TÜRK TIBBİ ONKOLOJİ DERNEĞİ
Hayat için bilimin izinde...

TÜRK TIBBİ ONKOLOJİ DERNEĞİ
SANAL KONGRESİ

Pandemi Gölgesinde Geçen 2020
Yılında Onkolojide Neler Değişti?

OTURUM 5

13-15 KASIM

GENİTOÜRİNER KANSERLER

«Üretelyal Tümörler: Yeni hedefler, Yeni stratejiler»

Arzu Yaren

Pamukkale Üniversitesi Tıbbi Onkoloji/Denizli

14 Kasım 2020

Üretelyal Kanser

- Mesane, renal pelvis, üreter ve üretra tümörleri
- %90 alt üriner trakt
- PS iyi, organ fx yeterli hastada ilk sıra tedavide platin bazlı kemoterapi

*Cisplatin + Gemsitabin veya (dd)MVAC

*mSK 12-17ay

- Cisplatin yerine carboplatin (mOS 9ay!!)
- İlk sıra tedaviden sonra 2. sıra tedavi yanıtları düşük
- Yeni tedavi hedefleri ve stratejileri

Cisplatin-Based CT for UC Yields Durable Responses: The Original "Tail on the Curve"

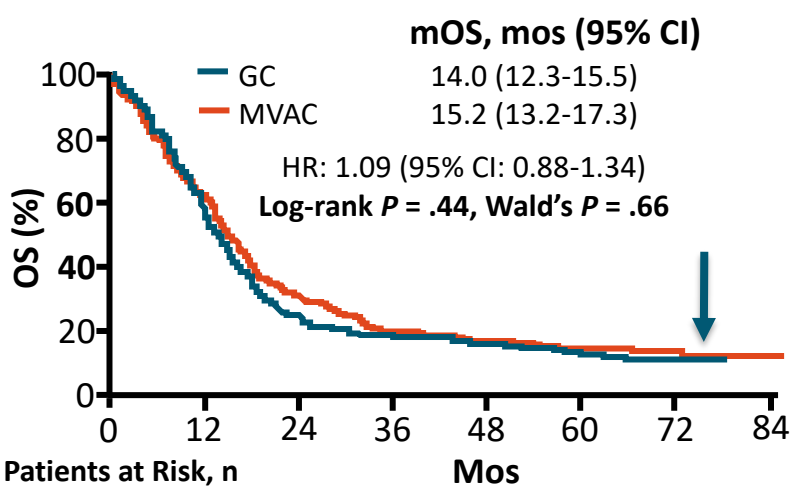
Cisplatin Eligible

Gemcitabine Cisplatin[1]

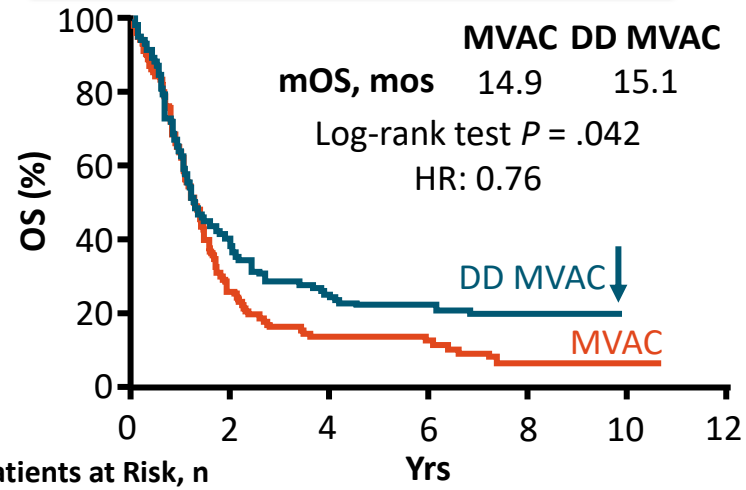
ORR	49%
CR	12%
mOS	14 mos

Dose-Dense MVAC[2]

ORR	72%
CR	25%
mOS	15.1 mos



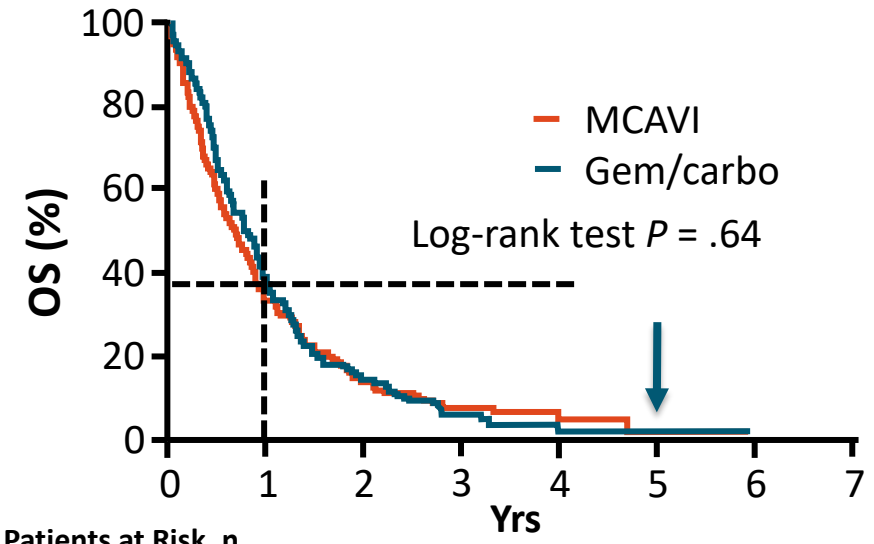
Patients at Risk, n							
GC **203**	118	52	36	30	23	7	0
MVAC **202**	125	62	40	34	29	9	1



Patients at Risk, n						
MVAC (n = 129)	32	15	11	4	2	
DD MVAC (n = 134)	45	29	23	8	0	

Gemcitabine Carboplatin[3]

ORR	36%
CR	3%
mOS	9.3 mos



Patients at Risk, n						
MCAVI (n = 119)	37	13	7	3	1	1
Gem/carbo (n = 119)	44	15	5	2	2	1

1. Von Der Masse. JCO. 2005;23:4602. 2. Sternberg. Eur J Ca. 2006;42:50. 3. De Santis. JCO. 2012;30:191.

İmmün checkpoint İnhibitörleri

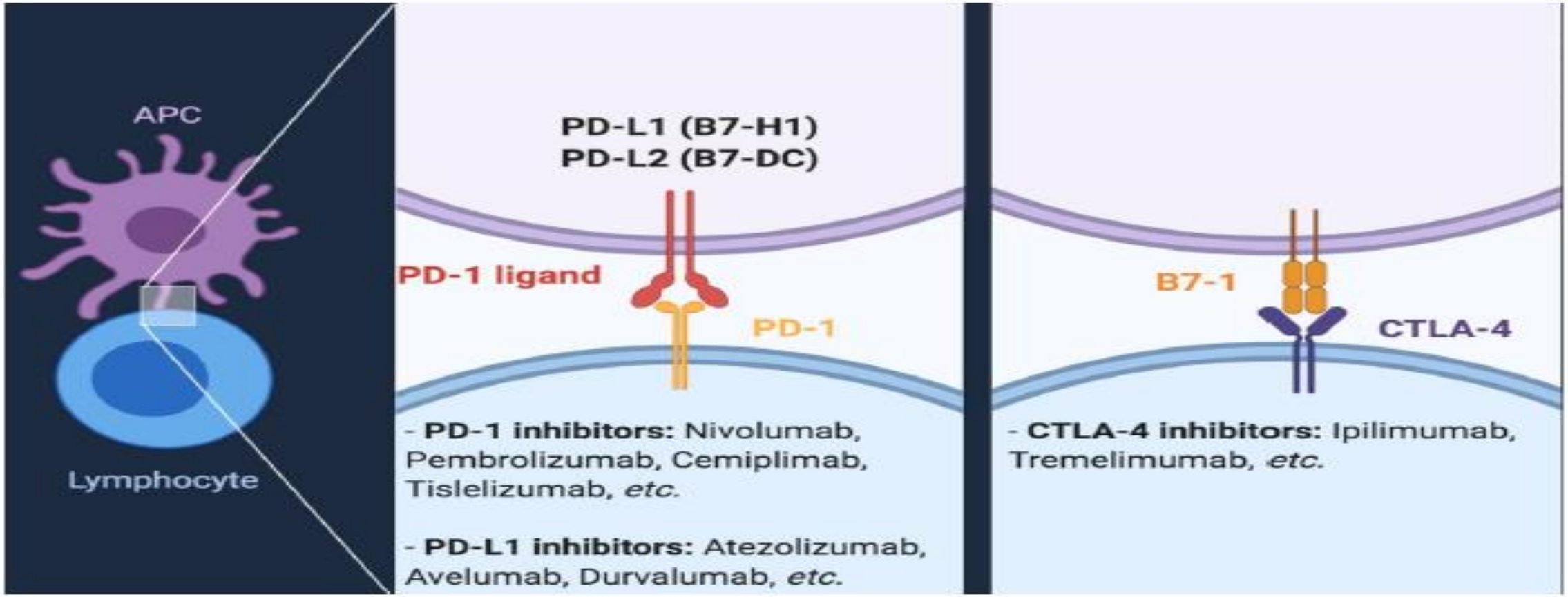


Figure 1. The interaction between PD-1/PD-L1 and CTLA-4/B7-1, a key mechanism exploited by immune checkpoint inhibitors. PD-1 inhibitors include nivolumab, pembrolizumab, cemiplimab, tislelizumab, and other agents currently in development; conversely, PD-L1 inhibitors encompass agents such as atezolizumab, avelumab, durvalumab, while CTLA-4 inhibitors encompass ipilimumab and tremelimumab.

Mollica V. Cancers 2020

Phase II Keynote-052: Long-term Outcomes With Pembrolizumab in Cisplatin-Ineligible Patients With mUC

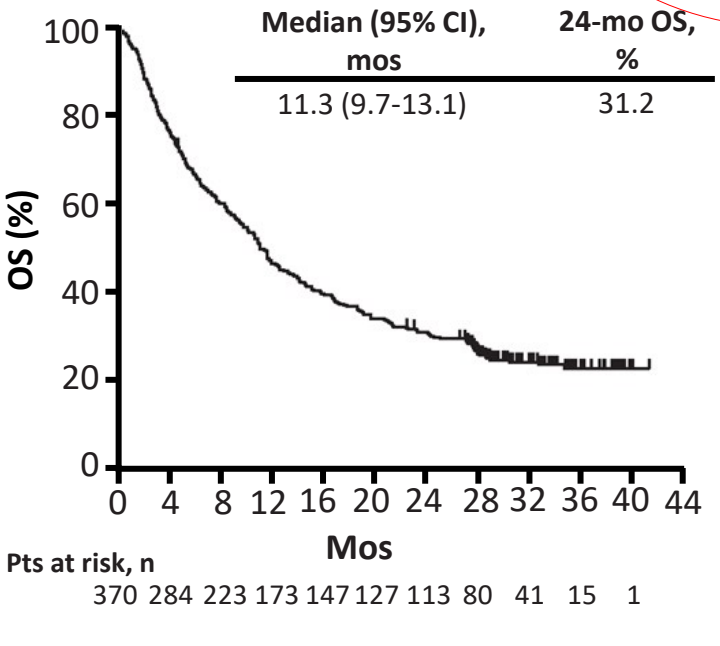
	All Treated Pts (N = 370)	CPS ≥ 10 (n = 11)
ORR, % (95% CI)	28.6 (24.1-33.5)	47.3 (37.7-57.0)
▪ CR	8.9 (6.2-12.3)	20.0 (13.0-28.7)
▪ PR	19.7 (15.8-24.2)	27.3 (19.2-36.6)

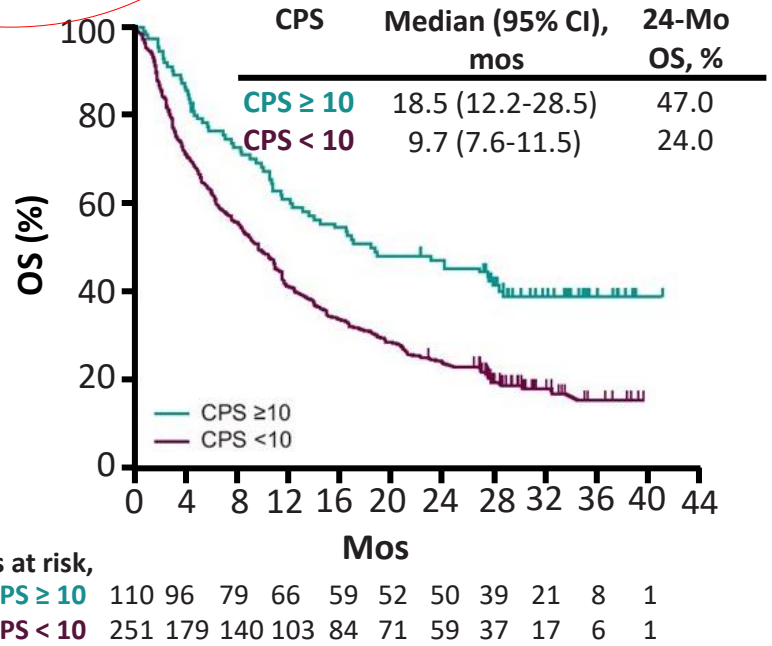
Median OS
11.3 mos

CPS ≥ 10% OS
18.5 mos

Inclusion criteria

- **Advanced urothelial cancer**
- **No prior chemotherapy for metastatic disease**
- **ECOG PS 0-2**
- **Ineligible for cisplatin based on ≥ 1 of the following:**
  - **CrCl < 60 mL/min**
  - **ECOG PS 2**
  - **≥ grade 2 neuropathy or hearing loss**
  - **NYHA class III CHF**





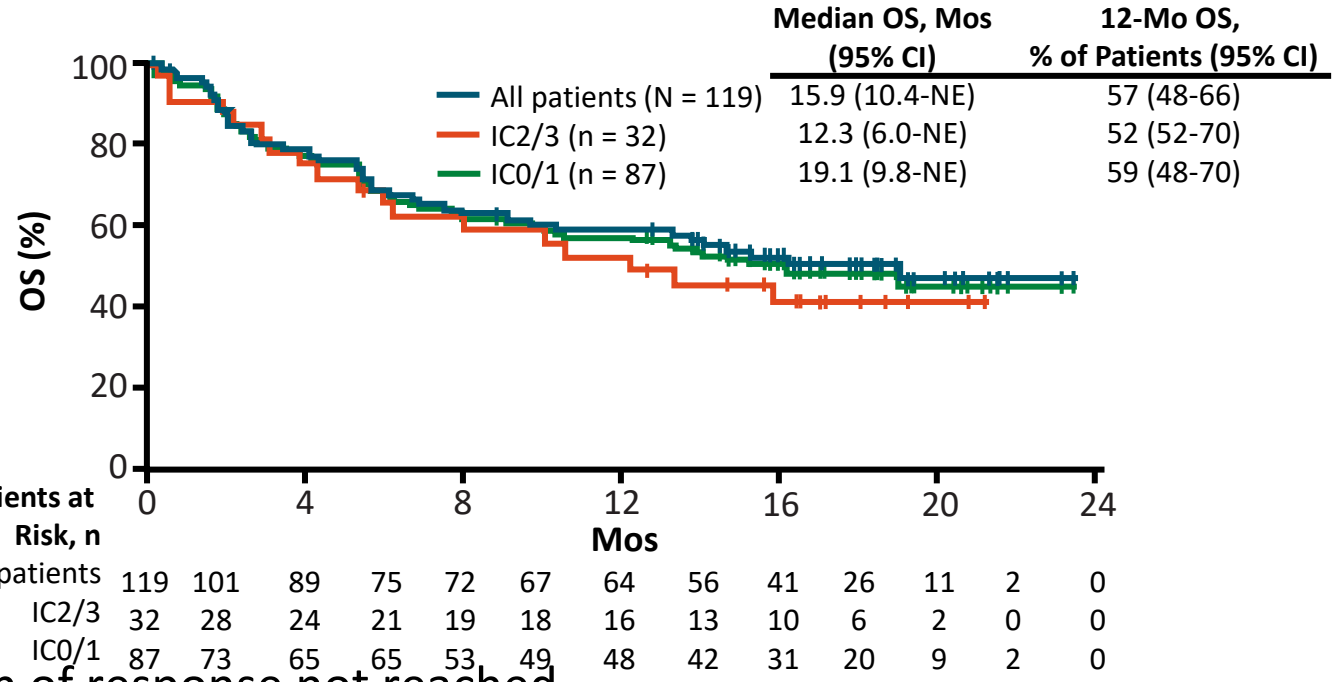
O'Donnell. ASCO 2019. Abstr 4546.

Phase II IMvigor210 Cohort 1: Accelerated FDA Approval for Atezolizumab in Cisplatin-Unfit UC (N = 119)

	IC2/3 (n = 32)	IC1/2/3 (n = 80)	All Pts (N = 119)	IC1 (n = 48)	IC0 (n = 39)
ORR, % (95% CI)	28 (14-47)	24 (15-35)	23 (16-31)	21 (11-35)	21 (9-37)
▪ CR	13	10	9	8	8
▪ PR	16	14	13	13	13

Cohort 1: specific inclusion criteria

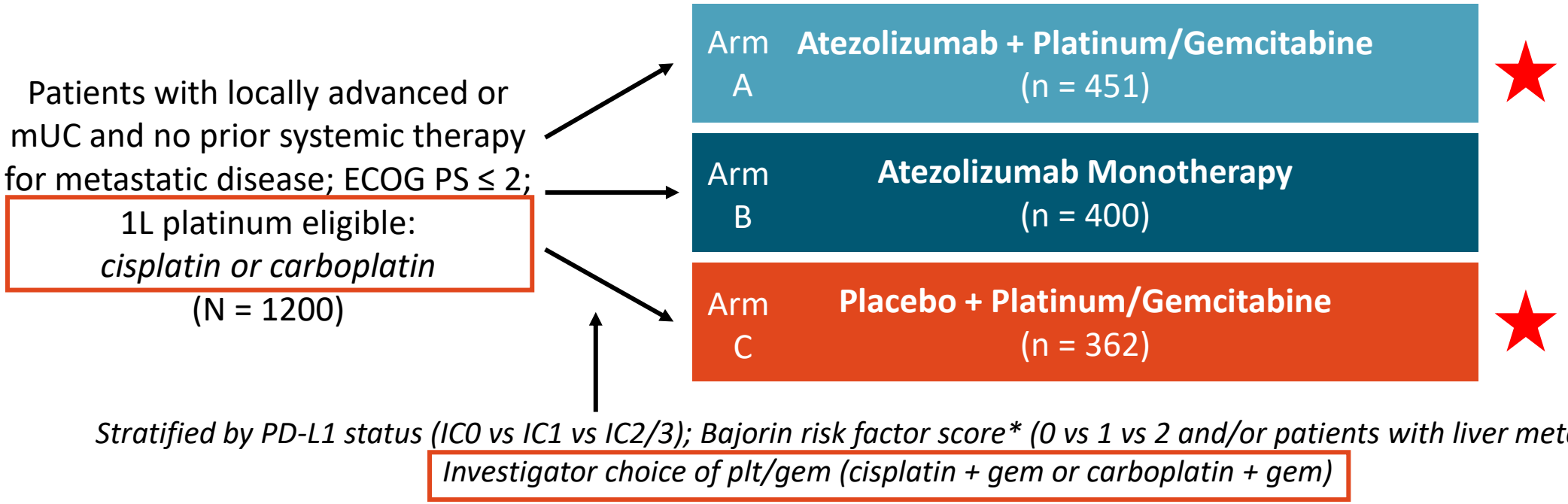
- **No prior treatment for mUC (> 12 mos since perioperative chemo)**
- **ECOG PS 0-2**
- **Cisplatin ineligibility based on ≥ 1 of the following:**
  - **Renal impairment: GFR < 60 and > 30 mL/min**
  - **≥ grade 2 hearing loss or peripheral neuropathy**
  - **ECOG PS 2**



Median duration of response not reached

Balar. Lancet. 2017;389:67.

Phase III IMvigor130: Atezolizumab ± Platinum-Based Chemotherapy for First-line Patients



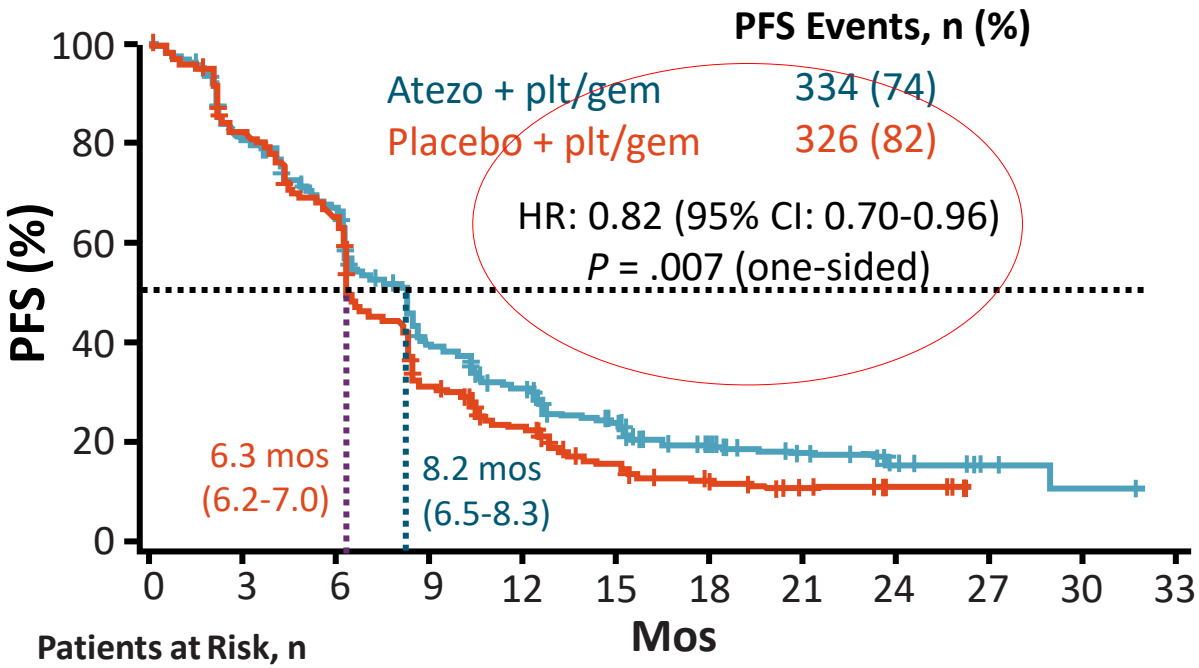
- Coprimary endpoints: investigator-assessed PFS and OS (Arm A vs C); OS (Arm B vs C; hierarchical approach)
- Key secondary endpoints: ORR, DoR, PFS, and OS (Arm B vs C; PD-L1 subgroups), safety

*Including KPS < 80% vs ≥ 80% and presence of visceral metastases.

Grande. ESMO 2019. Abstr LBA14_PR.

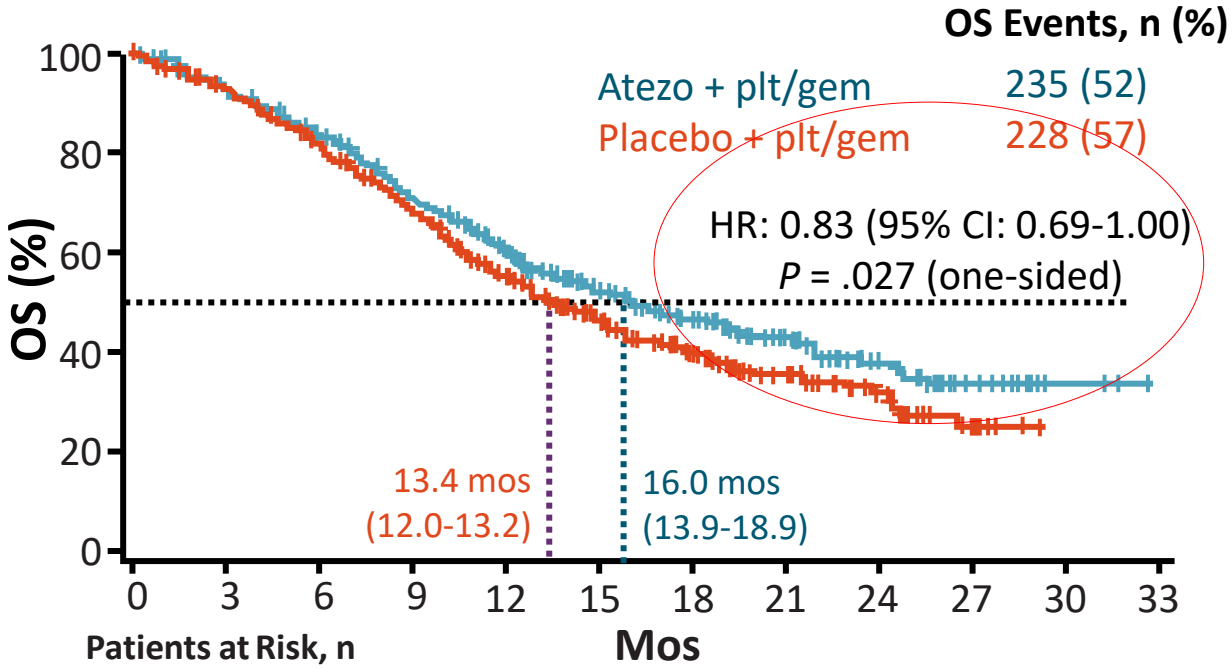
IMvigor130: Platinum-Based Chemotherapy ± Atezolizumab in Advanced UC

Final PFS (ITT)



Co-primary endpoint of PFS met

Interim OS (ITT)

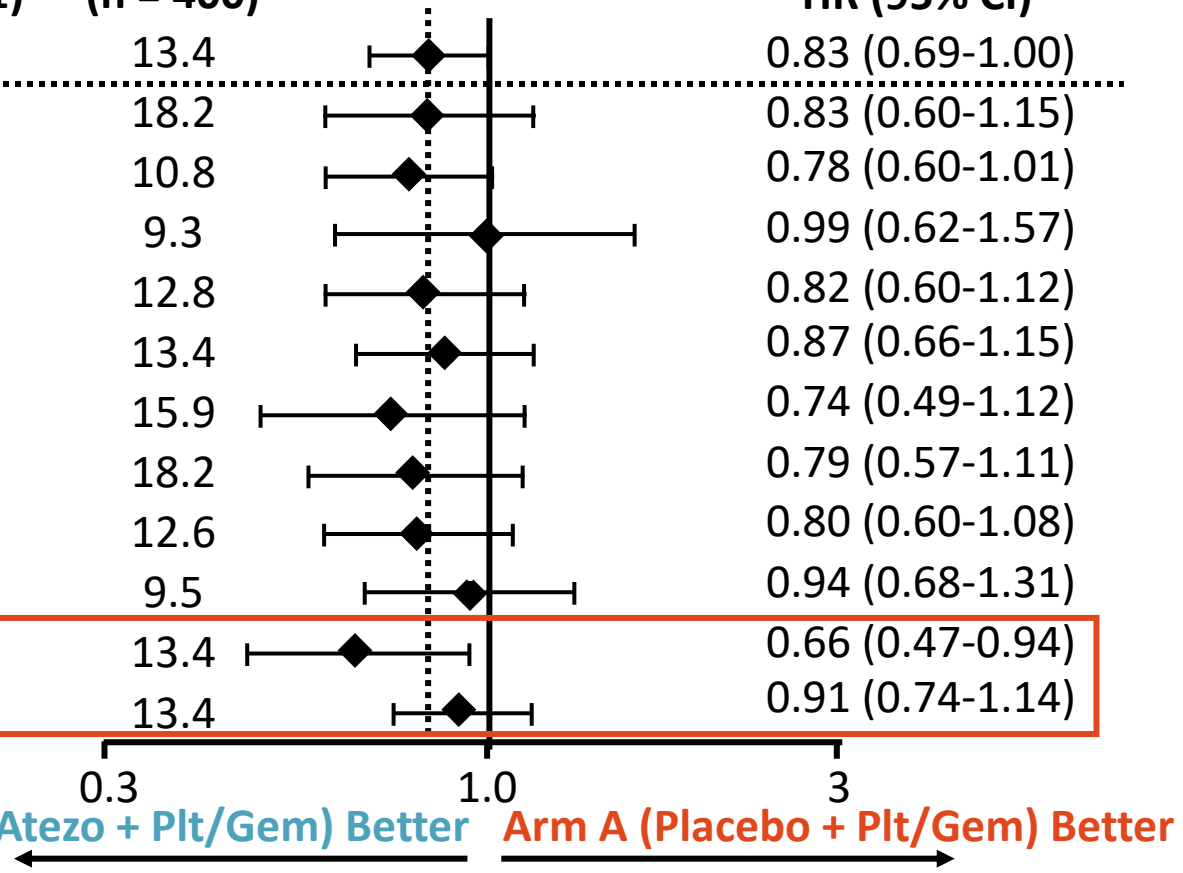


Co-primary endpoint of OS not (yet) met based on stats design, alpha spend

Grande. ESMO 2019. Abstr LBA14_PR.

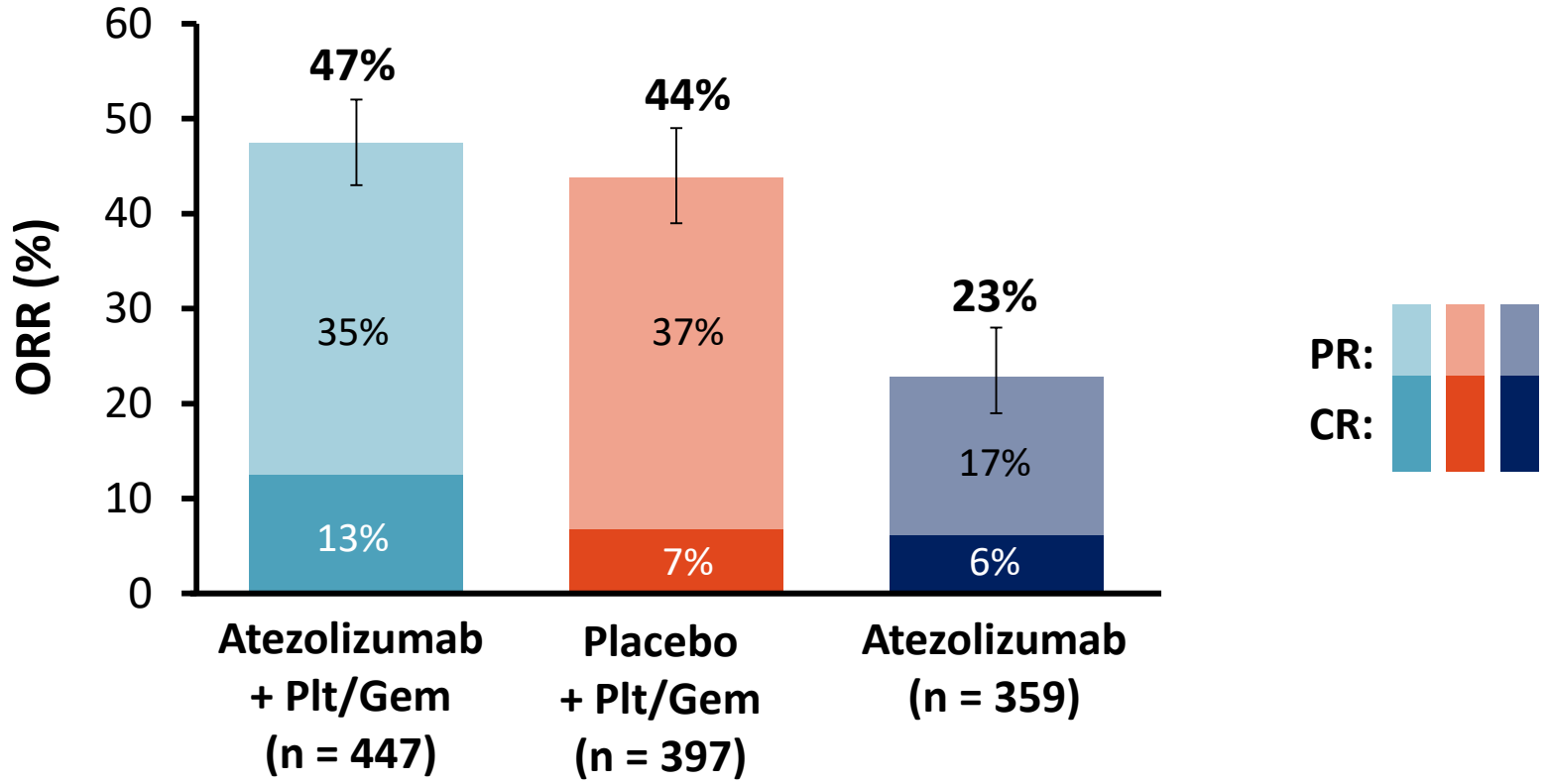
IMvigor130: OS by Patient Subgroups

Characteristic		Patients, n	Arm A mOS, Mos (n = 451)	Arm C mOS, Mos (n = 400)	HR (95% CI)
All patients		851	16.0	13.4	0.83 (0.69-1.00)
ECOG PS	0	355	22.0	18.2	0.83 (0.60-1.15)
	1	396	14.2	10.8	0.78 (0.60-1.01)
	2	100	7.4	9.3	0.99 (0.62-1.57)
PD-L1 status	0	278	14.2	12.8	0.82 (0.60-1.12)
	1	374	14.9	13.4	0.87 (0.66-1.15)
	2/3	199	23.6	15.9	0.74 (0.49-1.12)
Bajorin risk factor score	0	338	24.5	18.2	0.79 (0.57-1.11)
	1	318	15.8	12.6	0.80 (0.60-1.08)
	2 and/or liver mets	195	9.5	9.5	0.94 (0.68-1.31)
Investigator choice of chemo	Cisplatin	273	21.7	13.4	0.66 (0.47-0.94)
	Carboplatin	578	14.2	13.4	0.91 (0.74-1.14)



Grande. ESMO 2019. Abstr LBA14_PR.

IMvigor130: Confirmed ORR and DoR

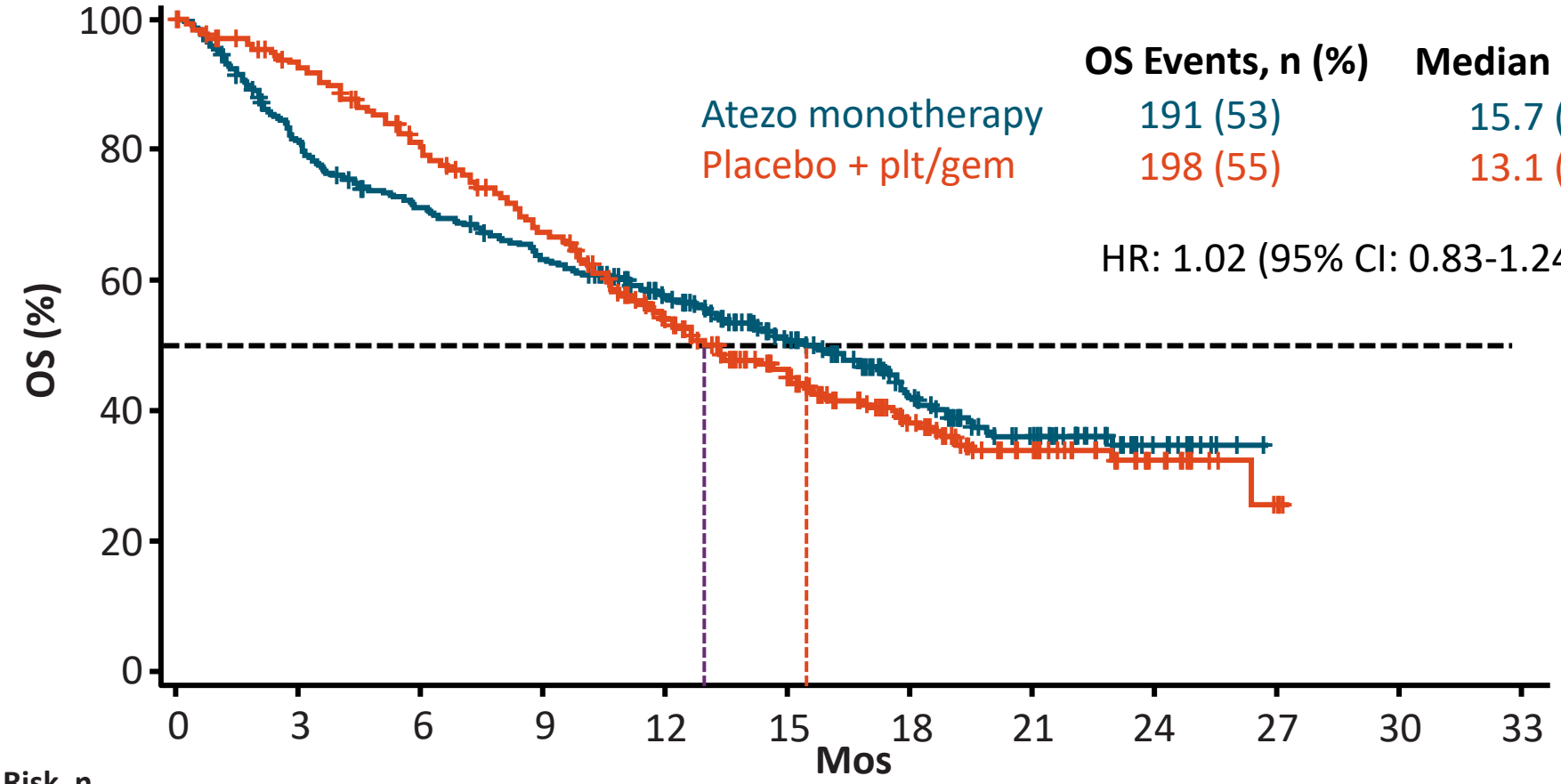


Median DoR,* mos (95% CI)	8.5 (7.2-10.4)	7.6 (6.3-8.5)	NE (15.9-NE)

*n = 212 in atezo + plt/gem, n = 174 in placebo + plt/gem, n = 82 in atezo.

Grande. ESMO 2019. Abstr LBA14_PR.

