Lung Cancer

A phase II study of nintedanib in patients with relapsed small cell lung cancer

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ABSTRACT

Objectives: Nintedanib is an oral triple angiokinase inhibitor. This study was conducted to evaluate the efficacy and safety of nintedanib in patients (pts) with relapsed/refractory small cell lung cancer (SCLC).
Patients and methods: Pts with an ECOG PS from 0 to 2 who exhibited progression after one or two prior chemotherapy or chemo/radiotherapy were enrolled. Pts received nintedanib 200 mg BID daily in a 4-week cycle until progression or intolerable toxicity. The primary end point was the objective response rate (ORR). A two-stage design was employed. To continue to stage 2, ≥2 responders out of 22 pts were required.
Results: From Dec 2011 to June 2014, 24 pts were enrolled. Twenty-two pts completed treatment and were evaluable for response. The median follow-up was 9.7 (0.5–19.8) months. The median age was 64 (46–77) years. Twenty-two pts were male. Six pts had sensitive relapse. Eight pts received one prior chemotherapy. A median of one (range 1–5) cycle was administered. One pt had a partial response, and seven pts exhibited stable disease. The ORR was 5% (95% confidence interval [CI], 0.1–22.8). Median progression-free survival was 1.0 (95% CI, 0.9–1.1) month, and overall survival was 9.8 (95% CI, 8.4–11.2) months. The response criteria to proceed to full accrual were not met. The most frequent drug-related adverse events (AE) included hepatic enzyme elevation (86%), anemia (73%), anorexia (59%), and nausea (50%). Most AEs were mild and manageable. Grade 3 hepatic enzyme elevation occurred in 5 pts (23%).
Conclusions: Nintedanib exhibited only limited activity with a manageable AE profile in relapsed or refractory SCLC (NCT01441297).

1. Introduction

Despite a high initial response rate to chemotherapy, most patients with small cell lung cancer (SCLC) experience relapse within a year of completing first-line therapy and die from systemic metastases [1]. Although topotecan is regarded as the standard second-line therapy, the response rate is modest, and survival rates remain unsatisfactory [2,3]. Therefore, more effective novel agents are required for relapsed SCLC.

Human SCLC cells express functional vascular endothelial growth factor receptor (VEGFR)-2, VEGFR-3 and platelet-derived growth factor receptor (PDGFR)-β [4,5]. In addition, stem cell factor (SCF) and its receptor KIT are co-expressed in up to 70% of SCLC cell lines and clinical SCLC samples [6]. Therefore, we previously conducted a phase II study on sunitinib, a multi-target tyrosine kinase inhibitor that is effective against VEGFR-1, VEGFR-2, VEGFR-3, PDGFR and KIT, in patients with relapsed or refractory SCLC. The response rate was 9% (2/23), and the disease control rate was 39% (9/23). However, most patients were unable to tolerate the sunitinib treatment due to significant toxicity, which resulted in frequent sunitinib dose interruptions. The actual dose intensity (the actual dose delivered as a proportion of the planned dose with or without delay) of sunitinib was 69.7%, which may have led to the relatively low efficacy [7]. In contrast, a recent randomized phase II trial demonstrated that maintenance sunitinib after chemotherapy improved progression-free survival (PFS) in untreated patients with extensive-disease (ED)-SCLC. In addition, the overall survival (OS) was promising despite the cross-over design. These findings suggest that multi-targeted VEGFR inhibitors may be effective against SCLC [8].

Nintedanib is a potent, oral angiokinase inhibitor that targets the pro-angiogenic pathways mediated by VEGFR1-3, fibroblast growth factor receptor (FGFR) 1-3, and PDGFR α and β [9]. *FGFR1* is amplified in 6% of SCLC, and sensitivity to FGFR inhibitors has

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Table 1
Baseline characteristics of patients.

