Immunotherapy in Kidney and Bladder Cancers

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Yale Cancer Center
July 19, 2019

Financial disclosures

Advisory Boards: Nektar Therapeutics, Janssen Pharmaceuticals, CRISPR Therapeutics

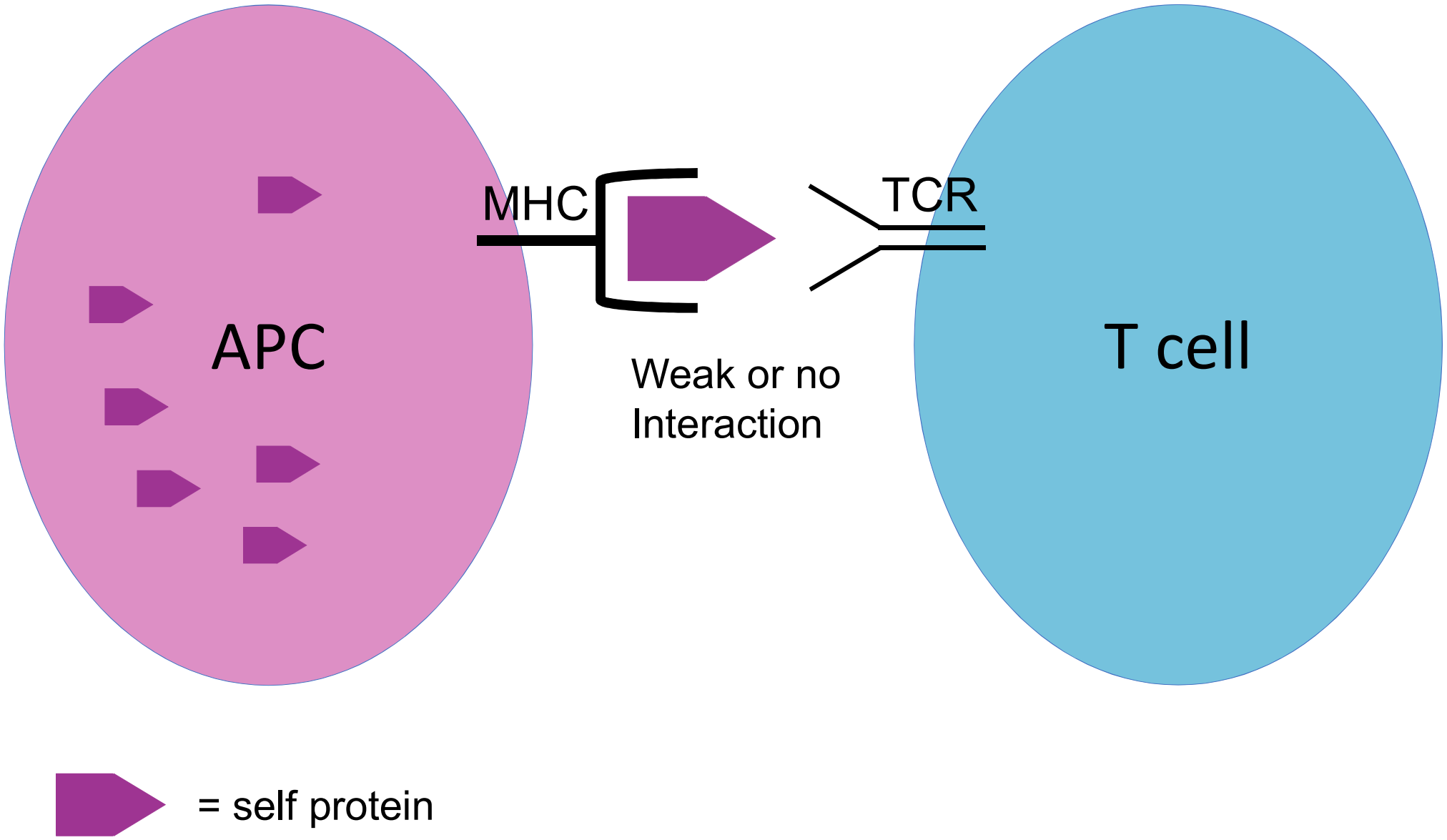
Research: Apexigen, Astellas, AstraZeneca, Bayer, Bristol Myer Squibb, Clovis, Corvus, Eli Lilly, Endocyte, Genentech, Genmab, Innocrin, Iovance, MedImmune, Merck, Nektar Therapeutics, Novartis, Pfizer, Progenics, Roche Laboratories, Sanofi Aventis, Seattle Genetics

Other: Gamida Cell

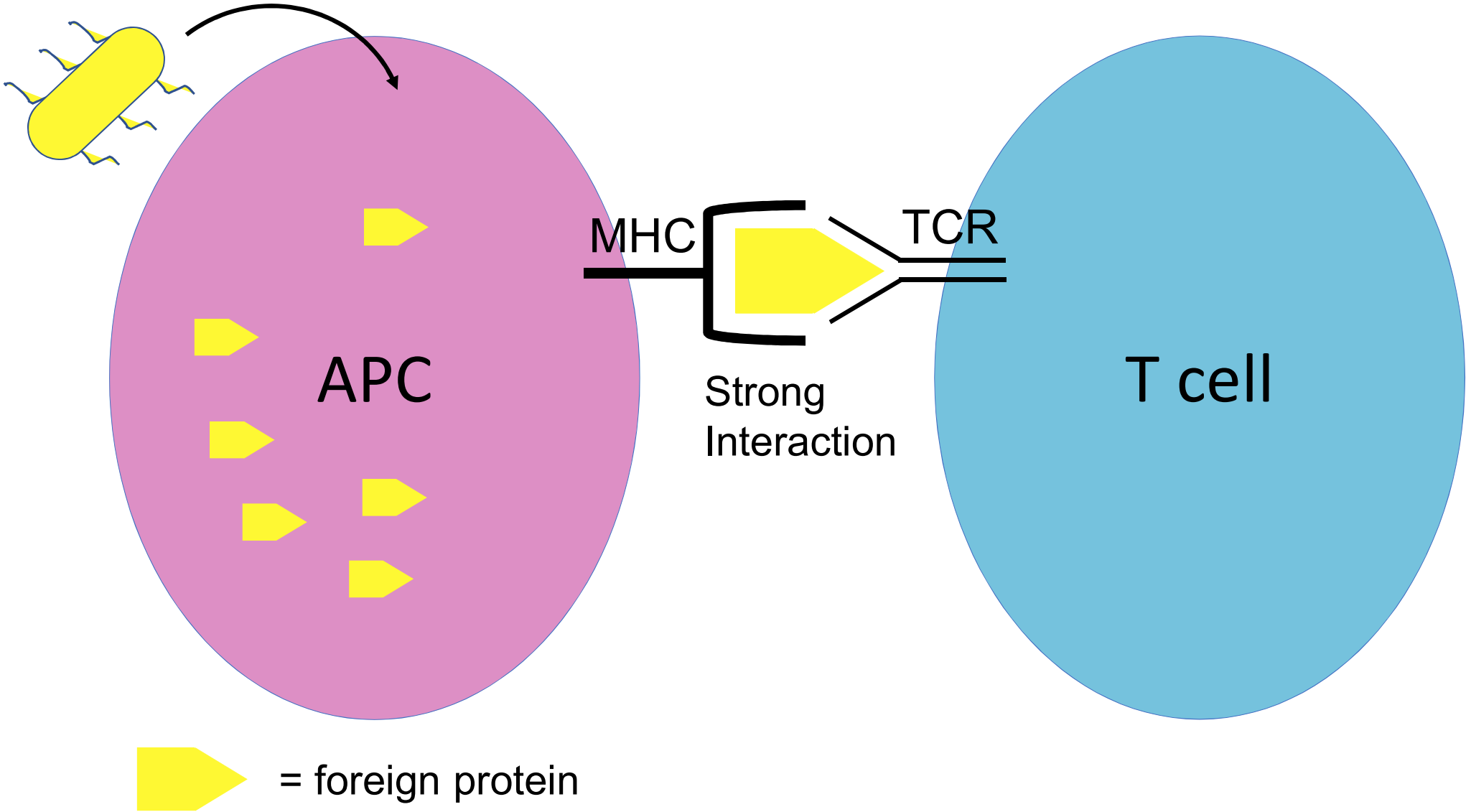
Talk outline

- Immunotherapy basics
- Bladder Cancer
- Kidney Cancer

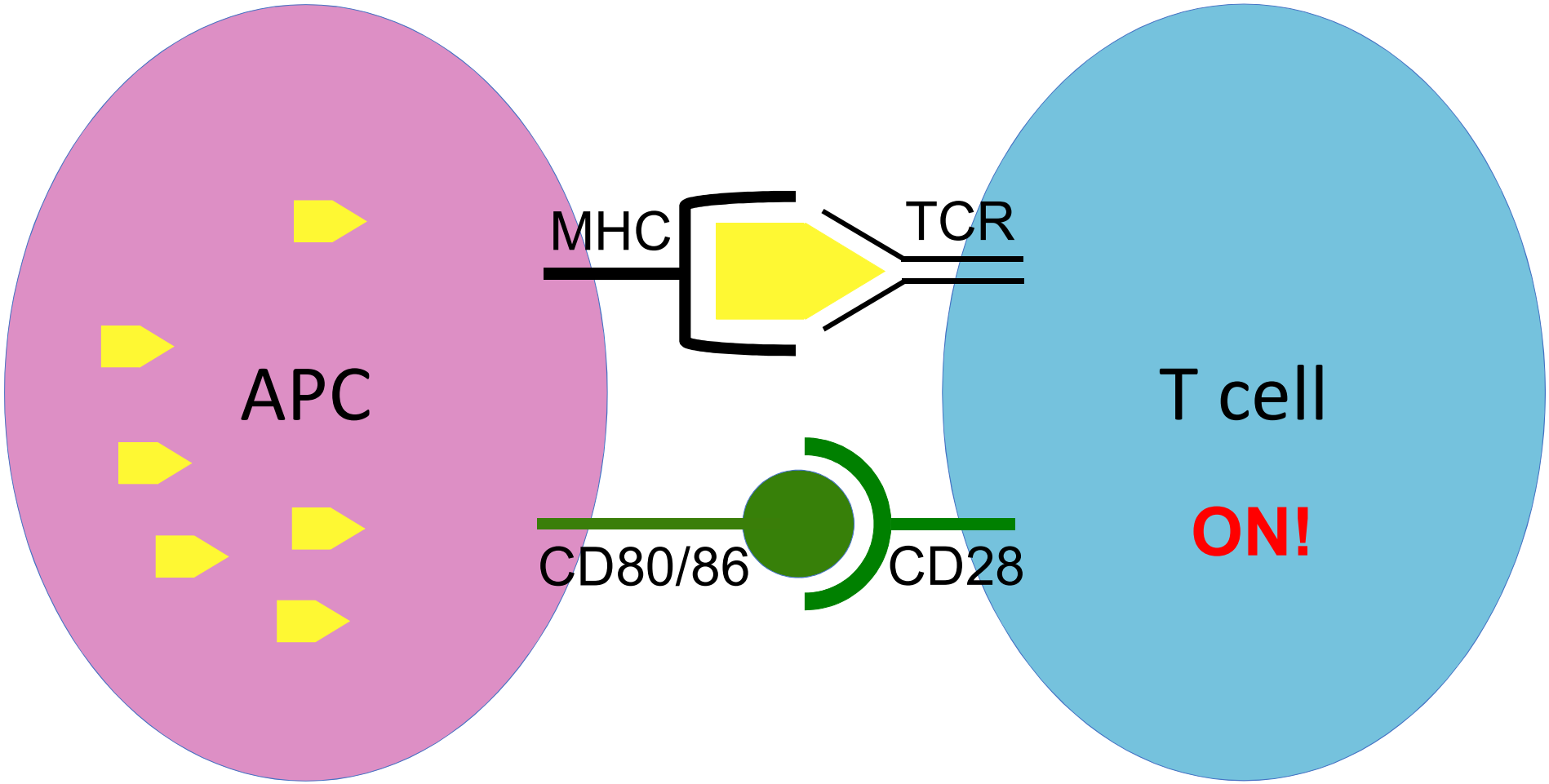
T cell activation: self-recognition



T cell activation: foreign recognition

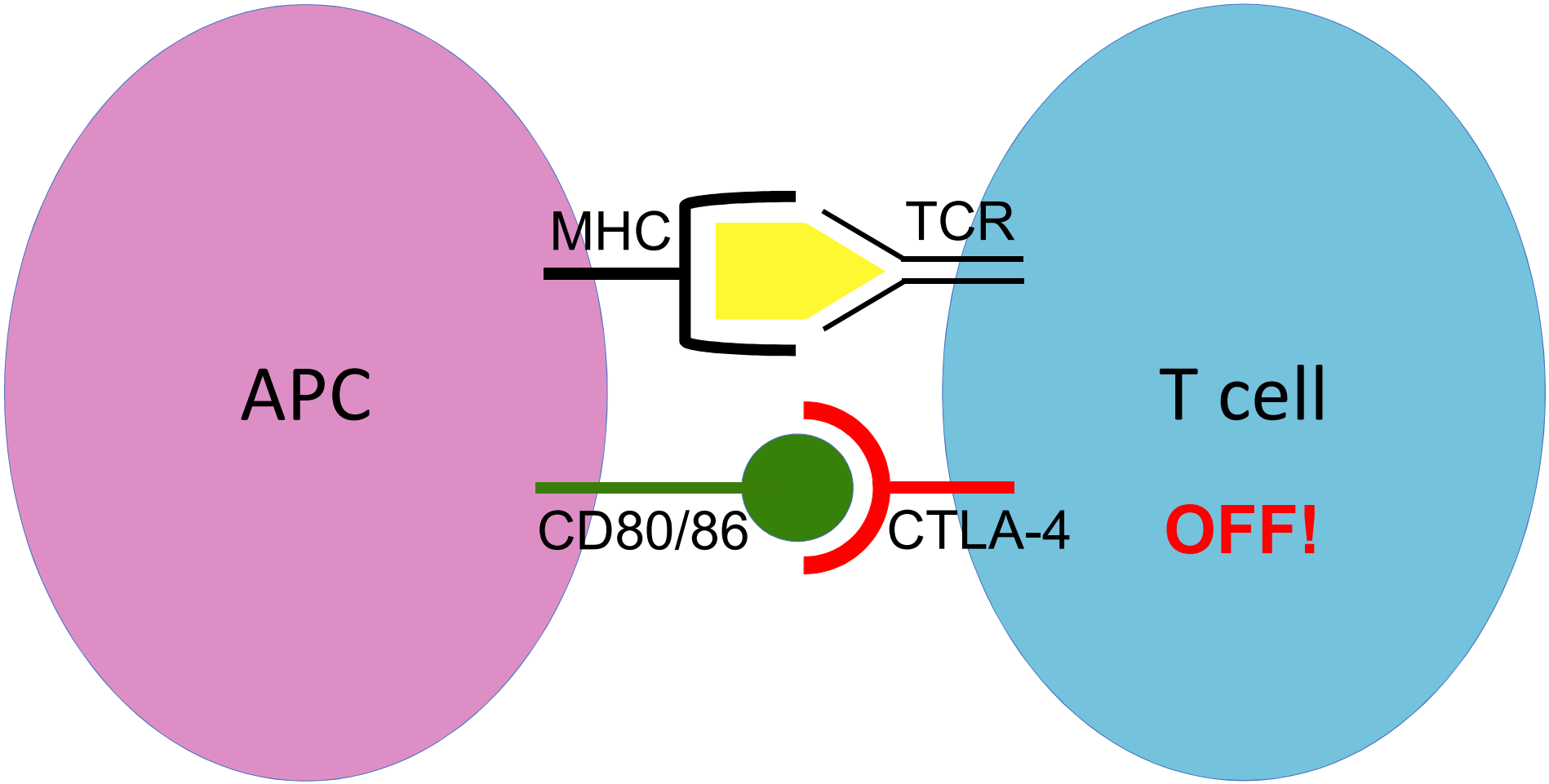


T cell activation: costimulation



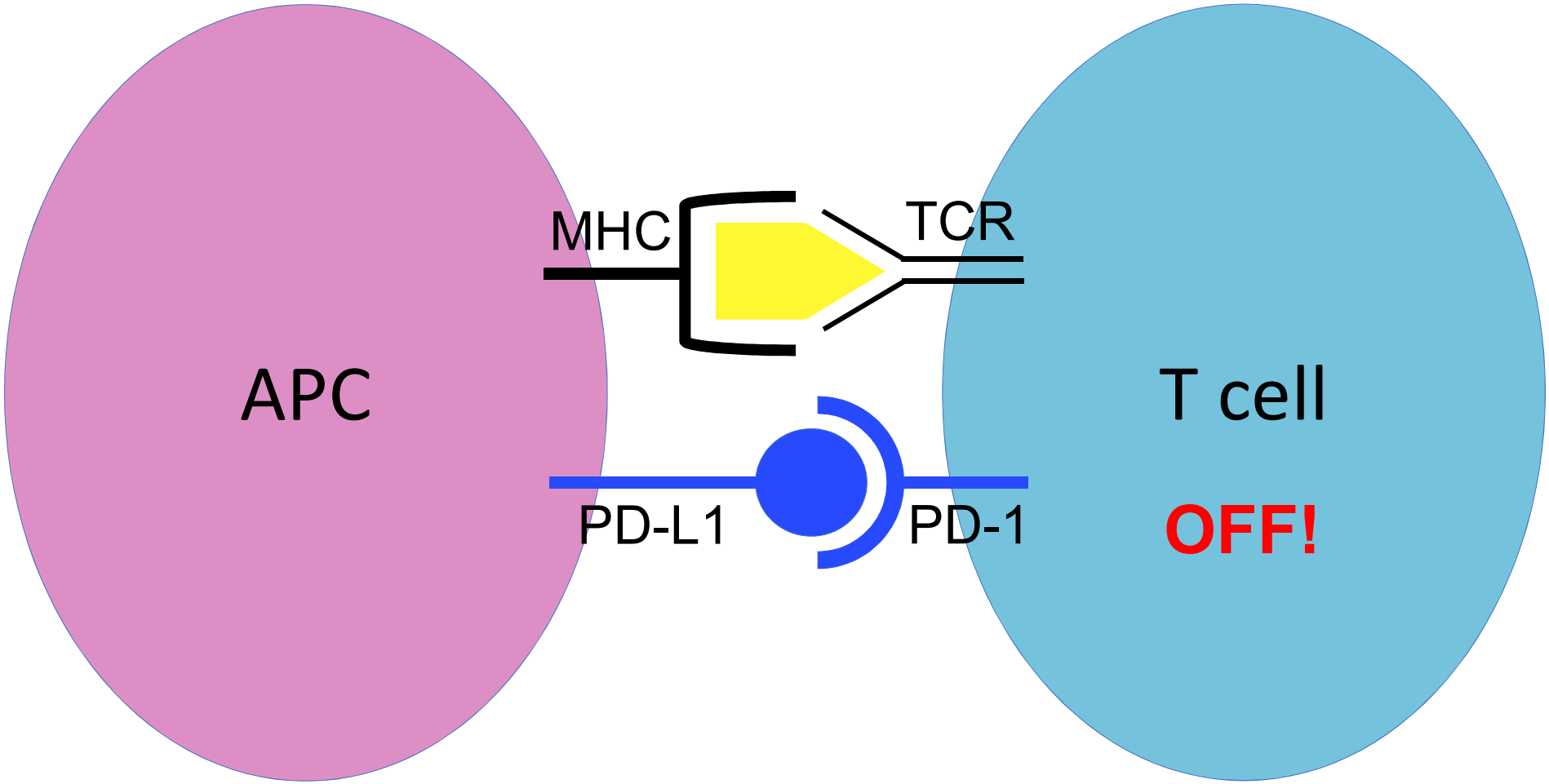
COSTIMULATION!

T cell inhibition: CTLA-4

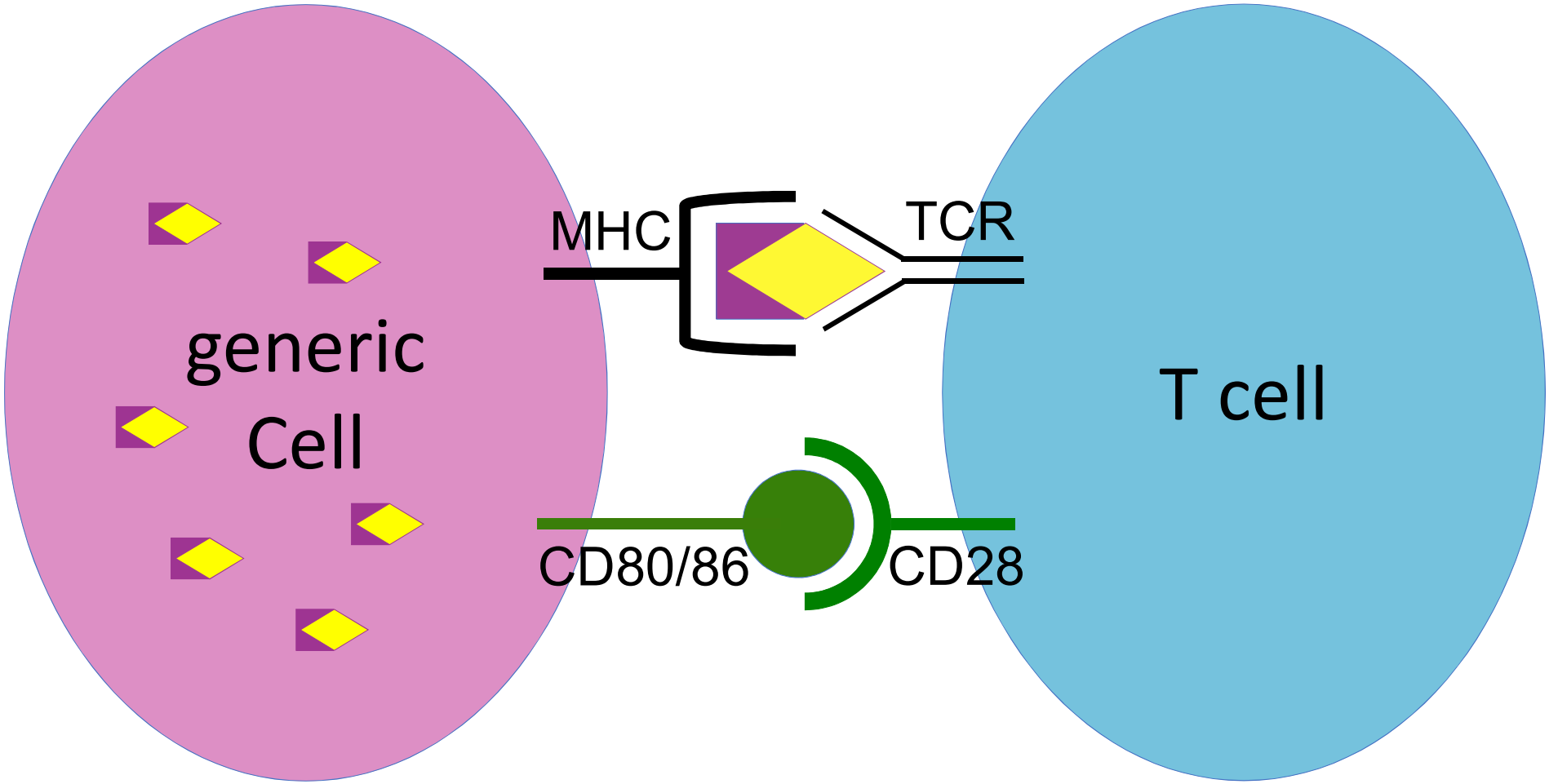


IMMUNE CHECKPOINT!

