Gynecologic Malignancies: Targeted Therapy-IO-Chemo Combinations

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Lecture outline

- Briefly discuss actionable immunotherapy targets
- Review immunotherapy/chemo combos for cervical cancer
- Review immunotherapy/chemo combos for endometrial cancer
- Review immunotherapy/chemo combos for ovarian cancer
- Questions

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Introduction

- **Once 1st line platinum based systemic therapy fails, there is no established 2nd line standard**

- **Pembrolizumab is approved in 2nd in patients with PD-L1 +ve tumors with a modest objective RR of 14%.**

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THE LANCET
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Articles

Efficacy and safety of tisotumab vedotin in previously treated recurrent or metastatic cervical cancer (innovaTV 204/GOG-3023/ENGOT-cx6): a multicentre, open-label, single-arm, phase 2 study

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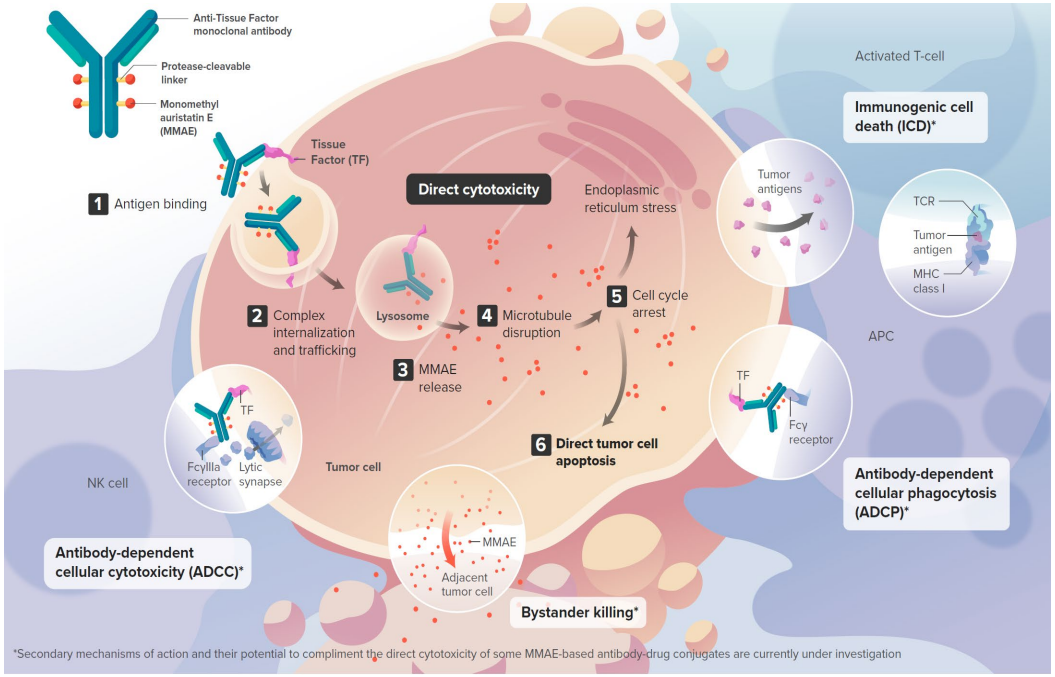
• Proposed MOA of Tisotumab Vedotin

- Tisotumab vedotin is an investigational antibody–drug conjugate directed to TF and covalently linked to the microtubule-disrupting agent MMAE via a protease-cleavable linker[1,2]
  - TF is a protein highly expressed in cervical cancer and other solid tumors[3-6]
- Multimodal MOA of tisotumab vedotin[1,2,7]
  - Direct cytotoxicity
  - Bystander killing
  - Immunogenic cell death
  - ADCC
  - ADCP



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. Forster Y et al. Clin Chim Acta. 2006;364:12-21. 4. Pan L et al. Mol Med Rep. 2019;19:2077-2086. 5. Cocco E et al. BMC Cancer. 2011;11:263. 6. Zhao X et al. Exp Ther Med. 2018;16:4075-4081. 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.

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• 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

→ **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

Primary Endpoint

- ORR[c] per RECIST v1.1, assessed by IRC

Secondary Endpoints

- ORR, 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]Responses were confirmed by subsequent repeat imaging performed ≥4 weeks after initial response assessment.
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; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; TTR, time to response.

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• Patient Disposition & Treatment Exposure

Patient Disposition[a]	N=101
Patients with ongoing treatment, n (%)	**4 (4)**
Patients 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 ongoing on 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.

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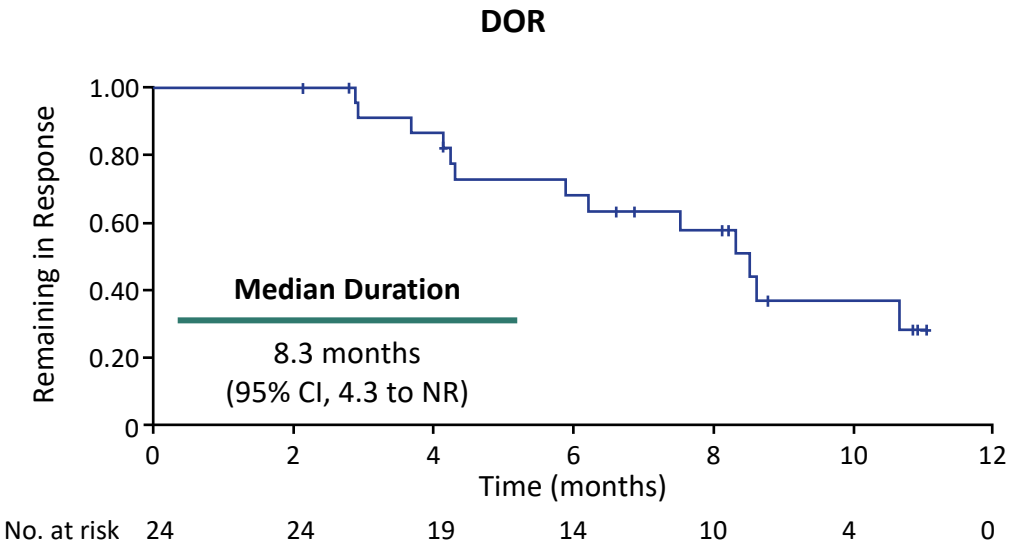
• Antitumor Activity by IRC Assessment

	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)
Disease control rate (95% CI),[b] %	72 (62.5−80.7)



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. [b]Patients with a confirmed response (CR or PR confirmed at least 4 weeks later) or SD (as measured at least 5 weeks after the first dose of tisotumab vedotin).
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.

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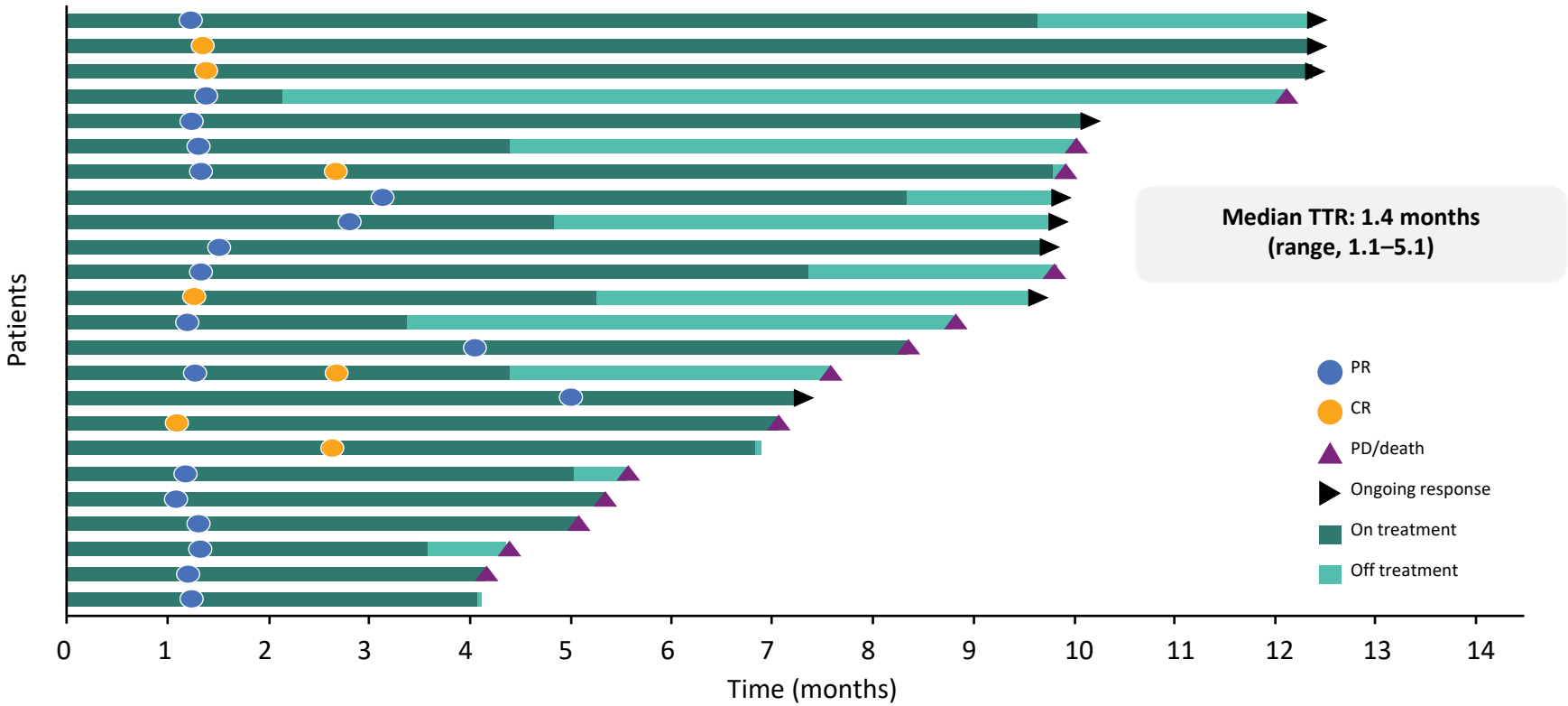
• Confirmed Responders by IRC Assessment



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.

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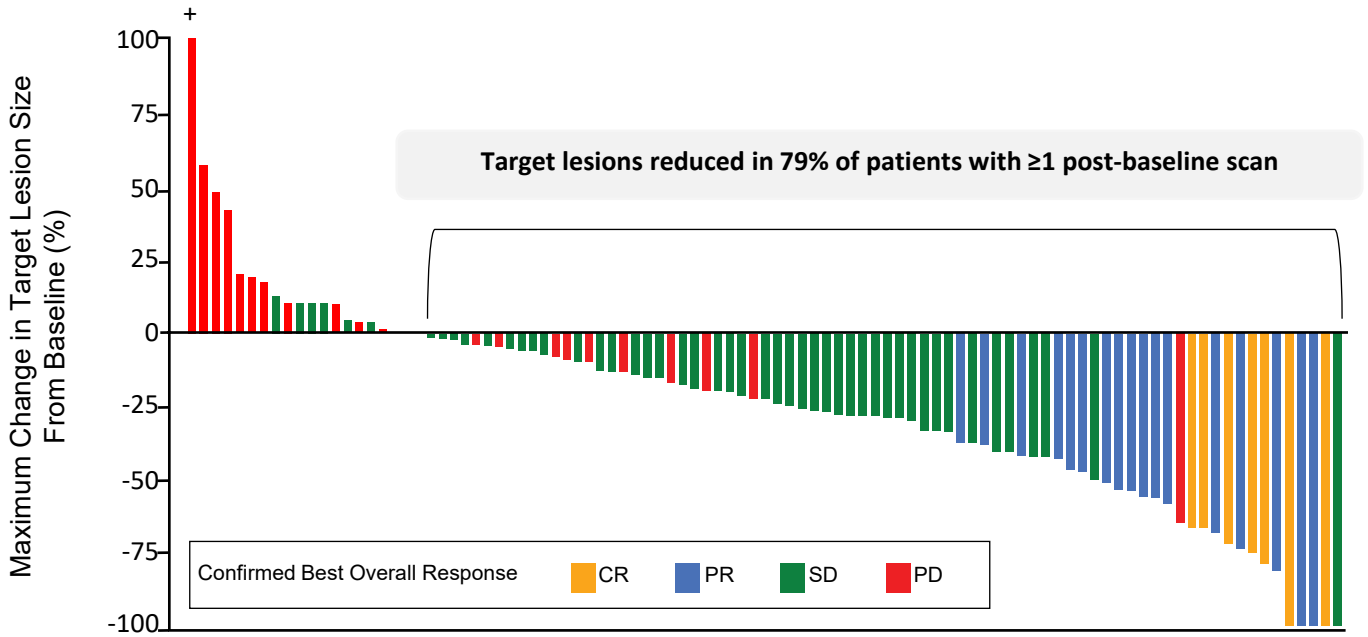
• Maximum Change in Target Lesion Size
• by IRC Assessment



Data cutoff: February 06, 2020. Median duration of follow-up: 10.0 months. + indicates a change greater than 100%.
The 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.

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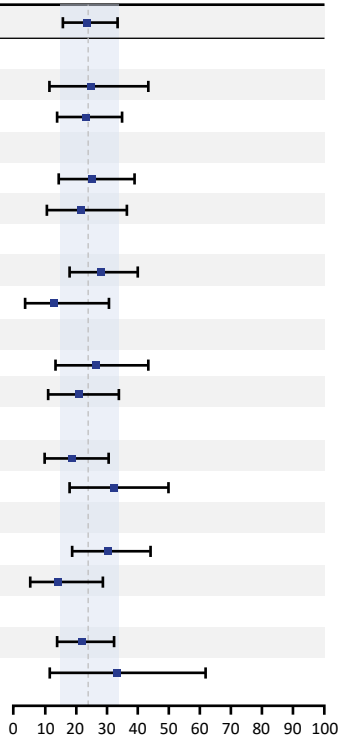
• ORR Subgroup Analysis

Subgroup	n/N	% (95% CI)	ORR% (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.

