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Primary results from IMagyn050/GOG 3015/ENGOT-OV39, a double-blind placebo-controlled randomised phase 3 trial of bevacizumab-containing therapy ± atezolizumab for newly diagnosed stage III/IV ovarian cancer

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Disclosures

- Dr Moore declares:
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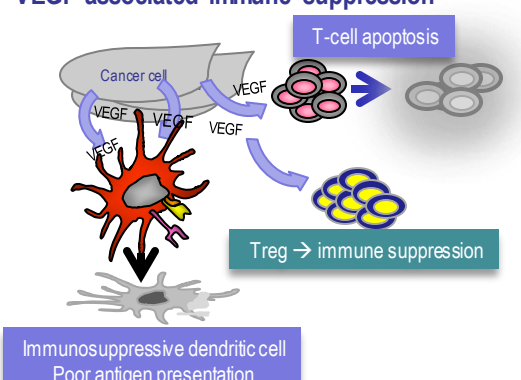
Rationale

- Atezolizumab, which targets PD-L1, has demonstrated efficacy in several cancers[1–6]
  - Immune cell PD-L1 expression is associated with greater atezolizumab effect in some tumours[1]
- Platinum–taxane chemotherapy combination with bevacizumab is an established front-line regimen for ovarian cancer (GOG-0218,[7] ICON7[8])
- Blocking tumour-associated VEGF may promote T-cell infiltration into the tumour bed and boost anti-tumour immune response, providing the rationale for combining atezolizumab with the anti-angiogenic agent bevacizumab[9,10]
- Combining anti-angiogenic approaches with PD-1/PD-L1 pathway blockade has shown clear anti-tumour efficacy in metastatic non-small-cell lung cancer,[2] unresectable hepatocellular cancer[5] and advanced endometrial cancer[13]

VEGF-associated immune suppression[11,12]



PD-1 = programmed death-1;
PD-L1 = programmed death-ligand 1;
Treg = regulatory T cell;
VEGF = vascular endothelial growth factor

[1]Schmid P et al. NEJM 2018; [2]Socinski MA et al. NEJM 2018; [3]Hom L et al. NEJM 2018; [4]Rittmeyer A et al. Lancet 2017; [5]Finn RS et al. NEJM 2020; [6]Powles T et al. Lancet 2018; [7]Burger RA et al. NEJM 2011; [8]Perren TJ et al. NEJM 2011; [9]Motz GT et al. Nat Med 2014; [10]Wallin J et al. Nat Commun 2016; [11]Coukos G et al. Adv Exp Med Biol 2007; [12]Shrimali RK et al. Cancer Res 2010; [13]Makker V et al. J Clin Oncol 2020

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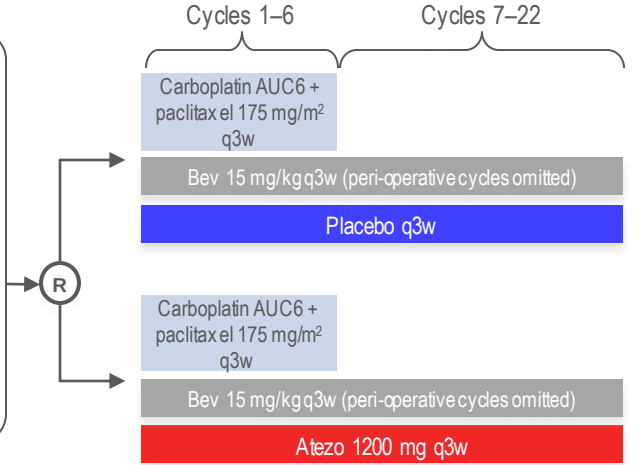
Trial design

- Previously untreated epithelial ovarian, primary peritoneal or fallopian tube cancer
- Post-operative stage III with macroscopic residual disease or stage IV or neoadjuvant candidate with planned interval surgery
- ECOG PS 0–2



