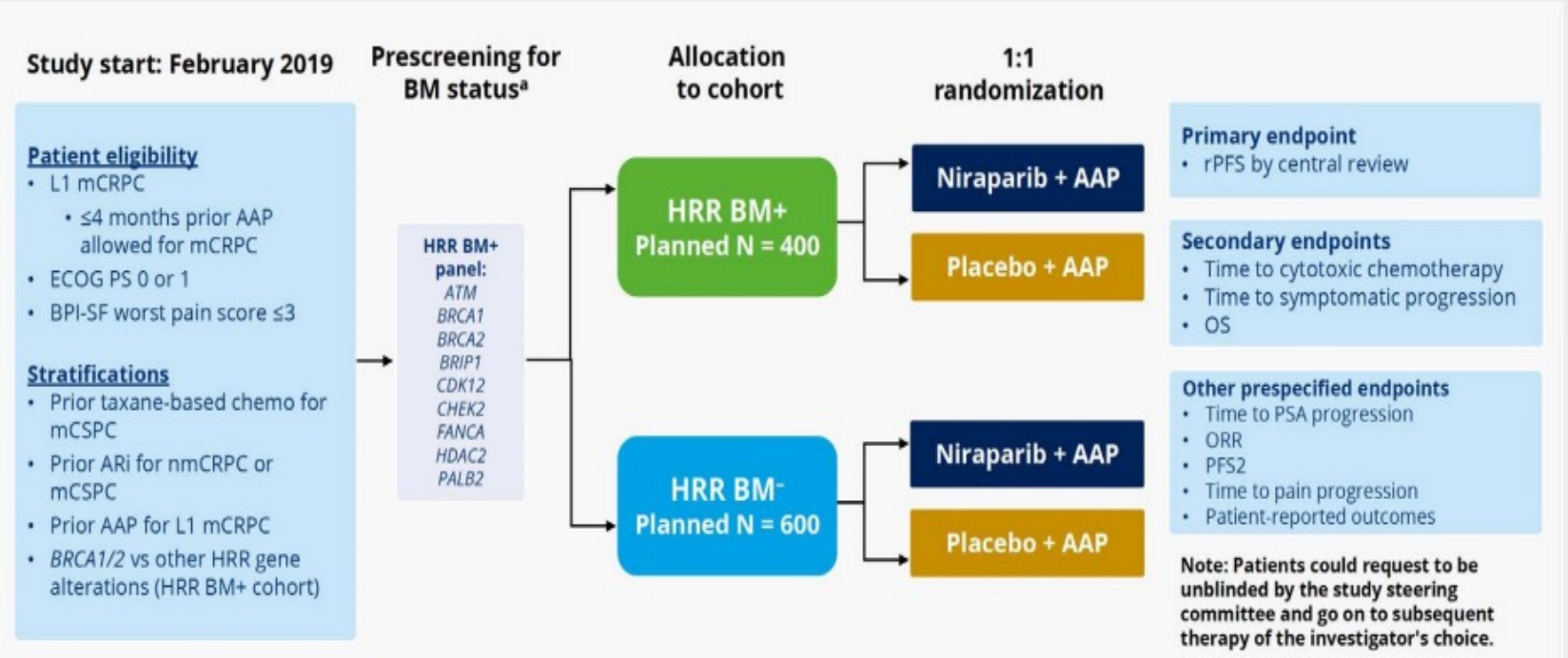
Saad F et al. Genitourinary Cancers Symposium 2022;Abstract 11.

PROpel Study



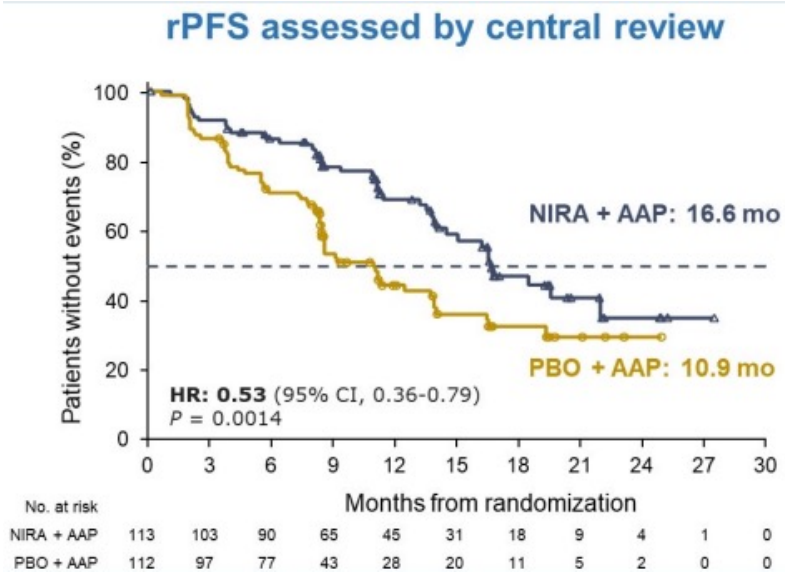
Saad F et al. Genitourinary Cancers Symposium 2022;Abstract 11.

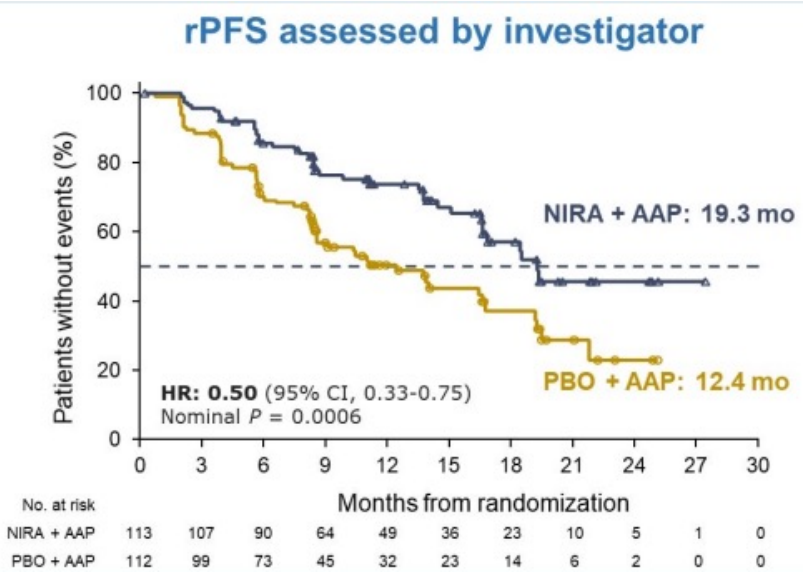
Magnitude Study



Chi et al Journal of Clinical Oncology 40, no. 6_suppl (February 20, 2022) 12-12.

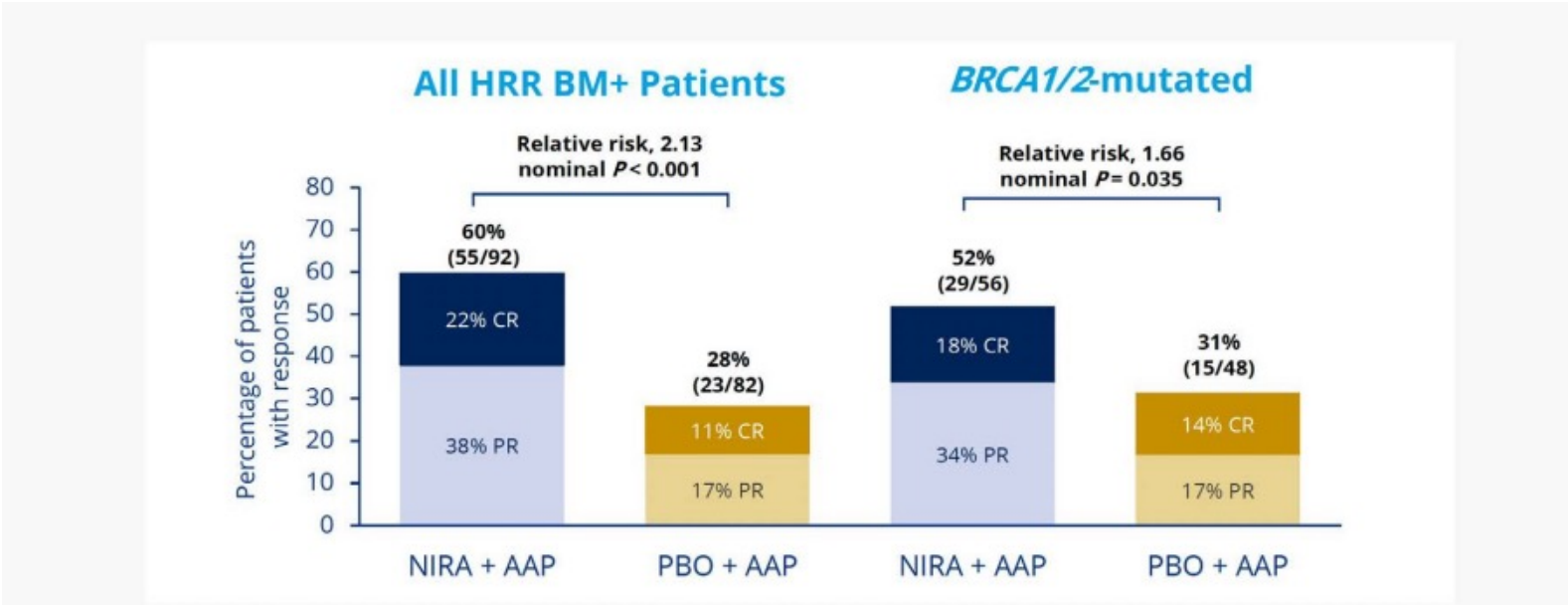
Magnitude study





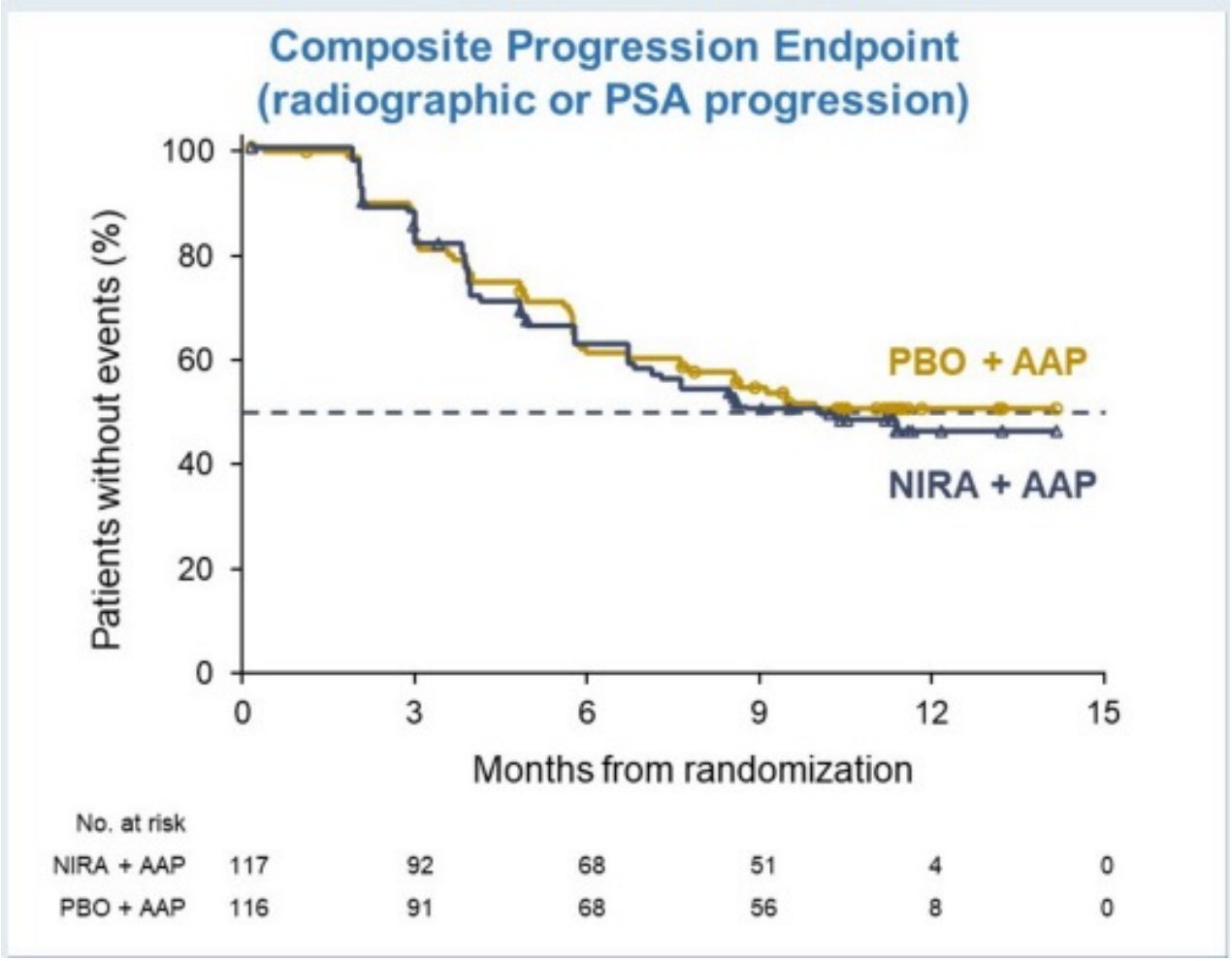
Chi et al Journal of Clinical Oncology *40, no. 6_suppl (February 20, 2022) 12-12.*

