

# Developing Targeted Therapy for GU Malignancies

## March 5, 2023

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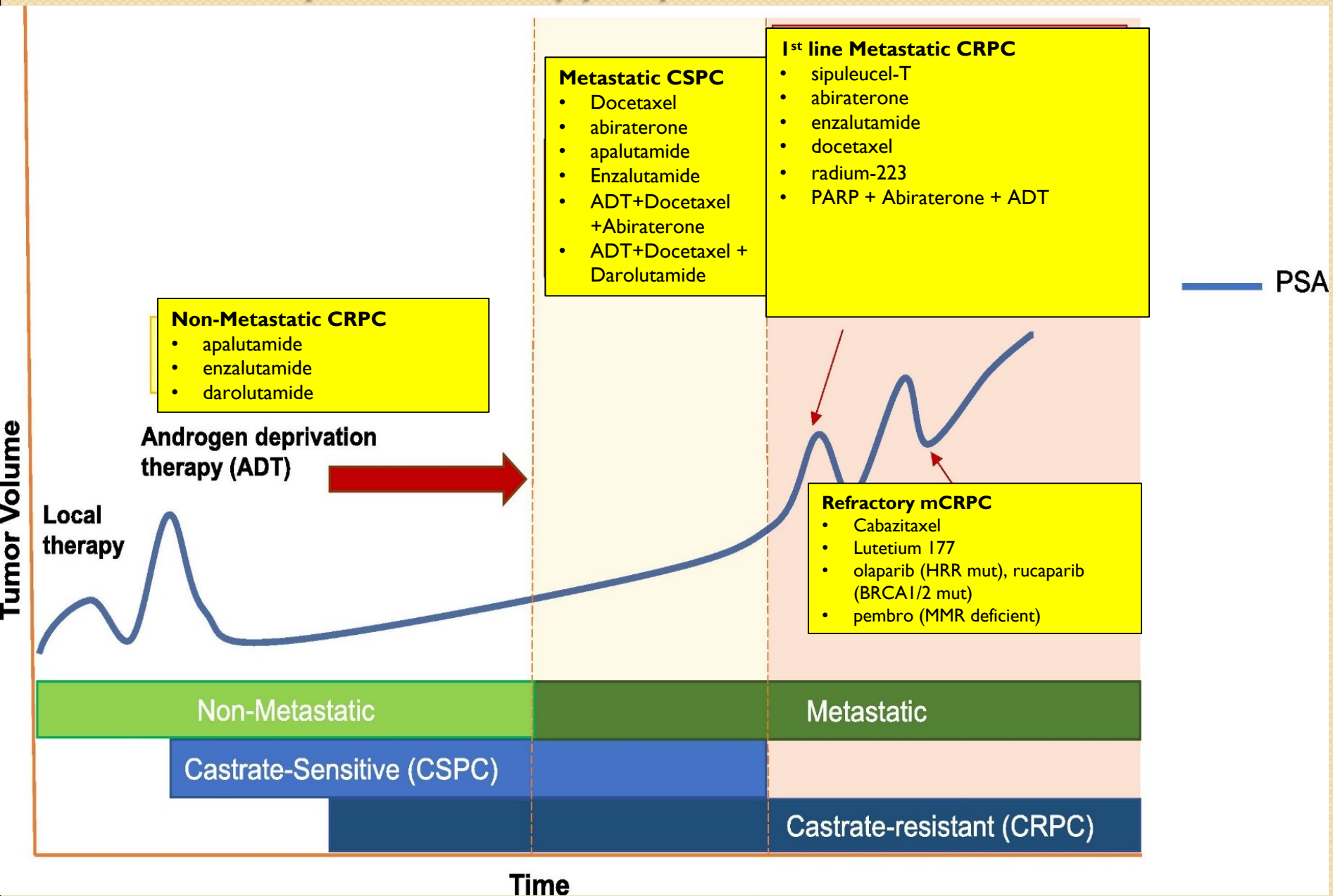


**NORTON**  
CANCER INSTITUTE

# 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

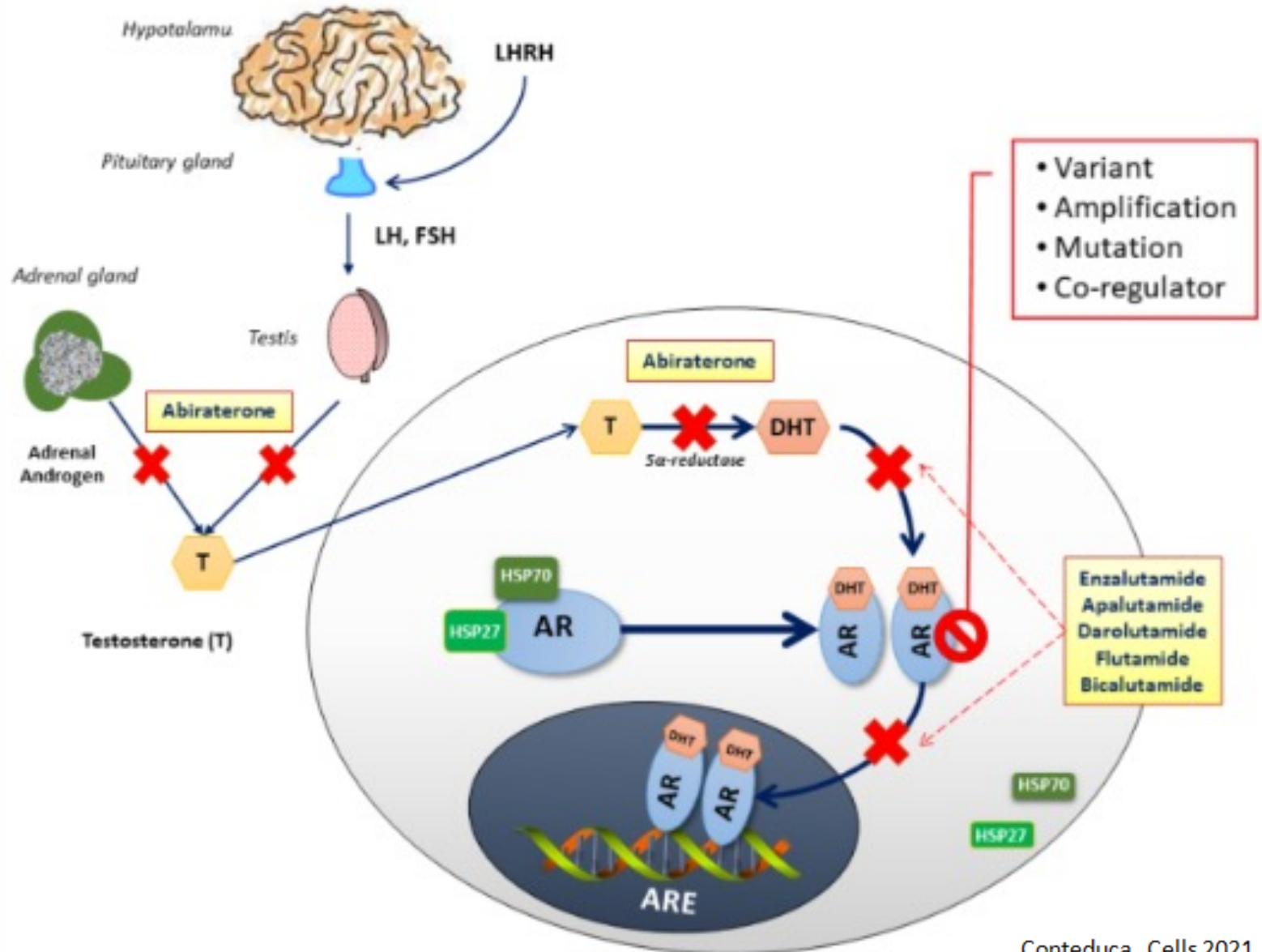
# Systemic therapy of prostate cancer 2023





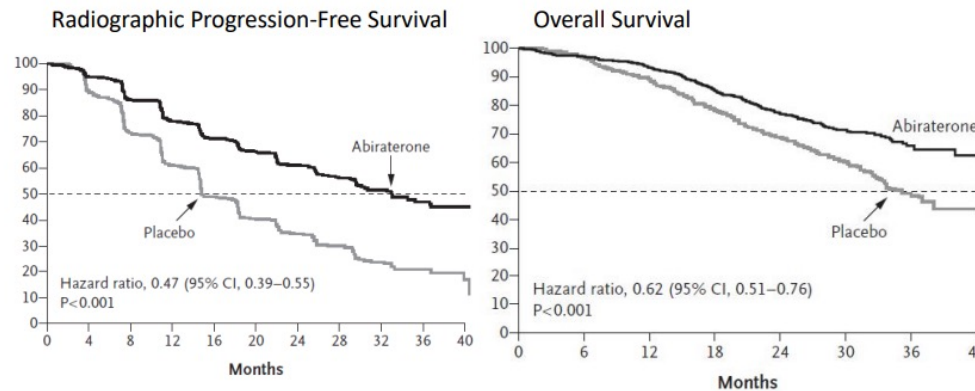
# I. Androgen Pathway Inhibitor





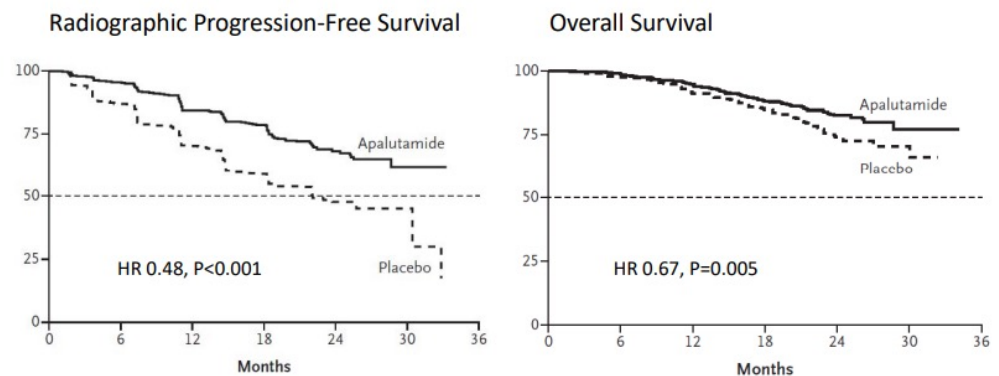
# Androgen Pathway Inhibitors

## LATITUDE: Abiraterone Acetate for mHSPC



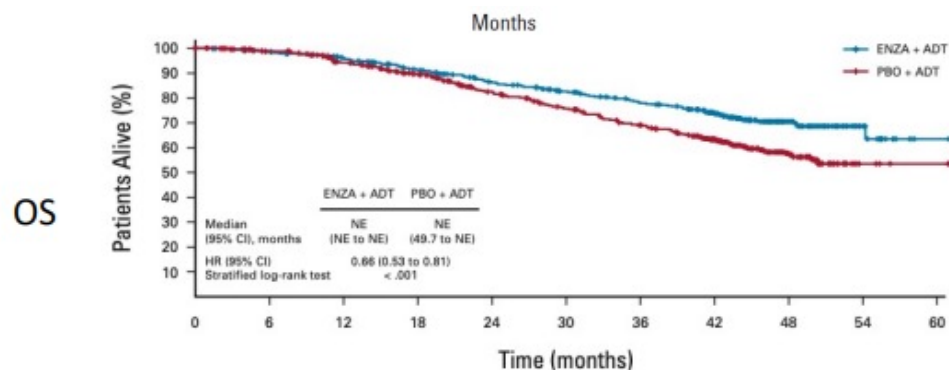
Fizazi et al (2017) *N Engl J Med* 377: 352-60

## TITAN: Apalutamide for mHSPC



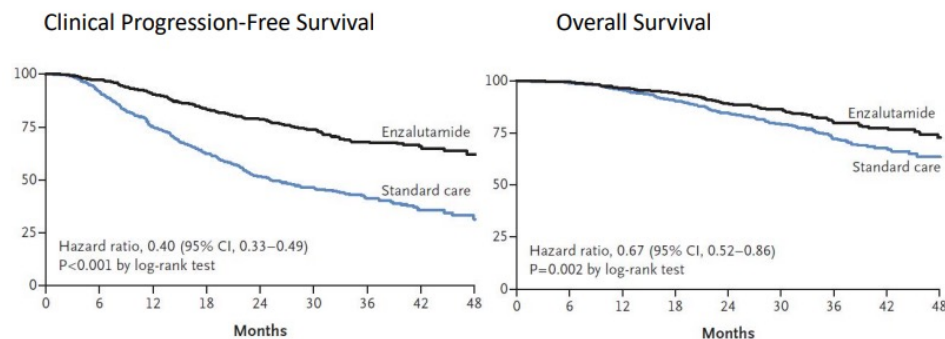
Chi et al (2019) *N Engl J Med* 381: 13-24

# ARCHES and ENZAMET



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 - I

## Key Eligibility Criteria

*De novo* mCSPC

Distant metastatic disease by  $\geq 1$  lesion on bone scan and/or CT scan

ECOG PS 0-2

## On-Study Requirement

Continuous ADT

## Permitted

ADT  $\leq 3$  months

## Stratification

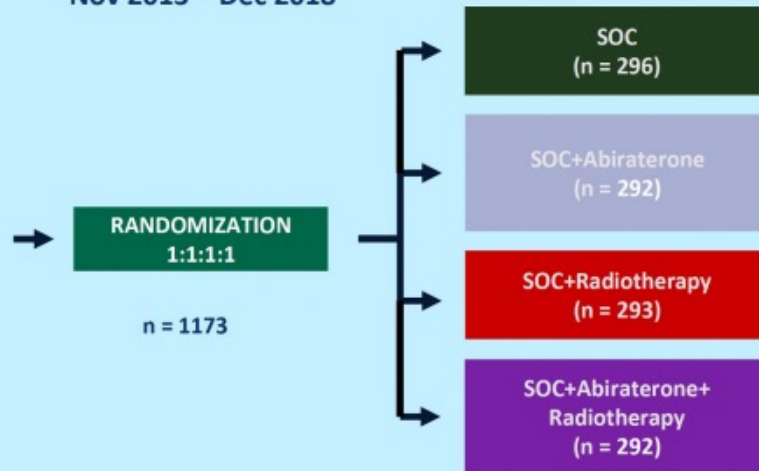
ECOG PS (0 vs 1-2)

Metastatic sites (LN vs bone vs visceral)

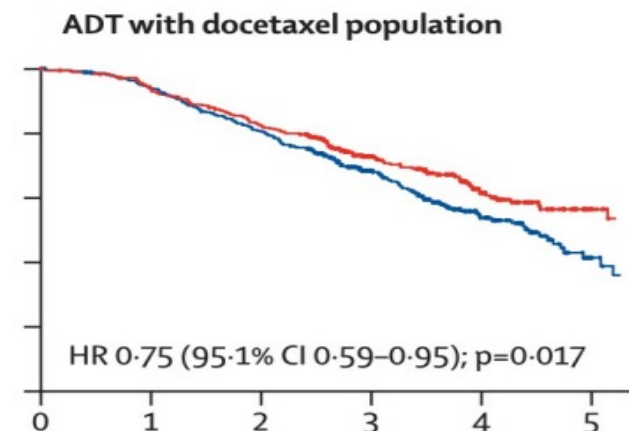
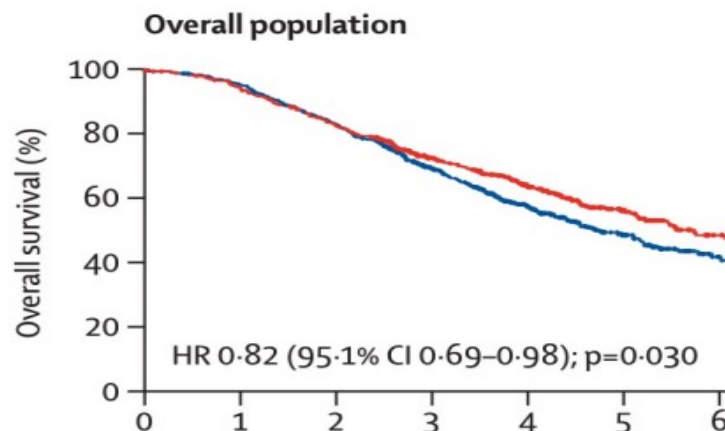
Type of castration (orchidectomy vs LHRH agonist vs LHRH antagonist)

Docetaxel (yes vs no)

Nov 2013 – Dec 2018



ECOG PS, Eastern Cooperative Oncology Group performance status





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 Montes-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

