Investigational New Drugs (2021) 39:1047–1056
https://doi.org/10.1007/s10637-021-01081-x

PHASE I STUDIES

First-in-human, phase I/IIa study of CRLX301, a nanoparticle drug conjugate containing docetaxel, in patients with advanced or metastatic solid malignancies

Sarina A. Piha-Paul[1] · Kyaw Z. Thein[1,2] · Paul De Souza[3] · Richard Kefford[4] · Tara Gangadhar[5] · Christopher Smith[6] · Shelly Schuster[6] · William C. Zamboni[7] · Claire E. Dees[8] · Ben Markman[9]

Received: 16 December 2020 / Accepted: 1 February 2021 / Published online: 16 February 2021

Summary

Background This was a phase I/IIa study to investigate the tolerability, efficacy and pharmacokinetics (PK)/ pharmacodynamics (PD) of CRLX301, CDP-based nanoparticle formulation of docetaxel. *Methods* The study was conducted in two parts. In part 1, dose-escalation using a standard 3 + 3 design was performed in two dosing schedules (every week (QW) and every 3 weeks (Q3W)). Part 2 was comprised of a dose expansion at 75 mg/m2 Q3W. PK studies were performed on both dosing schedules. *Results* Forty-two patients were recruited onto the study with a median age of 64(range 38–76); median number of prior systemic therapies was 5(range 0–10). Grade 3/4 treatment-related toxicities included: neutropenia (21.4 %), infusion related reaction (11.9 %), anemia (7.1 %), fatigue (4.8 %), diarrhea (4.8 %), and peripheral neuropathy (4.8 %). The maximum tolerated dose was 75 mg/m2 given on the Q3W schedule and was not determined on the QW schedule. In this heavily pre-treated population, four patients (12.9 %) achieved stable disease (SD) ≥ 4 months and 2 patients (6.5 %) achieved partial response (PR) for a clinical benefit rate (CBR) of 19.4 % (6/31 patients). The PRs were seen in prostate and breast adenocarcinoma (one each). CRLX301 exhibited some PK advantages over docetaxel including higher retention of drug in plasma, slower clearance and controlled slow release of docetaxel from the carrier. *Conclusions* In this heavily pretreated patient population, the safety profile was acceptable for CRLX301 therapy. There was some evidence of preliminary tumor efficacy, but further work is necessary to find the optimal dose and schedule of this formulation.

Clinicaltrials.gov trial registration number: NCT02380677 (Date of registration: March 2, 2015).

Keywords First-in-human study · Phase I/IIa study · CRLX301 · Nanoparticle · Docetaxel

Statement of Translational Relevance To mitigate the increased toxicities of commercially available docetaxel, cyclodextrin-containing polymer (CDPs)-based nanoparticles (CRLX301) was designed to produce docetaxel-containing nanoparticles. In this first-in-human, phase I/IIa study, dose-escalation was explored in two different dosing schedules (IV weekly (QW) or every 3 weeks (Q3W)). Forty-two patients were recruited onto the study with n = 37 patients in dose escalation (n = 17 on QW and n = 20 on Q3W) and n = 5 patients were treated during the expansion at 75 mg/m^2 Q3W. Four patients (12.9 %) achieved stable disease (SD) ≥ 4 months and 2 patients (6.5 %) had a partial response (PR) [total = 6/31 patients (19.4 %)]. The responses were seen primarily in prostate and breast adenocarcinoma. Clinical benefit rate (CBR; percentage of SD ≥ 4 months + PR) was 19.4 %. Interestingly, a higher number of instances of SD ≥ 4 months were achieved at lower doses of CRLX301. This may be explained by PK results which showed prolonged exposures of total and released docetaxel in plasma after administration of CRLX301 (7 days) when compared with docetaxel (24 h).

✉ Sarina A. Piha-Paul
spihapau@mdanderson.org

Extended author information available on the last page of the article

Introduction

Docetaxel is a member of the taxane family of antineoplastic agents that interferes with microtubule disassembly and causes cell death by apoptosis [1, 2]. Docetaxel is active against a variety of cancers and has been approved to treat several human solid malignancies including breast cancer, non-small cell lung cancer, hormone refractory prostate cancer, gastric adenocarcinoma and squamous cell carcinoma of the head and neck [3, 4]. However, therapeutic response to docetaxel is associated with dose-limiting toxicities, including fluid retention and myelosuppression [5, 6]. In addition to these toxicities, the poor aqueous solubility of docetaxel requires incorporation of non-ionic surfactants like polysorbate 80 (Tween 80) and cremophor EL (CrEL) as vehicles in the clinical formulation, leading to increased adverse effects including severe anaphylactoid hypersensitivity reactions, hyperlipidemia, and peripheral neuropathy [7, 8]. Both vehicles

have large spherical structures and are pharmacologically and biologically active, often predisposing to increased systemic drug accumulation and decreased cellular uptake of the drug [9]. To mitigate these drawbacks, there is an urgent need to develop less toxic and more efficient drug formulation vehicles.

One of the emerging platforms for drug delivery is the use of nanoparticles which significantly enhance bio-distribution, target-specificity and safety-profiles of many drugs [10, 11]. Among various types of nanoparticles, cyclodextrin-containing polymers (CDPs) are shown to integrate hydrophobic therapeutic drugs into nanoparticles by covalently attaching the drug payloads to the polymer and drastically improve solubility of the drugs by more than 100 fold [12]. Based on CDP polymer backbone technology, CRLX301 was designed to produce a docetaxel-containing nanoparticle. Preclinical studies have demonstrated that CRLX301 exhibits extended plasma stability by prolonging circulation time, avoiding rapid clearance, and creating greater accumulation within tumor tissue possibly through its enhanced permeability and retention effect [13]. To further investigate the safety, tolerability and clinical activity of CRLX301, we conducted a first-in-human, non-randomized, open-label phase I/IIa study of CRLX301 in patients with advanced solid tumors.

