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ORIGINAL REPORT

Italian, Multicenter, Phase III, Randomized Study of Cisplatin Plus Etoposide With or Without Bevacizumab as First-Line Treatment in Extensive-Disease Small-Cell Lung Cancer: The GOIRC-AIFA FARM6PMFJM Trial

Marcello Tiseo, Luca Boni, Francesca Ambrosio, Andrea Camerini, Editta Baldini, Saverio Cinieri, Matteo Brighenti, Francesca Zanelli, Efisio Defraia, Rita Chiari, Claudio Dazzi, Carmelo Tibaldi, Gianni Michele Turolla, Vito D'Alessandro, Nicoletta Zilembo, Anna Rita Trolese, Francesco Grossi, Ferdinando Riccardi, and Andrea Ardizzoni

Author affiliations and support information (if applicable) appear at the end of this article.

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Corresponding author: Marcello Tiseo, MD, Oncologia Medica, Azienda Ospedaliero-Universitaria, Via Gramsci 14, 43126 Parma, Italy; e-mail: mtiseo@ao.pr.it.

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A B S T R A C T

Purpose

Considering promising results in phase II studies, a randomized phase III trial was designed to assess the efficacy of adding bevacizumab to first-line cisplatin plus etoposide for treatment of extensive-disease (ED) small-cell lung cancer (SCLC).

Patients and Methods

Treatment-naive patients with ED-SCLC were randomly assigned to receive either cisplatin plus etoposide (arm A) or the same regimen with bevacizumab (arm B) for a maximum of six courses. In the absence of progression, patients in arm B continued bevacizumab alone until disease progression or for a maximum of 18 courses. The primary end point was overall survival (OS).

Results

Two hundred four patients were randomly assigned and considered in intent-to-treat analyses (103 patients in arm A and 101 patients in arm B). At a median follow-up of 34.9 months in arm A and arm B, median OS times were 8.9 and 9.8 months, and 1-year survival rates were 25% and 37% (hazard ratio, 0.78; 95% CI, 0.58 to 1.06; $P = .113$), respectively. A statistically significant effect of bevacizumab on OS in patients who received maintenance was seen (hazard ratio, 0.60; 95% CI, 0.40 to 0.91; $P = .011$). Median progression-free survival times were 5.7 and 6.7 months in arm A and arm B, respectively ($P = .030$). Regarding hematologic toxicity, no statistically significant differences were observed; for nonhematologic toxicity, only hypertension was more frequent in arm B (grade 3 or 4, 1.0% *v* 6.3% in arms A *v* B, respectively; $P = .057$).

Conclusion

The addition of bevacizumab to cisplatin and etoposide in the first-line treatment of ED-SCLC had an acceptable toxicity profile and led to a statistically significant improvement in progression-free survival, which, however, did not translate into a statistically significant increase in OS. Further research with novel antiangiogenic agents, particularly in the maintenance setting, is warranted.

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INTRODUCTION

Small-cell lung cancer (SCLC) currently accounts for approximately 12% to 15% of all bronchogenic tumors.[1] Despite its initial sensitivity to chemotherapy and radiotherapy, extensive-disease (ED) SCLC remains an incurable tumor.[2]

The standard-of-care first-line therapy for ED-SCLC is a combination chemotherapy regimen including cisplatin or carboplatin and etoposide.[3] Since the introduction of this combination chemotherapy in the early 1980s, other newer chemotherapy regimens or treatment strategies have not yielded any step forward.[2] Further treatment advances can probably be expected only from the development of novel nonchemotherapy strategies. However, so far, none of the biologic drugs tested has met the expectations.[4] Recently, there was a glimmer of hope that, perhaps, the antiangiogenic approach, which has allowed a significant step forward in other malignancies, would lead to an improved outcome in patients with SCLC.

ASSOCIATED CONTENT

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Data Supplement
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Vascular endothelial growth factor (VEGF) is the most important proangiogenic factor, and it is implicated in pathologic angiogenesis such as that associated with tumor growth.[5] Increased levels of VEGF have been found in most tumors, including lung cancer. Neoangiogenesis, evaluated through microvessel count and overexpression of VEGF, is abundant in SCLC and associated with poor prognosis.[6,7] For this reason, SCLC is believed to be an ideal model for testing antiangiogenic drugs.

Bevacizumab, a humanized monoclonal antibody directed against VEGF, is now indicated in the treatment of several tumor types including non–small-cell lung, breast, colorectal, kidney, and ovarian cancer. Considering positive signals in a few phase II studies,[8-12] we designed this randomized phase III trial to assess the efficacy of adding bevacizumab to first-line chemotherapy with cisplatin plus etoposide for treatment of ED-SCLC.