Characteristics		Patient No.
Age, years	Median (range)	64 (46–77)
Gender	Male	22
	Female	2
ECOG PS	0	1
	1	11
	2	12
Smoking	Median (range), pack-year	39 (11–94)
	Ever	21
	Never	3
Prior therapy No	One	8
	Two	16
Relapse pattern	Sensitive	6
	Resistant or refractory	18

Table 2
Adverse events.

	Grade 1	Grade 2	Grade 3	Grade 4
	N (%)	N (%)	N (%)	N (%)
Hematologic				
Anemia	12 (50)	6 (25)	0 (0)	0 (0)
Thrombocytopenia	6 (25)	0 (0)	0 (0)	0 (0)
Leukopenia	5 (21)	0 (0)	0 (0)	0 (0)
Neutropenia	0 (0)	2 (8)	1 (4)	0 (0)
Non-hematologic				
ALT elevation	5 (21)	9 (38)	5 (21)	0 (0)
AST elevation	5 (21)	9 (38)	2 (8)	0 (0)
Anorexia	6 (25)	7 (29)	0 (0)	0 (0)
Fatigue	7 (29)	5 (21)	1 (4)	0 (0)
Nausea	7 (29)	5 (21)	0 (0)	0 (0)
Diarrhea	8 (33)	1 (4)	0 (0)	0 (0)
Pain	4 (17)	5 (21)	0 (0)	0 (0)
Vomiting	5 (21)	1 (4)	0 (0)	0 (0)
Constipation	5 (21)	1 (4)	0 (0)	0 (0)
Abdominal pain	4 (17)	1 (4)	0 (0)	0 (0)
Epigastric soreness	3 (12)	3 (12)	0 (0)	0 (0)
Myalgia	2 (8)	2 (8)	0 (0)	0 (0)
Dyspepsia	3 (12)	0 (0)	0 (0)	0 (0)
Rash	2 (8)	1 (4)	0 (0)	0 (0)
Headache	2 (8)	1 (4)	0 (0)	0 (0)
Neuropathy-sensory	0	1 (4)	0 (0)	0 (0)
Mucositis	1 (4)	0 (0)	0 (0)	0 (0)
Dry mouth	1 (4)	0 (0)	0 (0)	0 (0)
Hand-foot syndrome	1 (4)	0 (0)	0 (0)	0 (0)
Hyponatremia	1 (4)	0 (0)	0 (0)	0 (0)
Hyperglycemia	1 (4)	0 (0)	0 (0)	0 (0)

been described in some, but not all, SCLC [10]. Recently, a randomized phase III study demonstrated a survival benefit of nintedanib in combination with docetaxel versus docetaxel alone in previously treated lung adenocarcinoma. In addition, nintedanib alone exhibited a manageable toxicity profile in phase I/II trials [11,12]. Given the potential activity through the inhibition of angiogenesis and a favorable toxicity profile, we conducted a phase II study of nintedanib in patients with relapsed or refractory SCLC.

2. Patients and methods

2.1. Eligibility criteria

Patients with ED-SCLC who progressed during or after treatment with at least one platinum-based chemotherapy were eligible for inclusion in the study. Patients, who have relapsed beyond 3 months of completing first-line treatment, were considered as the sensitive relapse. Patients who have progressed within 3 months were considered as the refractory relapse. Patients, who did not respond or relapsed during first-line treatment, were considered as resistant [13]. All patients displayed measurable disease by the Response Evaluation Criteria in Solid Tumors (RECIST), an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of less than or equal to 2, adequate hepatic, renal and hematologic function, and normal thyroid function. Additionally, all patients were at least 18 years of age. Patients were excluded if they presented a grade 3 hemorrhage based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) or gross hemoptysis (>5 mL of blood per episode and >10 mL of blood/d) less than 4 weeks prior to the onset of treatment. Prior treatment with anti-angiogenic agents was not permitted. Additional exclusion criteria included the following: uncontrolled hypertension; a diagnosis of any second malignancy within the preceding 3 years (except for adequately treated basal cell or squamous cell skin cancer or in situ carcinoma of the cervix uteri); a history of or current brain metastases, spinal cord compression, carcinomatous meningitis or evidence of brain or leptomeningeal disease; clinically significant cardiovascular disease (severe/unstable angina, myocardial infarction, coronary artery bypass graft, or symptomatic congestive heart failure); pulmonary embolism or cerebrovascular accident within the 12 months prior to the study drug administration; a history of a decline in the left ventricular ejection fraction below the lower limit of normal or ongoing cardiac dysrhythmias (NCI CTCAE grade ≥2), and atrial fibrillation or prolongation of the QTc interval. All patients with reproductive potential were required to use contraception during treatment. All patients were required to provide written informed consent prior to entry into the study.

