Abstract

Purpose: Response Evaluation Criteria in Solid Tumors (RECIST) may underestimate the efficacy of targeted therapies. In hepatocellular carcinoma (HCC) studies with sunitinib, RECIST-defined response rates are low, although hypodensity on computed tomography (CT) scans occurs more frequently. This exploratory analysis investigated tumor density as a surrogate endpoint of sunitinib activity in a phase II HCC study.

Experimental Design: Patients received sunitinib 50 mg/d (4 weeks on/2 weeks off). Tumor size and density were assessed on CT scans by using RECIST and Choi criteria, the latter of which classify a partial response as a 15% or more reduction in tumor density or a 10% or more reduction in tumor size. The overall percentage volume of tumor necrosis was calculated with volumetric reconstruction. Tumor perfusion parameters were assessed by using perfusion CT scans with specific acquisition.

Results: Among the 26 evaluable patients, 1 achieved a partial response and 22 had tumor stabilization by RECIST. In analysis of tumor density, 17 of 26 patients (65.4%) were responders by Choi criteria. Volumetric assessment showed major tumor necrosis (≥30% of tumor volume) in 10 of 21 patients (47.6%). Among four patients evaluated, tumor blood flow was reduced by 58.8% and blood volume by 68.4% after 4 weeks of treatment. The median time to progression (TTP) was 6.4 months. Patients with responses by Choi criteria had a significantly longer TTP (7.5 months) compared with nonresponders (4.8 months; HR = 0.33, two-sided P = 0.0182).

Conclusions: Tumor density assessment suggested that radiologic endpoints in addition to RECIST may be considered to capture sunitinib activity in HCC. Clin Cancer Res; 17(13); 4504–12. ©2011 AACR.
The identification of new anticancer agents brings many clinical challenges, including accurately assessing their clinical efficacy. The antitumor activity of targeted agents, such as sunitinib, sorafenib, and imatinib, may comprise changes in tumor vascularization, cavitation, and necrosis that do not significantly affect tumor size and are captured as stable disease by using Response Evaluation Criteria in Solid Tumors (RECIST). We evaluated changes in tumor density on computed tomography scans by using Choi criteria as a surrogate endpoint for sunitinib activity in a phase II study of patients with hepatocellular carcinoma (HCC). Compared with conventional RECIST-based measures, reductions in tumor density correlated notably better with improved time to progression. Our findings suggest that radiologic endpoints in addition to RECIST, or as an alternative to RECIST, need to be validated and integrated into HCC clinical trial design.

Patients and Methods

Study design and per-protocol assessments

The design and per-protocol results of this single-arm, multicenter trial (NCT00247676) have been described extensively in a recent publication (12).

This trial was approved by institutional review boards at all participating centers (in France, South Korea, and Taiwan), and all patients provided written informed consent. Eligible patients were aged 18 years or more with histologically proven HCC not amenable to curative surgery, life expectancy of 3 months or more, RECIST-defined measurable disease, Child–Pugh class A or B without ascites, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate organ function. Patients were not eligible if they had prior systemic therapy for HCC (including sorafenib) or liver transplantation. Prior treatment with lipiodol (or any other local therapy) was only permitted if patients had subsequent disease progression or recurrence that was accompanied by the development of at least one new measurable lesion.

Patients self-administered sunitinib orally at a starting dose of 50 mg daily for 4 weeks, followed by 2 weeks off treatment, in 6-week cycles until disease progression, unacceptable toxicity, or consent withdrawal. Dose reductions were acceptable toxicity, or consent withdrawal. Dose reductions were permitted if patients had subsequent disease progression or recurrence that was accompanied by the development of at least one new measurable lesion.

CT scans were conducted at screening, after the first 4 weeks on treatment, and then every 6 weeks (i.e., after each 4-week sunitinib treatment period). Efficacy analyses included all patients receiving sunitinib for at least one 4-week treatment period.

