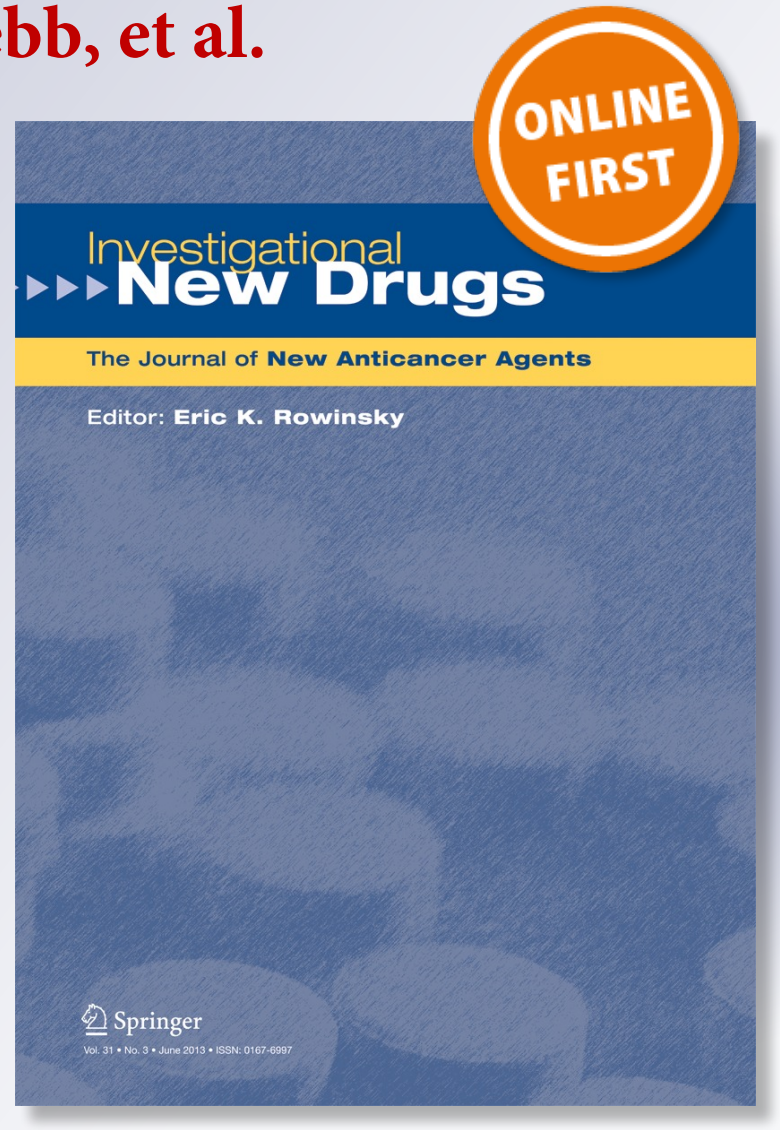
Patupilone in patients with pretreated metastatic/locally recurrent colorectal cancer: results of the Phase II CINATRA trial

S. Y. Moorcraft, I. Chau, C. Peckitt, D. Cunningham, S. Rao, K. L. Yim, A. Walther, C. G. C. A. Jackson, G. Stamp, J. Webb, et al.

Investigational New Drugs
The Journal of New Anticancer Agents

ISSN 0167-6997

Invest New Drugs
DOI 10.1007/s10637-013-9990-3



Springer

Invest New Drugs
DOI 10.1007/s10637-013-9990-3

PHASE II STUDIES

Patupilone in patients with pretreated metastatic/locally recurrent colorectal cancer: results of the Phase II CINATRA trial

S. Y. Moorcraft · I. Chau · C. Peckitt · D. Cunningham · S. Rao · K. L. Yim · A. Walther · C. G. C. A. Jackson · G. Stamp · J. Webb · G. Smith · A. Gillbanks · C. Swanton

Received: 14 May 2013 / Accepted: 12 June 2013

Summary *Background* Phase I trials of the microtubule stabilising agent patupilone showed encouraging tumour control and response rates in patients with metastatic colorectal cancer. *Methods* Patients with metastatic or locally recurrent colorectal cancer who had progressed following treatment with oxaliplatin, irinotecan and fluoropyrimidines were treated with patupilone (8 mg/m^2 IV every 3 weeks) in combination with dexamethasone or prednisolone. *Results* The trial was closed early after 29 patients had been enrolled due to concerns about toxicity. 20 patients (71.4 %) experienced at least one grade 3–5 toxicity, most commonly diarrhoea (14 patients), dehydration (7 patients) and lethargy (6 patients). The 12 week progression-free survival rate was 16.7 % (95 % CI 6.1 %–36.5 %) in the 24 patients with a 12 week scan available or who had died prior to the 12 week scan. No complete or partial responses were seen by 12 weeks. The median progression-free survival was 2.6 months (95 % CI 2.3–2.9) and median overall survival was 6.1 months (95 % CI 3.7–8.4). *Conclusion* Patupilone given at a dose of 8 mg/m^2 IV over 20 min every 3 weeks was associated with high levels of toxicity and no significant evidence of efficacy in patients with pre-treated colorectal cancer.

