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Randomized phase II–III study of bevacizumab in combination with chemotherapy in previously untreated extensive small-cell lung cancer: results from the IFCT-0802 trial†

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Background: This randomized phase II–III trial sought to evaluate the efficacy and safety of adding bevacizumab (Bev) following induction chemotherapy (CT) in extensive small-cell lung cancer (SCLC).

Patients and methods: Enrolled SCLC patients received two induction cycles of CT. Responders were randomly assigned 1:1 to receive four additional cycles of CT alone or CT plus Bev (7.5 mg/kg), followed by single-agent Bev until progression or unacceptable toxicity. The primary end point was the percentage of patients for whom disease remained controlled (still in response) at the fourth cycle.

Results: In total, 147 patients were enrolled. Partial response was observed in 103 patients, 74 of whom were eligible for Bev and randomly assigned to the CT alone group ($n = 37$) or the CT plus Bev group ($n = 37$). Response assessment at the end of the fourth cycle showed that disease control did not differ between the two groups (89.2% versus 91.9% of patients remaining responders in CT alone versus CT plus Bev, respectively; Fisher's exact test: $P = 1.00$). Progression-free survival (PFS) since randomization did not significantly differ, with a median PFS of 5.5 months [95% confidence interval (CI) 4.9% to 6.0%] versus 5.3 months (95% CI 4.8% to 5.8%) in the CT alone and CT plus Bev groups, respectively [hazard ratio (HR) for CT alone: 1.1; 95% CI 0.7% to 1.7%; unadjusted $P = 0.82$]. Grade ≥2 hypertension and grade ≥3 thrombotic events were observed in 40% and 11% of patients, respectively, in the CT plus Bev group. Serum vascular endothelial growth factor (VEGF) and soluble VEGF receptor titrations failed to identify predictive biomarkers.

Conclusion: Administering 7.5 mg/kg Bev after induction did not improve outcome in extensive SCLC patients.

Key words: small-cell lung cancer, chemotherapy, anti-angiogenesis therapy, bevacizumab

introduction

Chemotherapy still constitutes the backbone of small-cell lung cancer (SCLC) therapy, particularly in the extensive disease (ED) stage (ED-SCLC) [1]. SCLC clinically behaves aggressively, with a rapid growth and metastatic spread. As these features are thought to be angiogenesis-dependent processes, therapy targeting

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angiogenesis could be considered a putative therapeutic window [2]. Bevacizumab (Bev), a monoclonal antibody against vascular endothelial growth factor (VEGF), has been approved for treating metastatic non-SCLC [3], colon cancer, breast cancer, renal carcinoma, and some malignant brain tumors. In ED-SCLC, a recent randomized, placebo-controlled phase II study demonstrated that adding Bev to a PE doublet from treatment day 1 improved progression-free survival (PFS) from 4.4 to 5.5 months [4]. As has already been attempted with thalidomide, another possible schedule for adding an antiangiogenic therapy merits investigation, consisting in delivering the antiangiogenic drug firstly with chemotherapy cycle 3 in responders only [2]. This schedule has been designed in the attempt to minimize potential Bev-induced hemorrhage, as bulky mediastinal involvement is frequently observed with SCLC, as well as to select patients with putative long-term survival, namely those with rapid tumor response to conventional cytotoxic agents.

We hypothesized that the combination of an active chemotherapy and maintenance therapy using an antiangiogenic compound could improve the outcome of ED-SCLC patients. We therefore designed a two-step study as follows: (i) patients received two cycles of chemotherapy; (ii) responders then entered the second step and were randomly allocated to receive four additional cycles of chemotherapy alone or chemotherapy with Bev until progression or unacceptable toxicity. In this article, we present the final results of this French intergroup, prospective, randomized phase II–III study of Bev in ED-SCLC patients after response to chemotherapy.

patients and methods

patients

The following enrollment criteria were applied (step 1): patients with newly diagnosed, histologically confirmed ED-SCLC, defined according to the Veterans Administration Lung Cancer Group [5], and measurable disease, according to the response evaluation criteria in solid tumors (RECIST) Version 1.1. Other eligibility criteria consisted of Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2; ≤75 years of age; <10% weight loss during the preceding 3 months; normal hematological functions and blood chemistry; no prior treatment; no symptomatic brain metastases. Signed informed consent was required prior to commencing step 1 and the study was approved by a national ethics committee (Sud - Mediterranée IV, Montpellier University, Montpellier, France) and registered at clinicaltrials.gov under NCT00930891.

