Atezolizumab plus bevacizumab and chemotherapy for metastatic, persistent, or recurrent cervical cancer (BEATcc): a randomised, open-label, phase 3 trial

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Summary

Background The GOG240 trial established bevacizumab with chemotherapy as standard first-line therapy for metastatic or recurrent cervical cancer. In the BEATcc trial (ENGOT-Cx10–GEICO 68-C–JGOG1084–GOG-3030), we aimed to evaluate the addition of an immune checkpoint inhibitor to this standard backbone.

Methods In this investigator-initiated, randomised, open-label, phase 3 trial, patients from 92 sites in Europe, Japan, and the USA with metastatic (stage IVB), persistent, or recurrent cervical cancer that was measurable, previously untreated, and not amenable to curative surgery or radiation were randomly assigned 1:1 to receive standard therapy (cisplatin 50 mg/m² or carboplatin area under the curve of 5, paclitaxel 175 mg/m², and bevacizumab 15 mg/kg, all on day 1 of every 3-week cycle) with or without atezolizumab 1200 mg. Treatment was continued until disease progression, unacceptable toxicity, patient withdrawal, or death. Stratification factors were previous concomitant chemoradiation (yes *vs* no), histology (squamous cell carcinoma *vs* adenocarcinoma including adenosquamous carcinoma), and platinum backbone (cisplatin *vs* carboplatin). Dual primary endpoints were investigator-assessed progression-free survival according to Response Evaluation Criteria in Solid Tumours version 1.1 and overall survival analysed in the intention-to-treat population. This study is registered with ClinicalTrials.gov, NCT03556839, and is ongoing.

Findings Between Oct 8, 2018, and Aug 20, 2021, 410 of 519 patients assessed for eligibility were enrolled. Median progression-free survival was 13·7 months (95% CI 12·3–16·6) with atezolizumab and 10·4 months (9·7–11·7) with standard therapy (hazard ratio [HR]=0·62 [95% CI 0·49–0·78]; p<0·0001); at the interim overall survival analysis, median overall survival was 32·1 months (95% CI 25·3–36·8) versus 22·8 months (20·3–28·0), respectively (HR 0·68 [95% CI 0·52–0·88]; p=0·0046). Grade 3 or worse adverse events occurred in 79% of patients in the experimental group and in 75% of patients in the standard group. Grade 1–2 diarrhoea, arthralgia, pyrexia, and rash were increased with atezolizumab.

Interpretation Adding atezolizumab to a standard bevacizumab plus platinum regimen for metastatic, persistent, or recurrent cervical cancer significantly improves progression-free and overall survival and should be considered as a new first-line therapy option.

Funding F Hoffmann-La Roche.

Published **Online** December 1, 2023 https://doi.org/10.1016/S0140-6736(23)02405-4

See **Online/Comment** https://doi.org/10.1016/S0140-6736(23)02690-9

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Introduction

Vaccination against human papillomavirus (HPV) has resulted in substantial reductions in the incidence, morbidity, and mortality from cervical cancer.[1] Nevertheless, cervical cancer still causes an estimated 604 000 new cases and 342 000 deaths per year worldwide, making it the fourth most deadly cancer in women.[2] Patients diagnosed with metastatic, recurrent, or persistent cervical cancer not amenable to local control require systemic therapy and have a poor prognosis. The phase 3 Gynecologic Oncology Group (GOG) 240 trial combining bevacizumab with standard chemotherapy was the first study since trials of platinum agents to show significantly improved overall survival in this setting, but median overall survival in GOG240 was still less than 17 months.[3,4] In the subsequent phase 3 KEYNOTE-826 trial, addition of the immune checkpoint inhibitor pembrolizumab to first-line chemotherapy (with or without bevacizumab) significantly improved overall survival (median 26 months),[5,6] leading to regulatory approval of a pembrolizumab-containing regimen in many countries.

Both VEGF and PD-L1 play a role in cervical cancer pathogenesis.[7] Evidence suggests that peripheral immune tolerance and angiogenesis are closely connected and cooperate to sustain tumour growth.[8,9] Thus, inhibition of both angiogenesis and immunosuppression might result

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See Online for appendix

Research in context

Evidence before this study

When the BEATcc trial was designed in 2017, the standard of care therapy for metastatic, persistent, or recurrent cervical cancer was bevacizumab plus platinum-doublet chemotherapy, which showed an overall survival benefit compared with chemotherapy alone in the Gynecologic Oncology Group 240 trial. A PubMed search of clinical trial publications between 2001 and 2018 with the search terms "advanced cervical cancer" and "phase 3" identified no additional positive phase 3 trials.

Added value of this study

After the BEATcc trial was initiated, results from two phase 3 trials evaluating immune checkpoint blockade strategies (PD-1 inhibition) in cervical cancer were reported: KEYNOTE-826 in the first-line setting and EMPOWER-Cervical 1 after progression on platinum-based therapy. The KEYNOTE-826 trial showed significantly improved efficacy with the addition of the PD-1 inhibitor pembrolizumab to chemotherapy (with or without bevacizumab) for metastatic, persistent, or recurrent cervical cancer. Although the greatest benefit was observed in patients whose tumours had a PD-L1 combined positive score of 10 or more, the US Food and Drug Administration and the European Medicines Agency approved the combination for patients with persistent, recurrent, or metastatic cervical tumours with a PD-L1 combined positive score of 1 or more, on the basis of the perceived predictive role of PD-L1 for the efficacy of pembrolizumab. Bevacizumab was optional; therefore, the role of immune checkpoint blockade combined with bevacizumab and chemotherapy could only be inferred from subgroup analyses. In the EMPOWER-Cervical-1 trial, in which cemiplimab showed overall survival improvement compared with chemotherapy, patients were enrolled regardless of PD-L1 status.

BEATcc evaluated the PD-L1 inhibitor atezolizumab in a biomarker-unselected population and the use of bevacizumab was mandatory. BEATcc confirms the role of immune checkpoint blockade as first-line treatment for metastatic, persistent, or recurrent cervical cancer and is the first trial to show the efficacy of a PD-L1 inhibitor in cervical (or any other gynaecological) cancer.

Implications of all the available evidence

These results suggest that atezolizumab in combination with bevacizumab and platinum-based chemotherapy should be considered a new first-line treatment option for patients with metastatic, persistent, or recurrent cervical cancer.

in improved and more durable clinical benefit. In the KEYNOTE-826 trial, pembrolizumab was combined with a chemotherapy-alone backbone with optional bevacizumab;[5] thus, the role of immunotherapy with standard anti-angiogenic therapy was inferred only from subgroup analyses. The international BEATcc trial was designed to establish whether combining atezolizumab with bevacizumab plus chemotherapy improves efficacy in the setting of metastatic, persistent, or recurrent cervical cancer.

Methods

Study design and participants

This investigator-initiated, multicentre, randomised, open-label, phase 3 trial took place at 92 sites in Europe, Japan, and the USA, under the auspices of the European Network for Gynaecological Oncological Trial groups in collaboration with the GOG Foundation and the Japanese Gynecologic Oncology Group (appendix pp 3–4). The trial adhered to the ethical principles of the Declaration of Helsinki, Good Clinical Practice, International Conference on Harmonisation guidelines, and applicable national and local laws and regulations. The trial protocol including all amendments and relevant study documentation were approved by each participating site's independent ethics committee or review board. All patients provided written informed consent. The protocol is included in the appendix (pp 18–179).

Eligibility was defined with the following key inclusion criteria: adult patients (≥18 years) with measurable (according to Response Evaluation Criteria in Solid Tumours version 1.1 [RECIST]) metastatic (stage IVB), persistent, or recurrent cervical cancer not amenable to curative surgery or radiation, of squamous cell carcinoma or adenocarcinoma subtype (including adenosquamous carcinoma; adenocarcinoma including adenosquamous carcinoma was capped at 20% of the study population to enrol a population reflecting the typical distribution of histological subtypes in routine practice and to reduce the potential risk of diluting the atezolizumab treatment effect in case immune checkpoint blockade provided reduced benefit in this histological subtype with a lower prevalence of PD-L1 overexpression); with available archival or recently collected tumour tissue samples; and GOG or Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Key exclusion criteria included previous systemic therapy for metastatic, persistent, or recurrent disease (although concurrent chemoradiotherapy with curative intent or adjuvant chemoradiotherapy completed ≥3 months before enrolment were allowed); ongoing disease involving the bladder or rectum; previous treatment with any anti-VEGF therapy or immune checkpoint blockade; and other factors associated with an increased risk of bevacizumab-related or atezolizumab-related toxicity, such as a serious non-healing wound, ulcer, or bone fracture, history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess in the preceding 6 months, history of autoimmune disease, idiopathic pulmonary fibrosis, organising pneumonia, drug-induced pneumonitis, or idiopathic pneumonitis,

evidence of active pneumonitis, or administration of a live attenuated vaccine within the preceding 4 weeks (see appendix pp 110–111). The complete list of eligibility criteria is provided in the appendix (pp 66–74).

