Tisotumab Vedotin in Previously Treated Recurrent or Metastatic Cervical Cancer: Results From the Phase 2 innovaTV 204/GOG-3023/ ENGOT-cx6 Study

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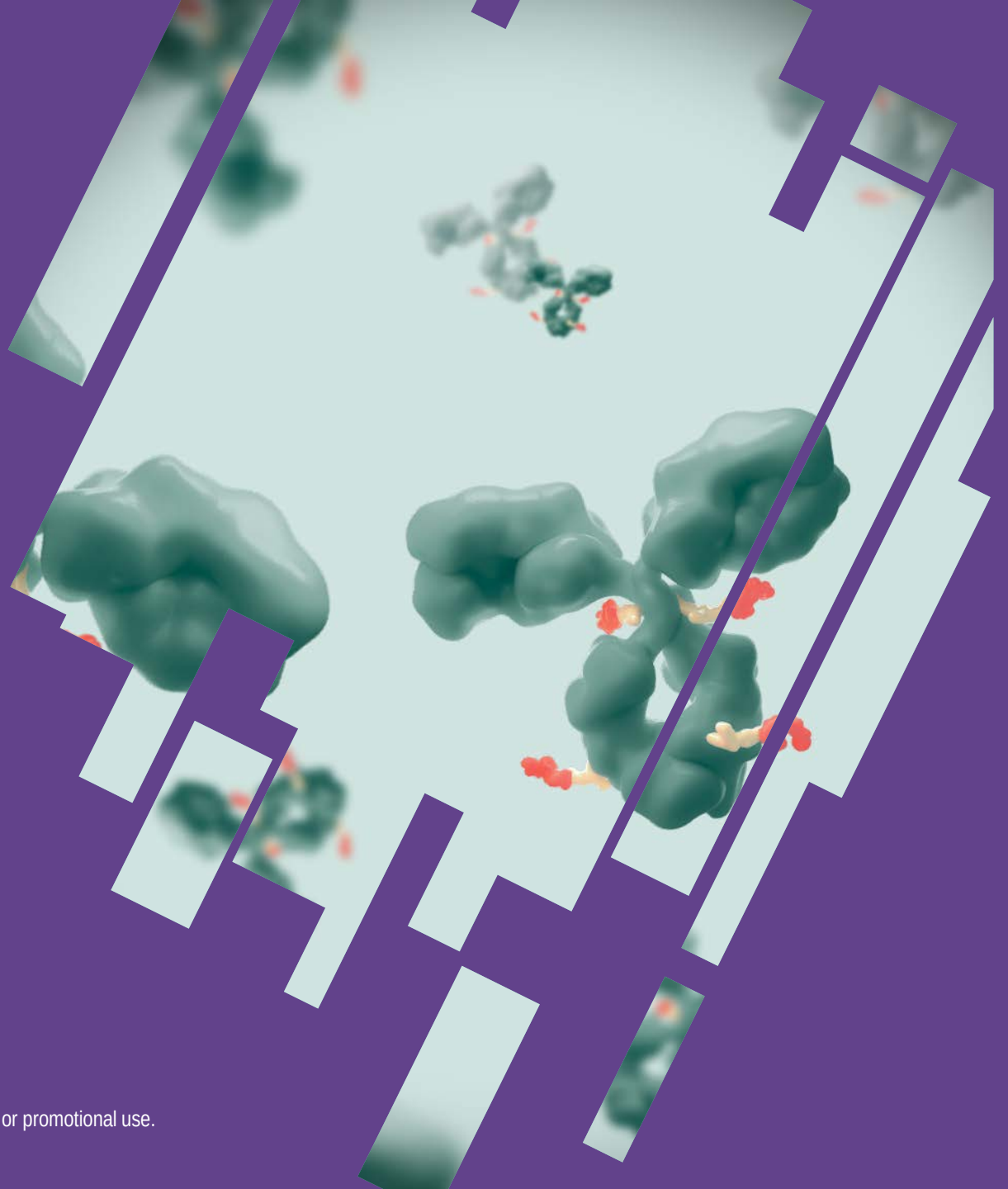

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Important Note

- This deck is intended for reactive scientific exchange
- Please note that tisotumab vedotin is under investigation and has not received FDA/EMA approval
- The safety and effectiveness of tisotumab vedotin has not been established
- Information about potential future uses are intended only for discussion
- Information should not be interpreted as an intent to promote unapproved uses
- The contents of this slide deck should not be used in any manner to directly or indirectly promote product for unapproved uses
- Seattle Genetics and Genmab prohibit the promotion of unapproved uses and comply with all applicable laws, regulations, and company policies

