Immunotherapy of Kidney and Bladder Cancer

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M-VAC vs Cisplatin Phase III
Long term survival

	Cisplatin	M-VAC
Evaluable	122	133
3 years	4	17
6 years*	2	9

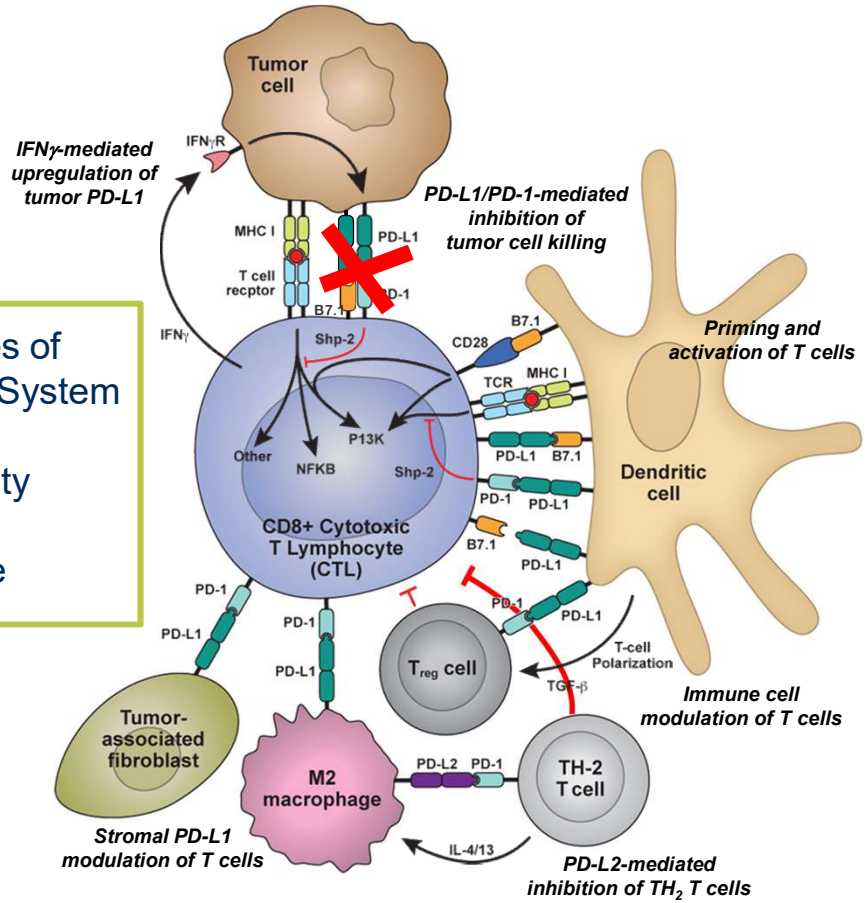
*6 patients died of TCC, 1 2nd Ca, 2 other, 1 lost to F/U

Saxman, JCO, 15:2564, 1997

Mechanism of Immune Checkpoint Inhibitors

Key Attributes of the Immune System

- Specificity
- Memory
- Adaptive



- Cancer cells develop many mutations that can make them appear foreign to the immune system
- T cells can recognize, attack and kill these “foreign” cancer cells
- Cancer cells can evade immune attack by expressing PD-L1
- Adaptive tumor expression of PD-L1 turns the immune system OFF
- Clinically, we want to block PD-1 or PD-L1 to reactivate the immune system
- PD-L1 plays an important role in dampening the anti-tumor immune response

Herbst RS et al. *J Clin Oncol* . 2013;31(suppl; abstr 3000)

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.

IMvigor210 (Cohort 1)

IMvigor210:

- Inoperable locally advanced or metastatic urothelial carcinoma
- Predominantly UC histology
- Tumor tissue evaluable for PD-L1 testing[a]

Cohort 1 (N = 119): 1L cisplatin-ineligible → Atezolizumab 1200 mg IV q3w until RECIST v1.1 progression

Cohort 2 (N = 310): Platinum-treated mUC → Atezolizumab 1200 mg IV q3w until loss of clinical benefit

Cohort 1–specific inclusion criteria

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

Key primary endpoint :

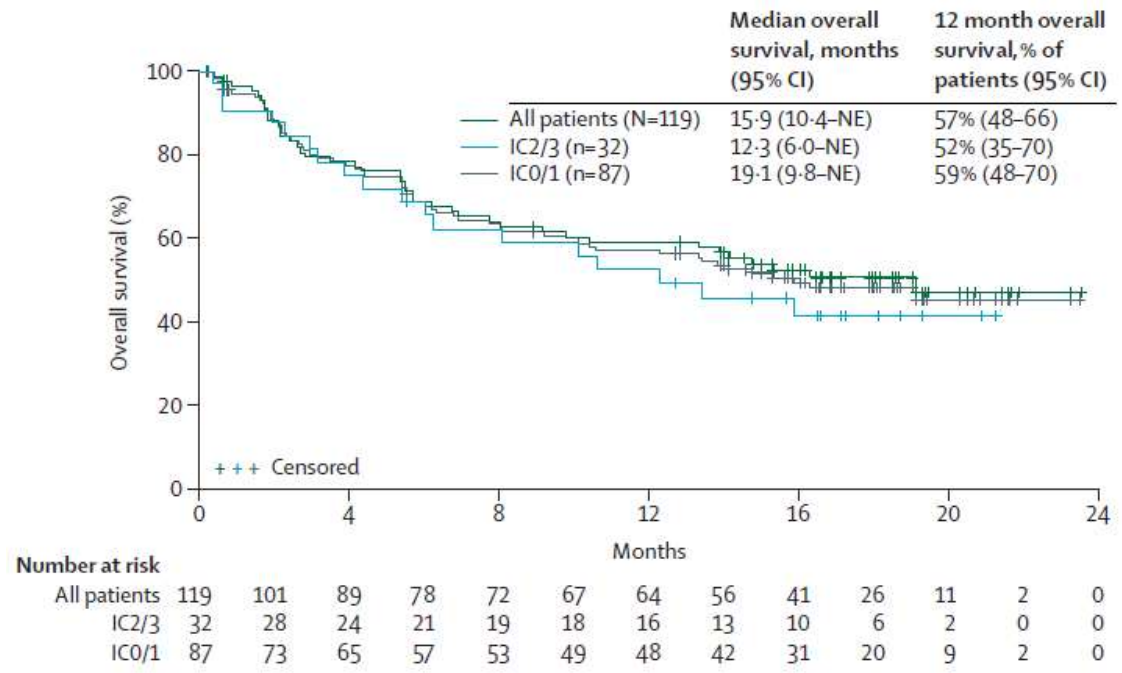
- Confirmed ORR: RECIST v1.1 (per central IRF)

Key secondary endpoints :

- DOR, PFS, OS, safety

IMvigor210 (Cohort 1)

- N = 119
- ORR = 23% (9% CR)



KEYNOTE-052: Pembrolizumab as 1st-Line Therapy for Cisplatin-Ineligible Advanced Urothelial Cancer

Patients (N = 350)

- 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

Pembrolizumab 200 mg Q3W

Primary Endpoints

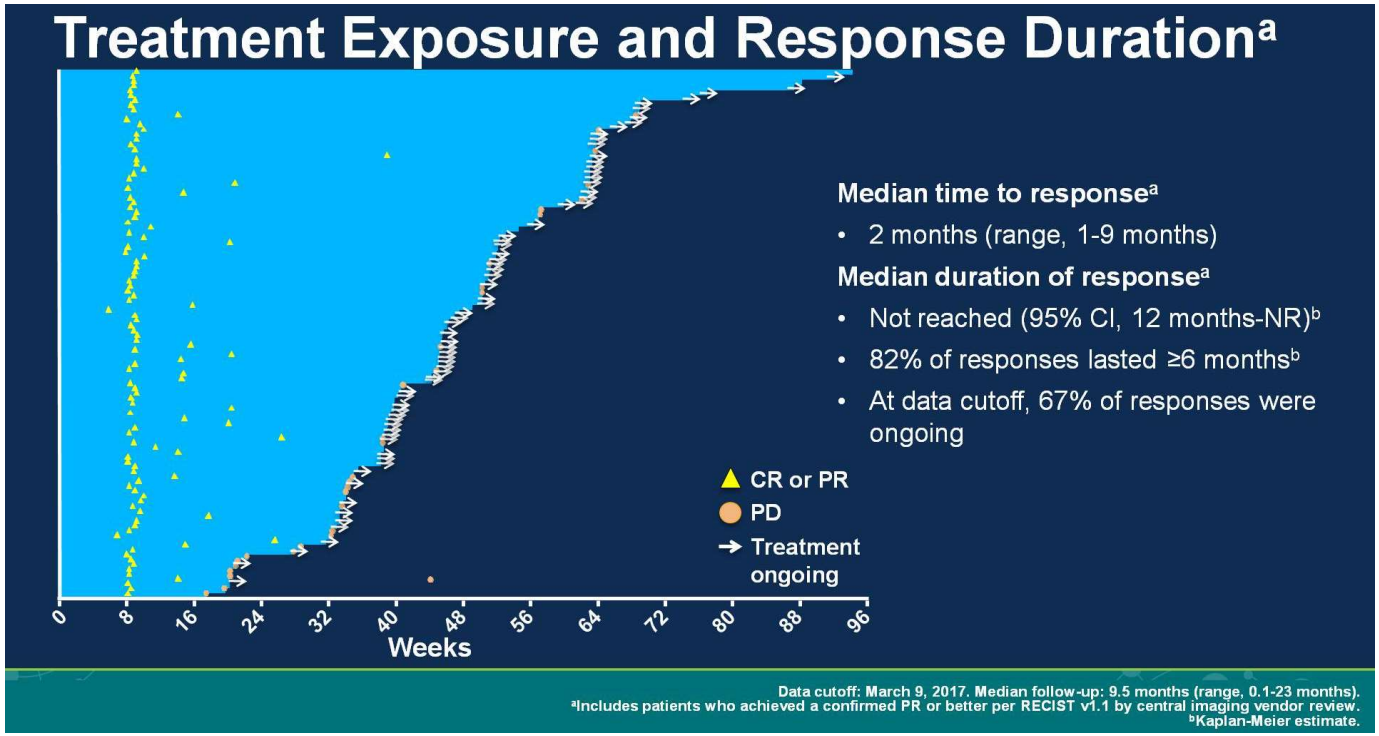
- ORR in all patients
- ORR in patients with PD-L1–positive tumors

Primary Endpoints:

- **Planned interim analysis in first 100 patients**
  - **Determine the PD-L1–high expression cutpoint**
- **ORR in all patients and PD-L1–positive population**

Secondary Endpoints: DOR, PFS, OS, and ORR in all patients, PD-L1–positive and PD-L1–high-expressing patients; safety and tolerability

KEYNOTE-052 (ASCO17 Update)



N = 370
ORR: 29%
CR: 7%

O'Donnell et al. ASCO 2017; Abstract 4502.

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.

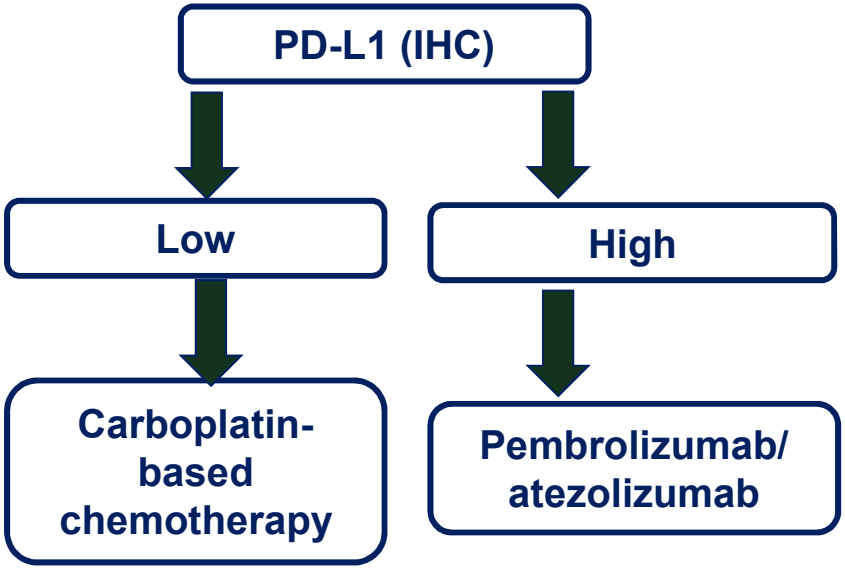
1. De Santis M, et al. J Clin Oncol. 2012;30(2):191-199; 2. Balar AV, et al. Lancet. 2017;389(10064):67-76; 3. Balar AV; et al. Lancet Oncol. 2017;18:1483-1492.

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.



First Line Chemotherapy +Checkpoint Therapy trials in Metastatic Urothelial Cancer

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

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.

IMvigor210 (Cohort 2)

IMvigor210:
- Inoperable locally advanced or metastatic urothelial carcinoma
- Predominantly UC histology
- Tumor tissue evaluable for PD-L1 testing[a]

Cohort 1 (N = 119): 1L cisplatin-ineligible → Atezolizumab 1200 mg IV q3w until RECIST v1.1 progression

Cohort 2 (N = 310): Platinum-treated mUC → Atezolizumab 1200 mg IV q3w until loss of clinical benefit

Cohort 2-Specific Inclusion Criteria
- Progression during/following platinum (no restrictions on # prior lines of therapy)
- ECOG PS 0-1
- CrCl ≥ 30 mL/min

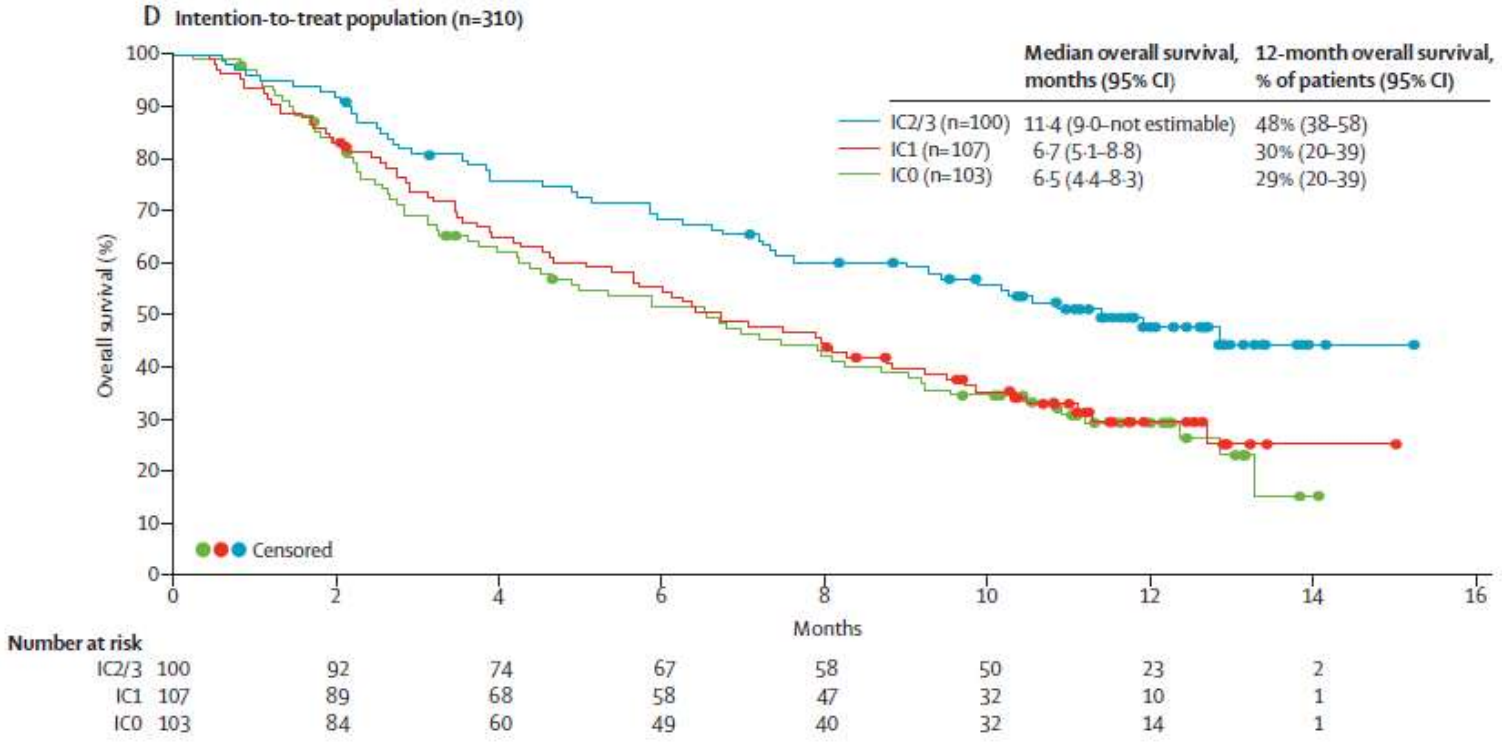
Key primary endpoint :

•Confirmed ORR: RECIST v1.1 (per central IRF)

Key secondary endpoints :