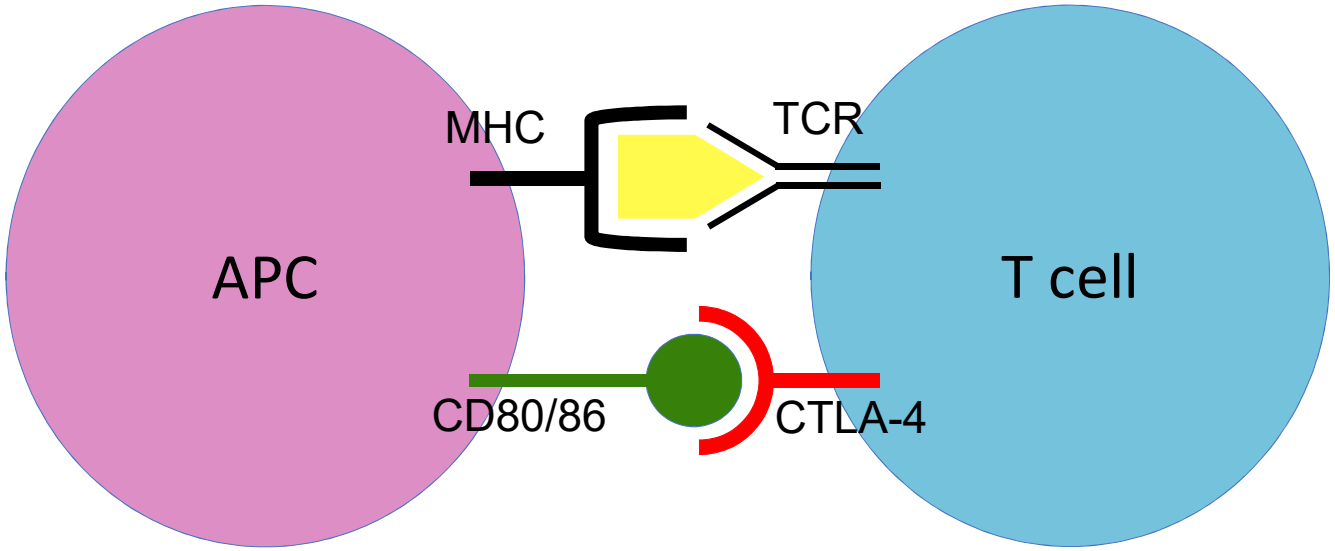
T cell inhibition: PD1 axis



T cell activation: cancer

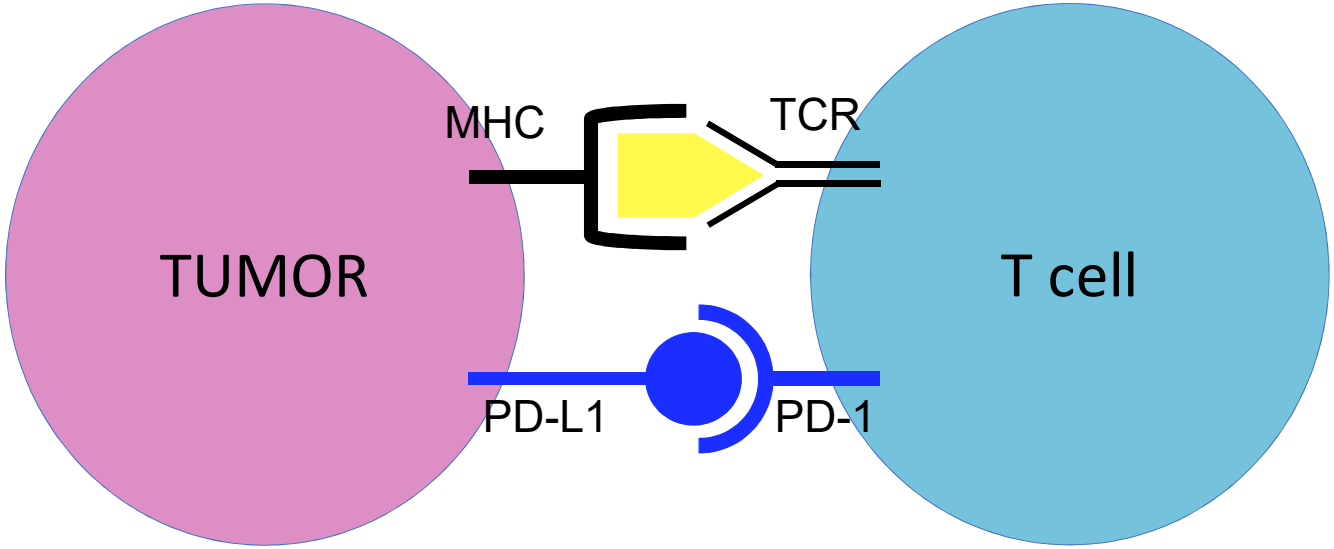


CTLA-4 vs PD-1/PD-L1



BLOCKS: ACTIVATION?

CELL: T_{reg}, T_{eff}



BLOCKS: ACTIVATION/ MAINTENANCE

CELL: T_{eff}

Immune checkpoint inhibitor side effects

System	Symptom/abnormality
General	Fatigue/asthenia
Skin	pruritis
	rash
GI	colitis: diarrhea, GI bleed
	nausea/vomiting
	decreased appetite/dysgeusia
	increased enzymes: LFTs/pancreatic
	Stomatitis/muscosal inflammation
Endocrine	hypothyroidism
	adrenal insufficiency
	type I diabetes mellitus
Cardiac	pericardial inflammation
	myocardial damage
Pulmonary	pneumonitis/fibrosis
Renal	nephritis
Nervous System	guillain-barre-like syndrome
Hematologic	Any lines decreased/aplastic anemia
	hemophagocytic syndrome

- PD1/PDL1 inhibitors alone:
  - 50-60% all grades AEs
  - 10-20% ≥ grade 3
- PD1/CTLA4 combination:
  - >90% all grades Aes
  - 50-70% ≥ grade 3
- Treatment
  - Prednisone 1-2 mg/kg or equivalent with slow taper
  - infliximab (not for liver)
  - MMF
  - IVIg, anti-IL6, etc
  - Endocrinopathies are not reversible
  - Side effects in red have been lethal

Bladder Cancer Treatment Basics

- Localized disease:
  - Non-muscle invasive bladder cancer (NMIBC)
  - Muscle-invasive bladder cancer (MIBC)
- Metastatic disease:
  - 1st line cisplatin eligible (GC or ddMVAC)
  - 1st line cisplatin ineligible (no standard)
  - 2nd line (no standard) or erdafitinib for FGFR mutant/overexpressed

How is immunotherapy used in each of these disease states?

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.

TCC selected single arm studies

Study name	Agent	n	ORR (%)	CR (%)	PFS	med OS	12 mo OS	DCR	DoR - % ongoing	median DoR	median TTR	ORR based on PD-L1 expression	Toxicity (Any Grade)	Toxicity (Grade 3-4)	Ref
JAVELIN	Avelumab	44	18.2	2.3	11.6 wks	13.7 mo	54.3%	52.3%	37% at 14.5 wks	36.4 wk	12 wks	<1% in TC: 4.5% ≥1% in TC: 50%	68%	9.1%	1
IMvigor210 (cohort 1; 1st line platinum ineligible)	Atezolizumab	119	23.0	9.0	2.7 mo	15.9 mo	57.0%	56.0%	75% at 14.4 mo	NR	2.1 mo	IC0: 21% IC1: 23% IC2/3: 28%	66%	15.0%	2
IMvigor210 (cohort 2) Rx beyond -> progresson ->	Atezolizumab	310	16.0	7.0	NR	7.9 mo	37.0%	49.0%	71% at 17.5 mo	NR	2.1 mo	IC0/1: 10% IC2/3: 28%	70%	16.0%	3
		126	19.0			11.4 mo	50%	47.0%							
Study 1108	Durvalumab	42	31.0	4.7	NR	NR	NR	>64%	92.3% at 26 wk	Not reached	~7 wks	TC and IC-: 0% TC and IC+: 46%	64%	5.0%	4
Checkmate 275	Nivolumab	265	19.0	2.0	NR	8.74 mo	NR	61%%	NR	Not reached	1.48 mo	<1%: 16.1% ≥1%: 23.8% ≥5%: 28.4%	63%	18.0%	5
Keynote-052	Pembrolizumab	370	29.0	7.0	NR	NR	52.9%	47.0%	82% at 6 mo	Not reached	2 mo	CPS <10%: 23% CPS ≥10%: 51%	66%	19.0%	6

NR = not reported; TC = PD-L1 expression on tumor cells, IC = PD-L1 expression on immune cells, IC0/1 = low expression by IHC, IC2/3 = high expression by IHC.

- ORR 16-29%
- CR <10%
- DCR 47-61%
- OS 7.9 mo – NR
- Some long durations of response

- Role of PDL1 status complex
- Toxicity
  - 63-70% all grades
  - 5-19% ≥ grade 3
- 19% ORR post progression (Imvigor210)

1. Apolo et al, JCO 2017 2. Balar et al, Lancet 2017 3. Rosenberg et al, Lancet 2016 4. Massard et al, JCO 2016 5. Sharma et al, Lancet Onc 2017 6. O'Donnell et al, ASCO 2017

PD-1/PD-L1 Inhibitors for NMIBC: Selected Trials

Trial ID	Phase	Regimen	Population
NCT02844816 (SWOG 1605)	II	Atezolizumab IV Infusion	BCG-resistant
NCT02625961 (Keynote 057)	II	Pembrolizumab IV Infusion	BCG-resistant
NCT02901548	II	Durvalumab IV Infusion	BCG-resistant CIS
NCT03317158 (ADAPT-Bladder)	I/II	Durvalumab IV Infusion Durvalumab + BCG Durvalumab + XRT	BCG-resistant
NCT03106610	I	Nivolumab IV Infusion	BCG-resistant
NCT02792192	I	Atezolizumab +/- BCG	BCG-naïve (or resistant)
Pending	I/II	Durvalumab + BCG	BCG-naive

KEYNOTE-057 Phase 2 Trial of Pembrolizumab for Patients With High-Risk Non–Muscle-Invasive Bladder Cancer Unresponsive to Bacillus Calmette-Guérin: Updated Interim Results

A. V. Balar[1]; G. S. Kulkarni[2]; E. Uchio[3]; J. L. Boormans[4]; L. Mourey[5]; L. Krieger[6]; E. A. Singer[7]; D. Bajorin[8]; A. Kamat[9]; P. Grivas[10]; H. K. Seo[11]; H. Nishiyama[12]; B. Konety[13]; K. Nam[14]; E. Kapadia[14]; T. Frenkl[14]; R. de Wit[4]

[1]Perlmutter Cancer Center at NYU Langone Health, New York, NY, USA; [2]UHN Princess Margaret Cancer Center, University of Toronto, Toronto, ON, Canada; [3]UC Irvine Health, Orange, CA, USA; [4]Erasmus University Medical Center, Rotterdam, Netherlands; [5]Institut Universitaire du Cancer Toulouse Oncopole, Toulouse, France; [6]Royal North Shore Hospital, Northern Cancer Institute, St Leonards, NSW, Australia; [7]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; [8]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [9]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [10]University of Washington, Seattle, WA, USA; [11]National Cancer Center, Goyang, Republic of Korea; [12]University of Tsukuba, Tsukuba, Ibaraki, Japan; [13]University of Minnesota, Minneapolis, MN, USA; [14]Merck & Co., Inc., Kenilworth, NJ, USA

Presented By Arjun Balar at 2019 Genitourinary Cancers Symposium

Keynote-057: Overall Response Rate at month 3

Response	Total Population (N = 102)		
	n	%	95% CI
CR	**41**	**40.2**	**30.6-50.4**
Non-CR	57	55.9	45.7-65.7
Persistent[b]	41	40.2	30.6-50.4
Recurrent[c]	6	5.9	2.2-12.4
NMIBC stage progression[d]	9	8.8	4.1-16.1
Non-bladder malignancy[e]	1	1.0	0.0-5.3
Progression to T2	0	0	NA-NA
Nonevaluable[f]	4	3.9	1.1-9.7

[a]Summary of overall responses of HR NMIBC per central assessment at month 3 in all patients who received ≥1 dose of trial treatment, had baseline evaluations, and also had ≥1 postbaseline disease assessment. [b]Defined as patients with CIS at baseline who at month 3 also had CIS ± papillary tumor. [c]Defined as pathologically confirmed appearance of papillary tumor (high-grade Ta or T1) without CIS at month 3.[d]Increase in stage from CIS and/or high-grade Ta at baseline to T1 disease. [e]Defined as presence of lesions suspicious for locally advanced or metastatic bladder cancer on imaging. Patient developed new liver lesions, as seen on imaging, and was later found to have a second primary malignancy of pancreatic cancer. Subsequent review of the baseline scan showed subtle findings that, in retrospect, could be attributed to pancreatic cancer. [f]Patients whose protocol-specified efficacy assessments were missing or who discontinued from the trial for reasons other than progressive disease were considered not evaluable for efficacy.
Database cutoff: September 14, 2018.

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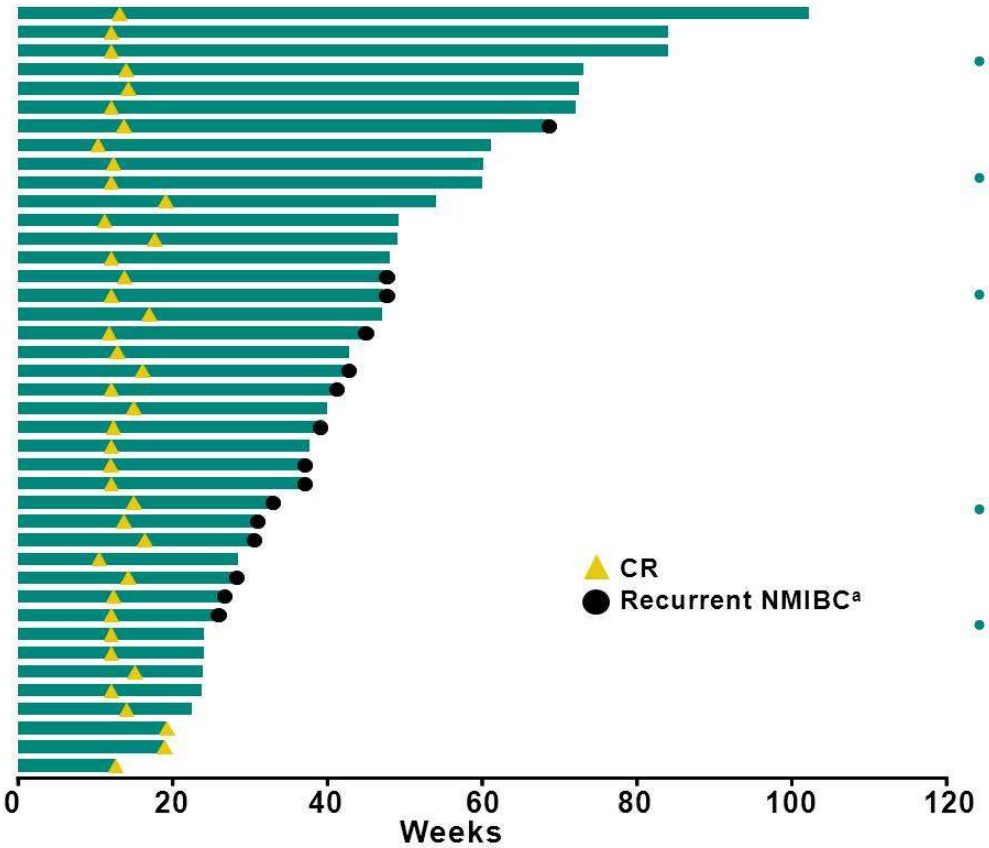
Keynote-057: time to response and recurrence

Time to CR and Development of Recurrent HR NMIBC



- Median follow-up for those in CR, 16.7 months (range, 5.9-28.2 months)
- 24 (58.5%) of complete responders had an ongoing response at time of data cutoff[b]
- 1 patient not represented in this figure was nonevaluable at week 12 but subsequently had confirmed CR beginning at week 24, with >12 months durability
- 15 (36.6%) of CRs subsequently experienced recurrent NMIBC after CR
- No patient developed muscle-invasive or metastatic disease

[a]Reappearance of HR NMIBC (CIS and/or high-grade Ta and/or T1 disease) after a disease-free interval (at each month or afterward). [b]One patient had ≥2 non-evaluable assessments. This patient discontinued after week 12 (censored at week 12) because of ongoing AEs and therefore did not complete the subsequent required efficacy assessments. Another patient with locally assessed CR underwent cystectomy. Database cutoff: September 14, 2018.

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Adjuvant PD-1/PD-L1 inhibitor phase III trials

Neo-adjuvant

	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

Adjuvant

Population	Control Arm	Experimental Arm	Primary Endpoint
Prior NAC- ≥pT2, no AC ≥pT3	No therapy	Atezolizumab	PFS
Prior NAC- ≥pT2, no AC ≥pT3	Placebo	Nivolumab	PFS
Prior NAC- ≥pT2, no AC ≥pT3	No therapy	Pembrolizumab	PFS/OS

PI: Apolo; SWOG PI: Sonpavde; ECOG PI: Srinivas.

First line chemotherapy + checkpoint therapy trials

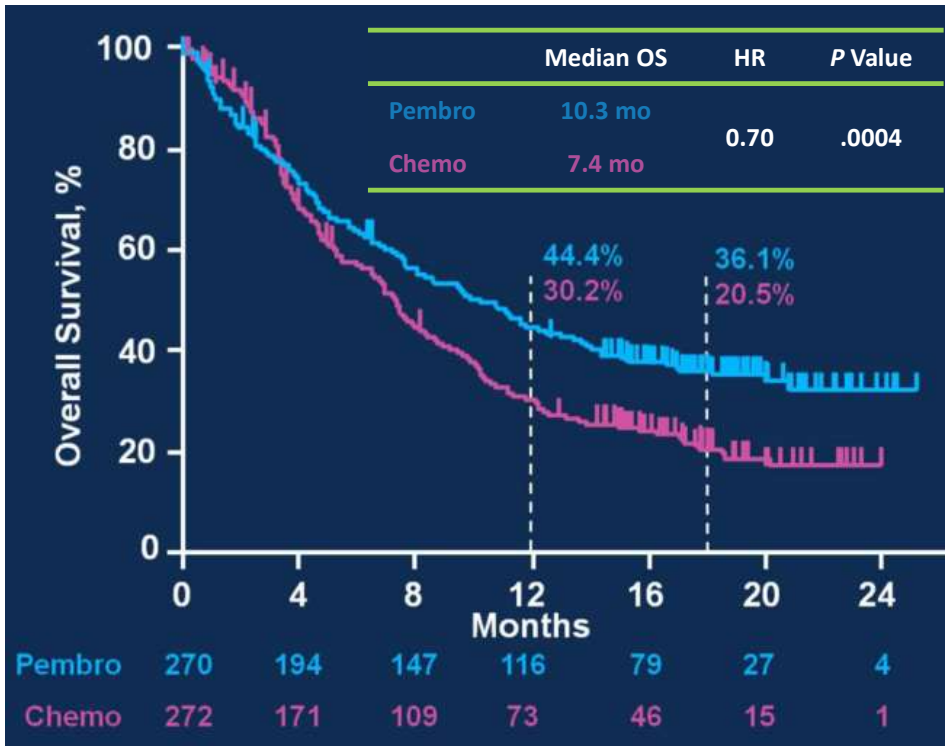
CT ID	Phase	Target	Experimental Arm(s)	Standard Arm
NCT02807636 IMvigor130	III	PD-L1	Atezo OR Atezo + Gem-Plat	Placebo + Gem-Plat
NCT02853305 KEYNOTE-361	III	PD-1	Pembro OR Pembro + Gem-Plat	Gem-Plat
NCT02516241 DANUBE	III	PD-L1 +/- CTLA-4	Durvalumab OR Durva + Treme	Gem-Plat
NCT03036098 CM-901	III	PD-1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

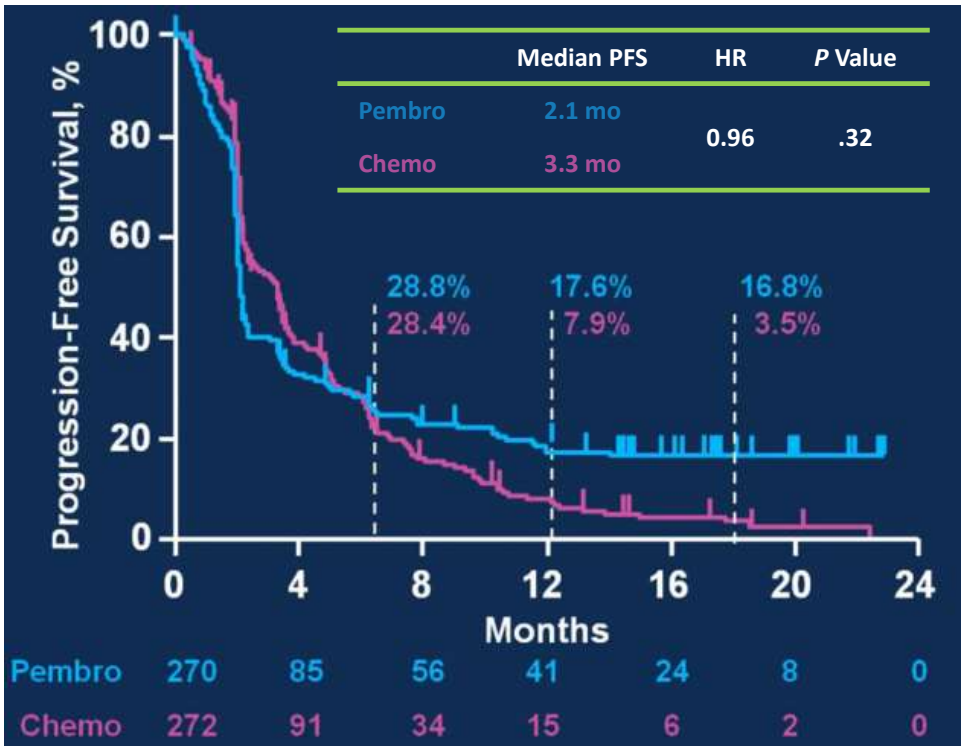
*This trial includes a substudy for cisplatin-eligible patients comparing gemcitabine + cisplatin +/- nivolumab.

Keynote-045 (n = 542): Randomized phase III post cisplatin

Arm	ORR (%)	PFS (mo)	1 yr PFS (%)	OS (mo)	1 yr OS (%)	DoR (mo)	All gr AEs (%)	Gr 3 AE (%)
Pembrolizumab	21.1	2.1	16.8	10.3	43.9	Not Reached	60.9	15
Chemotherapy	11.4	3.3	6.2	7.4	30.7	4.3	90.2	49

Chemotherapy = single agent therapies - docetaxel, paclitaxel or vinflunine





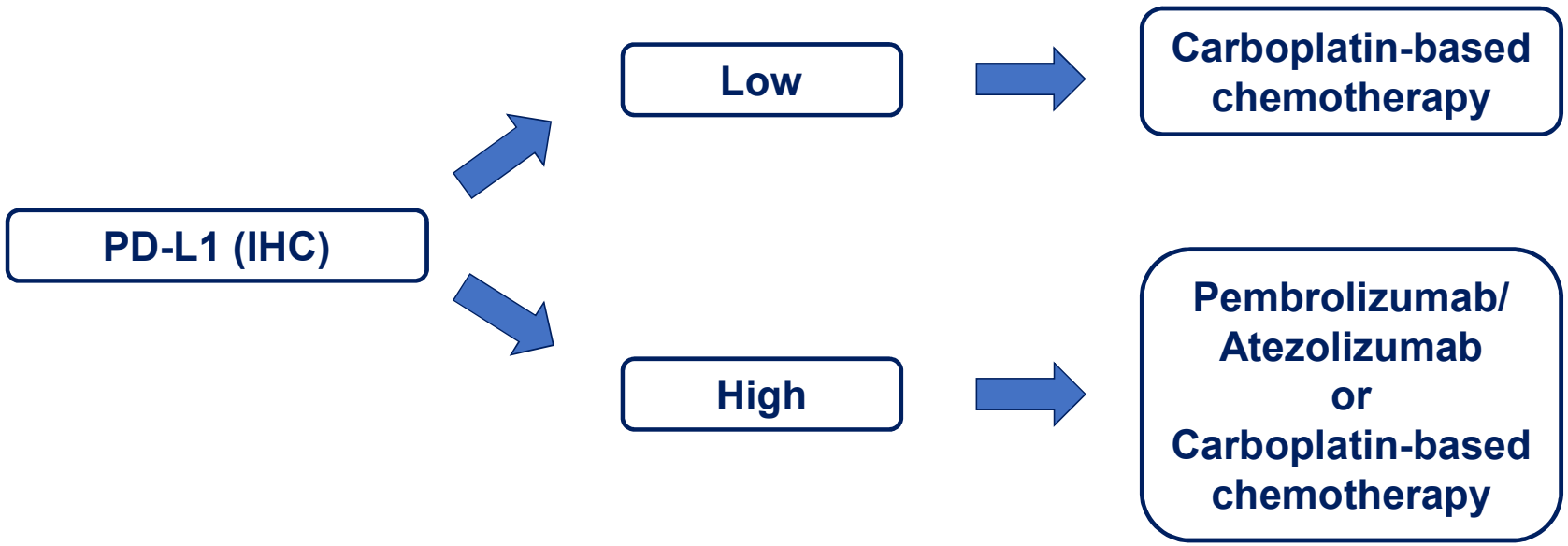
Bellmunt et al, NEJM 2017

PD-L1 expression to select therapy in cis-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.



For cis-ineligible: carbo/gem or PD-1/PD-L1 inhibitor?

