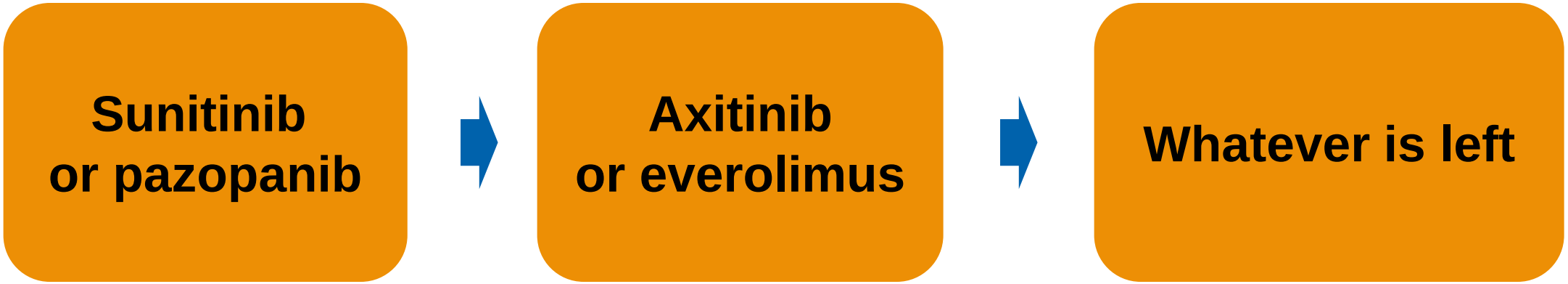
I checkpoint inhibitors nel trattamento di seconda linea del carcinoma renale metastatico

MG Vitale

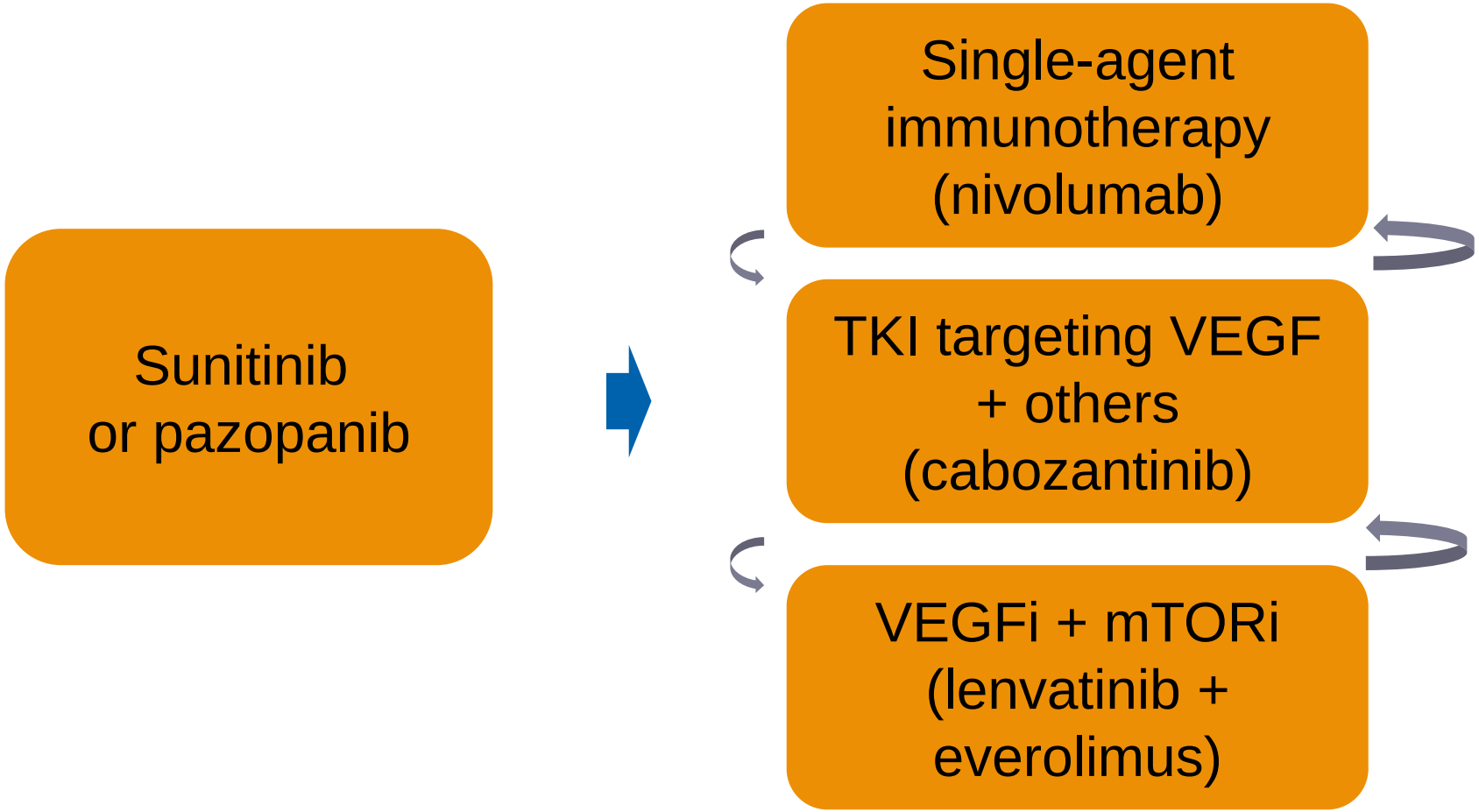
Oncologia Medica
Azienda Ospedaliera Universitaria
Policlinico di Modena

