

## A PHASE IIA STUDY OF TISOTUMAB VEDOTIN (HUMAX<sup>®</sup>-TF-ADC) IN PATIENTS WITH RELAPSED, RECURRENT AND/OR METASTATIC CERVICAL CANCER

Vergote I, Concin N, Dean E, Lassen U, Drew Y, Machiels JP, Nielsen D, Arkenau T, Forster M, Jones R, Slomovitz B, Spicer J, Johnson M, Cornez N, Gennigens C, Fulton B, Basse L, Lisby S, Coleman RL, Hong DS



## DISCLOSURES

- Disclosures include

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Linda	Basse	• Is a former employee of Genmab
Robert	Coleman	• Served on the scientific advisory committee for Genmab
Emma	Dean	• Has subsequently taken up employment with AstraZeneca
David	Hong	<ul style="list-style-type: none"> <li>• <i>Research/Grant Funding:</i> Bayer, Lilly, Genentech, LOXO, Pfizer, Amgen, Mirati, Ignyta, Merck, Daiichi-Sankyo, Eisai</li> <li>• <i>Travel, Accommodations, Expenses:</i> MiRNA, LOXO</li> <li>• <i>Consulting or Advisory Role:</i> Bayer, Baxter, Guidepoint Global</li> <li>• <i>Other ownership interests:</i> Oncoresponse (founder)</li> </ul>
Steen	Lisby	• Is a former employee of Genmab
Jean-Pascal	Machiels	<ul style="list-style-type: none"> <li>• <i>Advisory board:</i> MSD, AstraZeneca, Debio, Nanobiotix, Innate</li> <li>• <i>Grants:</i> Novartis, Roche, Janssen</li> </ul>
Ignace	Vergote	<ul style="list-style-type: none"> <li>• <i>Research/Grant Funding:</i> Genmab</li> <li>• <i>Consulting or Advisory Role:</i> Genmab</li> </ul>

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# CURRENT TREATMENT PARADIGM IN RECURRENT/ADVANCED CERVICAL CANCER

- **First-line standard of care** is paclitaxel-platinum in combination with bevacizumab<sup>1-3</sup>
- Second-line therapies have limited response rates<sup>1</sup>

Agent	Overall Response Rate (%) <sup>1</sup>	Agent	Overall Response Rate (%) <sup>1</sup>
Bevacizumab	11%	Pemetrexed	14%-15%
Topotecan	13%-19%	Irinotecan	21%
Vinorelbine	14%	Lapatinib	5%
Gemcitabine	5%	Pazopanib	9%
Albumin-bound paclitaxel <sup>a</sup>	29%	Pegylated liposomal doxorubicin	11%
Docetaxel	9%		

- There is **no standard of care in second-line** cervical cancer, creating an unmet medical need for new treatments<sup>1</sup>

<sup>a</sup>Dose dense regimen.

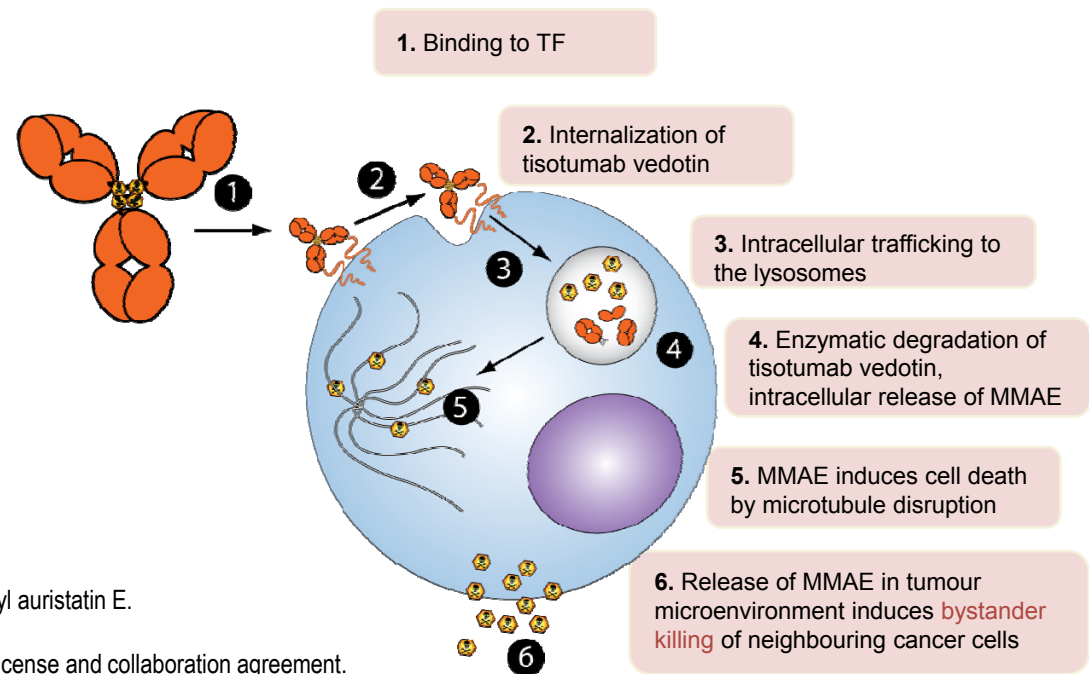
1. Marth C et al. *Ann Oncol.* 2017;28(suppl 4):iv72-iv83. 2. Tewari KS et al. *N Engl J Med.* 2014;370(8):734-743. 3. Koh WJ et al. *J Natl Compr Canc Netw.* 2015;13(4):395-404.



