Randomized phase II study of first-line everolimus (EVE) + bevacizumab (BEV) versus interferon alfa-2a (IFN) + BEV in patients (pts) with metastatic renal cell carcinoma (mRCC): RECORD-2

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Disclosure slide

- Member of Global, European and/or French boards for Pfizer, Novartis, Bayer Schering, GlaxoSmithKline, Astellas, Dendreon for renal cell carcinoma
- Meetings and travel support by Pfizer, Novartis
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- PI for international trials for Novartis, Pfizer

First-line Treatment of mRCC Efficacy Overview

Study	ORR, %	Median PFS, mo
Sunitinib vs IFN-α[1]	47 vs 12	11 vs 5 *P* < 0.001
Bevacizumab + IFN-α vs IFN-α[2]	31 vs 13	10.2 vs 5.4 *P* = 0.0001
Bevacizumab + IFN-α vs IFN-α[3]	25.5 vs 13.1	8.5 vs 5.2 *P* < 0.0001
Sorafenib vs IFN-α[4]	5.2 vs 8.7	5.7 vs 5.6* *P* = 0.50
Temsirolimus vs IFN-α[5]	8.6 vs 4.8	5.5 vs 3.1* *P* < 0.001
Pazopanib vs placebo[6]	32 vs 4	11.1 vs 2.8 *P* < 0.0001

*Independent assessment.

IFN, interferon; mRCC, metastatic renal cell carcinoma; ORR, objective response rate; PFS, progression-free survival.

1. Motzer RJ et al. *J Clin Oncol*. 2009; 27:3584-3590. 2. Escudier B et al. *Lancet*. 2007;370:2103-2111. 3. Rini B et al. *J Clin Oncol*. 2008;26:5422-5428. 4. Escudier B et al. *J Clin Oncol*. 2009;27:1280-1289. 5. Hudes G et al. *N Engl J Med*. 2007;356:2271-2281. 6. Sternberg C et al. *J Clin Oncol*. 2010;28:1061-1068.

Current Status for Patients With mRCC

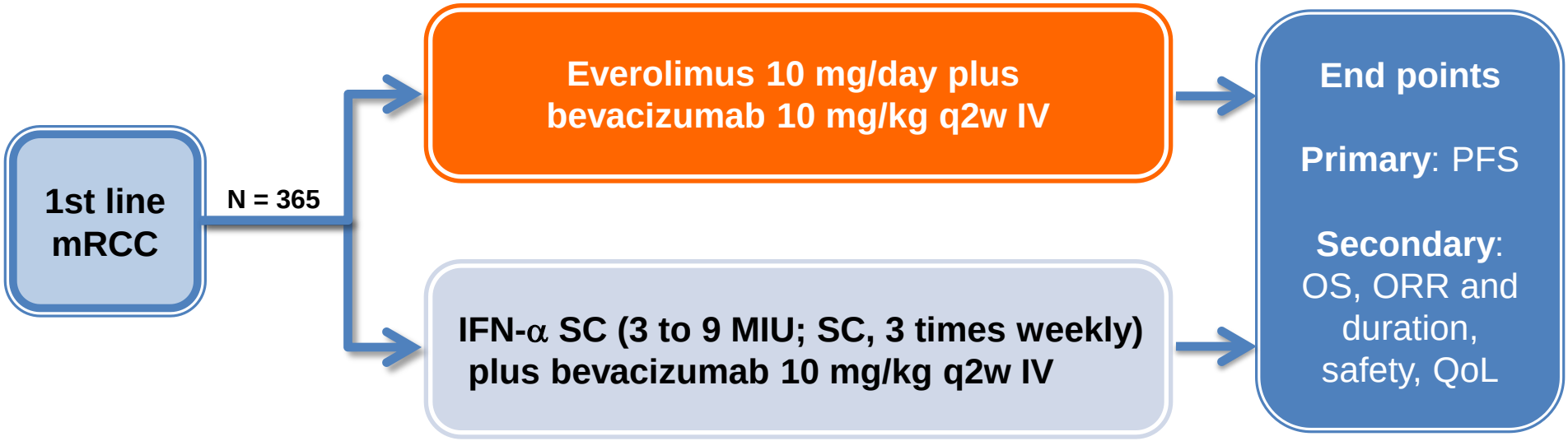
- The benefits of VEGF-based therapies are transient[1,2]
  - Durable response is rarely achieved, and most patients eventually develop progressive disease
  - Relapse is thought to occur via various escape mechanisms that allow for continued angiogenesis in spite of VEGF signaling blockade
- Current treatment strategies involve sequential administration of monotherapies[3,4]
- Combination therapy has the potential to substantially improve prognosis for patients with mRCC[5]
  - Everolimus and bevacizumab block different molecular targets[6,7]

