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TLD-1, a novel liposomal doxorubicin, in patients with advanced solid tumors: Dose escalation and expansion part of a multicenter open-label phase I trial (SAKK 65/16)

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ABSTRACT

Background: TLD-1 is a novel liposomal doxorubicin that compared favorably to conventional doxorubicin liposomal formulations in preclinical models. This phase I first-in-human study aimed to define the maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), safety and preliminary activity of TLD-1 in patients with advanced solid tumors.

Patients and methods: We recruited patients with advanced solid tumors who failed standard therapy and received up to 3 prior lines of palliative systemic chemotherapy. TLD-1 was administered intravenously every 3 weeks up to a maximum of 9 cycles (6 for patients with prior anthracyclines) from a starting dose of 10 mg/m^2, according to an accelerated titration design followed by a modified continual reassessment method.

Results: 30 patients were enrolled between November 2018 and May 2021. No dose-limiting toxicities (DLT) were observed. Maximum administered dose of TLD-1 was 45 mg/m^2, RP2D was defined at 40 mg/m^2. Most frequent treatment-related adverse events (TRAE) of any grade included palmar-plantar erythrodysesthesia (PPE) (50% of patients), oral mucositis (50%), fatigue (30%) and skin rash (26.7%). Most common G3 TRAE included PPE in 4 patients (13.3%) and oral mucositis in 2 (6.7%). Overall objective response rate was 10% in the whole population and 23.1% among 13 patients with breast cancer; median time-to-treatment failure was 2.7 months. TLD-1 exhibit linear pharmacokinetics, with a median terminal half-life of 95 h.

Conclusions: The new liposomal doxorubicin formulation TLD-1 showed a favourable safety profile and antitumor activity, particularly in breast cancer. RP2D was defined at 40 mg/m^2 administered every 3 weeks. (NCT03387917)

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1. Introduction

Targeted Liposomal Doxorubicin (TLD-1) is a novel PEGylated liposomal doxorubicin (PLD) formulation developed in order to improve the benefit-risk profile in comparison to conventional non-liposomal doxorubicin and existing liposomal doxorubicin formulations including Caelyx™ and Myocet™. Most important differences include a smaller particle size of about 35 nm as measured by cryoTEM [(or about 60 nm hydrodynamic diameter measured by dynamic light scattering (DLS)], a higher lipid-to-drug ratio, and a particularly dense, outward-only oriented PEGylation.

TLD-1 consists of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE)-mPEG2000 and ammonium sulphate, all of which are currently in use as part of approved liposomal doxorubicin formulations. The molar ratio of DSPC:cholesterol:DSPE-PEG is 58:37:5. With non-liposomal formulations, only a small fraction of doxorubicin accumulates in tumor tissues, resulting in substantial drug exposure in healthy tissue and subsequent toxicities [1]. In particular, accumulation of reactive oxygen species incardiac tissue may result in cardiomyocyte apoptosis and irreversible cardiac damage [2]. Doxorubicin cardiotoxicity is further amplified by doxorubicinol, the major circulating metabolite of doxorubicin [2–4].

Entrapping doxorubicin in polyethylene glycol-modified (PEGylated) liposomes substantially reduces cardiotoxicity [1] and significantly changes the drug's distribution pattern, thereby also increasing drug accumulation and release at the tumor site by approximately 10-fold compared to conventional doxorubicin [5–7]. PLD formulations exploit enhanced permeability and retention (EPR) effects [7,8] by preferentially extravasating in leaky tumor vasculature [9]. Major and most frequent toxicities of liposomal doxorubicin formulations include palmar-plantar erythrodysesthesia (PPE) and mucositis [1,10–13]. The clinical pharmacokinetics (PK) of PEGylated doxorubicin is significantly different from that of free doxorubicin [7,14–16] and is characterised by a small volume of distribution [17], slow clearance, long half-life ($t_{1/2}$) of 50 to 80 h and a roughly 300-fold increased area under the concentration-time curve ($AUC_{0–24}$) compared to non-PEGylated doxorubicin [7]. Compared to Caelyx™, TLD-1 has a smaller liposome diameter (60 nm versus 92 nm as measured by DLS), which may facilitate accumulation in poorly permeable tumors [5,18]. The comparatively high lipid-to-drug ratio primarily leads to a saturation of the clearance organs from the reticuloendothelial system (RES), particularly liver and spleen, with the goal of optimizing the drug delivery, maximizing the therapeutic effect and improving the safety profile [19,20]. Preclinical anti-tumor activity of TLD-1 was demonstrated in a syngeneic model of murine cancer (4T1), two models of human cancer cell lines (A2780, MDA MB231) and a patient-derived ovarian cancer xenograft model (MNI#124) *(Innomedica, data on file)*. TLD-1 preclinical PK was comparable to that of Caelyx™, with similar maximum plasma concentrations (C_{max}) and moderately lower drug exposure over 24 h (AUC_{24}). Repeated intravenous TLD-1 given over 4 weeks in Sprague Dawley rat at doses up to 6 mg/kg/week was devoid of dermal toxicity including PPE *(Innomedica, data on file)*.

We designed this first-in-human dose escalation and dose expansion phase I clinical trial aiming to define the MTD, RP2D, PK, safety and preliminary activity of TLD-1 in patients with adavanced solid tumors (SAKK 65/16, NCT03387917).