# TISOTUMAB VEDOTIN MECHANISM OF ACTION

## Mechanism of action<sup>1,2</sup>

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



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

<sup>a</sup>Tissue factor is known as TF, CD142, and thromboplastin.

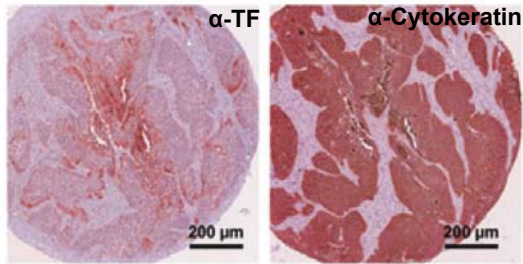
<sup>b</sup>MMAE-based ADC technology was licensed from Seattle Genetics, Inc., in a license and collaboration agreement.

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.

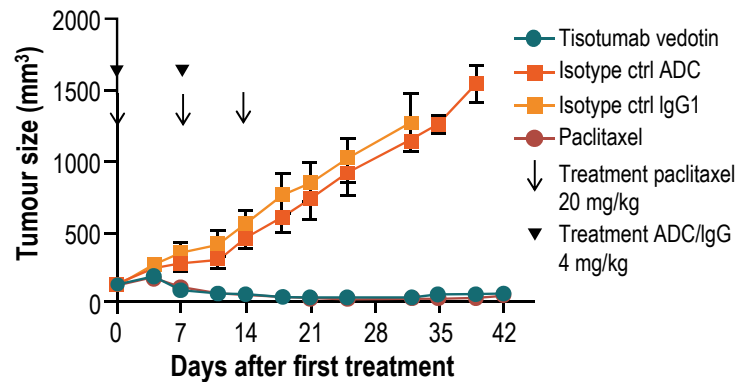
4. Förster Y et al. *Clin Chim Acta.* 2006;364(1-2):12-21. 5. Cocco E et al. *BMC Cancer.* 2011;11:263.

# ANTI-TUMOUR ACTIVITY IN A CERVICAL SQUAMOUS CELL CARCINOMA PDX MODEL: EFFICACY IN A TAXANE-RELAPSED SETTING

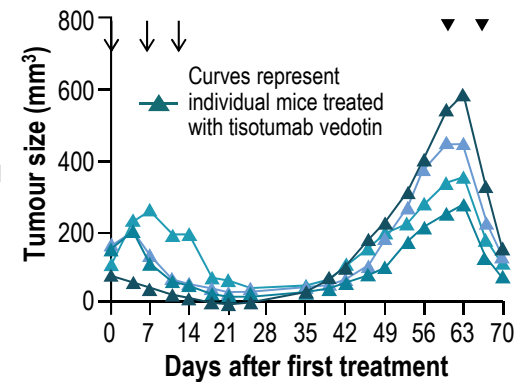
TF expression in a PDX model of cervical squamous cell carcinoma<sup>a</sup>



