innovaTV 301/ENGOT-cx12/GOG-3057: A Global, Randomized, Open-Label, Phase 3 Study of Tisotumab Vedotin vs Investigator's Choice of Chemotherapy in 2L or 3L Recurrent or Metastatic Cervical Cancer

Ignace Vergote, Antonio González Martín, Keiichi Fujiwara, Elsa Kalbacher, Andrea Bagaméri, Sharad Ghamande, Jung-Yun Lee, Susana Banerjee, Fernando Maluf, Domenica Lorusso, Kan Yonemori, Els Van Nieuwenhuysen, Luis Manso Sanchez, Linn Woelber, Anneke Westermann, Allan Covens, Elizabeth Whalley, Melinda Siew Leng Teng, Ibrahima Soumaoro, Brian M. Slomovitz

Seagen® | Genmab

Background

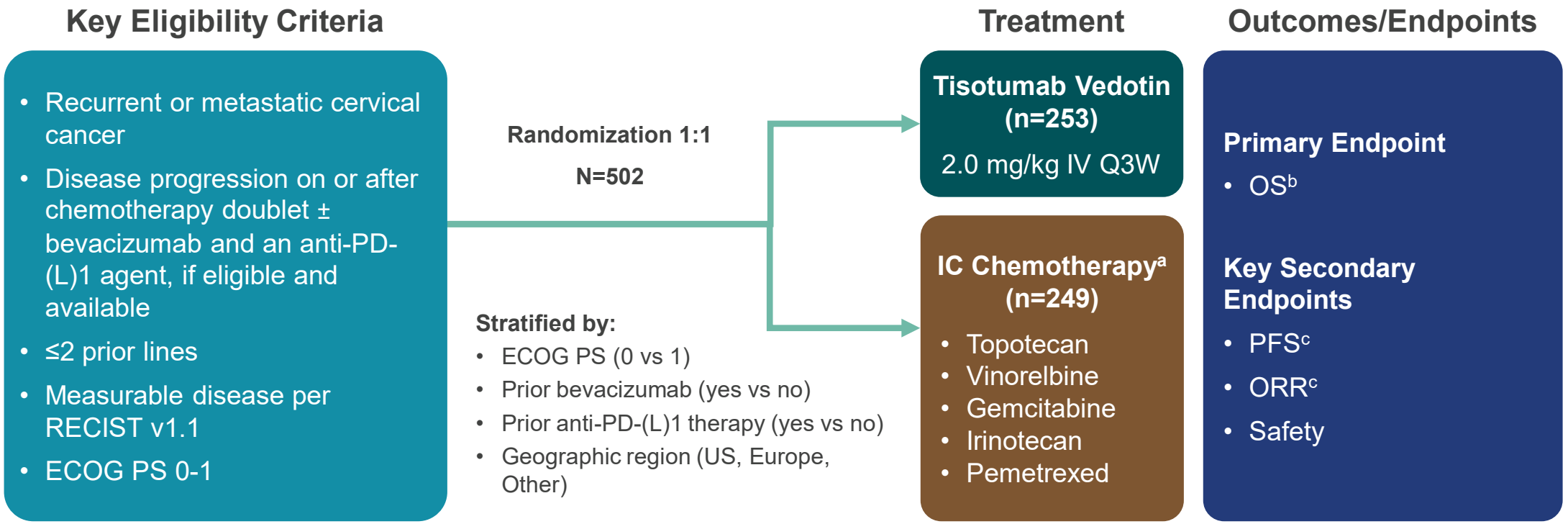
- Recurrent or metastatic cervical cancer (r/mCC) is a devastating disease globally that is associated with a poor prognosis and a high mortality rate[1-3]
  - Cervical cancer is the 4th most deadly cancer in female patients worldwide[4]
- Despite the addition of immunotherapy in the treatment of r/mCC, those who progress on or after 1L therapy continue to have a high unmet need
- Tisotumab vedotin is an investigational antibody-drug conjugate composed of a tissue factor-directed human monoclonal antibody covalently linked to the microtubule-disrupting agent MMAE
  - Tisotumab vedotin received FDA accelerated approval in the United States for the treatment of adult patients with r/mCC with disease progression on or after chemotherapy, based on the phase 2 innovaTV 204/GOG-3023/ENGOT-cx6 study[5,6]

1L, frontline; FDA, Food and Drug Administration; MMAE, monomethyl auristatin E

1. National Cancer Institute. SEER Cancer Stat Facts: Cervical Cancer. 2022. 2. Alholm Z. Gynecol Oncol. 2021:422-428 3. Tewari KS. N Engl J Med. 2022:544-555. 4. Sung H. CA Cancer J Clin. 2021:209-249. 5. Coleman RL. Lancet Oncol. 2021:609-619. 6. TIVDAK® (tisotumab vedotin-tftv) [prescribing information] Bothell, WA: Seagen Inc. 2023.

Seagen | Genmab

innovaTV 301: A Randomized, Open-Label, Phase 3 Trial



- Data presented herein are a planned interim analysis

IC, investigator's choice; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks
End of treatment visit occurred 30 days after the last dose of treatment. Survival follow-up occurred every 60 days after the last dose of treatment.
[a]Chemotherapy regimens were given at the following doses: topotecan 1 or 1.25 mg/m^2 IV on Days 1 to 5 of a 21-day cycle; vinorelbine 30 mg/m^2 IV on Days 1 and 8 of a 21-day cycle; gemcitabine 1000 mg/m^2 IV on Days 1 and 8 of a 21-day cycle; irinotecan 100 or 125 mg/m^2 IV weekly for 28 days every 42 days; pemetrexed 500 mg/m^2 on Day 1 of a 21-day cycle; [b]OS was defined as the time from the date of randomization to the date of death due to any cause; [c]Assessed by investigator.
Vergote I. ESMO 2023: Presidential Symposium (Oral Presentation) LBA9.

