A Phase IIa Study of Tisotumab Vedotin (HuMax®-TF-ADC) in Patients With Relapsed, Recurrent and/or Metastatic Cervical Cancer: Updated Safety and Efficacy

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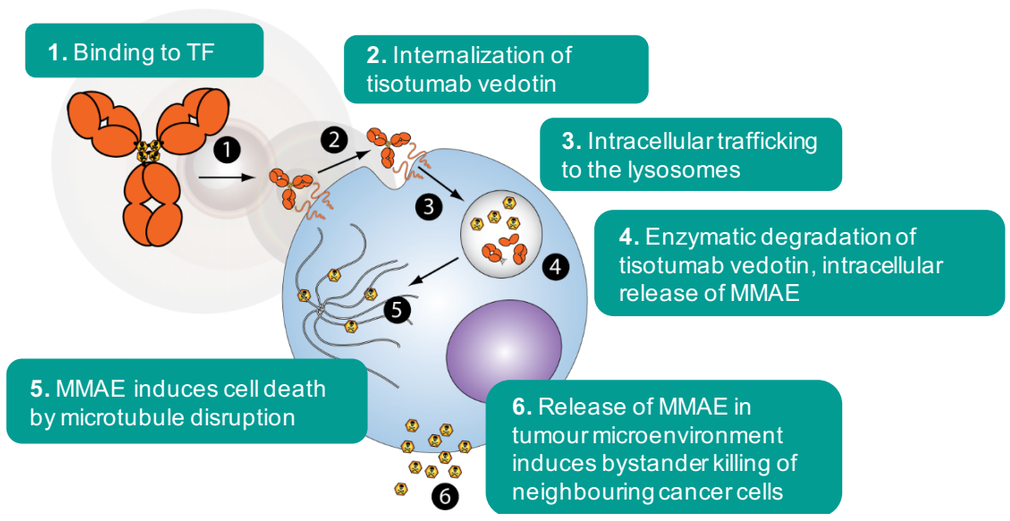
BACKGROUND

- Tisotumab vedotin is an ADC composed of a human mAb specific for TF, a protease-cleavable linker, and the microtubule disrupting agent MMAE[1,a]
- TF is a transmembrane protein that is the main physiological initiator of coagulation and is involved in angiogenesis, cell adhesion, motility, and cell survival[2]
- TF is aberrantly expressed in a broad range of solid tumours, including cervical cancer, and is associated with poor prognosis[3,4]
- Tisotumab vedotin selectively targets TF to deliver a clinically validated toxic payload to tumour cells **(Figure 1)**

Figure 1: Tisotumab Vedotin Mechanism of Action[1,5]



[a]MMAE-based ADC technology was licensed from Seattle Genetics, Inc., in a license and collaboration agreement.

PATIENT POPULATION

- A total of 34 patients were enrolled and received at least 1 dose of tisotumab vedotin (data cutoff date 24 July 2017)
- 7 patients (21%) are ongoing on treatment and 27 patients (79%) have withdrawn due to AE (n=5), disease progression (n=16), or other reasons (n=6)
- Patient demographics and baseline characteristics are shown in **Table 1**

Table 1: Patient Characteristics

		N=34
Age, median (range), y		43 (21-73)
ECOG score, n (%)	0	7 (21%)
	1	26 (76%)
	Missing	1 (3%)
Cancer type, n (%)	Adenocarcinoma	15 (44%)
	Adeno-squamous	3 (9%)
	Squamous	15 (44%)
	Missing	1 (3%)
Previous lines of systemic treatments, n (%)	0[a]	3 (9%)
	1	13 (38%)
	2	11 (32%)
	3	4 (12%)
	4	3 (9%)
Prior treatments, %[b]	Platinum	91%
	Taxane	91%
	Bevacizumab[c]	71%
	GOG 240 regimen[d]	68%
	≥1 platinum doublet	17%
Prior radiotherapy[e]		74%

[a]Patients progressed on therapy administered for treatment of locally advanced disease. [b]Missing data from 1 patient. [c]Including bevacizumab administered as combination therapy as either platinum/bevacizumab/paclitaxel or topotecan/bevacizumab/paclitaxel. [d]Combination therapy with cisplatin, paclitaxel, and bevacizumab. [e]External beam radiotherapy administered to the cervix or surrounding tissues.

METHODS

GEN701 Study Overview[6]

- First-in-human phase I/II dose-escalating (3 + 3 design) and expansion safety study of tisotumab vedotin in patients with locally advanced and/or metastatic solid tumours known to express TF
- Open-label, multicentre, single-arm study (NCT02001623)
- Safety and efficacy data are presented for only the cervical cancer expansion cohort (n=34)

