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European Association of Urology

Platinum Priority – Kidney Cancer

Editorial by Axel Bex on pp. 262–264 of this issue

Could Interferon Still Play a Role in Metastatic Renal Cell Carcinoma? A Randomized Study of Two Schedules of Sorafenib Plus Interferon-Alpha 2a (RAPSODY)

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Article info

Article history:
Accepted August 15, 2012
Published online ahead of print on August 23, 2012

Keywords:
Antiangiogenic therapy
Interferon-α2a
Renal cell carcinoma
Sorafenib

Abstract

Background: Sorafenib has proven efficacy in metastatic renal cell carcinoma (mRCC). Interferon (IFN) has antiangiogenic activity that is thought to be both dose- and administration-schedule dependent.
Objective: To compare two different schedules of IFN combined with sorafenib.
Design, setting, and participants: Single-stage, prospective, noncomparative, randomized, open-label, multicenter, phase 2 study on previously untreated patients with mRCC and Eastern Cooperative Oncology Group performance status 0–2.
Intervention: Sorafenib 400 mg twice daily plus subcutaneous IFN, 9 million units (MU) three times a week (Arm A) or 3 MU five times a week (Arm B).
Outcome measurements and statistical analysis: Primary end points were progression-free survival (PFS) for each arm and safety. Data were evaluated according to an intent-to-treat analysis.
Results and limitations: A total of 101 patients were evaluated. Median PFS was 7.9 mo in Arm A and 8.6 mo in Arm B ($p = 0.049$) and the median duration of response was 8.5 and 19.2 mo, respectively ($p = 0.0013$). Nine partial responses were observed in Arm A, and three complete and 14 partial responses were observed in Arm B (17.6% vs 34.0%; $p = 0.058$); 24 and 21 patients (47% and 42%), respectively, achieved stable disease. The most common grade 3–4 toxicities were fatigue plus asthenia (28% vs 16%; $p = 0.32$) and hand-foot skin reactions (20% vs 18%).
Conclusions: Sorafenib plus frequent low-dose IFN showed good efficacy and tolerability. Further investigations should be warranted to identify a possible positioning of this intriguing regimen (6% complete response rate) in the treatment scenario of mRCC.

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0302-2838/$ – see back matter
http://dx.doi.org/10.1016/j.eururo.2012.08.027

1. Introduction

The mainstay of medical treatment of metastatic renal cell carcinoma (mRCC) for >20 yr has been immunotherapy, often resulting in inadequate and/or contradictory response rates and severe toxicities [1,2]. Advances in the understanding of RCC molecular biology led to the development of new anticancer agents targeted directly against cell-specific pathways at a molecular level, including gene expression, growth regulation, cell-cycle control, apoptosis, and angiogenesis. These agents proved to be effective in terms of progression-free survival (PFS) and had acceptable toxicity profiles in the clinical setting [3,4].

Drug combination strategies were then developed to improve the inhibition of a single pathway (vertical blockade) or to hamper different pathways (horizontal blockade), in view of increased efficacy and reduced toxicity [5]. In this regard, the combination of interferon (IFN) with the targeted agent sorafenib, a Raf-kinase and vascular endothelial growth factor receptor 2 (VEGFR-2) inhibitor whose activity as a single agent has been widely documented in mRCC [3,6], appeared worthy of further investigation.

IFN-alpha is a pleiotropic molecule endowed with antiangiogenic activity: Early in vitro studies showed that IFN downregulates basic fibroblast growth factor expression in human cancer cells [7], and experimental studies in mice demonstrated that this antiangiogenic effect is optimal at frequent low doses, whereas it declines at higher doses [8]. The existence of schedule-dependent antiangiogenic activity of IFN, with possible increased activity when IFN is used at low frequent doses as compared with standard doses, was subsequently confirmed in humans by Judah Folkman, a pioneer in angiogenic studies [9]. With regard to advanced RCC, the combination of sorafenib plus IFN has previously been explored in experimental and phase 1 and 2 clinical studies using standard doses of IFN, demonstrating that this combination is effective and adequately tolerated [10–13]. The aim of the current study was to evaluate the efficacy and safety of two regimens consisting of sorafenib combined with either standard doses or frequent low doses of IFN.

