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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**

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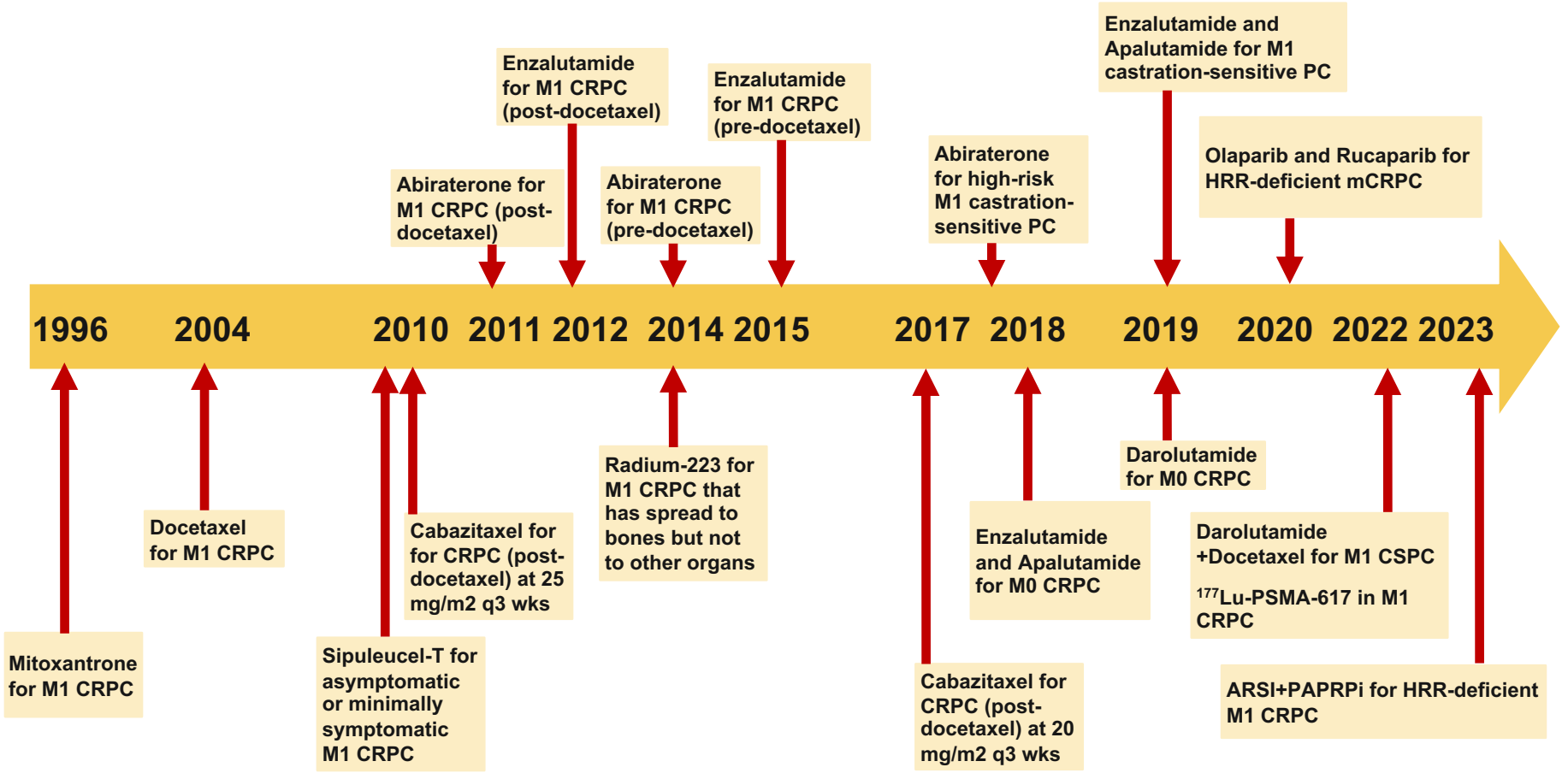
Timeline of FDA approvals in Prostate Cancer



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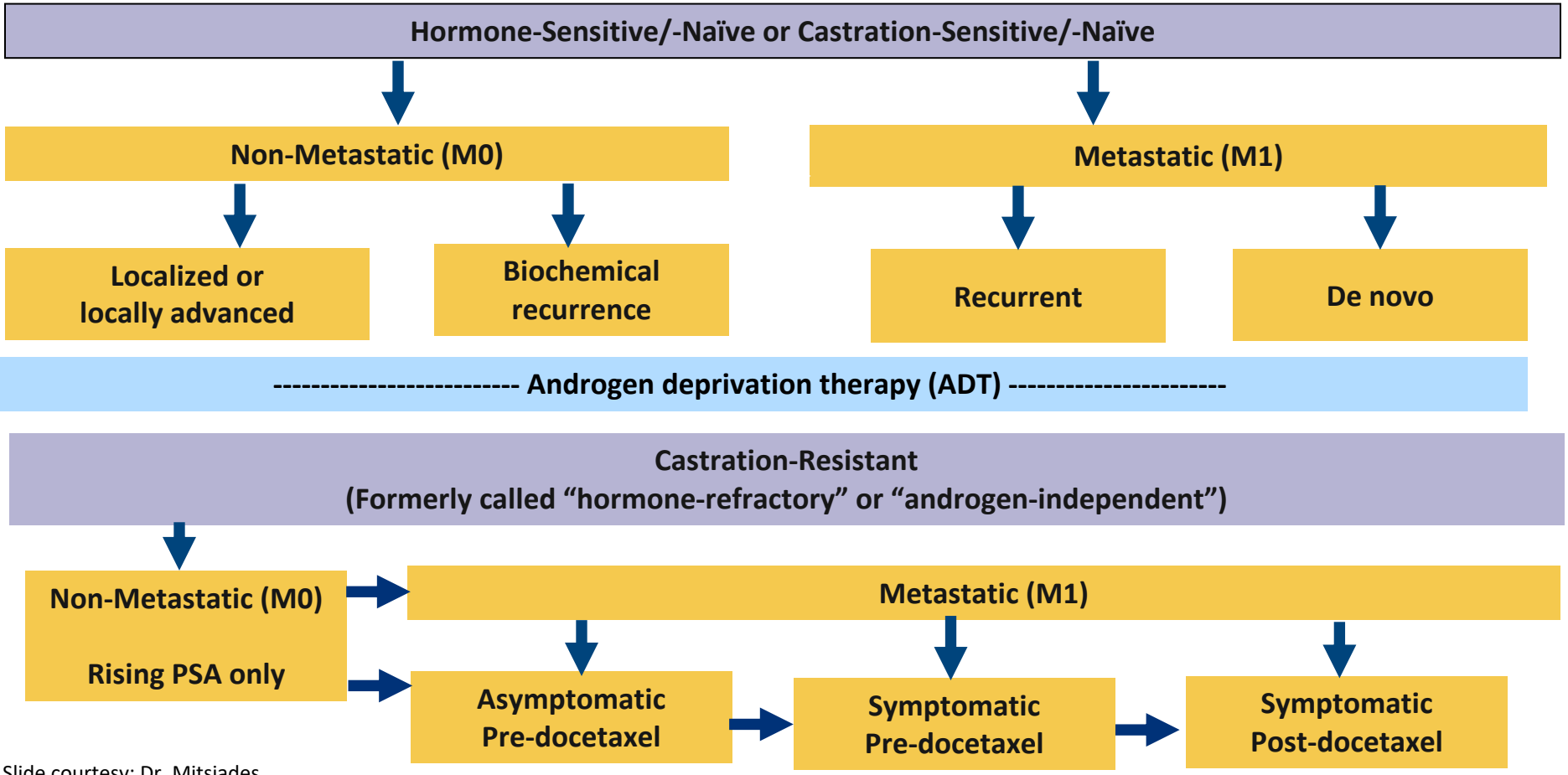
Prostate Cancer Disease States



Slide courtesy: Dr. Mitsiades

Enhancing frontline ADT: a) Docetaxel

M1 Disease

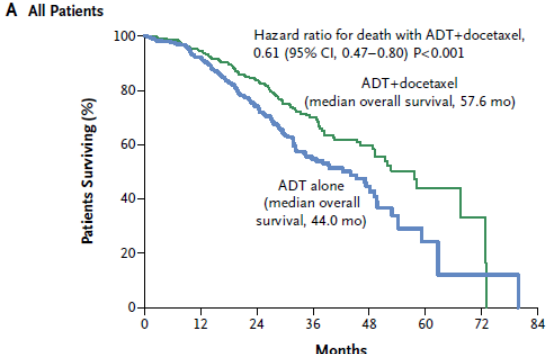
OS Hazard Ratio (HR)	
CHAARTED[a]	**0.61 (0.47-0.80)**
STAMPEDE[b]	**0.76 (0.62-0.93)**
GETUG-15[c]	0.90 (0.69-1.81)
Failure-free survival HR	
CHAARTED[a]	**0.61 (0.51-0.73)**
STAMPEDE[b]	**0.61 (0.53-0.71)**
GETUG-15[c]	**0.70 (0.57-0.86)**

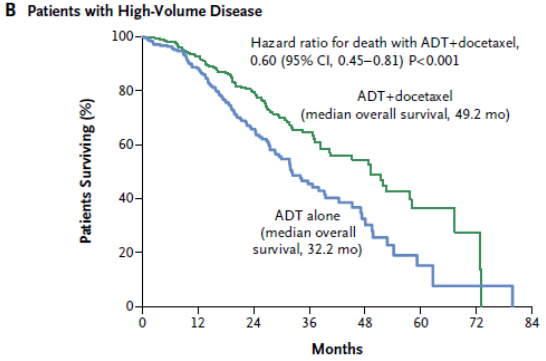
M0 Disease

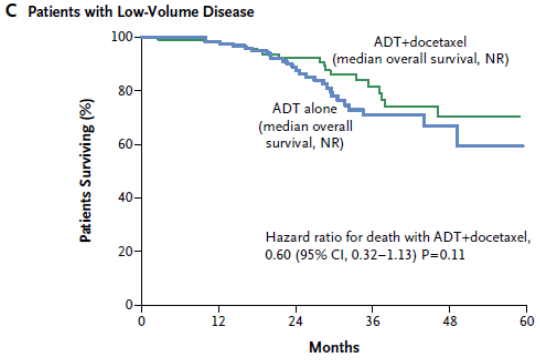
OS HR	
STAMPEDE[b]	0.95 (0.62-1.46)
GETUG-12[d]	0.94 (0.60-1.48)
Failure-free survival	
STAMPEDE[b]	**0.60 (045-0.80)**
GETUG-12[d]	**0.71 (0.54-0.94)**

(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.

CHAARTED: ADT + 6 cycles of Docetaxel





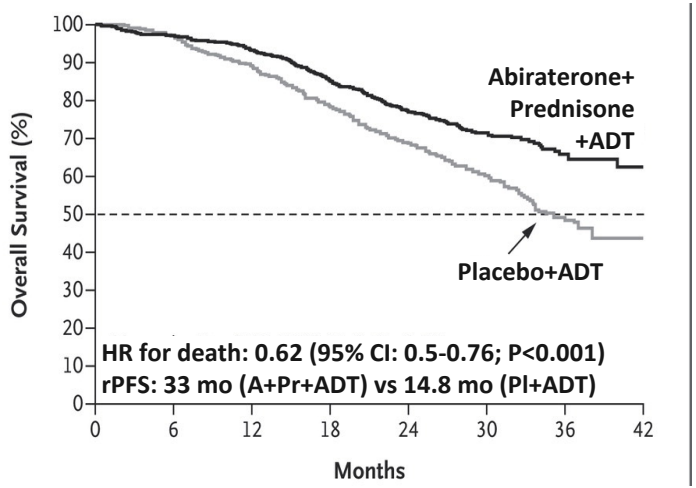


Stratification: high vs. low volume metastasis (high volume: visceral metastases OR four or more bone lesions with at least one beyond the vertebral bodies and pelvis)

CJ Sweeney, et al. N Engl J Med, 373 (2015), pp. 737-746

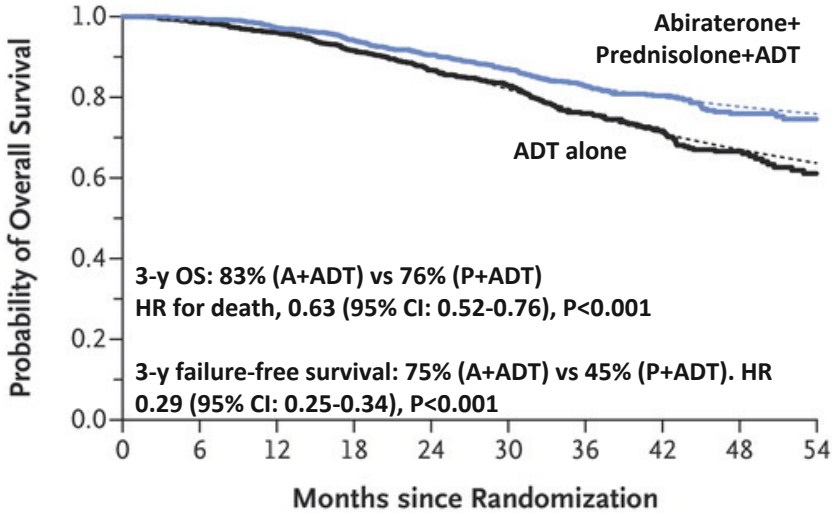
Enhancing frontline ADT: b) Abiraterone

LATITUDE



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

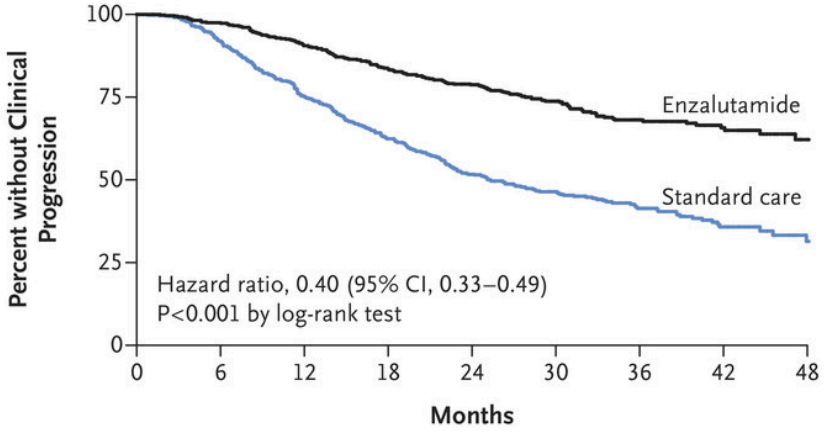
STAMPEDE (arm G)

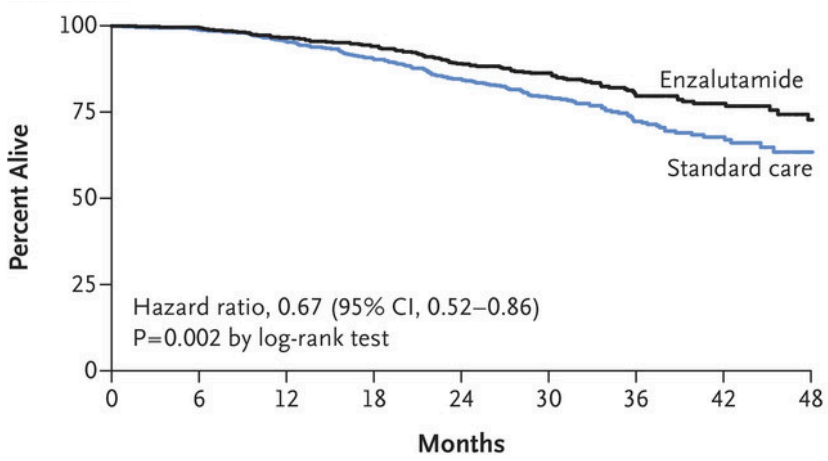


Patients had M1 disease (52%), N1 (or indeterminate) M0 disease (20%), and N0M0 disease (28%). XRT was mandatory for N0M0 and optional for N1M0 disease.