Co-primary endpoints

- **PFS** (per RECIST v1.1)
  (PD-L1+ and ITT populations tested simultaneously; p≤0.002 considered positive)
- **OS**
  (hierarchical testing, PD-L1+ then ITT)

Stratification factors

- Stage (III vs IV)
- ECOG PS (0 vs 1/2)
- Treatment approach (adjuvant vs neoadjuvant)
- PD-L1 status (IC <1% vs ≥1%; VENTANA SP142 assay)

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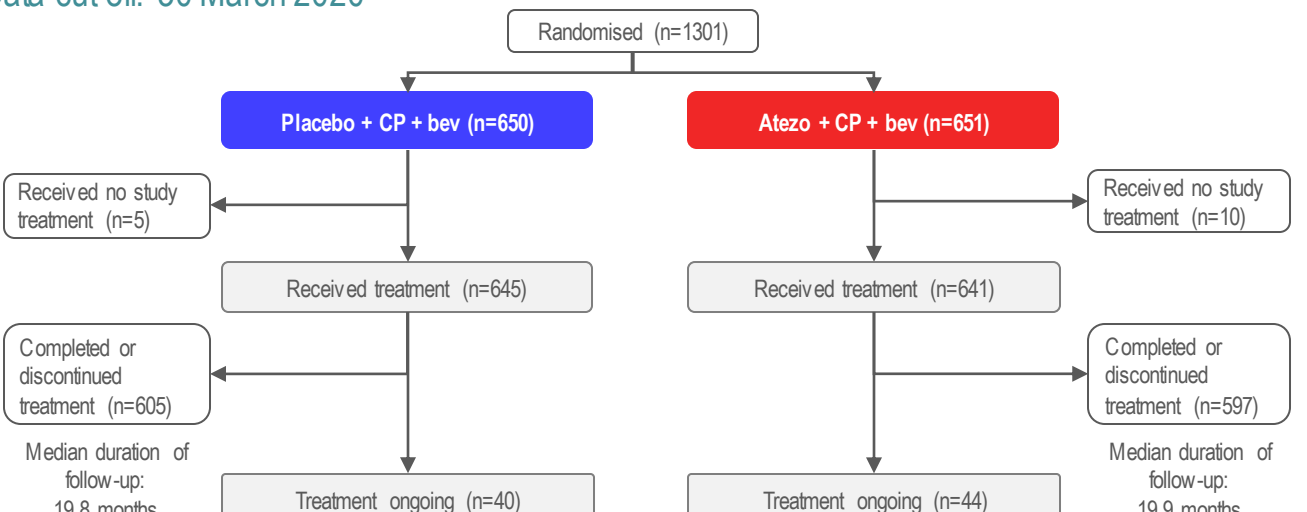
Atezo = atezolizumab; AUC = area under the curve; bev = bevacizumab; ECOG PS = Eastern Cooperative Oncology performance status; IC = immune cell; ITT = intent to treat; OS = overall survival; PFS = progression-free survival; q3w = every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumours

Patient flow

Data cut-off: 30 March 2020



CP = carboplatin + paclitaxel

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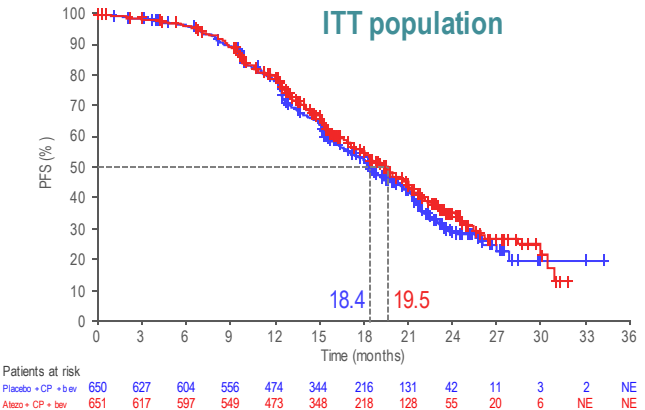
Baseline characteristics (ITT population)