Randomisation

Patients were randomly assigned in a 1:1 ratio to receive bevacizumab plus chemotherapy (henceforth referred to as standard therapy), with or without atezolizumab. Randomisation was done centrally by means of an interactive voice response–web system incorporating a standard procedure for generating random numbers and a permuted block design (block size of 4), with randomisation codes assigned sequentially within each stratum. Randomisation was stratified by previous concomitant chemoradiation (yes *vs* no), histological subtype (squamous cell carcinoma *vs* adenocarcinoma, including adenosquamous carcinoma), and platinum backbone (cisplatin *vs* carboplatin). An open-label design was considered appropriate because overall survival, which is not subject to investigator bias, was the sole primary endpoint before a protocol amendment (Aug 27, 2021) to assess overall survival and progression-free survival as dual primary endpoints. Furthermore, the risk of dropout among those randomly assigned to the standard group was assumed to be low given the proven efficacy of the standard regimen (including an overall survival benefit versus chemotherapy alone).[3]

Procedures

Standard therapy consisted of intravenous platinum (cisplatin 50 mg/m² or carboplatin area under the curve of 5), intravenous paclitaxel 175 mg/m², and intravenous bevacizumab 15 mg/kg, all on day 1 of every 3-week cycle. Initially, cisplatin use was mandatory, but following a protocol amendment (Feb 4, 2020), carboplatin was introduced as an alternative according to physician choice. Patients randomly assigned to the experimental group also received intravenous atezolizumab 1200 mg on day 1 of every 3-week cycle. Treatment was continued until disease progression, unacceptable toxicity, patient withdrawal, or death, whichever occurred first. Patients with a complete response after at least six cycles could discontinue chemotherapy and continue bevacizumab (and atezolizumab in the experimental group) as maintenance therapy. Patients who had unacceptable treatment-related toxicity could discontinue the relevant treatments and continue with the remaining drugs as planned and appropriate. The protocol details treatment modifications for toxicity (appendix pp 81–92, 143–174). Crossover from the standard group to atezolizumab at progression was not permitted.

Adverse events were recorded at every treatment cycle until 30 days after the last dose, initiation of new anticancer therapy, or death, whichever occurred first. Adverse events of special interest (appendix pp 108–111) were reported until 90 days after the last atezolizumab or bevacizumab dose (or the start of new anticancer therapy if earlier). After study treatment discontinuation, details of subsequent anticancer therapies continue to be collected until death or study end.

Outcomes

The dual primary endpoints were investigator-assessed progression-free survival, defined as the time between randomisation and the date of disease progression or death from any cause, whichever occurred first, and overall survival, defined as the time between randomisation and death from any cause (still being followed in this ongoing trial). Patients whose disease had not progressed were censored for progression-free survival at the date of last tumour assessment without documented progression. Patients who were alive at the data cutoff date (July 17, 2023) were censored at the date they were last known to be alive (for overall survival) or alive without progression (for progression-free survival). The secondary endpoints were objective response rate (according to RECIST), duration of response in responding patients, time from randomisation to first subsequent therapy or death, time from randomisation to second progression or death, frequency and severity of adverse events graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0), and tolerability. Secondary endpoints of role and physical functioning and global health status–health-related quality-of-life scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, serum concentration of atezolizumab at specified timepoints, and incidence of anti-therapeutic antibodies cannot be reported yet because these analyses are ongoing, and will be reported separately. Patients still on treatment continue to complete quality-of-life questionnaires.

Tumour imaging was done at screening, every 9 weeks during the first year, and every 12 weeks thereafter until disease progression, unacceptable toxicity, death, or patient withdrawal, whichever occurred first.

Statistical analysis

The overall 5% alpha was split between progression-free survival (2%) and overall survival (3%). The study was designed assuming a median progression-free survival of 9·1 months with standard therapy (on the basis of results from GOG240[3]), increasing to 13·5 months with the addition of atezolizumab (hazard ratio [HR]=0·675). To achieve 80% power, at least 280 progression-free survival events were required. Median overall survival with standard therapy was assumed to be 17·5 months (on the basis of GOG240[3,4]), increasing to 25·0 months with atezolizumab (HR=0·70). To detect this difference with 80% power and one interim analysis, at least 292 deaths were required at the final analysis. The target sample size with these assumptions was 404 patients.

The progression-free survival analysis was prespecified after at least 280 events, to be tested at a two-sided alpha

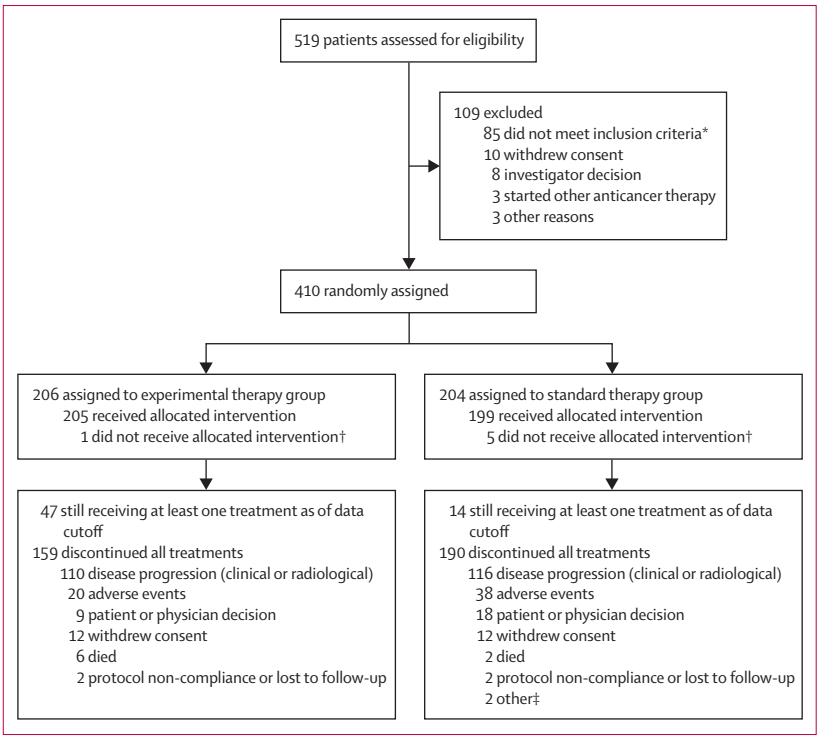

Figure 1: **Trial profile**
*Reasons related to medical unsuitability for bevacizumab in 28 patients. †Six patients did not start treatment because of investigator decision (n=1), withdrawal of consent (n=1), adverse event (n=2; one case each of ulcer and bone fracture), and missing reason (n=1) in the standard group, and investigator decision (n=1) in the experimental group. ‡Reason for end of treatment missing in two patients.

	Atezolizumab plus bevacizumab plus chemotherapy (experimental group; n=206)	Bevacizumab plus chemotherapy (standard group; n=204)
Age, years	51·0 (43·0–60·0)	52·5 (43·5–61·0)
Age group		
<65 years	171 (83%)	168 (82%)
≥65 years	35 (17%)	36 (18%)
Gynecologic Oncology Group or Eastern Cooperative Oncology Group performance status		
0	138 (67%)	128 (63%)
1	68 (33%)	73 (36%)
Missing data	0	3 (1%)
Race or ethnicity		
White	111 (54%)	113 (55%)
Asian	31 (51%)	27 (13%)
Latin	8 (4%)	10 (5%)
Arab	2 (1%)	3 (1%)
Black	3 (1%)	2 (1%)
Gypsy	1 (<1%)	0
Not available*	50 (24%)	49 (24%)
Geographical region		
Europe	166 (81%)	173 (85%)
Japan	30 (15%)	26 (13%)
USA	10 (5%)	5 (2%)

(Table 1 continues on next page)

of 2%. An interim overall survival analysis (reported here) with the same data cutoff was prespecified to occur at the same time. No hierarchical testing was done; the dual primary endpoints were examined simultaneously. The trial included alpha-spending to analyse overall survival and to control the overall two-sided type I error of 5% (appendix p 126). If one primary endpoint was significant, the corresponding alpha was recycled to the other primary endpoint. For the interim overall survival analysis, the critical level of significance was calculated by means of alpha-spending according to Lan–DeMets with O'Brien–Fleming boundaries. This value depended on the result of the progression-free survival analysis (owing to alpha re-allocation) and the number of deaths observed at the interim analysis. If the progression-free survival analysis was significant, the boundary for significance after 234 deaths (as observed in the present analysis) was $p<0·0238$; if the progression-free survival analysis was not significant, there would be no recycling of alpha and the boundary for significance would be $p=0·013$.

