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Everolimus in metastatic renal cell carcinoma: Subgroup analysis of patients with 1 or 2 previous vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapies enrolled in the phase III RECORD-1 study

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ABSTRACT

Introduction: In the phase III RECORD-1 trial (ClinicalTrials.gov: NCT00410124), patients with metastatic renal cell carcinoma (mRCC) who progressed on previous vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFr-TKI) therapy were randomised 2:1 to everolimus 10 mg once daily ($n = 277$) or placebo ($n = 139$). Median progression-free survival (PFS) was 4.9 months with everolimus and 1.9 months with placebo (hazard ratio [HR], 0.33; $P < .001$). This preplanned, prospective sub-analysis evaluated PFS benefit of everolimus versus placebo in patients who had previously received 1 or 2 VEGFr-TKIs.
Patients and methods: Median PFS was estimated using the Kaplan–Meier method, and Cox proportional hazards model was used to analyse differences in PFS.
Results: All patients (100%) received ⩾1 previous VEGFr-TKI; 26% of patients received 2 previous VEGFr-TKIs. Among patients who received 1 previous VEGFr-TKI, median PFS was 5.4 months with everolimus and 1.9 months with placebo (HR, 0.32; 95% confidence interval [CI], 0.24–0.43; $P < .001$). Among patients who received 2 previous VEGFr-TKIs,

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median PFS was 4.0 months with everolimus and 1.8 months with placebo (HR, 0.32; 95% CI, 0.19–0.54; $P < .001$). The everolimus safety profile was similar for both groups.

Conclusions: Everolimus was associated with prolonged PFS relative to placebo in patients who received 1 or 2 previous VEGFr-TKIs. Patients who received only 1 previous VEGFr-TKI had apparently longer PFS with everolimus in reference to those who received 2 previous VEGFr-TKIs. These results support the use of everolimus as the standard of care in patients who fail initial VEGFr-TKI therapy.

1. Introduction

Everolimus is a potent, orally administered inhibitor of the mammalian target of rapamycin (mTOR), which regulates cell growth, proliferation, survival, and angiogenesis.[1] Dysfunction within the mTOR pathway may play a role in the pathogenesis of renal cell carcinoma (RCC).[2,3] Everolimus is approved in the United States and Europe for the treatment of patients with metastatic RCC (mRCC) who have experienced disease progression following treatment with vascular endothelial growth factor receptor-tyrosine kinase inhibitors (VEGFr-TKIs).[4] Everolimus is the recommended standard of care for patients with mRCC whose disease has progressed after initial VEGFr-TKI therapy.[5–8]

The efficacy and safety of everolimus in patients with mRCC who were refractory to VEGFr-TKI therapy were demonstrated in the phase III RECORD-1 trial.[9,10] Median progression-free survival (PFS) was 4.9 months for patients who received everolimus plus best supportive care and 1.9 months for patients who received placebo plus best supportive care (hazard ratio [HR], 0.33; 95% confidence interval [CI], 0.25–0.43; $P < .001$).[10] Risk of disease progression was reduced by 67% for patients in the everolimus group compared with patients in the placebo group. The most commonly reported grade 3 or 4 adverse events (AEs) in the everolimus group were infections (10%), dyspnoea (7%), and fatigue (5%).[10]

Here we report results of a pre-planned, prospective subanalysis of the RECORD-1 trial that further examines PFS benefit of everolimus versus placebo in patients with mRCC who experienced disease progression after receiving either 1 or 2 previous VEGFr-TKIs.

2. Patients and methods

2.1. Patient population

The study design of RECORD-1 (ClinicalTrials.gov identifier: NCT00410124), an international, multicentre, double-blind, randomised phase III trial, has been previously reported.[9] Adult patients (aged 18 years and older) with measurable clear cell mRCC (according to RECIST 1.0[11]) who had progressed during or within 6 months of stopping treatment with sunitinib, sorafenib, or both were included in the study. Previous treatment with bevacizumab, immunotherapy (interleukin 2, interferon-α, or a combination of the two), or chemoimmunotherapy was also 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 Memorial Sloan-Kettering Cancer Center (MSKCC) risk categories (favourable, intermediate, 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 uncontrolled diabetes).

