Updates in Immunotherapy for Bladder Cancer

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Disclosure

- Consultant: Sanofi Aventis, Celgene, Pfizer, Millineum, Dendreon, Johnson and Johnson, Bayer, Medivation, Roche/Genetech, Bellcium, Tyme
- Research Support: Roche, Merck, Dendreon, Progenics, Lilly, Medivation, Agenysis, Astra Zenca, GSK, Bayer
- Stock Tyme, Bellicum

Checkpoint Inhibitors Approved for Use in Urothelial Carcinoma

7 US FDA Approvals May 2016-May 2017

Setting	Antibody	Approval Status
First-line (cisplatin-ineligible)	Atezolizumab	• Accelerated approval granted in April 2017.
	Pembrolizumab	• Accelerated approval granted in May 2017.
Platinum-pretreated	Atezolizumab	• Accelerated approval granted in May 2016. • In May 2017, the subsequent phase 3 IMvigor211 trial did not meet primary endpoint of overall survival.
	Nivolumab	• Accelerated approval granted in February 2017.
	Durvalumab	• Accelerated approval granted in May 2017.
	Avelumab	• Accelerated approval granted in May 2017.
	Pembrolizumab	• Full approval granted in May 2017.

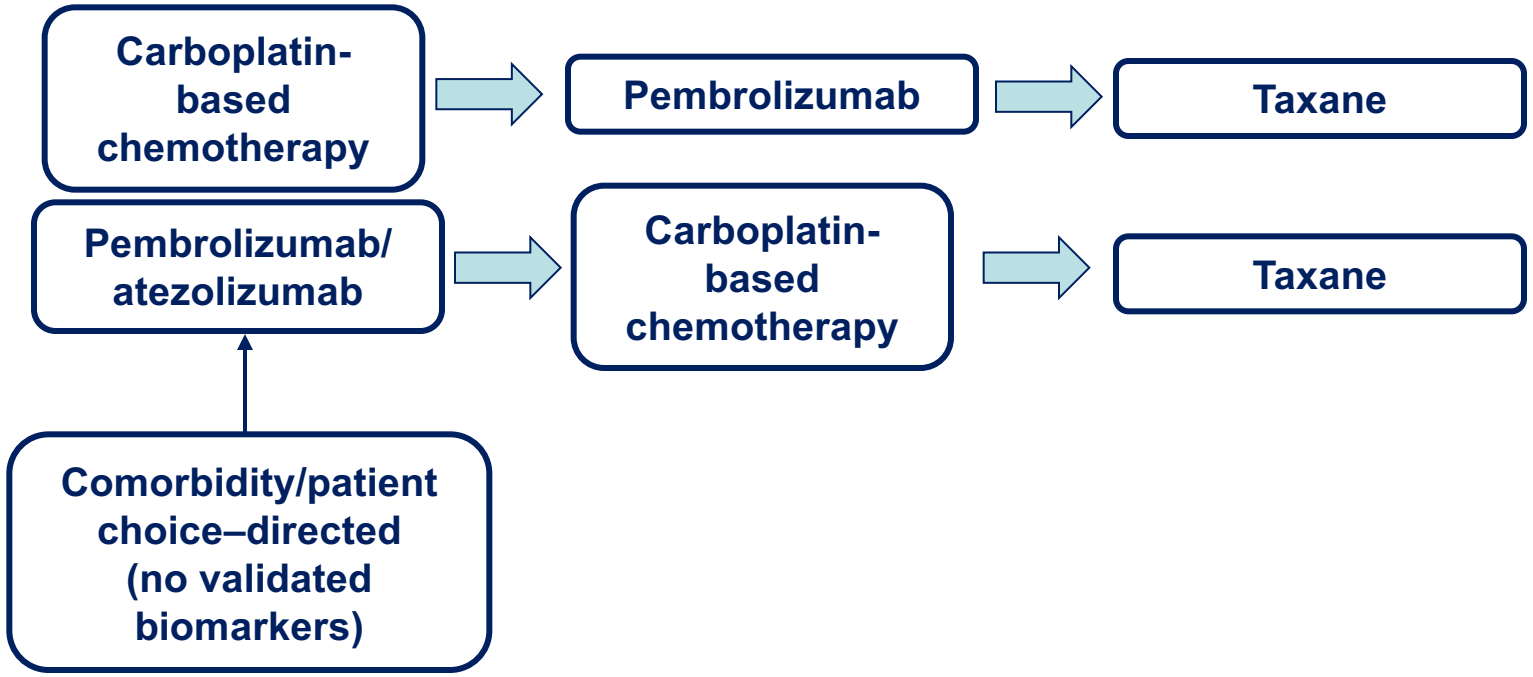
Approvals: First-line, Cisplatin-Ineligible

Apr 2017 — May 2017

Atezolizumab — Pembrolizumab

Above agents are indicated in patients with locally advanced or metastatic urothelial carcinoma not eligible for cisplatin-containing chemotherapy.

Sequence of Therapy for Cisplatin-Ineligible Patients



First-Line Therapy for Cisplatin-Ineligible Metastatic UC
PD-1/PD-L1 Inhibitor OR Gemcitabine-Carboplatin Based on Activity?

	Gem-Carbo (Ph III)[1]	Atezolizumab (Ph II)[2]	Pembrolizumab (Ph II)[3]
Number of patients	119	119	370
% with PS 2	44.5%	20%	42%
% CrCl <60 mL/min	55.5%[a]	70%	49%
% PS 2 + CrCl <60 mL/min	26.9%[a]	7%	9%
ORR	41.2% ✓	23%	24%
Median PFS	5.8 mo ✓	2.7 mo	2 mo; 3 mo on therapy
Median OS	9.3 mo	15.9 mo ✓	Not reported
Duration of response	Not reported	Not reached (median f/u 17.2 mo) ✓	Not reached (78% ≥6 months) ✓

[a]GFR 30-60 mL/min.

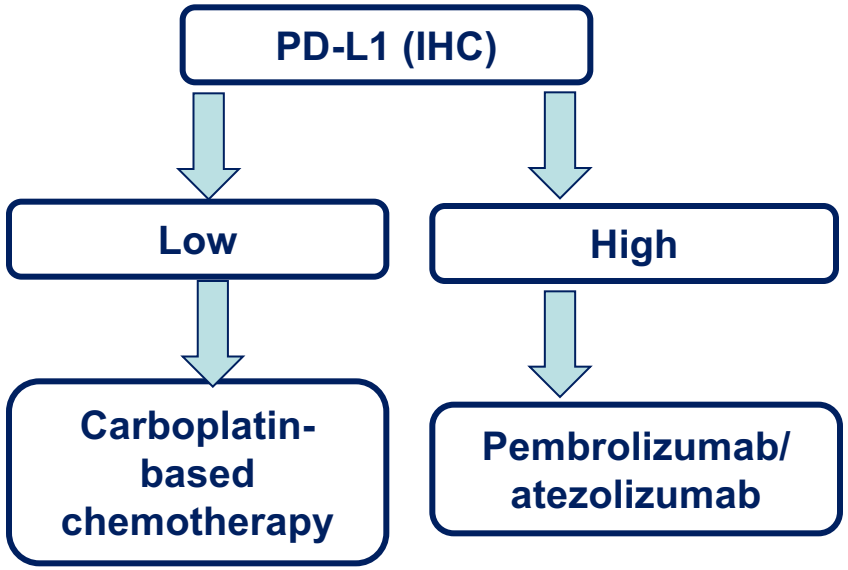
1. De Santis M, et al. J Clin Oncol. 2012;30(2):191-199; 2. Balar AV, et al. Lancet. 2017;389(10064):67-76; 3. Balar AV; et al. Lancet Oncol. 2017;18:1483-1492.

Use PD-L1 expression to select therapy for cisplatin-ineligible patients?