RCC: Sequential Monotherapy Treatment Paradigm in Early 2015

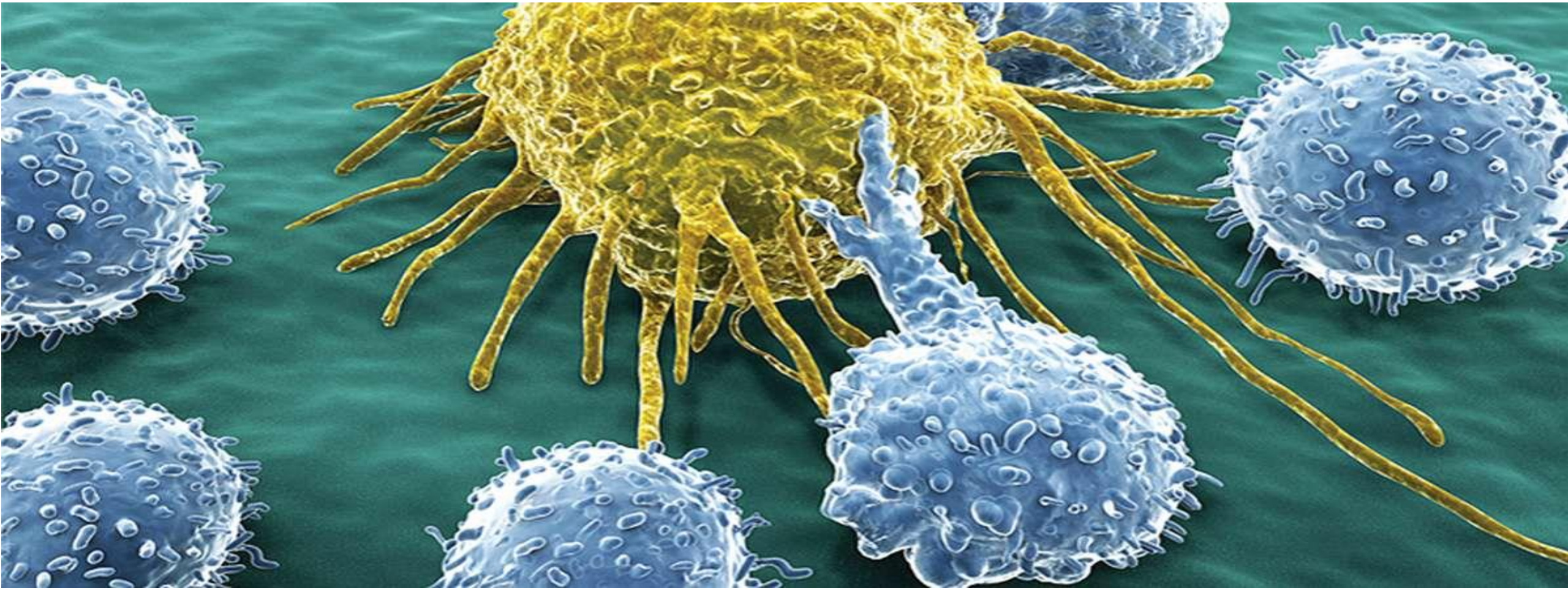


Paradigm of therapy in metastatic RCC
is an empiric sequence of monotherapies

New Treatment Options for Refractory Metastatic RCC in 2017

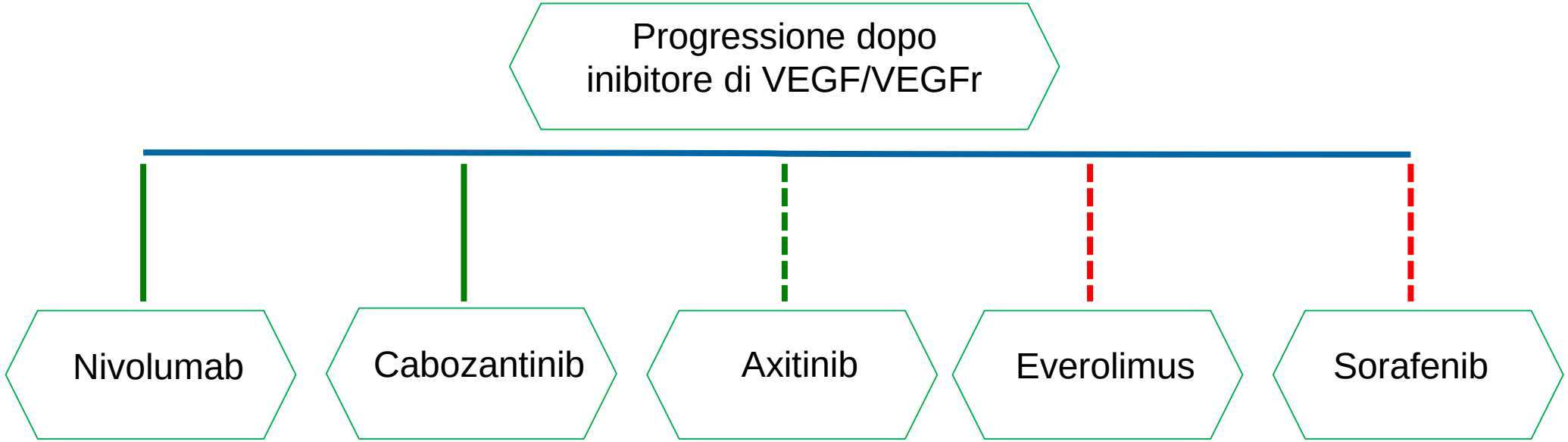


A new era in Renal Cancer Treatment



Trattamento medico della malattia avanzata

Opzioni terapeutiche successive alla prima linea dopo inibitori di VEGF/VEGFR



Positiva Forte

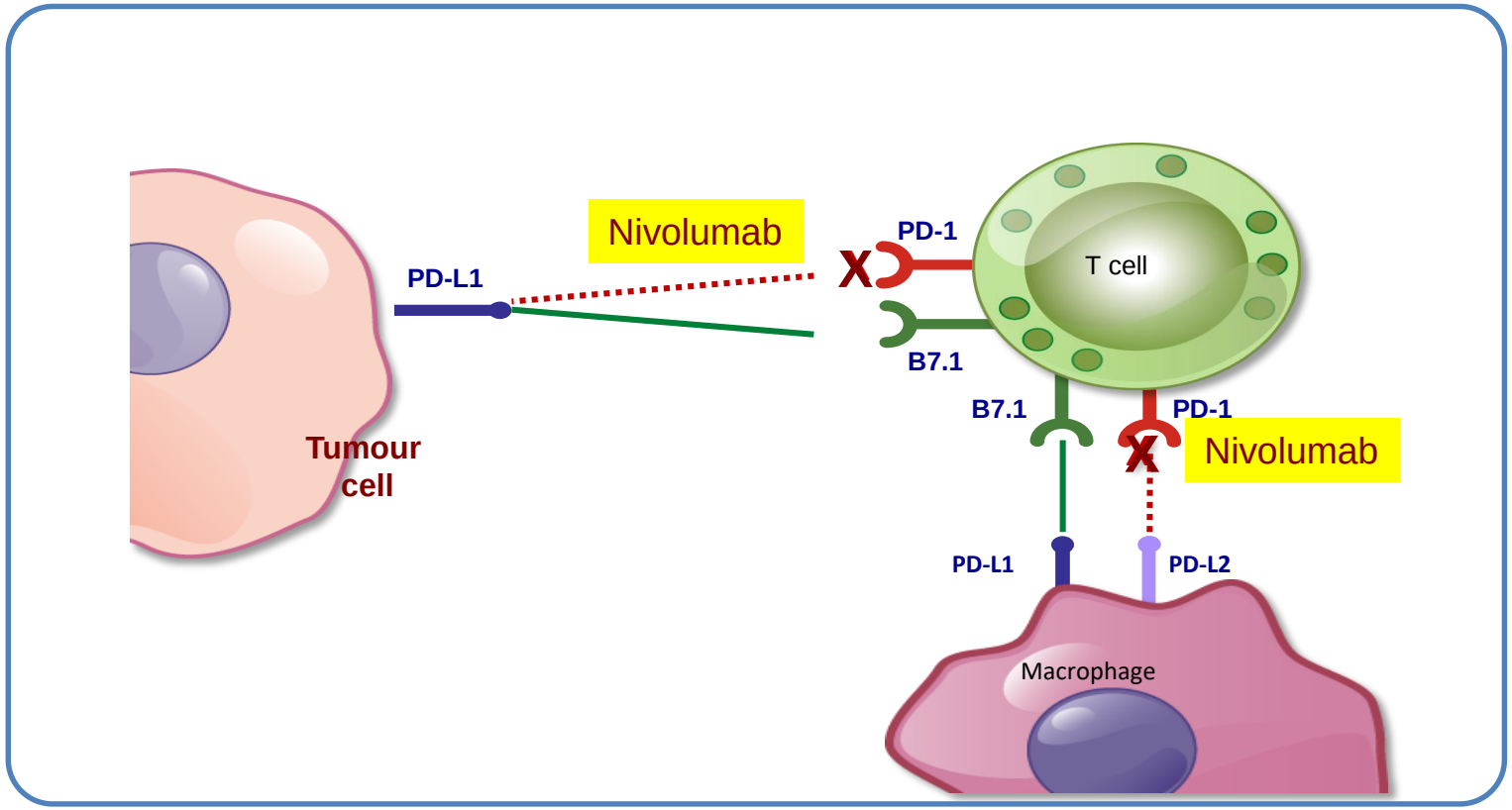
Positiva Debole

Negativa Debole

Negativa Forte

LG AIOM 2017

Nivolumab: targeting PD1



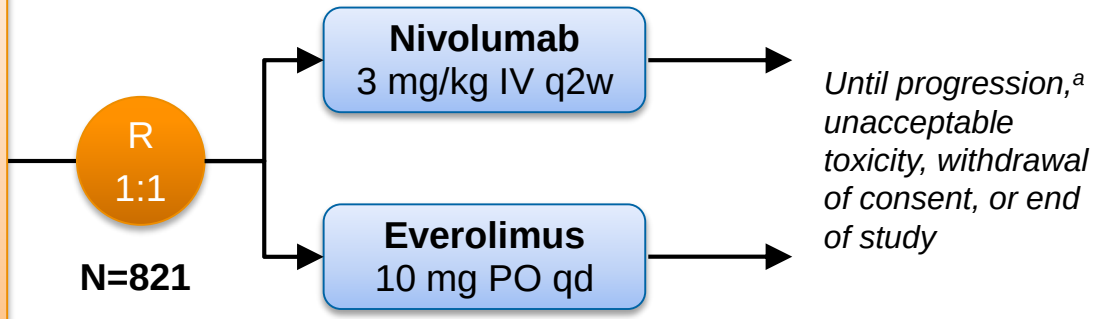
1. Chen, et al. 2012; 2. Paterson, et al. 2011
3. Yang, et al. 2011; 4. Brahmer, et al. 2012

CheckMate 025 Study Design

Phase 3, randomized, open-label study of nivolumab vs everolimus in patients with advanced or metastatic clear cell RCC who have received prior anti-angiogenic therapy.[1]

Key Inclusion Criteria[1]

- Advanced/metastatic clear cell RCC
- ≤3 total prior regimens
- 1 or 2 prior anti-angiogenic therapies
- Progression <6 months before enrollment
- KPS ≥70
- No CNS metastases
- No prior therapy with mTOR inhibitor
- No condition requiring glucocorticoids



Start Date: **September 2012[2]**
Estimated Trial Completion Date: **September 2018[2]**
Primary Completion Date: **May 2015[2]**
Status: **Ongoing but not recruiting[2]**
Trial Director: **Bristol-Myers Squibb[2]**

Primary Endpoint: **OS**
Secondary Endpoints: **ORR, PFS, OS by PD-L1 expression, incidence of AEs**

[a]Patients were allowed to continue treatment beyond progression if investigator-assessed clinical benefit was achieved and treatment had an acceptable side-effect profile.

AE, adverse event; CNS, central nervous system; IV, intravenous; KPS, Karnofsky performance status; mTOR, mammalian target of rapamycin; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; PO, oral; qd, once daily; q2w, every 2 weeks; R, randomized; RCC, renal cell carcinoma.

1. Motzer RJ et al. *N Engl J Med* 2015;373:1803–13. 2. Clinicaltrials.gov. NCT01668784. Accessed April 26, 2017.

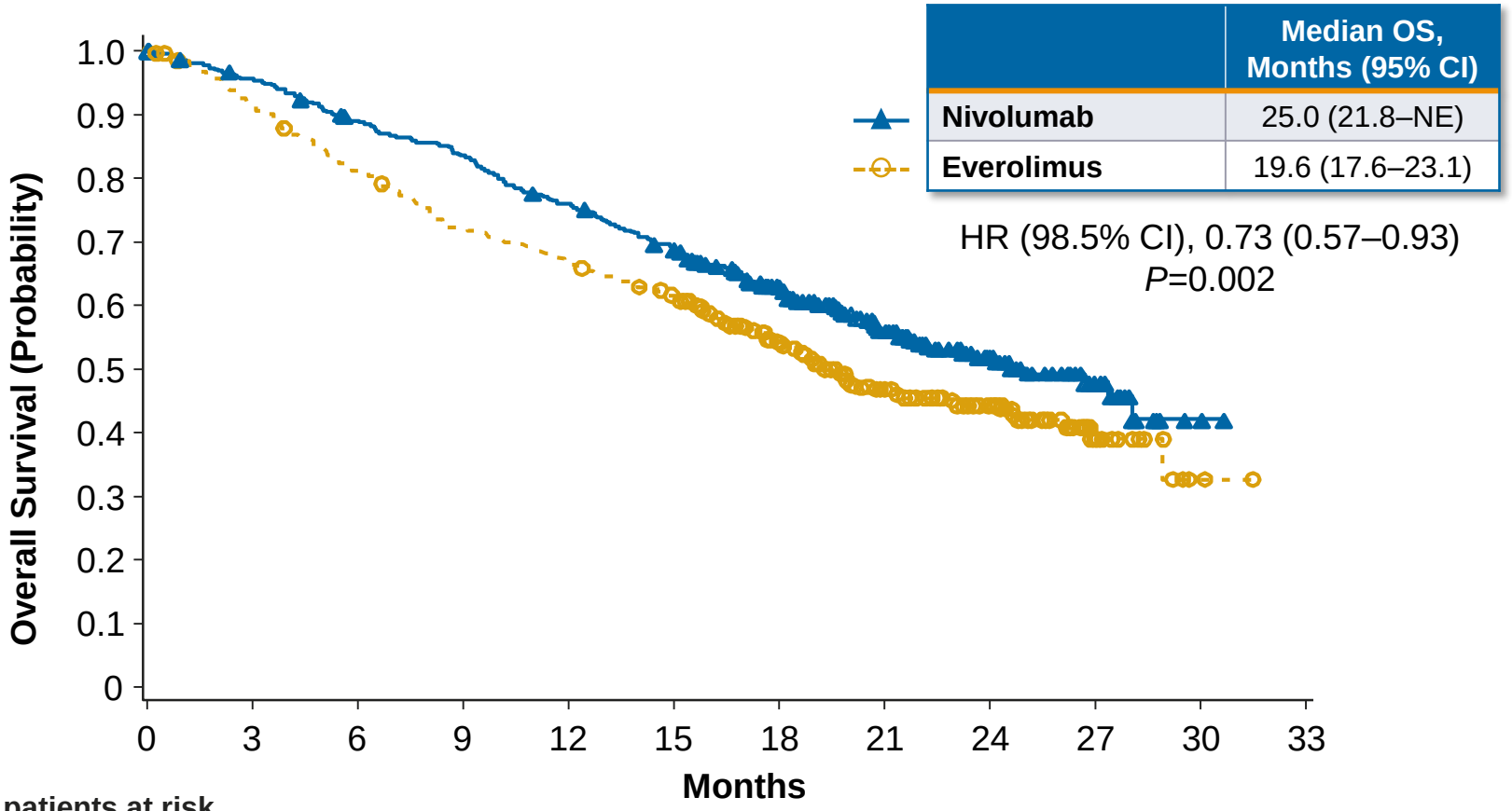
Baseline Characteristics

	Nivolumab N=410	Everolimus N=411
Median age (range), years	62 (23–88)	62 (18–86)
Sex, n (%)		
Male	315 (77)	304 (74)
Female	95 (23)	107 (26)
MSKCC risk group, n (%)[a]		
Favorable (0 factors)	145 (35)	148 (36)
Intermediate (1 factor)	201 (49)	203 (49)
Poor (2 or 3 factors)	64 (16)	60 (15)
No. of prior anti-angiogenic regimens in advanced setting, n (%)		
1	294 (72)	297 (72)
2	116 (28)	114 (28)
Most common previous systemic cancer therapy for metastatic RCC, n (%)		
Sunitinib	246 (60)	242 (59)
Pazopanib	119 (29)	131 (32)
Axitinib	51 (12)	50 (12)
Region, n (%)		
US/Canada	174 (42)	172 (42)
Western Europe	140 (34)	141 (34)
Rest of the world	96 (23)	98 (24)

Adapted from Motzer et al. *N Engl J Med* 2015 and Sharma et al. ESMO 2015.[1,2]

[a]Prognostic factors were anemia, hypercalcemia, and poor performance status.
MSKCC, Memorial Sloan Kettering Cancer Center; RCC, renal cell carcinoma.
1. Motzer RJ et al. *N Engl J Med* 2015;373:1803–13. 2. Sharma P et al. Oral presentation at ESMO 2015. 3LBA. 3. Data on File; Bristol-Myers Squibb.

Overall Survival



No. of patients at risk

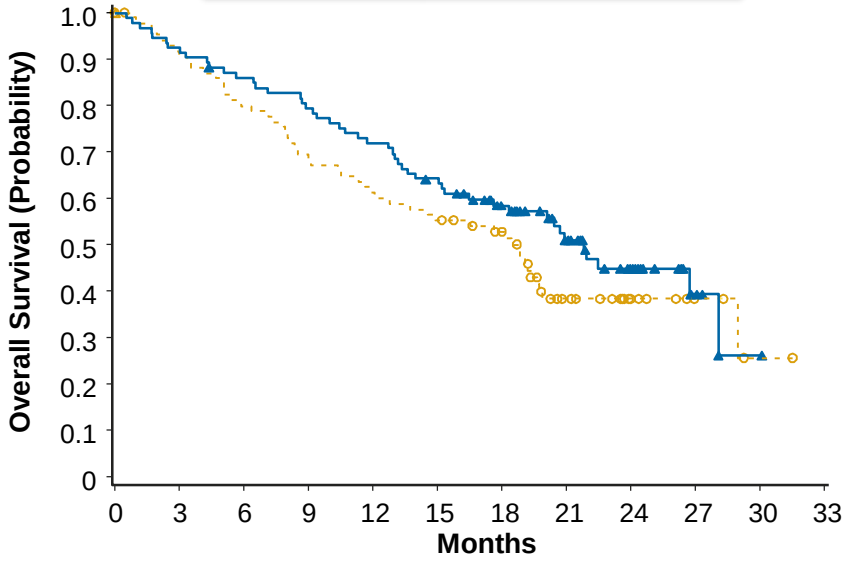
Nivolumab	410	389	359	337	305	275	213	139	73	29	3	0
Everolimus	411	366	324	287	265	241	187	115	61	20	2	0

Minimum follow-up: 14 months; reported as of June 2015.
CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival.
Motzer et al. *N Engl J Med* 2015;373:1803–13.

