Bladder cancer

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Bladder Cancer Advocacy Network BCAN
Leading the way to awareness and a cure

Seattle Cancer Care Alliance
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UNIVERSITY of WASHINGTON

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Disclosures (within 1 year)

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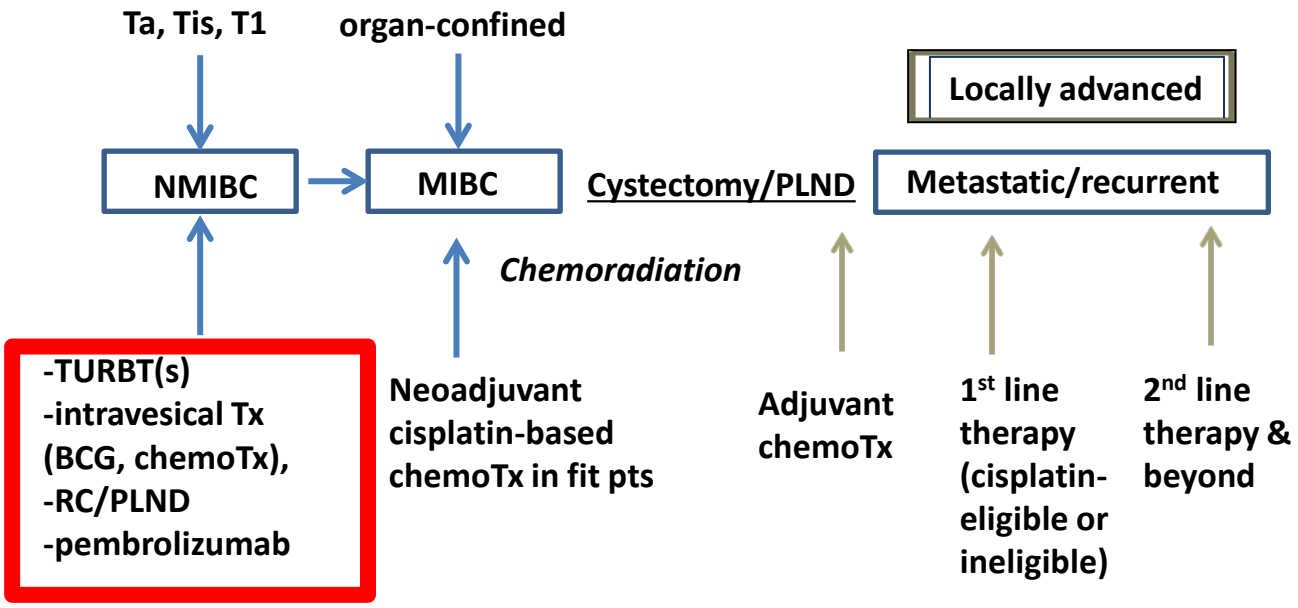
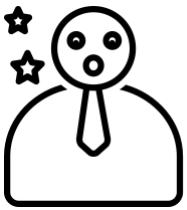
Disease / treatment settings



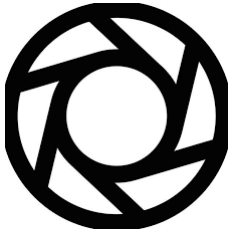
High risk NMIBC disease states defined by BCG

BCG Naïve



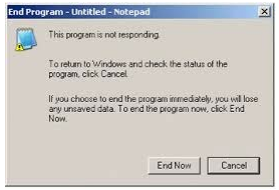
BCG 'Exposed'

- Induction only
- Late Relapse



BCG Unresponsive

- BCG Refractory
- Early Relapse



National BCG shortage in US: major issue!

What is BCG-unresponsive NMIBC?

Persistent Ta/CIS after induction and a round maintenance BCG

OR

Persistent T1after induction BCG

OR

After response to BCG, relapse of high grade Ta/T1 within 6 months or CIS within 12 months from last BCG dose

Adequate BCG therapy :

≥5 out of 6 doses of induction BCG + ≥ 2 additional doses of maintenance BCG

or

all 6 induction BCG doses and 1 maintenance BCG dose

UROLOGIC SCIENCES

BCG-unresponsive NMIBC

- **Radical Cystectomy & PLND**

What do many experts do?

- **Administer 1 more round of intravesical therapy before proceeding to radical cystectomy for HG Ta and/or CIS *(but RC for HG T1)***

Valrubicin

- **FDA-approved** in 1998 for BCG-refractory CIS in not candidates for radical cystectomy

- **CR at 6 months in 18% of pts**
- **2-year DFS only 4%**

Steinberg et al. J Urol, 1998;

Dinney et al. Urol Onc, 2013

Immune Checkpoint Inhibitors for

Keynote 057
Pembrolizumab
Cohort A: CIS

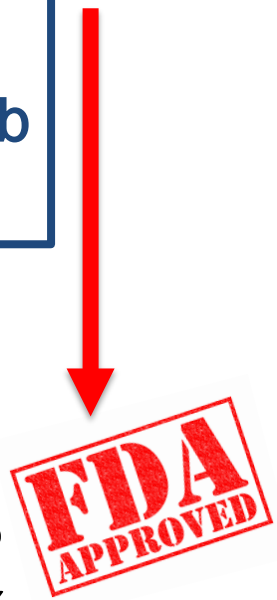
N=97

3 mo CR: 41%

6 mo CR: 31%

15 mo CR: 20%

Gr 3 TRAE: 13%



https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(21)00147-9/fulltext

Balar et al, GU ASCO 2019 ODAC Briefing Document

SWOG S1605
Atezolizumab

N=74

3 mo CR: 42%

6 mo CR: 27% (mandatory biopsy)

durability pending

Gr 3 TRAE: 17%

Black et al, ASCO 2020

Systemic Immune-Oncology Therapy for NMIBC after BCG: KEYNOTE-057 with Pembrolizumab

January 2020: FDA approved pembrolizumab for BCG-unresponsive CIS with or without papillary tumors who are ineligible for or have not elected to undergo radical cystectomy

de Wit R, et al. ESMO 2018
Balar A, et al. ASCO GU 2019

Examples of other novel therapies for NMIBC

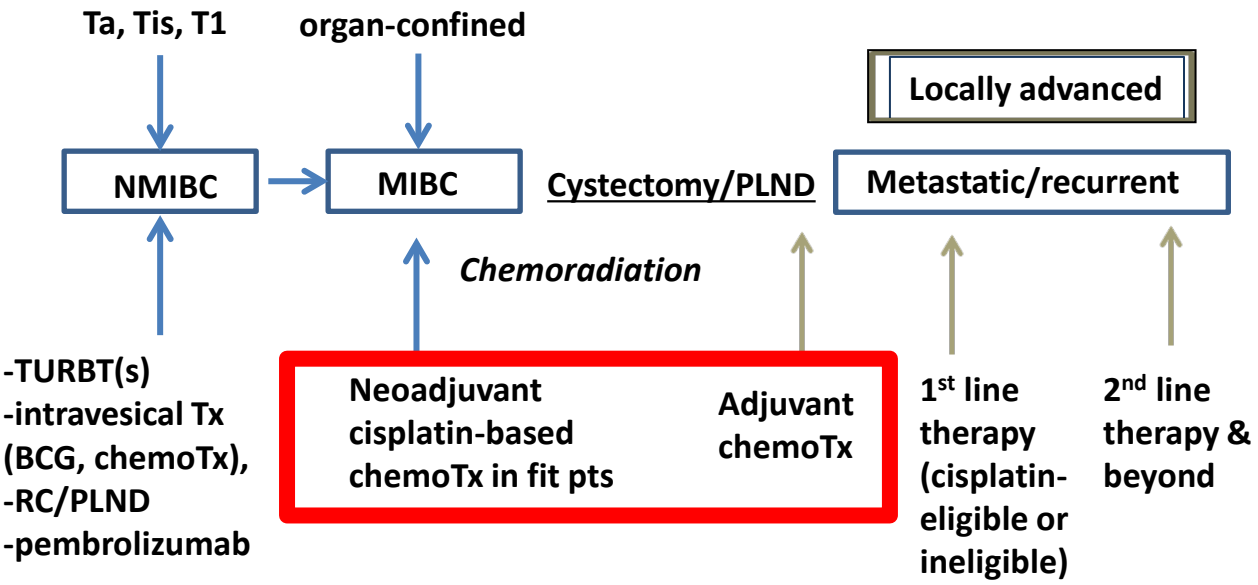
Oportuzumab monatox

Nadofaragene firadenovec

Photodynamic Therapy

ALT-803

Disease / treatment settings



Advantages of neoadjuvant systemic therapy

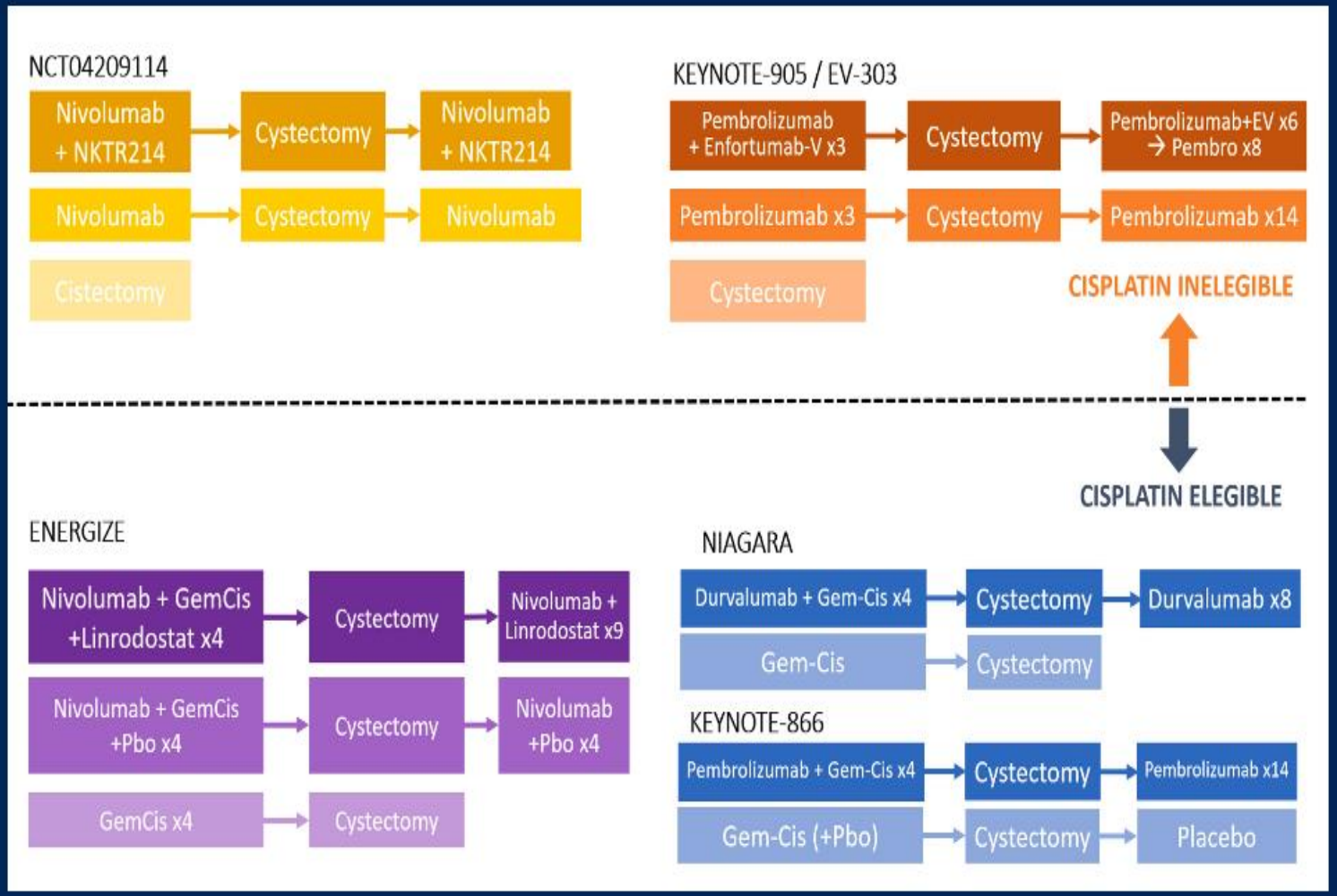
- Neoadjuvant cisplatin-based chemotherapy improves OS.
- Often better tolerated.
- Potential for maximizing impact on patient outcomes by administering drug at the earliest point in the natural history of the disease.
- Tissue availability from TURBT and RC offers opportunities to study biomarkers of response in clinical trials.
- Surrogate endpoints of responsiveness to therapy (pCR) enable early risk-stratification to select patients who could benefit from additional therapy.

Take Home Points on NAC

- **Disease-free and overall survival benefit from NAC with cisplatin-based combinations**
- **Non-cisplatin Tx in perioperative setting has no proven benefit**
- **Dose-dense MVAC may have less toxicity, shorter time to surgery**
- **Retrospective datasets & S1314 (COXEN trial presented at 2019 ASCO Meeting): comparable pCR % between gemcitabine/cisplatin & (dd)MVAC (+G-CSF); see also Vesper trial**
- **Novel trials focus on immunotherapy & biomarkers of response**

Smith D, J Urol. 2008; 180(6): 2384–2388
Grivas P, UROLOGY 82: 111e117, 2013
Choueiri T, *J Clin Oncol 32:1889–1894*
Plimack J, J Clin Oncol 32:1895–1901
Blick et al. 2012 Cancer

Phase III neoadjuvant IO trials



Rey-C´ardenas et al. Cancer Treatment Reviews, 2021.

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JOURNAL OF CLINICAL ONCOLOGY

EDITORIAL

Consider gemcitabine/cisplatin or accelerated/dose dense MVAC X 4 cycles for pT3/4 and/or pN+ who are cisplatin-fit and did not receive neoadjuvant chemoTx

Adjuvant Chemotherapy for Bladder Cancer: Using Population-Based Data to Fill a Void of Prospective Evidence

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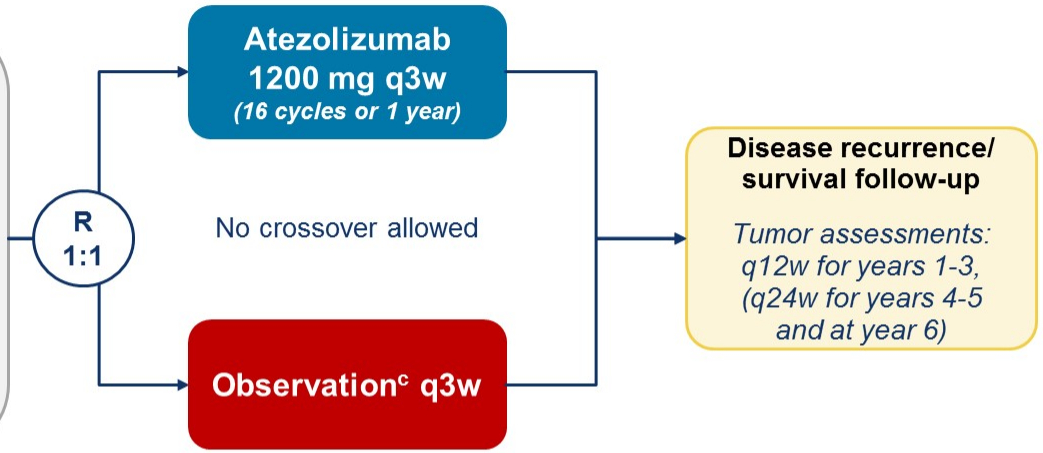
Neeraj Agarwal, *Huntsman Cancer Institute, University of Utah, Salt Lake City, UT*
Petros Grivas, *Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH*
Toni Choueiri, *Dana-Farber Cancer Institute, Boston, MA*

IMvigor010 Study Design

Key eligibility[a]

- **High-risk MIUC (bladder, renal pelvis, ureter)**
- **Radical cystectomy/nephroureterectomy with LN dissection** within ≤ 14 weeks
  - **ypT2-T4a or ypN+** for patients treated with **NAC**[b]
  - **pT3-T4a or pN+** for patients **not treated with NAC**[b]
- No postsurgical radiation or AC
- If no prior NAC given, patient had to be ineligible for, or declined, cisplatin-based AC
- ECOG PS 0-2
- **Tissue sample for PD-L1 testing**



Stratification factors

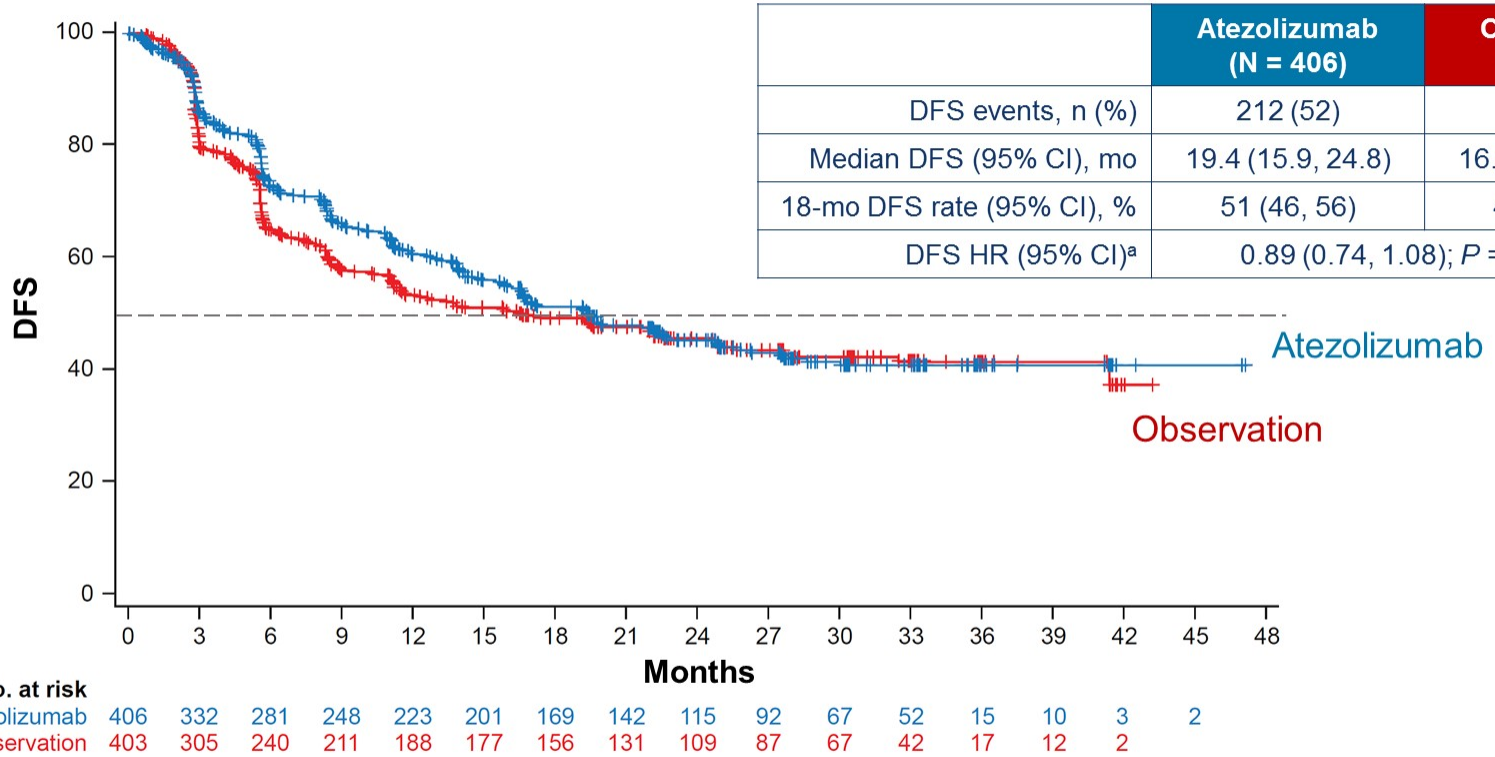
- Number of LNs resected (< 10 vs ≥ 10)
- Prior NAC (Yes vs No)
- LN status (+ vs –)
- Tumor stage (≤ pT2 vs pT3/pT4)
- PD-L1 status[a] (IC0/1 vs IC2/3)

- **Primary endpoint:** DFS (ITT population)
- **Key secondary endpoint:** OS (ITT population)
- **Exploratory analyses:** Biomarkers including PD-L1 status
- **Safety**

AC, adjuvant chemotherapy; DFS, disease-free survival; ITT, intention to treat; LN, lymph node; MIUC, muscle-invasive UC. [a] Protocol amendments broadened eligibility to "all-comers" (initially, only PD-L1–selected patients were enrolled [IC2/3: PD-L1 expression on tumor-infiltrating immune cells (IC) ≥ 5% of tumor area [VENTANA SP142 IHC assay]) and to patients with MIUC (initially, only patients with muscle-invasive bladder cancer were enrolled). [b] Upper-tract UC staging: ypT2-4 or ypN+ (with NAC) and pT3-4 or pN+ (without NAC). [c] Alternating clinic visits and phone calls.

Presented By Maha Hussain at TBD

DFS in ITT Population



	Atezolizumab (N = 406)	Observation (N = 403)
DFS events, n (%)	212 (52)	208 (52)
Median DFS (95% CI), mo	19.4 (15.9, 24.8)	16.6 (11.2, 24.8)
18-mo DFS rate (95% CI), %	51 (46, 56)	49 (44, 54)
DFS HR (95% CI)[a]	0.89 (0.74, 1.08); *P* = 0.2446[b]	

Data cutoff: November 30, 2019. Median follow-up: 21.9 mo. [a] Stratified by post-resection tumor stage, nodal status and PD-L1 status. [b] 2-sided.