PATIENTS AND METHODS

Patients and Eligibility

Study entry was limited to the patients with histologically or cytologically documented ED-SCLC, who were previously untreated with systemic therapy, were 18 years of age or older, had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, and had a life expectancy of greater than 12 weeks. Adequate bone marrow, renal, and liver functions were required. Patients with asymptomatic, treated brain metastases were eligible for trial participation. Exclusions included the following: mixed histologic diagnosis of SCLC and non–small-cell lung cancer; history of ≥ grade 2 hemoptysis; evidence of lung tumor cavitation; surgery; significant traumatic injury within the 4 weeks before first dose of study treatment; other active malignancies (previous or current); any underlying medical condition that might be aggravated by treatment; concomitant treatment with any other anticancer drug; nonhealing wound, ulcer, or bone fracture; history of thrombotic or hemorrhagic disorders; current or recent (within 10 days of first dose of study treatment) use of aspirin (> 325 mg/d) or other nonsteroidal anti-inflammatory drug with antiplatelet activity; and current or recent (within 10 days before study treatment start) use of full-dose oral or parenteral anticoagulants or thrombolytic agent for therapeutic (as opposed to prophylactic) purposes.

The study protocol was approved by ethics committee or institutional review board at each participating center (study protocol available online). The study was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent before initiation of any trial-specific procedure or treatment.

Study Design

Gruppo Oncologico Italiano di Ricerca Clinica–Agenzia Italiana del Farmaco FARM6PMFJM was a multicenter, open-label, randomized controlled phase III trial performed at 29 Italian centers (Appendix, online only). Patients received a combination of intravenous cisplatin (25 mg/m^2 on days 1 to 3), etoposide (100 mg/m^2 on days 1 to 3), and bevacizumab (7.5 mg/kg intravenously on day 1) administered every 3 weeks (experimental arm, arm B) or the same cisplatin and etoposide chemotherapy regimen alone given every 3 weeks (control arm, arm A). Carboplatin (area under the curve 5 on day 1) could be substituted for cisplatin in case of cisplatin contraindications or cisplatin-associated toxicity. Random allocation sequences were generated by a computer-based program under the supervision of the study statistician. Patients were randomly assigned (1:1) to one of the two treatment groups in a nonmasked fashion by a Web-based system, using the minimization algorithm. Stratification criteria were center, sex (female *v* male), age (≤ *v* > 65 years), and ECOG PS (0 or 1 *v* 2).

Platinum and etoposide treatment was given until progression of disease, unacceptable toxicity, or patient refusal or for a maximum of six courses. In the experimental arm, bevacizumab alone was continued as maintenance therapy until progression or for a maximum of 18 cycles (including the first six cycles) in patients with objective response or stable disease after the first six chemotherapy plus bevacizumab cycles.

Patients received full supportive care, including hematopoietic growth factors, transfusions of blood products, and antibiotics, when appropriate. Prophylactic cranial irradiation was permitted for patients with partial or complete responses. Other radiation therapy was permitted only for treatment of bone metastases.

Assessments and Data Collection

Tumor response, on the basis of investigator-assessed Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1), was evaluated every three cycles during chemotherapy treatment. After six cycles of chemotherapy, tumor assessment was performed every 9 weeks in both arms. Survival follow-up information was collected ≤ 6 months after treatment termination or last dose of study drug, until death or loss to follow-up.

Information on selected adverse events (AEs), serious AEs, and AEs leading to treatment discontinuation were recorded until approximately 30 days after the final treatment dose. The selected AEs were as follows: hypertension, proteinuria, hemorrhage, arterial and venous thromboembolic events (events known to be associated with bevacizumab), hematologic toxicity, febrile neutropenia, mucositis, nausea and vomiting, diarrhea, stypsis, fatigue, neurotoxicity, ototoxicity, hepatotoxicity, renal toxicity, and skin toxicity. All AEs were graded according to National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0. Safety evaluations at every cycle consisted of medical interviews, recording of AEs, physical examinations, blood pressure measurement, and laboratory measurements. Safety data are presented by incidence (numbers and percentages) in patients who received one or more doses of study treatments.

Statistical Considerations

The primary end point of this study was overall survival (OS), defined as the time interval between the date of random assignment and the date of death as a result of any cause or last follow-up (censored). The secondary end points of this study were response rate, defined as the sum of the complete and partial response rates according to RECIST criteria version 1.1; toxicity; and progression-free survival (PFS), defined as the time interval between the date of random assignment and the date of progression or death or the last known date progression free (censored). An administrative censoring at the cutoff date of December 31, 2015, was applied to all time-to-event analyses.