Efficacy data were analysed in the intention-to-treat population, defined as all randomly assigned patients regardless of treatment administration analysed according to the treatment assigned. Time-to-event endpoints were estimated by means of Kaplan-Meier analysis; a stratified Cox model was used to calculate HRs with 95% CIs, and a log-rank test stratified by the three factors used for randomisation was used for statistical comparisons. Sensitivity analyses were adjusted for missed tumour assessment visits, start of new anticancer therapy, and post-study immune checkpoint inhibitor therapy. The proportional hazards assumption was tested and inspected visually by means of Schoenfeld residuals. Subgroup analyses of the dual primary endpoints were prespecified in subgroups defined by the three stratification factors used for randomisation (previous concomitant chemoradiation, histological subtype, and chemotherapy backbone) and additional potentially prognostic baseline characteristics (age, race or ethnicity, ECOG performance status, disease status). Exploratory biomarker analyses, including for PD-L1 status, are planned and will be reported separately. Safety was analysed in the safety population, comprising all patients who received at least one dose of study drug, analysed according to the study treatment received. An independent data monitoring committee evaluated and monitored the safety of the study population, reviewing the safety data approximately every 6 months, or more frequently if appropriate. This study is registered with ClinicalTrials.gov, NCT03556839, and is ongoing.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Oct 8, 2018, and Aug 20, 2021, 519 patients were assessed for eligibility, and 410 were enrolled and randomly assigned: 206 to experimental therapy and 204 to standard therapy (figure 1). Baseline characteristics were generally well balanced (table 1). Overall, 263 (64%) of 410 patients had received previous chemoradiotherapy with or without surgery, and 90 (22%) of 410 had stage IVB disease at trial entry.

At the primary analysis data cutoff (July 17, 2023), median duration of follow-up was 32·9 months (95% CI 31·2–34·6) in the overall population. By this date, progression-free survival events had occurred in 304 (74%) of 410 patients (138 [67%] of 206 in the experimental group and 166 [81%] of 204 in the standard group). The HR for progression-free survival was 0·62 (95% CI 0·49–0·78; stratified log-rank p<0·0001; figure 2A). Median progression-free survival was 13·7 months (95% CI 12·3–16·6) with experimental therapy and 10·4 months (9·7–11·7) with standard therapy. Sensitivity analyses showed consistent results (appendix p 5). No evidence was seen of non-proportional hazards (p=0·27 for progression-free survival and p=0·81 for overall survival on the basis of Schoenfeld residuals).

After deaths in 234 (57%) of 410 patients (105 [51%] of 206 in the experimental group, 129 [63%] of 204 in the standard group), the overall survival HR was 0·68 (95% CI 0·52–0·88; stratified log-rank p=0·0046). Median overall survival at the interim analysis was 32·1 months (95% CI 25·3–36·8) with experimental therapy and 22·8 months (20·3–28·0) with standard therapy (figure 2B). The 2-year overall survival rate was 61% (95% CI 53–67) with experimental therapy and 49% (41–56) with standard therapy; 3-year overall survival rates were 42% (34–51) versus 26% (19–34), respectively. After disease progression on study therapy, similar proportions of patients in the two groups received at least one subsequent therapy (75 [54%] of 138 patients with disease progression in the experimental group, 97 [58%] of 166 in the standard group); however, considerably fewer patients in the experimental group (four [3%]) than in the standard group (55 [33%]) received an immune checkpoint inhibitor (appendix pp 6–9).

Subgroup analyses of progression-free survival and overall survival showed a consistent pattern favouring the experimental group in all prespecified subgroups (figure 3).

Objective responses were recorded in 173 (84%) of 206 patients (95% CI 79–89) in the experimental group versus 147 (72%) of 204 (66–78) in the standard group, including complete responses in 65 (32%) patients in the experimental group versus 41 (20%) in the standard group (appendix p 14). The HR for duration of response was 0·60 (95% CI 0·46–0·78). Median duration of response was 13·6 months (95% CI 10·6–21·3) in the experimental group and 8·6 months (8·0–10·6) in the standard group. At 2 years, response was maintained in 40% of patients responding to experimental therapy versus 19% of patients responding to standard therapy (appendix p 15). The HR for time to first subsequent therapy or death was 0·60 (95% CI 0·47–0·76). Median time to first subsequent therapy or death was 19·0 months (95% CI 16·4–24·0) with experimental therapy and 13·2 months (12·0–14·3) with standard therapy (appendix p 16). The HR for second progression or death was 0·61 (95% CI 0·48–0·79), with median second progression-free survival of 25·8 months (95% CI 22·1–32·1) in the experimental group versus 20·3 months (17·8–22·3) in the standard group (appendix p 17).

	Atezolizumab plus bevacizumab plus chemotherapy (experimental group; n=206)	Bevacizumab plus chemotherapy (standard group; n=204)
(Continued from previous page)		
Histological subtype		
Squamous cell carcinoma	164 (80%)	157 (77%)
Adenocarcinoma	36 (17%)	43 (21%)
Adenosquamous cell carcinoma	6 (3%)	4 (2%)
International Federation of Gynecology and Obstetrics stage at diagnosis		
I	31 (15%)	42 (21%)
II	61 (30%)	53 (26%)
III not otherwise specified	14 (7%)	12 (6%)
IIIA	2 (1%)	4 (2%)
IIIB	34 (17%)	22 (11%)
IV not otherwise specified	5 (2%)	8 (4%)
IVA	11 (5%)	6 (3%)
IVB	43 (21%)	50 (25%)†
Not assessed or pre-invasive	4 (2%)	5 (2%)
Missing	1 (<1%)	2 (1%)
Disease status at screening		
Newly diagnosed metastatic disease (stage IVB)	43 (21%)	47 (23%)
Recurrent (includes patients with distant disease)	150 (73%)	151 (74%)
Persistent	13 (6%)	6 (3%)
Disease location at screening		
Pelvic and distant	102 (50%)	90 (44%)
Distant only	71 (34%)	74 (36%)
Pelvic only	33 (16%)	40 (20%)
Initial therapy		
Concurrent chemoradiotherapy	70 (34%)	85 (42%)
Surgery	9 (4%)	14 (7%)
Surgery followed by chemoradiotherapy	64 (31%)	44 (22%)
Surgery followed by radiotherapy	5 (2%)	11 (5%)
Primary radiotherapy	2 (1%)	3 (1%)
None	56 (27%)	47 (23%)
Investigator-selected platinum backbone		
Cisplatin	124 (60%)	119 (58%)
Carboplatin	82 (40%)	85 (42%)

Data are median (IQR) or n (%). *Data not available for 99 patients in accordance with local legislation. †Stage IVB at diagnosis but recurrent at study entry.

