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Overall survival for sorafenib plus interleukin-2 compared with sorafenib alone in metastatic renal cell carcinoma (mRCC): final results of the ROSORC trial†

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Background: The ROSORC trial, a randomised, phase II trial comparing sorafenib plus interleukin (IL-2) versus sorafenib alone as first-line treatment of metastatic renal cell carcinoma (mRCC) failed to demonstrate differences in progression-free survival (PFS). Updated overall survival (OS) results are reported.
Patients and methods: In this study, 128 patients were randomised to receive sorafenib 400 mg twice daily plus subcutaneous IL-2 4.5 million international units (MIU) five times per week for 6 weeks every 8 weeks (arm A) or sorafenib alone (arm B). OS was estimated with the Kaplan–Meier method and compared with the two-sided log-rank test.
Results: After a median follow-up of 58 months (interquartile range: 28–63 months), the median OS was 38 and 33 months in arms A and B, respectively ($P = 0.667$). The 5-year OS was 26.3% [95% confidence interval (CI) 15.9–43.5) and 23.1% (95% CI 13.2–40.5) for the combination- and single-agent arm, respectively. Most of the patients who were refractory to first-line treatment were subsequently treated with different targeted agents; they had a median survival greater than expected.
Conclusions: This outcome suggests a synergistic effect of the subsequent therapies following sorafenib failure.
ClinicalTrials.gov Identifier: NCT00609401.
Key words: renal cell carcinoma, sorafenib, interleukin-2, first-line treatment, targeted therapies

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introduction

Following the introduction in the oncologic therapeutic scenario of new targeted agents (TTs), the oral tyrosine kinase inhibitor (TKI) sorafenib has represented a step forward in the treatment of metastatic renal cell carcinoma (mRCC). To improve sorafenib efficacy, association strategies with either other TTs or immunotherapy have been explored. These premises prompted the initiation of a multicentre prospective phase II randomised clinical study comparing sorafenib plus subcutaneous (sc) interleukin (IL-2) versus sorafenib alone in patients with mRCC previously untreated with systemic therapy (the ROSORC trial). Results of this study reported that sorafenib plus IL-2 did not demonstrate improved progression-free survival (PFS) (the main end point) versus sorafenib alone [1].

More recently, unexpected data concerning overall survival (OS) achieved with sorafenib were presented. A phase III trial comparing the two TKIs axitinib and sorafenib in a population of 723 patients previously treated with cytokines or other TTs (AXIS trial) was undertaken [2]. A statistically significant benefit in PFS (primary end point) in favour of axitinib was observed both in the general population and in a preplanned subgroup analysis according to previous treatments used in the first-line setting. Conversely, no advantage in OS was observed. However, in the group of patients treated with sunitinib as first-line treatment followed by sorafenib, a trend of an increase in OS was detected [3].

Another phase III study compared the target of rapamycin inhibitor temsirolimus versus sorafenib in 512 patients who relapsed from sunitinib (INTORSECT study) [4]. Although the study did not show any statistical differences in PFS between the two arms, the OS analysis showed a significant superiority of sorafenib (16.6 versus 12.7 months; $P = 0.0144$) [4]. Similar data were also reported in the study comparing sorafenib with the novel TKI tivozanib (TIVO-1) in a population mostly undergoing first-line treatment. Despite statistical differences in PFS in favour of tivozanib, the interim OS analysis did not report any difference [5].

The findings just described suggest that the correlation between PFS and OS could not be as unequivocal for TTs, so that, in contrast to studies using conventional chemotherapy, PFS may not represent a definite surrogate end point for OS [6]. Keeping these new developments in mind, the OS results of the full dataset of 128 patients of ROSORC trial are presented here.

patients and methods

patients

The study design and patient inclusion criteria for the ROSORC trial were previously described. Eligible patients were aged ≥18 years, with a life expectancy ≥3 months and an Eastern Cooperative Oncology Group performance status ≤2. They had a histologically based diagnosis of mRCC. All histologies had at least one measurable 1D lesion detected by computed tomography (CT) or magnetic resonance imaging (MRI) and were evaluated according to the Response Evaluation Criteria for Solid Tumours (RECIST) criteria v.1.0 [7]. Patients had not been previously treated with systemic therapy for metastatic disease, but they could have undergone nephrectomy.