Keywords Patupilone · Colorectal cancer · Toxicity · Diarrhoea

K. L. Yim, A. Walther and C. Jackson were working at The Royal Marsden at the time of this research.

S. Y. Moorcraft · I. Chau (✉) · C. Peckitt · D. Cunningham · S. Rao · G. Stamp · J. Webb · G. Smith · A. Gillbanks
The Royal Marsden, Downs Road, Sutton SM2 5PT, UK
e-mail: ian.chau@rmh.nhs.uk

K. L. Yim
Velindre Cancer Centre, Velindre Road, Cardiff CF14 2TL, UK

A. Walther
University Hospitals Bristol, Bristol BS2 8ED, UK

C. G. C. A. Jackson
Dunedin School of Medicine, University of Otago, PO Box 913, Dunedin, New Zealand

C. Swanton
Translational Cancer Therapeutics Laboratory, CR-UK London Research Institute, 44 Lincoln's Inn Fields, London WC2A 3PX, UK

Introduction

Although advances in treatment have improved the median survival for metastatic colorectal cancer (CRC) from 12 months with fluorouracil monotherapy to approximately 2 years [1], CRC remains the second most common cause of cancer death in Europe [2]. Therefore new treatments are required to further improve the outcomes of these patients.

Colorectal cancers are characterised by distinct, non-overlapping types of genomic instability: in chromosomal instability (CIN), occurring in the majority of CRC, the initial step is the loss or somatic mutation of *APC* leading to mutations in *KRAS*, loss of chromosome 18q with *SMAD4*, and mutations in *TP53* and many cytogenetic abnormalities. In microsatellite instability (MSI), defined as a tumour having instability in at least two of five standard microsatellite markers, loss of function in mismatch repair genes (e.g. *MLH1*) leads to mutations in *WNT, BRAF,* and *TGFβR2* with a diploid chromosome set [3]. It has been suggested that the high incidence of CIN in CRC may explain the resistance of CRC to taxane-based treatment [4] and that MSI-high tumours may be more sensitive to taxane-based therapy.

Published online: 26 June 2013

Patupilone is a novel microtubule stabilising agent with a similar mode of action to paclitaxel [5]. Paclitaxel binds to microtubules, which are important in the formation of the mitotic spindle and the subsequent separation of chromosomes during cell division. Abnormalities in spindle checkpoint regulators (e.g. AURORA-A) may promote chromosomal instability as well as confer resistance to taxanes [4, 6].

More than 1,200 patients have been treated with patupilone in phase I–III clinical trials in a variety of tumour types [5]. A phase I multi-centre dose escalation trial in patients with pre-treated metastatic CRC showed encouraging results [7]. Patients in this trial received patupilone once every 3 weeks as a 20 min infusion, 24 h infusion or 5 day intermittent 16 h infusion. Of 60 patients in the study, 4 had a partial response and 27 patients had stable disease [7]. Similarly, in another Phase 1 study of 39 patients with metastatic CRC who were treated with patupilone plus celecoxib there were 3 partial responses (9 %) and 13 patients (41 %) had stable disease [8].

Although 35–38 % of patients (excluding patients receiving the intermittent 5-day infusion) in these Phase I trials experienced grade 3–4 diarrhoea, this was felt to be manageable [7, 8]. Preclinical experiments in rats demonstrated that the concomitant administration of prednisolone significantly reduced patupilone-associated diarrhoea in a dose-dependent manner [9]. Furthermore, the use of prednisolone appeared to prevent diarrhoea in patients with prostate cancer treated with patupilone in a Phase I study [10] and therefore this appeared to be a promising strategy for the management of gastrointestinal toxicity.

