ORIGINAL ARTICLE

Antitumor activity of lurbinectedin (PM01183) and doxorubicin in relapsed small-cell lung cancer: results from a phase I study

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Background: Lurbinectedin (PM01183) has synergistic antitumor activity when combined with doxorubicin in mice with xenografted tumors. This phase I trial determined the recommended dose (RD) of doxorubicin (bolus) and PM01183 (1-h intravenous infusion) on day 1 every 3 weeks (q3wk), and obtained preliminary evidence of antitumor activity for this combination in small-cell lung cancer (SCLC).

Patients and methods: Patients with advanced solid tumors received doxorubicin and PM01183 following a standard dose escalation design and expansion at the RD. Twenty-seven patients had relapsed SCLC: 12 with sensitive disease (platinum-free interval ≥90 days) and 15 with resistant disease (platinum-free interval <90 days).

Results: Doxorubicin 50 mg/m^2 and PM01183 4.0 mg flat dose was the RD. In relapsed SCLC, treatment tolerance at the RD was manageable. Transient and reversible myelosuppression (including neutropenia, thrombocytopenia, and febrile neutropenia) was the main toxicity, managed with dose adjustment and colony-stimulating factors. Fatigue (79%), nausea/vomiting (58%), decreased appetite (53%), mucositis (53%), alopecia (42%), diarrhea/constipation (42%), and asymptomatic creatinine (68%) and transaminase increases (alanine aminotransferase 42%; aspartate aminotransferase 32%) were common, and mostly mild or moderate. Complete ($n = 2$, 8%) and partial response ($n = 13$, 50%) occurred in relapsed SCLC, mostly at the RD. Response rates at second line were 91.7% in sensitive disease [median progression-free survival (PFS)=5.8 months] and 33.3% in resistant disease (median PFS = 3.5 months). At third line, response rate was 20.0% (median PFS = 1.2 months), all in resistant disease.

Conclusion: Doxorubicin 50 mg/m^2 and PM01183 4.0 mg flat dose on day 1 q3wk has shown remarkable activity, mainly in second line, with manageable tolerance in relapsed SCLC, leading to further evaluation of this combination within an ongoing phase III trial.

Key words: lurbinectedin, PM01183, small-cell lung cancer, phase I study

Introduction

The synthetic tetrahydroisoquinoline lurbinectedin (PM01183; Pharma Mar S.A., Colmenar Viejo, Madrid, Spain) has broad *in vitro* activity in the low nanomolar range [1]. PM01183 inhibits active transcription in tumor cells through binding to CG-rich sequences, irreversible stalling and degradation of elongating RNA polymerase II on the DNA template, generation of XPF-dependent single- and double-strand DNA breaks, and subsequent apoptosis [2]. PM01183 also has a selective apoptotic-inducing effect on mononuclear phagocytes, and inhibits the production of inflammatory cytokines by these cells [3].

A study in mice bearing xenografted human tumors found strong dose-dependent antitumor activity for the combination of

PM01183 and doxorubicin, with a synergistic combination index ≤1. Doxorubicin has a different mechanism of action and its clinical toxicity profile does not completely overlap that of PM01183 [4]. A prior phase I trial found antitumor activity for single-agent PM01183 in patients with advanced solid tumors [5].

Based on these findings, this phase I trial was designed to determine the recommended dose (RD), and evaluate the safety and antitumor activity of doxorubicin combined with PM01183 administered every three weeks (q3wk) in selected advanced solid tumors. Tumor types for this study were selected based on preclinical evidence of potential activity of PM01183 and on the standard clinical use of doxorubicin in solid tumor patients. Of note, small-cell lung cancer (SCLC) cells are addicted to lineage-specific and proto-oncogenic transcription factors that support cell growth, hence further suggesting that PM01183 could play a role in the treatment of this tumor type. Due to the relevance of the antitumor activity observed during escalation, the results shown here are focused on relapsed SCLC patients.

Materials and methods

Patients were recruited in Spain and the UK. The study followed ICH Good Clinical Practice guidelines, and was approved by the respective Research Ethics Committees. Written informed consent was obtained from all patients before study-specific procedures. The study is registered at http://www.clinicaltrials.gov as NCT01970540.

