Developing Targeted Therapy for Genitourinary Malignancies

The 13th Annual Winter Cancer Symposium

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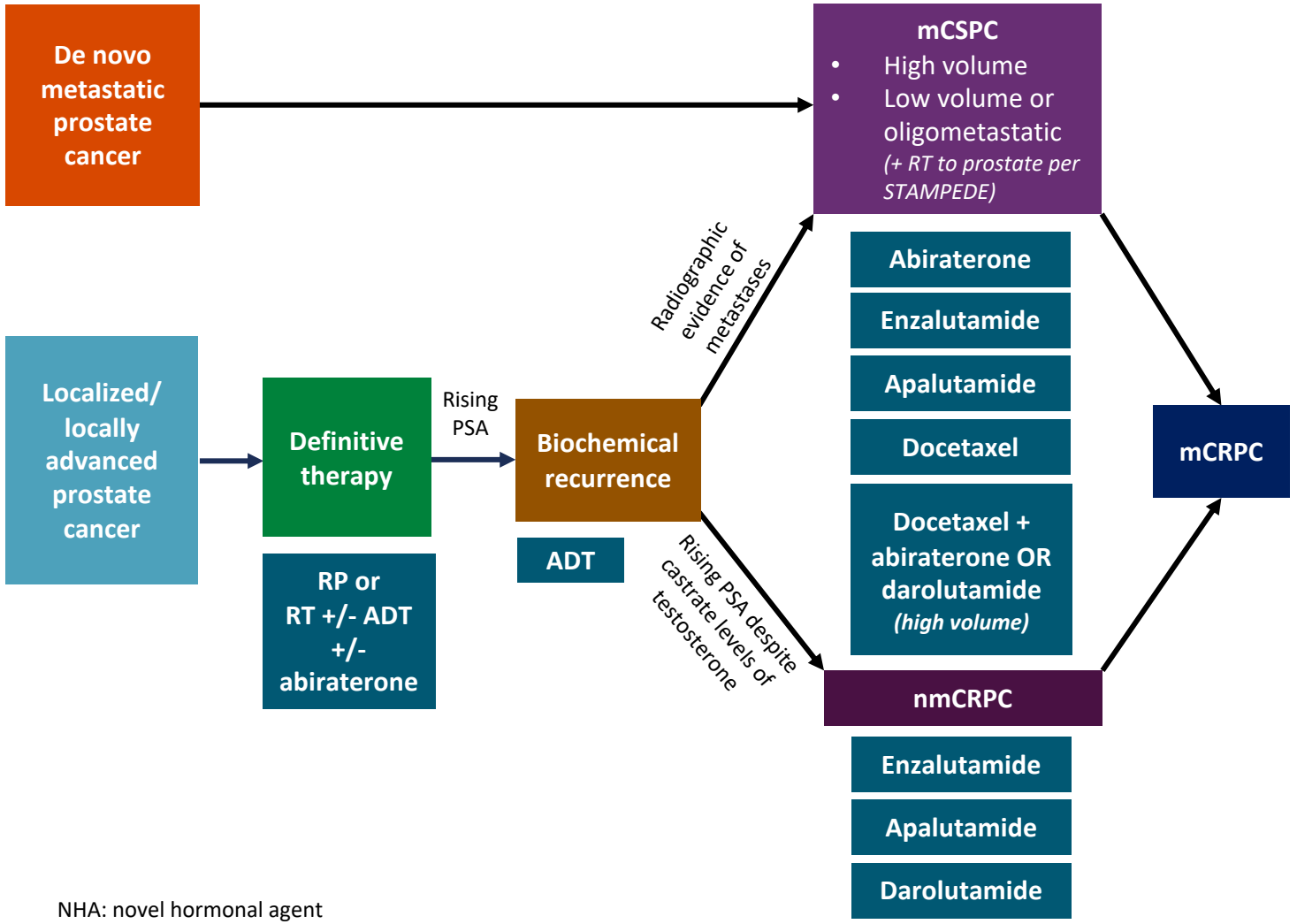
OUTLINE

- Targeted Therapies in Prostate Cancer (PCa)
- Targeted Therapies in Urothelial Cancer (UC)
- Targeted Therapies in Renal Cell Carcinoma (RCC)
- Summary

TREATMENT ACROSS THE CONTINUUM OF PCa

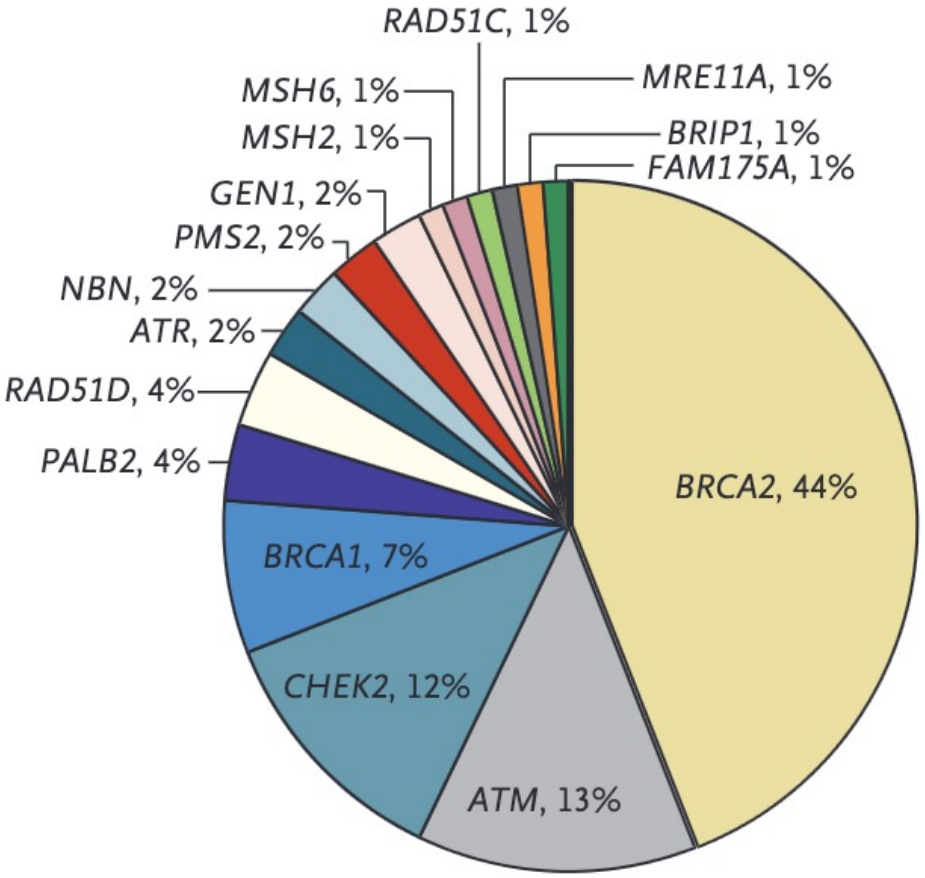


	No prior NHA	Prior NHA
No prior docetaxel	NHA monotherapy Abiraterone Enzalutamide Chemotherapy Docetaxel PARP inhibitor (PARPi) + NHA Niraparib + abiraterone (*BRCA*m) Olaparib + abiraterone (*BRCA*m) Talazoparib + enzalutamide (HRRm) Others Radium-223 (bone only mets) Sipuleucel-T	NHA monotherapy Abiraterone (if no prior abiraterone) Enzalutamide (if no prior enzalutamide) Chemotherapy Docetaxel PARPi + NHA Niraparib + abiraterone (*BRCA*m) Talazoparib + enzalutamide (HRRm) PARPi monotherapy Olaparib (HRRm) Rucaparib (*BRCA*m) Others ^{177}Lu-PSMA-617 (PSMA+) Radium-223 (bone only mets) Sipuleucel-T
Prior docetaxel	NHA monotherapy Abiraterone Enzalutamide Chemotherapy Cabazitaxel (+ carboplatin in select cases) PARPi + NHA Niraparib + abiraterone (*BRCA*m) Olaparib + abiraterone (*BRCA*m) Talazoparib + enzalutamide (HRRm) Others Radium-223 (bone only mets) Sipuleucel-T	NHA monotherapy Abiraterone (if no prior abiraterone) Enzalutamide (if no prior enzalutamide) Chemotherapy Cabazitaxel (+ carboplatin in select cases) PARPi + NHA Niraparib + abiraterone (*BRCA*m) Talazoparib + enzalutamide (HRRm) PARPi monotherapy Olaparib (HRRm) Rucaparib (*BRCA*m) Others ^{177}Lu-PSMA-617 (PSMA+) Radium-223 (bone only mets) Pembrolizumab (MSI-H, dMMR, or TMB ≥ 10)

NHA: novel hormonal agent

DNA DAMAGE RESPONSE & REPAIR (DDR) GENE MUTATIONS

DDR gene mutations are common in patients with metastatic prostate cancer



Germline

- 11.8% of men with metastatic prostate cancer[1]
- 6% with localized high-risk disease
- Regardless of age or family history of prostate cancer (but not of any cancer)[1]
- Prevalence in metastatic CRPC:[2,3]
  - ***BRCA2*: 3.5-5.3%**
  - ***BRCA1*: 0.9-1.3%**
  - ***ATM*: 0.3-2.0%**
  - ***PALB2*: 0.4-0.6%**

Somatic

- ~25-30% of metastatic CRPC[4]

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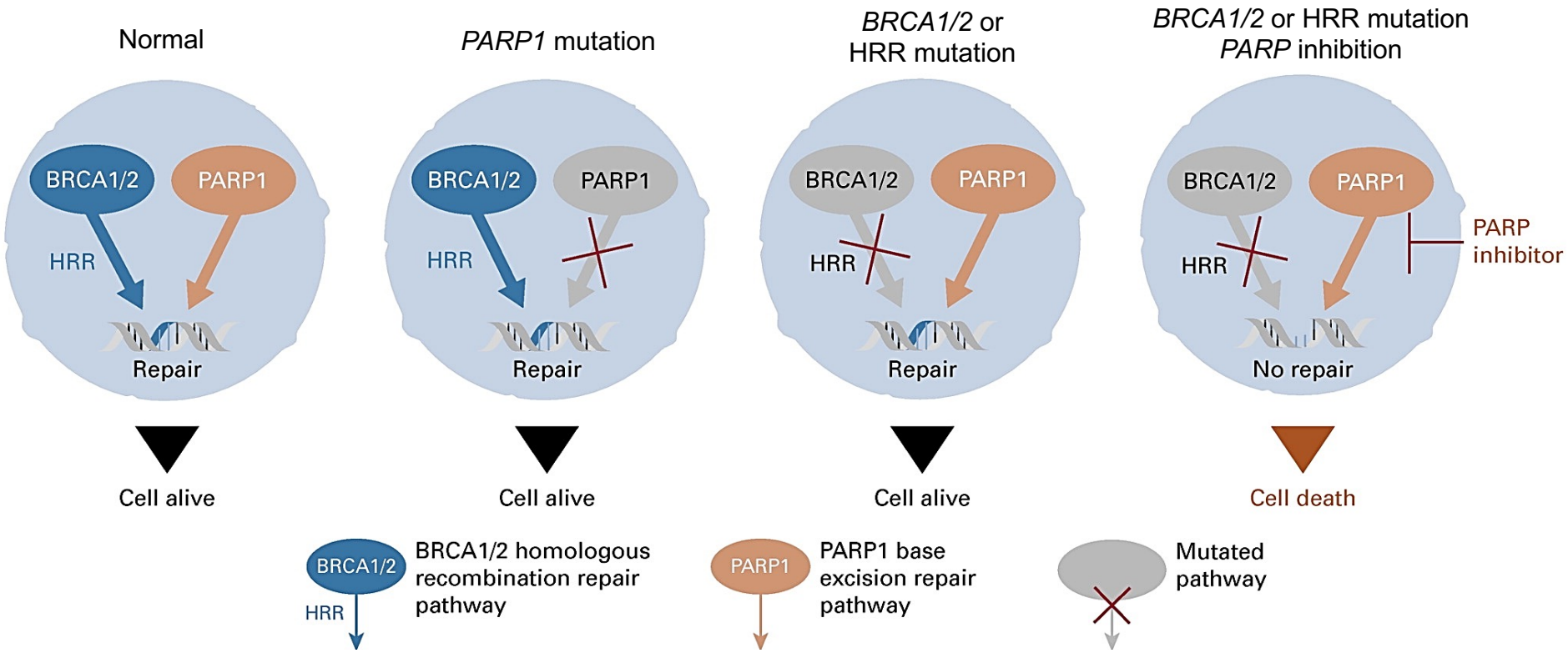
1. Pritchard CC. N Engl J Med. 2016. 2. Nicolsi P. JAMA Oncol. 2019. 3. Lang SH. Int J Oncol. 2019. 4. de Bono JS. Ann Oncol. 2019.

RATIONALE FOR PARP INHIBITORS (PARPi)

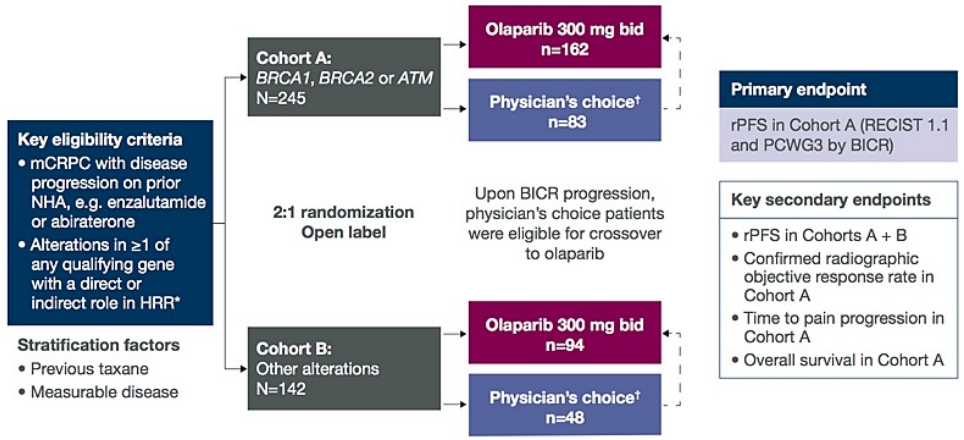


- Inhibition of PARP1 pathway leads to trapping of PARP on DNA
- In pts with HRR mutations → trapping of PARP results in synthetic lethality (cell marked for death)

Gourley C. J Clin Oncol. 2019.

