Current Treatment Landscape in First-line Urothelial Cancer

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A.5% of patients have metastatic disease at the time of diagnosis.

B.50 %patients relapse after cystectomy depending on the pathologic stage of the tumor and nodal status
1)10% to 30% Local recurrences
2)70 %-distant metastases.

	T	N	M
Stage IIIB	T1–T4a	N2,N3	M0
Stage IVA	T4b	Any N	M0
	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b

M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis
M1a	Distant metastasis limited to lymph nodes beyond the common iliacs
M1b	Non-lymph-node distant metastases

Some basic facts…

- 1. *Metastatectomy for oligometastatic disease -carefully select appropriate patients for metastasectomy,*

- 2. *If the evidence of spread is limited to nodes and biopsy is technically feasible, nodal biopsy should be considered and patients should be managed for positive nodal disease (stage IIIA, stage IIIB, or stage IVA).*

- 3. *Advanced urothelial cancers -93% of cases had at least one clinically relevant genetic alteration, with a mean of 2.6 clinically relevant genetic alterations per case.*

Broad scheme of discussion

- 1.Chemotherapy 1 st line
- 2.ICI – post chemotherapy- Maintenance
- 3.ICI – 1 st line when and how ?

1.Chemotherapy – 1 st line

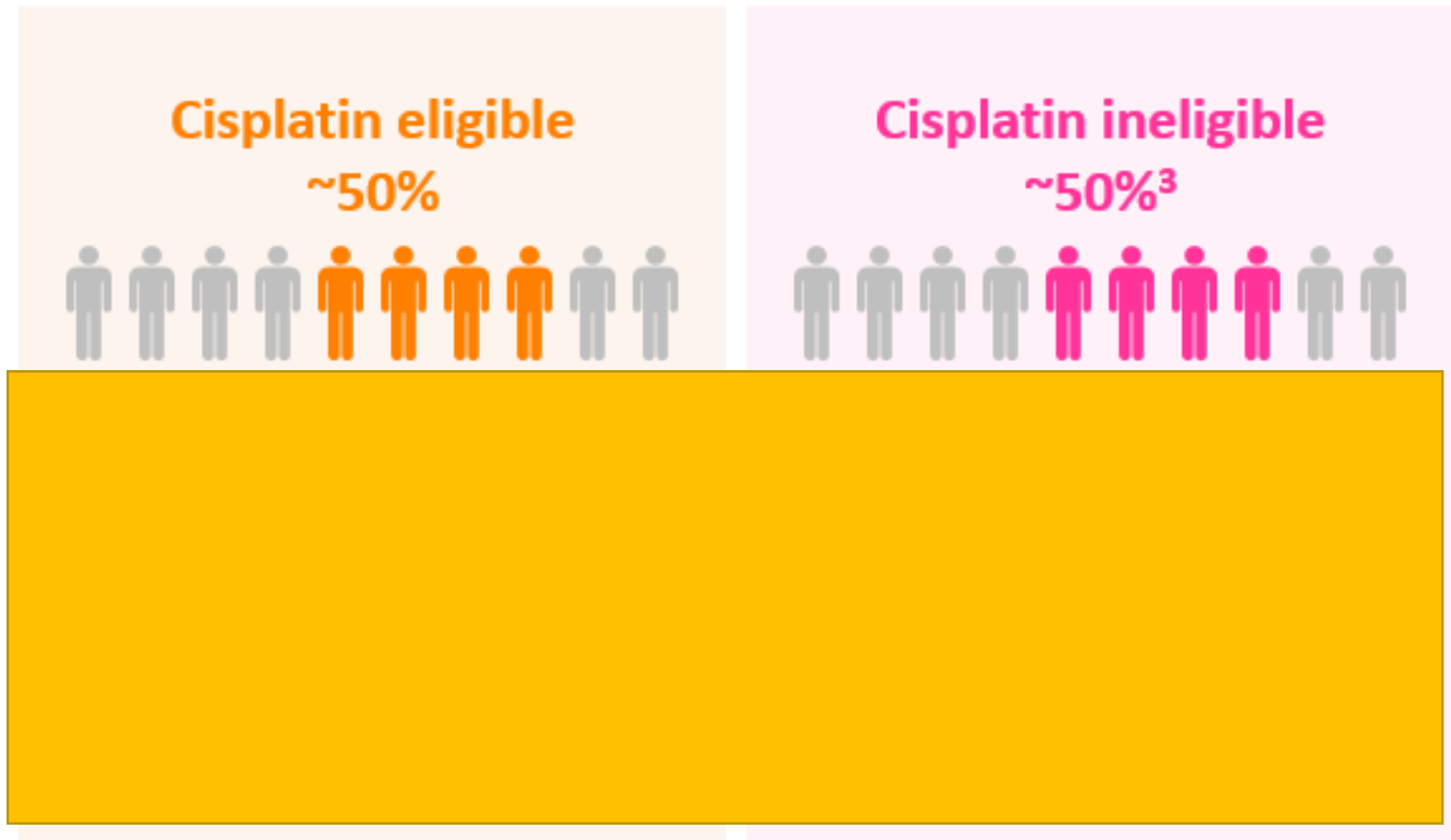
- 1. GC = standard MVAC @efficacy
- 2.GC >>>MVAC @ toxicity
- 3. ddMVAC >>> standard MVAC
- 4. Carboplatin can replace cisplatin in cisplatin ineligible patients
- 5.Addition of third drug – Taxanes – questionable benefits .

2.ICI Post chemotherapy- Avelumab Maintenance Therapy

- phase III JAVELIN Bladder 100 trial
- N= 700
- OS- 21.4 vs. 14.3 months; HR, 0.69; 95% CI, 0.56–0.86; P = .001).
- Toxicity – comparable
- PDL 1 agnostic
- Post Cisplatin based chemotherapy – category 1 recommendations

3.ICI – 1 st line when and how ?

- A. Platinum eligibility – patient selection
- B.ICI – evidence and action – Atezolizumab / Pembrolizumab



Galsky criteria for cisplatin eligibility[4]

- Creatinine clearance <60mL/min
- Grade ≥2 audiometric hearing loss
- NYHA Class III heart failure
- WHO or ECOG PS ≥2
- Grade ≥2 peripheral neuropathy

- 1. Bellmunt et al. Ann Oncol 2014 (eUpdate 2020)
  2. NCCN Guidelines – Bladder cancer v6.2020
- 3. Dash et al. Cancer 2006; 4. Galsky et al. J Clin Oncol 2011

Some basic facts ..

