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COMPREHENSIVE
CANCER CENTER

State of the Art in Genitourinary Cancers

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(and Many Thanks to
Dr Shuchi Gulati)

Presentation Outline

- **PROSTATE CANCER**
  - **Current status of approved drugs**
  - **Recent updates and upcoming trials**
  - **Treatment decisions**
- **KIDNEY CANCER**
- **UROTHELIAL CARCINOMA**

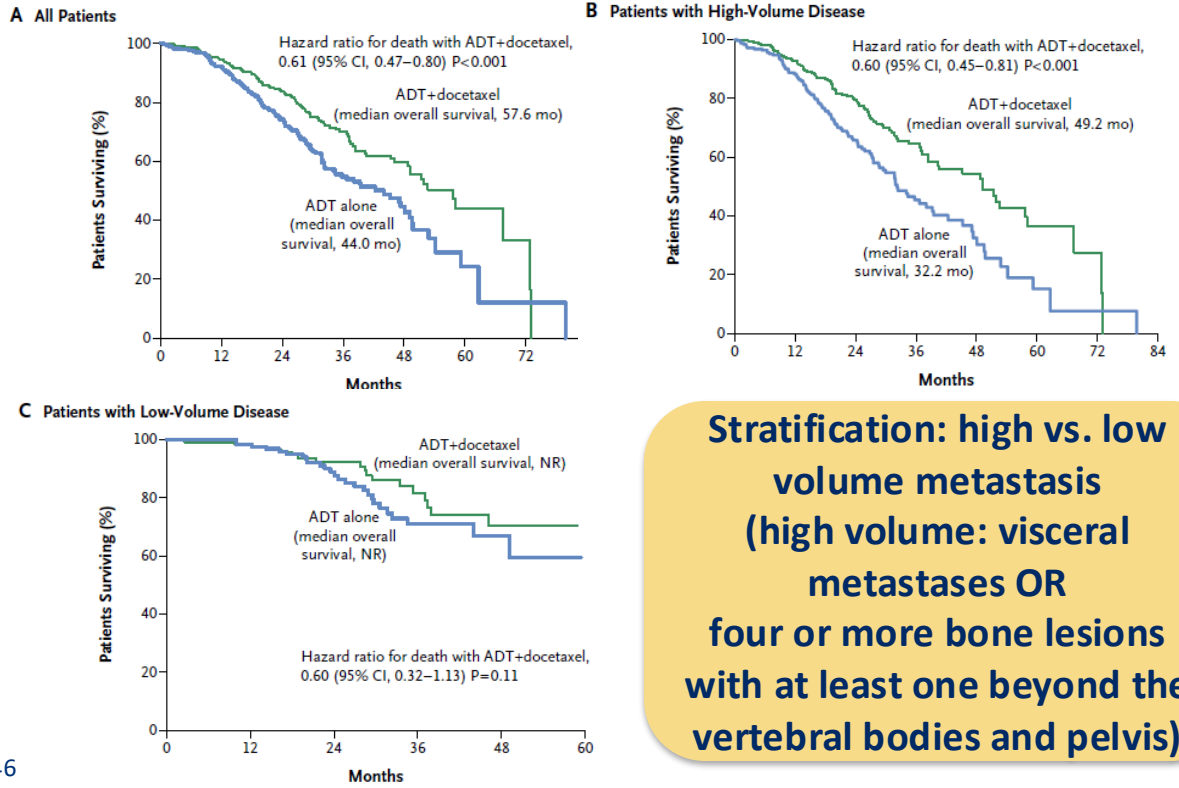
Enhancing frontline ADT for metastatic prostate cancer

a) Docetaxel

M1 Disease

OS Hazard Ratio (HR)	
CHAARTED[a]	**0.61 (0.47-0.80)**
STAMPEDE[b]	**0.76 (0.62-0.93)**
GETUG-15[c]	0.90 (0.69-1.81)
Failure-free survival HR	
CHAARTED[a]	**0.61 (0.51-0.73)**
STAMPEDE[b]	**0.61 (0.53-0.71)**
GETUG-15[c]	**0.70 (0.57-0.86)**

CHAARTED



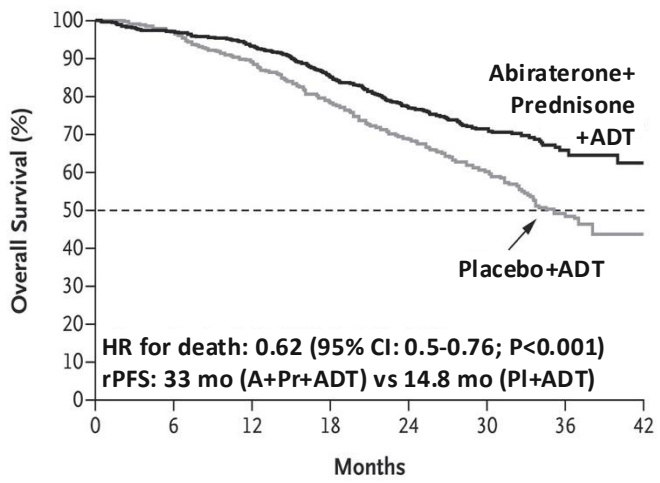
Stratification: high vs. low volume metastasis (high volume: visceral metastases OR four or more bone lesions with at least one beyond the vertebral bodies and pelvis)

(a) CJ Sweeney, et al. N Engl J Med, 373 (2015), pp. 737-746
(b) ND James, et al. Lancet 2016;387(10024):1163-77
(c) G Gravis, et al. Lancet Oncol, 14 (2013), pp. 149-158; G Gravis, et al. Proc Am Soc Clin Oncol, 33 (suppl 7) (2015) abstr 140.
(d) K Fizazi, et al. Proc Am Soc Clin Oncol, 32 (suppl) (2014) abstr 5005.

Enhancing frontline ADT for metastatic prostate cancer

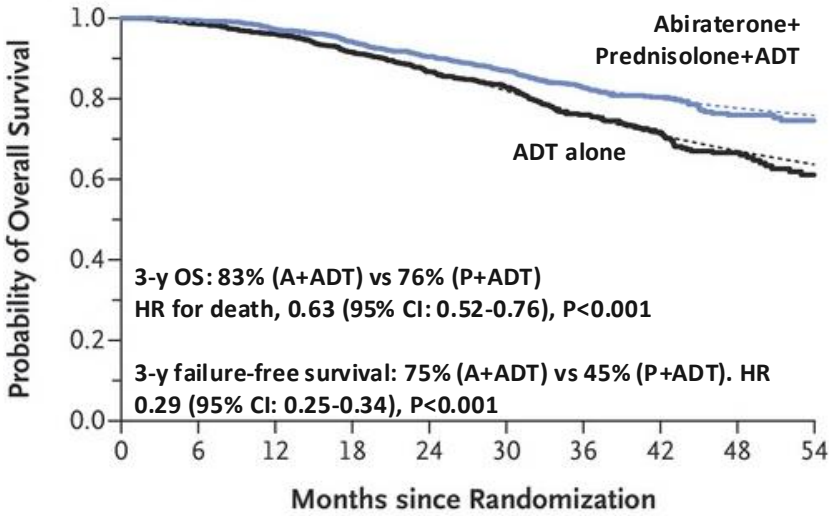
b) Abiraterone

LATITUDE



Patients had at least two of three risk factors: Gleason≥8, at least three bone lesions, or visceral metastasis.

STAMPEDE (arm G)



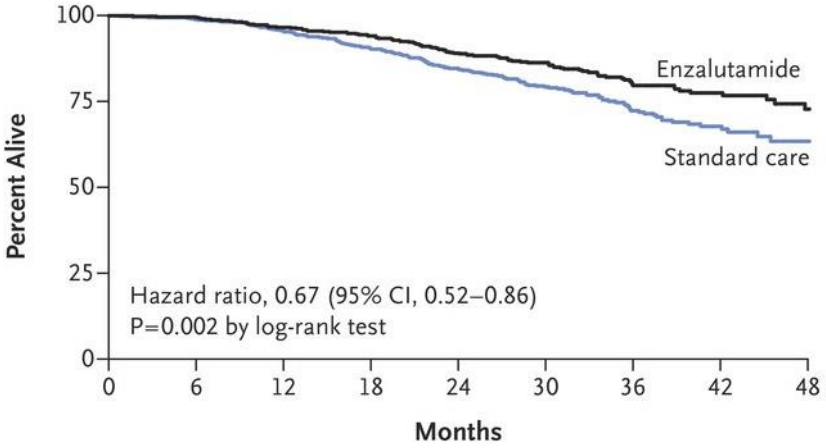
Patients had M1 disease (52%), N1 (or indeterminate) M0 disease (20%), and N0M0 disease (28%). XRT was mandatory for N0M0 and optional for N1M0 disease.

Fizazi K et al. NEJM 2017;377:352-360.
James ND et al. NEJM 2017;377:338-351.

Enhancing frontline ADT for metastatic prostate cancer

c) Enzalutamide

ENZAMET

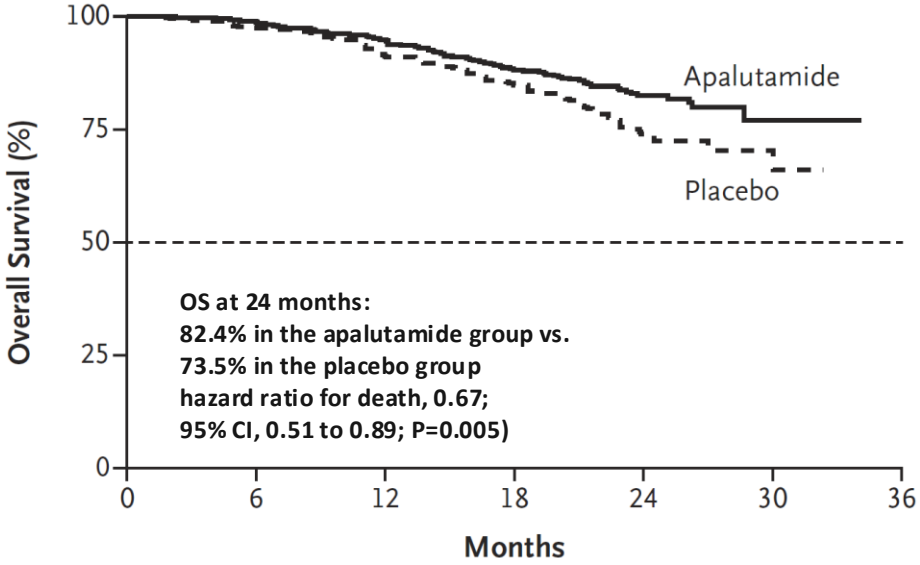


High-volume disease in 52% of the patients
The results were unaffected by adjustments for volume of disease and use of early docetaxel

ID Davis et al. N Engl J Med 2019;381:121-131

d) Apalutamide

TITAN



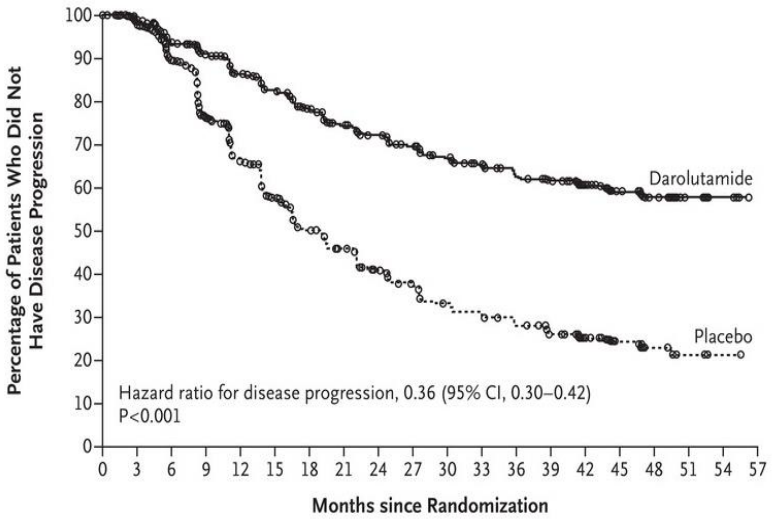
62.7% had high-volume disease, and 37.3% had low-volume disease
10.7% had received docetaxel