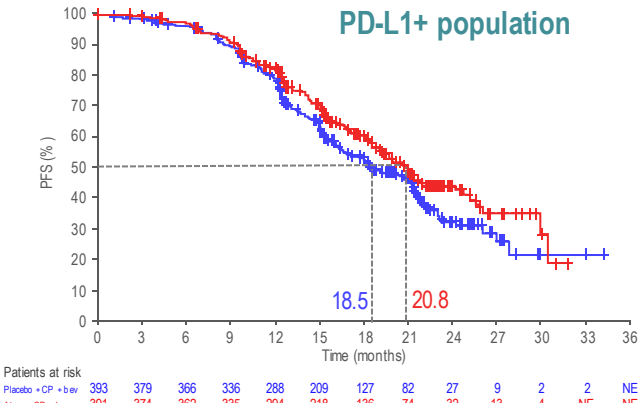
Characteristic, n (%)		Placebo + CP + bev (n=650)	Atezo + CP + bev (n=651)
Median age, years		59	60
Race	White	461 (71)	464 (71)
	Asian	155 (24)	150 (23)
	Black/African American	13 (2)	8 (1)
	Other	21 (3)	29 (4)
ECOG PS[a]	0	353 (54)	355 (55)
	1 or 2	297 (46)	296 (45)
Treatment approach[a]	Neoadjuvant	166 (25)	166 (25)
	Primary surgery	484 (74)	485 (75)
PD-L1[a]	IC <1%	257 (40)	260 (40)
	IC ≥1%	393 (60)	391 (60)
Stage[a,b]	III	448 (69)	448 (69)
	IV	201 (31)	203 (31)

Characteristic, n (%)		Placebo + CP + bev (n=650)	Atezo + CP + bev (n=651)
Primary tumour site[b]	Ovary	474 (73)	491 (75)
	Fallopian tube	111 (17)	100 (15)
	Primary peritoneal	64 (10)	60 (9)
Histology	High-grade serous	489 (75)	504 (77)
	Low-grade serous	58 (9)	67 (10)
	Endometrioid		
	Grade 3	5 (1)	7 (1)
	Grade 2	10 (2)	6 (1)
	Grade 1	6 (1)	1 (<1)
	Clear cell	22 (3)	29 (4)
	Mucinous/undifferentiated /mixed/other	60 (9)	37 (6)