The following criteria were applied at randomization following two cycles of chemotherapy (step 2): patients who had achieved a complete or partial response and recovered from any toxicity over grade 1 were evaluated for randomization. At this step, the following patients were not considered for randomization: patients with bulky mediastinal tumor burden invading or abutting large vessels, receiving anti-coagulant therapy, suffering from uncontrolled hypertension, having recently undergone surgery, or exhibiting active thrombotic event or hemoptysis. For these patients, treatment was continued at the discretion of the respective local center on a case-by-case basis, primarily consisting of four additional chemotherapy cycles. Other patients were then randomized to continue chemotherapy until the sixth cycle, with or without Bev.

treatment

Each center had the choice of one of the two modalities at the time of site initiation visit. Policy A (PE) consisted in each patient accrued by the center receiving PE combination, irrespective of PS. Policy B (PCDE/PE) consisted in patients with PS 0–1 receiving a four-drug regimen composed of cisplatin–cyclophosphamide–epidoxorubicin–etoposide (PCDE), whereas those with PS 2 received PE. A cycle started every 3 weeks (details of chemotherapy regimens are given in supplementary Table S1, available at *Annals of Oncology* online).

The patients randomly assigned to CT alone treatment, who achieved complete response, were put forward for prophylactic cranial irradiation. Those in the CT plus Bev group were excluded from this procedure due to the lack of available data regarding Bev and brain radiotherapy at the time of study design. Treatment at relapse was left to the discretion of each center's guidelines.

Bev was delivered at 7.5 mg/kg (Roche, France) on day 1 from cycle 3 to cycle 6, then every following 3 weeks. The first infusion lasted for 90 min; if tolerated, subsequent infusions lasted for 30 min. The postponement or discontinuation of Bev therapy was opted for in cases of specific toxicity or any serious adverse event (AE) not related to chemotherapy. The on-study drug was planned for a maximal duration of 2 years.

biomarkers

A blood sample was taken from each patient at step 1, prior to commencing the day 1 ($T_{baseline}$) first cycle of chemotherapy, and again at randomization (T_{random}), in order to test serum VEGF along with soluble VEGF receptor-1 and receptor-2 (sVEGFR-1, sVEGFR-2); details of titrations are indicated in supplementary Table S2, available at *Annals of Oncology* online.

study design and statistical considerations

Patients were randomly assigned 1:1 to receive chemotherapy alone (CT alone) or chemotherapy plus bevacizumab (CT plus Bev). Randomization was stratified (minimization) by PS [at time of randomization (0–1 versus 2)], gender, chemotherapy regimen (A versus B), liver metastasis, and center.

This open randomized study was planned in two phases: phases II and III. The response rate was used as primary end point in phase II and overall survival (OS) in phase III.

The end point for phase II was the proportion of patients for whom disease remained controlled (still exhibiting tumor response) at the end of the fourth cycle, i.e., 6 weeks after randomization. We hypothesized that a difference of at least 18% should be observed, 57% for CT alone and 75% for CT plus Bev, taking into account previous results produced with thalidomide [6]. The planned accrual was 74 randomized patients, taking into account a β risk of 20% and an α risk of 5%. Secondary objectives were to estimate PFS and OS, as well as to evaluate safety profile, biomarkers, and quality of life as assessed using Lung Cancer Symptom Scale (LCSS).

Survival analyses and response assessments (RECIST 1.1) were conducted on an intention-to-treat basis. Patients who had received at least one chemotherapy cycle after randomization were included in the safety and compliance analysis with the treatment population (toxicity criteria assessed using CTC-NCI Version 3.0). OS was defined as the time from randomization to the date of death. PFS was defined as the period lasting from randomization to the date of the first observation of progressive disease or death. Probability of survival was estimated by means of the Kaplan–Meier method and survival difference was analyzed using log-rank tests. The associations observed between treatment groups, stratification variables, and biomarkers with survival were tested via a Cox proportional hazards model. The variables to be tested in the model were selected using the results of univariate analysis ($P < 0.20$). The classical forward selection of variable procedure was used. A P-value <0.05 was considered significant. Assessments of response, toxicity, and quality of life are indicated in supplementary Table S3, available at *Annals of Oncology* online.