IMvigor130: Interim OS for Atezolizumab Monotherapy vs Platinum-Based Chemotherapy



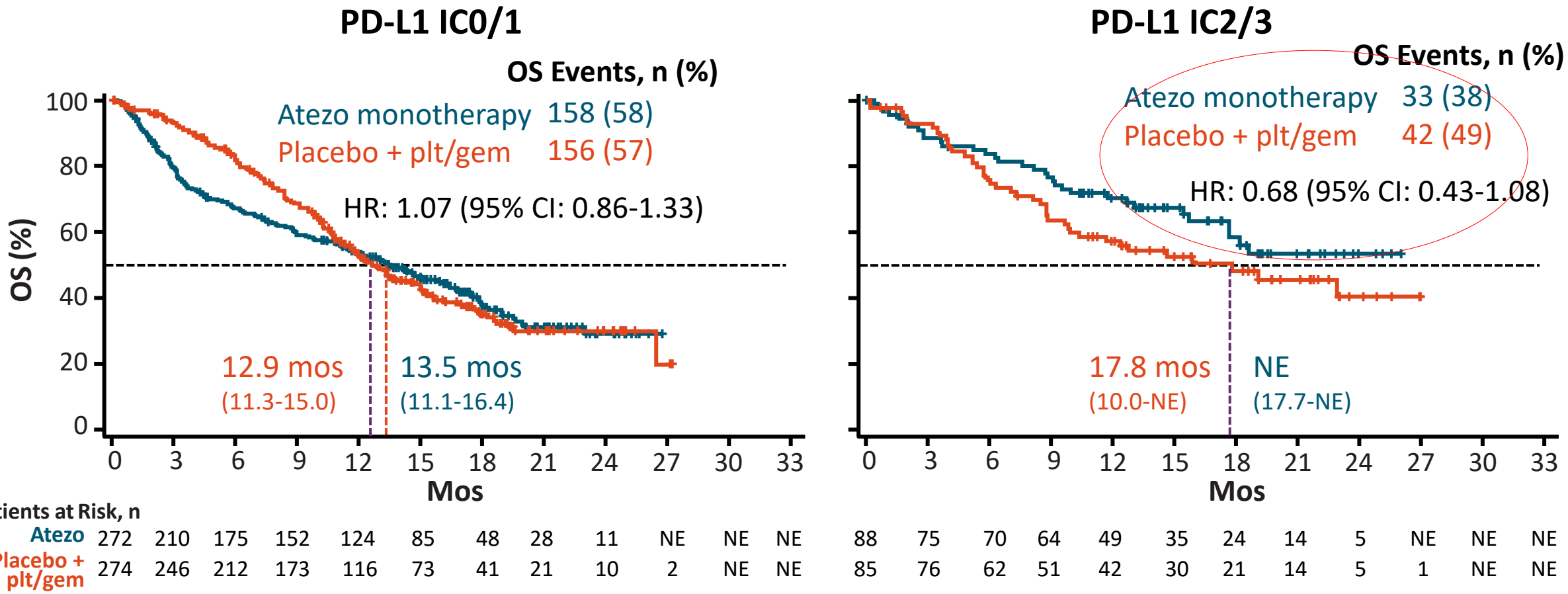
	OS Events, n (%)	Median OS, Mos (95% CI)
Atezo monotherapy	191 (53)	15.7 (13.1-17.8)
Placebo + plt/gem	198 (55)	13.1 (11.7-15.1)

HR: 1.02 (95% CI: 0.83-1.24)

Patients at Risk, n												
Atezo	360	285	245	216	173	120	72	42	16	NE	NE	NE
Placebo + plt/gem	359	322	274	224	158	103	62	35	15	3	NE	NE

Grande. ESMO 2019. Abstr LBA14_PR.

IMvigor130: Interim OS (Atezolizumab vs Platinum Chemotherapy) by PD-L1 Status



Patients at Risk, n

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

Grande. ESMO 2019. Abstr LBA14_PR.

IMvigor130: Safety

AE, n (%)	Atezo + Plt/Gem (n = 453)	Placebo + Plt/Gem (n = 390)	Atezo (n = 354)
Any AE	451 (100)	386 (99)	329 (93)
▪ Grade 3/4	383 (85)	334 (86)	148 (42)
▪ Grade 5	29 (6)	20 (5)	28 (8)
Any Tx-related AE	434 (96)	373 (96)	211 (60)
▪ Grade 3/4	367 (81)	315 (81)	54 (15)
▪ Grade 5	9 (2)	4 (1)	3 (1)
AE leading to Tx d/c	156 (34)	132 (34)	22 (6)
▪ Atezo/placebo	50 (11)	27 (7)	21 (6)
▪ Cisplatin	53 (12)	52 (13)	0
▪ Carboplatin	90 (20)	79 (20)	1 (< 1)
▪ Gemcitabine	117 (26)	100 (26)	1 (< 1)
AE leading to dose reduction/interruption	363 (80)	304 (78)	112 (32)

Any-Gr AE of Special Interest in ≥ 1% of Patients, n (%)	Atezo + Plt/Gem (n = 453)	Placebo + Plt/Gem (n = 390)	Atezo (n = 354)
Rash	137 (30)	74 (19)	45 (13)
Hepatitis*	82 (18)	49 (13)	50 (14)
▪ Lab abnormalities	79 (17)	44 (11)	46 (13)
▪ Diagnosis	6 (1)	8 (2)	6 (2)
Hypothyroidism	48 (11)	15 (4)	36 (10)
Hyperthyroidism	31 (7)	7 (2)	15 (5)
Pneumonitis	12 (3)	6 (2)	12 (3)
Infusion-related rxn	6 (1)	3 (1)	5 (1)
Pancreatitis	3 (1)	2 (1)	6 (2)

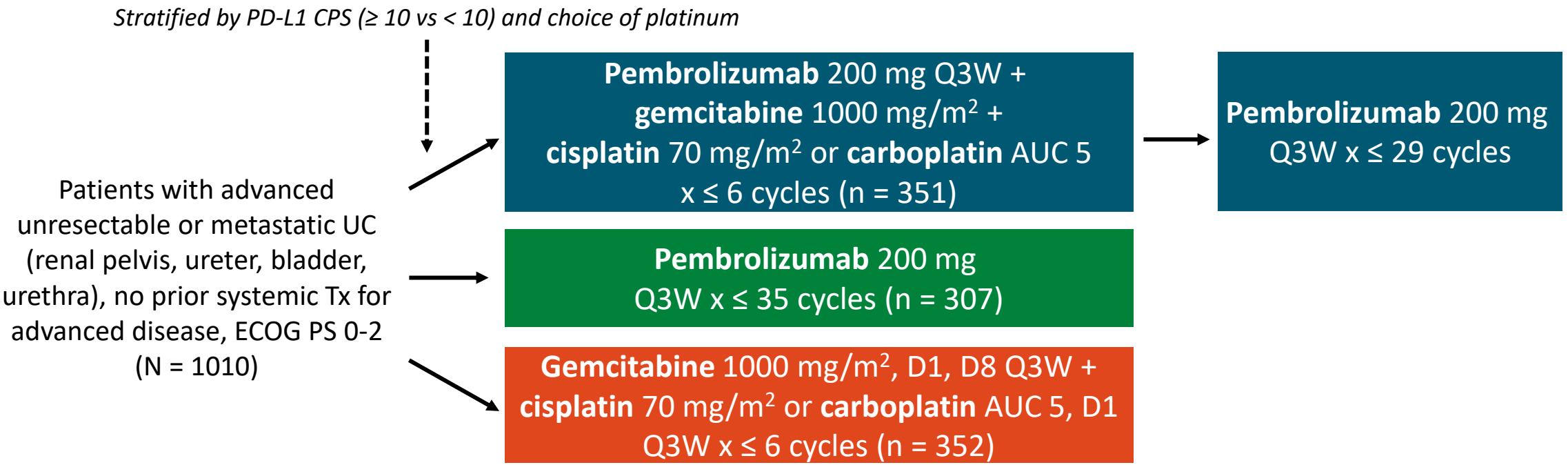
*Some patients are included in both categories.

- AEs requiring use of systemic corticosteroids: atezo + plt/gem, 12%; placebo + plt/gem, 6%; atezo alone, 8%

Grande. ESMO 2019. Abstr LBA14_PR.

KEYNOTE-361: First-line Pembrolizumab, Chemotherapy, or Both in Advanced Urothelial Carcinoma

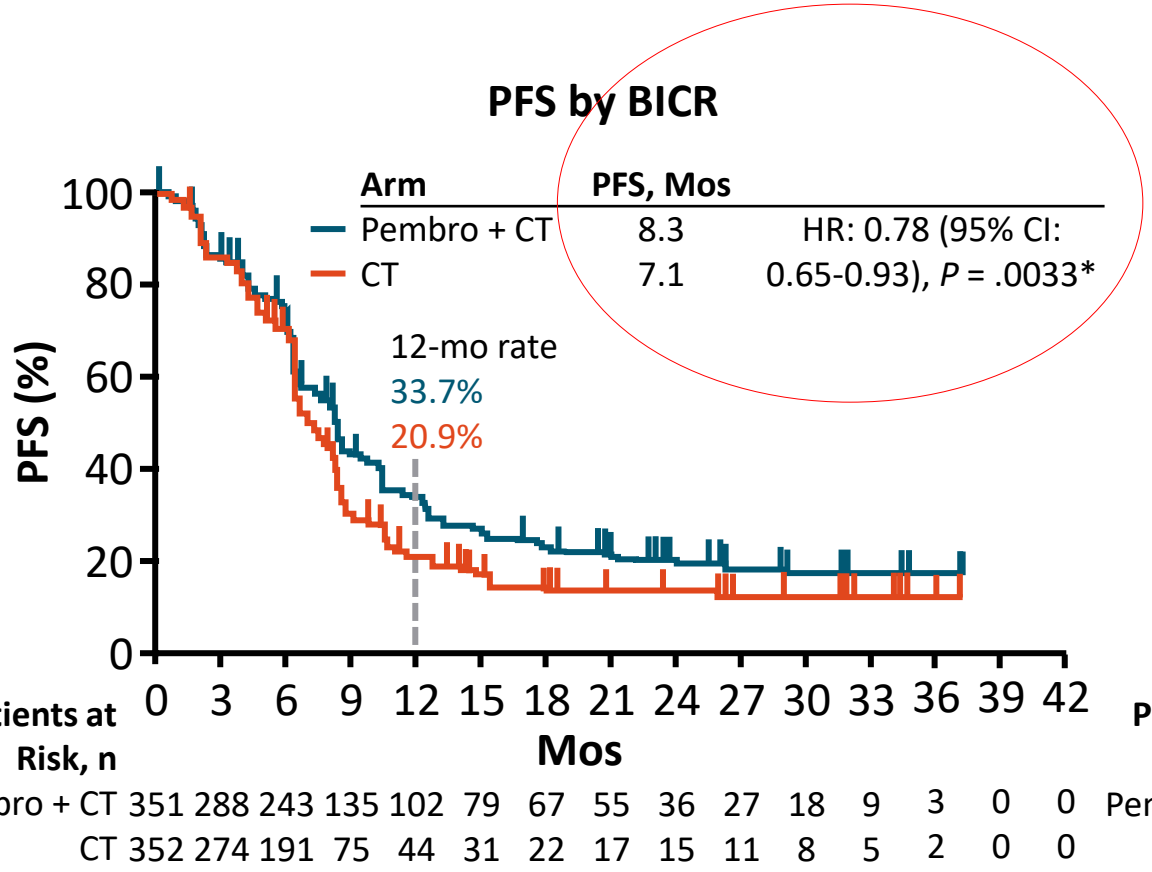
- Randomized, open-label phase III trial

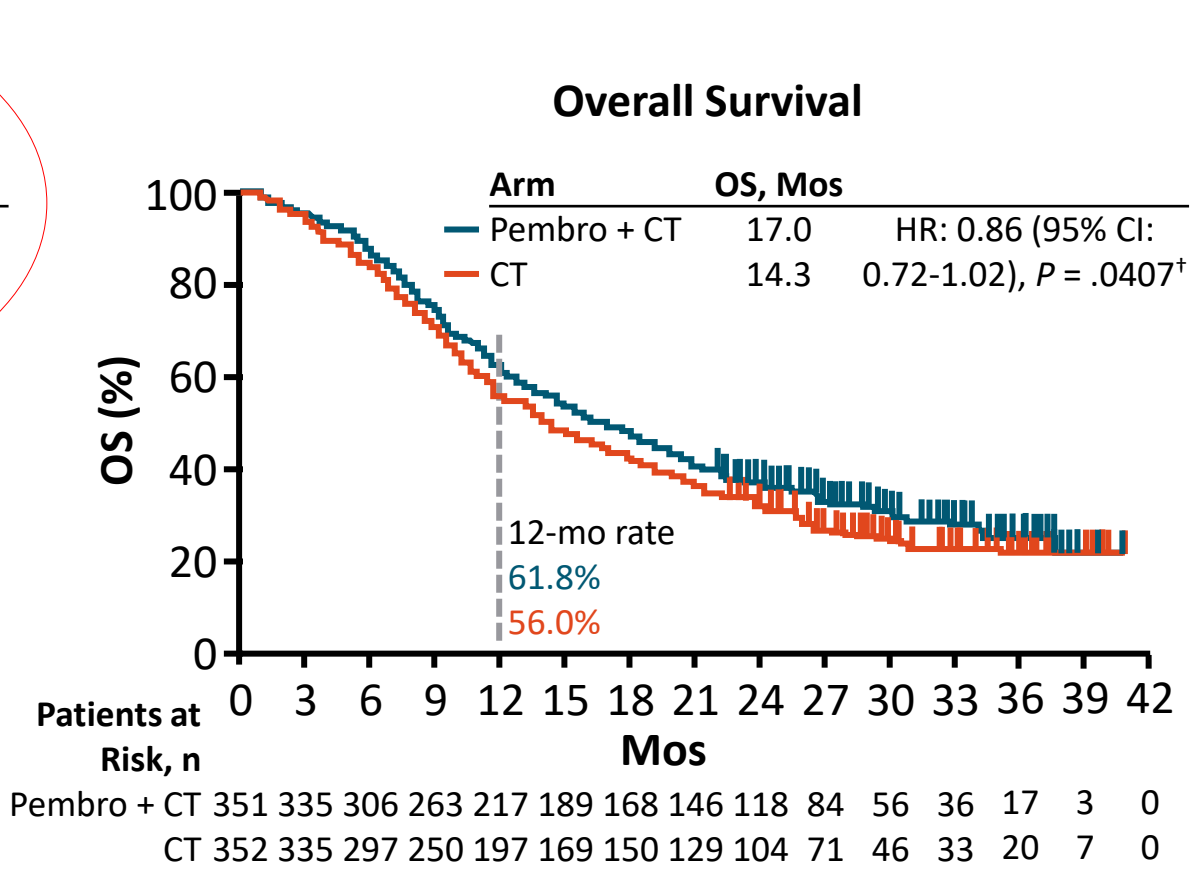


- Primary endpoints: PFS (BICR), OS
- Secondary endpoints: ORR, DCR, DOR (BICR); safety

Alva. ESMO 2020. Abstr LBA23.

KEYNOTE-361: PFS by BICR and OS, Primary Outcomes





- Median PFS by investigator 8.3 mos with pembro + CT vs 6.5 mos with CT; HR: 0.69 (95% CI: 0.59-0.82)

*Boundary for significance at final analysis $P \leq .0019$.

†Boundary for significance at final analysis $P \leq .0142$.

Alva. ESMO 2020. Abstr LBA23. Reproduced with permission.

KEYNOTE-361: OS With Pembrolizumab Alone vs Chemo (Secondary Endpoint)

Median OS, mos	Pembrolizumab (n = 307)	Chemotherapy (n = 352)
Total patient population	15.6	14.3
	HR: 0.92 (95% CI: 0.77-1.11)	

Median OS, mos	Pembrolizumab (n = 160)	Chemotherapy (n = 158)
Patients with PD-L1 CPS ≥ 10	16.1	15.2
	HR: 1.01 (95% CI: 0.77-1.32)	

Response Outcomes	Pembro + Chemo (n = 351)	Pembro (n = 307)	Chemo (n = 352)
ORR, %	54.7	30.3	44.9
DCR, %	80.3	47.2	75.9
Median DOR, mo	8.5	28.2	6.2
▪ 12-mo DOR, %	42.4	65.1	23.5

Alva. ESMO 2020. Abstr LBA23.

KEYNOTE-361: Safety

AE, %	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

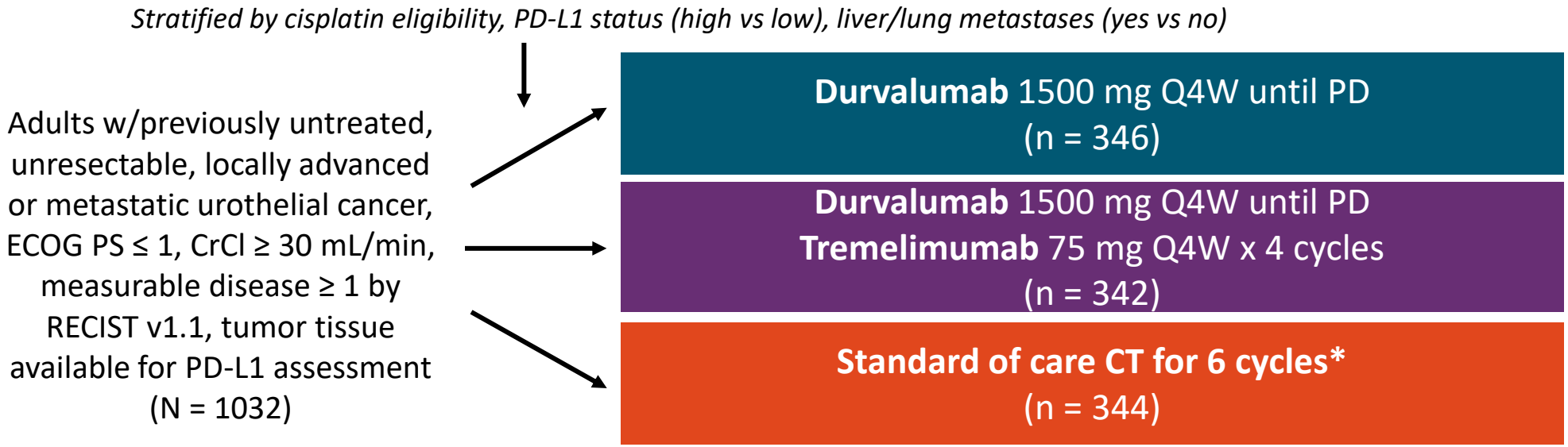
AE, %	Pembro	Chemo
Any grade	95.7	99.7
▪ Grade 3-5	62.9	81.9
Led to death	8.6	2.6
▪ Led to discontinuation	15.9	18.1

- Main AEs (all grades) seen with pembrolizumab + chemo:
  - Anemia
  - Nausea
  - Fatigue
  - Neutropenia
  - Constipation
  - Decreased appetite
  - Diarrhea
  - Vomiting

Alva. ESMO 2020. Abstr LBA23.

DANUBE: First-line Durvalumab ± Tremelimumab vs Chemo for Advanced Urothelial Carcinoma

- Randomized, open-label, multicenter phase III study

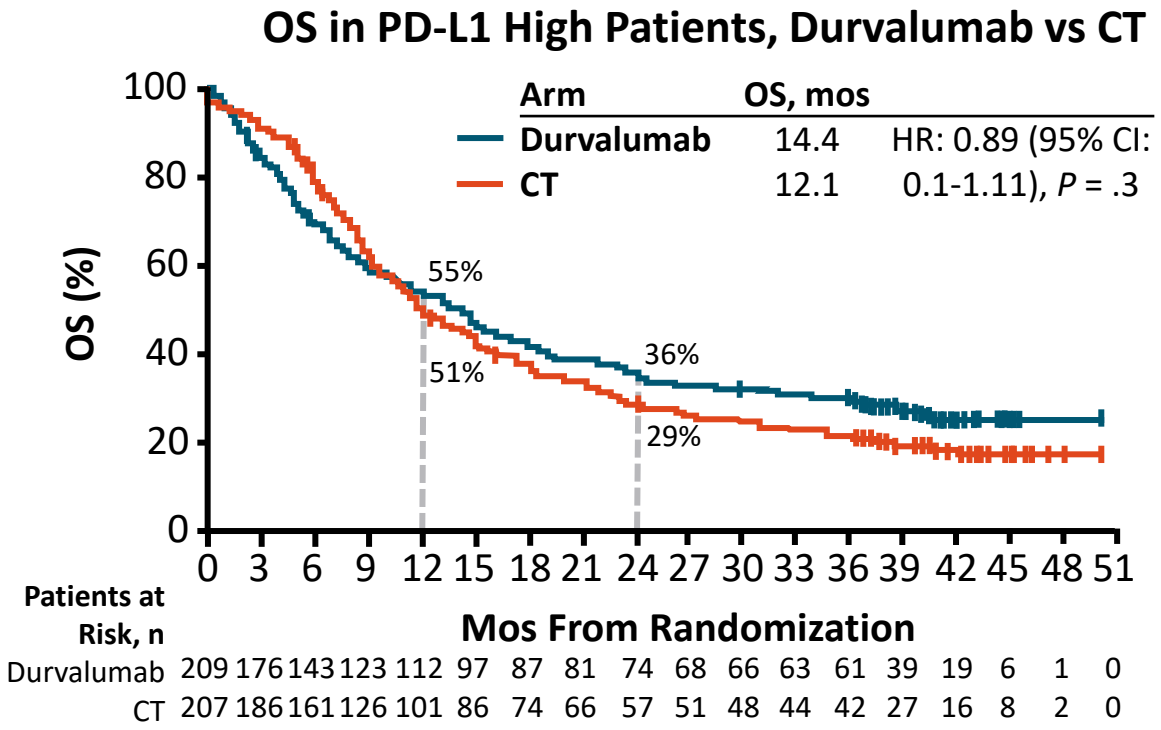


*Gemcitabine + cisplatin or carboplatin for up to 6 cycles.

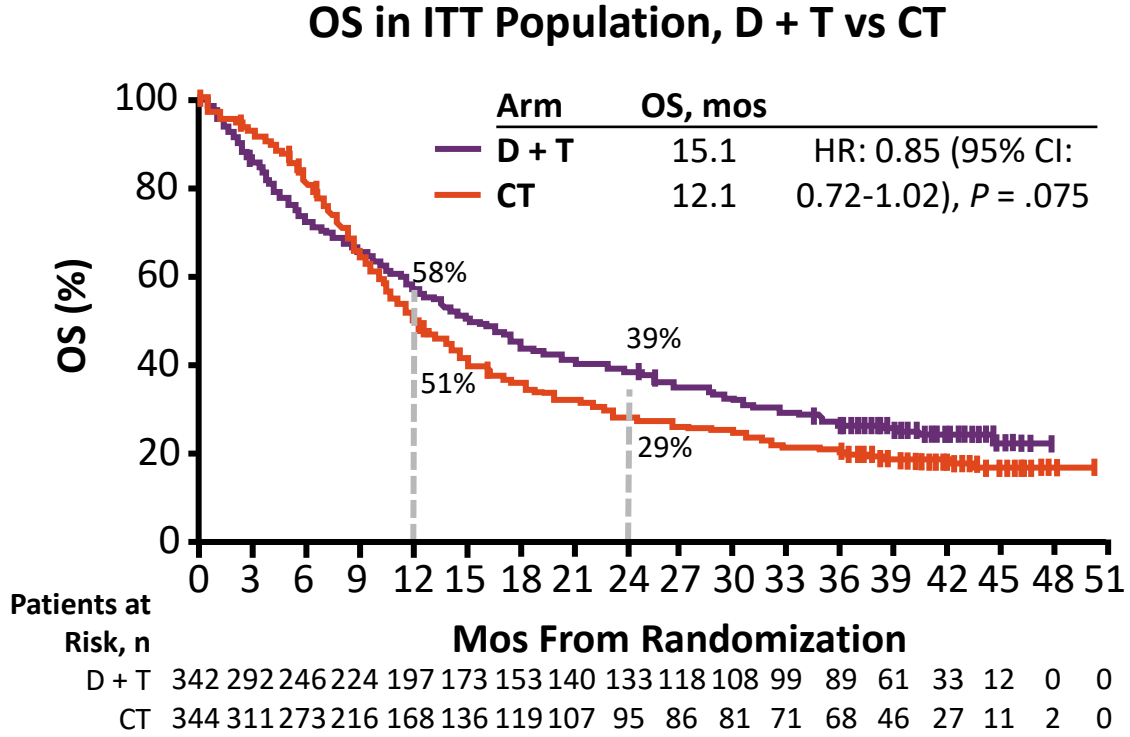
- Primary endpoints: OS with durvalumab vs CT in PD-L1 high patients, OS with durvalumab + tremelimumab vs CT in ITT population
- Secondary endpoints: OS with durvalumab vs CT in ITT population, OS with durvalumab + tremelimumab vs CT in PD-L1 high patients, PFS, ORR, DOR

Powles. ESMO 2020. Abstr 6790. Powles. Lancet Oncol. 2020;[Epub].

DANUBE: Overall Survival, Coprimary Endpoints



- Median OS with durvalumab + tremelimumab vs CT in PD-L1 high patients: 17.9 mos vs 12.1 mos; HR: 0.74 (0.59-0.93)



- Median OS with durvalumab vs CT in ITT population: 13.2 mos vs 12.1 mos; HR: 0.99 (0.83-1.17)

Powles. ESMO 2020. Abstr 6790. Powles. Lancet Oncol. 2020;[Epub].

DANUBE: ORR and PFS

	ITT Population			PD-L1 High Population		
	Durvalumab (n = 346)	Durvalumab + Tremelimumab (n = 342)	CT (n = 344)	Durvalumab (n = 209)	Durvalumab + Tremelimumab (n = 205)	CT (n = 207)
ORR, %	26	36	49	28	47	48
▪ CR, %	8	8	6	10	12	7
▪ PR, %	18	28	43	18	35	41
Median PFS, mos (95% CI)	2.3 (1.9-3.5)	3.7 (3.4-3.8)	6.7 (5.7-7.3)	2.4 (1.9-3.7)	4.1 (3.6-5.7)	5.8 (5.6-7.2)
12-mo PFS, % (95% CI)	16.8 (13.0-21.1)	21.4 (17.2-26.0)	15.3 (11.4-19.7)	21.2 (15.9-27.0)	25.6 (19.7-31.8)	15.0 (10.2-20.7)

Powles. ESMO 2020. Abstr 6790. Powles. Lancet Oncol. 2020;[Epub].

DANUBE: Safety

Events, %	Durvalumab (n = 345)	Durvalumab + Tremelimumab (n = 340)	CT (n = 313)
TRAEs	56	75	90
Grade 3/4	14	28	60
Grade 5	1	1	< 1
Serious TRAEs	9	23	16
TRAEs leading to d/c	6	16	12
TRAEs of special interest*	26	49	15
Grade 3/4	6	12	2
Systemic corticosteroid use	11	26	1

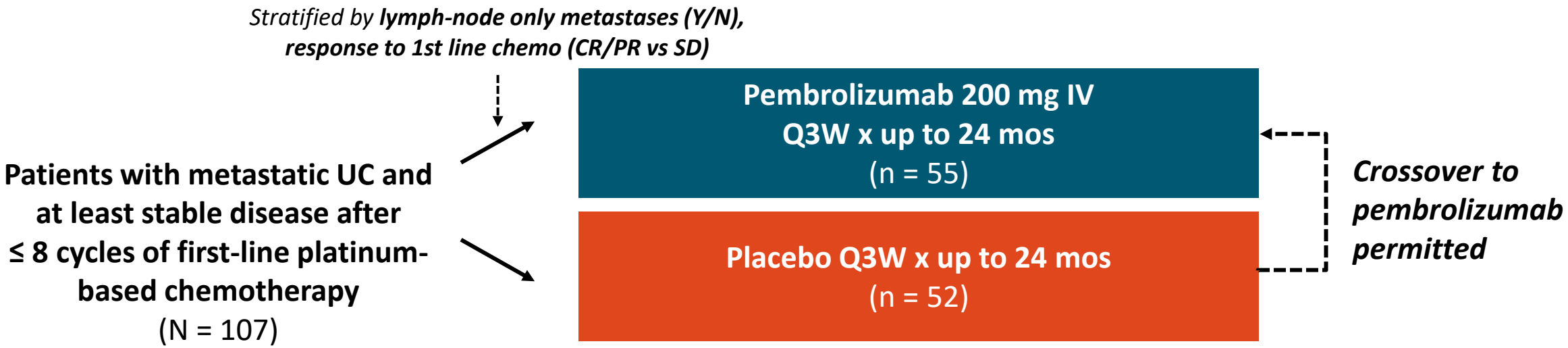
*Excluding infusion/hypersensitivity reactions.

- Most common grade 3/4 TRAEs: increased lipase (in both durvalumab-containing arms), neutropenia, anemia (in CT arm)

Powles. ESMO 2020. Abstr 6790. Powles. Lancet Oncol. 2020;[Epub].

HCRN GU14-182: Maintenance Pembrolizumab After First-line Platinum-Based CT for mUC

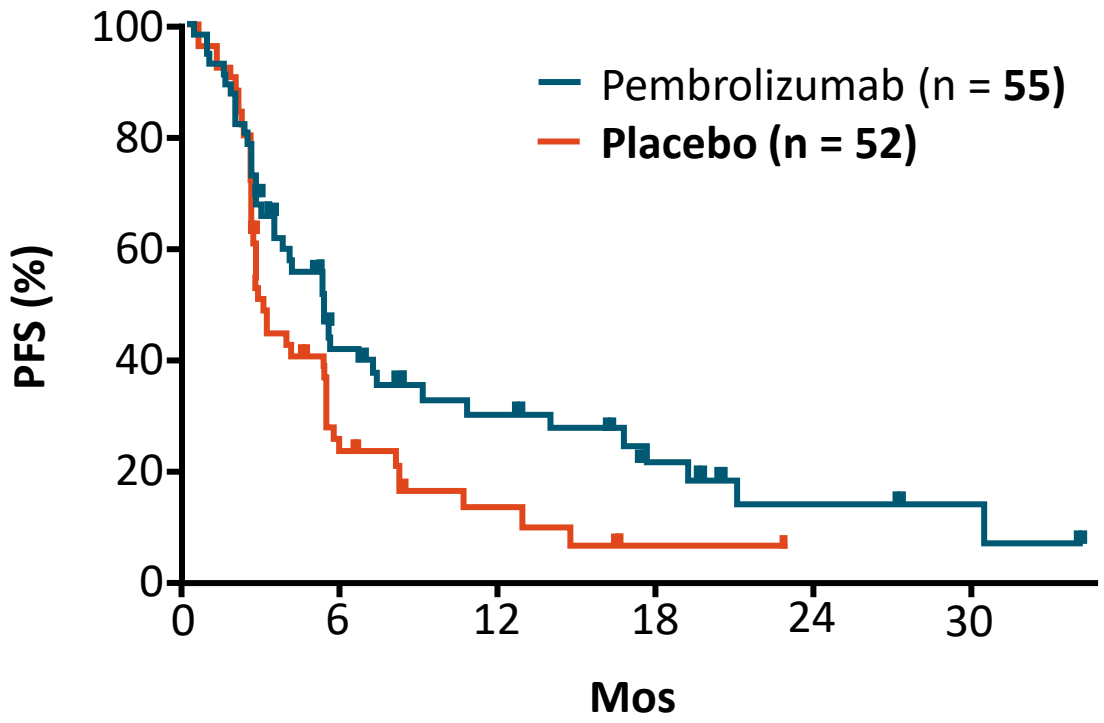
- Double-blind, randomized phase II trial



- Primary endpoint: PFS (irRECIST)
- Secondary endpoints: restricted mean PFS, PFS in PD-L1^{high}, PFS by RECIST 1.1, OS, ORR, and AEs

Galsky. ASCO 2019. Abstr 4504.

HCRN GU14-182: Progression-Free Survival



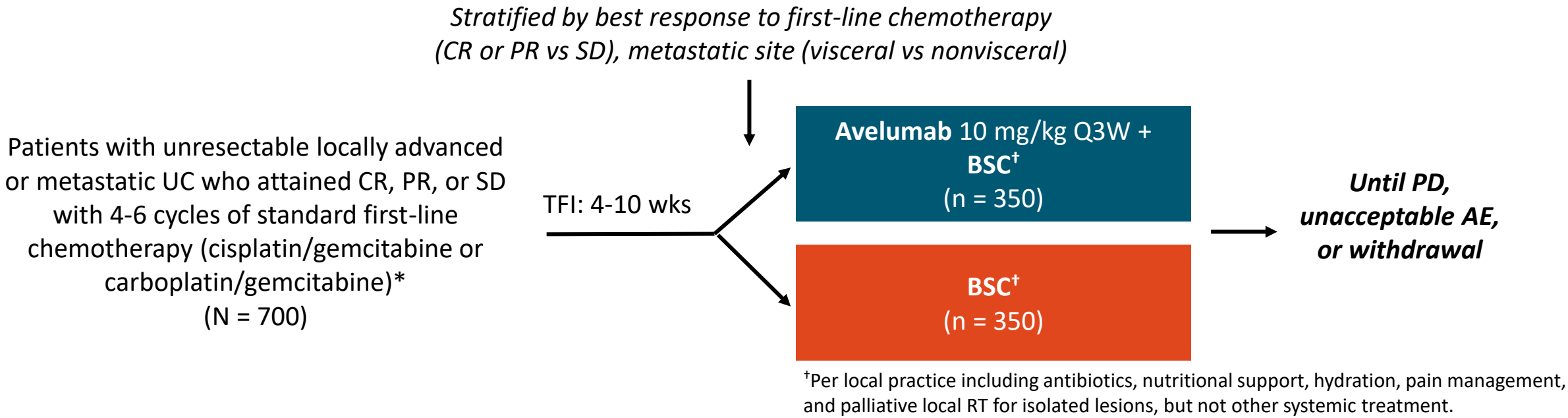
Patients at Risk, n						
Pembrolizumab	55	20	12	7	3	2
Placebo	52	12	4	1	0	0

- Median PFS, mos (95% CI)
  - Pembrolizumab: 5.4 (3.6-9.2)
  - Placebo: 3.2 (2.8-5.5)
- HR: 0.64 (95% CI: 0.41-0.98)
- Log rank *P* = .038

Galsky. ASCO 2019. Abstr 4504.

JAVELIN Bladder 100: Study Design

- Randomized, open-label phase III trial (data cutoff: October 21, 2019)



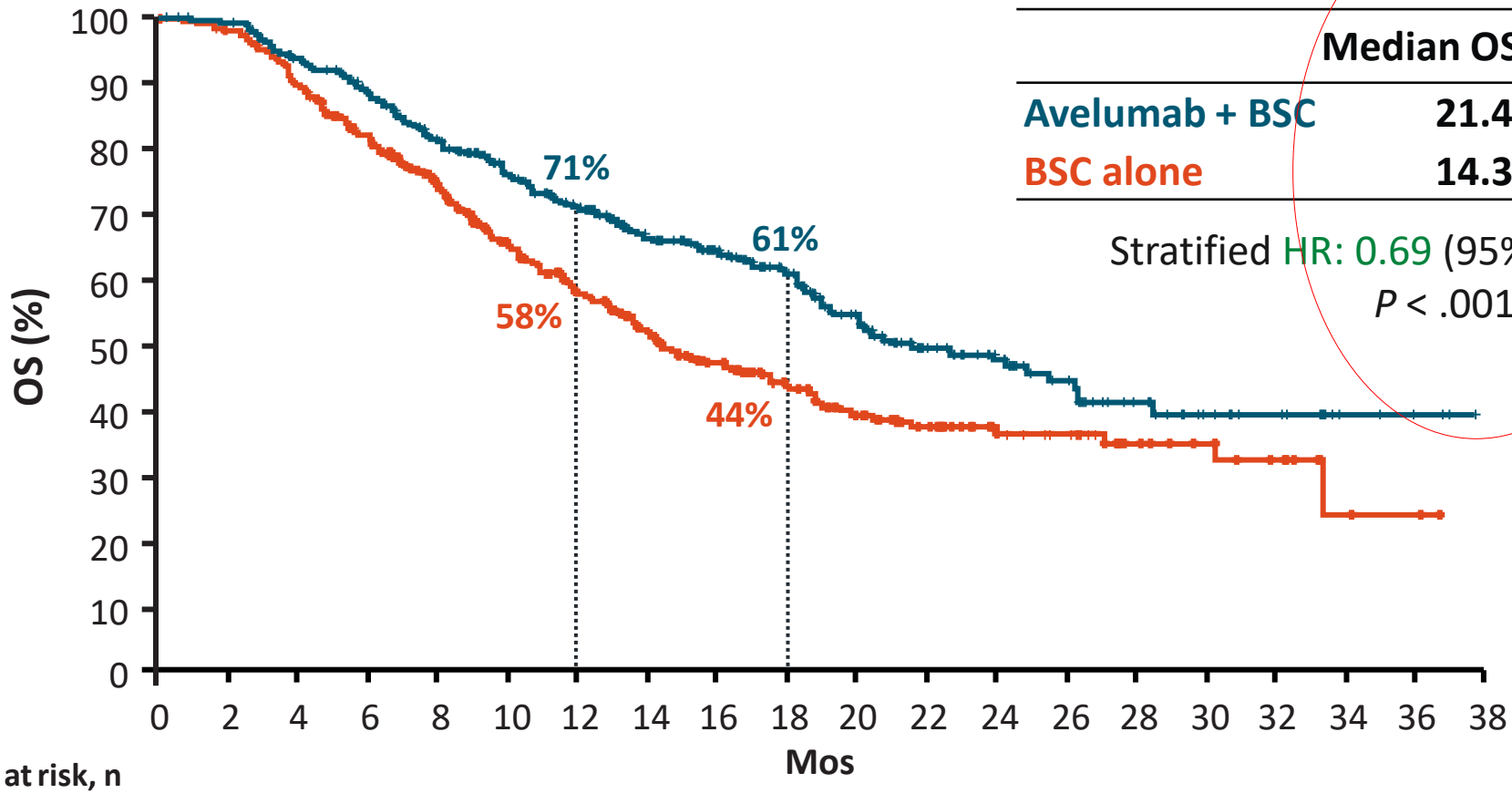
†Per local practice including antibiotics, nutritional support, hydration, pain management, and palliative local RT for isolated lesions, but not other systemic treatment.

- Primary endpoint: OS in all randomized patients, PD-L1+ population
- Secondary endpoints: PFS (RECIST v1.1), ORR (RECIST v1.1), safety and tolerability, PROs

*PD-L1+ status using SP263 assay, defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively

Powles. ASCO 2020. Abstr LBA1.