ASCO<sup>®</sup> Genitourinary  
Cancers Symposium

## Efficacy and Safety of Darolutamide in Combination With Androgen-Deprivation Therapy and Docetaxel by Disease Volume and Risk in the Phase 3 ARASENS Study

Maha Hussain, MD, FACP, FASCO,<sup>1</sup> Bertrand Tombal, MD, PhD,<sup>2</sup> Fred Saad, MD,<sup>3</sup> Karim Fizazi, MD, PhD,<sup>4</sup> Cora N. Sternberg, MD,<sup>5</sup> E. David Crawford, MD,<sup>6</sup> Neal Shore, MD,<sup>7</sup> Evgeny Kopyltsov, MD,<sup>8</sup> Arash Rezazadeh Kalebasty, MD,<sup>9</sup> Martin Bögemann, MD,<sup>10</sup> Dingwei Ye, MD,<sup>11</sup> Felipe Cruz, MD,<sup>12</sup> Hiroyoshi Suzuki, MD, PhD,<sup>13</sup> Shivani Kapur, MD,<sup>14</sup> Shankar Srinivasan, PhD,<sup>15</sup> Frank Verhulst, MD,<sup>16</sup> Iris Kuss, MD,<sup>17</sup> Heikki Joensuu, MD,<sup>18</sup> Matthew R. Smith, MD, PhD<sup>19</sup>

<sup>1</sup>Northwestern University, Feinberg School of Medicine, Chicago, IL; <sup>2</sup>Division of Urology, IREC, Cliniques Universitaires Saint Luc, UCLouvain, Brussels, Belgium; <sup>3</sup>University of Montreal Hospital Center, Montreal, Quebec, Canada; <sup>4</sup>Institut Gustave Roussy, University of Paris-Saclay, Villejuif, France; <sup>5</sup>Englander Institute for Precision Medicine, Weill Cornell Department of Medicine, Meyer Cancer Center, New York-Presbyterian Hospital, New York, NY; <sup>6</sup>UC San Diego School of Medicine, San Diego, CA; <sup>7</sup>Carolina Urologic Research Center/Genesis Care, Myrtle Beach, SC; <sup>8</sup>Clinical Oncological Dispensary of Omsk Region, Omsk, Russian Federation; <sup>9</sup>University of California Irvine, Division of Hematology/Oncology, Orange, CA; <sup>10</sup>Department of Urology, Münster University Medical Center, Münster, Germany; <sup>11</sup>Fudan University Shanghai Cancer Center, Xuhui District, Shanghai, China; <sup>12</sup>Núcleo de Pesquisa e Ensino da Rede São Camilo, São Paulo, Brazil; <sup>13</sup>Toho University Sakura Medical Center, Chiba, Japan; <sup>14</sup>Bayer SEA, Singapore; <sup>15</sup>Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ; <sup>16</sup>Bayer Consumer Care AG, Basel, Switzerland; <sup>17</sup>Bayer AG, Berlin, Germany; <sup>18</sup>Orion Corporation, Espoo, Finland; <sup>19</sup>Massachusetts General Hospital Cancer Center, Boston, MA

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#GU23

PRESENTED BY: Maha Hussain, MD, FACP, FASCO

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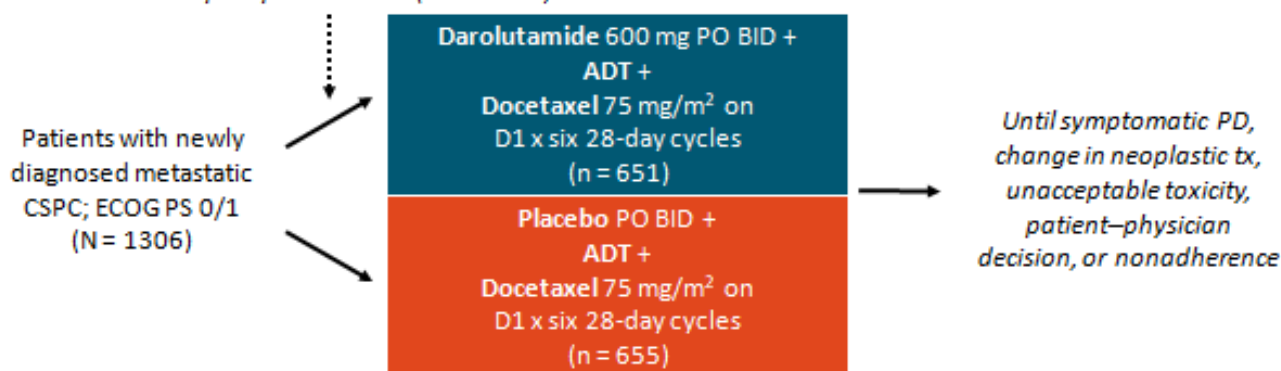


# ARASENS

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

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

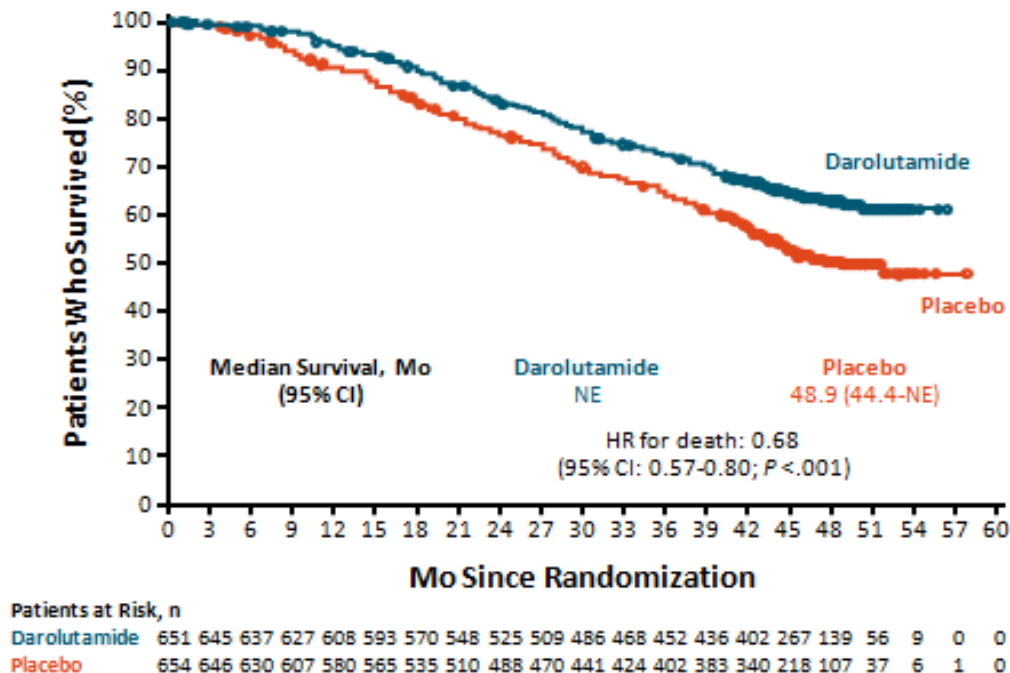
*Stratified by metastasis stage (M1a vs M1b vs M1c),  
alkaline phosphatase level (< vs ≥ ULN)*



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

# Overall Survival

## ARASENS: OS (Primary Endpoint)



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

# ARASENS Update

## Definition of Disease Volume and Risk Subgroups

High-Volume Disease: CHARTED Criteria <sup>1</sup>	High-Risk Disease: LATITUDE Criteria <sup>2</sup>
<ul style="list-style-type: none"><li>• Visceral metastases</li><li>• <math>\geq 4</math> bone metastases with <math>\geq 1</math> beyond the vertebral column/pelvis<sup>a</sup></li></ul>	<ul style="list-style-type: none"><li>• <math>\geq 2</math> risk factors:<ul style="list-style-type: none"><li>▪ Gleason score <math>\geq 8</math></li><li>▪ <math>\geq 3</math> bone metastases<sup>a</sup></li><li>▪ Visceral metastases</li></ul></li></ul>
<p>Low-volume and low-risk disease were defined as not meeting the respective high-volume and high-risk criteria</p> <p><sup>a</sup>Including those with diffusely increased skeletal metastases with superscan<sup>3</sup></p>	

- 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.

# 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 $\geq 8$ , n (%)	381 (76.7)	403 (79.3)	124 (80.5)	113 (77.4)
Metastasis stage at initial diagnosis, n (%) <sup>a</sup>				
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 $\pm$ LN)	386 (77.7)	390 (76.8) <sup>b</sup>	131 (85.1)	131 (89.7)
M1c (visceral $\pm$ LN or bone)	111 (22.3)	118 (23.2)	0	0
Serum PSA, median (range), ng/mL <sup>c</sup>	38.7 (0–9219.0)	27.9 (0–11,947.0)	11.7 (0–3771.0)	14.5 (0–3372.9)

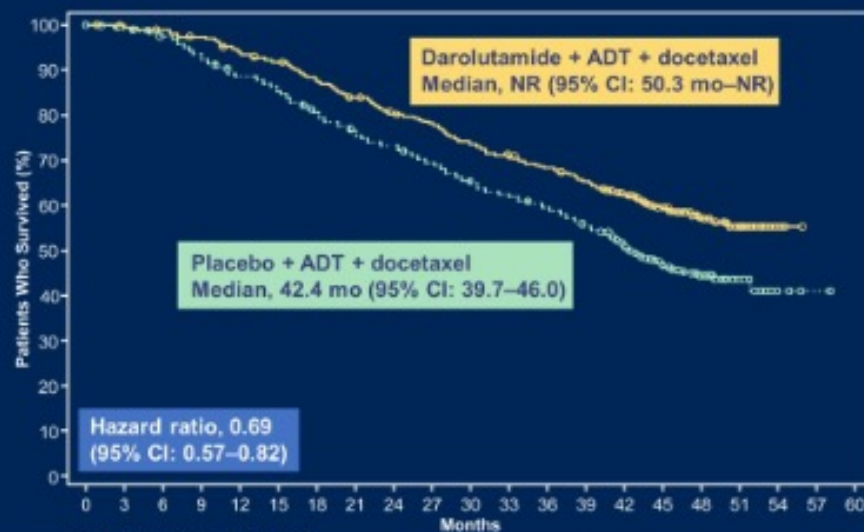
<sup>a</sup>Data on distant metastases were missing for 13 patients; <sup>b</sup>One patient had lymph node metastasis alone per direct entry in case report form but was categorized as M1b in the high-volume subgroup using detailed tumor data; <sup>c</sup>These values were centrally assessed. Samples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



# ARASENS Update

## ARASENS VOLUME Subgroups: Overall Survival

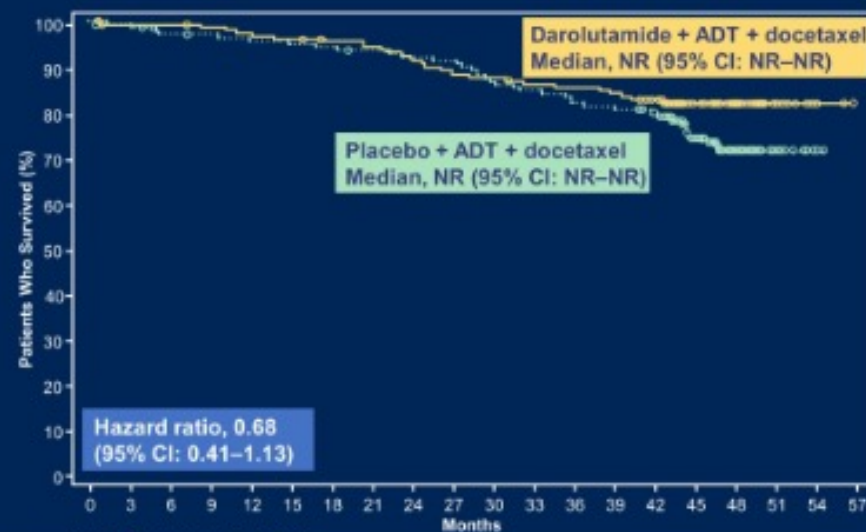
### High-volume mHSPC



Number of high-volume patients at risk

Darolutamide	497	494	486	479	462	449	429	408	389	378	356	341	326	312	285	193	103	43	6	0	0
Placebo	508	502	491	469	444	430	401	378	358	341	319	304	286	269	233	153	72	23	4	1	0

### Low-volume mHSPC



Number of low-volume patients at risk

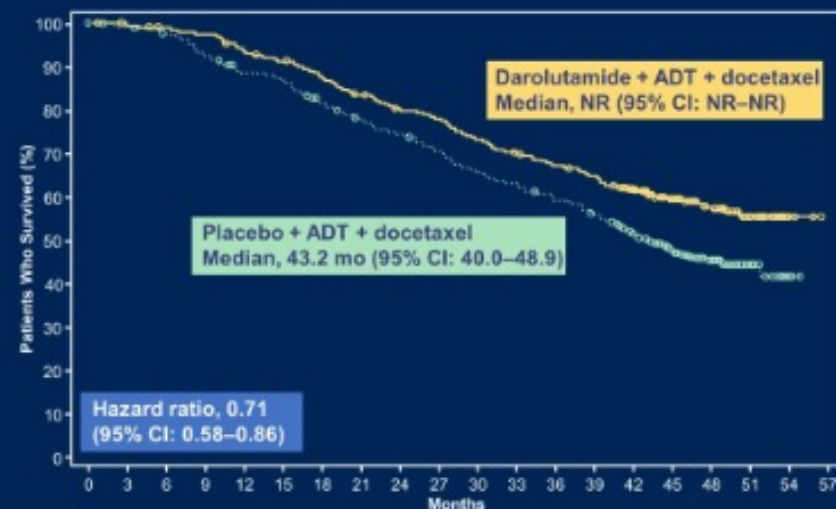
Darolutamide	154	151	151	148	146	144	141	140	136	131	130	127	126	124	117	74	36	13	3	0
Placebo	148	144	139	138	136	135	134	132	130	129	122	120	116	114	107	65	35	14	2	0

Analysis by unstratified Cox regression model. CI, confidence interval; NR, not reached.

# ARASENS Update

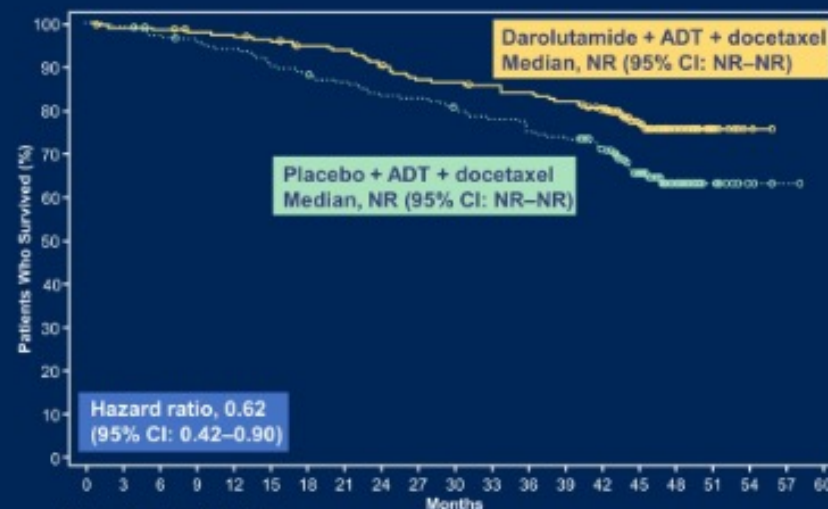
## ARASENS RISK Subgroups: Overall Survival

### High-risk mHSPC



	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
Darolutamide	452	450	443	437	419	407	389	369	352	344	322	308	294	282	257	177	99	42	6	0
Placebo	460	453	443	423	400	392	367	346	330	313	290	277	261	245	215	148	72	24	3	0

### Low-risk mHSPC



	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60
Darolutamide	199	195	194	190	189	186	181	179	173	165	164	160	158	154	145	90	40	14	3	0	0
Placebo	194	193	187	184	180	173	168	164	158	157	151	147	141	138	125	70	35	13	3	1	0



