Bladder Cancer Update

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Perioperative Therapy

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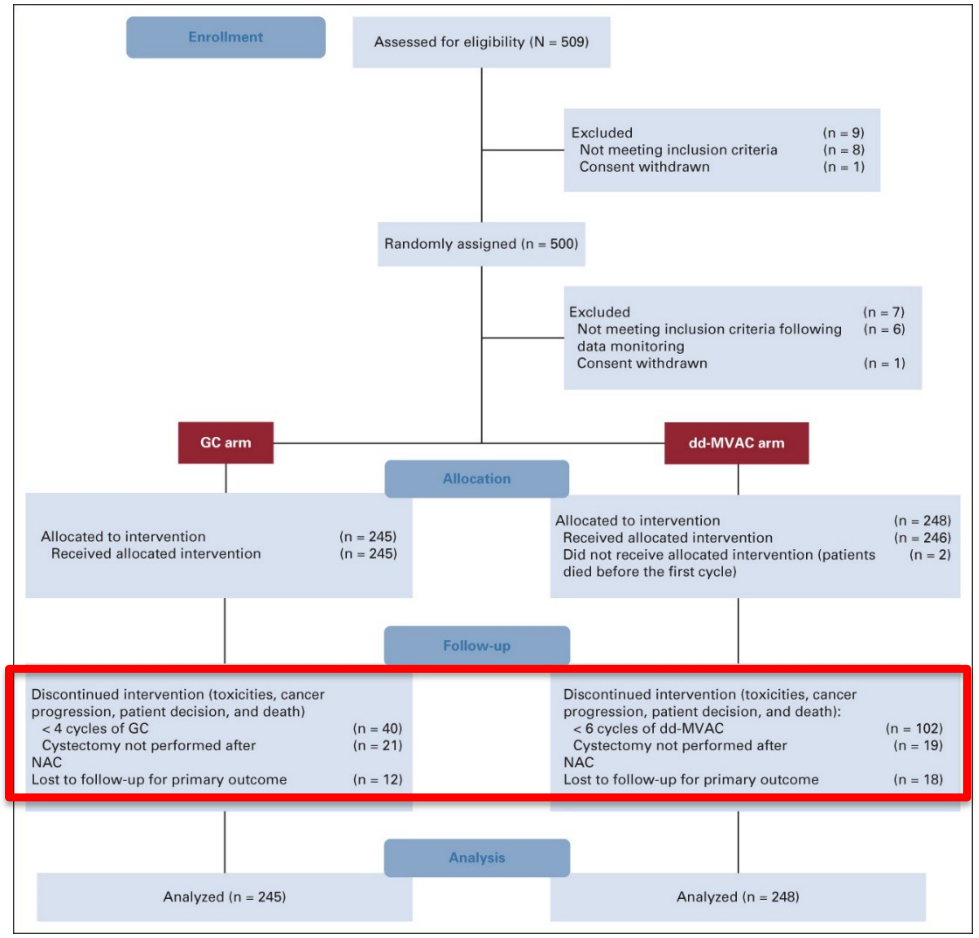
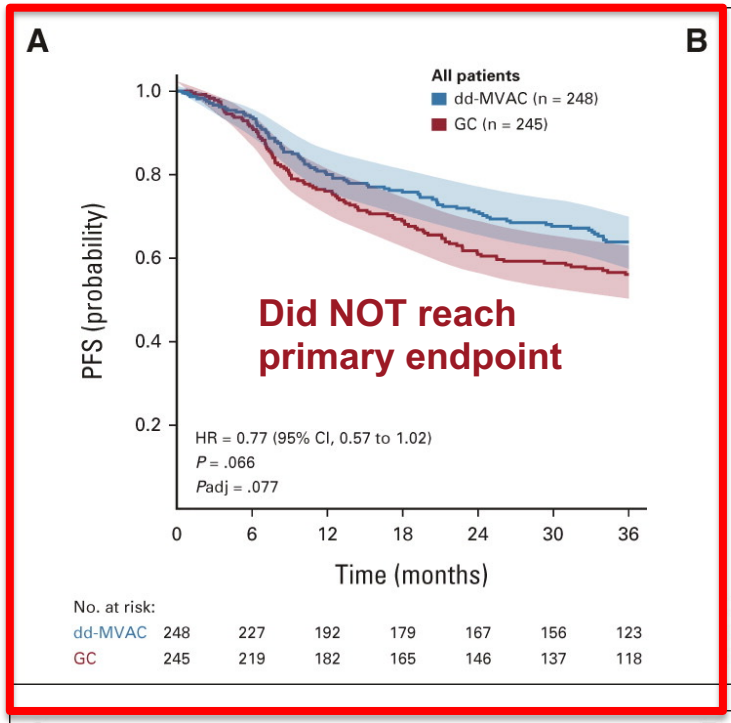
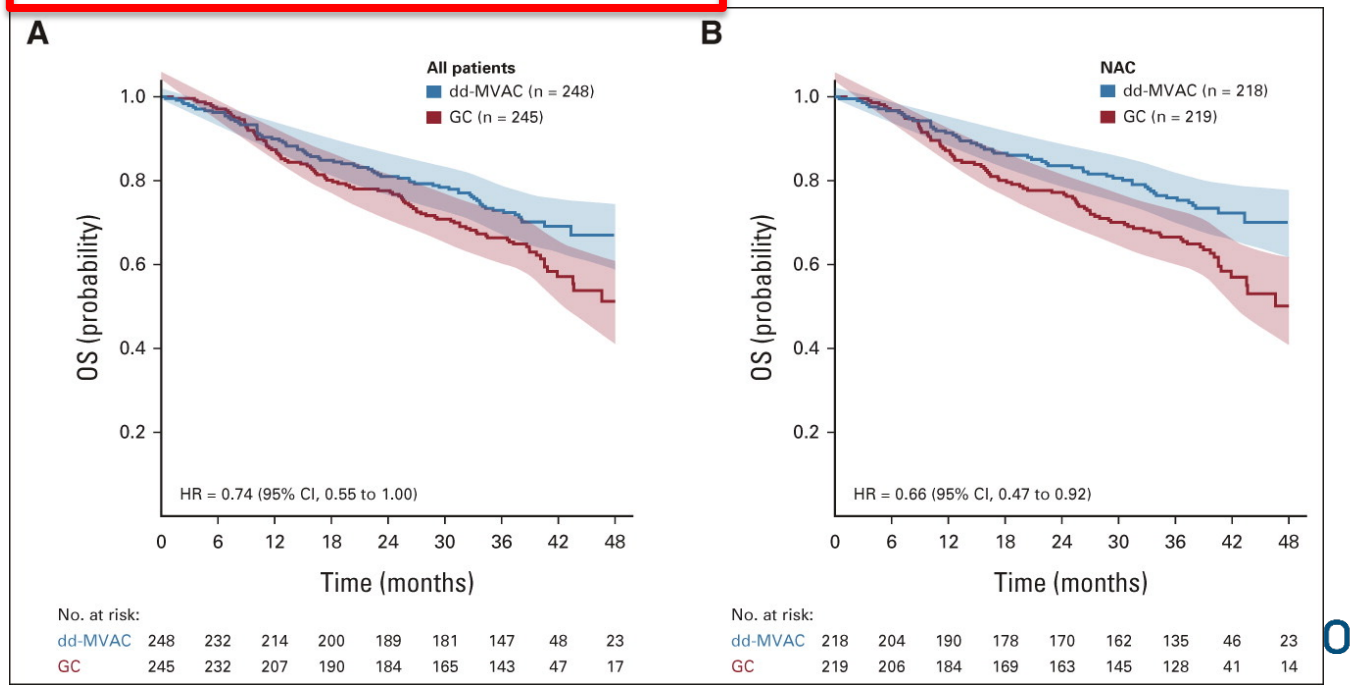
GETUG-AFU V05 VESPER Trial

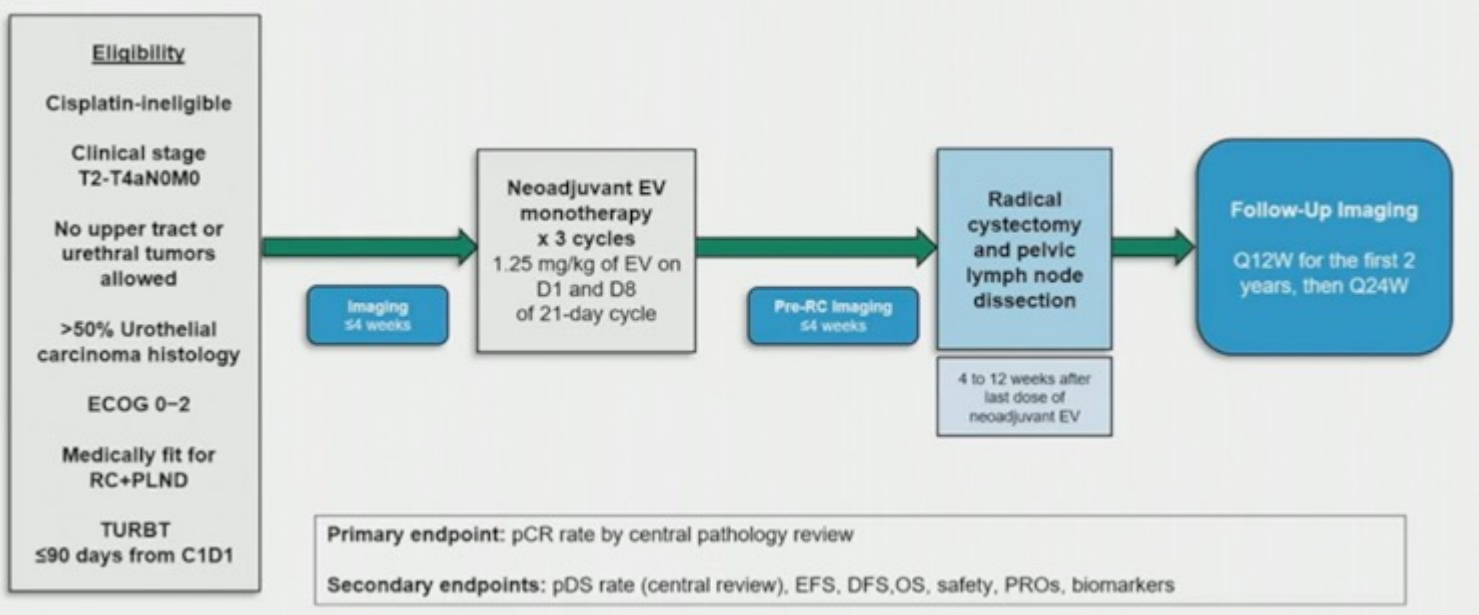


- 88% received NAC
  - 84% received GC x 4
  - 60% received ddMVAC x6
- Adjuvant Chemo
  - 81% received GC x 4
  - 40% received ddMVAC x6





Research Frontier:
EV-103 Cohort H: Neoadjuvant Enfortumab Vedotin



- 22 patients treated (68.2% cT2, 68.2% pure urothelial histology)
- 36.4% pCR, 50% pathological downstaging
- No surgical delays
- Cohort L, added in adjuvant treatment as well (x6 cycles)

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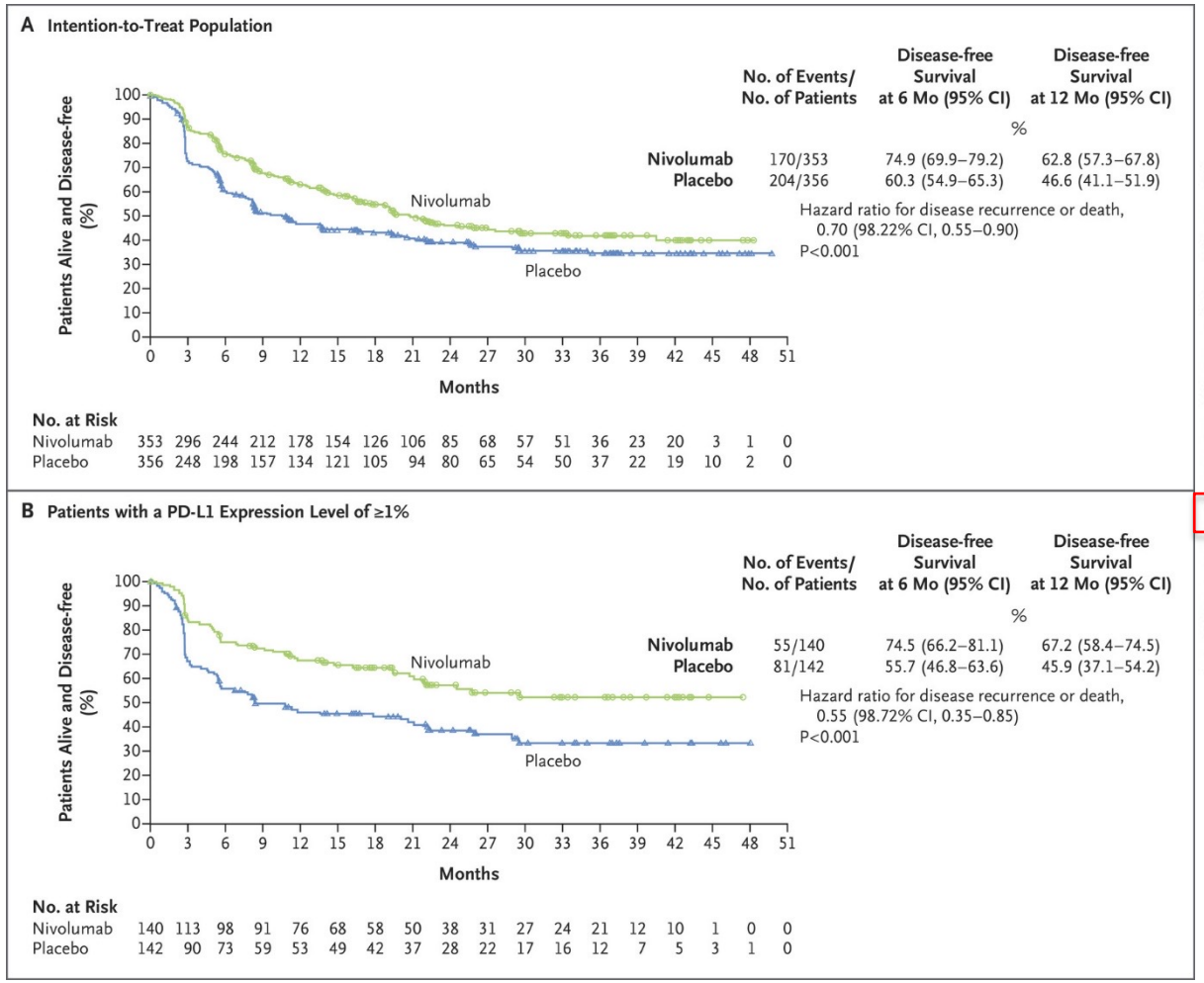
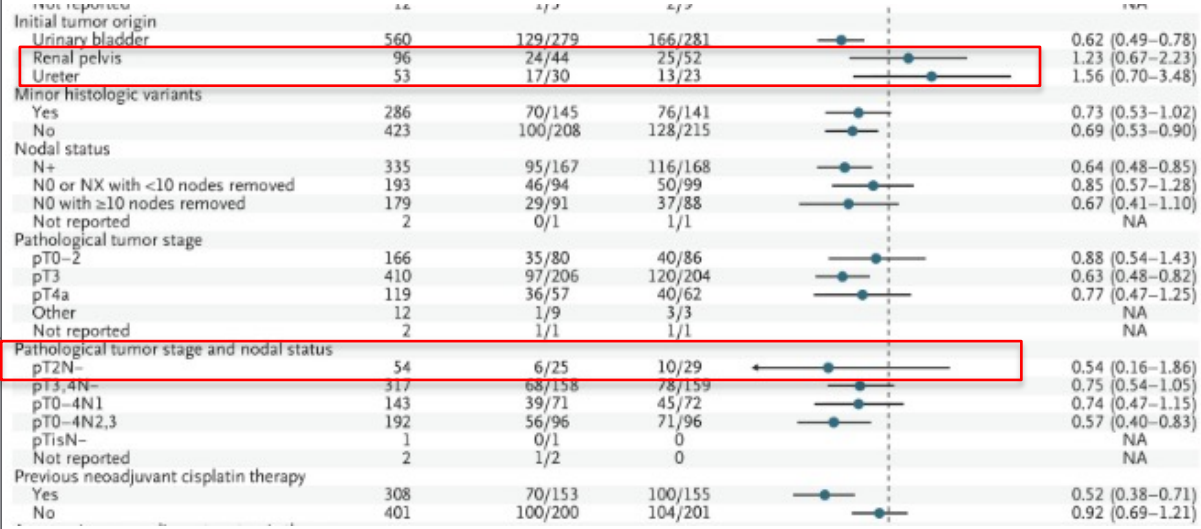
CheckMate 274 (Adjuvant Nivolumab)





