Immunotherapy for Kidney and Urothelial Cancer
15th Annual New Orleans Summer Cancer Meeting

New Orleans, 2.45 – 3.10pm, November 20th, 2020 {The Year of the Mask}

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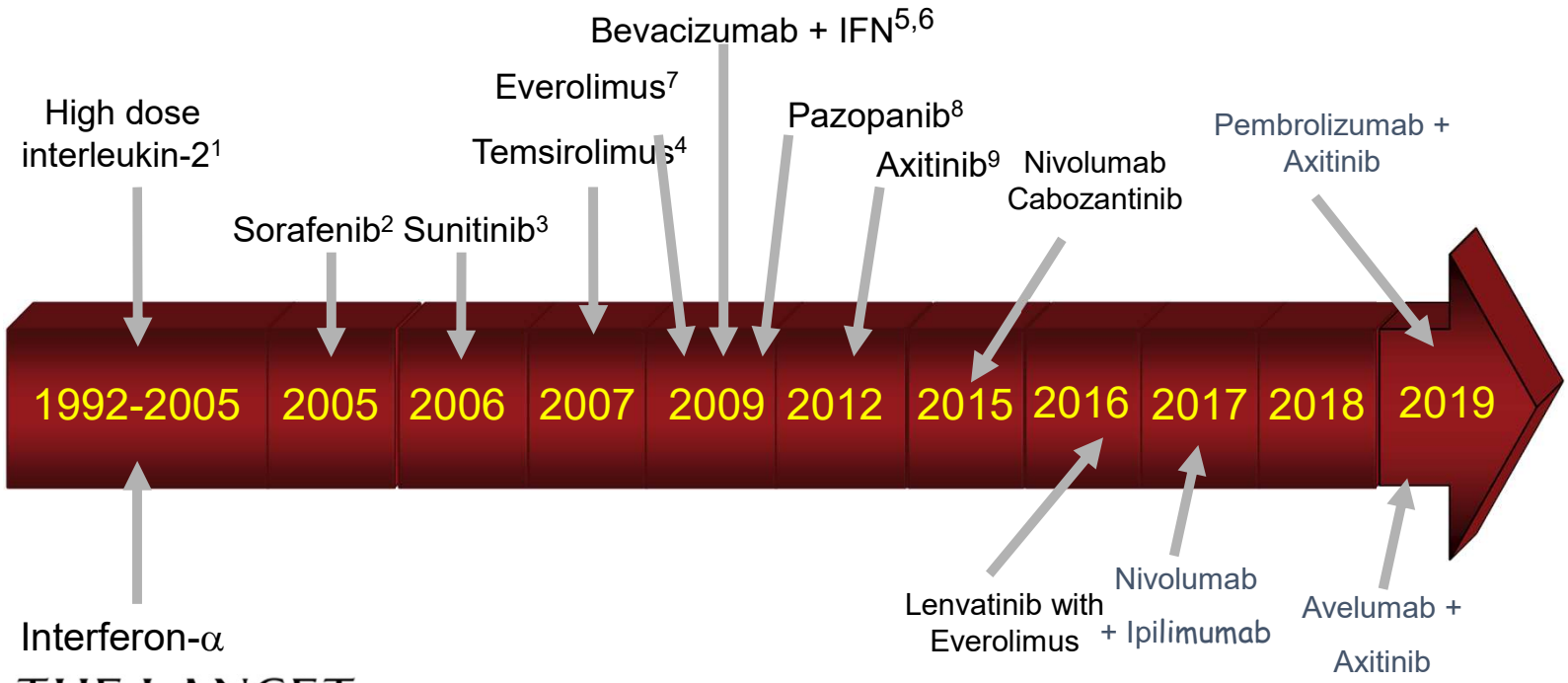
Treatment Options for RCC Have Been Changed Radically in the Last Decade…



THE LANCET

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Official Journal of the American Society of Clinical Oncology

The NEW ENGLAND JOURNAL of MEDICINE

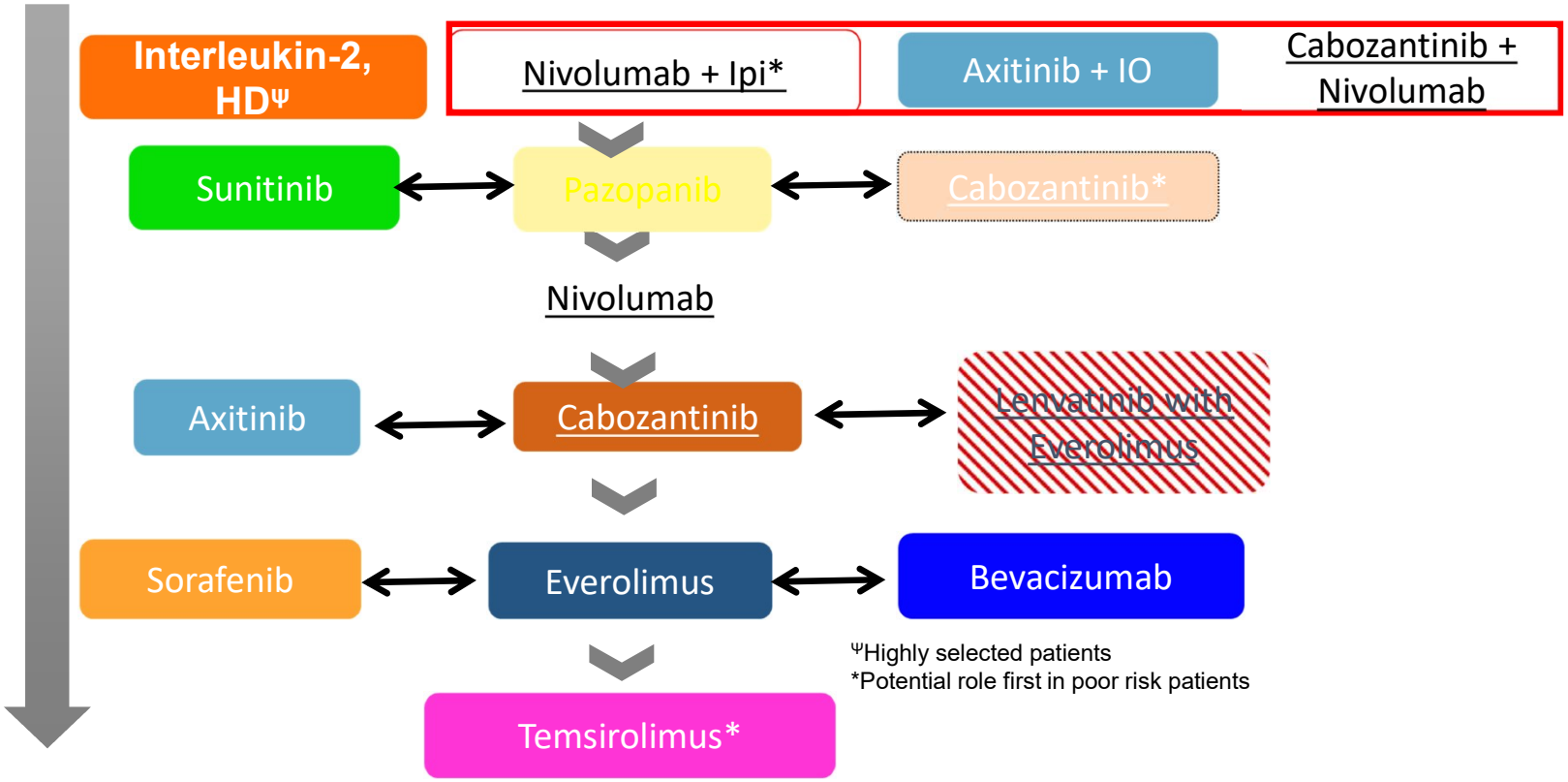
1. Fyfe G, et al. *J Clin Oncol*. 1995;13(3):688-696.
2. Escudier B, et al. *N Engl J Med*. 2007;356(2):125-134.
3. Motzer RJ, et al. *N Engl J Med*. 2007;356(2):115-124.
4. Hudes G, et al. *N Engl J Med*. 2007;356:2271-2281.
5. Escudier B, et al. *Lancet*. 2007;370(9605):2103-2111.
6. Rini BI, et al. *J Clin Oncol*. 2008;26(33):5422-5428.
7. Motzer RJ, et al. *Lancet*. 2008;372(9637):449-456.
8. Sternberg CN, et al. *J Clin Oncol*. 2010;28(6):1061-1068.
9. Rini BI, et al. *J Clin Oncol*. 2011;29(15S): Abstract 4503.

Caboxantinib + Nivoloumab

? Lenvatininib + Pembrolizumab

David Quinn's Preferred Therapeutic Sequencing and Decision Points for Metastatic RCC 2020

Baseline: ~~Cytoreductive nephrectomy~~; control critical metastases: brain, bone; general health measures: TSH, Vitamin D

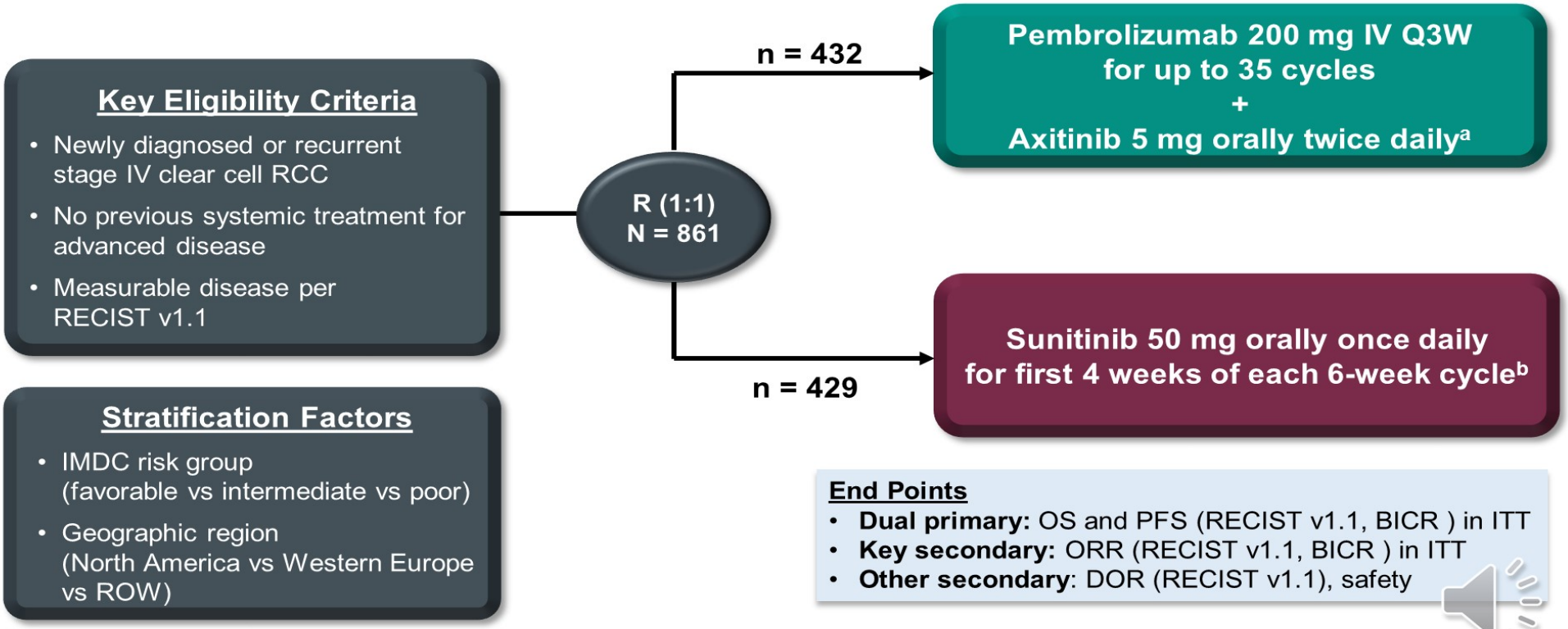


Introduction

- In the first interim analysis of KEYNOTE-426 (NCT02853331), pembrolizumab + axitinib demonstrated significant improvement versus sunitinib in treatment-naive patients with advanced RCC[1]:
  - OS: HR, 0.53 (95% CI, 0.38-0.74); *P* < 0.0001
  - PFS: HR, 0.69 (95% CI, 0.57-0.84); *P* < 0.001
  - ORR: 59.3% vs 35.7%; *P* < 0.001
- Updated efficacy and safety data from KEYNOTE-426 are presented herein with a minimum study follow-up of 23 months

1. Rini BI et al. *N Engl J Med.* 2019;380:1116-1127.

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 weeks of each 6-week cycle to manage toxicity. Data cutoff: January 6, 2020.

Baseline Characteristics

	Pembrolizumab + Axitinib n = 432	Sunitinib n = 429
Age, median (range), years	62 (30-89)	61 (26-90)
Male, n (%)	308 (71.3)	320 (74.6)
Region of enrollment, n (%)		
North America	104 (24.1)	103 (24.0)
Western Europe	106 (24.5)	104 (24.2)
ROW	222 (51.4)	222 (51.7)
IMDC risk category, n (%)		
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]	242/407 (59.5)	253/409 (61.9)
≥2 metastatic sites	315 (72.9)	331 (77.2)
Previous nephrectomy	359 (83.1)	359 (83.7)

Baseline Characteristics

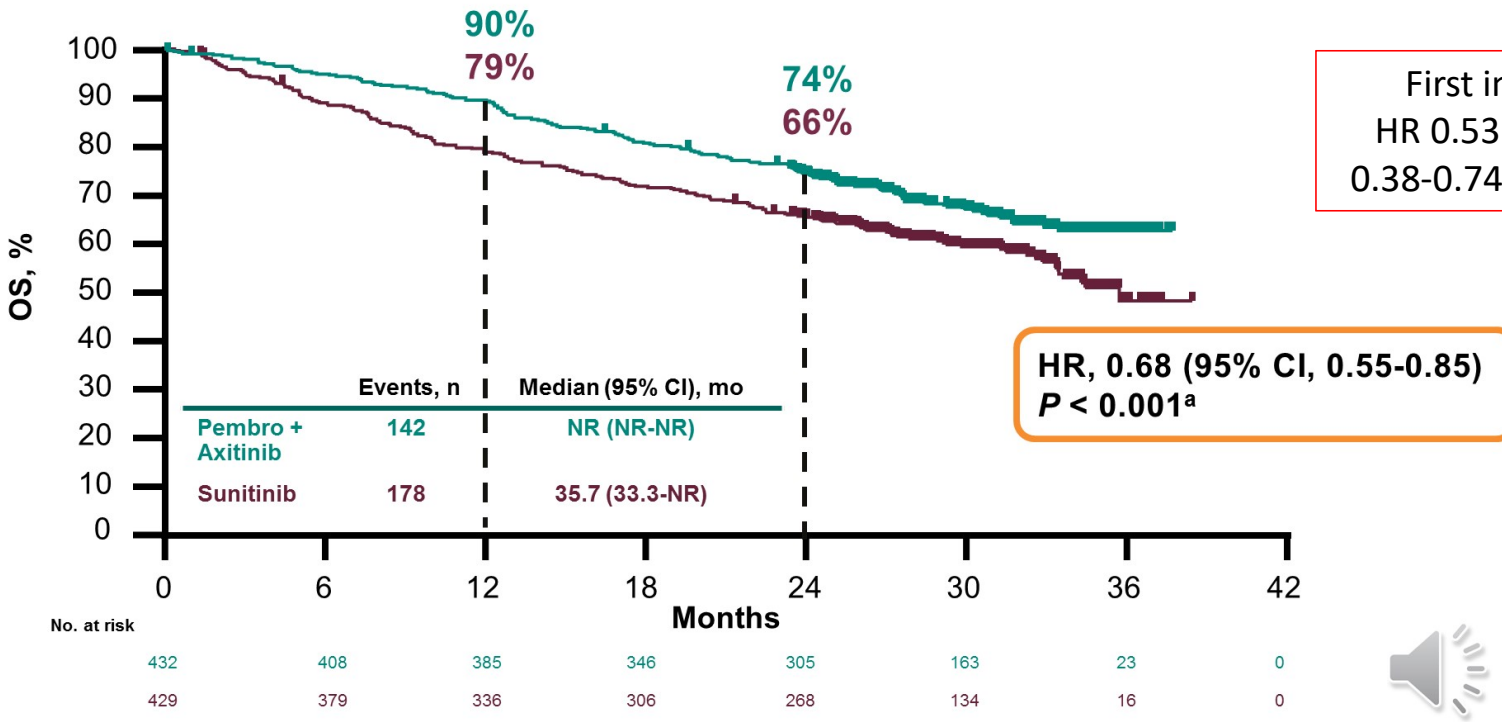
[a]Assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay (Agilent). CPS was defined as the number of PD-L1–positive cells (tumor cells, lymphocytes, macrophages) divided by the total number of tumor cells × 100. Data cutoff: January 6, 2020.

