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Everolimus in metastatic renal cell carcinoma patients intolerant to previous VEGFr-TKI therapy: a RECORD-1 subgroup analysis

S Bracarda*[,1], TE Hutson[2], C Porta[3], RA Figlin[4], E Calvo[5], V Grünwald[6], A Ravaud[7], R Motzer[8], D Kim[9], O Anak[10], A Panneerselvam[11] and B Escudier[12]

[1]Ospedale San Donato USL8, Istituto Toscano Tumori (ITT), Via Pietro Nenni, 20 52100 Arezzo, Italy; [2]US Oncology/Baylor–Sammons Cancer Center, 3535 Worth Street, Dallas, TX 75246, USA; [3]IRCCS San Matteo University Hospital Foundation, Piazzale C. Golgi 19, Pavia I-27100, Italy; [4]Samuel Oschin Comprehensive Cancer Institute, Cedars–Sinai Medical Center, 8700 Beverly Boulevard, AC 1085 North Tower, Los Angeles, CA 90048, USA; [5]START Madrid, Centro Integral Oncológico Clara Campal, Hospital Madrid Norte Sanchinarro, 28050 Madrid, Spain; [6]Medical School Hannover, Carl Neuberg Street 1, D-30627 Hannover, Germany; [7]Hôpital Saint André CHU, 1 rue Jean Burguet, 33075 Bordeaux, France; [8]Memorial Sloan–Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA; [9]Novartis Oncology Global Medical Affairs, One Health Plaza, East Hanover, NJ 07936, USA; [10]Novartis Oncology Global Development, CH-4002 Basel, Switzerland; [11]Novartis Oncology Biometrics and Data Management, 180 Park Avenue, Florham Park, NJ 07936, USA; [12]Institut Gustave Roussy, 114 rue Edouard Vaillant, 94805 Villejuif, France

BACKGROUND: A relevant percentage of patients with metastatic renal cell carcinoma develop intolerance to vascular endothelial growth factor receptor-tyrosine kinase inhibitors (VEGFr-TKIs) and require careful selection of subsequent treatment. This retrospective analysis evaluated the safety and efficacy of everolimus in patients enrolled in the phase-III RECORD-1 trial who discontinued previous VEGFr-TKI therapy because of toxicity.

METHODS: Patients with an adverse event (AE) as their primary reason for discontinuation of previous VEGFr-TKI therapy were included. Median progression-free survival (PFS) for VEGFr-TKI-intolerant patients in each arm was estimated using the Kaplan–Meier method, and effect on PFS (hazard ratio (HR)) was calculated using the Cox proportional hazard model.

RESULTS: In VEGFr-TKI-intolerant patients ($n = 58$, 14%), median PFS was 5.4 months with everolimus and 1.9 months with placebo (HR: 0.32; $P = 0.004$). In sunitinib-intolerant patients ($n = 26$), median PFS was 5.1 months with everolimus and 2.8 months with placebo (HR: 0.28; $P = 0.033$). Grade 3/4 AEs reported with everolimus in VEGFr-TKI-intolerant patients included infections (16%), fatigue (7%) and stomatitis (4%). The toxicity profile of everolimus was similar in the VEGFr-TKI-intolerant and overall study populations.

CONCLUSION: Everolimus is well tolerated and efficacious with no increased toxicity in patients intolerant to VEGFr-TKI therapy.
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Sequential treatment with targeted therapies is the current standard of care for patients with metastatic renal cell carcinoma (mRCC) (de Reijke *et al*, 2009; Escudier and Kataja, 2010; Ljungberg *et al*, 2010; National Comprehensive Cancer Network, 2012). Targeted therapies approved for use in patients with mRCC include the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab, the VEGF receptor-tyrosine kinase inhibitors (VEGFr-TKIs) sorafenib, sunitinib and pazopanib, and the mammalian target of rapamycin (mTOR) inhibitors everolimus and temsirolimus.

