GCT1021-01, a first-in-human, open-label, dose-escalation trial with expansion cohorts to evaluate safety of Axl-specific antibody-drug conjugate (HuMax®-AXL-ADC) in patients with solid tumors (NCT 02988817)

abstract TPS2605

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Background

HuMax-AXL-ADC is an antibody-drug conjugate (ADC) composed of an Axl-specific human monoclonal immunoglobulin G1 (IgG1y) conjugated via a protease-cleavable valine-citrulline linker to the microtubule disrupting agent monomethyl auristatin E (MMAE). *In vivo*, HuMax-AXL-ADC demonstrated therapeutic anti-tumor efficacy in patient-derived xenograft models representing a variety of solid cancers, including pancreas, thyroid, lung, esophageal, cervical cancers and malignant melanoma.
The non-clinical safety profile and pharmacokinetics (PK) of a once every 3 weeks (1Q3W) dosing schedule were established in cynomolgus monkeys.

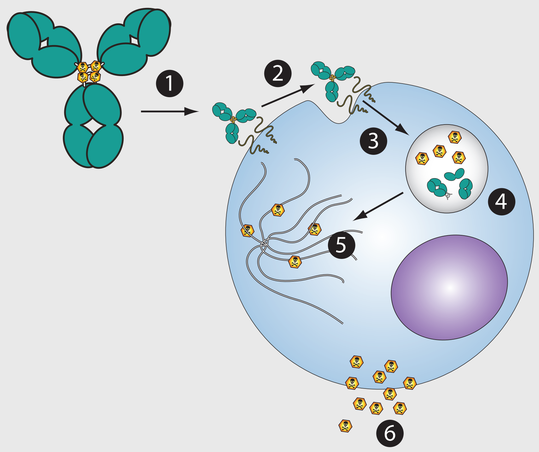

Figure 1. The dominant mechanism of action for HuMax AXL ADC is tumor cell killing by MMAE mediated interference with cell division.
1. Binding to Axl-positive tumor cells;
2. Internalization of HuMax-AXL-ADC;
3. Trafficking to the lysosomes;
4. Lysosomal degradation of HuMax-AXL-ADC and intracellular release of MMAE;
5. MMAE-mediated disruption of microtubules, resulting in apoptotic cell death of dividing cells;
6. Release of MMAE induces bystander killing of neighboring cancer cells.

Summary

This is the first-in-human open label, multi-center Phase I/IIa safety trial of HuMax-AXL-ADC in a mixed population of patients with solid tumors.
The primary objective is to determine the MTD and to establish the safety profile of HuMax-AXL-ADC, both in 1Q3W and 3Q4W dosing schedules. Dose escalation is currently ongoing.

Overview of trial design

The primary objective of this trial is to determine the MTD and to establish the safety profile of HuMax-AXL-ADC in a mixed population of patients with specified solid tumors, who have failed available therapies / are not candidates for standard therapies: ovarian, cervical, endometrial, thyroid cancer, NSCLC, and malignant melanoma.

The trial consists of two parts, a phase I dose escalation part and a phase IIa expansion part. The dose escalation part explores two different dosing frequencies in two arms: in the first arm, doses from 0.3 up to 2.8 mg/kg are administered 1Q3W (Figure 2).

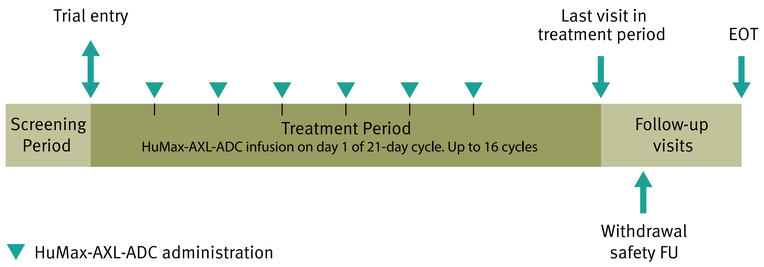

Figure 2. Trial flow for the 1Q3W dose escalation.

The second arm investigates doses in the range of 0.45 to 1.4 mg/kg to be administered weekly for 3 weeks followed by one treatment-free week (3Q4W dosing schedule, Figure 3).

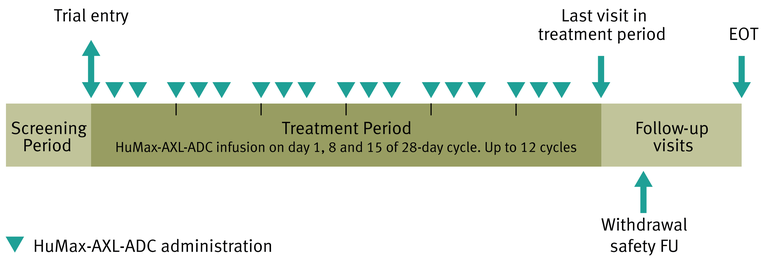

Figure 3. Trial Flow of the 3Q4W dose escalation.

The second arm will start when at least 8 patients have been evaluated for dose limiting toxicities, the 1.5 mg/kg cohort of the 1Q3W arm has been declared safe, and the predicted PK parameters of the starting dose in the 3Q4W arm are below pre-defined limits, the 3Q4W arm will be initiated.

The 1Q3W arm follows a modified Bayesian Continuous Reassessment Method including escalation with overdose control in up to 41 patients on up to 7 main and 4 intermediate dose levels while the 3Q4W arm is run as a standard 3+3 trial design on up to 5-6 dose levels (Figure 4).

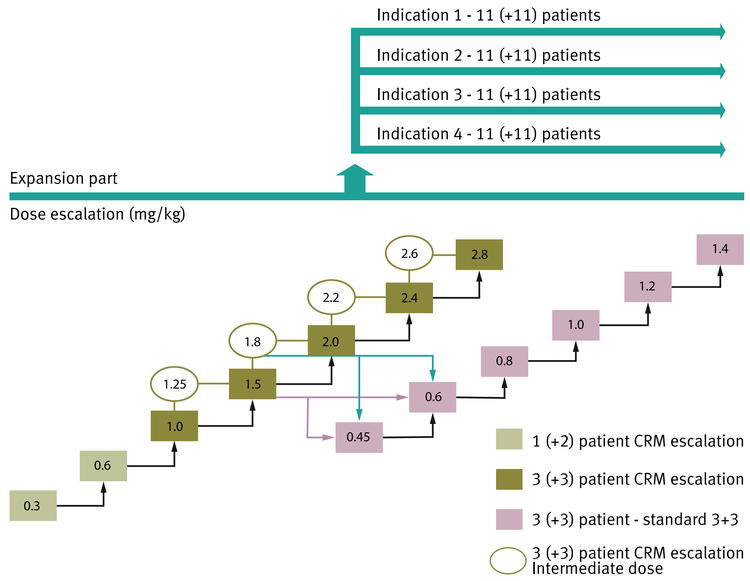

Figure 4. Overview of trial design.

In the phase IIa expansion part, further safety and biological activity data will be generated in selected indications using cohorts of 22 patients (11+11 patients in each cohort applying the Simon's two-stage design).