2.2. Study treatments

Patients were randomly assigned 2:1 to receive either continuous treatment with oral everolimus 10 mg once daily or placebo, both in conjunction with best supportive care. 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.

2.3. Assessments

All randomly assigned patients were assessable for efficacy. Patients were stratified according to the number of previous VEGFr-TKI therapies received and by MSKCC risk category (favourable, intermediate, poor). PFS, documented according to RECIST 1.0 and assessed via blinded, independent central review, was defined as the time from randomisation to the first documentation of disease progression or death from any cause. Tumour measurements, assessed by CT or MRI scans, were performed at screening and every 8 weeks thereafter. Additional scans were performed to confirm response (no sooner than 4 weeks and no later than 6 weeks after the initial observation) or whenever disease progression was suspected.

All patients who received at least one dose of study drug and who were followed up were assessed for safety. Safety was assessed every 14 days for the first three cycles and every 4 weeks thereafter. AEs and laboratory evaluations were monitored and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0.[12] Vital signs were measured, physical examinations were performed, and all concomitant medications and therapies were recorded.

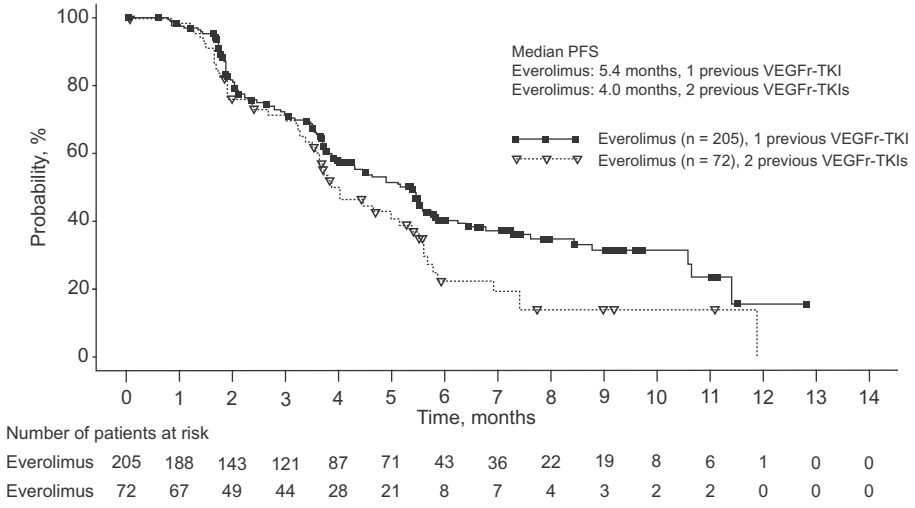

Fig. 1 – Kaplan–Meier estimates of PFS in patients treated with everolimus after progressing on treatment with 1 or 2 previous VEGFr-TKIs. PFS, progression-free survival; VEGFr-TKI, vascular endothelial growth factor receptor-tyrosine kinase inhibitor.

2.4. *Analysis*

Median PFS was estimated using the Kaplan–Meier method and Cox proportional hazards model was used to analyse the effect of everolimus treatment, compared with placebo, on PFS in patients who had received 1 previous VEGFr-TKI or 2 previous VEGFr-TKIs, as well as for patients who had favourable, intermediate, or poor MSKCC risk. Additional analyses of median PFS were also carried out on patient subgroups stratified by prior therapy (previous sunitinib or previous sorafenib). Most common AEs in the subgroups of patients treated with 1 or 2 previous VEGFr-TKIs were also reported.

2.5. *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.

3. Results

In the RECORD-1 population, 277 patients were randomly assigned to the everolimus group and 139 patients were randomly assigned to the placebo group. Baseline characteristics were similar between groups.[10] Overall, 79% of patients had received more than one previous systemic anti-cancer treatment, and all patients were treated with at least 1 prior VEGFr-TKI.[10]

When stratified by previous therapy, 74% ($n = 308$) of patients had received 1 previous VEGFr-TKI and 26% ($n = 108$) of patients had received 2 previous VEGFr-TKIs (Table 1). Among patients who had received 1 previous VEGFr-TKI, 60% ($n = 184$) had received previous sunitinib and 40% ($n = 124$) had received previous sorafenib.[10] Fifty-six patients of the total RECORD-1 population (13%) had received sunitinib as their only previous anti-neoplastic treatment (i.e. as first-line therapy).

