Continuous Sunitinib Treatment in Patients with Advanced Hepatocellular Carcinoma: A Swiss Group for Clinical Cancer Research (SAKK) and Swiss Association for the Study of the Liver (SASL) Multicenter Phase II Trial (SAKK 77/06)

DIETER KOEBERLE,^a MICHAEL MONTEMURRO,^b PANAGIOTIS SAMARAS,^c PIETRO MAJNO,^{d,e} MATHEW SIMCOCK,^f ANDREAS LIMACHER,^f STEFANIE LERCH,^f KATALIN KOVÁCS,^g ROMAN INAUEN,^a VIVIANNE HESS,^h PIERCARLO SALETTI,ⁱ MARKUS BORNER,^j ARNAUD ROTH,^d GYÖRGY BODOKY^g

^aKantonsspital, St. Gallen, Switzerland; ^bUniversity Hospital CHUV, Lausanne, Switzerland; ^cUniversity Hospital, Zurich, Switzerland; ^dUniversity Hospital, Geneva, Switzerland; ^eSASL, Zurich, Switzerland; ^fSAKK Coordinating Center, Bern, Switzerland; ^gSt. László Teaching Hospital, Budapest, Hungary; ^hUniversity Hospital, Basel, Switzerland; ⁱOncology Institute of Southern Switzerland, Bellinzona, Switzerland; ^jUniversity Hospital, Bern, Switzerland

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The paper discusses sunitinib (Pfizer, Inc.) as an investigational unlabeled product for hepatocellular carcinoma.

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ABSTRACT

Background. Sunitinib (SU) is a multitargeted tyrosine kinase inhibitor with antitumor and antiangiogenic activity. The objective of this trial was to demonstrate antitumor activity of continuous SU treatment in patients with hepatocellular carcinoma (HCC).

Patients and Methods. Key eligibility criteria included unresectable or metastatic HCC, no prior systemic anticancer treatment, measurable disease, and Child-Pugh class A or mild Child-Pugh class B liver dysfunction. Patients received 37.5 mg SU daily until progression or unacceptable toxicity. The primary end-

point was progression-free survival at 12 weeks (PFS12).

Results. Forty-five patients were enrolled. The median age was 63 years; 89% had Child-Pugh class A disease and 47% had distant metastases. PFS12 was rated successful in 15 patients (33%; 95% confidence interval, 20%–47%). Over the whole trial period, one complete response and a 40% rate of stable disease as the best response were achieved. The median PFS duration, disease stabilization duration, time to progression, and overall survival time were 1.5, 2.9, 1.5, and 9.3 months,

Correspondence: Dieter Koeberle, M.D., Department of Internal Medicine, Division Oncology/Hematology, Kantonsspital St. Gallen, CH-9007 St. Gallen, Switzerland. Telephone: 41-71-4941111; Fax: 41-71-4946325; e-mail: dieter.koeberle@kssg.ch Received December 10, 2009; accepted for publication January 28, 2010; first published online in *The Oncologist Express* on March 4, 2010. ©AlphaMed Press 1083-7159/2010/\$30.00/0 doi: 10.1634/theoncologist.2009-0316

respectively. Grade 3 and 4 adverse events were infrequent. None of the 33 deaths were considered drug related.

Conclusion. Continuous SU treatment with 37.5 mg daily is feasible and has moderate activity in patients with advanced HCC and mild to moderately impaired liver dysfunction. Under this trial design (>13 PFS12

successes), the therapy is considered promising. This is the first trial describing the clinical effects of continuous dosing of SU in HCC patients on a schedule that is used in an ongoing, randomized, phase III trial in comparison with the current treatment standard, sorafenib (ClinicalTrials.gov identifier, NCT00699374). *The Oncologist* 2010;15:285–292

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide [1], with approximately 500,000 new cases per year. Approximately 80% of cases arise in Asia and Africa [2], mainly as a result of chronic hepatitis B virus infection. Alcoholic cirrhosis is a main factor in HCC in western Europe and the U.S., where the incidence has increased in recent years, largely because of higher rates of chronic hepatitis C virus infections [3]. Surgical resection and liver transplantation are potentially curative options, but only approximately 15% of patients may benefit from these therapies [4]. Patients with unresectable or metastatic disease have a median survival duration of a few months [5]. Sorafenib (Nexavar®; Bayer Pharmaceuticals Corporation, West Haven, CT), an oral multitargeted tyrosine kinase inhibitor (TKI), was found to produce longer survival (OS) times in advanced-stage HCC patients (median OS, 10.7 months for sorafenib versus 7.9 months for placebo; $p = .0006$) [6]. Sorafenib has been approved for the treatment of HCC and has become the new standard systemic therapy for advanced stage HCC [7].