Presented By Maha Hussain at TBD

Study design

- CheckMate 274 is a phase 3, randomized, double-blind, multicenter study of adjuvant nivolumab versus placebo in patients with high-risk MIUC

N = 709

Key inclusion criteria

- Patients with ypT2-ypT4a or ypN+ MIUC who had neoadjuvant cisplatin chemotherapy
- Patients with pT3-pT4a or pN+ MIUC without prior neoadjuvant cisplatin chemotherapy and not eligible/refuse adjuvant cisplatin chemotherapy
- Radical surgery within the past 120 days
- Disease-free status within 4 weeks of dosing

Stratification factors

- PD-L1 status (<1% vs ≥ 1%)[a]
- Prior neoadjuvant cisplatin-based chemotherapy
- Nodal status

Treat for up to 1 year of adjuvant therapy

Minimum follow-up, 5.9 months
Median follow-up in ITT population, 20.9 months (NIVO) and 19.5 months (PBO)

Primary endpoints: DFS in ITT population and DFS in all randomized patients with tumor PD-L1 ≥ 1%
Secondary endpoints: NUTRFS, DSS, and OS[b]
Exploratory endpoints included: DMFS, safety, HRQoL

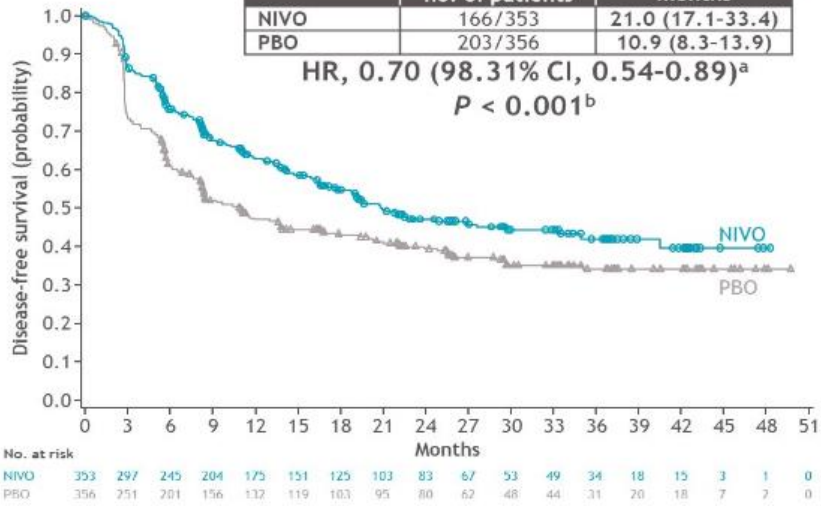
[a]Defined by the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells using the PD-L1 IHC 28-8 PharmDx immunohistochemistry assay.
[b]OS data were not mature at the time of the first planned interim analysis. OS and DSS data are not presented.
DFS, disease-free survival; DMFS, distant metastasis-free survival; DSS, disease-specific survival; HRQoL, health-related quality of life; IHC, immunohistochemistry; ITT, intent-to-treat; NUTRFS, non-urothelial tract recurrence-free survival; OS, overall survival; PD-L1, programmed death ligand 1; Q2W, every 2 weeks; R, randomized.

Disease-free survival

ITT

	No. of events/ no. of patients	Median (95% CI), months
NIVO	166/353	21.0 (17.1-33.4)
PBO	203/356	10.9 (8.3-13.9)

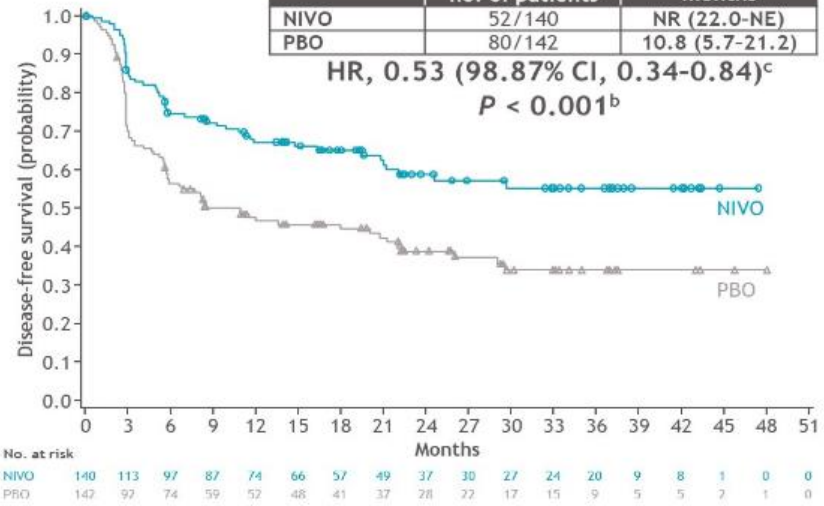
HR, 0.70 (98.31% CI, 0.54-0.89)[a]
P < 0.001[b]



PD-L1 ≥ 1%

	No. of events/ no. of patients	Median (95% CI), months
NIVO	52/140	NR (22.0-NE)
PBO	80/142	10.8 (5.7-21.2)

HR, 0.53 (98.87% CI, 0.34-0.84)[c]
P < 0.001[b]



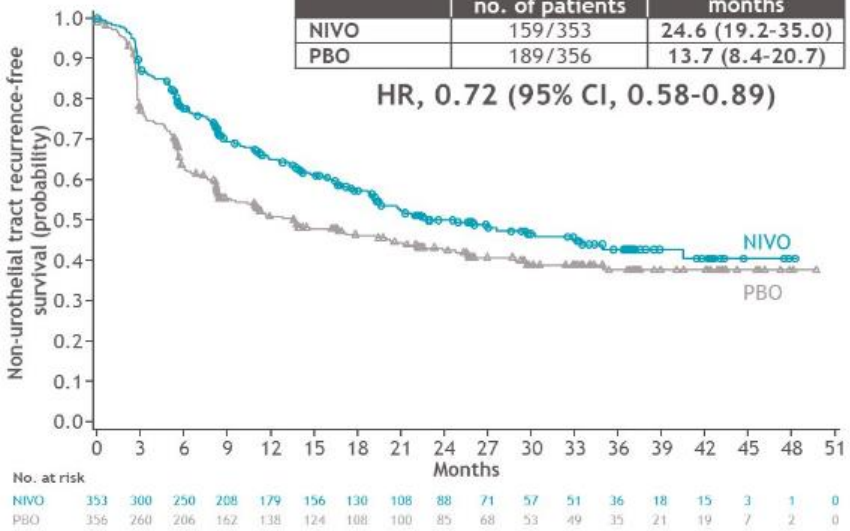
Minimum follow-up, 5.9 months.
DFS was defined as the time between the date of randomization and the date of first recurrence (local urothelial tract, local non-urothelial tract or distant) or death.
[a]HR, 0.695 (98.31% CI, 0.541-0.894). [b]Based on a 2-sided stratified logrank test. [c]HR, 0.535 (98.87% CI, 0.340-0.842).
CI, confidence interval; NE, not estimable; NR, not reached.

Non-urothelial tract recurrence-free survival

ITT

	No. of events/ no. of patients	Median (95% CI), months
NIVO	159/353	24.6 (19.2-35.0)
PBO	189/356	13.7 (8.4-20.7)

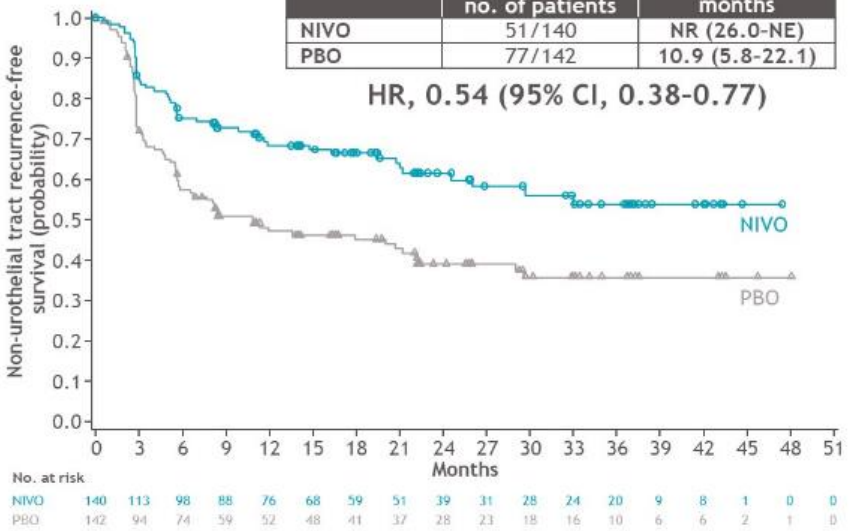
HR, 0.72 (95% CI, 0.58-0.89)



PD-L1 ≥ 1%

	No. of events/ no. of patients	Median (95% CI), months
NIVO	51/140	NR (26.0-NE)
PBO	77/142	10.9 (5.8-22.1)

HR, 0.54 (95% CI, 0.38-0.77)



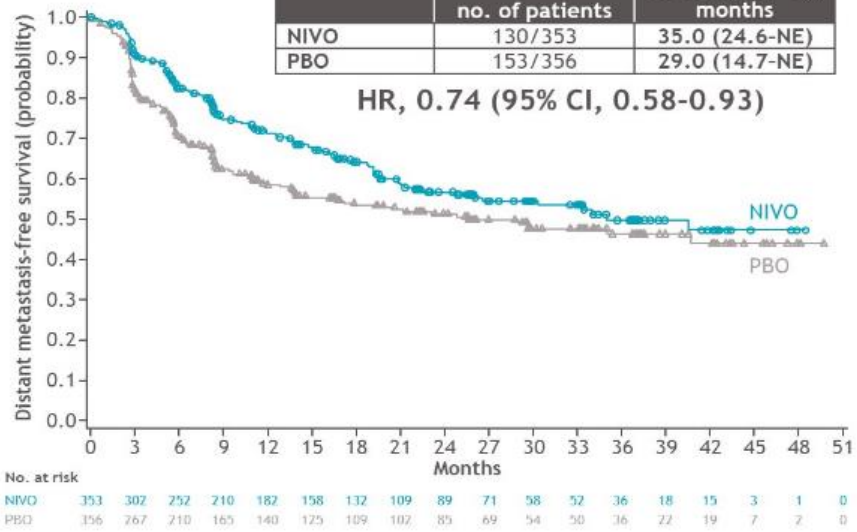
Minimum follow-up, 5.9 months.
NUTRFS was defined as the time between the date of randomization and the date of first local non-urothelial tract or distant recurrence or death.

Distant metastasis-free survival

ITT

	No. of events/ no. of patients	Median (95% CI), months
NIVO	130/353	35.0 (24.6-NE)
PBO	153/356	29.0 (14.7-NE)

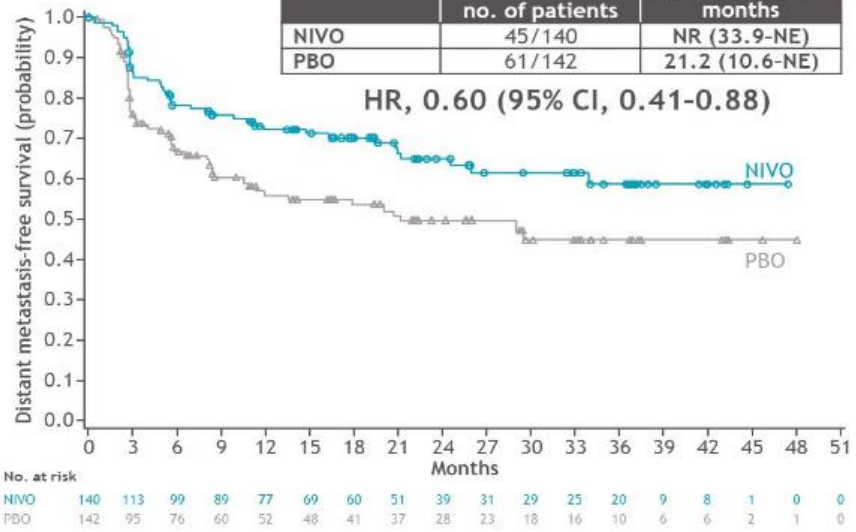
HR, 0.74 (95% CI, 0.58-0.93)



PD-L1 ≥ 1%

	No. of events/ no. of patients	Median (95% CI), months
NIVO	45/140	NR (33.9-NE)
PBO	61/142	21.2 (10.6-NE)

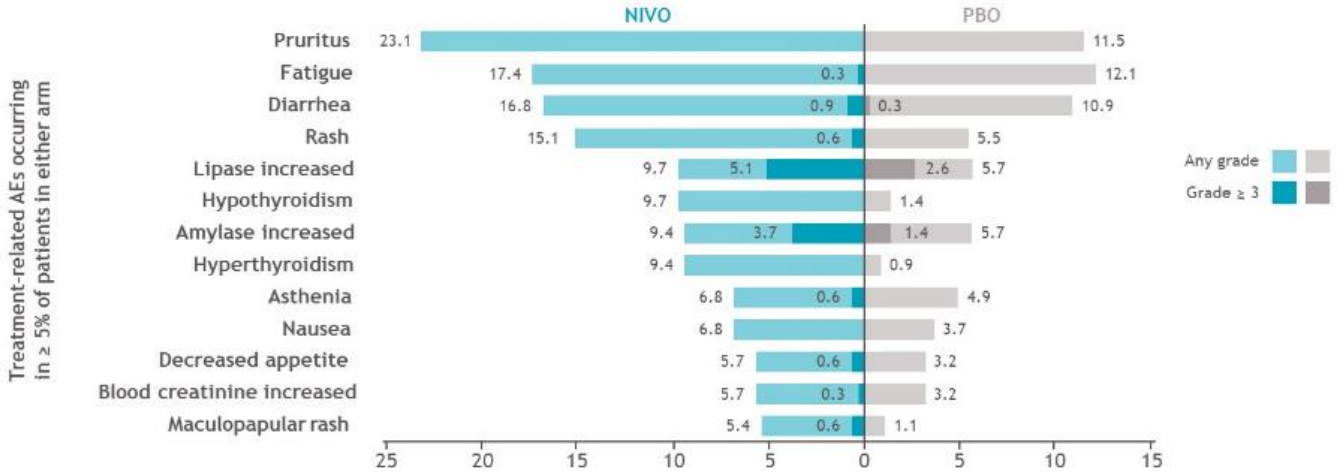
HR, 0.60 (95% CI, 0.41-0.88)



Minimum follow-up, 5.9 months.
DMFS was defined as the time between the date of randomization and the date of first distant recurrence (non-local) or date of death.

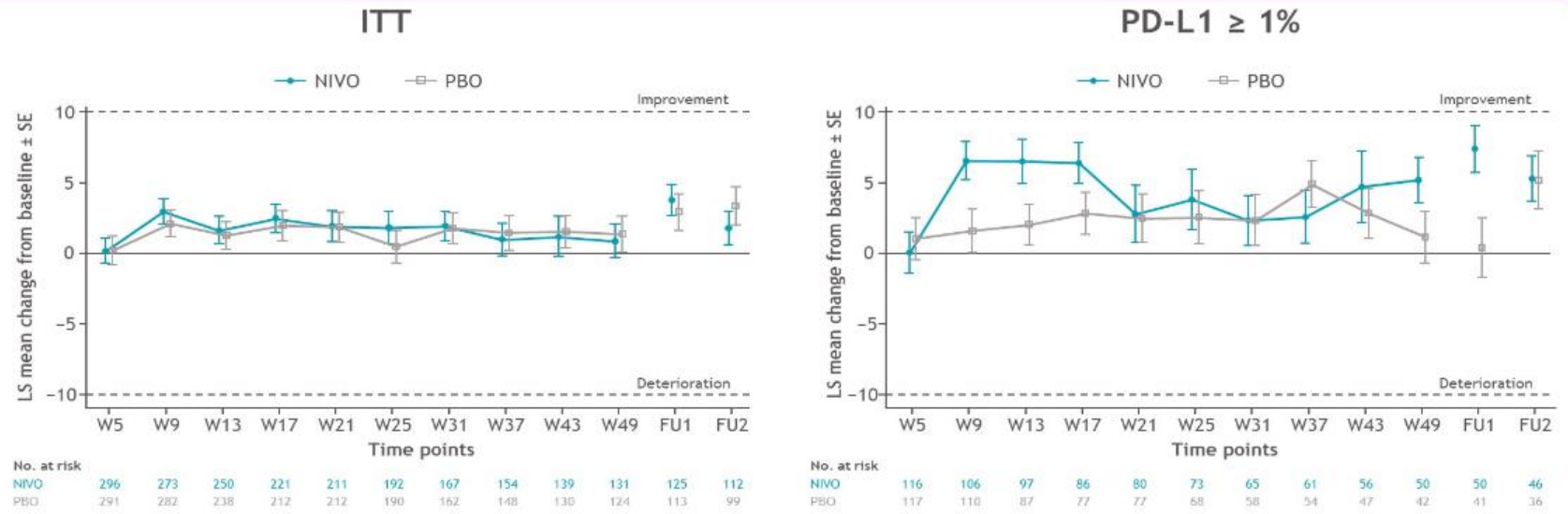
Safety summary in all treated patients

	NIVO (N = 351)[a]		PBO (N = 348)[a]	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Any-cause AEs, %	98.9	42.7	95.4	36.8
Treatment-related AEs,[b] %	77.5	17.9	55.5	7.2
Treatment-related AEs leading to discontinuation, %	12.8	7.1	2.0	1.4



[a]Includes all treated patients. [b]There were 2 treatment-related deaths due to pneumonitis in the NIVO arm. There were no treatment-related deaths in the PBO arm. Includes events reported between the first dose and 30 days after the last dose of study therapy.

Health-related quality of life: change from baseline in EORTC-QLQ-C30 global health status score



- No deterioration in HRQoL with NIVO versus PBO was observed in either the ITT or PD-L1 ≥ 1% populations

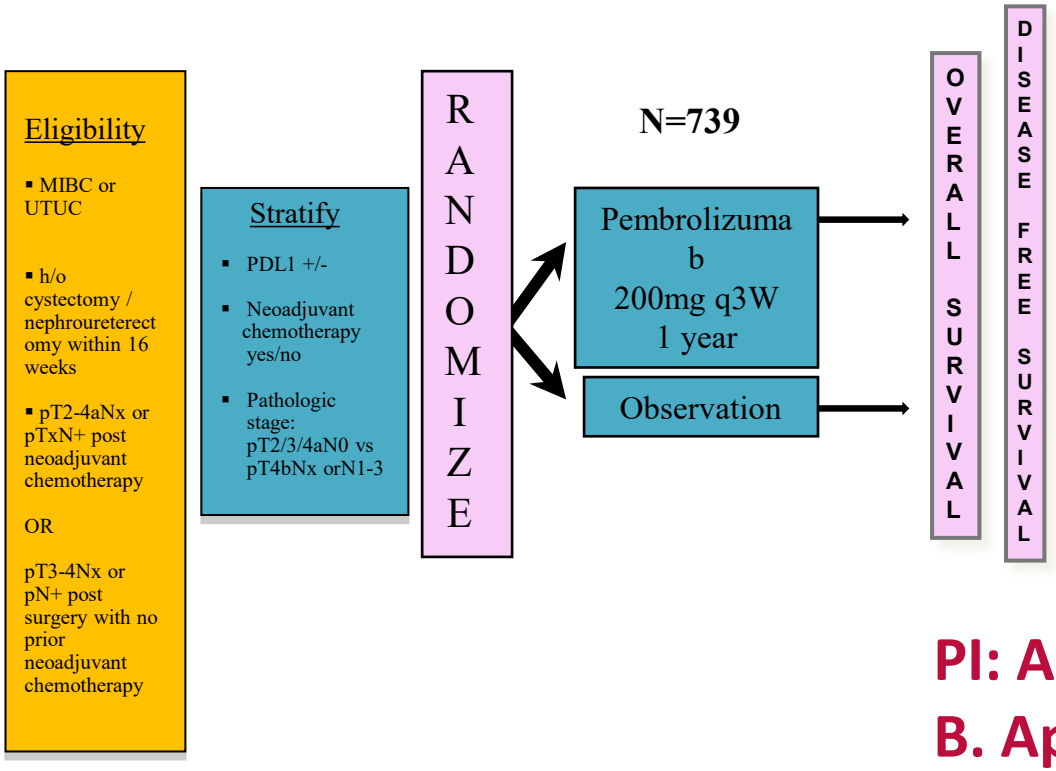
Number of patients displayed is the number of patients included in the mixed effects linear regression for repeated measures analysis at each visit. SE is the robust SE calculated using empirical variance estimator.
FU, follow-up visit; LS, least square; SE, standard error.

Summary

- Adjuvant NIVO significantly improved DFS in patients with high-risk MIUC after radical surgery, both in the ITT and PD-L1 ≥ 1% populations
- NUTRFS (secondary endpoint) and DMFS (exploratory endpoint) were also improved with NIVO versus PBO in both study populations
- The safety and tolerability of NIVO monotherapy was consistent with previous reports in other tumor types, including in patients with metastatic UC[1-3]
- No deterioration in HRQoL, as measured by change in EORTC QLQ-C30 global health status score, was observed with NIVO versus PBO
- NIVO is the first systemic immunotherapy to demonstrate a statistically significant and clinically meaningful improvement in outcomes when administered as adjuvant therapy to patients with MIUC[4,5]
- These results support NIVO monotherapy as a new standard of care in the adjuvant setting for patients with high-risk MIUC after radical surgery, regardless of PD-L1 status and prior neoadjuvant chemotherapy

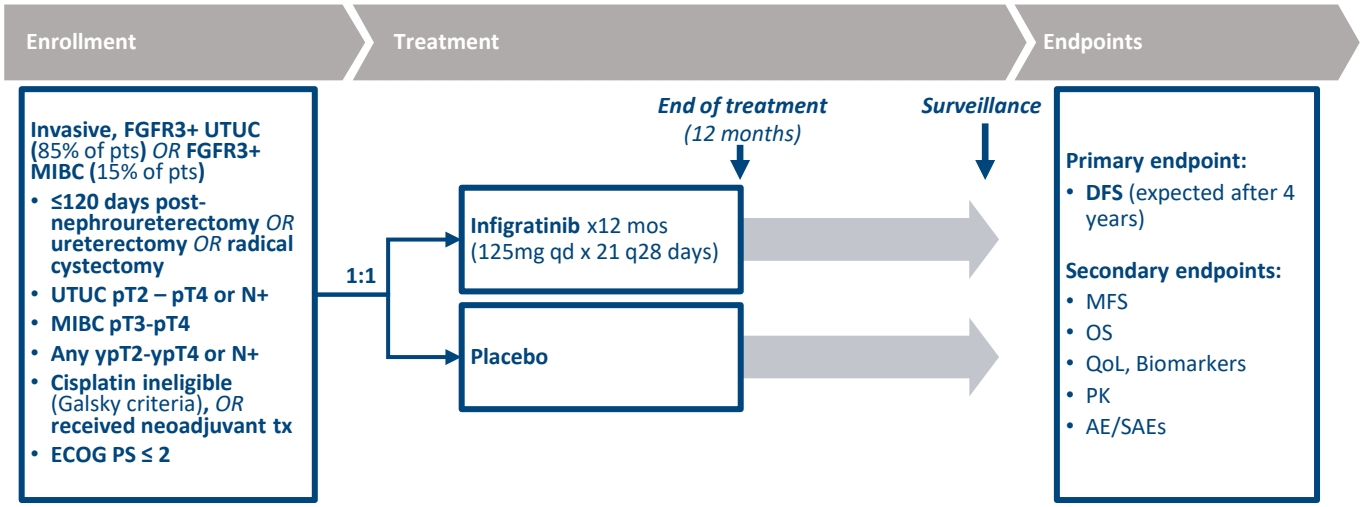
1. Sharma P et al. *Lancet Oncol* 2016;17:1590-1598. 2. Sharma P et al. *Lancet Oncol* 2017;18:312-322. 3. Motzer R et al. *N Engl J Med* 2015;373:1803-1813. 4. Kim HS et al. *Investig Clin Urol* 2018;59:285-296. 5. Hussain MHA et al. *J Clin Oncol* 2020;38(suppl 15):5000.