Primary treatment<sup>b</sup>



Re-treatment after paclitaxel (individual mice)<sup>c</sup>



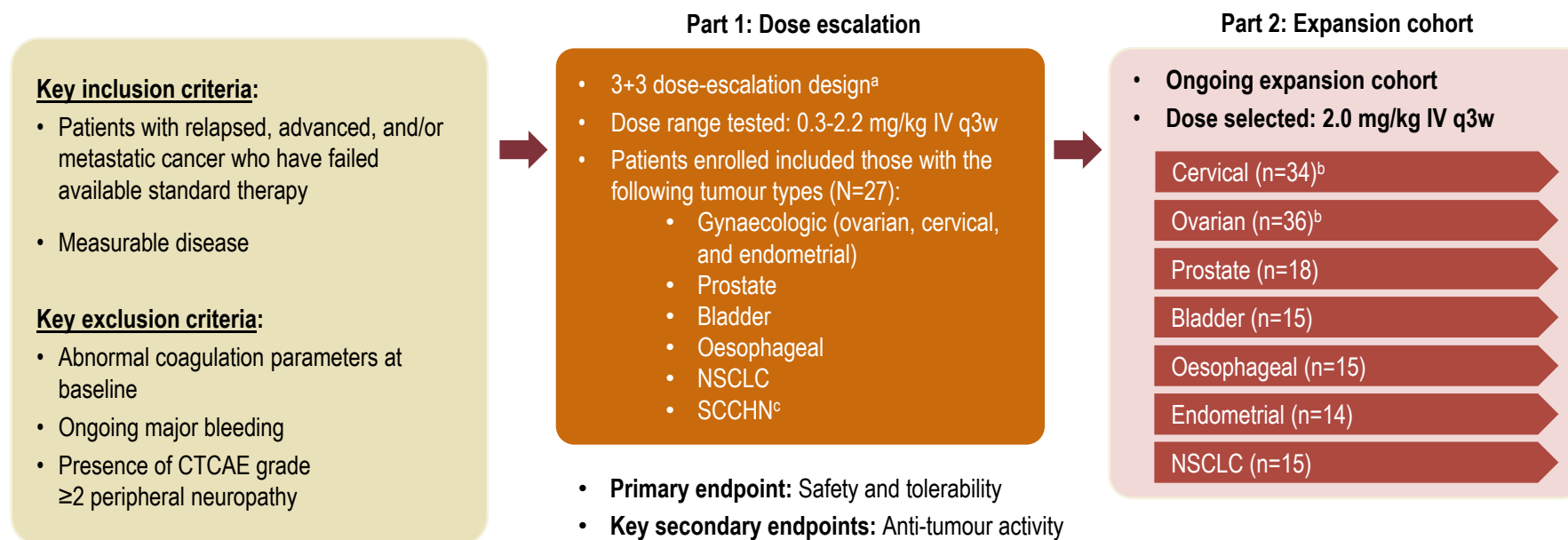
Despite heterogeneous TF expression, tisotumab vedotin induced robust tumour regression, event after paclitaxel, in cervical cancer PDX models

ADC=antibody-drug conjugate; IgG=immunoglobulin G; PDX=patient-derived xenograft; TF=tissue factor.

<sup>a</sup>A cervical squamous cell carcinoma PDX model was established by subcutaneous implantation of patient tumour fragments into mice. Immunohistochemistry analysis of PDX model using the TF human monoclonal antibody and human cytokeratin, which identifies human tumour cells. <sup>b</sup>Datapoints are the average tumour size per group, with 8 mice per group. <sup>c</sup>Curves and data points represent tumour size in individual mice. Patient-derived cervical squamous cell carcinoma cells were implanted in mice, and when the tumours reached a size of 80-200 mm<sup>3</sup>, mice were treated with 20 mg/kg of paclitaxel at the indicated time points. Upon tumour outgrowth following paclitaxel discontinuation, mice were treated with 2 doses of tisotumab vedotin 4 mg/kg at the indicated time points.

Breij EC et al. *Cancer Res.* 2014;74(4):1214-1226.