Radiologic analyses

At the end of the study, CT scan images were centralized for review by an independent radiologist (M.Z.) at Beaujon University Hospital (Clichy, France), who was blinded to the clinical data. One or two target lesions were defined at baseline and were followed up, regardless of their initial density. The tumor was delineated and the density in the overall lesions was measured. Tumor density was defined at baseline and compared with that observed at subsequent tumor evaluations. Imaging techniques are further defined in Supplementary Appendix S1. Correlative efficacy evaluations included tumor response according to changes in tumor density, volumetric measurement of tumor necrosis and the entire tumor, and tumor perfusion in a limited area. Tumor Imaging Assessments of Sunitinib in HCC

13 patients had stable disease for 3 months or more, resulting in a disease control rate of 37.8%.

Although the number of RECIST-defined objective responses was low in this trial (12), investigators observed that sustained tumor stabilization was usually associated with decreased tumor density on CT scans (13). This led us to conduct an ancillary study to quantify changes in tumor density on CT scans prior to and after treatment with sunitinib, in an attempt to identify patients who benefit from sunitinib therapy.

Patients self-administered sunitinib orally at a starting dose of 50 mg daily for 4 weeks, followed by 2 weeks off treatment, in 6-week cycles until disease progression, unacceptable toxicity, or consent withdrawal. Dose reductions were acceptable toxicity, or consent withdrawal. Dose reductions were permitted if patients had subsequent disease progression or recurrence that was accompanied by the development of at least one new measurable lesion.
number of patients. These analyses were not initially planned in the study protocol and were exploratory. For determination of changes in tumor density and volumetric measurement of tumor necrosis, 1 or more dominant hepatic mass of 2 cm or more was selected at baseline and followed every cycle.

Two-dimensional tumor density was assessed by using CT attenuation coefficients as described by Choi and colleagues in GIST (5, 6). These defined partial response as a decrease in tumor density [measured in Hounsfield units (HU)] of 15% or more on CT or a decrease in tumor size (sum of the largest diameters of target lesions as defined in RECIST, cm) of 10% or more (Supplementary Table S1; ref. 6).

Three-dimensional evaluation of tumor necrosis was also done. Tumor necrosis was defined as tumoral tissue that did not enhance on multiphasic CT examinations after contrast medium injection. We derived methods used for the measurement of liver volumetry and regeneration as described elsewhere (14, 15) to obtain a volumetric reconstruction of the tumor and of its inner volume of necrosis on CT scan. This was done by manually delineating the tumor and necrotic areas (Advantage Windows software version 4.2; GE Healthcare). A section thickness of 5 mm (without overlaps) was used for volumetry. The percentage volume of necrosis in the whole tumor was then calculated, with major and minor necrosis defined as ≥30% and ≥15% necrosis, respectively.

To establish whether changes in tumor density were due to hypovascularization, tumor blood perfusion parameters were determined by carrying out exploratory perfusion CT scans with specific acquisition in 4 patients. Using the deconvolution method for the perfusion CT, the following hemodynamic perfusion parameters were analyzed in regions of interest: blood flow, blood volume, mean transit time, arterial index, and permeability surface, as described elsewhere (16).

Statistical analysis
Calculation for comparison of tumor density and volumetric measurement of tumor necrosis before and after treatment were done by the Wilcoxon signed rank test (in which significance is defined by 2-sided P < 0.05). Time-to-event endpoints were summarized by using the Kaplan–Meier method and comparison of Kaplan–Meier curves used the log-rank (Mantel–Cox) test.

Results
Assessment of changes in tumor density
All 37 patients were followed until disease progression and/or occurrence of death. In total, 6 of 11 patients (54.6%) not included in the ancillary study to quantify changes in tumor density had progressed at the time of analysis, compared with 16 of 26 patients (61.5%) who were included. No significant differences in terms of RECIST response rate or PFS were detected in the 11 excluded patients compared with 26 patients who were included in this analysis. Twenty-six patients had CT scans available for assessment of tumor density, and their baseline characteristics are shown in Table 1. The remaining 11 patients were not evaluable for tumor density for the following reasons: density measurements could not be done due to software incompatibility (n = 5), adequate imaging not available at first evaluation (n = 5), and target lesions of 2 cm or less (n = 1).