Eligibility criteria

Eligible patients were aged 18–75 years with confirmed advanced solid tumors pre-treated with 1–2 cytotoxic-containing chemotherapy regimens for advanced disease (not anthracyclines); who had recovered from previous toxicities; ≥3 weeks since last anticancer therapy and ≥6 weeks since systemic nitrosoureas and mitomycin C; life expectancy ≥3 months; Eastern Cooperative Oncology Group performance status ≤1; normal left ventricular ejection fraction (LVEF); and adequate bone marrow, hepatic and renal function.

Patients were excluded if they had symptomatic progressive or corticosteroid-requiring brain metastases or leptomeningeal involvement; were pregnant or lactating women, or not using effective contraception; had prior radiation therapy (>35% of bone marrow), prior bone marrow/stem cell transplantation, relevant cardiac disease, alcohol consumption or cirrhosis, active uncontrolled infection, or any disease interfering with study outcome.

Study treatment

Treatment consisted of a fixed dose of doxorubicin 50 mg/m^2 as bolus followed by escalating doses of PM01183 intravenously (i.v.) over 1 h on day 1 q3wk. Doxorubicin was administered to a maximum cumulative dose of 450 mg/m^2. After reaching this, patients were switched to PM01183 alone at its single-agent RD of 7.0 mg flat dose (FD) on day 1 q3wk to prevent doxorubicin-induced cardiomyopathy [6]. Commercially available doxorubicin was provided. PM01183 was supplied as a lyophilized powder concentrate, reconstituted in sterile water for injection, and diluted with glucose 5% or sodium chloride 0.9% solution. All patients received standard antiemetic prophylaxis before each infusion. Treatment was given until disease progression, unacceptable toxicity, intercurrent illness precluding study continuation, patient refusal and/or non-compliance with study requirements, treatment delay >15 days (except if clear clinical benefit), and requirement of >2 dose reductions.

Dose escalation

Dose escalation followed a standard 3 + 3 design. Doxorubicin dose was standard for combination schedules. The starting PM01183 dose (3.5 mg FD daily) was 50% the RD defined for PM01183 alone on day 1 q3wk [5]. Dose-limiting toxicities were evaluated during cycle 1 and comprised grade 4 neutropenia >7 days, grade ≥3 febrile neutropenia, grade 4 thrombocytopenia (or grade 3 requiring transfusion), grade 4 transaminase increase (or grade 3 >14 days), grade ≥3 creatinine phosphokinase increase, and clinically relevant grade ≥3 non-hematological toxicities.

Study assessments

Hematology and biochemistry tests were done at baseline, weekly during cycle 1, and before each PM01183 infusion and on day 10 during subsequent cycles. Electrocardiograms and LVEF assessments were done at baseline and repeated at doxorubicin discontinuation or if clinically indicated.

Antitumor activity was evaluated every two cycles according to the Response Evaluation Criteria In Solid Tumors (RECIST) v.1.1 [7]. Overall response rate (ORR) was the percentage of patients with complete (CR) or partial response (PR), and disease control rate (DCR) was the percentage of patients with response or stable disease (SD). Time-to-event parameters were progression-free survival (PFS) and duration of response.

Adverse events (AEs) and laboratory abnormalities were graded with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.4 [8] and coded using the Medical Dictionary for Regulatory Activities (MedDRA) v.14.1.

Statistical analysis

Continuous variables were presented with summary statistics and categorical variables in frequency tables. Time-to-event variables were calculated using Kaplan–Meier approach. Binomial exact distribution was used to calculate 95% confidence intervals (95% CIs) for categorical variables.

Results

Dose escalation

Seventy-four patients were included during dose escalation. Most common tumor types were SCLC ($n = 28$, 38%), endometrial cancer ($n = 15$, 20%), neuroendocrine tumors ($n = 9$, 12%) and soft tissue sarcoma ($n = 8$, 11%). Four dose levels were evaluated. Most DLTs were hematological and mostly occurred at the highest dose level (doxorubicin 50 mg/m^2 and PM01183 5.0 mg FD), which was defined as the maximum tolerated dose. The RD was determined at doxorubicin 50 mg/m^2 and PM01183 4.0 mg FD [9].