Enhancing frontline ADT: c) Enzalutamide

ENZAMET



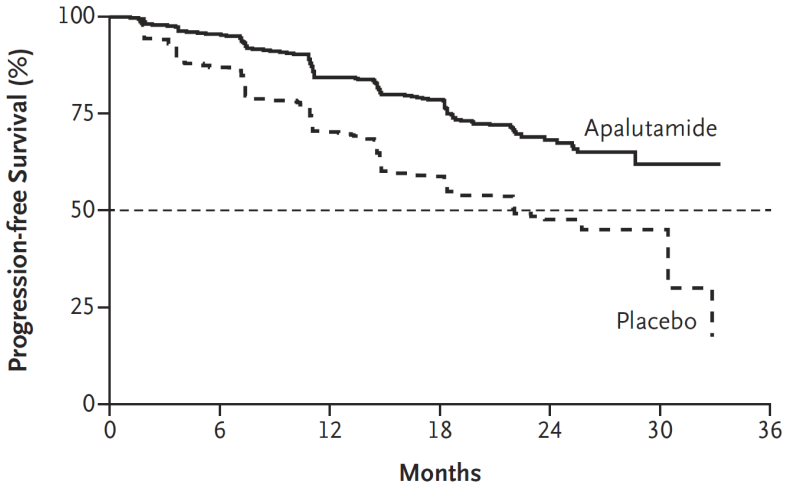


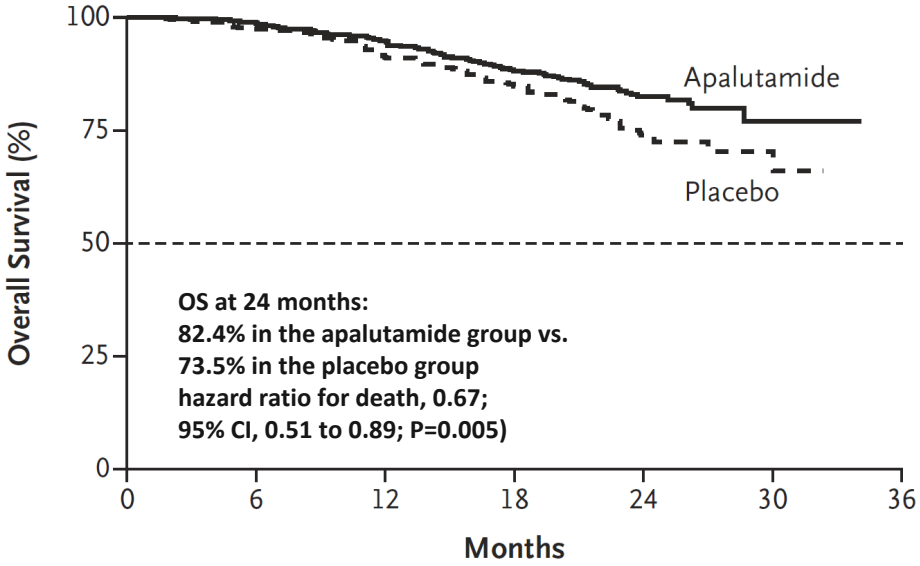
High-volume disease in 52% of the patients
The results were unaffected by adjustments for volume of disease and use of early docetaxel

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

Enhancing frontline ADT: d) Apalutamide

TITAN



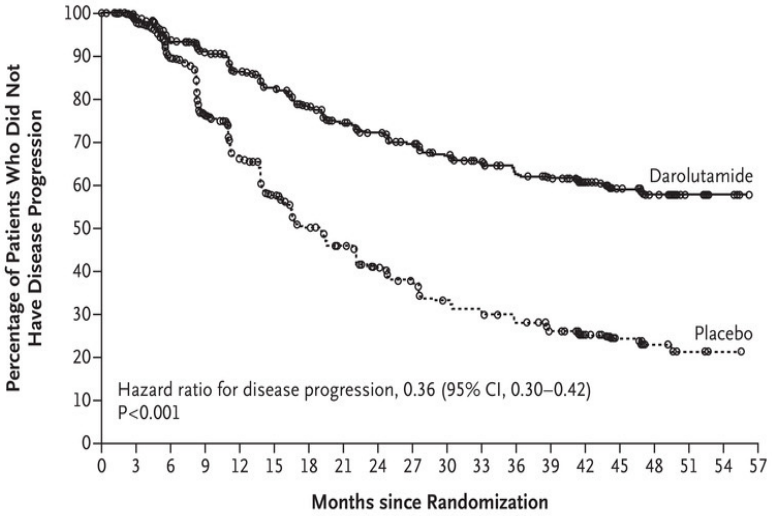


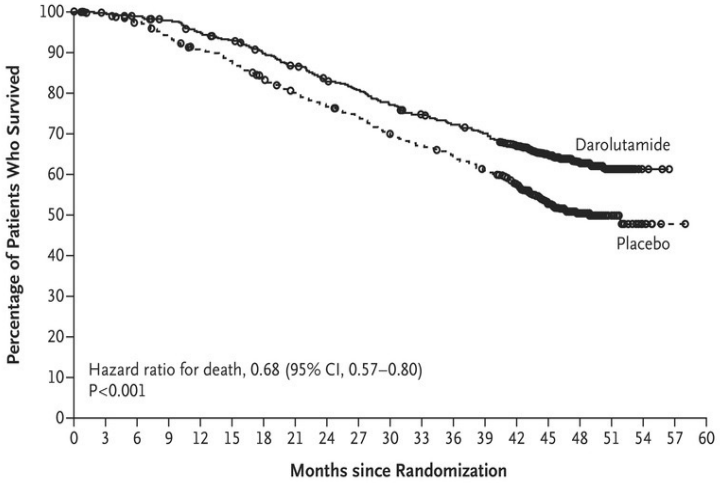
62.7% had high-volume disease, and 37.3% had low-volume disease
10.7% had received previous docetaxel therapy

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

Enhancing frontline ADT: e) Darolutamide + Docetaxel

ARASENS





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

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Summary and Thoughts on augmenting frontline ADT

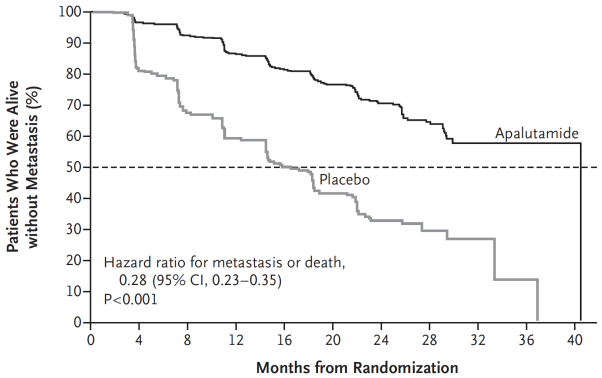
- Several options for M1 CSPC: ADT+Docetaxel (high volume disease), ADT+Abi, ADT+Enza, ADT+Apa and ADT+darolutamide+docetaxel

- 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.

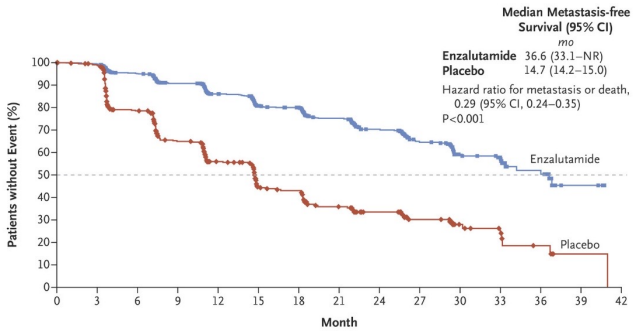
CRPC: Non-metastatic (PSA only)

SPARTAN



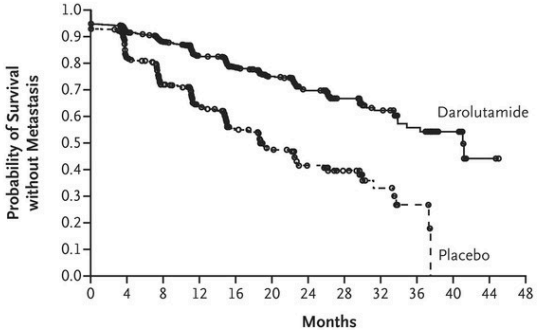
APALUTAMIDE*

PROSPER



ENZALUTAMIDE*

ARAMIS



DAROLUTAMIDE

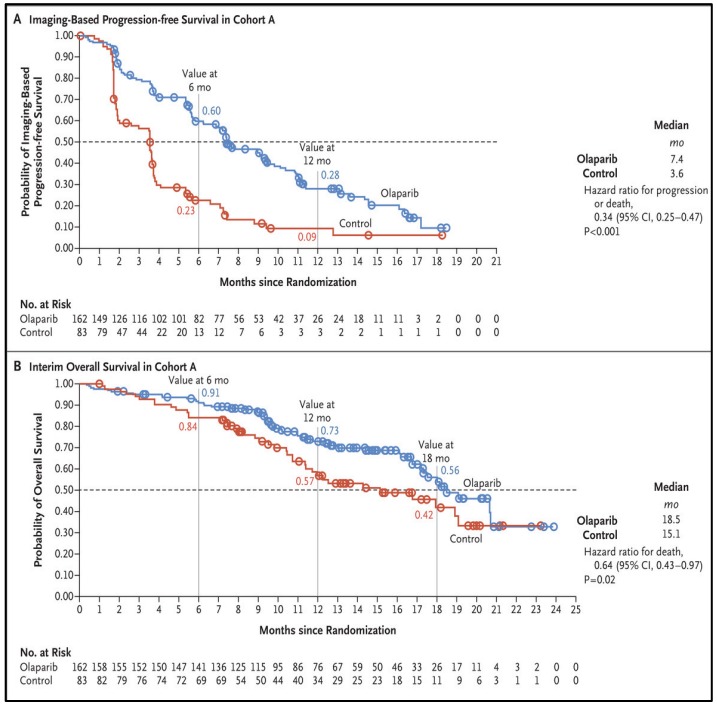
Significant fracture risk in both studies *
11.7% (apalutamide) vs. 6.5% (placebo) / 10% (enzalutamide) vs. 5% (placebo)

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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Guidelines and FDA approvals for single-agent PARP inhibitors in PC

- **Olaparib** is a treatment option for patients with mCRPC and a pathogenic mutation (germline and/or somatic) in a homologous recombination repair gene, **who have previously been treated with ADT.**

- Patients with **PPP2R2A mutations in the PROfound trial experienced an unfavorable risk-benefit profile. Therefore, olaparib is not recommended in patients with a PPP2R2A mutations.**

- FDA approval 5/15/2020: **Rucaparib** for mCRPC with BRCA mutation (germline and/or somatic) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy.

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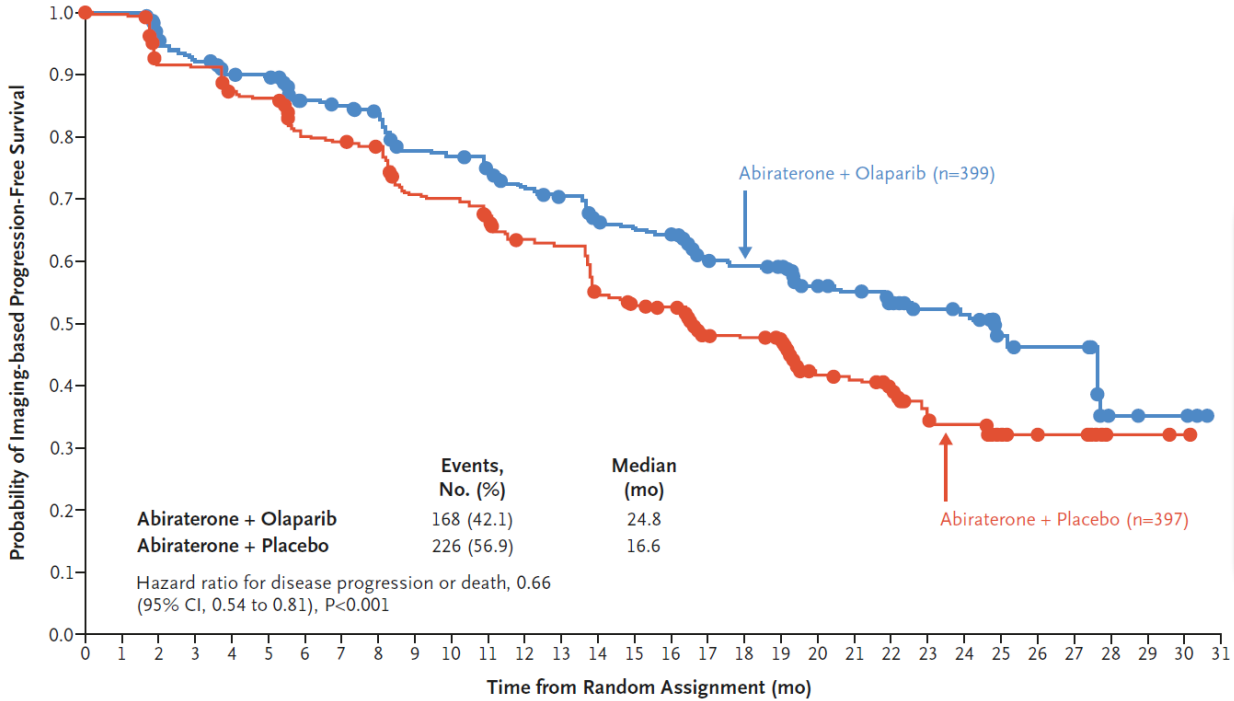
Do HRR-wild type PCs benefit from PARPis + ARSI?



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

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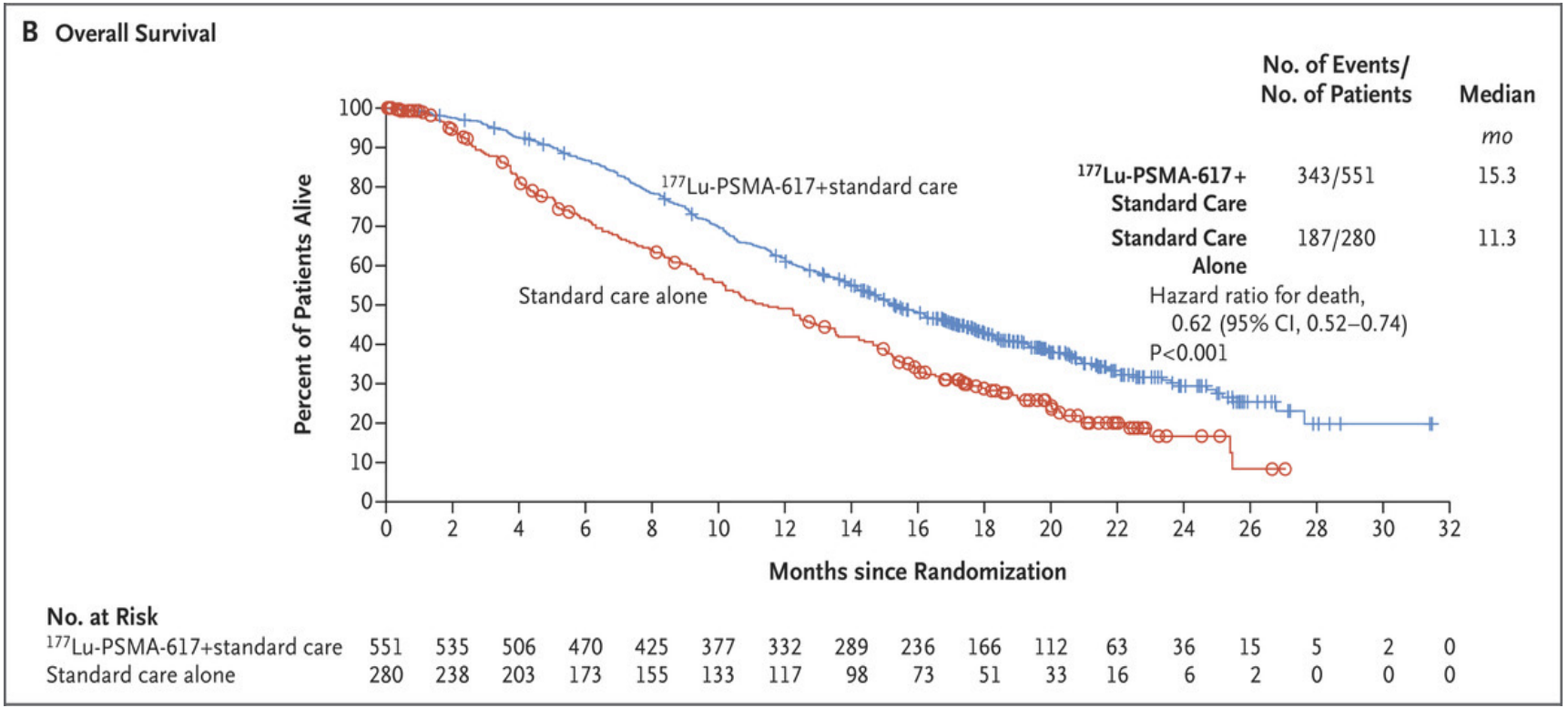
177Lu-PSMA-617 in mCRPC