Among patients who had received 1 previous VEGFr-TKI, median PFS was 5.4 months with everolimus and 1.9 months with placebo (HR, 0.32; 95% CI, 0.24–0.43; $P < .001$). Among patients who had received 2 previous VEGFr-TKIs, median PFS was 4.0 months in the everolimus group and 1.8 months in the placebo group (HR, 0.32; 95% CI, 0.19–0.54; $P < .001$). Kaplan–Meier curves for patients from the everolimus arm treated with 1 or 2 previous VEGFr-TKIs are shown in Fig. 1.

It is important to note that many of the patients in RECORD-1 who received only 1 previous VEGFr-TKI had also received 1 or more other previous anti-cancer treatments. In patients who had received sunitinib as their *only* previous anti-neoplastic therapy ($n = 56$), median PFS was 4.6 months with everolimus ($n = 43$) and 1.8 months with placebo ($n = 13$) (HR, 0.22; 95% CI, 0.09–0.55; $P < .001$), corresponding to a 78% reduction in risk of disease progression for patients receiving everolimus (Table 2).

Patients who were treated with everolimus had significantly longer median PFS than patients who received placebo, regardless of MSKCC risk category or previous VEGFr-TKI received (Table 2). When stratified by MSKCC risk category, patients treated with everolimus had apparently longer median PFS if they were of favourable (5.8 months) or intermediate MSKCC risk (4.5 months) than if they were of poor MSKCC risk (3.6 months). In patients who received sunitinib as their only previous VEGFr-TKI ($n = 124$), median PFS with everolimus was apparently longer for the subgroup of patients with favourable or intermediate MSKCC risk (5.2 months) than for patients of any MSKCC risk (3.9 months).

The safety profile of everolimus was similar among patients who had received 1 previous VEGFr-TKI compared with 2 previous VEGFr-TKIs (Tables 3 and 4). In patients who had received 1 previous VEGFr-TKI, the most commonly reported grade 3 or 4 AEs in the everolimus and placebo arms, respec-

Table 1 – Previous VEGFr-TKI therapy of patients enrolled in the RECORD-1 phase III trial.

Previous VEGFr-TKI therapy, *n* (%)	Everolimus + BSC, *n* = 277	Placebo + BSC, *n* = 139
1 previous VEGFr-TKI	205 (74)	103 (74)
Previous sunitinib only	124 (45)	60 (43)
Previous sorafenib only	81 (29)	43 (31)
Sunitinib as only previous anti-neoplastic therapy	43 (16)	13 (9)
2 previous VEGFr-TKIs	72 (26)	36 (26)

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

Table 2 – Analysis of PFS stratified by MSKCC risk category and by previous sunitinib or sorafenib.

	Everolimus + BSC, *n* = 277		Placebo + BSC, *n* = 139		Treatment effect	
	n (%)	Median PFS, months	*n* (%)	Median PFS, months	HR (95% CI)	*P*
MSKCC risk category						
Favourable	81 (29)	5.8	39 (28)	1.9	0.31 (0.19–0.50)	< .001
Intermediate	156 (56)	4.5	79 (57)	1.8	0.32 (0.22–0.44)	< .001
Poor	40 (14)	3.6	21 (15)	1.8	0.44 (0.22–0.85)	.007
Previous therapy by agent						
Sunitinib						
As only previous VEGFr-TKI						
All MSKCC risk groups	124 (45)	3.9	60 (43)	1.8	0.34 (0.23–0.51)	< .001
Favourable or intermediate MSKCC risk	111 (40)	5.2	51 (37)	1.8	0.31 (0.21–0.48)	< .001
As only previous anti-neoplastic therapy	43 (16)	4.6	13 (9)	1.8	0.22 (0.09–0.55)	< .001
Sorafenib						
As only previous VEGFr-TKI	81 (29)	5.9	43 (31)	2.8	0.25 (0.16–0.42)	< .001
As only previous anti-neoplastic therapy	18 (6)	3.8	12 (9)	1.9	0.35 (0.14–0.88)	.010

BSC, best supportive care; CI, confidence interval; HR, hazard ratio; MSKCC, Memorial Sloan-Kettering Cancer Center; PFS, progression-free survival; VEGFr-TKI, vascular endothelial growth factor receptor-tyrosine kinase inhibitor.