2. Patients and methods

This was in a single-stage, prospective, noncomparative, randomized, open-label, multicenter, phase 2, pick-the-winner trial [14]. The primary end points were PFS and safety. The main secondary end points were overall response rate, duration of response, and overall survival (OS). The study planned to enroll 100 patients over 18 mo in 11 centers located throughout Italy.

Eligible patients were aged ≥18 yr, had histologically or cytologically confirmed metastatic clear cell RCC with a clear cell component of ≥50%, measurable disease (at least one unidimensional lesion detected by computed tomography [CT] scan or magnetic resonance imaging [MRI]) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 criteria [15], life expectancy ≥3 mo, Eastern Cooperative Oncology Group (ECOG) performance status ≤2, baseline absolute neutrophil count $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l, hemoglobin values ≥10 g/dl, serum creatinine ≤2.0 times the upper limit of normal (ULN), total bilirubin ≤1.5 times ULN, and alanine aminotransferase or aspartate aminotransferase ≤2.5 times ULN (≤5.0 times ULN in the presence of liver metastases). All patients had undergone previous nephrectomy and none had been previously treated with any type of systemic therapy for metastatic disease.

Exclusion criteria were the following: history of brain metastases; concomitant important illnesses or medical conditions, such as serious respiratory or cardiovascular diseases, unstable diabetes mellitus, serious bacterial or fungal infections, and potentially life-threatening autoimmune disorders; pregnancy or breastfeeding (both women and men of reproductive potential must have agreed to use adequate barriers for birth control); and other prior malignancies, with the exception of adequately treated basal or squamous cell skin cancer or in situ cervical cancer. Following protocol approval by the ethical committees of each institution, each patient signed the written informed consent at the time of enrollment. Patient enrollment began in January 2006 and no clinical trial registration was needed. However, this study was registered in the Italian Health's Institute Study Registry with the number 0861.

Patients were randomly allocated to receive two 200 mg sorafenib tablets twice daily continuously combined with subcutaneous IFN at doses of either 9.0 million units (MU) three times a week (Arm A) or 3.0 MU five times a week (Arm B). The randomization list was generated according to random permuted blocks stratified by center, using a validated SAS program (SAS Institute Inc, Cary, NC, USA). Other stratification criteria were not applied. To increase patients' compliance, IFN administration could be initiated at lower doses (eg, 3.0 MU three times a week for Arm A, 1.5 MU five times a week for Arm B) provided that full doses would be achieved within the first 2 wk of treatment. Treatment was continued until tumor progression, symptomatic deterioration, or the onset of unacceptable toxicity requiring drug discontinuation and patient's withdrawal from the study. Each 4-wk (28-d) treatment period was considered one cycle.

Toxicity was assessed using the US National Cancer Institute Common Toxicity Criteria v.3.0. If grade 3–4 toxicity occurred that was probably correlated to sorafenib, treatment was discontinued temporarily, then continued at a reduced sorafenib dose of 600 mg once daily. If further dose reductions were required, doses of 400 mg or 200 mg once a day were applied. In the event of no recovery to grades 0–1 after a 2-wk discontinuation period, treatment with sorafenib was discontinued. If grade 3–4 toxicity probably correlated to IFN, the drug was initially reduced to 6.0 MU three times a week in Arm A and to 1.5 MU five times a week in Arm B. If required, 3.0 MU three times weekly in Arm A and 1.5 MU three times weekly in Arm B were applied. If no recovery to grades 0–1 was observed after 2 wk at reduced doses, IFN was discontinued. Patients who discontinued one drug during the study because of specific toxicities could, at the investigator's discretion, continue treatment with the other drug or withdraw from the study.

RECIST criteria 1.0 were used to assess response [15]. Tumor measurements were carried out by CT scan or MRI within the last 10 d of the third cycle and then every 12 wk. All evidence of complete and partial responses and of stable disease had to be confirmed 4 wk apart.

All clinical and instrumental variables and toxicity data were analyzed by usual descriptive statistics: mean, standard deviation, minimum and maximum values for continuous variables, and absolute and relative frequencies for categorical variables. All comparisons between groups were performed in an explorative fashion.

