Abstract No. 1487

Randomized Phase IIIb Trial of Temsirolimus and Bevacizumab versus Interferon and Bevacizumab in Metastatic Renal Cell Carcinoma: Results From INTORACT

B.I. Rini,[1] J. Bellmunt,[2] A.V. Alyzasova,[3] J. Clancy,[4] K. Wang,[5] A. Niethammer,[6] and B. Escudier[7]

[1]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH/UNITED STATES; [2]Hospital del mar de Barcelona, Barcelona/SPAIN; [3]Szpital Specjalistyczny Ludwika Rydygiera, Kraków/POLAND; [4]Pfizer Inc, Cambridge, MA/UNITED STATES; [5]Pfizer Inc, Pearl River, NY/UNITED STATES; [6]Pfizer Inc, La Jolla, CA/UNITED STATES; [7]Institut Gustave Roussy, Villejuif/FRANCE

VIENNA 2012 ESMO congress

Disclosures

- Conflict of Interest Disclosures

  Dr. Rini has received research funding and has served as a remunerated consultant for Pfizer Inc.

- Research Funding

  This study was sponsored by Pfizer Inc.

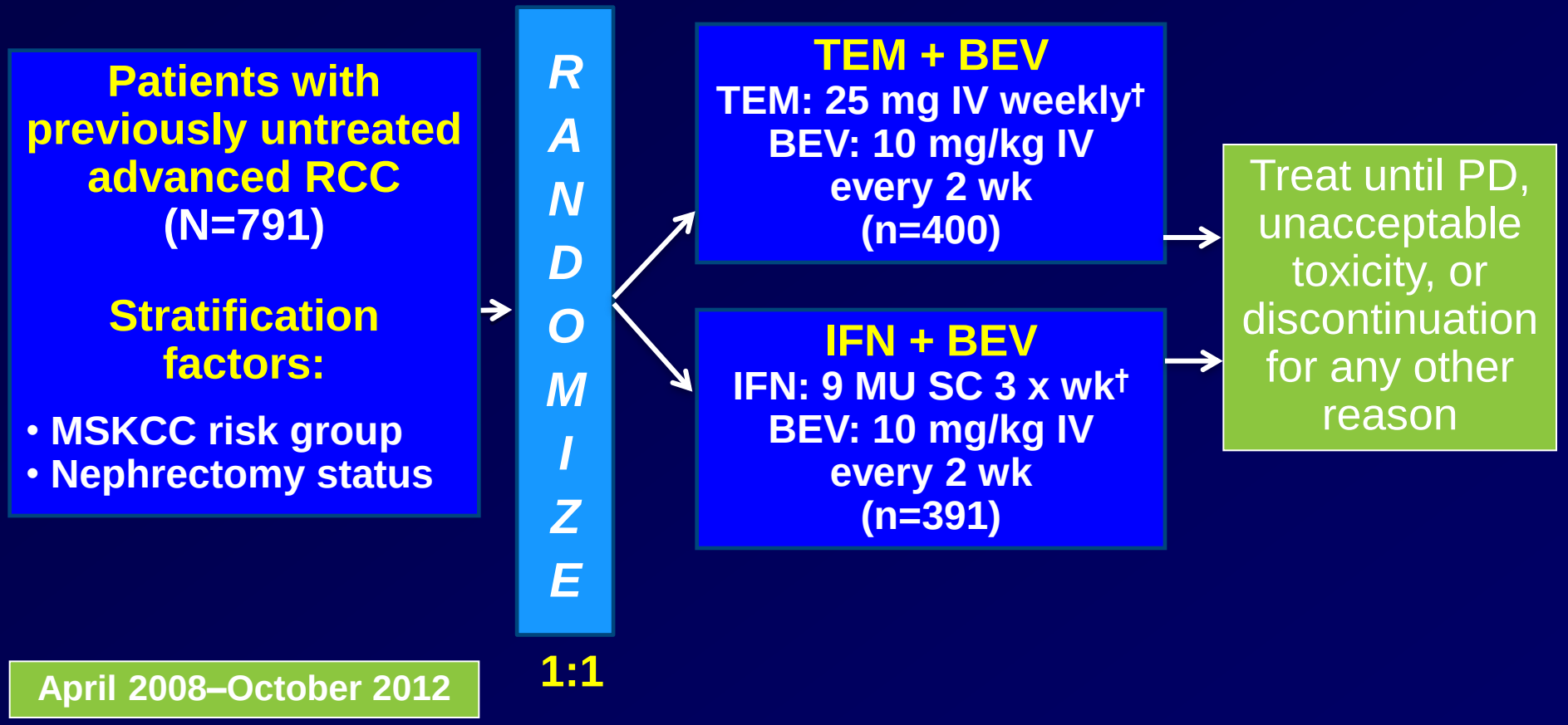
Background

- Bevacizumab (BEV) + interferon (IFN) has clinical activity as 1st-line treatment in patients with clear cell mRCC[1,2]
- Temsirolimus (TEM) has PFS and OS benefits vs IFN as 1st-line treatment in poor prognosis RCC[3]
- A phase I/II trial of TEM + BEV was conducted in previously treated RCC patients (N=46)[4]
  - 23% partial response rate
  - Median time to progression: 7.6 months
  - Median OS: 20.6 months
- TEM + BEV was also evaluated in untreated mRCC patients in the TORAVA randomized phase II trial[5]

mRCC, metastatic renal cell carcinoma; OS, overall survival; PFS, progression-free survival.

1. Escudier B, et al. *Lancet*. 2007;370:2103-11.
2. Rini BI, et al. *J Clin Oncol.* 2008;26:5422-28.
3. Hudes G, et al. *N Engl J Med.* 2007;356:2271-81.
4. Merchan JR, et al. *J Clin Oncol.* 2011;29(suppl; abstract 4548).
5. Escudier BJ, et al. *J Clin Oncol.* 2010;28(suppl; abstract 4516).

INTORACT* Study Design



*ClinicalTrials.gov Identifier: NCT00631371
†Dose reductions were allowed for TEM and IFN, but not for BEV

BEV, bevacizumab; IFN, interferon alfa; IRC, independent review committee; IV, intravenous; MSKCC, Memorial Sloan-Kettering Cancer Center; PFS, progression-free survival; RCC, renal cell carcinoma; SC, subcutaneously; TEM, temsirolimus.

Key Eligibility Criteria

- ≥18 years of age
- Histologically and/or cytologically confirmed advanced RCC of predominant clear cell type