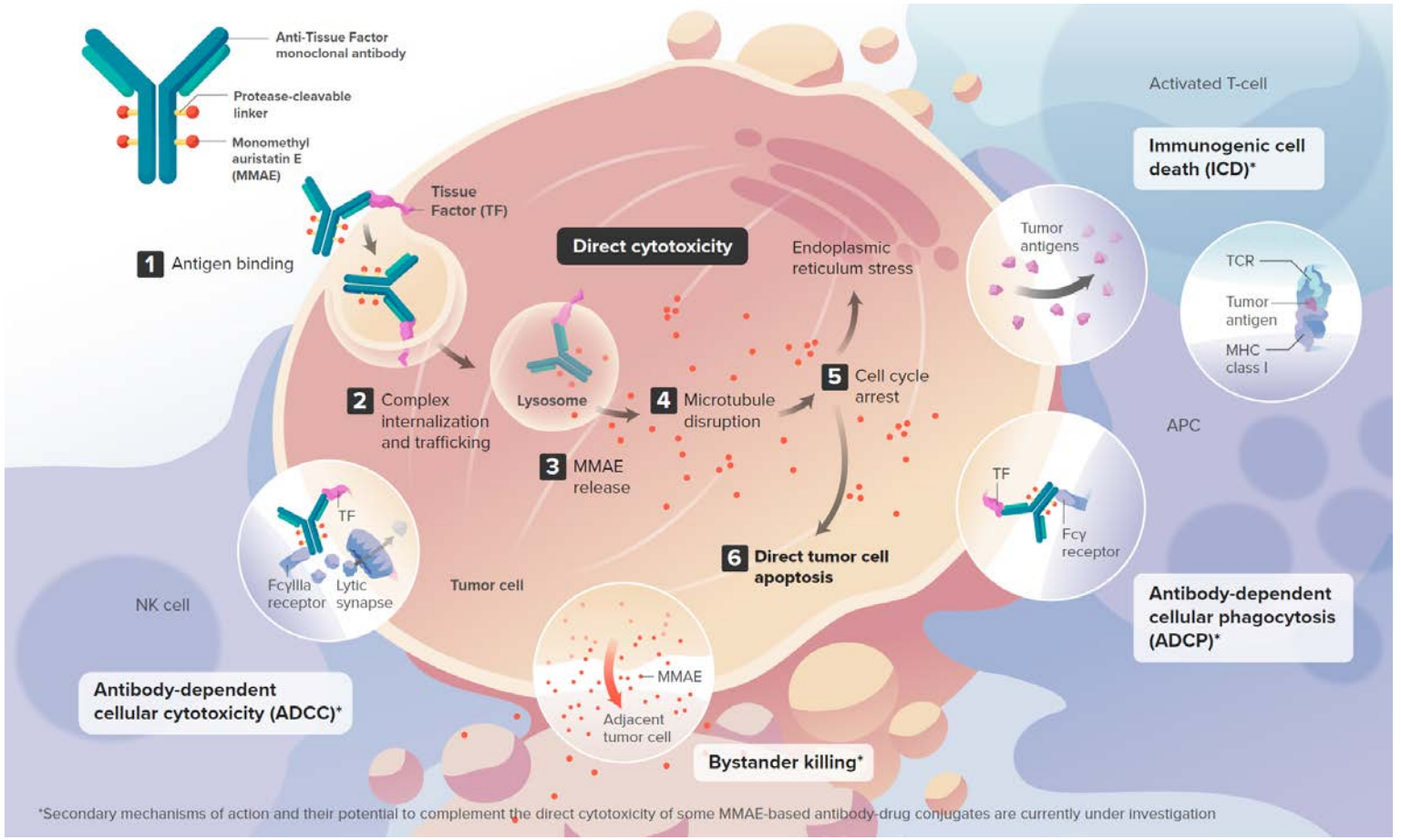
Background

- Recurrent and/or metastatic cervical cancer remains a significant cause of mortality in women[1]
- There is a high unmet need after resistance to or progression on 1L SOC (paclitaxel plus platinum/topotecan with bevacizumab, if eligible)[2,3]
- There is no currently established 2L+ SOC
  - Monotherapy cytotoxic agents have poor benefit/risk profiles with limited responses (ORR <5–15%)[4-11]
  - While pembrolizumab was approved in the United States under accelerated approval, only 14.3% of women with PD-L1+ tumors responded with DOR NR, and a median PFS of 2.1 months[12]
- Encouraging clinical activity for tisotumab vedotin in cervical cancer was initially observed in innovaTV 201, the first-in-human trial[13]

1. Bray F et al. *CA Can J Clin.* 2018;68:394-424. 2. Tewari KS et al. *N Engl J Med.* 2014;370:734-743. 3. Kitagawa R et al. *J Clin Oncol.* 2015;33:2129-2135. 4. Miller DS et al. *Gynecol Oncol*. 2008;110:65-70. 5. Lorusso D et al. *Ann Oncol*. 2010;21:61-66. 6. Muggia FM et al. *Gynecol Oncol*. 2004;92:639-643. 7.Bookman MA et al. *Gynecol Oncol*. 2000;77:446-449. 8. Monk BJ et al. *J Clin Oncol*. 2009;27:1069-1074. 9. Garcia AA et al. *Am J Clin Oncol*. 2007;30:428-431. 10. Schilder RJ et al. *Gynecol Oncol*. 2005;96:103-107. 11. Verschraegen CF et al. *J Clin Oncol*. 1997;15:625-631. 12. Chung HC et al. *J Clin Oncol.* 2019;37:1470-1478. 13. Hong DS et al. *Clin Cancer Res.* 2020;26:1220-1228.
1L, first-line; 2L, second-line; DOR, duration of response; NR, not reached; ORR, objective response rate; PD-L1, programmed death ligand 1; PFS, progression-free survival; SOC, standard of care.

Proposed MOA of Tisotumab Vedotin

- Tisotumab vedotin is an investigational antibody-drug conjugate directed to tissue factor (TF) and covalently linked to the microtubule-disrupting agent MMAE via a protease-cleavable linker[1,2]
- TF is highly prevalent in cervical cancer and other solid tumors and is associated with cancer pathophysiology and poor prognosis[3-5]
  - TF is co-opted by tumor cells to promote tumor growth, angiogenesis, and metastasis[6]
  - In normal physiology, TF's primary role is to initiate the coagulation cascade after vascular injury[6]
- Tisotumab vedotin has multiple anti-tumor effects[1,2,7]



Tisotumab vedotin is an investigational agent, and its safety and efficacy have not been established.

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. Pan L et al. *Mol Med Rep.* 2019;19:2077-2086. 4. Cocco E et al. *BMC Cancer.* 2011;11:263. 5. Zhao X et al. *Exp Ther Med.* 2018;16:4075-4081. 6. Forster Y et al. *Clin Chim Acta.* 2006;364:12-21 7. Alley SC et al. American Association for Cancer Research Annual Meeting; March 29 – April 3, 2019; Atlanta, GA, USA; Abstract #221.
ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; MMAE, monomethyl auristatin E; MOA, mechanism of action; TF, tissue factor.

innovaTV 204 Study Design

innovaTV 204 (NCT03438396) is a pivotal phase 2 single-arm, multicenter (United States and Europe) study evaluating tisotumab vedotin in patients with previously treated recurrent and/or metastatic cervical cancer

Key Eligibility Criteria

- Recurrent or extrapelvic metastatic cervical cancer
- Progressed during or after doublet chemotherapy[a] with bevacizumab (if eligible)
- Received ≤2 prior systemic regimens[b]
- ECOG PS 0-1

Enrolled: 102[c]
Treated: 101*

Tisotumab vedotin
2.0 mg/kg IV Q3W

Until PD or unacceptable toxicity

Tumor responses assessed using CT or MRI at baseline, every 6 weeks for the first 30 weeks, and every 12 weeks thereafter

*Study sample size calculated assuming a confirmed ORR of 21% to 25% with tisotumab vedotin and to provide ≥80% power to exclude an ORR of ≤11%[e]

Primary Endpoint

- ORR[d] per RECIST v1.1, by independent imaging review committee (IRC)

Secondary Endpoints

- ORR[d] per RECIST v1.1, by investigator
- DOR, TTR, and PFS, by IRC and investigator
- OS
- Safety

Exploratory Endpoints

- Biomarkers
- HRQoL

[a]Paclitaxel plus platinum (cisplatin or carboplatin) or paclitaxel plus topotecan. [b]Adjuvant or neoadjuvant chemotherapy or if administered with radiation therapy, was not counted as a prior systemic regimen. [c]June 2018 to April 2019. [d]Responses were confirmed by subsequent repeat imaging performed ≥4 weeks after initial response assessment. [e]Using one-sided exact binomial test at 0.025 significance level.
CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; IRC, independent review committee; IV, intravenous; MRI, magnetic resonance imaging; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; TTR, time to response.