Magnitude Study



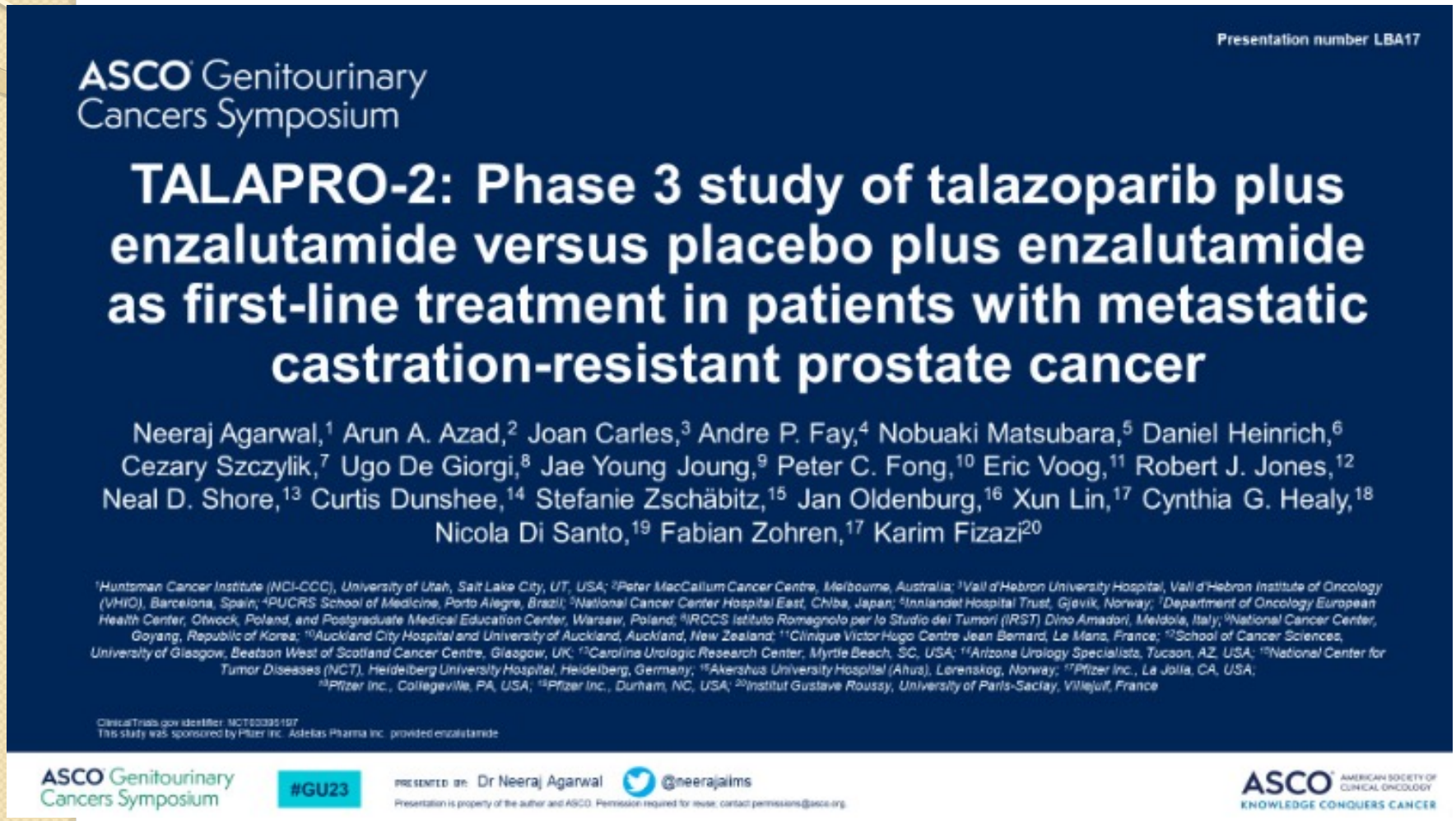
Chi et al Journal of Clinical Oncology 40, no. 6_suppl (February 20, 2022) 12-12.

MAGNITUDE study (HRR-)



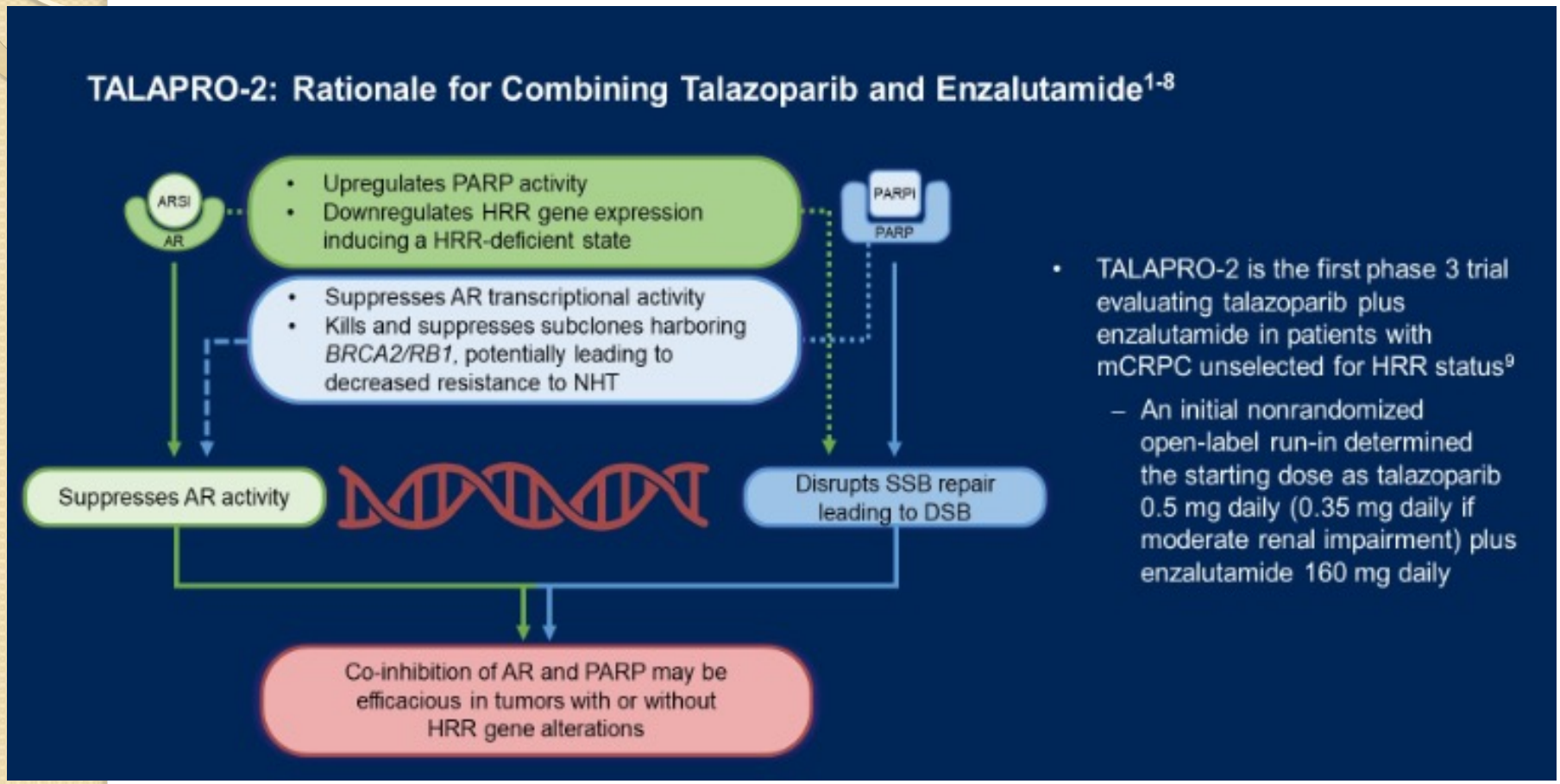
Chi et al Journal of Clinical Oncology *40, no. 6_suppl (February 20, 2022) 12-12.*