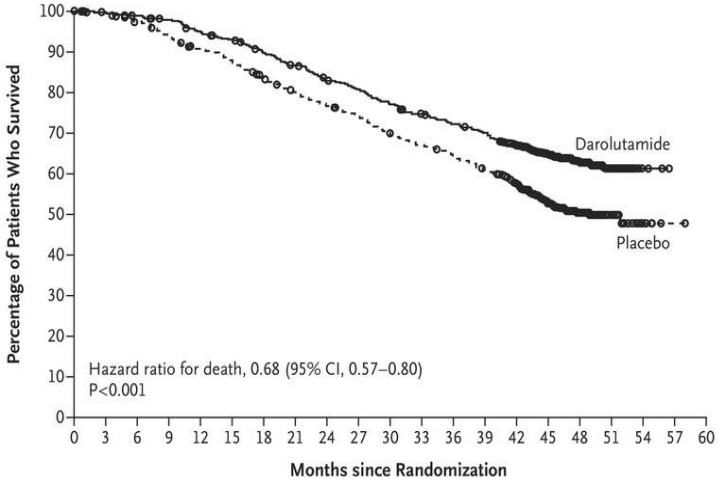
Chi KN et al. NEJM 2019;381(1):13-24

Enhancing frontline ADT for metastatic prostate cancer

e) Docetaxel + Darolutamide

ARASENS

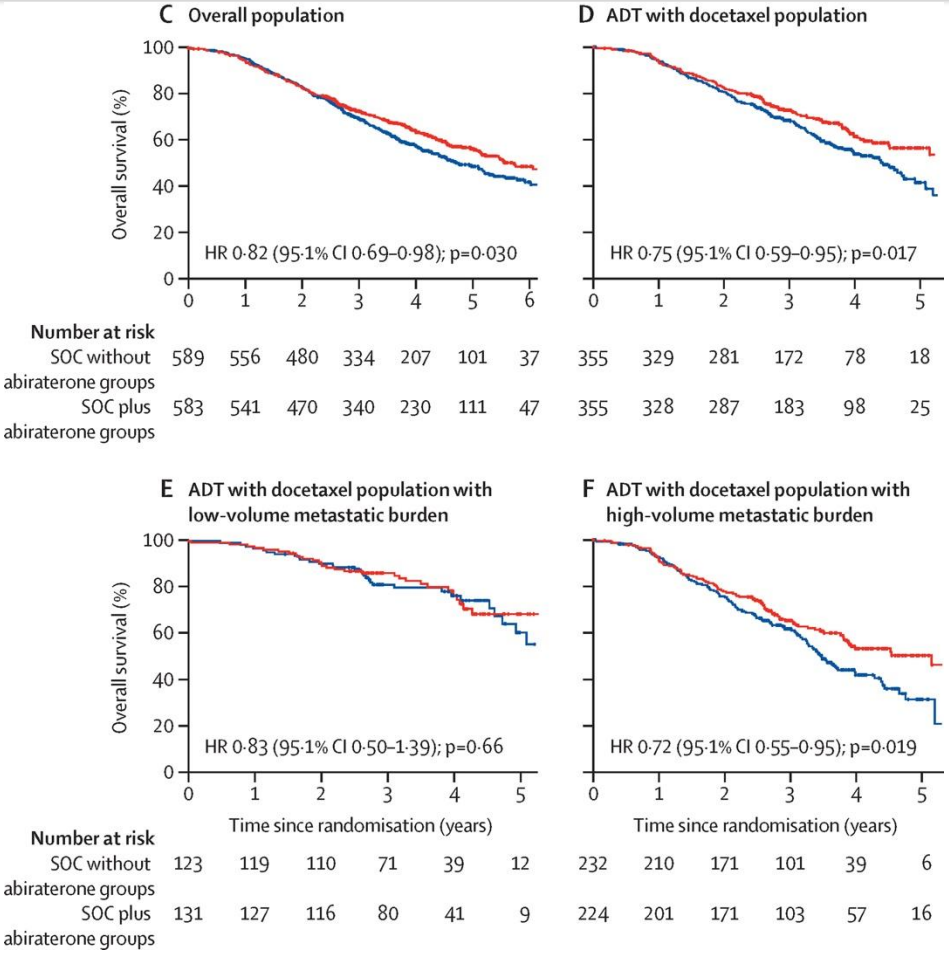




MR Smith et al. N Engl J Med 2022;386:1132-1142.

Enhancing frontline ADT: f) Docetaxel + Abiraterone

PEACE-1



Fizazi K, et al. Lancet. 2022:1695-1707

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Summary and Thoughts on augmenting frontline ADT

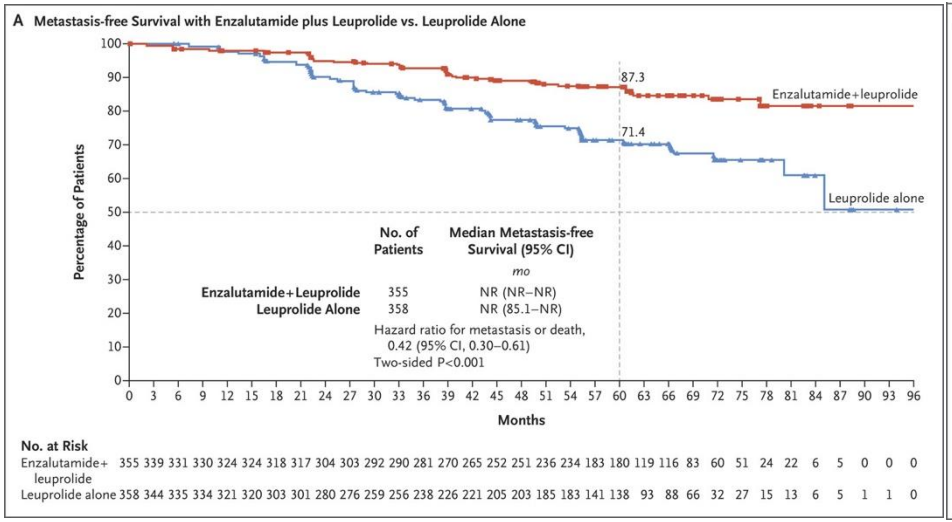
- Several options for M1 CSPC: ADT+Docetaxel (high volume disease), ADT+Abiraterone(+/-Docetaxel), ADT+Enzalutamide, ADT+Apalutamide and ADT+darolutamide+docetaxel

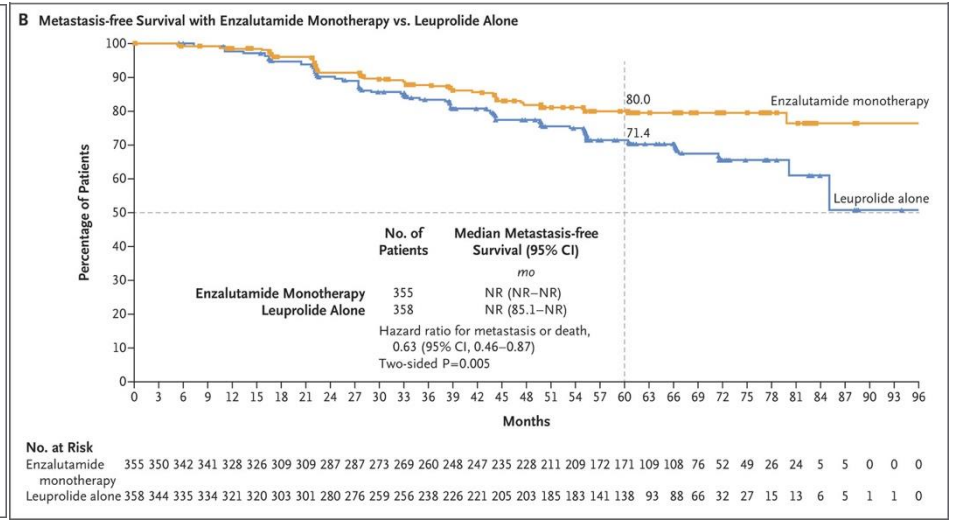
- Rapidly evolving field. Triplet or doublet therapy? Sequential?

- Adverse effects and other considerations:
  - Docetaxel: Peripheral neuropathy, myelosuppression, fatigue.
  - Abiraterone: HTN, hypokalemia, edema, liver toxicity, fatigue. Need for steroids
  - Enzalutamide/Apalutamide: Risk of seizure.
  - Darolutamide: Lower risk of seizures.

Biochemical Recurrence (High Risk)

EMBARK

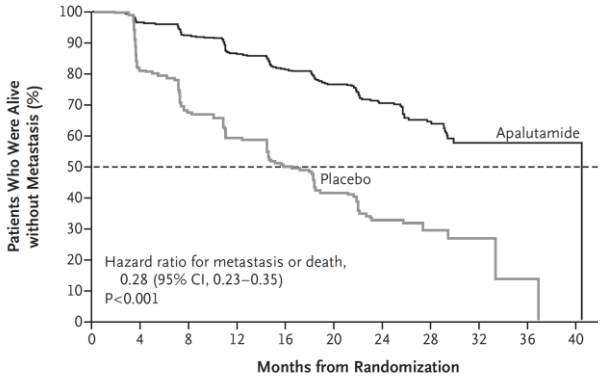




Freedland SJ et al. N Engl J Med2023;389:1453-1465

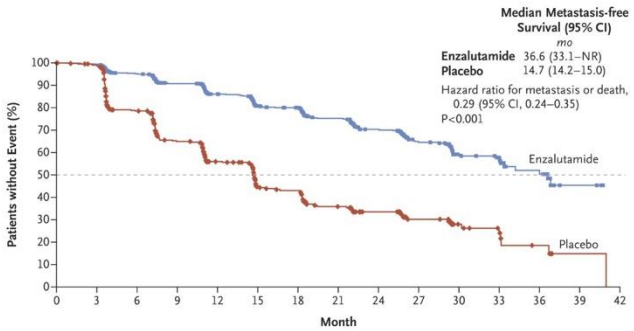
CRPC: Non-metastatic (PSA only)

SPARTAN



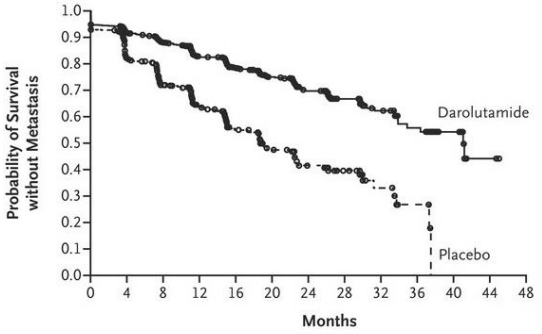
APALUTAMIDE*

PROSPER



ENZALUTAMIDE*

ARAMIS



DAROLUTAMIDE

Significant fracture risk in both studies *

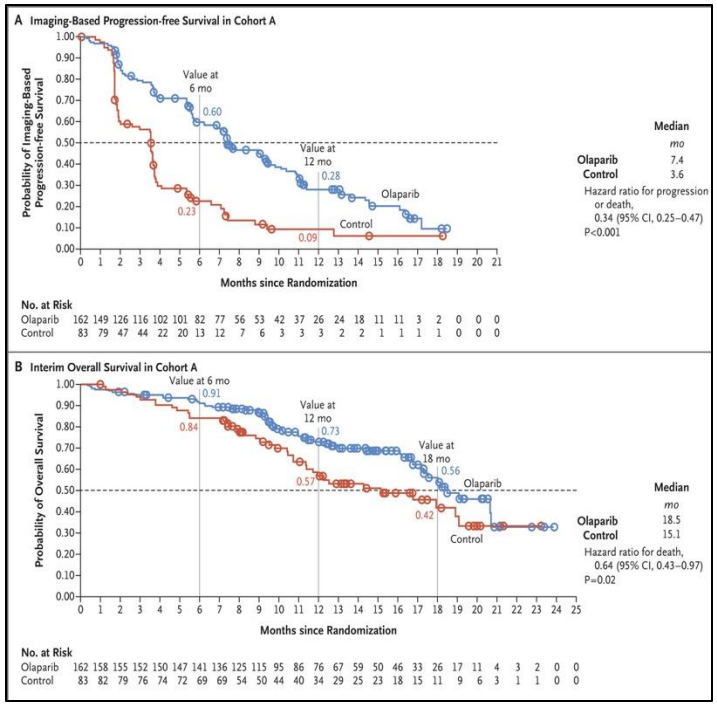
11.7% (apalutamide) vs. 6.5% (placebo) / 10% (enzalutamide) vs. 5% (placebo)

Darolutamide not associated with a higher incidence of seizures, falls, fractures, cognitive disorder

Smith MR, et al. NEJM 2018;378(15):1408-1418
Hussain M, et al. NEJM 2018;378(26):2465-2474
Fizazi K, NEJM 2019;380(13):1235-1246.

PARP inhibitors in CRPC

PROFOUND



OLAPARIB

Mutations:

Cohort A:

BRCA1, BRCA2, ATM

Cohort B:

BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D or RAD54L

PROfound is the first positive phase III biomarker-selected study evaluating a molecularly targeted treatment in patients with mCRPC

de Bono et al. NEJM 2020;382:2091-2102)

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Combinations of PARPis with ARSIs in mCRPC

- **Niraparib + abiraterone acetate in combination with prednisone**: Approved to treat deleterious or suspected deleterious BRCA-positive mCRPC.

- MAGNITUDE trial: Niraparib + abiraterone acetate plus prednisone reduced the risk of radiographic progression by 47% in the **BRCA1/2 subgroup**.

- Results of the futility analysis **in the HRR-wild type cohort demonstrated no benefit** for combination niraparib/abiraterone versus placebo/abiraterone.

- **Talazoparib + enzalutamide for the treatment of patients with HRR-mutant mCRPC**.