Phase III randomized “Adjuvant study of peMBrolizumAb in muScle invaSive and locAlly aDvanced urOthelial carcinoma” (AMBASSADOR) vs. observation



PI: Andrea B. Apolo

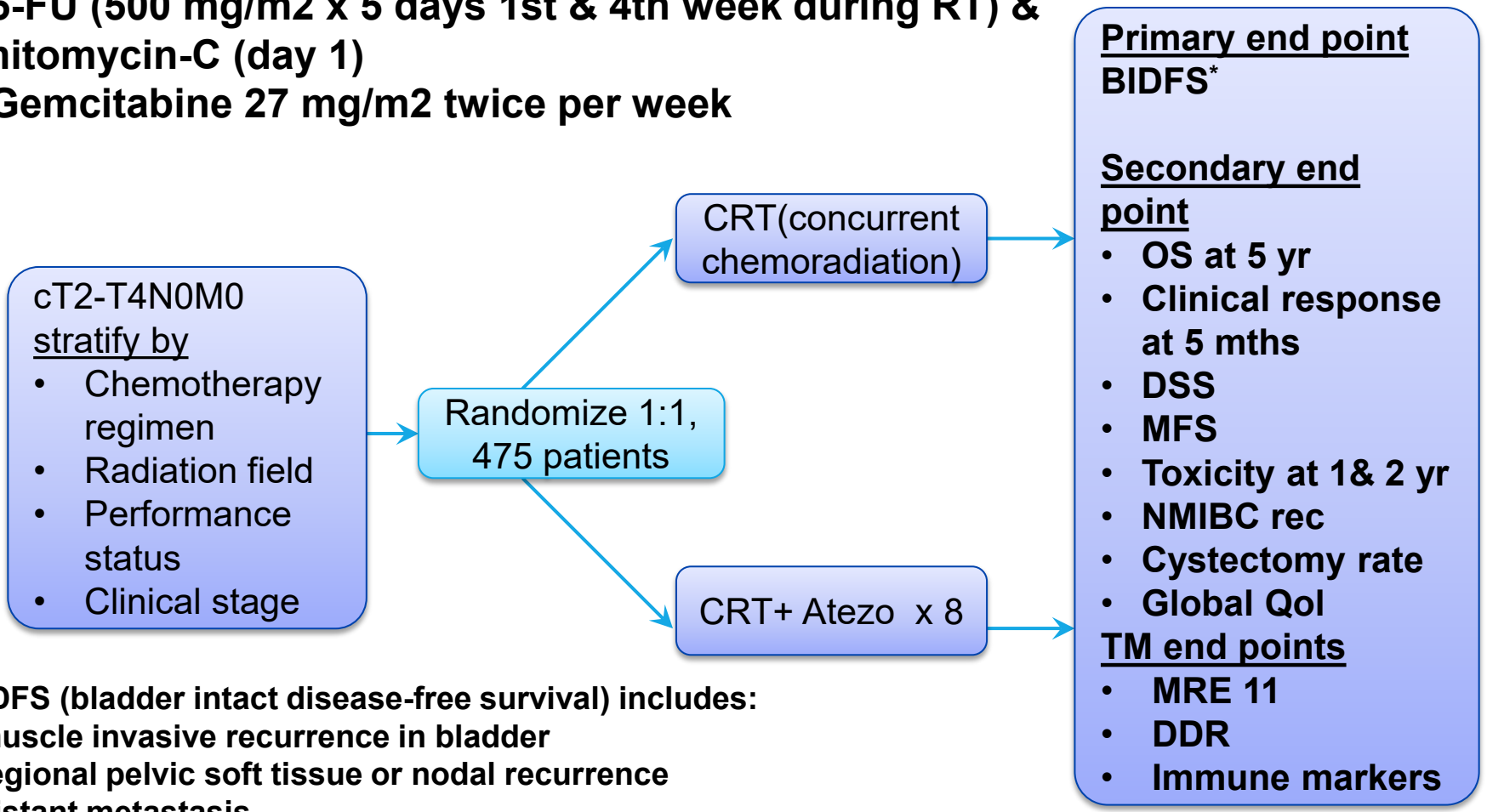
A Phase 3, double-blind, RCT trial of infigratinib



PIs: Dr. Pal & Dr. Daneshmand

SN1806 trial for bladder preservation

-Cisplatin 35 mg/m2 weekly (ideally Monday)
-5-FU (500 mg/m2 x 5 days 1st & 4th week during RT) & mitomycin-C (day 1)
-Gemcitabine 27 mg/m2 twice per week



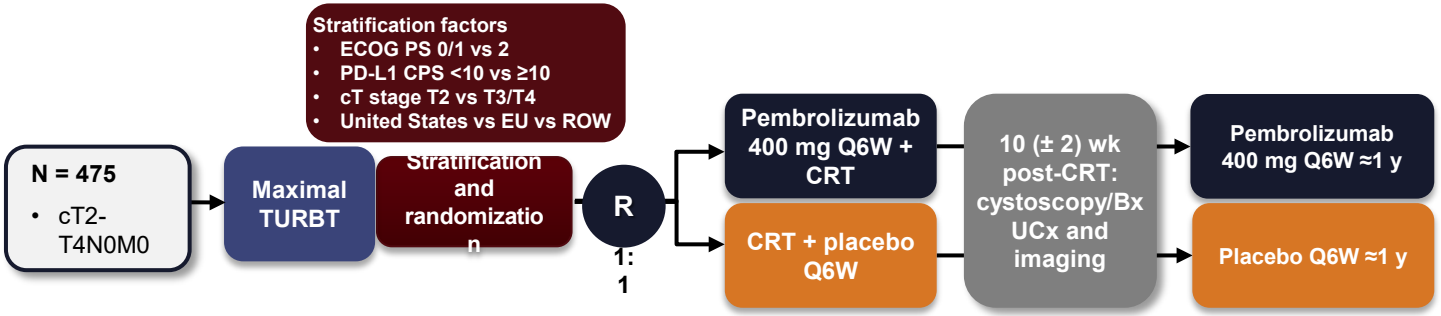
***BIDFS (bladder intact disease-free survival) includes:**
- **muscle invasive recurrence in bladder**
- **regional pelvic soft tissue or nodal recurrence**
- **distant metastasis**
- **bladder cancer or toxicity-related death or cystectomy**

PI: Parminder Singh

S1806

Southwest Oncology Group
A National Clinical Research Group

KN-992: Phase 3 Study of Pembrolizumab ± CRT for Bladder Preservation in Localized MIBC[1]

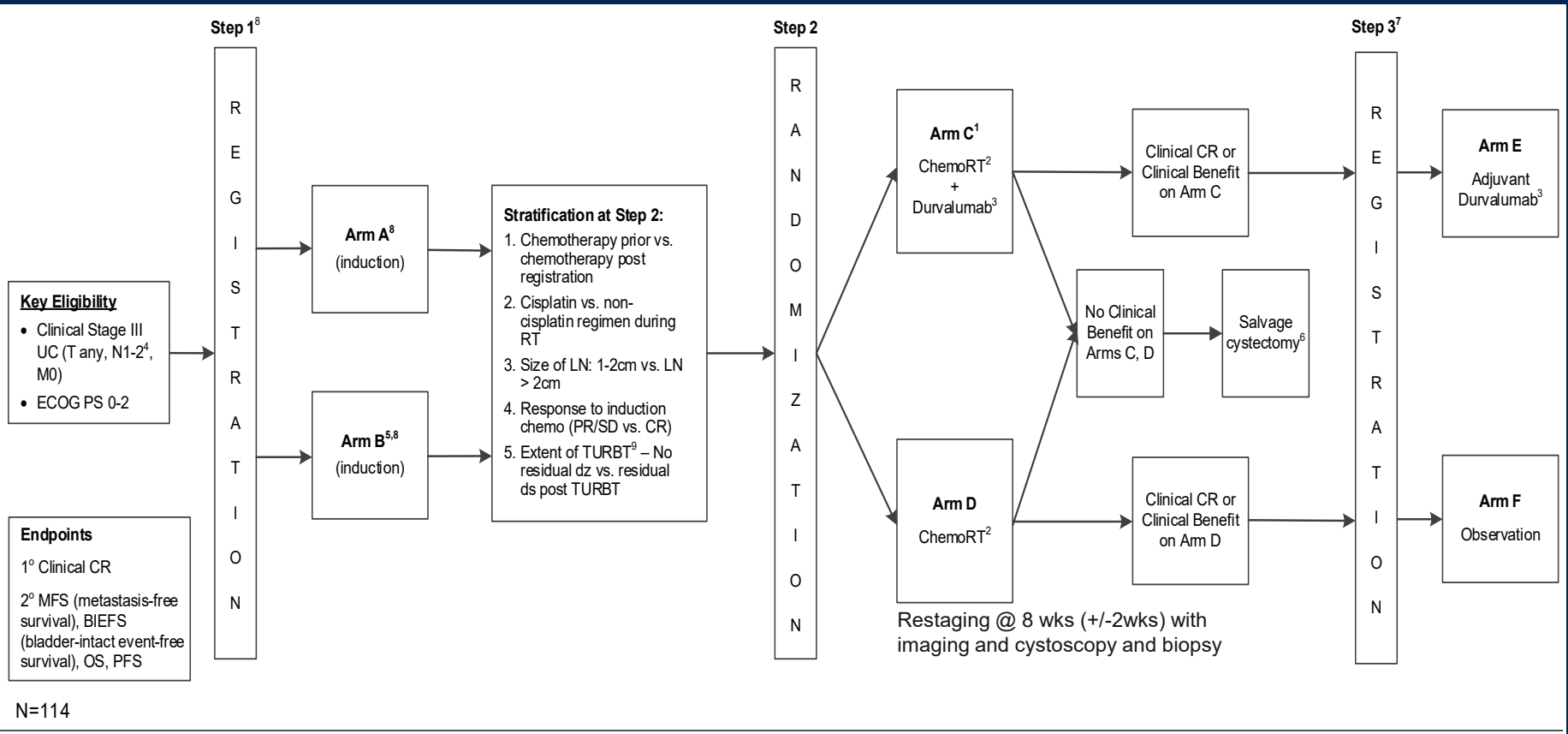


- **Primary endpoint:** BIEFS
- **Secondary endpoints:** OS, MFS, time to NMIBC, safety/tolerability, time to cystectomy, HRQOL
- **Biomarker endpoints:** blood/tissue DNA/RNA, IHC, proteomics
- **SAC chair: Arjun Balar**

- **Bladder-intact event-free survival**
- **Residual/recurrent MIBC (central pathology review)**
- **Metastases (nodal or distant)**
- **Radical cystectomy**
- **Death**

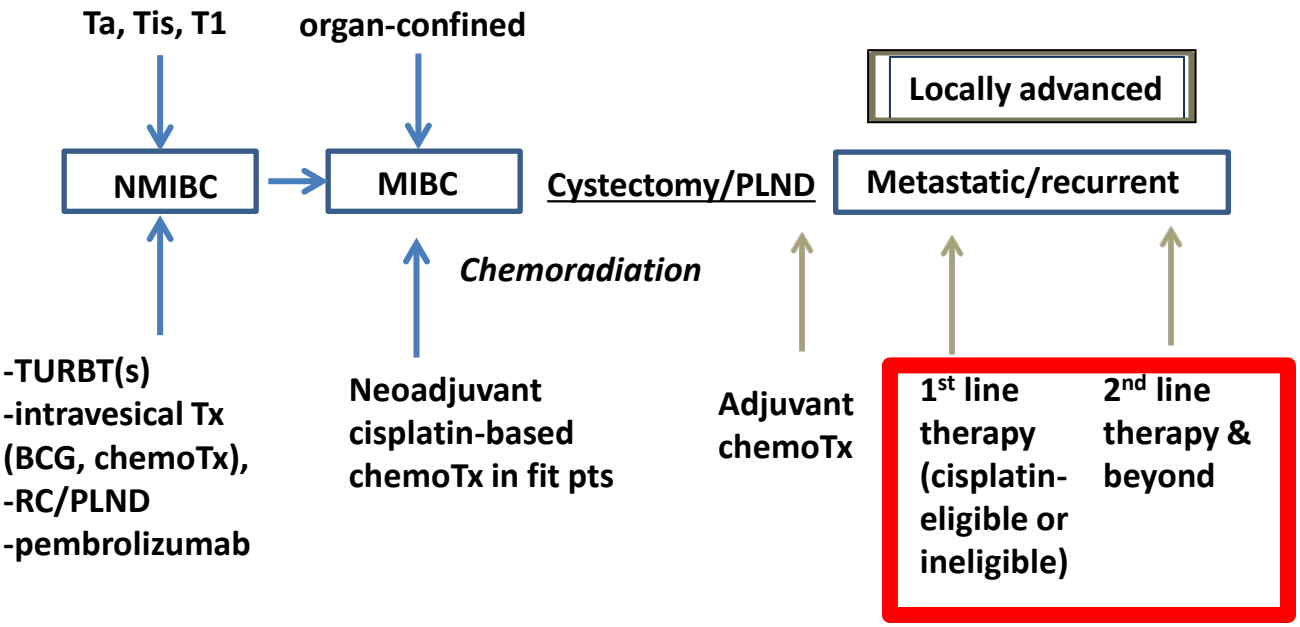
1. **https://clinicaltrials.gov/ct2/show/NCT04241185. Accessed February 7, 2020**

EA8185 (INSPIRE)



1. 1st 6 patients randomized to Arm C (ChemoRT + Durvalumab) will be evaluated for safety run.
2. Chemosensitizing options: (weekly Cisplatin or 5-FU+MMC, or twice weekly Gemcitabine) +EBRT. See section 5.2 for treatment options and descriptions.
3. Durvaluamb will be given Q3 weekly x 3 doses on Arm C and it will be given Q4 weekly x 9 doses on Arm E.
4. Node (N1-2) + status must be determined prior to starting induction chemotherapy (IC) and patients must not have PD during or post chemotherapy. N+ Defined > 1cm in short axis by imaging.
5. See section 5.1.1 for Induction chemotherapy options and descriptions.
6. Salvage cystectomy when possible.
7. Restaging 8 weeks (+/-2 weeks) with imaging and cystoscopy and biopsy.
8. Patients who have already completed ≥ 3 cycles of induction chemotherapy prior to study entry will be registered to Arm A and proceed directly to Step 2 randomization. Patients who are chemo naïve will be registered to Arm B and will undergo induction chemotherapy for 3 cycles before proceeding to Step 2 randomization.
9. TURBT: trans-urethral resection of bladder tumor.

Disease / treatment settings



Metastatic disease (1st line)

- Comparable ORR between GC & 'classic' MVAC
- Median PFS: 7.7m (GC) and 8.3 m (MVAC)
- Median OS (14 vs. 15 months)
- Similar 5-y OS rate (13-15%) (p=0.53)
- Less G ¾ AEs with GC, e.g. neutropenia (71 vs. 82%), neutropenic sepsis (2% vs 14%), mucositis (1% vs 22%)
- Trial was designed to assess if GC is superior and was not powered to demonstrate non-inferiority

Most patients get GC (dose dense MVAC easier & better than older 'classic' MVAC)

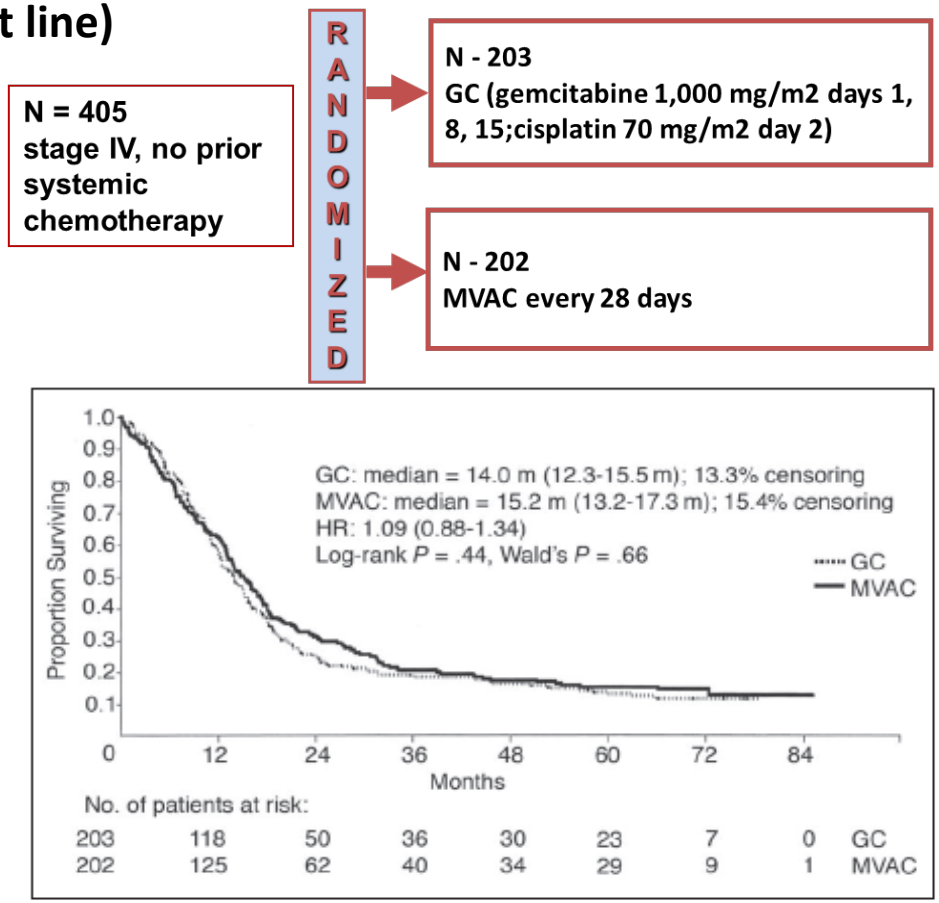
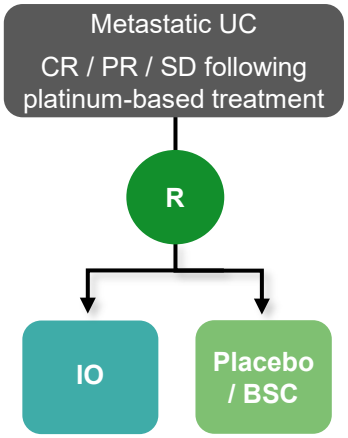


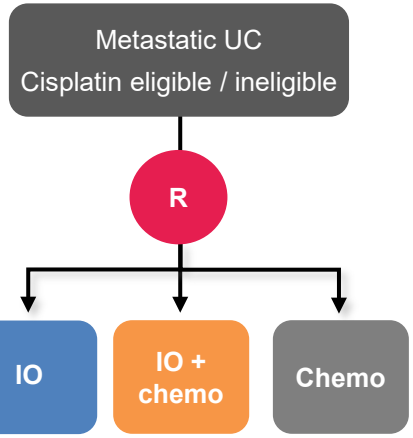
Fig 1. Kaplan-Meier curves for overall survival. GC, gemcitabine/cisplatin; MVAC, methotrexate/vinblastine/doxorubicin/cisplatin; HR, hazard ratio; Pts, patients.

Von der Maase H et al, JCO, 2000 (17): 3068-77

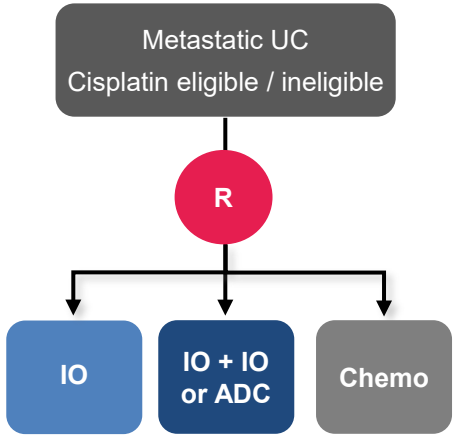
Different strategies aiming to impact 1L SoC



JB100 [NCT02603432]	avelumab	BSC	OS
HOOSIER [NCT02500121]	pembro	placebo	6-mo PFS



KN361 [NCT02853305]	pembro	pembro + chemo	chemo	OS, PFS
CM901 [NCT03036098]	--	nivo + chemo*	chemo	OS, PFS
IMvigor130 [NCT02807636]	atezo	atezo + chemo	chemo	OS, PFS, safety

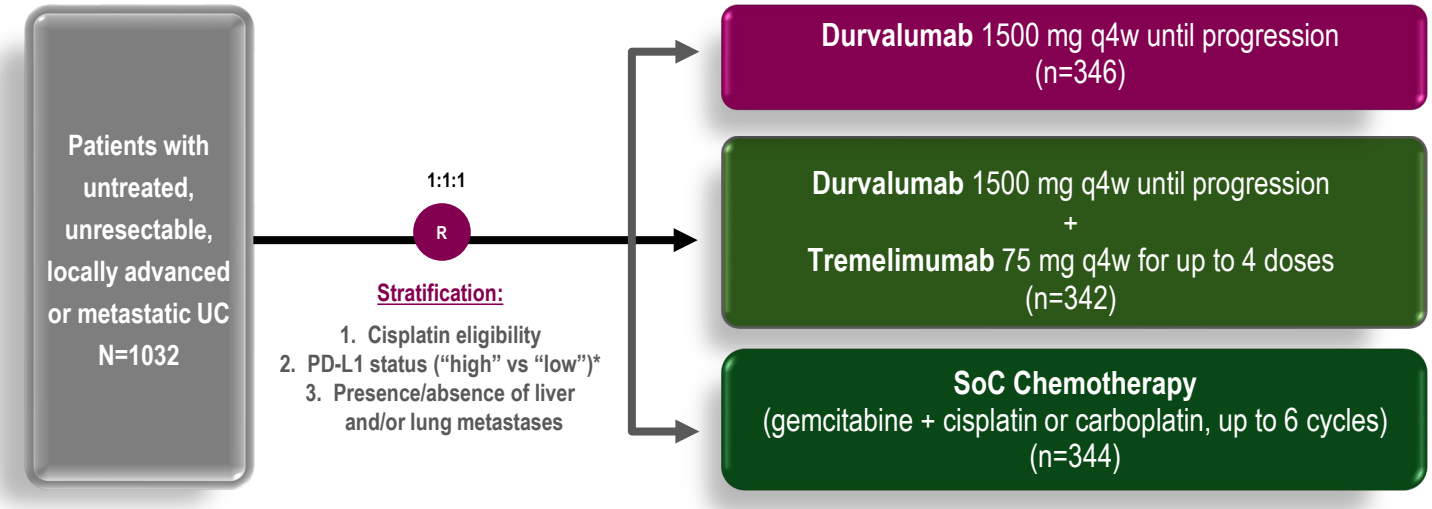


DANUBE [NCT02516241]	durva	durva + treme	chemo	OS
CM901 [NCT03036098]	--	nivo + ipi	chemo	OS, PFS
EV-302 [NCT04223856]	--	pembro + EV	chemo	OS, PFS

*For cisplatin-eligible patients only

1L, first-line; ADC, antibody-drug conjugate; atezo, atezolizumab; BSC, best supportive care; EV, enfortumab vedotin; chemo, chemotherapy; CR, complete response; durva, durvalumab; IO, immuno-oncology; ipi, ipilimumab; OS, overall survival; nivo, nivolumab; pembro, pembrolizumab; PFS, progression-free survival; PR, partial response; R, randomisation; SD, stable disease; SoC, standard of care; treme, tremelimumab; UC, urothelial carcinoma. NCT entries available at https://clinicaltrials.gov/ [Accessed August 2020].

