IMmotion151: A Randomized Phase III Study of Atezolizumab Plus Bevacizumab vs Sunitinib in Untreated Metastatic Renal Cell Carcinoma

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PRESENTED AT: 2018 Genitourinary Cancers Symposium | #GU18

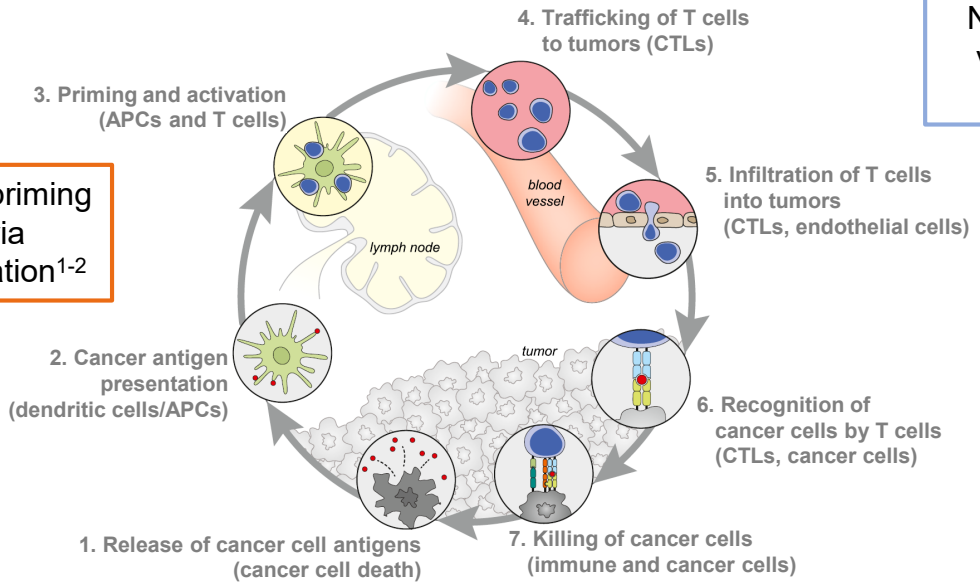
Introduction

- Bevacizumab (VEGF inhibitor) + IFN-α-2a is approved for use in first-line mRCC. Bevacizumab also has single-agent activity[1-4]
- Atezolizumab (anti–PD-L1) demonstrated anti-tumor activity and a tolerable safety profile in mRCC[5-7]
- In a randomized Phase II study, atezolizumab + bevacizumab resulted in encouraging efficacy vs sunitinib in patients whose disease expresses PD-L1, indicating a complementary effect when combining the two agents[7]

mRCC, metastatic renal cell carcinoma.

1. Yang JC, et al. *N Engl J Med.* 2003; 2. Bukowski RM, et al. *J Clin Oncol.* 2007; 3. Flaherty KT, et al. *J Clin Oncol.* 2015, 4. Escudier B, et al. *J Clin Oncol.* 2010; 5. Herbst RL, et al. *Nature.* 2014; 6. McDermott DF, et al. *J Clin Oncol.* 2016; 7. McDermott DF, et al. ASCO-GU 2017.

Rationale for Combining Atezolizumab + Bevacizumab



Normalization of the tumor vasculature for increased T-cell tumor infiltration[3-6]

Promotion of T-cell priming and activation via dendritic cell maturation[1-2]

Establishing an immune-permissive tumor microenvironment by decreasing MDSC and Treg populations[6-10]

- Atezolizumab's T-cell mediated cancer cell killing may be enhanced through bevacizumab's reversal of VEGF-mediated immunosuppression

1. Gabrilovich DI, et al. *Nat Med*, 1996. 2. Oyama T, et al. *J Immunol*, 1998. 3. Goel S, et al. *Physiol Rev*, 2011. 4. Motz GT, et al. *Nat Med*, 2014. 5. Hodi FS, et al. *Cancer Immunol Res*, 2014.
6. Wallin JJ, et al. *Nat Commun*, 2016. 7. Gabrilovich DI, Nagaraj S. *Nat Rev Immunol*, 2009. 8. Roland CL, et al. *PLoS One*, 2009. 9. Facciabene A, et al. *Nature*, 2011. 10. Voron T, et al. *J Exp Med*, 2015.
Figure adapted from Chen DS, Mellman I. *Immunity*, 2013.

Study Objectives

- A randomized Phase III study of atezolizumab + bevacizumab vs sunitinib was conducted in patients with treatment-naive advanced or metastatic RCC

- **Primary Endpoints**
  - PFS by investigator-assessment in PD-L1+ patients, defined as ≥ 1% expression on tumor-infiltrating immune cells (IC) as determined by immunohistochemistry (IHC)[a]
  - OS in ITT

- **Key Secondary Endpoints**
  - PFS in ITT
  - OS in PD-L1+
  - ORR and DOR
  - Independent radiology committee (IRC)-assessed PFS and ORR
  - Patient-reported outcomes
  - Safety

DOR, duration of response; ITT, intent-to-treat; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; [a] Using SP142 IHC assay.