ASCO GU 2023



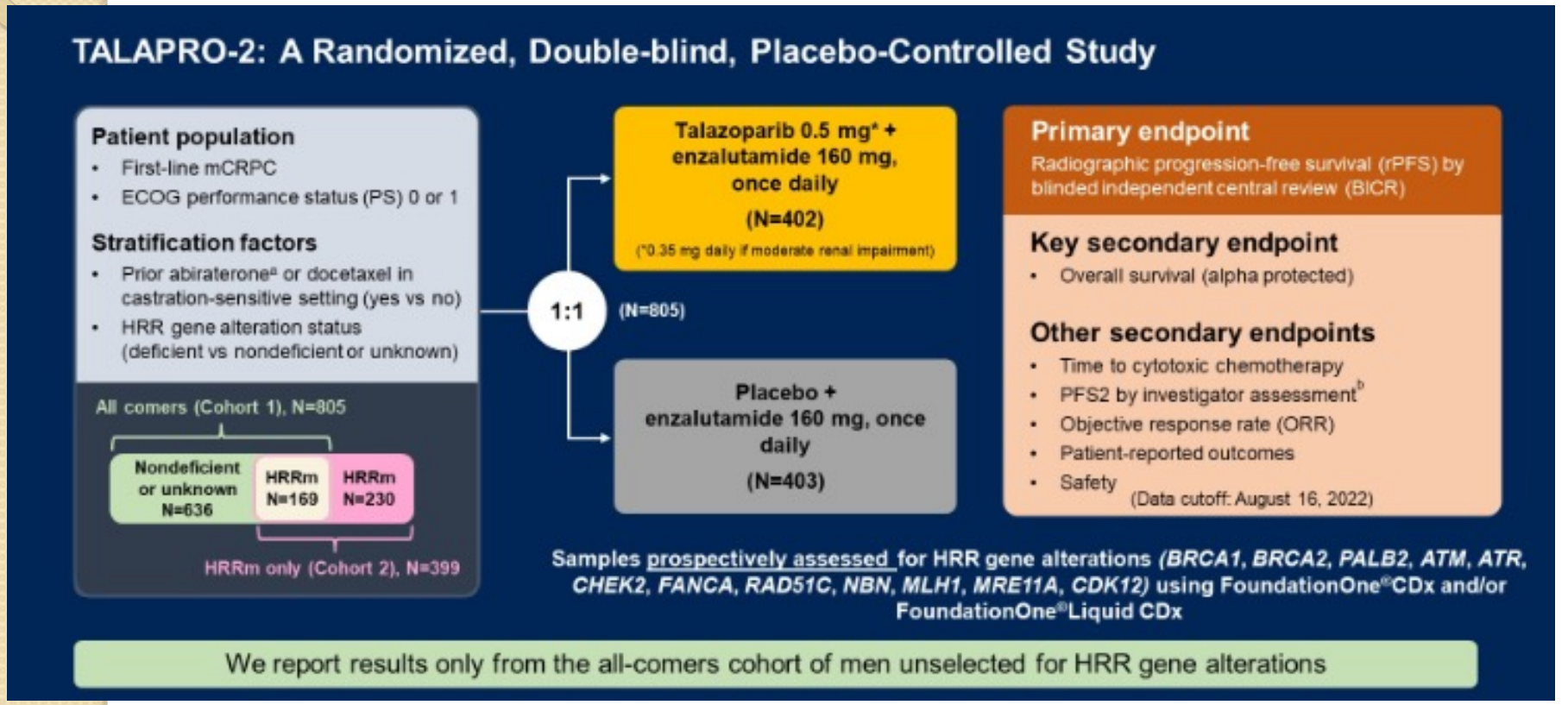
Agarwal, ASCO GU 2023

TALAPRO-2



Agarwal, ASCO GU 2023

TALAPRO-2



Agarwal, ASCO GU 2023

TALAPRO-2

TALAPRO-2: Baseline Demographics and Disease Characteristics

These were well-balanced between treatment arms

	Talazoparib + Enzalutamide (N=402)	Placebo + Enzalutamide (N=403)
Age, median (range), years	71 (41–90)	71 (36–91)
Prostate-specific antigen (PSA), median (range), ng/mL	18.2 (0.1–2796.0)	16.2 (0.1–2285.1)
Disease site, n (%)		
Bone	349 (86.8)	342 (84.9)
Lymph node	147 (36.6)	167 (41.4)
Visceral (lung)	45 (11.2)	61 (15.1)
Visceral (liver)	12 (3.0)	16 (4.0)
ECOG PS 0/1, n (%)	259 (64.4)/143 (35.6)	271 (67.2)/132 (32.8)
Prior abiraterone[a] or docetaxel, n (%)	109 (27.1)	110 (27.3)
Abiraterone	21 (5.2)	25 (6.2)
Docetaxel	86 (21.4)	93 (23.1)
HRR gene alteration status (for prospective stratification), n (%)		
Deficient	85 (21.1)	84 (20.8)
Nondeficient or unknown	317 (78.9)	319 (79.2)

[a]Two patients in each treatment arm received prior orteronel.

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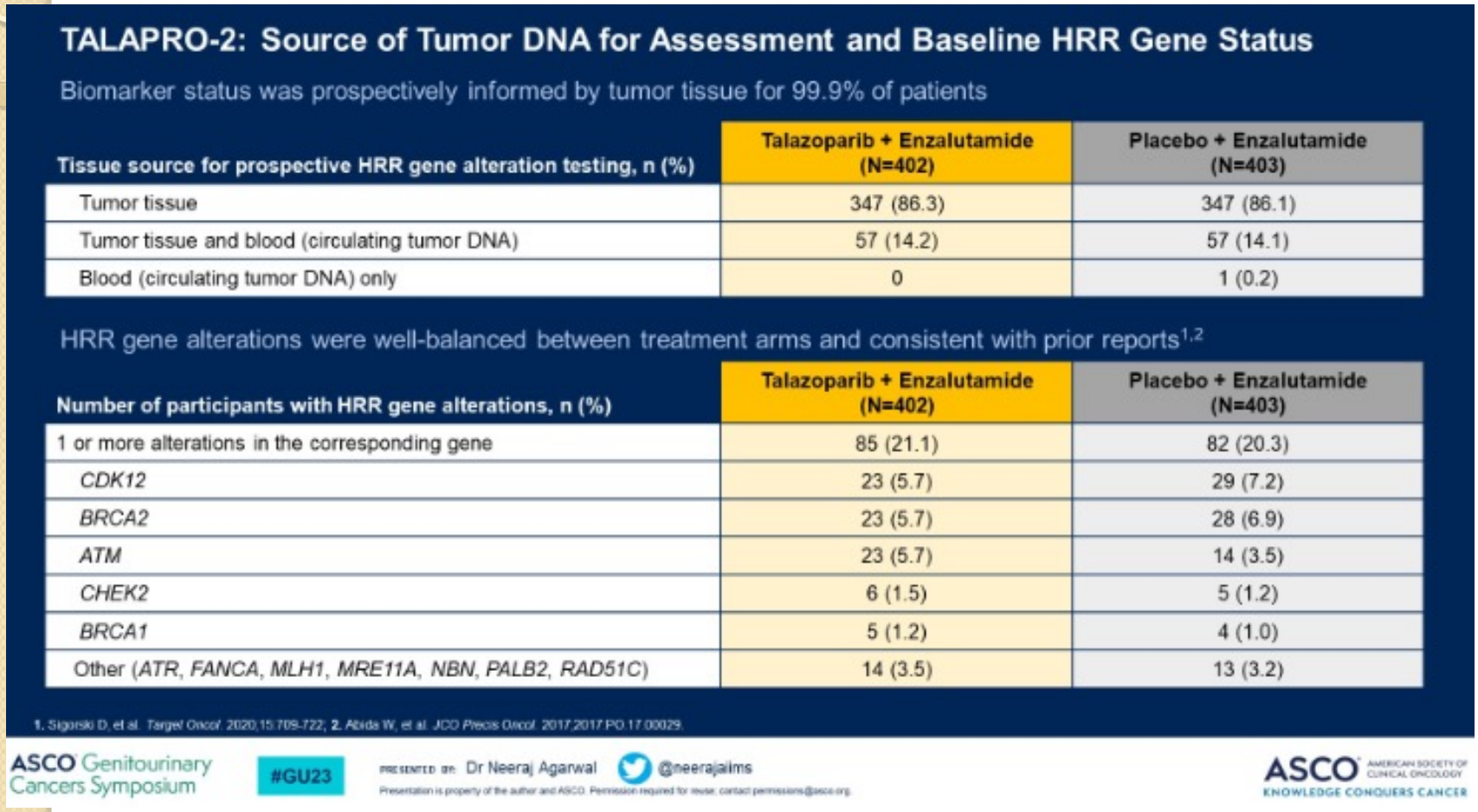
TALAPRO-2



TALAPRO-2: Source of Tumor DNA for Assessment and Baseline HRR Gene Status

Biomarker status was prospectively informed by tumor tissue for 99.9% of patients

Tissue source for prospective HRR gene alteration testing, n (%)	Talazoparib + Enzalutamide (N=402)	Placebo + Enzalutamide (N=403)
Tumor tissue	347 (86.3)	347 (86.1)
Tumor tissue and blood (circulating tumor DNA)	57 (14.2)	57 (14.1)
Blood (circulating tumor DNA) only	0	1 (0.2)

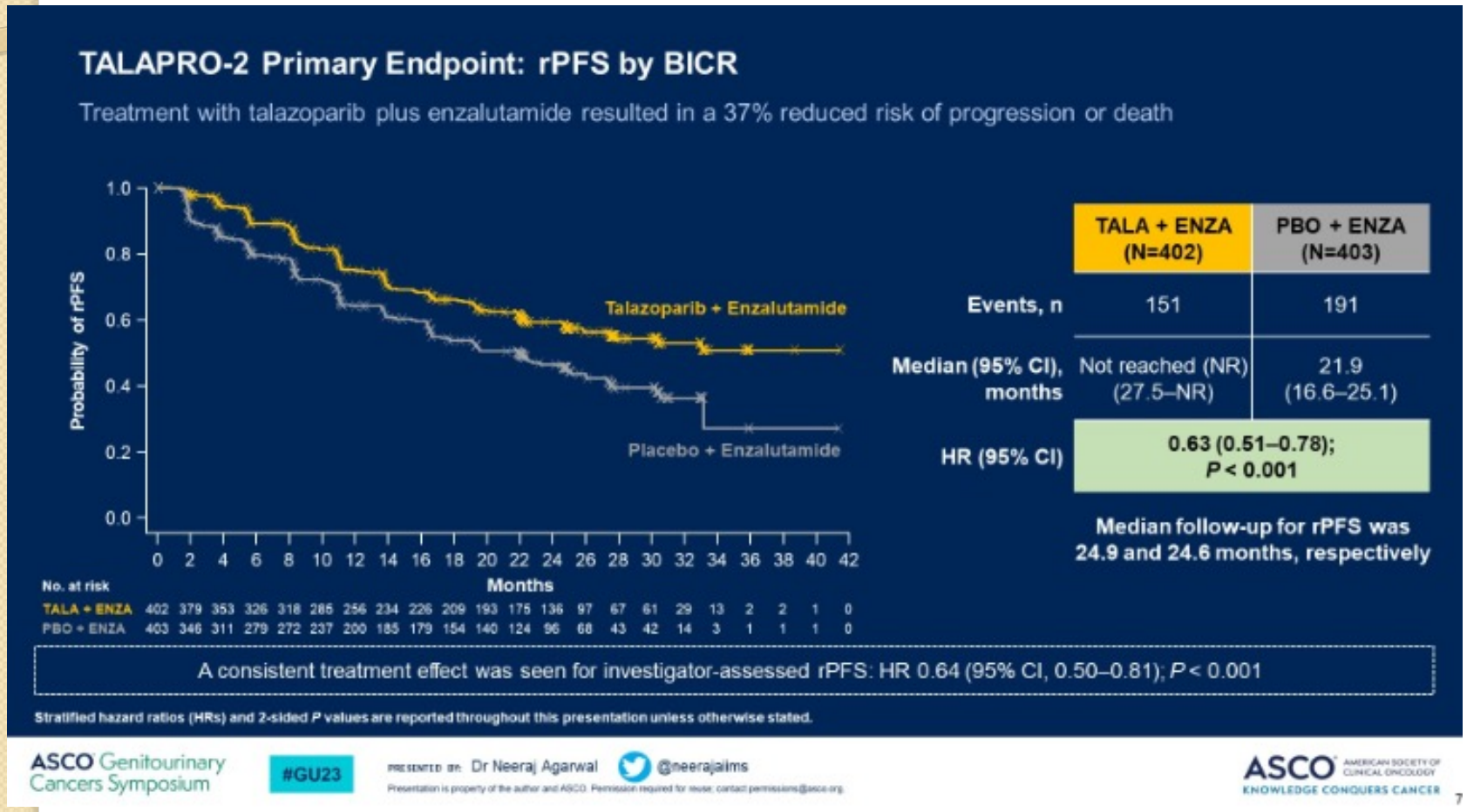
HRR gene alterations were well-balanced between treatment arms and consistent with prior reports[1,2]

Number of participants with HRR gene alterations, n (%)	Talazoparib + Enzalutamide (N=402)	Placebo + Enzalutamide (N=403)
1 or more alterations in the corresponding gene	85 (21.1)	82 (20.3)
CDK12	23 (5.7)	29 (7.2)
BRCA2	23 (5.7)	28 (6.9)
ATM	23 (5.7)	14 (3.5)
CHEK2	6 (1.5)	5 (1.2)
BRCA1	5 (1.2)	4 (1.0)
Other (*ATR*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, *RAD51C*)	14 (3.5)	13 (3.2)