Baseline Demographics & Disease Characteristics

	N=101
Age, median (range), years	50 (31-78)
Race, n (%)	
White	96 (95)
Asian	2 (2)
Black or African American	1 (1)
Other	2 (2)
ECOG PS, n (%)	
0	59 (58)
1	42 (42)
Histology, n (%)	
Squamous cell carcinoma	69 (68)
Adenocarcinoma	27 (27)
Adenosquamous carcinoma	5 (5)
Extrapelvic metastatic disease at baseline, n (%)	95 (94)

	N=101
Prior cisplatin plus radiation, n (%)	
Yes	55 (54)
No	46 (46)
Prior lines of systemic regimen for recurrent/metastatic disease,[a] n (%)	
1	71 (70)
2	30 (30)
Prior bevacizumab plus doublet chemotherapy as 1L therapy,[b] n (%)	64 (63)
Response to last systemic regimen,[a] n (%)	
Yes	38 (38)
No	57 (56)
Unknown	6 (6)
Biopsy evaluable, n (%)	80 (79)
Positive membrane TF expression,[c] n (%)	77 (96)

Data cutoff: February 06, 2020.
[a]Systemic regimen administered in the metastatic or recurrent setting. [b]Doublet chemotherapy defined as paclitaxel-platinum or paclitaxel-topotecan. [c]Positive TF expression defined as any positive membrane staining on tumor cells out of biopsy-evaluable population (n=80).
1L, first-line; ECOG PS, Eastern Cooperative Group performance status; TF, tissue factor.

Baseline Demographics & Disease Characteristics

Patient Disposition[a]	N=101
Patients with ongoing treatment, n (%)	**4 (4)**
Patients with discontinued treatment, n (%)	**97 (96)**
Radiographic disease progression	66 (65)
AEs	13 (13)
Clinical progression	8 (8)
Withdrawal of consent	5 (5)
Death	4 (4)
Investigator decision	1 (1)
Patients in survival follow up, n (%)	**33 (33)**

Treatment Exposure[a]	
Median treatment duration	4.2 months (range, 1–16)
Median tisotumab vedotin doses received	6 (range, 1–21)
Relative dose intensity	95.9% (range, 44–114)

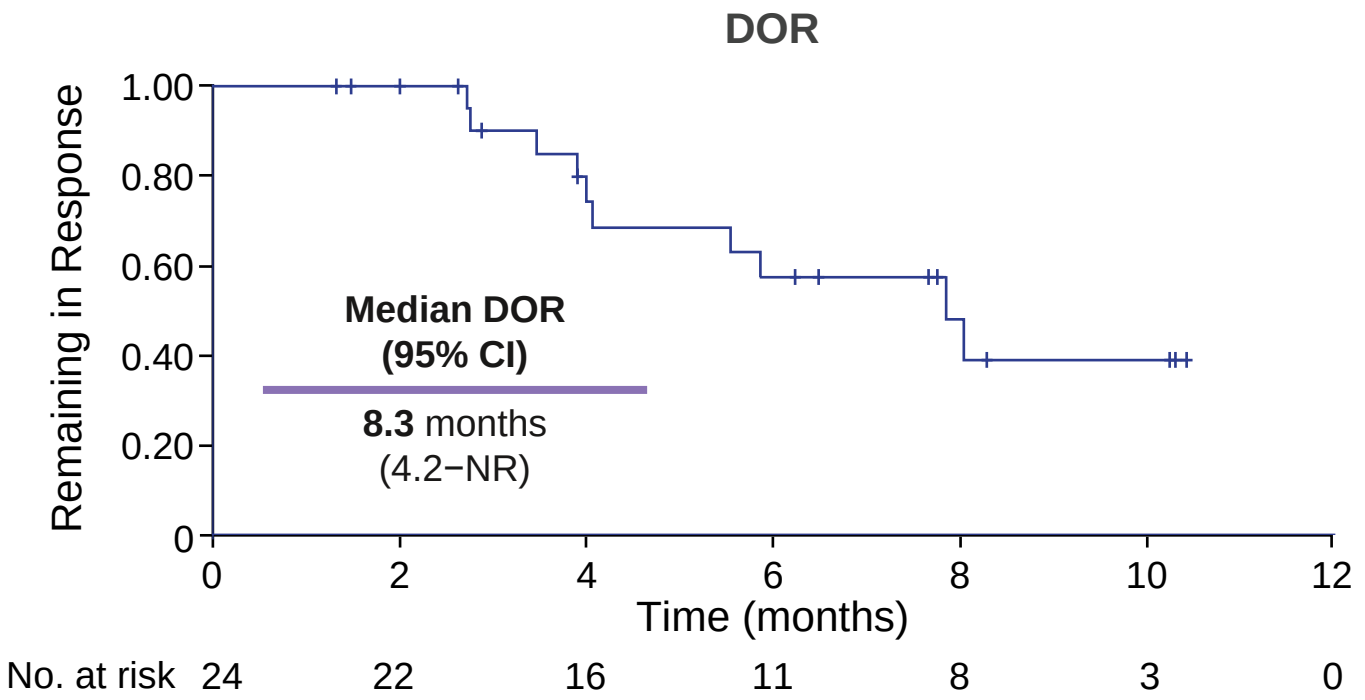
Median duration of follow-up: 10.0 months (range, 0.7–17.9)

[a]Based on data cutoff: February 06, 2020.
AE, adverse event.