- TALAPRO-2 trial: Improvement in median rPFS **for both HRR-mutated and HRR-wild type** (or unknown) cohorts. The benefit of talazoparib was larger, as anticipated, in patients harboring known alteration in HRR-mediating genes (27.9 v 16.4 months, HR 0.46 [0.30-70], $p<0.001$).

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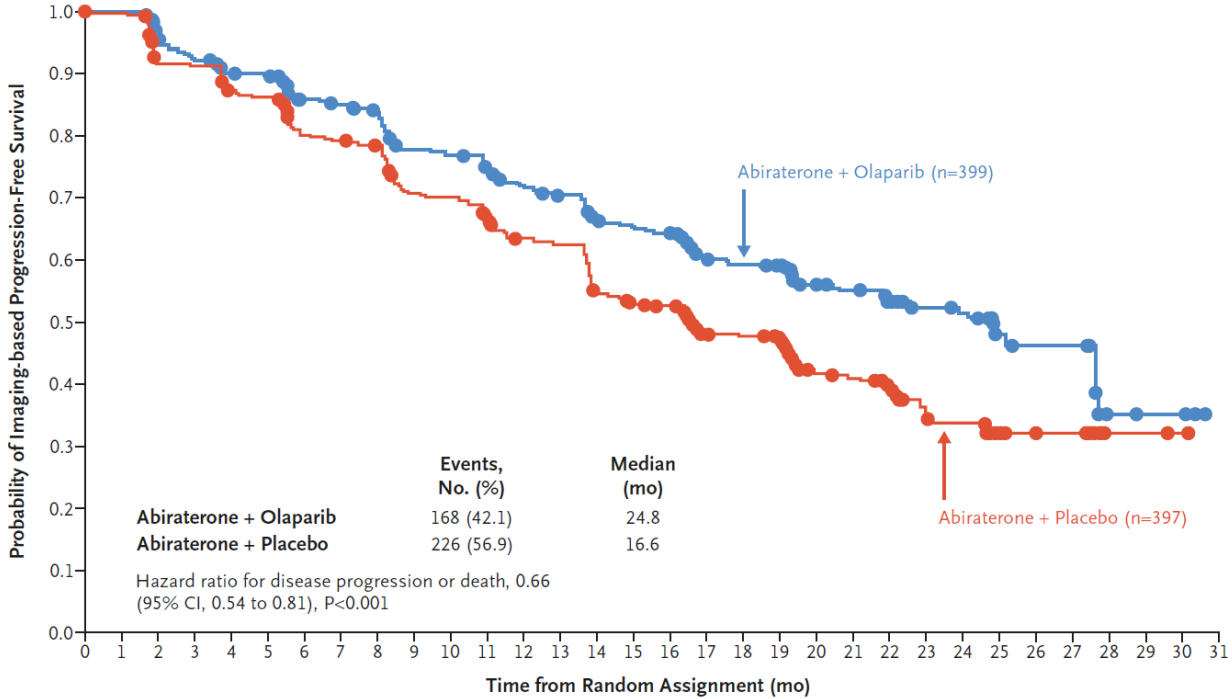
Do HRR-wild type PCs benefit from PARPis + ARSI?



No. at Risk

Abiraterone + Olaparib	399	395	367	354	340	337	313	309	301	277	274	265	251	244	227	221	219	170	167	163	104	100	87	59	57	28	26	26	5	4	4	0
Abiraterone + Placebo	397	393	359	356	338	334	306	303	297	266	264	249	232	228	198	190	186	143	141	137	87	84	73	45	43	21	17	16	2	2	1	0

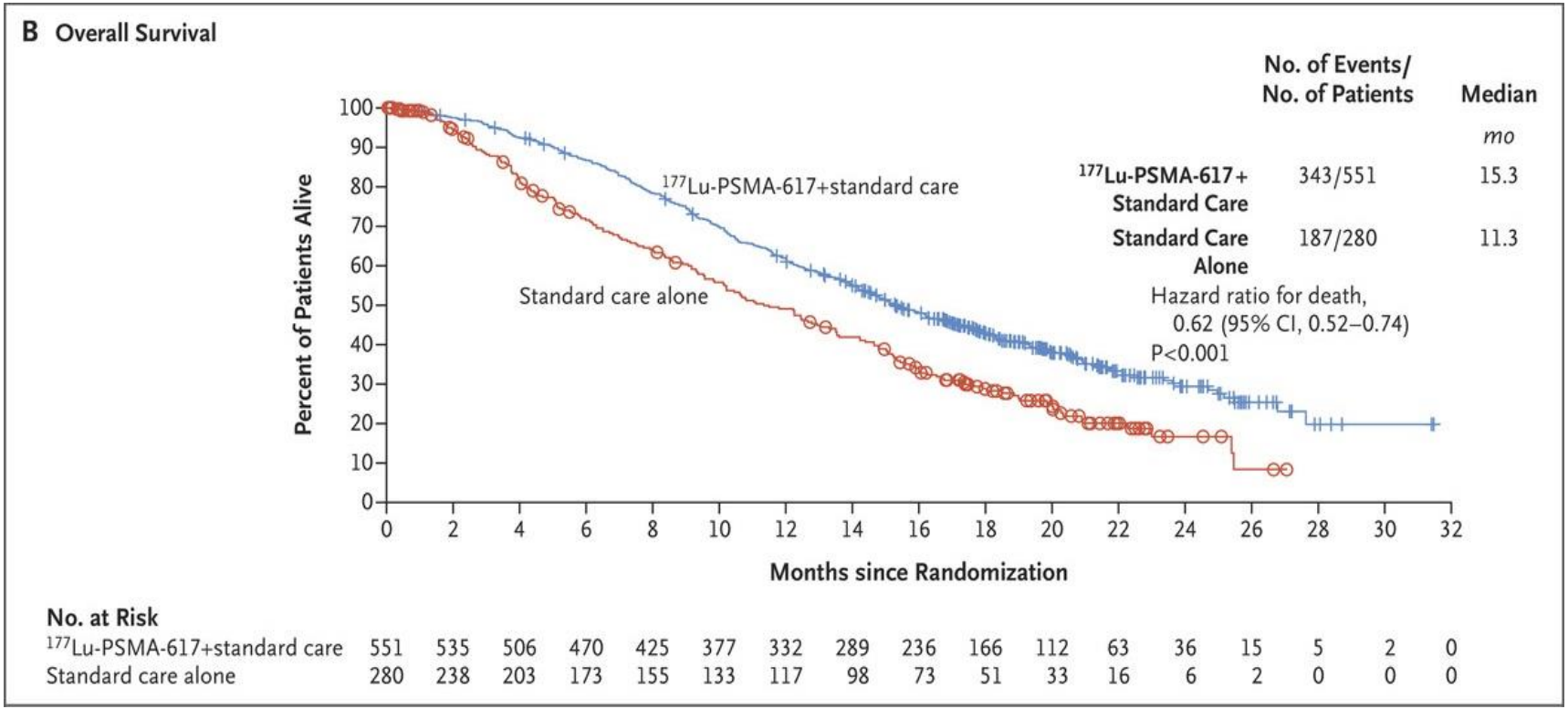
PROpel trial:

Patients with mCRPC, regardless of HRR gene mutation status, received either abiraterone and olaparib or abiraterone and placebo in the first-line setting.

Noel W. Clarke, et al. NEJM Evid; Volume 1(9):EVIDoa2200043, August 23, 2022

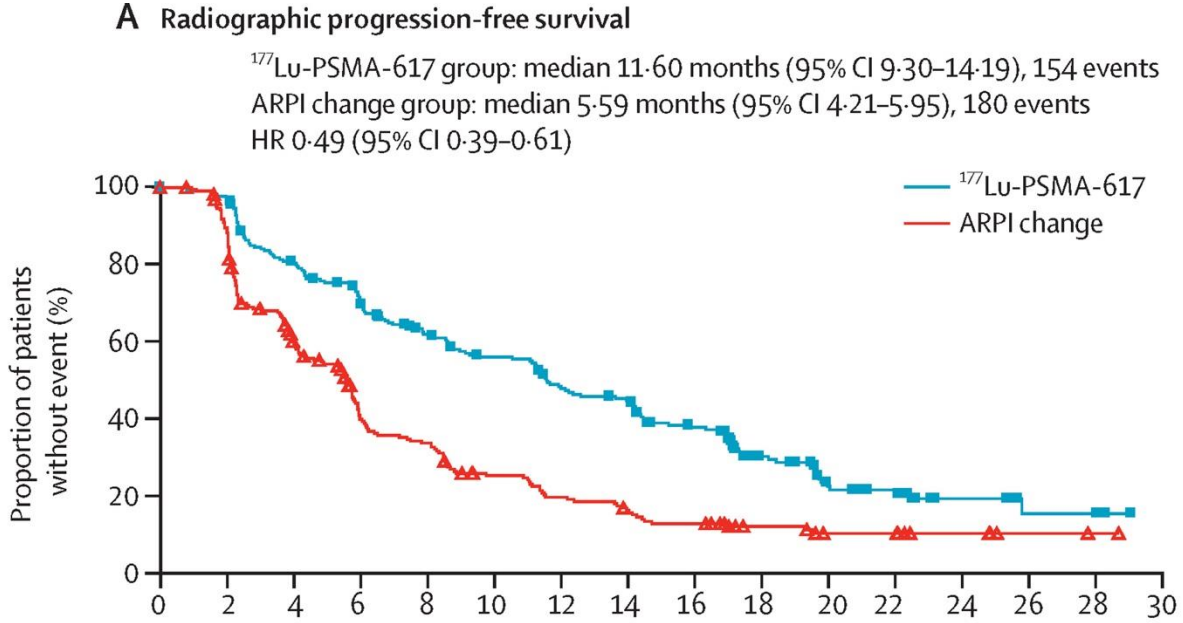
177Lu-PSMA-617 in mCRPC

VISION



O Sartor et al. N Engl J Med 2021;385:1091-1103.
Armstrong AJ et al. JCO. 2022

PSMAfore: ^{177}Lu-PSMA-617 in taxane-naïve mCRPC



Number at risk (number censored)																
^{177}Lu-PSMA-617 group	234	217	175	152	126	111	94	86	67	39	25	20	8	4	4	0
	(0)	(12)	(5)	(3)	(6)	(3)	(2)	(1)	(6)	(16)	(6)	(3)	(10)	(3)	(0)	(4)
ARPI change group	234	197	126	79	65	45	35	28	22	14	9	9	5	2	1	0
	(0)	(14)	(7)	(9)	(0)	(4)	(0)	(1)	(0)	(7)	(3)	(0)	(4)	(3)	(1)	(1)

However:

- No OS benefit
- No docetaxel arm

Morris MJ, et al. ^{177}Lu-PSMA-617 versus a change of androgen receptor pathway inhibitor therapy for taxane-naive patients with progressive metastatic castration-resistant prostate cancer (PSMAfore): a phase 3, randomised, controlled trial. Lancet. 2024 Sep 28;404(10459):1227-1239

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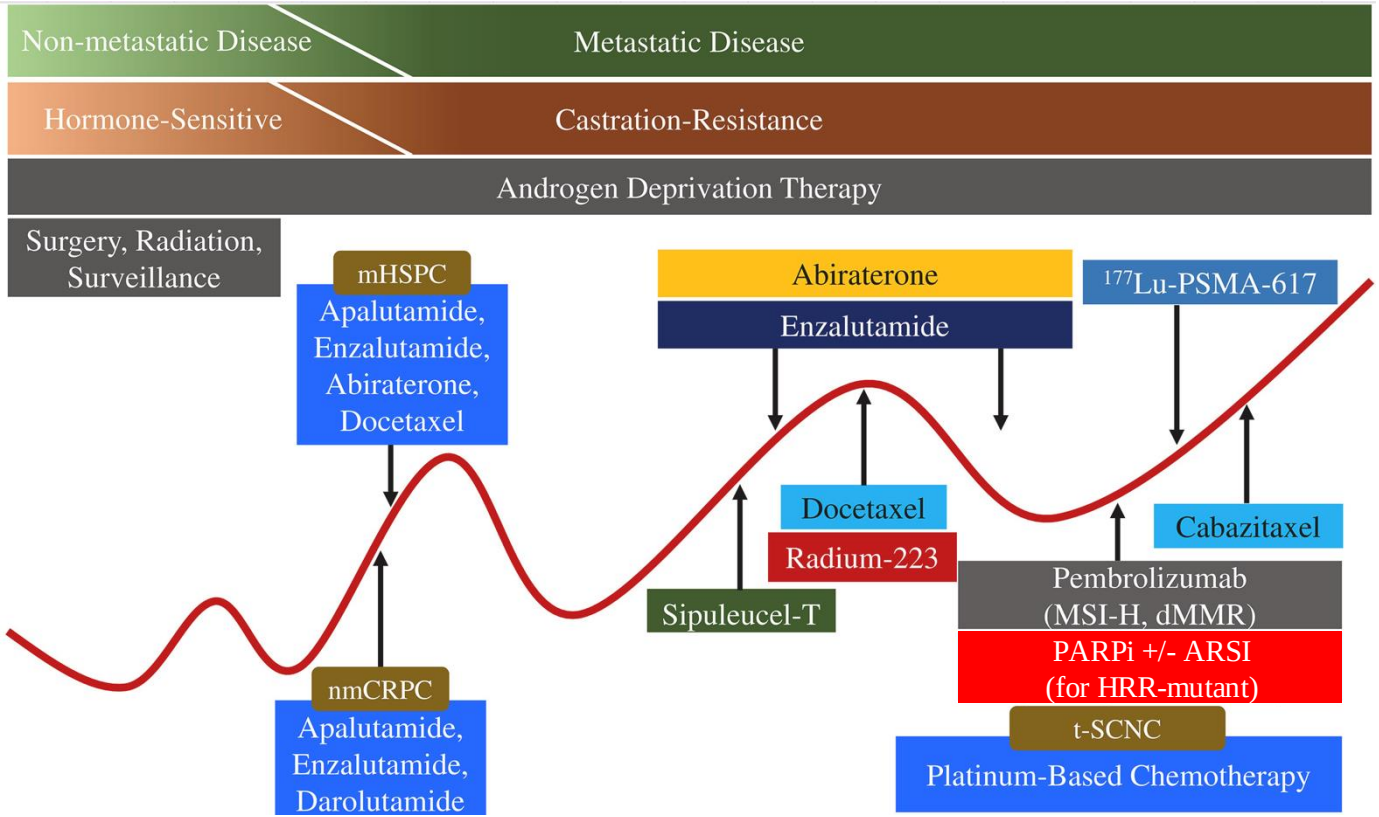
Summary



