A phase I combination dose-escalation study of eribulin mesylate and gemcitabine in patients with advanced solid tumours: a study of the Princess Margaret Consortium

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Background: Eribulin mesylate is a synthetic microtubule inhibitor that showed cytotoxic synergy in combination with gemcitabine preclinically. This combination was assessed in a Phase I dose-finding trial in patients diagnosed with advanced solid tumours who had received up to two prior chemotherapy regimens for metastatic disease (CP cohort).

Methods: Dose escalation was performed in a 3 + 3 design to identify the recommended phase II dose (RP2D). Two additional expansion cohorts in women with gynaecologic cancers at the RP2D (G), and further dose escalation of metastatic chemotherapy-naive patients (CN), were evaluated.

Results: 45 patients were treated: 21 (CP), 10 (G) and 14 (CN). The initial combination of eribulin and gemcitabine was administered on days 1, 8, and 15 of a 28-day cycle; however, due to 2 out of 6 dose-limiting haematological toxicities at the first dose level, a reduced dose-intense schedule was assessed. The RP2D was defined at $1.0 \, \mathrm{mg \, m^{-2}}$ eribulin and $1000 \, \mathrm{mg \, m^{-2}}$ gemcitabine day 1 and 8 q3 weeks. No other significant toxicities were observed in the G expansion cohort. Neutropenia prevented further dose escalation in the CN cohort. Objective responses were seen in all three cohorts – 2/21 (CP), 1/10 (G) and 2/14 (CN).

Conclusions: The combination of eribulin and gemcitabine was well tolerated at the RP2D.

Eribulin mesylate is a non-taxane, synthetic microtubule inhibitor developed from halichondrin B, a natural marine product. Eribulin inhibits microtubule dynamics by binding to a unique site on tubulin (Dabydeen *et al*, 2006; Okouneva *et al*, 2008), resulting in the suppression of microtubule polymerisation, without effects on depolymerisation (Jordan *et al*, 2005). Eribulin exhibited *in vitro* and *in vivo* activities against a wide number of malignancies (Towle *et al*, 2001), particularly in disease models in which microtubule inhibitors have a therapeutic role such as in breast or ovarian cancers (Shablak, 2013). Eribulin has been recently approved as a third-line therapy for metastatic breast cancer

patients, who have previously been treated with an anthracycline and a taxane (Swami *et al*, 2012). Eribulin monotherapy is administered as intravenous (IV) dose of $1.4 \, \mathrm{mg \, m^{-2}}$ on days 1 and 8 of a 21-day cycle. The predominant toxicities are neutropenia and fatigue.

Preclinical studies show synergy when eribulin is combined with gemcitabine, inducing tumour regression in non-small cell lung cancer (NSCLC) xenografts (Towle *et al*, 2003; Kuznetsov *et al*, 2009). Gemcitabine is a cell cycle-dependent antineoplastic chemotherapeutic agent of the antimetabolite class. Gemcitabine exerts cytotoxicity through apoptosis following inhibition of DNA

synthesis with incorporation of pyrimidine analogues into DNA (Plunkett *et al*, 1995). Gemcitabine is commonly used at a dose of 1000 mg m^{-2} IV in several malignancies such as advanced NSCLC (Abratt *et al*, 1944; Gatzemeier *et al*, 2004), pancreatic (Carmichael *et al*, 1996; Mattiucci *et al*, 2013), ovarian, breast (Lorusso *et al*, 2003) and bladder cancers (Von der Maase *et al*, 2000). Common toxicities of gemcitabine include myelosuppression, gastrointestinal toxicity such as nausea, vomiting and diarrhoea, rash, flu like symptoms and abnormalities in liver function tests (Aapro *et al*, 1998). A phase I clinical trial was conducted to determine the safety and tolerability of the combination of eribulin with gemcitabine in patients with refractory or advanced solid tumours. No pharmacokinetics data were done as this combination was not expected to be at risk for drug–drug interaction.