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Metastatic Urothelial Carcinoma

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Cisplatin or Carboplatin Chemotherapy

(Cis preferred)

PD-1/PD-L1 Inhibitors
(2nd Line or Maintenance)

(1st: If Cis ineligible and PDL1+)

Enfortumab Vedotin

Erdafitinib
(*FGFR* mut)

Sacituzumab Govitecan

CLINICAL TRIALS

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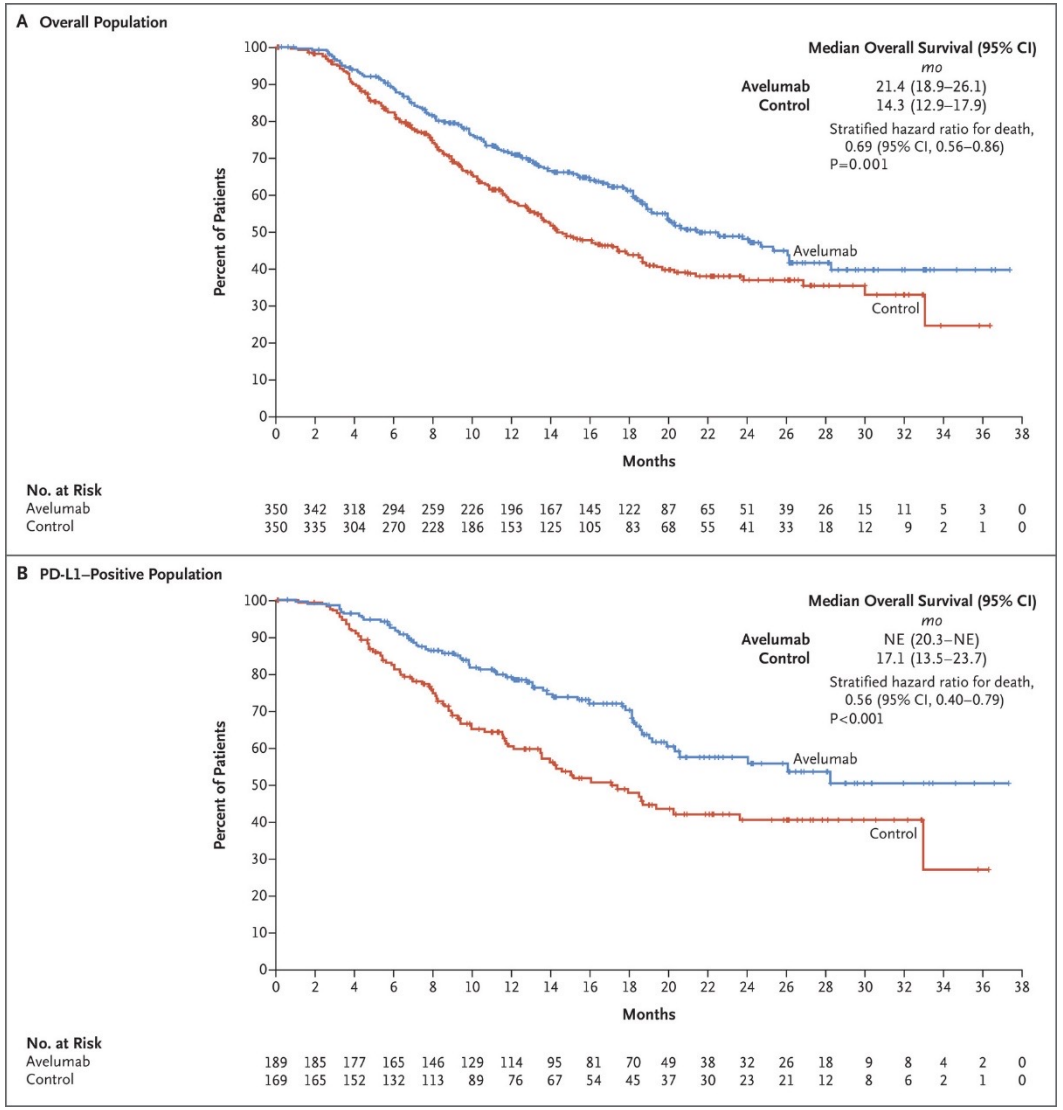
JAVELIN Bladder 100: Avelumab Maintenance



	All pts		Pts with PD-L1+ tumors	
	Avelumab + BSC (n = 350)	BSC alone (n = 350)	Avelumab + BSC (n = 189)	BSC alone (n = 169)
Median OS (95% CI), months	23.8 (19.9-28.8)	15.0 (13.5-18.2)	30.9 (24.0-39.8)	18.5 (14.1-24.2)
HR for OS (95% CI); 2-sided p value	0.76 (0.631-0.915); p = 0.0036		0.69 (0.521-0.901); p = 0.0064	
30-month OS rate, % (95% CI)	43.7 (38.2-49.0)	33.5 (28.4-38.7)	51.3 (43.7-58.4)	38.5 (30.9-46.1)
Restricted mean survival time (95% CI), months; 2-sided p value	28.8 (26.6-31.0); p = 0.0029	24.1 (21.9-26.3)	32.4 (29.4-35.4) p = 0.0080	26.4 (23.2-29.7)
Median PFS by investigator (95% CI), months	5.5 (4.2-7.2)	2.1 (1.9-3.0)	7.5 (5.5-11.1)	2.8 (2.0-3.7)
HR for PFS (95% CI); 2-sided p value	0.54 (0.457-0.645); p < 0.0001		0.46 (0.360-0.588); p < 0.0001	
30-month PFS rate, % (95% CI)	19.3 (15.0-24.0)	6.3 (3.8-9.5)	25.1 (18.6-32.2)	6.7 (3.3-11.6)

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Powles T et al. NEJM 2020.
Powles T et al. ASCO Annual Meeting 2022

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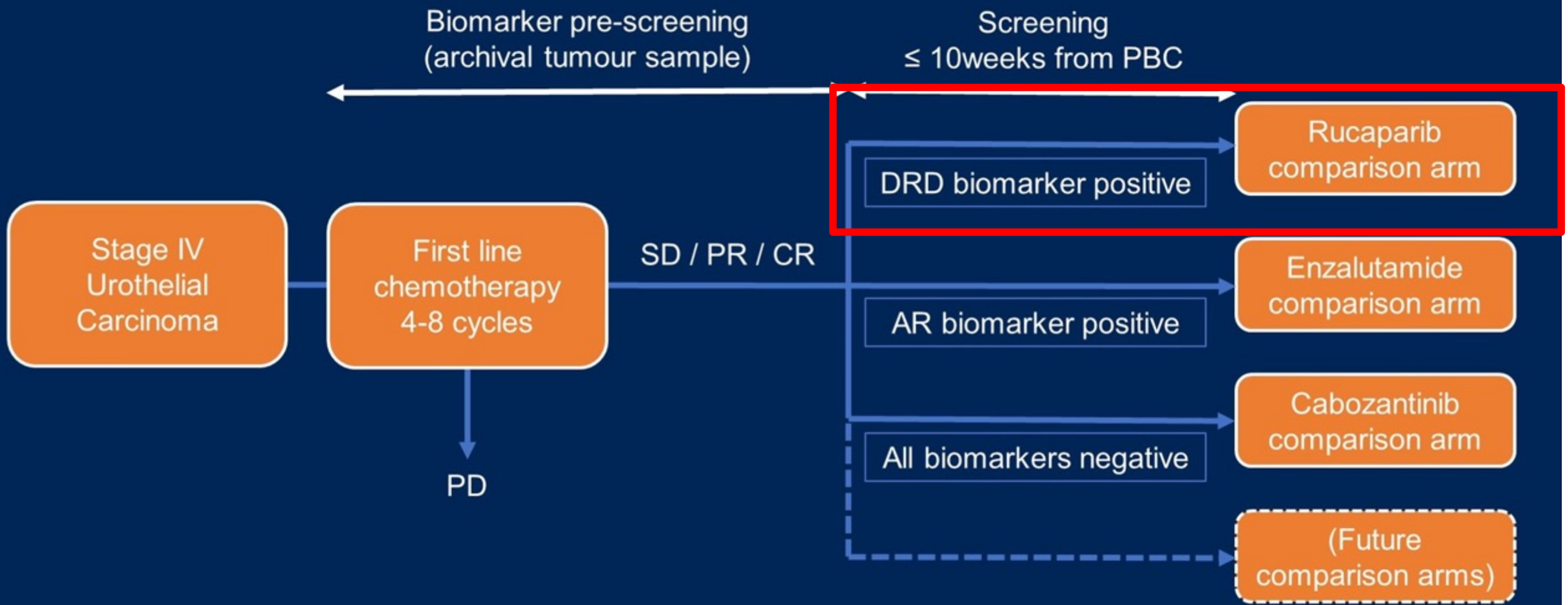
The ATLANTIS trial platform[1]



[1]Fulton et al, Trials. 2020 Apr 19;21(1):344

SD, stable disease; PR, partial response; CR, complete response; PD, progressive disease; DRD, DNA repair deficiency; AR, androgen receptor

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CONSORT and DRD biomarker

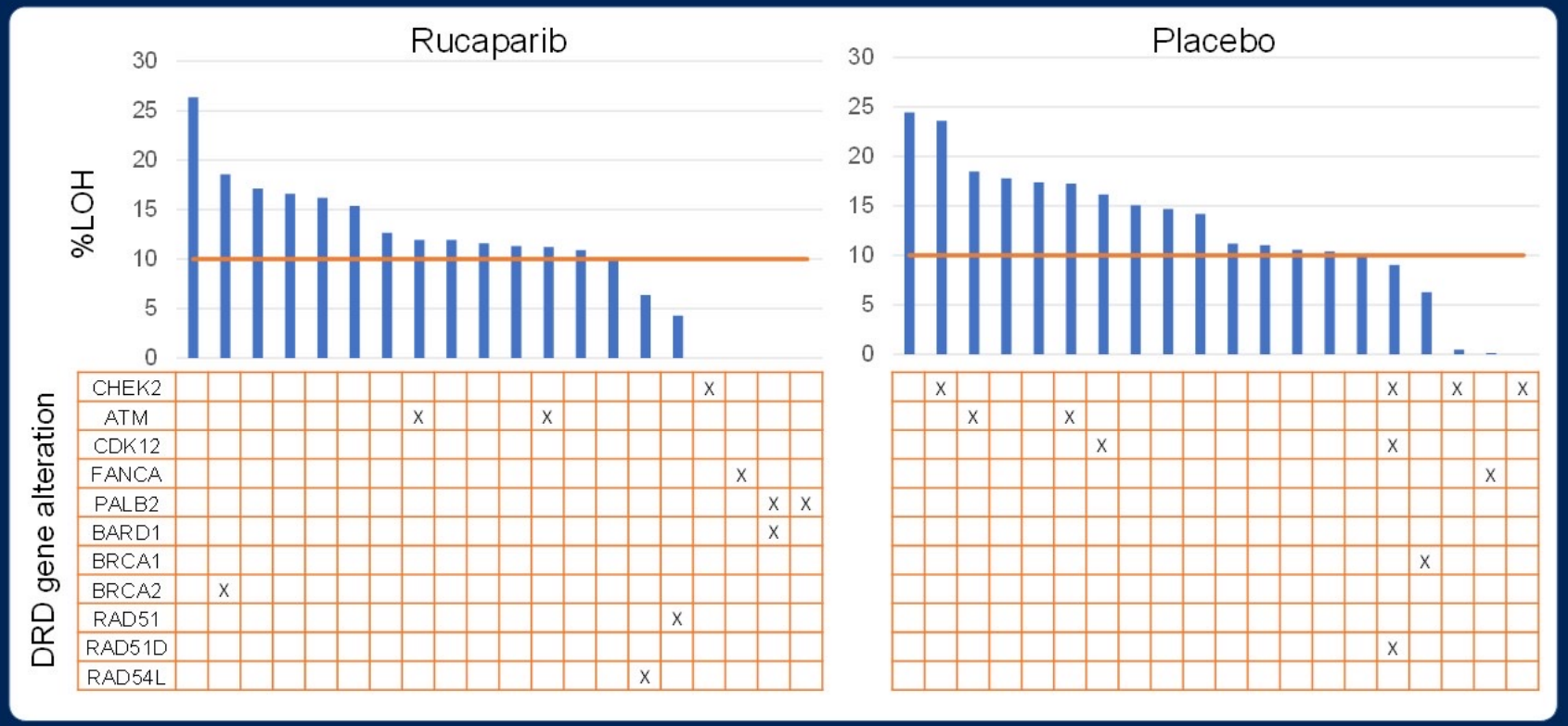
279 registered to ATLANTIS*

248 pre-screened for rucaparib comparison

74 DRD biomarker positive

40 randomised to rucaparib comparison

- ≥10% LOH: 22 / 40 (55%)
- DRD gene altered: 11 / 40 (27.5%)
- Both: 7 / 40 (17.5%)



*31 patients were screened for ATLANTIS prior to the first site opening the rucaparib comparison arm. DRD, DNA repair deficiency; %LOH, percentage of genome-wide loss of heterozygosity

