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E5501 - Phase II Study of Topotecan Sequenced with Etoposide/ Cisplatin, and Irinotecan/Cisplatin Sequenced with Etoposide for Extensive Stage Small Cell Lung Cancer

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Abstract

Purpose—Sequence dependent improved efficacy of topoisomerase I followed by topoisomerase 2 inhibitors was assessed in a randomized phase II study in extensive-stage small cell lung cancer (SCLC).

Methods—Patients with previously untreated extensive stage SCLC with measurable disease, ECOG performance status of 0 to 3 and stable brain metastases were eligible. Arm A consisted of topotecan (0.75 mg/m^2) on days 1, 2 and 3, etoposide (70 mg/m^2) and cisplatin (20 mg/m^2) [PET] on days 8, 9 and 10 in a 3-week cycle. Arm B consisted of irinotecan (50 mg/m^2) and cisplatin (20 mg/m^2) on days 1 and 8 followed by etoposide (85 mg/m^2 PO bid) on days 3 and 10 [PIE] in a 3-week cycle.

Results—We enrolled 140 patients and randomized 66 eligible patients to each arm. Only 54.5% of all patients completed the planned maximum 6 cycles. There were grade ≥3 treatment-related adverse events in approximately 70% of the patients on both arms including 6 treatment-related grade 5 events. The overall response rates (CR+PR) were 69.7% (90% CI: 59.1–78.9%, 95% CI: 57.1–80.4%) for arm A and 57.6% (90% CI: 46.7–67.9%, 95% CI:44.8–69.7%) for arm B. The median PFS and OS were 6.4 months (95% CI: 5.4–7.5 months) and 11.9 months (95% CI: 9.6–13.7 months) for arm A and 6.0 months (95% CI: 5.4–7.0 months) and 11.0 months (95% CI: 8.6–13.1 months) for arm B.

Conclusion—Sequential administration of topoisomerase inhibitors did not improve on the historical efficacy of standard platinum-doublet chemotherapy for extensive stage SCLC.

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Keywords

small cell; topoisomerase; clinical trial; topotecan; irinotecan; sequential administration; survival

Introduction

Small cell lung cancer (SCLC) constitutes approximately 10–15% of all cases of lung cancer diagnosed in the US.[1,2] A large majority, more than two-thirds, of the SCLC patients present with extensive stage disease, indicating disease spread beyond the primary hemithorax and contiguous regional lymph nodes.[3,4] The initial chemotherapy responsiveness in SCLC and improved survival fueled the early optimism that SCLC is potentially curable with systemic therapy.[5] The two drug regimen, cisplatin plus etoposide, became the most commonly employed systemic therapy due to its improved toxicity profile and efficacy in comparison to the older CAV or CAE regimens.[6,7]

Despite the high response rate associated with frontline regimens, extensive stage SCLC essentially remains an incurable disease. Patients with resistant disease suffer early relapse with disease progression occurring within a year of treatment. Those with initially chemosensitive disease achieve longer time to disease progression but show diminished tumor responsiveness to chemotherapy at the time of recurrence. Despite the use of second line therapy or retreatment with the frontline regimen in cases with durable response off chemotherapy lasting more than 90 days, the overall survival at 5 years remains less than 5%.[8–10] New approaches explored in the last two decades have yielded no major therapeutic breakthroughs in this disease. While topoisomerase 2 (TOP-2) active agents such as etoposide and doxorubicin have long showed activity, the topoisomerase-1 (TOP-1) camptothecin derivatives inhibitors: topotecan and irinotecan, also later showed activity initially in the salvage setting and subsequently as part of frontline therapy.[11–14] The empiric addition of topotecan to frontline therapy in extensive stage SCLC failed to improve on the efficacy of cisplatin/etoposide, but substitution of irinotecan for etoposide in combination with cisplatin produced superior outcome in Japanese patients.[15,16] However, large randomized studies in the Western population failed to reproduce this efficacy benefit of irinotecan, and demonstrated greater toxicity.[17,18]

Rubin et al. explored the mechanism of action and development of resistance to the TOP-1 agents, camptothecins in preclinical models. These studies provided strong rationale for the further integration of these agents into the frontline therapy of extensive stage SCLC. This preclinical work showed that resistance to TOP-1 inhibitors may be mediated in part, by the down-regulation of the TOP-1 target, along with a compensatory increase in TOP-2 expression. Conversely, treatment with TOP-2 inhibitors results in a down-regulation of TOP-2 and compensatory up-regulation of TOP-1.[19,20] Furthermore, point mutations in TOP-1 resulted in increased sensitivity to cisplatin,[21] thus suggesting that intercalating cisplatin within the TOP-1, TOP-2 alternations might further enhance drug activity and overcome resistance. Initial validation of this preclinical observations was carried out in several phase I studies.[22–25] Consistent with the preclinical model prediction, peripheral blood monocytes showed reciprocal changes in the expression of TOP-1 and TOP-2

enzymes with sequential administration of their inhibitors. Since both TOP-1 and TOP-2 inhibitors are effective SCLC therapy, we expected a systematic exploitation of this mechanism to induce greater susceptibility of SCLC to the cytotoxicity of these agents and result in improved response and survival. The Eastern Cooperative Oncology Group therefore conducted this randomized phase II study to evaluate the triple regimens of topotecan followed by etoposide plus cisplatin (PET) as well as the combination of irinotecan plus cisplatin followed by oral etoposide (PIE) in patients with previously untreated extensive stage SCLC.