- No prior systemic treatment for RCC
- ≥1 measurable lesion per RECIST criteria[1]
- Karnofsky PS ≥70%
- Adequate blood counts and organ function
- No evidence of current or prior CNS metastases

CNS, central nervous system; PS, performance score; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors.

1. Therasse P, et al. *J Natl Cancer Inst* 2000;92:205-16.

Study Objectives

- **Primary objective**
  - To compare independently assessed PFS with TEM + BEV vs IFN + BEV as 1st-line treatment for patients with advanced predominantly clear cell RCC

- **Secondary objectives**
  - Safety
  - Investigator-assessed PFS
  - Objective response rate (CR + PR) per RECIST
  - Overall survival

BEV, bevacizumab; CR, complete response; IFN, interferon alfa; PFS, progression-free survival; PR, partial response; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors; TEM, temsirolimus.

Statistical Methods

- **Primary end point: PFS (assessed by blinded IRC)**
  - Analysis based on ITT population
    - 80% power to observe a 30% improvement in PFS while maintaining a significance level of 2.5% in a 1-sided stratified log-rank test
    - Sample size of 800 patients required to observe 472 progression events (per IRC) for final analysis
- **Secondary end point: OS**
  - 80% power to observe a 30% improvement in median OS while maintaining a significance level of 2.5% in a 1-sided stratified log-rank test
  - Number of OS events required at the final OS analysis was approximately 512

IRC, independent review committee; ITT, intent to treat; OS, overall survival; PFS, progression-free survival.

Key Assessments

- **Treatment phase**
  - Physician/clinical assessment every month
  - Radiographic tumor assessments every 8 weeks
    - Bone scan required at baseline for all patients and post-baseline if indicative of metastatic disease or if signs/symptoms of bone metastases developed
- **Posttreatment phase (long-term follow-up)**
  - Survival status every 8 weeks

Patient Characteristics

Characteristic	TEM + BEV (n=400)	IFN + BEV (n=391)
Median age, y (range)	59 (22–87)	58 (23–81)
Gender (%)		
Male	72	69
Female	28	31
Race (%)		
White	82	85
Asian	12	13
Other/unspecified	5	2
Karnofsky PS (%)		
70	5	8
80	25	18
≥90	70	74

BEV, bevacizumab; IFN, interferon alfa; PS, performance score.