Methods

Patients

Adult (age ≥ 18 years) patients were eligible for the study if they had histologically documented, advanced or metastatic solid tumors refractory to standard treatment or for which no standard therapy was available. Key inclusion criteria included Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate organ function. The number of prior treatments was not limited. Patients in phase IIa (part 2 dose expansion) of the study had to have at least one measurable target lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [14, 15], except for patients with castrate resistant prostate cancer (CRPC) where prostate cancer working group 2 (PCWG2) criteria was utilized.[16] Key exclusions were patients with uncontrolled > grade 2 toxicity from any prior treatment including any active peripheral neuropathy with ≥ grade 2 neurosensory symptoms. In part 2 dose expansion, patients could not have had treatment with a taxane within 6 months of the first dose of CRLX301 and patients with CRPC had to be taxane-naïve.

Study design and treatment

This was an international, multi-center, open-label, phase I/IIa study to determine the dose-limiting toxicities (DLTs) and maximum tolerated dose/ recommended phase 2 dose (MTD/ RP2D) of CRLX301 and to further explore the safety and tolerability of the MTD/RP2D (ClinicalTrial.gov identifier NCT02380677). The study was conducted in two parts. In part 1, dose-escalation was explored in two different dosing schedules. In schedule 1, CRLX301 was given every 3 weeks (Q3W; cycle = 21 days)) IV over 120 minutes and in schedule 2, it was given weekly (QW; cycle = 28 days) IV over 120 minutes. During dose escalation in schedule 1 (Q3W), patients were accrued in a stepwise manner into two initial cohorts of one patient each. Starting from cohort 3, a 3 + 3 dose escalation design was employed for all subsequent cohorts. During dose escalation for schedule 2 (QW), a 3 + 3 dose escalation design was utilized from the beginning. In part 2 of the study, patients were enrolled into an expansion cohort of the Q3W dosing schedule at the RP2D. The study protocol was approved by the Institutional Review Board or Independent Ethics Committee at each participating site and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and all local and federal regulatory guidelines. All patients signed informed consent prior to enrolling onto the study.

Study assessments

Tumor response was assessed using RECIST v1.1. Baseline imaging was performed within 30 days of treatment initiation. Repeat imaging (using the same methodology as at baseline) was obtained every 8–9 weeks. Treatment emergent adverse events (TEAEs) were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. A DLT was defined as any CRLX301-related adverse event ≥ grade 3 in severity, excluding the following: grade 3 fatigue lasting < 7 days, grade 3 anorexia or constipation, grade 3 dehydration as a result of nausea and vomiting, grade 3–4 hypersensitivity/infusion reaction, grade 3 electrolyte disturbance resolving to ≤ grade 1 or baseline within 7 days. The MTD was defined as the highest dose level at which fewer than 2 out of 6 patients experiences a DLT during Cycle 1 or the first 3 weeks. After the MTD was defined in each schedule, the study was extended to include additional evaluable patients at the MTD. A safety monitoring committee comprised of investigators and the study sponsor reviewed all safety information and made consensus decisions about dose escalation.

Pharmacokinetic analyses

Pharmacokinetic (PK) studies of CRLX301 in plasma were performed during dose escalation on both the QW and Q3W dosing schedule regimens. For the Q3W regimen, PK samples were collected on cycle 1, 3 and 6 prior to administration, at 0.5 and 1 hour (h) after the start of the infusion, at the end of

the infusion (EOI), and at 0.5, 1, 3, 6, 24, 48, 168, and 336 h after the EOI, and prior to the next dose. For the QW regimen, PK samples were collected on weeks 1, 4 and 7 prior to administration, at 0.5, 1 and 2 h after start of infusion, and at 0.5, 1, 3, 6, and 24 h after EOI, and prior to the next dose.

Total (conjugated + released) and released docetaxel in plasma were measured by liquid chromatography/tandem mass spectrometry (LC-MS/MS). The lower limits of quantification for total and released docetaxel in plasma were 50 ng/mL and 1 ng/mL, respectively. The following plasma PK parameters were calculated by using non-compartmental methods: maximum concentration (C_{max}), time of C_{max} (T_{max}), area-under the concentration versus time curve (AUC) from 0 to infinity, volume of distribution (Vd), clearance (CL) and elimination half-life (t½).

Statistical methods

Statistical analyses were performed using the Statistical Analysis System (SAS®) software Version 9.4 or higher (SAS Institute, Cary, North Carolina, USA). All quantitative variables are summarized by descriptive statistics, including mean, median and standard deviation (SD).

Results

Patient characteristics

Overall, forty-two patients with advanced, metastatic malignancies were enrolled between November 2014 and August 2017. Twenty patients were enrolled in part 1, schedule 1 (Q3W dosing) and 17 patients were enrolled in part 1, schedule 2 (QW dosing). Five patients were enrolled into an expansion cohort during part 2 of the study (Q3W dosing at RP2D).

Demographic and clinical characteristics of all patients enrolled are summarized in Table 1. The median age of patients was 64 years (range, 38–76 years). The median number of prior systemic therapies was 5 (range, 0–10). The most common types of cancer enrolled were head and neck cancer (n = 6), and CRPC (n = 5) followed by HCC and gynecological cancers (n = 4 each). The median number of cycles for part 1, schedule 1 and part 2 (cycle = 21 days) completed for all patients was 3 (range, 1–17). The median number of treatments during part 1, schedule 2 (treatment given every 7 days; cycle = 28 days) completed for all patients was 11 (range, 7–18). Fifteen of 42 patients (35.7 %) had received prior taxane (1 patient in part 2, dose expansion). For patients with SD > 4 months or better, the median number of cycles completed was 14 (range, 11–17; n = 2) in the Q3W schedule and the median number of treatments completed was 16.5 (range, 9–18; n = 4) in the QW schedule.

Safety and tolerability

All 42 patients are no longer on study. Clinically unacceptable TEAEs and disease progression accounted for the majority of patient withdrawals from the study. Toxicities accounted for withdrawals in 15 (35.7 %): 7 in part 1 schedule 1 (Q3W), 6 in schedule 2 (QW) and 2 in part 2 (Q3W). Progression of disease contributed to withdrawals in 8 patients in schedule 1, 7 in schedule 2 and 1 in part 2.