results

patients

From September 2009 to October 2011, 147 patients were admitted to 49 French centers. At the time of randomization, 103 patients (70.1%) had achieved partial response, and no complete responses were observed. Of these, 74 were randomized (Figure 1; CONSORT—Consolidated Standards of Reporting Trials). One patient had withdrawn his consent before receiving any treatment. Four patients (2.7%) were ineligible due to limited disease ($n = 2$), or non-SCLC histology ($n = 2$). In addition, three patients randomly allocated to the CT plus Bev group were found to be ineligible, one having exhibited persistent grade 2 thrombocytopenia following step 1, a second presenting with congenital cerebrovascular hemangioma, making them ineligible for Bev therapy, and a third only achieving stable disease at the end of step 1. Only the third patient received the allocated treatment (CT plus Bev). Table 1 displays patient demographics and disease characteristics for the step 1 population and the two randomized groups. Variable distributions were well balanced between the two groups.

efficacy and compliance at step 2

Response assessment at the end of the fourth chemotherapy cycle showed that disease control did not significantly differ between the two groups (89.2% versus 91.9% of patients remaining responders receiving CT alone versus CT plus Bev, respectively; Fisher's exact test: $P = 1.00$; Table 2). With regard to compliance with the chemotherapy program, 83.8% of patients in the CT alone group completed the entire six-cycle program, when compared with 91.4% patients in the CT plus Bev group. For the patients receiving CT plus Bev, the median number (range) of Bev infusions received was nine (4–16), including four cycles of maintenance where Bev was received after the end of chemotherapy. Mean ± SD dose intensity was 100 ± 9.5%. With regard to compliance with the chemotherapy program, the cisplatin dose intensity was significantly higher in the CT plus Bev group at 0.96 versus 0.99 for CT alone versus CT plus Bev, respectively (Mann–Whitney: $P = 0.008$). The dose intensity for etoposide did not significantly differ (0.98 versus 0.97 for CT alone versus CT plus Bev, respectively; $P = 0.32$). Four patients (five cycles) in the CT alone group and two patients (four cycles) in the CT plus Bev group required treatment switch from cisplatin to carboplatin.

Disease progression was the main reason for protocol discontinuation, indistinctly affecting both groups, with 91.9% and 91.4% for the CT alone and CT plus Bev groups, respectively. The other reasons for discontinuation were death ($n = 2$), toxicity ($n = 2$), and protocol violation ($n = 2$).

safety

In step 1, three toxic deaths occurred due to severe myelosuppression. These patients had received the conventional PE doublet (supplementary Table S1, available at *Annals of Oncology* online).

In Step 2, myelosuppression was mild to moderate and manageable (Table 3). Of the total 416 cycles administered during step 2, 205 (49.3%) were delivered with a G-CSF prophylaxis, corresponding to 103 (50%) and 102 cycles (48.6%) in the CT alone and CT plus Bev groups, respectively. Red blood cell and platelet transfusion requirements did not differ between the two groups. In the CT alone group, red blood cell and platelet transfusions were required for 5.3% and 0.5%, respectively, of the 206 cycles delivered, versus 4.3% and 1.9% of the 210 cycles received in the CT plus Bev group. During step 2, hematological toxicity did not differ between the two groups.

In Table 3, selected toxicity, namely any potential Bev-induced toxicity, are shown. No unexpected toxicity occurred. A 57-year-old patient, however, experienced severe hypertension after the 10th Bev administration. A subdural hematoma occurred despite antihypertensive therapy, causing death. At the