The primary objective of the Phase II Chromosomal Instability and Anti-Tubulin Response Assessment (CINATRA) study (ISRCTN58864837) was to determine the anti-tumour activity of patupilone in patients with pretreated metastatic or locally recurrent CRC. Secondary objectives included the stratification of response according to MSI and CIN status by comparing outcomes in a genetically unselected Cohort A to Cohort B, selected based on the presence of mismatch repair deficiency. The safety of patupilone was also evaluated as a secondary objective.

Materials and methods

Patients

This study was sponsored by The Royal Marsden NHS Foundation Trust. Protocol design, statistical analysis and data interpretation were all performed by the academic investigators. Patupilone was provided free by Novartis together with an educational grant. Novartis was not involved in the protocol design, statistical design or data analysis. All patients were treated at The Royal Marsden NHS Foundation Trust. The study was approved by a Research Ethics Committee and all patients provided written informed consent.

The eligibility criteria for this single-arm, phase II study included: 18 years of age or older, histologically confirmed metastatic or locally recurrent carcinoma of the colon or rectum, prior therapy with oxaliplatin, a fluoropyrimidine and irinotecan for CRC, ECOG performance status 0 or 1, measurable disease and satisfactory haematological, renal and liver function. Patients with persistent toxicity from previous treatment were excluded. The trial was designed with 2 cohorts: Cohort A comprised genetically unselected patients. Once recruitment to Cohort A was complete, patients with MSI-high tumours were to be recruited to Cohort B.

Treatment and response assessment

Patients were treated with patupilone for a total of 8 cycles unless there was clinical or radiological evidence of disease progression or unacceptable toxicity. Patupilone was administered at a dose of 8 mg/m^2 IV over 20 min on day 1 of each 3-week cycle. There was an optional escalation to 10 mg/m^2 of patupilone after 2 cycles if no toxicities were greater than grade 1, but only after consultation with the chief investigator. The first 24 patients were also treated with dexamethasone 20 mg IV as premedication followed by a reducing course of oral dexamethasone (4 mg bd day on day 1 to 7, 4 mg od on day 8 and 2 mg od on day 9). Following a protocol amendment, the dexamethasone was changed to a reducing course of oral prednisolone (25 mg bd on day 1 to day 8, 20 mg bd on day 9, 15 mg bd on day 10, 10 mg bd on day 11 and 5 mg bd on day 12). Before each cycle of treatment patients had a physical examination and their full blood count and biochemistry was checked. Response was assessed according to RECIST criteria by computed tomography (CT) scans every 4 cycles during chemotherapy until disease progression or discontinuation of chemotherapy.

Assessment and management of toxicity

Toxicity was assessed according to the NCI Common Toxicity Criteria, Version 3.0. Patients experiencing unacceptable toxicity directly associated with treatment had treatment temporarily suspended and modified according to the protocol. Toxicities had to have resolved to at least grade 1 or baseline in order for treatment to be recommenced. Intensive management of diarrhoea was instituted at the first sign of abdominal cramping, loose stools or diarrhoea. An anti-diarrhoeal treatment algorithm was incorporated into the protocol based on guidelines for the management of chemotherapy-induced diarrhoea [11, 12].

Patients were advised to take loperamide (initial administration of 4 mg, then 2 mg every 4 h up to a maximum of 16 mg per day), at the first sign of loose stools or symptoms of abdominal pain. If the diarrhoea did not resolve within 24 h, dihydrocodeine tartrate tablets/injections were started and a stool sample was required. Grade 3 or 4 diarrhoea was treated with high dose loperamide (initial 4 mg then 2 mg

every 2 h), dihydrocodeine tartrate tablets/injections and IV fluids/antibiotics as required. Patients were started on octreotide 500–1,000 μg tds if diarrhoea persisted for more than 12–24 h. An interim safety analysis, to be reviewed by an independent data monitoring committee (IDMC), was planned following the recruitment of the first 30 patients.

Statistical considerations

The primary endpoint for this study was 12 week progression-free survival (PFS). Secondary endpoints included overall survival (OS), response rate and the incidence of serious toxicity with patupilone therapy. PFS was calculated from the date of study registration to the date of first documented progression or death, and any patients who were alive and progression free at the time of analysis were censored at last follow-up. OS was calculated from the date of registration until death from any cause and any patients who were alive were censored at last follow-up. Survival was calculated according to the Kaplan–Meier method. Toxicities were summarised, overall and by individual toxicities, as the percentage of patients with any grade and grade 3+ toxicity.

Assuming a 10 % 12 week PFS as standard for best supportive care, a 12 week PFS rate from the time of trial registration of ≥25 % was considered to be acceptable evidence of efficacy. If ≥13 out of 75 patients were free from progression at 12 weeks, then the treatment would be considered suitable for evaluation in definitive phase 3 studies (1-sided α=0.034, >95 % power).