Subsequent Anticancer Therapy Among Patients Who Discontinued Study Treatment

n (%)	Pembrolizumab + Axitinib n = 312	Sunitinib n = 349
Received any subsequent therapy	170 (54.5)	242 (69.3)
By type of treatment		
Any PD-1/PD-L1 inhibitor	25 (8.0)	169 (48.4)
Any VEGF/VEGFR inhibitor	153 (49.0)	159 (45.6)
Other	47 (15.1)	54 (15.5)

Data cutoff: January 6, 2020.

OS in the ITT Population



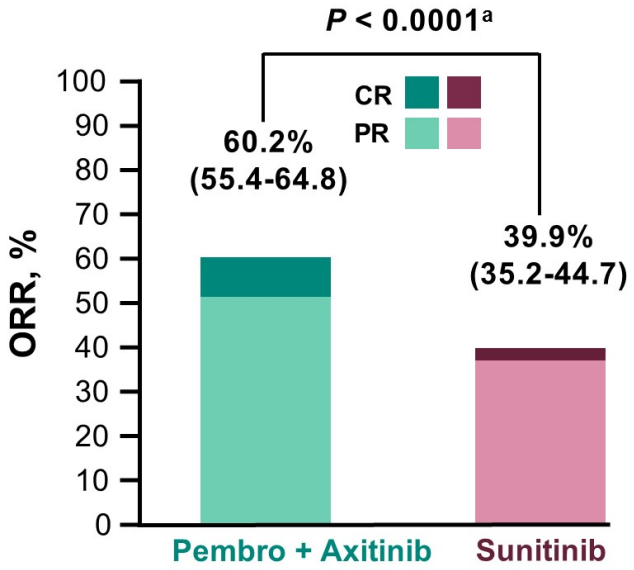
First interim:
HR 0.53 (95% CI, 0.38-0.74) p<0.001

HR, 0.68 (95% CI, 0.55-0.85)
***P* < 0.001[a]**

[a]Because superiority of pembrolizumab + axitinib was shown at the first interim analysis, no alpha was allocated to OS; only nominal *P* values are reported. Data cutoff: January 6, 2020.

Presented By Elizabeth Plimack at TBD

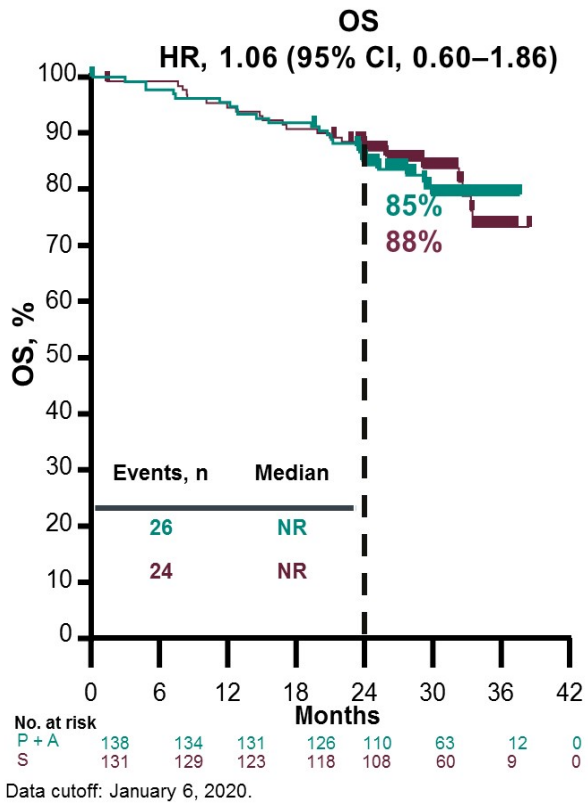
Confirmed Objective Response Rate
ITT Population

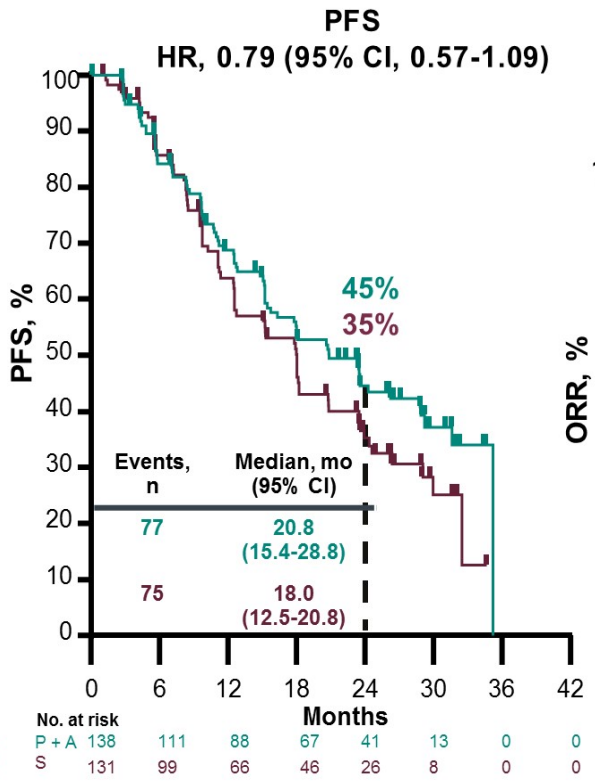


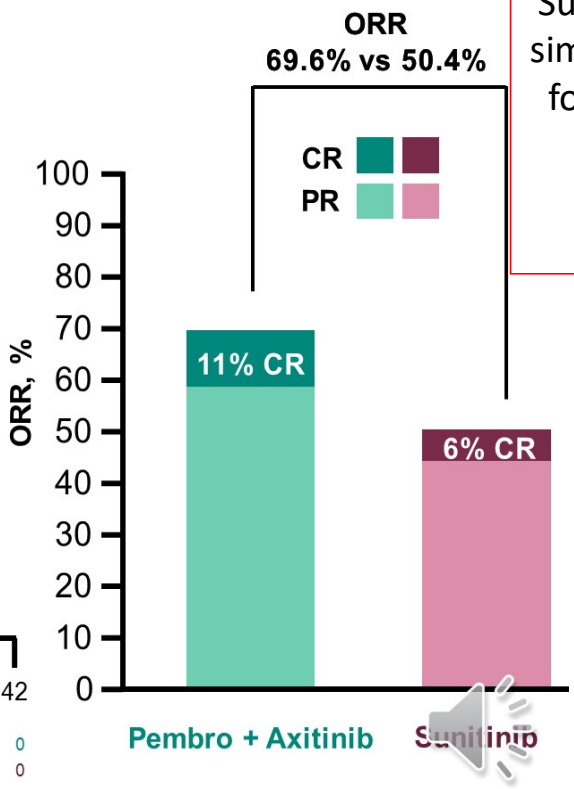
	Pembro + Axitinib n = 432	Sunitinib n = 429
Best response, n (%)		
CR	38 (8.8)	13 (3.0)
PR	222 (51.4)	158 (36.8)
SD	100 (23.1)	150 (35.0)
PD	49 (11.3)	74 (17.2)
NE[b]	16 (3.7)	28 (6.5)
NA[c]	7 (1.6)	6 (1.4)
Duration of response, median (range), mo	23.5 (1.4+ to 34.5+)	15.9 (2.3 to 31.8+)

[a]Because superiority of pembrolizumab + axitinib was shown at the first interim analysis, no alpha was allocated to confirmed objective response; only nominal *P* values are reported. [b]Postbaseline assessment available but not evaluable (ie, all postbaseline assessments with insufficient data for assessment of response per RECIST v1.1 or CR/PR/SD <6 weeks from randomization).
[c]No postbaseline assessment available for response evaluation; + indicates an ongoing response at time of last disease assessment. Data cutoff: January 6, 2020.

IMDC Favorable Risk: OS, PFS, and ORR







Data cutoff: January 6, 2020.

Superior ORR but similar OS and PFS for Ax + Pembro compared to Sunitinib

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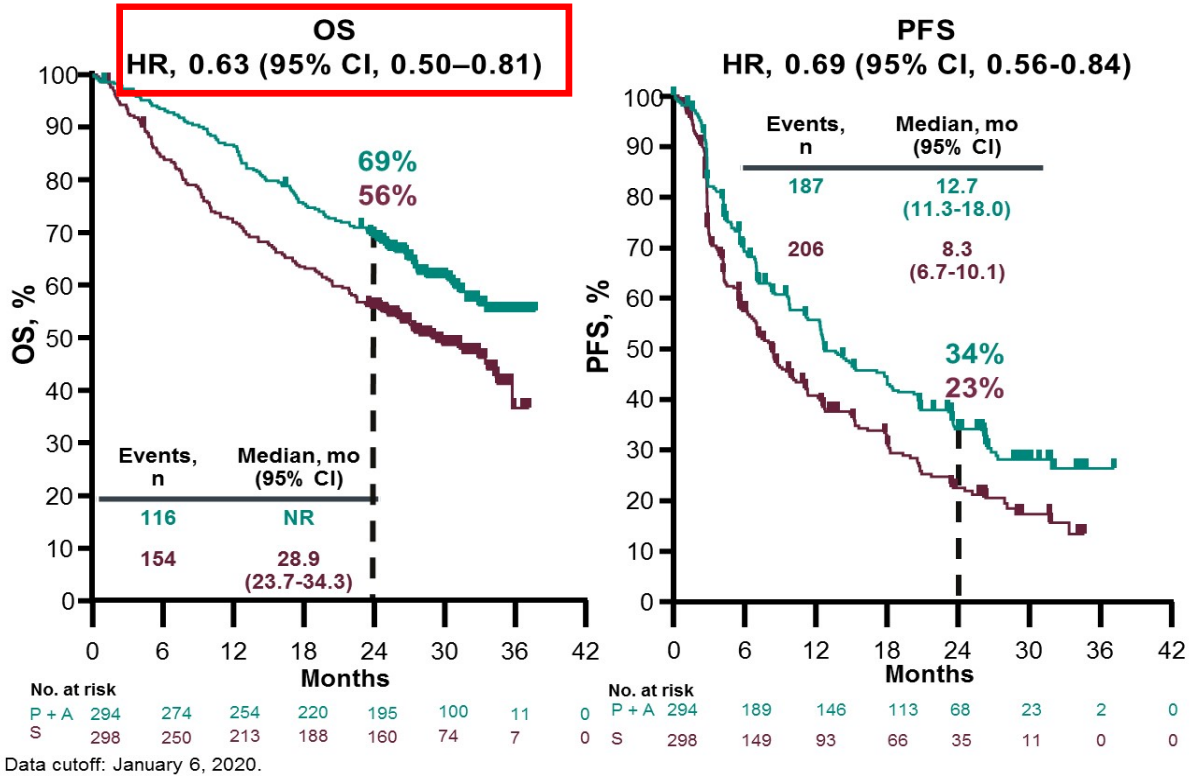
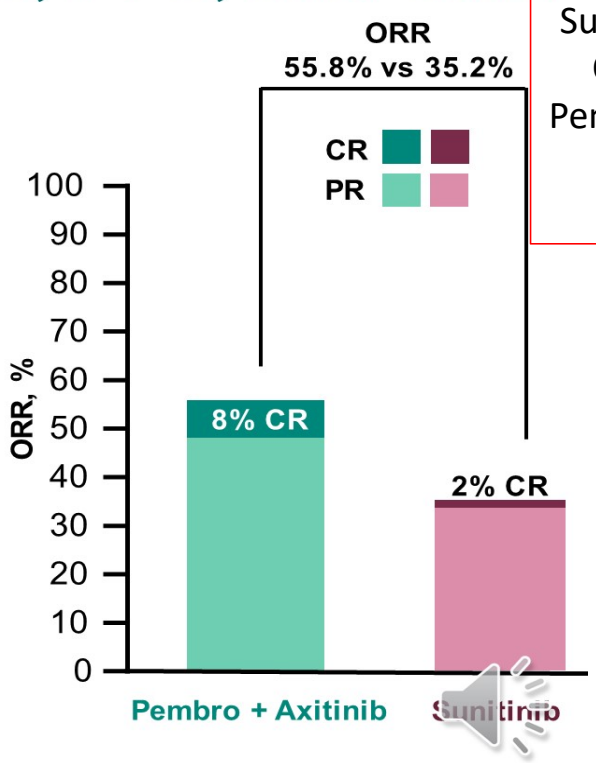
IMDC Intermediate/Poor Risk: OS, PFS, and ORR



Data cutoff: January 6, 2020.