Materials and Methods

Eligibility

Eligibility included extensive stage SCLC with measurable disease and an ECOG performance status of 0–3. Prior systemic chemotherapy or thoracic irradiation was not allowed but prior radiotherapy for CNS metastasis was permitted, provided the patient had no evidence of progression in the brain before enrolment. Other salient eligibility requirements included: adequate hematologic, hepatic, and renal function within 4 weeks before randomization defined as WBC > 4000/mm^3 and platelets > 100,000/mm^3, bilirubin < 2×upper limit of normal, SGPT (ALT) and SGOT (AST) < 2.5×upper limit of normal or < 5 times upper limit of normal in patients with liver metastases; calculated creatinine clearance > 30mls/minute. Patients with prior diagnosis of any other type of malignancies within 5 years of enrolment were excluded except for treated basal or squamous cell skin cancer, or carcinoma in situ of the cervix.

Treatment

Eligible patients were randomized to one of two arms (A or B). Patients on arm A received topotecan (0.75 mg/m^2 IV) on days 1, 2 and 3 followed one week later by etoposide (70 mg/m^2 IV) and cisplatin (20 mg/m^2 IV) on days 8, 9 and 10 in a 3-week cycle schedule (PET). G-CSF: 5mcg/kg/day subcutaneously was administered starting day 11 of each cycle until WBC recovery > 10,000/mm^3. Treatment on arm B consisted of irinotecan (50 mg/m^2 IV) and cisplatin (20 mg/m^2 IV) on days 1 and 8 and etoposide (85 mg/m2 PO bid) on days 3 and 10 of each cycle (PIE). Cycles were repeated every 3 weeks for a total of 6 cycles in the absence of disease progression, withdrawal of consent or intolerable toxicities that, in the opinion of the treating physician, threatened the well-being of the patient.

Dose Modification

Before starting a new cycle, patients were evaluated for treatment emergent toxicities graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 2. In addition to instituting appropriate supportive care measures, dose modification was effected as appropriate for the agent presumed most likely responsible for the toxicity. Accordingly, topotecan dose was reduced by 25% for febrile neutropenia, or a nadir absolute neutrophil count of <500/mm^3 for 5 days or more during the previous cycle, and by 50% for nadir platelets count <25,000/mm^3.

Irinotecan dose was reduced by 25% for febrile neutropenia, a nadir absolute neutrophil count of < 500/mm^3 lasting ≥5 days or nadir platelets <25,000/mm^3 during the previous cycle. Etoposide dose was reduced by 25% for febrile neutropenia or nadir ANC of 750–999/mm^3. A 50% dose reduction was instituted for ANC <750/mm^3 and platelets <50,000/mm^3 while a 25–50% dose reduction was required for hepatic toxicity. Renal toxicity with creatinine elevation above 2mg/dL, grade 2 neurotoxicity or grade 3 gastrointestinal toxicity required a 50% reduction in the dose of cisplatin.

Dose re-escalation was allowed in cases of hematologic toxicities as tolerated but not in cases of grade 3 or 4 non-hematologic toxicities.

Efficacy

All enrolled patients had documented measurable disease on cross sectional anatomic imaging at baseline (not more than two weeks before randomization). Follow-up scans were obtained after every 2 cycles during treatment. Post treatment follow up scans were obtained once every 3 months for 2 years from study entry and once every 6 months between 2 and 3 years from study entry. Efficacy was assessed and graded according to the RECIST 1.0 guidelines as Complete Response (CR), Partial Response (PR), Stable Disease (SD) or Progressive Disease (PD). Confirmation of objective response classification (CR or PR) was required on a follow up scan obtained not earlier than four weeks from when the patient first met the objective response criteria.

Survival

All patients, including those whose protocol therapy was discontinued, were followed for response until progression and for survival for 3 years from the date of randomization. There were no specific follow-up requirements for patients surviving more than 3 years from study entry.

Statistics

Patients were randomized to the two treatment arms in equal numbers using permuted blocks without stratification with dynamic balancing on main institutions. The primary study endpoint was objective response frequency. The secondary efficacy endpoint was response duration. The study design called for a total accrual of 70 patients in each arm in order to have 63 eligible patients in the primary analysis. A treatment would be considered efficacious if the true response rate exceeded 35%. Using a two-stage design, a treatment arm was to be terminated if fewer than 6 objective responses were observed in the first 27 eligible patients enrolled in that arm. The treatment arm was to be declared efficacious if a total of 16 or more objective responses were observed.

