A Phase I, First-in-Human Study to Evaluate the Tolerability, Pharmacokinetics and Preliminary Efficacy of HuMax®-TF-ADC in Patients with Solid Tumors

abstract number
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Background

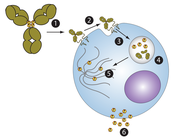
HuMax®-TF-ADC is an antibody drug conjugate (ADC) composed of:
- A human monoclonal antibody specific for tissue factor (TF).
- A protease-cleavable valine-citrulline linker.
- The microtubule disrupting agent monomethyl auristatin E (MMAE), a dolastatin analogue.

Tissue Factor (TF; CD142; thromboplastin) is:
- A transmembrane protein, sequestered from the circulation under normal conditions.
- The main physiological initiator of coagulation.
- Aberrantly expressed and associated with poor prognosis in solid cancers.
- An attractive ADC target due to optimal internalization characteristics.

HuMax-TF-ADC showed potent anti-tumor activity in xenograft models derived from a broad range of solid cancers, including PDX models (Breij, EC et al., Cancer Res. 2014;74:1214-26).

Mechanism of action - HuMax-TF-ADC

1. Binding to TF-positive tumor cells
2. Internalization of HuMax-TF-ADC
3. Trafficking to the lysosomes
4. Lysosomal degradation of HuMax-TF-ADC, release of MMAE
5. MMAE-mediated disruption of microtubules, resulting in cell death
6. Diffusion of free MMAE across the plasma membrane may cause “bystander cytotoxicity” in neighboring tumor cells



Study objectives

Primary Study Objective
- To establish the tolerability of HuMax-TF-ADC in a mixed population of patients with specified solid tumors.

Secondary Study Objectives
- To establish the long term tolerability of HuMax-TF-ADC in a mixed population of patients with specified solid tumors.
- To determine the MTD and the recommended dose for phase II trials with HuMax-TF-ADC.
- To establish the PK profile of HuMax-TF-ADC after single and multiple infusions.
- To evaluate the anti-tumor activity of HuMax-TF-ADC in a mixed population of patients with specified solid tumors.

Methods

Study design
Open-label dose escalation (traditional 3+3 design) followed by a 30 patient cohort expansion.
- Dose schedule q3wk for 4 cycles. In patients with clinical benefit (defined as SD or better) the possibility to continue dosing for additionally 8 cycles is available as per protocol.

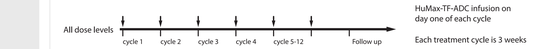


Figure 1: Dose Escalation Part: Dose levels and cohorts - dosing period (cycles 1-4) and extended dosing period (cycles 5-12).

Patient population

Patients: advanced (locally advanced and/or metastatic) cancer of the ovary, cervix, endometrium, bladder, prostate (CRPC), esophagus, head and neck (SCCHN) or lung (NSCLC) who have failed available standard treatments or who are not candidates for standard therapy.

Key inclusion criteria include
Acceptable liver function defined as:
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 times the upper limit of normal (ULN); if liver tumor/ metastases are present, then ≤ 5 x ULN is allowed.
- Bilirubin ≤ 1.5 x ULN, except, in patients diagnosed with Gilbert’s syndrome, direct bilirubin ≤ 2 x ULN.

Acceptable kidney function defined as:
- Glomerular filtration rate (Cockroft-Gault) › 45 mL/min

Acceptable hematological status (without hematologic support) defined as:
- Hemoglobin ≥ 5.6 mmol/L (~ 9 g/dL)
- Absolute neutrophil count (ANC) ≥ 1500/µL (1.5 x 10^9/L)
- Platelet count ≥ 100 x 10^9/L

Acceptable coagulation status defined as:
- INR ≤ 1.2 (without anticoagulant therapy)
- aPTT ≤ ULN

Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

Key exclusion criteria include
- Known past or current coagulation defects
- Ongoing major bleedings
- Tumor located adjacent to or invading large vessels
- Known past or current malignancy other than inclusion diagnosis, except for superficial cancers
- Radiographic evidence of cavitating pulmonary lesions
- Presence of CTCAE grade ≥ 2 peripheral neuropathy
- Ongoing inflammatory disease in bowel, lung or skin

Safety assessments
According to Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03, (data cut as per April 30, 2015)

Efficacy assessments
According to RESIST ver. 1.1 (data cut as per April 30, 2015). In order to qualify for SD, CT scan scheduled for week 6 needs to be SD or better. Two CT scans were performed outside the per protocol defined window. For patients with CRPC and ovarian cancer, changes in PSA and CA125 were also evaluated.