PARPi MONOTHERAPY IN mCRPC

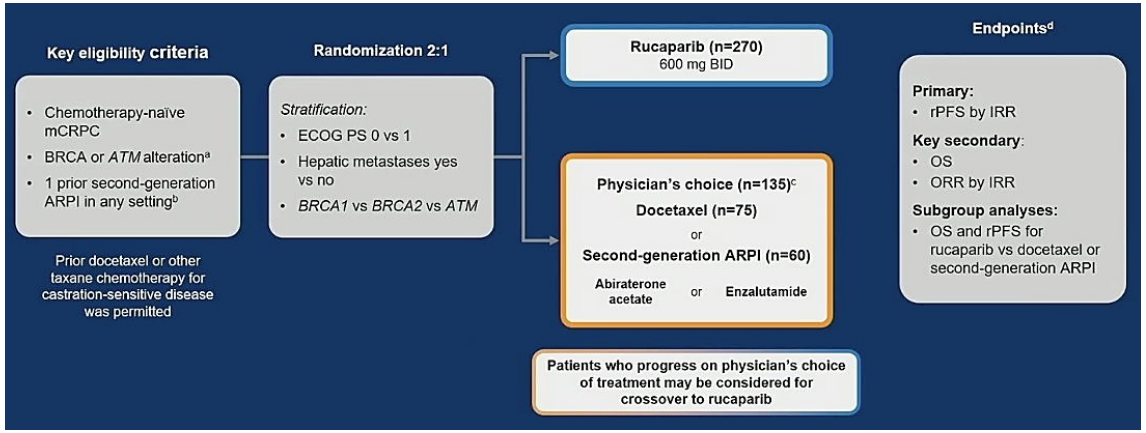
PROfound[1,2] (olaparib)



Median rPFS & OS longer with olaparib in the ***BRCA1/2*m subgroup**

	Cohort A (*BRCA1/2*m or *ATM*m)		Overall population Cohort A + Cohort B (other HRRm)	
	Olaparib (n=162)	Physician's choice‡ (n=83)	Olaparib (n=94)	Physician's choice‡ (n=48)
mrPFS, mos	**7.4**	3.6	5.8	3.5
mOS, mos	**19.1**	14.7	17.3 Cohort B: 14.1	14.0 Cohort B: 11.5

TRITON-3[3] (rucaparib)



Superior efficacy with rucaparib vs. docetaxel in patients with ***BRCA*m**

	*BRCA*m subgroup		ITT population (*BRCA*m + *ATM*m)	
	Rucaparib (n=201)	Physician's choice* (n=101)	Rucaparib (n=270)	Physician's choice* (n=135)
mrPFS, mos	**11.2**	6.4	10.2	6.4
mOS, mos	24.3	20.8	23.6	20.9

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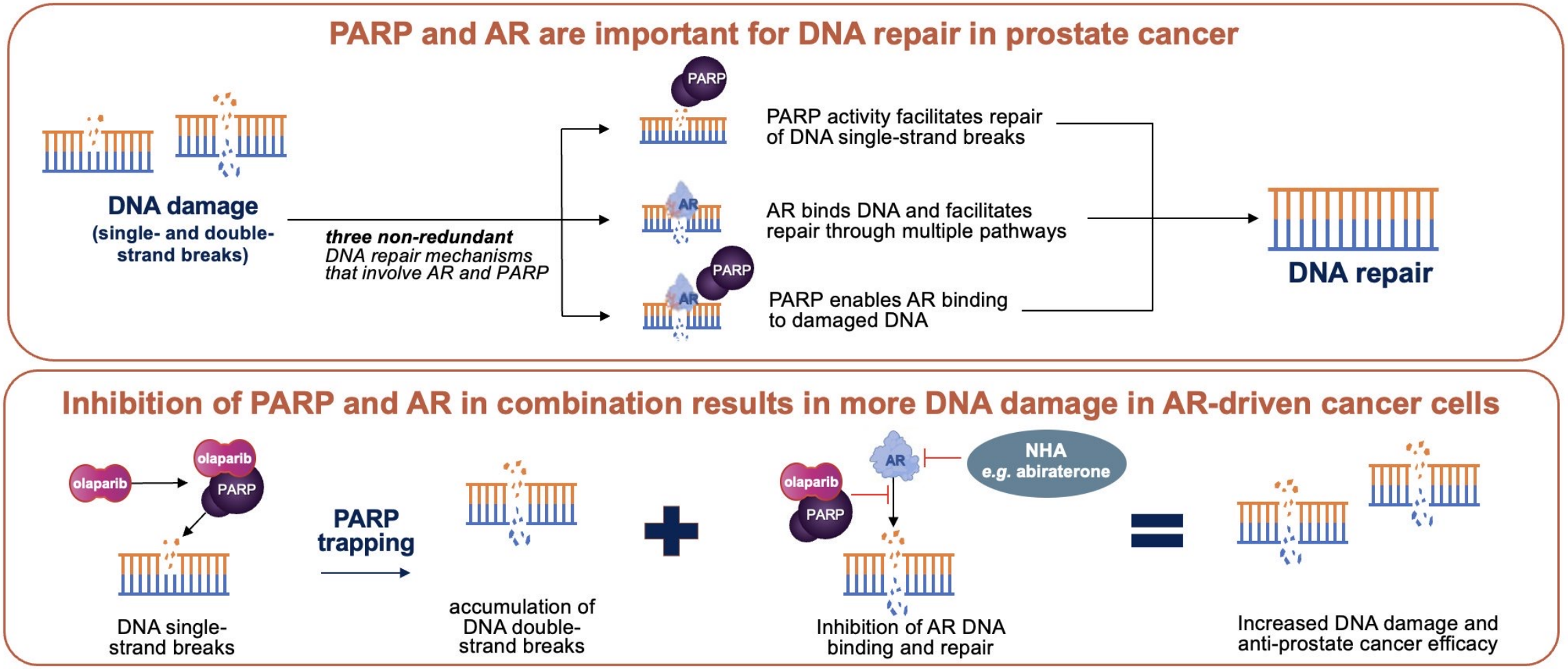
‡Physician's choice: NHA (abiraterone or enzalutamide)
*Physician's choice: Docetaxel or NHA (abiraterone or enzalutamide)

1. de Bono JS. N Engl J Med. 2020. 2. Hussain MHA. N Engl J Med. 2020.
3. Fizazi K. N Engl J Med. 2023.

RATIONALE FOR COMBINING PARPi + NHAs



AR, androgen receptor; DNA, deoxyribonucleic acid; NHA, novel hormonal agent; PARP, poly(ADP-ribose) polymerase

Figure courtesy of Hannah Dzimitrowicz McManus, MD & Andrew Armstrong, MD.

PARPi + NHA COMBINATIONS IN mCRPC

	PROpel[1] (Olaparib + abiraterone/prednisone vs. placebo + abiraterone/prednisone)	TALAPRO-2[2] (Talazoparib + enzalutamide vs. placebo + enzalutamide)	MAGNITUDE[3,4] (Niraparib + abiraterone/prednisone vs. placebo + abiraterone/prednisone)
Study population	All comers (biomarker unselected)	All comers (biomarker unselected) Biomarker testing completed prior to enrollment	Biomarker stratified a priori HRRm- (Cohort 2) discontinued due to futility
Prior therapies	• Prior docetaxel in mCSPC setting • No prior abiraterone • Other prior NHA allowed in CSPC setting if stopped ≥ 12 months before randomization	• Prior docetaxel or abiraterone allowed in mCSPC setting • No prior systemic therapy for nmCRPC or mCRPC	• ≤ 4-month prior abiraterone at mCRPC • Allowed prior treatments for nmCRPC or mCSPC: enzalutamide, apalutamide, darolutamide, taxane chemotherapy
Primary endpoint	• rPFS by investigator assessment in unselected patients	• rPFS by BICR per RECIST 1.1 (soft tissue disease) & PCWG3 (bone disease) in unselected patients (Cohort 1) & in patients with DDR alterations (Cohort 2)	• rPFS by BICR
Stratification factors	• Site of metastases • Prior taxane for mCSPC	• Prior docetaxel or abiraterone for mCSPC • DDR alteration status	• Prior taxane in mCSPC • Prior NHA in nmCRPC or mCSPC settings • Abiraterone in 1L mCRPC • *BRCA*m in HRRm cohort
Screening assay	• FoundationOne® CDx test • FoundationOne® Liquid CDx test	• FoundationOne® CDx test • FoundationOne® Liquid CDx test	• FoundationOne® CDx test • Resolution Bioscience liquid test (ctDNA)

1. Clarke N. N Engl J Med. 2022. 2. Agarwal N. Lancet. 2023. 3. Chi KN. J Clin Oncol. 2023. 4. Chi KN. Ann Oncol. 2023.

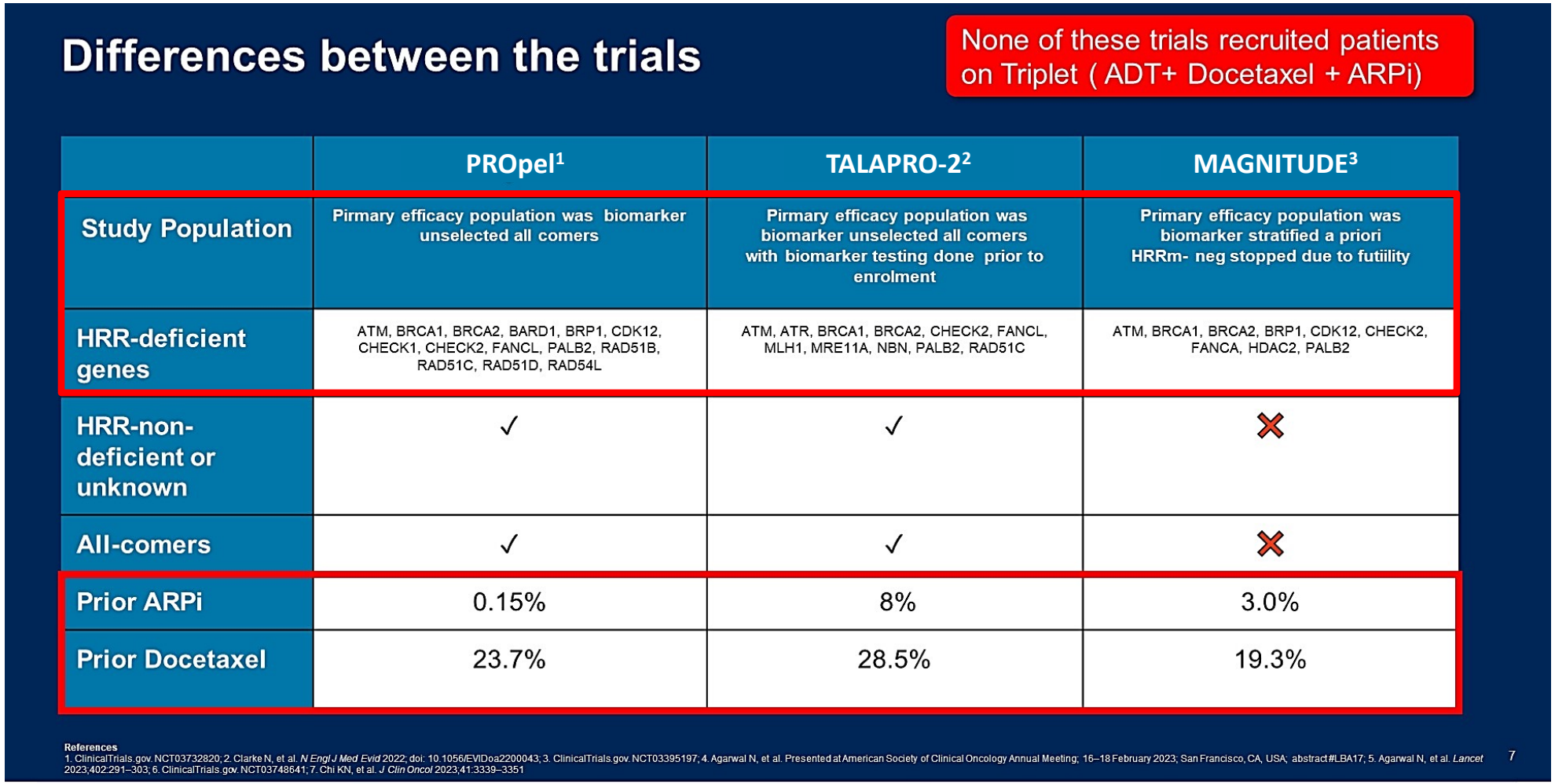
PARPi + NHA COMBINATIONS IN mCRPC

	PROpel[1] (Olaparib + abiraterone/prednisone vs. placebo + abiraterone/prednisone)	TALAPRO-2[2-5] (Talazoparib + enzalutamide vs. placebo + enzalutamide)	MAGNITUDE[6,7] (Niraparib + abiraterone/prednisone vs. placebo + abiraterone/prednisone)
HRRm	mrPFS: NR vs. 13.9 months **HR 0.50** (95% CI: 0.34-0.74) mOS: NR vs. 28.5 months **HR 0.66** (95% CI: 0.45-0.95)	mrPFS: 27.9 vs. 16.4 months **HR 0.46** (95% CI: 0.30-0.70); p<0.0003 mOS: NR vs. 33.7 months* **HR 0.69** (95% CI: 0.46-1.03); p=0.068	mrPFS: 16.5 vs. 13.7 months **HR 0.73** (95% CI: 0.56-0.96); p=0.0217 mOS: 29.3 vs. 32.2 months **HR 1.01** (95% CI: 0.75-1.36); p=0.948
Non-HRRm	mrPFS: 24.1 vs. 19.0 months **HR 0.76** (95% CI: 0.60-0.97) mOS: 42.1 vs. 38.9 months **HR 0.89** (95% CI: 0.70-1.14)	mrPFS: NR vs. 22.5 months **HR 0.70** (95% CI: 0.54-0.89); p=0.0039 mOS: NR vs. 38.7 months* **HR 0.93** (95% CI: 0.73-1.19); p=0.56	mrPFS: NR vs. NR **HR 1.09** (95% CI: 0.75-1.57); p=0.66
***BRCA*m**	mrPFS: NR vs. 8.4 months **HR 0.23** (95% CI: 0.12-0.43) mOS: NR vs. 23.0 months **HR 0.29** (95% CI: 0.14-0.56)	mrPFS: NR vs. NR **HR 0.23** (95% CI: 0.10-0.53); p<0.0002 mOS: NR vs. NR* **HR 0.61** (95% CI: 0.31-1.23); p=0.16	mrPFS: 16.6 vs. 10.9 months **HR 0.53** (95% CI: 0.36-0.79); p=0.001 mOS: 30.4 vs. 28.6 months **HR 0.79** (95% CI: 0.55-1.12); p=0.183
Non-*BRCA*m	mrPFS: 24.1 vs. 19.0 months **HR 0.76** (95% CI: 0.61-0.94) mOS: 39.6 vs. 38.0 months **HR 0.91** (95% CI: 0.73-1.13)	mrPFS: NR vs. NR **HR 0.66** (95% CI: 0.39-1.12); p=0.12	----------