Results

Patient characteristics

The trial planned to recruit 75 genetically unselected patients into Cohort A and 35 patients with MSI into Cohort B. However, at the Trial Management Group (TMG) meeting in January 2010, following recruitment of the 24th patient, there were concerns over the levels of diarrhoea experienced in the trial. An amendment replaced dexamethasone with prednisolone in the hope that this would reduce the diarrhoea levels. Following the recruitment of a further 5 patients the TMG felt that the level of toxicity remained too high to justify continued recruitment to the study. The IDMC approved this decision and the trial was closed in June 2010. Of the 29 registered patients, one patient withdrew from the study prior to receiving treatment. Patient characteristics are indicated in Table 1.

Table 1 Patient baseline characteristics

	N (%) (*n*=29)
Age (years)	
Median	66.2
Range	28–77
Gender	
Male	21 (72.4)
Female	8 (27.6)
Performance status	
0	4 (13.8)
1	25 (86.2)
Site of Primary	
Ascending colon	2 (6.9)
Transverse colon	1 (3.4)
Descending colon	1 (3.4)
Sigmoid colon	9 (31.0)
Recto-sigmoid junction	3 (10.3)
Rectum	13 (44.8)
Differentiation	
Poor	2 (6.9)
Moderate	22 (75.9)
Well	5 (17.2)
Prior surgery to primary site	25 (86.2)
Prior surgery for metastatic disease	8 (27.6)
Prior radical chemoradiotherapy or radiotherapy	10 (34.5)
Previous lines of chemotherapy	
2	11 (37.9)
3	12 (41.4)
4	6 (20.7)

Treatment

The median number of completed cycles of patupilone per patient was 3 (range 1–7) (see Fig. 1). Eight patients withdrew from the study after starting treatment. The reasons for withdrawal were adverse events (3 patients), patient choice (3 patients) and clinician decision due to lack of efficacy or clinical deterioration (2 patients). No patients had the dose escalated to 10 mg/m^2. Nine of the 28 patients had the dose of patupilone reduced by 25–50 %. The majority of dose reductions occurred following cycle 2 (3 patients) or cycle 3 (5 patients). In addition, 7 patients had dose delays, again most commonly following cycle 2 (2 patients, median delay 5.5 days, range 4–7 days) or cycle 3 (3 patients, median delay 20 days, range 7–42 days). The median relative dose intensity for the number of cycles received was 99.2 % (range 57.7 %–103.3 %). The median delivered relative dose intensity of the protocol-planned 8 cycles of treatment was 34.4 % (range 12.5–84.4 %).

Patupilone-related toxicity

Toxicity is summarised in Table 2. Twenty patients (71.4 %) experienced one or more grade 3+ toxicities. The most

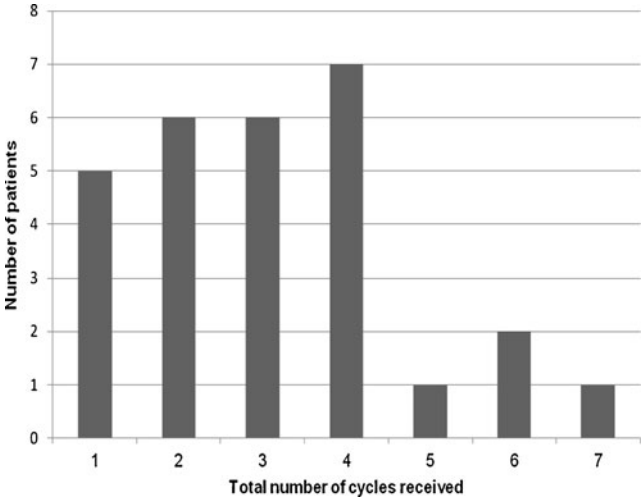


Fig. 1 Total number of cycles of patupilone received per patient

significant common adverse events were grade 3 diarrhoea (n=13, 46 %), grade 3 dehydration (n=6, 21 %) and grade 2 (n=10, 36 %) and 3 (n=4, 14 %) lethargy. One patient died following admission to a local hospital with grade 5 dehydration and grade 3–4 diarrhoea, nausea, vomiting and hypotension. Although this was reported as a Suspected Unexpected Serious Adverse Reaction (SUSAR), disease progression was felt to contribute to the patient's death. There were a total of 22 serious adverse events.

