Results of a phase I study of sorafenib in combination with pemetrexed and carboplatin (PECASO) as first-line treatment of advanced non-small cell lung cancer

Background: Lung cancer is the leading cause of cancer death worldwide and the majority of patients present with locally advanced or metastatic disease. Novel treatment regimens combining multi-kinase inhibitors with platinum-based chemotherapy may increase efficacy without additional toxicity.

Methods: Twelve patients (median age 62 years, range 44-77; 4/12 females, 7/12 ECOG 0) with previously untreated NSCLC (stage IIIB with pleural effusion or IV; 7/12 non-squamous histology) were enrolled in a phase I dose escalation trial and received sorafenib 200 mg bid (n=3) to 400 mg bid (n=9) on days 2-19 following pemetrexed 500 mg/m^2 and carboplatin AUC 6 on day 1. The primary objective was to determine the dose of sorafenib for a planned phase-II trial. Secondary endpoints were safety and efficacy.

Results: A total of 52 treatment cycles were administered. Eleven patients experienced grade 3/4 hematologic toxicity (83% thrombocytopenia, 83% neutropenia, 92% leukopenia), requiring one (n=2) or two dose reductions (n=7). Most dose reductions were caused by grade 3/4 thrombocytopenia (82%). Four patients were withdrawn from the trial after experiencing grade 3/4 thrombocytopenia in three consecutive cycles despite two dose reductions. Other grade 3/4 adverse events were infrequent (25%). Best response according to RECIST criteria included a partial response in 3 patients (25%), stable disease in 8 patients (67%), and progression in 1 patient (8%). Median progression-free survival was 6.3 months (95% confidence interval [CI] 3.7-8.9) and median OS was 14.7 months (95% CI 6.8-22.6). There were no differences in safety and efficacy between the sorafenib dose cohorts (200 mg bid vs. 400 mg bid) and histology subsets (squamous vs. non-squamous NSCLC) ($p>0.1$ for all comparisons).

Conclusions: The combination of sorafenib and carboplatin-pemetrexed was active and safe, both in squamous and non-squamous metastatic NSCLC, except for excessive hematologic toxicity. Sorafenib given in this combination and administration schedule appears to enhance thrombocytopenia compared with other published reports.

Introduction

The prognosis of advanced non-small cell lung cancer (NSCLC) still remains very poor, and the majority of patients treated with platinum-based chemotherapy ultimately develop disease progression. Therefore, new active therapies with improved risk-benefit ratio are clearly needed for these patients. Preliminary data indicates that molecularly targeted therapies might improve survival when administered in combination with standard chemotherapy while minimizing toxicity and without compromising quality of life. Sorafenib is an oral multi-kinase inhibitor targeting several intracellular and receptor protein kinases. As an inhibitor of signal transduction, sorafenib prevents tumor cell proliferation and angiogenesis via its effects on the RAF/MEK/ERK pathway at the level of Raf kinase, tyrosine kinases, vascular endothelial growth factor receptor-2 (VEGFR-2) and platelet-derived growth factor receptor-ß (PDGFR-β) [1, 2, 3]. Sorafenib demonstrated broad-spectrum anti-tumor activity in preclinical studies *in vitro* and *in vivo*, including xenograft models of human renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), breast cancer, colon cancer, pancreatic cancer, NSCLC and melanoma [4]. Based on the results of clinical trials of the clinical efficacy and safety of sorafenib, this agent has been approved by the European Medicines Agency (EMA) for the treatment of patients with HCC and those with advanced RCC who had failed prior IFN-α or interleukin-2-based therapy. When planning this sorafenib study in patients with advanced NSCLC, preliminary clinical data had also indicated activity of sorafenib in NSCLC. In addition, two phase II trials had shown that the combination of carboplatin and pemetrexed had comparable efficacy to other standard platinum doublets in this setting but a more favorable toxicity profile [5, 6]. These features made the regimen an attractive partner for combination with novel agents. We therefore initiated a randomized phase II study to evaluate the carboplatin-pemetrexed combination with or without sorafenib in patients with advanced NSCLC. As an additional safety measure, the study was preceded by a two-step dose escalation phase I study of sorafenib in combination with carboplatin-pemetrexed. The study was discontinued after phase I due to unexpectedly severe hematologic toxicity.