Study Design

Key Eligibility:

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

Stratification:

- •MSKCC risk score
- •Liver metastases
- •PD-L1 IC IHC status (< 1% vs ≥ 1%)[a]

N = 915

R 1:1

Atezolizumab 1200 mg IV q3w[b]
+
Bevacizumab 15 mg/kg IV q3w[b]

Sunitinib 50 mg/day orally (4 wk on, 2 wk off)

[a] ≥ 1% IC: 40% prevalence using SP142 IHC assay; [b] No dose reduction for atezolizumab or bevacizumab.

Statistical Design and Conduct

- IMmotion151 enrolled 915 randomized patients, 362 (40%) of whom had PD-L1+ disease[a]
- Primary analysis of PFS in the PD-L1+ subgroup was triggered by 236 PFS events (65% event-to-patient ratio) at the data cutoff date of September 29, 2017
- First OS interim analysis was also conducted with the same cutoff date
- Stratified HR and log-rank test were used for primary analyses
- 5% alpha was split: 4% for PFS in PD-L1+ and 1% for OS in ITT populations
  - The *P* value boundary at the first OS interim analysis was alpha = 0.0009

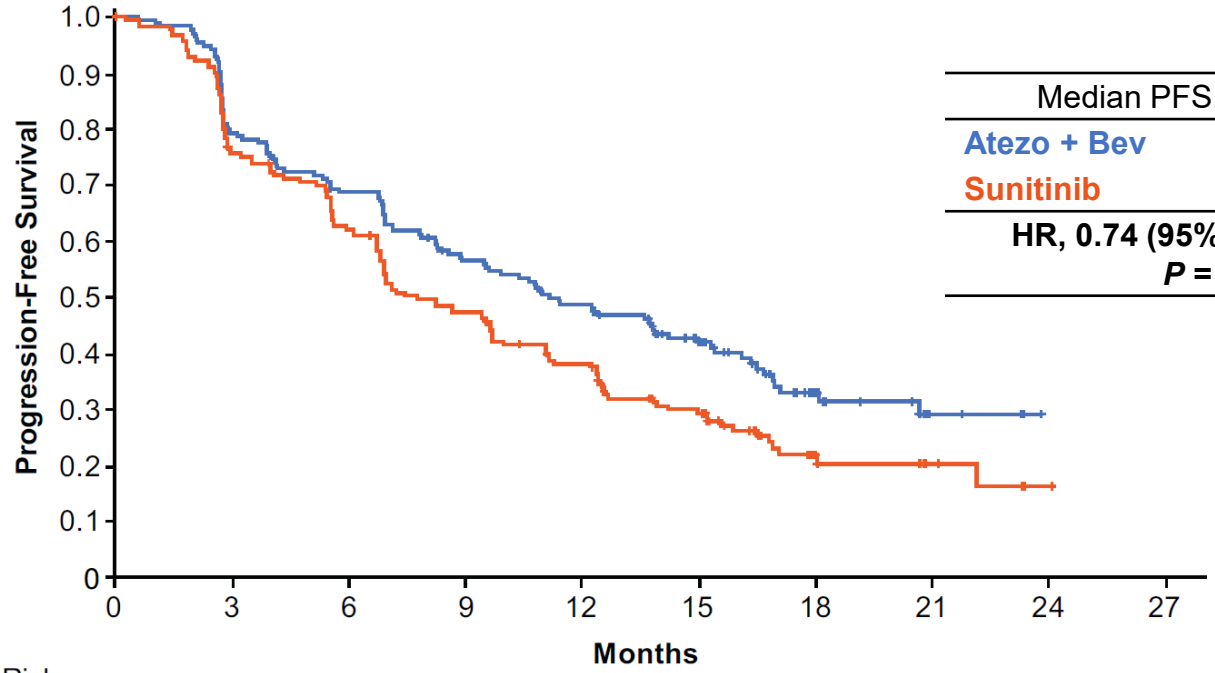
[a] ≥ 1% IC using SP142 IHC assay.

Baseline Characteristics

	PD-L1+ (n = 362)		ITT (N = 915)	
Characteristic	**Atezo + Bev n = 178**	**Sunitinib n = 184**	**Atezo + Bev n = 454**	**Sunitinib n = 461**
Age, median (range)	62 y (33-84)	59 y (23-80)	62 y (24-88)	60 y (18-84)
Male	67%	79%	70%	76%
KPS ≥ 80	95%	95%	91%	92%
Liver metastasis	17%	18%	17%	18%
Prior nephrectomy	84%	83%	74%	72%
Predominant clear cell histology	92%	87%	93%	92%
Sarcomatoid component	20%	27%	15%	16%
≥ 1% of IC expressing PD-L1 (PD-L1+)	-	-	39%	40%
MSKCC risk category				
Favorable (0)	17%	18%	20%	20%
Intermediate (1 or 2)	74%	73%	71%	70%
Poor (≥ 3)	8%	9%	10%	10%