2.2. Study design

This was an open-label, single-arm, phase II study conducted at a single center (National Cancer Center, Goyang, Korea). The primary end point was the objective response rate (ORR), defined as the percentage of all patients who experienced a confirmed complete response or partial response (PR) based on RECIST1.1 [14]. The secondary end points included safety and tolerability, PFS and OS. The protocol was approved by an independent ethics committee/institutional review board and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice.

2.3. Study treatment

The patients received nintedanib 200 mg orally twice daily every 4 weeks. In the case of treatment-related adverse events, nintedanib dose reductions were performed accordingly by 25% for each additional toxicity grade (i.e., 25% for grade 2 and 50% for grade 3 toxicity). Treatment was continued until tumor progression, withdrawal of consent or unacceptable toxicity, defined as grade 4 hematologic toxicity and grade ≥ 3 non-hematologic toxicity inducing a persistent delay in administration of the next cycle beyond day 42 of each cycle.

2.4. Assessment

The baseline evaluations included medical history, physical examination, tumor imaging with computed tomography or a magnetic resonance imaging scan, laboratory tests (hematology, urinalysis, coagulation, blood chemistry and pregnancy tests), three 12-lead electrocardiogram (ECGs) and echocardiography. Hematology, blood chemistry and thyroid function (T3, thyroid-stimulating hormone (TSH), and free T4) evaluations were performed before each treatment cycle. The response assessment was performed at the end of dosing in cycles 1 and 2 followed by every two cycles according to the RECIST criteria 1.1. Initially, tumor responses were evaluated by the investigator. Subsequent to the evaluation
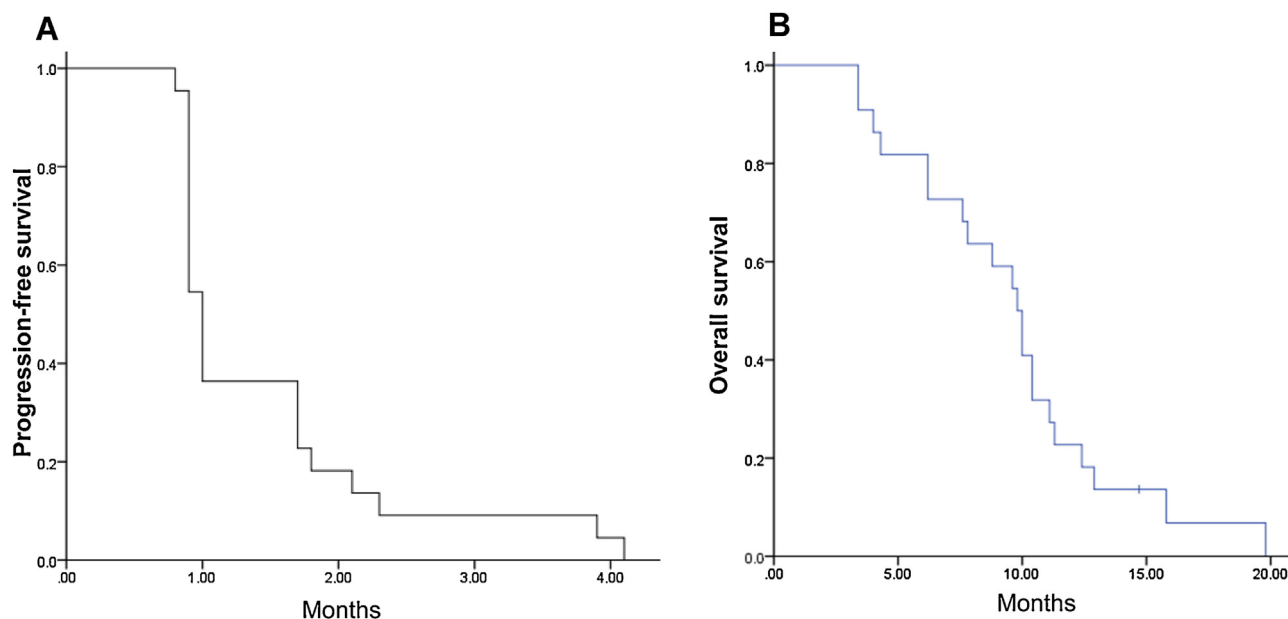
Fig. 1. Patient survival. (A) Progression-free survival. (B) Overall survival.

