Temsirolimus and bevacizumab, or sunitinib, or interferon alfa and bevacizumab for patients with advanced renal cell carcinoma (TORAVA): a randomised phase 2 trial

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Summary

Background Combining targeted treatments for renal cell carcinoma has been suggested as a possible method to improve treatment efficacy. We aimed to assess the potential synergistic or additive effect of the combination of bevacizumab, directed against the VEGF receptor, and temsirolimus, an mTOR inhibitor, in metastatic renal cell carcinoma.

Methods TORAVA was an open-label, multicentre randomised phase 2 study undertaken in 24 centres in France. Patients aged 18 years or older who had untreated metastatic renal cell carcinoma were randomly assigned (2:1:1) to receive the combination of bevacizumab (10 mg/kg every 2 weeks) and temsirolimus (25 mg weekly; group A), or one of the standard treatments: sunitinib (50 mg/day for 4 weeks followed by 2 weeks off; group B), or the combination of interferon alfa (9 mIU three times per week) and bevacizumab (10 mg/kg every 2 weeks; group C). Randomisation was done centrally and independently from other study procedures with computer-generated permuted blocks of four and eight patients stratified by participating centre and Eastern Cooperative Oncology Group performance status. The primary endpoint was progression-free survival (PFS) at 48 weeks (four follow-up CT scans), which was expected to be above 50% in group A. Analysis was by intention to treat. The study is ongoing for long-term overall survival. This study is registered with ClinicalTrials.gov, number NCT00619268.

Findings Between March 3, 2008 and May 6, 2009, 171 patients were randomly assigned: 88 to the experimental group (group A), 42 to group B, and 41 to group C. PFS at 48 weeks was 29·5% (26 of 88 patients, 95% CI 20·0–39·1) in group A, 35·7% (15 of 42, 21·2–50·2) in group B, and 61·0% (25 of 41, 46·0–75·9) in group C. Median PFS was 8·2 months (95% CI 7·0–9·6) in group A, 8·2 months (5·5–11·7) in group B, and 16·8 months (6·0–26·0) in group C. 45 (51%) of 88 patients in group A stopped treatment for reasons other than progression compared with five (12%) of 42 in group B and 15 (38%) of 40 in group C. Grade 3 or worse adverse events were reported in 68 (77%) of 88 patients in group A versus 25 (60%) of 42 in group B and 28 (70%) of 40 in group C. Serious adverse events were reported in 39 (44%) of 88, 13 (31%) of 42, and 18 (45%) of 40 patients in groups A, B, and C, respectively.

Interpretation The toxicity of the temsirolimus and bevacizumab combination was much higher than anticipated and limited treatment continuation over time. Clinical activity was low compared with the benefit expected from sequential use of each targeted therapy. This combination cannot be recommended for first-line treatment in patients with metastatic renal cell carcinoma.

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Introduction

The standard of care for renal cell carcinoma has evolved rapidly with the approval of six targeted therapies by the US Food and Drug Administration and European Medicines Agency since 2006. All these new treatments, to different amounts, aim to block the activity of VEGF,[1] which has neoangiogenic effects on tumour endothelial cells and is also a major tumour growth factor for renal cell carcinoma.[2,3] Some drugs, such as the anti-VEGF antibody bevacizumab or tyrosine kinase inhibitors that block VEGF receptors (sorafenib, sunitinib, and pazopanib), act directly on VEGF; others are mainly mTOR inhibitors (temsirolimus and everolimus), with indirect effects on the VEGF pathway.[4–9] All of these six approved targeted drugs have been shown to be better than placebo or interferon alfa in terms of progression-free survival (PFS), and one (temsirolimus) has shown a gain in overall survival.[8] Because of limited cross-resistance between drugs, some patients are eligible for a second-line treatment.[10,11] Survival of these patients before targeted therapies were available was not more than 18 months in the most selective studies, whereas median overall survival in the main first-line treatment trials is now more than 23 months.[12]

Despite these improvements in survival with targeted treatment, most patients eventually become resistant to treatment after 6 months to 3 years of disease control and ultimately die from the disease. Better treatment strategies are thus needed. A potential benefit from

combinations of the newly approved drugs has been suggested on the biological rationale that they have different targets or different mechanisms of action aimed at different malignant processes. As a consequence, phase 1 trials have assessed the tolerance of combination therapies, but because of dose-limiting toxicities, some combinations, such as temsirolimus and sunitinib,[13] and bevacizumab and sunitinib,[14] had to be stopped early.[15] Nevertheless, the combination of bevacizumab with an mTOR inhibitor, either temsirolimus or everolimus, was tolerable at the maximum doses available on label and showed good response rates in phase 1–2 trials.[16–18]

The combination of bevacizumab and temsirolimus should inhibit separate pathways critical to the survival of the tumour. The combined treatment regimen could thus represent a means to achieve a larger proportion of complete responses, which represents a first step toward a putative eradication of the disease.[19] We therefore undertook the TORAVA trial to assess the potential synergistic or additive efficacy and long-term tolerance of the combination of temsirolimus and bevacizumab for first-line treatment of patients with metastatic renal cell carcinoma.