# 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

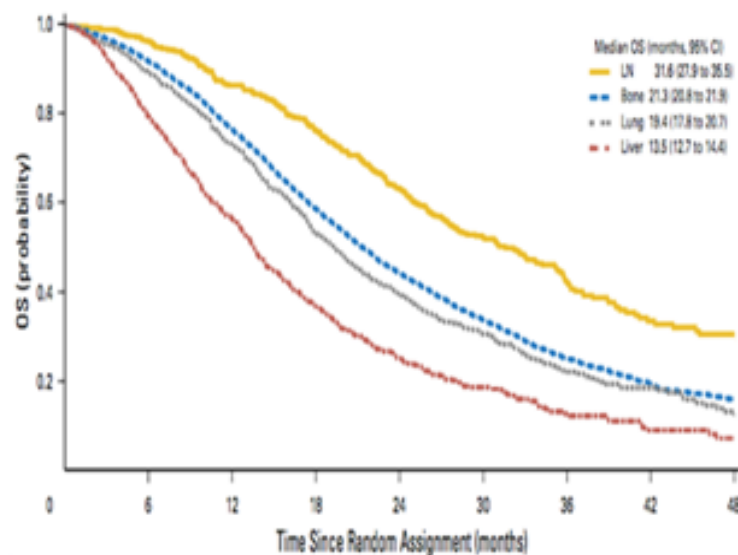
## Synchronous

- 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 ( <u>Metachronous</u> ) Low Volume	~8 y
Relapsed ( <u>Metachronous</u> ) Low Volume	4.5
De Novo ( <u>Synchronous</u> ) Low Volume	4.5
De Novo ( <u>Synchronous</u> ) 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,  
RBI, PTEN  
mutation**

**Metachronous  
Low Volume**

**Androgen  
Pathway  
Inhibitor and  
ADT**

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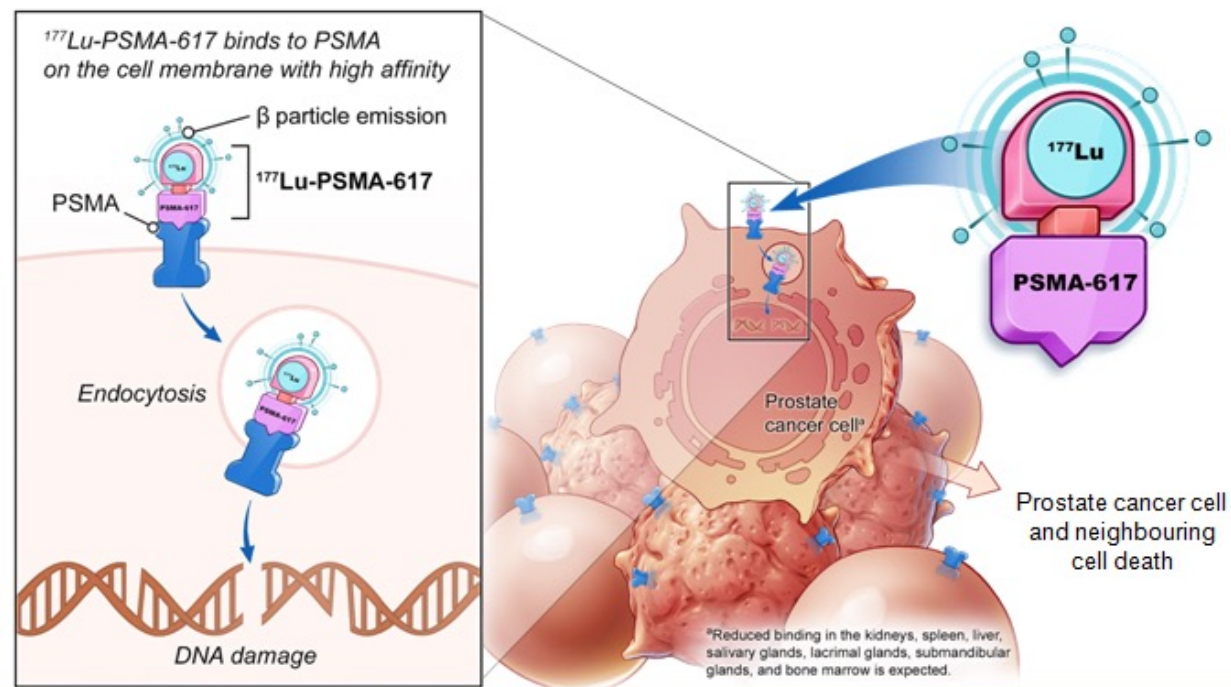


## 2. Radioligand Therapy



# Radioligand Therapy

## $^{177}\text{Lu}$ -PSMA-617 targeted radioligand therapy



Presented By: Michael J. Morris

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2021 ASCO  
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# 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<sup>\*</sup>

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September 16, 2021

N Engl J Med 2021; 385:1091-1103

DOI: 10.1056/NEJMoa2107322

Chinese Translation 中文翻译

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# VISION Study

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

### Eligible patients

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

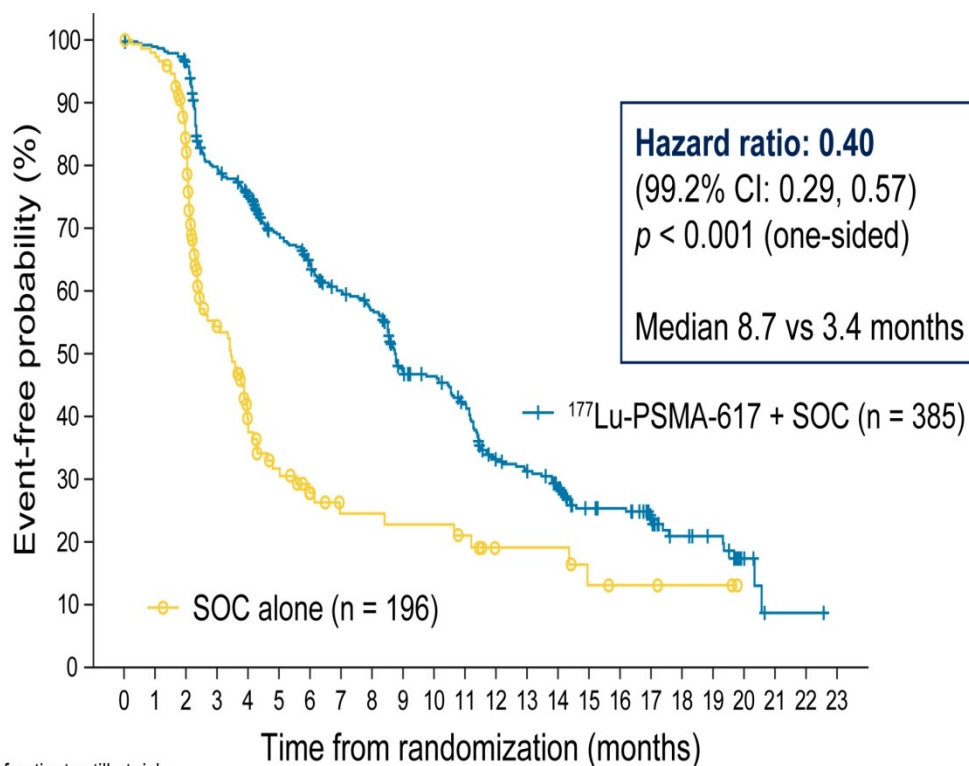


- Randomization stratified by
  - ECOG status (0–1 or 2)
  - LDH (high or low)
  - Liver metastases (yes or no)
  - Androgen receptor pathway inhibitors in SOC (yes or no)
- CT/MRI/bone scans
  - Every 8 weeks (treatment)
  - Every 12 weeks (follow-up)
  - Blinded independent central review

## Primary endpoints: $^{177}\text{Lu}$ -PSMA-617 improved rPFS

Primary  
analysis

rPFS  
analysis set  
(n = 581)



Number of patients still at risk

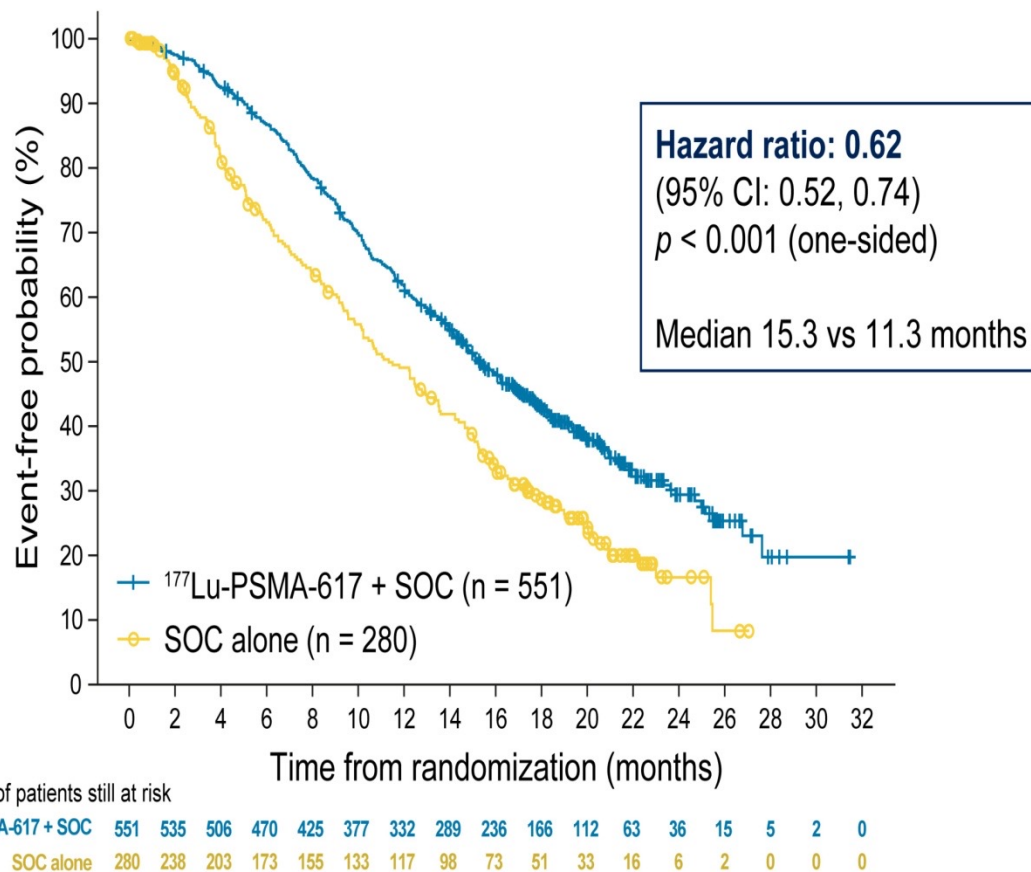
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
$^{177}\text{Lu}$ -PSMA-617 + SOC	385	373	362	292	272	235	215	194	182	146	137	121	88	83	71	51	49	37	21	18	6	1	1	0



# Primary endpoints: $^{177}\text{Lu}$ -PSMA-617 prolonged OS

## Primary analysis

All randomized patients  
(N = 831)



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

Patients, n (%)	All grades		Grade 3–5	
	<sup>177</sup> Lu-PSMA-617 + SOC (n = 529)	SOC alone (n = 205)	<sup>177</sup> 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)



# VISION study

- $^{177}\text{Lu}$ -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

2022 ASCO<sup>®</sup>  
ANNUAL MEETING

ANZUP<sup>®</sup>  
Cancer Trials Group Limited

## **<sup>177</sup>Lu-PSMA-617 (LuPSMA) versus cabazitaxel in metastatic castration resistant prostate cancer (mCRPC) progressing after docetaxel: overall survival after median follow-up of 3 years**

(TheraP ANZUP 1603)

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

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

Clinicaltrials.gov NCT03392428

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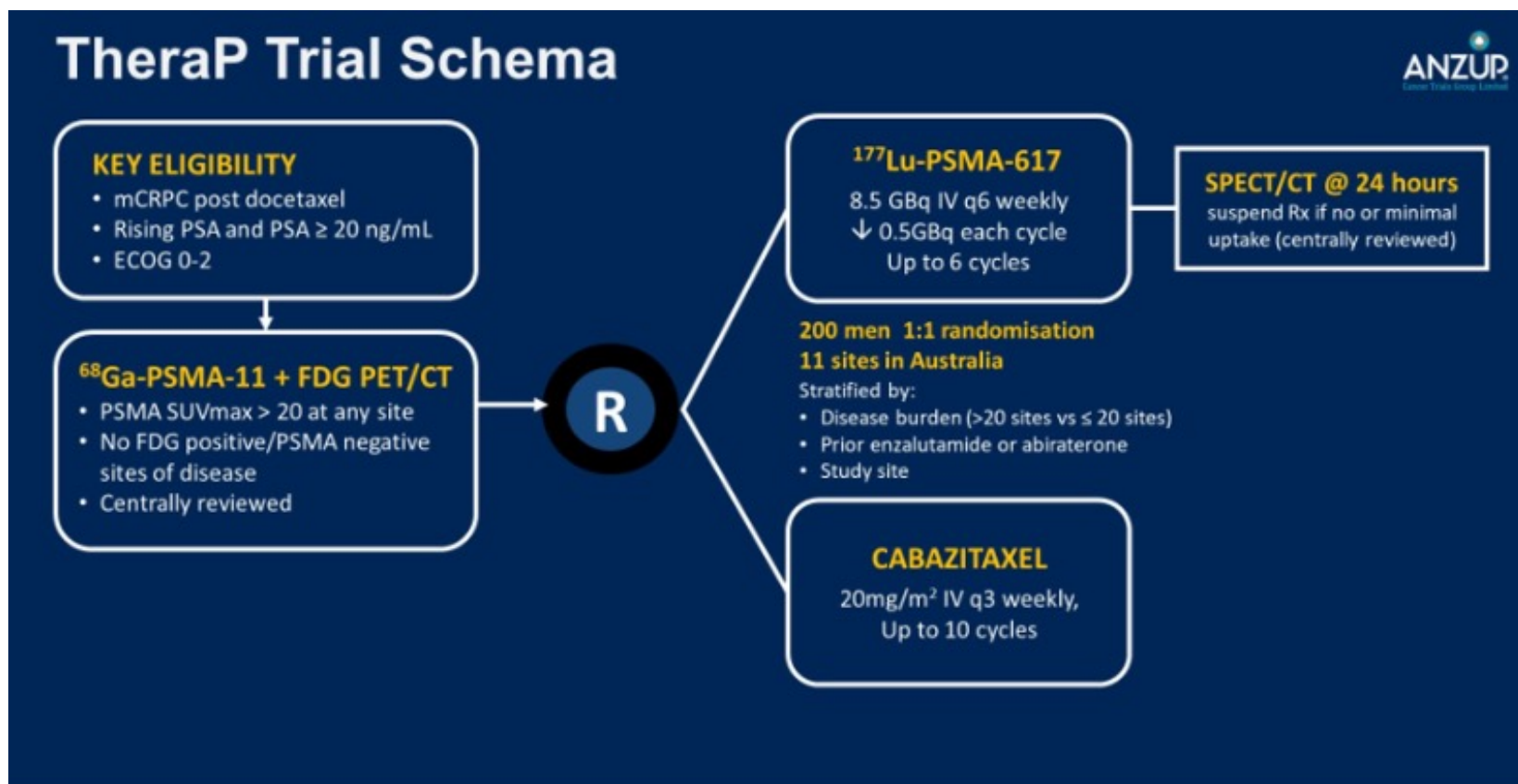
PRESENTED BY:  
Michael Hofman, MBBS @DrMHofman

#TheraP

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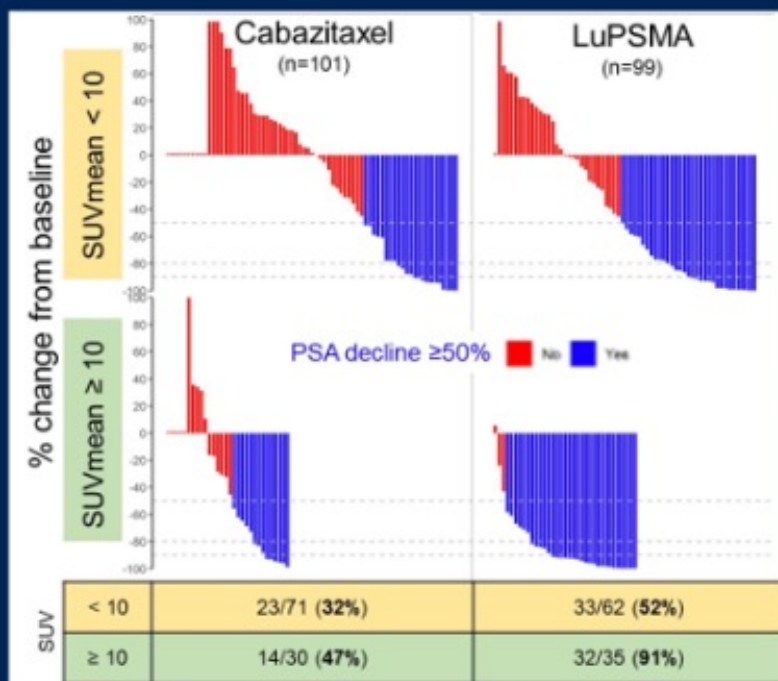
# TheraP Trial Study Design