VEGF, vascular endothelial growth factor.

1. Escudier B et al. *N Engl J Med*. 2007;356:125-134. 2. Motzer RJ et al. *N Engl J Med*. 2007;356:115-124. 3. Porta C et al. *Med Oncol*. 2011:DOI 10.1007/s12032-011-0016-8. 4. *Annals of Oncology*. 2012; 23 (Suppl 7): vii65–vii71.. 5. Hutson TE. *Oncologist*. 2011;16(suppl 2):14-22. 6. Brugarolas J. *N Engl J Med*. 2007;356:185-187. 7. Mulders P. *BJU Int*. 2009;104:1585-1589.

RECORD-2: Study Design

Randomized, open-label, phase II study



Key eligibility criteria:

- Age ≥ 18 years with confirmation of advanced metastatic clear-cell RCC
- ≥ 1 measurable lesion per RECIST criteria
- Prior nephrectomy
- KPS ≥ 70%

Key exclusion criteria:

- Prior systemic treatment for mRCC, including prior therapy with VEGF or mTOR inhibitor

KPS, Karnofsky Performance Status; mTOR, mammalian target of rapamycin; OS, overall survival; QoL, quality of life; IFN, interferon; RECIST, Response Evaluation Criteria In Solid Tumors.

RECORD-2: Statistical Methods

- The primary objective was treatment effect on PFS per central review based on an estimate of the probability of success (PoS) in a subsequent phase III trial
  - The protocol-defined criterion for phase II success was: PoS ≥ 50%
  - The protocol-defined median PFS assumptions were: 10.2 months in the IFN-α + bevacizumab treatment arm vs 13.6 months in the everolimus + bevacizumab arm, leading to a hazard ratio of 1.33
- QoL was measured using 2 validated patient self-reported questionnaires
  - The FKSI-DRS assesses patient symptoms, including pain, fatigue, shortness of breath, fever, weight loss, coughing, and blood in urine
    - The total score can range from 0 (worst) to 36 (best)
    - A decrease by at least 2 score units represents deterioration
  - The EORTC QLQ-C30 assesses patients' physical, emotional, cognitive, social, and role function, global quality of life, and several specific symptoms
    - A 10% decrease from baseline represents deterioration

PFS, progression-free survival; IFN, interferon; QoL, quality of life; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Physical Functioning Subscale and Global Health Status/QoL Scale; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index Disease-Related Symptoms.

Patient Disposition

Disposition Reason		Everolimus + bevacizumab (n = 182)	IFN + bevacizumab (n = 183)
Patients randomized, %	Untreated	1	1
	Treated	99	99
Patients treated, %	Treatment ongoing*	8	10
	End of treatment	92	90
Primary reasons for end of treatment, %	Disease progression	59	61
	AEs	23	26
	Death	8	6
	Withdrew consent	7	4
	New cancer therapy	2	1
	Protocol deviation	1	1
	Lost to follow-up	1	1
	Administrative problems	0	1
Analysis set, %	Full analysis set	100	100
	Safety set	99	99