[a]Stratification factor. [b]Missing in 1 patient in the placebo arm

Progression-free survival

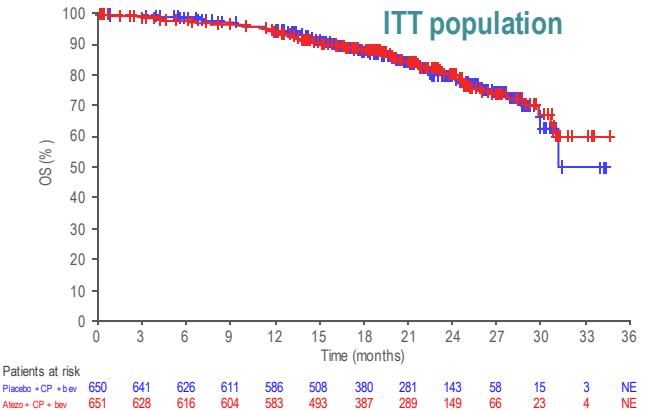


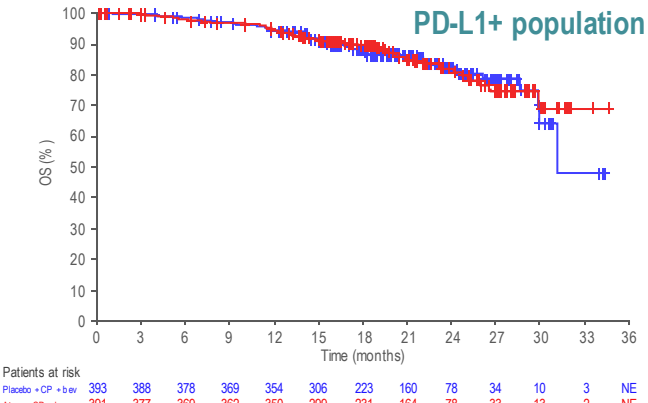


PFS	ITT population		PD-L1+ population	
	Placebo + CP + bev (n=650)	Atezo + CP + bev (n=651)	Placebo + CP + bev (n=393)	Atezo + CP + bev (n=391)
Patients with events, n (%)	341 (52.5)	323 (49.6)	199 (50.6)	167 (42.7)
Median PFS, months (95% CI)	18.4 (17.2–19.8)	19.5 (18.1–20.8)	18.5 (16.6–21.4)	20.8 (19.1–24.2)
Stratified HR (95% CI)	0.92 (0.79–1.07)		0.80 (0.65–0.99)	
Stratified log-rank p-value	0.2785		0.0376	
2-year event-free rate (95% CI)	29.1 (23.9–34.3)	35.1 (30.0–40.3)	32.2 (25.4–39.0)	43.9 (37.2–50.5)

CI = confidence interval; HR = hazard ratio

Overall survival: first interim analysis[a]





OS	ITT population		PD-L1+ population	
	Placebo + CP + bev (n=650)	Atezo + CP + bev (n=651)	Placebo + CP + bev (n=393)	Atezo + CP + bev (n=391)
Patients with events, n (%)	110 (16.9)	109 (16.7)	59 (15.0)	57 (14.6)
Median OS, months (95% CI)	NE	NE	31.2 (30.0–NE)	NE
Stratified HR (95% CI)	0.96 (0.74–1.26)		0.98 (0.68–1.41)	
Stratified log-rank p-value	0.7887		0.9083	
2-year event-free rate (95% CI)	79.4 (75.4–83.3)	80.6 (76.8–84.5)	82.5 (77.8–87.3)	82.1 (77.2–87.0)

[a]Information fraction: 41% (ITT population) and 37% (PD-L1+ population). NE = not estimable

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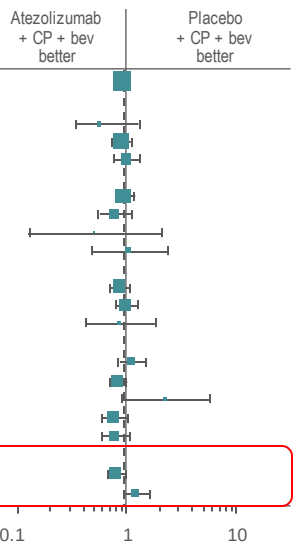
Subgroup analyses of PFS by baseline characteristics

ITT population

Baseline risk factors	Total n	Placebo + CP + bev (n=650) n	Placebo + CP + bev (n=650) Median (months)	Atezolizumab + CP + bev (n=651) n	Atezolizumab + CP + bev (n=651) Median (months)	HR (95% Wald CI)
All patients	1301	650	18.4	651	19.5	0.92 (0.79–1.07)
Age (by group)						
18–40 years	66	30	19.6	36	20.6	0.58 (0.35–1.30)
41–64 years	813	399	18.2	414	19.6	0.90 (0.74–1.10)
≥65 years	422	221	18.8	201	18.0	1.01 (0.78–1.32)
Race						
White	925	461	18.1	464	18.2	0.97 (0.82–1.16)
Asian	305	155	21.2	150	21.6	0.78 (0.55–1.10)
Black/African American	21	13	19.1	8	24.2	0.52 (0.13–2.07)
Other	50	21	18.2	29	19.7	1.06 (0.48–2.32)
Baseline ECOG PS						
0	708	353	18.4	355	20.2	0.87 (0.70–1.07)
1	529	266	18.7	263	18.3	1.00 (0.79–1.27)
2	64	31	18.2	33	17.1	0.87 (0.42–1.81)
Treatment approach						
Neoadjuvant	332	166	17.2	166	16.6	1.12 (0.85–1.47)
Primary surgery	969	484	18.4	485	19.8	0.84 (0.70–1.01)
No gross residual disease	72	41	22.1	31	19.3	2.27 (0.89–5.77)
Residual disease ≤1 cm	499	245	18.3	254	21.1	0.78 (0.60–1.01)
Residual disease >1 cm	398	198	17.1	200	18.6	0.80 (0.61–1.05)
Disease stage						
Stage III	896	448	18.4	448	20.6	0.80 (0.67–0.97)
Stage IV	404	201	18.4	203	17.1	1.24 (0.95–1.63)