Both PFS and OS were calculated using the Kaplan-Meier method in the Statistical Package for the Social Sciences (SPSS) v.15.0 (IBM Corp., Armonk, NY, USA) [16]. PFS was defined from the date of the first dose of sorafenib to death from any cause or disease progression. Duration of response was defined from the date of response to disease progression in responding patients. OS was defined from the date of the first dose of sorafenib to death from any cause. The number of patients to be accrued was calculated by hypothesizing a median PFS treatment period of 6 mo for Arm A with a hazard ratio of 1.5 between the worst and best arm.

Taking into consideration $\alpha = 0.05$ and $\beta = 0.20$ (Dupont design) [17] and assuming an accrual period of 18 mo, a total of 100 patients (50 in each arm, including five withdrawals per arm) was set as the accrual total. All efficacy data deriving from the study were evaluated and reported according to an intent-to-treat analysis (ITT).

3. Results

From January 2006 to March 2007, 102 patients from 11 Italian centers were enrolled. Of these, one patient was ineligible because of multiple inclusion-criteria violations, and 101 patients (51 in Arm A and 50 in Arm B) were considered suitable for evaluation (ITT analysis) (Fig. 1). Main, baseline, patient characteristics are reported in Table 1. Treatment groups were reasonably well matched; however, at baseline, fewer patients in Arm A versus Arm B had an ECOG performance status of 0 (31 vs 39), more had an ECOG performance status of 2 (3 vs 0), and more had a *poor* Memorial Sloan-Kettering Cancer Center score (13 vs 5). The median numbers of cycles of sorafenib and IFN singularly administered in each experimental arm were as follows: Arm A, nine cycles of sorafenib (range: 1–38) and eight cycles of IFN (range: 1–26); Arm B, 10.5 cycles of sorafenib (range: 1–32) and 10 cycles of IFN (1–28).

Overall, confirmed objective responses were achieved in 26 patients: 9 of 51 patients in Arm A and 17 of 50 patients in Arm B (17.6% vs 34%; $p = 0.058$), while 24 (47%) and 21 (42%) patients, respectively, showed stable disease, resulting in an overall disease-control rate (or clinical benefit) of 65% for Arm A and 76% for Arm B ($p = 0.21$). Of note, 3 of the 17 responses (6%) in Arm B were confirmed complete responses (CR). As shown in Figure 2, the median duration of confirmed responses was 8.5 mo for Arm A (95% confidence interval [CI], 4.1–18.6) and 19.2 mo for Arm B (95% CI, 7.9–32.9) ($p = 0.0013$). The median PFS (Fig. 3) was