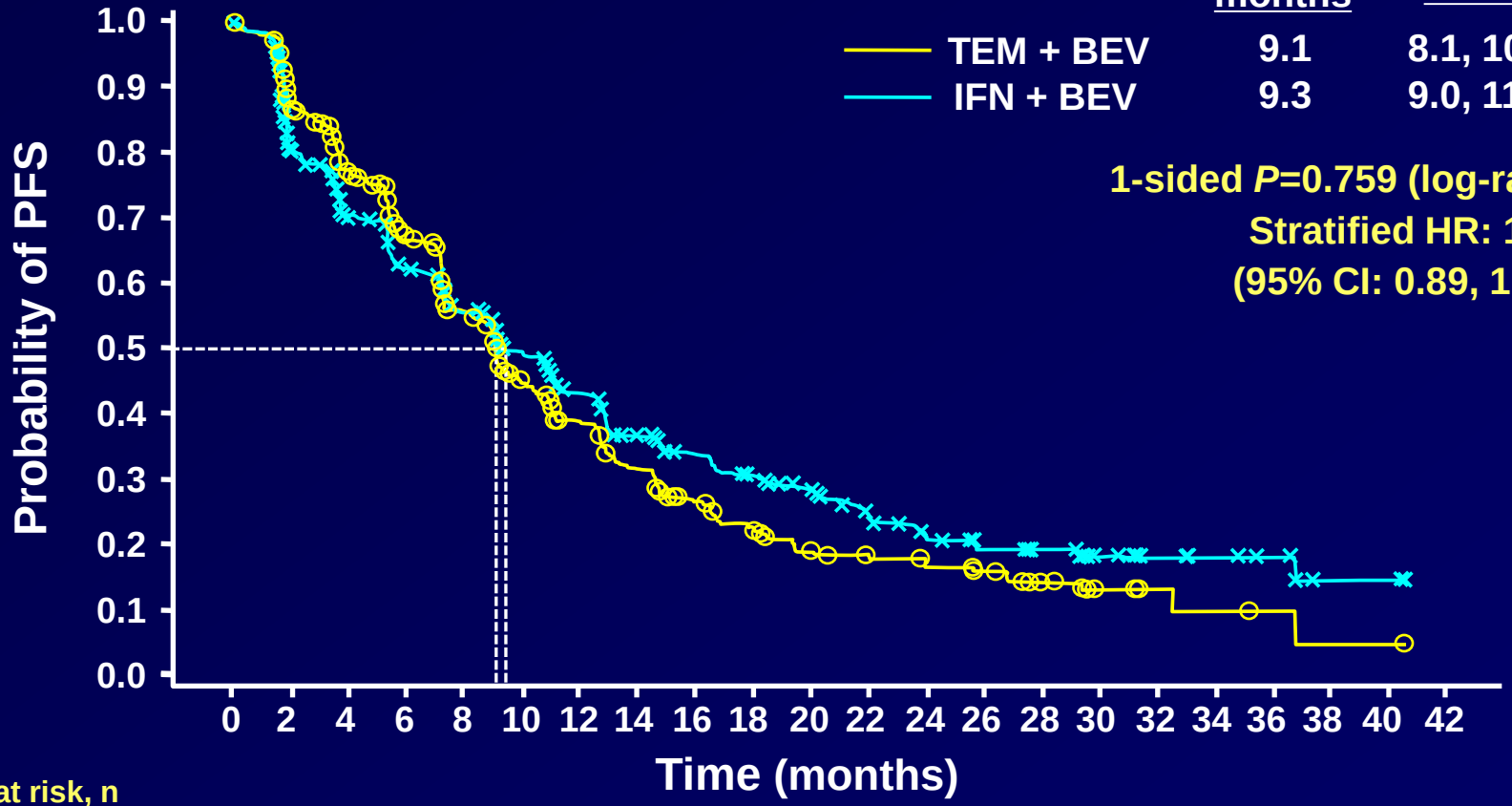
Patient Characteristics, cont'd

Characteristic	TEM + BEV (n=400)	IFN + BEV (n=391)
Prior nephrectomy, %	85	86
MSKCC risk factors,[1] %		
0 (good)	28	27
1–2 (intermediate)	65	65
≥3 (poor)	8	8

BEV, bevacizumab; IFN, interferon alfa; MSKCC, Memorial Sloan-Kettering Cancer Center; TEM, temsirolimus.