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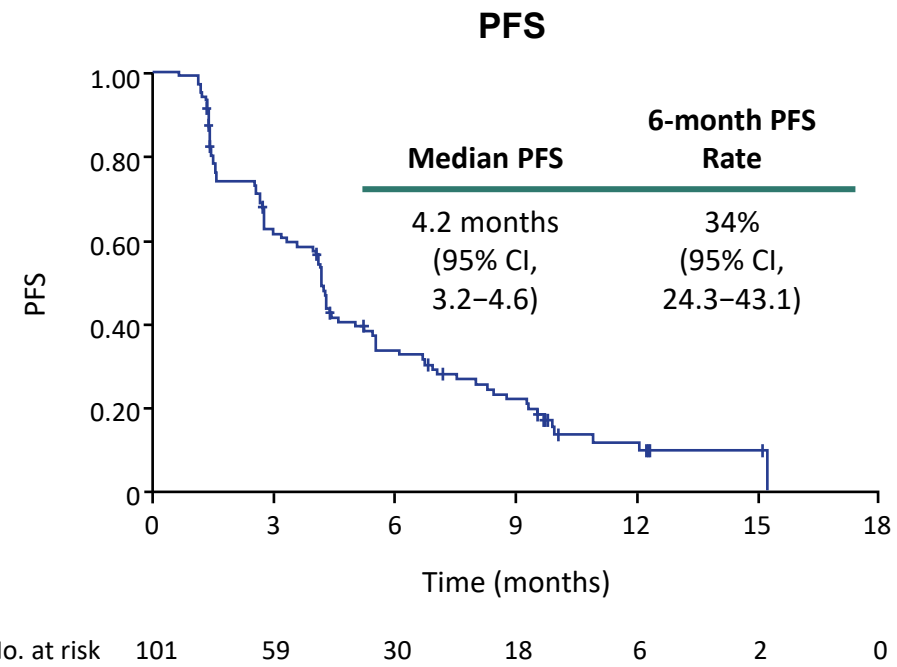
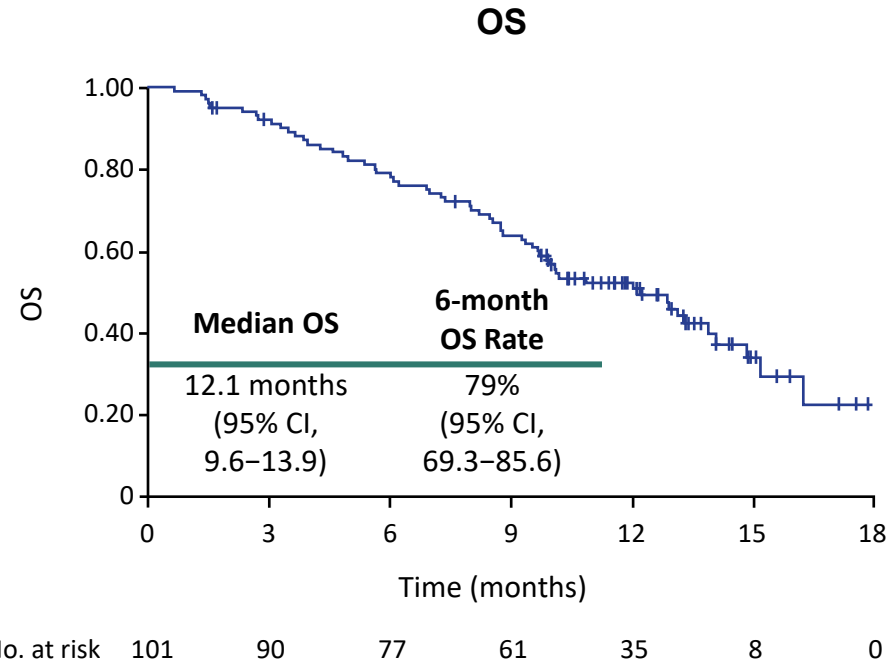
• PFS by IRC Assessment and OS





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

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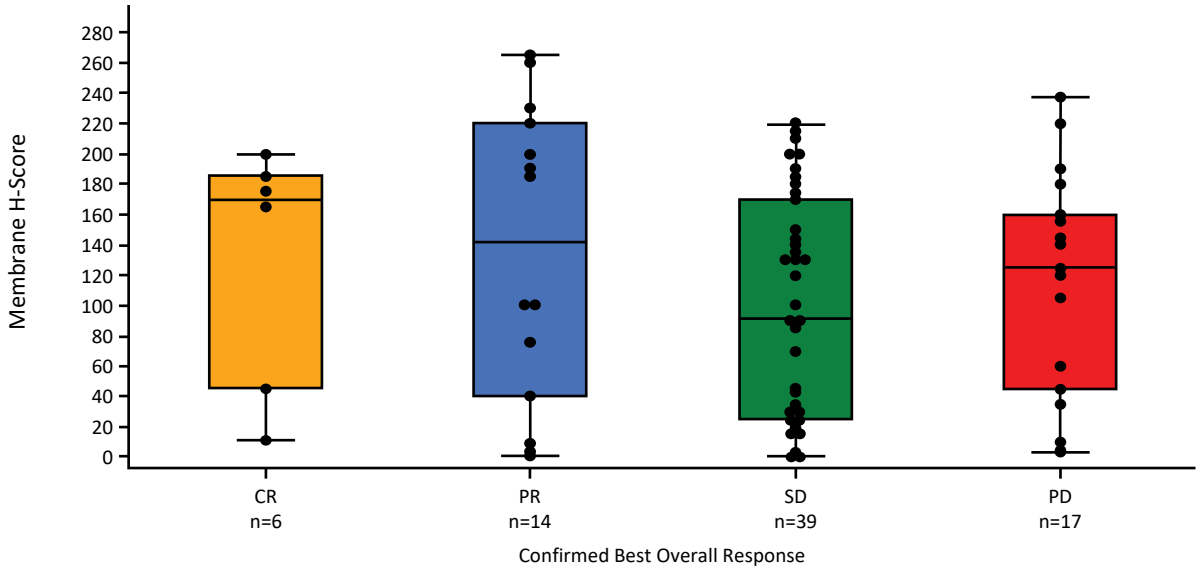
• Tissue Factor Expression Analyses

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

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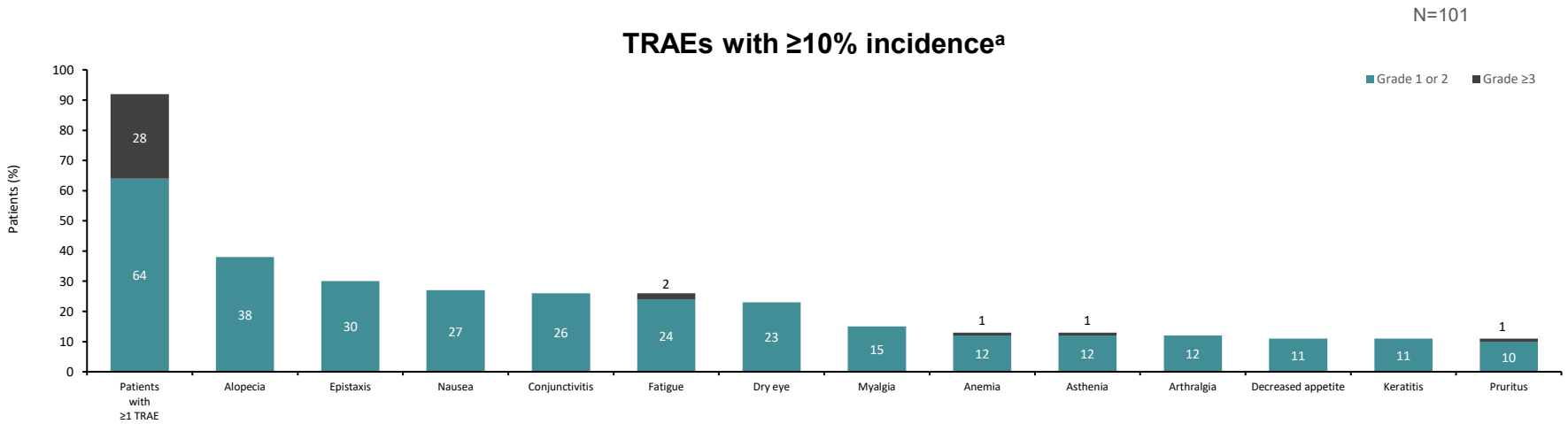
• Most Common TRAEs



- **Most TRAEs with tisotumab vedotin were grade 1/2 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.

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer

N. Colombo, C. Dubot, D. Lorusso, M.V. Caceres, K. Hasegawa, R. Shapira-Frommer, K.S. Tewari, P. Salman, E. Hoyos Usta, E. Yañez, M. Gümüş, M. Olivera Hurtado de Mendoza, V. Samouëlian, V. Castonguay, A. Arkhipov, S. Toker, K. Li, S.M. Keefe, and B.J. Monk, for the KEYNOTE-826 Investigators*

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ESMO 2021 LB

Pembrolizumab plus Chemotherapy versus Placebo plus Chemotherapy for Persistent, Recurrent, or Metastatic Cervical Cancer: Randomized, Double-Blind, Phase 3 KEYNOTE-826 Study

Nicoletta Colombo,[1] Coraline Dubot,[2] Domenica Lorusso,[3] Valeria Caceres,[4] Kosei Hasegawa,[5] Ronnie Shapira-Frommer,[6] Krishnansu S. Tewari,[7] Pamela Salman,[8] Edwin Hoyos Usta,[9] Eduardo Yañez,[10] Mahmut Gümüş,[11] Mivael Olivera Hurtado de Mendoza,[12] Vanessa Samouëlian,[13] Vincent Castonguay,[14] Alexander Arkhipov,[15] Sarper Toker,[16] Kan Li,[16] Stephen M. Keefe,[16] Bradley J. Monk,[17] on behalf of the KEYNOTE-826 Investigators

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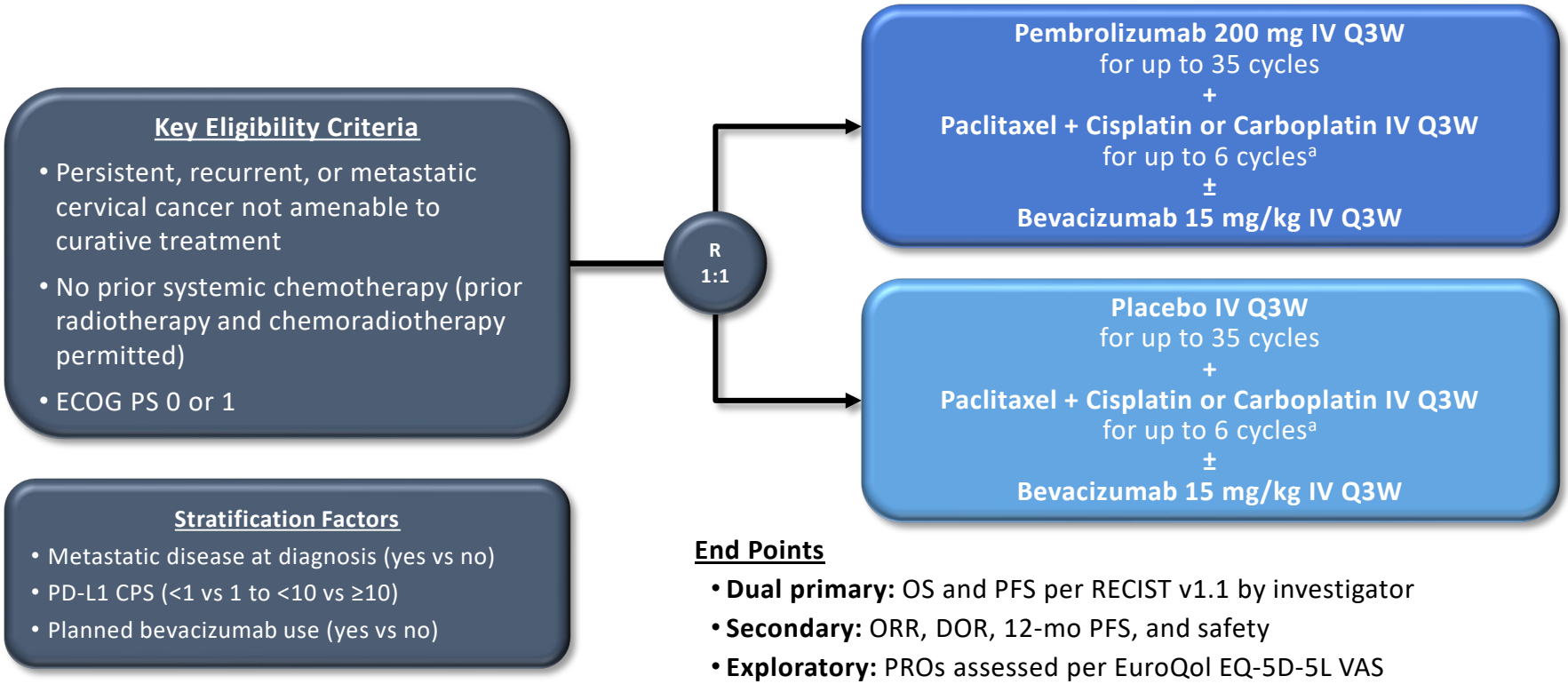
KEYNOTE-826: Randomized, Double-Blind, Phase 3 Study



End Points

- **Dual primary:** OS and PFS per RECIST v1.1 by investigator
- **Secondary:** ORR, DOR, 12-mo PFS, and safety
- **Exploratory:** PROs assessed per EuroQol EQ-5D-5L VAS

[a]Paclitaxel: 175 mg/m^2. Cisplatin: cisplatin 50 mg/m^2. Carboplatin: AUC 5 mg/mL/min. The 6-cycle limit was introduced with protocol amendment 2, although participants with ongoing who were tolerating chemotherapy could continue beyond 6 cycles after sponsor consultation.
CPS, combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100); PROs, patient-reported outcomes; VAS, visual analog scale. KEYNOTE-826 ClinicalTrials.gov identifier, NCT03635567.

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Baseline Characteristics, All-Comer Population

	Pembro Arm[a] (N = 308)	Placebo Arm[a] (N = 309)
Age, median (range)	51 y (25-82)	50 y (22-79)
ECOG PS 1	128 (41.6%)	139 (45.0%)
Squamous cell carcinoma	235 (76.3%)	211 (68.3%)
PD-L1 CPS		
<1	35 (11.4%)	34 (11.0%)
1 to <10	115 (37.3%)	116 (37.5%)
≥10	158 (51.3%)	159 (51.5%)
Prior therapy		
Chemoradiation or radiation with surgery	71 (23.1%)	79 (25.6%)
Chemoradiation or radiation only	156 (50.6%)	142 (46.0%)
Surgery only	23 (7.5%)	24 (7.8%)
None	58 (18.8%)	64 (20.7%)

	Pembro Arm[a] (N = 308)	Placebo Arm[a] (N = 309)
Stage at initial diagnosis (FIGO 2009/NCCN 2017 criteria)		
I	67 (21.8%)	58 (18.8%)
II	85 (27.6%)	93 (30.1%)
III	5 (1.6%)	8 (2.6%)
IIIA	4 (1.3%)	8 (2.6%)
IIIB	46 (14.9%)	42 (13.6%)
IVA	7 (2.3%)	4 (1.3%)
IVB	94 (30.5%)	96 (31.1%)
Disease status at study entry		
Metastatic[b]	58 (18.8%)	64 (20.7%)
Persistent or recurrent with distant metastases	199 (64.6%)	179 (57.9%)
Persistent or recurrent without distant metastases	51 (16.6%)	66 (21.4%)
Bevacizumab use during the study	196 (63.6%)	193 (62.5%)

[a]The treatment regimen in both arms included chemo ± bev.
[b]Includes participants with para-aortic lymph node involvement. These participants were diagnosed with stage IVB disease and entered the study with no prior treatment for cervical cancer.
Data cutoff date: May 3, 2021.