Efficacy

The primary endpoint was progression-free survival (PFS) at 12 weeks. At 12 weeks, 17 patients had disease progression by RECIST criteria, 1 patient had progressed clinically and 2 patients had died. This meant that 8 patients (28.6 %) were progression free (95 % CI 15.1 %–47.2 %). However, of these 8 patients, 4 had withdrawn from the study prior to the 12 week response assessment and information on response or progression was unavailable. The 12 week PFS rate for the 24 patients who had either died or had a CT assessment of response was 16.7 % (95 % CI 6.1 %–36.5 %). 4 patients had stable disease and no complete or partial responses were seen by 12 weeks (response rate 0 %). At the time of analysis, all 28 patients had died. The median PFS was 2.6 months (95 % CI 2.3–2.9) and median overall survival (OS) was 6.1 months (95 % CI 3.7–8.4) (see Fig. 2). The planned assessment of MSI and CIN was not performed as due to the premature closure of the study the number of patients was insufficient for a formal analysis according to MSI status.

Table 2 Number (%) of subjects experiencing adverse events with patupilone in the CINATRA trial

Adverse event	Any grade N (%)	Grade 3–5 N (%)
Lethargy	28 (100)	6 (21.4)
Diarrhoea	23 (82.1)	14 (50)
Anorexia	18 (64.3)	1 (3.6)
Peripheral neuropathy	16 (57.1)	0 (0)
Abdominal pain	13 (46.4)	3 (10.7)
Nausea	12 (42.9)	1 (3.6)
Dehydration	10 (35.7)	7 (25.0)
Skin toxicity	11 (39.3)	0 (0)
Vomiting	9 (32.1)	2 (7.1)
Dyspnoea	7 (25.0)	0 (0)
Infection	3 (10.7)	1 (3.6)
Alopecia	3 (10.7)	0 (0)
Dysgeusia	3 (10.7)	0 (0)
Hypotension	2 (7.1)	2 (7.1)
Any	**28 (100)**	**20 (71.4)**

Discussion

Diarrhoea is known to be a common side effect of patupilone and is characterised by necrosis and apoptosis of bowel crypt cells, disturbances in water absorption and inflammation [5]. However, the gastrointestinal toxicity seen in the CINATRA trial was more severe than has previously been reported, with grade 3–4 diarrhoea seen in 50 % of patients and diarrhoea of any grade in 82.1 % of patients. In comparison, although 80 % of patients treated by Melichar et al. with a 3-weekly schedule of patupilone had diarrhoea, only 35 % (11 patients) had grade 3–4 diarrhoea, and 10 of these patients were

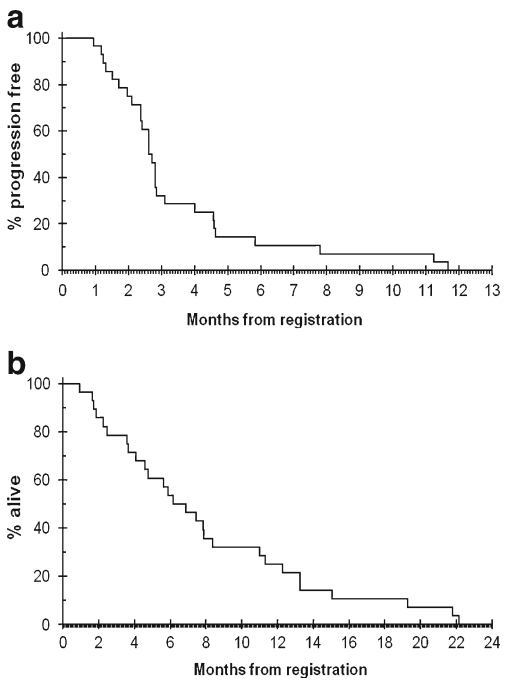


Fig. 2 Kaplan-Meier curves of progression-free survival (**a**) and overall survival (**b**) for patients with metastatic colorectal cancer treated with patupilone (n=28)

treated at higher doses (9 or 10 mg/m^2) than given in the CINATRA trial [7].

The incidence and severity of other toxicities, such as nausea and vomiting, were consistent with those previously reported [7, 8, 13, 14]. One of the other major adverse effects was lethargy, which was grade 2 in 36 % and grade 3–4 in 21.4 % of patients. The diarrhoea is likely to have contributed to this, although the level of grade 3–4 lethargy is comparable to that seen in other studies (10.4–21 %) [14–17]. The combination of diarrhoea, lethargy and/or other toxicities resulted in 3 patients being withdrawn from the study due to adverse events and a further 3 patients decided to withdraw from the study. We have not formally reported the quality of life data in this paper because this was incomplete.