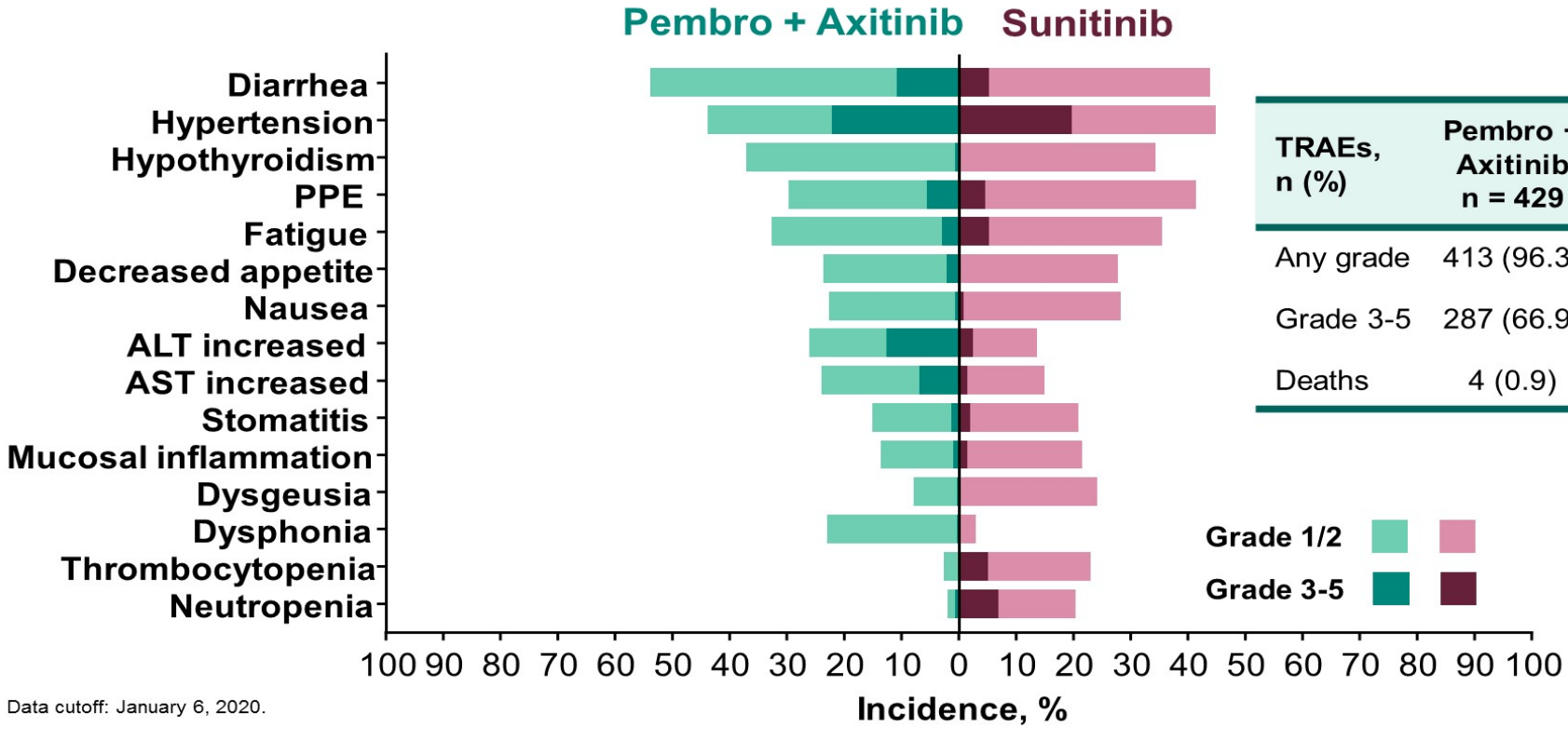


Superior OS, PFS, ORR for Ax + Pembro compared to Sunitinib

Presented By Elizabeth Plimack at TBD

Treatment-Related Adverse Events

Incidence ≥ 20% Within Either Treatment Arm



TRAEs, n (%)	Pembro + Axitinib n = 429	Sunitinib n = 425
Any grade	413 (96.3)	415 (97.6)
Grade 3-5	287 (66.9)	265 (62.4)
Deaths	4 (0.9)	6 (1.4)

Data cutoff: January 6, 2020.

Presented By Elizabeth Plimack at TBD

Summary and Conclusions

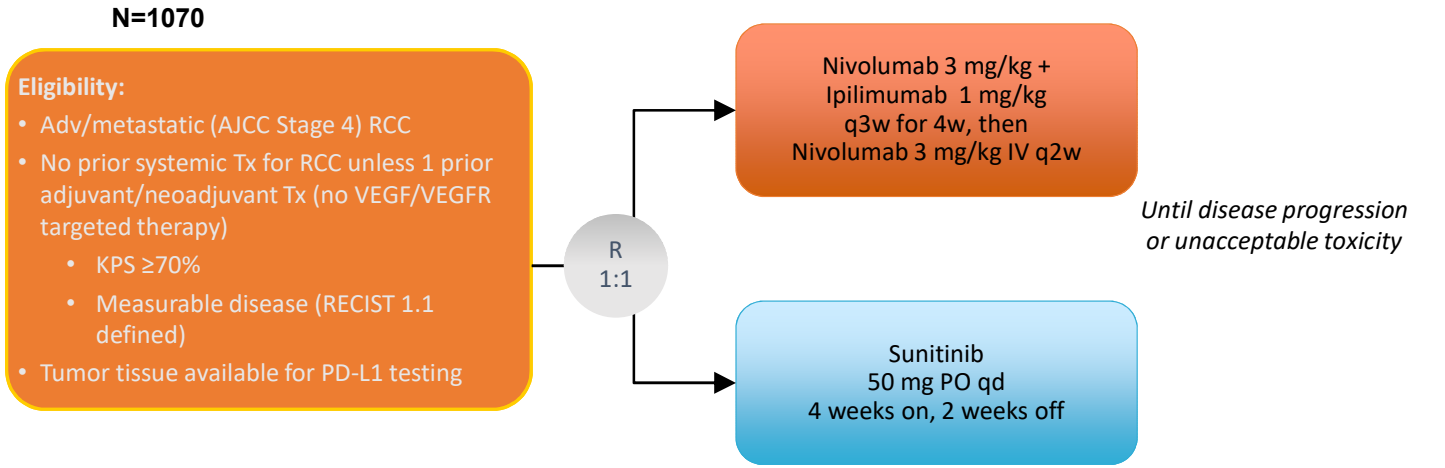
- With extended follow-up, pembrolizumab + axitinib continued to demonstrate clinically significant improved efficacy compared with sunitinib for previously untreated, advanced RCC
  - OS: HR, 0.68; $P < 0.001$[a]; 24-month rate, 74% vs 66%
  - PFS: HR, 0.71; $P < 0.0001$[a]; 24-month rate, 38% vs 27%
  - ORR: 60% vs 40%; $P < 0.0001$[a]
  - CR rate: 9% vs 3%
- Exploratory landmark analysis demonstrated that greater depth of tumor shrinkage was associated with increased OS in the pembrolizumab + axitinib arm
  - Patients with ≥80% tumor reduction had similar survival rates as patients who achieved confirmed CR by RECIST v1.1 within 6 months after randomization
- These results continue to support pembrolizumab + axitinib as a standard of care for patients with previously untreated advanced RCC

Limited benefit differential in favorable risk patients

[a]Because superiority of pembrolizumab + axitinib was shown at the first interim analysis, no alpha was allocated; only nominal *P* values are reported.

Checkmate 214: Phase 3 Study of Nivolumab + Ipilimumab vs Sunitinib in 1L Advanced/Metastatic RCC[1,2]

For perspective ….



Primary Outcome Measure: PFS, OS, ORR
Secondary Outcome Measures: Safety
Key Exploratory Measures: antitumor activity (ORR, PFS, OS) in favorable risk patients, outcomes by tumor PD-L1 expression level, health-related QoL based on FKSI-19

1. Escudier B et al. Oral Presentation at ESMO 2017. LBA5. 2. Clinicaltrials.gov. NCT02231749. Accessed on October 23, 2017.

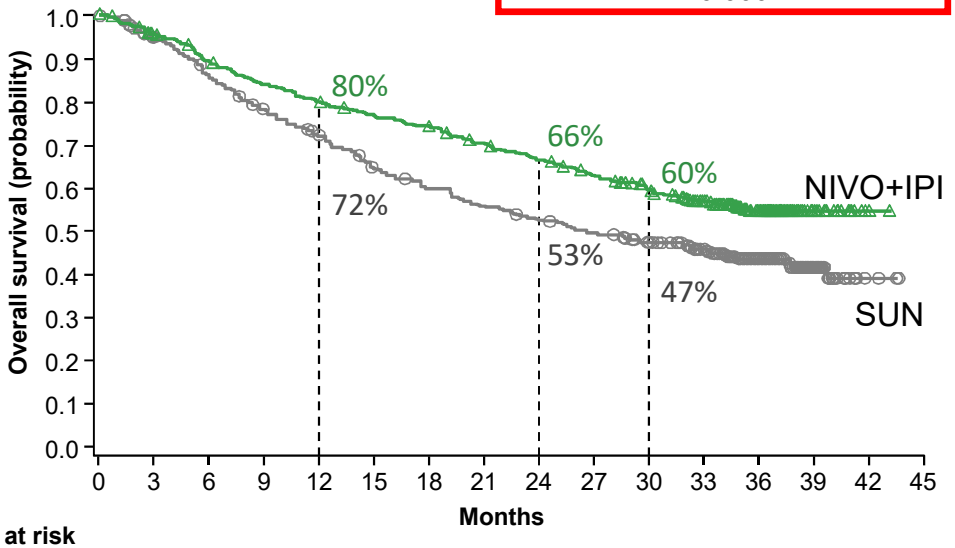
CM214: Overall Survival: by IMDC Risk

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

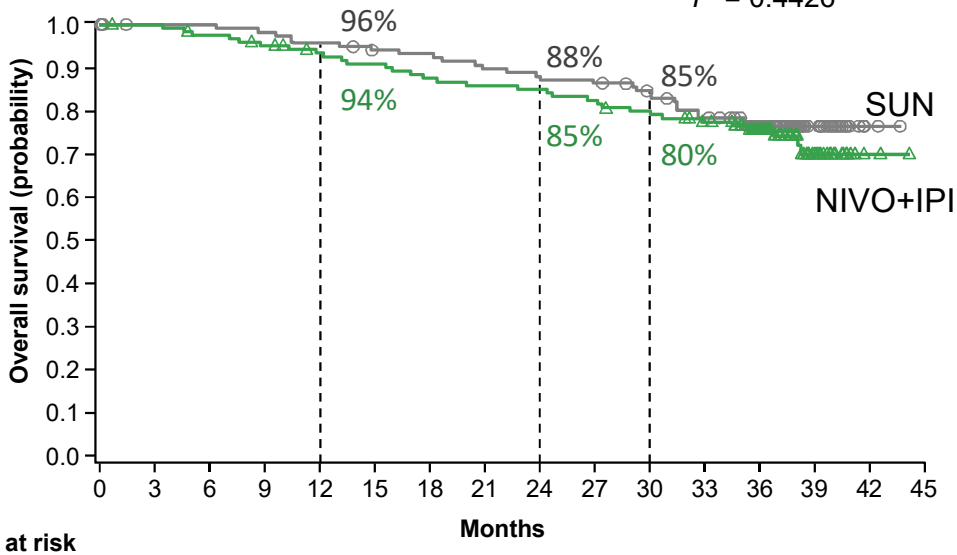
NIVO+IPI	425	399	372	348	332	317	306	287	270	253	233	183	90	34	2	0
SUN	422	388	353	318	290	257	236	220	207	194	179	144	75	29	3	0

Favorable risk

Median OS, months (95% CI)

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

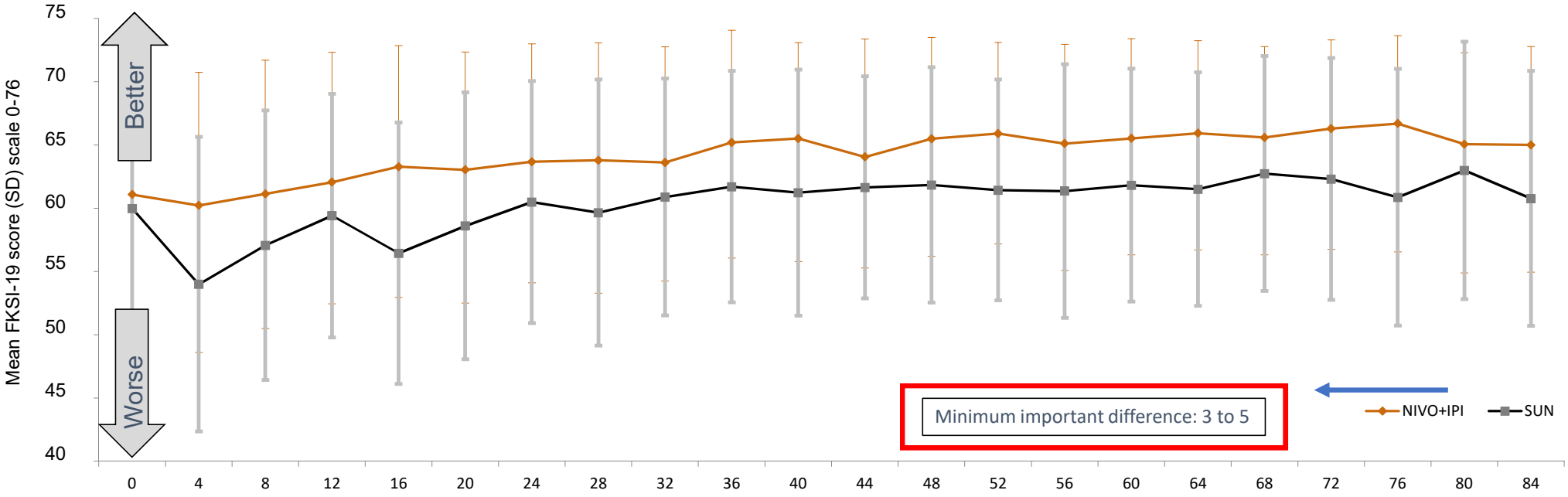
HR (95% CI), 1.22 (0.73–2.04)
P = 0.4426



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

CM214: Exploratory endpoint
Health-related quality of life: Intention to treat



No. at Risk

NIVO+IPI	532	502	399	350	323	298	288	188	142	190	126	118	154	118	103	114	108	104	119	89	90	103
SUN	515	502	460	402	383	294	311	169	111	215	134	98	173	103	92	156	91	71	132	82	64	106

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VIRTUAL ESMO congress 2020

Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma: first results from the randomized phase 3 CheckMate 9ER trial

Toni K. Choueiri,[1] Thomas Powles,[2] Mauricio Burotto,[3] Maria T. Bourlon,[4] Bogdan Zurawski,[5] Víctor Manuel Oyervides Juárez,[6] James J. Hsieh,[7] Umberto Basso,[8] Amishi Y. Shah,[9] Cristina Suarez,[10] Alketa Hamzaj,[11] Carlos Barrios,[12] Martin Richardet,[13] David Pook,[14] Yoshihiko Tomita,[15] Bernard Escudier,[16] Joshua Zhang,[17] Burcin Simsek,[17] Andrea B. Apolo,[18] Robert J. Motzer[19]

