Contemporary Management of Advanced Bladder Cancer

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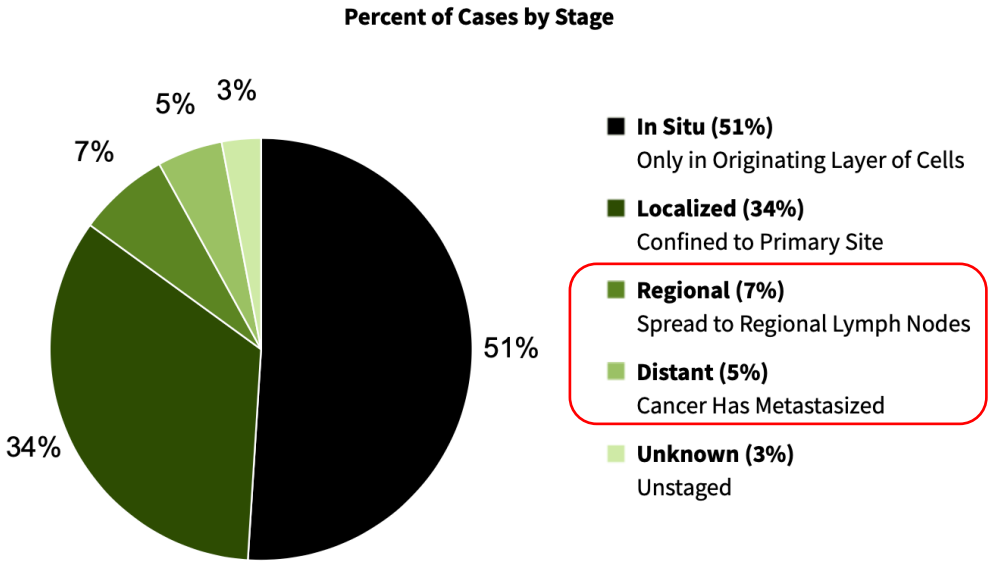
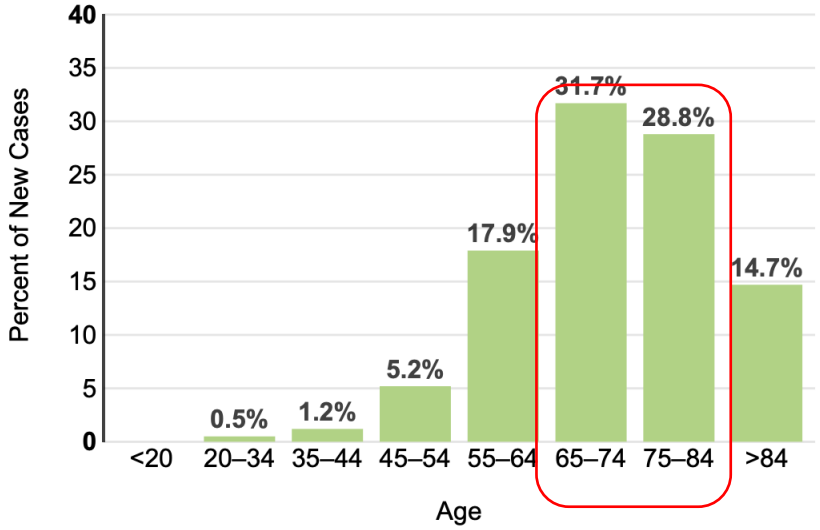
Advanced UC is a heterogenous disease





Heterogeneity in initial stage of diagnosis: ?? biology

Heterogeneity in initial treatment of localized disease

Majority of cases diagnosed 65-85

Significant variation in comorbidities

Bladder Cancer Advocacy Network. Siegel RL, et al. *CA Cancer J Clin*. 2022;72(1):7-33. SEER 17.

Patient considerations in advanced UC

- Hearing loss
- Renal dysfunction
- Congestive heart failure
- Peripheral neuropathy
- Poor performance status

→ Cisplatin-ineligible (40-50%)

- ECOG PS ≥ 3
- Cr Cl < 30 ml/min
- Peripheral neuropathy ≥ Grade 2
- NYHA Heart Failure Class ≥ 3
- ECOG PS 2 AND Cr Cl < 30 ml/min

→ Platinum-ineligible (10-15%)

Galsky et al. Lancet Oncol 2011; Gupta et al. ASCO 2022

Platinum chemotherapy in advanced UC

Cisplatin-eligible patients: GC vs. MVAC

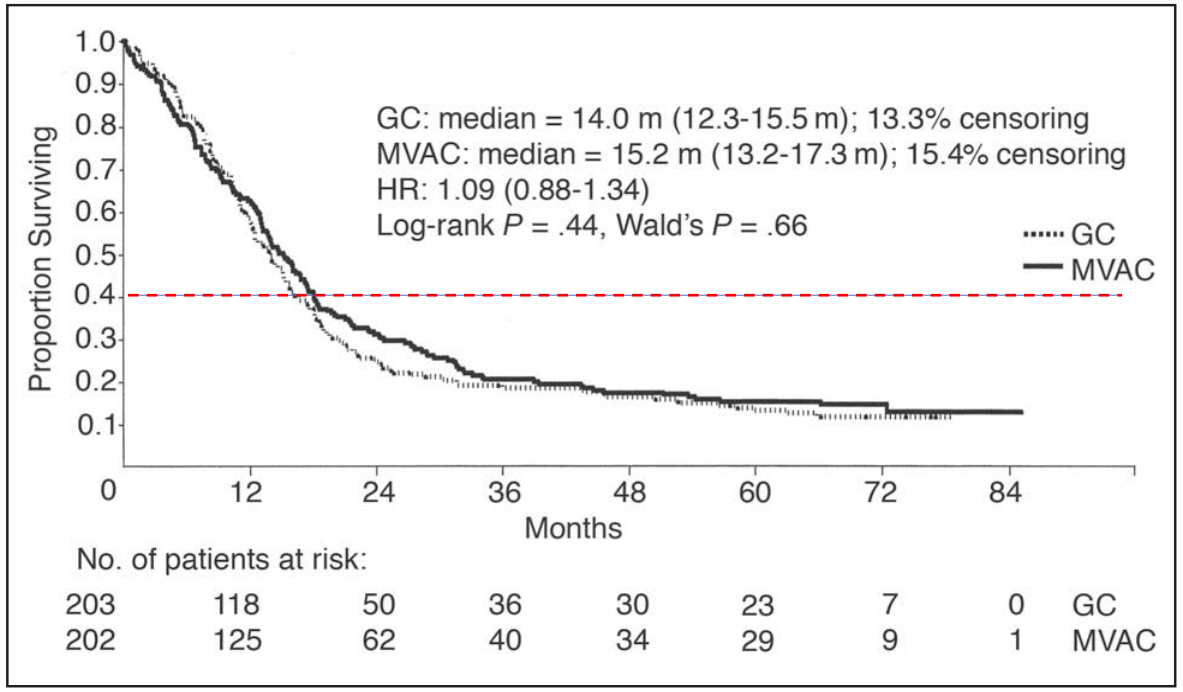


Fig 1. Kaplan-Meier curves for overall survival. GC, gemcitabine/cisplatin; MVAC, methotrexate/vinblastine/doxorubicin/cisplatin; HR, hazard ratio;

Cisplatin in-eligible: EORTC 30986

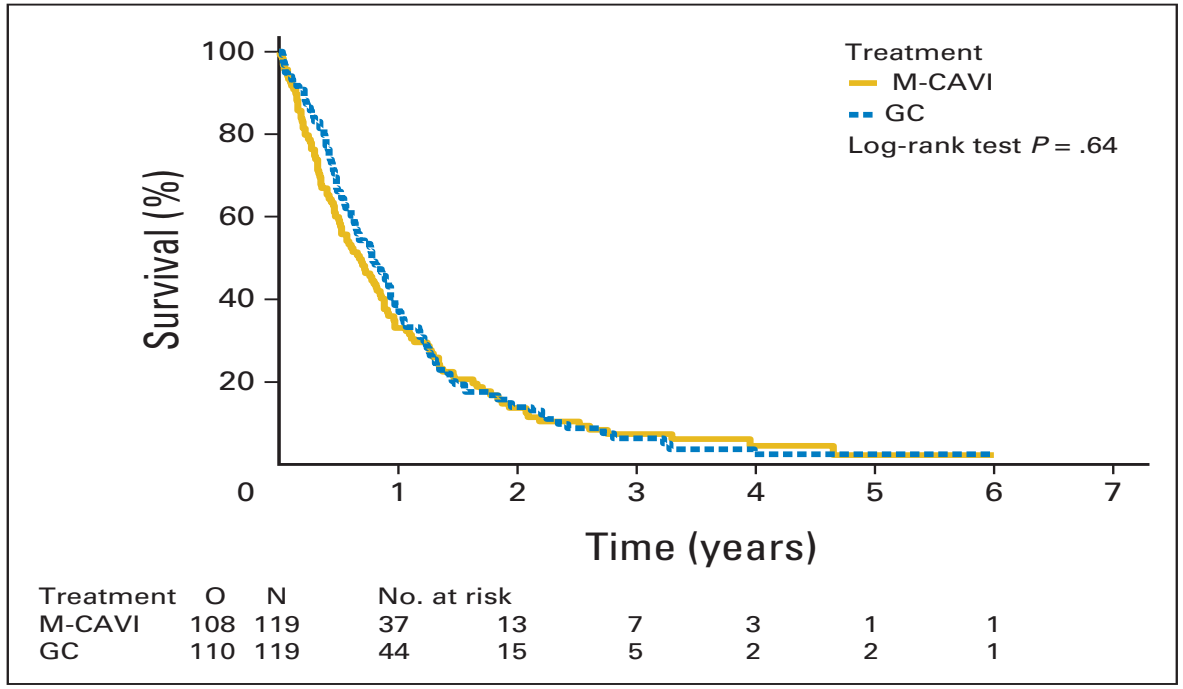


Fig 2. Duration of survival by treatment group. GC, gemcitabine/carboplatin; M-CAVI, methotrexate/carboplatin/vinblastine; O, observed number of deaths.

von der Masse JCO 2005; De Santis et al. JCO 2012

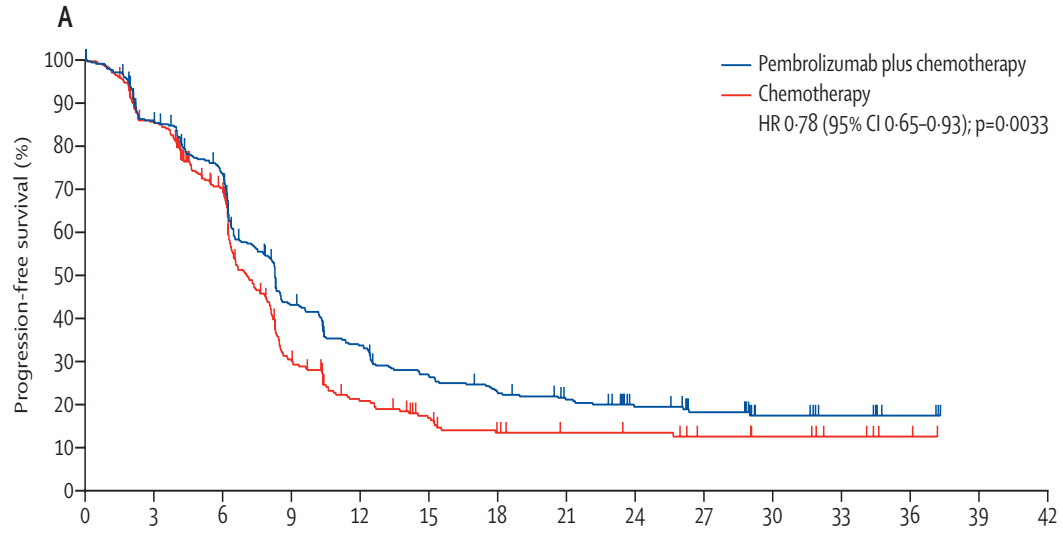
Chemo +/- pembrolizumab in untreated UC

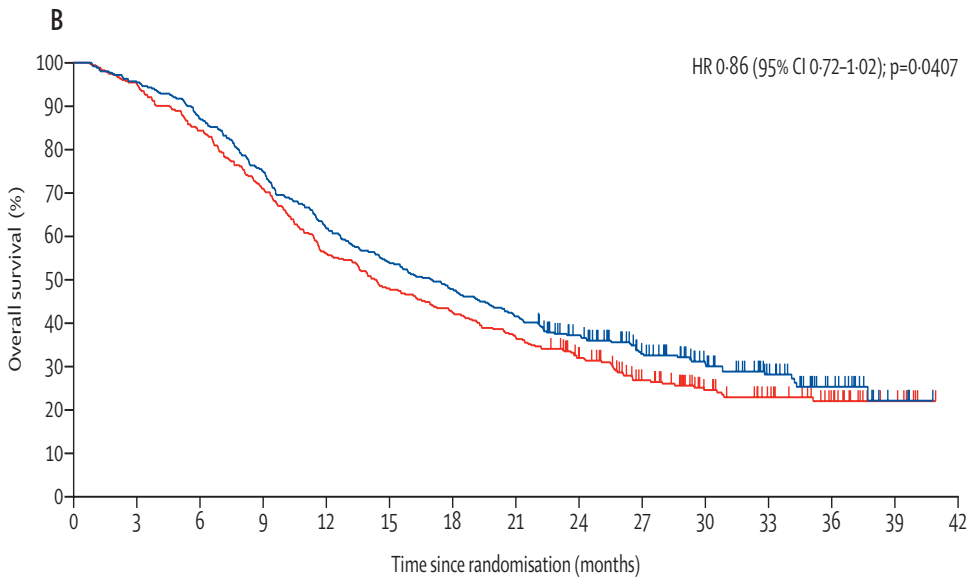
Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): a randomised, open-label, phase 3 trial