It is unclear what led to the increased level of toxicity seen in the CINATRA trial. Our patients were treated with a dose of 8 mg/m^2 every 3 weeks, which is a lower dose than that used in other studies (although the Phase I data has to be interpreted with care due to the dose escalation nature of the trials). For example, many trials chose a dose of 10 mg/m^2 3 weekly, but despite this the rates of grade 3–4 diarrhoea were 11–32 % [10, 14, 16, 18–21]. In one Phase II trial in patients with prostate cancer, the dose of patupilone was reduced from 10 mg/m^2 to 8 mg/m^2 due to toxicity, but the rate of diarrhoea at 8 mg/m^2 was 22 % [17]. Therefore the dose and schedule of patupilone chosen for this trial appeared reasonable based on the data available.

Patupilone is metabolised by the liver [5]. Although patupilone clearance is reduced by approximately 50 % in patients with liver impairment, leading to increased systemic exposure [22], patients had to have a bilirubin of <1.5 times the upper limit of normal and an AST and ALT ≤5 times the upper limit of normal to be eligible for this trial.

Patients with CRC may be at increased risk of gastrointestinal toxicities compared to patients with other types of cancer, due to previous bowel surgery, chemotherapy and/or radiotherapy. The baseline characteristics of patients in the CINATRA trial were different to those in the Phase I trial reported by Melichar et al. and the combination of one or more of these factors may account for the increased level of toxicity seen. Our patients were slightly older (median 66.2 years vs 59 years) and although all patients were PS 0 or 1, our patients were more likely to be PS 1 (86.2 % vs 19 %). Our patients were also more likely to have received more lines of chemotherapy as 37.9 % of our patients had received 2 previous lines of chemotherapy and 62.1 % of our patients had received ≥3 previous lines of chemotherapy, compared to 19 % and 29 % in the 20 min infusion arm of the phase I trial [7]. In addition, 44.8 % of patients had rectal tumours and these patients may have an increased risk of diarrhoea, particularly as 34.5 % of patients had previously received radical radiotherapy or chemoradiotherapy (and would therefore have been excluded from the Phase I trial).

Various strategies have been tried to reduce the incidence and severity of patupilone-associated diarrhoea. Although steroids had been shown in animal models and a phase I trial in patients in prostate cancer to reduce the incidence of patupilone-associated diarrhoea [10], this approach was not effective in this study. In a phase I trial of patients with metastatic CRC treated with patupilone and celecoxib, the maximum tolerated dose was higher than previously reported, suggesting a benefit from the addition of celecoxib and diarrhoea management [8]. Melichar et al. gave patients a nutritional supplement, but this did not appear to be of benefit. However, given the lack of therapeutic efficacy, strategies to reduce patupilone-associated diarrhoea in patients with metastatic CRC are unlikely to be further evaluated.

The efficacy data from this trial was disappointing, with no objective responses and only 4 patients with RECIST confirmed stable disease at 12 weeks. This may be due to our patients having more previous lines of treatment, as 3 of the 4 patients with a partial response in the Phase I trial had only received one previous line of chemotherapy for metastatic disease [7]. In addition, response was assessed after 2 cycles in the phase I trial, whereas our planned response assessment was after 4 cycles. However, it is unlikely that any early responses were missed as many patients were scanned prior to 12 weeks and had RECIST confirmed progression, and the median PFS of 2.6 months also compares unfavourably with the median time to progression of 4.3 months in the Phase I setting [7]. One of the limitations of this study is that not all of the patients who withdrew from the study had CT scans performed to assess response at the time of study withdrawal or at 12 weeks. This was often because the patients had clinical deterioration and their subsequent care was handed over to the community palliative care team, therefore further outpatient oncology follow-up was not arranged. However, this is unlikely to have significantly impacted on the overall conclusions from this trial.

One potential reason for the disappointing efficacy results could be the amount of patupilone received by patients. Dose reductions were common and significant dose delays also occurred. Although the median relative dose intensity for the number of cycles received was 99.2 %, it should be noted that as all patients were started at the planned 8 mg/m^2 dose, this figure is artificially elevated due to the number of patients who discontinued treatment following cycle 1 or 2. A clearer indication of the amount of patupilone received is provided by the 34.4 % median delivered dose intensity of the protocol-planned 8 cycles of treatment. However, as many patients had CT scans performed due to toxicity concerns prior to cycle 4 and these showed disease progression, it seems unlikely that further patupilone would have been beneficial. In addition, due to the toxicity experienced by patients in this trial, dose escalation is not an option.