Statistical Considerations

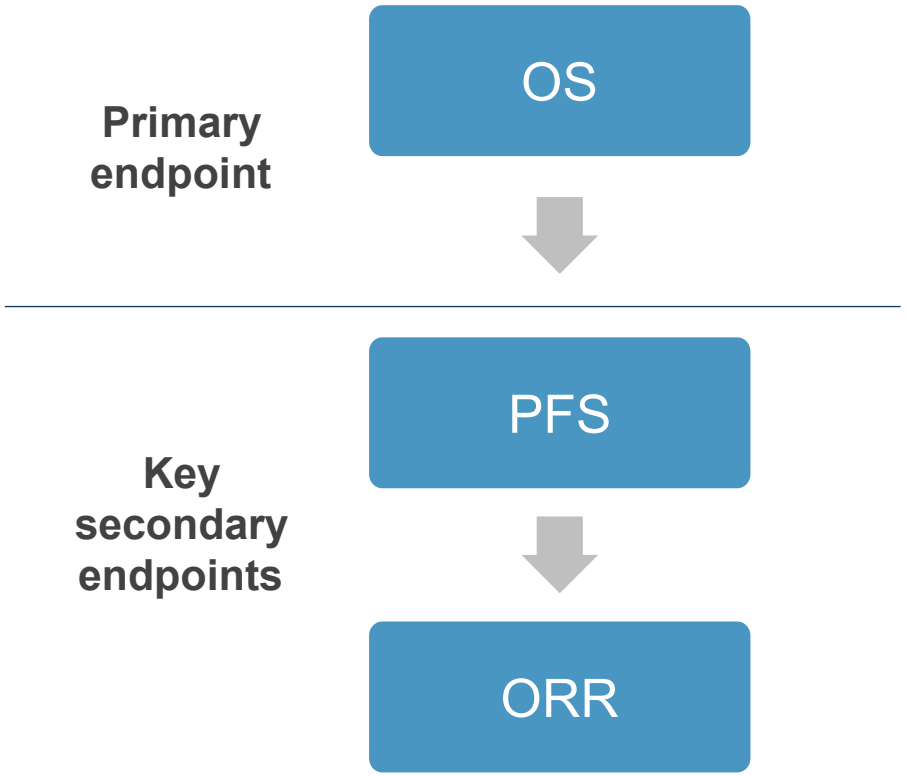
Planned sample size of approximately 482 patients

- Sample size powered at 90% with 336 OS events
- Interim analysis planned for 252 OS events
- Assumed HR of 0.7
- Drop-out rate of 5% per year
- Overall statistical level of significance = 0.05 (2-sided)

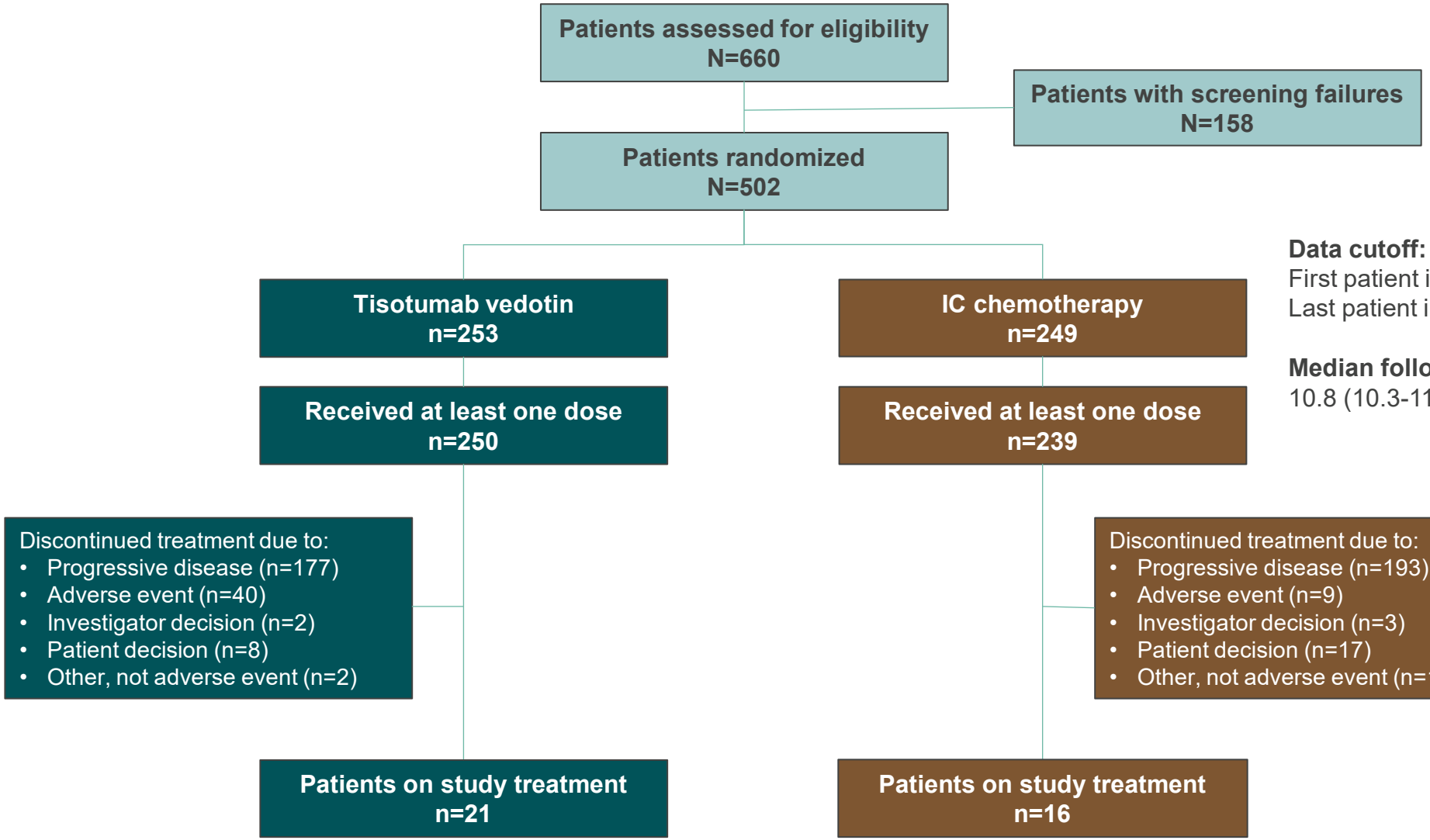
Based on actual number of events at interim analysis, the P value boundary for:

