Immunotherapy for the Treatment of Kidney and Bladder Cancer

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Immunotherapy for Kidney and Bladder Cancer

Overview

Update of Recently Approved Therapies in First and Second Line Settings

Rationale for New Combination Therapies

Future Strategies

ALAN KOLETSKY, MD

Immunotherapy in Kidney & Bladder Cancers

Relevant Financial Relationships in the Past Twelve Months By Presenter or Spouse /Partner

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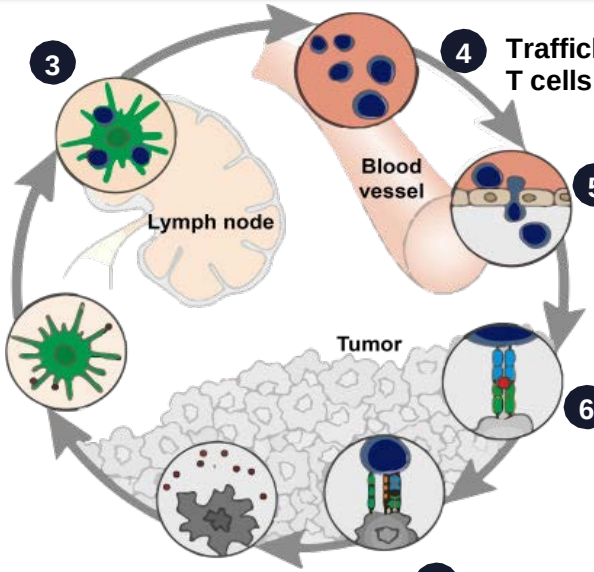
Multiple Steps Required for Anticancer Activity[1]

Priming and activation
- Anti–CTLA-4
- Anti-CD137 (agonist)
- Anti-OX40 (agonist)
- Anti-CD27 (agonist)
- IL-2
- IL-12

Cancer antigen presentation
- Vaccines
- IFN-α
- GM-CSF/T-VEC
- Anti-CD40 (agonist)
- TLR agonists

Release of cancer cell antigens
- Chemotherapy
- Radiation therapy
- Targeted therapy



Trafficking of T cells to tumors

Infiltration of T cells into tumors
- Anti-VEGF
- Anti-CXCR4

Recognition of cancer cells by T cells
- CAR-T cell therapy
- HDAC inhibitors

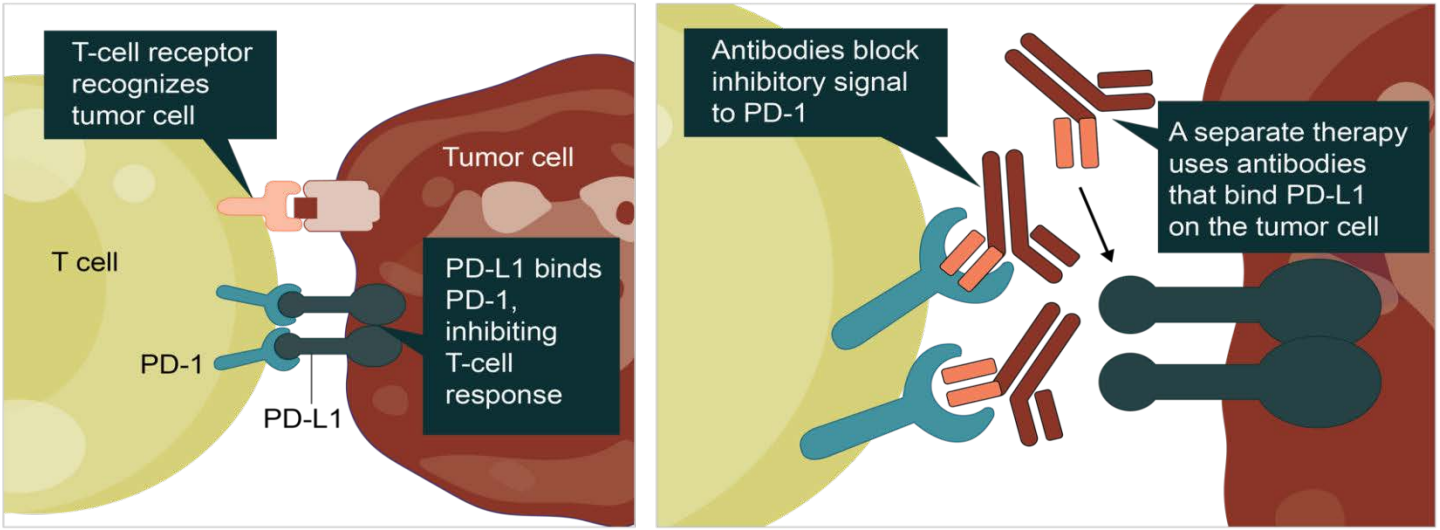
Killing of cancer cells and tolerance
- Anti–PD-1/PD-L1
- IDO inhibitors
- Anti–LAG-3

- **Multiple processes are required to establish and maintain an effective immune response**
- **Determinants of sensitivity and resistance not clearly defined yet**

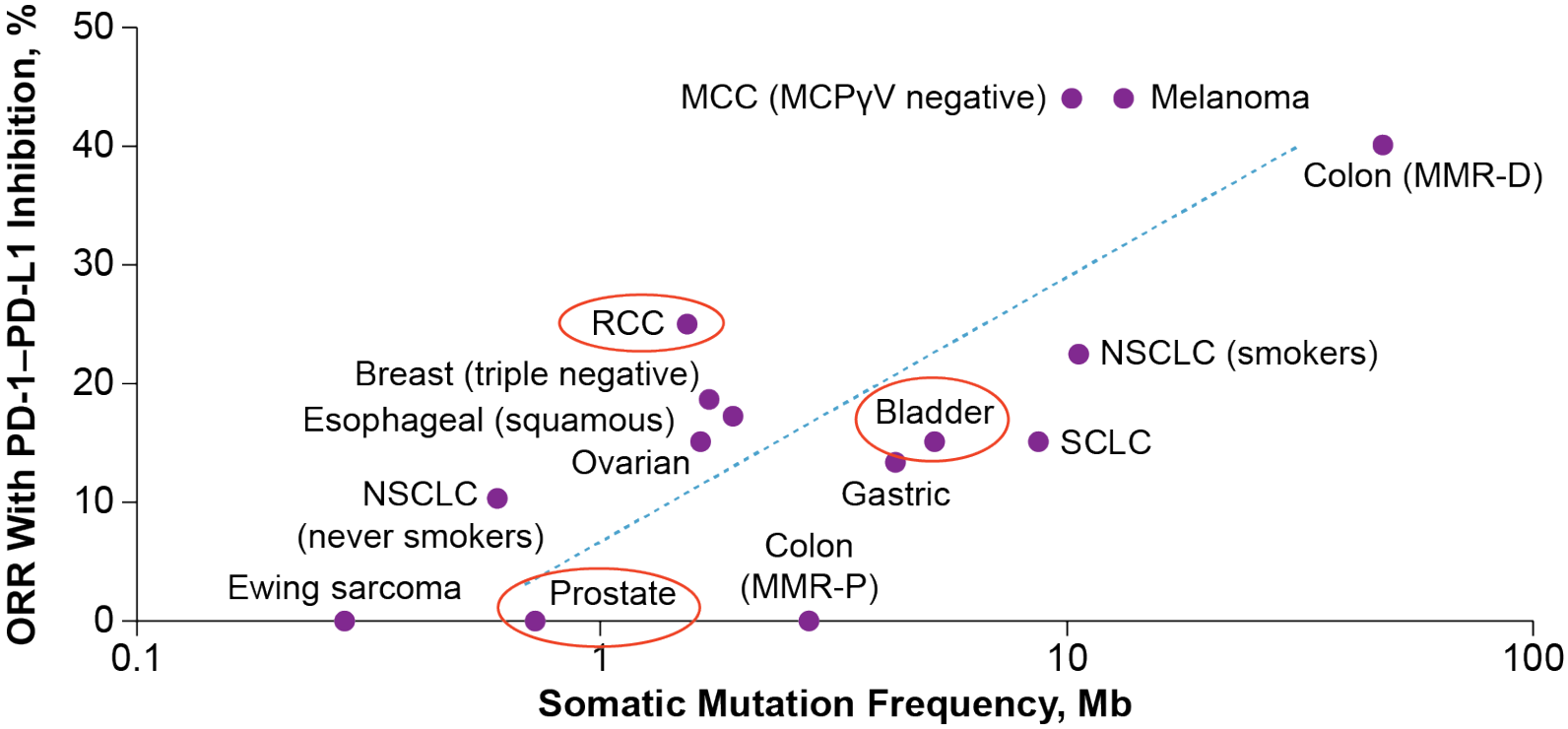
1. Chen DS et al. *Immunity*. 2013;39:1-10.

Immune Checkpoint Blockade in Cancer

Tumor cells can inhibit the body's immune response by binding to proteins, such as PD-1, on the surface of T cells; antibody therapies that block this binding reactivate the immune response



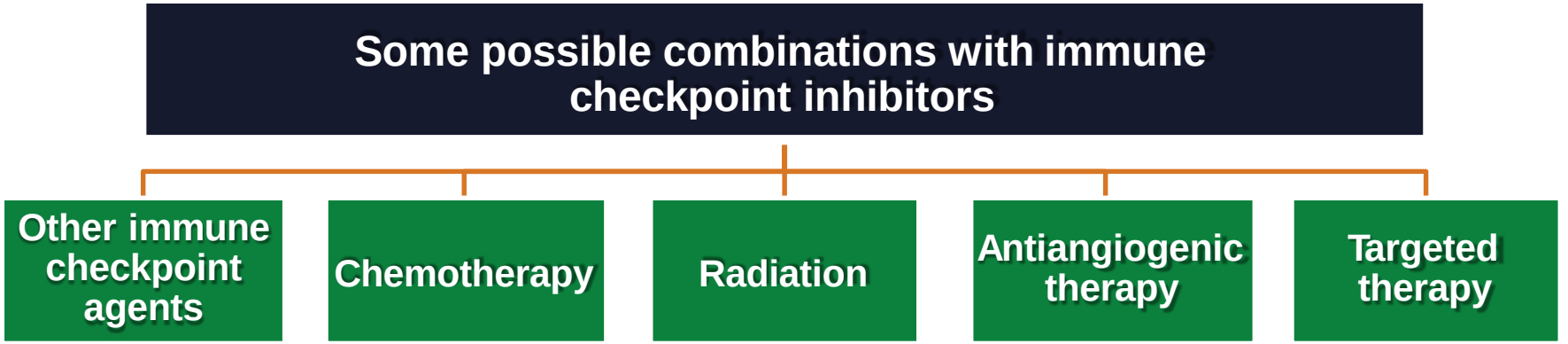
Response Rate and Tumor Mutational Burden[1]



1. Yarchoan M et al. *Nature Rev Cancer*. 2017;17:209-222.

Overcoming Immunotherapy Resistance

- Multiple strategies may be considered
- Tip balance away from tumor-protective mechanisms and towards antitumor immunity
- Rational combinations are required to move the field forward
- Some are leading to improved survival



Targeting the PD-1/PD-L1 Axis Has Activity in GU Cancers

5 anti–PD-1/anti–PD-L1 drugs now approved for advanced urothelial carcinoma

Atezolizumab, nivolumab, durvalumab, avelumab, pembrolizumab

Nivolumab approved for kidney cancer

Two positive phase 3 trials for combination therapy:

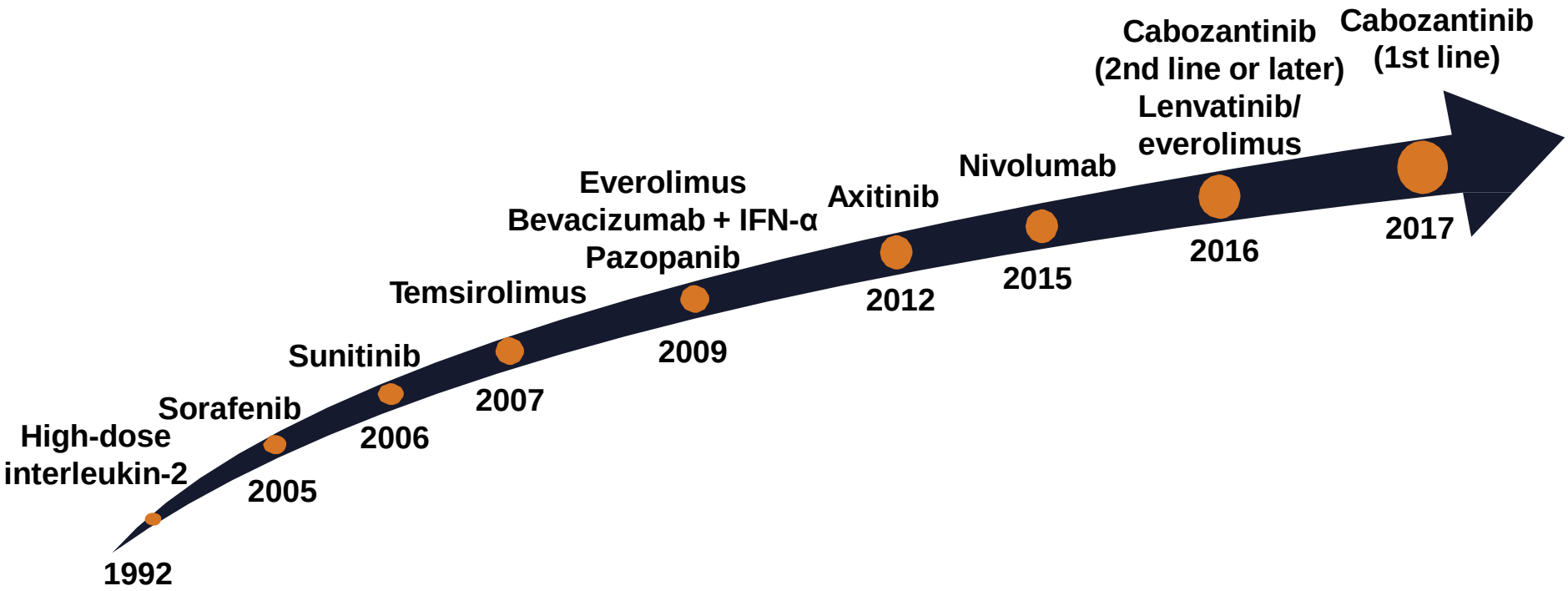
- Ipilimumab/nivolumab in first-line therapy
- Atezolizumab/bevacizumab as first-line therapy in PD-L1–positive tumors

Provocative data with enzalutamide-resistant cancers responding to pembrolizumab

Multiple large trials ongoing

Immunotherapy for the Treatment of Renal Cell Carcinoma

Approved Therapies for Renal Cell Carcinoma



1. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed January 26, 2018.