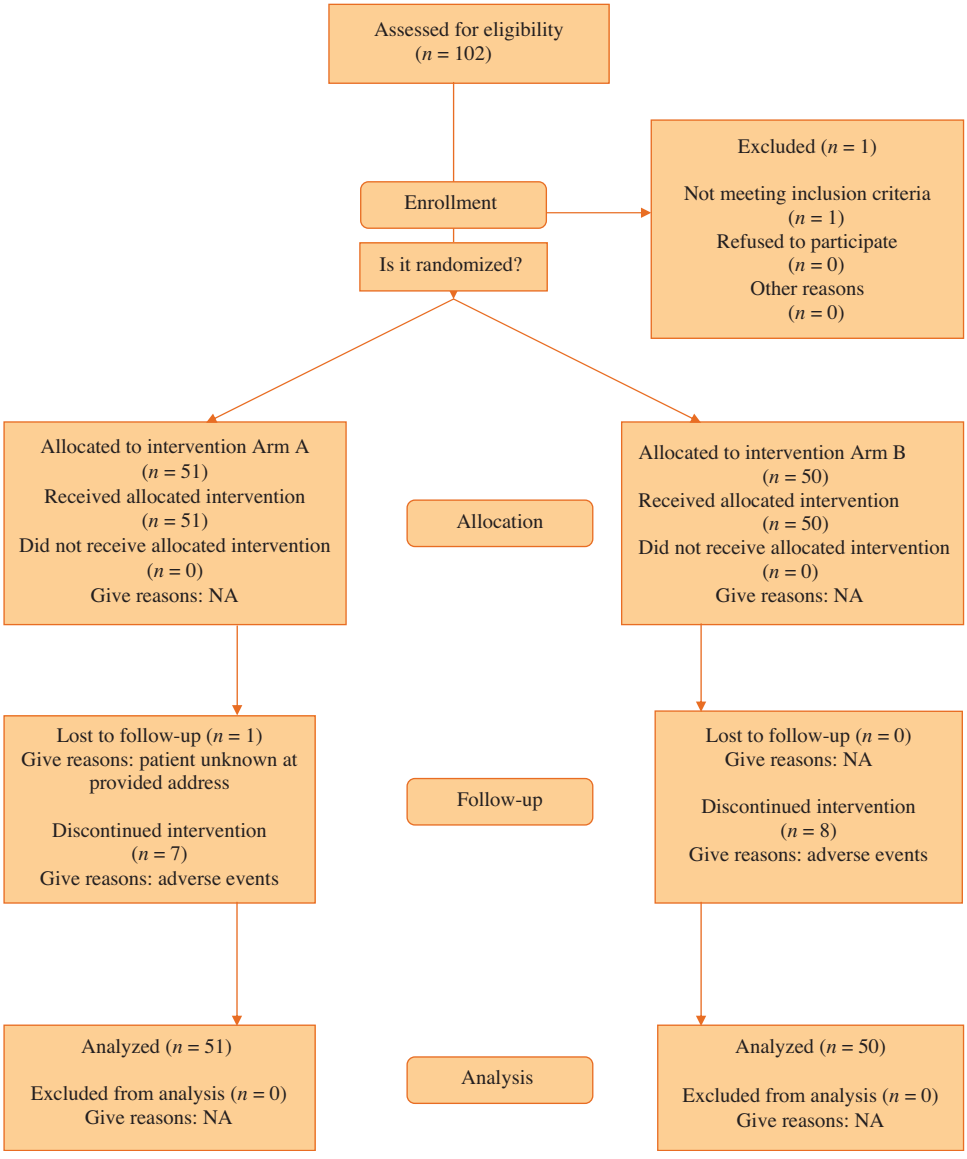

Fig. 1 – RAPSODY: the Consolidated Standards of Reporting Trials e-flowchart. NA = not applicable.

Table 1 – Baseline patient characteristics in the two treatment arms

Characteristic	Treatment arm	
	Sorafenib + HD IFN (n = 51)	Sorafenib + LD IFN (n = 50)
Age, yr		
Median	64.0	64.0
Range	34.0–79.0	39.0–82.0
Sex, no. (%)		
Male	34 (66.7)	38 (76.0)
Female	17 (33.3)	12 (24.0)
ECOG performance status, no. (%)		
0	31 (61.0)	39 (78.0)
1	17 (33.0)	11 (22.0)
2	3 (6.0)	0 (0.0)
MSKCC score, no. (%)		
Favorable	7 (13.7)	10 (20.0)
Intermediate	31 (60.8)	35 (70.0)
Poor	13 (25.5)	5 (10.0)
Prior radiotherapy, no. (%)	5 (9.8)	6 (12.0)
Disease-free interval ≤1 yr, no. (%)	32 (62.8)	27 (54.0)
Metastatic sites*, no. (%)		
1	4 (8.2)	4 (8.2)
>1	45 (91.8)	45 (91.8)
Metastatic sites, no. (%)		
Lung	76 (34.9)	77 (36.0)
Lymph node	46 (21.0)	49 (22.9)
Liver	22 (10.1)	18 (8.4)
Bone	20 (9.2)	33 (15.4)
Other	54 (24.8)	37 (17.3)

HD = high dose; LD = low dose; IFN = interferon; ECOG = Eastern Cooperative Oncology Group; MSKCC = Memorial Sloan-Kettering Cancer Center.
* Information missing for three patients.