Table 1: **Baseline characteristics**

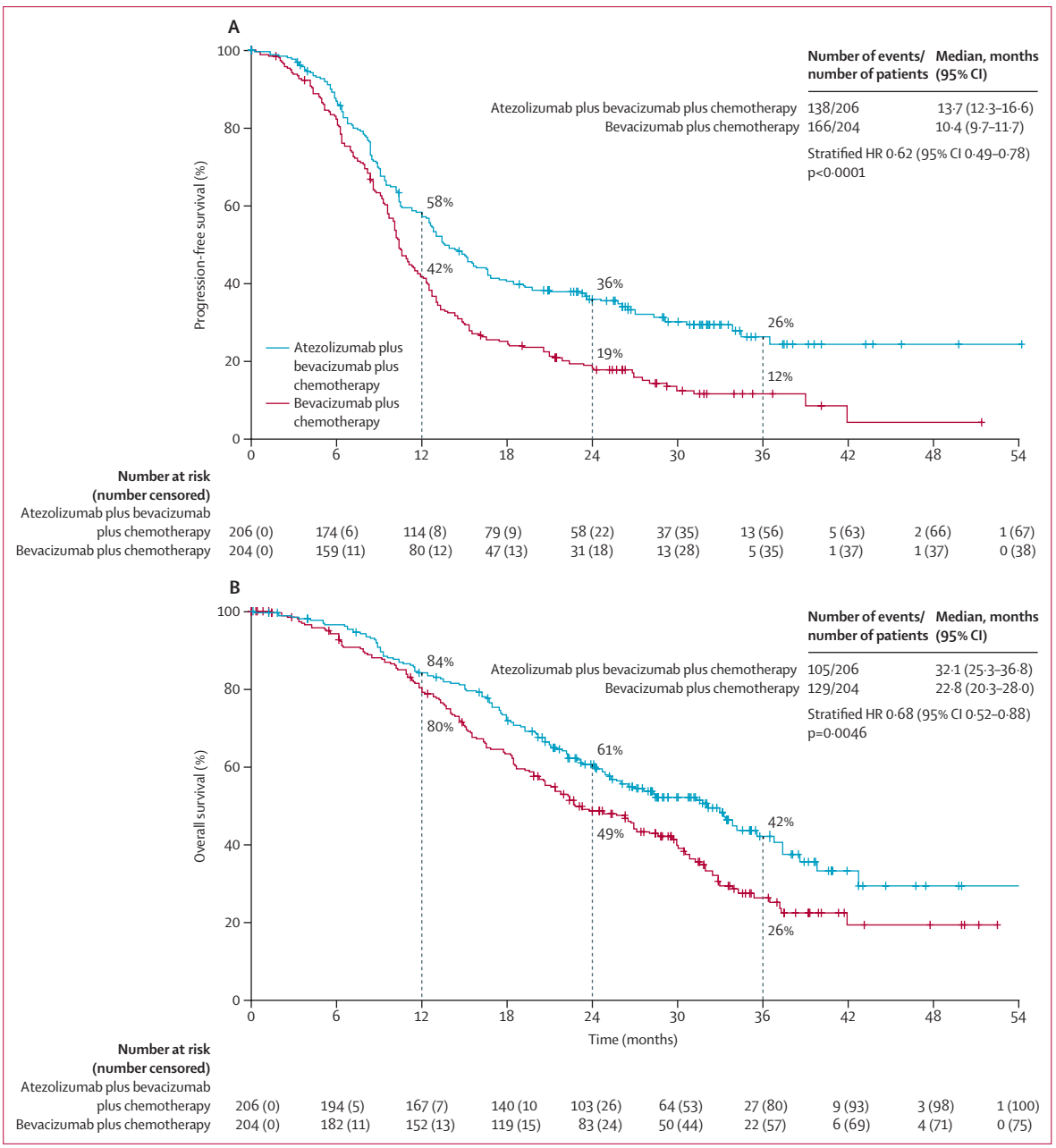

Figure 2: **Kaplan-Meier estimates of (A) progression-free survival and (B) overall survival in the intention-to-treat population**
The boundary for significance at the interim overall survival analysis was p=0·024.

At the data cutoff, 47 (23%) of 206 patients were still receiving experimental therapy and 14 (7%) of 204 patients were still receiving standard therapy. Median treatment duration was 12·7 months (IQR 7·6–24·8) in the experimental group versus 8·5 months (5·1–13·9) in the standard group. Median duration of chemotherapy was six cycles (IQR 6–8) in both groups, whereas median bevacizumab duration was longer in the experimental group (14 cycles [IQR 7–25]) than the standard group (ten cycles [6–18]). Median atezolizumab duration was 16 cycles (IQR 8–32).

The most common all-grade adverse events with both treatments were peripheral or sensory neuropathy, asthenia, nausea, alopecia, neutropenia, and anaemia (and constipation and diarrhoea with experimental therapy; table 2). Incidences of all-grade diarrhoea, arthralgia, pyrexia, rash, hypothyroidism, constipation, and myalgia were numerically higher in the experimental group. Grade 3 or worse adverse events occurred in 161 (79%) of 205 patients receiving experimental therapy and 149 (75%) of 199 receiving standard therapy, most commonly hypertension, haematological events, and

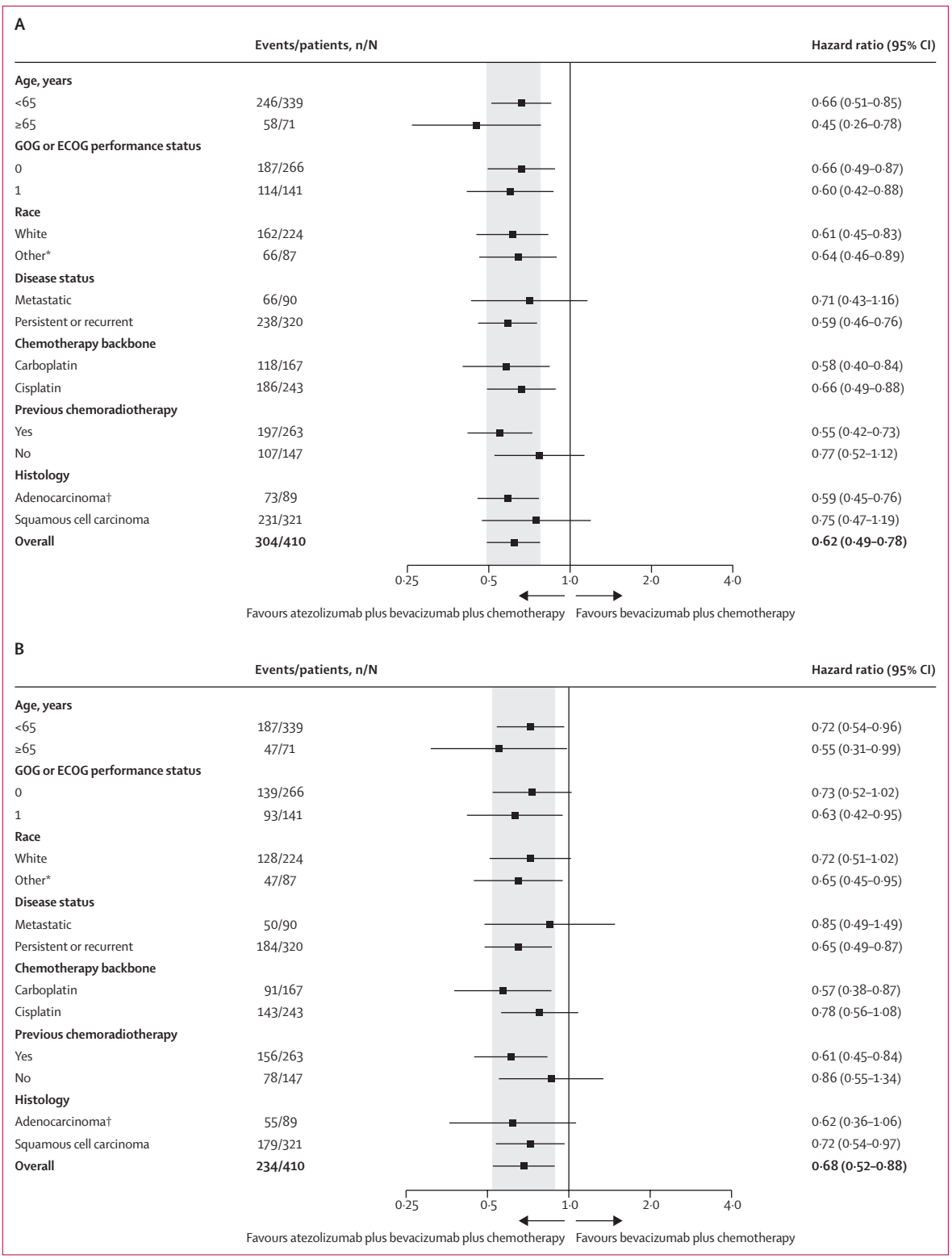

Figure 3: **Subgroup analyses of (A) progression-free survival and (B) overall survival in the intention-to-treat population**
ECOG=Eastern Cooperative Oncology Group. GOG=Gynecologic Oncology Group. *Other includes Asian (n=58), Latin (n=18), Arab (n=5), Black (n=5), and Gypsy (n=1); not available in 99 patients according to local legislation. †Adenocarcinoma includes adenosquamous carcinoma.

