Nivolumab with or without ipilimumab in patients with recurrent or metastatic cervical cancer (CheckMate 358): a phase 1–2, open-label, multicohort trial

Ana Oaknin, Kathleen Moore, Tim Meyer, José López-Picazo González, Lot A Devriese, Asim Amin, Christopher D Lao, Valentina Boni, William H Sharfman, Jong Chul Park, Makoto Tahara, Suzanne L Topalian, Manuel Magallanes, Alejandro Molina Alavez, Tariq Aziz Khan, Catherine Copigneaux, Michelle Lee, Charlie Garnett-Benson, Xuya Wang, R Wendel Naumann

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Medical Oncology Service, Vall d'Hebron Institute of Oncology, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain (A Oaknin MD); **Stephenson Cancer Center, Oklahoma City, OK, USA** (K Moore MD); **Sarah Cannon Research Institute, Nashville, TN, USA** (K Moore); **University College London, London, UK** (Prof T Meyer MD); **Clinica Universidad de Navarra, Navarra, Spain** (J López-Picazo González MD); **Universitair Medisch Centrum Utrecht, Utrecht, Netherlands** (L A Devriese MD); **Levine Cancer Institute, Atrium Health, Charlotte, NC, USA** (Prof A Amin MD, R W Naumann MD); **Rogel Cancer Center, University of Michigan, Ann Arbor, MI, USA** (C D Lao MD); **Medical Oncology, START Madrid, Centro Integral Oncológico Clara Campal, Hospital Madrid Norte Sanchinarro, Madrid, Spain** (V Boni MD); **Johns Hopkins Bloomberg-Kimmel Institute for Cancer Immunotherapy and Kimmel Cancer Center, Baltimore, MD, USA** (Prof W H Sharfman MD, Prof S L Topalian MD); **Massachusetts General Hospital, Boston, MA, USA** (J C Park MD); **National Cancer Center Hospital East, Kashiwa, Japan** (M Tahara MD); **Centro Oncológico Internacional, Mexico City, Mexico** (M Magallanes MD); **Centro de Atención e Investigación Clínica en Oncología, Mérida, Mexico** (A Molina Alavez MD); **Bristol Myers Squibb, Princeton, NJ, USA** (T A Khan MD, C Copigneaux PhD, M Lee MS,

Summary

Background In preliminary findings from the recurrent or metastatic cervical cancer cohort of CheckMate 358, nivolumab showed durable anti-tumour responses, and the combination of nivolumab plus ipilimumab showed promising clinical activity. Here, we report long-term outcomes from this cohort.

Methods CheckMate 358 was a phase 1–2, open-label, multicohort trial. The metastatic cervical cancer cohort enrolled patients from 30 hospitals and cancer centres across ten countries. Female patients aged 18 years or older with a histologically confirmed diagnosis of squamous cell carcinoma of the cervix with recurrent or metastatic disease, an Eastern Cooperative Oncology Group performance status of 0 or 1, and up to two previous systemic therapies were enrolled into the nivolumab 240 mg every 2 weeks group, the randomised groups (nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks [NIVO3 plus IPI1] or nivolumab 1 mg/kg every 3 weeks plus ipilimumab 3 mg/kg every 3 weeks for four cycles then nivolumab 240 mg every 2 weeks [NIVO1 plus IPI3]), or the NIVO1 plus IPI3 expansion group. All doses were given intravenously. Patients were randomly assigned (1:1) to NIVO3 plus IPI1 or NIVO1 plus IPI3 via an interactive voice response system. Treatment continued until disease progression, unacceptable toxicity, or consent withdrawal, or for up to 24 months. The primary endpoint was investigator-assessed objective response rate. Anti-tumour activity and safety were analysed in all treated patients. This study is registered with ClinicalTrials.gov (NCT02488759) and is now completed.

Findings Between October, 2015, and March, 2020, 193 patients were recruited in the recurrent or metastatic cervical cancer cohort of CheckMate 358, of whom 176 were treated. 19 patients received nivolumab monotherapy, 45 received NIVO3 plus IPI1, and 112 received NIVO1 plus IPI3 (45 in the randomised group and 67 in the expansion group). Median follow-up times were 19·9 months (IQR 8·2–44·8) with nivolumab, 12·6 months (7·8–37·1) with NIVO3 plus IPI1, and 16·7 months (7·2–27·5) with pooled NIVO1 plus IPI3. Objective response rates were 26% (95% CI 9–51; five of 19 patients) with nivolumab, 31% (18–47; 14 of 45 patients) with NIVO3 plus IPI1, 40% (26–56; 18 of 45 patients) with randomised NIVO1 plus IPI3, and 38% (29–48; 43 of 112 patients) with pooled NIVO1 plus IPI3. The most common grade 3–4 treatment-related adverse events were diarrhoea, hepatic cytolysis, hyponatraemia, pneumonitis, and syncope (one [5%] patient each; nivolumab group), diarrhoea, increased gamma-glutamyl transferase, increased lipase, and vomiting (two [4%] patients each; NIVO3 plus IPI1 group), and increased lipase (nine [8%] patients) and anaemia (seven [6%] patients; pooled NIVO1 plus IPI3 group). Serious treatment-related adverse events were reported in three (16%) patients in the nivolumab group, 12 (27%) patients in the NIVO3 plus IPI1 group, and 47 (42%) patients in the pooled NIVO1 plus IPI3 group. There was one treatment-related death due to immune-mediated colitis in the NIVO1 plus IPI3 group.

Interpretation Nivolumab monotherapy and nivolumab plus ipilimumab combination therapy showed promise in the CheckMate 358 study as potential treatment options for recurrent or metastatic cervical cancer. Future randomised controlled trials of nivolumab plus ipilimumab or other dual immunotherapy regimens are warranted to confirm treatment benefit in this patient population.

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Introduction

Cervical cancer is associated with substantial morbidity and is the fourth leading cause of cancer-related mortality in women worldwide.[1,2] Human papillomavirus (HPV) infection causes almost all cervical cancers.[3] Immunotherapy is a promising treatment option for virus-induced cancers because viral proteins are strong immune stimulants.[4] Additionally, upregulation of PD-L1

Research in context

Evidence before this study

We searched PubMed on Sept 12, 2022, using the search terms "cervical cancer or cervical carcinoma" in the title or abstract and "programmed death-1 or PD-1 or programmed cell death ligand-1 or PD-L1" for English language articles. Our search identified several publications reporting on various therapies in patients with recurrent or metastatic cervical cancer. Bevacizumab plus platinum-paclitaxel has been the first-line treatment of choice in this patient population for the past decade. Over the past few years, PD-1 inhibition has emerged as the standard of care, with efficacy reported with pembrolizumab (a PD-1 inhibitor) monotherapy and in combination with platinum-based chemotherapy with or without bevacizumab, cemiplimab (a PD-1 inhibitor), dual immunotherapy with balstilimab (a PD-1 inhibitor) and zalifrelimab (a CTLA-4 inhibitor), and cadonilimab (a bispecific antibody targeting PD-1 and CTLA-4); the results are specific to patient populations based on the line of therapy and PD-L1 status. However, chemotherapy-free first-line treatment options, efficacious second-line or later-line treatment options, and PD-L1-agnostic options remain unmet medical needs.

Added value of this study

The CheckMate 358 study aimed to address this unmet need by evaluating nivolumab monotherapy as well as two regimens of nivolumab plus ipilimumab in the first-line and second-line or later-line settings in patients with recurrent or metastatic cervical cancer. Treatment with nivolumab plus ipilimumab was associated with durable antitumour activity in the first-line and second-line or later-line settings, and in patients with PD-L1 expression on tumour cells of 1% or higher or less than 1%. Additionally, the durability of response previously reported with nivolumab monotherapy was maintained in this analysis. Although the incidence of overall and grade 3–4 treatment-related adverse events was highest with the higher-dose ipilimumab regimen, all treatments were associated with a manageable safety profile.

Implications of all the available evidence

Our findings of durable activity and manageable safety with nivolumab plus ipilimumab regimens suggest that these dual immunotherapy regimens could potentially be investigated as chemotherapy-free first-line or second-line or later-line treatment options or as an immunotherapy backbone for the treatment of patients with recurrent or metastatic cervical cancer. Additionally, nivolumab monotherapy is a viable treatment option for second-line or later-line treatment of recurrent or metastatic cervical cancer. Studies on predictive biomarkers to identify patients likely to benefit from nivolumab monotherapy or nivolumab plus ipilimumab treatments are warranted.