Sunitinib (Sutent®; Pfizer, Inc., New York) is a selective TKI of vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, platelet-derived growth factor (PDGFR)- α , PDGFR- β , and several other related tyrosine kinases with antitumor and antiangiogenic activities [8, 9]. Sunitinib was recently approved for the treatment of both advanced renal cell carcinoma (RCC) and gastrointestinal stromal tumors (GISTs) after disease progression or intolerance to imatinib.

Evidence for clinical activity in HCC patients was recently reported in two phase II trials using sunitinib at a starting daily dose of 37.5 mg [10] or 50 mg [11] for 4 weeks followed by 2 weeks off treatment in repeated 6-week cycles. At the 50-mg daily dose, sunitinib treatment in HCC patients induced a higher rate of grade 3 and 4 toxicities and a death rate of 10% [11]. The optimal treatment dose schedule for sunitinib in advanced HCC is currently unknown. Preclinical studies indicate that continuous exposure of the tumor to an agent that inhibits angiogenesis might be more effective than intermittent dosing [12]. Fur-

thermore, it is unknown if treatment interruption favors progression of HCC, and experimental data suggest that this strategy might be counterproductive [13].

Phase II trials in patients with cytokine-refractory metastatic RCC [14] and imatinib-resistant GISTs [15] were performed with a continuous daily dose of 37.5 mg sunitinib, and they demonstrated that this schedule is well tolerated and seems to be at least equally active to a 4-weeks-on, 2-weeks-off dosing regimen of sunitinib. Therefore, the current trial was designed to evaluate the antitumor activity and tolerability of continuous dosing of sunitinib in patients with incurable HCC.

PATIENTS AND METHODS

Eligibility Criteria

Patients eligible for the study had histologically, cytologically, or radiologically [16] diagnosed, measurable, unresectable or metastatic HCC. No prior therapy other than liver-directed therapies (chemoembolization was limited to five treatments) was allowed, provided that previously treated lesions remained separate from the target lesions measured for this trial. Other eligibility criteria included age ≥ 18 years, World Health Organization performance status score of 0–1, Child-Pugh class A or mild Child-Pugh class B liver dysfunction [17], adequate bone marrow, hepatic, and renal function as indicated by an absolute neutrophil count $\geq 1,500/\mu\text{l}$, a platelet count $\geq 75,000/\mu\text{l}$, a total bilirubin level $\leq 2 \times$ the upper limit of normal (ULN), a serum alanine aminotransferase level $\leq 7 \times$ ULN, and a calculated creatinine clearance ≥ 40 ml/minute according to the Cockcroft–Gault formula.

Exclusion criteria included: known central nervous system metastases, a history of other primary malignancy within 5 years except for nonmelanomatous skin cancer or adequately treated in situ cervical cancer, prior organ transplantation, known fibrolamellar HCC or mixed cholangiocarcinoma/HCC, documented variceal hemorrhage within 3 months before registration, clinical ascites of any grade, encephalopathy, current use or anticipated need for drugs that are known cytochrome P450 3A4 inhibitors or induc-

ers, QTc prolongation >500 msec in a screening electrocardiogram (ECG) or family history of long QT syndrome, and any serious underlying medical condition that could impair the patient from participating in the trial or taking oral medication. The protocol was approved by local ethics review boards and all patients gave written informed consent. The trial was registered with the National Institutes of Health (ClinicalTrials.gov identifier, NCT00514228).

Treatment Plan

Treatment consisted of sunitinib at a dose of 37.5 mg daily given orally in the evening until disease progression, unacceptable toxicity, or withdrawal of patient consent. The occurrence of grade 3 or 4 adverse events (AEs) necessitated interruption of treatment until toxicities had been resolved below grade 2. If this was not achieved within 3 weeks, the study treatment was discontinued. The sunitinib dose was reduced to 25 mg for grade 4 AEs or in cases of recurrence of a grade 3 AE. The best possible palliative and supportive care for disease-related symptoms was offered to all patients.