New Options for Pretreated Patients

NCCN recommended parameters of risk stratification

Poor-Prognosis patients are defined as those with 3 or more predictors of short survival

Karnofsky performance score of 70 or less

Corrected Serum Calcium level > 10 mg/dl (2.5 mmol/liter)

Lactate dehydrogenous level > 1.5 times upper limit of normal

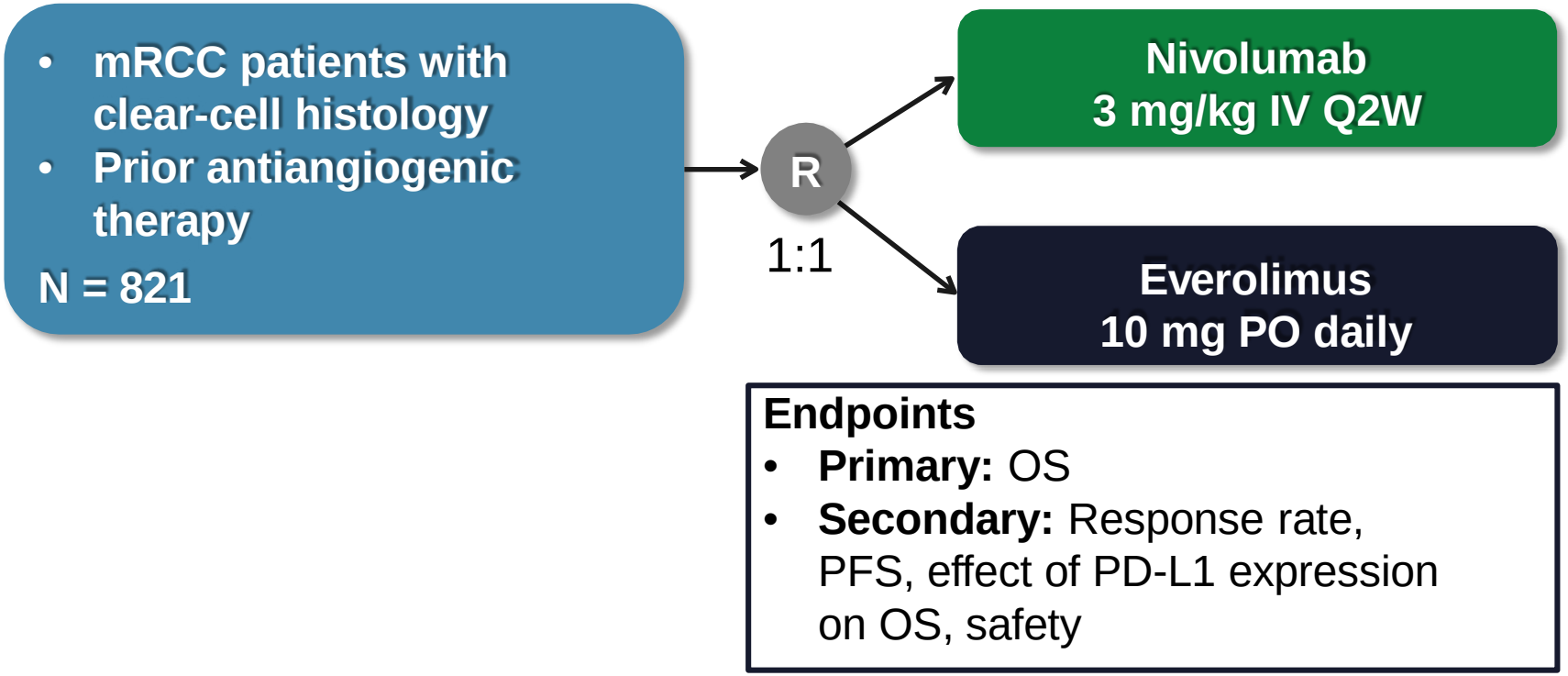
Hemoglobin Level < lower Limit of normal

Interval less than a year from original diagnosis to start of systemic therapy

2 or more sites of organ metastasis

***NCCN Guidelines 2013 Kidney Cancer**

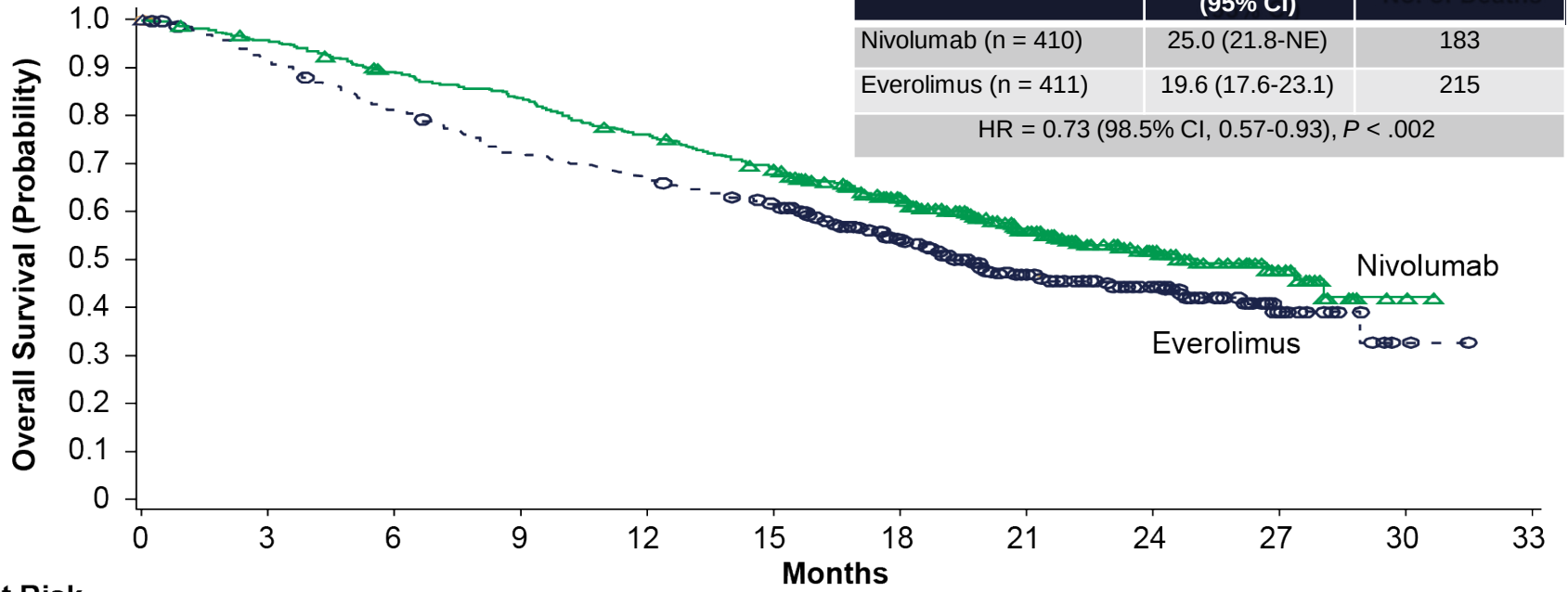
CheckMate-025: Phase 3 Study of Nivolumab vs Everolimus[1]



1. Motzer RJ et al. *N Engl J Med*. 2015;373:1803-1813.

CheckMate-025: Overall Survival[1]

	Median OS, mo (95% CI)	No. of Deaths
Nivolumab (n = 410)	25.0 (21.8-NE)	183
Everolimus (n = 411)	19.6 (17.6-23.1)	215
HR = 0.73 (98.5% CI, 0.57-0.93), *P* < .002		



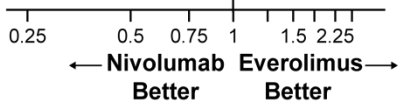
No. at Risk

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

1. Motzer RJ et al. *N Engl J Med*. 2015;373:1803-1813.

CheckMate-025: Subgroup Analysis of OS[1]

Subgroup	Nivolumab	Everolimus	Unstratified Hazard Ratio for Death (95% CI)
Overall	183/410	215/411	0.76 (0.62-0.92)
MSKCC risk group			
Favorable	45/145	52/148	0.89 (0.59-1.32)
Intermediate	101/201	116/203	0.76 (0.58-0.99)
Poor	37/64	47/60	0.47 (0.30-0.73)
Prior anti-angiogenic regimens			
1	128/294	158/297	0.71 (0.56-0.90)
2	55/116	57/114	0.89 (0.61-1.29)
Region			
US/Canada	66/174	87/172	0.66 (0.48-0.91)
Western Europe	78/140	84/141	0.86 (0.63-1.16)
Rest of the world	39/96	44/98	0.78 (0.51-1.20)
Age, years			
<65	111/257	118/240	0.78 (0.60-1.01)
≥65 to <75	53/119	77/131	0.64 (0.45-0.91)
≥75	19/34	20/40	1.23 (0.66-2.31)
Sex			
Female	48/95	56/107	0.84 (0.57-1.24)
Male	135/315	159/304	0.73 (0.58-0.92)



1. Adapted from: Motzer RJ et al. *N Engl J Med*. 2015;373:1803-1813.

ORR by Risk Level[1]

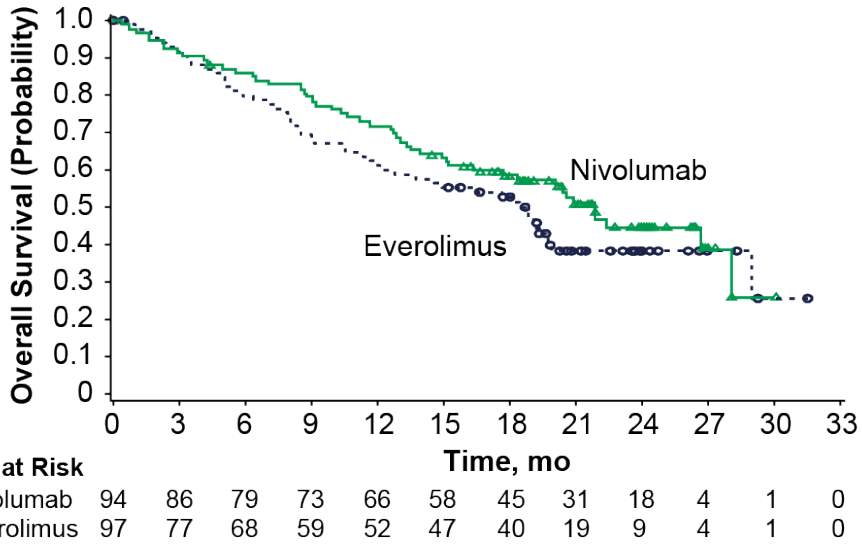
MSKCC Risk Group	Nivolumab, %	Everolimus, %
Favorable	24	8
Intermediate	25	5
Poor	27	3

1. Escudier B et al. *Eur Urol*. 2017;72:962-971.

Overall Survival by Tumoral PD-L1 Expression[1]

Patients With ≥1% PD-L1 Expression

	Median OS, mo (95% CI)	No. of Deaths
Nivolumab (n = 94)	21.8 (16.5-28.1)	48
Everolimus (n = 87)	18.8 (11.0-19.9)	51

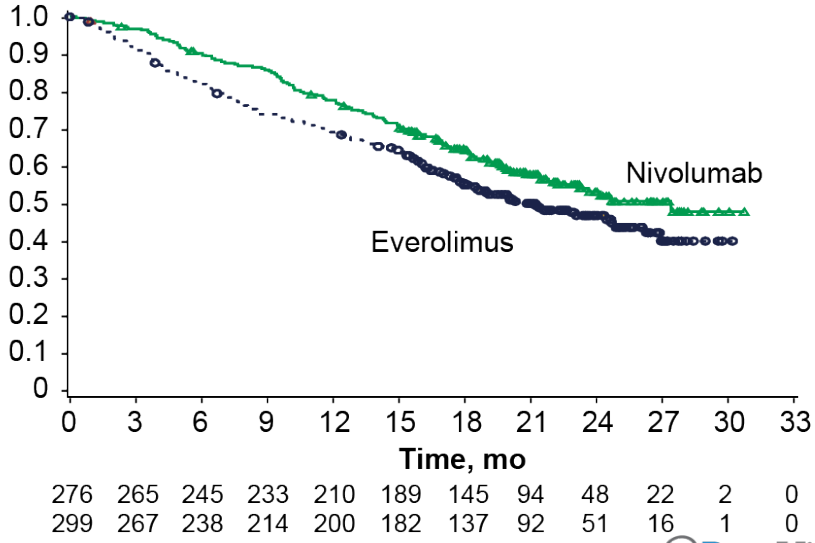


No. at Risk

Nivolumab	94	86	79	73	66	58	45	31	18	4	1	0
Everolimus	97	77	68	59	52	47	40	19	9	4	1	0

Patients With <1% PD-L1 Expression

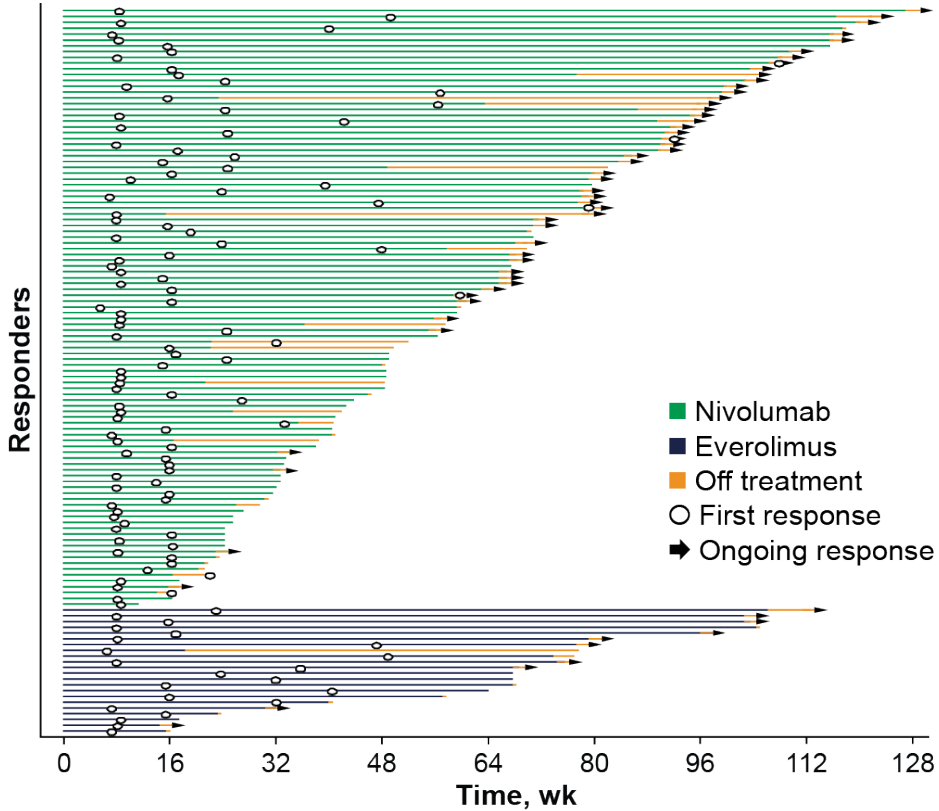
	Median OS, mo (95% CI)	No. of Deaths
Nivolumab (n = 276)	27.4 (21.4-NE)	118
Everolimus (n = 299)	21.2 (17.7-26.2)	150



Nivolumab	276	265	245	233	210	189	145	94	48	22	2	0
Everolimus	299	267	238	214	200	182	137	92	51	16	1	0

1. Motzer RJ et al. *N Engl J Med*. 2015;373:1803-1813.

CheckMate-025: Duration of Response[1]



Response Rate
Nivolumab 21.5%
Everolimus 3.9%

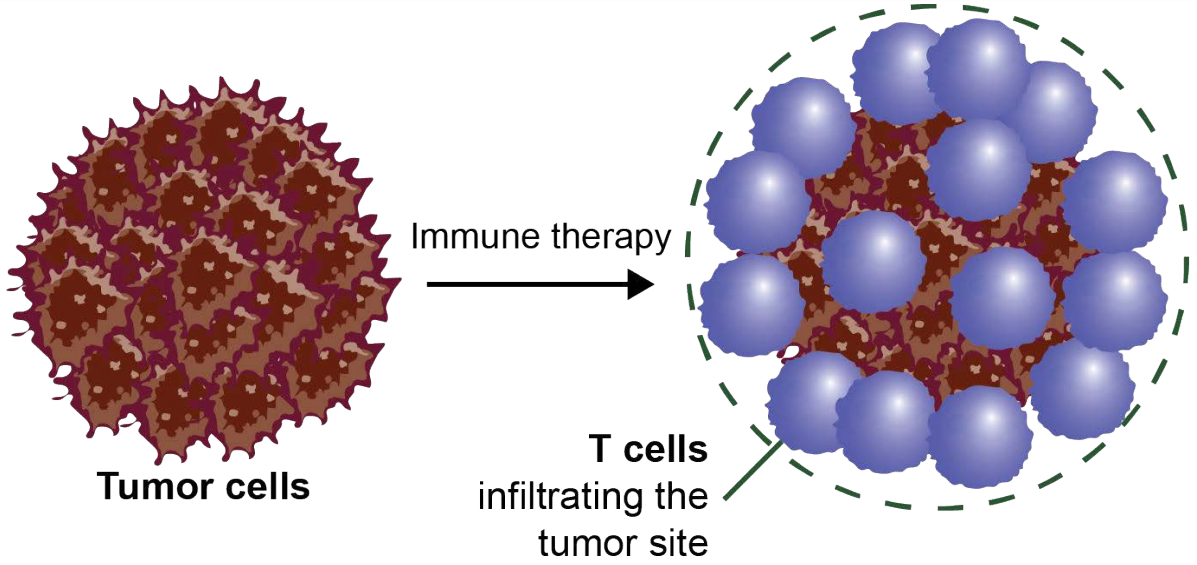
DOR
Nivolumab 23.0 months
Everolimus 13.7 months