•DOR, PFS, OS, safety

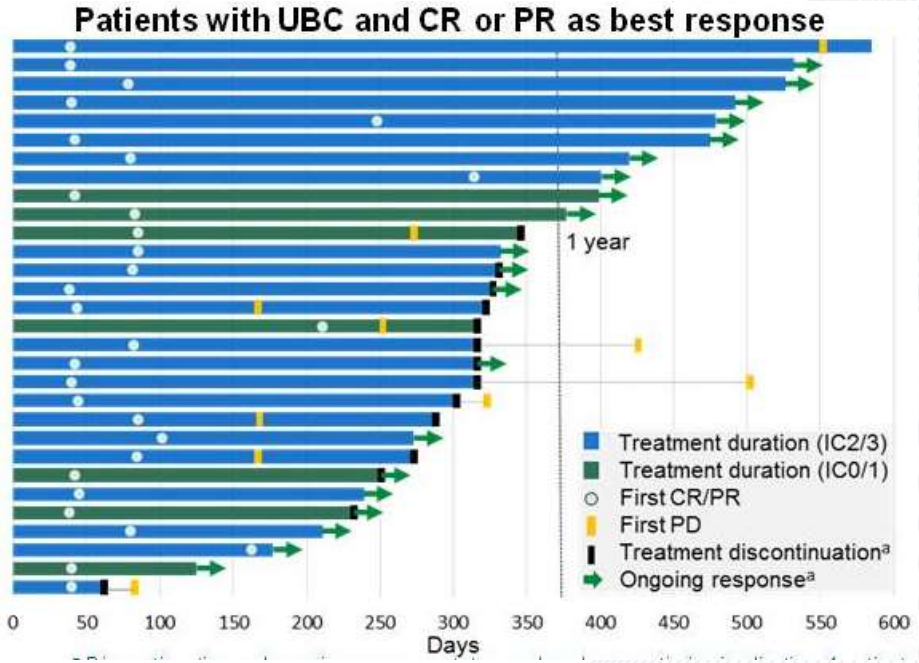
IMvigor210 (Cohort 2)



Phase Ia Trial of Atezolizumab in Pretreated Bladder Cancer

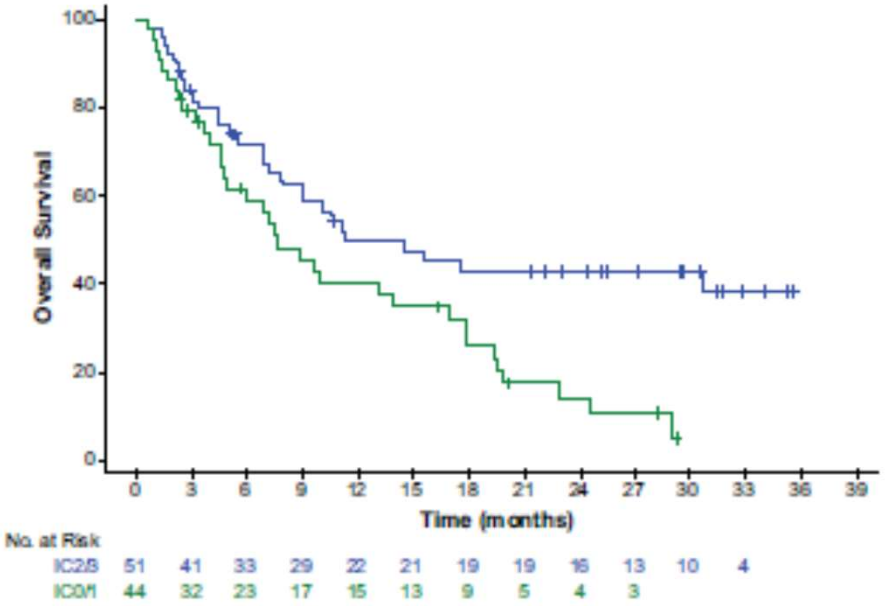
92

- 72% with ≥2 prior systemic therapies
- **ORR 50% in PD-L1 high (IC2/3)**
- **ORR 17% in PD-L1 low (IC0/1)**

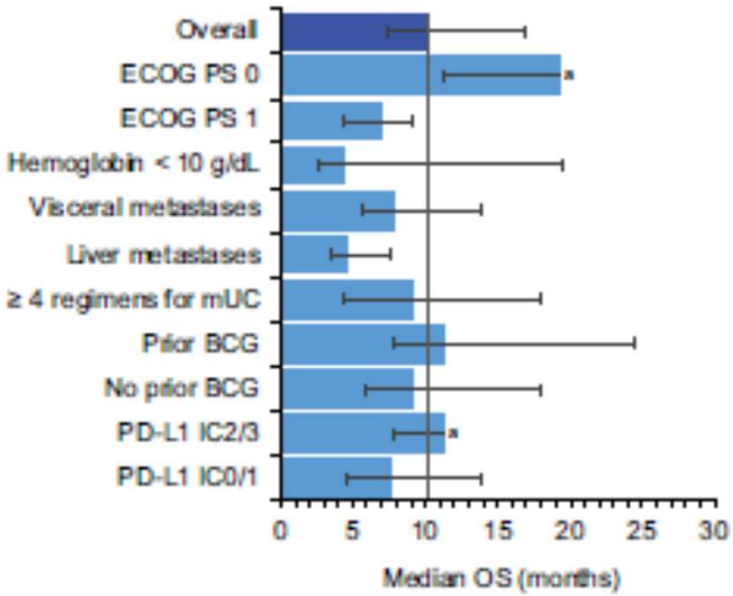


Petrylak et al. ASCO 2015; Abstract

OS by PD-L1 Status



Median Survival by Baseline Characteristics



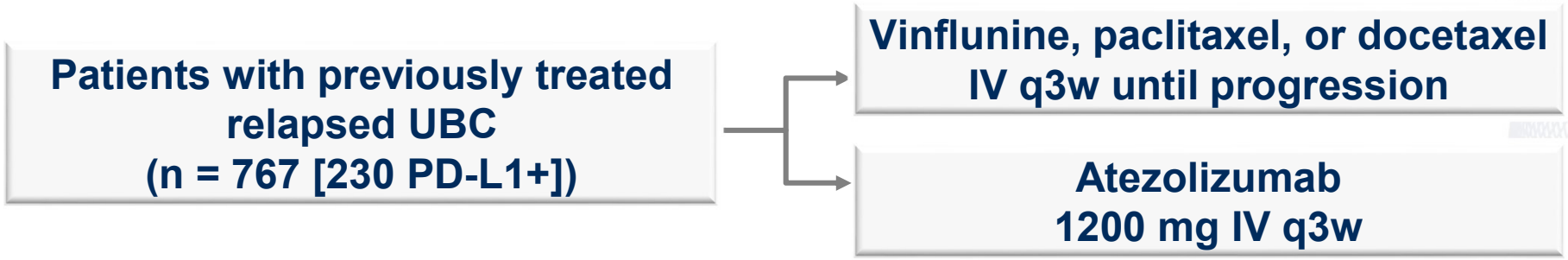
Patterns of AE Occurrence

Time Following Initiation of Atezolizumab*	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%

* 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

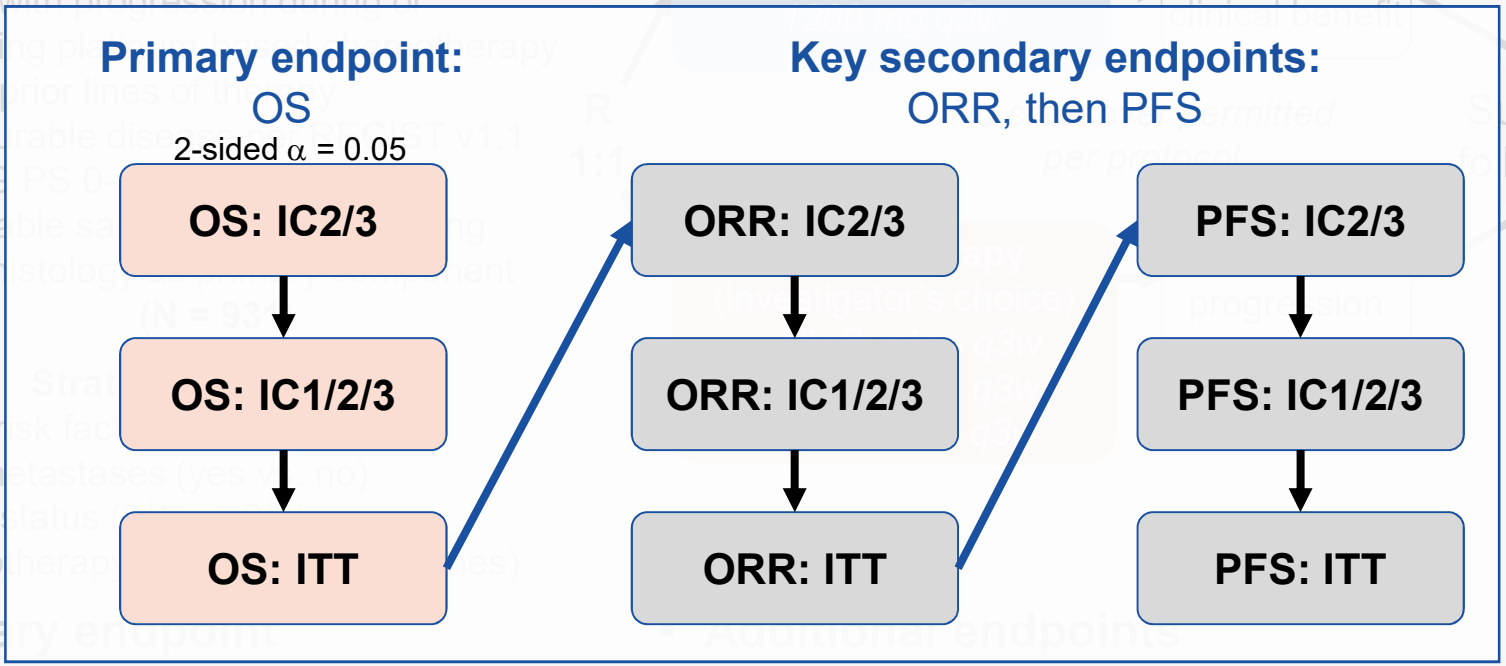
IMvigor211 Phase III Trial in Previously-treated Urothelial Cancer



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

2nd Special Conference
EACR
AACR
SIC

IMvigor211 Study Design

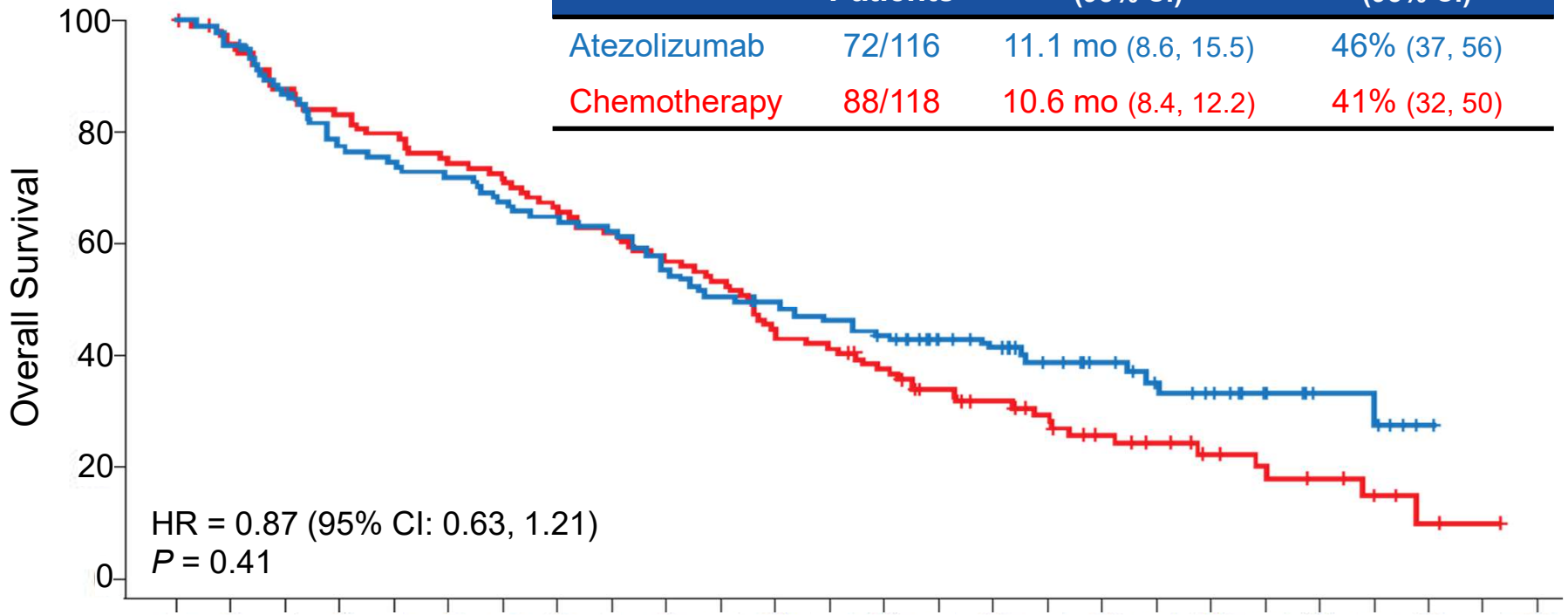


DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; PRO, patient-reported outcome; q3w, every three weeks; RECIST, Response Evaluation Criteria In Solid Tumors; TCC, transitional cell carcinoma. [a] ClinicalTrials.gov, 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)



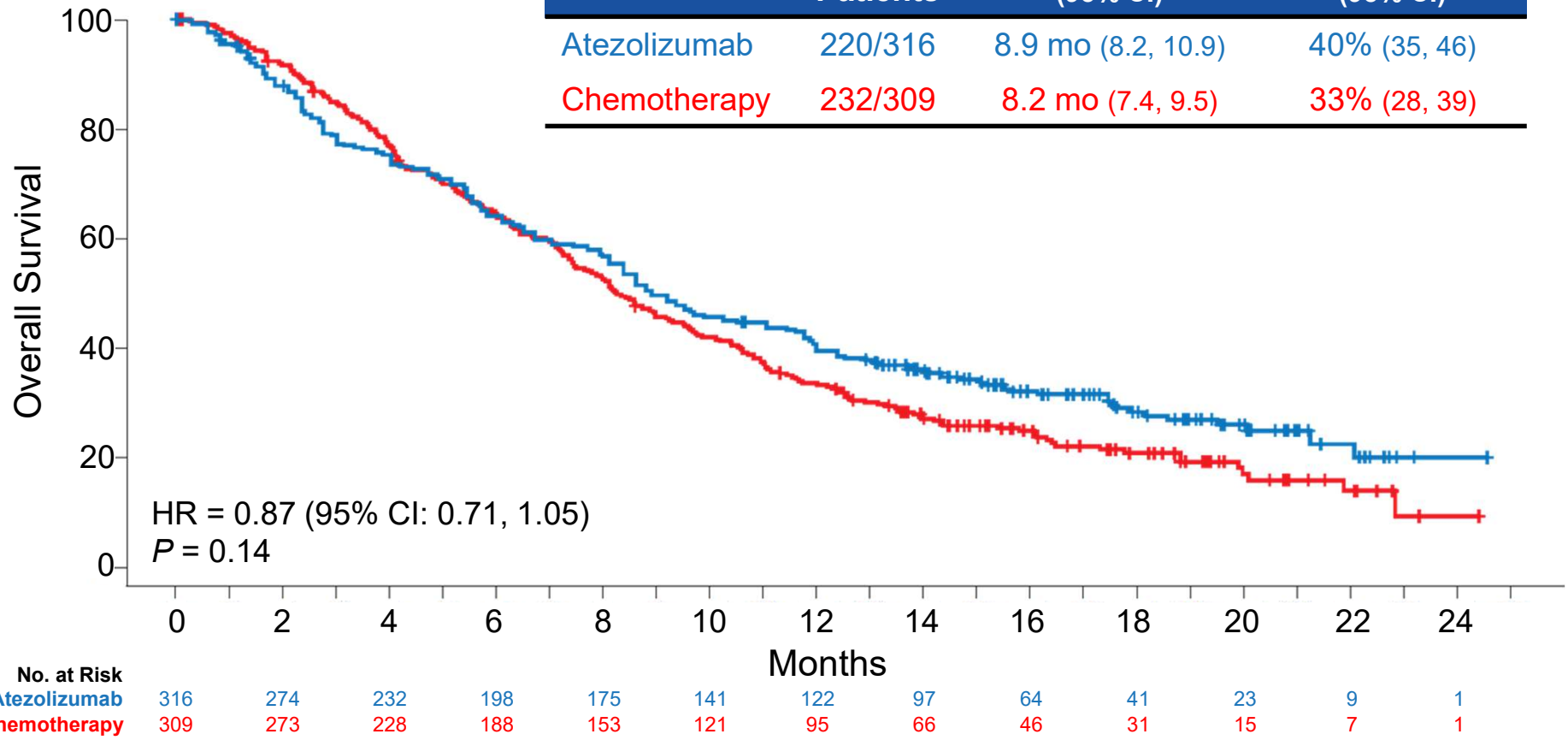
No. at Risk													
Atezolizumab	116	100	85	77	71	58	51	39	27	19	11	6	0
Chemotherapy	118	100	91	82	71	61	47	32	24	15	9	5	1

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.