Methods

Patients. Patients with unresectable, histologically or cytologically confirmed stage IIIB (with pleural or pericardial effusion) or stage IV NSCLC who were medically fit for treatment with pemetrexed and carboplatin were eligible for the study. Other inclusion criteria were age ≥18 years; no prior systemic anticancer therapy and no investigational therapy or participation in a clinical trial within 30 day before the start of trial; measurable disease (at least one lesion with a greatest diameter ≥2 cm as measured by conventional techniques or ≥1 cm as measured by spiral CT); Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1; life expectancy of at least 12 weeks; adequate bone marrow, renal and hepatic function (hemoglobin ≥ 9.0 g/dl, absolute neutrophil count ≥1,500/mm³, platelet count ≥100,000/mm³, total bilirubin ≤1.5 times the upper limit of normal [ULN], ALT and AST ≤2.5 times ULN or ≤5 times ULN in patients with liver involvement, normal coagulation status, serum creatinine ≤1.5 times ULN, creatinine clearance ≥45 mL/min); no active serious infection or any other serious concomitant systemic disorder that, in the opinion of the investigator, would compromise the patient's ability to adhere to the protocol; no brain metastases. Pregnant and breast-feeding women were excluded, and adequate contraception was required for both women of childbearing potential and male patients for the duration of the study. Males had to continue contraception for at least six months after the last administration of sorafenib. Prior local radiotherapy was allowed if it was completed at least 3 weeks prior to the first dose of study medication. Concomitant palliative radiation therapy to an existing bone lesion for pain control was also allowed. Prior surgery was allowed if it was performed at least 4 weeks prior to the first dose of study medication and the patient had fully recovered. All patients gave written informed consent prior to the study. The study was conducted in accordance with the Declaration of Helsinki.

Objectives The primary objective of the phase-I part of the study was to determine the recommended sorafenib dose for the randomized phase II study to evaluate the carboplatin-pemetrexed combination with or without sorafenib in patients with advanced NSCLC. Therefore the randomized phase II trial was preceded by a run-in two-step dose escalation phase of sorafenib to exclude any unexpected toxicities of

the combination with carboplatin-pemetrexed. Secondary objectives were to determine DLTs and the safety and efficacy of the treatment regimen.
The primary objective of the planned randomized phase II study was to compare progression-free survival (PFS) between the two study arms. Secondary objectives were to compare overall survival (OS), objective response rate, disease control rate (CR + PR + SD), time to and duration of response, quality of life, feasibility and toxicity of the regimens, and to determine biomarkers from the tumor biopsy or resections specimens that were predictive of response to treatment.

Study design and treatment.

On dose level 1 of the run-in dose escalation phase, three patients were planned to receive pemetrexed 500 mg/m² as a 10-min intravenous (IV) infusion followed immediately by carboplatin AUC 6 given IV over 30 minutes on day 1 of a 21-day cycle, and sorafenib 200 mg bid given orally from day 2 to 19. All patients received premedication including an intramuscular injection of 1000 µg of vitamin B12 (One to 2 weeks before day 1 every 9 weeks) and 400 µg of folic acid p.o. given daily on at least 5 of the 7 days preceding day 1 of each cycle; doses were continued throughout treatment until at least 21 days after the last dose of chemotherapy. In addition, patients received premedication with oral doses of 4 mg of dexamethasone every 12 hours for a total of 6 doses, starting 24 hours prior to each pemetrexed infusion. Dose adjustments and treatment delays due to severe or intolerable toxicities were performed according to predefined criteria.