# GEN701 IS THE FIRST-IN-HUMAN STUDY OF TISOTUMAB VEDOTIN



CTCAE=Common Terminology Criteria for Adverse Events; IV=intravenous; NSCLC=non-small cell lung cancer; SCCHN=squamous cell carcinoma of the head and neck.

<sup>a</sup>Subjects were enrolled into cohorts at increasing dose levels of tisotumab vedotin in 21-day treatment cycles. <sup>b</sup>In phase 2, ovarian and cervical cohorts were expanded to approximately 30 patients based on preliminary efficacy observed in the first 14 patients enrolled. <sup>c</sup>The SCCHN cohort was closed by protocol amendment 4 due to an event of pharyngeal tumour haemorrhage with fatal outcome. The event was deemed to be most likely related to the disease itself.

Clinicaltrials.gov. <https://clinicaltrials.gov/ct2/show/NCT02001623>. Accessed August 7, 2017.

## PATIENT DISPOSITION IN THE CERVICAL CANCER COHORT

Treated	N=34
Ongoing on treatment	7
Withdrawn from trial	27
Due to adverse event <sup>a</sup>	5
Due to progressive disease	16
Other <sup>b</sup>	6
Died	0

<sup>a</sup>Including patients who experienced peripheral neuropathy (n=2), peripheral neuropathy and arthralgia (n=1), peripheral neuropathy and reduced visual acuity (n=1), and conjunctivitis (n=1).

<sup>b</sup>Including patients who withdrew due to patient choice (n=1), investigator judgement (n=1), non-radiographic clinical progression (n=1), and other reasons (n=3).

Data cutoff date July 24, 2017.



## BASELINE PATIENT CHARACTERISTICS IN CERVICAL CANCER COHORT

	Cervical (N=34)
Age (median, range), y	→ 43 (21-73)
ECOG score, no (%)	
0	7 (21%)
1	→ 26 (76%)
Missing	1 (3%)
Cancer type, no (%)	
Adenocarcinoma	→ 15 (44%)
Adeno-squamous	3 (9%)
Squamous	15 (44%)
Missing/TBD	1 (3%)
Previous lines of systemic treatments, no (%)	
0 <sup>a</sup>	3 (9%)
1	13 (38%)
2	→ 11 (32%)
3	4 (12%)
4	3 (9%)

	Cervical (N=34)
Prior treatments, % <sup>b</sup>	
Platinum	91%
Taxane	91%
Bevacizumab <sup>c</sup>	71%
GOG 240 regimen <sup>d</sup>	68%
≥1 platinum doublet	17%
Prior radiotherapy <sup>e</sup>	74%

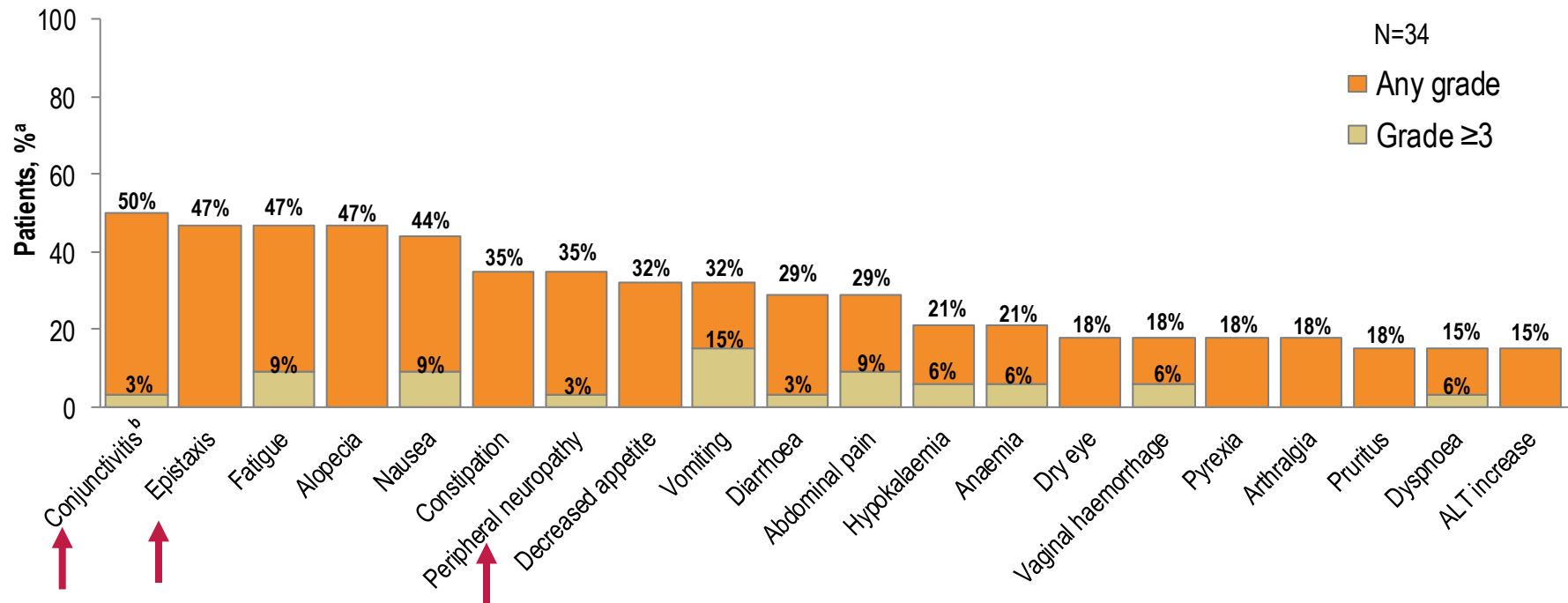
ECOG=Eastern Cooperative Oncology Group; TBD=to be determined.