Results

Table 1. Patient demographics

	Cohort	Mean Age (at screening)	Sex (% male)	White (%)	Location of primary tumor (indication)	Stage of disease	Response to last therapy	Previous Taxane (%)	N previous therapies (mean (median)	Mean weight (kg)	Mean height (cm)
1					bladder	4	PD				
2	0.3 mg/kg	61	67	100	esophageal	4a	PD	67	2 (2)	69	171
3					esophageal	4	PR				
4					CRPC	4	PD				
5	0.6 mg/kg	67	67	100	ovarian	4	PD	100	8 (6)	76	170
6					SCCHN	3	NA				
7					esophageal	4	SD				
8	0.9 mg/kg	56	67	100	esophageal	4	PD	100	4 (3)	65	166
9					CRPC	2	PD				
10					CRPC	4	PD				
11	1.2 mg/kg	50	33	100	ovarian	4	PR	100	3 (3)	82	168
12					cervical	4	NA				
13					ovarian	3c	PD				
14	1.5 mg/kg	57	33	100	bladder	4	SD	33	3 (2)	67	173
15					CRPC	4	PD				
16					NSCLC	4	PD				
17	1.8 mg/kg	65	0	100	ovarian	3c	PD	67	4 (4)	67	163
18					endometrial	1b	PD				
19					NSCLC	4	PD				
20					NSCLC	3a	SD				
21	2.2 mg/kg	63	17	100	ovarian	3c	PD	100	6 (5)	79	167
22					endometrial	3c	PD				
23					ovarian	4	SD				
24					cervical	2b	PD				

Safety

- 24 patients have been administered HuMax-TF-ADC at doses up to and including 2.2 mg/kg every 3 weeks.
- Three DLTs were observed in 3 patients at the highest dose level (mucositis, diabetes and neutropenic fever , all CTCAE grade 3). Intermediate dose of 2.0 mg/kg is being explored.
- One event of fatal pharyngeal hemorrhage in the 0.6 mg/kg cohort has been reported in an SCCHN patient with normal coagulation values, who was previously treated with 3 lines of therapy including radical radiotherapy. Relationship of this event to the trial drug could not be excluded. All other AE’s related to bleeding were of CTCAE grade 1 except for 1 event of grade 2 hematuria in a patient with bladder cancer.
- The most commonly reported AEs seen in at least 5 patients were constipation, nausea, abdominal pain, anemia, epistaxis, fatigue, decreased appetite, pyrexia and alopecia.
- Elevation in liver enzymes was seen in 16 patients, mainly of grade 1.
- A total of 25 serious adverse events (SAEs) have been reported of which 9 were treatment related (pharyngeal hemorrhage, fever, myalgia, dyspnea, hyponatremia, fatigue, gastritis, mucosal inflammation and diabetes mellitus type II).
- No CTCAE grade 4 AEs have been reported.
- Ten patients reported ≥ grade 3 related adverse events (Table 2). Three patients reported events of fatigue. All other ≥ grade 3 related events were reported in 1 patient only.
- No significant changes in coagulation parameters have been observed.
- No major AEs (defined as CTCAE grade ≥ 3) of kidney toxicity, cardiac toxicity or skin rash have been reported.

