Ongoing Trials – status update

ENGOT-cx1 Randomized Phase II of paclitaxel-carboplatin +/- Nintedanib

- Advanced stage IVB, or recurrent cx ca
- **Up to one prior line of chemotherapy for metastatic cervical cancer now allowed***
- **Prior treatment with angiogenesis inhibitors now allowed***

n = 105/120

Randomization 1:1

Stratification

1. Primary advanced Stage IVB versus recurrent disease.
2. Previous line of chemotherapy for metastatic disease

Carboplatin AUC5 + paclitaxel 175 mg/m2 (tri)weekly + Nintedanib 200mg

followed by Nintedanib maintenance

Carboplatin AUC5 + paclitaxel 175 mg/m2 (tri)weekly + Placebo

followed by Placebo maintenance

* Protocol v5.0 or above

Trial setting: Cervix/ primary stage IVB, recurrent
Sponsor(s): BGOG
Planned No. of patients: 120
Current accrual: 105
FPI: Mar 2014 ; LPI: expected July 2018
Primary endpoint: PFS Secondary endpoint: OS, toxicity, safety, QOL and RR

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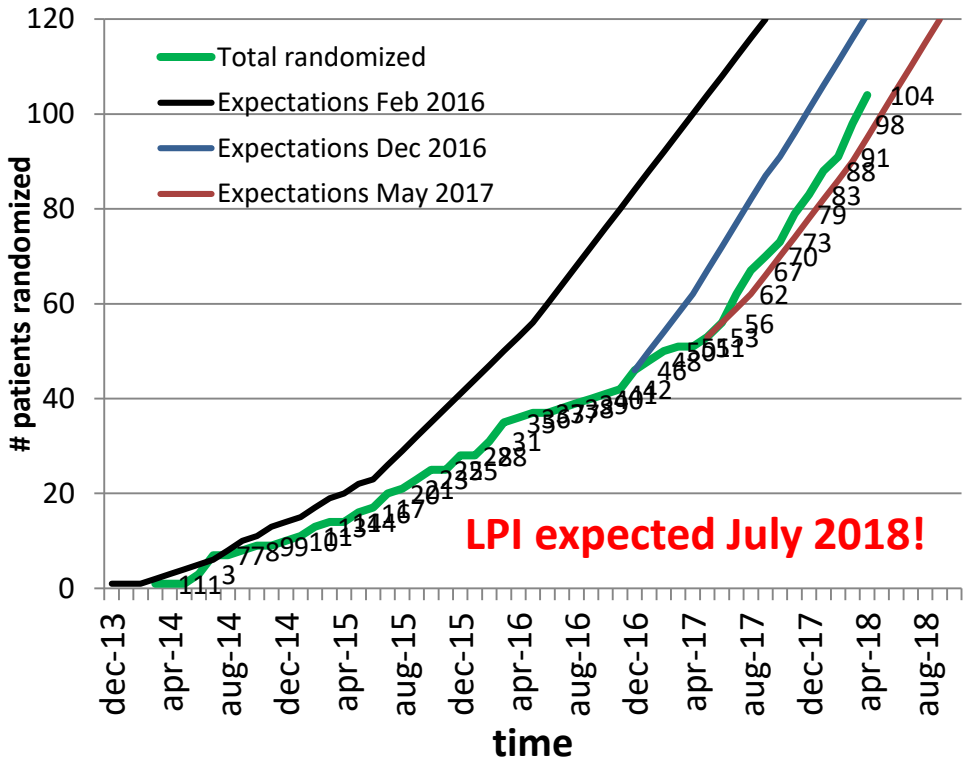
ENGOT-cx1 Randomized Phase II of paclitaxel-carboplatin +/- Nintedanib