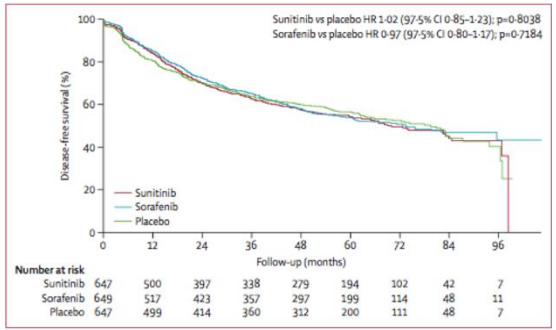
Yasutaka Yamada, Himisha Beltran. Cancer Letters, 2021 (updated for 2024)

Presentation Outline

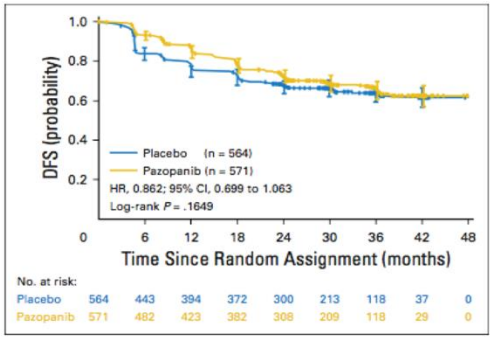
- PROSTATE CANCER
- KIDNEY CANCER
  - The state of perioperative therapies in RCC
  - Current Status Front-Line Metastatic RCC : Doublets and Triplet
  - Recent updates and upcoming trials
  - Treatment decisions (?biomarkers or lack thereof)
- UROTHELIAL CARCINOMA

Perioperative Management: VEGFi/ TKIs

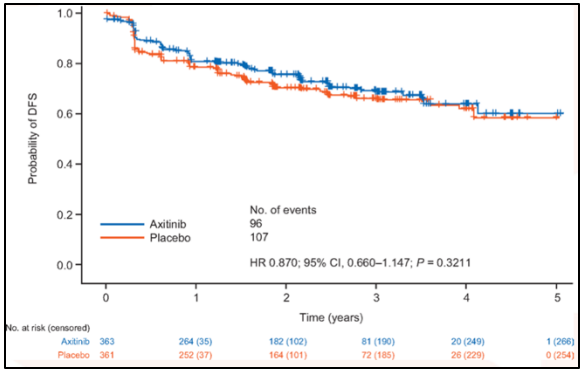
ASSURE DFS



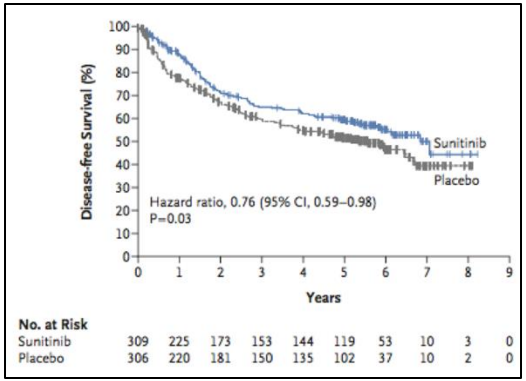
PROTECT DFS



ATLAS DFS



S-TRAC DFS

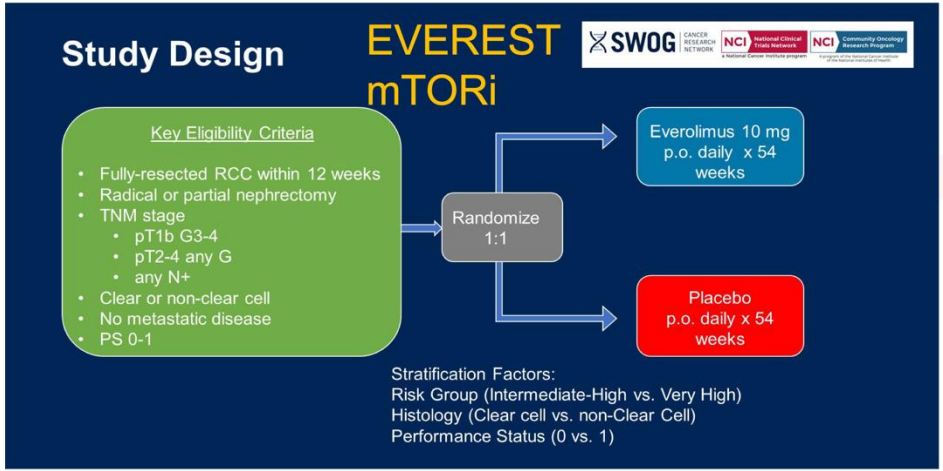


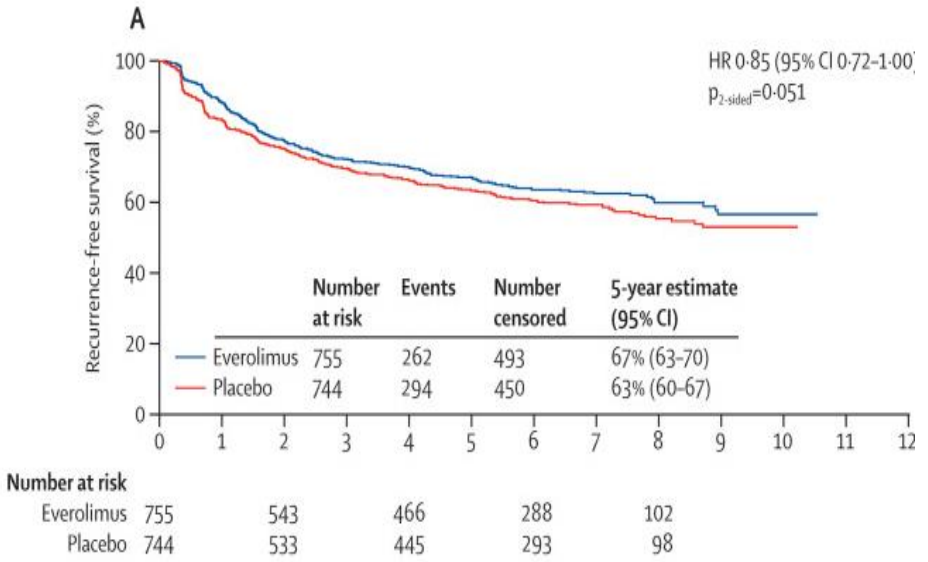
- Heterogeneity
- ASSURE- lower T stage, clear and non clear
- PROTECT/ S-TRAC- pT3, higher grade and higher risk tumors
- S-TRAC the only positive trial for DFS (HR 0.76)
- Sunitinib approved by the FDA but not the EMA
- OS benefit not seen in any

Haas NB, et al. *Lancet*. 2016;387(10032):2008-16. Motzer RJ, et al. *J Clin Oncol*. 2017;35(35):3916-3923. Ravaud A, et al. *N Engl J Med*. 2016;375(23):2246-2254. Gross- Goupil M, et al. *Ann Oncol*. 2018;29(12):2371-2378.

Perioperative Management: Everolimus (mTOR inhibitor)

EVEREST TRIAL





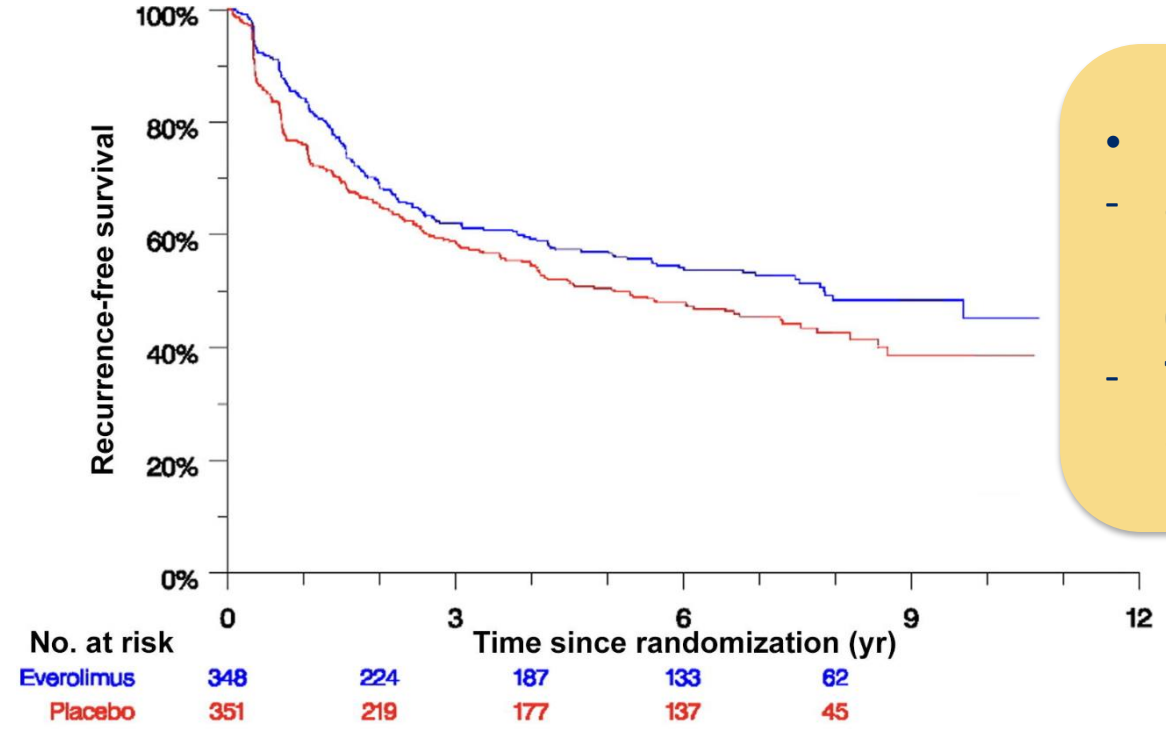
RFS *p-value did not cross the prespecified boundary for statistical significance (p=0.044)

No improvement in RFS in papillary or chromophobe subgroups

Ryan CW, *et al. The Lancet*. 2023
Gulati, *et al.* JAMA Network Open. 2024

Perioperative Management: Everolimus (mTOR inhibitor)

EVEREST TRIAL: Subgroup analyses in very-high risk patients



- In the very-high-risk population:
  - Significant improvement in RFS (HR 0.80, 95% CI 0.65–0.99; p = 0.041)
  - There was no statistically significant difference in OS