VISION



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

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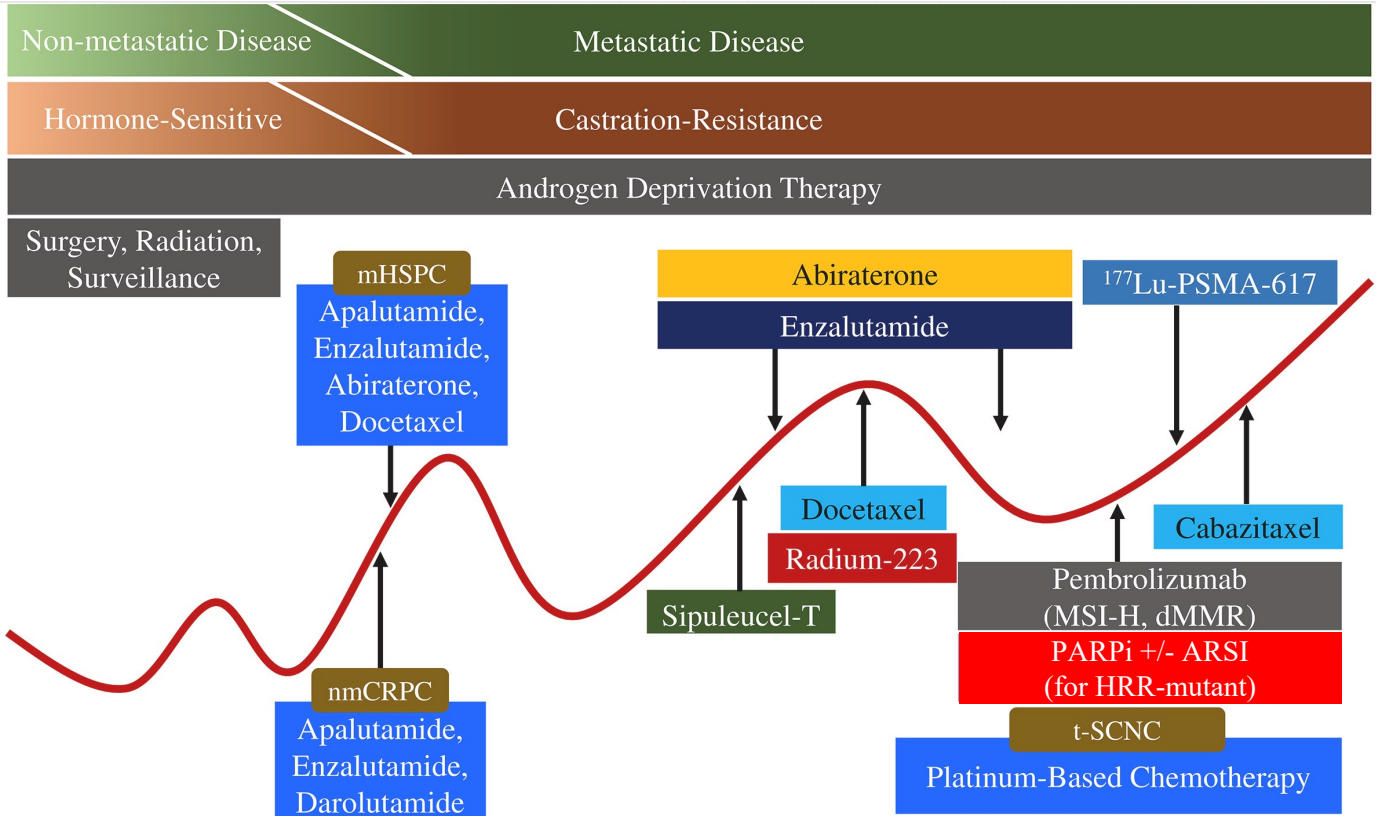
Summary



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

Presentation Outline

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

International Metastatic Database Consortium Risk Stratification

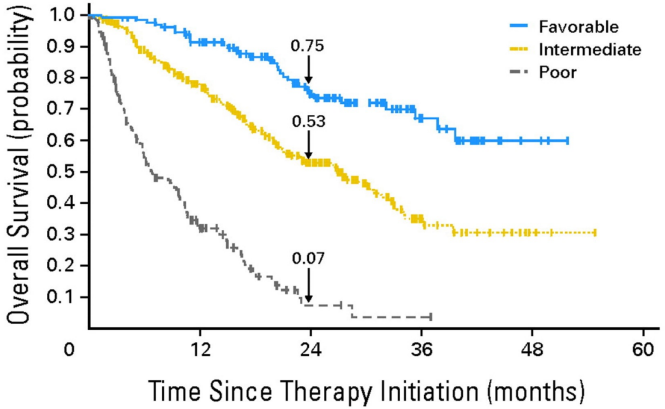
- **Clinical**

- Karnofsky Performance Status <80%
- Time from diagnosis to treatment <1 year

- **Laboratory**

- Hemoglobin <LLN
- Calcium > ULN
- Neutrophil count > ULN

- Platelet count > ULN

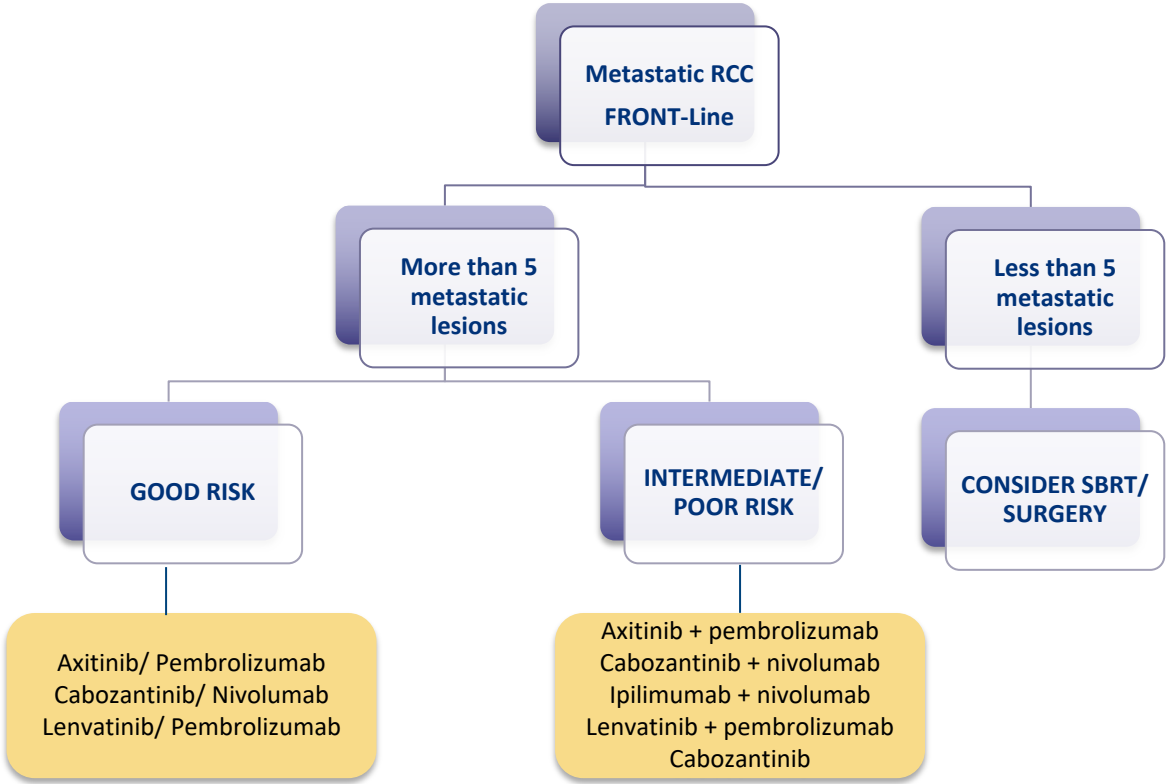


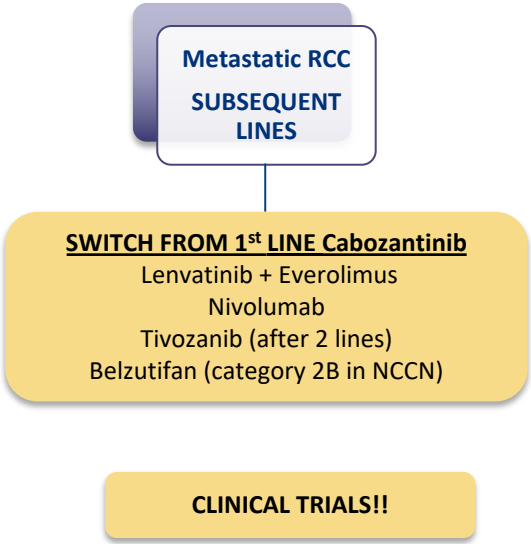
No. of events/No. at risk					
Favorable	11/133	16/110	4/62	2/22	0/3
Intermediate	61/301	50/182	17/82	2/18	0/3
Poor	94/152	19/36	1/3	0/1	0/0

Favorable: 0 risk factors → means slow-growing and/or VEGF-responsive
Intermediate: 1-2 risk factors → medium growth rate and somewhat VEGF- responsive
Poor: 3-6 risk factors → fast-growing and VEGF-unresponsive

Heng DYC, et al. *J Clin Oncol*. 2009;27(34):5794-9.

Metastatic Kidney Cancer: TREATMENT LANDSCAPE





NCCN [nccn.org]

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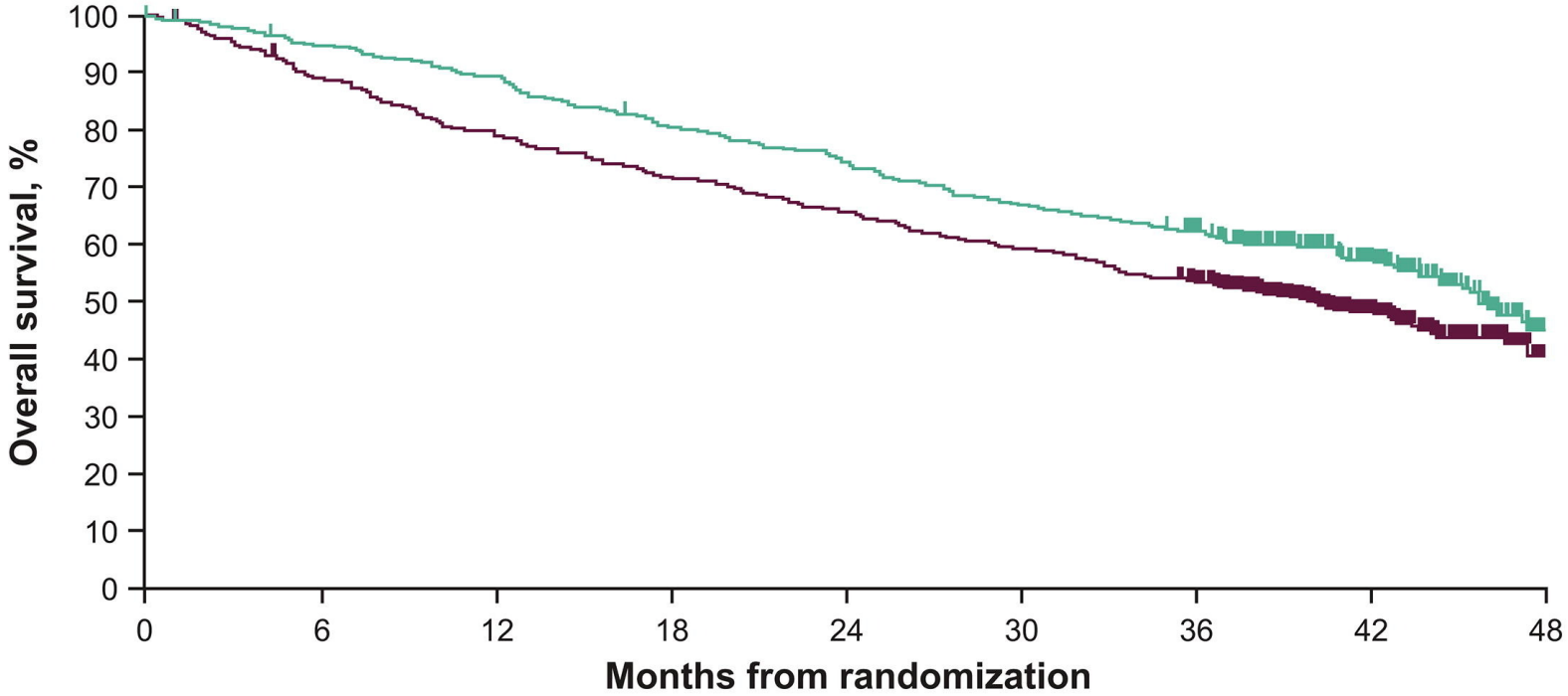
KEYNOTE-426: Pembrolizumab plus Axitinib versus Sunitinib



No. at risk

432	407	384	345	318	286	259	141	16
429	379	336	306	279	252	224	110	12

Plimack ER, et al. Eur Urol. 2023 Nov;84(5):449-454.

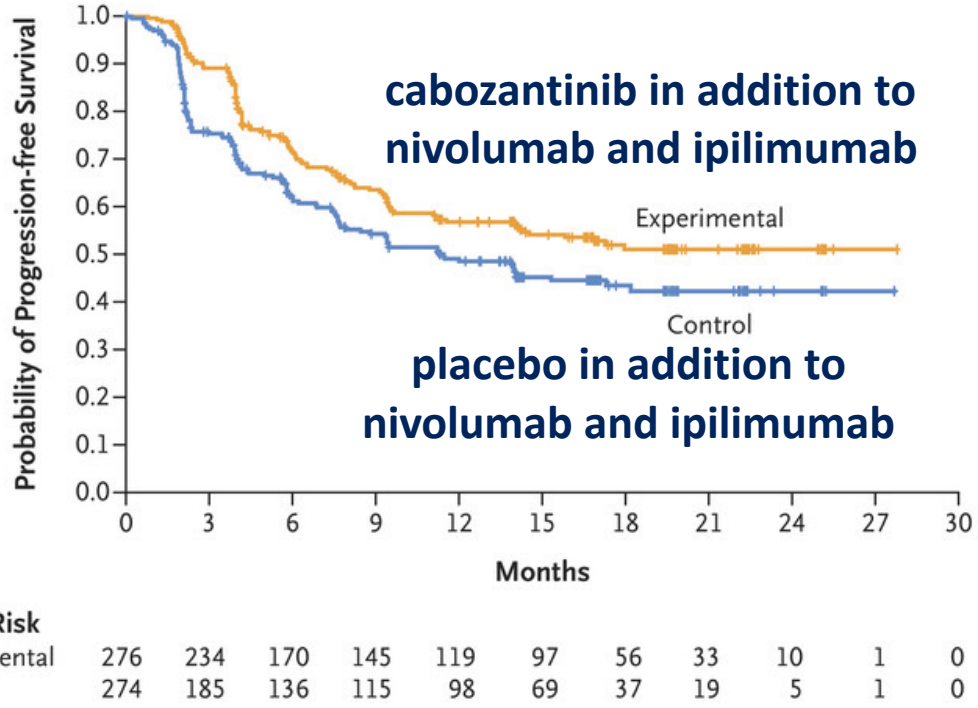
KEYNOTE-426: Pembrolizumab plus Axitinib versus Sunitinib

Conclusions

- KEYNOTE-426 represents the longest follow-up to date of the combination of a checkpoint inhibitor plus a VEGFR TKI for first-line clear cell RCC
- Pembrolizumab plus axitinib continued to demonstrate improved OS, PFS, and ORR versus sunitinib for patients with previously untreated clear cell RCC
  - Benefit was observed despite a greater proportion of patients in the sunitinib arm receiving subsequent therapy, including predominantly PD-1/L1 inhibitors, and more lines of therapy
- A substantial percentage of patients completed 35 cycles of pembrolizumab with good long-term outcomes
- These data continue to support pembrolizumab + axitinib as a standard of care for patients with previously untreated advanced clear cell RCC

Plimack ER, et al. Eur Urol. 2023 Nov;84(5):449-454.