1. Motzer RJ, et al. *J Clin Oncol* 2004;22:454-463.

Progression-Free Survival
(IRC Assessment)

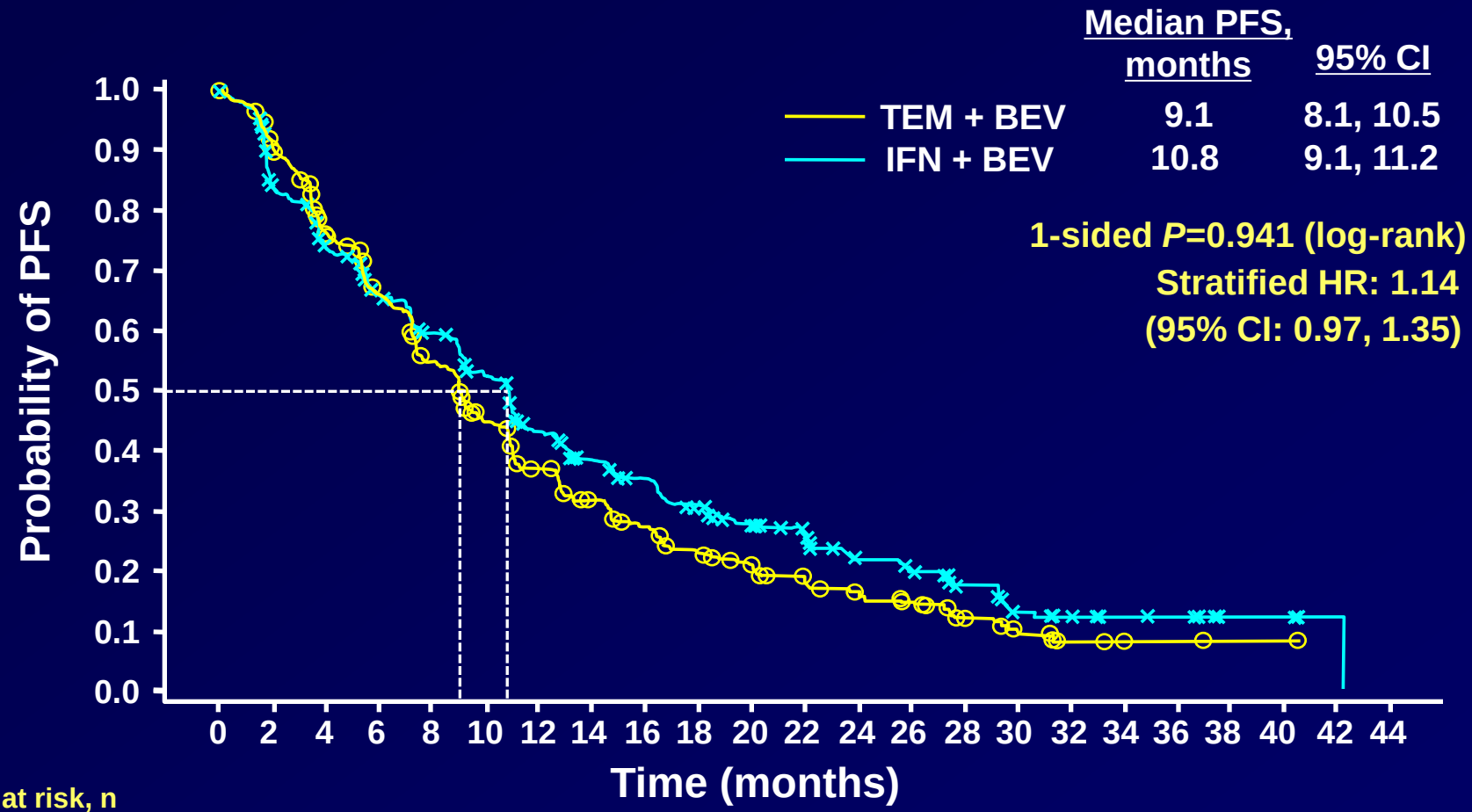


Patients at risk, n

TEM + BEV	400	316	256	208	161	120	95	76	59	48	36	31	26	21	14	9	4	3	2	1	1
IFN + BEV	391	280	230	196	167	138	114	92	78	68	60	42	32	26	22	16	12	9	6	2	2

BEV, bevacizumab; CI, confidence interval; HR, hazard ratio; IFN, interferon alfa; IRC, Independent Review Committee; PFS, progression-free survival; TEM, temsirolimus.