7.9 mo in Arm A (95% CI, 5.1–10.9) and 8.6 mo in Arm B (95% CI, 2.2–15.1), (log-rank, p = 0.049) with an actual OS (Fig. 4) of 20.3 mo (95% CI, 20.5–32.4) versus 19.4 mo (95% CI, 23.4–36.8) (log-rank, p = not significant).

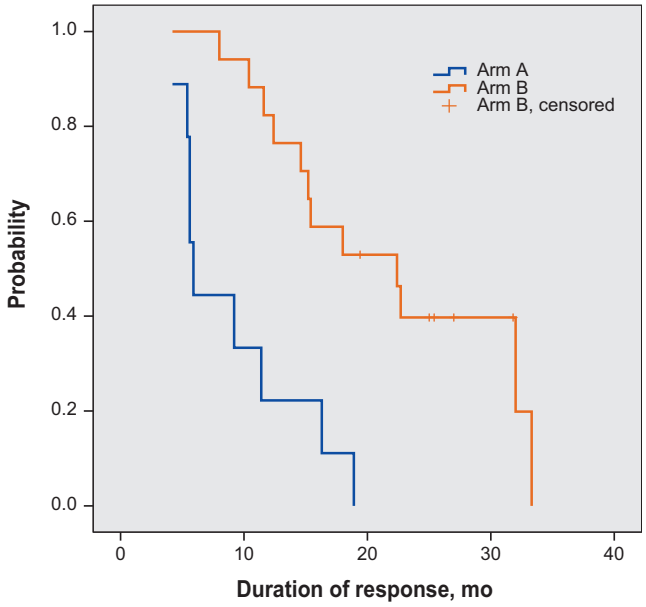

Fig. 2 – Median duration of response.

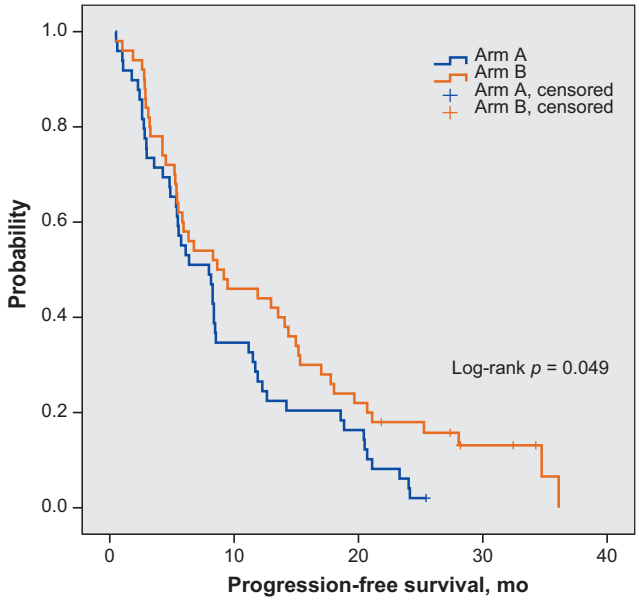

Fig. 3 – Median progression-free survival.

With regard to toxicity, 1188 events of any grade (539 in Arm A and 649 in Arm B) were recorded during the study (Table 2). Of these, only 173 were grade 3–4 events (88 in Arm A and 85 in Arm B; p = 0.71). The most common treatment-related grade 3–4 toxicity observed in both arms was fatigue plus asthenia, with lower incidence in the frequent low-dose IFN schedule (28% vs 16%; p = 0.32). Other reported grade 3–4 side effects were hypophosphatemia (17% vs 21%), hand-foot skin reaction or skin rash (14% vs 13%), diarrhea (6% vs 10.%), leukopenia (5% vs 3%), and thrombocytopenia (5% vs 0%). Dose reductions were applied in 41 cases in Arm A and in 39 cases in Arm B, and treatment discontinuation due to adverse events occurred in 7 and 8 cases, respectively.

4. Discussion

Our results confirmed that the combination of sorafenib with IFN is highly active in the treatment of mRCC in a nonstrictly selected population (eg, ECOG performance status 0-2 vs 0-1 in many other trials). Indeed, the results achieved in both treatment groups showed consistent PFS values, 7.9 mo in Arm A and 8.6 mo in Arm B, in agreement with studies comparing the combination sorafenib plus IFN with sorafenib alone (PFS 8.5 vs 5.5 mo) [11–13,18].