All 42 patients treated with CRLX 301 experienced at least one TEAE. TEAEs related to CRLX301 were reported in 95.2 % of all patients. Serious adverse events (SAEs) occurred in 40.5 % of all patients; 55 % in schedule 1, 23.5 % in schedule 2 and 40 % in part 2 dose expansion. Treatment-related adverse events (TRAE) of all grades in each treatment arm are described in detail in Table 2. The most common TRAEs were fatigue (66.7 %), dysgeusia (38.1 %), diarrhea (33.3 %), nausea (33.3 %), decreased appetite (30.9 %), infusion related reaction (30.9 %), neutropenia (26.2 %), and peripheral neuropathy (23.8 %). Grade 3/4 TRAEs were seen in 22/42 (52.4 %) of patients. The most common grade 3/4 toxicities related to CRLX301 were neutropenia (21.4 %), infusion related reaction (11.9 %), anemia (7.1 %), fatigue (4.8 %), diarrhea (4.8 %), and peripheral neuropathy (4.8 %).

DLTs occurred in 2 out of 6 patients enrolled in part 1, schedule 1 (Q3W) cohort 7 (90 mg/m^2). One patient experienced febrile neutropenia requiring hospitalization. The second patient had abnormally elevated liver function tests (grade 3) resulting in hospitalization and permanent discontinuation of therapy. Seventeen SAE were reported, and nine were considered related to study drug: 5 cases of infusion related reaction, 1 case of sensory and motor neuropathy, 1 febrile neutropenia, 1 anemia, and 1 elevated liver enzyme. Overall, 6 (14.2 %) patients died during the course of the study and none of the fatalities were causally related to CRLX301. Out of six, 4 were due to disease progression and the cause of death was unknown in 2 patients.

Antitumor activity

Thirty-one of the 42 patients (74 %) were evaluable for tumor response with both pre- and post-baseline target lesion measurements by RECIST v1.1. Best overall tumor response is shown in Fig. 1. In the Q3W schedule, one patient achieved partial responses (PR), 8 patients had SD and 7 patients had progressive disease (PD) as their best response per RECIST v1.1. The PR was in a prostate adenocarcinoma patient who progressed on 8 prior lines of therapies (taxane-naïve) treated at 75 mg/m^2 – the patient received a total of 11 cycles (33 weeks) of treatment prior to disease progression. In the QW

Table 1 Patient baseline demographic and disease characteristics

Characteristic n (%)[a]	CRLX301 Part 1, Schedule 1- dose escalation (Q3W) dosing						CRLX301 Part 1, Schedule 2- dose escalation (QW) dosing					Part 2* (Q3W)	Overall
	7.5 mg/m^2 (N=1)	15 mg/m^2 (N=1)	30 mg/m^2 (N=3)	60 mg/m^2 (N=3)	75 mg/m^2 (N=6)	90 mg/m^2 (N=6)	25 mg/m^2 (N=3)	35 mg/m^2 (N=4)	45 mg/m^2 (N=4)	54 mg/m^2 (N=2)	54 mg/m^2 (N=4)**	75 mg/m^2 (N=5)	N=42
Age (years) at consent													
Median (Range)	74 (74–74)	43 (43–43)	64 (38–75)	67 (66–69)	65.5 (47–74)	58.5 (43–76)	64 (63–68)	56.5 (43–68)	51.5 (44–69)	72.5 (71–74)	61 (56–63)	67 (60–71)	64 (38–76)
Gender													
Male	1 (100)	1 (100)	1 (33.3)	2 (66.7)	4 (66.7)	2 (33.3)	0	3 (75)	2 (50)	2 (100)	3 (75)	5 (100)	26 (61.9)
Female	0	0	2 (66.7)	1 (33.3)	2 (33.3)	4 (66.7)	3 (100)	1 (25)	2 (50)	0	1 (25)	0	16 (38.1)
Race													
White	1 (100)	1 (100)	3 (100)	3 (100)	6 (100)	4 (66.7)	3 (100)	3 (75)	3 (75)	1 (50)	4 (100)	5 (100)	37 (88.1)
Black	0	0	0	0	0	1 (16.7)	0	1 (25)	0	1 (50)	0	0	3 (7.1)
Other	0	0	0	0	0	1 (16.7)	0	0	1 (25)	0	0	0	2 (4.8)
ECOG performance status at baseline													
0	0	0	2 (66.7)	1 (33.3)	4 (66.7)	3 (50)	1 (33.3)	1 (25)	3 (75)	0	1 (25)	1 (20)	17 (40.5)
1	1 (100)	1 (100)	1 (33.3)	2 (66.7)	2 (33.3)	3 (50)	2 (66.7)	3 (75)	1 (25)	2 (100)	3 (75)	4 (80)	25 (59.5)
Primary site of disease at baseline													
Abdomen/ peritoneum	2 (10)						1 (5.9)					0	3 (7.1)
Bladder	0						1 (5.9)					0	1 (2.4)
Bone	0						1 (5.9)					0	1 (2.4)
Breast	0						1 (5.9)					0	1 (2.4)
Colorectal/ anus	1 (5)						1 (5)					0	2 (4.8)
Esophagus/ GEJ	2 (10)						1 (5)					0	3 (7.1)
Head and neck	2 (10)						3 (17.6)					1 (5)	6 (14.3)
Liver	4 (20)						0					0	4 (9.5)
Lung	2 (10)						1 (5.9)					0	3 (7.1)
Lymph node	1 (5)						0					1 (20)	2 (4.8)
Pancreas	1 (5)						1 (5.9)					0	2 (4.8)
Pleura	1 (5)						0					0	1 (2.4)
Prostate	0						2 (11.8)					3 (60)	5 (11.9)
Salivary Gland[b]	1 (5)						2 (11.8)					0	3 (7.1)
Gynecological[c]	2 (10)						2 (11.8)					0	4 (9.5)
Others	1 (5)[d]						0					0	1 (2.4)
Median number of prior therapies													
0–2	5 (25)						4 (23.5)					0	9 (21.4)

Table 1 (continued)