Co-Primary Endpoint

Progression-Free Survival in PD-L1+

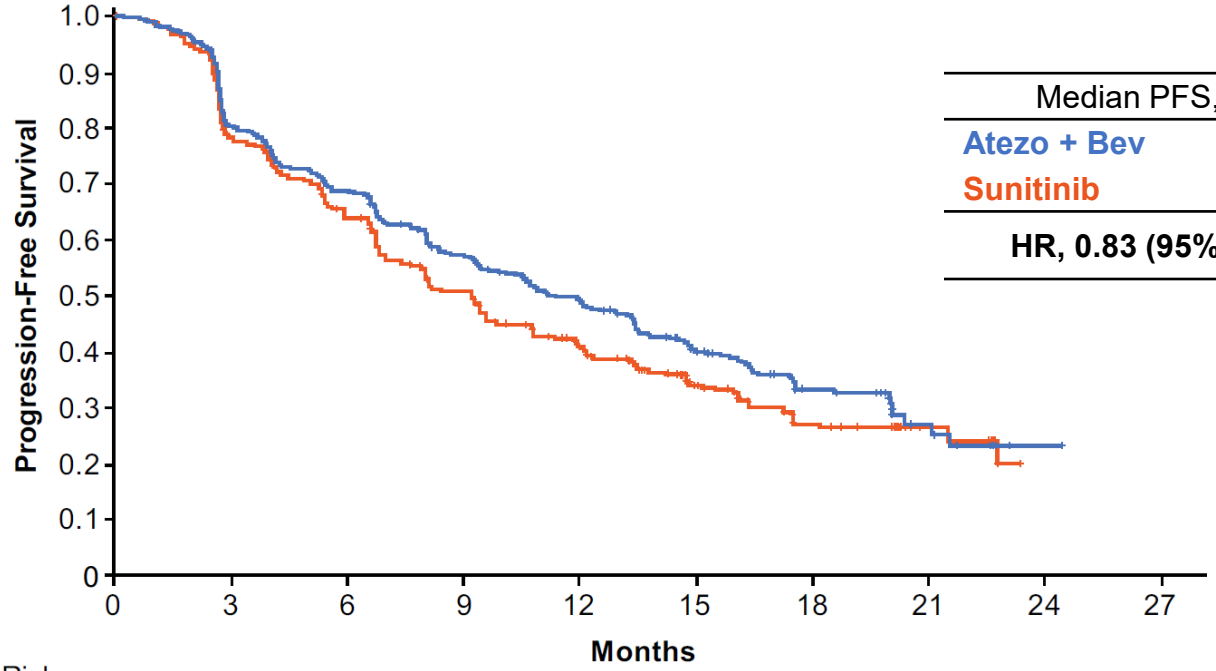


Median PFS, mo (95% CI)	
Atezo + Bev	11.2 (8.9, 15.0)
Sunitinib	7.7 (6.8, 9.7)
HR, 0.74 (95% CI: 0.57, 0.96) *P* = 0.02	

No. at Risk									
Atezo + Bev	178	137	117	94	79	55	22	5	
Sunitinib	184	135	110	83	64	44	15	7	1

PFS assessed by investigators. Minimum follow-up, 12 mo. Median follow-up, 15 mo.
The PFS analysis passed the pre-specified *P* value boundary of alpha = 0.04.

Progression-Free Survival in ITT



Median PFS, mo (95% CI)	
Atezo + Bev	**11.2 (9.6, 13.3)**
Sunitinib	**8.4 (7.5, 9.7)**
HR, 0.83 (95% CI: 0.70, 0.97)	

No. at Risk									
Atezo + Bev	454	355	294	236	196	126	57	15	1
Sunitinib	461	346	281	211	166	105	42	14	1

PFS assessed by investigators. Minimum follow-up, 12 mo. Median follow-up, 15 mo.

Objective Response Rate

	PD-L1+	
	Atezo + Bev n = 178	Sunitinib n = 184
Confirmed ORR, % 95% CI	43% (35, 50)	35% (28, 42)
Complete response	9%	4%
Partial response	34%	30%
Stable disease	32%	35%
Progressive disease	19%	21%
Not evaluable[a]	7%	10%

[a] Including patients with no post-baseline tumor assessment. ORR assessed by investigators in patients with measurable disease at baseline.