5/18/2018

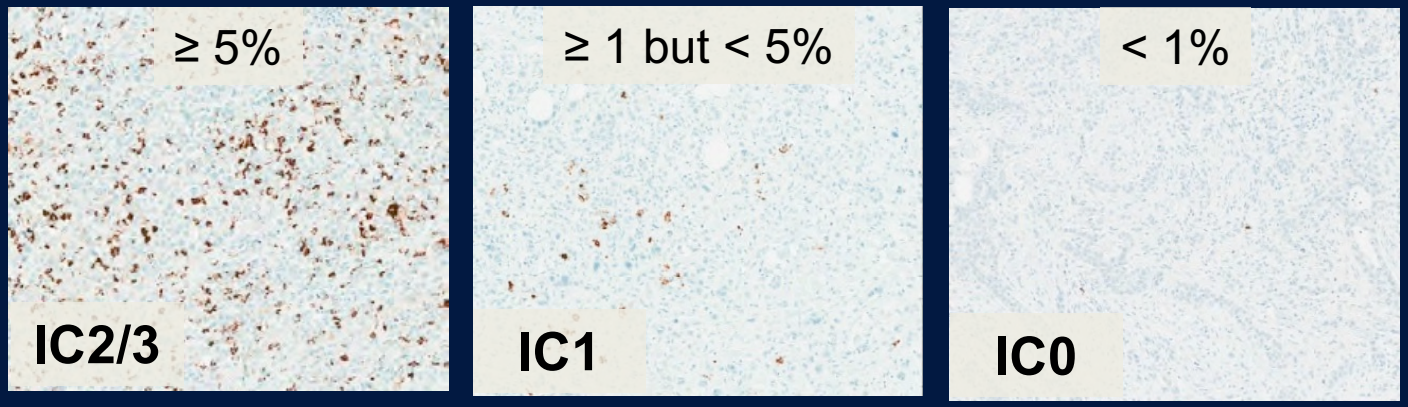
FDA Alert

- In two ongoing clinical trials (KEYNOTE-361 and IMVIGOR-130), the Data Monitoring Committees' (DMC) found patients in the **monotherapy arms of both trials with PD-L1 low status had decreased survival compared to patients who received cisplatin- or carboplatin-based chemotherapy.**
- Both trials have stopped enrolling patients whose tumors have PD-L1 low status to the Keytruda or Tecentriq monotherapy arms.
- The monotherapy arms remain open only to patients whose tumors have PD-L1 high status.



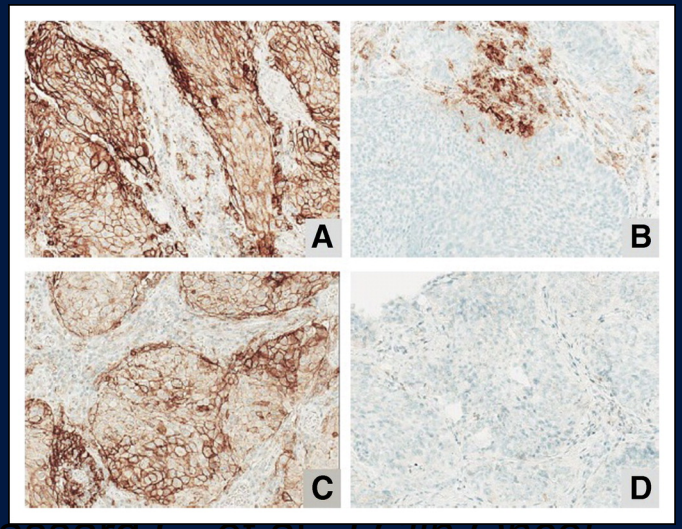
Examples of Different Staining Patterns and Antibodies

SP-142



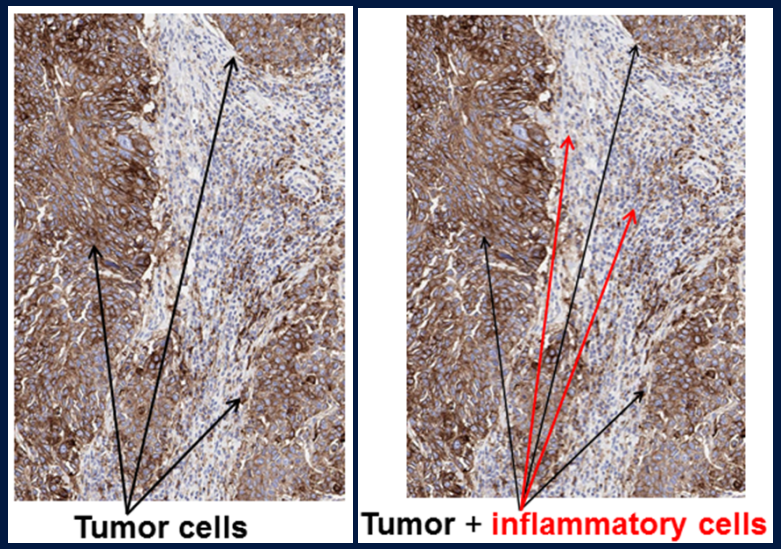
Rosenberg et al. ESMO 2016 Abstract

SP263



Massard C, et al. *J Clin Oncol*. 2016;34(26):3119-2125.

22C3



c/o E. Plimack

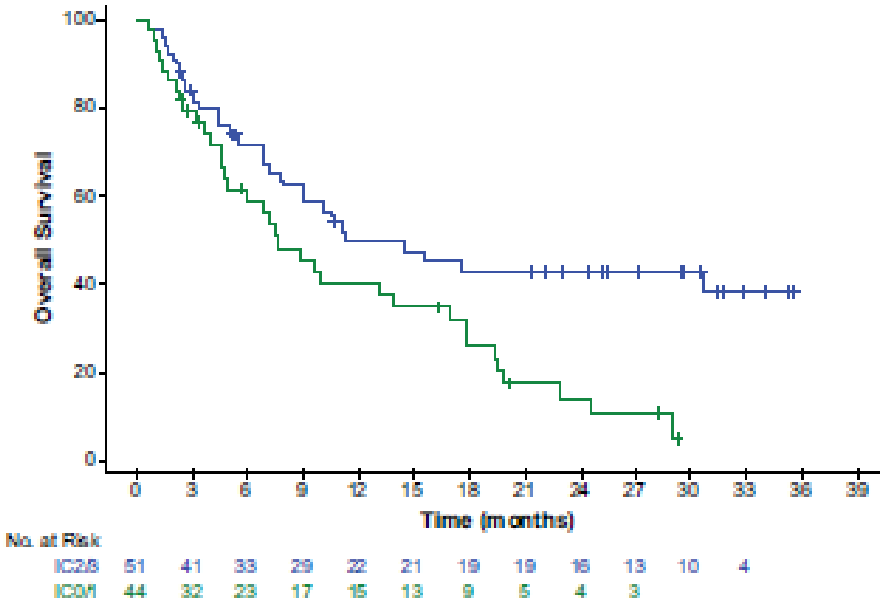
Approvals: Previously-treated Disease

May 2016 Feb 2017 May 2017

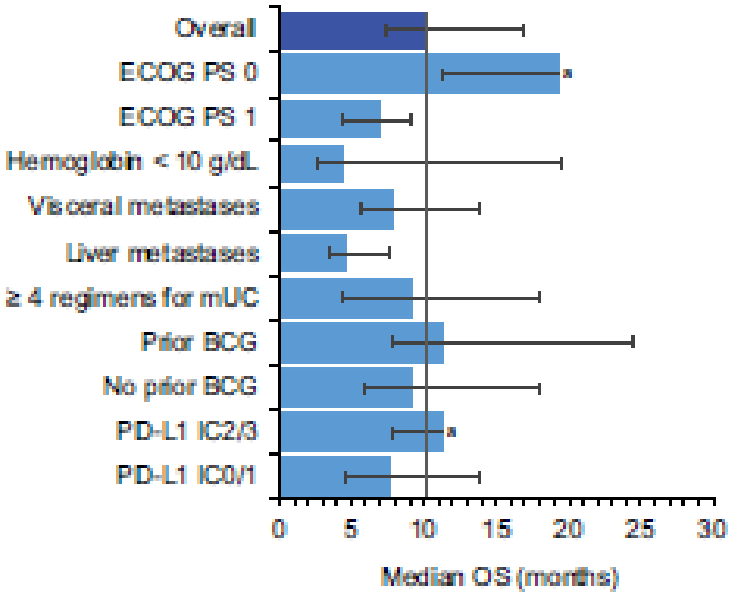
Atezolizumab Nivolumab Durvalumab Avelumab Pembrolizumab

Above agents are indicated in patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with (platinum-containing) chemotherapy.