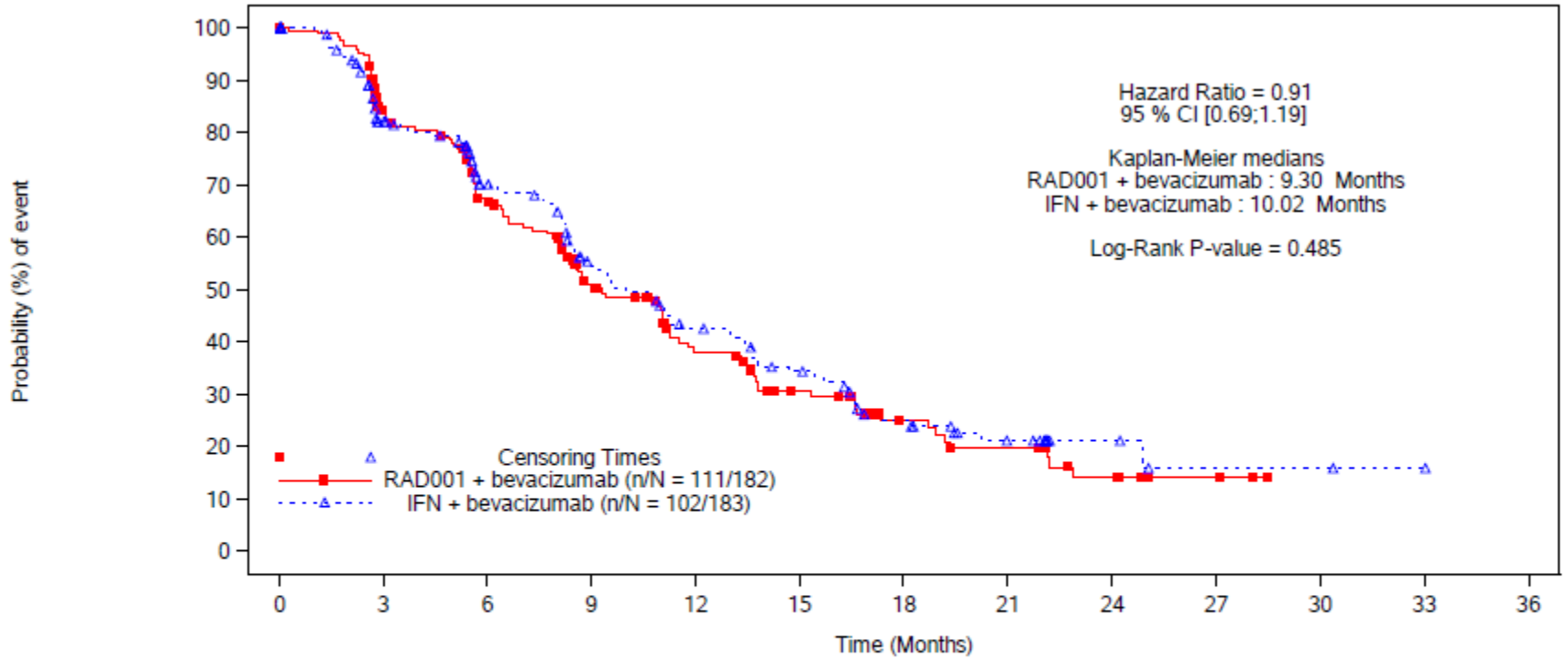
*Patients ongoing at time of cut-off (12/31/2011).
AEs, adverse events.

Demographics and Baseline Characteristics

Variable		Everolimus + bevacizumab (n = 182)	IFN + bevacizumab (n = 183)	All patients (N = 365)
Age, years	**Median (range)**	60 (20-84)	60 (31-81)	60 (20-84)
Male gender, %		76	72	74
MSKCC risk, %	**Favorable** **Intermediate** **Poor**	36 57 7	36 57 7	36 57 7
Metastatic sites, %	**Lung** **Lymph node** **Bone** **Liver** **Mediastinum**	83 47 26 23 15	73 54 30 20 20	78 50 28 21 17