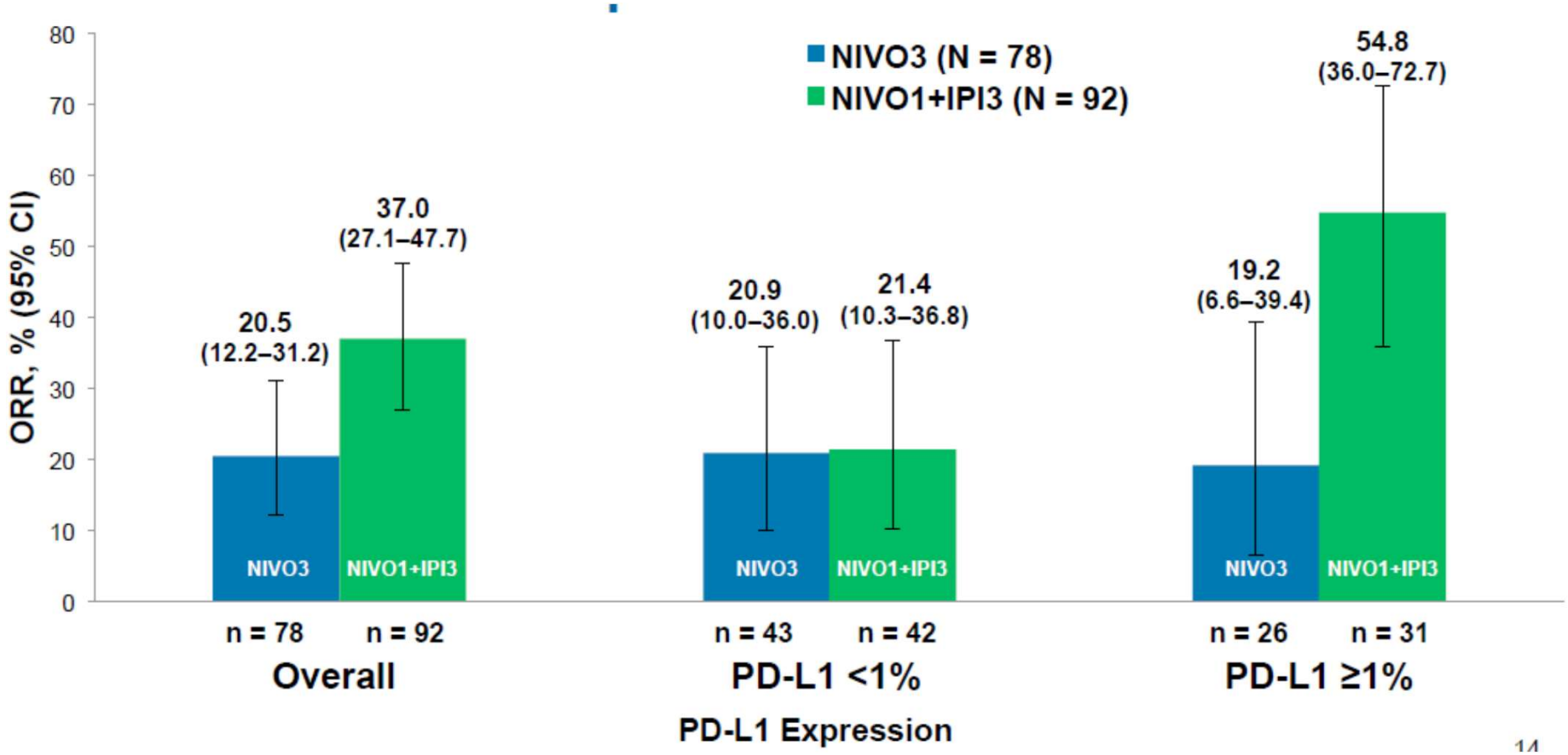
	Gem-Carbo (Ph III)[1]	Atezolizumab (Ph II)[2]	Pembrolizumab (Ph II)[3]
Number of patients	119	119	370
% with PS 2	44.5%	20%	42%
% CrCl <60 mL/min	55.5%[a]	70%	49%
% PS 2 + CrCl <60 mL/min	26.9%[a]	7%	9%
ORR	41.2% ✓	23%	24%
Median PFS	5.8 mo ✓	2.7 mo	2 mo; 3 mo on therapy
Median OS	9.3 mo	15.9 mo ✓	Not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

Checkmate 032: nivolumab vs ipilimumab/nivolumab

Arm	ORR	PFS	OS
Nivolumab 3 mg/kg	26%	2.8 mo	9.9 mo
Nivo 1 mg/kg and Ipi 3 mg/kg	27%	2.6 mo	7.4 mo
Nivo 3 mg/kg and Ipi 1 mg/kg	38%	4.9 mo	15.3 mo



Randomized double-blind phase II study of maintenance pembrolizumab versus placebo after first-line chemotherapy in patients with metastatic urothelial cancer: HCRN GU14-182

Matthew D. Galsky, Sumanta K. Pal, Amir Mortazavi, Matthew I. Milowsky, Saby George, Sumati Gupta, Mark T. Fleming, Long H. Dang, Daniel M. Geynisman, Radhika Walling, Robert S. Alter, Erwin L. Robin, Jue Wang, Shilpa Gupta, David D. Chism, Joel Picus, George Philips, David I. Quinn, Noah M. Hahn, Menggang Yu

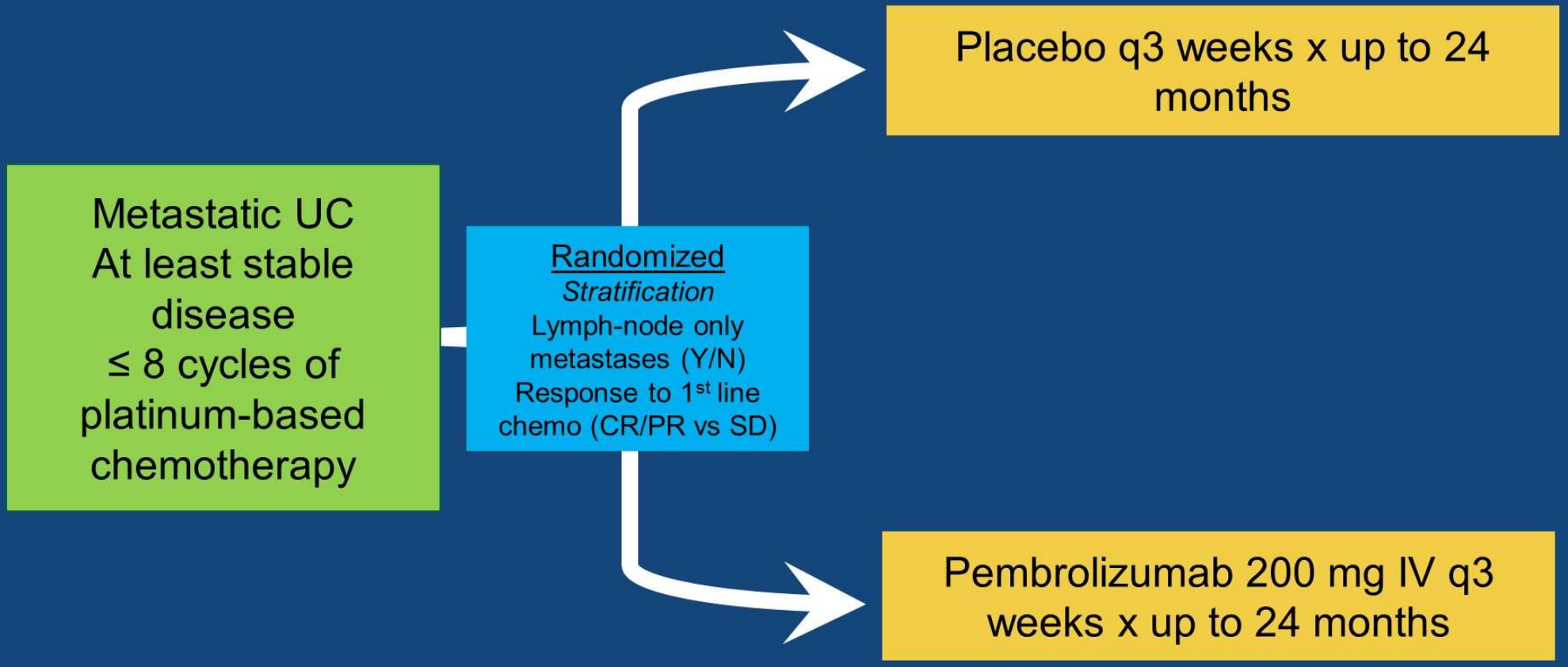
Icahn School of Medicine at Mount Sinai; City of Hope National Medical Center, Duarte, CA; Ohio State University; University of North Carolina at Chapel Hill School of Medicine; Roswell Park Cancer Institute; Huntsman Cancer Institute-University of Utah Health Care; Virginia Oncology Associates; University of Florida; Fox Chase Cancer Center; Community Cancer Center; John Theurer Cancer Center at Hackensack University Medical Center; University of Arizona Cancer Center at Dignity Health St. Joseph's Hospital and Medical Center; Masonic Cancer Center, University of Minnesota; Vanderbilt University Medical Center; Washington University School of Medicine; Georgetown University Hospital; USC Norris Comprehensive Cancer Center; Johns Hopkins University School of Medicine; University of Wisconsin; Hoosier Cancer Research Network

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

PRESENTED BY: Matthew D. Galsky, MD

Presented By Matt Galsky at 2019 ASCO Annual Meeting

HCRN GU14-182



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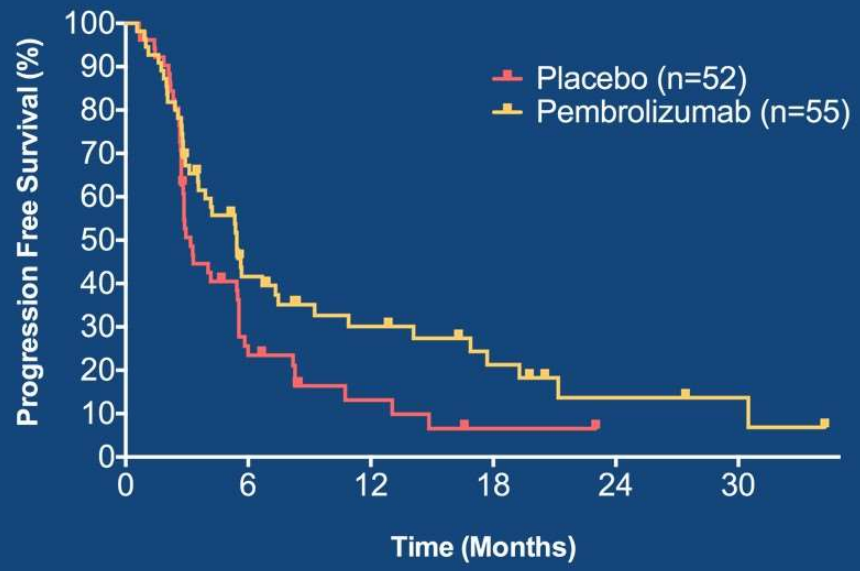
Progression-free Survival



Number at Risk						
Placebo	52	12	4	1	0	0
Pembrolizumab	55	20	12	7	3	2

Median PFS and 95% CI
Placebo: 3.2 (2.8, 5.5)
Pembrolizumab: 5.4 (3.6, 9.2)

Hazard Ratio: 0.64 (0.41, 0.98)

Log rank $p = 0.038$

EV-201: Results of Enfortumab Vedotin Monotherapy for Locally Advanced or Metastatic Urothelial Cancer Previously Treated with Platinum and Immune Checkpoint Inhibitors (NCT03219333)

Daniel P. Petrylak, Arjun V. Balar, Peter H. O'Donnell, Bradley A. McGregor, Elisabeth I. Heath, Evan Y. Yu, Matthew D. Galsky, Noah M. Hahn, Elaina M. Gartner, Juan M. Pinelli, Shang-Ying Liang, Amal Melhem-Bertrandt, and Jonathan E. Rosenberg

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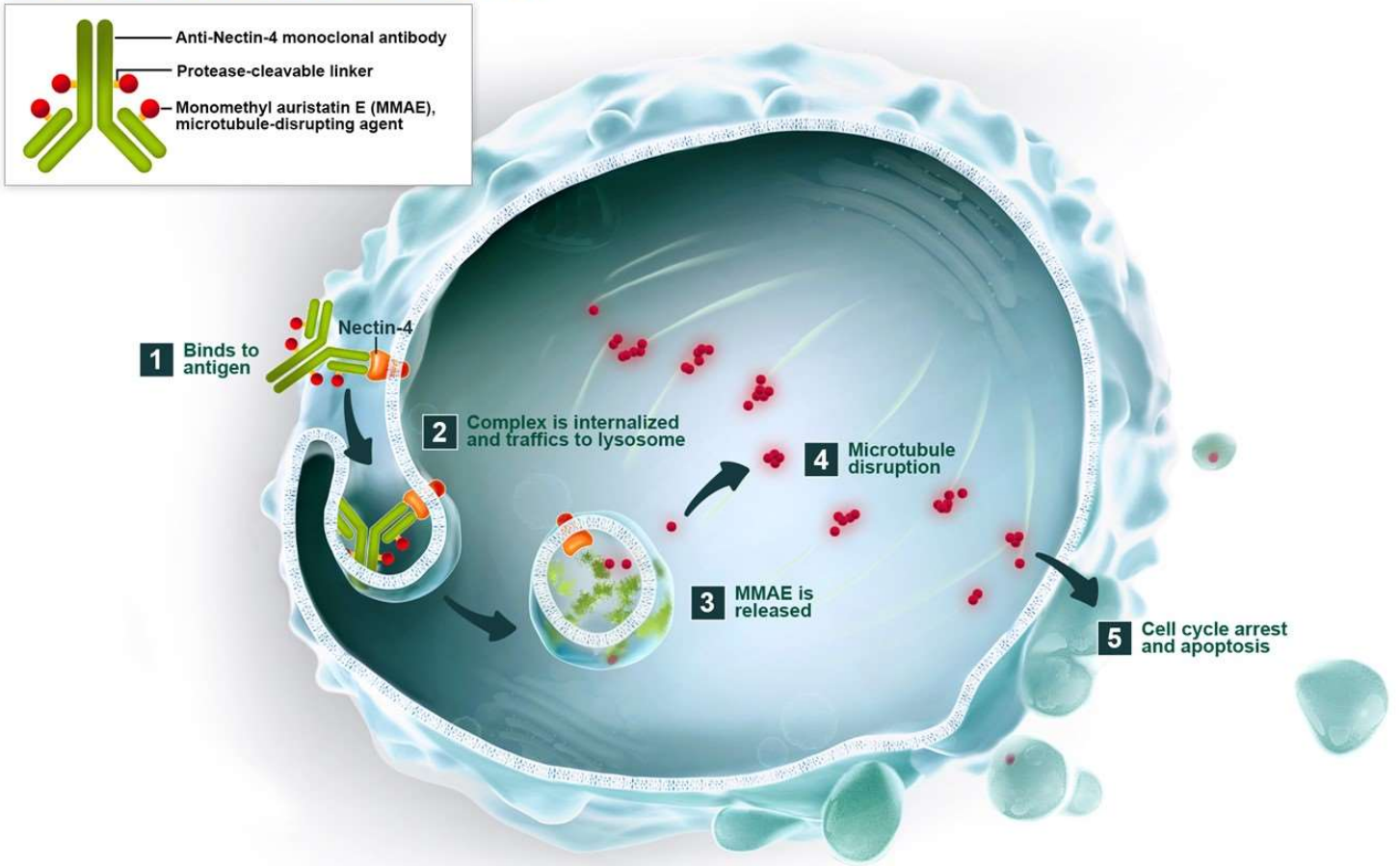
Enfortumab Vedotin: Nectin-4 Targeted Therapy

Proposed Mechanism of Action



Enfortumab vedotin (ASG-22ME) is an investigational agent, and its safety and efficacy have not been established.
Enfortumab vedotin is being developed in collaboration with Astellas Pharma Inc.

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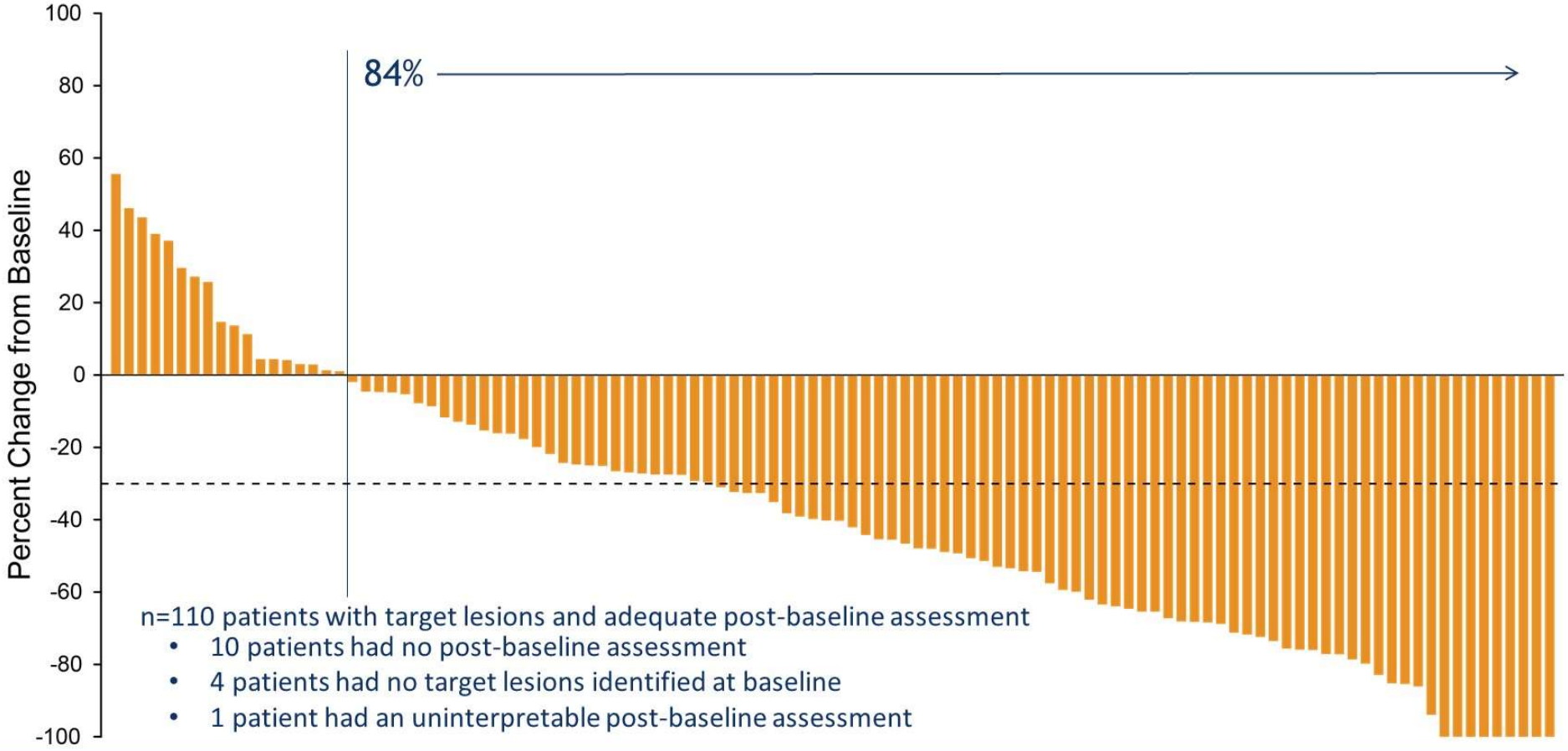
EV-201: Cohort 1 Change in Tumor Measurements per BICR



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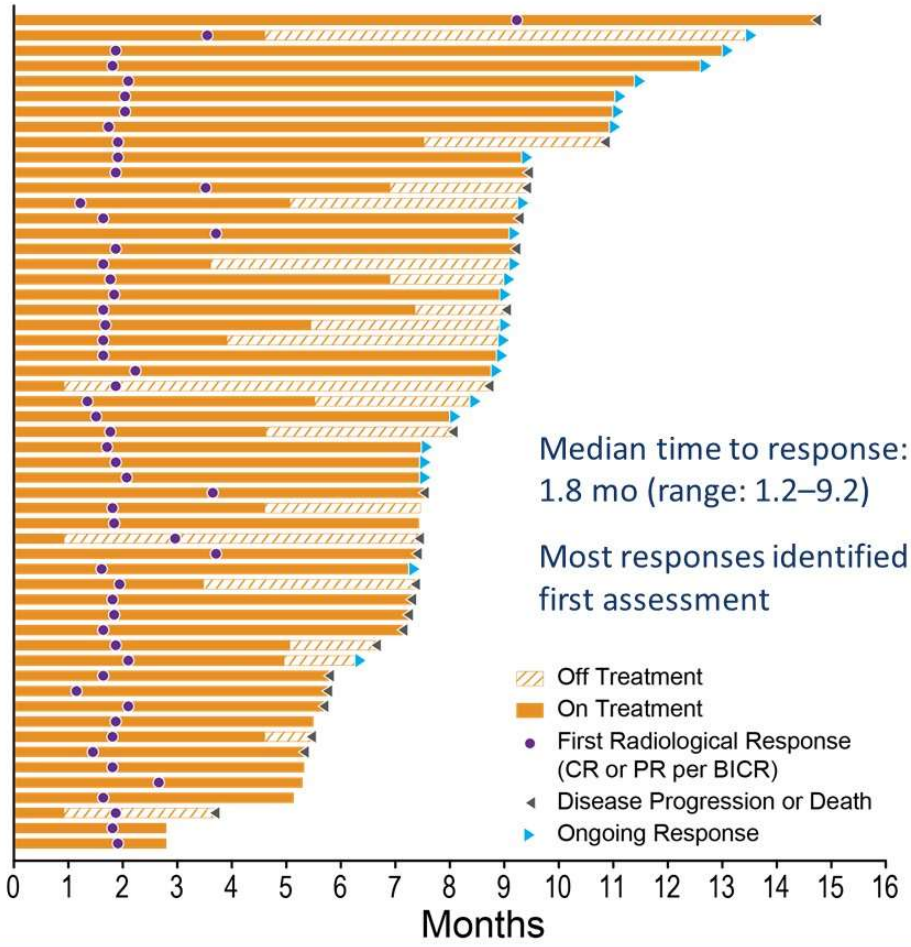
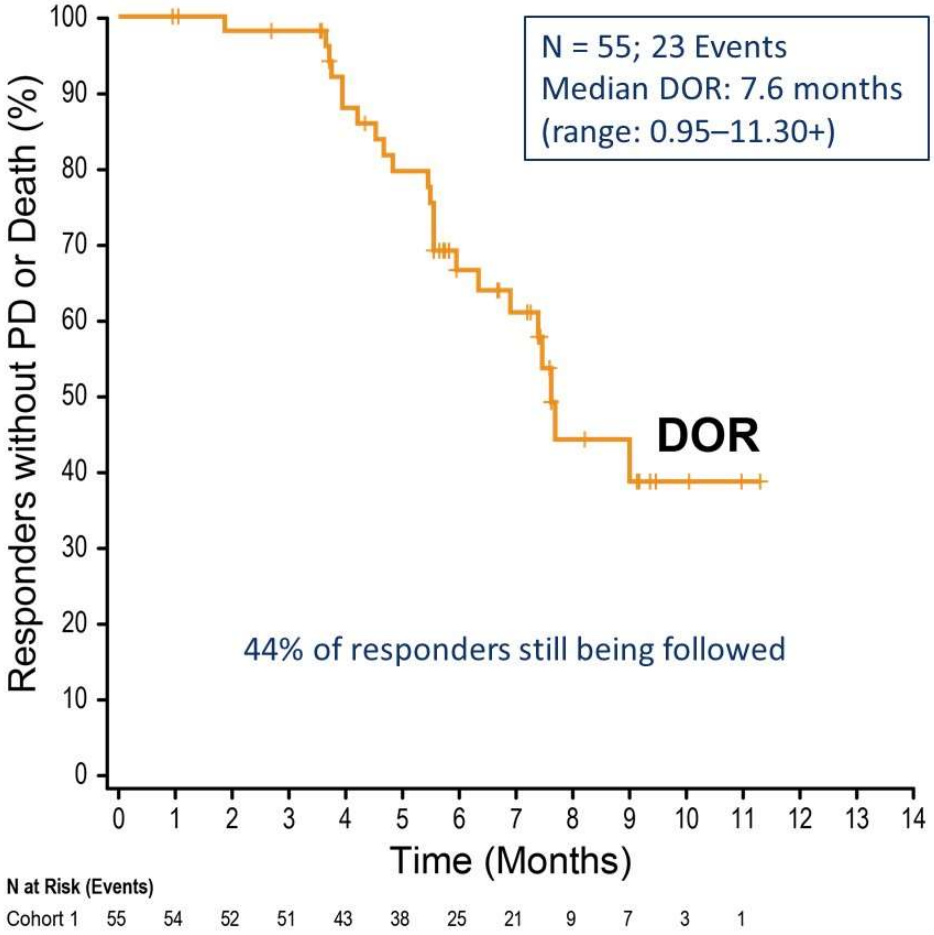
EV-201: Cohort 1 Duration of Response with Enfortumab Vedotin