OS by PD-L1 Status



Median Survival by Baseline Characteristics



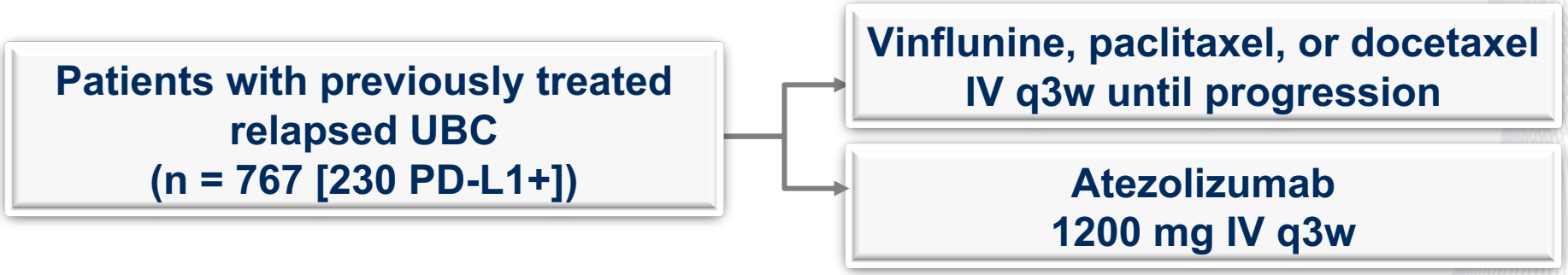
Patterns of AE Occurrence

Time Following Initiation of Atezolizumab[a]	All Treatment-Related AEs		Serious Treatment-Related AEs	
	All Grade	Grade 3-4	All Grade	Grade 3-4
Within year 1 (N = 95)	66%	7%	5%	0%
Beyond year 1 (n = 37)	35%	5%	0%	0%
Year 2 (n = 37)	32%	5%	0%	0%
Year 3 (n = 20)	10%	0%	0%	0%

[a] Values in parentheses refer to the number of patients evaluable for safety at the beginning of each period.

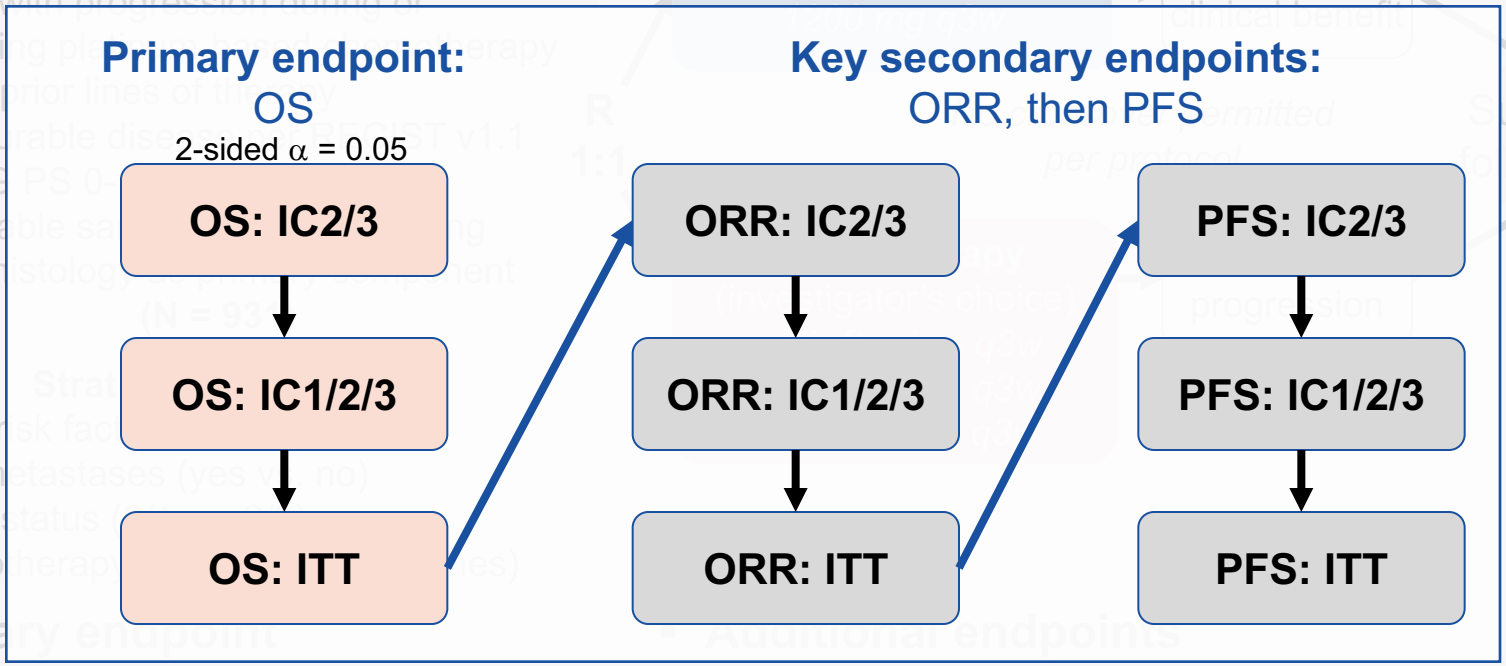
- Most treatment-related AEs occurred within the first year following initiation of treatment, with the AE incidence in year 2 approximately half that in year 1
- No serious treatment-related AEs occurred beyond year 1

IMvigor211 Phase III Trial in Previously-treated Urothelial Cancer



- **Primary endpoint**: OS in IHC 2/3→1/2/3→ITT
- **Secondary endpoints**: PFS, ORR, DOR
- FPI: Q4 2014

IMvigor211 Study Design

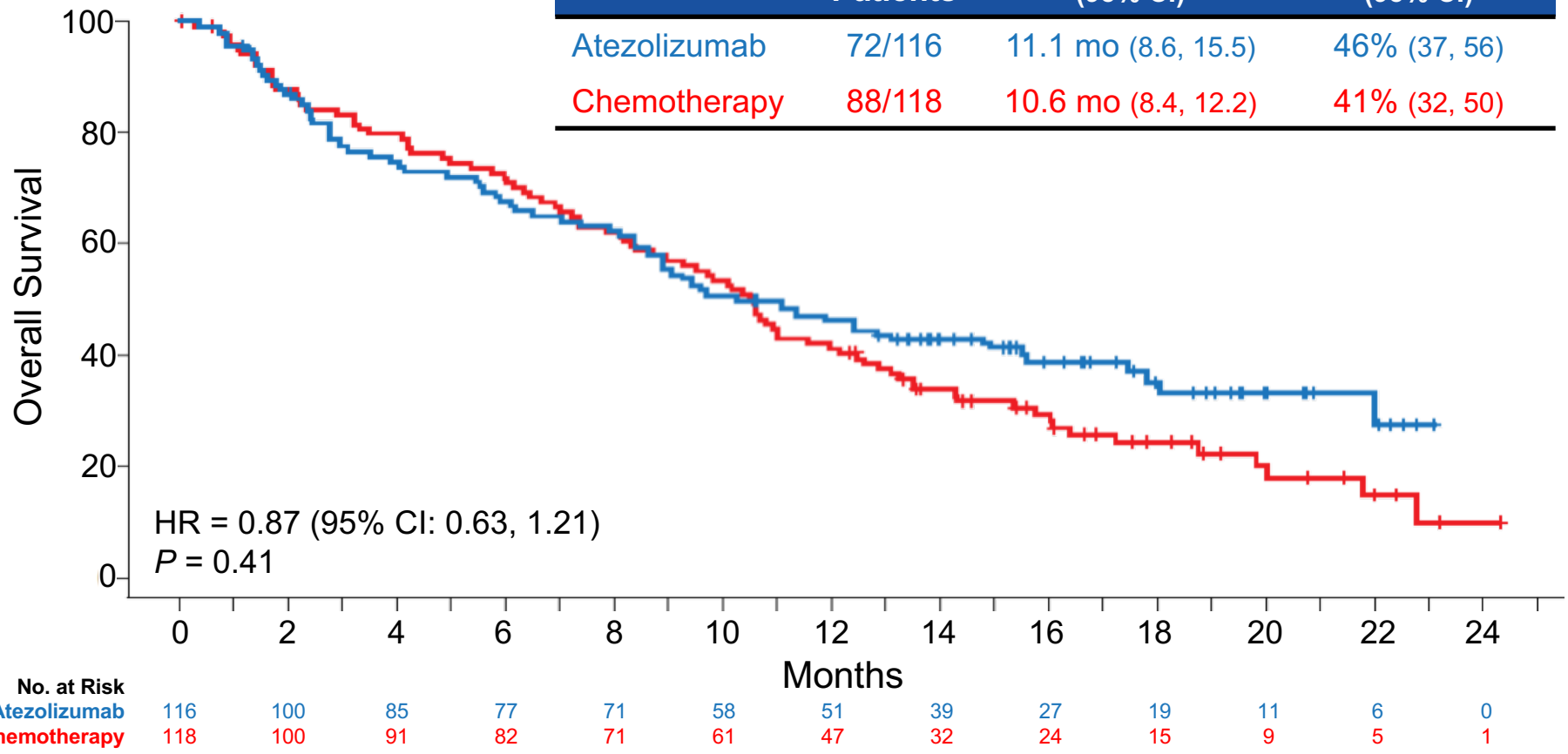


DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; PRO, patient-reported outcome; q3w, every three weeks; RECIST, Response Evaluation Criteria In Solid Tumors; TCC, transitional cell carcinoma. [a] ClinicalTrials.gov, NCT02302807. [b] Defined by time from prior chemotherapy < 3 mo, ECOG performance status > 0 and hemoglobin < 10 g/dL. [c] Confirmed response was not required for secondary efficacy endpoints. This analysis reports exploratory confirmed responses.