	Atezolizumab plus bevacizumab plus chemotherapy (experimental group; n=205)				Bevacizumab plus chemotherapy (standard group; n=199)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Peripheral or sensory neuropathy	96 (47%)	15 (7%)	0	0	94 (47%)	8 (4%)	0	0
Asthenia	84 (41%)	22 (11%)	1 (<1%)	0	86 (43%)	17 (9%)	0	0
Nausea	92 (45%)	9 (4%)	0	0	88 (44%)	8 (4%)	0	0
Alopecia	87 (42%)	1 (<1%)	1 (<1%)	0	75 (38%)	2 (1%)	1 (<1%)	0
Anaemia	58 (28%)	28 (14%)	1 (<1%)	0	58 (29%)	14 (7%)	1 (<1%)	0
Constipation	83 (40%)	3 (1%)	0	0	65 (33%)	2 (1%)	0	0
Diarrhoea	73 (36%)	8 (4%)	1 (<1%)	0	45 (23%)	6 (3%)	0	0
Neutropenia	44 (21%)	24 (12%)	13 (6%)	0	33 (17%)	36 (18%)	13 (7%)	0
Hypertension	37 (18%)	36 (18%)	0	0	46 (23%)	32 (16%)	0	0
Arthralgia	65 (32%)	2 (1%)	0	0	39 (20%)	0	0	0
Proteinuria	45 (22%)	13 (6%)	1 (<1%)	0	44 (22%)	7 (4%)	0	0
Pyrexia	46 (22%)	3 (1%)	0	0	21 (11%)	1 (1%)	0	0
Urinary tract infection	41 (20%)	7 (3%)	0	0	33 (17%)	8 (4%)	0	0
Myalgia	46 (22%)	2 (1%)	0	0	31 (16%)	1 (1%)	0	0
Thrombocytopenia	32 (16%)	10 (5%)	1 (<1%)	0	19 (10%)	8 (4%)	4 (2%)	0
Rash	38 (19%)	4 (2%)	0	0	17 (9%)	0	0	0
Headache	39 (19%)	1 (<1%)	0	0	30 (15%)	2 (1%)	0	0
Abdominal pain lower	35 (17%)	4 (2%)	0	0	40 (20%)	5 (3%)	0	0
Vomiting	34 (17%)	3 (1%)	0	0	28 (14%)	7 (4%)	0	0
Decreased appetite	32 (16%)	5 (2%)	0	0	26 (13%)	1 (<1%)	0	0
Back pain	35 (17%)	1 (<1%)	0	0	29 (15%)	3 (2%)	0	0
Fatigue	26 (13%)	6 (3%)	0	0	21 (11%)	6 (3%)	0	0
Hypothyroidism	30 (15%)	0	0	0	12 (6%)	0	0	0
Musculoskeletal pain	24 (12%)	2 (1%)	0	0	19 (10%)	1 (<1%)	0	0
Neurotoxicity	21 (10%)	4 (2%)	0	0	23 (12%)	5 (3%)	0	0
Blood creatinine increased	24 (12%)	0	0	0	22 (11%)	1 (<1%)	0	0
Stomatitis	22 (11%)	1 (<1%)	0	0	13 (7%)	0	0	0
COVID-19	23 (11%)	0	0	0	12 (6%)	2 (1%)	0	0
Dysuria	23 (11%)	0	0	0	15 (8%)	1 (<1%)	0	0
Dyspnoea	20 (10%)	2 (1%)	0	0	14 (7%)	2 (1%)	0	0
Hypomagnesaemia	21 (10%)	1 (<1%)	0	0	13 (7%)	1 (<1%)	1 (<1%)	0
Dysgeusia	22 (11%)	0	0	0	16 (8%)	0	1 (<1%)	0
Pelvic pain	18 (9%)	3 (1%)	0	0	16 (8%)	2 (1%)	0	0
Abdominal pain upper	19 (9%)	1 (<1%)	0	0	17 (9%)	0	0	0
Paraesthesia	17 (8%)	2 (1%)	0	0	17 (9%)	0	0	0
Infusion-related reaction	14 (7%)	3 (1%)	0	0	13 (7%)	1 (<1%)	0	0
Rash maculopapular	14 (7%)	3 (1%)	0	0	2 (1%)	0	0	0
White blood cell count decreased	9 (4%)	5 (2%)	1 (<1%)	0	13 (7%)	5 (3%)	0	0
Platelet count decreased	10 (5%)	4 (2%)	0	0	15 (8%)	3 (2%)	0	0
Vaginal haemorrhage	9 (4%)	2 (1%)	1 (<1%)	1 (<1%)	5 (3%)	1 (<1%)	0	0
Pain in extremity	12 (6%)	0	0	0	15 (8%)	2 (1%)	0	0
Febrile neutropenia	1 (<1%)	6 (3%)	4 (2%)	0	0	4 (2%)	0	0
Female genital tract fistula	3 (1%)	8 (4%)	0	0	1 (<1%)	8 (4%)	0	0
Haematuria	9 (4%)	2 (1%)	0	0	10 (5%)	1 (<1%)	0	0
Pain	10 (5%)	1 (<1%)	0	0	8 (4%)	2 (1%)	0	0
Peripheral oedema	11 (5%)	0	0	0	9 (5%)	2 (1%)	0	0
Alanine aminotransferase increased	11 (5%)	0	0	0	19 (10%)	2 (1%)	0	0
Hyponatraemia	7 (3%)	1 (<1%)	1 (<1%)	0	3 (2%)	2 (1%)	1 (<1%)	0
Lymphopenia	6 (3%)	3 (1%)	0	0	8 (4%)	0	0	0
Hypersensitivity	3 (1%)	5 (2%)	0	0	5 (3%)	3 (2%)	0	0

(Table 2 continues on next page)

	Atezolizumab plus bevacizumab plus chemotherapy (experimental group; n=205)				Bevacizumab plus chemotherapy (standard group; n=199)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Polyneuropathy	5 (2%)	3 (1%)	0	0	1 (<1%)	3 (2%)	0	0
Pyelonephritis	3 (1%)	4 (2%)	0	0	1 (<1%)	4 (2%)	0	0
Hydronephrosis	4 (2%)	3 (1%)	0	0	1 (<1%)	3 (2%)	0	0
Malaise	6 (3%)	1 (<1%)	0	0	8 (4%)	3 (2%)	0	0
Leukopenia	1 (<1%)	5 (2%)	0	0	5 (3%)	5 (3%)	0	0
Intestinal obstruction	0	4 (2%)	0	1 (<1%)	0	1 (<1%)	0	0
Urinary tract obstruction	1 (<1%)	4 (2%)	0	0	1 (<1%)	0	0	0
Renal colic	2 (1%)	3 (1%)	0	0	1 (<1%)	0	0	0
Hepatotoxicity	2 (1%)	1 (<1%)	1 (<1%)	0	2 (1%)	0	0	0
Colitis	1 (<1%)	3 (1%)	0	0	0	1 (<1%)	0	0
Acute kidney injury	1 (<1%)	3 (1%)	0	0	1 (<1%)	2 (1%)	0	0
Lymphocyte count decreased	2 (1%)	2 (1%)	1 (<1%)	0	5 (3%)	3 (2%)	0	0
Enteritis	2 (1%)	2 (1%)	0	0	2 (1%)	0	0	0
General physical health deterioration	2 (1%)	2 (1%)	0	0	0	1 (<1%)	0	0
Dehydration	2 (1%)	2 (1%)	0	0	1 (<1%)	0	0	0
Hypoalbuminaemia	2 (1%)	2 (1%)	0	0	5 (3%)	0	0	0
Intestinal perforation	0	0	3 (1%)	0	0	0	0	1 (<1%)
Sepsis	0	3 (1%)	0	0	0	3 (2%)	1 (<1%)	0
Malnutrition	0	3 (1%)	0	0	0	1 (<1%)	0	0
Pulmonary embolism	1 (<1%)	2 (1%)	0	0	1 (<1%)	1 (<1%)	0	0
Enterovesical fistula	0	1 (<1%)	1 (<1%)	0	0	1 (<1%)	0	0
Urogenital fistula	0	2 (1%)	0	0	1 (<1%)	0	0	0
Pancytopenia	0	2 (1%)	0	0	0	0	0	0
Urinary retention	0	2 (1%)	0	0	1 (<1%)	1 (<1%)	0	0
Febrile infection	0	2 (1%)	0	0	0	0	0	0
Infection	0	2 (1%)	0	0	0	0	0	0
Urosepsis	0	2 (1%)	0	0	0	0	0	0
Hypertriglyceridaemia	2 (1%)	0	0	0	1 (<1%)	2 (1%)	0	0
Subileus	0	1 (<1%)	0	0	0	2 (1%)	0	0
Ileus	0	1 (<1%)	0	0	0	2 (1%)	0	0
Deep vein thrombosis	0	0	0	0	3 (2%)	2 (1%)	0	0
Cholelithiasis	0	0	0	0	0	2 (1%)	0	0
General physical condition abnormal	0	0	0	0	0	2 (1%)	0	0