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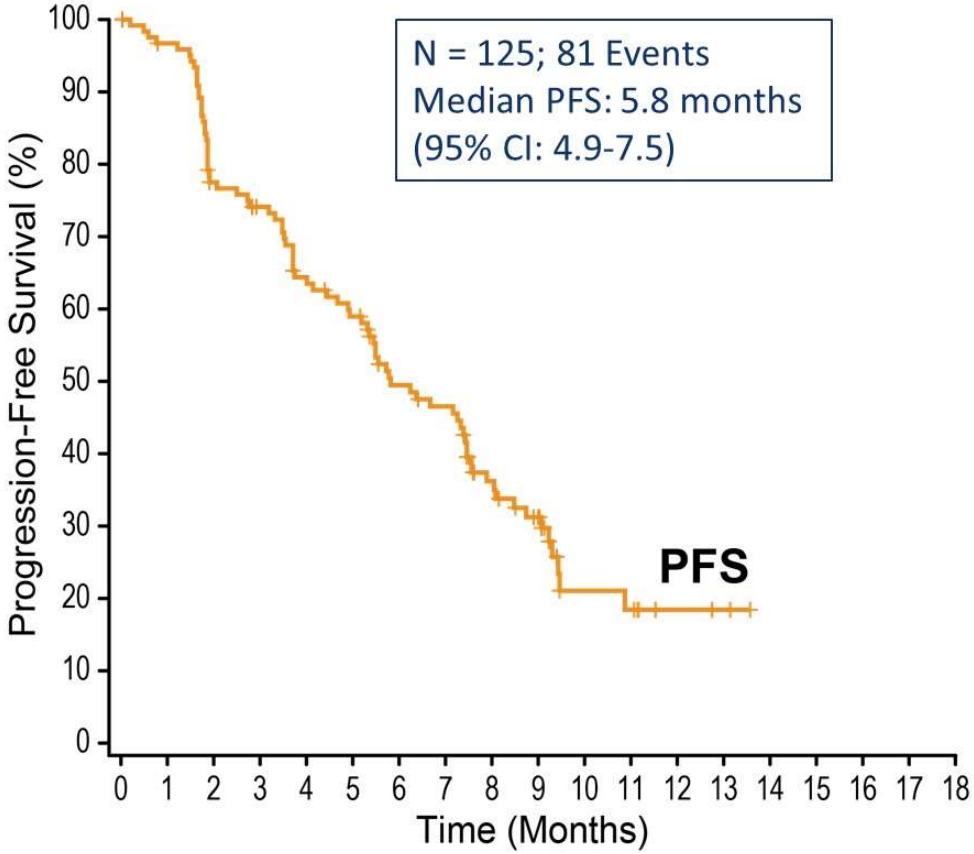
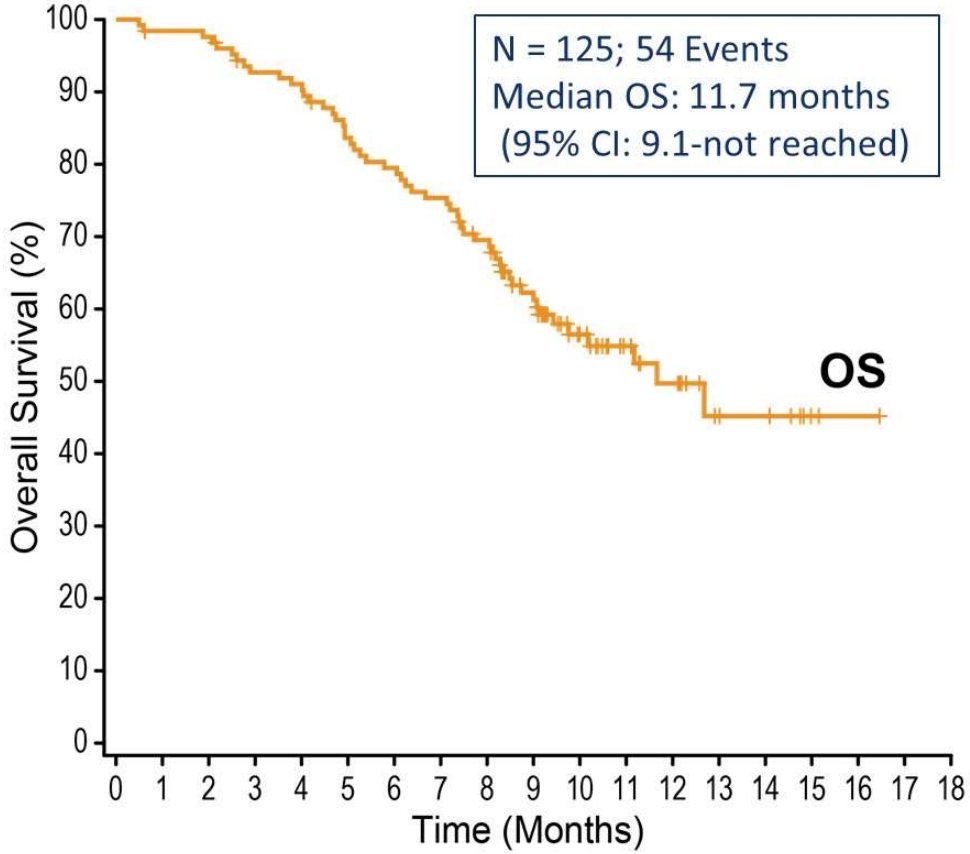
EV-201: Cohort 1 Kaplan-Meier Estimates of Survival



N at Risk (Events)

Cohort 1	125	116	91	84	72	65	51	47	30	22	8	7	3	2



N at Risk (Events)

Cohort 1	125	122	121	113	111	101	96	91	82	61	36	24	18	9	8	2	1

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EV-201: Cohort 1 Treatment-Related Adverse Events

Treatment-related AEs by preferred term in ≥20% of patients (any Grade) or ≥5% (≥Grade 3)	Patients (N=125) n (%)	
	Any Grade	≥Grade 3
Fatigue	62 (50)	7 (6)
Alopecia	61 (49)	–
Decreased appetite	55 (44)	1 (1)
Dysgeusia	50 (40)	–
Peripheral sensory neuropathy	50 (40)	2 (2)
Nausea	49 (39)	3 (2)
Diarrhea	40 (32)	3 (2)
Dry skin	28 (22)	0
Weight decreased	28 (22)	1 (1)
Rash maculo-papular	27 (22)	5 (4)
Anemia	22 (18)	9 (7)
Neutropenia	13 (10)	10 (8)

- Treatment-related AEs led to few discontinuations (12%)
  - Peripheral sensory neuropathy was the most common (6%)
- 1 treatment-related death reported by the investigator
  - Interstitial lung disease
  - Confounded by high-dose corticosteroid use and suspected *pneumocystis jiroveci* pneumonia

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Sequencing therapies in bladder cancer

for Cisplatin-Eligible Patients:

for Cisplatin-Ineligible Patients:

or

For PD-L1+ cisplatin-ineligible patients, choice is comorbidity/patient choice-directed (no validated biomarkers)

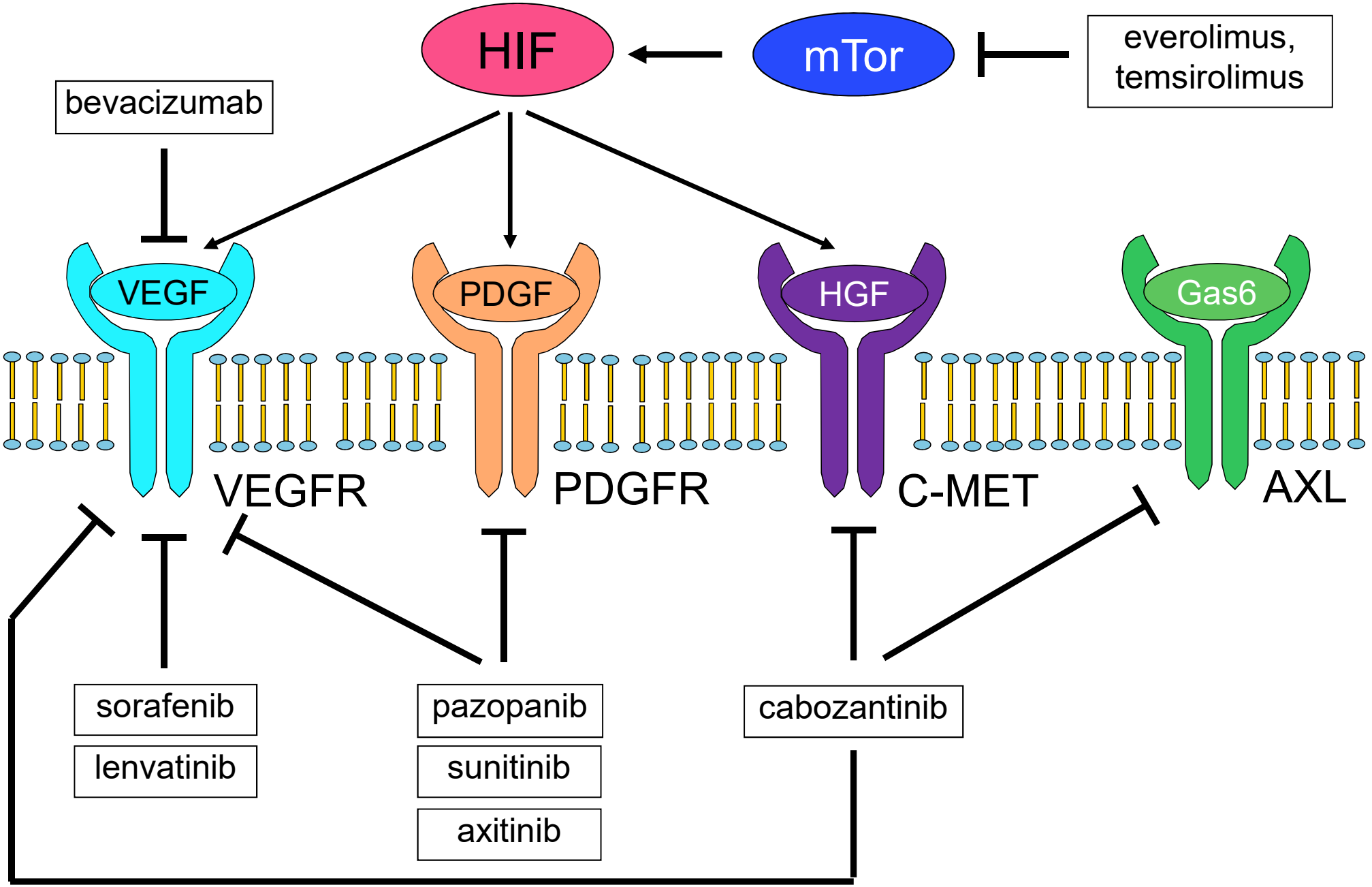
Kidney Cancer Treatment Basics

- Localized disease:
  - Nephrectomy (partial or radical)

- Metastatic disease:
  - Cytoreductive nephrectomy?
  - Systemic therapies
  - Clear cell vs non-clear cell

How is immunotherapy used in each of these disease states?

Signaling pathways and inhibitors in RCC



Adjuvant therapy

RCC Adjuvant Trials

Clinical Trial	Study Intervention	Duration (years)	N	Clear Cell	Patient Population	Primary Endpoint	Time	Stratification during Study	Imaging	NCT Identifier
ASSURE	Sunitinib vs. sorafenib vs. placebo	1	1943	Or nccRCC	pT1b (G3–4), pT2-4, pN+	DFS	Apr 2006-Sep 2010	Histology, Surgery, ECOG PS, Risk	q4.5mo x 1 yr, then q6mo x 2 yr, then q12mo	NCT00326898
S-TRAC	Sunitinib vs. placebo	1	615	Only	pT3-4, pN+	DFS	Jul 2007-Nov 2015	UISS Risk, ECOG PS, Country of residence	q3mo x 3 yr, then q6mo	NCT00375674
ARISER	Girentuximab vs. placebo	0.5	864	Only	pT1b-2 (G3-4), pT3-4, pN+	DFS + OS	Jun 2004-Apr 2013	UISS Risk, Region of the world	q3mo x 2 yr, then q6mo x 2 yr, then q12mo	NCT00087022
PROTECT	Pazopanib vs. placebo	1	1540	Only	pT2 (G3–4), pT3-4, pN+	DFS	Nov 2010-Oct 2015	Surgery, Risk	~q4mo x 1 yr, then q6mo x 4 yr, then q12mo	NCT01235962
EVEREST	Everolimus vs. placebo	1	1545	Or nccRCC	pT1b (G3–4), pT2-4, pN+	DFS	Apr 2011-Oct 2021	Histology, ECOG PS, Risk	q4mo x 1yr,then q6mo x 2yr,then q12mo	NCT01120249
SORCE	Sorafenib (1 vs 3 y) vs. placebo	1	1656	Or nccRCC	Intermediate- or high-risk RCC (Leibovich score, 3–11)	DFS	Jun 2007-Aug 2012	Yes (factors N/A)	q6mo x 3 yr	NCT00492258
ATLAS	Axitinib vs. placebo	3	700	Only	pT2-4, pN+	DFS	Apr 2012-Jun 2017	N/A	N/A	NCT01599754
IMmotion 010	Atezolizumab vs. placebo	1	664	Or sarcomatoid dedifferentiation	pT2 (G3-4), pT3a (G4), pT3b-4, pN+, NED after mets surgery	DFS	Jan 2017-Jun 2024	Risk, Region of the world, PD-L1 IHC	q3mo x 3 yr, then q6mo	NCT03024996
PROSPER	Nivolumab (neoadj+adj) vs. observation	0.8	766	Or nccRCC	cT2-4, cN+	RFS	Feb 2017-July 2022	Histology, cT, cN	q4.5mo twice, then q6mo x 1 yr, then q12mo	NCT03055013

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Adjuvant Therapy of Renal Cell Carcinoma: Current Controversies – Presented by: Jose A. Karam, MD, FACS

- Only positive study is S-TRAC and only for PFS (not for OS): 6.8 vs 5.6 mo
- Ongoing adjuvant trials with immunotherapy

Ravaud et al, NEJM 2016

Cytoreductive nephrectomy

Treatment	n	Response Rate	Overall Survival	Ref
IFN alfa-2B IFN alfa-2B + nephrectomy	85	12% 19%	7 mo 17 mo	1
IFN alfa-2B IFN alfa-2B + nephrectomy	120	3.6% 3.3%	8.1 mo 11.1 mo	2
IFN alfa-2B IFN alfa-2B + nephrectomy	331	5.7% 6.9%	7.8 mo 13.6 mo	3
IL-2 + nephrectomy (retrospective)	89		16.7 mo	4
Sunitinib Sunitinib + nephrectomy	450	29.1% 27.4%	18.4 mo 13.9 mo	5, 6

- Given newest data, cytoreductive nephrectomy should only be done after multidisciplinary discussion with experienced RCC team
- MD Anderson experience[7]: for ≥4 risk factors, no benefit over systemic therapy alone – albumin <normal, symptoms present, liver mets, RP adenopathy, supradiaphragmatic adenopathy, tumor ≥T3, LDH > normal
- Unclear how this relates to immunotherapy – which is now the standard of care!

1. Mickisch et al, Lancet 2001, 2. Flanigan et al, NEJM 2001, 3. Flanigan et al, J. Urol 2004, 4. Pantuck et al, NEJM 2001, 5. Méjean et al, NEJM 2018, 6. Motzer and Russo, NEJM 2018, 7. Culp et al, Cancer 2010

Systemic therapy

- Cytokines (IL-2, IFNα)
- Tyrosine kinase inhibition (VEGFR and MET)
- mTor inhibition
- Immune checkpoint inhibition
- Chemotherapy: doesn't work (high MDR expression)

Motzer et al, JCO 1995

Risk stratification: MSKCC and IMDC criteria

Risk factors	MSKCC	IMDC
Hgb <normal	+	+
Karnofsky < 80	+	+
Corrected Ca > normal	+	+
Time from dx to rx < 1 yr	+	+
LDH > 1.5x normal	+	-
Neutrophils > normal	-	+
Platelets > normal	-	+

Risk	# of risk factors	Overall survival (med/2 yr)		
		MSKCC (med)	IMDC (med)	IMDC (2 yr)
Favorable	0	30 mo	Not reached	75%
Intermediate	1-2	14 mo	27 mo	53%
Poor	>2	5 mo	8.8 mo	7%

- MSKCC criteria were for cytokine era; IMDC for TKI era
- There are other risk factors: eg bony, liver metastases

Motzer et al, JCO 2002; Heng et al, JCO 2009

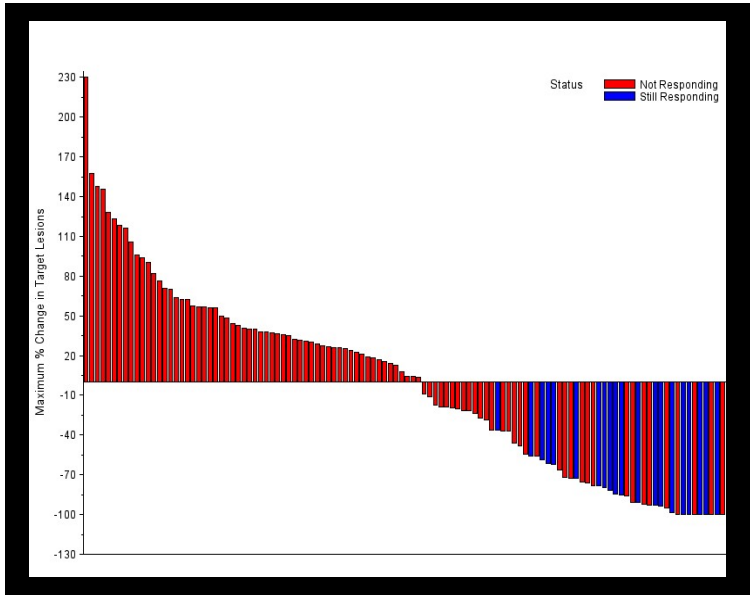
Cytokine therapies: interleukin-2 and interferon alfa-2B

- Both drugs have broadly activating effects on innate and adaptive immunity
- Both drugs cause flu-like syndromes at low doses
- IL-2 has multiple other effects at high doses
- Rarely used anymore

1. Muss et al, JCO 1987; 2. Minasian et al, JCO 1993; 3. Fyfe et al, JCO 1995; 4. Fyfe et al, JCO 1996; 5. Fisher et al, Cancer J Sci Am 1997; 6. Negrier et al, NEJM 1998; 7. MRCRCC, Lancet 1999; 8. Yang et al, JCO 2003; 9. Negrier et al, Cancer 2007 10. McDermott et al, Clin Cancer Res 2015

IL-2 trials

Treatment	n	RR	OS	notes	Ref
High dose IL-2	255	14%	16.3 mo	4% toxicity-related death Responses at all dz sites	1-3
High dose IL-2 Low dose IL-2 Low dose SQ IL-2	400	21% 13% 10%	No sig diff	Durability of CR responses better w/ HD (p = 0.04)	4
High dose IL-2	120	28%	42.8 mo	7% CR 18% durable responders	5



CWG trial

- 70% MSKCC intermediate risk
- No difference in RR by risk group
- 11% disease free at 3 years

1. Fyfe et al, JCO 1995; 2. Fyfe et al, JCO 1996; 3. Fisher et al, Cancer J Sci Am 1997; 4. Yang et al, JCO 2003; 5. McDermott et al, Clin Cancer Res 2015

IL-2 treatment and toxicity

- Given as inpatient:
  - 600,000 or 720,000 IU/kg over 15 minutes q8h
  - Up to 14 doses, skip doses for tolerance
  - Repeat in 5-9 days
  - New cycle q8-12 weeks
- Highly toxic: should only be given at experienced centers
- Toxicities:
  - Capillary leak syndrome
  - Sepsis
  - Hypotension
  - renal failure
  - Confusion/neurotoxicity
  - Cardiac disease

McDermott et al, Clin Cancer Res 2015

30-Month Follow-Up of the Phase 3 CheckMate 214 Trial of First-Line Nivolumab Plus Ipilimumab or Sunitinib in Patients With Advanced Renal Cell Carcinoma

Nizar M. Tannir,[1] Osvaldo Arén Frontera,[2] Hans J. Hammers,[3] Michael Carducci,[4] David F. McDermott,[5] Pamela Salman,[6] Bernard Escudier,[7] Benoit Beuselinck,[8] Asim Amin,[9] Camillo Porta,[10] Saby George,[11] Sergio Bracarda,[12] Scott S. Tykodi,[13] Thomas Powles,[14] Brian I. Rini,[15] Yoshihiko Tomita,[16] M. Brent McHenry,[17] Sabeen Mekan,[17] Robert J. Motzer[18]

[1]University of Texas MD Anderson Cancer Center, Houston TX, USA; [2]Centro Internacional de Estudios Clínicos, Santiago, Chile; [3]UT Southwestern, Dallas, TX, USA; [4]Johns Hopkins Medicine - The Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA; [5]Beth Israel Deaconess Medical Center, Dana-Farber/Harvard Cancer Center, Boston, MA, USA; [6]Fundación Arturo López Pérez, Santiago, Chile; [7]Gustave Roussy, Villejuif, France; [8]University Hospitals Leuven, Leuven, Belgium; [9]Levine Cancer Institute, Charlotte, NC, USA; [10]University of Pavia, Pavia, Italy; [11]Roswell Park Cancer Institute, Buffalo, NY, USA; [12]Ospedale San Donato, Azienda Ospedaliera S.Maria, Terni, Italy; [13]University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [14]Barts Cancer Institute, London, UK; [15]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA; [16]Niigata University, Niigata, Japan; [17]Bristol-Myers Squibb, Princeton, NJ, USA; [18]Memorial Sloan Kettering Cancer Center, New York, NY, USA

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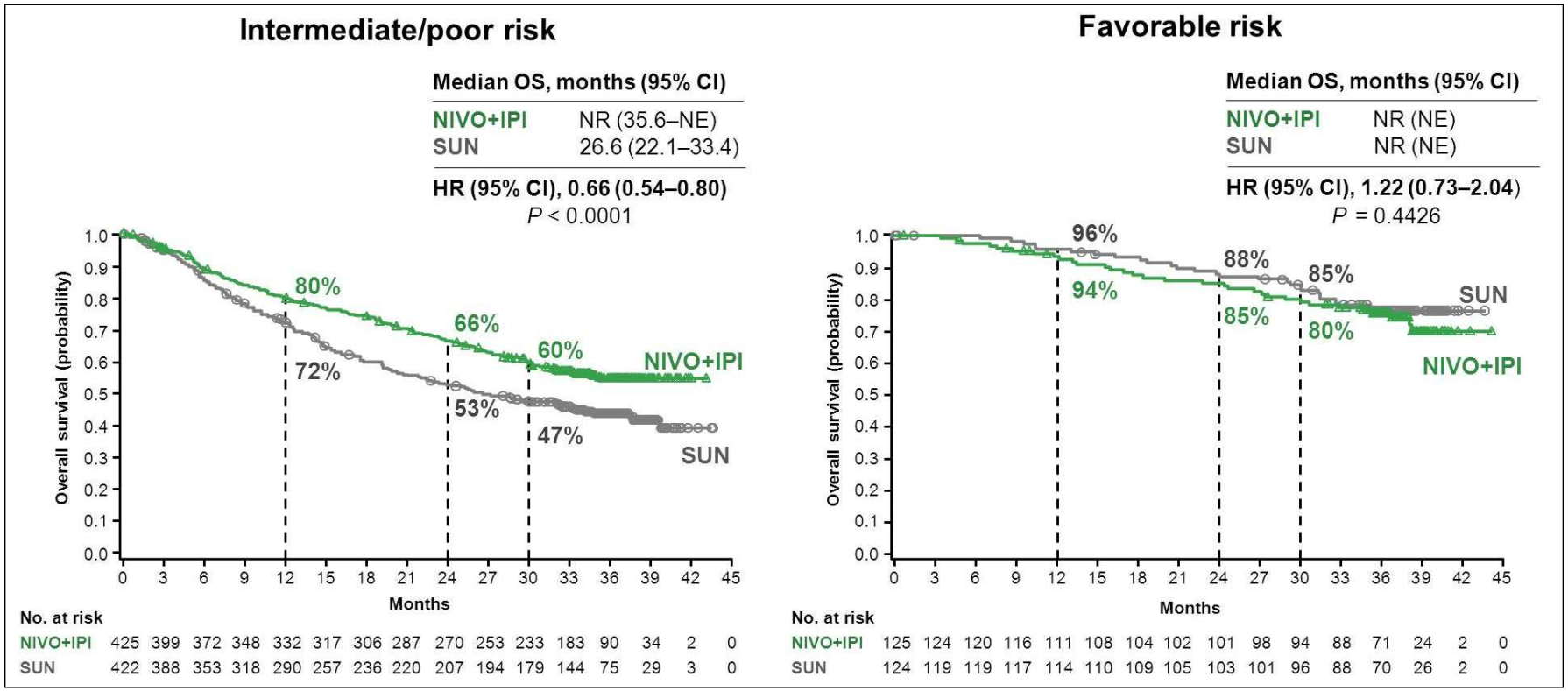
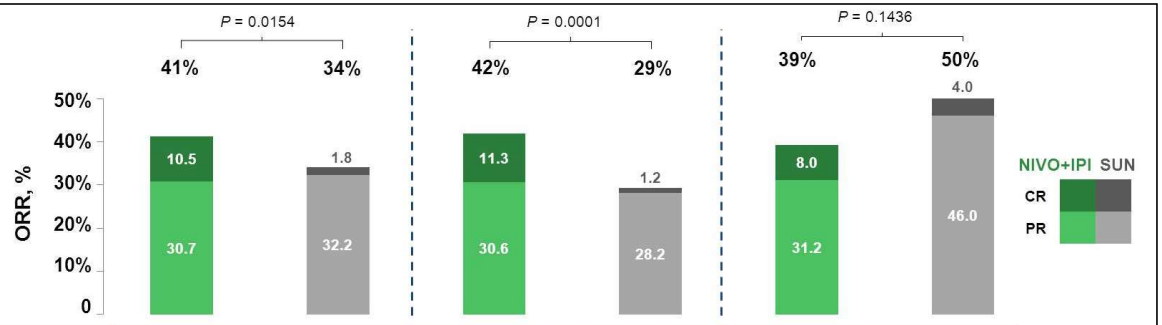
Presented By Nizar Tannir at 2019 Genitourinary Cancers Symposium