Characteristics of SCLC patients and treatment

All 28 SCLC patients were treated with doxorubicin/PM01183, and 27 of them were included in the present analysis (Table 1); one patient was considered not evaluable because he had leptomeningeal carcinomatosis in cycle 1 that had not been evaluated at baseline. Median age was 62 years (range, 48–73 years) and many were male ($n = 17$, 63%). At baseline, 18 (67%) had bulky disease (target lesion >50 mm), 6 (22%) had brain metastases, and 13 (48%) had received prophylactic cranial irradiation.

Twelve patients (44%) had sensitive disease [defined as platinum-free interval (PFI) ≥90 days] and received doxorubicin/PM01183 as second-line therapy. The other 15 (56%) had resistant

Table 1. Baseline characteristics of patients with relapsed SCLC

	Doxorubicin+PM01183					
	Second line				Third or fourth line[a]	
	Sensitive (n=12)		Resistant (n=9)		Resistant (n=6)	
	n	%	n	%	n	%
Gender						
Male	10	83	6	67	1	17
Female	2	17	3	33	5	83
Median age (range) (years)	62.5 (48–73)		62.0 (50–70)		58.5 (50–63)	
ECOG performance status						
0	8	67	1	11	3	50
1	4	33	8	89	3	50
Median BSA (range) (m^2)	1.9 (1.3–2.0)		1.9 (1.7–2.3)		1.7 (1.5–1.8)	
Median albumin (range) (g/dl)	4.1 (3.2–4.8)		4.2 (2.5–4.5)		4.0 (3.6–4.5)	
Median hemoglobin (range) (g/dl)	13.5 (10.5–15.2)		12.1 (9.2–17.7)		11.6 (9.6–13.2)	
Median LDH (range) (x ULN)	0.6 (0.3–1.6)		1.1 (0.5–3.4)		1.7 (0.7–2.8)	
Smoker						
Current	2	17	4	44	2	33
Former[b]	10	83	5	56	4	67
Median number of sites of disease involvement (range)	2.5 (1–4)		3 (1–5)		2.5 (2–7)	
Metastasis at baseline						
Visceral	6	50	8	89	3	50
Liver	6	50	3	33	2	33
Bone	3	25	4	44	2	33
CNS	–	–	4	44	2	33
Bulky disease (any target lesion >50 mm)	5	42	8	89	5	83
PCI	10	83	1	11	2	33
Prior therapy						
Platinum compound	12	100	9	100	6	100
Etoposide	12	100	9	100	6	100
Topotecan	–	–	–	–	3	50
Irinotecan	–	–	–	–	2	33
Other (investigational drugs)	1[c]	8	1[d]	11	–	–
PFI[e]						
<90 days	–	–	9	100	6	100
90–179 days	7	58	–	–	–	–
≥180 days	5	42	–	–	–	–
TTP to prior therapy (months)	7.7 (2.1–13.6)		4.5 (1.2–6.0)		3.3 (1.6–6.4)	

[a]Only one patient with resistant disease received the combination as fourth-line therapy.
[b]Defined as an adult patient who used to smoke but who had quit smoking by the time of registration into this trial.
[c]LY2940680.
[d]Nivolumab.
[e]Time from the last prior platinum therapy before inclusion in the study.
BSA, body surface area; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PCI, prophylactic cranial irradiation; PFI, platinum-free interval; SCLC, small-cell lung cancer; TTP, time to progression; ULN, upper limit of normal.

disease (defined as PFI <90 days) and received it as second line (n=9), third line (n=5) or fourth line (n=1).

Six patients were treated below the RD, 19 at the RD (doxorubicin 50 mg/m^2 + PM01183 4.0 mg FD), and 2 above the RD. A total of 126 cycles of doxorubicin/PM01183 were administered at all dose levels (101 cycles at the RD). Median relative dose intensity at the RD was 95.8% (range, 78.6%–103.1%) for doxorubicin, and 94.5% (range, 70.1%–101.2%) for PM01183. Eight patients (29.6%) received 45 cycles of single-agent PM01183 after doxorubicin discontinuation [median relative dose intensity = 87.4% (range, 76.5%–100.0%), including seven patients previously treated with the combination at the RD]. Total median of cycles (combination and single-agent PM01183) per patient was 4 (range, 1–33 cycles) at all dose levels and 6 (range, 1–33 cycles) at the RD.