Powles T, et al. EAS 2017, IMvigor211.

OS Analysis: IC2/3 Population

	Events/ Patients	Median OS (95% CI)	12-mo OS Rate (95% CI)
Atezolizumab	72/116	11.1 mo (8.6, 15.5)	46% (37, 56)
Chemotherapy	88/118	10.6 mo (8.4, 12.2)	41% (32, 50)

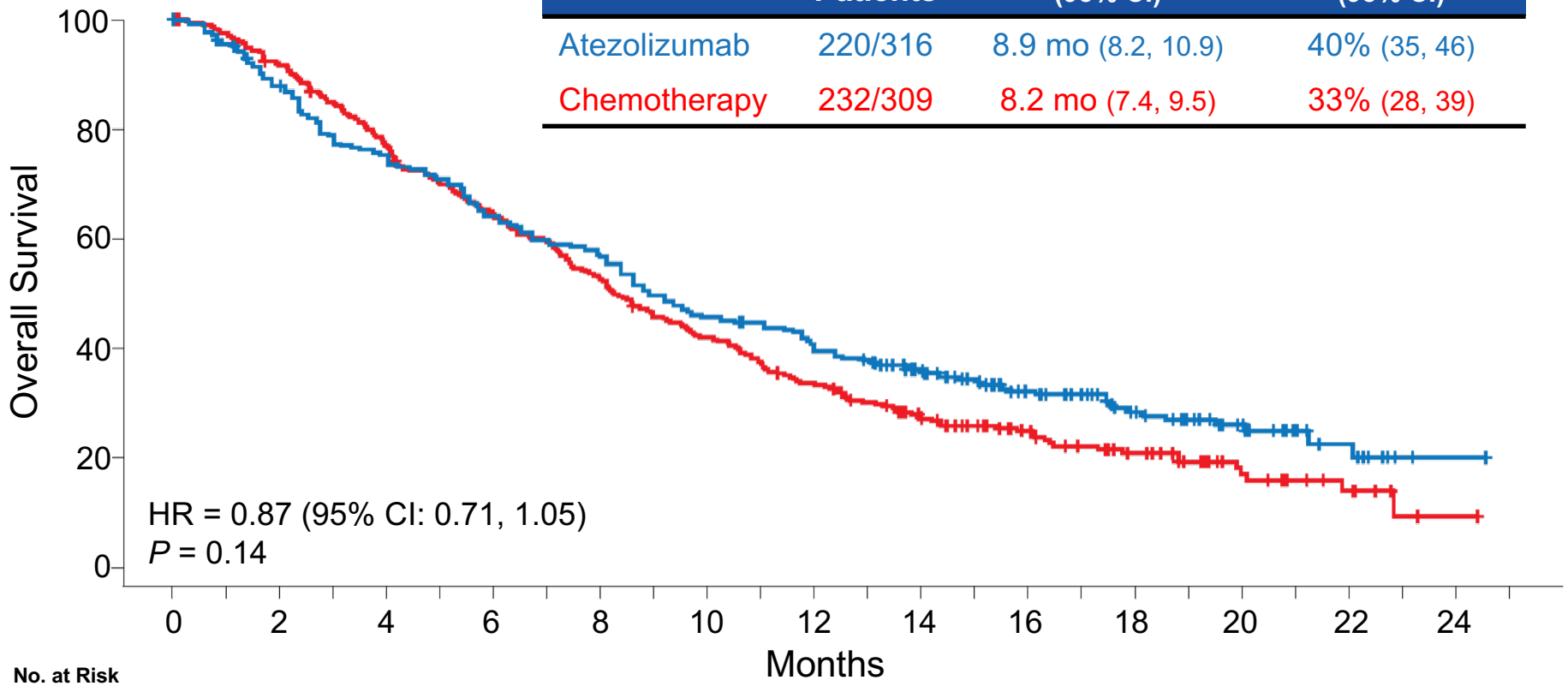


HR, hazard ratio.

Powles T, et al. EAS 2017, IMvigor211.

OS Analysis: IC1/2/3 Population

	Events/ Patients	Median OS (95% CI)	12-mo OS Rate (95% CI)
Atezolizumab	220/316	8.9 mo (8.2, 10.9)	40% (35, 46)
Chemotherapy	232/309	8.2 mo (7.4, 9.5)	33% (28, 39)

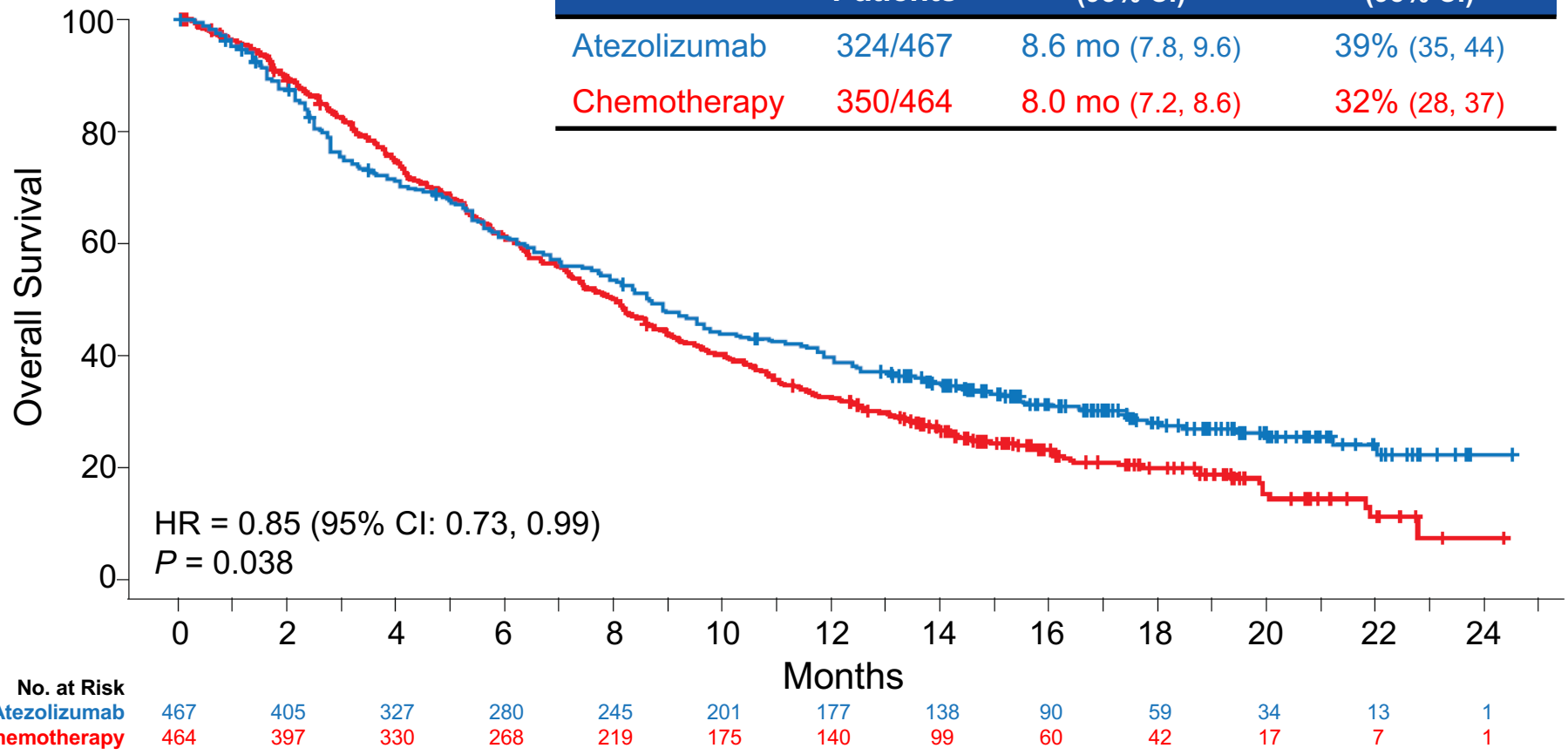


No. at Risk													
Atezolizumab	316	274	232	198	175	141	122	97	64	41	23	9	1
Chemotherapy	309	273	228	188	153	121	95	66	46	31	15	7	1

Powles T, et al. EAS 2017, IMvigor211.