MATERIALS AND METHODS

Patient eligibility. Adult patients (>18 years) with histologically confirmed metastatic or unresectable malignancy with no curative treatment options were eligible. Other eligibility criteria included the following: measurable disease, ECOG performance status 0 to 2, maximum of two prior chemotherapy regimens for metastatic disease, prior therapy completed at least 4 weeks prior to registration, adequate bone marrow and organ function (leukocytes $>3 \times 10^9 l^{-1}$, absolute neutrophil count (ANC) $\geqslant 1.5 \times 10^9 l^{-1}$, platelets $\geqslant 100 \times 10^9 l^{-1}$, total bilirubin within normal institutional limits, AST/ALT $\leqslant 2.5 \times$ institutional upper limit of normal, creatinine clearance $\geqslant 60$ ml min$^{-1} 1.73$ m^{-2}). Prior treatment with gemcitabine or eribulin was not allowed. Prior radiation could not have encompassed more than 40% of a patient's bone marrow. Patients had to have recovered from any toxicity related to prior therapy at the time of registration. As CYP3A4 appears to be the major enzyme responsible for hepatic metabolism of eribulin, the concurrent use of inhibitors and inducers of CYP3A4 were prohibited. All patients gave informed written consent. The study was approved by the Ontario Cancer Research Ethics Board and registered on ClinicalTrials.gov (NCT00410553) and was conducted in accordance with Good Clinical Practice guidelines.

Trial design and procedures. This was an open-label, phase I, dose-escalation trial conducted by the Princess Margaret Phase II Consortium in conjunction with the US National Cancer Institute Cancer Therapy Evaluation Program, and was performed at two participating institutions, the Ottawa Hospital (Ottawa, ON, Canada) and Princess Margaret Cancer Centre (Toronto, ON, Canada). The primary objectives were to determine the dose-limiting toxicities (DLT) and recommended phase II dosing (RP2D) of the eribulin/gemcitabine combination. Secondary objectives included the assessment of treatment-related toxicities and preliminary assessment of clinical activity as measured by response rate and progression-free survival (PFS), defined as time from initiation of therapy to disease progression or death from any cause. Patients were treated with eribulin as an IV bolus and gemcitabine IV over 30 min, after completion of the eribulin infusion. The starting dose level (DL) 1 was eribulin 0.7 mg m^{-2} and gemcitabine 800 mg m^{-2}, on day 1, 8, and 15 for the 28-day schedule (Q4W). This was switched to a 21-day cycle (Q3W) on day 1 and 8 after two DLT were seen in DL 1 on the 28-day schedule. Patients were premedicated with dexamethasone 10 mg IV plus additional antiemetics according to institutional guidelines before eribulin IV bolus. Dose escalation occurred in the standard 3 + 3 design. Treatment continued until disease progression, unacceptable toxicity or patient withdrawal. Dose escalation was continued until DLT was observed in two or more of the 3–6 patients. The RP2D was defined as the highest dose level with at

least six patients where one or fewer patients experienced a DLT. Once RP2D was determined, two expansion cohorts of patients were planned in ovarian/endometrial cancer and in patients who were chemotherapy naive for the setting of metastatic disease. Patients remained on treatment until progression, unless they had unmanageable adverse events (AEs), or requested to discontinue therapy. In the first gynaecological cohort (limited to ovarian/ endometrial cancer), patients received both drugs at the RP2D. In the second metastatic chemotherapy-naive cohort, patients were treated at dose levels above the RP2D on the 21-day cycle. It was felt that such patients would tolerate higher doses of the study regimen drugs.

Toxicity criteria and dose modifications. DLT was based on cycle 1 and defined as any grade 3 or 4 non-haematologic toxicity (with the exception of alopecia, or nausea/vomiting unless the latter occurs despite maximal supportive measures), any grade 4 haematologic toxicity lasting for more than 7 days, febrile neutropenia, inability to deliver days 8 and/or 15 in a 28-day cycle (during cycle 1) or day 8 in a 21-day cycle (during cycle 1), or the inability to initiate study drugs on day 1 of cycle 2 for more than 2 weeks from the scheduled date due to drug-related AEs. Toxicities were graded using the National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0 (DCTD, NCI, NIH, DHHS; http://ctep.cancer.gov). Doses of eribulin and gemcitabine were adjusted according to the set criteria based on the degree of haematologic and non-haematologic toxicities observed in the previous cycle. In order to be eligible to start the next cycle, patients were required to have adequate haematologic parameters: ANC $\geqslant 1.5 \times 10^9 l^{-1}$ and platelets $\geqslant 100 \times 10^9 l^{-1}$. In order to proceed with day 8 treatment (and day 15 treatment in the 28-day schedule), patients were required to have ANC $\geqslant 1.0 \times 10^9 l^{-1}$ and platelets $\geqslant 50 \times 10^9 l^{-1}$.