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

Data cutoff date July 24, 2017.



## ADVERSE EVENTS (≥15% OF PATIENTS) IN CERVICAL CANCER COHORT



ALT=alanine aminotransferase.

<sup>a</sup>Adverse events with events of any grade occurring in ≥15% of patients or of grade ≥3 in 2 or more patients. <sup>b</sup>Grade 2 conjunctivitis was reported in 32% of patients.

Data cutoff date July 24, 2017.



## ADVERSE EVENTS OF SPECIAL INTEREST IN CERVICAL CANCER COHORT

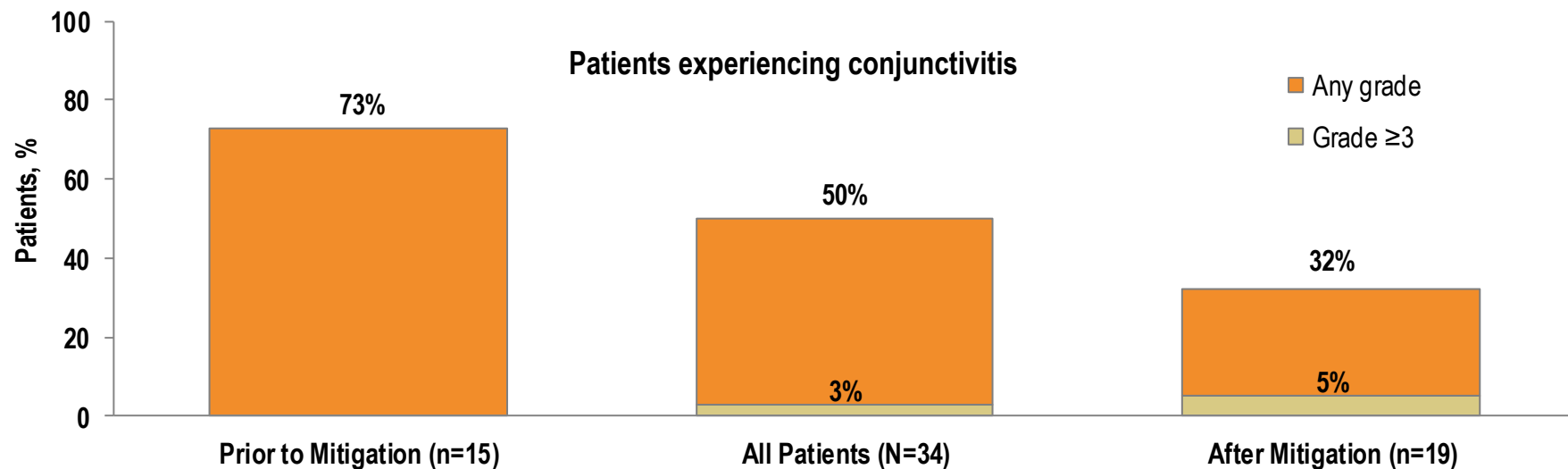
AEOSI Term	N=34	
	Any Grade, n (%)	Grade ≥3, n (%)
Ocular (any) <sup>a</sup>	18 (53%)	1 (3%)
Conjunctivitis	17 (50%)	1 (3%)
Conjunctivitis scar	1 (3%)	0
Conjunctivitis viral	1 (3%)	0
Conjunctival ulceration	0	0
Keratitis	1 (3%)	0
Ulcerative keratitis	2 (6%)	0
Symblepharon	0	0
Neuropathy (any)	12 (35%)	2 (6%)