The following grade 3 adverse events occurred in one patient each in the experimental group: mucosal inflammation, urinary incontinence, dizziness, abdominal pain lower, weight decreased, renal failure, upper respiratory tract infection, thrombosis, respiratory tract infection, sciatica, device-related infection, flushing, nasal congestion, urine leukocyte esterase positive, cellulitis, hyperhidrosis, procedural pain, nail toxicity, cell death, vitamin D deficiency, pyelocaliectasis, rectal ulcer, adverse drug reaction, *Clostridium* colitis, flank pain, glomerular filtration rate decreased, weight increased, syncope, nephritis, dermatitis, psoriasis, illness, cystitis *Klebsiella*, vaginal fistula, cholecystitis, acute pyelonephritis, fistula, presyncope, lymph node pain, immune-mediated thyroiditis, iridocyclitis, uveitis, diverticular perforation, immune-mediated nephritis, intestinal pseudo-obstruction, hyperthermia, performance status decreased, hepatobiliary disease, COVID-19 pneumonia, cervicitis, influenza, *Pseudomonas* infection, vascular access complication, myositis, metastases to central nervous system, hydrocephalus, device dislocation, immune-mediated nephritis, tubulointerstitial nephritis, urethral obstruction, urinary bladder haemorrhage, urinary fistula, urinary tract injury, pustular psoriasis, skin reaction, and toxic skin eruption. The following grade 3 adverse events occurred in one patient each in the standard group: aspartate aminotransferase increased, dry skin, intermenstrual bleeding, vulvovaginal pain, radiation gastroenteritis, urine leukocyte esterase positive, glomerular filtration rate decreased, cancer pain, neuralgia, anal ulcer, embolism, aspiration, hypocalcaemia, illness, cholecystitis, acute pyelonephritis, fistula, discomfort, urticaria, vasculitis, extravasation, blood cholesterol increased, migraine, gastrointestinal disorder, vena cava thrombosis, bacteraemia, osteonecrosis of jaw, incontinence, orthostatic intolerance, conduction disorder, ototoxicity, gastrointestinal perforation, small intestinal perforation, condition aggravated, oedema, suprapubic pain, bile duct stenosis, cholangitis, soft tissue infection, streptococcal bacteraemia, urethritis, fibula fracture, food intolerance, hyperlipasaemia, bladder neoplasm, nephrotic syndrome, and hypertensive crisis. The following grade 4 adverse events occurred in one patient each in the experimental group: respiratory failure, septic shock, large intestine perforation, *Aspergillus* infection, pelvic abscess, pelvic infection, peritonitis, blood creatinine phosphokinase increased, petit mal epilepsy, and posterior reversible encephalopathy syndrome. The following grade 4 adverse events occurred in one patient each in the standard group: septic shock, fistula of small intestine, rectal perforation, and hypokalaemia. The following grade 5 adverse events occurred in one patient each in the experimental group: ileal perforation, disease progression (death reason recorded by the investigator as disease progression not adverse event), jaundice cholestatic, and aspiration. Two additional deaths from adverse events (nausea and vomiting in one patient, septic shock in one patient, both considered unrelated to treatment) occurred >60 days after the last dose and are therefore outside the reporting window for adverse events. The following grade 5 adverse events occurred in one patient each in the standard group: cardiorespiratory arrest, respiratory tract infection, respiratory failure, metastases to meninges, and neoplasm progression.

Table 2: **All-cause adverse events in the safety population (events occurring in ≥10% of participants, or any grades 3–5)**

asthenia. Adverse events led to discontinuation of any treatment in 31 (15%) of 205 patients in the experimental group versus 31 (16%) of 199 in the standard group (appendix p 10). The most common adverse events of special interest for atezolizumab were grade 1–2 hypothyroidism (17 [8%] of 205), grade 1–2 hyperthyroidism (seven [3%]), and infusion-related reaction (seven [3%]; appendix p 11). The most common adverse events of special interest for bevacizumab were grade 1–3 hypertension (52 [25%] of 205 patients in the experimental group and 50 [25%] of 199 in the standard group), proteinuria (46 [22%] in the experimental group *vs* 41 [21%] in the standard group), and grade 1–2 epistaxis (16 [8%] *vs* 19 [10%], respectively). Gastrointestinal fistulae occurred in two patients (1%) receiving experimental therapy and one (1%) receiving standard therapy; genitourinary fistulae occurred in nine (4%) versus five (3%) patients, respectively (appendix p 12). Adverse events were fatal in 13 patients (seven [3%] of 205 receiving experimental therapy, six [3%] of 199 receiving standard therapy); of these, three deaths (1%) in the experimental group were considered treatment-related (obstructive jaundice after cycle 1, ileal perforation after cycle 25, vaginal haemorrhage after clinical progression).

Discussion

To the best of our knowledge, this investigator-initiated phase 3 trial (BEATcc) is the first to evaluate the addition of a PD-L1 inhibitor (atezolizumab) to the standard of care established in the GOG240 trial (bevacizumab and chemotherapy) for metastatic, persistent, or recurrent cervical cancer. The BEATcc trial met both of its dual primary objectives, showing significant and clinically meaningful improvements in progression-free survival and overall survival with the addition of atezolizumab to first-line bevacizumab and chemotherapy in patients with metastatic, persistent, or recurrent cervical cancer. The threshold for significance was met at the interim overall survival analysis, with an increase in median overall survival of almost 10 months. Median overall survival exceeding 2·5 years, with 61% of patients alive at 2 years, represents the current benchmark for first-line treatment of advanced cervical cancer. This improvement was shown despite the better-than-expected performance of standard therapy (median overall survival of 23 months *vs* 17·5 months in GOG240[4]), which might reflect more effective subsequent therapies, enrolment of a better-selected patient population with a more favourable prognosis, or both. Remarkably, the magnitudes of the progression-free and overall survival benefits from the addition of atezolizumab to bevacizumab plus chemotherapy (HR=0·62 and 0·68, respectively) were at least as large as those observed one decade ago with the addition of bevacizumab to chemotherapy in GOG240 (HR=0·67 and 0·71, respectively),[3] which led to the regulatory approval of a new standard of care in cervical cancer. Secondary efficacy endpoints also showed consistently more favourable outcomes in the experimental group. Of note, 84% of patients responded to atezolizumab-containing therapy (32% with a complete response), representing clinically meaningful tumour shrinkage in this typically symptomatic disease. Overall survival follow-up continues and final results are expected in 2024.

The safety profiles of both regimens were as expected with atezolizumab, bevacizumab, and a platinum–paclitaxel backbone. Importantly, following lessons learned from GOG240 (with cisplatin)[3] and CECILIA (with carboplatin in a more selected population),[10] patient selection in BEATcc led to a lower incidence of grade 3 or worse fistulae (3% overall *vs* 6% in GOG240[4]), which is one of the most concerning adverse events in patients with cervical cancer treated with bevacizumab. Consistent with previous phase 3 trials of atezolizumab in gynaecological cancers,[11–13] hypothyroidism and rash (both predominantly grade 1–2) were more common in the experimental group.

Until recently, the success of immunotherapy for recurrent or metastatic cervical cancer was limited to therapies targeting the PD-1 receptor given as monotherapy[14–17] or with anti-cytotoxic T-lymphocyte-associated protein 4 agents.[18,19] Phase 3 trials have explored the PD-1 inhibitor pembrolizumab with first-line platinum-based chemotherapy (KEYNOTE-826),[5] the PD-1 inhibitor cemiplimab versus chemotherapy after progression on platinum-based therapy (EMPOWER-Cervical 1–GOG-3016–ENGOT-cx9),[20] and the PD-L1 inhibitor durvalumab given concurrently with chemoradiotherapy followed by maintenance for locally advanced cervical cancer (CALLA).[21] In KEYNOTE-826, benefit from pembrolizumab was most apparent in patients with PD-L1-positive tumours (89% of the population),[5] leading to regulatory approval in PD-L1-positive cervical cancer.[22] In the EMPOWER-Cervical 1 trial, cemiplimab was more effective than chemotherapy irrespective of PD-L1 status;[20] consequently, cemiplimab received approval from the European Medicines Agency on Nov 23, 2022, for all patients with recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy.[23] Finally, durvalumab failed to improve progression-free survival when added to standard chemoradiotherapy in an almost entirely (92%) PD-L1-positive population.[21]

The BEATcc trial enrolled an all-comer population with no biomarker selection, which could be considered a limitation; however, without a robust biomarker to identify those patients deriving greater or lesser benefit from the experimental regimen, the value of enrolling a biomarker-selected population is questionable. In addition, 80% of the population had squamous histology, which is characterised by higher PD-L1 expression than in adenocarcinoma.[7] Despite this, the HRs for the dual primary endpoints in BEATcc favoured the experimental group in the subgroup of patients with adenocarcinoma

(0·59 for progression-free survival, 0·62 for overall survival) as well as those with squamous cell carcinoma. These and previously reported results for other agents raise the question of whether PD-L1 is necessary to select patients deriving greatest benefit from immunotherapy for cervical cancer, or whether the relationship between PD-L1 and HPV infection makes it a less discerning biomarker. Another potential limitation is the lack of a placebo in the control group. However, although progression-free survival might be affected by investigator bias, overall survival is not, and was one of the two dual endpoints of this trial showing a robust HR and superiority of the experimental group. Bevacizumab was mandatory; therefore, patients for whom bevacizumab was contraindicated were not enrolled in this trial, resulting in a more selected population, which might marginally reduce the generalisability of the trial results. On the other hand, mandatory bevacizumab provides a clean and statistically rigorous trial design to confirm the biological hypothesis forming the premise of our clinical trial. Angiogenesis and immune suppression are two facets of a linked biological programme;[24] given the intimate relationship between angiogenesis and immunosuppression, inhibiting both pathways might potentially result in an improved and more durable clinical benefit. BEATcc outcomes allow firm conclusions to be drawn on the role of immunotherapy combined with bevacizumab and platinum-containing therapy. Finally, little is known about the efficacy of PD-L1 inhibition after previous PD-1 inhibitor therapy, which might become more relevant if the ENGOT-cx11–GOG-3047–KEYNOTE-A18 trial evaluating pembrolizumab with chemoradiation for newly diagnosed high-risk locally advanced cervical cancer shows an overall survival benefit in the future. Targeting PD-L1 rather than PD-1 might be of interest rather than re-exposure to PD-1 in patients progressing after initial PD-1 therapy, thus these first data on the use of PD-L1 are an important addition to immune checkpoint strategies.