Kidney Cancer: METASTATIC TRIPLET OR DOUBLET: COSMIC 313



	No. of Patients	No. of Events	Median Progression-free Survival
			mo
Experimental	276	116	NR (14.0–NE)
Control	274	133	11.3 (7.7–18.2)

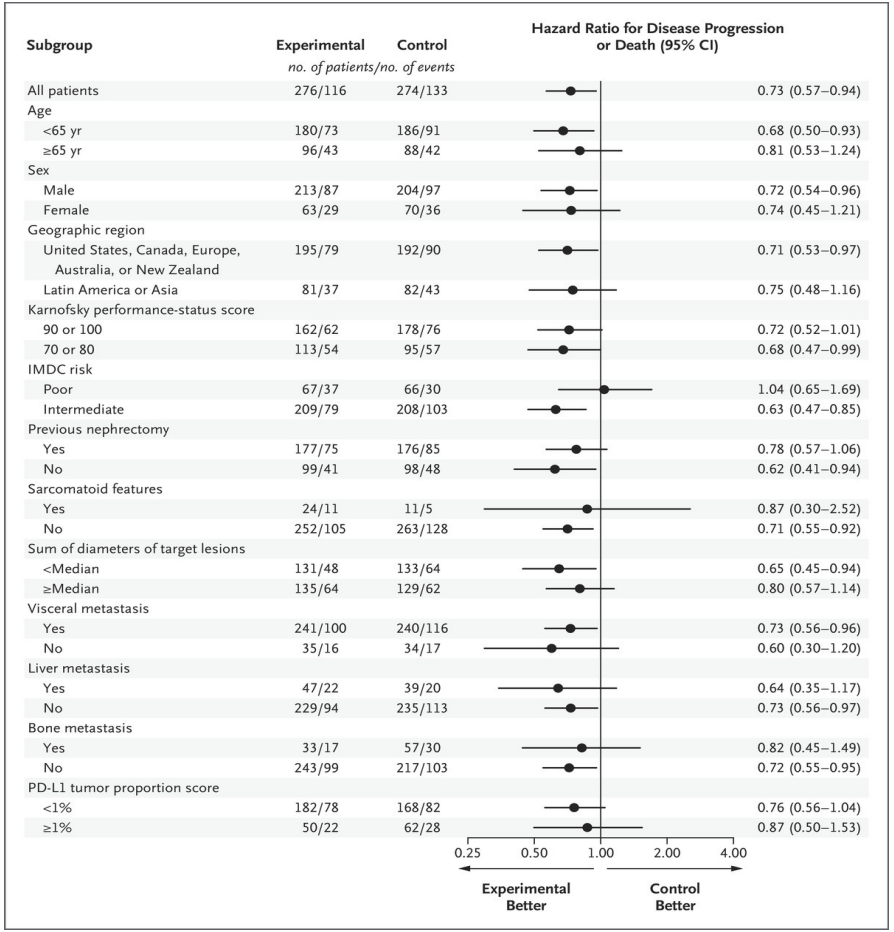
Hazard ratio for disease progression or death, 0.73 (95% CI, 0.57–0.94)
P=0.01

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

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

Kidney Cancer: METASTATIC TRIPLET OR DOUBLET: COSMIC 313

PFS in Prespecified Subgroups



Subgroup	Experimental	Control	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients/no. of events		
All patients	276/116	274/133	0.73 (0.57–0.94)
Age			
<65 yr	180/73	186/91	0.68 (0.50–0.93)
≥65 yr	96/43	88/42	0.81 (0.53–1.24)
Sex			
Male	213/87	204/97	0.72 (0.54–0.96)
Female	63/29	70/36	0.74 (0.45–1.21)
Geographic region			
United States, Canada, Europe, Australia, or New Zealand	195/79	192/90	0.71 (0.53–0.97)
Latin America or Asia	81/37	82/43	0.75 (0.48–1.16)
Karnofsky performance-status score			
90 or 100	162/62	178/76	0.72 (0.52–1.01)
70 or 80	113/54	95/57	0.68 (0.47–0.99)
IMDC risk			
Poor	67/37	66/30	1.04 (0.65–1.69)
Intermediate	209/79	208/103	0.63 (0.47–0.85)
Previous nephrectomy			
Yes	177/75	176/85	0.78 (0.57–1.06)
No	99/41	98/48	0.62 (0.41–0.94)
Sarcomatoid features			
Yes	24/11	11/5	0.87 (0.30–2.52)
No	252/105	263/128	0.71 (0.55–0.92)
Sum of diameters of target lesions			
<Median	131/48	133/64	0.65 (0.45–0.94)
≥Median	135/64	129/62	0.80 (0.57–1.14)
Visceral metastasis			
Yes	241/100	240/116	0.73 (0.56–0.96)
No	35/16	34/17	0.60 (0.30–1.20)
Liver metastasis			
Yes	47/22	39/20	0.64 (0.35–1.17)
No	229/94	235/113	0.73 (0.56–0.97)
Bone metastasis			
Yes	33/17	57/30	0.82 (0.45–1.49)
No	243/99	217/103	0.72 (0.55–0.95)
PD-L1 tumor proportion score			
<1%	182/78	168/82	0.76 (0.56–1.04)
≥1%	50/22	62/28	0.87 (0.50–1.53)

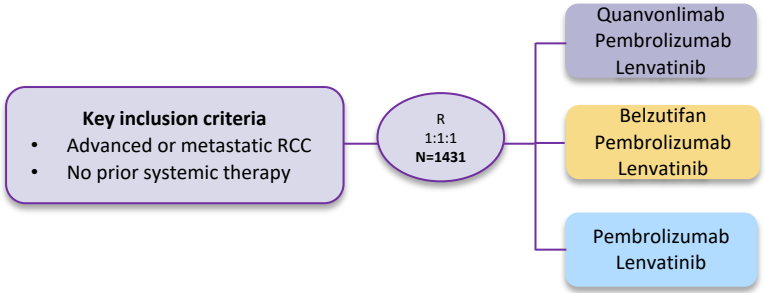
TK Choueiri et al. N Engl J Med 2023;388:1767-1778.

Kidney Cancer: METASTATIC TRIPLET OR DOUBLET: COSMIC 313

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

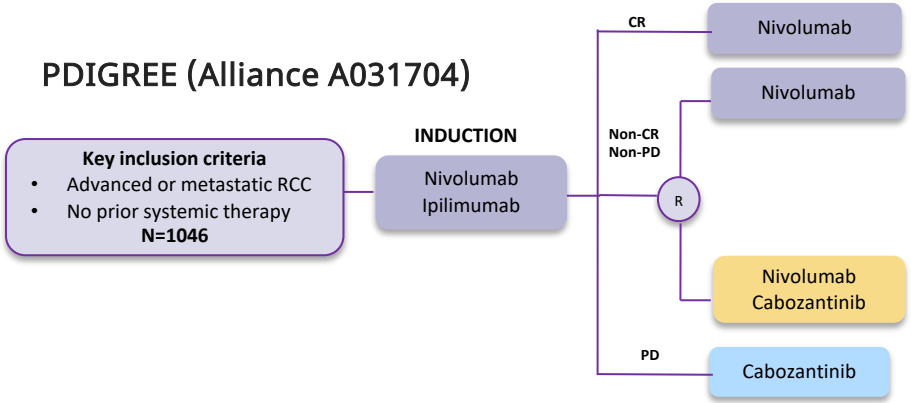
Metastatic Kidney Cancer: Next Steps (Trials)

- Trials evaluating other Triplets

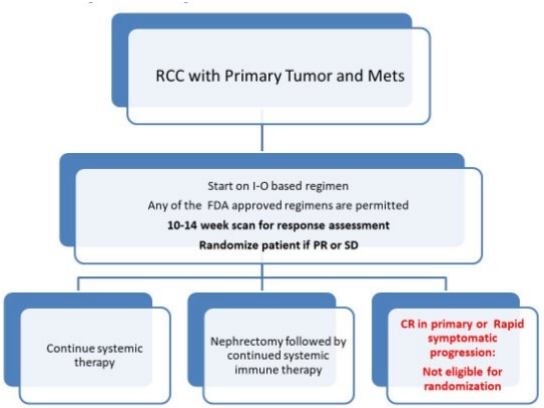


- Trials evaluating a "Risk-Adapted" Approach

PDIGREE (Alliance A031704)



PROBE (SWOG S1931)

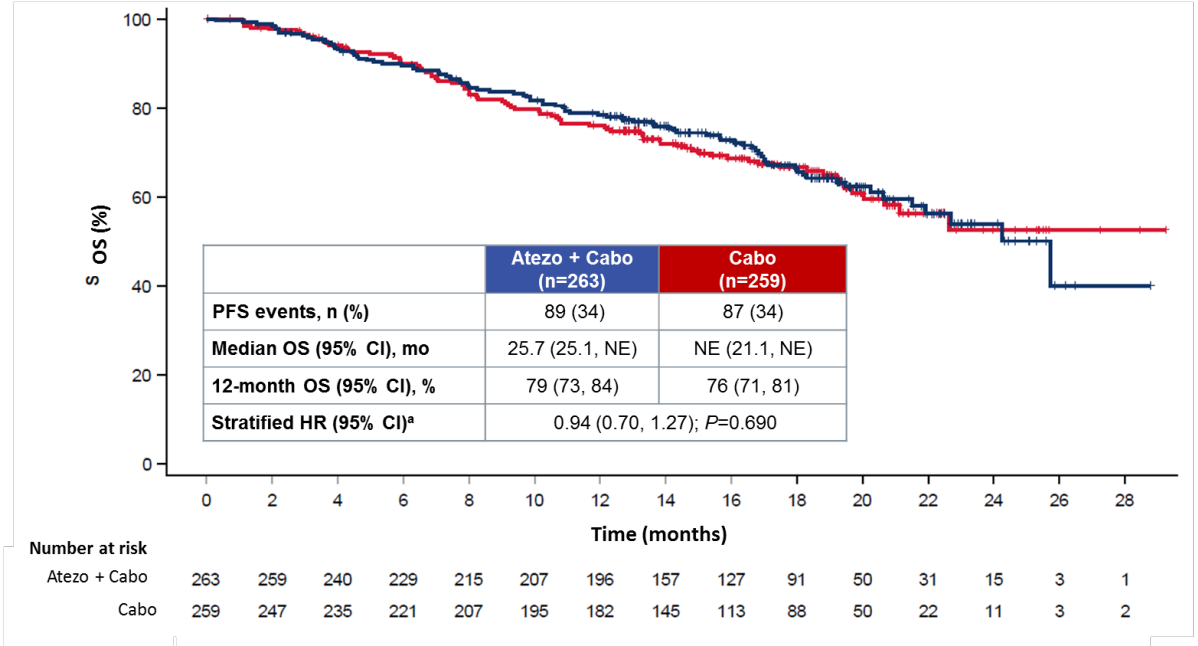


Choueiri, et al. Poster presented at: GU ASCO 2022
Zhang et al. Poster presented at GU ASCO 2022
Vaishampayan. Poster presented at GU ASCO 2022

Kidney Cancer: 2L therapy after ICI ?

- The introduction of ICIs as 1L treatment has led to questions around optimal 2L therapy.
- CONTACT-03 compared the efficacy of atezolizumab (anti–PD-L1) plus cabozantinib vs cabozantinib alone in the post-ICI setting in patients with mRCC.

Interim analysis of OS (primary endpoint)



	Atezo + Cabo (n=263)	Cabo (n=259)
PFS events, n (%)	89 (34)	87 (34)
Median OS (95% CI), mo	25.7 (25.1, NE)	NE (21.1, NE)
12-month OS (95% CI), %	79 (73, 84)	76 (71, 81)
Stratified HR (95% CI)[a]	0.94 (0.70, 1.27); *P*=0.690	

Kidney Cancer: 2L therapy after ICI ?

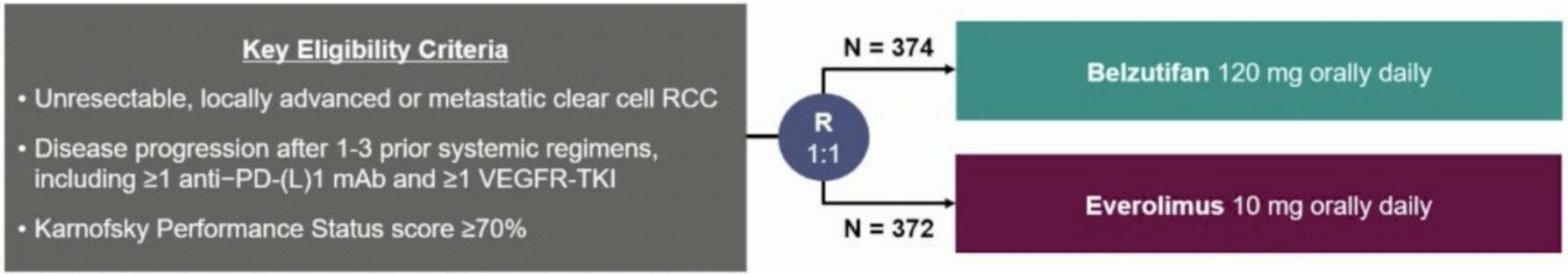
Atezolizumab plus cabozantinib versus cabozantinib monotherapy for patients with renal cell carcinoma after progression with previous immune checkpoint inhibitor treatment (CONTACT-03): a multicentre, randomised, open-label, phase 3 trial

Sumanta Kumar Pal, Laurence Albiges, Piotr Tomczak, Cristina Suárez, Martin H Voss, Guillermo de Velasco, Jad Chahoud, Anastasia Mochalova, Giuseppe Procopio, Hakim Mahammedi, Friedemann Zengerling, Chan Kim, Takahiro Osawa, Martín Angel, Suyasha Gupta, Omara Khan, Guillaume Bergthold, Bo Liu, Melania Kalaitzidou, Mahrukh Huseni, Christian Scheffold, Thomas Powles, Toni K Choueiri

"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."