Clinical activity. Clinical response was assessed by RECIST version 1.0 (Therasse *et al*, 2000). Imaging assessments were performed by CT scanner at baseline and every 2 cycles. Any partial or complete response required confirmatory imaging $\geqslant 4$ weeks after the initial imaging demonstrating response.

RESULTS

The study was activated is November 2006 and was closed permanently to accrual on June 2012.

Patient characteristics. In the dose-escalation cohort (21- and 28-day schedule), 21 patients were enroled and all received at least one dose of the combination eribulin and gemcitabine. Baseline characteristics are presented in Table 1. After establishing RP2D, 10 women with gynaecologic malignancies were treated in an expansion cohort. Nine of these patients had ovarian cancer and one had endometrial cancer. All patients had been pretreated with systemic therapy for metastatic disease with a median number of two prior regimens. Fourteen chemo-naive patients were accrued and further dose escalation was attempted.

Dose escalation. Dose escalation and toxicities are shown on Table 2. Six patients were treated at DL 1 on the 28-day cycle schedule. At this DL 1, two DLTs occurred (grade 3 and 4 thrombocytopenia leading to reduced dose-intensity treatment on cycle 1 or delay in the initiation of cycle 2); subsequent patients were accrued to dose levels on the 21-day cycle regimen. Three patients were treated on the Q3W DL 1, 2 and 3 each with no DLT observed (Table 2). At DL 4, two patients developed DLT (grade 3 diarrhoea and grade 3 fatigue). Therefore, three more patients were treated on DL 3 and one patient developed DLT (grade 4 neutropenia with missing dose on cycle 1) over a total of six patients in this dose level. Thus, DL 3 defined by 1.0 mg m^{-2}

eribulin with 1000 mg m^{-2} gemcitabine; both day 1 and 8 every 21 days, was considered as the RP2D. Haematologic toxicity was not dose-limiting when the chemotherapy regimen was given in a 21-day cycle; however, increasing dose of chemotherapy regimen from DL 1 to DL 3 was associated with a trend towards increasing myelosuppression, with a drop in the median nadir levels of haemoglobin, leukocyte and neutrophil counts (Supplementary Table 1A). A total of 77 cycles of treatment were administered to the 21 patients enroled, with a median number of 2 cycles (1–12). Sixteen and five patients discontinued study due to disease progression and toxicity respectively.

Expansion cohorts

Gynaecologic cohort. Ten patients treated at the RP2D received a total of 75 cycles of chemotherapy administered with a median number of 6 cycles (2–18). No DLT was observed. Eight and two patients discontinued study due to disease progression and toxicity, respectively. The toxicity profile was not significantly different from the patients in the dose-escalation cohort.

Metastatic chemotherapy-naive cohort. Fourteen patients were enroled from DL 4–6, these additional dose escalations were used for this cohort as patients were not exposed to previous chemotherapy in the metastatic setting (two patients received adjuvant chemotherapy). A total of 90 cycles of treatment were given with a median number of 5 cycles (1–16). Only two patients were enroled at DL 6 as the second patient experienced severe neutropenia G4. Ten and three patients discontinued due to progressive disease and toxicity, respectively. The major limitation beyond RP2D in the metastatic chemotherapy-naive cohort patients was myelosuppression in either the first cycle (Supplementary Table 1B) or later cycles. Based on the increased frequency of grade 3 and 4 neutropenia observed at DL 4, 5 or 6, the RP2D remained DL 3 even for the metastatic chemotherapy-naive patients.

Safety profile. The most common grade 3 or 4 toxicities were haematologic (Tables 3 and 4). The most common grade 3 or 4 biochemical toxicities were reversible elevation of liver transaminases. The main grade 3 or 4 non-hematolgic toxicities – observed in at least two cycles of therapy – were fatigue, diarrhoea, nausea and vomiting. There was no death attributable to chemotherapy-related toxicity.