Methods

Patients

TORAVA was an open-label multicentre randomised phase 2 trial. We included patients from 24 centres in France. Patients aged 18 years or older who had histologically proven metastatic renal cell carcinoma of any subtype except papillary carcinomas (which were investigated in a concomitant specific trial; ClinicalTrials.gov number NCT00541008); an Eastern Cooperative Oncology Group (ECOG) performance status score of two or less; no brain metastases; measurable metastases (Response Evaluation Criteria In Solid Tumors [RECIST] criteria[20]); liver, renal, and haematological functions in the range of 1·5 to two times above or below normal values; normal lipid and glycaemic concentrations; normal cardiac function within 6 weeks before randomisation; and no hypertension were included. Other inclusion criteria were no systemic treatment for the disease and no history of arterial or venous thrombosis in the past 6 months.

This trial was approved by the local ethics committee according to French laws and followed good clinical practice guidelines. All patients gave written informed consent before enrolment.

Randomisation and masking

Initially, we designed a single-arm phase 2 trial, but because few results from controlled trials of the two standard treatment regimens were available at the time, we finally decided to add two control groups. These control groups ensured that the experimental treatment was not done in a selection-biased population.

Patients were randomly assigned (2:1:1) to the experimental combination of temsirolimus and bevacizumab (group A) or one of the standard treatment regimens: sunitinib (group B) or interferon alfa plus bevacizumab (group C). This randomisation ratio was chosen because the control treatments had already been studied in depth. Randomisation was done centrally, so that the next treatment could not be known in advance, via a computer-generated system with permuted blocks