2. Materials and methods

2.1. Study design and treatment

SAKK 65/15 is an open label, multicentre first-in-human phase I dose-escalation and dose-expansion study of TLD-1 in patients with advanced solid tumors. Dose escalation was conducted according to an accelerated dose titration (ADT) followed by a modified continual reassessment method (mCRM) design. The primary objective was to define the MTD and RP2D of TLD-1. Secondary objectives included safety, preliminary activity and PK of TLD-1. TLD-1 was administered as a 3-weekly intravenous (iv) infusion over 60 to 90 min (depending on the absolute dose) starting at 10 mg/m^2 until disease progression, unacceptable toxicity or consent withdrawal for a maximum of 6 or 9 cycles (depending on prior anthracycline exposure). Choice of TLD-1 starting dose was based on No Observed Adverse Effect Level (NOAEL) from preclinical testing and calculated using FDA guidelines [21]. Patients received premedication with dexamethasone 8 mg before TLD-1 infusion. Planned dose levels ranged from 10 to 80 mg/m^2. TLD-1 was escalated in single-patient cohorts until the occurrence of the first dose-limiting toxicity (DLT) for the ADT followed by dosing cohorts of 3 patients for the mCRM part. For the mCRM part, decision to escalate/de-escalate TLD-1 dose was based on all prior toxicity data using a mathematical model for the association between dose and toxicity and a target toxicity level of 0.25. Infusion time was 60 min for doses at 10–40 mg/m^2 and 90 min for doses $>$ 40 mg/m^2. No central line was required for TDL-1 administration. No granulocyte-colony stimulating factors (G-CSF) was allowed during cycle 1.

2.2. Study population

Eligible patients were $\geq$ 18 years of age, had histologically or cytologically confirmed advanced or recurrent solid tumors, had received up to 3 prior lines of palliative systemic chemotherapy, had measurable or evaluable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1, Eastern Cooperative Oncology Group (ECOG) performance status $\leq$ 1, adequate bone marrow, hepatic and renal function and a left ventricular ejection fraction (LVEF) $\geq$ 50% as determined by either echocardiography (ECHO) or radionuclide angiocardiography (MUGA). After the inclusion of 21 patients, the protocol was amended to include only patients with sarcoma, breast, ovarian and uterine cancer, based on the established antracycline sensitivity of these tumor entities. Key exclusion criteria included known symptomatic central nervous system or leptomeningeal metastases, malignant primary brain tumors, clinically relevant secondary malignancies, prior cumulative doses of $>$ 250 mg/m^2 for non-liposomal doxorubicin, $>$ 300 mg/m^2 for liposomal doxorubicin or $>$ 400 mg/m^2 for epirubicin or being refractory (progression during first 3 months of treatment) to prior anthracyclines, unresolved drug-associated toxicities Common Terminology Criteria for Adverse Events (CTCAE) grade (G) $>$ 1 from prior treatment, significant cardiac disease including Fredericia-corrected QTc interval $>$ 470 ms for female and $>$ 450 ms for male patients. Approval was obtained from the ethics committee at the participating institutions and regulatory authorities. All patients provided written informed consent. The study was conducted according the Declaration of Helsinki and Good Clinical Practice Guidelines.

2.3. Definition of dose-limiting toxicity

Dose-limiting toxicity was defined as any of the following toxicities occurring during the first 3 weeks (cycle 1) of study treatment and related to TLD-1. Definition of DLT included G4 neutropenia lasting for $\geq$ 5 days, G3 febrile neutropenia, G4 thrombocytopenia or G3 thrombocytopenia with bleeding, G3 QTc prolongation, any drop of LVEF $<$ 50% or $\geq$ 10% from baseline, any symptomatic LVEF deterioration, G4 non-hematological toxicity or G3 lasting lasting for more than 7 days with the exception of anorexia and adequatly treated nausea, vomiting and diarrhoea, G3 skin toxicity not resolving to G2 within $\leq$ 1 week, G2 PPE not resolving to G1 within $\leq$ 2 weeks and any treatment related AE (TRAE) leading to a delay in starting cycle 2 $>$ 14 days.

2.4. Safety and response assessments

Clinical and laboratory assessments were conducted at baseline,

before each weekly visit and at the end of the study. Echocardiogram or MUGA were performed at baseline, day 15 of every 3rd cycle and at the end of study treatment. Electrocardiograms were done at baseline and on day 1 of every treatment cycle. AEs were recorded and graded using NCI-CTCAE v5.0, and assessed by the investigator for any relationship with TLD-1 treatment. Tumor response was assessed according to RECIST v1.1 at baseline and every 6 weeks thereafter. For stable disease (SD), patients had to meet SD criteria at least once after study entry at a minimum interval between measurements of 6 weeks.

2.5. Pharmacokinetic assessments

Blood samples for PK analyses were collected on days 1, 2, 3 (cycle 1 only), 8 and 15 of the first 2 treatment cycles. On day 1, PK samples were taken at the following time points: immediately before administration of TLD-1, at half and end of infusion and 1, 3, 5 and 7 h after end of TLD-1 infusion. Plasma concentrations of doxorubicin (free and total) and doxorubicinol were determined using a validated high-performance liquid chromatographic method according to GLP regulations, with a detection limit of 2.0 ng/mL for doxorubicin and 0.5 for doxorubicinol. To assess the PK of TLD-1, a non-compartmental analysis of the total doxorubicin plasma concentrations (entrapped + free doxorubicin) was performed using the package *pkr* in R [22]. Raw and dose-normalized maximum concentration (C_{max}), raw and dose-normalized area under the concentration-time curve from t = 0 until infinity ($AUC_{0\text{-}inf}$), the time at C_{max} (t_{max}), the volume of distribution (V_D) and the terminal half-lives were calculated for every patient and cycle.