Assessments

Tumor response was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) [18] based on computed tomography (CT) or magnetic resonance imaging (MRI) scans performed at baseline and every 6 weeks until week 18, and every 8 weeks thereafter during treatment administration. Objective responses (complete or partial) were confirmed after a minimum of 4 weeks. Original CT and MRI scans were reviewed for tumor response (RECIST) and change in tumor density (Choi criteria) [19] by two independent radiologists who were blinded to the investigator's evaluation. Clinical visits included assessment of AEs, serial laboratory testing (biochemical, hematological, and coagulation parameters, serum vitamin B₁₂ [cobalamin] and α -fetoprotein [AFP] levels), and 12-lead ECG. Physical examinations were required once every 2 weeks. Thyroid function testing was done every eighth week. Patients were followed up quarter-yearly after treatment discontinuation for their survival status.

Statistics

The primary endpoint, progression-free survival at 12 weeks (PFS12), was defined as a "success" if the patient was alive and without tumor progression 12 weeks (± 7 days) after trial registration. A PFS12 rate $\leq 20\%$ was considered uninteresting and a PFS12 rate $\geq 40\%$ was considered promising. Using Simon's minimax two-stage design [19] with 90% power and a 5% significance level, the sample size required was 45 patients. At the final analysis, if

≤ 13 patients remained progression free and alive after 12 weeks, the treatment was considered uninteresting, otherwise it was considered promising for further investigation.

AEs, graded using the Common Terminology Criteria for Adverse Events (version 3.0), were summarized by event type and worst recorded grade per patient across all therapy cycles administered. Secondary efficacy endpoints consisted of the best objective response during therapy as well as the following time-to-event analyses: time to progression (TTP), PFS, duration of disease stabilization (DDS), and OS, all assessed by the Kaplan-Meier method based on an intention-to-treat analysis. The OS time was defined as the time from trial registration until death resulting from any cause. TTP and the PFS time were read as the time from trial registration until either disease progression, death (tumor-related for TTP), or symptomatic deterioration in the event of no response being measured. DDS was recorded from the moment of a complete or partial remission, or stable disease until progression. If no event was reached, the patient was censored at the last known follow-up for OS and either the last tumor assessment or start of second-line therapy for TTP, PFS, and DDS.

Descriptive analyses included assessment of repeated measurements of serum AFP (if AFP $\geq 1.5 \times$ ULN at baseline), vitamin B₁₂, and tumor density.

Statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

Patient Characteristics

In total, 45 patients were enrolled from nine Swiss centers and one center in Hungary between September 2007 and August 2008. All patients were eligible and evaluable for safety, response, and OS. Table 1 lists the patients demographic and pretreatment characteristics.

Treatment Administration

Patients received a total of 113 cycles (each cycle was 4 weeks long) of sunitinib with a median of 2.9 (range, 1–12) cycles given per patient. Dose reductions to 25 mg/day of sunitinib were necessary in 24.6% of all cycles and in 10 patients. Ten of 45 patients never had an omission or dose reduction. This translates into 609 of 2,551 days when the drug was reduced and 616 of 2,551 days when the drug was omitted. Of the 45 patients, 29 discontinued treatment as a result of disease progression, eight discontinued because of symptomatic deterioration, five discontinued because of AEs, and two patients refused further treatment unrelated to any AE. One discontinuation was the result of a death resulting from tumor progression.

Table 1. Baseline patient characteristics (*n* = 45)

Characteristic	Frequency (%)
Median age, yrs (range)	63 (37–83)
Gender	
Male	39 (87)
Female	6 (13)
World Health Organization performance status score	
0	21 (47)
1	24 (53)
Child-Pugh class	
A	39 (87)
B	6 (13)
Etiology of underlying liver disease ^a	
Hepatitis B	6 (13)
Hepatitis C	8 (18)
Alcoholism	21 (47)
Hemochromatosis	2 (4)
Other/unknown	13 (29)
Metastatic disease	21 (47)
Portal vein invasion	
Yes	12 (27)
No	26 (58)
Unknown	7 (15)
Median diameter of longest lesion, mm (range)	84 (18–280)
Previous treatment	
Resection	5 (11)
Chemoembolization	8 (18)
Embolization	6 (13)
Radiofrequency ablation	2 (4)

^aReflecting clinical practice, multiple etiologies were allowed to be considered in a single patient, thus explaining the difference between the sum of etiologies and patient number.