Table 3
Clinical trials of antiangiogenic agents in relapsed small cell lung cancer.

Authors	Study drug		Study design	Relapse pattern	Patients (n)	ORR (%)	mPFS (mo)	mOS (mo)
Jadal et al.	Bevacizumab	Paclitaxel	Single arm, phase II	Sensitive	34	18	3.4	6.9
Mountzios et al.	Bevacizumab	Paclitaxel	Single arm, phase II	Resistant	30	20	2.7	6.3
Allen et al.	Aflibercept	Topotecan	Two arms, randomized phase II	Sensitive or resistant	189	2	1.8	6.0
Ramalingam et al.	Cediranib	–	Single arm, phase II	Sensitive or resistant	25	0	2.0	6.0
Han et al.	Sunitinib	–	Single arm, phase II	Sensitive or resistant	25	9	1.4	5.6
This study	Nintedanib	–	Single arm, phase II	Sensitive or resistant	22	5	1.0	9.8

ORR, overall response rate; mPFS, median progression-free survival; mOS, median overall survival.

by the investigator; all measurable and non-measurable lesions were independently assessed by two referee radiologists who were blinded to the treatment assignment (Kim HY, Lim KY). Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 4.0.

2.5. Statistical analyses

The primary objective of this phase II trial was to assess the overall ORR in patients with relapsed SCLC treated with single agent nintedanib. It was hypothesized that nintedanib would result in an objective response of >20% (single agent topotecan activity in relapse SCLC) in the intent-to-treat population. This trial employed a Simon optimal design. For a total of 41 evaluable subjects, 22 were accrued during stage 1, and 19 were accrued during stage 2. If fewer than 2 patients respond to therapy during stage 1, accrual was stopped, and it would be concluded that this therapy regimen would not merit further study. The alpha level of the design is 0.05; and the power is 0.9. Efficacy outcomes are based on intent-to-treat analyses. PFS is defined as the interval between the start date of treatment and the date of occurrence of PD or death. OS is measured from the date of study entry until the date of death. Dose-intensity was calculated by using the method of Hryniuk and Bush [15].

3. Results

3.1. Patient characteristics

From Dec 2011 to June 2014, 24 patients were enrolled, and 22 received at least one cycle of nintedanib. Two patients withdrew

from the study within 1 week after the first dose of nintedanib. The baseline characteristics of the enrolled patients are listed in Table 1. The median age was 64 years, and 22 of the patients were male. Eight patients who received one platinum-based chemotherapy exhibited resistant relapse. Among 16 patients who received two prior chemotherapy regimens, 10 exhibited refractory relapses.

3.2. Toxicity

All patients who received at least one dose of therapy were assessable for toxicity. Toxicity was reported as the maximum toxicity experienced during the study treatment (Table 2). The most common adverse event (AE) was hepatic enzyme elevation (80%). A grade 3 hepatic enzyme elevation occurred in 5 patients (21%). Most AEs were mild and manageable. No treatment-related deaths were noted.