For each arm, if the true response frequency was 0.2, the probability of stopping early was 0.54, and the probability of declaring the treatment efficacious was 0.1. If the true response frequency was 0.35, the probability of stopping early was 0.05, and the probability of declaring the treatment efficacious was 0.9. This design had 0.44, 0.72 and 0.93 probabilities to declare at least one treatment arm efficacious when the true response rates were 0.20 and 0.25, 0.20 and 0.30, and 0.20 and 0.35 in the two arms, respectively. The corresponding

conditional probabilities of selecting the correct treatment arm were 0.82, 0.93 and 0.98. These probabilities were determined by simulations. After a total of 9 months of treatment plus follow-up on 63 patients, the null hypothesis of a 9-month median survival was to be rejected in favor of the alternative that median survival exceeds 9 months if 38 patients were still alive. This test had a 0.04 significance level (exact binomial) and an 80% power to detect survival distributions where the 33rd percentile was 9 months or longer.

The data cut-off date for this analysis was January 24, 2012. The primary efficacy analyses excluded ineligible patients, while the toxicity analysis included all treated patients. Overall survival (OS) is defined as the time from randomization to death from any cause, with follow-up censored at the date of last contact. Progression free survival (PFS) was defined as time from randomization to documented progression or death without progression. Patients without documented progression or death reported were censored at the time of last documented disease evaluation. Duration of response was defined as the length of time between the date of confirmed response and the date of disease progression. Patients without documented progression were censored at the time of last documented disease evaluation.

Kaplan-Meier estimates were used for event-time distributions. Fisher's exact test (categorical variable with two categories), χ^2 test (categorical variable with three or more categories) and Wilcoxon test (continuous variable) were used to test for differences in baseline characteristics between the two arms. Confidence intervals for response frequencies were computed using the method of Atkinson and Brown.[26]

Results

The study was conducted between March 2004 and April 2008, and accrued a total of 140 patients. There were 6 ineligible patients and 2 patients who never started treatment, leaving 132 cases in the primary analysis (Figure 1 is a consort diagram summarizing the patient enrollment and randomization procedures).

Patient Characteristics

Full patient demographic factors and disease characteristics at the time of enrollment are presented in Table 1. The two study arms were well matched except for significant difference in age at enrollment (median age higher in arm B than arm A; Wilcoxon test p = 0.039) and better kidney function in patients in arm A than in arm B (Wilcoxon test p = 0.046).

Treatment

54.5% of the enrolled patients received the planned maximum 6 cycles of treatment (59.1% in arm A and 50% in arm B). Two eligible patients never started treatment; one due to withdrawal of consent, the other because of an elevated liver function test. One of 6 ineligible patients did not receive treatment.

Adverse Events

All patients who started assigned treatment, including ineligible patients, were included in the analysis of adverse events, giving 69 patients on arm A (PET) and 68 patients on arm B (PIE) for the adverse event analysis. More than 70% of the patients on both arms experienced treatmentrelated adverse events of grade 3 or higher. There were 6 treatment-related grade 5 events, all of which were due to infectious complication and neutropenia. Eight additional grade 5 events were considered unrelated to treatment. Details of all grades 3, 4 & 5 adverse events are provided in Table 2.

Response

Primary efficacy analysis was based on the 66 patients enrolled on each arm of the study. There were 46 PRs on arm A (PET) and 1 CR and 37 PRs on B (PIE). The overall response rates (CR+PR) were 69.7% (90% CI: 59.1–78.9%, 95% CI: 57.1–80.4%) for arm A (PET), and 57.6% (90% CI: 46.7–67.9%, 95% CI: 44.8–69.7%) for arm B (PIE), all adjusted for the two-stage design. Based on a prespecified response rate of 35%, both arms of the study met the required efficacious threshold defined in the study design. Twenty seven cases were inevaluable (13 on arm A, 14 on arm B). The median response duration was 6.0 months (95% CI: 5.0–7.0 months) for arm A and 6.0 months (95% CI: 5.0–8.3 months) for arm B (Figure 2).

Survival

The median OS was comparable between both arms, 11.9 months (95% CI: 9.6–13.7 months) for arm A and 11.0 months (95% CI: 8.6–13.1 months) for arm B (Figure 3). Similarly, median PFS was 6.4 months (95% CI: 5.4–7.5 months) for arm A and 6.0 months (95% CI: 5.4–7.0 months) for arm B (Figure 4). There were 43 patients in arm A (PET) and 39 patients in arm B (PIE) who survived more than 9 months. Under the null hypothesis of a 9-month median survival, the probabilities of having 39 or more, and 43 or more patients alive after 9 months were 0.009 and 0.088 for patients treated with the PET and PIE regimens, respectively (exact binomial).

Discussion

The sequence dependent potentiation of TOP-1 and TOP-2 inhibitors provided sufficient rationale to test the regimens of etoposide /cisplatin combination alternating with topotecan as well as the combination of irinotecan/cisplatin followed by oral etoposide in extensive SCLC patients. The study met the prespecified statistical endpoints of response rate of 35% but did not confer any significant improvement in progression free or overall survival when compared to the historical efficacy data of standard cisplatin /etoposide doublet chemotherapy. Despite the preclinical rationale, the strategy of alternating topoisomerase inhibitors in order to improve clinical efficacy could not be validated in this study.