OS by PD-L1 Expression

PD-L1 ≥1% (n=181; 24%)

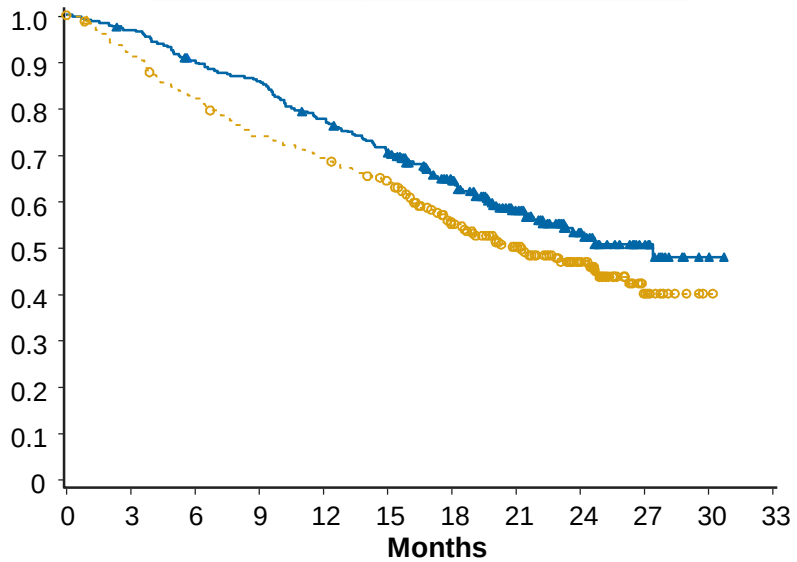
	Median OS, Months (95% CI)
Nivolumab	21.8 (16.5–28.1)
Everolimus	18.8 (11.9–19.9)



No. of patients 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

PD-L1 <1% (n=575; 76%)

	Median OS, Months (95% CI)
Nivolumab	27.4 (21.4–NE)
Everolimus	21.2 (17.7–26.2)

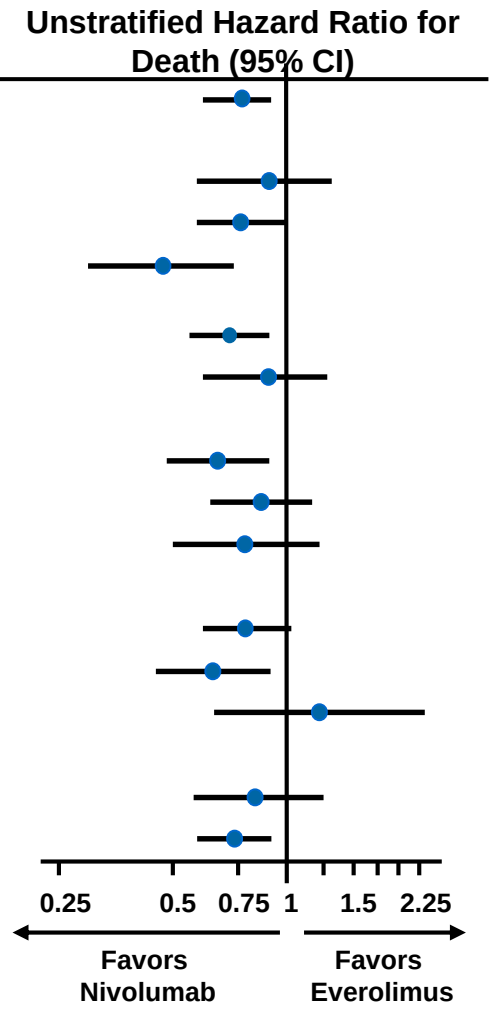


Nivolumab	276	265	245	233	210	189	145	94	48	22	2	0
Everolimus	299	267	238	214	200	192	137	92	51	16	1	0

Minimum follow-up: 14 months; reported as of June 2015.
CI, confidence interval; NE, not estimable; OS, overall survival; PD-L1, programmed death ligand 1.
Motzer et al. *N Engl J Med* 2015;373:1803–13.

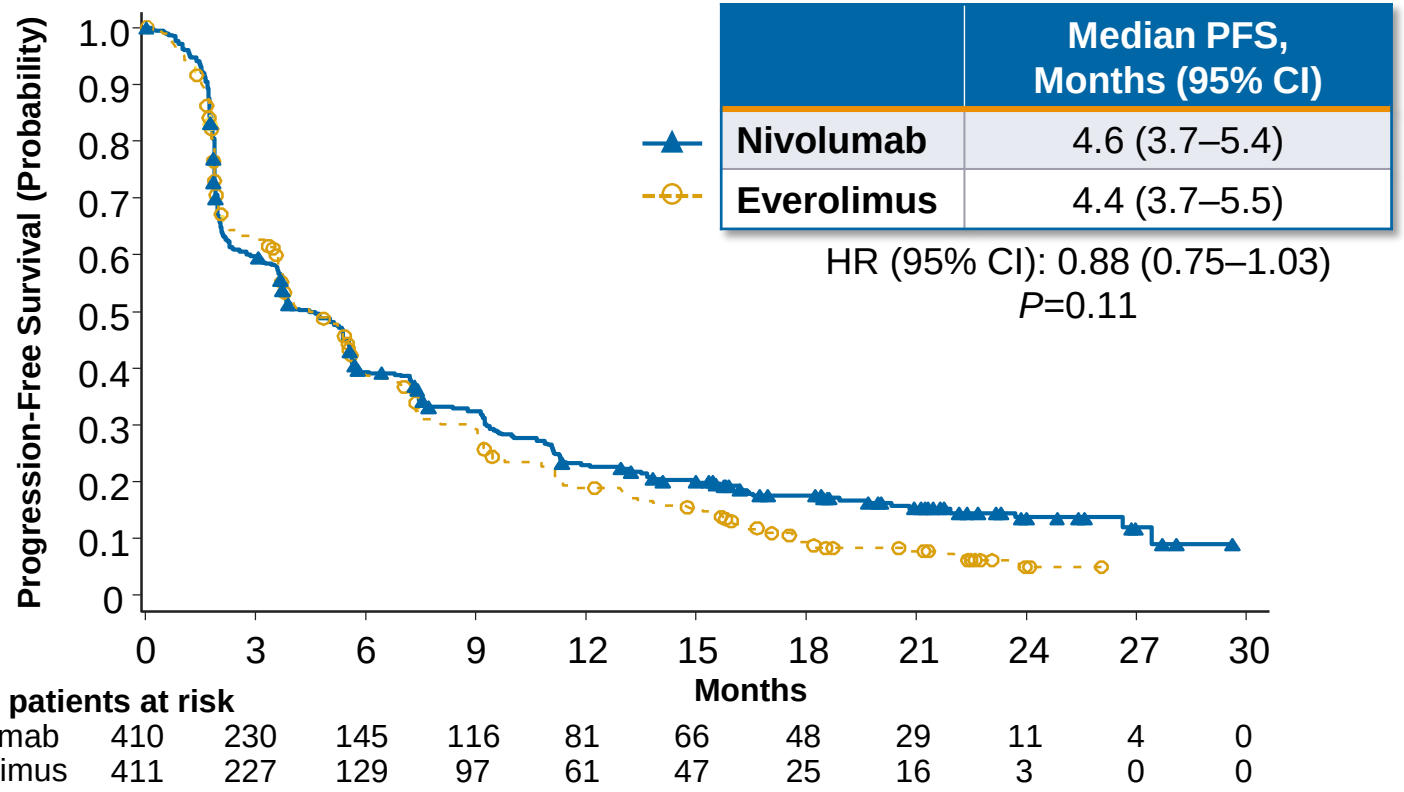
OS by Subgroup[a]

Subgroup	Nivolumab n/N	Everolimus n/N
Overall	183/410	215/411
MSKCC prognostic score		
Favorable	45/145	52/148
Intermediate	101/201	116/203
Poor	37/64	47/60
Previous anti-angiogenic regimens		
1	128/294	158/297
2	55/116	57/114
Region		
United States/Canada	66/174	87/172
Western Europe	78/140	84/141
Rest of the world	39/96	44/98
Age category, n (%)		
<65 years	111/257	118/240
≥65–<75 years	53/119	77/131
≥75 years	19/34	20/40
Sex		
Female	48/95	56/107
Male	135/315	159/304



Minimum follow-up: 14 months; reported as of June 2015.
[a]Analyses are based on interactive voice response system data.
CI, confidence interval; MSKCC, Memorial Sloan Kettering Cancer Center; OS, overall survival.
Adapted from Motzer et al. *N Engl J Med* 2015;373:1803–13.

Progression-Free Survival



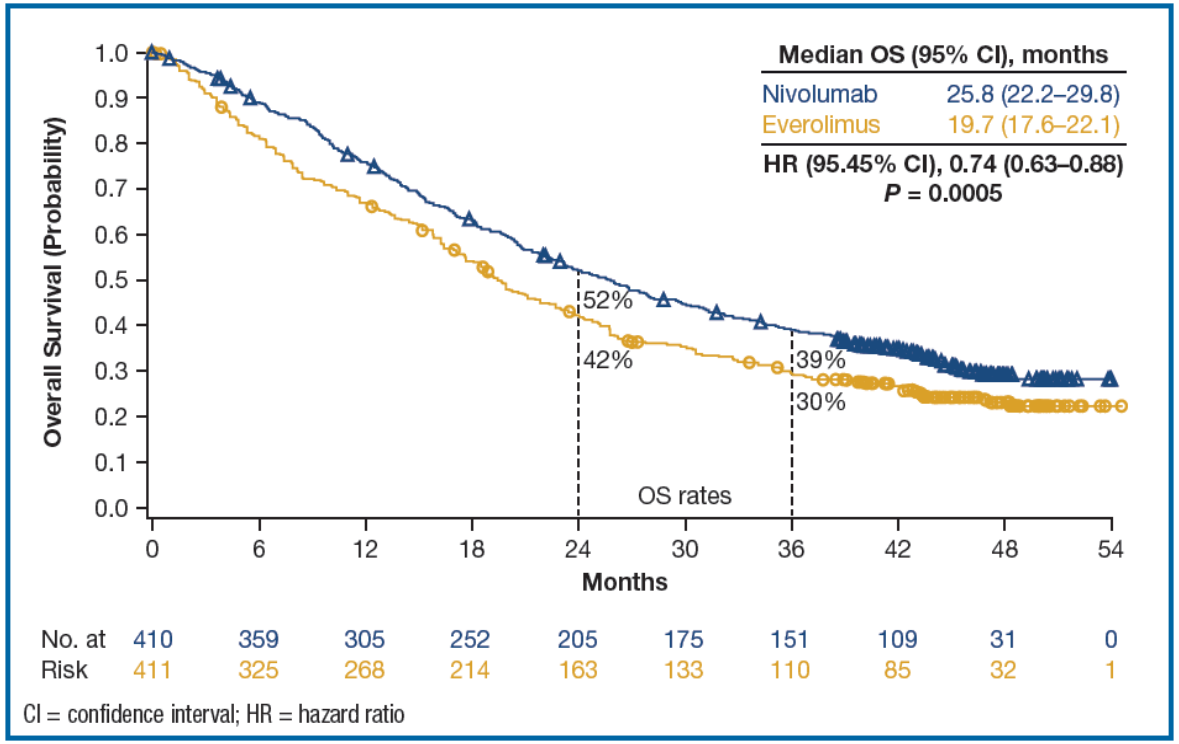
	Median PFS, Months (95% CI)
Nivolumab	4.6 (3.7–5.4)
Everolimus	4.4 (3.7–5.5)