1.decreased survival –ICI -first-line monotherapy compared to those receiving cisplatin- or carboplatin-based therapy

2. Choose chemotherapy even for PDL 1 high platinum eligible patient .

3. Do we need PD L1 checking at all? – Yes - for Atezolizumab

4. Chemotherapy + ICI << ICI monotherapy.

a. Atezolizumab- IMVIGOR 210/ 130
b. Pembrolizumab- Keynote 052/ 361

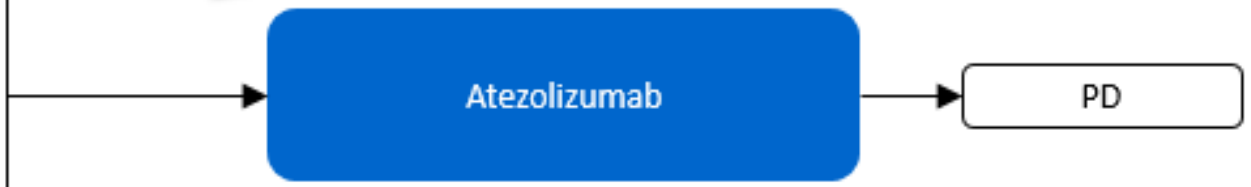
IMvigor210 Cohort 1: phase II single-arm study of atezolizumab in mUC

Key Cohort 1-specific inclusion criteria

- Locally advanced/metastatic transitional cell carcinoma of the urothelium
- FFPE tissue specimen for PD-L1 analysis
- No prior treatment for mUC (>12 months since perioperative chemotherapy)
- ECOG PS 0–2
- Cisplatin ineligibility based on ≥1 of: impaired renal function (GFR >30 and <60mL/min); Grade ≥2 hearing loss; Grade ≥2 peripheral neuropathy; ECOG PS 2

N=119

Data from IMvigor210 Cohort 1 supported the FDA accelerated and EMA approvals of atezolizumab for 1L, cisplatin-ineligible mUC[2,3]



1 **Primary endpoint**

- ORR (IRF assessed by RECIST v1.1)

2 **Secondary endpoints**

- PFS and DOR (IRF assessed by RECIST v1.1 and investigator assessed by modified RECIST*); ORR, DOR and PFS (investigator assessed by RECIST v1.1); OS and safety, tolerability, PKs and ATAs

- Patients with CR/PR/SD followed every 12 weeks (follow-up until death, loss to follow-up or study termination). Response assessed by CT scan (RECIST v1.1 and modified RECIST. *Modified RECIST criteria account for possible appearance of new lesions and allow radiological progression to be confirmed at a subsequent assessment

1. NCT02951767; 2. Atezolizumab PI 3. Atezolizumab SmPC

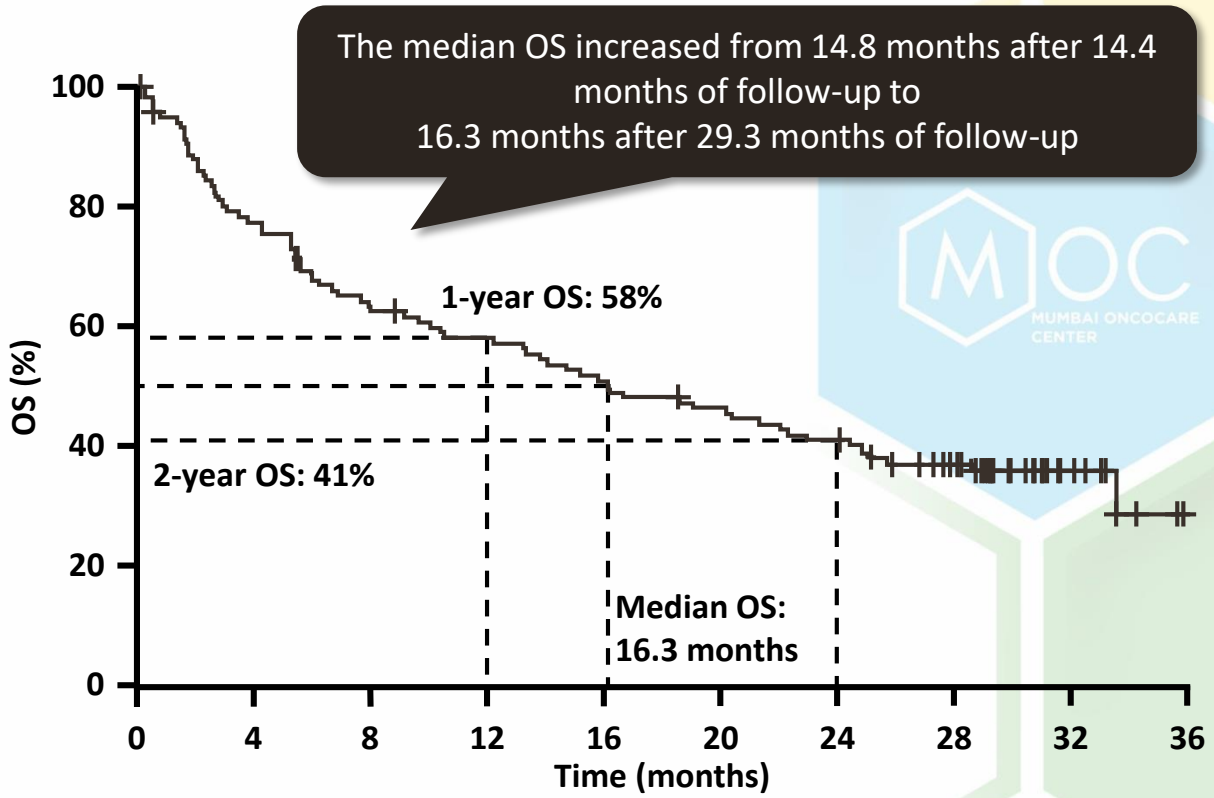
IMvigor210 Cohort 1: ORR and OS in the ITT population

ORR

	Atezolizumab N=119
Median duration of follow-up, months	29.3
ORR (95% CI), %* CR, %	24 (16–32) 8
DOR, median (95% CI), months	NE (30.4–NE)
Patients with ongoing response†	19 of 28
Median DOR in patients with CR (95% CI), months	Not reached (NE–NE)
Median duration of CR (95% CI), months	Not reached (NE–NE)
Ongoing CR at data cut-off, n (%)	8 (80)

- *19 patients with missing or unevaluable response status. †No death or IRF-assessed PD events (RECIST v1.1). Data cut-off: 12 July 2017; median duration of follow-up: 29.3 months

OS



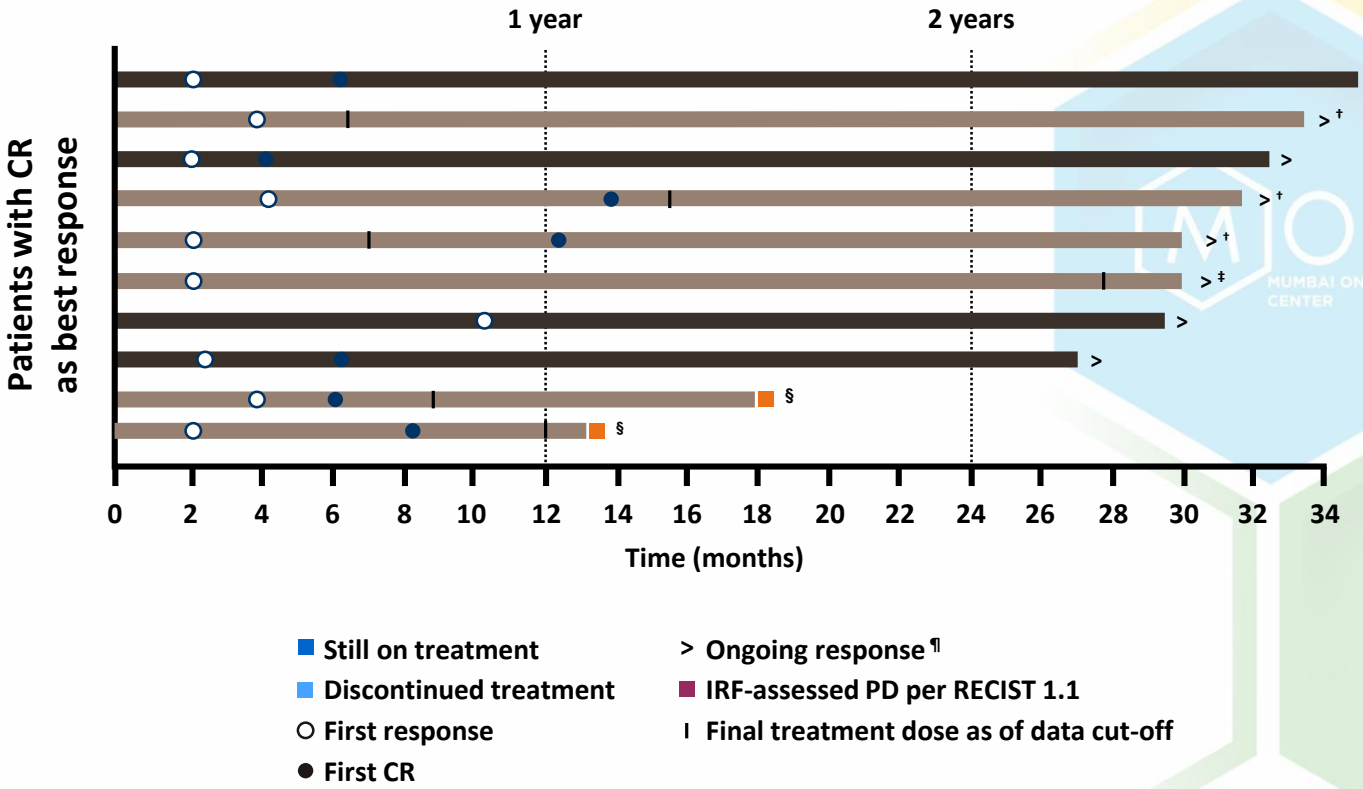
- 1. Balar et al. ASCO 2018; 2. Loriot et al. ASCO 2019