DANUBE Study Design[1]



CO-PRIMARY ENDPOINTS

- OS (D vs SoC in PD-L1 high)
- OS (D+T vs SoC in all comers)

SELECT SECONDARY ENDPOINTS

- OS (D vs SoC in all comers)
- OS (D+T vs SoC in PD-L1 high)
- PFS, ORR, and DoR

Data cutoff date (final analysis): January 27 2020

Minimum follow-up from date last patient randomised: 34 months

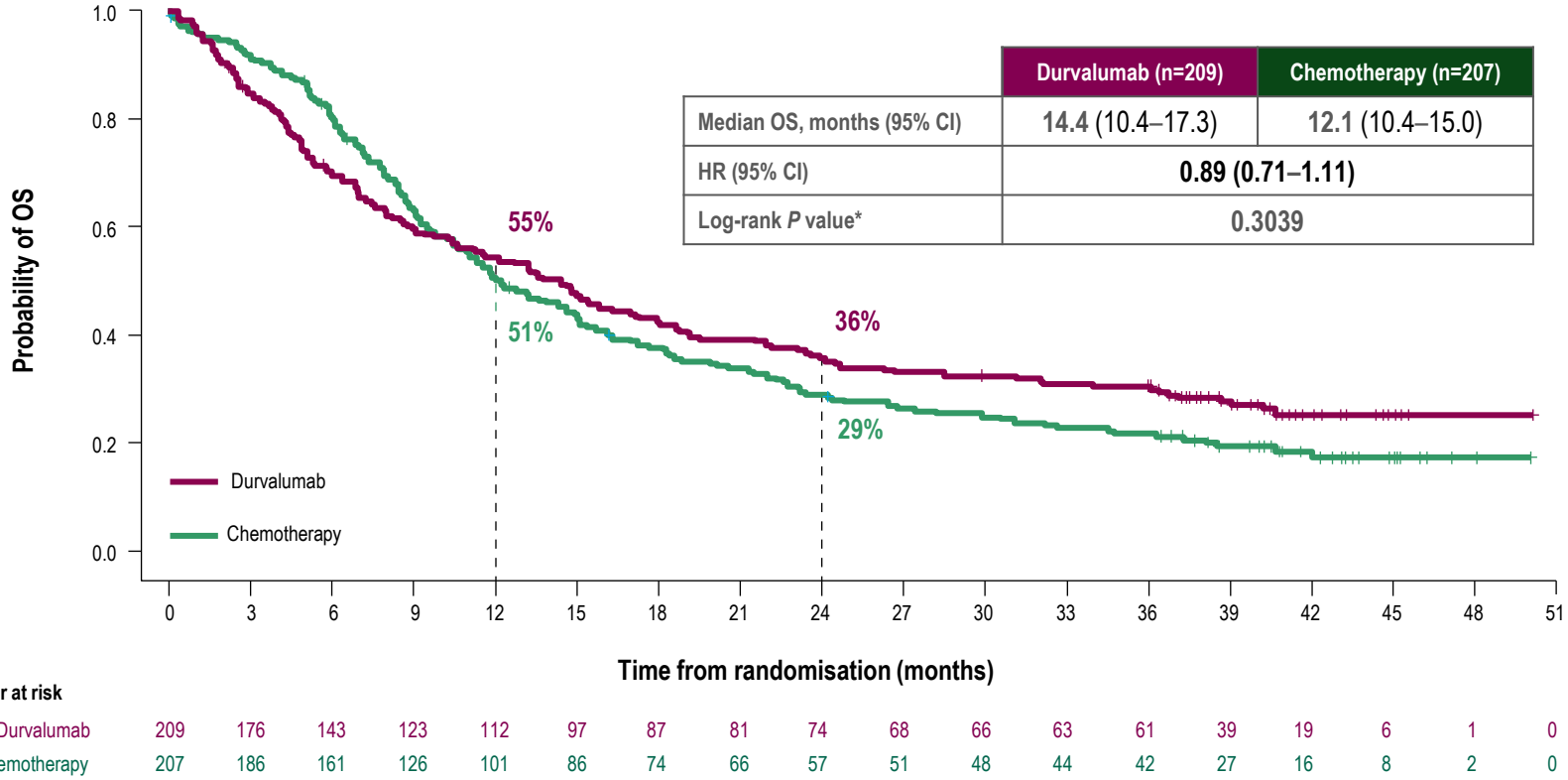
Median follow-up for survival: 41.2 months for all patients

*PD-L1 assessed using the VENTANA PD-L1 (SP263) Assay (Ventana Medical Systems, Tucson, AZ)[2]

- High PD-L1 expression:[3] either ≥25% of tumour cells (TCs) with membrane staining or ≥25% of immune cells (ICs) staining for PD-L1 at any intensity

1. Powles T, et al. Presented at ESMO 2020 697O; 2. Zajac M, et al. Arch Pathol Lab Med 2019;143:722–31; 3. Ventana Medical Systems. VENTANA PD-L1 (SP263) Assay. https://www.accessdata.fda.gov/cdrh_docs/pdf16/p160046c.pdf.

Co-primary Endpoint: OS With Durvalumab vs Chemotherapy in the PD-L1 High Population



	Durvalumab (n=209)	Chemotherapy (n=207)
Median OS, months (95% CI)	14.4 (10.4–17.3)	12.1 (10.4–15.0)
HR (95% CI)	0.89 (0.71–1.11)	
Log-rank *P* value*	0.3039	

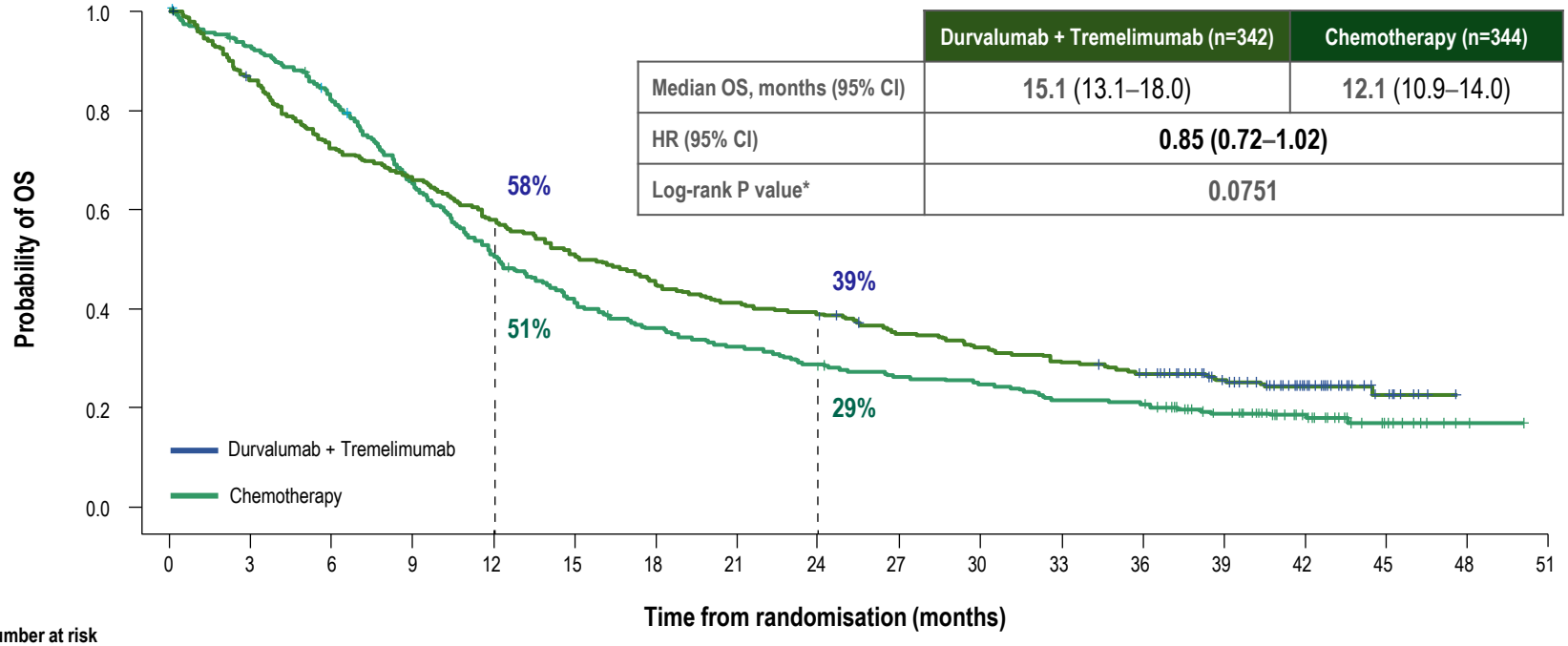
Number at risk

Durvalumab	209	176	143	123	112	97	87	81	74	68	66	63	61	39	19	6	1	0
Chemotherapy	207	186	161	126	101	86	74	66	57	51	48	44	42	27	16	8	2	0

*Considered statistically significant if p<0.0301.

Powles T, et al. Presented at ESMO 2020 697O.

Co-primary Endpoint – OS with Durvalumab + Tremelimumab vs Chemotherapy in the ITT Population



	Durvalumab + Tremelimumab (n=342)	Chemotherapy (n=344)
Median OS, months (95% CI)	15.1 (13.1–18.0)	12.1 (10.9–14.0)
HR (95% CI)	0.85 (0.72–1.02)	
Log-rank P value*	0.0751	

Number at risk

Durvalumab + Tremelimumab	342	292	246	224	197	173	153	140	133	118	108	99	89	61	33	12	0	0
Chemotherapy	344	311	273	216	168	136	119	107	95	86	81	71	68	46	27	11	2	0

*Considered statistically significant if p<0.0301.

Powles T, et al. Presented at ESMO 2020 697O.

Safety Summary

	Durvalumab n=345	Durvalumab + Tremelimumab n=340	Chemotherapy n=313
Treatment-related AEs			
Any grade	56%	75%	90%
Grade 3 or 4	14%	28%	60%
Grade 5	1%	1%	<1%
Treatment-related serious AEs	9%	23%	16%
Treatment-related AEs leading to discontinuation	6%	16%	12%
Treatment-related AEs of special interest*			
Any grade	26%	49%	15%
Grade 3 or 4	6%	12%	2%
Systemic corticosteroid use	11%	26%	1%

*Excluding infusion/hypersensitivity reactions.

Most common treatment-related AEs of Grade 3 or 4 was increased lipase (in both the durvalumab and durvalumab + tremelimumab groups) and neutropenia and anemia (in the chemotherapy group)

Powles T, et al. Presented at ESMO 2020 697O.

IMvigor130: chemo/atezo vs chemo; atezo vs chemo[1,2]

- **Locally advanced or mUC**
- **No prior systemic therapy in the metastatic setting**
- **ECOG PS ≤2**
- **1L platinum-eligible**
- **N=1213**
- **Randomised 1:1:1**

→ **Arm A**
Atezo + plt/gem

→ **Arm B**
Atezo monotherapy[a]

→ **Arm C**
Placebo + plt/gem

Stratification factors:
- PD-L1 IC status (IC0 vs IC1 vs IC2/3)
- Bajorin risk factor score including KPS < 80% vs ≥ 80% and presence of visceral metastases (0 vs 1 vs 2 ± patients with liver metastases)
- Investigator choice of plt/gem (gem + carbo or gem + cis)

Co-primary endpoints:
- INV-assessed PFS[b] and OS (Arm A vs C)
- OS (Arm B vs C, hierarchical approach)

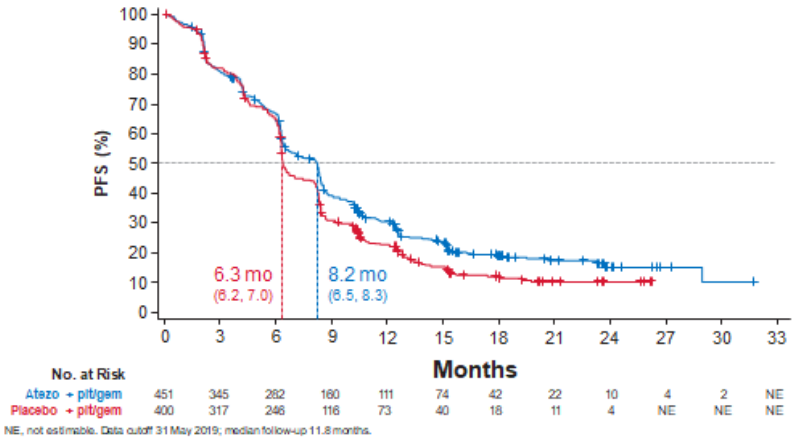
Key secondary endpoints:
- INV-ORR[b] and DOR
- PFS[b] and OS (Arm B vs C; PD-L1 IC2/3 subgroup)
- Safety

[a]The first 129 patients were randomised 2:1 to Arm A and Arm C per initial study design; Arm B enrolled later. PD-L1 status was unblinded in the final protocol amendment per IMDC recommendation, such that IC0/1 patients received atezo + plt/gem and IC2/3 patients received atezo monotherapy (n=6). [b]per RECIST 1.1.

Atezo, atezolizumab; carbo, carboplatin; cis, cisplatin; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; gem, gemcitabine; IC, immune cells; INV, investigator; KPS; Karnofsky performance status; mUC, metastatic urothelial carcinoma; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; plt, platinum; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumours. 1. Galsky MD et al. Lancet 2020;395:1547–57; 2. Grande E, et al. Presented at ESMO 2019 LBA14.

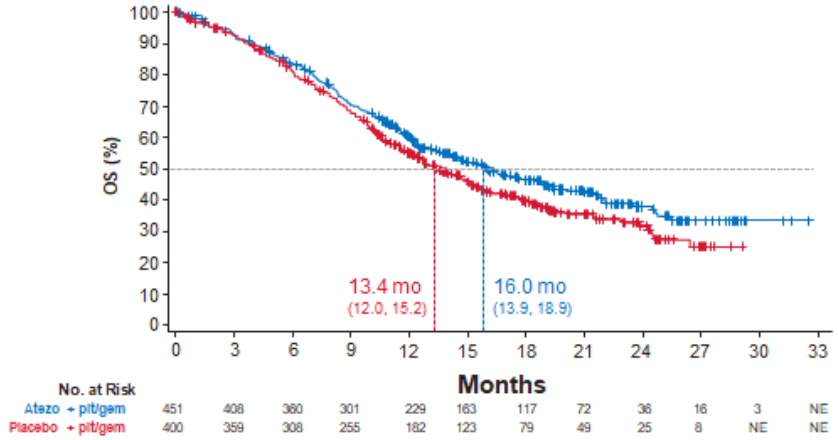
Progression free & overall survival (Arm A vs Arm C)[1,2]

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)

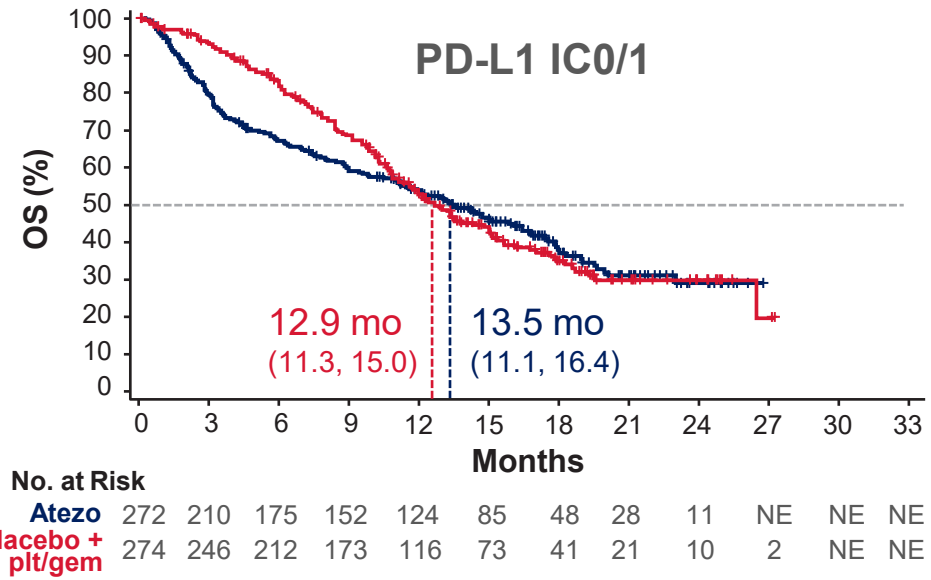


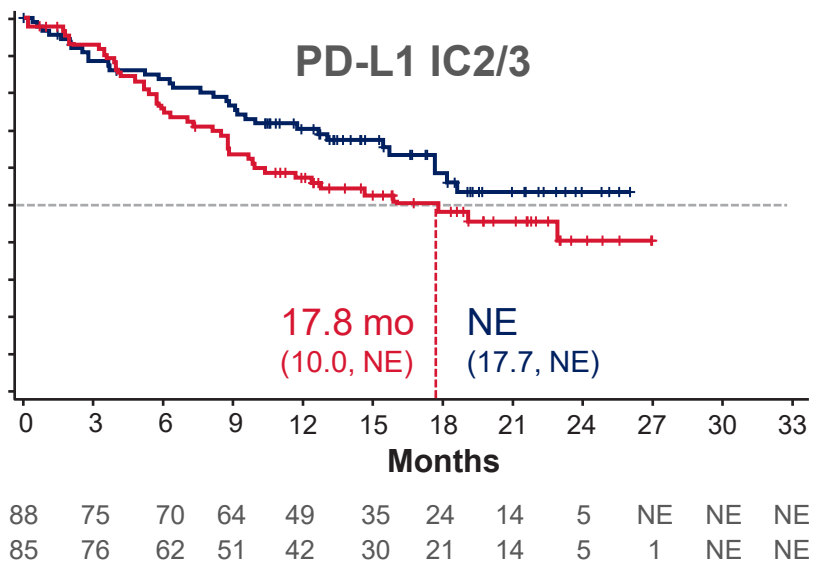
	Arm A Atezo + plt/gem (n=451)	Arm C Placebo + plt/gem (n=400)
OS events[a], n (%)	235 (52)	228 (57)
Stratified HR (95% CI)	**0.83 (0.69, 1.00)** P=0.027 (one-sided)[b]	

Did not cross the interim efficacy boundary of 0.007 per the O'Brien-Fleming alpha spending function.

Atezo, atezolizumab; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; mo, months; PFS, progression-free survival; plt/gem, platinum/gemcitabine; UC, urothelial carcinoma. 1. Galsky MD et al. Lancet 2020;395:1547–57; 2. Grande E, et al. Presented at ESMO 2019 LBA14.

IMvigor130 interim OS: PD-L1 status (Arm B vs Arm C)





No. at Risk

Atezo	272	210	175	152	124	85	48	28	11	NE	NE	NE	88	75	70	64	49	35	24	14	5	NE	NE	NE
Placebo + plt/gem	274	246	212	173	116	73	41	21	10	2	NE	NE	85	76	62	51	42	30	21	14	5	1	NE	NE

	Arm B Atezo (n=272)	Arm C Placebo + plt/gem (n=274)
OS events, n (%)	158 (58)	156 (57)
Unstratified HR (95% CI)	1.07 (0.86, 1.33)	

	Arm B Atezo (n=88)	Arm C Placebo + plt/gem (n=85)
OS events, n (%)	33 (38)	42 (49)
Stratified HR (95% CI)	0.68 (0.43, 1.08)	

Data cutoff 31 May 2019; median follow-up 11.8 months.
Atezo, atezolizumab; CI, confidence interval; HR, hazard ratio; IC, immune cells; mo, months; NE, non-estimable; OS, overall survival; PD-L1, programmed death-ligand 1; plt/gem, platinum/gemcitabine. Galsky MD et al. Lancet 2020;395:1547–57.