Progression-Free Survival
(Investigator Assessment)



Patients at risk, n

TEM + BEV	400	336	273	229	189	146	116	96	81	67	57	45	36	31	20	14	5	3	3	2	2	0
IFN + BEV	391	304	261	227	202	176	140	121	109	92	78	62	46	40	29	19	16	12	10	3	3	1

BEV, bevacizumab; CI, confidence interval; HR, hazard ratio; IFN, interferon alfa; PFS, progression-free survival; TEM, temsirolimus.

PFS by Stratification Factors

Median PFS, mo (95% CI)	TEM + BEV (n=400)	IFN + BEV (n=391)
Nephrectomy		
No	9.2 (7.2, 11.1)	6.8 (2.4, 7.5)
Yes	9.1 (8.1, 10.4)	10.9 (9.0, 12.7)
MSKCC status		
Good	11.0 (9.0, 14.5)	11.2 (10.7, 14.9)
Intermediate	9.2 (8.1, 10.9)	9.1 (7.3, 12.7)
Poor	4.0 (3.4, 7.2)	2.1 (1.8, 5.4)

BEV, bevacizumab; CI, confidence interval; IFN, interferon alfa; MSKCC, Memorial Sloan-Kettering Cancer Center; PFS, progression-free survival; TEM, temsirolimus.

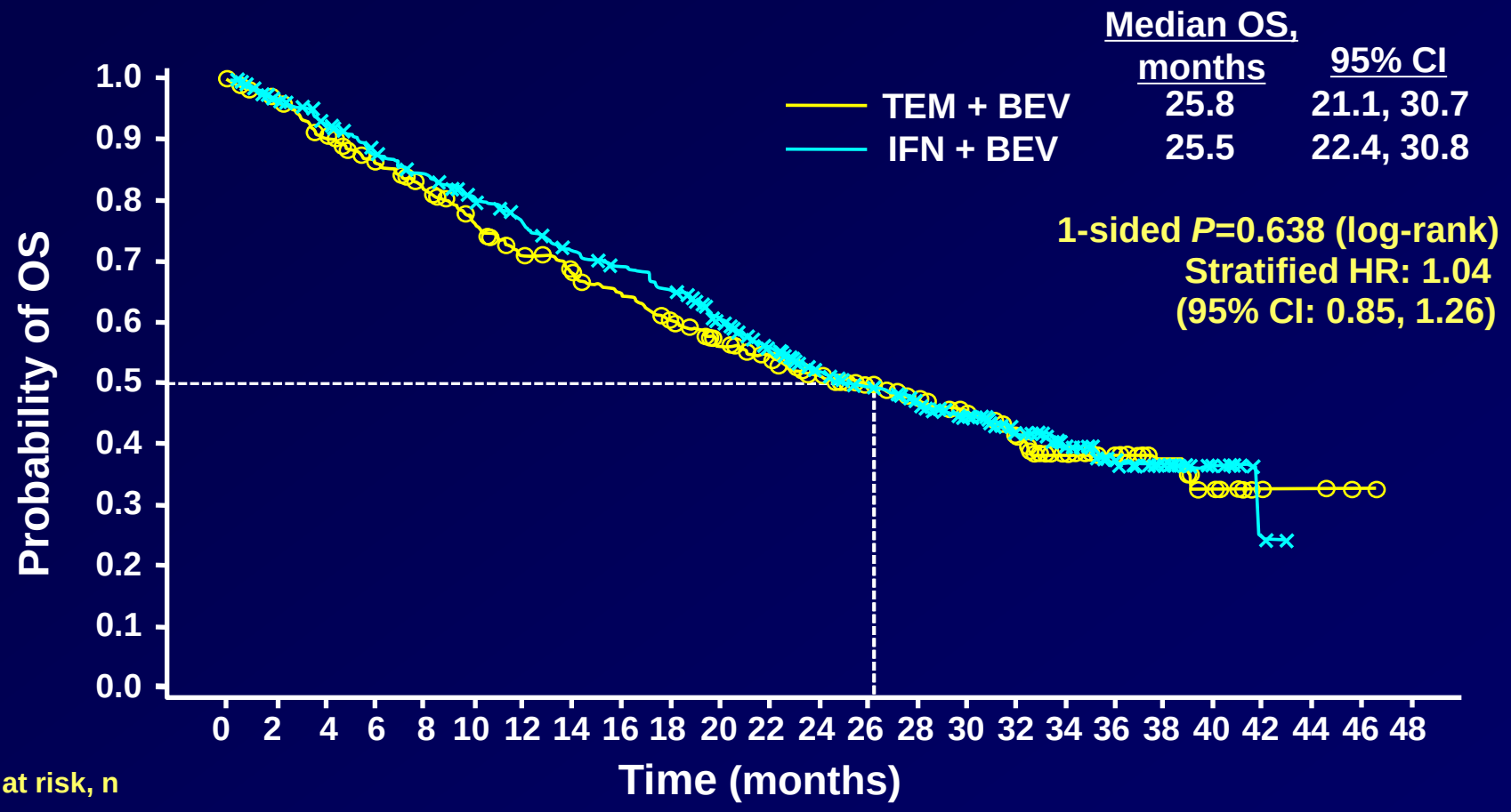
Best Response by RECIST
(IRC Assessment)