Number of patients with durable benefit off therapy

Optimal duration of therapy unknown

1. Motzer RJ et al. *N Engl J Med*. 2015;373:1803-1813.

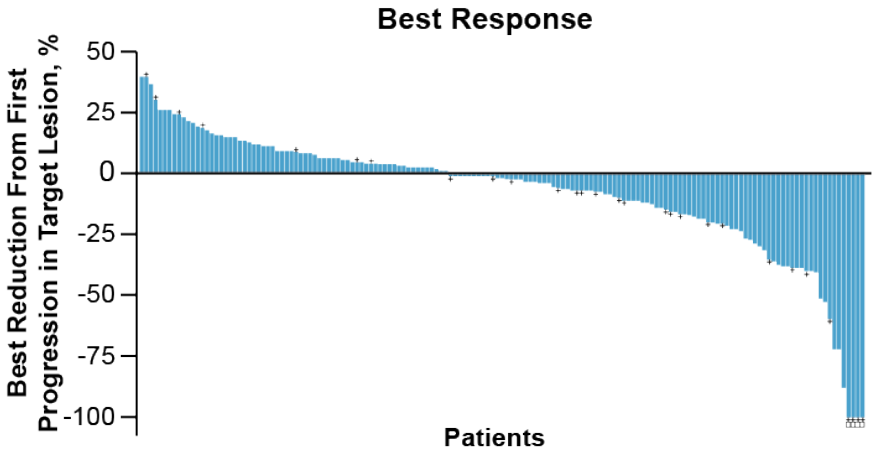
Tumor Flare With Immunotherapy[1]

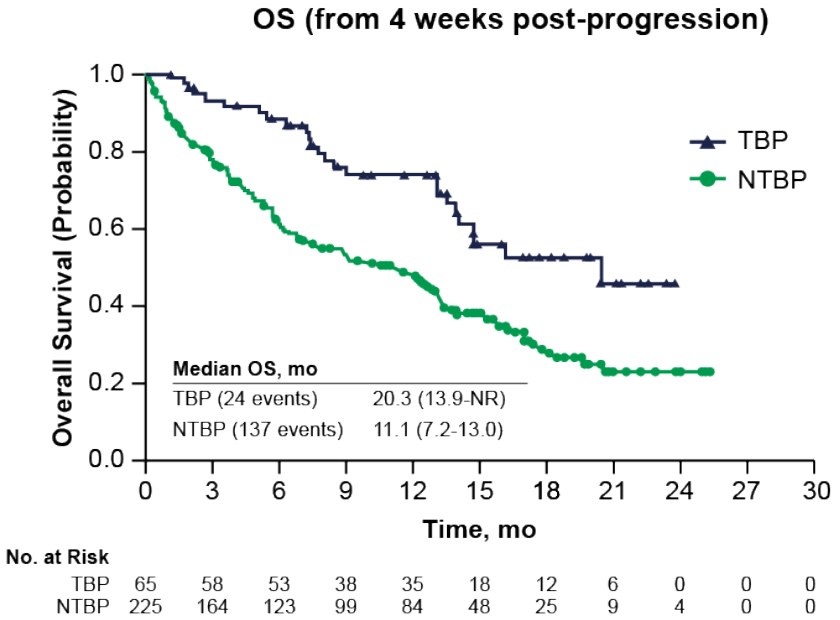


- In patients on immunotherapy, tumor flare or the appearance of new lesions may precede antitumor effects
  - This phenomenon may be characterized as a RECIST-defined progression and may result in premature discontinuation of therapy

1. Wolchok JD et al. *Clin Cancer Res*. 2009;15:7412-7420.

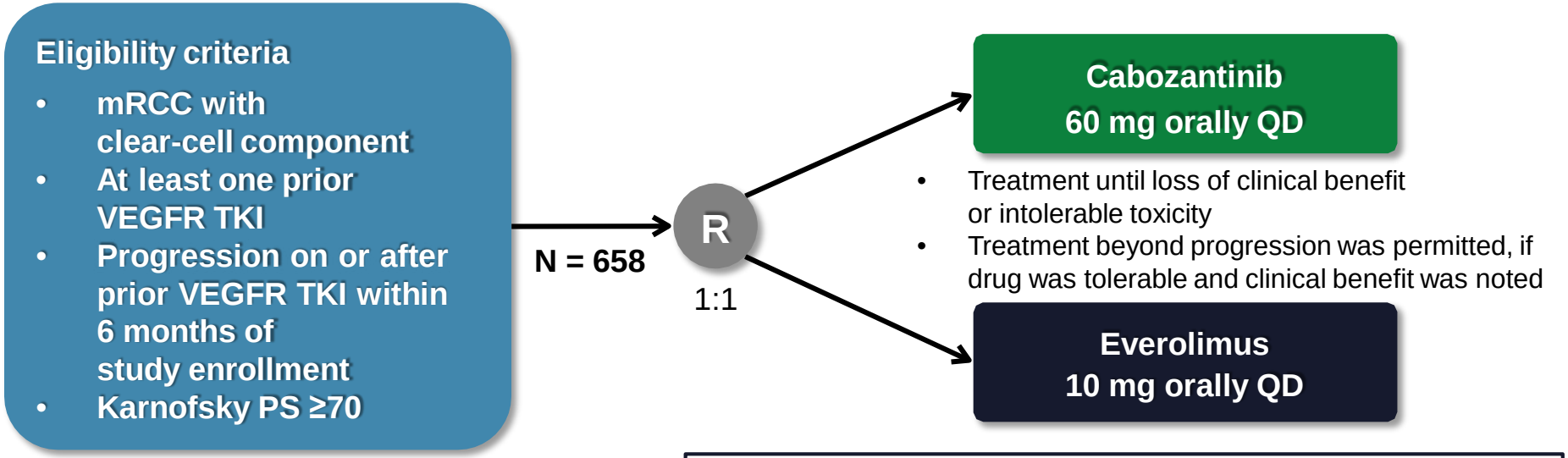
CheckMate-025: Treatment Beyond Progression[1]





1. Escudier B et al. *Eur Urol*. 2017;72:368-376.

METEOR: Phase 3 Study of Cabozantinib vs Everolimus[1]

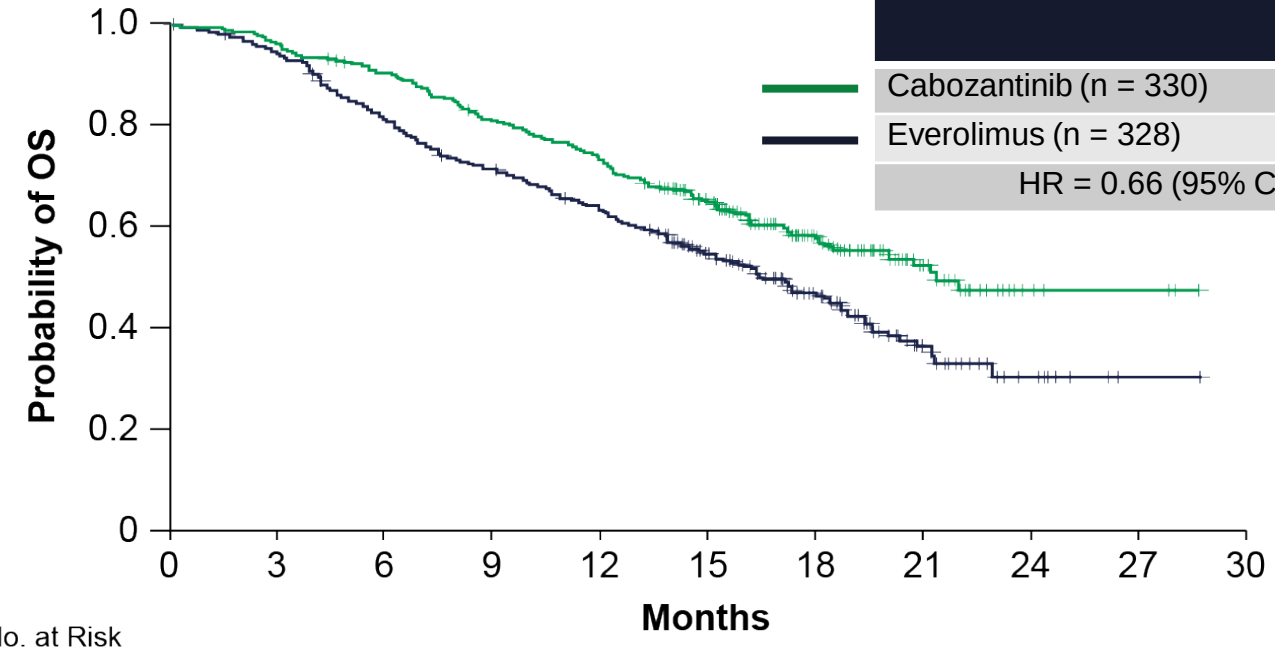


Stratification: MSKCC risk criteria; number of prior VEGFR TKIs

- **Primary endpoint:** PFS
- **Secondary endpoints:** OS, ORR
- **Exploratory endpoints:** Safety, tolerability, tumour MET status, circulating tumour cells, serum bone markers and plasma biomarkers, skeletal-related events, and HRQOL

1. Choueiri TK et al. *N Engl J Med.* 2015;373:1814-1823.

METEOR: OS[1,a]



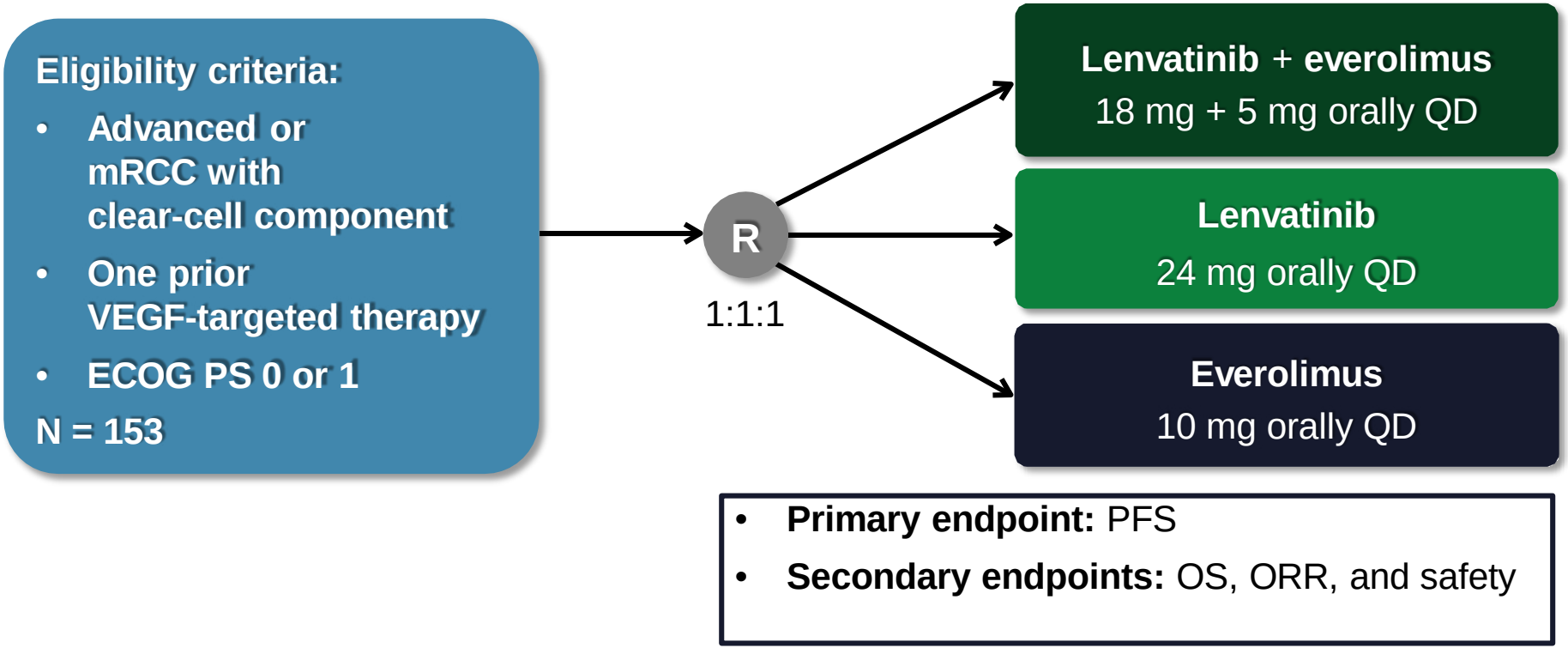
	Median OS, mo (95% CI)	No. of Deaths
Cabozantinib (n = 330)	21.4 (18.7-NE)	140
Everolimus (n = 328)	16.5 (14.7-18.8)	180
HR = 0.66 (95% CI, 0.53-0.83) , *P* = .00026		

No. at Risk											
Cabozantinib	330	318	296	264	239	178	105	41	6	3	0
Everolimus	328	307	262	229	202	141	82	32	8	1	0

[a] Cut-off: December 31, 2015.

1. Choueiri TK et al. *Lancet Oncol*. 2016;17:917-927.

Lenvatinib Alone or Plus Everolimus vs Everolimus Randomized Phase 2 Trial[1]



1. Motzer RJ et al. *Lancet Oncol*. 2016;17:e4-e5.

Phase 2 Lenvatinib Plus Everolimus: Efficacy

Primary Analysis	Lenvatinib + Everolimus (n = 51)	Lenvatinib (n = 52)	Everolimus (n = 50)
Median PFS, mo (95% CI)[1,a]	12.8 (7.4-17.5)	9.0 (5.6-10.2)	5.6 (3.6-9.3)
Median OS, mo (95% CI)[2]	25.5 (20.8-25.5)	18.4 (13.3-NE)	17.5 (11.8-NE)
ORR, n (%)[1,a]	18 (35)	20 (39)	0 (0)
Median duration of response, mo (95% CI)[2]	13.1 (3.8-NE)	7.5 (3.8-NE)	8.5 (7.5-9.4)
Median number of cycles (range)[2]	9.0 (1-25)	8.5 (1-25)	5.0 (1-22)

[a] As assessed by an independent radiologic review.