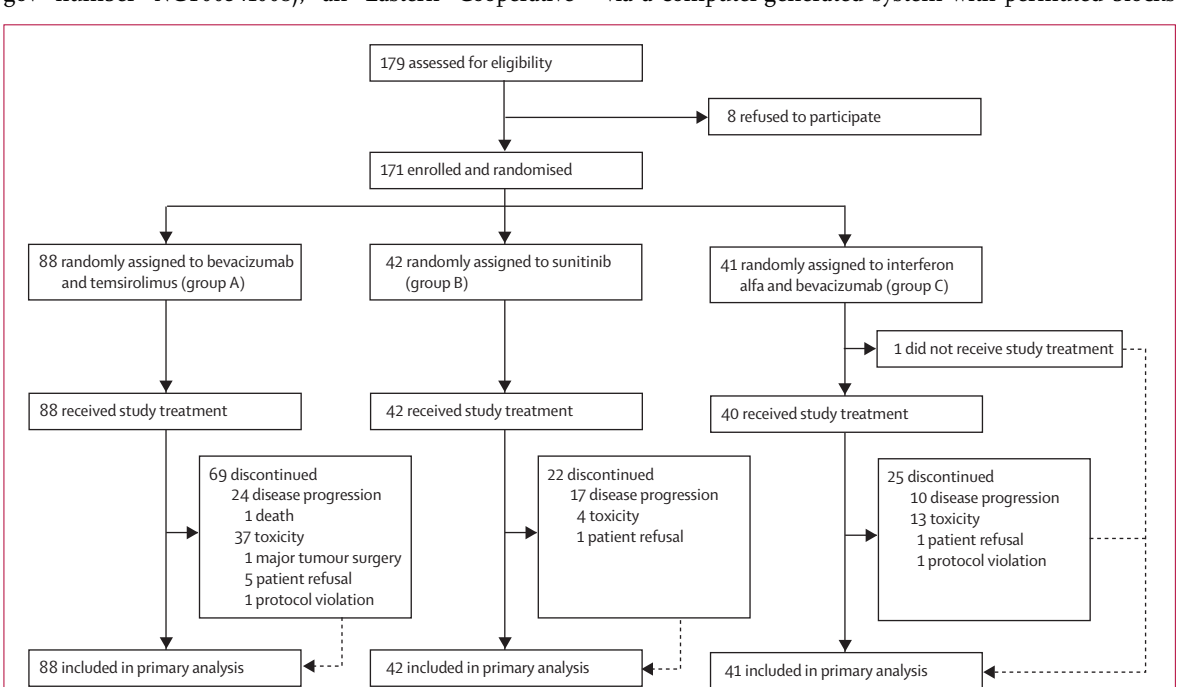

Figure 1: **Trial profile**

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of four and eight patients. Stratification was done by participating centre and performance status (ECOG performance status 0 or 1 *vs* 2). The allocation list was generated by a statistician from the coordination centre (Biostatistics Unit, Centre Léon Bérard, Lyon) who was not involved in study data analysis. Investigators applied to the website for treatment allocation. All patients and investigators were unmasked to treatment allocation.

Procedures

Patients in group A received intravenous temsirolimus (Wyeth Pharmaceuticals, Paris, France) 25 mg weekly and intravenous bevacizumab (Roche, Neuilly, France) 10 mg/kg every 2 weeks; doses were chosen on the basis of satisfactory results of a previous phase 1 trial.[16] Patients in group B received oral sunitinib (Pfizer, Paris, France) at doses previously reported (50 mg/day for 4 weeks followed by 2 weeks off).[5] Patients in group C received intravenous bevacizumab (Roche) and subcutaneous interferon alfa (Roche), at doses previously reported (10 mg/kg every 2 weeks for bevacizumab and 9 mIU three times per week for interferon alfa).[7] All treatments were continued until disease progression, unacceptable toxicity, or protocol violation.

The baseline tumour work-up included thoracic, abdominal, and pelvic CT scan, brain MRI or CT scan, and bone scan. Tumours were assessed at baseline and then every 12 weeks until progression during the first year, and then every 3 months thereafter. Patients who discontinued study treatment were assessed until progression. Further treatments were recorded, whatever the randomisation group. All imaging documents were centrally reviewed by an independent assessment committee masked to treatment allocation.

The primary endpoint was 48-week PFS (four follow-up CT scans) according to RECIST (version 1.0) guidelines.[20] This endpoint was chosen because: (1) tumour response has failed to predict survival benefit in renal cancer;[21] (2) PFS is the preferred endpoint for phase 2 trials of targeted drugs;[22] and (3) the main limitation of PFS for a randomised phase 2 design—the need for larger samples[23]—can be overcome by using PFS at a pre-specified timepoint as the primary endpoint.[24] Secondary endpoints were the rate and duration of objective responses, the rates of PFS and overall survival, and the tolerance profile of each regimen.

Dose modifications were made by the treating physician on the basis of adverse events or laboratory abnormalities. Temsirolimus could be reduced from 25 mg to 15 mg by 5 mg decrements (ie, to 20 mg and then 15 mg weekly); no dose reduction was allowed for bevacizumab but one injection could be skipped. Consistent with the primary objective, more than a 1-month interruption of one or both drugs in group A was classified as a treatment failure. Two levels of dose reduction were permitted for groups B and C. Sunitinib dose reductions by 12·5 mg decrements (ie, to 37·5 and 25 mg/day) to a minimum of 25 mg/day and interferon alfa by 3 mIU decrements to a minimum of 3 mIU were allowed.

	Group A (n=88)*	Group B (n=42)†	Group C (n=41)‡
Age (years)	62·0 (33–83)	61·2 (33–83)	61·9 (40–79)
Sex (male)	65 (74%)	32 (76%)	27 (66%)
ECOG PS			
0 or 1	77 (88%)	37 (88%)	36 (88%)
2	11 (13%)	5 (12%)	5 (12%)
History of hypertension	42 (48%)	20 (48%)	20 (49%)
Clear-cell carcinoma	84 (95%)	40 (95%)	40 (98%)
>1 metastatic site	48 (55%)	22 (52%)	20 (49%)
Hepatic metastases	5 (6%)	8 (19%)	6 (15%)
Bone metastases	23 (26%)	8 (19%)	12 (29%)
Metastasis-free interval >12 months	33 (38%)	12 (29%)	16 (39%)
Nephrectomy	73 (83%)	41 (98%)	35 (85%)
MSKCC classification§			
Good risk	25 (32%)	12 (31%)	14 (39%)
Intermediate risk	41 (53%)	23 (59%)	16 (44%)
Poor risk	11 (14%)	4 (10%)	6 (17%)

Data are median (range) or number (%). Percentages do not add up to 100 in some cases because of rounding. ECOG PS=Eastern Cooperative Oncology Group performance status. MSKCC=Memorial Sloan Kettering Cancer Center. *Bevacizumab and temsirolimus. †Sunitinib. ‡Interferon alfa and bevacizumab. §Data missing for 11 patients in group A, three in group B, and five in group C.