Topotecan as a single agent showed promising single agent activity with objective response in approximately 40% of previously untreated patients,[27] and comparable efficacy with better tolerability than multi-agent chemotherapy, CAV, in the salvage setting.[28] The integration of topotecan into the frontline as part of a triplet therapy in the form of

maintenance therapy, or in combination with other classes of cytotoxic chemotherapy was not promising and led to increased toxicity and diminished quality of life.[15,29–33] Similarly a phase III study compared topotecan/cisplatin to topotecan/etoposide or cisplatin/etoposide in chemotherapy-naïve extensive stage SCLC and showed the topotecan/etoposide as inferior. Topotecan/cisplatin was superior to cisplatin/etoposide (median survival: 44.9 vs. 40.9 weeks; p = 0.40; median TTP: 27.4 vs. 24.3 weeks, p = 0.01) and showed significantly higher overall response rates for the (55.5% vs. 45.5%, p = 0.01). However, increased hematologic toxicity did not support the standard use of this for SCLC.[34] The combination of oral topotecan with IV cisplatin appeared better tolerated, but survival was not superior to standard regimen of etoposide/cisplatin.[35] The Hellenic Oncology Research Group studied sequential (4 cycles of cisplatin etoposide followed by 4 cycles of topotecan) versus alternating (1 cycle of cisplatin/etoposide alternating with 1 cycle of topotecan) schedule but showed no significant difference in response rates, median time to progression (TTP) or OS.[36]

Irinotecan is an established frontline agent for the treatment of SCLC in Japanese patients, with comparable activity but greater toxicity than etoposide –cisplatin in Western populations. Irinotecan is likewise frequently used as a salvage regimen in the US patient population.[16,8] The result of our study is not superior to the clinical efficacy observed with irinotecan as part of a doublet chemotherapy.[37–40] Similarly, the incorporation of irinotecan into a triplet regimen of carboplatin, etoposide and irinotecan failed to improve the clinical efficacy in a prior study.[41] Given the disparity between the preclinical and clinical findings, it seems worthwhile to explore the potential reasons for the failure of these two sequential combinations to improve on outcome results. First, one may question whether reduced dose intensity of cisplatin to minimize toxicity might have compromised the overall efficacy, but a randomized study by Ihde et al showed no dose-dependent effect over a 2-fold range of the cisplatin dose intensity.[42] Secondly, while our patient population, was mostly Caucasian, SWOG study 0124 showed the outcome with cisplatin/irinotecan to be similar to cisplatin/etoposide in this population.

Finally, pharmacokinetic and pharmacodynamic correlation in surrogate samples analyzed in the course of phase I clinical trials showed that TOP-2 expression induced by TOP-1 inhibitor therapy is short-lasting (<24 hours) such that for optimal efficacy, the administration of a TOP-2 inhibitor should be scheduled to occur within this narrow window following the administration of the TOP-1 inhibitor.[43,23] In a study testing sequential alternation of TOP-1 and TOP-2 inhibitors in acute leukemia, Saraiya et al showed by sequential study of the target leukemia cells that the optimal timing of the sequential administration of TOP-1 and TOP-2 inhibitors was approximately 6 hours, and much longer interval lacked the reciprocal target modulation and clinical efficacy.[44] In an attempt to minimize toxicity, the TOP-2 inhibitor, etoposide, was administered after 72 hours of the TOP-1 inhibitor administration in both arms of our study. In conclusion, our results along with published reports from other phase II and phase III trials do not support the incorporation of topotecan or irinotecan along with standard cisplatin/etoposide regimen in the frontline treatment of extensive stage SCLC. The 72 hour based sequential use ofTOP-1 and TOP-2 inhibitors failed to improve outcomes and produced more toxicity than socalled standard etoposide cisplatin. The results from the original phase I study and those from

leukemia patients suggest that the 72 hour based sequencing to reduce potential toxicities may not have been an adequate test of this hypothesis derived from intriguing preclinical observations of a potential mechanism of drug resistance