JAVELIN Bladder 100: Avelumab Improves OS in the Overall Study Population



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

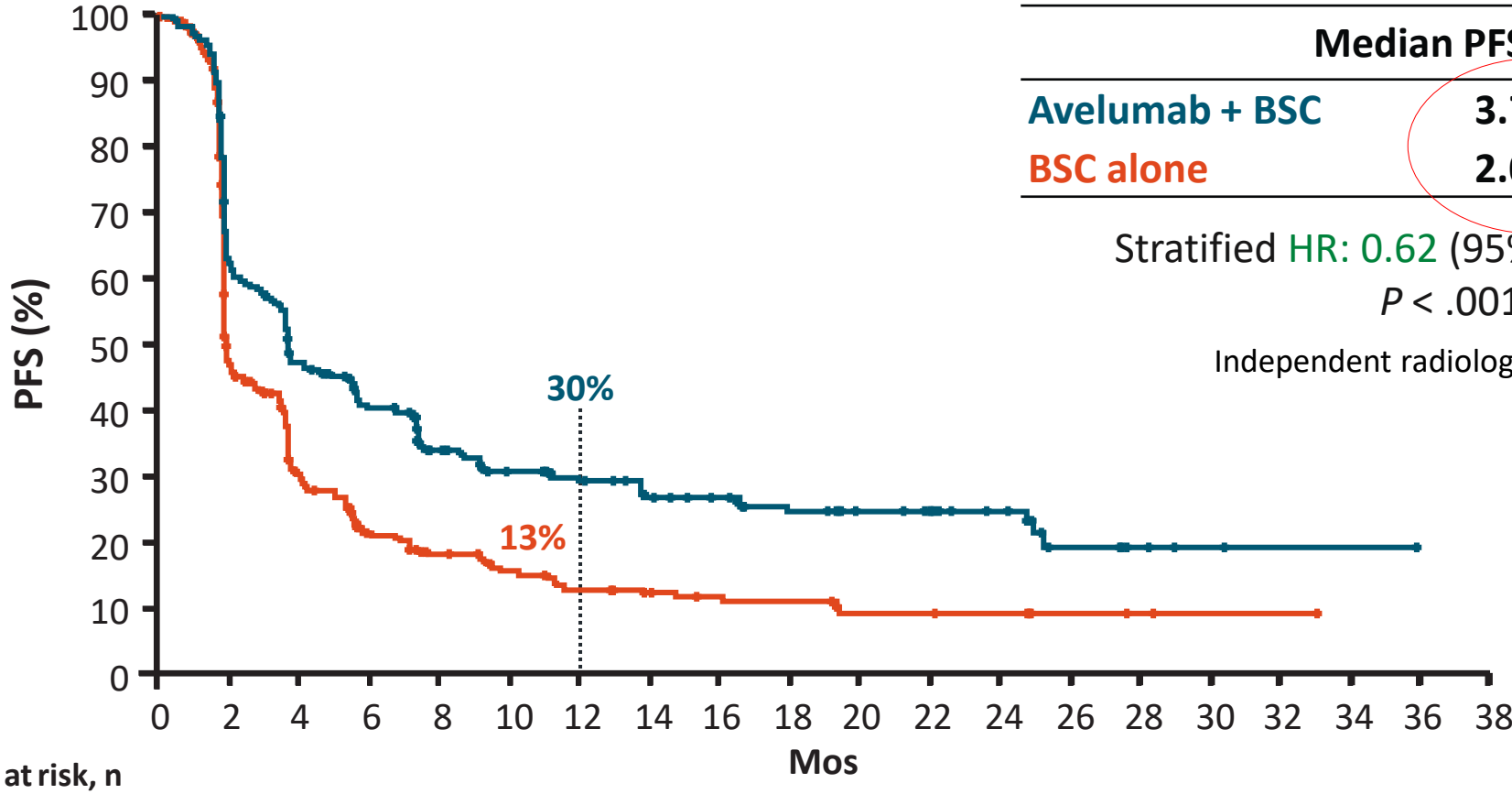
Stratified HR: 0.69 (95% CI: 0.56-0.86)
P < .001

Patients at risk, n																			
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 randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (*P* < .0053)

Powles. ASCO 2020. Abstr LBA1.

JAVELIN Bladder 100: Avelumab Improves PFS in the Overall Study Population



	Median PFS (95% CI), Mos
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 < .001

Independent radiology review

Patients at risk, n																		
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	

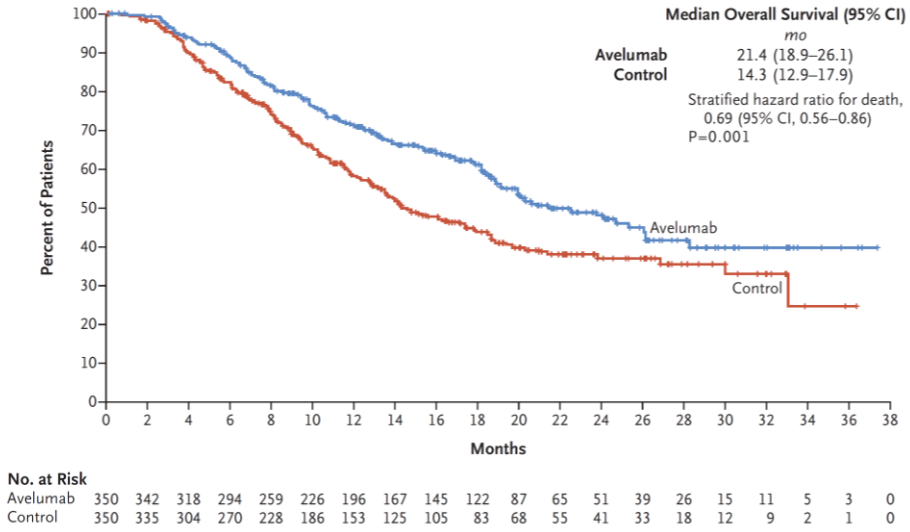
OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (*P* < .0053)

Powles. ASCO 2020. Abstr LBA1.

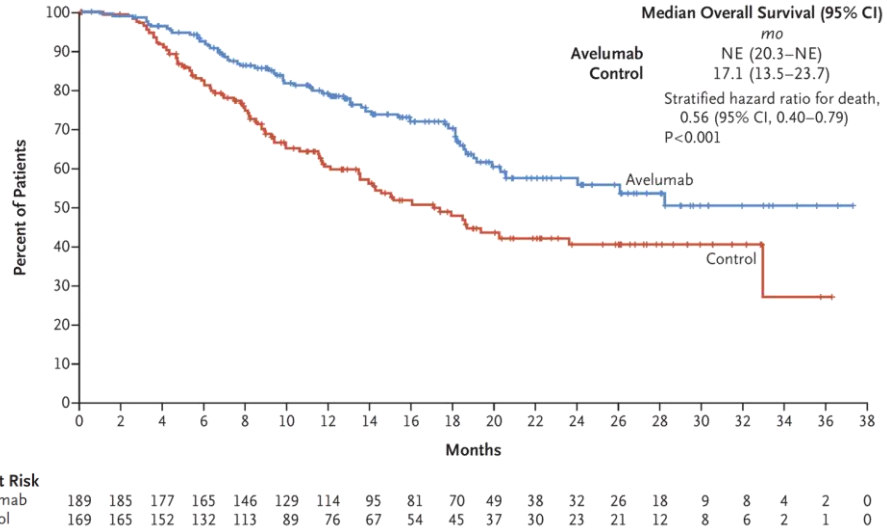
Results: efficacy

OS

Overall Population



PD-L1–Positive Population



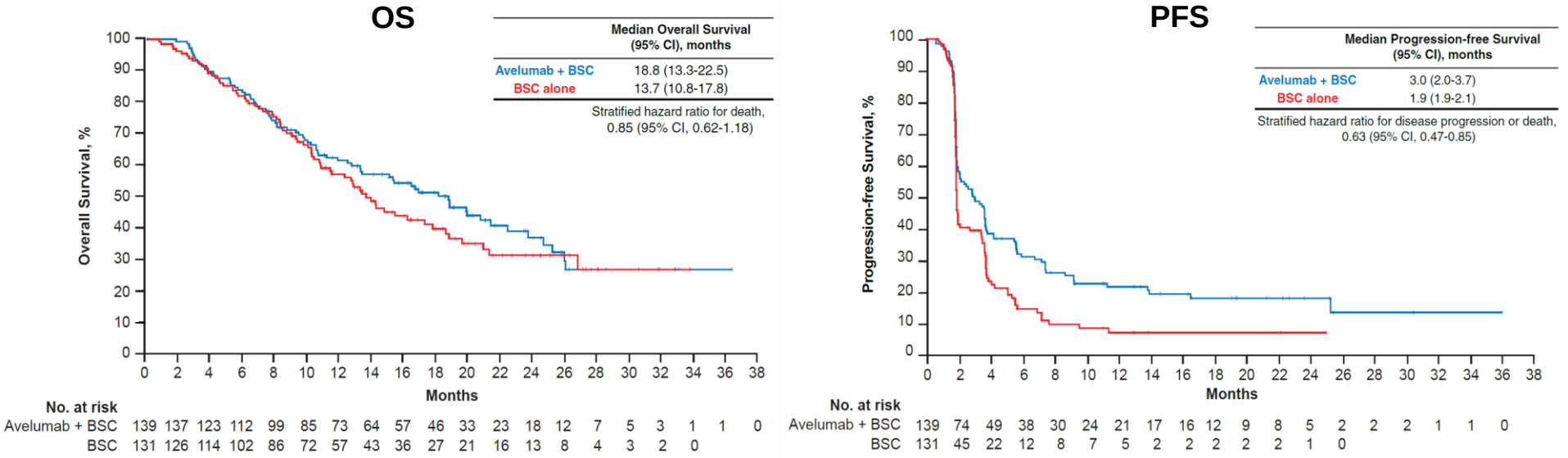
- **In the overall population, OS was significantly longer in the avelumab arm vs the control arm (stratified HR, 0.69; 95% CI, 0.56-0.86; 2-sided P=0.001)**
- **OS at 1-year was 71.3% (95% CI, 66.0-76.0) vs 58.4% (95% CI, 52.7-63.7), respectively**

- **In the PD-L1–positive population, OS was also significantly longer in the avelumab arm vs the control arm (stratified HR, 0.56; 95% CI, 0.40-0.79; 2-sided P<0.001)**
- **OS at 1-year was 79.1% (95% CI, 72.1-84.5) vs 60.4% (95% CI, 52.0-67.7), respectively**

OS was measured from randomization (after chemotherapy).

Results: efficacy

OS and PFS in the PD-L1–negative population

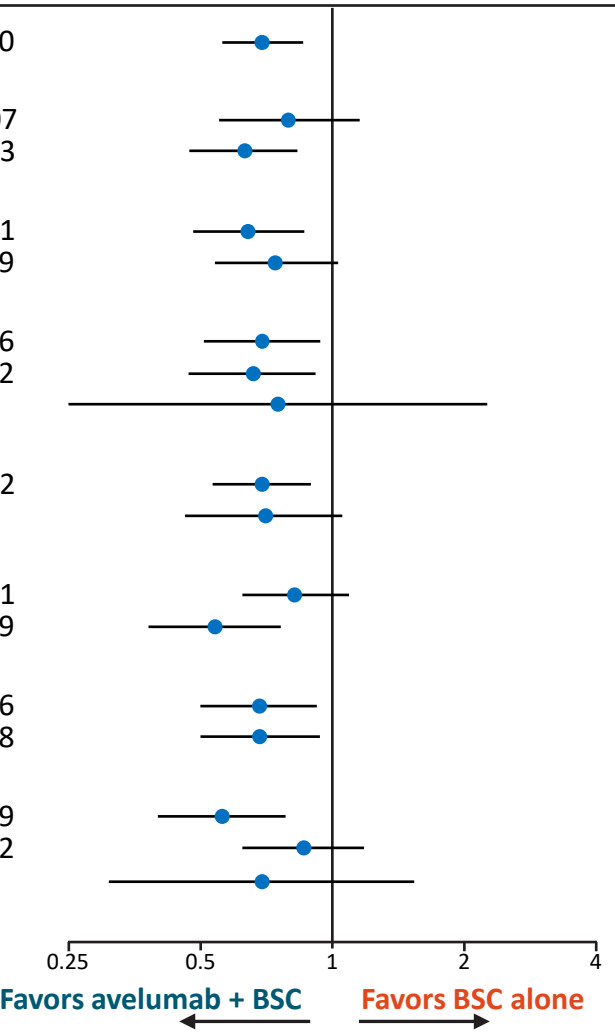


- **Among patients with PD-L1–negative tumors, the stratified HR for OS was 0.85 (95% CI, 0.62-1.18)**
- **In patients with PD-L1–negative tumors, the stratified HR for PFS was 0.63 (95% CI, 0.47-0.85)**

OS and PFS were measured from randomization (after chemotherapy); patient numbers may impact interpretability of subgroup analyses. Exploratory subgroup not part of the planned statistical analyses.

JAVELIN Bladder 100: Subgroup Analysis of OS in the Overall Population

Subgroup		Events/Patients, n: Avelumab + BSC	Events/Patients, n: BSC alone	HR (95% CI)
All patients		145/350	179/350	**0.69** (0.56, 0.86)*
Age	< 65 yrs	61/129	53/107	**0.79** (0.55, 1.15)
	≥ 65 yrs	84/221	126/243	**0.63** (0.47, 0.83)
ECOG PS score	0	77/213	101/211	**0.64** (0.48, 0.86)
	≥ 1	68/137	78/139	**0.74** (0.54, 1.03)
1st-line chemotherapy regimen	Gemcitabine + cisplatin	71/183	98/206	**0.69** (0.51, 0.94)
	Gemcitabine + carboplatin	68/147	73/122	**0.66** (0.47, 0.91)
	Gemcitabine + cisplatin/carboplatin	6/20	7/20	**0.75** (0.25, 2.25)
Best response to 1st-line chemotherapy	CR or PR	104/253	127/252	**0.69** (0.53, 0.89)
	SD	41/97	52/98	**0.70** (0.46, 1.05)
Site of baseline metastasis	Visceral	93/191	101/191	**0.82** (0.62, 1.09)
	Nonvisceral	52/159	78/159	**0.54** (0.38, 0.76)
Creatinine clearance	≥60 mL/min	74/181	97/196	**0.68** (0.50, 0.92)
	<60 mL/min	71/168	81/148	**0.68** (0.50, 0.94)
PD-L1 status	Positive	61/189	82/169	**0.56** (0.40, 0.78)
	Negative	76/139	72/132	**0.86** (0.62, 1.18)
	Unknown	8/22	25/49	**0.69** (0.31, 1.53)



Error bars show 95% CI

*Stratified (all other analyses are unstratified)

Powles. ASCO 2020. Abstr LBA1.

JAVELIN Bladder 100: Avelumab Improves Response

Response	Overall Population (N = 700)		PD-L1+ Population (n = 358)	
	Avelumab + BSC (n = 350)	BSC (n = 350)	Avelumab + BSC (n = 189)	BSC (n = 169)
ORR, % (95% CI)	9.7 (6.8-13.3)	1.4 (0.5-3.3)	13.8 (9.2-19.5)	1.2 (0.1-4.2)
Stratified odds ratio (95% CI)	7.464 (2.824-24.445)		12.669 (3.160-114.115)	
Best overall response, %				
▪ CR	6.0	0.9	9.5	0.6
▪ PR	3.7	0.6	4.2	0.6
▪ SD	12.6	13.1	10.1	13.6
▪ Non-CR/non-PD	18.9	12.9	20.1	13.0
▪ PD	37.1	48.3	31.2	48.5
▪ Not evaluable	21.7	24.3	24.9	23.7
DCR, %	41.1	27.4	43.9	27.8

Powles. ASCO 2020. Abstr LBA1.

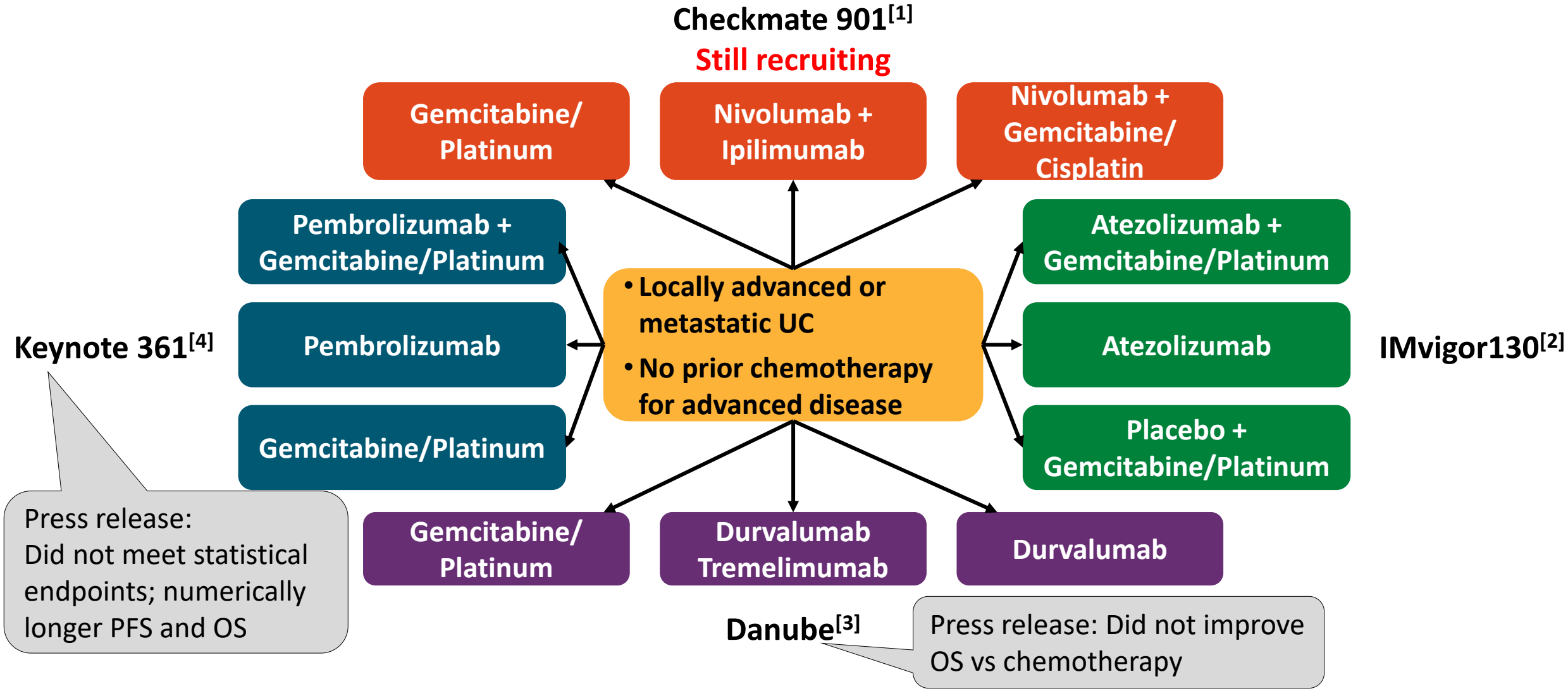
JAVELIN Bladder 100: Immune-Related AEs

Immune-Related AEs, %	Avelumab + BSC (n = 344)	
	Any Grade	Grade ≥ 3
Any	29.4	7.0
Hypothyroidism	10.2	0.3
Rash	4.9	0.3
Hyperthyroidism	4.7	0
Rash maculopapular	2.3	0.3
Pruritus	2.0	0
Pneumonitis	1.5	0.3
Colitis	0.9	0.6
Increased ALT	0.9	0.9
Increased AST	0.6	0.6
Hyperglycemia	0.9	0.9
Myositis	0.6	0.6

- No grade 4/5 immune-related AEs reported
- 9.0% of patients in avelumab arm received high-dose corticosteroids (≥ 40 mg total daily prednisone or equivalent) for management of immune-related AEs

Powles. ASCO 2020. Abstr LBA1.

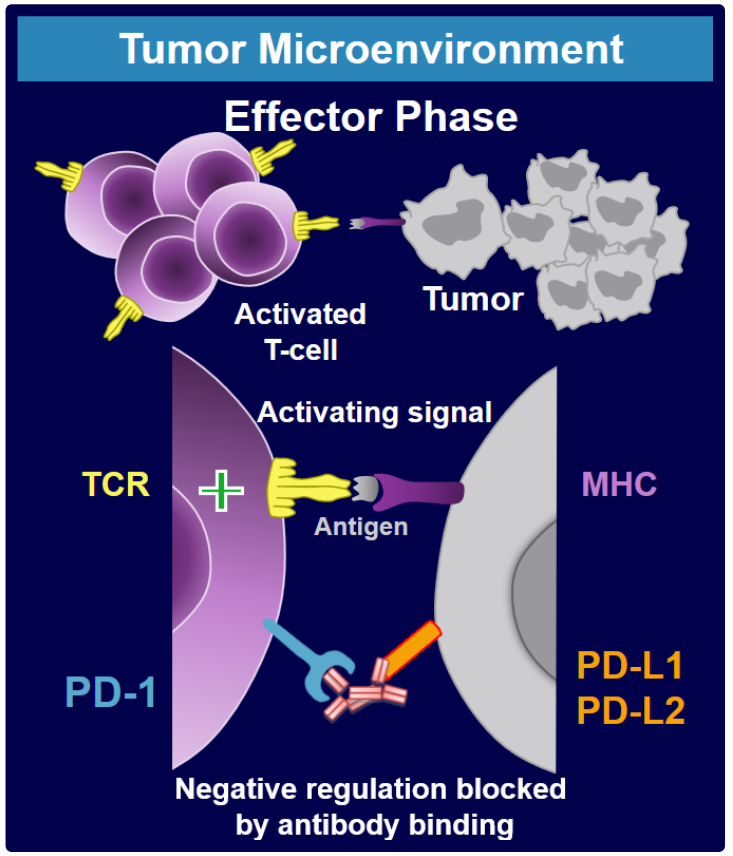
İlk sıra tedavi



1. NCT03036098. 2. Grande. ESMO 2019. Abstr LBA14_PR. 3. NCT02516241. 4. NCT02853305.

Platin bazlı tedavi sonrası tedavi (2.sıra tedavi)

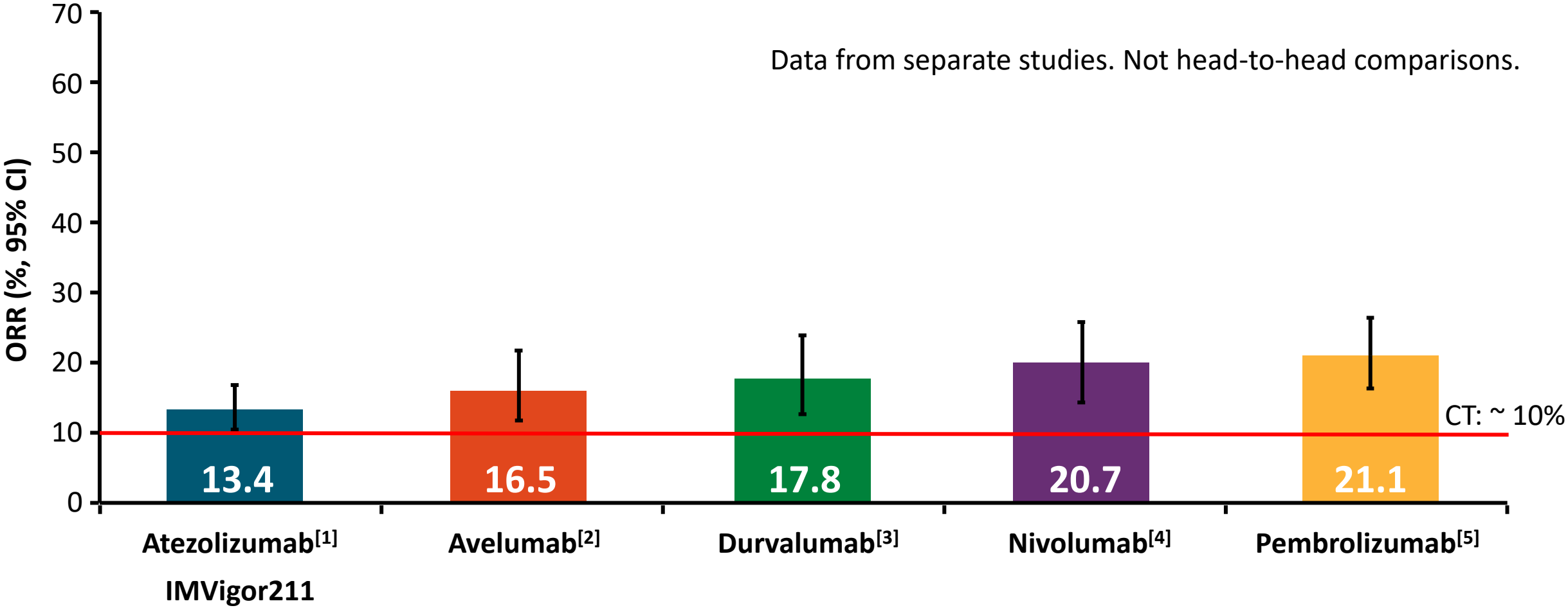
Agent	Target	Dosing Schedule	Post Platinum
Atezolizumab	PD-L1	840 mg Q2W 1200 mg Q3W 1680 mg Q4W	Accelerated
Nivolumab	PD-1	240 mg Q2W 480 mg Q4W	Accelerated
Durvalumab	PD-L1	10 mg/kg Q2W	Accelerated
Avelumab	PD-L1	800 mg Q2W	Accelerated
Pembrolizumab	PD-1	200 mg Q3W 400 mg Q6W	Level 1*



*Dosing regimen of 400 mg every 6 wks is approved under accelerated approval.

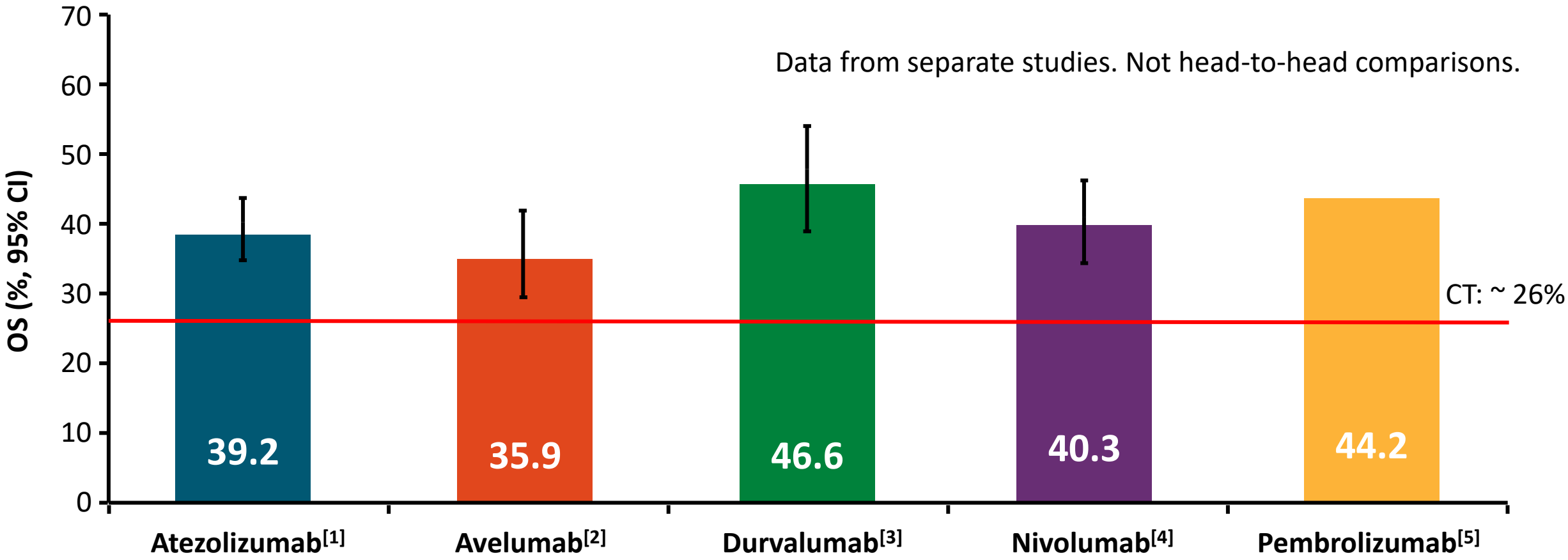
Image adapted from Ribas. NEJM. 2012;366:2517.

Overall Response to Immunotherapy in Bladder Cancer After Platinum Therapy



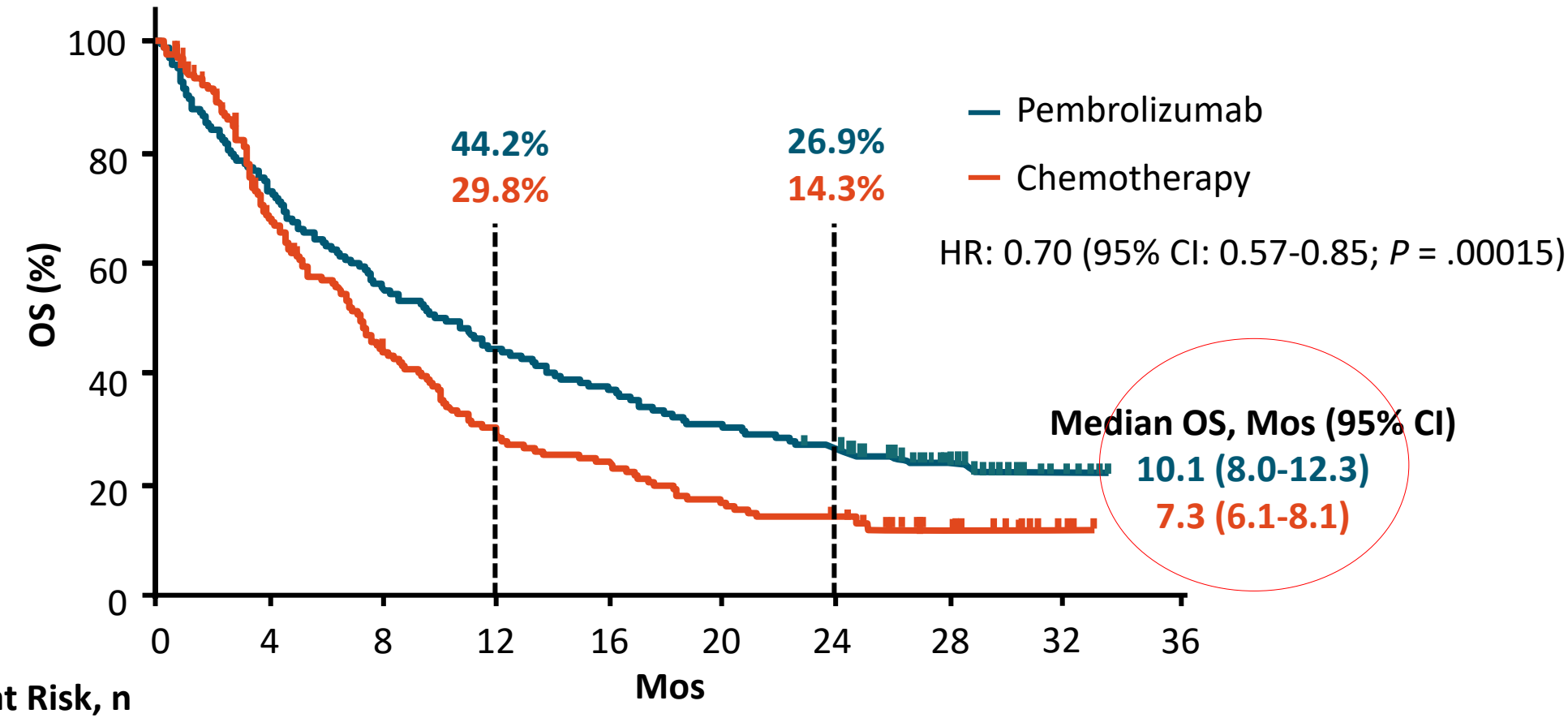
1. Powles. Lancet. 2018;391:748. 2. Apolo. GU ASCO 2019. Abstr 425. 3. Powles. JAMA Oncol. 2017;3:e172411.
4. Siefker-Radtke. ASCO 2019. Abstr 4524. 5. Fradet. Ann Oncol. 2019;30:970.

12-Mo OS in Bladder Cancer After Platinum Therapy



1. Powles. Lancet. 2018;391:748. 2. Apolo. GU ASCO 2019. Abstr 425. 3. O'Donnell. AACR 2018. Abstract CT031.
4. Siefker-Radtke. ASCO 2019. Abstr 4524. 5. Fradet. Ann Oncol. 2019;30:970.

Phase III KEYNOTE-045: OS with Pembrolizumab in Recurrent UC

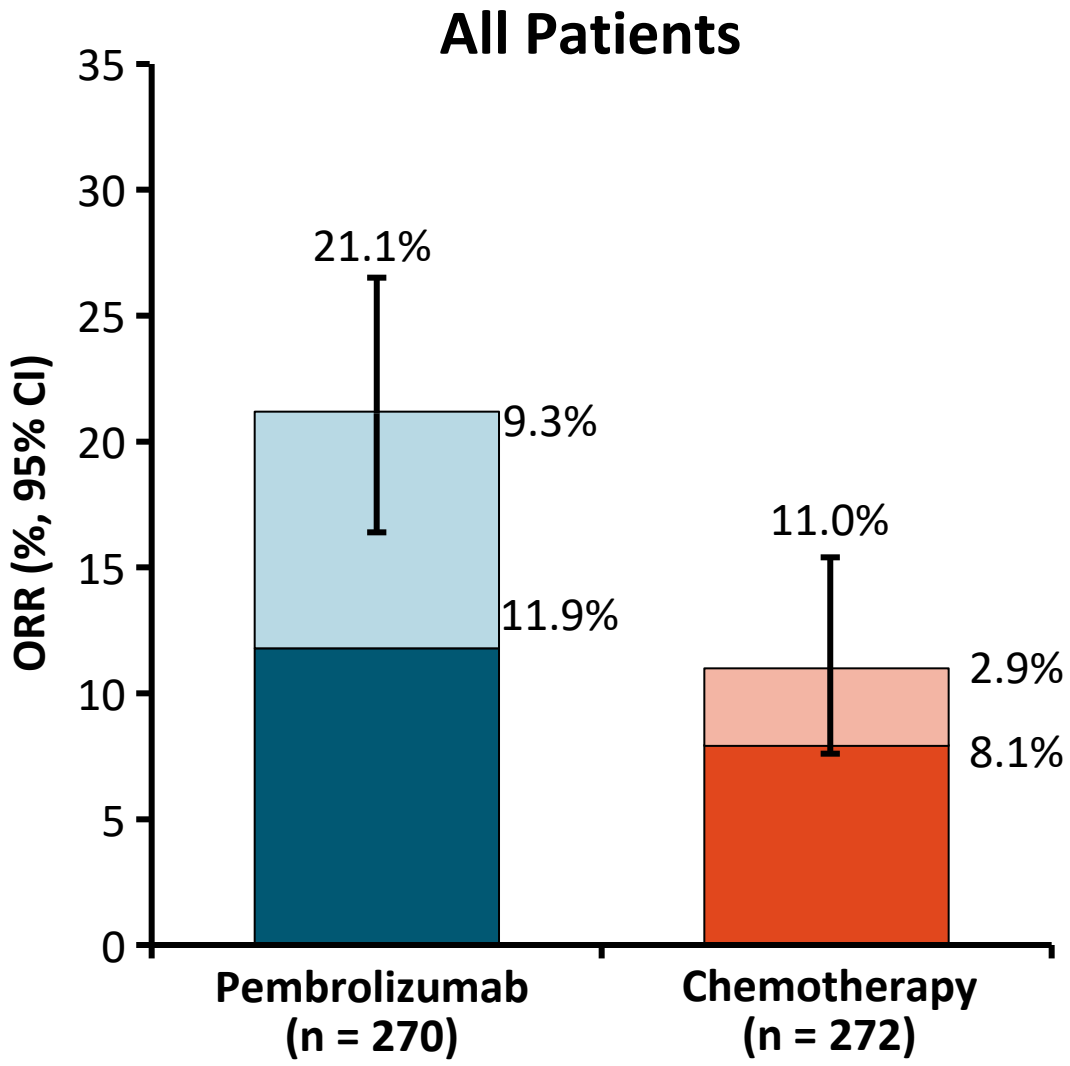


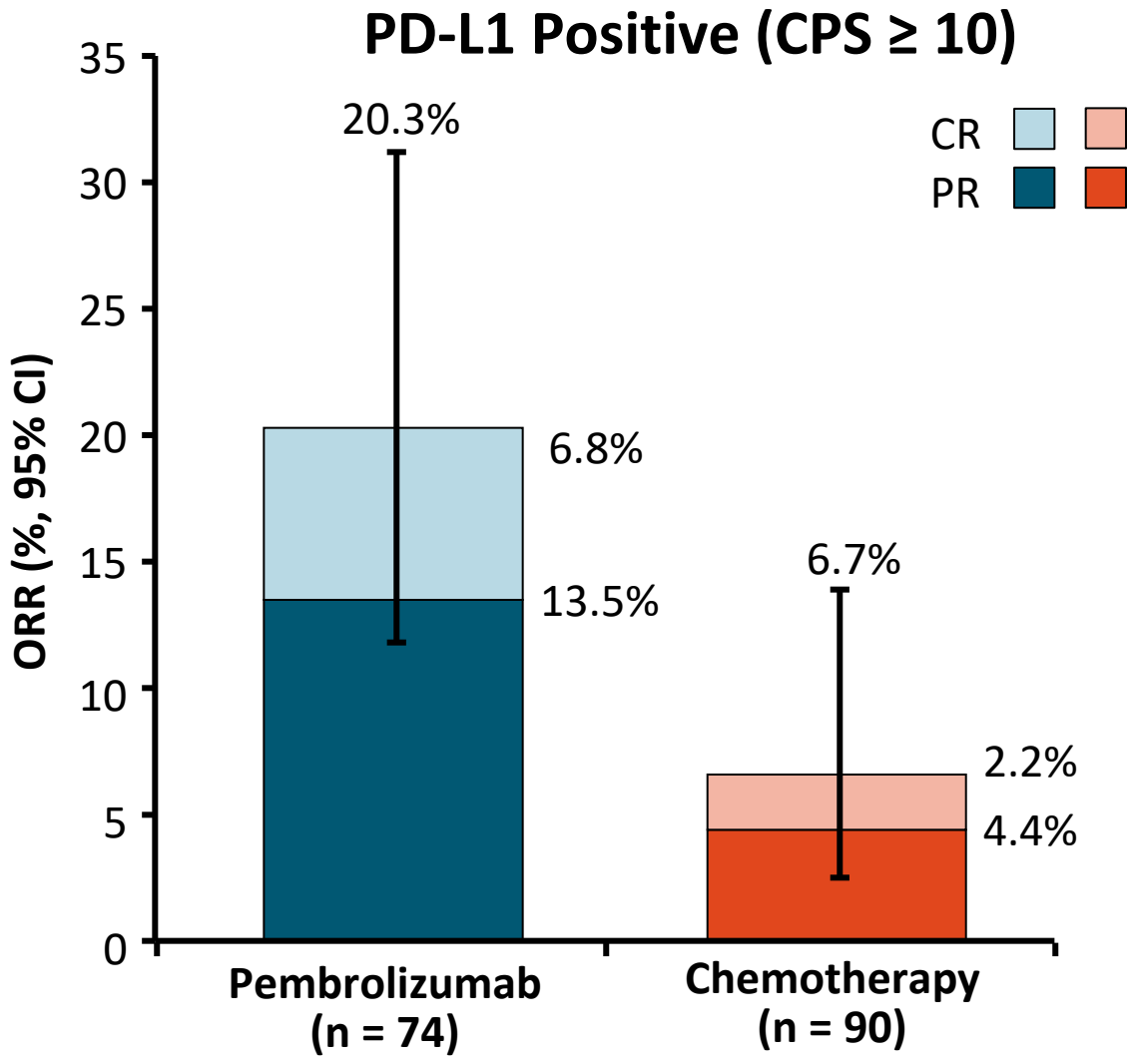
Patients at Risk, n

Pembrolizumab	270	195	148	116	98	80	67	33	7	0
Chemotherapy	272	173	109	73	59	42	34	18	4	0

Fradet. Ann Oncol. 2019;30:970.