Objective Response Rate

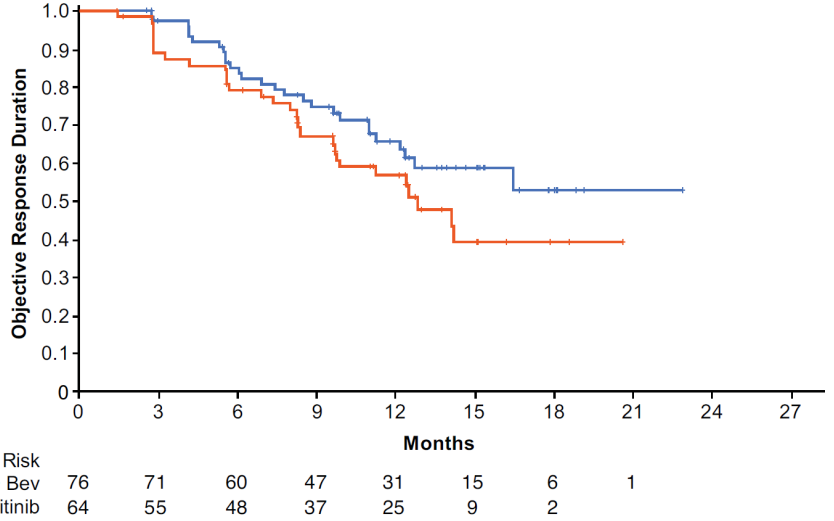
	PD-L1+		ITT	
	Atezo + Bev n = 178	Sunitinib n = 184	Atezo + Bev n = 454	Sunitinib n = 460
Confirmed ORR, % 95% CI	43% (35, 50)	35% (28, 42)	37% (32, 41)	33% (29, 38)
Complete response	9%	4%	5%	2%
Partial response	34%	30%	31%	31%
Stable disease	32%	35%	39%	39%
Progressive disease	19%	21%	18%	19%
Not evaluable[a]	7%	10%	7%	9%

[a] Including patients with no post-baseline tumor assessment. ORR assessed by investigators in patients with measurable disease at baseline.

Objective Response Rate

	PD-L1+	
	Atezo + Bev n = 178	Sunitinib n = 184
Confirmed ORR, % 95% CI	43% (35, 50)	35% (28, 42)
Complete response	9%	4%
Partial response	34%	30%
Stable disease	32%	35%
Progressive disease	19%	21%
Not evaluable[a]	7%	10%

PD-L1+	Median DOR, mo (95% CI)	Ongoing Responders, n (%)
Atezo + Bev	NR (12.4, NR)	49 (65%)
Sunitinib	12.9 (9.8, NR)	34 (53%)



NR, not reached. [a] Including patients with no post-baseline tumor assessment. ORR assessed by investigators in patients with measurable disease at baseline. Minimum follow-up, 12 mo. Median follow-up, 15 mo.