- OS is 0.0226 (2-sided)
- PFS is 0.0453 (2-sided)
- ORR is 0.05 (2-sided)

Hierarchical Testing



CONSORT Diagram



Data cutoff: 24Jul2023
First patient in: 9Mar2021
Last patient in: 16May2023

Median follow-up, mo (95% CI):
10.8 (10.3-11.6)

Baseline Patient and Disease Characteristics

	Tisotumab Vedotin (N=253)	IC Chemotherapy (N=249)
Age, years, median (range)	51 (26-80)	50 (27-78)
Baseline ECOG PS, n (%)		
0	137 (54.2)	136 (54.6)
1	116 (45.8)	113 (45.4)
Region, n (%)		
United States	16 (6.3)	14 (5.6)
Europe	106 (41.9)	104 (41.8)
Asia	85 (33.6)	88 (35.3)
Other	46 (18.2)	43 (17.3)
Histology, n (%)		
Squamous cell carcinoma	160 (63.2)	157 (63.1)
Adenocarcinoma	85 (33.6)	75 (30.1)
Adenosquamous carcinoma	8 (3.2)	17 (6.8)
Disease status at study entry, n (%)		
Pelvic recurrent only	27 (10.7)	24 (9.6)
Extra-pelvic metastatic	226 (89.3)	225 (90.4)

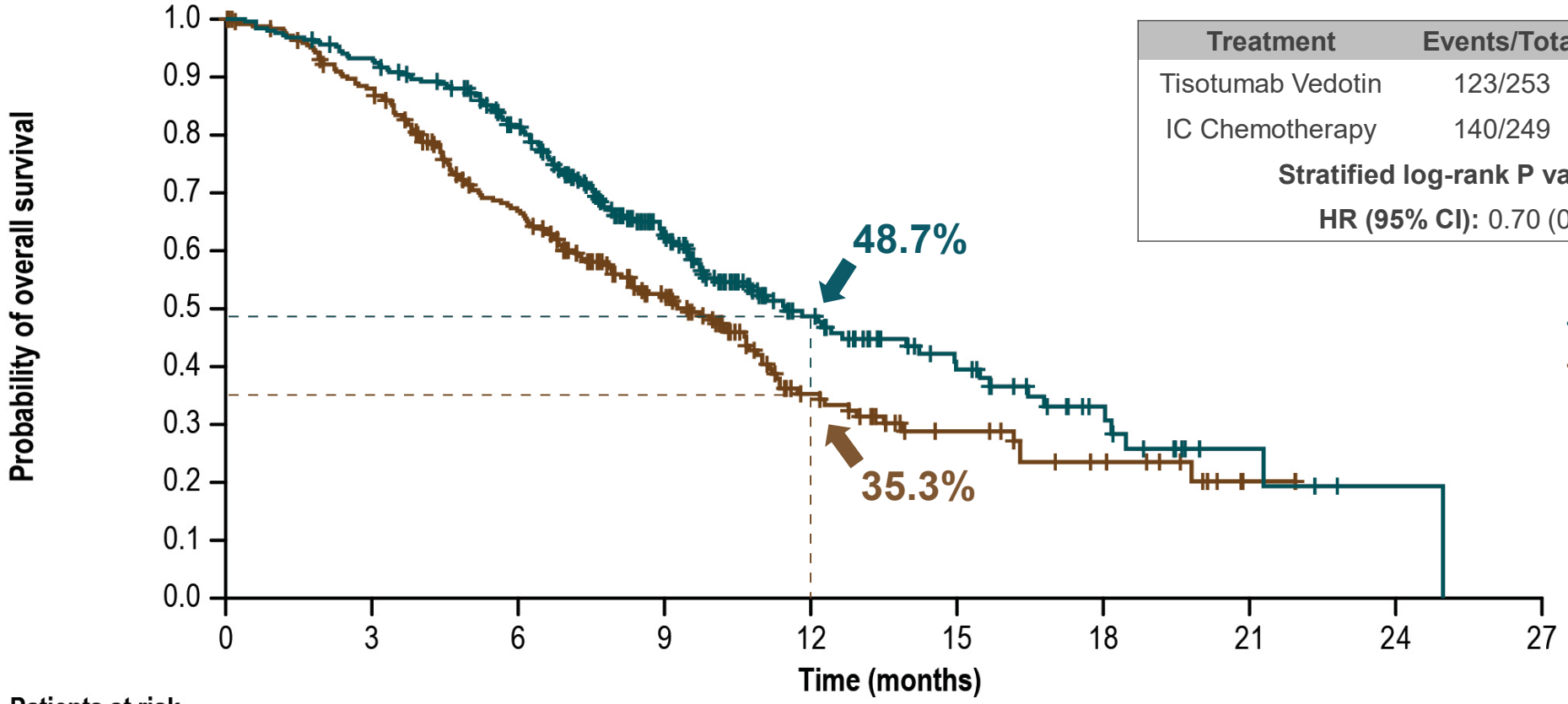
	Tisotumab Vedotin (N=253)	IC Chemotherapy (N=249)
Number of prior r/m systemic regimens, n (%)		
1	159 (62.8)	149 (59.8)
2	93 (36.8)	100 (40.2)
Unknown	1 (0.4)	0
Prior bevacizumab, n (%)	164 (64.8)	157 (63.1)
Prior anti-PD-(L)1 therapy, n (%)	71 (28.1)	67 (26.9)
Prior radiation therapy for cervical cancer, n (%)	205 (81.0)	203 (81.5)
Biopsy evaluable, n (%)	210 (83.0)	194 (77.9)
Positive membrane TF expression[a]	194 (92.4)	183 (94.3)