Safety

AEs per patient of any grade are summarized in Table 2. The most common AEs were anemia, thrombocytopenia, and fatigue. Most events were grade 1 or 2 in severity. Grade 3 or 4 events occurred in ≤9% of patients, with the exception of thrombocytopenia (18%) and fatigue (26%). No patient experienced liver failure and there were no treatment-related deaths. At least one serious adverse event (SAE) was recorded in 11 patients (24%) during the study. In total, 14 SAEs were reported, the most common of which were hemorrhage from esophageal varices (three patients) and worsening in general condition (three patients).

Table 2. Adverse events

Adverse event	CTCAE grade (maximum grade observed per patient), <i>n</i> (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	23 (51)	13 (29)	3 (7)	1 (2)
Neutropenia	6 (13)	7 (16)	3 (7)	–
Thrombocytopenia	18 (40)	8 (18)	8 (18)	–
Bilirubin	8 (18)	13 (29)	3 (7)	1 (2)
Alanine aminotransferase	16 (36)	6 (13)	2 (4)	–
Anorexia	20 (44)	12 (27)	–	–
Diarrhea	15 (33)	6 (13)	–	–
Mucositis	6 (13)	3 (7)	1 (2)	–
Taste alteration	11 (24)	4 (9)	–	–
Fatigue	8 (18)	12 (27)	11 (24)	1 (2)
Hand–foot syndrome	2 (4)	2 (4)	–	–
Rash	2 (4)	2 (4)	3 (7)	–
Hypertension	7 (29)	5 (21)	4 (17)	–
Hypothyroidism	2 (4)	3 (7)	–	–
Prolonged QTc	4 (9)	2 (4)	2 (4)	–

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events.

Efficacy

PFS12 was rated by the investigators as a success in 15 patients (33%; Clopper–Pearson 95% confidence interval [CI], 20%–47%) and as a failure in 27 patients (60%); three patients were alive without evaluation. The independent reviewers rated PFS12 as a success in 17 patients (38%; Clopper–Pearson 95% CI, 24%–52%) and as a failure in 24 patients (53%), with four patients considered not evaluable.

Concerning the best objective response during therapy, one patient (2%) achieved a complete response whereas no patient achieved a partial response. Eighteen patients (40%) achieved stable disease (Table 3) (Fig. 1). With a median follow-up time of 15.8 months (range, 1.4–18.6 months), the median PFS time was 1.5 months (95% CI, 1.38–2.83 months), the median TTP was 1.5 months (95% CI, 1.38–2.83 months), the median DDS was 2.9 months (95% CI, 1.5–3.3 months), and the median OS time was 9.3 months (95% CI, 5.6–12.9 months) (Fig. 2).

Correlative Studies

Change in tumor density, assessed by an independent reviewer based on CT scans at baseline and 6 and 12 weeks after treatment initiation according to the Choi criteria [20], was available in 29 patients. No statistically significant association between the Choi criteria and RECIST response at

Table 3. Best objective response during therapy according to the RECIST and the Choi criteria [19]

Response type	n (%)
RECIST response (n = 45)	
Complete response	1 (2)
Partial response	—
Stable disease	18 (40)
Disease progression	18 (40)
No assessment performed ^a	8 (18)
Choi response (n = 29)	
Decrease in tumor density (HU $\geq$ 15%)	14/29 (48)
Reduction in tumor size $\geq$ 10%	8/29 (28)
Partial response (either decreased HU $\geq$ 15% or tumor size reduction $\geq$ 10%)	18/29 (62)
	18/29 (86)

^aAs a result of symptomatic deterioration (five patients), death (one patient), patient refusal because of toxicity (one patient), and patient refusal not because of toxicity (one patient).
Abbreviations: HU, Hounsfield Unit; RECIST, Response Evaluation Criteria in Solid Tumors.

either week 6 or 12 was found. Furthermore, neither the RECIST nor the Choi criteria predicted any of the outcome parameters studied (PFS12, TTP, DDS, OS).

Thirty-one (69%) patients had elevated baseline AFP levels, of which nine showed a decrease $\geq$ 50% at some stage during treatment administration.

Predefined baseline characteristics were assessed against the primary endpoint, PFS12, using odds ratios. The predefined variables were: gender, age (>65 years versus <65 years), performance status, Child Pugh class, and hepatitis C and AFP level. Changes in AFP level from baseline to the 12-week follow-up were also considered. A decrease in AFP $>50\%$ or no change of AFP at any of the measurements up to week 12 was found to be significantly associated with PFS12: the odds ratio for a more favorable response in those with AFP stabilization or an AFP decrease was 0.17 (95% CI, 0.03–0.93). No correlations were found between the other prespecified variables and PFS12.