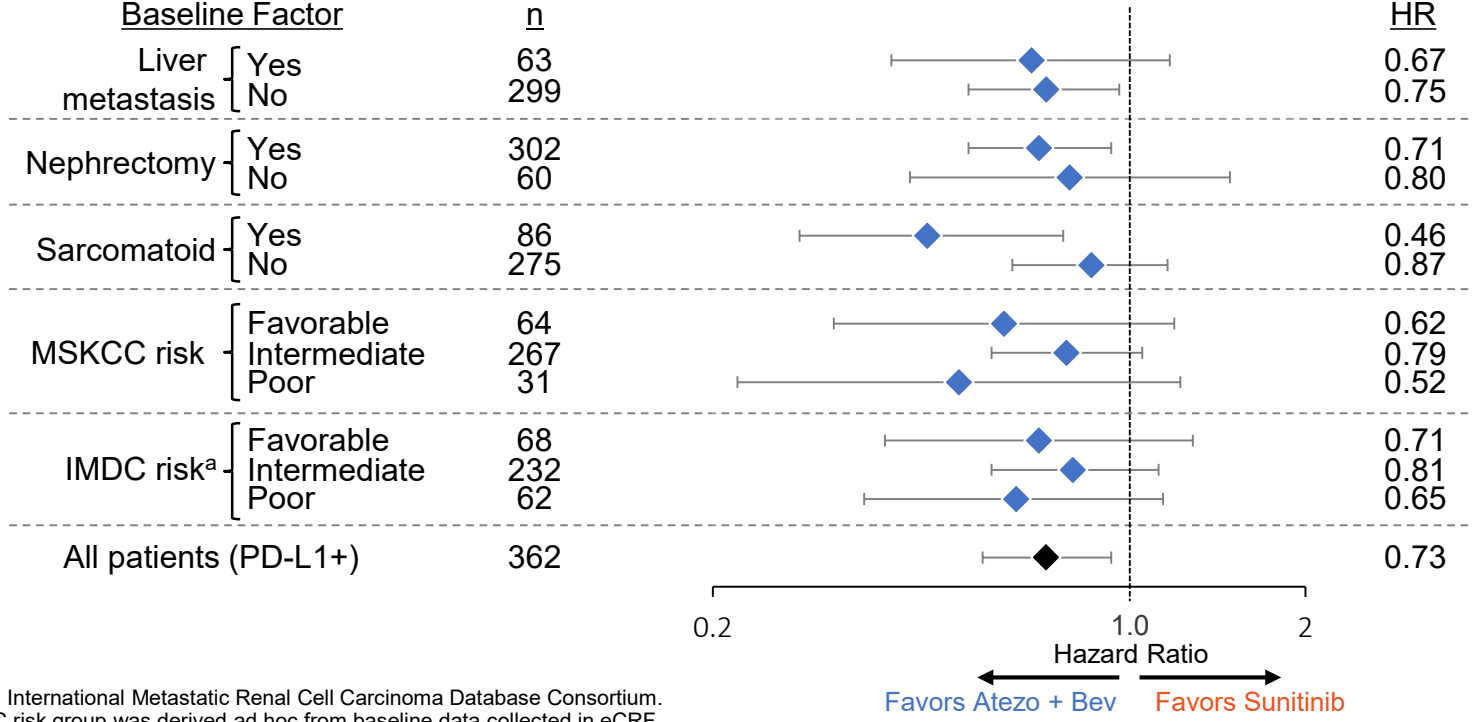
PFS and ORR by IRC

	PD-L1+		PD-L1−[a]		ITT	
	Atezo + Bev n = 178	Sunitinib n = 184	Atezo + Bev n = 276	Sunitinib n = 277[b]	Atezo + Bev n = 454	Sunitinib n = 461
Median PFS, mo (95% CI)	8.9 (6.9, 12.5)	7.2 (6.1, 11.1)	11.0 (8.3, 13.3)	8.4 (7.4, 10.1)	9.6 (8.3, 11.5)	8.3 (7.0, 9.7)
Stratified HR (95% CI)	0.93 (0.72, 1.21)		0.84 (0.67, 1.04)		0.88 (0.74, 1.04)	
Confirmed ORR, % (95% CI)	36% (29, 44)	33% (26, 40)	32% (26, 37)	30% (25, 36)	33% (29, 38)	31% (27, 36)
CR rate	15%	8%	8%	6%	11%	7%

- IRC and investigator assessment of PFS benefit was generally consistent in the ITT population; however, results differed from investigator assessment in patients with PD-L1+ disease
- Investigators, IRC reviewers and the sponsor were blinded to PD-L1 status

[a] PD-L1 negative tumors had a PD-L1 IC IHC expression < 1%. [b] n = 276 for ORR.

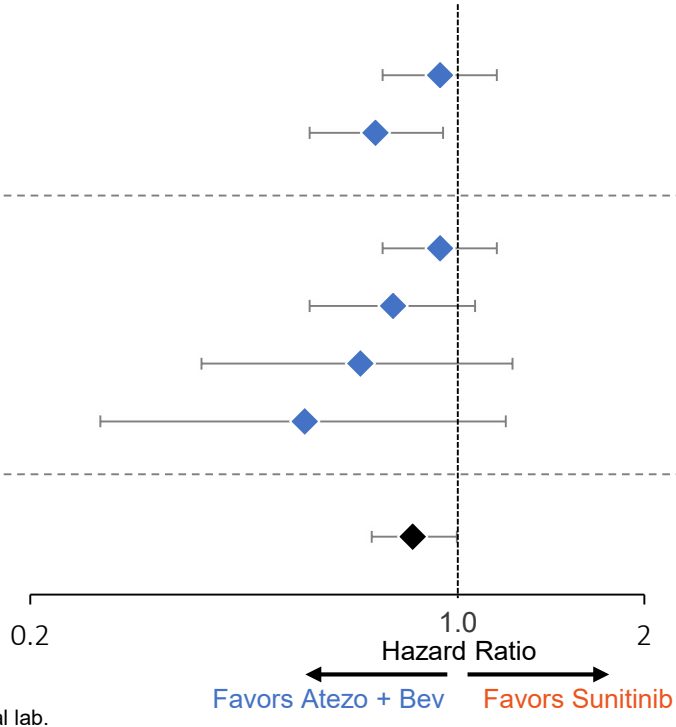
PFS in Key Subgroups (PD-L1+)



IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.
[a] IMDC risk group was derived ad hoc from baseline data collected in eCRF.
PFS assessed by investigators.

PFS in PD-L1 Subgroups (ITT)