Exclusion criteria included a history of brain metastases, presence of concomitant illnesses, or medical conditions like unstable angina, uncontrolled hypertension, unstable diabetes mellitus, or potentially life-threatening autoimmune disorders.

study design

This prospective randomised, open-label, multicentre phase II study was designed to evaluate the efficacy and safety of the combination of sorafenib plus IL-2 versus sorafenib alone in untreated patients with mRCC. The primary end point of the study was PFS, and the secondary end points included objective response rate, OS and the safety profile of the two therapeutic regimens. Sample size was calculated according to a phase 2.5 design [8], considering PFS as the end point (progression or death without progression, whichever occurred first).

Patients were randomly allocated (1:1) to treatment with either oral sorafenib 400 mg (200 mg tablets) twice daily for the entire study period combined with sc IL-2 at a dose of 4.5 MIU 5 days per week for 6 weeks with treatment repeated every 8 weeks or with sorafenib alone at the same dose. However, after treatment of the first 40 patients, of whom 20 were randomised to the combination treatment arm, the protocol was amended to reduce the dose of IL-2 to 3 million IU 5 days per week, 2 weeks on and 2 weeks off, because of the onset of adverse events (AEs). Patients received study treatment until tumour progression or the onset of unacceptable toxicity.

The study design was approved by the local ethical committees and carried out in accordance with the Declaration of Helsinki and good clinical practice guidelines. At enrolment, each patient gave written informed consent. Randomisation was carried out centrally at the Italian Trials in Medical Oncology office. To ensure balance between the treatment arms with respect to centre, Memorial Sloan-Kettering Cancer Center risk group (low, intermediate, or high), and histologic type (clear cell versus non-clear cell), the minimisation method was applied using the Minim program [9].

safety and efficacy assessments

Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria (v.3.0). In the case of severe toxic effects (grade 3–4) that were deemed likely related to sorafenib treatment, such as haematologic toxicity, hypertension, and skin reactions, sorafenib was reduced to a dose of 400 mg once daily or every other day, or was temporarily discontinued. If a further dose reduction was required, or if no recovery (grade 0–1) was evident after a 2-week discontinuation of sorafenib, treatment was discontinued. No dose reduction of IL-2 was initially defined in the protocol; in the case of AEs related to IL-2, drug administration was temporarily stopped and then restarted at the same dosage after AE resolution. After the protocol amendment, the occurrence of grade 3–4 AEs resulted in dose reduction of IL-2 to 2 million IU 5 days per week, 2 weeks on and 2 weeks off. If after 2 weeks no recovery (grade 0–1) was observed, the patient was withdrawn from the study.

RECIST criteria v.1.0 was used for response assessments. Evaluations were carried out every 8 weeks during the first 24 weeks of treatment and then every 12 weeks thereafter. Tumour measurements were carried out by CT or MRI scan, with all initial diagnoses of complete and partial responses confirmed 4 weeks later.

statistical analysis

OS time was computed from the randomisation date to the date of death for any cause or censored at the last follow-up assessment in alive patients. For four patients (three undergoing sorafenib and one the combination), it was not possible to retrieve the date of death. Therefore, OS time was censored at

the last follow-up date. OS curves were estimated using the Kaplan–Meier method [10] and compared using the log-rank test.