TF, tissue factor

[a]TF expression is defined as TF membrane expression ≥1% with immunohistochemistry; percentages are calculated based on number of evaluable biopsies.

Seagen | Genmab

Overall Survival (Primary Endpoint)



Treatment	Events/Total	Median (95% CI)
Tisotumab Vedotin	123/253	11.5 (9.8, 14.9)
IC Chemotherapy	140/249	9.5 (7.9, 10.7)
Stratified log-rank P value[a]: 0.0038		
HR (95% CI): 0.70 (0.54, 0.89)		

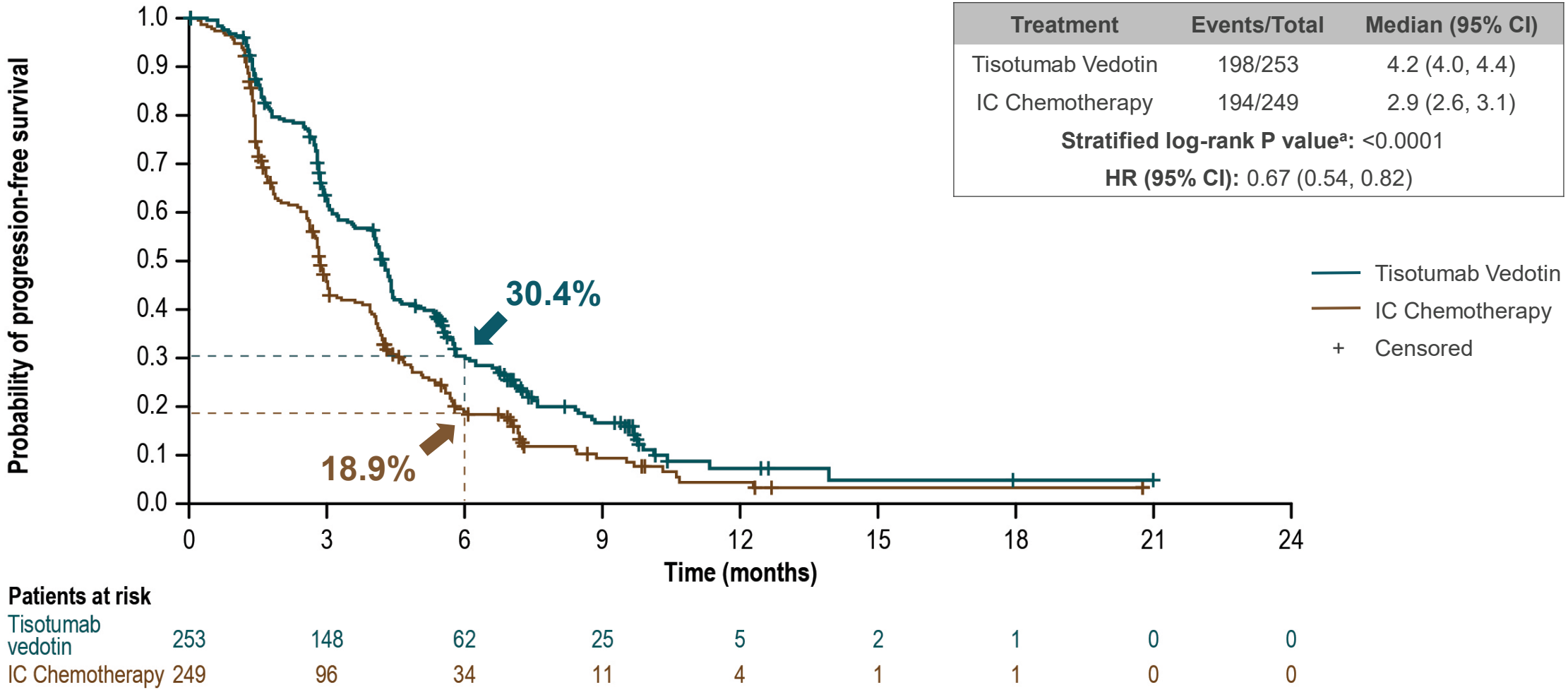
Patients at risk

Tisotumab vedotin	253	234	191	109	52	29	14	4	1	0
IC Chemotherapy	249	212	150	87	37	19	11	1	0	0

[a]The threshold for statistical significance is 0.0226 (2-sided), based on the actual number of OS events at interim analysis.