OS Analysis: ITT Population

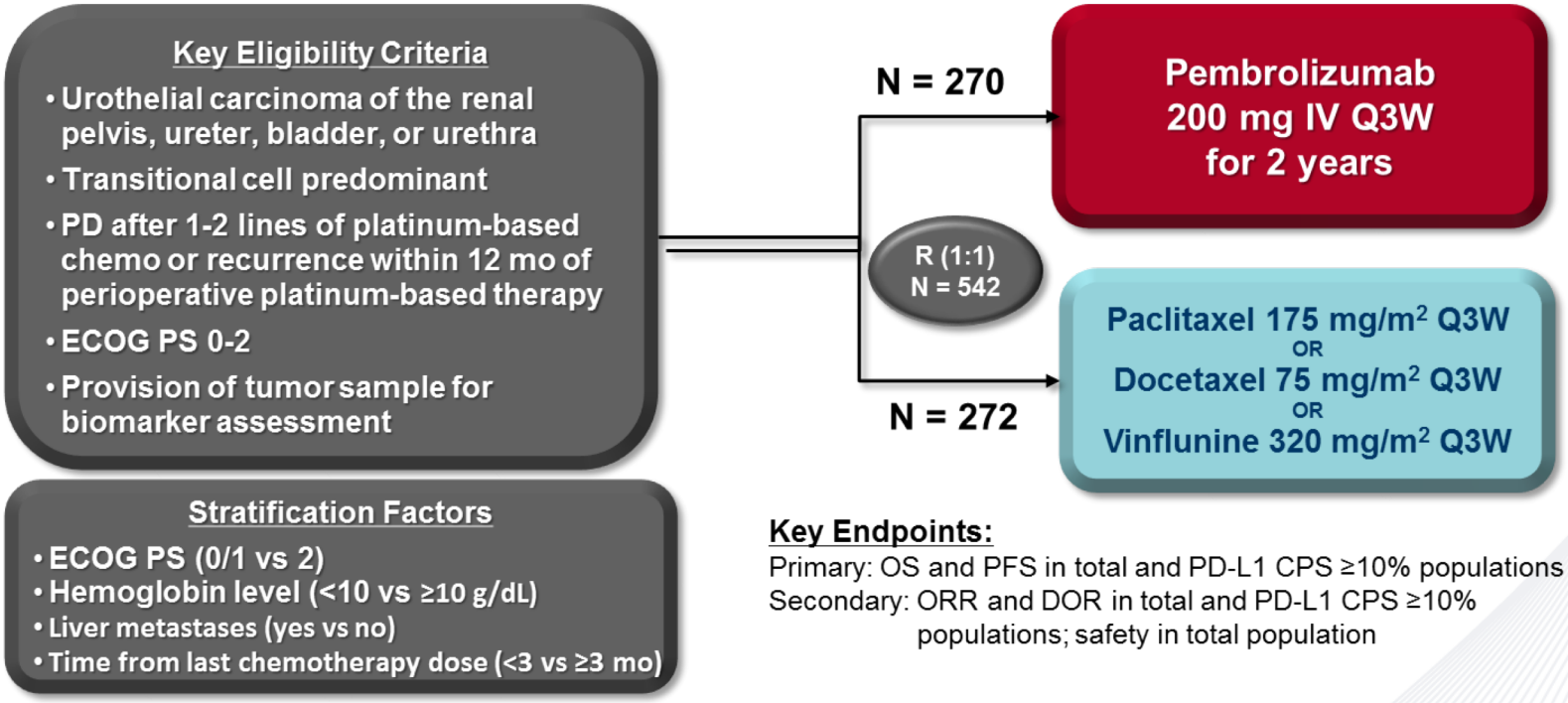
	Events/ Patients	Median OS (95% CI)	12-mo OS Rate (95% CI)
Atezolizumab	324/467	8.6 mo (7.8, 9.6)	39% (35, 44)
Chemotherapy	350/464	8.0 mo (7.2, 8.6)	32% (28, 37)



- Median follow-up duration in ITT population: 17.3 mo (range, 0 to 24.5 mo)

Powles T, et al. EAS 2017, IMvigor211.

KEYNOTE-045: Phase III Study Design

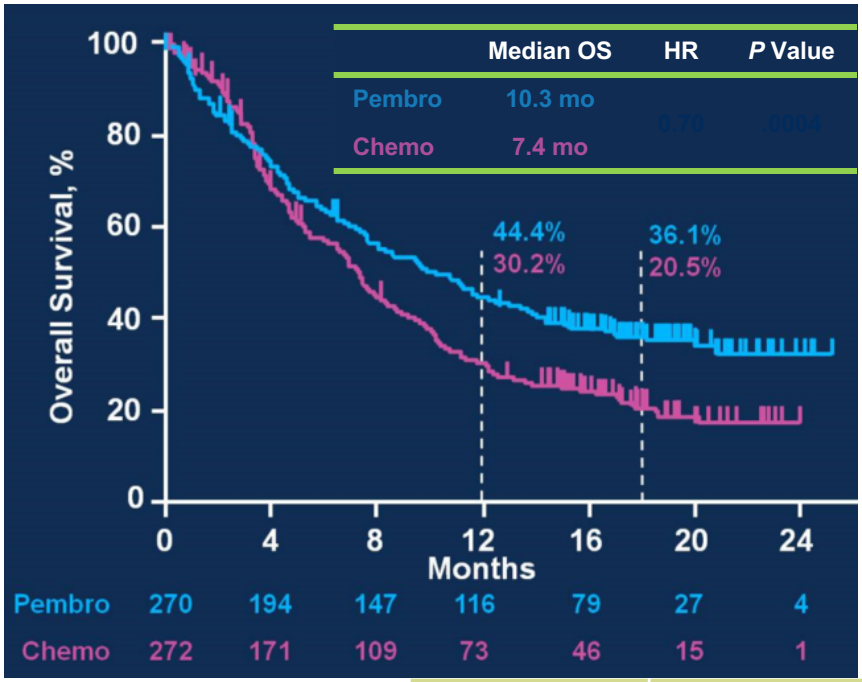


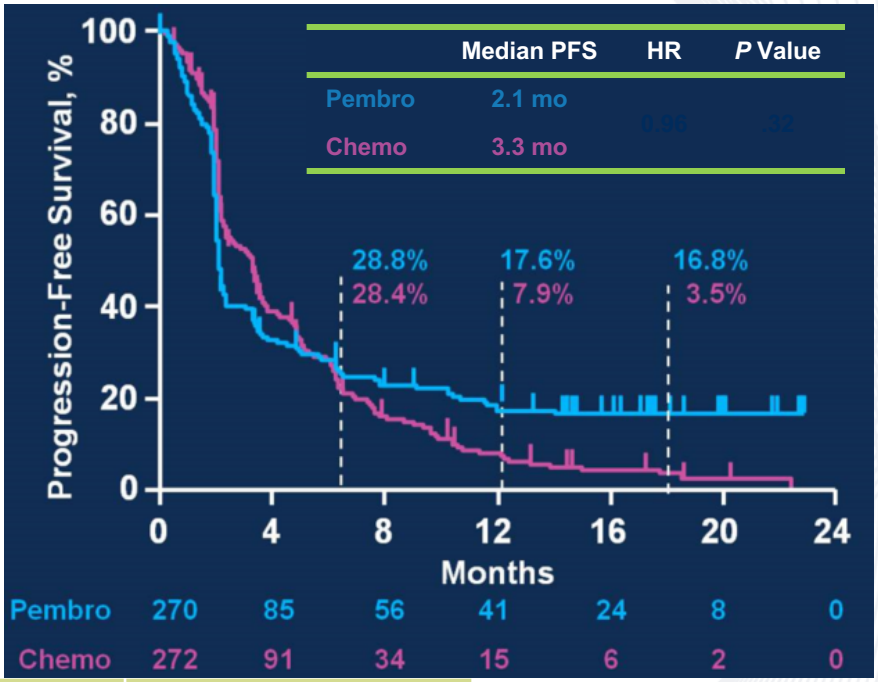
Key Endpoints:

Primary: OS and PFS in total and PD-L1 CPS ≥10% populations

Secondary: ORR and DOR in total and PD-L1 CPS ≥10% populations; safety in total population

CPS, combined positive score; PD, progressive disease.