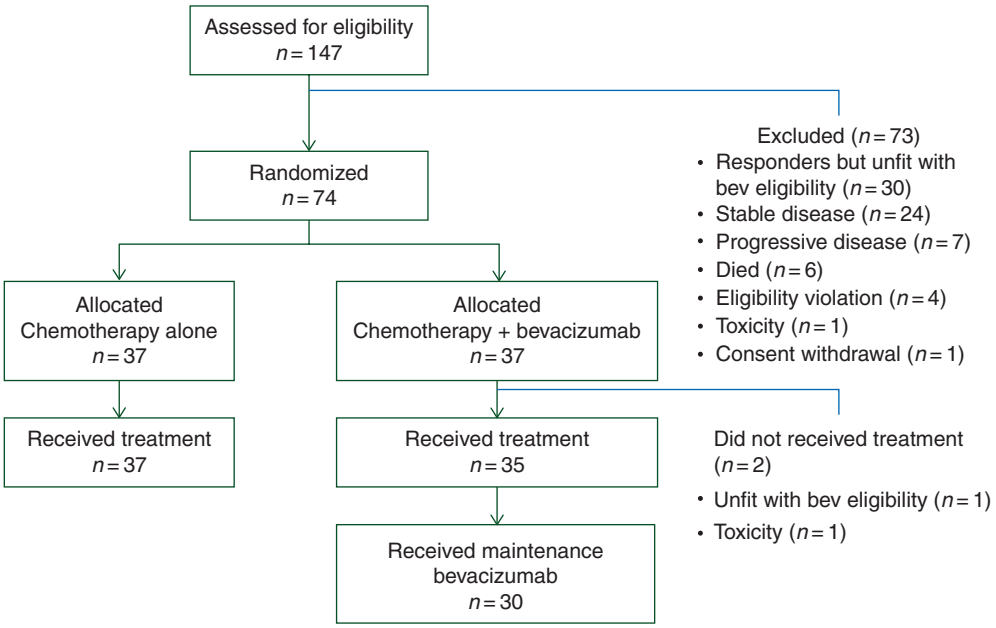

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram of the phase II clinical trial to evaluate chemotherapy alone versus chemotherapy plus bevacizumab.

Table 1. Comparison of patient demography and disease characteristics at time of enrollment and time of randomization for patients with extensive small-cell lung cancer (SCLC) randomly assigned to chemotherapy alone versus chemotherapy plus bevacizumab

	Step 1 ($n = 147$)	Randomization ($n = 74$)	CT alone ($n = 37$)	CT plus Bev ($n = 37$)	P
Male gender (%)	108 (73.5%)	51 (68.9%)	26 (70.3%)	25 (67.6%)	0.80
Mean age (range) (years)	60.5 (24–75)	60.6 (43–75)	60.1 (46–72)	61.2 (43–75)	0.52
ECOG PS (%)[a]					
0–1	118 (80.3%)	68 (91.9%)[b]	35 (94.6%)	33 (89.2%)	0.11
2	29 (19.7%)	5 (6.8%)	2 (5.4%)	3 (8.1%)	
Mean weight loss prior to therapy ±SD (kg)	3.8 ± 4.2	3.3 ± 4.0	3.1 ± 4.4	3.4 ± 3.6	0.96
Site of metastases (%), *n*					
Liver	83 (56.5%)	37 (50.0%)	18 (48.6%)	19 (51.4%)	0.82
Adrenal gland	31 (21.1%)	12 (16.2%)	4 (10.8%)	8 (21.6%)	0.21
Bone	42 (28.6%)	25 (33.8%)	11 (29.7%)	14 (37.8%)	0.46
Brain	22 (15.0%)	7 (9.5%)	5 (13.5%)	2 (5.4%)	0.43
Other	13 (8.8%)	8 (10.8%)	3 (8.1%)	5 (13.5%)	0.71
Type of chemotherapy					
PE	127 (86.4%)	60 (81.1%)	29 (78.4%)	31 (83.8%)	0.55
PCDE	20 (13.6%)	14 (18.9%)	8 (21.6%)	6 (16.2%)	

[a]Step 1 PS values correspond to observed PS at time of inclusion; other PS values correspond to PS at randomization.
[b]PS at randomization missing for one patient.
ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation; Bev, bevacizumab; CT, chemotherapy; PE, cisplatin–etoposide; PCDE, cisplatin–etoposide–4′-epidoxorubicin–cyclophosphamide.

Table 2. Patients with disease remaining controlled according to treatment group: number and percentage of affected patients at the end of the fourth cycle (end point) and after cycle 6, i.e., two cycles and four cycles post-randomization

	Response evaluation at the end of cycle 4		Response evaluation at the end of cycle 6	
	CT alone ($n = 34$)	CT plus Bev ($n = 35$)	CT alone ($n = 31$)	CT plus Bev ($n = 32$)
Patients remaining responders (%)	89.2	91.9	62.2	78.4
95% CI	74.6–97.0	78.1–98.3	44.8–77.5	61.8–90.2
P[‡]	1.000		0.13	