Efficacy: PFS

Based on central review



Number of patients still at risk

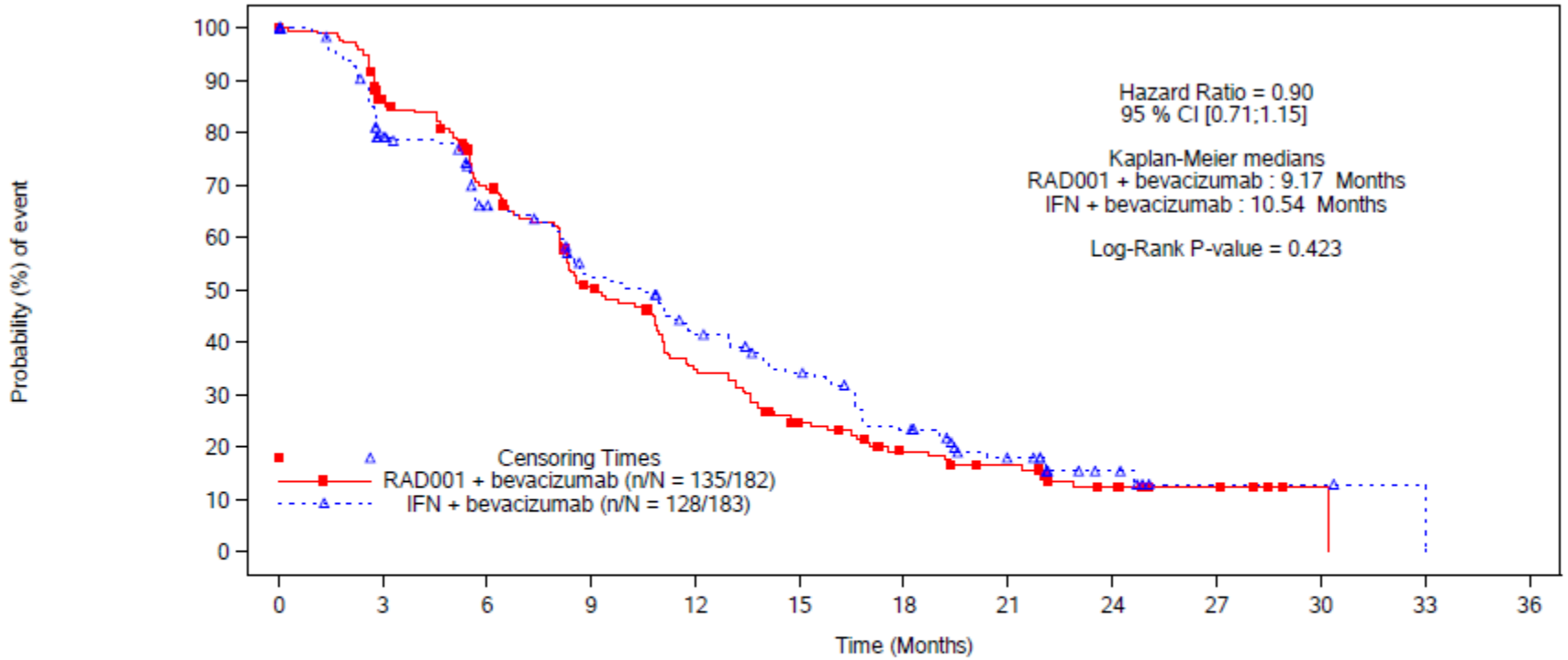
Time (Months)	0	3	6	9	12	15	18	21	24	27	30	33	36
RAD001 + bevacizumab	182	135	98	65	43	29	19	14	7	3	0	0	0
IFN + bevacizumab	183	126	93	66	48	36	22	13	5	2	2	1	0

Log-Rank P-value is obtained from a Log-Rank test stratified by MSKCC criteria
Hazard ratio IFN/RAD is obtained from an unadjusted Cox model stratified by MSKCC criteria
In the expression (n/N), n represents the number of patients who experienced an event.

RAD001, everolimus.