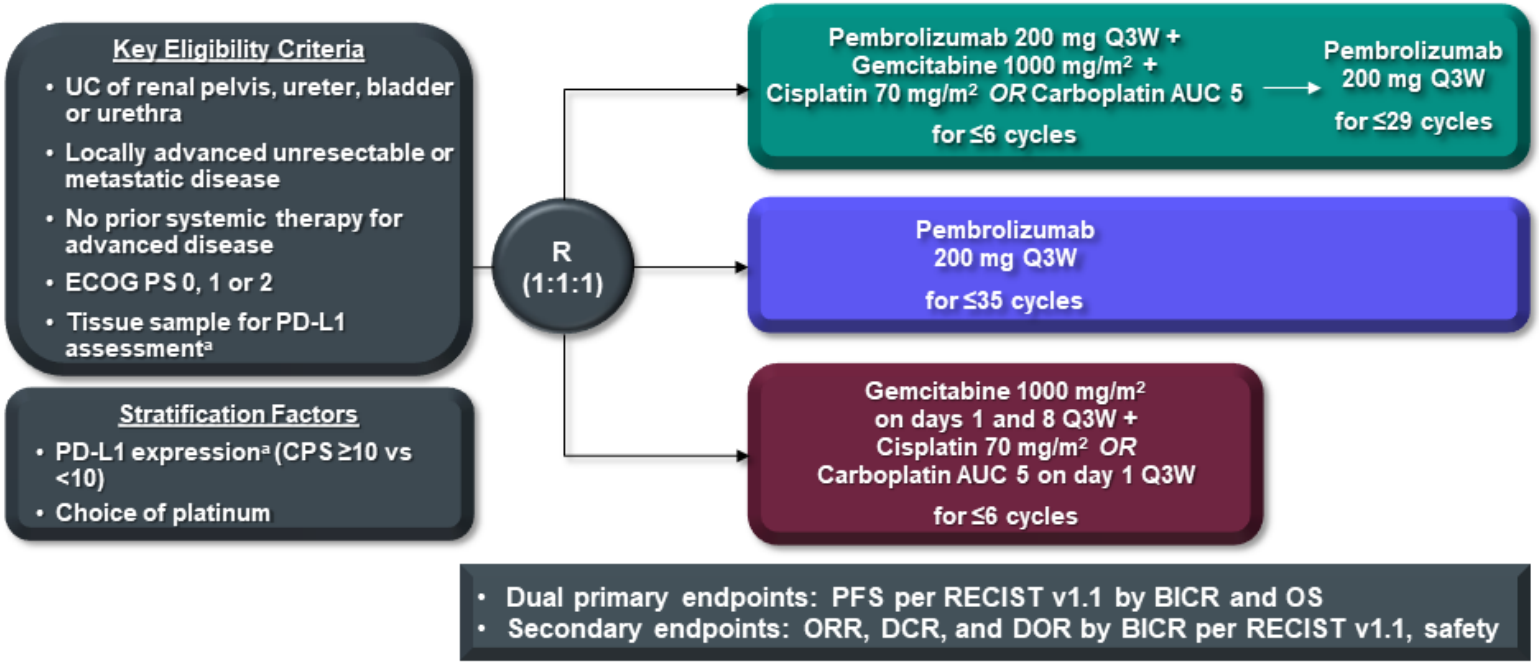
Safety summary

AE, n (%)	Atezo + plt/gem (n = 453)	Placebo + plt/gem (n = 390)	Atezo (n = 354)
Any grade, all cause	451 (100)	386 (99)	329 (93)
Grade 3-4	383 (85)	334 (86)	148 (42)
Grade 5	29 (6)	20 (5)	28 (8)
Any grade, treatment related	434 (96)	373 (96)	211 (60)
Grade 3-4	367 (81)	315 (81)	54 (15)
Grade 5	9 (2)	4 (1)	3 (1)
Any grade, serious	234 (52)	191 (49)	152 (43)
Treatment-related serious AEs	144 (32)	101 (26)	44 (12)
Any grade leading to any treatment discontinuation	156 (34)	132 (34)	22 (6)
Atezo or placebo discontinuation	50 (11)	27 (7)	21 (6)
Cisplatin discontinuation	53 (12)	52 (13)	0
Carboplatin discontinuation	90 (20)	79 (20)	1 (< 1)[a]
Gemcitabine discontinuation	117 (26)	100 (26)	1 (< 1)[a]
Any grade leading to any dose reduction or interruption	363 (80)	304 (78)	112 (32)

AE, adverse event. Safety-evaluable population.
Data cutoff, 31 May 2019; median survival follow-up 11.8 months (all patients).
[a] This patient was randomised to atezo + plt/gem and received atezo; they had an AE of pyrexia that day, and gemcitabine and carboplatin were marked as 'drug withdrawn'. Since no chemotherapy was given, this patient was included in the atezo monotherapy arm for safety analysis.

Galsky MD et al. Lancet 2020;395:1547–57.

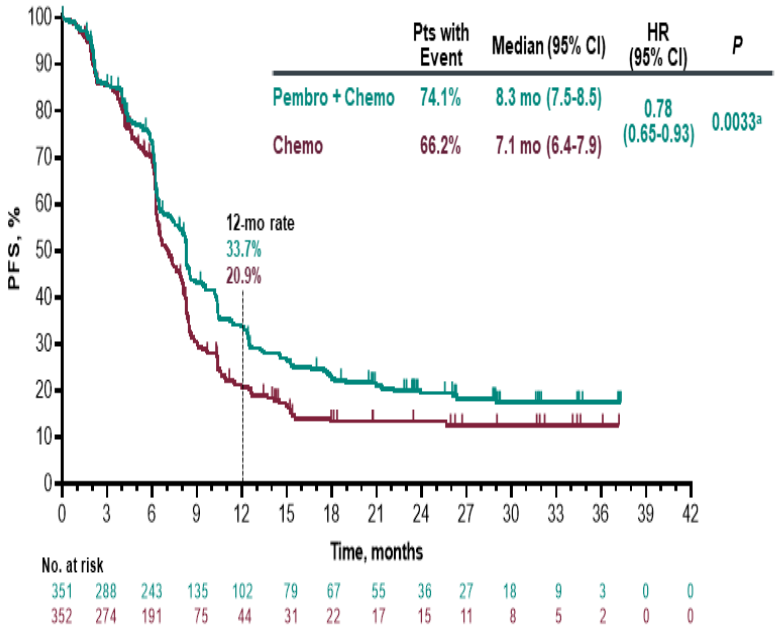
KEYNOTE-361 Study Design (NCT02853305)



[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay. CPS (combined positive score) is the number of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100.
BICR, blinded independent central review.

Alva A, et al. Presented at ESMO 2020 LBA23.

PFS by BICR: Pembro + Chemo vs Chemo, ITT Population (Primary Endpoint)

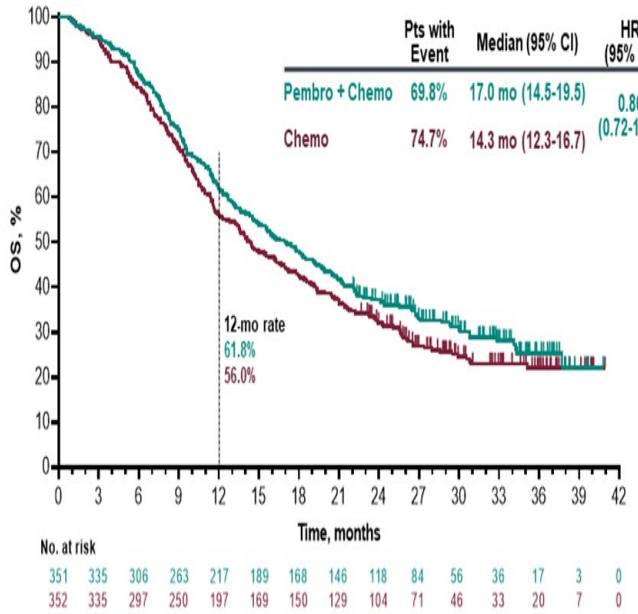


	Pts with Event	Median (95% CI)	HR (95% CI)	P
Pembro + Chemo	74.1%	8.3 mo (7.5-8.5)	0.78 (0.65-0.93)	0.0033[a]
Chemo	66.2%	7.1 mo (6.4-7.9)		

[a]*P*-value boundary of significance at final analysis ≤0.0019.
PFS assessed per RECIST v1.1. Data cutoff date: April 29, 2020.

Alva KN361 ESMO 2020

OS: Pembro + Chemo vs Chemo, ITT Population



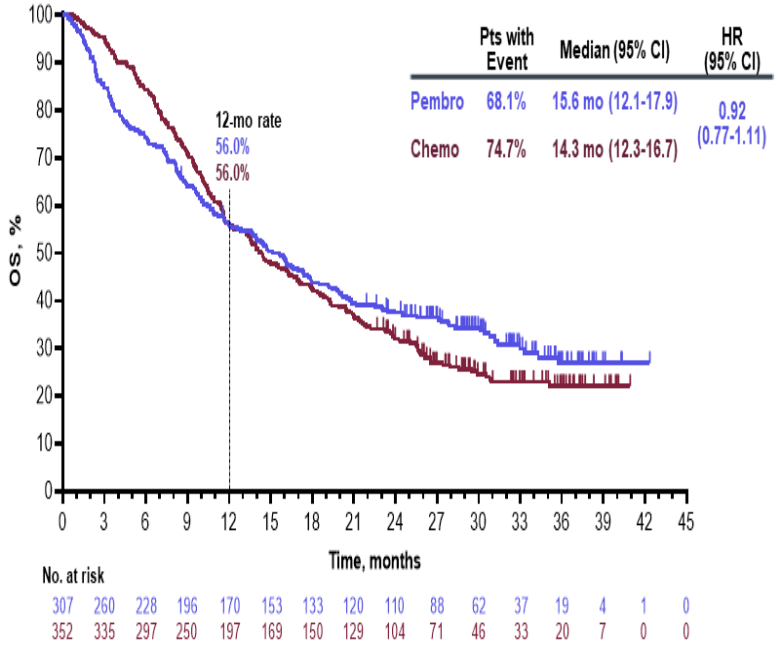
	Pts with Event	Median (95% CI)	HR (95% CI)	P
Pembro + Chemo	69.8%	17.0 mo (14.5-19.5)	0.86 (0.72-1.02)	0.0407[a]
Chemo	74.7%	14.3 mo (12.3-16.7)		

[a]*P*-value boundary of significance at final analysis ≤0.0142. Per the statistical analysis plan, no further formal statistical testing was performed.
Data cutoff date: April 29, 2020.

Alva A, et al. Presented at ESMO 2020 LBA23.

Alva KN361 ESMO 2020

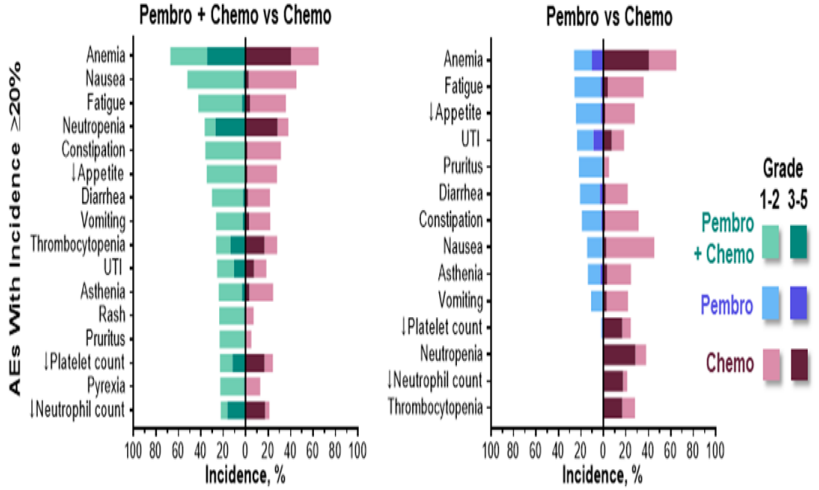
OS: Pembro vs Chemo, ITT Population



	Pts with Event	Median (95% CI)	HR (95% CI)
Pembro	68.1%	15.6 mo (12.1-17.9)	0.92 (0.77-1.11)
Chemo	74.7%	14.3 mo (12.3-16.7)	

Data cutoff date: April 29, 2020.

All-Cause AEs, As-Treated Population



All AEs	Pembro + Chemo	Chemo
Any grade	99.7%	99.7%
Grade 3-5	87.4%	81.9%
Led to death	9.2%	2.6%
Led to discontinuation	30.9%	18.1%

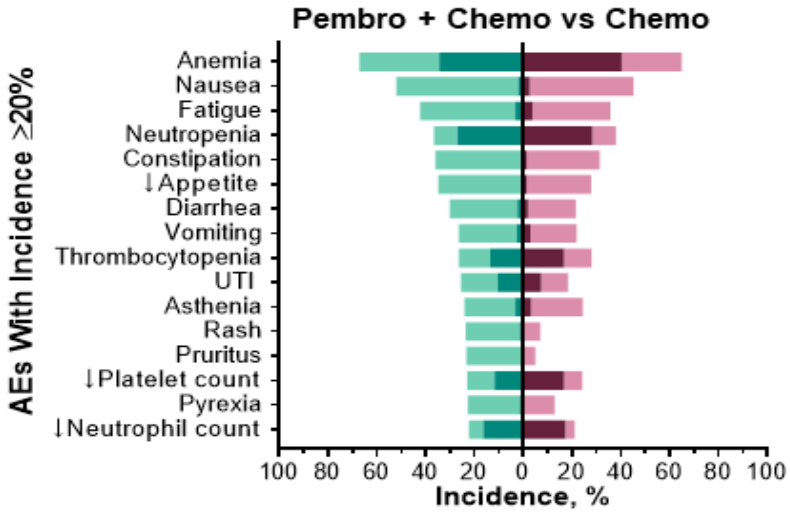
All AEs	Pembro	Chemo
Any grade	95.7%	99.7%
Grade 3-5	62.9%	81.9%
Led to death	8.6%	2.6%
Led to discontinuation	15.9%	18.1%

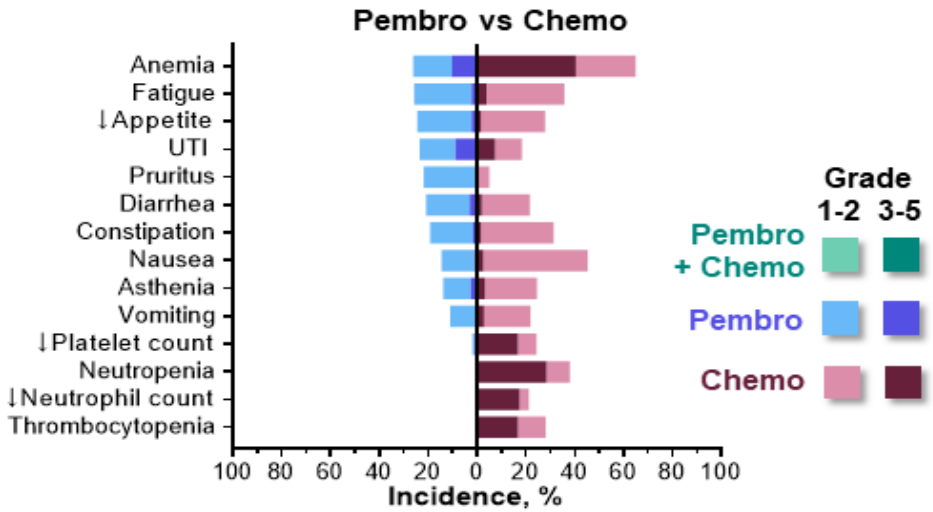
Median (range) duration of treatment was 7.7 (0-27.8) months for pembro + chemo, 4.2 (0-28.1) months for pembro, and 3.7 (0-7.2) months for chemo. As-treated population includes all patients who received ≥1 dose of trial treatment. Data cutoff date: April 29, 2020.

Alva A, et al. Presented at ESMO 2020 LBA23.

Alva KN361 ESMO 2020

All-Cause AEs, As-Treated Population





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ORIGINAL ARTICLE

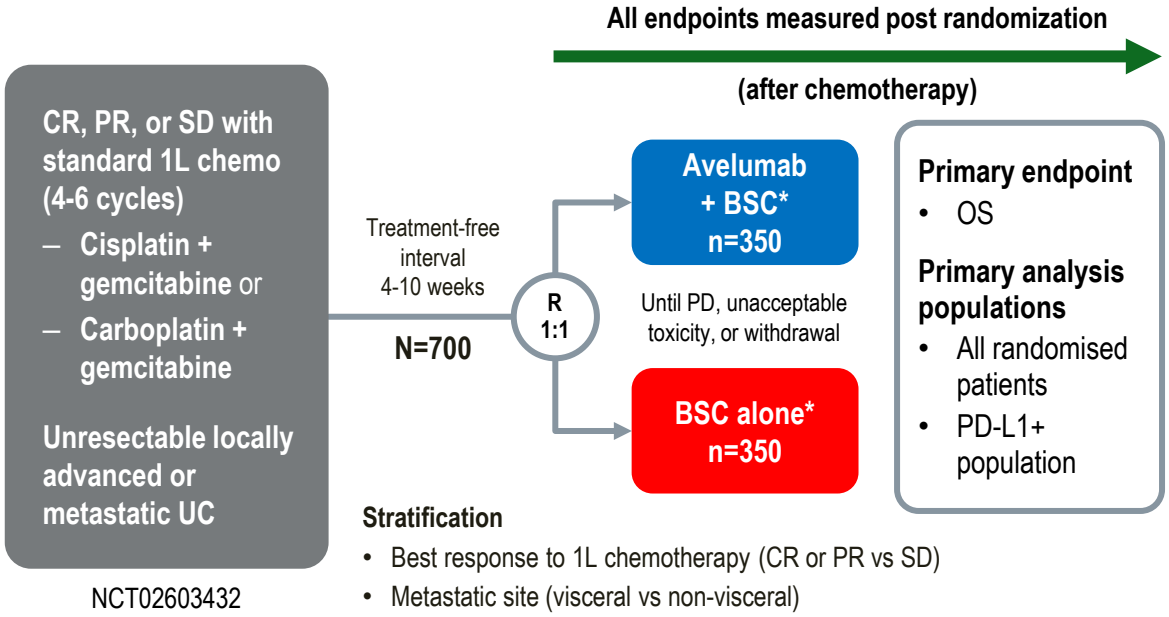
Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma

Thomas Powles, M.D., Se Hoon Park, M.D., Ph.D., Eric Voog, M.D., Claudia Caserta, M.D., Begoña P. Valderrama, M.D., Howard Gurney, M.D., Haralabos Kalofonos, M.D., Ph.D., Siniša Radulović, M.D., Ph.D., Wim Demey, M.D., Anders Ullén, M.D., Ph.D., Yohann Loriot, M.D., Ph.D., Srikala S. Sridhar, M.D., et al.

Thomas Powles,[1] Se Hoon Park,[2] Eric Voog,[3] Claudia Caserta,[4] Begoña P. Valderrama,[5] Howard Gurney,[6] Haralabos Kalofonos,[7] Sinisa Radulovic,[8] Wim Demey,[9] Anders Ullén,[10] Yohann Loriot,[11] Srikala S. Sridhar,[12] Norihiko Tsuchiya,[13] Evgeny Kopyltsov,[14] Cora N. Sternberg,[15] Joaquim Bellmunt,[16] Jeanny B Aragon-Ching,[17] Daniel P. Petrylak,[18] Alessandra di Pietro,[19] Petros Grivas[20]

[1]Barts Cancer Institute, Experimental Cancer Medicine Centre, Queen Mary University of London, St Bartholomew's Hospital, London, UK; [2]Sungkyunkwan University Samsung Medical Center, Seoul, Korea; [3]Centre Jean Bernard Clinique Victor Hugo, Le Mans, France; [4]Medical Oncology Unit, Azienda Ospedaliera S. Maria, Terni, Italy; [5]Department of Medical Oncology, Hospital Universitario Virgen del Rocío, Sevilla, Spain; [6]Department of Clinical Medicine, Macquarie University, Sydney, New South Wales, Australia; [7]Medical Oncology, University General Hospital of Patras, Patras, Greece; [8]Institute for Oncology and Radiology of Serbia, Belgrade, Serbia; [9]Department of Medical Oncology, AZ KLINA, Brasschaat, Belgium; [10]Patient Area Pelvic Cancer, Theme Cancer, Karolinska University Hospital and Department of Oncology-Pathology, Karolinska Institute, Solna, Sweden; [11]Gustave Roussy, INSERMU981, Université Paris-Saclay Villejuif, France; [12]Princess Margaret Cancer Center, University Health Network, Toronto, Ontario, Canada; [13]Department of Urology, Yamagata University Faculty of Medicine, Yamagata, Japan; [14]State Institution of Healthcare Regional Clinical Oncology Dispensary, Omsk, Russia; [15]Weill Cornell Medicine, Hematology/Oncology, New York, New York, USA; [16]Department of Medical Oncology, Beth Israel Deaconess Medical Center; Harvard Medical School, Boston, Massachusetts, USA; [17]Inova Schar Cancer Institute, Fairfax, Virginia, USA; [18]Yale Cancer Center, New Haven, Connecticut, USA; [19]Pfizer srl, Milano, Italy; [20]Department of Medicine, Division of Oncology, University of Washington, Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA

Avelumab 1L maintenance + BSC significantly prolonged OS vs BSC alone in the JAVELIN Bladder 100 phase 3 trial[1]

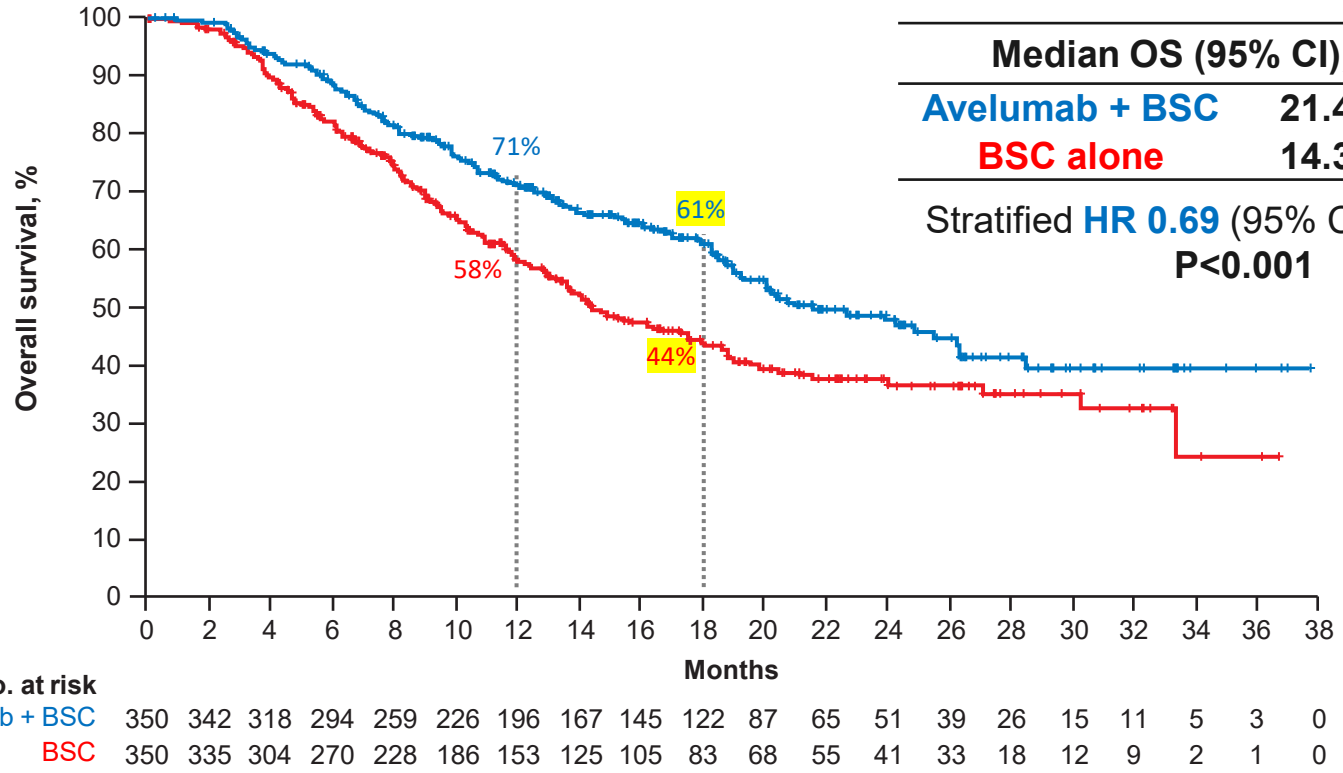


- Median OS in all randomised patients[1]
  - **Avelumab 1L maintenance + BSC**: **21.4 months** (95% CI, 18.9, 26.1)
  - **BSC alone**: **14.3 months** (95% CI, 12.9, 17.9)
  - **HR 0.69** (95% CI, 0.56, 0.86); P<0.001
- The safety profile of avelumab 1L maintenance was manageable and consistent with previous studies of avelumab monotherapy[1,2]

OS benefit with avelumab + BSC vs BSC alone were analysed in patient subgroups

1L, first line; BSC, best supportive care; CR, complete response; HR, hazard ratio; OS, overall survival; PR, partial response; R, randomisation; SD, stable disease; UC, urothelial carcinoma ·BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other systemic antitumour therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable. 1. Powles T, et al. New Engl J Med 2020.