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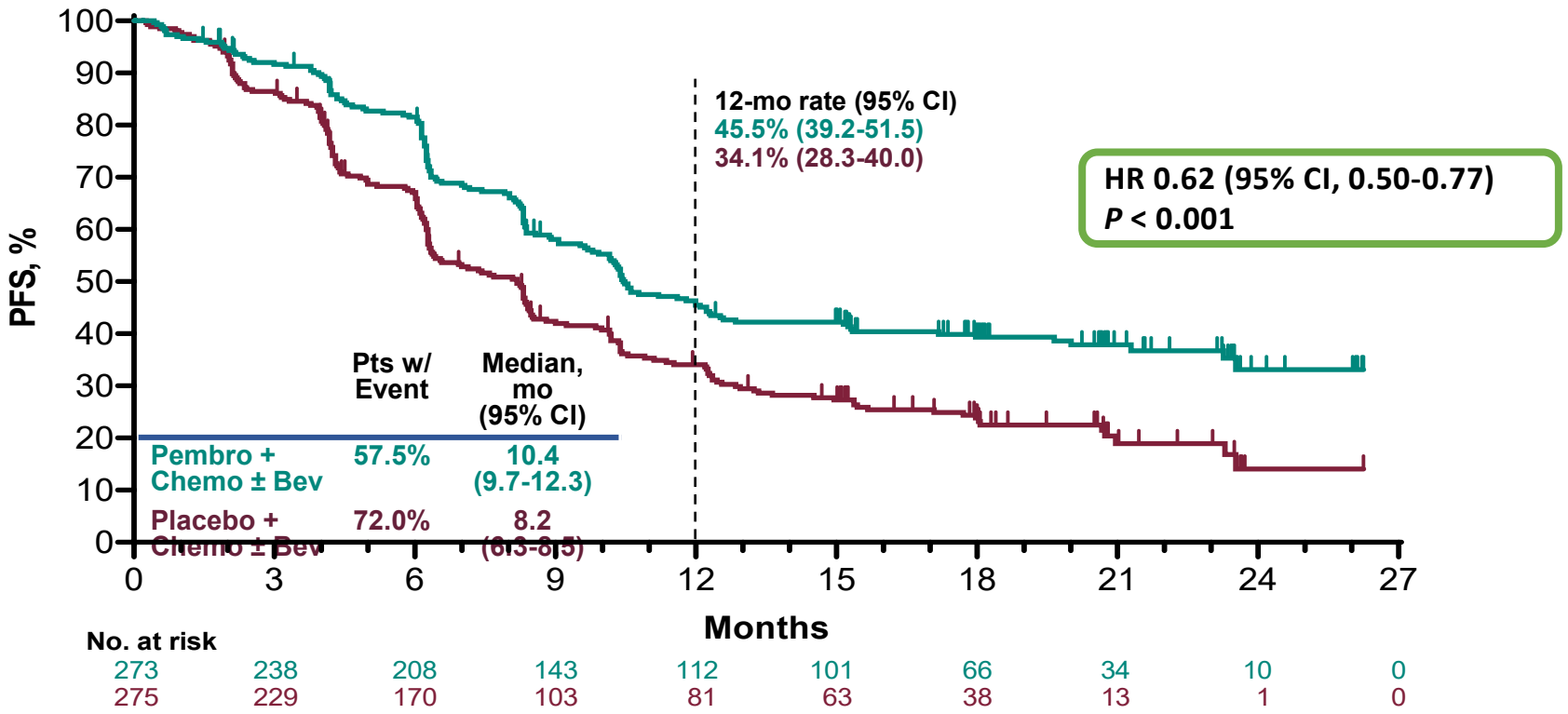
PFS: PD-L1 CPS ≥1 Population



Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: May 3, 2021.

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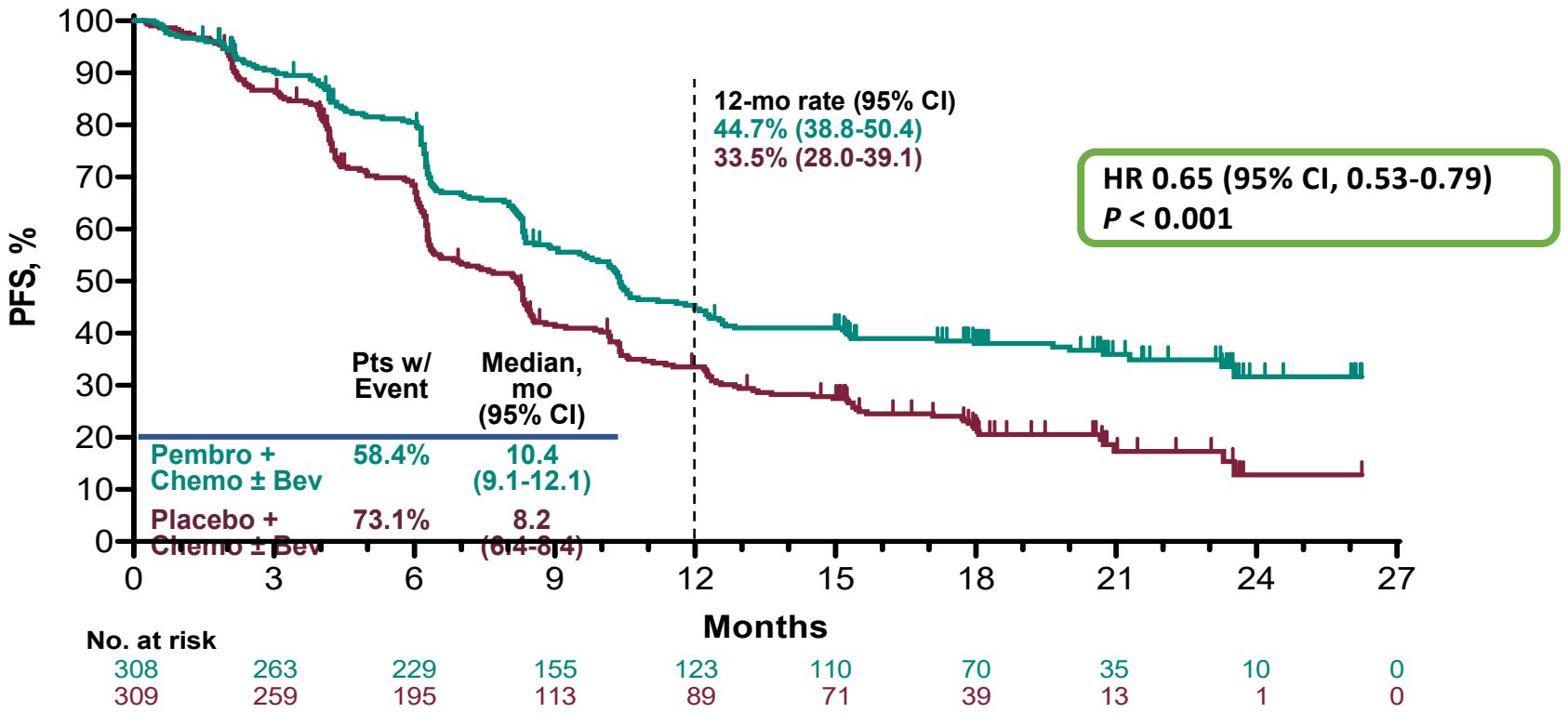
PFS: All-Comer Population



Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: May 3, 2021.

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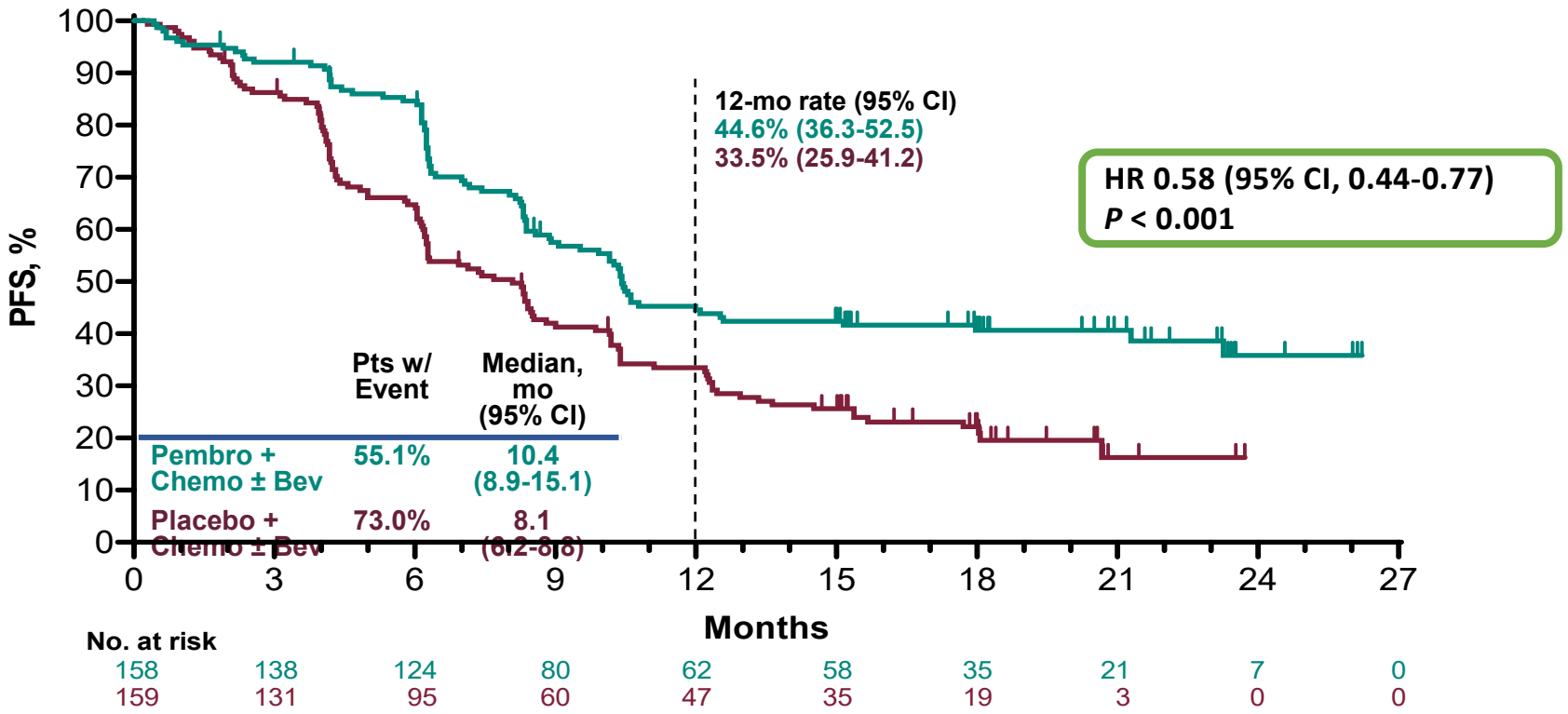
PFS: PD-L1 CPS ≥10 Population



Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: May 3, 2021.

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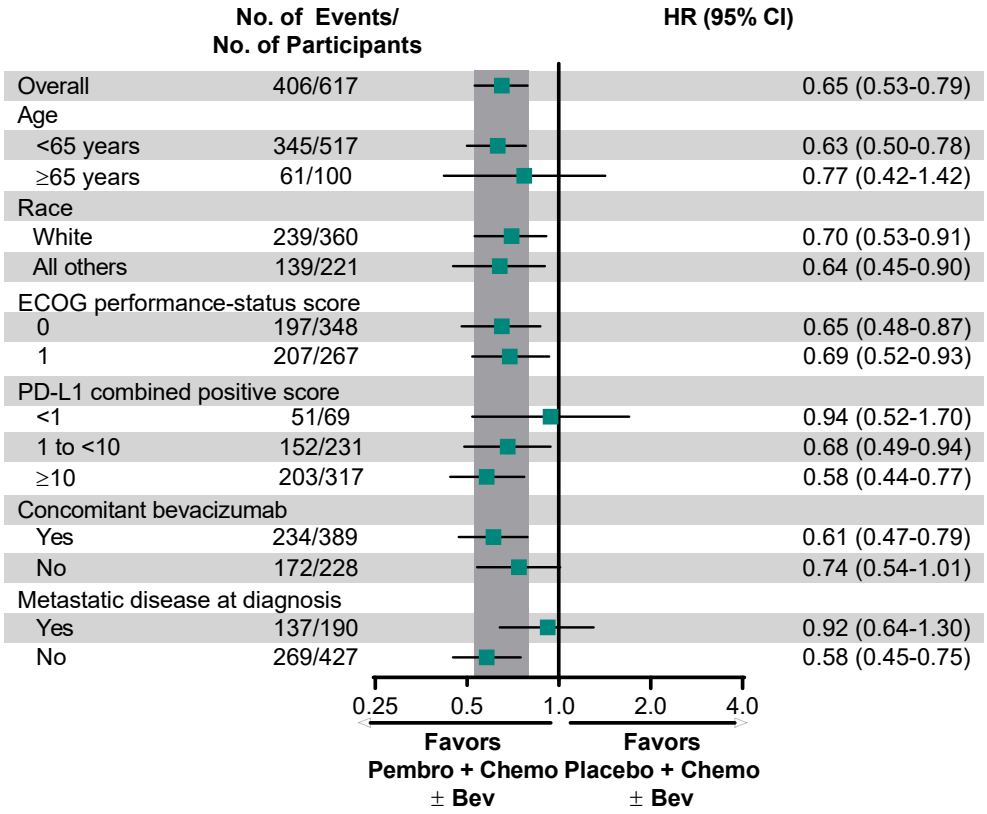
PFS: Protocol-Specified Subgroups, All-Comer Population



Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: May 3, 2021.