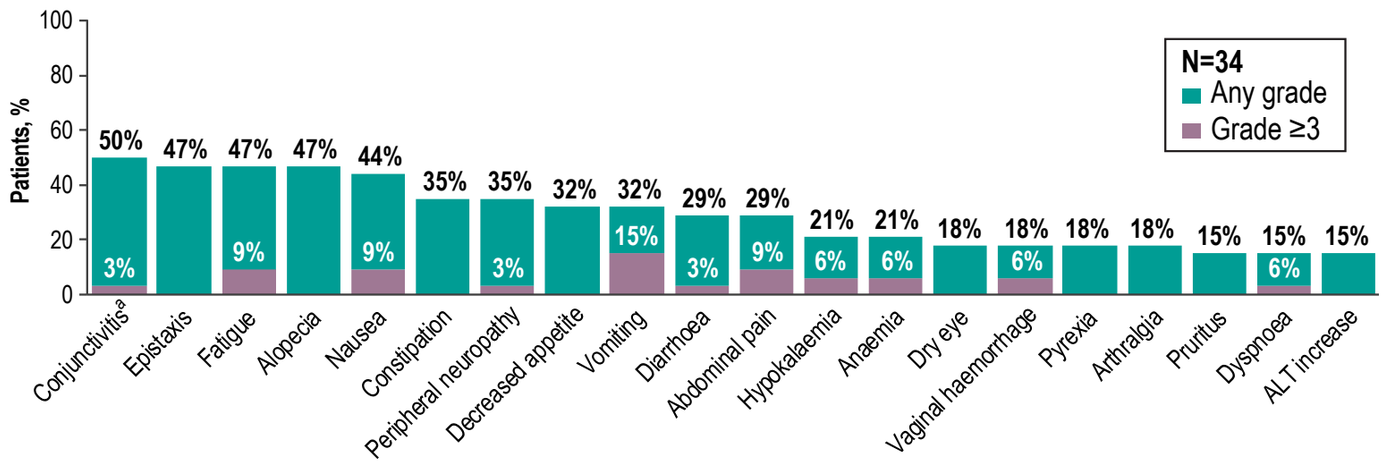
GEN701 Part 2, Cervical Cancer Expansion Cohort

- **Patient population:** patients with relapsed, recurrent, and/or metastatic cervical cancer
- **Dosage and administration:** based on the dose escalation portion of the GEN701 study, tisotumab vedotin was administered by IV infusions at 2.0 mg/kg q3w
- **Primary objective:** assess safety and tolerability (AE severity was graded according to CTCAE v4.03)
- **Secondary objective:** evaluate preliminary antitumour activity (assessed according to RECIST v1.1; tumour evaluations were performed by CT scans every 6 weeks)

SAFETY

- Common (≥15%) TEAEs following tisotumab vedotin monotherapy are summarized in **Figure 2**
- Grade 3 TEAEs were reported in 16 patients (47%); there were no grade 4-5 events
- Compound-specific conjunctival toxicity was observed; however, mitigation measures substantially reduced conjunctival toxicity in patients
  - Prior to mitigation (n=15), 73% of patients experienced conjunctivitis of any grade
  - After mitigation (n=19), 32% of patients experienced conjunctivitis of any grade, and 5% at grade ≥3
  - Risk mitigation measures involved a prophylactic steroid, lubricating eye drops, and cooling eye masks worn during treatment infusion, as well as stricter dose adjustment guidance

Figure 2: Most Common TEAEs (Any Grade ≥15%)



[a]Grade 2 conjunctivitis was reported in 32% of patients.

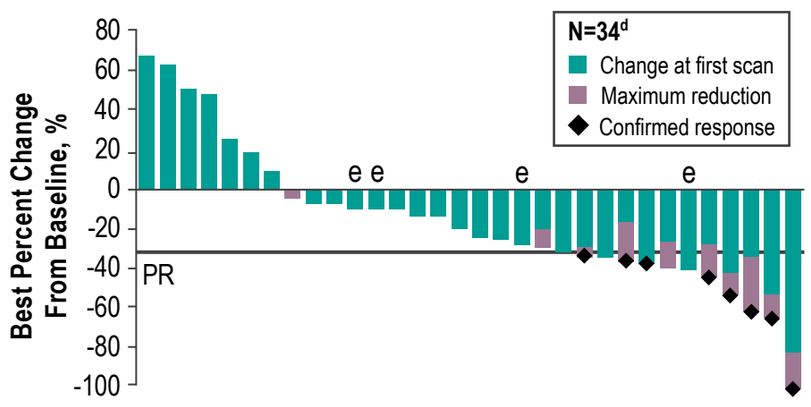
EFFICACY

- Efficacy for the cervical cancer cohort is displayed in **Table 2** and **Figure 3**
- 7 patients are ongoing on treatment

Table 2: Tumour Response, PFS and DoR

	N=34
ORR, n (%) (95% CI)	11 (32) (17%-50%)
PR, n (%)[a]	11 (32)
DCR (CR+PR+SD)[b], n (%) (95% CI)	17 (50) (35%-65%)
Median DoR, mo[c]	8.3
Median PFS, mo	6.4

Figure 3: Change From Baseline in Target Lesion



[a]Including 8 confirmed PR and 3 unconfirmed PR (1 of which is still ongoing). [b]Clinical benefit, after 12 weeks. [c]Median DoR of 5.4 months for confirmed and unconfirmed responses. [d]Two patients were withdrawn prior to CT scan, and so are not represented in the graph. [e]PD due to new lesion at same scan.

CONCLUSIONS

- Tisotumab vedotin demonstrated robust efficacy and a manageable safety profile in the cervical cancer expansion cohort
- The safety profile of tisotumab vedotin in recurrent cervical cancer was generally consistent with other MMAE-based ADCs
- Compound-specific conjunctival events were observed; however, mitigation measures substantially reduced rates of toxicity
- The substantial efficacy and the manageable safety profile warrant further development of tisotumab vedotin in previously treated recurrent/advanced cervical cancer patients
- An additional dosing schedule is being evaluated in a cervical cancer expansion cohort in study GEN702 (NCT0255121)

ABBREVIATIONS

ADC=antibody-drug conjugate; AE=adverse event; ALT=alanine aminotransferase; CR=complete response; CT=computerized tomography; CTCAE=Common Terminology Criteria for Adverse Events; DCR=disease control rate; DoR=duration of response; ECOG=Eastern Cooperative Oncology Group; IV=intravenous; mAb=monoclonal antibody; MMAE=monomethyl auristatin E; ORR=overall response rate; PD=progressive disease; PFS=progression-free survival; PR=partial response; q3w=every 3 weeks; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease; TEAE=treatment-emergent AE; TF=tissue factor.

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