Antitumor Activity by IRC Assessment

Primary and Secondary Endpoints

	N=101
Confirmed ORR (95% CI),[a] %	24 (15.9–33.3)
CR, n (%)	7 (7)
PR, n (%)	17 (17)
SD, n (%)	49 (49)
PD, n (%)	24 (24)
Not evaluable, n (%)	4 (4)

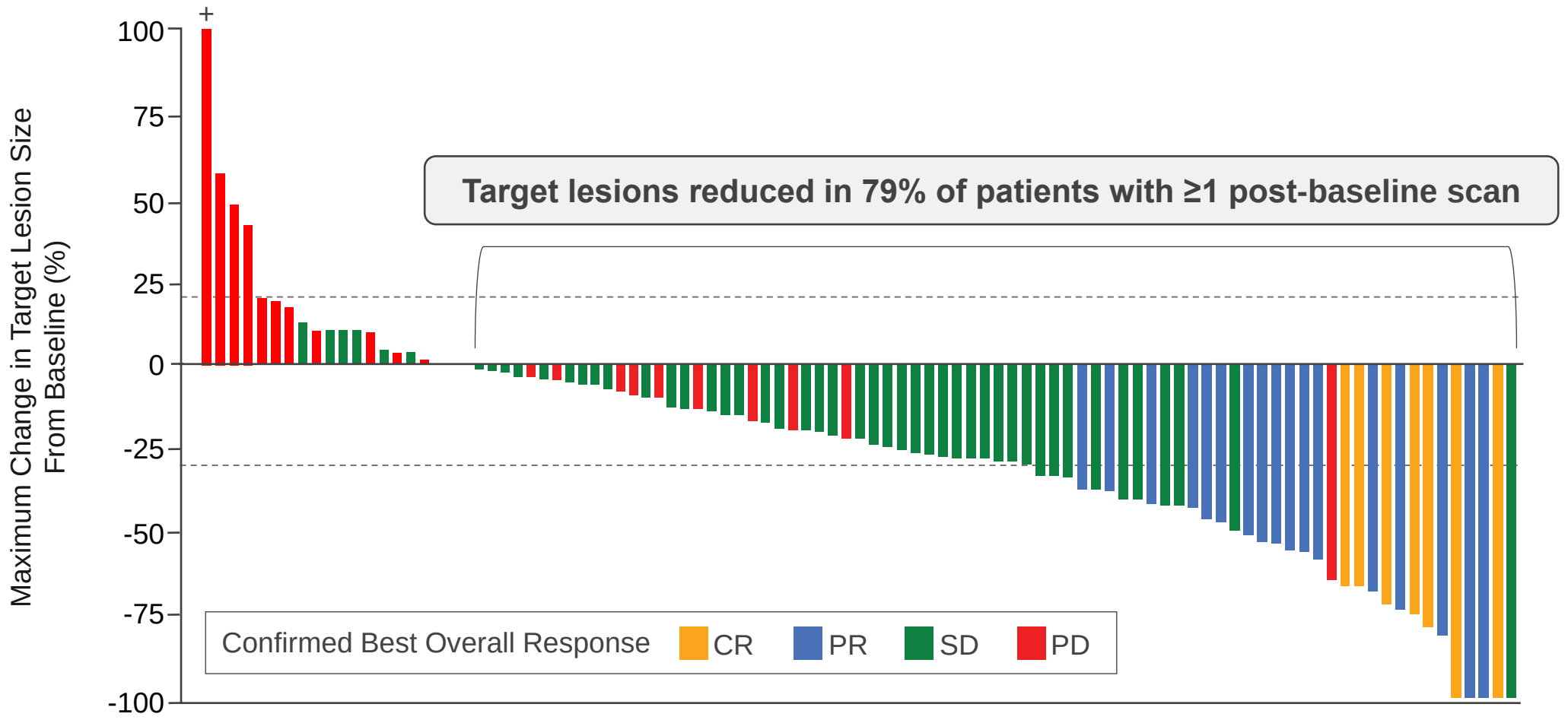


Clinically meaningful and durable responses were observed

Data cutoff: February 06, 2020. Median duration of follow-up: 10.0 months.
[a]Based on the Clopper-Pearson method.
CI, confidence interval; CR, complete response; DOR, duration of response; IRC, independent review committee; NR, not reached; ORR, objective response rate; PD, disease progression; PR, partial response; SD, stable disease.