1. Sigorski D, et al. *Target Oncol*. 2020;15:709-722; 2. Abida W, et al. *JCO Precis Oncol*. 2017;2017:PO.17.00029.

Agarwal, ASCO GU 2023

TALAPRO-2



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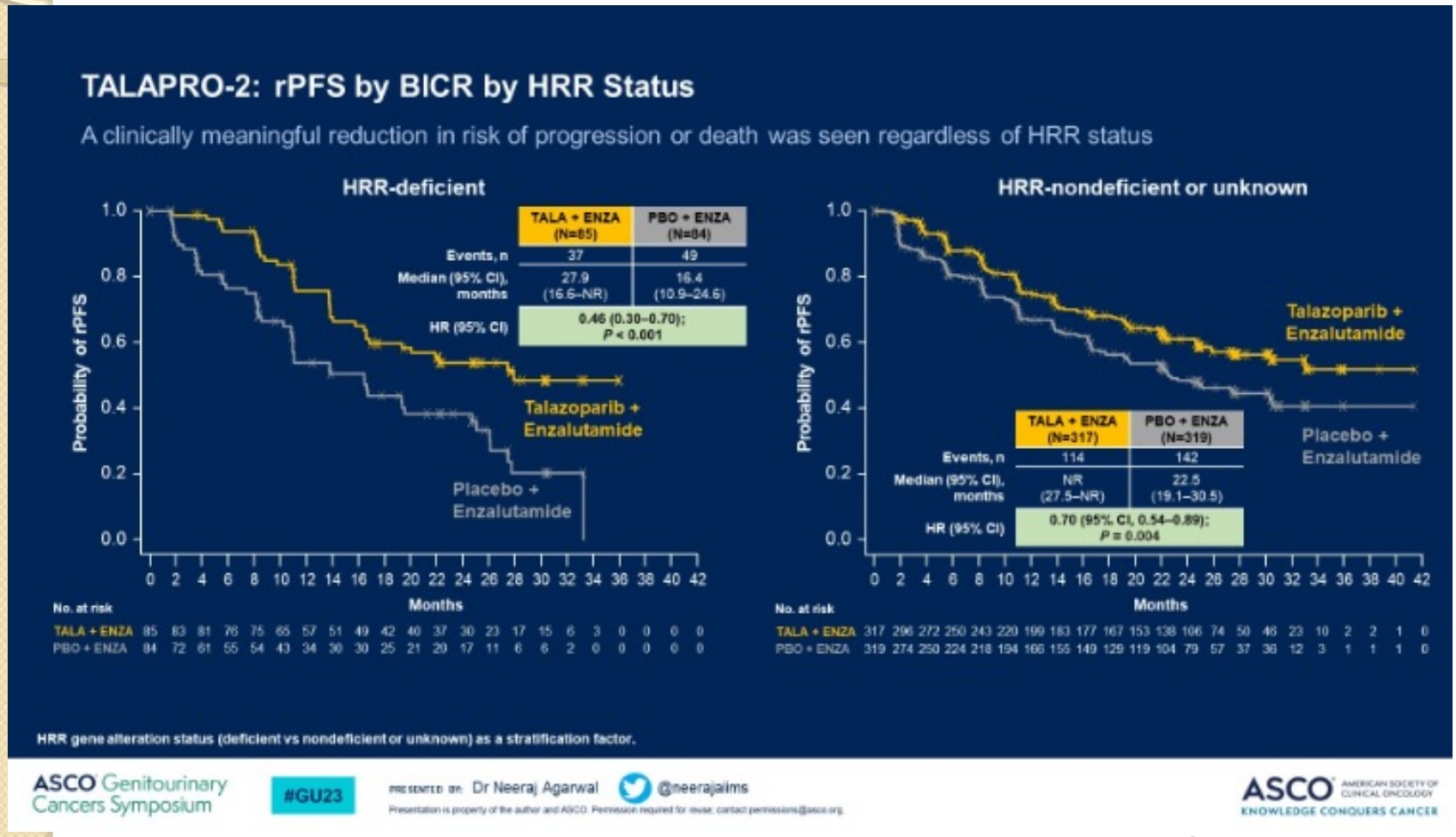
TALAPRO-2



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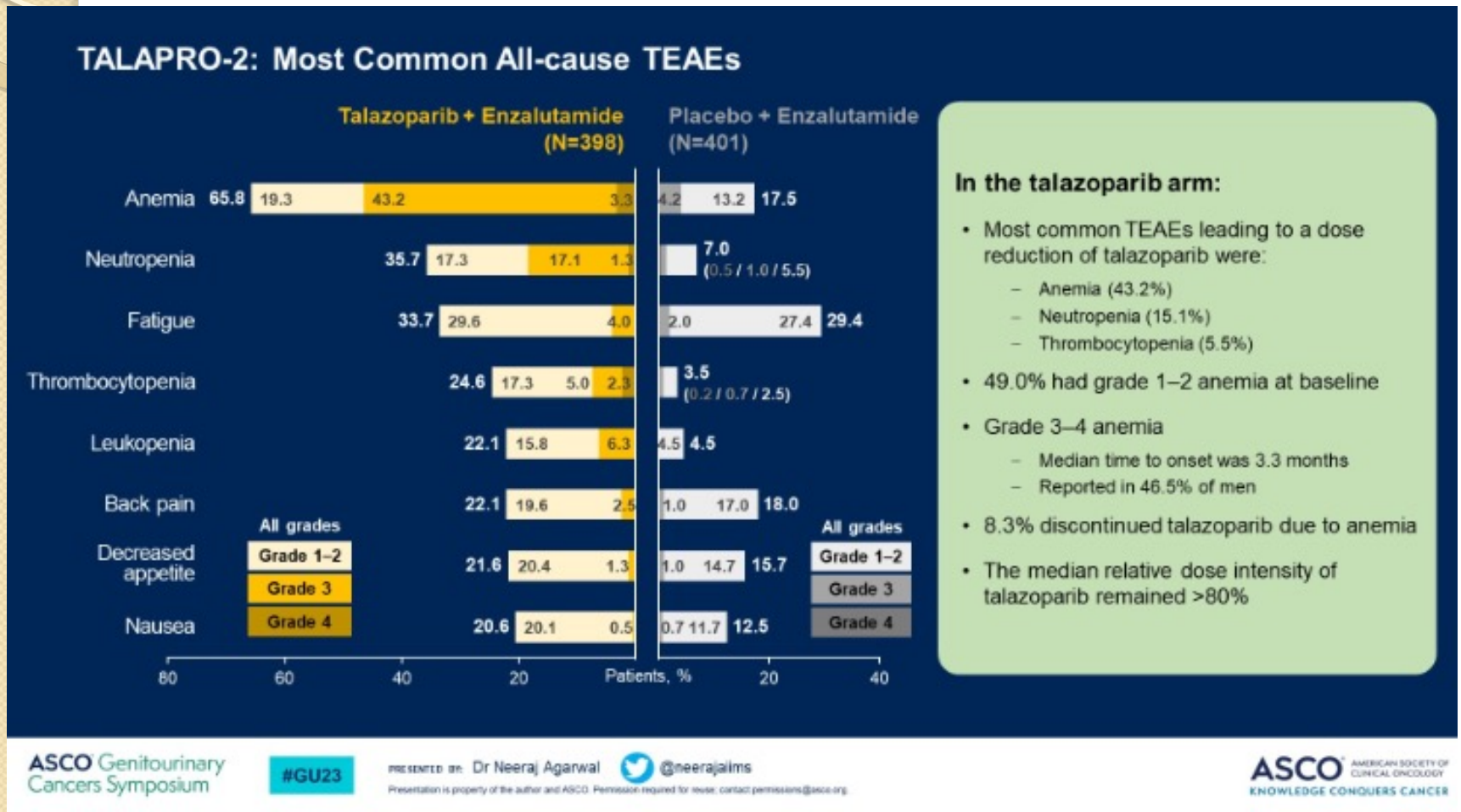
TALAPRO-2



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PARP + Androgen Pathway Inhibitor

- **PROpel**
  - rPFS benefit for olaparib + Abi/Pred + ADT vs placebo + Abi/Pred + ADT in overall population
  - Patients were not stratified by HRR status
  - Benefit across unselected patients

- **MAGNITUDE Study**
  - rPFS benefit for niraparib + Abi/Pred + ADT vs placebo + Abi/Pred + ADT
  - No benefit in HRRmut -ve cohort

- **TALAPRO-2 Study**
  - rPFS benefit for Talazoparib + Enzalutamide + ADT vs Enzalutamide +ADT
  - Benefit across unselected patients

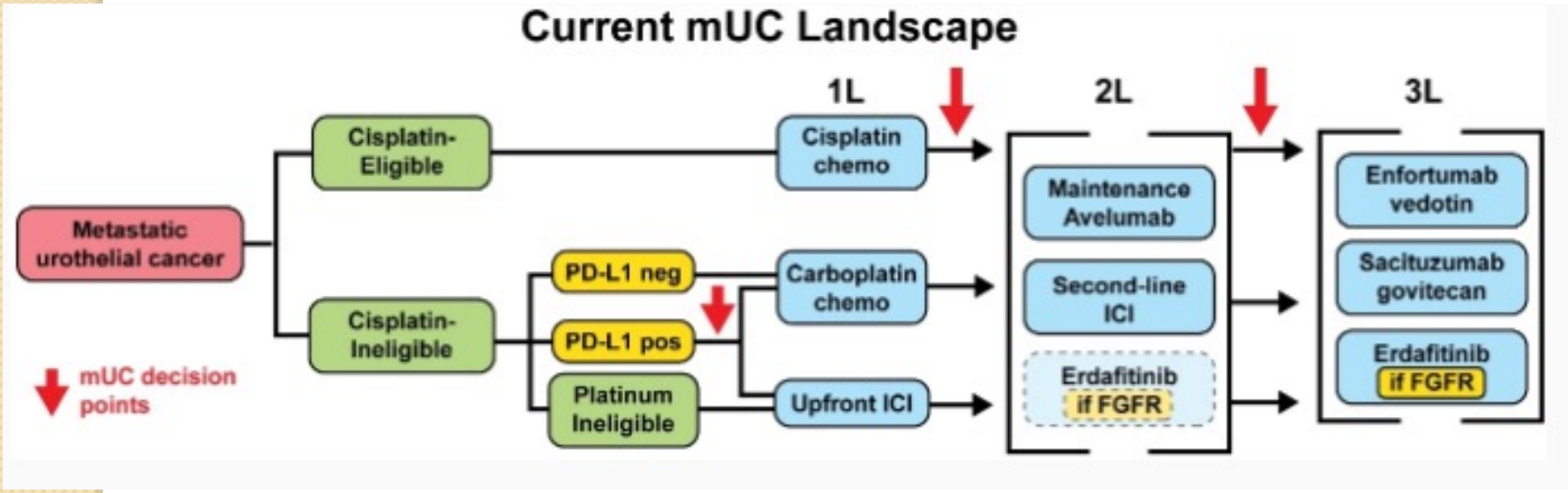
My practice

- I would consider PARP + Androgen Pathway Inhibitor + ADT for patients with metastatic castrate resistant prostate cancer with BRCA2 mutation
- Will await follow up studies with Enzalutamide + Rucaparib (CASPAR trial) since there appears to be discordance with MAGNITUDE, PROpel, and TALAPRO-2 for unselected patients