*OS from interim analysis

1. Clarke N. N Engl J Med. 2022. 2. Agarwal N. Lancet. 2023. 3. Fizazi K. ASCO 2023. Abstract 5004. 4. Matsubara N. ESMO 2023. Abstract 1870P. 5. Fizazi K. Nat Medicine. 2023. 6. Chi KN. J Clin Oncol. 2023. 7. Chi KN. Ann Oncol. 2023.

PARPi + NHA COMBINATIONS IN mCRPC



Differences between the trials

None of these trials recruited patients on Triplet (ADT+ Docetaxel + ARPi)

	PROpel[1]	TALAPRO-2[2]	MAGNITUDE[3]
Study Population	Pirmary efficacy population was biomarker unselected all comers	Pirmary efficacy population was biomarker unselected all comers with biomarker testing done prior to enrolment	Primary efficacy population was biomarker stratified a priori HRRm- neg stopped due to futiility
HRR-deficient genes	ATM, BRCA1, BRCA2, BARD1, BRP1, CDK12, CHECK1, CHECK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L	ATM, ATR, BRCA1, BRCA2, CHECK2, FANCL, MLH1, MRE11A, NBN, PALB2, RAD51C	ATM, BRCA1, BRCA2, BRP1, CDK12, CHECK2, FANCA, HDAC2, PALB2
HRR-non-deficient or unknown	✓	✓	✗
All-comers	✓	✓	✗
Prior ARPi	0.15%	8%	3.0%
Prior Docetaxel	23.7%	28.5%	19.3%

References
1. ClinicalTrials.gov. NCT03732820; 2. Clarke N, et al. *N Engl J Med Evid* 2022; doi: 10.1056/EVIDoa2200043; 3. ClinicalTrials.gov. NCT03395197; 4. Agarwal N, et al. Presented at American Society of Clinical Oncology Annual Meeting; 16–18 February 2023; San Francisco, CA, USA; abstract #LBA17; 5. Agarwal N, et al. *Lancet* 2023;402:291–303; 6. ClinicalTrials.gov. NCT03748641; 7. Chi KN, et al. *J Clin Oncol* 2023;41:3339–3351

7

ASCO Genitourinary Cancers Symposium #GU24

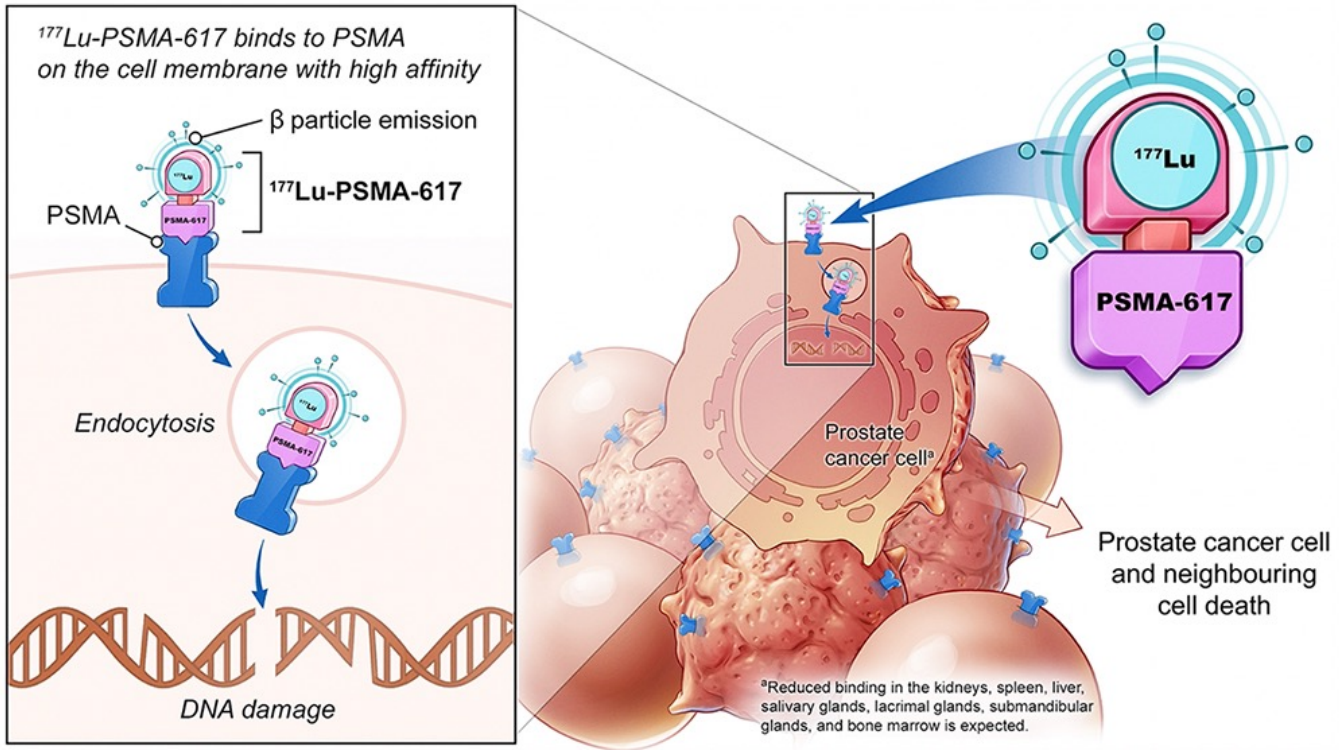
Note that head-to-head studies were not conducted between these products.

PRESENTED BY: Ravindran Kanesvaran, MD

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

1. Clarke N. N Engl J Med. 2022. 2. Agarwal N. Lancet. 2023. 3. Chi KN. J Clin Oncol. 2023.
Slide credit: Kanesvaran R. ASCO GU 2024.

RADIOLIGAND THERAPIES (RLTs) IN mCRPC

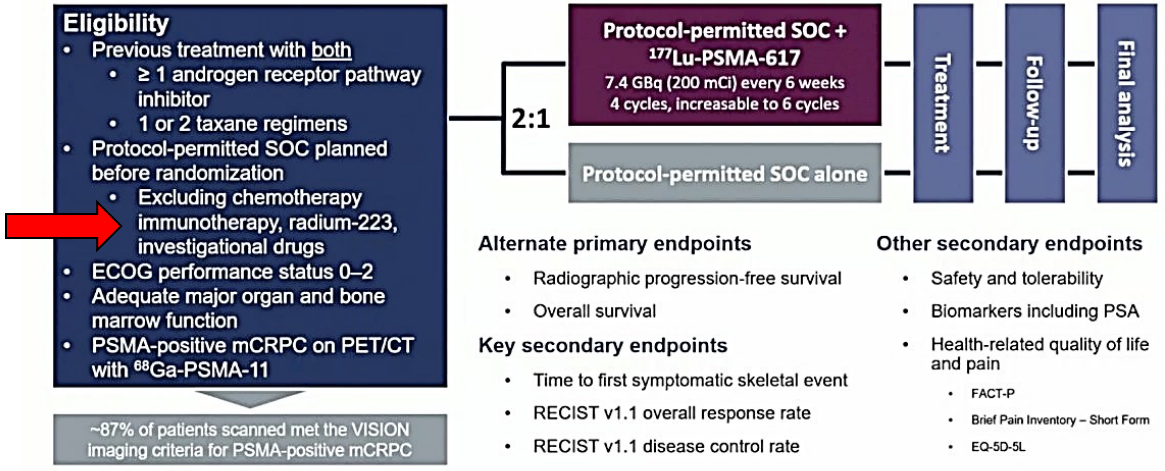


- Prostate-specific membrane antigen (**PSMA**) highly expressed on prostate cancer cells
- **^{177}Lu** is a β-emitting radioisotope
- Radioligand therapies
  - Bind to target on prostate cancer cell (e.g., PSMA)
  - Enveloped into cell → emitted radiation induces cell death
- Different target-radioisotope conjugations under investigation

Morris MJ. ASCO 2021. Abstract LBA4.

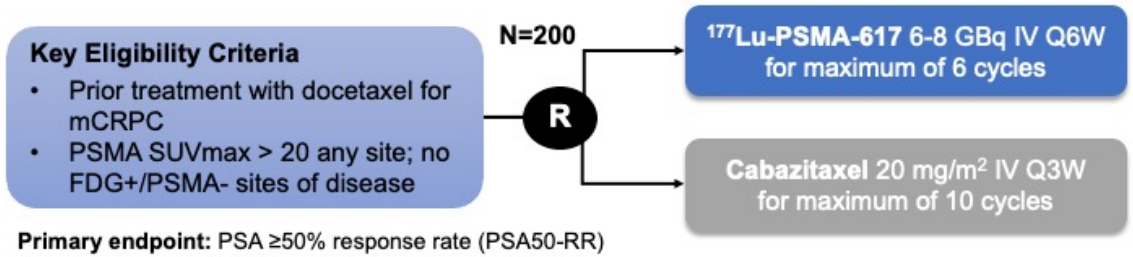
RADIOLIGAND THERAPIES IN mCRPC

VISION[1,2] (^{177}Lu-PSMA-617 + SOC)



	^{177}Lu-PSMA-617 + SOC (n=551)	SOC (n=280)	Hazard Ratio (95 % CI)	p-value
PSA50-RR	46%	33%	N/A	N/A
mrPFS, mos	**8.7**	3.4	0.40 (0.29-0.57)	<0.001
mOS, mos	**15.3**	11.3	0.62 (0.52-0.74)	<0.001

TheraP[3,4] (^{177}Lu-PSMA-617)



Primary endpoint: PSA ≥50% response rate (PSA50-RR)

	^{177}Lu-PSMA-617 (n=99)	Cabazitaxel (n=101)	Difference (95 % CI)	p-value
PSA50-RR	**66%**	37%	29% (95% CI: -3.7-2.7)	<0.0001
mrPFS, mos	**5.1**	5.1	HR 0.64 (95% CI: 0.46-0.88)	0.007
OS (RMST), mos	19.1	19.6	-0.5 mos (95% CI: -3.7-2.7)	0.77

1. Morris MJ. ASCO 2021. Abstract LBA4. 2. Sartor O. N Engl J Med. 2021. 3. Hofman MS. Lancet. 2021. 4. Hofman MS. Lancet Oncol. 2023.