Table 3 – Most commonly reported grades 3 and 4 adverse events in patients treated with 1 previous VEGFr-TKI[a].

Adverse event	Everolimus + BSC, *n* = 205		Placebo + BSC, *n* = 103	
	Grade 3, *n* (%)	Grade 4, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)
Anaemia	18 (8.8)	1 (0.5)	3 (2.9)	1 (1.0)
Dyspnoea	11 (5.4)	3 (1.5)	4 (3.9)	0
Infection	10 (4.9)	3 (1.5)	1 (1.0)	0
Fatigue	12 (5.9)	0	3 (2.9)	0
Hyperglycaemia	12 (5.9)	0	2 (1.9)	0
Hypercholesterolaemia	9 (4.4)	0	0	0
Lymphopaenia	9 (4.4)	0	0	0
Pneumonitis	8 (3.9)	0	0	0
Stomatitis	7 (3.4)	1 (0.5)	0	0
Abdominal pain	7 (3.4)	0	0	0
Asthaenia	5 (2.4)	1 (0.5)	4 (3.9)	0
Dehydration	6 (2.9)	0	2 (1.9)	0
Elevated gamma-glutamyltransferase	6 (2.9)	0	1 (1.0)	0
Back pain	2 (1.0)	1 (0.5)	0	0
Mucosal inflammation	1 (0.5)	0	0	0

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

[a] Grade 3 and grade 4 adverse events reported in ⩾3% (combined grades 3 and 4 incidence) of everolimus-treated patients who received either 1 or 2 VEGFr-TKIs are shown. A patient with multiple occurrences of an adverse event is counted only once in the adverse event category for that treatment. Adverse events occurring more than 28 days after discontinuation of study treatment are not presented. The adverse event with maximum severity is counted for patients who experienced multiple episodes of an event.

Table 4 – Most commonly reported grades 3 and 4 adverse events in patients treated with 2 previous VEGFr-TKIs[a].

Adverse event	Everolimus + BSC, *n* = 72		Placebo + BSC, *n* = 36	
	Grade 3, *n* (%)	Grade 4, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)
Anaemia	8 (11.1)	1 (1.4)	3 (8.3)	0
Dyspnoea	6 (8.3)	1 (1.4)	0	0
Infection	5 (6.9)	1 (1.4)	0	0
Fatigue	3 (4.2)	0	1 (2.8)	1 (2.8)
Hyperglycaemia	5 (6.9)	0	0	0
Hypercholesterolaemia	0	0	0	0
Lymphopaenia	3 (4.2)	0	0	0
Pneumonitis	2 (2.8)	0	0	0
Stomatitis	4 (5.6)	0	0	0
Abdominal pain	2 (2.8)	0	0	0
Asthaenia	2 (2.8)	1 (1.4)	2 (5.6)	0
Dehydration	4 (5.6)	1 (1.4)	0	0
Elevated gamma-glutamyltransferase	4 (5.6)	0	1 (2.8)	0
Back pain	2 (2.8)	1 (1.4)	0	0
Mucosal inflammation	3 (4.2)	0	0	0

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

[a] Grade 3 and grade 4 adverse events reported in ⩾3% (combined grades 3 and 4 incidence) of everolimus-treated patients who received either 1 or 2 VEGFr-TKIs are shown. A patient with multiple occurrences of an adverse event is counted only once in the adverse event category for that treatment. Adverse events occurring more than 28 days after discontinuation of study treatment are not presented. The adverse event with maximum severity is counted for patients who experienced multiple episodes of an event.

tively, were anaemia (9.3% versus 3.9%), dyspnoea (6.9% versus 3.9%), infection (6.4% versus 1.0%), fatigue (5.9% versus 2.9%), and hyperglycaemia (5.9% versus 1.9%). In patients who had received 2 previous VEGFr-TKIs, the most commonly reported grade 3 or 4 AEs in the everolimus and placebo arms, respectively, were anaemia (12.5% versus 8.3%), dyspnoea (9.7% versus 0%), infection (8.3% versus 0%), dehydration (7.0% versus 0%), and hyperglycaemia (6.9% versus 0%).