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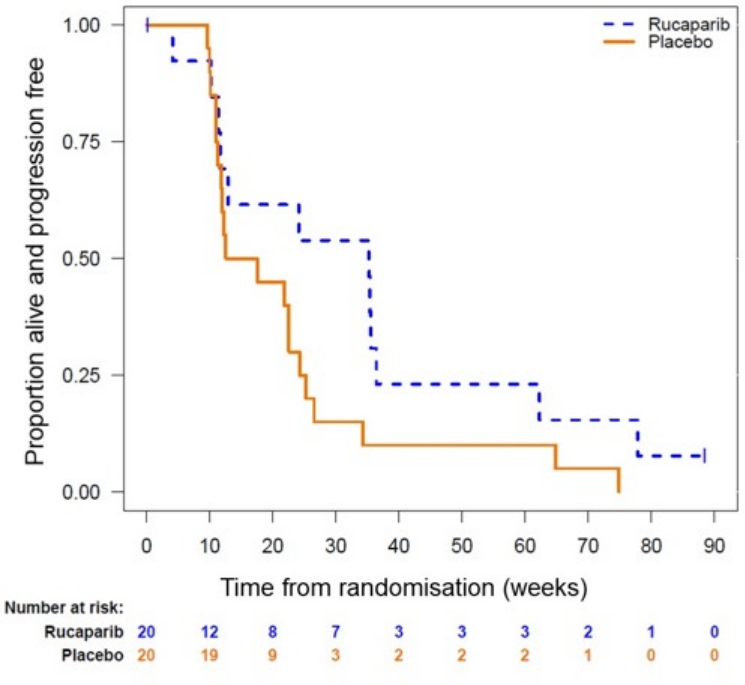
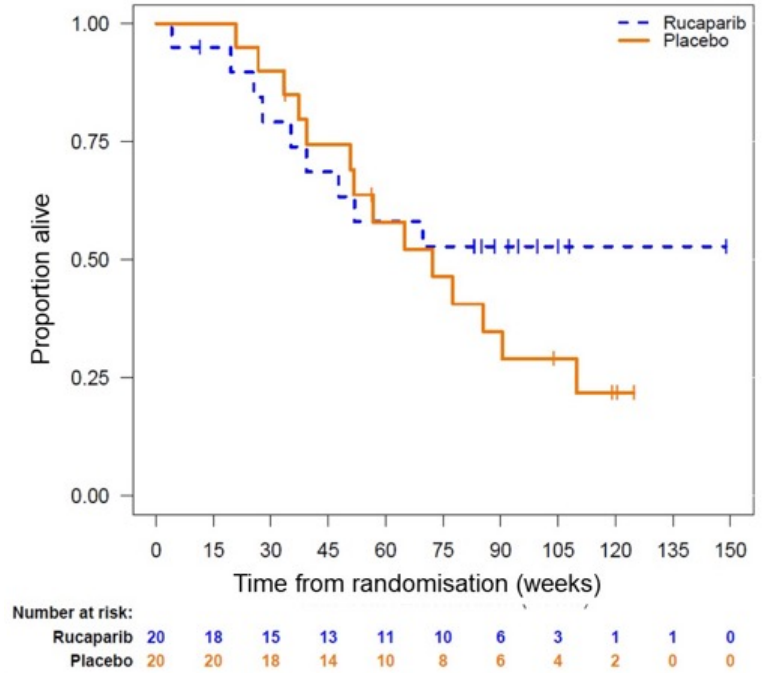
Progression Free Survival (PE) and Overall Survival (Secondary EP)



	Rucaparib	Placebo	p
PFS events	12 (60%)	20 (100%)	
Median PFS, weeks	35.3 (80% CI 11.7-35.6)	15.1 (80% CI 11.9-22.6)	
Hazard ratio	0.53 (80% CI 0.30-0.92)		0.07



	Rucaparib	Placebo	p
OS events	9 (45%)	14 (70%)	
Median OS, weeks	Not reached	72.3 (80% CI 51.7-85.4)	
Hazard ratio	1.22 (80% CI 0.62-2.38)		0.35

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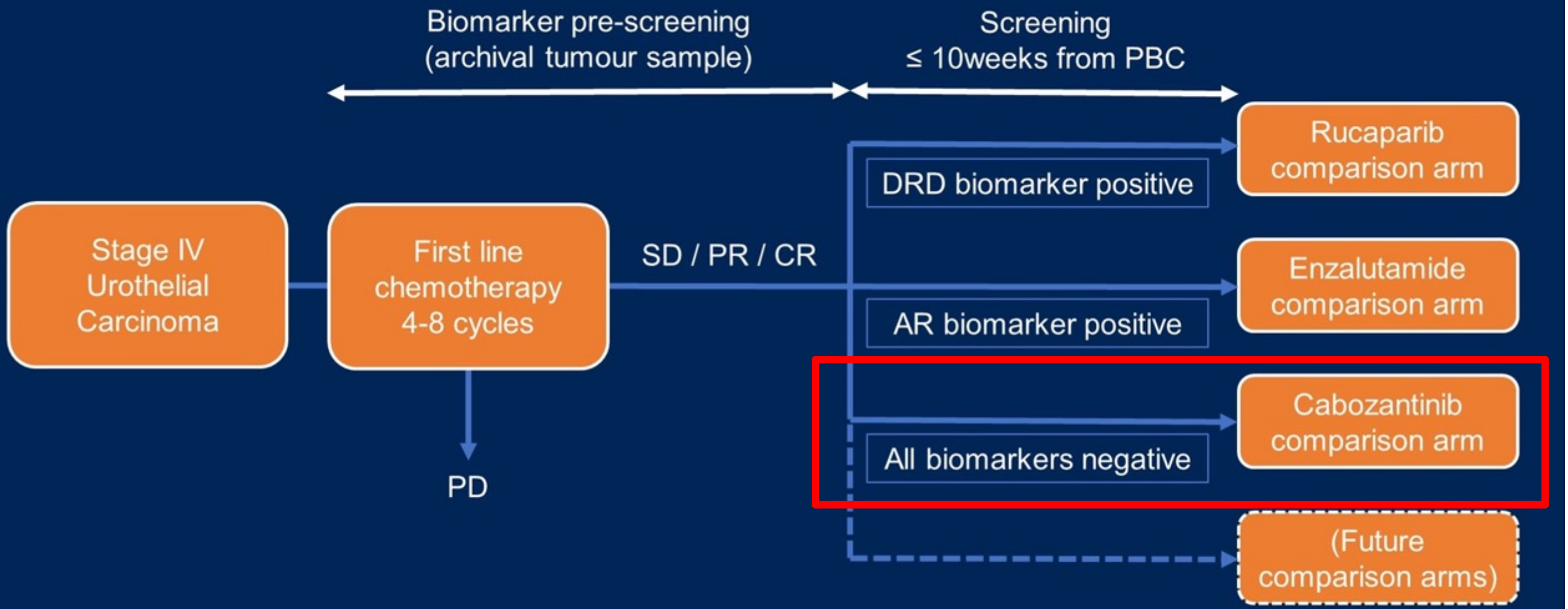
The ATLANTIS trial platform[1]



[1]Fulton et al, Trials. 2020 Apr 19;21(1):344

SD, stable disease; PR, partial response; CR, complete response; PD, progressive disease; DRD, DNA repair deficiency; AR, androgen receptor

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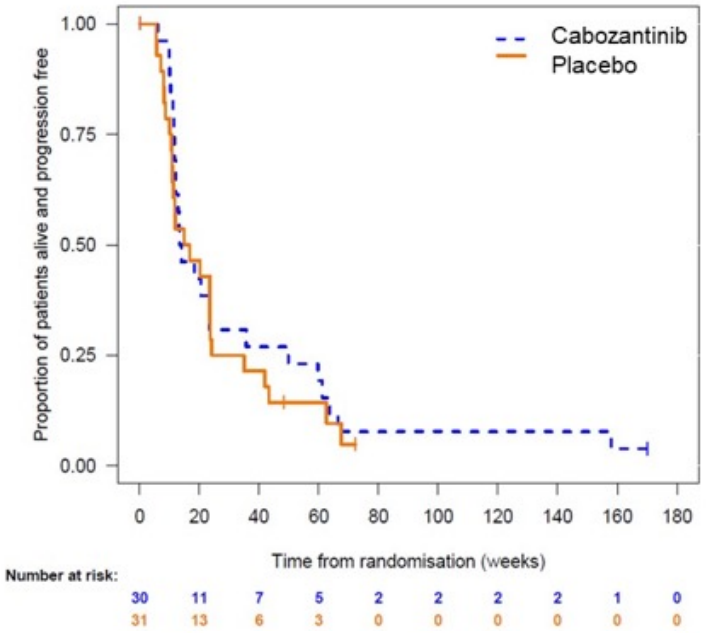
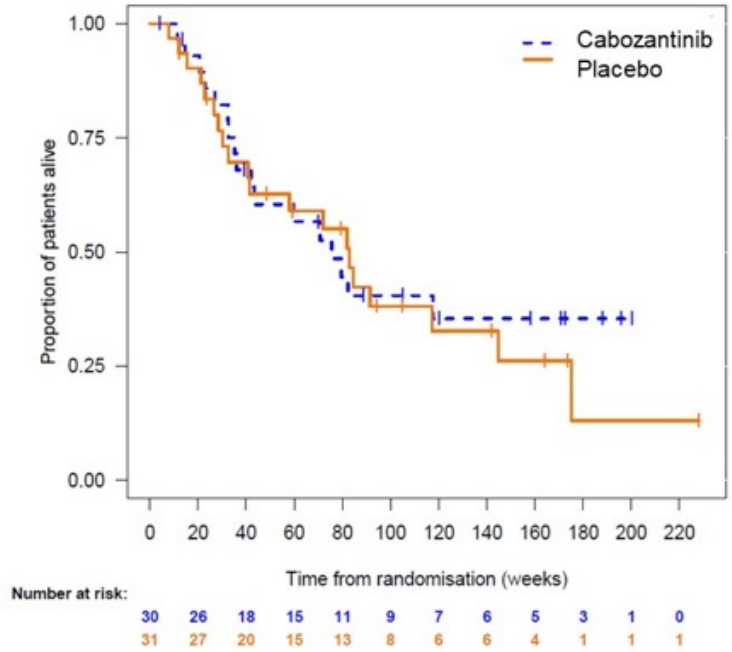
Progression Free Survival (PE) and Overall Survival (Secondary EP)



	Cabozantinib	Placebo	p
PFS events	25 (83%)	26 (84%)	
Median PFS, weeks	13.7 (80% CI 12.1, 23.3)	15.8 (80% CI 11.3, 23.6)	
Hazard ratio*	0.89 (80% CI 0.61, 1.30)		0.35



	Cabozantinib	Placebo	p
OS events	17 (57%)	20 (65%)	
Median OS, weeks	75.5 (80% CI 43.4, 117.6)	82.9 (80% CI 58.0, 117.1)	
Hazard ratio*	0.80 (80% CI 0.52, 1.30)		0.25

***adjusted for minimization factors**

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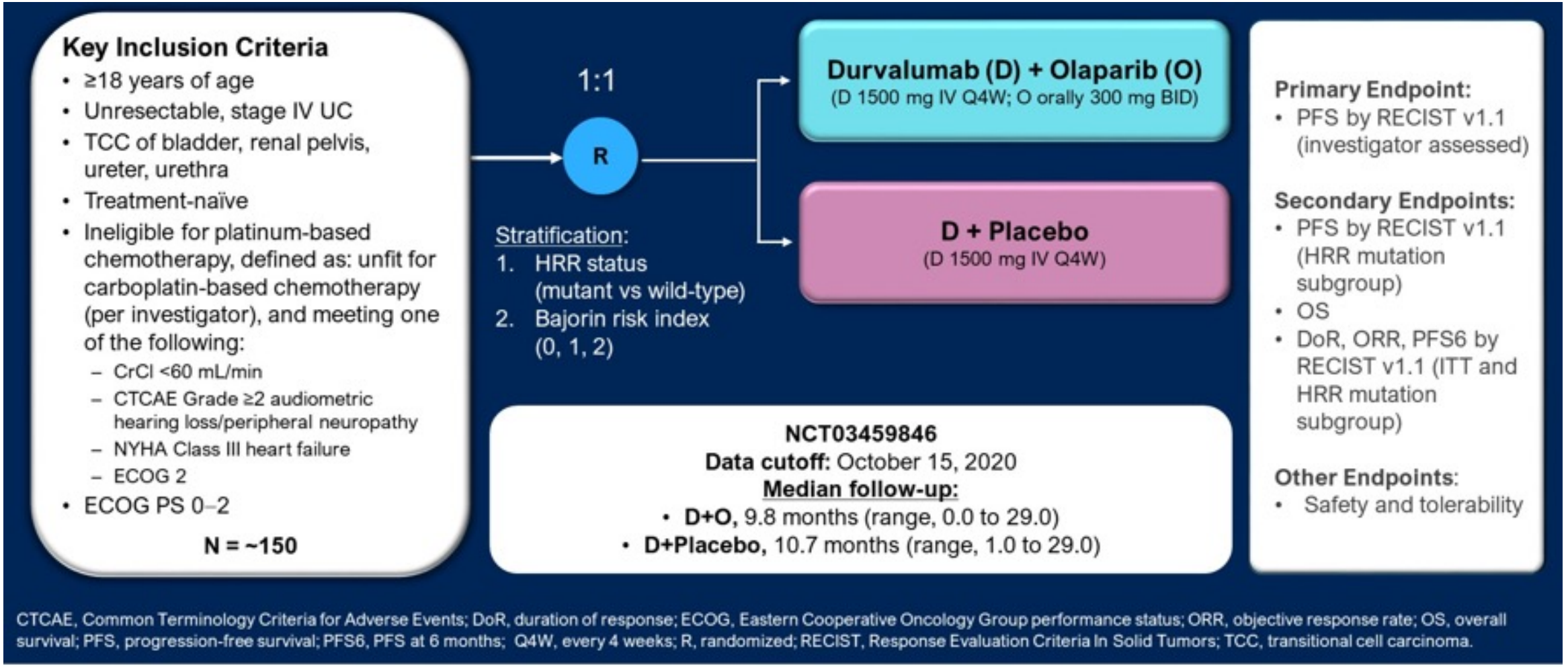
BAYOU: Phase 2 Study Design



CTCAE, Common Terminology Criteria for Adverse Events; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS6, PFS at 6 months; Q4W, every 4 weeks; R, randomized; RECIST, Response Evaluation Criteria In Solid Tumors; TCC, transitional cell carcinoma.

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BAYOU: Select Baseline Characteristics in (IIT Population)

	D+O (n = 78)	D+Placebo (n = 76)
Bajorin risk factors, n (%)		
0	16 (21)	18 (24)
1	38 (49)	36 (47)
2	24 (31)	22 (29)
Previous therapy, n (%)	9 (11.5)	8 (10.5)
HRR status, n (%)		
Mutant	17 (22)	14 (18)
Wild-type	61 (78)	62 (82)
PD-L1 status,* n (%)		
High expression	34 (44)	32 (42)
Low expression	27 (35)	22 (29)
Missing	17 (22)	22 (29)

*High PD-L1 expression was defined as described in Powles, T et al *Lancet Oncol* 21(12):1574-1588 (2020): ≥25% of tumor cells with membrane staining or ≥25% of immune cells staining for PD-L1 at any intensity if >1% of the tumor area contained immune cells, or 100% of immune cells staining for PD-L1 at any intensity if 1% of the tumor area contained immune cells.