Targeted therapy in Urothelial Cancers

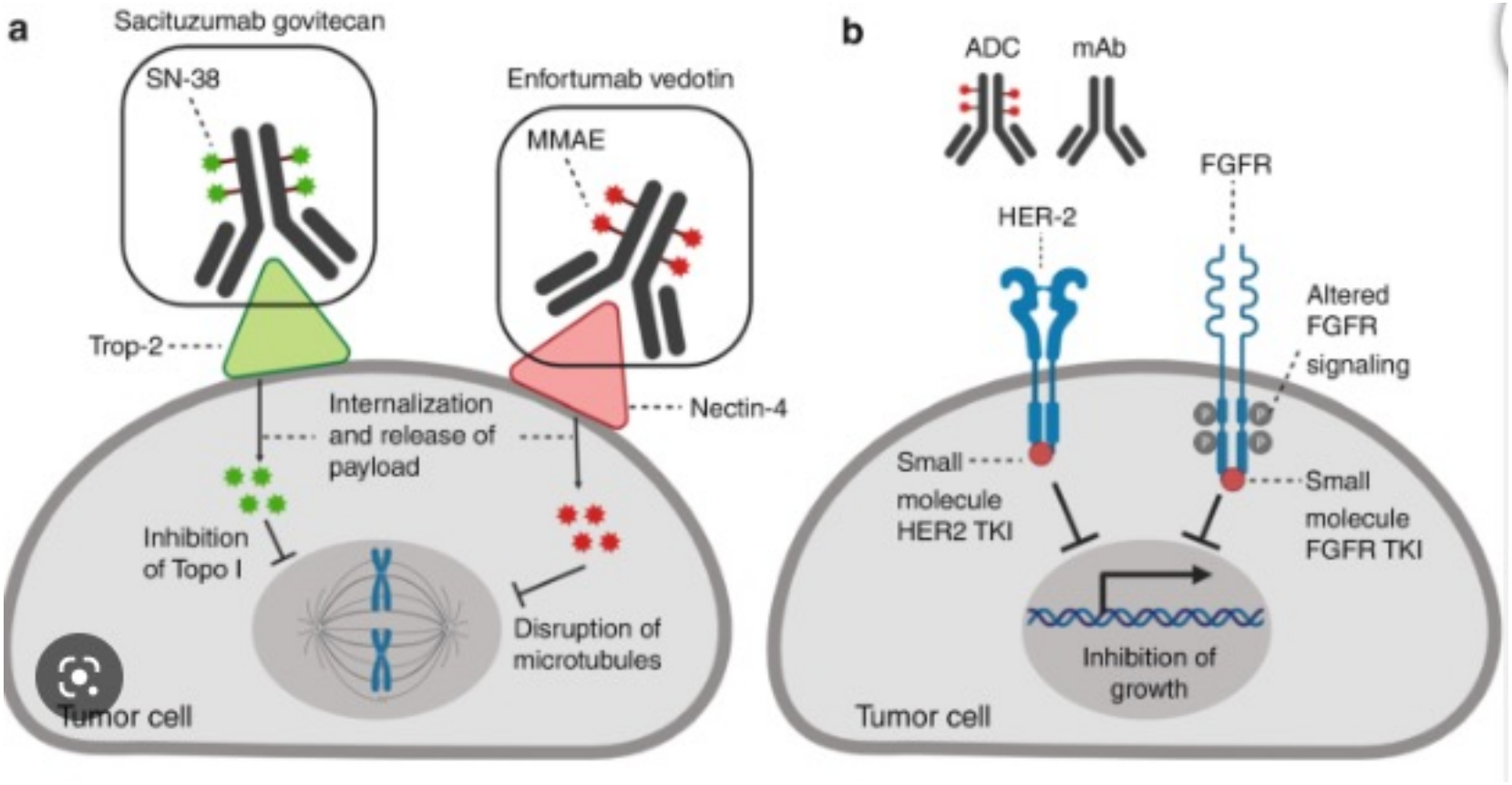
- FGFR 2/FGFR 3 inhibitor
- Nectin-4 directed therapy
- TROP 2 directed therapy,
- HER 2 directed therapy

Urothelial Cancer Algorithm



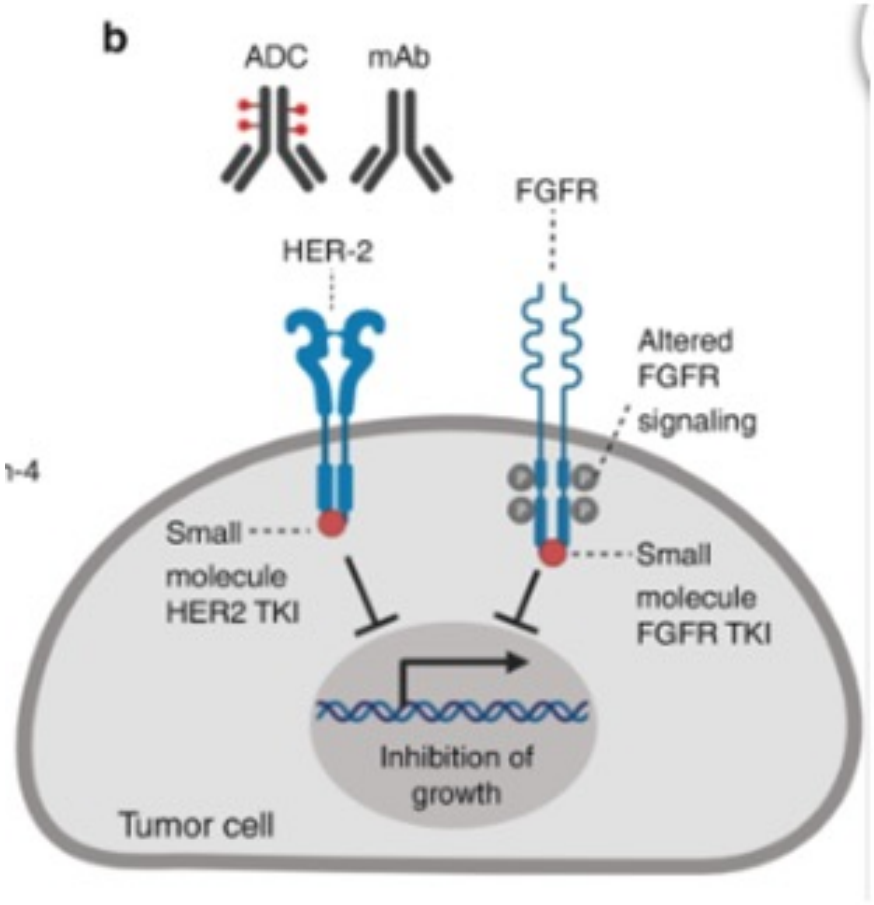
Jun, *J Cancer Metastasis Treat* 2022

Targeted Therapies



Alhalabi, Urinary Bladder Pathology, pp 199-209, 2021

Erdafitinib

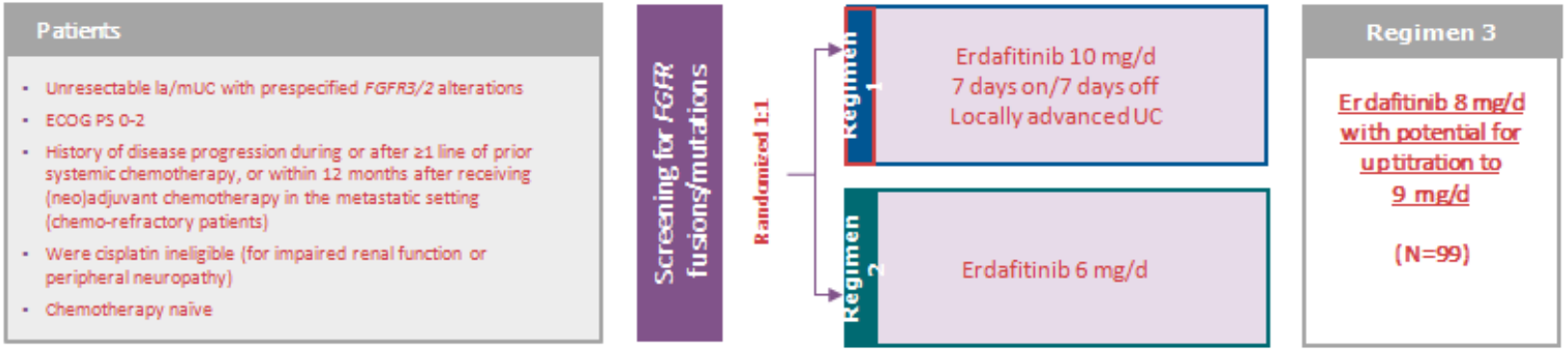


Alhalabi, Urinary Bladder Pathology, pp 199-209, 2021

Erdafitinib

BLC2001: Phase 2 Trial of Erdafitinib[1]

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



Primary endpoint

- Confirmed ORR

Secondary endpoints

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

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

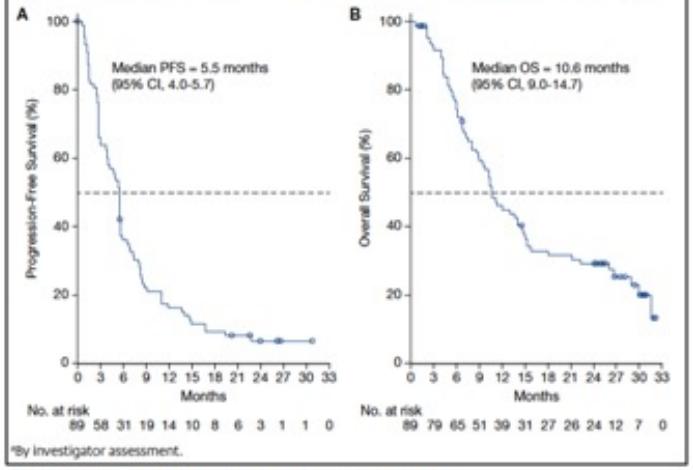
1. Loriot Y, et al. *N Engl J Med*. 2019;381(4):338-348.
2. Helsten T, et al. *Clin Cancer Res*. 2016;22(1):259-267.

Erdafitinib

BCL2001: Efficacy

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

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



[a]By investigator assessment.

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

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

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

Table 2. Efficacy Outcomes by Subgroup

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

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

Erdafitinib

BCL2001: Safety

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

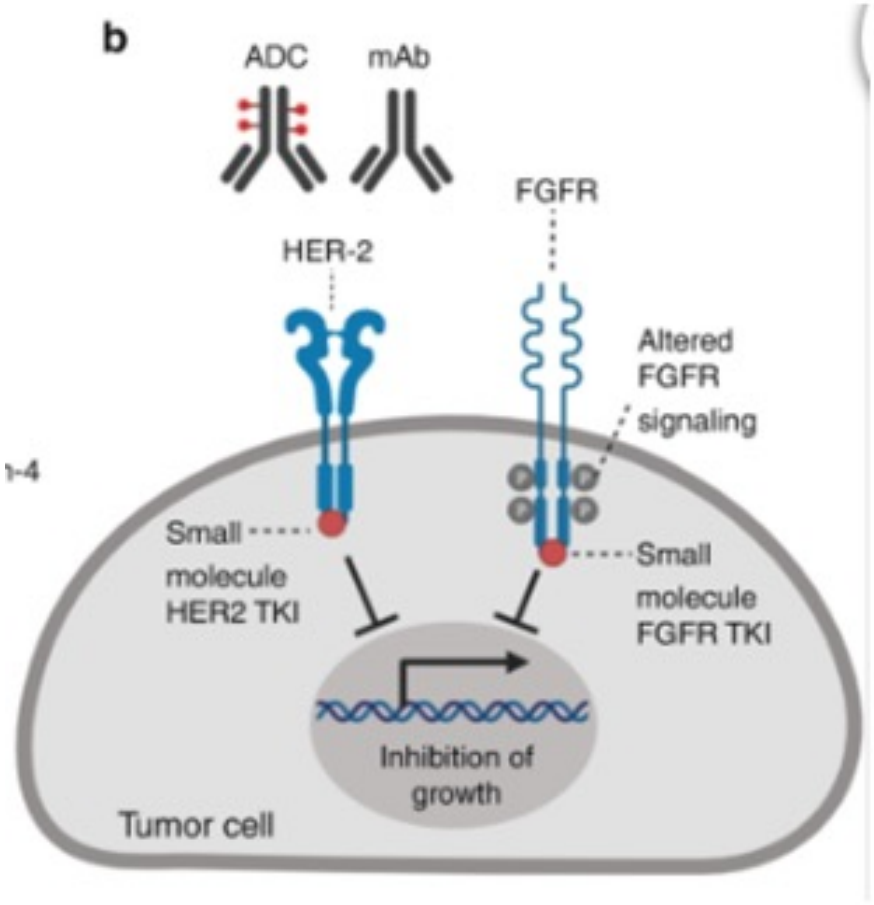
Final Analysis (n=101)