4. Discussion

Sequential treatment with targeted agents is the actual standard of care for patients with mRCC.[5–8] First-line treatment with a VEGFr-TKI is recommended for most patients with mRCC; however, development of resistance to these agents is common. None of the existing VEGFr-TKIs completely block all angiogenic signalling pathways.[13] Tumour cells can adapt to this incomplete inhibition of angiogenesis, leading to resistance and disease progression.[14] Tumour adaptation and evasion may occur via multiple mechanisms. For example, reestablishment of angiogenesis can occur via mutation, epigenetic programming, or remodelling of the stromal microenvironment, leading to renewed tumour growth.[14] Alternatively, tumour cells may reduce their dependence on angiogenesis and subsequently upregulate other pathways involved in tumour survival and invasiveness.[15] In addition, hypoxia induced by VEGF inhibition triggers activation of signalling pathways that result in enhanced tumour aggressiveness and metastasis.[13] Eventual resistance to initial VEGFr-TKI therapy and subsequent disease progression will occur in the majority of patients with mRCC; as such, optimal selection of second-line therapy in these patients is of critical importance. Choice of subsequent therapy should be made with careful consideration of each patient's unique profile, including experience with first-line therapy (i.e. efficacy and toxicities), the aggressiveness of their disease, their performance status, and comorbidities.

Clinical practice guidelines released in the United States and Europe uniformly recommend everolimus in patients with VEGFr-TKI-refractory mRCC,[5–8] based on high-level clinical evidence from RECORD-1.[9,10] Results of this preplanned, prospective sub-analysis of RECORD-1 demonstrate that the PFS benefit of everolimus versus placebo extends to patients with mRCC who were previously treated with either 1 or 2 previous VEGFr-TKIs. Everolimus appears to afford a longer PFS in patients who have received only 1 previous VEGFr-TKI (5.4 months) than in those who have received 2 previous VEGFr-TKIs (4.0 months). Although this analysis was not designed to allow a statistical comparison of PFS values between subgroups, it should be noted that median PFS was similar in the placebo arms of the two sub-groups (1.9 versus 1.8 months). Thus, this result forms a basis for non-statistical comparison of median PFS for patients in the everolimus arm of the two sub-groups. In addition, HRs for median PFS in the everolimus arm compared with the placebo arm for both 1 and 2 previous VEGFr-TKI subgroups were nearly identical to that of the overall RECORD-1 population (HR, 0.33; 95% CI, 0.25–0.43: $P < .001$).[10] A significantly increased PFS benefit was observed in patients treated with everolimus compared with patients who received placebo, regardless of MSKCC risk category or previous VEGFr-TKI received. Of particular note, in the subset of patients who had received sunitinib as their only previous anti-neoplastic therapy (i.e. as first-line therapy), everolimus was associated with a median PFS of 4.6 months, and a 78% reduced risk of disease progression compared with placebo (HR, 0.22; 95% CI, 0.09–0.55; $P < .001$).

Recent interim results from a prospective, non-interventional, observational study of everolimus in routine clinical practice have provided additional clinical evidence of the effi-

cacy of everolimus in mRCC following initial VEGFr-TKI failure. This study has a higher percentage of patients receiving everolimus as pure second-line therapy compared with RECORD-1 (66% versus 21%[10]). On interim analysis, median time to disease progression (TTP) with everolimus was 9.7 months for patients with mRCC who had failed treatment with 1 previous anti-VEGF targeted therapy (either a VEGFr-TKI or bevacizumab).[16] Although this result is subject to bias given the non-randomised, observational study design, the lack of standardised assessment of disease progression, and the interim nature of the results, it appears consistent with our current results in suggesting that patients may achieve increased efficacy if they are treated with everolimus after only 1 previous VEGFr-TKI therapy.

Recent results of the phase III AXIS trial of axitinib versus sorafenib in patients who received 1 previous anti-cancer therapy demonstrated a median PFS of 6.7 months for axitinib and 4.7 months for sorafenib (HR, 0.665; $P < .0001$).[17] However, when patients were stratified by previous therapy, median PFS of patients who were previously treated with 1 VEGFr-TKI was 4.8 months for axitinib and 3.4 months for sorafenib (HR, 0.74; $P = .011$).[17] Safety results for the sub-group of patients previously treated with a VEGFr-TKI in AXIS have yet to be reported.