C Garnett-Benson PhD, X Wang PhD); **Syneos Health, Morrisville, NC, USA** (M Lee)

Correspondence to:
Dr Ana Oaknin, Medical Oncology Service, Vall d´Hebron Institute of Oncology, Vall d´Hebron Barcelona Hospital Campus, Barcelona 08035, Spain
aoaknin@vhio.net

has been reported in the epithelial cells of the majority of patients with HPV-induced cervical intraepithelial neoplasias and HPV-induced squamous cell cancers of the cervix.[5]

Based on the results of the GOG-240 study, platinum-paclitaxel plus bevacizumab became the first-line standard of care for all patients with recurrent or metastatic cervical cancer who were able to tolerate bevacizumab.[6,7] Over the past few years, PD-1 inhibitor-based regimens have shown efficacy in the treatment of recurrent or metastatic cervical cancer and have been incorporated in both first-line and second-line or later-line settings. For the first-line treatment of patients with recurrent or metastatic cervical cancer who have a PD-L1 combined positive score (CPS) of 1 or higher, pembrolizumab in combination with platinum plus paclitaxel with or without bevacizumab has been approved by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).[8,9] For second-line or later-line treatment, pembrolizumab monotherapy is approved by the FDA for patients with a PD-L1 CPS of 1 or higher, or with microsatellite instability-high or deficient mismatch repair tumours.[8] Additionally, cemiplimab has been approved as a second-line treatment for patients with recurrent or metastatic cervical cancer (regardless of PD-L1 expression on tumour cells) following the results of a randomised phase 3 study.[10] Despite the available treatment options for patients with recurrent or metastatic cervical cancer, chemotherapy-free first-line options, efficacious second-line or later-line options, and PD-L1-agnostic options remain unmet medical needs.

Nivolumab is a fully human PD-1 inhibitor that has been approved as a monotherapy and in combination with ipilimumab, a fully human CTLA-4 inhibitor, for the treatment of multiple tumour types including melanoma, renal cell carcinoma, squamous cell carcinoma of the head and neck, non-small-cell lung cancer, malignant pleural mesothelioma, and oesophageal squamous cell carcinoma.[11,12] The phase 1–2 CheckMate 358 trial aimed to assess the anti-tumour activity of nivolumab-based therapies, including monotherapy and dual immunotherapy with ipilimumab, in patients with virus-associated solid tumours. We previously reported preliminary results with nivolumab monotherapy in the recurrent or metastatic cervical cancer cohort of this trial, which showed an objective response rate of 26%, with the median duration of response not reached (NR; range 23·3 to >29·5; ongoing response at last observation).[13] Durable responses were observed in this heavily treated population, which included 79% of patients who had previously received systemic therapy for metastatic disease; efficacy was observed in patients with PD-L1 expression of 1% or higher or less than 1% on tumour cells. Preliminary data also suggested clinical activity with nivolumab plus ipilimumab regimens in patients with recurrent or

metastatic cervical cancer, with objective response rates ranging from 32% to 46% in the first-line setting and 23–36% in the second-line or later-line settings.[14] Here, we report long-term outcomes in patients with recurrent or metastatic cervical cancer treated with nivolumab alone or in combination with ipilimumab in CheckMate 358.

Methods

Study design and participants

CheckMate 358 was a phase 1–2, open-label, multicohort trial. The recurrent or metastatic cervical cancer cohort of the study, which enrolled patients from 30 hospitals and cancer centres across ten countries (appendix p 2), was initiated in October, 2015. This cohort initially included only nivolumab monotherapy, but a protocol amendment resulted in initiation of randomisation into one of two nivolumab plus ipilimumab treatment groups in August, 2016. The treatment cohorts did not enroll in parallel but in sequence (ie, enrolment to the combination therapy cohorts opened after enrolment to monotherapy was completed). Patients were eligible for enrolment into any treatment group of the study if they were female, aged 18 years or older, had a histologically confirmed diagnosis of squamous cell carcinoma of the cervix with recurrent or metastatic disease, had received up to two previous systemic therapies, had an Eastern Cooperative Oncology Group performance status of 0 or 1, and had a positive or unknown tumour HPV status. Patients who had previously undergone experimental antitumour vaccine treatment or immune checkpoint inhibitor treatment were not eligible, nor were patients with active brain metastases, or those with a previous malignancy active within the past 3 years, or active autoimmune disease, or those who needed systemic immunosuppressive medication within 2 weeks of receiving study drug treatment. Patients were required to have adequate organ function based on laboratory testing requirements. Full details of patient eligibility criteria are included in the protocol (appendix).

See Online for appendix

An early antitumour activity signal along with a manageable safety profile was noted in patients randomly allocated to nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, leading to the addition of a non-randomised expansion group for this treatment schedule in October, 2018. Once the expansion cohort opened, all patients receiving nivolumab 1 mg/kg plus ipilimumab 3 mg/kg were entered into this cohort. This group enrolled two sets of patients: treatment-naive patients who were unsuitable for platinum-based therapy (for first-line treatment) and patients who had previously received systemic therapy for metastatic disease, regardless of their eligibility for platinum-based therapy (for second-line or later-line treatment).

CheckMate 358 was conducted in accordance with the ethical principles of the European Union Directive, the US Code of Federal Regulations, the Declaration of Helsinki, and Good Clinical Practice guidelines as defined by the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. The study protocol was approved by an institutional review board or an independent ethics committee at each site before study initiation. All patients provided written informed consent.

Additional details of the study methodology are included in the study protocol (appendix) and have been previously published.[13]

Randomisation and masking

Randomisation (1:1) into one of the two nivolumab plus ipilimumab treatment groups was done via an interactive voice response system, with the allocation sequence generated by the Bristol Myers Squibb (Princeton, NJ, USA) interactive response technology team and transferred to a third-party vendor for patient enrolment and assignment to trial groups in collaboration with study site investigators. This was an open-label study, so no masking was done.

Procedures

In the monotherapy group, patients received nivolumab 240 mg every 2 weeks. After a protocol amendment, patients were randomly allocated to receive nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks (NIVO3 plus IPI1 group) or nivolumab 1 mg/kg every 3 weeks plus ipilimumab 3 mg/kg every 3 weeks for four cycles, followed by nivolumab 240 mg every 2 weeks (NIVO1 plus IPI3 group; appendix p 7). Patients enrolled in the NIVO1 plus IPI3 expansion group received the same dose schedule as those in the randomly allocated group.

Both drugs were administered intravenously. Patients were treated until disease progression, unacceptable toxicity, or withdrawal of consent, or for a maximum of 24 months. Dose delays were permitted for both nivolumab and ipilimumab for management of adverse events; dose reductions were not allowed for either drug.

Tumour assessments (by CT or MRI) were performed at screening (within 35 days of first dose), then every 8 weeks during year 1 of treatment and every 12 weeks thereafter until treatment discontinuation. Overall survival was monitored 35 days after the last treatment (first follow-up assessment), 80 days after the first follow-up assessment, and every 3 months thereafter. Safety was monitored throughout the study until 100 days after the last dose of study treatment.[13] Adverse events were coded with the Medical Dictionary for Regulatory Activities (version 24.1) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Immune-mediated adverse events were defined as adverse events, regardless of causality and occurring within 100 days of the last dose, for which patients received immunosuppressive medications. Endocrine events (hypothyroidism or thyroiditis, hyperthyroidism, hypophysitis, diabetes

mellitus, and adrenal insufficiency) were included as immune-mediated adverse events regardless of treatment, as they are often managed without immunosuppression. Diarrhoea and colitis were listed separately in the reporting of treatment-related adverse events; however, in the reporting of immune-mediated adverse events, they were grouped together as per the protocol-specified definition of immune-mediated adverse events.

PD-L1 expression on tumour cells and PD-L1 CPS in fresh or archival tumour biopsy specimens were assessed before and during treatment with the PD-L1 IHC 28-8 pharmDx immunohistochemical assay (Dako-Agilent Technologies, Santa Clara, CA, USA).[15,16] Interferon-γ (IFN-γ)-induced chemokine (CXC motif chemokine ligand10 [CXCL10] and CXCL9) concentrations and C-reactive protein (CRP) concentrations in peripheral blood samples were measured by the Luminex immunoassay (Luminex, Austin, TX, USA) with multiplex panels before treatment and during subsequent cycles of treatment. Human leukocyte antigen-DR isotype (HLA-DR)-negative CD14+ myeloid-derived suppressor cell (MDSC) frequencies in peripheral blood samples were measured by flow cytometry before administration of the first dose of the study drug and during subsequent treatment cycles. Freshly collected, whole-blood samples from patients before treatment were sent for analysis (real time) using flow cytometry at Serametrix (Carlsbad, CA, USA). Data output "MDSC frequencies (%)" was defined as the percentage of Lineage Cocktail negative (LIN-), CD14 positive events that are low or negative for the surface marker HLA-DR. The Lineage Cocktail comprised a custom collection of markers for the negative selection of non-myeloid cells.