Lara PN, et al. *European Urology*. 2024

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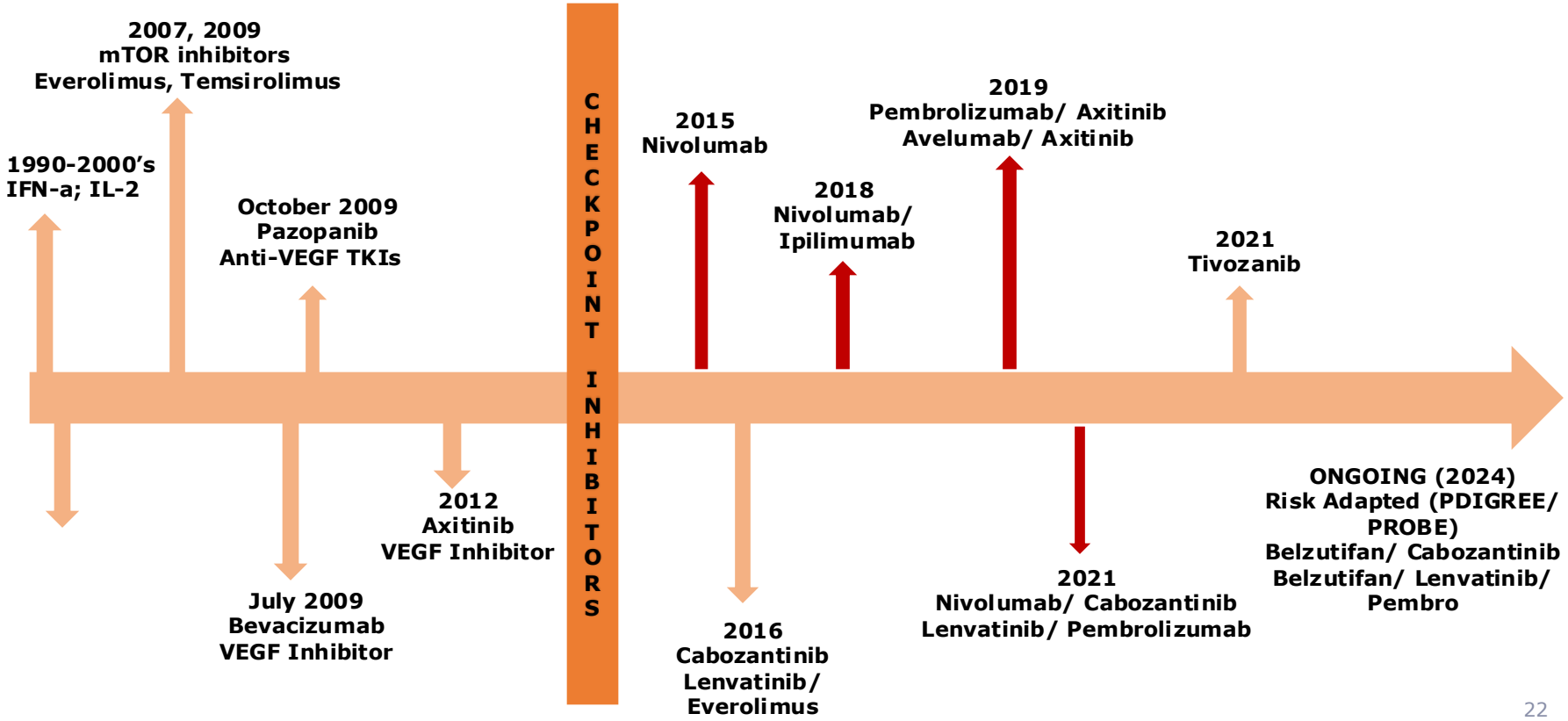
Perioperative Management: Immune checkpoint inhibitors

	KEYNOTE - 564 PEMBROLIZUMAB	PROSPER (EA8143) NIVOLUMAB	IMMotion 010 ATEZOLIZUMAB	CHECKMATE-914 NIVO/ IPI
RANDOMIZATION	Adjuvant Pembrolizumab Vs. Placebo	Neoadjuvant and adjuvant Nivolumab vs. surgical SOC	Adjuvant Atezolizumab Vs. Placebo	Adj Nivolumab + Ipilimumab vs Placebo (nivolumab alone added)
HISTOLOGY	cRCC with a component of clear cell histology w or w/out sarcomatoid histology	Clear and nonclear cell	Component of either ccRCC histology or sarcomatoid histology	ccRCC predominant with or without sarcomatoid histology
SARCOMATOID?	YES	YES	YES	YES
T/N	pT2, grade 4 and higher Any N	cT2 and higher Any N	pT2, grade 4 and higher Any N	pT2 grade3-4 and higher Any N
OLIGOMETS	M1 resected within 12 months of primary tumor	Oligomets ablated or resected within 12 weeks of primary	Lung or soft tissue oligomets >12 months	NO
PFS HR P-value	**0.63 p<0.0001**	0.97 p= 0.43	0.93 p= 0.49	0.92 P= 0.53
OS HR P-value	**0.62; (95% CI, 0.44 to 0.87) P=0.005**	NS	NS	NS

Choueiri et al. NEJM 2021, 2023; Allaf M, et al. Presented at: ESMO;2022; Pal M, Lancet 9-11-22. Bex A, et al. Presented at: ESMO 2022; Motzer RJ, et al. Presented at: ESMO;2022; Choueiri et al. NEJM 2024

Systemic Therapies for Advanced/ Metastatic RCC in 2024



Published doublet trials

	CHECKMATE- 214	KEYNOTE-426	CLEAR	CHECKMATE- 9ER
DRUGS	**Nivolumab + ipilimumab (N = 1096)**	**Pembrolizumab + Axitinib (N = 861)**	**Pembrolizumab + Lenvatinib (N = 1069)**	**Nivolumab + Cabozantinib (N = 651)**
Median follow-up (months)	**68 months**	**67 months**	**48 months**	**44 months**
mPFS (mo)	12.2 vs. 12.3	15.7 vs. 11.1	**23.9 vs. 9.2**	16.6 vs. 8.4
HR (95% CI)	**0.86 (0.73-1.01) (0.73 for Int/Poor)**	**0.69 (0.59-0.81)**	**0.47 (0.38-0.57)**	**0.59 (0.49-0.71)**
Median OS (mo)	**55.7 vs. 38.4**	**47.2 vs. 40.8**	**53.7 vs. 54.3**	**49.5 vs. 35.5**
HR (95% CI)	**0.72 (0.62-0.85) (0.68 for Int/Poor)**	**0.84 (0.71-0.99)**	**0.79 (0.63-0.99) (0.74 for Int/Poor)**	**0.70 (0.56-0.87)**
ORR	39 vs. 32%	61% vs. 40%	**71% vs. 37%**	56% vs. 28%
CR	12% vs. 3%	12% vs. 3%	**18% vs. 5%**	13% vs. 5%
Sarcomatoid features (%)	16	12	8	11.5
% pts discontinuation of both drugs	22% vs. 12%	7% vs. 12%	**37% vs. 14%**	20% vs. 17%
QOL (vs. Sunitinib)	Improved	Similar	Similar to improved	Improved

Kidney Cancer: METASTATIC TRIPLET OR DOUBLET: COSMIC 313

COSMIC-313: TRIPLET Therapy in mRCC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

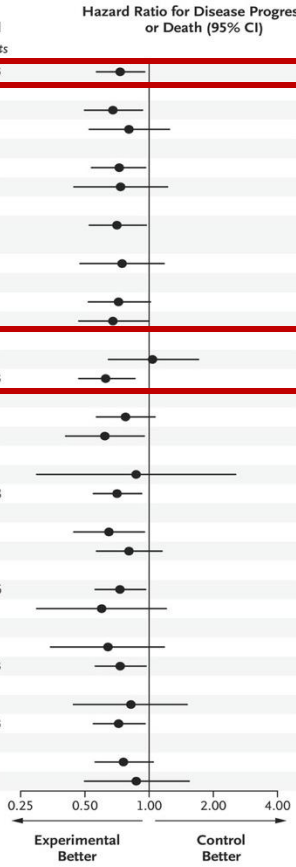
Cabozantinib plus Nivolumab and Ipilimumab in Renal-Cell Carcinoma

T.K. Choueiri, T. Powles, L. Albiges, M. Burotto, C. Szczylik, B. Zurawski, E. Yanez Ruiz, M. Maruzzo, A. Suarez Zaizar, L.E. Fein, F.A. Schutz, D.Y.C. Heng, F. Wang, F. Mataveli, Y.-L. Chang, M. van Kooten Losio, C. Suarez, and R.J. Motzer, for the COSMIC-313 Investigators*

FIRST trial to compare a triplet to a doublet
FIRST trial with ipilimumab/ nivolumab as the comparator

PFS in Prespecified Subgroups

Subgroup	Experimental	Control
	no. of patients/no. of events	
All patients	276/116	274/133
Age		
<65 yr	180/73	186/91
≥65 yr	96/43	88/42
Sex		
Male	213/87	204/97
Female	63/29	70/36
Geographic region		
United States, Canada, Europe, Australia, or New Zealand	195/79	192/90
Latin America or Asia	81/37	82/43
Karnofsky performance-status score		
90 or 100	162/62	178/76
70 or 80	113/54	95/57
IMDC risk		
Poor	67/37	66/30
Intermediate	209/79	208/103
Previous nephrectomy		
Yes	177/75	176/85
No	99/41	98/48
Sarcomatoid features		
Yes	24/11	11/5
No	252/105	263/128
Sum of diameters of target lesions		
<Median	131/48	133/64
≥Median	135/64	129/62
Visceral metastasis		
Yes	241/100	240/116
No	35/16	34/17
Liver metastasis		
Yes	47/22	39/20
No	229/94	235/113
Bone metastasis		
Yes	33/17	57/30
No	243/99	217/103
PD-L1 tumor proportion score		
<1%	182/78	168/82
≥1%	50/22	62/28



TK Choueiri et al. N Engl J Med 2023;388:1767-1778.

COSMIC-313: Adverse Event Data

Treatment Exposure and Discontinuation (Safety Population)

	Cabo+Nivo+Ipi (N=426)	Pbo+Nivo+Ipi (N=424)
Median duration of exposure of study treatment (range), mo	10.9 (0.2–28.5)	10.3 (0.1–28.1)
Median average daily dose (range) of Cabo or Pbo, mg	23.2 (3.6–40.0)	36.1 (0.8–40.0)
Median Nivo infusions (range) received, no	10 (1–27)	9 (1–27)
Doses of Ipi received, %		
4	58	73
3	13	14
2	22	7
1	7	6
Any dose hold due to an AE, %	90	70
Any dose reduction of Cabo or Pbo due to an AE, %	54	20
Treatment-related AE leading to discontinuation, %		
Any study treatment	45	24
Cabo or Pbo	28	14
Nivo	26	18
Ipi	30	12
All treatment components (due to the same AE)	12	5

Data cut-off: Jan 31, 2022

TK Choueiri et al. N Engl J Med 2023;388:1767-1778.

Kidney Cancer: METASTATIC TRIPLET OR DOUBLET: COSMIC 313

- Positive trial for PFS (HR 0.73) to support the triplet
- However, looking at the HR in the FORREST PLOT: poor risk patients DO NOT benefit
- Low response rates
- Use of high dose corticosteroids (≥ 40mg/day) in 58% patients and a 45% rate of discontinuation due to AEs
- TOXICITY GETS IN THE WAY!!!

BELZUTIFAN: LITESPARK 005

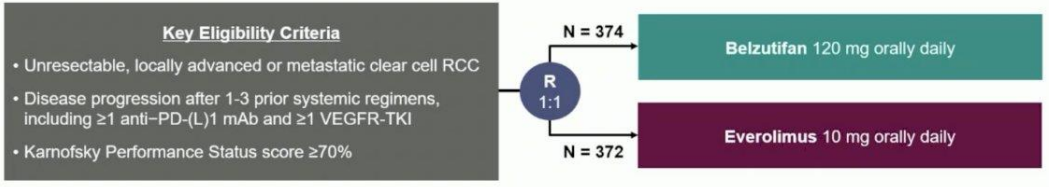
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Belzutifan versus Everolimus for Advanced Renal-Cell Carcinoma

T.K. Choueiri, T. Powles, K. Peltola, G. de Velasco, M. Burotto, C. Suarez, P. Ghatalia, R. Iacovelli, E.T. Lam, E. Verzoni, M. Gümüş, W.M. Stadler, C. Kollmannsberger, B. Melichar, B. Venugopal, M. Gross-Goupil, A. Poprach, M. De Santis, F.A. Schutz, S.H. Park, D.A. Nosov, C. Porta, J.L. Lee, X. Garcia-del-Muro, E. Biscaldi, R. Manneh Kopp, M. Oya, L. He, A. Wang, R.F. Perini, D. Vickery, L. Albiges, and B. Rini, for the LITESPARK-005 Investigators*

LITESPARK-005 Study (NCT04195750)



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

Choueiri *et al.* NEJM. Aug 2024

BELZUTIFAN: LITESPARK 005

A Progression-free Survival

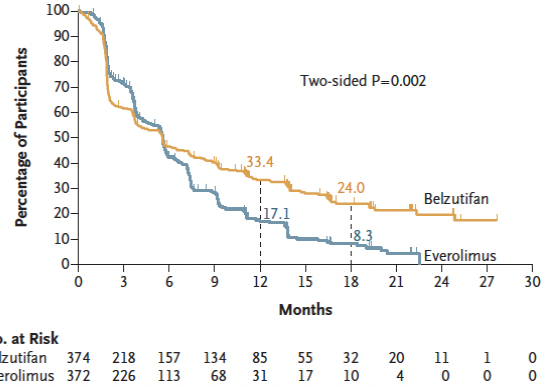
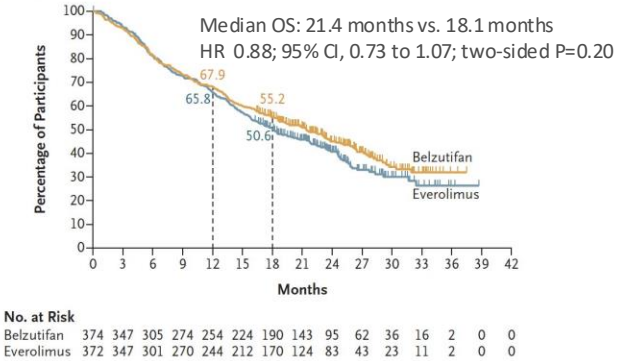