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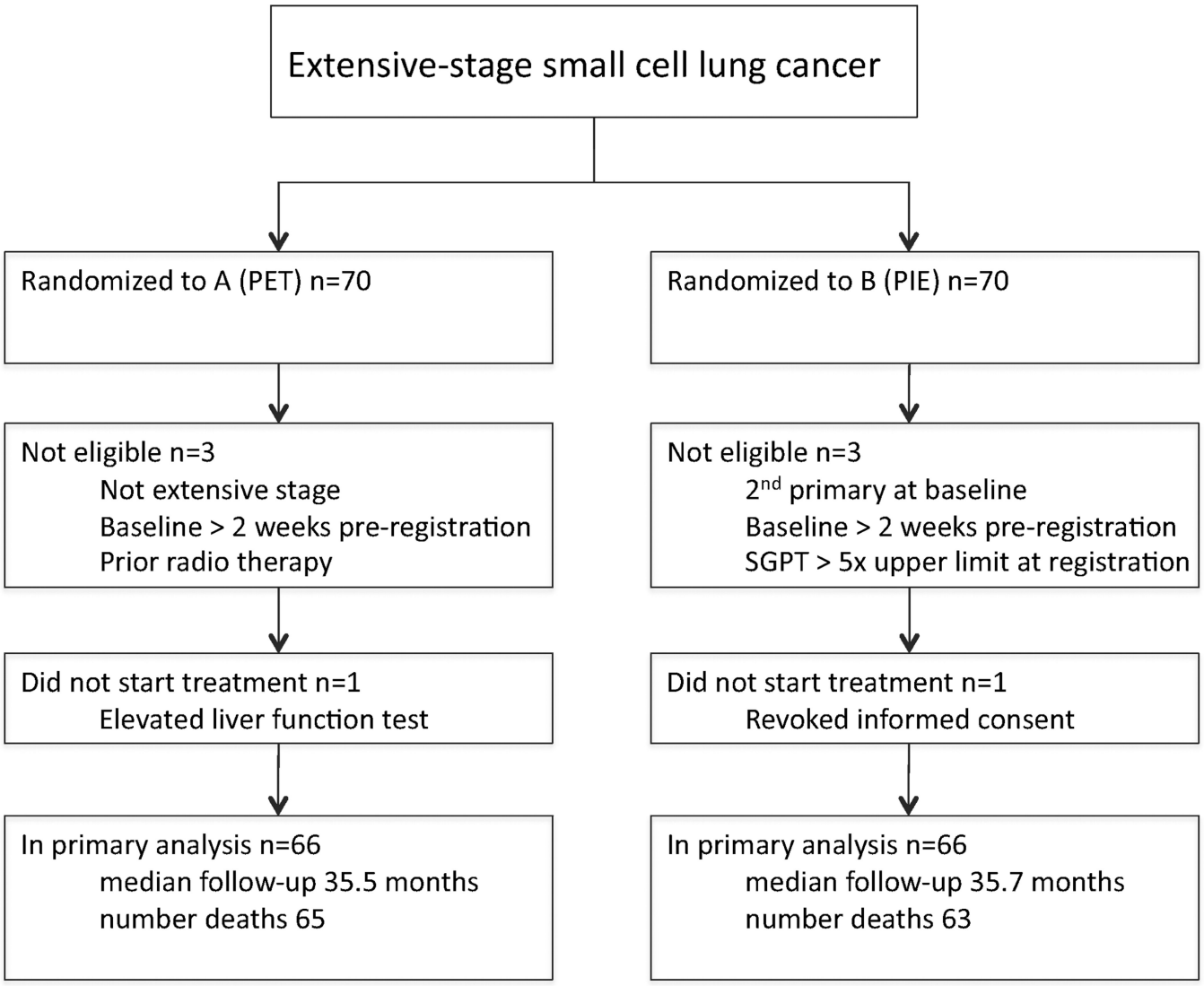

Figure 1.
Consort diagram showing enrolment, eligibility and randomization of patients on the study