The OS hazard ratio (HR) for sorafenib plus IL-2 versus sorafenib alone was estimated by using a Cox model, in which proportional hazard (PH) assumption was checked by statistical tests based on scaled Schoenfeld residuals [11]. We also estimated HR as a function of time. Such estimation was based on the Poisson approximation of the Cox model. Preliminary record splitting on monthly intervals was carried out. Then, a generalised linear model with Poisson error was fitted including as covariates the treatment arm, time, and the interaction terms treatment by time; the latter was modelled with 4-knot cubic spline transformation [12]. P values <0.05 were considered significant. The SAS statistical package (v.6, SAS Institute, Inc., Cary, NC) and R software (R Foundation for Statistical Computing; http://www.R-project.org/, Vienna, Austria) were used for the statistical analyses.

results

patients

From October 2006 to February 2008, 128 patients entered the ROSORC study; 66 were allocated to treatment with sorafenib plus IL-2 and 62 to sorafenib alone (Figure 1). Table 1 summarises baseline characteristics. At relapse, 49 patients (74%) of the combination arm and 48 (77%) of the sorafenib-alone arm underwent at least one subsequent therapy (second line). Additional therapies included sunitinib, everolimus, axitinib, and temsirolimus administered as second or further lines (Table 2). Eight patients were lost during follow-up. The remaining 23 patients did not receive subsequent lines of therapy because of treatment toxicity ($N = 10$) or early disease progression within 3 months from first-line therapy start ($N = 13$). The median PFS was 7.3 versus 6.9 months, showing a trend in favour of the combination arm ($P = 0.109$) [1]. The most common AEs were asthenia, hand-foot syndrome, hypertension, and diarrhoea. Grade 3–4 AEs were documented for 38% and 25% of the patients receiving combination- and single-agent treatment, respectively.

In the present update on OS, all enrolled patients were included in the intent-to-treat analysis: 85 of them died. In the sorafenib arm, 42 of 62 patients died; in the combination arm, 43 of 66 patients died.

survival

OS data were updated on September 30, 2012. Median follow-up was 58 months (interquartile range: 28–63 months), survival curves were evaluated to the perspective of 60 months (5 years), which is ~75% of the follow-up duration.

Figure 2 shows OS in the entire population. Median OS was 38 months [95% confidence interval (CI) 18–50] in the combination arm versus 33 months (95% CI 16–43) in the sorafenib-alone arm (log-rank test $P = 0.667$). Considering only the combination arm, the 5-year OS outlook was 26.3% (95% CI 15.9–43.5). For patients receiving sorafenib alone, the 5-year OS outlook was 23.1% (95% CI 13.2–40.5). The HR for sorafenib plus IL-2 versus sorafenib alone, as estimated from the Cox model, was 0.91 (95% CI 0.59–1.41), indicating a negligible effect of IL-2 on OS.

Cox model PH assumption was verified; coherently, no statistical evidence of treatment effect modification with time was shown in the model set up for investigating the HR time trend ($P = 0.923$ for the time by treatment interaction).

discussion

The extent of PFS observed in the ROSORC trial was definitely in line with those reported in previous or recent studies using sorafenib as a single agent in first-line treatment (Table 3, upper panel). Conversely, the median OS benefit of 33 months achieved in this trial represents the only evidence coming from a first-line prospective study, and, to our knowledge, its extent is