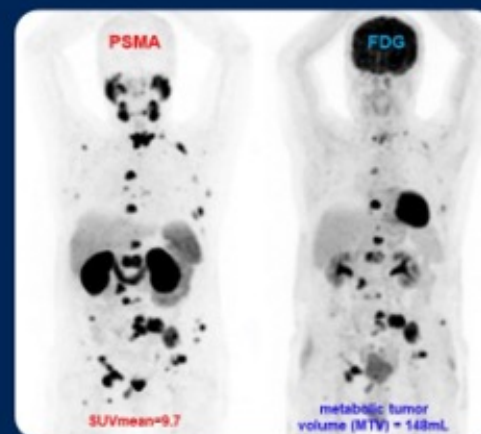


# ASCO 2022:TheraP Study

## Discussion: PSMA as predictive biomarker<sup>1</sup> (PSA50-RR)<sup>11</sup>



<sup>1</sup>Bateau J et al, ASCO GU 2022. doi:10.1200/JCO.2022.40.6\_suppl.010



### Odds of PSA50-RR to LuPSMA vs cabazitaxel

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

P=0.03

Further analysis to be performed including OS

# <sup>177</sup>Lu-PSMA-617 vs Cabazitaxel.

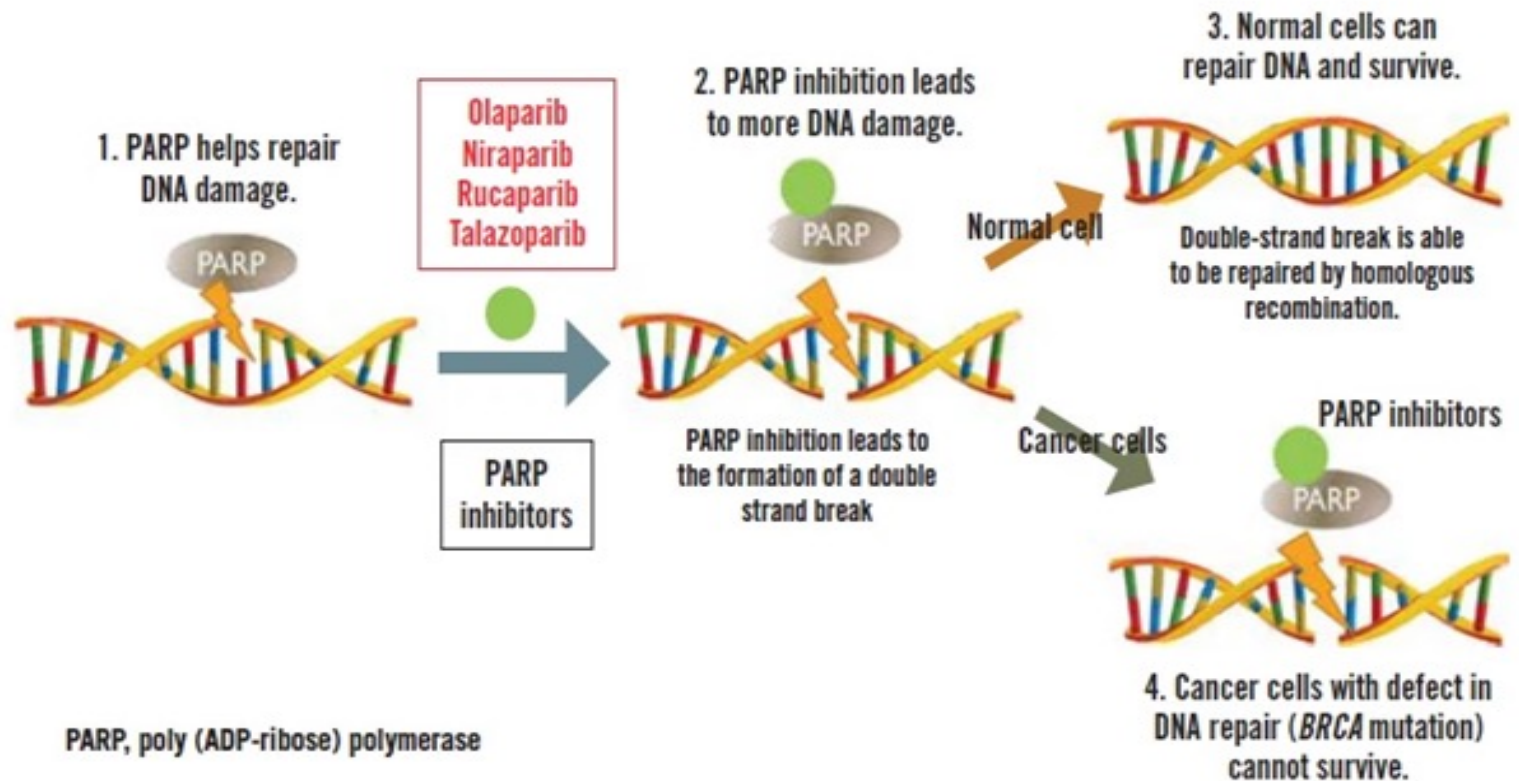
- PSMA PET scan is a biomarker. If SUV >10 I favor Lu-PSMA 617
- If patient progresses in less than 12 months on androgen pathway inhibitor I favor Cabazitaxel based on CARD Trial
- Phase III PSMAfore trial met primary endpoint. (pre-taxane indication)



### 3. PARP inhibitor



# Mechanism of Action



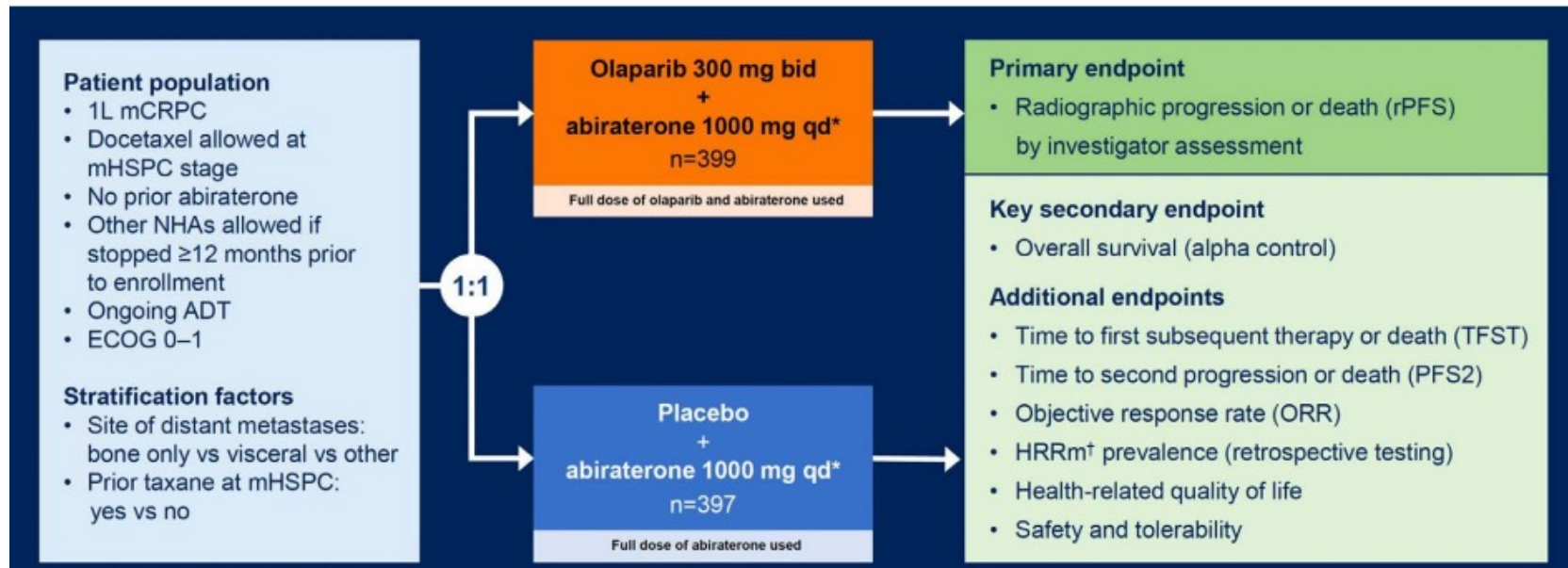
# PROpel Study

ASCO Genitourinary  
Cancers Symposium 2022;Abstract 11

## **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 Loreda, 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

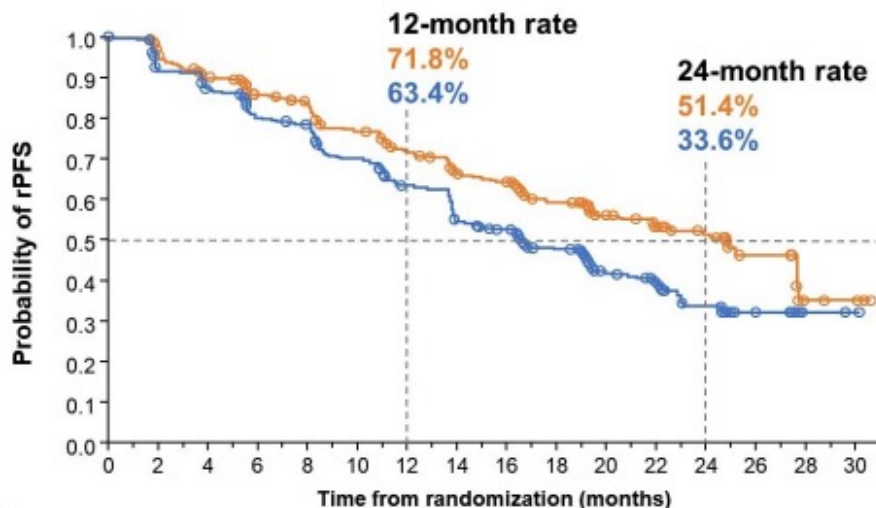
# PROpel Study





# PROpel study

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



No. at risk

Olaparib + abiraterone 399 395 367 354 340 337 313 309 301 277 274 265 251 244 277 221 219 170 167 163 104 100 87 59 57 28 25 25 5 4 4 0  
Placebo + abiraterone 397 393 359 356 336 334 306 303 297 266 264 249 232 226 196 190 186 143 141 137 87 84 73 45 43 21 17 16 2 2 1 0

Events: 394; Maturity 49.5%

\*In combination with prednisone or prednisolone

CI, confidence interval; HR, hazard ratio.

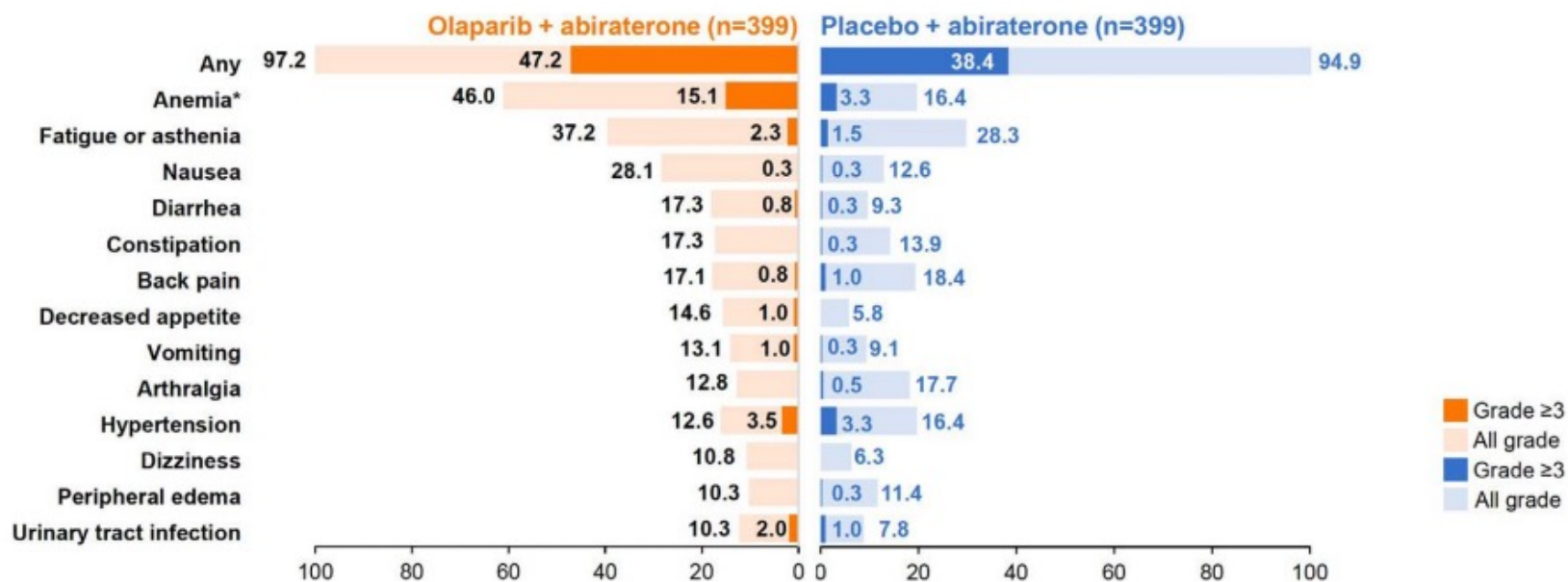
	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Events, n (%)	168 (42.1)	226 (56.9)
Median rPFS (months)	24.8	16.6
HR (95% CI)	0.66 (0.54–0.81); P<0.0001	

Pre-specified 2-sided alpha: 0.0324

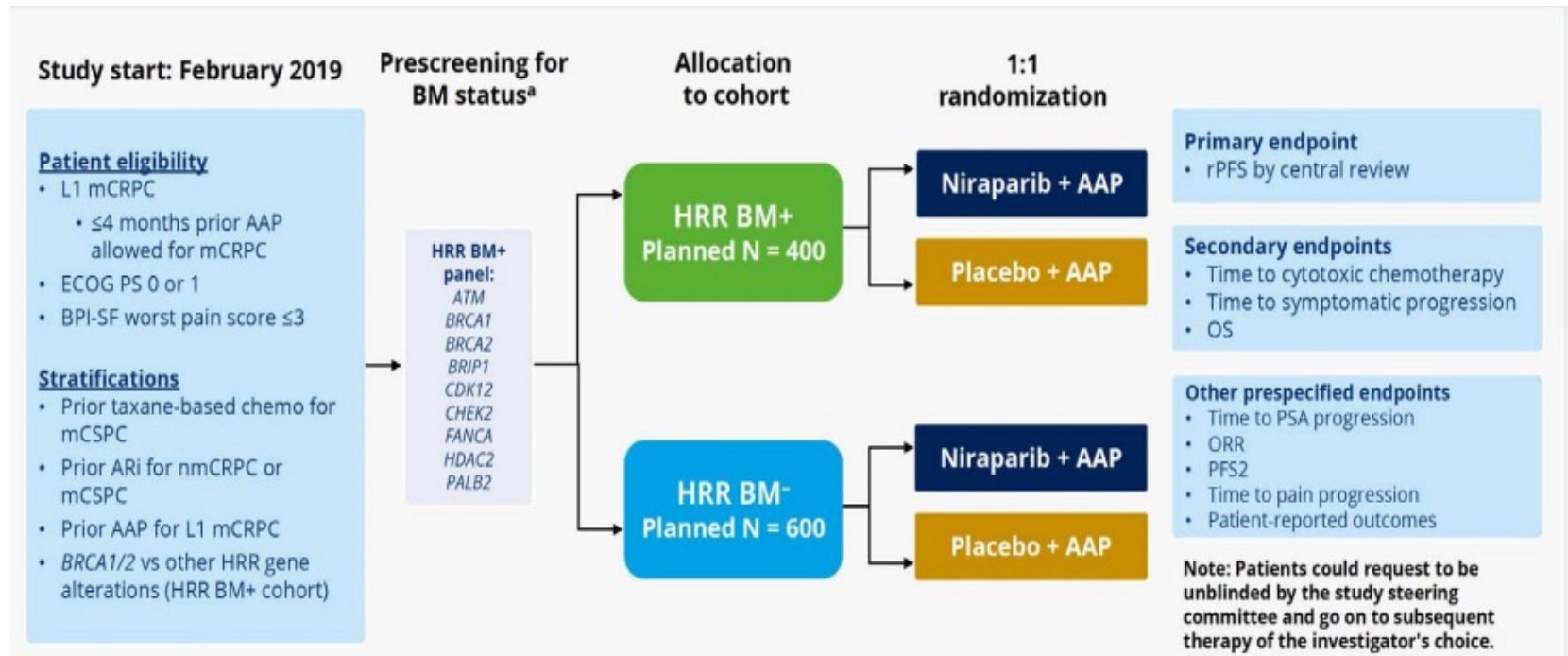
**Median rPFS improvement of 8.2 months  
favors olaparib + abiraterone\***