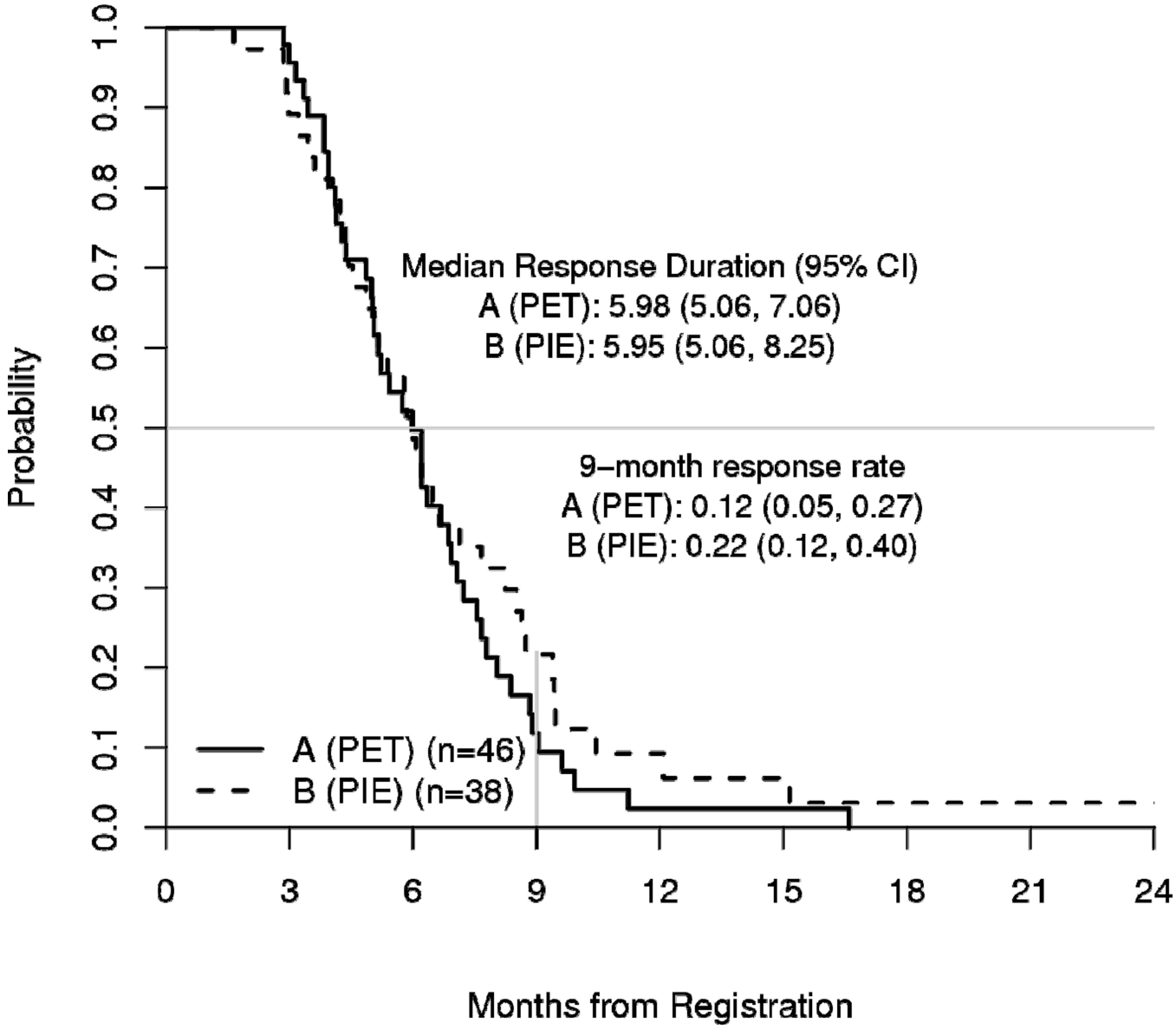

Figure 2.

Kaplan-Meier curves showing the duration of response in patients who achieved objective responses on both arms of the study