Table 2. Best tumor response according to Response Evaluation Criteria In Solid Tumors (RECIST)

	Doxorubicin + PM01183						Total (n=26)[a]	
	Second line				Third line			
	Sensitive (n=12)		Resistant (n=9)		Resistant (n=5)			
	n	%	n	%	n	%	n	%
CR	2	16.7	–	–	–	–	2	7.7
PR	9[b]	75.0	3	33.3	1	20.0	13	50.0
SD	1	8.3	2	22.2	–	–	3	11.5
PD	–	–	4	44.4	4	80.0	8	30.8
ORR (95% CI)	91.7% (61.5%–99.8%)		33.3% (7.5%–70.1%)		20.0% (–)		57.7% (36.9%–76.6%)	
DCR (95% CI)	100.0% (73.5%–100.0%)		55.6% (21.2%–86.3%)		20.0% (–)		69.2% (48.2%–85.6%)	
Median duration of response (months) (95% CI)	4.5 (2.1–9.1)		6.7 (2.3–7.2)		2.8 (–)		4.5 (2.3–7.8)	

[a]One patient, who was the only one in this study who received the combination as fourth-line therapy, was not evaluable for efficacy and has been excluded.

[b]Partial response could not be confirmed in one patient.

CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Efficacy

Twenty-six patients were evaluable for efficacy. Overall, ORR was 57.7% (95% CI, 36.9%–76.6%) and DCR was 69.2% (95% CI, 48.2%–85.6%) (Table 2).

As second line, 14 of 21 patients (ORR = 66.7%; 95% CI, 43.0%–85.4%) had response. ORR was 91.7% (95% CI, 61.5%–99.8%) in sensitive disease [two CRs (16.7%) and nine PRs (75.0%) among 12 patients], and 33.3% (95% CI, 7.5%–70.1%) in resistant disease (three PRs among nine patients). Most responses were confirmed (14 of 15). One patient with sensitive disease and two with resistant disease had SD; DCR was 100.0% (95% CI, 73.5%–100.0%) in sensitive disease and 55.6% (95% CI, 21.2%–86.3%) in resistant disease (Table 2).

As third line (all resistant disease), ORR/DCR was 20.0% (95% CI, 0.5%–71.6%) (one PR among five patients) (Table 2).

Tumor shrinkage occurred in 20 of 26 patients (77%) (Figure 1): all 12 with sensitive disease, and 7 of 9 (78%) with resistant disease as second line; and 1 of 5 (20%) with resistant disease as third line. Target lesion size decrease was maintained in seven of eight (88%) patients treated with single-agent PM01183.

Median PFS was 4.1 months (95% CI, 1.4–5.8 months) in all patients: 4.7 months (95% CI, 3.5–8.4 months) as second line [sensitive disease: 5.8 months (95% CI, 3.6–10.9 months); resistant disease: 3.5 months (95% CI, 1.1–8.0 months)], and 1.2 months (95% CI, 0.6–4.1 months) as third line (Figure 2). Seven patients achieved PFS >6 months (Figure 1), including one with sensitive disease who received 33 cycles as second line and had CR and a PFS of 23.6 months before discontinuing due to disease progression (time-to-progression after first-line therapy had been 2.1 months).

Median duration of response was 4.5 months (95% CI, 2.3–7.8 months) in all patients and as second line [sensitive disease: 4.5 months (95% CI, 2.1–9.1 months); resistant disease: 6.7 months

(95% CI, 2.3–7.2 months)]; and 2.8 months in one patient as third line.