SELECT PARPi COMBOS IN DEVELOPMENT IN mPCa

	NHA	Immunotherapy		Other targeted pathways		
Olaparib	Ph III PROpel ***Met primary endpoint*** **Abiraterone**	Ph III KEYLYNK-010 ***Results negative*** **Pembrolizumab**	Ph II NCT03810105 **Durvalumab**	Ph I/II COMRADE NCT03317392 **Radium-223**	Ph I LuPARP NCT03874884 **^{177}Lu-PSMA-617**	Ph II NCT02893917 **Cediranib (VEGFRi)**
Talazoparib	Ph III TALAPRO-3 NCT04821622 Ph III TALAPRO-2 ***Met primary endpoint*** **Enzalutamide**			Ph II NCT04824937 **Telaglenastat (GLSi)**	Ph I NCT04846478 **Tazemetostat (EZH2i)**	Ph I NCT04703920 **Belinostat (HDACi)**
Rucaparib	Ph III CASPAR ***Closed to accrual*** **Enzalutamide**	Ph II CheckMate 9KD NCT03338790 **Nivolumab**		Ph II PLATI-PARP NCT03442556 **Chemotherapy**	Phase I/II NCT04253262 **Copanlisib (PI3Ki)**	
Niraparib	Ph III AMPLITUDE NCT04497844 Ph III MAGNITUDE ***Met primary endpoint*** **Abiraterone**	Ph I/II QUEST NCT03431350 **Cetrelimab**		Ph I NiraRad NCT03076203 **Radium-223**	Ph II NCT04592237 **Chemotherapy + Cetrelimab**	
AZD5305 (Saruparib)	Ph III EvoPAR-PR01 NCT06120491	**Abiraterone or Enzalutamide or Darolutamide**				

mCSPC setting

mCRPC setting

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SELECT TARGETED THERAPIES IN DEVELOPMENT IN PCa

Targeted Agents & Combinations

Androgen Receptor Pathway
- ARV-110
- ARV-766
- ODM-208

Other targeted agent combinations
- Abemaciclib (CDK4/6 inhibitor) +/- abiraterone
- Cabozantinib + atezolizumab
- Capivasertib + abiraterone
- PARPi combos in earlier PCa

Radioligand Therapies (RLTs)

Novel Radioligands
- ^{177}Lu-PSMA-I&T
- ^{177}Lu-DOTA-rosopatamab
- ^{225}Ac-PSMA-617
- ^{225}Ac-PSMA-I&T

Radioligand combinations
- ^{177}Lu-PSMA-617 + olaparib
- ^{177}Lu-PSMA-617 + enza
- ^{177}Lu-J591 + docetaxel
- ^{225}Ac-J591 + pembro + NHA
- ^{177}Lu-PSMA-I&T + ^{223}Radium

Bispecific T-cell engagers & CAR-T

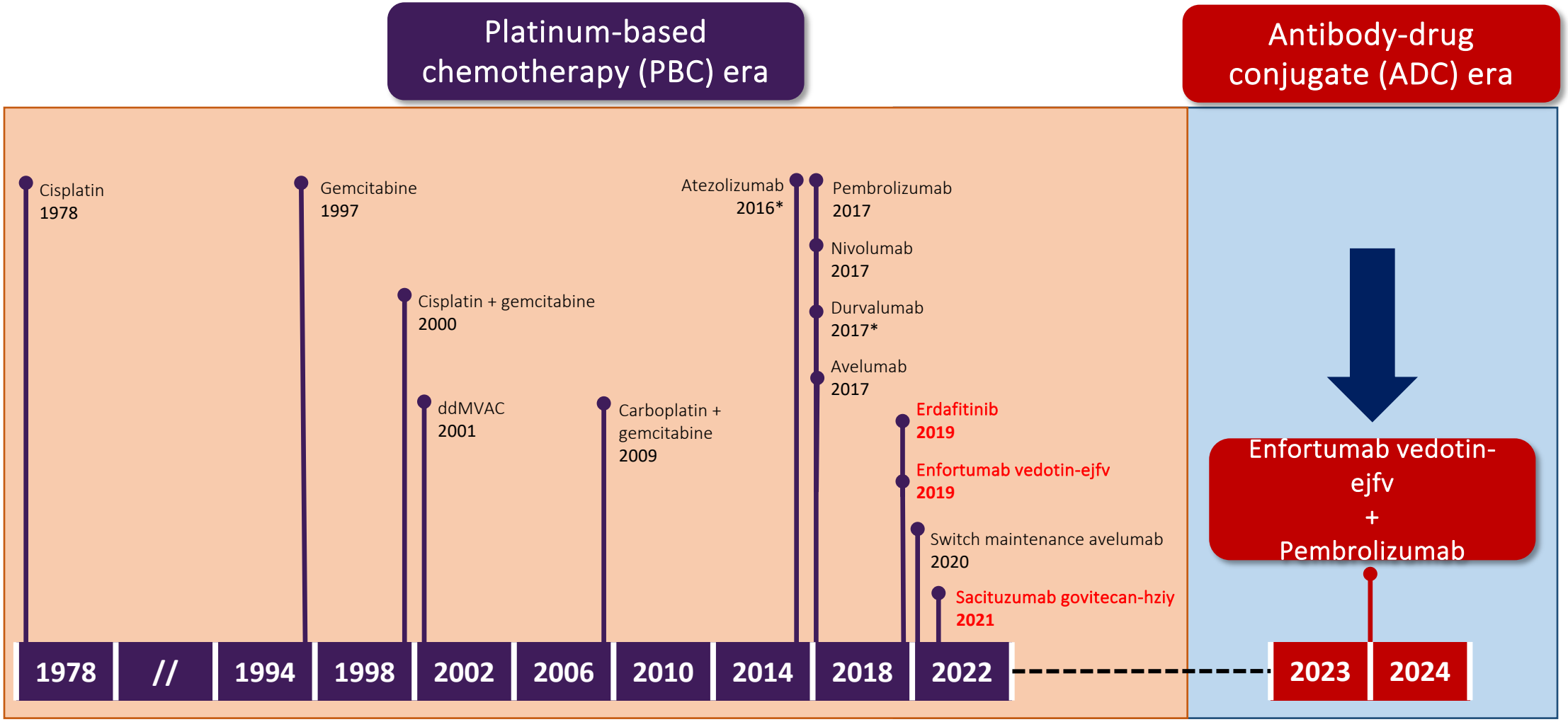
Bispecific T-cell engagers
- Acapatamab (PSMA x CD3)
- REGN5678 (PSMA x CD28)
- AMG 509 (STEAP-1 x CD3)

CAR-T cell therapy
- CART-PSMA-TGFβRDN
- P-PSMA-101 CAR-T cells
- 4SCAR-PSMA T cells
- Non-viral PD1 integrated anti-PSMA CAR-T cells

OUTLINE

- Targeted Therapies in Prostate Cancer (PCa)
- Targeted Therapies in Urothelial Cancer (UC)
- Targeted Therapies in Renal Cell Carcinoma (RCC)
- Summary

THE ERA OF NOVEL THERAPEUTICS IN ADVANCED UC (aUC)



*FDA approval voluntarily withdrawn due to confirmatory Phase III trials not meeting primary endpoints

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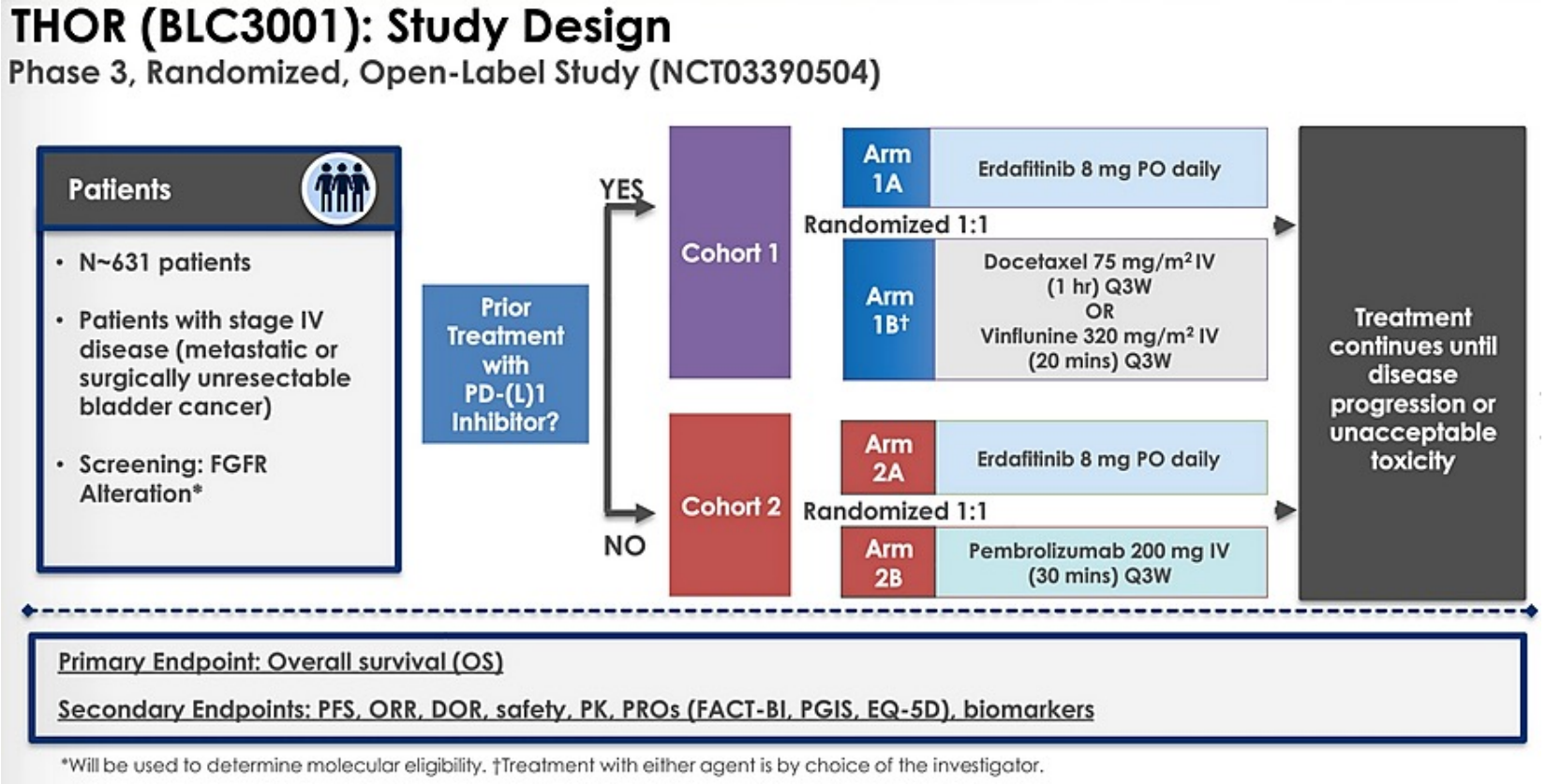
Slide adapted with permission from Parminder Singh, MD.

ERDAFITINIB



*Translocations: *FGFR2-BICC1*, *FGFR2-CASP7*, *FGFR3-TACC3_V1*, *FGFR3-TACC3_V3*, *FGFR3-BAIAP2L1*; *FGFR* mutations: R248C, S249C, G370C, Y373C.

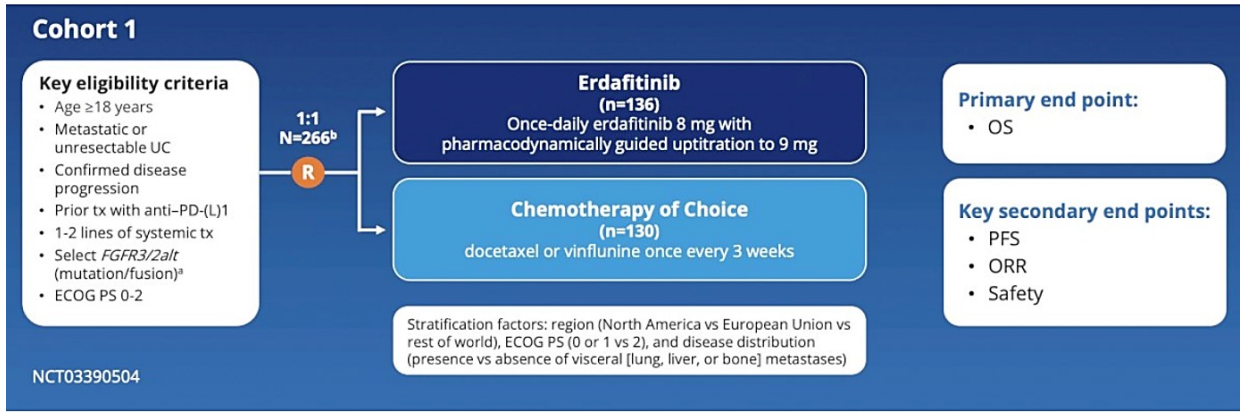
- *FGFR* alterations (alt) present in 15-20% of aUC[1,2]
  - *FGFR3* alt more prevalent in UTUC (37%) vs. 22% across all UC[3]
  - More common in low-grade vs. high-grade UC[4]
- Erdafitinib is a potent *FGFR1-4* tyrosine kinase inhibitor[5]
- **4/2019:** Erdafitinib gained accelerated FDA approval in the post-PBC setting based on the Ph II BLC2001 trial[5]

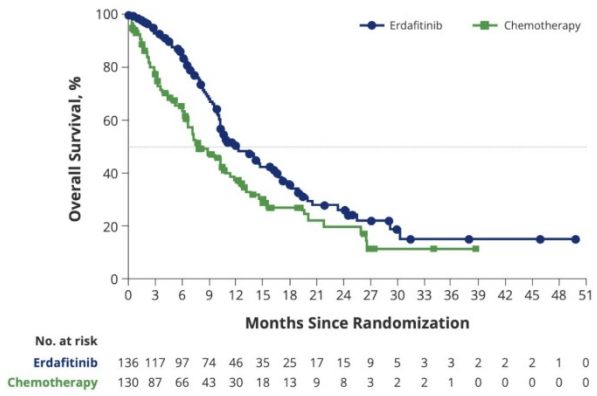
1. The Cancer Genome Atlas Research Network. Nature. 2014. 2. Helsten T. Clin Cancer Res. 2016.
3. Li Q. Curr Urol Rep. 2016. 4. Pandith AA. Urol Oncol. 2013. 5. Loriot Y. N Engl J Med. 2019.

ERDAFITINIB

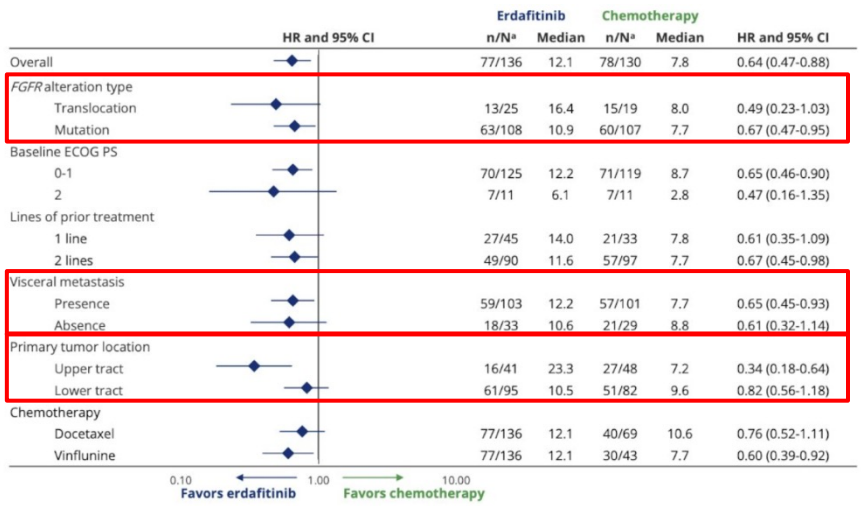
THOR (Cohort 1)[1,2]

Median follow up: 15.9 months





	Erdafitinib	Chemo
mOS, mos	12.1	7.8
HR (95% CI); p-value	0.64 (0.47-0.88); p=0.005	



4/2019: Erdafitinib gained accelerated FDA approval for pts with *FGFR2/3* alt post-PBC based on Ph II BLC2001

1/2024: Full FDA approval **only for pts with *FGFR3* alt** after ≥ 1 prior therapy line based on Cohort 1 of Ph III THOR

All patients (N=266)	Erdafitinib (n=136)	Chemotherapy (n=130)
Prior therapy lines, n (%)		
1	45 (33.1)	33 (25.4)
2	90 (66.2)	97 (74.6)
FGFR2/3* alterations, n (%)	(n=135)	(n=129)
Mutations	108 (79.4)	107 (82.3)
Fusions	25 (18.4)	19 (14.6)
Mutations and fusions	2 (1.5)	3 (2.3)
Objective response rate	46%	12%
CR	7%	1%
PR	39%	11%
Median PFS, mos	5.6 mos	2.7 mos
Median OS, mos	12.1 mos	7.8 mos

*Translocations: *FGFR2-BICC1*, *FGFR2-CASP7*, *FGFR3-TACC3_V1*, *FGFR3-TACC3_V3*, *FGFR3-BAIAP2L1*; *FGFR* mutations: R248C, S249C, G370C, Y373C.

