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Sorafenib in combination with erlotinib or with gemcitabine in elderly patients with advanced non-small-cell lung cancer: a randomized phase II study

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Background: Sorafenib is a small-molecule multitargeted kinase inhibitor that blocks the activation of C-RAF, B-RAF, c-KIT, FLT-3, RET, vascular endothelial growth factor receptor 2 (VEGFR-2), VEGFR-3 and platelet-derived growth factor receptor β. The aim of this multicenter, randomized phase II study was to evaluate clinical activity and safety of sorafenib in combination with erlotinib or gemcitabine in unselected untreated elderly patients with non-small-cell lung cancer (NSCLC).

Methods: The trial was designed to select the most promising sorafenib-containing combination in previously untreated elderly (≥70 years) stage IIIB or IV NSCLC patients, with performance status of zero to two. Patients were randomly assigned to one of the following combinations: gemcitabine, 1200 mg/m^2 days 1 and 8, every 21 days, for a maximum of six cycles, plus sorafenib, 800 mg/day, until disease progression or unacceptable toxicity (arm 1); or erlotinib, 150 mg/day, plus sorafenib, 800 mg/day, until disease progression or unacceptable toxicity (arm 2). A selection design was applied with 1-year survival rate as the primary end point of the study, requiring 58 patients.

Results: Sixty patients were randomly allocated to the study (31 patients in arm 1 and 29 patients in arm 2). After a median follow-up of 15 months, 10 patients [32%, 95% confidence interval (CI) 16% to 49%] in arm 1 and 13 patients (45%, 95% CI 27% to 63%) in arm 2 were alive at 1 year. Median overall survival was 6.6 and 12.6 months in arm 1 and arm 2, respectively. Observed toxic effects were consistent with the expected drug profiles.

Conclusions: The combination of erlotinib and sorafenib was feasible in elderly patients with advanced NSCLC and was associated with a higher 1-year survival rate than the other arm. According to the selection design, this combination warrants further investigation in phase III trials.

Key words: elderly, erlotinib, gemcitabine, NSCLC, sorafenib

introduction

Non-small-cell lung cancer (NSCLC) is the leading cause of cancer-related deaths in Western countries [1]. At diagnosis, the majority of patients have metastatic disease and two-thirds of them are older than 65 years [2]. On the basis of current evidence, chemotherapy treatment appears justified in elderly patients with advanced NSCLC. Single-agent chemotherapy (gemcitabine, vinorelbine, taxanes) may be the preferred option for palliative treatment of these patients [3, 4]. In selected fit patients with performance status (PS) of zero to one and adequate organ functions, combination chemotherapy is a valid option [5]. However, new treatment strategies to improve prognosis of elderly patients are strongly needed.

Sorafenib is a small-molecule multitargeted kinase inhibitor that blocks the activation of C-RAF, B-RAF (both the wild-type and the activated V600E mutant), c-KIT, FLT-3, RET, vascular endothelial growth factor receptor 2 (VEGFR-2), VEGFR-3 and platelet-derived growth factor receptor β [6]. Sorafenib is currently approved for the treatment of metastatic renal cell carcinoma and for advanced hepatocellular carcinoma and is under investigation in other malignancies, including NSCLC. Sorafenib affects tumor growth by directly inhibiting tumor cell proliferation and promoting apoptosis in a variety of tumor

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types as well as by inhibiting tumor-induced neoangiogenesis. As single agent, sorafenib has demonstrated activity in patients with refractory or recurrent NSCLC, although it acted primarily by inducing disease stabilization [7]. Sorafenib has been tested also in combination with cytotoxic drugs. Based on the preliminary activity and the acceptable safety profile of the combination of paclitaxel and carboplatin with sorafenib [8, 9], two phase III studies in unselected advanced NSCLC patients have been conducted. The ESCAPE (Evaluation of Sorafenib, Carboplatin and Paclitaxel Efficacy) trial, which compared a chemotherapy doublet with paclitaxel and carboplatin versus the same regimen with the addition of sorafenib in chemo-naive patients with advanced disease, was stopped prematurely because of the evidence at a planned interim analysis of a detrimental effect in patients with squamous cell histology and a clear inferiority of the experimental arm [10]. Another phase III trial, the NExUS (NSCLC research Experience Utilizing Sorafenib) trial, which compared the combination of gemcitabine plus cisplatin versus the same regimen with the addition of sorafenib in the first-line treatment of patients with advanced NSCLC, recently failed to meet the primary end point of overall survival (OS) [11]. Additional studies are currently ongoing to further characterize the safety and efficacy of combinations of sorafenib with various cytotoxic regimens in patients with metastatic NSCLC [12].