Twelve responses (including both CRs) occurred at the RD. ORR was 64.7% (95% CI, 38.3%–85.7%) as second line [sensitive disease: 88.9% (95% CI, 51.7%–99.7%); resistant disease: 37.5% (95% CI, 8.5%–75.5%)]; and 50.0% (95% CI, 1.2%–98.7%) as third line. Median PFS was 4.1 months (95% CI, 1.4–9.0 months) as second line [sensitive disease: 9.0 months (95% CI, 3.3–11.7 months); resistant disease: 2.4 months (95% CI, 1.1–8.0 months)]; and 2.4 months (95% CI, 0.6–4.1 months) as third line. Median duration of response was 6.7 months (95% CI, 2.1–9.1 months) as second line [sensitive disease: 5.6 months (95% CI, 1.0–9.8 months); resistant disease: 6.7 months (95% CI, 2.3–7.2 months)].

Six patients at all dose levels had brain metastases at baseline that were considered non-target lesions for the evaluation of the disease. Of these six patients, four received the doxorubicin/PM01183 combination as second-line therapy and two as third-line therapy. All six patients discontinued treatment due to disease progression. In three of these patients, disease progression consisted of the appearance of new tumor lesions after two to six cycles while the brain lesions at baseline remained apparently stable (n = 2) or were not evaluated again while on treatment (n = 1). Two patients showed progression in baseline brain lesions after two and five cycles. Finally, one patient had clinical deterioration after three cycles while the baseline brain lesions remained apparently stable.