Outcomes

Outcomes are presented by treatment group: nivolumab monotherapy, randomised NIVO3 plus IPI1, randomised NIVO1 plus IPI3, and pooled NIVO1 plus IPI3 (randomised plus expansion). The primary endpoint of the recurrent or metastatic cervical cancer cohort of CheckMate 358 was investigator-assessed objective response rate (as per Response Evaluation Criteria in Solid Tumours version 1.1 [RECIST 1.1], defined as the proportion of patients with a best overall response of confirmed complete or partial response). Secondary endpoints were investigator-assessed duration of response (assessed in patients with confirmed complete or partial responses; defined as the time from first confirmed complete or partial response to tumour progression or death due to any cause), investigator-assessed progression-free survival (defined as the time from the first dosing date to the date of the first documented tumour progression, per RECIST 1.1, or death due to any cause; patients who did not undergo disease progression or die were censored on the date of their last tumour assessment before any subsequent anticancer therapy), and overall survival (defined as the

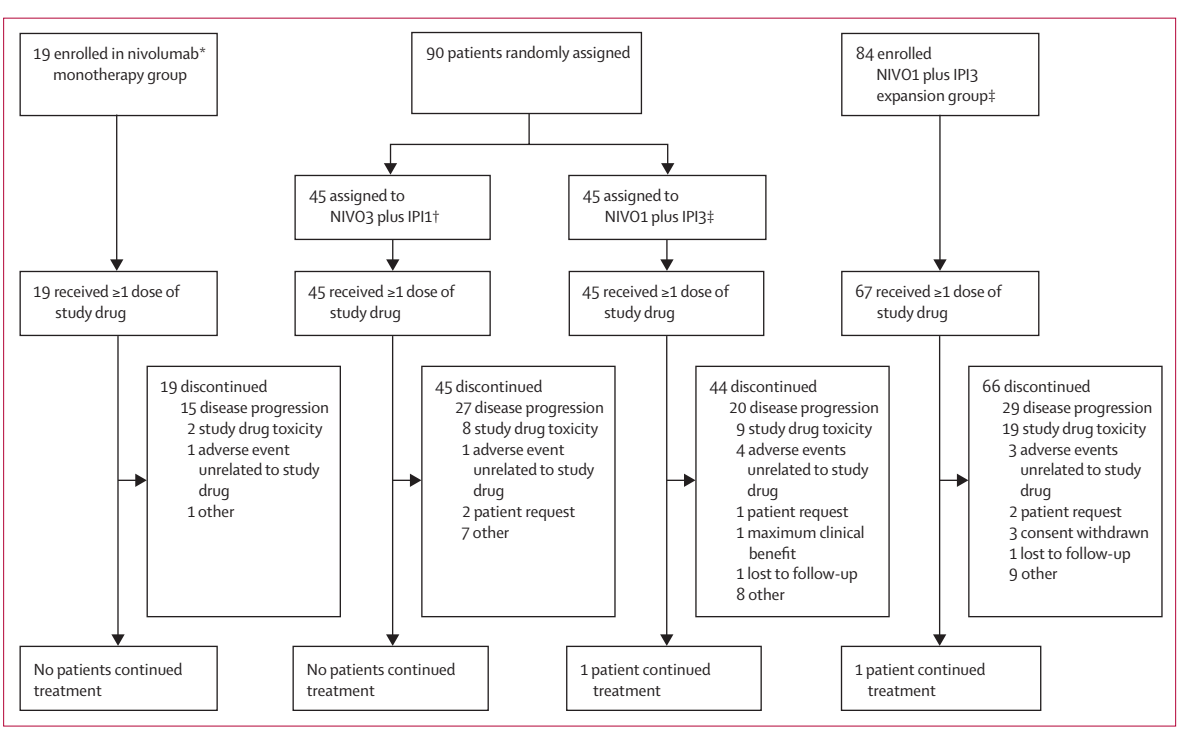

Figure 1: **Trial profile**

*Intravenous nivolumab 240 mg every 2 weeks. †Intravenous nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks (NIVO3 plus IPI1). ‡Intravenous nivolumab 1 mg/kg every 3 weeks plus ipilimumab 3 mg/kg every 3 weeks for four cycles, followed by nivolumab 240 mg every 2 weeks (NIVO1 plus IPI3).

	Nivolumab* (n=19)	NIVO3 plus IPI1 (randomised; n=45)†	NIVO1 plus IPI3 (randomised; n=45)‡	NIVO1 plus IPI3 (pooled; n=112)‡§
Median age (IQR), years	51·0 (43·0–57·0)	48·0 (41·0–55·0)	44·0 (36·0–49·0)	46·0 (38·5–54·0)
Sex				
Female	19 (100%)	45 (100%)	45 (100%)	112 (100%)
Region				
USA or Canada	1 (5%)	16 (36%)	15 (33%)	29 (26%)
Europe	18 (95%)	25 (56%)	27 (60%)	51 (46%)
Rest of the world	0	4 (9%)	3 (7%)	32 (29%)
Race				
White	17 (89%)	34 (76%)	34 (76%)	95 (85%)
Asian	1 (5%)	5 (11%)	8 (18%)	10 (9%)
American Indian or Alaska Native	1 (5%)	0	1 (2%)	2 (2%)
Black	0	6 (13%)	2 (4%)	5 (4%)
AJCC stage¶				
I–IIA2	1 (5%)	1 (2%)	1 (2%)	6 (5%)
IIB–IIC	1 (5%)	1 (2%)	0	3 (3%)
III–IIIC	2 (11%)	3 (7%)	7 (16%)	15 (13%)
IV–IVC	15 (79%)	40 (89%)	37 (82%)	88 (79%)
ECOG performance status				
0	10 (53%)	23 (51%)	25 (56%)	52 (46%)
1	8 (42%)	22 (49%)	20 (44%)	60 (54%)
Not reported	1 (5%)	0	0	0
PD-L1 expression on tumour cells**				
Quantifiable	18 (95%)	40 (89%)	35 (78%)	89 (79%)
≥1%††	11 (61%)	25 (62%)	23 (66%)	53 (60%)
<1%††	7 (39%)	15 (38%)	12 (34%)	36 (40%)
Not tested‡‡ or not evaluable§§	1 (5%)	5 (11%)	10 (22%)	23 (21%)
PD-L1 CPS¶¶				
Quantifiable	16 (84%)	37 (82%)	34 (76%)	67 (60%)
≥1††	16 (100%)	35 (95%)	31 (91%)	60 (90%)
<1††	0	2 (5%)	3 (9%)	7 (10%)
≥10††	14 (88%)	25 (68%)	21 (62%)	36 (54%)
<10††	2 (12%)	12 (32%)	13 (38%)	31 (46%)
Not tested‡‡ or not evaluable§§	3 (16%)	8 (18%)	11 (24%)	45 (40%)
Sites of metastatic disease***				
Lymph node	12 (63%)	25 (56%)	24 (53%)	63 (56%)
Lung	8 (42%)	13 (29%)	14 (31%)	30 (27%)
Pelvis	5 (26%)	15 (33%)	13 (29%)	27 (24%)
Uterus	3 (16%)	5 (11%)	6 (13%)	24 (21%)
Peritoneum	2 (11%)	3 (7%)	5 (11%)	13 (12%)
Bone with no soft tissue component	2 (11%)	3 (7%)	3 (7%)	9 (8%)
Bone with soft tissue component	1 (5%)	1 (2%)	2 (4%)	4 (4%)
Chest wall	1 (5%)	1 (2%)	0	0
Skin or soft tissue	1 (5%)	5 (11%)	7 (16%)	13 (12%)
Liver	0	8 (18%)	6 (13%)	23 (21%)
Kidney	0	2 (4%)	0	2 (2%)
Mediastinum	0	2 (4%)	4 (9%)	4 (4%)
Ovary	0	2 (4%)	0	3 (3%)
Pleura	0	2 (4%)	1 (2%)	2 (2%)
Adrenal gland	0	1 (2%)	0	3 (3%)
Ascites	0	1 (2%)	2 (4%)	3 (3%)

(Table 1 continues on next page)

	Nivolumab* (n=19)	NIVO3 plus IPI1 (randomised; n=45)†	NIVO1 plus IPI3 (randomised; n=45)‡	NIVO1 plus IPI3 (pooled; n=112)‡§
(Continued from previous page)				
Intestine	0	0	0	3 (3%)
Bladder	0	1 (2%)	1 (2%)	1 (1%)
Bone marrow	0	1 (2%)	0	0
Pancreas	0	1 (2%)	0	0
Visceral, other	0	1 (2%)	1 (2%)	8 (7%)
Effusion	0	0	1 (2%)	1 (1%)
Gastric	0	0	0	1 (1%)
Spleen	0	0	0	1 (1%)
Ureter	0	0	0	1 (1%)
Other	5 (26%)	13 (29%)	12 (27%)	26 (23%)
Previous radiotherapy	17 (89%)	38 (84%)	39 (87%)	90 (80%)
Previous systemic therapy in the metastatic setting	15 (79%)	27 (60%)	20 (44%)	40 (36%)
Previous lines of systemic therapy for metastatic disease				
0	4 (21%)	18 (40%)	25 (56%)	72 (64%)†††
1	8 (42%)	20 (44%)	15 (33%)	31 (28%)†††
2	7 (37%)	7 (16%)	5 (11%)	9 (8%)†††