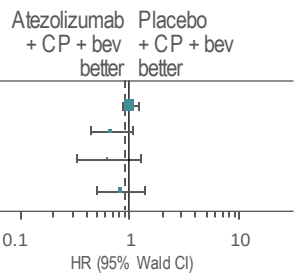


Subgroups may not total 1301 because of patients with 'unknown' category

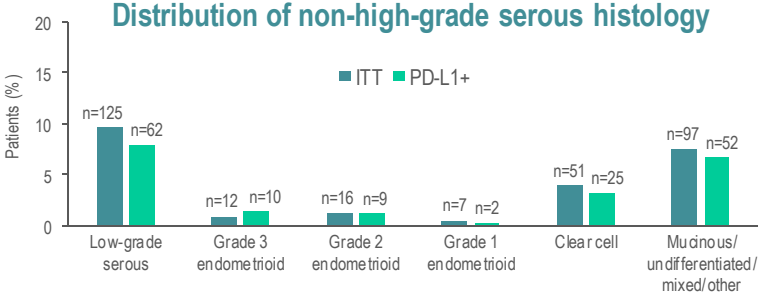
Subgroup analyses of PFS by histology

ITT population

Histological type	Total n	Placebo+ CP + bev (n=650) n	Placebo+ CP + bev (n=650) Median (months)	Atezolizumab + CP + bev (n=651) n	Atezolizumab + CP + bev (n=651) Median (months)	HR (95% Wald CI)
High-grade serous	993	489	19.0	504	19.3	1.01 (0.84–1.20)
High-grade non-serous	155	87	15.7	68	19.9	0.69 (0.45–1.07)
Clear cell	51	22	12.3	29	13.6	0.64 (0.33–1.24)
Low-grade serous	125	58	20.4	67	19.7	0.83 (0.50–1.38)

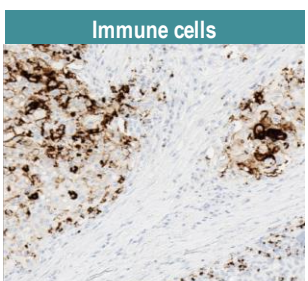


Distribution of non-high-grade serous histology



VENTANA SP142 PD-L1 immunohistochemistry

Ovarian cancer:
PD-L1 expression
mainlyon IC



IMagyn050 PD-L1 analyses

Co-primaryendpoint:

PD-L1 IC positive — IC ≥1%

Exploratory analysis:

PD-L1 IC negative	IC <1%	PD-L1 TC negative	TC<1%
IC positive-low	IC ≥1–<5%	TC positive	TC≥1%
IC positive-high	IC ≥5%		

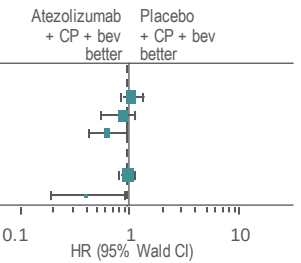
Scoring:
PD-L1 IC: area of PD-L1-stained tumour-infiltrating immune cells (ICs) as a percentage of tumour area
PD-L1 TC: percentage of PD-L1-stained tumour cells (TCs)