Efficacy: PFS

Based on investigator assessment

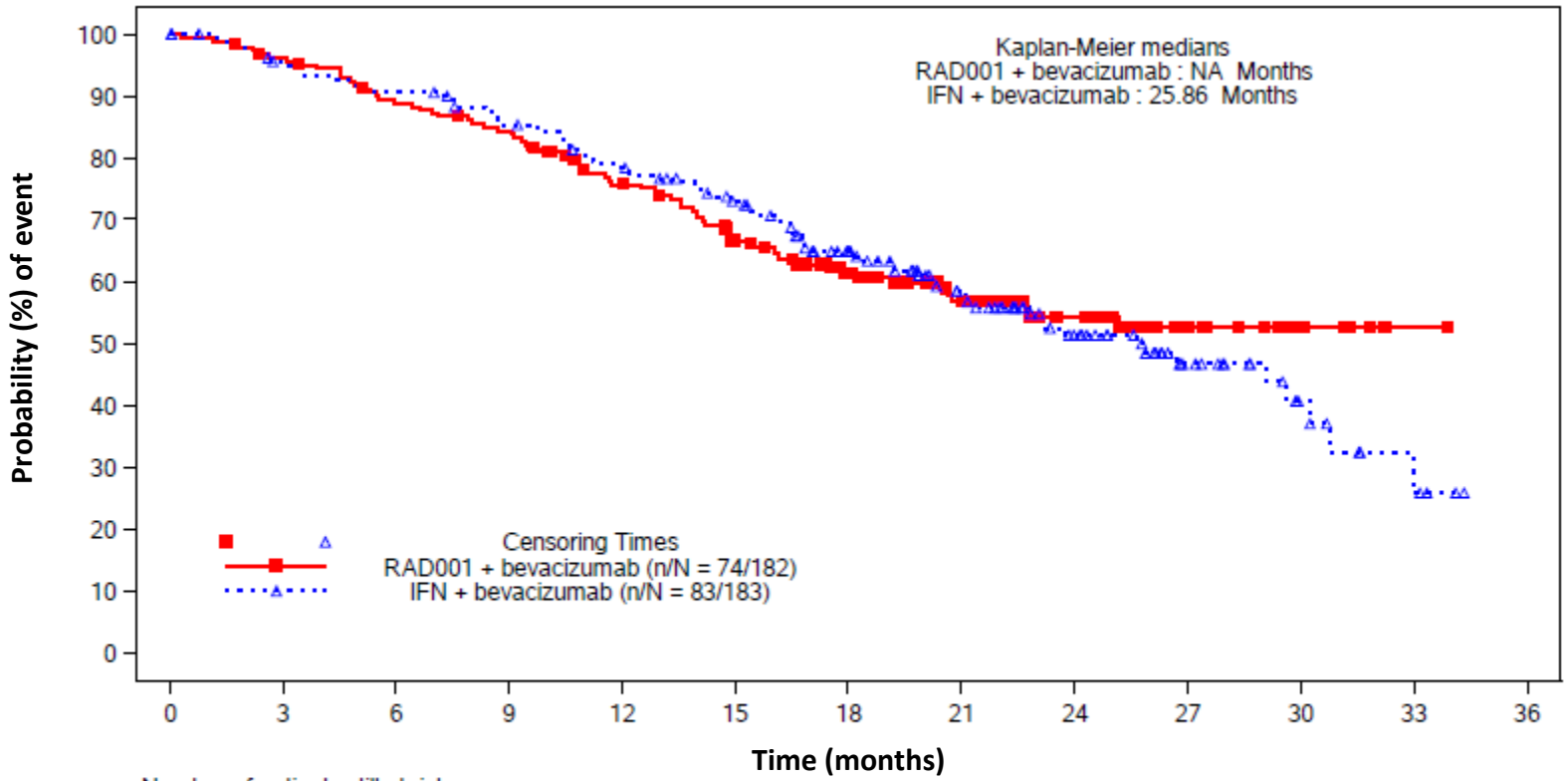


Number of patients still at risk

Time (Months)	0	3	6	9	12	15	18	21	24	27	30	33	36
RAD001 + bevacizumab	182	145	111	78	52	33	22	17	9	5	1	0	0
IFN + bevacizumab	183	133	104	79	59	46	30	17	7	2	2	1	0

Log-Rank P-value is obtained from a Log-Rank test stratified by MSKCC criteria
Hazard ratio IFN/RAD is obtained from an unadjusted Cox model stratified by MSKCC criteria
In the expression (n/N), n represents the number of patients who experienced an event.