The major progresses in the knowledge of cancer biology and of mechanisms of oncogenesis have allowed the discovery of several potential molecular targets for NSCLC treatment, which are components of signaling pathways or metabolic processes contributing to the acquisition of the cancer phenotype. Blockade of the epidermal growth factor receptor (EGFR) by the tyrosine kinase inhibitor (TKI) erlotinib has been demonstrated as a potential therapeutic tool in elderly patients due to the activity and to the manageable toxicity achieved in first-line setting [13].

The combined blockade of two distinct but related signaling pathways in cancer and in endothelial cells, such as the EGFR and the VEGFR, could represent a better strategy to obtain a more sustained control of tumor growth and of tumor-induced angiogenesis [14, 15]. There is a biologic rationale for the addition of sorafenib to agents that target the EGFR. First, sorafenib blocks B-RAF, a downstream serine threonine kinase to K-RAS, and its addition to EGFR-TKIs could overcome resistance in patients whose tumors express activating K-RAS mutations. Secondly, since sorafenib is a multitargeted kinase inhibitor blocking several growth factor-receptor-driven signals, the simultaneous EGFR inhibition could be additive or synergistic.

Our laboratory has recently provided evidence of a synergistic interaction between sorafenib and erlotinib or between sorafenib and cetuximab, a chimeric anti-EGFR blocking monoclonal antibody, in a panel of human NSCLC and colorectal cancer cell lines, *in vitro* and *in vivo*, which is accompanied by a marked and sustained inhibition of the mitogen-activated protein kinase and of the phosphoinositide 3-kinase/Akt-dependent intracellular signals [16].

A phase I study has established the safety and the tolerability of combining sorafenib and erlotinib with promising antitumor activity for solid tumors, while preclinical data show synergism also in EGFR-inhibitor-resistant NSCLC cells [17]. More recently, the same combination has been evaluated in a phase II study in chemo-naive stage IIIB/IV NSCLC patients, showing clinical activity and an acceptable safety profile [18].

The aim of this multicenter, randomized phase II study was to evaluate the clinical activity and the safety of sorafenib in combination with either erlotinib or gemcitabine in unselected untreated elderly patients with advanced NSCLC. The primary objective of the study was to evaluate the 1-year survival rate in order to define the potentially more active treatment among the two sorafenib-containing regimens.

methods

study design and patients

This was an investigator-initiated, multicenter randomized phase II trial (EUDRACT number: 2007-002941-20). Ten Italian centers participated in this study. The study protocol was approved by the ethics committee of each participating institution and all patients provided written informed consent.

Inclusion criteria were as follows: patients aged ≥70 years, with Eastern Cooperative Oncology Group (ECOG) PS of zero to two, cytological or histological diagnosis of NSCLC with stage IV or IIIB disease with malignant pleural effusion or supraclavicular nodes, no prior chemotherapy, presence of at least one target lesion, life expectancy of ≥3 months, neutrophils ≥1.5 × 10^9/l, platelets ≥100 × 10^9/l, hemoglobin ≥9 g/dl, bilirubin level either normal or <1.5 × upper limit of normal (ULN), aspartate aminotransferase and alanine aminotransferase ≤2.5 × ULN (≤5 × ULN if liver metastasis are present), serum creatinine <1.5 × ULN, alkaline phosphatase ≤4 × ULN, protrombine time, International normalized ratio/partial protrombine time <1.5 × ULN, and effective contraception for both male and female patients if the risk of conception existed.