2.6. Statistical analysis

A two-part modified continual reassessment method was used. It started with an accelerated titration design for dose escalation up to the occurrence of the first DLT. The maximum number of patients to be enrolled was 30 and the minimum number of patients at the tentative RP2D was 15. Patients were considered evaluable for the primary endpoint if they had received at least one infusion of TLD-1 and were followed for the DLT period of 21 days. Patients were evaluable for antitumor activity if at least one post-baseline tumor assessement was performed. Response was evaluated according to RECIST 1.1 criteria and objective radiological response (ORR) was defined as complete response (CR) or partial response (PR) during trial treatment. Time-to-treatment failure (TTF) was defined as time from registration until premature treatment discontinuation due to any reason. Patients who completed study treatment as per protocol without tumor progression were censored at the date of their last treatment plus 21 days. For categorical variables, the results were summarized by frequencies and percentages and were presented together with their exact 2-sided 95% Clopper-Pearson confidence intervals (CI). For continuous variables, the results were summarized by descriptive statistics. Time-to-event endpoints were presented using the the Kaplan-Meier methodology. AEs are presented by type and grade showing frequency and proportions of worst grade AE.

All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA) and R 4.1.2 (The R Fundation; www.r-project.org).

3. Results

3.1. Patients characteristics and treatment

A total of 30 patients were enrolled across 4 Swiss sites between November 2018 and May 2021. Most frequent tumor entities included breast cancer (BC) in 13 and ovarian cancer in 6 patients. Most patients were heavily pretreated, having received a median of 4 prior lines (including treatment in the adjuvant setting) of systemic treatment including 13 (43%) patients previously treated with anthracyclines. Baseline demographic and disease characteristics are outlined in Table 1.

Table 1
Patient demographics and clinical characteristics.

Patient characteristics	Total (N = 30)
Median age (years)	67.5
range	38-83
ECOG performance status, n (%)	
0	18 (60)
1	12 (40)
Gender, n (%)	
female	24 (80)
male	6 (20)
Tumor type, n (%)	
breast cancer	13 (43)
ovarian cancer	6 (20)
cervical cancer	2 (7)
uterine cancer	2 (7)
cholangiocarcinoma	2 (7)
other	5 (17)
Prior anthracyclines, n (%)	13 (43)
Prior systemic anticancer treatments, n (%)	
1	4 (13)
2	3 (10)
3	5 (17)
≥4	18 (60)

Enrolled patients were included in 7 dose escalation cohorts as described in Fig. 1. All patients received at least one cycle of TLD-1. Patients received a median of 4 cycles (range 1–9) with a total number of 128 administered cycles. Reasons for treatment discontinuation included progressive disease in 18 patients (60%), maximum number of cycles reached in 6 (20%), patient's decision in 3 (10%), unacceptable toxicity and physician's decision in one patient each (3.3%).

3.2. Safety

None of the enrolled patients experienced a DLT. TRAE of any grade were documented in 28 (93.3%) patients; the most frequent were PPE (50%), oral mucositis (50%), fatigue (30%), skin rash (26.7%) presenting more frequently after cycle 1 and at higher doses (Fig. 2). Most frequent TRAE G3 were PPE in 4 patients (13.3%) and oral mucositis in 2 (6.7%); G3 hematological toxicity included one case of anemia and one of neutropenia (Table 2). Thirteen SAEs were reported and 2 were considered possibly related to TLD-1, i.e. one case of heart failure G3 (in a patient with preexisting valvular heart-disease) and one case of shingles G3. There were no study-related deaths. Dose modifications or delays of TLD-1 occurred in 7/50 (14%) cycles at the dose of 40 mg/m^2 and in 12/61 (19.7%) cycles at the dose of 45 mg/m^2. At least one dose modification due to treatment-emergent AE (TEAE) occurred in 9 patients (30%) in total, 2 at DL6 and 7 at DL7. Dose delay due to TEAE occurred in 14 (46.7%) patients, including 5 at DL6 and 8 at DL7. TRAE leading to discontinuation of TLD-1 occurred in 1 (3.3%) patient at the 45 mg/m^2 dose (DL 7). At DL7, 66.7% of patients (10/15) experienced PPE of any grade including 3 (20%) patients with PPE G3 resulting in TLD-1 dose delays and/or dose reductions. Despite the absence of DLTs and thus not meeting the criteria for the definition of MTD, DL7 was considered not safe due to the rate of PPE and dose reductions. DL6 was expanded to enrol 9 additional patients and the RP2D was defined as 40 mg/m^2 every 3 weeks. At DL6, PPE of any grade occurred in 40% (4/10) of patients.