3.3. Treatment adherence

Patients received a median of one (range 1–5) cycle. Overall, a total of 38 treatment cycles were administered as per protocol, among which 9 (24%) were delayed. The main reason for treatment delay and subsequent dose modifications were aspartate transaminase (AST)/alanine transaminase (ALT) elevations (n = 7) and neutropenia (n = 2). The median dose-intensity was 372 mg/day (93% of the planned dose). The reason for treatment discontinuation was disease progression during treatment in all cases.

3.4. Response and survival

A total of 22 patients were evaluable for response. One patient exhibited a PR, and seven exhibited stable disease (SD). Among 7 patients with SD, three showed some dregree of tumor shrinkage. The ORR was 5% (95% confidence interval (CI), 0.1–22.8) and the disease control rate (PR + SD) was 36% (95% CI, 17–59). The cutoff for the OS update was June 25, 2015, and the median follow-up time was 9.7 months (range, 0.5–19.8 months). The median PFS and OS were 1.0 (95% CI, 0.9–1.1) month and 9.8 (95% CI, 8.4–11.2) months, respectively (Fig. 1A, B).

4. Discussion

Despite the substantial scientific rationale for antiangiogenic agents in SCLC, few studies have demonstrated a clinical benefit. So far, topotecan is the only agent approved for second-line therapy for sensitive relapsed SCLC. In an early phase II study of topotecan as a second-line therapy in both platinum-sensitive and refractory patients, ORRs of 37.8% and 6.4%, respectively, were reported. The overall median time to progression was 2.8 months and the OS was 5.4 months [2,3]. Recently, a randomized phase II study compared topotecan with or without aflibercept, a recombinant fusion protein consisting of VEGF-binding portions from the extracellular domains of human VEGFR1 and 2 that are fused to the Fc portion of human IgG1. Although aflibercept improved 3-month PFS in platinum-refractory SCLC (27% vs. 10%, P = 0.02), no significant difference in OS was noted. In the study, the median PFS and median OS were 1.3 months and 4.6 months, respectively, in sensitive relapsed SCLC. These values were 1.4 months and 4.2 months, respectively, in refractory relapsed SCLC with topotecan alone [16]. Table 3 summarized the clinical trials of antiangiogenic agents in relapsed SCLC [7,16–19]. All studies demonstrated only modest activity; however, these results are comparable with topotecan alone in patients with relapsed SCLC.

The primary endpoint of this study was RR. However, the surrogate endpoints have not been widely established for SCLC. Additionally, a decrease in response rate (RR) has been noted over the past 25 years in SCLC studies, which has been well demonstrated in topotecan efficacy in relapsed SCLC. It is likely that the use of more sensitive imaging technology to evaluate the response may contribute to the decreased RR in SCLC [20]. Moreover, antiangiogenic agents can result in increased efficacy in the absence of a robust response based on RECIST. This phenomenon has been well demonstrated in a phase III study of sorafenib in hepatocellular carcinoma, in which sorafenib improved PFS and OS despite an RR of only 2.3% [21]. Although our study did not meet the efficacy criteria to proceed to full accrual after interim analysis, the median OS of 9.8 months observed in our study may suggest a potential survival benefit from nintedanib in SCLC.

In contrast to the limited activity of antiangiogenic agents in relapsed SCLC, sunitinib as a maintenance therapy after induction chemotherapy improved PFS in ED-SCLC. The median OS for the sunitinib maintenance arm was 2.1 months longer than the placebo arm, but the difference was not statistically significant. Although the authors concluded that sunitinib maintenance was safe and feasible, grade 3 or 4 toxicities were reported in 39% (17/44) of patients who received sunitinib. In addition, 21 (48%) patients required sunitinib dose modifications [8]. Previously, we also reported that sunitinib was not tolerated mainly due to thrombocytopenia, asthenia and neutropenia. [7] In this study, the main reason for treatment delay and subsequent dose modifications were AST/ALT elevations and neutropenia. However, most patients tolerated nintedanib treatment. No cases of treatment interruption due to unacceptable toxicity were reported. The median dose-intensity was 372 mg/day, which accounts for 93% of planned doses. Given the manageable toxicity profile and the potential OS benefit, nintedanib could be considered as a maintenance therapy in SCLC.