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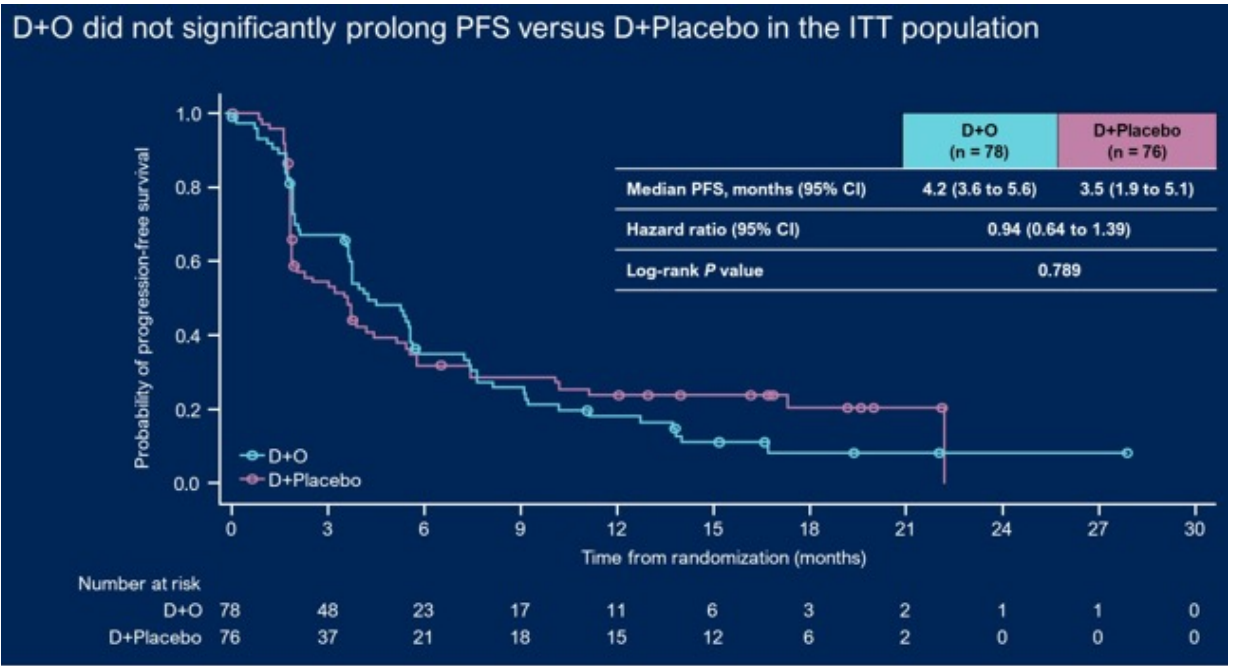
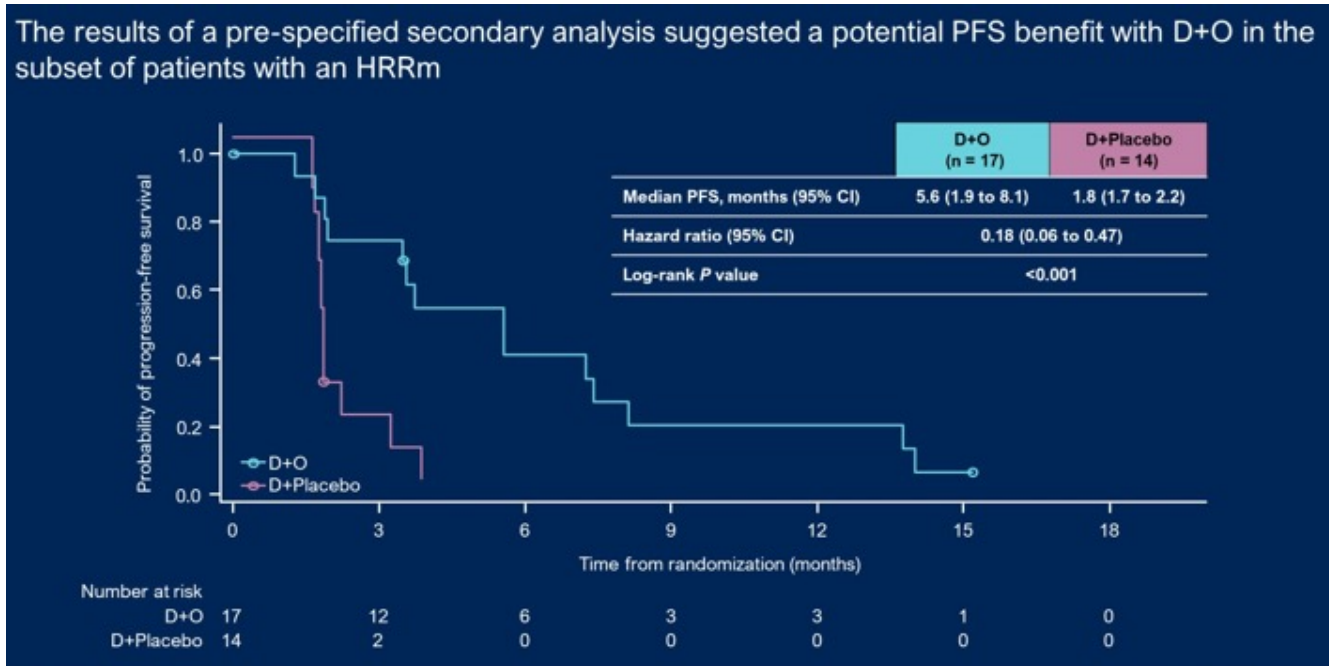
BAYOU: PFS

D+O did not significantly prolong PFS versus D+Placebo in the ITT population



	D+O (n = 78)	D+Placebo (n = 76)
Median PFS, months (95% CI)	4.2 (3.6 to 5.6)	3.5 (1.9 to 5.1)
Hazard ratio (95% CI)	0.94 (0.64 to 1.39)	
Log-rank *P* value	0.789	

The results of a pre-specified secondary analysis suggested a potential PFS benefit with D+O in the subset of patients with an HRRm



	D+O (n = 17)	D+Placebo (n = 14)
Median PFS, months (95% CI)	5.6 (1.9 to 8.1)	1.8 (1.7 to 2.2)
Hazard ratio (95% CI)	0.18 (0.06 to 0.47)	
Log-rank *P* value	<0.001	

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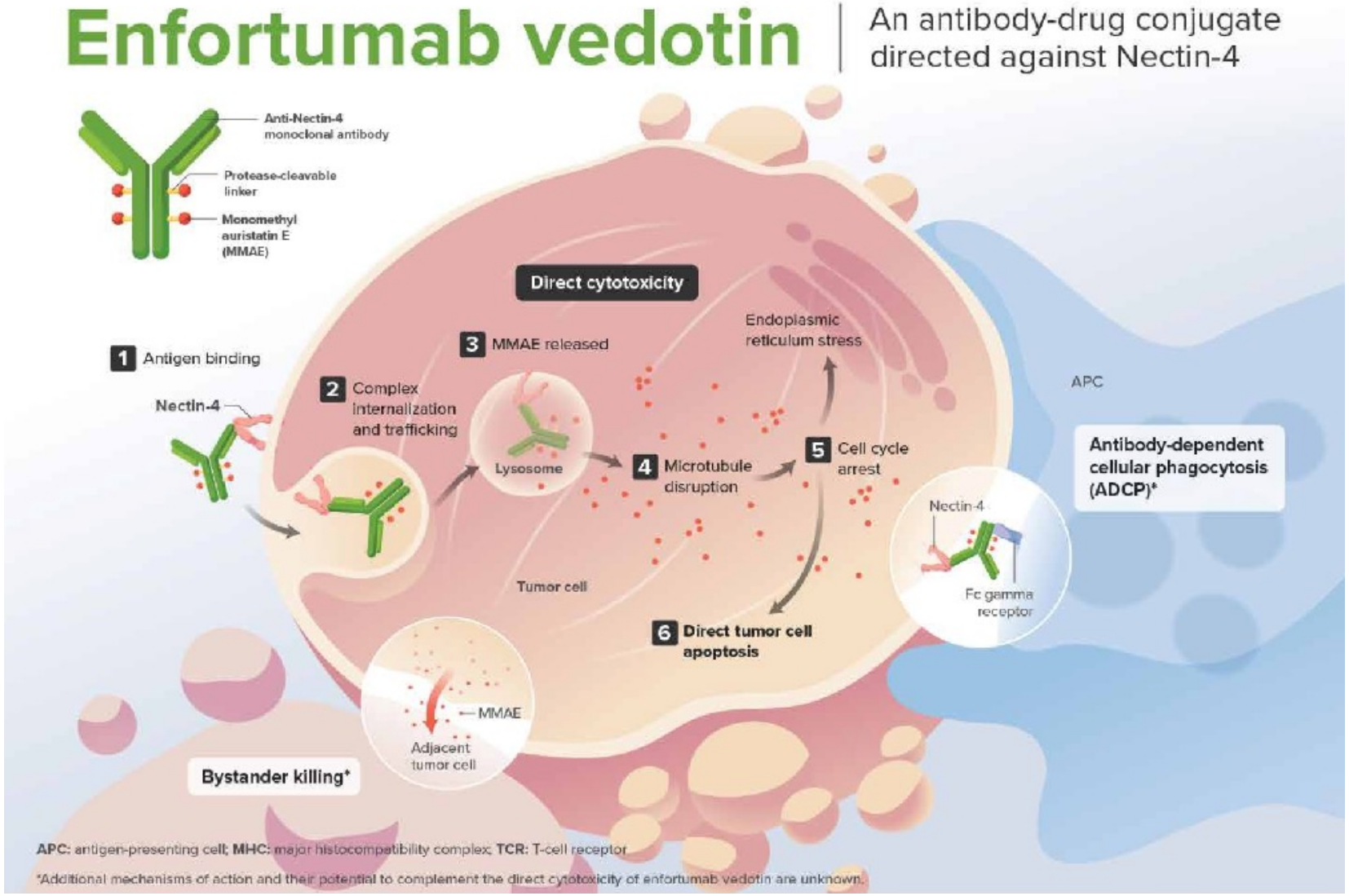

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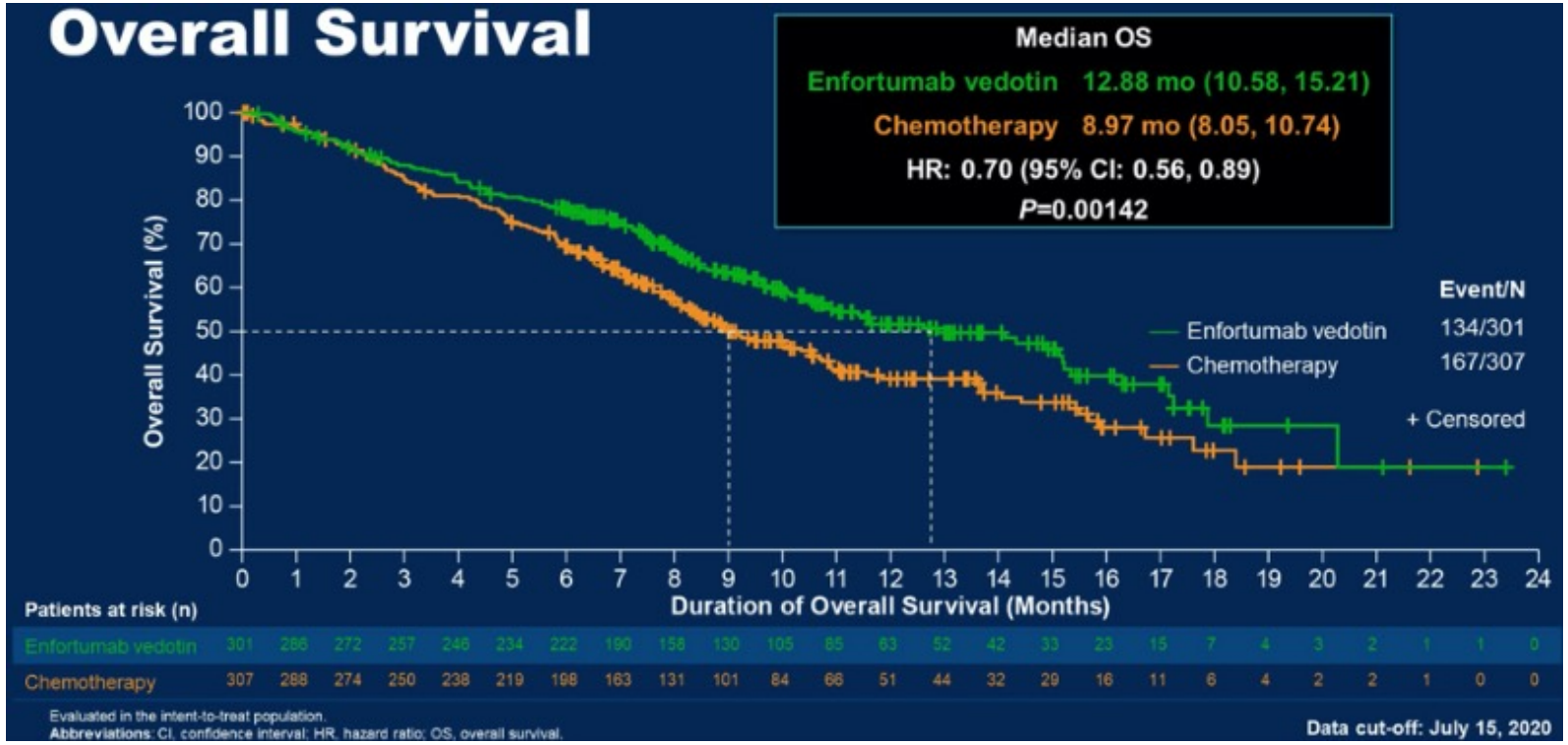
EV-301: Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma



Update at 24 months – ASCO 2022:

- mOS: 12.9 vs 8.9 m (HR 0.70)
- mPFS: 5.6 vs 3.7 m (HR 0.63)
- No new safety signals

Powles et al. GU ASCO 2021.
Rosenberg et al. ASCO 2022.