3.3. Antitumor activity

29 (93.7%) of 30 patients were evaluable for radiological response assessment, with one patient not evaluable because of the lack of radiological restaging. Investigator-assessed ORR was 10% (95% CI: 2.1%, 26.5%) in all patients, 10 (34.5%) patients had stable disease (SD) lasting ≥ 12 weeks (Figure 3). The median TTF was 2.7 months (95% CI: 1.6, 4.1). In patients with BC the ORR was 23.1%, while no responses

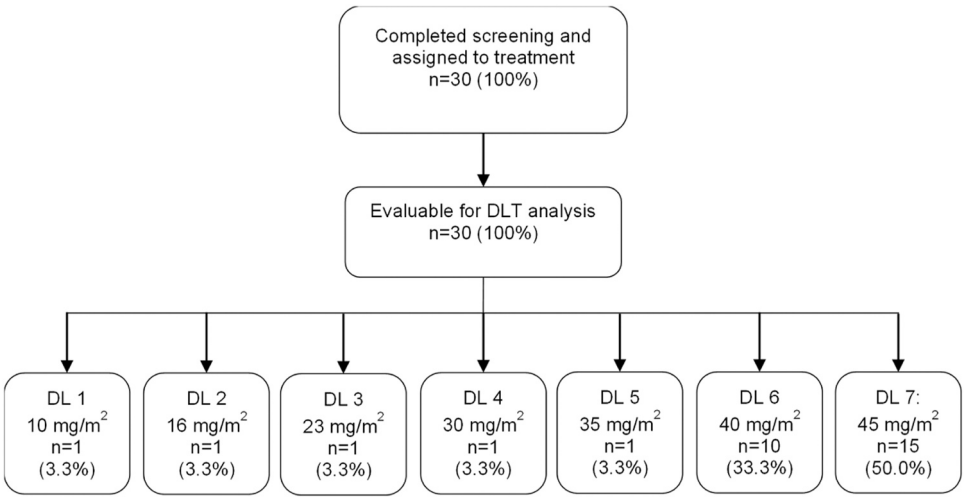

Fig. 1. Patients disposition. Dose escalation was conducted according to an accelerated dose titration (ADT), followed by a modified continual reassessment method (mCRM) design. One patient was enrolled in each dose level (DL) from DL1 to DL6 and 15 patients at 45 mg/m^2. Due to emergent toxicities in later cycles at 45 mg/m^2 leading to dose delays or reductions, 9 additional patients were enrolled in DL 6 cohort (40 mg/m^2).

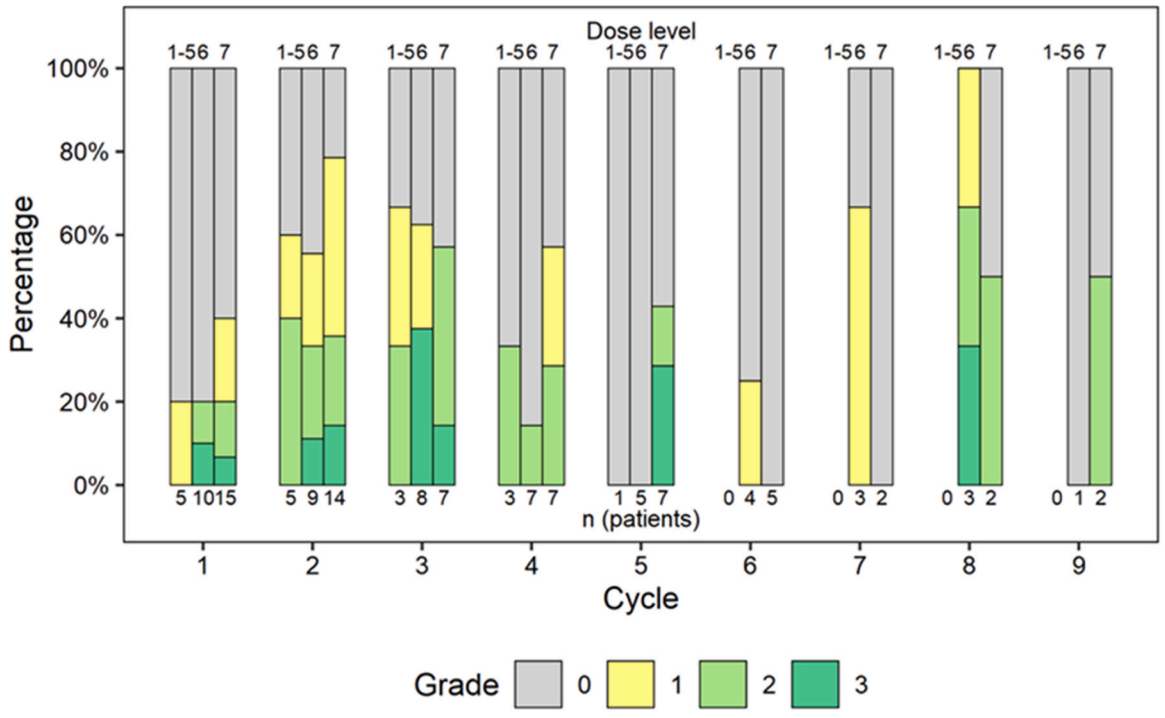

Fig. 2. Treatment-related adverse events (TRAEs) by dose-level (highest grade per patient and cycle).

were seen among 6 patients with platinum-resistant ovarian cancer. TTF was 4.1 and 1.4 months in patients with BC and ovarian cancer respectively.