The main exclusion criteria were the following: brain metastases, previous chemotherapy for advanced disease, previous treatment with anti-EGFR drugs, history of cardiac disease (congestive heart failure >NYHA class 2); active cardiac disease (myocardial infarct >6 months before study entry was allowed); cardiac arrhythmias requiring antiarrhythmic therapy (β-blockers or digoxin were permitted) or uncontrolled hypertension; patients with evidence or history of bleeding diathesis, history of HIV infection or chronic hepatitis B or C, patients undergoing renal dialysis, acute intestinal occlusion or history of inflammatory bowel disease, known grade 3 or 4 allergic reaction to any of the components of the treatment, known drug abuse/alcohol abuse, inability to follow protocol rules, clinically relevant peripheral neuropathy, any concurrent malignancy (other than non-melanoma skin cancer or carcinoma in situ of the cervix) or patients with a previous malignancy but without evidence of disease before ≥5 years.

Patients were randomly assigned using a 1 : 1 allocation to sorafenib in combination with gemcitabine (arm 1) or sorafenib in combination with erlotinib (arm 2). Patients assigned to arm 1 received oral sorafenib, 400 mg twice daily, until disease progression or unacceptable toxicity, plus gemcitabine: 1200 mg/m^2, i.v., days 1 and 8, every 3 weeks, for a maximum of six cycles. Patients assigned to arm 2 received oral sorafenib, 400 mg twice daily, until disease progression or unacceptable toxicity, plus oral erlotinib 150 mg per day, until disease progression or unacceptable toxicity. The cycle duration was 21 days in both treatment arms.

efficacy and safety evaluations

All assessments were planned to be the same across all treatment groups. Staging included complete history and physical examination, blood count and biochemistry analyses, brain, thoracic and abdominal computed tomography (CT) scans and bone scan. Blood counts were repeated weekly. Tumor response with CT scans of the brain, chest and abdomen was

assessed every third cycle (9 weeks of treatment). Response was measured by the use of the RECIST. No central or independent verification of response was used. Toxicity was assessed before each cycle of therapy and was coded according to the National Cancer Institute—Common Terminology Criteria Adverse Events, version 3.0. For toxicity analysis, the worst data for each patient were gauged.

statistical analysis

The sample size for this randomized phase II study was calculated on the basis of the theory of selection [19]. By recruiting 29 patients for each arm (sorafenib plus gemcitabine or sorafenib plus erlotinib), there was a 90% of probability to select the best treatment if it induced a percent rate of patients alive at 1 year, which was superior of at least 15% as compared with an expected percent rate of patients alive at 1 year of 20% with the worst treatment.

The primary variable of interest for the analysis was represented by the proportion of patients alive at 1 year since the enrollment in the study. According with the design of selection, the treatment that would produce the higher percentile of patients alive will be considered the best candidate for a following randomized phase III study. In the main analysis, the evaluation of this percentile was done on the principle of 'intention to treat', splitting the number of patients alive at 1 year by the number of patients enrolled. Confidence intervals (CI) were described at 95%. The principal analysis of the study did not consider the application of statistical tests of comparison between the two treatments. The OS curves were estimated by the Kaplan–Meier, with an exclusive descriptive role.

results

Patients were enrolled in this study from September 2007 through May 2009. Since on 21 February 2008, sorafenib was withdrawn from the treatment of squamous NSCLC, after the release of the preliminary results of the ESCAPE trial [10], the current study continued as planned, but patients with squamous histology were excluded from enrollment. Since at this time point, two patients with a squamous histology NSCLC had been randomized, the number of patients to recruit was extended from 58 to 60 patients, in order to include in the final intention-to-treat analysis also these two patients with squamous histology. Thirty-one patients were assigned to the combination of sorafenib and gemcitabine (arm 1) and 29 patients to the combination of sorafenib and erlotinib (arm 2).

The median age of patients was 74 years (range 70–86 years) (Table 1). The majority were males (62%). Approximately 73% of the patients had an ECOG PS of one or two at baseline (70% of patients were PS 1 and 3% were PS 2), with only 27% of the patients having a PS 0. PS 0 patients were slightly more frequent in the arm 1.