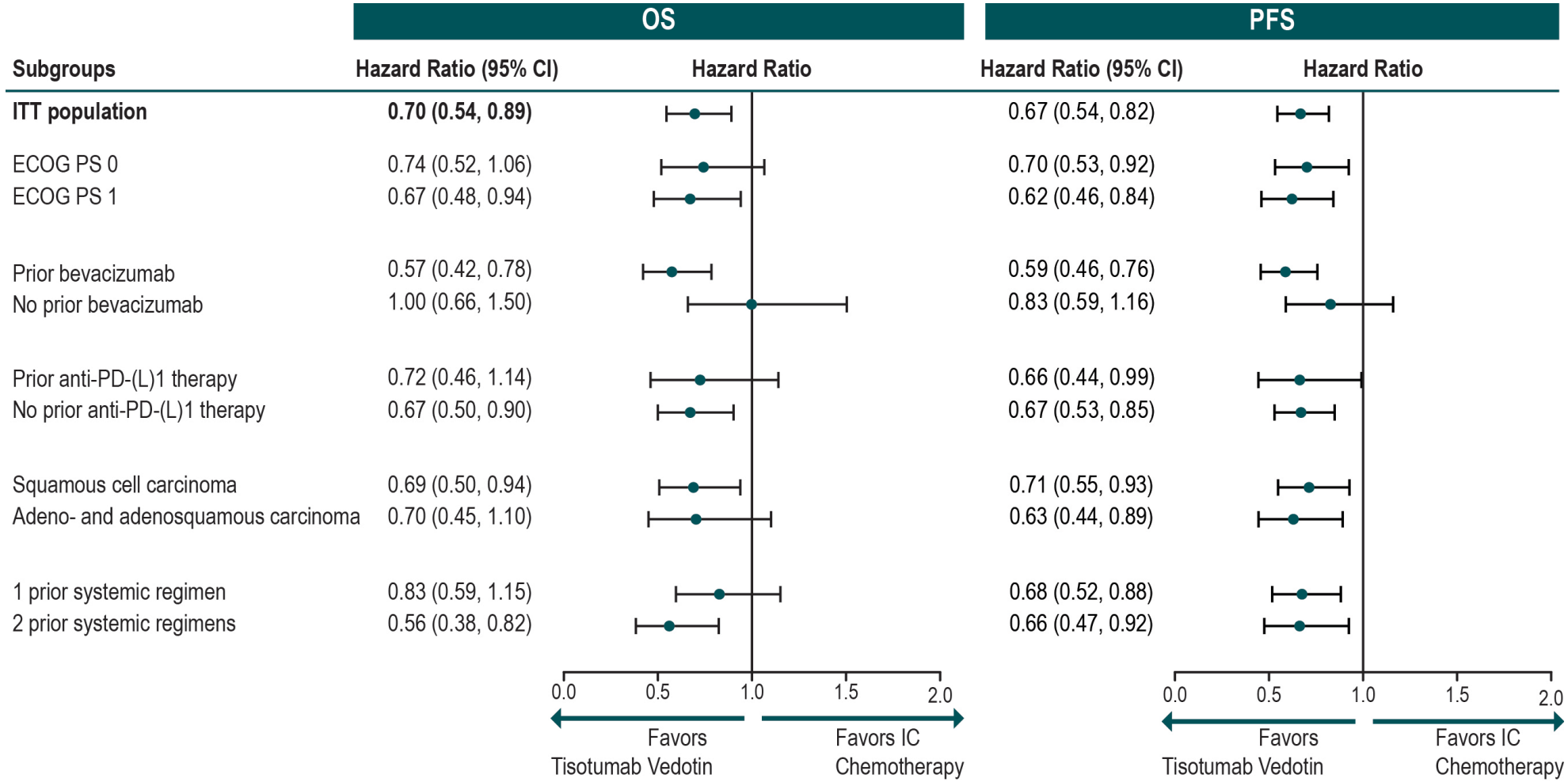
Progression-Free Survival Per Investigator

Treatment	Events/Total	Median (95% CI)
Tisotumab Vedotin	198/253	4.2 (4.0, 4.4)
IC Chemotherapy	194/249	2.9 (2.6, 3.1)
Stratified log-rank P value[a]: <0.0001		
HR (95% CI): 0.67 (0.54, 0.82)		



[a]The threshold for statistical significance is 0.0453 (2-sided), based on the actual number of PFS events at interim analysis.