1. Loriot Y. ASCO 2023. Abstract LBA4619. 2. Loriot Y. N Engl J Med. 2023.

ERDAFITINIB

THOR (Cohort 2)[1,2]

Key eligibility criteria
- Age ≥18 years
- Metastatic or unresectable UC
- Confirmed disease progression on 1 prior tx
- Naive to anti–PD-(L)1 tx
- Select *FGFR3/2alt* (mutation/fusion)[a]
- ECOG PS 0-2

1:1
N=351[b]
R

Erdafitinib
(n=175)
Once-daily erdafitinib 8 mg with pharmacodynamically guided uptitration to 9 mg

Pembrolizumab
(n=176)
200 mg once every 3 weeks

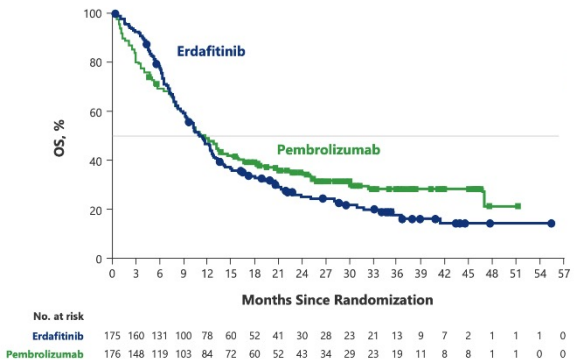
Stratification factors: region (North America vs European Union vs rest of world), ECOG PS (0 or 1 vs 2), and disease distribution (presence vs absence of visceral [lung, liver, or bone] metastases)

Primary end point
- OS

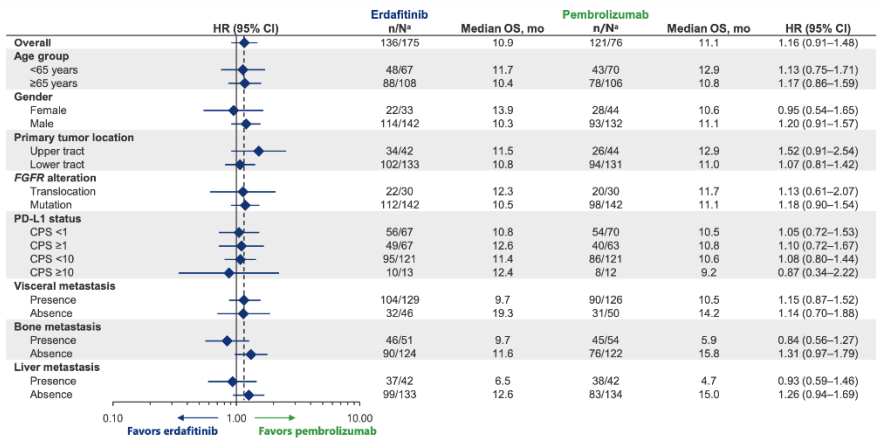
Secondary end points
- PFS
- ORR
- Safety

Primary endpoint not met

NCT03390504



	Erdafitinib	Pembrolizumab
mOS, mos	10.9	11.1
HR (95% CI); p-value	1.18 (0.9-1.5); p=0.18	



Hazard Ratio for OS was similar across subgroups

Median follow up: 33.0 months

All patients (N=351)	Erdafitinib (n=175)	Pembrolizumab (n=176)
FGFR2/3* alterations, n (%)	(n=175)	(n=176)
Mutations	142 (81.1)	142 (80.7)
Fusions	29 (16.6)	30 (17.0)
Mutations and fusions	4 (2.3)	4 (2.3)
Objective response rate	40%	22%
Median PFS, mos	4.4 mos	2.7 mos
Median OS, mos	10.9 mos	11.1 mos

*Translocations: *FGFR2-BICC1*, *FGFR2-CASP7*, *FGFR3-TACC3_V1*, *FGFR3-TACC3_V3*, *FGFR3-BAIAP2L1*; *FGFR* mutations: R248C, S249C, G370C, Y373C.

1. Siefker-Radtke AO. ESMO 2023. Abstract 2395O. 2. Siefker-Radtke AO. Ann Oncol. 2024.

Cleveland Clinic

ANTIBODY-DRUG CONJUGATES (ADCs) in aUC

ENFORTUMAB VEDOTIN (EV)

Target: Nectin-4, a type 1 transmembrane cell adhesion molecule overexpressed in epithelial cancers
Linker: Protease cleavable
Payload: MMAE

EV-301[1,2]

Phase III EV-301[2,3]
- 1-2 lines of prior Tx including PBC & CPI

R 1:1

N=608

- **Enfortumab vedotin**
- **Investigator's choice chemo (docetaxel, paclitaxel, or vinflunine)**

Primary endpoint: OS

Secondary endpoints: PFS, DCR, ORR, safety

All patients (N=608)	EV (n=301)	Chemo (n=307)
ORR	41%	18%
Median PFS, mos	5.6	3.7
Median OS, mos	12.9	8.9

Median Follow Up
23.8 mos

SACITUZUMAB GOVITECAN (SG)

Target: Trop-2, an epithelial cell-surface glycoprotein highly expressed in muscle-invasive disease
Linker: Hydrolysable
Payload: SN-38, the active metabolite of irinotecan

TROPHY-U-01 (Cohorts 1 & 2)[3-5]

- **Cohort 1 (N=113)**
  - aUC with PD after PBC & CPI
- **Cohort 2 (N=38)***
  - Platinum-ineligible aUC with PD after CPI

→ **Sacituzumab govitecan**

Primary endpoint: ORR

Secondary endpoints: DOR, PFS, OS, safety

*Not FDA approved for this indication

Median Follow Up
Cohort 1: 10.5 mos
Cohort 2: 9.3 mos

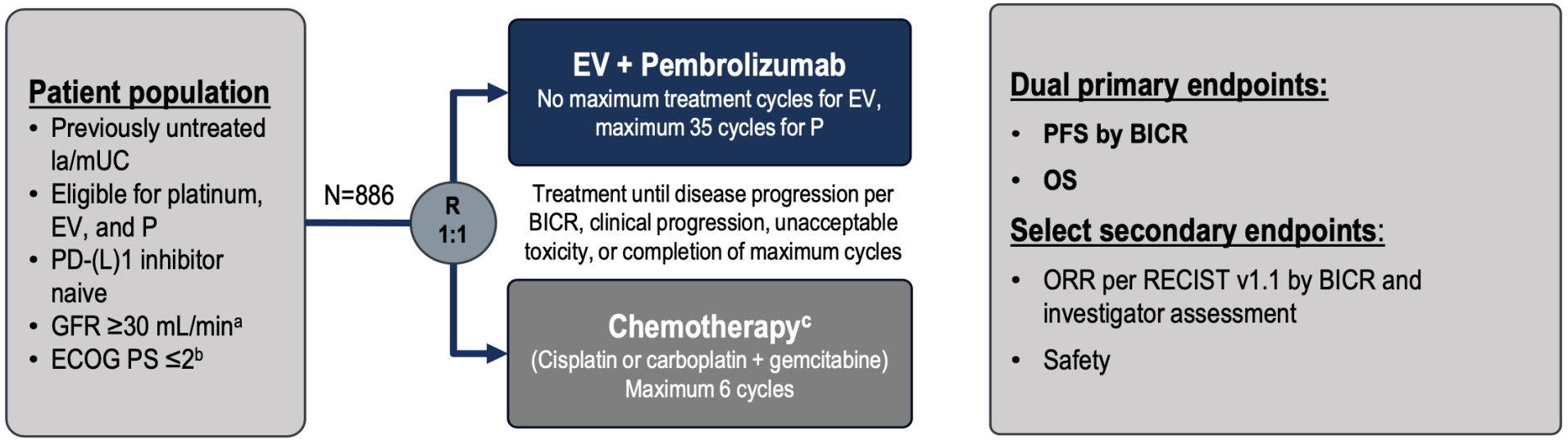
	SG Cohort 1 (N=113)	SG Cohort 2 (N=38)
ORR	28%	32%
Median PFS, mos	5.4	5.6
Median OS, mos	10.9	13.5

Cleveland Clinic

1. Powles T. N Engl J Med. 2021. 2. Rosenberg JE. Ann Oncol. 2023. 3. Tagawa S. JCO. 2021. 4. Tagawa S. ASCO GU 2023. Abstract 526. 5. Petrylak D. ASCO GU 2023. Abstract 520.

ENFORTUMAB VEDOTIN + PEMBROLIZUMAB

EV-302/KEYNOTE-A39 (NCT04223856)



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

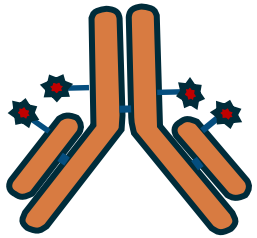
	EV + Pembrolizumab (n=442)	Chemotherapy (n=444)	Hazard Ratio (95% CI)	p-value
ORR	68%	44%	N/A	<0.00001
Median PFS, mos	12.5	6.3	0.45 (0.38-0.54)	<0.00001
Median OS, mos	31.5	16.1	0.47 (0.38-0.58)	<0.00001

Powles T. ESMO 2023. Abstract LBA6.

HER2-TARGETED ADCs IN aUC

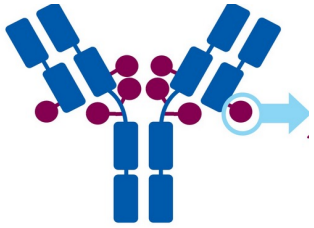
Major HER2-targeted ADCs in aUC

Disitimab vedotin (RC48 or DV)[1]



Fully Humanized ADC
Target: HER2
Linker: Protease cleavable
Payload: MMAE (microtubule-disrupting agent)

Trastuzumab deruxtecan (T-DXd)[2]



Fully Humanized ADC
Target: HER2
Linker: Tetrapeptide-based cleavable
Payload: Deruxtecan (topoisomerase I inhibitor)

HER2 Expression in aUC[3]

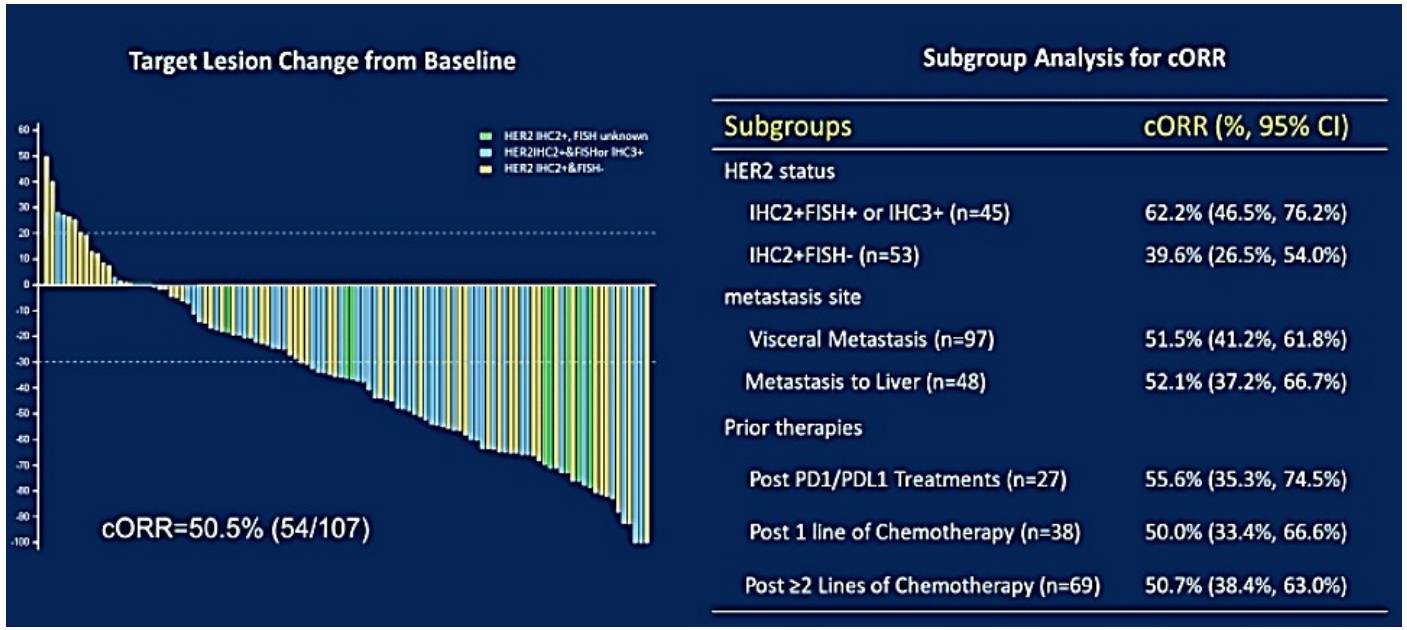
- ~13-25% HER2-positive (IHC 3+ or IHC 2+/FISH+)
- Up to ~20% HER2-low (IHC 2+/FISH- or IHC 1+)
- Ongoing studies to define prevalence of HER2 expressing tumors