Efficacy analyses were based on the intent-to-treat population, which included all randomly assigned patients. Patients who received at least one cycle of study treatment were included in the safety population. Assuming a cumulative probability of survival at 1 year from the entry onto the study in the control arm of 40% (corresponding to a median survival of 9 months), the experimental treatment would be considered more effective if associated with a relative reduction of the risk (hazard) of death of at least 40% with respect to the control arm. This would correspond to an absolute cumulative probability of survival at 1 year from the entry onto the study in the experimental arm ≥ 58% (corresponding to a median survival of ≥ 15 months). Fixing the type I error rate to 5% for a two-tail log-rank test and the type II error rate to 10% (power of 90%), before progressing to the final results analysis, it would be necessary to observe a total of 169 deaths and enroll 206 patients (103 patients for each arm).

Summary statistics by treatment group for demographic and baseline characteristics are presented to describe the study population. The median period of follow-up and its interquartile range were calculated for the entire study cohort according to the reverse Kaplan-Meier method. Distributions of OS and PFS times were estimated using the Kaplan-Meier

method. OS and PFS were compared between the treatment groups using the unstratified log-rank test. The hazard ratio (HR) and 95% CI were provided. Response rates were compared using the χ^2 test for heterogeneity. Subgroup analyses of OS and PFS were performed by means of an interaction test to determine the consistency of the treatment effect according to key baseline characteristics. All reported *P* values and CIs were two-sided. SAS software version 9.2 (SAS Institute, Cary, NC) was used for the statistical analysis.

A futility analysis, on the basis of the conditional power approach, and a safety analysis were performed by an independent data monitoring committee after the enrollment of two thirds of the total planned sample size; the committee recommended that the study be continued. The study is registered in the European Clinical Trials Database (EudraCT No. 2007-007949-13).

RESULTS

The study was conducted from November 16, 2009, to October 1, 2015, in 29 Italian centers. A total of 205 patients were randomly assigned in the two arms; 204 patients were considered in the intent-to-treat analysis (103 patients in arm A and 101 patients in arm B; one patient was randomly assigned twice by mistake; Fig 1). Median duration of follow-up was 34.9 months (interquartile range, 22.5 to 41.5 months). Patients characteristics were as follows: 68.0% and 68.3% men and 89.3% and 94.1% with ECOG PS of 0 to 1 in arm A and arm B, respectively; median age was 64 years (range, 41 to 81 years; Table 1).

Six patients (one in arm A and five in arm B) did not receive the assigned treatment as a result of refusal after random assignment. The median number of chemotherapy courses administered was six in both arms. Cisplatin was used in 93 and 91 patients in arms A and B, respectively; four patients (three in arm A and one in arm B) switched to carboplatin after receiving cisplatin. Average relative dose-intensities for all drugs were 87.6% and 89.2% in arms A and B, respectively. Average relative dose-intensity for each drug was as follows: in arm A, 87.6% for etoposide and 87.5% for platinum, and in arm B, 90.1% for etoposide, 90.3% for platinum, and 88.6% for bevacizumab. Dose reductions and delays were performed in 30.1% *v* 35.8% and 60.2% *v* 58.9% of patients in arm A versus arm B, respectively. A lower percentage of patients in arm B (14.7%) than in arm A (22.3%) discontinued treatment because of radiologic disease progression, which was the main reason for treatment discontinuation.