[1]Dana-Farber Cancer Institute, The Lank Center for Genitourinary Oncology, Boston, MA, USA; [2]Barts Cancer Institute, Queen Mary University of London, Royal Free NHS Trust, London, UK; [3]Bradford Hill Clinical Research Center, Santiago, Chile; [4]Urologic Oncology Clinic, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; [5]Professor Franciszek Lukaszczyk Oncology Centre, Bydgoszcz, Poland; [6]Centro Universitario contra el Cáncer Hospital Universitario "Dr. José Eleuterio González" Universidad Autónoma de Nuevo León, Nuevo León, Mexico; [7]Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO, USA; [8]Istituto Oncologico Veneto IOV IRCCS, Padova, Italy; [9]MD Anderson Cancer Center, Houston, TX, USA; [10]Vall d'Hebron Institute of Oncology, Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [11]Ospedale San Donato, Istituto Toscano Tumori, Arezzo, Italy; [12]Oncology Research Center, Hospital São Lucas, PUCRS, Porto Alegre, Brazil; [13]Fundacion Richardet Longo, Instituto Oncologico de Cordoba, Cordoba, Argentina; [14]Cabrini Monash University Department of Medical Oncology, Cabrini Health, Malvern, VIC, Australia; [15]Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; [16]Gustave Roussy, Villejuif, France; [17]Bristol Myers Squibb, Princeton, NJ, USA; [18]Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA; [19]Memorial Sloan Kettering Cancer Center, New York, NY, USA

Presentation Number 696O

CheckMate 9ER: Study design

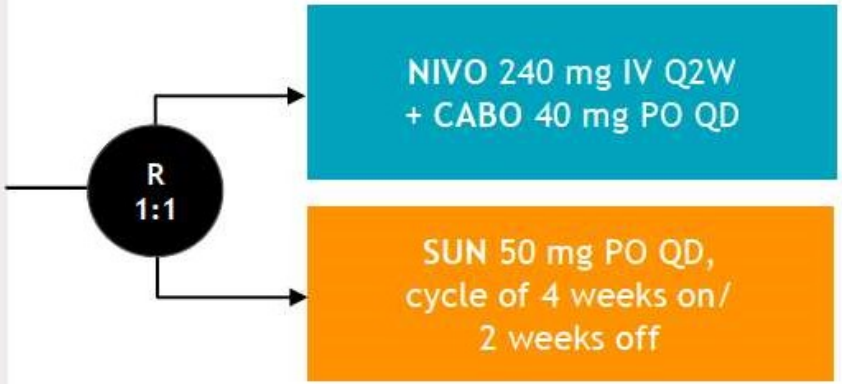
N = 651

Key inclusion criteria[1,2]

- Previously untreated advanced or metastatic RCC
- Clear cell component
- Any IMDC risk group

Stratification factors:

- IMDC risk score
- Tumor PD-L1 expression[a]
- Geographic region



Treat until RECIST v1.1-defined progression or unacceptable toxicity[b]

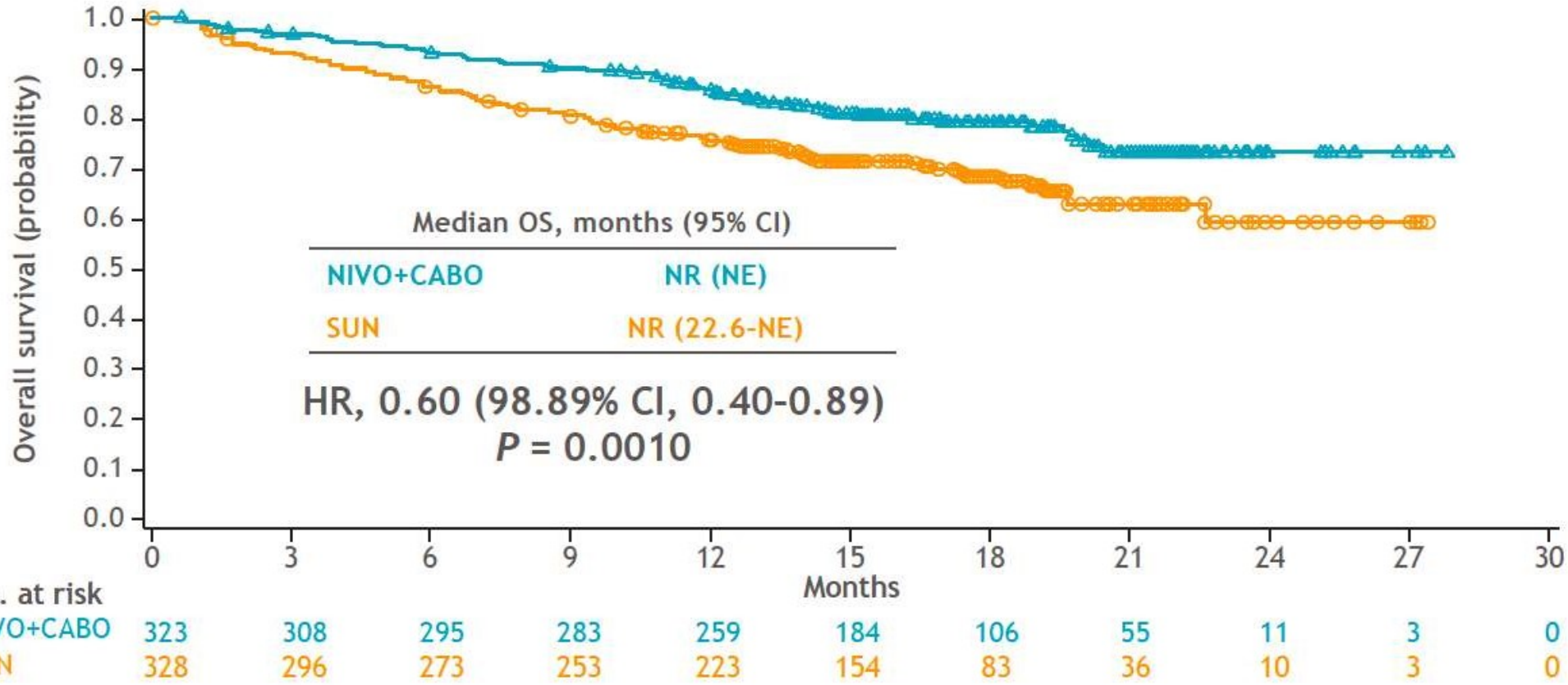
Median study follow-up, 18.1 months (range, 10.6-30.6 months)

Primary endpoint: PFS

Secondary endpoints: OS, ORR, and safety

[a]Defined as the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 immunohistochemistry 28-8 pharmDx assay.
[b]NIVO dosing may not exceed a total of 2 years (from cycle 1); CABO and SUN treatment may continue beyond 2 years in the absence of progression or unacceptable toxicity. Patients may be treated beyond progression.
IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IV, intravenously; ORR, objective response rate; PD-L1, programmed death ligand 1; PFS, progression-free survival; PO, orally; Q2W, every 2 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.
1. Clinicaltrials.gov/ct2/show/NCT03141177. Accessed June 8, 2020; 2. Choueiri TK et al. Poster presented at the American Society of Clinical Oncology Annual Meeting 2018. TPS4598.

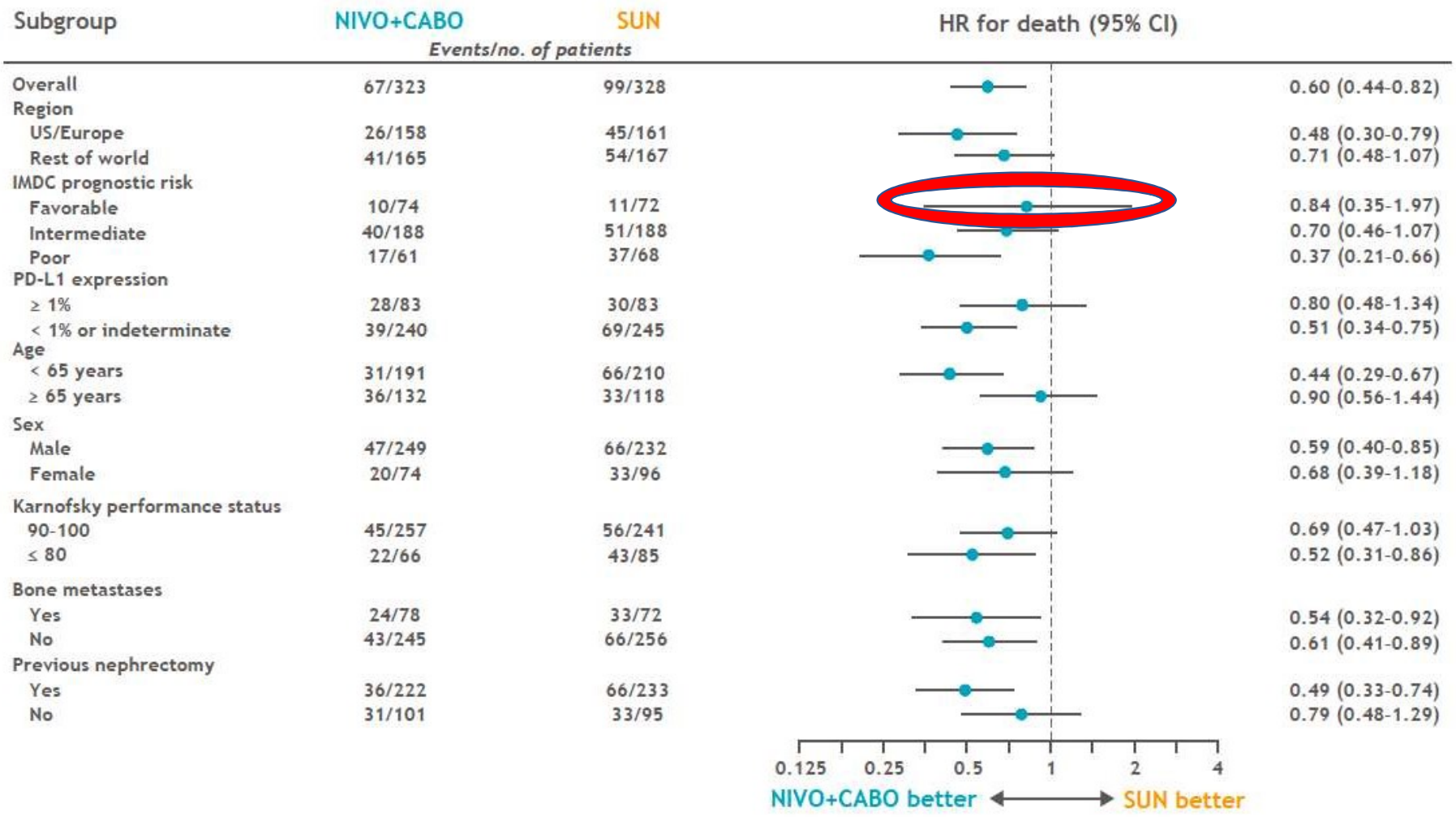
Overall survival



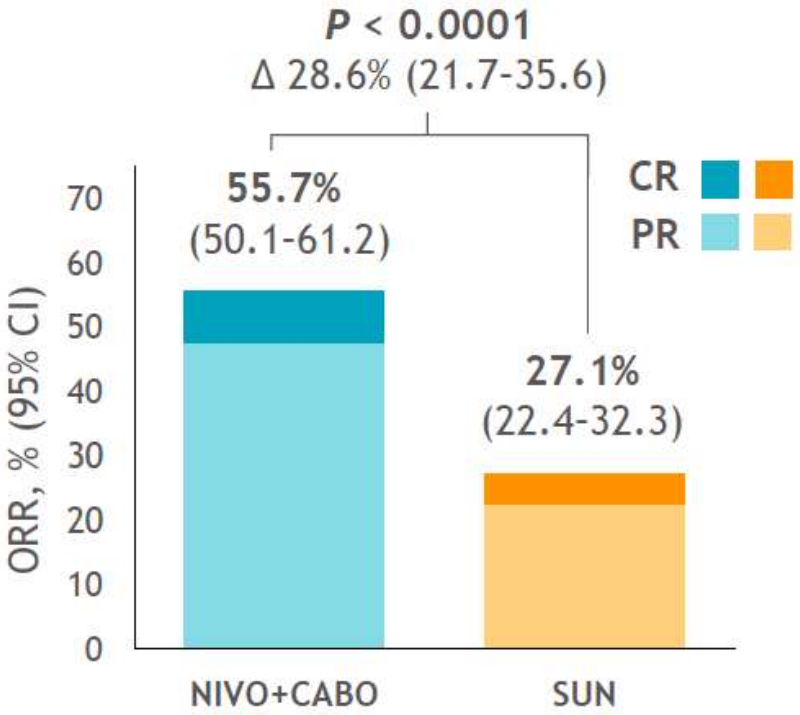
No. at risk											
NIVO+CABO	323	308	295	283	259	184	106	55	11	3	0
SUN	328	296	273	253	223	154	83	36	10	3	0

Minimum study follow-up, 10.6 months.
NE, not estimable; NR, not reached.

Overall survival in subgroups



Objective response and best overall response per BICR



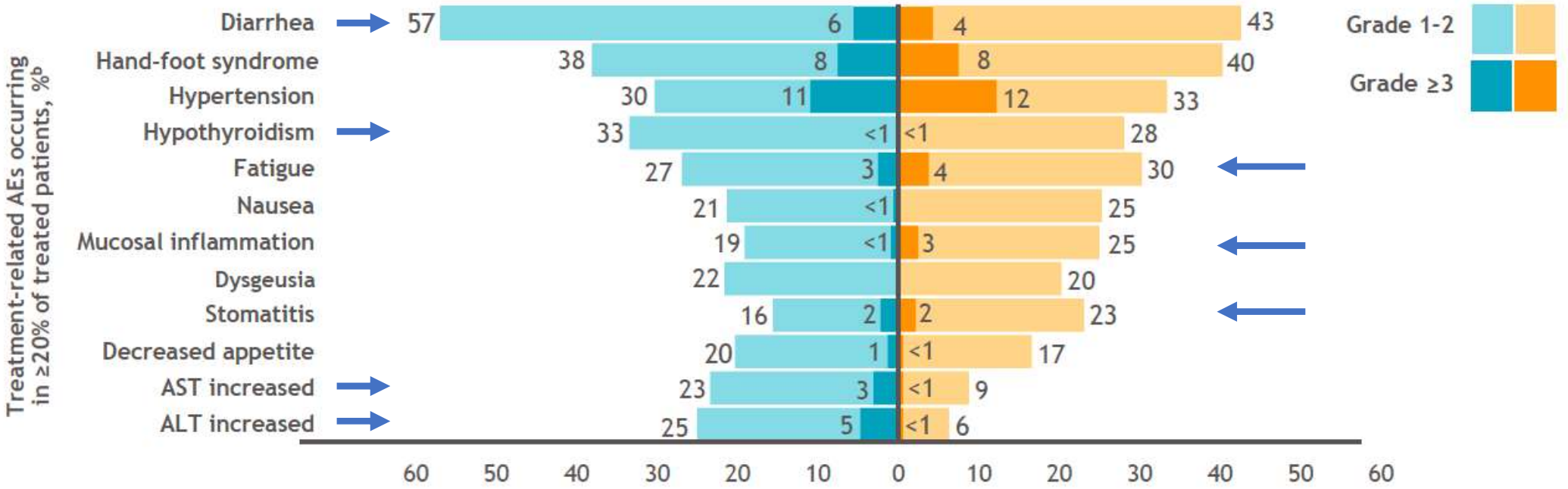
Outcome, %	NIVO+CABO (n = 323)	SUN (n = 328)
Complete response	8.0	4.6
Partial response	47.7	22.6
Stable disease	32.2	42.1
Progressive disease	5.6	13.7
Not evaluable/not assessed[a]	6.5	17.1
Median time to response (range), months[b]	2.8 (1.0-19.4)	4.2 (1.7-12.3)
Median duration of response (95% CI), months[b]	20.2 (17.3-NE)	11.5 (8.3-18.4)

- ORR favored NIVO+CABO over SUN across subgroups including by IMDC risk status, tumor PD-L1 expression (≥ 1% vs < 1%), and bone metastases

BICR-assessed ORR and BOR by RECIST v1.1.
[a]Includes patients who were never treated, those who discontinued/died before disease assessment, those without measurable disease at baseline per BICR, or other reason not reported/specified; [b]Median time to and duration of response were calculated for patients who had a complete or partial response (n = 180 with NIVO+CABO, n = 89 patients with SUN).