Characteristic n (%)[a]	CRLX301 Part 1, Schedule 1- dose escalation (Q3W) dosing						CRLX301 Part 1, Schedule 2- dose escalation (QW) dosing				Part 2* (Q3W)	Overall
	7.5 mg/m^2 (N = 1)	15 mg/m^2 (N = 1)	30 mg/m^2 (N = 3)	60 mg/m^2 (N = 3)	75 mg/m^2 (N = 6)	90 mg/m^2 (N = 6)	25 mg/m^2 (N = 3)	35 mg/m^2 (N = 4)	45 mg/m^2 (N = 4)	54 mg/m^2 (N = 2)	75 mg/m^2 (N = 5)	N = 42
3–5	9 (45)					6 (35.3)				2 (40)	17 (40.5)	
≥6	6 (30)					7 (41.2)				3 (60)	16 (38.1)	

54 mg/m^2 (N = 4)-**

Abbreviations:

n, number of patients; Q3W, 3 weekly dosing schedule; QW, weekly dosing schedule including 3 weeks on/ 1 week off; GEJ, gastroesophageal junction; ECOG, Eastern Cooperative Oncology Group

* denotes CRLX301 Part 2 – dose expansion at 75 mg/m2 (Q3W) dosing

** denotes CRLX301 QW (3 Weeks On/ 1 Week Off)

[a] Unless otherwise specified, figures represent n (%)

[b] Includes adenoid cystic carcinoma

[c] Includes vagina, endometrial and ovarian carcinoma

[d] Includes melanoma

schedule, one patient had a PR and 12 patients achieved SD as their best response per RECIST v1.1. The PR was in a breast adenocarcinoma patient who was exposed to 5 prior lines of therapies including taxane in the adjuvant setting, treated at 45 mg/m^2 – the patient received a total of 12 treatments (12 weeks) of treatment prior to disease progression. No patients had achieved complete response (CR) in this study. Details regarding patients who achieved SD > 4 months or PR including dose level, schedule and duration of treatment are described in Table 3.

Pharmacokinetics

For the Q3W regimen, the plasma concentration versus time profile of total and released docetaxel from 0 to 168 h for CRLX301 at 75 mg/m^2 after the dose on day 1 is presented in Fig. 2. Total and released docetaxel were detectable in plasma from 0 to 48 h and 0-168 h, respectively. The shorter duration of exposure of total docetaxel compared to released docetaxel in plasma is due to the higher lower limit of quantitation (LLQ) for total docetaxel compared to released docetaxel. For the Q3W regimen, the plasma PK parameters are summarized in Supplemental Table 1. Plasma PK of total and released docetaxel were linear after CRLX301 from 7.5 to 75 mg/m^2. CRLX301 plasma PK was similar on cycles 1, 3 and 6 suggesting no accumulation after multiple doses. For CRLX301 at 75 mg/m^2 on cycle 1, mean ± SD plasma AUC0-inf of total and released docetaxel were 312,237 ± 14,816 and 3,613 ± 1054 ng/mL•h, respectively. Mean ± SD % of docetaxel released from CRLX301 into the plasma was 1.0 ± 0.2 %, which is consistent with most of the drug in the plasma remains in the conjugated form.

For the QW regimen, the plasma PK AUC parameters are summarized in Supplement Table 2. There was prolonged exposure of total and released docetaxel in plasma on weeks 1, 4 and 7 with most of the drug exposure remaining as conjugated docetaxel. There is an approximate linear relationship between CRLX301 dose and total and released docetaxel AUCs on week 1. The total docetaxel AUC is relatively constant over weeks 1, 4 and 7 suggesting no accumulation of drug with repeated weekly dosing of CRLX301.

Discussion

Employing nanoparticle-based strategies into cancer therapy is of interest. Nanoparticles are designed to enhance the pharmacokinetic and pharmacodynamic properties of neoplastic agents by increasing drug solubility and enriching bio-distribution. Successful examples of nanoparticle technologies being employed include those incorporating doxorubicin, paclitaxel, cytarabine, irinotecan and vincristine.[17] Among the

Table 2 Summary of treatment related adverse events of all grades of severity in treatment groups

n (%)	CRLX301 Part 1, Schedule 1- dose escalation (Q3W) n=20		CRLX301 Part 1, Schedule 2- dose escalation (QW) n=17		CRLX301 Part 2 –dose expansion at 75 mg/m^2 (Q3W) n=5		Total N=42	
	All	Grade 3/4	All	Grade 3/4	All	Grade 3/4	All	Grade 3/4
Anemia	2 (10)	0	4 (23.5)	3 (17.6)	0	0	6 (14.3)	3 (7.1)
Febrile neutropenia	1 (5)	1 (5)*	0	0	0	0	1 (2.4)	1 (2.4)
Neutropenia	5 (25)	3 (15)	3 (17.6)	3 (17.6)	3 (60)	3 (60)	11 (26.2)	9 (21.4)
Thrombocytopenia	1 (5)	0	0	0	0	0	1 (2.4)	0
Constipation	1 (5)	0	3 (17.6)	0	0	0	4 (9.5)	0
Diarrhea	6 (30)	0	7 (41.2)	1 (5.9)	1 (20)	1 (20)	14 (33.3)	2 (4.8)
Nausea	7 (35)	0	7 (41.2)	0	0	0	14 (33.3)	0
Vomiting	3 (15)	0	2 (11.8)	0	0	0	5 (11.9)	0
Elevated LFT or bilirubin	2 (10)	1 (5)*	2 (11.8)	0	1 (20)	0	5 (11.9)	1 (2.4)
Stomatitis	3 (15)	0	1 (5.9)	0	0	0	4 (9.5)	0
Fatigue	14 (70)	0	12 (70.6)	2 (11.8)	2 (40)	0	28 (66.7)	2 (4.8)
Decreased appetite	7(35)	0	6 (35.3)	0	0	0	13 (30.9)	0
Infections/ infestations	1 (5)	0	1 (5.9)	0	0	0	2 (4.8)	0
Infusion related reaction	8 (40)	3 (15)	4 (23.5)	1 (5.9)	1 (20)	1 (20)	13 (30.9)	5 (11.9)
Peripheral neuropathy	4 (20)	1 (5)	4 (23.5)	1 (5.9)	2 (40)	0	10 (23.8)	2 (4.8)
Dysgeusia	7 (35)	0	9 (52.9)	0	0	0	16 (38.1)	0
Cough	1 (5)	0	1 (5.9)	0	0	0	2 (4.8)	0
Alopecia	5 (25)	0	7 (41.2)	0	0	0	12 (28.6)	0
Arthralgia	5 (25)	0	4 (23.5)	0	1 (20)	0	10 (23.8)	0
Palmar-plantar erythrodysesthesia	2 (10)	0	1 (5.9)	0	0	0	3 (7.1)	0