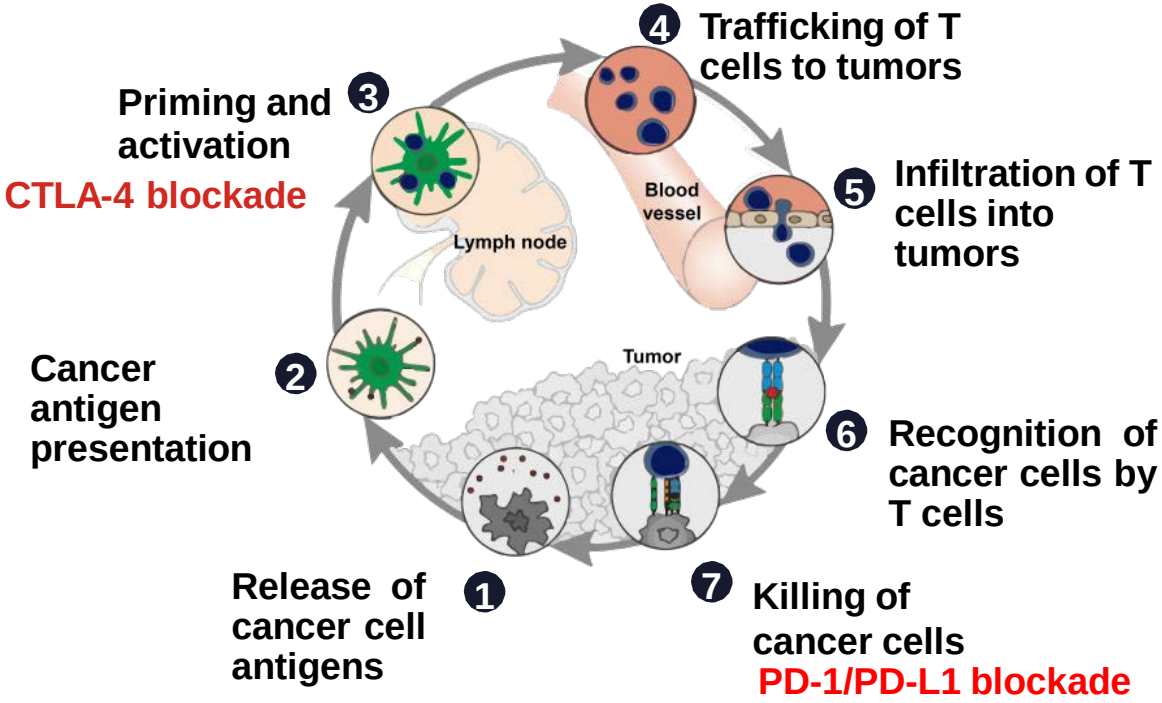
1. Motzer RJ et al. *Lancet Oncol.* 2016;17:e4-e5. 2. Motzer RJ et al. *Lancet Oncol*. 2015;6:1473-1482.

Key Points: Second-Line Therapy

- Level 1 data supports use of nivolumab OR cabozantinib
- Toxicities vary between VEGF pathway– versus PD-1 pathway–directed therapy
- No clear evidence for clinical choice
- No definitive biomarkers
- Role of additional combinations being tested
- Phase 3 confirmatory trial of lenvatinib + everolimus pending

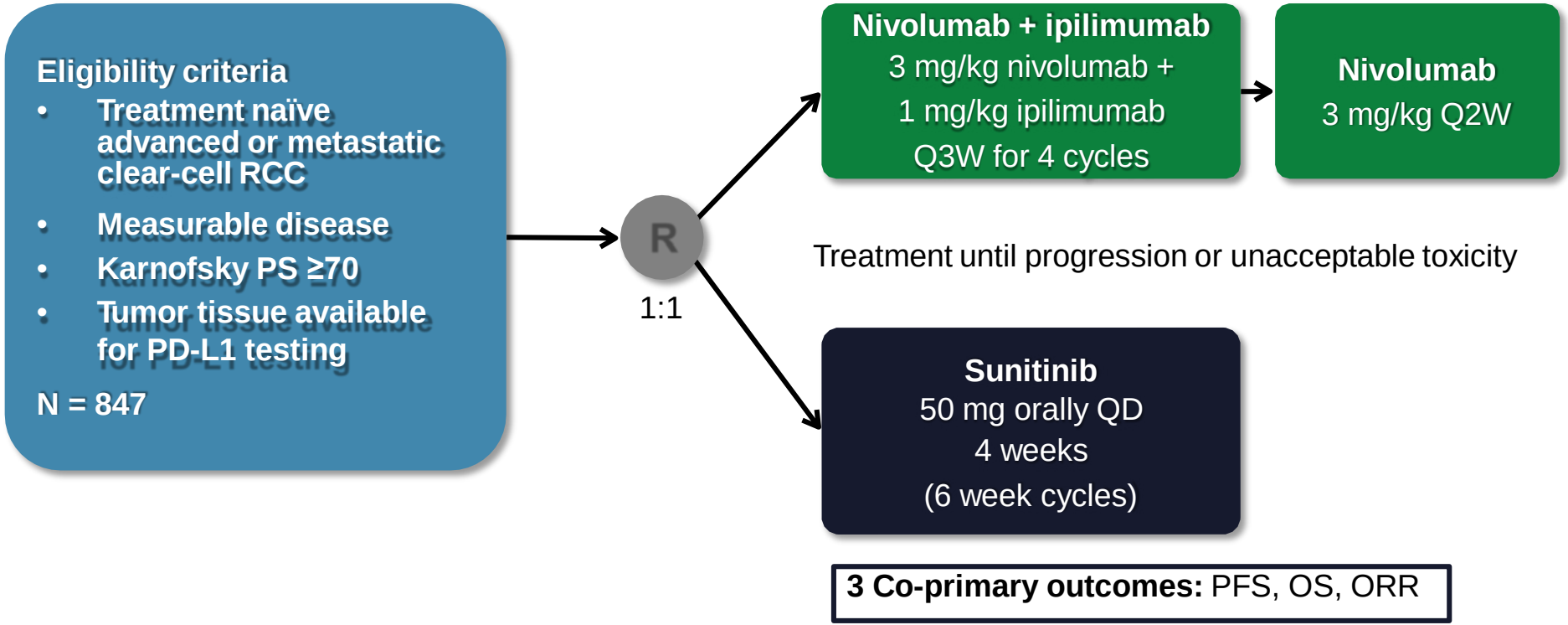
What About Front-Line Therapy?

Is CTLA-4 Blockade Synergistic With Anti–PD-1?[1]



1. Chen DS, Mellman I. *Immunity*. 2013;39:1-10.

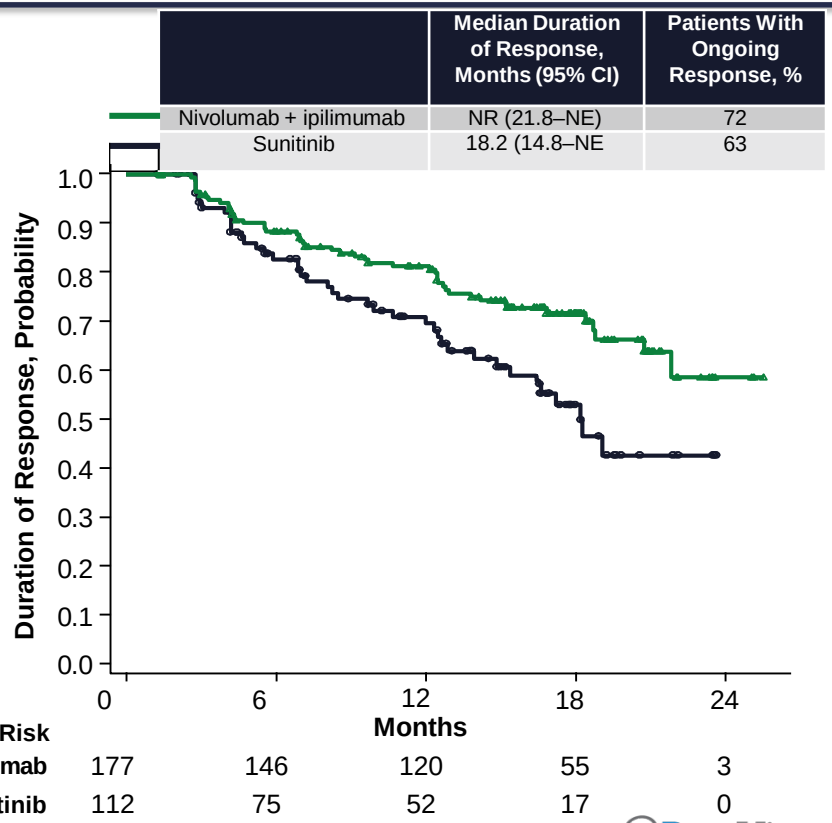
CheckMate-214: Phase 3 Trial[1]



1. Escudier B et al. ESMO 2017. Abstract LBA5.

CheckMate-214: ORR per IRCC
IMDC Intermediate-Risk/Poor-Risk Patients[1]

Outcome (N = 847)	Nivolumab + ipilimumab (n = 425)	Sunitinib (n = 422)
Confirmed ORR,[a] % (95% CI)	42 (37–47)	27 (22–31)
	P < .0001	
Confirmed BOR,[a] %		
Complete response	9[b]	1[b]
Partial response	32	25
Stable disease	31	45
Progressive disease	20	17
Unable to determine/not reported	8	12

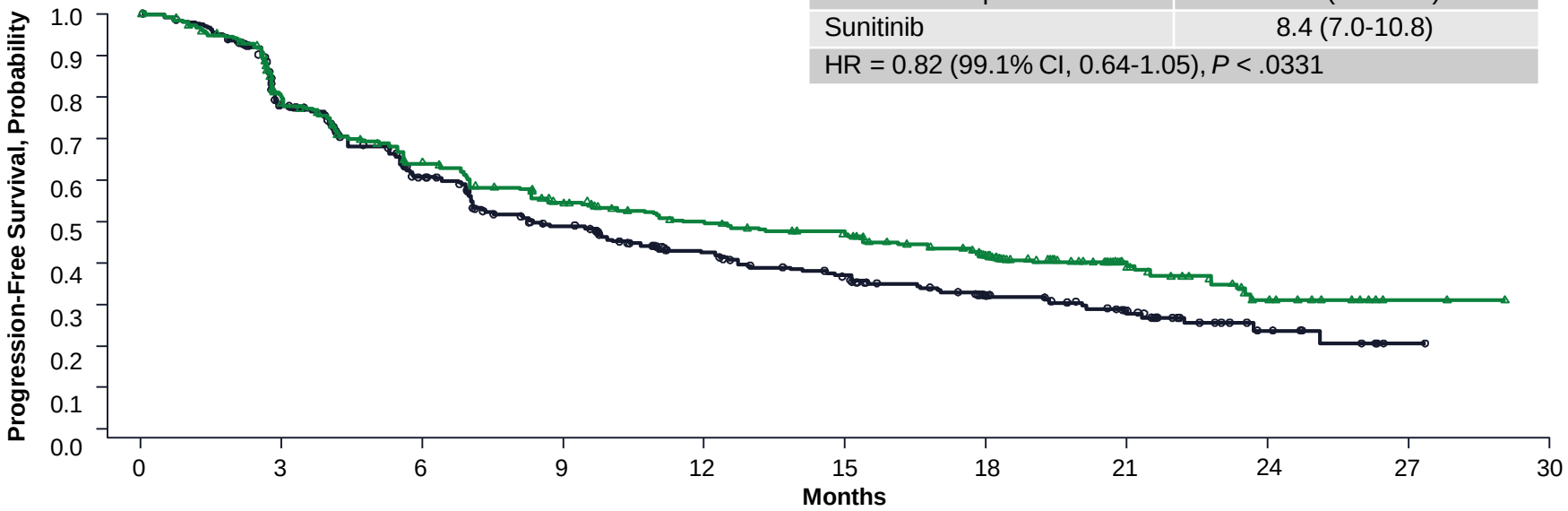


[a] IRRC-assessed ORR and BOR by RECIST v1.1. [b] *P* < 0.0001.

1. Escudier B et al. ESMO 2017. Abstract LBA5.

CheckMate-214: PFS per IRRC
IMDC Intermediate-Risk/Poor-Risk Patients[1]

	Median PFS (95% CI), mo
Nivolumab + ipilimumab	11.6 (8.7-15.5)
Sunitinib	8.4 (7.0-10.8)
HR = 0.82 (99.1% CI, 0.64-1.05), *P* < .0331	



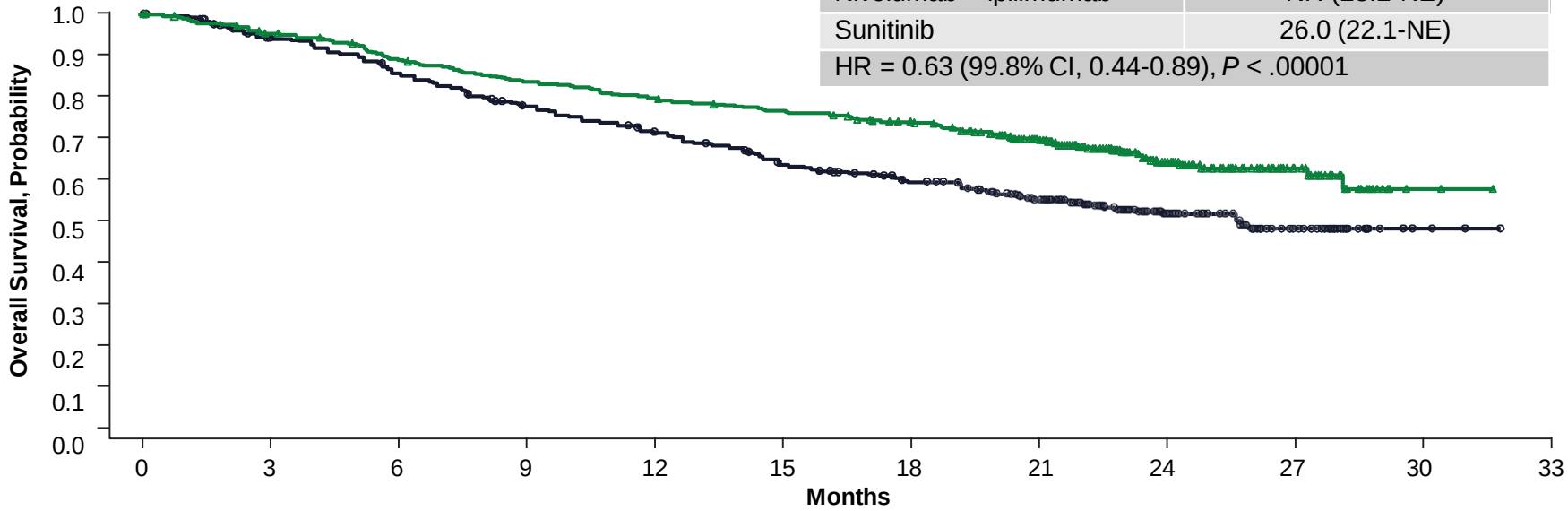
No. at Risk											
Nivolumab + ipilimumab	425	304	233	187	163	149	118	46	17	3	0
Sunitinib	422	282	191	139	107	86	57	33	11	1	0

1. Escudier B et al. ESMO 2017. Abstract LBA5.

CheckMate-214: OS

IMDC Intermediate-Risk/Poor-Risk Patients[1]

	Median OS (95% CI), mo
Nivolumab + ipilimumab	NR (28.2-NE)
Sunitinib	26.0 (22.1-NE)
HR = 0.63 (99.8% CI, 0.44-0.89), *P* < .00001	



No. at Risk												
Nivolumab + ipilimumab	425	399	372	348	332	318	300	241	119	44	2	0
Sunitinib	422	387	352	315	288	253	225	179	89	34	3	0

1. Escudier B et al. ESMO 2017. Abstract LBA5.

CheckMate 214: ORR and PFS per IRRC
IMDC Favorable Risk[1]

Outcome, N = 249[a]	Nivolumab + Ipilimumab (n = 125)	Sunitinib (n = 124)
Confirmed ORR,[b] % (95% CI)	29 (21–38)	52 (43–61)
	P = .0002	
PFS,[c] median (95% CI), months	15.3 (9.7–20.3)	25.1 (20.9–NE)
	HR (99.1% CI) 2.18 (1.29–3.68) *P* < .0001	

[a] 11% of patients in both arms had tumor PD-L1 expression ≥1%. [b] IRRC assessed by RECIST v1.1. [c] IRRC assessed.

1. Escudier B et al. ESMO 2017. Abstract LBA5.

CheckMate-214: Treatment-Related Adverse Events[1]

Event, %	Nivolumab + Ipilimumab (n = 547)		Sunitinib (n = 535)	
	Any Grade	Grade 3–5	Any Grade	Grade 3–5[a]
Treatment-related adverse events in ≥25% of patients	93	46	97	63
Fatigue	37	4	49	9
Pruritus	28	<1	9	0
Diarrhea	27	4	52	5
Nausea	20	2	38	1
Hypothyroidism	16	<1	25	<1
Decreased appetite	14	1	25	1
Dysgeusia	6	0	33	<1
Stomatitis	4	0	28	3
Hypertension	2	<1	40	16
Mucosal inflammation	2	0	28	3
Palmar-plantar erythrodysesthesia syndrome	1	0	43	9
Treatment-related AEs leading to discontinuation, %	22	15	12	7
Treatment-related deaths	n = 7[b]		n = 4[c]	

[a] Two patients had grade 5 cardiac arrest. [b] Pneumonitis, immune-mediated bronchitis, lower GI hemorrhage, hemophagocytic syndrome, sudden death, liver toxicity, lung infection. [c] Cardiac arrest (n = 2), heart failure, multiple organ failure.