# PROpel Study

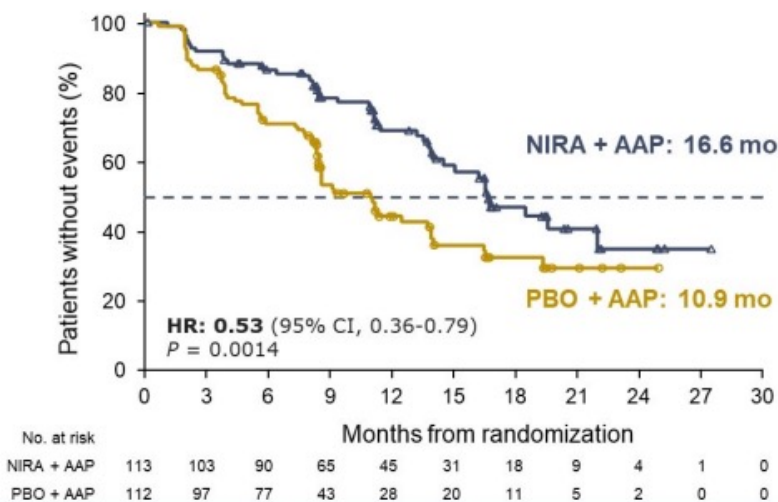


# Magnitude Study

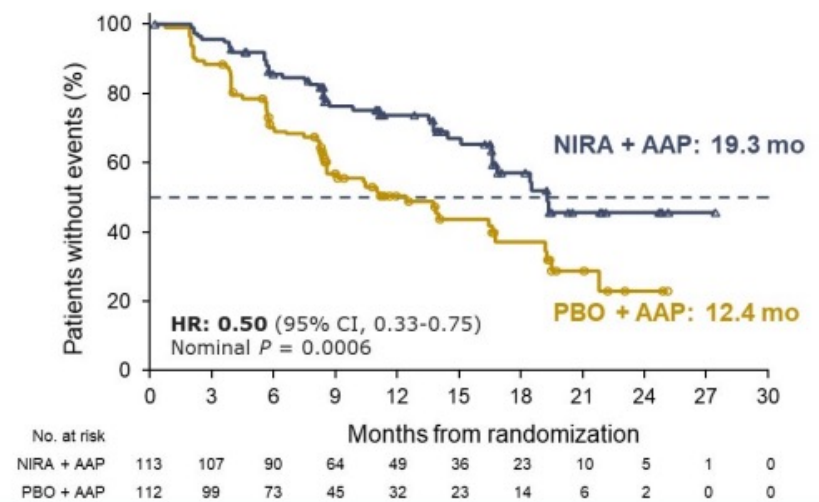


# Magnitude study

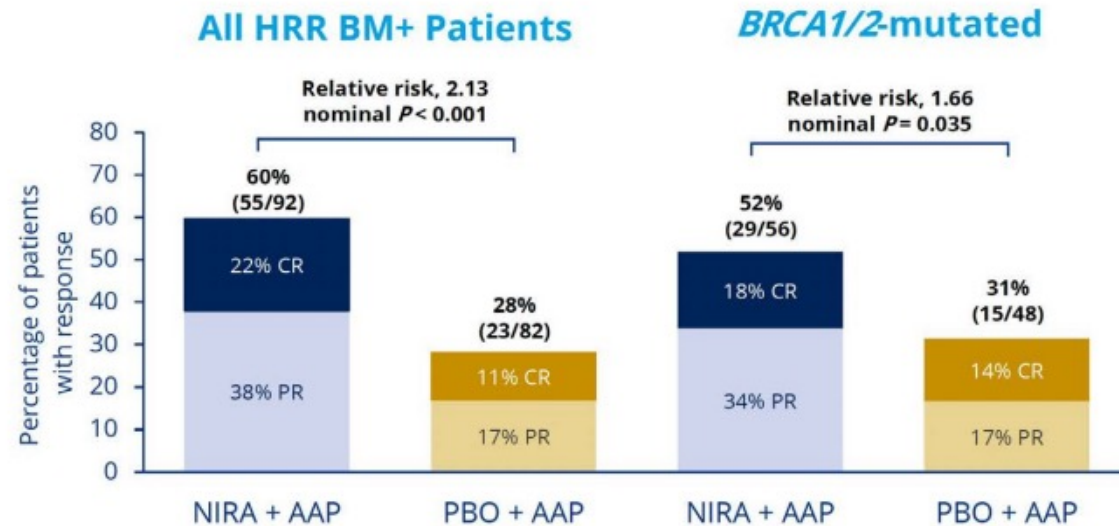
rPFS assessed by central review



rPFS assessed by investigator

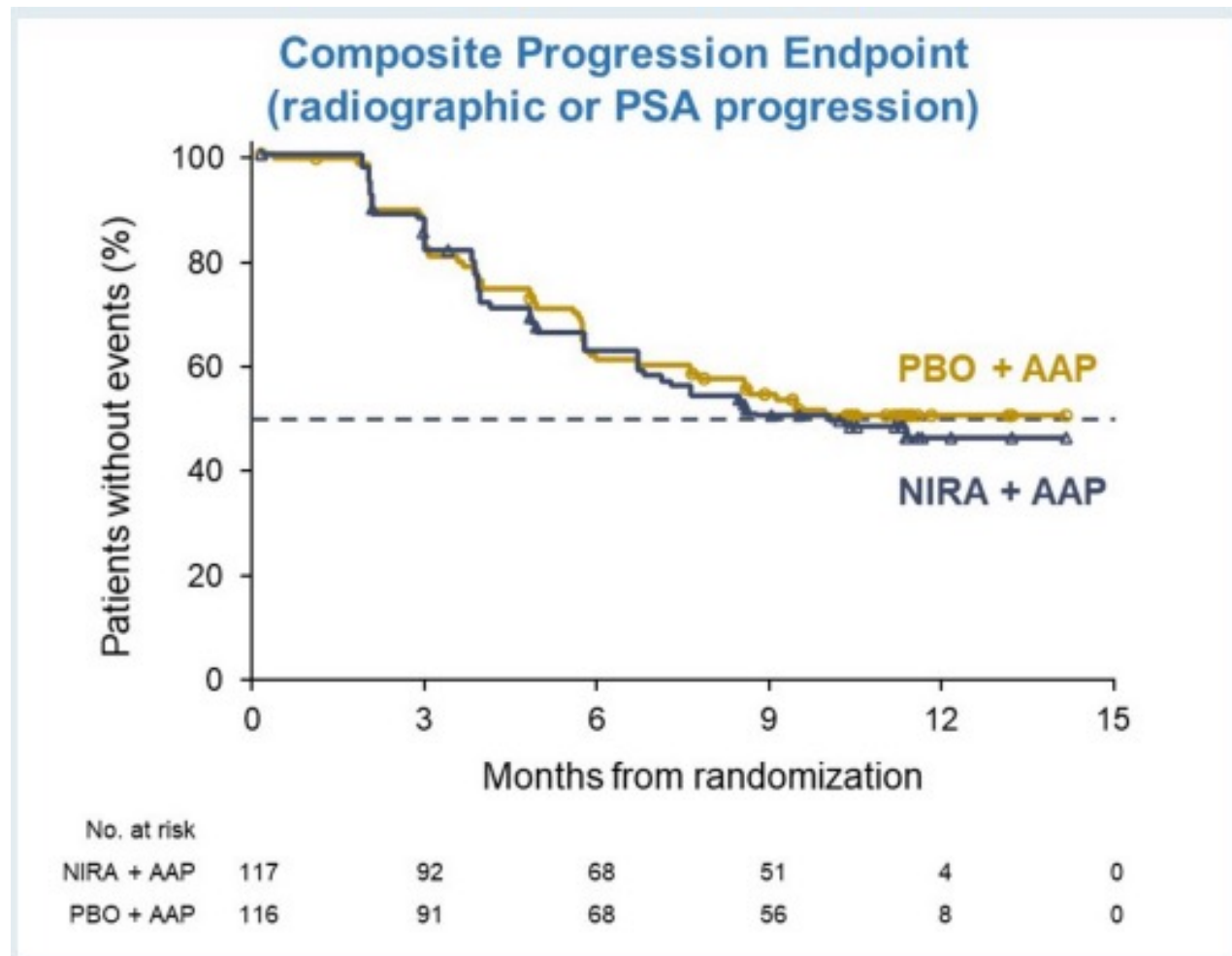


# Magnitude Study





# MAGNITUDE study (HRR-)



# ASCO GU 2023

Presentation number LBA17

ASCO<sup>®</sup> Genitourinary  
Cancers Symposium

## TALAPRO-2: Phase 3 study of talazoparib plus enzalutamide versus placebo plus enzalutamide as first-line treatment in patients with metastatic castration-resistant prostate cancer

Neeraj Agarwal,<sup>1</sup> Arun A. Azad,<sup>2</sup> Joan Carles,<sup>3</sup> Andre P. Fay,<sup>4</sup> Nobuaki Matsubara,<sup>5</sup> Daniel Heinrich,<sup>6</sup> Cezary Szczylik,<sup>7</sup> Ugo De Giorgi,<sup>8</sup> Jae Young Joung,<sup>9</sup> Peter C. Fong,<sup>10</sup> Eric Voog,<sup>11</sup> Robert J. Jones,<sup>12</sup> Neal D. Shore,<sup>13</sup> Curtis Dunshee,<sup>14</sup> Stefanie Zschäbitz,<sup>15</sup> Jan Oldenburg,<sup>16</sup> Xun Lin,<sup>17</sup> Cynthia G. Healy,<sup>18</sup> Nicola Di Santo,<sup>19</sup> Fabian Zohren,<sup>17</sup> Karim Fizazi<sup>20</sup>

<sup>1</sup>Huntsman Cancer Institute (NCI-CCC), University of Utah, Salt Lake City, UT, USA; <sup>2</sup>Peter MacCallum Cancer Centre, Melbourne, Australia; <sup>3</sup>Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; <sup>4</sup>PUCRS School of Medicine, Porto Alegre, Brazil; <sup>5</sup>National Cancer Center Hospital East, Chiba, Japan; <sup>6</sup>Inlandet Hospital Trust, Gjøvik, Norway; <sup>7</sup>Department of Oncology European Health Center, Otwock, Poland, and Postgraduate Medical Education Center, Warsaw, Poland; <sup>8</sup>IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) Dino Amadori, Meldola, Italy; <sup>9</sup>National Cancer Center, Goyang, Republic of Korea; <sup>10</sup>Auckland City Hospital and University of Auckland, Auckland, New Zealand; <sup>11</sup>Clinique Victor Hugo Centre Jean Bernard, Le Mans, France; <sup>12</sup>School of Cancer Sciences, University of Glasgow, Beatson West of Scotland Cancer Centre, Glasgow, UK; <sup>13</sup>Carolina Urologic Research Center, Myrtle Beach, SC, USA; <sup>14</sup>Arizona Urology Specialists, Tucson, AZ, USA; <sup>15</sup>National Center for Tumor Diseases (NCT), Heidelberg University Hospital, Heidelberg, Germany; <sup>16</sup>Akershus University Hospital (Ahus), Lørenskog, Norway; <sup>17</sup>Pfizer Inc., La Jolla, CA, USA; <sup>18</sup>Pfizer Inc., Collegeville, PA, USA; <sup>19</sup>Pfizer Inc., Durham, NC, USA; <sup>20</sup>Institut Gustave Roussy, University of Paris-Saclay, Villejuif, France

ClinicalTrials.gov identifier: NCT03390197  
This study was sponsored by Pfizer Inc. Astellas Pharma Inc. provided enzalutamide

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Cancers Symposium

#GU23

PRESENTED BY: Dr Neeraj Agarwal



@neerajalms

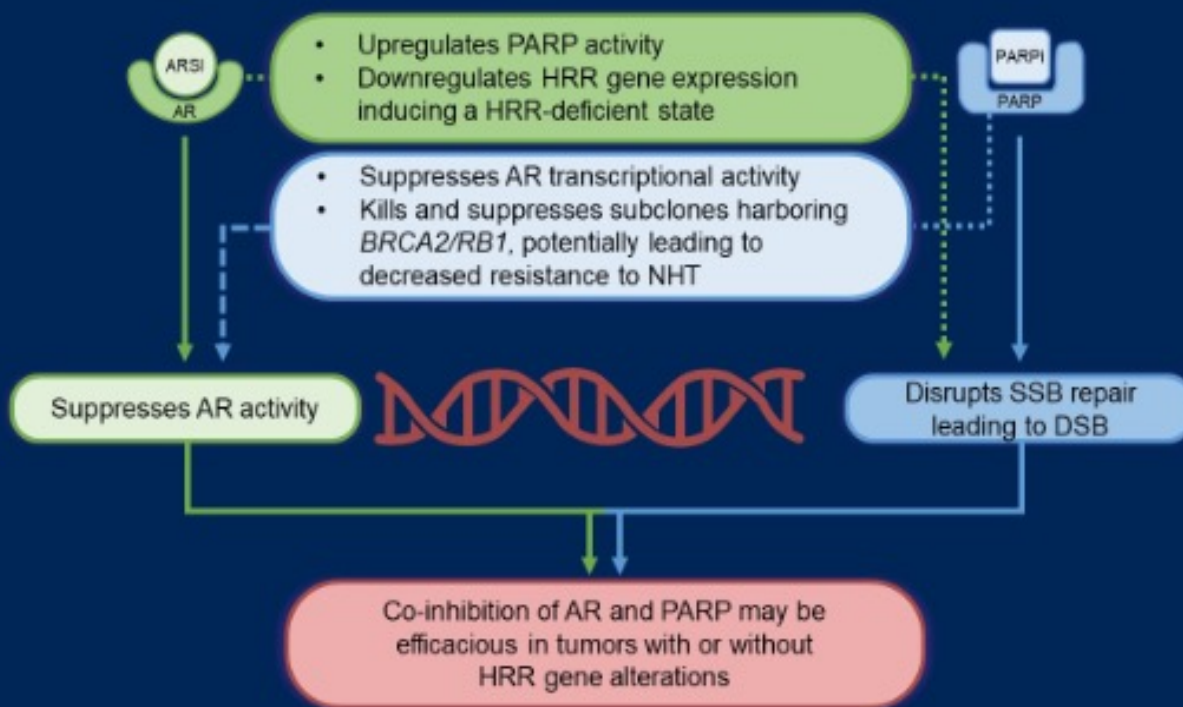
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Agarwal, ASCO GU 2023

# TALAPRO-2

## TALAPRO-2: Rationale for Combining Talazoparib and Enzalutamide<sup>1-8</sup>



- TALAPRO-2 is the first phase 3 trial evaluating talazoparib plus enzalutamide in patients with mCRPC unselected for HRR status<sup>9</sup>
  - An initial nonrandomized open-label run-in determined the starting dose as talazoparib 0.5 mg daily (0.35 mg daily if moderate renal impairment) plus enzalutamide 160 mg daily



# TALAPRO-2

## TALAPRO-2: A Randomized, Double-blind, Placebo-Controlled Study

### Patient population

- First-line mCRPC
- ECOG performance status (PS) 0 or 1

### Stratification factors

- Prior abiraterone<sup>a</sup> or docetaxel in castration-sensitive setting (yes vs no)
- HRR gene alteration status (deficient vs nondeficient or unknown)

All comers (Cohort 1), N=805

Nondeficient  
or unknown  
N=636

HRRm  
N=169

HRRm  
N=230

HRRm only (Cohort 2), N=399

1:1

(N=805)

Talazoparib 0.5 mg\* +  
enzalutamide 160 mg,  
once daily

(N=402)

(\*0.35 mg daily if moderate renal impairment)

Placebo +  
enzalutamide 160 mg, once  
daily

(N=403)

### Primary endpoint

Radiographic progression-free survival (rPFS) by blinded independent central review (BICR)

### Key secondary endpoint

- Overall survival (alpha protected)

### Other secondary endpoints

- Time to cytotoxic chemotherapy
- PFS2 by investigator assessment<sup>b</sup>
- Objective response rate (ORR)
- Patient-reported outcomes
- Safety

(Data cutoff: August 16, 2022)

Samples prospectively assessed for HRR gene alterations (*BRCA1, BRCA2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MLH1, MRE11A, CDK12*) using FoundationOne<sup>®</sup>CDx and/or FoundationOne<sup>®</sup>Liquid CDx

We report results only from the all-comers cohort of men unselected for HRR gene alterations



# TALAPRO-2

## TALAPRO-2: Baseline Demographics and Disease Characteristics

These were well-balanced between treatment arms

	Talazoparib + Enzalutamide (N=402)	Placebo + Enzalutamide (N=403)
<b>Age, median (range), years</b>	71 (41–90)	71 (36–91)
<b>Prostate-specific antigen (PSA), median (range), ng/mL</b>	18.2 (0.1–2796.0)	16.2 (0.1–2285.1)
<b>Disease site, n (%)</b>		
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)
<b>ECOG PS 0/1, n (%)</b>	259 (64.4)/143 (35.6)	271 (67.2)/132 (32.8)
<b>Prior abiraterone* or docetaxel, n (%)</b>	109 (27.1)	110 (27.3)
Abiraterone	21 (5.2)	25 (6.2)
Docetaxel	86 (21.4)	93 (23.1)
<b>HRR gene alteration status (for prospective stratification), n (%)</b>		
Deficient	85 (21.1)	84 (20.8)
Nondeficient or unknown	317 (78.9)	319 (79.2)

\*Two patients in each treatment arm received prior enzalutamide.