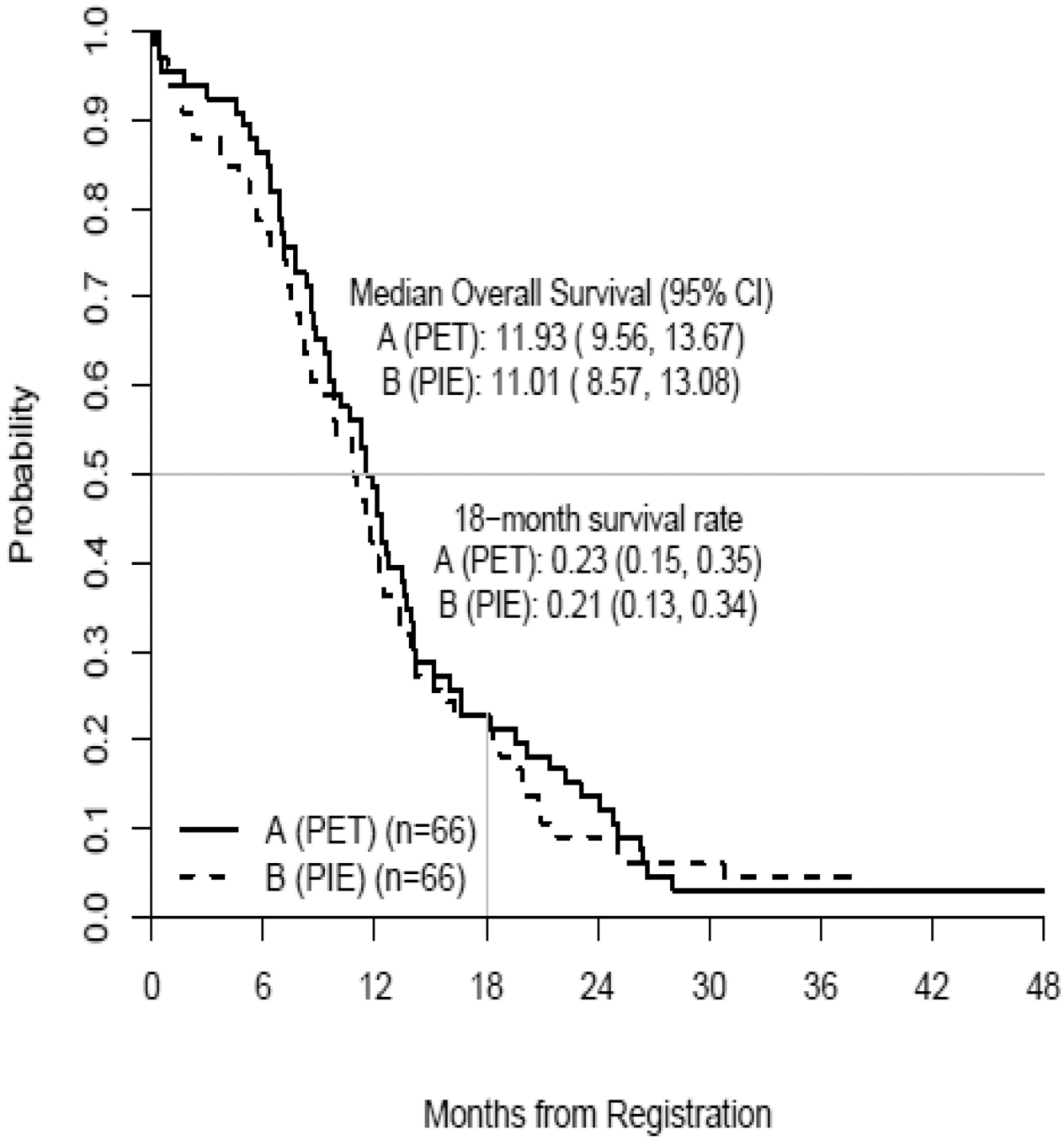

Figure 3.
Kaplan-Meier curves for overall survival measured from randomization until death or censorship for all eligible patients treated on both arms of the study.

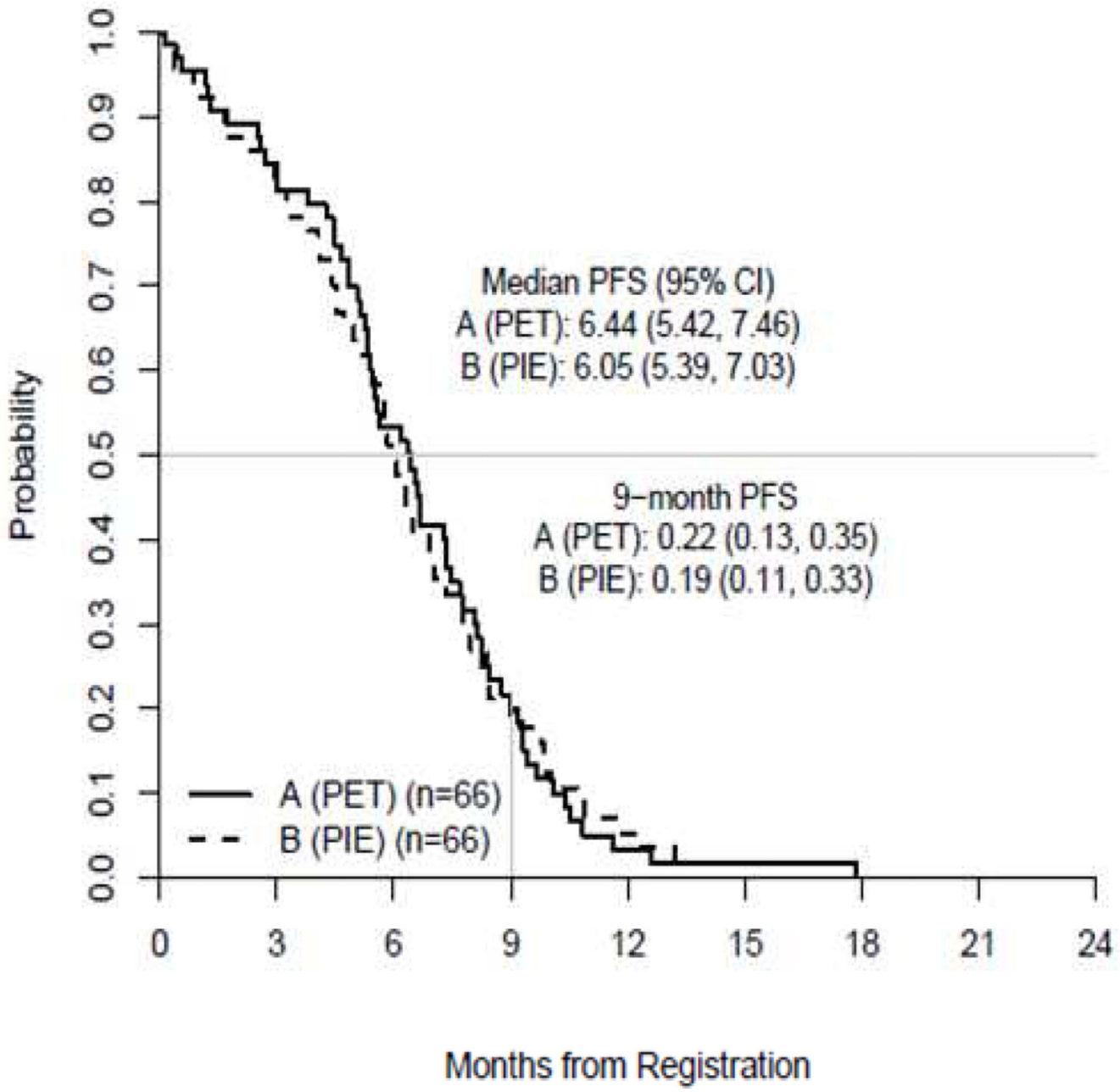

Figure 4.