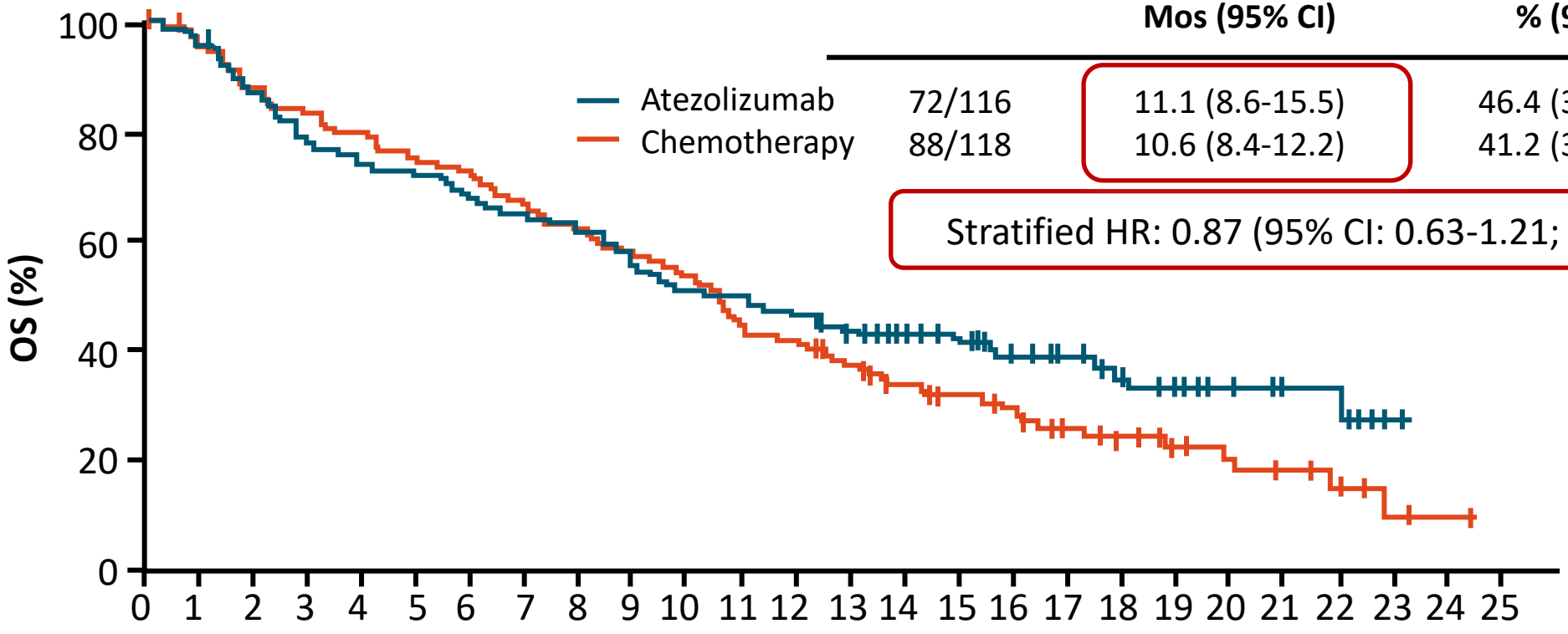
Phase III KEYNOTE-045: Objective Response Rate with Pembrolizumab in Recurrent UC





Fradet. Ann Oncol. 2019;30:970.

Phase III IMvigor211: OS With Atezolizumab vs Chemotherapy for PD-L1+ Postplatinum Advanced UC



	Events/Pts, n	Median OS, Mos (95% CI)	12-Mo OS Rate, % (95% CI)
Atezolizumab	72/116	11.1 (8.6-15.5)	46.4 (37.3-55.6)
Chemotherapy	88/118	10.6 (8.4-12.2)	41.2 (32.2-50.3)

Stratified HR: 0.87 (95% CI: 0.63-1.21; *P* = .41)

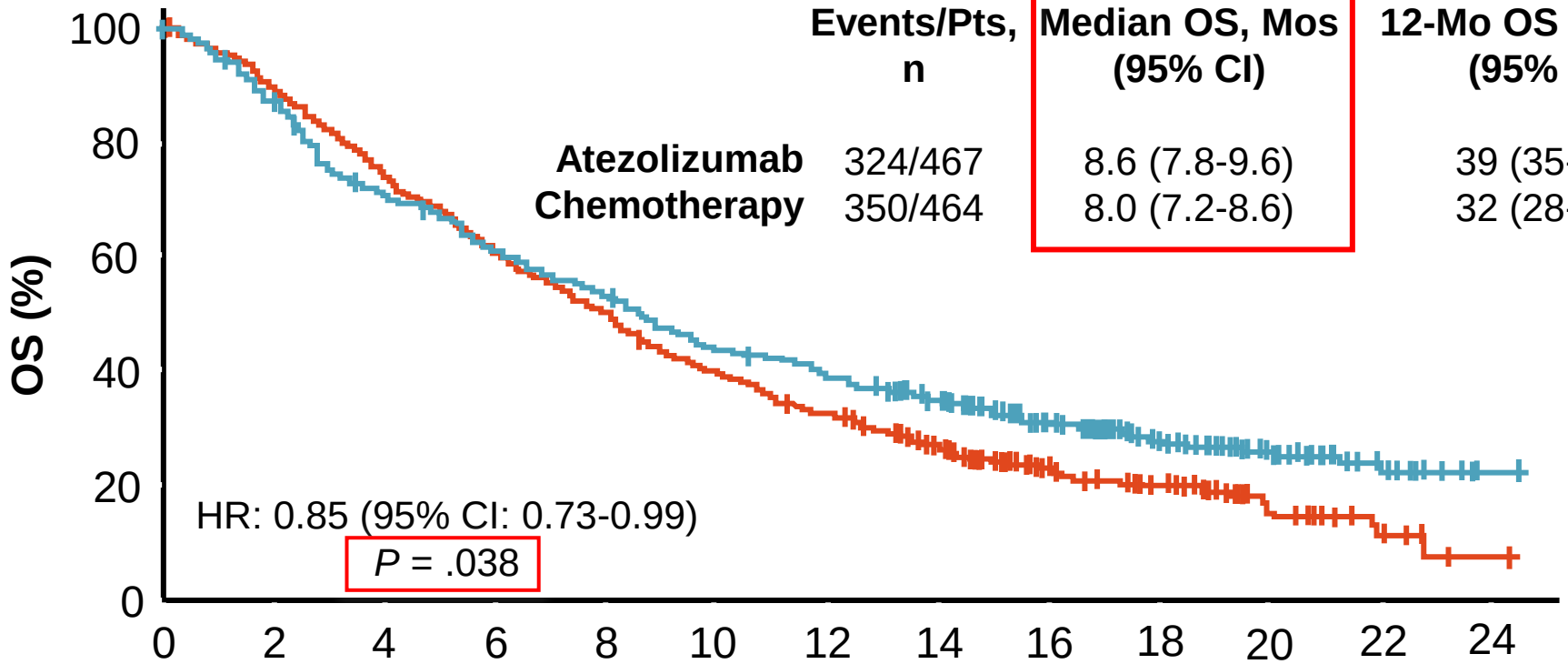
Patients at Risk, n

Atezolizumab	116	112	100	88	85	82	77	73	71	63	58	55	51	47	39	35	27	23	19	15	11	6	6	1	-	-
Chemotherapy	118	109	100	95	91	85	82	75	71	65	61	51	47	41	32	28	24	18	15	11	9	7	5	2	1	-

Powles. Lancet. 2018;391:748.

IMvigor211: OS (ITT Population)

- Median follow-up: 17.3 mos (range: 0-24.5)



	Events/Pts, n	Median OS, Mos (95% CI)	12-Mo OS Rate, % (95% CI)
Atezolizumab	324/467	8.6 (7.8-9.6)	39 (35-44)
Chemotherapy	350/464	8.0 (7.2-8.6)	32 (28-37)

Pts at Risk, n													
Atezolizumab	467	405	327	280	245	201	177	138	90	59	34	13	1
Chemotherapy	464	397	330	268	219	175	140	99	60	42	17	7	1

Powles T, et al. EAS 2017. Powles T, et al. Lancet. 2017;[Epub ahead of print].

Checkmate-275: Study Design

- A multicenter, single-arm phase II trial

Pts with measurable metastatic or locally advanced urothelial carcinoma after recurrence or progression following ≥ 1 platinum-based chemotherapy; ECOG PS 0 or 1; evaluable tumor tissue for biomarker testing (N = 270)

→

Nivolumab
3 mg/kg Q2W
(N = 270)

→

Treated PD and clinical deterioration, unacceptable AE, or protocol-defined decision*

- Primary endpoints: ORR in all pts, ORR in pts with PD-L1 ≥ 5% or ≥ 1%
- Secondary endpoints: PFS, OS, TTR, DoR, safety, QoL

*Pts allowed to continue treatment beyond initial radiographic progression if well tolerated and clinical benefit was noted.

Sharma P, et al. Lancet Oncol. 2017;[Epub ahead of print].

Bladder Cancers With Higher Tumor Mutational Burden Have Higher Response Rates With Nivolumab

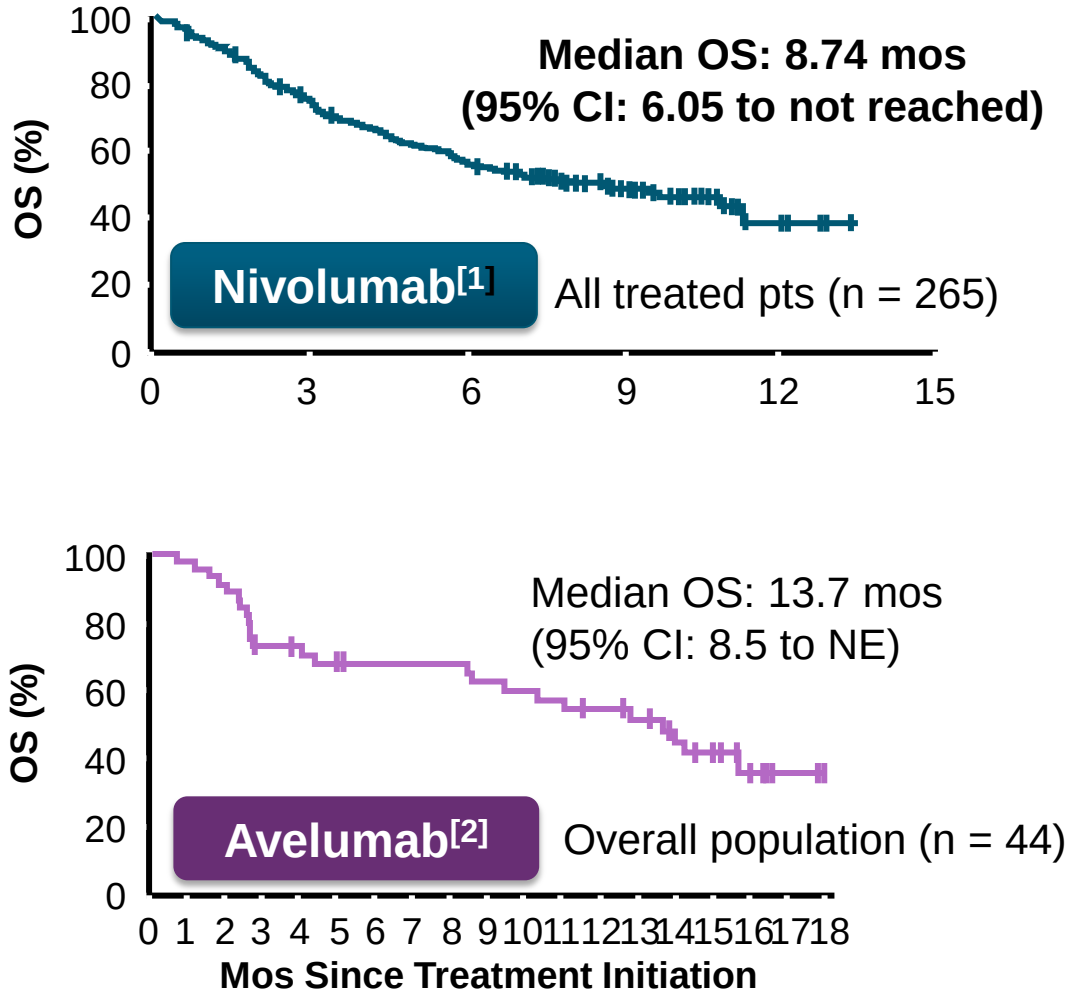
- Exploratory analysis from phase II CheckMate 275 study

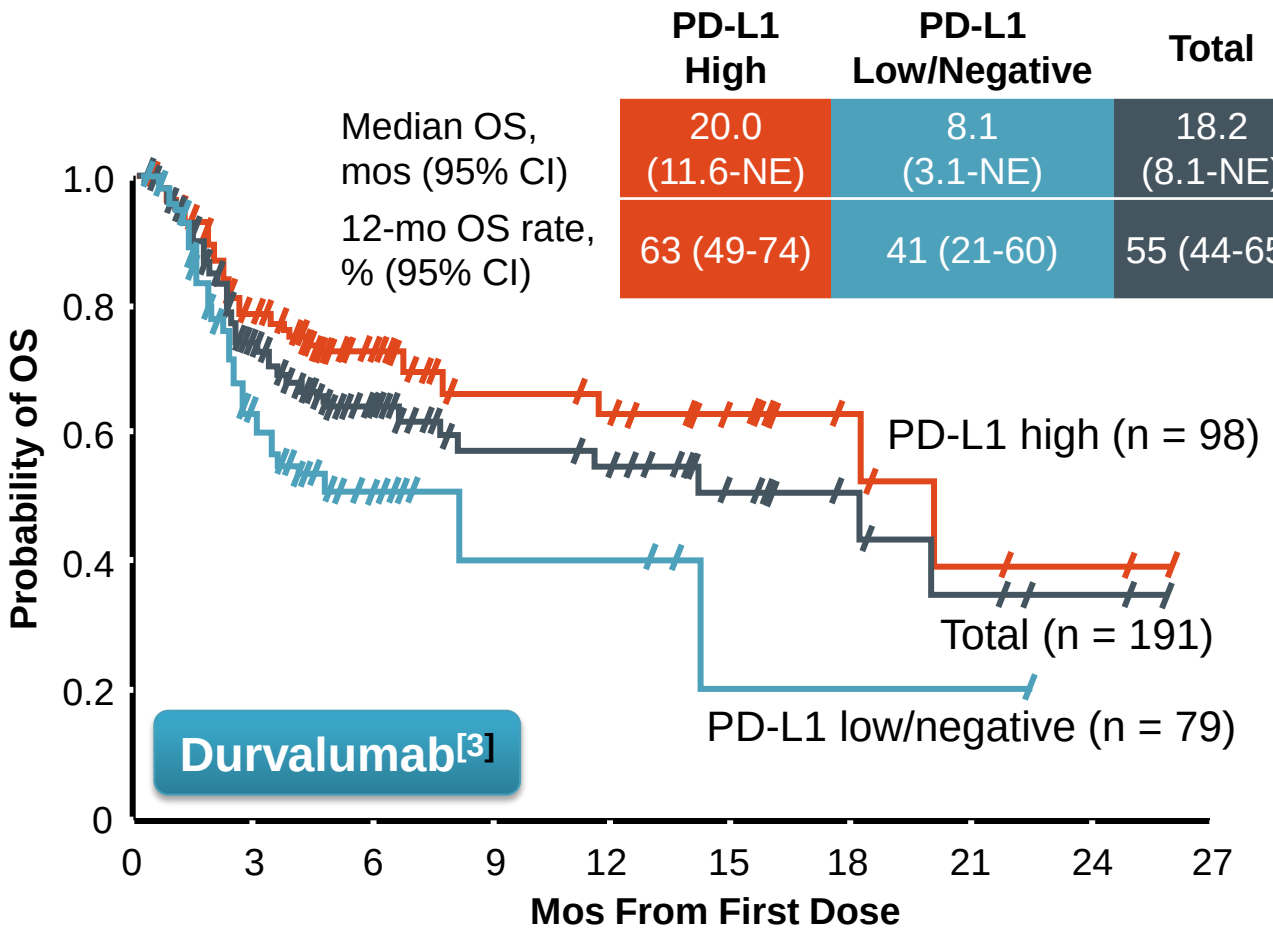
TMB	ORR, %	Median OS, Mos (95% CI)
TMB high (n = 47)	31.9	11.63 (5.82-NR)
TMB medium (n = 46)	17.4	9.66 (4.76-NR)
TMB low (n = 46)	10.9	5.72 (4.21-11.30)

ORR was significantly higher in the subgroup of patients with PD-L1 expression 5% (28.4%) compared to the PD-L1 1% (23.8%) and the PD-L1 negative (16.1%) cohorts.

Galsky. ESMO 2017. Abstract 4951.

Phase II Studies of Immune Checkpoint Inhibitors





Pts at Risk, n 44 43 40 31 30 28 25 25 25 23 22 21 19 17 14 10 6 2 0

1. Sharma P, et al. Lancet Oncol. 2017;18:312-322. 2. Apolo AB, et al. J Clin Oncol. 2017;35:2117-2124.
3. Powles T, et al. JAMA Oncol. 2017 Sep 14;3(9):e172411.

PD-1/PD-L1 Inhibitors in Pts With Advanced UC After Pt-Based Chemotherapy

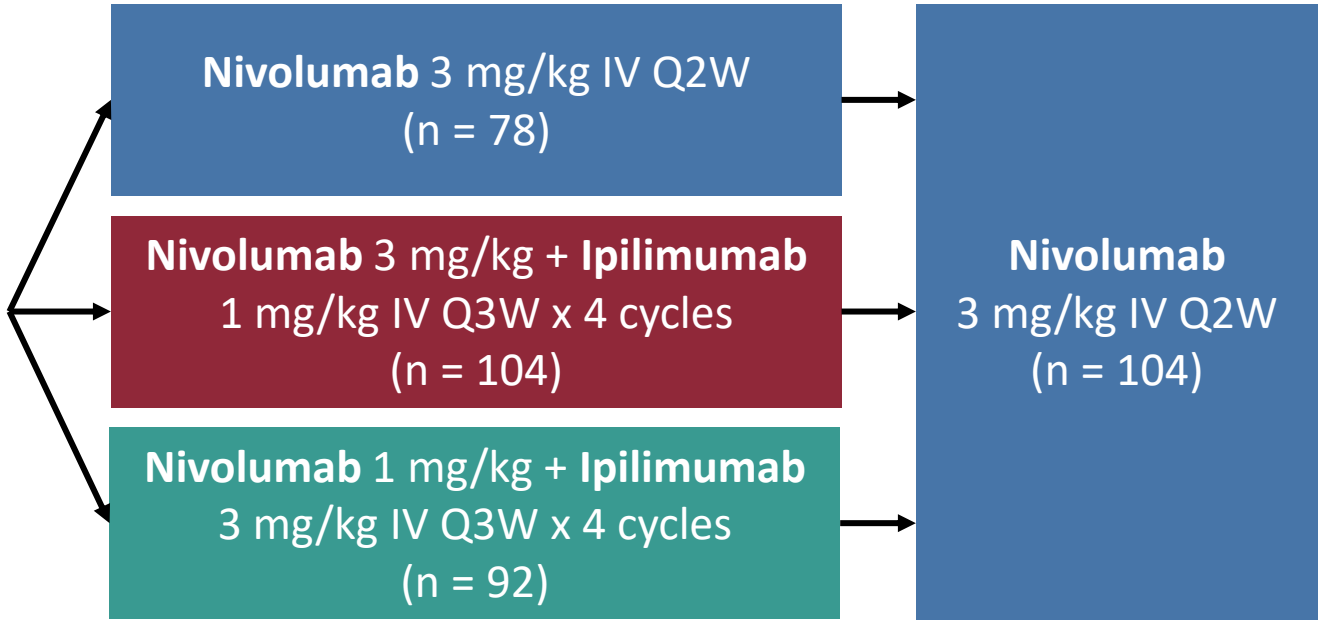
Agent	Phase	N (evaluable)	ORR, % (95% CI)	CR, %	12-Mo OS, % (95% CI)	mOS, Mos	mPFS, Mos
Atezolizumab[1] (IMvigor210)	II	310	16.0 (12.0-20.0)	6.0	37.0 (31.0-42.0)	7.90	2.1
Pembrolizumab[2] (KEYNOTE-045)	III	270	21.1 (16.4-26.5)	7.0	43.9 (37.8-49.9)	10.30	2.1
Durvalumab[3] ENRICHED	I/II	103	20.4 (13.1-29.5)	3.9	51.0 (39.0-62.0)	14.10	2.2
Nivolumab[4] (Checkmate-275)	II	265	19.6 (15.0-24.9)	2.3		8.74	2.0
Avelumab[5] (JAVELIN)	Ib	153	17.6 (12.0-24.6)	5.9			1.6

1. Loriot Y, et al. ESMO 2016. Abstract 783PD. 2. Bellmunt J, et al. N Engl J Med. 2017;[Epub ahead of print].
3. Powles T, et al. ASCO GU 2017. Abstract 286. 4. Sharma P, et al. Lancet Oncol. 2017;[Epub ahead of print].
5. Patel M, et al. ASCO GU 2017. Abstract 330.

CheckMate-032: Nivolumab vs Nivolumab + Ipilimumab in Locally Advanced or Metastatic Urothelial Carcinoma

- Multicenter, international, open-label, randomized phase I/II trial in several tumor types

Locally advanced or metastatic UC; PD within 1 yr of ≥ 1 platinum agent or not chemotherapy candidate; ECOG PS 0-1; brain metastases and autoimmune disease not allowed
(N = 274)

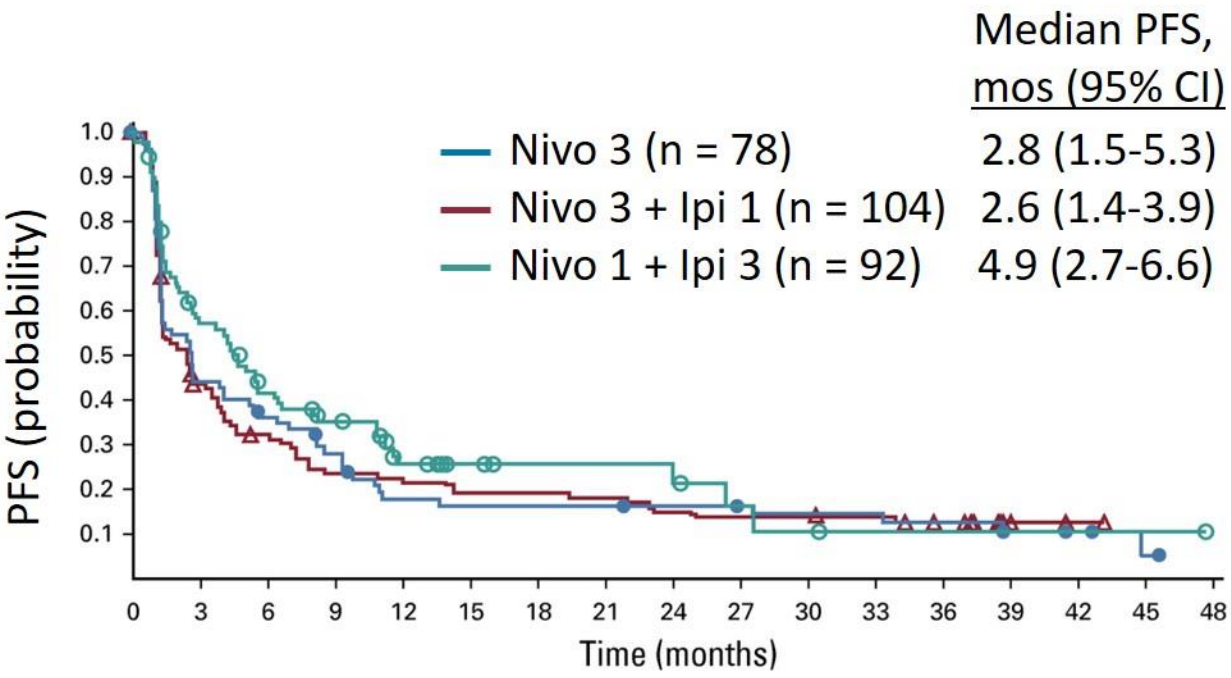


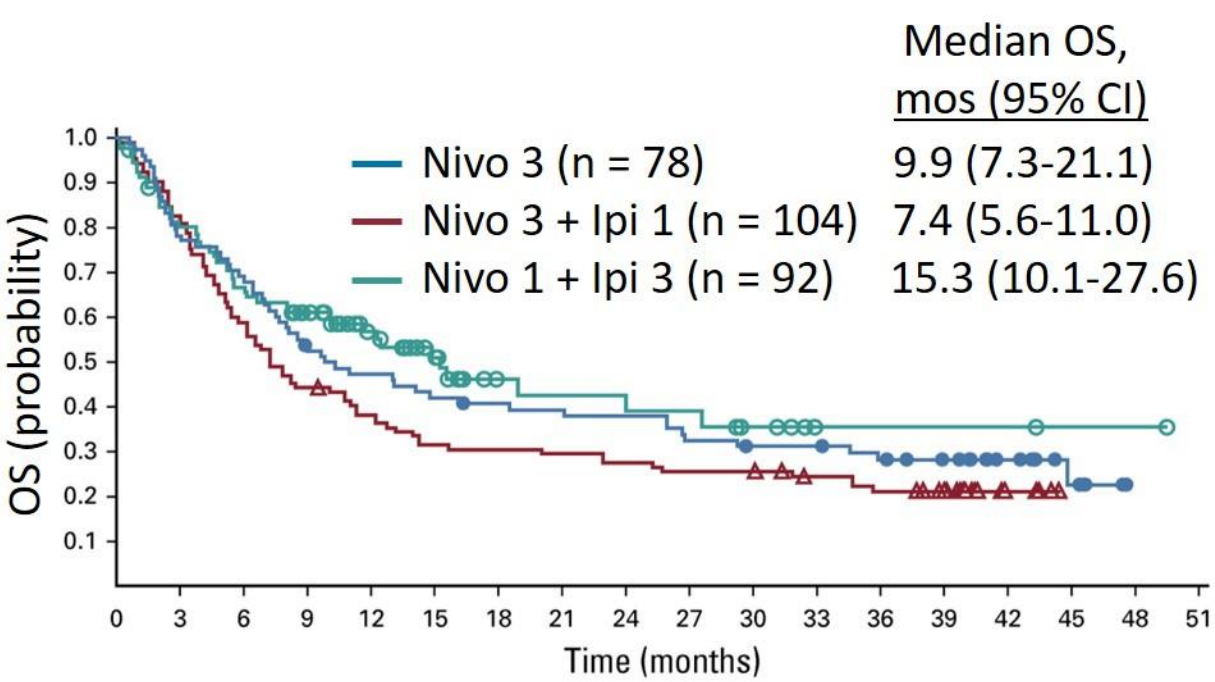
- Primary endpoints: ORR (Investigator, per RECIST 1.1), DoR
- Key secondary endpoints: PFS, OS, safety

Sharma. JCO. 2019;37:1608.

CheckMate-032: Efficacy With Nivolumab ± Ipilimumab in Previously Treated Metastatic Urothelial Carcinoma

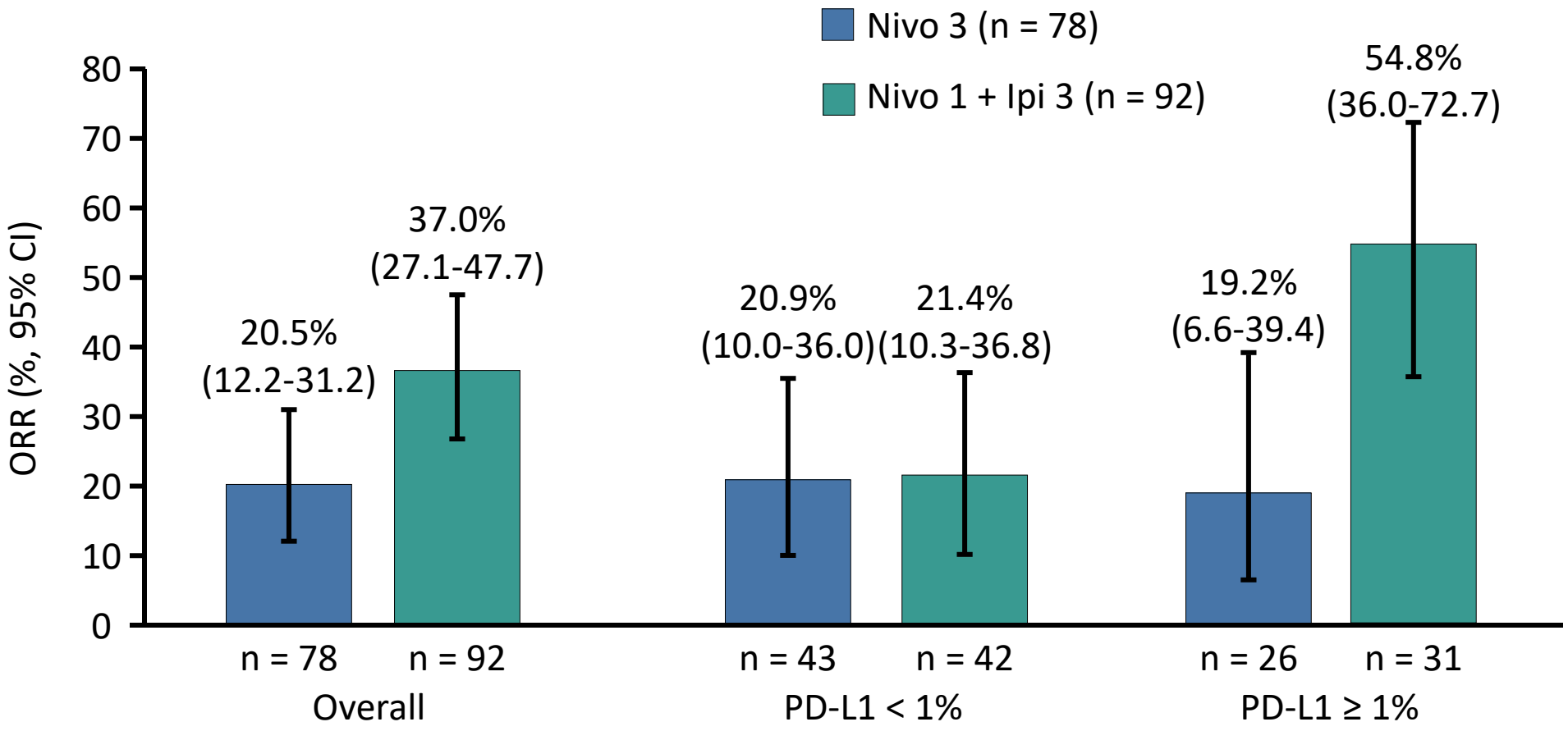
- Confirmed ORR: 25.6% with Nivo alone vs 26.9% with Nivo 3 mg/kg and + Ipi 1 mg/kg vs 38.0% with Nivo 1 mg/kg and + Ipi 3 mg/kg





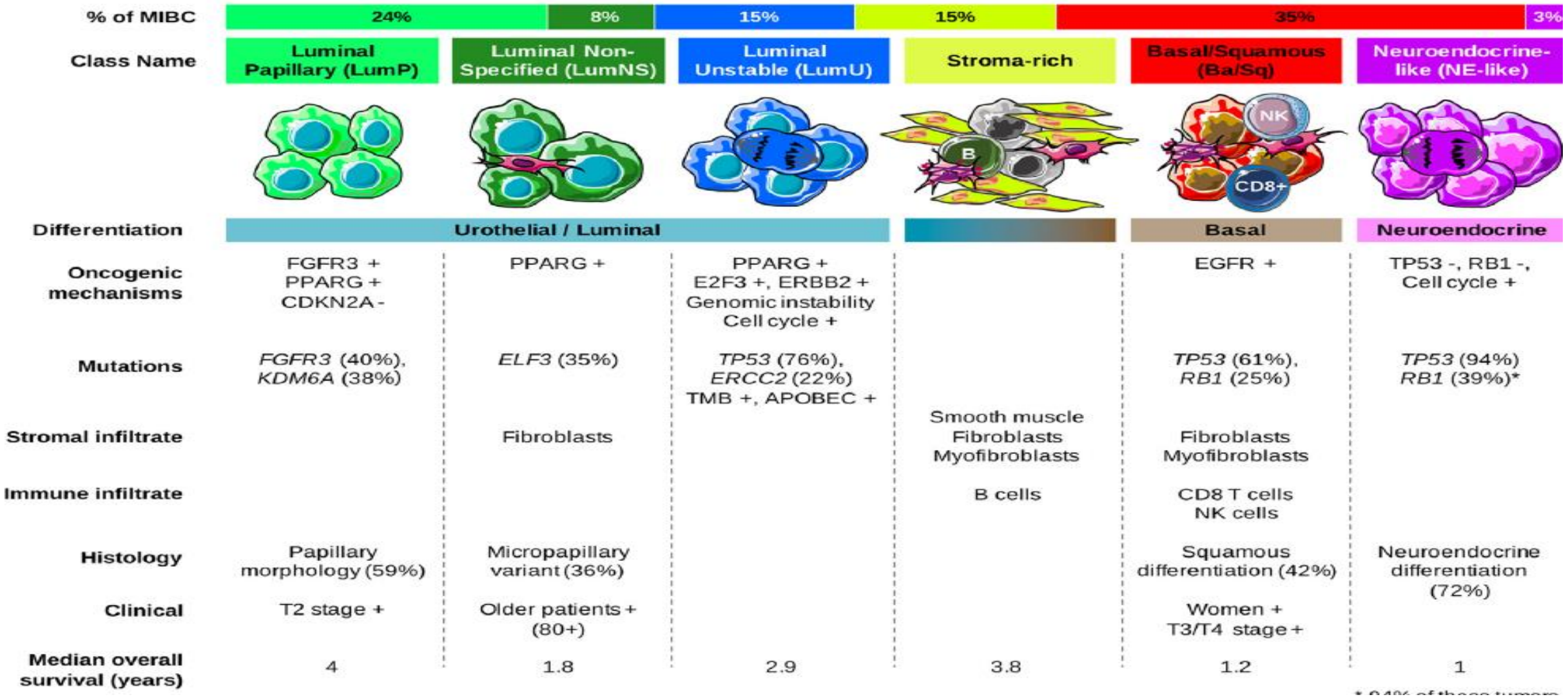
Sharma. JCO. 2019;37:1608.

CheckMate-032: Response to Nivolumab ± Ipilimumab by PD-L1 Expression



Sharma. JCO. 2019;37:1608.