First-line systemic treatment options supported by the highest level of clinical evidence for patients with mRCC are the VEGF-targeted agents sunitinib, pazopanib and bevacizumab (plus interferon-α) for patients of good or intermediate Memorial Sloan–Kettering Cancer Center (MSKCC) risk and the mTOR inhibitor temsirolimus for patients of poor MSKCC risk (de Reijke *et al*, 2009; Escudier and Kataja, 2010; Ljungberg *et al*, 2010; National Comprehensive Cancer Network, 2012). Although many patients obtain significant clinical benefit in terms of progression-free survival (PFS) from treatment with VEGF-targeted therapies, these agents are not well tolerated by all patients, leading to treatment discontinuation in a relevant percentage of cases.

Adverse events (AEs) commonly observed in patients treated with VEGFr-TKIs include hypertension, hand-foot skin reaction (palmoplantar erythrodysesthesia), rash/desquamation, alopecia, diarrhoea, fatigue, hyponatremia, neutropenia and thrombocytopenia (Ravaud, 2011). The onset of treatment-related AEs may necessitate dose interruptions, dose adjustments and/or treatment discontinuation in some patients. In a phase-III trial of patients with mRCC treated with sunitinib ($n = 375$) or interferon-α ($n = 375$), 8% and 13% of patients, respectively, discontinued treatment because of AEs (Motzer *et al*, 2007). In the phase-III TARGET trial of patients with mRCC receiving sorafenib ($n = 451$) or placebo ($n = 452$), 21% of sorafenib-treated patients required dose interruptions primarily because of the occurrence of hand-foot skin reaction, whereas 6% of patients in the placebo group

*Correspondence: Dr S Bracarda;
E-mail: sergio.bracarda@usl8.toscana.it
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required dose interruptions (Escudier *et al*, 2007). In a phase-III study of patients with mRCC who received pazopanib ($n = 290$) or placebo ($n = 145$), 14% and 3% of patients, respectively, discontinued treatment because of AEs (Sternberg *et al*, 2010). Tolerability of first-line VEGFr-TKIs may be an even more relevant issue in clinical practice compared with clinical trials (Choueiri *et al*, 2010; Porta *et al*, 2011b). Results of two retrospective chart reviews from tertiary oncology centres in the United States (Choueiri *et al*, 2010) and Italy (Porta *et al*, 2011b) found that 26–37% of patients treated with first-line sunitinib or sorafenib required dose reductions because of AEs, 19–32% of patients required dose interruptions because of AEs and 5–18% discontinued treatment because of AEs.

For patients who are intolerant to first-line VEGF-targeted therapy (i.e., discontinue therapy because of unacceptable toxicity), careful selection of second-line treatment is particularly critical in order to achieve maximum clinical benefit while minimising the occurrence of further treatment-related AEs. VEGF-targeted agents and mTOR inhibitors have distinct class effect toxicities (Ravaud, 2011); thus, patients who are intolerant to first-line VEGF-targeted therapy may be less likely to experience significant toxicity with a second-line mTOR inhibitor than a second-line VEGF-targeted agent. The phase-III RECORD-1 study evaluated the efficacy of the oral mTOR inhibitor everolimus in patients with mRCC whose disease had progressed on, or who were intolerant to, previous VEGFr-TKI therapy (sunitinib and/or sorafenib) (Motzer *et al*, 2008, 2010). Median PFS was prolonged from 1.9 months (95% CI: 1.8–1.9) to 4.9 months (95% CI: 4.0–5.5) for patients who received placebo or everolimus, respectively (Motzer *et al*, 2010). Risk of disease progression was reduced by 67% for patients in the everolimus group, compared with patients in the placebo group (hazard ratio (HR): 0.33; $P < 0.001$). Based on these results, current clinical practice guidelines recommend everolimus as the standard of care for patients with mRCC who have failed initial VEGFr-TKI therapy (de Reijke *et al*, 2009; Escudier and Kataja, 2010; Ljungberg *et al*, 2010; National Comprehensive Cancer Network, 2012).

Herein we present the results of a retrospective analysis of RECORD-1 that evaluated the efficacy and safety of everolimus in the subgroup of patients who discontinued previous VEGFr-TKI therapy because of toxicity.