Belzutifan as 2L therapy after ICI (Phase III)

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:

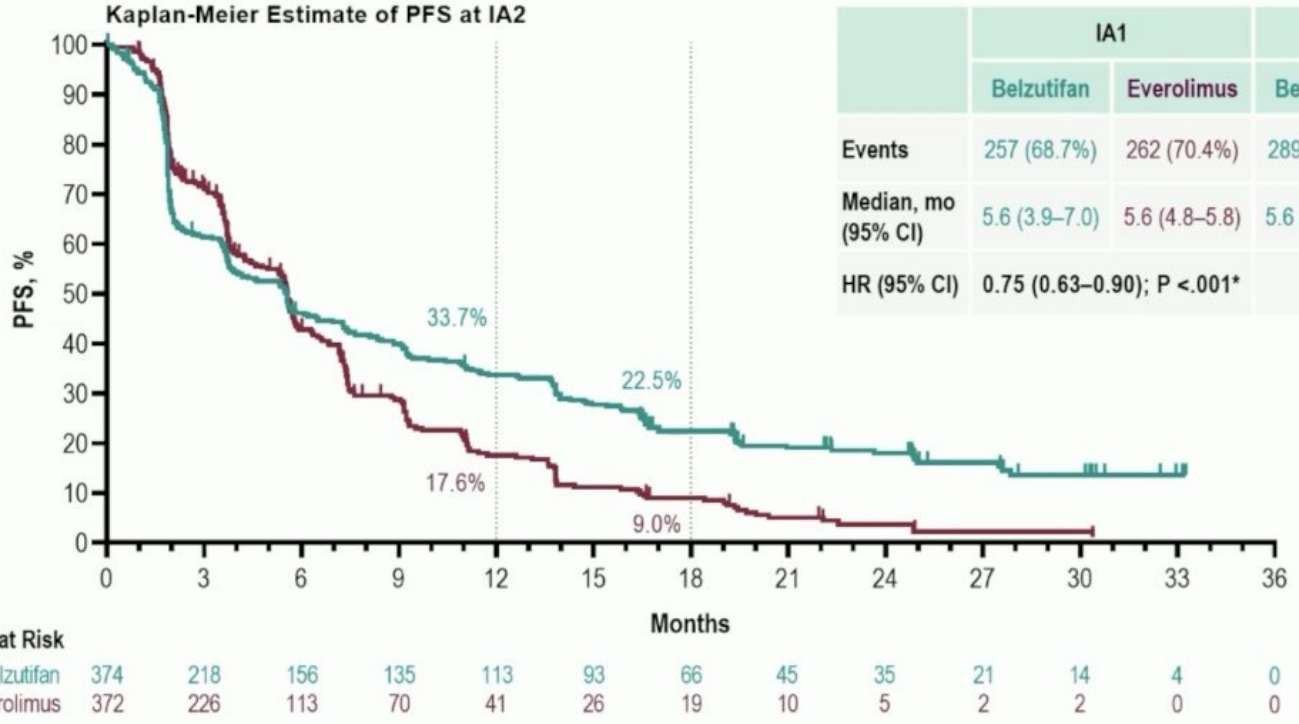
- ORR per RECIST 1.1 by BICR

Other Secondary Endpoints Include:

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

Belzutifan as 2L therapy after ICI (Phase III)

Primary Endpoint: PFS per RECIST 1.1 by BICR



	IA1		IA2	
	Belzutifan	Everolimus	Belzutifan	Everolimus
Events	257 (68.7%)	262 (70.4%)	289 (77.3%)	276 (74.2%)
Median, mo (95% CI)	5.6 (3.9–7.0)	5.6 (4.8–5.8)	5.6 (3.8–6.5)	5.6 (4.8–5.8)
HR (95% CI)	0.75 (0.63–0.90); P <.001*		0.74 (0.63–0.88)	

* denotes statistical significance. Primary PFS endpoint was met at IA1 and was not formally statistically tested at IA2. Data cutoff date for IA1: November 1, 2022. Data cutoff date for IA2: June 13, 2023.

ESMO 2023: LBA87

Belzutifan as 2L therapy after ICI (Phase III)

PFS by BICR per RECIST 1.1 in Subgroups

	Events/Participants	Hazard Ratio (95% CI)
Overall	565/746	0.74 (0.63-0.88)
Age		
<65 years	328/433	0.82 (0.66-1.03)
≥65 years	237/313	0.65 (0.50-0.84)
Sex		
Male	448/581	0.76 (0.63-0.92)
Female	117/165	0.70 (0.49-1.02)
Race		
White	450/588	0.75 (0.62-0.91)
All others	84/121	0.67 (0.43-1.05)
Region		
North America	116/164	0.71 (0.49-1.02)
Western Europe	292/373	0.85 (0.67-1.08)
Rest of world	157/209	0.63 (0.46-0.88)
IMDC risk categories		
Favorable	111/162	0.74 (0.51-1.09)
Intermediate	382/493	0.75 (0.61-0.92)
Poor	72/91	0.67 (0.41-1.09)
# Prior VEGF/VEGFR therapies		
1	288/377	0.77 (0.61-0.98)
2-3	277/369	0.73 (0.57-0.93)
# Prior lines of therapy		
1	72/98	0.54 (0.34-0.87)
2	244/323	0.81 (0.62-1.05)
3	243/319	0.77 (0.59-1.00)

utoff date for IA2: June 13, 2023.

ESMO 2023: LBA87

Belzutifan as 2L therapy after ICI (Phase III)

Safety Summary

	Belzutifan (N = 372)	Everolimus (N = 360)
Median duration of therapy, mo (range)	7.6 (0.1–35.8)	3.9 (0.0–33.2)
All-cause AEs, n (%)	369 (99.2%)	357 (99.2%)
Grade ≥3	230 (61.8%)	225 (62.5%)
Serious	157 (42.2%)	137 (38.1%)
Led to discontinuation	22 (5.9%)	53 (14.7%)
Led to death	13 (3.5%)	19 (5.3%)
Treatment-related AEs, n (%)	331 (89.0%)	322 (89.4%)
Grade ≥3	144 (38.7%)	142 (39.4%)
Serious	49 (13.2%)	47 (13.1%)
Led to death	1 (0.3%)[a]	2 (0.6%)[b]

[a] Multiple organ dysfunction syndrome. [b] Sepsis (n = 1) and acute kidney injury (n = 1).

ESMO 2023: LBA87

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

ESMO 2023: LBA87

New combinations: LITESPARK-003 Phase 2 Study of Belzutifan+Cabozantinib

Study Design of LITESPARK-003 (NCT03634540)

Key Eligibility Criteria
- Have locally advanced or metastatic ccRCC
- Is either treatment naive or has received prior immunotherapy and ≤2 regimens for metastatic RCC
- ECOG PS 0 or 1

Cohort 1:
Treatment-naive

Belzutifan 120 mg/day PO
+
Cabozantinib 60 mg/day PO
N ≈ 50[a]

Cohort 2:
Prior immunotherapy treatment ± prior targeted treatment[b]

Belzutifan 120 mg/day PO
+
Cabozantinib 60 mg/day PO
N ≈ 50[a]

Tumor Assessments
- Week 9, then Q8W for 12 months and Q12W thereafter

End Points
- Primary: ORR per RECIST v1.1 by investigator
- Secondary: PFS, DOR, and TTR per RECIST v1.1 by investigator, OS, safety/tolerability

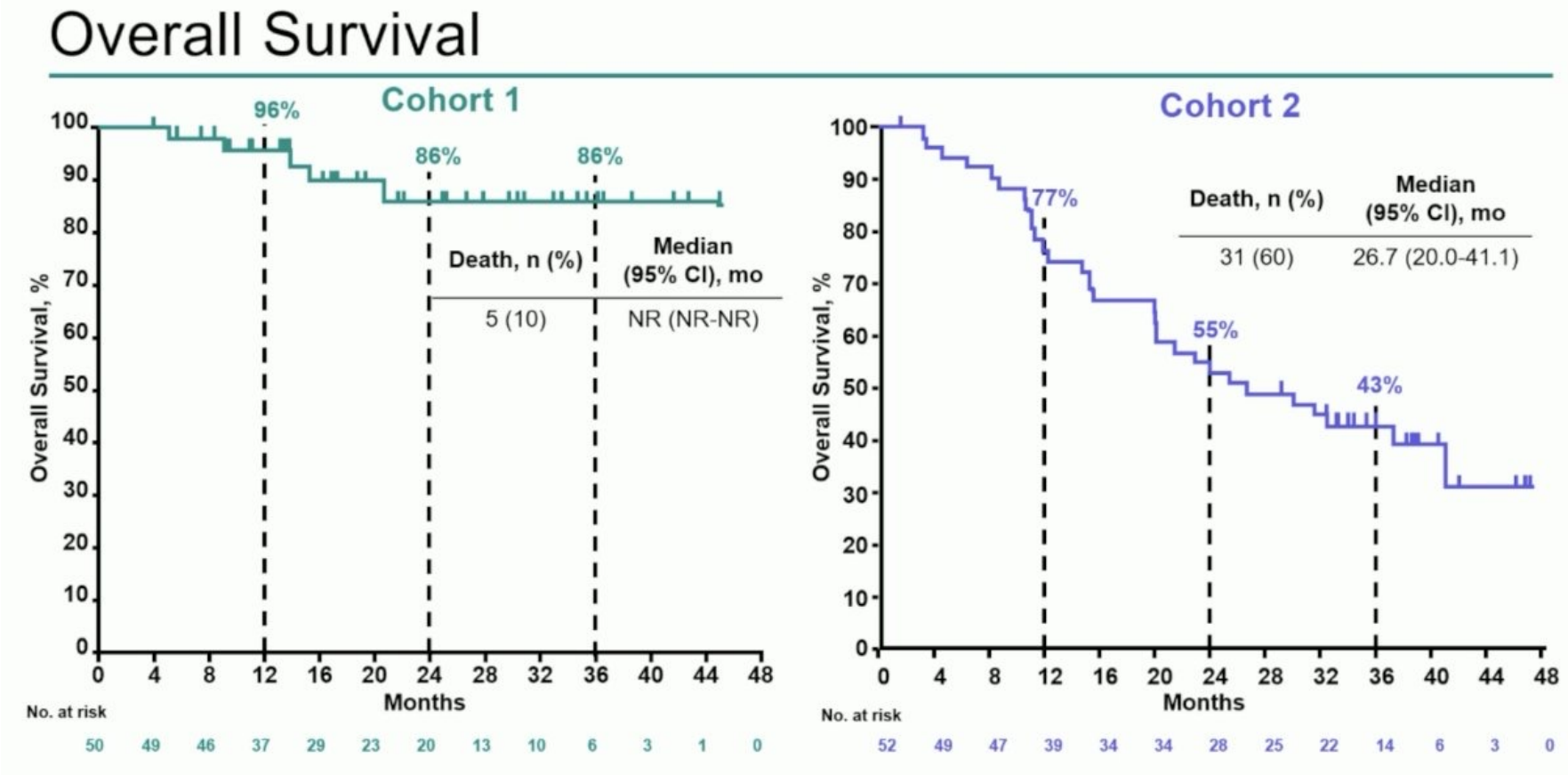
New combinations: LITESPARK-003 Phase 2 Study of Belzutifan+Cabozantinib

ORR by Investigator in All Patients and by IMDC Risk

	Cohort 1			Cohort 2		
	Overall N = 50	IMDC risk category		Overall N = 52	IMDC risk category	
		Favorable n = 28	Intermediate/ poor n = 22		Favorable n = 11	Intermediate/ poor n = 41
ORR (CR + PR)	**35 (70)**	22 (79)	13 (59)	**16 (31)**	3 (27)	13 (32)
DCR (CR + PR + SD)	49 (98)	28 (100)	21 (96)	48 (92)	11 (100)	37 (90)
Best response						
CR	4 (8)	3 (11)	1 (5)	2 (4)	0	2 (5)
PR	31 (62)	19 (68)	12 (55)	14 (27)	3 (27)	11 (27)
SD	14 (28)	6 (21)	8 (36)	32 (62)	8 (73)	24 (59)
PD	1 (2)	0 (0)	1 (5)	3 (6)	0 (0)	3 (7)
Not available[a]	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	1 (2)

ESMO 2023: LBA87

New combinations: LITESPARK-003 Phase 2 Study of Belzutifan+Cabozantinib



ESMO 2023: LBA87

New combinations: LITESPARK-003 Phase 2 Study of Belzutifan+Cabozantinib

Summary of Treatment-Related Adverse Events

	Cohort 1 N = 50	Cohort 2 N = 52
Any-grade treatment-related AE	50 (100)	51 (98)
Grade ≥3 treatment-related AE	23 (46)	33 (64)
Grade 5 treatment-related AE	0 (0)	1 (2)[a]
Discontinued any drug because of a treatment-related AE	7 (14)	11 (21)
Serious treatment-related AE	7 (14)	16 (31)
Dose reduction because of a treatment-related AE	38 (76)	37 (71)

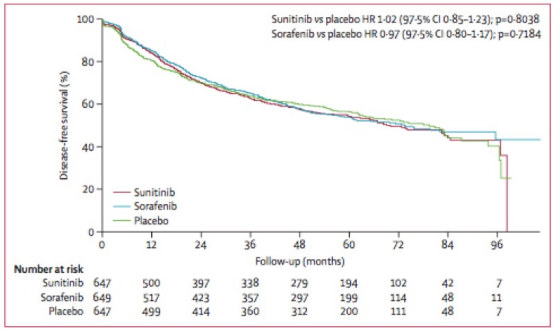
ESMO 2023: LBA87

Kidney Cancer: Perioperative Management

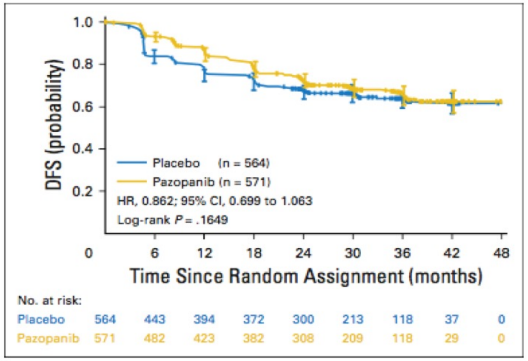
- Remains controversial in 2023!
- Rapidly evolving landscape
- Identification of patients most likely to benefit remains a challenge (no biomarkers)

Perioperative Management: VEGF-TKI Trials

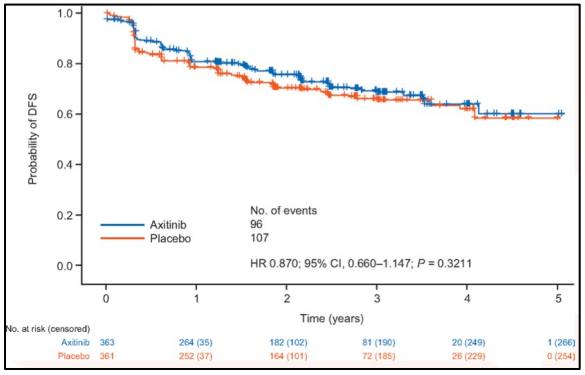
ASSURE DFS



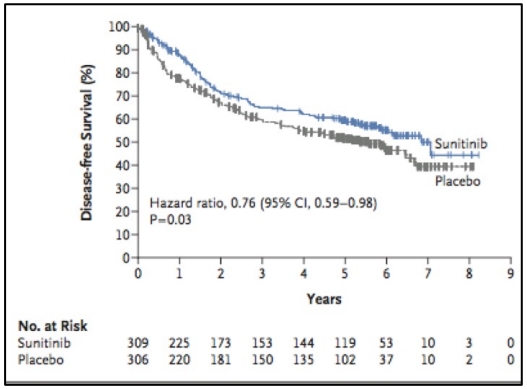
PROTECT DFS



ATLAS DFS



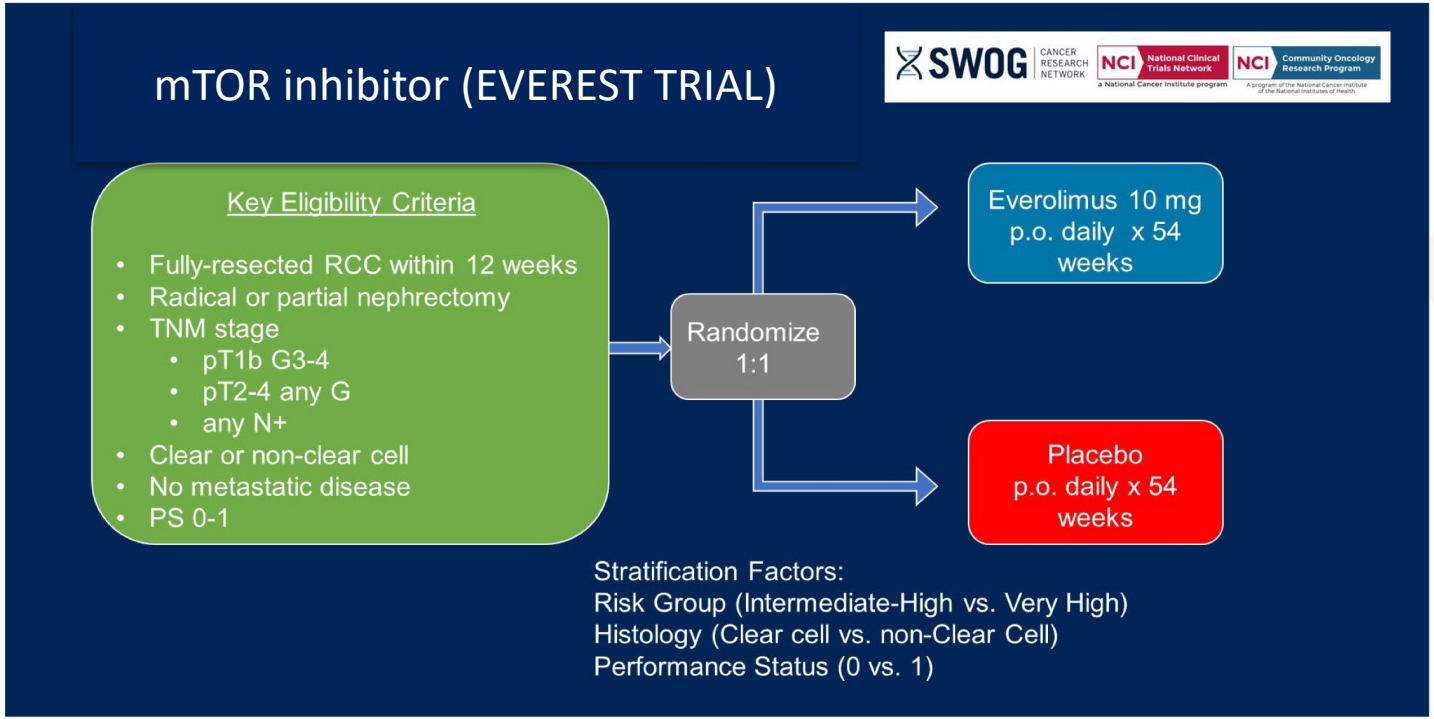
S-TRAC DFS



- 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.