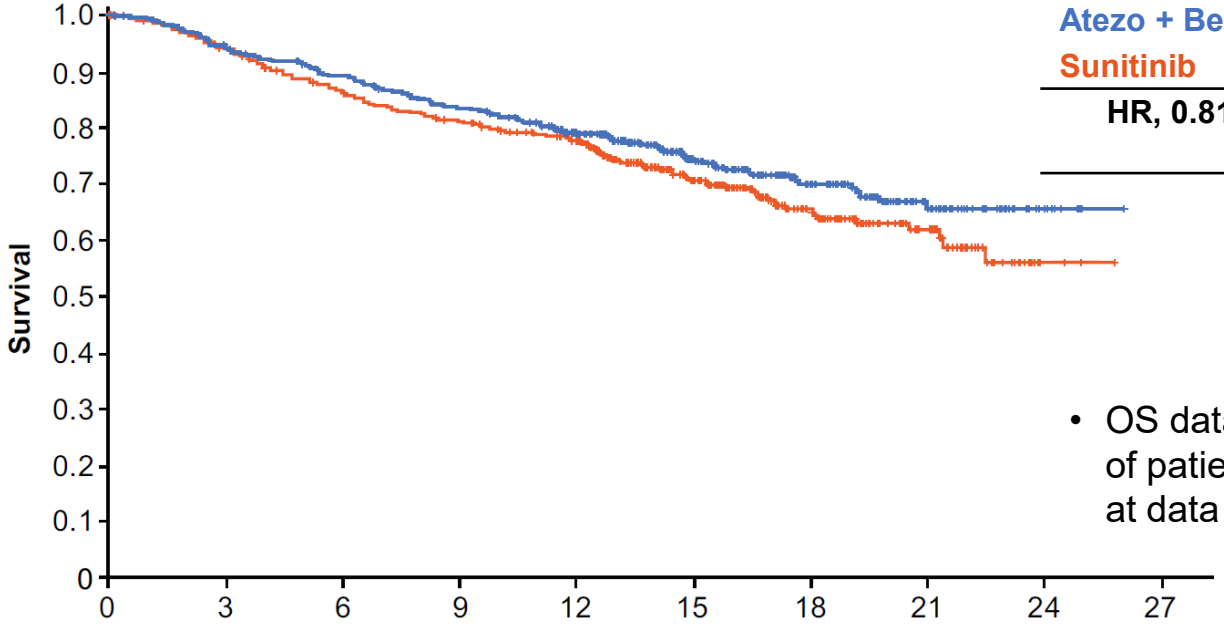
IC expressing PD-L1[a]	n	HR
0 (< 1%)	552	0.93
1/2/3 (≥ 1%)	363[b]	0.73
0 (< 1%)	552	0.93
1 (≥ 1% and < 5%)	253	0.78
2 (≥ 5% and < 10%)	72	0.69
3 (≥ 10%)	38	0.56
All patients (ITT)	915	0.84



[a] Per central lab. [b] One patient had PD-L1 IC0 per IxRS and IC123 per central lab.
PFS assessed by investigators.

Overall Survival in ITT

Median OS, mo (95% CI)	
Atezo + Bev	Not reached
Sunitinib	Not reached
HR, 0.81 (95% CI: 0.63, 1.03)	
***P* = 0.09**	



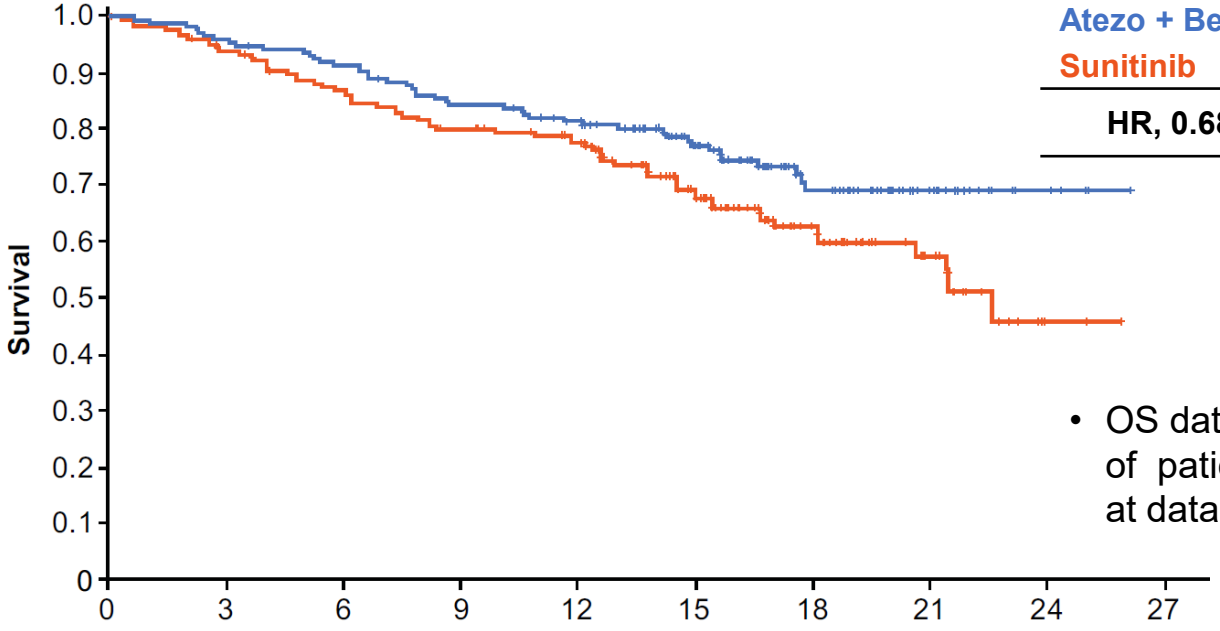
No. at Risk									
Atezo + Bev	454	428	398	371	341	246	141	69	18
Sunitinib	461	422	384	357	331	227	126	65	15

- OS data are immature; 29% of patients had an OS event at data cutoff

Minimum follow-up, 12 mo. Median of follow-up, 15 mo. Event/patient ratio: 27% for atezo + bev, 31% for sunitinib.
The OS analysis did not pass the *P* value boundary of alpha = 0.0009 at the first interim analysis.