Efficacy: Overall Survival



Number of patients still at risk

Time (Months)	0	3	6	9	12	15	18	21	24	27	30	33	36
RAD001 + bevacizumab	182	173	158	149	128	108	82	57	40	19	7	1	0
IFN + bevacizumab	183	170	161	149	135	119	92	67	43	23	11	4	0

n represents the number of patients in the population with an event

RAD001, everolimus; IFN, interferon-α; NA, not available.

Efficacy: Response Rates

Best overall response,* n (%)	Everolimus + bevacizumab (n = 182)	IFN + bevacizumab (n = 183)
Complete response	0 (0.0)	1 (0.5)
Partial response	49 (26.9)	50 (27.3)
Stable disease	90 (49.5)	84 (45.9)
Progressive disease	25 (13.7)	26 (14.2)
Unknown	18 (9.9)	22 (12.0)
Objective response rate (ORR)†	49 (26.9)	51 (27.9)

*Best overall response as per central radiology review by treatment (Full Analysis Set)
†ORR = complete + partial response.

Efficacy: Comparison With Previous Studies

- PFS and response rates with everolimus + bevacizumab were higher than those obtained with single-agent bevacizumab
- Results were within the range of those reported in prior studies in patients with treatment-naïve mRCC

Outcomes	Phase II				Phase III					
	RECORD-2		BEV[1]	EVE + BEV[2]	IFN ± BEV[3]		IFN ± BEV[4]		SUN vs IFN[5]	
	EVE + BEV	IFN + BEV	BEV	EVE + BEV	IFN + BEV	IFN	IFN + BEV	IFN	SUN	IFN
ORR, %	26.9	27.9	10	30	31	13	25.5	13.1	47	12
Median PFS, mo	9.3	10.0	4.8*	9.1	10.2	5.4	8.5	5.2	11	5

*Time-to-progression.
ORR, objective response rate; PFS, progression-free survival; BEV, bevacizumab; EVE, everolimus; IFN, interferon-α; SUN, sunitinib.

1. Yang JC et al. *N Engl J Med*. 2003;349:427-434. 2. Hainsworth JD et al. *J Clin Oncol*. 2010;28:2131-2136.
3. Escudier B et al. *Lancet*. 2007;370:2103-2111. 4. Rini BI et al. *J Clin Oncol*. 2008;26:5422-5428. 5. Motzer RJ et al. *J Clin Oncol*. 2009;27:3584-3590.

Safety: Summary

Category, %	Everolimus + BEV (n = 180)	IFN + BEV (n = 181)
Deaths		
All	41	46
On-treatment[a]	11	9
AEs	**99**	**99**
Suspected to be drug related	96	90
Grade 3/4	**80**	**76**
Suspected to be drug related	64	58
Clinically notable[b]	92	82
Suspected to be drug related	89	70
Leading to discontinuation[c]	24	24
Suspected to be drug related	16	17
Requiring dose interruption and/or reduction	80	76
Requiring additional therapy[d]	94	88
SAEs	**43**	**39**
Suspected to be drug related	21	18