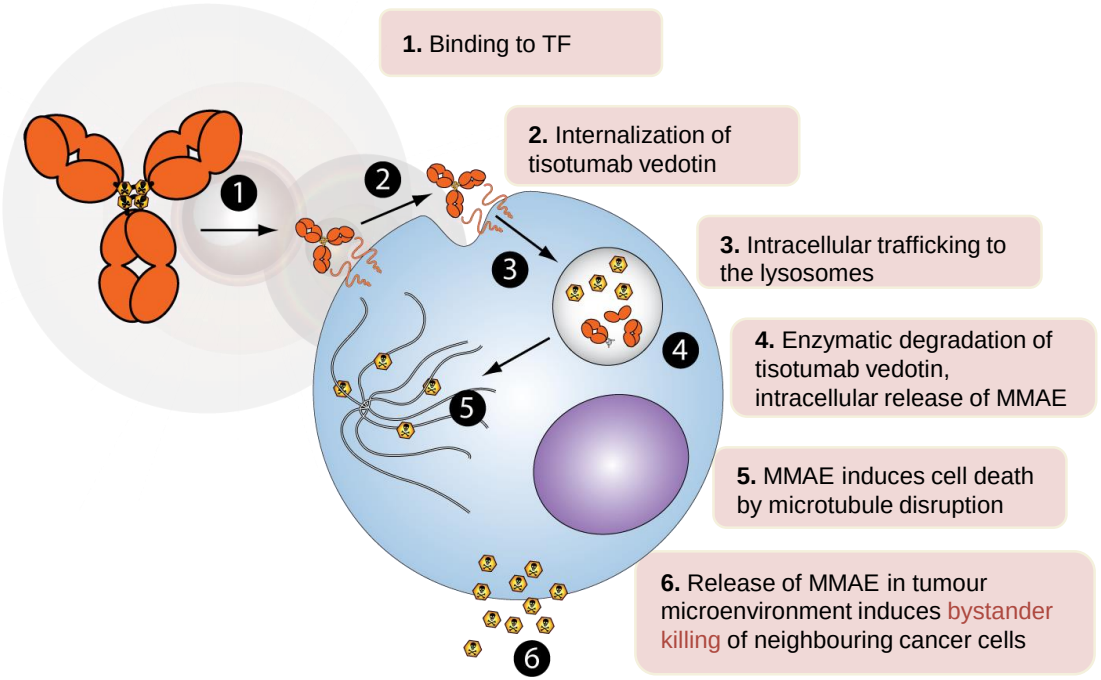
GROUP	SITES ACTIVATED	SUBJECT ENROLLMENT
GEICO	5/5	25
BGOG	10/10	43
NOGGO	6/6	19
MITO/MANGO	7/9	18
Total	28/30	105/120

IDMC	First interim analysis	interim analysis – patients on weekly TC
How many patients?	First 40 evaluable patients	First 3, 6, 9 and 18 evaluable patients
When?	After 2 months of treatment	After 6 weeks of treatment
What kind of analysis?	Safety	Safety
19/09/2017	51 patients included (including 40 > 2 months of treatment)	3 patients included (>6 weeks of treatment)
Conclusion	No safety issues - Recommendation to continue the study received on 6 Feb 2018	
Planned May 2018		9 patients (>6 weeks of treatment)



Mechanism of action Tisotumab Vedotin

- Tisotumab vedotin is an Antibody-Drug Conjugate (ADC) composed of a human mAb specific for Tissue Factor (TF= TROMBOPLASTIN), a protease-cleavable linker, and the microtubule disrupting agent MMAE[1,a,b]
- TF is a transmembrane protein that is the main physiological initiator of coagulation and is involved in angiogenesis, cell adhesion, motility, and cell survival[3]
- TF is aberrantly expressed in a broad range of solid tumours, including cervical cancer, and is associated with poor prognosis[4,5]



ADC=antibody-drug conjugate; mAb=monoclonal antibody; MMAE=monomethyl auristatin E.