Data cutoff: Jan 18, 2017
Median follow-up: 18.5 mo

	Pembrolizumab	Chemotherapy
ORR	**21%**	**11%**
CR	8%	3%

Bajorin et al. ASCO 2017, Abstract 4501.

Future Directions

Combinations

Adjuvant therapy

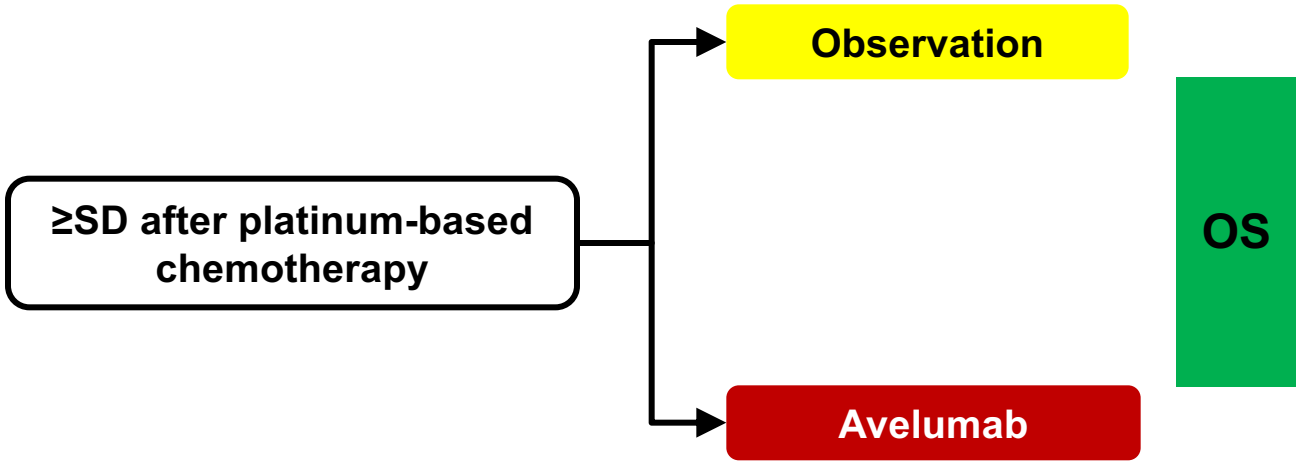
Biomarkers

Ongoing First-Line Phase III Trials Incorporating IO for Advanced UC: Including Cisplatin-Eligible and -Ineligible Patients in the Same Trial!

CT ID	Phase	Target	Experimental Arm(s)	Standard Arm
NCT02807636 IMvigor130	III	PD-L1	Atezo OR Atezo + Gem-Plat	Placebo + Gem-Plat
NCT02853305 KEYNOTE-361	III	PD-1	Pembro OR Pembro + Gem-Plat	Gem-Plat
NCT02516241 DANUBE	III	PD-L1 +/- CTLA-4	Durvalumab OR Durva + Treme	Gem-Plat
NCT03036098 CM-901	III	PD-1 + CTLA	Nivo + Ipi*	Gem-Plat

***This trial includes a substudy for cisplatin-eligible patients comparing gemcitabine + cisplatin +/- nivolumab.**

Second-Line Switch Maintenance: Avelumab Undergoing Evaluation in Phase III JAVELIN Bladder 100 Trial



NCT02603432

Adjuvant PD-1/PD-L1 Inhibitor Phase III Trials

PI	Population	Control Arm	Experimental Arm	Primary Endpoint
Industry	All-comers MIUC Prior NAC- ≥pT2 No AC ≥pT3	No therapy	Atezolizumab	PFS
Industry	All-comers MIUC Prior NAC- ≥pT2 No AC ≥pT3	Placebo	Nivolumab	PFS
Intergroup[a]	All-comers MIUC Prior NAC- ≥pT2 No AC ≥pT3	No therapy	Pembrolizumab	PFS/OS

[a]PI: Apolo; SWOG PI: Sonpavde; ECOG PI: Srinivas.

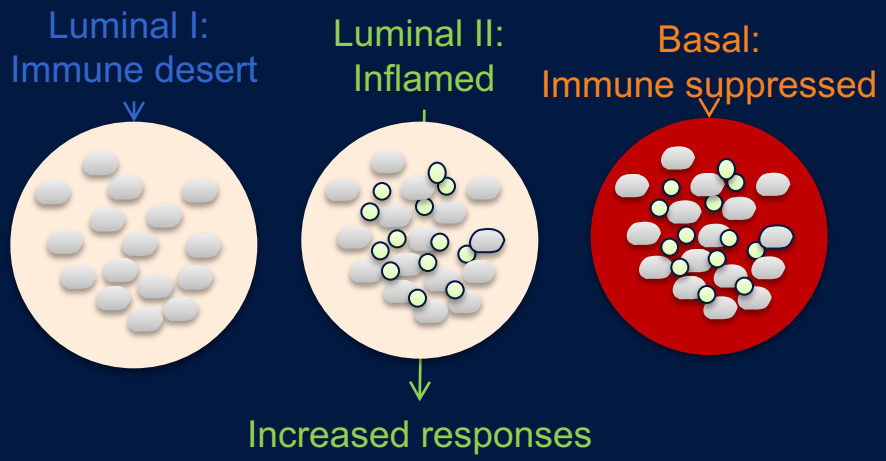
Neoadjuvant Therapy With IO Agents
Selected Phase I-II Trials

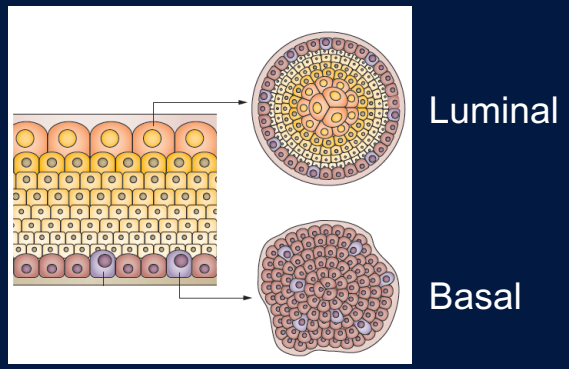
	Trial ID	Phase	Regimen	Primary Endpoint
Chemo-IO	NCT03294304	II	GC-Nivolumab	pCR
	NCT02690558	II	GC-Pembrolizumab	pCR
	NCT02365766	I/II	G/GC-Pembrolizumab	Feasibility, pCR
IO	NCT02451423	II	Atezolizumab	pCR, immune response
	NCT02736266	II	Pembrolizumab	pCR
IO-IO	NCT02812420	II	Durvalumab + Tremelimumab	Feasibility
	NCT02845323	II	Nivolumab +/- Urelumab	Immune response
	Pending	I	Durvalumab +/- CD73i	Feasibility, Immune response

Biomarkers

- In bladder cancer, PD-L1 staining appears to be associated with higher response rate, and may be linked to overall survival;[1] however, multiple assays exist and are under evaluation in bladder cancer.
- Other biomarkers beyond PD-L1 are needed.
  - Data in multiple cancer types suggests that mutation load is associated with treatment outcome with immune checkpoint blockade.[2,3]