***Table 1*: Baseline characteristics of patients**

Patients on study medication were assessed at day 15 and then at least every 6 weeks for toxicity with the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE; version 3.0). Survival was assessed until death or end of clinical data collection.

An independent data safety monitoring committee regularly examined the severe adverse events reported and the rates of four specific grade 3 or higher events (haemorrhage; venous or arterial thromboembolism; pulmonary interstitial syndrome; and gastrointestinal perforation) that were classified as critical complications that needed intervention. Another independent committee controlled the quality of the study, especially regarding data monitoring and statistical analysis, and proposed conclusions to the investigators.

Statistical analysis

We calculated the sample size by Fleming's single stage design for phase 2 trials,[25] with the hypothesis that the temsirolimus and bevacizumab combination should result in a PFS at 48 weeks of at least 50% to be judged appropriate for further investigation. Despite more optimistic expectations from the investigators, this threshold was calculated on the basis of PFS rates of 42% (95% CI 33–51)[5] and 46% (41–51)[7] from PFS curves in previous randomised trials that used standard treatments. The upper bound of the 95% CI for PFS at 48 weeks reported in these two trials was 51%, which is close to the 50% cutoff defined as the expected minimum efficacy threshold in the experimental arm. A PFS at 48 weeks of 35% or less would mean that the

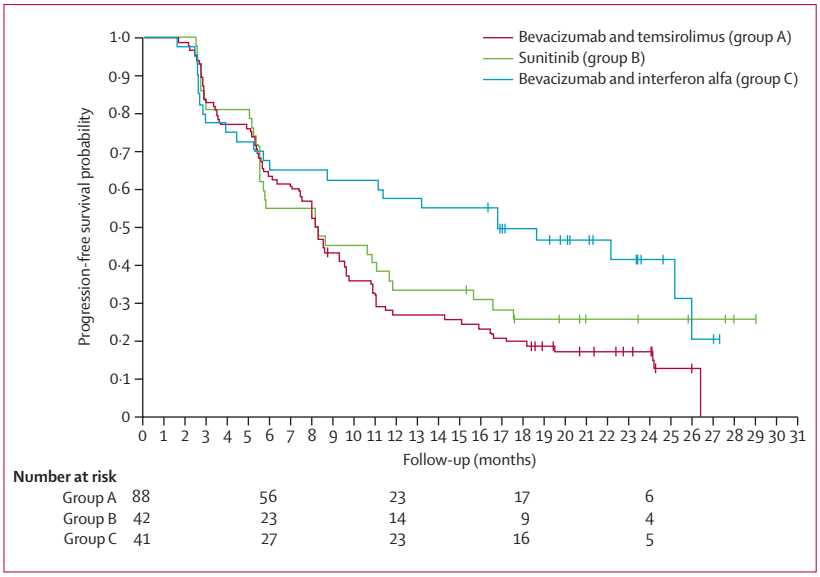

Figure 2: **Kaplan-Meier estimates of progression-free survival**
74 of 88 patients in group A, 31 of 42 in group B, and 24 of 41 in group C progressed.

	Group A (n=88)*	Group B (n=42)†	Group C (n=40)‡
Patients receiving second-line therapy	61 (69%)	20 (48%)	27 (68%)
Bevacizumab§	9 (10%)	0 (0%)	7 (18%)
Tyrosine kinase inhibitor¶	49 (56%)	16 (38%)	19 (48%)
mTOR inhibitor‖	3 (3%)	4 (10%)	1 (3%)

Data are number (%). *Bevacizumab and temsirolimus. †Sunitinib. ‡Interferon alfa and bevacizumab. §Bevacizumab with or without interferon alfa in group A; bevacizumab alone in group C. ¶Sunitinib, sorafenib, or axitinib. ‖Temsirolimus.

Table 2: **Second-line treatments after study treatment failure**

temsirolimus and bevacizumab combination did not warrant further investigation.

A sample size of 76 patients provided 85% power to reject the null hypothesis with a one-sided, type 1 error of 5%, 34 patients being the lower cutoff point of decision making.[7] To account for a non-assessable patient rate of 5%, four patients were added in the experimental arm (total 80 patients).