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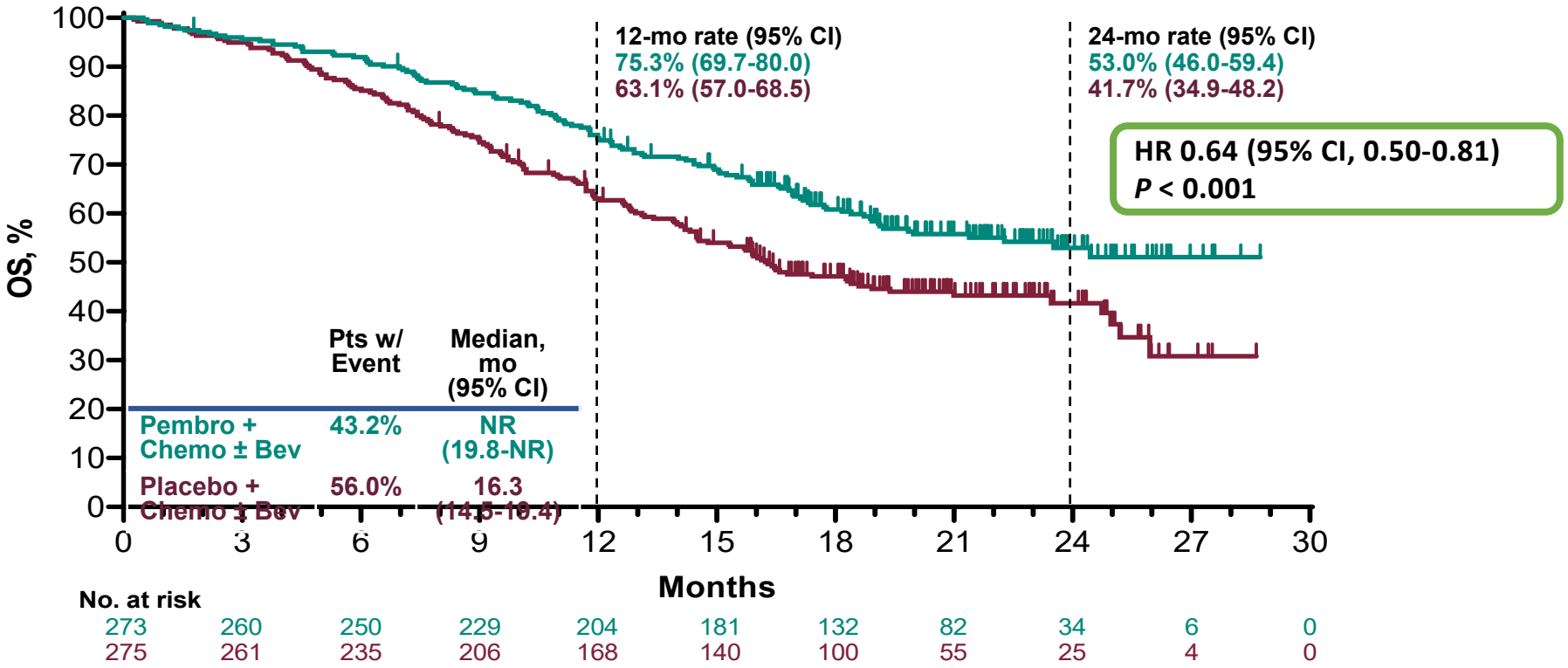
OS: PD-L1 CPS ≥1 Population



Data cutoff date: May 3, 2021.

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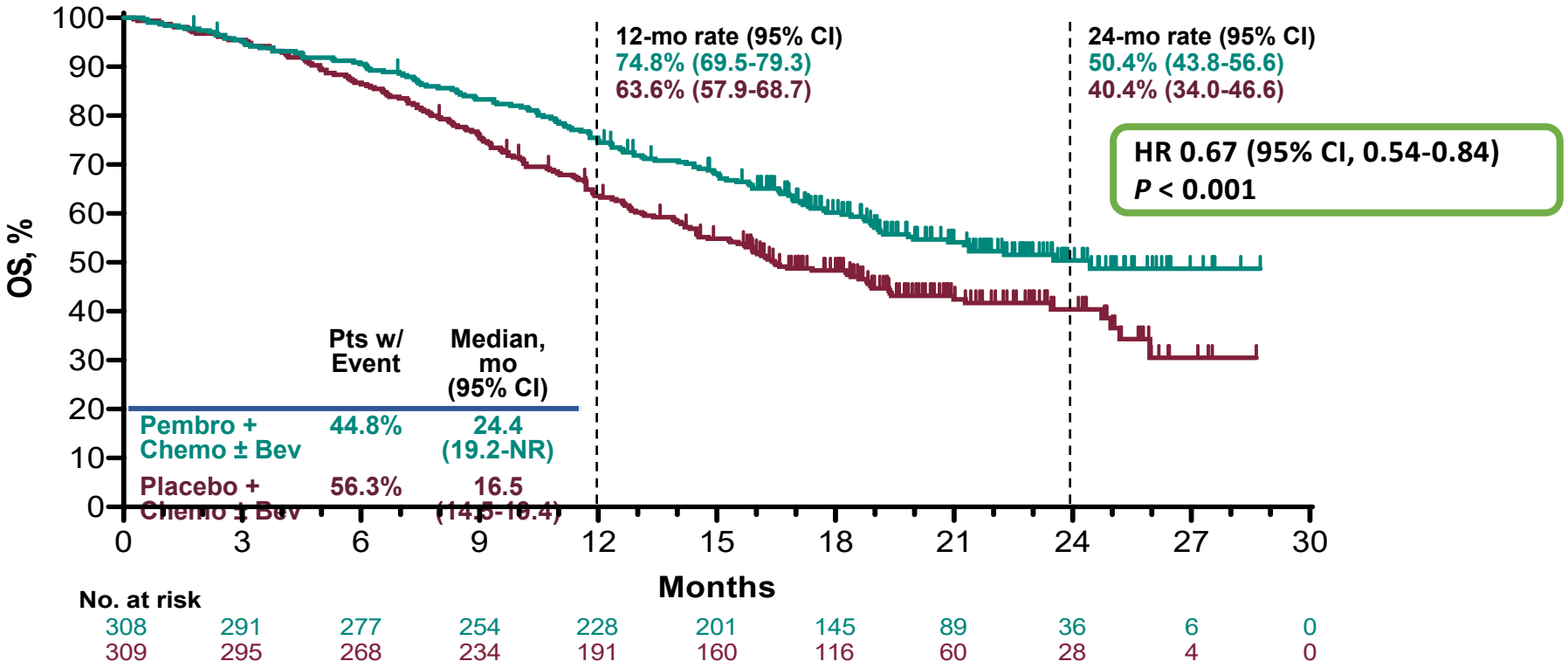
OS: All-Comer Population



Data cutoff date: May 3, 2021.

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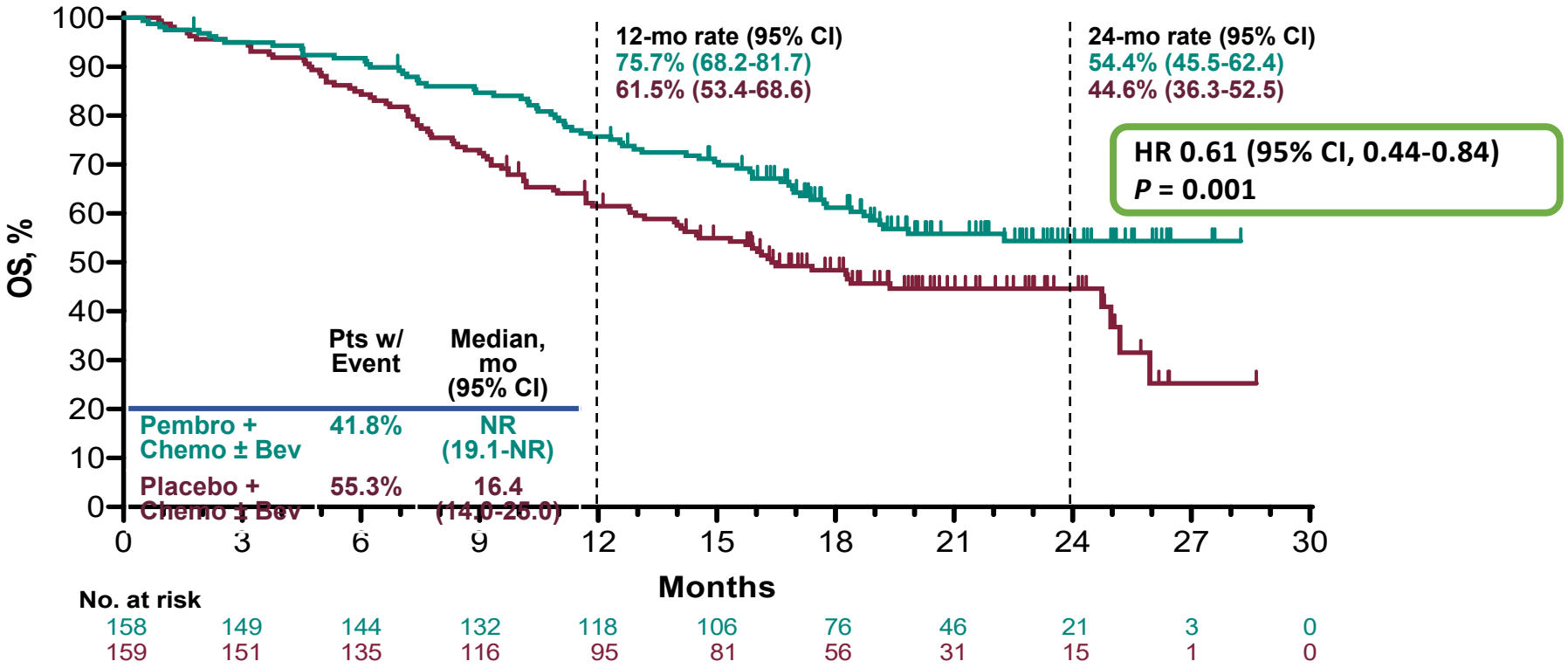
OS: PD-L1 CPS ≥10 Population



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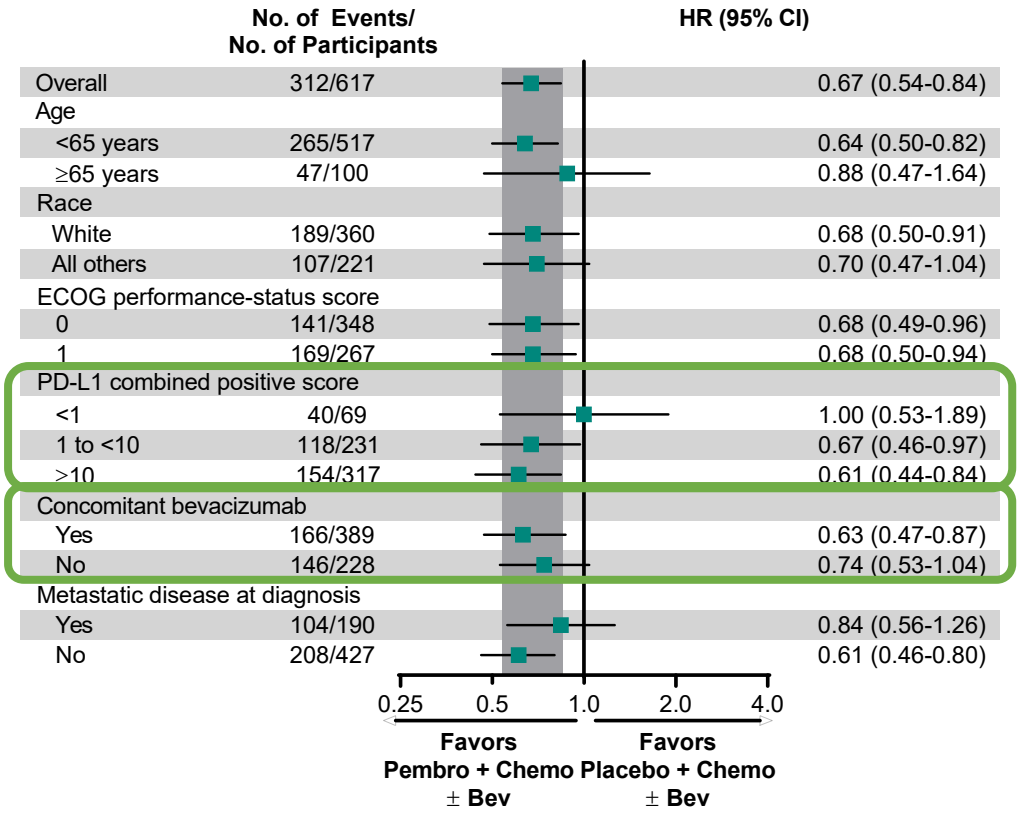
OS: Protocol-Specified Subgroups, All-Comer Population



Data cutoff date: May 3, 2021.

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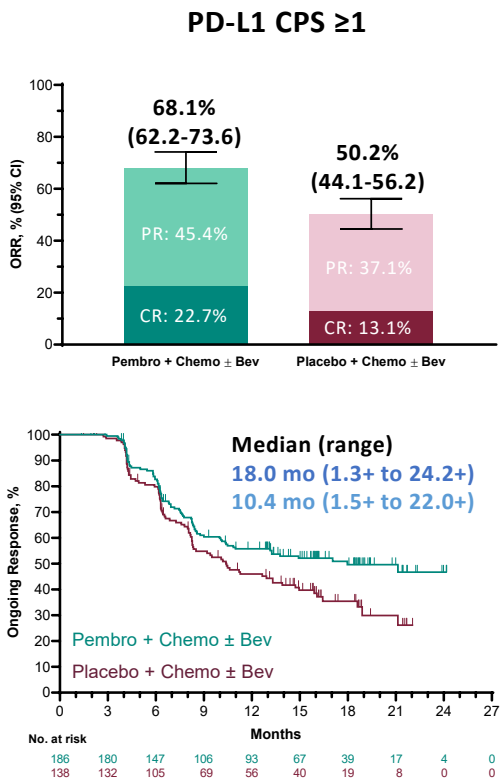
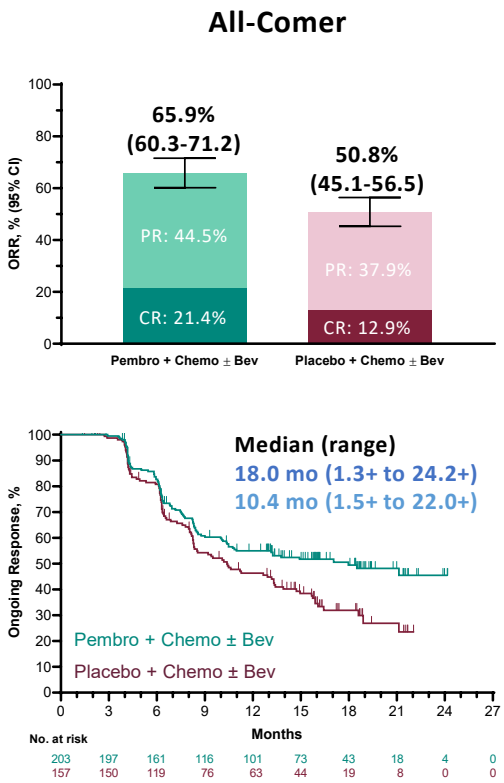
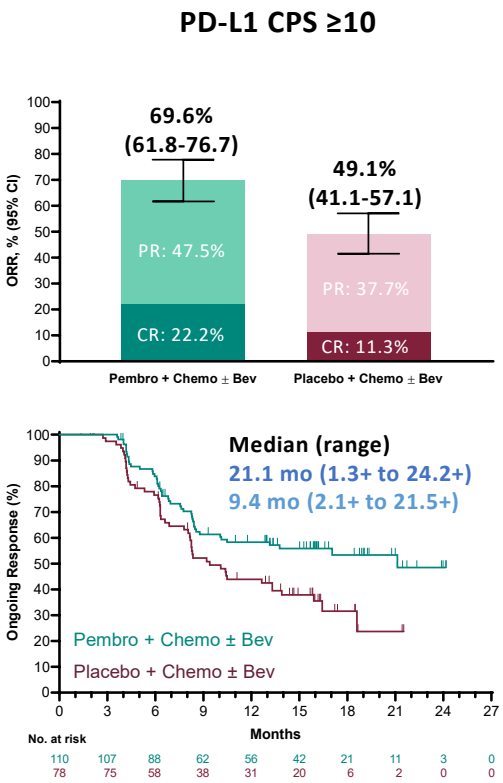
ORR and DOR: All Analysis Populations







Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: May 3, 2021.