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

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

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

HER 2 Targeted treatment

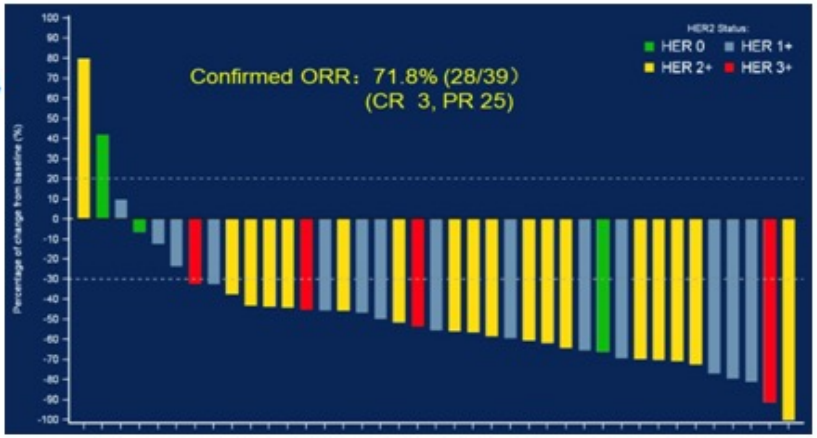


Alhalabi, Urinary Bladder Pathology, pp 199-209, 2021

HER2 antibody drug conjuage

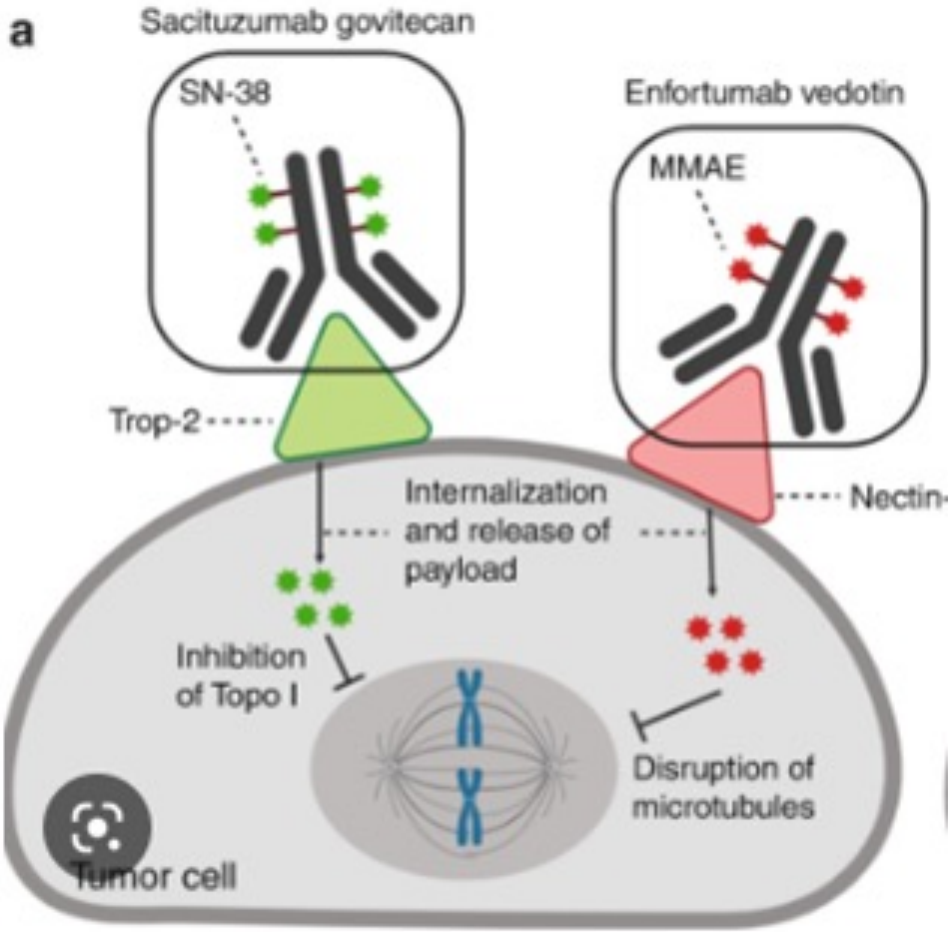
Disitamab Vedotin with Anti-PD-1 (Toripalimab) in mUC

- Pts with locally advanced or metastatic UC
- 41 pts (25 treatment-naïve / 16 with 1+ lines of therapy)
  - 39 pts evaluable for response
- Confirmed ORR: 72% (28/39)
  - cORR in IHC 0 or 1+ pts: 9/17 (53%)
- Median PFS: 9.2 months
- Median OS: NR (86% 12-month OS)



Promising results with DV trials in China led to a Breakthrough Therapy Designation by FDA
Phase II & III registrational trials (monotherapy & combo with anti-PD-1) pending

Antibody drug conjugate



ASCO 2022

Enfortumab Vedotin for Previously Treated Advanced UC

- The 5-year relative survival rate for metastatic bladder cancer is ≈8%[1]
- Enfortumab vedotin (EV), an antibody–drug conjugate directed against Nectin-4, demonstrated overall survival (OS) and progression-free survival (PFS) benefit in patients with locally advanced or metastatic (la/m) urothelial carcinoma (UC) in the open-label, confirmatory phase 3 EV-301 trial (NCT03474107) at the prespecified interim analysis[2]

Efficacy and safety are presented for EV vs chemotherapy over a median follow-up period of ≈2 years

Key eligibility criteria:
- Histologically/Cytologically confirmed UC
- Radiographic progression/ relapse during or after PD-1/L1 treatment for advanced UC
- Prior platinum-containing regimen for advanced UC
- ECOG PS 0–1

1:1 randomization with stratification

Enfortumab vedotin (N=301)
1.25 mg/kg on days 1, 8, and 15 of each 28-d cycle

Preselected chemotherapy (N=307)
Docetaxel 75 mg/m² or paclitaxel 175 mg/m² or vinflunine 320 mg/m² on day 1 of each 21-d cycle

Primary end point: Overall survival

Secondary end points:
- Progression-free survival
- Disease control rate
- Overall response rate
- Safety

Investigator-assessed per RECIST v1.1

Findings from the prespecified, event-driven OS analysis when 439 deaths occurred are presented

y Group performance status; EV, enfortumab vedotin; la/m, locally advanced or metastatic; OS, overall survival; PD-1/L1, programmed cell death protein-1/programmed death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; UC, urothelial carcinoma.

1. National Cancer Institute. https://seer.cancer.gov/statfacts/html/urinb.html. 2. Powles T, et al. *N Engl J Med.* 2021;384:1125-1135.

PRESENTED BY: Jonathan E. Rosenberg, MD

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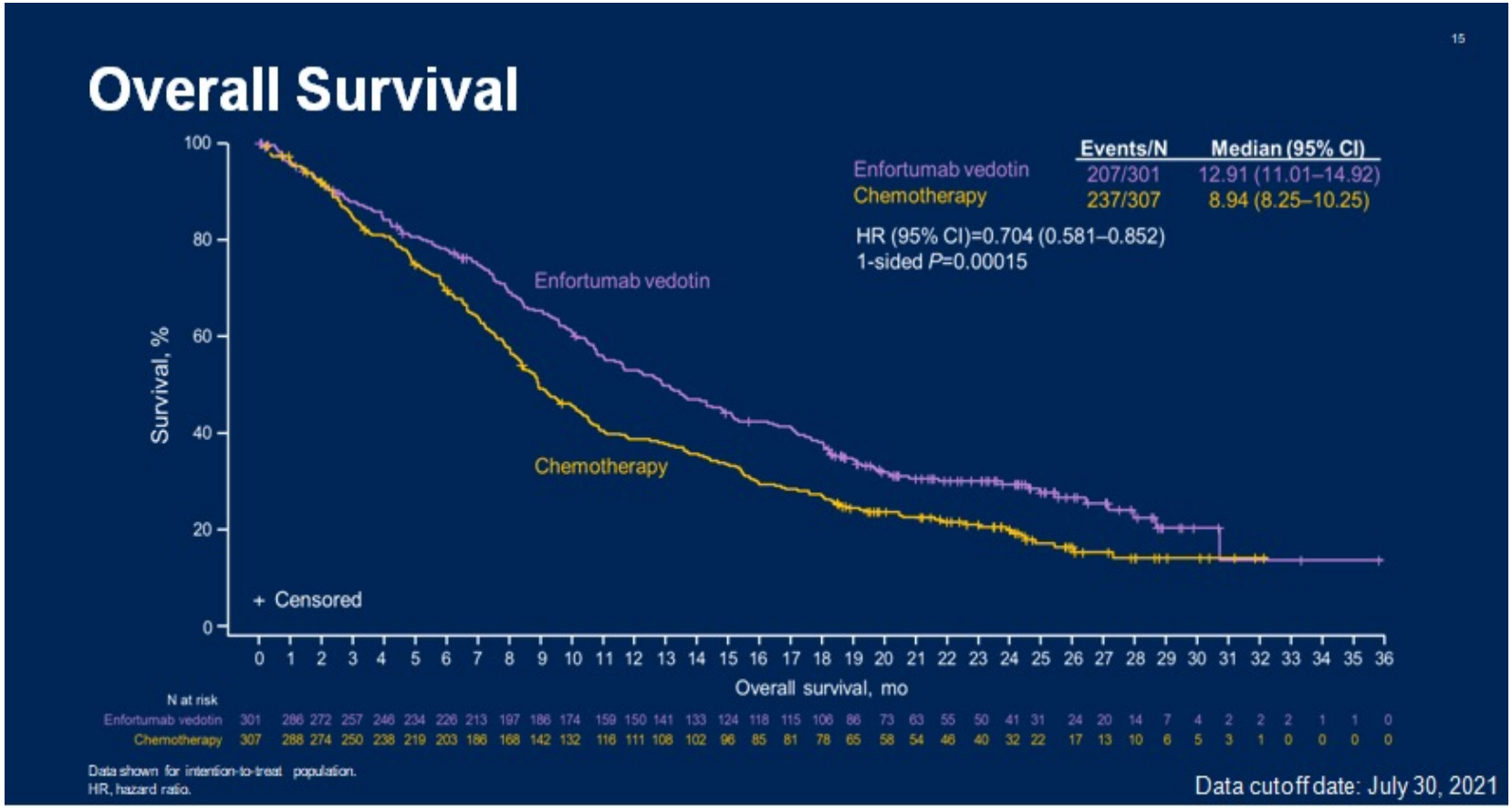

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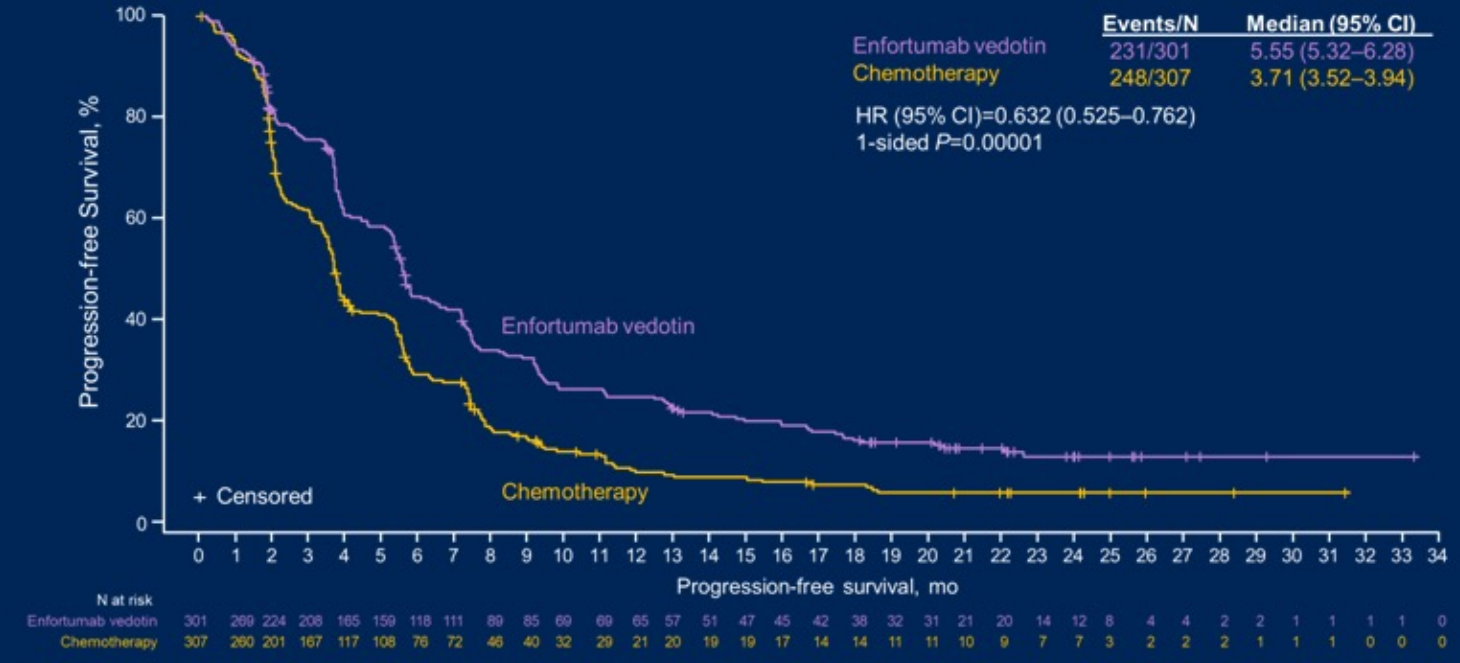
Progression-Free Survival



Data shown for intention-to-treat population.
HR, hazard ratio.