IMvigor210 Cohort 1: DOR in responders

DOR in patients with CR (n=10)

	N=119
Median duration of follow-up, months	29.3
Median duration of follow-up for patients with CR, months	31.7
ORR (95% CI), %*	24 (16–32)
CR, %	8
Median duration of response in patients with CR (95% CI), months	Not reached (NE–NE)
Median duration of complete response (95% CI), months	Not reached (NE–NE)
Ongoing CR at data cut-off, n (%) ¶	8 (80)

Time to response and DOR among patients with CR (n=10)

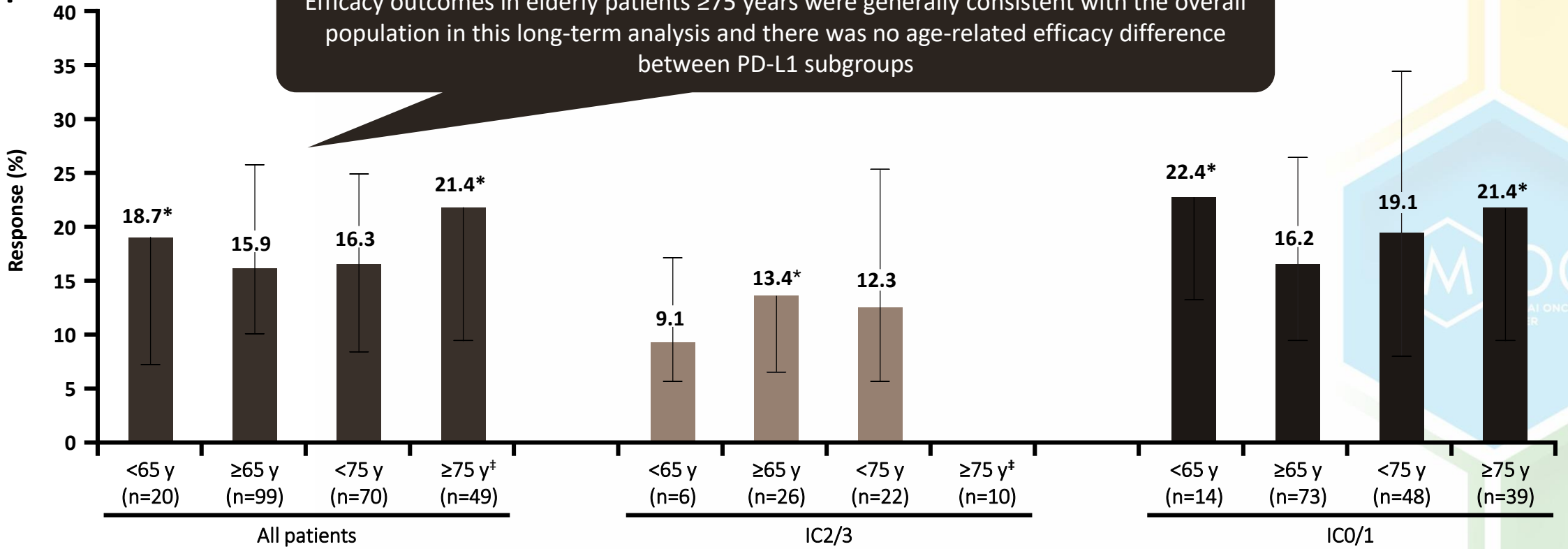


- *19 patients with missing or unevaluable response status
†Discontinued due to an AE. ‡Discontinued due to other reasons. §Discontinued due to patient withdrawal
¶Refers to no PD or death only. Data cut-off: 12 July 2017; median follow-up: 29.3 months

- Loriot et al. ASCO 2019

IMvigor210 Cohort 1: efficacy in elderly patients

Efficacy outcomes in elderly patients ≥75 years were generally consistent with the overall population in this long-term analysis and there was no age-related efficacy difference between PD-L1 subgroups



ORR, %	25	23	20	29	17	31	18	50	29	21	21	23
CR rate, %	20	6	9	8	17	12	9	20	21	4	8	5

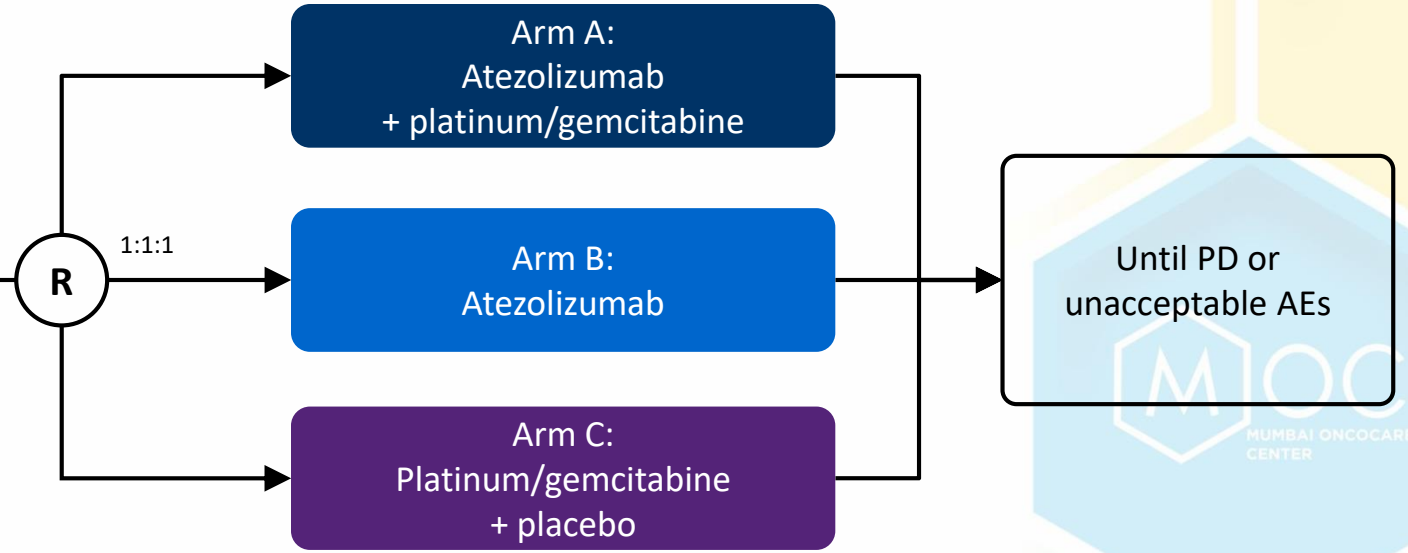
- Error bars refer to 95% CI for median OS; *upper CI is NE; ‡median is NE. Data cut-off: 12 July 2017; median follow-up: 29.3 months