Toxicity

All patients were evaluable for safety. At the RD, the most common combination-related non-hematological AEs were fatigue (n = 15; 79%), nausea/vomiting (n = 11; 58%), decreased
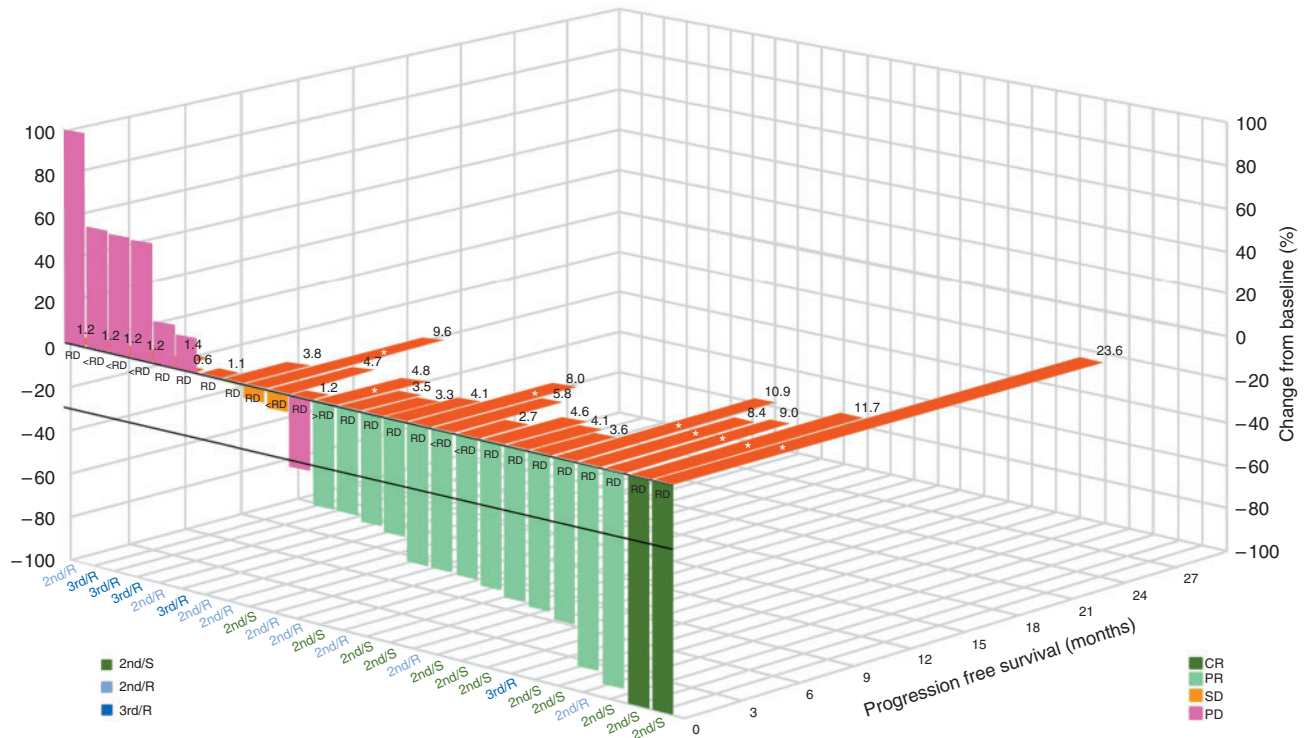
Figure 1. Waterfall plot showing maximum variation of target lesions and progression-free survival in patients with at least one radiological tumor assessment (n = 26). Sixteen patients had target lesion decrease >30%: 15 with CR or PR, and 1 with PD who had response in extracranial lesions and disease progression in the brain. Red stars = treatment switch to PM01183 alone. 2nd/R, second-line therapy and resistant disease; 2nd/S, second-line therapy and sensitive disease; 3rd/R, third-line therapy and resistant disease; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.
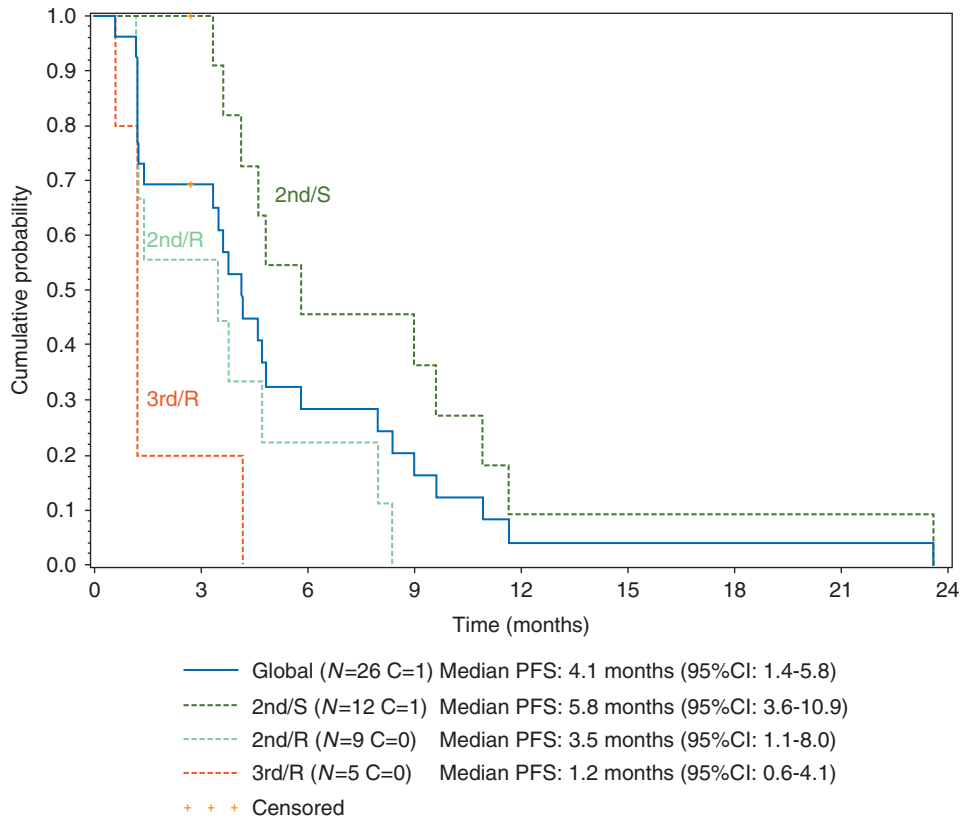

Figure 2. Kaplan–Meier plot of progression-free survival with doxorubicin/PM01183. 2nd/R, second-line therapy and resistant disease; 2nd/S, second-line therapy and sensitive disease; 3rd/R, third-line therapy and resistant disease; C, censored; CI, confidence interval; PFS, progression-free survival.