AEOSI=adverse events of special interest.

<sup>a</sup>Most patients who experienced other events than conjunctivitis also experienced conjunctivitis.

Data cutoff date July 24, 2017.

## MITIGATION MEASURES SUBSTANTIALLY REDUCED CONJUNCTIVAL TOXICITY IN CERVICAL CANCER COHORT

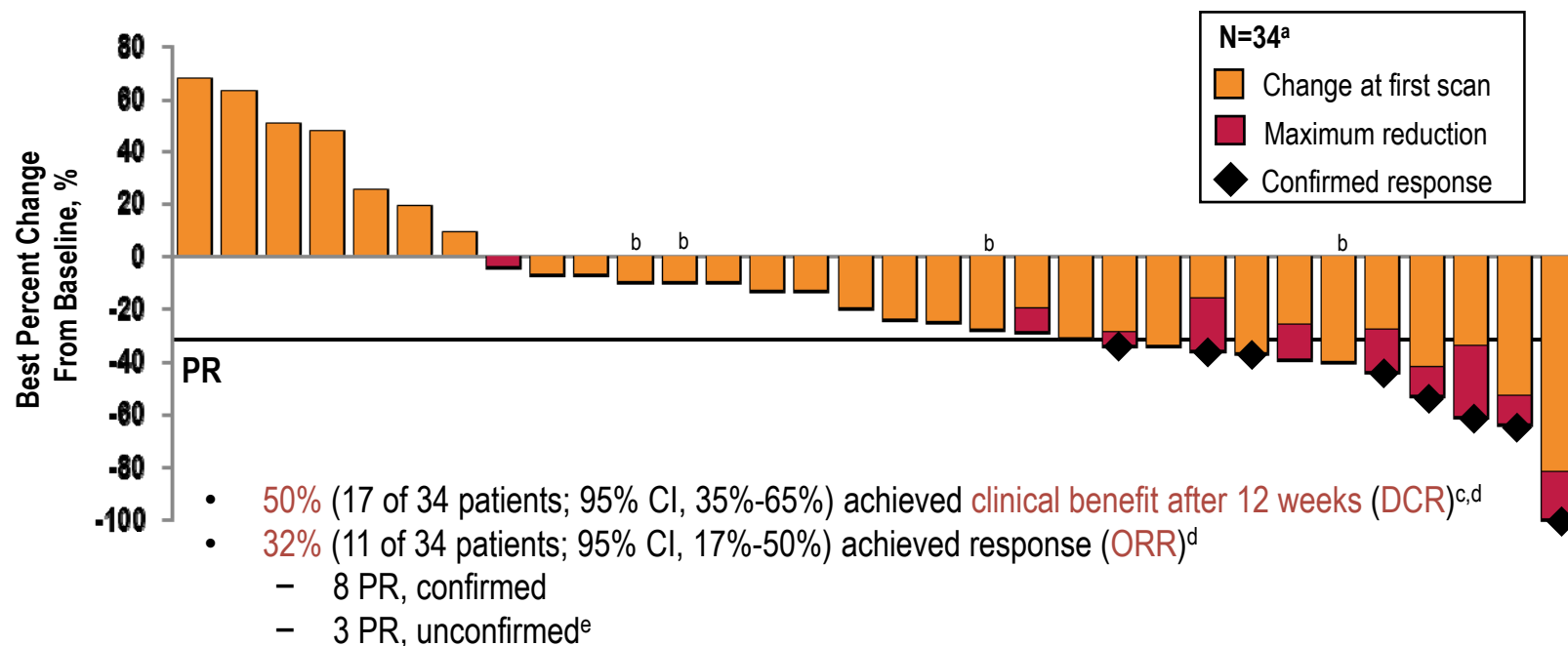


- Risk mitigation measures involved a **prophylactic steroid**, **lubricating eye drops**, and **cooling eye masks** worn during treatment infusion, as well as **stricter dose adjustment guidance**
- Mitigation measures substantially reduced the rates of conjunctival toxicity

Data cutoff date July 24, 2017.