- Balar et al. ASCO GU 2019

IMvigor130: phase III study of atezolizumab ± platinum-based chemotherapy for 1L mUC

- Locally advanced or mUC
- No prior systemic therapy in the metastatic setting
- ECOG PS ≤2
- Eligible for platinum-based chemotherapy (cisplatin or carboplatin with gemcitabine)
- Tissue sample available for PD-L1 testing (VENTANA SP142 IHC assay)

N=1213



1 **Primary endpoints**

- Investigator-assessed PFS* and OS (Arm A vs C); OS (Arm B vs C; hierarchical approach)

2 **Secondary endpoints**

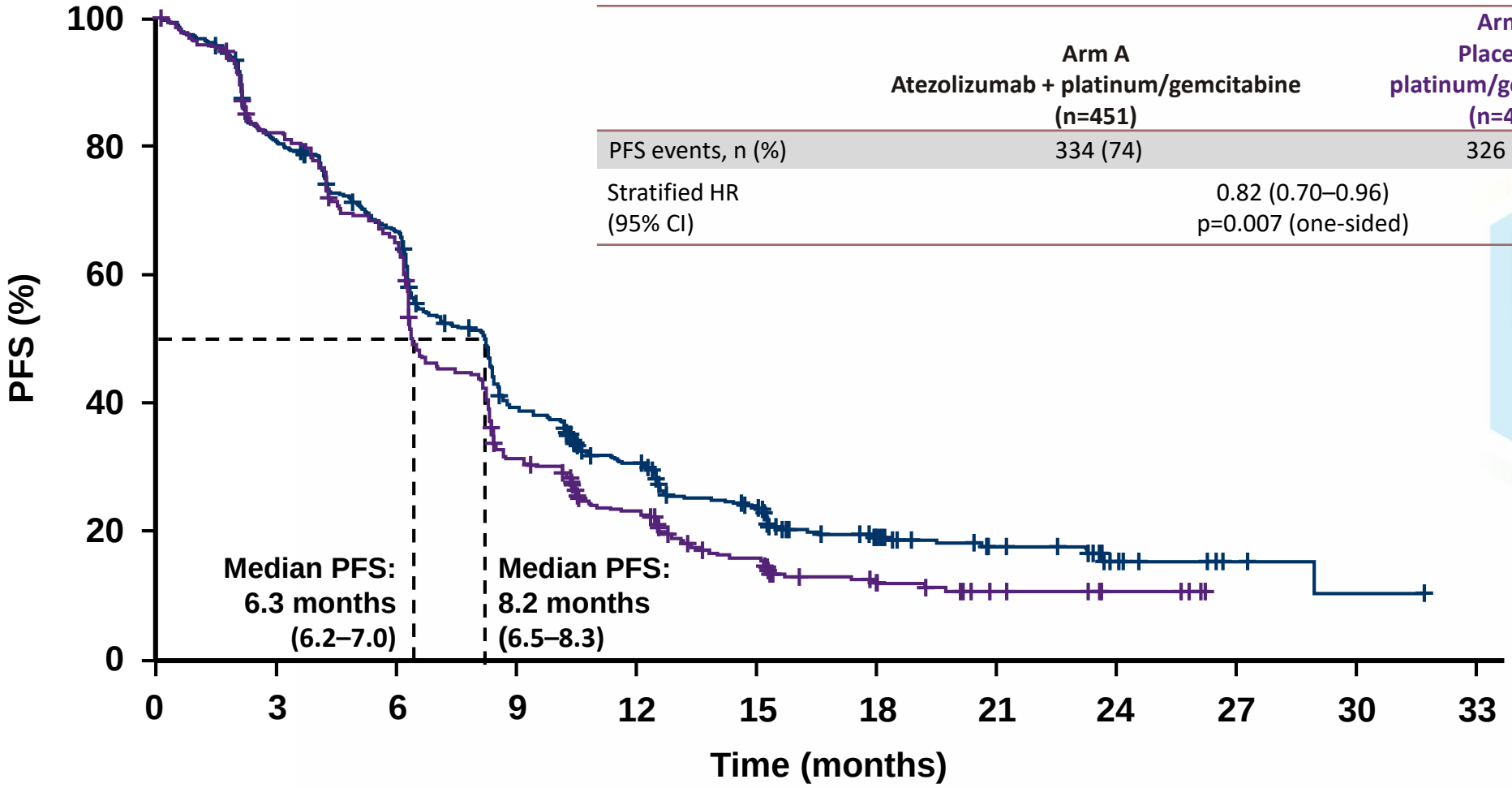
- INV-ORR*, DOR
- PFS, and OS (Arm B vs C; PD-L1 subgroups)
- Safety

- *per RECIST v1.1

- 1. NCT02807636; 2. Grande et al. ESMO 2019

IMvigor130: PFS (ITT, Arm A vs Arm C, co-primary endpoint)