A sample size of 40 evaluable patients was used in control groups B and C, according to the 2:1:1 randomisation ratio. No comparative hypothesis was formulated and no statistical comparison between these two groups and the experimental arm was planned. These groups were only included to check the similarity between the enrolled patients and historical controls with respect to clinical outcome when given standard treatments.[22]

All patients who received at least one dose of the study drug were included in safety analyses. Efficacy data were analysed in the intent-to-treat population. The proportions of patients who were progression free at 48 weeks were calculated with their respective 95% CIs for the intention-to-treat population. Time to progression was calculated from data confirmed by central review by an independent committee. Response duration was the time from documented evidence of complete or partial response to progression or death. PFS duration was the time from randomisation to disease progression or death from any cause. Overall survival duration was the time from randomisation to death from any cause. Patients with no reported event at the time of analysis were censored at the date of last follow-up. PFS, overall survival, and time of exposure to study medication were estimated according to time with the Kaplan-Meier method.[26] Median follow-up was calculated by a reverse Kaplan-Meier estimate.[27] We used non-parametric methods to calculate the median duration of study treatment (Kruskal-Wallis one-way analysis of variance by ranks) or reasons for treatment interruption (Fisher's exact test) among groups. Because of the large dropout rate in the experimental arm, we did additional post-hoc analyses of treatment failures in all patients with progressive disease, whether on study treatment or not, or starting another treatment, within 48 weeks.

All analyses were done with SAS (version 9.1). This study is registered with ClinicalTrials.gov, number NCT00619268.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 3, 2008 and May 6, 2009, 171 patients were randomly assigned to group A (88 patients), group B (42 patients), or group C (41 patients; figure 1). All but one patient (group C) received the allocated treatment. Median follow-up was 23·2 months (range 2·0–29·9) at time of analysis. Table 1 shows the main patient characteristics at baseline. No significant differences were noted between groups, except for a lower percentage of patients with hepatic metastases in group A than in groups B and C and a higher percentage of patients with nephrectomy in group B than in groups A and C. We also noted some clinical differences—eg, patients in group C had less aggressive tumours (longer metastasis-free intervals) and more were in the low-risk group according to the Memorial Sloan Kettering Cancer Center (MSKCC) score[28] than those in groups A or B.

Masked central review of CT scans was done in 153 (89%) of 171 patients. Investigators' notification was used in the remaining patients for whom independent review was not possible. PFS at 48 weeks in the

experimental group was 29·5% (26 of 88 patients, 95% CI 20·0–39·1). PFS at 48 weeks was 35·7% in group B (15 of 42 patients, 95% CI 21·2–50·2) and 61·0% in group C (25 of 41, 46·0–75·9). Figure 2 shows PFS curves according to treatment group. Median PFS was 8·2 months (95% CI 7·0–9·6) in group A, 8·2 months (5·5–11·7) in group B, and 16·8 months (6·0–26·0) in group C.

Table 2 shows the second-line treatments that patients received after study treatment failure because of toxicity or progression. A greater proportion of patients in groups A and C had had second-line treatment than in group B.

The analysis on treatment administration and safety focused on the first 48 weeks. At 48 weeks, 41 patients (12 of 88 in group A, 16 of 42 in group B, and 13 of 41 in group C) were still on study treatment. The median time on treatment was shorter in the experimental group (20·5 weeks, range 0–48) than in the standard treatment groups B (41·6 weeks, 2–48) and C (28·9 weeks, 4–48; Kruskal-Wallis test p=0·020; figure 3).

Table 3 describes the reasons for early treatment interruptions and the main types of adverse events. More patients stopped treatment for other reasons than progression in group A than in groups B or C (Fisher's exact test p<0·0001). All definitive interruptions except three (major protocol violation in two patients and major tumour surgery in one patient) were deemed to be treatment related. Grade 3 or worse adverse events were reported in 68 (77%) of 88, 25 (60%) of 42, and 28 (70%) of 40 patients in groups A, B, and C, respectively. Grade 4 adverse events were reported in 11 (13%) of 88 patients in group A, one (2%) of 42 in group B, and three (8%) of 40 in group C. Serious adverse events were reported in 39 (44%) of 88, 13 (31%) of 42, and 18 (45%) of 40 patients in groups A, B and C, respectively.

Two non-disease related deaths occurred after 14 weeks of temsirolimus plus bevacizumab: one sudden death in a patient with good performance status on the day before death, and one respiratory failure. No non-disease related deaths occurred in the other groups. A high proportion of patients in group A had oral, anal, or digestive fistulas or abscesses; ten events were of at least grade 3 severity. These events were also reported, although in a smaller proportion of patients, with interferon and bevacizumab (group C; table 3).