3.4. Pharmacokinetics

All 30 patients were evaluable for cycle 1 PK analysis, while cycle 2 PK data were not available in 2 patients. Median dose-normalized area under the plasma concentration-time curve from time zero to infinity ($AUC_{0\text{-inf}}$) and the median dose-normalized C_{max} were 37.4 h/L (range, 17.3 h/L to 79.3 h/L) and 0.328 1/L (0.211 1/L to 0.859 1/L), respectively, in cycle 1, and 43.4 h/L (range, 16.7 h/L to 79.5 h/L) and 0.360 1/L (0.195 1/L to 0.809 1/L), respectively, in cycle 2. The median $t_{1/2}$ was 89 h with a large variability (range, 46 h to 132 h) in cycle 1 and 104 h with a large variability (range, 49 h to 213 h) in cycle 2. PK parameters of total doxorubicin obtained from the non-compartimental analysis were stratified by dose-level and are displayed in Table 3. Plasma concentration-time profiles of entrapped and free doxorubicin as well as doxorubicinol for each dose-level are shown in Supplementary Figs. 1–3. More detailed results of TLD-1 population analysis will be reported separately.

Table 2
Treatment-related adverse events (TRAE) according to dose level and grade.

n (%)	DL 1-5 n = 5		DL 6 n = 10		DL 7 n = 15		Total n = 30	
TRAE	Any G	G3	Any G	G3	Any G	G3	Any G	G3
PPE	1 (20)		4 (40)	1 (10)	10 (66.7)	3 (20)	15 (50)	4 (13.3)
mucositis	2 (40)		5 (50)	1 (10)	8 (53)	1 (6.7)	15 (50)	2 (6.7)
fatigue	2 (40)		1 (10)		6 (40)	1 (6.7)	9 (30)	1 (3.3)
maculo-papular rash			3 (30)		5 (33.3)		8 (26.7)	
nausea	1 (20)		1 (10)		3 (20)		5 (16.6)	
anorexia	1 (20)		1 (10)		2 (13.3)		4 (13.3)	
neutropenia			1 (10)	1 (10)	3 (20)		4 (13.3)	1 (3.3)
urinary tract infection			2 (20)	1 (10)	1 (6.7)		3 (10)	1 (3.3)
vomiting			1 (10)		1 (6.7)		2 (6.7)	
anemia	1 (20)		1 (10)	1 (10)			2 (6.7)	1 (3.3)
dysphagia					2 (6.7)		2 (6.7)	
limb edema	1 (20)				1 (6.7)		2 (6.7)	
alopecia			1 (10)		1 (6.7)		2 (6.7)	
leucopenia	1 (20)						1. (3.3)	
hearth failure			1 (10)	1 (10)			1 (3.3)	1 (3.3)
abdominal pain					1 (6.7)		1 (3.3)	
constipation	1 (20)						1 (3.3)	
diarrhea	1 (20)						1 (3.3)	
dyspepsia					1 (6.7)		1 (3.3)	
gastritis					1 (6.7)		1 (3.3)	
esophageal infection					1 (6.7)		1 (3.3)	
herpes simplex reactivation					1 (6.7)		1 (3.3)	
nail infection			1 (10)				1 (3.3)	
shingles					1 (6.7)	1 (6.7)	1 (3.3)	1 (3.3)
vulvar infection					1 (6.7)		1 (3.3)	
increased creatinine	1 (20)						1 (3.3)	
headache	1 (20)						1 (3.3)	
nephritis	1 (20)						1 (3.3)	
genital edema	1 (20)						1 (3.3)	
sore throat					1 (6.7)		1 (3.3)	
eczema			1 (10)				1 (3.3)	

PPE: Palmar-plantar erythrodysesthesia; DL: dose level; G: grade

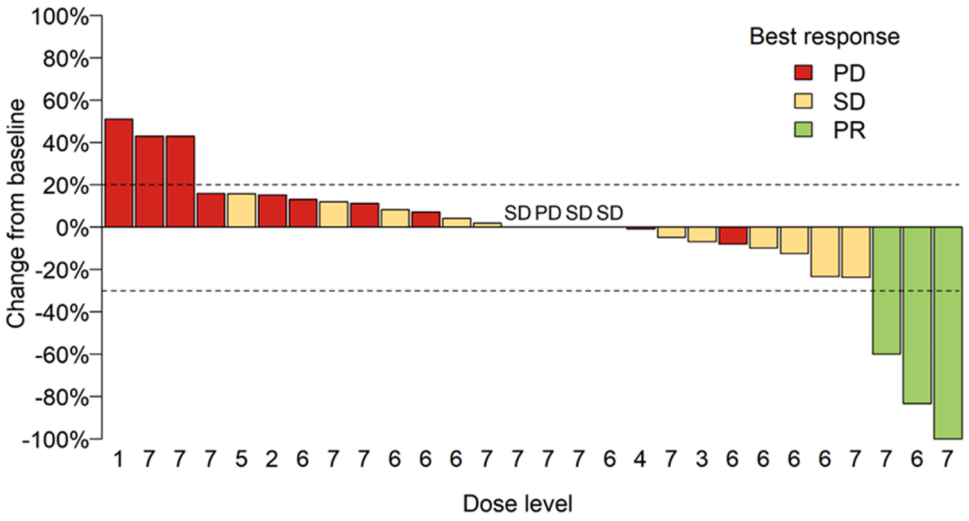

Fig. 3. Maximum reduction of the sum of target lesions and best response according RECIST 1.1. PD: progressive disease; SD: stable disease; PR: partial response.