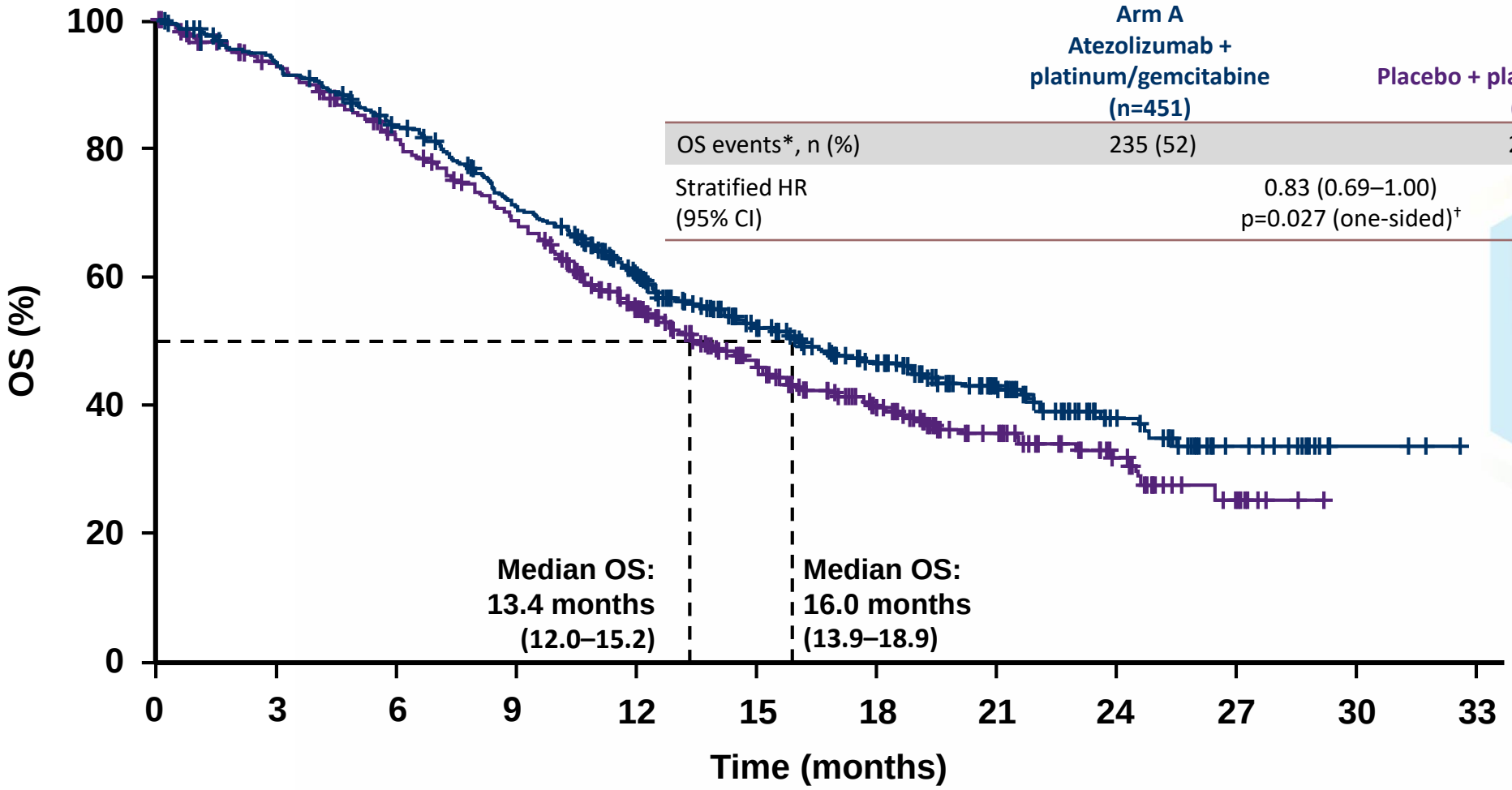
	Arm A Atezolizumab + platinum/gemcitabine (n=451)	Arm C Placebo + platinum/gemcitabine (n=400)
PFS events, n (%)	334 (74)	326 (82)
Stratified HR (95% CI)	0.82 (0.70–0.96) p=0.007 (one-sided)	



- Data cut-off 31 May 2019; median survival follow-up 11.8 months (all patients)
- Grande et al. ESMO 2019; Galsky et al. Lancet 2020

IMvigor130: interim OS analysis (ITT, Arm A vs Arm C)

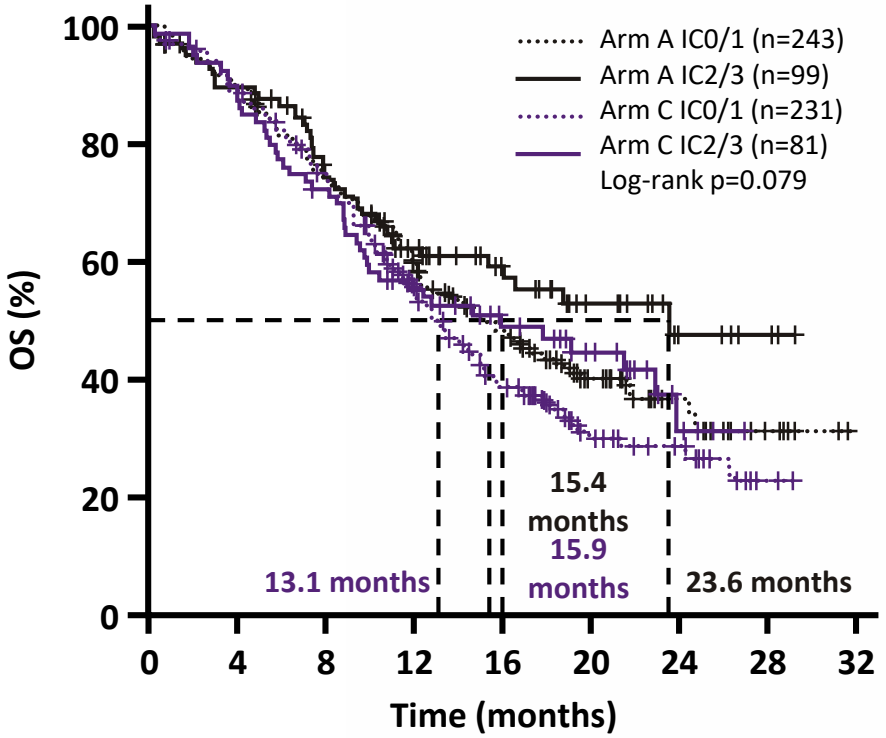
	Arm A Atezolizumab + platinum/gemcitabine (n=451)	Arm C Placebo + platinum/gemcitabine (n=400)
OS events*, n (%)	235 (52)	228 (57)
Stratified HR (95% CI)	0.83 (0.69–1.00) p=0.027 (one-sided)†	



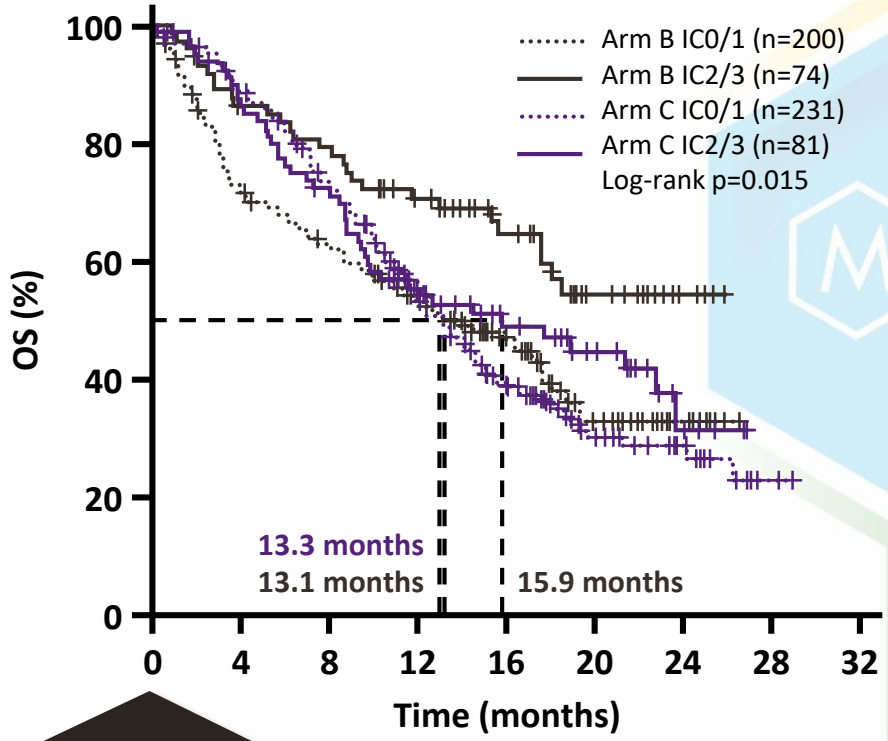
- Data cut-off 31 May 2019; median survival follow-up 11.8 months (all patients)
  *5% of patients from Arm A and 20% of patients from Arm C crossed over to non-protocol immunotherapy
  †Did not cross the interim efficacy boundary of 0.007 per the O'Brien-Fleming alpha spending function
- Grande et al. ESMO 2019; Galsky et al. Lancet 2020

IMvigor130: interim OS by PD-L1 status

Arm A (atezolizumab + platinum/gemcitabine) vs Arm C (placebo + platinum/gemcitabine)



Arm B (atezolizumab) vs Arm C (placebo + platinum/gemcitabine)



Improved OS for patients in the atezolizumab monotherapy arm was associated with PD-L1 IC2/3 status

- P values are displayed for exploratory/descriptive purposes only
- Baseline PD-L1 expression in tumour specimens was evaluated using the
- Galsky et al. ASCO 2020

Atezolizumab – 1 st line

1) are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 as measured by PD-L1–TPS 5 % (SP 142)

2) are not eligible for any platinum- containing chemotherapy regardless of the level of tumor PD-L1 expression.