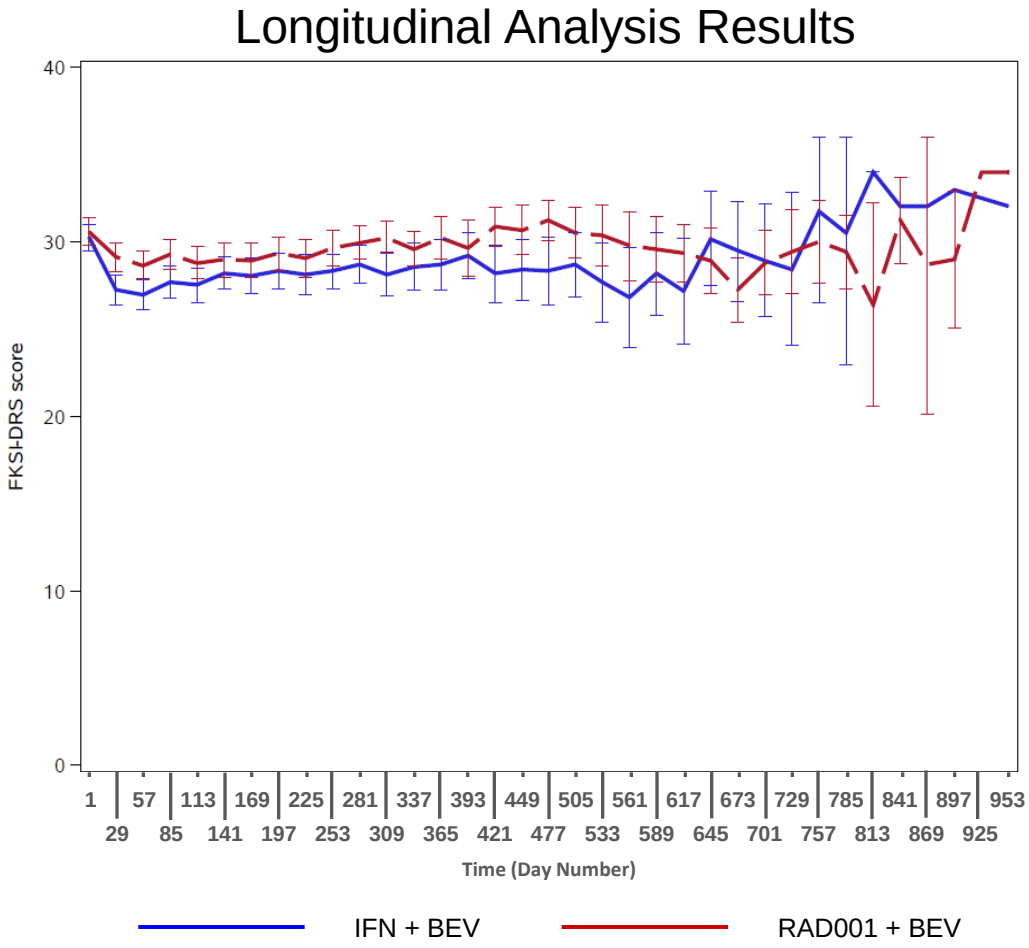
[a]Occurring up to 28 days after discontinuation of study treatment.
[b]Events of specific clinical interest in connection with everolimus or events which are similar in nature.
[c]Discontinuation defined as stopping of both drugs of the combined treatment.
[d]Includes all non-drug therapy and concomitant medications.
SAEs, serious adverse events.

Safety: Most Common AEs

AEs (≥ 25% in either group) regardless of relationship to study drug						
AE, %	Everolimus + BEV (n = 180)			IFN + BEV (n = 181)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Stomatitis	63	10	1	23	2	0
Proteinuria	49	22	1	37	9	1
Diarrhea	39	2	1	27	1	0
Hypertension	38	7	0	21	6	0
Epistaxis	35	3	0	21	0	0
Fatigue	32	5	0	41	17	0
Cough	31	2	0	19	1	0
Weight decreased	28	1	0	32	3	0
Decreased appetite	27	3	0	45	5	0
Asthenia	22	4	0	34	13	1
Nausea	22	1	0	28	1	0
Pyrexia	15	0	0	35	1	0