Abbreviations: Q3W, 3 weekly dosing schedule; QW, weekly dosing schedule including 3 weeks on/ 1 week off; LFT, liver function test; n, number of patients

*denotes a dose-limiting toxicity. Two patients experienced DLT at dose 90 mg/m^2 ; one had febrile neutropenia and other had grade 3 elevated liver function test

various types of nanoparticles used to deliver antineoplastic agents, cyclodextrin-based formulation and drug delivery have shown immense potential in preclinical studies, mainly due to their preferential accumulation in the tumor microenvironment potentially resulting in less off-target toxicities. [18–20] Cyclodextrin-containing polymers are composed of β-cyclodextrin and polyethylene glycol where the structure of the hydrophilic exterior layers over the hydrophobic interior where the hydrophobic drug resides resulting in improved drug solubility and stability, and ultimately increased bioavailability.[12].

The first CDP-based nanoparticle camptothecin conjugate (CRLX101) was evaluated in a first-in-human phase I/IIa trial by Weiss and Chao et al.[21] In total 62 patients (24 in dose escalation and 38 in expansion) were enrolled onto study. The MTD was defined at 15 mg/m^2 twice weekly (BIW). Among all patients in the study receiving dosing at the MTD (n = 44), the most common grade 3/4 TRAEs were fatigue (37 %), cystitis (27 %), anemia (26 %) and neutropenia (21 %) − 3 patients experienced DLTs of myelosuppression. Median progression free survival (PFS) for patients treated at the MTD was 3.7 months with 28 (64 %) patients having SD as their best response. Six patients went on to have SD > 6 months. In a subset of 22 NSCLC patients, the median PFS was 4.4 months with 16 patients (73 %) having SD as their best response.

CRLX301, a docetaxel-containing nanoparticle, was created based on the technology behind the production of CRLX101 and eliminates the need for polysorbate 80 (Tween 80) and cremophor EL (CrEL) in the infusion. [9] However, we did not see a significant reduction in the incidence of hypersensitivity/infusion reactions when compared to the commercial formulations using polysorbate. In fact, the incidence of hypersensitivity/infusion reactions was higher with CRLX301 treatment at 30.9 % when compared with Sanofi's docetaxel formulation (Sanofi Product Information) at 25 %. In our study, infusion-related reactions were more common in Q3W regimen (36 %) compared to QW schedule