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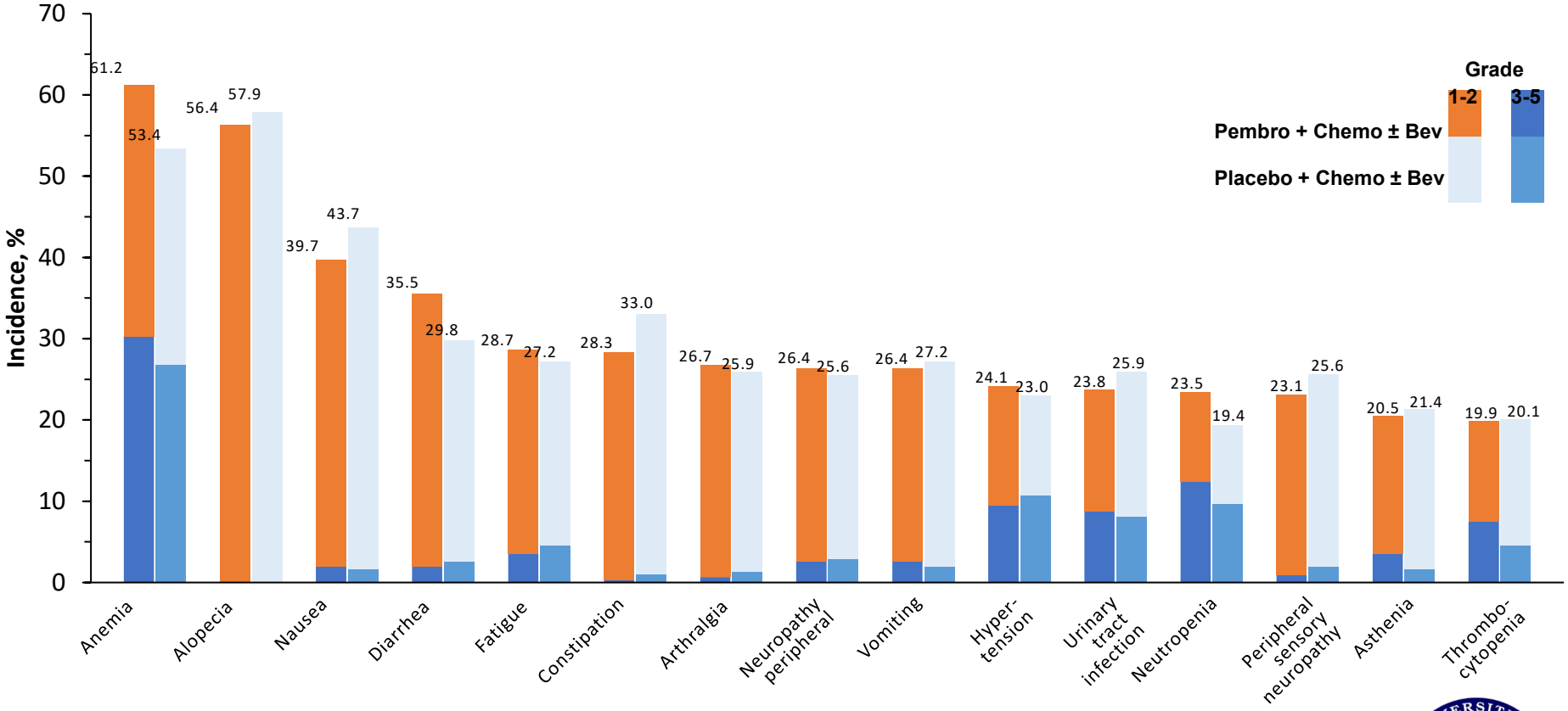
All-Cause AEs, Incidence ≥20% in Either Arm



Data cutoff date: May 3, 2021.

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ENDOMETRIAL CANCER

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ENDOMETRIAL CANCER

- **Most common gynecologic cancer**
- **Active chemotherapeutic agents: paclitaxel + carboplatin, doxorubicin**
- **For patients whose tumors are MSH, PD-L1 or high TMB, pembrolizumab is an option once chemo has failed. This group is approximately 25% of patients.**

Additional options are therefore highly desirable

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A multicenter, open-label, randomized, phase 3 study to compare the efficacy and safety of lenvatinib in **combination with pembrolizumab vs treatment of physician's choice in patients with advanced endometrial cancer: Study 309/KEYNOTE-775**

Vicky Makker[1]; Nicoletta Colombo[2]; Antonio Casado Herráez[3]; Alessandro D. Santin[4]; Emeline Colomba[5]; David S. Miller[6]; Keiichi Fujiwara[7]; Sandro Pignata[8]; Sally Baron-Hay[9]; Isabelle Ray-Coquard[10]; Ronnie Shapira-Frommer[11]; Kimio Ushijima[12]; Jun Sakata[13]; Kan Yonemori[14]; Yong Man Kim[15]; Eva M. Guerra[16]; Ulus A. Sanli[17]; Mary M. McCormack[18]; Jie Huang[19]; Alan D. Smith[20]; Stephen Keefe[21]; Lea Dutta[19]; Robert J. Orlowski[21]; Domenica Lorusso[22]

SGO 2021 VIRTUAL ANNUAL MEETING ON WOMEN'S CANCER®

Society of Gynecologic Oncology

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Introduction

- There is a high unmet need for effective therapies to treat advanced/recurrent endometrial cancer (EC); no standard second-line treatments have been identified following platinum-based CT[1,2]
- Checkpoint inhibitors have previously shown benefit in MSI-H/ dMMR tumors[3-5]
- Lenvatinib (LEN) + pembrolizumab (pembro) showed compelling efficacy and manageable safety profiles in previously treated advanced/recurrent endometrial carcinoma[6]
- In this phase 3 study (NCT03517449), we compare the efficacy and safety of LEN + pembro versus treatment of physician's choice ([TPC] doxorubicin or paclitaxel) following platinum-based therapy in advanced/recurrent EC

CT, chemotherapy; dMMR, mismatch repair-deficient; MSI-H, microsatellite instability-high.

1.Koh WJ, et al. *J Natl Compr Canc Netw*. 2018;16(2):170-199. 2. Concin N, et al. *Int J Gynecol Cancer*. 2021;31(1):12-39. 3. Marabelle A, et al. *J Clin Oncol*. 2020;38(1):1-10. 4. Oaknin A, et al. *JAMA Oncol*. 2020;6(11):1-7. 5. Azad NS, et al. *J Clin Oncol*. 2020;38(3):214-222. 6. Makker V et al. *J Clin Oncol*. 2020;38:2981-2992.

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Study Design

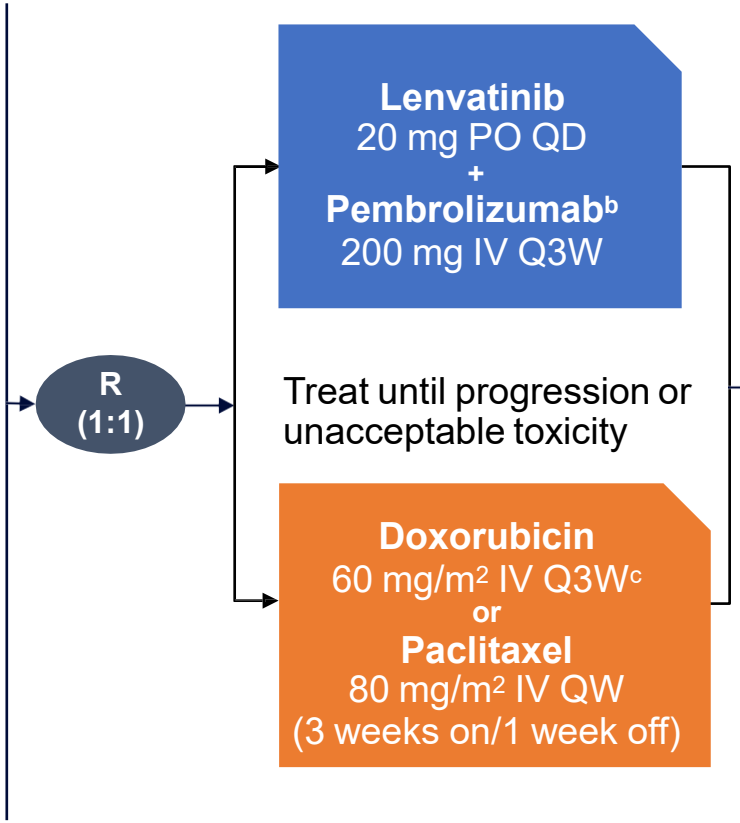
Key eligibility criteria

- Advanced, metastatic, or recurrent endometrial cancer
- Measurable disease by BICR
- 1 Prior platinum-based CT[a]
- ECOG PS 0-1
- Tissue available for MMR testing

Stratification factors

MMR status (pMMR vs dMMR) and further stratification within pMMR by:

- Region (R1: Europe, USA, Canada, Australia, New Zealand, and Israel, vs R2: rest of the world)
- ECOG PS (0 vs 1)
- Prior history of pelvic radiation (Y vs N)



Primary endpoints

- PFS by BICR
- Overall survival

Secondary endpoints

- ORR
- HRQoL
- Pharmacokinetics
- Safety

Key exploratory endpoint

- Duration of response

[a]Patients may have received up to 2 prior platinum-based CT regimens if 1 is given in the neoadjuvant or adjuvant treatment setting. [b]Maximum of 35 doses. [c]Maximum cumulative dose of 500 mg/m^2.

BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; IV, intravenous; PFS, progression-free survival; pMMR, mismatch repair-proficient; ORR, objective response rate; PO, per os (by mouth); QD, once; Q3W, every 3 weeks; QW, once weekly.

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Baseline Characteristics

	LEN + pembro (n = 411)	TPC (n = 416)
Median age (range), years	64 (30-82)	65 (35-86)
MMR status: pMMR / dMMR, %	84.2 / 15.8	84.4 / 15.6
Prior history of pelvic radiation, %	40.9	41.6
ECOG 0 / 1, %[a]	59.9 / 39.9	57.9 / 42.1
Race: White / Black / Asian / other, %[b]	63.5 / 4.1 / 20.7 / 2.9	59.1 / 3.4 / 22.1 / 4.8
Histology at diagnosis, %[c]		
Endometrioid carcinoma High-grade / low-grade / not specified[d]	22.9 / 14.4 / 21.9	21.6 / 13.0 / 26.4
Serous carcinoma	25.1	27.6
Clear cell carcinoma	7.3	4.1
Mixed	5.4	3.8
Prior lines of systemic treatment 1 / ≥ 2, %	72.3 / 27.7	66.6 / 33.4
Prior lines of platinum-based treatment 1 / 2, %[e]	79.3 / 20.2	75.7 / 24.3
Prior neo-adjuvant and/or adjuvant treatment, %	54.5	60.3

[a]0.2% of patients in the LEN + pembro group had an ECOG score deviation of 3. [b]Includes American Indian or Alaska native, native Hawaiian or other Pacific islander and multi-racial patients; 8.8% of patients in the LEN + pembro group and 10.6% of patients in the TPC group were missing information on race. [c]Other histology at diagnosis included mucinous, undifferentiated, and neuroendocrine (LEN + pembro: 1.7%; TPC: 0.96%). Histology was unclassifie d for 0% patients in the LEN + pembro arm, and 0.7% in the TPC arm. [d]The "not specified" category includes endometrioid (grade not specified) and endometrioid with squamous differentia
[e]1 patient in the LEN + pembro arm had ≥ 3 prior lines of platinum-based therapy.

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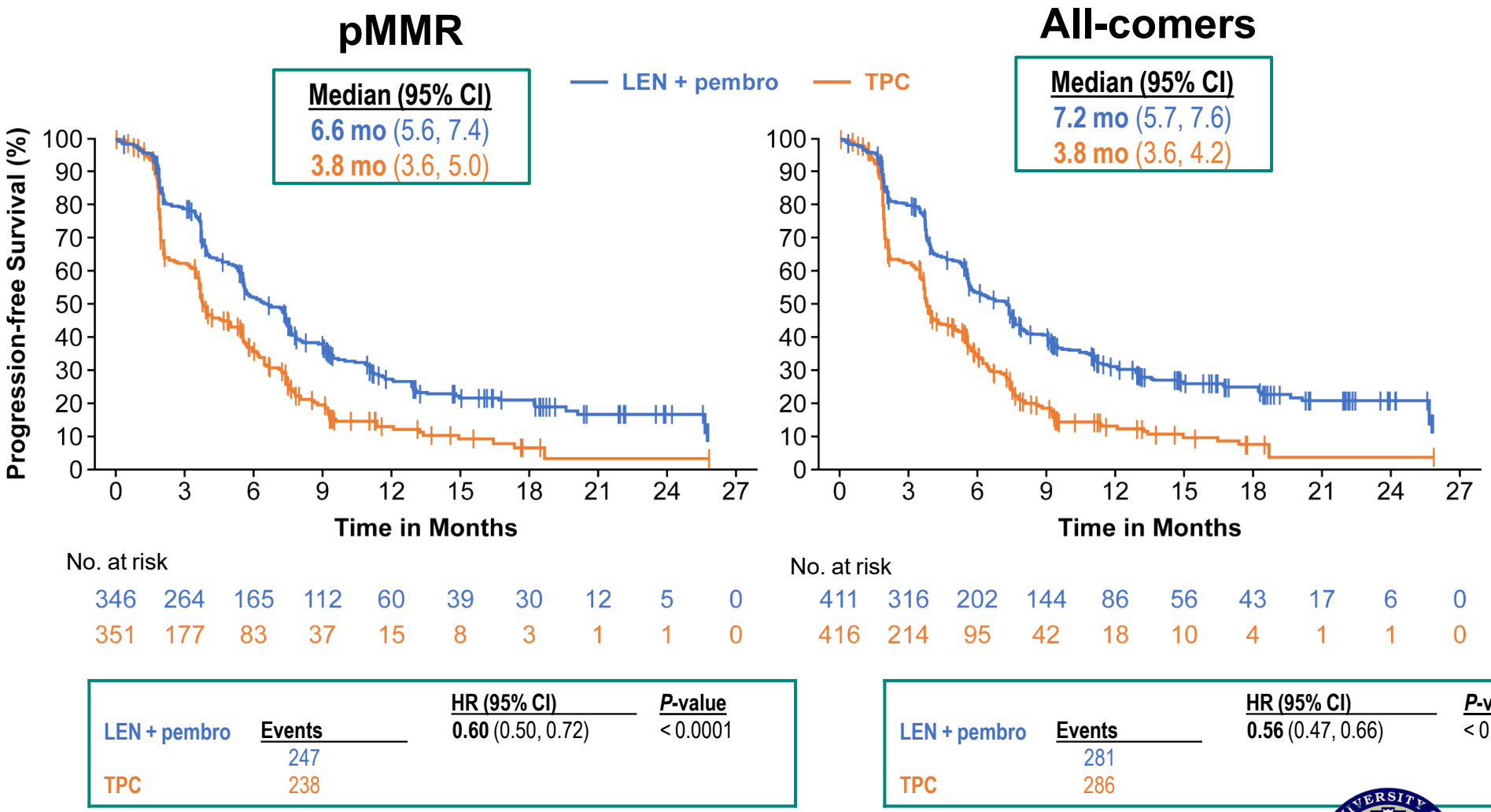
Progression-free Survival[a]



	Events	HR (95% CI)	*P*-value
LEN + pembro	247	**0.60** (0.50, 0.72)	< 0.0001
TPC	238		

	Events	HR (95% CI)	*P*-va
LEN + pembro	281	**0.56** (0.47, 0.66)	< 0.0
TPC	286		

[a]By BICR per Response Evaluation Criteria in Solid Tumors version 1.1.