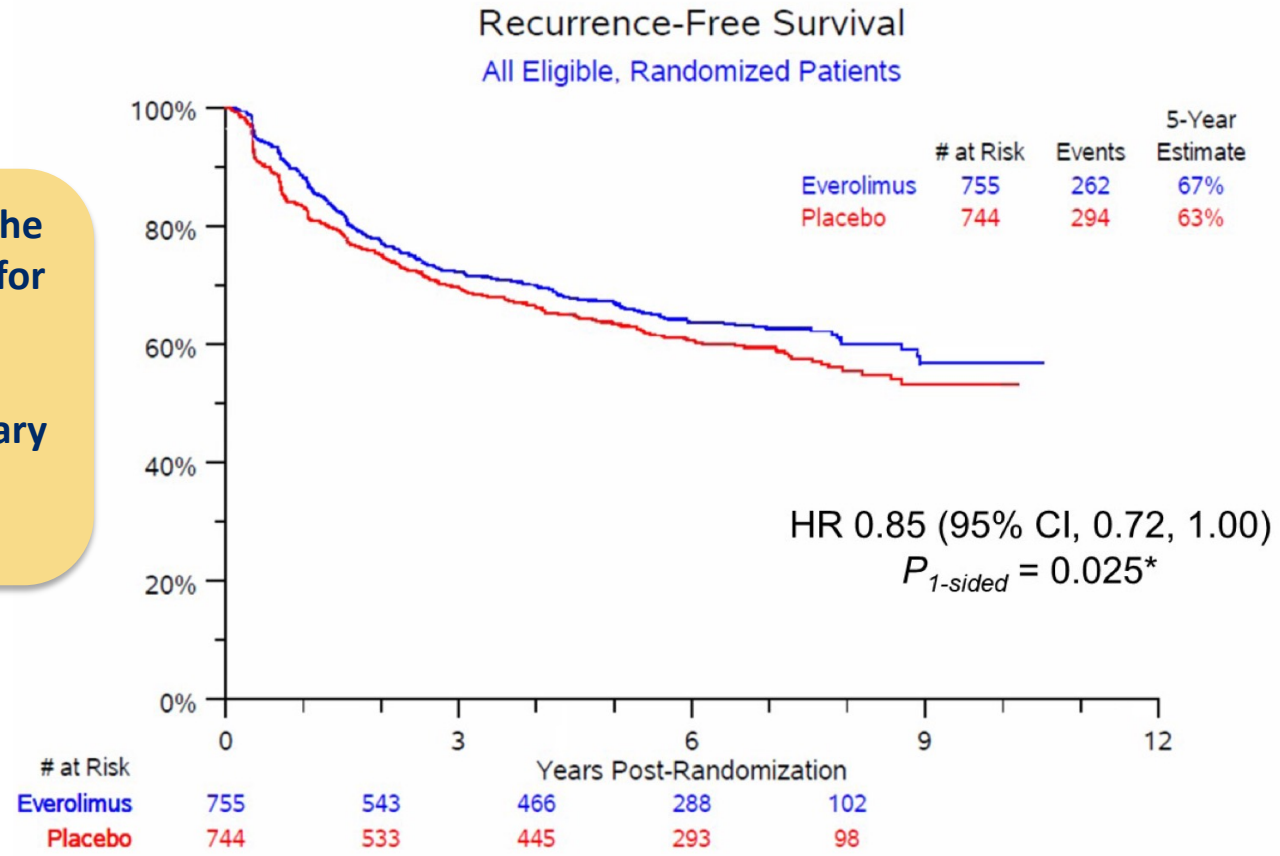
Kidney Cancer: Perioperative Management (EVEREST TRIAL)



Ryan CW, et al. *J Clin Oncol*. 2022;40(17_suppl):LBA4500. Presented at: ASCO 2022.

Kidney Cancer: Perioperative Management (EVEREST TRIAL)

- ***p-value did not cross the prespecified boundary for statistical significance**
- **DID NOT reach its primary RFS endpoint**



Ryan CW, et al. *J Clin Oncol*. 2022;40(17_suppl):LBA4500. Presented at: ASCO 2022.

UCDAVIS COMPREHENSIVE CANCER CENTER

Perioperative Management: Immune Checkpoint Inhibitor Trials

	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
SACRCOMATOID?	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	0.70	-Lung or soft tissue oligomets >12 months	NO
PFS HR P-value	**0.63, p<0.0001 (**and OS benefit!!!*)**	0.97 p= 0.43	0.93 p= 0.49	0.92 P= 0.53

Choueiri et al. Presented at ASCO GU 2022; 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

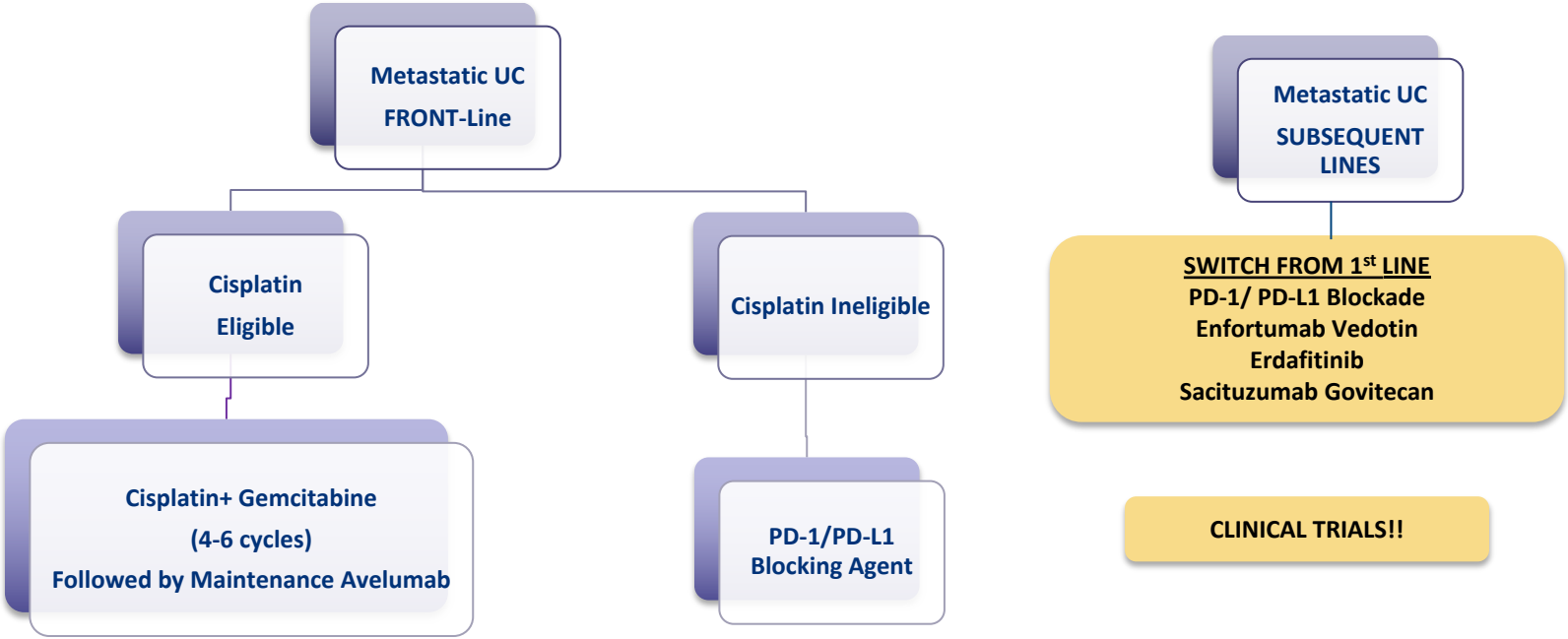
Kidney Cancer: Perioperative Management FINAL CONCLUSIONS

- Pembrolizumab and sunitinib showed improvement in DFS and are approved in the adjuvant setting
- Detailed biomarker analysis even from the “negative” studies will be helpful to elucidate tumor/host factors that may determine response
- Standardization of eligibility criteria for future studies will be helpful

Presentation Outline

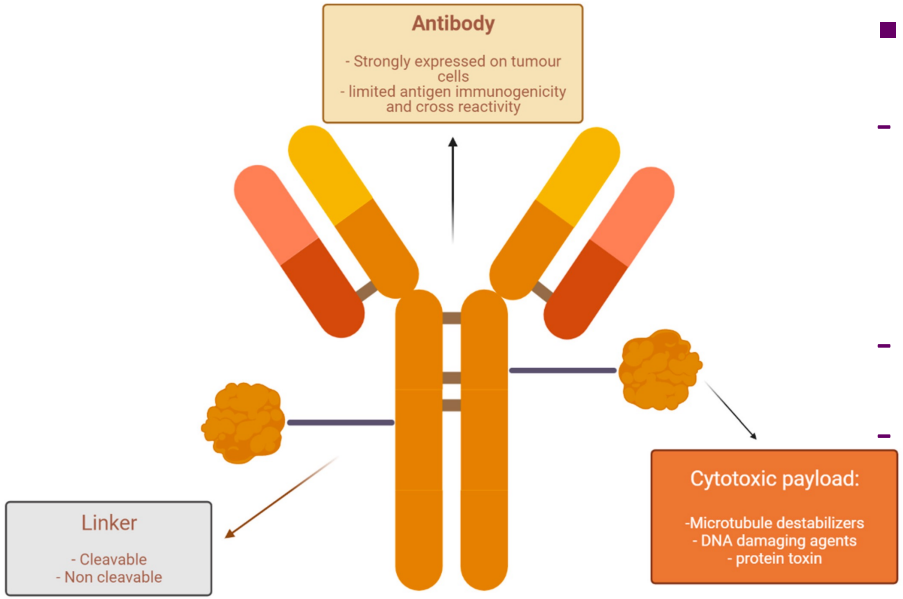
- PROSTATE CANCER
- KIDNEY CANCER
- **UROTHELIAL CARCINOMA**
  - Current Status of approved drugs for metastatic urothelial carcinoma
  - Recent updates and upcoming trials
  - The state of perioperative therapies
  - Treatment decisions

Metastatic Urothelial Cancer: TREATMENT LANDSCAPE IN 2022



NCCN [nccn.org]