Biomarkers Beyond PD-L1

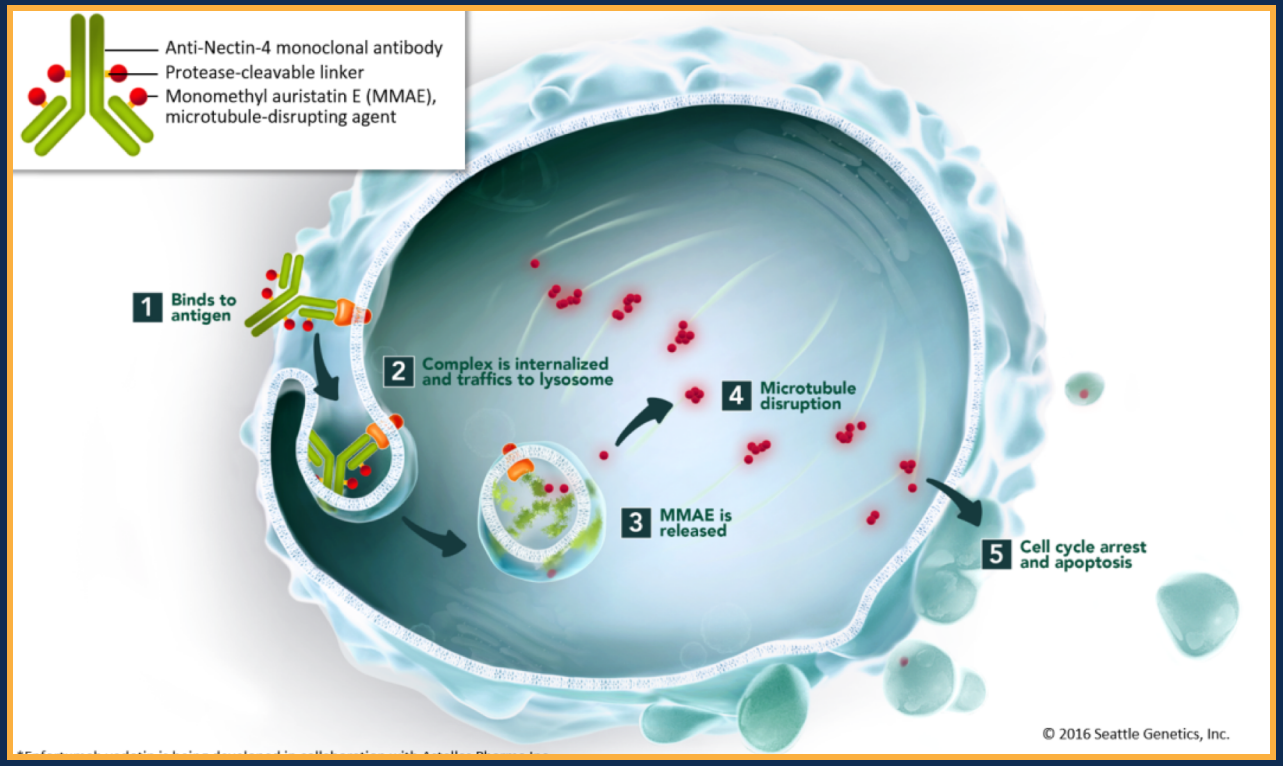




- Luminal I tumors have low T_{eff} expression
- Luminal II tumors have high T_{eff} and low stromal gene expression
- Basal tumors have high T_{eff} and high stromal gene expression

Rosenberg JE, et al. Presented at: ASCO 2016; June 3-7, 2016; Chicago, IL. Abstract 104.

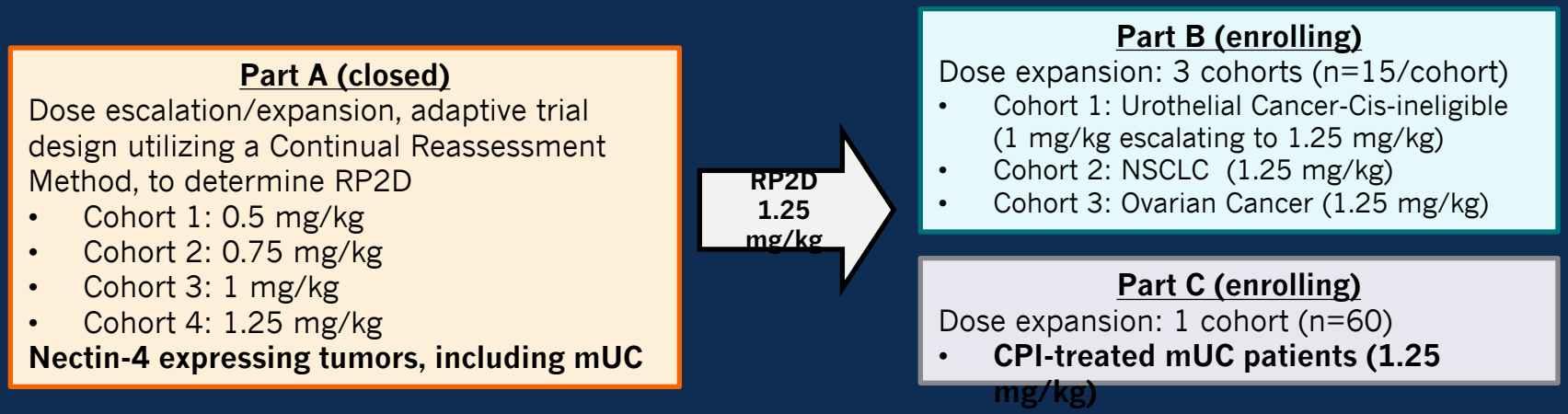
Enfortumab Vedotin: Proposed Mechanism of Action



Enfortumab Vedotin is being co-developed by Seattle Genetics, Inc. and Astellas Pharma Inc.

Study Design

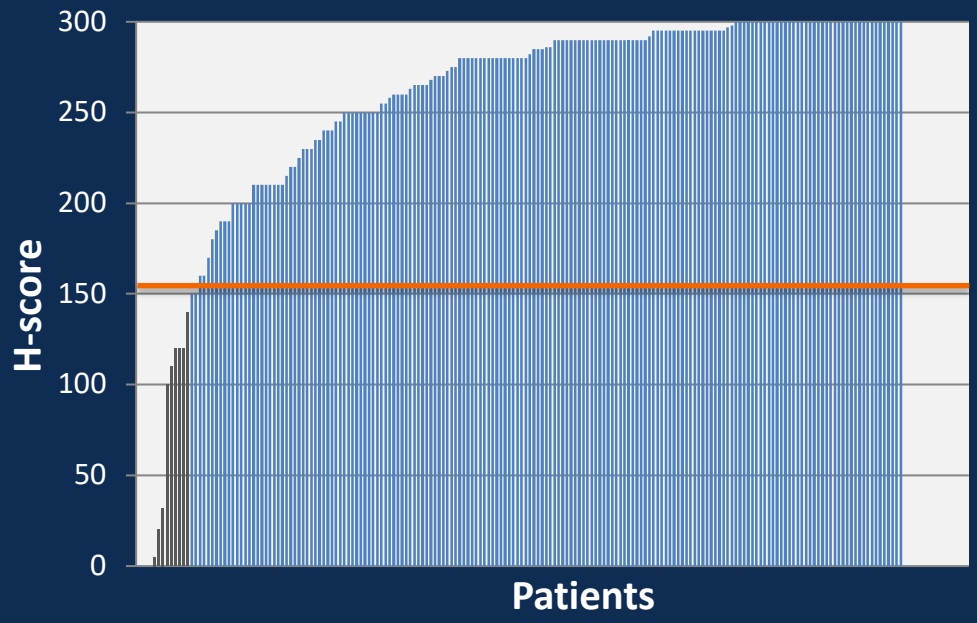
- This phase 1, 3-part study (NCT02091999) enrolled patients with metastatic malignant solid tumors treated with ≥1 prior chemotherapy regimen
- IV administration over 30 minutes on Days 1, 8, and 15 every 28 days
- Study enrollment in Parts B and C ongoing



https://www.clinicaltrials.gov. Accessed 12 May 2017.

Screening of Nectin-4 Expression in mUC

- At screening, patients with mUC had samples that were centrally assessed by immunohistochemistry (IHC) for Nectin-4
  - Almost all patient (97%) samples showed Nectin-4 expression
  - Expression of Nectin-4 was high (median H-score 280 out of a 300 maximum score)
- Due to the above findings, pre-screening for Nectin-4 is no longer an eligibility requirement for subjects with mUC



Gray bars indicate patients with Nectin-4 H-score <150
Blue bars indicate patients with H-scores of ≥150
Note: data cutoff November 2016, N=186

Clinical Response With Enfortumab Vedotin in mUC Patients With or Without Prior CPI or Liver Metastases

	Prior CPI Treatment[a]	CPI-Naïve[a]	Liver Metastases[a]
	1.25 mg/kg (n=89)	1.25 mg/kg (n=23)	1.25 mg/kg (n=33)
Confirmed CR	**3.4%**	9%	0
Confirmed PR	**37%**	35%	39%
Confirmed ORR[b] (95% CI)	**40% (30.2, 51.4)**	44% (23.2, 65.5)	39% (22.9, 57.9)
SD	**34%**	17%	21%
DCR[b] (95% CI)	**74% (63.8, 82.9)**	61% (38.5, 80.3)	60% (42.1, 77.1)

Data cut-off date is April 9, 2018.
Data presented as n (%), unless otherwise indicated.
CR, complete response; CPI, checkpoint inhibitor, DCR, disease control rate (DCR=CR+PR+SD); PR, partial response; ORR, overall response rate (ORR=CR+PR); SD, stable disease.
[a]Evaluable patients must have at least one post-baseline assessment; responses assessed per RECIST 1.1.
[b]Data presented as % (95% CI); 95% CI based on the Clopper-Pearson method.