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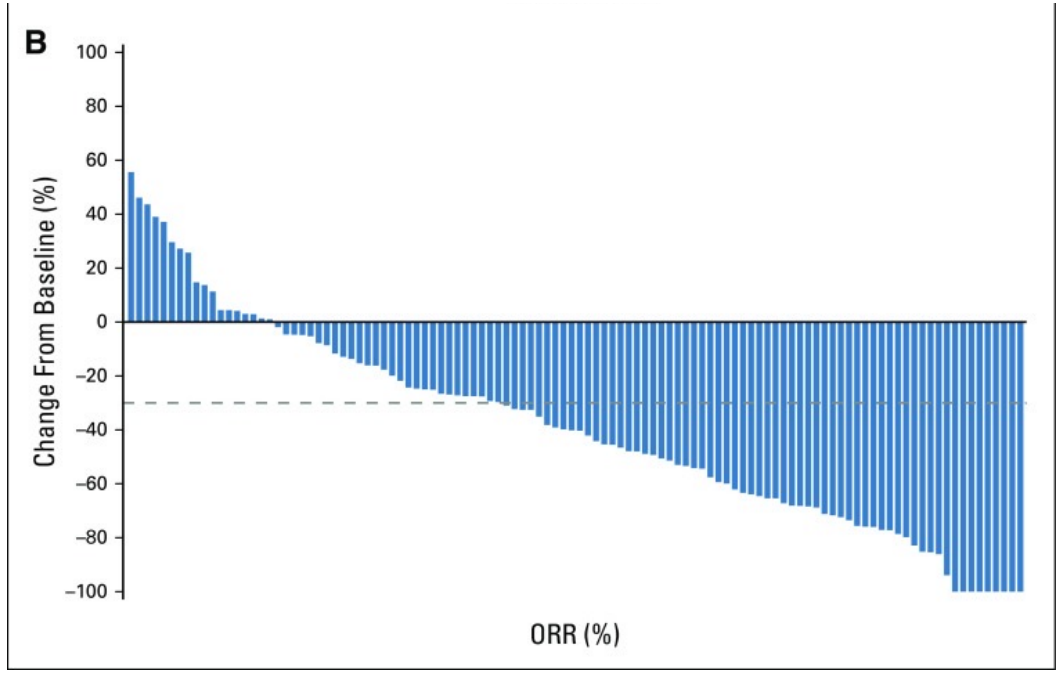
EV-201: Cohort 1: Enfortumab Vedotin Phase II Trial



- Patients treated with prior Chemo and IO
- 92 of 110 patients evaluable
- Target lesions reduced in 84%
- ORR 55%
  - 56% in IO responders
  - 41% in IO non-responders

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Table 2. Treatment-Related Adverse Events (Safety Population).*

Adverse Event	Enfortumab Vedotin Group (N=296)		Chemotherapy Group (N=291)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	278 (93.9)	152 (51.4)	267 (91.8)	145 (49.8)
Alopecia	134 (45.3)	0	106 (36.4)	0
Peripheral sensory neuropathy†	100 (33.8)	9 (3.0)	62 (21.3)	6 (2.1)
Pruritus	95 (32.1)	4 (1.4)	13 (4.5)	0
Fatigue	92 (31.1)	19 (6.4)	66 (22.7)	13 (4.5)
Decreased appetite	91 (30.7)	9 (3.0)	68 (23.4)	5 (1.7)
Diarrhea	72 (24.3)	10 (3.4)	48 (16.5)	5 (1.7)
Dysgeusia	72 (24.3)	0	21 (7.2)	0
Nausea	67 (22.6)	3 (1.0)	63 (21.6)	4 (1.4)
Maculopapular rash	48 (16.2)	22 (7.4)	5 (1.7)	0
Anemia	34 (11.5)	8 (2.7)	59 (20.3)	22 (7.6)
Decreased neutrophil count	30 (10.1)	18 (6.1)	49 (16.8)	39 (13.4)
Neutropenia	20 (6.8)	14 (4.7)	24 (8.2)	18 (6.2)
Decreased white-cell count	16 (5.4)	4 (1.4)	31 (10.7)	20 (6.9)
Febrile neutropenia	2 (0.7)	2 (0.7)	16 (5.5)	16 (5.5)

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EV-301: Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma

Treatment-Related Adverse Event	Enfortumab Vedotin N=296		Chemotherapy N=291	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Skin Reactions[a]	**47%**	**15%**	**16%**	**1%**
Rash	44%	15%	10%	0[c]
Severe cutaneous adverse reactions[b]	20%	5%	8%	1%
Peripheral neuropathy	**46%**	**5%**	**31%**	**2%**
Sensory events	44%	4%	30%	2%
Motor events	7%	2%	2%	0
Hyperglycemia	**6%**	**4%**	**0[c]**	**0**

The majority of TRAEs of special interest were mild-to-moderate in severity.

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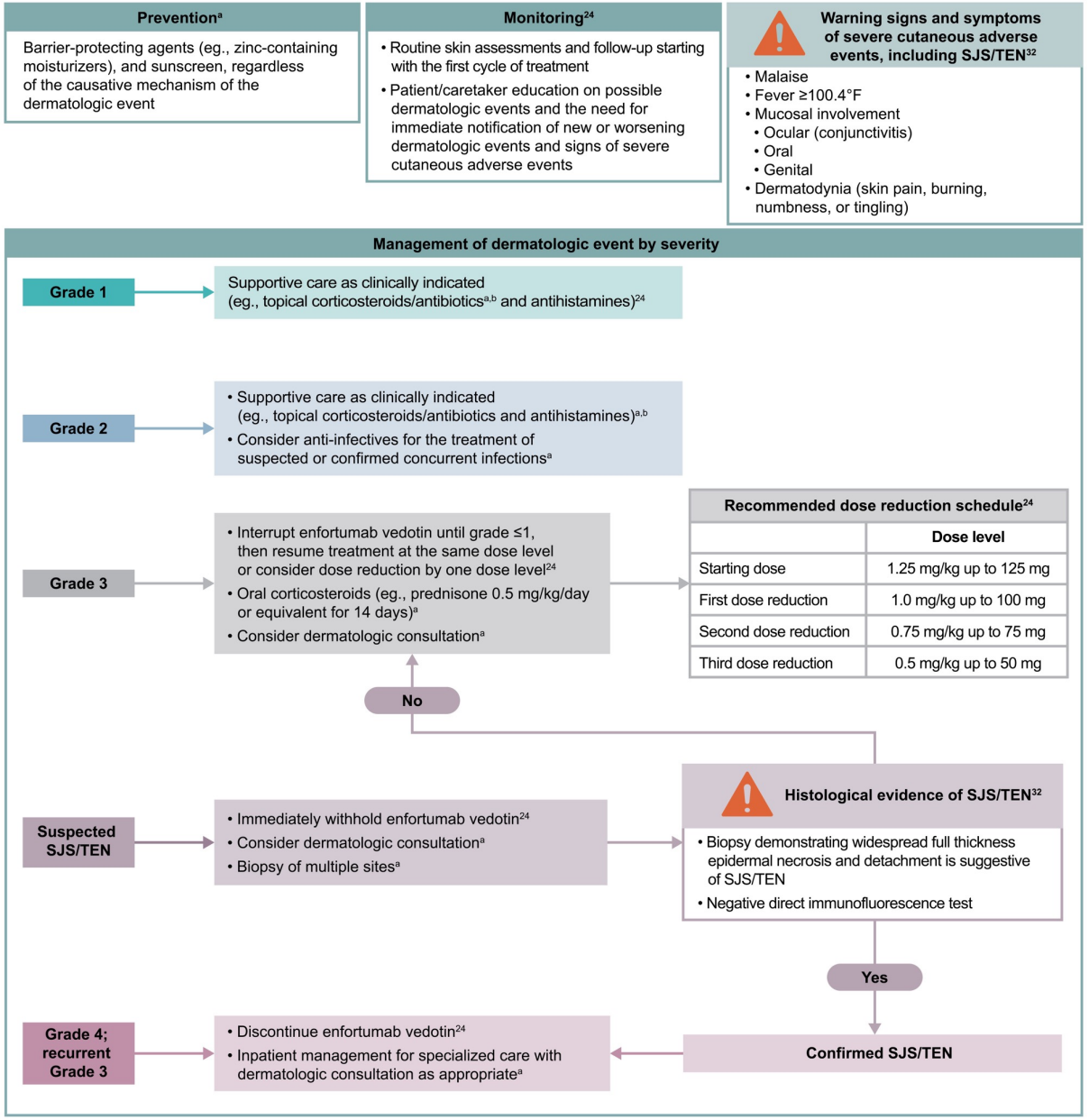
Enfortumab Vedotin Skin Toxicity



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Expression of Nectin-4 and PD-L1 in bladder cancer with variant histology.

Nectin-4 and PD-L1 staining results among BCVH subtypes.

			Nectin-4 H-score		PD-L1
Histology	No. of specimens	% of total (N = 117)	Mean	Median (range)	CPS ≥ 10 n(%)
Squamous	31	26.5	207.7	219.5 (17-300)	15/30 (50)
Adenocarcinoma	24	20.5	166.9	140.0 (45-299)	4/24 (16.7)
Sarcomatoid	24	20.5	52.3	2.5 (0-300)	17/24 (70.8)
Plasmacytoid	20	17.1	253.5	257.5 (108-300)	1/20 (5)
Small cell	10	8.5	46.8	0 (0-233)	2/10 (20)
Mixed	8	6.8	122	105 (20-265)	2/8 (25)

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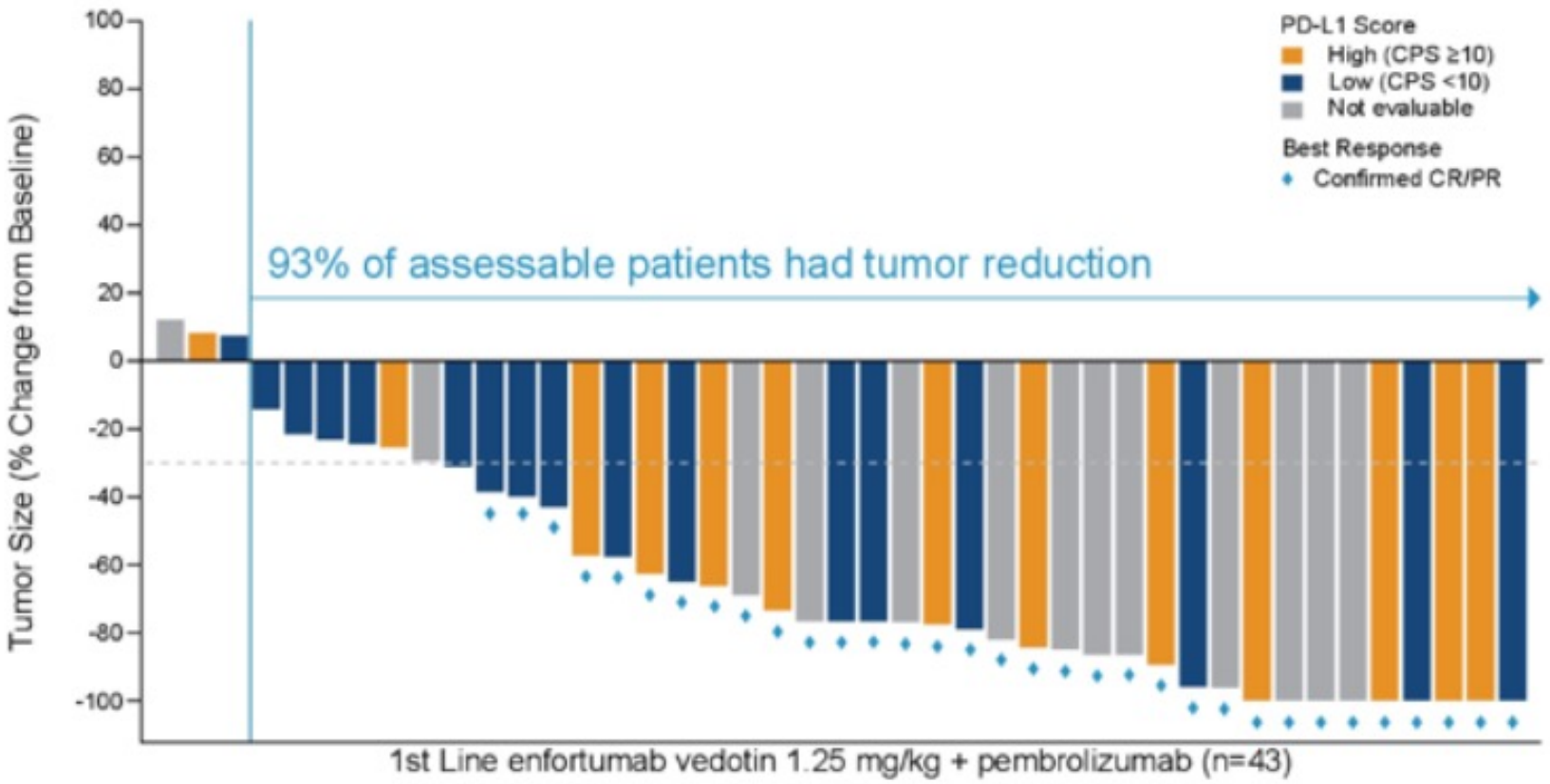
EV-103: Cohort A: Enfortumab Vedotin + Pembrolizumab



- 45 patients
- Front-line Cis-ineligible
- ORR 73.3%
- 17.8% CR
- mDOR: 25.6 months
- mPFS 12.3 months
- mOS 26.1 months

Phase 3 EV-302 is randomizing EV + P vs Gem + cis/carbo in front-line aUC

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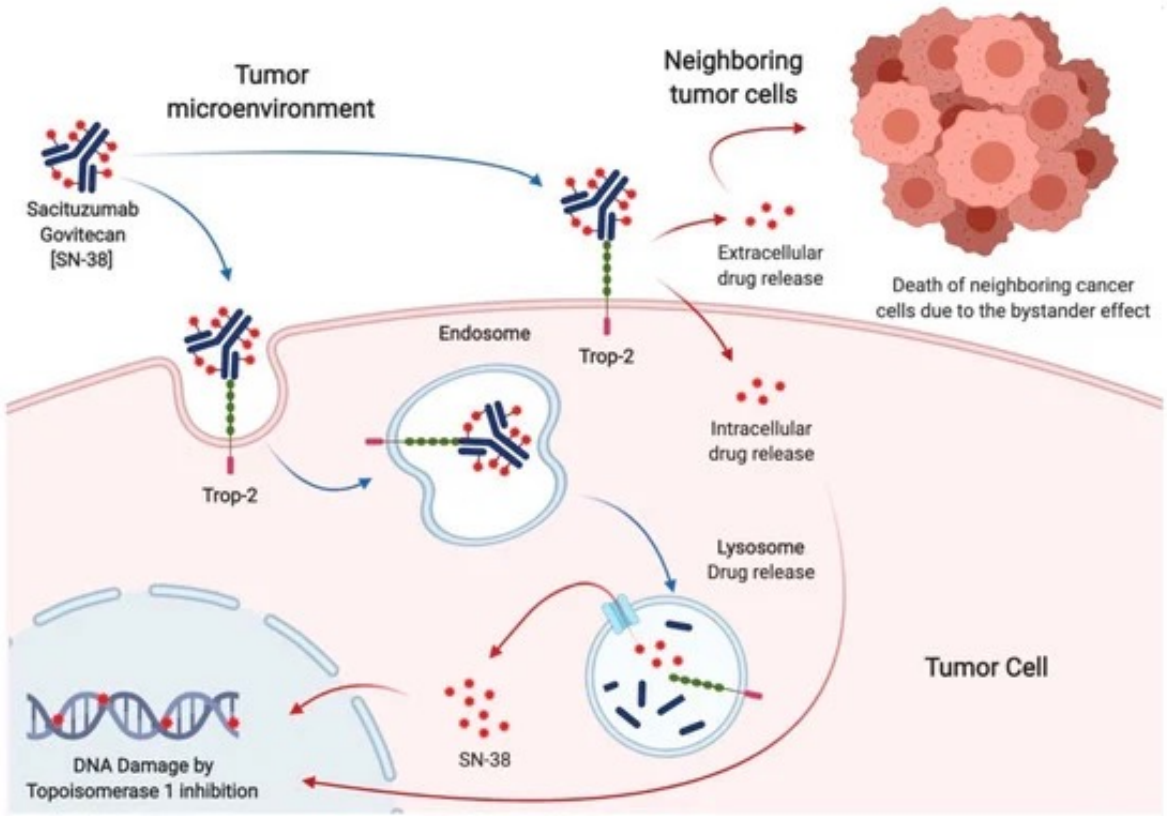
Sacituzumab Govitecan (SG): Trop-2-Directed ADC