Subgroup analyses of PFS by PD-L1 status

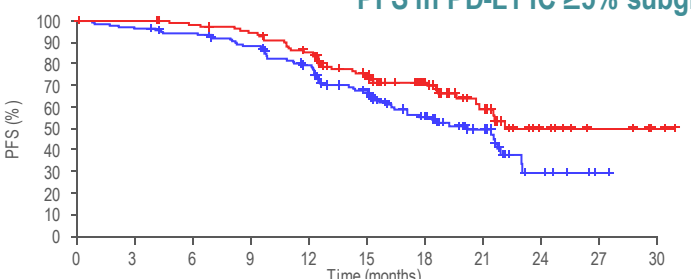
ITT population

PD-L1 status	Total n	Placebo + CP + bev (n=650) n	Placebo + CP + bev (n=650) Median (months)	Atezolizumab + CP + bev (n=651) n	Atezolizumab + CP + bev (n=651) Median (months)	HR (95% Wald CI)
PD-L1 IC status						
IC <1%	517 (40%)	257	18.3	260	17.4	1.06 (0.84–1.33)
IC ≥1% to <5%	524 (40%)	252	18.2	272	19.3	0.89 (0.55–1.13)
IC ≥5%	260 (20%)	141	20.2	119	NE	0.64 (0.43–0.96)
PD-L1 TC status						
TC <1%	1228 (94%)	610	18.4	618	19.2	0.96 (0.82–1.12)
TC ≥1% [a]	73 (6%)	40	15.0	33	NE	0.41 (0.19–0.90)

[a]PD-L1 TC ≥1% and IC ≥1%: n=67. PD-L1 TC ≥1% and IC <1%: n=6



PFS in PD-L1 IC ≥5% subgroup



	Placebo + CP + bev (n=141)	Atezo + CP + bev (n=119)
Patients with events, n (%)	66 (46.8)	39 (32.8)
Median PFS, months (95% CI)	20.2 (17.1–21.9)	NE (20.8–NE)
Unstratified HR (95% CI)	0.64 (0.43–0.96)	
Unstratified log-rank p-value	0.0278	

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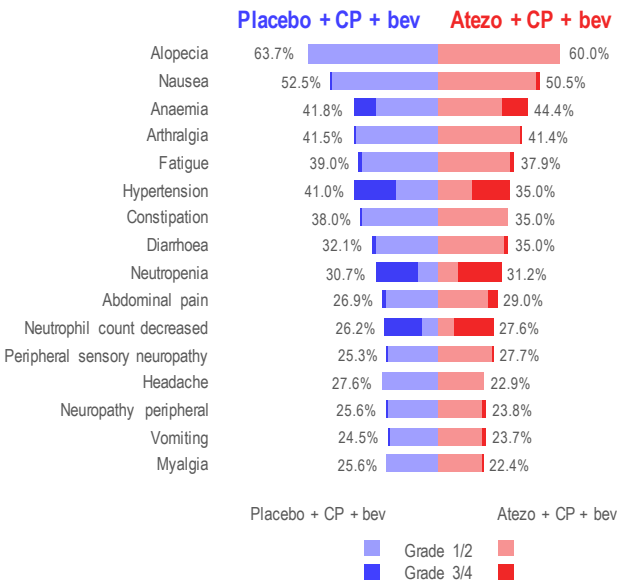
Overall safety profile

AEs, n (%)	Placebo + CP + bev (n=644)	Atezo + CP + bev (n=642)
All-grade AEs	643 (100)	642 (100)
AE with fatal outcome	8 (1)	9 (1)
Related AE with fatal outcome	5 (0.8)	4 (0.6)
SAE	211 (33)	304 (47)
Related SAE	135 (21)	222 (35)
Grade 3/4 AE[a]	471 (73)	509 (79)
Related grade 3/4 AE	429 (67)	479 (75)
AE leading to any treatment discontinuation	140 (22)	167 (26)
AE leading to atezo/placebo discontinuation	40 (6)	98 (15)
AE leading to bev discontinuation	109 (17)	116 (18)
AE leading to atezo dose interruption	385 (60)	425 (66)
AESI for atezo	336 (52)	469 (73)
AESI with fatal outcome[b]	0	1 (0.2)
Grade 3/4 AESI[a]	38 (6)	109 (17)