HR (95% CI): 0.88 (0.75–1.03)
P=0.11

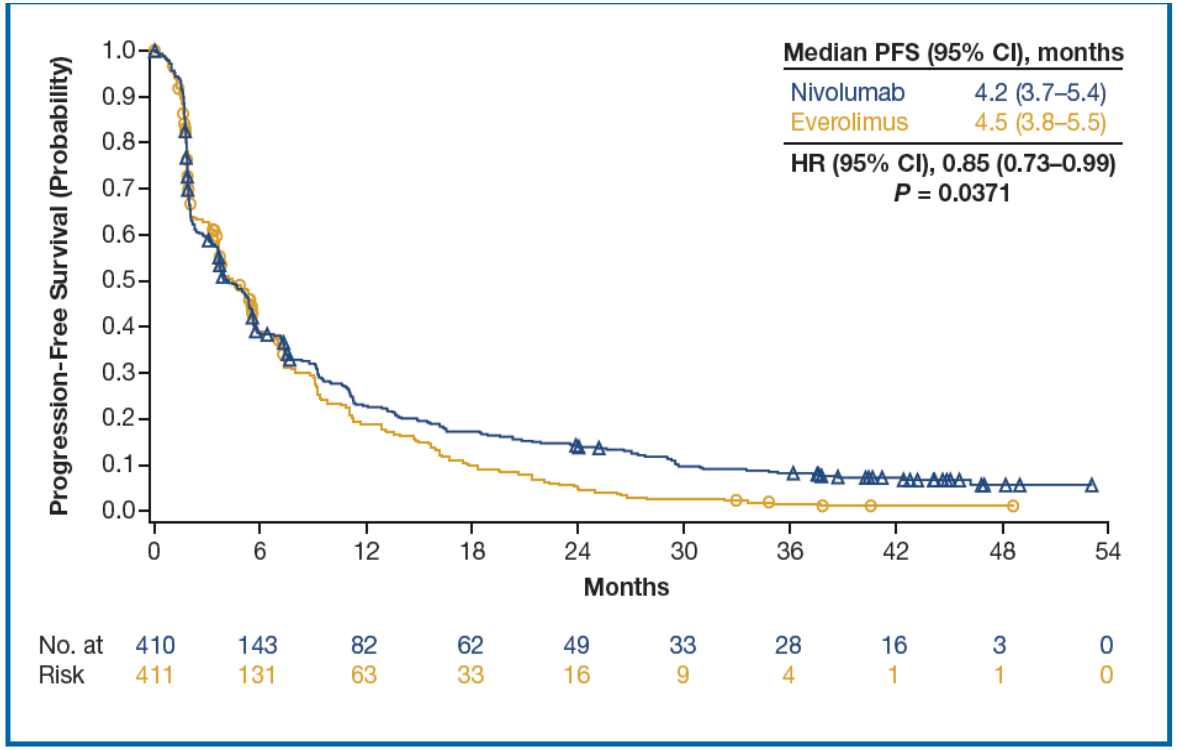
- **In a post-hoc analysis of the patients who had not progressed or died at 6 months (145 with nivolumab, 129 with everolimus), median PFS (95% CI) was 15.6 months (11.8–19.6) for nivolumab vs 11.7 months (10.9–14.7) for everolimus (HR [95% CI], 0.64 [0.47–0.88])**

Minimum follow-up: 14 months; reported as of June 2015.
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.
Motzer et al. *N Engl J Med* 2015;373:1803–13.

Three-Year Efficacy Update From the Phase III CheckMate 025



mOS remained significantly longer with nivolumab versus everolimus, with 3-year OS rates of 39% versus 30%, respectively



A delayed benefit with nivolumab versus everolimus was seen in PFS

Sharma P., et al Int Kidney cancer Symposium, Miami, 2017

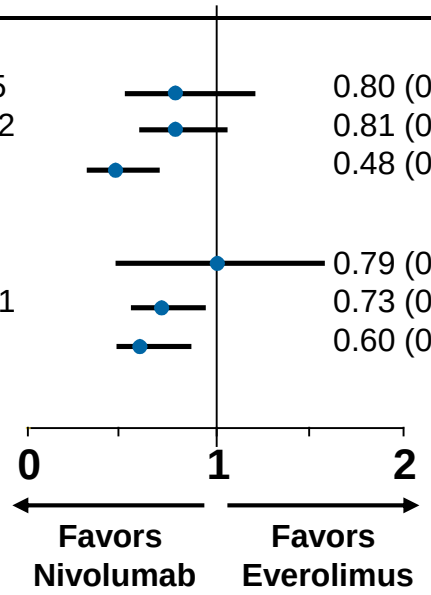
Antitumor Activity

	Nivolumab N=410	Everolimus N=411
Investigator-assessed ORR, n (%)	103 (25)	22 (5)
Odds ratio (95% CI), *P* value	5.98 (3.68–9.72), *P*<0.001	
Investigator-assessed best overall response, n (%) **Complete response** **Partial response** **Stable disease** **Progressive disease** **Not evaluated**	 4 (1) 99 (24) 141 (34) 143 (35) 23 (6)	 2 (1) 20 (5) 227 (55) 114 (28) 48 (12)
Investigator-assessed mDOR, months (range)	12.0 (0–27.6)	12.0 (0–22.2)
Median time to response, months (range)	3.5 (1.4–24.8)	3.7 (1.5–11.2)
Ongoing response, n/N (%)	49/103 (48)	10/22 (45)

Minimum follow-up: 14 months; reported as of June 2015.
CI, confidence interval; mDOR, median duration of response; ORR, objective response rate.
Adapted from Motzer RJ et al. *N Engl J Med* 2015;373:1803–13, supplemental materials.

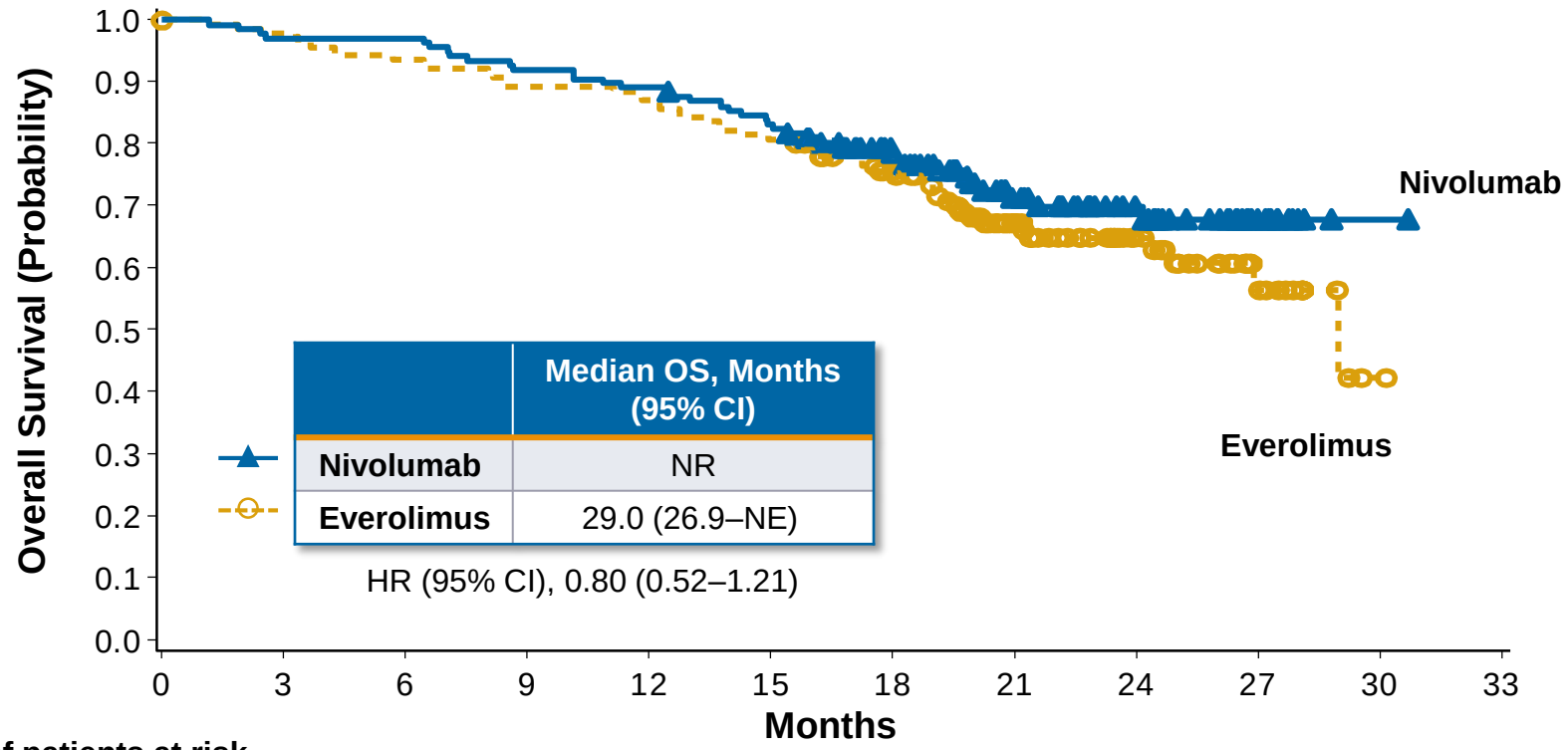
OS Subgroup Analysis: Risk Group

Subgroup	Events/Pts Nivo	Events/Pts Eve	Unstratified Hazard Ratio for Death (95% CI)	Mortality Rate at Month 12, % Nivo	Mortality Rate at Month 12, % Eve	Diff. in Mortality Rate (95% CI)
MSKCC risk score						
Favorable	38/137	50/145	0.80 (0.52–1.21)	11	13	–1.8 (–9.4 to 5.8)
Intermediate	95/193	104/192	0.81 (0.61–1.06)	25	37	–11.2 (–20.5 to –1.9)
Poor	50/79	61/74	0.48 (0.32–0.70)	44	66	–21.8 (–37.5 to –6.2)
IMDC risk score						
Favorable	13/55	21/70	0.79 (0.39–1.58)	6	10	–4.8 (–14.2 to 4.6)
Intermediate	102/242	123/241	0.73 (0.56–0.95)	21	31	–10.5 (–18.3 to –2.6)
Poor	61/96	61/83	0.60 (0.42–0.86)	43	63	–20.1 (–34.8 to –5.5)



Minimum follow-up: 14 months; reported as of June 2015.
Analyses based on case report form data.
CI, confidence interval; Eve, everolimus; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Center; OS, overall survival; Nivo, nivolumab; Pts, patients.
Included with permission from Escudier B et al. *Eur Urol* 2017. http://dx.doi.org/10.1016/j.eururo.2017.02.010.