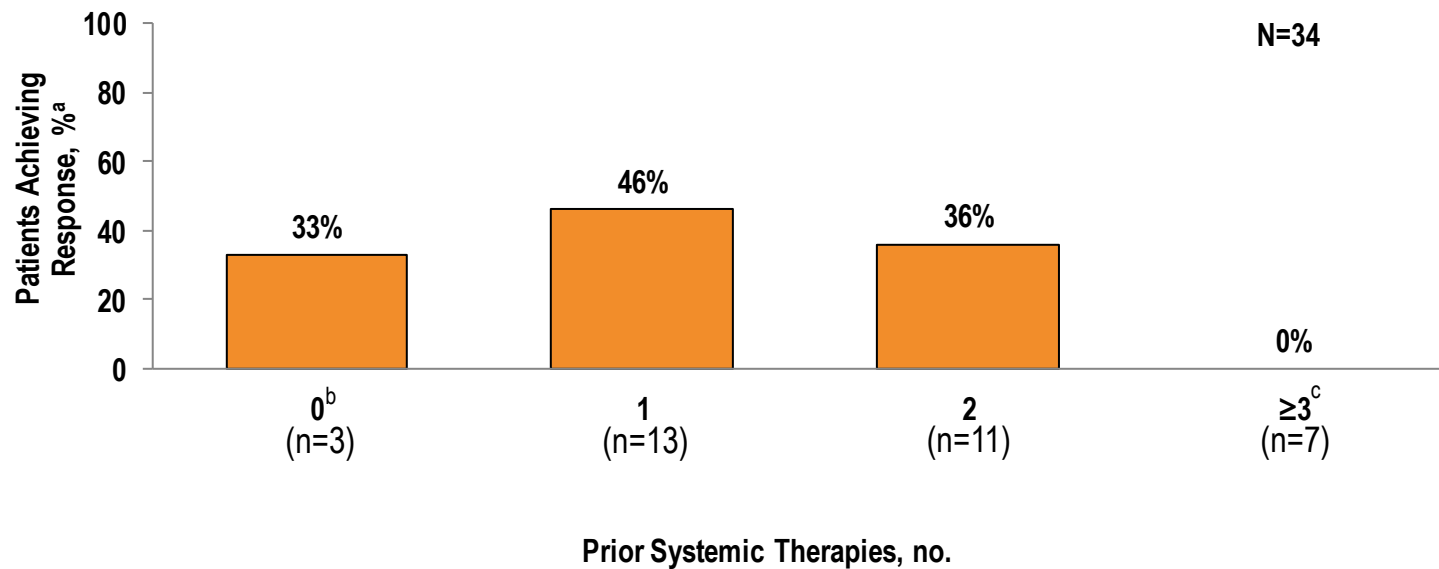
## 32% OF PATIENTS WITH RECURRENT/ADVANCED CERVICAL CANCER ACHIEVED RESPONSE WITH TISOTUMAB VEDOTIN



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.