- The addition of atezolizumab did not compromise delivery of backbone therapy

[a]Grade 3/4 AE refers to highest grade experienced. [b]The fatal AESI myasthenia gravis was considered by investigator as related to atezolizumab
AE = adverse event; AESI = adverse event of special interest; SAE = serious adverse event

Most common AEs



SAEs with ≥2% incidence in either arm

SAEs	Placebo + CP + bev (n=644)	Atezo + CP + bev (n=642)
Febrile neutropenia	3.7%	8.4%
Pyrexia	1.2%	4.0%

AEs of special interest for atezolizumab (>2 patients in either arm)

Immune-mediated AEs by medical concept, n (%)	Placebo + CP + bev (n=644)		Atezo + CP + bev (n=642)	
	Any grade	Grade 3/4[a]	Any grade	Grade 3/4[a]
Hepatitis	14 (2.2)	4 (0.6)	17 (2.6)	7 (1.1)
Pneumonitis	4 (0.6)	0	12 (1.9)	1 (0.2)
Hypothyroidism	83 (12.9)	1 (0.2)	166 (25.9)	3 (0.5)
Hyperthyroidism	23 (3.6)	0	51 (7.9)	0
Adrenal insufficiency	2 (0.3)	0	5 (0.8)	1 (0.2)
Infusion-related reactions	49 (7.6)	2 (0.3)	78 (12.1)	5 (0.8)
Colitis	11 (1.7)	7 (1.1)	21 (3.3)	11 (1.7)
Rash	165 (25.6)	6 (0.9)	265 (41.3)	41 (6.4)
Severe cutaneous reactions	3 (0.5)	0	15 (2.3)	8 (1.2)
Myositis	5 (0.8)	0	4 (0.6)	2 (0.3)
Meningoencephalitis[b]	3 (0.5)	0	3 (0.5)	1 (0.2)
Pancreatitis	0	0	5 (0.8)	4 (0.6)

[a]Grade 3/4 AE refers to highest grade experienced. [b]No cases of meningitis, 1 patient with encephalitis, remaining events were photophobia. In the atezo arm there was one (fatal) case of myasthenia gravis and two cases of systemic immune activation (one grade 4, both resolved). Diabetes mellitus and rhabdomyolysis each occurred in 2 patients (0.3%) in the atezo arm (grade 3/4 in 1 patient; 0.2%) and there were three cases of diabetes mellitus (0.5%) in the placebo arm (no grade 3/4). Myocarditis and Guillain–Barré syndrome each occurred in 1 patient (0.2%) in each arm, at grade 3/4 in all cases except for myocarditis in the atezo arm. There were no cases of haemophagocytic lymphohistiocytosis or hypophysitis in either arm

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Conclusions

- IMagyn050/GOG 3015/ENGOT-OV39 is a global randomised phase III trial powered to assess treatment effect in PD-L1+ ovarian cancer
- The addition of atezolizumab to a chemotherapy + bevacizumab backbone did not significantly improve PFS vs chemotherapy + bevacizumab alone in the ITT or PD-L1+ (IC ≥1%) populations
  - ITT population: HR = 0.92 (95% CI 0.79–1.07); median PFS: 19.5 vs 18.4 months
  - PD-L1+ population: HR = 0.80 (95% CI 0.65–0.99); median PFS 20.8 vs 18.5 months
  - Exploratory PFS analyses in the PD-L1 IC ≥5% subgroup showed a trend favouring atezolizumab
- First interim OS analysis did not show a significant OS benefit with the addition of atezolizumab to chemotherapy + bevacizumab
  - Final OS results are expected in 2023
- Safety of atezolizumab in combination with bevacizumab and chemotherapy was consistent with the known safety profile of individual drugs and their combination