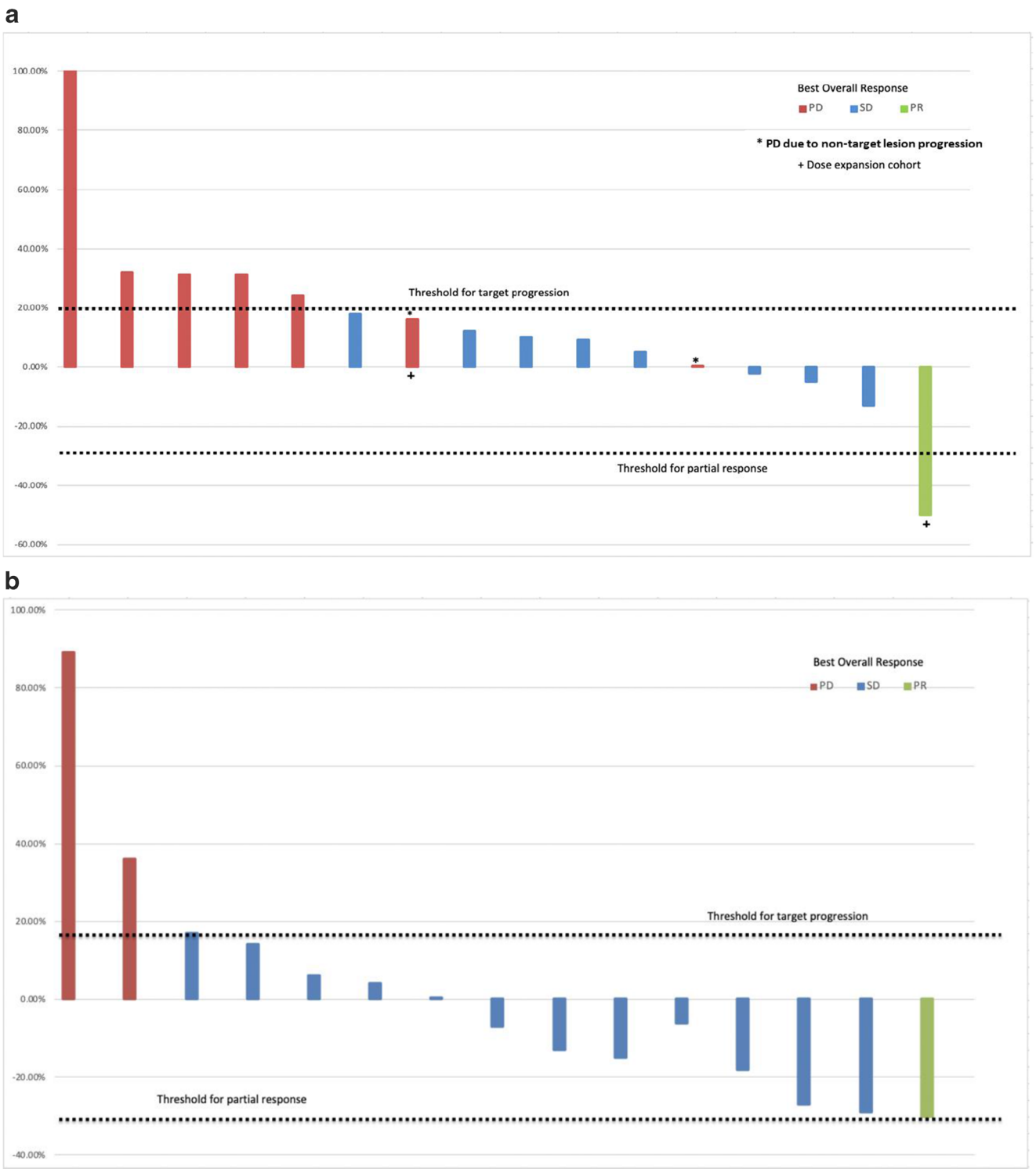

Fig. 1 Individual patients/best response are represented by vertical bars on the X-axis. The best RECIST response (%) is depicted on the Y-axis. Thirty-one of the 42 patients were evaluable for tumor response with both pre- and post-baseline target lesion measurements by RECIST v1.1. **a** Evaluble patients on the Q3W dosing schedule (cycle = 21 days). Patients on part 2, dose expansion, are marked with a "+." **b** Evaluable patients on the QW dosing schedule (cycle = 28 days). Abbreviations: Q3W, 3 weekly dosing schedule; QW, weekly dosing schedule; PD, progressive disease; SD, stable disease; PR, partial response

(23.5 %). Additionally, we did not see a significant reduction in peripheral neuropathy. In a phase 3 study by Rivera et al. comparing the docetaxel schedule of Q3W vs. QW in breast cancer, the reported incidence of neuropathy was 10 % and 5 %, respectively. [22] In our study, we found the incidence of neuropathy in the Q3W vs. QW schedule to be 24 % and

Table 3 Stable disease > 4 months (SD) or partial response (PR) by RECIST v1.1 and characterization by patient

Cancer Type	CRLX301 Dose (mg/m^2)	Schedule (QW vs. Q3W)	Best Response by RECIST v1.1	Number of Prior Systemic Therapies	Prior Taxane (Y/N)	Duration of Treatment (cycles[a] or weeks[b])
Adenoid cystic carcinoma	30	Q3W	SD	0	N	17
Prostate Adenocarcinoma	75*	Q3W	PR	8	N	11
Head and neck squamous cell carcinoma	54	QW**	SD	5	Y	16
Vagina adenocarcinoma	54	QW**	SD	9	Y	17
Adenoid cystic carcinoma	25	QW	SD	0	N	18
Breast Adenocarcinoma	45	QW	PR	5	Y	9

Abbreviations: Q3W, every 3 week dosing schedule; QW, weekly dosing schedule including **3 weeks on/ 1 week off; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; Y, Yes; N, No

* denotes CRLX301 Part 2 – dose expansion at 75 mg/m^2 (Q3W) dosing

** denotes CRLX301 QW (3 Weeks On/ 1 Week Off)

[a] Q3W dosing schedule (cycle = 21 days) and [b] QW dosing schedule (week = 7 days and cycle = 28 days)

23.4 %, respectively. Peripheral neuropathy also increased with increasing duration of CRLX301 administration and led us to change the QW dosing schedule to 3 weeks on/1 week off. It is unclear as to why we saw increased peripheral neuropathy in patients treated with CRLX301, however, we cannot discount the heavy pre-treatment of patients enrolled on this study with a median of 5 prior lines of therapy.

CRLX301 had a lower incidence of high-grade neutropenia, febrile neutropenia and fluid retention when compared with previous docetaxel studies. [22, 23] For high-grade neutropenia, when comparing the Q3W vs. QW schedule, CRLX301 had an incidence of 24 % and 18 % respectively when compared with docetaxel at 81 % and 10 %, respectively. Febrile neutropenia was reported at 4 % and 0 %, respectively in CRLX301 when compared to docetaxel at 10 % and 3 %, respectively. Fluid retention in CRLX301 across patients was 14 % compared to 47 % for docetaxel. Overall though, CRLX301 did not prove to be less toxic compared with docetaxel as had been hoped, possibly compounded by prior therapy. TRAEs due to CRLX301 were reported in 95 % of all patients and were as high as 96 % and 94 % when comparing the Q3W vs. QW schedule, respectively. In Rivera et al.'s work, TRAE in the Q3W vs. QW schedule were 88.1 % and 55.9 %, respectively. However, the numbers of patients treated in our study are too small to draw any true conclusions. Further, it is important to note that this was not a comparative study.

CRLX301 showed preliminary signals of efficacy with 71 % of patients achieving SD or PR as their best RECIST

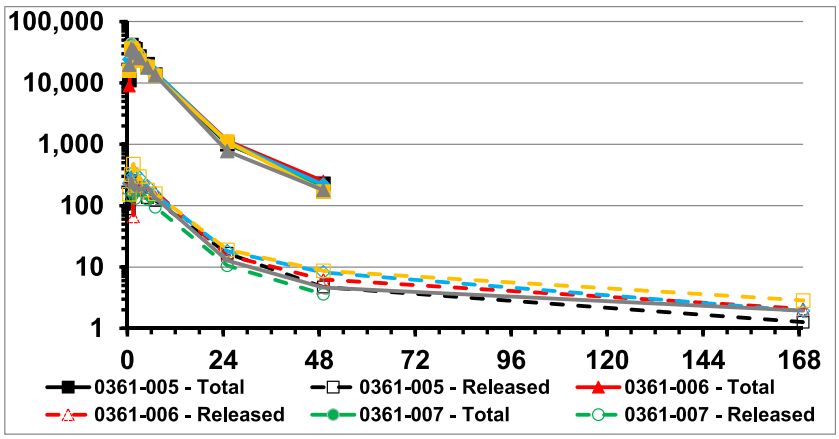

Fig. 2 Plasma concentration versus time profile of total and released docetaxel from 0 to 168 h for CRLX301 at 75 mg/m^2 after the dose on day 1 of the Q3W regimen. Solid and dashed lines represent the total and released docetaxel in plasma, respectively. Total and released docetaxel were detectable in plasma from 0-48 h and 0-168 h, respectively. The shorter duration of exposure of total docetaxel compared to released docetaxel in plasma is due to the higher lower limit of quantitation (LLQ) for total docetaxel (50 ng/mL) compared to released docetaxel (1 ng/mL). In summary, most of CRLX301 remains as the conjugated from in plasma