Moleküler Sınıflama



Kamoun A. Eur Urology 2020

Hedefler

- Phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) yolağı
- Receptor tyrosine kinase/MAPK yolağı
- FGFR3-TACC3 füzyon aktivasyonu
- …

- PIK3CA mutasyonu
- TSC1 veya TSC2 mutasyon veya delesyonu
- AKT3 overekspresyonu
- FGFR3 aktivasyonu
- EGFR amplifikasyonu
- ERBB3 mutasyonu
- ERBB2 mutasyon ve amplifikasyonu
- …

Hedefli tedaviler

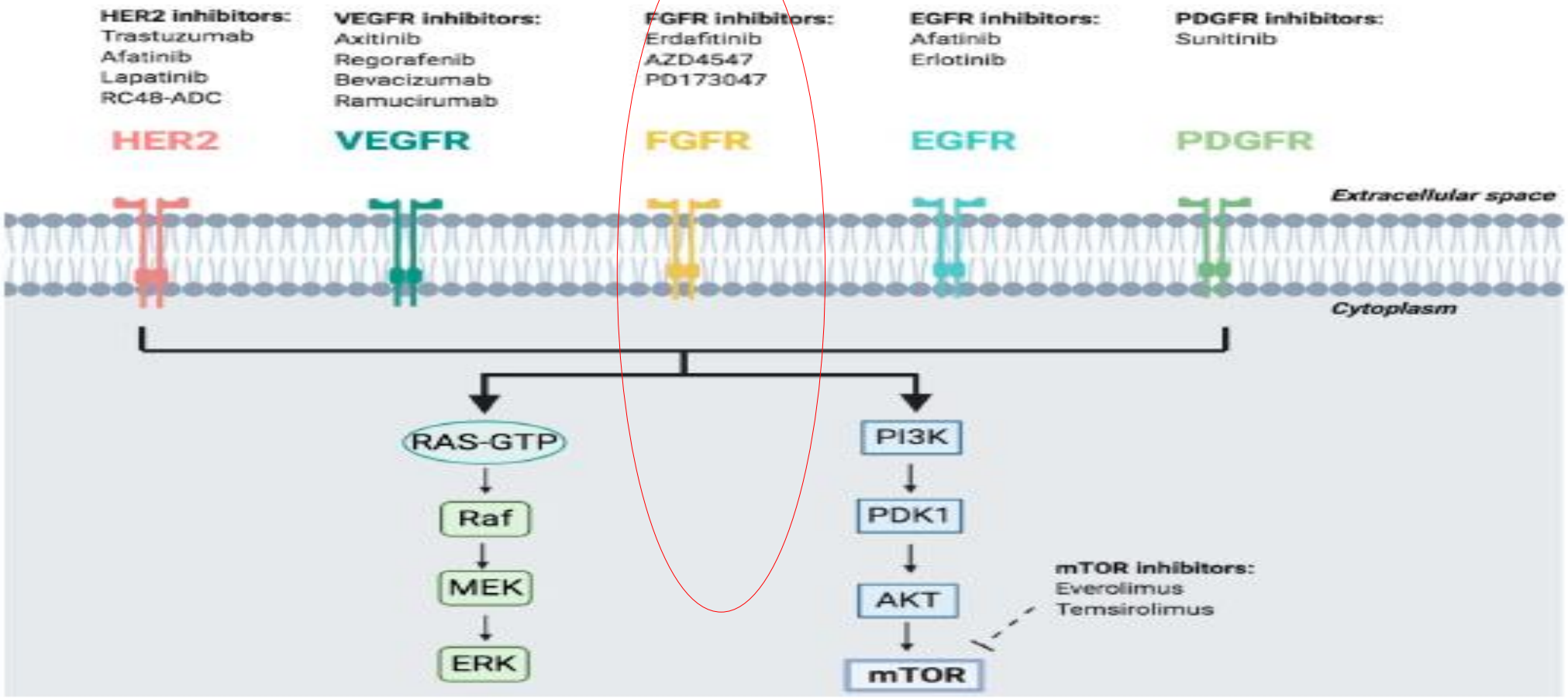
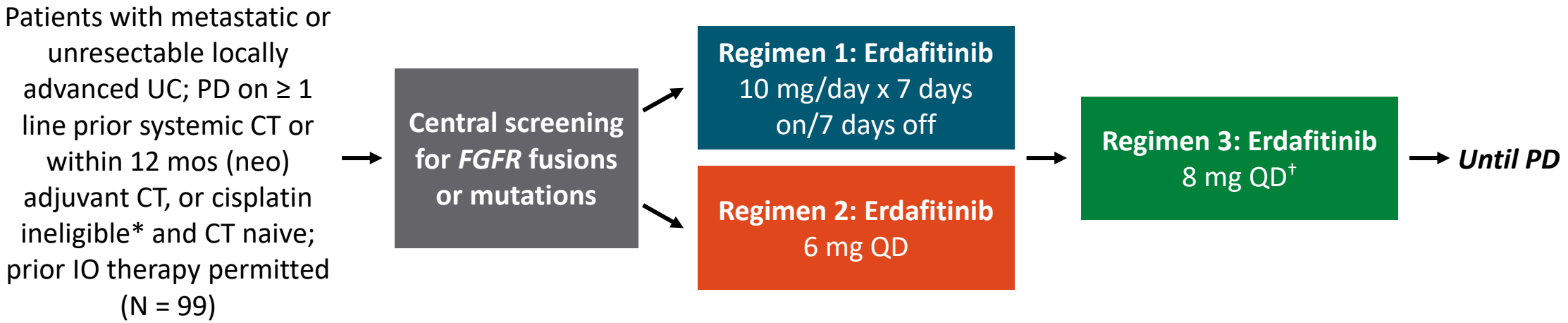


Figure 2. Frequent potentially actionable mutations and pathways involved in UC. EGFR: epidermal growth factor receptor; ERK: mitogen-activated protein kinase; FGFR: fibroblast growth factor receptor; HER2: receptor tyrosine-protein kinase ERBB2; MAPK: mitogen-activated protein kinase; MEK: dual-specificity mitogen-activated protein kinase; mTOR: mammalian target of rapamycin; PDGFR: platelet-derived growth factor receptor; PI3K: phosphoinositide 3-kinase; PTEN: phosphatase and tensin homologue; VEGFR: vascular endothelial growth factor receptor.

Mollica V. Cancers 2020

BLC2001: Study Design

- International, open-label phase II trial



*Defined as peripheral neuropathy or impaired renal function. †Titration up to 9 mg QD if target not reached for serum phosphate (≥ 5.5 mg/dL) by Day 14 and no TRAEs.

- Primary endpoint: ORR
  - Study has 85% power with 1-sided α = 0.025 to test primary hypothesis that ORR > 25% in Regimen 3
- Secondary endpoints: PFS, OS, safety, DoR, PK, predictive biomarker evaluation

Siefker-Radtke AO, et al. ASCO 2018. Abstract 4503. Siefker-Radtke AO, et al. ASCO 2016. Abstract TPS4575. ClinicalTrials.gov. NCT02365597.

BLC2001: Antitumor Activity

Response,*† n (%)	Patients (N = 99)
ORR	40 (40.4)
▪ CR	3 (3.0)
▪ PR	37 (37.4)
SD	39 (39.4)
PD	18 (18.2)
Median TTR, mos	1.4
Median DoR, mos	5.6

*Investigator-assessed response confirmed with second scan ≥ 6 wks after first observation of response. †Response unknown, n = 2.

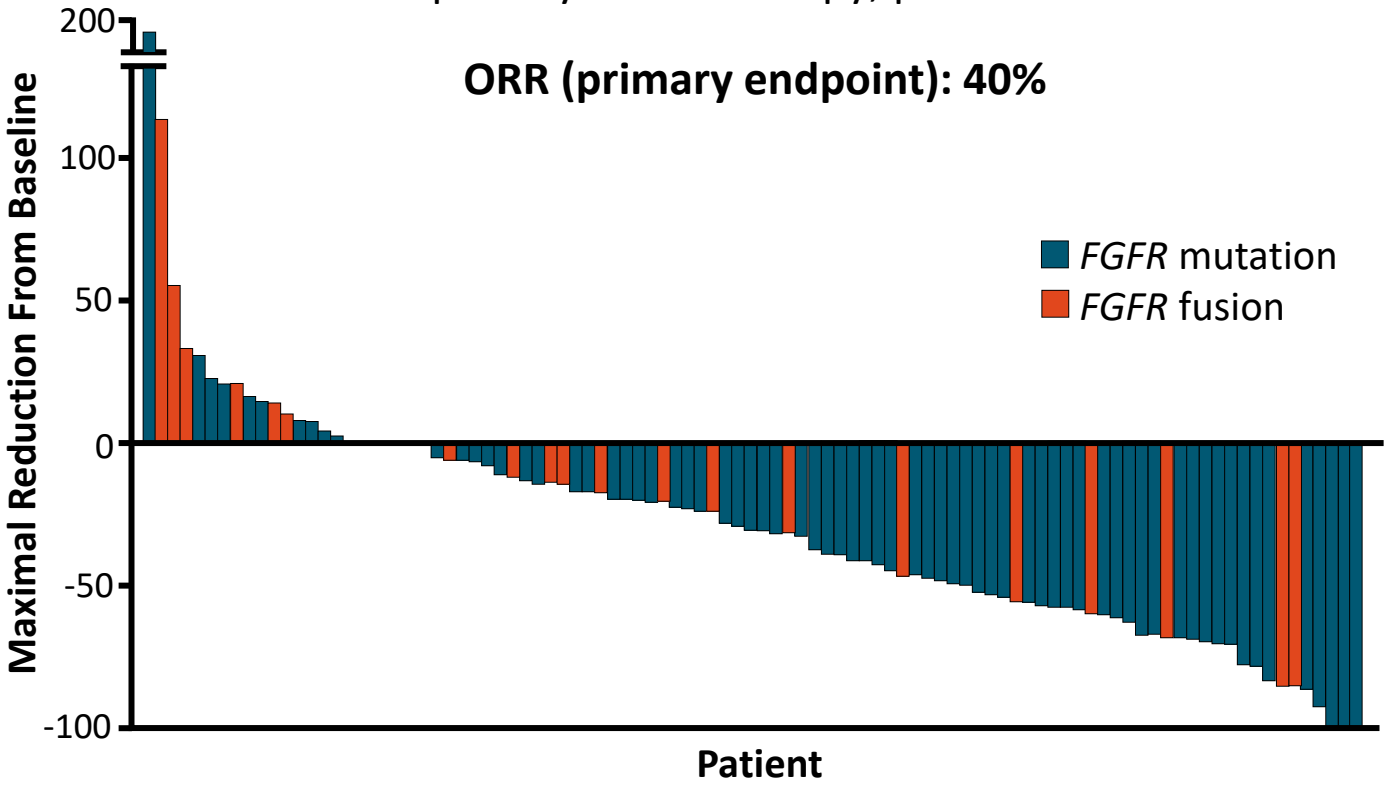
- Tumor shrinkage observed in 76% of evaluable patients receiving erdafitinib 8 mg QD
- Reponses were durable

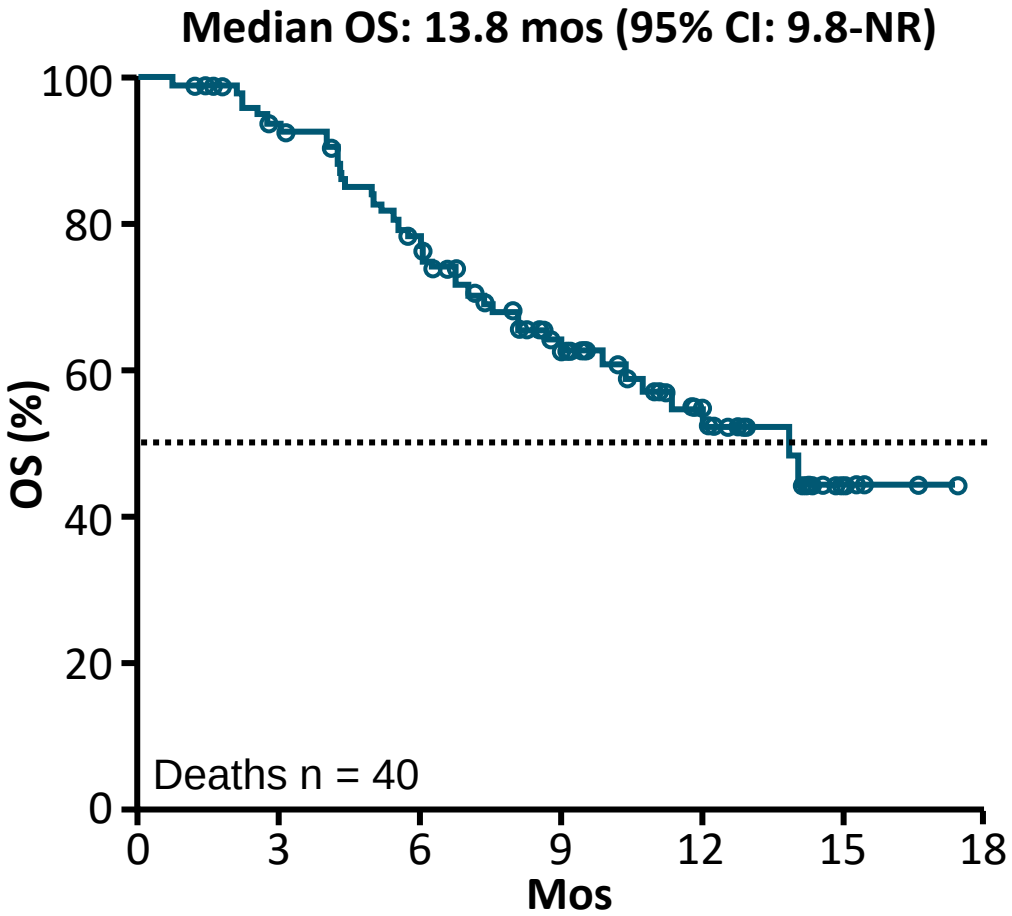
Response, %	Patient Subgroups				
	CT Naive (n = 12)	PD/Relapse After CT (n = 87)	Visceral Mets (n = 78)	No Visceral Mets (n = 21)	Prior IO (n = 22)
ORR to erdafitinib	41.7	40.2	38.5	47.6	59.0
ORR to prior IO	--	--	--	--	5

Siefker-Radtke AO, et al. ASCO 2018. Abstract 4503.

Pivotal Phase II Erdafitinib Study in *FGFR*-Positive Metastatic UC After ≥ 1 Line Platinum-Based Chemo

- Erdafitinib: oral pan-FGFR (1-4) inhibitör (8mg/d continuous)
- Patients with metastatic UC and *FGFR* mutation or fusion (prevalence in metastatic UC: 15% to 20%)
  - At least 1 prior systemic therapy; prior ICI allowed





Siefker-Radtke. ASCO 2018. Abstr 4503. Loriot. NEJM. 2019;381:338.

Pivotal Phase II Erdafitinib Study: Most Common TRAEs

- Most TRAEs were grade 1/2
  - No grade 4/5 TRAEs observed
- Serious TRAEs observed in 9 patients (9%)
  - No serious TRAE observed in ≥ 1 patient

TRAEs in > 20% of Patients, n (%)	Erdafitinib 8 mg QD (N = 99)	
	Any Grade	Grade 3
Hyperphosphatemia	72 (73)	2 (2)
Stomatitis	54 (55)	9 (9)
Dry mouth	43 (43)	0
Diarrhea	37 (37)	4 (4)
Dysgeusia	35 (35)	1 (1)
Dry skin	32 (32)	0
Alopecia	27 (27)	0
Decreased appetite	25 (25)	0
Hand–foot syndrome	22 (22)	5 (5)
Fatigue	21 (21)	2 (2)

Siefker-Radtke. ASCO 2018. Abstr 4503.

Pivotal Phase II Erdafitinib Study: TRAEs of Special Interest or Clinical Importance

- Most TRAEs of special interest or clinical importance were grade 1/2[1]
- CSR an established class effect of MAPK pathway inhibitors[2,3]
- D/c due to AEs of special interest in 7 patients[1]
  - D/c due to CSR in 3 patients (no retinal vein or artery occlusion observed)
- All AEs of special interest manageable with supportive treatment and dose interruption or modification[1]
  - Patients were monitored routinely

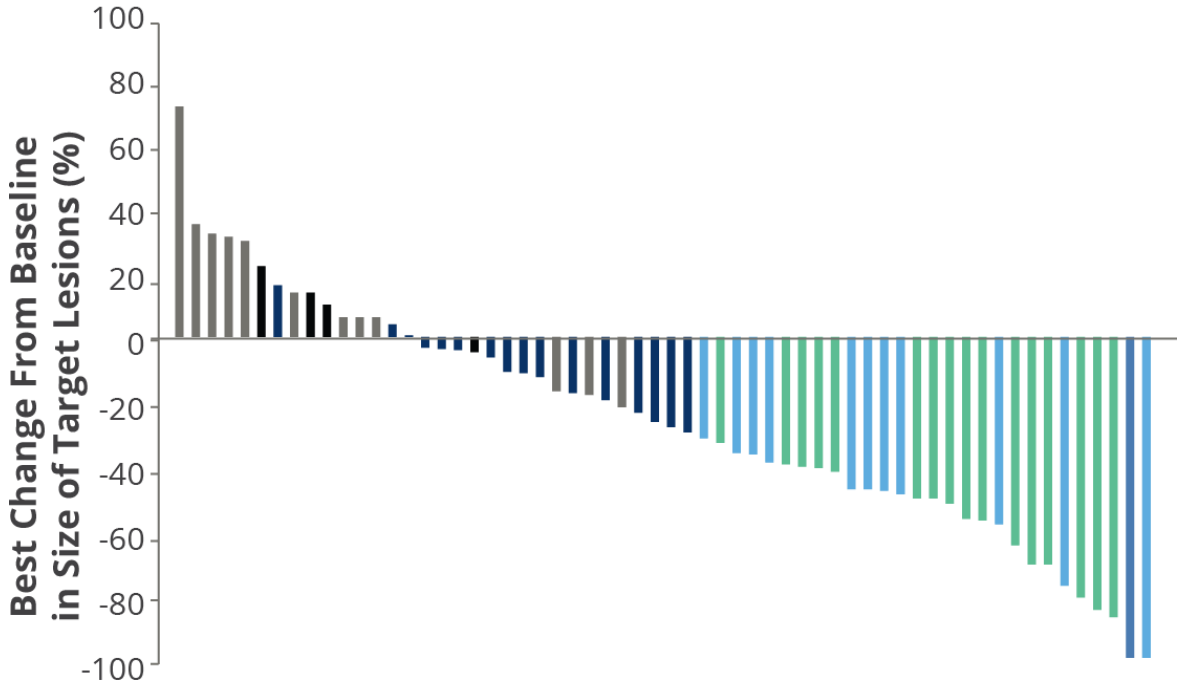
TRAEs of Special Interest or Clinical Importance, n (%)[1]	Erdafitinib 8 mg QD (n = 99)	
	Any Grade	Grade ≥ 3
Hyperphosphatemia	72 (73)	2 (2)
Skin events	48 (49)	6 (6)
▪ Dry skin	32 (32)	0
▪ Hand–foot syndrome	22 (22)	5 (5)
Nail events	51 (52)	14 (14)
▪ Onycholysis	16 (16)	2 (2)
▪ Paronychia	14 (14)	3 (3)
▪ Nail dystrophy	16 (16)	6 (6)
Ocular events		
▪ CSR	21 (21)	3 (3)
▪ Non-CSR events*	51 (52)	5 (5)

*Most common non-CSR events: dry eye, 19%; blurry vision, 16%; increased lacrimation, 11%; conjunctivitis, 9%.

1. Siefker-Radtke. ASCO 2018. Abstr 4503. 2. van der Noll. Cancer Treat Rev. 2013;39:664. 3. Stjepanovic. Ann Oncol. 2016;27:998.

Other Investigational FGFR Inhibitors

Phase I Study of Infigratinib (BGJ398125)[1]



Phase II/III FORT Study of Rogaratinib[2]

FGFR1 or 3+ tumors (by mRNA expression)
LA or mUC
≥1 platinum CT
≤2 prior lines of systemic therapy
N=400

1:1

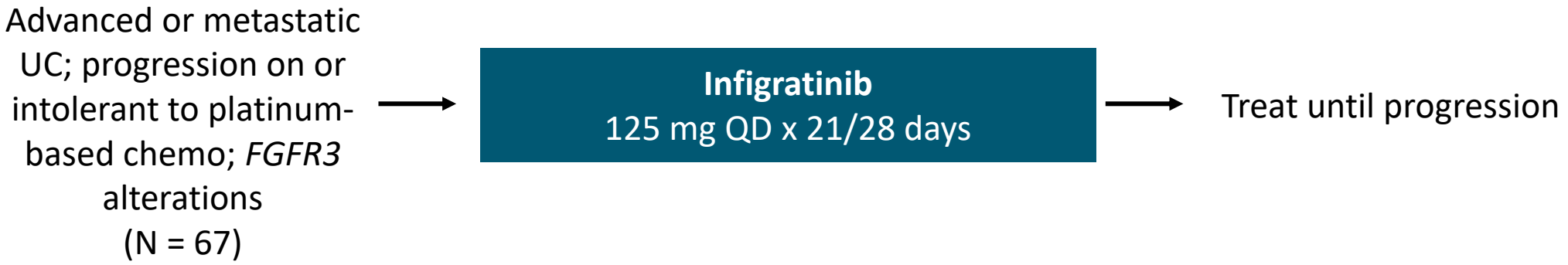
Oral Rogaritinib
BID continuously

Active Comparator
Taxane or vinflunine IV Q3W

Primary Outcome Measure: OS
Secondary Outcome Measures: PFS, ORR, DCR, DoR, AEs

1. Pal. Cancer Discov. 2018;8;812. 2. NCT03410693.

Phase I Trial of Novel FGFR1-3 Inhibitor Infigratinib: Cohort of Patients With Advanced UC



- Primary endpoint: ORR with infigratinib as first-line treatment vs later lines
- Secondary endpoints: PFS, DCR, BOR, OS, safety, PK

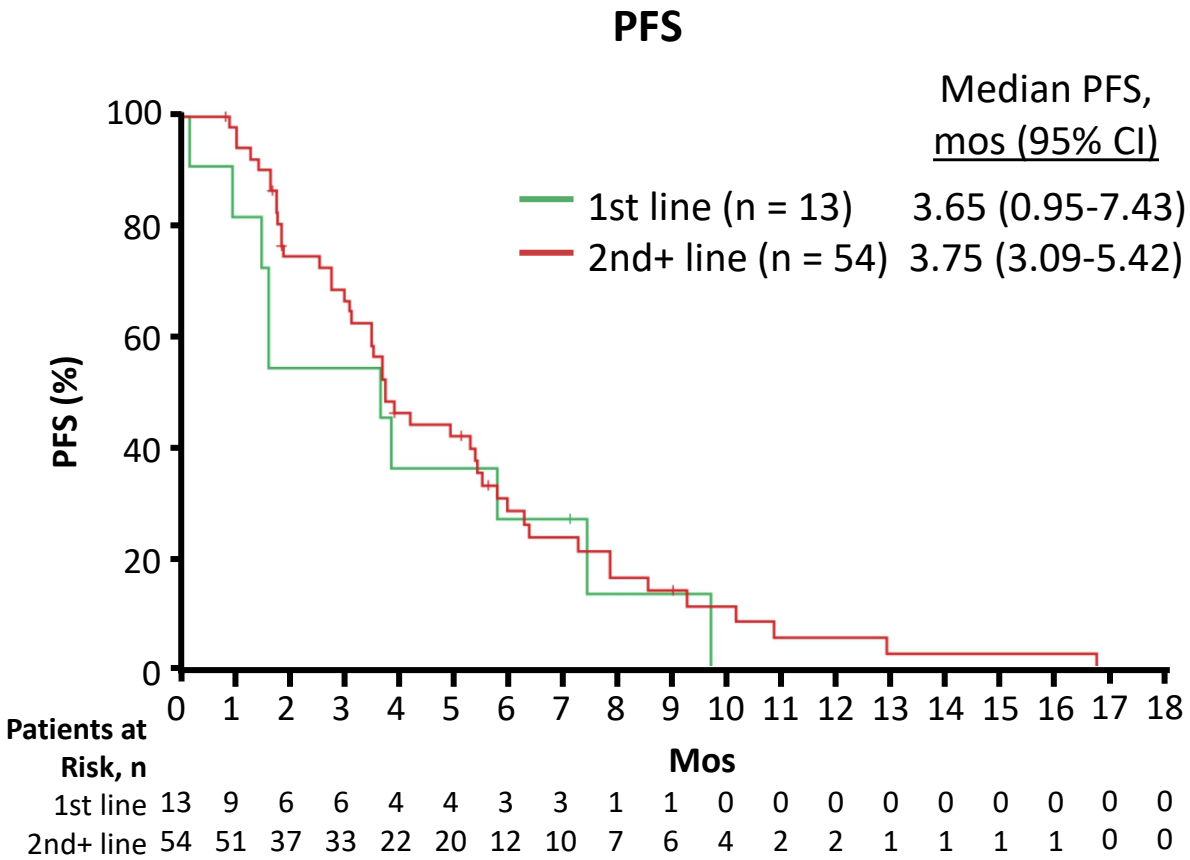
Lyou. ASCO 2020. Abstract 5038.

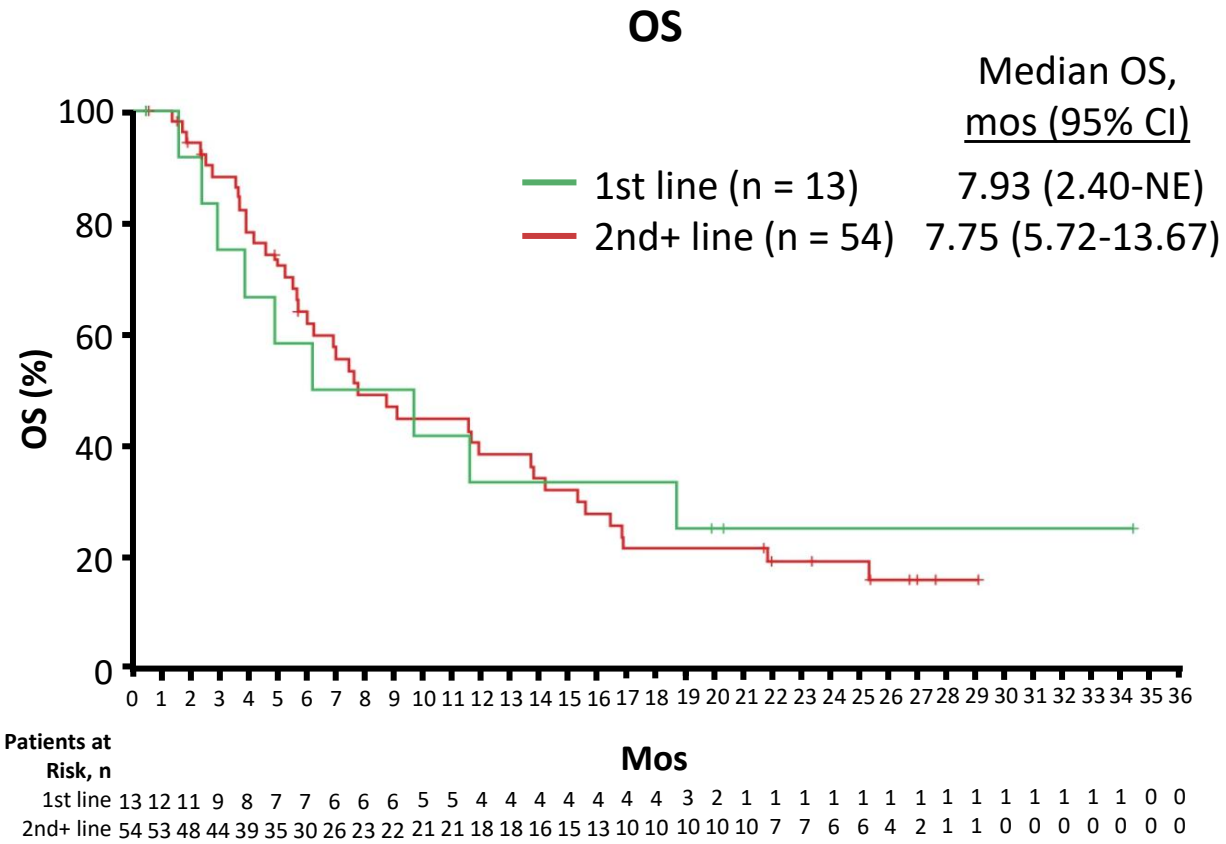
Phase I Study of Infigratinib in UC: Responses

Response, n (%)	First Line (n = 13)	Second or Later Lines (n = 54)	Total (N = 67)
Response Assessment			
▪ CR	0	1 (1.9)	1 (1.5)
▪ PR	4 (30.8)	12 (22.2)	16 (23.9)
▪ SD	2 (15.4)	24 (44.4)	26 (38.8)
▪ Unconfirmed CR/PR	1 (7.7)	10 (18.5)	11 (16.4)
▪ PD	6 (46.2)	12 (22.2)	18 (26.9)
▪ Unknown	1 (7.7)	5 (9.3)	6 (9.0)
Confirmed objective response (CR or PR)	4 (30.8) [95% CI: 9.1-61.4]	13 (24.1) [95% CI: 13.5-37.6]	17 (25.4) [95% CI: 15.5-37.5]
Best overall response (CR or PR, confirmed or unconfirmed)	5 (38.5) [95% CI: 13.9-68.4)	23 (42.6) [95% CI: 29.2-56.8]	28 (41.8) [95% CI: 29.8-54.5]
DCR (CR/PR/SD)	6 (46.2) [95% CI: 19.2-74.9]	37 (68.5) [95% CI: 54.4-80.5]	43 (64.2) [51.5-75.5]

Lyou. ASCO 2020. Abstract 5038.

Phase I Trial of Infigratinib: Cohort of Patients With Advanced UC





Lyou. ASCO 2020. Abstract 5038.

VEGF/VEGFR inhibitors

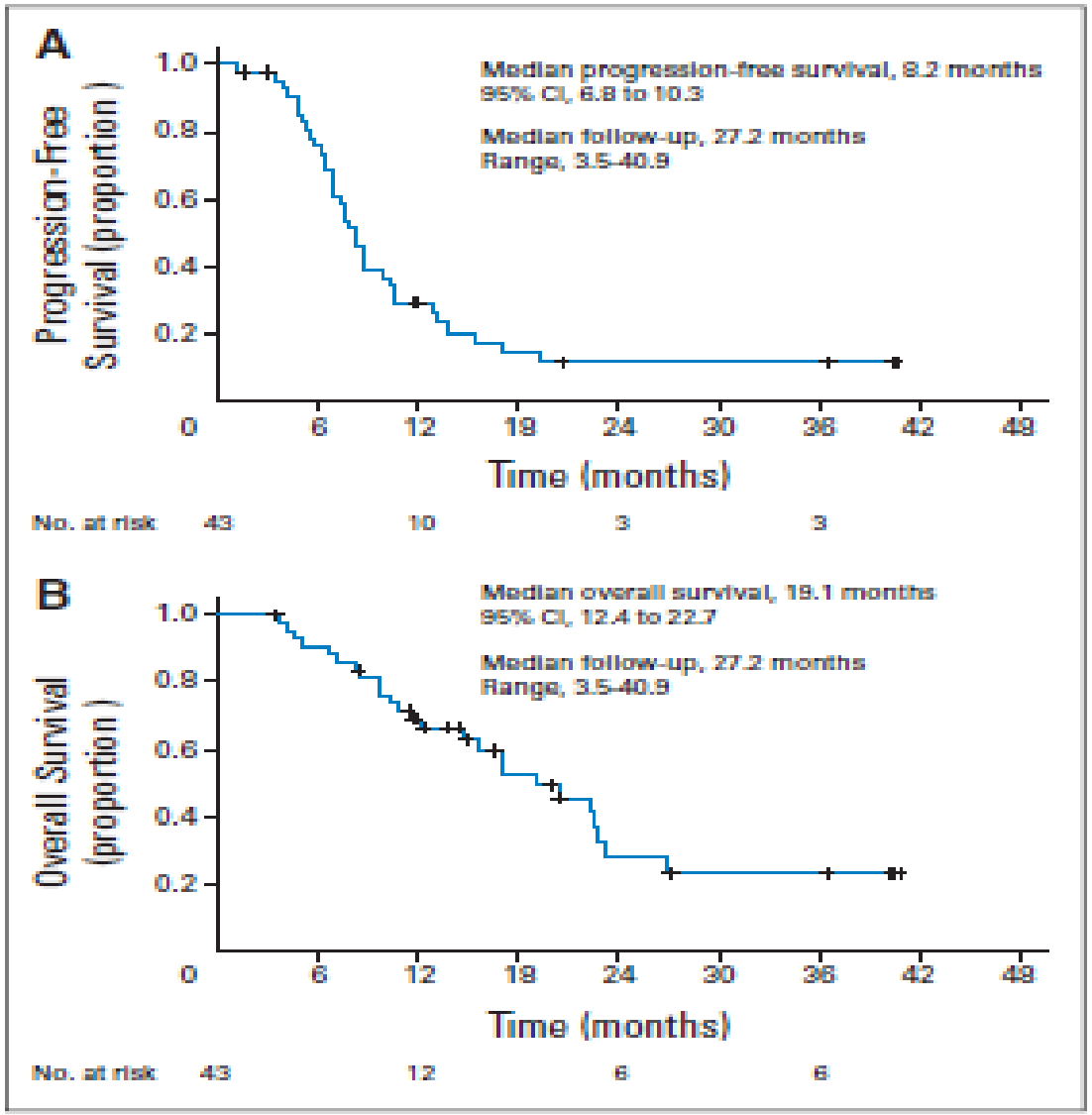


Fig 1. (A) Progression-free survival (PFS). (B) Overall survival (OS).

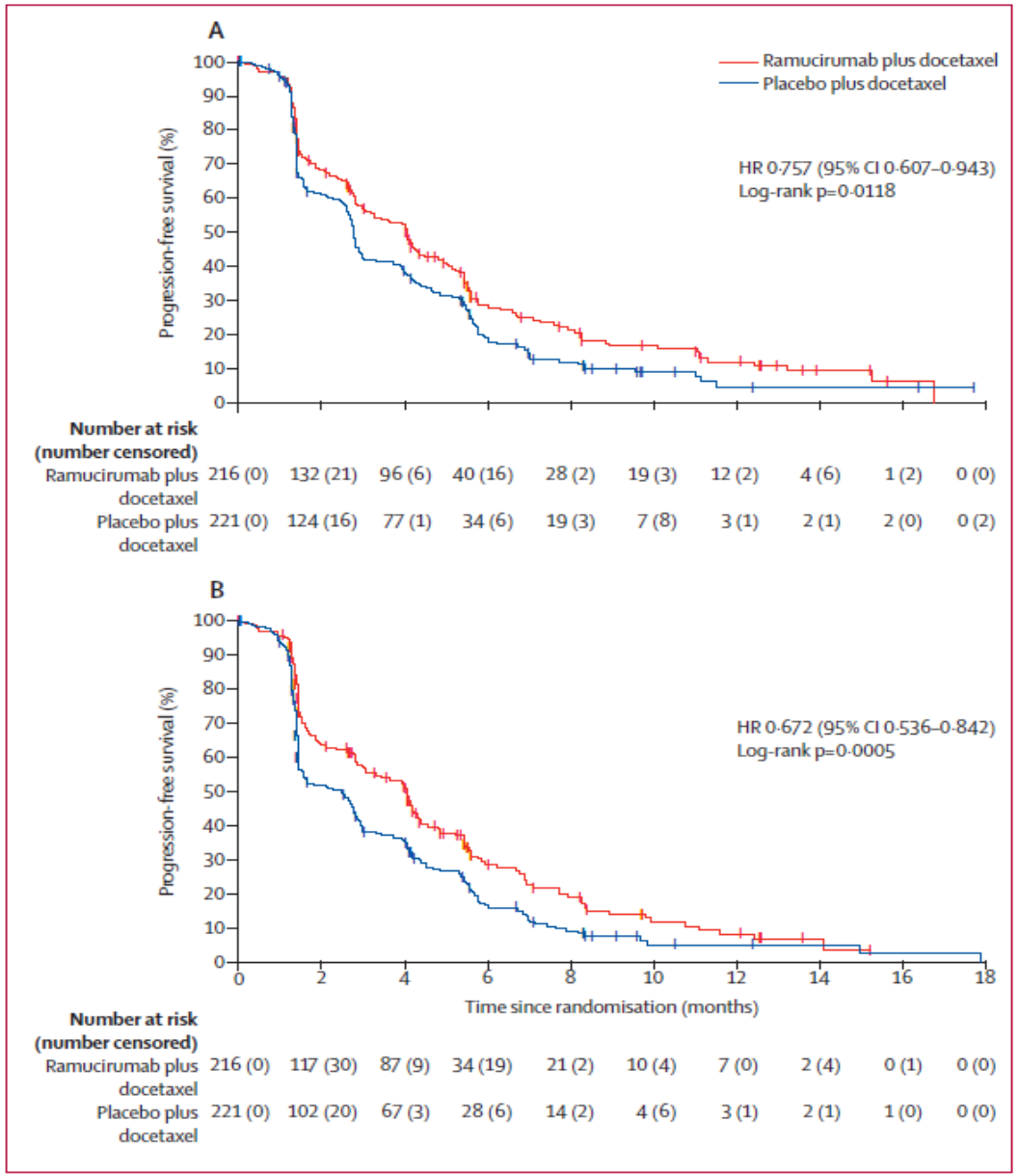
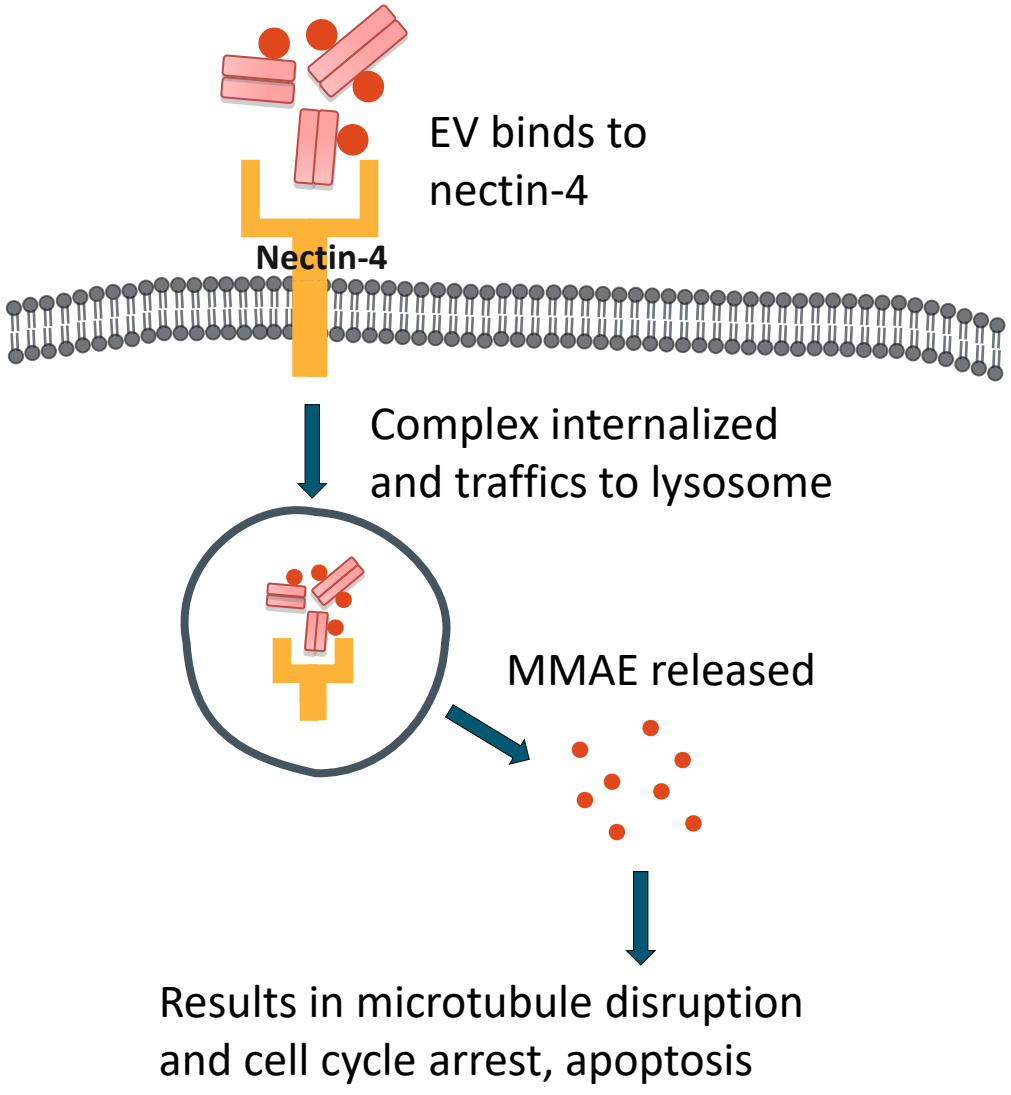


Figure 2: **Kaplan-Meier plots for progression-free survival in the first 437 randomised patients (intention-to-treat population)**
(A) Investigator-assessed. (B) Independent central review. HR=hazard ratio.