*Thomas Powles, Tibor Csőszi, Mustafa Özgüroğlu, Nobuaki Matsubara, Lajos Géczi, Susanna Y-S Cheng, Yves Fradet, Stephane Oudard, Christof Vulsteke, Rafael Morales Barrera, Aude Fléchon, Seyda Gunduz, Yohann Loriot, Alejo Rodriguez-Vida, Ronac Mamtani, Evan Y Yu, Kijoeng Nam, Kentaro Imai, Blanca Homet Moreno, Ajjai Alva, for the KEYNOTE-361 Investigators**

No significant improvement in PFS (pre-specified P value threshold: 0.0019)

No significant improvement in OS (pre-specified P value threshold: 0.0142)

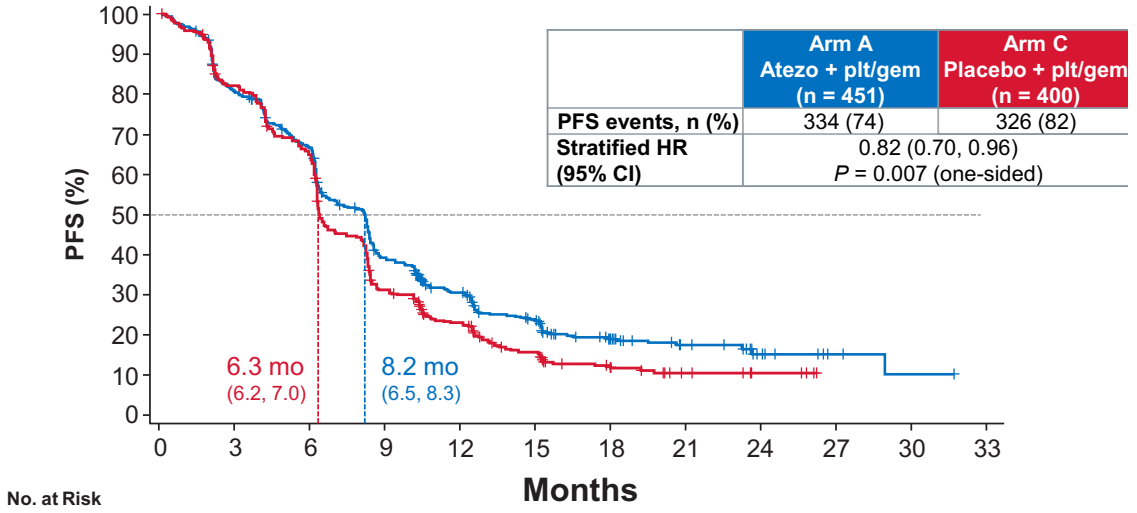




Powles et al. Lancet Oncol, 2021

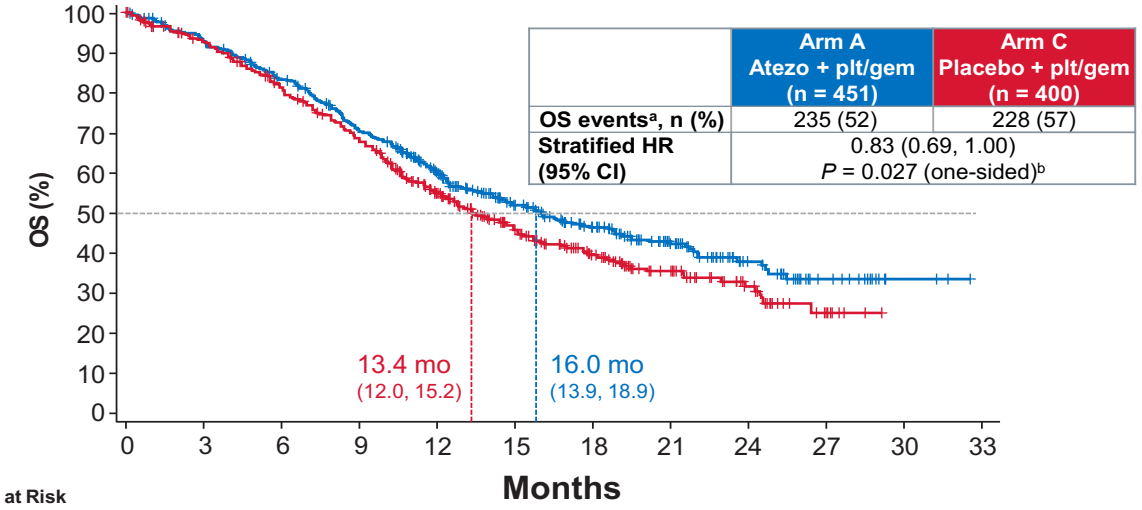
Chemo +/- atezolizumab in untreated UC

Final PFS: ITT (Arm A vs Arm C)



	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
PFS events, n (%)	334 (74)	326 (82)
Stratified HR (95% CI)	0.82 (0.70, 0.96) *P* = 0.007 (one-sided)	

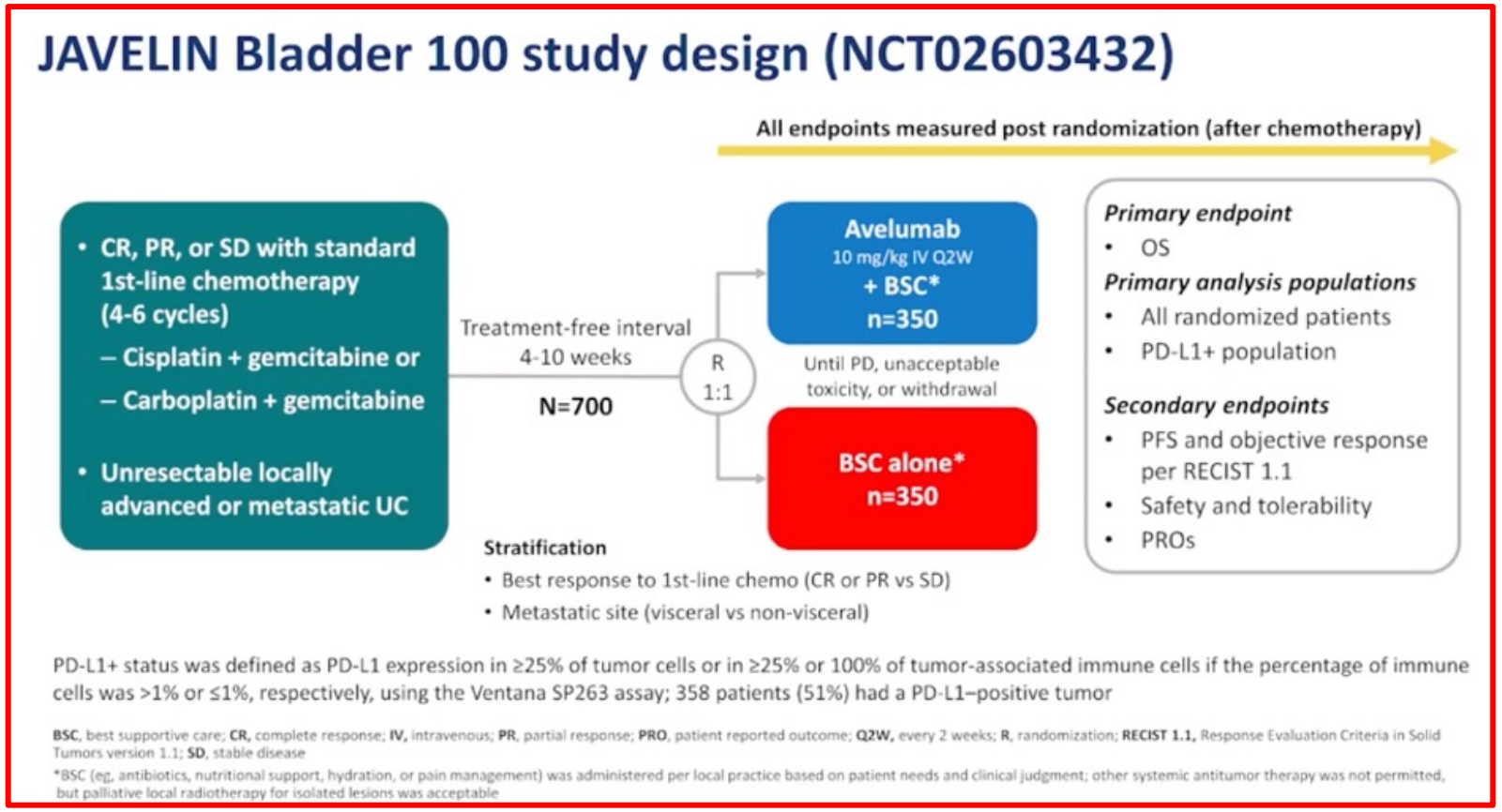
Interim OS: ITT (Arm A vs Arm C)



	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
OS events[a], n (%)	235 (52)	228 (57)
Stratified HR (95% CI)	0.83 (0.69, 1.00) *P* = 0.027 (one-sided)[b]	