1. Escudier B et al. ESMO 2017. Abstract LBA5.

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Hypothyroidism	16	<1	25	<1
Decreased appetite	14	1	25	1
Dysgeusia	9	0	33	<1
Stomatitis	4	0	28	3
Hypertension	2	<1	40	16
Mucosal inflammation	2	0	28	3
Palmar-plantar erythrodysesthesia syndrome	1	0	43	9
Treatment-related AEs leading to discontinuation, %	22	15	12	7
Treatment-related deaths	n = 7[b]		n = 4[c]	

60% of patients treated with nivolumab + ipilimumab required systemic corticosteroids,

45% high dose steroids for an adverse event

[a] Two patients had grade 5 cardiac arrest. [b] Pneumonitis, immune-mediated bronchitis, lower GI hemorrhage, hemophagocytic syndrome, sudden death, liver toxicity, lung infection. [c] Cardiac arrest (n = 2), heart failure, multiple organ failure.

1. Escudier B et al. ESMO 2017. Abstract LBA5.

CABOSUN: Randomized Phase 2 Assessment of Front-Line Cabozantinib[1]

Multicenter, randomized, phase 2 study

- Clear-cell RCC
- Intermediate or poor risk
- No prior systemic therapy

N = 157

R

Cabozantinib 60 mg/d (Continuous dosing) (n = 79)

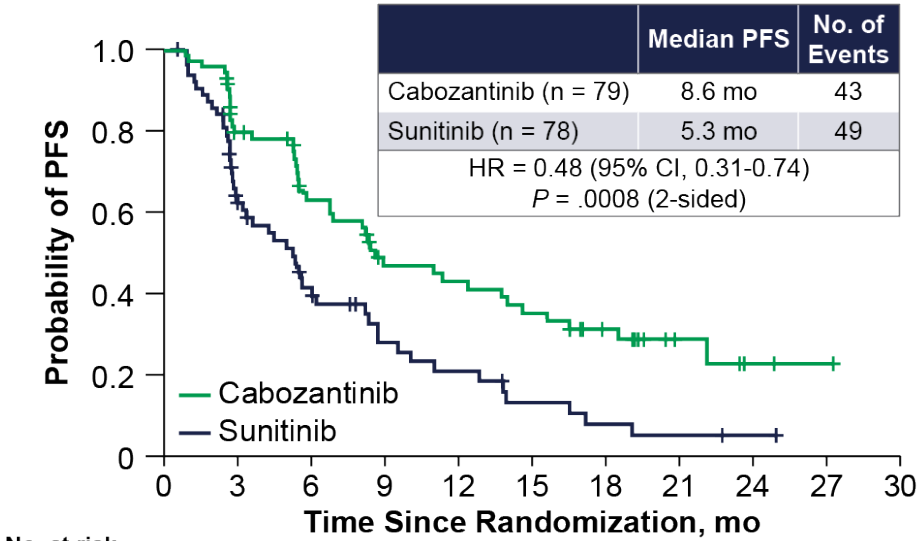
Sunitinib 50 mg/d (4/2 dosing) (n = 78)

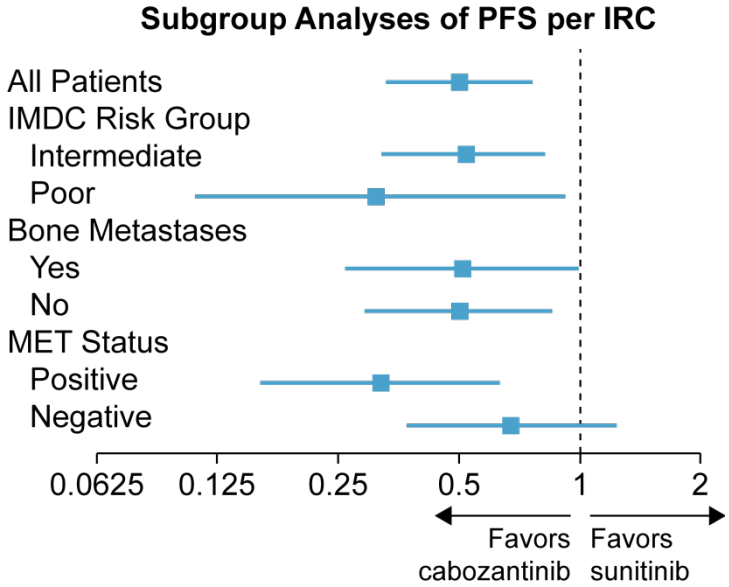
Stratified by:
- International Metastatic Renal Cell Carcinoma Database Consortium risk group (intermediate vs poor)
- Bone metastasis (yes/no)

Primary endpoint: PFS

1. Choueiri TK et al. *J Clin Oncol.* 2016;35:591-597.

CABOSUN: PFS per IRC and OS[1,a]



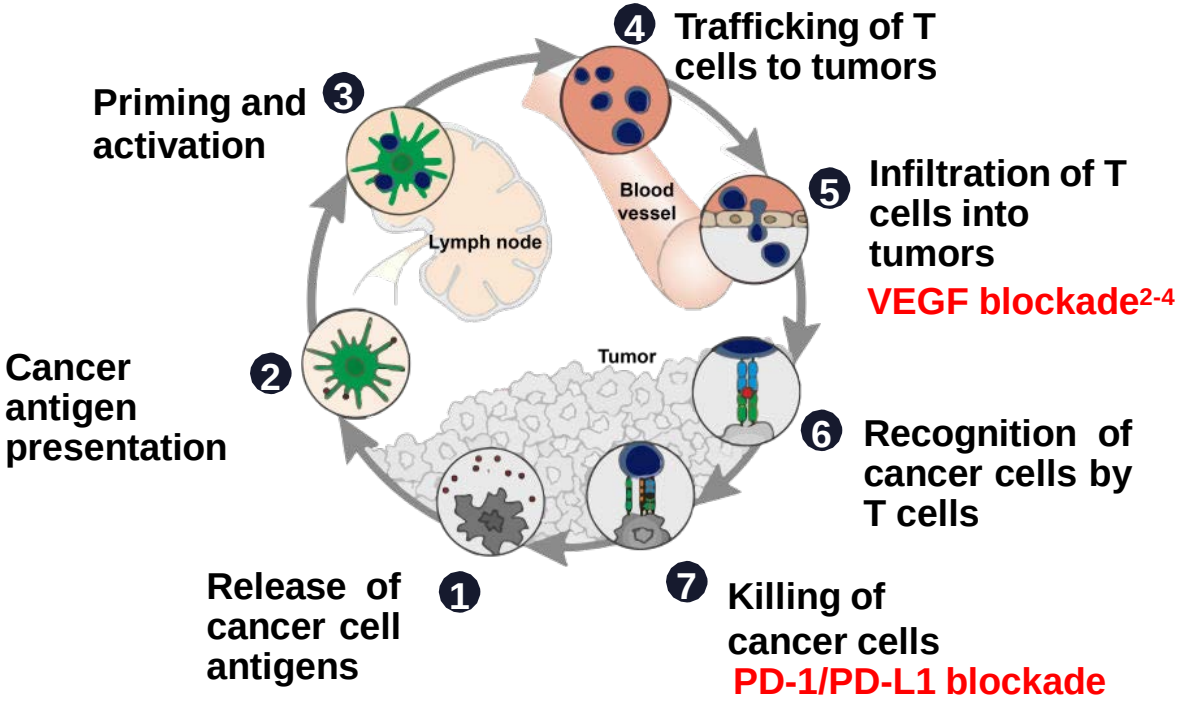


OS
HR = 0.80 (95% CI, 0.53-1.21)
P = .29 (2-sided)
Median OS: cabozantinib, 26.6 mo; sunitinib, 21.2 mo

[a] Data cutoff: PFS, September 15, 2016; OS, July 1, 2017.

1. Choueiri TK et al. ESMO 2017. Abstract LBA38.

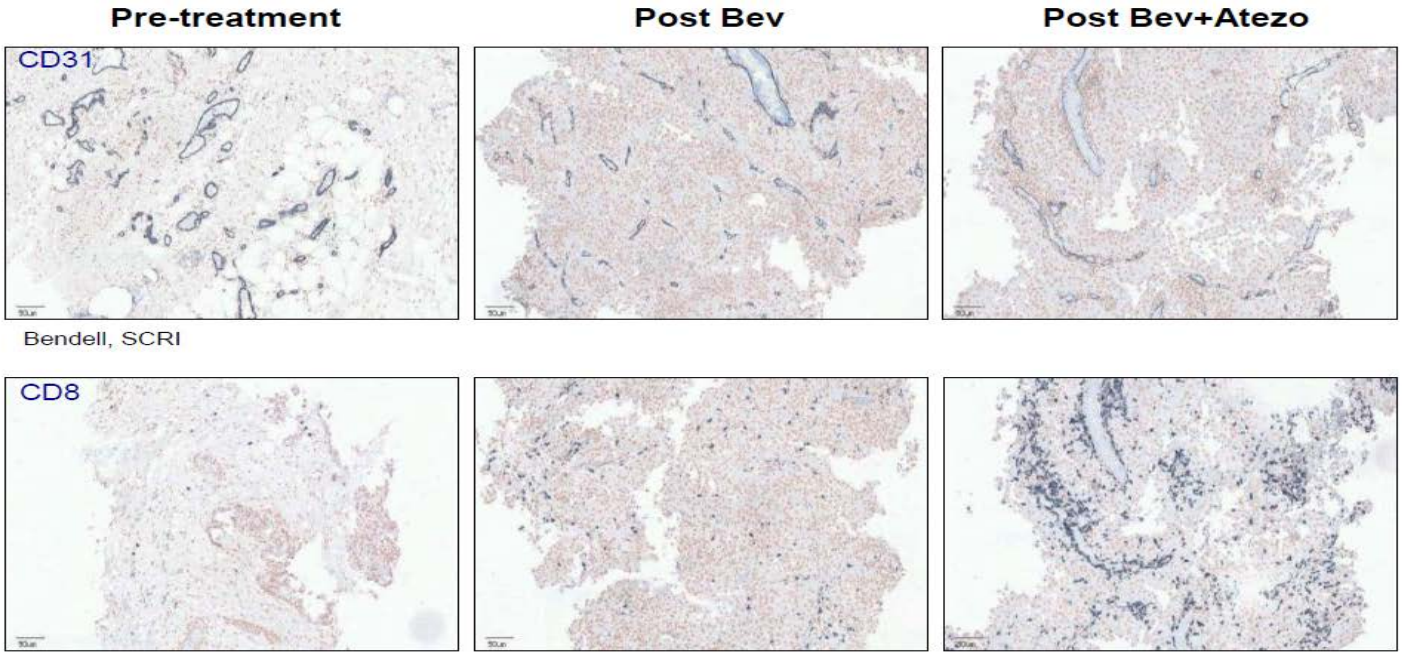
Is VEGF Inhibition Synergistic With Anti–PD-1?[1]



1. Chen DS, Mellman I. *Immunity*. 2013;39:1-10. 2. Shrimali RK et al. *Can Res.* 2010;70:6171-6180. 3. Manning EA et al. *Clin Cancer Res.* 2007;13:3951-3959. 4. Motz GT et al. *Nat Med.* 2014;20:607-615.

Increases in CD8⁺ T cells are observed with treatments

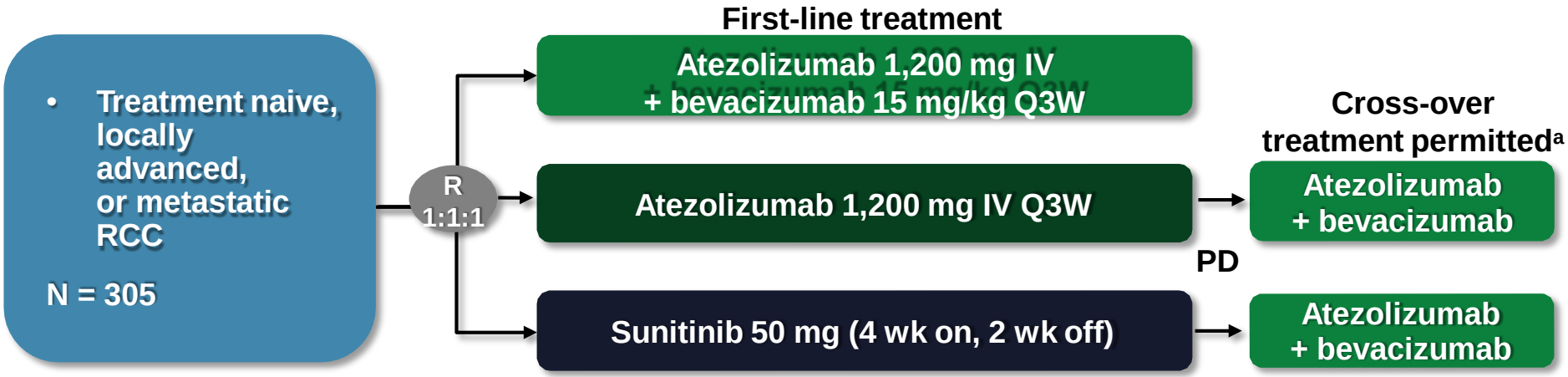
Patient 3, Female, 62 years old



- **83%** (5/6) of **bev + atezo** RCC patients had increases in tumor CD8⁺ T cells
- **11%** (1/9) of RCC patients had increased tumor CD8⁺ T cells following **monotherapy atezo** (PCD4989g)

Wallin et al, Nat Comm, 2016

Phase 2 IMmotion150 Trial Design[1,2]

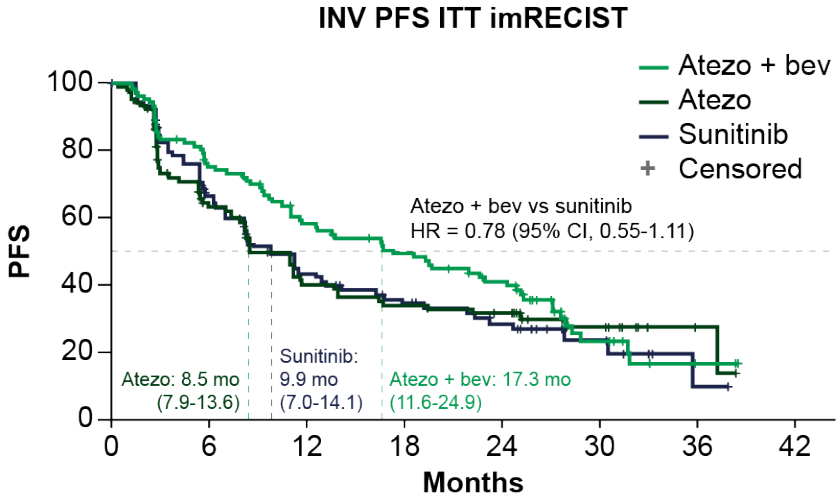


- IMmotion150 was designed to be hypothesis generating and inform the phase 3 study IMmotion151
- Co-primary endpoints were PFS (RECIST v1.1 by IRF) in ITT patients and patients with ≥1% of IC expressing PD-L1
- Exploratory endpoints included interrogation of the association between outcome and TME gene signatures[3]

[a] Crossover from atezolizumab monotherapy not allowed in Europe.