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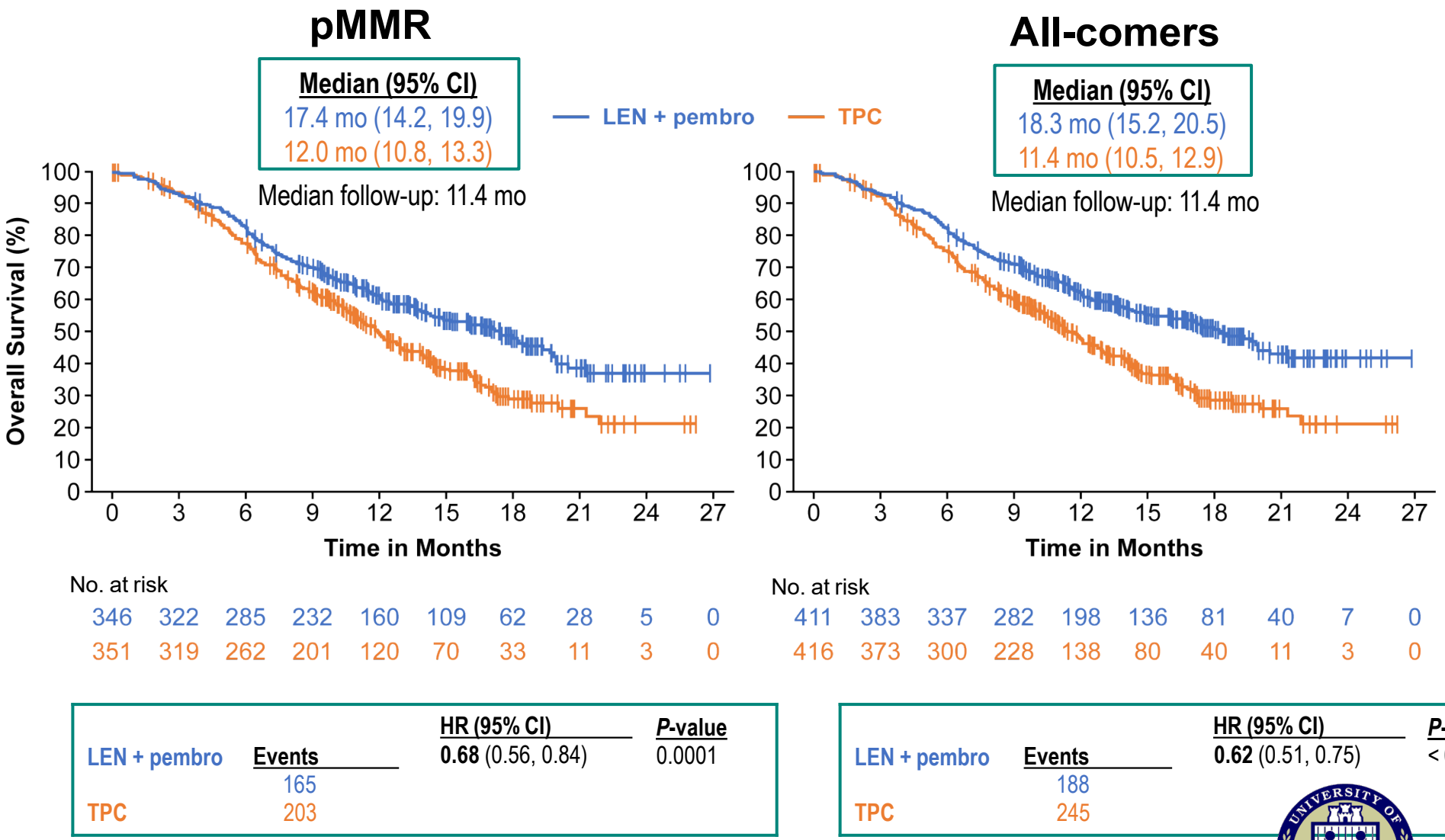
Overall Survival



	Events	HR (95% CI)	*P*-value
LEN + pembro	165	**0.68** (0.56, 0.84)	0.0001
TPC	203		

	Events	HR (95% CI)	*P*-v
LEN + pembro	188	**0.62** (0.51, 0.75)	< 0
TPC	245		

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TEAEs With Frequency ≥ 25% in All-comers

	LEN + pembro (n = 406)		TPC (n = 388)	
	Any Grade	Grade ≥3[a]	Any Grade	Grade ≥3[a]
Patients with any TEAEs, %	99.8	88.9	99.5	72.7
Hypertension	64.0	37.9	5.2	2.3
Hypothyroidism[b]	57.4	1.2	0.8	0.0
Diarrhea	54.2	7.6	20.1	2.1
Nausea	49.5	3.4	46.1	1.3
Decreased appetite	44.8	7.9	21.1	0.5
Vomiting	36.7	2.7	20.9	2.3
Weight decrease	34.0	10.3	5.7	0.3
Fatigue	33.0	5.2	27.6	3.1
Arthralgia	30.5	1.7	8.0	0.0
Proteinuria	28.8	5.4	2.8	0.3
Anemia	26.1	6.2	48.7	14.7
Constipation	25.9	0.7	24.7	0.5
Urinary tract infection	25.6	3.9	10.1	1.0
Headache	24.9	0.5	8.8	0.3
Asthenia	23.6	5.9	24.5	3.9
Neutropenia	7.4	1.7	33.8	25.8
Alopecia	5.4	0.0	30.9	0.5

[a]In the LEN + pembro arm, 5.7% of patients died due to grade 5 events (gastrointestinal disorders: 1.2%, cardiac disorders: 0.5%, general disorders: 1.5%, infections: 0.7%, decreased appetite: 0.2%, neoplasms, nervous system, psychiatric, renal, reproductive, or respiratory disorders: 0.2% each. In the TPC arm, 4.9% of p due to grade 5 events (cardiac disorders: 1%, general disorders: 1.3%, infections, 1.5%, subdural hematoma: 0.3%, respiratory disorders: 0.8%). [b]Adverse a of interest for pembro.

OVARIAN CANCER

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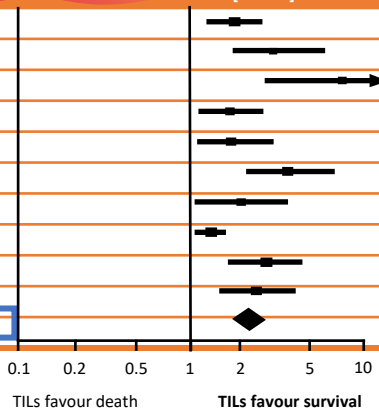
Immunotherapy in Ovarian Cancer: What is the rationale? Correlation between TILs and Survival

Independent of tumour grade, stage or histologic subtype[1]

Study or Subgroup	Log [HR]	SE	Weight (%)	HR [95% CI]
Zhang (2003)	0.61	0.18	12.5	1.84 [1.29–2.62]
Sato (2005)	1.11	0.307	8.8	3.03 [1.66–5.54]
Hamanishi (2007)	2.031	0.518	4.8	7.62 [2.76–21.04]
Callahan (2008)	0.548	0.222	11.2	1.73 [1.12–2.67]
Han (2008)	0.563	0.258	10.1	1.76 [1.06–2.91]
Tomsova (2008)	1.308	0.296	9.1	3.70 [2.07–6.61]
Adams (2009)	0.694	0.315	8.6	2.00 [1.08–3.71]
Clarke (2009)	0.282	0.106	14.5	1.33 [1.08–1.63]
Leffers (2009)	1.02	0.251	10.3	2.77 [1.70–4.54]
Stumpf (2009)	0.895	0.258	10.1	2.45 [1.48–4.06]
Total (95% CI)			**100.0**	**2.24 [1.71–2.92]**



Test for overall effect: p<0.00001
CI, confidence interval; HR, hazard ratio; OC, ovarian cancer;
SE, standard error; TILs, tumour-infiltrating lymphocytes

Hwang et al. Gynecol Oncol 2012

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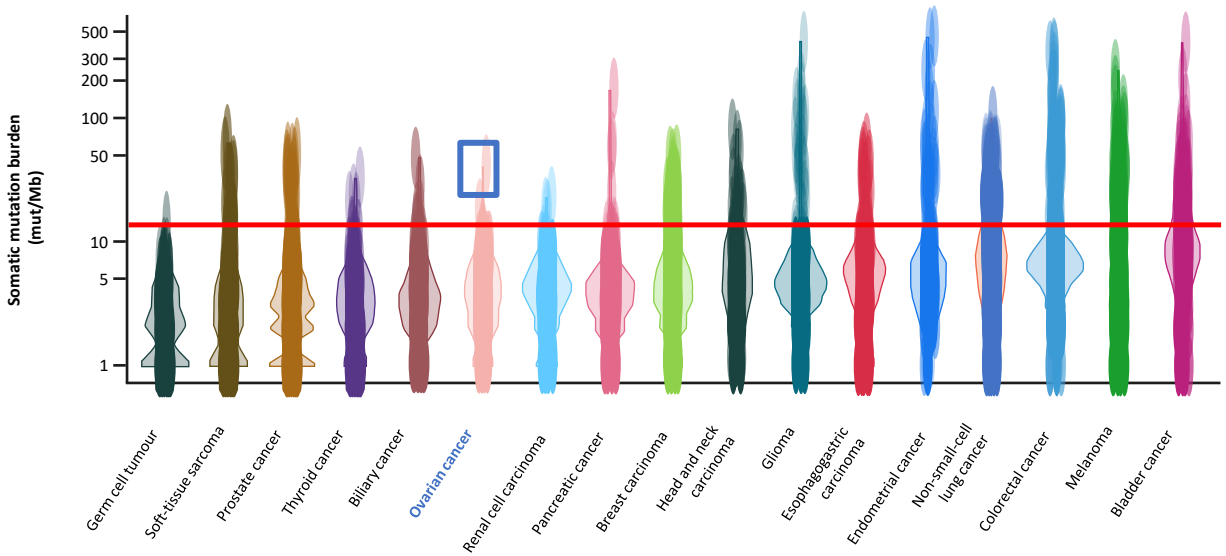
Immunotherapy in Ovarian Cancer: What is the rationale?

OC carries significant levels of mutational load



Red line indicates the threshold for samples with a high mutational burden (13.8 mutations/Mb)
Mb, megabase; OC, ovarian cancer

Zehir et al. Nat Med 2017

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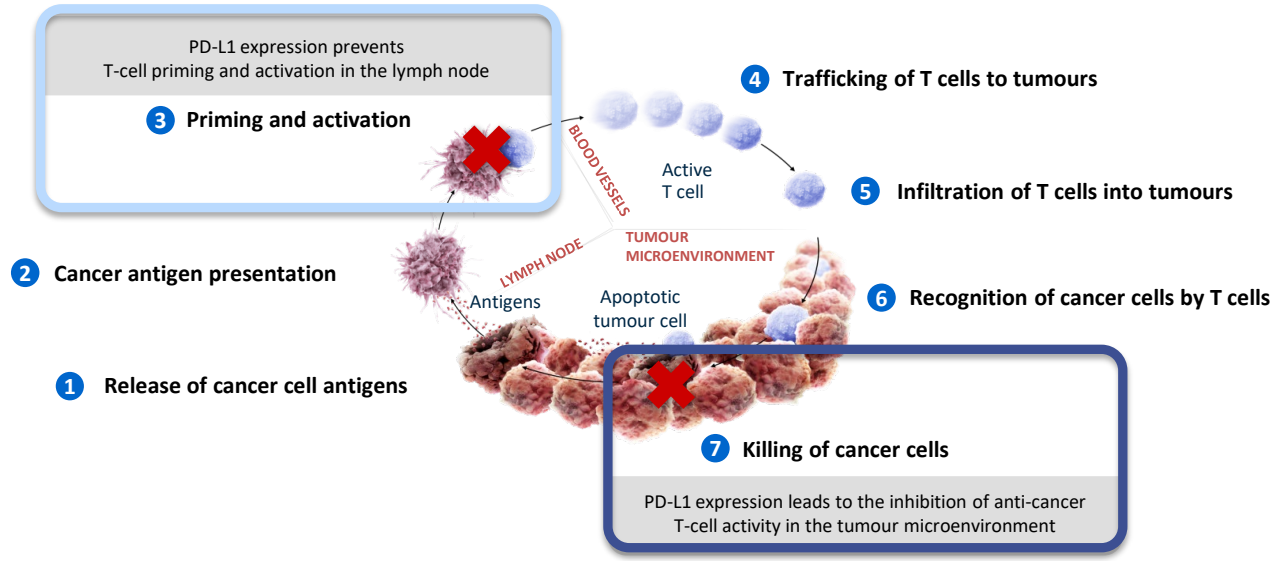
Immunotherapy in Ovarian Cancer: What is the rationale?
PD-L1 and its role in cancer[1–5]



PD-L1, programmed death ligand 1

1. Keir et al. Annu Rev Immunol 2008; 2. Park et al. Blood 2010; 3. Chen et al. Clin Cancer Res 2012
4. Rozali et al. Clin Dev Immunol 2012; 5. Topalian et al. New Engl J Med 2012