Galsky et al. Lancet Oncol 2020

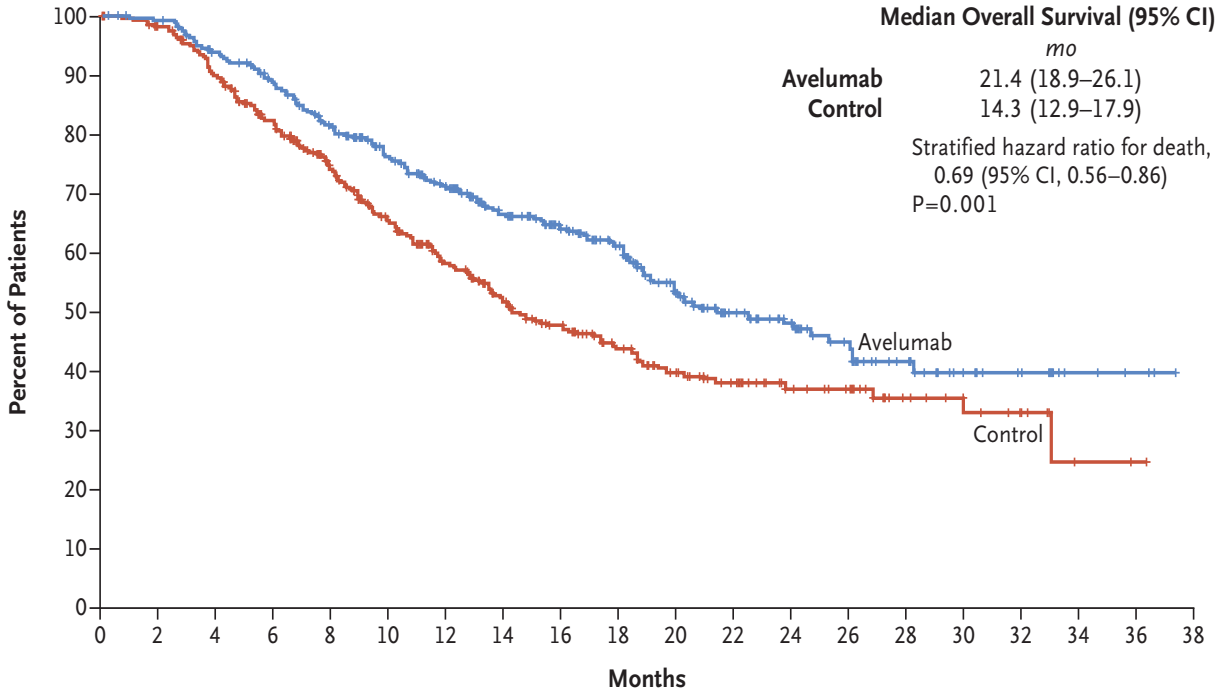
Switch maintenance: JAVELIN 100 Bladder



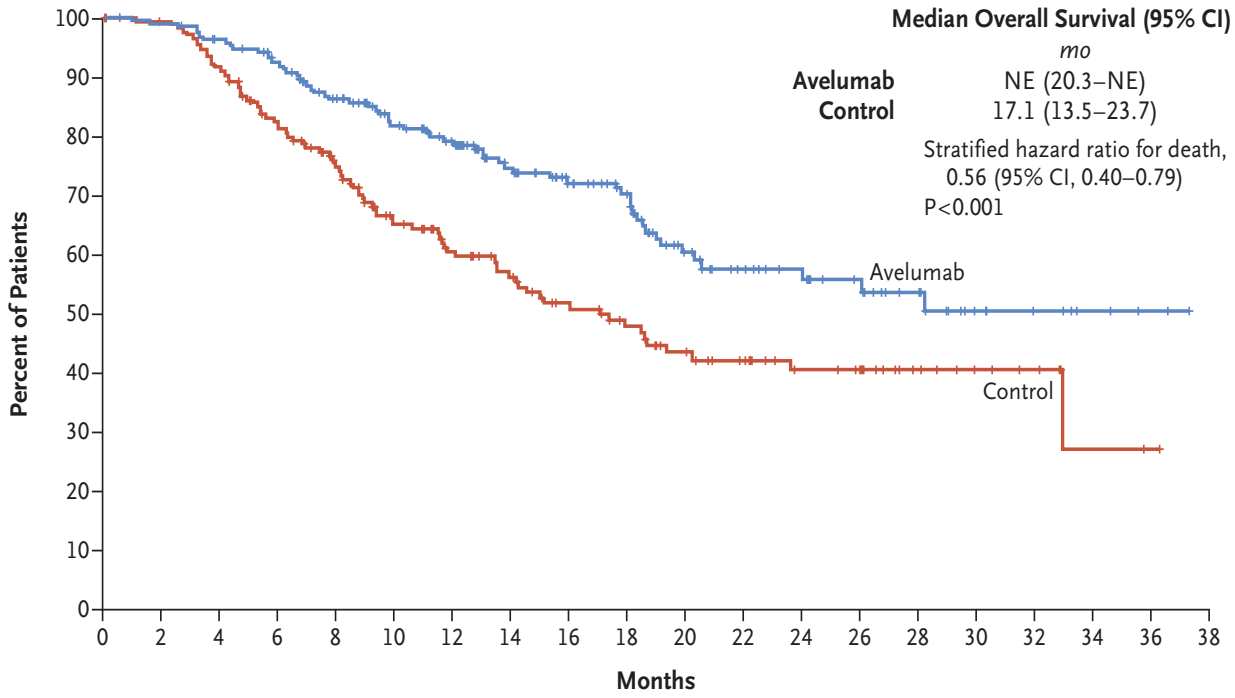
Powles et al. NEJM 2020

Switch maintenance: JAVELIN 100 Bladder

OS in ITT patients

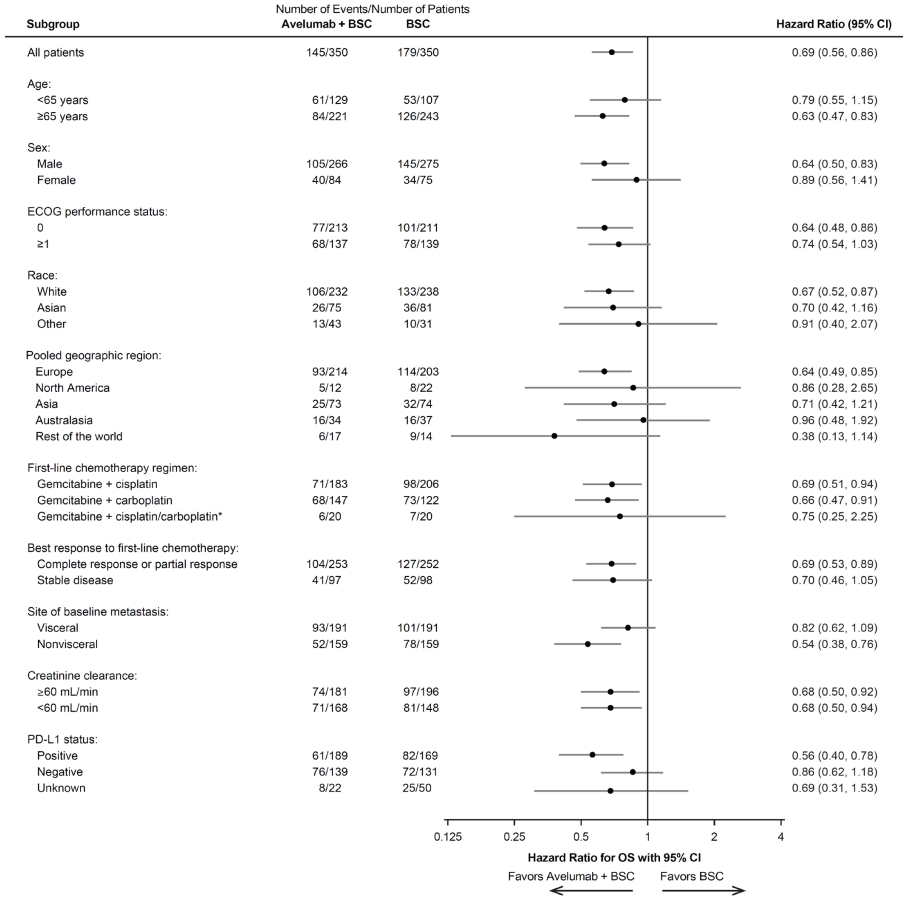


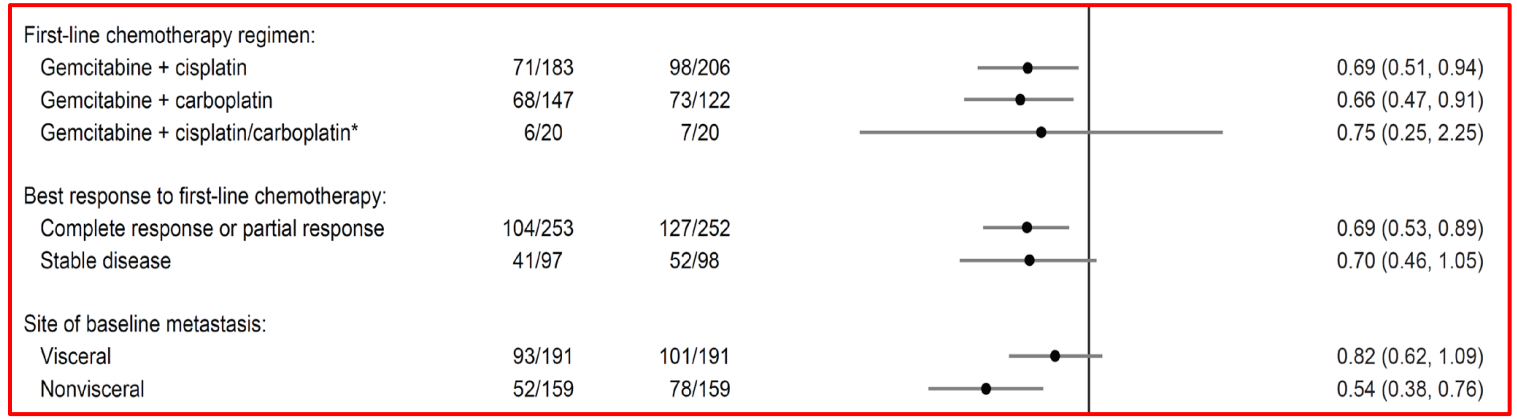
OS in PD-L1 high patients



Powles et al. NEJM 2020

Switch maintenance: JAVELIN 100 Bladder

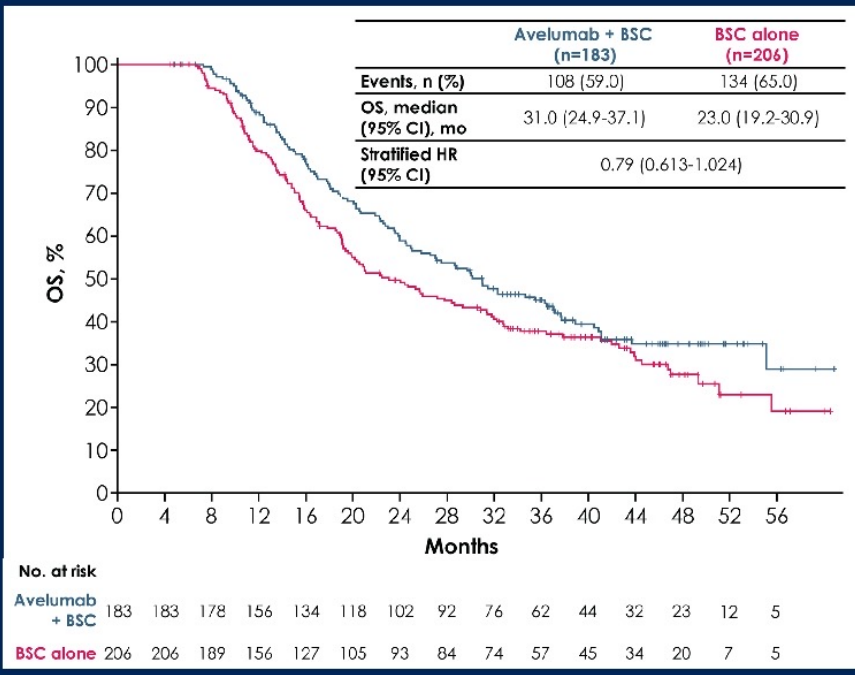




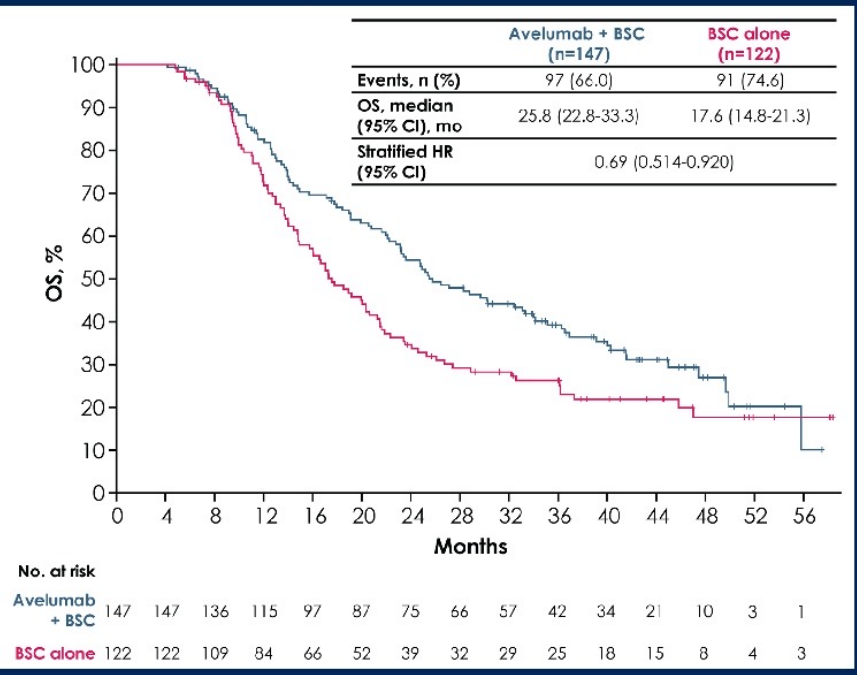
Powles et al. NEJM 2020

OS from start of 1L chemotherapy

Cisplatin + gemcitabine



Carboplatin + gemcitabine



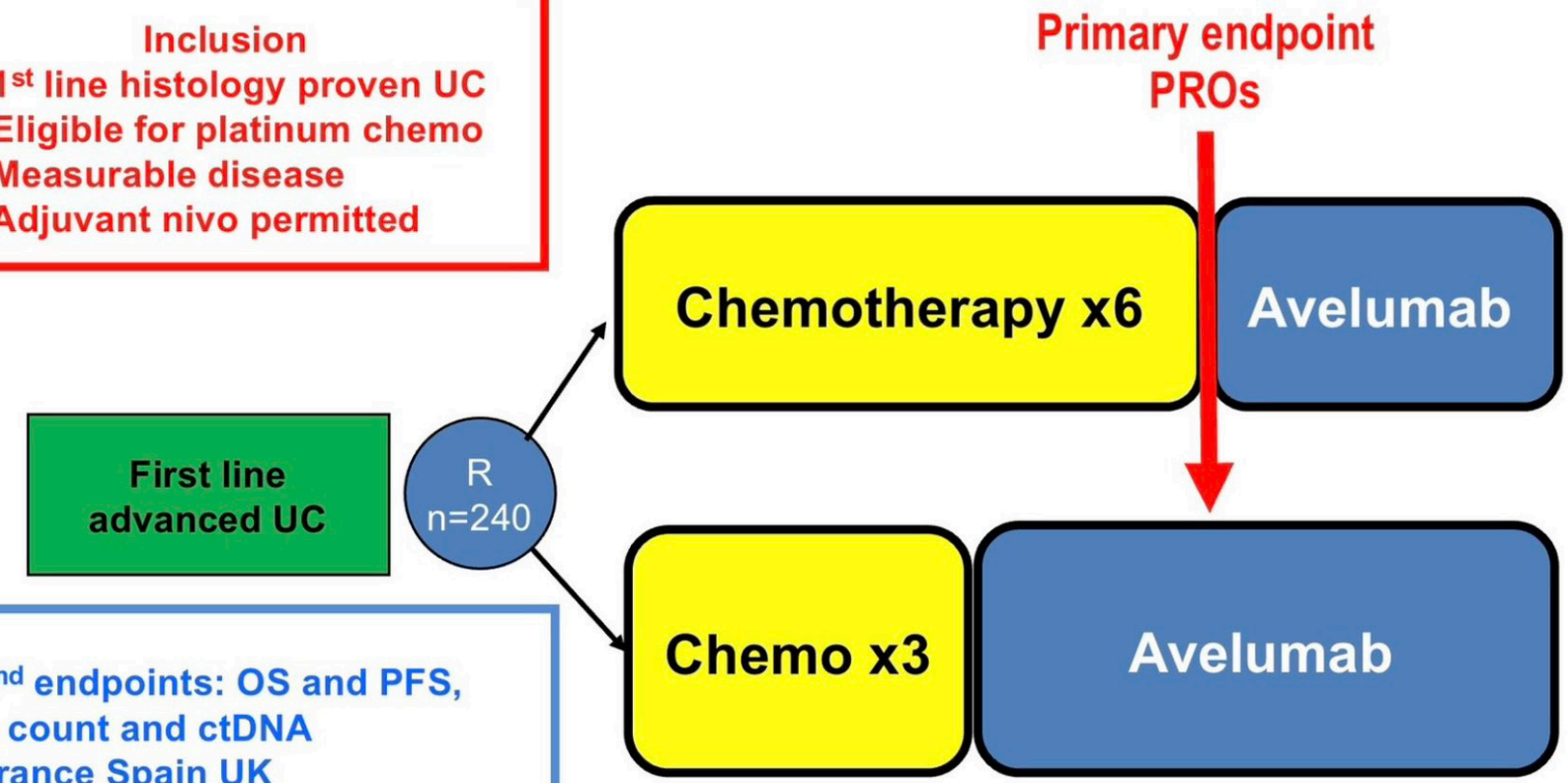
- In the overall population, median OS measured from the start of 1L chemotherapy was 29.7 months with avelumab + BSC and 20.5 months with BSC alone
- OS measured from the start of 1L chemotherapy was also longer with avelumab + BSC vs BSC alone irrespective of 1L chemotherapy regimen

1L, first line; **BSC,** best supportive care; **HR,** hazard ratio; **OS,** overall survival.