In this single-arm phase II study, nintedanib exhibited limited activity but was well tolerated in patients with relapsed SCLC. Although the primary end point of ORR and thus the prerequisite to proceed with full accrual as per the trial design was not achieved, it is worth noting that seven patients had stable disease, and one patient exhibited a partial response following nintedanib treatment. Furthermore, the median OS of 9.8 months observed in these patients with a poor prognosis appears promising.

Competing interest

There are no financial disclosures and conflicts of interest.

Acknowledgments

References

[1] G.R. Simon, A. Turrisi, American College of Chest P: Management of small cell lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition), Chest 132 (3 Suppl) (2007) 324S–339S.

[2] J. von Pawel, J.H. Schiller, F.A. Shepherd, S.Z. Fields, J.P. Kleisbauer, N.G. Chrysson, D.J. Stewart, P.I. Clark, M.C. Palmer, A. Depierre, Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer, J. Clin. Oncol. 17 (2) (1999) 658–667.

[3] A. Ardizzoni, H. Hansen, P. Dombernowsky, T. Gamucci, S. Kaplan, P. Postmus, G. Giaccone, B. Schaefer, J. Wanders, J. Verweij, Topotecan, a new active drug in the second-line treatment of small-cell lung cancer: a phase II study in patients with refractory and sensitive disease. The European Organization for Research and Treatment of Cancer Early Clinical Studies Group and New Drug Development Office, and the Lung Cancer Cooperative Group, J. Clin. Oncol. 15 (5) (1997) 2090–2096.

[4] S. Tanno, Y. Ohsaki, K. Nakanishi, E. Toyoshima, K. Kikuchi, Human small cell lung cancer cells express functional VEGF receptors, VEGFR-2 and VEGFR-3, Lung Cancer 46 (1) (2004) 11–19.

[5] M. Ioannou, R. Papamichali, E. Kouvaras, I. Mylonis, D. Vageli, T. Kerenidou, S. Barbanis, A. Daponte, G. Simos, K. Gourgoulianis, et al., Hypoxia inducible factor-1 alpha and vascular endothelial growth factor in biopsies of small cell lung carcinoma, Lung 187 (5) (2009) 321–329.

[6] G.W. Krystal, S.J. Hines, C.P. Organ, Autocrine growth of small cell lung cancer mediated by coexpression of c-kit and stem cell factor, Cancer Res. 56 (2) (1996) 370–376.

[7] J.Y. Han, H.Y. Kim, K.Y. Lim, J.H. Han, Y.J. Lee, M.H. Kwak, H.J. Kim, T. Yun, H.T. Kim, J.S. Lee, A phase II study of sunitinib in patients with relapsed or refractory small cell lung cancer, Lung Cancer 79 (2) (2013) 137–142.

[8] N.E. Ready, H.H. Pang, L. Gu, G.A. Otterson, S.P. Thomas, A.A. Miller, M. Baggstrom, G.A. Masters, S.L. Graziano, J. Crawford, et al., Chemotherapy with or without maintenance sunitinib for untreated extensive-stage small-cell lung cancer: a randomized, double-blind, placebo-controlled phase II study-cALGB 30504 (Alliance), J. Clin. Oncol. 33 (15) (2015) 1660–1665.

[9] M. Reck, R. Kaiser, A. Mellemgaard, J.Y. Douillard, S. Orlov, M. Krzakowski, J. von Pawel, M. Gottfried, I. Bondarenko, M. Liao, et al., Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-lung 1): a phase 3, double-blind, randomised controlled trial, Lancet Oncol. 15 (2) (2014) 143–155.