Data are n (%), unless otherwise indicated. AJCC=American Joint Committee on Cancer. CPS=combined positive score. ECOG=Eastern Cooperative Oncology Group. *Intravenous nivolumab 240 mg every 2 weeks. †Intravenous nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks. ‡Intravenous nivolumab 1 mg/kg every 3 weeks plus ipilimumab 3 mg/kg every 3 weeks for four cycles, followed by nivolumab 240 mg every 2 weeks. §The pooled NIVO1 plus IPI3 group comprised 45 patients from the randomised group and 67 patients from the expansion group. ¶Aligned with Fédération Internationale de Gynécologie et d'Obstétrique staging. **PD-L1 expression on tumour cells was defined as the percentage of tumour cells with plasma membrane staining at any intensity. ††Calculated as a proportion of patients with quantifiable data. ‡‡Sample not available. §§Less than 100 viable tumour cells present on the stained slide. ¶¶Defined as the number of PD-L1-positive cells, including tumour cells, lymphocytes, and macrophages, divided by the total number of viable tumour cells × 100. ***Including target and non-target lesions; patients could have had lesions at more than one site. †††At enrolment, 69 patients were classified as receiving first-line treatment and 43 patients as receiving second-line or later-line treatment. Following subsequent database entries, it was determined that three patients in the latter group did not previously receive therapy in the metastatic setting and they were reclassified as receiving first-line treatment (reflected in this table).

Table 1: **Baseline characteristics**

time from the first dosing date to the date of death; patients who did not die were censored at the last known date alive). Safety, assessed as an exploratory endpoint, comprised evaluation of adverse events, including treatment-related adverse events and immune-mediated adverse events. Exploratory biomarker analyses included association of best overall response, progression-free survival, and overall survival with PD-L1 expression on tumour cells (before treatment) and association of best overall response with circulating MDSC frequencies (before and after treatment).

Statistical analysis

As this was a signal-seeking study, sample size determination was not based on statistical power calculations and the study was not designed for statistical comparisons. Activity analyses were done in all treated patients, with tumour response evaluated in those patients with tumour measurements at baseline and at least one on-study timepoint, or those with tumour measurements at baseline who had disease progression or died before any on-study tumour assessment. For patients who received NIVO1 plus IPI3, analyses were conducted on the randomised and pooled datasets. The objective response rate was summarised by frequency distributions and 95% CIs with the Clopper-Pearson method.[17] Per protocol, an objective response rate of 10% or higher was considered to be of clinical interest and an objective response rate of 25% or higher was considered to be of strong clinical interest. Duration of response (for responders), overall survival, and progression-free survival were estimated with Kaplan-Meier analyses,[18] with two-sided 95% CIs calculated by use of the Brookmeyer and Crowley method, based on a log-log transformed confidence interval for the survivor function. Progression-free survival and overall survival at 1-year and 2-year timepoints (prespecified in the protocol) were estimated by the Kaplan-Meier method with 95% CIs based on the Greenwood formula. Safety was summarised for all treated patients with descriptive statistics.

Pre-specified exploratory subgroup activity analyses included association of best overall response, progression-free survival, and overall survival with pre-treatment PD-L1 expression on tumour cells and association of best overall response with MDSC concentrations (before and after treatment). Post-hoc analyses evaluated on-treatment PD-L1 expression on

tumour cells and PD-L1 CPS, association of best overall response, progression-free survival, and overall survival with line of therapy, and association of best overall response with pre-treatment PD-L1 CPS, IFN-γ-induced chemokine concentrations (before and after treatment), and CRP concentrations (before and after treatment). Potential associations of best overall response with IFN-γ-induced chemokine, CRP, and MDSC concentrations across different timepoints were summarised graphically. Pre-treatment and post-treatment PD-L1 expression on tumour cells and PD-L1 CPS were also summarised graphically.

All statistical analyses were done with SAS (version 9.02). This study is registered with ClinicalTrials.gov (NCT02488759) and is now completed.

Role of the funding source

The funders were involved in the design and conduct of the study, data analysis and interpretation, development of the manuscript, and the decision to submit the manuscript for publication. The funders did not have a role in data collection. Financial support for editorial and writing assistance was provided by the funders.

Results

Between October, 2015, and March, 2020, 193 patients were recruited and 176 patients treated in the recurrent or metastatic cervical cancer cohort of CheckMate 358. 19 patients received nivolumab monotherapy and 45 patients each were randomised to the NIVO3 plus IPI1 and NIVO1 plus IPI3 groups. In the subsequent NIVO1 plus IPI3 expansion group, 67 additional patients were treated, resulting in a total of 112 patients in the pooled NIVO1 plus IPI3 group (figure 1). A much lower proportion of patients received nivolumab in the first-line setting (four [21%] of 19) compared with NIVO3 plus IPI1 (18 [40%] of 45) or pooled NIVO1 plus IPI3 (72 [64%] of 112). Baseline characteristics are shown in table 1. Among patients with quantifiable data, PD-L1 expression on tumour cells was 1% or higher in 11 (61%) of 18 patients in the nivolumab group, 25 (62%) of 40 patients in the NIVO3 plus IPI1 group, and 53 (60%) of 89 patients in the pooled NIVO1 plus IPI3 group.

As of the Dec 13, 2021, database lock, median follow-up times were 19·9 months (IQR 8·2–44·8) for the nivolumab group, 12·6 months (7·8–37·1) for the NIVO3 plus IPI1 group, and 16·7 months (7·2–27·5) for the pooled NIVO1 plus IPI3 group. Minimum follow-up times (ie, the time period between the last patient's first-dose date and last patient's last-contact date) for overall survival were 67·4 months for the nivolumab group, 36·9 months for the NIVO3 plus IPI1 group, and 17·9 months for the pooled NIVO1 plus IPI3 group. Disease progression was the main cause of treatment discontinuation in all treatment groups (figure 1). At database lock, no patient remained on treatment in the nivolumab and NIVO3 plus IPI1 groups, while two (2%) of 112 patients remained on treatment in the pooled NIVO1 plus IPI3 group. No patient completed the maximum permitted treatment of 2 years in the nivolumab group, compared with six (13%) of 45 in the NIVO3 plus IPI1 group and 15 (13%) of 112 in the pooled NIVO1 plus IPI3 group. Treatment exposure and subsequent systemic therapies are summarised in the appendix (pp 3–4).

Objective response rates with nivolumab (26% [95% CI 9–51]; five of 19 patients), NIVO3 plus IPI1 (31% [18–47];

	Nivolumab (n=19)			NIVO3 plus IPI1 (randomised; n=45)			NIVO1 plus IPI3 (randomised; n=45)			NIVO1 plus IPI3 (pooled; n=112)		
	All treated (n=19)	First-line (n=4)	Second-line or later-line (n=15)	All treated (n=45)	First-line (n=18)	Second-line or later-line (n=27)	All treated (n=45)	First-line (n=25)	Second-line or later-line (n=20)	All treated (n=112)	First-line (n=69)	Second-line or later-line (n=43)
Best overall response												
Complete response	4 (21%)	1 (25%)	3 (20%)	3 (7%)	2 (11%)	1 (4%)	5 (11%)	3 (12%)	2 (10%)	8 (7%)	4 (6%)	4 (9%)
Partial response	1 (5%)	0	1 (7%)	11 (24%)	5 (28%)	6 (22%)	13 (29%)	9 (36%)	4 (20%)	35 (31%)	24 (35%)	11 (26%)
Stable disease	8 (42%)	1 (25%)	7 (47%)	14 (31%)	6 (33%)	8 (30%)	14 (31%)	6 (24%)	8 (40%)	32 (29%)	18 (26%)	14 (33%)
Progressive disease	6 (31%)	2 (50%)	4 (27%)	16 (36%)	5 (28%)	11 (41%)	11 (24%)	6 (24%)	5 (25%)	32 (29%)	20 (29%)	12 (28%)
Unable to determine	0	0	0	1 (2%)	0	1 (4%)	2 (4%)	1 (4%)	1 (5%)	5 (4%)	3 (4%)	2 (5%)
Objective response rate; (95% CI)	5 (26%; 9–51)	1 (25%; 1–81)	4 (27%; 8–55)	14 (31%; 18–47)	7 (39%; 17–64)	7 (26%; 11–46)	18 (40%; 26–56)	12 (48%; 28–69)	6 (30%; 12–54)	43 (38%; 29–48)	28 (41%; 29–53)	15 (35%; 21–51)
Median duration of response, months (95% CI)	NR (35·3–NR)	NA*	NR	24·4 (8·7–NR)	34·6 (6·6–NR)	21·1 (7·5–NR)	34·1 (15·3–NR)	34·1 (5·8–NR)	NR (2·6–NR)	34·1 (11·5–NR)	25·6 (9·2–NR)	NR (5·2–NR)
Median progression-free survival, months (95% CI)	5·1 (1·9–9·1)	NA†	5·5 (1·8–9·1)	3·8 (2·1–10·3)	17·1 (2·1–36·4)	3·6 (1·8–5·1)	7·2 (3·8–17·2)	8·8 (3·7–35·9)	5·8 (2·0–14·1)	5·8 (3·8–9·3)	7·0 (3·8–10·4)	4·7 (3·2–10·0)
Median overall survival, months (95% CI)	21·6 (8·3–46·9)	NA†	21·9 (8·3–NR)	15·2 (9·0–36·2)	36·2 (17·1–NR)	10·3 (7·8–15·2)	24·7 (16·6–49·1)	27·4 (13·9–NR)	24·7 (13·0–NR)	20·9 (14·4–32·8)	20·9 (13·9–NR)	19·9 (7·8–32·8)

Data are n (%), unless otherwise indicated. NA=not applicable. NR=not reached. *Duration of response of the responder (n=1) was 35·3 months. †Sample size (n=4) is too small to report median progression-free survival and median overall survival.