OS Subgroup Analysis: Favorable MSKCC risk

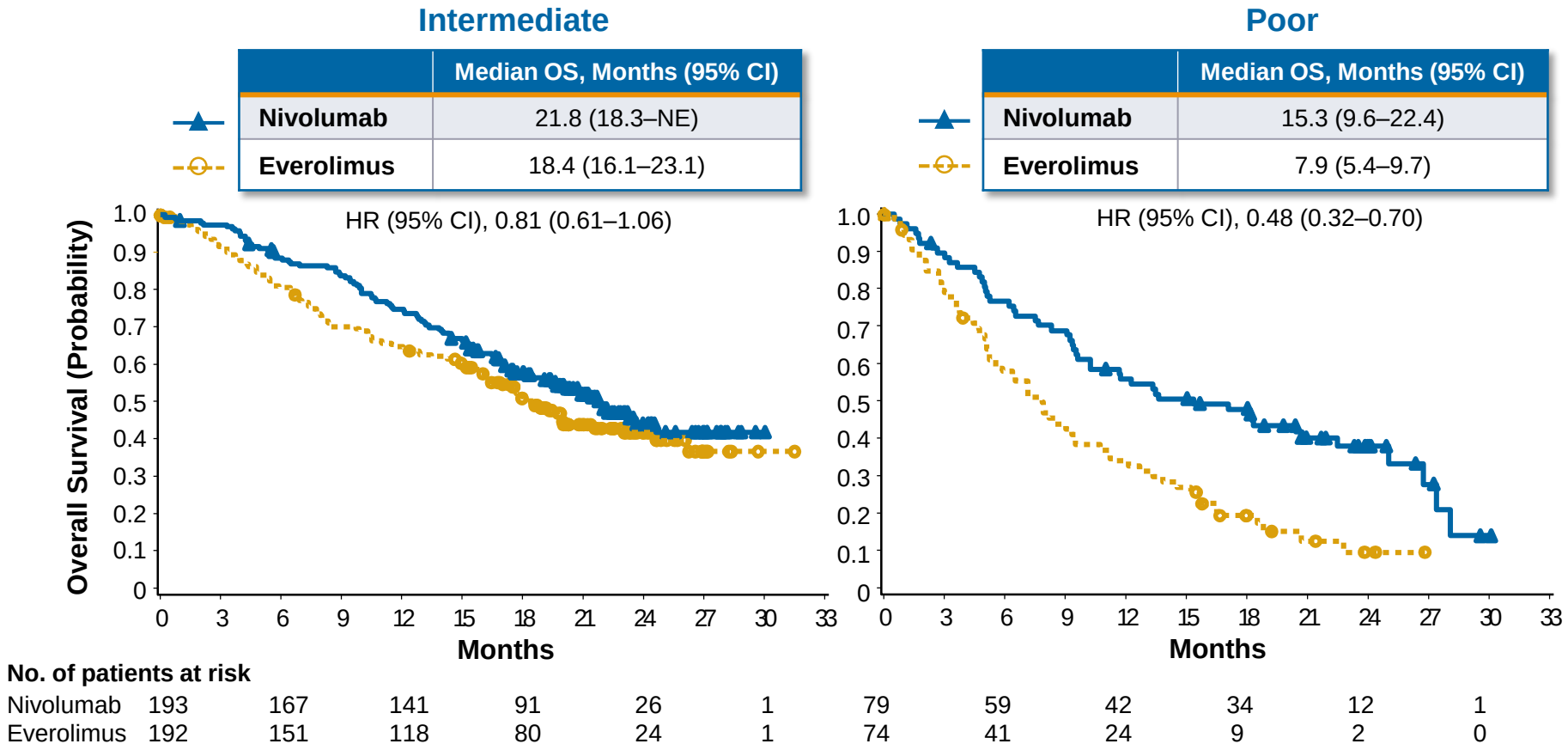


No. of patients at risk

Nivolumab	137	133	122	88	35	1
Everolimus	145	132	123	98	35	1

Minimum follow-up: 14 months; reported as of June 2015.
Analyses based on case report form data.
CI, confidence interval; HR, hazard ratio; MSKCC, Memorial Sloan Kettering Cancer Center; NE, not estimable; NR, not reached; OS, overall survival.
Escudier B et al. *Eur Urol* 2017. http://dx.doi.org/10.1016/j.eururo.2017.02.010.

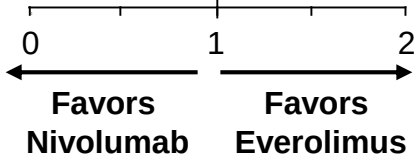
OS Subgroup Analysis: Intermediate and Poor MSKCC Risk



Minimum follow-up: 14 months; reported as of June 2015.
Analyses based on case report form data.
CI, confidence interval; HR, hazard ratio; MSKCC, Memorial Sloan Kettering Cancer Center; NE, not estimable; OS, overall survival.
Escudier B et al. *Eur Urol* 2017. http://dx.doi.org/10.1016/j.eururo.2017.02.010.

OS Subgroup Analysis: Number and Site of Metastases

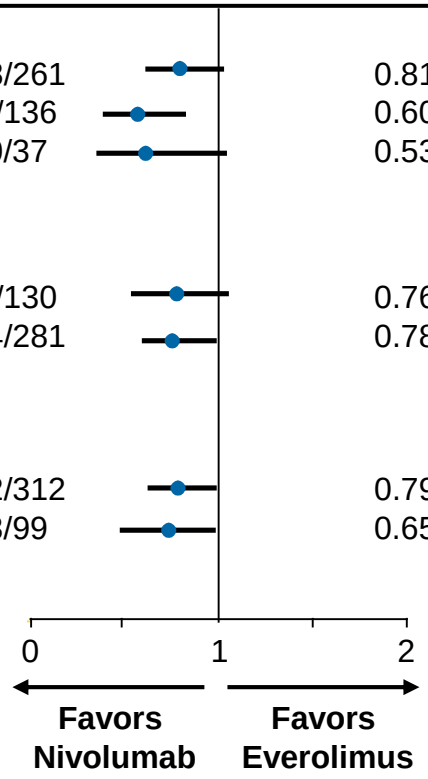
Subgroup	Events/Pts Nivo	Events/Pts Eve	Unstratified Hazard Ratio for Death (95% CI)	Mortality Rate at Month 12, % Nivo	Mortality Rate at Month 12, % Eve	Diff. in Mortality Rate (95% CI)
No. of sites of metastases						
1	14/68	21/71	0.68 (0.34–1.35)	10	13	–2.7 (–13.6 to 8.1)
≥2	168/341	194/338	0.74 (0.60–0.91)	27	38	–11.2 (–18.2 to –4.1)
Bone metastases						
Yes	42/76	45/70	0.72 (0.47–1.09)	39	48	–9.3 (–25.5 to 6.9)
No	141/334	170/341	0.76 (0.61–0.95)	21	30	–9.7 (–16.4 to –3.1)
Liver metastases						
Yes	54/100	52/87	0.81 (0.55–1.18)	36	40	–4.6 (–18.7 to 9.6)
No	129/310	163/324	0.73 (0.58–0.92)	20	32	–11.2 (–18.0 to –4.4)
Lung metastases						
Yes	125/278	150/273	0.72 (0.56–0.91)	23	35	–11.5 (–19.1 to –3.9)
No	58/132	65/138	0.85 (0.60–1.21)	26	31	–4.9 (–15.7 to 5.9)



Minimum follow-up: 14 months; reported as of June 2015.
CI, confidence interval; Eve, everolimus; Nivo, nivolumab; OS, overall survival; Pts, patients.
Included with permission from Escudier B et al. *Eur Urol* 2017. http://dx.doi.org/10.1016/j.eururo.2017.02.010.

OS Subgroup Analysis: Prior Therapy

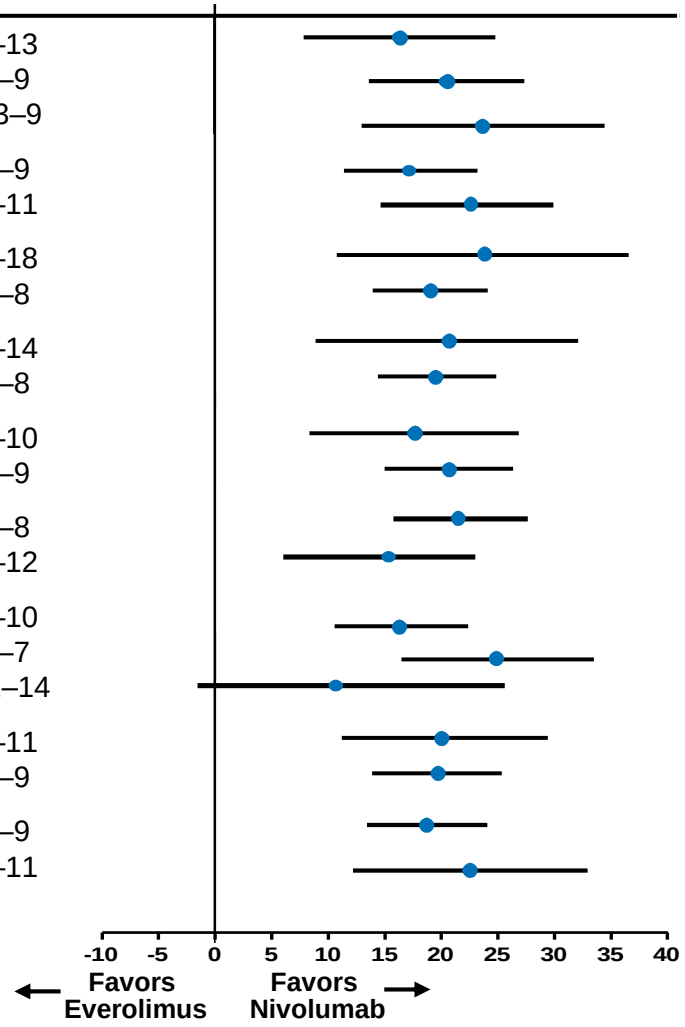
Subgroup	Events/Pts Nivo	Events/Pts Eve	Unstratified Hazard Ratio for Death (95% CI)	Mortality Rate at Month 12, % Nivo	Mortality Rate at Month 12, % Eve	Diff. in Mortality Rate (95% CI)
Prior therapy						
Sunitinib	123/257	138/261	0.81 (0.64–1.04)	24	33	–8.0 (–15.9 to –0.2)
Pazopanib	53/126	79/136	0.60 (0.42–0.84)	25	38	–12.6 (–23.9 to –1.3)
Interleukin-2	15/42	20/37	0.53 (0.27–1.04)	17	32	–15.3 (–34.8 to 4.2)
Months on first-line therapy						
<6	61/110	81/130	0.76 (0.55–1.06)	36	46	–10.0 (–22.6 to 2.7)
≥6	122/300	134/281	0.78 (0.61–0.99)	20	27	–7.9 (–14.8 to –0.9)
Prior anti-angiogenic therapies						
1	144/317	162/312	0.79 (0.63–0.99)	25	33	–8.1 (–15.2 to –0.9)
2	37/90	53/99	0.65 (0.43–0.99)	21	35	–13.9 (–26.6 to –1.1)



Minimum follow-up: 14 months; reported as of June 2015.
Analyses based on case report form data.
CI, confidence interval; Eve, everolimus; Nivo, nivolumab; OS, overall survival; Pts, patients.
Included with permission from Escudier B et al. *Eur Urol* 2017. http://dx.doi.org/10.1016/j.eururo.2017.02.010.

ORR Subgroup Analysis

		Nivolumab		Everolimus	
		ORR, %	95% CI	ORR, %	95% CI
MSKCC risk group	Favorable	24	17–32	8	4–13
	Intermediate	25	19–32	5	2–9
	Poor	27	17–38	3	0.3–9
Age group	<65 years	23	18–29	5	3–9
	≥65 years	29	22–37	6	3–11
No. of sites of metastases	1	32	22–45	9	3–18
	≥2	24	19–29	5	3–8
Bone metastases	Yes	26	17–38	6	2–14
	No	25	20–30	5	3–8
Liver metastases	Yes	21	14–30	3	1–10
	No	27	22–32	6	4–9
Lung metastases	Yes	27	22–33	5	3–8
	No	21	15–29	7	3–12
Prior therapy	Sunitinib	23	18–28	6	4–10
	Pazopanib	28	20–37	3	1–7
	Interleukin-2	14	5–29	3	0.1–14
Months on first-line therapy	<6	26	18–35	5	2–11
	≥6	25	20–30	5	3–9
Prior anti-angiogenic therapies	1	24	20–29	5	3–9
	2	28	19–38	5	2–11



Minimum follow-up: 14 months; reported as of June 2015.
Analyses based on case report form data.
CI, confidence interval; MSKCC, Memorial Sloan Kettering Cancer Center; ORR, objective response rate.

Treatment-Related AEs in ≥10% of Patients

%	Nivolumab N=406			Everolimus N=397		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Treatment-related AEs	79	18	1	88	33	4
Fatigue	33	2	0	34	3	0
Nausea	14	<1	0	17	1	0
Pruritus	14	0	0	10	0	0
Diarrhea	12	1	0	21	1	0
Decreased appetite	12	<1	0	21	1	0
Rash	10	<1	0	20	1	0
Cough	9	0	0	19	0	0
Anemia	8	2	0	24	8	<1
Dyspnea	7	1	0	13	<1	0
Edema peripheral	4	0	0	14	<1	0
Pneumonitis	4	1	<1	15	3	0
Mucosal inflammation	3	0	0	19	3	0
Dysgeusia	3	0	0	13	0	0
Hyperglycemia	2	1	<1	12	3	<1
Stomatitis	2	0	0	29	4	0
Hypertriglyceridemia	1	0	0	16	4	1
Epistaxis	1	0	0	10	0	0

- **No treatment-related deaths were reported with nivolumab, and 2 deaths were reported with everolimus (1 from septic shock and 1 from bowel ischemia)**

Minimum follow-up: 14 months; reported as of June 2015.
AE, adverse event.
Included with permission from Sharma P et al. Oral presentation at ESMO 2015. 3LBA.