In total, 46 target lesions in 26 patients were measured (median, 2 lesions/patient; range, 1–4) at baseline and

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Evaluable patients (N = 26)</th>
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<tbody>
<tr>
<td>Median age, y (range)</td>
<td>61 (34–79)</td>
</tr>
<tr>
<td>Male/female, n (%)</td>
<td>23 (88.5)/3 (11.5)</td>
</tr>
<tr>
<td>Patients enrolled by region, n (%)</td>
<td>18 (69.2)/8 (30.8)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td>0 (15)/1 (57.7)</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td>8 (30.8)/13 (50.0)/5 (19.2)</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>10 (38.5)/9 (34.6)/7 (26.9)</td>
</tr>
<tr>
<td>Viral hepatitis B</td>
<td>4 (15.4)/14 (53.8)/8 (30.8)</td>
</tr>
<tr>
<td>Viral hepatitis C</td>
<td>7 (26.9)/14 (53.8)/5 (19.2)</td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
<td>13 (50.0)/10 (38.5)/3 (11.5)</td>
</tr>
<tr>
<td>Ascites</td>
<td>1 (3.8)/25 (96.2)/0</td>
</tr>
<tr>
<td>Child–Pugh status, n (%)</td>
<td>A (24/92.3)</td>
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<tr>
<td>A</td>
<td>2 (7.7)</td>
</tr>
<tr>
<td>B</td>
<td>2 (7.7)</td>
</tr>
<tr>
<td>Differentiation grading at initial diagnosis, n (%)</td>
<td>15 (57.7)/11 (42.3)</td>
</tr>
<tr>
<td>Well differentiated</td>
<td>10 (38.5)</td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>11 (42.3)</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>3 (11.5)</td>
</tr>
<tr>
<td>Not assessable</td>
<td>2 (7.7)</td>
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<tr>
<td>Extrahepatic spread, n (%)</td>
<td>15 (57.7)/11 (42.3)</td>
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<td>BCLC stage, n (%)</td>
<td>24 (92.3)</td>
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<tr>
<td>C</td>
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<tr>
<td>B</td>
<td>1 (3.8)</td>
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<tr>
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<tr>
<td>Number of disease sites, n (%)</td>
<td>13 (50.0)</td>
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<tr>
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<td>9 (34.6)</td>
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<td>≥3</td>
<td>4 (15.4)</td>
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<tr>
<td>Prior treatment, n (%)</td>
<td>7 (26.9)</td>
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<tr>
<td>Surgery</td>
<td>1 (3.8)</td>
</tr>
<tr>
<td>Locoregional therapy</td>
<td>11 (42.3)</td>
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</tbody>
</table>

*Complete portal vein thrombosis: n = 2; partial portal vein thrombosis: n = 11.
after cycle 1. The median number of treatment cycles was 3 (range, 1–7). As some patients discontinued after cycle 1; 32 target lesions (19 patients) were evaluated after cycle 2; 28 (16 patients) after cycle 3; and 21 (11 patients) after cycle 4.

Using the best response at any cycle as an endpoint, no significant change in tumor size (as measured based on largest diameters) from baseline (mean size, 54.5 ± 8.1 mm; *P* = 0.7) to the time of best response (mean size, 54.3 ± 8.3 mm) was detectable among evaluable lesions (Supplementary Fig. S1).

Figure 1A and B represent scans from a patient who displayed no change in tumor diameter after 4 weeks of treatment, but a significant (*P* < 0.05) decrease in tumor density that coincided with normalization of α-fetoprotein levels. This patient experienced 33 months of disease control.

Most changes in whole tumor density seemed to occur early, as illustrated in Figure 1C. Median tumor density at baseline was 86.0 HU (range, 39–162) and decreased significantly to 55.0 HU (range, 27–147) after cycle 1 (*P* < 0.001). Median tumor densities after cycles 2, 3, and 4 were 68.0 HU (range, 27–155), 76.5 HU (range, 40–178), and 70.0 HU (range, 40–141), respectively. None of these values differed significantly from baseline values (*P* > 0.05). Density seemed to increase markedly after cycle 3, as mean values were significantly higher after cycles 3 and 4 than the first cycle evaluation (*P* < 0.01 and 0.05, respectively).