Table 3. Treatment-related adverse events and laboratory abnormalities regardless of relationship at the RD ($\geq$10% of patients or grade 3/4)						
	Doxorubicin 50.0 mg/m^2+PM01183 4.0 mg FD (n=19)					
	NCI-CTCAE grade					
	3		4		All	
	n	%	n	%	n	%
Treatment-related AEs						
Alopecia	–	–	–	–	8	42
Conjunctivitis	–	–	–	–	2	11
Decreased appetite	–	–	–	–	10	53
Diarrhea/constipation	–	–	–	–	8	42
Dizziness	–	–	–	–	2	11
Dry mouth	–	–	–	–	2	11
Dry skin	–	–	–	–	2	11
Dysgeusia	–	–	–	–	7	37
Esophageal candidiasis	1	5	–	–	1	5
Fatigue	2	11	–	–	15	79
Hypokalemia	1	5	–	–	1	5
Hypomagnesemia	1	5	–	–	1	5
Mucositis	2	11	–	–	10	53
Myalgia	–	–	–	–	3	16
Nail disorder	–	–	–	–	2	11
Nausea/vomiting	–	–	–	–	11	58
Neutropenic infection	1	5	–	–	1	5
Pneumonia	2	11	–	–	2	11
Pyrexia	–	–	–	–	2	11
Somnolence	–	–	–	–	2	11
Hematological abnormalities						
Anemia	9	47	–	–	18	95
Febrile neutropenia	4	21	1	5	5	26
Leukopenia	9	47	6	32	19	100
Neutropenia	3	16	15	79	19	100
Thrombocytopenia	2	11	3	16	17	90
Biochemical abnormalities						
ALP increased	–	–	–	–	5	26
ALT increased	1	5	–	–	8	42
AST increased	1	5	–	–	6	32
Bilirubin increased	1	5	–	–	5	26
Creatinine increased	–	–	–	–	13	68

AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FD, flat dose; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; RD, recommended dose.

appetite, mucositis (n = 10 each; 53%), alopecia and diarrhea/constipation (n = 8 each; 42%) (Table 3). Most AEs were grade 1/2. Grade $\geq$3 related AEs comprised febrile neutropenia, fatigue, mucositis and pneumonia. The only related grade 4 AE was one febrile neutropenia episode. Regardless of relationship, hematological abnormalities were common and severe cases comprised neutropenia (n = 18; 95%) [grade 4 lasting a median of 4 days (range, 2–13 days)], leukopenia (n = 15; 79%), anemia (n = 9; 47%), and thrombocytopenia (n = 5; 26%) (Table 3). Most biochemical abnormalities were grade 1/2; the most frequent were creatinine (n = 13; 68%), alanine aminotransferase (n = 8; 42%) and aspartate aminotransferase (n = 6; 32%) increases. Grade 3

increases in transaminases and bilirubin occurred in one patient and were concomitant with bile duct obstruction unrelated to treatment.

At the RD, nine patients required red blood cell transfusions, one had platelets transfusions, and seven required granulocyte colony-stimulating factor support. Treatment-related AEs resulted in 12 delays, two dose reductions, and one discontinuation. No toxic deaths occurred.

Most common AEs related to single-agent PM01183 were fatigue (all eight patients), decreased appetite (n = 4; 50%) and alopecia (n = 3; 38%). Most were grade 1/2; single episodes of grade 3 febrile neutropenia, grade 3 hypomagnesemia, and grade 4

hypokalemia occurred. Severe hematological abnormalities comprised neutropenia (75% of patients), anemia (63%), leukopenia and thrombocytopenia (50% each). All biochemical abnormalities were grade 1/2.

Discussion

Remarkable antitumor activity was found for the doxorubicin/PM01183 combination in relapsed SCLC. At the RD, ORR was 65% as second line (sensitive disease: 89%; resistant disease: 38%); and 50% as third line. Most responses occurred at the RD and were durable. Median PFS was 5.8 months (sensitive disease) and 3.5 months (resistant disease) as second line, and 1.2 months as third line. Median duration of response was 4.5, 6.7 and 2.8 months, respectively. One CR lasted almost two years in a patient with sensitive disease. Tumor shrinkage was maintained in 88% of patients who switched to PM01183 alone.