MATERIALS AND METHODS

Patient population

The study design of RECORD-1, an international, multicentre, double-blind, randomised phase-III trial, has been previously reported (Motzer *et al*, 2008). Adult patients (aged $\geqslant 18$ years) with measurable clear cell mRCC (according to RECIST 1.0 (Therasse *et al*, 2000)), which had progressed within 6 months of stopping treatment with sunitinib, sorafenib or both were included in the study. Previous treatment with bevacizumab, interleukin 2 or interferon-α also was permitted. Other key inclusion criteria were a Karnofsky performance status of at least 70% (scale 0–100, higher scores indicated better performance) and adequate bone marrow, hepatic and renal function. Patients in all MSKCC-risk categories (favourable, intermediate and poor) were included. Key exclusion criteria were previous treatment with temsirolimus, untreated central nervous system metastases and uncontrolled medical conditions (e.g., unstable angina pectoris, symptomatic congestive heart failure, recent myocardial infarction or diabetes).

Study treatments

Patients were stratified according to whether they received one or two previous VEGFr-TKIs and by MSKCC-risk group. Patients were then randomly assigned 2:1 to receive either continuous treatment with oral everolimus 10 mg once daily ($n = 277$) or placebo ($n = 139$), both in conjunction with best supportive care (Motzer *et al*, 2010). A cycle was 28 days of treatment. Doses were delayed or reduced (to 5 mg once daily) if patients had clinically significant haematological or other AEs that were considered by the investigator to be related to everolimus. Treatment continued until disease progression, unacceptable toxicity, death or discontinuation for any other reason. Patients randomly assigned to placebo who experienced disease progression were permitted to cross over to open-label everolimus.

Assessments

The primary reason for discontinuation of each previous antineoplastic therapy (AE, disease progression or other) was collected for all patients. Patients for whom an AE was the primary reason for discontinuation of previous sunitinib therapy, sorafenib therapy or both (i.e., discontinuation of previous VEGFr-TKI therapy because of unacceptable toxicity) were included in this subgroup analysis and assessed for PFS and safety. PFS was defined as the time from randomisation to the first documentation of disease progression or death from any cause and was documented according to RECIST 1.0 and assessed via blinded, independent central review (Motzer *et al*, 2008). Tumour measurements were assessed by CT or MRI scans and were performed at screening and every 8 weeks thereafter.

Safety was assessed in all patients who received at least one dose of study drug. AEs and laboratory evaluations were monitored and graded according to the National Cancer Institute's Common Terminology Criteria for AEs, version 3.0 (National Cancer Institute, 2006). Vital signs were measured, physical examinations were performed and all concomitant medications and therapies were recorded.

Analysis

The Kaplan–Meier method was used to estimate median PFS for patients intolerant to previous VEGFr-TKI therapy in each treatment arm and the Cox proportional hazard model was used to calculate the HR of treatment effect on PFS.

Ethical conduct

RECORD-1 was conducted according to the ethical principles of the Declaration of Helsinki. The study protocol was reviewed by the independent ethics committee or institutional review board for each centre. Each patient provided written informed consent before screening procedures were initiated.

RESULTS

In the overall RECORD-1 population, 14% of patients ($n = 58$) discontinued previous VEGFr-TKI therapy because of unacceptable toxicity. Among the subgroup of 58 patients who were intolerant to previous VEGFr-TKI therapy, 45 patients and 13 patients were randomly assigned to everolimus and placebo, respectively. Baseline characteristics in this subgroup of patients were generally similar to those of the overall study population; however, some differences between placebo-treated patients who were VEGFr-TKI-intolerant and all placebo-treated patients were noted (e.g., younger median age and higher percentage of women) (Table 1). When stratified by previous VEGFr-TKI therapy, of the 45 patients who received everolimus, 21 were intolerant to previous sunitinib, 19 were intolerant to previous sorafenib and 5 were intolerant to previous sunitinib and sorafenib. Of the

Table 1 Patient demographics in the subgroup of patients who were intolerant of previous VEGFr-TKI therapy and all patients in the RECORD-1 trial