In a post hoc analysis, we observed a significant association between baseline serum vitamin B₁₂ level and OS (Fig. 3). Kaplan–Meier curves for OS were plotted against dichotomized vitamin B₁₂ levels at baseline. In this exploratory analysis, patients with baseline vitamin B₁₂ levels $\leq$ 600 ng/l had an 11.5-month median OS time (95% CI, 6.1–14.5 months), compared with 4.0 months (95% CI, 2.2–5.3 months) in patients with vitamin B₁₂ levels >600 ng/l ($p = .002$). The cutoff value of 600 ng/l was chosen because one quarter of the patients were below this value and one third of the deaths occurred under this value. At the

Figure 1. Waterfall plot of the maximum percentage change in the sum of the largest diameter of target lesions.

same time, it provided the clearest difference between survival times, although a significant difference in survival curves was maintained as the cutoff value was increased, but with fewer patients, which made the difference unreliable to interpret. No significant association was observed between vitamin B₁₂ level above and below 600 ng/l and any other factor.

DISCUSSION

Targeted-therapies that specifically inhibit growth factor receptors and their related pathways have emerged as a promising systemic treatment for advanced HCC [21, 22].

We report the results of a phase II trial evaluating the safety and efficacy of continuous dosing of sunitinib with 37.5 mg daily in 45 patients with advanced HCC and mild to moderate liver dysfunction. On independent review, 38% of the patients had controlled/stable disease at week 12 (PFS12), which was considered per protocol as promising, a figure that is similar to the 43% disease control rate in the recently reported Sorafenib HCC Assessment Randomized Protocol (SHARP) trial [6]. When this trial was planned, our primary endpoint of PFS12 appeared reasonably accurate for screening a new treatment regarding antitumor activity. Based on a publication of an expert panel convened by the American Association for the Study of Liver Diseases, it is now generally accepted that PFS, a composite endpoint, should no longer be used as a primary endpoint for trials testing new compounds in HCC [7].

The median TTP (1.5 months), DDS (2.9 months), and PFS time (1.5 months) were shorter than reported elsewhere [10, 11]. The evaluation of symptomatic deterioration as disease progression, in accordance with recent

Figure 2. Kaplan–Meier estimates of progression-free survival (PFS) and overall survival (OS).

updated guidelines [7], in 18% of patients might explain, at least in part, these differences. Twenty-eight patients went on to receive second-line therapy, mainly sorafenib, which might have influenced the observed difference between the TTP of 1.5 months and the OS time of 9.3 months, which is consistent with other published data.

Trial comparisons are usually difficult and may be inappropriate given differences in the definition of endpoints, sample size, and patient population. The median OS time of 10.7 months in the sorafenib SHARP trial [6] and the median OS time of 6.5 months in the sorafenib Asia-Pacific Liver Cancer study [23] demonstrated the strong influence of differences in baseline patient characteristics, and perhaps also medical practice, on final outcome.

Therefore, sunitinib data should be carefully interpreted until results from the ongoing, large, multicenter, randomized phase III study comparing sunitinib with sorafenib (ClinicalTrials.gov identifier, NCT00699374) are available.

Consistent with the known safety profile of sunitinib in HCC, the most common AEs were fatigue and thrombocytopenia; other toxicities were generally moderate but may well affect quality of life. We used more stringent eligibility criteria, with a bilirubin level of 2. This may explain the relatively fair tolerability profiles. Importantly, we did not observe irreversible liver failure during sunitinib treatment, and none of the deaths were considered drug related. The number of early treatment discontinuations as a result of symptomatic deterioration, eight (18%), seems high, but

these should not be interpreted as being all treatment related. Certainly, a lower tolerance to the drug in some of the patients related to a lower drug clearance rate cannot be formally excluded. There might be a causal relationship between the timing of sunitinib intake and the frequency of fatigue/asthenia, as suggested by two randomized phase II trials in RCC and GIST patients. In those trials, patients were randomized to receive sunitinib at a dose of 37.5 mg daily either in the morning or in the evening. The patients receiving sunitinib in the evening had a higher frequency of grade 3 asthenia (23% in both trials) than those in the morning group (9% and 10%, respectively) [14, 15]. The consistently higher number of asthenia cases following the evening dosing of sunitinib is in line with observations in our trial, with 24% of patients with grade 3 asthenia.