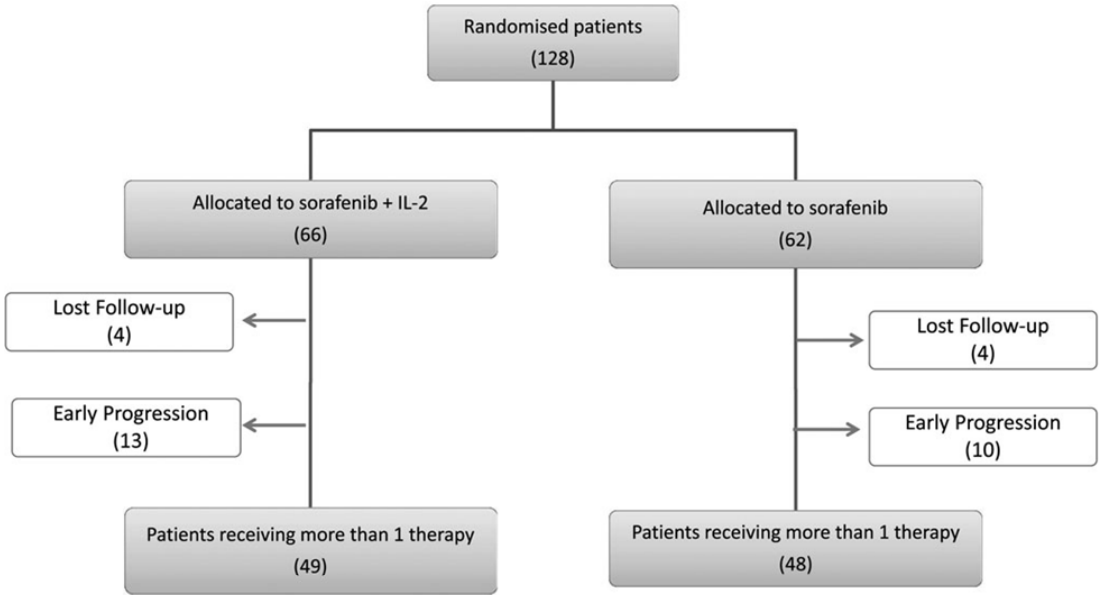

Figure 1. Flow of patients through the study.

Table 1. Patient characteristics at baseline

	Sorafenib + IL-2 ($n = 66$)	Sorafenib ($n = 62$)
Age at randomisation (years)		
Median (interquartile range)	64 (57–69)	62 (52–69)
Gender, *n* (%)		
Male	52 (79)	43 (69)
Female	14 (21)	19 (31)
Tumour stage at diagnosis, *n* (%)		
I	5 (8)	3 (5)
II	17 (26)	10 (16)
III	14 (21)	24 (39)
IV	28 (42)	25 (40)
Missing	2 (3)	0
MSKCC risk group, *n* (%)		
Low	36 (55)	34 (55)
Intermediate	27 (41)	24 (39)
High	3 (5)	4 (6)
Histologic type, *n* (%)		
Clear cell	58 (88)	56 (90)
Non-clear cell	8 (12)	6 (10)
Previous nephrectomy, *n* (%)		
No	18 (27)	16 (26)
Yes	48 (73)	46 (74)
Sites of disease, *n* (%)		
Lung	20 (30)	9 (15)
Liver	1 (2)	3 (5)
Lymph nodes	7 (11)	10 (16)
Kidney	1 (2)	1 (2)
Bone	2 (3)	3 (5)
Other site	4 (6)	4 (6)
Multiple sites	31 (47)	32 (52)

Table 2. Subsequent therapies

	Sorafenib + IL-2 ($n = 66$) Patients	Sorafenib ($n = 62$) Patients
Therapy after first line		
Any systemic therapy	49 (74%)	48 (77%)
Sunitinib	43 (65%)	41 (66%)
Everolimus	16 (24%)	14 (22%)
Temsirolimus	2 (3%)	4 (6%)
Axitinib	3 (4%)	1
Sorafenib	3 (4%)	2 (3%)
Other	5 (7%)	2 (3%)
Number of subsequent anticancer therapies		
1	24 (36%)	28 (45)
≥2	25 (38%)	20 (32%)

Table 3. PFS and OS in different trials with TTs in treatment-naive patients

Study	Year or name	Patients	Median (months)
Progression-free survival (PFS)			
Escudier (2007)	2005–2006	96	5.7
Jonasch (2009)	2005–2007	40	7.4
Bellmunt (2009)	2006	26	7.5
ROSORC	2006–2008	62	7.3
AMG 386	2007–2008	51	9.0
TIVO-1*	2010–2011	257	9.1
Overall survival (OS)			
Sunitinib	Phase III	375	26.4
	COMPARZ	553	29.3
Temsirolimus	Phase III	209	10.9
Bevacizumab	AVOREN	327	23.3
	CALGB	369	18.3
Pazopanib	Phase III	135	22.9
	COMPARZ	557	28.4
Sorafenib	ROSORC	62	33.0