The majority of patients were former smokers (61% in arm 1 and 59% in arm 2), whereas approximately one-third (32%) of the patients were never smokers (Table 1).

All patients received at least one dose of the assigned treatment, and four patients, all in arm 2 (sorafenib plus erlotinib), were still on treatment at the last follow-up (31 May 2010).

In the gemcitabine plus sorafenib combination (arm 1), all patients received sorafenib. Eight patients completed the planned six cycles of gemcitabine and continued the treatment with single-agent sorafenib for a median of 20 weeks. Chemotherapy was discontinued earlier than planned in 23 patients (10 patients after one cycle, 5 patients after two cycles, 5 patients after three cycles and 3 patients after five cycles). Overall, 101 courses of chemotherapy were delivered (median, three cycles for patient). Gemcitabine administration on day 8 was omitted 17 times because of lack of hematologic recovery. Of a total of 31 patients, 12 patients interrupted the treatment for disease progression, 7 patients for adverse events (AEs) and 1 patient for PS deterioration (Table 2). Time-to-treatment failure (TTF) was 8.1 weeks (95% CI 1.0–65.0) for the combination of gemcitabine plus sorafenib (Table 3).

Table 1. Baseline characteristics of patients by treatment arm

	Arm 1 (gemcitabine + sorafenib)	Arm 2 (erlotinib + sorafenib)	Total
No. of patients	31	29	60
Age, years			
Median (range)	74 (69–82)	76 (70–86)	74 (69–86)
Gender, *n* (%)			
Male	20 (65)	17 (59)	37 (62)
Female	11 (35)	12 (41)	23 (38)
ECOG PS, *n* (%)			
0	12 (39)	4 (14)	16 (27)
1	17 (55)	25 (86)	42 (70)
2	2 (6)	–	2 (3)
Race, *n* (%)			
Caucasian	31 (100)	29 (100)	60 (100)
Smoking history, *n* (%)			
Never smoker	9 (29)	10 (34)	19 (32)
Former smoker	19 (61)	17 (59)	36 (60)
Current smoker	3 (10)	2 (7)	5 (8)
Histotype, *n* (%)			
Squamous	2 (6)	–	2 (3)
Adenocarcinoma	25 (81)	25 (86)	50 (83)
BAC	1 (3)	–	1 (2)
Large cell	2 (6)	1 (3)	3 (5)
Mixed	–	–	–
Not defined	1 (3)	3 (10)	4 (7)

In the erlotinib plus sorafenib combination (arm 2), all patients received sorafenib and erlotinib. Of the 29 patients randomized in this arm, 4 patients were still on treatment without evidence of disease progression at the closure of the follow-up (31 May 2010), 6 patients stopped treatment for progression of the disease, 6 patients for AEs and 1 patient for PS deterioration (Table 2). TTF was 12.7 weeks (95% CI 2.0–69.4) for the combination of sorafenib plus erlotinib (Table 3).

After a median follow-up of 15 months, 10 patients (32%, 95% CI 16% to 49%) in arm 1 and 13 patients (45%, 95% CI 27% to 63%) in arm 2 were alive at 1 year, with 21 and 16 failures (dead or lost) before 1 year, respectively (Table 3). The median OS were 6.55 months for arm 1 (gemcitabine plus sorafenib) and 12.6 months for arm 2 (erlotinib plus sorafenib) (Figure 1).

The observed response rate was 6.5% (0.8%–21.4%) for the combination of gemcitabine plus sorafenib (arm 1) and 10.3% (2.2%–27.4%) for the combination of erlotinib plus sorafenib (arm 2), with two and three partial responses recorded in arm 1 and arm 2, respectively. Stable disease and progression of disease were observed in 11 (35.5%) and 6 (19.4%) patients in

Table 2. Treatment received and causes of treatment interruption

	Arm 1 (gemcitabine + sorafenib)	Arm 2 (erlotinib + sorafenib)
Received treatment	31	29
Gemcitabine	31	–
Erlotinib	–	29
Sorafenib	31	29
Last information about experimental treatment (cut-off data 31 May 2010)		
Stopped	31	25
Ongoing	–	4
Causes of treatment interruption		
Non-compliance	1	2
Adverse event	7	6
Disease progression/death	15	10
Consent withdrawn	3	1
Lost to follow-up	0	1
Interruption >21 days	2	3
Squamous histology	1	1
Medical decision	1	0
Deterioration	1	1