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AACR
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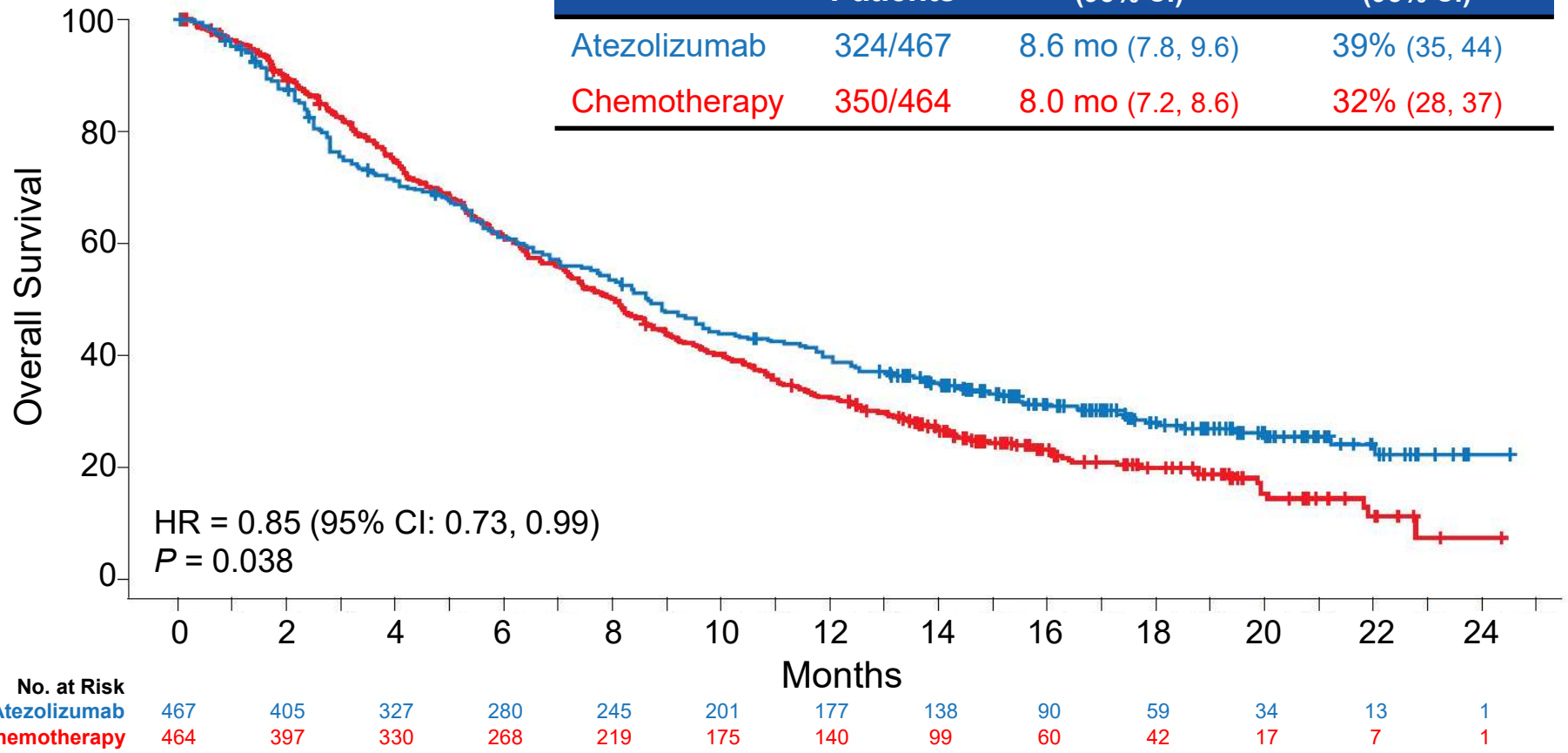
OS Analysis: ITT Population

	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)



No. at Risk													
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

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

Powles T, et al. EAS 2017, IMvigor211.

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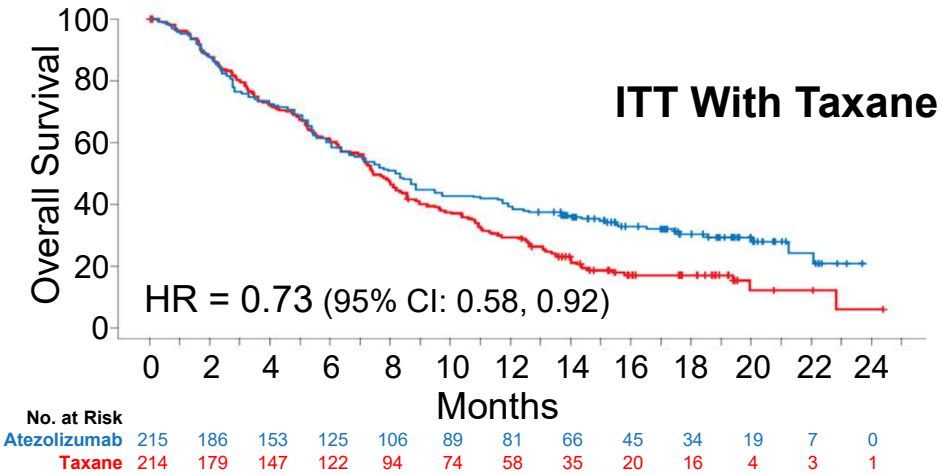
OS by Chemotherapy Type



- OS was also examined in subgroups based on chemotherapy type at randomization
  - Improved OS was observed with atezolizumab vs. taxanes

Subgroup	Median OS (95% CI)
Atezolizumab	8.3 mo (6.6, 9.8)
Taxane	7.5 mo (6.7, 8.6)

Powles T, et al. EAS 2017, IMvigor211.

Phase Ib JAVELIN Solid Tumor Trial of Avelumab: Trial Schema

- Open-label, multicenter phase Ib study in pts with confirmed solid tumors

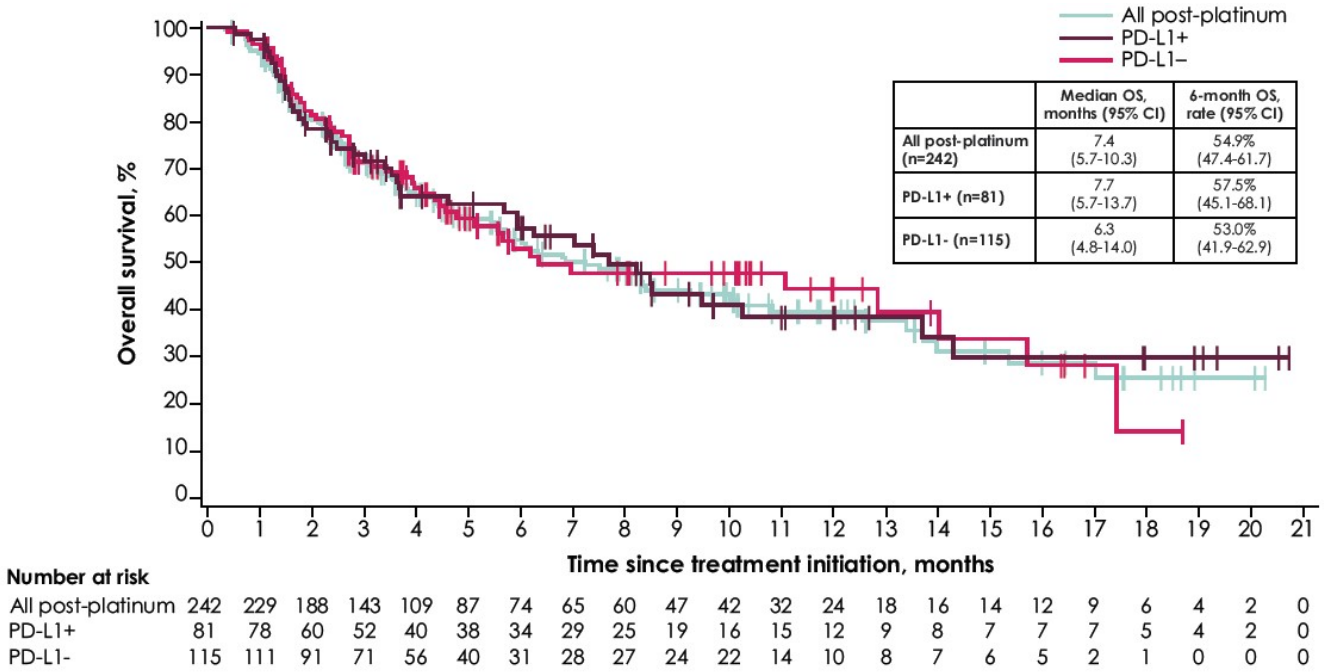
histology or cytology confirmed metastatic UC after progression on or ineligible for platinum-based chemotherapy for metastatic disease; ECOG PS 0-1
(N = 241)

Avelumab
10 mg/kg IV Q2W

Treated until PD, unacceptable AE, or investigator decision

- Primary endpoint: ORR, safety
- Secondary endpoints: PFS, OS, and association of PD-L1 expression on tumor cells with clinical activity of avelumab

Phase Ib JAVELIN Solid Tumor Trial of Avelumab (ASCO17 Update)



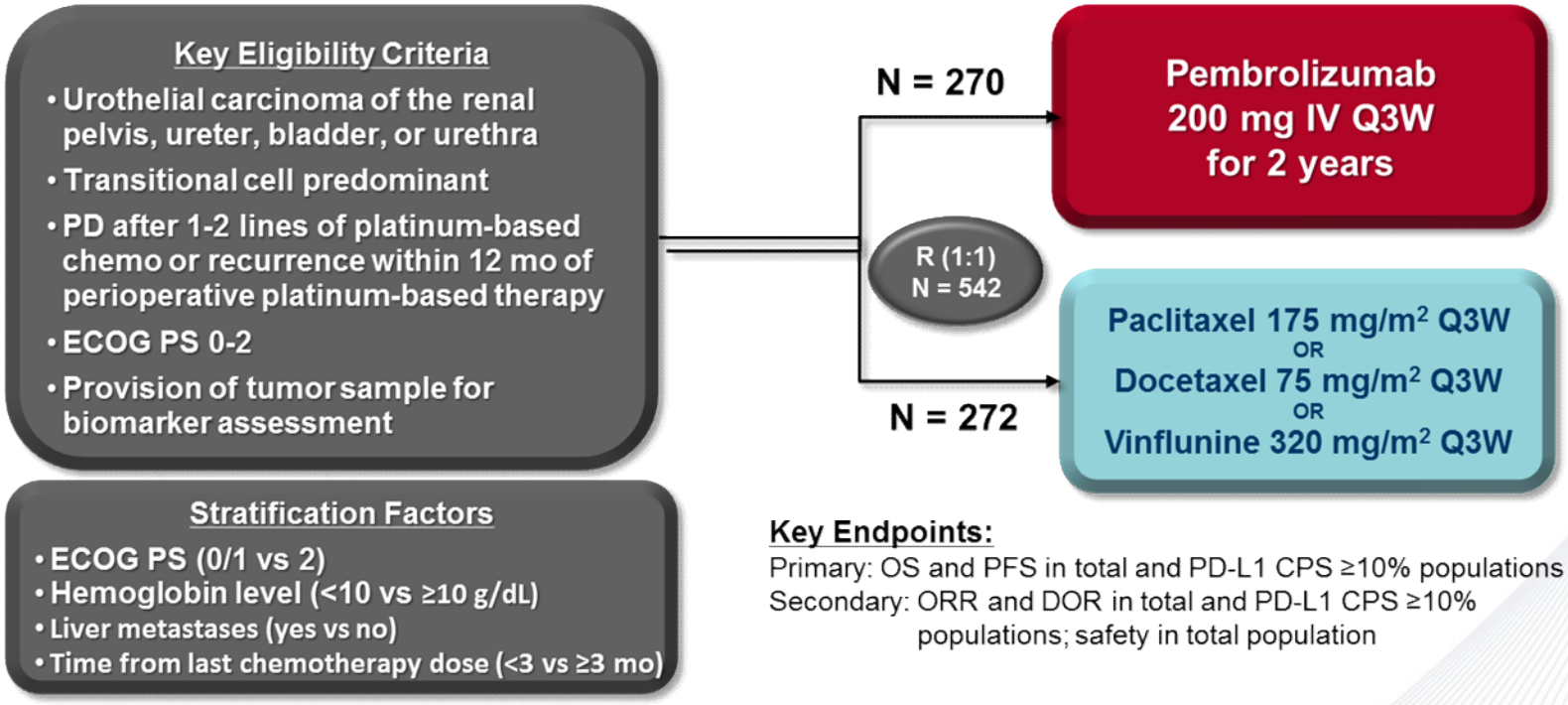
	Median OS, months (95% CI)	6-month OS, rate (95% CI)
All post-platinum (n=242)	7.4 (5.7-10.3)	54.9% (47.4-61.7)
PD-L1+ (n=81)	7.7 (5.7-13.7)	57.5% (45.1-68.1)
PD-L1- (n=115)	6.3 (4.8-14.0)	53.0% (41.9-62.9)

Number at risk

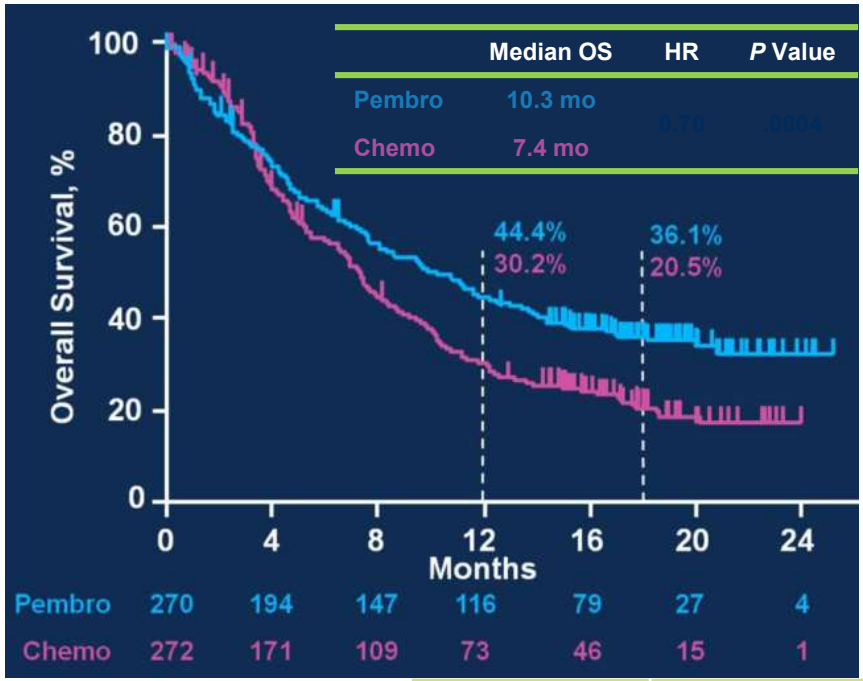
All post-platinum	242	229	188	143	109	87	74	65	60	47	42	32	24	18	16	14	12	9	6	4	2	0
PD-L1+	81	78	60	52	40	38	34	29	25	19	16	15	12	9	8	7	7	7	5	4	2	0
PD-L1-	115	111	91	71	56	40	31	28	27	24	22	14	10	8	7	6	5	2	1	0	0	0

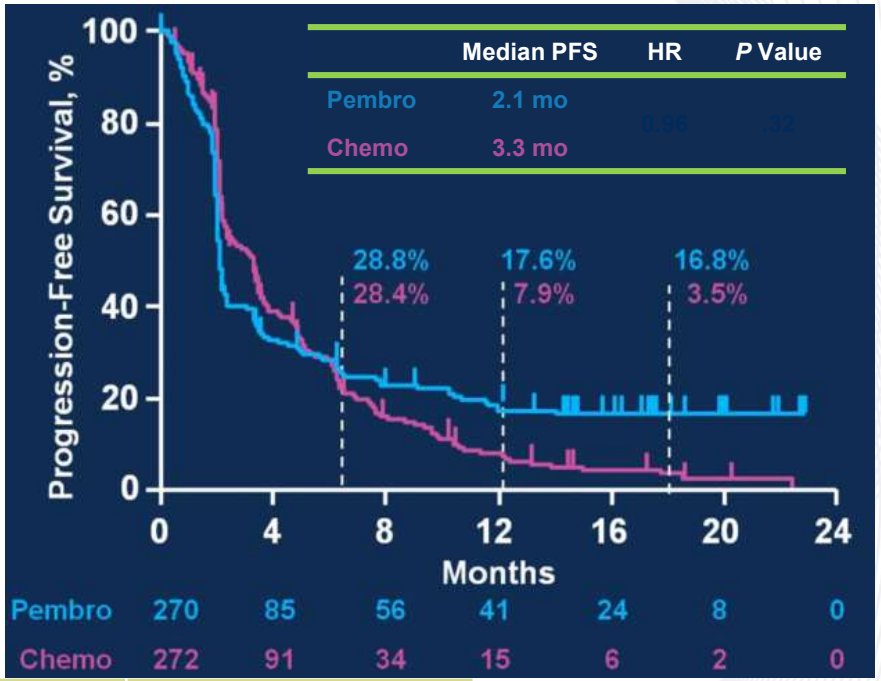
	N = 242
mOS	7.4 mo
mPFS	1.5 mo (6.6 wk)