Treatment Duration and Discontinuation

	Nivolumab	Everolimus
Randomized/treated, N/n	410/406	411/397
Median duration of treatment, months (range)	5.5 (<0.1–29.6)	3.7 (0.2–25.7)
Continuation of treatment, %	17	7
Dose delay,[a] %	51	66
≥1 dose reduction, %	Not allowed	26
Treatment-related adverse events leading to treatment discontinuation, %	8	13

- **Minimum follow-up was 14 months**
- **Primary reason for discontinuation of treatment was disease progression, occurring in 70% with nivolumab and 69% with everolimus**

Minimum follow-up: 14 months; reported as of June 2015.
[a]Includes interruptions for everolimus.
Motzer et al. *N Engl J Med* 2015;373:1803–13.

Results

- Treatment-related AEs occurred in 80% and 89% of patients treated with nivolumab and everolimus, respectively (Table 2)
- Incidence of treatment-related select AEs is shown in Table 2

Table 2. Treatment-related AE summary

n (%)	Nivolumab N = 406		Everolimus N = 397	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Treatment-related AEs	325 (80)	84 (21)	352 (89)	147 (37)
Treatment-related AEs leading to discontinuation	34 (8)	20 (5)	50 (13)	27 (7)
Treatment-related select AEs				
Hepatic	46 (11)	12 (3)	31 (8)	2 (<1)
Skin	110 (27)	5 (1)	152 (38)	5 (1)
GI	56 (14)	9 (2)	86 (22)	6 (2)
Renal	28 (7)	4 (1)	36 (9)	2 (<1)
Endocrine	45 (11)	4 (1)	11 (3)	1 (<1)
Pulmonary	20 (5)	6 (1)	69 (17)	13 (3)

GI = gastrointestinal

Sharma P., et al Int Kidney cancer Symposium, Miami, 2017

Three-Year Safety Update From the Phase III CheckMate 025

	Median (range) time to onset, weeks	Median (range) time to resolution, weeks	Resolution rates, %
Hepatic	7.6 (2.0–200.4)	9.7 (1.6–163.3+)	80
Skin	8.6 (0.1–195.9)	16.0 (0.1-215.4+)	78
GI	10.1 (0.1–122.1)	8.4 (0.1–191.3+)	84
Renal	10.6 (4.0–79.1)	26.1 (0.6–165.0+)	67
Endocrine	18.4 (2.1–187.6)	NA[a] (1.9–194.9+)	38
Pulmonary	18.9 (1.9–162.4)	5.6 (1.3–154.1+)	85

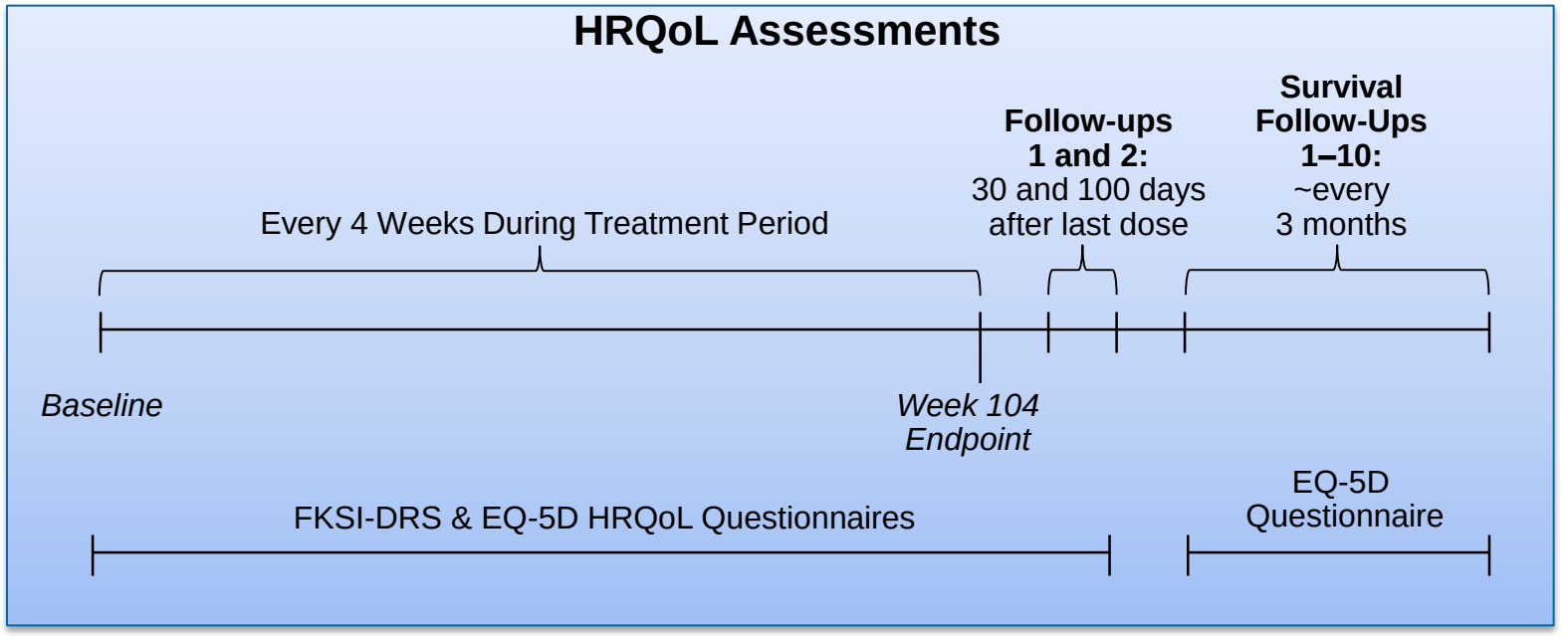
[a]Median time to resolution of endocrine AEs was not available (NA) at the June 2017 data cutoff. + Indicates a censored value

The majority of nivolumab-related select AEs resolved (within 5.6–26.1 weeks), with the exception of endocrine events

Sharma P., et al Int Kidney cancer Symposium, Miami, 2017

HRQoL Assessments and Schedule

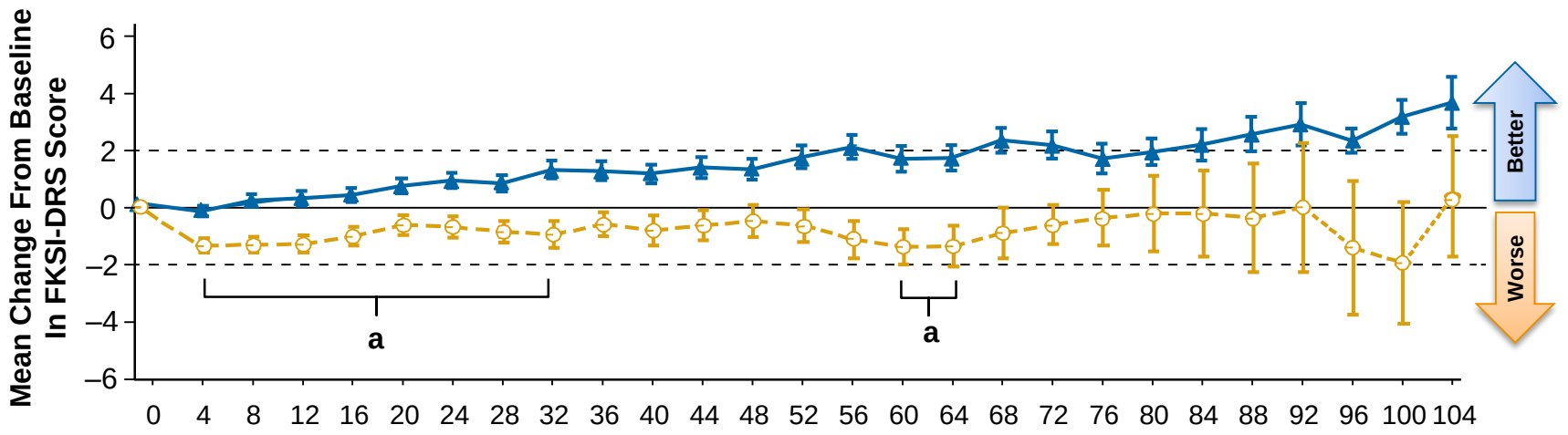
- **FKSI-DRS (higher scores indicate better health state)**
  - **Consists of 9 symptom-specific questions that address lack of energy, pain, weight loss, bone pain, fatigue, dyspnea, cough, fever, and hematuria**
- **EQ-5D Utility Index (higher scores indicate better health state)**
- **EQ-5D Visual analog scale (higher scores indicate better health state)**



EQ-5D, European Quality of Life-5 Dimensions; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms; HRQoL, health-related quality of life.
Adapted from Cella DF et al. *Lancet Oncol* 2016;17:994–1003.

Change From Baseline in HRQoL by FKSI-DRS

- **Within the nivolumab arm, improvement from baseline in HRQoL was observed starting at week 20 (*P*=0.031) and mean change from baseline differed significantly from the everolimus arm at each assessment through week 76 (*P*=0.043)**
- **Deterioration in HRQoL from baseline was observed in the everolimus arm (bracket a)**



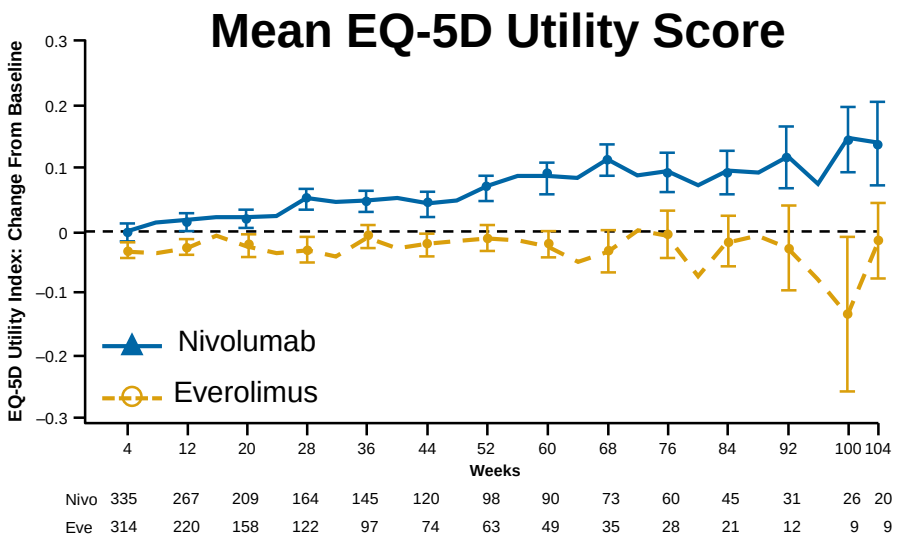
No. of patients at risk

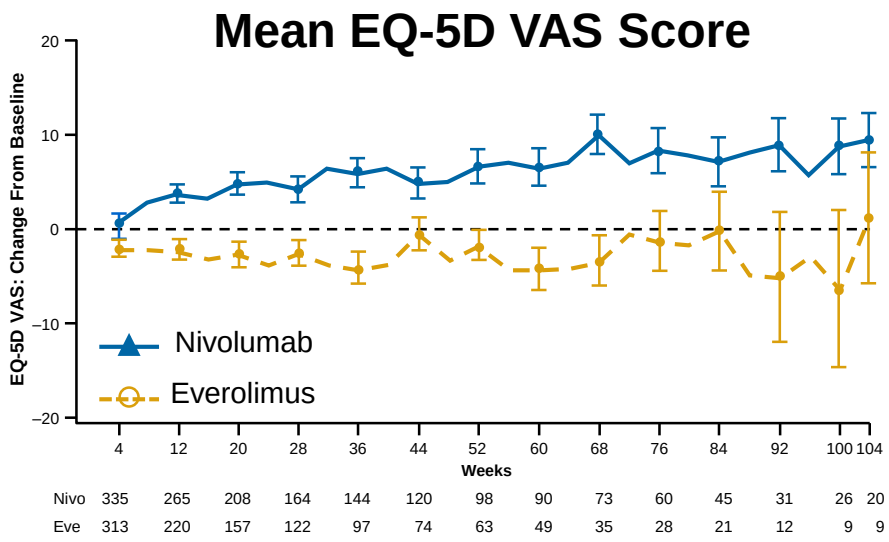
Nivolumab	361	334	302	267	236	208	186	164	159	144	132	119	112	97	90	89	81	72	63	59	53	44	43	31	30	26	20
Everolimus	343	316	270	219	191	157	143	122	102	97	87	74	73	63	58	49	44	35	30	28	24	21	15	12	12	9	9

Minimum follow-up: 14 months; reported as of June 2015.
Only time points where data were available for 5 or more patients are shown. Number at risk shows the number of randomized patients with baseline plus at least 1 post-baseline HRQoL assessment with non-missing patient-reported outcome data. Important difference consists of a change of ≥2 points. Bars show standard error.
FKSI-DRS, Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms; HRQoL, health-related quality of life.
Adapted from Cella DF et al. *Lancet Oncol* 2016;17:994–1003.