Key Subgroups: OS and PFS

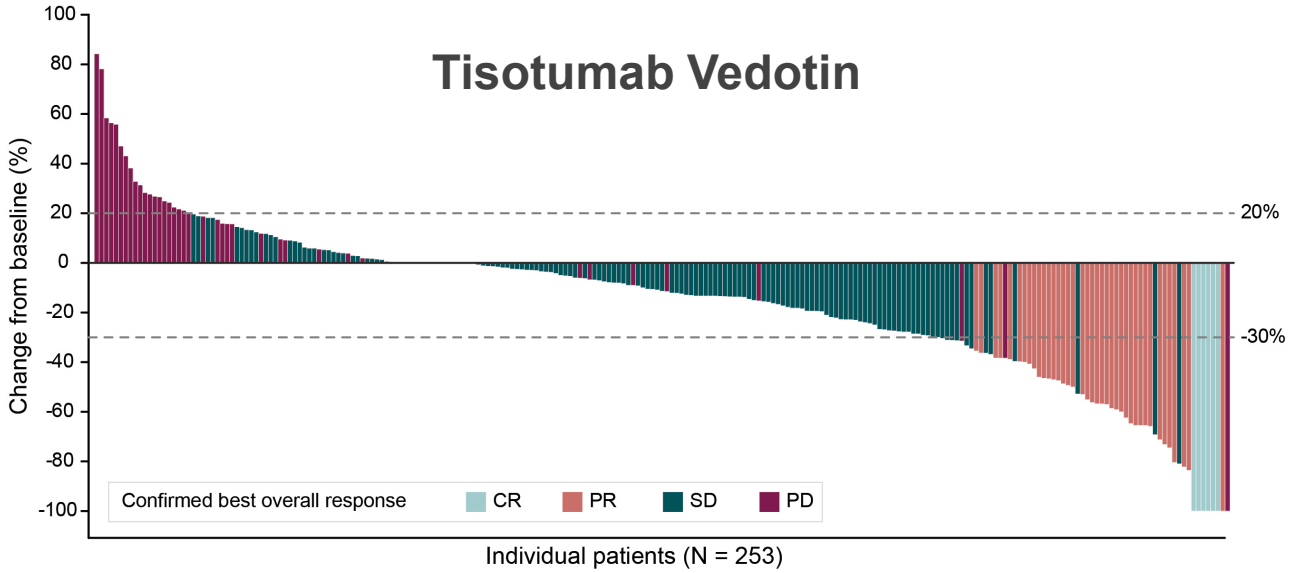


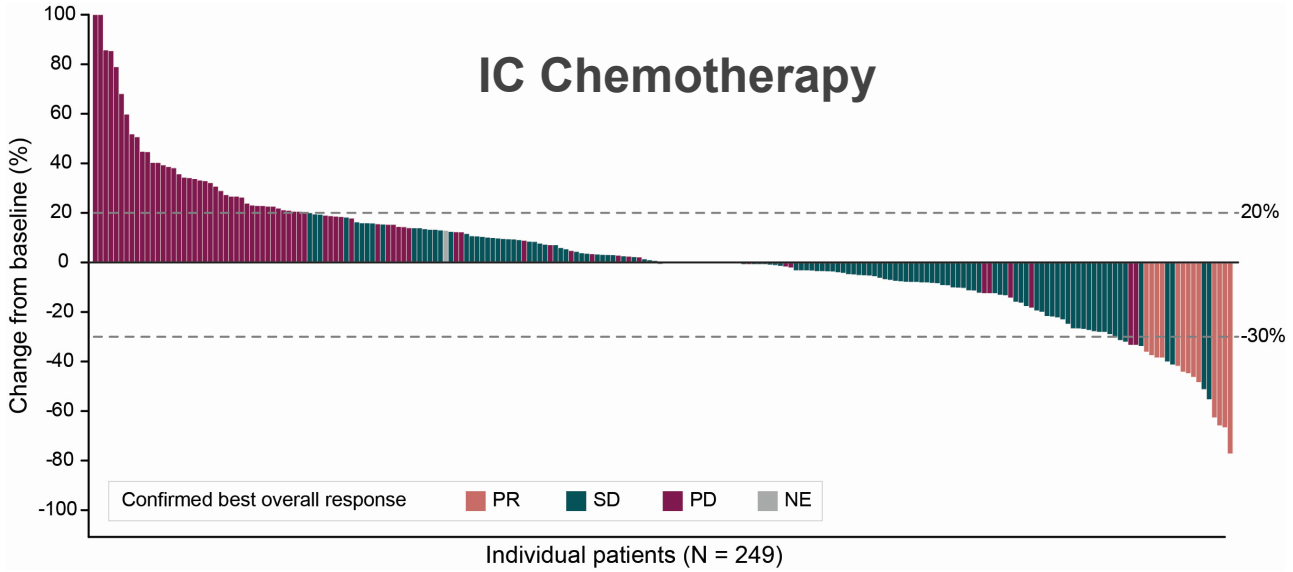
OS and PFS benefit was generally consistent across key subgroups

Seagen | Genmab

Antitumor Activity

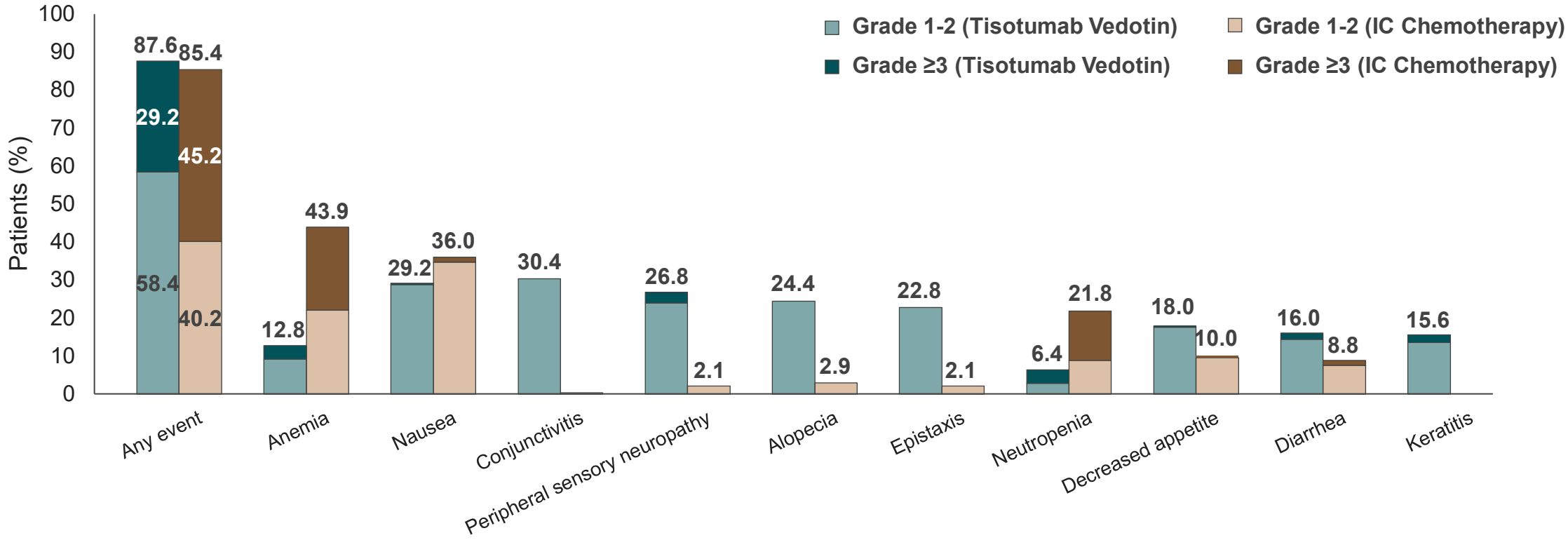
	Tisotumab Vedotin (N=253)	IC Chemotherapy (N=249)
ORR, % (95% CI)	17.8 (13.3-23.1)	5.2 (2.8-8.8)
Odds ratio (95% CI)	4.0 (2.1-7.6)	
P value	p<0.0001	
Best Overall Response, n (%)		
CR	6 (2.4)	0
PR	39 (15.4)	13 (5.2)
SD	147 (58.1)	132 (53.0)
PD	46 (18.2)	74 (29.7)
Not evaluable/Not available	15 (5.9)	30 (12.0)
DCR[a], % (95% CI)	75.9 (70.1-81.0)	58.2 (51.8-64.4)
Median DOR (95% CI)	5.3 (4.2-8.3)	5.7 (2.8-NR)