4. Discussion

This trial explored the safety, tolerability, PK and preliminary clinical activity of the new liposomal doxorubicin formulation TLD-1 in patients with advanced solid tumors. Based on AEs observed at 45 mg/m^2, the dose of 40 mg/m^2 every 3 weeks was selected as the RP2D of TLD-1. Evidence of antitumor activity was observed in patients who had failed standard chemotherapy, including patients with advanced BC. At 40 mg/m^2, the two most prevalent mild and severe TRAE included PPE in 30% and 10% of patients, stomatitis in 40% and 10% of patients, respectively. These toxicity data are comparable to those reported for Caelyx™ when administered at the approved dose of 50 mg/m^2 [13]. In a randomized clinical trial in 509 patients with metastatic BC, Caelyx™ at 50 mg/m^2 every 4 weeks resulted in mild and severe PPE in 48% and 17% of patients, mild and severe mucositis in 23% and 4% of patients, respectively [1]. Higher rates of Caelyx™-associated PPE and stomatitis were reported by Harbeck et al. in 210 patients with metastatic BC receiving Caelyx™ at 50 mg/m^2 every 4 weeks, with mild and severe PPE in 66% and 39% of patients, mild and severe stomatitis in 40% and 6% of patients, respectively [23].

With regards to antitumor activity, we report a radiological response rate of 23.1% (3/13 patients) in patients with advanced BC with a TTP of

Table 3
Pharmacokinetic data of TLD-1 in cycle 1*.

Dose level	N	Results	$AUC_{0\text{-}inf}$	$AUC_{0\text{-}inf}$/Dose	C_{max}	C_{max}/Dose	t_{max}	V_D	$t_{1/2}$
			$h{\cdot}mg{\cdot}L^{-1}$	$h{\cdot}L^{-1}$	$mg{\cdot}L^{-1}$	L^{-1}	h	L	h
1 (10 mg/m^2)	1	mean ± SD	558	31.9	4.98	0.28	1.52	3.66	81.0
		% CV	0	0	0	0	0	0	0
2 (16 mg/m^2)	1	mean ± SD	726	23.4	6.61	0.21	2.25	4.81	78.0
		% CV	0	0	0	0	0	0	0
3 (23 mg/m^2)	1	mean ± SD	1172	31.3	9.4	0.25	4	4.37	94.8
		% CV	0	0	0	0	0	0	0
4 (30 mg/m^2)	1	mean ± SD	2334	38.6	16.8	0.28	1.42	3.51	93.9
		% CV	0	0	0	0	0	0	0
5 (35 mg/m^2)	1	mean ± SD	1970	36.1	18.0	0.33	2.23	3.09	77.1
		% CV	0	0	0	0	0	0	0
6 (40 mg/m^2)	10	mean ± SD	2192 ± 1172	32.8 ± 17.6	20.0 ± 4.73	0.299 ± 0.069	2.97 ± 2.19	4.06 ± 0.91	84.2 ± 20.6
		% CV	53.5	53.7	23.6	23.1	83.3	22.4	24.5
7 (45 mg/m^2)	15	mean ± SD	4151 ± 1115	52.3 ± 16.0	36.2 ± 10.7	0.45 ± 0.134	3.70 ± 1.79	2.81 ± 0.61	96.9 ± 21.6
		% CV	26.9	30.5	29.5	29.7	29.5	21.7	22.3

*Values are reported for total doxorubicin, i.e., the sum of entrapped + free doxorubicin.

4.1 months. This compares to response rates ranging between 7–27% in patients with BC treated with Caelyx™ at the approved dose [11–13,23]. However due to the lack of head-to-head comparison and the limited number of patients treated with TLD-1 to date, no formal comparison between TLD-1 and Caelyx™ has been estabilshed yet.

The key rationale for TLD-1's design was to maximize the pharmacological potential of PEGylated liposomal doxorubicin by making use of a smaller nanoparticle diameter, potentially allowing a greater tumor uptake by transcytotic processes across tumor blood vessels [24–26] and potentially improving the therapeutic benefit-risk ratio. However, our understanding of the association between PEGylated liposomal nanoparticle characteristics, their pharmacology, PK and clinical effects is still incomplete. TLD-1 terminal half-life at the RP2D of 84.2 h (+/- 20.6) is moderately longer compared to Caelyx™ average terminal half-life of roughly 74 h (range, 24 h – 231 h), potentially allowing for increased tumor uptake of liposomal doxorubicin from TLD-1 compared to Caelyx™. A more comprehensive TLD-1 PK analysis using a compartmental population PK model of entrapped doxorubicin, free doxorubicin, and doxorubicinol will be reported separately.

In conclusion, this phase I study demonstrated that the new liposomal doxorubicin formulation TLD-1 is safe and well tolerated at a dose of 40 mg/m^2 every 3 weeks, with antitumor activity in patients with pretreated advanced BC and a potentially favourable PK profile of TLD-1. An amended ongoing part of this study is currently comparing TLD-1 at 40 mg/m^2 versus Caelyx™ at 40 mg/m^2 in a randomized intrapatient cross-over design to further characterize the PK of the two liposome formulations in patients with advanced BC and platinum-resistant ovarian cancer.