Data cutoff date: July 30, 2021

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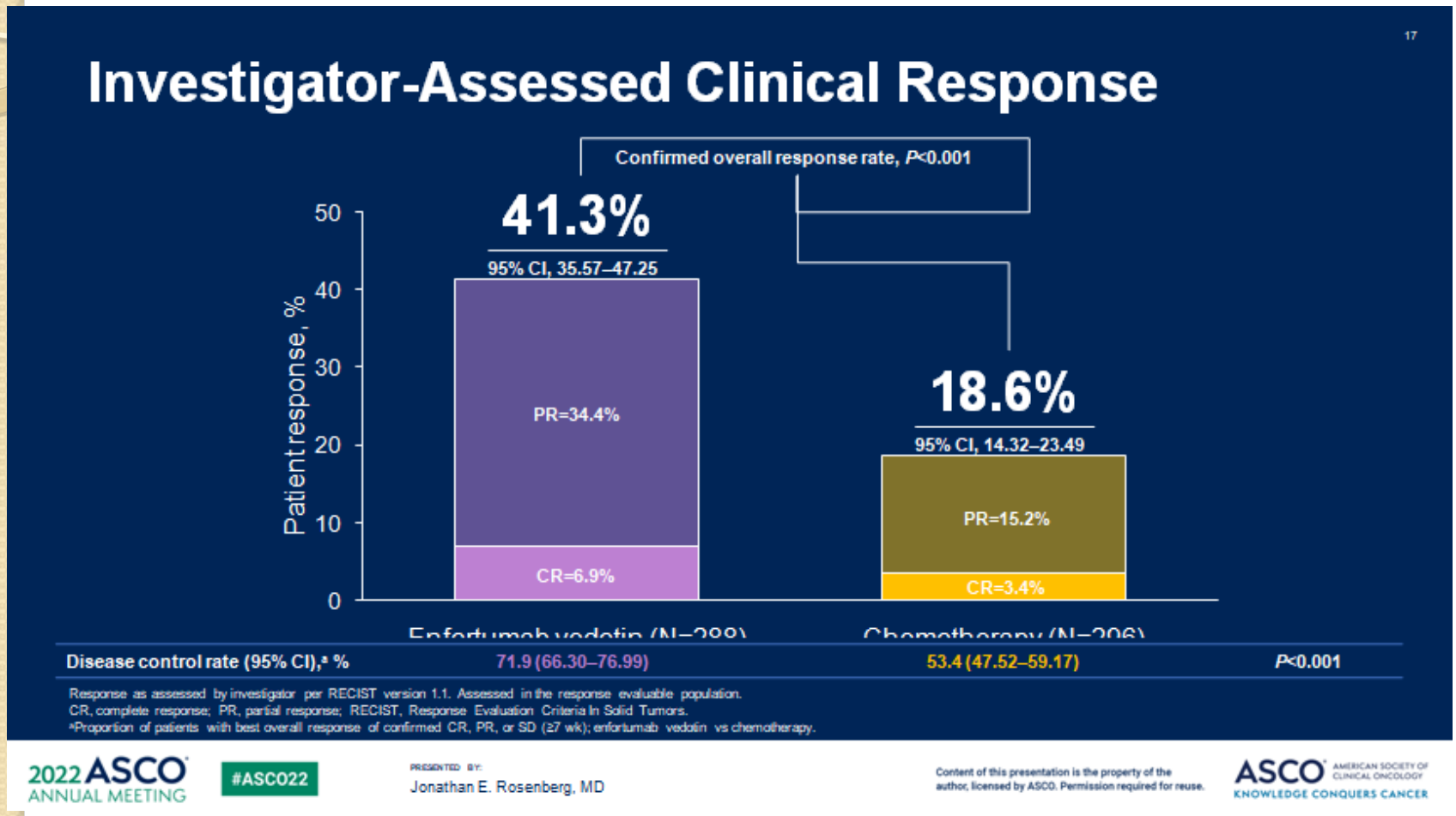
17
Investigator-Assessed Clinical Response
Confirmed overall response rate, P<0.001
41.3%
95% CI, 35.57–47.25
PR=34.4%
CR=6.9%
18.6%
95% CI, 14.32–23.49
PR=15.2%
CR=3.4%
Patient response, %
50
40
30
20
10
0
Disease control rate (95% CI),[a] %
71.9 (66.30–76.99)
53.4 (47.52–59.17)
P<0.001
Response as assessed by investigator per RECIST version 1.1. Assessed in the response evaluable population.
CR, complete response; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors.
[a]Proportion of patients with best overall response of confirmed CR, PR, or SD (≥7 wk); enfortumab vedotin vs chemotherapy.
2022 ASCO ANNUAL MEETING
#ASCO22
PRESENTED BY:
Jonathan E. Rosenberg, MD
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KNOWLEDGE CONQUERS CANCER

ASCO 2022

Safety/Tolerability

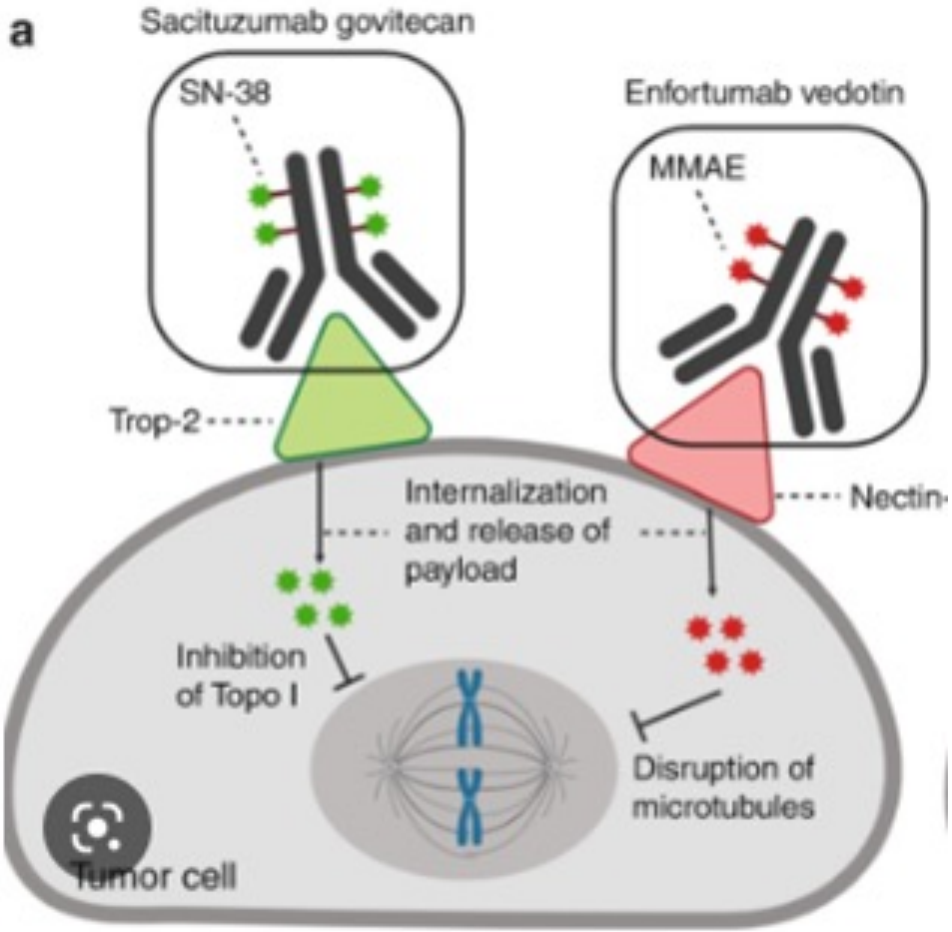
- Median (range) duration rates of treatment were 4.99 mo (0.5-29.9) for EV and 3.45 mo (0.2–26.4) for chemotherapy
- Rates of treatment-related adverse events (TRAEs; 93.9% vs 91.8%) and serious TRAEs (22.6% vs 23.4%) were comparable between EV and chemotherapy groups

	Enfortumab vedotin (N=296)		Chemotherapy (N=291)	
Treatment-related adverse event, n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
Alopecia	135 (45.6)	NR	108 (37.1)	NR
Peripheral sensory neuropathy	103 (34.8)	15 (5.1)	63 (21.6)	6 (2.1)
Pruritus	96 (32.4)	4 (1.4)	14 (4.8)	1 (0.3)
Fatigue	93 (31.4)	20 (6.8)	66 (22.7)	13 (4.5)
Decreased appetite	92 (31.1)	9 (3.0)	69 (23.7)	5 (1.7)
Diarrhea	74 (25.0)	10 (3.4)	49 (16.8)	5 (1.7)
Dysgeusia	73 (24.7)	NR	22 (7.6)	NR
Nausea	71 (24.0)	3 (1.0)	64 (22.0)	4 (1.4)
Maculopapular rash	50 (16.9)	22 (7.4)	5 (1.7)	NR
Anemia	34 (11.5)	8 (2.7)	63 (21.6)	23 (7.9)
Decreased neutrophil count	31 (10.5)	18 (6.1)	51 (17.5)	41 (14.1)
Neutropenia	20 (6.8)	14 (4.7)	25 (8.6)	18 (6.2)
Decreased white blood cell count	15 (5.1)	4 (1.4)	32 (11.0)	21 (7.2)
Febrile neutropenia	2 (0.7)	2 (0.7)	16 (5.5)	16 (5.5)

Occurring in ≥20% of patients in either treatment group or grade ≥3 TRAEs occurring in ≥5% of patients in either treatment group. Data shown for safety population.

Data cutoff date: July 30, 2021

Antibody drug conjugate



Sacituzumab Govitecan

TROPHY-U-01 Is a Registrational, Open-Label, Multicohort Phase 2 Trial in Patients With mUC

TROPHY U-01

Cohort 1* (~100 patients): patients with mUC who progressed after prior platinum-based and CPI-based therapies — SG 10 mg/kg Days 1 and 8, every 21 days

Cohort 2 (~40 patients): patients with mUC ineligible for platinum-based therapy and who progressed after prior CPI-based therapies — SG 10 mg/kg Days 1 and 8, every 21 days

Cohort 3[a] (up to 61 patients): mUC CPI naïve patients who progressed after prior platinum-based therapies — SG 10 mg/kg Days 1 and 8, every 21 days; Pembrolizumab 200 mg day 1 every 21 days

Cohort 4 (up to 60 patients): mUC platinum-naïve patients — SG Days 1 and 8, every 21 days; Cisplatin[b]

Cohort 5 (up to 60 patients): mUC platinum-naïve patients — SG Days 1 and 8, every 21 days; Cisplatin[c]; Avelumab 800 mg every 2 weeks

Continue treatment in the absence of unacceptable toxicity or disease progression

Continue until a maximum of 6 cycles has been completed,[d] disease progression, lack of clinical benefit, toxicity, or withdrawal of consent → Maintenance avelumab (800 mg every 2 weeks) with SG (Days 1 and 8 every 21 days) for those without disease progression

Primary Endpoint:
Objective response rate per RECIST 1.1 criteria

Key Secondary Endpoints:
Safety/tolerability, DOR, PFS, OS

Key Inclusion Criteria: Age ≥18 years, ECOG of 0/1, creatinine clearance (CrCl) ≥30 mL/min,[b,c] adequate hepatic function
Key Exclusion Criteria: Immunodeficiency, active Hepatitis B or C, active secondary malignancy, or active brain metastases

***Accelerated FDA approval for treatment of patients with locally advanced or mUC who previously received platinum-containing chemotherapy and PD-1/L1 inhibitor[1]**

[a]Exclusions for Cohort 3 only: active autoimmune disease or history of interstitial lung disease. [b]In patients with CrCl ≥60 mL/min. [c]In patients with creatinine clearance 50–60 mL/min. [d]For patients who have not progressed, maintenance therapy will begin with infusions of avelumab (800 mg every 2 weeks beginning cycle 1, day 1 and every 2 weeks thereafter) followed by SG on days 1 and 8 every 21 days.
CBR, clinical benefit rate; CPI, checkpoint inhibitor; CrCl, creatinine clearance; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; mUC, metastatic urothelial cancer; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SG, sacituzumab govitecan.