Overall Survival in PD-L1+

Median OS, mo (95% CI)	
Atezo + Bev	**Not reached**
Sunitinib	**23.3 (21.3, NR)**
HR, 0.68 (95% CI: 0.46, 1.00)	



No. at Risk									
Atezo + Bev	178	169	160	147	139	109	55	26	6
Sunitinib	184	169	154	141	134	96	51	27	6

- OS data are immature; 30% of patients had an OS event at data cutoff

NR, not reached. Minimum follow-up, 12 mo. Median follow-up, 15 mo. Event/patient ratio: 25% for atezo + bev, 35% for sunitinib.

Safety Summary in All-Treated Patients

Treatment-related AEs

All treated	Atezo + Bev n = 451	Sunitinib n = 446
Median treatment duration (range), mo	12.0 (0-26.2)	9.2 (0-26.6)
AEs, % Grade 3-4, %	91% 40%	96% 54%
AEs leading to discontinuation of treatment regimen, %	5%	8%
AEs leading to discontinuation of any treatment component, %[a]	12%	8%
Deaths, n	5[b]	1[c]

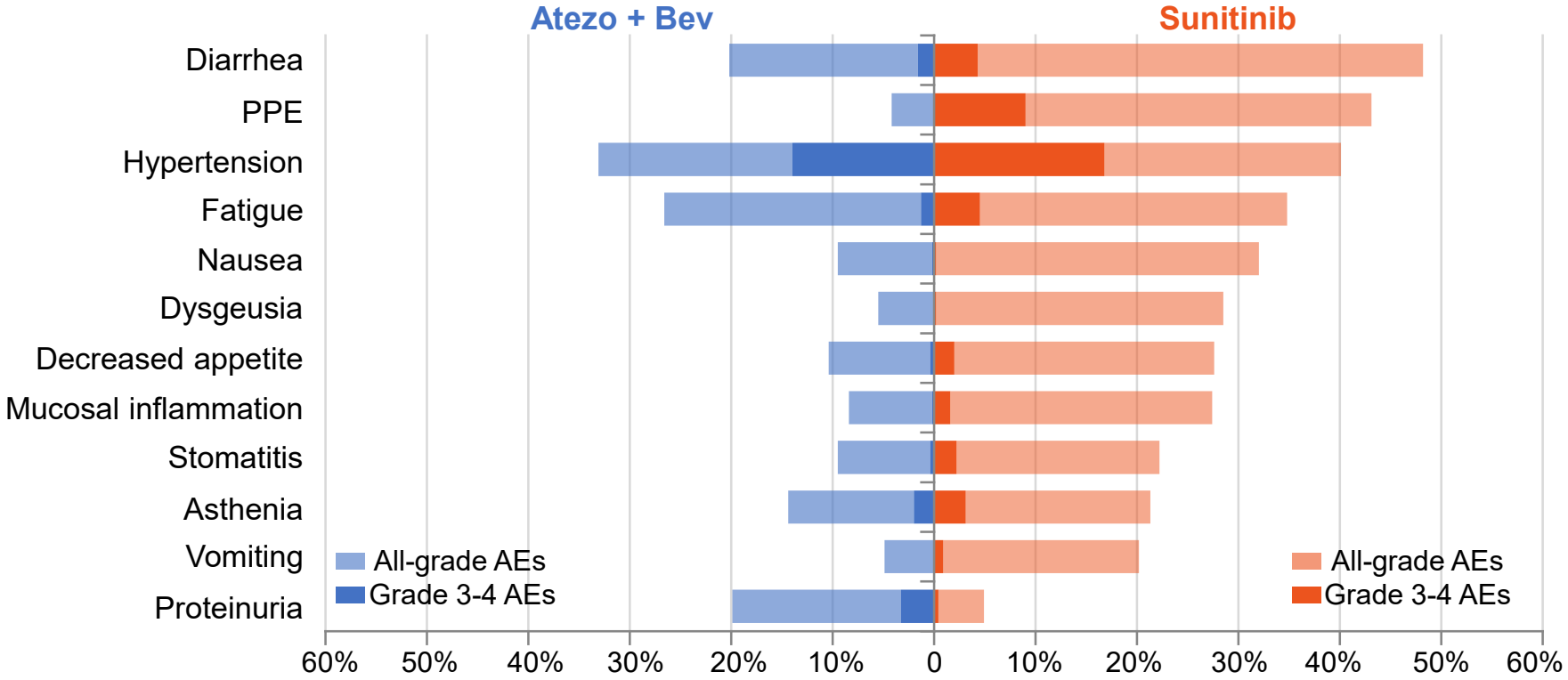
- Safety results were similar in all-treated patients and in those with PD-L1+ disease

AEs, adverse events.
[a] Atezo + bev, 5%; atezo only, 2%; bev only, 5%.
[b] Cerebral infarction, intracranial haemorrhage, adrenal insufficiency, multiple organ dysfunction syndrome, sepsis. [c] Cardiac arrest.