v1.1 response. Across the study, the clinical benefit rate (CBR; percentage of SD ≥ 4 months + PR) was 19.4 %. Notably, 35.7 % had received prior taxane including a breast cancer patient receiving 45 mg/m^2 QW who achieved PR. Interestingly, in the Q3W schedule, there is a suggestion of a higher percentage of patients having SD as their best response at doses less than the MTD (75 mg/m^2 Q3W) – 4/7 (57 %) at dose levels 1–4 vs. 3/7 (43 %) at the MTD. However, the one PR on this schedule was seen in a taxane-naïve prostate cancer patient treated at the MTD. The higher number of instances of SD > 4 months achieved at lower doses of CRLX301 may be explained by our PK analysis findings which showed prolonged exposures of total and released docetaxel in plasma after administration of CRLX301 (7 days) when compared with docetaxel (24 h). This may have allowed for an anti-tumor effect even at lower doses. CRLX301 exhibited PK advantages over docetaxel such as higher retention of drug in plasma, slower clearance and controlled slow release of docetaxel from the carrier. In addition, the mean ± SD % of docetaxel released from CRLX301 into the plasma was 1.0 ± 0.2 %, which is consistent with most of the drug in the plasma remaining in the conjugated form.

The QW schedule was not pursued for dose expansion and no MTD was declared. We were able to escalate to the highest planned dose of 54 mg/m^2 QW. However, due to a recurring need for dose hold due to cytopenias along with increasing incidence of peripheral neuropathy with cumulative dosing, a different schedule was evaluated at 3 weeks on/1 week off. Despite the toxicity issues, the QW schedule did have a trend toward a greater number of patients deriving clinical benefit when compared to the Q3W schedule – 4/15 (26.7 %) for QW vs. 2/16 (12.5 %) for Q3W despite the AUC of the weekly infusion being less.

In conclusion, the CDP-based nanoparticle formulation of docetaxel, CRLX301, did show some preliminary efficacy though this was at the expense of toxicity. However, the data from this study is based on small numbers. The altered kinetics of the nanoparticle formulation does appear to influence the toxicity profile. Further work is needed to find the optimal dosing regimen and schedule of this formulation.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10637-021-01081-x.

Acknowledgements We thank the patients who participated in this study and their families for supporting them.

Author contributions All the authors have contributed to the preparation of this manuscript and approved the final version.

Funding Cerulean Pharma Inc.

Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Declarations The study protocol was approved by the Institutional Review Board or Independent Ethics Committee at each participating site and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and all local and federal regulatory guidelines. All patients signed informed consent prior to enrolling onto the study.

Conflicts of Interest/Competing Interests None of the authors have any conflict of interest relevant to the subject of this manuscript.

Sarina A. Piha-Paul receives Research/Grant Funding through the institution from the following sources: AbbVie, Inc.; ABM Therapeutics, Inc.; Acepodia, Inc; Alkermes; Aminex Therapeutics; Amphivena Therapeutics, Inc.; BioMarin Pharmaceutical, Inc; Boehringer Ingelheim; Bristol Myers Squib; Cerulean Pharma, Inc.; Chugai Pharmaceutical Co., Ltd; Curis, Inc.; Daiichi Sankyo; Eli Lilly; ENB Therapeutics; Five Prime Therapeutics; Gene Quantum; Genmab A/S; GlaxoSmithKline; Helix BioPharma Corp.; Incyte Corp.; Jacobio Pharmaceuticals Co., Ltd.; Medimmune, LLC.; Medivation, Inc.; Merck Sharp and Dohme Corp.; Novartis Pharmaceuticals; Pieris Pharmaceuticals, Inc.; Pfizer; Principia Biopharma, Inc.; Puma Biotechnology, Inc.; Rapt Therapeutics, Inc.; Seattle Genetics; Silverback Therapeutics; Taiho Oncology; Tesaro, Inc.; TransThera Bio; NCI/NIH; P30CA016672 – Core Grant (CCSG Shared Resources).

Paul De Souza receives funding through his institution as a consultant for BioSceptre.

Tara Gangadhar receives honoraria for scientific advisory board participation from Merck, and BMS.

Christopher Smith and **Shelly Schuster** were employees of and held stock in NewLink Genetics Corporation.

William C. Zamboni receives research funding from: Apollomics (formally CBT Pharma); Meryx Pharma; OBI Pharma; ChemoGLO, LLC; Glolytics, LLC; Nemucore, Inc; NexImmune; ZY Therapeutics; Merrimack Pharma; Genentech. **Has worked or is working as a consultant**: Cerulean Pharma; BlueLink Pharmaceuticals; Ellipses Pharma; Syros Pharmaceuticals; OBI Pharmaceuticals; Akagera Medicines; Merrimack Pharmaceuticals. **Additional positions held**: CEO, MediGLO - Medical and Pharmaceutical Consulting, LLC; CSO, ChemoGLO, LLC; CSO, Glolytics, LLC.

All remaining authors have declared no conflicts of interest.

References

1. Herbst RS, Khuri FR (2003) Mode of action of docetaxel - a basis for combination with novel anticancer agents. Cancer Treat Rev 29(5):407–415
2. Aapro M (1996) The scientific rationale for developing taxoids. Anti-Cancer Drugs 7(Suppl 2):33–36
3. Montero A, Fossella F, Hortobagyi G, Valero V (2005) Docetaxel for treatment of solid tumours: a systematic review of clinical data. Lancet Oncol 6(4):229–239. https://doi.org/10.1016/s1470-2045(05)70094-2
4. Saloustros E, Mavroudis D, Georgoulias V (2008) Paclitaxel and docetaxel in the treatment of breast cancer. Expert Opin Pharmacother 9(15):2603–2616. https://doi.org/10.1517/14656566.9.15.2603
5. Kuppens IE (2006) Current state of the art of new tubulin inhibitors in the clinic. Curr Clin Pharmacol 1(1):57–70
6. Baker J, Ajani J, Scotte F, Winther D, Martin M, Aapro MS, von Minckwitz G (2009) Docetaxel-related side effects and their