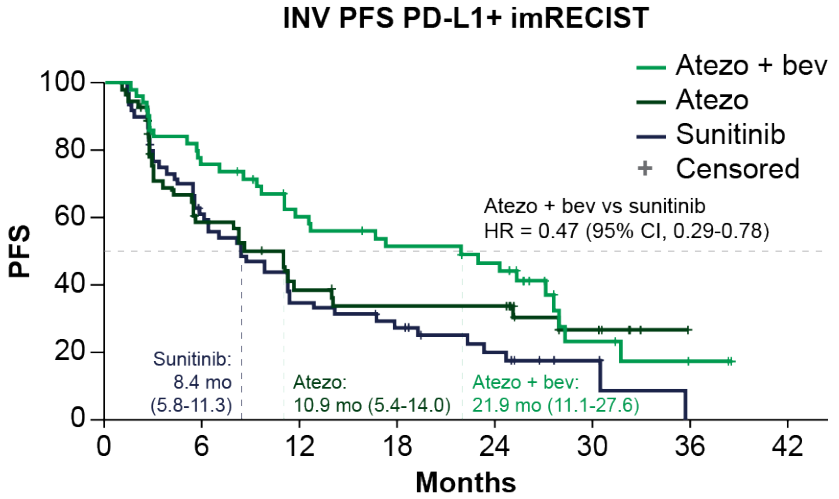
1. McDermott DF et al. *J Clin Oncol.* 2016;34:833-842. 2. McDermott DF et al. American Society for Clinical Oncology 2017 Genitourinary Symposium (ASCO GU 2017). Abstract 431. 3. McDermott D et al. American Association for Cancer Research Annual Meeting 2017 (AACR 2017). Abstract CT081.

Bevacizumab + Atezolizumab – Phase 2 Efficacy[1]



No. at risk

Atezo + bev	101	73	54	44	33	10	2
Atezo	103	56	34	28	25	11	2
Sunitinib	101	59	37	26	18	7	1



No. at risk

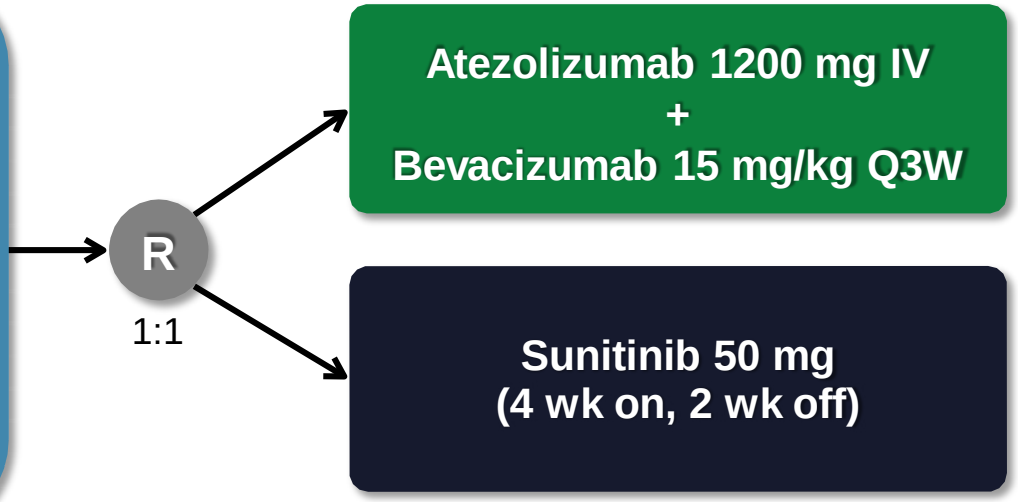
Atezo + bev	50	37	27	22	19	5	2
Atezo	54	28	17	14	14	6	–
Sunitinib	60	35	20	14	8	3	–

1. Pal SK et al.16th International Kidney Cancer Symposium 2017.

IMmotion151: Phase 3 Assessment of Bevacizumab/Atezolizumab[1]

- Treatment-naïve advanced or metastatic RCC
- Clear-cell and/or sarcomatoid histology
- KPS ≥ 70
- Tumor tissue available for PD-L1 staining

N = 915



Stratification:
- MSKCC risk score
- Liver metastases
- PD-L1 IC IHC status (< 1% vs ≥ 1%)

Co-primary endpoints: Investigator-assessed PFS in patients with PD-L1 expression ≥1; OS in ITT population

1. https://clinicaltrials.gov/ct2/show/NCT02420821. Accessed February 6, 2018.

IMmotion151: Efficacy and Safety[1]

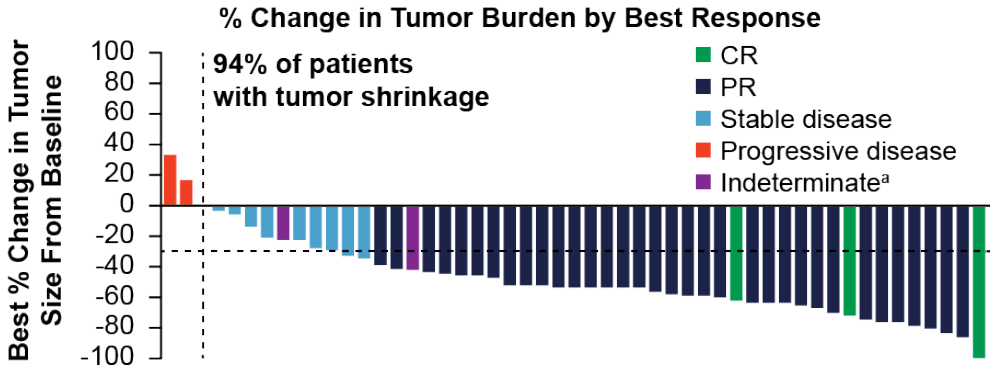
	PD-L1+, (n = 362)[a]		ITT (N = 915)	
	Sunitinib (n = 184)	Atezolizumab + Bevacizumab (n = 178)	Sunitinib (n = 461)	Atezolizumab + bevacizumab (n = 454)
mPFS (95% CI)	7.7 (6.8-9.7)	11.2 (8.9-15.0)	8.4 (7.5-9.7)	11.2 (9.6-13.3)
HR (95% CI), *P*	0.74 (0.57-0.96), 0.0217		0.83 (0.70-0.97), 0.219[b]	
ORR, %	35 (28-42)	43 (35-50)	33 (29-38)	37 (32-41)
DOR, months (95% CI)	1.29 (9.8-NE)	NE (12.4-NE)	14.2 (11.3-NE)	16.6 (15.4-NE)

Treatment-related grade 3-4 AEs: 40% atezolizumab/bevacizumab; 54% sunitinib
Treatment-related any grade AE leading to discontinuation: 12% atezolizumab/bevacizumab; 8% sunitinib

[a] PD-L1 expression on ≥1% on tumor infiltrating immune cells, SP142 IHC assay. [b] Descriptive purposes only.

1. Motzer RJ et al. ASCO GU. 2018. Abstract 578.

VEGFR-TKI + Anti–PD-1: Axitinib + Pembrolizumab—Efficacy[1]



- Median PFS was 15.1 mo (11.4-NR) in overall population
- **UPDATED PFS: 20.9 months[2]**
- Of 11 pts enrolled in the dose-finding phase, median PFS not yet reached
- 9 of 48 (18.8%) evaluable tumor specimens were PD-L1–positive

N = 52	Axitinib + Pembrolizumab
Pts with baseline assessment	52 (100)
Pts with measurable disease at BL	52 (100)
Best overall response, n (%)	
CR	3 (5.8)
PR	34 (65.4)
Stable disease	10 (19.2)
Progressive disease	2 (3.8)
Indeterminate[b]	3 (5.8)
ORR (CR + PR)	37 (71.2)
95% exact CI	56.9-82.9
UPDATED ORR[2]	**73.1%**

[a] Stable disease or PR not confirmed. [b] 2 patients indeterminate and 1 patient with no follow-up assessment.

1. Atkins MB et al. *Ann Oncol.* 2016;27:266-295. 2. Atkins MB et al. ASCO GU 2018. Abstract 579.

VEGFR-TKI + Anti–PD-1: Axitinib + Pembrolizumab—Safety[1]

Dosage[a] (N = 52)	Pembrolizumab Average Dose per Cycle, mg/kg	Axitinib Average Daily Dose, mg	Days on Treatment
Mean (SD)	1.9 (0.1)	8.5 (1.7)	318.5 (124.7)
Median	2.0	8.9	316.0
Range	1.6-2.1	4.7-13.8	22.0-656.0

Update[2]

- Most common grade ≥ 3 AEs
  - Hypertension (23%), diarrhea (10%) fatigue (10%)
- Immune-related AEs
  - Diarrhea (29%), increased ALT 17%, increased AST(13%), hypothyroidism (13%), fatigue (12%)

	AEs in ≥20% of Pts, n (%)	Immune-Related AEs, n (%)[b]
Any AE	34 (65.4)	10 (19.2)
Diarrhea	5 (9.6)	4 (7.7)
Fatigue	3 (5.8)	2 (3.8)
Decreased appetite	1 (1.9)	0
Hypertension	9 (17.3)	0
Increased ALT	3 (5.8)	2 (3.8)
Hypothyroidism	0	2 (3.8)
Nausea	1 (1.9)	0
PPE syndrome	2 (3.8)	0
Increased AST	2 (3.8)	2 (3.8)
Headache	4 (7.7)	0
Dizziness	1 (1.9)	0
Dyspnea	2 (3.8)	0
Weight loss	3 (5.8)	1 (1.9)
Vomiting	1 (1.9)	0
Oral pain	1 (1.9)	0
Proteinuria	1 (1.9)	0
Hyperthyroidism	1 (1.9)	0
Colitis	2 (3.8)	2 (3.8)

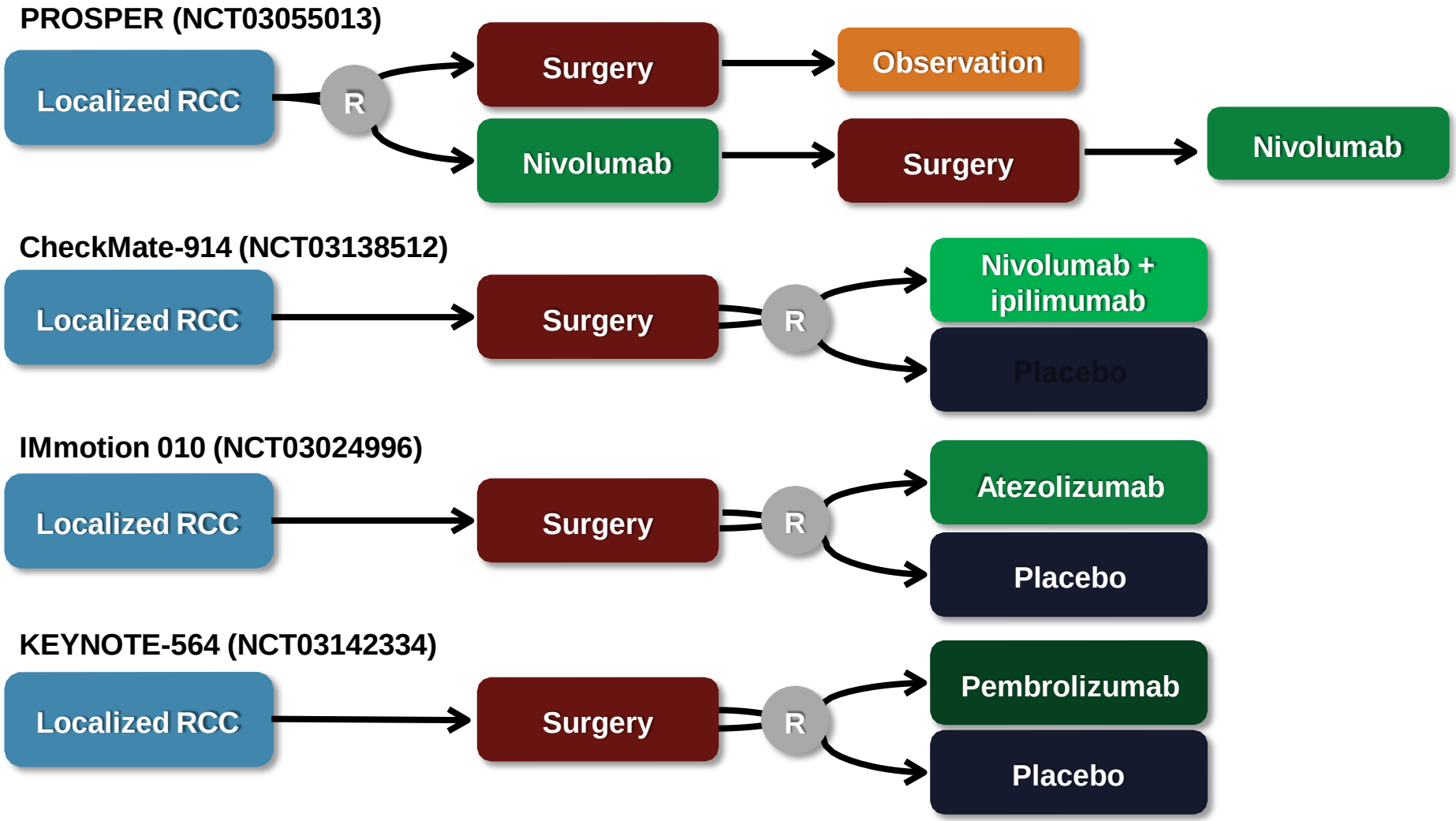
[a] Dosage: 2 mg/kg IV pembrolizumab every 3 weeks + 5 mg axitinib twice daily. [b] No immune-related grade ≥4 AEs reported.

1. Atkins MB et al. *Ann Oncol.* 2016;27:266-295. 2. Atkins MB et al. ASCO GU 2018. Abstract 579.

First-Line Phase 3 Trials in Advanced RCC[1]

Experimental Arm	Primary Endpoint	Estimated N	Trial	ClinicalTrials.gov ID
Axitinib + avelumab	PFS	583	JAVELIN Renal 101	NCT02684006
Axitinib + pembrolizumab	PFS, OS	840	KEYNOTE-426	NCT02853331
Bevacizumab + atezolizumab	PFS, OS in PD-L1–detectable tumors	900	IMmotion151	NCT02420821
Nivolumab + ipilimumab	PFS, OS	1,070	CheckMate 214	NCT02231749
Nivolumab + cabozantinib or nivolumab + ipilimumab + cabozantinib	PFS in intermediate-risk/ poor-risk patients	1,014	CheckMate 9ER	NCT03141177
Lenvatinib/pembrolizumab or lenvatinib/everolimus	PFS	735	CLEAR	NCT02811861
Sunitinib + AGS-003	OS	450	ADAPT	NCT01582672

1. www.clinicaltrials.gov. Accessed February 6, 2018.