# 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<sup>1,2</sup>

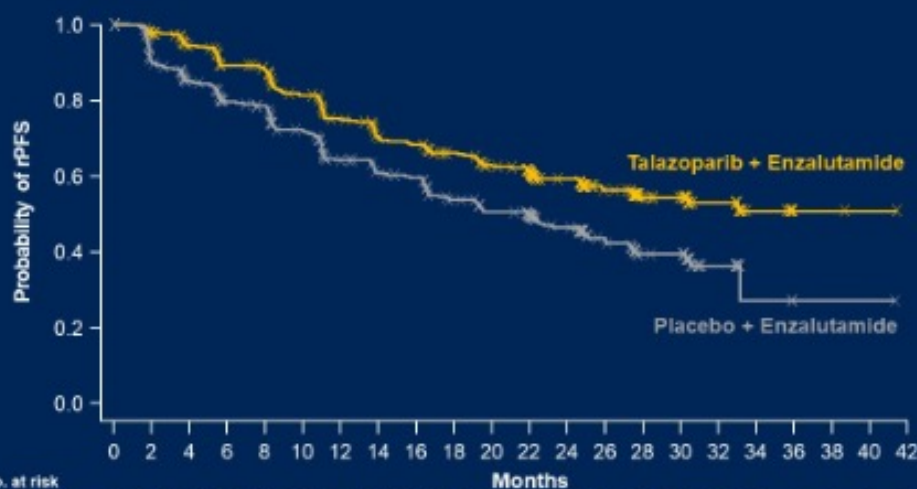
Number of participants with HRR gene alterations, n (%)	Talazoparib + Enzalutamide (N=402)	Placebo + Enzalutamide (N=403)
1 or more alterations in the corresponding gene	85 (21.1)	82 (20.3)
<i>CDK12</i>	23 (5.7)	29 (7.2)
<i>BRCA2</i>	23 (5.7)	28 (6.9)
<i>ATM</i>	23 (5.7)	14 (3.5)
<i>CHEK2</i>	6 (1.5)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

1. Sigarski D, et al. *Target Oncol*. 2020;15:705-722; 2. Abida W, et al. *JCO Precis Oncol*. 2017;2017:PO.17.00029.

# TALAPRO-2

## TALAPRO-2 Primary Endpoint: rPFS by BICR

Treatment with talazoparib plus enzalutamide resulted in a 37% reduced risk of progression or death



	TALA + ENZA (N=402)	PBO + ENZA (N=403)
Events, n	151	191
Median (95% CI), months	Not reached (NR) (27.5–NR)	21.9 (16.6–25.1)
HR (95% CI)	0.63 (0.51–0.78); P < 0.001	

Median follow-up for rPFS was 24.9 and 24.6 months, respectively

A consistent treatment effect was seen for investigator-assessed rPFS: HR 0.64 (95% CI, 0.50–0.81); P < 0.001

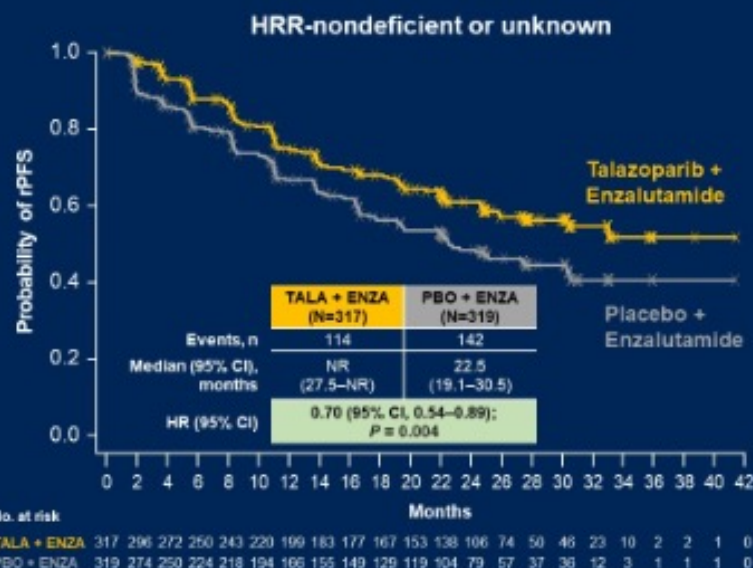
Stratified hazard ratios (HRs) and 2-sided P values are reported throughout this presentation unless otherwise stated.



# TALAPRO-2

## TALAPRO-2: rPFS by BICR by HRR Status

A clinically meaningful reduction in risk of progression or death was seen regardless of HRR status



HRR gene alteration status (deficient vs nondeficient or unknown) as a stratification factor.



# TALAPRO-2

## TALAPRO-2: Most Common All-cause TEAEs



### In the talazoparib arm:

- Most common TEAEs leading to a dose reduction of talazoparib were:
  - Anemia (43.2%)
  - Neutropenia (15.1%)
  - Thrombocytopenia (5.5%)
- 49.0% had grade 1–2 anemia at baseline
- Grade 3–4 anemia
  - Median time to onset was 3.3 months
  - Reported in 46.5% of men
- 8.3% discontinued talazoparib due to anemia
- The median relative dose intensity of talazoparib remained >80%

# 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

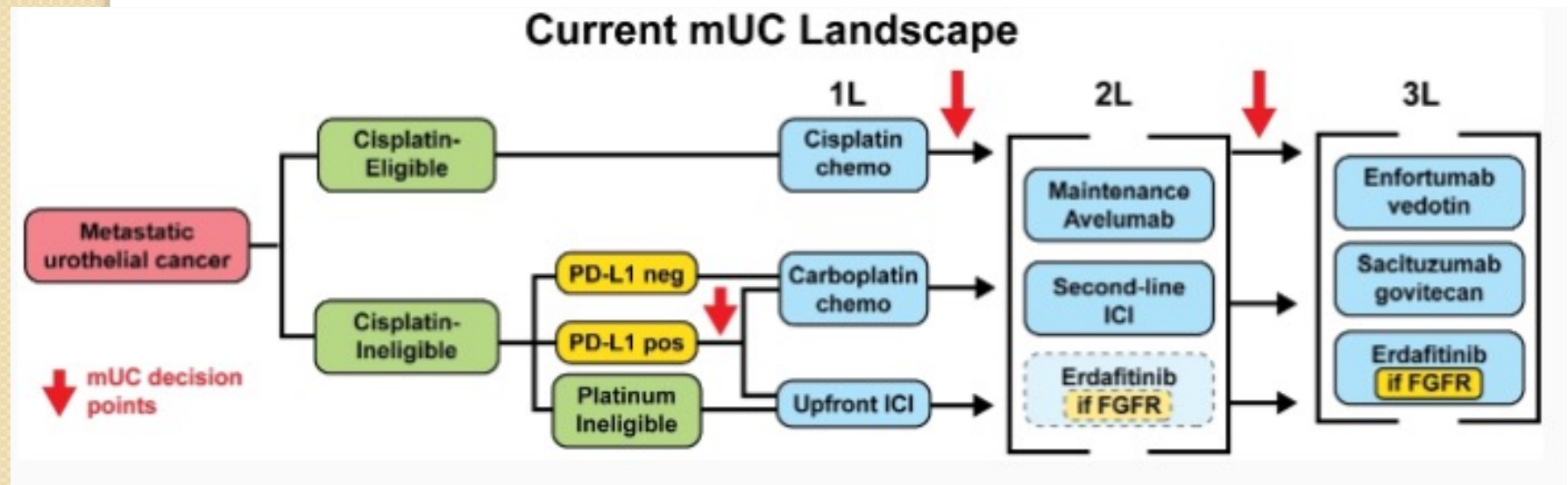
- I would consider PARP + Androgen Pathway Inhibitor + ADT for patients with metastatic castrate resistant prostate cancer with BRCA2 mutation
- Will await follow up studies with Enzalutamide + Rucaparib (CASPAR trial) since there appears to be discordance with MAGNITUDE, PROpel, and TALAPRO-2 for unselected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

# Targeted therapy in Urothelial Cancers

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

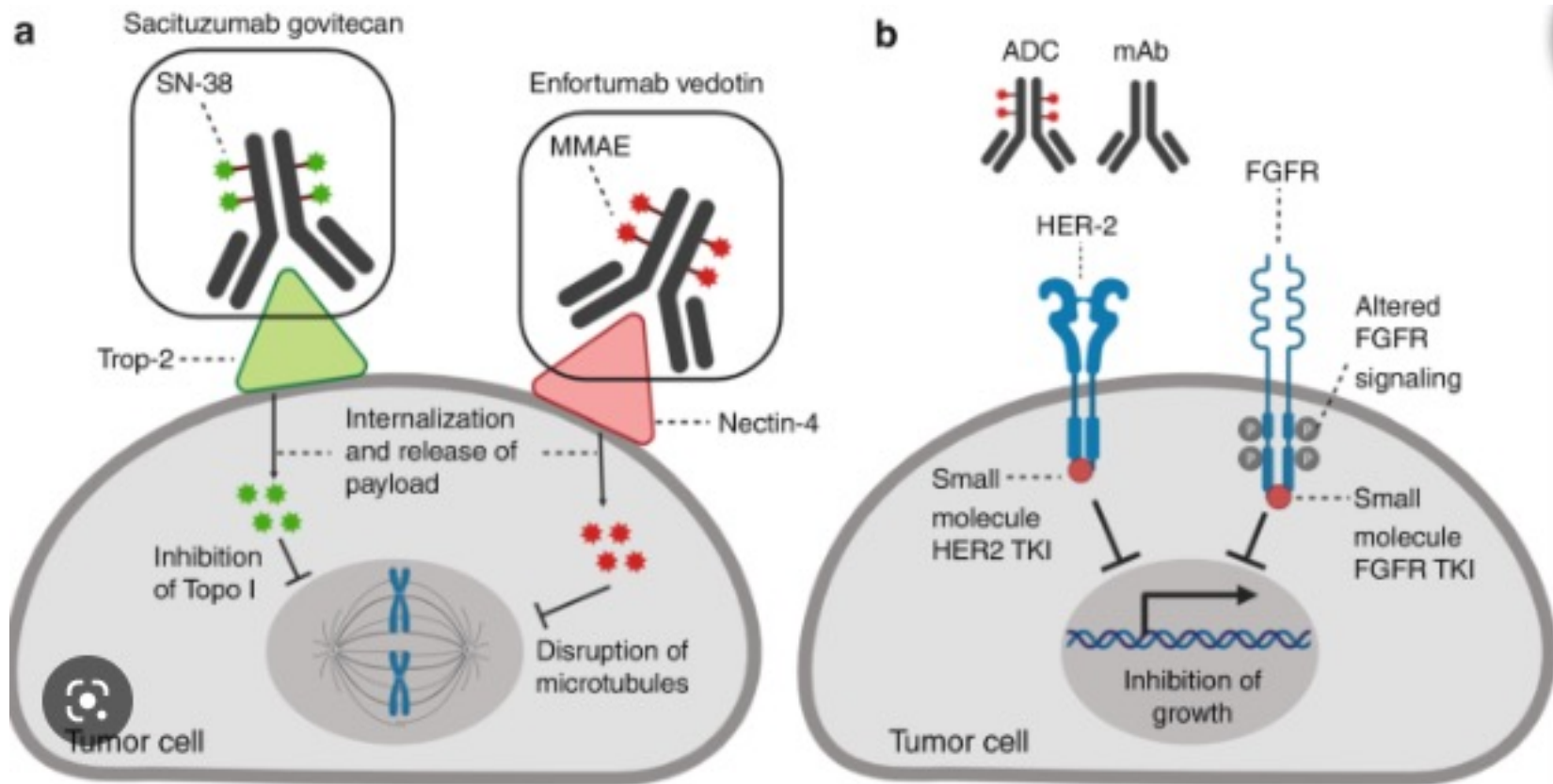


# Urothelial Cancer Algorithm

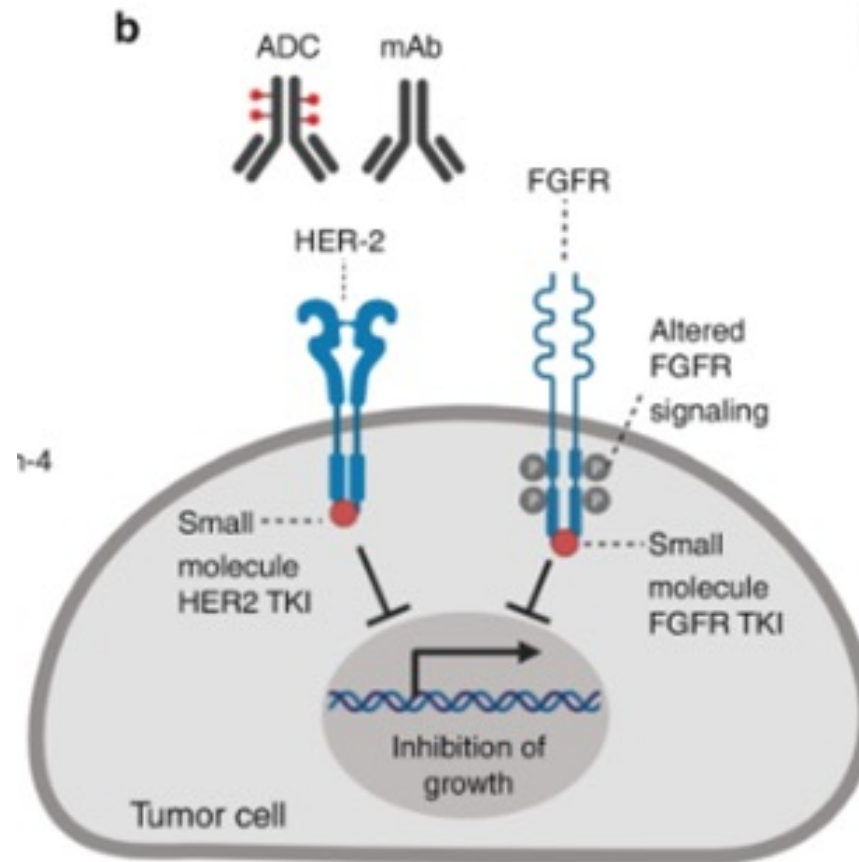


Jun, *J Cancer Metastasis Treat* 2022

# Targeted Therapies



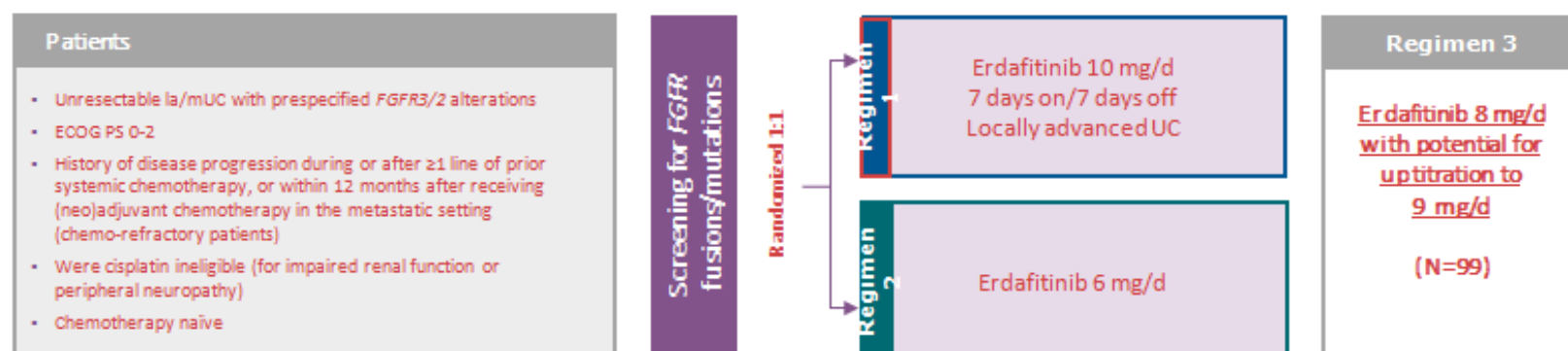
# Erdafitinib



# Erdafitinib

## BLC2001: Phase 2 Trial of Erdafitinib<sup>1</sup>

- Fifteen percent of patients with MIBC have *FGFR* alterations<sup>2</sup>



### Primary endpoint

- Confirmed ORR

### Secondary endpoints

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

### *FGFR* Alterations (n=99)

<i>FGFR2</i> or <i>FGFR3</i> fusion, No. (%)	25 (25)
<i>FGFR3</i> mutation, No. (%)	74 (75)
<i>FGFR2/3</i> 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.