Table 1. Patient characteristics			
Cohorts	**Dose escalation**	**Gynaecologic**	**Chemotherapy-naïve**
Total number of patients (*n*) (Male : female)	21 (11 : 10)	10	14 (7 : 7)
Median age	59 (32, 84)	53 (45, 70)	63 (46, 79)
Performance status (0, 1, 2)	1, 13, 7	5, 4, 1	7, 5, 2
Median prior lines of therapy for metastatic disease (not including prior neoadjuvant/adjuvant chemotherapy)	2	2	0
Prior therapy for metastatic disease			
Chemotherapy (*n*, patients) Radiation (*n*, patients) Immunotherapy (*n*, patients)	21 8 1	10 1 0	
Disease origin	NSCLC 4 Ovarian 3 Head/neck 3 Colon 2 Endometrial 3 Gastric 3 Breast 1 Carcinoid 1 Unknown 1	Ovarian 9 (2 platinum sensitive and 7 platinum resistant) Endometrial 1	Pancreas 7 Head/neck 4 Melanoma 1 NSCLC 1 Unknown primary 1
Abbreviation: NSCLC = non-small cell lung carcinoma.			

Table 2. Dose, schedule and dose-limiting toxicities (DLT)					
Dose level (DL)	**Eribulin dose (mg m^{-2})**	**Gemcitabine dose^a mg m^{-2}**	**Number of patients**	**DLT number**	**DLT toxicity and grade (G)**
1 (28-day)	0.7	800	6	2	Thrombocytopenia G3 and G4 with reduced dose intensity and/or delay in the initiation of cycle 2
1 (21-day)	0.7	800	3	0	
2 (21-day)	0.7	1000	3	0	
3 (21-day)	1.0	1000	6	1	Neutropenia G4 with reduced dose intensity Recommended phase II dose
4 (21-day)	1.4	1000	3	2	Diarrhoea G3 Dizziness/fatigue G3
Gynaecologic cohort – DL3	1.0	1000	10	0	
Chemotherapy-naive (CN) cohort – DL 4	1.4	1000	7	1	1 G3 increase aspartate transaminase (AST)
CN – DL 5	1.6	1000	5	0	Post cycle 1 haematological toxicities
CN – DL 6	1.8	1000	2	1	Severe neutropenia G4
^{a}Gemcitabine administered on day 1, 8, 15 in DL 1 (28-day cycle) and on day 1, 8 (21-day cycle).					

Table 3. All grades adverse events suspected to be study drug related occurring in at least 10% of all enroled patients (escalation and expansion cohorts)

	DL 1 Q4W n = 6	DL 1 Q3W n = 3	DL 2 Q3W n = 3	DL 3 Q3W n = 16	DL 4 Q3W n = 10	DL 5 Q3W n = 5	DL 6 Q3W n = 2	All pts (n = 45)
Event	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Neutrophil count decreased	3 (50)	3 (100)	3 (100)	13 (81)	8 (80)	4 (80)	2 (100)	36 (80)
White blood cell decreased	3 (50)	3 (100)	3 (100)	12 (75)	7 (70)	5 (100)	2 (100)	35 (78)
Lymphocyte count decreased	4 (67)	1 (33)	1 (33)	8 (50)	5 (50)	4 (80)	1 (50)	24 (53)
Platelet count decreased	5 (83)	2 (67)	3 (100)	13 (81)	6 (60)	5 (100)	2 (100)	36 (80)
Anaemia	4 (67)	1 (33)	3 (100)	9 (56)	5 (50)	5 (100)	2 (100)	29 (64)
Alanine aminotransferase increased	6 (100)	2 (67)	1 (33)	14 (88)	9 (90)	1 (20)	1 (50)	34 (76)
Aspartate aminotransferase increased	5 (83)	0	2 (67)	13 (81)	8 (80)	2 (40)	1 (50)	31 (69)
Alkaline phosphatase increased	1 (17)	0	0	1 (6)	3 (30)	1 (20)	1 (50)	7 (16)
GGT increased	0	0	0	4 (25)	0	1 (20)	0	5 (11)
Hypoalbuminemia	1 (17)	0	0	8 (50)	4 (40)	3 (60)	0	16 (36)
Hyperglycaemia	0	1 (33)	0	3 (19)	2 (20)	1 (20)	0	7 (16)
Hyponatremia	0	0	0	2 (13)	2 (20)	1 (20)	1 (50)	6 (13)
Hypophosphatemia	0	0	0	3 (19)	2 (20)	1 (20)	0	6 (13)
Hypocalcaemia	0	0	0	5 (31)	0	0	0	5 (11)
Fatigue	3 (50)	0	0	10 (63)	6 (60)	4 (80)	1 (50)	24 (53)
Alopecia	0	0	0	9 (56)	4 (40)	5 (100)	2 (100)	20 (44)
Nausea	4 (67)	1 (33)	1 (33)	7 (44)	3 (30)	2 (40)	0	18 (40)
Vomiting	1 (17)	0	0	5 (31)	3 (30)	0	0	9 (20)
Diarrhoea	0	1 (33)	0	2 (13)	1 (10)	1 (20)	0	5 (11)
Anorexia	2 (33)	0	0	5 (31)	5 (50)	4 (80)	0	16 (36)
Mucositis oral	1 (17)	0	0	1 (6)	4 (40)	2 (40)	1 (50)	9 (20)
Peripheral sensory neuropathy	1 (17)	1 (33)	0	3 (19)	3 (30)	1 (20)	1 (50)	10 (22)
Fever	0	0	0	1 (6)	3 (30)	2 (40)	2 (100)	8 (18)
Headache	1 (17)	0	0	1 (6)	2 (20)	1 (20)	0	5 (11)
Rash maculo-papular	1 (17)	0	0	1 (6)	2 (20)	1 (20)	0	5 (11)