First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study

Arjun V Balar, Daniel Castellano, Peter H O'Donnell, Petros Grivas, Jacqueline Vuky, Thomas Powles, Elizabeth R Plimack, Noah M Hahn, Ronald de Wit, Lei Pang, Mary J Savage, Rodolfo F Perini, Stephen M Keefe, Dean Bajorin, Joaquim Bellmunt

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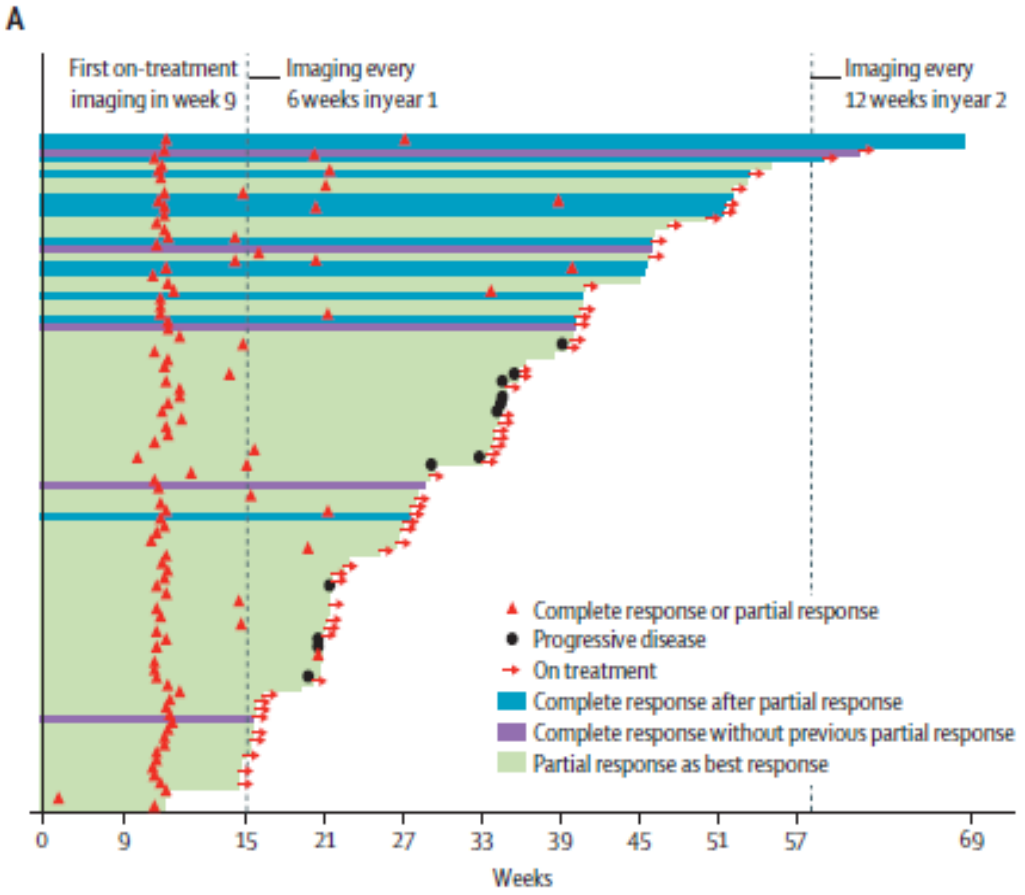