KEYNOTE-045: Phase III Study Design



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

Non Muscle Invasive Disease

Combinations

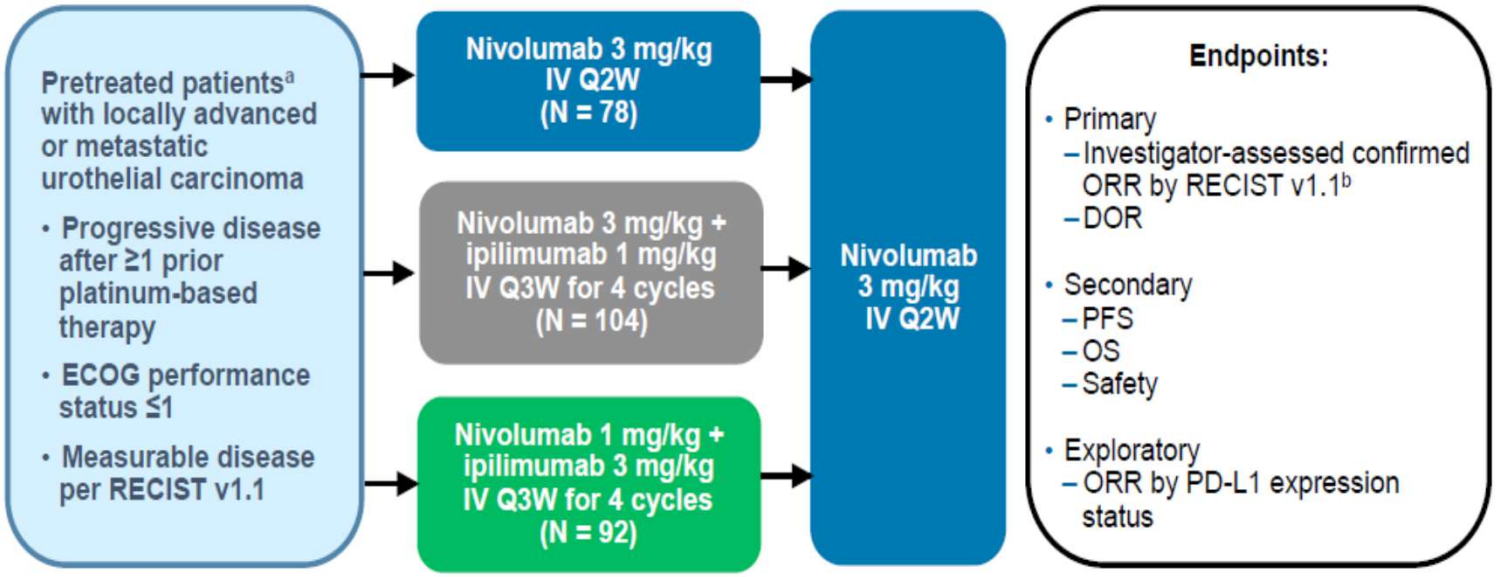
Adjuvant therapy

Biomarkers

Checkmate 032

Study Design

Open-label, multicenter, phase 1/2 study (NCT01928394)

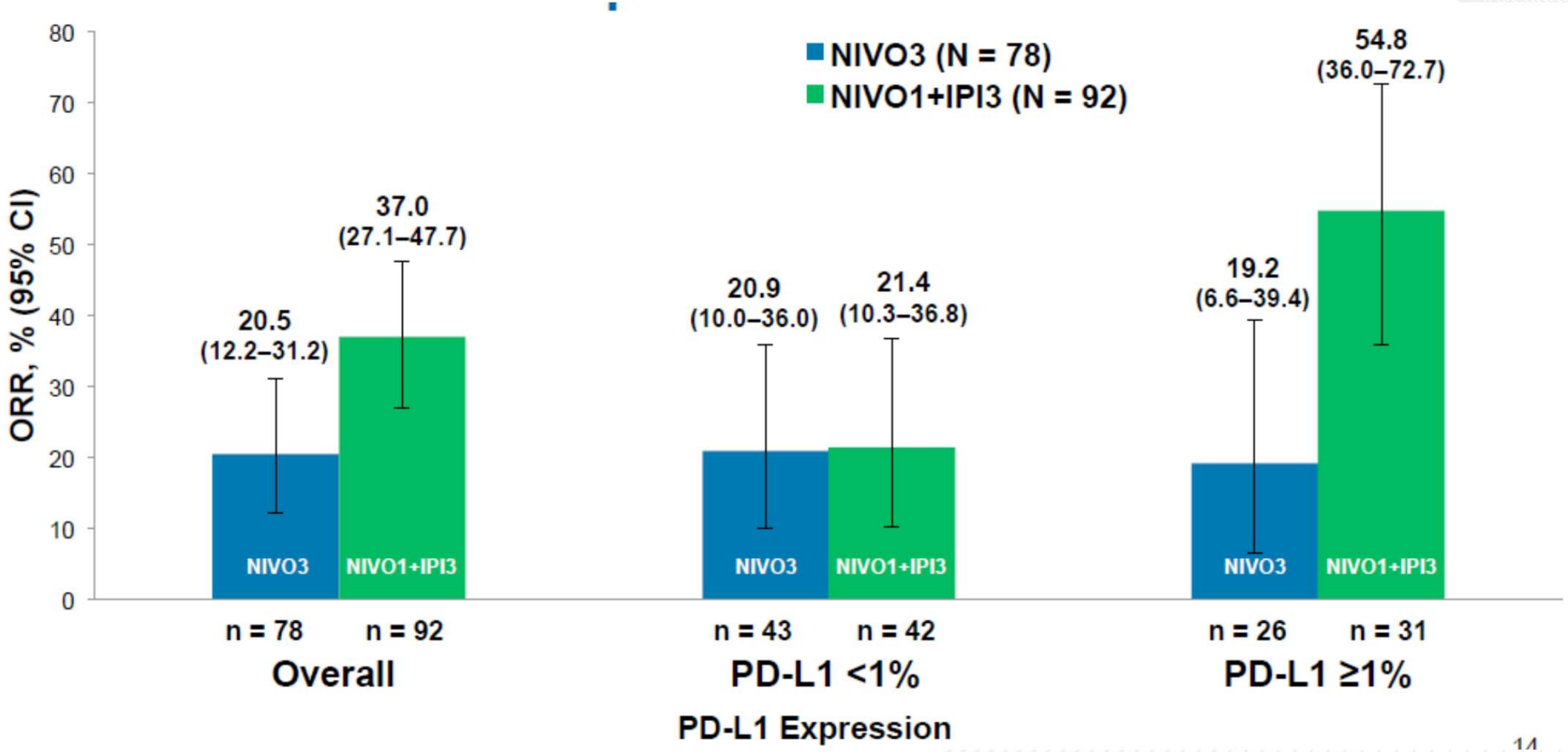


- Tumor measurements: CT or MRI every 6 weeks (±1 week) from first dose for the first 24 weeks, then every 12 weeks (±1 week)

Checkmate 032
Ipilimumab(Ipi) +Nivolumab(N)

	ORR	PFS	OS
N 3 mg/kg	26%	2.8	9.9
N+ Ipi 3 mg/kg	27%	2.6	7.4
N+ Ipi 1 mg/kg	38%	4.9	15.3

PDL-1 Expression and ORR



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

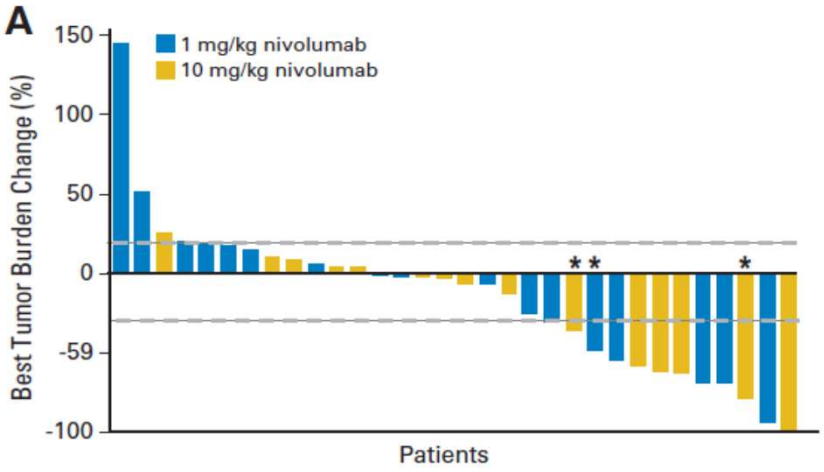
[a]**PI: Apolo; SWOG PI: Sonpavde; ECOG PI: Srinivas.**

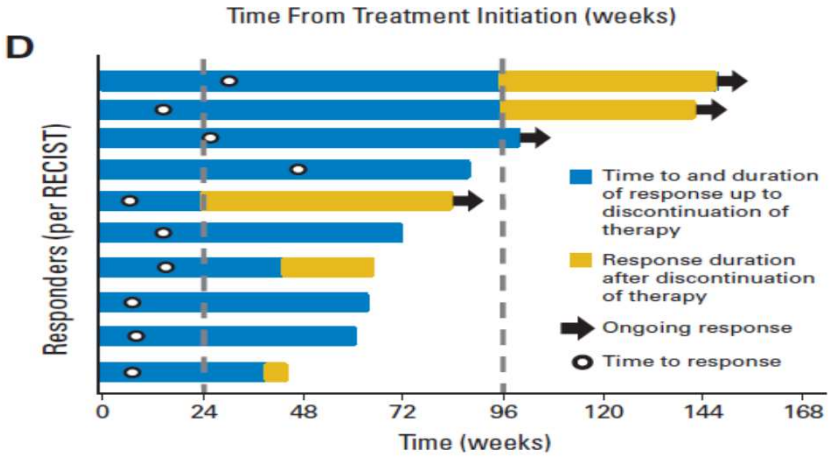
Neoadjuvant Therapy With IO Agents
Selected Phase I-II Trials

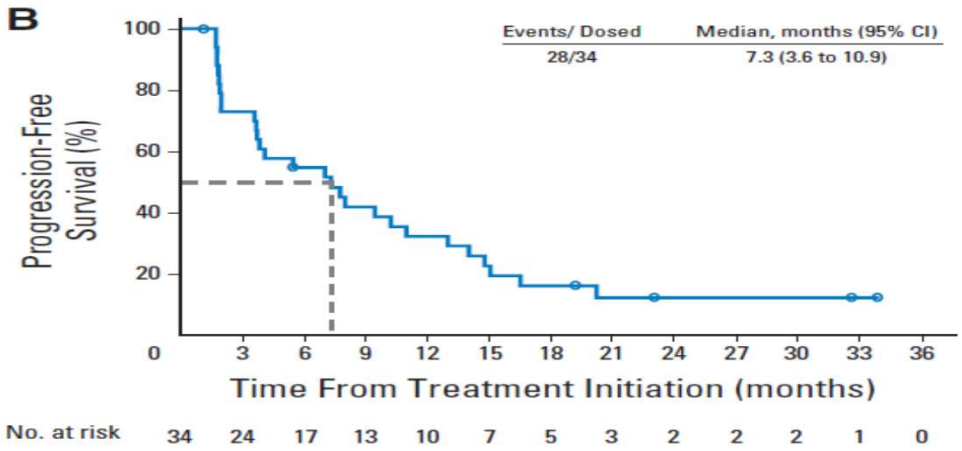
	Trial ID	Phase	Regimen	Primary Endpoint
Chemo-IO	NCT03294304	II	GC-Nivolumab	pCR
	NCT02690558	II	GC-Pembrolizumab	pCR
	NCT02365766	I/II	G/GC-Pembrolizumab	Feasibility, pCR
IO	NCT02451423	II	Atezolizumab	pCR, immune response
	NCT02736266	II	Pembrolizumab	pCR
IO-IO	NCT02812420	II	Durvalumab + Tremelimumab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

Planned Phase III Trial by NRG, SWOG
ChemoRT +/- Concurrent → Adjuvant Atezolizumab

Activity of Nivolumab in Phase 1 Multi-Dose Trial







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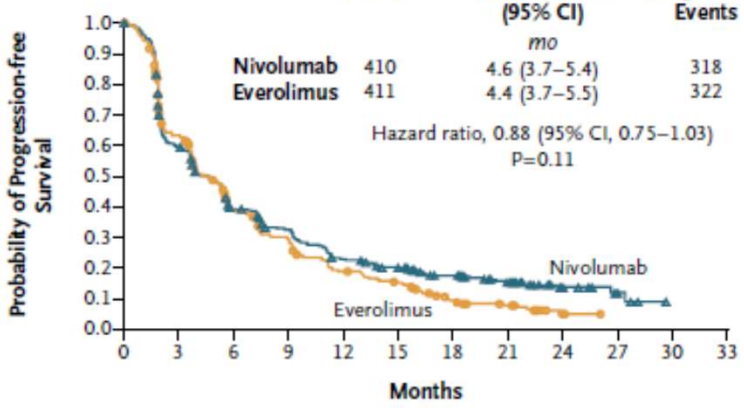
Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

N ENGL J MED 373;19 NEJM.ORG NOVEMBER 5, 2015

R.J. Motzer, B. Escudier, D.F. McDermott, S. George, H.J. Hammers, S. Srinivas, S.S. Tykodi, J.A. Sosman, G. Procopio, E.R. Plimack, D. Castellano, T.K. Choueiri, H. Gurney, F. Donskov, P. Bono, J. Wagstaff, T.C. Gauler, T. Ueda, Y. Tomita, F.A. Schutz, C. Kollmannsberger, J. Larkin, A. Ravaud, J.S. Simon, L.-A. Xu, I.M. Waxman, and P. Sharma, for the CheckMate 025 Investigators*

Kaplan–Meier Curve for Progression-free Survival

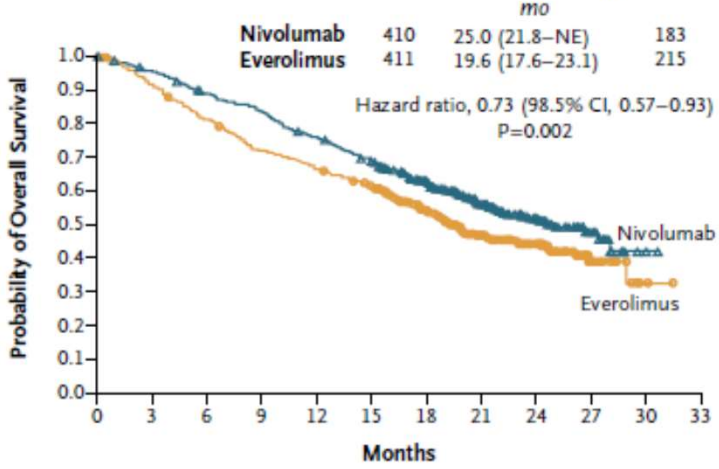


	No. of Patients	Median Progression-free Survival (95% CI)	No. of Progression Events
		mo	
Nivolumab	410	4.6 (3.7–5.4)	318
Everolimus	411	4.4 (3.7–5.5)	322

Hazard ratio, 0.88 (95% CI, 0.75–1.03)
P=0.11

No. at Risk

Nivolumab	410	230	145	116	81	66	48	29	11	4	0	0
Everolimus	411	227	129	97	61	47	25	16	3	0	0	0



	No. of Patients	Median Overall Survival (95% CI)	No. of Deaths
		mo	
Nivolumab	410	25.0 (21.8–NE)	183
Everolimus	411	19.6 (17.6–23.1)	215

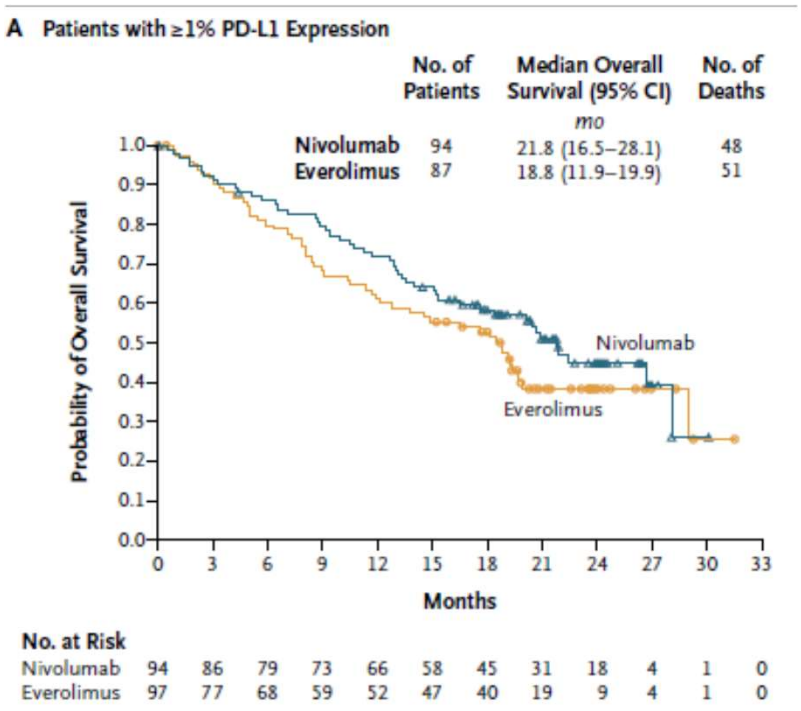
Hazard ratio, 0.73 (98.5% CI, 0.57–0.93)
P=0.002