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

## RESPONSES WITH TISOTUMAB VEDOTIN BY PRIOR LINES IN CERVICAL CANCER COHORT

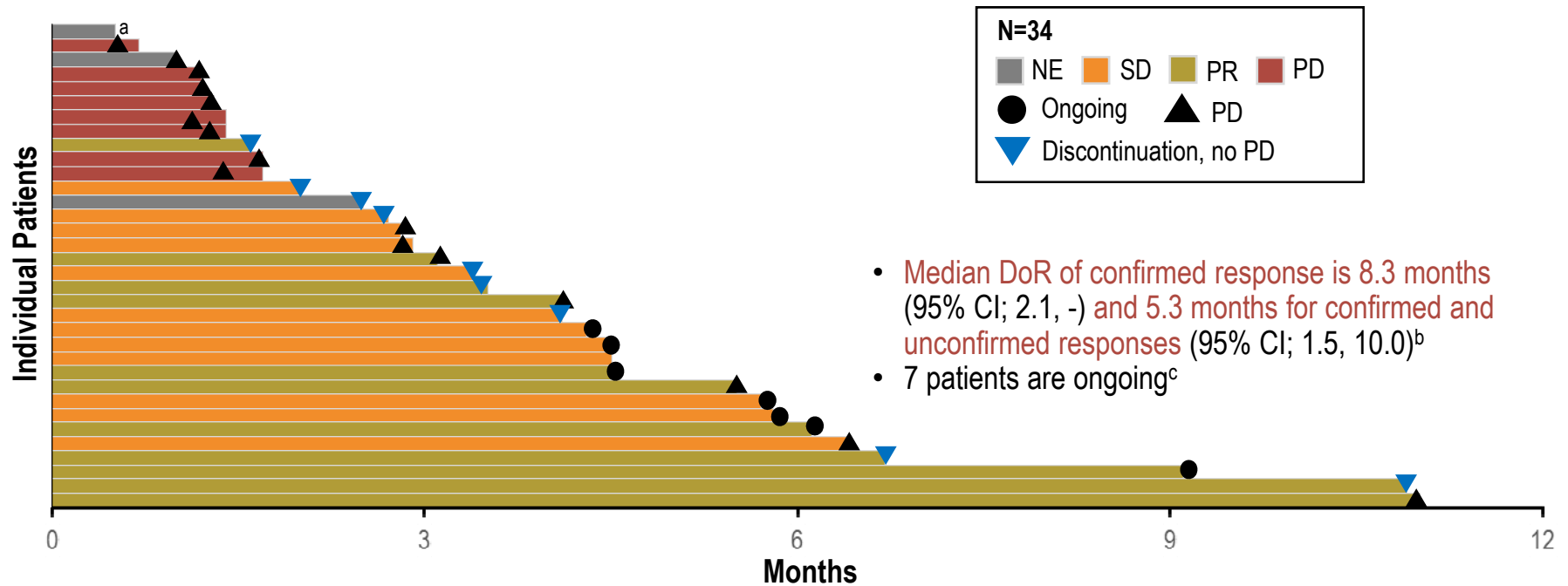


<sup>a</sup>Including confirmed and unconfirmed responses. <sup>b</sup>Patients were refractory to therapy administered for early stage disease. <sup>c</sup>Patients received either 3 (n=4) or 4 (n=3) prior systemic therapies.

Data cutoff date July 24, 2017.



## DURATION OF RESPONSE WITH TISOTUMAB VEDOTIN IN CERVICAL CANCER COHORT



DoR=duration of response; NE=not evaluated; PD=progressive disease; PFS=progression-free survival; PR=partial response; SD=stable disease.

<sup>a</sup>Patient withdrawn. <sup>b</sup> 4 responders have progressed as of the data cutoff of July 24, 2017 and 4 have been withdrawn because of other reasons and are thus censored for DoR.

<sup>c</sup>Estimated median PFS was 6.4 months.

Data cutoff date July 24, 2017.



## TISOTUMAB VEDOTIN DEMONSTRATED ROBUST EFFICACY AND A MANAGEABLE SAFETY PROFILE IN THE CERVICAL CANCER EXPANSION COHORT

- Tisotumab vedotin is an **ADC** composed of a human mAb specific for **TF**, a protease cleavable linker, and the microtubule disrupting agent MMAE
- The **safety** profile of tisotumab vedotin in recurrent cervical cancer was **generally consistent** with other MMAE-based ADCs
  - Conjunctivitis was the most common TEAE
  - The mitigation measures substantially reduced conjunctival toxicity
- **ORR** (confirmed + unconfirmed responders) is **32%** and median DoR (confirmed responders) is 8.3 months
- The substantial efficacy and the manageable safety warrants **further development of tisotumab vedotin in previously treated recurrent/advanced cervical cancer patients**

ADC=antibody-drug conjugate; DoR=duration of response; mAb=monoclonal antibody; MMAE=monomethyl auristatin E; ORR=overall response rate; TEAE=treatment-emergent adverse event; TF=tissue factor.

Data cutoff date July 24, 2017.

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