- SG is a novel ADC composed of Trop-2 antibody coupled to SN-38, the active metabolite of irinotecan
- SG was granted FDA –accelerated approval for patients with locally advanced or mUC who have previously received a platinum-chemotherapy and a CPI.
- In the mUC cohort (N=45) of IMMU-132-01 with a median of 2 prior therapies, SG showed an ORR of 29% and median DOR of 12.9 months.[2]
- In the Phase 2 registrational TROPHY-U-01 study, SG monotherapy resulted in 27% ORR and a median DOR of 7.2 months in heavily pretreated patients with mUC (N-113; cohort 1). [3]

1. Pavone, G. et al. Molecules. 2021.
2. Bardia, A. et al. Ann Oncol. 2021.
3. Tagawa, ST. et al. J Clin Oncol. 2021.

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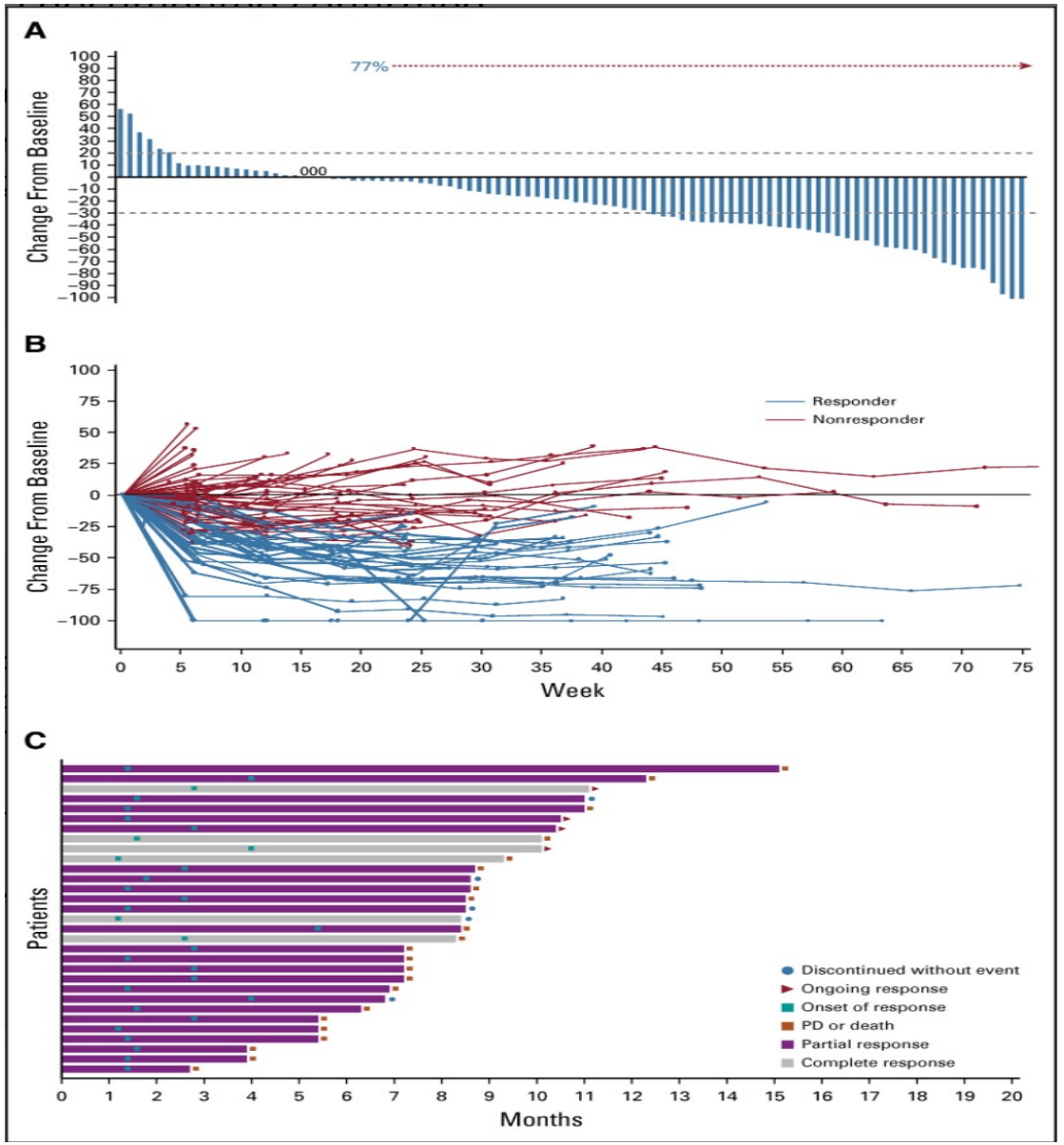
TROPHY-U-01 Cohort 1
Prior Platinum and IO

- 113 patients
- ORR 27.4%, including 6 CR (5.3%) and 25 PR (22.1%)
- Median DOR 7.2 mo (95% CI, 4.7 – 8.6m)
- mPFS 5.4mo (95% CI, 3.5 - 7.2 m; range 2.4 - 8.9)
- mOS 10.9mo (95% CI 9 - 13 m; range 3.8 -19.8



1. Petrylak, DP. ASCO.2020 (Abstract 5027)
2. Tagawa, ST. et al. J Clin Oncol. 2021.

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TROPHY-U-01 Cohort 1

TABLE 3. Most Common TRAEs of Any Grade (Observed in ≥ 20% of Patients) orTRAEs Grade ≥ 3 (Observed in ≥ 5% of Patients) (N = 113)

Category	Event	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Hematologic[a]	Neutropenia	46	22	12
	Leukopenia	25	12	5
	Anemia	33	14	0
	Lymphopenia	11	5	2
	Febrile neutropenia	10	7	3
GI	Diarrhea	65	9	1
	Nausea	60	4	0
	Vomiting	30	1	0
General disorders and administrative site conditions	Fatigue	52	4	0
Skin and subcutaneous tissue	Alopecia	47	0	0
Metabolism and nutrition	Decreased appetite	36	3	0
Infections and infestations	Urinary tract infection	8	6	0

Abbreviation: TRAEs, treatment-related adverse events.

[a]Neutrophil count decreased, WBC count decreased, lymphocyte count decreased, and hemoglobin decreased have been recoded to neutropenia, leukopenia, lymphopenia, and anemia, respectively, for summary purposes.

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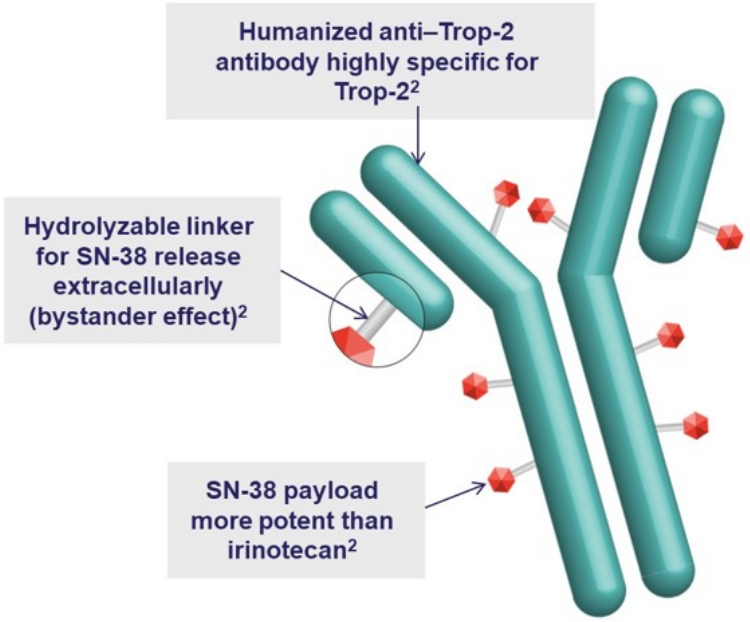
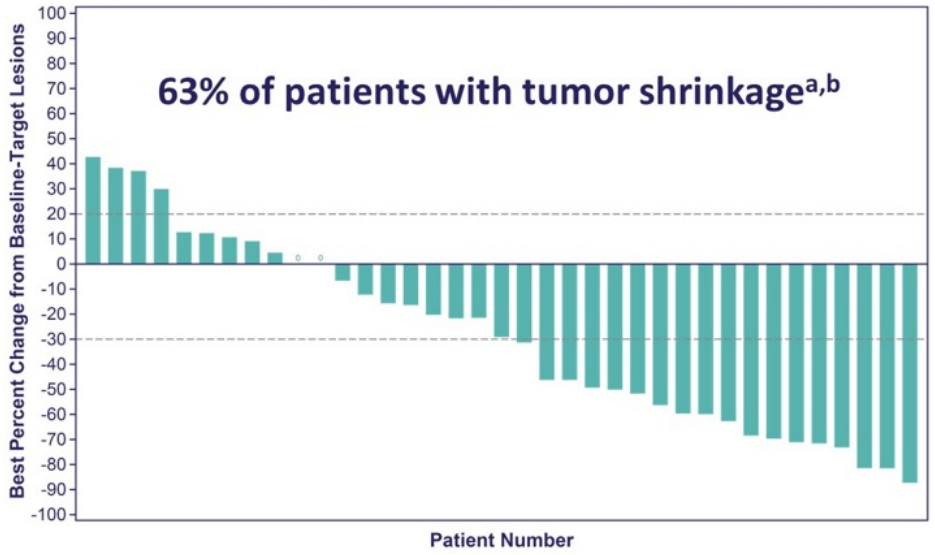
Early Results of TROPHY-U-01 Cohort 3: SG in combo with Pembro in pts with mUC who progressed after PLT-based regimens



Overall Response and Best % Change From Baseline in Tumor Size

- Median follow-up: 5.8 months (data cutoff date: 2021-09-24)
- Median time to response: 2 months (1.3–2.8; n=14)
- Median DOR not yet reached: N/A (2.80-N/A)
- Median PFS (95% CI), 5.5 months (1.7–NR); median OS, not reached



	Cohort 3[a] (N=41)
Objective response rate (CR + PR), n (%) [95%CI]	14 (34) [20.1-50.6]
Objective response rate (CR + PR), evaluable patients, n (%)	14 (38)
Best overall response, n (%)	
CR	1 (2)
PR	13 (32)
SD	11 (27)
SD ≥ 6 months	*4 (10)*
PD	12 (29)
Not assessed	4 (10)
Clinical Benefit Rate (CR + PR + SD), n (%) [95%CI]	25 (61) [44.5-75.8]

- Treatment-related Gr 3-4 AEs in 59% of patients. 39% of pts had SG dose reduction due to TRAE.
- No treatment-related death occurred.

Presented by Petros Grivas at GU ASCO 2022. Abstract #434

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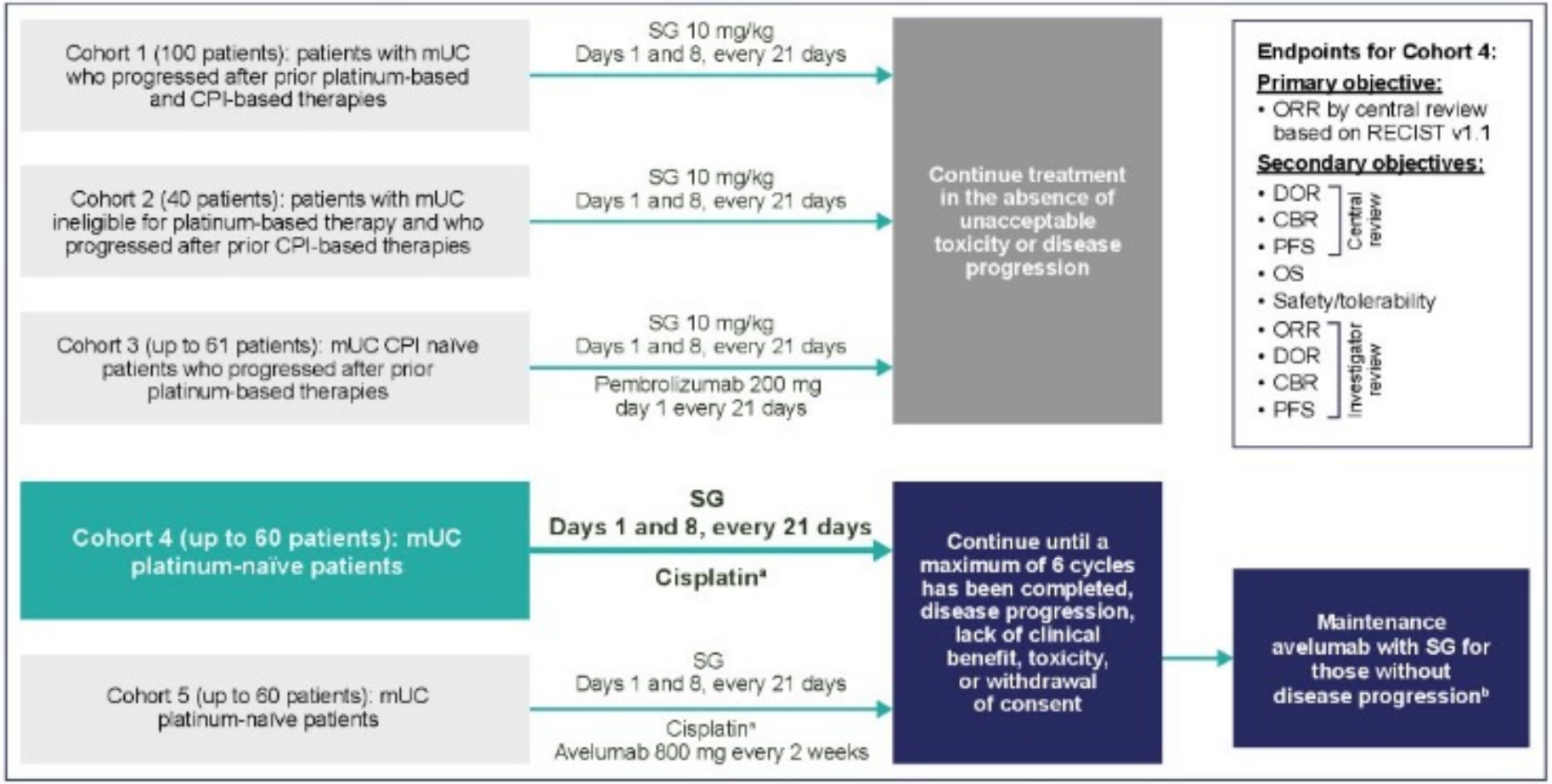
TROPHY-U-01

Figure 3. TROPHY-U-01 (NCT03547973)