[‡]Fisher's exact test for response evaluation at the end of cycle 4 and chi-square test for response at cycle 6.
CT, chemotherapy; Bev, bevacizumab; CI, confidence interval.

time of tumor progression, 83% and 75% of patients in the CT alone and CT plus Bev groups, respectively, received second-line chemotherapy, primarily consisting of topotecan.

survival

Median follow-up was 37.7 months (25–50 months). PFS from the date of randomization did not significantly differ between the two groups, with a median PFS of 5.5 months (95% CI 4.9% to 6.0%) versus 5.3 months (95% CI 4.8% to 5.8%) in the CT alone and CT plus Bev groups, respectively (HR for CT alone: 1.1; 95% CI 0.7% to 1.7%; unadjusted $P = 0.82$; Figure 2A). Randomization was found to have no effect on OS, calculated from the date of randomization, with a median OS of 13.3 months (95% CI 9.8% to 16.6%) versus 11.1 months (95% CI 8.7% to 14.0%) in the CT alone and CT plus Bev groups, respectively (HR for CT alone: 0.8; 95% CI 0.5% to 1.3%; unadjusted $P = 0.35$; Figure 2B). In subgroup analyses, the selected chemotherapy regimen constituted the only significant prognostic determinant of PFS, with a median PFS in policy A (PE) of 5.3 months (95% CI 4.9% to 5.5%) versus 5.6 months in policy B (PE/PCDE) (95% CI 4.9% to 7.9%) (HR for policy B: 0.5; 95% CI 0.3% to 0.9%; unadjusted $P = 0.02$).

The median OS from enrollment was 11.0 months (95% CI 9.9% to 12.6%) in the entire population, namely all patients accrued into step 1. OS from the sixth week following enrollment (landmark) was 8.3 months (95% CI 6.8% to 10.1%) and 12.4 months (95% CI 10.3% to 14.1%) in the non-randomized and randomized populations, respectively.

The mean LCSS score improved during the run-in period and remained stable in both groups after randomization (supplementary Figure S1, available at *Annals of Oncology* online).

biomarkers

Serum samples for biomarker analysis were available in 61 of the 74 patients (82.4%) at baseline and in 43 (58.1%) at randomization. The mean value of serum VEGF did not substantially

Table 3. Adverse events according to treatment group: number and percentage of affected patients

	CT alone cycles 3–6								CT plus Bev cycles 3–6 and maintenance							
	Grade 1		Grade 2		Grade 3		Grade 4		Grade 1		Grade 2		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Hematological																
Anemia	7	18.9	19	51.4	6	16.2	0	0	12	34.3	19	54.3	3	8.6	0	0
Neutrophil count decrease	0	0	4	10.8	8	21.6	5	13.5	2	5.7	5	14.3	7	20.0	8	22.9
Thrombocytopenia	11	29.7	10	27.0	4	10.8	0	0	16	45.7	5	14.3	3	8.6	4	11.4
Non-hematological																
Auditory/Ear	1	2.7	1	2.7	1	2.7	0	0	3	8.6	2	5.7	0	0	0	0
Cardiac	3	8.1	0	0	0	0	0	0	1	2.9	0	0	0	0	0	0
Neurological (without peripheral)	5	13.5	3	8.1	1	2.7	0	0	8	22.9	3	8.6	1	2.9	1	2.9
Neurological peripheral	8	21.6	4	10.8	0	0	0	0	9	25.7	3	8.6	0	0	0	0
Gastrointestinal	12	32.4	8	21.6	3	8.1	0	0	9	25.7	16	45.7	3	8.6	0	0
General	13	35.1	13	35.1	4	10.8	0	0	4	11.4	16	45.7	8	22.9	1	2.9
Hemorrhage	2	5.4	0	0	0	0	0	0	6	17.1	1	2.9	0	0	0	0[a]
Hypertension	3	8.1	2	5.4	0	0	0	0	4	11.4	12	34.3	2	5.7	0	0
Infection	2	5.4	2	5.4	0	0	0	0	3	8.6	6	17.1	2	5.7	0	0
Metabolic disorders	5	13.5	4	10.8	2	5.4	1	2.7	6	17.1	3	8.6	4	11.4	0	0
Occular	0	0	0	0	0	0	0	0	1	2.9	0	0	0	0	0	0
Pain	8	21.6	6	16.2	0	0	0	0	10	28.6	13	37.1	1	2.9	0	0
Proteinuria	0	0	0	0	0	0	0	0	1	2.9	2	5.7	0	0	0	0
Renal	6	16.2	2	5.4	0	0	0	0	6	17.1	3	8.6	0	0	0	0
Renal other (cystitis and urinary retention)	0	0	0	0	0	0	0	0	2	5.7	2	5.7	2	5.7	0	0
Respiratory	5	13.5	6	16.2	3	8.1	0	0	8	22.9	8	22.9	0	0	0	0
Skin	6	16.2	8	21.6	1	2.7	0	0	4	11.4	8	22.9	0	0	0	0
Venous thromboembolism	1	2.7	3	8.1	0	0	2	5.4	0	0	1	2.9	4	11.4	0	0