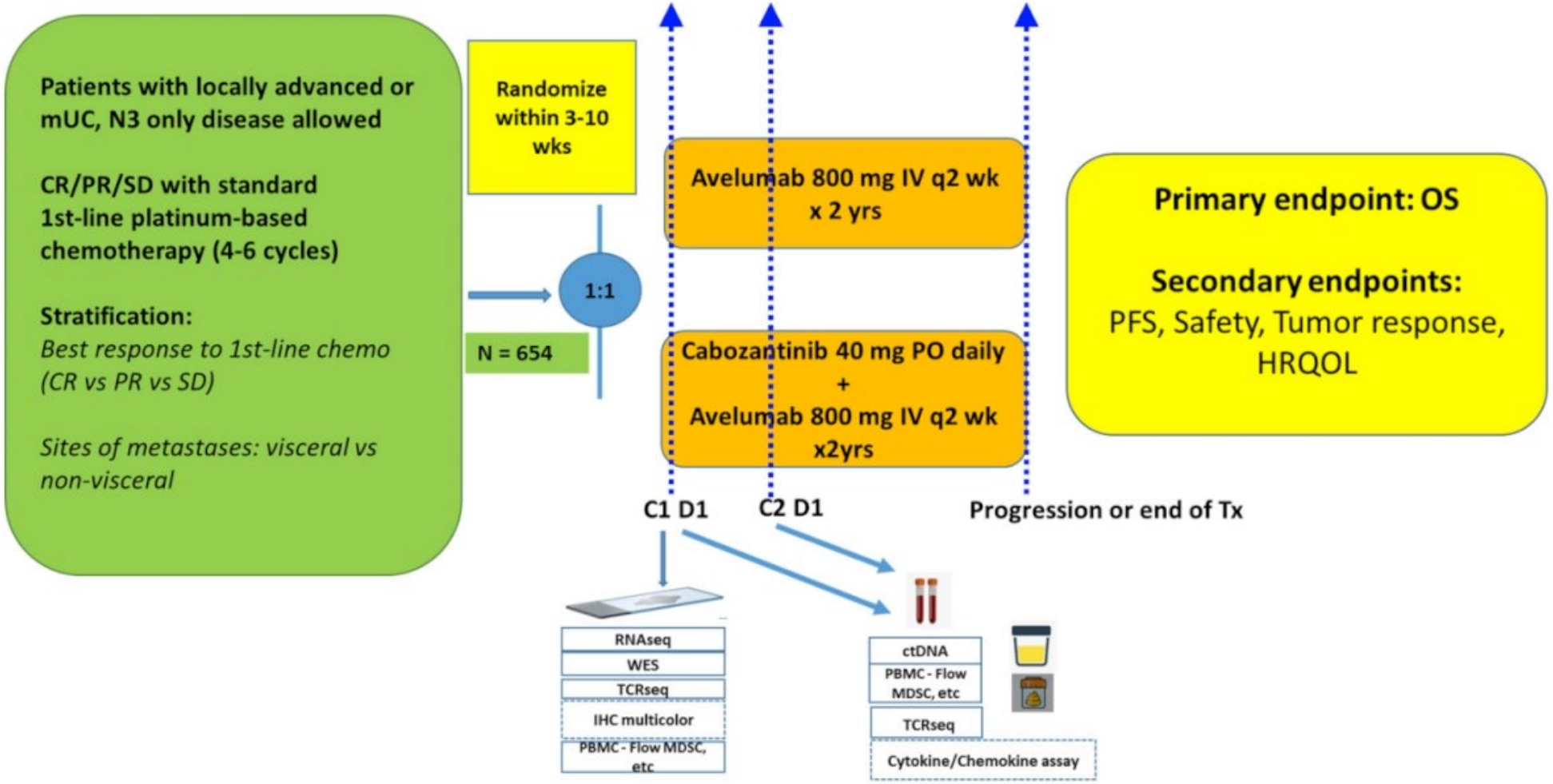
The DISCUS TRIAL: 3 vs 6 cycles of platinum chemotherapy and maintenance avelumab

Inclusion

- 1st line histology proven UC
- Eligible for platinum chemo
- Measurable disease
- Adjuvant nivo permitted



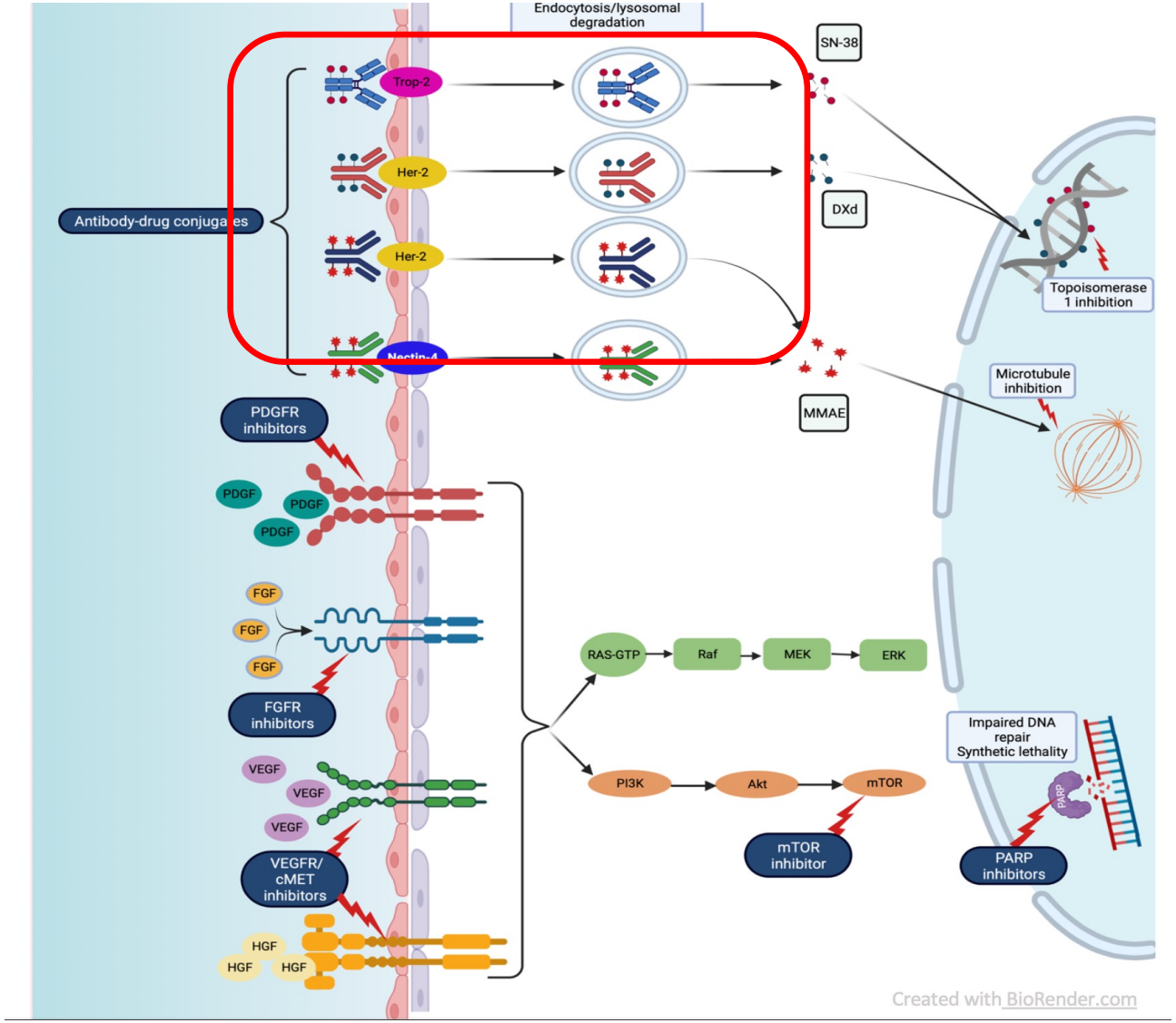
- 2nd endpoints: OS and PFS, step count and ctDNA
- France Spain UK
- Sponsor: Barts Cancer Institute



PI: Shilpa Gupta MD

Beyond chemotherapy/IO

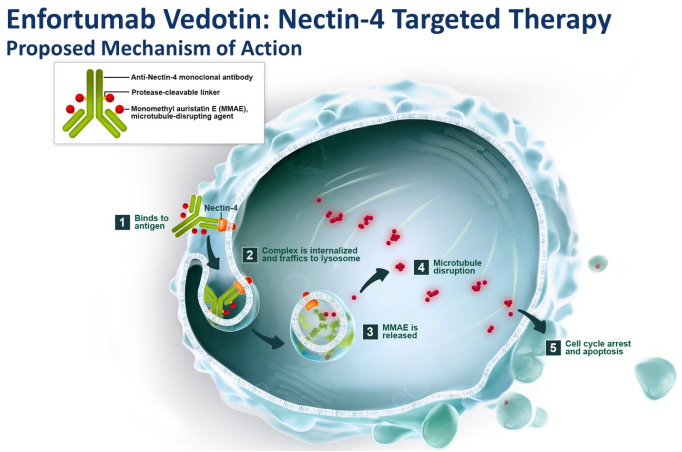
- Antibody-drug conjugates
  - Enfortumab vedotin
  - Sacituzumab govitecan
  - HER-2-targeted ADCs
- Kinase inhibition:
  - FGFR inhibition
  - Multi-kinase inhibitors

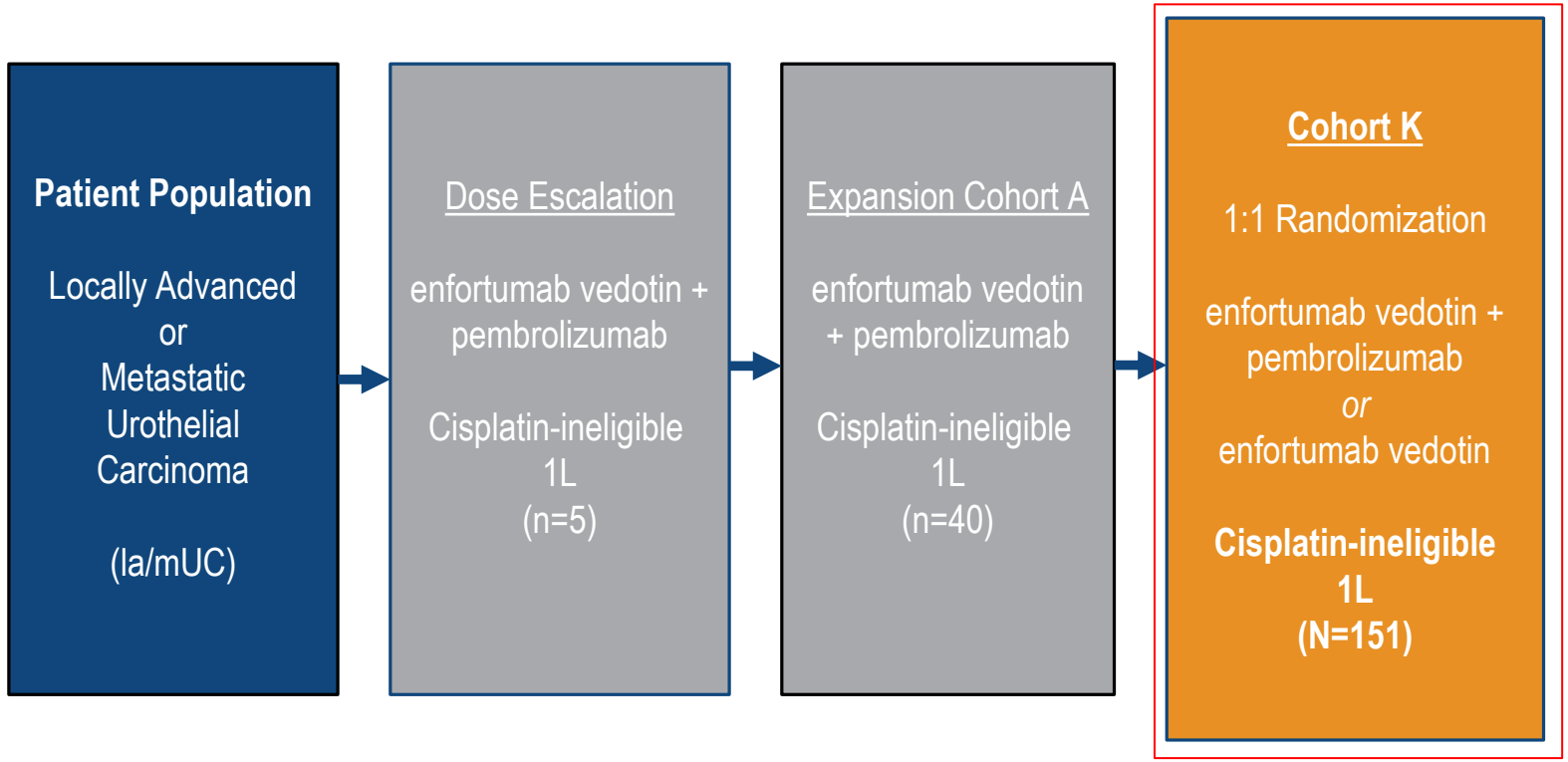


Tripathi et al. Drugs 2022

Novel combinations: EV +/- pembrolizumab

Study EV-103 Cohort K: Antitumor activity of enfortumab vedotin monotherapy or in combination with pembrolizumab in previously untreated cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer (la/mUC)





- **Primary endpoint:** confirmed ORR by RECIST v1.1 per BICR

Key secondary endpoints: confirmed ORR per RECIST v1.1 by investigator, DOR, DCR, PFS, OS, safety/ tolerability, and lab abnormalities