The response rate was higher in Arm B, with a trend towards a statistical significance (34% vs 17.6%; p = 0.058) and three confirmed CRs, two of which were long term (one 36 mo and the other on course at the time of this article), were observed in Arm B versus none (one unconfirmed CR) in Arm A. Duration of response was significantly higher in Arm B, suggesting that patients who achieve an objective response (CR plus partial response with the sorafenib plus frequent low-dose IFN combination (one-third of the sample) may derive substantial benefits in terms of

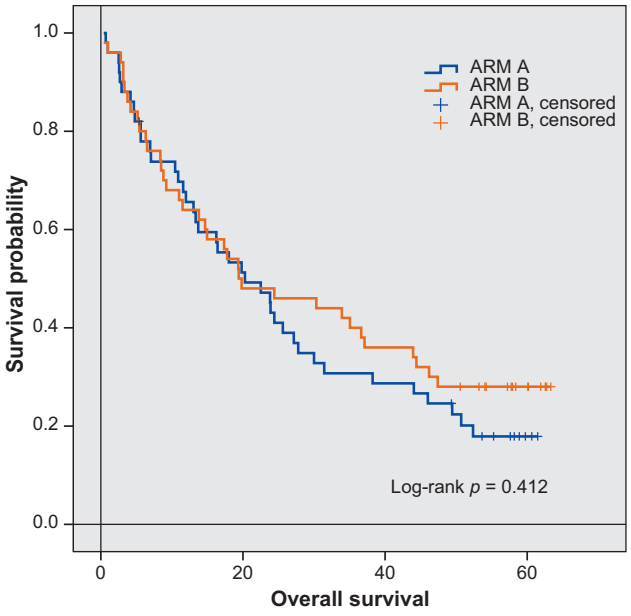

Fig. 4 – Median overall survival.

extended disease control with respect to patients simply achieving a stable disease. However, the advantage in terms of median PFS reported in Arm B was less pronounced (+0.7 mo vs Arm A). This discrepancy might be attributed, at least in part, to the fact that the number of patients who experience an objective response is too low to generate a marked effect on PFS in the global population. We can speculate, therefore, that the sorafenib plus frequent low-dose IFN regimen may exert an improved antiangiogenic activity in some specific subpopulations of patients. The potential identification of these subpopulations was not a goal of our study and might deserve investigation in future trials. No differences were observed between the two treatment groups for OS.

We paid a particular attention to safety issues, with continuous monitoring for adverse events: Data suggest that safety is increased by frequent administration of IFN as IFN-related adverse events were less frequent in Arm B than in Arm A, although not significantly. The reported cumulative incidence of grade 3–4 fatigue and asthenia was rather high in both arms (although 50% lower in Arm B). The possible onset of these conditions should be taken into account when planning further studies on the tested, or similar, combinations.

A major limitation of the study is lack of definitive evidence for the choice of the IFN dose and schedule. However, we have based our decision for IFN doses and schedule on previous studies, using them as a guide to define a range of IFN dosages that could potentially be associated with a favorable safety/efficacy ratio. The combination of sorafenib and IFN was initially tested in a phase 1 dose-finding study by Escudier [11], with suggested doses for phase 2 studies being 400 mg twice daily for sorafenib and 9 MU three times a week for IFN. In this dose-finding study, however, IFN was initiated at the dose of 6 MU three times a week, which did not allow for evaluation of the activity and safety of lower doses—possibly the most interesting from an antiangiogenic point of view as suggested by Folkman et al. [9,19]. Based on these data, two, single-arm, phase 2 studies were conducted, both of which showed a significant improvement in response rates and median PFS as compared with the pivotal, second-line, phase 3 trial with sorafenib alone [3,12,13] and the recently published first-line, randomized, phase 2 trial with sorafenib versus IFN [18]. However, both of these single-arm studies showed a relevant increase in toxicity, highlighting the difficulty of using this combination in clinical practice [20]. This prompted Brian Rini to suggest the need for controlled studies to verify the results [21].