JAVELIN Bladder 100: OS in the overall population



Median OS (95% CI), months	
Avelumab + BSC	**21.4** (18.9, 26.1)
BSC alone	**14.3** (12.9, 17.9)

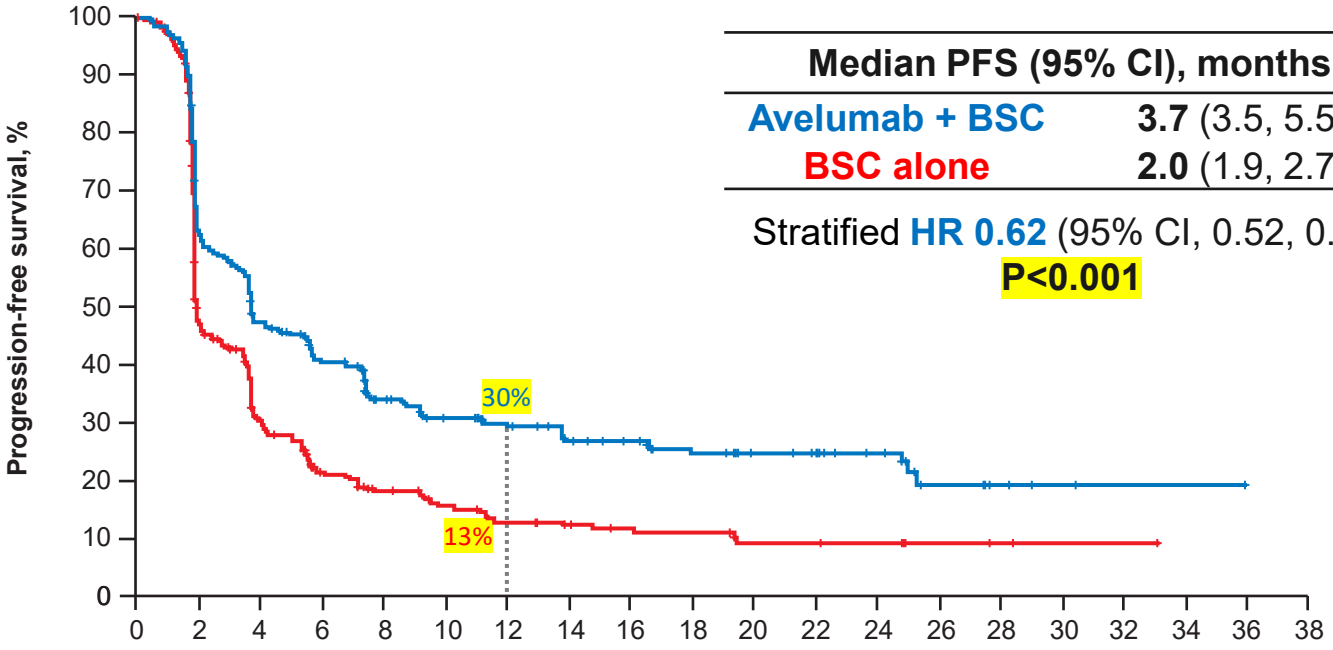
Stratified **HR 0.69** (95% CI, 0.56, 0.86)
P<0.001

No. at risk																				
Avelumab + BSC	350	342	318	294	259	226	196	167	145	122	87	65	51	39	26	15	11	5	3	0
BSC	350	335	304	270	228	186	153	125	105	83	68	55	41	33	18	12	9	2	1	0

OS was measured post randomisation (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0053)

BSC, best supportive care; CI, confidence interval; HR, hazard ratio; OS, overall survival.
Powles T, et al. New Engl J Med 2020.

JAVELIN Bladder 100:
PFS by independent radiology review in the overall population



Median PFS (95% CI), months	
Avelumab + BSC	**3.7** (3.5, 5.5)
BSC alone	**2.0** (1.9, 2.7)

Stratified **HR 0.62** (95% CI, 0.52, 0.75)

P<0.001

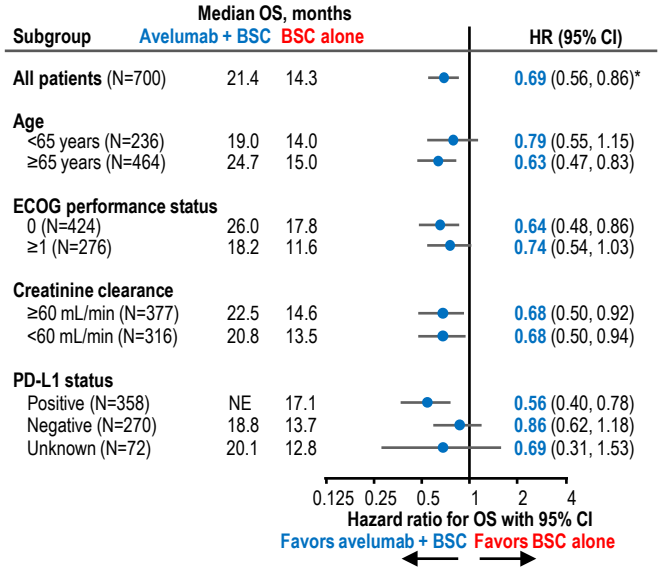
No. at risk																			
Avelumab + BSC	350	198	145	118	90	72	59	49	45	34	27	25	17	9	4	2	1	1	0
BSC	350	144	87	52	39	31	24	20	17	16	10	10	7	3	2	1	1	0	

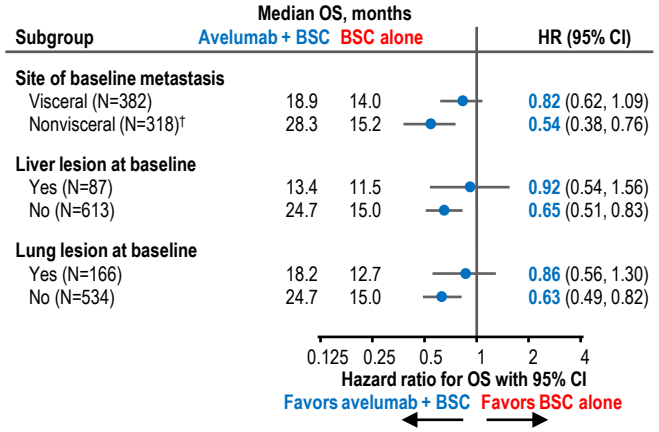
PFS was measured post randomisation (from end of chemotherapy)

BSC, best supportive care; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Powles T, et al. New Engl J Med 2020.

OS benefit with avelumab 1L maintenance was observed across additional prespecified subgroups





No significant treatment-by-subgroup interaction (at 0.05 level) was observed for any subgroup variable

OS was measured post randomization (after chemotherapy)
* Stratified (all other analyses are unstratified)
† Nonvisceral includes patients with locally advanced disease or only nonvisceral disease, including bone metastasis

Treatment-emergent AEs (any causality)

	Avelumab + BSC (N=344)		BSC alone (N=345)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TEAE, %	**98.0**	**47.4**	**77.7**	**25.2**
Fatigue	17.7	1.7	7.0	0.6
Pruritus	17.2	0.3	1.7	0
UTI	17.2	4.4	10.4	2.6
Diarrhea	16.6	0.6	4.9	0.3
Arthralgia	16.3	0.6	5.5	0
Asthenia	16.3	0	5.5	1.2
Constipation	16.3	0.6	9.0	0
Back pain	16.0	1.2	9.9	2.3
Nausea	15.7	0.3	6.4	0.6
Pyrexia	14.8	0.3	3.5	0
Decreased appetite	13.7	0.3	6.7	0.6
Cough	12.8	0.3	4.6	0
Vomiting	12.5	1.2	3.5	0.6
Hypothyroidism	11.6	0.3	0.6	0
Rash	11.6	0.3	1.2	0
Anemia	11.3	3.8	6.7	2.9
Hematuria	10.5	1.7	10.7	1.4
IRR	10.2	0.9	0	0

- TEAEs led to discontinuation of avelumab in 11.9%
- Death was attributed by the investigator to study treatment toxicity in 2 patients (0.6%) in the avelumab + BSC arm
  - Due to sepsis (in Cycle 10) and ischemic stroke (100 days after a single dose of avelumab)

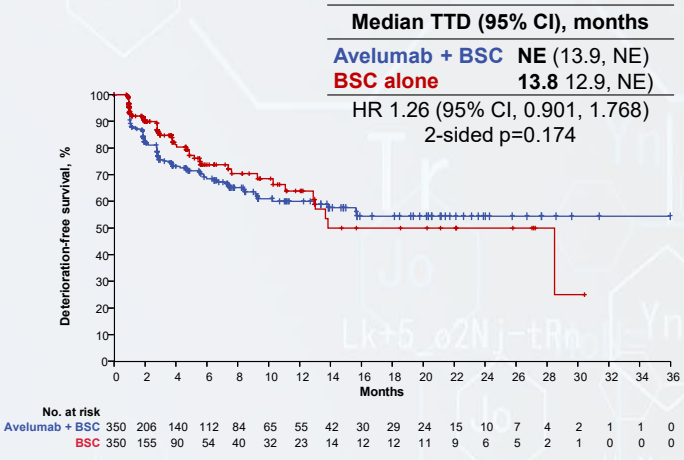
Table shows TEAEs of any grade occurring in ≥10% or grade ≥3 TEAEs occurring in ≥5% in either arm

AE, adverse event; **IRR**, infusion-related reaction; **TEAE**, treatment-emergent adverse event; **UTI,** urinary tract infection
Safety was assessed in all patients who received ≥1 dose of avelumab in the avelumab arm, or who completed the cycle 1 day 1 visit in the BSC arm (N=689)

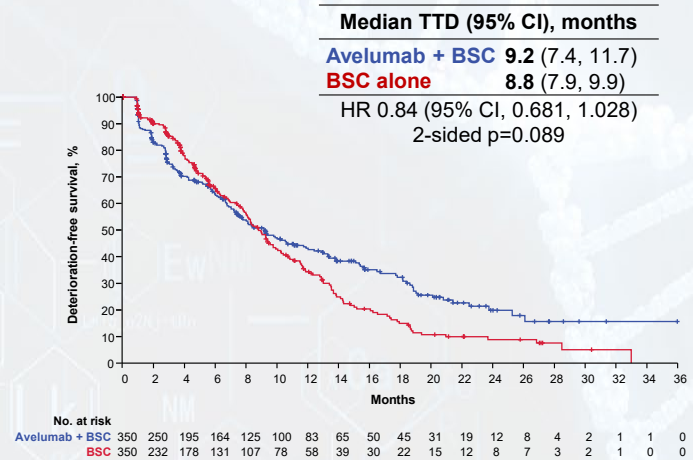
Presented By Thomas Powles at TBD

TTD in FBISI-18 DRS-P scores (A) and TTD in FBISI-18 DRS-P scores or death (B) in the overall population

A



B



•**NE**, not estimable

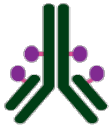
•Crossing of curves, inconsistency between HRs, and differences in median TTD suggest that HRs may be nonproportional; therefore results should be interpreted with caution

	Atezolizumab[1]	Nivolumab[2]	Pembrolizumab[3]	Avelumab[4]	Durvalumab[5]
Phase	Phase III Randomized vs chemotherapy	Phase II Single Arm	Phase III Randomized vs Chemotherpay	Phase Ib	Phase I/II
Number of Patients	931	265	542	249 (161 pts ≥ 6 mos f/u)	191
Dosing	1200mg every 3 weeks	3mg/kg every 2 weeks	200mg every 3 weeks	10mg/kg every 2 weeks	10mg/kg every 2 weeks
ORR	13.4%	19.6%	21.1%	17%	17.8%
Duration of Response	63% of responses ongoing at median f/u of 21.7 mos	77% of responses ongoing at median f/u of 7 mos	72% of responses ongoing at median f/u of 14.1 mos	96% of responses ongoing at 6 mos f/u	50% of responses lasting ≥ 6 mos
Median OS	8.6 mos	8.7 mos	10.3 mos	6.5 mos	18.2 mos
Median PFS	2.1 mos	2.0 mos	2.1 mos	1.5 mos	1.5 mos
Rate of Grade 3/4 Treatment-related AEs	20%	18%	15%	8%	6.8%

1Powles T, et al. Lancet. 2018;391(10122):748-757.; 2Sharma P, et al. Lancet Oncol. 2017;18(3):312-322.; 3Bellmunt J, et al. N Engl J Med. 2017;376(11):1015-1026.; 4Patel MR, et al. Lancet Oncol. 2018;19(1):51-64.; 5Powles T, et al. JAMA Oncol. 2017;3(9):e172411

Antibody–Drug Conjugates in Bladder Cancer

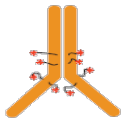
Enfortumab vedotin[1]



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

FDA approved: For treatment of patients with locally advanced or metastatic urothelial cancer who had prior treatment with PD-(L)1 inhibitor and platinum-containing chemotherapy regimen

Sacituzumab govitecan (IMMU-132)[2]

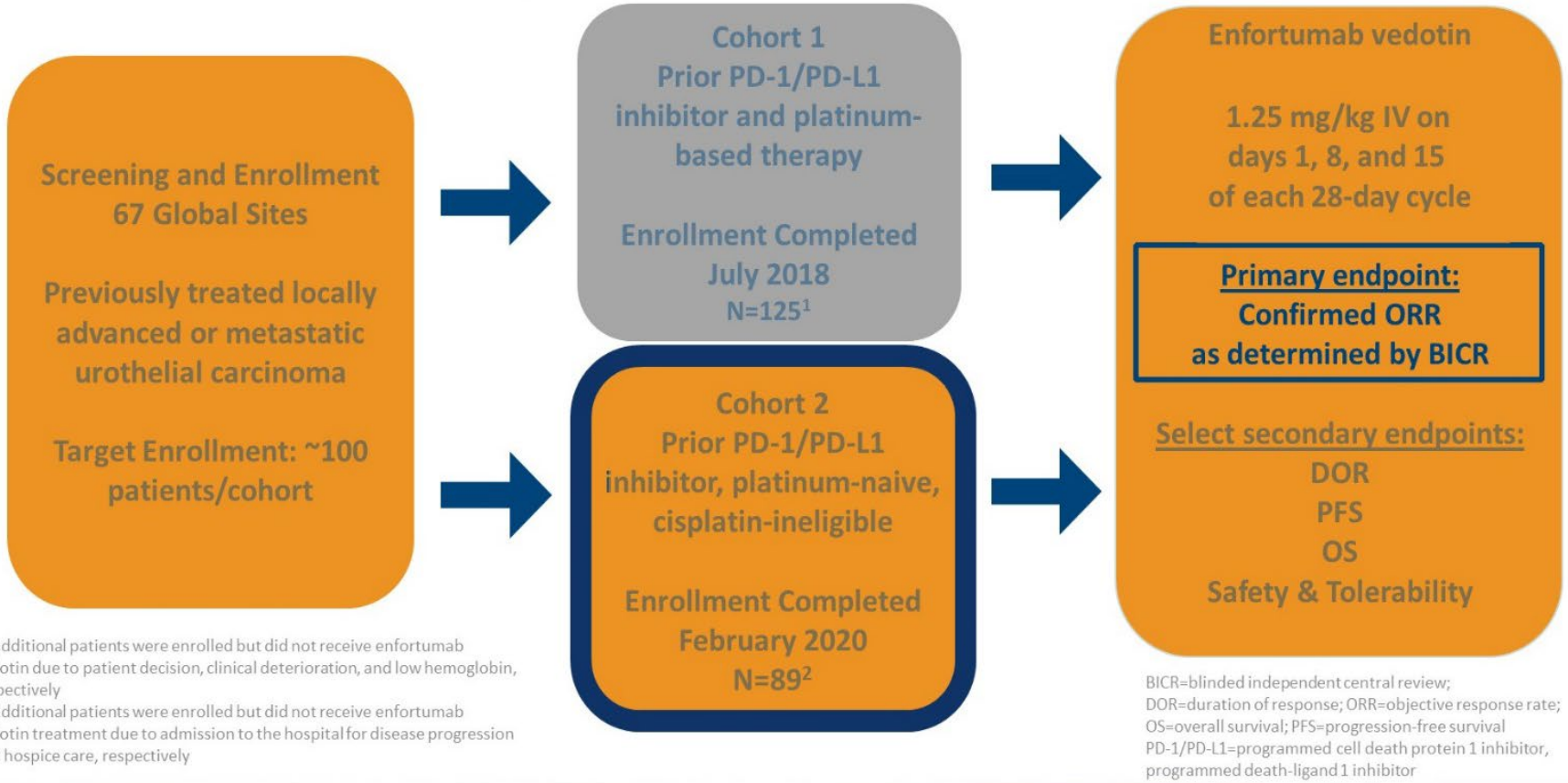


Target: Trop-2, an epithelial cell-surface glycoprotein highly expressed in muscle-invasive disease
Linker: Hydrolysable
Payload: SN-38, the active metabolite of irinotecan

FDA Fast-Track Designation: For treatment of patients with locally advanced or metastatic urothelial cancer who had prior treatment with PD-(L)1 inhibitor and platinum-containing chemotherapy regimen

1. Rosenberg JE et al. ASCO 2018. Abstract 4504. 2. Avellini C et al. *Oncotarget.* 2017;8:58642-58653.

EV-201: Non-Comparative, Pivotal Phase 2 Trial



[1]3 additional patients were enrolled but did not receive enfortumab vedotin due to patient decision, clinical deterioration, and low hemoglobin, respectively

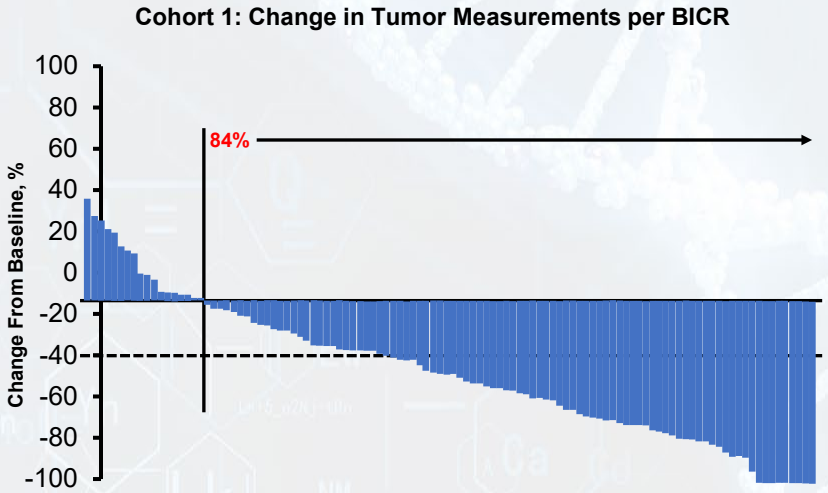
[2]2 additional patients were enrolled but did not receive enfortumab vedotin treatment due to admission to the hospital for disease progression and hospice care, respectively

BICR=blinded independent central review; DOR=duration of response; ORR=objective response rate; OS=overall survival; PFS=progression-free survival PD-1/PD-L1=programmed cell death protein 1 inhibitor, programmed death-ligand 1 inhibitor

Balar AV, et al. Virtual oral presentation at ASCO GU 2021; abstract 394

EV-201: Evidence Supporting Enfortumab Vedotin in Previously Treated mUC[1]

ORR per RECIST v1.1 Assessed by BICR	Patients (N = 125) n (%)
Confirmed ORR (95% CI)[1]	55 (44) (35.1-53.2)
Best overall response per RECIST v1.1, n (%)	
Complete response	15 (12)
Partial response	40 (32)
Stable disease	35 (28)
Progressive disease	23 (18)
Not evaluable	12 (10)



- N = 110 pts with target lesions and adequate post-baseline assessment
- 10 pts had no post-baseline assessment
- 4 pts had no target lesions identified at baseline
- 1 pt had uninterpretable post-baseline assessment

1. Rosenberg JE et al. *J Clin Oncol*. 2019;37:2592-2600

EV-201: Primary endpoint ORR positive with majority of patients experiencing tumour reduction

EV-201 cohort 2: Confirmed best overall response per BICR

ORR per RECIST v 1.1 assessed by BICR	Patients (N=89) %
Confirmed ORR, 95% CI[1]	52 (40.8, 62.4)
Best overall response[2]	
Complete response	20
Partial response	31
Stable disease	30
Progressive disease	9
Not evaluable[3]	9

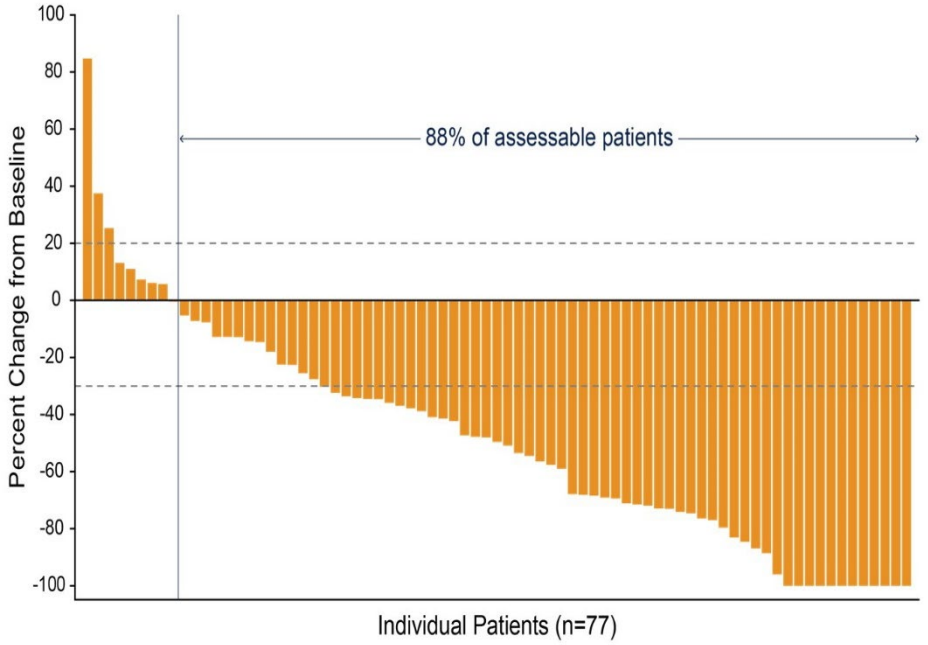
ORR = Objective Response Rate; RECIST = Response Evaluation Criteria in Solid Tumors; BICR = Blinded Independent Central Review

[1]CI = Confidence Interval, Computed using the Clopper-Pearson method

[2]Best overall response according to RECIST v1.1. CR and PR were confirmed with repeat scans ≥28 days after initial response.