Powles T, et al. *J Clin Oncol.* 2021

EV103: EV+/- pembrolizumab in cis-ineligible UC

	EV+P (N=76)	EV Mono (N=73)
Male sex, n (%)	54 (71.1)	56 (76.7)
Age (yrs), median (range)	71 (51, 91)	74 (56, 89)
White race, n (%)	61 (80.3)	55 (75.3)
ECOG PS, n (%)		
0	33 (43.4)	28 (38.4)
1	33 (43.4)	35 (47.9)
2	10 (13.2)	10 (13.7)
Primary tumor location, n (%)		
Lower tract	46 (60.5)	51 (69.9)
Upper tract	30 (39.5)	21 (28.8)
Metastasis disease sites, n (%)		
Bone	19 (25.0)	21 (28.8)
Liver	13 (17.1)	13 (17.8)
Lung	37 (48.7)	30 (41.1)
Metastasis category, n (%)		
Lymph node only	10 (13.2)	12 (16.4)
Visceral disease	64 (84.2)	60 (82.2)
Not applicable[1]	2 (2.6)	1 (1.4)
PD-L1 status by combined positive score,[2] n (%)		
CPS<10	44 (57.9)	38 (52.1)
CPS≥10	31 (40.8)	28 (38.4)
Not Evaluable	1 (1.3)	7 (9.6)

	EV+P (N=76) n (%)	EV Mono (N=73) n (%)
Patient meeting at least one of the following Galsky criteria	76 (100%)	72 (98.6)
CrCL <60 and ≥30mL/min[1]	48 (63.2)	44 (60.3)
Grade ≥2 hearing loss	11 (14.5)	11 (15.1)
ECOG PS of 2	6 (7.9)	9 (12.3)
CrCL <60 and ≥30mL/min[1] and Grade ≥2 hearing loss	7 (9.2)	7 (9.6)
CrCL <60 and ≥30mL/min[1] and ECOG PS of 2	4 (5.3)	1 (1.4)
Patient considered cisplatin-ineligible by the investigator although not meeting Galsky criteria[2]	0	1 (1.4)

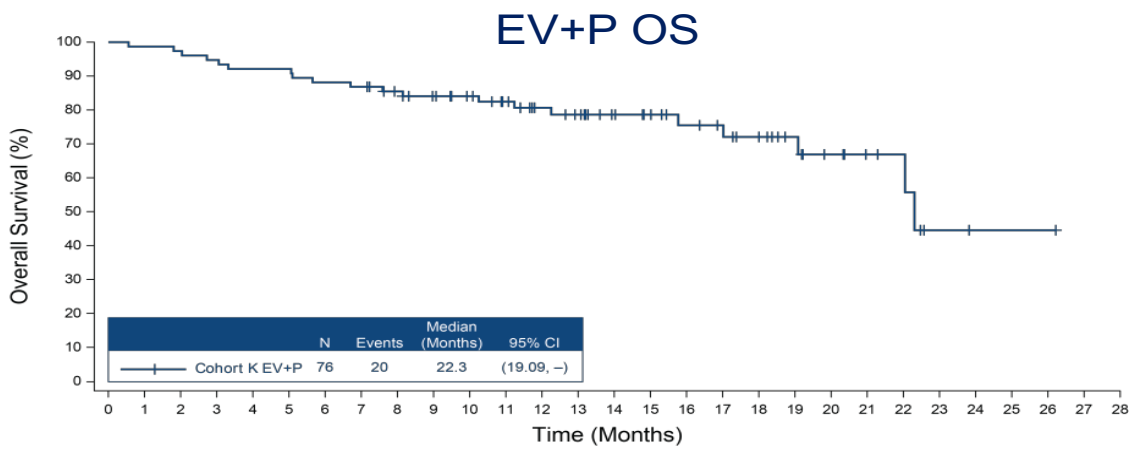
CrCL: Creatinine Clearance; ECOG PS: Eastern Cooperative Oncology Group Performance Status; Mono: Monotherapy
[1]Estimated creatinine clearance per Cockcroft-Gault formula or 24-hr urine collection or MDRD equation.
[2]One patient in the EV Mono arm was considered cisplatin-ineligible by the investigator due to age and Grade 1 hearing loss.

Powles T, et al. *J Clin Oncol.* 2021

EV103: EV+/- pembrolizumab in cis-ineligible UC

	EV+P (N=76)	EV Mono (N=73)
Confirmed ORR, n (%) (95% CI)	49 (64.5) (52.7, 75.1)	33 (45.2) (33.5, 57.3)
Best overall response, n (%)		
Complete Response	8 (10.5)	3 (4.1)
Partial Response	41 (53.9)	30 (41.1)
Stable Disease	17 (22.4)	25 (34.2)
Progressive Disease	6 (7.9)	7 (9.6)
Not Evaluable	3 (3.9)	5 (6.8)
No Assessment	1 (1.3)	3 (4.1)
Median time to objective response (range), mos	2.07 (1.1, 6.6)	2.07 (1.9, 15.4)
Median number of treatment cycles (range)	11.0 (1, 29)	8.0 (1, 33)

	EV+P (N=76)	EV Mono (N=73)
Responders, n	49	33
Progression events, n	13	14
mDOR (95% CI), mos	- (10.25, -)	13.2 (6.14, 15.97)
DOR ≥12 mos, %	65.4%	56.3%



	EV+P (N=76)		EV Mono (N=73)	
	Any Grade n (%)	**Grade ≥3 n (%)**	**Any Grade n (%)**	**Grade ≥3 n (%)**
Skin reactions	51 (67.1)	16 (21.1)	33 (45.2)	6 (8.2)
Peripheral neuropathy	46 (60.5)	2 (2.6)	40 (54.8)	2 (2.7)
Ocular disorders	20 (26.3)	0	21 (28.8)	0
Dry eye	18 (23.7)	0	9 (12.3)	0
Blurred vision	9 (11.8)	0	10 (13.7)	0
Corneal disorders	0	0	4 (5.5)	0

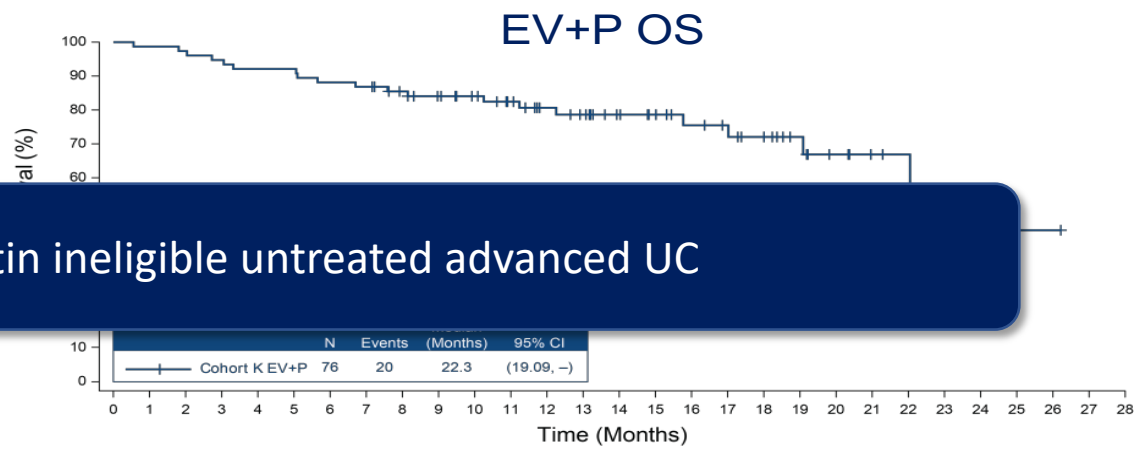
Powles T, et al. *J Clin Oncol.* 2021

EV103: EV+/- pembrolizumab in cis-ineligible UC

	EV+P (N=76)	EV Mono (N=73)
Confirmed ORR, n (%) (95% CI)	49 (64.5) (52.7, 75.1)	33 (45.2) (33.5, 57.3)
Best overall response, n (%)		
Complete Response	[illegible]	[illegible]
Partial Response	[illegible]	[illegible]
Stable Disease	[illegible]	[illegible]
Progressive Disease	[illegible]	[illegible]
Not Evaluable	3 (3.9)	5 (6.8)
No Assessment	1 (1.3)	3 (4.1)
Median time to objective response (range), mos	2.07 (1.1, 6.6)	2.07 (1.9, 15.4)
Median number of treatment cycles (range)	11.0 (1, 29)	8.0 (1, 33)

Received accelerated approval for cisplatin ineligible untreated advanced UC

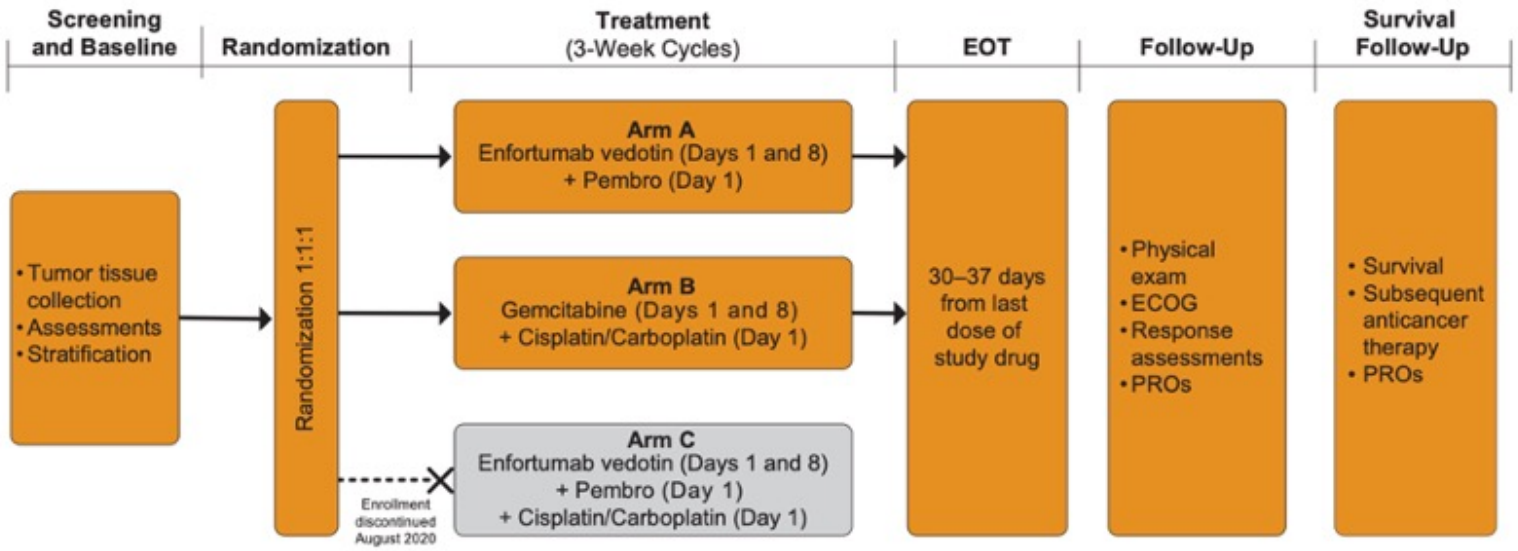
	EV+P (N=76)	EV Mono (N=73)
Responders, n	49	33
Progression events, n	13	14
mDOR (95% CI), mos	- (10.25, -)	13.2 (6.14, 15.97)
DOR ≥12 mos, %	65.4%	56.3%



	EV+P (N=76)		EV Mono (N=73)	
	Any Grade n (%)	**Grade ≥3 n (%)**	**Any Grade n (%)**	**Grade ≥3 n (%)**
Skin reactions	51 (67.1)	16 (21.1)	33 (45.2)	6 (8.2)
Peripheral neuropathy	46 (60.5)	2 (2.6)	40 (54.8)	2 (2.7)
Ocular disorders	20 (26.3)	0	21 (28.8)	0
Dry eye	18 (23.7)	0	9 (12.3)	0
Blurred vision	9 (11.8)	0	10 (13.7)	0
Corneal disorders	0	0	4 (5.5)	0