Results of the post-hoc analyses showed that 70 of 88 patients (79·5%, 95% CI 71·1–88·0) had progressed or started another treatment within 48 weeks in group A, compared with 28 of 42 (66·7%, 52·4–80·9) in group B and 21 of 41 (51·2%, 35·9–66·5) in group C.

Table 4 shows the rates of responses to treatment. The median response duration was 7·7 months (range 0·5–23·8) in group A, versus 13·3 months (0·1–18·1) in group B and 13·9 months (2·9–23·2) in group C (Kruskal-Wallis test p=0·52). 12-month overall survival was 77% (95% CI 67–85), 74% (59–85), and 90% (77–96) in groups A, B, and C, respectively. This study is ongoing for long-term overall survival.

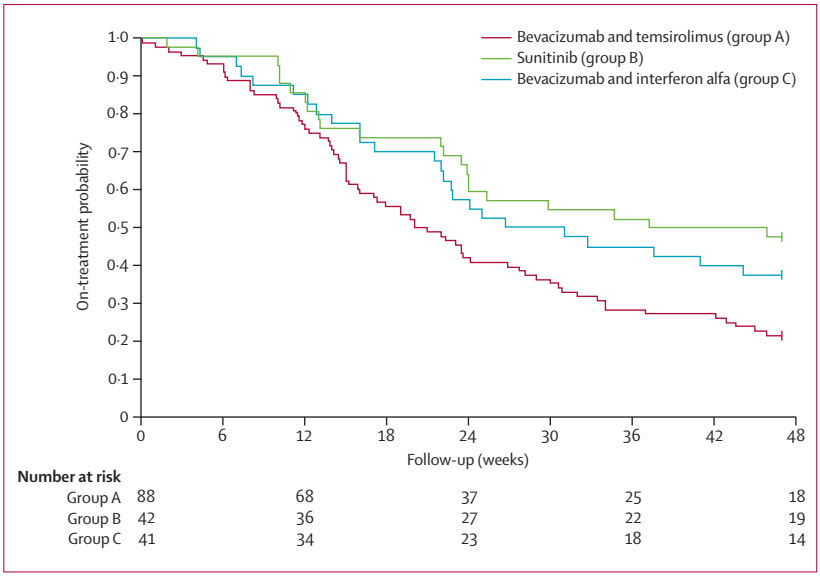

Figure 3: **Kaplan-Meier estimates of exposure to study medication**

	Group A (n=88)*	Group B (n=42)†	Group C (n=40)‡
Interruptions			
Total	45 (51%)	5 (12%)	15 (38%)
Death	1 (1%)	0 (0%)	0 (0%)
Toxicity	37 (42%)	4 (10%)	13 (33%)
Others§	7 (8%)	1 (2%)	2 (5%)
Adverse events			
Fatigue, asthenia, or malaise	67 (76%)	34 (81%)	36 (90%)
Proteinuria	36 (41%)	2 (5%)	10 (25%)
Hypertension	29 (33%)	13 (31%)	17 (43%)
Venous thromboembolism	1 (1%)	3 (7%)	1 (3%)
Gastrointestinal perforation	2 (2%)	0 (0%)	0 (0%)
Oral, anal, or digestive fistula or abscess	18 (20%)	2 (5%)	5 (13%)
Diarrhoea	29 (33%)	25 (60%)	17 (43%)
Vomiting	19 (22%)	12 (29%)	9 (23%)
Nausea	27 (31%)	14 (33%)	16 (40%)
Skin disorders	60 (68%)	27 (64%)	18 (45%)
Anaemia	10 (11%)	8 (19%)	5 (13%)
Neutropenia	4 (5%)	11 (26%)	11 (28%)
Thrombopenia	10 (11%)	8 (19%)	5 (13%)

Data are number (%). *Bevacizumab and temsirolimus. †Sunitinib. ‡Interferon alfa and bevacizumab. §Patient refusals (five in group A; one in group B; and one in group C), severe protocol violations (one in group A and one in group C), and major tumour surgery (one in group A).

Table 3: **Reasons for treatment interruption, except progression, and main types of adverse events (all grades)**

Discussion

To our knowledge, TORAVA is the first prospective randomised trial to assess a combination of registered targeted drugs in metastatic renal cell carcinoma (panel). There was no additive or synergistic effect of the combination of temsirolimus and bevacizumab, whereas the efficacy of the standard treatments was within

	Group A (n=88)*	Group B (n=42)†	Group C (n=40)‡
Best objective response	24 (27%)	12 (29%)	17 (43%)
Complete response	2 (2%)	0 (0%)	0 (0%)
Partial response	22 (25%)	12 (29%)	17 (43%)
Stable disease	46 (52%)	20 (48%)	13 (33%)
Progressive disease	15 (17%)	8 (19%)	8 (20%)

Data are number (%). *Bevacizumab and temsirolimus. †Sunitinib. ‡Interferon alfa and bevacizumab.