Table 2. Patients with grade ≥3, related AEs

Preferred term	Dose (mg/kg)							
	0.3	0.6	0.9	1.2	1.5	1.8	2.2	Total
N	3	3	3	3	3	3	6	24
Type II Diabetes mellitus*	0	0	0	0	0	0	1	1
Fatigue	1	0	0	0	0	0	2	3
Gastritis **	0	0	0	0	0	1	0	1
Hyperglycaemia*	0	0	0	0	0	0	1	1
Hyponatraemia	0	0	0	0	1	0	0	1
Mucosal inflammation	0	0	0	0	0	0	1	1
Neuropathy peripheral **	0	0	0	0	0	1	0	1
Pharyngeal haemorrhage	0	1	0	0	0	0	0	1
Platelet count decreased	0	1	0	0	0	0	0	1
Transaminases increased	0	1	0	0	0	0	0	1

*: same event, **: same patient

Anti-tumor activity

- Overall, patients had received a mean of 4.5 (range 1-14, median 4) prior lines of therapy. In the 2.2 mg/kg cohort, a mean of 6 (median 5) prior lines of therapy was recorded. In addition, the vast majority of patients had experienced a PD to their last treatment (Table 1).
- Encouraging evidence of efficacy seen in 11 patients of which 10 SD and 1PR were observed according to RESIST (Fig.2).
- Clinically meaningful, long term disease control seen in 6 patients including 5 pts with SD hereof 2 patients with CRPC (18 and 50 wks), 1 patient with ovarian cancer (27 wks), 1 patient with endometrial cancer (17 wks) and 1 patient with NSCLC (22 wks) and 1 cervical cancer patient with a confirmed PR (19 wks and ongoing).

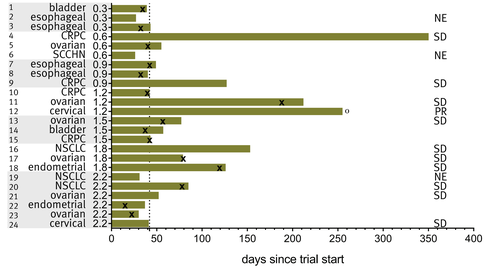


Figure 2. Best response and duration of follow-up

Footnote: X denotes time of disease progression. Patients still in the trial have an “O” following the end of their bar. Dashed vertical line at 6 weeks denotes the SD-threshold: “SD: follow-up measurements must have met the SD criteria at least once and for a minimum time period of 6 weeks (≥ 3 days) after first treatment.” Not evaluable (because of insufficient follow-up) patients are denoted with an NE. SD: stable disease, PR: partial response.

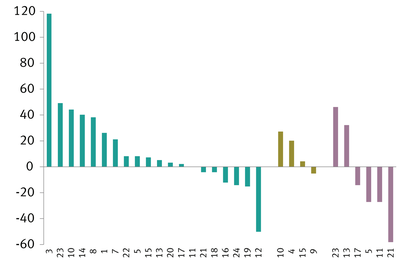


Figure 3. Best % reduction from baseline

Footnote: as per RECIST 1.1 (green), PSA (CRPC patients only, yellow), CA125 (ovarian cancer patients only, purple).

Pharmacokinetics

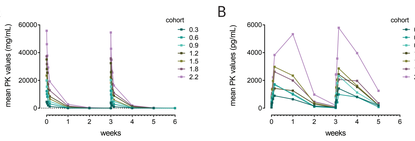


Figure 4. Mean plasma HuMax-TF-ADC and free MMAE concentration-time profiles
A. HuMax-TF-ADC mean PK values by cohort and cycles, B. Cytotoxic payload (MMAE) mean PK values by cohort and cycles.

Footnote: The figure presents mean plasma concentrations by cohort and cycle for cycles 1 and 2 based on the nominal sampling times.

Conclusions

- Encouraging early antitumor activity observed in this heavily pretreated, unmet medical need patient population.
- Clinically meaningful, long term disease control seen in 6 patients including 5 patients with SD (range 17-50 wks) and 1 patient with a confirmed PR (19 wks, patient is ongoing in trial).
- HuMax-TF-ADC is well tolerated at doses up to and including 1.8 mg/kg.
  - No concern regarding bleeding for doses up to and including 1.8 mg/kg.
  - No significant changes in coagulation parameters observed.
- Due to observed DLTs in the 2.2 mg/kg dose cohort, an intermediate dose of 2.0 mg/kg is being explored to define MTD.
- Next step: include extra 50 patients in dose cohort expansion part (80 patients in total).

The study is sponsored by Genmab A/S.