Therapeutic options for SCLC relapsing after first-line therapy are few. Currently approved second-line therapies resulted in ORRs of 7%–44% (sensitive disease: 25%–53%; resistant disease: 10%–18%) and median PFS of 2.2–4.5 months in patients with PFIs of 45–90 days or no brain metastases [10–12]. Immunotherapy drugs currently under evaluation for relapsed SCLC have resulted in ORRs of 10%–33% for the monoclonal antibody nivolumab alone or with ipilimumab [13] and ~33% for the monoclonal antibody pembrolizumab in selected patients with PDL1-positive disease [14]. The antibody-drug conjugate rovalpituzumab tesirine has been described to have an ORR of 18% in relapsed SCLC, with an ORR of 38% in highly selected patients with high DLL3 expression [15]. In contrast, in the present study second-line doxorubicin/PM01183 combination resulted in higher ORRs compared to currently approved therapies in unselected patients with sensitive (91.7%) and resistant (33.3%) disease. Median PFS was also longer. Of note, the 5.8 months achieved with second-line doxorubicin/PM01183 in sensitive disease was similar to the median PFS of 5.5 months reported with platinum/etoposide rechallenge in a retrospective analysis [16]. Remarkably, one-third of patients in this current study showed longer PFS with second-line doxorubicin/PM01183 than with first-line therapy.

Reversible myelosuppression was the most common toxicity with the doxorubicin/PM01183 combination. Episodes of severe neutropenia, thrombocytopenia and febrile neutropenia were transient and successfully managed with cycle delays, dose reductions and colony-stimulating factors. Most other toxicities were mild or moderate. Median dose intensities at the RD were 96% for doxorubicin and 95% for PM01183. No toxic deaths occurred.

Toxicities with doxorubicin/PM01183 were more frequent than with single-agent PM01183 in a previous phase I study [5]; e.g. nausea/vomiting (58% versus 47%), mucositis (53% versus <10%) and alopecia (42% versus <10%). Severe hematological toxicity was generally more frequent with doxorubicin/PM01183 than with doxorubicin alone at 60 or 70 mg/m^2 q3wk in other tumors [17, 18] and similar than with approved second-line therapies [19]. Some non-hematological toxicities were more common with doxorubicin/PM01183 (anorexia, 53% versus 30%) than with doxorubicin alone; others occurred at similar frequencies (nausea/vomiting, 58% versus 30%–75%; stomatitis/mucositis, 53% versus 62%) or were less common (alopecia, 42% versus 97%) [17, 18]. The safety profile of single-agent PM01183 in this study generally agrees with that reported previously [5].

In summary, this doxorubicin/PM01183 q3wk regimen has remarkable antitumor activity in relapsed SCLC that appears to be meaningfully higher compared to standard second-line therapies, particularly in sensitive disease. Tolerance suggested a positive risk-benefit profile for doxorubicin/PM01183 in relapsed SCLC. This trial is currently evaluating the combination in an expanded cohort of SCLC patients at a reduced doxorubicin dose (40 mg/m^2) and with PM01183 transformed to a dose of 2.0 mg/m^2 to improve safety over the profile described herein. An ongoing randomized phase III trial is evaluating doxorubicin/PM01183 versus cyclophosphamide, doxorubicin and vincristine (CAV) or topotecan, with primary colony-stimulating factor support as second-line treatment of SCLC.

Disclosure

EC has been consultant for Novartis, Pierre Fabre, Boehringer Ingelheim, EUSA and Seattle Genetics, and has participated in a speaker's bureau for Novartis. MPLC has been paid travel accommodation and expenses by Bristol. MF has been consultant for Eli-Lilly, Pfizer, Clovis, Boehringer Ingelheim, Novartis, Merck, AstraZeneca, BMS and MSD; has received research funding from AstraZeneca and Boehringer Ingelheim; and has been paid travel accommodation and expenses by Boehringer Ingelheim, BMS, Celgene, Eli Lilly, Merck, MSD and Roche. In addition, MF is supported by the UCL/UCLH NIHR Biomedical Research Centre and runs early phase studies in the NIHR UCLH Clinical Research Facility supported by the UCL ECMC. CK, MS, CFT, MCY, and ASM-P are employees and stock owners of Pharma Mar S.A. JAL-V is an employee of Pharma Mar S.A. All remaining authors have declared no conflicts of interest.

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