Change From Baseline in HRQoL Scores by EQ-5D

- **Differences favored nivolumab when compared with everolimus (not all time points were statistically significant)**
- **For nivolumab vs everolimus:**
  - **More patients experienced a clinically meaningful HRQoL improvement (*P*=0.0001) assessed by EQ-5D VAS (53% vs 39%) and shorter time (*P*=0.0054) to improvement (6.5 months vs 23.1 months)**





Minimum follow-up: 14 months; reported as of June 2015.
Note: Important difference consists of a change of ≥0.08 points for EQ-5D utility index or ≥7 points for EQ-5D VAS.
EQ-5D, European Quality of Life-5 Dimensions; EQ-5D VAS, European Quality of Life-5 Dimensions visual analogue scale; FKSI-DRS, Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms; HRQoL, health-related quality of life.
Adapted from Cella DF et al. *Lancet Oncol* 2016;17:994–1003, supplemental materials.

Nivolumab vs Everolimus (CheckMate-025): Subgroup Analyses

Pts with advanced RCC with clear-cell component, KPS ≥ 70%, 1-2 previous antiangiogenic agents, progression ≤ 6 mos before enrollment (N = 803)

Nivolumab
3 mg/kg IV Q2W
(n = 406)

- Progressed (n = 316)
  - Treated beyond progression (n = 153)
  - Treated briefly beyond progression (n = 18)
  - Not treated beyond progression (n = 145)
- Did not progress (n = 90)

Everolimus
10 mg PO QD
(n = 397)

- Progressed (n = 320)
  - Treated beyond progression (n = 65)
  - Treated briefly beyond progression (n = 111)
  - Not treated beyond progression (n = 144)
- Did not progress (n = 77)

Primary endpoint: OS

Secondary endpoints: ORR, safety

Subgroup analyses: efficacy, safety from baseline to first progression, safety at and after first progression

Escudier BJ, et al. ASCO 2016. Abstract 4509.

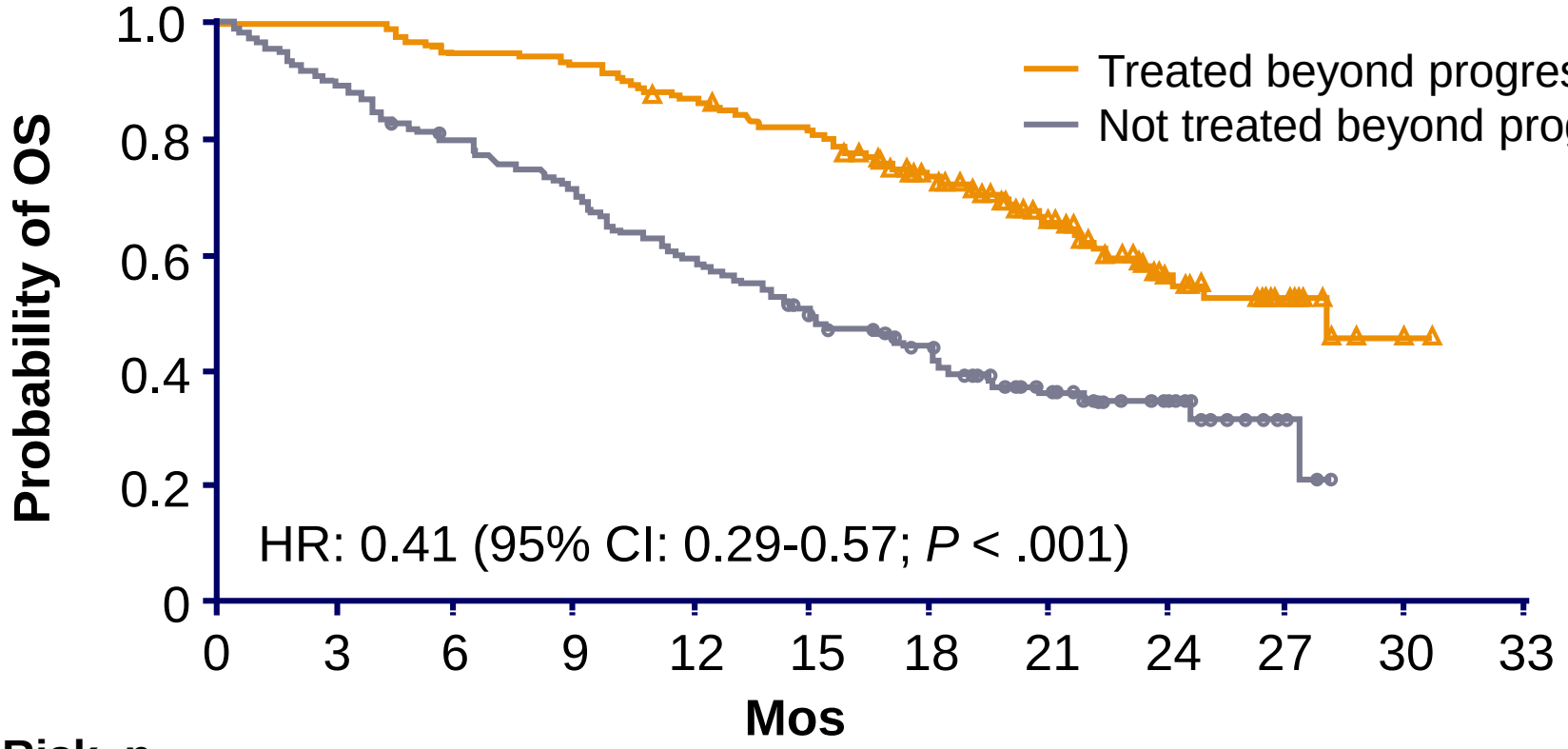
Nivolumab vs Everolimus (CheckMate-025): Patient Population for Subgroup Analysis

Disease Characteristics at First Progression	TBP (n = 153)	NTBP (n = 145)
Median age, yrs (range)	62 (29-85)	63 (23-85)
Male, %	76	80
Quality-of-life score (FKSI-DRS),* median (range)	31.0 (28.0-33.0)	27.0 (24.0-32.5)
KPS: ≥ 90/70 or 80/< 70, %	73/27/1	48/50/2
Change in KPS: deterioration/improvement, %	17/16	27/8
Target lesion status at progression, % ▪ Increase in target lesions† ▪ Appearance of new lesions ▪ Both of above	 55 41 12	 43 44 15
Site of new lesions‡: lung/node/bone/liver, %	14/10/5/5	12/10/14/8
Change in tumor burden,§ % ▪ Bulky to small ▪ Small to bulky	 4 7	 3 13

*TBP, n = 135; NTBP, n = 52. †≥ 20% increase in smallest SOD of target lesions.
‡Based on all pts treated and not treated beyond progression. §Bulky: ≥13 cm; small: < 13 cm.

Escudier BJ, et al. ASCO 2016. Abstract 4509.

CheckMate 025 Subgroup Analysis: OS



	Median OS, Mos (95% CI)
Treated beyond progression	28.1 (23.2-NE)
Not treated beyond progression	15.0 (12.1-18.2)

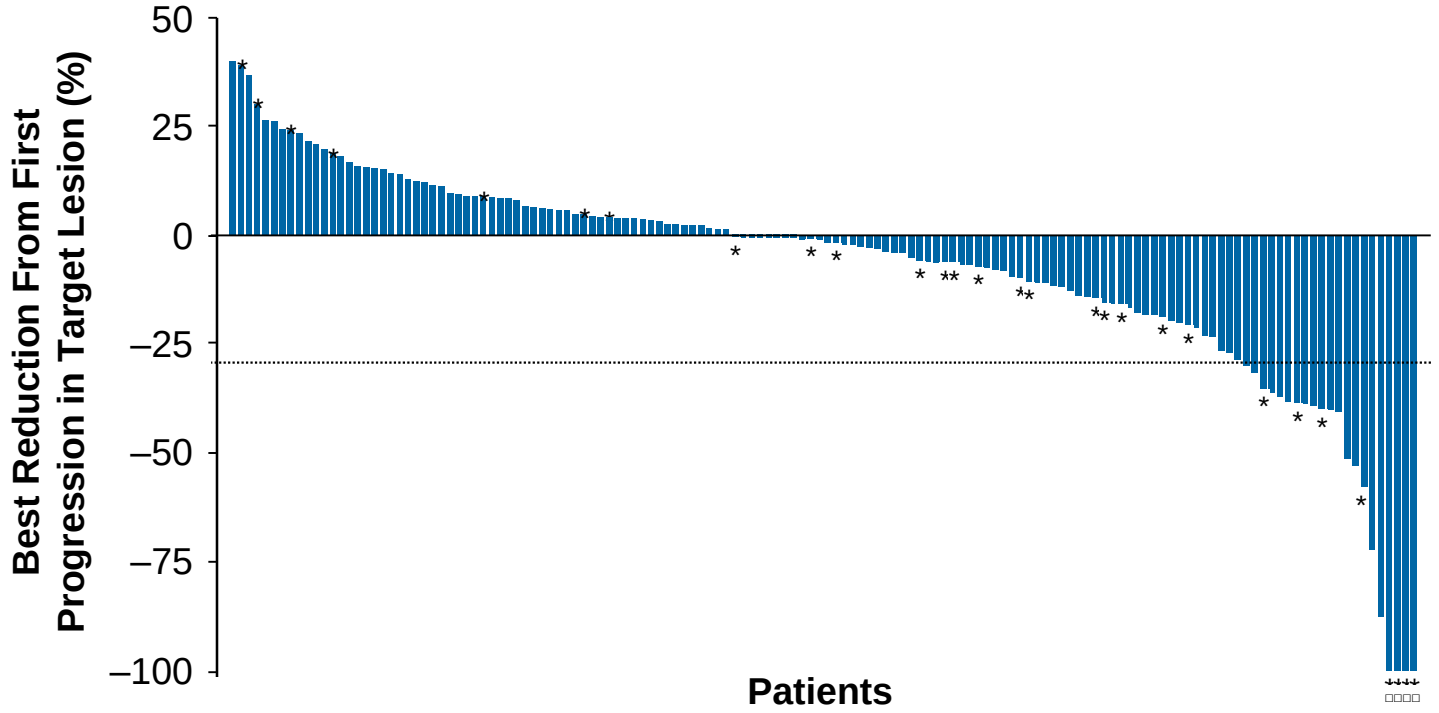
Pts at Risk, n

TBP	153	153	146	142	132	123	96	65	30	17	2	0
NTBP	145	131	113	101	84	69	54	29	16	3	0	0

Escudier BJ, et al. ASCO 2016. Abstract 4509.

Target Lesion Change Post-Progression

- **Of the 153 patients treated with nivolumab beyond progression, 48% (n=74; 95% CI, 40.2–56.6) had any tumor burden reduction post-progression and 13% (n=20; 95% CI, 8.2–19.5) had a ≥30% reduction in tumor burden post-progression[a]**



Minimum follow-up: 14 months; reported as of June 2015.
Asterisks represent responders before first progression. Square symbols represent % change truncated to 100%. Excludes patients who were treated beyond progression but did not have scans beyond first progression to document tumor burden.
[a]11 of 153 patients did not have tumor measurements before and after first progression.
CI, confidence interval.
Included with permission from Escudier B et al. *Eur Urol* 2017. http://dx.doi.org/10.1016/j.eururo.2017.03.037.