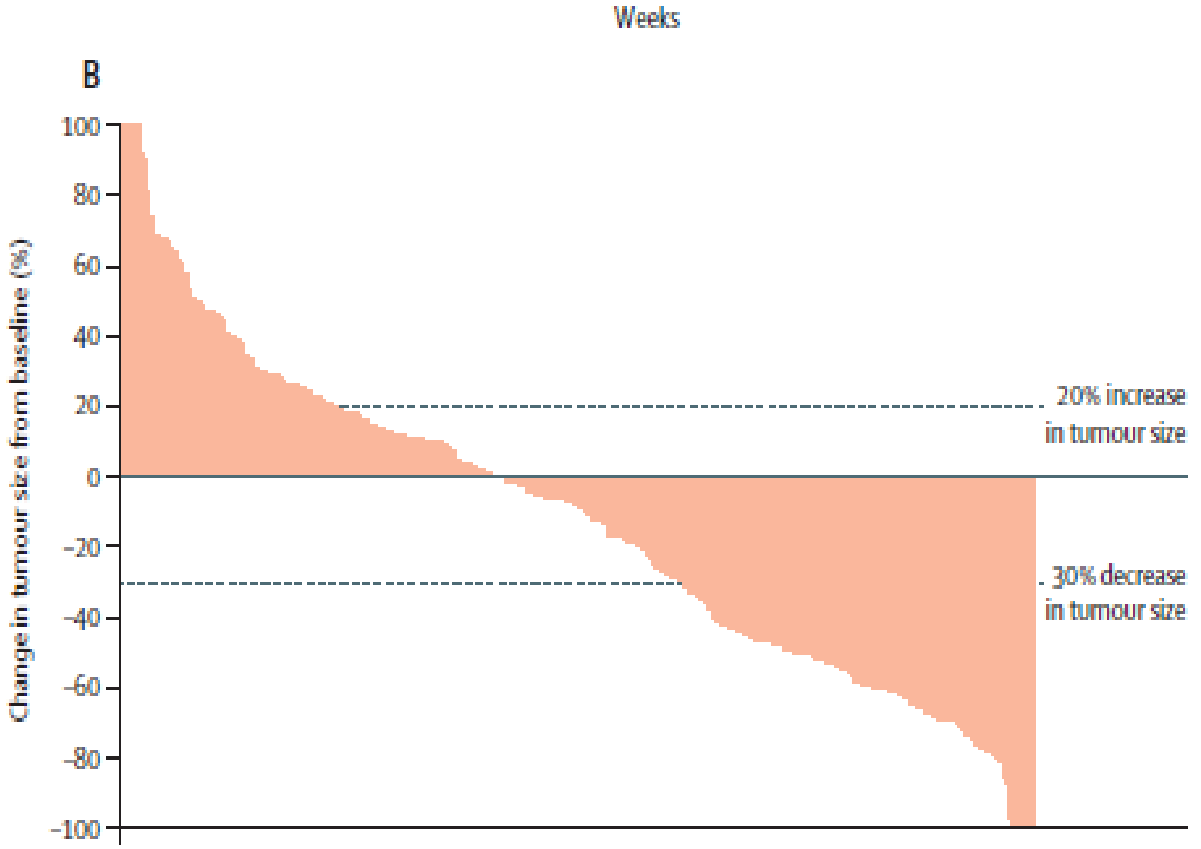
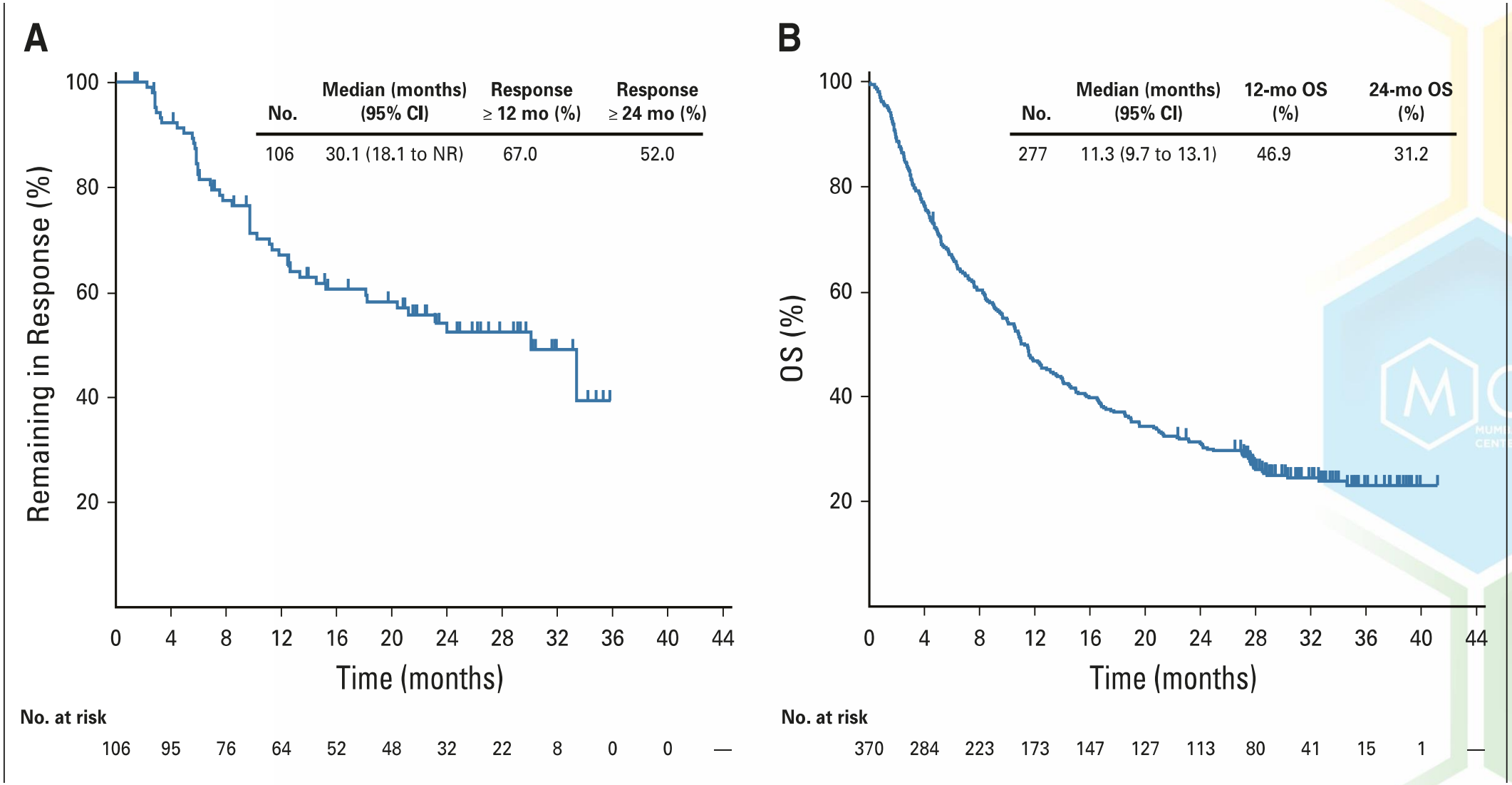
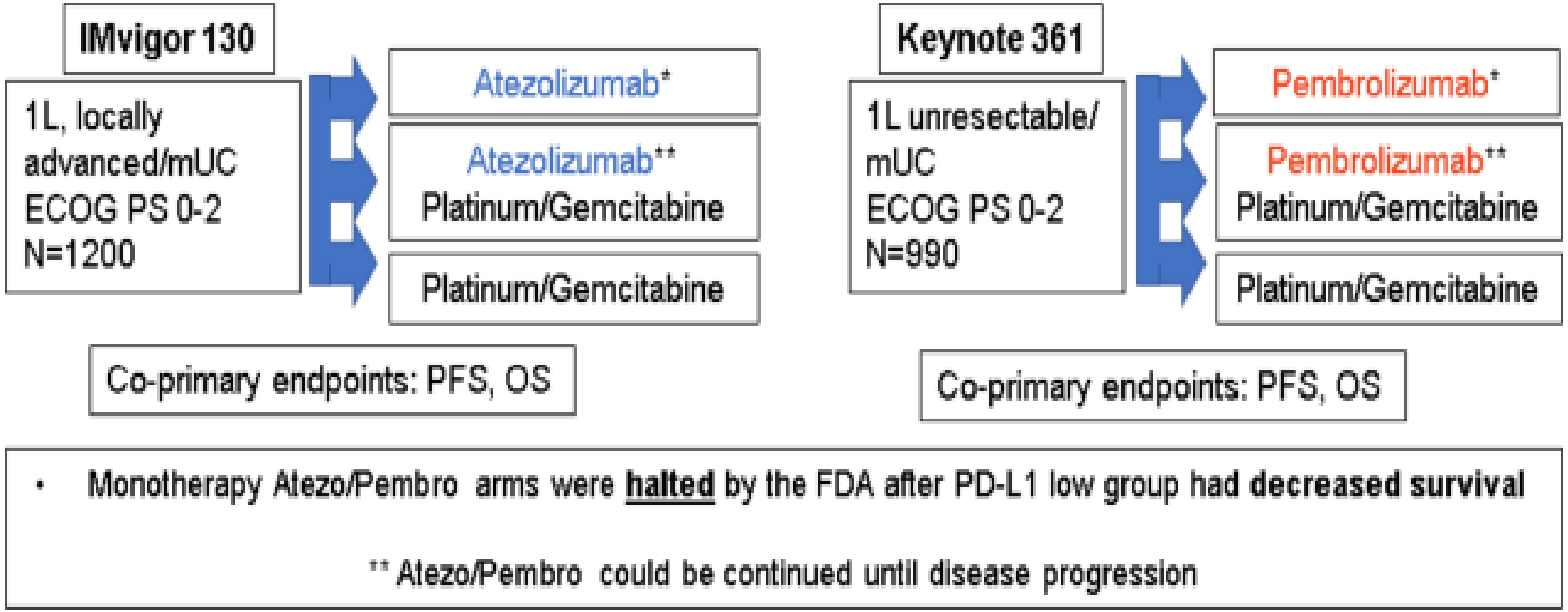


***Figure 2*: Centrally assessed tumour response to pembrolizumab according to Response Evaluation Criteria in Solid Tumors (version 1.1)**
(A) Treatment exposure and duration of response in patients achieving a partial response or complete response (n=89). (B) Best percentage change from baseline in target lesions (n=331). Patients who had measurable disease at baseline and at least one post-baseline scan are included.