[a]One patient randomly allocated to the CT plus Bev group died following subdural hemorrhage.

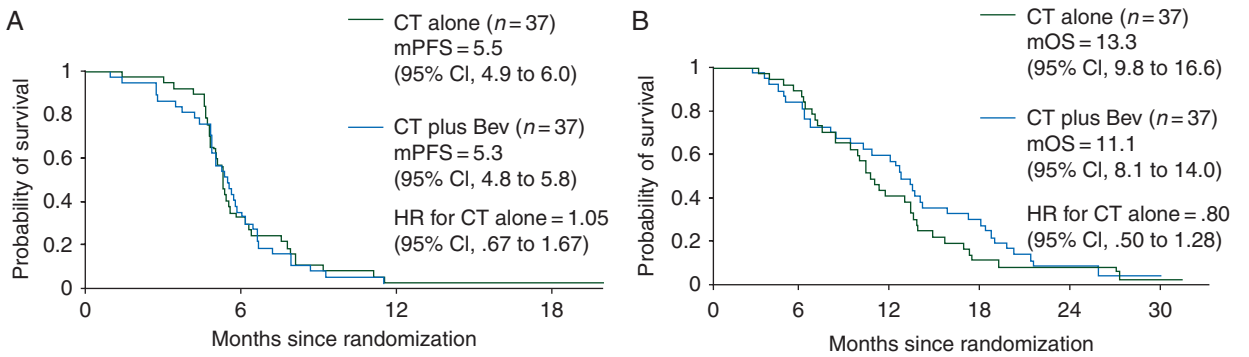

Figure 2. Survival from date of randomization: (a) progression-free survival (PFS); (b) overall survival (OS).

change from the time of enrollment to the time of randomization, with a $T_{baseline}$ mean (IR) of 390.1 pg/ml (188.4–441.8) and a T_{random} median (IR) of 357.8 pg/ml (171.6–627.8); Student's *t*-test: $P = 0.42$ (supplementary Table S2 and Figure S2, available at *Annals of Oncology* online).

The randomized patients exhibiting a T_{random} serum VEGF >300 pg/ml achieved a longer PFS from randomization onwards when compared to randomized patients exhibiting a T_{random} serum VEGF ≤300 pg/ml, though the difference did not reach statistical significance. The median PFS in patients with high T_{random} serum VEGF was 5.5 months (95% CI 4.9% to 6.5%) versus 5.3 months in patients with low T_{random} serum VEGF (95% CI 4.8% to 5.6%) (HR for high serum VEGF: 0.5; 95% CI 0.3% to 1.1%; unadjusted $P = 0.07$; supplementary Figure S3, available at *Annals of Oncology* online). In the Cox model, the marker was not a significant prognostic determinant of PFS. Subgroup analyses by randomized arm did not reveal any statistical differences in T_{random} serum VEGF level (data not shown). The T_{random} serum VEGF level did not influence OS.

Neither the $T_{baseline}$ serum VEGF level nor the $T_{baseline}$ or T_{random} sVEGFR-1 or sVEGFR-2 levels constituted prognostic variables of PFS or OS, and none of the tested biomarkers was found to be predictors of Bev's effect on survival.

discussion

In this randomized study, the adjunction of 7.5 mg/kg Bev administered after induction chemotherapy did not improve the outcome in ED-SCLC patients. The disease control rate in the CT plus Bev arm was higher than the one expected in our hypothesis insofar as 91.9% of the patients still remained in response at the end of CT cycle 4, whereas a 75% control rate was anticipated. Nevertheless, the hypothesis was not verified because of the high control rate also observed in the CT alone arm (89.2%). Consequently, the phase II part of the study failed to detect a positive signal, favoring the CT plus Bev regimen and the phase III part of the study was canceled. In addition, serum VEGF and soluble VEGF receptor titrations failed to identify a biomarker profile able to predict response or survival. The safety of the drug was not a factor in this negative result, insofar as compliance with Bev was acceptable and no unexpected toxicity was observed.