Maximum Change in Target Lesion Size by IRC Assessment

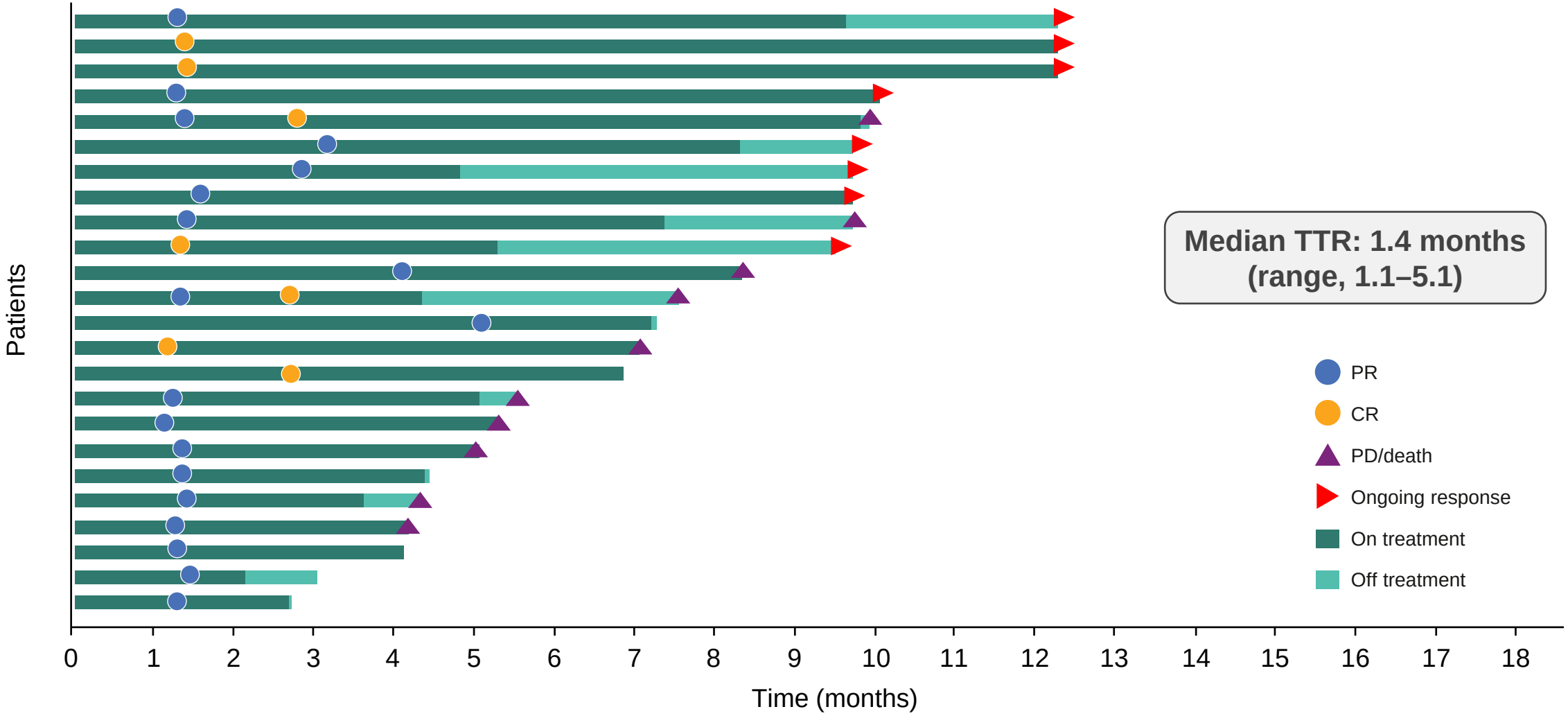
Secondary Endpoint



Data cutoff: February 06, 2020. Median duration of follow-up: 10.0 months. + indicates a change greater than 100%. Horizontal dashed lines indicate 20% increase and 30% decrease in target lesion diameters from baseline for RECIST v1.1 assessment. Colored bars represent the best overall confirmed response. CR, PR, SD, and PD were based on RECIST v1.1 as evaluated by IRC.
CR, complete response; IRC, independent review committee; PD, disease progression; PR, partial response; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; SD, stable disease.

Confirmed Responders by IRC Assessment

Secondary Endpoint

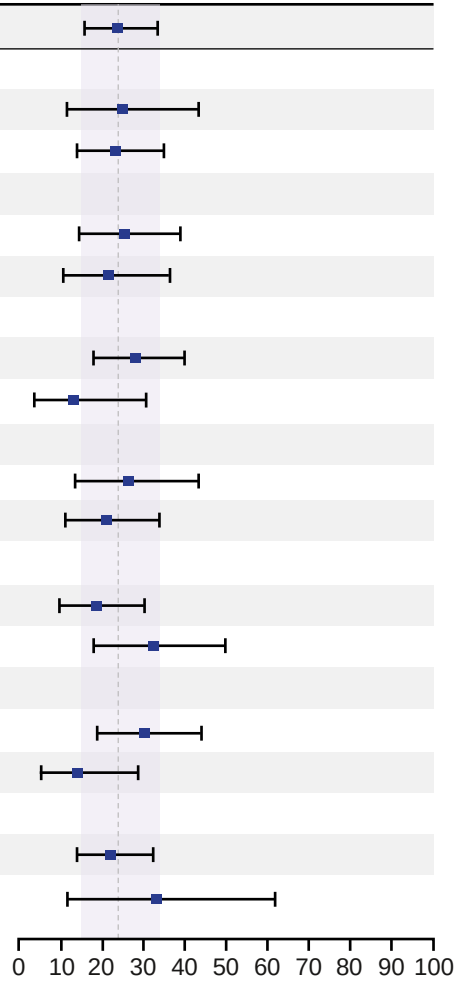


Data cutoff: February 06, 2020. Median duration of follow-up: 10.0 months.
Symbols closest to the Y-axis indicate the first response. A second symbol on a lane indicates a response that improved from a PR to a CR.
CR, complete response; IRC, independent review committee; PD, disease progression; PR, partial response; TTR, time to response.

ORR Subgroup Analysis

Primary Endpoint

Subgroup	n/N	% (95% CI)
Overall	24/101	24 (15.9–33.3)
Histology		
Nonsquamous	8/32	25 (11.5–43.4)
Squamous	16/69	23 (13.9–34.9)
Prior cisplatin + radiation		
Yes	14/55	26 (14.7–39.0)
No	10/46	22 (10.9–36.4)
Prior lines of systemic regimen		
1 line	20/71	28 (18.1–40.1)
2 lines	4/30	13 (3.8–30.7)
Response to last systemic regimen[a]		
Yes	10/38	26 (13.4–43.1)
No	12/57	21 (11.4–33.9)
Bevacizumab in combination with chemotherapy doublet as 1L therapy[b]		
Yes	12/64	19 (10.1–30.5)
No	12/37	32 (18.0–49.8)
ECOG performance status		
0	18/59	31 (19.2–43.9)
1	6/42	14 (5.4–28.5)
Region		
European Union	19/86	22 (13.9–32.3)
United States	5/15	33 (11.8–61.6)