Abbreviations: DL = dose level; GGT = gamma glutamyl transpeptidase; pts = patients.

Of the 45 patients in total (over all the investigated cohorts), 15 patients had dose reductions, 23 patients missed a dose and 28 patients had dose delays. All 45 patients experienced at least one treatment-related AE, with the most frequently occurring treatment-related AEs being haematological toxicities.

Clinical activity. In the dose escalation cohort, among the RECIST-evaluable patients (17 of 21 patients), the best responses observed were two partial responses (PR) in one patient diagnosed with ovarian cancer and the second patient with head and neck carcinoma (10% of patients) and eight stable disease (SD; 38% of patients) with a median duration of 6.2 months (1.5–14.6). In the gynaecological expansion cohort, there was one PR (ovarian cancer) and seven SD (six SD in the ovarian subgroup and one SD with endometrial cancer) with a median SD duration of 6 months (2.9–15). In the chemotherapy-naive cohort, two PR (patients with unknown primary and pancreatic cancer) and eight SD with a median duration of 5.9 months (2.3–14.3) were observed (Table 5). Overall, the median PFS was 3.7 months (1.6–5.8). In the specific ovarian cancer subgroup, the median PFS was 4.5 months (1.6–15.2; Figure 1). No patients remain on treatment.

DISCUSSION

This trial demonstrated a RP2D of the combination of eribulin 1.0 mg m^{-2} and gemcitabine 1000 mg m^{-2} on days 1 and 8 every 21 days. This combination was feasible and toxicity was generally manageable. Haematologic toxicity prevented further dose escalation. The RP2D was defined at the same dose level in the chemo-naive expansion cohort based on the myelosuppression observed beyond cycle 1. Myelosuppression, fatigue and biochemical liver enzyme changes were the most commonly observed AEs in this study, consistent with previously reported toxicities of these drugs. Haematological toxicities and fatigue, which have been observed with both eribulin and gemcitabine in single agent studies, may have been more prominent due to overlapping toxicity. Indeed, eribulin inhibits cancer cell growth via induction of irreversible complete mitotic block at G2–M (prometaphase blockage), disruption of mitotic spindles formation and initiation of apoptosis following prolonged mitotic blockage (Kuznetsov et al, 2004). Gemcitabine is an antimetabolite (incorporation of pyrimidine analogues into DNA) that primarily kills cells undergoing DNA synthesis (S phase) and blocks the progression of cells through the G1/S phase boundary (Bookman, 2005). The synergistic action on the cell cycle may explain the rate of haematological toxicities observed. Diarrhoea was infrequent and manageable with loperamide, although it was a defined DLT at DL 4 (grade 3 in one patient). The peripheral neuropathy appears to be lower with eribulin than other microtubule inhibitor agents (Shablak, 2013). Preliminary signs of activity were observed even in pretreated patients. As eribulin inhibits cancer cell proliferation via cell cycle arrest at G2–M phase (Towle et al, 2001; Jordan et al, 2005;

Table 4. Grade 3 and 4 adverse events suspected to be study drug related (dose escalation and dose expansion cohorts)