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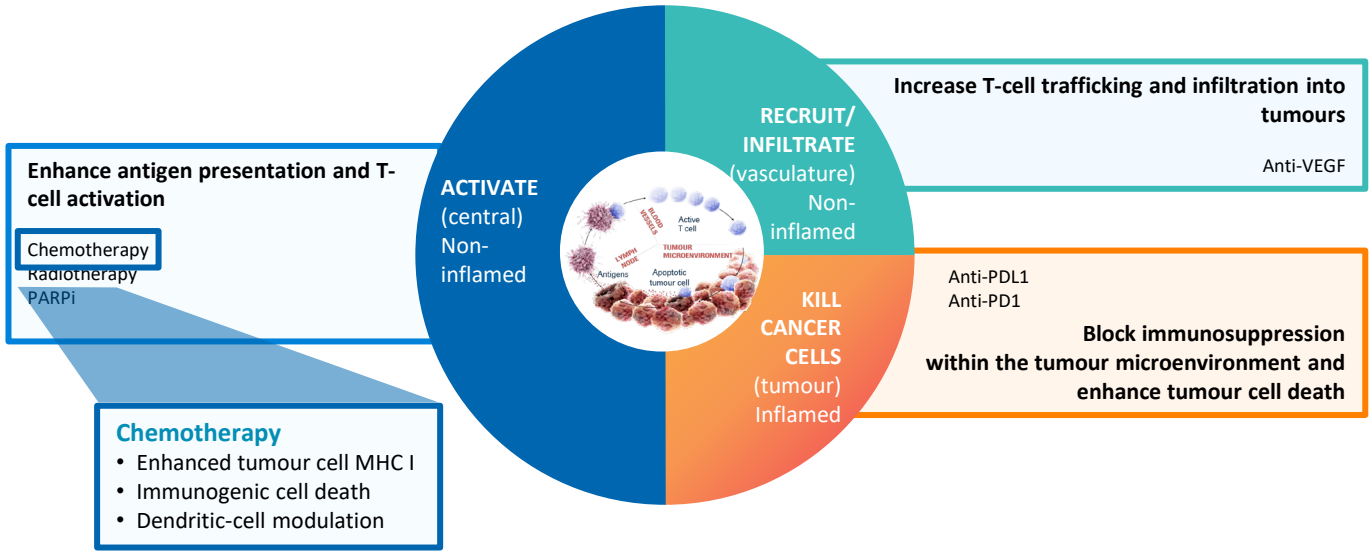
Combination opportunities in ovarian cancer immunotherapy



Chen & Mellman. Immunity 2013
Galluzzi, et al. Nat Rev Drug Discov 2012
Hannani, et al. Cancer J 2011; Vanneman and Dranoff. Nat Rev Cancer 2012

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Rationale for Combining Chemotherapy and IO in Ovarian Cancer

Study	Disease Site	Drug Combination
CheckMate 012	Advanced stage NSCLC	Nivolumab + platinum based doublet chemotherapy
Keynote 021	Chemotherapy naïve non squamous NSCLC	Pembrolizumab + Carboplatin + Pemetrexed
Keynote 189	Advanced stage NSCLC	Pembrolizumab + Platinum based chemo + Pemetrexed
Keynote 407	Metastatic squamous NCSLC	Pembrolizumab + carboplatin + taxane
I-SPY2	High risk locally advanced breast cancer	Pembrolizumab + paclitaxel followed by AC
Impower 133	Advanced stage small cell lung cancer	Atezolizumab + Carboplatin + Etoposide

Slide Courtesy of Ramez Eskander, MD

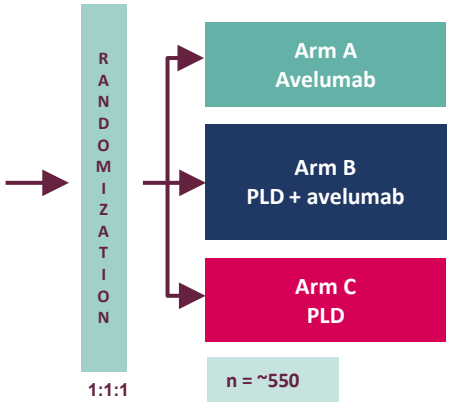
S7

JAVELIN Ovarian 200 Avelumab PROC

Randomized Phase 3 Study (NCT02580058)

Enrollment Criteria

- Progression ≤6 mo or no response to most recent platinum-based therapy
- Up to 3 lines of chemotherapy for platinum-sensitive disease, most recently platinum-containing, and no prior therapy for platinum-resistant disease
- Measurable disease
- ECOG PS 0 or 1
- No prior immune checkpoint inhibitor therapies
- Doxil-resistant (disease progression within 6 mo) excluded
- Mandatory archival tissue
- Baseline biopsy required unless contraindicated



Stratification: Platinum refractory vs resistant, number of prior therapies, bulky disease

Primary Endpoint:	OS, PFS
Secondary Endpoints:	ORR, PFS, duration of response, PROs, safety

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S7

JAVELIN Ovarian 200 Avelumab PROC

11/19/2018: " the Phase III JAVELIN Ovarian 200 trial evaluating avelumab alone or in combination with pegylated liposomal doxorubicin …compared with PLD did not meet the pre-specified primary endpoints of OS or PFS…."

Avelumab + PLD vs. PLD: HR 0.78 (0.587-1.244) for PFS and HR 0.89 (.744-1.2) for OS
Avelumab vs. PLD: HR 1.68 (1.3-2.6)for PFS and HR 1.14 (.95 -1.6) for OS

ORR: 13.3% PLD + Avelumab vs. 3.7% Avelumab alone vs. 4.2% for PLD alone

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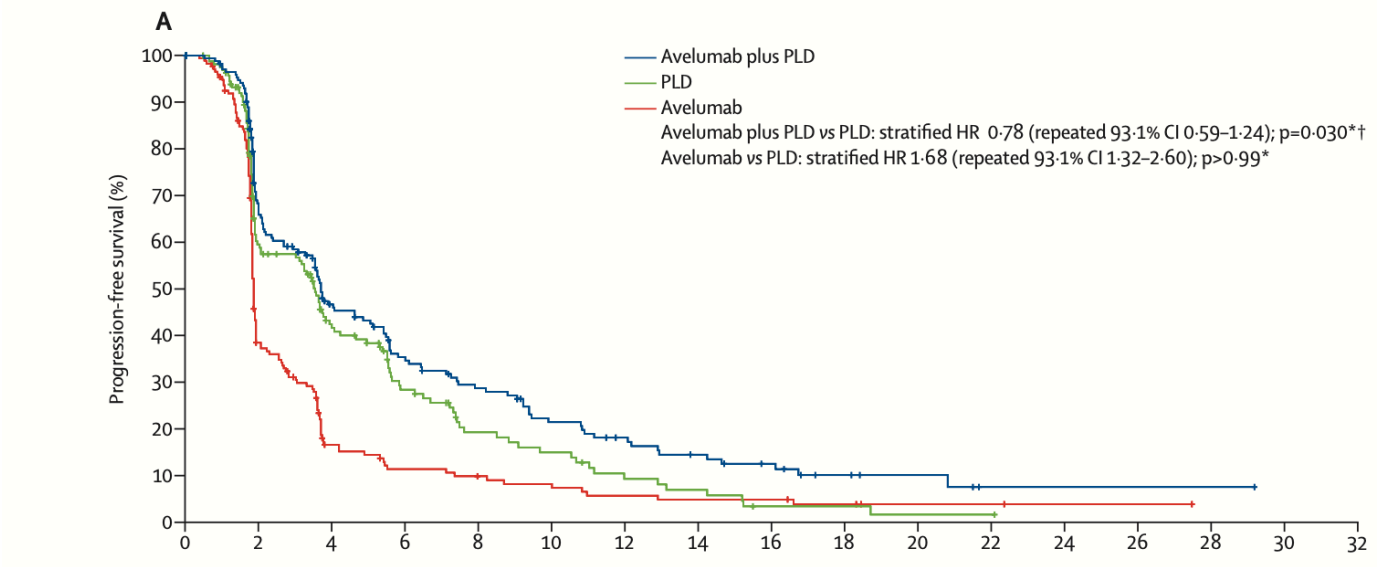
Javelin 200: Avelumab vs. PLD vs. PLD+Avelumab PROC-Progression-Free Survival



1: Avelumab alone or in combination with chemotherapy versus chemotherapy alone in platinum-resistant or platinum-refractory ovarian cancer (JAVELIN Ovarian 200): an open-label, three-arm, randomised, phase 3 study.
Pujade-Lauraine E, Fujiwara K, Ledermann JA, Oza AM, Kristeleit R, Ray-Coquard IL, Richardson GE, Sessa C, Yonemori K, Banerjee S, Leary A, Tinker AV, Jung KH, Madry R, Park SY, Anderson CK, Zohren F, Stewart RA, Wei C, Dychter SS, Monk BJ.
Lancet Oncol. 2021 Jul;22(7):1034-1046.

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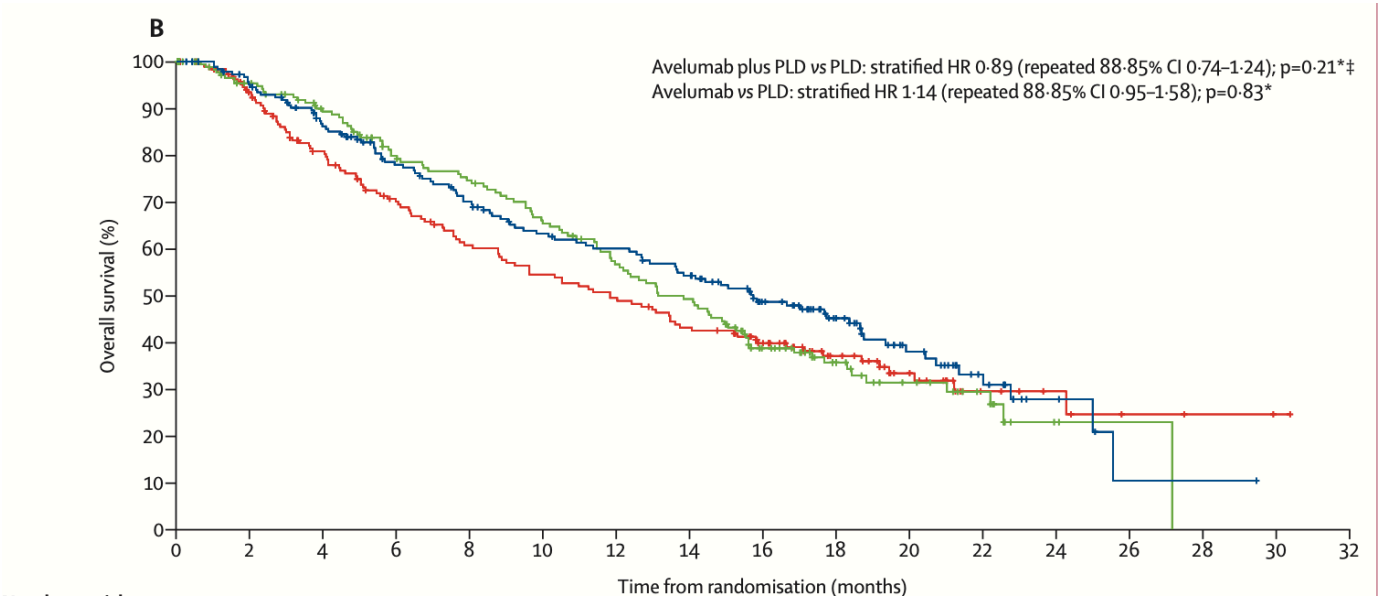
Javelin 200: Avelumab vs. PLD vs. PLD+Avelumab PROC-Overall Survival



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Pujade-Lauraine E, Fujiwara K, Ledermann JA, Oza AM, Kristeleit R, Ray-Coquard IL, Richardson GE, Sessa C, Yonemori K, Banerjee S, Leary A, Tinker AV, Jung KH, Madry R, Park SY, Anderson CK, Zohren F, Stewart RA, Wei C, Dychter SS, Monk BJ.
Lancet Oncol. 2021 Jul;22(7):1034-1046.

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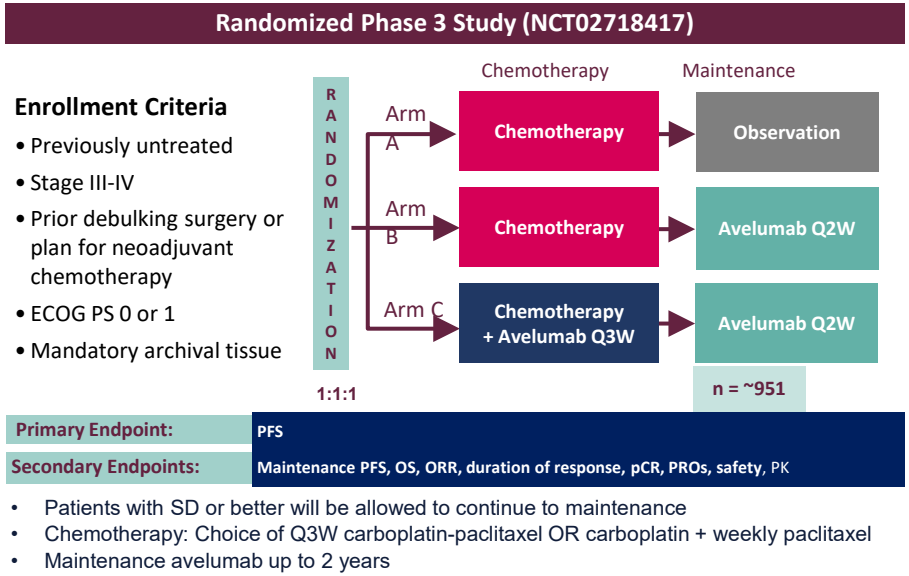
JAVELIN Ovarian 100 Avelumab + Chemo (Frontline)



- Patients with SD or better will be allowed to continue to maintenance
- Chemotherapy: Choice of Q3W carboplatin-paclitaxel OR carboplatin + weekly paclitaxel
- Maintenance avelumab up to 2 years

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S7

JAVELIN Ovarian 00 Avelumab PROC

12/21/2018: “Data from a planned interim analysis of the Phase III JAVELIN Ovarian 100 study of avelumab **did not support** the study’s initial hypothesis and therefore the alliance made the decision to terminate the trial in alignment with the independent Data Monitoring Committee. “

