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

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## Background

- Doxorubicin is an established anthracycline used in the treatment of several different malignancies.
- TLD-1 is a novel liposomal doxorubicin that compared favourably to conventional liposomal formulations of doxorubicin in preclinical in vivo models.
- This phase I first-in-human trial is aiming to determine the maximum tolerated dose (MTD), the recommended phase II dose (RP2D), toxicity profile, pharmacokinetics and preliminary activity in advanced solid tumors.

## Methods

- **Main Eligibility Criteria**:

a) Patients with advanced solid tumors , a maximum of 3 prior lines of systemic chemotherapy and ECOG PS ≤ 1
b) Adequate bone marrow, hepatic and renal function
c) Limitation of cumulative prior anthracycline treatment
d) Absence of significant cardiac disease

- **Treatment**: TLD-1 was administered on day 1 iv over 60-90 minutes (depending on individual dose) q 21 days, for up to 6 or 9 cycles (depending on prior exposure to anthracyclines) with premedication of 8mg dexamethasone.
- **Design**: An accelerated titration design (ATD) was used, treating one patient at each dose level (DL) up to DL6, followed by a modified continual reassessment method at DL7.
- **Primary endpoint**: DLT
- **Secondary endpoints**: additional safety data, preliminary activity and pharmacokinetics (PK)

## Results

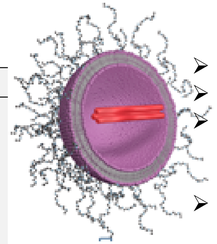
Starting in Nov. 2018, 12 patients were enrolled, all evaluable for primary and secondary endpoints.

**Tab 1. Baseline patient demographics**

| Variable | N=12 |
|---|---|
| • Age: Median (Min-Max) | 67y (39-83) |
| • Gender | F=8 / M=4 |
| • Type of solid tumor | |
| Breast cancer | 3 |
| Ovarian cancer | 4 |
| Cholangio cancer | 1 |
| Colon cancer | 1 |
| Pancreatic cancer | 1 |
| Mesothelioma | 1 |
| Uterine cancer | 1 |
| • Previous anthracyclines | Yes=5 / No=7 |

**Tab 2. Dose-levels, Toxicity and Treatment Modifications**

| Dose level | N pts | Toxicity | Delay / dose modifications |
|---|---|---|---|
| DL 1 (10 mg/m$^2$) | 1 | No | No |
| DL 2 (16 mg/m$^2$) | 1 | No | No |
| DL 3 (23 mg/m$^2$) | 1 | No | No |
| DL 4 (30 mg/m$^2$) | 1 | Mucositis G2 (C3)<br>PPE G2 (C4),<br>WBC G2 (C2) | Delay of subsequent cycle |
| DL 5 (35 mg/m$^2$) | 1 | Mucositis G2 (C2) | No |
| DL 6 (40 mg/m$^2$) | 1 | Rash G2 (C3)<br>PPE G3 (C3) | Dose reduction and delay of subsequent cycle |
| DL 7 (45 mg/m$^2$) | 3/6 | Rash G2 (C3)<br>PPE G2 (C3)<br>PPE G3 (C3) | Dose reduction and delay of subsequent cycle |



- Patients received a median of 4 cycles (2-6).
- No DLT occurred in cycle 1
- Skin and mucosa toxicity was categorized as related to TLD-1 and started within C3/4 and led to a delay of subsequent cycles and dose reductions
- No other clinically relevant AE's were observed

### Blood sampling and pharmacokinetic analysis

- Blood samples were taken in the first two cycles at multiple timepoints up to 48h and at days 8 and 15 after infusion.
- The PK showed full dose linearity (Figure 1).
- The mean apparent half-life was 96 hours (CV 23.8%).
- No carry-over effect from previous cycles was observed.
- A 4-compartment parent-metabolite PK model was developed to describe the concentration time-profiles of all three analytes, measured by using LC-MS/MS

**Fig 1. PK for pts 1-6**

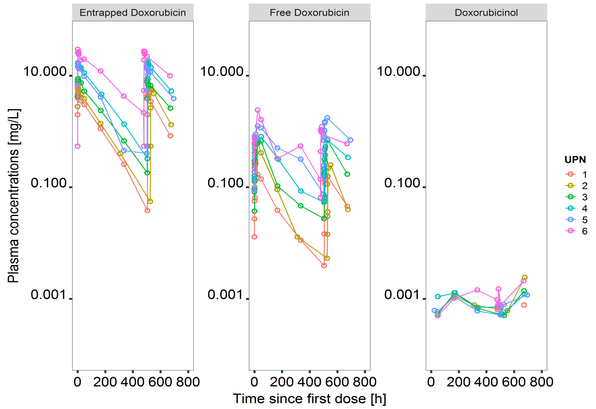
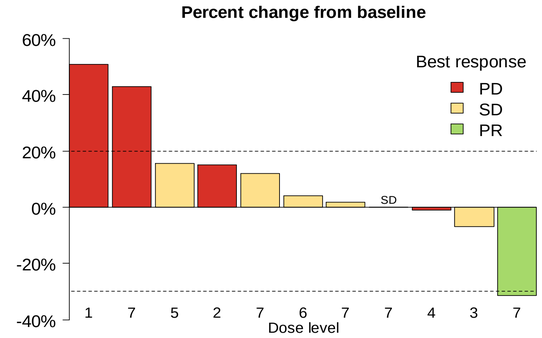



**Fig 2. Maximum reduction of target lesion sum**




One patient with only non-target lesions omitted

## Conclusion

- TLD-1 can be safely administered up to a dose of 45mg/m$^2$, however, G2/3 cumulative skin and mucosa toxicity was observed in 6/12 pts. mainly starting with cycle 3.
- TLD-1 shows dose-linear PK and early activity in anthracycline-sensitive tumors (1 PR in a pt with breast cancer at DL7).
- The trial is currently being expanded to gain more information on cumulative toxicities and to better define the RP2D.

## Conflicts of Interest

1. D.Hess: shareholder values
2. S.Haefliger: advisory boards
3. A.Stathis: institutional research funding
4. C.Kloft: grants from an industry consortium

**All COIs are outside the submitted work**

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