	VEGFr-TKI-intolerant patients		All patients (Motzer *et al*, 2010)	
	Everolimus+BSC ***n*** **= 45**	**Placebo+BSC** ***n*** **= 13**	**Everolimus+BSC** ***n*** **= 277**	**Placebo+BSC** ***n*** **= 139**
Age in years, median (range)	66 (44–81)	41 (29–74)	61 (27–85)	60 (29–79)
Sex, n (%)				
Men	28 (62)	5 (39)	216 (78)	106 (76)
Women	17 (38)	8 (62)	61 (22)	33 (24)
KPS score, n (%)				
100	10 (22)	1 (8)	78 (28)	41 (30)
90	16 (36)	6 (27)	98 (35)	53 (38)
80	18 (40)	5 (22)	72 (26)	30 (22)
70	1 (2)	1 (8)	28 (10)	15 (11)
Missing	0	0	1 (<1)	0
MSKCC-risk group, n (%)				
Favourable	13 (29)	3 (23)	81 (29)	39 (28)
Intermediate	30 (67)	8 (62)	156 (56)	79 (57)
Poor	2 (4)	2 (15)	40 (14)	21 (15)

Abbreviations: BSC = best supportive care; KPS = Karnofsky performance status; MSKCC = Memorial Sloan–Kettering Cancer Center; VEGFr-TKI = vascular endothelial growth factor receptor-tyrosine kinase inhibitor.

Table 2 Rates and reasons for discontinuation of everolimus or placebo in patients who were intolerant of previous VEGFr-TKI therapy

Discontinuations, *n* (%)	**Everolimus+BSC** ***n*** **= 45**	**Placebo+BSC** ***n*** **= 13**
	30 (66.7)	12 (92.3)
Reason for discontinuation, n (%)		
Disease progression	19 (42.2)	11 (84.6)
Adverse event	6 (13.3)	0
Consent withdrawn	3 (6.7)	0
Abnormal laboratory value	1 (2.2)	0
Lost to follow-up	1 (2.2)	0
Death	0	1 (7.7)

Abbreviations: BSC = best supportive care; VEGFr-TKI = vascular endothelial growth factor receptor-tyrosine kinase inhibitor.

13 patients who received placebo, 5 were intolerant to previous sunitinib and 8 were intolerant to previous sorafenib.

Among patients who were intolerant to previous VEGFr-TKI therapy and subsequently received everolimus or placebo, 42.2% and 84.6%, respectively, discontinued treatment because of disease progression, whereas 13% and 0%, respectively, discontinued treatment because of AEs (Table 2). AEs that led to discontinuation of everolimus treatment were asthenia, increased blood creatinine, dehydration, dyspnoea, increased gamma-glutamyltransferase, general physical health deterioration, pathological fracture, pleural effusion and pneumonitis.

As was observed in the overall RECORD-1 population, everolimus significantly prolonged PFS compared with placebo in patients who were intolerant to previous VEGFr-TKI therapy (Figure 1). Median PFS was 5.4 months (95% CI: 3.8–5.9) with everolimus and 1.9 months (95% CI: 1.8–3.7) with placebo. Risk of disease progression was decreased by 68% with everolimus compared with placebo (HR: 0.32; 95% CI: 0.13–0.77; $P = 0.004$).

PFS benefit of everolimus compared with placebo was similar for patients who were intolerant to previous sunitinib or sorafenib therapy (Table 3). Among patients who were intolerant to previous sunitinib therapy, median PFS was 5.1 months (95% CI: 3.7–not available) with everolimus and 2.8 months (95% CI: 1.9–3.7) with placebo (HR: 0.28; 95% CI: 0.07–1.18; $P = 0.033$). Among patients who were intolerant to previous sorafenib therapy, median PFS was 5.6 months