Table 2: **Anti-tumour activity by line of therapy**

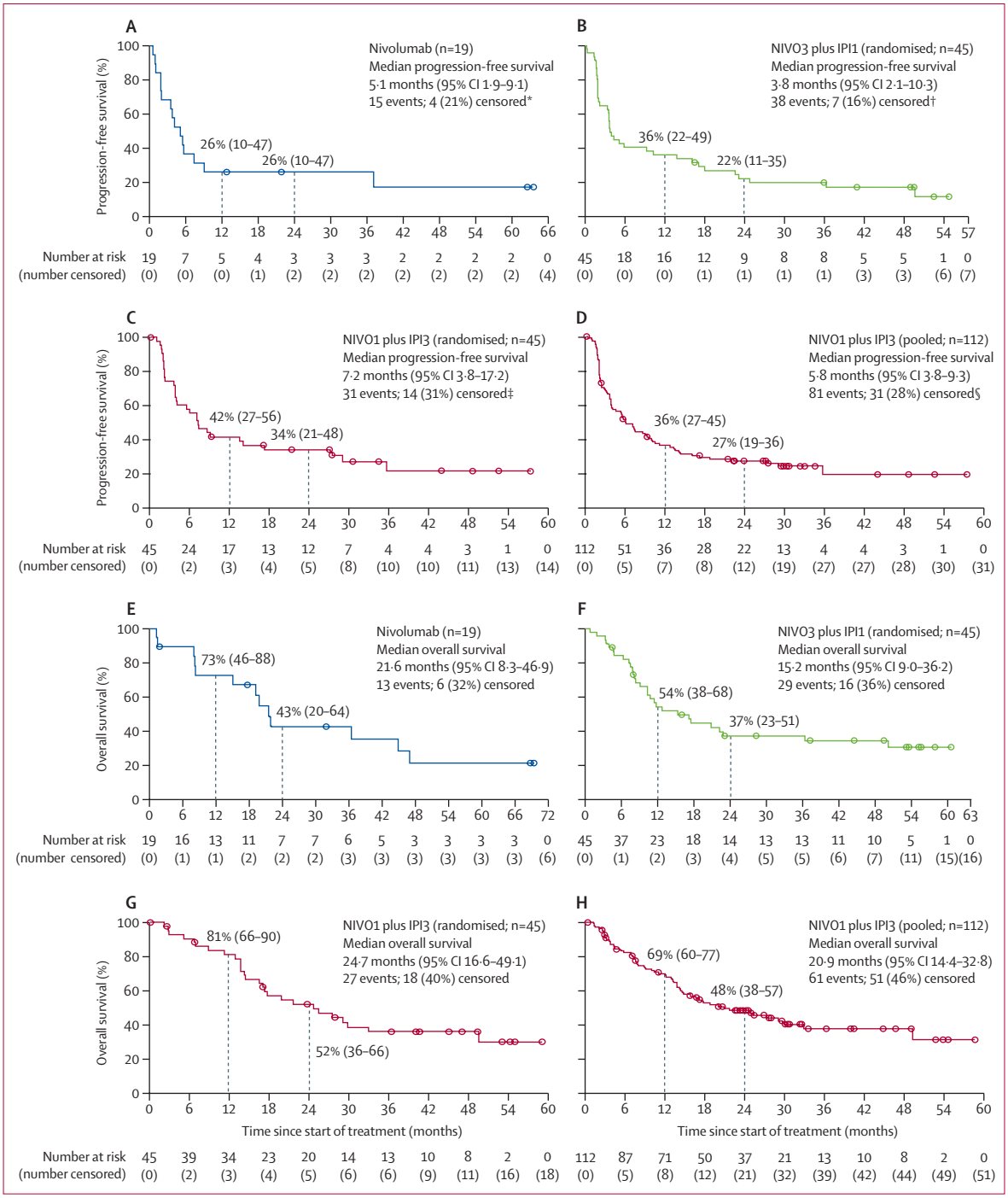

Figure 2: **Investigator-assessed progression-free survival and overall survival**

Progression-free survival in the nivolumab group (A), NIVO3 plus IPI1 (randomised) group (B), NIVO1 plus IPI3 (randomised) group (C), and NIVO1 plus IPI3 (pooled) group (D). Overall survival in the nivolumab group (E), NIVO3 plus IPI1 (randomised) group (F), NIVO1 plus IPI3 (randomised) group (G), and NIVO1 plus IPI3 (pooled) group (H). The open circles in the plots represent censored data points. The rates shown in the plots are point estimates of the 1-year and 2-year survival proportions; 95% CIs are shown in parentheses. *All patients were censored on the date of their last tumour assessment (one received subsequent radiotherapy, one received subsequent surgery, and two were in follow-up). †All patients were censored on the date of their last tumour assessment (one received subsequent surgery and six were in follow-up). ‡Two patients were censored at randomisation (due to no on-study tumour assessment or no death) and 12 were censored on the date of their last tumour assessment (one received subsequent surgery, one was still on treatment at time of database lock, six were in follow-up, and four were off study). §Two patients were censored at randomisation (due to no on-study tumour assessment or no death) and 29 were censored on the date of their last tumour assessment (one received subsequent surgery, one was still on treatment, 21 were in follow-up, and six were off study).

14 of 45 patients), randomised NIVO1 plus IPI3 (40% [26–56]; 18 of 45 patients), and pooled NIVO1 plus IPI3 (38% [29–48]; 43 of 112 patients) were higher than the protocol-defined threshold of 25% (table 2). Responses were durable; median duration of response was NR in the nivolumab group and ranged between 24·4 months and 34·1 months in the nivolumab plus ipilimumab groups (table 2). Best change from baseline in tumour burden over time for individual patients with an evaluable response in target lesions (19 patients in the nivolumab group, 42 in the NIVO3 plus IPI1 group, 42 in the randomised NIVO1 plus IPI3 group, and 105 in the pooled NIVO1 plus IPI3 group) indicates similar depths of response across the combination therapy groups (appendix p 8). Median progression-free survival was 5·1 months (95% CI 1·9–9·1) in the nivolumab group, with 15 events reported; 3·8 months (2·1–10·3) in the NIVO3 plus IPI1 group, with 38 events reported; 7·2 months (3·8–17·2) in the randomised NIVO1 plus IPI3 group, with 31 events reported; and 5·8 months (3·8–9·3) in the pooled NIVO1 plus IPI3 group with 81 events reported (table 2; figure 2). Median overall survival was 21·6 months (95% CI 8·3–46·9) in the nivolumab group, with 13 events reported; 15·2 months (9·0–36·2) in the NIVO3 plus IPI1 group, with 29 events reported; 24·7 months (16·6–49·1) in the randomised NIVO1 plus IPI3 group, with 27 events reported; and 20·9 months (14·4–32·8) in the pooled NIVO1 plus IPI3 group, with 61 events reported (table 2; figure 2).

Tumour response by PD-L1 status is summarised in tables 3, 4, and 5. Low patient numbers precluded response assessment in patients with CPS less than 1; in other subgroups, responses were seen regardless of PD-L1 status.