1. Shi F. Drug Deliv. 2022. 2. Tarantino P. Nat Rev Clin Oncol. 2023. 3. Scherrer E. Front Oncol. 2022.

DISITIMAB VEDOTIN (DV) IN aUC WITH HER2 EXPRESSION

Activity in HER2-positive patients (IHC 2+ or 3+)

RC48-C005 & RC48-C009 Trials in China (N=107)[1,2]



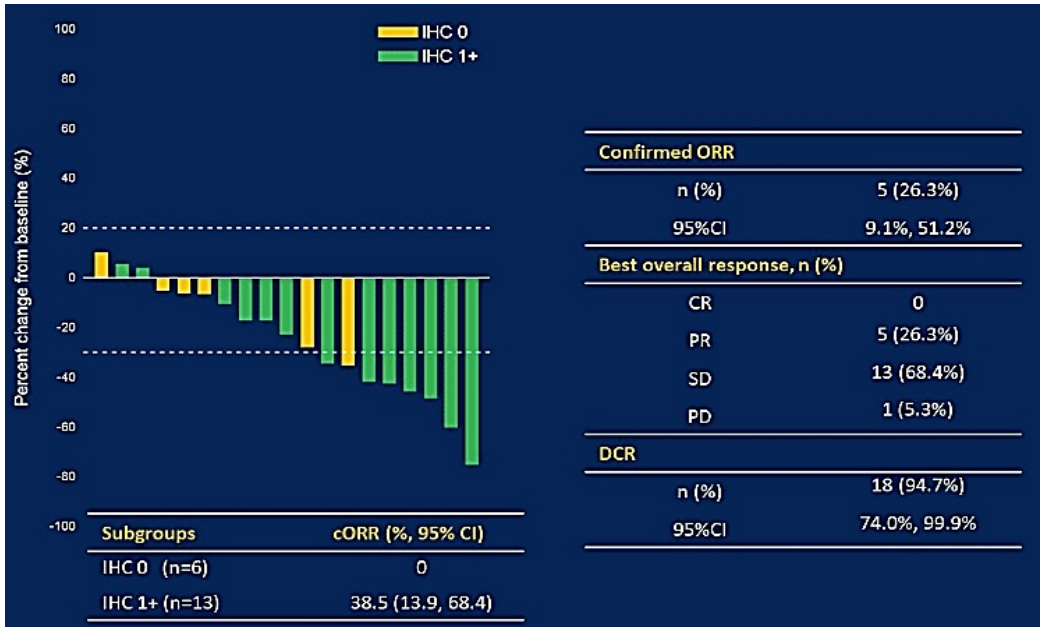
Subgroup Analysis for cORR

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

mPFS: 5.9 months
mOS: 14.2 months

Activity in HER2-low patients (IHC 0 or 1+)

RC48-C011 Trial in China (N=19)[3]



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

Confirmed ORR	
n (%)	5 (26.3%)
95%CI	9.1%, 51.2%
Best overall response, n (%)	
CR	0
PR	5 (26.3%)
SD	13 (68.4%)
PD	1 (5.3%)
DCR	
n (%)	18 (94.7%)
95%CI	74.0%, 99.9%

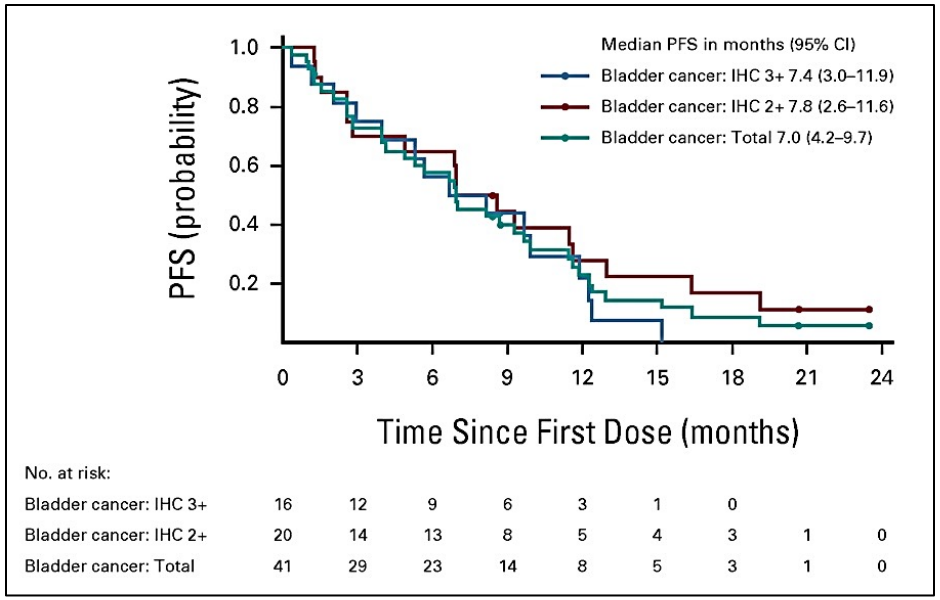
mPFS: 5.5 months
mOS: 16.4 months

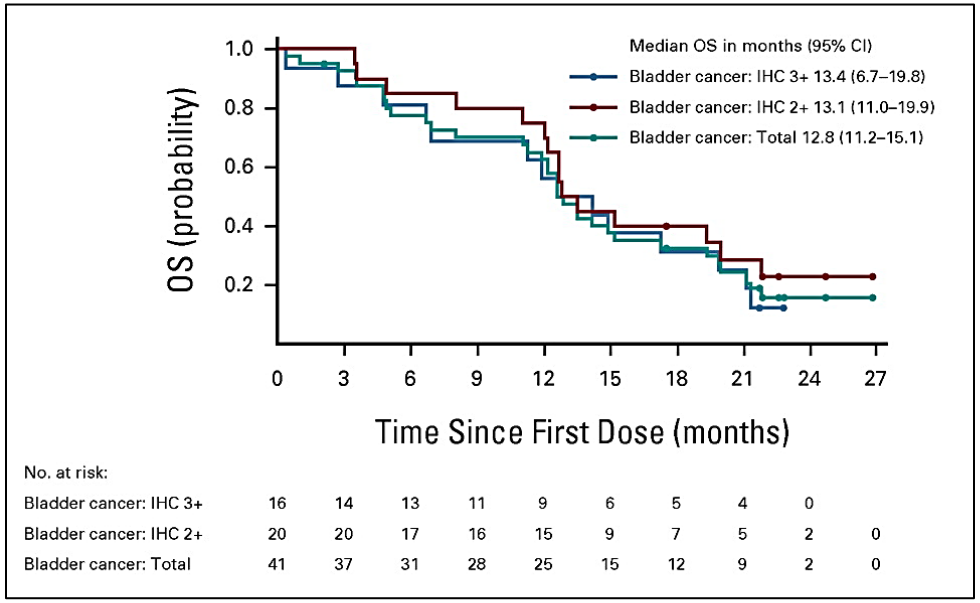
- Promising results from DV trials in China led to a Breakthrough Therapy designation by the FDA in 9/2020
- Phase II & III global registrational studies (DV monotherapy post-PBC & in combination with pembrolizumab) are accruing

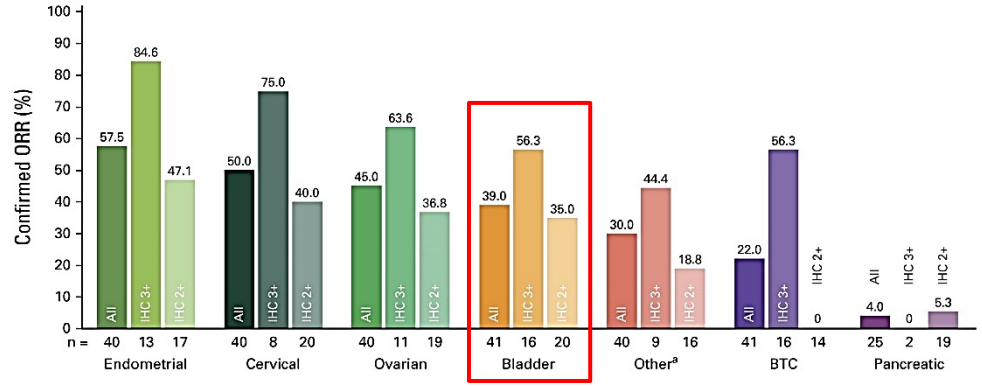
1. Sheng X. ASCO 2022. Abstract 4520. 2. Sheng X. J Clin Oncol. 2023. 3. Xu H. ASCO 2022. Abstract 4519.
Slide adapted with permission from Vadim Koshkin, MD.

TRASTUZUMAB DERUXTECAN (T-DXd) IN HER2-EXPRESSING aUC

DESTINY-PanTumor02: Phase II Trial of T-DXd Monotherapy in HER2-Expressing Solid Tumors







Bladder Cohort Population: progression after ≥ 1 prior therapy line(s)

Bladder Cohort	All (n=41)	IHC 3+ (n=16)	IHC 2+ (n=20)
Investigator-assessed ORR	39%	56%	35%
Median PFS, mos	7.0	7.4	7.8
Median OS, mos	12.8	13.4	13.1

Cleveland Clinic

Meric-Bernstam F. J Clin Oncol. 2024.

OTHER ADC + CHECKPOINT INHIBITOR (CPI) COMBINATIONS

Trial	Regimen	N	ADC Target	Payload	Population	ORR	mPFS, mos.	mOS, mos.
Phase II TROPHY-U-01 (Cohort 3)[1] NCT03547973	Sacituzumab govitecan + pembrolizumab	41	Trop-2	SN38 (topo-isomerase I)	• Platinum-refractory • CPI-naïve	**34%**	**5.3**	**12.7**
Phase Ib/II RC48-C014[2] NCT04264936	Disitamab vedotin + toripalimab	41	HER2	MMAE (tubulin)	• 25 (61%) treatment-naïve • 16 (39%) with 1+ lines of therapy	**73%**	**9.2**	**NR** **2-yr OS: 63%**
Phase Ib DS8201-A-U105[3] NCT03523572	Trastuzumab deruxtecan + nivolumab	30	HER2	DxD (topo-isomerase I)	• HER2-expressing • Platinum-refractory • CPI-naïve	**37%**	**6.9**	**11.0**

1. Grivas P. J Clin Oncol. 2024. 2. Sheng X. ASCO 2023. Abstract 4566. 3. Galsky MD. ASCO GU 2022. Abstract 438.
Slide adapted with permission from Vadim Koshkin, MD.

SELECT TARGETED THERAPIES IN DEVELOPMENT IN UC

Non-muscle invasive bladder cancer (NMIBC)

- Intravesical gemcitabine (TAR-200) +/- cetrelimab
- Intravesical erdafitinib (TAR-210)
- Pembrolizumab + vibo-stolimab or favezelimab
- Tislelizumab + disitimab vedotin
- RT + tislelizumab
- Oportuzumab monatox

Muscle-invasive UC (perioperative setting)

- EV + pembrolizumab
- EV + durvalumab + tremelimumab
- Nivolumab + relatlimab
- ChemoRT + CPIs
- ChemoRT + ADCs
- ChemoRT + ADCs + CPIs

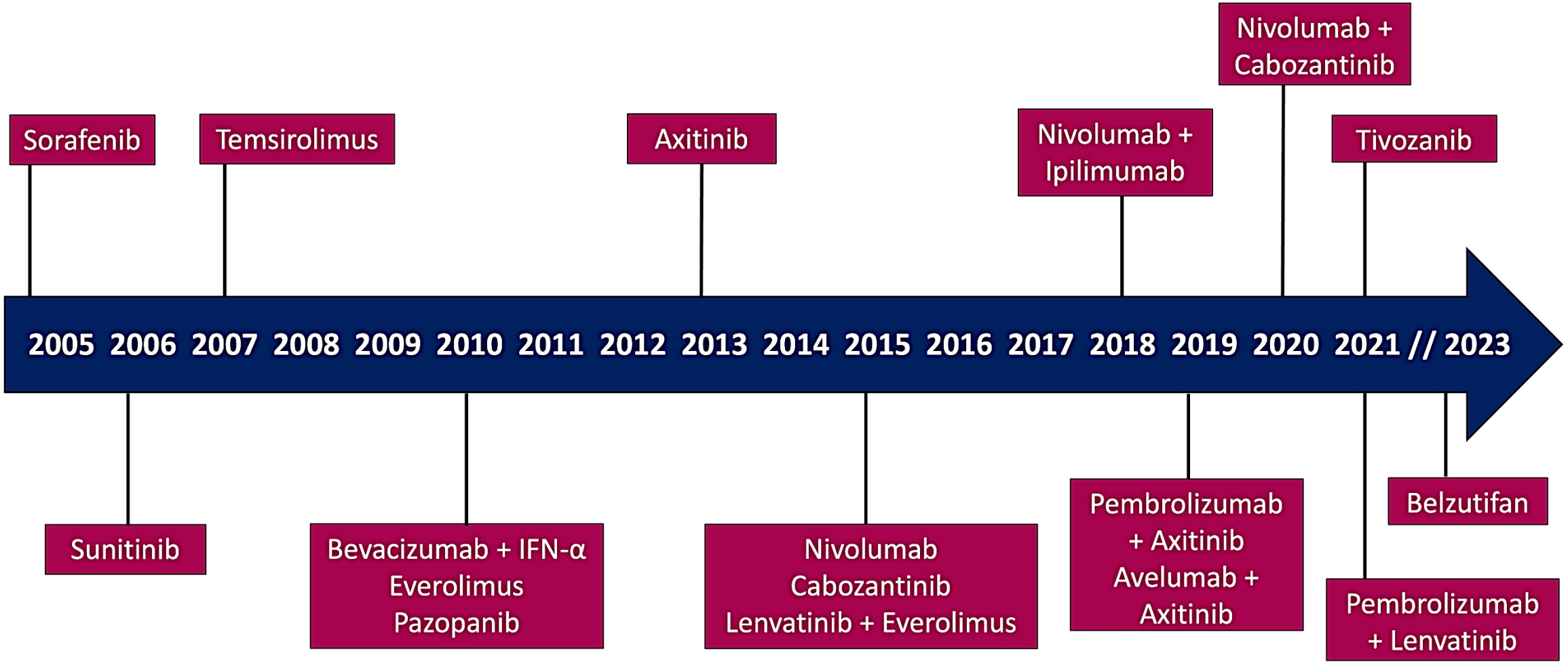
Locally advanced/metastatic UC

- ADCs + novel dual-CPI compounds
- EV + SG + CPI
- Erdafitinib + EV
- sEphB4-HSA (EphrinB2 inh.) + pembrolizumab
- Avelumab + various targeted Tx (maint. setting)
- BT8009 (Nectin-4 targeted bicycle toxin conjugate)