Checkmate 214 Overall Survival and Response Rates



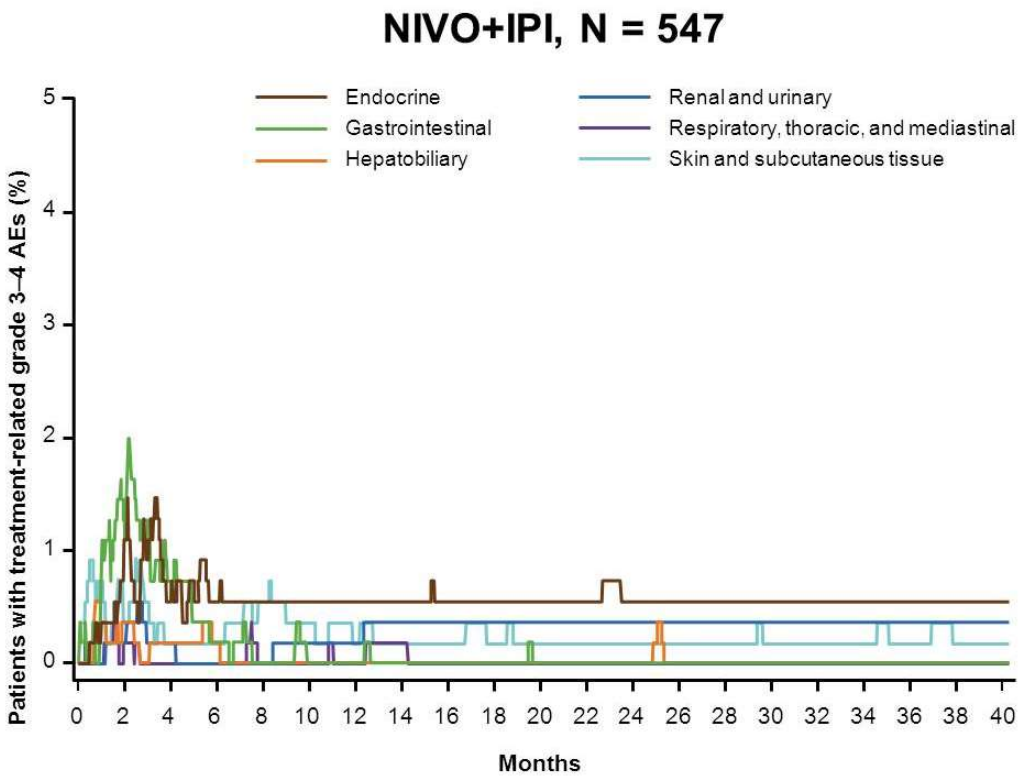


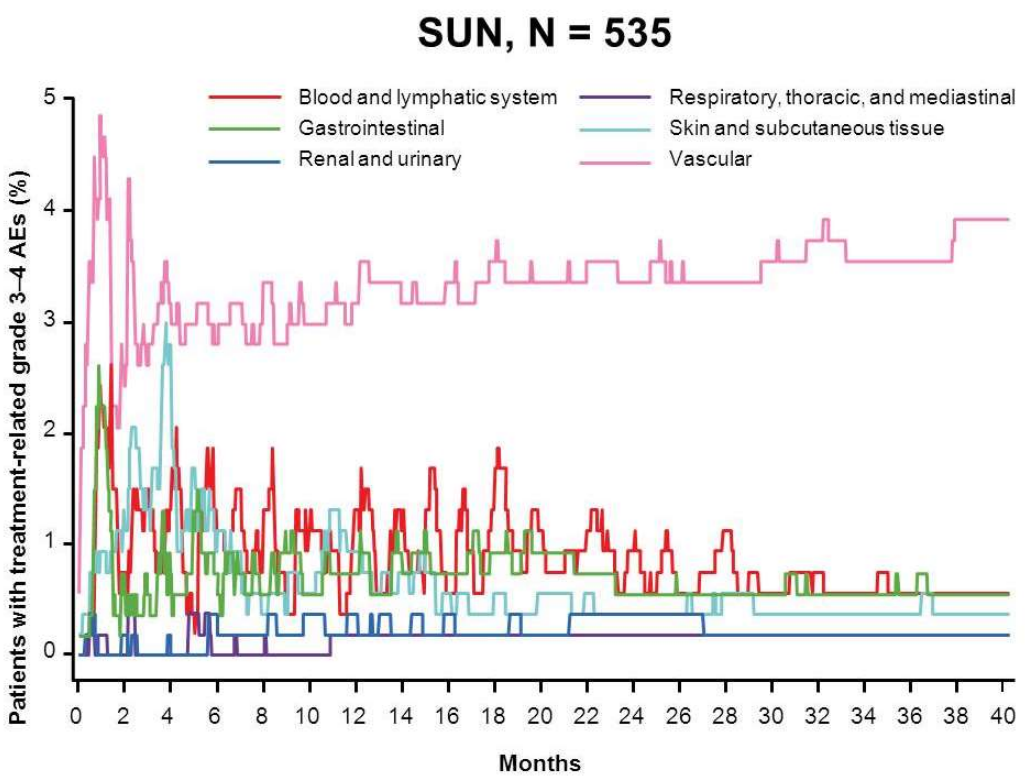
	ITT population		Intermediate/poor risk[1]		Favorable risk	
	NIVO+IPI N = 550	SUN N = 546	NIVO+IPI N = 425	SUN N = 422	NIVO+IPI N = 125	SUN N = 124
DOR ≥18 months, %	53	39	52	28	57	60
Ongoing CR, n/N (%)	51/58 (88)	6/10	42/48 (88)	4/5	9/10	2/5

- Among ITT patients, 185 (34%) versus 114 (21%) achieved ≥50% best tumor burden reduction with NIVO+IPI versus SUN

Tanir et al, GU ASCO 2019

CM214: treatment-related AEs by common organ system





- In the NIVO+IPI arm, 35% of patients received high-dose glucocorticoids (≥40 mg of prednisone per day or equivalent) for select treatment-related AE management
- No additional treatment-related deaths occurred

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Subgroup analysis from JAVELIN Renal 101: outcomes for avelumab + axitinib vs sunitinib in advanced renal cell carcinoma

Toni K. Choueiri,[1] Robert J. Motzer,[2] Matthew T. Campbell,[3] Boris Y. Alekseev,[4] Motohide Uemura,[5] Christian K. Kollmannsberger,[6] Gwenaelle Gravis,[7] Georg A. Bjarnason,[8] Howard Gurney,[9] Jinsoo Chung,[10] John Haanen,[11] Brian I. Rini,[12] James Larkin,[13] Manuela Schmidinger,[14] Franco Nole,[15] Aleksander Chudnovsky,[16] Bo Huang,[17] Subramanian Hariharan,[18] Alessandra di Pietro,[19] and Laurence Albiges[20]

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Presented by: Toni K. Choueiri, MD

Abstract no. 544

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JAVELIN Renal 101 efficacy summary[1]

	PD-L1+ group (N = 560)		Overall population (N = 886)	
	Avelumab + axitinib (N = 270)	Sunitinib (N = 290)	Avelumab + axitinib (N = 442)	Sunitinib (N = 444)
PFS per IRC				
Median, months	13.8	7.2	13.8	8.4
95% CI	11.1, NE	5.7, 9.7	11.1, NE	6.9, 11.1
Benefit vs sunitinib (HR; P value)	0.61; P < .0001	-	0.69; P = .0001	-
ORR per IRC, %	55.2	25.5	51.4	25.7
95% CI	49.0, 61.2	20.6, 30.9	46.6, 56.1	21.7, 30.0
PFS per investigator assessment				
Median, months	13.3	8.2	12.5	8.4
95% CI	9.8, NE	6.9, 8.5	11.1, 15.2	8.2, 9.7
Benefit vs sunitinib (HR; P value)	0.51; P < .0001	-	0.64; P < .0001	-
ORR per investigator assessment, %	61.9	29.7	55.9	30.2
95% CI	55.8, 67.7	24.5, 35.3	51.1, 60.6	25.9, 34.7

IRC, independent review committee; **NE**, not estimable; **ORR**, objective response rate.
Data cutoff date: June 20, 2018; median follow-up, 12.0 months (avelumab + axitinib) and 11.5 months (sunitinib).

1. Motzer RJ, et al. ESMO 2018:LBA6_PR.

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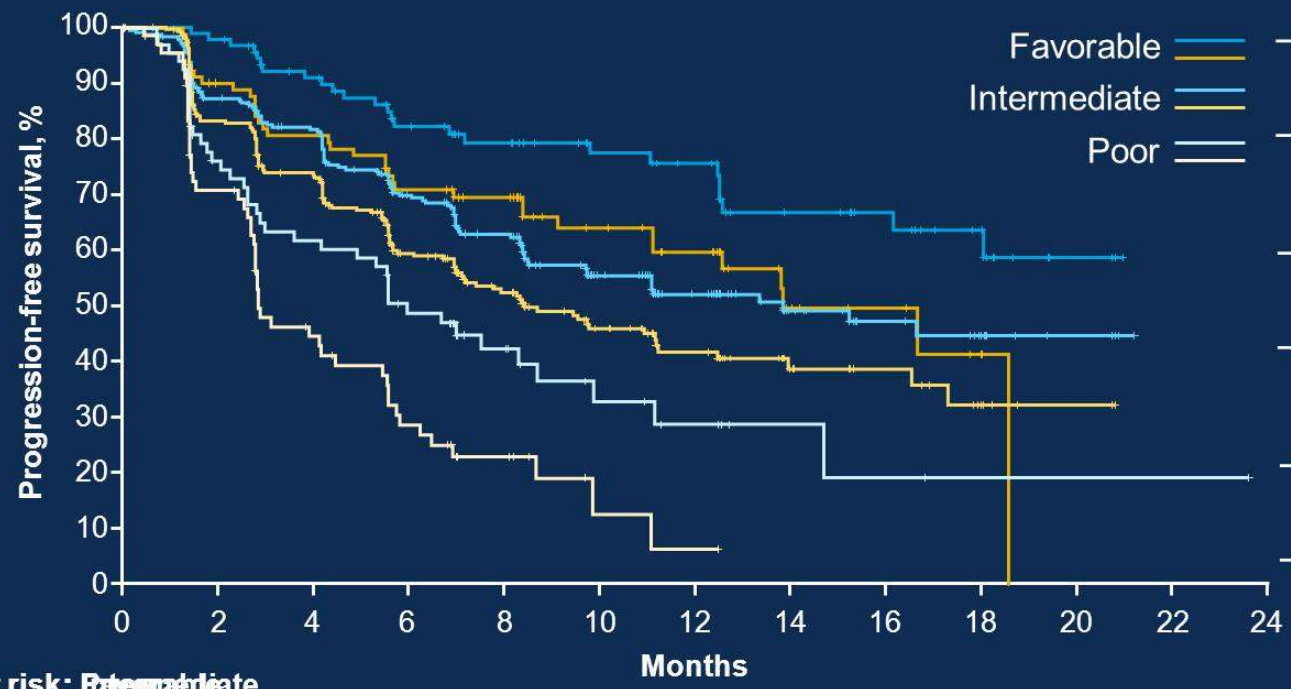
PFS per IRC in IMDC prognostic risk groups in the overall population



Median PFS (95% CI), months	
Avelumab + axitinib	NE (16.1, NE)
Sunitinib	13.8 (11.1, 18.6)
Unstratified HR, 0.54 (95% CI: 0.321, 0.907)	

Median PFS (95% CI), months	
Avelumab + axitinib	13.8 (9.7, NE)
Sunitinib	8.4 (7.0, 11.2)
Unstratified HR, 0.74 (95% CI: 0.570, 0.950)	

Median PFS (95% CI), months	
Avelumab + axitinib	6.0 (3.6, 8.7)
Sunitinib	2.9 (2.7, 5.5)
Unstratified HR, 0.57 (95% CI: 0.375, 0.880)	

Number at risk: Favorable / Intermediate / Poor

Avel + axit	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0
Sunitinib	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0	

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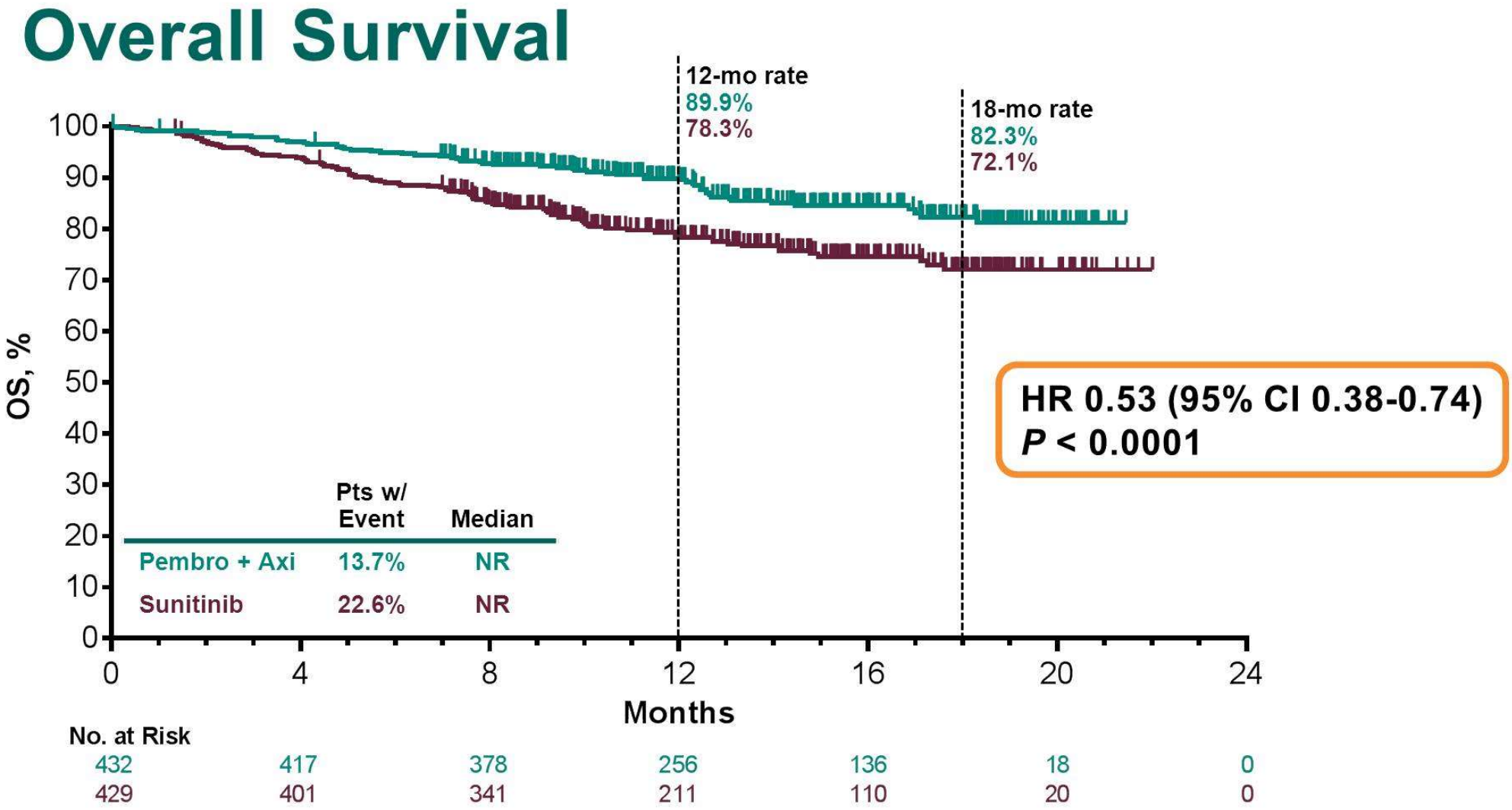
Pembrolizumab plus Axitinib as First-Line Therapy for mRCC: Outcomes in the Combined IMDC Intermediate/Poor Risk and Sarcomatoid Subgroups of KEYNOTE-426

Brian I. Rini,[1] Elizabeth R. Plimack,[2] Viktor Stus,[3] Rustem Gafanov,[4] Robert Hawkins,[5] Dmitry Nosov,[6] Frédéric Pouliot,[7] Denis Soulières,[8] Bohuslav Melichar,[9] Ihor Vynnychenko,[10] Sergio J. Azevedo,[11] Delphine Borchiellini,[12] Raymond S. McDermott,[13] Jens Bedke,[14] Satoshi Tamada,[15] Shuyan Wan,[16] Scot Ebbinghaus,[16] Rodolfo F. Perini,[16] Mei Chen,[16] Michael B. Atkins,[17] Thomas Powles[18]

[1]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA; [2]Fox Chase Cancer Center, Philadelphia, PA, USA; [3]Dnipropetrovsk Medical Academy of Ministry of Health of Ukraine, Dnipro, Ukraine; [4]Russian Scientific Center of Roentgenoradiology, Moscow, Russia; [5]The Christie NHS Foundation Trust, Manchester, UK; [6]Central Clinical Hospital with Outpatient Clinic, Moscow, Russia; [7]CHU de Québec and Université Laval, Quebec City, QC, Canada; [8]Centre Hospitalier de l'Universitaire de Montréal, Montréal, QC, Canada; [9]Palacky University Medical School and Teaching Hospital, Olomouc, Czech Republic; [10]Sumy State University, Sumy Regional Oncology Center, Sumy, Ukraine; [11]Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil; [12]Centre Antoine Lacassagne, Université Côte d'Azur, Nice, France; [13]Adelaide and Meath Hospital and University College Dublin, Dublin, Ireland; [14]Department of Urology, Eberhard-Karls University Tübingen, Tübingen, Germany; [15]Osaka City University Hospital, Osaka, Japan; [16]Merck & Co., Inc., Kenilworth, NJ, USA; [17]Georgetown–Lombardi Comprehensive Cancer Center, Washington, D.C., USA; [18]Barts Health and the Royal Free NHS Trusts, Barts Cancer Institute, and Queen Mary University of London, London, UK

Presented By Brian Rini at 2019 ASCO Annual Meeting

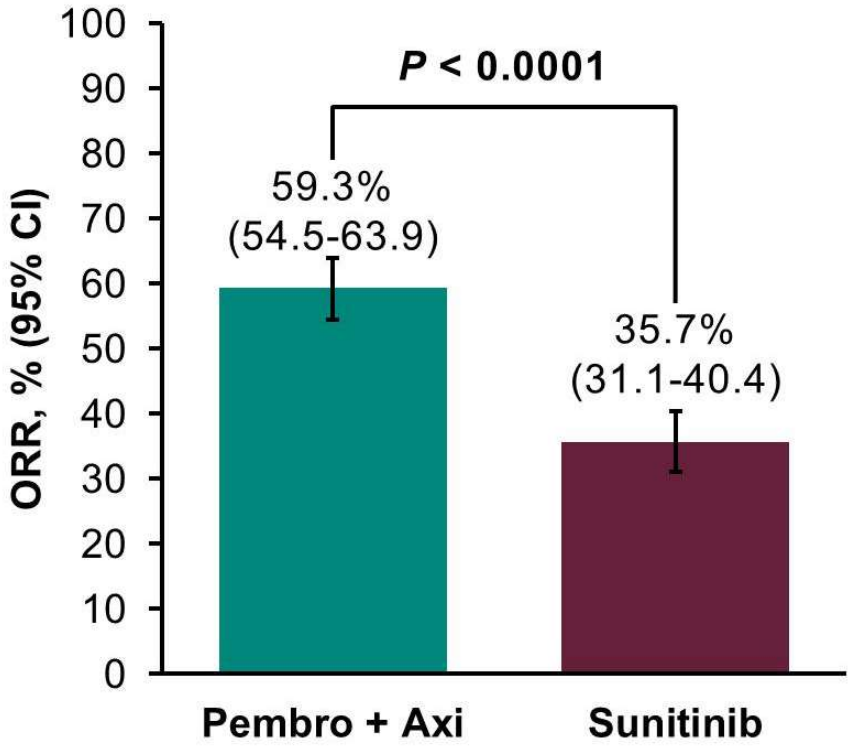
Keynote-426: overall survival



Data cutoff date: Aug 24, 2018.

Presented By Thomas Powles at 2019 Genitourinary Cancers Symposium

Keynote-426: confirmed objective response rate



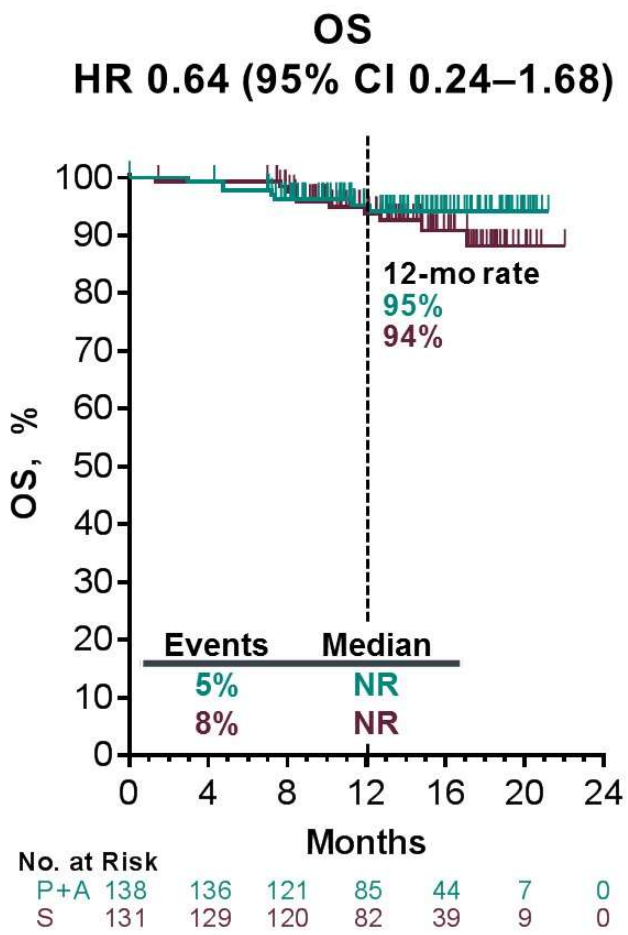
Best Response	Pembro + Axi N = 432	Sunitinib N = 429
CR	25 (5.8%)	8 (1.9%)
PR	231 (53.5%)	145 (33.8%)
SD	106 (24.5%)	169 (39.4%)
PD	47 (10.9%)	73 (17.0%)
NE[a]	8 (1.9%)	6 (1.4%)
NA[b]	15 (3.5%)	28 (6.5%)
Response Duration	**N = 256**	**N = 153**
Median (range), mo	NR (1.4+ to 18.2+)	15.2 (1.1+ to 15.4+)

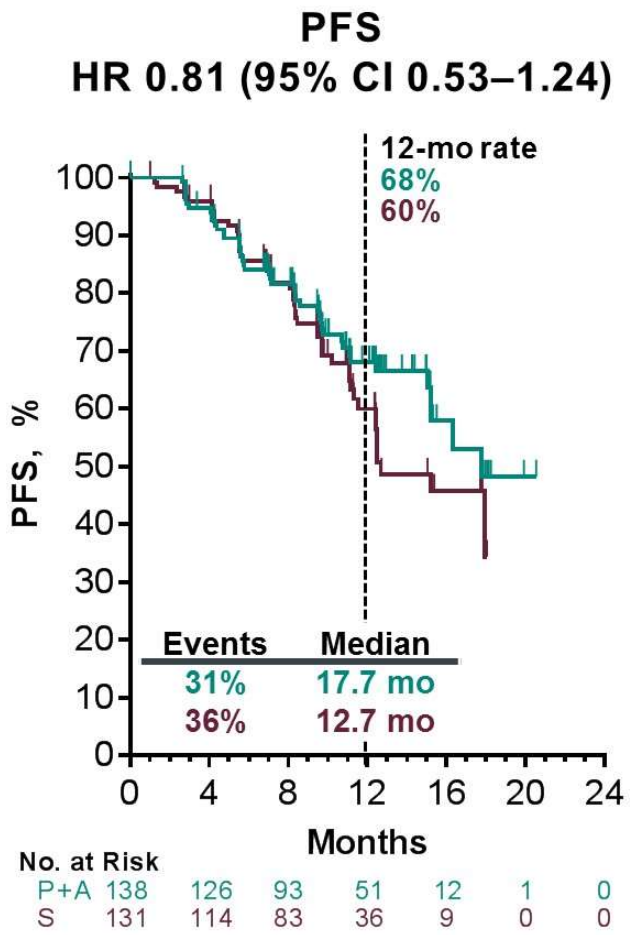
[a]Patients who had ≥1 post-baseline imaging assessment, none of which were evaluable per RECIST v1.1 by BICR. [b]Patients who did not have ≥1 post-baseline imaging assessment.
Data cutoff date: Aug 24, 2018.