Table 2. Best Response in the Intention-to-Treat Population.[a]

Response	First Interim Analysis			Second Interim Analysis		
	Belzutifan (N=374)	Everolimus (N=372)	Estimated Difference	Belzutifan (N=374)	Everolimus (N=372)	Estimated Difference
Objective response — % (95% CI)	21.9 (17.8–26.5)	3.5 (1.9–5.9)	18.4 (14.0–23.2)†	22.7 (18.6–27.3)	3.5 (1.9–5.9)	19.2 (14.8–24.0)
Confirmed best overall response — no. (%)						
Complete response	10 (2.7)	0		13 (3.5)	0	
Partial response	72 (19.3)	13 (3.5)		72 (19.3)	13 (3.5)	
Stable disease‡	147 (39.3)	245 (65.9)		143 (38.2)	245 (65.9)	
Progressive disease	126 (33.7)	80 (21.5)		127 (34.0)	80 (21.5)	
Not evaluable§	5 (1.3)	8 (2.2)		5 (1.3)	8 (2.2)	
No assessment¶	14 (3.7)	26 (7.0)		14 (3.7)	26 (7.0)	

B Overall Survival



ADVERSE EVENTS:

- Grade 3+ adverse events were ~62% in both treatment arms
- Most common AEs with belzutifan were anemia and hypoxia
- AEs led to discontinuation of treatment in 5.9% and 14.7% of pts on BEL and EVE, respectively

Choueiri *et al*. NEJM. Aug 2024

Belzutifan as 2L therapy after ICI (Phase III)

Conclusions:

- LITESPARK-005 establishes HIF-2a inhibition as a novel therapeutic MOA in advanced clear cell RCC.
- Belzutifan demonstrated a statistically significant improvement in progression-free survival and objective response rate versus everolimus.
- 25% reduction in risk for progression or death with belzutifan.
- OS difference has not reached statistical significance; final analysis pending.
- Belzutifan was well tolerated.
- LITESPARK-005 is the first positive phase 3 study in patients with advanced RCC following immune checkpoint and anti-angiogenic therapies

Other Subsequent Lines of Therapy for mccRCC

Study	Treatment evaluated	Prior treatment	Number of patients	PFS (months)	ORR (%)
METEOR (post-hoc)[6]	Cabozantinib (vs. everolimus)	Anti-PD-1/PD-L1 subgroup	32	Not reached vs. 4.1 mos (HR 0.22)	22% vs. 0%
Phase II study[3]	Axitinib	IO alone: 71% IO-TKI or IO/IO: 31%	40	8.8 months	38%
BREAKPOINT (Phase II)[1]	Cabozantinib	74%: IO/IO 17%: IO-TKI 9%: adjuvant IO	48	9.3 months	43%
INMUNOSUN-SOGUG (Phase II)[2]	Sunitinib	IO combinations and monotherapy	21	5.6 months	19%
CANTATA (Phase III)[4]	Cabozantinib vs. Cabozantinib+ Telaglenastat	IO alone or IO combinations	91	9.2 months vs. 9.3 months	31% vs. 28%
TIVO-3 (Phase III)[5]	Tivozanib vs. Sorafenib	≥3rd line, IO in 27%	350	7.3 months vs. 5.1 months	NR
Phase II[8]	Cabozantinib+ Belzutifan	65%: IO/IO 35%: IO-TKI 14%: IO after TKI or vice versa	52	1 year PFS: 65%	22%

TIVOZANIB: TIVO-3

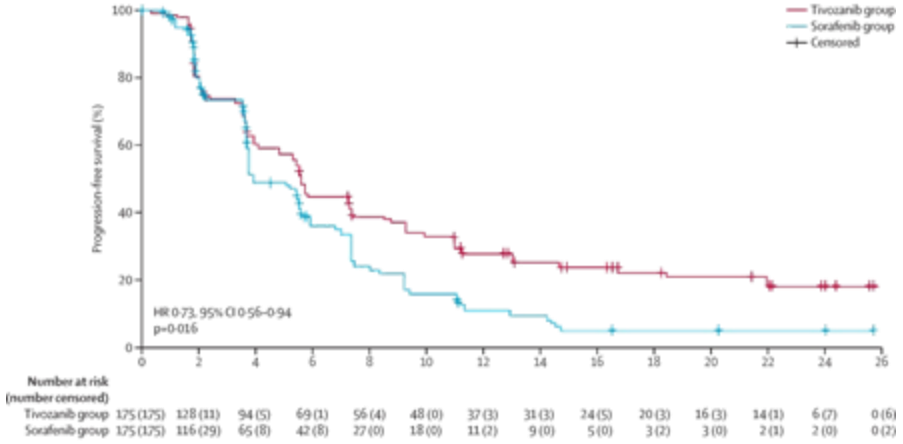
Key eligibility criteria
- Metastatic clear cell RCC
- Received at least 2 lines of prior systemic therapy (including 1 VEGFRi/ TKI)
- Measurable disease per RECIST
- ECOG PS 0 or 1

R
(1:1)
N = 350

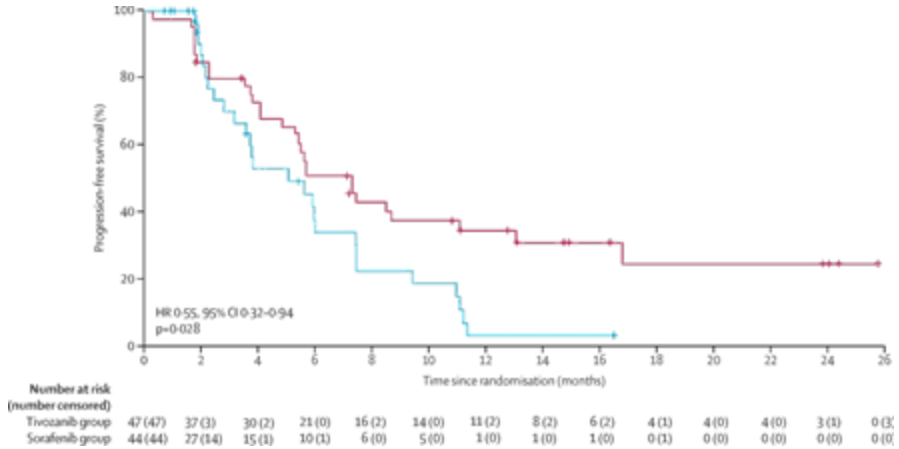
Tivozanib 1.34 mg PO daily
21 days on and 7 days off

Sorafenib 400mg PO BID
(1 cycle = 28 days)

Primary endpoint: PFS
Secondary endpoint: OS, ORR, duration of response and safety



PFS in ITT population:
mPFS 5.6 months with tivozanib vs. 3.9 months



PFS after an ICI and TKI combination:
mPFS 7.3 months for tivozanib vs. 5.1 months

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

Rechallenge with an IO-based Regimen: CONTACT-03

Key eligibility criteria

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

R
1:1

N=522

Atezolizumab 1200 mg IV q3w + Cabozantinib 60 mg daily PO

Cabozantinib 60 mg daily PO

Stratification factors

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

Primary endpoints

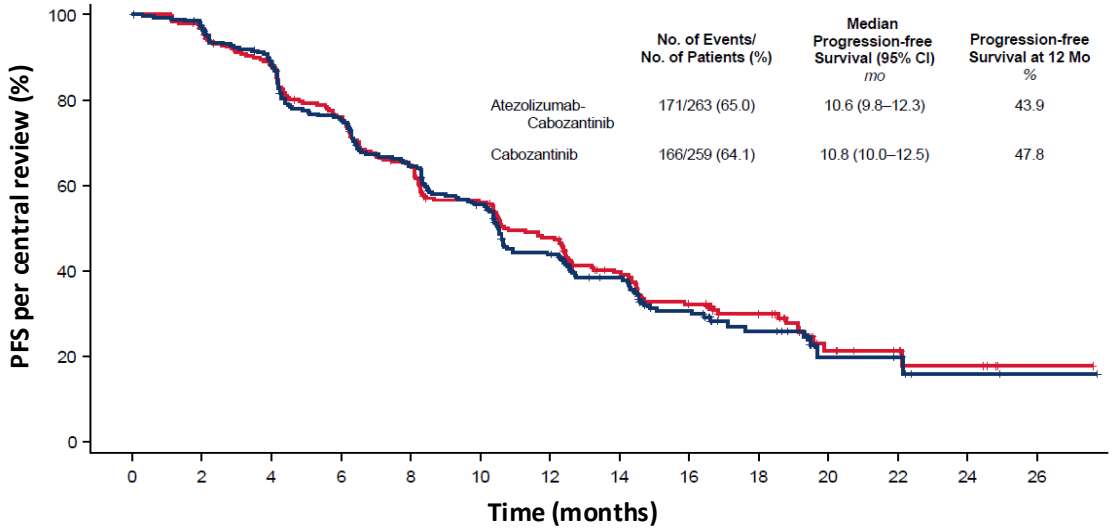
- Independent centrally-assessed PFS[c]
- OS

Key secondary endpoints

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

Choueiri et al. ASCO 2023

CONTACT-03: Primary analysis of centrally reviewed PFS (primary endpoint)



"The addition of atezolizumab to cabozantinib did not improve clinical outcomes and led to increased toxicity. These results should discourage sequential use of immune checkpoint inhibitors in patients with renal cell carcinoma outside of clinical trials."

Choueiri et al. ASCO 2023

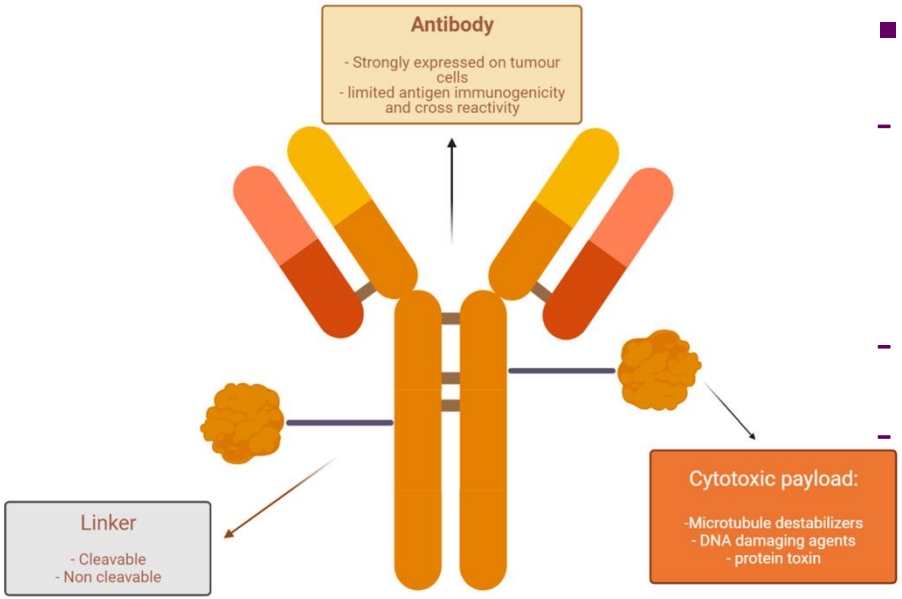
Management of RCC in 2024: CONCLUSIONS

- Perioperative treatment of RCC has evolved to adjuvant pembrolizumab with OS benefit reported
- Doublet regimens remain standard of care in the front-line setting (no triplets)
- We do not have biomarkers to select for specific regimens
- CONTACT3 and TiNivo-2 data DO NOT support re-challenge with an ICI after progression (and there is no data to address the same question after adjuvant pembrolizumab)

Presentation Outline

- PROSTATE CANCER
- KIDNEY CANCER
- **UROTHELIAL CARCINOMA**
  - Current Status of approved drugs for metastatic urothelial carcinoma
  - Recent updates and upcoming trials
  - The state of perioperative therapies
  - Treatment decisions