If none out of 3 patients experienced a dose-limiting toxicity (DLT) during cycle 1 of the phase I part of the study, the subsequent patients were to start on level 2. If one out of 3 patients developed a DLT, three additional patients were to be treated on dose level 1. If 2 or more out of 6 patients at this dose level experienced a DLT, the study had to be terminated; if not, dose escalation of sorafenib was to proceed to level 2. On level 2, 6 patients were to receive sorafenib 400 mg bid orally from day 2 to 19 in combination with unchanged doses of pemetrexed and carboplatin. If 2 or more patients treated with this dose regimen developed a DLT, dose level 1 should be administered during the phase II portion of the study. Alternatively, at the request of the data monitoring committee (DMC), an additional 3 patients could be treated on dose level 2 in order to reach a more solid dose recommendation for phase II.

Patients on each dose level could receive a maximum of 6 treatment cycles, with no maintenance sorafenib. After all patients had completed the first 21-day chemotherapy cycle of the phase I portion of the study, the DMC would decide whether to proceed to phase II or terminate the study. Phase II was designed as a randomized, double-blind, placebo-controlled, multicenter trial of combination chemotherapy with carboplatin-pemetrexed as described above, given with or without sorafenib at the recommended phase II dose. It was planned to enroll a total of 130 patients and administer up to 6 cycles of study therapy. Patients achieving a complete response (CR), partial response (PR) or stable disease (SD) were to receive maintenance therapy with daily sorafenib or placebo for a maximum of one year or until disease progression. Additional antiemetic prophylaxis was strongly recommended. Granulocyte colony-stimulating factor (G-CSF) was not allowed in cycle 1 but could be administered in subsequent cycles if clinically indicated.

Toxicity was graded according to the Common Toxicity Criteria for Adverse Events v. 3.0 (CTCAE). DLT was defined as one of the following events occurring during cycle 1 of the phase I study: Grade 4 neutropenia (ANC $<0.5 \times 10^9$/L) for ≥7 days; febrile grade 4 neutropenia; grade 4 thrombocytopenia (platelet count $<25.0 \times 10^9$/L); grade ≥3 hemorrhage with grade ≥3 thrombocytopenia ($\leq 50.0 \times 10^9$/L); any grade ≥3 nonhematologic drug-related adverse event other than unpremedicated hypertension or nausea/vomiting; or grade 4 hypertension.

Statistical analysis. The number of patients enrolled in the phase I portion of the study was determined by the traditional dose escalation schedule as described above. Accordingly, a minimum number of 3 patients and a maximum of 6 patients per dose level were required for an overall maximum number of 12 patients. Evaluation of patient outcome was performed on a descriptive basis.

Results

Patients. Twelve patients treated in the phase I part of the study were evaluated for the appropriate dose of sorafenib and the safety and efficacy of the sorafenib-carboplatin-pemetrexed combination. The baseline characteristics of the patients are

shown in **Table 1**. Three patients were treated on dose level 1 and nine on dose level 2.

Primary endpoint of the phase I part of the study. According to the protocol, the dose limiting toxicities (DLT) were determined in cycle 1. No DLT occurred among three patients treated on dose level 1 of the phase I study (sorafenib 200 mg bid), and one DLT (CTCAE grade 4 thrombocytopenia) occurred among nine patients treated on the extended dose level 2 (**table 2**). Thus, formally, 400 mg of sorafenib given orally twice daily from day 2 to 19 of each cycle was defined as the recommended phase II dose for combination therapy with carboplatin and pemetrexed.

Secondary endpoints of the phase I part of the study.

Treatment exposure. Twelve patients received a total of 52 cycles (median 4, range 1-6). Five patients (42%) completed all 6 cycles of study treatment. Three patients (25%) had no dose reductions of carboplatin-pemetrexed during the course of treatment, 2 patients (17%) had one dose reduction (level 1, -25%), and 7 patients (58%) had two dose reductions (level 2, -50%). Thrombocytopenia grade 3/4 was the reason for 82% of all dose reductions. Study treatment was discontinued prematurely in 7 patients (58%); the reason for discontinuation was hematologic toxicity in 4 patients (grade 3/4 thrombocytopenia in three consecutive cycles despite two dose reductions in all cases), disease progression in 2 patients and intercurrent illness (cardiac ischemia) in one patient. Nine of the 12 patients (75%) received second-line therapy, and of these, 2 (17%) received third-line therapy and one (8%) fourth-line therapy. All but one of the second-line regimens included docetaxel. Due to progressive disease in the brain, palliative radiation was necessary in one patient.