Table 4: **Responses to treatment**

expected ranges. In addition to poor PFS rates at 48 weeks, which were 20% below the minimum prespecified rate of 50% to conclude efficacy, the median PFS of 8·2 months was disappointing. The combination of interferon alfa and bevacizumab in phase 3 has achieved a median PFS of 8·5–10·2 months,[7,32] whereas sunitinib has a median PFS of 11 months.[5] The combination of interferon alfa and bevacizumab achieved favourable survival results, which could partly be because of a more favourable patient selection in this group and also a good long-term tolerance of this regimen. No conclusions of superiority of any group can be made because this study was not intended or powered to address this issue.

The toxicity of the experimental regimen was much higher than anticipated, with over 50% of patients unable to tolerate the combination of bevacizumab and temsirolimus over several months. The combination regimen caused more severe toxic effects than did the standard treatments. The high dropout rate could also indicate the cumulative effect of several subacute or chronic toxicities.

This dropout rate is also a result of the strict rules that were chosen by the investigators. For example, patients who skipped more than one injection of bevacizumab were deemed unable to receive the combination. Otherwise, the study would have included patients who had been off bevacizumab for at least 1·5 months, which was judged too long a period of time to not receive the combined treatment. The combination was supposed to have at least an additive effect and this effect could be missed in cases of successive treatment or long interruptions of one of the drugs.

No significant differences were observed in the baseline characteristics of the three patient groups except a lower proportion of patients with hepatic metastases in the experimental arm. However, this difference did not affect performance status, and clearly did not work in favour of the activity of the combined treatment. Thus, the results observed with the experimental treatment were unlikely to have been affected by patient selection bias.

By contrast with other combinations of angiogenesis inhibitors,[14] our experimental regimen induced no new or unexpected adverse effects. However, many different local abscesses or fistulas occurred in more patients in the experimental group than in the interferon alfa and bevacizumab group. This finding is probably a result of the defect in healing caused by angiogenesis inhibition, especially with bevacizumab, and the immunosuppressive and proinfectious effect of temsirolimus.[33,34]

The fact that half of the patients in the bevacizumab and temsirolimus group discontinued shows the failure of the treatment strategy, independently of any treatment effect. At least two reasons might explain why this higher toxicity was not anticipated at the phase 1 stage. First, the results of the two phase 1 trials testing the combination of bevacizumab with an mTOR inhibitor were preliminary and patients had only been followed up for a limited time when TORAVA was designed.[16,17] One of these trials has been published since TORAVA was designed, and reported a median duration of treatment of only 6 months after a longer follow-up (14 months), which is close to what we reported in our experimental group.[31] Second, these early-phase trials were done in fewer centres than TORAVA. The different TORAVA investigators might not have accepted treatment-related toxicities as readily as those from the early-phase trials; however, the situation of the TORAVA investigators was closer to what could eventually have become a routine situation for use if the results from the trial had shown an additive or synergistic effect.

The difference between the TORAVA findings and those from the phase 1 trials emphasises that the classical design of phase 1 oncology trials, which mostly investigate chemotherapy drugs, is not adapted to testing the tolerance of targeted drugs because cumulative and combined mild toxicities are underestimated. Like chemotherapy, targeted drugs might induce acute toxicities that can be avoided by use of the maximum tolerated dose, but, because these treatments must be continued over time, subacute or chronic toxicities of lesser severity might occur. Most phase 1 trials focus on acute toxicities that are often treatment limiting, and assess the toxicity profile as a function of the different percentages and grades of toxicities rather than of the late dropout rate. This limitation of phase 1 trial results has already been acknowledged by others, including for combinations of angiogenesis inhibitors in patients with advanced renal cancer.[14,35] Therefore, specific trials with more patients than usually planned at each dose level in phase 1 trials and with sufficient follow-up to assess long-term tolerance are very important.