Kaplan-Meier curves for progression-free survival measured from time of randomization until disease progression, death or censorship for all eligible patients treated on both arms of the study

Table 1
Patient demographics and disease characteristics

Demographic details and comparison of salient patient and tumor characteristics between the 2 arms of the study

Variable	Category	A (PET) N=66	B (PIE) N=66	Total N=132
Age	Median (IQR)	60 (53,68)	64 (58,70)	63 (56,69)
Age	<65	39(59.1)	33(50.0)	72(54.5)
	>=65	27(40.9)	33(50.0)	60(45.5)
Gender	Male	41(62.1)	33(50.0)	74(56.1)
	Female	25(37.9)	33(50.0)	58(43.9)
Race	White	63(95.5)	63(95.5)	126(95.5)
	Black	3(4.5)	3(4.5)	6(4.5)
Performance Status	0	27(40.9)	19(28.8)	46(34.8)
	1	29(43.9)	35(53.0)	64(48.5)
	2	6(9.1)	8(12.1)	14(10.6)
	3	4(6.1)	4(6.1)	8(6.1)
Weight Loss in Previous 6 Months	<5%	46(69.7)	39(60.9)	85(65.4)
	5–<10%	14(21.2)	13(20.3)	27(20.8)
	10–<20%	4(6.1)	9(14.1)	13(10.0)
	>=20%	2(3.0)	3(4.7)	5(3.8)
Degree of Involvement of Metastatic Sites	Single Lesion	3(4.5)	5(7.6)	8(6.1)
	Single Site	17(25.8)	16(24.2)	33(25.0)
	Multiple Lesions and Sites	46(69.7)	45(68.2)	91(68.9)
Pleural effusion present	No	39(59.1)	44(66.7)	83(62.9)
	Yes	27(40.9)	22(33.3)	49(37.1)
Pleural effusion malignant	No	5(18.5)	0(0.0)	5(10.2)
	Yes	5(18.5)	7(31.8)	12(24.5)
	Unknown	17(63.0)	15(68.2)	32(65.3)
	No	64(97.0)	62(93.9)	126(95.5)
Previous Radiation	Yes	5(7.6)	6(9.1)	11(8.3)

Variable	Category	A (PET) N=66	B (PIE) N=66	Total N=132
	No	65(98.5)	63(95.5)	128(97.0)
Previous Surgery	Yes	1(1.5)	3(4.5)	4(3.0)
	No	61(92.4)	60(90.9)	121(91.7)
CNS Metastases	Yes	5(7.6)	6(9.1)	11(8.3)

Randomization was balanced except for age and kidney function

Table 2

Grade 3, 4 & 5 Adverse Events

Details of all grade 3, 4 and 5 toxicities recorded on both arms of the study. Toxicity grading was according to the NCI CTCAE guidelines version 2

Adverse Event	Treatment Arms					
	A (PET)			B (PIE)		
	Grade			Grade		
	3 (%)	4 (%)	5 (%)	3 (%)	4 (%)	5 (%)
Hemoglobin	19	1		6	1	
Leukocytes	12	7		28	4	
Neutrophils	20	13		37	9	
Platelets	20	1		4		
Transfusion – Platelets	1					
Transfusion - PRBC	26			16		
SVT - Arrhythmia				1		
Hypotension	1				1	
Thrombosis/Embolism				1		
Visceral arterial ischemia		1				
Cardiac - other	1					
Fatigue	12	3		15	1	
Weight loss	1			1		
Constitutional						1
Skin – other				1		
SIADH				1		
Anorexia	4			9	3	
Constipation				1		
Dehydration	6			12		
Dyspepsia	1					
Ileus				1		
Nausea	4			7		
Vomiting	4			7		

Adverse Event	Treatment Arms					
	A (PET)			B (PIE)		
	Grade			Grade		
	3 (%)	4 (%)	5 (%)	3 (%)	4 (%)	5 (%)
Diarrhea	3			24	1	
GI-other					1	
Hemorrhage				1		
CNS hemorrhage						1
Epistaxis	1					
Hemoptysis	1					
Alkaline phosphatase	1			1		
Bilirubin	1			1		
SGOT	1	1		1		
SGPT	3	1		4	1	
Febrile Neutropenia			1	4		
Infection with grade 3 or 4 neutropenia	1	3	1	4		3
Infection without neutropenia	4			3	1	1
Hyperkalemia	1					
Hypermagnesemia		1				
Hypokalemia	3			1		
Hypomagenesemia	3			6		
Hyponatremia	1			3	1	
Hypophosphatemia					1	
Muscle weakness	1			4		
Confusion					3	
Depressed level of consciousness				1		
Depression				1		
Motor neuropathy	1			1		
Syncope	1					
Abdominal pain				4		

Adverse Event	Treatment Arms					
	A (PET)			B (PIE)		
	Grade			Grade		
	3 (%)	4 (%)	5 (%)	3 (%)	4 (%)	5 (%)
Earache				1		
Myalgia	1			1		
Dyspnea	4			4	1	
hypoxia	1			1	1	
Pneumonitis/Pulmonary Infiltrates				1		
Pulmonary -Other						1
Renal failure					1	