Table 3. Efficacy outcome by treatment arms and objective responses according to the RECIST criteria

	Arm 1	Arm 2
No. of patients	31	29
Primary outcome		
Alive at 1 year	10 (32%) (95% CI 16% to 49%)	13 (45%) (95% CI 27% to 63%)
Complete response	0	0
Partial response	2 (6.5%)	3 (10.3%)
Stable disease	11 (35.5%)	10 (34.5%)
Progressive disease	6 (19.4%)	5 (17.2%)
Not evaluated	12 (38.7%)	11 (37.9%)
Objective response rate		
	2 (6.5%)	3 (10.3%)
95% CI	0.8% to 21.4%	2.2% to 27.4%
Median TTF (weeks)	8.1 (1.0–65.0)	12.7 (2.0–69.4)

CI, confidence interval; TTF, time-to-treatment failure.

arm 1 and in 10 (34.5%) and 5 (17.2%) patients in arm 2 (Table 3). The observed toxic effects were consistent with the expected drug profiles (Table 4).

The combination of erlotinib and sorafenib resulted in more skin rash (26% in arm 1 and 48% in arm 2, all grades), hand and foot skin reaction (20% in arm 1 and 31% in arm 2, all grades), grade 3 diarrhea (3% in arm 1 and 14% in arm 2), grade 4 bleeding (3%), grade 3 hypertransaminasemia (3%), grade 4 hyperbilirubinemia (3%) and grade 4 hyperamylase lipase (3%). The combination of sorafenib with gemcitabine resulted in a more pronounced hematological toxicity, in particular, in grade 4 neutropenia (3%) and grade 4 thrombocytopenia (3%). Grade 3–4 fatigue was equally recorded in both arms (13% and 14%, respectively).

Seven and six patients, in arm 1 and arm 2, respectively, discontinued therapy because of AEs. Two deaths were possibly treatment related, both in the sorafenib plus gemcitabine combination arm. A 73-year-old Caucasian male with a stage IV large cell carcinoma of the lung developed tumor cavitation and fatal pulmonary hemorrhage after two cycles of treatment with gemcitabine and sorafenib. The second case occurred in a 74-year-old Caucasian female with a stage IV lung adenocarcinoma that developed colon perforation after five cycles of treatment with gemcitabine and sorafenib.

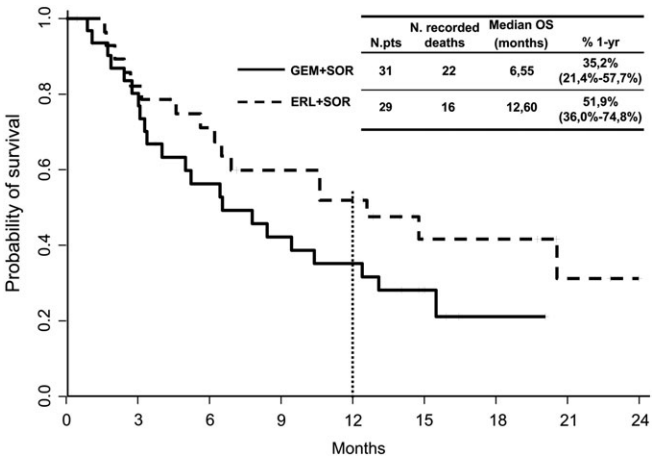

Figure 1. Kaplan–Meier's estimated curves of overall survival (OS) for elderly patients by treatment arm. Pts, patients, yr, year.

discussion

At diagnosis, the majority of NSCLC patients have metastatic disease, and two-thirds of them are older than 65 years. In consideration of the concomitant comorbidities and the decrease of organ function, single-agent chemotherapy with a third-generation drug (gemcitabine, vinorelbine or taxanes) is currently the treatment in unselected patients, which is supported by prospective elderly-specific clinical studies [3, 4].