Safety summary

Events, %[a]	NIVO+CABO, n = 320		SUN, n = 320	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
All-cause AEs	100	75	99	71
Treatment-related AEs	97	61	93	51



[a]Includes events that occurred on therapy or within 30 days after the end of the treatment period of all treated patients. Treatment-related deaths per investigator: NIVO+CABO n = 1 (small intestine perforation), SUN n = 2 (pneumonia, respiratory distress); [b]Total bar represents treatment-related AEs of any grade ≥ 20% in either treatment arm; of these events, none were grade 5.

Renal cell cancer: where to in 2020?

- **We have a wealth of agents with IO, VEGF and mTORi mechanism of action**
- **For first line IO eligible patients who are intermediate to poor risk, Nivo + Ipi, Pembro + Axitinib and Cabo + Nivo provide a robust OS benefit**
- **These are regimens of first choice**
- **Therapy selection may be based on the toxicity of the drug add to the PD-1 agent at the start of treatment**

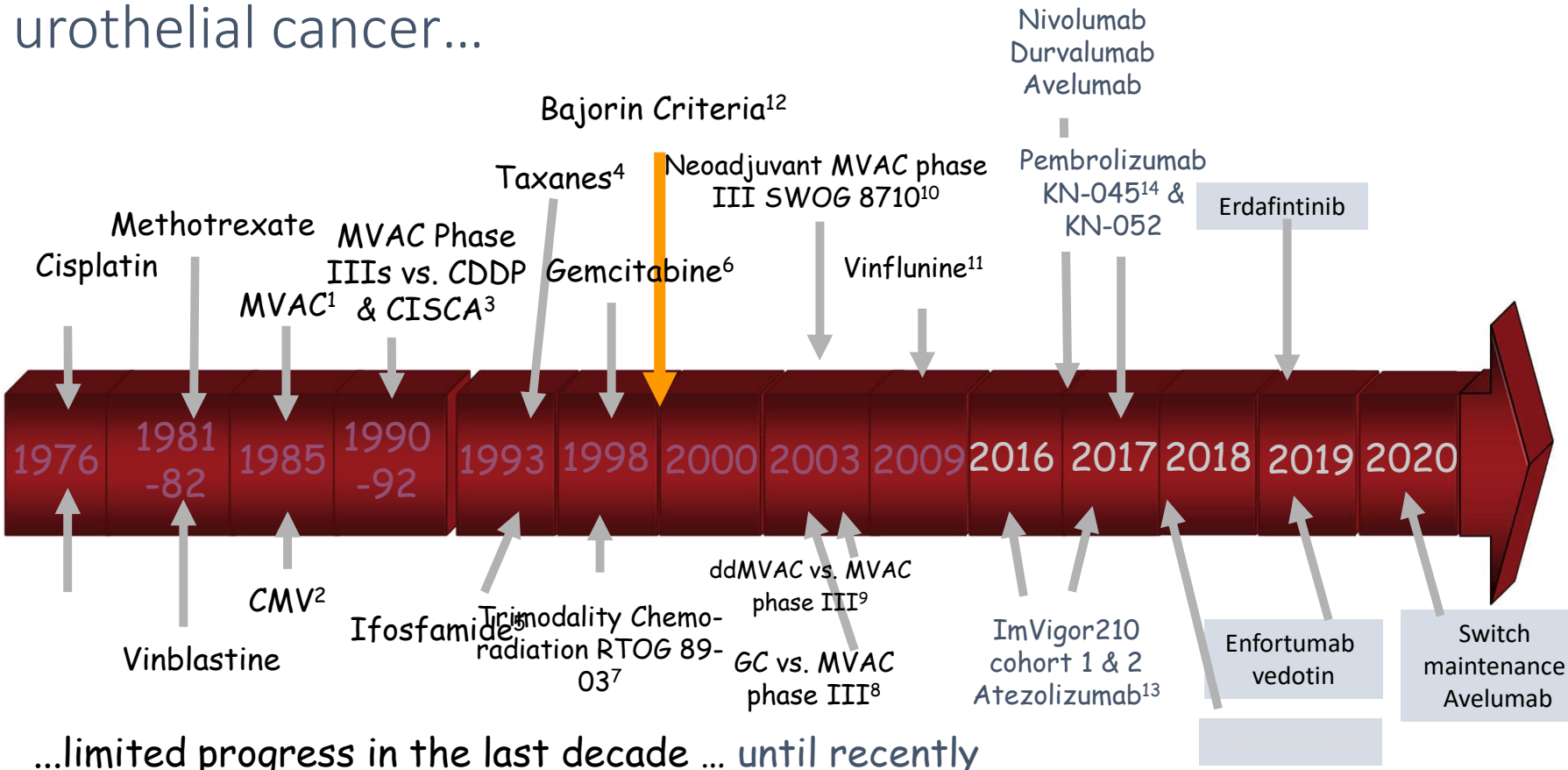
- **For good risk metastatic patients, IO therapy is an option but first line VEGFrTKI followed by other agent including IO therapy results in a similar OS outcome.**
- **The addition of Ipi to Nivolumab in patients with stable disease or progression produces an incremental response in 10-15% of patients. (GU 16-260, German Urology Group data)**

- **Caboxantinib is an excellent alternative or salvage option, relative to IO therapy in intermediate and poor risk cases. Axitinib and other VEGFrTKIs are active if the patient has not had prior exposure.**

- **More data to follow …**

Urothelial cancer

Timeline for systemic therapy development in urothelial cancer…



…limited progress in the last decade … until recently

1. Sternberg CN et al. J Urol 133: 403-7, 1985
2. Harker WG et al. J Clin Oncol 3: 1463-70, 1985
3. Logothetis CJ et al. J Clin Oncol 8:1050-5, 1990
4. Roth BJ et al J Clin Oncol 12: 2264-70, 1994
5. Witte RS et al J Clin Oncol 15: 589-93, 1997
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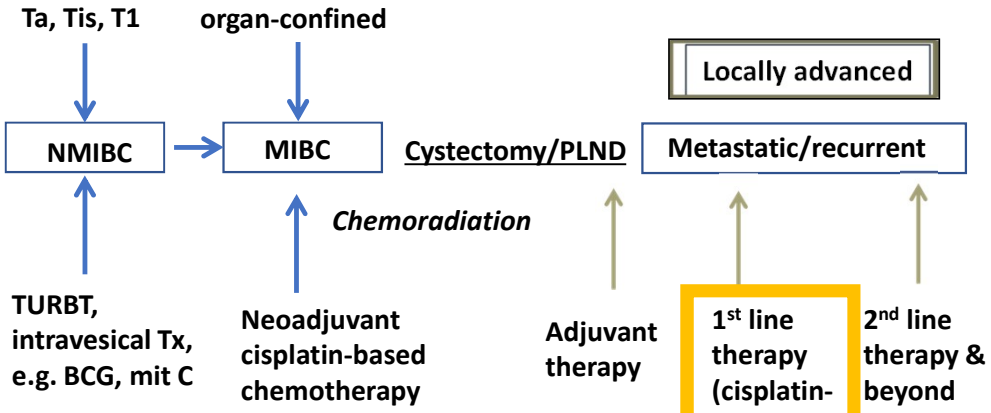
12. Bajorin DF et al J Cline Oncol 17: 3173-81, 1999
13. Rosenberg J et al Lancet 2016
14. Bellmunt J et al. N Engl J Med 2017

Urothelial cancer: treatment settings



Approved going into 2020

Pembrolizumab

Pembrolizumab
Atezolizumab

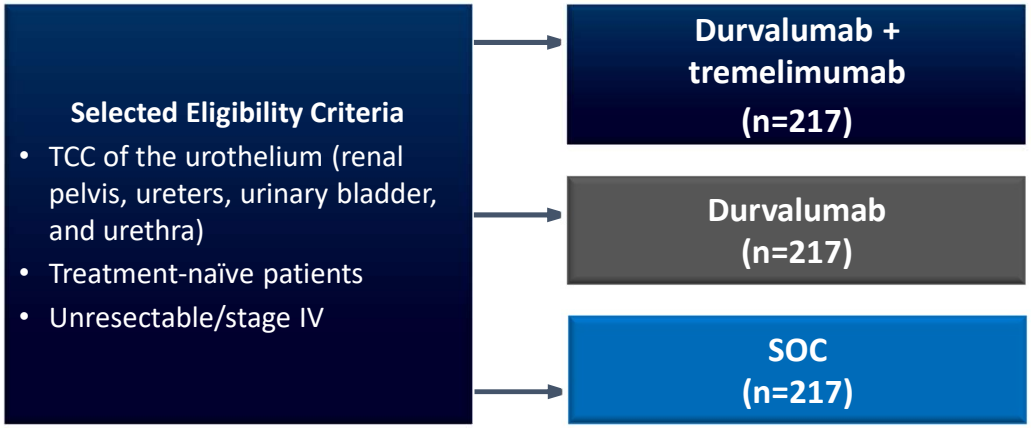
Pembrolizumab
Atezolizumab
Nivolumab
Durvalumab
Avelumb

Immune Checkpoint Inhibitors in Front-Line In Cisplatin-Ineligible Setting

	Atezolizumab[1]	Pembrolizumab[2]
Phase	Phase II (IMvigor Cohort 1)	Phase II (Keynote-052)
Number of Patients	119	370
Dosing	1200mg every 3 weeks	200mg every 3 weeks
ORR	23% (9% CR)	29% (7% CR)
Duration of Response	70% of responses ongoing at 17.2 months	82% of responses ongoing at ≥ 6 months
Median OS	15.9 months	Not reached
Median PFS	2.7 months	2 months
Rate of Grade 3/4 Treatment-related AEs	16%	19%

1. Balar et al. 2017 Lancet 2. Balar et al. 2017 Lancet Oncology

DANUBE: Phase 3 Study of Durvalumab ± Tremelimumab vs SOC in First-line A



Randomization stratification factors:

- Cisplatin eligibility (eligible vs ineligible)
- PD-L1 status (positive vs negative)
- Visceral metastasis (presence or absence; ie, bone, lung, or liver)

Primary endp

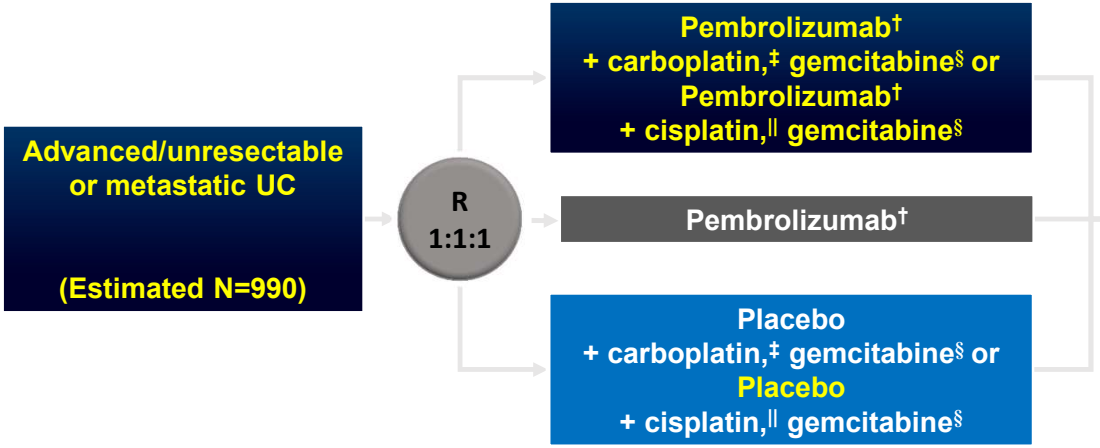
PFS, OS (

Secondary e

PFS (single
PFS (PD-L1
ORR (comb
FACT-BL
Immunogenicity

Did not reach primary endpoint
Did not appear to validate durvalumab over SOIC chemo in PD-L1 high subset
ESMO 2020

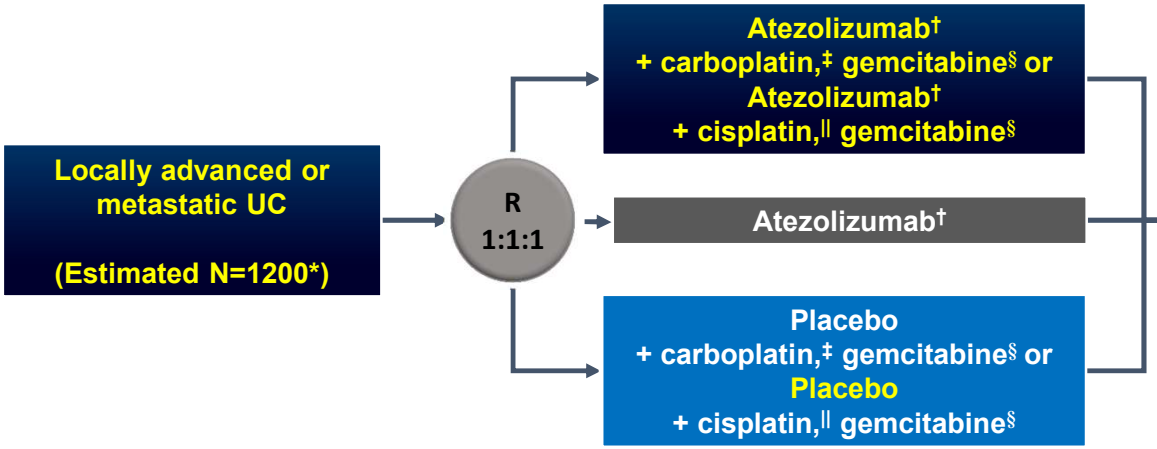
KEYNOTE-361: Phase III Pembrolizumab With or Without Platinum-Based Combination Chemotherap
Chemotherapy in Patients With Advanced c