Enfortumab Vedotin: An Antibody–Drug Conjugate Targeting Nectin-4

- Enfortumab vedotin[1]
  - A fully humanized monoclonal antibody against nectin-4
  - Conjugated with microtubule-disrupting agent, monomethyl auristatin E (MMAE), by a protease-cleavable linker
- Nectin-4 is a transmembrane cell adhesion molecule[2] that is highly expressed in 97% of mUC patient samples[3]



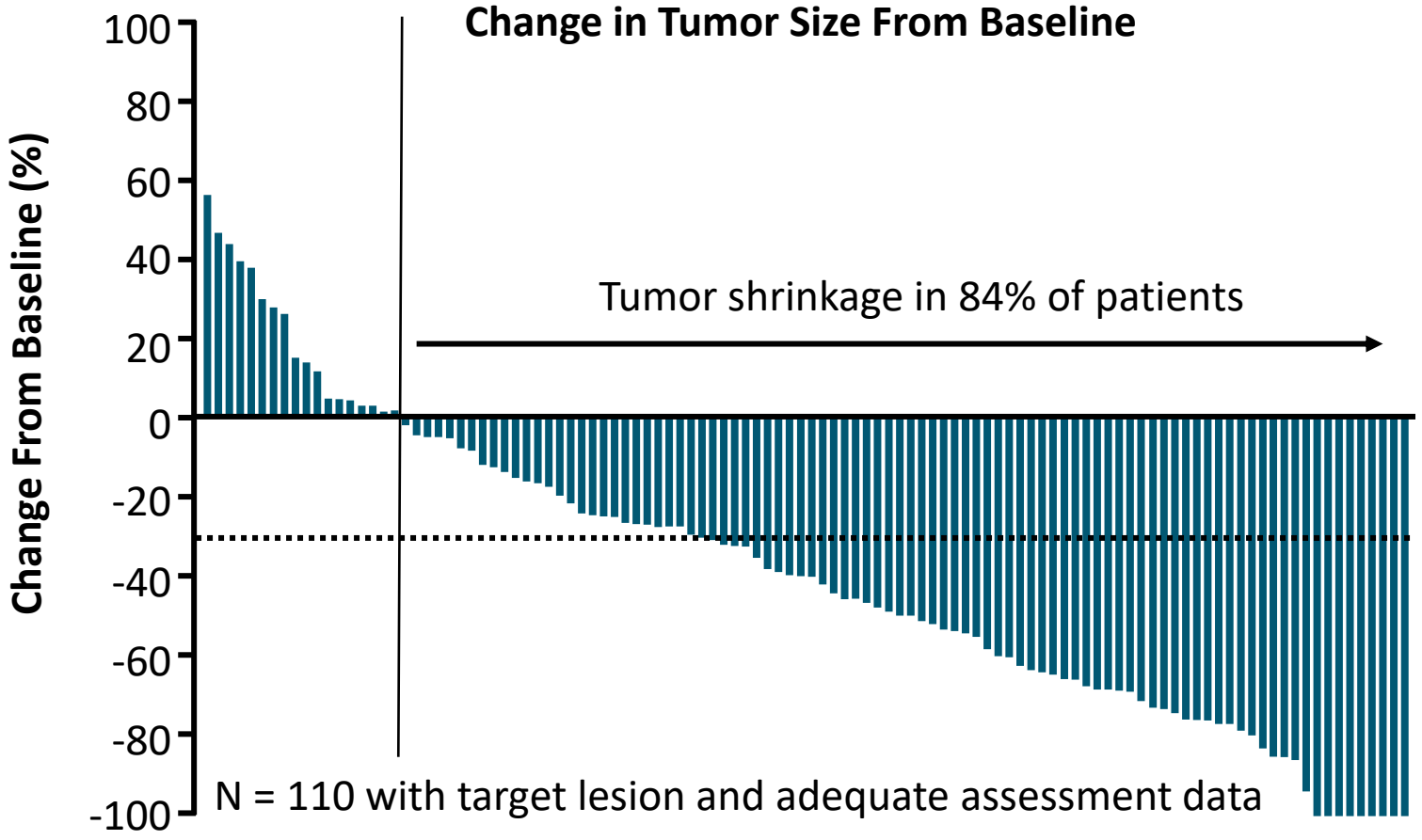
1. Challita-Eid. Cancer Res. 2016;76:3003. 2. Samanta. Cell Mol Life Sci. 2015;72:645. 3. Petrylak. JCO. 2017;35:106.

EV-201 Cohort 1: Response to Enfortumab Vedotin Monotherapy in Metastatic UC

- Pivotal phase II trial of enfortumab vedotin 1.25 mg/kg in mUC after platinum-based chemo and immune checkpoint inhibitor

Response, n (%)	Cohort 1 (n = 125)
Confirmed ORR	55 (44)
Best overall response per RECIST 1.1	
▪ CR	15 (12)
▪ PR	40 (32)
▪ SD	35 (28)
▪ PD	23 (18)

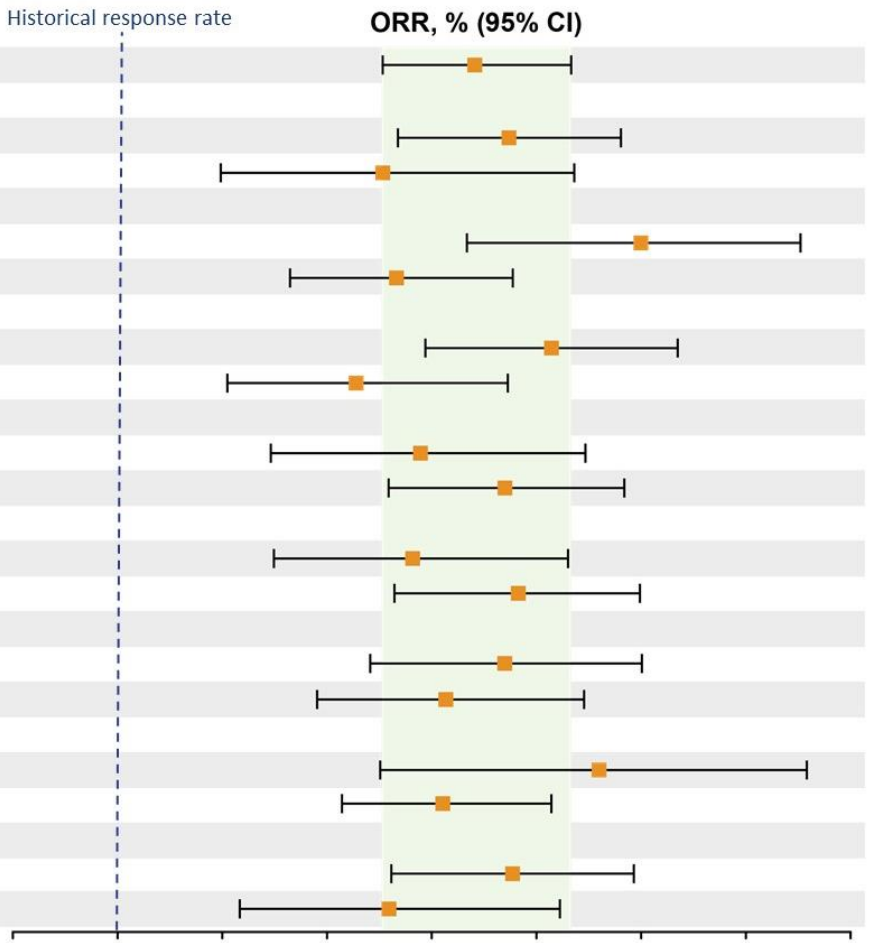
All patients had previous platinum and checkpoint therapy



Rosenberg. JCO. 2019;37:2592.

EV-201 Cohort 1: Response to Enfortumab Vedotin Monotherapy by Subgroup

Subgroup	n/N	% (95% CI)
Overall	55/125	44 (35.1, 53.2)
Age		
<75	43/91	47 (36.7, 58.0)
≥75	12/34	35 (19.7, 53.5)
ECOG performance status, n (%)		
Grade 0	24/40	60 (43.3, 75.1)
Grade 1	31/85	36 (26.3, 47.6)
Bellmunt risk score[1]		
0−1	37/72	51 (39.3, 63.3)
≥2	17/52	33 (20.3, 47.1)
Primary tumor sites		
Upper tract	17/44	39 (24.4, 54.5)
Bladder/Other	38/81	47 (35.7, 58.3)
Liver metastasis		
Yes	19/50	38 (24.7, 52.8)
No	36/75	48 (36.3, 59.8)
Number of prior therapies in metastatic UC setting		
1−2	29/62	47 (34.0, 59.9)
≥3	26/63	41 (29.0, 54.4)
Best response to prior PD-1/L1[2]		
Responder	14/25	56 (34.9, 75.6)
Non-responder	41/100	41 (31.3, 51.3)
PD-L1 expression[3]		
CPS <10	37/78	47 (36.0, 59.1)
CPS ≥10	15/42	36 (21.6, 52.0)

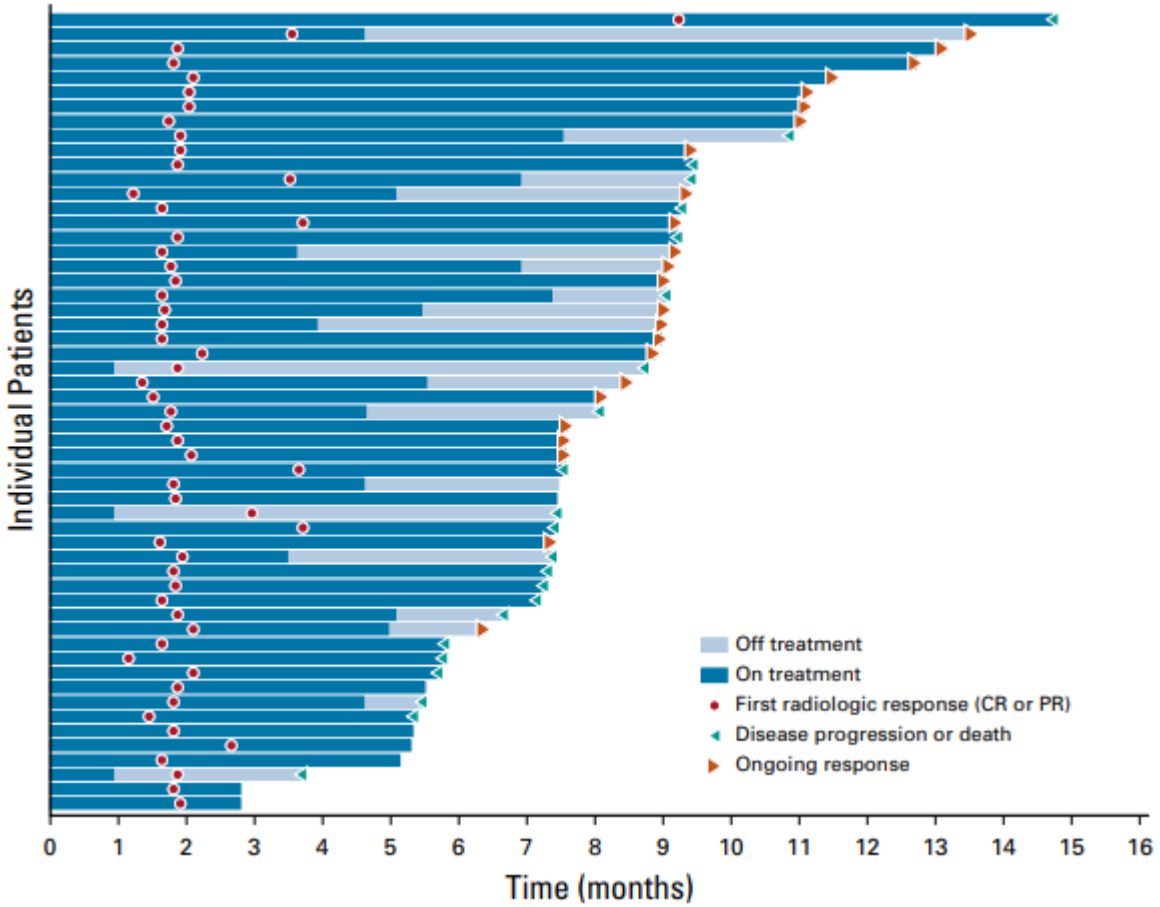


[1] Bellmunt risk score was not available for 1 patient; [2] Anti-PD-1 or anti-PD-L1 therapy;
[3] Five patients were not evaluable for PD-L1 expression levels.

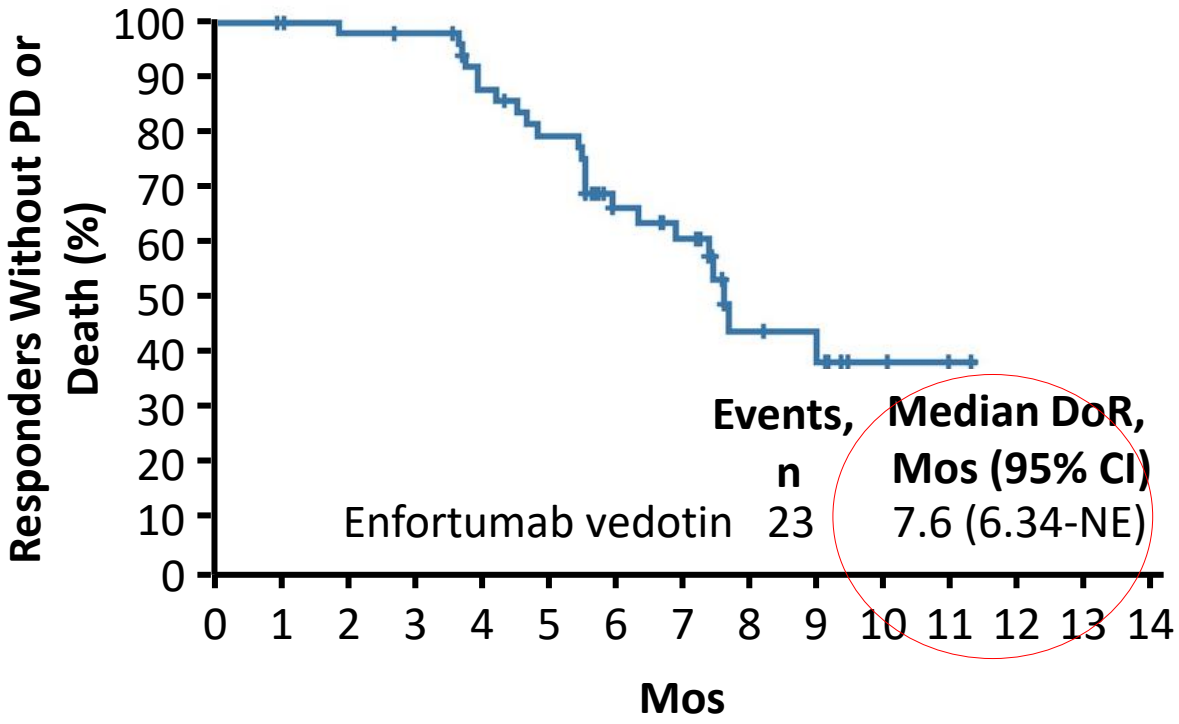
Rosenberg. JCO. 2019;37:2592.

EV-201 Cohort 1: Duration of Response to Enfortumab Vedotin

Objective Responses



Duration of Response

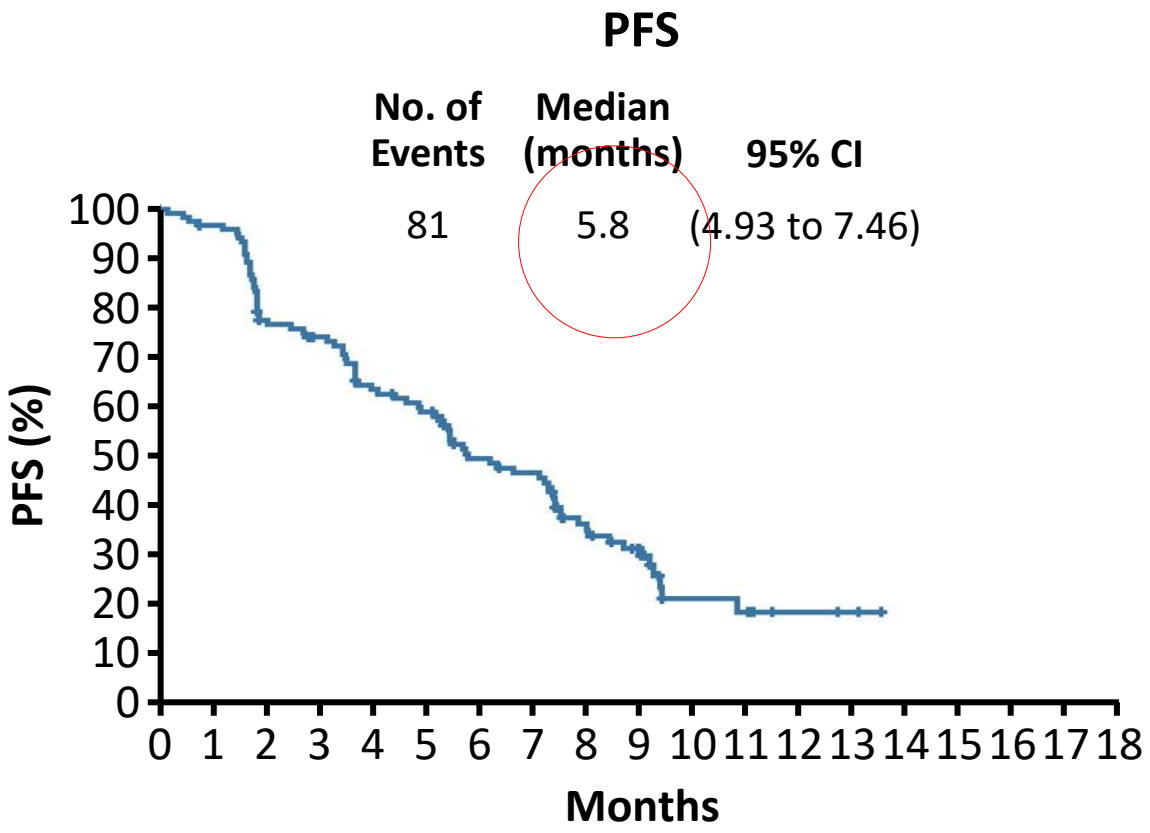


Patients at Risk, n

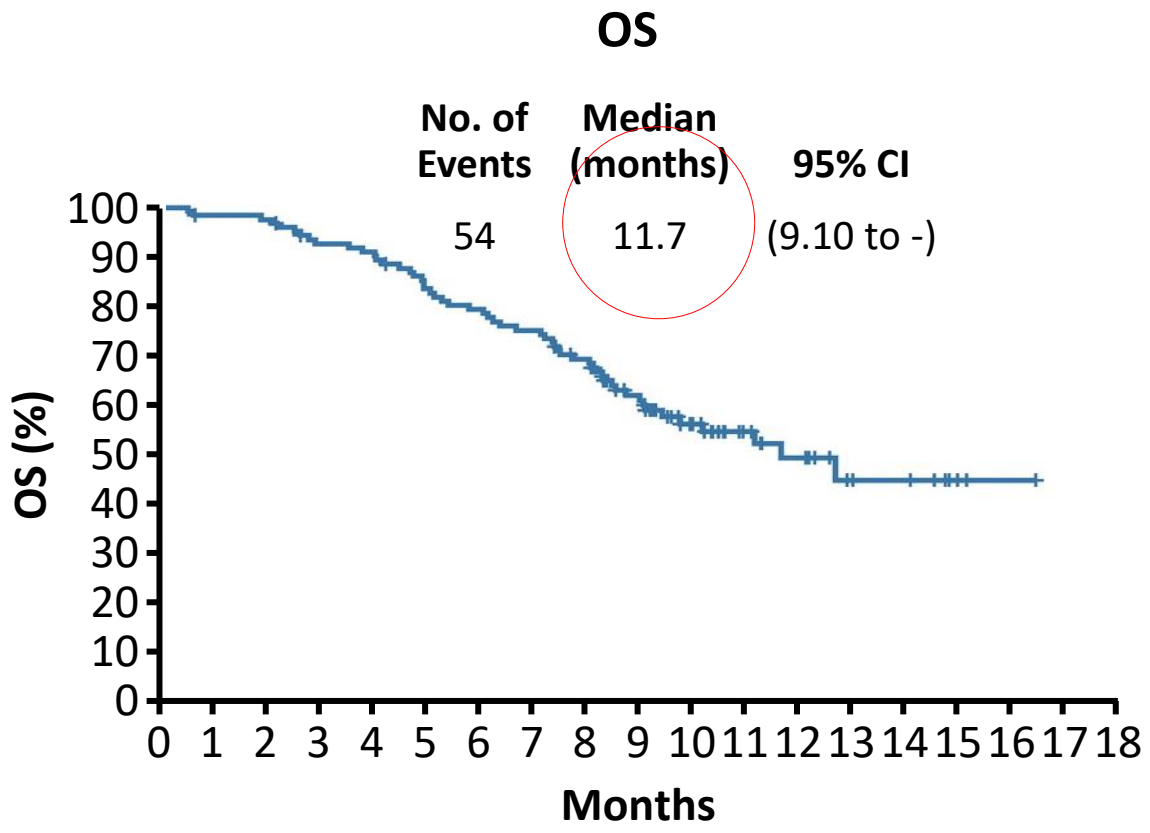
Cohort 1	55	54	52	51	43	38	25	21	9	7	3	1

Rosenberg. JCO. 2019;37:2592.

EV-201 Cohort 1: PFS and OS with Enfortumab Vedotin



No. at risk: 125 116 91 84 72 65 51 47 30 22 8 7 3 2



No. at risk: 125 122 121 113 111 101 96 91 82 61 36 24 18 9 8 2 1

Rosenberg. J Clin Oncol. 2019;37:2592.

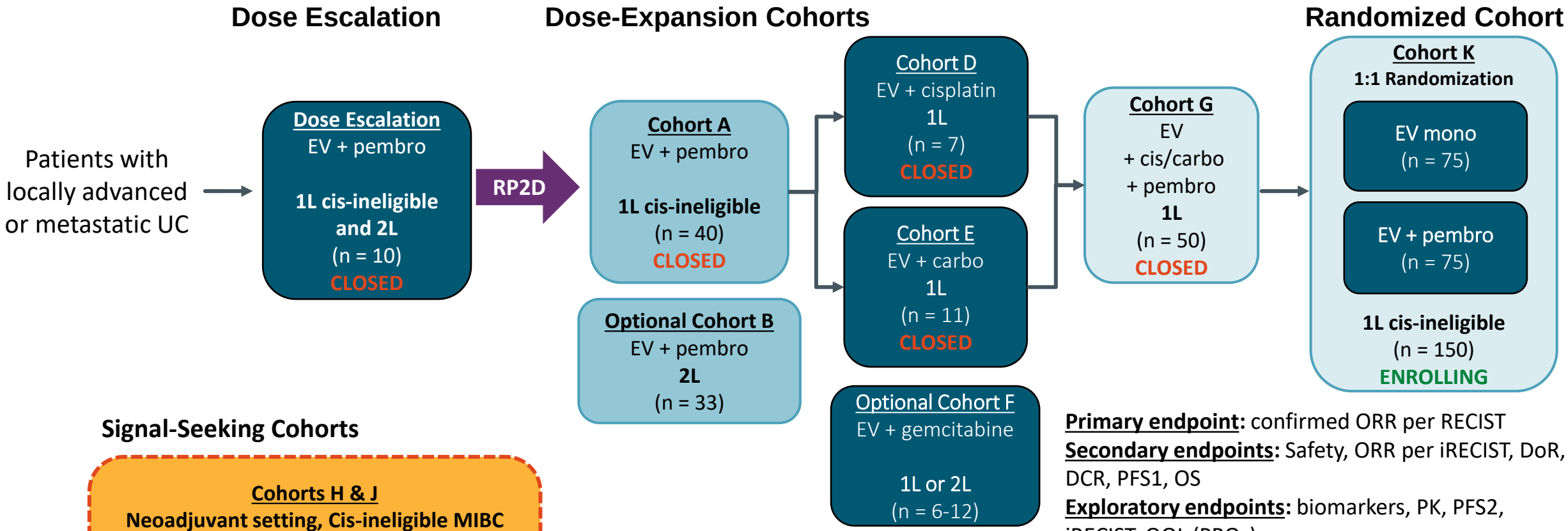
EV-201 Cohort 1: Treatment-Related AEs With Enfortumab Vedotin

TRAE in ≥ 10%, n (%)	Patients (n = 125)	
	Any Grade	Grade ≥ 3
Overall	117 (94)	68 (54)
Fatigue	62 (50)	7 (6)
Alopecia	61 (49)	0
Decreased appetite	55 (44)	1 (1)
Dysgeusia	50 (40)	0
Peripheral sensory neuropathy	50 (40)	2 (2)
Nausea	49 (39)	3 (2)
Diarrhea	40 (32)	3 (2)
Weight decreased	28 (22)	1 (1)
Dry skin	28 (22)	0
Rash maculopapular	27 (22)	5 (4)
Dry eye	24 (19)	0
Anemia	22 (18)	9 (7)

TRAE in ≥ 10%, n (%)	Patients (n = 125)	
	Any Grade	Grade ≥ 3
Pruritis	21 (17)	0
Vomiting	18 (14)	3 (2)
Lacrimation increased	18 (14)	0
AST increased	17 (14)	4 (3)
Constipation	15 (12)	0
Vision blurred	15 (12)	0
Rash erythematous	14 (11)	4 (3)
Edema peripheral	14 (11)	1 (1)
Neutropenia	13 (10)	10 (8)
Hyperglycemia	12 (10)	5 (4)
Amylase increased	12 (10)	2 (2)
Pruritis generalized	12 (10)	2 (2)
ALT increased	12 (10)	2 (2)

Rosenberg. J Clin Oncol. 2019;37:2592.

Phase Ib/II EV-103: Enfortumab Vedotin Alone or in Combinations in Metastatic UC and MIBC



Signal-Seeking Cohorts

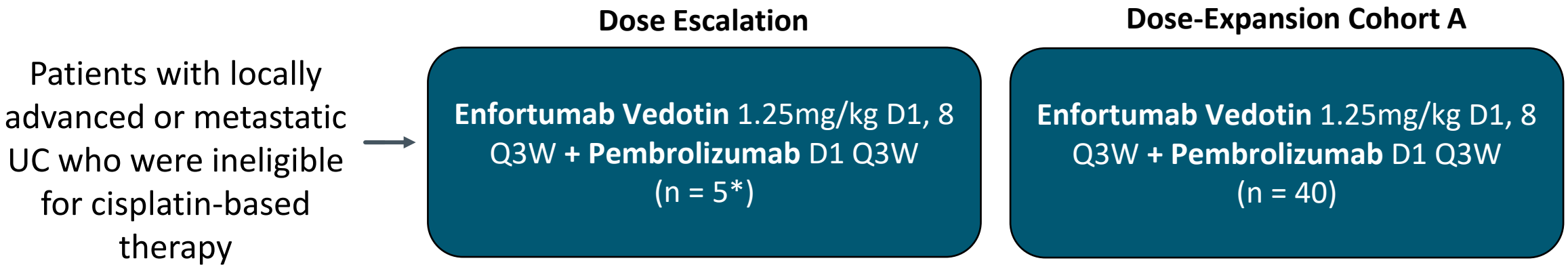
Cohorts H & J
Neoadjuvant setting, Cis-ineligible MIBC
EV mono (Cohort H)
EV + pembro (Cohort J)
(n = 20 in each cohort)
Cohort H ENROLLING

Primary endpoint: pCR by local review
Secondary endpoints: pCR by central review, downstaging, DFS, PFS, OS, safety, rate of delayed surgery due to TRAEs

Primary endpoint: confirmed ORR per RECIST
Secondary endpoints: Safety, ORR per iRECIST, DoR, DCR, PFS1, OS
Exploratory endpoints: biomarkers, PK, PFS2, iRECIST, QOL (PROs)

ClinicalTrials.gov. NCT03288545. Rosenberg. ASCO 2020. Abstr 5044.

Phase Ib/II EV-103 Cohort A : First-line Enfortumab Vedotin + Pembrolizumab in Cisplatin-Ineligible mUC



- Primary endpoints: AEs, lab abnormalities
- Key secondary endpoints: DLTs, ORR, DCR, DoR, OS

*Not included in the current analysis: 3 patients treated with EV 1 mg/kg + pembro 200 mg as first-line therapy and 2 patients treated with EV 1.25 mg/kg + pembro 200 mg as second-line therapy

Rosenberg. ASCO 2020. Abstr 5044.

Phase Ib/II EV-103 Cohort A: Response With Enfortumab Vedotin + Pembrolizumab

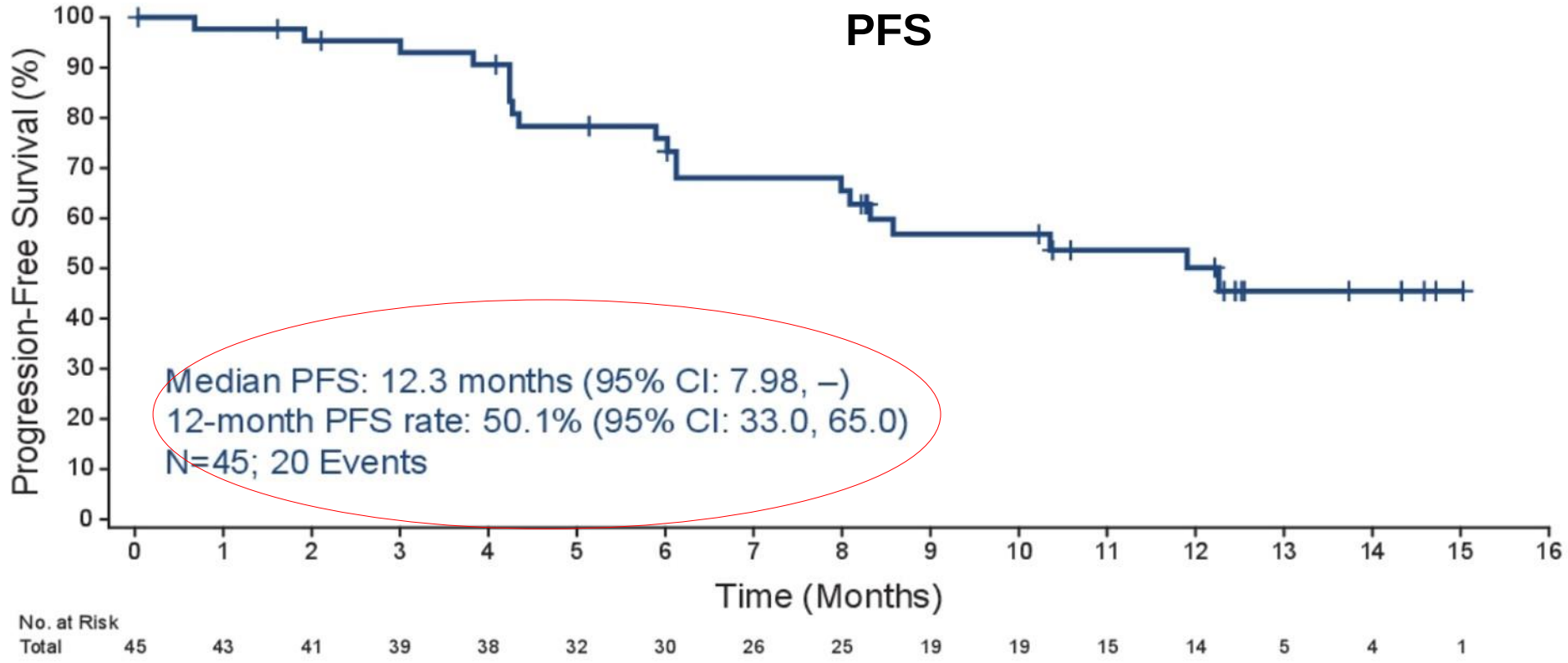
- ORR: 73.3% as first-line therapy for cisplatin-ineligible patients with mUC
- Response observed regardless of PD-L1 expression

Best Overall Response, n (%)	Total (N = 45)
Confirmed ORR, n (%) [95% CI]	33 (73.3) [58.1-85.4]
▪ CR	7 (15.6)
▪ PR	26 (57.8)
SD	9 (20.0)
PD	1 (2.2)
NE	2 (4.4)
ORR in patients with liver mets	8/15 (53.5)
ORR by PD-L1 expression	
▪ High	11/14 (78.6)
▪ Low	12/19 (63.2)

Rosenberg. ASCO 2020. Abstr 5044.

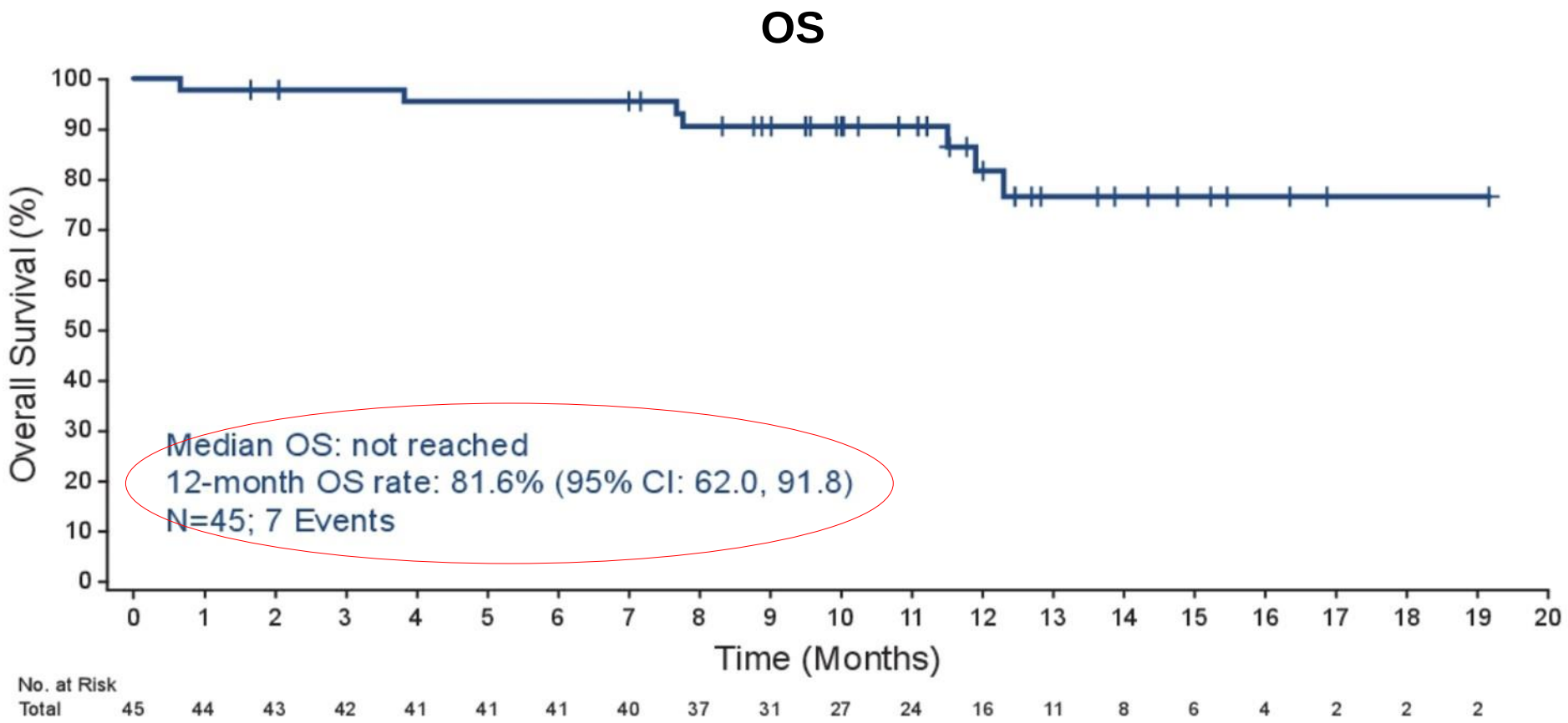
Phase Ib/II EV-103 Cohort A: DoR and PFS With Enfortumab Vedotin + Pembrolizumab

- Median DoR not reached with median follow-up of 10.4 mos
  - 12-mo DoR rate: 53.7% (95% CI: 27.4-74.1)



Rosenberg. ASCO 2020. Abstr 5044.

Phase Ib/II EV-103 Cohort A: OS With Enfortumab Vedotin + Pembrolizumab



Rosenberg. ASCO 2020. Abstr 5044.

TROPHY-U-01: Sacituzumab Govitecan in mUC After Platinum-Based or Anti–PD-1/PD-L1—Based Therapy

- An international, single-arm, open-label phase II trial
- Sacituzumab govitecan: antibody-drug conjugate; Trop-2 antibody coupled to cytotoxic agent SN-38 via hydrolyzable linker

Pts with advanced or metastatic UC

- ***Cohort 1***: progression after platinum-based and PD-1/PD-L1–targeted agents (n = 100)
- ***Cohort 2***: platinum-ineligible with progression after PD-1/PD-L1–targeted agents (n = 40)

→ **Sacituzumab Govitecan**
10 mg/kg
Days 1 and 8, every 21 days
→ Continue treatment in the absence of unacceptable toxicity or PD

- Primary endpoints: ORR, DoR, PFS, OS

Tagawa. ASCO GU 2019. Abstr 354. Petrylak. ASCO 2020. Abstr 5027.