Best Overall Response, %	TEM + BEV (n=400)	IFN + BEV (n=391)
Complete response (CR)	1	2
Partial response (PR)*	27	26
Stable disease	55	47
Progressive disease	10	18
Indeterminate	1	0
ORR (CR + PR)*	27	28
Risk ratio (95% CI)	0.99 (0.8, 1.3)	
Median duration of response, mo	11	17

**P*=0.965.
Note: numbers have been rounded.

BEV, bevacizumab; CI, confidence interval; IFN, interferon alfa; IRC, Independent Review Committee; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors; TEM, temsirolimus.

Overall Survival*



*409 patients had died as of the date of data cutoff (TEM + BEV: 210; IFN + BEV: 199).

BEV, bevacizumab; CI, confidence interval; HR, hazard ratio; IFN, interferon alfa; OS, overall survival; TEM, temsirolimus.

Anticancer Therapy Post-treatment
(Safety Population)

Anticancer Therapy Posttreatment (%)	TEM + BEV (n=393)	IFN + BEV (n=391)
Anticancer medication	43	43
Radiotherapy	15	13
Surgery	9	5

BEV, bevacizumab; IFN, interferon alfa; TEM, temsirolimus.

Drug Delivery and Modifications
(Safety Population)

Parameter	TEM + BEV (n=393)	IFN + BEV (n=391)
Dose delay due to AE* (%)	69.7	61.6
Dose reduction due to AE* (%)	30.3	38.1
Discontinuation due to treatment-related AEs* (%)	11.7	9.7

*Adverse events as determined by investigators.

AE, adverse event; BEV, bevacizumab; IFN, interferon alfa; RDI, relative dose intensity; TEM, temsirolimus.

Adverse Events*

Event, %	TEM + BEV (n=393)		IFN + BEV (n=391)		P value†
	All Grades	Grade 3/4	All Grades	Grade 3/4	
Any	98	80	97	76	0.142
Proteinuria	36	16	27	13	0.269
Hypertension	32	11	26	11	0.818
Anemia	21	9	17	8	0.704
Mucosal inflammation	27	8	10	0.3	<0.001
Hypertriglyceridemia	29	7	21	4	0.116
Stomatitis	26	7	10	2	<0.001
Asthenia	24	6	28	10	0.035
Hypercholesterolemia	32	6	10	1	<0.001
Hyperglycemia	22	6	5	1	<0.001
Hypophosphatemia	10	6	4	1	<0.001
Fatigue	23	5	32	11	0.001
Lymphopenia	<10	3	<10	6	0.036
Neutropenia	5	2	17	8	<0.001
Pneumonitis	5	1	0	0	0.062

*Grade 3/4 events with incidence of ≥5% in either treatment arm, with corresponding incidence for all-grade events.
†Fisher's exact test (2-tail) comparing incidence of grade 3 or 4 AEs; TEM + BEV vs IFN + BEV.