Changes in tumor density measured with contrast-enhanced CT may be a better early indicator of tumor response to TKIs than RECIST [18, 20]. In our study, about 60% of patients experienced a partial response according to the Choi criteria [20], which include a decrease in tumor density $\geq 15\%$ or a reduction in tumor size $\geq 10\%$, measured within 12 weeks of therapy initiation. However, within the limitations of this small series, the Choi criteria did not appear to correlate with the RECIST-defined response, nor with TTP or the OS time.

This is disappointing, because despite promising preliminary data [26], thus far, no validated radiologic criteria or tumor markers exist that reliably predict response to TKI treatment in HCC patients. Given the costs of treatment and

Figure 3. Kaplan–Meier estimates of overall survival stratified by baseline vitamin B₁₂ level.

large differences in individual treatment benefits, better tools to guide TKI treatment will be crucial in future drug development. Although the Choi criteria did not add any prognostic information in this series, it might still be interesting to further investigate their value in a larger series.

Decreases in AFP levels following TKI therapy [27] or chemotherapy [28] appear to predict longer survival. This was confirmed in this series: a decrease of $\geq 50\%$ from baseline, observed in 24% of our patients, correlated with PFS12.

In a clinical trial evaluating the efficacy and safety of continuous sunitinib at a dose of 37.5 mg daily in patients with metastatic RCC, vitamin B₁₂ deficiency was observed [29]. The serum vitamin B₁₂ levels of six patients who were treated for >5 months were analyzed and found to be lower in all these patients. Because baseline B₁₂ levels were unavailable, it was unclear whether sunitinib lowered vitamin B₁₂ levels, for example, by lowering gastrointestinal absorption, or whether patients with low levels have a better prognosis or better therapeutic response. We could not strictly replicate this finding in our trial, that is, we didn't find a lower vitamin B₁₂ level later in the treatment course,

but B₁₂ supplementation and the shorter treatment duration in HCC patients might have diluted any possible effect of sunitinib on B₁₂ homeostasis. Interestingly, however, we were able to demonstrate a large difference in OS by stratifying patients' baseline vitamin B₁₂ levels above or below the threshold of 600 ng/l. It has long been recognized that HCC can be accompanied by an increase in circulating vitamin B₁₂ [30]. Possible causes for raised vitamin B₁₂ levels include vitamin B₁₂ release during hepatic cytolysis and lower vitamin B₁₂ clearance by the cirrhotic liver. This finding has to be replicated in a larger series before any prognostic or predictive role of vitamin B₁₂ in HCC and TKI treatment can be established.

In summary, the results of this trial suggest that continuous sunitinib treatment with 37.5 mg daily is feasible and has moderate activity. Continuous sunitinib treatment is currently being investigated in a randomized phase III trial in comparison with the current treatment standard, sorafenib (ClinicalTrials.gov identifier, NCT00699374).

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AUTHOR CONTRIBUTIONS

Conception/Design: Dieter Koeberle, Stefanie Lerch, Michael Montemurro, Pietro Majno, Mathew Simcock, Andreas Limacher

Provision of study material or patients: Dieter Koeberle, Katalin Kovács, Roman Inauen, Markus Borner, Vivianne Hess, György Bodoky, Michael Montemurro, Panagiotis Samaras, Piercarlo Saletti, Arnaud Roth

Collection and/or assembly of data: Dieter Koeberle, Stefanie Lerch, Mathew Simcock, Andreas Limacher

Data analysis and interpretation: Dieter Koeberle, Stefanie Lerch, Katalin Kovács, Roman Inauen, Markus Borner, Michael Montemurro, Panagiotis Samaras, Pietro Majno, Mathew Simcock, Andreas Limacher

Manuscript writing: Dieter Koeberle, Stefanie Lerch, Vivianne Hess, György Bodoky, Michael Montemurro, Panagiotis Samaras, Pietro Majno, Mathew Simcock, Piercarlo Saletti, Andreas Limacher

Final approval of manuscript: Dieter Koeberle, Stefanie Lerch, Katalin Kovács, Roman Inauen, Markus Borner, Vivianne Hess, György Bodoky, Michael Montemurro, Panagiotis Samaras, Pietro Majno, Mathew Simcock, Piercarlo Saletti, Andreas Limacher, Arnaud Roth

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