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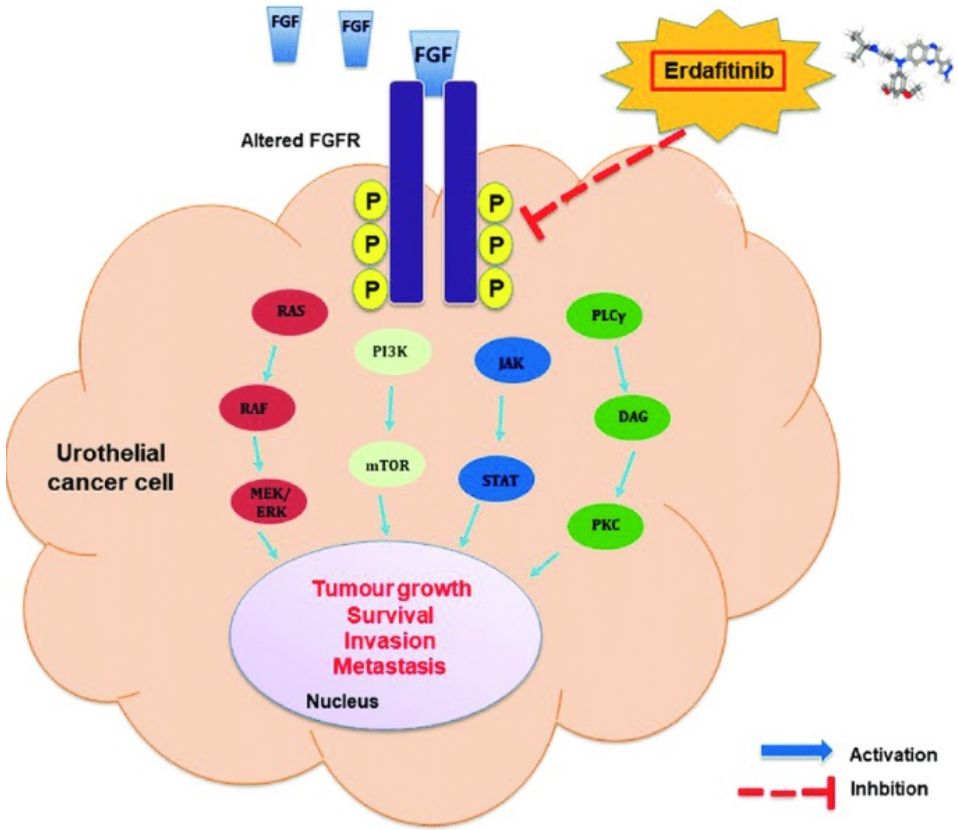
Erdafitinib



- FDA approved for patients with susceptible FGFR3 or FGFR2 alterations that have progressed following platinum

Table 1. Demographic and Clinical Characteristics of the 99 Patients in the Selected-Regimen Group at Baseline.*

Characteristic	Value
Age — yr	
Median	68
Range	36–87
ECOG performance-status score — no. (%)†	
0	50 (51)
1	42 (42)
2	7 (7)
Treatment history — no. (%)	
Progression or relapse after chemotherapy	87 (88)
No previous chemotherapy	12 (12)
Progression or relapse after immunotherapy	22 (22)
No. of previous treatments — no. (%)	
0	11 (11)
1	45 (45)
≥2	43 (43)
Visceral metastasis — no. (%)	
Present‡	78 (79)
Absent	21 (21)
Creatinine clearance rate — no. (%)	
<60 ml/min	52 (53)
≥60 ml/min	47 (47)

Loriot et al. NEJM 2019.
D'Angelo A er al. Expert Rev Clin Pharmacol. 2020.

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Erdafitinib

Update 2022:
Siefker-Radtke et al,
The Lancet Oncology

- ORR 40% (40/101)
- No new safety signals

Table 2. Antitumor Activity of Erdafitinib in the 99 Patients in the Selected-Regimen Group.*

Variable	Value	Rate of Response (95% CI)
		percent
Response per investigator assessment — no. of patients†		
Any objective response	40	40 (31–50)
Complete response	3	3
Partial response	37	37
Stable disease	39	39
Progressive disease	18	18
Could not be evaluated or unknown	2	2
Median time to response — mo	1.4	
Median duration of response (95% CI) — mo	5.6 (4.2–7.2)	
Response according to daily dose of erdafitinib — no./total no.		
8 mg	20/58	34 (22–47)
8 mg with dose escalation to 9 mg	20/41	49 (34–64)
Response according to genetic alteration — no./total no.		
FGFR3 mutation	36/74	49 (37–60)
FGFR2/3 fusion	4/25	16 (2–30)

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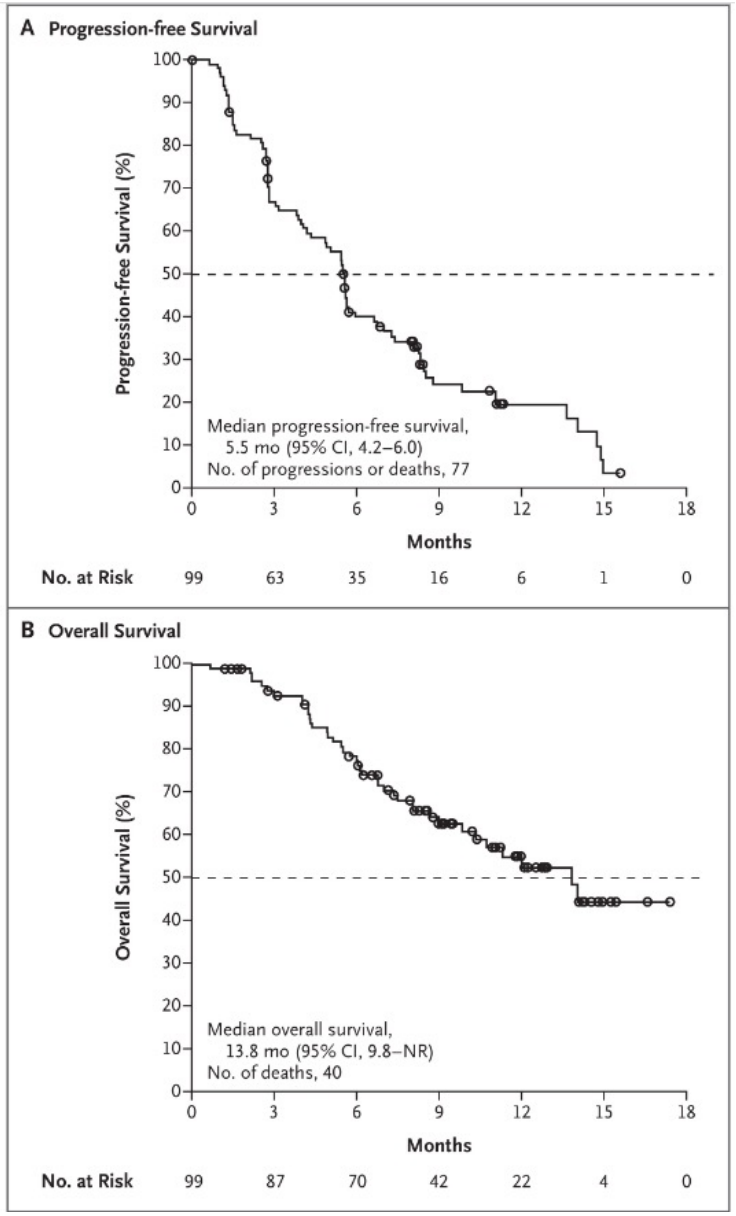
Erdafitinib



Loriot et al. NEJM 2019.

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Erdafitinib

Table 3. Adverse Events in the 99 Patients in the Selected-Regimen Group.*

Adverse Event	Any Grade	Grade 1	Grade 2	Grade ≥3
		number of patients (percent)		
Hyperphosphatemia	76 (77)	53 (54)	21 (21)	2 (2)
Stomatitis	57 (58)	21 (21)	26 (26)	10 (10)
Diarrhea	50 (51)	31 (31)	15 (15)	4 (4)
Dry mouth	45 (46)	34 (34)	11 (11)	0
Decreased appetite	38 (38)	18 (18)	20 (20)	0
Dysgeusia	37 (37)	23 (23)	13 (13)	1 (1)
Fatigue	32 (32)	12 (12)	18 (18)	2 (2)
Dry skin	32 (32)	24 (24)	8 (8)	0
Alopecia	29 (29)	23 (23)	6 (6)	0
Constipation	28 (28)	19 (19)	8 (8)	1 (1)
Hand–foot syndrome	23 (23)	6 (6)	12 (12)	5 (5)
Anemia	20 (20)	9 (9)	7 (7)	4 (4)
Asthenia	20 (20)	2 (2)	11 (11)	7 (7)
Nausea	20 (20)	13 (13)	6 (6)	1 (1)
Dry eye	19 (19)	14 (14)	4 (4)	1 (1)
Onycholysis	18 (18)	6 (6)	10 (10)	2 (2)
Alanine aminotransferase increased	17 (17)	13 (13)	2 (2)	2 (2)
Paronychia	17 (17)	3 (3)	11 (11)	3 (3)
Blurred vision	17 (17)	10 (10)	7 (7)	0
Nail dystrophy	16 (16)	5 (5)	5 (5)	6 (6)
Urinary tract infection	16 (16)	0	11 (11)	5 (5)
Vomiting	13 (13)	10 (10)	1 (1)	2 (2)
Hyponatremia	12 (12)	1 (1)	0	11 (11)

Loriot et al. NEJM 2019.

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Research Frontiers: HER 2 Targeting

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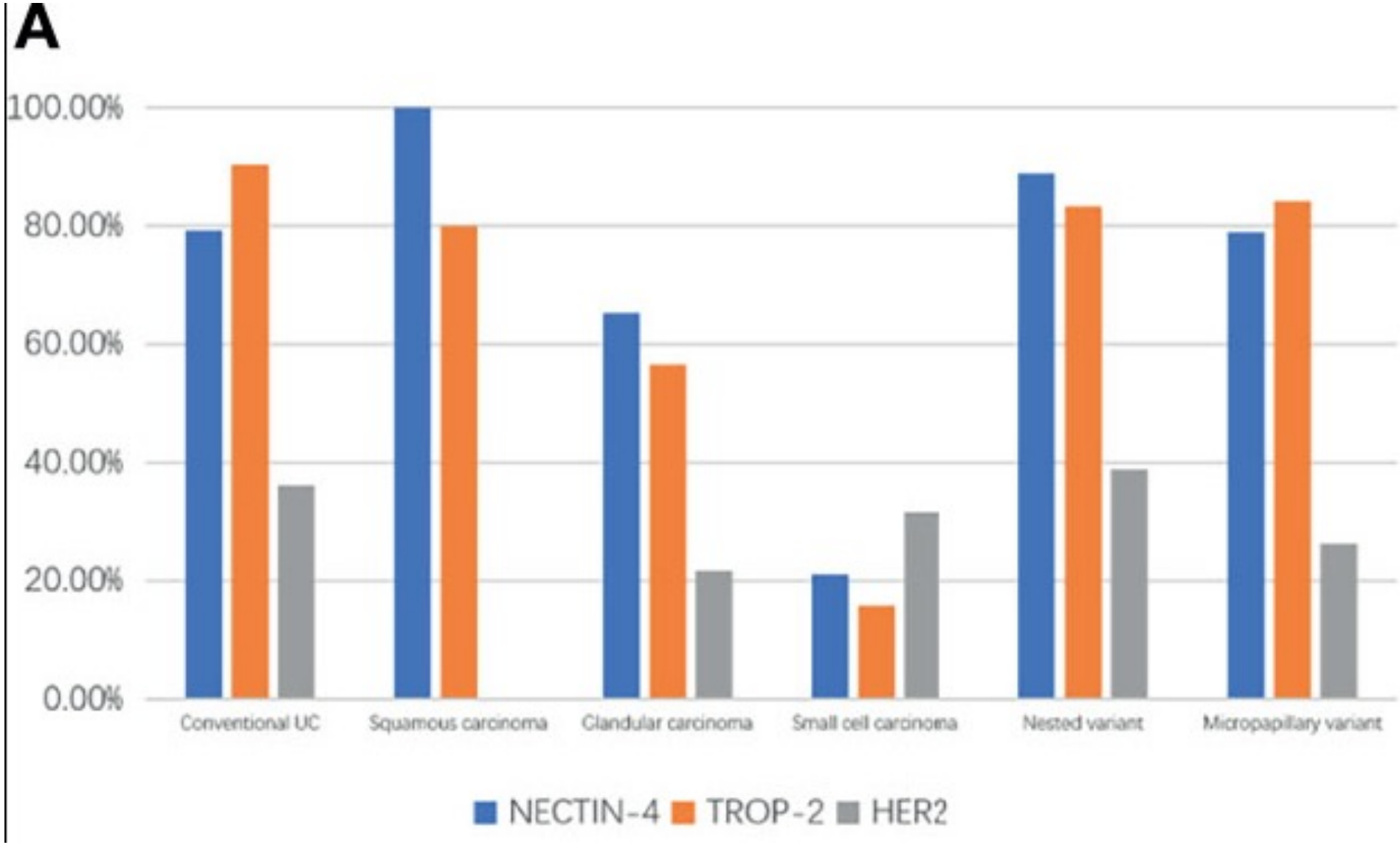

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HER2 Failures

- Trastuzumab + Carboplatin, Paclitaxel, Gemcitabine
  - 22.7% suffered cardiac toxicity, 2 deaths
- Platinum/Gemcitabine ± Trastuzumab: No PFS difference (10.2 vs 8.2 m)
- Lapatanib: 3% PR as single-agent
- Lapatanib as maintenance post-chemo (Phase III). No PFS or OS benefit
- Afatanib: 21.7% had a 3 month PFS
- TDM1 basket study without much efficacy in urothelial cancer
- Tucatanib + Trastuzumab basket study ongoing

Hussain MH et al. JCO 2007.
Oudard S et al. European Journal of Cancer. 2015.
Wulfing C et al. Cancer. 2009
PowelsvT et al. JCO. 2017.
Hyman DM et al. Cancer Res. 2017

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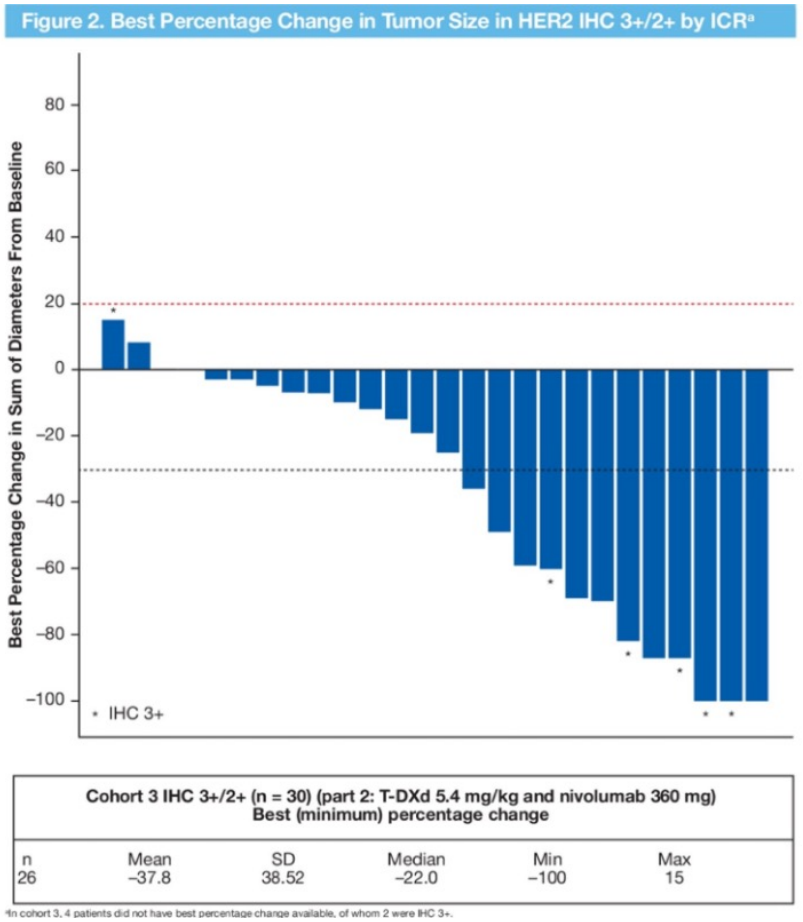
Trastuzumab Deruxtecan + Nivolumab (DS8201-a-U105)

- Cohort 3, UC HER2 IHC 2/3+ (n=30)
- ORR 36.7%
  - CR 13.3%
  - PR 23.3%
  - SD 40%
- mPFS 6.9m
- mOS 11 m
- No previous IO
- Most common TEAEs: Nausea (73.5%), Fatgiue (52.9%), Vomitting (44.1%).
  - ILD/Pneumonitis in 23.5%. 1 G5.