AE, adverse event; BEV, bevacizumab; IFN, interferon alfa; TEM, temsirolimus.

Adverse Events*

Event, %	TEM + BEV (n=393)		IFN + BEV (n=391)		P value†
	All Grades	Grade 3/4	All Grades	Grade 3/4	
Any	98	80	97	76	0.142
Proteinuria	36	16	27	13	0.269
Hypertension	32	11	26	11	0.818
Anemia	21	9	17	8	0.704
Mucosal inflammation	27	8	10	0.3	<0.001
Hypertriglyceridemia	29	7	21	4	0.116
Stomatitis	26	7	10	2	<0.001
Asthenia	24	6	28	10	0.035
Hypercholesterolemia	32	6	10	1	<0.001
Hyperglycemia	22	6	5	1	<0.001
Hypophosphatemia	10	6	4	1	<0.001
Fatigue	23	5	32	11	0.001
Lymphopenia	<10	3	<10	6	0.036
Neutropenia	5	2	17	8	<0.001
Pneumonitis	5	1	0	0	0.062

*Grade 3/4 events with incidence of ≥5% in either treatment arm, with corresponding incidence for all-grade events.
†Fisher's exact test (2-tail) comparing incidence of grade 3 or 4 AEs; TEM + BEV vs IFN + BEV.

AE, adverse event; BEV, bevacizumab; IFN, interferon alfa; TEM, temsirolimus.

Adverse Events*

Event, %	TEM + BEV (n=393)		IFN + BEV (n=391)		P value†
	All Grades	Grade 3/4	All Grades	Grade 3/4	
Any	98	80	97	76	0.142
Proteinuria	36	16	27	13	0.269
Hypertension	32	11	26	11	0.818
Anemia	21	9	17	8	0.704
Mucosal inflammation	27	8	10	0.3	<0.001
Hypertriglyceridemia	29	7	21	4	0.116
Stomatitis	26	7	10	2	<0.001
Asthenia	24	6	28	10	0.035
Hypercholesterolemia	32	6	10	1	<0.001
Hyperglycemia	22	6	5	1	<0.001
Hypophosphatemia	10	6	4	1	<0.001
Fatigue	23	5	32	11	0.001
Lymphopenia	<10	3	<10	6	0.036
Neutropenia	5	2	17	8	<0.001
Pneumonitis	5	1	0	0	0.062

*Grade 3/4 events with incidence of ≥5% in either treatment arm, with corresponding incidence for all-grade events.
†Fisher's exact test (2-tail) comparing incidence of grade 3 or 4 AEs; TEM + BEV vs IFN + BEV.

AE, adverse event; BEV, bevacizumab; IFN, interferon alfa; TEM, temsirolimus.

Conclusions

- TEM + BEV was not superior to IFN + BEV as 1st-line treatment for patients with clear cell mRCC
  - Response rates >25% were observed in both treatment groups
  - Duration of response was longer with IFN + BEV vs TEM + BEV (17 months vs 11 months)
  - In IFN + BEV arm, longer PFS was observed in patients with prior nephrectomy vs those with no prior nephrectomy (10.9 months vs 6.8 months)

BEV, bevacizumab; IFN, interferon alfa; mRCC, metastatic renal cell carcinoma; PFS, progression-free survival; TEM, temsirolimus.

Conclusions, cont'd

- Safety data were consistent with known profiles
  - Grade ≥3 mucosal inflammation, stomatitis, hyperglycemia, hypophosphatemia, and hypercholesterolemia were more common with TEM + BEV ($P<0.001$); pneumonitis was lower than expected (1%)
  - Grade ≥3 neutropenia and fatigue were more common with IFN + BEV ($P\leq0.001$)

- IFN + BEV remains a treatment option in mRCC, but other combination therapies remain investigational

BEV, bevacizumab; IFN, interferon alfa; mRCC, metastatic renal cell carcinoma; TEM, temsirolimus.

Acknowledgments

We thank the patients, their families, and the clinical personnel and investigators who participated in this study.

Editorial support was provided by Peloton Advantage and was funded by Pfizer Inc.