- Key inclusion criteria: No prior systemic chemotherapy for advanced or metastatic UC neoadjuvant and adjuvant Pt-based CT); ECOG ≤2
- Primary endpoints: PFS (investigator-assessed), OS
- Secondary endpoints: Safety, ORR, DCR, PFS as assessed by BICR
- Estimated primary completion date: March 2019

Did not reach primary endpoint Did not appear to validate pembrolizumab over chemo in PD-L1 high subset ESMO 2020

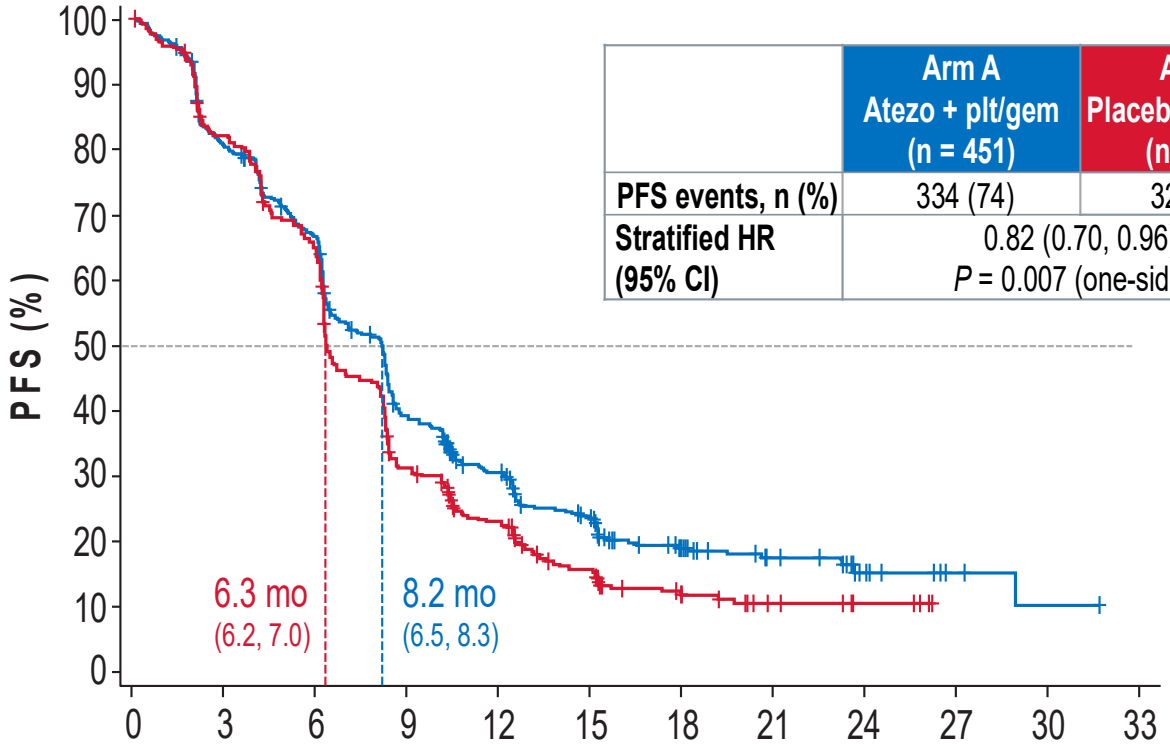
IMvigor 130 (WO30070): Phase III Atezolizumab vs Atezolizumab + Platinum-Based Chemotherapy in Untreated Locally Advanced or Metastatic UC – Study Design



- Key inclusion criteria: First-line platinum-eligible; evaluable for tumor PD-L1 prior CT for inoperable, locally advanced, or metastatic UC; ECOG ≤2
- Primary endpoints: PFS (investigator-assessed), OS, safety
- Secondary endpoints: ORR, DOR, QOL, PK, ATA

Did reach a co-primary endpoint
Did appear to validate atezolizumab over chemo in PD-L1 hgh subset
ESMO 2019

Final PFS: ITT (Arm A vs Arm C)



	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
PFS events, n (%)	334 (74)	326 (82)
Stratified HR (95% CI)	0.82 (0.70, 0.96) *P* = 0.007 (one-sided)	

No. at Risk												
Atezo + plt/gem	451	345	282	160	111	74	42	22	10	4	2	NE
Placebo + plt/gem	400	317	246	116	73	40	18	11	4	NE	NE	NE

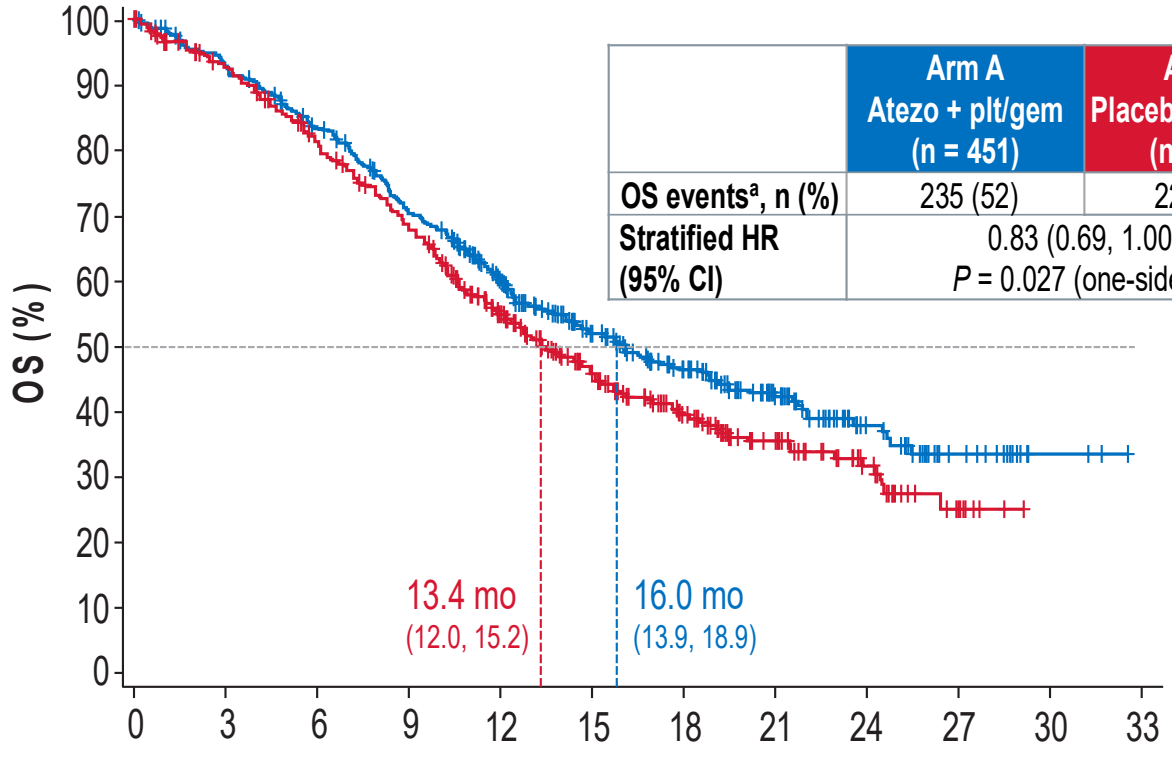
NE, not estimable. Data cutoff 31 May 2019; median survival follow-up 11.8 months (all patients).

IMvigor130—ESMO 2019 (LBA14): presented by Dr Enrique Grande

http://bit.ly/2Z1bPbD

Interir

Interim OS: ITT (Arm A vs Arm C)



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

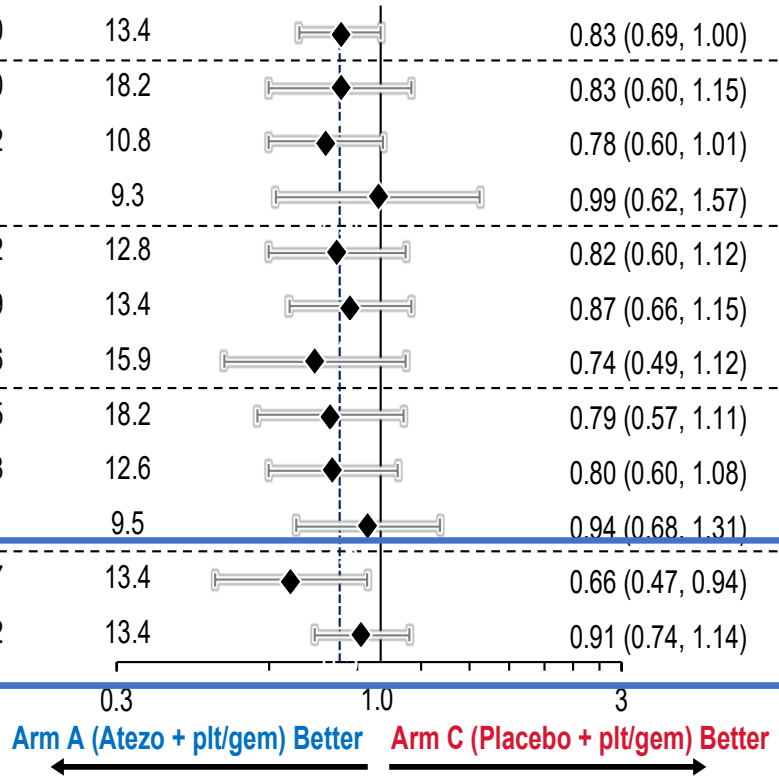
No. at Risk												
Atezo + plt/gem	451	408	360	301	229	163	117	72	36	16	3	NE
Placebo + plt/gem	400	359	308	255	182	123	79	49	25	8	NE	NE

Data cutoff 31 May 2019; median survival follow-up 11.8 months (all patients). [a] 5% of patients from Arm A and 20% of patients from Arm C received non-protocol immunotherapy. [b] Did not cross the interim efficacy boundary of 0.007 per the O'Brien-Fleming alpha spending function.

IMvigor130—ESMO 2019 (LBA14): presented by Dr Enrique Grande http://bit.ly/2Z1bPbD

Interim OS subgroups: ITT (Arm A vs Arm C)

Characteristic		Patients (n)	Arm A mOS, mo (n = 451)	Arm C mOS, mo (n = 400)	HR (95% CI)[a]
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)



[a] Unstratified HR shown for all characteristics except for 'All Patients', where stratified HR is shown.

IMvigor130—ESMO 2019 (LBA14): presented by Dr Enrique Grande

http://bit.ly/2Z1bPbD

IMvigor010: Primary Analysis From a Phase III Randomized Study of Adjuvant Atezolizumab vs Observation in High-Risk Muscle-Invasive Urothelial Carcinoma

Maha H.A. Hussain,[1] Thomas Powles,[2] Peter Albers,[3] Daniel Castellano,[4] Siamak Daneshmand,[5] Jürgen E. Gschwend,[6] Hiroyuki Nishiyama,[7] Stephane Oudard,[8] Darren Tayama,[9] Nicole Davarpanah,[9] Viraj Degaonkar,[9] Yi Shi,[9] Sanjeev Mariathasan,[9] Petros Grivas,[10] Peter H. O'Donnell,[11] Jonathan E. Rosenberg,[12] Daniel M. Geynisman,[13] Jean H. Hoffman-Censits,[14] Daniel P. Petrylak,[15] Joaquim Bellmunt[16]

[1]Robert H Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL; [2]Barts Cancer Institute, Queen Mary University of London, St Bartholomew's Hospital, London, UK; [3]Heinrich-Heine University Düsseldorf, Medical Faculty, Department of Urology, University Hospital Düsseldorf, Germany; [4]University Hospital 12 de Octubre, Medical Oncology Department CIBER-ONC, Madrid, Spain; [5]USC Norris Comprehensive Cancer Center, Los Angeles, CA; [6]Technical University of Munich, Munich, Germany; [7]University of Tsukuba, Ibaraki, Japan; [8]Georges Pompidou European Hospital, Paris Descartes University, Paris, France; [9]Genentech, Inc., South San Francisco, CA; [10]University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA; [11]The University of Chicago, Chicago, IL; [12]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; Weill Cornell Medical College, New York, NY; [13]Department of Hematology/Oncology, Fox Chase Cancer Center, Philadelphia, PA; [14]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; [15]Yale Cancer Center, New Haven, CT; [16]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

PRESENTED BY: Hussain M. IMvigor010 primary analysis [abs 5000]. https://bit.ly/2SKSAD3

Presented By Maha Hussain at TBD

IMvigor010 Study Design

Key eligibility[a]

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

R 1:1

Atezolizumab 1200 mg q3w *(16 cycles or 1 year)*

No crossover allowed

Observation[c] **q3w**

Disease recurrence/ survival follow-up

Tumor assessments: q12w for years 1-3, (q24w for years 4-5 and at year 6)

Stratification factors

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

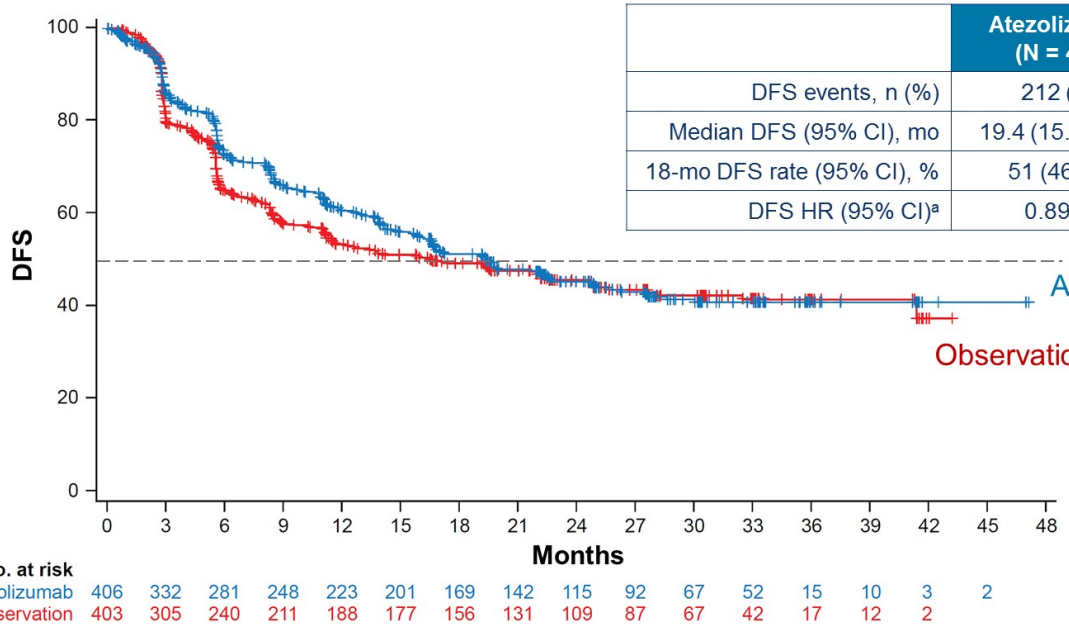
- **Primary endpoint:** DFS (ITT population)
- **Key secondary endpoint:** OS (ITT population)
- **Exploratory analyses:** Biomarkers including PD-L1 status
- **Safety**