[10] M.C. Pietanza, L.A. Byers, J.D. Minna, C.M. Rudin, Small cell lung cancer: will recent progress lead to improved outcomes? Clin. Cancer Res. 21 (10) (2015) 2244–2255.

[11] K. Mross, M. Stefanic, D. Gmehling, A. Frost, F. Baas, C. Unger, R. Strecker, J. Henning, B. Gaschler-Markefski, P. Stopfer, et al., Phase I study of the angiogenesis inhibitor BIBF 1120 in patients with advanced solid tumors, Clin. Cancer Res. 16 (1) (2010) 311–319.

[12] M. Reck, R. Kaiser, C. Eschbach, M. Stefanic, J. Love, U. Gatzemeier, P. Stopfer, J. von Pawel, A phase II double-blind study to investigate efficacy and safety of two doses of the triple angiokinase inhibitor BIBF 1120 in patients with relapsed advanced non-small-cell lung cancer, Ann. Oncol.: Off. J. Eur. Soc. Med. Oncol./ESMO 22 (6) (2011) 1374–1381.

[13] J.L. Hurwitz, F. McCoy, P. Scullin, D.A. Fennell, New advances in the second-line treatment of small cell lung cancer, Oncologist 14 (10) (2009) 986–994.

[14] E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, et al., New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1), Eur. J. Cancer 45 (2) (2009) 228–247.

[15] W. Hryniuk, H. Bush, The importance of dose intensity in chemotherapy of metastatic breast cancer, J. Clin. Oncol. 2 (11) (1984) 1281–1288.

[16] J.W. Allen, J. Moon, M. Redman, S.M. Gadgeel, K. Kelly, P.C. Mack, H.M. Saba, M.K. Mohamed, M. Jahanzeb, D.R. Gandara, Southwest Oncology Group S0802: a randomized, phase II trial of weekly topotecan with and without ziv-aflibercept in patients with platinum-treated small-cell lung cancer, J. Clin. Oncol. 32 (23) (2014) 2463–2470.

[17] S. Jalal, P. Bedano, L. Einhorn, S. Bhatia, R. Ansari, N. Bechar, K. Koneru, R. Govindan, J. Wu, M. Yu, Paclitaxel plus bevacizumab in patients with chemosensitive relapsed small cell lung cancer : a safety, feasibility, and efficacy study from the Hoosier Oncology Group, J. Thorac. Oncol. 5 (12) (2010) 2008–2011.

[18] G. Mountzios, C. Emmanouilidis, N. Vardakis, E. Kontopodis, D. Hatzidaki, E. Popis, N. Karachaliou, A. Kotsakis, M. Agelidou, V. Georgoulias, Paclitaxel plus bevacizumab in patients with chemoresistant relapsed small cell lung cancer as salvage treatment: a phase II multicenter study of the Hellenic Oncology Research Group, Lung Cancer 77 (1) (2012) 146–150.

[19] S.S. Ramalingam, C.P. Belani, P.C. Mack, E.E. Vokes, J. Longmate, R. Govindan, M. Koczywas, S.P. Ivy, D.R. Gandara, Phase II study of Cediranib (AZD 2171), an inhibitor of the vascular endothelial growth factor receptor, for second-line therapy of small cell lung cancer (National Cancer Institute #7097), J. Thorac. Oncol. 5 (8) (2010) 1279–1284.

[20] M. Nickolich, S. Babakoohi, P. Fu, A. Dowlati, Clinical trial design in small cell lung cancer: surrogate end points and statistical evolution, Clin. Lung Cancer 15 (3) (2014) 207–212.

[21] J.M. Llovet, S. Ricci, V. Mazzaferro, P. Hilgard, E. Gane, J.F. Blanc, A.C. de Oliveira, A. Santoro, J.L. Raoul, A. Forner, et al., Sorafenib in advanced hepatocellular carcinoma, N. Engl. J. Med. 359 (4) (2008) 378–390.