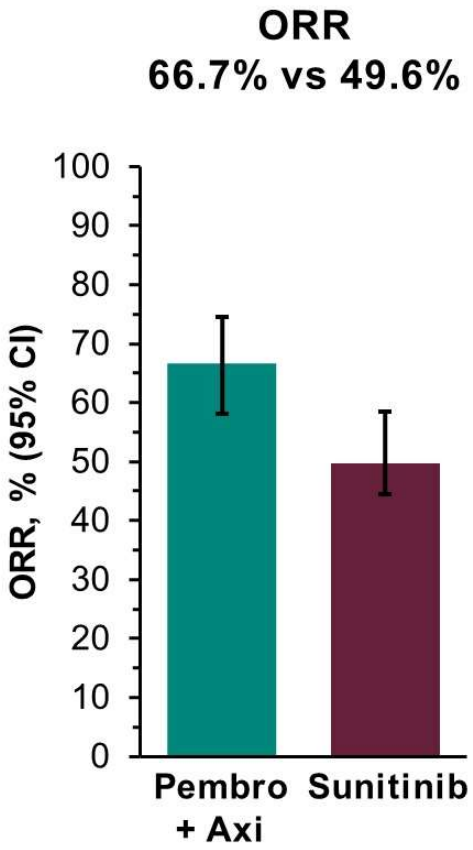
Presented By Thomas Powles at 2019 Genitourinary Cancers Symposium

Keynote-426: favorable risk disease

IMDC Favorable Risk: OS, PFS, and ORR







Data cutoff date: Aug 24, 2018.

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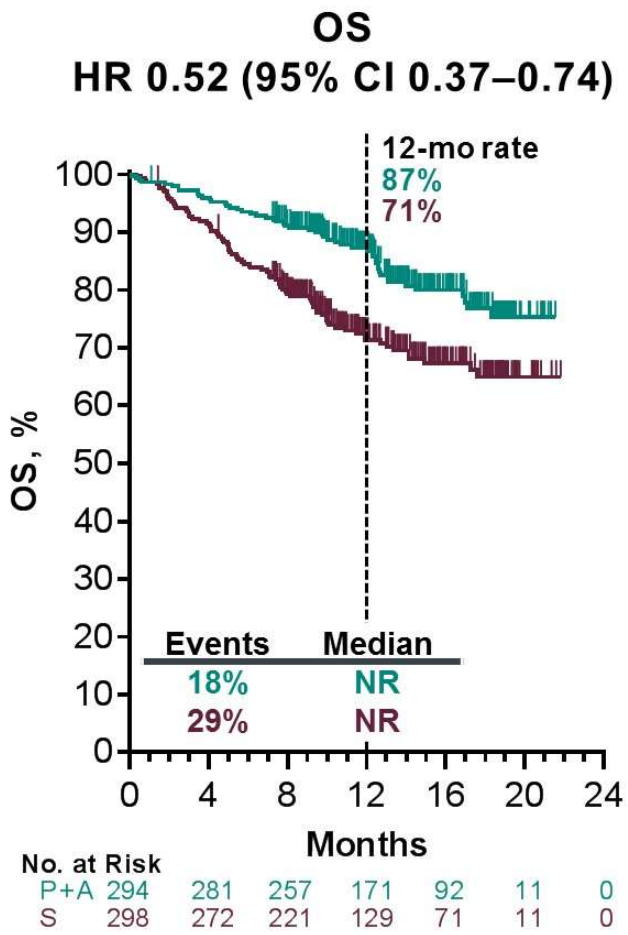
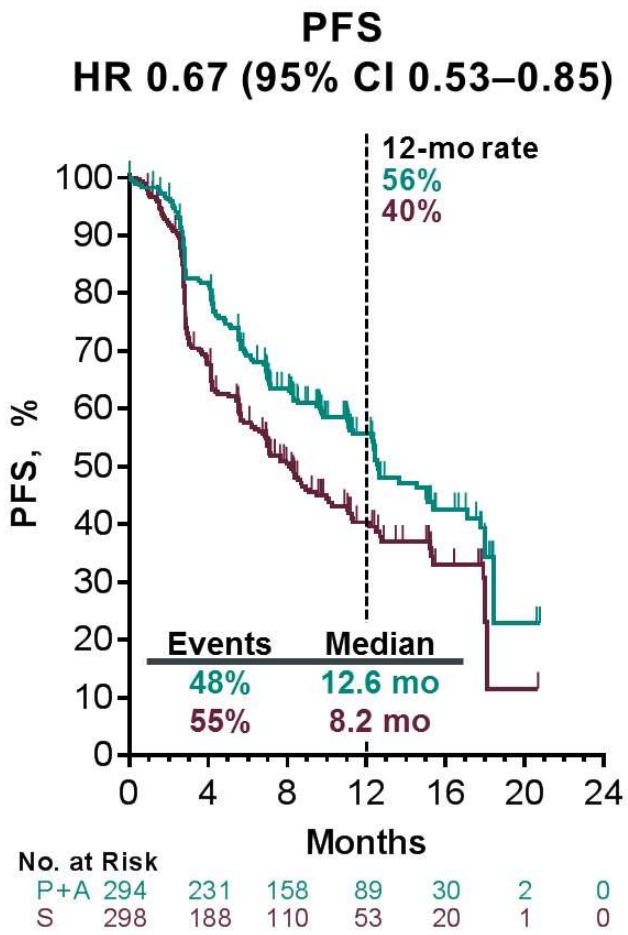
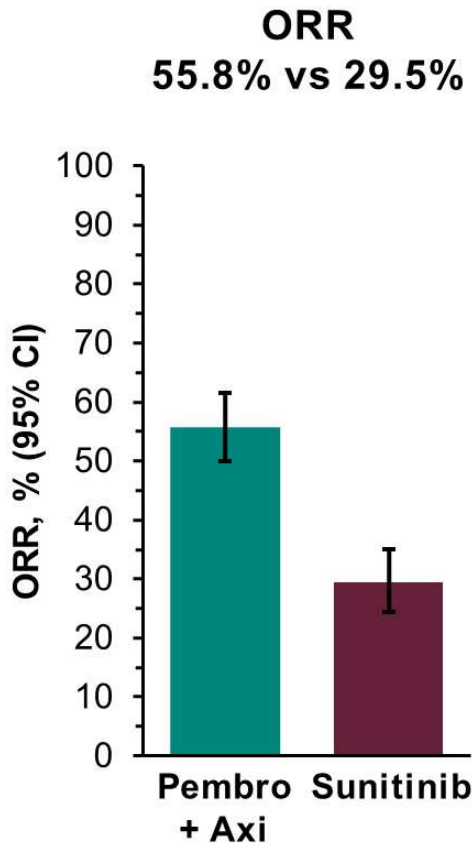
Keynote-426: intermediate/poor risk disease

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



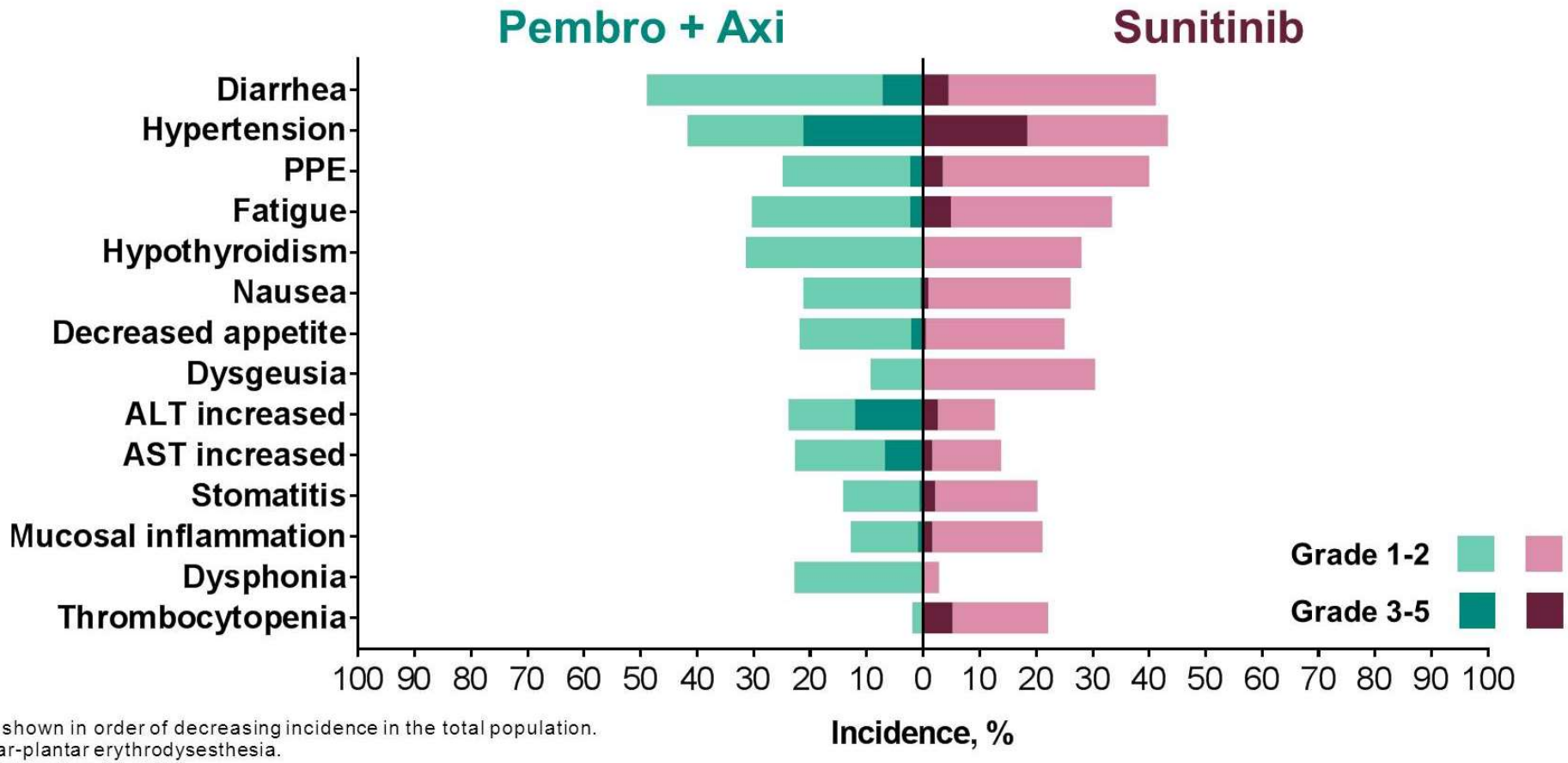




Data cutoff date: Aug 24, 2018.

Presented By Brian Rini at 2019 ASCO Annual Meeting

Keynote-426: treatment-related AEs (≥20% incidence)

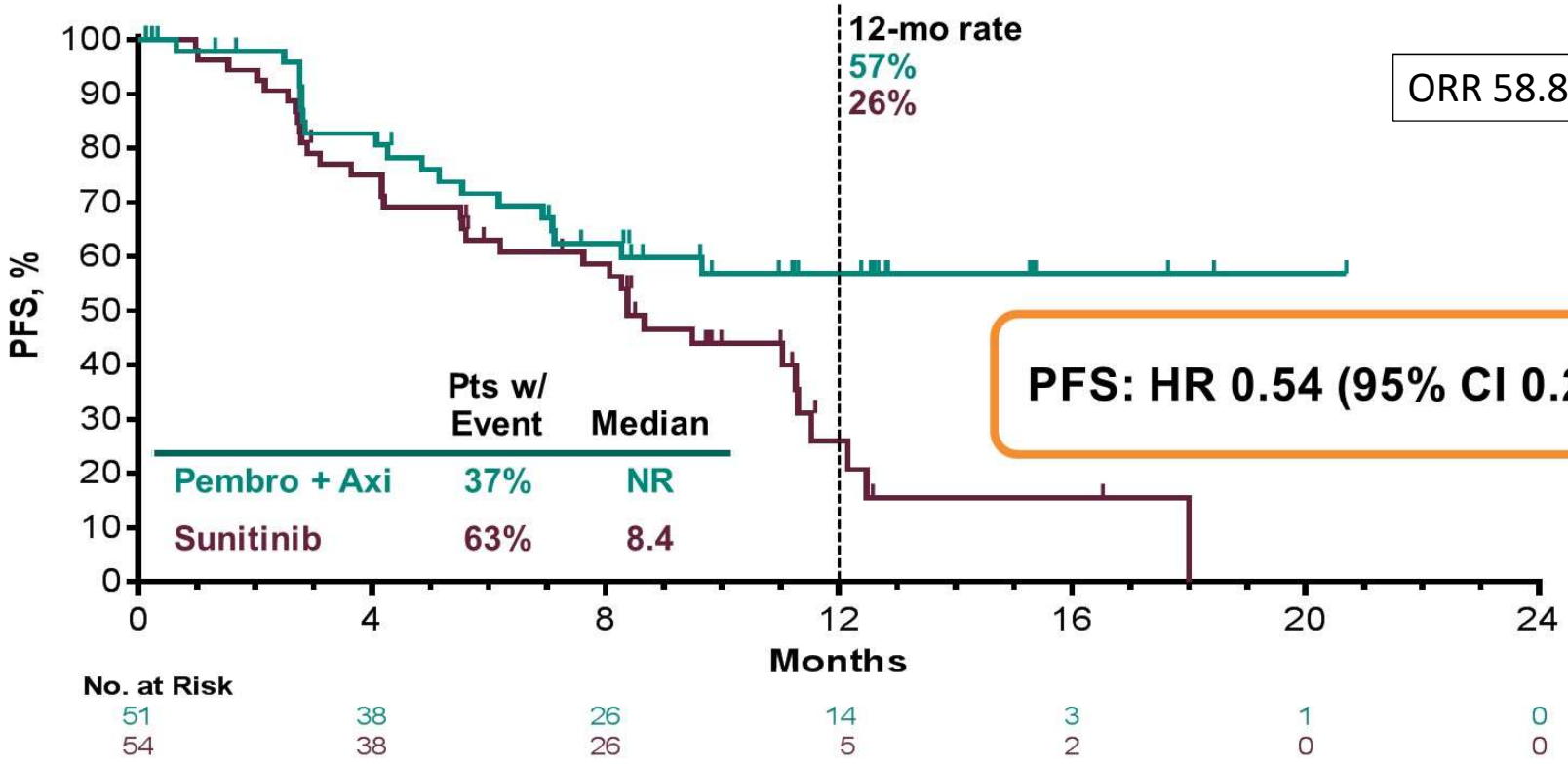


Events are shown in order of decreasing incidence in the total population.
PPE, palmar-plantar erythrodysesthesia.
Data cutoff date: Aug 24, 2018.

Presented By Thomas Powles at 2019 Genitourinary Cancers Symposium

Keynote-426: sarcomatoid disease

PFS: Presence of Sarcomatoid Features[a]



ORR 58.8% vs 31.5%

PFS: HR 0.54 (95% CI 0.29–1.00)

OS: HR 0.58 (95% CI 0.21–1.59); median NR in either arm[b]

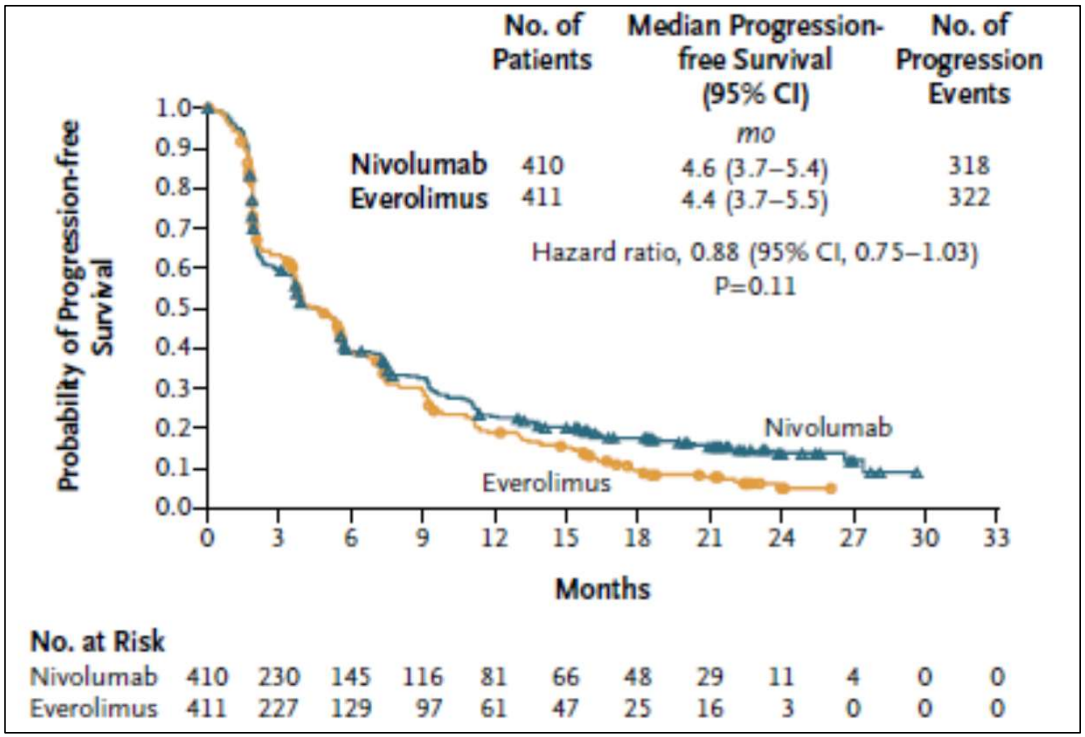
[a]Among the 578 participants with known status assessed by local pathology review and as indicated on the eCRF. [b]Pts who died: 16% in the pembro + axi arm, 20% in the sunitinib arm. Data cutoff date: Aug 24, 2018.

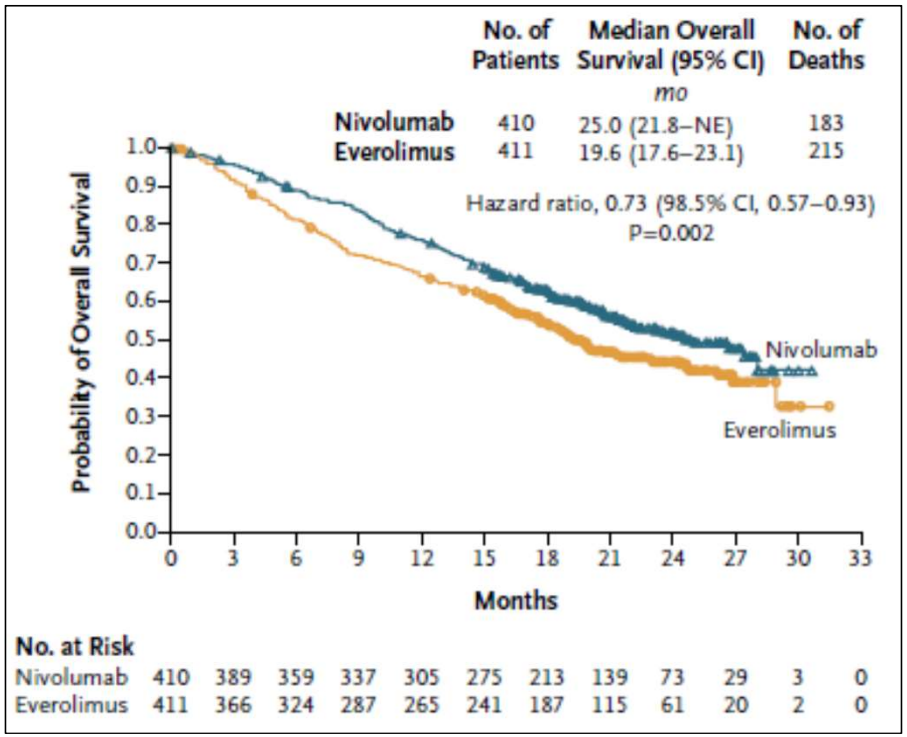
Presented By Brian Rini at 2019 ASCO Annual Meeting

nivolumab vs everolimus (2nd or 3rd line IO naive)

Treatment	n	RR	PFS	OS	≥G3 AEs
nivolumab 3 mg/kg q3 wk	410	25%	4.6 mo	25.0 mo	19%
temsirolimus 10 mg po qd	411	5%	4.4 mo	19.6 mo	37%

OS HR 0.73, p=0.002

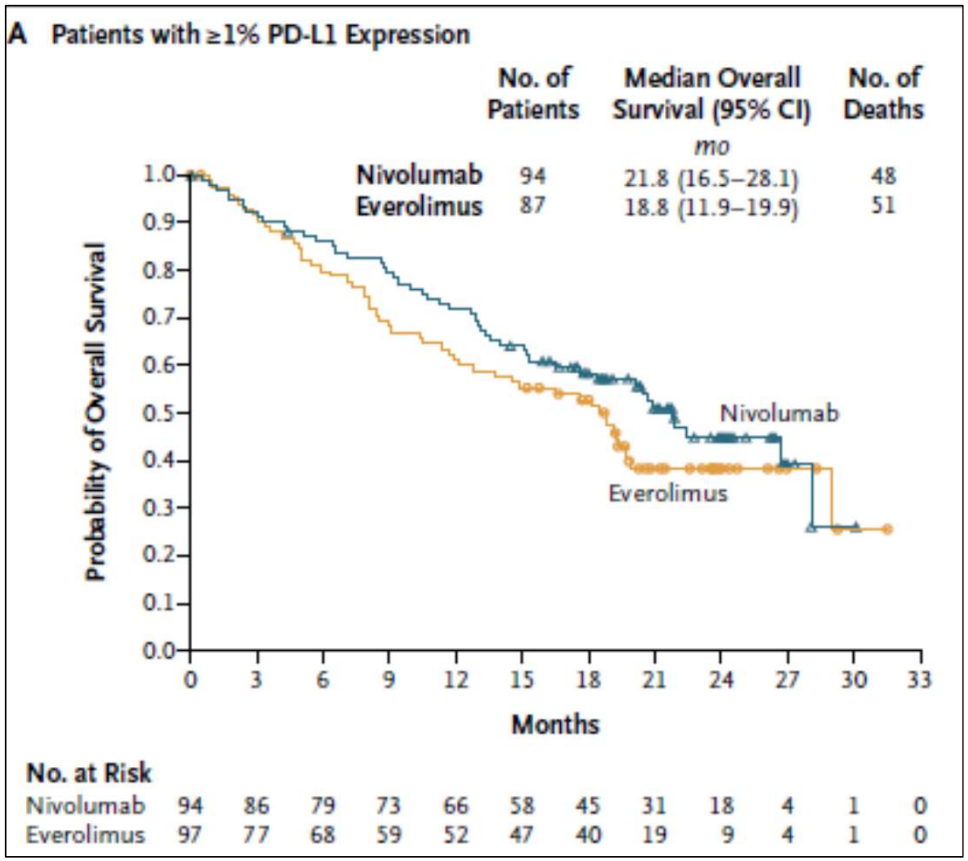


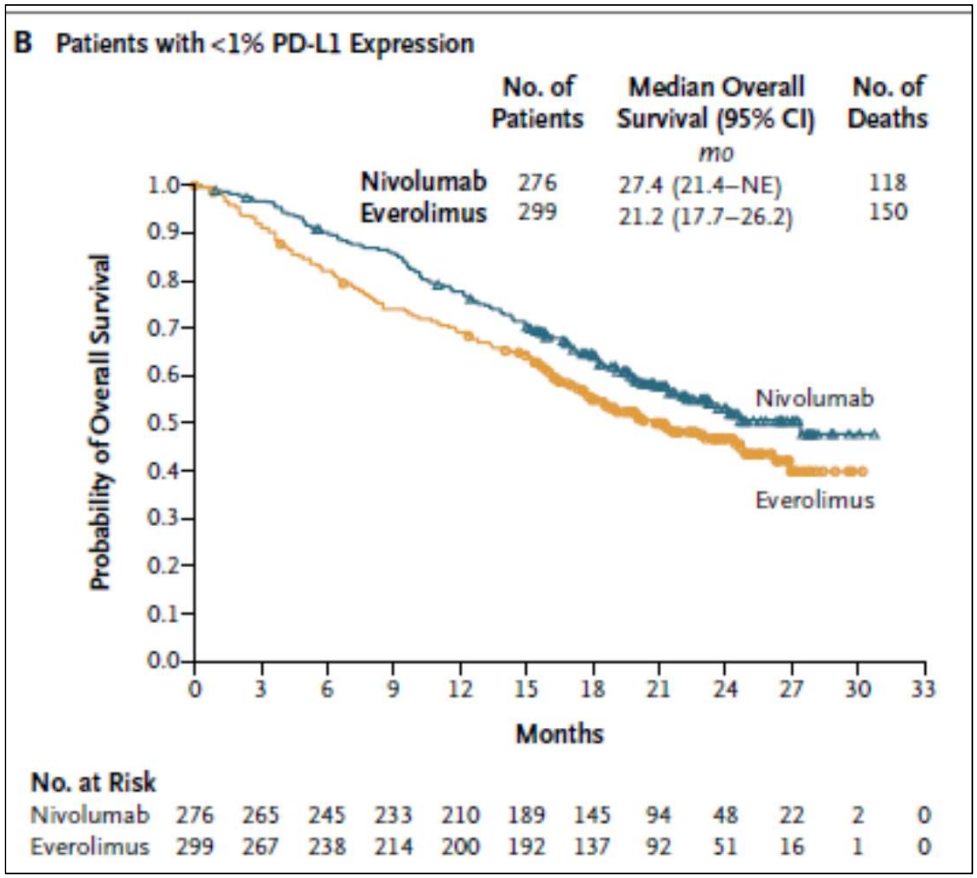


- OS benefit, but no PFS benefit!