An inverse approach was employed by the MD Anderson Group, which investigated sorafenib alone versus a

Table 2 – Drug-related adverse events

Adverse event	Adverse event grade by treatment arm							
	Sorafenib + HD INF				Sorafenib + LD INF			
	Any grade		Grade ≥3		Any grade		Grade ≥3	
	No.	%	No.	%	No.	%	No.	%
Fatigue and asthenia	34	68	14	28	39	76	8	16
Anorexia	24	48	5	10	22	43	7	14
Anemia	19	38	3	6	19	37	2	4
Amylase	13	26	3	6	14	27	4	8
Diarrhea	26	52	5	10	33	65	9	18
Hypophosphatemia	16	32	11	22	15	29	10	20
Rash	30	60	8	16	24	47	7	14
Leukopenia	13	26	4	8	12	23	2	4
Piastrinopenia	20	40	3	6	14	27	0	0
Fever	22	44	3	6	12	23	2	4
Neutropenia	10	20	6	12	10	20	4	8
Lipase elevation	12	24	3	6	11	22	2	4
Hand-foot skin reaction	22	44	10	20	23	45	9	18
Stomatitis	12	24	4	8	15	29	4	8

HD = high dose; LD = low dose; IFN = interferon.

combination of sorafenib with very-low-dose IFN (0.5 MU twice daily) in a randomized phase 2 study. Results of the study, as presented by Jonasch et al. at the American Society of Clinical Oncology (ASCO) annual meeting of 2007 [22], updated by Tannir et al. at ASCO 2008 [23], and recently published [24], were disappointing for this combination, with an increased and unexpected high response rate in patients treated with sorafenib alone and without any evident advantage for patients in the combination arm. A possible interpretation of these data is that the selected dosage of IFN was suboptimal. If IFN truly acts as an antiangiogenic agent at frequent low doses, a range of active dosages needs to be identified and a lower cut-off point should exist. As such, and notwithstanding the encouraging results we achieved in the current study, we believe that the optimal dose of IFN and optimal schedule of administration still need to be identified.

We acknowledge further limitations. Patient sample sizes were relatively small; the low number of patients enrolled did not allow the stratification of patients at randomization for any factor, with the exception of stratification by the enrollment center. In addition, the differences in disease status between patients in Arm A and Arm B at baseline may have had a major impact on the results. We cannot rule out, in fact, that the more favorable prognostic factors reported in arm B could explain, at least in part, the enhanced efficacy of sorafenib with frequent low-dose IFN observed in this treatment group. We also acknowledge that the results were not corrected by any baseline parameter.

Despite these limitations, at the present time and to the best of our knowledge, this study is unique compared to previous trials in verifying the potential advantages and pitfalls of two schedules of sorafenib plus IFN with a randomized pick-the-winner design. This design is useful in phase 2 clinical development, especially when there are uncertainties regarding the dose levels, as in our case [14]. The combination of sorafenib plus frequent low-dose IFN confirms the possibility of a clinically relevant disease control rate in mRCC, along with the possibility of achieving CRs—a rare entity in this disease—and a long duration of response. Last, but not least, this combination has an acceptable safety profile because of a reduced incidence of IFN-related high-grade toxicities. While the exact mechanism of the antiangiogenic action of IFN still needs clarification, according to the findings reported in this study the sorafenib plus frequent low-dose IFN combination may deserve further assessment in randomized, phase 3, comparative, clinical trials.