	Nivolumab (n=19)		NIVO3 plus IPI1 (randomised; n=45)		NIVO1 plus IPI3 (randomised; n=45)		NIVO1 plus IPI3 (pooled; n=112)	
	PD-L1 ≥1% (n=11)	PD-L1 <1% (n=7)	PD-L1 ≥1% (n=25)	PD-L1 <1% (n=15)	PD-L1 ≥1% (n=23)	PD-L1 <1% (n=12)	PD-L1 ≥1% (n=53)	PD-L1 <1% (n=36)
Best overall response								
Complete response	2 (18%)	1 (14%)	3 (12%)	0	1 (4%)	1 (8%)	4 (8%)	1 (3%)
Partial response	1 (9%)	0	6 (24%)	3 (20%)	5 (22%)	3 (25%)	15 (28%)	10 (28%)
Stable disease	5 (45%)	3 (43%)	6 (24%)	5 (33%)	8 (35%)	4 (33%)	18 (34%)	10 (28%)
Progressive disease	3 (27%)	3 (43%)	9 (36%)	7 (47%)	8 (35%)	3 (25%)	13 (25%)	13 (36%)
Unable to determine	0	0	1 (4%)	0	1 (4%)	1 (8%)	3 (6%)	2 (6%)
Objective response rate (95% CI)	3 (27%; 6–61)	1 (14%; <1–58)	9 (36%; 18–58)	3 (20%; 4–48)	6 (26%; 10–48)	4 (33%; 10–65)	19 (36%; 23–50)	11 (31%; 16–48)
Median duration of response, months (95% CI)	NR (35·3–NR)	NA*	34·6 (7·5–NR)	NR (24·4–NR)	NR (5·8–NR)	10·2 (2·6–NR)	NR (8·0–NR)	11·5 (5·2–NR)
Median progression-free survival, months (95% CI)	5·6 (0·9–NR)	3·5 (1·0–5·1)	3·9 (1·9–18·0)	3·6 (1·6–5·8)	3·9 (2·0–13·5)	5·8 (1·9–17·2)	5·5 (3·7–10·0)	5·2 (2·1–9·3)
Median overall survival, months (95% CI)	21·6 (8·2–NR)	19·2 (1·5–NR)	17·1 (8·3–NR)	9·0 (4·7–22·1)	17·5 (9·1–49·1)	18·8 (13·0–32·8)	18·8 (11·5–49·1)	15·5 (10·0–21·6)

Data are n (%) unless otherwise indicated. NA=not applicable. NR=not reached. *Duration of response of the responder (n=1) was 62·1 months.

Table 3: **Anti-tumour activity by PD-L1 expression on tumour cells pre-treatment**

	Nivolumab (n=19)		NIVO3 plus IPI1 (randomised; n=45)		NIVO1 plus IPI3 (randomised; n=45)		NIVO1 plus IPI3 (pooled; n=112)	
	CPS ≥1 (n=16)	CPS <1 (n=0)	CPS ≥1 (n=35)	CPS <1 (n=2)	CPS ≥1 (n=31)	CPS <1 (n=3)	CPS ≥1 (n=60)	CPS <1 (n=7)
Best overall response								
Complete response	3 (19%)	..	3 (9%)	0	2 (6%)	0	4 (7%)	0
Partial response	1 (6%)	..	8 (23%)	1 (50%)	8 (26%)	0	19 (32%)	0
Stable disease	8 (50%)	..	11 (31%)	0	9 (29%)	2 (67%)	19 (32%)	4 (57%)
Progressive disease	4 (25%)	..	12 (34%)	1 (50%)	11 (35%)	0	15 (25%)	2 (29%)
Unable to determine	0	..	1 (3%)	0	1 (3%)	1 (33%)	3 (5%)	1 (14%)
Objective response rate (95% CI)	4 (25%; 7–52)	..	11 (31%; 17–49)	1 (50%; 1–99)	10 (32%; 17–51)	0 (0%; 0–71)	23 (38%; 26–52)	0 (0%; 0–41)
Median duration of response, months (95% CI)	NR	..	34·6 (14·6–NR)	NA*	NR (2·6–NR)	..	NR (6·7–NR)	..
Median progression-free survival, months (95% CI)	5·3 (2·0–9·1)	..	3·9 (2·1–16·2)	NR (0·2–NR)	3·9 (2·1–13·5)	9·7 (5·4–14·1)	5·4 (3·5–11·1)	5·3 (1·6–14·1)
Median overall survival, months (95% CI)	21·9 (8·3–NR)	..	15·2 (9·0–22·7)	NR (0·8–NR)	17·5 (13·9–32·8)	19·9 (17·8–25·4)	20·9 (13·9–49·1)	16·6 (7·0–25·4)

Data are n (%) unless otherwise indicated. CPS=combined positive score. NA=not applicable. NR=not reached. *Duration of response of the responder (n=1) was 45·6 months.

Table 4: **Anti-tumour activity by PD-L1 on tumour and immune cells (ie, CPS cutoff of 1) pre-treatment**

	Nivolumab (n=19)		NIVO3 plus IPI1 (randomised; n=45)		NIVO1 plus IPI3 (randomised; n=45)		NIVO1 plus IPI3 (pooled; n=112)	
	CPS ≥10 (n=14)	CPS <10 (n=2)	CPS ≥10 (n=25)	CPS <10 (n=12)	CPS ≥10 (n=21)	CPS <10 (n=13)	CPS ≥10 (n=36)	CPS <10 (n=31)
Best overall response								
Complete response	3 (21%)	0	3 (12%)	0	2 (10%)	0	4 (11%)	0
Partial response	1 (7%)	0	5 (20%)	4 (33%)	4 (19%)	4 (31%)	9 (25%)	10 (32%)
Stable disease	6 (43%)	2 (100%)	7 (28%)	4 (33%)	7 (33%)	4 (31%)	13 (36%)	10 (32%)
Progressive disease	4 (29%)	0	9 (36%)	4 (33%)	8 (38%)	3 (23%)	8 (22%)	9 (29%)
Unable to determine	0	0	1 (4%)	0	0	2 (15%)	2 (6%)	2 (6%)
Objective response rate (95% CI)	4 (29%; 8–58)	0 (0%; 0–84)	8 (32%; 15–54)	4 (33%; 10–65)	6 (29%; 11–52)	4 (31%; 9–61)	13 (36%; 21–54)	10 (32%; 17–51)
Median duration of response, months (95% CI)	NR	..	27·9 (7·5–NR)	NR (24·4–NR)	NR (5·8–NR)	10·2 (2·6–NR)	NR (6·0–NR)	NR (2·6–NR)
Median progression-free survival, months (95% CI)	5·3 (1·9–NR)	NA*	3·9 (1·9–17·1)	4·4 (1·4–49·9)	3·8 (1·9–NR)	5·8 (2·0–14·1)	5·7 (3·2–14·3)	5·4 (2·3–9·9)
Median overall survival, months (95% CI)	21·6 (8·3–NR)	NA*	12·6 (7·2–NR)	18·7 (7·8–NR)	14·6 (7·2–NR)	20·8 (13·9–32·8)	14·6 (7·4–NR)	19·9 (13·0–32·8)

Data are n (%) unless otherwise indicated. CPS=combined positive score. NA=not applicable. NR=not reached. *Sample size (n=2) is too small to report median progression-free survival and median overall survival.

Table 5: **Anti-tumour activity by PD-L1 on tumour and immune cells (ie, CPS cutoff of 10) pre-treatment**

Any-grade treatment-related adverse events were reported in 12 (63%) of 19 patients in the nivolumab group, 36 (80%) of 45 patients in the NIVO3 plus IPI1 group, and 99 (88%) of 112 patients in the pooled NIVO1 plus IPI3 group; grade 3–4 treatment-related adverse events were reported in four (21%) patients in the nivolumab group, 13 (29%) patients in the NIVO3 plus IPI1 group, and 52 (46%) patients in the pooled NIVO1 plus IPI3 group (table 6). Treatment discontinuation due to any-grade treatment-related adverse events occurred in two (11%) patients in the nivolumab group, eight (18%) patients in the NIVO3 plus IPI1 group, and 27 (24%) patients in the pooled NIVO1 plus IPI3 group, with the most common events being Sjogren's syndrome and pneumonitis in one (5%) patient each in the nivolumab group, gastritis in two (4%) patients in the NIVO3 plus IPI1 group, and colitis in seven (6%) patients in the pooled NIVO1 plus IPI3 group. Serious treatment-related adverse events were reported in three (16%) patients in the nivolumab group, 12 (27%) patients in the NIVO3 plus IPI1 group, and 47 (42%) patients in the pooled NIVO1 plus IPI3 group, with the most common events being diarrhoea, hepatic cytolysis, and pneumonitis (one [5%] patient each; nivolumab group), diarrhoea (three [7%] patients; NIVO3 plus IPI1 group), and colitis and pneumonitis (nine [8%] and eight [7%] patients, respectively; pooled NIVO1 plus IPI3 group).

Immune-mediated adverse events reported in the study are summarised in the appendix (p 5). Grade 3–4 immune-mediated adverse events leading to treatment discontinuation included pneumonitis (one [5%] patient) in the nivolumab group; hepatitis (two [4%] patients) and nephritis or renal dysfunction (one [2%] patient) in the NIVO3 plus IPI1 group; and hepatitis (nine [8%] patients), diarrhoea or colitis (three [3%] patients), pneumonitis (three [3%] patients), and rash (one [1%] patient) in the pooled NIVO1 plus IPI3 group. There was one treatment-related death (one [4%] patient) in the pooled NIVO1 plus IPI3 group, which was due to immune-mediated colitis. A summary of deaths in the study is included in the appendix (p 6).