Motzer et al, NEJM 2015

Nivolumab: PD-L1 expression prognostic but not predictive





Motzer et al, NEJM 2015

Non-clear cell carcinoma response rates

Treatment	unclassified	papillary	chromophobe	sarcomatoid
atezolizumab/ bevacizumab	26%	25%	10%	44%
savolitinib/ durvalumab		27%		
pembrolizumab	34.6%	25.4%	9.5%	
pembrolizumab/ axitinib				58.8%
sunitinib				31.5%

Treatment	PDL1+	PDL1-	ref
atezolizumab/ bevacizumab	64%	20%	1
savolitinib/ durvalumab	38%	24%	2
pembrolizumab	33%	10%	3

1. McKay et al, GU ASCO 2019; 2. Powles et al, GU ASCO 2019; 3. McDermott et al, GU ASCO 2019

Treatment: intermediate/poor risk clear cell RCC

1st line	2nd line
Ipilimumab/Nivolumab →	TKI or High dose IL-2
Axitinib/Pembrolizumab or Axitinib/Avelumab? →	Sunitinib Pazopanib Cabozantinib High dose IL-2
Cabozantinib →	Axitinib Nivolumab Ipi/Nivo Axi/Pembro Axi/Avelumab?
High Dose IL-2 →	TKI or Ipi/Nivo Nivo Axi/Pembro Axi/Avlumab?

3rd line

If patient has not seen IO:

- Nivo or Ipi/Nivo

If patient has had IO and TKI:

- 2nd line TKI or
- Lenvatinib/Everolimus

4th + lines

- Temsirolimus
- Everolimus
- Bevacizumab/IFN
- Or retry IO (Nivo)

Voss et al, JCO 2016

Treatment: good risk clear cell RCC

1st line	2nd line
Axitinib/Pembrolizumab or Axitinib/Avelumab?	Sunitinib Pazopanib Cabozantinib High dose IL-2? Ipi/Nivo
Ipilimumab/Nivolumab	Sunitinib Pazopanib Cabozantinib High dose IL-2
High Dose IL-2	Ipi/Nivo Nivo Axi/Pembro Sunitinib Pazopanib Cabozantinib Axi/Avelumab?
Cabozantinib	Ipi/Nivo Axi/Pembro Axitinib Nivolumab Axi/Avelumab?

3rd line

If patient has not seen IO:

- Nivo or Ipi/Nivo

If patient has had IO and TKI:

- 2nd line TKI: Axitinib, Cabozantinib, Lenvatinib/Everolimus

4th + lines

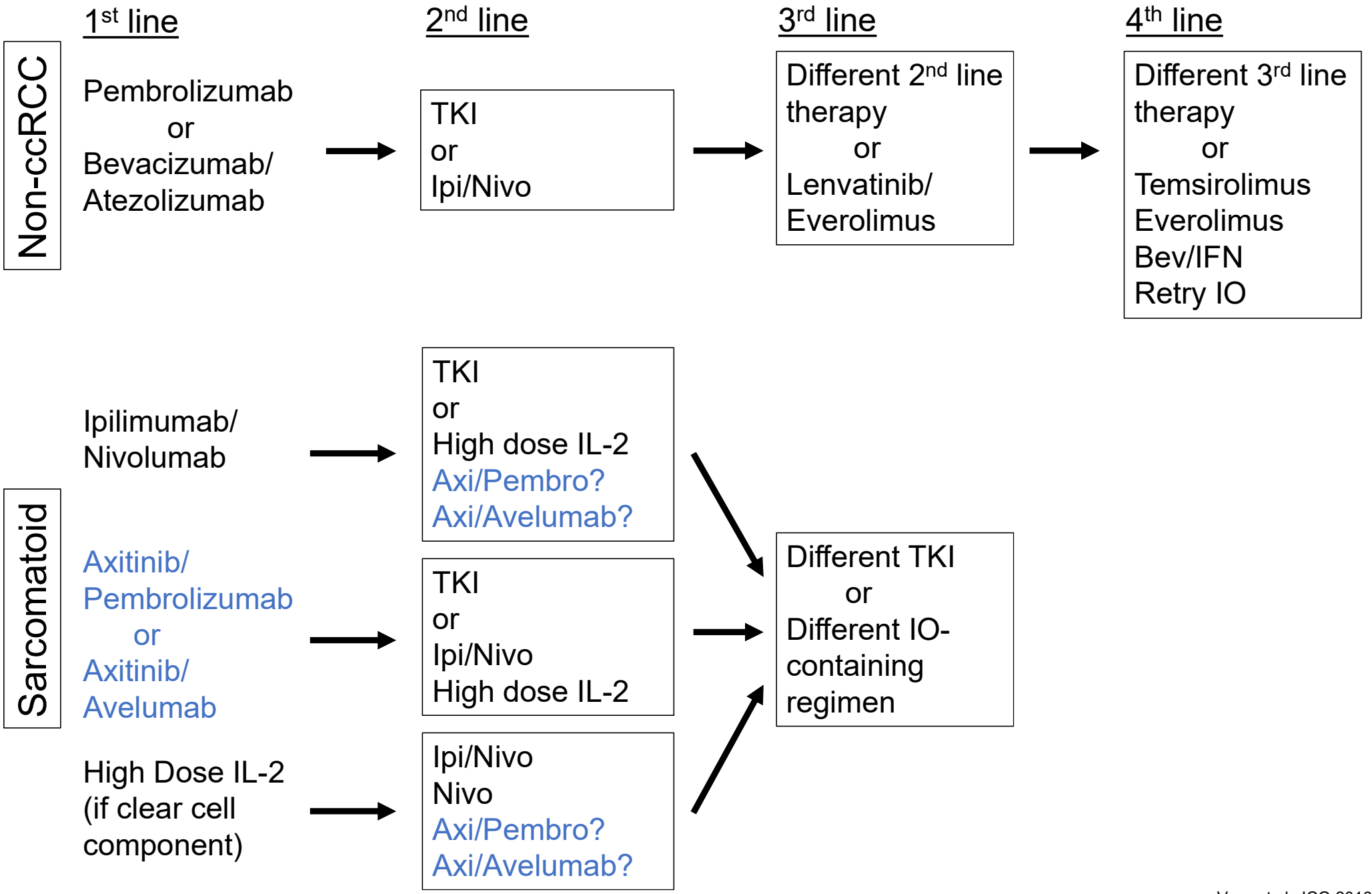
- Temsirolimus
- Everolimus
- Bevacizumab/IFN
- Or retry IO (nivo, pembro)

Other considerations:

- For Good Risk, can sometimes observe at first
- IL-2 might have worse outcomes after TKI

Voss et al, JCO 2016

Treatment: non-clear cell or sarcomatoid



Voss et al, JCO 2016

Thanks for listening

Targeted Therapies: TKIs and mTor inhibitors

	Treatment	n	RR	PFS	OS	ref
Post-cytokine	IFNα	363	NR	NR	17.4 mo	1
	IFNα + bevacizumab	369	NR	NR	18.3 mo	
	IFNα	327	NR	NR	21.3 mo	2
	IFNα + bevacizumab	322	NR	NR	23.3 mo	
1st line	IFNα	375	6%	5 mo	22 mo	3
	Sunitinib	375	31%	11 mo	26 mo*	
	placebo	145	3%	4.2 mo	NR	4
	Pazopanib	290	30%	9.2 mo*	NR	
	Sunitinib	78	18%	5.6 mo	21.8 mo	5
	Cabozantinib	79	46%	8.2 mo*	30.3 mo	
	IFNα	207	4.8%	1.9 mo	7.3 mo	6
	Temsirolimus/IFNα	209	8.1%	3.7 mo	8.4 mo	
	Temsirolimus	210	8.6%	3.8 mo*	10.9 mo*	
2nd line	Sorafenib	362	9%	4.7 mo	NR	7
	Axitinib	362	19%	6.7 mo*	NR	
	Everolimus	328	5%	3.8 mo	NR	8
	Cabozantinib	330	21%	7.4 mo*	NR	
	Lenvatinib	52	27%	7.4 mo	18.4 mo	9
	Everolimus	50	6%	5.5 mo	17.5 mo	
	Lenvatinib/Everolimus	51	43%	14.6 mo*	25.5 mo*	
	Placebo	138	0%	1.9 mo	8.8 mo	10
	Everolimus	272	1%	4.0 mo*	not reached	

*statistically significant

1. Rini et al, JCO 2010; 2. Escudier et al, JCO 2010; 3. Motzer et al, NEJM 2007; 4. Sternberg et al, JCO 2010; 5. Choueiri et al, JCO 2016; 6. Hudes et al, NEJM 2007; 7. Rini et al, Lancet 2011; 8. Chouieri et al, NEJM 2015; 9. Motzer et al, Lancet Oncology 2015; 10. Motzer et al. Lancet 2008

Adverse effects of non-immune therapies

Tyrosine Kinase Inhibitors

Side effect	management
Fatigue	Supportive
Diarrhea	Anti-diarrheals
Nausea	Anti-nausea meds
Dyspepsia	Supportive
Stomatitis	Supportive
Hypertension	Anti-hypertensive
Proteinuria	Dose reduction
Decreased EF	Hold medication
Hypothyroidism	Replacement
Lymphopenia	Monitor
Hyperlipasemia	Monitor

mTor inhibitors

Side effect	Laboratory Abnormalities
Stomatitis	Hypercholesterolemia
Rash	Hypertriglyceridemia
Fatigue	Hyperglycemia
Asthenia	Hypophosphatemia
Diarrhea	
Pneumonitis	

Chen and Cleck, Nature Rev Clin Oncol 2009; Jonasch et al, JCO 2018

Adverse Events (select treatment-emergent in ≥5%)

AE Term	Placebo (n=52)			Pembrolizumab (n=55)		
	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Any adverse event	58%	35%	0%	38%	42%	11%
Fatigue	39%	0%	0%	31%	7%	0%
Anorexia	14%	0%	0%	16%	2%	0%
Dry mouth	0%	0%	0%	11%	0%	0%
ALT increased	2%	0%	0%	11%	4%	2%
AST increased	10%	0%	0%	15%	5%	0%
Diarrhea	19%	0%	0%	35%	0%	0%
Hypothyroidism	4%	0%	0%	9%	0%	0%
Pruritis	13%	0%	0%	22%	2%	0%
Rash	8%	0%	0%	22%	0%	0%
Dyspnea	14%	0%	0%	22%	5%	0%
Renal insufficiency	24%	0%	0%	29%	2%	0%

* One patient randomized to pembrolizumab developed fatal immune-related hepatitis

Objective Response Rate (RECIST 1.1)

Characteristic	Placebo (n=52)	Pembrolizumab (n=55)
Not evaluable (baseline CR)	10	9
Overall response	12%	22%
Partial response	12%	13%
Complete response	0	9%
Stable disease	29%	35%
Progressive disease	54%	33%
Unknown	5%	10%

Adding ipilimumab to nivolumab at progression?

- 10 patients with progression of disease on nivolumab
- 1 PR, 4 SD after addition of ipilimumab
- Modest increase in grade 3/4 toxicities

Callahan et al. ASCO GU 2017; Abstract 384.

Safety and efficacy of nivolumab in metastatic renal cell carcinoma Final analysis from the NIVOREN GETUG AFU 26 study

L. Albiges, S. Negrier, C. Dalban, C. Chevreau, G. Gravis, S. Oudard, B. Laguerre, P. Barthelemy, D. Borchiellini, M. Gross-Goupil, L. Geoffrois, F. Rolland, A. Thiery-Vuillemin, F. Joly, S. Ladoire, F. Tantot, B. Escudier
on behalf of the GETUG

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Presented By Laurence Albiges at 2019 Genitourinary Cancers Symposium

Nivolumab monotherapy: real-world results

Summary of the findings

	CheckMate 025	GETUG- AFU 26 NIVOREN
n	406	**720**
Median FUp	14 mo (minimum Fup)	**23.9 mo**
Median PFS	4.6 mo	**3.7 mo**
Median OS	25.0 mo	**24.5 mo**
ORR SD PD	25% 34% 35%	**21.0%** **31.1%** **47.9%**
Ttt beyond progression	44%	**47.0%**
Grade ≥3 TRAEs	19%	**17.9%**

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Presented by: Laurence Albiges, MD PhD

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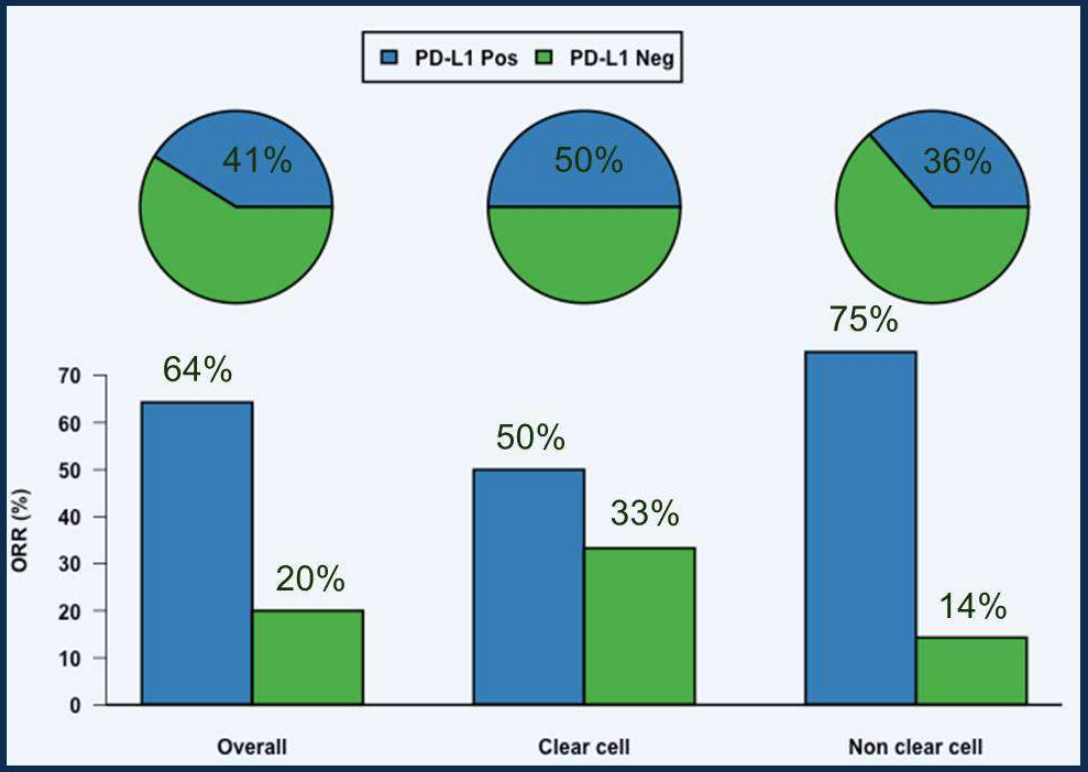
Atezo/Bev in non-clear cell and/or sarcomatoid RCC

ORR by PD-L1 Staining Status



	Non-Clear Cell (n=22)	Clear Cell SD (n=12)	Total (n=34)
PD-L1+	36% (n=8/22)	50% (n=6/12)	41% (n=14/34)

SD=Sarcomatoid differentiation; PD-L1=Programmed death ligand 1. 9A11 antibody used for PD-L1 staining. The percent PD-L1 positive tumor cells (score) was calculated using the formula: Number PD-L1 Positive Tumor Cells/Total Number Tumor Cells . A score ≥1 was positive (Yes versus No).

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Presented by: Rana R. McKay

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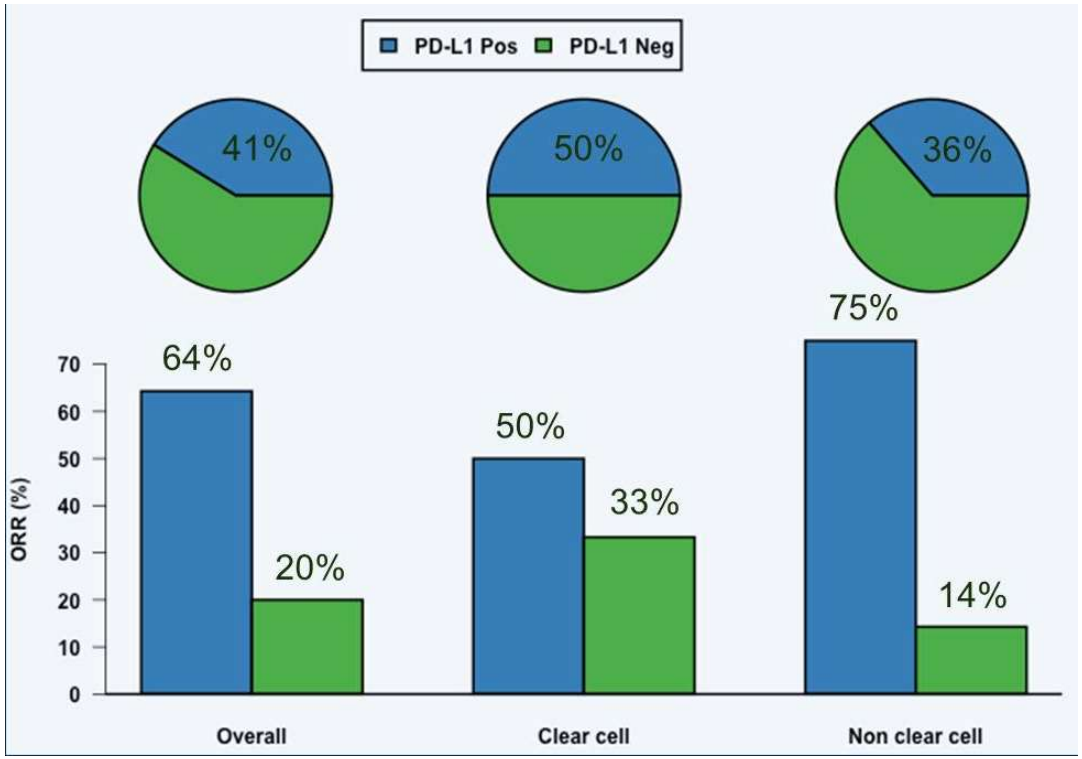
Atezo/Bev in non-clear cell and/or sarcomatoid RCC



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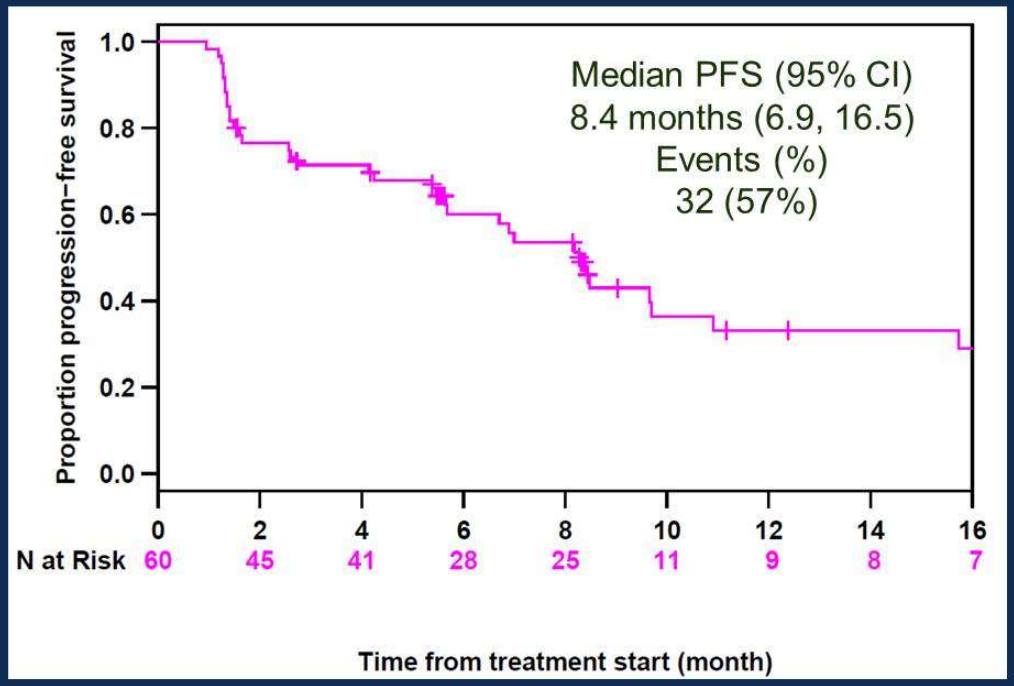
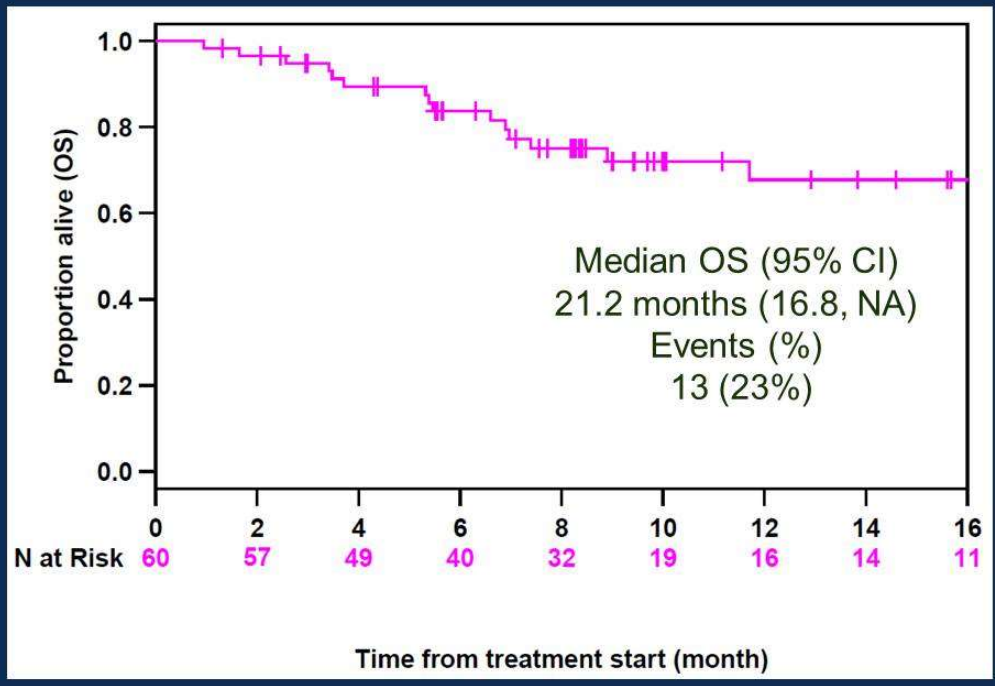
Atezo/Bev in non-clear cell and/or sarcomatoid RCC

PFS and OS





PFS=Progression-free survival; CI=Confidence interval, OS=Overall survival. Median follow-up time is 9.7 months.