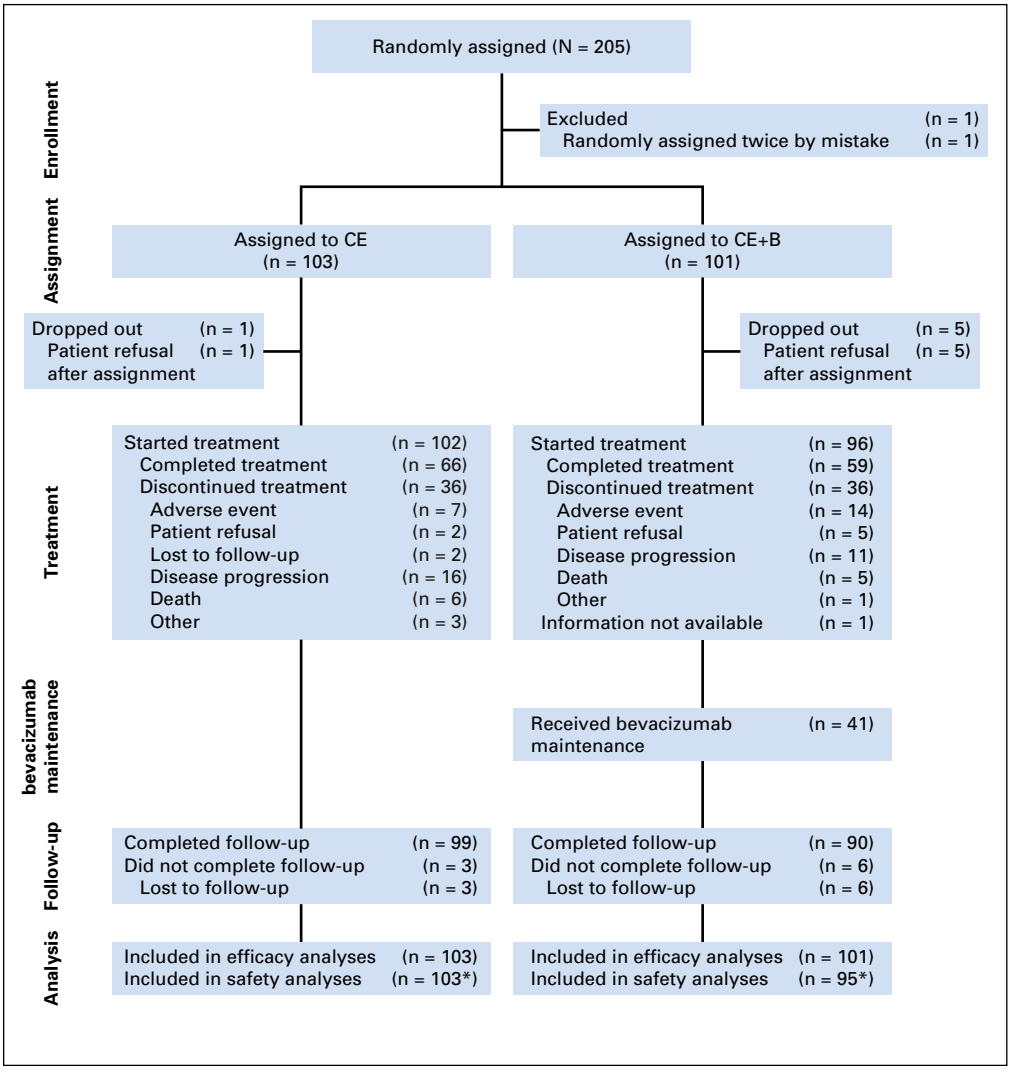

Fig 1. Trial profile. (*) One patient assigned to the cisplatin and etoposide plus bevacizumab (CE+B) treatment arm never received bevacizumab. CE, cisplatin and etoposide.

Table 1. Baseline Characteristics of the Patients in the Intent-to-Treat Population

Characteristic	CE Alone (n = 103)	CE Plus Bevacizumab (n = 101)
Age, years		
Median	63.0	64.0
Range	41-81	45-79
Sex, No. (%)		
Male	70 (68.0)	69 (68.3)
Female	33 (32.0)	32 (31.7)
ECOG performance status, No. (%)		
0	57 (55.3)	53 (52.5)
1	35 (34.0)	42 (41.6)
2	11 (10.7)	6 (5.9)

Abbreviations: CE, cisplatin and etoposide; ECOG, Eastern Cooperative Oncology Group.

Among 96 patients enrolled onto arm B, 41 patients (42%) continued bevacizumab beyond the sixth cycle of therapy. The other 55 patients did not continue bevacizumab because of medical decision (n = 10), disease progression (n = 20), AEs (n = 13), death (n = 6), patient refusal (n = 5), or other reasons (n = 1). A median of four cycles of bevacizumab maintenance were administered (range, one to 12 cycles); this treatment was interrupted in 27 patients (65.8%) as a result of disease progression. Prophylactic cranial irradiation (PCI) was administered in 28 patients (17 in arm A and 11 in arm B; Table 2).

Grade 3 to 5 AEs were reported in 64 patients (62.1%) who received only chemotherapy, compared with 52 patients (54.7%) who were also treated with bevacizumab ($P = .291$; Table 3). The majority of AEs reported during the study were grade 1 or 2. The study treatment was interrupted for AEs in 6.8% *v* 14.7% of patients in arm A versus arm B, respectively. Concerning the hematologic toxicity, no statistically significant differences were observed between the two arms. Concerning the nonhematologic toxicity, only hypertension was more frequent in the bevacizumab arm (grade 3 or 4, 1% *v* 6.3% of patients in arm A *v* arm B, respectively; $P = .057$); no grade 3 or 4 proteinuria or hemorrhage was documented in either arm.