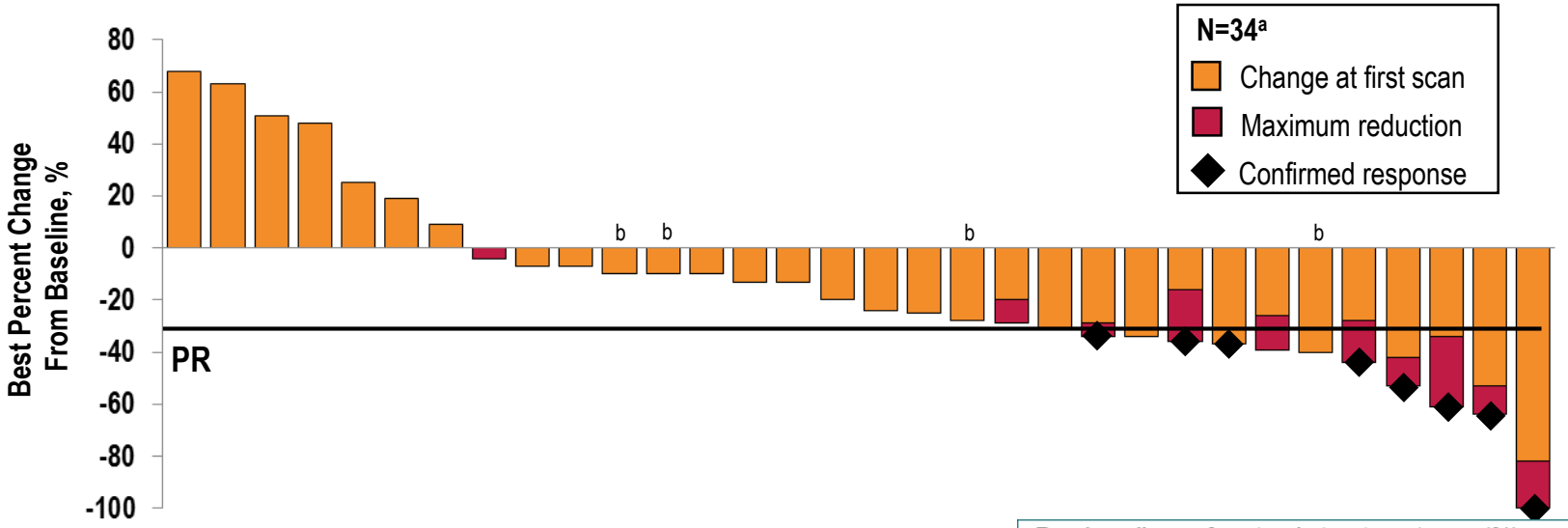
[a]Tissue factor is known as TF, CD142, and thromboplastin.

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

1. Breij EC et al. *Cancer Res.* 2014;74(4):1214-1226. **2.** De Goeij BE et al. *Mol Cancer Ther*. 2015;14(5):1130-1140. **3.** Chu AJ. *Int J Inflam*. 2011;2011. doi: 10.4061/2011/367284. **4.** Förster Y et al. *Clin Chim Acta*. 2006;364(1-2):12-21. **5.** Cocco E et al. *BMC Cancer*. 2011;11:263.

Phase I expansion in ≥ 2nd line recurrent Cxca (Vergote et al ESMO 2017)

32% OF PATIENTS WITH RECURRENT/ADVANCED CERVICAL CANCER ACHIEVED RESPONSE WITH TISOTUMAB VEDOTIN



- 50% (17 of 34 patients; 95% CI, 35%-65%) clinical benefit after 12 wks (DCR)[c,d]
- 32% (11 of 34 patients; 95% CI, 17%-50%) response (ORR)[d]
  - 8 PR, confirmed
  - 3 PR, unconfirmed[e]

Previous lines of systemic treatments, no (%)	
0[a]	3 (9%)
1	13 (38%)
2	11 (32%)
3	4 (12%)
4	3 (9%)

CI=confidence interval; CR=complete response; CT=computed tomography; DCR=disease control rate; ORR=overall response rate; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease.

[a]Two patients were withdrawn prior to CT scan, and so are not represented in the graph. [b]PD due to new lesion at same scan. [c]Clinical benefit was defined as the DCR rate, the proportion of patients who achieved a CR, PR, or SD after 12 weeks. [d]Response was as assessed by investigators using standard RECIST 1.1 criteria. [e]One of which is still ongoing. Data cutoff date July 24, 2017.

ENGOT-cx6/GOG lead: Tisotumab Vedotin in Previously treated recurrent or metastatic cervical cancer

STUDY DESIGN

Patients with recurrent or metastatic cervical cancer who have received **at least one prior line** of systemic therapy.