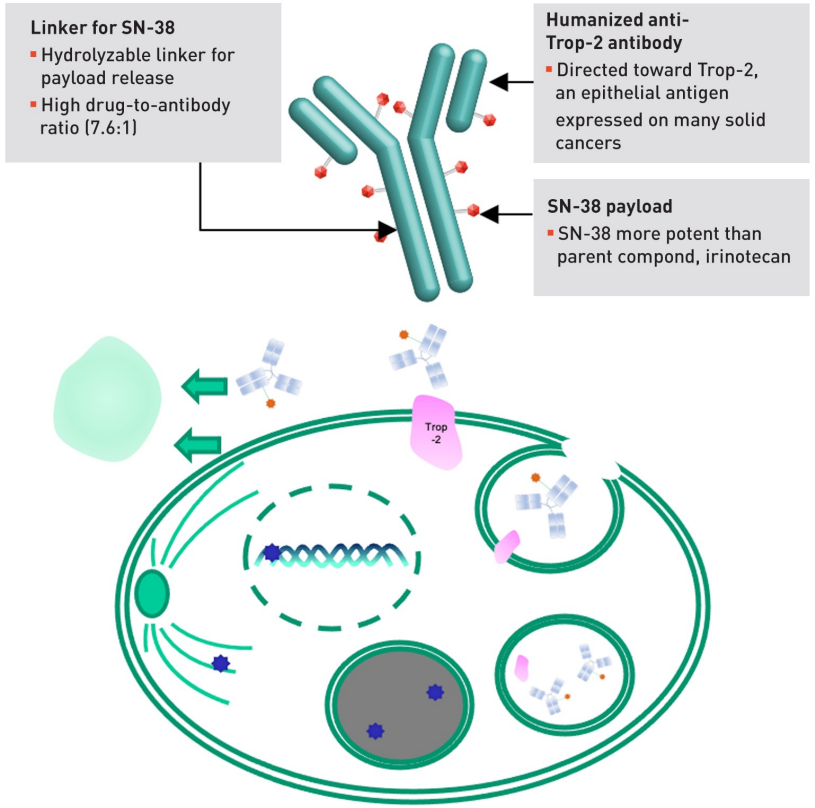
Powles T, et al. *J Clin Oncol.* 2021

EV 302: EV+/- pembrolizumab in platinum eligible UC

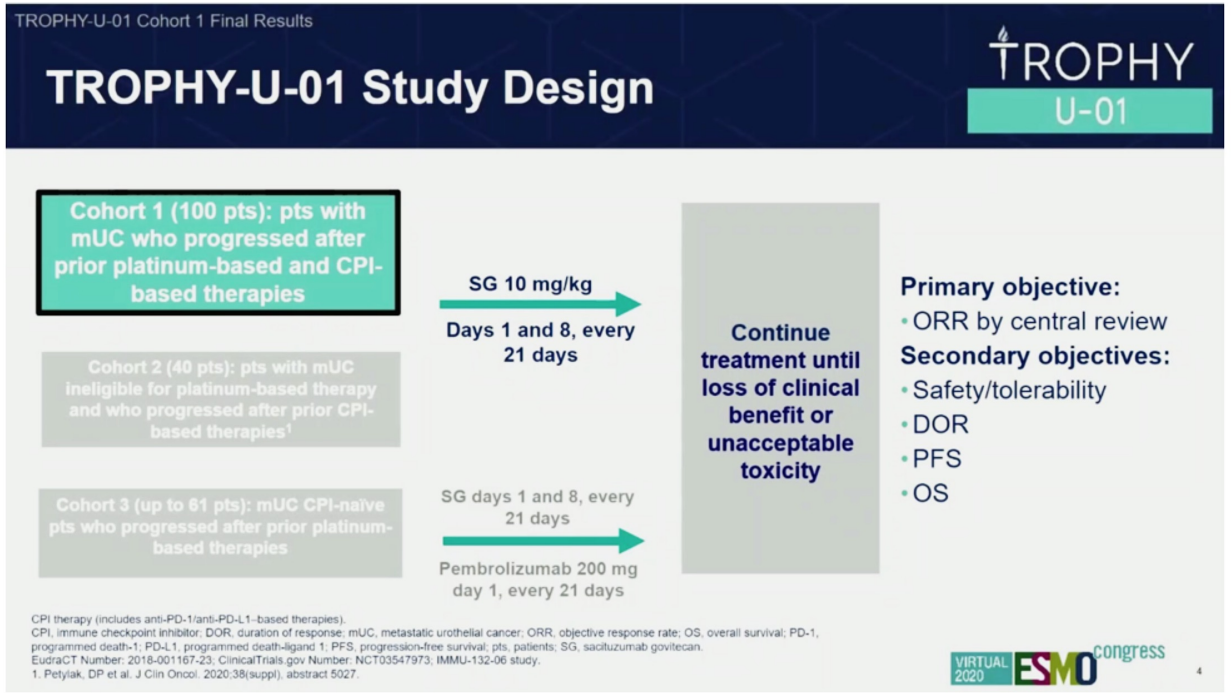


- Stratification Factors for Randomization: cisplatin eligibility (eligible/ineligible), liver metastases (present/absent), PD-L1 expression (high/low)
- Follow-up until disease progression, death, consent withdrawal, or study closure

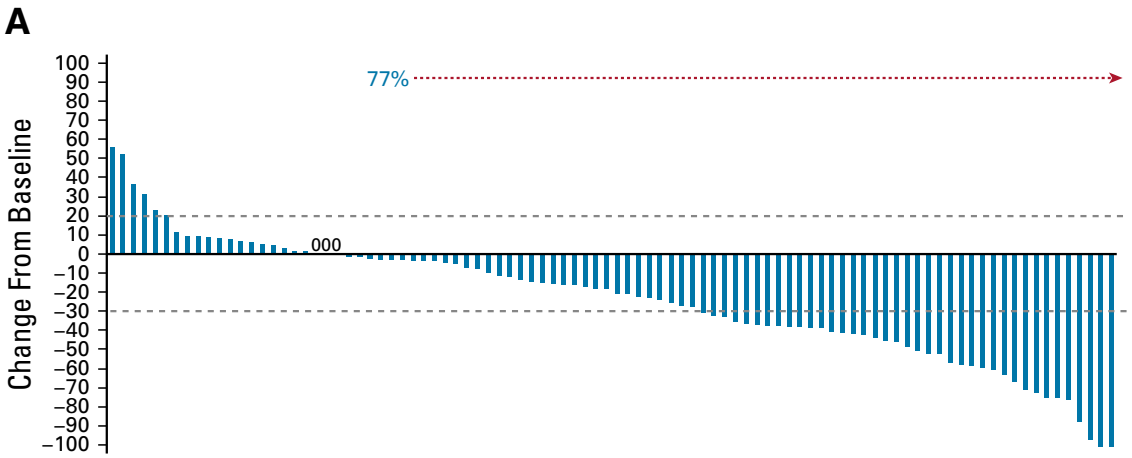
Sacituzumab Govitecan in Refractory UC

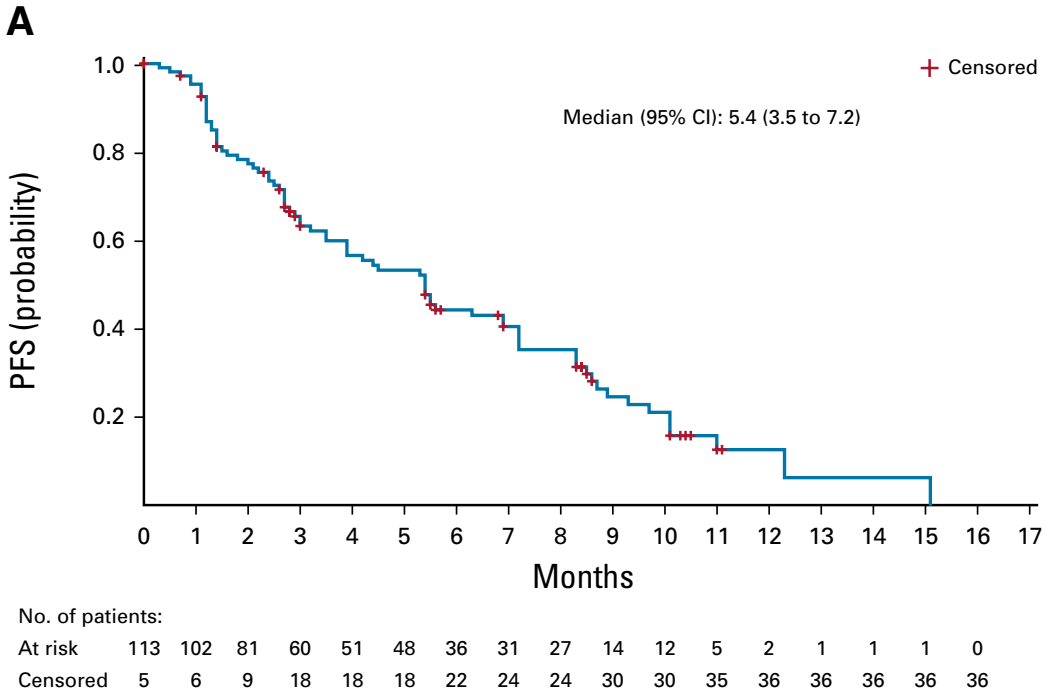


Nagayama, A, Ellisen L, Chabner B, Bardia A. Target Oncol. 2017



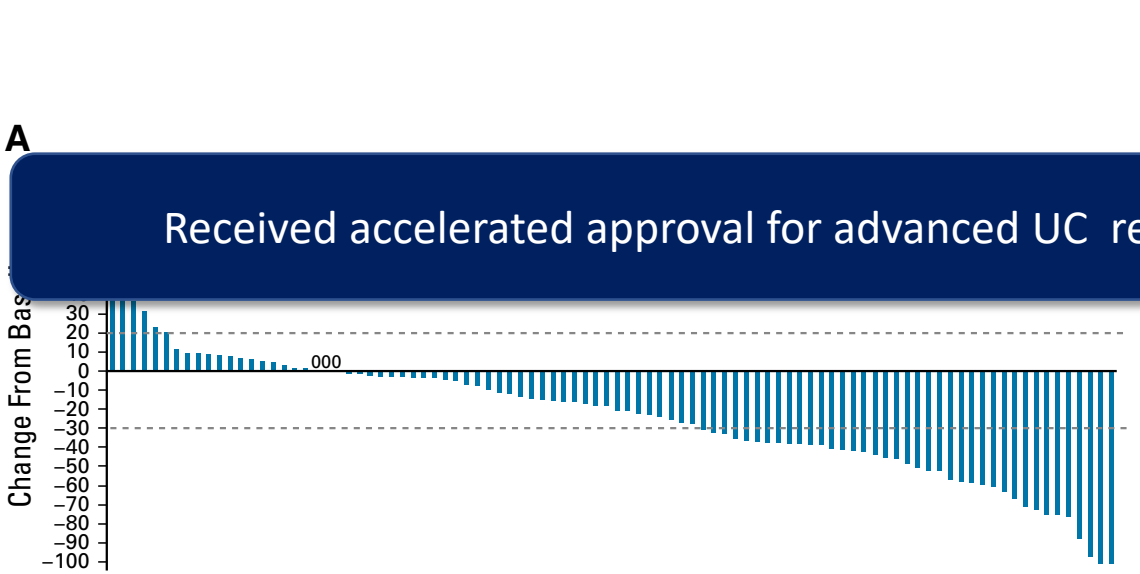
Sacituzumab Govitecan in Refractory UC

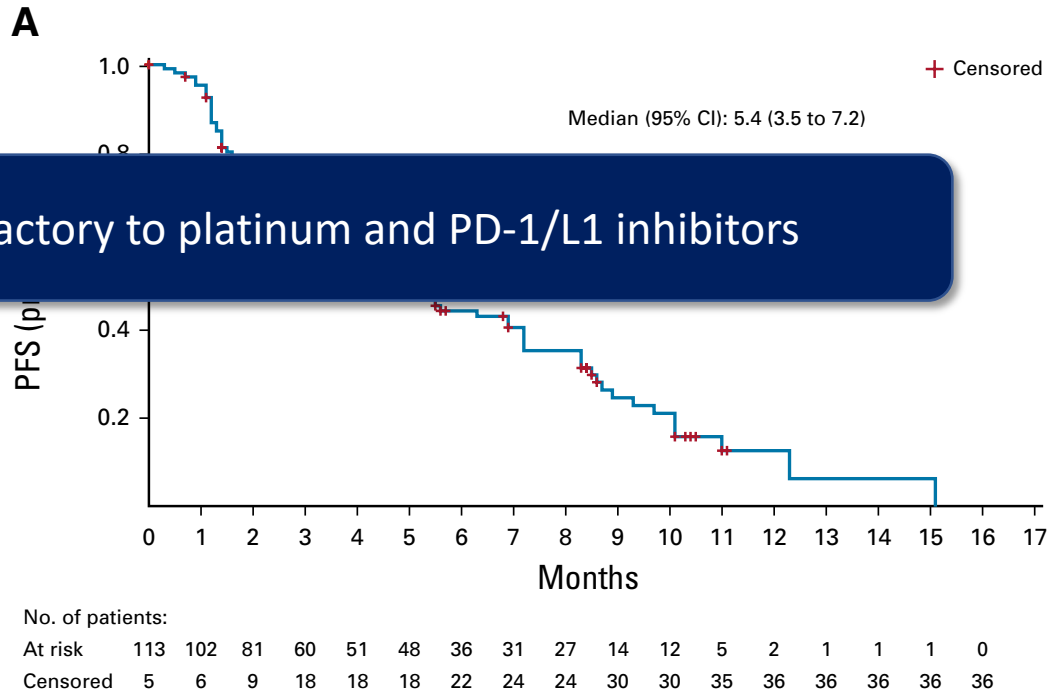




Sacituzumab Govitecan in Refractory UC

Received accelerated approval for advanced UC refractory to platinum and PD-1/L1 inhibitors

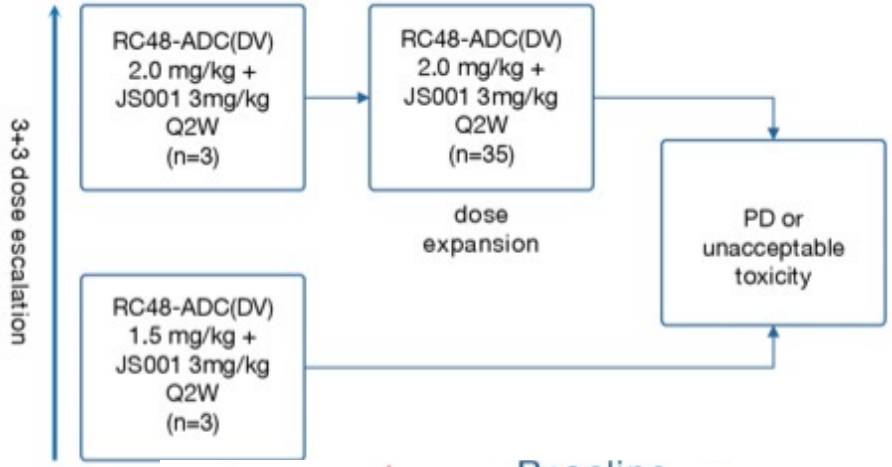


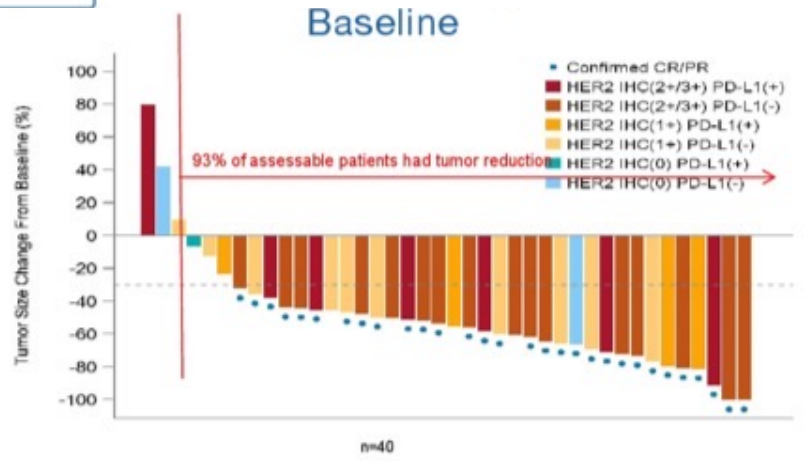


Anti-HER-2-ADC: Disitamab vedotin

Key Inclusion Criteria

- unresectable la/m UC[a]
- Prior ≥ 0 lines[b]
- Measurable lesions per RECIST v1.1
- ECOG PS 0-1
- Had tissue samples for the detection of PD-L1 and HER2