Although the disappointing results of the experimental combination are partly due to the high number of treatment interruptions related to toxicity, the additional post-hoc efficacy analyses among all patients who progressed on treatment confirmed the limited activity of the study combination. A recent phase 2 trial testing the combination of bevacizumab and everolimus in advanced renal cancer has reported similar disappointing PFS results.[31]

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Panel: Research in context

Systematic review

In 2007, when TORAVA was planned, we did a systematic review before designing the trial. We searched for published papers as well as important and well-designed presentations in peer-reviewed symposia or meetings. The different mechanisms of actions or cellular targets of the new therapeutic drugs have been reported.[3] Additionally, large randomised trials have been done and showed evidence of a significant clinical activity of the different drugs that have been or will be registered for the treatment of metastatic renal cell carcinoma.[4-8] Overall, these data have given rise to the hypothesis that drugs targeting different pathways (ie, survival and angiogenesis) might have additional or synergistic activity.[19,29,30] This strategy has been discussed within international expert groups at the Fifth Kidney Cancer Association Symposium, Chicago, IL, USA, Sept 22–23, 2006. Experts participating in this symposium acknowledged that (1) combining drugs could be an interesting way to increase treatment activity; (2) combining drugs that target different pathways that are crucial for tumour cell survival might represent one of the best approaches; and (3) combining two drugs that have different targets would probably reduce the risk of severe toxicity caused by overlapping mechanisms of action. The hypothesis of potential synergy or an additive effect of the combination of anti-VEGF drugs and mTOR inhibitors was then accepted by the investigators as a valid hypothesis that might help improve patient outcome.

Interpretation

This randomised phase 2 trial provides the first results of combination treatment with an antiangiogenesis inhibitor (bevacizumab) and an mTOR inhibitor (temsirolimus) for first-line treatment of metastatic renal cell carcinoma. The absence of an additive or synergistic effect and the limitation of treatment duration because of toxicities observed here confirm the results obtained with a similar combination in a smaller group of patients.[31] As a consequence, clinicians should be aware that combining these drugs, which are both registered for the initial treatment of metastatic renal cell carcinoma, might cause additional toxicities and that these combinations are not to be used outside of clinical trials. The combination of bevacizumab and temsirolimus does not seem to be a major advance for initial treatment of metastatic renal cell carcinoma.

Despite a biological rationale based on the hypothesis of complementary effects by targeting different cellular pathways, the superiority of the combination of two targeted drugs in clinical practice for treatment of renal cell carcinoma remains to be shown. Disappointing results, sometimes after encouraging preliminary reports, have been reported with other combinations. For example, combinations of interferon alfa and temsirolimus[8] and bevacizumab and the EGFR inhibitor erlotinib[36] have been tested but finally abandoned.

There is no perfect way to verify the efficacy of a new strategy that uses new drugs, but undertaking a phase 2 trial seems crucial to test the activity of a new combination before launching randomised comparative trials. Randomised phase 2 trials cannot replace phase 3 trials, but could be useful to verify that the experimental treatment results are not obtained in a selection biased population. As such, TORAVA has fulfilled its methodology objectives and shows clear evidence that the combination of temsirolimus with bevacizumab does not represent a major advance for first-line treatment in patients with metastatic renal cell carcinoma.

Whereas the combination of targeted drugs seems disappointing, their sequential use seems much more appropriate for the control of advanced disease over time and could help to improve overall survival.[9,10,32,37] Promising results have been reported with the addition of one targeted drug to another one already in use, when the initial treatment started to lose control over disease progression.[38] Such salvage additions of targeted drugs used sequentially could possibly be of interest before switching to another treatment. Such a strategy is already in use in advanced prostate cancer when the disease becomes resistant to initial hormonal therapy.[39]

In conclusion, the toxicity profile of the combination of temsirolimus and bevacizumab at full doses of each drug was much higher than anticipated and limited treatment continuation over time. This combination has failed to show any beneficial activity when used as first-line treatment in patients with metastatic renal cell carcinoma and cannot be recommended for this indication.

Contributors

SN, DP, and BE designed the study, interpreted the data and drafted the manuscript. All authors collected data, reviewed the draft, provided comments or substantive revisions, and approved the final manuscript.

Conflicts of interest

SN has received honoraria from Novartis, Wyeth, Pfizer, GlaxoSmithKline, and Roche; and has received research funding from Wyeth, Roche, and Novartis. DP has received honoraria from Bayer, Eli Lilly, and Roche. J-OB has received honoraria from Amgen and is a consultant with Novartis. LG and BL have received honoraria from Novartis. BE has received honoraria from Bayer, Roche, Pfizer, Genentech, Novartis, GlaxoSmithKline, and Aveo; and is a consultant with Bayer, Pfizer, and Roche. All other authors declared no conflicts of interest.

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See Online for webappendix

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