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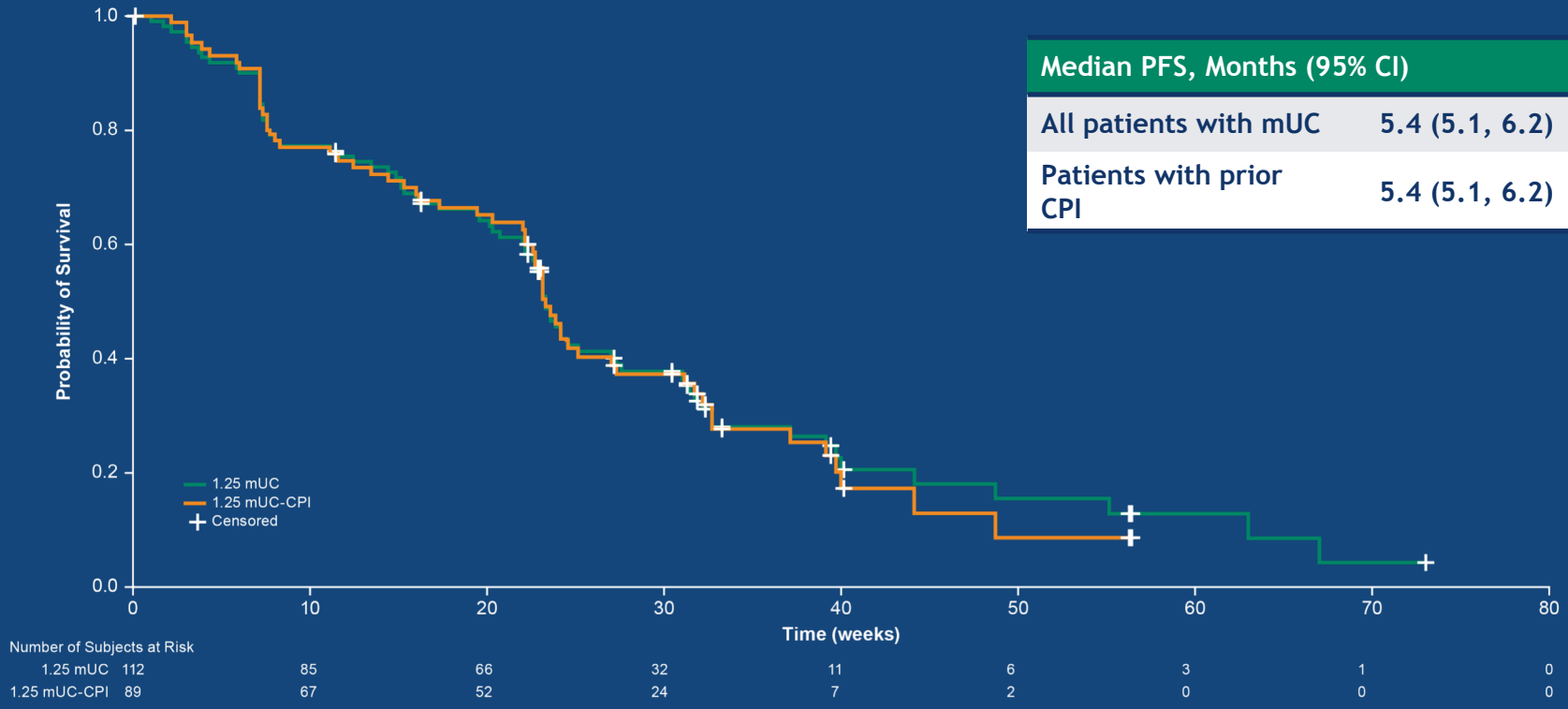
Progression-Free Survival in Patients With mUC Treated With Enfortumab Vedotin 1.25 mg/kg



Median PFS, Months (95% CI)	
All patients with mUC	5.4 (5.1, 6.2)
Patients with prior CPI	5.4 (5.1, 6.2)

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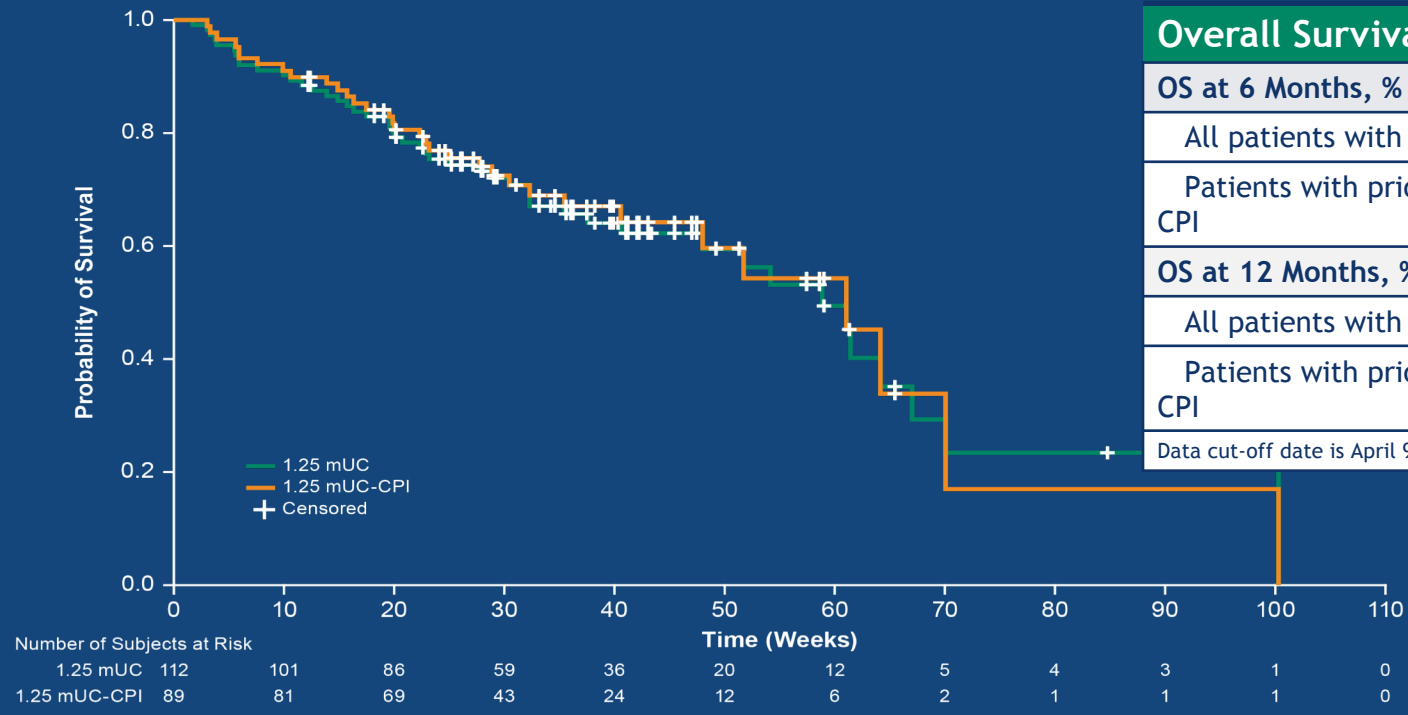
Preliminary Overall Survival in Patients With mUC Treated With Enfortumab Vedotin 1.25 mg/kg



Overall Survival	
OS at 6 Months, %	
All patients with mUC	74.4
Patients with prior CPI	75.6
OS at 12 Months, %	
All patients with mUC	56.3
Patients with prior CPI	54.2
Data cut-off date is April 9, 2018.	

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Conclusions

- Checkpoint inhibition therapy demonstrates significant antitumor activity in advanced urothelial carcinoma:
  - As initial therapy in cisplatin-ineligible patients.
  - In patients with cisplatin-pretreated disease.
- Trials are ongoing to explore immunotherapy-based combinations and the use of immunotherapy in earlier stages of disease.
- A thorough understanding of the markers of resistance and response will help to designing future trials in earlier disease.