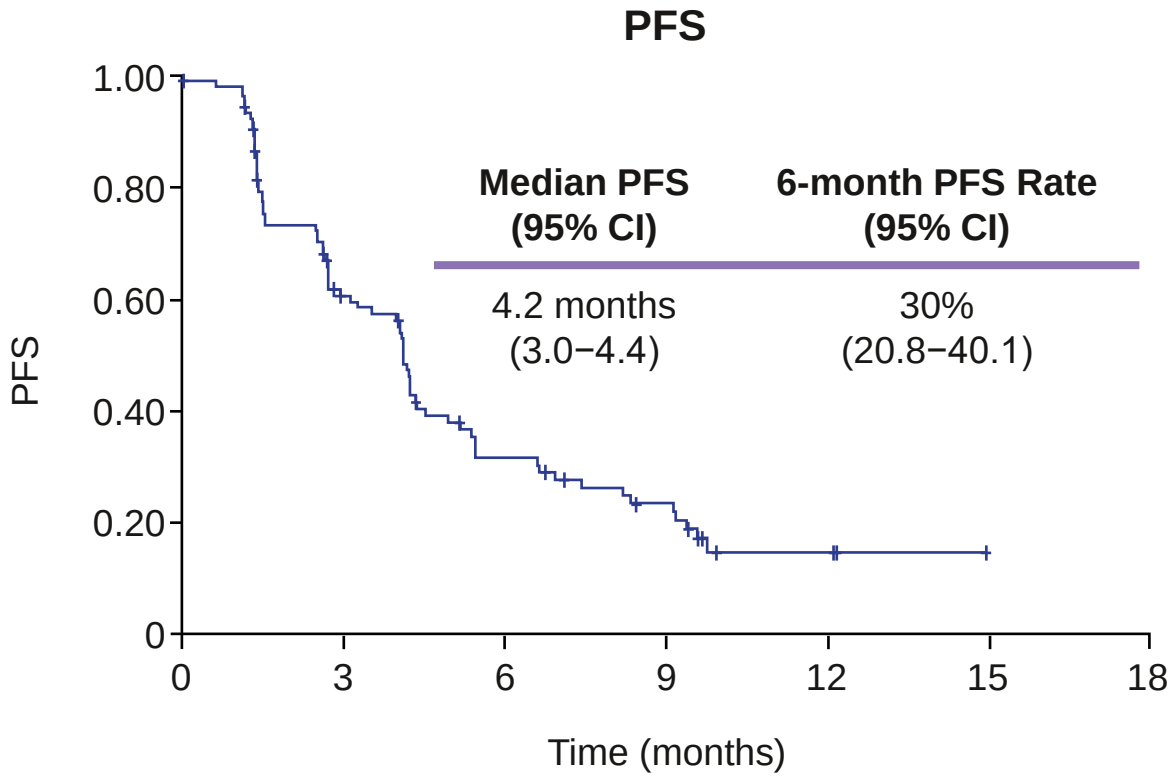
Responses generally consistent across subgroups regardless of:

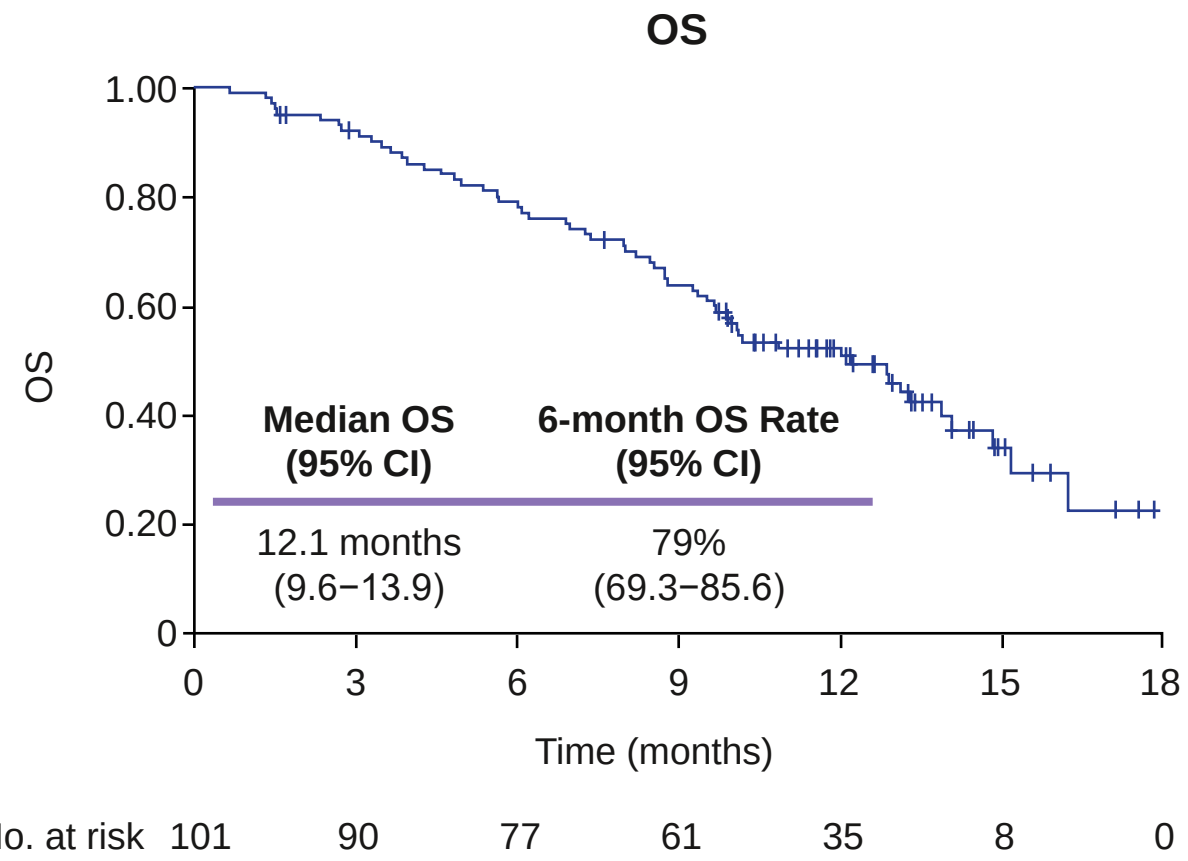
- **Tumor histology**
- **Lines of prior therapy**
- **Responses to prior systemic regimen**
- **Doublet chemotherapy with bevacizumab as 1L treatment**

Data cutoff: February 06, 2020. Median duration of follow-up: 10.0 months. The vertical line indicates 24%, which was the ORR of the entire study cohort.
[a]Response to last systemic regimen was not available for 6 subjects. [b]The term chemotherapy doublet includes either paclitaxel plus cisplatin or carboplatin or paclitaxel plus topotecan.
1L, first-line; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate.