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CRediT authorship contribution statement

Ilaria Colombo: Data curation, Formal analysis, Investigation, Project administration, Resources, Visualization, Writing original draft. **Kira-Lee Koster:** Data curation, Formal analysis, Investigation, Project administration, Validation, Writing review & editing. **Lisa Holer**: Data curation, Formal analysis, Methodology, Project administration, Resources, Software, Validation, Writing – review & editing. **Simon Haefliger**: Investigation, Project administration, Writing – review & editing. **Manuela Rabaglio:** Investigation, Project administration, Writing – review & editing. **Sara Bastian**: Investigation, Project administration, Writing – review & editing. **Michael Schwitter:** Investigation, Project administration, Writing – review & editing. **Katrin Eckhardt**: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Writing – review & editing. **Stefanie Hayoz:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Writing – review & editing. **Anna M. Mc Laughlin**: Data curation, Formal analysis, Methodology, Software, Validation, Visualization, Writing – review & editing., **Charlotte Kloft**: Data curation, Formal analysis, Methodology, Software, Validation, Visualization, Writing – review & editing. **Marian Klose:** Data curation, Formal analysis, Methodology, Software, Validation, Visualization, Writing – review & editing. **Stefan Halbherr**: Conceptualization, Methodology, Resources, Writing – review & editing. Christian Baumgartner: Conceptualization, Methodology, Resources, Writing – review & editing. **Cristiana Sessa:** Conceptualization, Data curation, Formal analysis, Methodology, Validation, Writing – review & editing. **Anastasios Stathis:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing. **Dagmar Hess**: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing. **Markus Joerger**: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing.

Declaration of Competing Interest

Ilaria Colombo: Travel grants: Tesaro, Janssen, AZ, GSK. Honoraria for consultancy or expert opinion: AZ, GSK, Novartis, MSD, BionTech. Institutional grants for clinical trials (PI): MSD, Bayer, Vivesto, Incyte, AZ, Orion.

Kira-Lee Koster: Travel grants for congress visits from Takeda Pharma AG und Janssen-Cilag AG (paid to institution).

Lisa Holer: no conflict of interest.

Simon Haefliger: no conflict of interest.

Manuela Rabaglio: no conflict of interest.

Sara Bastian: no conflict of interest.

Michael Schwitter: no conflict of interest.

Katrin Eckhardt: no conflict of interest.

Stefanie Hayoz: no conflict of interest.

Anna M. Mc Laughlin: current employee of Pharmetheus AB and a paid consultant to multiple pharmaceutical companies.

Charlotte Kloft: no conflict of interest.

Marian Klose: no conflict of interest.

Stefan Halbherr: Stefan Halbherr owns shares of InnoMedica Holding AG and functions as part of the executive management of the firm.

Christian Baumgartner: Christian Baumgartner hold shares of Innomedica and is a former employee of the firm. He has received advisory fees from Boehringer Ingelheim.

Cristiana Sessa: no conflict of interest.

Anastasios Stathis: Institutional funding for clinical trials: Innomedica, Abbvie; ADC Therapeutics; Amgen, Astra Zeneca; Bayer; Cellestia; Incyte, Loxo Oncology; Merck MSD; Novartis; Pfizer; Philogen; Roche. Consultant/expert testimony/advisory board (institutional): Debiopharm, Janssen, AstraZeneca, Incyte, Eli Lilly, Novartis, Roche, Loxo Oncology. Travel grant: Incyte; Astra Zeneca.

Dagmar Hess: no conflict of interest.

Markus Joerger: Advisory role (institutional): Novartis, Astra Zeneca, Basilea Pharmaceutica, Bayer, BMS, Debiopharm, MSD, Roche, Sanofi; research funding: Swiss Cancer Research; travel grants: Roche, Sanofi, Takeda.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.113588.

References

[1] O'Brien ME, Wigler N, Inbar M, Rosso R, Grischke E, Santoro A, et al. Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. Ann Oncol 2004;15(3):440–9. https://doi.org/10.1093/annonc/mdh097.

[2] Rahman AM, Yusuf SW, Ewer MS. Anthracycline-induced cardiotoxicity and the cardiac-sparing effect of liposomal formulation. Int J Nanomed 2007;2(4):567–83.

[3] Olson RD, Mushlin PS, Brenner DE, Fleischer S, Cusack BJ, Chang BK, et al. Doxorubicin cardiotoxicity may be caused by its metabolite, doxorubicinol. Proc Natl Acad Sci USA 1988;85(10):3585–9. https://doi.org/10.1073/pnas.85.10.3585.

[4] Boucek Jr RJ, Olson RD, Brenner DE, Ogunbunmi EM, Inui M, Fleischer S. The major metabolite of doxorubicin is a potent inhibitor of membrane-associated ion pumps. A correlative study of cardiac muscle with isolated membrane fractions. J Biol Chem 1987;262(33):15851–6.

[5] Symon Z, Peyser A, Tzemach D, Lyass O, Sucher E, Shezen E, et al. Selective delivery of doxorubicin to patients with breast carcinoma metastases by stealth liposomes. Cancer 1999;86(1):72–8.

[6] Gabizon A, Catane R, Uziely B, Kaufman B, Safra T, Cohen R, et al. Prolonged circulation time and enhanced accumulation in malignant exudates of doxorubicin encapsulated in polyethylene-glycol coated liposomes. Cancer Res 1994;54(4):987–92.