Although crossover to atezolizumab was not permitted in BEATcc, 33% of patients whose disease progressed on standard therapy subsequently received immune checkpoint inhibitors, which could confound survival given the efficacy of immune checkpoint inhibitors after platinum-based therapy.[14,20] Nevertheless, the observed improvement in median overall survival was almost 10 months with atezolizumab.

In conclusion, these results provide clear evidence that the addition of atezolizumab significantly improves the efficacy of first-line bevacizumab and chemotherapy for metastatic, persistent, or recurrent cervical cancer. This benefit was shown in a patient population that was unselected for PD-L1 status. We believe that atezolizumab with bevacizumab and platinum-based chemotherapy should be considered as a new first-line option for patients with metastatic, persistent, or recurrent cervical cancer.

Contributors

AO was the principal investigator for the study. AO, LG, JM-G, MT, UDG, KL, LW, NC, LD, AL, AG-O, SN, AA, MJR, LF-M, SY, DL, IR-C, LM, FJ, JA, PF, IR, CL, JAP-F, MY, HD, VD'H, and LMR enrolled patients and collected data. GV analysed and visualised the data. AO and GV interpreted the results, wrote the original draft of the manuscript with the support of a professional medical writer, and directly accessed and verified the underlying data reported in the manuscript. Trial conduct and statistical analyses were the responsibility of Grupo Español de Investigación en Cáncer ginecologico. Representatives of the funder had the opportunity to review the manuscript for accuracy but had no involvement in writing or deciding to submit the manuscript for publication. All authors had full access to all the data in the study and had final responsibility to submit the Article for publication.

Declaration of interests

AO reports personal fees for participation in the advisory boards of AstraZeneca, Clovis Oncology, Deciphera, Genmab, GSK, Immunogen, Mersana Therapeutics, PharmaMar, MSD de España, Agenus, Sutro, Corcept Therapeutics, EMD Serono, Novocure, Shattuck Labs, iTeos, and Eisai; travel and accommodation support from AstraZeneca, PharmaMar, and Roche; and funding paid to institution from AbbVie Deutschland, Advaxis, Aeterna Zentaris, Amgen, Aprea Therapeutics AB, Clovis Oncology, Eisai, F Hoffmann-La Roche, Regeneron Pharmaceuticals, Immunogen, MSD de España, Takeda, PharmaMar, Tesaro, and Bristol Myers Squibb. LG reports support for attending meetings or travel from Viatris, GSK, and MSD; consulting fees paid to institution for participation in the advisory boards of Clovis, GSK, AstraZeneca, and Seagen; and speaker honoraria paid to institution from AstraZeneca, GSK, and Eisai. JM-G reports personal fees for participation in the advisory boards of AstraZeneca, Clovis, GSK, and PharmaMar; research grants paid to institution from GSK and Roche; and travel and accommodation expenses from GSK–Tesaro, Pfizer, and PharmaMar. GV reports honoraria for speaker engagements from MSD, Pierre Fabre, GSK, and Pfizer; and consulting fees from Reveal Genomics. UDG reports personal consulting fees from Amgen, AstraZeneca, Pfizer, BMS, Clovis Oncology, Dompé Farmaceutici, Merck, MSD, PharmaMar, Astellas, Bayer, Ipsen, Novartis, Eisai, and Janssen; other funding paid to institution from AstraZeneca, Sanofi, and Roche; and support for attending meetings or travel from Pfizer, Ipsen, and AstraZeneca. KL reports personal honoraria from Eisai; participation on data safety monitoring or advisory boards of Eisai, MSD, Nykode, AstraZeneca, and GSK (honoraria paid to institution); and funding paid to institution from GSK. LW reports personal honoraria for participation in the advisory boards of AstraZeneca, Pfizer, GSK, Roche, MSD–Merck, Eisai, and Seagen; personal honoraria for speaker engagements from AstraZeneca, Eisai, GSK, Pfizer, Roche, MSD–Merck, and Seagen; and support for attending meetings or travel from GSK and MSD. NC reports consultancy or advisory roles for AstraZeneca, Clovis Oncology, Eisai, GSK, Immunogen, Mersana, MSD–Merck, Nuvation Bio, OncXerna, Pfizer, Pieris, and Roche; promotional speaker roles for AstraZeneca, Novartis, Clovis Oncology, MSD–Merck, and GSK; research grants from AstraZeneca, GSK, and Roche; and support for attending meetings or travel from AstraZeneca and GSK. LD reports personal fees for scientific advisory boards from Aadi Bioscience and Regeneron; fees paid to institution for scientific advisory boards from Merck; membership of the *British Journal of Obstetrics and Gynaecology* Editorial Board; personal royalties for writing expert content for UpToDate, Wiley, and the American Society of Clinical Oncology; personal fees for continuing medical education activities for Advance Medical, CEA Group, and Clinical Care Options; research funding paid to institution for investigator-initiated trials from Merck; clinical trial grants paid to institution from Genentech–Roche, AbbVie (GOG 3005), Acrivon, Advaxis, Aduro BioTech, Alkermes, Blueprint, Constellation, Eisai, GSK–Novartis, Immunogen, Inovio, Iovance, Karyopharm, KSQ Therapeutics, Lycera, Merck, Morab, MorphoTek, Naveris, Nurix, OncoQuest, Pfizer, Syndax, Tesaro, and Zentalis; and fees paid to institution for membership of data and safety monitoring committees for Agenus and Inovio. AL reports personal fees for presentations or educational events from Medscape and PeerVoice; consulting fees paid to institution from Owkin; speaker honoraria paid to institution from

MSD, GSK, AstraZeneca, and Eisai; fees paid to institution for participation in the advisory boards of AstraZeneca, MSD, Seagen, GSK, Genmab, Zentalis, and Blueprint; non-remunerated independent data safety monitoring board participation for Clovis and BMS; an educational grant paid to institution from AstraZeneca; and support for attending meetings or travel from OSE Immunotherapeutics. AG-O reports honoraria paid to institution for participation in the advisory board of Novartis; personal honoraria for speaker engagements from AstraZeneca, Pfizer, Novartis, and Lilly; and support for attending meetings or travel from Pfizer and Novartis. MJR reports personal fees for participation in the advisory boards of AstraZeneca, Clovis Oncology, GSK, PharmaMar, MSD de España, Eisai, and Roche; personal fees for speaker engagements from MSD, AstraZeneca, Clovis Oncology, GSK, and PharmaMar; and travel and accommodation from AstraZeneca, PharmaMar, Roche, GSK, and MSD de España. LF-M reports honoraria paid to institution for participation in the advisory boards of GSK; honoraria paid to institution for speaker engagements from GSK, AstraZeneca–MSD, and Eisai; and support for attending meetings or travel from AstraZeneca–MSD and GSK. DL reports personal fees for participation in the advisory boards of AstraZeneca, Clovis Oncology, Corcept, Genmab, GSK, Immunogen, MSD, Oncoinvent, PharmaMar, Seagen, and Sutro; personal fees for consultancy roles from AstraZeneca, Clovis Oncology, Genmab, GSK, Immunogen, MSD, Novartis, PharmaMar, and Seagen; clinical trial or research funding to institution from Clovis Oncology, GSK, MSD, and PharmaMar; other financial or non-financial interests from AstraZeneca, Clovis Oncology, Corcept, Genmab, GSK, Immunogen, Incyte, MSD, Novartis, Oncoinvent, PharmaMar, Roche, Seagen, and Sutro; and travel grants from AstraZeneca, Clovis Oncology, and GSK. IR-C reports personal honoraria for participation in the advisory boards of Adaptimmune, Agenus, Amgen, AstraZeneca, BMS, Clovis, Daiichi Sankyo, Deciphera, Eisai, EQRx, GSK, Merck Serono, MacroGenics, Mersana, Novartis, Onxeo, Roche, and Sutro Biopharma; honoraria paid to institution for participation in the advisory boards of MSD (translational research); and funding paid to institution for translational research from BMS. LM reports participation in the advisory board of Roche; and honoraria for speaker engagements from Roche, GSK, Clovis Oncology, AstraZeneca, Pfizer, Novartis, and Lilly. FJ reports honoraria for lectures, expert boards, and educational events from AstraZeneca, Clovis Oncology, GSK, and Seagen; travel and accommodation support from GSK, Eisai, and MSD; and financial support for national academic GINECO trials from GSK and AstraZeneca. JA reports honoraria for speaker bureaus from GSK, Roche, AstraZeneca, MSD, PharmaMar, and Clovis; and advisory boards for GSK, MSD, AstraZeneca, and Clovis. PF reports personal fees for expert testimony from Daiichi; personal fees for invited speaker engagements from GSK and MSD; and support for attending meetings or travel from Lilly, Novartis, and GSK. IR reports personal fees for advisory boards from AstraZeneca, Clovis Oncology, GSK, PharmaMar, Roche, and MSD; and travel and accommodation from AstraZeneca, PharmaMar, Roche, and GSK. CL reports honoraria for advisory board participation from GSK; personal honoraria for speaker engagements from GSK, Clovis Oncology, Eisai, and MSD; and support for attending meetings or travel from MSD and GSK. JAP-F reports honoraria for speaker engagements from AstraZeneca, PharmaMar, Pharma&, Clovis, and GSK; payment for expert testimony from AstraZeneca, GSK, Roche, and PharmaMar; support for attending meetings or travel from Karyopharm, AstraZeneca, Roche, and PharmaMar; grants paid to institution from GSK and PharmaMar; equipment, materials, drugs, medical writing, gifts, or other services paid to institution from GSK; participation on data safety monitoring or advisory boards for Ability Pharma; and has a patent pending in breast cancer. HD reports personal honoraria for advisory board participation from AstraZeneca. LMR reports honoraria for speaker engagements from Genmab–Seagen, Blueprint Oncology, Curio Science, and Physicians Education Resource; honoraria for participation in the advisory boards of AstraZeneca, Clovis Oncology, GOG Foundation, Aadi Biosciences, Seagen, OnTarget Laboratories, Merck, Mersana, Rubius Therapeutics, Myriad Genetics, Genentech–Roche, Eisai, Novocure, and Immunogen; consulting fees from the GOG Foundation; and funding paid to institution from Genentech–Roche, On Target Laboratories, Pfizer, Aivita Biomedical, Tesaro, AstraZeneca, Merck, Akeso Biopharma, and Grupo Español de Investigación en Cáncer ginecologico. All other authors declare no competing interests.