### Volumetric changes in tumor density in whole tumors

Because measurement of tumor density could be affected by subjectively positioning an area of interest on tumor slides, we analyzed changes in tumor density in 3 dimensions. Twenty-one patients had a total of 32 tridimensional measurable lesions evaluable for changes in tumor volume. No significant changes in mean tumor volume were observed from baseline (295.0 ± 587.0 mm$^3$) to the time of best tumor response (321.8 ± 573.5 mm$^3$; *P* = 0.58).

At baseline, the mean volume of tumor necrosis was 44.5 ± 9.2 mm$^3$ (15.1% ± 21.6 of tumor volume) and increased significantly to 129.4 ± 70.3 mm$^3$ (40.2% ± 30.5 of tumor volume) after cycle 1 (*P* = 0.001). Major necrosis (≥30% of tumor volume) was observed in 10 of 21 patients (47.6%), whereas minor necrosis (≥15% of tumor volume) was induced in 13 patients (61.9%).

### Assessment of tumor perfusion on CT scan

To determine whether changes in tumor density were due to reductions in tumor vascularization, additional investigations by perfusion CT scans were done in 4 patients. Among these patients, all of whom had RECIST-defined stable disease, blood flow was reduced by 58.8% (range, 39.3–71.1) and blood volume by 68.4% (range, 58.1–74.3) after 4 weeks of sunitinib treatment, compared with baseline. Figure 2 shows CT scans conducted before and after 4 weeks of sunitinib treatment, showing a significant decrease in tumor density suggestive of a large area of tumor necrosis. Three-dimensional reconstruction of hepatic vascularization before and after sunitinib revealed a number of changes in macro- and microvascularization, with devascularized areas and the occurrence of large blood spaces. Perfusion CT scans conducted before and after sunitinib in the same patient showed a significant decrease in blood flow, as indicated in Figure 2E and F by the blue areas. As shown in Figure 2, perfusion parameters including blood volume and blood flow seemed to increase by 34.7% and 14.8%, respectively, in nontumor liver tissues during sunitinib treatment.

### Response assessed by Choi criteria versus RECIST

Figure 3 shows changes in tumor size according to RECIST or variations in tumor density measured by CT scan at baseline and after 4 weeks of sunitinib treatment in all evaluable patients. Among 26 patients evaluated in this trial, 1 (3.8%) presented a partial response, 22 (84.6%) had tumor stabilization, and 3 (11.5%) experienced disease progression according to RECIST. On the
basis of Choi criteria (5), 17 of 26 evaluable patients (65.4%) were responders. The remaining 9 of 26 patients (34.6%) were considered nonresponders: 1 patient with stable disease and 8 with tumor progression. Table 2 compares best response by RECIST versus response by Choi criteria in the 26 evaluable patients at the time of first evaluation. In total, 16 of 22 patients who had a best response of stable disease by RECIST were responders according to Choi criteria, whereas 6 patients with RECIST-defined stable disease were nonresponders using Choi criteria. Three patients had progressive disease according to both criteria.

Activity assessed by RECIST or Choi criteria versus time to progression

Among the 26 evaluable patients in this study, the median time to progression (TTP) was 6.4 months by RECIST, with 10 patients presenting new lesions as a cause of progression, 6 patients having an increase of 20% or more in tumor size, and 10 patients remaining stable. The median TTP of patients with a partial response or tumor stabilization by RECIST was 7.5 months and was significantly higher than the 0.9-month TTP observed in patients with a best response of progressive disease (HR = 0.21; 95% CI, 0.001–0.48; 2-sided P = 0.0153).

Figure 2. Representative changes in the tumor vascularization during treatment with sunitinib in patients with HCC. CT scans showing tumor density and inner tumor vascularization, respectively, at baseline (A and C) and after 4 weeks of sunitinib therapy (B and D). After sunitinib treatment, decreased tumor density (B, arrow) was associated with changes in the inner tumor vascularization (D), with occurrence of wide blood spaces (arrow). Perfusion CT scans performed at the same time points [baseline (E) and after 4 weeks of treatment (F)] showed a decrease in tumor blood flow after sunitinib therapy (arrows and blue areas).
This confirms that progression by RECIST predicts a poor outcome in HCC. The outcome of 17 patients with responses according to Choi criteria was compared with that of the 9 patients classed as nonresponders (Fig. 4). Patients with a response according to Choi criteria experienced a significantly longer median TTP (7.5 months), compared with nonresponders (4.8 months; HR = 0.33; 95% CI, 0.04–0.75, 2-sided \( P = 0.0182 \)). No significant difference in median OS was observed between Choi responders (9.3 months) and nonresponders (4.8 months; HR = 0.70; 95% CI, 0.3–1.6; \( P = 0.56 \)).