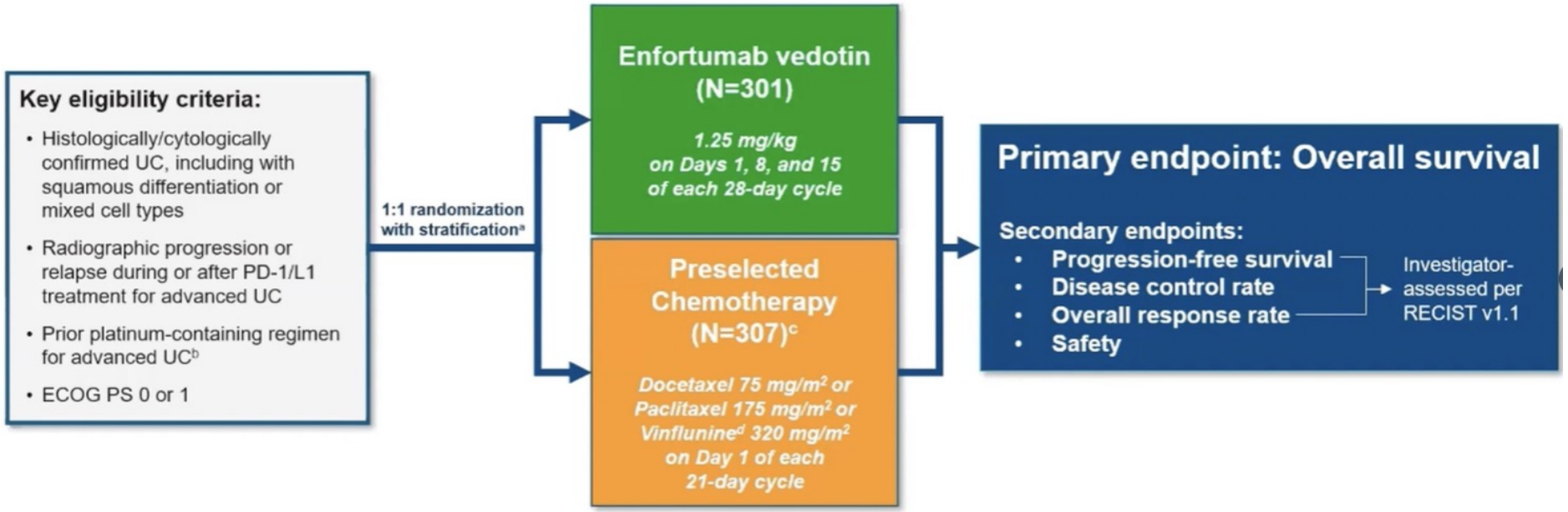
Antibody Drug Conjugates



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

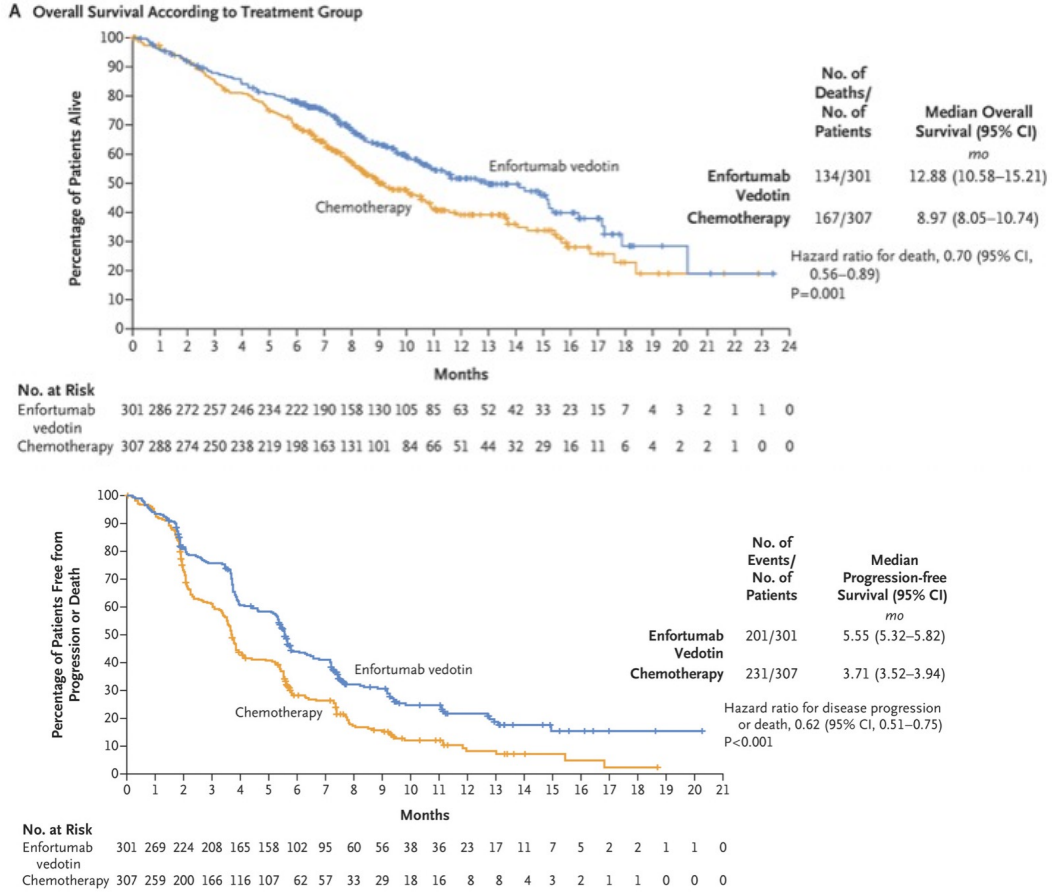
Ungaro et al. MDPI. 2022

Enfortumab Vedotin: EV-301



Powels et al. Presented at GU-ASCO 2021; NEJM 2021

Enfortumab Vedotin: Phase-III Trial (EV-301): Improved OS and PFS



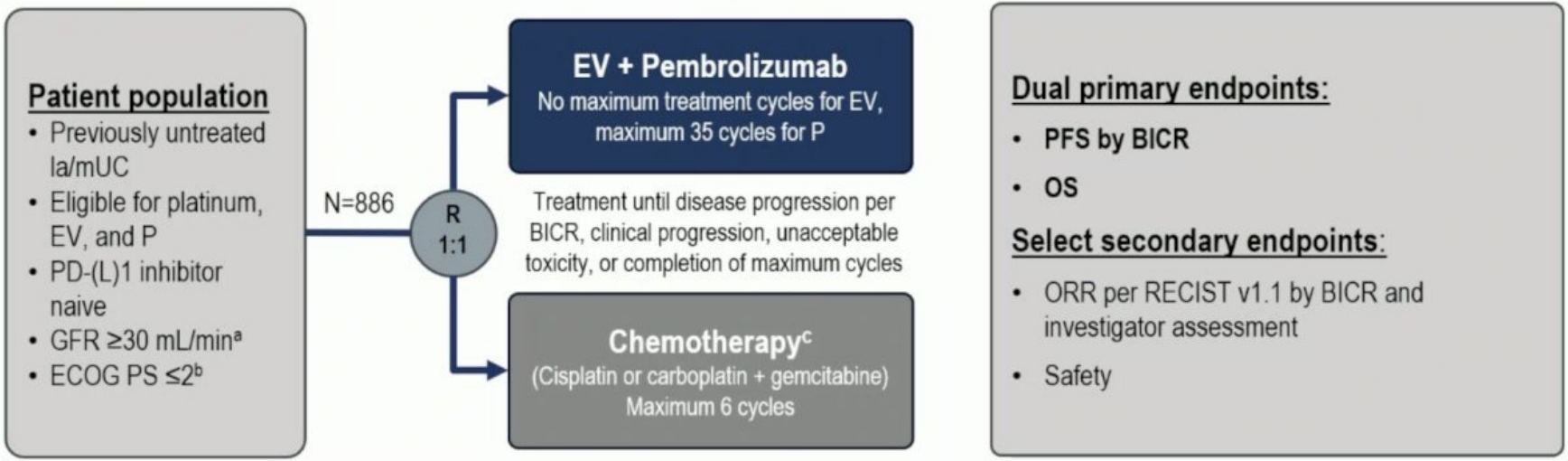
This study led to FDA approval for:

- Patients who have previously received IO and platinum-based chemotherapy
- Patients ineligible for cisplatin-based chemotherapy and have previously received one or more prior lines of therapy

Powels et al. Presented at GU-ASCO 2021; NEJM 2021

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

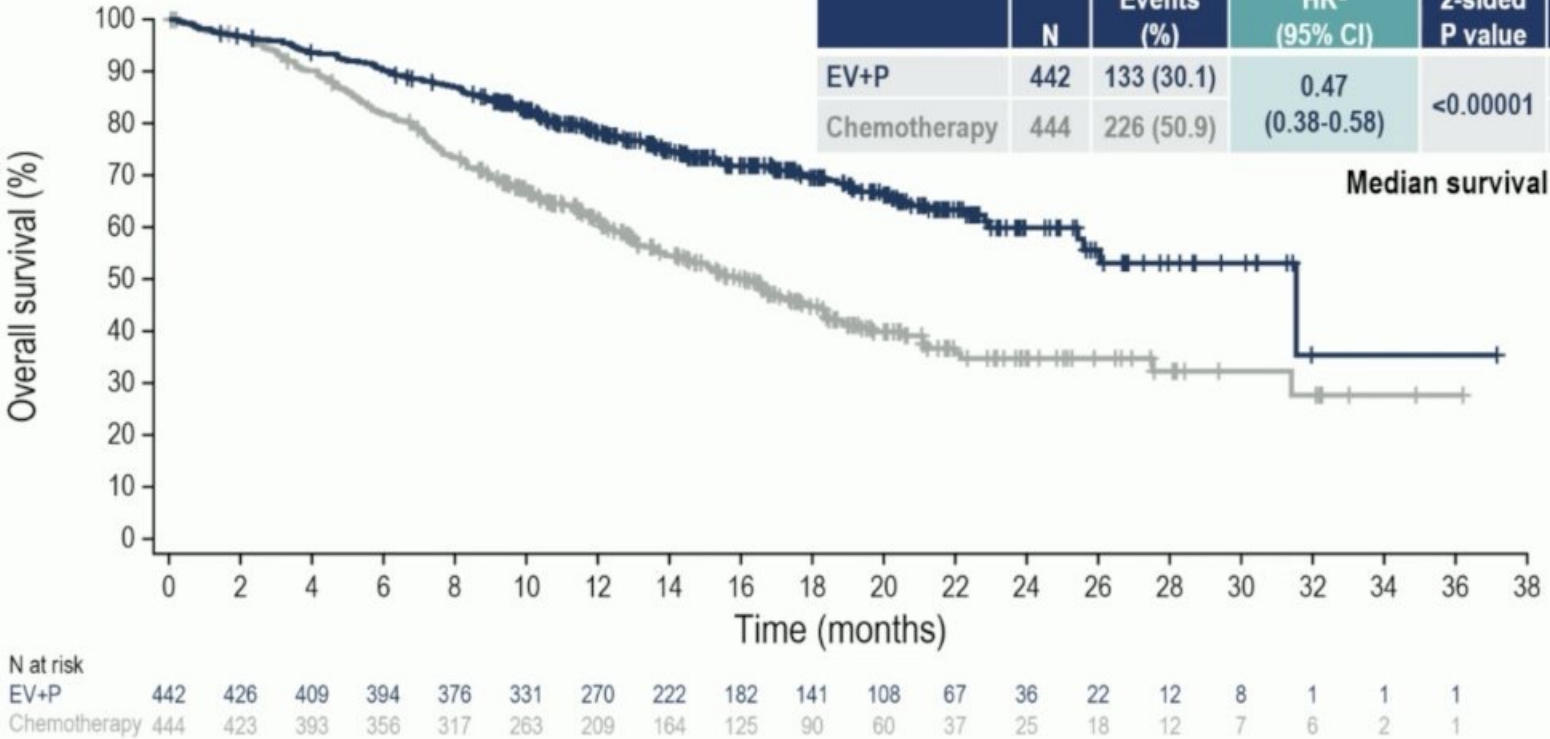
EV-302/KEYNOTE-A39: First time that platinum-based CT has been surpassed in OS

Overall Survival

Risk of death was reduced by 53% in patients who received EV+P

	N	Events (%)	HR[a] (95% CI)	2-sided P value	mOS (95% CI), months
EV+P	442	133 (30.1)	0.47 (0.38-0.58)	<0.00001	31.5 (25.4-NR)
Chemotherapy	444	226 (50.9)			16.1 (13.9-18.3)

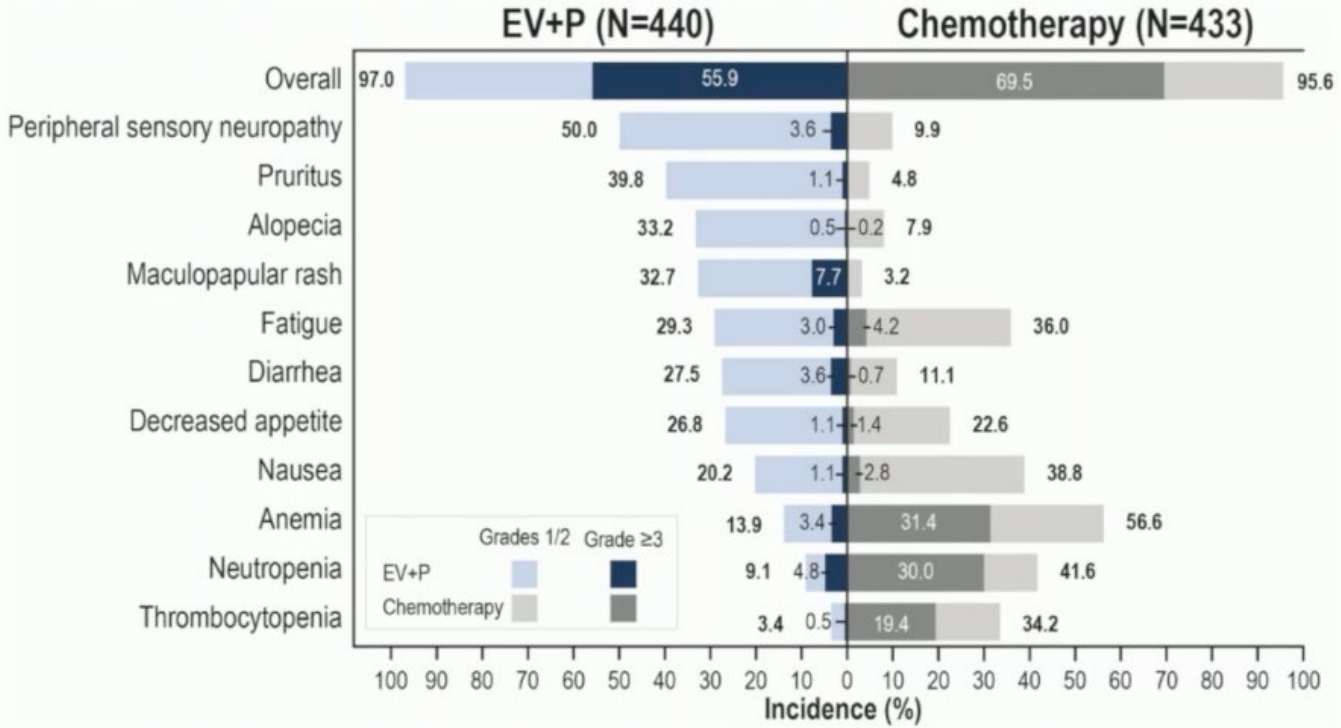
Median survival follow-up: 17.2 months



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

Further Development of Immunotherapy in UC
SWITCH TO MAINTAINENCE IO (JAVELIN 100)

Javelin Bladder-100 Randomized Phase 3

- CR, PR, or SD with standard 1L chemotherapy (4-6 cycles)
  - – Cisplatin + gemcitabine or
  - – Carboplatin + gemcitabine
- Unresectable locally advanced or metastatic UC

Treatment-free interval 4-10 weeks

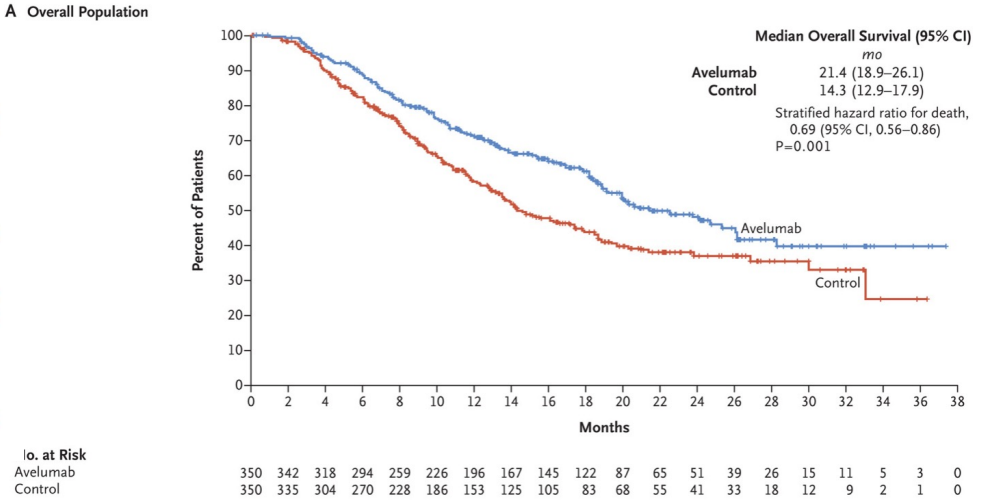
N=700

R 1:1

Avelumab
10 mg/kg IV Q2W
+ BSC*
n=350

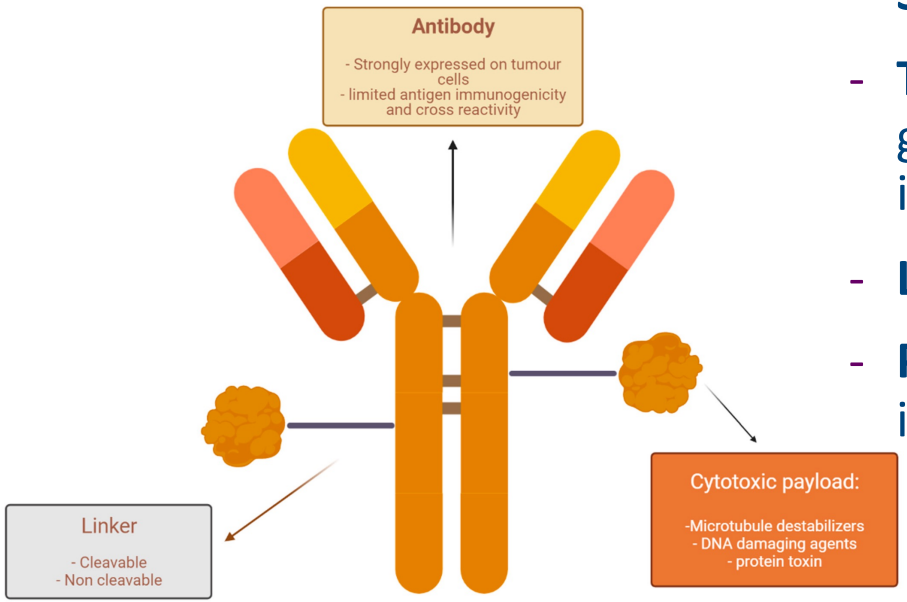
Until PD, unacceptable toxicity, or withdrawal

BSC alone*
n=350



Grivas et al. Presented at ASCO 2020. Powles T, et al. *N Engl J Med*. 2020;383(13):1218-1230