Antibody Drug Conjugates

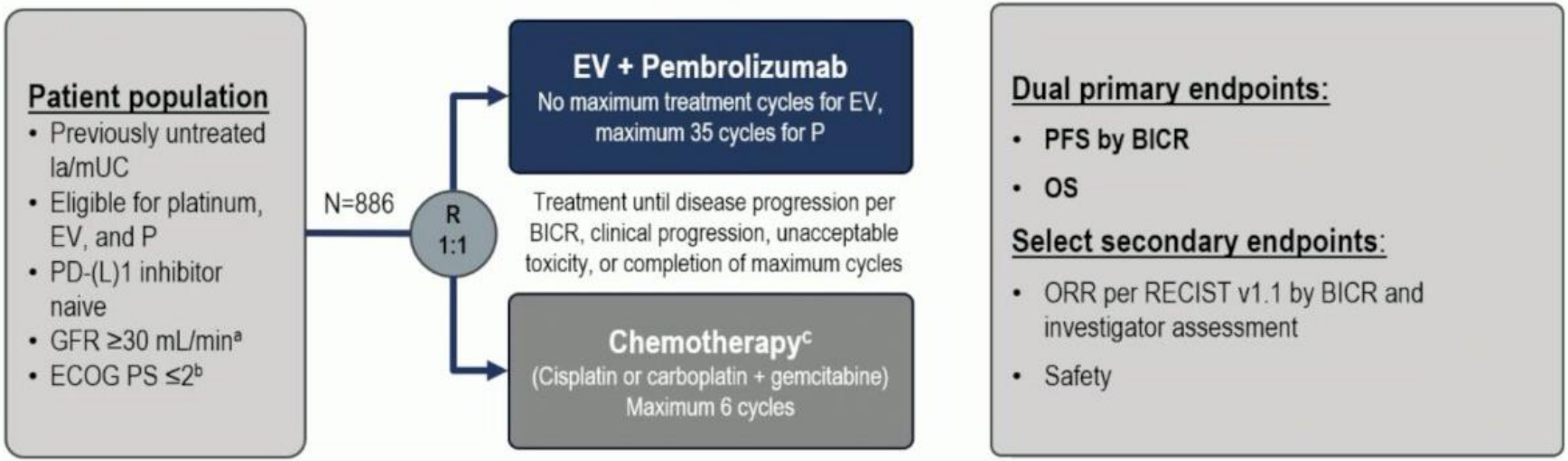


- **ENFORTUMAB VEDOTIN**
- **Target:** Nectin-4 (transmembrane cell adhesion molecule overexpressed in epithelial cancers)
- **Linker:** Protease cleavable
- **Payload:** Monomethyl auristatin E (MMAE)

Ungaro et al. MDPI. 2022

EV-302/KEYNOTE-A39: First time that platinum-based CT has been surpassed in OS

EV-302/KEYNOTE-A39 (NCT04223856)



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

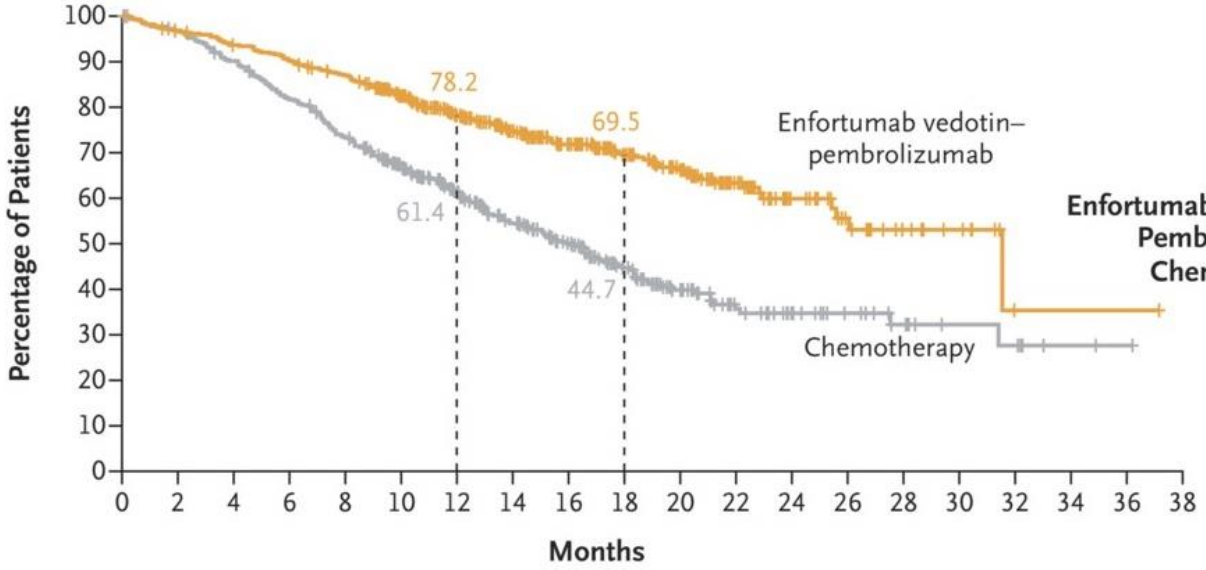
Cisplatin eligibility and assignment/dosing of cisplatin vs carboplatin were protocol-defined; patients received 3-week cycles of EV (1.25 mg/kg; IV) on Days 1 and 8 and P (200 mg; IV) on Day 1

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

ESMO 2023: LBA-6 and Powles T, et al. N Engl J Med. 2024;390(10):875-888.

EV-302/KEYNOTE-A39: First time that platinum-based CT has been surpassed in OS

A Overall Survival



	No. of Events/ No. of Patients	Median Overall Survival (95% CI)
		mo
Enfortumab Vedotin–Pembrolizumab	133/442	31.5 (25.4–NE)
Chemotherapy	226/444	16.1 (13.9–18.3)

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

No. at Risk

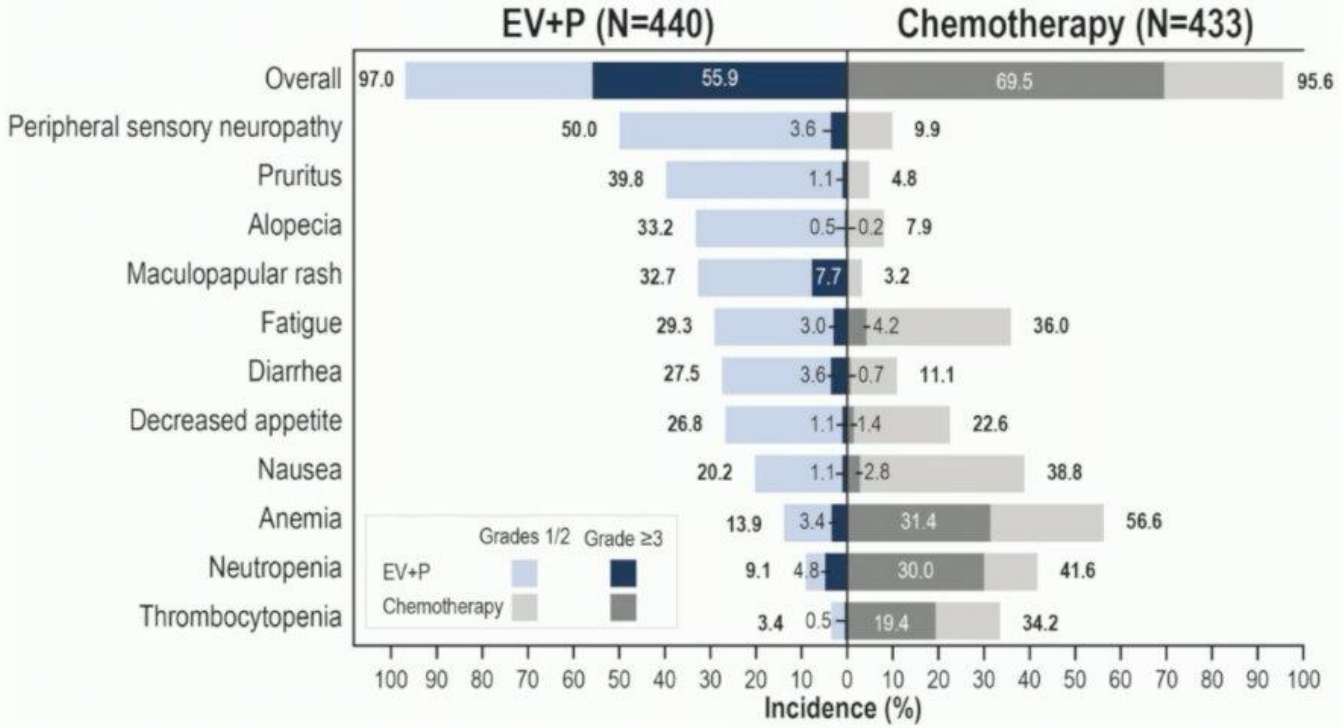
Enfortumab vedotin–pembrolizumab	442	426	409	394	376	331	270	222	182	141	108	67	36	22	12	8	1	1	1
Chemotherapy	444	423	393	356	317	263	209	164	125	90	60	37	25	18	12	7	6	2	1

Powles T, et al. N Engl J Med. 2024;390(10):875-888.

EV-302/KEYNOTE-A39: First time that platinum-based CT has been surpassed in OS

Treatment-Related Adverse Events

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



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

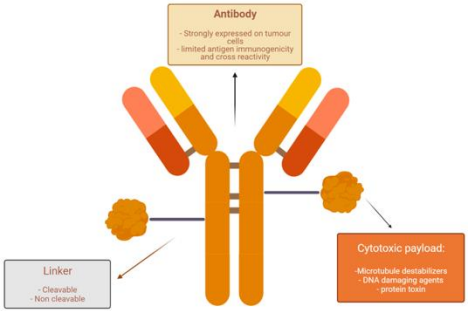
TRAEs leading to death (per investigator):

EV+P: 4 (0.9%)
- Asthenia
- Diarrhea
- Immune-mediated lung disease
- Multiple organ dysfunction syndrome

Chemotherapy: 4 (0.9%)
- Febrile neutropenia
- Myocardial infarction
- Neutropenic sepsis
- Sepsis

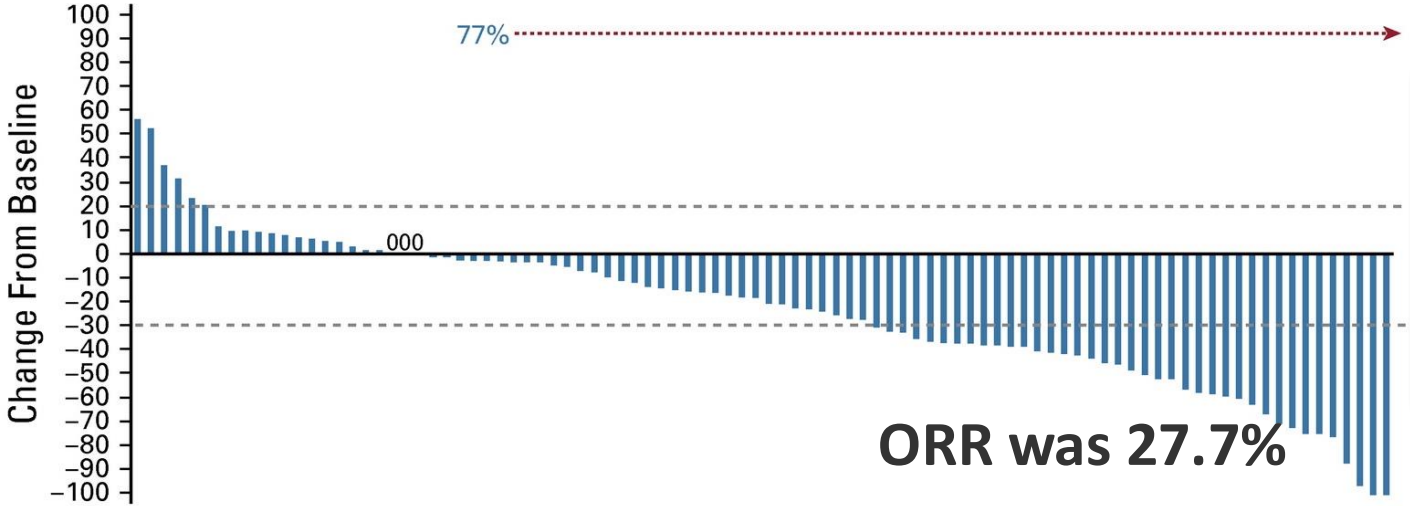
ESMO 2023: LBA-6 and Powles T, et al. N Engl J Med. 2024;390(10):875-888.