Characteristics	Total (N=41)
HER2 Expression(n,%)	
IHC 3+	5 (12.2%)
IHC 2+	19 (46.3%)
IHC 1+	14 (34.1%)
IHC 0	3 (7.3%)

Subgroups	cORR (%, 95% CI)
HER2 & PD-L1 Expression	
HER2 IHC(2+/3+), PD-L1(+) (n=8)	75.0(34.9~96.8)
HER2 IHC(2+/3+), PD-L1(-) (n=16)	87.5(61.7~98.4)
HER2 IHC(1+), PD-L1(+) (n=4)	50.0(6.8~93.2)
HER2 IHC(1+), PD-L1(-)(n=10)	70.0(34.8~93.3)
HER2 IHC(0), PD-L1(+)(n=1)	0.0(0.0~97.5)
HER2 IHC(0), PD-L1(-)(n=2)	50.0(1.3~98.7)

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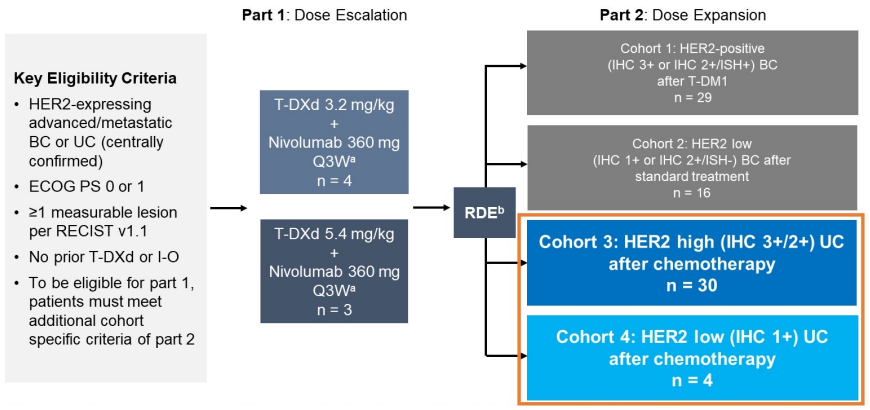
Anti-HER-2-ADC: TxD



4

Summary of Efficacy Results in UC Cohorts

	Cohort 3 HER2 IHC 3+/2+ n = 30
Confirmed ORR by ICR (ORR, CR + PR)	
n (%)	**11 (36.7)**
95% CI	(19.9-56.1)
Best overall response, n (%)	
CR	4 (13.3)
PR	7 (23.3)
SD	12 (40.0)
PD	5 (16.7)
NE[a]	2 (6.7)
DOR, median (95% CI), months	13.1 (4.1-NE)
PFS, median (95% CI), months	6.9 (2.7-14.4)
TTR, median (95% CI), months	1.9 (1.2-6.9)
OS, median (95% CI), months	11.0 (7.2-NE)
Treatment duration, median (range), months	
T-DXd	3.9 (1-21)
Nivolumab	4.1 (1-20)

- Data cutoff: July 22, 2021
- In cohort 3:
  - HER2 IHC 3+: 62.5% (5/8) patients had a confirmed objective response, including 2 CR (25%)
  - HER2 IHC 2+: 27.3% (6/22) patients had a confirmed objective response, including 2 CR (9.1%)
- In cohort 4 (HER2 IHC 1+)[b]:
  - 2 patients had a PR
  - 1 patient had SD
  - 1 patient had PD

CR, complete response; DOR, duration of response; ICR, independent central review; NE, nonevaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TTR, time to response.
[a]Patients were missing postbaseline scans.
[b]For cohort 4, efficacy endpoints are not summarized because of the small sample size (n = 4).

PRESENTED BY: Matthew D. Galsky, MD

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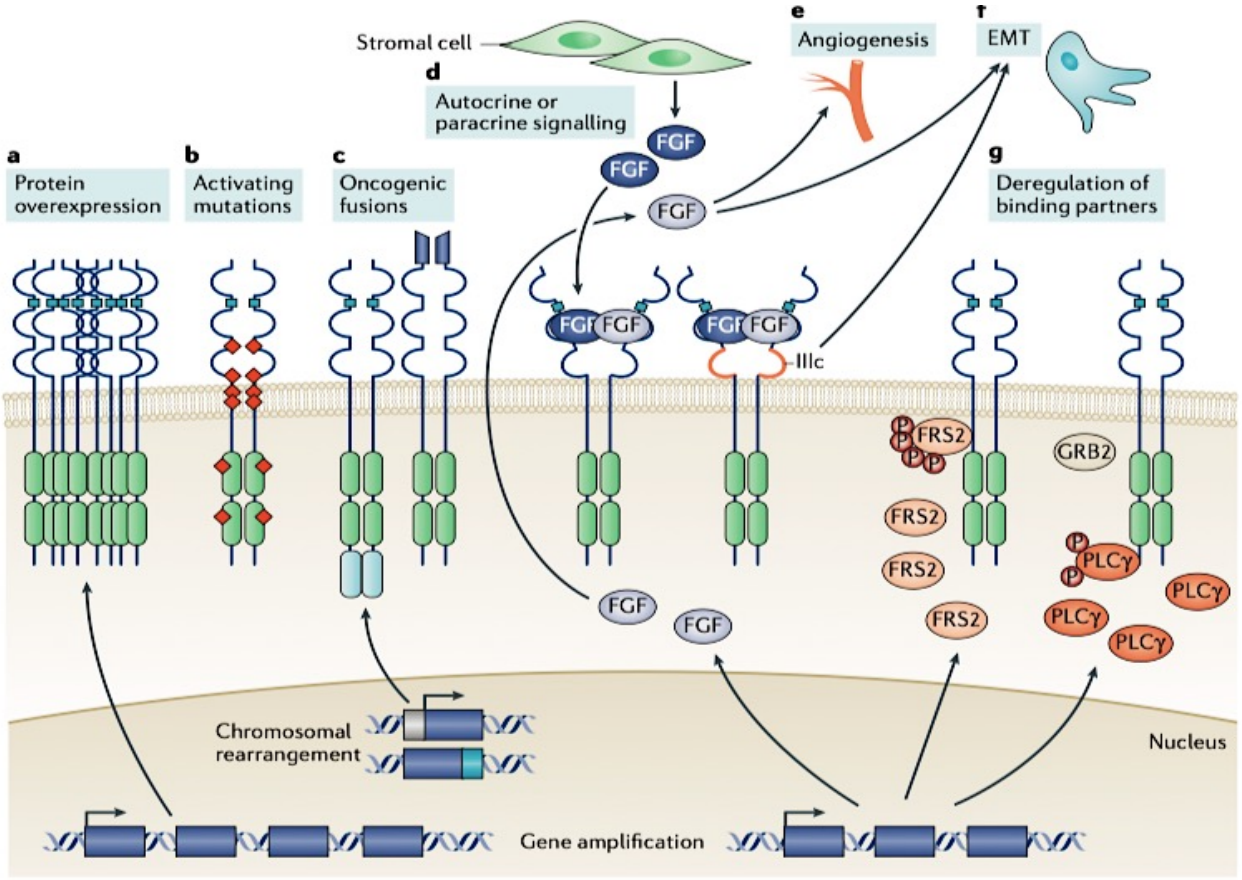
FGFR Inhibitors in Advanced UC

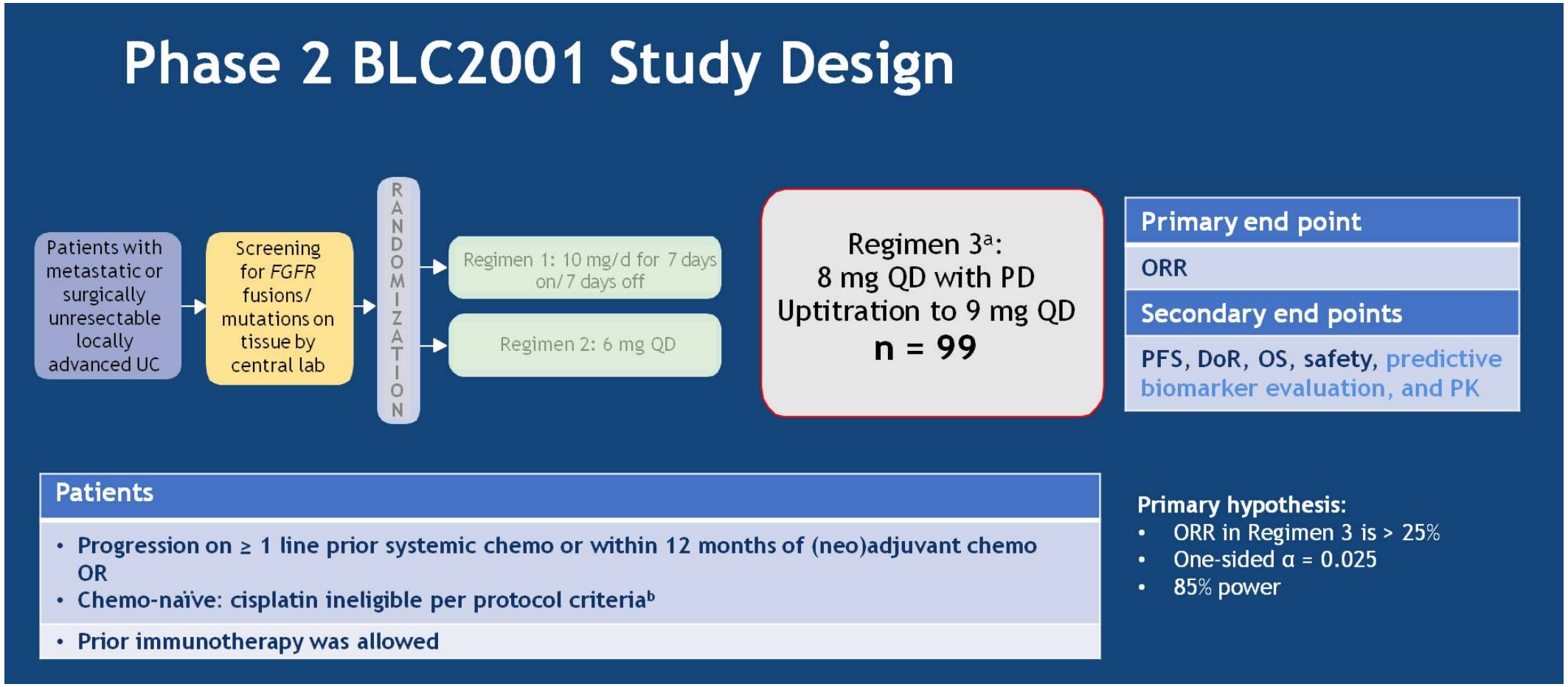
- FGFR (1-3) mutations can be seen in 15-20% of patients with advanced UC
- Enriched in upper tract and luminal papillary subtypes



FGFR = fibroblast growth factor receptor.

Robinson BD, et al. *Nat Commun*. 2019;10(1):2977. Babina IS, et al. *Nat Rev Cancer*. 2017;17(5):318-332.

Erdafitinib in Advanced UC with FGFR Alterations



QD = daily; ORR = overall response rate; DoR = duration of response; PK = pharmacokinetic.

Siefker-Radtke AO, et al. *J Clin Oncol.* 2018;36(15 Suppl):4503.