Data sharing

The data will be available for academic purposes after completion of the trial and finalisation of the clinical study report. Requests should be sent to ipuebla@grupogeico.net and will be considered on a case-by-case basis.

Acknowledgments

The trial was funded by F Hoffmann-La Roche and sponsored by the Grupo Español de Investigación en Cáncer ginecologico. The authors thank all patients and their families; the study investigators (listed in the appendix pp 3–5); the staff from the participating study groups, particularly the project managers Yanina Brauer and Gabriele Elser (Arbeitsgemeinschaft Gynaekologische Onkologie), Iratxe Puebla and Carmen Marqués (Grupo Español de Investigación en Cáncer ginecologico), Sixtine Genel (Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens), Tetsuo Seki and Seiichiro Takahashi (Japanese Gynecologic Oncology Group), Giuseppe Funari (Mario Negri Gynecologic Oncology group), Anna Miserocchi and Bernadette Vertogen (Multicenter Italian Trials in Ovarian cancer and gynecologic malignancies), and Johanne Hestvang (Nordic Society of Gynecological Oncology); the GOG Foundation and GOG Partners; members of the independent data monitoring committee (Ignace Vergote [Chair], Susana Banerjee, and Andrew Embleton); and F Hoffmann-La Roche for financial support and drug supply. The authors also thank Jennifer Kelly (Medi-Kelsey, Ashbourne, UK) for medical writing assistance, funded by GEICO, and Ana Moreno, Laura Fuentes, and Susana Vara (APICES, Madrid, Spain) for their support with the study setup, coordination, and project management, monitoring, pharmacovigilance, data management, and statistical analysis.

References

1 Lei J, Ploner A, Elfström KM, et al. HPV vaccination and the risk of invasive cervical cancer. *N Engl J Med* 2020; **383:** 1340–48.

2 Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; **71:** 209–49.

3 Tewari KS, Sill MW, Long HJ 3rd, et al. Improved survival with bevacizumab in advanced cervical cancer. *N Engl J Med* 2014; **370:** 734–43.

4 Tewari KS, Sill MW, Penson RT, et al. Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). *Lancet* 2017; **390:** 1654–63.

5 Colombo N, Dubot C, Lorusso D, et al. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. *N Engl J Med* 2021; **385:** 1856–67.

6 Monk BJ, Colombo N, Tewari KS, et al. First-line pembrolizumab + chemotherapy versus placebo + chemotherapy for persistent, recurrent, or metastatic cervical cancer: final overall survival results of KEYNOTE-826. *J Clin Oncol* 2023; published online Nov 1. https://ascopubs.org/doi/10.1200/JCO.23.00914.

7 Mezache L, Paniccia B, Nyinawabera A, Nuovo GJ. Enhanced expression of PD L1 in cervical intraepithelial neoplasia and cervical cancers. *Mod Pathol* 2015; **28:** 1594–602.

8 Shrimali RK, Yu Z, Theoret MR, Chinnasamy D, Restifo NP, Rosenberg SA. Antiangiogenic agents can increase lymphocyte infiltration into tumor and enhance the effectiveness of adoptive immunotherapy of cancer. *Cancer Res* 2010; **70:** 6171–80.

9 Kandalaft LE, Motz GT, Busch J, Coukos G. Angiogenesis and the tumor vasculature as antitumor immune modulators: the role of vascular endothelial growth factor and endothelin. *Curr Top Microbiol Immunol* 2011; **344:** 129–48.

10 Redondo A, Colombo N, McCormack M, et al. Primary results from CECILIA, a global single-arm phase II study evaluating bevacizumab, carboplatin and paclitaxel for advanced cervical cancer. *Gynecol Oncol* 2020; **159:** 142–49.

11 Kurtz JE, Pujade-Lauraine E, Oaknin A, et al. Atezolizumab combined with bevacizumab and platinum-based therapy for platinum-sensitive ovarian cancer: placebo-controlled randomized phase III ATALANTE/ENGOT-ov29 trial. *J Clin Oncol* 2023; **41:** 4768–78.

12 Pignata S, Bookman M, Sehouli J, et al. Overall survival and patient-reported outcome results from the placebo-controlled randomized phase III IMagyn050/GOG 3015/ENGOT-OV39 trial of atezolizumab for newly diagnosed stage III/IV ovarian cancer. *Gynecol Oncol* 2023; **177:** 20–31.

13 Moore KN, Bookman M, Sehouli J, et al. Atezolizumab, bevacizumab, and chemotherapy for newly diagnosed stage III or IV ovarian cancer: placebo-controlled randomized phase III trial (IMagyn050/GOG 3015/ENGOT-OV39). *J Clin Oncol* 2021; **39:** 1842–55.

14 Chung HC, Ros W, Delord JP, et al. Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: results from the phase II KEYNOTE-158 study. *J Clin Oncol* 2019; **37:** 1470–78.

15 O'Malley DM, Oaknin A, Monk BJ, et al. Phase II study of the safety and efficacy of the anti-PD-1 antibody balstilimab in patients with recurrent and/or metastatic cervical cancer. *Gynecol Oncol* 2021; **163:** 274–80.

16 Naumann RW, Hollebecque A, Meyer T, et al. Safety and efficacy of nivolumab monotherapy in recurrent or metastatic cervical, vaginal, or vulvar carcinoma: results from the phase I/II CheckMate 358 trial. *J Clin Oncol* 2019; **37:** 2825–34.

17 Santin AD, Deng W, Frumovitz M, et al. Phase II evaluation of nivolumab in the treatment of persistent or recurrent cervical cancer (NCT02257528/NRG-GY002). *Gynecol Oncol* 2020; **157:** 161–66.

18 O'Malley DM, Neffa M, Monk BJ, et al. Dual PD-1 and CTLA-4 checkpoint blockade using balstilimab and zalifrelimab combination as second-line treatment for advanced cervical cancer: An open-label phase II study. *J Clin Oncol* 2022; **40:** 762–71.

19 Oaknin A, Moore KN, Meyer T, et al. Safety and efficacy of nivolumab (NIVO) ± ipilimumab (IPI) in patients (pts) with recurrent/metastatic cervical cancer (R/M Cx Ca) in checkmate 358. *Ann Oncol* 2022; **33** (suppl 7)**:** S782 (abstr 520MO).

20 Tewari KS, Monk BJ, Vergote I, et al. Survival with cemiplimab in recurrent cervical cancer. *N Engl J Med* 2022; **386:** 544–55.

21 Monk BJ, Toita T, Wu X, et al. Durvalumab versus placebo with chemoradiotherapy for locally advanced cervical cancer (CALLA): a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2023; **24:** 1334–48.

22 Merck, Sharp & Dohme. Keytruda summary of product characteristics. June 29, 2022. https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf (accessed Sept 3, 2023).

23 Regeneron. July 18, 2023. https://www.ema.europa.eu/en/documents/product-information/libtayo-epar-product-information_en.pdf (accessed Sept 3, 2023).

24 Motz GT, Santoro SP, Wang L-P, et al. Tumor endothelium FasL establishes a selective immune barrier promoting tolerance in tumors. *Nat Med* 2014; **20:** 607–15.