[3]Includes five subjects who did not have response assessment post-baseline, two subjects whose post-baseline assessment did not meet the minimum interval requirement for stable disease, and one subject whose response cannot be assessed due to incomplete anatomy.

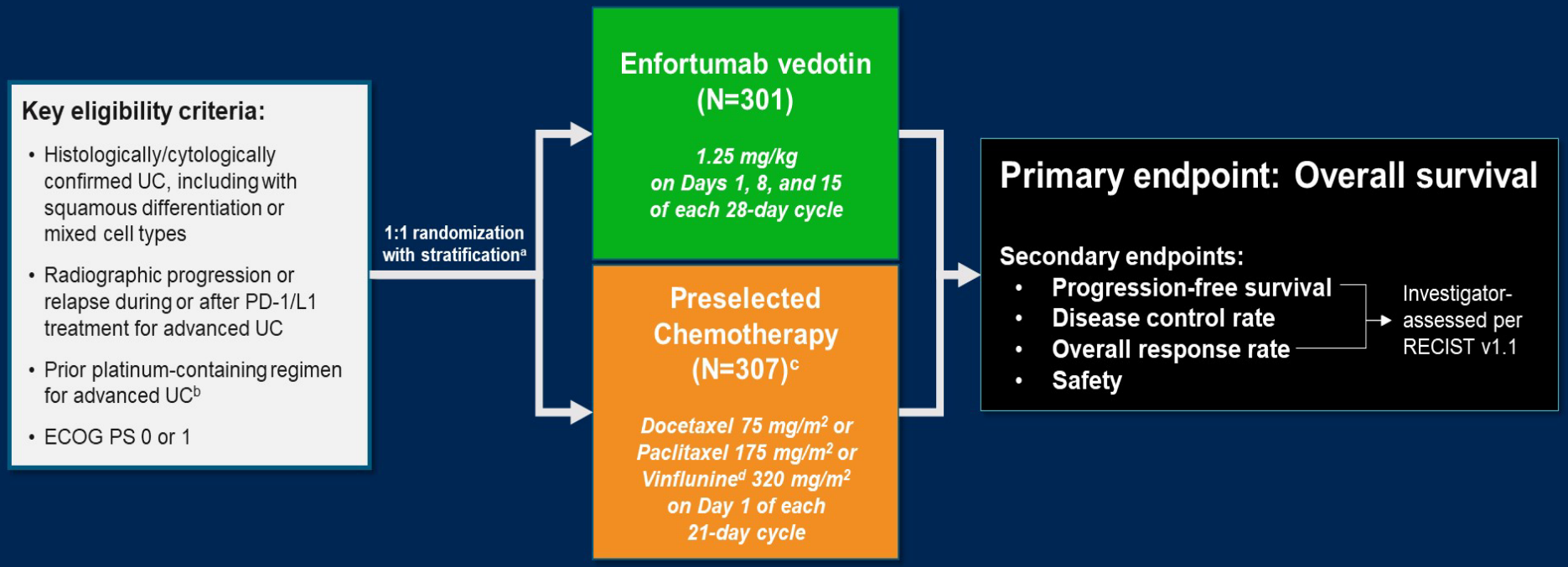
EV-201 cohort 2: Change in tumour measurements per BICR



Data are not available for 12 subjects due to no response assessment post-baseline (n=5), incomplete assessment of target lesions post-baseline (n=1), or no measurable disease at baseline per BICR (n=6).

Balar AV, et al. Virtual oral presentation at ASCO GU 2021; abstract 394

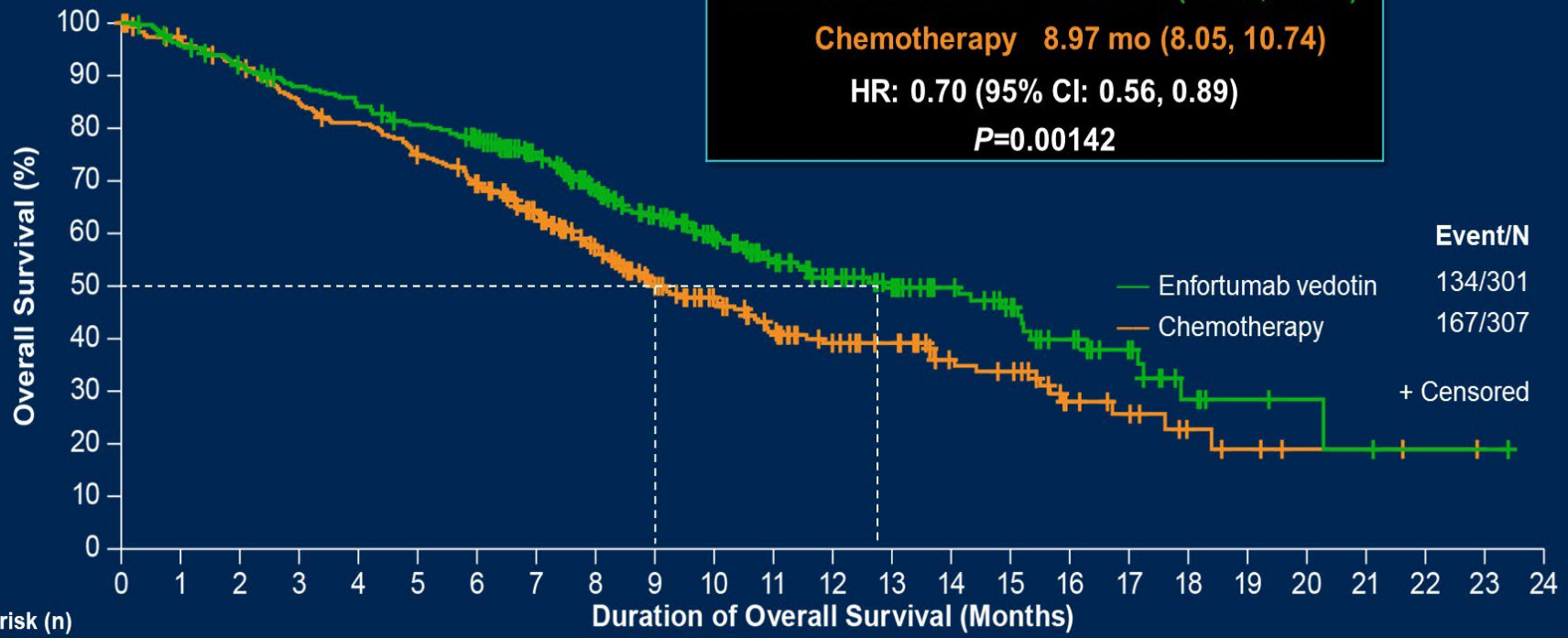
EV-301 Open-Label Phase 3 Trial Design



[a]Stratification variables were ECOG performance status (0 or 1), regions of the world (United States, western Europe, or rest of world), liver metastasis (yes or no).
[b]If used in the adjuvant/neoadjuvant setting, progression must be within 12 months of completion.
[c]Investigator selected prior to randomization.
[d]In countries where approved; overall proportion of patients receiving vinflunine capped at 35%.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PD-1/L1, programmed cell death protein-1/programmed death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; UC, advanced urothelial carcinoma.

Powles T, et al. Virtual oral presentation at ASCO GU 2021; abstract 393.

Overall Survival



Patients at risk (n)

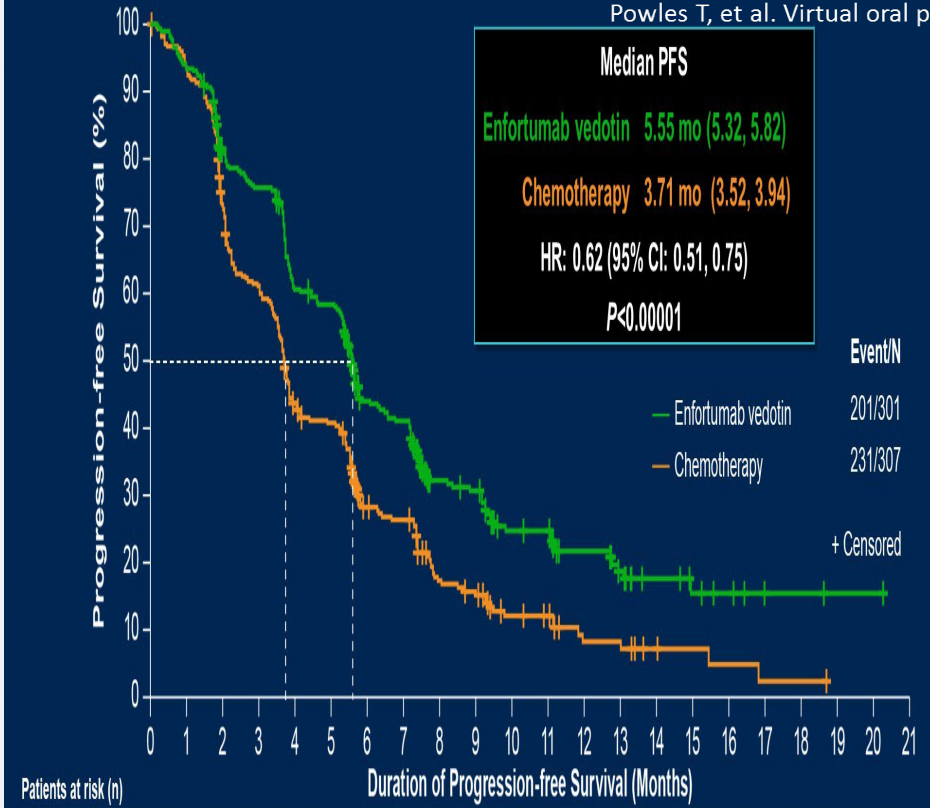
Enfortumab vedotin	301	286	272	257	246	234	222	190	158	130	105	85	63	52	42	33	23	15	7	4	3	2	1	1	0
Chemotherapy	307	288	274	250	238	219	198	163	131	101	84	66	51	44	32	29	16	11	6	4	2	2	1	0	0

Evaluated in the intent-to-treat population.
Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.

Data cut-off: July 15, 2020

Progression-free Survival

Powles T, et al. Virtual oral presentation at ASCO GU 2021; abstract 393

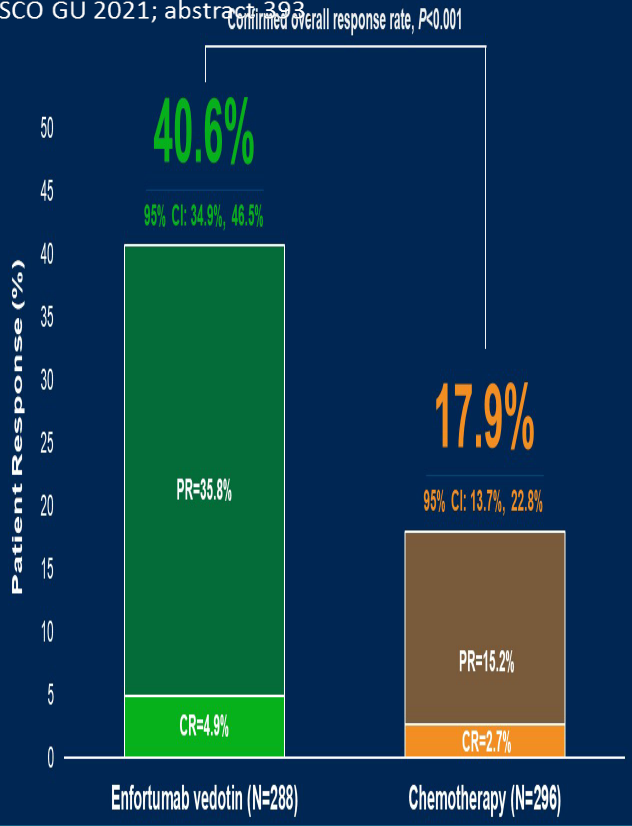


Patients at risk (n)																				
Enfortumab vedotin	301	269	224	208	165	158	102	95	60	56	38	36	23	17	11	7	5	2	2	1	1	0
Chemotherapy	307	259	200	166	116	107	62	57	33	29	18	16	8	8	4	3	2	1	0	0	0	0

Evaluated in the intent-to-treat population.
Abbreviations: CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival.

Data cut-off: July 15, 2020

Investigator-Assessed Overall Response



	Enfortumab vedotin (N=288)	Chemotherapy (N=296)	
Disease control rate,[a] % (95% CI)	71.9 (66.3, 77.0)	53.4 (47.5, 59.2)	P<0.001

Evaluated in the response-evaluable population. Response is as assessed by the investigator per RECIST v1.1.
[a]Indicates the proportion of patients who had a best overall response of confirmed CR, PR, or SD (at least 7 weeks); enfortumab vedotin vs chemotherapy.
Abbreviations: CI, confidence interval; CR, complete response; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Data cut-off: July 15, 2020

EV-201 cohort 2

	Patients (N=89) n (%)	
	Any Grade	≥Grade 3
Overall TRAEs	86 (97)	49 (55)
TRAEs[1] by preferred term in ≥20% of patients (any Grade) or ≥5% (≥Grade 3)	Any Grade	≥Grade 3
Alopecia	45 (51)	–
Peripheral sensory neuropathy	42 (47)	3 (3)
Fatigue	30 (34)	6 (7)
Decreased appetite	29 (33)	5 (6)
Pruritus	27 (30)	3 (3)
Rash maculo-papular	27 (30)	7 (8)
Dysgeusia	24 (27)	–
Weight decreased	23 (26)	1 (1)
Anemia	22 (25)	5 (6)
Diarrhea	20 (22)	5 (6)
Nausea	20 (22)	1 (1)
Neutropenia	11 (12)	8 (9)
Hyperglycemia	8 (9)	5 (6)
Lipase increased	7 (8)	5 (6)

- TRAEs led to discontinuations in 16% of patients
  - Peripheral sensory neuropathy was the most common reason (4%)

TRAEs leading to death:

4 deaths considered to be treatment related by the investigator:
- acute kidney injury
- metabolic acidosis
- multiple organ dysfunction syndrome
- pneumonitis (occurred >30 days of last dose)

3 of these deaths occurred within 30 days of first dose of EV occurred in patients with BMI ≥30 kg/m^2

All 4 deaths: confounded by age (≥75 years) and other comorbidities

[1]Treatment-related Adverse Events

Balar AV, et al. Virtual oral presentation at ASCO GU 2021; abstract 394.
Powles T, et al. Virtual oral presentation at ASCO GU 2021; abstract 393.

EV-301

Adverse Events of Special Interest

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.

Evaluated in the safety population; displaying selected TRAEs of special interest to EV. Differences between AE rates in current and prior slide may be due to preferred term groupings.
TRAE are events with a reasonable possibility of relationship to study treatment as assessed by the investigator or missing relationship.
[a]Encompasses rash and severe cutaneous adverse reactions.
[b]Severe cutaneous adverse reactions included the following (by Preferred Term): stomatitis, drug eruption, conjunctivitis, blister, dermatitis bullous, skin exfoliation, erythema multiforme, exfoliative rash, fixed eruption, mouth ulceration, pemphigus, and toxic skin eruption.
[c]One patient had the TRAE that is listed.
Abbreviations: EV, enfortumab vedotin; TRAE, treatment-related adverse event.

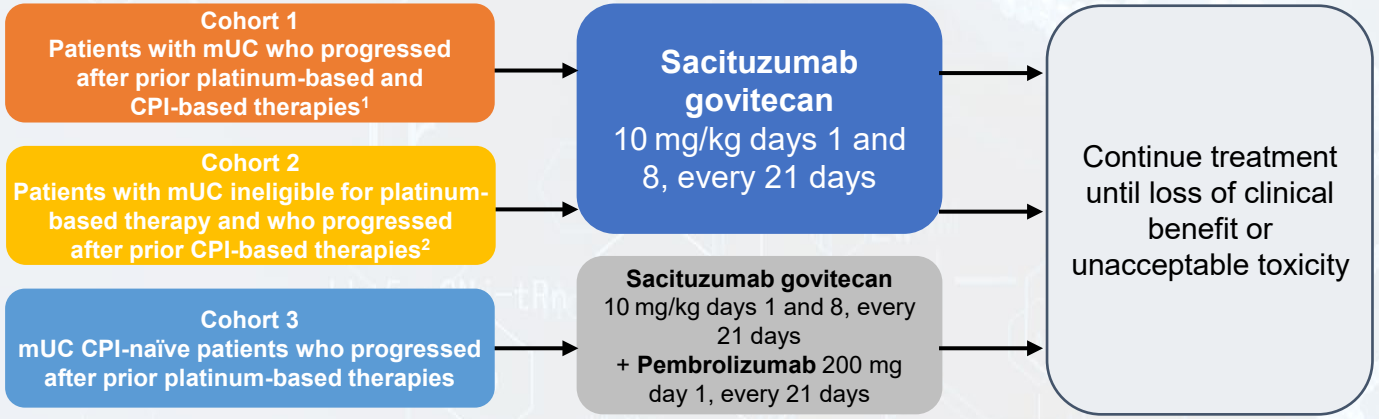
Data cut-off: July 15, 2020

original reports

TROPHY-U-01: A Phase II Open-Label Study of Sacituzumab Govitecan in Patients With Metastatic Urothelial Carcinoma Progressing After Platinum-Based Chemotherapy and Checkpoint Inhibitors

Scott T. Tagawa, MD, MS[1]; Arjun V. Balar, MD[2]; Daniel P. Petrylak, MD[3]; Arash Rezazadeh Kalebasty, MD[4]; Yohann Loriot, MD, PhD[5]; Aude Fléchon, MD, PhD[6]; Rohit K. Jain, MD[7]; Neeraj Agarwal, MD[8]; Manojkumar Bupathi, MD, MS[9]; Philippe Barthelemy, MD, PhD[10]; Philippe Beuzeboc, MD, PhD[11]; Phillip Palmbos, MD, PhD[12]; Christos E. Kyriakopoulos, MD[13]; Damien Pouessel, MD, PhD[14]; Cora N. Sternberg, MD[1]; Quan Hong, MD[15]; Trishna Goswami, MD[15]; Loretta M. Itri, MD[15]; and Petros Grivas, MD, PhD[16]

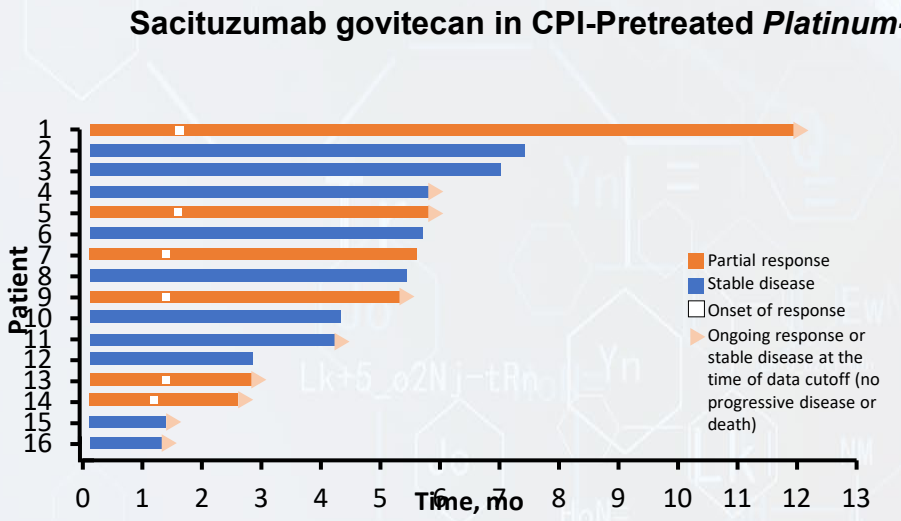
Sacituzumab Govitecan in Pretreated Locally Advanced Metastatic Urothelial Carcinoma



- **Primary endpoint: ORR by central review**
- **Secondary endpoints:** PFS, DOR, OS, and safety/tolerability

Loriot et al. ESMO 2020

TROPHY-U-01- Cohort 2[1]