TROPHY-U-01 Cohort 1: Adverse Events With Sacituzumab Govitecan

Adverse Event, %		All Grade	Grade 3	Grade 4
Hematologic	Neutropenia	66	29	26
	Leukopenia	40	20	9
	Anemia	34	17	0
	Febrile neutropenia	11	9	3
	Lymphocytosis	11	6	3
Gastrointestinal	Diarrhea	57	6	3
	Nausea	43	0	0
	Abdominal pain	20	3	0
General disorders	Fatigue	54	6	0
Infections/infestations	UTI	14	11	0
Skin and subcutaneous tissue	Alopecia	74	0	0
Metabolism/nutrition	Decreased appetite	20	0	0

- Median treatment cycles: 5 (range: 1-11)
- 3 patients discontinued due to TRAEs
- Other key TRAEs: ≤ grade 2 rash (n = 5)
  - No cases of ILD, ocular toxicities, or hyperglycemia
  - No peripheral neuropathy > G2
- **No treatment-related deaths**

Tagawa. ESMO 2019. Abstract 354.

TROPHY-U-01 Cohort 1: Response With Sacituzumab Govitecan

Response Outcomes

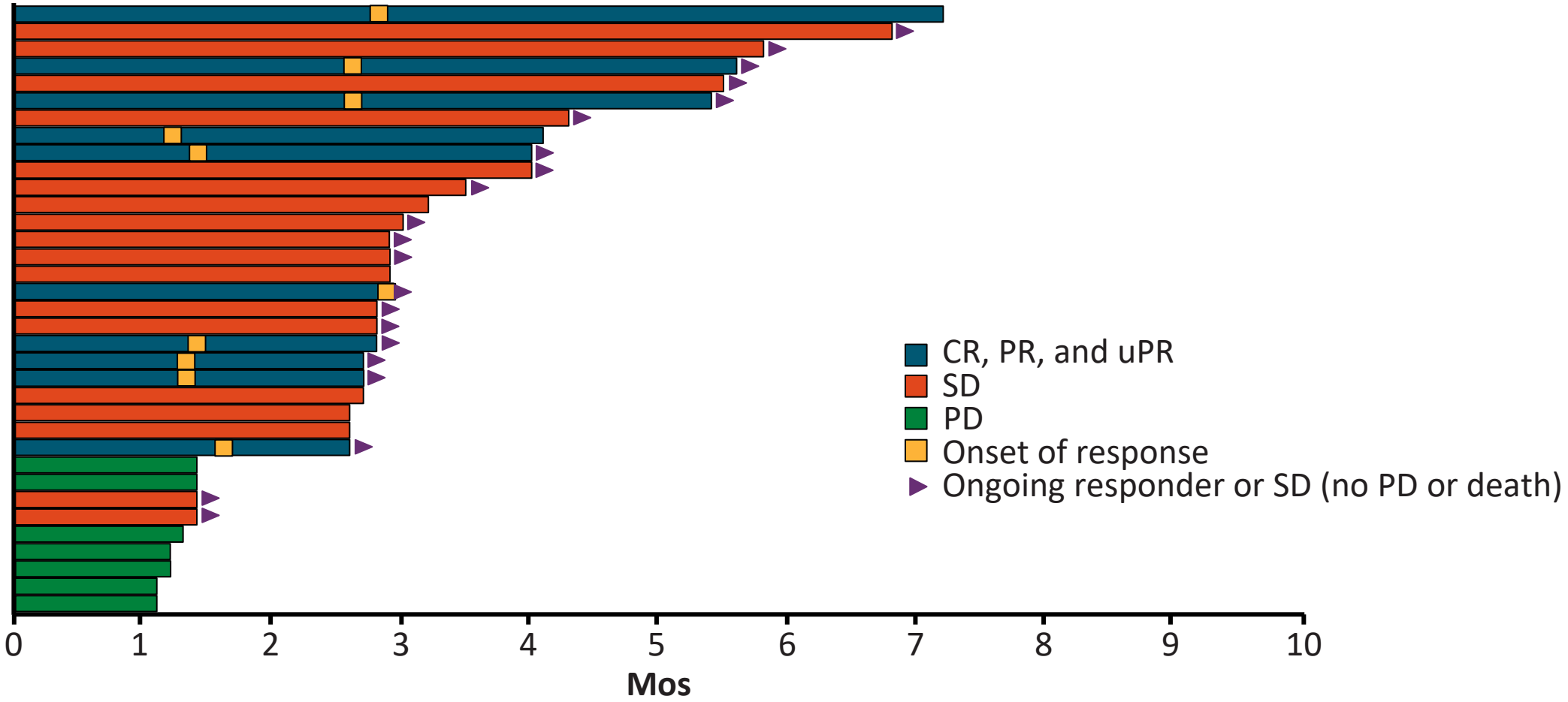
N = 35	
Median follow-up, mos	4.1
Pts continuing treatment, n (%)	20 (57)
ORR, n (%)	10 (29) [95% CI: 15-46]
▪ CR	2 (6)
▪ PR	6 (17)
▪ uPR (pending confirmation)	2 (6)
Median time to response, mos (range)	1.5 (1.2-2.8)

ORR by Subgroup

Category		ORR, % (n/N)
Overall	--	29 (10/35)
Age, yrs	< 75 ≥ 75	29 (8/28) 29 (2/7)
ECOG PS	0 1	33 (5/15) 25 (5/20)
Prior regimens, n	2 ≥ 3	18 (2/11) 33 (8/24)
Visceral involvement at study entry	Yes Liver No	23 (5/22) 25 (2/8) 39 (5/13)
Bellmunt risk factors	0-1 2-3	35 (10/29) 0 (0/6)

Tagawa. ESMO 2019. Abstract 354.

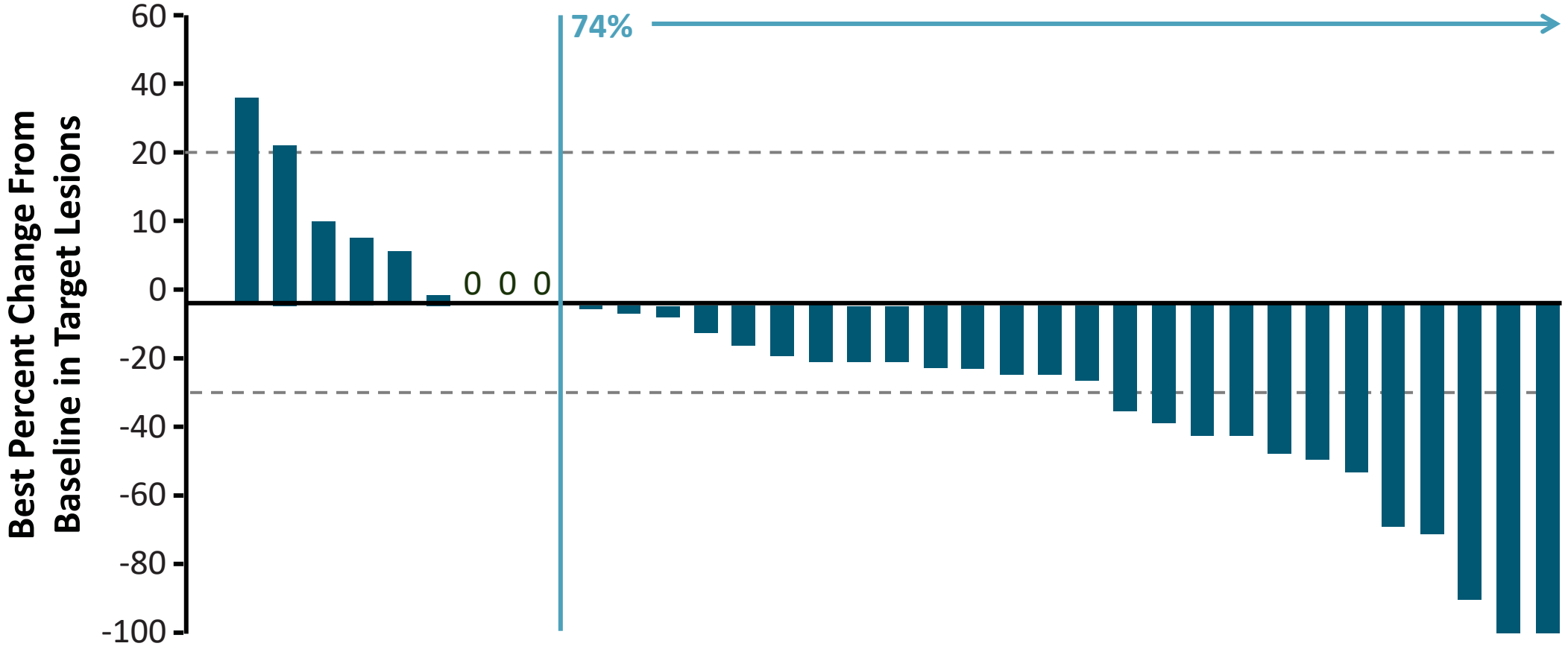
TROPHY-U-01 Cohort 1: DoR With Sacituzumab Govitecan



- 8 of 10 responders have ongoing response at data cutoff

Tagawa. ESMO 2019. Abstract 354.

TROPHY-U-01 Cohort 1: Tumor Reduction With Sacituzumab Govitecan



Tagawa. ESMO 2019. Abstract 354.

TROPHY-U-01: Sacituzumab Govitecan in mUC After Platinum-Based or Anti–PD-1/ PD-L1—Based Therapy

- An international, single-arm, open-label phase II trial
- Sacituzumab govitecan: antibody-drug conjugate; Trop-2 antibody coupled to cytotoxic agent SN-38 via hydrolyzable linker

Pts with advanced or metastatic UC

- ***Cohort 1***: progression after platinum-based and PD-1/PD-L1–targeted agents (n = 100)
- ***Cohort 2***: platinum-ineligible with progression after PD-1/PD-L1–targeted agents (n = 40)

→ **Sacituzumab Govitecan**
10 mg/kg
Days 1 and 8, every 21 days
→ Continue treatment in the absence of unacceptable toxicity or PD

- Primary endpoints: ORR, DoR, PFS, OS

Tagawa. ASCO GU 2019. Abstr 354. Petrylak. ASCO 2020. Abstr 5027.

TROPHY-U-01 Cohort 2: Exposure and Response Outcomes Sacituzumab Govitecan in Metastatic UC

- Median treatment cycles, n (range): 5 (1-15)
- Median duration of treatment, n (range): 4.5 mos (0.3-15.6)
- Median dose intensity: 92%

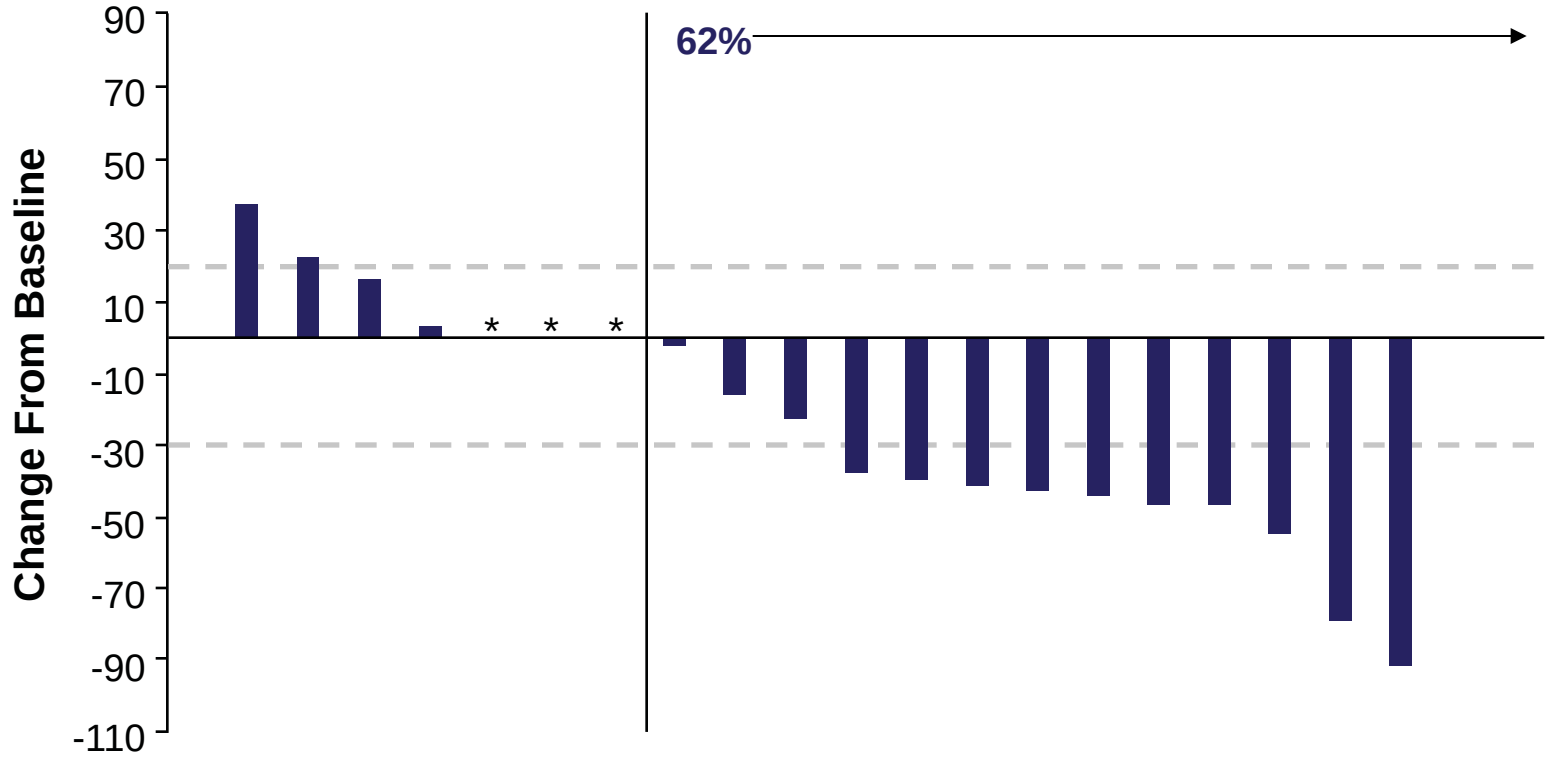
	N = 21
Median follow-up, mos (range)	6.8 (1.6-18.9)
Patients continuing Tx, n (%)	9 (43)
ORR, n (%) ▪ CR ▪ PR ▪ SD	6 (29) [95% CI: 12-54] 0 6 (29) 10 (48)
Median TTR, mos (range)	1.3 (1.1-1.5)
CBR*, n (%)	7 (33) [95% CI: 15-59]
Median DoR, mos (range)	NR (4.3-NR)

*CR + uCR + PR + uPR or (SD ≥ 6 mos)

Petrylak. ASCO 2020. Abstract 5027.

TROPHY-U-01 Cohort 2: Tumor Size Reduction With Sacituzumab Govitecan in Metastatic UC

- 62% (13/21) demonstrated a reduction in tumor size

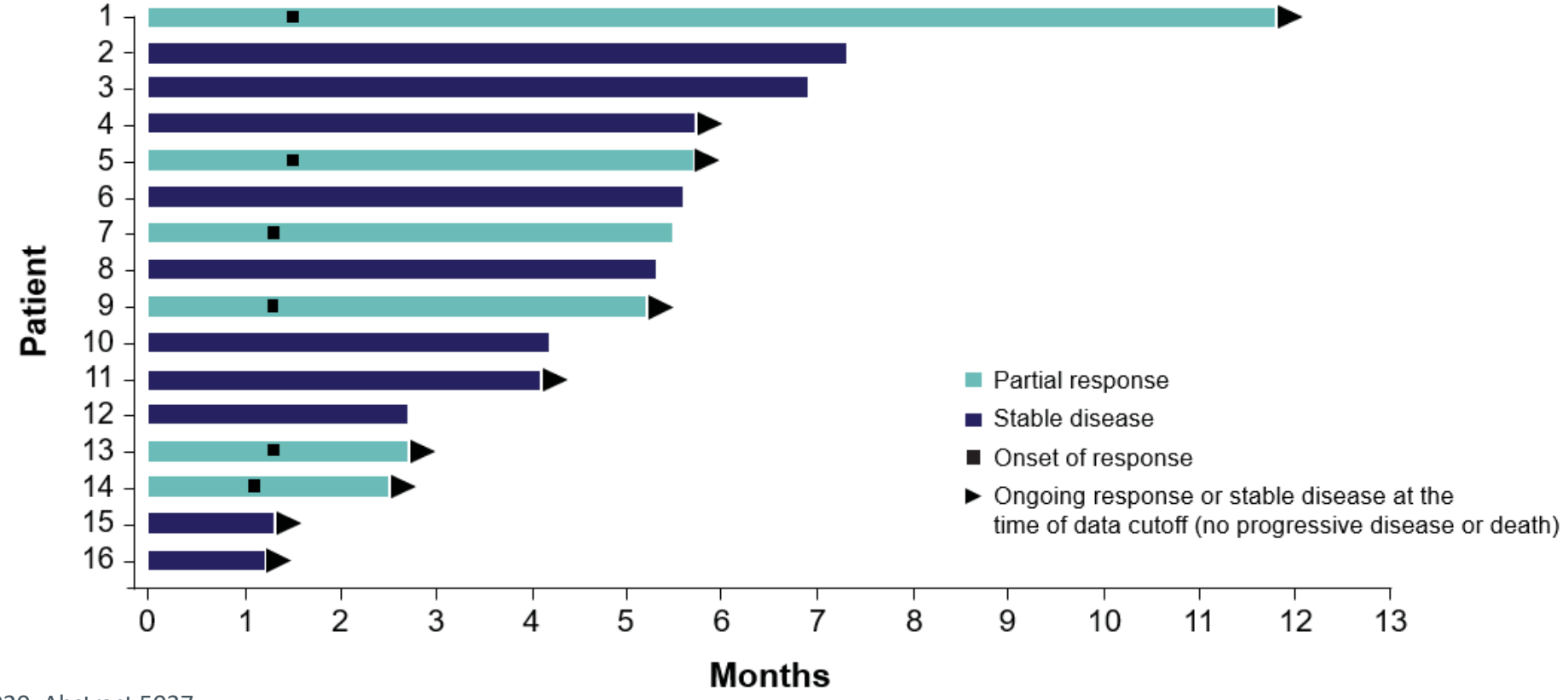


*0% change

Petrylak. ASCO 2020. Abstract 5027.

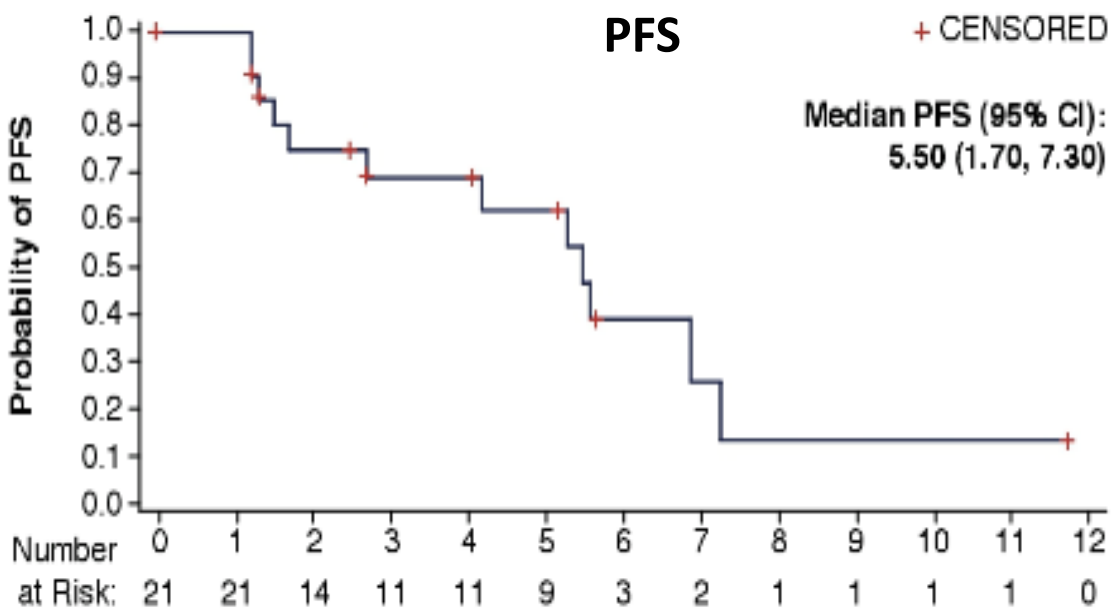
TROPHY-U-01 Cohort 2: DoR (Local Assessment) With Sacituzumab Govitecan in Metastatic UC

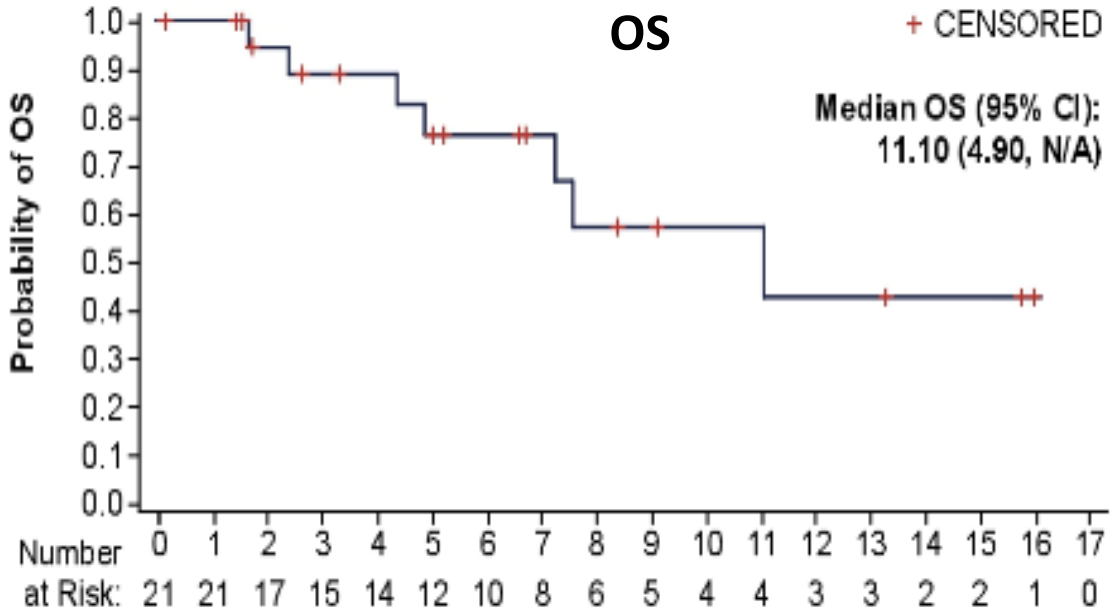
- Median DoR: not reached; range: 1.4+ to 10.4+ mos
- 3 or 6 responding pts w/DoR ≥ 4 mos; 5 of 6 responders w/ongoing response



Petrylak. ASCO 2020. Abstract 5027.

TROPHY-U-01 Cohort 2: PFS and OS With Sacituzumab Govitecan in Metastatic UC





- At this early follow-up, the median PFS and OS compare favorably to current standards of care for platinum-ineligible patients with metastatic UC who have progressed after checkpoint inhibitor therapy
- OS (95% CI) at 6 mos and 12 mos: 76.4% (48.4-90.5) and 43.0% (13.1-70.4), respectively

Petrylak. ASCO 2020. Abstract 5027.

PIVOT-02: Bempegaldesleukin (NKTR-214) in Metastatic UC and Other Solid Tumors

DOSE ESCALATION (multiple tumor types)

Bempegaldesleukin 0.003 mg/kg Q2W
Nivolumab 240 mg Q2W

Bempegaldesleukin 0.006 mg/kg Q2W
Nivolumab 240 mg Q2W

Recommended phase II dose

Bempegaldesleukin 0.006 mg/kg Q2W
Nivolumab 360 mg Q2W

DOSE EXPANSION

Unresectable, locally advanced or metastatic UC; cisplatin ineligible or eligible and refused SoC; ECOG PS 0-1

Bempegaldesleukin 0.006 mg/kg Q2W
Nivolumab 240 mg Q2W

Other tumor types being evaluated in separate expansion arms

Bempegaldesleukin 0.009 mg/kg Q3W
Nivolumab 360 mg Q3W

- Primary endpoints: safety/tolerability, ORR
- Secondary/exploratory endpoints: DoR, OS, PFS, CBR, PK, ORR by irRECIST
- Biomarker endpoints: ALC, blood immunophenotyping; biopsies at baseline and Wk 3 where feasible
- ≥ 1 dose bempegaldesleukin in mUC cohort: n = 41
  - Efficacy evaluable: n = 27

Siefker-Radtke. ASCO GU 2019. Abstract 388.

PIVOT-02: Treatment-Related Adverse Events With Bempegaldesleukin in Metastatic UC

Treatment-Related AE, n (%)	N = 45
≥ 1 TRAE	36 (88)
Grade 1/2 AEs in > 15% of patients	
▪ Flu-like symptoms	29 (71)
▪ Fatigue	23 (56)
▪ Rash	19 (46)
▪ Pruritis	13 (32)
▪ Decreased appetite	11 (27)
▪ Nausea	9 (22)

Treatment-Related AE, n (%)	N = 45
Grade 3 TRAE in at least 1 patient	6 (15)
▪ Flu-like symptoms	2 (5)
▪ Hypotension	1 (2)
▪ Reaction with eosinophilia, systemic symptoms	1 (2)
▪ Encephalopathy	1 (2)
▪ Hypereosinophilic syndrome	1 (2)
▪ Myasthenic syndrome	1 (2)
▪ Complete atrioventricular block	1 (2)
▪ Myocarditis	1 (2)
▪ Myositis	
Grade 4/5 TRAE	0
Discontinued due to TRAE	4 (10)

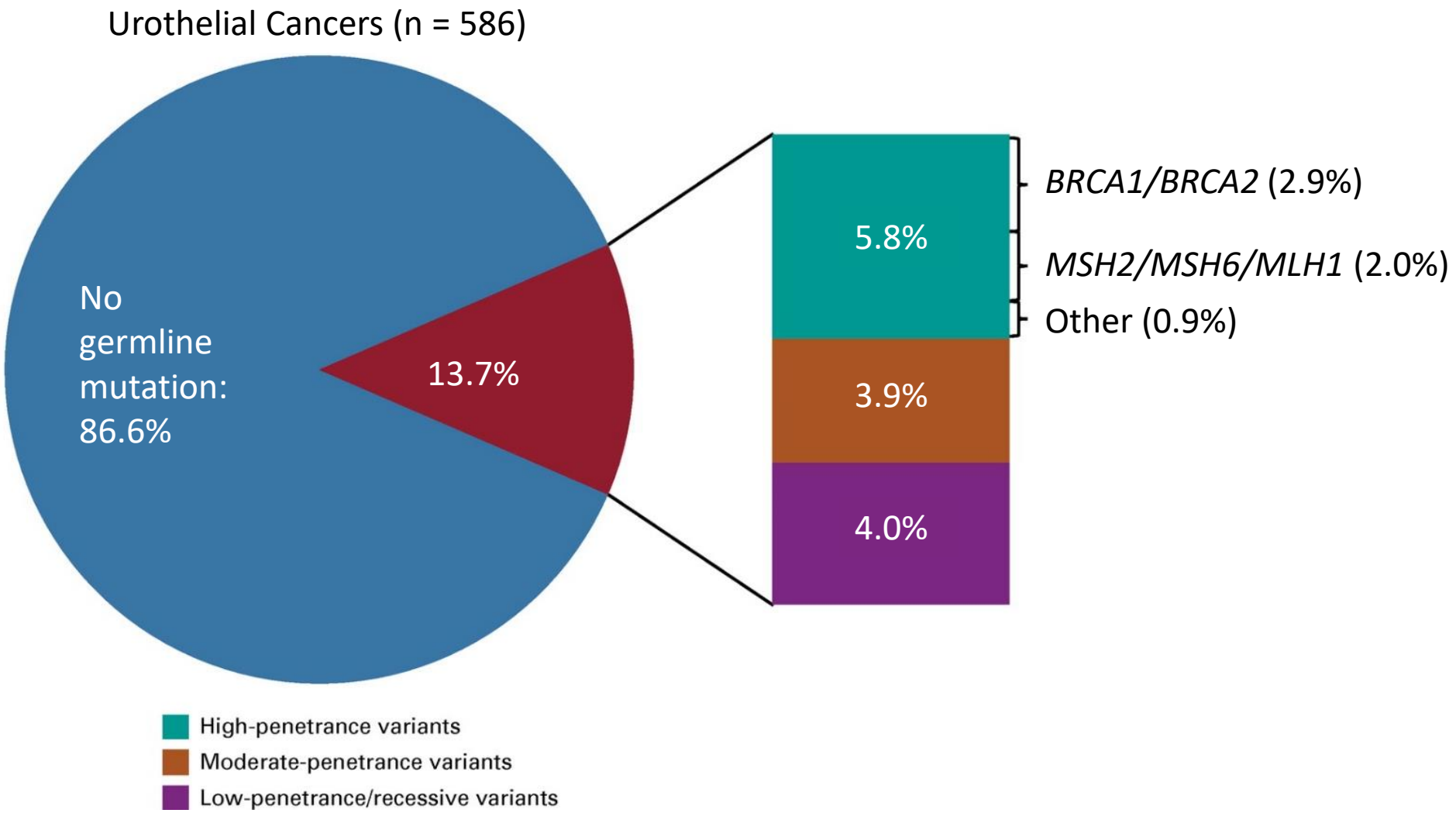
Siefker-Radtke. ASCO GU 2019. Abstract 388.

PIVOT-02: Response With Bempegaldesleukin in Metastatic UC

Response, n (%)	Total Efficacy Evaluable (N = 27)	PD-L1 < 1% (n = 11)	PD-L1 ≥ 1% (n = 12)	PD-L1 Unknown (n = 4)
ORR (CR + PR)	13 (48)	5 (45)	6 (50)	2 (50)
▪ CR	5 (19)	2 (18)	3 (25)	0
▪ PR	8 (30)	3 (27)	3 (25)	2 (50)
DCR (CR + PR + SD)	19 (70)	8 (73)	9 (75)	2 (50)
▪ SD	6 (22)	3 (27)	3 (25)	0
▪ PD	8 (30)	3 (27)	3 (25)	2 (50)

Siefker-Radtke. ASCO GU 2019. Abstract 388.

Germline Variants in Urothelial Cancer: Frequency and Penetrance

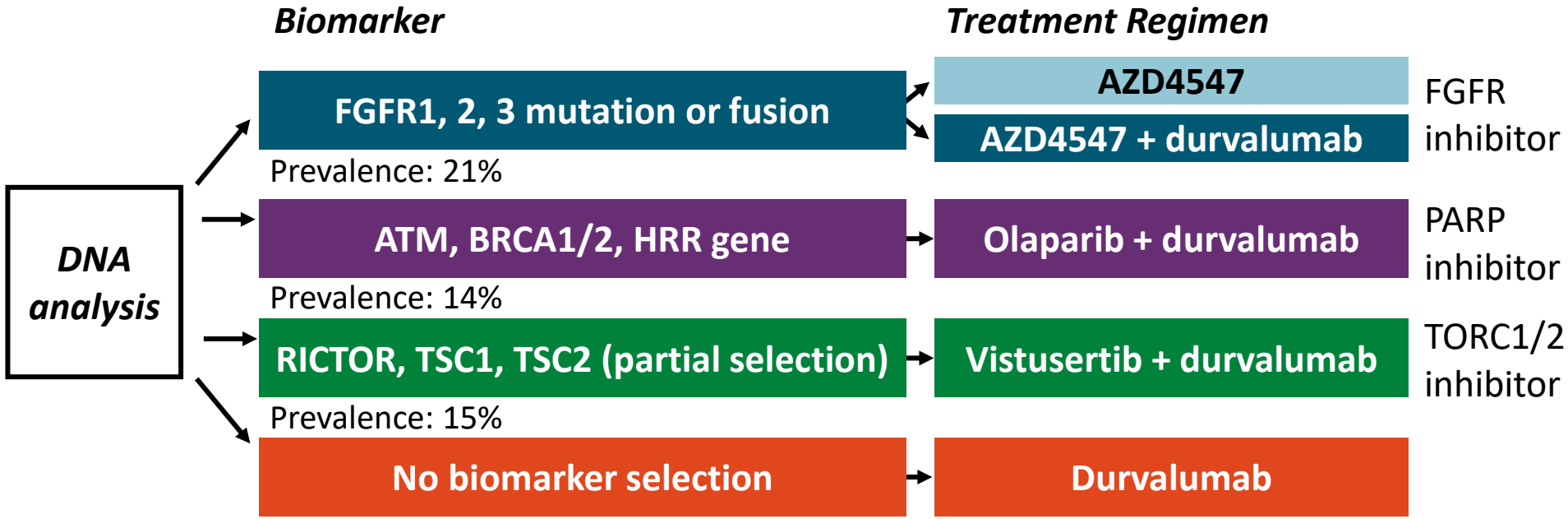


Carlo. JCO. 2020;38:406.

BISCAY: Durvalumab-Based, Biomarker-Directed Randomized Trial in Metastatic UC

- Open-label, randomized, biomarker directed, multiarm phase Ib trial

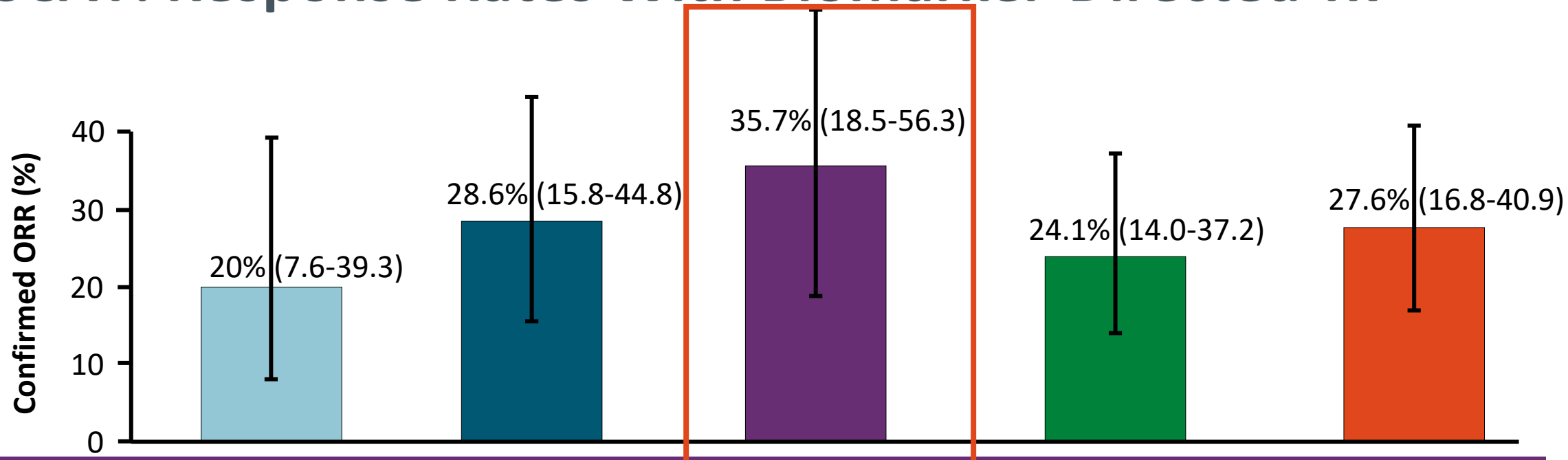
Patients with metastatic UC and ≥ 1 previous line of platinum-based CT for mUC or PD < 1 yr of perioperative platinum-based CT; WHO PS 0/1; archived tissue for biomarker assessment (N = 108)



- Primary endpoint: safety and tolerability
- Secondary endpoints: efficacy (ORR, DCR, PFS, DoR, OS) of durvalumab alone or in combination; immunogenicity of durvalumab; pharmacokinetics

Powles. ESMO 2019. Abstr 902O.

BISCAY: Response Rates With Biomarker-Directed Tx



	AZD4547 (n = 15)	AZD4547 + Durvalumab (n = 21)	Olaparib + Durvalumab (n = 14)	Vistusertib + Durvalumab (n = 29)	Durvalumab (n = 29)
Durvalumab*	80 mg BID	80 mg BID	300 mg PO	150 mg BID D1,2/wk	--
PD-L1+, %	25	23	50	50	54
tTMB ≥ 10, %	23	5	54	43	18

*Dose of durvalumab: 1500 mg Q4W IV.

Powles. ESMO 2019. Abstr 902O.

COSMIC-021 Cohort 2 Expansion: Study Design

- Ongoing, multicenter, single-arm phase Ib study

Patients with locally advanced or metastatic UC with transitional cell histology, radiographic evidence of progression on/after platinum-containing CT,* ECOG PS 0/1, and no prior ICIs or cabozantinib
(N = 30)

→

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

→

Until loss of clinical benefit or unacceptable AE

Follow-up: every 6 wks in Yr 1 and every 12 wks thereafter

*Patients eligible if they had radiographic evidence of recurrent disease within 12 mos from the end of previous (neo)adjuvant platinum-containing therapy.

- Primary endpoint: investigator-assessed ORR per RECIST v1.1 criteria
- Secondary/exploratory endpoints: safety, DoR, investigator-assessed PFS per RECIST v.1.1 criteria, OS, biomarkers

Pal. ASCO 2020. Abstr 5013.

COSMIC-021 Cohort 2 Expansion: Efficacy

Investigator-Assessed Tumor Response (RECIST v1.1 Criteria)	UC Cohort 2 (N = 30)
ORR, % (80% CI)	27 (16-40)
Best overall response, n (%) ▪ CR ▪ PR ▪ SD ▪ PD ▪ Missing	 2 (6.7) 6 (20) 11 (37) 7 (23) 4 (13)
DCR (CR + PR + SD), n (%)	19 (63)
Median DoR, mos (range)	NR (1.4+ to 15.6+)
Median time to objective response, mos (range)	3 (1-6)

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

Pal. ASCO 2020. Abstr 5013.