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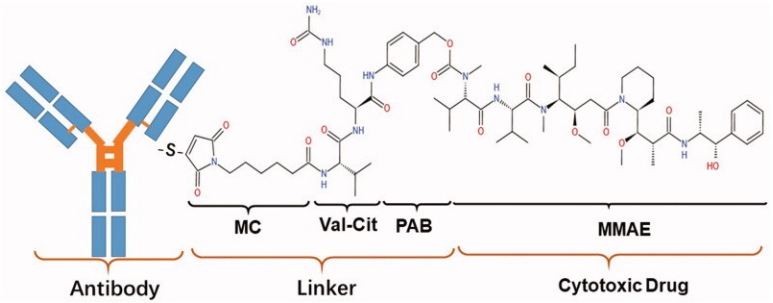
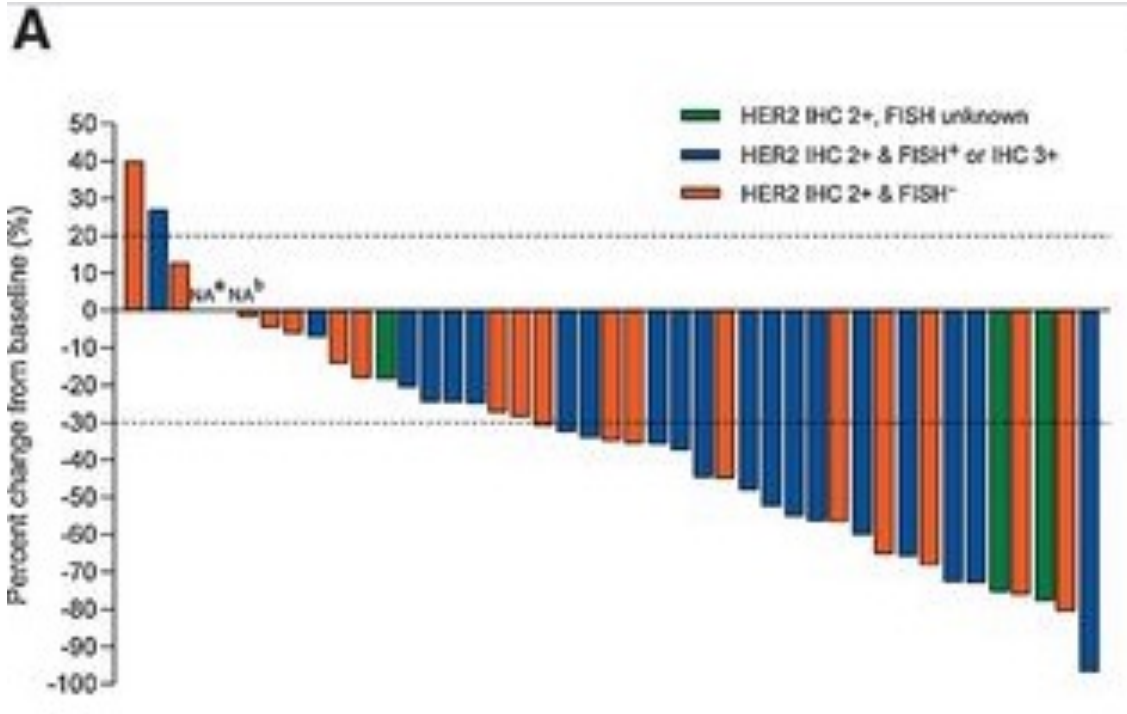
Disitamab vedotin (RC-48)



- mPFS 6.9 months
- mOS 13.9 motns

43 Patients
- CR 0%
- PR 51%
- SD 40%

Duration of Response 6.9 m



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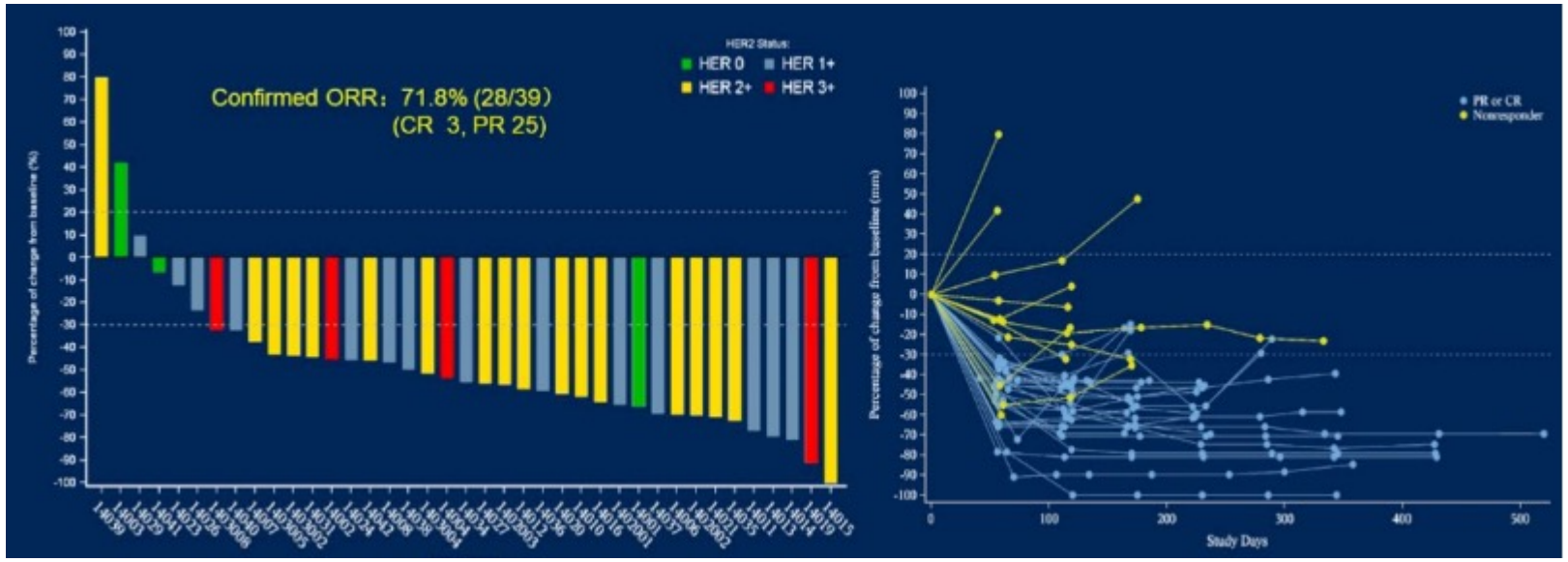
Disitamab vedotin (RC-48) + Toripalimab (anti-PD1)

- Phase 1b/II Trial of 41 patients
  - 61% had NOT received prior systemic therapy
  - 54% HAD visceral metastases; 24% had liver mets
  - HER2 IHC 2/3+ in 59%; PD-L1 CPS ≥10 in 32%



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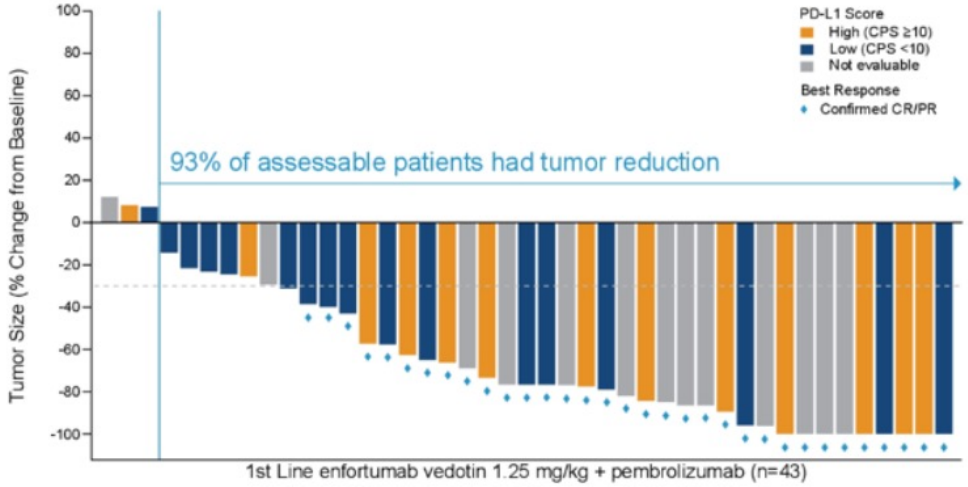
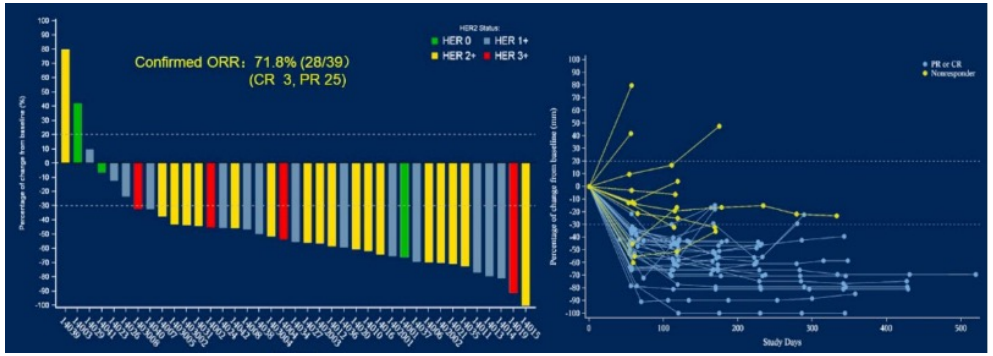
MMAE Payload (Blocks polymerization of tubulin)

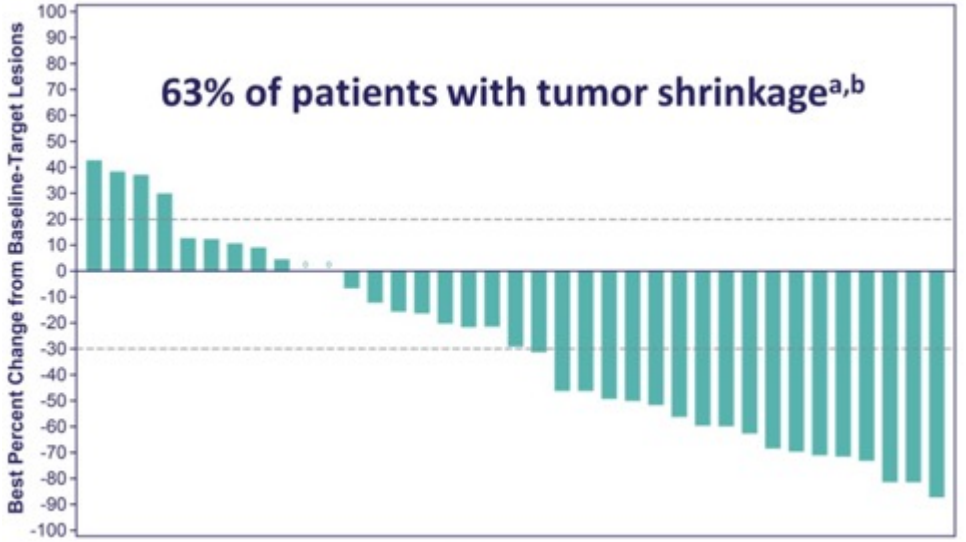


EV + PD1: OR 73%



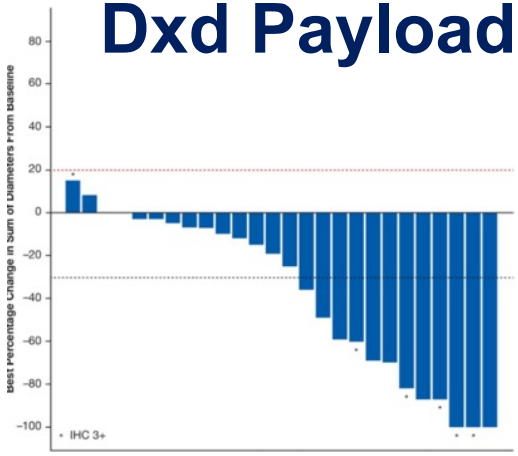
RC-48 + PD1: OR 72%

SN-38 Payload (Topo-1 inh)



SG + PD1: OR 34%

Dxd Payload (Topo-1 inh)



T-Dxd + PD1: OR 37%

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Research Frontiers: TKI + IO

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Cosmic-021 Cohort 2: Cabozantinib + Atezolizumab in patients previously treated with platinum

Cabozantinib 40 mg QD PO +
Atezolizumab 1200 mg Q3W IV
(N = 30)

Single-arm Phase 1b

Patients with locally advanced or metastatic UC with transitional cell histology, radiographic evidence of progression on/after platinum-containing CT, and no prior ICIs or cabozantinib (N = 30)

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COSMIC-021 Cohort 2 Expansion: Efficacy

Tumor Response per Investigator by RECIST v1.1	UC Cohort 2 (N=30)
Objective response rate (80% CI), %	27 (16–40)
Best overall response, n (%)	
Complete response	2 (6.7)
Partial response	6 (20)
Stable disease	11 (37)
Progressive disease	7 (23)
Missing	4 (13)
Disease control rate, n (%)	19 (63)
Duration of objective response, median (range), months	NR (1.4+–15.6+)
Time to objective response, median (range), months	3.0 (1–6)

Disease control rate = complete response + partial response + stable disease; NR, not reached

- Median PFS: 5.4 mos (95% CI: 1.5-7.6)
- 27% with response
- Reduction in target lesion size observed in 16 (53%) patients
- No association between PD-L1 expression and tumor response based on preliminary data

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COSMIC-021 Cohorts 3, 4, 5

	C3 (cisplatin ineligible) (N = 30)	C4 (cisplatin eligible) (N = 30)	C5 (received prior ICI) (N = 31)
ORR, % (95% CI)	20 (8, 39)	30 (15, 49)	10 (2, 26)
Best overall response, n (%)			
Complete response (CR)	1 (3)	2 (7)	0
Partial response (PR)	5 (17)	7 (23)	3 (10)
Stable disease (SD)	18 (60)	10 (33)	16 (52)
Progressive disease	3 (10)	7 (23)	8 (26)
Disease control rate, % (95% CI)*	80 (61, 92)	63 (44, 80)	61 (42, 78)
Median DOR, mo (95% CI)	7.1 (2.8, NE)	NE (7.2, NE)	4.1 (2.6, NE)
Median PFS, mo (95% CI)	5.6 (3.1, 11.1)	7.8 (1.6, 13.8)	3.0 (1.8, 5.5)
Median OS, mo (95% CI)	14.3 (8.6, NE)	13.5 (7.8, 23.2)	8.2 (5.5, 9.8)

*CR + PR + SD.

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