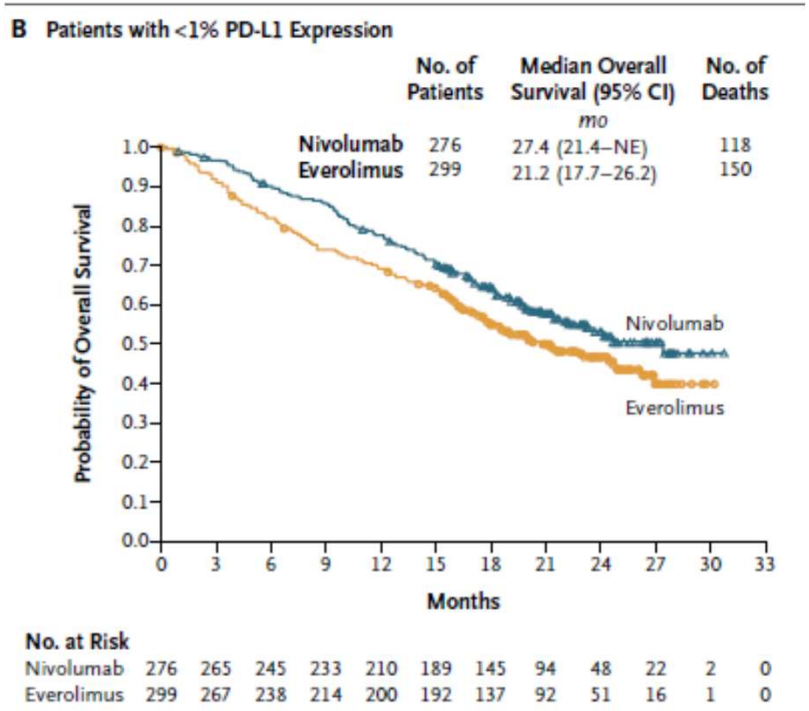
No. at Risk

Nivolumab	410	389	359	337	305	275	213	139	73	29	3	0
Everolimus	411	366	324	287	265	241	187	115	61	20	2	0

Tumor PD-L1 is not Predictive

N ENGL J MED 373;19 NEJM.ORG NOVEMBER 5, 2015





Survival by MSKCC Score

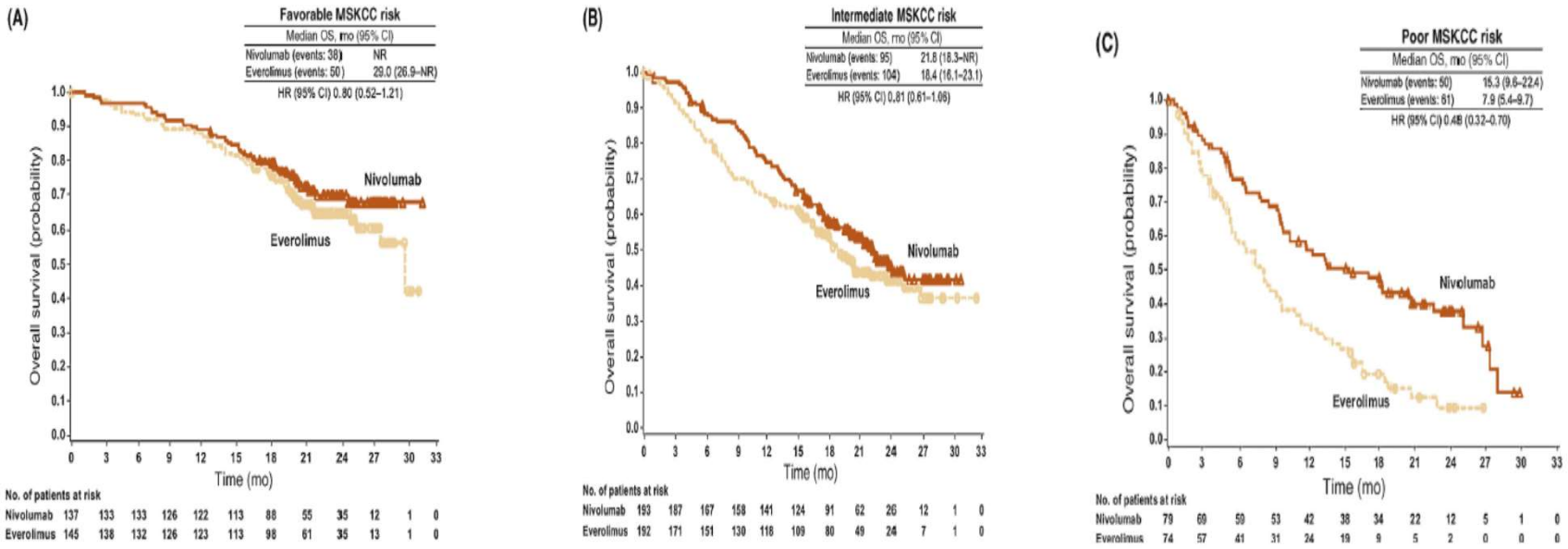
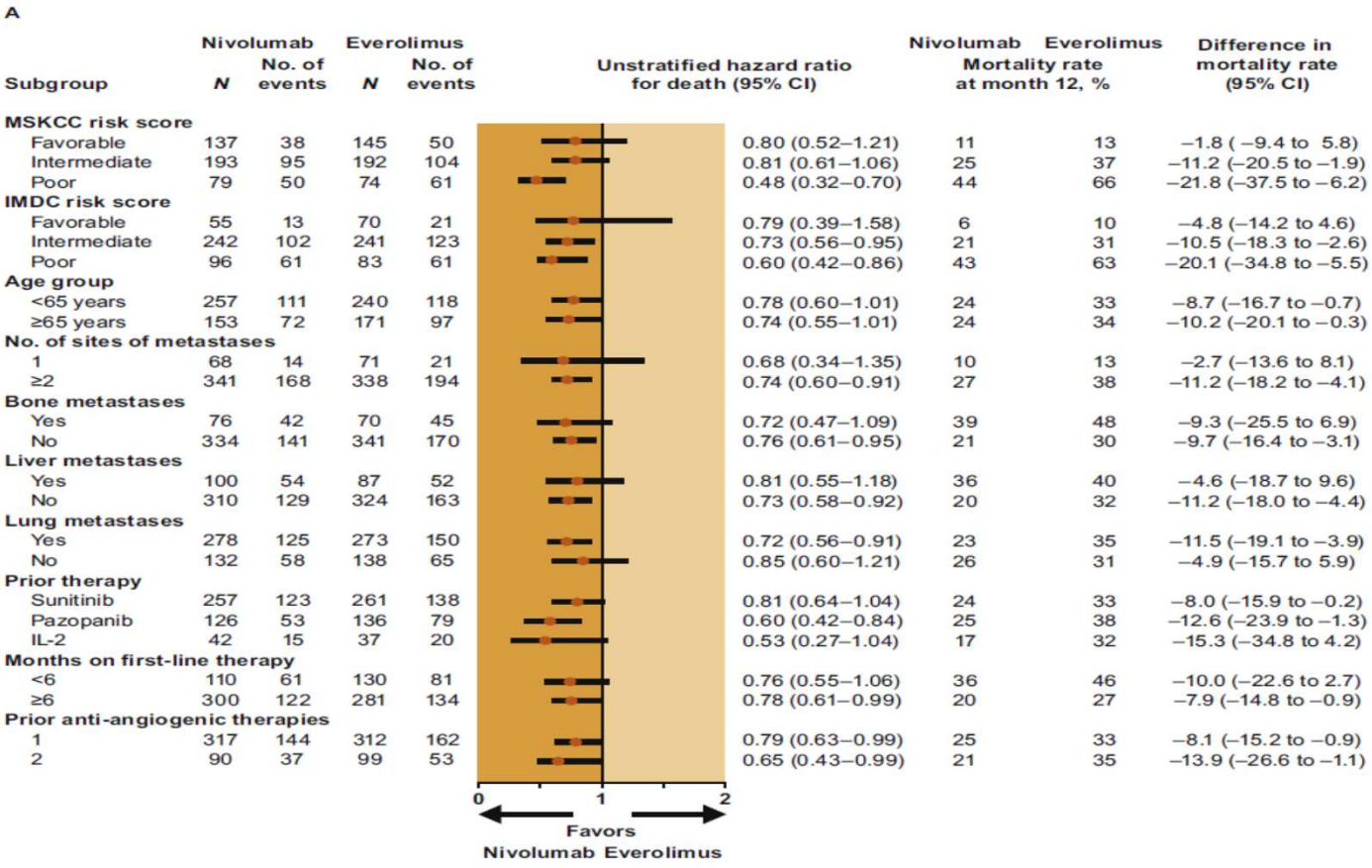


Fig. 2 – Kaplan-Meier curves for overall survival by (A) favorable, (B) intermediate, and (C) poor MSKCC risk group. CI = confidence interval; HR = hazard ratio; MSKCC = Memorial Sloan Kettering Cancer Center; NR = not reached; OS = overall survival.

EUROPEAN UROLOGY 72 (2017) 962–971

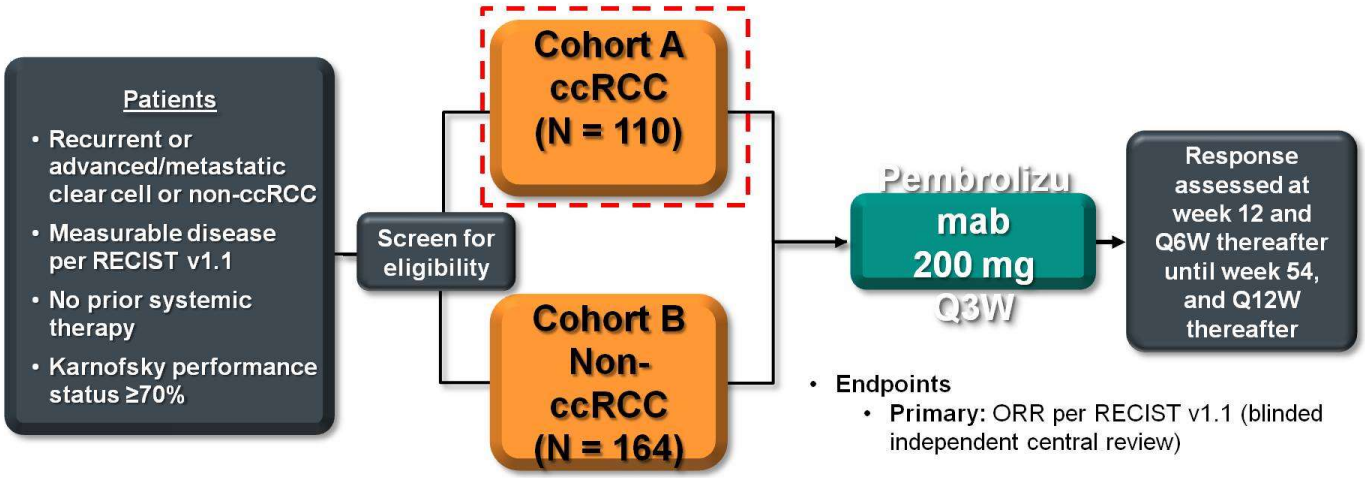
Survival by Patient Characteristics – Checkmate 025



A

Subgroup	Nivolumab N	Nivolumab No. of events	Everolimus N	Everolimus No. of events	Unstratified hazard ratio for death (95% CI)	Nivolumab Mortality rate at month 12, %	Everolimus Mortality rate at month 12, %	Difference in mortality rate (95% CI)
MSKCC risk score								
Favorable	137	38	145	50	0.80 (0.52–1.21)	11	13	–1.8 (–9.4 to 5.8)
Intermediate	193	95	192	104	0.81 (0.61–1.06)	25	37	–11.2 (–20.5 to –1.9)
Poor	79	50	74	61	0.48 (0.32–0.70)	44	66	–21.8 (–37.5 to –6.2)
IMDC risk score								
Favorable	55	13	70	21	0.79 (0.39–1.58)	6	10	–4.8 (–14.2 to 4.6)
Intermediate	242	102	241	123	0.73 (0.56–0.95)	21	31	–10.5 (–18.3 to –2.6)
Poor	96	61	83	61	0.60 (0.42–0.86)	43	63	–20.1 (–34.8 to –5.5)
Age group								
<65 years	257	111	240	118	0.78 (0.60–1.01)	24	33	–8.7 (–16.7 to –0.7)
≥65 years	153	72	171	97	0.74 (0.55–1.01)	24	34	–10.2 (–20.1 to –0.3)
No. of sites of metastases								
1	68	14	71	21	0.68 (0.34–1.35)	10	13	–2.7 (–13.6 to 8.1)
≥2	341	168	338	194	0.74 (0.60–0.91)	27	38	–11.2 (–18.2 to –4.1)
Bone metastases								
Yes	76	42	70	45	0.72 (0.47–1.09)	39	48	–9.3 (–25.5 to 6.9)
No	334	141	341	170	0.76 (0.61–0.95)	21	30	–9.7 (–16.4 to –3.1)
Liver metastases								
Yes	100	54	87	52	0.81 (0.55–1.18)	36	40	–4.6 (–18.7 to 9.6)
No	310	129	324	163	0.73 (0.58–0.92)	20	32	–11.2 (–18.0 to –4.4)
Lung metastases								
Yes	278	125	273	150	0.72 (0.56–0.91)	23	35	–11.5 (–19.1 to –3.9)
No	132	58	138	65	0.85 (0.60–1.21)	26	31	–4.9 (–15.7 to 5.9)
Prior therapy								
Sunitinib	257	123	261	138	0.81 (0.64–1.04)	24	33	–8.0 (–15.9 to –0.2)
Pazopanib	126	53	136	79	0.60 (0.42–0.84)	25	38	–12.6 (–23.9 to –1.3)
IL-2	42	15	37	20	0.53 (0.27–1.04)	17	32	–15.3 (–34.8 to 4.2)
Months on first-line therapy								
<6	110	61	130	81	0.76 (0.55–1.06)	36	46	–10.0 (–22.6 to 2.7)
≥6	300	122	281	134	0.78 (0.61–0.99)	20	27	–7.9 (–14.8 to –0.9)
Prior anti-angiogenic therapies								
1	317	144	312	162	0.79 (0.63–0.99)	25	33	–8.1 (–15.2 to –0.9)
2	90	37	99	53	0.65 (0.43–0.99)	21	35	–13.9 (–26.6 to –1.1)

KEYNOTE-427: (NCT02853344)



- **Endpoints**
  - **Primary:** ORR per RECIST v1.1 (blinded independent central review)
  - **Secondary:** DOR, DCR, PFS, OS, safety, and tolerability
  - **Exploratory:** tissue based biomarkers (e.g. IHC, RNA sequencing)

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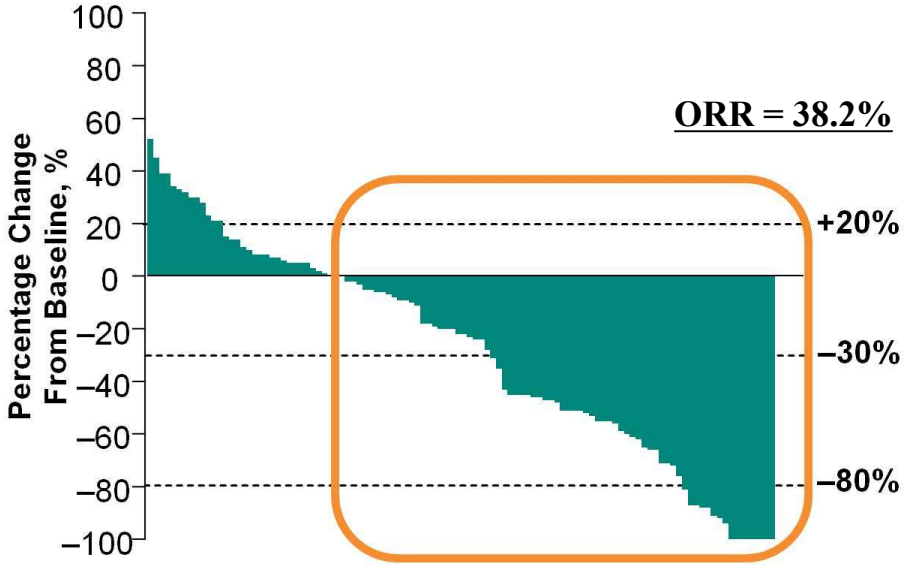
Maximum Change From Baseline in Target Lesions by Central Review

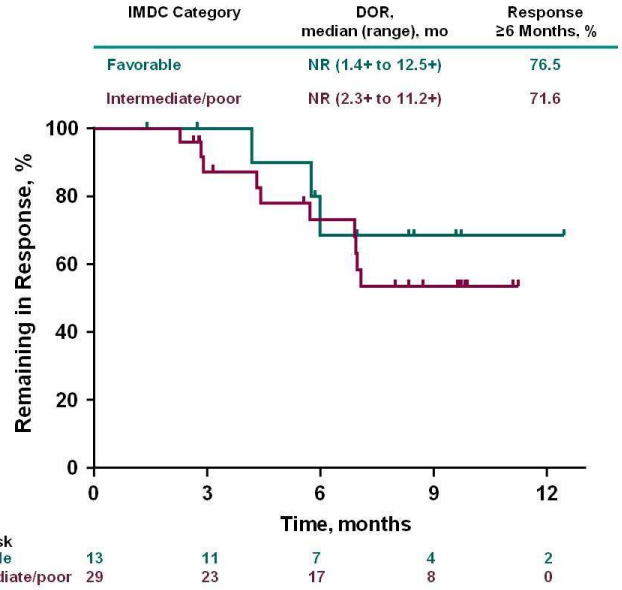


- 74 of 110 (67.3%) patients experienced a reduction in tumor burden
- 16 of 110 patients (14.5%) experienced a tumor burden reduction ≥80%
- 8 of 110 patients (7.3%) experienced 100% tumor burden reduction

Includes patients who received ≥1 dose of pembrolizumab, had a baseline scan with measurable disease per RECIST v1.1, and had a postbaseline assessment (n = 108).
Database cutoff: March 12, 2018.