[a]DCR defined as CR+PR+SD; CR and PR were confirmed responses. The minimum criteria for SD duration was ≥5 weeks after the date of randomization.

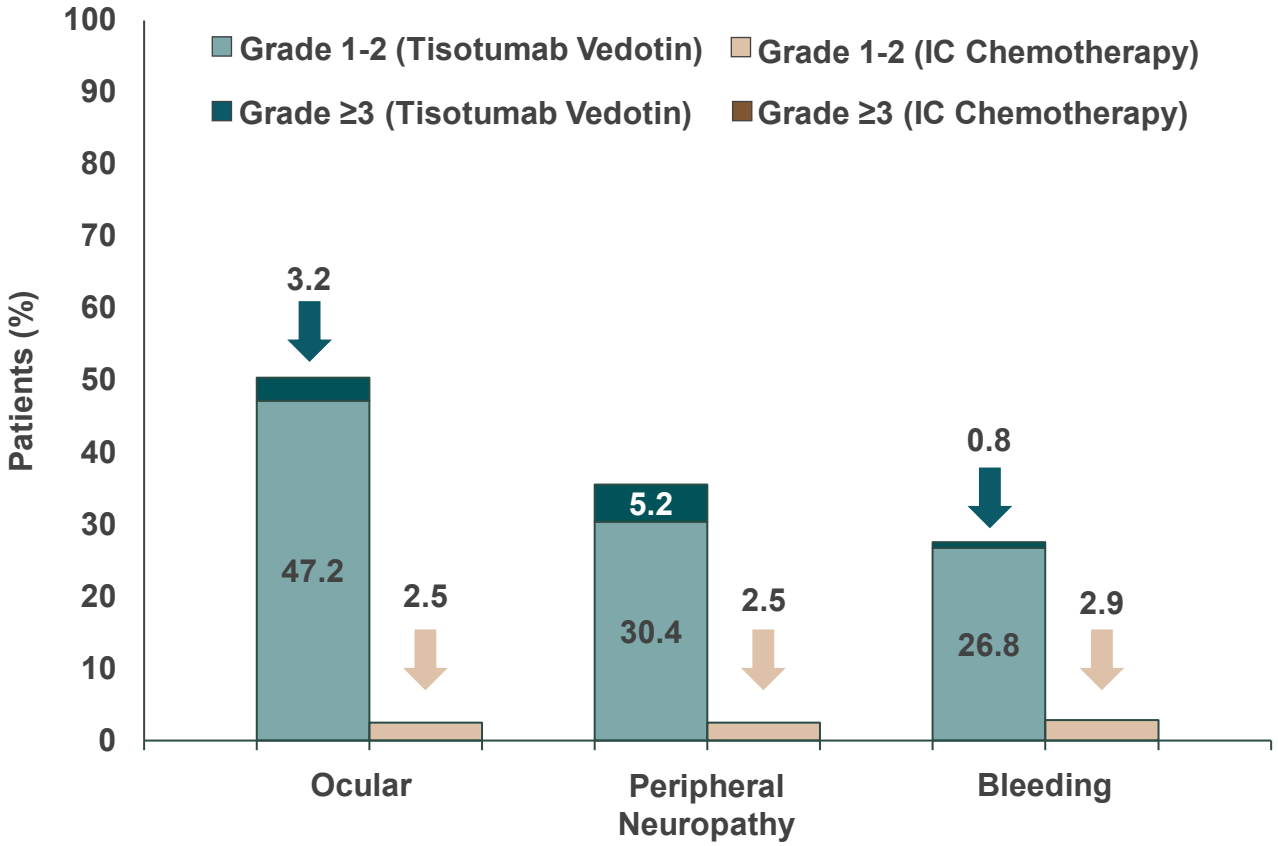
Most Common Treatment-Related Adverse Events[a]



- Grade 5 TRAEs occurred in 2 (0.8%) and 1 (0.4%) patients in the tisotumab vedotin and IC chemotherapy arms, respectively[b]
- Median relative dose intensity was 96.1% and 90.0% in the tisotumab vedotin and IC chemotherapy arms, respectively

[a]TRAEs listed are those occurring in ≥15% of patients on either arm; [b]Grade 5 TRAEs included acute kidney injury (n=1) and Stevens-Johnson syndrome (n=1) in the tisotumab vedotin arm and pancytopenia (n=1) in the IC chemotherapy arm.