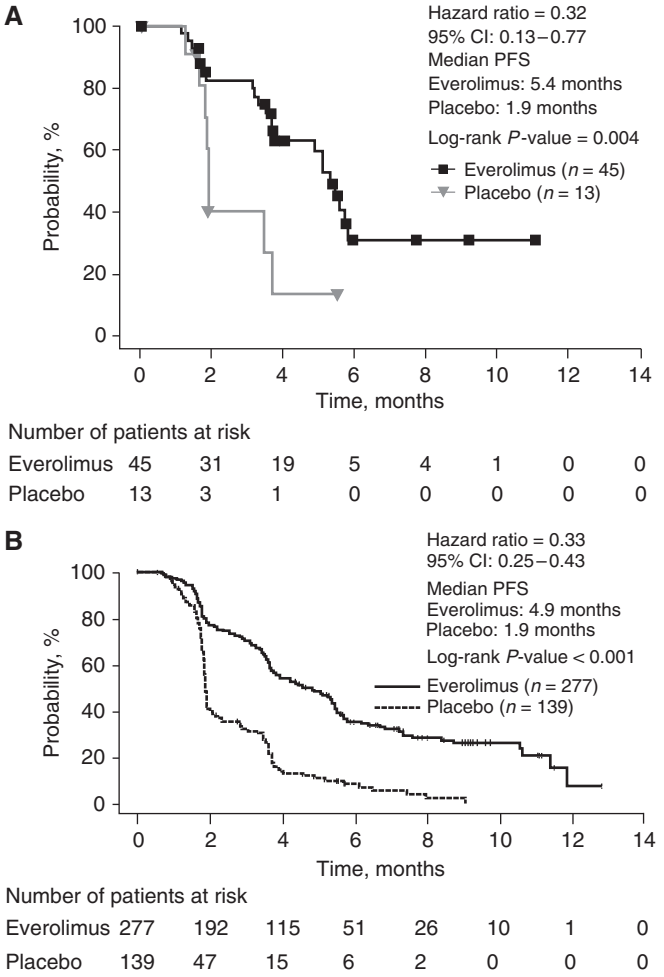

Figure 1 Kaplan–Meier estimates of PFS by treatment group in the patients intolerant of previous VEGFr-TKI therapy (**A**) and the overall RECORD-1 population (**B**) (Motzer *et al*, 2010). Figure 1B was reprinted from Motzer *et al*, 2010, copyright (2010), with permission from John Wiley & Sons (Hoboken, NJ, USA). Abbreviations: PFS = progression-free survival; VEGFr-TKI = vascular endothelial growth factor receptor-tyrosine kinase inhibitor.

Table 3 PFS in patients intolerant to previous sunitinib and/or sorafenib therapy

	Intolerant to previous sunitinib[a]		Intolerant to previous sorafenib[b]	
	Everolimus+BSC	**Placebo+BSC**	**Everolimus+BSC**	**Placebo+BSC**
Patients, *n*	26[c]	5	24[c]	8
PFS in months, median (95% CI)	5.1 (3.7–NA)	2.8 (1.9–3.7)	5.6 (3.8–NA)	1.9 (1.7–3.5)
Hazard ratio (95% CI)	0.28 (0.07–1.18), $P=0.033$		0.29 (0.09–0.91), $P=0.012$	

Abbreviations: BSC = best supportive care; CI = confidence interval; NA = not available; PFS = progression-free survival. [a]Patients who had an adverse event (AE) as the primary reason for discontinuation of previous sunitinib. Patients may have also received previous sorafenib. [b]Patients who had an AE as the primary reason for discontinuation of previous sorafenib. Patients may have also received previous sunitinib. [c]Of the 45 VEGFr-TKI-intolerant patients randomly assigned to everolimus, 5 patients were intolerant to both previous sunitinib and sorafenib and were included in both previous treatment groups.

Table 4 Commonly reported adverse events and laboratory abnormalities, irrespective of relation to treatment, in patients intolerant to previous VEGFr-TKI therapy and the overall RECORD-1 population

	Patients intolerant to previous VEGFr-TKI therapy						All patients (Motzer *et al*, 2010)					
	Everolimus+BSC, $n=45$			Placebo+BSC, $n=13$			Everolimus+BSC, $n=274$			Placebo+BSC, $n=137$		
	All grade	**Grade 3**	**Grade 4**	**All grade**	**Grade 3**	**Grade 4**	**All grade**	**Grade 3**	**Grade 4**	**All grade**	**Grade 3**	**Grade 4**
Adverse event, %												
Stomatitis[a]	49	4	0	15	0	0	44	4	<1	8	0	0
Fatigue	38	7	0	0	0	0	31	5	0	27	3	<1
Infections[b]	33	9	7	31	0	0	37	7	3	18	1	0
Diarrhoea	31	2	0	0	0	0	30	1	0	7	0	0
Rash	31	0	0	0	0	0	29	1	0	7	0	0
Nausea	27	0	0	23	0	0	26	1	0	19	0	0
Asthenia	24	2	0	23	0	0	33	3	<1	23	4	0
Peripheral oedema	24	0	0	15	0	0	25	<1	0	8	<1	0
Mucosal inflammation	16	2	0	0	0	0	19	1	0	1	0	0
Laboratory abnormality, %												
Haemoglobin decreased	96	13	2	92	8	0	92	12	1	79	5	<1
Cholesterol increased	78	4	0	38	0	0	77	4	0	35	0	0
Triglycerides increased	76	0	0	0	0	0	73	<1	0	34	0	0
Glucose increased	64	20	0	23	0	0	57	15	<1	25	1	0
Lymphocytes decreased	64	18	2	31	0	0	51	16	2	28	5	0
Creatinine increased	60	0	0	31	0	0	50	1	0	34	0	0
Platelets decreased	40	0	2	8	0	8	23	1	0	2	0	<1