Table 2. Treatment Characteristics of the Patients in the As-Treated Population

Characteristic	CE Alone (n = 103)	CE Plus Bevacizumab (n = 95)
Median No. of chemotherapy courses	6	6
Type of platinum, No. (%)		
Cisplatin	93 (90.3)	91 (95.8)
Carboplatin	7 (6.8)	3 (3.1)
Both	3 (2.9)	1 (1.1)
Overall relative dose-intensity (%)		
Average	87.6	89.2
Range	56.3-100	40.8-100
Dose reduction, No. (%)	31 (30.1)	34 (35.8)
Dose delay, No. (%)	62 (60.2)	56 (58.9)
Maintenance treatment, No. (%)	NA	41 (43.2)
No. of maintenance treatment courses		
Median	NA	4
Range	NA	1-12
Prophylactic cranial irradiation, No. (%)	17 (16.5)	11 (11.6)

Abbreviations: CE, cisplatin and etoposide; NA, not applicable.

Table 3. Most Common Grade 3 or 4 Adverse Events Observed in the Safety Population

Adverse Event	No. of Patients (%)		
	CE Alone (n = 103)	CE Plus Bevacizumab (n = 95)	*P**
Anemia	10 (9.7)	3 (3.2)	.063
Leukopenia	14 (13.6)	14 (14.7)	.817
Neutropenia	47 (45.6)	44 (46.3)	.923
Thrombocytopenia	11 (10.7)	4 (4.2)	.086
Nausea	5 (4.9)	1 (1.1)	.214
Vomiting	3 (2.9)	3 (3.2)	1.000
Fatigue	15 (14.6)	8 (8.4)	.178
Hypertension	1 (1.0)	6 (6.3)	.057
Thrombosis	3 (2.9)	5 (5.3)	.484
All events	64 (62.1)	52 (54.7)	.291

NOTE. Events listed are those that occurred in at least 3% of patients in either treatment group.
Abbreviation: CE, cisplatin and etoposide.
*According to the χ^2 test for heterogeneity or Fisher's exact test.

The response rate was 55.3% *v* 58.4% in arm A versus arm B, respectively (odds ratio, 1.13; 95% CI, 0.65 to 1.97; $P = .657$). At a median follow-up of 34.9 months, median PFS was 5.7 *v* 6.7 months (HR, 0.72; 95% CI, 0.54 to 0.97; $P = .030$; Fig 2A), median OS was 8.9 *v* 9.8 months, and 1-year survival rate was 25% *v* 37% (HR, 0.78; 95% CI, 0.58 to 1.06; $P = .113$; Fig 2C; Table 4) in arm A versus arm B, respectively.

A significant effect of the maintenance treatment on OS (HR, 0.60; 95% CI, 0.40 to 0.91; likelihood ratio test, $P = .011$), with only a borderline effect on PFS (HR, 0.72; 95% CI, 0.48 to 1.07; likelihood ratio test, $P = .095$), was shown including this factor in the Cox model as a time-dependent covariate. Comparable results were observed with the landmark analysis based on a limited sample of 78 patients who achieved an objective response or showed stable disease at the end of the induction phase. HRs were 0.71 (95% CI, 0.43 to 1.18) and 0.65 (95% CI, 0.40 to 1.07) for OS and PFS, respectively. The results obtained with both approaches were similar after the adjustment for sex, age, and ECOG PS at random assignment.

A subgroup analysis was performed to assess the possibility that some specific subgroup might have derived more benefit from the addition of bevacizumab to chemotherapy (Figs 2B and 2D). This analysis showed a statistically significant interaction for OS only between treatment and sex; in fact, the addition of bevacizumab led to a significant survival benefit in men (HR, 0.55) and to a possible detrimental effect in women (HR, 1.55; interaction test, $P = .003$).

Possible candidates for PCI included 42 and 41 patients in arms A and B, respectively. However, in arm A, only 14 selected patients received PCI, and in arm B, only eight patients received PCI. The delivery of PCI was associated with a survival benefit; in fact, after adjustment according treatment arm, the estimated HR was 0.53 (95% CI, 0.29 to 0.98; $P = .034$).

DISCUSSION

To our knowledge, this is the first randomized, prospective, comparative phase III study assessing the role of adding bevacizumab to standard platinum plus etoposide chemotherapy on