These results, however, should be considered in the context of the continuously changing treatment scenario of mRCC. For instance, pegylated IFNs present comparable efficacy and safety in the treatment of mRCC compared with standard IFN, with the advantage of a weekly administration [25]. Therefore, we speculate that the use of pegylated IFN in combination with a targeted therapy might deserve investigation. In addition, anti-VEGF agents other than sorafenib can be tested in combination with the frequent low-dose IFN regimen, thanks to their pharmacologic properties and therapeutic efficacy. The combination of bevacizumab with IFN has shown efficacy in the first-line treatment of mRCC [26,27], and this finding was confirmed when bevacizumab was combined with low-dose IFN [28]. Sunitinib has a superior potency compared with sorafenib, is associated with a high rate of CR [29], and the use of this drug in clinical practice is well-established [30]. Unlike sorafenib [31], sunitinib can improve type 1 T-cell cytokine response in mRCC patients while reducing function of regulatory T cells [32], and can promote tumor infiltration by lymphocytes [33]. Thanks to these immunomodulating properties, a rationale for the combination of sunitinib and IFN might exist. However, the initial clinical results obtained in mRCC patients treated with this combination did not reveal a favorable safety profile [34]. Pazopanib presents a marked efficacy in the treatment of mRCC [35], and a recent meta-analysis has suggested that this molecule may be a suitable first-line option in mRCC patients, although a direct comparison with other tyrosine kinase inhibitors is still awaited [36]. In addition, new and more potent second-generation tyrosine kinase inhibitors, like tivozanib or axitinib, were introduced to the pharmacologic armamentarium for mRCC after the completion of our study. These molecules showed very promising results in RCC patients [37,38], and their combination with the frequent low-dose IFN regimen suggested by our study might be worth investigation. The potential immunomodulating properties of these agents should also be investigated. Last, recent clinical results also support the use of antibody-mediated blockade of programmed cell-death ligand 1 to induced durable tumor regression and prolonged stabilization of disease in several types of solid tumors, including mRCC [39]. These agent will likely become of interest in future clinical trials in mRCC.

5. Conclusions

Sorafenib plus frequent low-dose IFN showed enhanced efficacy and tolerability in comparison with sorafenib and standard-dose IFN. Therefore, further investigations should be warranted to compare this intriguing regimen (6% CR rate) with other treatments for mRCC and to identify its possible positioning in the treatment scenario of this disease. Alternatively, frequent low-dose IFN, or pegylated IFN, may be tested in combination with other available anti-VEGF agents for the treatment of mRCC.

Author contributions: Sergio Bracarda had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Bracarda.
Acquisition of data: Bracarda, Porta, Boni, Santoro, Mucciarini, Pazzola, Cortesi, Gasparro, Labianca, Di Costanzo, Falcone, Caserta, Paglino.
Analysis and interpretation of data: Cinquini, De Angelis.
Drafting of the manuscript: Bracarda.
Critical revision of the manuscript for important intellectual content: Bracarda, Caserta.
Statistical analysis: Cinquini, De Angelis.

Obtaining funding: Bracarda, Boni.
Administrative, technical, or material support: Bracarda.
Supervision: Bracarda.
Other (specify): None.

Financial disclosures: Sergio Bracarda certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Sergio Bracarda has received honoraria from Novaris and served as a board member of Pfizer, Bayer-Schering Pharma, Novartis, GSK, and Aveo/Astellas. Camillo Porta has received honoraria from Pfizer, Roche, Novartis, Bayer-Schering Pharma, and Wyeth; and served as a board member of Pfizer, Bayer-Schering Pharma, Roche, Novartis, GSK, and Aveo/Astellas. Corrado Boni, Armando Santoro, and Enrico Cortesi have served as board members of Bayer-Schering Pharma. Chiara Paglino has received honoraria from Bayer-Schering Pharma.

Funding/Support and role of the sponsor: The Italian Oncology Group for Clinical Research (GOIRC) received an unrestricted grant by Bayer Pharmaceuticals S.p.A to partially support the study. Editorial assistance was provided by Content Ed Net and Luca Giacomelli, PhD. This activity was funded by Bayer Pharmaceuticals S.p.A.

Acknowledgment statement: This study was presented in part at the 43rd Annual Meeting of the American Society of Clinical Oncology, June 1–5, 2007, Chicago, IL, USA, and at the 2008 ASCO Genitourinary Symposium, February 14–16, 2008, San Francisco, CA, USA. The following authors participated in the RAPSODY Study Group: Marta Rossi and Alketa Hamzaj in Perugia, Italy; Ilaria Imarisio in Pavia, Italy; Ermanno Rondini in Reggio Emilia, Italy; Fabio De Vincenzo in Milan, Italy; and Caterina Messina in Bergamo, Italy.

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