PFS by IRC Assessment and OS

Secondary Endpoints





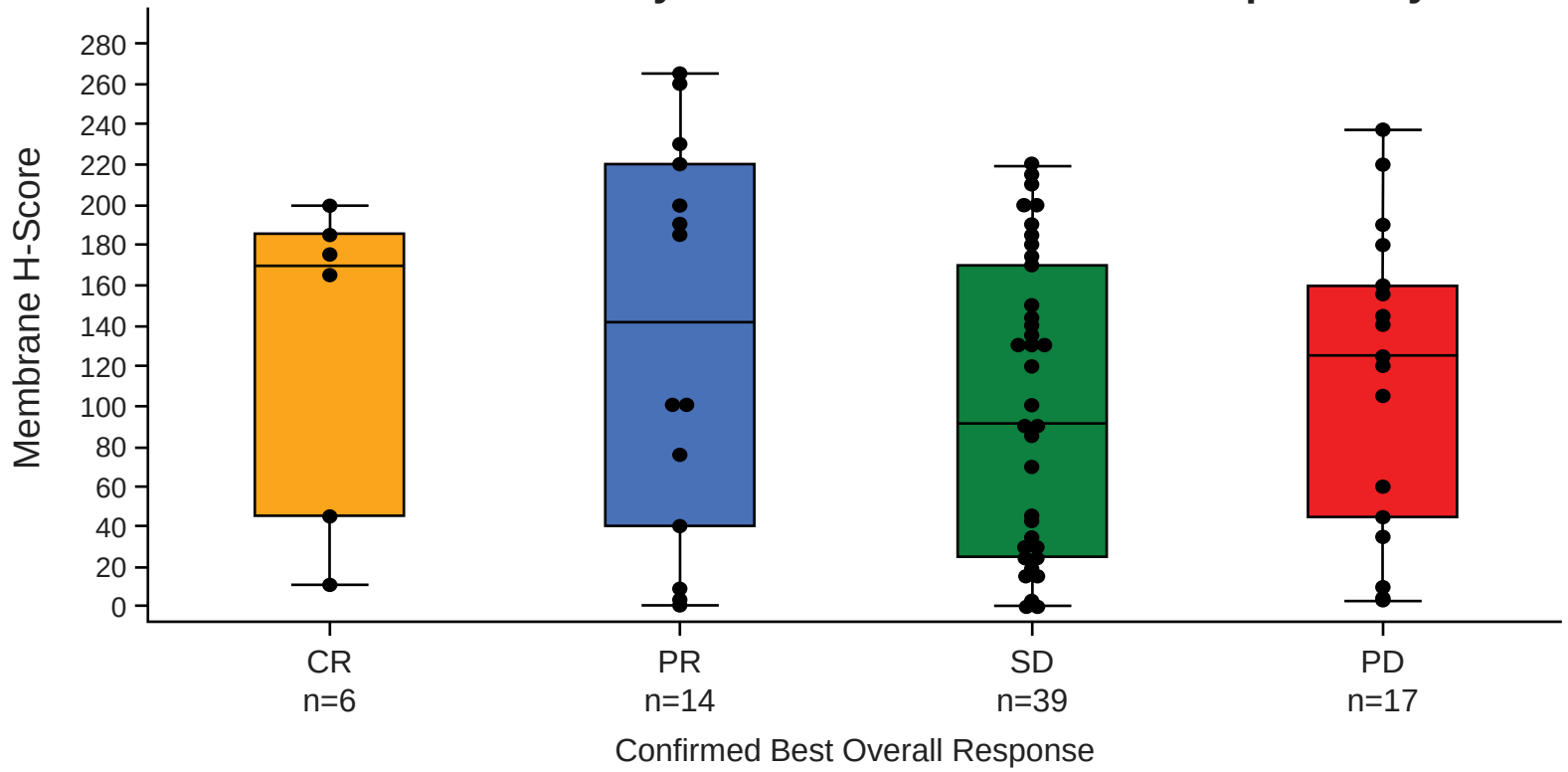
Data cutoff: February 06, 2020. Median duration of follow-up: 10.0 months.
CI, confidence interval; OS, overall survival; PFS, progression-free survival.

Tissue Factor Expression Analyses

Exploratory Endpoint

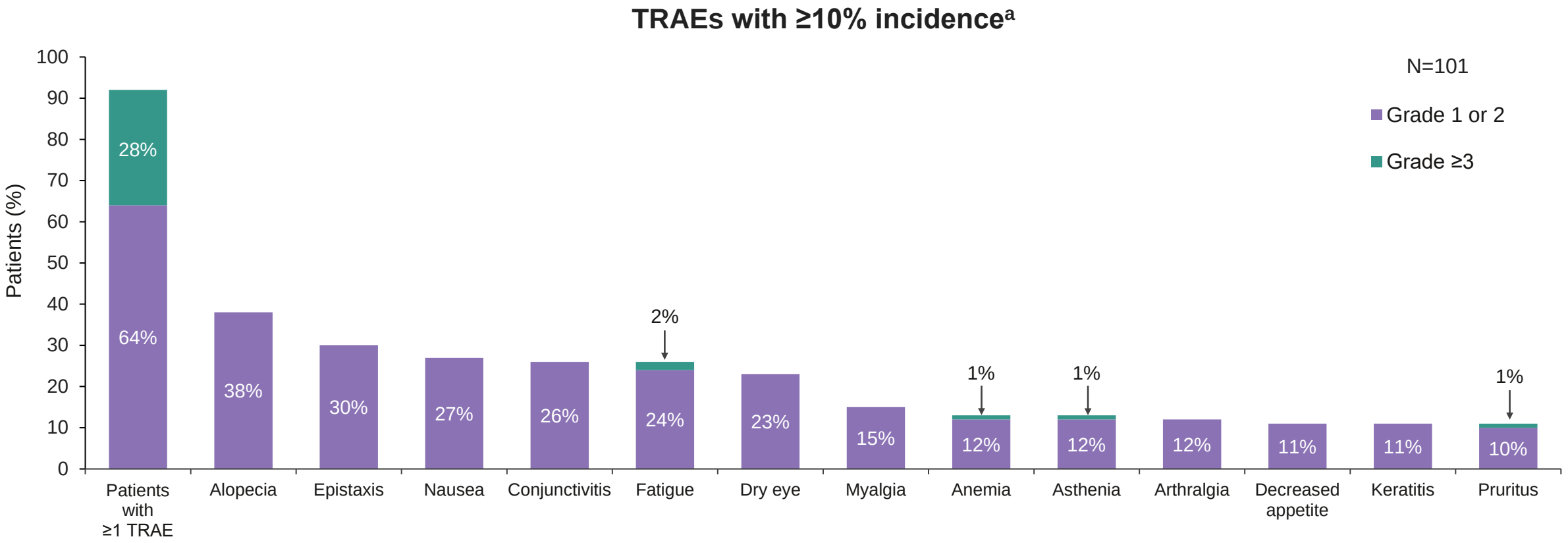
- **Response to tisotumab vedotin was observed regardless of membrane TF expression level**
- **Of the 80 patients for whom TF expression data were available, 76 (95%) were also evaluable for response**
- **Similar distribution of TF expression was observed between the different response groups**

Tumor Membrane H-Score at Baseline by Confirmed Best Overall Response by IRC Assessment



Data cutoff: February 06, 2020. Median duration of follow-up: 10.0 months.
CR, complete response; IRC, independent review committee; PD, disease progression; PR, partial response; SD, stable disease; TF, tissue factor.