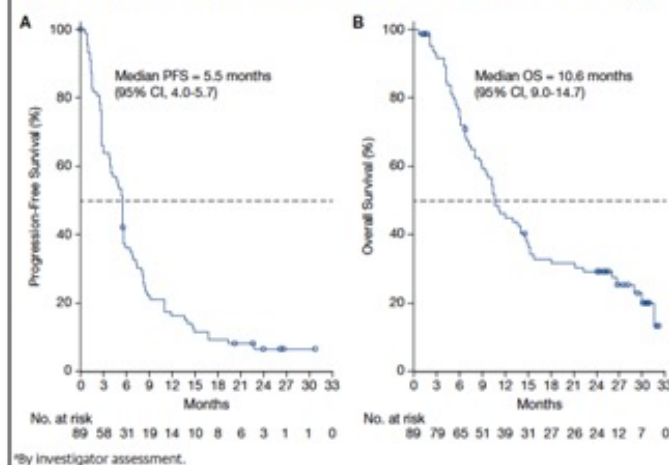


# Erdafitinib

## 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\* and B) OS in Patients Who Had Prior Chemotherapy



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 <sup>a</sup> , mo	n <sup>b</sup>	Median PFS <sup>a</sup> , 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

<sup>a</sup>By investigator assessment. <sup>b</sup>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)

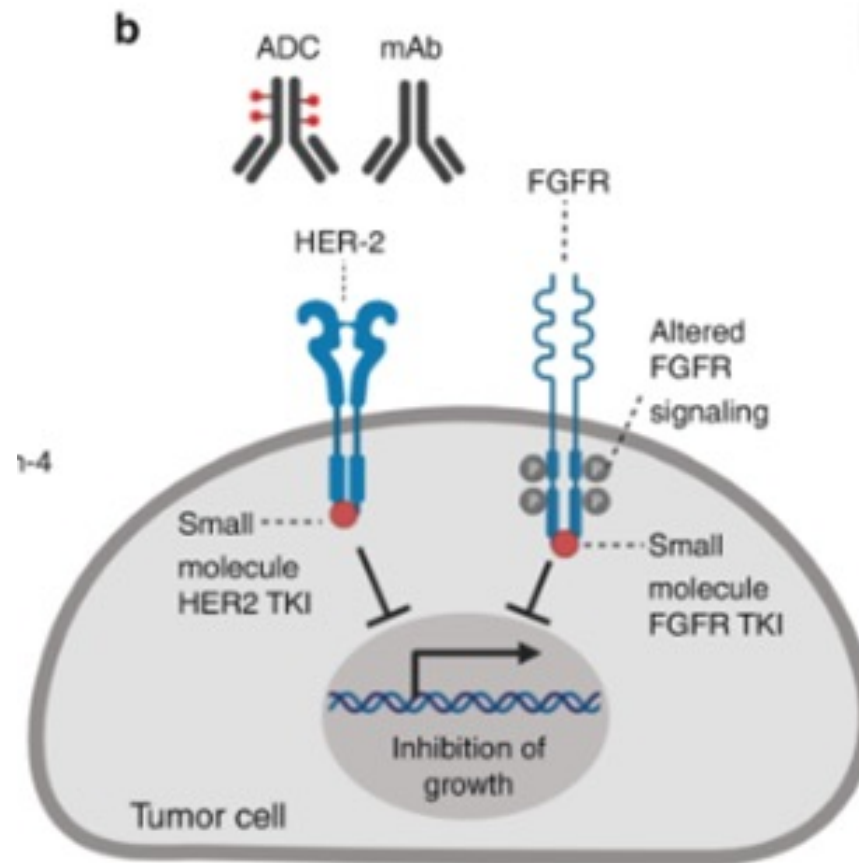
### Final Analysis (n=101)

TEAE of Interest	Overall Incidence n (%)
<u>Hyperphosphatemia<sup>a</sup></u>	79 (78%)
Stomatitis	60 (59%)
Nail disorders	60 (59%)
Skin disorders	55 (55%)
Central serous retinopathy	27 (27%)

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

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

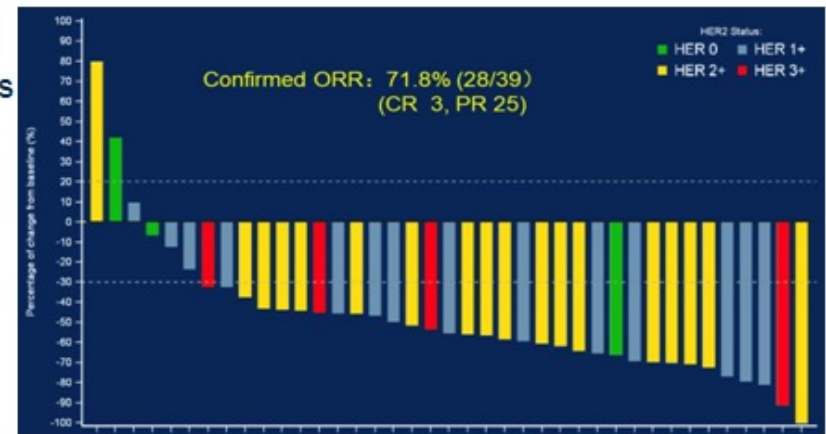
# HER 2 Targeted treatment



# HER2 antibody drug conjugate

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

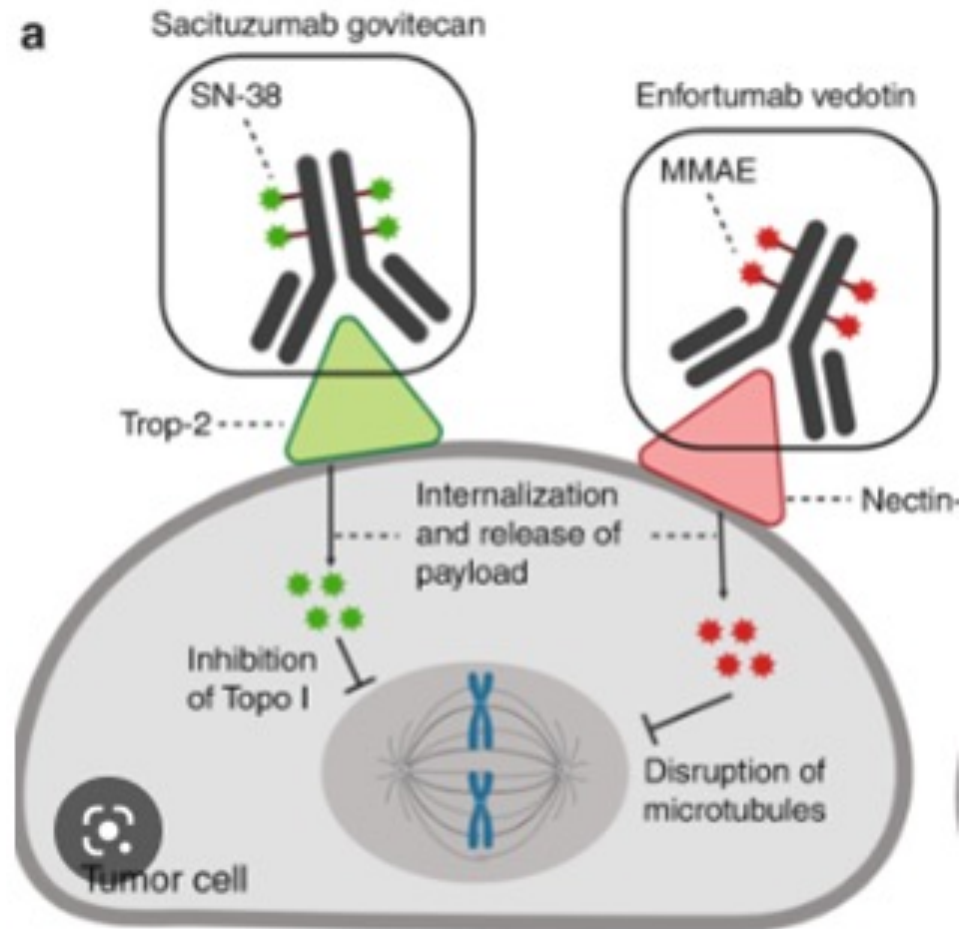
- Pts with locally advanced or metastatic UC
- 41 pts (25 treatment-naïve / 16 with 1+ lines of therapy)
  - 39 pts evaluable for response
- Confirmed ORR: 72% (28/39)
  - cORR in IHC 0 or 1+ pts: 9/17 (53%)
- Median PFS: 9.2 months
- Median OS: NR (86% 12-month OS)



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

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## Enfortumab Vedotin for Previously Treated Advanced UC

- The 5-year relative survival rate for metastatic bladder cancer is  $\approx 8\%$ <sup>1</sup>
- 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<sup>2</sup>

**Efficacy and safety are presented for EV vs chemotherapy over a median follow-up period of  $\approx 2$  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/m<sup>2</sup> or paclitaxel 175 mg/m<sup>2</sup> or  
vinflunine 320 mg/m<sup>2</sup>  
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

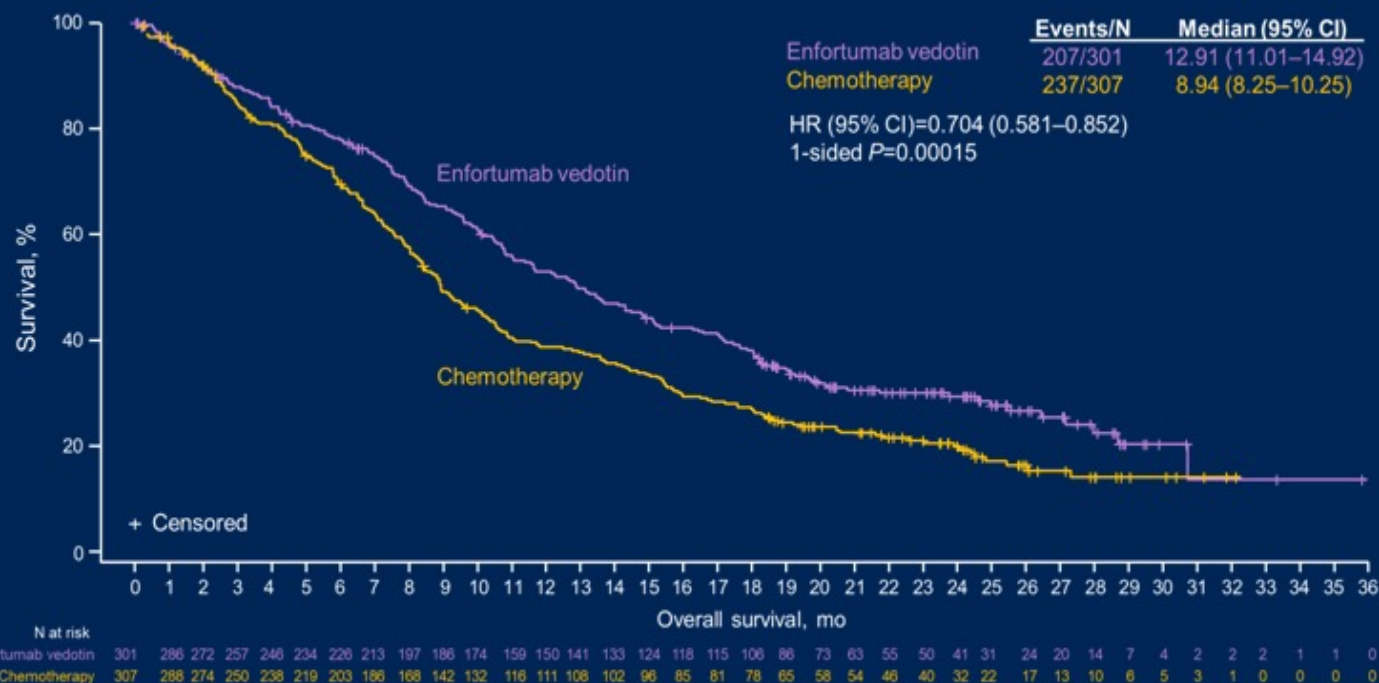
Investigator-  
assessed per  
RECIST v1.1

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

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.

# ASCO 2022

## Overall Survival



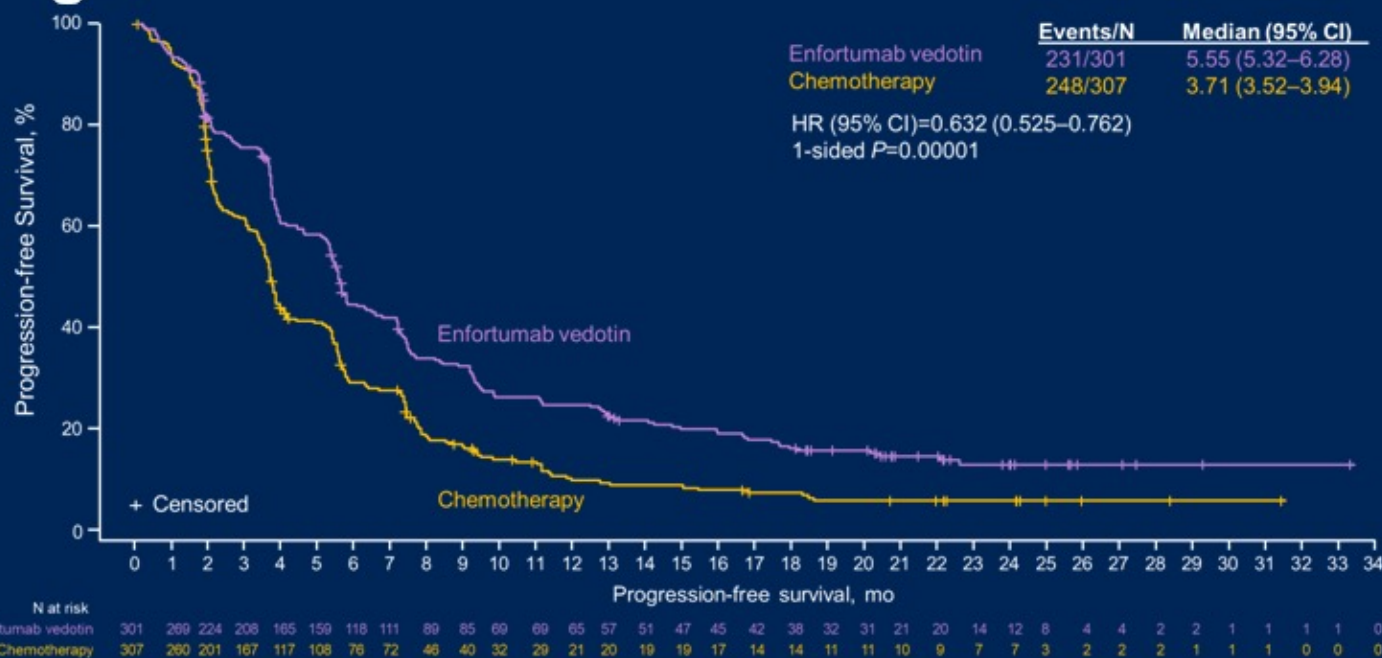
Data shown for intention-to-treat population.  
HR, hazard ratio.