	DL 1 Q4W n = 6	DL 1 Q3W n = 3	DL 2 Q3W n = 3	DL 3 Q3W n = 16	DL 4 Q3W n = 10	DL 5 Q3W n = 5	DL 6 Q3W n = 2	All pts (n = 45)
Event	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Neutrophil count decreased	0	0	1 (33)	11 (69)	7 (70)	3 (60)	2 (100)	24 (53)
White blood cell decreased	2 (33)	0	0	5 (31)	5 (50)	3 (60)	1 (50)	16 (36)
Lymphocyte count decreased	3 (50)	0	0	3 (19)	4 (40)	1 (20)	1 (50)	12 (27)
Alanine aminotransferase increased	0	0	0	4 (25)	3 (30)	0	0	7 (16)
Fatigue	0	0	0	4 (25)	2 (20)	0	1 (50)	7 (16)
Aspartate aminotransferase increased	0	0	0	3 (19)	2 (20)	0	0	5 (11)
Platelet count decreased	2 (33)	0	0	1 (6)	1 (10)	0	0	4 (9)
Anaemia	0	0	0	1 (6)	0	0	1 (50)	2 (4)
Nausea	0	1 (33)	0	1 (6)	0	0	0	2 (4)
Vomiting	0	0	0	1 (6)	1 (10)	0	0	2 (4)
Diarrhoea	0	0	0	1 (6)	1 (10)	0	0	2 (4)
GGT increased	0	0	0	0	0	1 (20)	0	1 (2)
Hypophosphatemia	0	0	0	1 (6)	0	0	0	1 (2)

Abbreviations: DL = dose level; GGT = gamma glutamyl transpeptidase; pts = patients.

Table 5. Anti-tumour activity

Cohort (n)	Partial response (% evaluable)	Stable Disease (median duration (months)) (% evaluable)	Progressive disease (% evaluable)	Non-evaluable (no data to assess response)
Dose escalation (21)	2 (12%)	8 (6.2 (1.5–14.6)) (47%)	7 (41%)	4
Gynaecologic (10)	1 (10%)	7 (6 (2.9–15)) (70%)	2 (20%)	0
Metastatic Chemotherapy-naive (14)	2 (15%)	8 (5.9 (2.3–14.3)) (62%)	3 (23%)	1
Overall (45)	5 (11%)	23 (62%)	12 (27%)	5

Response based on RECIST version 1.0.

Kuznetsov *et al*, 2009) and gemcitabine blocks the progression of cells through the G1/S phase (Plunkett *et al*, 1995; Mini *et al*, 2006), the drug combination may increase apoptosis by targeting two different checkpoints of the cell cycle, as demonstrated in preclinical models (Towle *et al*, 2003). Given the limited simple size and the dose-escalation nature of this trial, it is difficult to draw conclusions regarding the activity of this drug combination in patients. The lower incidence and grade of neuropathy with this combination and initial signal of activity may make this combination of interest in ovarian cancer given the efficacy of microtubule inhibitors in this disease such as paclitaxel but for which peripheral neuropathy is the main DLT (Gornstein and Schwarz, 2014); however, a dedicated phase II trial is needed to assess activity.

Eribulin is the only 'classical' cytotoxic agent approved for the treatment of breast cancer in the last 7 years over the new era of molecularly targeted agents. Eribulin was responsible for prolonging overall survival (OS) of heavily pretreated metastatic breast cancer patients in a large Phase III trial (Cortes *et al*, 2011) and is now under clinical development in earlier settings such as neoadjuvant and adjuvant settings. Furthermore, its unique mechanism of action and the absence of cross-resistance with taxanes have led to the design of clinical trials in multiple indications including: bladder, lung and prostate cancers (Polastro *et al*, 2014; Swami *et al*, 2015). On the basis of the promising results from the phase II (Schöffski *et al*, 2011), a randomised, open-label, multicenter phase III trial of eribulin mesylate in patients with locally advanced or recurrent and/or metastatic adipocytic sarcoma or leiomyosarcoma was conducted (NCT01327885). This trial enroled 452 patients who had disease progression following two

standard therapies, which must have included an anthracycline and at least one additional regimen after anthracycline failure. Eribulin was given on day 1 and 8 of a 21-day cycle *vs* dacarbazine given on day 1, every 21 days. The primary endpoint of the study was to compare OS between treatment arms. Recent data showed that the primary endpoint in this trial was met, demonstrating a statistically significant improvement in OS in patients treated with eribulin *vs* Dacarbazine (Schöffski *et al*, 2015).