Discussion

The aims of phase II trials include detecting indications of antitumor activity and providing information that can be used for further clinical development. Phase II studies with sunitinib in HCC were designed using response rate according to RECIST as a primary conservative endpoint for efficacy. However, regardless of doses and schedules used in the recently reported phase II trials, response rates of sunitinib in HCC were generally less than 10%, which is below the 20% threshold usually acknowledged to define active anticancer agents (12, 17–19). Despite limited changes in HCC tumor sizes, striking appearances of large areas of tumor hypodensity were frequently reported during treatment with sunitinib. Using DC-MRI, Zhu and colleagues (17) reported that sunitinib significantly reduced intratumor vascularization, leading to significant changes in the transfer constant \( K_{\text{trans}} \), a surrogate endpoint for vessel leakage, in patients with partial responses or sustained tumor stabilization. In our study using contrast-enhanced CT scans, we also reported sunitinib-associated changes in inner tumor density accompanied by reduced tumor blood flow and volume that suggest the occurrence of extensive tumor necrosis. In this population of patients with unresectable liver cancer, it was not possible to obtain pathologic specimens that would have confirmed the presence of tumor necrosis. Instead, tumor blood flow analysis provided a noninvasive method to evaluate the effect of sunitinib on tumor vascularization in a small subset of patients. Limited changes in tumor size with possible reduction in tumor density were also observed with sorafenib, despite additional evidence showing that this drug improved survival of patients with HCC (8, 9, 20, 21). In the phase III SHARP and Asia-Pacific trials, RECIST-defined response rates with sorafenib were 2% and 3.3%, respectively (20, 21), which are in the same order of magnitude as response rates with sunitinib in this study (12). These clinical reports with multitargeted inhibitors seem to indicate that changes in intratumor vascularization did not modify overall tumor size and were not associated with significant tumor shrinkage, resulting in limited numbers of objective responses according to RECIST.

<table>
<thead>
<tr>
<th>Table 2. Best response by RECIST versus response by Choi criteria in 26 evaluable patients</th>
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<tr>
<td><strong>RECIST, n (%)</strong></td>
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<tr>
<td>Partial response</td>
</tr>
<tr>
<td>Stable disease</td>
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<td>Progressive disease</td>
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Figure 3. Waterfall plot of changes in tumor size, using sums of largest diameters of target lesions (RECIST; A) or mean tumor density change in target lesions (B), after 4 weeks of sunitinib treatment (\( n = 26 \) evaluable matched patients).
Lack of enhancement and/or decreased tumor density has been previously used in transarterial chemoembolization and local ablation to define responders and nonresponders. This method was shown to provide early evidence of clinical activity (22), and has also been used to monitor activity of targeted agents. Choi and colleagues (6) first reported changes in tumor density in patients with GIST tumors treated with imatinib. They showed that a ≥15% reduction of tumor density or a ≥10% reduction in tumor size correlated better with PFS than RECIST. Another approach, revisiting RECIST using modified criteria (mRECIST), has been recommended by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases (23). Both mRECIST and Choi criteria recognize that changes in overall tumor size, as measured by the largest tumor diameters, may not be appropriate for evaluating the antitumor effects of antiangiogenic agents in HCC, and consider the occurrence of hypodense areas. Additionally, Response Evaluation Criteria in Cancer of the Liver (RECICL) proposed by the Liver Cancer Study Group of Japan captures tumor necrosis based on 2-dimensional measurements (24). These novel criteria should be incorporated prospectively in future clinical trials and validated as surrogate endpoints for survival parameters.