Devam eden çalışmalar (KT + İmmünoterapi)

								Safety		
NCT02853305 (KEYNOTE-361)	III	First-line	All	Pembrolizumab	Pembrolizumab + gemcitabine + cisplatin (or carboplatin)	Placebo + gemcitabine + cisplatin (or carboplatin)	Pembrolizumab: anti-PD-1	990	PFS OS	Active, not recruiting	May 2020
NCT02807636 (IMvigor130 trial)	III	First-line	All	Atezolizumab	Atezolizumab + gemcitabine + cisplatin (or carboplatin)	Placebo + gemcitabine + cisplatin (or carboplatin)	Atezolizumab: anti-PD-L1	1200	PFS OS Safety	Active, not recruiting	November 2020
NCT03093922	II	First-line	All	Atezolizumab + gemcitabine + cisplatin	Atezolizumab + gemcitabine + cisplatin (modified schedule)	Atezolizumab + gemcitabine + cisplatin (modified schedule)	Atezolizumab: anti-PD-L1	74	ORR	Recruiting	March 2021
NCT03967977	III	First-line	All	Tislelizumab + gemcitabine + cisplatin (or carboplatin)	Placebo + gemcitabine + cisplatin (or carboplatin)		Tislelizumab: humanized monoclonal PD-1 antibody	420	OS	Recruiting	July 2022
NCT03737123	II	Second-line (no prior platinum chemotherapy)	Cisplatin ineligible	Atezolizumab + chemotherapy (docetaxel or gemcitabine + carboplatin)			Atezolizumab: anti-PD-L1	33	PFS	Recruiting	January 2022

NCT03682068 (NILE)	III	First-line	All	Durvalumab + gemcitabine + cisplatin (or carboplatin)	Durvalumab + tremelimumab + gemcitabine + cisplatin (or carboplatin)	Gemcitabine + cisplatin (or carboplatin)	Durvalumab: anti-PD-L1. Tremelimumab: anti-CTLA-4.	885	PFS OS	Recruiting	April 2022
NCT03036098 (CheckMate-901)	III	First-line	All	Nivolumab + ipilimumab	Gemcitabine + cisplatin (or carboplatin)	Nivolumab + gemcitabine + cisplatin (or carboplatin)	Nivolumab: anti-PD-1. Ipilimumab: anti-CTLA-4	990	OS in cisplatin ineligible OS in PD-L1 ≥ 1%	Recruiting	December 2022
NCT03219775, (TITAN-TCC)	II	First- or later-line	All	Nivolumab + ipilimumab			Nivolumab: anti-PD-1. Ipilimumab: anti-CTLA-4.	80	ORR	Recruiting	December 2020
NCT02516241 (DANUBE)	III	First-line	All	Durvalumab + tremelimumab	Durvalumab	Gemcitabine + cisplatin (or carboplatin)	Durvalumab: anti-PD-L1. Tremelimumab: anti-CTLA-4.	1126	OS	Active, not recruiting	May 2020

İmmünoterapi + Antianjiojenik ajanlar

NCT03272217	II	First-line	Cisplatin ineligible	Atezolizumab + bevacizumab		Bevacizumab: anti-VEGF	70	OS	Recruiting	June 2021
NCT03472560 (JAVELIN Medley VEGF)	II	Second- or later-line	Cisplatin ineligible	Avelumab + axitinib		Avelumab: anti-PD-L1. Axitinib: tyrosine kinase inhibitor.	61	OR	Active, not recruiting	September 2020
NCT03898180 (LEAP-011 trial)	III	First-line, PD-L1 ≥ 10%	Cisplatin ineligible	Pembrolizumab + lenvatinib	Pembrolizumab + placebo	Lenvatinib: tyrosine kinase inhibitor	694	PFS OS	Recruiting	December 2022
NCT03534804 (PemCab)	II	First-line	Cisplatin ineligible	Pembrolizumab + cabozantinib		Cabozantinib: tyrosine kinase inhibitor	39	ORR	Recruiting	September 2023
NCT03824691 (ARCADIA)	II	Second-line or third-line	All	Durvalumab + cabozantinib		Durvalumab: anti-PD-L1. Cabozantinib: tyrosine kinase inhibitor.	122	OS	Recruiting	February 2023
NCT03866382	II	First- or later-line	All	Nivolumab + ipilimumab + cabozantinib		Nivolumab: anti-PD-1. Ipilimumab: anti-CTLA-4. Cabozantinib: tyrosine kinase inhibitor.	186	ORR	Recruiting	February 2023
NCT04066595 (CabUC)	II	Second-line or third-line	All	Cabozantinib		Cabozantinib: tyrosine kinase inhibitor	88	ORR 6-month	Recruiting	September 2024

İmmünoterapi + Yeni ajanlar

NCT03361865 (KEYNOTE-672/ECHO-307)	III	First-line	Cisplatin ineligible	Pembrolizumab + epacadostat	Pembrolizumab + placebo	Epacadostat: IDO1 inhibitor. Pembrolizumab: anti-PD-1.	93	ORR	Active, not recruiting	September 2020
NCT03374488	III	Second- or later-line	All	Pembrolizumab + epacadostat	Pembrolizumab + placebo	Epacadostat: IDO1 inhibitor. Pembrolizumab: anti-PD-1.	84	ORR	Active, not recruiting	August 2020
NCT02554812 (JAVELIN Medley)	II	Second- or third-line	All	6 cohorts, different combinations with avelumab, PF-04518600 and utomilumab (PF-05082566)		PF-04518600: OX40 agonist. Utomilumab: 4-1BB agonist. Avelumab: anti-PD-L1.	620	Safety OR	Recruiting	December 2022
NCT03785925 (PIVOT-10)	II	First-line	Cisplatin ineligible	Nivolumab + Bempegaldesleukin (NKTR-214)		Bempegaldesleukin (NKTR-214): IL-2 pathway agonist designed to target CD122. Nivolumab: anti-PD-1.	205	ORR	Recruiting	March 2022
NCT03513952	II	Second- or later-line (prior platinum chemotherapy)	All	Atezolizumab + CYT-107	Atezolizumab	CYT-107: glycosylated recombinant human interleukin-7. Atezolizumab: anti-PD-L1.	54	ORR	Recruiting	December 2020

NCT02795156	II	Second-line	All	Afatinib or Regorafenib or Cabozantinib (based on specific genomic alterations on next-generation sequencing)			Afatinib, Regorafenib, Cabozantinib: tyrosine kinase inhibitor	160	ORR	Recruiting	December 2020
NCT02872714 (FIGHT-201)	II	Second- or later-line	All	Pemigatinib			Pemigatinib: FGFR inhibitor	240	ORR	Recruiting	August 2020
NCT03410693 (FORT-1)	II/III	Second- or later-line	All	Rogaratinib (BAY1163877)	Chemotherapy		Rogaratinib: FGFR inhibitor	171	OS	Active, not recruiting	November 2020
NCT04003610 (FIGHT-205)	II	First-line	Cisplatin ineligible	Pemigatinib + Pembrolizumab	Pemigatinib	Chemotherapy or pembrolizumab	Pemigatinib: FGFR inhibitor. Pembrolizumab: anti-PD-1.	372	PFS	Recruiting	June 2024
NCT03190174	I/II	Second- or later-line	All	Nivolumab + ABI-009 (Nab-rapamycin)			ABI-009 (Nab-rapamycin): mTOR inhibitor. Nivolumab: anti-PD-1.	40	Safety	Recruiting	April 2021

NCT03547973	II	First-line (in platinum unfit) or second- or later-line (with prior platinum-based chemotherapy or ICI)	All	Sacituzumab govitecan (IMMU-132)			Sacituzumab govitecan (IMMU-132): Anti-Trop-2/SN-38 Antibody-Drug Conjugate	201	ORR	Recruiting	September 2021
NCT04223856 (EV-302)	III	First-line	Cisplatin or carboplatin eligible	Enfortumab vedotin + pembrolizumab	Enfortumab vedotin + pembrolizumab + cisplatin or carboplatin	Gemcitabine + cisplatin or carboplatin	Enfortumab vedotin: anti nectin-4 monoclonal antibody liked to a micro-tubule-disrupting agent (monomethyl auristatin E). Pembrolizumab: anti-PD-1.	1095	PFS, OS	Recruiting	November 2023
NCT03474107 (EV-301)	III	Third- or later-line	All	Enfortumab vedotin	Chemotherapy (docetaxel, vinflunine, paclitaxel)		Enfortumab vedotin: anti nectin-4 monoclonal antibody liked to a micro-tubule-disrupting agent (monomethyl auristatin E)	608	OS	Active, not recruiting	September 2021

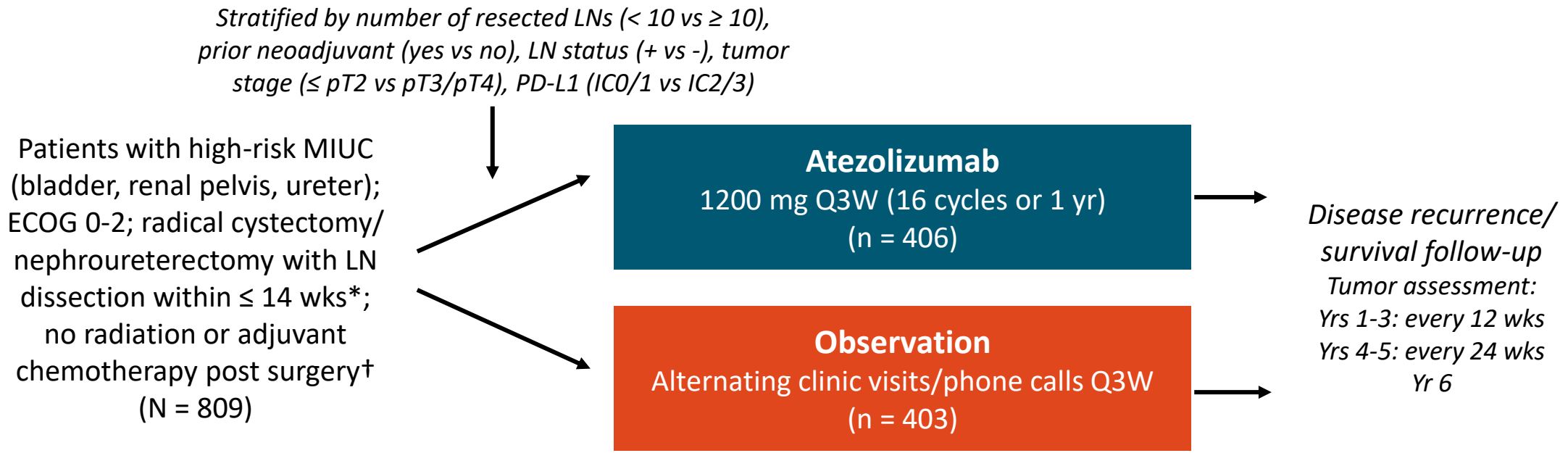
Adjuvan PD-1/PD-L1 İnhibitörleri Faz III çalışmalar

Trial	Population	Control Arm	Experimental Arm	Primary Endpoint
IMvigor010[1] **PI: Apolo**	All-comers MIUC Prior NAC: ≥ pT2 No AC: ≥ pT3	No therapy	Atezolizumab	DFS
CheckMate 274[2] **PI: Sonpavde**	All-comers MIUC Prior NAC: ≥ pT2 No AC: ≥ pT3	Placebo	Nivolumab	PFS
AMBASSADOR[3] **Intergroup trial** **ECOG PI: Srinivas**	All-comers MIUC Prior NAC: ≥ pT2 No AC: ≥ pT3	No therapy	Pembrolizumab	DFS/OS

1. NCT02450331. 2. NCT02632409. 3. NCT03244384.

IMvigor010: Adjuvant Atezolizumab vs Observation in Patients With High-Risk MIUC

- International, open-label, randomized phase III study



*Upper tract UC staging eligibiity cirteria: For patients given neoadjuvant chemotherapy: ypT2-T4a or ypN+. For patients *not* given neoadjuvant chemotherapy: pT3-T4a or pN+. †To be enrolled, patients who were not given neoadjuvant chemotherapy also must have been ineligible or declined adjuvant cisplatin-based therapy.

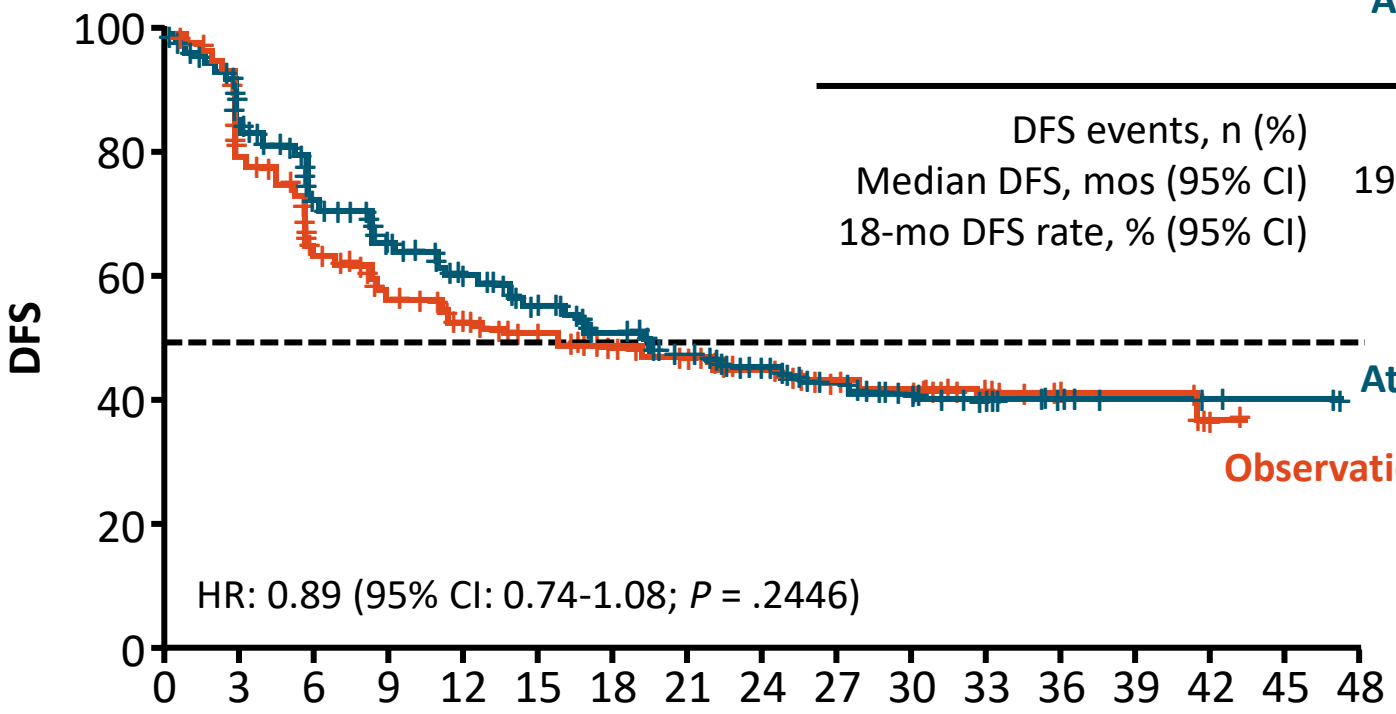
- Primary endpoint: DFS (ITT)

Data cutoff: November 30, 2019

- Secondary endpoints: OS (ITT), safety; exploratory: biomarkers including PD-L1 status

Hussain. ASCO 2020. Abstr 5000.

IMvigor010: Similar DFS With Adjuvant Atezolizumab vs Observation in High-Risk MIUC (ITT; Primary Endpoint)



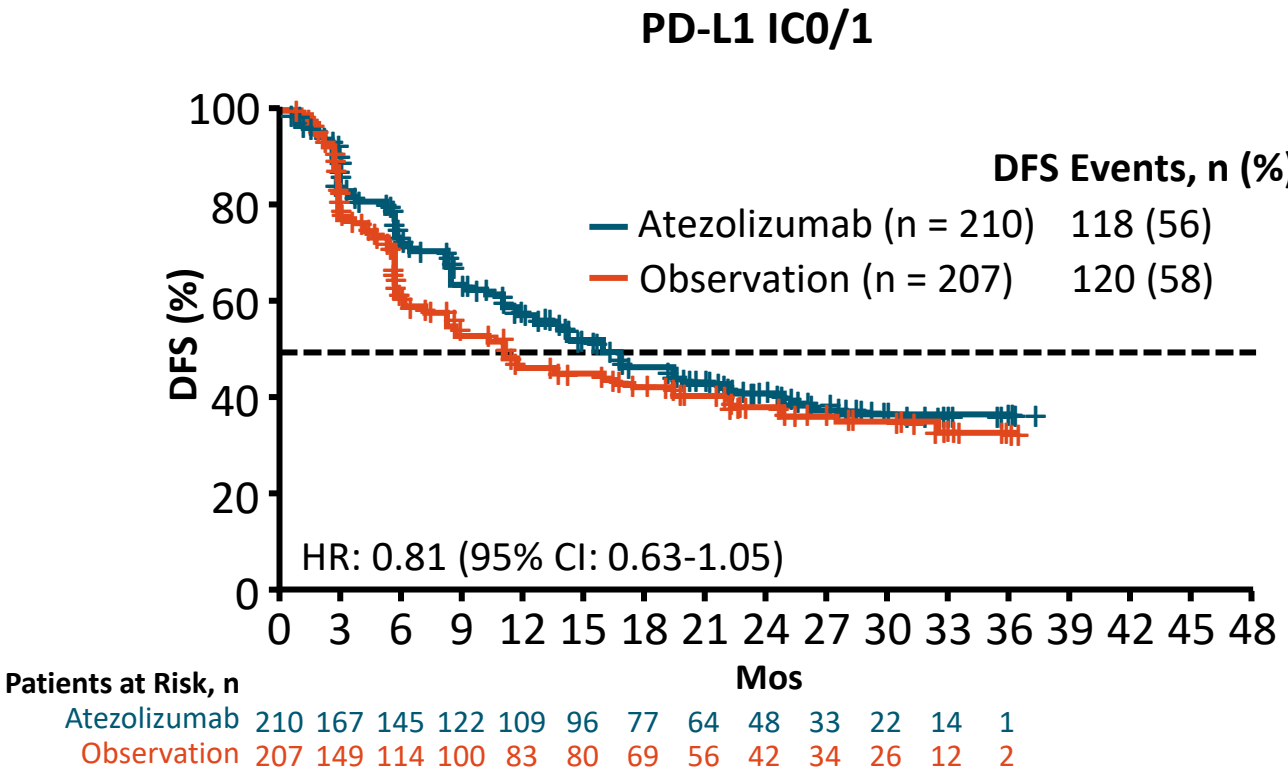
	Atezolizumab (n = 406)	Observation (n = 403)
DFS events, n (%)	212 (52)	208 (52)
Median DFS, mos (95% CI)	19.4 (15.9-24.8)	16.6 (11.2-24.8)
18-mo DFS rate, % (95% CI)	51 (46-56)	49 (44-54)

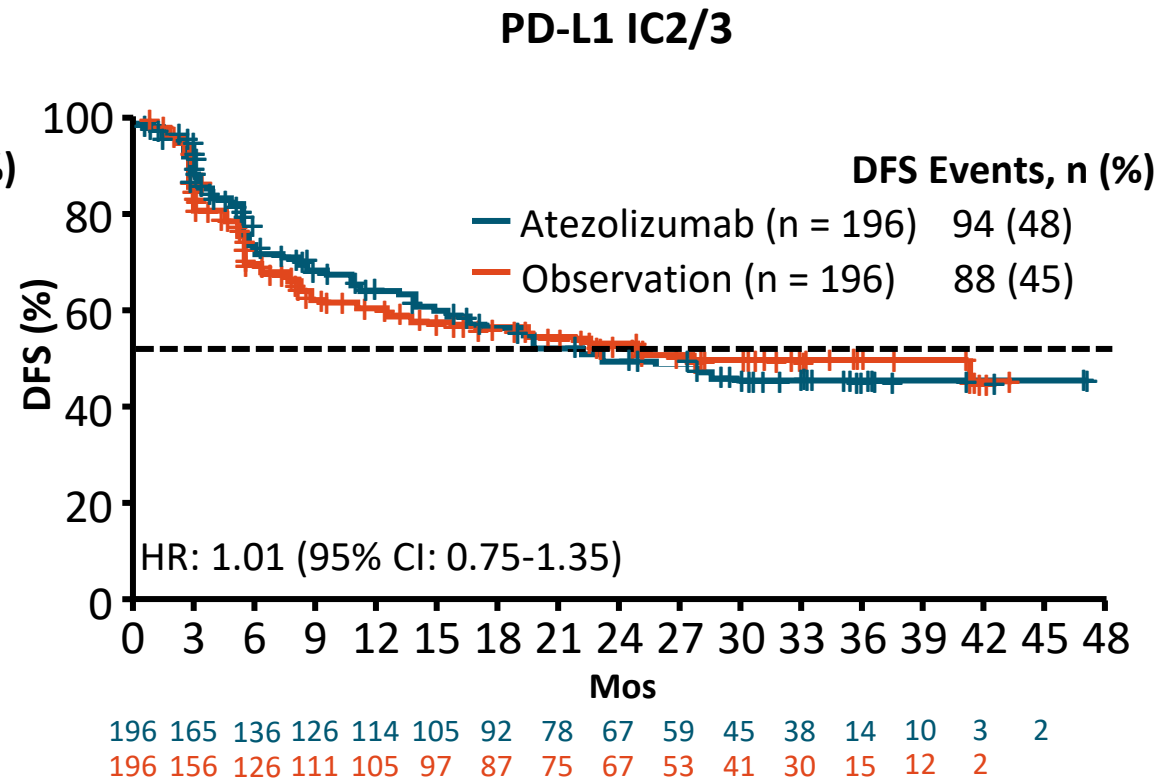
Patients at Risk, n

Atezolizumab	406	332	281	248	223	201	169	142	115	92	67	52	15	10	3	2
Observation	403	305	240	211	188	177	156	131	109	87	67	42	17	12	2	

Hussain. ASCO 2020. Abstr 5000.

IMvigor010: Similar DFS With Atezolizumab vs Observation in High-Risk MIUC Regardless of PD-L1 Expression



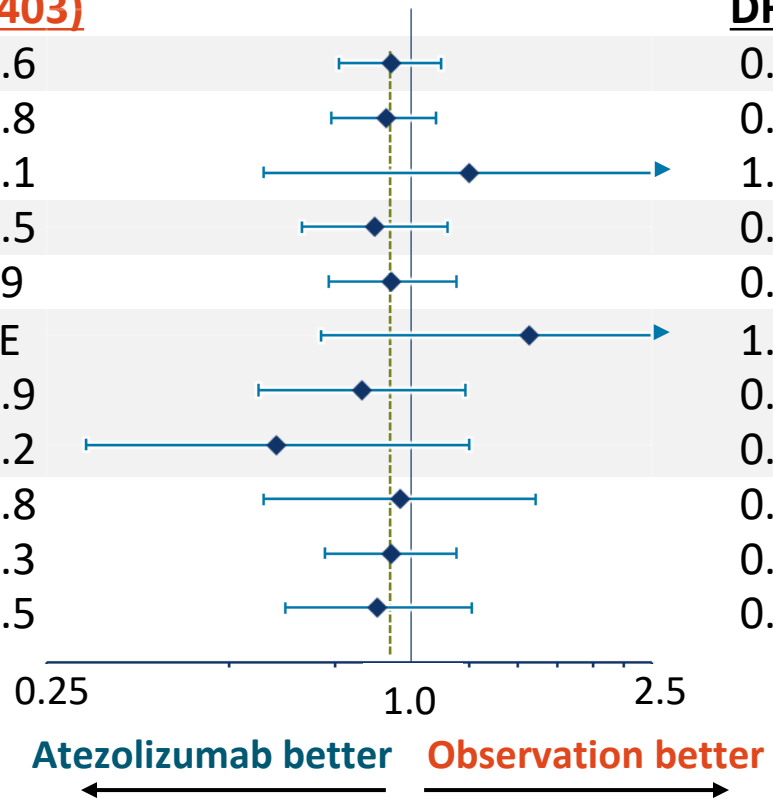


Data cutoff: November 30, 2019. IC2/3, PD-L1–expressing IC on ≥ 5% of tumor area (VENTANA SP142 assay); IC0/1, < 5%. [a] Stratified by tumor stage and nodal status.

Hussain. ASCO 2020. Abstr 5000.

IMvigor010: DFS With Atezolizumab vs Observation By Clinical Subgroup

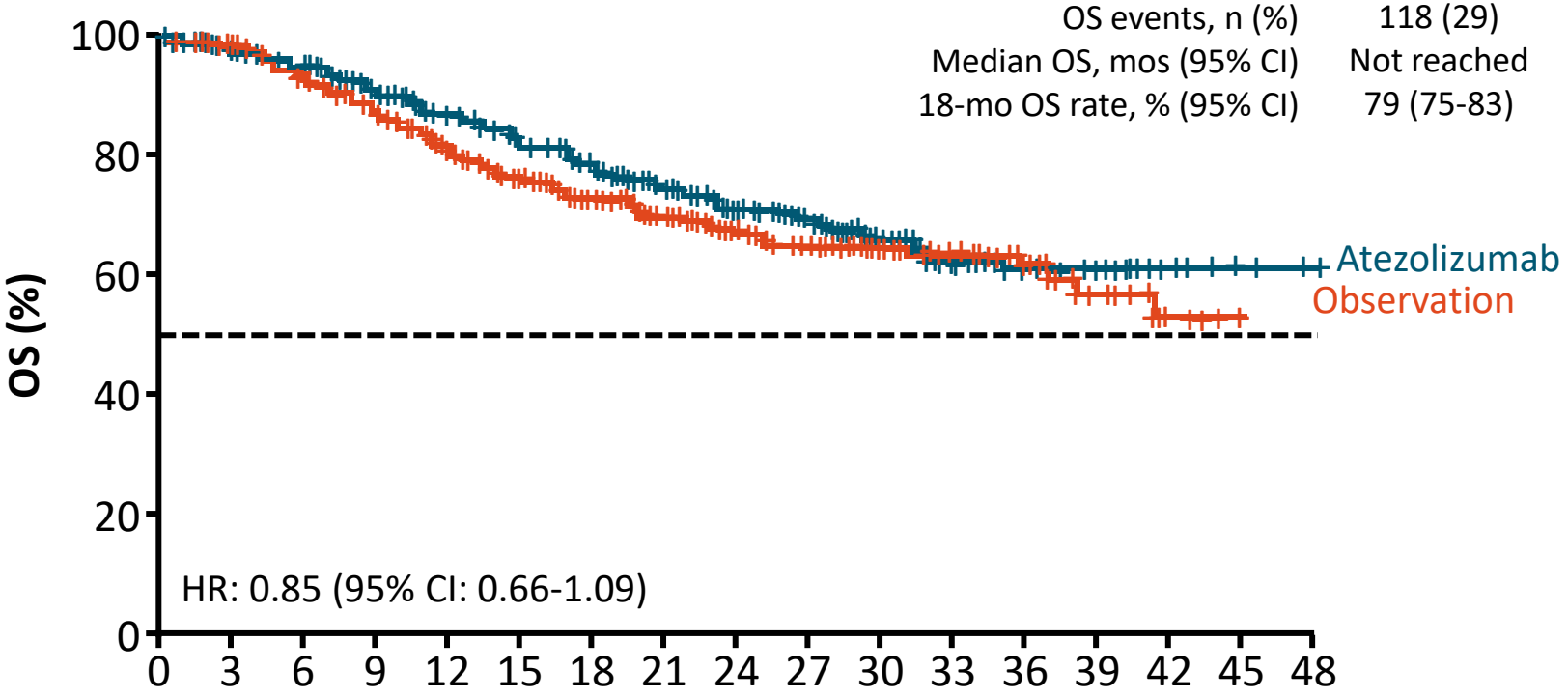
Population (n)	Median DFS, mo: Atezolizumab (N = 406)	Median DFS, mo: Observation (N = 403)	DFS HR (95% CI)[c]
All patients (809)	19.4	16.6	0.93 (0.76-1.12)
Bladder (755)	19.6	15.8	0.91 (0.74-1.10)
Upper tract (ureter, renal pelvis) (54)	14.2	28.1	1.25 (0.57-2.74)
Prior neoadjuvant chemotherapy (385)	19.8	16.5	0.87 (0.66-1.15)
Positive pathologic node status (420)	13.9	8.9	0.93 (0.73-1.19)
pT2N0 (73)	NE	NE	1.57 (0.71-3.46)
pT3N0 (243)	NE	24.9	0.83 (0.56-1.23)
pT4N0 (65)	NE	14.2	0.60 (0.29-1.25)
Asia (125)	23.1	24.8	0.96 (0.57-1.61)
Europe (437)	19.1	12.3	0.93 (0.72-1.19)
North America (241)	19.8	16.5	0.88 (0.62-1.26)



Hussain. ASCO 2020. Abstr 5000.

IMvigor010: OS With Adjuvant Atezolizumab vs Observation in High-Risk MIUC (ITT; Secondary Endpoint)

	Atezolizumab (n = 406)	Observation (n = 403)
OS events, n (%)	118 (29)	124 (31)
Median OS, mos (95% CI)	Not reached	Not reached
18-mo OS rate, % (95% CI)	79 (75-83)	73 (69-78)



Patients at Risk, n																	
Atezolizumab	406	383	369	350	328	306	267	229	185	144	100	72	35	22	8	4	2
Observation	403	377	345	318	289	270	235	199	163	134	100	65	36	20	6	1	

Hussain. ASCO 2020. Abstr 5000.

KEYNOTE-057: Pembrolizumab in Patients With High-Risk NMIBC Unresponsive to BCG

- Single-arm, open-label, phase II study

Patients with high-risk NMIBC who are unresponsive to BCG who are ineligible for or refuse cystectomy

Cohort A: CIS with or without papillary disease* (high-grade Ta or T1) (n = 130)

Cohort B: papillary disease* (high grade Ta or any T1) without CIS (n = 130)

→ **Pembrolizumab**
200 mg Q3W for up to 24 mos →

Eval with cystoscopy, cytology with or without biopsy Q12W x 2 yrs, then Q24W x 2 yrs and once yrly thereafter

CT urogram Q24W x 2 yrs or more frequently as clinically indicated →

If no persistence or recurrence of HR NMIBC, treat until PD, toxicity, death or completion of 2 yrs of treatment
OR
Discontinue *if HR NMIBC present at any assessment*

*Patients with papillary disease must have fully resected disease at study entry.

- Primary endpoint: CR (absence of HR NMIBC) in Cohort A; DFS in Cohort B
- Secondary endpoints: CR (absence of any disease, high or low risk NMIBC) in cohort A, DoR in cohort A, safety

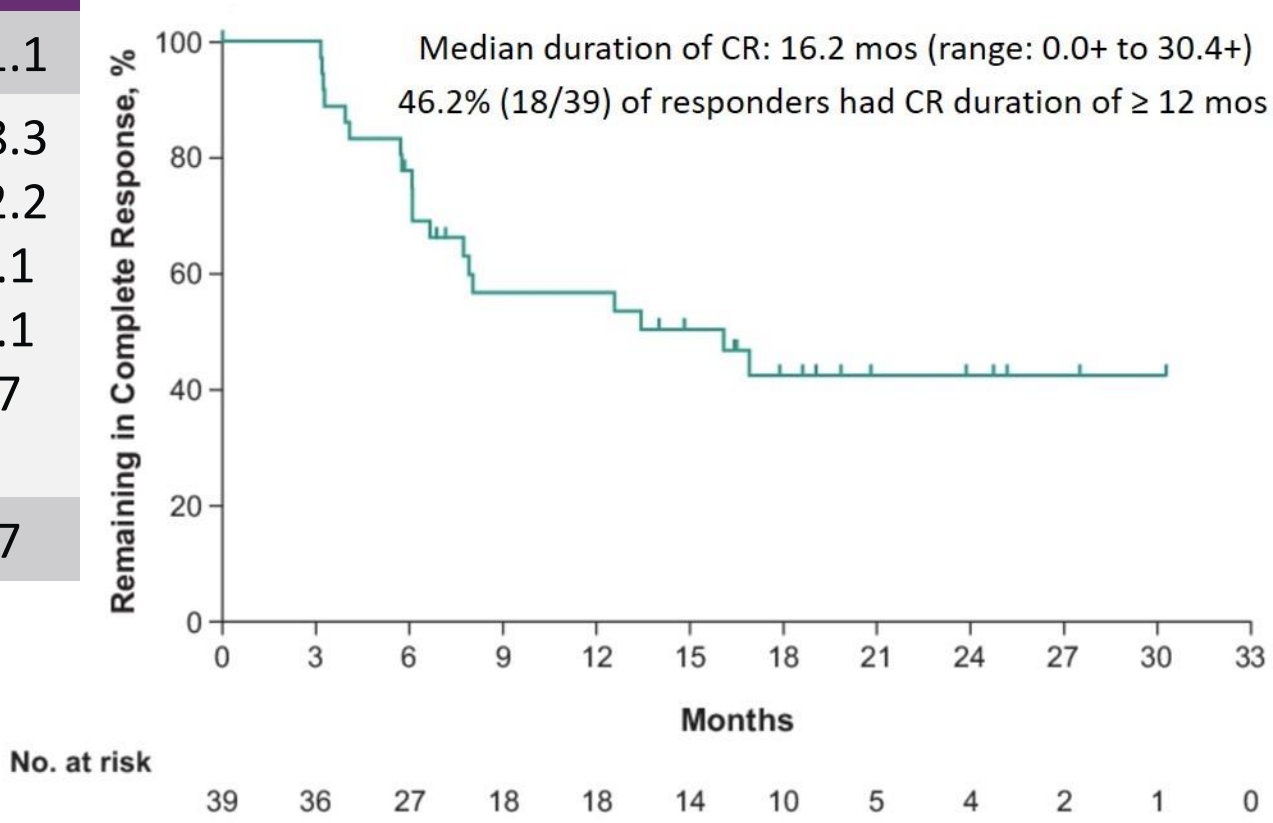
De Wit. ESMO 2018. Abstr. Balar ASCO 2020. Abstr 5041.

KEYNOTE-057: ORR at First Evaluable Assessment

Response (N = 96)	N	%	95% CI
CR	39	40.6	30.7-51.1
Non-CR	56	58.3	47.8-68.3
▪ Persistent	40	41.7	31.7-52.2
▪ Recurrent	6	6.3	2.3-13.1
▪ NMIBC stage progression	9	9.4	4.4-17.1
▪ Non-bladder malignancy	1	1.0	0.0-5.7
▪ Progression to T2	0	0	NA
Nonevaluable	1	1.0	0.0-5.7

- Of 96 patients, 86 discontinued study therapy, most due to persistent disease (n = 38) or recurrent disease/stage progression (n = 33)

DoR in Patients With CR



Balar ASCO 2020. Abstr 5041.

Phase II SWOG S1605 Study: Atezolizumab in BCG-Unresponsive NMIBC

- Single arm phase II registration trial of atezolizumab (1200 mg IV) every 3 wks for 1 yr
- BCG-unresponsive high risk NMIBC; unfit for or declined radical cystectomy
- This report includes patients with CIS (with or without concomitant Ta/T1)
- Primary endpoint: pCR at 6 Mos

Characteristic	Patients (N = 74)
Median age, yrs (range)	73.4 (47.4-90.8)
Male, %	85
White race, %	95
ECOG PS 0/1, n (%)	77 / 23
Median BCG instillations, n (range)	12 (6-29)
Median days since last BCG dose, n (range)	154 (5-346)
Histology, % ▪ TIS ▪ TIS/Ta ▪ TIS/T1 ▪ TIS/Ta/T1	 58 19 18 5

Black. ASCO 2020. Abstr 5022.

Phase II SWOG S1605 Study: Atezolizumab in BCG-Unresponsive NMIBC

- CIS efficacy population N = 74

Event, n	3-Mo	6-Mo
CR	31	20
Persistent CIS	22	31
CIS + Ta/T1	5	0
Recurrent Ta/T1	4	14
Recurrent T2	1	0
Recurrent, unknown stage	3	3
Recur, positive cytology only	2	0
Not assessable	6*	6§

*Due to death (n = 1), site error (n = 2), declining PS from brain tumor (n = 1), grade 3 AE (n = 1).
§Due to death (n = 1), declining PS from brain tumor (n = 1), physician choice (n = 1), withdrew consent (n = 1), grade ≥ 2 AE (n = 2).

- pCR at 3 mos: 42% (95% CI: 31-54)
- **pCR at 6 mos: 27% (95% CI: 17-39)**
- At 3 mos, 32 pts had recurrence (HG Ta or CIS, n = 28; T1, n = 3; T2, n = 1)
  - 9 of 28 with HG Ta/CIS stayed on therapy and 2 experienced CR at 6 mos

Black. ASCO 2020. Abstr 5022.

Neoadjuvan Çalışmalar: Faz I-II

	Trial ID	Name	Phase	Regimen	Primary Endpoint
Chemo-IO	NCT03294304	BLASST-1	II	GC + Nivolumab	pCR
	NCT02690558	LCC 1520	II	GC + Pembrolizumab	pCR
	NCT02365766	HCRN GU14-188	I/II	G/GC + Pembrolizumab	Feasibility, pCR
IO	NCT02451423	Study 14524	II	Atezolizumab	pCR, immune response
	NCT02736266	PURE-01	II	Pembrolizumab	pCR
IO-IO	NCT02812420	Study 2016-0033	II	Durvalumab + Tremelimumab	Feasibility
	NCT02845323	J1682	II	Nivolumab +/- Urelumab	Immune response
	Pending	--	I	Durvalumab +/- CD73i	Feasibility, Immune response

ABACUS and PURE-01: Phase II Trials of Neoadjuvant Checkpoint Inhibition in MIBC

	ABACUS: Atezolizumab (n = 95)[1]	PURE-01: Pembrolizumab (n = 50)[2]
Eligibility	T2-T3b N+ not allowed T4b allowed	T2-T3b N1 allowed (4%) T4b not allowed
Cisplatin ineligible patients, %	100	8
Patients who also received NAC, %	0	10
Duration of neoadjuvant ICP therapy, cycles (wks)	2 (6)	3 (9)
Primary endpoint	pCR, TILs	pCR
	pCR: 31%	**pCR: 42%**

1. Powles. Nat Med. 2019;[Epub]. 2. Necchi. J Clin Oncol. 2018;36:3353.

Sonuç;

- Metastatik hastalıkta ilk sıra tedavi platin bazlı kemoterapi standart, hangi hastalarda immünoterapi eklenebilir?
- Cisplatin uygulaması uygun olmayan hastalarda;

*carboplatin bazlı KT veya non-platin bazlı KT

*PD-L 1 yüksek olan hastalarda immünoterapi veya nonplatin bazlı KT+ immünoterapi(pembro veya Atezo)?

- İlk sıra platin bazlı KT sonrası idame tedavide avelumab idamesi OS uzatıyor

Sonuç;

- İkinci sıra tedavide immünoterapi (pembro, ipi +nivo,??),

*FGFR 2veya 3 genetik alterasyonu olanlarda erdatifinib, olmayanlarda enfortumab vedotin?

- 3.sıra tedavi seçenekleri? Sacituzumab govitecan?
- Devam eden çalışmaların sonuçları klinik pratiğimize etkisi
- Adjuvan ve Neoadjuvan Faz III çalışmaların sonuçları ???


Teşekkürler