Toxicity. In general, the combination was well tolerated. Toxicities experienced during cycle 1 and all cycles are summarized in **Table 4**. However, hematologic toxicity, especially thrombocytopenia, was higher than anticipated. This prompted the DMC to discontinue the study after phase I and recommend a modified sorafenib schedule for combination with carboplatin-pemetrexed chemotherapy. Overall, grade 3 or 4 hematologic toxicity occurred in 11 patients (92%) and 33 cycles (63%) of study treatment. There were no significant differences between the two sorafenib

dose levels in the overall frequency of hematologic toxicities or in the frequency of neutropenia/granulocytopenia or thrombocytopenia (data not shown). Treatment cycles and dose reductions are displayed in **Table 3**. Moreover, none of the baseline or treatment-related variables examined (age, stage, histology, number of completed cycles, cycles with dose reductions, PR as best response, ECOG performance status, weight loss during therapy) predicted for the occurrence of enhanced hematologic toxicity (Exact Fisher test p > 0,1, all comparions). Low platelet numbers prior to chemotherapy also did not predict the incidence of grade 3/4 thrombocytopenia. However, patient numbers were small, and an increased incidence of grade 4 thrombocytopenia on the 400-mg dose level of sorafenib (18% compared with 7% on level 1) cannot be fully excluded.

Except one patient with grade 3 arthralgia and one patient experiencing grade 3 cardiac ischemia there no episodes of grade 3/4 non-hematologic toxicity throughout the trial.

Efficacy. Three patients (25%) achieved a PR as best response according to RECIST criteria, eight patients (67%) had SD, and one patient (8%) progressed after the first two cycles of study treatment (**Figure 1**) Median PFS in this small patient population was 6.3 months (95% confidence interval [CI] 3.7 to 8.9), and median OS was 14.7 months (95% CI 8.6 to 20.8). The Kaplan-Meier estimates of PFS and OS are shown in **Figure 2**. Outcome was similar for patients with squamous and those with non-squamous histology and also independent of sex, age, stage, best response, weight loss during the course of the study and treatment exposure (total number of treatment cycles, number of treatment cycles at full doses, number of dose reductions, or premature termination of the study due to repeated hematologic toxicity). Although PFS was favorable for patients with an ECOG performance status of 0 vs. 1 (log-rank p=0.009), this advantage did not translate into improved OS.

Discussion

Our study was originally planned as a randomized, placebo-controlled phase II trial with a run-in phase I part to determine whether sorafenib at daily oral doses of 200 or 400 mg would offer the best benefit-risk ratio when combined with carboplatin-pemetrexed chemotherapy. Although only one DLT occurred among nine patients

treated at the 400-mg dose level of sorafenib, the DMC decided to terminate the study after phase I because of unexpectedly severe hematologic toxicity, particularly thrombocytopenia. The efficacy of the combination, however, was encouraging and warrants future studies of a modified sorafenib-chemotherapy regimen in patients with advanced NSCLC, ie. with respect to molecular defined NSCLC phenotypes.