In our trial, we showed that sunitinib was capable of inducing a reduction of 15% or more in tumor density or a 10% or more reduction in tumor size in 65.4% of patients. Likewise, the study reported by Koeberle and colleagues (19) using sunitinib 37.5 mg on a continuous daily dosing schedule also found responses in 62% of patients according to Choi criteria, whereas RECIST captured an objective response rate of only 2%. In our study, perfusion CT scans also showed an early reduction in blood flow to the tumor site after 1 month of treatment with sunitinib, indicative of direct and rapid effects on tumor vasculature. Similarly, in a phase II study using bevacizumab, Zhu and colleagues reported a significant decrease in tumor perfusion parameters including blood flow and blood volume within 2 weeks after bevacizumab administration in patients with advanced HCC (25).

Interestingly, using Choi criteria, modifications in density seemed to occur early, with best responses observed at the first imaging assessment in 20 of 26 evaluable patients and after cycle 2 in the remaining 6 patients, despite a best response of tumor stabilization by RECIST. In our experience, Choi criteria were associated with a better outcome, as reflected by a marked increase in TTP among responders versus nonresponders. Although the number of patients in this study was limited, these data also strongly suggest that endpoints evaluating intratumor vascularization, such as the measurement of tumor density, would be more appropriate to capture the effects of sunitinib than RECIST. As 2-dimensional decreases in tumor density seem to correlate favorably (P = 0.04) with volumetric reconstructions of areas of tumor necrosis in our study (data not shown), 2-dimensional measurements are likely more appropriate for future trials because of their greater ease of use. However, the small sample size and unplanned nature of the analyses reported here need to be taken into account. At this time, measurements of tumor density remain exploratory endpoints in a limited number of patients, and further work is needed to determine whether density changes correlate with clinical efficacy in HCC in larger clinical trials.

Among the 26 patients evaluated in this trial, 22 (84.6%) had tumor stabilization according to RECIST. In the absence of a control group, one may consider that disease stabilization might have been related to the presence of indolent disease. Although cross-study comparisons should be interpreted with care, it may be useful to note that our study population primarily comprised patients with Barcelona Clinic Liver Cancer (BCLC) stage C disease (92.3%; ref. 12), and was similar to that of the SHARP trial (81.6% of patients with BCLC stage C disease) in which TTP in the placebo group was only 2.8 months (20, 21). Moreover, PFS in this study showed that more than 50% of patients had progressed at 6 months, suggesting that patients entered in this trial had disease forms associated with poor prognosis.

Criteria for progression are not unequivocally defined by Choi criteria. Therefore, in this study, we were unable to define PFS or TTP according to Choi criteria. Considering that 10 patients presented new lesions as a cause of progression, 6 patients had an increase of 20% or more in tumor size, and 10 patients remained stable according to RECIST, it is likely that RECIST and Choi criteria would converge in defining similar rates of progression. Importantly, although we cannot define PFS according to Choi criteria in this trial, our data suggest that early occurrence of response by Choi criteria at the first tumor evaluation defines patients who will experience a better outcome with
sunitinib therapy. This early identification of responders is also supported by the immediate divergence of the TTP curves in Figure 4.

In summary, these analyses provide further evidence that conventional imaging strategies relying on changes in tumor dimensions may not be sufficient to capture the antitumor activity of targeted antiangiogenic agents in HCC. Additional or alternative endpoints to RECIST-defined objective response need to be validated and integrated into HCC clinical trial design.

Disclosure of Potential Conflicts of Interest

S. Faivre has received honoraria from Pfizer Inc., Bayer, Schering, Merck Serono, and Sanofi-Aventis, and has had a consultant/advisory role with Amgen. J.Y. Douillard and E. Raymond have had a consultant/advisory role with Pfizer Inc. Y.K. Kang has received honoraria from and has had a consultant/advisory role with Pfizer Inc. and Bayer. A-L. Cheng has received consultant/advisory role with Pfizer Inc. Y-K. Kang has received honoraria from and has had a consultant/advisory role with Pfizer Inc. S. Lanzalone, X. Lin, and M.J. Lechuga are employees of Pfizer Inc.

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References

Changes in Tumor Density in Patients with Advanced Hepatocellular Carcinoma Treated with Sunitinib

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