Secondary Endpoint

Treatment-related AEs

≥ 20% frequency in either arm and > 5% difference between arms



PPE, palmar-plantar erythrodysesthesia.

AEs of Special Interest

	Atezo + Bev n = 451		Sunitinib n = 446	
	All grades	Grade 3-4	All grades	Grade 3-4
Rash	19%	< 1%	15%	< 1%
Hypothyroidism	22%	< 1%	26%	< 1%
Hyperthyroidism	7%	< 1%	3%	0%
Adrenal insufficiency	2%	0%	0%	0%
LFT abnormalities	10%	3%	18%	4%
Colitis	2%	< 1%	< 1%	< 1%
Pneumonitis	3%	< 1%	0%	0%

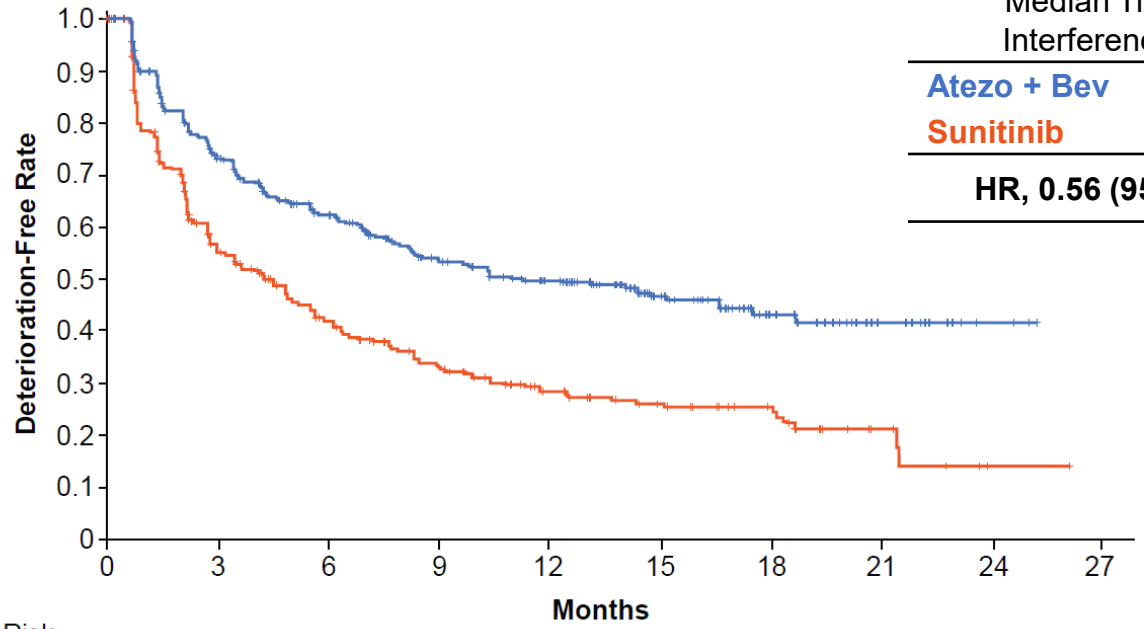
- 16% of patients treated with atezolizumab + bevacizumab required systemic corticosteroid use within 30 days of an AE of special interest

LFT, liver function test.
Occurring in > 1% of patients in the atezo + bev arm.

Time to Symptom Interference With Activities of Daily Living in ITT

Secondary Endpoint

Median Time to Symptom Interference, mo (95% CI)	
Atezo + Bev	11.3 (8.3, 17.5)
Sunitinib	4.3 (3.1, 5.6)
HR, 0.56 (95% CI: 0.46, 0.68)	



No. at Risk									
Atezo + Bev	454	256	196	154	128	74	35	12	3
Sunitinib	461	178	119	87	60	38	25	7	1

Per the MD Anderson Symptom Interference Scale, event defined as a ≥ 2-point score increase (on a 10-point scale) from baseline.

Conclusions

- IMmotion151 met its co-primary PFS endpoint, demonstrating improved PFS for atezolizumab + bevacizumab over sunitinib in patients with PD-L1+ disease
- Response outcomes and encouraging immature OS results support improved efficacy for atezolizumab + bevacizumab. IRC-assessed PFS results differed from investigator assessment in patients with PD-L1+ disease
- Atezolizumab + bevacizumab had fewer high-grade treatment-related AEs, low steroid use and delayed symptom interference with daily life vs sunitinib
- These study results support atezolizumab + bevacizumab as a first-line treatment option for patients with PD-L1+ advanced RCC

Acknowledgements

- The patients and their families
- Participating study investigators and clinical sites
- This study is sponsored by F. Hoffmann-La Roche, Ltd
- Medical writing assistance for this presentation was provided by Paige S. Davies, PhD, of Health Interactions and funded by F. Hoffmann-La Roche, Ltd