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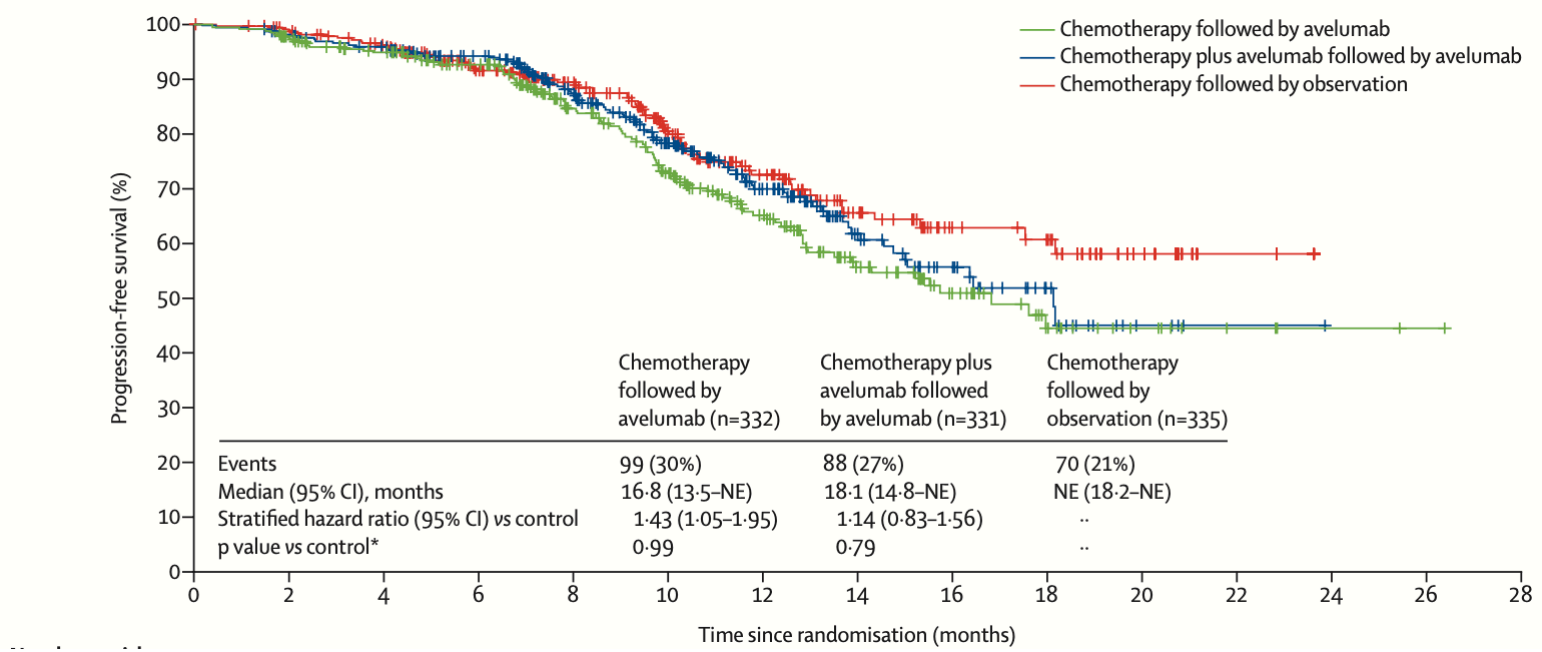
Javelin 100: CT vs CT+ avelumab vs CT followed by avelumab



	Chemotherapy followed by avelumab (n=332)	Chemotherapy plus avelumab followed by avelumab (n=331)	Chemotherapy followed by observation (n=335)
Events	99 (30%)	88 (27%)	70 (21%)
Median (95% CI), months	16·8 (13·5–NE)	18·1 (14·8–NE)	NE (18·2–NE)
Stratified hazard ratio (95% CI) *vs* control	1·43 (1·05–1·95)	1·14 (0·83–1·56)	..
p value *vs* control*	0·99	0·79	..

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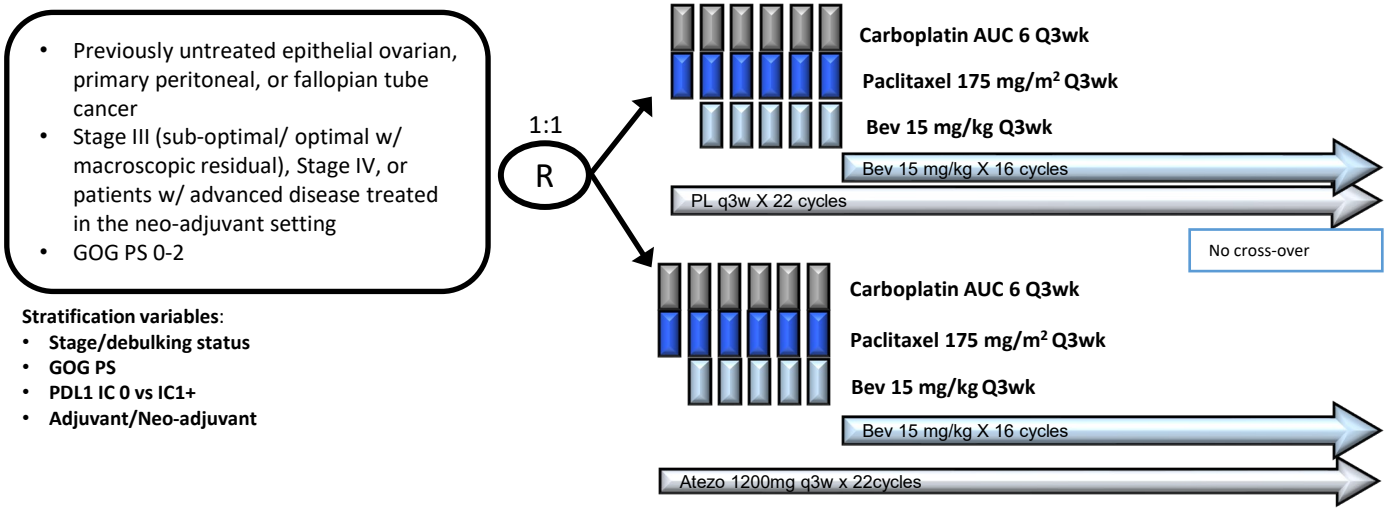
S9

IMaGYN050 Study Design - GOG 3015

Double blinded, 1:1 randomized, placebo-controlled multi-center study, primary surgery cohort



Stratification variables:
- **Stage/debulking status**
- **GOG PS**
- **PDL1 IC 0 vs IC1+**
- **Adjuvant/Neo-adjuvant**

Co-Primary endpoint: PFS &OS in all comers and Dx+ (IC 1+)

ClinicalTrials.gov Identifier: NCT03038100

NB1: Atezolizumab is not registered in Australia and efficacy and safety for this medicine is not yet established.
NB2: Bevacizumab is TGA-approved in combination with Carboplatin and Paclitaxel.

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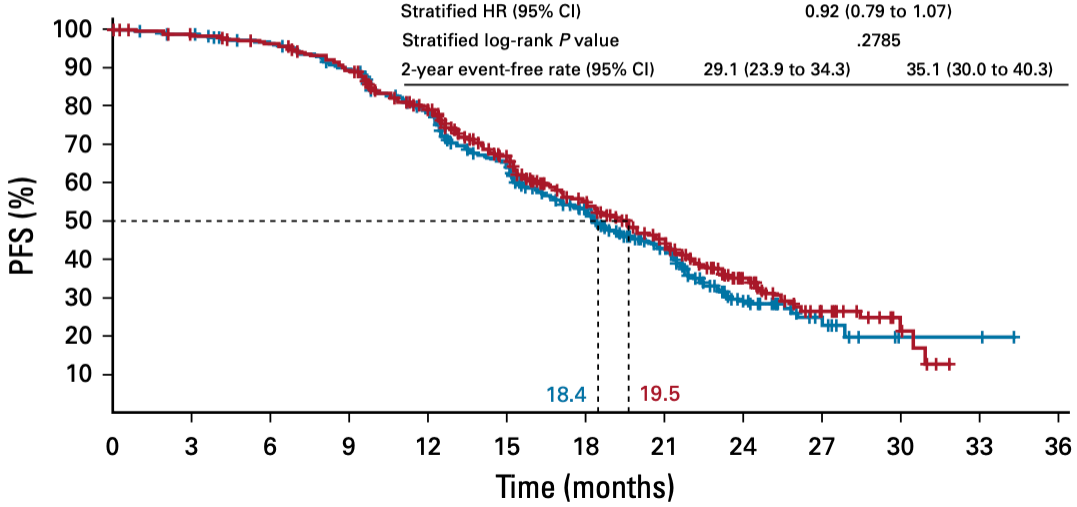
IMAGYN 50

PFS in ITT

PFS	Placebo Plus CP Plus Bevacizumab (n = 650)	Atezolizumab Plus CP Plus Bevacizumab (n = 651)
Events, n (%)	341 (52.5)	323 (49.6)
Median PFS, months (95% CI)	18.4 (17.2 to 19.8)	19.5 (18.1 to 20.8)
Stratified HR (95% CI)	0.92 (0.79 to 1.07)	
Stratified log-rank *P* value	.2785	
2-year event-free rate (95% CI)	29.1 (23.9 to 34.3)	35.1 (30.0 to 40.3)



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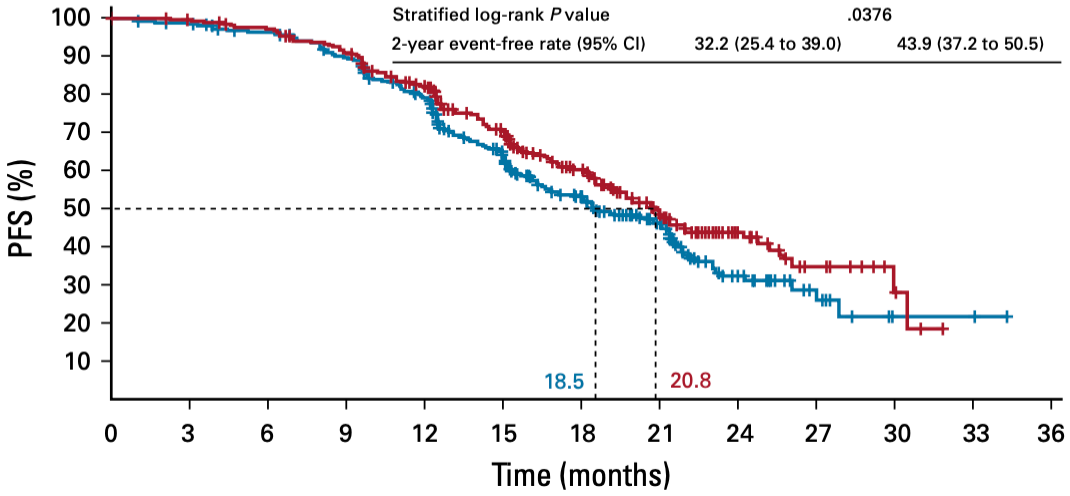
IMAGYN 50

PFS in PDL1+

PFS	Placebo Plus CP Plus Bevacizumab (n = 393)	Atezolizumab Plus CP Plus Bevacizumab (n = 391)
Events, n (%)	199 (50.6)	167 (42.7)
Median PFS, months (95% CI)	18.5 (16.6 to 21.4)	20.8 (19.1 to 24.2)
Stratified HR (95% CI)	0.80 (0.65 to 0.99)	
Stratified log-rank *P* value	.0376	
2-year event-free rate (95% CI)	32.2 (25.4 to 39.0)	43.9 (37.2 to 50.5)



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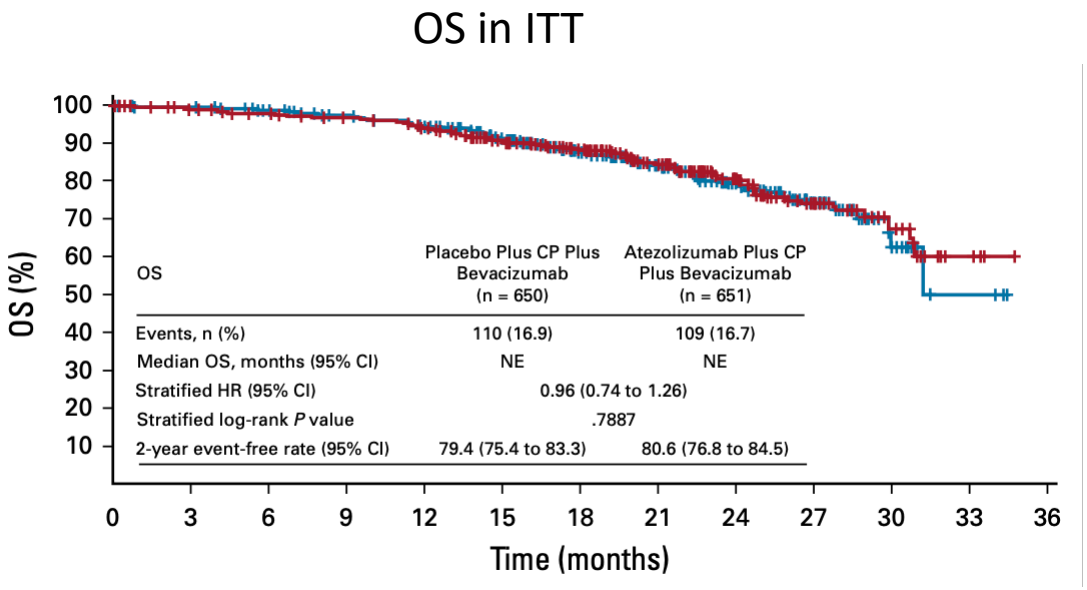

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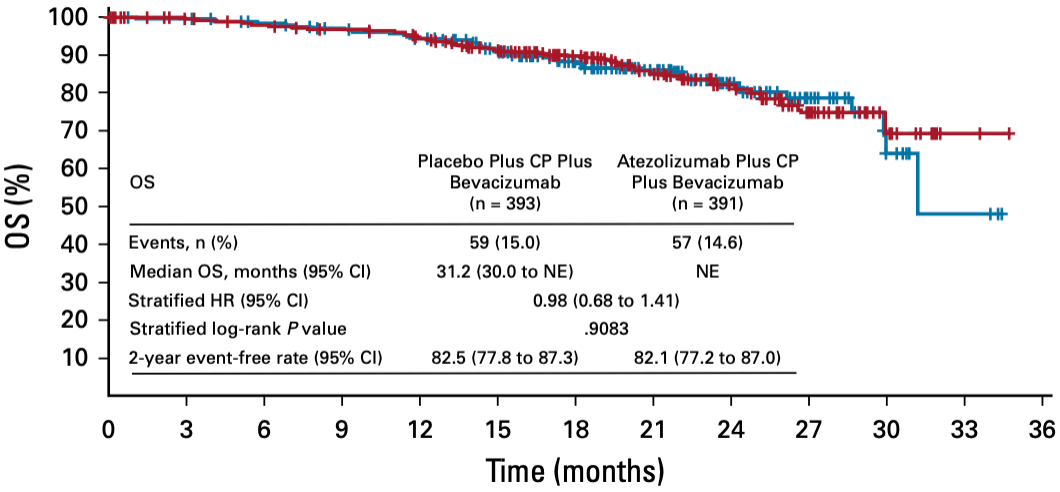
OS in PDL1+



OS	Placebo Plus CP Plus Bevacizumab (n = 393)	Atezolizumab Plus CP Plus Bevacizumab (n = 391)
Events, n (%)	59 (15.0)	57 (14.6)
Median OS, months (95% CI)	31.2 (30.0 to NE)	NE
Stratified HR (95% CI)	0.98 (0.68 to 1.41)	
Stratified log-rank *P* value	.9083	
2-year event-free rate (95% CI)	82.5 (77.8 to 87.3)	82.1 (77.2 to 87.0)

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Conclusions

- **Immunomodulation is a viable treatment strategy for gynecologic cancers**
- **When tumor responds, the response durable**
- **There are opportunities to be explored for optimizing immune therapy benefits in gynecologic cancers**
- **Combination of chemotherapy with immune therapy is an attractive strategy that should be explored further**

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Thank you