Abbreviations: BSC = best supportive care; VEGFr-TKI = vascular endothelial growth factor receptor-tyrosine kinase inhibitor. [a]Stomatitis (including aphthous stomatitis), mouth ulceration and tongue ulceration. [b]All infections reported, including pneumonia, aspergillosis, candidiasis and sepsis.

(95% CI: 3.8–not available) with everolimus and 1.9 months (95% CI: 1.7–3.5) with placebo (HR: 0.29; 95% CI: 0.09–0.91; $P=0.012$).

Everolimus was generally well tolerated in patients who were intolerant to previous VEGFr-TKI therapy, with low rates of grade 3 and grade 4 AEs, and the safety profile was similar to that observed in the overall RECORD-1 population (Table 4). In the everolimus cohort of patients intolerant to previous VEGFr-TKI therapy, the most common AEs (all grade and grade $\geqslant 3$ incidence, respectively) were stomatitis (49% and 4%), fatigue (38% and 7%) and infections (33% and 16%), and the most commonly reported grade $\geqslant 3$ laboratory abnormalities were hyperglycaemia (20%), lymphopenia (20%) and anaemia (15%).

DISCUSSION

Targeted therapies in mRCC are rarely curative, and patients often rely on multiple lines of therapy to derive sustained clinical benefit (Oudard and Elaidi, 2012). In patients with mRCC who are intolerant to first-line VEGF-targeted therapy and must discontinue treatment before disease progression, tolerability of subsequent therapy is of particular importance. Patients who require dose reductions/interruptions or cessation of treatment to manage toxicity associated with VEGF-targeted therapy may experience reduced efficacy of that agent. A recent pharmacokinetic/pharmacodynamic meta-analysis of sunitinib-treated patients with various types of cancer, including mRCC, demonstrated a positive relationship between drug exposure and time to progression or overall survival (Houk *et al*, 2010). However, increased sunitinib exposure was also associated with increased incidence of class-effect toxicities such as hypertension, neutropenia and fatigue.

In previous studies of sequential administration of VEGF-targeted agents, overlapping toxicity profiles of these agents have resulted in high incidences of certain treatment-related AEs, such as hypertension, skin toxicities, fatigue and gastrointestinal toxicities, some of which have required dose modifications (Rini *et al*, 2008, 2011; Di Lorenzo *et al*, 2009; Garcia *et al*, 2010). The AXIS phase-III trial evaluated the safety and efficacy of axitinib *vs* sorafenib in patients with mRCC who had failed first-line treatment with a sunitinib-, bevacizumab-, temsirolimus- or cytokine-based regimen; 62% of patients received first-line VEGF-targeted therapy (sunitinib or bevacizumab) (Rini *et al*, 2011). In the overall AXIS population, class-effect AEs reported in the axitinib and sorafenib arms included diarrhoea (55% and 53%, respectively), hypertension (40% and 29%, respectively), fatigue (39% and 32%, respectively), palmar-plantar erythrodysaesthesia

(27% and 51%, respectively), rash (13% and 32%, respectively) and alopecia (4% and 32%, respectively) (Rini *et al*, 2011). One or more dose reduction was reported in 31% and 52% of patients in the axitinib and sorafenib arms, respectively, and 77% and 80% of patients in each arm, respectively, had one or more dose interruption (Rini *et al*, 2011). Safety data for the subgroup of patients who failed previous VEGFr-TKI therapy (54%) has yet to be reported.