Most Common TRAEs with Tisotumab Vedotin

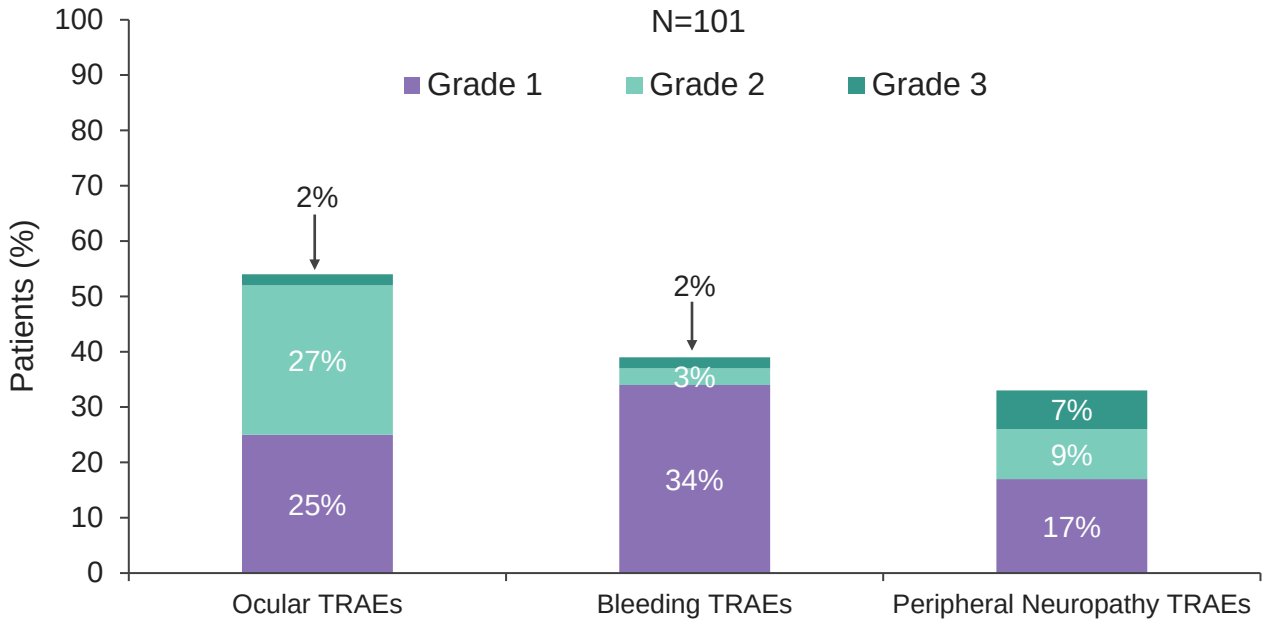


- **Most TRAEs were grade 1 or 2 and no new safety signals were reported**
- **One death due to septic shock was considered by the investigator to be related to therapy[b]**

Data cutoff: February 06, 2020. Median duration of follow-up: 10.0 months. Median duration of treatment: 4.2 months (range, 1–16).
[a]Any-grade AEs included if ≥10%. [b]Three treatment-emergent deaths unrelated to therapy included one case of ileus and two with unknown causes.
TRAE, treatment-related adverse event.

Prespecified AEs of Interest of Tisotumab Vedotin

Ocular,[a] bleeding,[b] and peripheral neuropathy[c] TRAEs



	Ocular	Bleeding	Peripheral Neuropathy
Time to onset (median, months)	1.4	0.3	3.1
Events resolved, %	86	90	21
Time to resolution[d] (median, months)	0.7	0.5	0.6

- Ocular AEs were mostly mild to moderate, resolved, and were manageable with an eye care plan
- Most bleeding events were grade 1 epistaxis (28%) of which majority resolved
- Most peripheral neuropathy events (known MMAE-related toxicity) were grade 1 and manageable with dose modifications; resolution was limited by follow-up period

Data cutoff: February 06, 2020. Median duration of follow-up: 10.0 months.
[a]Any ocular SMQ (conjunctival disorders SMQ, corneal disorders SMQ, scleral disorders SMQ, retinal disorders SMQ, periorbital and eyelid disorders SMQ, ocular infections SMQ, optic nerve disorders SMQ, glaucoma SMQ, lacrimal disorders SMQ, and eye disorders SMQ). [b]Hemorrhage SMQ. [c]Peripheral neuropathy SMQ. [d]Assessment limited by the protocol-defined follow-up period for AE of only 30 days after the last dose.
AE, adverse event; MMAE, monomethyl auristatin E; SMQ, standardized MedDRA queries; TRAE, treatment-related adverse events.

Author's Conclusions

- Tisotumab vedotin demonstrated compelling (ORR: 24%; CR: 7%) and durable (median DOR: 8.3 months) antitumor activity in recurrent and/or metastatic cervical cancer previously treated with doublet chemotherapy with bevacizumab (if eligible)
  - Most responses were rapid (median TTR: 1.4 months), with activity observed within the first 2 treatment cycles
  - Median PFS (4.2 months) and OS (12.1 months) are encouraging
  - Clinically meaningful responses were observed regardless of TF expression, histology subtype, or prior therapy
- Tisotumab vedotin had a manageable and tolerable safety profile with no new safety signals
  - Most treatment-related adverse events were Grade 1 or 2
  - Ocular (Grade 1: 25%, Grade 2: 27%, Grade 3: 2%), bleeding (Grade 1: 34%, Grade 2: 3%, Grade 3: 2%), and peripheral neuropathy (Grade 1: 17%, Grade 2: 9%, Grade 3: 7%) treatment-related adverse events were generally mild and effectively managed with dose modifications
  - An eye care plan was implemented to mitigate and manage ocular events
- Tisotumab vedotin is a potential novel treatment* for women with previously treated recurrent and/or metastatic cervical cancer

Evaluation is ongoing in 37 (37%) patients.
* If approved by relevant regulatory authorities, including FDA/EMA.
AE, adverse event; CR, complete response, DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TF, tissue factor; TTR, time to response.

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The following principal investigators participated in the innovaTV 204/GOG-3023/ENGOT-cx6 study

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