Thanks to

- The patients and their families
- The investigators and clinical study sites

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Bookman, Anderson, Myers, Thomes-Pepin, Willmott, Robison, Sharma, Gold, Reid, Moore K, Darus, Green, Aghajanian, Thaker, Ueland, Buscema, Lim, O'Malley, Shahin, Rutledge, Lee, Carney, Behbakht, Blank, Bell, Mchale, Kumar, Barlin, Tierney, Santillan-Gomez, Celano, Moore T, McCluskey, Pothuri, Tewari D, Fiorica, Bender, Fleming, Diaz, Fauci, Morgan, Morris, Spirtos, Waggoner, McNamara, Teneriello, John, Chen, Rodabaugh, Alvarez-Secord, Indermaur, Lentz, McCarthy, Landen, Rose, Geller, Olawaiye, Ma, Frederickson, Liu, Schilder, Trinidad, Moroney, Holschneider, Kamat, Jackson, Messing, Gray, Krivak, Cloven, Lea, Werner, Warshal, Barroilhet, Seago, Schuler, Hernandez, Cohen, Dorigo, Castro, Westin, Podzielinski, Evans, Bottsford-Miller, Ahuja, Richards, Tewari K, Yost, Fields, Fishman, Slater, Dewdney, Elsahwi, Roman, McCollum, Houck, Wassenaar, Mahmood, Chan, Rivard, Farley, Rhodes, Callahan, Tenney, Crane, Griffin, Gao, Williams-Brown, Lewin, Boardman, Miller, Wolfson, Mansky

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Scambia, Mangili, Raspagliesi, Zola, Tognon, Pignata, Colombo, Siena, Conte, Zamagni, Bologna, Tamberi, Lissoni, Ferrero, De Placido, Cinieri, Mosconi, De Giorgi

NOGGO

Ataseven, Schneeweiss, De Gregorio, Hanker, Eichbaum, Sehouli, Bossart, Wimberger, Burges, Dieterich, Buderath, Schmalfeldt, Park-Simon, Bronger, Hasenburg, Alwafai

TÜRK JİNEKOLOJİK ONKOLOJİ DERNEĞİ

Bese, Kose, Taskiran, Saip, Ayhan, Akbulut

NSGO

Auranen, Hietanen, Anttila, Lindemann, Aune, Fernebro, Lindahl, Nøttrup

HeCOG Hellenic Cooperative Oncology Group

Bamias, Fountzilas, Kkalofonos, Aravantinos

GEICO Grupo Español de Investigación en Cáncer de Ovario

Alarcon Company, Herrero Ibañez, Martinez Bueno, Garcia Garcia, Garcia Donas, Santaballa Bertran, Hernando Polo, Arranz Arija, Bermejo Perez

PGOG

Bidzinski, Madry, Chudecka-Glaz, Iwanska

ARCAGY - GINECO

Lortholary, Bonnin, Selle, Bourgeois, Ray-Coquard, Dubot, Leary

CEEGOG Central and Eastern European Gynecologic Oncology Group

Cibula, Klat, Melichar, Prausova

The Israeli Society of Gynecologic החברה הישראלית לגינקולוגיה אונקולוגית

Korach, Beiner, Bruchim, Rosengarten

AGO AUSTRIA

Marth, Koch, Reinthaller, Schauer

BGOG

Van Nieuwenhuysen, Denys, Dirix, Vulsteke

Wu, Zhu, Cao, Lou, Gao, Zhou, Cheng X, Cai, Yin, Cheng W, Wang, Liu, Li

Ushijima, Takeshima, Kajiyama, Okadome, Matsumoto, Takehara, Oda, Kato, Kobayashi, Okamoto, Tokunaga, Aoki, Hamanishi, Enomoto, Takekuma, Kamiura, Itamochi, Kondo, Yahata, Mizushima, Nagao, Nakamura

Safin, Lisyanskaya, Stroyakovskii, Smolin

Kim Y-M, Kim J-W, Kim B-G, Lim

Richardson, Baron-Hay, Grossi

Hegg, Melo

- Vidya Maiya, Danh Huynh, David Tesarowski, Ignacio Dolado, Michelle Brockman (F. Hoffmann-La Roche Ltd/Genentech, Inc)