PROSPER (NCT03055013)
Localized RCC
R
Surgery
Observation
Nivolumab
Surgery
Nivolumab
CheckMate-914 (NCT03138512)
Localized RCC
Surgery
R
Nivolumab + ipilimumab
Placebo
IMmotion 010 (NCT03024996)
Localized RCC
Surgery
R
Atezolizumab
Placebo
KEYNOTE-564 (NCT03142334)
Localized RCC
Surgery
R
Pembrolizumab
Placebo

Immunotherapy for the Treatment of Bladder Cancer

Immune Checkpoint Blockade Has Revolutionized the Treatment of Advanced Urothelial Carcinoma[1]

- Before 2016, cytotoxic chemotherapy was the only option for patients with locally advanced or metastatic urothelial carcinoma
- Cisplatin-based combination chemotherapy remains the standard of care for eligible patients
- Outcomes with carboplatin-based chemotherapy are poor, with median survival about 9 months in phase 3 trials
- After failure of platinum-based chemotherapy, survival was short, and available treatments (taxanes, pemetrexed, vinflunine [EU]) were toxic

1. Abida W et al. *Hematol Oncol Clin North Am*. 2015;29:319-328.

Proposed Criteria for Definition of Cis-Platinum Ineligible Patients for CDDP-Based Regimens

1. Poor Performance Status (ECOG 2 or higher)

2. CrCl <60 ml/min

3. Hearing Loss or Neuropathy (Grade 2 or Worse)

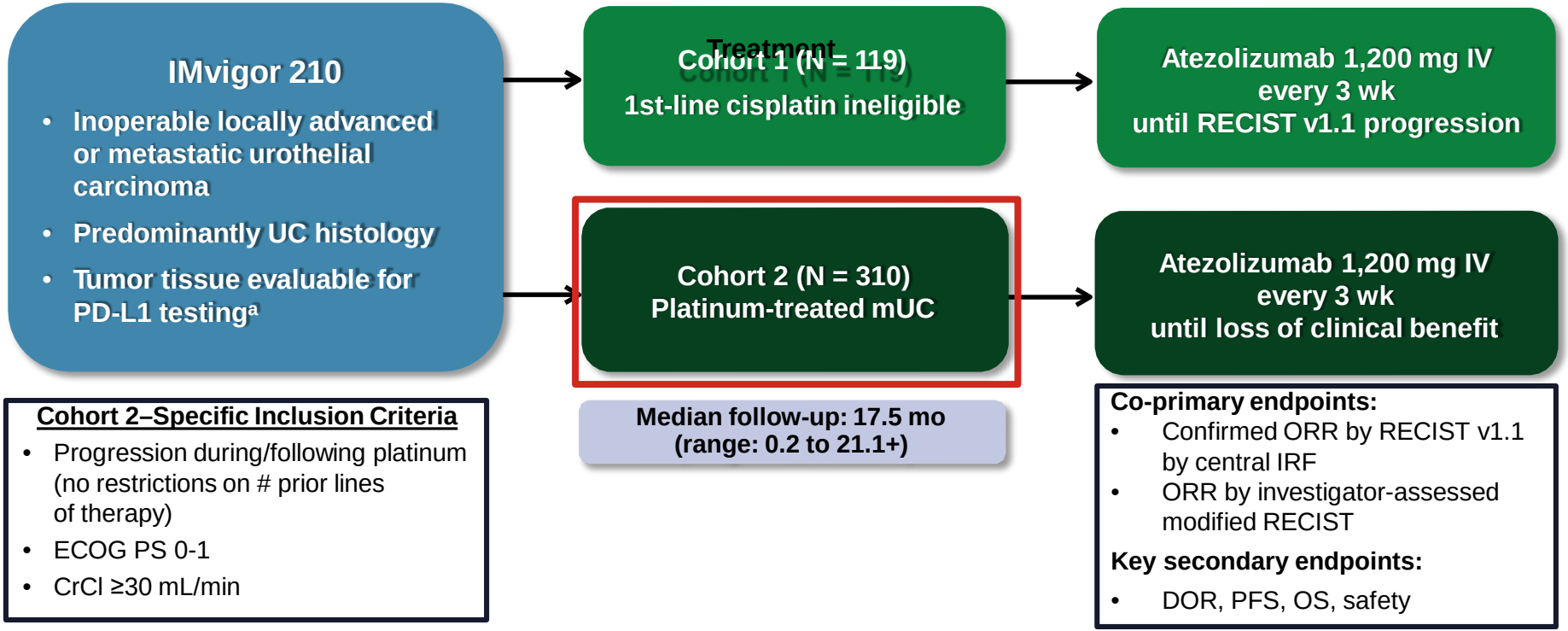
4. NYHA Class III Heart Failure

Rapid Development of Immunotherapy in Bladder Cancer

5 drugs approved in 13 months

Agent	Mechanism	Schedule	Post Platinum	Frontline Cis Ineligible
Atezolizumab	Anti–PD-L1	Q3W	Accelerated approval	Accelerated approval
Nivolumab	Anti–PD-1	Q2W	Accelerated approval	-
Durvalumab	Anti–PD-L1	Q2W	Accelerated approval	-
Avelumab	Anti–PD-L1	Q2W	Accelerated approval	-
Pembrolizumab	Anti–PD-1	Q3W	Full approval	Accelerated approval

IMvigor210 Cohort 2 Study Design: Basis for Accelerated Approval[1,2]

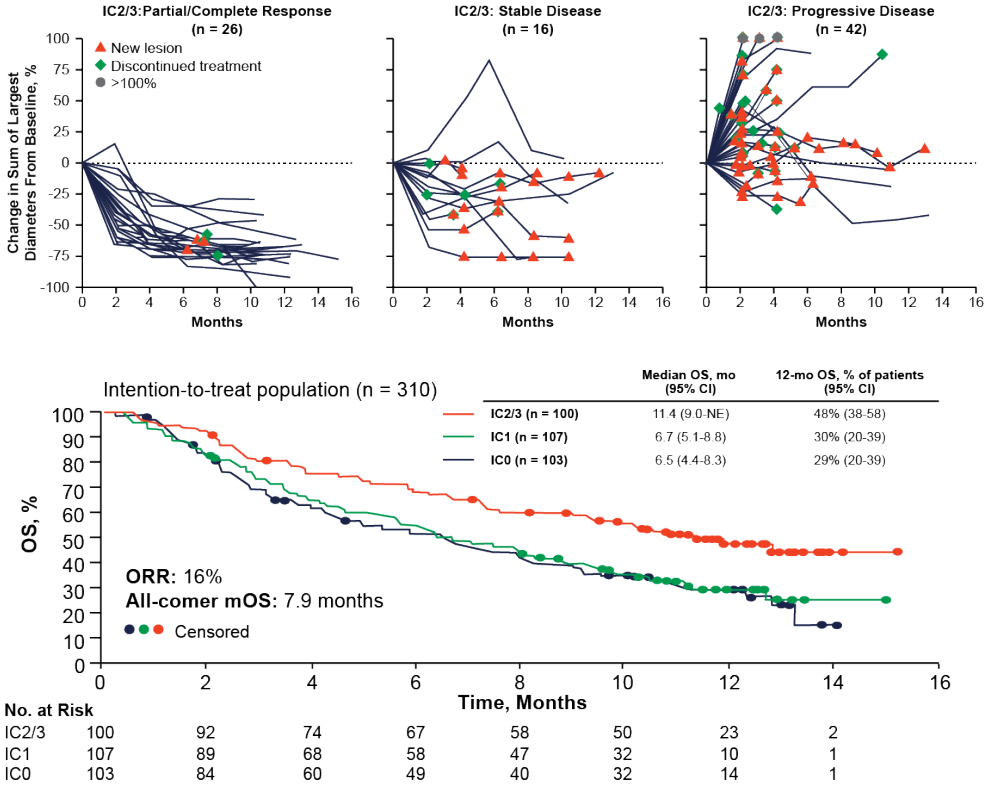


[a] PD-L1 prospectively assessed by a central laboratory, with patients and investigators blinded.

1. Dreicer R et al. ASCO 2016. Abstract 4515. 2. Rosenberg JE et al. *Lancet*. 2016;387:1909-1920.

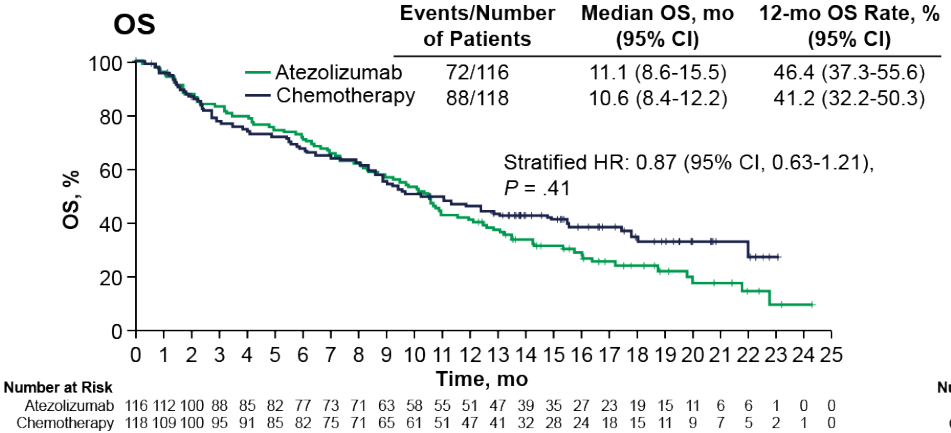
IMvigor210: Atezolizumab Approved for Prior Platinum-Treated Patients[1]

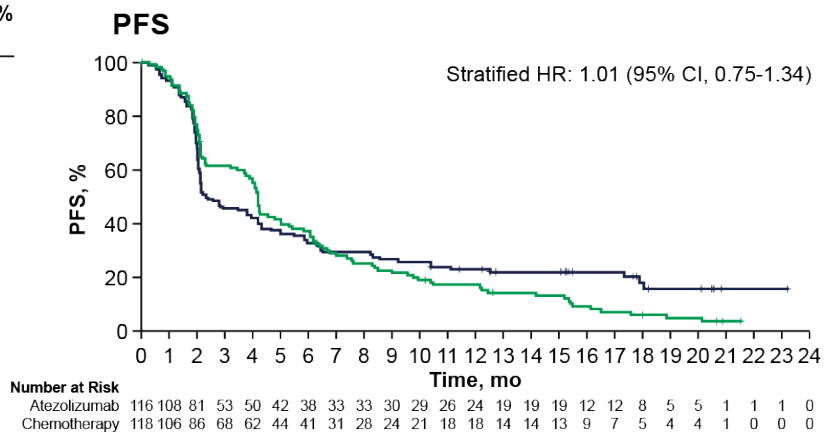
- 40% had 2 or more prior regimens
- ORR: 14.8%
- Median OS: 7.9 mo
- Modest toxicity
- Higher levels of PD-L1 staining on immune cells are associated with higher response rate and longer survival (SP142 assay)



1. Rosenberg JE et al. *Lancet*. 2016;387:1909-1920.

Atezolizumab Did Not Improve OS in the PD-L1–Positive Population[1]

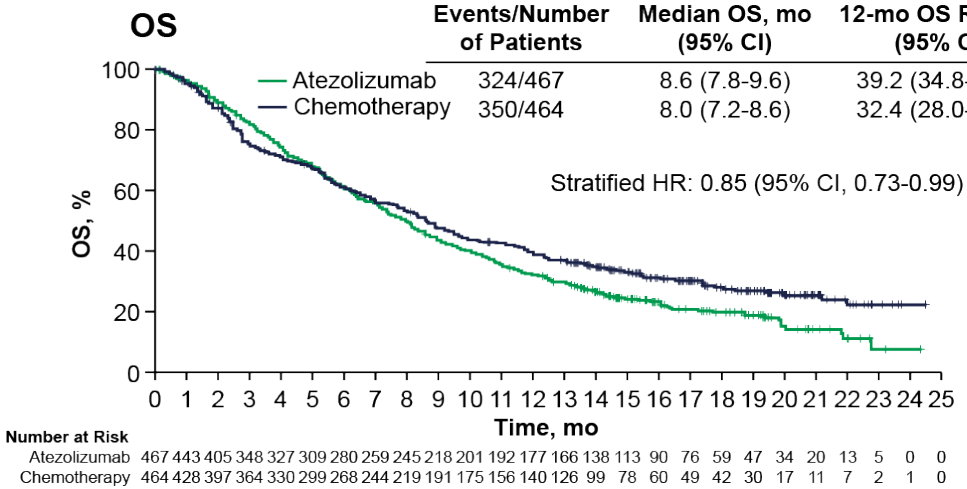


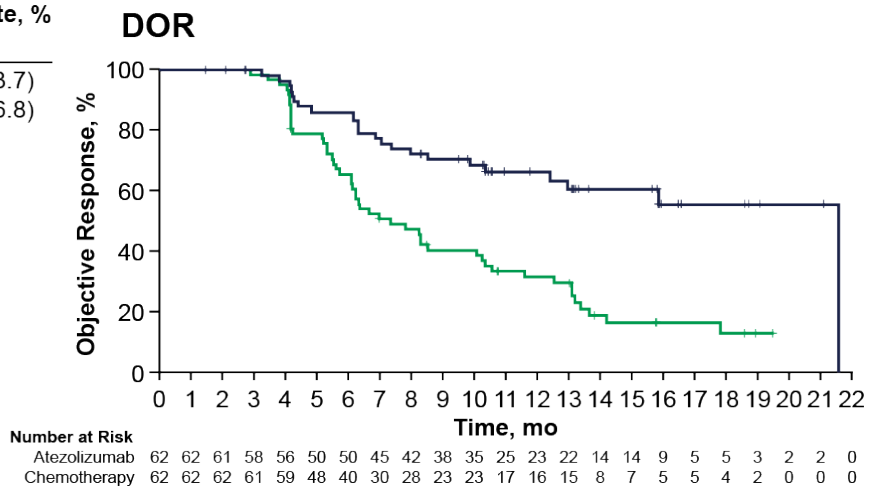


PD-L1 staining enriched for response and survival for both chemotherapy and atezolizumab

1. Powles T et al. *Lancet*. 2017 Dec 18 [Epub ahead of print].

IMvigor211:Outcomes in the ITT Population[1]

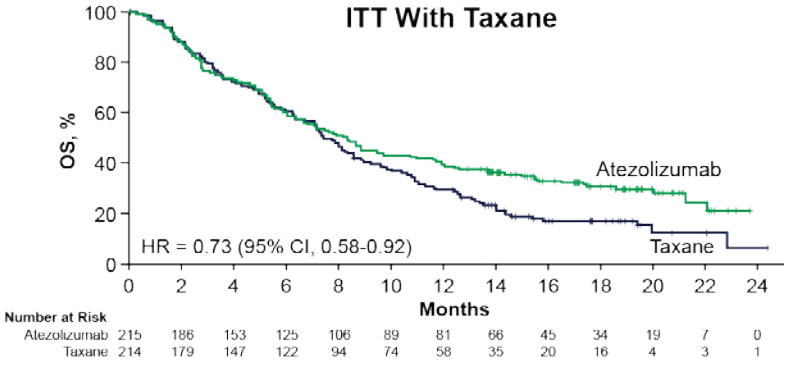


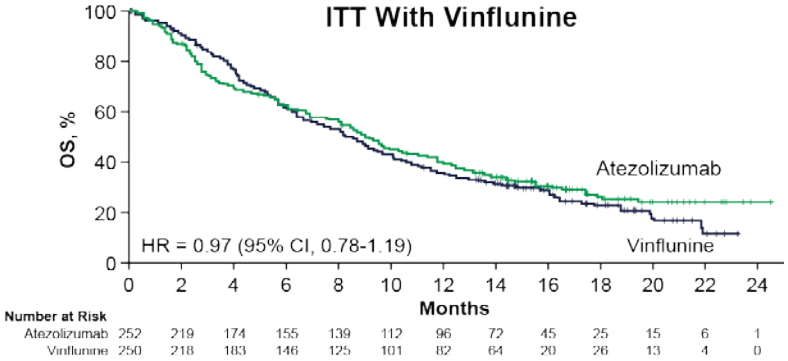


- Study design did not allow formal assessment of OS in the entire study population
  - HR and long-term survival favored atezolizumab
- DOR was dramatically longer in patients treated with atezolizumab

1. Powles T et al. *Lancet*. 2017 Dec 18 [Epub ahead of print].

IMvigor211: Subgroup Analysis by Chemotherapy Type[1]





OS was also examined in subgroups based on chemotherapy type at randomization

- **Improved OS was observed with atezolizumab vs taxanes**

Subgroup	Median OS, mo (95% CI)
Atezolizumab	8.3 mo (6.6-9.8)
Taxane	7.5 mo (6.7-8.8)

Subgroup	Median OS, mo (95% CI)
Atezolizumab	9.2 mo (7.9-10.4)
Vinflunine	8.3 mo (6.9-9.6)

1. Adapted from Powles T et al. European Association for Cancer Research, American Association for Cancer Research, and Italian Cancer Society (EACR-AACR-SIC) 2017 Special Conference. Abstract 606.

What Does This Mean?