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Presented By Rana McKay at 2019 Genitourinary Cancers Symposium

A phase I/II study investigating the safety and efficacy of savolitinib and durvalumab in metastatic papillary renal cancer (CALYPSO)

Thomas Powles[1], James M. G. Larkin[2], Poulam Patel[3], Begoña Pérez-Valderrama[4], Alejo Rodriguez-Vida[5], Hilary Glen[6], Fiona Thistlethwaite[7], Christy Ralph[8], Gopalakrishnan Srinivasan[9], Maria Jose Mendez-Vidal[10], Wing-Kin Liu[11], Aaron Prendergast[1], Laura Vosper[1], Kelly Mousa[1], Cristina Suárez[12]

Presented by: Dr Cristina Suárez, MD PhD
Hospital Universitari Vall d´Hebron – Vall d´Hebron Institute of Oncology

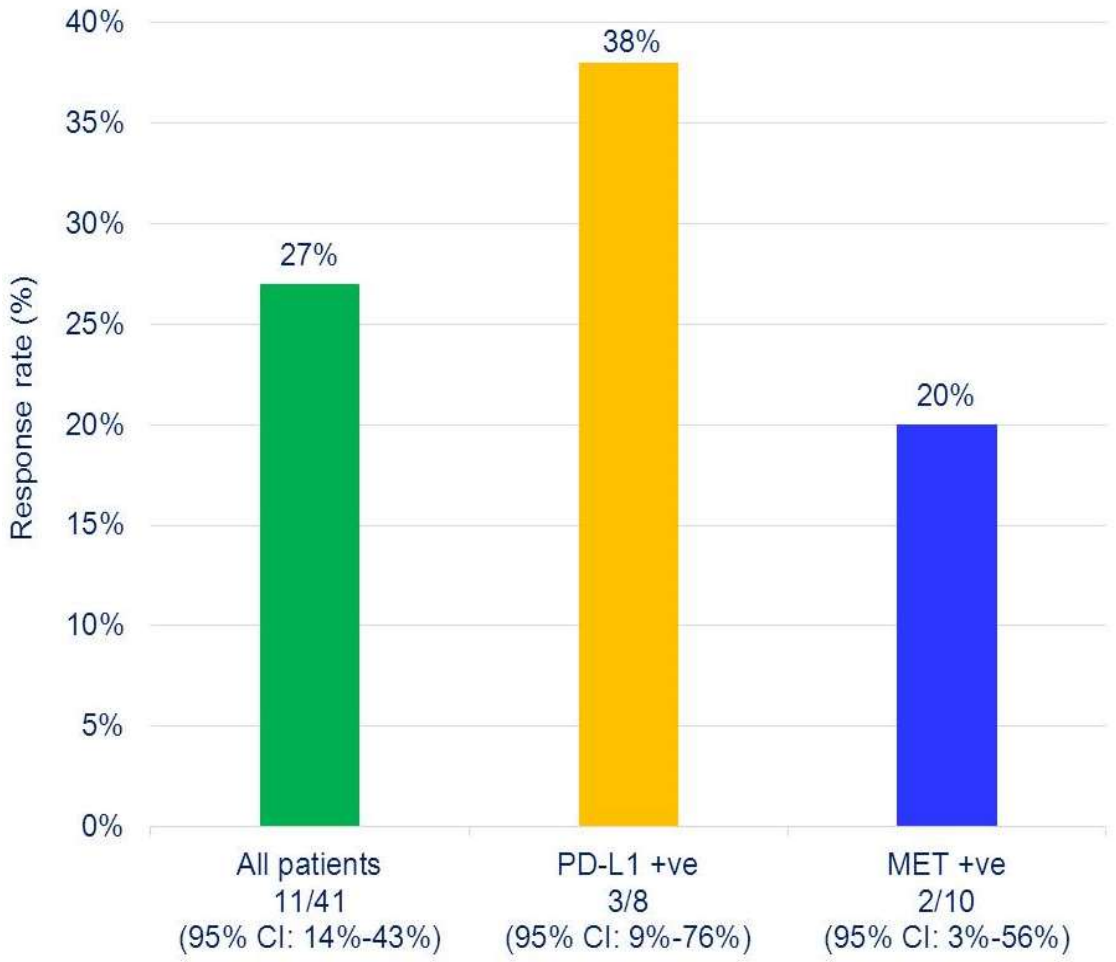
[1]Barts Cancer Institute, Queen Mary University of London, London, UK; [2] The Royal Marsden NHS Foundation Trust, London, UK; [3] Nottingham University Hospital NHS Trust, Nottingham, UK; [4] Hospital Universitario Virgen del Rocío, Seville, Spain; [5]Hospital del Mar, Barcelona, Spain; [6]Beatson West of Scotland Cancer Centre, Glasgow, UK; [7]The Christie NHS Foundation Trust and University of Manchester, UK; [8]St. James's Institute of Oncology, University of Leeds, Leeds, UK; [9]Mid-Essex Hospital Services NHS Trust, Broomfield, UK; [10]Hospital Reina Sofia, Cordoba, Spain; [11]Barts Hospital NHS Trust, London, UK; [12]Hospital University Vall D Hebron General, Barcelona, Spain

Presented at: 2019 Genitourinary Cancers Symposium | #GU19

Presented by: Dr Cristina Suárez

Presented By Cristina Suarez at 2019 Genitourinary Cancers Symposium

Calypso (savolitinib/durvalumab): response rates



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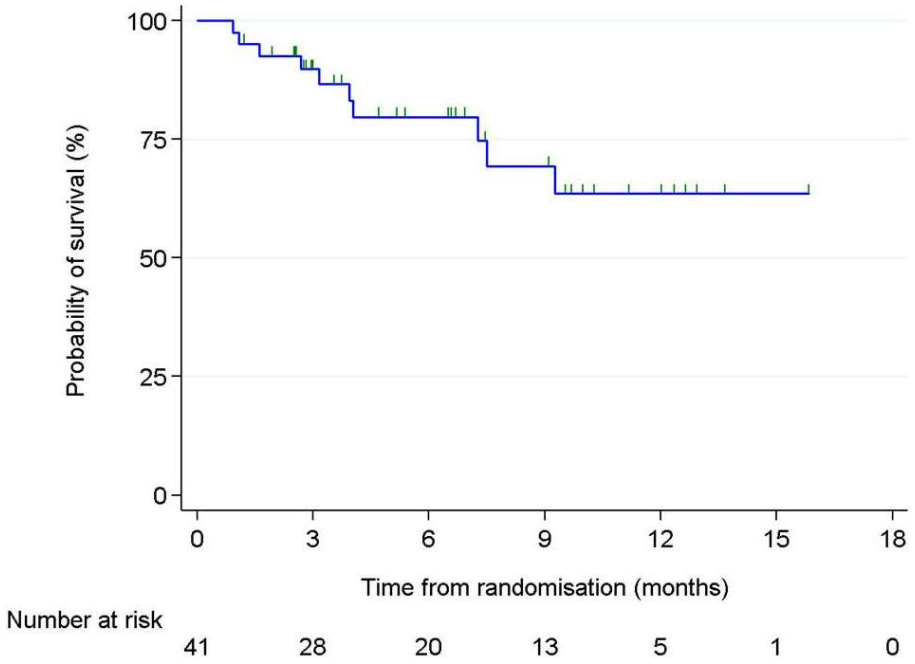
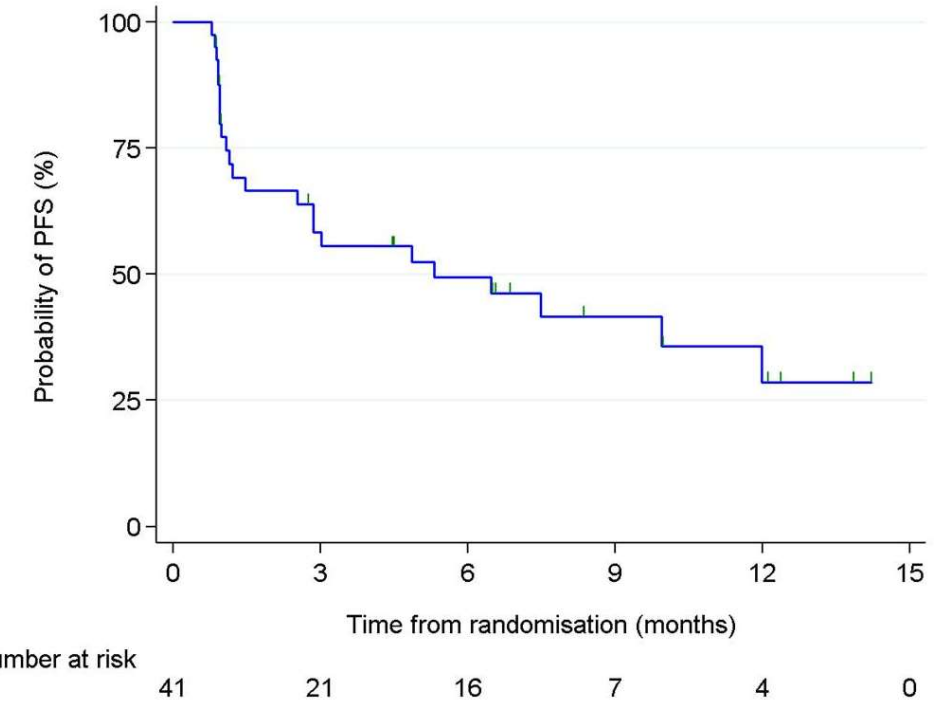
Calypso: interim survival analyses

Median OS in months (95% CI) = NR (7.5 – NR)



Median PFS (95% CI) = **5.3 months** (1.5 – 12.0)



Presented By Cristina Suarez at 2019 Genitourinary Cancers Symposium

First-Line Pembrolizumab Monotherapy for Advanced Non–Clear Cell Renal Cell Carcinoma: Results From KEYNOTE-427 Cohort B

D. McDermott[1]; J.-L. Lee[2]; M. Ziobro[3]; R. Gafanov[4]; V. B. Matveev[5]; C. Suarez[6]; F. Donskov[7]; F. Pouliot[8]; B. Y. Alekseev[9]; P. Wiechno[10]; P. Tomczak[11]; M. A. Climent[12]; S. J. Shin[13]; R. Kloss Silverman[14]; R. F. Perini[14]; C. Schloss[14]; M. B. Atkins[15]

[1]Beth Israel Deaconess Medical Center, Boston, MA, USA; [2]Asan Medical Center and University of Ulsan College of Medicine, Seoul, Republic of Korea; [3]Centrum Onkologii-Instytut im. Marii Sklodowskiej, Cracow, Poland; [4]Russian Scientific Center of Roentgenoradiology, Moscow, Russian Federation; [5]N.N. Blokhin Russian Cancer Research Center, Moscow, Russia Federation; [6]Vall d'Hebron University Hospital and Institute of Oncology, Universitat Autònoma de Barcelona, Barcelona, Spain; [7]Aarhus University Hospital, Aarhus, Denmark; [8]CHU de Quebec and Laval University, Quebec, ON, Canada; [9]P. A. Herzen Moscow Oncology Research Institute, Ministry of Health of the Russian Federation, Moscow, Russian Federation; [10]Maria Sklodowska-Curie Memorial Cancer Center, Warsaw, Poland; [11]Clinical Hospital No. 1 of the Poznan University of Medical Sciences, Poznan, Poland; [12]Instituto Valenciano de Oncología, Valencia, Spain; [13]Yonsei University College of Medicine, Seoul, Republic of Korea; [14]Merck & Co., Inc., Kenilworth, NJ, USA; [15]Georgetown Lombardi Comprehensive Cancer Center, Washington, DC, USA

Presented By David McDermott at 2019 Genitourinary Cancers Symposium

Keynote-427: pembrolizumab in non-clear cell RCC

ORR by Confirmed RCC Histology per Blinded Independent Central Review

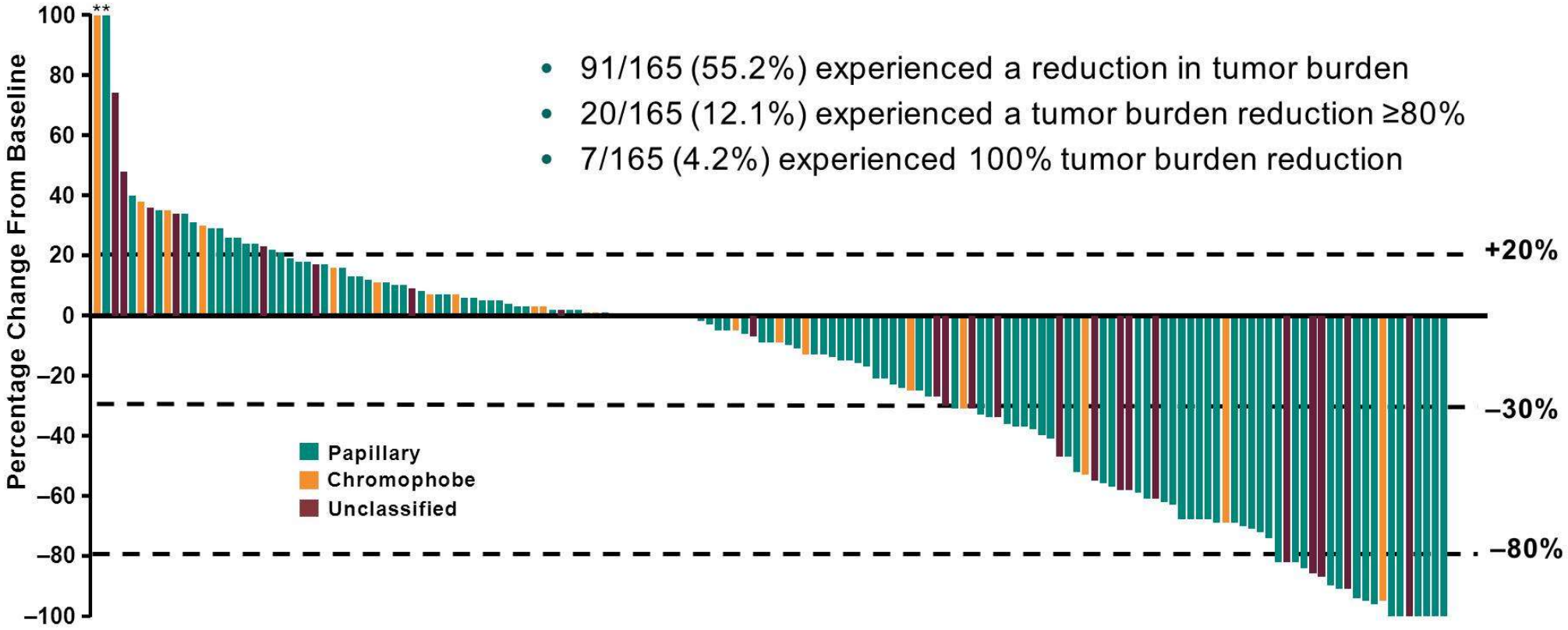
	Papillary n = 118	Chromophobe n = 21	Unclassified n = 26
Confirmed ORR, % (95%CI)	**25.4 (17.9-34.3)**	**9.5 (1.2-30.4)**	**34.6 (17.2-55.7)**
DCR, % (95%CI)[a]	**43.2 (34.1-52.7)**	**33.3 (14.6-57.0)**	**34.6 (17.2-55.7)**
Confirmed BOR, %			
CR	4.2	4.8	7.7
PR	21.2	4.8	26.9
SD	34.7	47.6	7.7
PD	33.9	42.9	46.2
No assessment[b]	5.1	0.0	7.7
Not evaluable[c]	0.8	0.0	3.8

[a]DCR = CR + PR + SD ≥6 months. [b]Includes patients who discontinued or died before first postbaseline scan. [c]Includes patients with insufficient data for response assessment.
Database cutoff: September 7, 2018.

Presented By David McDermott at 2019 Genitourinary Cancers Symposium

Keynote-427: pembrolizumab in non-clear cell RCC

Maximum Change From Baseline in Target Lesions by Central Review



- 91/165 (55.2%) experienced a reduction in tumor burden
- 20/165 (12.1%) experienced a tumor burden reduction ≥80%
- 7/165 (4.2%) 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 = 155).
*Patient had an increase in target lesions above 100%.
Database cutoff: September 7, 2018.

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Keynote-427: pembrolizumab in non-clear cell RCC

ORR by PD-L1 Expression

	CPS ≥1 n = 102	CPS <1 n = 58
Confirmed ORR, % (95%CI)	**33.3 (24.3-43.4)**	**10.3 (3.9-21.2)**
DCR, % (95%CI)[a]	**49.0 (39.0-59.1)**	**25.9 (15.3-39.0)**
Confirmed BOR, %		
CR	5.9	3.4
PR	27.5	6.9
SD	26.5	41.4
PD	33.3	43.1
No assessment[b]	4.9	5.2
Not evaluable[c]	2.0	0.0

[a]DCR = CR + PR + SD ≥6 months. [b]Includes patients who discontinued or died before first postbaseline scan. [c]Includes patients with insufficient data for response assessment.
Database cutoff: September 7, 2018.

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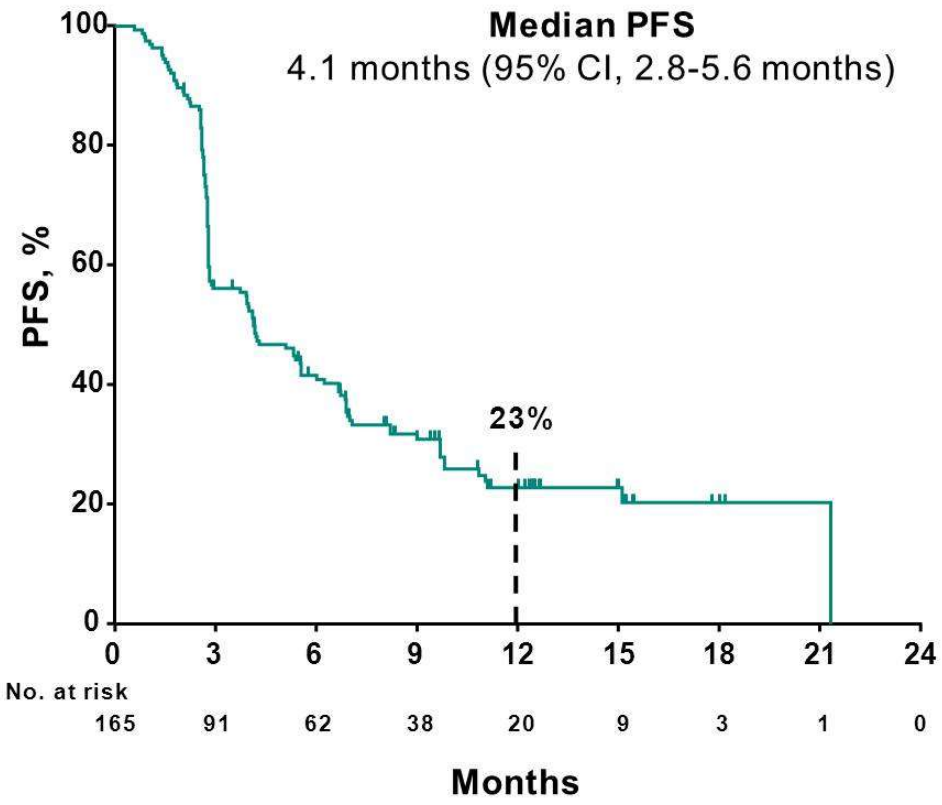
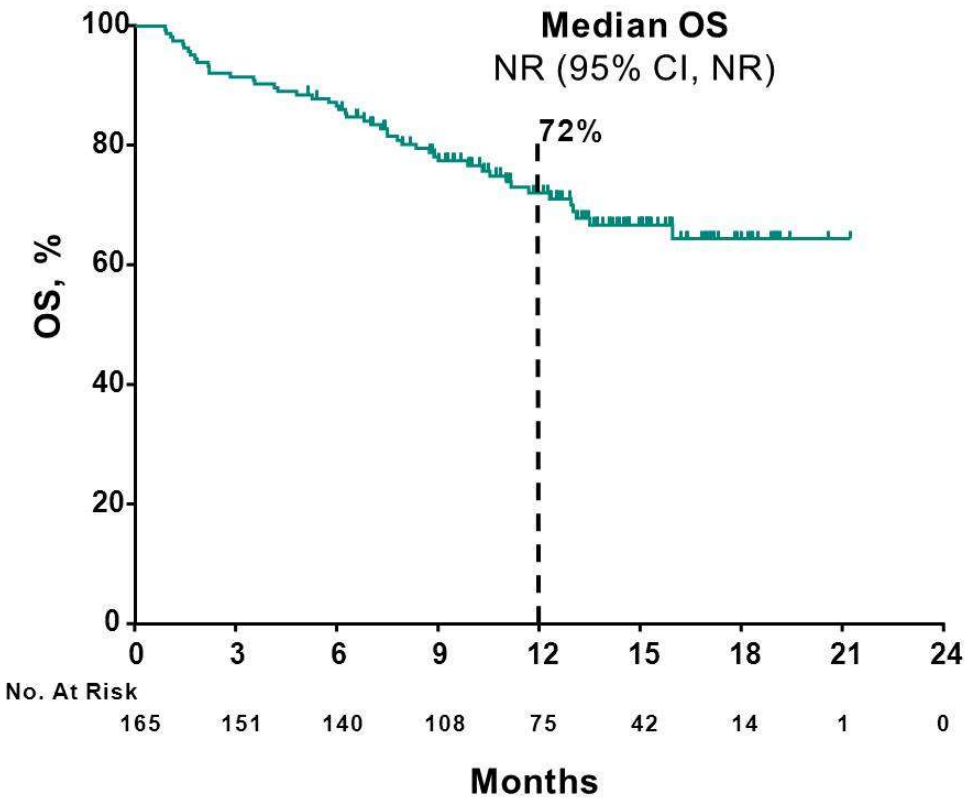
Keynote-427: pembrolizumab in non-clear cell RCC

Progression-Free Survival and Overall Survival in the Total Population





Database cutoff: September 7, 2018.

Presented By David McDermott at 2019 Genitourinary Cancers Symposium

Abstract 548 (244057): Results of a Phase II Study of Atezolizumab and Bevacizumab in Non-Clear Cell Renal Cell Carcinoma and Clear Cell Renal Cell Carcinoma with Sarcomatoid Differentiation

NCT02724878

Rana R. McKay, Bradley A. McGregor, Kathryn Gray, John A. Steinharter, Meghara K. Walsh, David A. Braun, Abdallah Flaifel, Eliezer M. Van Allen, Xiao X. Wei, Sabina Signoretti, Lauren C. Harshman, Ulka N. Vaishampayan, Toni K. Choueiri

University of California San Diego, San Diego, CA; Dana-Farber Cancer Institute, Boston, MA; Karmanos Cancer Institute, Detroit, MI

PRESENTED AT: 2019 Genitourinary Cancers Symposium | #GU19

Presented by: Rana R. McKay

Presented By Rana McKay at 2019 Genitourinary Cancers Symposium

Atezo/Bev in non-clear cell and/or sarcomatoid RCC

Objective Response Rate

	ORR
Overall	34% (n=19/56)*
Prior Treatment	
Treatment Naïve	31% (n=11/36)
Previously Treated	40% (n=8/20)
IMDC Risk Group	
IMDC Favorable Risk	33% (n=3/9)
IMDC Intermediate Risk	42% (n=14/33)
IMDC Poor Risk	14% (n=2/14)

	ORR
Clear Cell SD	53% (n=9/17)
Non-Clear	26% (n=10/39)
Sarcomatoid Present	44% (n=11/25)
Sarcomatoid Absent	26% (n=8/31)
Papillary	25% (n=3/12)
Chromophobe	10% (n=1/10)
Unclassified	29% (n=2/7)
Other#	30% (n=3/10)

Analytical cohort includes patient with at least 1 scan assessment. *Confirmed 23% (n=13/56). Complete response=2 (3.6%). #Translocation, Collecting Duct, Medullary. IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; SD=Sarcomatoid Differentiation.

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Presented by: Rana R. McKay

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