Enrollment

N ~ 100

Treatment

- **Tisotumab vedotin (TV) 2.0 mg/kg 1Q3W**
- Imaging every **6 weeks** first 30 weeks and every 12 weeks thereafter.
- Imaging assessed locally (by PI) and centrally (by IRC*).

Design

- Continue TV treatment **until IRC verified PD or until pt. fulfils other treatment discontinuation criteria** e.g. unacceptable adverse events.
- Pt. is followed up for survival and new anti-cancer treatment until the pt. dies or until withdrawal from the trial.

ENGOT Model C

*IRC: Independent review committee

- Data obtained from central IRC review will be used in the analysis and reporting of trial results.

ENGOT-cx6: Tisotumab Vedotin in Previously treated recurrent or metastatic cervical cancer

STUDY STATUS

EU (7)
Belgium (BGOG) – 10 sites
Spain (GEICO) – 8 sites
Sweden (NSGO) – 3 sites
Germany (AGO) – 9 sites
Italy (MITO) – 8 sites

Americas (1)
US

US (GOG-3023) – Site ID ongoing

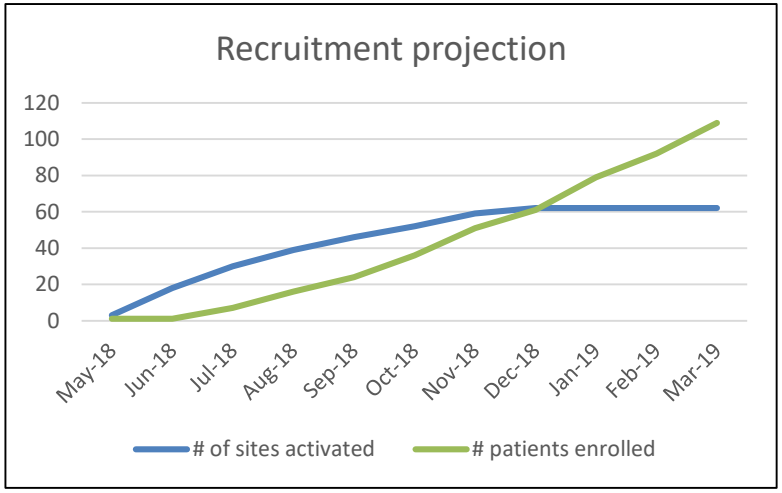
SAVE THE DATE: INVESTIGATOR MEETING 19-20th of JUNE 2018, BRUSSELS

22 sites

EU ENGOT cx_6 - Site ID complete

49 sites returned feasibility questionnaire

42 sites confirmed as selected



- ➔ In CZ, Italy, Spain and Germany, the contract negotiation is a rate limiter
- ➔ Germany DRG opinion: planned examinations require BfS approval

ENGOT-cx8

A phase 2 Open-label Trial of Tisotumab Vedotin (HuMax®-TF-ADC) alone or in Combination in First Line Recurrent or Stage IVB Cervical Cancer