TARGET
HR 0.75

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

Presented By Maha Hussain at TBD

DFS in ITT Population

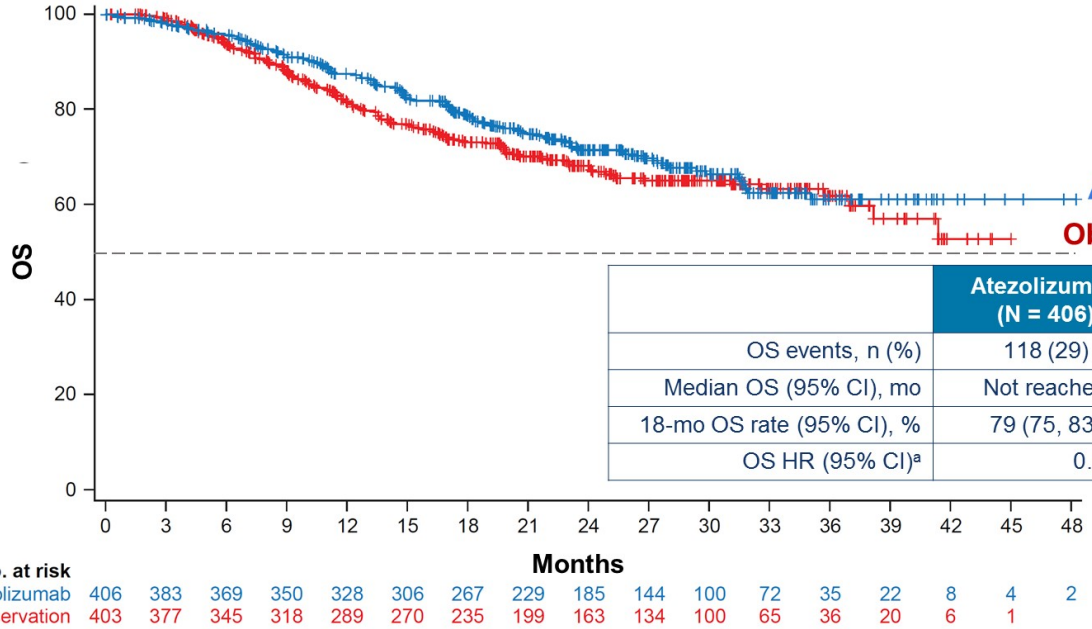


	Atezolizumab (N = 406)	Observation (N = 403)
DFS events, n (%)	212 (52)	208 (52)
Median DFS (95% CI), mo	19.4 (15.9, 24.8)	16.6 (11.2, 24.8)
18-mo DFS rate (95% CI), %	51 (46, 56)	49 (44, 54)
DFS HR (95% CI)[a]	0.89 (0.74, 1.08); *P* = 0.2446[b]	

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

Presented By Maha Hussain at TBD

Interim OS Analysis in ITT Population



	Atezolizumab (N = 406)	Observation (N = 403)
OS events, n (%)	118 (29)	124 (31)
Median OS (95% CI), mo	Not reached	Not reached
18-mo OS rate (95% CI), %	79 (75, 83)	73 (69, 78)
OS HR (95% CI)[a]	0.85 (0.66, 1.09)	

Data cutoff: November 30, 2019. Median follow-up: 21.9 mo. Most common subsequent non-protocol therapies included immunotherapy (9% in atezolizumab arm vs 21% in observation arm), chemotherapy (27% vs 25%) and targeted therapy (5% vs 2%). [a] OS results are shown for descriptive purposes only. HR stratified by tumor stage, nodal status and PD-L1 status.

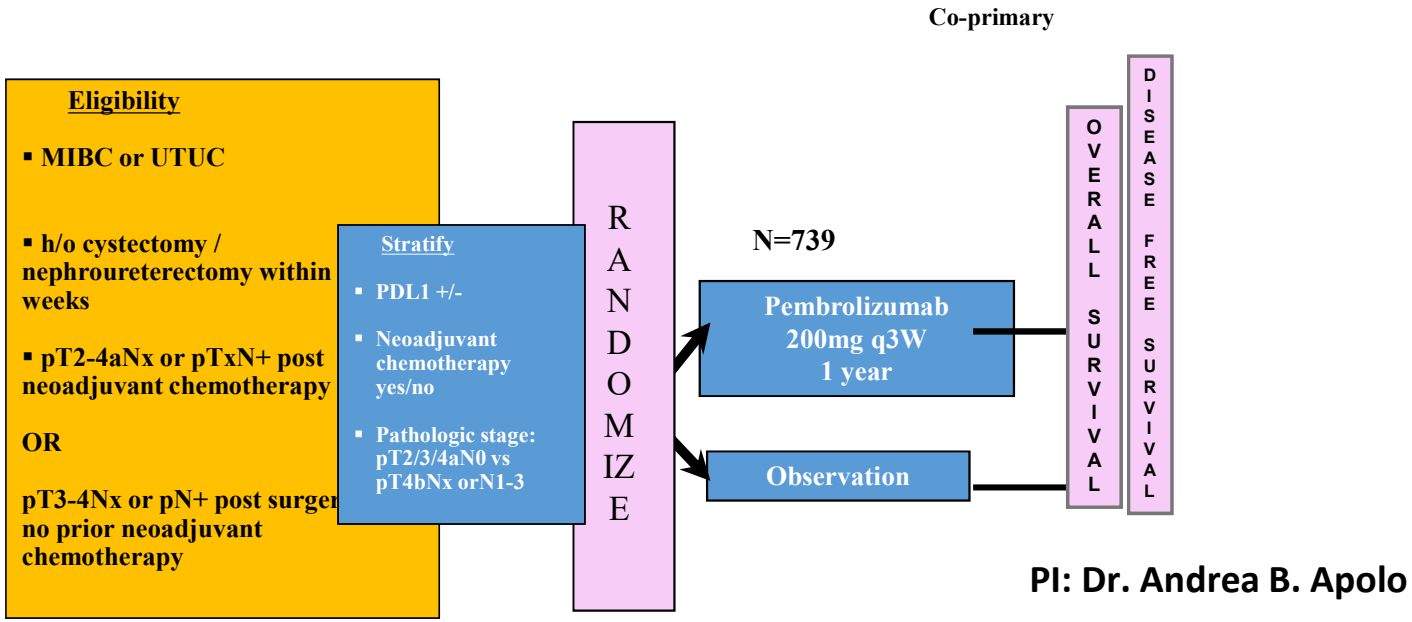
Presented By Maha Hussain at TBD

IMvigor010: Conclusions

- IMvigor010 is the first Phase III study evaluating the benefit of an adjuvant CPI in MIUC
- The safety profile for atezolizumab monotherapy was consistent with that in prior studies in the advanced setting, with no new safety concerns
  - Higher frequencies of AESIs (mainly Grade 1-2), and treatment discontinuation due to AEs (mainly skin and gastrointestinal) were seen, while corticosteroid use was lower in IMvigor010
- IMvigor010 did not meet its primary endpoint of DFS
  - No pre-specified subgroups (including higher PD-L1 status) showed treatment benefit with atezolizumab
  - OS follow-up is ongoing; additional exploratory biomarker and subgroup analyses may warrant further study
- Other clinical trials with atezolizumab as monotherapy and combination therapy are underway in the metastatic, non-muscle invasive, and bladder-preservation UC settings

Presented By Maha Hussain at TBD

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



PI: Dr. Andrea B. Apolo

Press release 9/24/20: Nivolumab Significantly Improves Disease Free-Survival vs. Placebo as Adjuvant Therapy for Patients with High-Risk, Muscle-Invasive Urothelial Carcinoma in Phase 3 CheckMate -274 Trial


I'll Show Him
High Maintenance

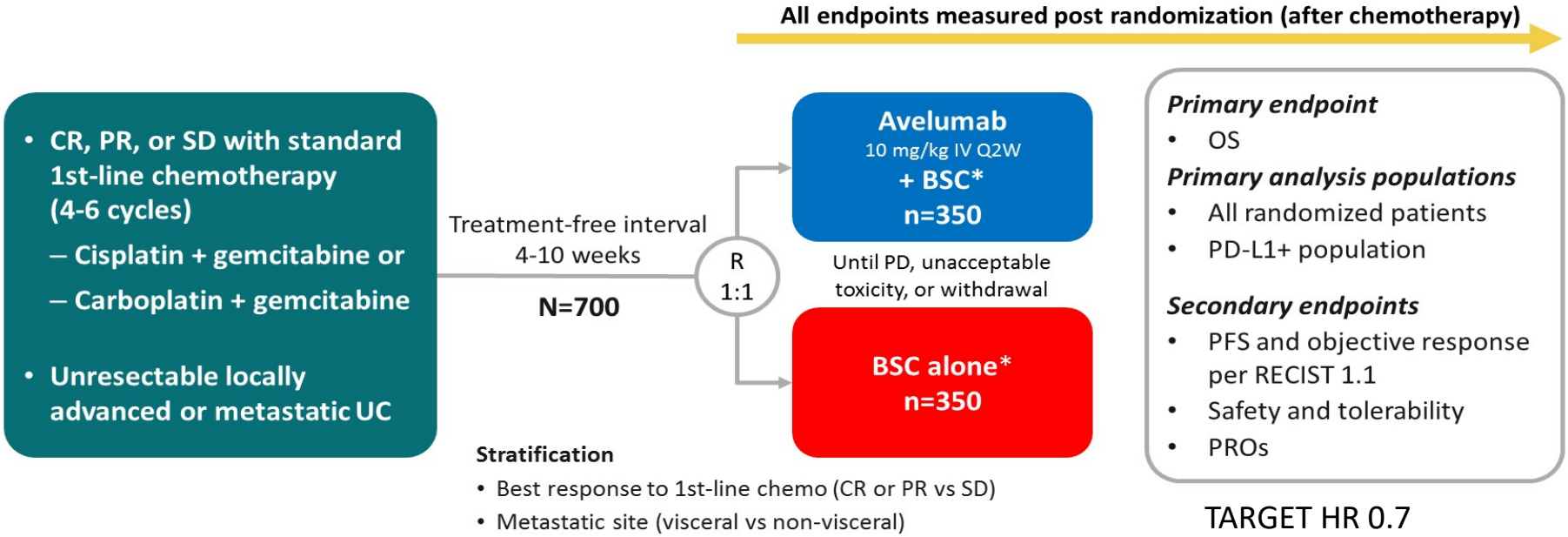
Maintenance avelumab + best supportive care (BSC) versus BSC alone after platinum-based first-line chemotherapy in advanced urothelial carcinoma: JAVELIN Bladder 100 phase III results

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

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

Presented By Thomas Powles at TBD

JAVELIN Bladder 100 study design (NCT02603432)



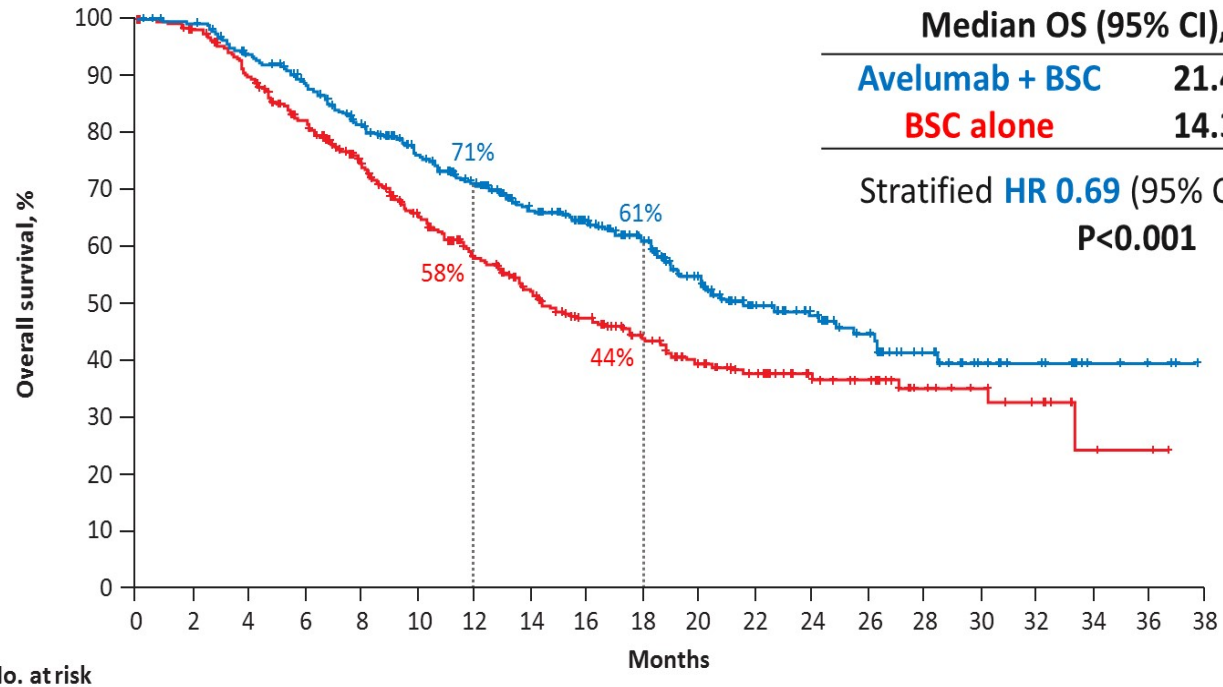
PD-L1+ status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively, using the Ventana SP263 assay; 358 patients (51%) had a PD-L1–positive tumor

BSC, best supportive care; **CR,** complete response; **IV,** intravenous; **PR**, partial response; **PRO**, patient reported outcome; **Q2W,** every 2 weeks; **R**, randomization; **RECIST 1.1,** Response Evaluation Criteria in Solid Tumors version 1.1; **SD**, stable disease

*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other systemic antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable

Presented By Thomas Powles at TBD

OS in the overall population



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

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

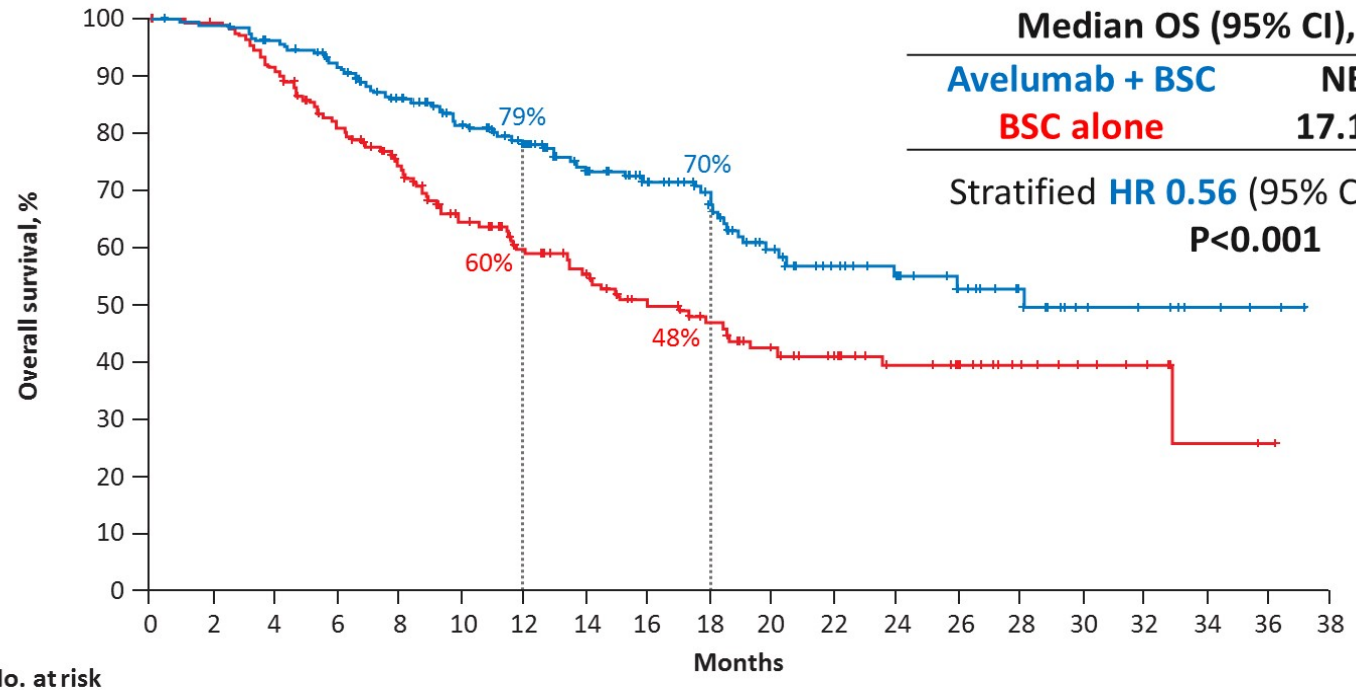
P<0.001

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

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

Presented By Thomas Powles at TBD

OS in the PD-L1+ population



Median OS (95% CI), months	
Avelumab + BSC	**NE** (20.3, NE)
BSC alone	**17.1** (13.5, 23.7)

Stratified **HR 0.56** (95% CI, 0.40, 0.79)
P<0.001

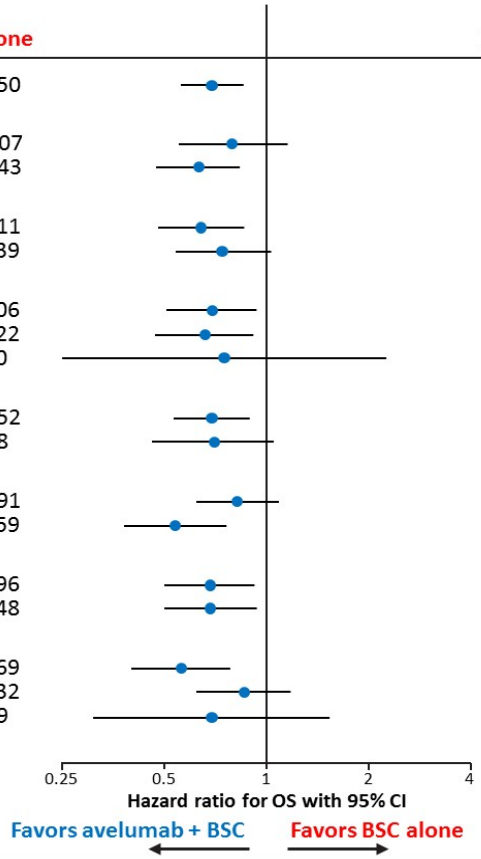
No. at risk																				
Avelumab + BSC	189	185	177	165	146	129	114	95	81	70	49	38	32	26	18	9	8	4	2	0
BSC	169	165	152	132	113	89	76	67	54	45	37	30	23	21	12	8	6	2	1	0

OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0014). **NE**, not estimable

Presented By Thomas Powles at TBD

Subgroup analysis of OS in the overall population

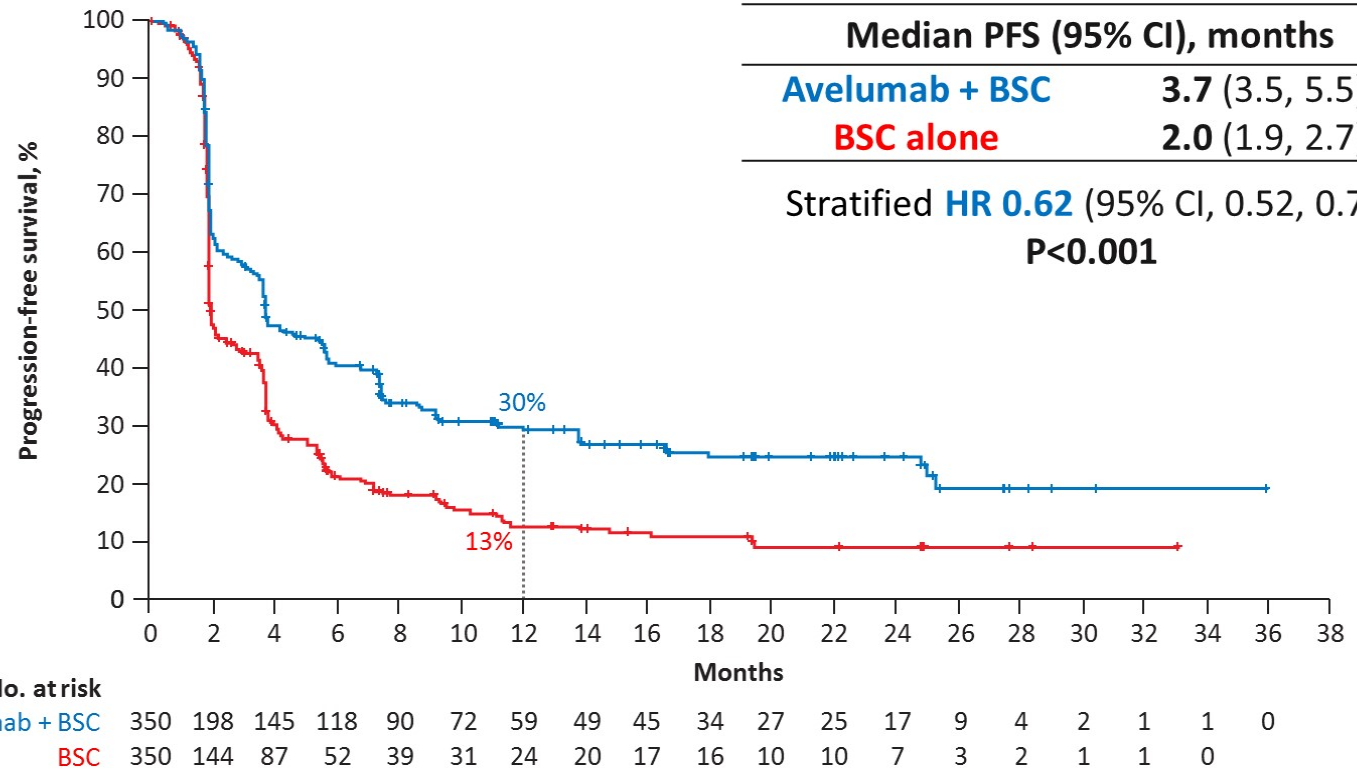
Subgroup		Events/patients, n: Avelumab + BSC	Events/patients, n: BSC alone	Hazard ratio (95% CI)
All patients		145/350	179/350	**0.69** (0.56, 0.86)*
Age	<65 years	61/129	53/107	**0.79** (0.55, 1.15)
	≥65 years	84/221	126/243	**0.63** (0.47, 0.83)
ECOG PS score	0	77/213	101/211	**0.64** (0.48, 0.86)
	≥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)

Presented By Thomas Powles at TBD

PFS by independent radiology review in the overall population



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

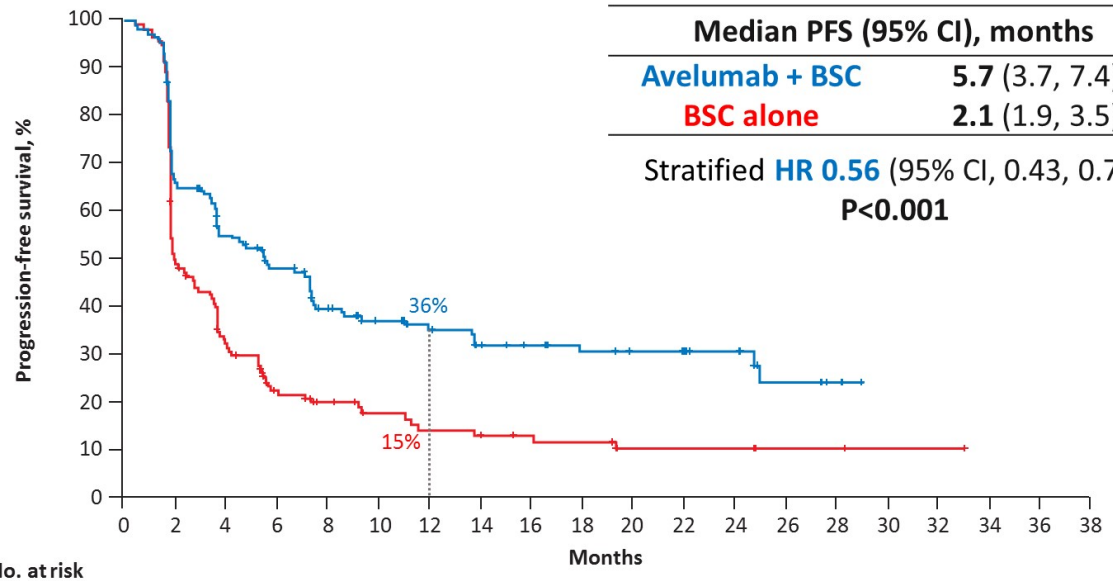
Stratified **HR 0.62** (95% CI, 0.52, 0.75)
P<0.001

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

PFS was measured post randomization (from end of chemotherapy)

Presented By Thomas Powles at TBD

PFS by independent radiology review in the PD-L1+ population



Median PFS (95% CI), months	
Avelumab + BSC	**5.7** (3.7, 7.4)
BSC alone	**2.1** (1.9, 3.5)

Stratified **HR 0.56** (95% CI, 0.43, 0.73)
P<0.001

No. at risk																	
Avelumab + BSC	189	114	89	73	55	45	35	29	26	20	17	17	12	7	2	0	
BSC	169	80	51	28	21	16	13	12	10	9	5	5	5	2	2	1	1	0

PFS was measured post randomization (from end of chemotherapy)

Presented By Thomas Powles at TBD

Confirmed objective response

Response to maintenance therapy post randomization

	Overall population		PD-L1+ population	
	Avelumab + BSC (N=350)	BSC alone (N=350)	Avelumab + BSC (N=189)	BSC alone (N=169)
ORR, %	**9.7**	**1.4**	**13.8**	**1.2**
(95% CI)	(6.8, 13.3)	(0.5, 3.3)	(9.2, 19.5)	(0.1, 4.2)
Stratified odds ratio (95% CI)	7.464 (2.824, 24.445)		12.699 (3.160, 114.115)	
Best overall response, %				
Complete response	6.0	0.9	9.5	0.6
Partial response	3.7	0.6	4.2	0.6
Stable disease	12.6	13.1	10.1	13.6
Non-CR/non-PD	18.9	12.9	20.1	13.0
Progressive disease	37.1	48.3	31.2	48.5
Not evaluable*	21.7	24.3	24.9	23.7
Disease control, %†	41.1	27.4	43.9	27.8

PD, progressive disease
Objective response was assessed by independent radiology review; in patients with a CR after chemotherapy, best overall response was not evaluable if no evidence of disease at baseline was maintained after randomization, or PD if disease progression occurred after randomization
*Reasons for not evaluable included no evidence of disease at baseline; no post-baseline assessments; SD <6 weeks after randomization; PD >12 weeks after randomization; new anticancer therapy started before first post-baseline assessment; or all post-baseline assessments have objective response of not evaluable
†Patients with a best overall response of CR, PR, SD, or non-CR/non-PD

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Treatment-emergent AEs (any causality)

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

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

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

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

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Immune-related AEs

	Avelumab + BSC (N=344)	
	Any grade	**Grade 3**
Any irAE, %	**29.4**	**7.0**
Hypothyroidism	10.2	0.3
Rash	4.9	0.3
Hyperthyroidism	4.7	0
Rash maculopapular	2.3	0.3
Pruritis	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

irAEs were identified according to a prespecified case definition
ALT, alanine aminotransferase; **AST**, aspartate aminotransferase; **irAE,** immune-related adverse event

- No grade 4/5 irAEs occurred
- High-dose corticosteroids (≥40 mg total daily prednisone or equivalent) were administered following irAE in 9.0% of avelumab-treated patients

Table shows irAEs of any grade occurring in ≥1% or grade ≥3 irAEs occurring in ≥0.5% in either arm

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Conclusions

- JAVELIN Bladder 100 met its primary endpoint by showing significantly longer OS with avelumab 1st-line maintenance vs control, both in the overall population and PD-L1+ population
- OS was longer with avelumab vs control across all prespecified subgroups
  - Includes subgroups defined by cisplatin-based or carboplatin-based chemotherapy, or response or SD with 1st-line induction chemotherapy
- The safety profile of avelumab as 1st-line maintenance was manageable and consistent with previous studies of avelumab monotherapy[1]
- Avelumab 1st-line maintenance in patients whose disease has not progressed with platinum-based induction chemotherapy represents a new 1st-line standard of care for advanced UC

1. Kelly K, et al. Cancer. 2018;124:2010-17.

Javelin 100 - Key points:

Paradigm shift for clinical practice in advanced UC
Relatively large OS effect: 7 months
    Selected population
Lesser used IO agent
    2 weekly
    Infusion reactions

Urothelial cancer immunotherapy: where to in 2020?

- **Platinum is still king; Cisplatin may be king of kings**
- **Immunotherapy is useful as**
- **salvage and maintenance after platinum**
- **in some instances as an alternative**
  - **PD-L1 marker is useful in this setting but we need further follow up**

- **UC is not Lung Cancer: Is IO + concurrent chemotherapy a viable first line option?**

- **nmInvasive, Neoadjuvant and Adjuvant settings will be explored.**
  - **Accelerated approval for Pembrolizumab in BCG refractory carcinoma in situ**

Regarding first line combinations of ICI with other agents in urothelial and renal cell cancer, which of the following is does NOT produce a definitive overall survival advantage:

A. Nivolumab + ipilimumab in first line intermediate/poor risk RCC
B. Pembrolizumab + Axitninib in first line intermediate/poor risk RCC
C. Cabozantinib + Nivolumab in first line intermediate/poor risk RCC
D. Switch maintenance Avelumab after platinum based chemotherapy in urothelial cancer
E. ICI combined with platinum based chemotherapy in urothelial cancer