Lenvatinib + Pembrolizumab in Metastatic RCC: Phase I/II Study

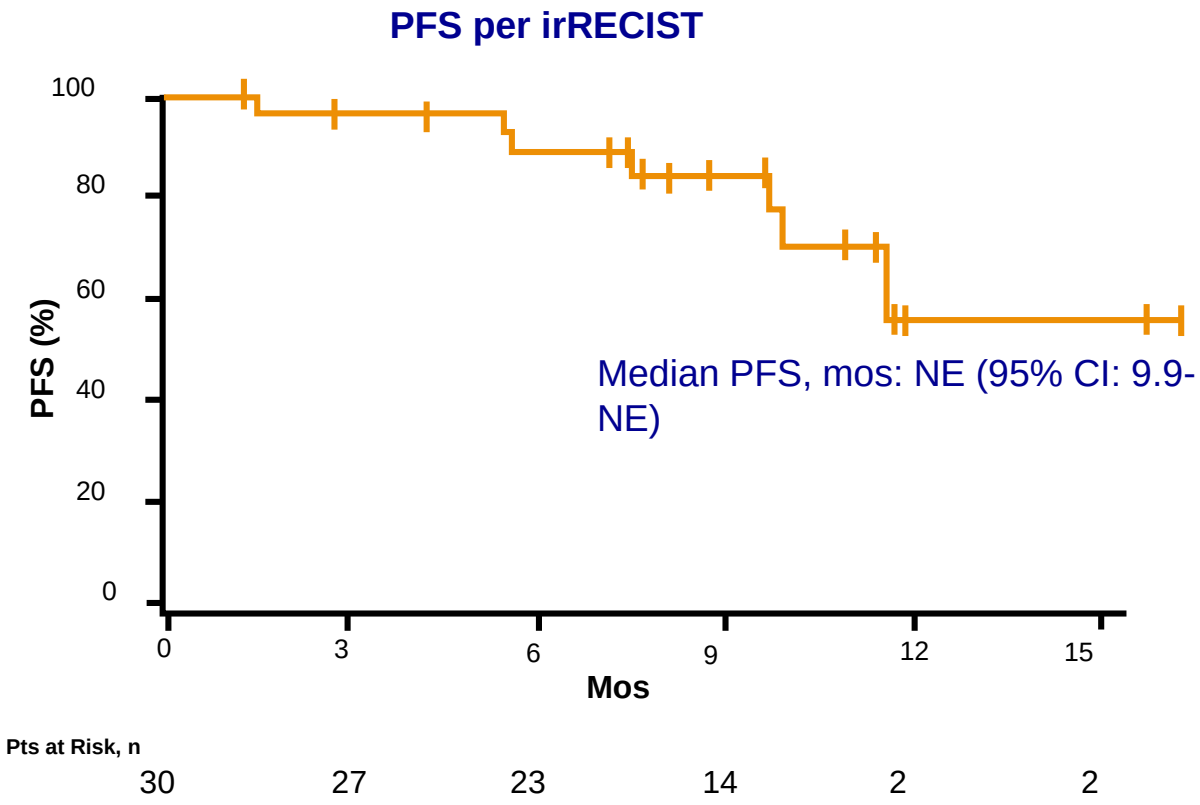
- **Combined analysis of phase I/II data from RCC cohort (N = 30)**
  - **Phase I: enrolled previously treated pts with selected metastatic solid tumors (n = 8 with RCC)**
    - Lenvatinib 24 mg QD (reduced to 20 mg based on DLT) + pembrolizumab 200 mg Q3W on 21-day cycles
    - MTD/RP2D: lenvatinib 20 mg QD + pembrolizumab 200 mg Q3W on 21-d cycles
  - **Phase II (n = 22): enrolled pts with metastatic clear-cell RCC, 0-2 prior systemic treatment, measurable disease**
    - **Treated with MTD**

Lee C, et al. ESMO 2017. Abstract 847O

Phase I/II: Lenvatinib + Pembrolizumab in Metastatic RCC Efficacy Outcomes

Pts	ORR at Wk 24,* n (%)
All (N = 30)	19 (63)
Treatment naive (n = 12)	10 (83)
Previously treated	
▪ 1 regimen (n = 10)	5 (50)
▪ ≥ 2 regimens (n = 8)	4 (50)
PD-L1 status	
▪ Positive (n = 12)	7 (58)
▪ Negative (n = 14)	10 (71)
▪ Unknown (n = 4)	2 (50)

*All PR per irRECIST.



Lee C, et al. ESMO 2017. Abs 847O

Lenvatinib + Pembrolizumab in Metastatic RCC: Select TEAE in ≥ 15% of Pts

TEAE, n (%)	Pts (N = 30)		
	Any	Grade 3	Grade 4
Any	30 (100)	16 (53)	2 (7)
Diarrhea	25 (83)	1 (3)	0
Fatigue	21 (70)	2 (7)	0
Hypothyroidism	20 (67)	0	0
Stomatitis	18 (60)	0	0
Hypertension	17 (57)	3 (10)	0
Nausea	17 (57)	1 (3)	0
Proteinuria	11 (37)	2 (7)	0
Lipase elevation	5 (17)	4 (13)	1 (3)

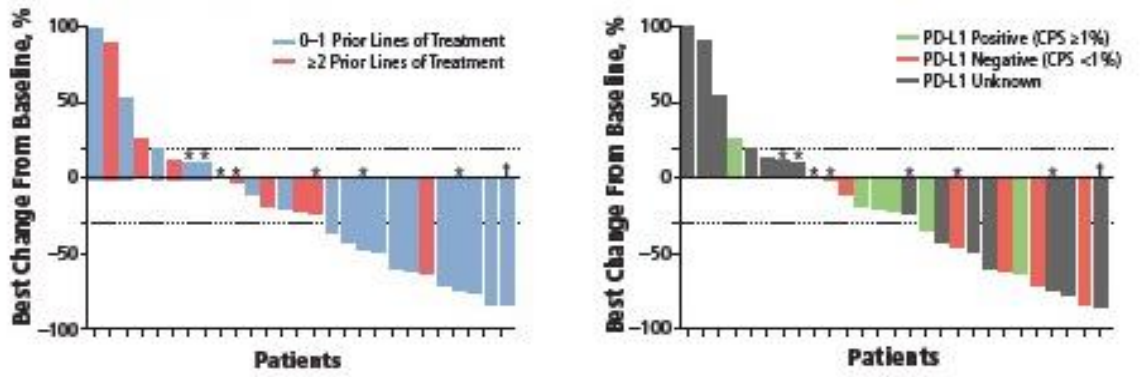
Lee C, et al. ESMO 2017. Abstract 847O

Epacadostat Plus Pembrolizumab in Patients With Advanced RC: Preliminary Phase 1/2 Results From ECHO-202/KEYNOTE-037

During phase 1 dose escalation, 46 pts received oral epacadostat 25 mg BID, 50 mg BID, 100 mg BID, or 300 mg BID in combination with IV pembrolizumab 2 mg/kg or 200 mg Q3W

The maximum tolerated dose of epacadostat was not exceeded during phase 1 evaluation7; epacadostat 100

Variable	Total (N=46)
Median (range) age, y	63 (37–81)
Sex, n (%)	
Men	29 (63)
Women	17 (37)
Race, n (%)	
White	43 (93)
Asian	3 (7)
ECOG PS, n (%)	
0	28 (61)
1	17 (37)
Not done	1 (2)
MSKCC score, n (%)	
Favorable	4 (9)
Intermediate	34 (74)
Poor	8 (17)
Prior radiation therapy, n (%)	13 (28)
Prior surgery, n (%)	44 (96)*
Number of prior treatments for advanced disease, n (%)	
0	14 (30)
1	18 (40)
≥2	14 (30)
PD-L1 expression†	
Positive (CPS ≥1%)	6/30 (20)
Negative (CPS <1%)	7/30 (23)
Unknown‡	17/30 (57)

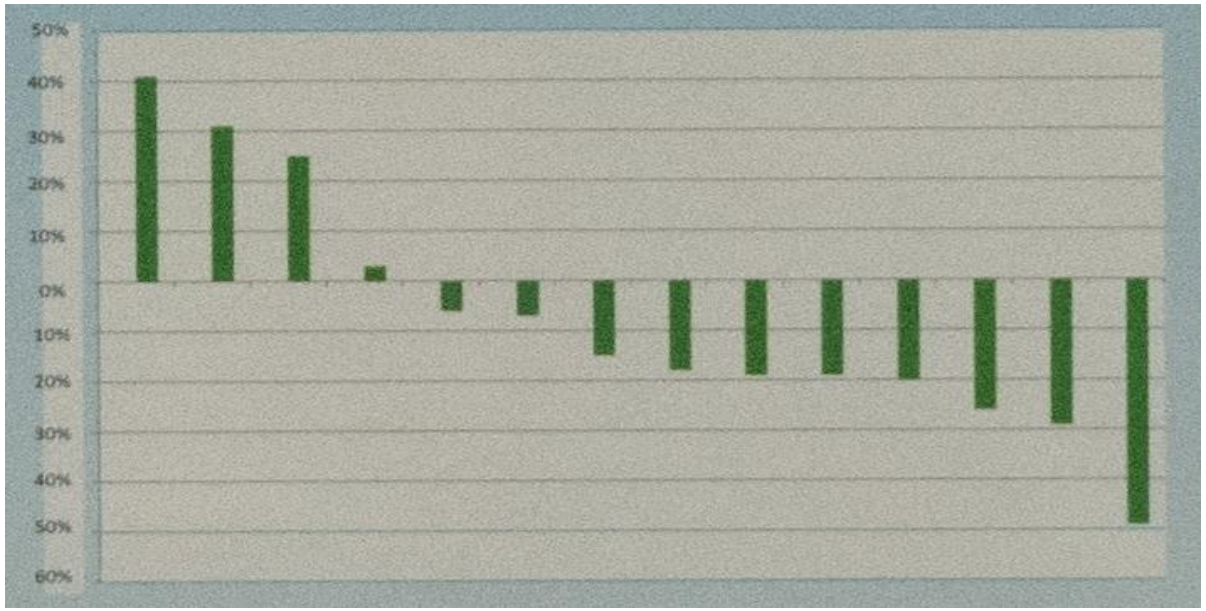


Patients, n (%)	Total* (n=30)	Number of Prior Lines of Treatment		PD-L1 Expression†	
		0–1 (n=19)	≥2 (n=11)	Positive (n=6)	Negative (n=7)
ORR (CR+PR)	10 (33)	9 (47)	1 (9)	2 (33)	3 (43)
CR	1 (3)	1 (5)	0	0	0
PR	9 (30)	8 (42)	1 (9)	2 (33)	3 (43)
SD	5 (17)	2 (11)	3 (27)	3 (50)	1 (14)
DCR (CR+PR+SD)	15 (50)	11 (58)	4 (36)	5 (83)	4 (57)
PD	12 (40)	8 (42)	4 (36)	1 (17)	2 (29)
Not evaluable	3 (10)	0	3 (27)	0	1 (14)

Lara PN., et al, Chicago ASCO 2017 abs 4515

Phase I study of Pembrolizumab in combination with Bevacizumab for treatment of mRCC. Big Ten Research Consortium BTCRC-GU14-003

16 pts with mRCC (mean age 59, median 61 yr) after failure of at least one systemic therapy, were included in this analysis



Tumor Volume Reduction (% below baseline)

Patient #	Cell Reduction(%)	Tumor Reduction (%)
2	18	29
6	50	7
9	78	18
1	79	49
8	88	20
14	92	19
10	94	26
3	96	15

Circulating Tumor Cells

Dudek AZ, ASCO-GU 2016

Management of Advanced RCC in 2017

	First-line Therapy	Second-line Therapy
Favorable risk	Sunitinib or pazopanib	Nivolumab, cabozantinib, lenvatinib/everolimus, or axitinib
Intermediate risk	Sunitinib or pazopanib	Nivolumab, cabozantinib, lenvatinib/everolimus or axitinib
Poor risk	Sunitinib or pazopanib Can consider temsirolimus	Nivolumab, cabozantinib, lenvatinib/everolimus or axitinib

Conclusions

- Numerous new treatment options with proven role in advanced RCC now available
- VEGF and mTOR pathways are important targets in this disease
- Checkpoint inhibition has proven survival benefit in RCC in second-line therapy and beyond
  - Substantial percentage of pts may have durable benefit with minimal toxicity
- Clinicians must be able to use novel therapies sequentially with optimal dosing and management in order to maintain long-term disease control and increased QoL