Currently, in this patient population, the expected median survival following vinorelbine or gemcitabine single-agent treatment is ∼28–36 weeks, with a probability of being alive at 1 year of ∼28%–38% [20, 21].

Retrospective analyses showed a similar outcome of platinum-based therapy for elderly patients compared with their younger counterparts, both in terms of response rate and OS, with similar toxicity and no significant adverse effect on quality of life [22].

However, the only prospective study carried out in elderly NSCLC patients to compare single-agent versus platinum-based chemotherapy has been recently presented at the 2010 Annual American Society of Clinical Oncology meeting by Quoix et al. [5]. In this multicenter, randomized phase III study, patients aged from 70–89 years, PS of zero to two, with advanced NSCLC were randomized to receive a 3-weekly single-agent therapy (gemcitabine 1150 mg/m^2 or vinorelbine 30 mg/m^2, days 1 and 8) or a doublet combination with carboplatin area under the curve 6, every 4 weeks plus paclitaxel 90 mg/m^2 (days 1, 8 and 15) with OS as the main end point. OS of the 313 patients analyzed was significantly longer for patients treated with a platinum-based chemotherapy (median OS: 10.4 versus 6.2 months, hazard ratio 0.60, $P < 0.0001$). However, as

Table 4. Worst grade of toxicity according to treatment arm

Toxicity	NCI–CTC grade, *n* (%) of patients									
	Gemcitabine + sorafenib (*n* = 31)					Erlotinib + sorafenib (*n* = 29)				
	1	2	3	4	5	1	2	3	4	5
Anemia	1 (3)							1 (3)		
Leucopenia	2 (6)	3 (10)								
Neutropenia	2 (6)	4 (13)		1 (3)						
Thrombocytopenia	1 (3)	1 (3)		1 (3)		1 (3)				
Bleeding						1 (3)			1 (3)	
Allergy	1 (3)									
Heart, rhythm			1 (3)						1 (3)	
Heart, general (CV)			1 (3)						1 (3)	
Fatigue	1 (3)	5 (16)	4 (13)			2 (7)	6 (21)	4 (14)		
Fever	1 (3)						1 (3)			
Hair loss	2 (6)					1 (3)				
Skin rash	3 (10)	5 (16)				6 (21)	4 (14)	3 (10)	1 (3)	
Hand–foot skin reaction	3 (10)	3 (10)				4 (14)	2 (7)	3 (10)		
Paronychia	1 (3)					1 (3)				
Anorexia	1 (3)					4 (14)				
Constipation	1 (3)									
Diarrhea	2 (6)	1 (3)	1 (3)			6 (21)	5 (17)	4 (14)	1 (3)	
Nausea	3 (10)					1 (3)	1 (3)			
Vomiting						1 (3)	1 (3)			
Stomatitis	2 (6)	2 (6)				1 (3)				
Mucositis	1 (3)	3 (10)				1 (3)	1 (3)			
Hypertransaminasemia	2 (6)					1 (3)	1 (3)	2 (7)		
Hyperbilirubinemia						1 (3)	1 (3)		1 (3)	
Itching		1 (3)								
Dysphonia		1 (3)								
Neuropathy										
Hypertension			1 (3)				2 (7)			
Endobronchial cavitation		1 (3)								
Colon perforation				1 (3)						
Hyperamylase lipase									1 (3)	

NCI–CTC, National Cancer Institute—Common Terminology Criteria; CV, cardiovascular.

expected, grade 3–4 hematologic toxic effects and treatment-related deaths were significantly more frequent in patients treated with carboplatin and paclitaxel as compared with single-agent gemcitabine or vinorelbine. In this regard, a platinum-based doublet chemotherapy can be suggested to elderly NSCLC patients who are more fit for such therapy (PS of zero to one and with an adequate organ function), but it requires further clinical investigations.