ORR and Response Duration: IMDC Categories

	Favorable n = 41	Intermediate/Poor n = 69
Confirmed ORR, % (95% CI)	**31.7 (18.1-48.1)**	**42.0 (30.2-54.5)**
DCR, % (95% CI)[a]	**65.9 (49.4-79.9)**	**55.1 (42.6-67.1)**
Confirmed BOR, %		
CR	2.4	2.9
PR	29.3	39.1
SD	51.2	20.3
PD	17.1	34.8
NA	0	2.9



BOR, best overall response; IMDC, International Metastatic RCC Database Consortium.
[a]DCR = CR + PR + SD ≥6 months.
Database cutoff: March 12, 2018.

Presented By David McDermott at 2018 ASCO Annual Meeting

ORR by PD-L1 Expression

	CPS ≥1 n = 46	CPS <1 n =53	Missing n = 11
Confirmed ORR, % (95%CI)	**50.0 (34.9-65.1)**	**26.4 (15.3-40.3)**	**45.5 (16.7-76.6)**
DCR, % (95%CI)[a]	**67.4 (52.0-80.5)**	**49.1 (35.1-63.2)**	**72.7 (39.0-94.0)**
Confirmed BOR, %			
CR	6.5	0	0
PR	43.5	26.4	45.5
SD	26.1	35.8	36.4
PD	23.9	34.0	18.2
NA	0	3.8	0

[a]DCR = CR + PR + SD ≥6 months.
Database cutoff: March 12, 2018.

Ipilimumab + Nivolumab in mRCC

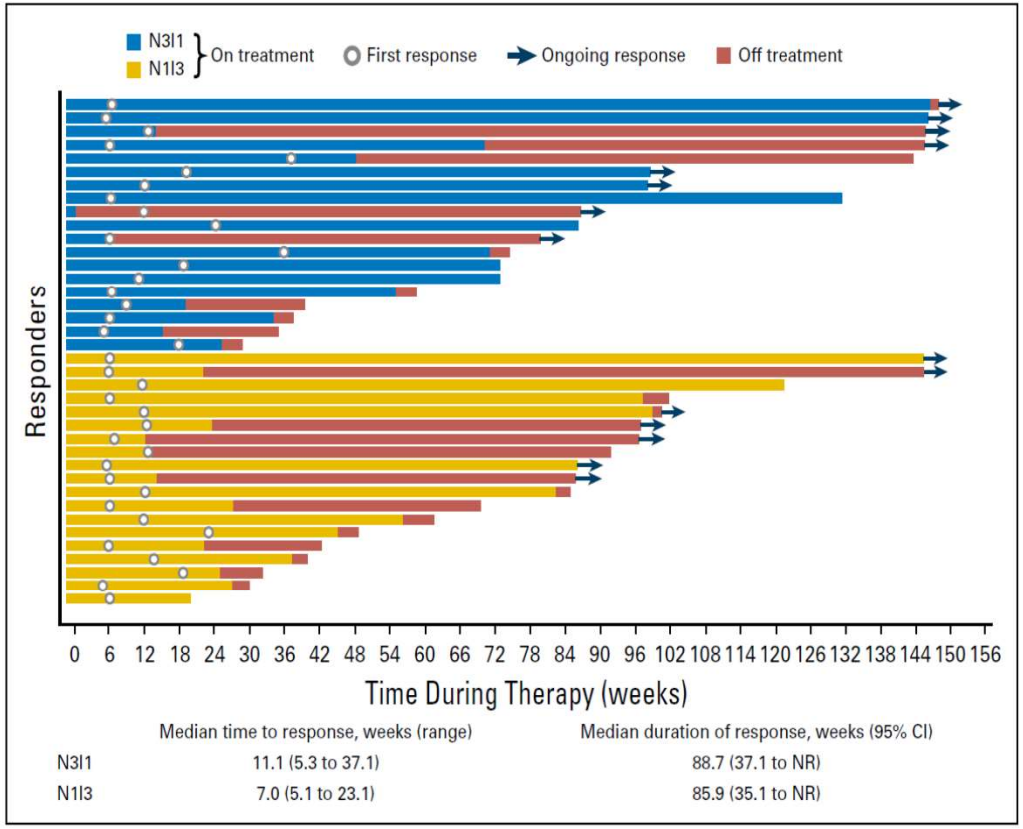
Approx 50% no prior Rx

Approx 50% good risk

Table 3. ORRs by Treatment Arm

Response	Treatment Arm, No. (%) N3I1 (n = 47)	N1I3 (n = 47)
Confirmed ORR	19 (40.4)	19 (40.4)
95% CI	26.4 to 55.7	26.4 to 55.7
BOR		
Complete response	5 (10.6)	0 (0.0)
Partial response	14 (29.8)	19 (40.4)
Stable disease	19 (40.4)	17 (36.2)
Disease progression	8 (17.0)	8 (17.0)
Unable to determine	1 (2.1)	3 (6.4)

Abbreviations: BOR, best overall response; N1I3, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg; N3I1, nivolumab 3 mg/kg plus ipilimumab 1 mg/kg; ORR, objective response rate.



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JOURNAL OF CLINICAL ONCOLOGY

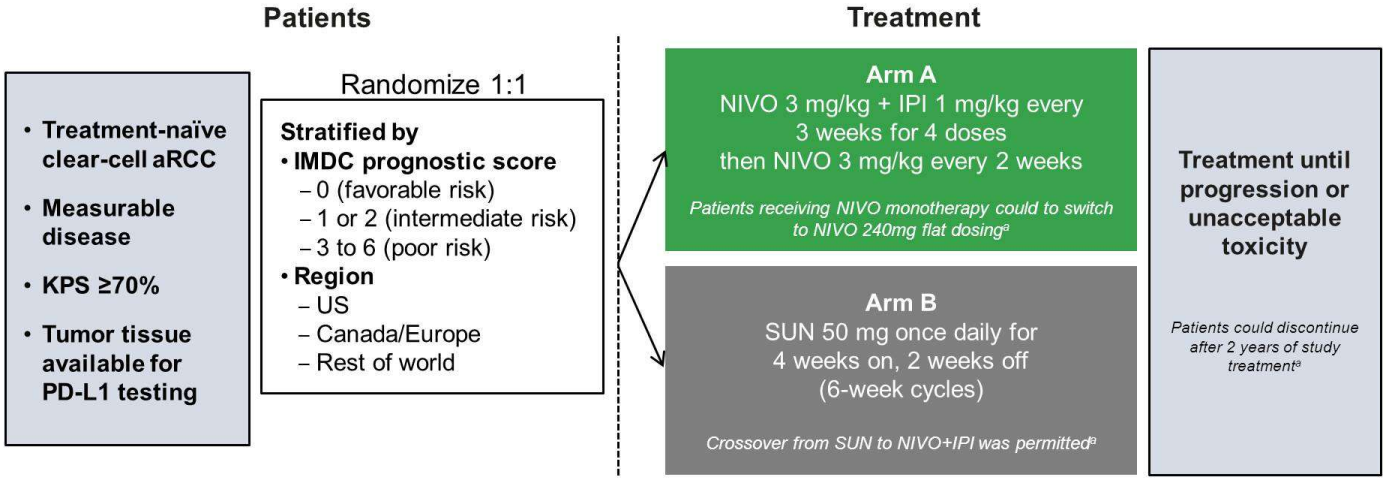
Less toxicity for Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg

Table 2. Treatment-Related AEs Reported in 20% or More of Patients (N3I1 and N1I3 Arms), Grade 3 or 4 AEs Reported in Two or More Patients (Any Arm), and Select Treatment-Related AEs

	Treatment Arm, No. (%)					
	N3I1 (n = 47)		N1I3 (n = 47)		N3I3 (n = 6)	
Treatment-Related AE	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Preferred term*						
Total patients with an event	43 (91.5)	18 (38.3)	45 (95.7)	29 (61.7)	6 (100.0)	5 (83.3)
Select AE, organ class†						
Skin	23 (48.9)	0	28 (59.6)	1 (2.1)	3 (50.0)	0
Endocrine	13 (27.7)	2 (4.3)	19 (40.4)	0	6 (100.0)	0
GI	12 (25.5)	2 (4.3)	21 (44.7)	11 (23.4)	3 (50.0)	2 (33.3)
Hepatic	9 (19.1)	3 (6.4)	13 (27.7)	8 (17.0)	3 (50.0)	1 (16.7)
Renal	9 (19.1)	2 (4.3)	6 (12.8)	1 (2.1)	2 (33.3)	0
Pulmonary	3 (6.4)	0	5 (10.6)	0	0	0

N Engl J Med. 2018 Apr 5;378(14):1277-1290. doi: 10.1056/NEJMoa1712126. Epub 2018 Mar 21.

CheckMate 214: Study Design



[a]As of a November 2017 protocol amendment.
IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; KPS, Karnofsky performance status; PD-L1, programmed death ligand 1.

N Engl J Med. 2018 Apr 5;378(14):1277-1290. doi: 10.1056/NEJMoa1712126. Epub 2018 Mar 21.

Baseline Characteristics

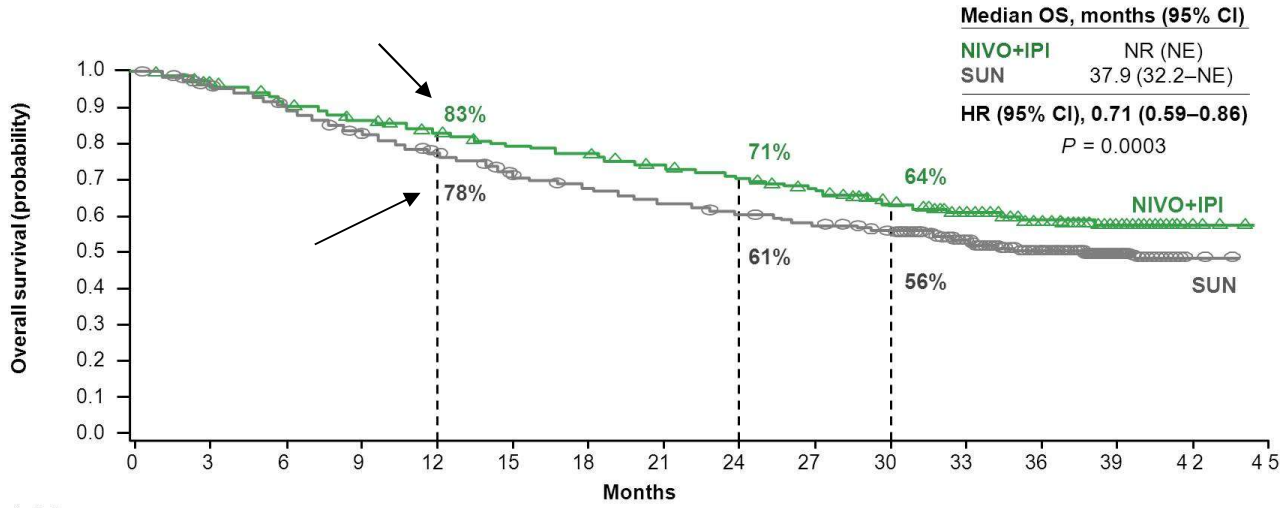
	ITT population		Intermediate/poor risk		Favorable risk	
	NIVO+IPI N = 550	SUN N = 546	NIVO+IPI N = 425	SUN N = 422	NIVO+IPI N = 125	SUN N = 124
IMDC prognostic score, %						
Favorable (0)	23	23	0	0	100	100
Intermediate (1–2)	61	61	79	79	0	0
Poor (3–6)	17	16	21	21	0	0
Region, %						
USA	28	28	26	26	34	34
Canada/Europe	37	36	35	35	42	43
Rest of the world	35	36	39	39	24	23

Percentages may not total 100 because of rounding. Information shown in the table is based on data collected with the use of an interactive voice-response system.
ITT, intention to treat.
1. Motzer RJ, et al. *N Engl J Med* 2018;378:1277–1290.

N Engl J Med. 2018 Apr 5;378(14):1277-1290.

CheckMate 214

Overall Survival: ITT Patients



No. at risk																
NIVO+IPI	550	523	492	464	443	425	410	389	371	351	327	271	161	58	4	0
SUN	546	507	472	435	404	367	345	325	310	295	275	232	145	55	5	0

CI, confidence interval; NE, not estimable; NR, not reached.

5

Presented By Nizar Tannir at 2019 Genitourinary Cancers Symposium

N Engl J Med. 2018 Apr 5;378(14):1277-1290.

CheckMate 214

Overall Survival: by IMDC Risk

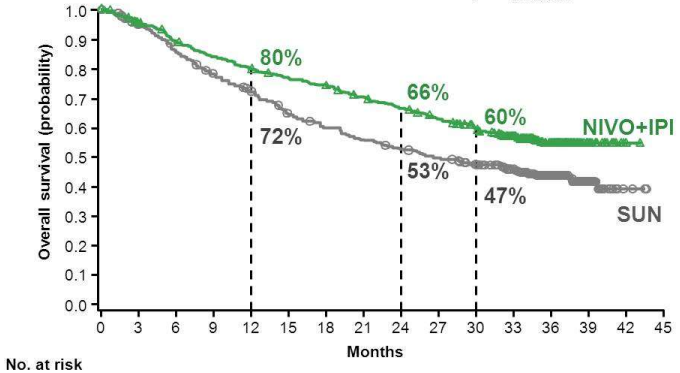
95.2% vs 93.8% in pembro/axitinib vs sunitinib, HR 0.64

Intermediate/poor risk

Median OS, months (95% CI)

NIVO+IPI	NR (35.6–NE)
SUN	26.6 (22.1–33.4)

HR (95% CI), 0.66 (0.54–0.80)
P < 0.0001



No. at risk

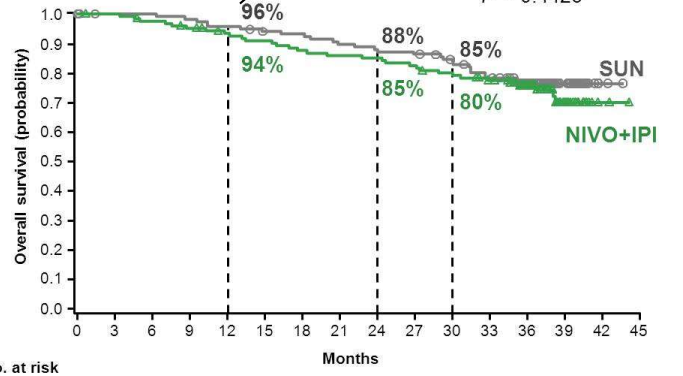
NIVO+IPI	425	399	372	348	332	317	306	287	270	253	233	183	90	34	2	0
SUN	422	388	353	318	290	257	236	220	207	194	179	144	75	29	3	0

Favorable risk

Median OS, months (95% CI)

NIVO+IPI	NR (NE)
SUN	NR (NE)