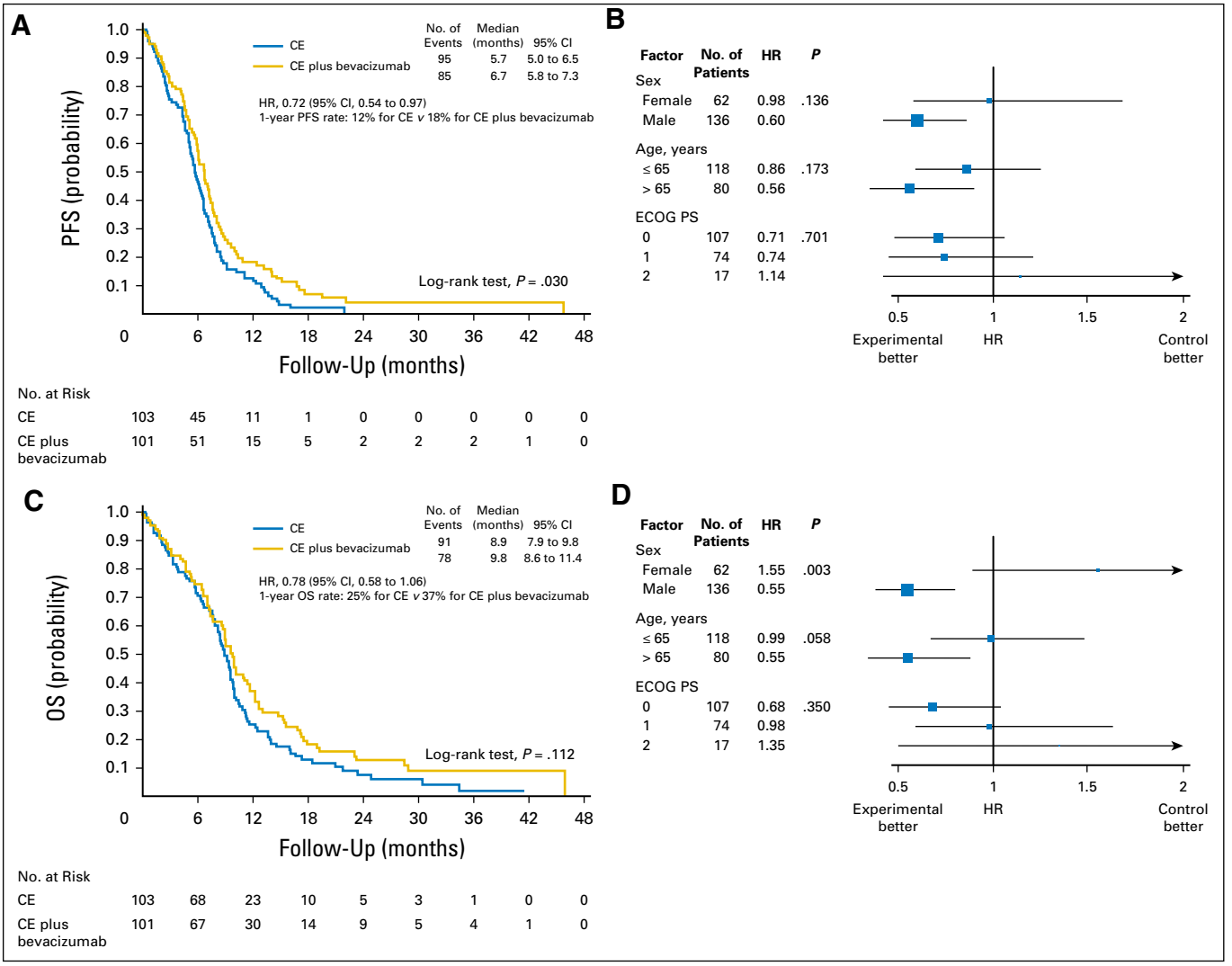

Fig 2. Kaplan-Meier estimates of progression-free survival (PFS) and overall survival (OS) according to treatment group. (A) Kaplan-Meier curves and (B) forest plot are shown for PFS in the chemotherapy (cisplatin and etoposide [CE]) and CE plus bevacizumab groups for each stratum of the stratification factors. (C) Kaplan-Meier curves and (D) forest plot are shown for OS in the CE and CE plus bevacizumab groups for each stratum of the stratification factors. ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio.

survival outcome in the first-line treatment of ED-SCLC. The results of our trial indicate that this combined treatment is feasible and well tolerated and leads to a small statistically significant improvement in PFS. However, the primary end point of the study (ie, survival rate increase at 1 year from 40% to 58%) was not met.

The expected survival improvement was indeed rather optimistic, and the relatively small sample size of our trial does not allow us to prove a possible smaller survival gain if any. Such a large survival improvement was chosen on purpose when planning this study, in agreement with the government funding body (Agenzia Italiana del Farmaco), because it was believed that, given the added toxicity and cost of bevacizumab, only a clinically meaningful survival improvement would have been considered practice changing in Italy.