A
Remaining in Response (%)
100
80
60
40
20
No.
Median (months) (95% CI)
Response ≥ 12 mo (%)
Response ≥ 24 mo (%)
106
30.1 (18.1 to NR)
67.0
52.0
0
4
8
12
16
20
24
28
32
36
40
44
Time (months)
No. at risk
106
95
76
64
52
48
32
22
8
0
0
—
B
OS (%)
100
80
60
40
20
No.
Median (months) (95% CI)
12-mo OS (%)
24-mo OS (%)
277
11.3 (9.7 to 13.1)
46.9
31.2
0
4
8
12
16
20
24
28
32
36
40
44
Time (months)
No. at risk
370
284
223
173
147
127
113
80
41
15
1
—

First Line combination trials



Pembrolizumab – 1 st line

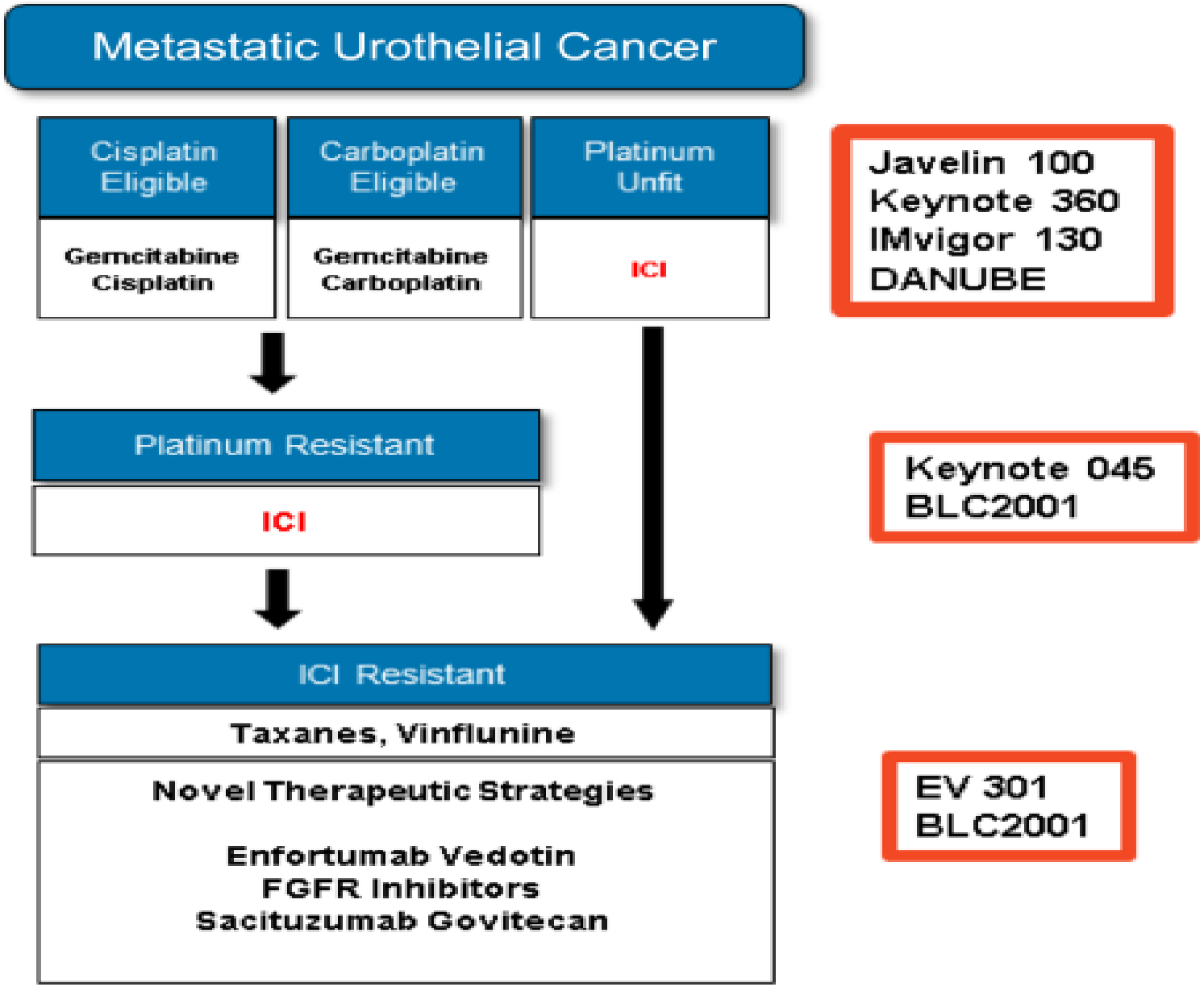
Only patients who were not eligible for any platinum-containing chemotherapy

First Line immune checkpoint inhibitors

	Pembrolizumab	Atezolizumab
Phase	Phase II (Keynote-052)	Phase II (IMvigor 210, Cohort 1)
Patients	370	119
Dosing	200 mg every 3 weeks	1200 mg every 3 weeks
ORR	28.9% (9.5% CR)	23% (9% CR)
Duration of response	39.4% responses ongoing at ≥48 months	70% responses ongoing at 17.2 months
Median OS	11.3 months	15.9 months
Median PFS	2 months	2.7 months
Rate of grade 3/4 treatment-related AEs (%)	19	16

AE, adverse events; CR, complete response; ORR, objective response rate; OS, overall survival; PFS, progression free survival

Management algorithm



Recruiting trials in 1L setting for advanced urothelial carcinoma

Study name/ID	Investigational drug	Phase	Primary end point
EV-301 (Clinicaltrial.gov identifier: NCT04223856)	Enfortumab-vedotin	III	OS, PFS
LEAP-011 (NCT03898180)	Sacituzumab-govitecan	III	OS, PFS
NCT03967977	Tislelizumab	III	OS
NCT04486781	sEphB4-HAS + pembrolizumab	II	ORR
NCT04601857	Futibatinib + pembrolizumab	II	ORR
AUREA (NCT04602078)	Atezolizumab + split dose cisplatin/gemcitabine	II	ORR
NCT04264936	RC48-ADC and JS001	Ib/II	Adverse events and maximal tolerated dose
NCT03534804	Cabozantinib + pembrolizumab	II	ORR
FORT-2 (NCT03473756)	Rogaratinib + atezolizumab	II	Dose-limiting toxicity, TRAE, PFS
NCT03237780	Eribulin mesylate + atezolizumab	II	ORR, TRAE, OTR
GCISAVE (NCT03324282)	Avelumab + chemotherapy	II	ORR, proportion of severe toxicity
NCT03272217	Atezolizumab + Bevacizumab	II	OS

OS, overall survival; ORR, objective tumor response; PFS, progression free survival; TRAE, treatment related adverse events.

PD-L1/PD-1 inhibitors have been approved for 1L mUC

	1L PD-L1+ cisplatin-eligible	1L PD-L1+ cisplatin-ineligible	1L platinum-ineligible	1L maintenance
	Gemcitabine/cisplatin	**Pembrolizumab** **Atezolizumab** Gemcitabine/carboplatin		
	Gemcitabine/cisplatin	**Pembrolizumab** **Atezolizumab** Gemcitabine/carboplatin	**Pembrolizumab** **Atezolizumab** *Regardless of tumor PD-L1 expression*	**Avelumab**

Thank you

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