The safety profile of mTOR inhibitors generally does not overlap with that of VEGFr-TKIs (Escudier *et al*, 2007; Motzer *et al*, 2007, 2010), thus, patients who experience intolerance to VEGFr-TKI therapy may benefit from switching to an mTOR inhibitor. Most common grade $\geqslant 3$ AEs with everolimus in the overall RECORD-1 population were infections (10%), dyspnoea (7%), fatigue (5%) and stomatitis ($\sim 5\%$), and most common grade $\geqslant 3$ laboratory abnormalities were lymphopenia (18%), hyperglycaemia ($\sim 16\%$) and anaemia (13%) (Motzer *et al*, 2010). Noninfectious pneumonitis, a class effect of mTOR inhibitors, was reported in 13.5% of patients in the everolimus group of the RECORD-1 study (grade 1, 3.3%; grade 2, 6.6%; grade 3, 3.6%; and grade 4, 0%) (Motzer *et al*, 2010; White *et al*, 2010; Porta *et al*, 2011a). Cardiovascular toxicity (hypertension, reduced left ventricular ejection fraction, cardiac ischaemia and infarction) and hand-foot skin reaction are not commonly observed in patients treated with everolimus (Escudier *et al*, 2007; Motzer *et al*, 2007, 2010).

Results of this subgroup analysis of RECORD-1 demonstrate that everolimus is well tolerated and efficacious in patients who are intolerant to VEGFr-TKI therapy. VEGFr-TKI-intolerant patients, who may be at risk for experiencing treatment-related AEs, did not experience increased toxicity and, notably, did not experience increased rates of pneumonitis relative to the overall RECORD-1 population (Motzer *et al*, 2010). In this analysis, 13.3% of patients discontinued treatment with everolimus because of AEs, thus, the majority (86.7%) of VEGFr-TKI-intolerant patients did tolerate treatment with everolimus. Additionally, the median PFS of everolimus in patients who were intolerant to previous VEGFr-TKI therapy (5.4 months) was similar to the median PFS of all everolimus-treated patients in RECORD-1 (4.9 months) (Motzer *et al*, 2010).

The retrospective nature of this analysis, small sample size, and lack of patient stratification within the subgroup suggest use of caution when interpreting these results. Furthermore, this analysis was not powered or designed to enable statistical comparison of efficacy or safety profiles between patients intolerant to VEGFr-TKI therapy and the overall RECORD-1 population. Further studies of everolimus in patients intolerant to VEGF-targeted therapy are warranted to confirm our observations.

Recent evidence has indicated that sequential treatment with a VEGFr-TKI and an mTOR inhibitor may permit eventual rechallenge with a third-line VEGFr-TKI. A subset of RECORD-1 patients from French sites ($n = 36$) demonstrated a median PFS of 5.3 months for sorafenib, 8 months for sunitinib and 12 months for dovitinib (TKI258) after disease progression on at least one VEGFr-TKI and everolimus (Blesius *et al*, 2010). Another subset of RECORD-1 patients from a German institution ($n = 39$) achieved a median PFS of 5.1 months after receiving sorafenib, sunitinib or dovitinib following previous treatment with at least one VEGFr-TKI and everolimus (Gruenwald *et al*, 2010). In a retrospective Italian study ($n = 34$), third-line sorafenib after sequential therapy with sunitinib followed by everolimus or temsirolimus was associated with a median PFS of 4 months and a median overall survival of 7 months from initiation of sorafenib treatment (Di Lorenzo *et al*, 2010). A phase-III study designed to compare the safety and efficacy of dovitinib and sorafenib in patients with mRCC whose disease has progressed on one previous VEGFr-TKI and one previous mTOR inhibitor is currently ongoing (ClinicalTrials.gov identifier: NCT01223027).

In conclusion, appropriate selection of second-line therapy to maximise clinical benefit and minimise the occurrence of treatment-related AEs for patients who are intolerant of initial VEGF-targeted therapy is a key clinical issue. Results of this subgroup analysis of the phase-III RECORD-1 study demonstrate that everolimus can be safely given to patients with a previous intolerance to VEGFr-TKI therapy. These results further support everolimus as the treatment of choice in patients who have failed initial VEGFr-TKI therapy.

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