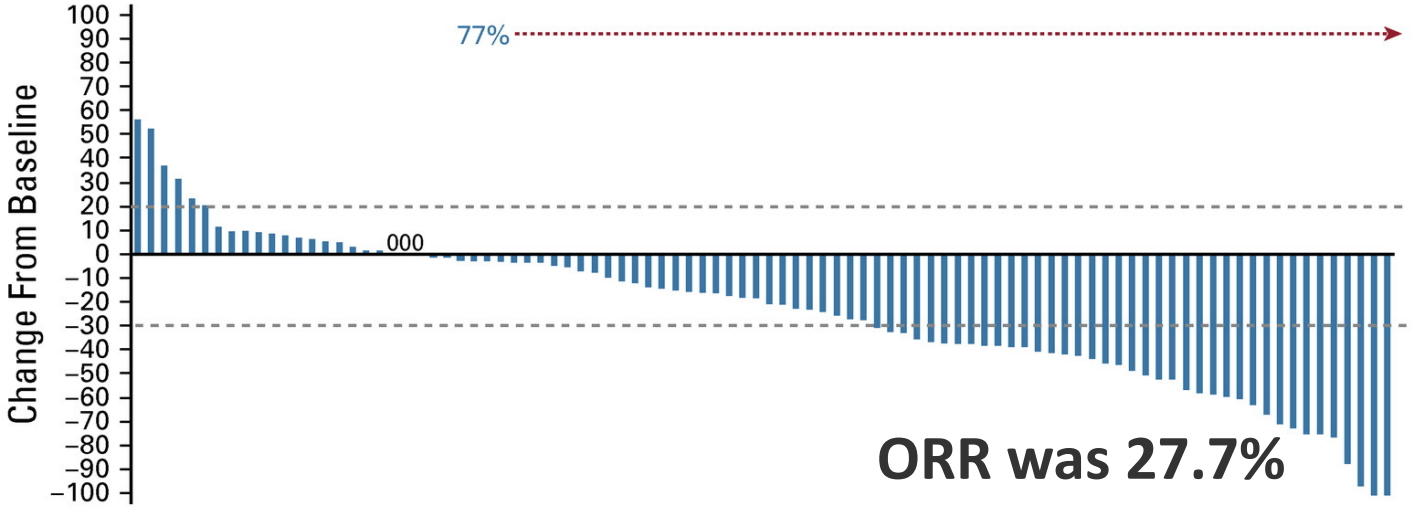
Antibody Drug Conjugates



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

Ungaro et al. MDPI. 2022

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

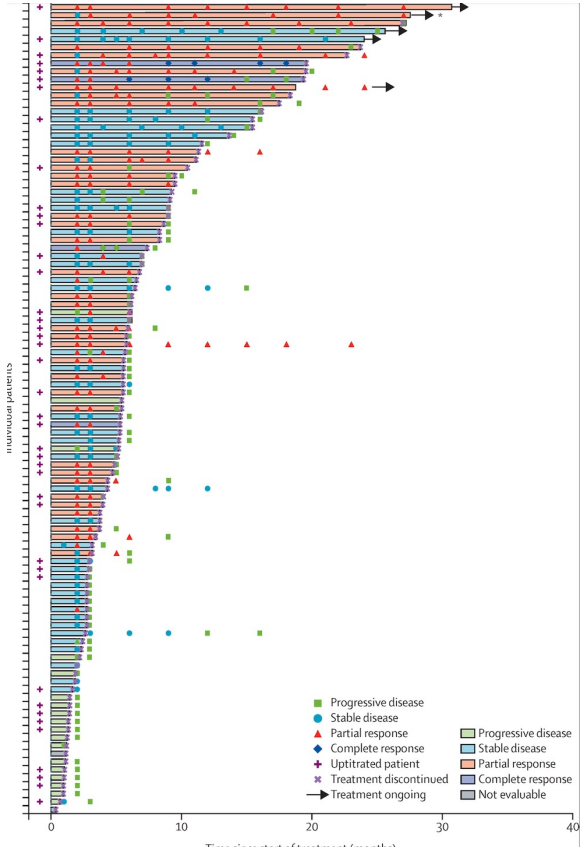


FDA Approved for:
Patients who have have previously received IO and platinum-based chemotherapy

Tagawa et al. JCO. 2021

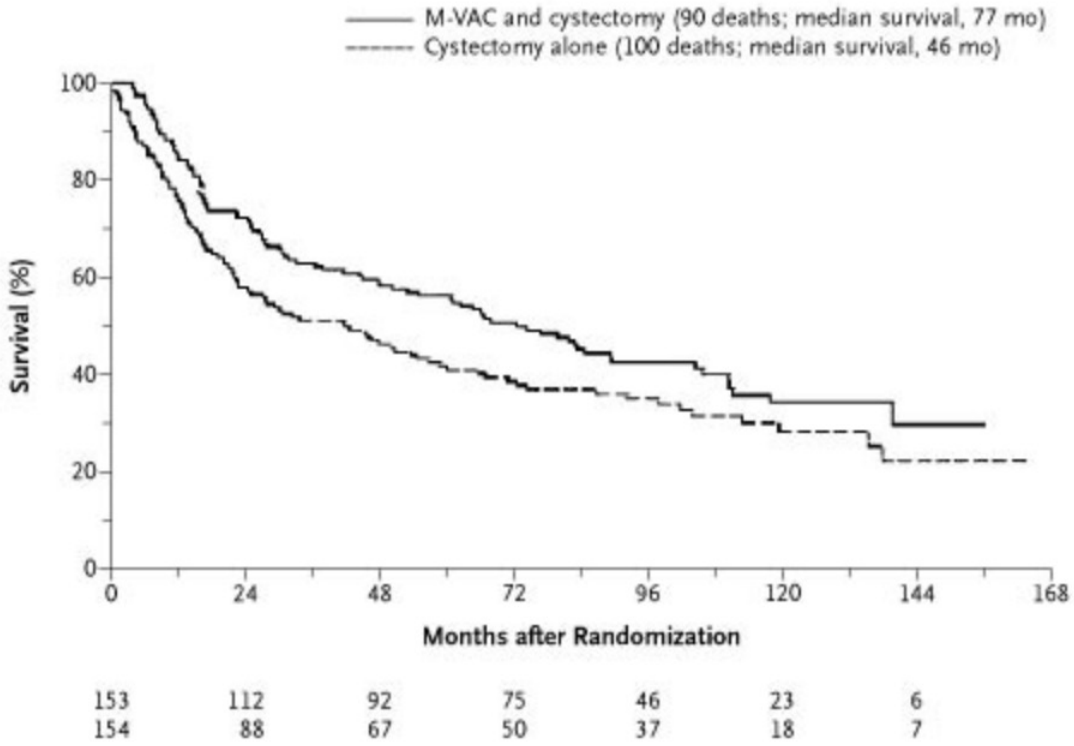
FGFR3 Inhibitors

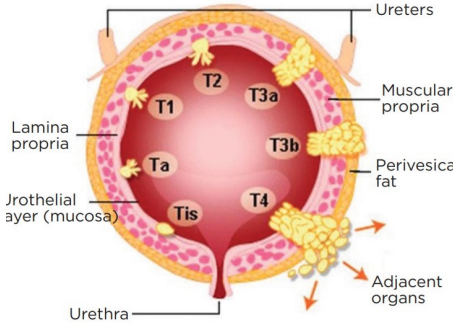
- **FGFR3 mutated in 15-20% patients**
- Targeted therapy: **ERDAFITINIB**
- ORR 33%
- **FDA approved for patients with**
  - locally advanced or metastatic urothelial carcinoma
  - with susceptible FGFR3 or FGFR2 genetic alterations
  - progressed during or following platinum-containing chemotherapy



Siefker-Radtke et al. Lancet Oncology, 2022

Urothelial Cancer: Perioperative Management





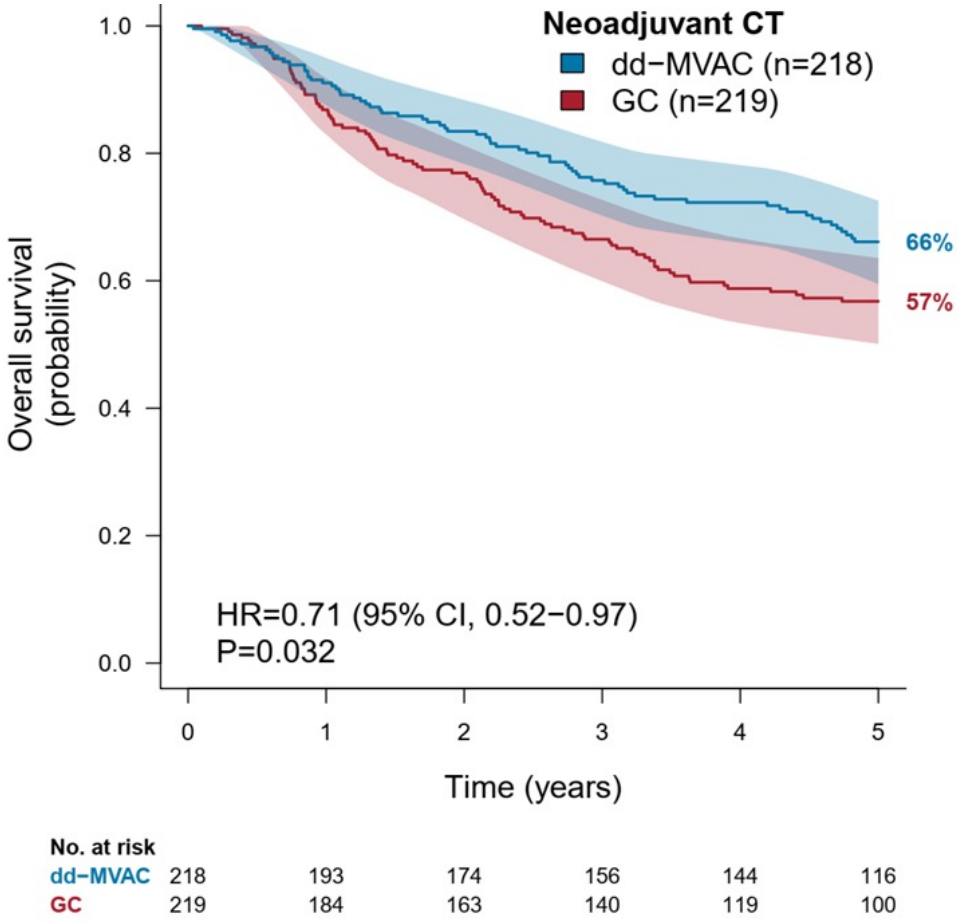
UP TO 50% PATIENTS: CISPLATIN INELIGIBLE

- ECOG PS ≥ 2
- Creatinine clearance < 60 mL/min
- Grade ≥ 2 hearing loss
- Grade ≥ 2 neuropathy
- New York Heart Association class III CHF

NEOADJUVANT PLATINUM-BASED CHEMOTHERAPY IS THE GOLD STANDARD !
Adjuvant chemotherapy has low evidence (but is still frequently used)

Grossman et al. NEJM, 2003
Galsky et al. Lancet Oncol, 2011

VESPER: RANDOMIZED PHASE III OF DOSE DENSE MVAC OR GC AS PERIOPERATIVE CHEMOTHERAPY FOR MUSCLE INVASIVE BLADDER CANCER



Pfister et al. ASCO 2023

VESPER: RANDOMIZED PHASE III OF DOSE DENSE MVAC OR GC AS PERIOPERATIVE CHEMOTHERAPY FOR MUSCLE INVASIVE BLADDER CANCER

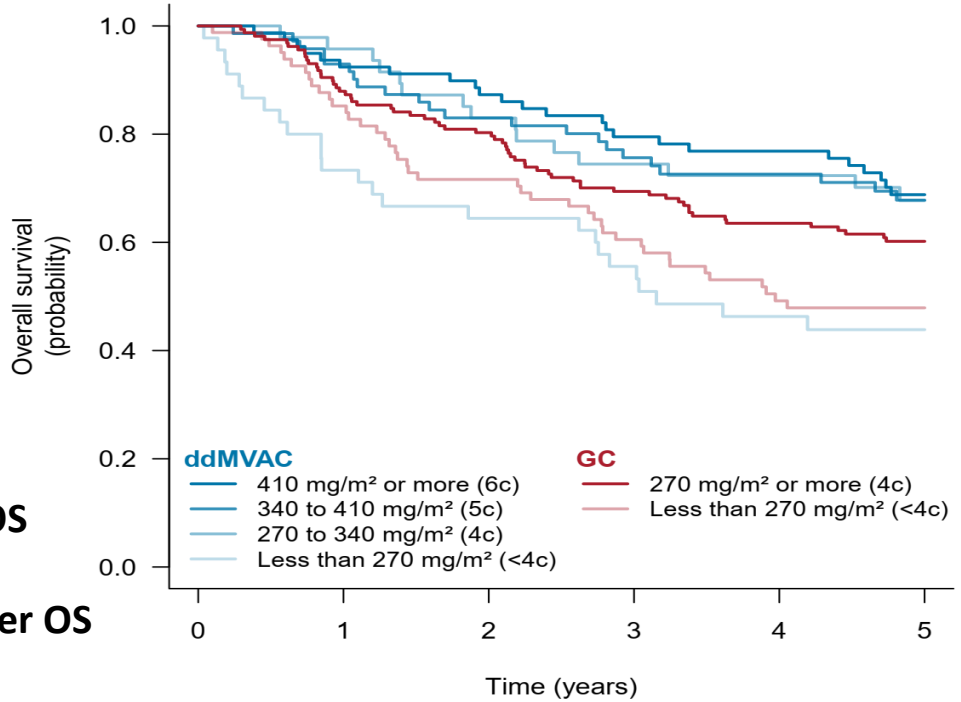
OS stratified by CT arm and number of cycles delivered

Importance of <u>cumulative cisplatin dose</u>

Less than 4 full doses cisplatin: **Poor OS**

GC arm with 4 full doses cisplatin: **Intermediate OS**

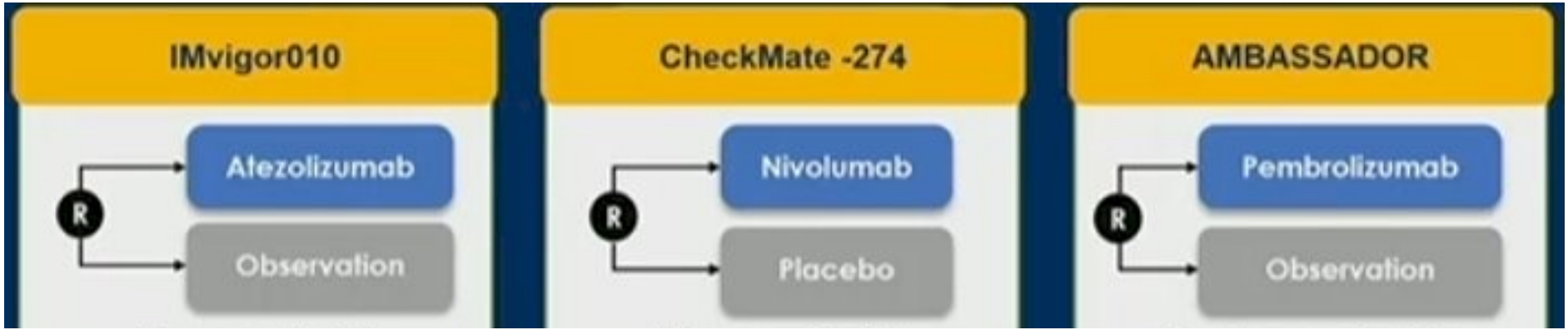
dd-MVAC arm 4 or more full doses cisplatin: **Higher OS**



No. at risk							
ddMVAC	6c	79	73	68	61	58	47
	5c	71	66	57	51	47	38
	4c	47	45	39	35	33	26
	<4c	51	33	29	24	19	15
GC	4c	159	138	126	108	96	82
	<4c	86	69	58	49	38	30

Pfister et al. ASCO 2023

Urothelial Cancer: Adjuvant IO Therapies?



No DFS or OS improvement

DFS improvement Waiting for OS data

DFS improvement Waiting for OS data

Bellmunt J, et al. Lancet Oncol. 2021;22(4):525-537.
Bajorin DF, et al. *N Engl J Med.* 2021;384(22):2102-2114.

Thank You!

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(and Many Thanks to Dr Shuchi Gulati)