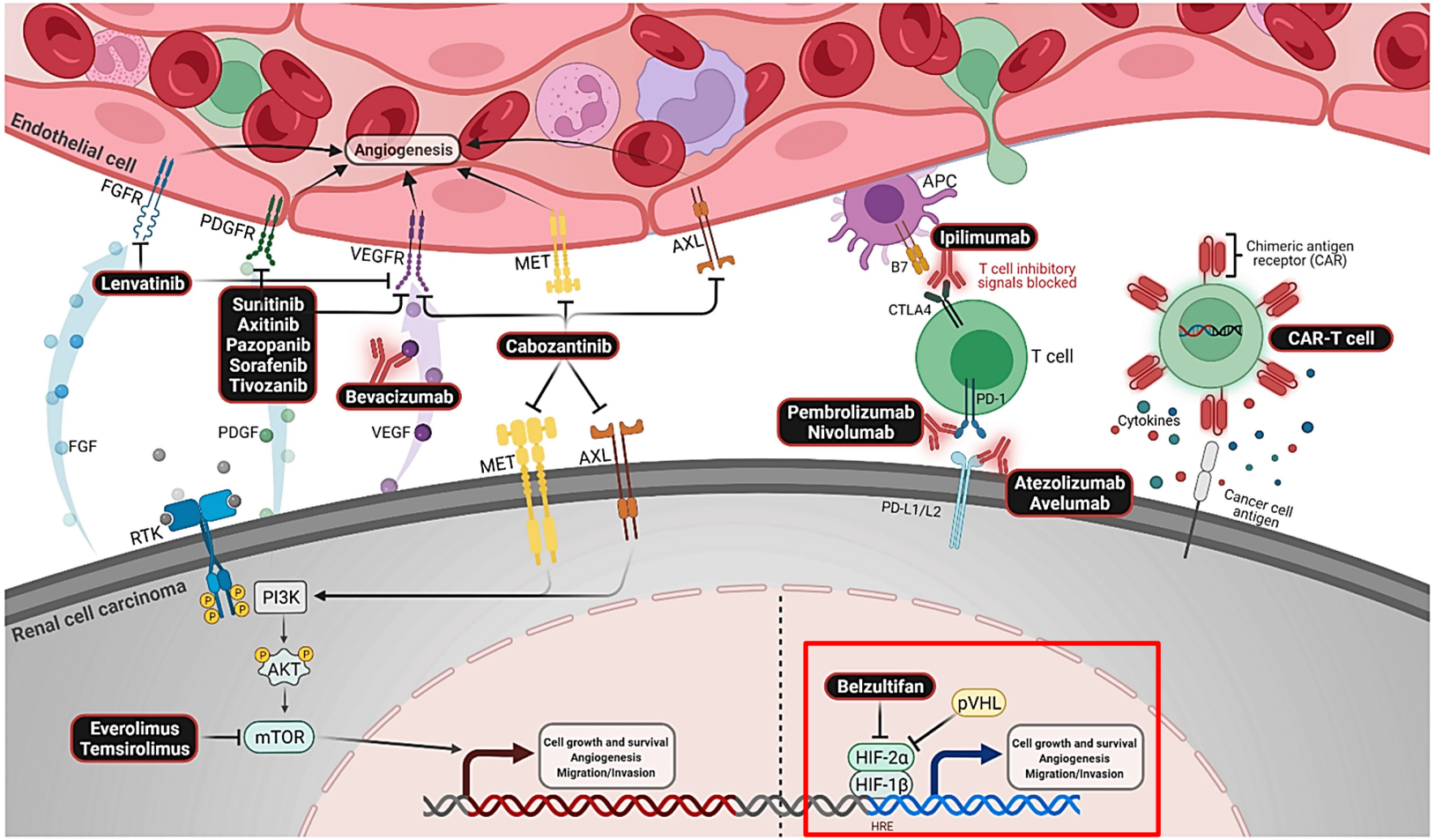
OUTLINE

- Targeted Therapies in Prostate Cancer (PCa)
- Targeted Therapies in Urothelial Cancer (UC)
- Targeted Therapies in Renal Cell Carcinoma (RCC)
- Summary

SYSTEMIC THERAPY APPROVALS IN mRCC



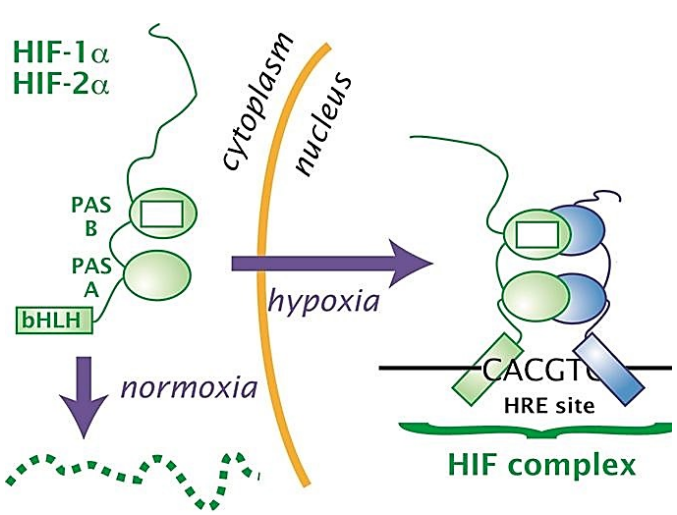
TARGETED THERAPIES IN mRCC

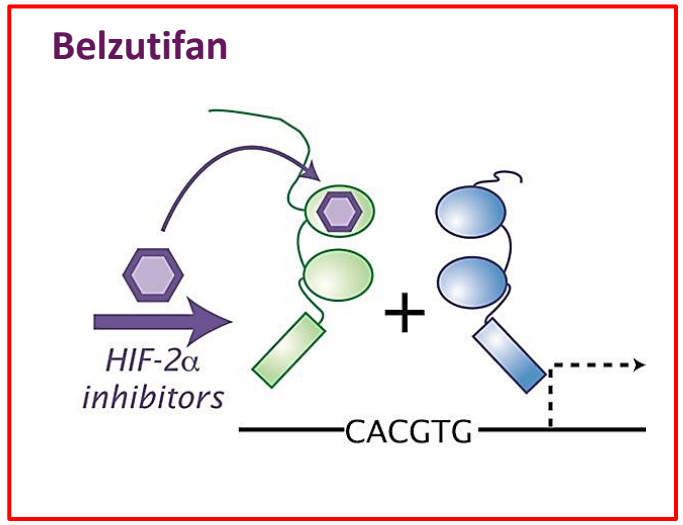


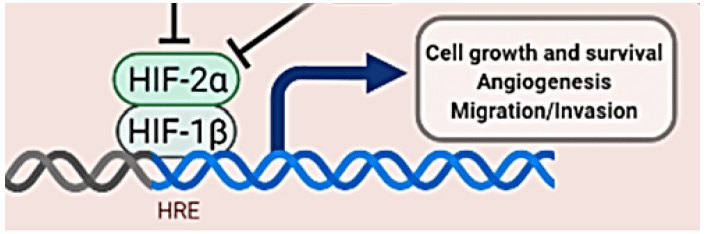
- Tyrosine kinase inhibitors (TKI) have been the backbone of therapy for mRCC for ~20 years
- Current SOC for 1L mRCC:
  - TKI + CPI regimens
  - Ipilimumab + nivolumab
- **Belzutifan**: **HIF-2α inhibitor**
- First studied in patients with von Hippel-Lindau (VHL) disease-associated tumors

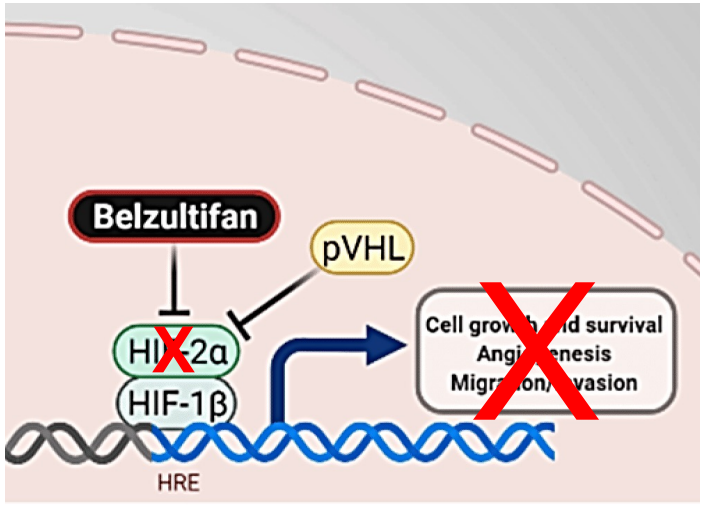
Govindarajan A. Cancers. 2022.

BELZUTIFAN







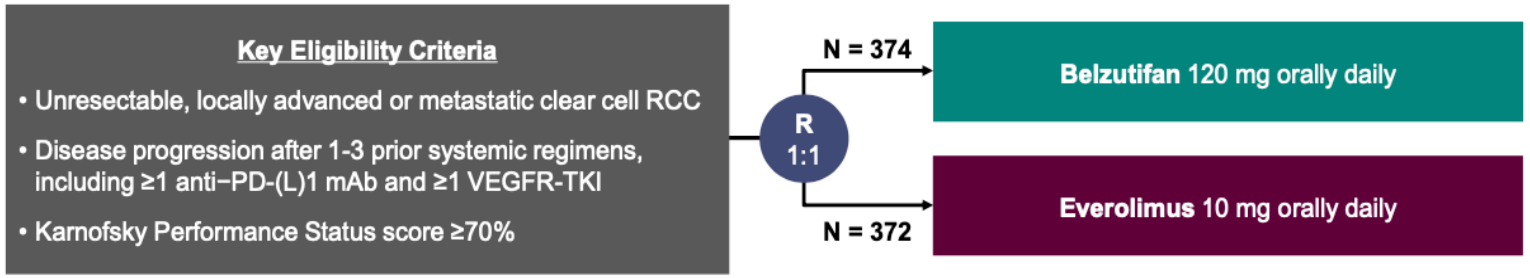


- HIF pathway is critical in the pathophysiology of clear cell RCC (ccRCC) & VHL disease[1]
- Belzutifan inhibits HIF's tumor-promoting activity
- **8/2021:** Belzutifan approved in patients with VHL-associated tumors (incl. RCC)
- Up to 90% of sporadic, non-familial ccRCC harbor somatic *VHL* mutations[1]
- → Belzutifan investigated in sporadic ccRCC

1. Gossage L. Nat Rev Cancer. 2015.
Top figure: Bruick R, Gardner K, UTSW Medical Center.
Bottom figure: modified from Govindarajan A. Cancers. 2022.

BELZUTIFAN

LITESPARK-005: Phase III Randomized Open-Label Trial of Belzutifan Versus Everolimus in Patients With Previously Treated Advanced Clear Cell RCC



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

Dual Primary Endpoints:
- PFS per RECIST 1.1 by BICR
- OS

Key Secondary Endpoint:
- ORR per RECIST 1.1 by BICR

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

	Belzutifan (n=374)	Everolimus (n=372)	Hazard Ratio (95% CI)	p-value
ORR	**22%**	4%	N/A	<0.00001
Median PFS, mos	**5.6**	5.6	0.75 (0.63-0.90)	<0.001
Median OS, mos	21.4 (immature)	18.1 (immature)	0.88 (0.73-1.07)	0.099

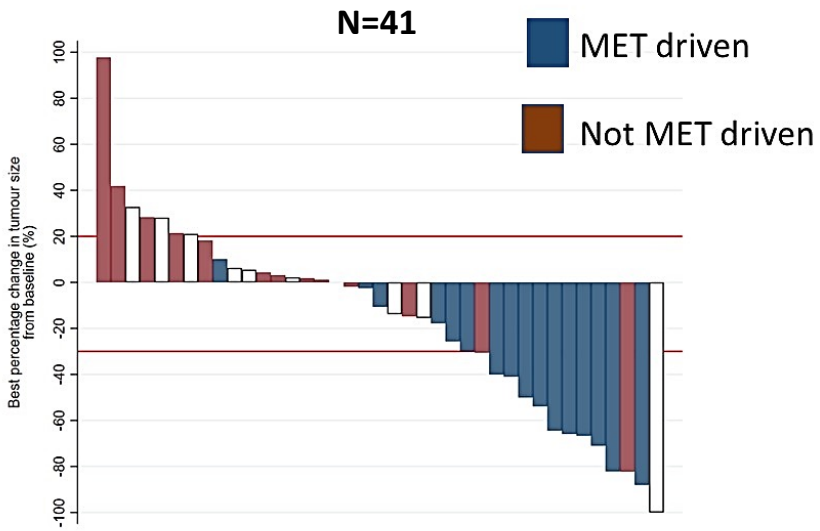
12/2023: Belzutifan FDA approved for patients with sporadic advanced RCC post-TKI & CPI

Albiges L. ESMO 2023. Abstract LBA88.