Biomarker analyses included patients with available data at each timepoint, as indicated in the appendix (pp 9–12). Concentrations of IFN-γ-induced chemokines CXCL10 and CXCL9 increased after treatment with nivolumab plus ipilimumab compared with pre-treatment values (appendix p 9). However, similar on-treatment changes were observed in responders and non-responders. CRP concentrations decreased after treatment with nivolumab plus ipilimumab among responders, but no change in CRP concentrations was observed in non-responders (appendix p 10). Although frequencies of circulating MDSCs were lower following treatment with nivolumab plus ipilimumab compared with pre-treatment frequencies, there were no substantial differences between responders and non-responders. Diminishing patient numbers in successive treatment cycles limited data interpretation (appendix p 11). No consistent changes in PD-L1 expression on tumour cells were noted on treatment with nivolumab plus ipilimumab; by contrast, the PD-L1 CPS was higher after treatment than before treatment (appendix p 12). Biomarker analyses could not be performed for the nivolumab monotherapy group owing to limited sample availability.

Discussion

In the CheckMate 358 study, nivolumab monotherapy and nivolumab plus ipilimumab treatment regimens were associated with durable anti-tumour activity in patients with recurrent or metastatic cervical cancer. The findings with nivolumab monotherapy, reported here at a median follow-up of 19·9 months (IQR 8·2–44·8), are an update to previously published results at a median follow-up of

	Nivolumab (n=19)			NIVO3 plus IPI1 (randomised; n=45)			NIVO1 plus IPI3 (pooled; n=112)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Summary of treatment-related adverse events									
Any*	8 (42%)	4 (21%)	0	23 (51%)	8 (18%)	5 (11%)	47 (42%)	35 (31%)	17 (15%)
Led to discontinuation*	1 (5%)	1 (5%)	0	4 (9%)	2 (4%)	2 (4%)	6 (5%)	11 (10%)	10 (9%)
Serious treatment-related adverse events*	0	3 (16%)	0	4 (9%)	5 (11%)	3 (7%)	13 (12%)	20 (18%)	14 (12%)
Treatment-related adverse events*†									
Diarrhoea	3 (16%)	1 (5%)	0	6 (13%)	1 (2%)	1 (2%)	25 (22%)	2 (2%)	0
Fatigue	3 (16%)	0	0	8 (18%)	0	0	17 (15%)	4 (4%)	0
Arthralgia	3 (16%)	0	0	1 (2%)	1 (2%)	0	12 (11%)	0	0
Pneumonitis	2 (11%)	1 (5%)	0	1 (2%)	0	0	8 (7%)	4 (4%)	1 (1%)
Abdominal pain	2 (11%)	0	0	3 (7%)	1 (2%)	0	4 (4%)	0	0
Stomatitis	2 (11%)	0	0	1 (2%)	0	0	2 (2%)	0	0
Dry eye	2 (11%)	0	0	0	0	0	0	0	0
Pruritus	1 (5%)	0	0	11 (24%)	0	0	21 (19%)	0	0
Hypothyroidism	1 (5%)	0	0	8 (18%)	1 (2%)	0	25 (22%)	0	0
Increased AST	1 (5%)	0	0	8 (18%)	0	0	11 (10%)	4 (4%)	0
Increased ALT	1 (5%)	0	0	7 (16%)	1 (2%)	0	13 (12%)	4 (4%)	0
Nausea	1 (5%)	0	0	6 (13%)	1 (2%)	0	14 (12%)	3 (3%)	0
Asthenia	1 (5%)	0	0	5 (11%)	0	0	7 (6%)	0	0
Maculo-papular rash	1 (5%)	0	0	4 (9%)	0	0	20 (18%)	3 (3%)	0
Anaemia	1 (5%)	0	0	3 (7%)	1 (2%)	0	4 (4%)	6 (5%)	1 (1%)
Dyspnoea	1 (5%)	0	0	2 (4%)	1 (2%)	0	2 (2%)	0	0
Macular rash	0	0	0	2 (4%)	0	0	2 (2%)	0	1 (1%)
Vomiting	1 (5%)	0	0	1 (2%)	2 (4%)	0	6 (5%)	2 (2%)	0
Hyponatremia	0	1 (5%)	0	0	0	0	2 (2%)	0	1 (1%)
Hepatic cytolysis	0	1 (5%)	0	0	0	0	0	0	0
Syncope	0	1 (5%)	0	0	0	0	0	0	0
Hyperthyroidism	0	0	0	4 (9%)	1 (2%)	0	15 (13%)	1 (1%)	0
Pyrexia	0	0	0	4 (9%)	0	0	16 (14%)	0	0
Increased amylase	0	0	0	4 (9%)	0	0	6 (5%)	2 (2%)	0
Increased lipase	0	0	0	2 (4%)	1 (2%)	1 (2%)	3 (3%)	6 (5%)	3 (3%)
Gastritis	0	0	0	2 (4%)	0	0	1 (1%)	2 (2%)	0
Hypokalaemia	0	0	0	2 (4%)	0	0	0	1 (1%)	0
Type 1 diabetes	0	0	0	1 (2%)	1 (2%)	0	0	0	0
Hyperglycaemia	0	0	0	1 (2%)	0	1 (2%)	4 (4%)	1 (1%)	0
Increased aminotransferase	0	0	0	1 (2%)	0	1 (2%)	0	4 (4%)	0
Increased GGT	0	0	0	0	2 (4%)	0	0	1 (1%)	0
Colitis	0	0	0	0	1 (2%)	0	7 (6%)	6 (5%)	0
Premature menopause	0	0	0	0	1 (2%)	0	0	0	0
Proctitis	0	0	0	0	1 (2%)	0	0	0	0
Polyarthritis	0	0	0	0	1 (2%)	0	0	0	0
Renal failure	0	0	0	0	1 (2%)	0	0	0	0
Autoimmune hepatitis	0	0	0	0	0	1 (2%)	0	1 (1%)	2 (2%)
Abnormal lipase	0	0	0	0	0	1 (2%)	0	0	1 (1%)
Hypophysitis	0	0	0	0	0	0	3 (3%)	0	1 (1%)
Hypoalbumaenia	0	0	0	0	0	0	2 (2%)	1 (1%)	0
Infusion-related reaction	0	0	0	0	0	0	2 (2%)	1 (1%)	0
Pruritic rash	0	0	0	0	0	0	2 (2%)	1 (1%)	0
Acute kidney injury	0	0	0	0	0	0	1 (1%)	1 (1%)	1 (1%)
Autoimmune cholangitis	0	0	0	0	0	0	0	1 (1%)	0
Autoimmune nephritis	0	0	0	0	0	0	0	1 (1%)	0
Encephalitis	0	0	0	0	0	0	0	1 (1%)	0

(Table 6 continues on next page)

	Nivolumab (n=19)			NIVO3 plus IPI1 (randomised; n=45)			NIVO1 plus IPI3 (pooled; n=112)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
(Continued from previous page)									
Female genital tract fistula	0	0	0	0	0	0	0	1 (1%)	0
Hypertension	0	0	0	0	0	0	0	1 (1%)	0
Increased LFT	0	0	0	0	0	0	0	1 (1%)	0
Pancreatitis	0	0	0	0	0	0	0	1 (1%)	0
Pleural effusion	0	0	0	0	0	0	0	1 (1%)	0
Rash erythematous	0	0	0	0	0	0	0	1 (1%)	0
Thrombocytopenia	0	0	0	0	0	0	0	1 (1%)	0
Hepatotoxicity	0	0	0	0	0	0	0	0	4 (4%)
Diabetic ketoacidosis	0	0	0	0	0	0	0	0	1 (1%)
Hypertransaminasaemia	0	0	0	0	0	0	0	0	1 (1%)
Inappropriate ADH secretion	0	0	0	0	0	0	0	0	1 (1%)
Pericardial effusion	0	0	0	0	0	0	0	0	1 (1%)

Data are n (%). ADH=antidiuretic hormone. ALT=alanine aminotransferase. AST=aspartate aminotransferase. GGT=gamma-glutamyl transferase. LFT=liver function test. *Includes events reported between the first dose and 30 days after last dose of treatment. †Includes all grade 3–4 treatment-related adverse events and grade 1–2 occurrences of these events. For other grade 1–2 treatment-related adverse events, events occurring in ≥10% of patients (in any treatment group) are included.