Several studies of sorafenib alone or in combination with various agents and regimens in patients with advanced NSCLC have been reported in the literature.
In a phase II study by Blumenschein et al. [7], 51 evaluable patients with relapsed or refractory advanced NSCLC received single agent sorafenib at 400 mg bid. No patient achieved an objective response, but 30 patients (59%) had SD, including 4 patients (8%) whose tumor shrank by 30% or more. Median PFS and OS was 2.7 and 6.7 months, respectively. The most common grade 3 or 4 adverse event was hand-foot syndrome occurring in 5 patients (10%).
In another phase II study single agent sorafenib (400 mg bid continuously) was given as front-line therapy for advanced NSCLC. The trial was closed because of lack of efficacy. Only 3 (12%) out of 25 previously untreated patients achieved a PR, and 6 (24%) had SD. Median time to progression was 2.8 months and median OS 8.8 months. Seven patients (28%) were progression-free at 24 weeks of treatment. No grade 3/4 hematologic toxicities were observed in this study,. Thirteen patients (52%) experienced a grade 3 nonhematologic adverse event, with fatigue (20%), diarrhea (8%) and dyspnea (8%) being the most common.
In two reported studies, sorafenib was given in combination with carboplatin-paclitaxel. The phase I study by Flaherty et al. [8] mainly included patients with advanced melanoma, and among others, 4 patients with advanced NSCLC. The dose of sorafenib was increased in three steps from 100 mg bid to 400 mg bid given from day 2 to 19 every 3 weeks, while the dose of carboplatin (AUC 6) and paclitaxel (225 mg/m²) was held constant. The most common treatment-related adverse events were hematologic (95%), dermatologic (85%), fatigue (59%), sensory neuropathy (59%), nausea (56%) and arthralgia (26%), with no clear relationship to the dose of sorafenib. Although no cases of grade 4 thrombocytopenia occurred in the study, grade 3 thrombocytopenia was observed in 16 patients (41%) in the first treatment cycle across all dose levels. Overall response rate among 39 patients was 26% (1

CR, 9 PR). All responses were seen in the 24 melanoma patients. However, no efficacy details were reported for the NSCLC patients.

The Evaluation of Sorafenib, Carboplatin and Paclitaxel Efficacy in NSCLC (ESCAPE) phase III trial randomized a total of 926 previously untreated advanced stage NSCLC patients to receive either sorafenib (400 mg orally bid on days 2 to 19) or matching placebo added to paclitaxel 200 mg/m² and carboplatin AUC 6 [9]. After an interim analysis in 2008, the trial was stopped prematurely because in the subset of patients with squamous-cell histology (n=223), the addition of sorafenib appeared to have a detrimental effect on survival (median OS 8.9 months vs. 13.6 months in the placebo group). In the total population, median OS was virtually identical in the sorafenib and placebo group (10.7 vs. 10.6 months). Main grade 3/4 toxicities related to sorafenib included rash (8%), hand-foot syndrome (8%), diarrhea (3.5%) and hypertension (3%). The incidence of drug-related hematologic adverse events was similar in the two groups except for thrombocytopenia which was significantly more common in the sorafenib group (any grade, 8% vs. 3%; grade 3/4, 4% vs. 1%). Although the rate of all drug-related hemorrhage/bleeding events was significantly higher in the sorafenib group compared with placebo (10% vs. 5%; p=0.004), this did not explain the excess mortality observed among patients with squamous-cell histology treated with the sorafenib combination. Actually, fatal bleeding events were more common in the patient subset with squamous-cell NSCLC, but these events were equally distributed between the treatment groups. Therefore, no reasonable explanation for the disappointing results of this trial has been found to date.

Given the small number of evaluable patients in our phase I study of sorafenib plus carboplatin-pemetrexed, the results regarding safety and efficacy of this combination must be interpreted with caution. However, the median OS of 14.7 months achieved in PECASO is the best outcome ever reported for a sorafenib combination in advanced NSCLC, suggesting good activity of the regimen. Moreover, median OS among the 5 patients with squamous-cell histology was comparable to the 7 patients with non-squamous histology (14.7 vs. 14.8 months), leaving room for speculation about the role of the specific chemotherapy regimen used in combination with sorafenib. The main problem we faced with sorafenib-carboplatin-pemetrexed in the treatment of patients with advanced NSCLC was the severe hematologic toxicity,

especially thrombocytopenia. This could be related to a sorafenib-platinum interaction, e.g. on PDGFR and cKit, resulting in an additive or synergistic toxic effect on the hematopoietic stem cell pool when both agents are administered consecutively without a treatment pause. However, in previous sorafenib monotherapy studies or combination trials with platinum compounds, severe hematotoxicity as observed in this trail cound not be demonstrated.