Data cutoff date: July 30, 2021

# ASCO 2022

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## Progression-Free Survival



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

Data cutoff date: July 30, 2021

2022 ASCO  
ANNUAL MEETING

#ASCO22

PRESENTED BY:  
Jonathan E. Rosenberg, MD

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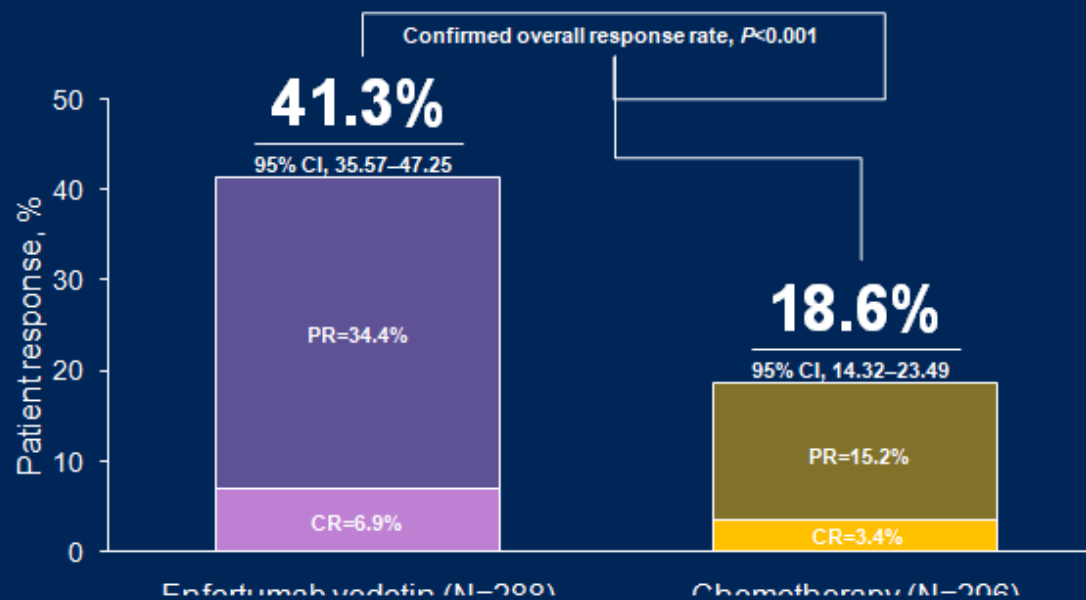
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## Investigator-Assessed Clinical Response



Disease control rate (95% CI),\* %

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.

\*Proportion of patients with best overall response of confirmed CR, PR, or SD (≥7 wk); enfortumab vedotin vs chemotherapy.

# ASCO 2022

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## 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

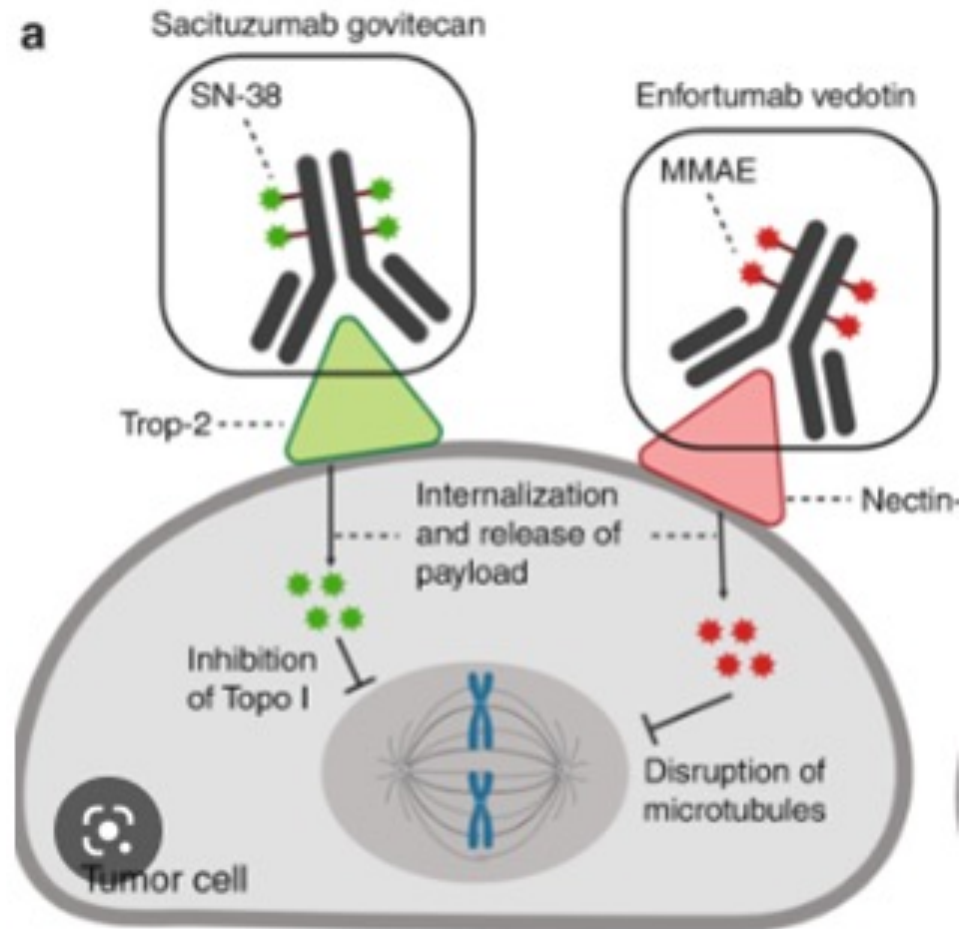
Treatment-related adverse event, n (%)	Enfortumab vedotin (N=296)		Chemotherapy (N=291)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Alopecia	135 (45.6)	NR	108 (37.1)	NR
Peripheral sensory neuropathy	103 (34.8)	15 (5.1)	63 (21.6)	6 (2.1)
Pruritus	96 (32.4)	4 (1.4)	14 (4.8)	1 (0.3)
Fatigue	93 (31.4)	20 (6.8)	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)

NR=Not Reported. TRAEs=treatment-related adverse events.

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

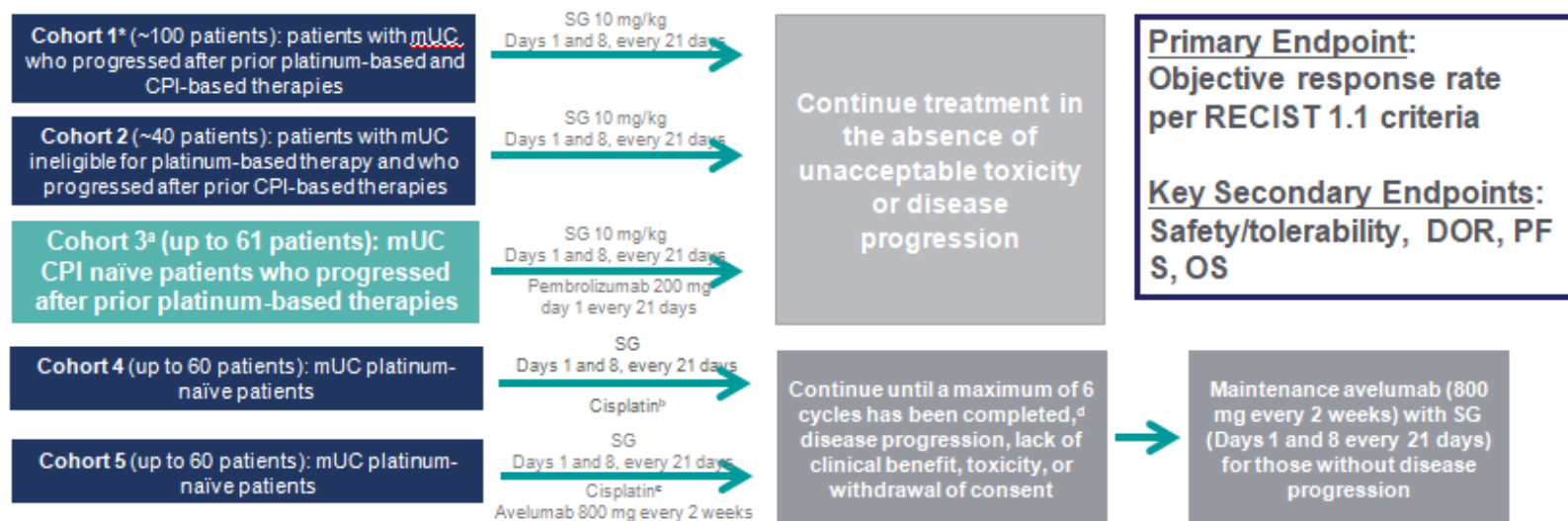
# Antibody drug conjugate



# Sacituzumab Govitecan

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

TROPHY  
U-01



**Key Inclusion Criteria:** Age ≥18 years, ECOG of 0/1, creatinine clearance (CrCl) ≥30 mL/min,<sup>e,f</sup> 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<sup>1</sup>**

<sup>a</sup>Exclusions for Cohort 3 only: active autoimmune disease or history of interstitial lung disease. <sup>b</sup>In patients with CrCl ≥60 mL/min; <sup>c</sup>In patients with creatinine clearance 50–60 mL/min. <sup>d</sup>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-hzyl). Prescribing Information. Immunomedics, Inc.; April 2021; EudraCT Number: 2018-001167-23; ClinicalTrials.gov Number: NCT03547973. IMMU-132-06 study.

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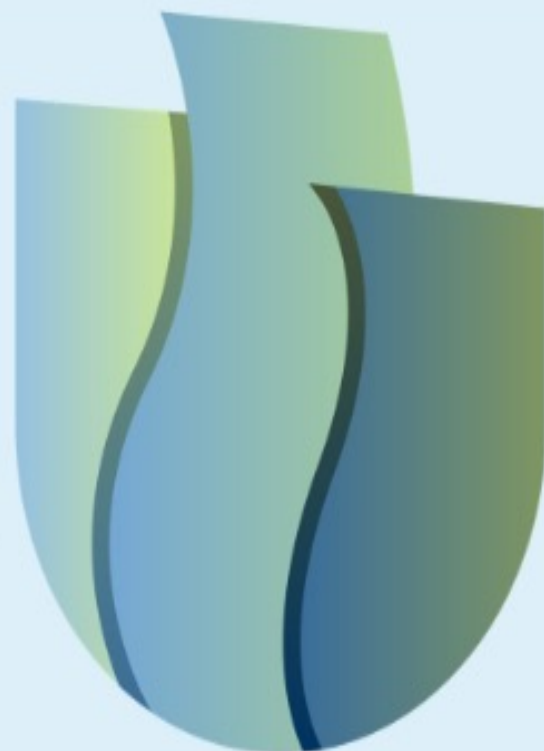
ASCO Genitourinary  
Cancers Symposium



# ASCO GU 2023

## 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) <sup>a</sup>
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) <sup>b,c</sup>
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, <sup>d</sup> n (%)	
Complete response	1 (3)
Partial response	6 (16)
Stable disease	13 (34)
Disease progression	22 (58)

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

# TROPHY-U-01 Cohort 2

## Best Overall Responses<sup>a</sup>

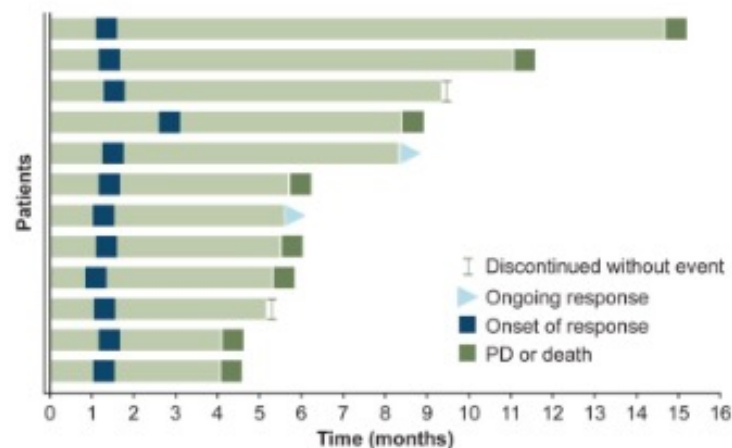
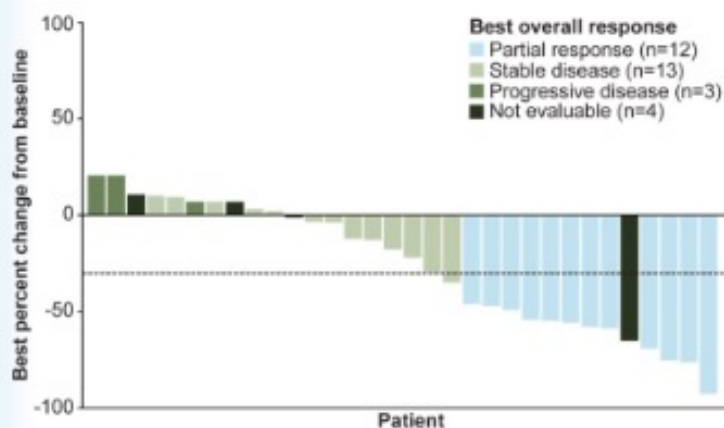
Best Overall Responses	Cohort 2 (N=38)
Objective response rate (CR + PR), n (%) [95%CI]	12 (32) [17.5-48.7]
Best overall response, n (%)	
CR	0
PR	12 (32)
SD	13 (34)
SD ≥6 months	4 (11)
PD	4 (11)
Not evaluable <sup>b</sup>	4 (11)
Not assessed <sup>c</sup>	5 (13)
Clinical benefit rate (CR + PR + SD ≥6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

<sup>a</sup>Responses assessed by independent review assessment <sup>b</sup>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". <sup>c</sup>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.

# TROPHY-U-01 Cohort 2

## Best Change in Target Lesions<sup>a</sup>, and Response Assessment From Start of Treatment to Progression



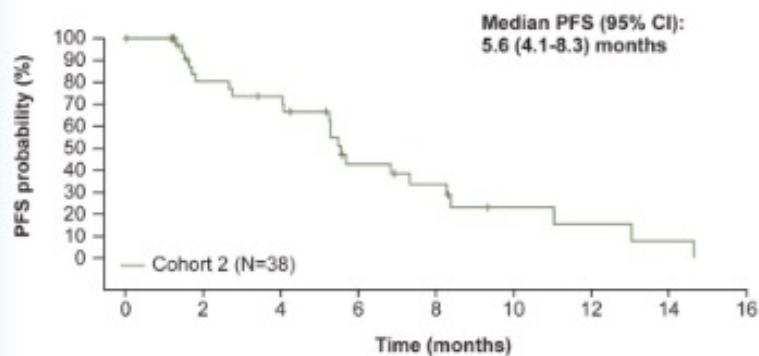
- 69% of assessed patients (22/32) experienced target lesion reduction
- 2 patients had an ongoing response at data cutoff

<sup>a</sup>Patients with missing percent change from baseline are not reported.  
PD, progressive disease.

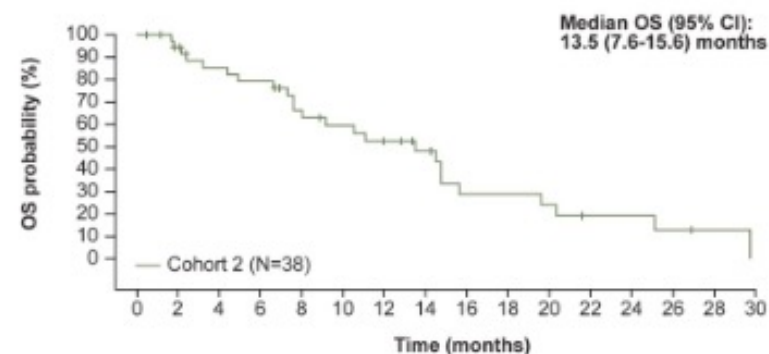


# TROPHY-U-01 Cohort 2

## Progression-Free Survival and Overall Survival



No. of patients still at risk  
Cohort 2 38 24 21 10 7 3 2 1 0



No. of patients still at risk  
Cohort 2 38 33 28 26 20 17 14 11 6 6 5 3 3 2 1 0

- Median follow-up was 9.3 months
- Median PFS was 5.6 months (95% CI, 4.1-8.3)
- Median OS was 13.5 months (95% CI, 7.6-15.6)

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

# 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

# TROPHY-U-01 Cohort 2

## Conclusions

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- 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)<sup>1</sup>



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