[7] Gabizon A, Shmeeda H, Barenholz Y. Pharmacokinetics of pegylated liposomal Doxorubicin: review of animal and human studies. Clin Pharm 2003;42(5):419–36. https://doi.org/10.2165/00003088-200342050-00002.

[8] Maeda H, Wu J, Sawa T, Matsumura Y, Hori K. Tumor vascular permeability and the EPR effect in macromolecular therapeutics: a review. J Control Release 2000;65(1-2):271–84. https://doi.org/10.1016/s0168-3659(99)00248-5.

[9] Rosenblum D, Joshi N, Tao W, Karp JM, Peer D. Progress and challenges towards targeted delivery of cancer therapeutics. Nat Commun 2018;9(1):1410. https://doi.org/10.1038/s41467-018-03705-y.

[10] Gordon AN, Fleagle JT, Guthrie D, Parkin DE, Gore ME, Lacave AJ. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. J Clin Oncol 2001;19(14):3312–22. https://doi.org/10.1200/JCO.2001.19.14.3312.

[11] Coleman RE, Biganzoli L, Canney P, Dirix L, Mauriac L, Chollet P, et al. A randomised phase II study of two different schedules of pegylated liposomal doxorubicin in metastatic breast cancer (EORTC-10993). Eur J Cancer 2006;42(7):882–7. https://doi.org/10.1016/j.ejca.2005.12.011.

[12] Fiegl M, Mlineritsch B, Hubalek M, Bartsch R, Pluschnig U, Steger GG. Single-agent pegylated liposomal doxorubicin (PLD) in the treatment of metastatic breast cancer: results of an Austrian observational trial. BMC Cancer 2011;11:373. https://doi.org/10.1186/1471-2407-11-373.

[13] Keller AM, Mennel RG, Georgoulias VA, Nabholtz JM, Erazo A, Lluch A, et al. Randomized phase III trial of pegylated liposomal doxorubicin versus vinorelbine or mitomycin C plus vinblastine in women with taxane-refractory advanced breast cancer. J Clin Oncol 2004;22(19):3893–901. https://doi.org/10.1200/JCO.2004.08.157.

[14] Speth PA, van Hoesel QG, Haanen C. Clinical pharmacokinetics of doxorubicin. Clin Pharm 1988;15(1):15–31. https://doi.org/10.2165/00003088-198815010-00002.

[15] Joerger M, Huitema AD, Meenhorst PL, Schellens JH, Beijnen JH. Pharmacokinetics of low-dose doxorubicin and metabolites in patients with AIDS-related Kaposi sarcoma. Cancer Chemother Pharm 2005;55(5):488–96. https://doi.org/10.1007/s00280-004-0900-4.

[16] Amantea MA, Forrest A, Northfelt DW, Mamelok R. Population pharmacokinetics and pharmacodynamics of pegylated-liposomal doxorubicin in patients with AIDS-related Kaposi's sarcoma. Clin Pharm Ther 1997;61(3):301–11. https://doi.org/10.1016/S0009-9236(97)90162-4.

[17] Xu L, Wang W, Sheng YC, Zheng QS. Pharmacokinetics and its relation to toxicity of pegylated-liposomal doxorubicin in Chinese patients with breast tumours. J Clin Pharm Ther 2010;35(5):593–601. https://doi.org/10.1111/j.1365-2710.2009.01128.x.

[18] (EMA) EMA. Caelyx summary of product characteristics.

[19] Liu D, Mori A, Huang L. Role of liposome size and RES blockade in controlling biodistribution and tumor uptake of GM1-containing liposomes. Biochim Et Biophys Acta 1992;1104(1):95–101. https://doi.org/10.1016/0005-2736(92)90136-a.

[20] Sun X, Yan X, Jacobson O, Sun W, Wang Z, Tong X, et al. Improved Tumor Uptake by Optimizing Liposome Based RES Blockade Strategy. Theranostics 2017;7(2):319–28. https://doi.org/10.7150/thno.18078.

[21] (FDA) USFDA. Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. 2005.

[22] R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, 2022.https://www.r-project.org/.

[23] Harbeck N, Saupe S, Jager E, Schmidt M, Kreienberg R, Muller L, et al. A randomized phase III study evaluating pegylated liposomal doxorubicin versus capecitabine as first-line therapy for metastatic breast cancer: results of the PELICAN study. Breast Cancer Res Treat 2017;161(1):63–72. https://doi.org/10.1007/s10549-016-4033-3.

[24] Ouyang B, Poon W, Zhang YN, Lin ZP, Kingston BR, Tavares AJ, et al. The dose threshold for nanoparticle tumour delivery. Nat Mater 2020;19(12):1362–71. https://doi.org/10.1038/s41563-020-0755-z.

[25] Sindhwani S, Syed AM, Ngai J, Kingston BR, Maiorino L, Rothschild J, et al. The entry of nanoparticles into solid tumours. 566-75 Nat Mater 2020;19(5). https://doi.org/10.1038/s41563-019-0566-2.

[26] Kingston BR, Lin ZP, Ouyang B, MacMillan P, Ngai J, Syed AM, et al. Specific endothelial cells govern nanoparticle entry into solid tumors. ACS Nano 2021;15(9):14080–94. https://doi.org/10.1021/acsnano.1c04510.