management. Eur J Oncol Nurs 13(1):49–59. https://doi.org/10.1016/j.ejon.2008.10.003
7. Engels FK, Mathot RA, Verweij J (2007) Alternative drug formulations of docetaxel: a review. Anti-Cancer Drugs 18(2):95–103. https://doi.org/10.1097/CAD.0b013e3280113338
8. Gelderblom H, Verweij J, Nooter K, Sparreboom A (2001) Cremophor EL: the drawbacks and advantages of vehicle selection for drug formulation. Eur J Cancer 37 (13):1590–1598. https://doi.org/10.1016/s0959-8049(01)00171-x
9. ten Tije AJ, Verweij J, Loos WJ, Sparreboom A (2003) Pharmacological effects of formulation vehicles. Clin Pharmacokinet 42(7):665–685. https://doi.org/10.2165/00003088-200342070-00005
10. Wilczewska AZ, Niemirowicz K, Markiewicz KH, Car H (2012) Nanoparticles as drug delivery systems. Pharmacol Rep 64(5): 1020–1037
11. Din FU, Aman W, Ullah I, Qureshi OS, Mustapha O, Shafique S, Zeb A (2017) Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors. Int J Nanomed 12:7291–7309. https://doi.org/10.2147/ijn.S146315
12. Heidel JD, Schluep T (2012) Cyclodextrin-containing polymers: versatile platforms of drug delivery materials. J Drug Deliv 2012: 262731. https://doi.org/10.1155/2012/262731
13. Lazarus D, Kabir S, Eliasof S (2012) Abstract 5643: CRLX301, a novel tumor-targeted taxane nanopharmaceutical. Can Res 72(8 Supplement):5643–5643. https://doi.org/10.1158/1538-7445.Am2012-5643
14. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45(2):228–247. https://doi.org/10.1016/j.ejca.2008.10.026
15. Nishino M, Jagannathan JP, Ramaiya NH, Van den Abbeele AD (2010) Revised RECIST guideline version 1.1: What oncologists want to know and what radiologists need to know. AJR Am J Roentgenol 195(2):281–289. https://doi.org/10.2214/ajr.09.4110
16. Sonpavde G, Pond GR, Armstrong AJ, Galsky MD, Leopold L, Wood BA, Wang SL, Paolini J, Chen I, Chow-Maneval E, Mooney DJ, Lechuga M, Smith MR, Michaelson MD (2014) Radiographic progression by Prostate Cancer Working Group (PCWG)-2 criteria as an intermediate endpoint for drug development in metastatic castration-resistant prostate cancer. BJU Int 114(6b):E25–E31. https://doi.org/10.1111/bju.12589
17. Tran S, DeGiovanni PJ, Piel B, Rai P (2017) Cancer nanomedicine: a review of recent success in drug delivery. Clin Transl Med 6(1): 44. https://doi.org/10.1186/s40169-017-0175-0
18. Varan G, Benito JM, Mellet CO, Bilensoy E (2017) Development of polycationic amphiphilic cyclodextrin nanoparticles for anticancer drug delivery. Beilstein J Nanotechnol 8:1457–1468. https://doi.org/10.3762/bjnano.8.145
19. Erdogar N, Varan G, Bilensoy E (2017) Amphiphilic cyclodextrin derivatives for targeted drug delivery to tumors. Curr Top Med Chem 17(13):1521–1528. https://doi.org/10.2174/1568026616666161222101104
20. Stella VJ, He Q (2008) Cyclodextrins. Toxicol Pathol 36(1):30–42. https://doi.org/10.1177/0192623307310945
21. Weiss GJ, Chao J, Neidhart JD, Ramanathan RK, Bassett D, Neidhart JA, Choi CHJ, Chow W, Chung V, Forman SJ, Garmey E, Hwang J, Kalinoski DL, Koczywas M, Longmate J, Melton RJ, Morgan R, Oliver J, Peterkin JJ, Ryan JL, Schluep T, Synold TW, Twardowski P, Davis ME, Yen Y (2013) First-in-human phase 1/2a trial of CRLX101, a cyclodextrin-containing polymer-camptothecin nanopharmaceutical in patients with advanced solid tumor malignancies. Investig New Drugs 31(4):986–1000. https://doi.org/10.1007/s10637-012-9921-8
22. Rivera E, Mejia JA, Arun BK, Adinin RB, Walters RS, Brewster A, Broglio KR, Yin G, Esmaeli B, Hortobagyi GN, Valero V (2008) Phase 3 study comparing the use of docetaxel on an every-3-week versus weekly schedule in the treatment of metastatic breast cancer. Cancer 112(7):1455–1461. https://doi.org/10.1002/cncr.23321
23. Belfiglio M, Fanizza C, Tinari N, Ficorella C, Iacobelli S, Natoli C (2012) Meta-analysis of phase III trials of docetaxel alone or in combination with chemotherapy in metastatic breast cancer. J Cancer Res Clin Oncol 138(2):221–229. https://doi.org/10.1007/s00432-011-1091-0

Affiliations

Sarina A. Piha-Paul[1] · Kyaw Z. Thein[1,2] · Paul De Souza[3] · Richard Kefford[4] · Tara Gangadhar[5] · Christopher Smith[6] · Shelly Schuster[6] · William C. Zamboni[7] · Claire E. Dees[8] · Ben Markman[9]

1 Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA

2 Division of Hematology and Medical Oncology, Oregon Health and Science University/ Knight Cancer Institute, Portland, OR, USA

3 Department of Medical Oncology, Liverpool Hospital, Sydney, Australia

4 Department of Medicine and Health Sciences, Macquarie University, Sydney, Australia

5 Department of Hematology and Medical Oncology, University of Pennsylvania, Philadelphia, PA, USA

6 NewLink Genetics Corporation, Ames, IA, USA

7 UNC Eshelman School of Pharmacy, UNC Lineberger Comprehensive Cancer Center, Carolina Institute of Nanomedicine, Chapel Hill, NC, USA

8 Division of Medical Oncology, University of North Carolina, Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA

9 Department of Medical Oncology, Monash Health/Monash University, Melbourne, Australia