For a recently initiated successor phase I trial we have therefore introduced 3-day treatment-free periods before and after administration of sorafenib, i.e., restricting the use of sorafenib to 14 days (days 5 to 18, with chemotherapy given on day 1 and repeated every 22 days). Additional preventive safety measures were the substitution of carboplatin by cisplatinum, the exclusion of patients with squamous-cell histology, and the implementation of dose adjustment rules for sorafenib based on the hematologic nadir values in preceding cycles.

In conclusion, the combination of the multikinase inhibitor sorafenib with carboplatin-pemetrexed chemotherapy was found to be effective both in patients with squamous and non-squamous cell NSCLC. Moreover, the combination was generally safe except for excessive hematologic toxicity. In particular, sorafenib appeared to enhance carboplatin-induced thrombocytopenia, indicating the need for a modified schedule of administration of sorafenib when given in combination with hematotoxic chemotherapy.

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Tables

Table 1. Baseline characteristics of 12 patients with NSCLC treated in the phase I part of the study.

	No. of patients (%)
Total	12 (100)
Gender	
Male	8 (67)
Female	4 (33)
Age, years	
Mean	62.3
Median (range)	62 (44-77)
ECOG performance status	
0	7 (58)
1	5 (42)
Histology	
Squamous	5 (42)
Non-squamous	7 (58)
Adenocarcinoma	6 (50)
Large cell	1 (8)

Table 2: Events defined as dose limiting toxicity (DLT). * None of the three patients in the sorafenib 200mg bid dose group, and 1/9 in the sorafenib 400mg bid group experienced grade 4 thrombocytopenia.

Events defined as DLT	Event occurred
CTCAE grade 4 neutropenia for ≥7 d	no
Febrile Grade 4 neutropenia	no
CTCAE Grade 4 thrombocytopenia	Yes (1/12)*
CTCAE Grade ≥3 hemorrhage with Grade ≥3 thrombocytopenia	no
CTCAE Grade ≥3 nonhematologic drug related adverse events	no
CTCAE Grade 4 hypertension	no

Table 3. Delivered dose. Dose modifications* applied only for carboplatin and pemetrexed (level1: -25%; level 2:-50%). Sorafenib was not reduced.

Completed cycles and dose reductions	Patients (%)
1-2 cycle(s) completed	2 (16)
3-4 cycles completed	4 (42)
5-6 cycles completed	5 (42)
Median number of cycles (range)	4
No dose reduction due to toxicity	3 (25)
1 dose reduction* during trial	2 (17)
2 dose reductions* during trial	7 (58)
Median (range)	2
CTCAE Grade 3 and 4 hematotoxicity during study treatment	11 (92)

Table 4. Adverse events occurring on study treatment (1st cycle vs. all cycles)

	1st cycle (n=12 patients)			All cycles (n=52 cycles)		
Adverse event	**CTC grade n (%)**			**CTC grade n (%)**		
	3	**4**	**3/4**	**3**	**4**	**3/4**
Hematologic						
Febrile neutropenia	0	0	**0**	1 (2)	0	**1 (2)**
Neutropenia/granulocytopenia	5 (42)	0	**5 (42)**	13 (25)	4 (8)	**17 (33)**
Leukopenia	4 (33)	0	**4(33)**	15 (29)	3 (6)	**18 (35)**
Thrombocytopenia	1 (11)	1 (11)	**2 (17)**	14 (27)	8 (15)	**22 (42)**
Anemia	0	0	**0**	6* (12)	0	**6* (12)**
Dermatologic						
Alopecia	0	0	**0**	0	0	**0**
Rash/desquamation	0	0	**0**	0	0	**0**
Hand-foot syndrome	0	0	**0**	0	0	**0**
Others						
Fatigue	0	0	**0**	0	0	**0**
Nausea	0	0	**0**	0	0	**0**
Diarrhea	0	0	**0**	1 (2)	0	**1 (2)**
Constipation	0	0	**0**	0	0	**0**
Sensory neuropathy	0	0	**0**	0	0	**0**
Arthralgia	1	0	**1† (8)**	1	0	**1† (2)**
Hypertension	0	0	**0**	0	0	**0**
Cardiac ischemia	1	0	**1‡ (8)**	1	0	**1‡ (2)**
Bleeding/pulmonary hemorrhage	0	0	**0**	0	0	**0**

* These patients were anemic (grade 1 or 2) prior to therapy.