1. TRODELVY™ (sacituzumab govitecan-hziy). Prescribing Information. Immunomedics, Inc.; April 2021; EudraCT Number: 2018-001167-23; ClinicalTrials.gov Number: NCT03547973. IMMU-132-06 study.

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TROPHY-U-01 Cohort 2, a Phase 2 Study of Sacituzumab Govitecan in Platinum-Ineligible Patients With Metastatic Urothelial Cancer who Progressed After Prior Checkpoint Inhibitor Therapy

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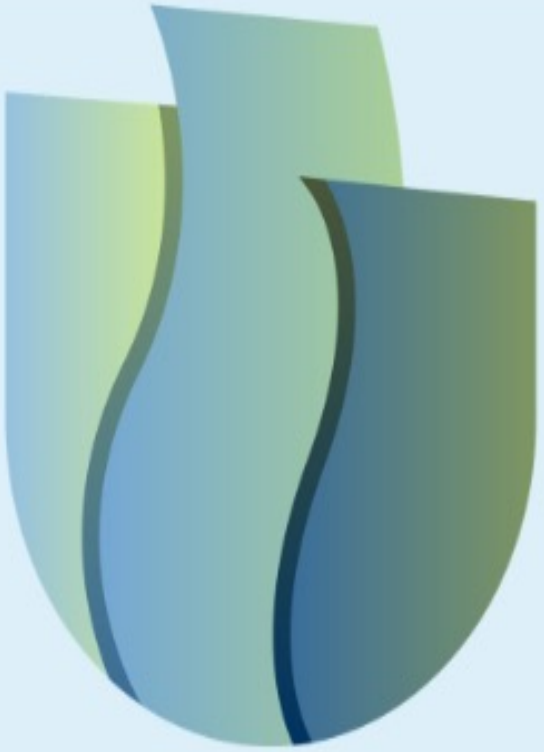

TROPHY-U-01 Cohort 2

Baseline Characteristics and Prior Therapies

Baseline Characteristics	Cohort 2 (N=38)
Male, n (%)	23 (61)
Median age, y (range)	73 (41-87)
ECOG PS 1, n (%)	19 (50)
Tumor stage at screening, n (%)	
Locoregional only	13 (34)
Distant metastasis	25 (66)
Site of disease at baseline, n (%)	
Visceral	25 (66)
Liver metastasis at baseline	11 (29)
Nonvisceral	13 (34)
Bellmunt risk factor, n (%)	
0	11 (29)
1	19 (50)
2	8 (21)

Prior Therapies	Cohort 2 (N=38)[a]
Median prior anticancer regimens, (range)	2 (1-5)
≤2 prior anticancer regimens, n (%)	28 (74)
Median time since last prior anticancer regimen, months (range)	1.6 (1-8)
Prior CPI, n (%)	37 (97)[b,c]
Pembrolizumab	22 (58)
Atezolizumab	10 (26)
Nivolumab	5 (13)
Durvalumab	1 (3)
Ipilimumab	1 (3)
Prior (neo)adjuvant platinum therapy, n (%)	19 (50)
Prior enfortumab vedotin, n (%)	7 (18)
Prior erdafitinib, n (%)	1 (3)
Best response to prior systemic therapy,[d] n (%)	
Complete response	1 (3)
Partial response	6 (16)
Stable disease	13 (34)
Disease progression	22 (58)

[a]Percentages are based on big N. [b]One patient was missing data (n=1). [c]Patients may have been treated with more than one prior CPI. [d]Responses are to all prior systemic therapies for each patient.
CPI, checkpoint inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status.

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TROPHY-U-01 Cohort 2

Best Overall Responses[a]

Best Overall Reponses	Cohort 2 (N=38)
Objective response rate (CR + PR), n (%) [95%CI]	12 (32) [17.5-48.7]
Best overall response, n (%)	
CR	0
PR	12 (32)
SD	13 (34)
SD ≥6 months	4 (11)
PD	4 (11)
Not evaluable[b]	4 (11)
Not assessed[c]	5 (13)
Clinical benefit rate (CR + PR + SD ≥6 months), n (%) [95%CI]	16 (42) [26.3-59.2]

- An ORR of 32% was observed (32% PR rate and 42% CBR)
  - An ORR of 53.8% was observed in patients without prior platinum or EV (N=13)
- Median time to response was 1.4 months
- Median DOR was 5.6 months (95% CI, 2.8-13.3; n=12)
- ORRs were largely similar across prespecified subgroups, regardless of number of prior anticancer therapies, though some subgroups had limited patient numbers

[a]Responses assessed by independent review assessment [b]Patients who did have one postbaseline imaging assessment but were assigned a BOR "not evaluable" per BICR assessment due to imaging quality issue or other reasons not currently provided in the BICR datasets are counted as "not evaluable". [c]Patients without postbaseline assessments are counted as "not assessed".
BICR, blinded independent central review; BOR, best overall response; CBR, clinical benefit rate; CR, complete response; DOR, duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

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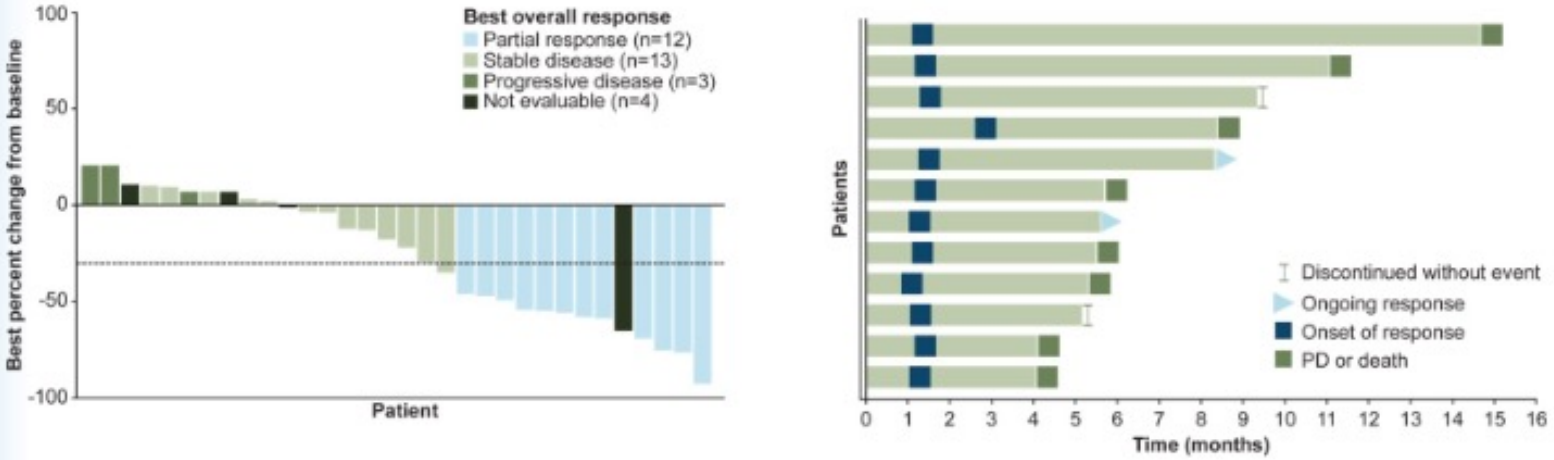
TROPHY-U-01 Cohort 2

Best Change in Target Lesions[a], and Response Assessment From Start of Treatment to Progression



- 69% of assessed patients (22/32) experienced target lesion reduction
- 2 patients had an ongoing response at data cutoff

[a]Patients with missing percent change from baseline are not reported.
PD, progressive disease.

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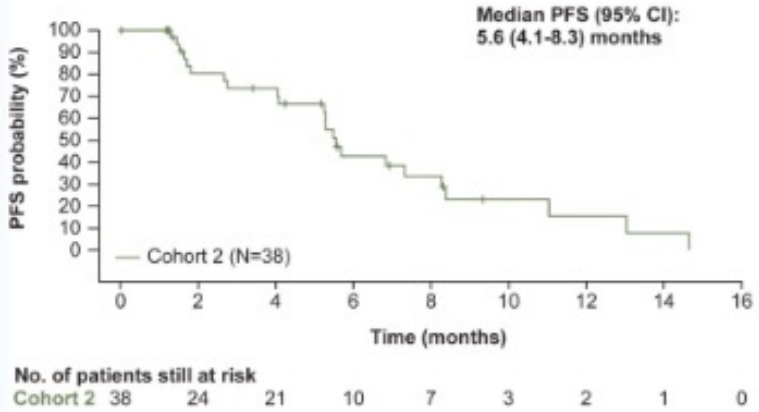
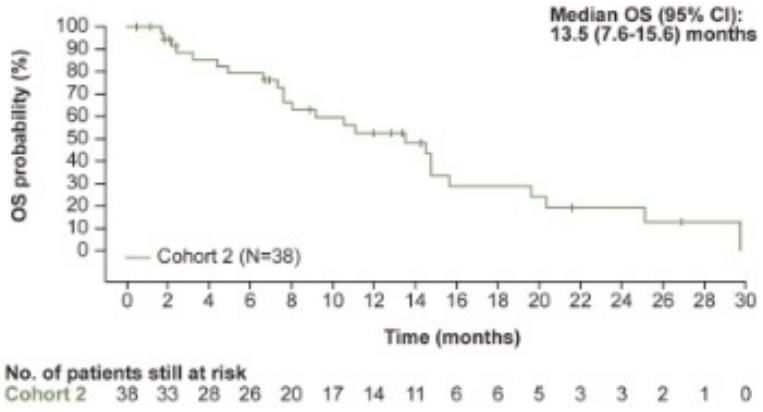
TROPHY-U-01 Cohort 2

Progression-Free Survival and Overall Survival





- Median follow-up was 9.3 months
- Median PFS was 5.6 months (95% CI, 4.1-8.3)
- Median OS was13.5 months (95% CI, 7.6-15.6)

OS, overall survival; PFS, progression-free survival.

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TROPHY-U-01 Cohort 2

Updated Safety Outcomes

TRAEs Occurring in >20% of Patients, n (%)	Cohort 2 (N=38)	
	All Grade	Grade ≥3
Diarrhea	24 (63)	6 (16)
Alopecia	19 (50)	0
Nausea	18 (47)	0
Neutropenia	17 (45)	13 (34)
Fatigue	16 (42)	7 (18)
Anemia	14 (37)	8 (21)
Leukopenia	13 (34)	7 (18)
Decreased appetite	10 (26)	0

- 26 (68%) patients had grade ≥3 TRAEs
  - The most common were neutropenia (34%), anemia (21%), leukopenia (18%), fatigue (18%), diarrhea (16%)
- 3 (8%) patients had treatment-related febrile neutropenia (2 with grade 3; 1 with grade 4)
- 14 (37%) patients had SG dose reduction due to TRAEs
- 7 (18%) patients discontinued treatment due to TRAEs
- No treatment-related death occurred
- G-CSF was received by 7 (18%) patients for primary prophylaxis and 10 (26%) patients for secondary prophylaxis

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TROPHY-U-01 Cohort 2

Conclusions

- In PT-ineligible patients with mUC who progressed following CPI therapy, an ORR of 32% was observed in all patients. Chemotherapy/EV naïve patients had an ORR of 53.8%. The CBR was 42%
- At 9.3 months of median follow-up, the median PFS was 5.6 months and median OS was 13.5 months
- SG had a manageable safety profile with no new safety signals and no treatment-related deaths
- Data support further evaluation of SG (alone and in combination) in patients with mUC who progressed after prior CPI therapy
- Cohorts 4, 5 and 6 for 1L mUC remain open and are currently enrolling
- The TROPiCS-04 randomized phase 3 randomized trial of SG vs single-agent chemotherapy of physician's choice after progression after prior PT & CPI therapies is ongoing (NCT04527991)[1]

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