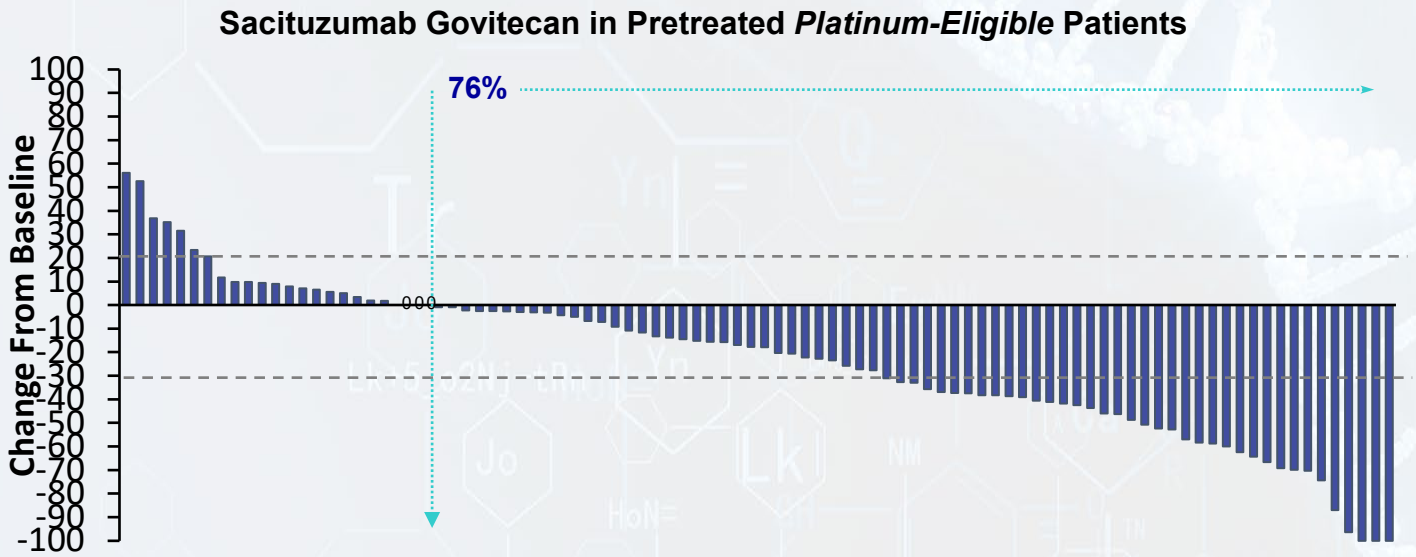


At median follow-up of 6.8 months:

- **ORR 29% (6/21)**
- **6 confirmed PRs**
- **Median DOR not reached**
- **mPFS 5.5mo (95% CI 1.70, 7.30)**
- **mOS 11.1 mo (95% CI 4.90, N/A)**
- **62% (13/21) of pts demonstrated reduction in tumor size**

Petrylak et al. ASCO 2020

TROPHY-U-01 – Reduction in Tumor Size[1,a]



Loriot et al. ESMO 2020

Treatment-Related Adverse Events ≥20% Any Grade or ≥5% Grade ≥3 (N=113)

Loriot et al. ESMO 2020

Category	Event	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Hematologic[a]	**Neutropenia**	**46**	**22**	**12**
	Leukopenia	26	12	5
	Anemia	34	14	0
	Lymphopenia	12	5	2
	Febrile neutropenia	**10**	**7**	**3**
Gastrointestinal	**Diarrhea[b]**	**65**	**9**	**1**
	Nausea	**58**	**4**	**0**
	Vomiting	28	1	0
General disorders & administrative site conditions	**Fatigue**	**50**	**4**	**0**
Skin & subcutaneous tissue	**Alopecia**	**47**	**0**	**0**
Metabolism & nutrition	Decreased appetite	36	3	0
Infections & infestations	Urinary tract infection	8	6	0

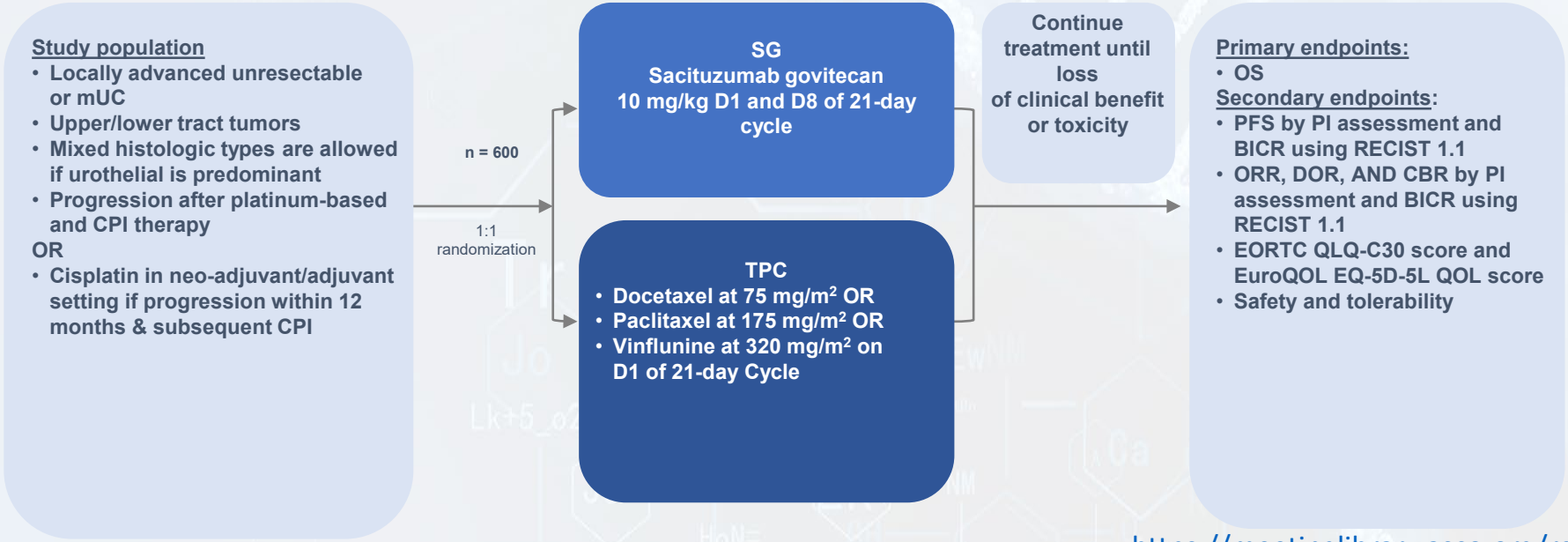
Median treatment cycles: 6 (range: 1–22); worst grade CTCAE reported

- **7 (6%) pts discontinued due to TRAEs**
  - **3 discontinued due to neutropenia or its complications**
- **30% GCSF usage**
- **One treatment-related death (sepsis due to febrile neutropenia)**

[a]"Neutrophil count decreased," "White blood cell count decreased," "Lymphocyte count decreased," and "Hemoglobin decreased" have been re-coded to Neutropenia, Leukopenia, Lymphopenia, and Anemia, correspondingly, for summary purposes. [b]15% of patients treated with SG experienced grade 2 treatment-related diarrhea.

CTCAE, Common Terminology Criteria for Adverse Events; GCSF, granulocyte colony-stimulating factor; pt, patient; TRAEs, treatment-related adverse events.

TPS498 – Petros Grivas – TROPiCS-04: Study of sacituzumab govitecan in metastatic or locally advanced unresectable urothelial cancer that has progressed after platinum and checkpoint inhibitor therapy



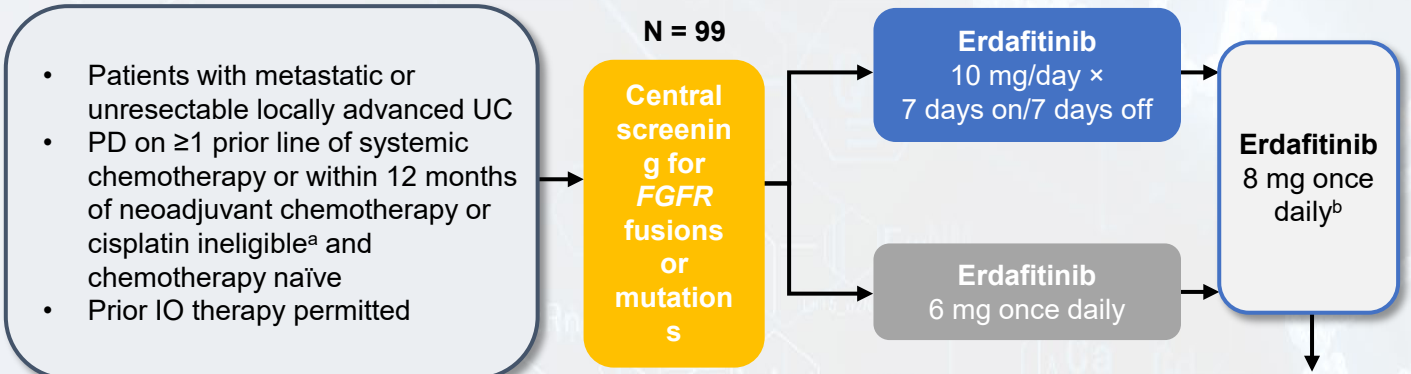
BICR, blinded independent central review; CBR, clinical benefit rate; CPI, checkpoint inhibitor; D, Day; DOR, duration of response; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EuroQOL EQ-5D-5L, European Quality of Life 5-dimensions 5-levels; mUC, metastatic urothelial cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed death-ligand 1; PFS, progression-free survival; PI, prinical investigator; QOL, Quality of Life; RECIST, Response Evaluation Criteria in Solid Tumors; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

https://meetinglibrary.asco.org/record/194773/abstract

Grivas P, et al. Virtual poster presentation at ASCO GU 2021; abstract TPS498

BLC2001: Study Design[1]

Pivotal Phase 2 Trial of Erdafitinib in *FGFR*-Altered Metastatic or Unresectable UC



- **Primary endpoint:** ORR
- **Secondary endpoints:** PFS, OS, safety, DOR, PK, predictive biomarker evaluation

- Study has 85% power with 1-sided α = .025 to test primary hypothesis that ORR >25% in erdafitinib 8-mg arm
- Patients with ≥2 prior therapies, n = 43
- Patients with visceral metastases, n = 78

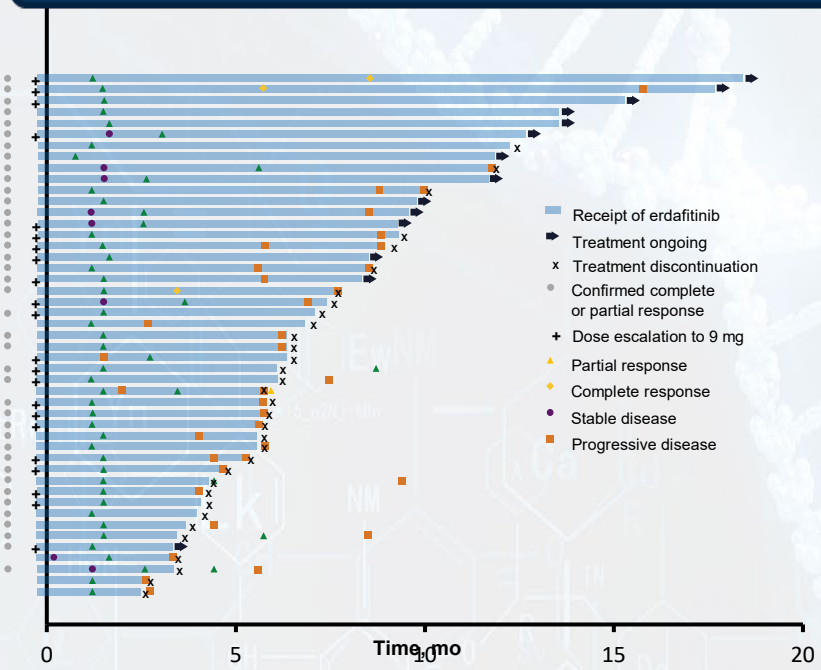
[a] Peripheral neuropathy or impaired renal function. [b] Titration up to 9 mg once daily if target not reached for serum phosphate (≥5.5 mg/dL) by day 14 and no TRAEs.

1. Loriot Y et al. *N Engl J Med*. 2019;381:338-48

BLC2001: Response[1]

- **Confirmed response rate 40% (3% CR; 37% PR)**
- **Among 22 pts with prior ICI, confirmed response rate 59%**

Results led to FDA approval of erdafitinib for locally advanced UC or mUC with *FGFR3* or *FGFR2* mutation or fusion after progression on ≥1 line of prior platinum-containing chemotherapy



Loriot Y et al. N Engl J Med. 2019;381:338-48

BLC2001: Subgroup Analyses of Long-Term Efficacy Outcomes[1]

	n	Median DoR, months	n	Median PFS, months	Median OS, months
FGFR alteration					
*FGFR*m+f-	33	6.0	70	5.6	12.0
*FGFR*m-f+	4	6.2	25	2.8	10.3
FGFRm+f+	3	5.6	6	6.9	15.0
Primary tumour location					
Upper tract	11	6.7	25	4.2	10.3
Lower tract	29	6.0	76	5.6	13.8
Presence of visceral metastases					
Yes	30	6.0	78	5.5	10.3
No	10	5.3	23	5.8	14.1
Prior systemic therapy					
None	4	10.9	10	9.8	18.1
1 line	17	6.0	48	5.5	11.3
2 lines	10	6.1	28	5.5	8.0
3 lines	7	4.4	11	5.7	11.2
≥3 lines	2	4.8	4	3.4	12.4
Use of prior chemotherapy					
Prior chemotherapy	35	5.6	89	5.5	10.6
Chemotherapy naïve	5	14.3	12	14.9	20.8
Use of prior IO					
Prior IO	14	6.5	24	5.7	10.9
No prior IO	26	5.6	77	5.5	12.0

Pts derived benefit regardless of *FGFR* alteration type, tumor location, presence of visceral metastases, or prior treatment with immunotherapy

1. **Necchi A et al. *Ann Oncol*. 2020;31(suppl 4):s583.**

BLC2001: TEAEs of Interest from the Final Analysis

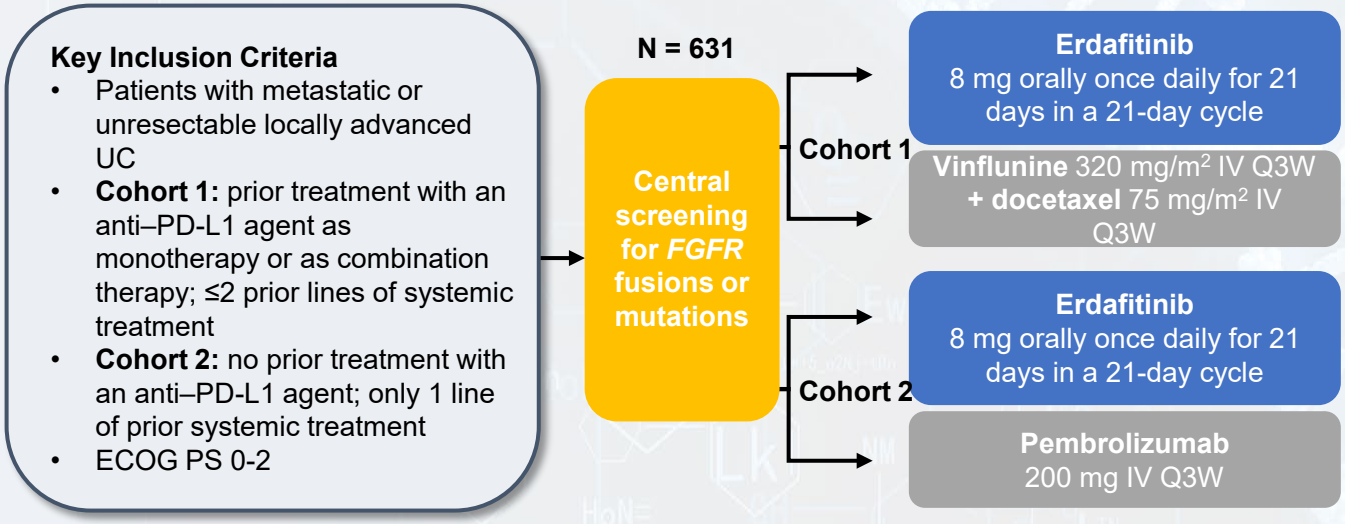
TEAE of Interest	Overall Incidence n (%)
Hyperphosphatemia[a]	79 (78%)
Stomatitis	60 (59%)
Nail disorders	60 (59%)
Skin disorders	55 (55%)
Central serous retinopathy	27 (27%)

N = 101[b]
Median follow-up: 24.0 months
Median treatment duration: 5.4 months

Few TEAEs were grade 3; none were grade ≥ 4

The most common and FGFRi class effect TEAEs were generally reversible and managed by supportive care and dose modification

Phase 3 THOR: Study Design[1]



- **Primary endpoint:** OS
- **Secondary endpoints:** PFS, ORR, PROs, DOR, safety

1. https://clinicaltrials.gov/ct2/show/NCT03390504

Numerous agents being evaluated in mUC: combos *vs* sequential Tx

Conventional Cytotoxic Agents	Immunotherapy	Targeted Therapies
• Chemotherapy • Antibody-Drug Conjugates • Radiation Tx	• Checkpoint inhibitors • Vaccines • Cytokines • Adoptive cell-based therapy • Other immuno-modulating agents	• Anti-angiogenesis • FGFR inhibitors • HER family inhibitors • PARP inhibitors • Chromatin remodeling, i.e. HDAC inhibitors • Other, i.e. mAbs, TKIs, etc.

- Patient selection / precision oncology
- Tumor tissue & ctDNA analysis
- **Targets and predictive biomarkers** with:
  - Analytical validity
  - Clinical validity (biological relevance)
  - **Clinical utility**

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Advanced Urothelial Ca Treatment Algorithm

Disease State	Setting	Preferred Option	Standard Options
Metastatic, no prior chemotherapy	Cisplatin-eligible	Cisplatin/gemcitabine f/b avelumab maintenance	Cisplatin-based combination chemotherapy f/b avelumab maintenance
Metastatic, no prior chemotherapy	Cisplatin-ineligible	Gemcitabine/Carboplatin (PD-L1 low tumors in fit patients) f/b avelumab maintenance	Gemcitabine/Carboplatin f/b avelumab maintenance *Pembrolizumab* *umab* gent chemotherapy
Metastatic, prior platinum chemotherapy or relapse within 1 year of perioperative cisplatin-based therapy		OR Erdafitinib (tumors with FGFR2/3 alterations)	umab Avelumab Durvalumab Nivolumab
Metastatic, prior chemotherapy & immunotherapy		Enfortumab vedotin OR Sacituzumab govitecan OR Erdafitinib (tumors with FGFR2/3 alterations)	Taxane (US) Vinflunine (EU)

Clinical trials are critical throughout disease spectrum & treatment settings!

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SCCA/UWMC Bladder/Urothelial Cancer Trials

Ta, Tis, T1 **NMIBC**	**Neoadjuvant for MIBC**	**Chemoradiation OR Adjuvant Therapy**	**Metastatic** Locally Advanced / Unresectable ***First Line***	**Metastatic** ***Second Line +***
Pembro for BCG-Unresponsive NMIBC (accruing only in cohort B for non-CIS) NCT02625961	**Neoadjuvant+Adjuvant Nivolumab +/- NKTR-214 vs no (neo)adjuvant in Cisplatin-ineligible pts NCT04209114**	**AMBASSADOR adjuvant pembro vs observation NCT03244384**	**Pembrolizumab + Neutrons NCT03486197**	
THOR-2 BCG unresponsive, & tumor FGFR mutation + NCT04172675	**Keynote 866: neoadj gemcitabine/cisplatin +/- Pembro in Cisplatin-eligible pts NCT03924856**	**SWOG S1806 Chemoradiation with or without atezolizumab (bladder preservation) NCT03775265**	**Mirati Sitravatinib in Combination with PD-(L)1 Checkpoint Inhibitor Regimens in advanced or metastatic urothelial carcinoma NCT03606174**	
	Pembro + aMVAC chemo in pure or predominant non-urothelial MIBC NCT04383743	**PROOF302 (adjuvant infigratinib vs placebo for FGFR3 mutation or fusion tested by Foundation) NCT04197986**	**Immunomedics: IMMU-132 post-CPI; pembro+IMMU-132 in platinum refractory, cohort 4 Cisplatin + Sacituzumab govitecan (first line) NCT03547973**	
		SWOG 1600 nutritional therapy in bladder cancer before and after surgery NCT03757949	**Merck 7902-LEAP-011 Pembro / Lenvatinib vs Pembro / Placebo in PD-L1-high (CPS ≥10) Cisplatin-ineligible or Platinum-Ineligible pts NCT03898180**	**Atezolizumab + IL-7 (2nd line after platinum-based therapy) NCT03513952**
			SeaGen GN22E-003 Previously untreated locally advanced or metastatic UC NCT04223856	**GSK Phase 1b Bintrafusp Alfa NCT04349280**
			ATTAMAGE-A1 Ph1 CD8+ and CD4+ Transgenic T-cells expressing TCR + Atezolizumab in metastatic MAGE-A1 cancer NCT04639245	**MAGEA1 TCR Cell Therapy Study NeoTCR-P1 +/- Anti-PD-1 in solid tumors NCT03970382**

KEY: Open: **Green or Bold**
Not Yet Open: *Blue or Italicized*

Updated: 7/30/2021

Take home messages

- **Clinical trials or cisplatin-based chemoTx for cisplatin-eligible pts**
- **Pembrolizumab has FDA approval in BCG-unresponsive high-risk CIS for pts who refuse of cannot undergo RC**
- **Neoadjuvant cisplatin-based chemotherapy is the SOC prior to RC in fit patients**
- **Bladder preservation should be considered as an option in appropriate patients**
- **Adjuvant nivolumab prolonged DFS in the CM-274 trial (no OS data yet)**
- **Atezolizumab & pembrolizumab: phase II trial single arm data in 1L cisplatin-ineligible for *PD-L1+ (or 'platinum-unfit' pts in US only)***
- **JavelinBladder100 trial met primary endpoint of OS with switch maintenance avelumab/BSC vs BSC→ level I evidence as 1L maintenance after CR/PR/SD on platinum-based chemoTx**
- **Level I evidence *for pembrolizumab in* platinum-refractory setting (KN045 trial)**
- **Role of anti-CTLA4 is only experimental in UC (awaiting CM901 & NILE trials)**
- ***EV: impressive ORR in 2L after 1L ICI; OS/PFS benefit in 3L vs taxane/vinflunine (EV-301)***
- ***EV / SG FDA approved; Erdafitinib FDA approved for FGFR2/3 mutation/fusion after PD on platinum***
- **Biomarker validation is the *Holy Grail*: variability among trials**

Thanks much ☺

Patient and families!

Collaborators, sponsors, institutions, foundations, colleagues, research, admin & clinical staff: Teams!

@PGrivasMDPhD