D.Hess\(^1\), Ilaria Colombo\(^2\), Simon Haefliger\(^3\), Manuela Rabaglio\(^4\), Sara Bastian\(^5\), Yannis Metaxas\(^6\), Katrin Eckhardt\(^7\), Stefanie Hayoz\(^3\), Christoph Kopp\(^5\), Anna Mueller-Schoeff\(^7\), Charlotte Klotz\(^8\), Cristiana Sessa\(^3\), Anastasios Statthis\(^9\), Markus Joerger\(^1\) for the Swiss Group for Clinical Cancer research (SAKK) Abstract: \# 1863

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) 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.

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 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

**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.Statthis: institutional research funding
4. C.Klotz: grants from an industry consortium

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