The aim of the present multicenter, randomized phase II trial was to evaluate and eventually select the most promising sorafenib-containing combination (with gemcitabine or with erlotinib) in unselected elderly patients with previously untreated advanced NSCLC. A selection design, with 1-year survival rate as the primary end point, was applied [19]. The advantage of a randomized phase II selection designed study over separate studies includes less selection bias due to changing natural history or outcome improvements over time in sequentially conducted phase II studies and the ability to ensure that uniform evaluation criteria are used. In this type of phase II trial, two experimental treatments are studied and no standard treatment arm is considered. With this type of design, it will be possible to select as 'best' the arm with the best efficacy level, which deserves further evaluation in phase III study, regardless of the magnitude of the difference. The present study suggests that combination of erlotinib and sorafenib is feasible in elderly patients with advanced NSCLC and is associated with a median OS of 12.6 months and an approximately 52% probability of being alive at 1 year.

In phase II trials in unselected patients with pretreated advanced NSCLC, sorafenib as single agent has demonstrated a promising antitumor activity, with a median OS of 6.8 months and a median progression-free survival of 2.8 months with a manageable toxicity [23, 24]. However, the randomized phase III ESCAPE and NExUS studies (carboplatin plus paclitaxel or cisplatin gemcitabine, respectively, with and without sorafenib in first-line advanced NSCLC) failed to met the primary end point of an increase in OS as compared with standard platinum-based doublet chemotherapy [10, 11].

On the other hand, a phase II study was conducted in 80 unselected elderly patients with advanced NSCLC treated with erlotinib in first-line treatment and resulted in a median survival of 10.9 months [13].

More recently, a phase II study evaluating the combination of erlotinib and sorafenib in chemo-naive patients with advanced

NSCLC reported a median survival of 10.9 months, with a nonprogression rate at 6 weeks (the primary end point of the study) of 74% and a response rate of 28% [18]. In the present study, the combination of sorafenib and erlotinib obtained a median survival of 12.6 months and a response rate of 10.3%. The difference in response rate with the previous study may be related to the patient population, being the present study carried out in an elderly population, which was predominantly with a PS 1 (70%) and PS 2 (3%).

In the present study, the treatment was generally well tolerated and the AEs observed were similar to those reported in other trials with these drugs. Given their age and concomitant comorbidities, patients on the current trial were expected to have a higher incidence of AEs than younger patients receiving this combination. Nevertheless, 20% of patients in this study required toxicity-related discontinuation compared with the 16% of patients in the previously mentioned phase II study of sorafenib plus erlotinib, which was carried out in a younger patient population [18].

There were two deaths in patients during the combined treatment with gemcitabine and sorafenib. The first was a result of hemoptysis, which occurred in a patient with nonsquamous histology. It is known that patients with squamous cell carcinoma are at greater risk than those with nonsquamous cell histologies for serious tumor-related bleeding when treated with angiogenesis inhibitors, such as sorafenib [23]. The second potentially treatment-related death was a result of colon perforation. Proposed risk factors for gastrointestinal perforation in patients treated with antiangiogenic drugs include a variety of local phenomena, such as peptic ulcer disease, diverticulitis, carcinomatosis, bowel obstruction, chemotherapy-induced colitis, prior bowel irradiation and bowel ischemia [25].

This study does not provide information on the role of the combination treatment with erlotinib and sorafenib in NSCLC patients with EGFR-sensitizing mutations to small-molecules EGFR-TKIs. This is largely due to the lack of adequate tissue sampling for such tests in a patient population in which the age, the poorer PS (73% patients included in this study had a PS 1 or a PS 2) and the presence of comorbidities often preclude the possibility of a relatively invasive diagnostic bioptic procedure. Probably, a better selection of patients based on the presence or absence of prognostic and predictive biologic markers may further improve the outcome of this study.

Nevertheless, the results of the present study suggest that the combination of erlotinib and sorafenib is feasible as first-line treatment of unselected elderly patients with advanced NSCLC and that is associated with a promising therapeutic efficacy (median OS of 12.6 months). Therefore, according to the selection design of this exploratory randomized phase II study, the combination of erlotinib and sorafenib warrants further investigation in a larger patient sample and therefore in randomized phase III trials as compared with standard treatment for these patients.

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disclosure

MDM acted as a consultant for Bayer Schering Pharma and for Eli Lilly Italia and is member of the speaker's bureau for Bayer Schering Pharma.

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