On the basis of scientific rationale, the combination of eribulin and gemcitabine is under investigation in several different ongoing clinical trials. For example, based on the RP2D defined in our phase I trial, a randomised phase II trial is open to accrual comparing eribulin and gemcitabine chemotherapy with paclitaxel and gemcitabine chemotherapy for patients with HER-2-negative metastatic breast cancer as first-line chemotherapy (NCT02263495). The combination of gemcitabine and eribulin is also under investigation in a phase II trial for patients with bladder cancer that is advanced or cannot be removed by surgery (NCT02178241).

Further development of eribulin is assessed in combination with other agents. A phase I trial showed that on the 21-day cycle, eribulin mesylate $1.2\,mg\,m^{-2}$, administered on days 1 and 8, in combination with cisplatin $75\,mg\,m^{-2}$, administered on day 1 is well tolerated and showed preliminary anticancer activity (Koczywas *et al*, 2014). Eribulin combined with standard gemcitabine/cisplatin chemotherapy was also shown to be feasible with encouraging clinical activity for locally advanced or metastatic bladder cancer with haematologic toxicity remaining the main limiting factor (Vogelzang *et al*, 2012). The RP2D of eribulin in combination with standard doses of gemcitabine ($1000\,mg\,m^{-2}$,
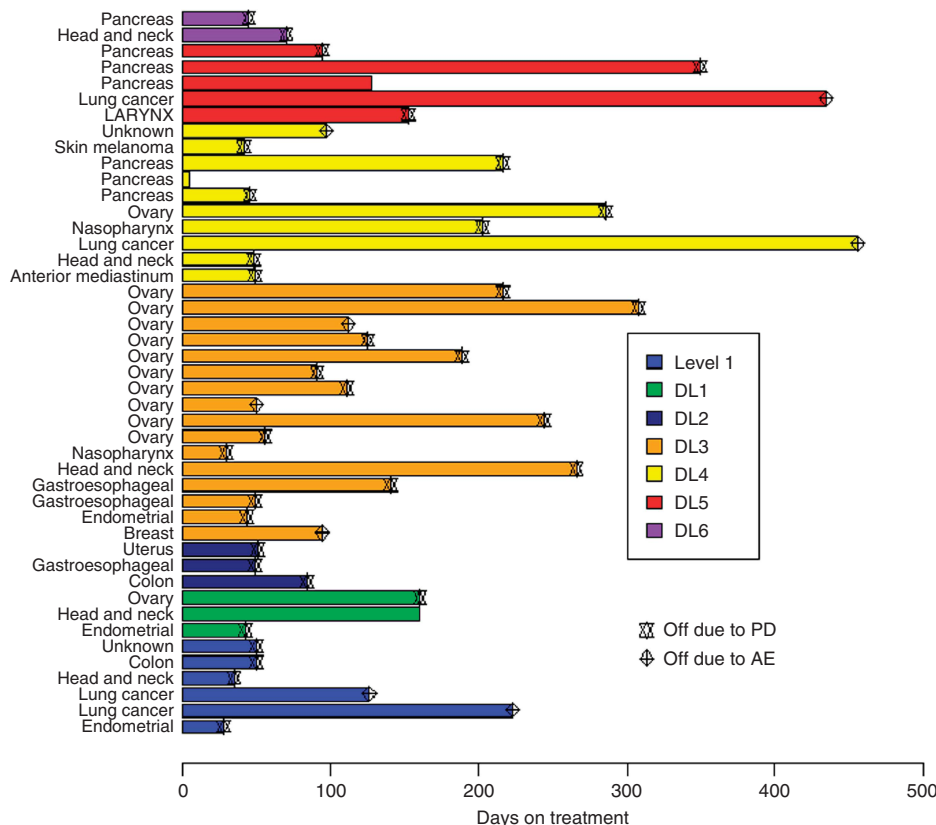
Figure 1. Time on treatment for the all enroled patients (dose escalation and expansion cohort).

days 1 and 8 every 21 days) and cisplatin (70 mg m^{-2}, day 1) was also established at 1.0 mg m^{-2} on the same schedule at day 1 and 8 every 21 days. These findings corroborate our findings and the RP2D.

CONCLUSION

The RP2D of eribulin and gemcitabine combination is 1.0 mg m^{-2} of eribulin and 1000 mg m^{-2} of gemcitabine at day 1 and 8 every 21 days. Clinical benefits were reported with manageable toxicity.

ACKNOWLEDGEMENTS

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies this paper on British Journal of Cancer website (http://www.nature.com/bjc)