Sacituzumab Govitecan: TROPHY-U-1 (Phase-II trial)



Ungaro et al. MDPI. 2022

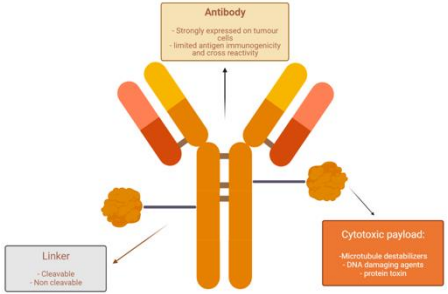
- **Target:** Trop-2, an epithelial cell-surface glycoprotein highly expressed in muscle-invasive disease
- **Linker:** Hydrolysable
- **Payload:** SN-38, the active metabolite of irinotecan



Accelerated FDA Approval for: Patients who have have previously received IO and platinum-based chemotherapy

Tagawa et al. JCO. 2021

Sacituzumab Govitecan: TROPHY-U-1 (Phase-II trial)



Ungaro et al. MDPI. 2022

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

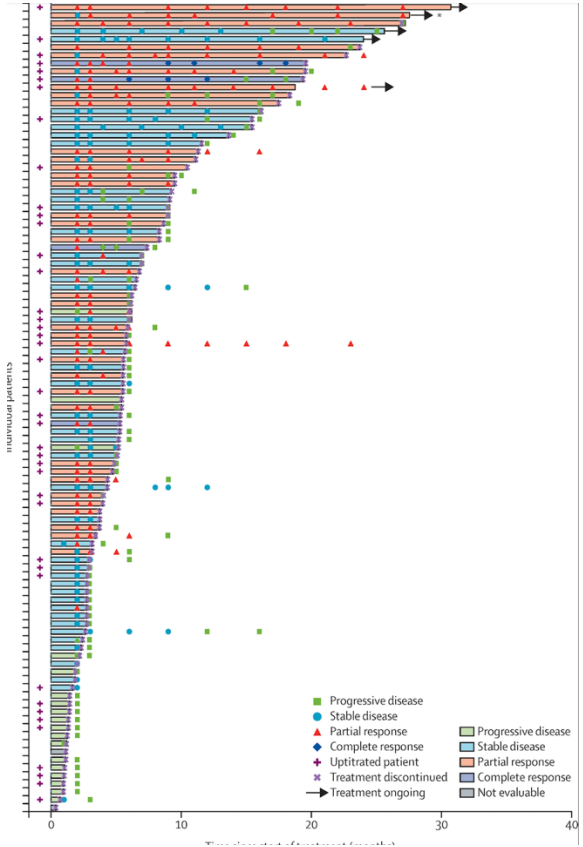
HOWEVER

The confirmatory TROPiCS-04 study did not meet the primary endpoint of OS

The manufacturer voluntarily withdrew the U.S. accelerated approval

FGFR3 Inhibitors

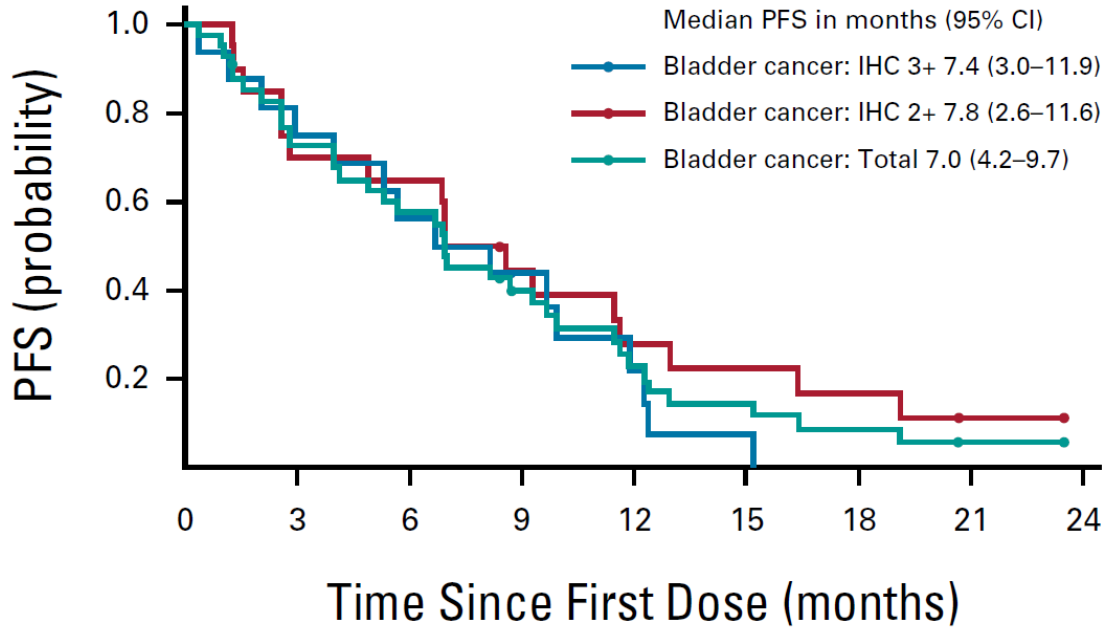
- **FGFR3 mutated in 15-20% patients**
- Targeted therapy: **ERDAFITINIB**
- ORR 33%
- **FDA approved for patients with**
  - locally advanced or metastatic urothelial carcinoma
  - with susceptible FGFR3 or FGFR2 genetic alterations
  - progressed during or following platinum-containing chemotherapy



Siefker-Radtke et al. Lancet Oncology, 2022

Trastuzumab Deruxtecan (T-DXd) in Patients With HER2-Expressing Bladder Cancer (DESTINY-PanTumor02 Phase II Trial)

D



No. at risk:

Bladder cancer: IHC 3+	16	12	9	6	3	1	0		
Bladder cancer: IHC 2+	20	14	13	8	5	4	3	1	0
Bladder cancer: Total	41	29	23	14	8	5	3	1	0

Meric-Bernstam F, et al. Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial. J Clin Oncol. 2024 Jan 1;42(1):47-58.

Trastuzumab Deruxtecan (T-DXd) in Patients With HER2-Expressing Bladder Cancer (DESTINY-PanTumor02 Phase II Trial)

	All Pts	HER2 IHC 3+	HER2 IHC 2+	HER2 IHC 1+	HER2 IHC 0
n	41	16	20	2	2
Pts with OR, n	16	9	7	0	0
ORR, % (95% CI)	39.0 (24.2, 55.5)	56.3 (29.9, 80.2)	35.0 (15.4, 59.2)	0	0
mDOR, months (95% CI)	8.7 (4.3, 11.8)	8.7 (2.8, 10.6)	10.3 (4.3, 17.8)	-	-
mPFS, months (95% CI)	7.0 (4.2, 9.7)	7.4 (3.0, 11.9)	7.8 (2.6, 11.6)	5.5 (4.0, NE)	2.6 (1.0, NE)
DCR at 12 weeks, % (95% CI)	70.7 (54.5, 83.9)	75.0 (47.6, 92.7)	70.0 (45.7, 88.1)	100 (15.8, 100)	50.0 (1.3, 98.7)

By INV. Local HER2 status confirmed by central testing; upon reanalysis, some pts were IHC 1+/0/unknown. 1 pt: central IHC unknown. DOR was assessed in pts with an OR. CIs omitted: 0%. NE, not evaluable.

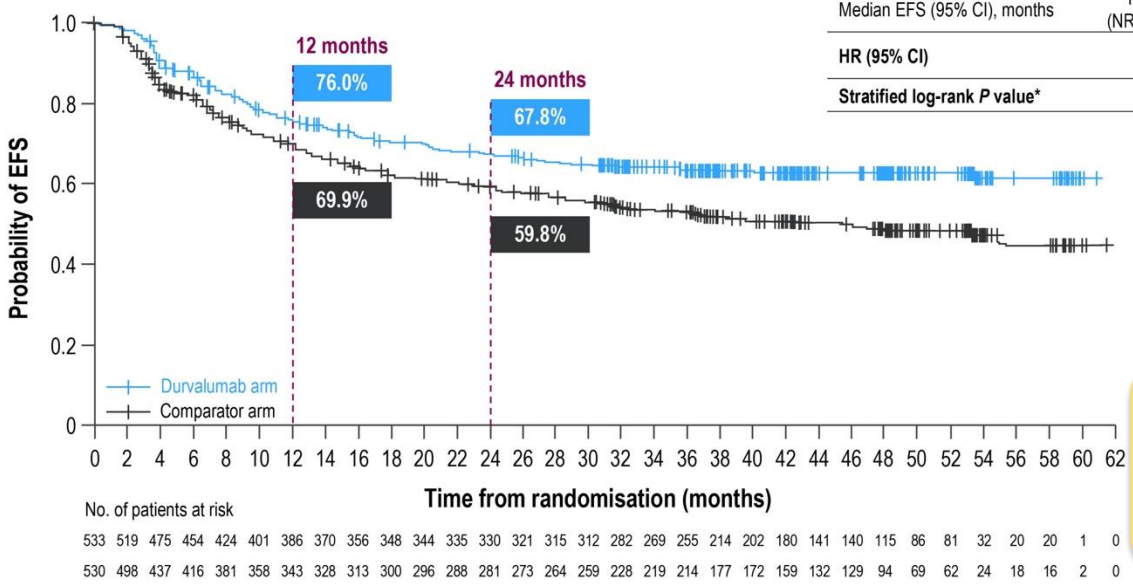
Piotr Jan Wysocki et al., Efficacy and safety of trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-expressing solid tumors: Results from the bladder cohort of the DESTINY-PanTumor02 (DP-02) study.. JCO 42, 4565-4565(2024).

4/5/24: Trastuzumab deruxtecan was approved for adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumours who have received prior systemic treatment and have no satisfactory alternative treatment options.

Urothelial Cancer: Perioperative Management

NIAGARA: Event-free Survival by Blinded Independent Central Review (ITT)

	Durvalumab arm N=533	Comparator arm N=530
Number of events, n (%)	187 (35.1)	246 (46.4)
Median EFS (95% CI), months	NR (NR–NR)	46.1 (32.2–NR)
HR (95% CI)	**0.68 (0.56–0.82)**	
Stratified log-rank *P* value*	**<0.0001**	



Median follow-up in censored patients: 42.3 months (range, 0.03–61.3)

Maturity: 39%

Also, OS benefit!

(HR 0.75; 95% CI 0.59–0.93; p=0.0106

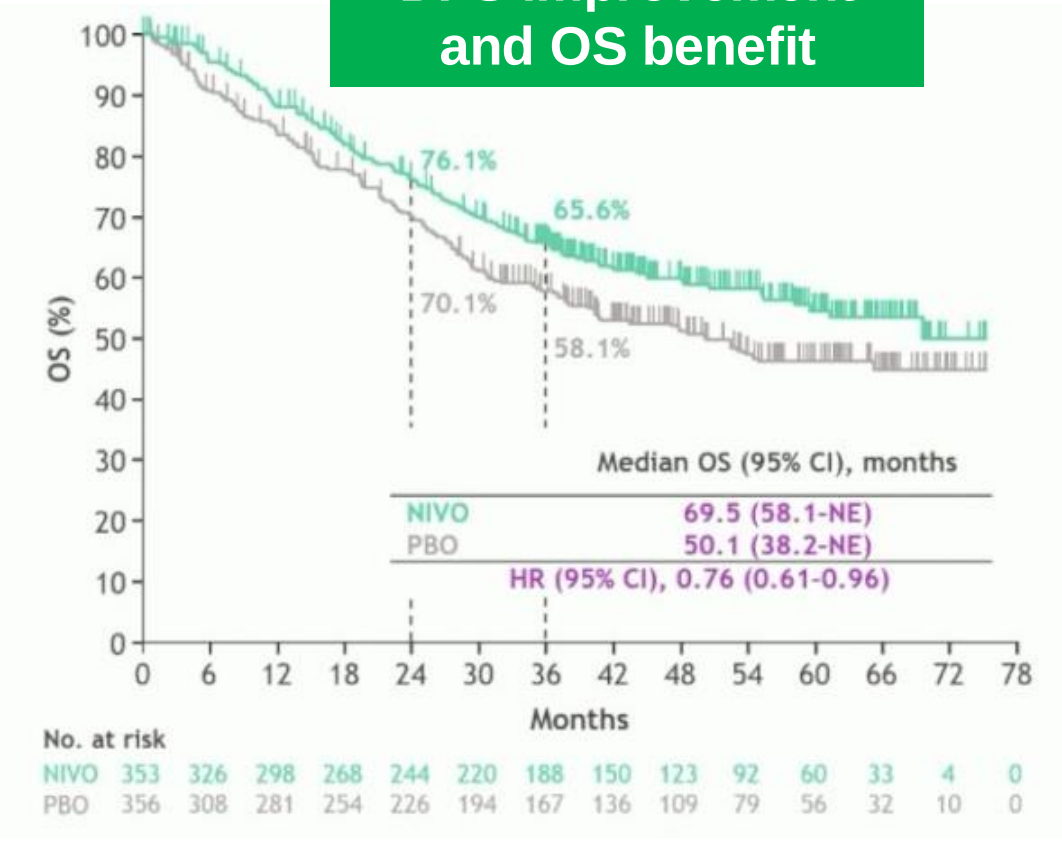
EFS was assessed using RECIST v1.1. EFS is defined as the time from randomisation to the first: 1) progressive disease that precluded RC; 2) recurrence after RC; 3) date of expected surgery in patients who did not undergo RC; 4) death from any cause.*The threshold to declare statistical significance was based on a Lan-DeMets alpha spending function with O'Brien-Fleming boundary – with the observed number of events, the boundary for declaring statistical significance was 0.04123 for a 4.9% overall 2-sided alpha. Data cutoff 29 Apr 2024. BICR, blinded independent central review; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; ITT, intent-to-treat population; NR, not reached; RC, radical cystectomy; RECIST, Response Evaluation Criteria In Solid Tumors.

Powles TB, et al. ESMO Congress 2024, LBA5

Urothelial Cancer: Adjuvant IO Therapies?

EAU 2024

CheckMate 274
DFS improvement and OS benefit



However:

AMBASSADOR (pembrolizumab) DFS improvement No OS benefit

IMvigor010 (atezolizumab) No DFS or OS improvement

Thank You!

Questions: nmitsiades@ucdavis.edu

(and Many Thanks to Dr Shuchi Gulati)