In conclusion, patupilone given at a dose of 8 mg/m^2 IV over 20 min every 3 weeks was associated with high levels of

toxicity and no significant evidence of efficacy in patients with pretreated CRC. Since recruitment was terminated prematurely, formal assessment of progression free survival intervals according to MSI and CIN status could not be performed.

Acknowledgements We acknowledge National Health Service funding to the National Institute for Health Research Biomedical Research Centre and Novartis who provided an educational grant and patupilone.

Ethical standards The study was approved by a Research Ethics Committee and all patients provided written informed consent.

Conflicts of interest IC has received research funding from Novartis, Merck-Serono and Roche, and has advisory roles (compensated) with Roche, Sanofi-Aventis, Novartis and Eli Lilly. DC has received research funding from Amgen, Roche, Sanofi-Aventis, Merck-Serono, Novartis, and Celgene, and has had advisory roles (uncompensated) with Roche and Amgen. SR has received research funding from GlaxoSmithKline and has advisory roles (uncompensated) with Roche, Sanofi-Aventis, Merck-Serono and Celgene. CS sat on a global advisory board for Novartis 3 years ago and receives research funding from Novartis. SYM, CP, KLY, AW, CJ, GS, JW, GSm and AG have no conflicts of interest to declare.

References

1. Cunningham D, Atkin W, Lenz HJ, Lynch HT, Minsky B, Nordlinger B, Starling N (2010) Colorectal cancer. Lancet 375(9719):1030–1047. doi:10.1016/S0140-6736(10)60353-4
2. Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P (2007) Estimates of the cancer incidence and mortality in Europe in 2006. Annal Oncol Off J Eur Soc Med Oncol / ESMO 18(3):581–592. doi:10.1093/annonc/mdl498
3. Walther A, Johnstone E, Swanton C, Midgley R, Tomlinson I, Kerr D (2009) Genetic prognostic and predictive markers in colorectal cancer. Nat Rev Cancer 9(7):489–499. doi:10.1038/nrc2645
4. Swanton C, Tomlinson I, Downward J (2006) Chromosomal instability, colorectal cancer and taxane resistance. Cell cycle 5(8):818–823
5. Bystricky B, Chau I (2011) Patupilone in cancer treatment. Expert Opin Investigational Drugs 20(1):107–117. doi:10.1517/13543784.2011.542148
6. Anand S, Penrhyn-Lowe S, Venkitaraman AR (2003) AURORA-A amplification overrides the mitotic spindle assembly checkpoint, inducing resistance to Taxol. Cancer cell 3(1):51–62
7. Melichar B, Casado E, Bridgewater J, Bennouna J, Campone M, Vitek P, Delord JP, Cerman J Jr, Salazar R, Dvorak J, Sguotti C, Urban P, Viraswami-Appanna K, Tan E, Tabernero J (2011) Clinical activity of patupilone in patients with pretreated advanced/metastatic colon cancer: results of a phase I dose escalation trial. Br J Cancer 105(11):1646–1653. doi:10.1038/bjc.2011.438
8. Iqbal S, El-Khoueiry AB, Yang D, Cole S, Boswell W, Shriki J, Ning Y, Agafitei RD, Menendez X, Lenz H (2010) A phase I study of celecoxib (C) and patupilone (EPO906) in patients (pts) with metastatic colorectal cancer (mCRC). J Clin Oncol Off J Am S Clin Oncol 28 (suppl; abstr 2533)
9. McSheehy P, Becquet M, Boisclair J, Bizot MN (2008) Prednisolone abrogates patupilone (EPO906)-induced diarrhoea in rats without impacting on patupilone PK or efficacy. Proc 20th EORTC-NCI-AACR Symp Mol Targets Cancer Ther EJC Suppl 6:451
10. Sridhar SS, Hotte SJ, Kollmannsberger CK, Mukherjee SD, Capier K, Barclay J, Adams L, Weber D, Chi KN (2010) Preventing patupilone-induced diarrhea with high-dose corticosteroids. J Clin Oncol Off J Am S Clin Oncol 28 (suppl; abstr e13069)
11. Kornblau S, Benson AB, Catalano R, Champlin RE, Engelking C, Field M, Ippoliti C, Lazarus HM, Mitchell E, Rubin J, Stiff PJ, Vokes E, Wadler S (2000) Management of cancer treatment-related diarrhea. Issues and therapeutic strategies. J Pain Symptom Manag 19(2):118–129