When sequential VEGFr-TKIs are administered to patients with mRCC as first- and second-line therapy, cumulative toxicity associated with the occurrence of AEs common to these agents may result.[18,19] AEs that are commonly associated with VEGFr-TKIs include hypertension, cardiac events, and hand-foot skin reaction.[10,20,21] The safety profile of VEGFr-TKIs[20,21] generally does not overlap with the safety profile of mTOR inhibitors.[22,23] In this sub-analysis, the safety profile of everolimus was similar for patients who had received 1 or 2 previous VEGFr-TKIs and was consistent with that of the overall RECORD-1 population.

While results of the current study provide valuable information to physicians who treat VEGFr-TKI-refractory patients with mRCC, definitive guidance on the benefits of sequencing with an mTOR inhibitor versus a VEGFr-TKI following progression on an initial VEGFr-TKI must come from randomised, controlled clinical trials in a purely second-line setting. Such direct comparisons will provide improved understanding of the efficacy and safety of sequential therapy in this patient population.

Currently, there are no definitive guidelines regarding choice of third-line treatment in patients who have progressed on a VEGFr-TKI and an mTOR inhibitor; however, recent evidence has demonstrated that reintroduction of a TKI following treatment with a VEGFr-TKI and an mTOR inhibitor offers significant clinical benefit in patients with mRCC.[18,19] In addition, a prospective, randomised phase III study evaluating this approach is currently ongoing that will compare the safety and efficacy of the TKIs dovitinib and sorafenib in patients with mRCC whose disease has progressed on 1 previous VEGFr-TKI and 1 previous mTOR inhibitor (clinicaltrials.gov identifier: NCT01223027).

In conclusion, results from this pre-planned, prospective sub-analysis of RECORD-1 demonstrate that everolimus is associated with a longer PFS than placebo, irrespective of whether patients received 1 or 2 previous VEGFr-TKIs, and that PFS is apparently longer in patients who receive everolimus after only 1 previous VEGFr-TKI. These results further support the use of everolimus as the present standard of care in patients with mRCC whose disease has progressed after initial VEGFr-TKI therapy.

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This work was supported by Novartis Pharmaceuticals Corporation. Novartis-affiliated authors had a role in formulating the study concepts and design, coordinating data acquisition, performing quality control, data analysis and interpretation, and statistical analysis, and editing and reviewing the manuscript. All authors participated in the decision to submit this manuscript for publication.

Conflict of interest statement

E. Calvo has served as a consultant to and received honoraria from Novartis and Pfizer, and has received investigational grants from Pfizer, Novartis, Roche, GlaxoSmithKline, and Bayer. B. Escudier has served as a consultant to and received honoraria from Bayer, Pfizer, Roche, Novartis, GlaxoSmith Kline, and Aveo. R.J. Motzer has served as a consultant to and received honoraria from Pfizer, and has received research funding from Novartis, Pfizer, GlaxoSmithKline, Aveo, and Bristol-Myers Squibb. S. Oudard has received honoraria from Bayer, Novartis, Pfizer, Roche, and Sanofi-Aventis. T.E. Hutson has served as a consultant to and received honoraria and research funding from Pfizer, Bayer, Novartis, GlaxoSmithKline, and Genentech, and has received honoraria and research funding from GlaxoSmithKline. C. Porta has received honoraria from Novartis, Bayer-Schering, Pfizer, Hoffman La Roche, and GlaxoSmithKline, and has received research funding from Novartis and Bayer-Schering. S. Bracarda has served as an advisory board member to Pfizer, GlaxoSmithKline, Novartis, and Bayer, and has received honoraria from Pfizer and Novartis. V. Grünwald has served as a consultant to Roche, Bayer, Novartis, Pfizer, GlaxoSmithKline, and Aveo/Astellas, has received honoraria from GlaxoSmithKline, Novartis, and Pfizer, and has received research funding from Pfizer and GlaxoSmithKline. J.A. Thompson has no conflicts of interest to declare. A. Ravaud is a member of global, European, and/or French boards on urological tumours for Pfizer, Novartis, GlaxoSmithKline, Bayer-Schering, and Dendreon, and has received institutional grant support from Pfizer, Novartis, and Roche. D. Kim is an employee of and owns stock in Novartis. A. Panneerselvam and O. Anak are employees of Novartis. R.A. Figlin has served as a consultant to Aveo and Argos.

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