A preplanned subgroup analysis seems to indicate an interaction between bevacizumab and sex, with women experiencing even a detrimental effect with bevacizumab added to chemotherapy. We verified that this result was not attributable to the association between sex and the other clinical factors for which information was available. Even if this observation is subject to the issue of multiplicity tests and does not seem to have a plausible biologic explanation, other bevacizumab trials have come to similar conclusions.[13]

Interestingly, maintenance bevacizumab turned out to be associated with a better survival outcome. This finding might be influenced by selection bias because only the best patients (ie, those who did not experience progression after induction chemotherapy combined with bevacizumab) had access to maintenance therapy. However, we tried to limit the influence of such a bias with proper statistical analyses; in particular, the HR for OS estimated with the landmark analysis was equal to 0.71 (95% CI, 0.43 to 1.18). Even acknowledging the limitation of this observation, it raises the issue of the optimal timing of bevacizumab administration. Given the lack of a statistically significant benefit in terms of response rate in all the trials studying the concurrent use of chemotherapy, our data, together with those of the Cancer and Leukemia Group B 30504

Table 4. Efficacy in the Intent-to-Treat Population According to Treatment Group

Variable	CE Alone (n = 103)	CE Plus Bevacizumab (n = 101)	Odds Ratio or Hazard Ratio (95% CI)*	*P*
Response, No. (%)				
Complete response	2 (1.9)	1 (1.0)		
Partial response	55 (53.4)	58 (57.4)		
Stable disease	16 (15.5)	9 (8.9)		
Progressive disease	13 (12.6)	7 (6.9)		
Not evaluated	17 (16.5)	26 (25.7)		
Overall response rate			1.13 (0.65 to 1.97)	.657
No. (%)	57 (55.3)	59 (58.4)		
95% CI (%)	45.2 to 65.0	48.2 to 68.0		
Progression-free survival			0.72 (0.54 to 0.97)	.030
No. of events (%)	98 (95.1)	85 (84.2)		
Median, months (95% CI)	5.7 (5.0 to 6.5)	6.7 (5.8 to 7.3)		
Overall survival			0.78 (0.58 to 1.06)	.113
No. of deaths (%)	91 (88.3)	78 (77.2)		
Median, months (95% CI)	8.9 (7.9 to 9.8)	9.8 (8.6 to 11.4)		

Abbreviation: CE, cisplatin and etoposide.
*The ratios listed are hazard ratios, except for the overall response rate, for which the odds ratio is shown.

sunitinib maintenance trial,[14] generate the hypothesis that a sequential use could be a better and safer strategy to deliver antiangiogenic drugs in SCLC.

In the literature, we could identify only two other smaller comparative trials on the same subject.[10,15] The SALUTE (Study of Bevacizumab in Previously Untreated Extensive-Stage Small Cell Lung Cancer) phase II randomized trial enrolled a total of 102 patients with ED-SCLC to either cisplatin 75 mg/m^2 or carboplatin (area under the curve 5) and etoposide 100 mg/m^2 over 3 days for four cycles alone or combined with placebo or bevacizumab 15 mg/kg until disease progression.[10] The results of this study are remarkably similar to those of our trial. In fact, median PFS was significantly improved from 4.4 to 5.5 months (HR, 0.53), whereas median survival was numerically worse in the experimental arm (10.9 and 9.4 months in control and experimental arms, respectively; HR, 1.16). The authors concluded that a larger phase III trial was needed.

The only other published comparative trial available was conducted by the French Cooperative Thoracic Intergroup and has a rather different trial design.[15] In this trial, 147 patients with ED-SCLC were enrolled and treated with induction chemotherapy (cisplatin plus etoposide or cisplatin, etoposide, cyclophosphamide, and epidoxorubicin) for two cycles, and only 74 of 103 responding patients were then randomly assigned to receive or not receive bevacizumab 7.5 mg/kg until disease progression. The primary end point of this trial, the percentage of patients who were still in response after the fourth cycle, was not met because both arms had superimposable disease control. Similarly, the PFS outcome did not differ in the two arms (5.3 *v* 5.5 months in the experimental and control arms, respectively). In addition, neither serum VEGF nor soluble VEGF receptor (sVEGFR) concentration was predictive of bevacizumab benefit. Determination of the baseline serum levels of VEGF, sVEGFR1, sVEGFR2, E-selectin, basic fibroblast growth factor, and intercellular adhesion molecule was planned in this trial and is presently ongoing; the results will be the subject of a separate publication.