Sponsor: Genmab

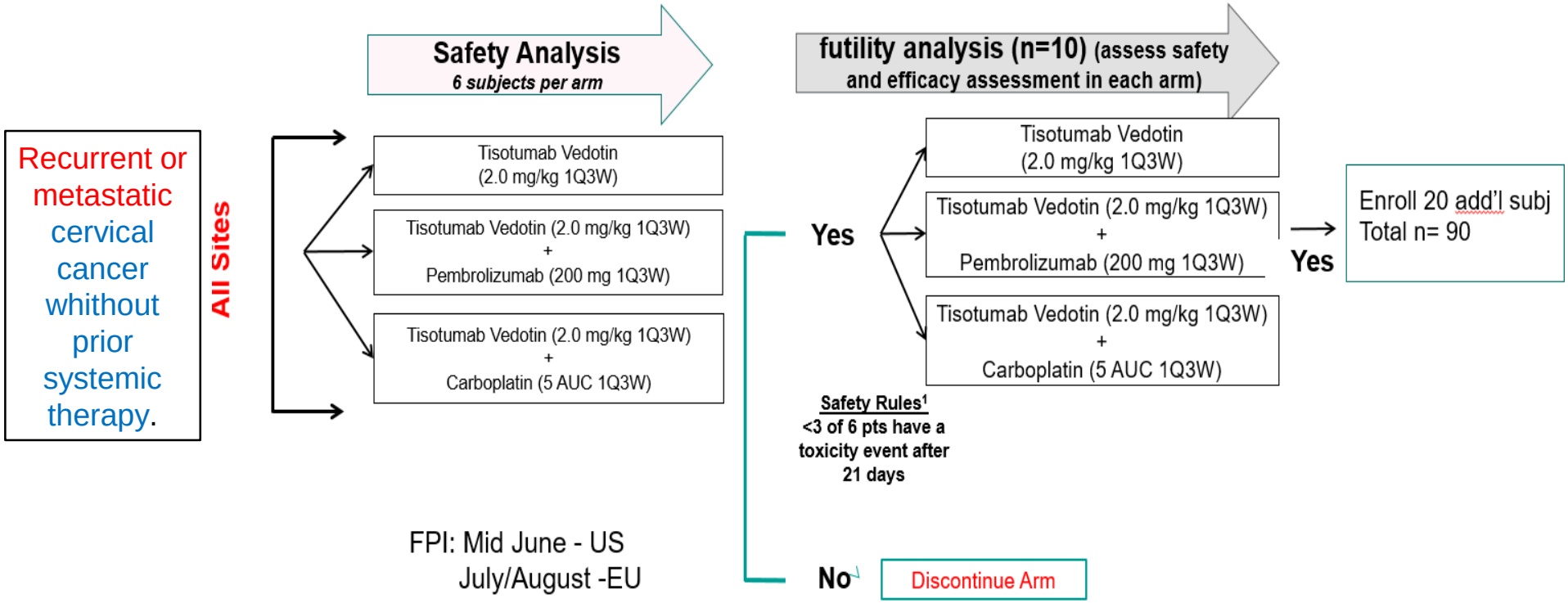
ENGOT lead

ENGOT Model C

Activating Trials – status update

ENGOT-cx8: Randomized, open label, phase II first line trial

STUDY DESIGN



Patients continue therapy until toxicity or PD; scan frequency is every 6 weeks.

ENGOT-cx8: Randomized, open label, phase II first line trial

Key Inclusion Criteria:

- Must have **not received prior systemic therapy for recurrent or Stage IV disease**. Chemotherapy administered in combination with radiation therapy will not be counted as a prior systemic therapy.
- Must have baseline **measurable** disease per RECIST v1.1
- Life expectancy of ≥ 3 months

Key Exclusion Criteria:

- Previously treated with chemotherapy except when used concurrently with radiation therapy.
- Active **ocular surface disease** at baseline. Subjects with prior history of cicatricle conjunctivitis or Steven Johnson Syndrome (as evaluated by the Investigator)

ENGOT-cx8: Randomized, open label, phase II first line trial

STUDY DESIGN (continued)

- Randomization will be stratified by disease status (metastatic/recurrent Y/N) and histology (squamous/non-squamous Y/N).
- Subjects participating in the tisotumab vedotin + pembrolizumab treatment group, treatment with pembrolizumab will be discontinued after the subject has completed 35 treatments (approximately 2 years) with pembrolizumab.
- Subjects may continue to receive tisotumab vedotin monotherapy after the discontinuation of pembrolizumab if the subject has achieved stable disease (SD) or better.
- A futility analysis will be conducted for each treatment group after enrollment of the first 10 pts/arm. If < 2/10 pts respond (unconfirmed or confirmed) in a treatment group, discontinuation for futility will be considered. Enrollment to the trial will continue while the interim analysis is being performed.

ENGOT-cx8: Randomized, open label, phase II first line trial

Study status

- A total of 60-70 sites will be selected: ~ 20 in the US and ~ 40 in Europe.
- European countries: **BGOG, NOGGO, DGOG, NSGO (Denmark, Sweden), ICORG, CEEGOG, MITO, TGOG, NCRI**
- VHP submission occurred end of March; submission has been successfully validated
- EU: SIVs expected July-Nov 2018
- Expected **FPI: Q3 (EU) 2018**

- Investigator meeting will be planned in **September 2018**
- **Interested groups can contact BGOG@ENGOT.eu or Ignace.vergote@uzleuven.be**