TARGETED THERAPIES IN NON-CLEAR CELL RCC

Savolitinib + durvalumab in MET driven advanced papillary RCC

Phase II CALYPSO Trial[1]



- **53% response rate in MET driven pts**
  (29% in overall population)
- **mPFS: 12.0 mos in MET driven pts**
  (4.9 mos in overall population)
- **mOS: 27.4 mos in MET driven pts**
  (14.1 mos in overall population)

Phase III SAMETA Trial[2]

Timeframe: 28 months post first subject randomized
Responsible Party: AstraZeneca (multi-center study)

SAMETA Trial
N = 220

Key Inclusion Criteria
- *MET driven, unresectable and locally advanced/metastatic papillary RCC
- No prior systemic anti-cancer treatment in the metastatic setting

R 2:1:1

- **Savolitinib** (600 mg PO QD) + **Durvalumab** (1500 mg IV Q4W)
- **Sunitinib** (50mg PO 4 weeks on /2 weeks off)
- **Durvalumab** (1500mg IV Q4W)

Treat until progression per RECIST 1.1 as assessed by BICR

Primary Endpoint: PFS (Savolitinib plus Durvalumab relative to Sunitinib)
Secondary Endpoint: OS, ORR, DoR, DCR

*MET-driven, without co-occurring FH mutations; PD, progressive disease; IV, intravenously; PO, orally; Q4W, every 4 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; PFS, progression free survival; OS, overall survival; ORR, objective response rate; DoR, duration of response; DCR, disease control rate

1. Suárez C. J Clin Oncol. 2023. 2. Clinical Trials.gov NCT05043090.

TARGETED THERAPIES IN NON-CLEAR CELL RCC

Phase II KEYNOTE-B61 Trial

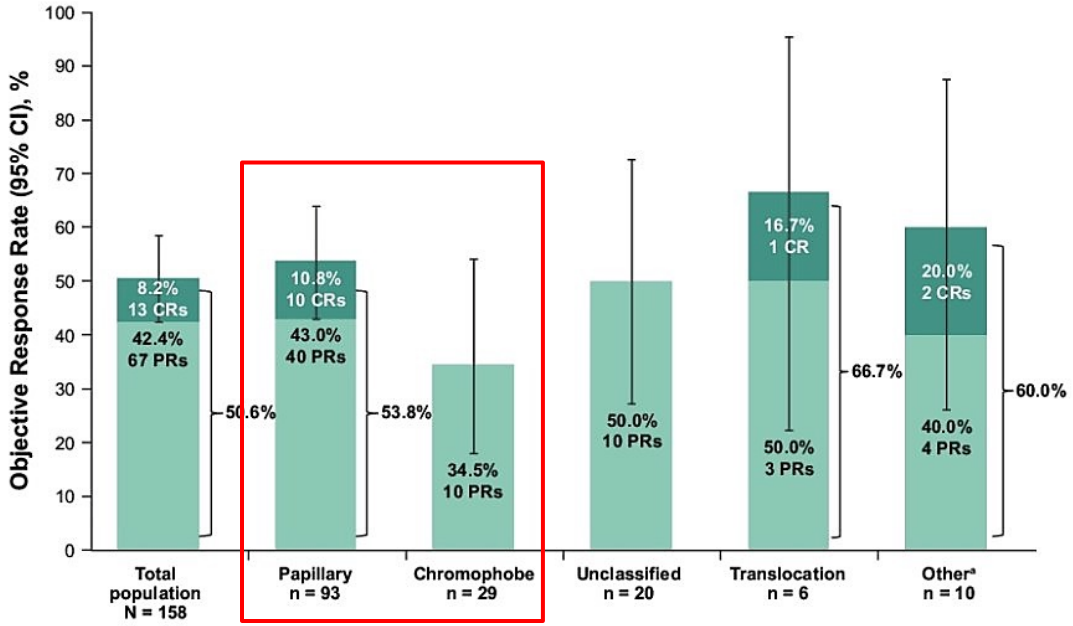
Key Eligibility Criteria
- Histologically confirmed diagnosis of non–clear cell RCC (per investigator)
- Locally advanced/metastatic disease
- No prior systemic therapy
- Measurable disease per RECIST v1.1
- Tumor tissue sample available
- KPS ≥70%

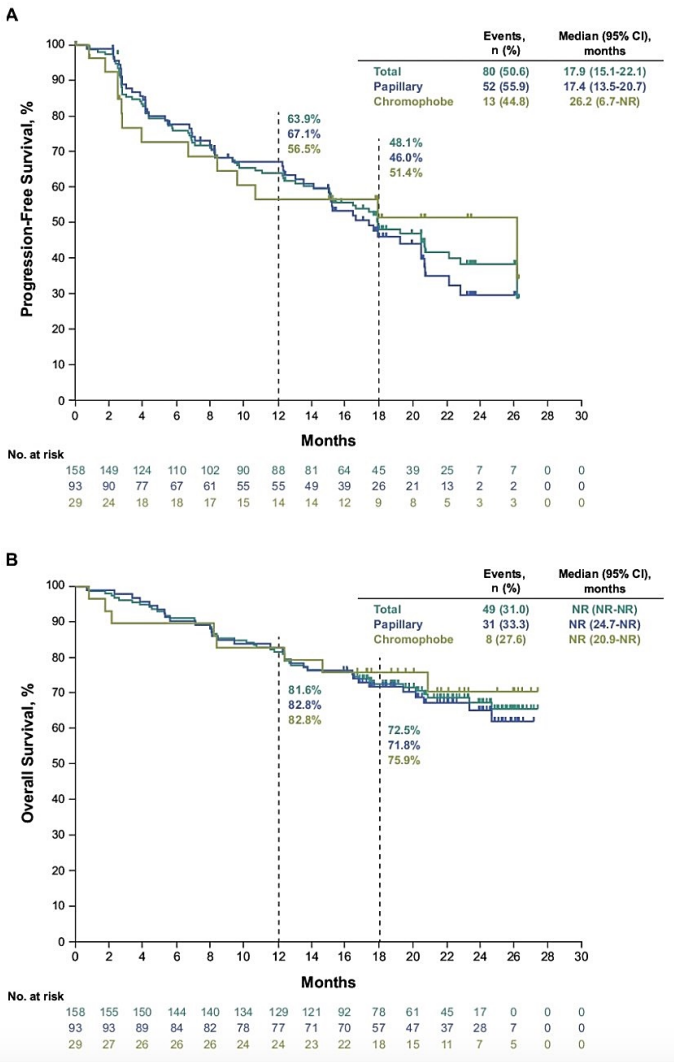
N = 158

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

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

Figure 3. Confirmed ORR by histology per RECIST v1.1 by BICR





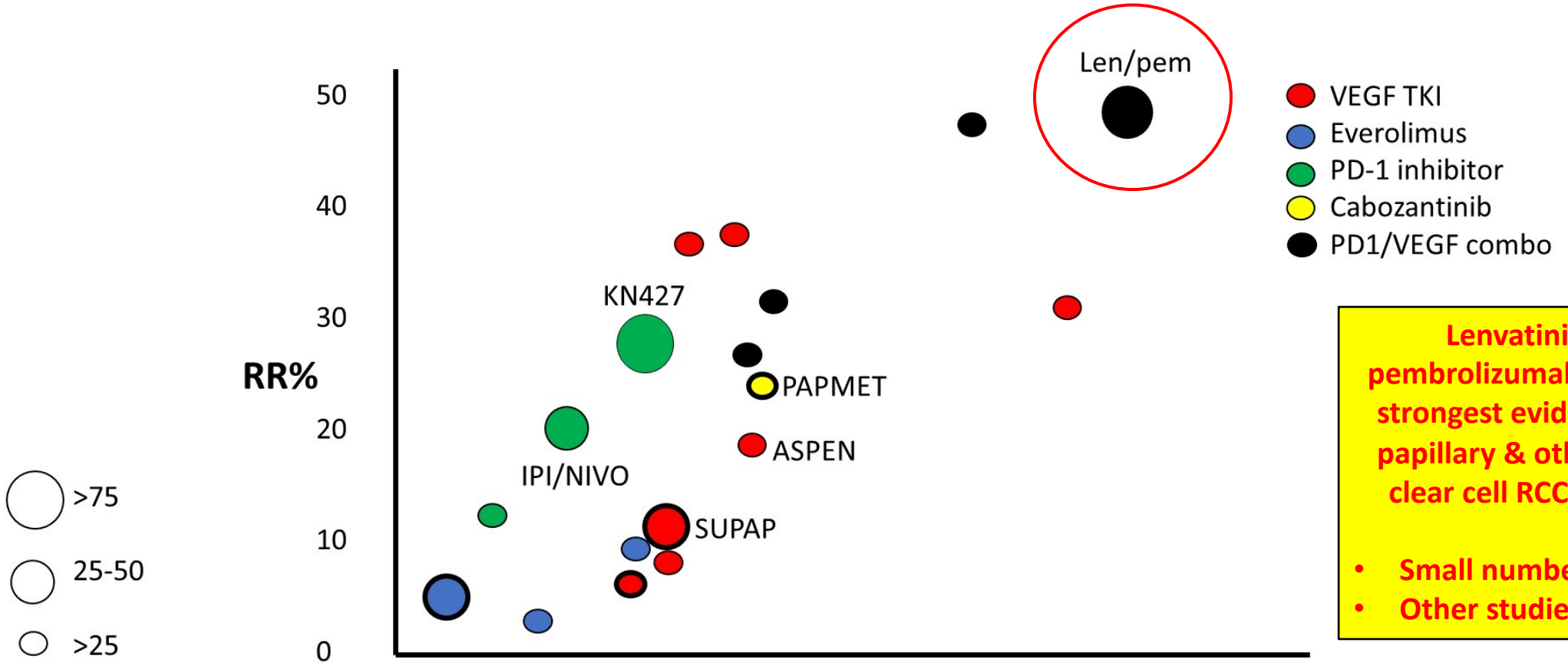
ORR (all): 51% (8% CRs)
- Papillary: 54% (11% CRs)
- Chromophobe: 35% (no CRs)

mPFS (all): 17.9 mos
- Papillary: 17.4 mos
- Chromophobe: 26.2 mos

mOS (all): NR
- Papillary: NR
- Chromophobe: NR

Voss MH. ASCO GU 2024. Abstract 2.

TARGETED THERAPIES IN NON-CLEAR CELL mRCC



Lenvatinib + pembrolizumab has the strongest evidence for papillary & other non-clear cell RCCs, but…

- **Small numbers**
- **Other studies ongoing**

Black ring around cycle = papillary only studies/cohorts
Cross trial comparison-handle with caution
Not all trials had all data points available and some were<25 pts
Some studies had inconsistence in reporting related to multipe data cuts or different analysis

Tannir 2016, Armstrong 2016, Bergmann 2020, Jung 2018
Park 2018, Vogelzang 2020, Mcgregor 2020, Pal 2021, Lee 2022
Albiges 2023, Pal 2021 Ravaud 2015, Escudier 2015 McDermott 2015

Powles T. ASCO GU 2024.

SELECT TARGETED THERAPIES IN DEVELOPMENT IN RCC

Targeted Therapy Combinations

- Belzutifan + cabozantinib
- Belzutifan + lenvatinib + pembrolizumab
- Savolitinib + durvalumab
- Ciforadenant + ipilimumab + nivolumab
- Batiraxcept + cabozantinib + nivolumab
- Zanzalintinib + nivolumab
- Pazopanib + abexinostat

Bispecific Antibodies & CAR-T

- MEDI5752 (bispecific anti-PD-1/CTLA-4 Ab) + lenvatinib
- ALLO-316: CD70-targeted CAR-T cell therapy

OUTLINE

- Targeted Therapies in Prostate Cancer (PCa)
- Targeted Therapies in Urothelial Cancer (UC)
- Targeted Therapies in Renal Cell Carcinoma (RCC)
- Summary

SUMMARY: TARGETED THERAPIES IN GU MALIGNANCIES

PROSTATE CANCER

- PARPi + NHA → SOC for 1L mCRPC with HRRm or ***BRCA1/2*m** and no prior NHA
- PARPi monotherapy → option for HRRm or ***BRCA1/2*m** mCRPC post-triplet therapy in mCSPC
- Ongoing trials of novel RLT- & PARPi-based combinations in mCSPC → future shift in mCRPC landscape
- Bispecific T-cell engagers & CAR-T cell therapy → early promising results in refractory mCRPC

UROTHELIAL CANCER

- Erdafitinib is the only targeted therapy approved in aUC (select *FGFR3* alterations; after ≥ 1 therapy line)
- ADCs: the new backbone of therapy → different ADC-CPI combinations yield very different results
- Next targeted approach: HER2-targeted ADCs → efforts underway to characterize HER2 expression in UC

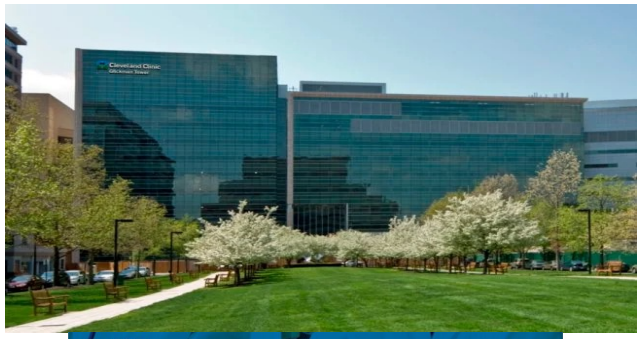
RENAL CELL CANCER

- Belzutifan, first-in-class drug, now approved in sporadic mRCC → several combinations under investigation
- Next targeted approach: MET inhibition + CPI? → results of Phase III SAMETA trial awaited

THANK YOU!

Our patients, families, patient advocates, & cancer advocacy organizations!

Cleveland Clinic
Taussig Cancer Institute



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