Table 6: **Treatment-related adverse events**

19·2 months (range 1·4–31·4).[13] Although the study was not statistically powered to assess an improvement in objective response rate, nivolumab monotherapy resulted in an objective response rate (26% [95% CI 9–51]) that was greater than the protocol-defined threshold of 25%, indicative of strong clinical interest. Durability of response with nivolumab continued to be maintained in the current analysis; overall survival (median 21·6 months in the current analysis *vs* 21·9 months in the previous analysis) and progression-free survival (median 5·1 months in both analyses) results were also maintained. The NIVO1 plus IPI3 expansion group was added to the study on the basis of promising signals in the randomised NIVO1 plus IPI3 group. However, results in the expansion group were not consistent with that in the randomised group, potentially due to a mixed patient population resulting from differences in geographical regions (due to the addition of new sites in the expansion group) and previous lines of therapy. Nonetheless, objective response rates with NIVO3 plus IPI1 (31% [95% CI 18–47]) and pooled NIVO1 plus IPI3 (38% [29–48]) were indicative of strong clinical interest. 2-year progression-free survival and overall survival were promising; however, the study was not powered to assess an improvement in progression-free survival or overall survival. Anti-tumour activity in all treatment groups was promising in patients with PD-L1 expression on tumour cells less than 1% and 1% or higher, CPS less than 10 and 10 or higher, as well as CPS 1 or higher, but could not be determined in patients with CPS less than 1 owing to small patient numbers.

In the study, treatment was administered in the first-line setting in 21% of patients in the nivolumab group, 40% of patients in the NIVO3 plus IPI1 group, and 64% of patients in the pooled NIVO1 plus IPI3 group. This is likely to be due to the evolution of the use of immunotherapy over the course of the study.

The incidence of treatment-related adverse events, immune-mediated adverse events, and treatment discontinuation due to treatment-related adverse events was higher in the NIVO1 plus IPI3 group than in the NIVO3 plus IPI1 group; these results were generally consistent with previous observations from other studies in patients with melanoma, non-small-cell lung cancer, and urothelial carcinoma, which showed that higher ipilimumab doses led to increased toxicity.[19–21] Immune-mediated adverse events across all three treatment groups were primarily grade 1–2, with a 5% or lower incidence of grade 3–4 immune-mediated adverse events except for hepatitis in the NIVO3 plus IPI1 group (7%) and pooled NIVO1 plus IPI3 group (16%); overall, immune-mediated adverse events were adequately managed through established protocols.[22]

Currently, pembrolizumab plus chemotherapy with or without bevacizumab is approved by the FDA and the EMA for the treatment of PD-L1-expressing (CPS 1 or higher), persistent, recurrent, or metastatic cervical cancer in the first-line setting.[8] In the KEYNOTE-826 study, pembrolizumab plus chemotherapy with or without bevacizumab significantly improved overall survival versus chemotherapy with or without bevacizumab in the PD-L1 CPS 1 or higher, intention-to-treat, and PD-L1 CPS 10 or higher populations; however, no improvement in overall survival was reported in patients with CPS less than 1.[23] The results from CheckMate 358 suggest durable anti-tumour activity with first-line nivolumab and ipilimumab dual immunotherapy in patients with recurrent or metastatic cervical cancer, including those with PD-L1 expression on tumour

cells of 1% or higher or less than 1%. All current recommendations for the first-line treatment of recurrent or metastatic cervical cancer include a platinum-based chemotherapy component. However, based on our results, dual immunotherapy could potentially be investigated as the backbone for future trials of novel combination therapies.

In the second-line or later-line setting following disease progression after chemotherapy, pembrolizumab is approved as a monotherapy for patients with PD-L1-expressing (CPS 1 or higher) recurrent or metastatic cervical cancer.[8] In patients with previously treated recurrent or metastatic cervical cancer with PD-L1 CPS 1 or higher, pembrolizumab monotherapy showed an objective response rate of 15% and median duration of response NR (range ≥3·7 months to ≥18·6 months) in the phase 2 KEYNOTE-158 study.[24] Dual immunotherapy with the investigational agents balstilimab (a PD-1 inhibitor) plus zalifrelimab (a CTLA-4 inhibitor) in the second-line setting resulted in an objective response rate of 26% in the overall population (median duration of response in months NR [95% CI 9·7–NR]), with an objective response rate of 33% in patients with a PD-L1 CPS of 1 or higher and 9% in patients with PD-L1 CPS less than 1.[25] In a phase 2 study, second-line or later-line cadonilimab (a first-in-class bispecific antibody targeting PD-1 and CTLA-4) was associated with an objective response rate of 33·0% and median duration of response NR at a median follow-up of 9·6 months in the overall patient population, including those with PD-L1 CPS 1 or higher and less than 1; patients with CPS 1 or higher had an objective response rate of 43·8%.[26] In the phase 3 EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9 study, cemiplimab (a PD-1 inhibitor) showed improved overall survival versus the investigator's choice of single-agent chemotherapy in the second-line setting, regardless of PD-L1 expression on tumour cells. Median overall survival was significantly higher for cemiplimab versus chemotherapy (12·0 months *vs* 8·5 months) in the overall population; the objective response rate was 16·4% with cemiplimab versus 6·3% with chemotherapy and the median duration of response was 16·4 months versus 6·9 months.[27] Taken together with the above first-line treatment data, results from CheckMate 358 in the second-line or later-line setting suggest that chemotherapy-free regimens including dual immunotherapy might provide benefit to patients with recurrent or metastatic cervical cancer, including those with PD-L1 expression on tumour cells 1% or higher or less than 1%; further evaluation is needed to confirm treatment benefit. Additionally, it is not known how these regimens would perform in patients with disease progression or after PD-1 inhibitor treatment. It would be worth investigating whether a dual immunotherapy combination could overcome the resistance seen with single-agent treatment.

In this study, all biomarker analyses were exploratory or conducted post hoc. Although interesting changes in serum cytokine concentrations were observed, linking such changes to drug mechanism of action would require parallel assessment of broader immune cell changes in the periphery and in the tumour microenvironment, which were not assessed here. Furthermore, although there were some signs of modulation of MDSCs, this observation would be more informative relative to frequencies of other immune cell subsets to understand the full spectrum of immunological changes associated with the treatment. A unique aspect of ipilimumab's mechanism of action is its potential to increase inflammatory cell infiltrates in the tumour microenvironment.[28] Comparison of pre-treatment and on-treatment PD-L1 expression on tumour cells and PD-L1 CPS in this study showed that nivolumab plus ipilimumab induced an increase in PD-L1 CPS but not in PD-L1 expression on tumour cells, suggesting that nivolumab plus ipilimumab selectively modulates PD-L1 expression on tumour-infiltrating immune cells. Further biomarker research such as deeper characterisation of the tumour microenvironment to identify patients most likely to benefit from immunotherapy, elucidating how differences in response are related to tumour cell versus combined tumour and immune cell PD-L1 expression, understanding whether the ability of dual immunotherapy regimens to increase PD-L1 concentrations is observable in a larger dataset and whether this modulation affects the clinical utility of baseline expression, will be of value.

Study limitations include the absence of a comparator group, accrual via a phased approach, as well as absence of independent radiological review for assessment of tumour response.

In summary, our results suggest that nivolumab plus ipilimumab or other dual immunotherapy regimens should be further investigated as a potential backbone of immunotherapy for patients with recurrent or metastatic cervical cancer. Additionally, long-term data for the nivolumab monotherapy group show that this agent continues to be a viable treatment option in the second-line or later-line setting for patients with recurrent or metastatic cervical cancer. Identification of predictive biomarkers to select patients most likely to benefit from nivolumab alone or in combination with ipilimumab remains an unmet medical need.

Contributors

AO was responsible for the conception or design of the study, data acquisition, data analysis, data interpretation, and writing (review and editing) of the manuscript. KM was responsible for the conception or design of the study, data acquisition, data interpretation, and writing (review and editing) of the manuscript. TM, JL-PG, LAD, AA, CL, VB, WHS, JCP, MT, MM, and AMA were responsible for data acquisition, data interpretation, and writing (review and editing) of the manuscript. SLT was responsible for the conception or design of the study, data interpretation, and writing (review and editing) of the manuscript. TAK, CC, ML, CG-B, and XW were responsible for data analysis, data interpretation, and writing (review and editing) of the manuscript. RWN was responsible for the conception or design of the study, data acquisition, data analysis, data interpretation, and writing (review and editing) of the manuscript.

TAK, CC, ML, CG-B, and XW verified all data in the study. All authors had full access to all the data in the study and had full responsibility for the decision to submit the manuscript for publication.

Declaration of interests

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Data sharing

Bristol Myers Squibb's data sharing policy is available online. De-identified and anonymised datasets of clinical trial information, including patient-level data, will be shared with external researchers for proposals that are complete and for which the scientific request is valid and the data are available, consistent with safeguarding patient privacy and informed consent. Upon execution of an agreement, the de-identified and anonymised datasets can be accessed via a secured portal that provides an environment for statistical programming with R as the programming language. The protocol and statistical analysis plan will also be available. Data will be available for 2 years from the study completion date of Oct 24, 2022.

For the **data sharing policy** see https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html

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