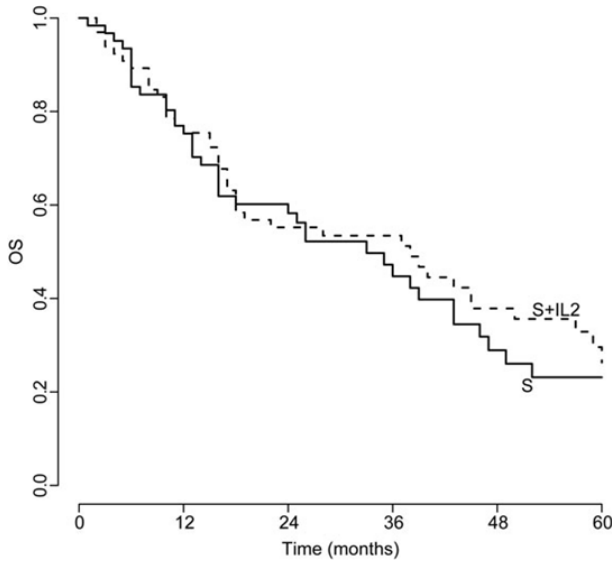

Figure 2. OS curves in patients treated with the combination of sorafenib plus IL-2 or sorafenib alone.

the larger so far observed in the treatment of mRCC (Table 3, lower panel). As reported by different authors [3, 6], this survival benefit should be correlated with, and ascribed to, the efficacy of the subsequent therapies administered to patients who relapsed after first-line treatment. It cannot be excluded, however, that some differences exist between the present and the series of large phase III trials that may lead to such a variance of results. In addition, it must be emphasised that the patients enrolled in this study were treated for conditions corresponding to everyday clinical practice without undergoing the restricted selection criteria typical of the phase III pivotal clinical trials. In this regard, well-balanced rates of patients with non-clear cell histology (12% in the combination arm versus 10% in the sorafenib alone) and with a poor prognosis (5% versus 6%) were accrued in both arms.

The limited extent of PFS as opposed to longer survival needs explanation. A first hypothesis could be an inaccurate PFS evaluation, likely due to the fact that some patients whose disease was stable were assessed as progressed. Consequently, this evaluation could have favoured the efficacy of subsequent

therapies because the resistance to sorafenib was still incomplete.

When the study was undertaken, the experience concerning the evaluation of responses induced by TTs was not yet fully understood. The ROSORC study started in October 2006 and ended in February 2008, a period in which physicians had just begun to evaluate the response to sorafenib in a different way than the dimensional reduction observed with chemotherapy. Experience gathered over time showed that a correct evaluation of the sorafenib response should consider the density alteration observed in the core of the tumour during the follow-up [13, 14].

A second explanation for this extended survival could also be related to the selection of the therapeutic sequence. Retrospective data have shown that first-line therapy with sorafenib followed by subsequent therapy with sunitinib could be related to a better overall PFS when compared with the reverse sequence [15, 16]. This evidence is also supported by preclinical data indicating the administration of a molecule with a lower anti-angiogenic activity can limit the anti-angiogenic resistance to subsequent therapies [17]. In line with these data, it must be considered that the unexpected OS of 33 months could have been reached because all of the patients enrolled received as first line, an anti-angiogenic drug with a lower affinity for vascular endothelial growth factor receptors. Therefore, the sequence of sorafenib followed by sunitinib could help achieve a prolonged OS, although a more detailed analysis on second-line therapies (e.g., a survival analysis in the interval between discontinuation of primary therapy until death) was not carried out. It is likely that only the ongoing phase III randomised trial (NCT00732914) comparing the two sequences, sorafenib followed by sunitinib and vice versa, might be able to confirm or discard this hypothesis.

In conclusion, our study suggests a synergistic effect of the subsequent therapies following sorafenib failure.

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disclosure

The authors have declared no conflicts of interest.

appendix

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