In 2011, Spigel et al. [4] published a randomized phase II trial that demonstrated that the triplet cisplatin–etoposide–bevacizumab combination improves PFS in ED-SCLC when compared with PE alone. However, this study was unable to prove any benefit with this regimen in terms of OS. Their study differed from our trial in several aspects. Firstly, the Bev dose used in the Spigel study was double that of the IFCT 0802. Nevertheless, in non-SCLC, no difference in terms of efficacy was observed when comparing patients receiving chemotherapy with 7.5 mg/kg Bev to those receiving 15 mg/kg [6]. Secondly, there was a difference in Bev therapy design, with our study delaying initiation until after the two-cycle induction.

Among the classical drugs with antiangiogenic properties that have been tested in SCLC using the two-step design, marimastat [7] (a matrix metalloproteinase inhibitor) and thalidomide failed to demonstrate sufficient efficacy in modifying the standard of care I [2, 8]. The most extensively studied antiangiogenic drug in SCLC to date is Bev. Although signals of activity have been observed in Spigel's, a clear impact on survival remains to be established. In addition, the ECOG 3501 [9] phase II study investigated the etoposide cisplatin doublet combined with Bev, whereas the CALGB 3036 study evaluated a combination of irinotecan cisplatin and Bev [10]. Both non-randomized studies failed to detect a meaningful outcome improvement in ED-SCLC. Numerous other compounds have been tested, such as cediranib, another anti-VEGF, yet their development has, to our knowledge, been discontinued after phase II [11].

Hitherto, the corpus of data from the published clinical studies (including our study) precludes further research on Bev chemotherapy combination in SCLC.

In conclusion, administering Bev after induction chemotherapy is not an option in ED-SCLC. The identification of biomarkers able to select patients who could potentially benefit from antiantigenic therapy is thus warranted.

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Effect of BRCA1 and XPG mutations on treatment response to trabectedin and pegylated liposomal doxorubicin in patients with advanced ovarian cancer: exploratory analysis of the phase 3 OVA-301 study†

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Background: We investigated the association of BRCA1 and XPG mutations with response rate (RR), progression-free survival (PFS) and overall survival (OS) in a subset of patients from a phase 3 clinical trial comparing the efficacy and safety of trabectedin + pegylated liposomal doxorubicin (PLD) versus PLD alone in patients with recurrent ovarian cancer.

Patients and methods: A candidate array was designed based on the Breast Cancer Information Core database for BRCA mutation analyses. An exploratory analysis of BRCA1/XPG mutation status was conducted using a two-sided log-rank test and 0.05 significance in germline DNA samples from 264 women with failed first-line platinum-based chemotherapy, randomized (1 : 1) to trabectedin + PLD or PLD alone.

Results: Overall, 41 (16%) of the 264 women had $BRCA1^{mut}$ (trabectedin + PLD: $n = 24/135$, 18%; PLD: $n = 17/129$; 13%) and 17 (6%) had XPG^{mut} (trabectedin + PLD: $n = 8/135$, 6%; PLD: $n = 9/129$, 7%). A higher RR was observed in $BRCA1^{mut}$ patients (20/41; 49%) versus $BRCA1^{wt}$ patients (62/223; 28%). Within the $BRCA1^{mut}$ group, trabectedin + PLD-treated patients had longer PFS and longer OS than PLD-treated patients (median PFS 13.5 versus 5.5 months, $P = 0.0002$; median OS 23.8 versus 12.5 months, $P = 0.0086$), whereas in $BRCA1^{wt}$ patients, OS was not significantly different (median OS: 19.1 versus 19.3 months; $P = 0.9377$). There were no differences in OS or PFS of patients with XPG^{mut} between the two treatment arms. However, trabectedin + PLD-treated patients with XPG^{mut} had a trend toward shorter PFS (median PFS: 1.9 versus 7.5 months; $P = 0.1666$) and OS (median OS: 14.5 versus 20.7 months; $P = 0.1774$) than those with XPG^{wt}.

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