HR (95% CI), 1.22 (0.73–2.04)
P = 0.4426



No. at risk

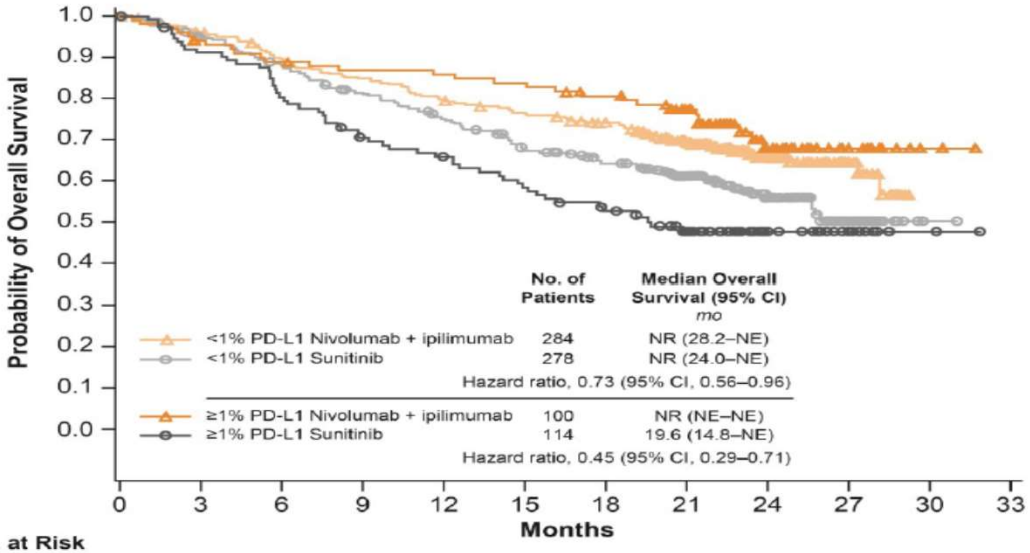
NIVO+IPI	125	124	120	116	111	108	104	102	101	98	94	88	71	24	2	0
SUN	124	119	119	117	114	110	109	105	103	101	96	88	70	26	2	0

6

- **Sunitinib ORR and PFS > ipi/nivo in favorable risk**
- **89% of favorable risk had PD-L1< 1%**

Presented By Nizar Tannir at 2019 Genitourinary Cancers Symposium

Figure S4. Kaplan–Meier Curves for Overall Survival According to PD-L1 Expression Level in IMDC Intermediate- and Poor-risk Patients

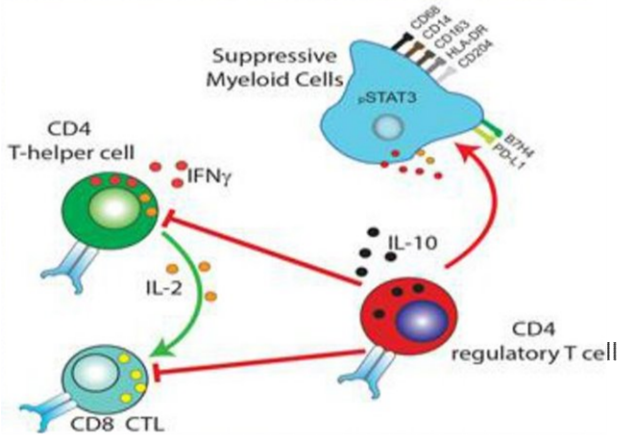


No. at Risk						
NIVO + IPI <1% PD-L1	284	251	223	200	76	0
SUN <1% PD-L1	278	239	198	157	61	1
NIVO + IPI ≥1% PD-L1	100	87	83	76	33	2
SUN ≥1% PD-L1	114	90	72	55	21	2

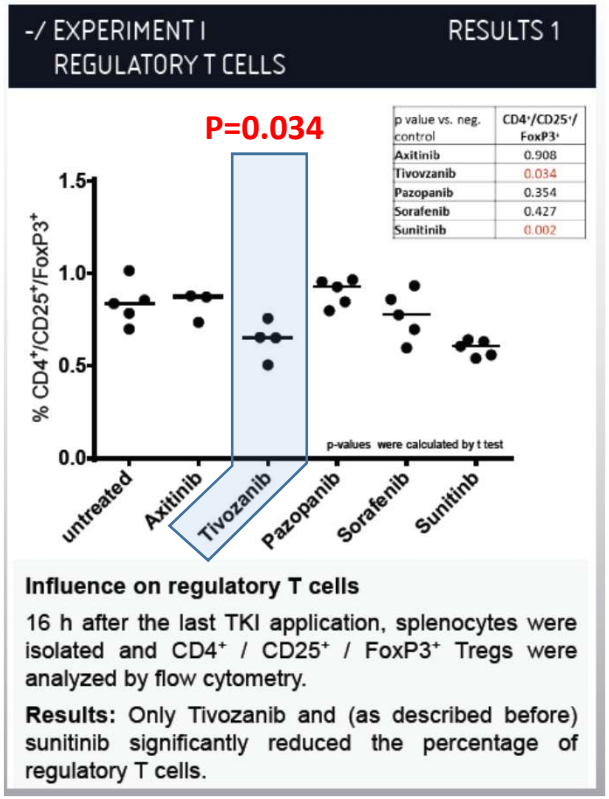
Supplement to: Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 2018;378:1277-90. DOI: 10.1056/NEJMoa1712126

VEGFRi produce immunomodulatory effects; but may differ depending on the individual agent

Regulatory T cells suppress or downregulate induction and proliferation of effector T cells (e.g. CD4 and CD8)



Other Immune effects:
-Changes in MDSC populations
-Induce T-cell attracting chemokines within tumor
-Block inhibitory effects of VEGF on dendritic cells



Pawlowski N et al. AACR 2013. Poster 3971.

AVEO ONCOLOGY

Phase 1b of Avelumab + Axitinib in mRCC

Axitinib + Pembrolizumab – ORR-> 73%, 2018 ASCO GU,
Atkins et al

Best overall response

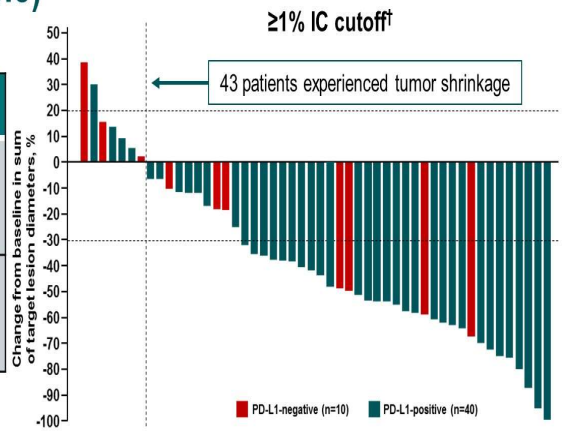
- 32 patients had a confirmed objective response
  - Confirmed ORR was 58.2% (95% CI, 44.1–71.3)
  - An additional patient with ongoing therapy had an unconfirmed response
- Disease control was achieved in 78.2% of patients

Confirmed best OR*, n (%)	Overall population (N=55)
Complete response	3 (5.5)
Partial response	29 (52.7)
Stable disease	11 (20.0)
Progressive disease	10 (18.2)
Nonevaluable†	2 (3.6)
ORR, % (95% CI)	58.2 (44.1–71.3)

* According to RECIST v1.1 per investigator assessment.
† 1 patient died due to myocarditis prior to the first oncologic assessment, and 1 patient had a first oncologic assessment prior to the protocol-specified time window and then died due to disease progression.

ORR and percent change from baseline in sum of target lesion diameters according to PD-L1 IHC expression on ICs (n=52 PD-L1 evaluable)*

Cutoff	PD-L1 status	ORR (n/evaluable patients*)	Odds ratio (95% CI)
≥1%	+	**65.9% (27/41)**	**3.38 (0.70–18.12)**
	-	**36.4% (4/11)**	
≥5%	+	67.9% (19/28)	2.11 (0.60–7.57)
	-	50.0% (12/24)	



* Expression of PD-L1 on ICs within the tumor microenvironment was assessed via IHC using the Ventana SP263 assay.
† 1 patient in the ≥1% cutoff with a BOR of SD was excluded due to start of a new anticancer therapy on the day of tumor assessment.
IC, immune cell; **IHC**, immunohistochemistry.

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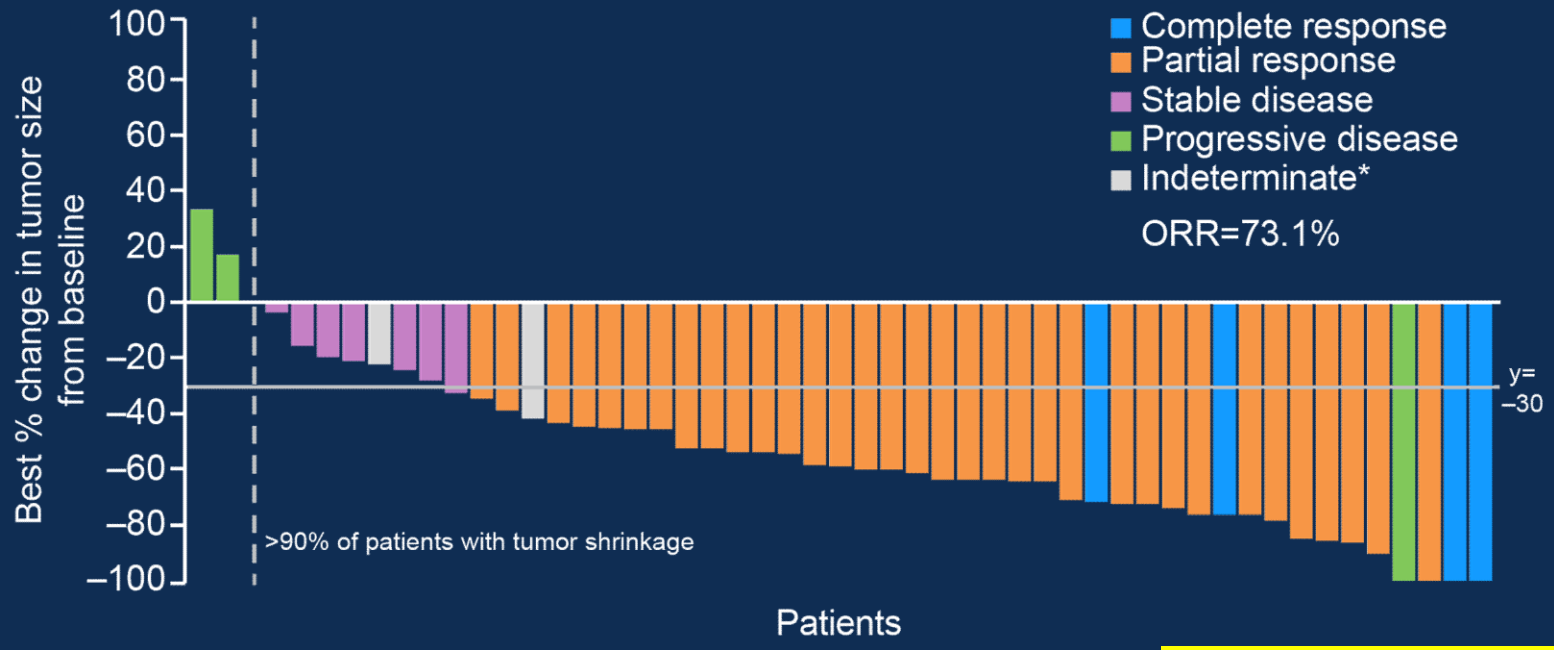
Phase 2 - pembrolizumab + axitinib Tumor Response

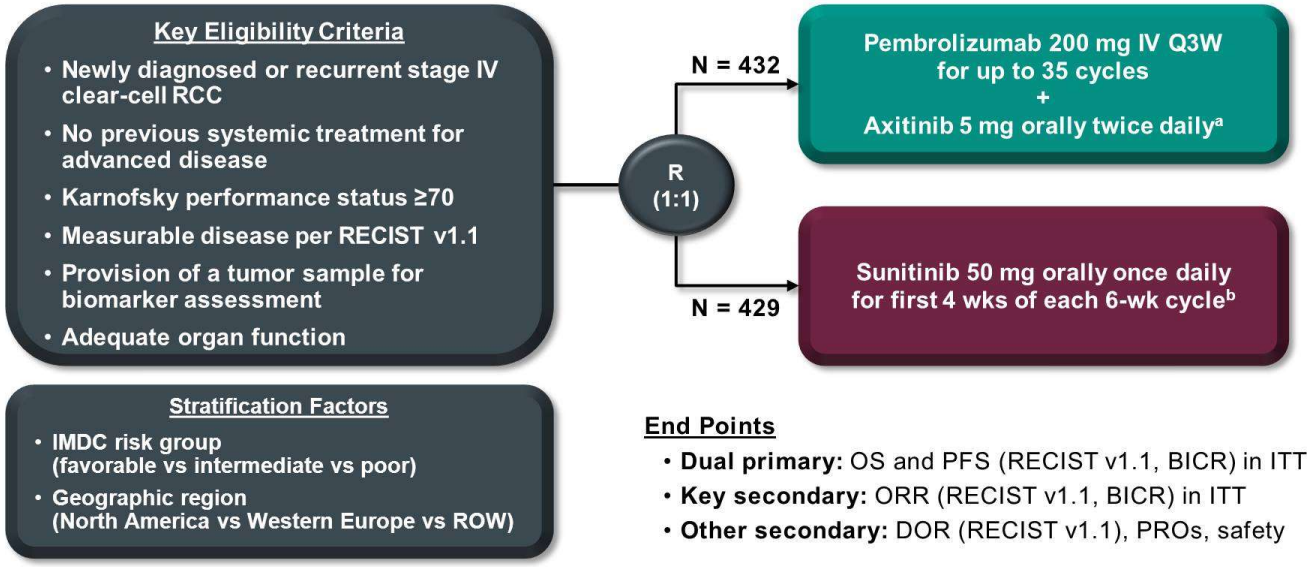


Median PFS 20.9 months,
approx. 90% survival at 18 months

* Stable disease or partial response not confirmed, or no follow-up scans available.
ORR=objective response rate

N Engl J Med. 2019 Feb 16. doi: 10.1056/NEJMoa1816714. [Epub ahead of print]

KEYNOTE-426 Study Design



[a]Axitinib dose could be increased to 7 mg, then 10 mg, twice daily if safety criteria were met; dose could be reduced to 3 mg, then 2 mg, twice daily to manage toxicity.
[b]Sunitinib dose could be decreased to 37.5 mg, then 25 mg, once daily for the first 4 wks of each 6-wk cycle to manage toxicity.
BICR, blinded independent central radiologic review; DOR, duration of response; PROs, patient-reported outcomes; ROW, rest of world.
KEYNOTE-426 is a randomized, open-label, phase 3 study (ClinicalTrials.gov identifier NCT02853331).

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Keynote-426: Pembro/axitinib versus sunitinib

Baseline Characteristics

	Pembrolizumab + Axitinib N = 432	Sunitinib N = 429
Age, median (range)	62 yrs (30-89)	61 yrs (26-90)
Male	308 (71.3%)	320 (74.6%)
Region of enrollment		
North America	104 (24.1%)	103 (24.0%)
Western Europe	106 (24.5%)	104 (24.2%)
Rest of world	222 (51.4%)	222 (51.7%)
IMDC risk category		
Favorable	138 (31.9%)	131 (30.5%)
Intermediate	238 (55.1%)	246 (57.3%)
Poor	56 (13.0%)	52 (12.1%)
Sarcomatoid features	51/285 (17.9%)	54/293 (18.4%)
PD-L1 CPS ≥1[a]	243/410 (59.3%)	254/412 (61.7%)
≥2 metastatic organs	315 (72.9%)	331 (77.2%)
Previous nephrectomy	357 (82.6%)	358 (83.4%)

More favorable risk than ipi/nivo checkmate-214 trial

Approx 33% in ipi/nivo checkmate-214 trial

[a]Assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay. CPS = combined positive score = number of PD-L1–positive cells (tumor cells, lymphocytes, macrophages) divided by total number of tumor cells × 100.
Data cutoff date: Aug 24, 2018.