Adverse Events of Special Interest for Tisotumab Vedotin[a]



- There were no grade 4 or 5 AESIs
- Dose discontinuation due to ocular and peripheral neuropathy events occurred in 5.6% of patients for each

Three most common preferred terms for each AESI	
Ocular	Conjunctivitis (30.4%), keratitis (15.6%), dry eye (13.2%)
Peripheral neuropathy	Peripheral sensory neuropathy (26.8%), paresthesia (2.8%), muscular weakness (2.4%), peripheral sensorimotor neuropathy (2.4%)
Bleeding	Epistaxis (22.8%), hematuria (3.2%), vaginal hemorrhage (3.2%)

AESI, adverse event of special interest
[a]Treatment-related AESIs

Authors' Conclusions

- Tisotumab vedotin showed a statistically significant and clinically meaningful improvement in OS
  - The hazard ratio for OS was 0.70, demonstrating a 30% reduction in the risk of death
- Consistent benefit in PFS and confirmed ORR were also observed and supportive of the observed OS benefit with tisotumab vedotin
- The safety profile of tisotumab vedotin was manageable and tolerable, and consistent with previous experience[1]
- Based on these data, tisotumab vedotin should be considered a potential new standard of care for patients who have progressed after 1L systemic therapy

1. Coleman RL. Lancet Oncol. 2021:609-619.

Acknowledgements

- Thank you to the 502 patients and their families for their participation.
- This study was funded by Genmab (Copenhagen, Denmark) and Seagen Inc. (Bothell, WA, USA). Tisotumab vedotin is being co-developed by Genmab and Seagen Inc.
- Jennifer Yang, PhD, of Seagen Inc. provided medical writing and editorial support with funding from Seagen Inc., in accordance with Good Publication Practice guidelines.

A-AGO	AGO	BGOG	CEEGOG	DGOG	GEICO	GINECO	NSGO-CTU	LACOG	GOTIC	KGOG	GOG
Petru Polterauer	Woelber Mach Heitz Trillsch	Vergote Baurain Denys Gennigens Henry Honhon Palastro Teurfs Van Nieuwenhuysen Van Gorp	Cibula Melichar Zikan Bagameri Poka Kocsis Bednarikova	Westermann Lalisang Ottevanger Boere Witteveen	Perez-Fidalgo Garcia Perez Oaknin Manso Sanchez Redondo Sanchez Gonzalez-Martin	Angelergues Lebreton Gladieff Joly Kalbacher Leary Lortholary Eberst Hardy-Bessard Kaminsky	Mirza Hietanen Auranen Lindemann Sundset Bjurberg Dahlstrand Lindahl Anttila Koliadi	Raimondo Cruz Reyes Contreras Baltz Hehn Giornelli Molina Damian Melo Maluf da Silveira Nogueira Ribeiro Franke Pimentel Oppermann Calle	Fujiwara Yonemori Miyagi Nakai Yokota Hasegawa Kamiura Matsumoto Nakamura Iwata Yamaguchi Nakamura Watari Okamoto Kiuchi Nishio Katsumata Takhara Suzuki Nakamura Aoki Mochizuki Toshiaki Nagao Baba Harano Yunokawa Kobayahi Kato Hidenori Kato Hisamori Taira Takano	Lee JY Kim BG Kim HS Jeon Lim No Kim MK Kim JH Choi Kim YH Kim MH Jeong Lee SJ Kim YM Shin	Slomovitz Randall Tewari Leath Ghamande Boyd Van Le Cosgrove Duska Holschneider Barroilhet Fishman Zakhour Thaker Gordinier Roque Walters Haygood Santin Monk Teneriello Thomes-Pepin Anderson Buscema Cloven Lee C Black Aylesworth Salinas Priebe McCollum Schiavone Reid Bixel Rose Jordan

CTI	MITO	NCRI	PGOG	Canada	China	Singapore	Taiwan
Calvert	De Giorgi Lorusso Mangili De Vivo Scollo	Forrest Barraclough Banerjee Sadozye Ang	Mackowiak-Matejczyk	Covens Kolinsky Lheureux Tinker Hopkins Samouelian	Li Chen Wu Zhou	Chay Lim	Chao Wang PH Chang

Study Sponsor

Nicacio
Whalley
Markle
Chen
Teng
Soumaoro

ENGOT Statistician

Laenen

IDMC

Reed
Cho
George
Gillen
Wenham

Plain Language Summary

innovaTV 301/ENGOT-cx12/GOG-3057: A Global, Randomized, Open-Label, Phase 3 Study of Tisotumab Vedotin vs Investigator's Choice of Chemotherapy in 2L or 3L Recurrent or Metastatic Cervical Cancer

Vergote et al. ESMO 2023

Why was this research needed?

- Few treatment options are available for patients with recurrent or metastatic cervical cancer (r/mCC) whose disease persists or comes back after being treated
- Previously, tisotumab vedotin received accelerated approval in the United States for previously treated r/mCC based on lasting response and treatable side effects
- In this study, tisotumab vedotin was compared to chemotherapy for the treatment of r/mCC with the goal of showing improved survival

What were the results and why are the findings meaningful?

- In patients with previously treated r/mCC, tisotumab vedotin treatment resulted in lower risk of death or disease progression. As a whole, patients who got tisotumab vedotin lived longer and had better tumor response compared to patients who got chemotherapy
- Treatment with tisotumab vedotin is tolerable and side effects can be managed
- Tisotumab vedotin is a potential new standard of care for patients with r/mCC who progressed after the first-line treatment

Where can I find more information?

clinicaltrials.gov/ct2/show/NCT04697628

Seagen | Genmab