12. Wadler S, Benson AB 3rd, Engelking C, Catalano R, Field M, Kornblau SM, Mitchell E, Rubin J, Trotta P, Vokes E (1998) Recommended guidelines for the treatment of chemotherapy-induced diarrhea. J Clin Oncol Off J Am S Clin Oncol 16(9):3169–3178
13. Poplin E, Moore M, O'Dwyer P, Clarke S, Hill M, Sessa C, Rothermel J, Mull R, Miller J, L; R (2003) Safety and efficacy of EPO906 in patients with advanced colorectal cancer: A review of 2 phase II trials Proc Am Soc Clin Oncol 22 (abstr 1135)
14. Colombo N, Kutarska E, Dimopoulos M, Bae DS, Rzepka-Gorska I, Bidzinski M, Scambia G, Engelholm SA, Joly F, Weber D, El-Hashimy M, Li J, Souami F, Wing P, Engelholm S, Bamias A, Schwartz P (2012) Randomized, open-label, phase III study comparing patupilone (EPO906) with pegylated liposomal doxorubicin in platinum-refractory or -resistant patients with recurrent epithelial ovarian, primary fallopian tube, or primary peritoneal cancer. J Clin Oncol Off J Am S Clin Oncol 30(31):3841–3847. doi:10.1200/JCO.2011.38.8082
15. Hussain A, DiPaola RS, Baron AD, Higano CS, Tchekmedyian NS, Johri AR (2009) Phase II trial of weekly patupilone in patients with castration-resistant prostate cancer. Annal Oncol Off J Eur Soc Med Oncol / ESMO 20(3):492–497. doi:10.1093/annonc/mdn665
16. Reid TR, Takimoto CH, Verschraegen CF, Sarantopoulos J, Cheung W, Allen-Freda E, Li J, Xu Y, Ko J, Johri A (2008) Evaluation of safety, tolerability and pharmacokinetics (PK) of patupilone in patients (pts) with advanced solid tumors and varying degrees of hepatic function: An open-label phase I study. J Clin Oncol Off J Am S Clin Oncol 26: (May 20 suppl; abstr 2557)
17. Chi KN, Beardsley E, Eigl BJ, Venner P, Hotte SJ, Winquist E, Ko YJ, Sridhar SS, Weber D, Saad F (2012) A phase 2 study of patupilone in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel: Canadian Urologic Oncology Group study P07a. Annal Oncol Off J Eur Soc Med Oncol / ESMO 23(1):53–58. doi:10.1093/annonc/mdr336
18. Abrey LE, Wen P, Govindan R, Reimers H, Rigas JR, Robins HI, Allen-Freda E, Gao B, Ko J, Johri A (2008) Patupilone for the treatment of recurrent/progressive brain metastases in patients (pts) with non-small cell lung cancer (NSCLC): An open-label phase II study. J Clin Oncol Off J Am S Clin Oncol 26: (May 20 suppl; abstr 2033)
19. De Souza PL, Mellado B, Pfister C, Rosenthal M, Castellano DE, Weber D, Ferrara S, Shaik N, Tan E, S.G; P (2010) Randomized phase II trial of patupilone plus prednisone versus docetaxel plus prednisone in patients with chemotherapy-naïve, metastatic, castrate-resistant prostate cancer (CRPC). J Clin Oncol Off J Am S Clin Oncol 28 (suppl; abstr 4553)
20. Oehler C, Frei K, Rushing EJ, McSheehy PM, Weber D, Allegrini PR, Weniger D, Lutolf UM, Knuth A, Yonekawa Y, Barath K, Broggini-Tenzer A, Pruschy M, Hofer S (2012) Patupilone (epothilone B) for recurrent glioblastoma: clinical outcome and translational analysis of a single-institution phase I/II trial. Oncology 83(1):1–9. doi:10.1159/000339152
21. Conlin AK, D'Andrea G, Hudis CA, Robson ME, Drullinsky P, Theodoulou M, Lis E, Kang TY, Peereboom DM, Seidman AD (2008) Phase II trial of patupilone in patients (pts) with breast cancer brain metastases (BCBM) progressing or recurring after whole brain radiation therapy (WBXRT) Journal of Clinical Oncology 26 (May 20 Suppl;1086)
22. Rubin EH, Rothermel J, Tesfaye F, Chen T, Hubert M, Ho YY, Hsu CH, Oza AM (2005) Phase I dose-finding study of weekly single-agent patupilone in patients with advanced solid tumors. J Clin Oncol Off J Am S Clin Oncol 23(36):9120–9129. doi:10.1200/JCO.2005.03.0981