QoL as Measured by the FKSI-DRS Risk Score

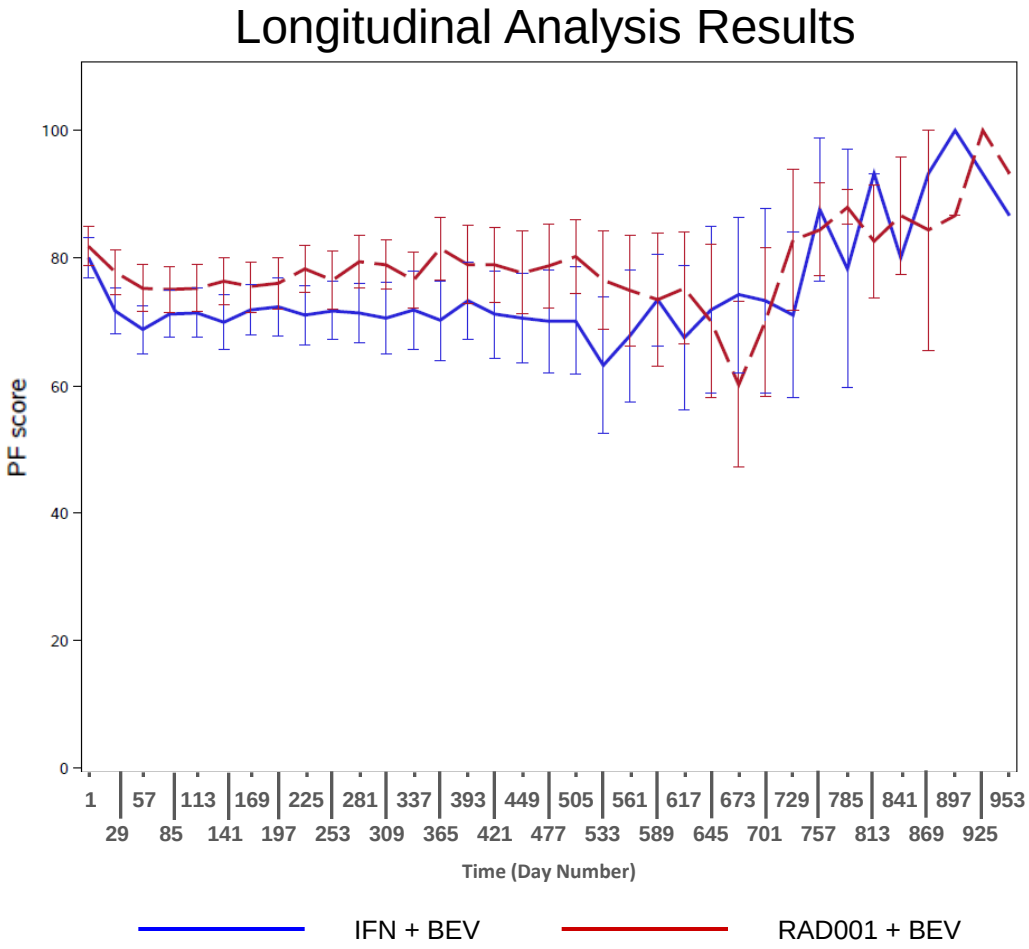
- FKSI mean score is significantly better over the time for patients treated with everolimus compared with the IFN arm ($P < 0.001$)
- However, no significant difference between arms was shown in the time to definitive deterioration analysis ($P = 0.782$)



QoL, quality of life; IFN, interferon-α; BEV, bevacizumab; RAD001; everolimus;
FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index—Disease-Related Symptoms.

QoL as Measured by the EORTC QLQ-C30

- PF mean score is significantly better over time for patients treated with everolimus compared with the IFN arm ($P = 0.032$)
- However, no significant difference between arms was shown in the time to definitive deterioration analysis ($P = 0.533$)
- For the global health status/QoL score, longitudinal analysis and time to definitive deterioration analysis did not show any significant treatment effect



QoL, quality of life; PF, physical functioning; IFN, interferon-α; BEV, bevacizumab; RAD001; everolimus;
EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Physical Functioning Subscale and Global Health Status/QoL Scale.

Summary

- The combination of everolimus with bevacizumab did not show superiority over the combination of interferon-α with bevacizumab
  - Both study arms performed similarly in terms of PFS and response rates
  - Optimization of sequencing of single-agent treatments may have a greater chance to improve treatment outcomes compared with combination approaches
- The combination of everolimus with bevacizumab was generally well tolerated in patients with treatment-naïve RCC
- No significant difference between treatment arms was observed in the time to definitive deterioration analysis. However, the physical functioning from EORTC QLQ-C30 and FKSI mean score is significantly better over time for patients treated with everolimus
- Final OS and safety updates for RECORD-2 are expected in Q4 2012

Countries Participating in the RECORD-2 Study

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