Besides bevacizumab, other antiangiogenic agents have been tested in ED-SCLC as an adjunct to chemotherapy, mainly in the setting of maintenance therapy, with mixed results. Thalidomide has been studied in two randomized trials.[16,17] Although the French Cooperative Thoracic Intergroup found a non–statistically significant 3-month increase in median survival,[16] a larger randomized study conducted in the United Kingdom did not show any benefit in terms of either PFS or OS with the addition of thalidomide maintenance for a maximum of 2 years.[17] The Canadian BR.20 randomized phase II trial examined whether vandetanib, an inhibitor of the VEGF and epidermal growth factor receptors, could prolong PFS in responding patients with SCLC; in a planned subgroup analysis, limited-stage patients treated with vandetanib had longer OS, whereas patients with ED treated with vandetanib had shorter survival compared with placebo.[18] Finally, the Cancer and Leukemia Group B 30504 randomized phase II placebo-controlled study tested another antiangiogenic multitarget tyrosine kinase inhibitor, sunitinib, as maintenance therapy in 144 patients with ED-SCLC patients without progressive disease after standard chemotherapy; PFS was prolonged with maintenance sunitinib from 2.1 months to 3.7 months (P = .02), and median OS was 6.9 months for placebo compared with 9.0 months for sunitinib (P = .16).[14]

In summary, the results of our trial, together with the available knowledge in this field, overall support the conclusion that combining bevacizumab with standard platinum plus etoposide chemotherapy does not lead to meaningful survival improvement in ED-SCLC. However, the finding of a statistically improved PFS in this trial, as in others performed with the same class of agents, justifies, in our opinion, further studies with novel and better antiangiogenic agents in ED-SCLC, particularly in the maintenance setting.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Marcello Tiseo, Luca Boni, Andrea Ardizzoni
Provision of study materials or patients: Marcello Tiseo, Francesca Ambrosio, Andrea Camerini, Editta Baldini, Saverio Cinieri, Matteo Brighenti, Francesca Zanelli, Efisio Defraia, Rita Chiari, Claudio Dazzi, Carmelo Tibaldi, Gianni Michele Turolla, Vito D'Alessandro, Nicoletta Zilembo, Anna Rita Trolese, Francesco Grossi, Ferdinando Riccardi, Andrea Ardizzoni
Collection and assembly of data: All authors
Data analysis and interpretation: Marcello Tiseo, Luca Boni, Andrea Ardizzoni
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Affiliations

Marcello Tiseo, Azienda Ospedaliero-Universitaria, Parma; **Luca Boni**, Clinical Trials Coordinating Center, Istituto Toscano Tumori, Azienda Ospedaliero-Universitaria Careggi, Firenze; **Francesca Ambrosio** and **Ferdinando Riccardi**, Azienda Ospedaliera di Rilievo Nazionale Cardarelli, Napoli; **Andrea Camerini**, Ospedale della Versilia, Lido di Camaiore; **Editta Baldini** and **Carmelo Tibaldi**, Ospedale San Luca, Lucca; **Saverio Cinieri**, Ospedale Perrino, Brindisi; **Matteo Brighenti**, Azienda Socio-Sanitaria Territoriale di Cremona, Cremona; **Francesca Zanelli**, Istituti di Ricovero e Cura a Carattere Scientifico (IRCCS), Ospedale Santa Maria Nuova, Reggio Emilia; **Efisio Defraia**, Ospedale Businco, Cagliari; **Rita Chiari**, Azienda Ospedaliero-Universitaria, Perugia; **Claudio Dazzi**, Ospedale Santa Maria delle Croci, Ravenna; **Gianni Michele Turolla**, Ospedale Civile Umberto I, Lugo di Romagna; **Vito D'Alessandro**, IRCCS Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo; **Nicoletta Zilembo**, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano; **Anna Rita Trolese**, Ospedale Mater Salutis di Legnago, Legnago; **Francesco Grossi**, Azienda Ospedaliera Universitaria San Martino IST-Istituto Nazionale per la Ricerca sul Cancro, Genova; and **Andrea Ardizzoni**, Azienda Ospedaliero-Universitaria Sant'Orsola Malpighi, Bologna, Italy.

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Marcello Tiseo
Consulting or Advisory Role: AstraZeneca, Eli Lilly, Boehringer Ingelheim, Novartis, Bristol-Myers Squibb, Pierre Fabre, Otsuka

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Francesca Ambrosio
No relationship to disclose

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Consulting or Advisory Role: Roche, Pfizer, AstraZeneca, Pierre Fabre

Editta Baldini
No relationship to disclose

Saverio Cinieri
Travel, Accommodations, Expenses: Genentech

Matteo Brighenti
No relationship to disclose

Francesca Zanelli
No relationship to disclose

Efisio Defraia
No relationship to disclose

Rita Chiari
No relationship to disclose

Claudio Dazzi
No relationship to disclose

Carmelo Tibaldi
No relationship to disclose

Gianni Michele Turolla
No relationship to disclose

Vito D'Alessandro
No relationship to disclose

Nicoletta Zilembo
No relationship to disclose

Anna Rita Trolese
No relationship to disclose

Francesco Grossi
No relationship to disclose

Ferdinando Riccardi
No relationship to disclose

Andrea Ardizzoni
Honoraria: Eli Lilly, Bristol-Myers Squibb, MSD, Boehringer Ingelheim
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Participating Institutions

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