† Not drug-related.

‡ Not drug-related; the patient was symptomatic during cycle 1 but did not report concurrent cardiac ischemia prior to therapy and was therefore withdrawn after cycle 1. The patient died 15 months after PECASO from a heart attack.

Figures

Figure 1. Waterfall-plot analysis of treatment response

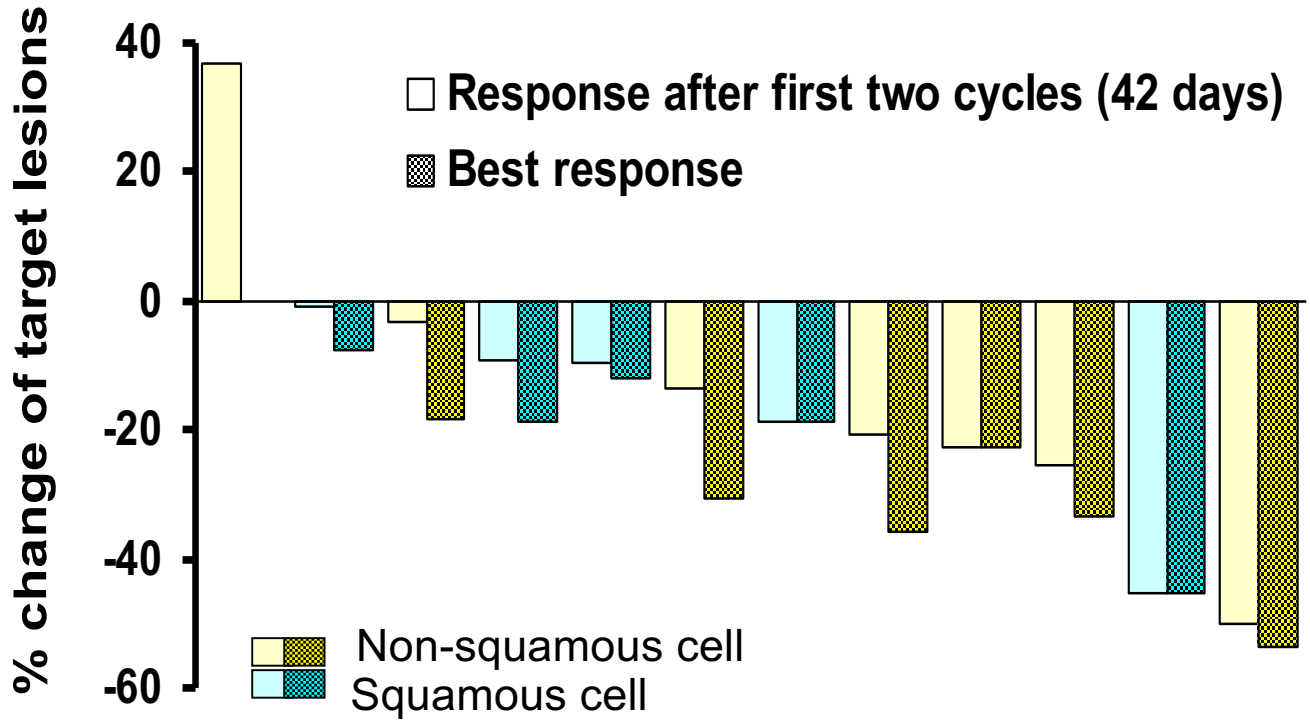

Figure 2. Progression-free survival (PFS) and overall survival (OS)