Atezolizumab is an active drug

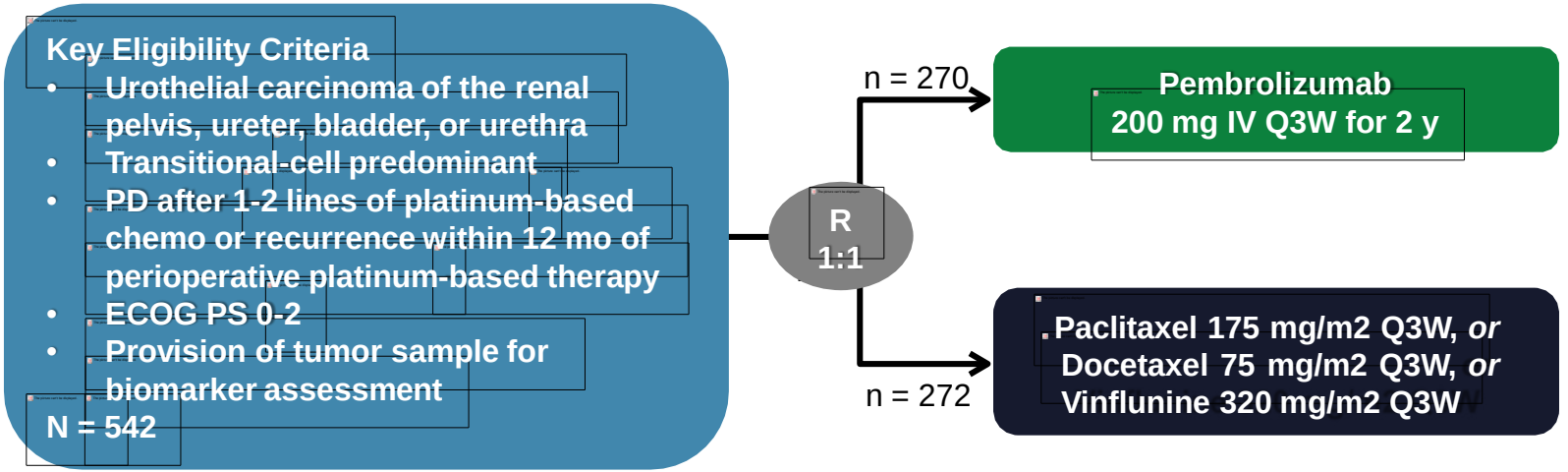
- Phase 3 trial showed that vinflunine is a more active agent than previously thought
- Atezolizumab activity recapitulated earlier data

SP142 PD-L1 biomarker did not perform as predicted

- IC2/3 predicted both chemotherapy and immunotherapy response

Level 1 evidence (randomized phase 3 trial) supports pembrolizumab as second-line therapy

KEYNOTE-045 Phase 3 Trial (NCT02256436)[1]



Stratification Factors

- ECOG PS (0/1 vs 2)
- Hemoglobin level (<10 vs ≥10 g/dL)
- Liver metastases (yes vs no)
- Time from last chemotherapy dose (<3 vs ≥3 mo)

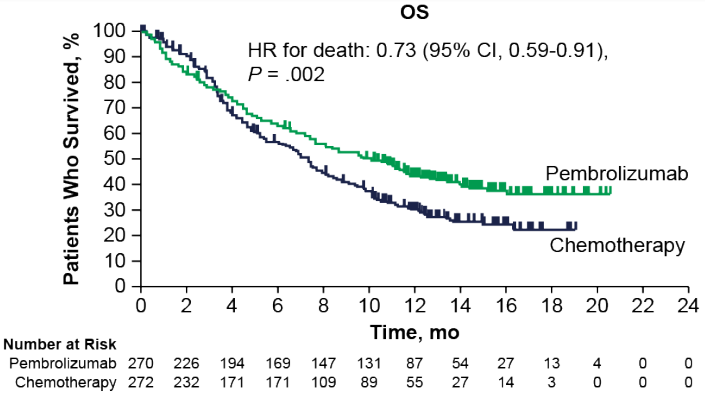
Key Endpoints

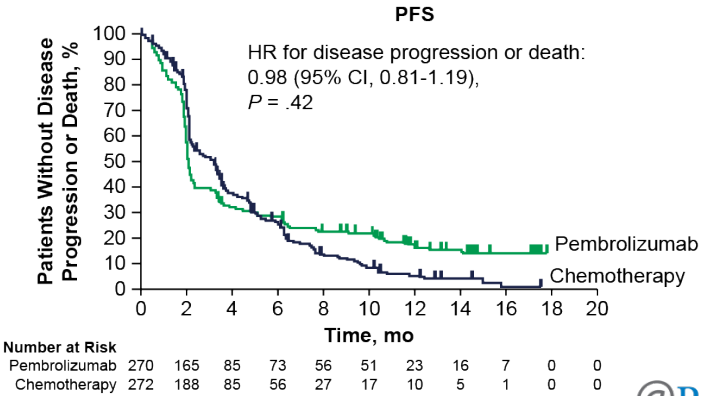
- **Primary:** OS and PFS in total and in PD-L1 combined positive score ≥10% populations
- **Secondary:** ORR and DOR in total and in PD-L1 combined positive score ≥10% populations; safety in total population

1. Bellmunt J et al. *N Engl J Med*. 2017;376:1015-1026.

KEYNOTE-045: Pembrolizumab Improves OS vs Chemotherapy in the Second or Third Line[1]

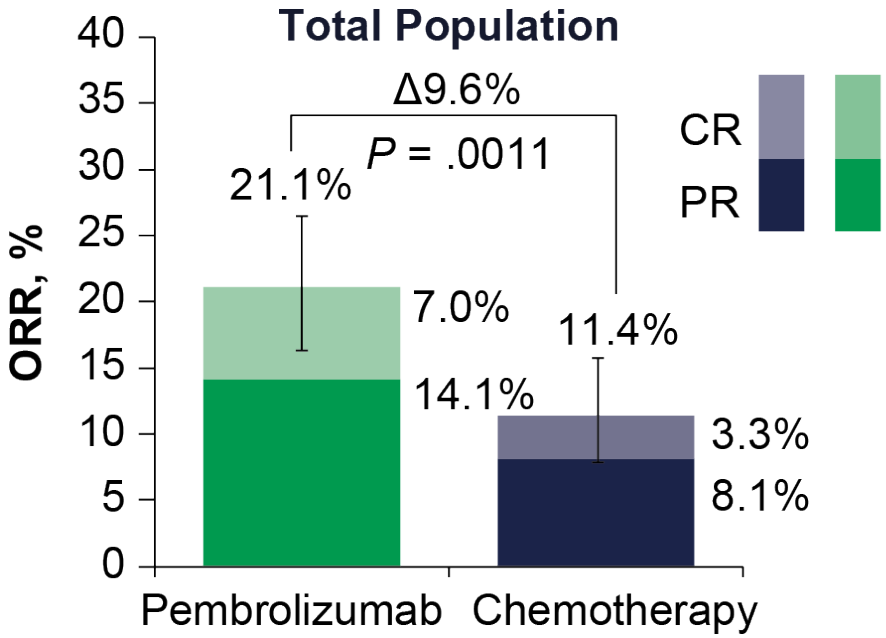
- Median OS 10.3 months for pembrolizumab vs 7.4 for chemo (HR = 0.73)
- **Updated: 10.3 mo vs 7.3 mo (HR = 0.70)[2]**
- PFS short, and not different between the two arms
- PD-L1 expression with this assay was a poor prognostic biomarker and does not help with patient selection

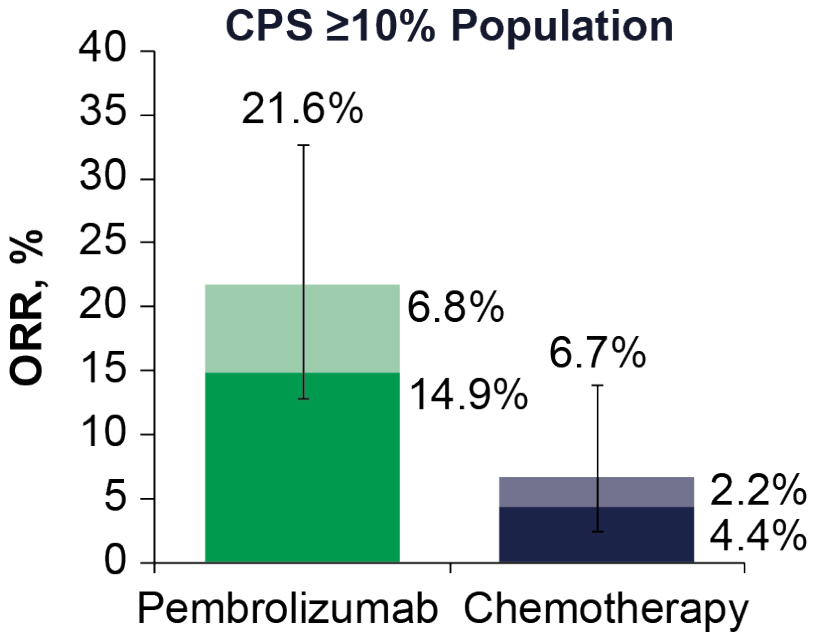




1. Bellmunt J et al. *N Engl J Med*. 2017;376:1015-1026. 2. Bellmunt J et al. ASCO GU 2018. Abstract 410.

KEYNOTE-045: Confirmed Objective Response Rate[1]

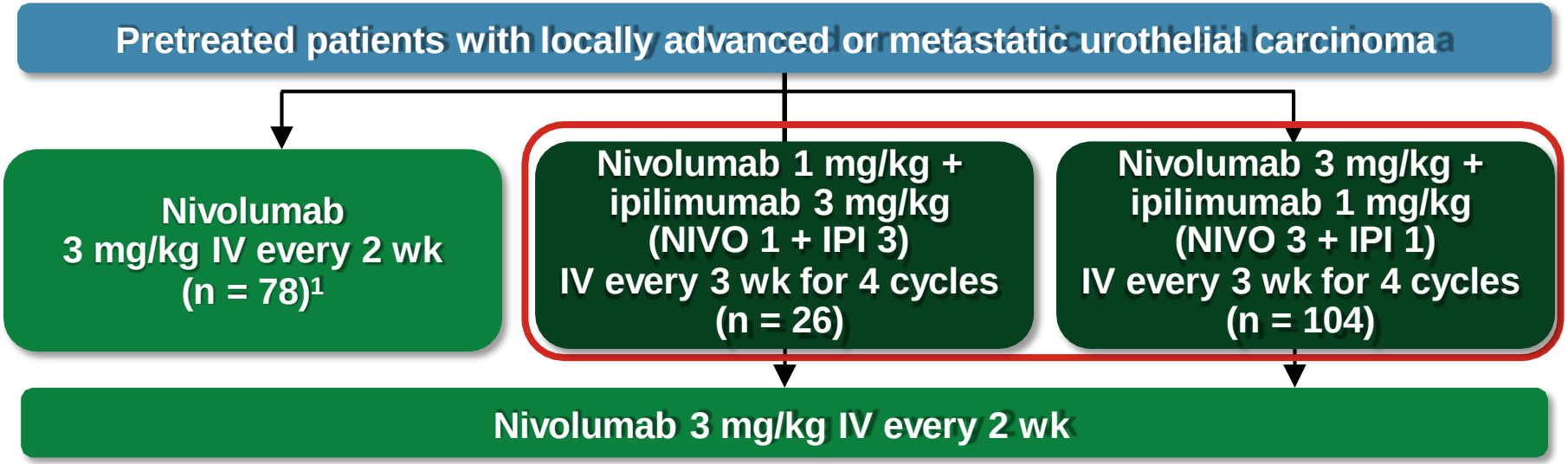




1. Bellmunt J et al. *J Immunother Cancer*. 2016;4(suppl. 2):O2.

Anti–CTLA-4 and Anti–PD-1: CheckMate-032: Study Design[1,2]

Open-label, multicenter, phase 1/2 study



- Treatment beyond progression was permitted if treatment was tolerated and prespecified clinical benefit was noted
- Tumor measurements: CT or MRI every 6 wk (±1 wk) from first dose for the first 24 wk, then every 12 wk (±1 wk)

1. Sharma P et al. *Lancet Oncol*. 2016;17:1590-1598. 2. https://clinicaltrials.gov/ct2/show/NCT01928394. Accessed January 28, 2018.

Anti–CTLA-4 and Anti–PD-1: CheckMate-032: Antitumor Activity[1]

Outcome, %	Nivolumab 1 + Ipilimumab 3 (n = 26)	Nivolumab 3 + Ipilimumab 1 (n = 104)	Nivolumab Monotherapy (n = 78)
Confirmed ORR, %	38.5	26.0	24.4
95% CI	20.2-59.4	17.9-35.5	15.3-35.4
Best overall response, %			
Complete response	3.8	2.9	6.4
Partial response	34.6	23.1	17.9
Stable disease	19.2	25.0	28.2
Progressive disease	26.9	41.3	38.5

1. Sharma P et al. 31st Annual Meeting & Associated Programs of the Society for Immunotherapy of Cancer (SITC 2016). Abstract O3.

Immune–Immune Combinations Hold Significant Promise

- CTLA-4, PD-1 pathway combinations have significant toxicity
- Identification of agents with less toxicity in combination is warranted
  - Advanced bladder cancer patients tend to be older and sicker
- Multiple different classes of agents are being tested

Approved Checkpoint Inhibitors for Platinum-Refractory mUC

M Ornstein JTT online Feb 13, 2018 with permission

	Atezolizumab	*Nivolumab*	*Pembrolizumab*	*Avelumab*	*Durvalumab*
Phase (no. of pts)	**Phase II (310)**	**Phase II (265)**	**Phase III (270)**	**Phase 1b (241)**	**I/II (191)**
Dosing	**1200 mg Q 3wk**	**240 mg Q 2wk**	**200 mg Q 3wk**	**10mg/kg Q 2wk**	**10 mg/kg Q 2w**
ORR	**15%**	**24%**	**29%**	**18%**	**18%**
mPFS/OS (months)	**2.1/7.9**	**2.0/8.7**	**2.1/10.3**	**1.8/13.7**	**1.5/18.2**
Grade 3/4 Rx-Related AEs	**16%**	**18%**	**15%**	**8%**	**7%**
Most Common Rx-related AEs	**Fatigue (30%)** **Nausea (14%)** **Pruritis (10%)**	**Fatigue (17%)** **Pruritis (9%)** **Diarrhea (9%)**	**Pruritis (19.5%)** **Fatigue (13.9%)** **Nausea (10.9%)**	**Infusion-related reaction (22.8%)** **Fatigue (12%)**	**Fatigue (19.4%)** **Decrease appetite (9%)** **Diarrhea 8.4%)**
FDA Approval	May18,2016 (accelerated)	February 2, 2017 (accelerated)	May 18, 2017 (regular approval)	May 9, 2017 (accelerated)	May 1, 2017 (accelerated)

Future Strategies

Indoleamine 2,3-Dioxygenase 1 (IDO1)[1]

Resistance to PD-1 pathway inhibition may be mediated in part by IDO1 activity

IDO1:
- Depletes tryptophan and increases kynurenine levels
- Leads to an immunosuppressive tumor microenvironment

This leads to:
- Decreased effector T-cell function
- Differentiation of regulatory T cells

Inhibitors of this pathway are being tested in mUC

1. Mellor AL et al. *Front Immunol*. 2017;8:1360.

Epacadostat and Pembrolizumab[1]

40 patients treated in expansion cohort at 100 mg PO BID

ORR is 35%

Tolerability appears similar to PD-1 therapy alone

80% had 1 or fewer prior regimens in metastatic setting

- Relatively lightly pretreated cohort compared with IMvigor210 (59%), but similar to KEYNOTE-045 (80%) and Checkmate-275 (71%)

Promising ORR worthy of further investigation in a planned large randomized trial

1. Smith DC et al. ASCO 2017. Abstract 4503.

Nivolumab and BMS986205[1]

25 bladder cancer patients treated in a multicohort phase 1/2a dose-escalation and expansion study (CA017-003)

ORR was 32%

Kynurenine levels were decreased in pre- and on-treatment tumor biopsies

Toxicity seemed similar to single agent therapy

1. Luke JJ et al. SITC 2017. Abstract O41.