Presented By Thomas Powles at 2019 Genitourinary Cancers Symposium

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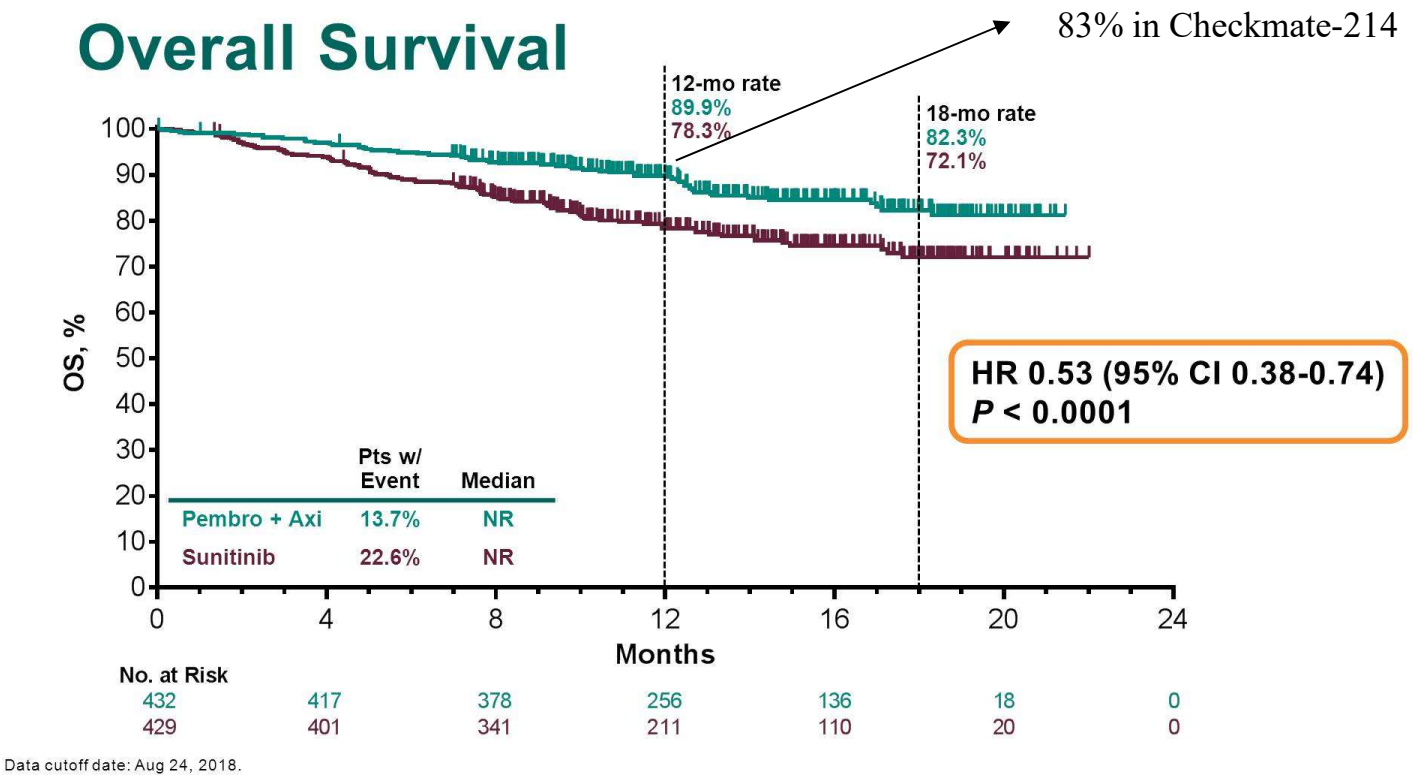
Keynote-426: Pembro/axitinib versus sunitinib



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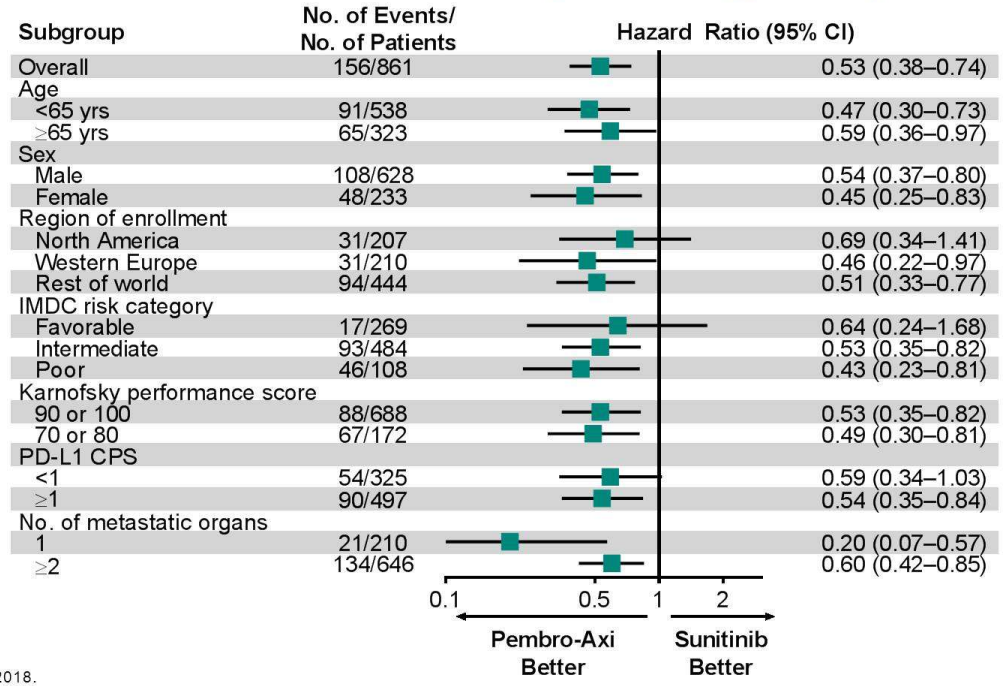
Keynote-426: Pembro/axitinib versus sunitinib

Overall Survival in Key Subgroups



Data cutoff date: Aug 24, 2018.

HR 0.71 in Checkmate-214

No effect in checkmate-214

HR 0.66 for this group in Checkmate-214

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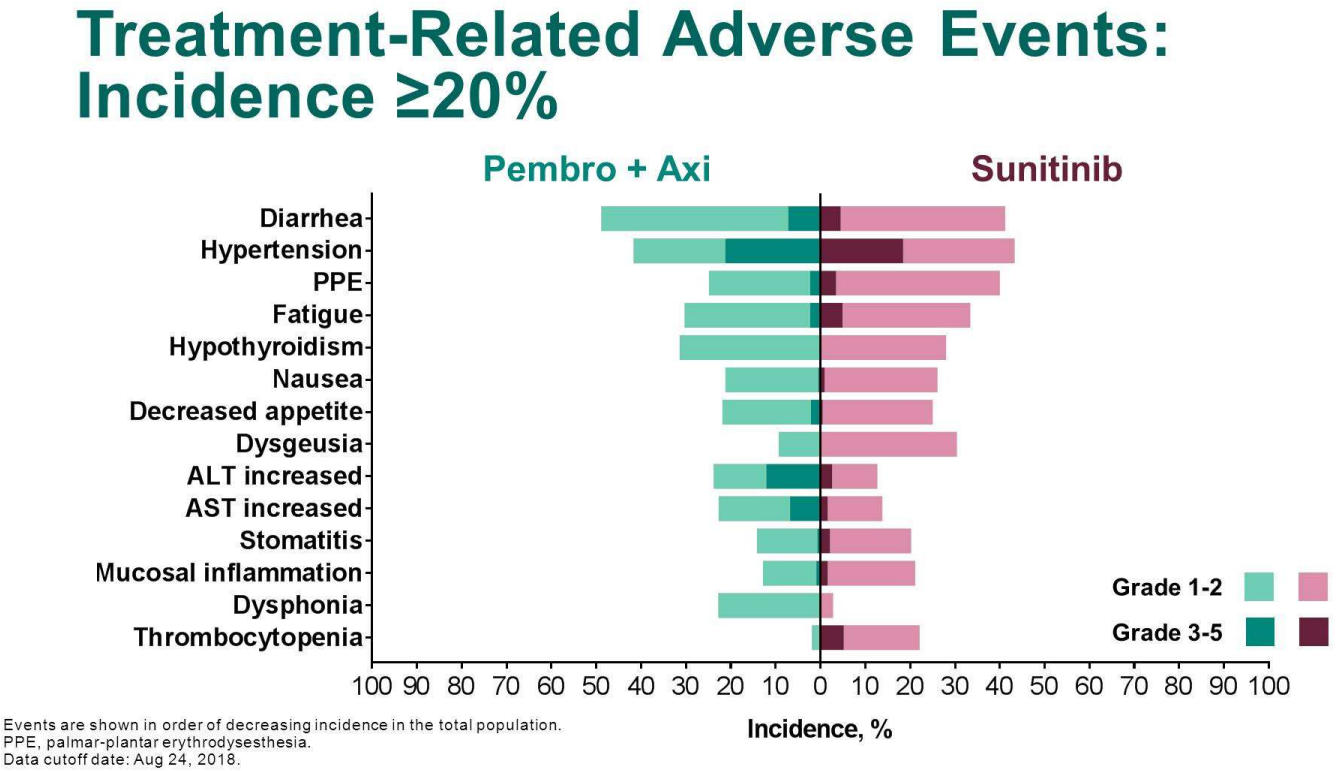

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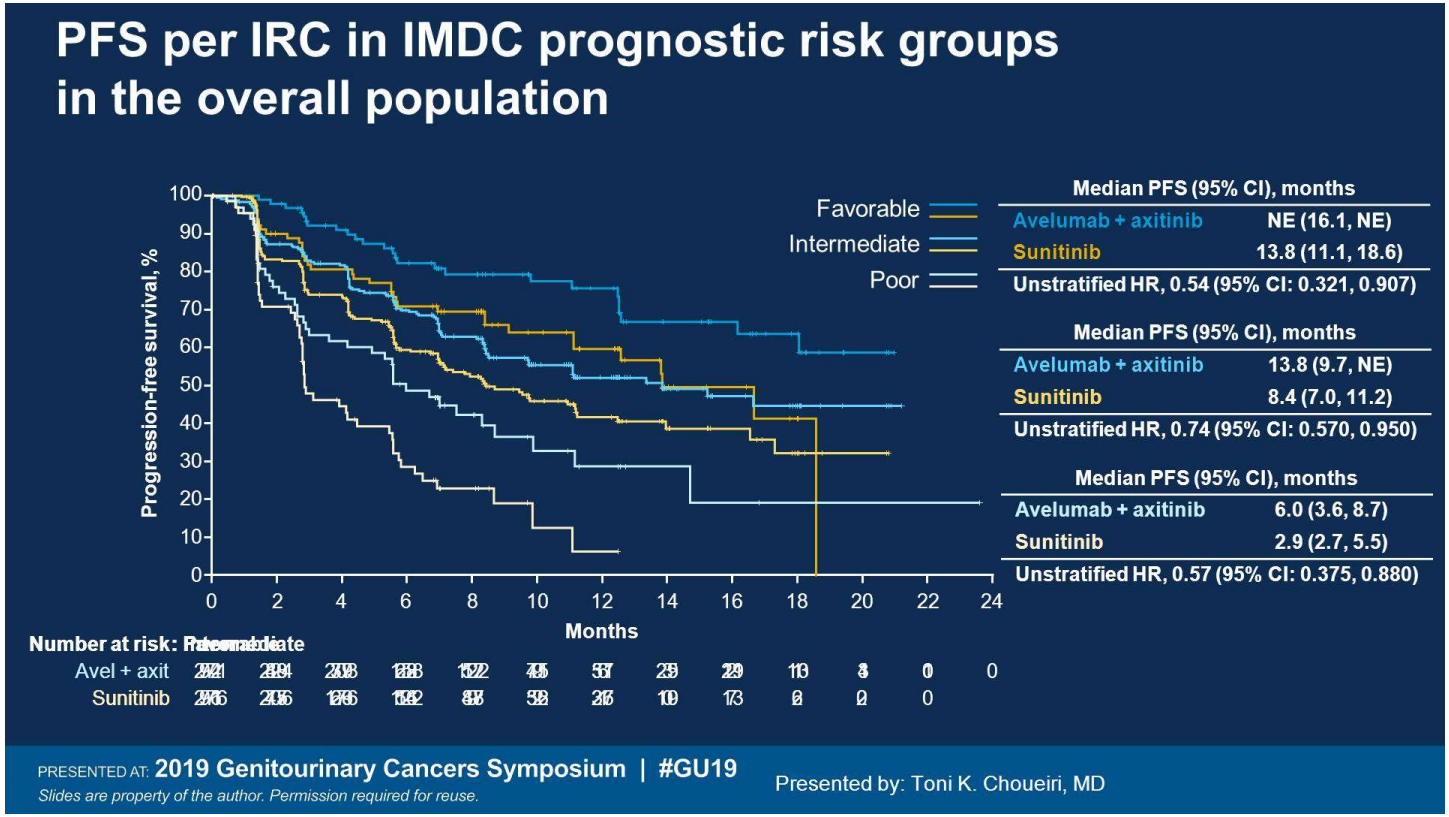
Avelumab/Axitinib versus Sunitinib



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OS data NA

Presented By Toni Choueiri at 2019 Genitourinary Cancers Symposium

Response Endpoints in Trials:

- ORR
- PFS
- OS

Metastatic Clear Cell Renal Carcinoma

Sunitinib
Pazopanib
Cabozantinib
Axitinib
Lenvatinib + everolimus

Ipilimumab/nivolumab
Nivolumab
Pembrolizumab
High-dose Interleukin-2?

VEGFRi +/- Nivolumab or pembrolizumab or avelumab

Ipilimumab + nivolumab

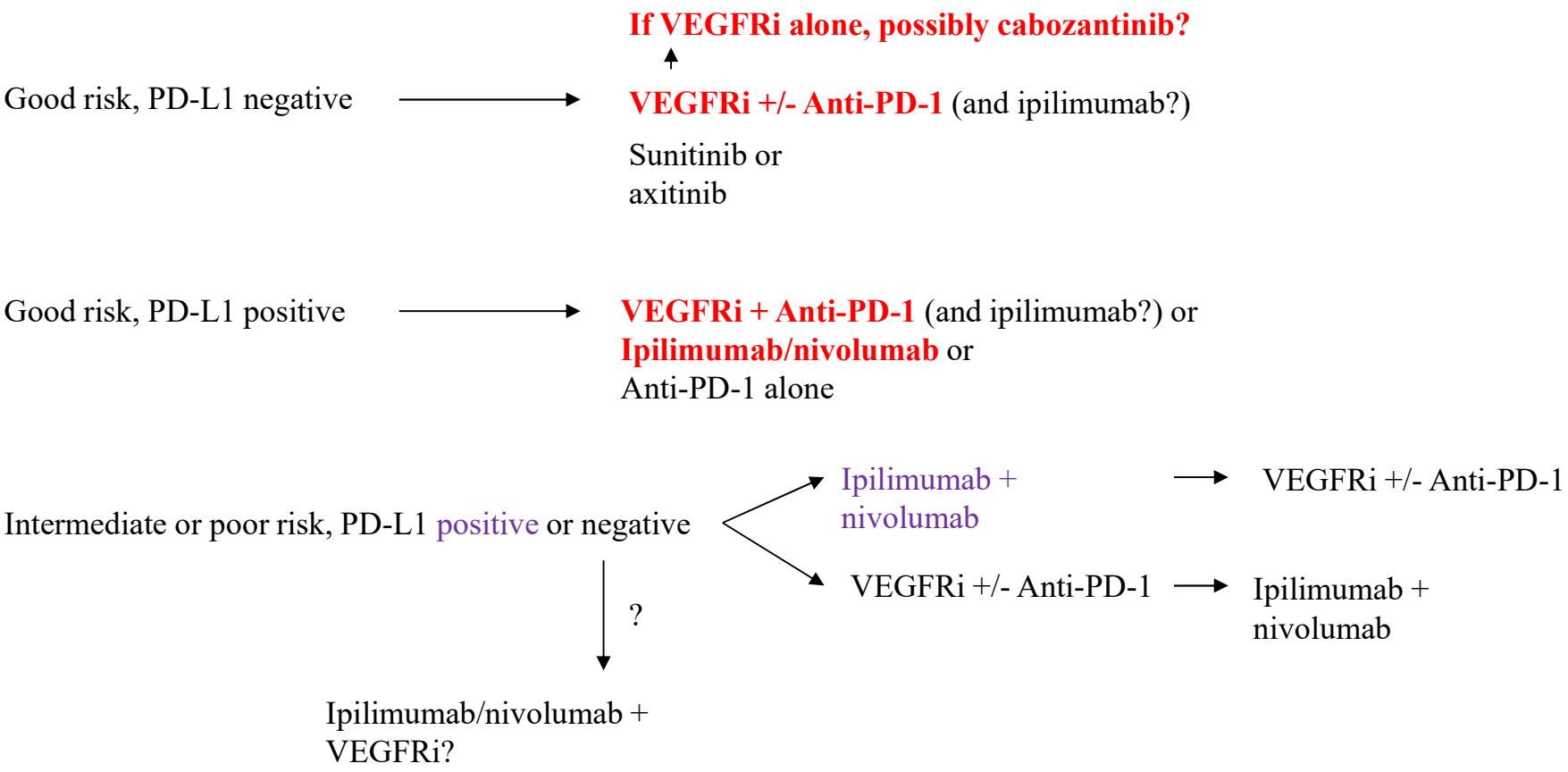
Ipilimumab/nivolumab (post anti-PD-1 alone)
VEGFRi +/- Nivolumab or pembrolizumab or avelumab

Ipilimumab + nivolumab
Nivolumab
Pembolizumab

+/- VEGFRi

How to select patients for best outcome?

- PD-L1
- IMDC or Motzer Risk
- Gene signature?


If VEGFRi alone, possibly cabozantinib?
Good risk, PD-L1 negative
VEGFRi +/- Anti-PD-1 (and ipilimumab?)
Sunitinib or
axitinib
Good risk, PD-L1 positive
VEGFRi + Anti-PD-1 (and ipilimumab?) or
Ipilimumab/nivolumab or
Anti-PD-1 alone
Intermediate or poor risk, PD-L1 positive or negative
Ipilimumab +
nivolumab
VEGFRi +/- Anti-PD-1
VEGFRi +/- Anti-PD-1
Ipilimumab +
nivolumab
?
Ipilimumab/nivolumab +
VEGFRi?

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.

Conclusions

- Anti-PD-1 demonstrates clinically meaningful activity in previously untreated and previously treated patients with mRCC
  - A subset (perhaps 30%) of responders can achieve long-term objective responses
  - Effects on overall survival may be greater in IMDC (or Motzer) intermediate and poor risk groups
- Ipilimumab + nivolumab improves survival compared to sunitinib in IMDC intermediate/poor risk groups regardless of PD-L1 expression
  - Greater survival effect in PD-L1+ group
  - Amount of anti-tumor activity contributed by Ipilimumab is not conclusively determined
- In good risk groups, ORR and PFS for anti-angiogenesis agents may be greater than for immune checkpoint inhibitors