Phase 3 THOR Study: Erdafitinib Versus Chemotherapy of Choice in Patients With Advanced Urothelial Cancer and Selected FGFR Aberrations

Cohort 1

Key eligibility criteria

- Age ≥18 years
- Metastatic or unresectable UC
- Confirmed disease progression
- Prior tx with anti–PD-(L)1
- 1-2 lines of systemic tx
- Select *FGFR3/2alt* (mutation/fusion)[a]
- ECOG PS 0-2

1:1
N=266[b]

R

Erdafitinib
(n=136)
Once-daily erdafitinib 8 mg with pharmacodynamically guided uptitration to 9 mg

Chemotherapy of Choice
(n=130)
docetaxel or vinflunine once every 3 weeks

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

Primary end point:
- OS

Key secondary end points:
- PFS
- ORR
- Safety

NCT03390504

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Demographics and Disease Characteristics

Characteristic	Erdafitinib (n=136)	Chemotherapy (n=130)
Age, median (range), years	66 (32-85)	69 (35-86)
Men, n (%)	96 (70.6)	94 (72.3)
Race, n (%)		
White	81 (59.6)	63 (48.5)
Asian	37 (27.2)	40 (30.8)
Black or African American	0	1 (0.8)
Multiple	0	1 (0.8)
Not reported	18 (13.2)	25 (19.2)
Presence of visceral metastases, n (%)	101 (74.3)	97 (74.6)
Liver	31 (22.8)	38 (29.2)

Characteristic	Erdafitinib (n=136)	Chemotherapy (n=130)
ECOG PS 0-1, n (%)	124 (91.2)	117 (90)
Primary tumor upper tract, n (%)	41 (30.1)	48 (36.9)
PD-L1 low (CPS <10), n (%)	89 (92.7)[a]	68 (86.1)[a]
FGFRalt, n (%)[b]	(n=135)	(n=129)
Mutations	108 (79.4)	107 (82.3)
Fusions	25 (18.4)	19 (14.6)
Mutations and fusions	2 (1.5)	3 (2.3)
Prior lines of systemic therapy[c]		
1 line	45 (33.1)	33 (25.4)
2 lines	90 (66.2)	97 (74.6)

- Patient baseline characteristics were generally balanced between treatment arms

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All Patients Enrolled in the Study Had Received Anti–PD-1 in the First- or Second-Line Setting

Patients receiving prior therapy, n (%)	Erdafitinib (n=136)[a]	Chemotherapy (n=130)
1 line of prior systemic therapy	**45 (33.1)**	**33 (25.4)**
Chemotherapy + anti–PD-(L)1[b]	33 (24.3)	15 (11.5)
Anti–PD-(L)1[c]	11 (8.1)	16 (12.3)
Chemotherapy	1 (0.7)	2 (1.5)
2 lines of prior systemic therapy	**90 (66.2)**	**97 (74.6)**
First line of therapy		
Chemotherapy	77 (56.6)	76 (58.5)
Chemotherapy + anti–PD-(L)1	6 (4.4)	10 (7.7)
Other	7 (5.1)	11 (8.5)
Second line of therapy		
Anti–PD-(L)1	76 (55.9)	76 (58.5)
Chemotherapy	10 (7.4)	14 (10.8)
Other	4 (2.9)	7 (5.4)

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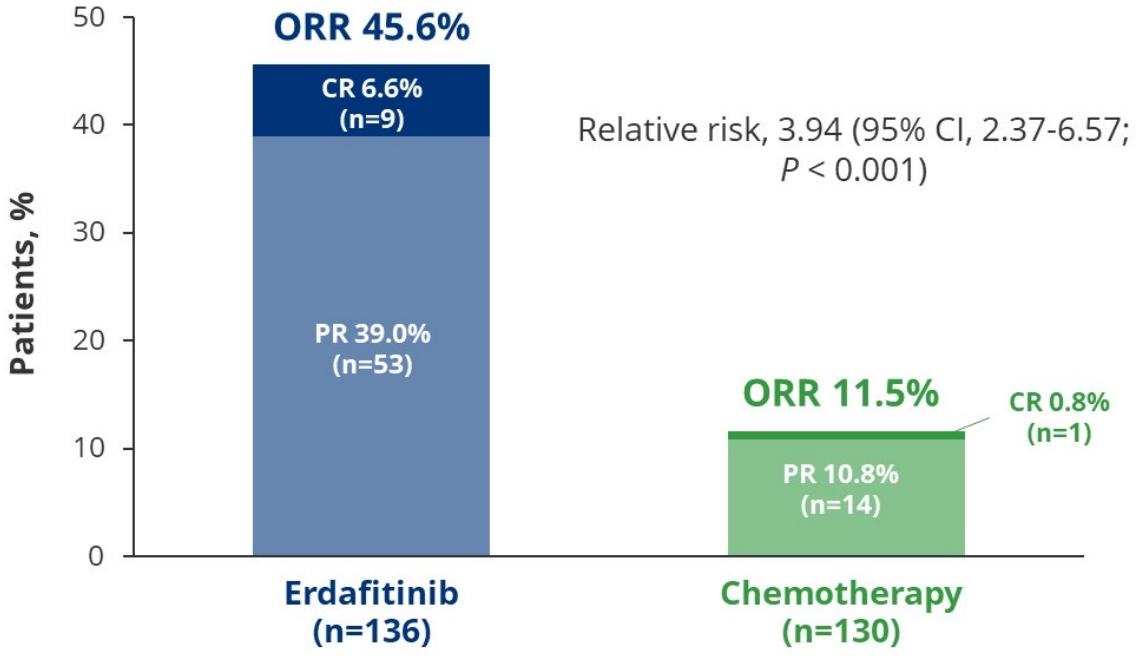
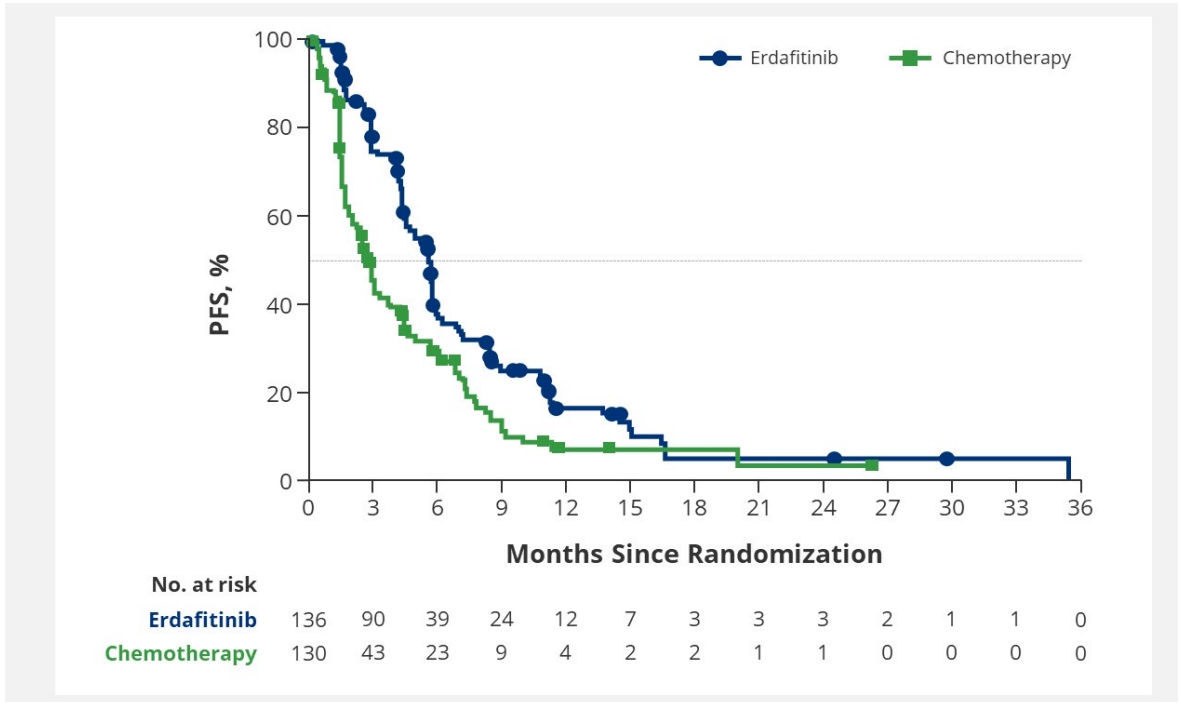
Phase 3 THOR Study: Erdafitinib Versus Chemotherapy of Choice in Patients With Advanced Urothelial Cancer and Selected FGFR Aberrations





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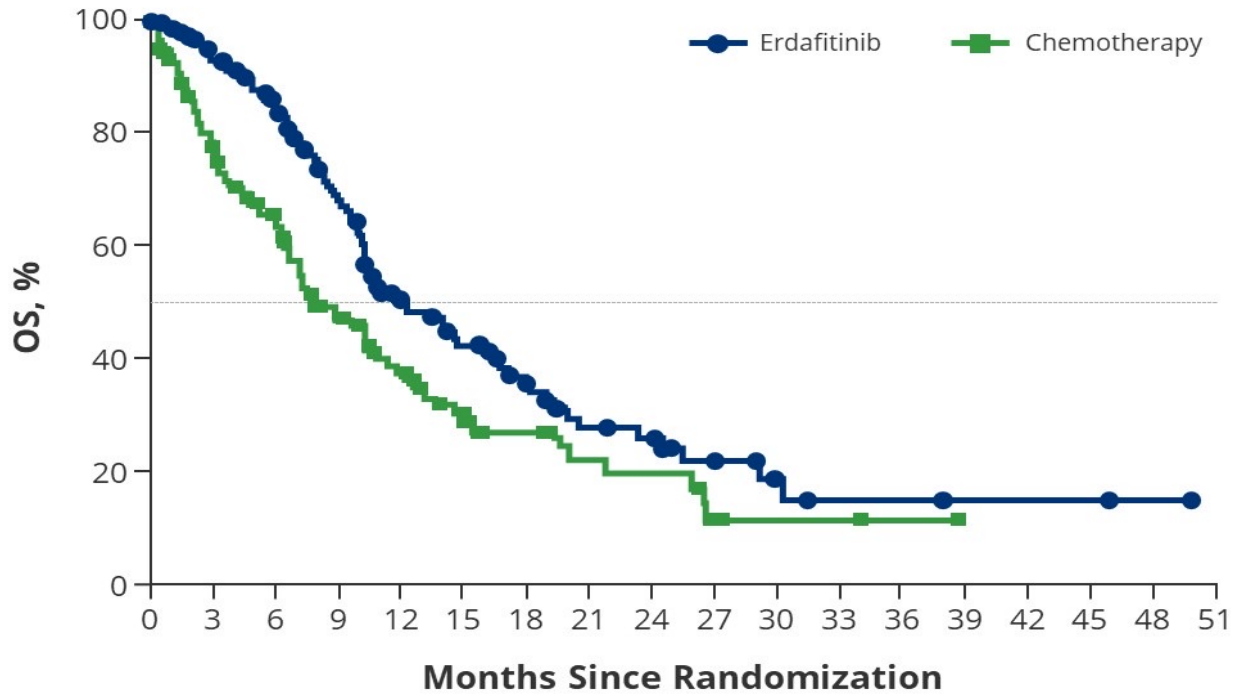
Overall Survival for Erdafitinib Was Superior to Investigator's Choice of Chemotherapy



No. at risk																		
Erdafitinib	136	117	97	74	46	35	25	17	15	9	5	3	3	2	2	2	1	0
Chemotherapy	130	87	66	43	30	18	13	9	8	3	2	2	1	0	0	0	0	0

- Median follow-up was 15.9 months
- Median OS was 12.1 months for erdafitinib versus 7.8 months for chemotherapy
- Erdafitinib reduced the risk of death by 36% versus chemotherapy
  - HR, 0.64 (95% CI, 0.47-0.88; $P = 0.005$)[a]
- Based on these interim analysis results, the IDMC recommended to stop the study, unblind data, and cross over patients from chemotherapy to erdafitinib

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The Safety Profiles Were Consistent With the Known Profiles of Erdafitinib and Chemotherapy (1/2)

Patients with AEs, n (%)[a]	Erdafitinib (n=135)	
	Any grade	Grade 3-4
≥1 treatment-related AE	**131 (97.0)**	**62 (45.9)**
Hyperphosphatemia	**106 (78.5)**	**7 (5.2)**
Diarrhea	**74 (54.8)**	**4 (3.0)**
Stomatitis	**62 (45.9)**	**11 (8.1)**
Dry mouth	**52 (38.5)**	**0**
PPE syndrome	**41 (30.4)**	**13 (9.6)**
Onycholysis	**31 (23.0)**	**8 (5.9)**
Patients who discontinued study treatment, n (%)		
Discontinuation due to treatment-related AEs	**11 (8.1%)[b]**	

- **In the erdafitinib group:**
  - 18 patients (13.3%) had treatment-related serious AEs
  - 1 treatment-related death occurred[c]
  - AEs with erdafitinib were mostly manageable with dose modifications and supportive care
- **In the chemotherapy group:**
  - 27 patients (24.1%) had treatment-related serious AEs
  - 6 treatment-related deaths occurred[d]

Patients with AEs, n (%)[e]	Chemotherapy (n=112)	
	Any grade	Grade 3-4
≥1 treatment-related AE	**97 (86.6)**	**52 (46.4)**
Anemia	**31 (27.7)**	**7 (6.3)**
Alopecia	**24 (21.4)**	**0**
Nausea	**22 (19.6)**	**2 (1.8)**
Neutropenia	**21 (18.8)**	**15 (13.4)**
Leukopenia	**13 (11.6)**	**9 (8.0)**
Febrile neutropenia	**9 (8.0)**	**10 (8.9)**
Patients who discontinued study treatment, n (%)		
Discontinuation due to treatment-related AEs	**15 (13.4)[f]**	

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Sequencing agents in second line setting (post platinum and PD-1)

- Limited prospective data!

- Factors to consider:
  - Prior line of therapy
  - Level of evidence
  - Genomic characteristics
  - Patient comorbidity/preference

Summary of agents in post platinum/IO space

	Enfortumab	Sacituzumab	Erdafitinib
Level of evidence	Randomized phase 3	Non-randomized	Randomized phase 3
Biomarker selection	n/a	n/a	+
Mode of administration	IV	IV	Oral
Patient out of pocket cost	+	+	++
Toxicity	Peripheral neuropathy, rash, hyperglycemia	Myelosuppression, GI toxicity	Diarrhea, hyperPHOS, mucositis
Limited data suggests efficacy of SG after enfortumab			

Remaining questions…

- Accelerated approval of EV/Pembrolizumab introduces additional sequencing challenges
- Role/tolerability and efficacy of platinum in post EV/Pembro setting needs to be evaluated
- Efficacy of erdafitinib after sequential ADC use needs to be better evaluated
- ? Therapy de-escalation in durable responders

Take home message

- EV/pembrolizumab poised to disrupt frontline treatment landscape
  - Could bring change to cisplatin eligible/in-eligible paradigm
- Sequential ADCs with different targets/payloads likely to play role in relapsed refractory setting
- FGFR inhibitors first targeted therapy to demonstrate improved OS
-
- Utilization of NGS crucial to identify patients likely to benefit from targeted therapy/clinical trials

Thank You

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