THERAPEUTIC ADVANCES in
Medical Oncology

Original Research

Xevinapant plus avelumab in advanced solid tumours, with a dose expansion in advanced non-small-cell lung cancer: exploratory biomarker, safety and efficacy analyses from an open-label, nonrandomised phase Ib study

Ther Adv Med Oncol

2025, Vol. 17: 1–17

DOI: 10.1177/17588359251332154

Glenwood Goss, Tudor Ciuleanu, Rodryg Ramlau, Daniel J. Renouf, Quincy Chu, Ewa Kalinka, Piotr Sawrycki, Jonathan Bramson, Brad H. Nelson, Rafael Crabbé, Eric LaCasse, Bryan Lo, Daniela A. Sahlender, Philippa Crompton, Franck Brichory, Luke Piggott, Michael Schenker and Rosalyn Juergens

Correspondence to:
Glenwood Goss
Department of Medicine, University of Ottawa, and the Ottawa Hospital Research Institute, 501 Smyth Road, Ottawa, ON K1H8L6, Canada
ggoss@toh.ca

Tudor Ciuleanu
Department of Oncology, 'Iuliu Haţieganu' University of Medicine and Pharmacy, Cluj-Napoca, Romania

Rodryg Ramlau
Oncology Department, Poznan University of Medical Sciences, Poznan, Poland

Daniel J. Renouf
Department of Medicine, Faculty of Medicine, University of British Columbia, BC Cancer, Vancouver, BC, Canada

Quincy Chu
Department of Oncology, University of Alberta, Cross Cancer Institute, Edmonton, AB, Canada

Ewa Kalinka
Department of Oncology, Polish Mother's Memorial Hospital, Lodz, Poland

Piotr Sawrycki
Wojewódzki Szpital Zespolony im. L. Rydygiera w Toruniu, Torun, Poland

Jonathan Bramson
Centre for Discovery in Cancer Research and Department of Medicine, McMaster University, Hamilton, ON, Canada

Brad H. Nelson
Deeley Research Centre, BC Cancer – Victoria, Victoria, BC, Canada

Rafael Crabbé
RC Consultancy, Bassins, Switzerland

Eric LaCasse
CHEO Research Institute, Ottawa, ON, Canada

Abstract

Background: Xevinapant, an inhibitor of apoptosis protein (IAP) inhibitor, has shown promising activity in combination with anticancer agents, including radiotherapy, and, in preclinical studies, anti-PD-(L)1 antibodies. This, in part, is due to its ability to restore apoptosis and increase antitumour immunity.

Objectives: We report efficacy, safety and exploratory biomarker analyses of xevinapant plus avelumab (anti-PD-L1) in a two-part, open-label, nonrandomised, phase Ib study.

Design: Part A assessed patients with advanced solid tumours who received xevinapant (100, 150, 200 or 250 mg/day, with no random allocation, on Days 1–10 and 15–24) in combination with avelumab (10 mg/kg) on Days 1 and 15 in 28-day cycle. Part B assessed patients with advanced non-small-cell lung cancer (NSCLC) who received xevinapant at the recommended phase II dose (RP2D) plus avelumab (maximum 26 cycles).

Methods: Part A assessed the safety and tolerability of the combination and established the maximum tolerated dose (MTD) and RP2D of xevinapant. Part B assessed the antitumour activity of xevinapant at the RP2D combined with avelumab compared with a historical control (avelumab alone). Exploratory biomarker analyses were also conducted.

Results: In part A ($n = 16$), xevinapant 200 mg/day was established as the RP2D with avelumab and the MTD was not reached. The most common treatment-emergent adverse events (TEAEs) irrespective of xevinapant dose were nausea and fatigue ($n = 11$ (68.8%) each). In part B ($n = 38$; four patients received prior anti-PD-(L)1 antibody), the objective response rate (ORR) was 10.5% (95% confidence interval (CI), 2.9–24.8; partial response, $n = 4$) and the most common TEAE was decreased appetite ($n = 13$ (34.2%)). Levels of plasma IL-10, IL-1β, IL-13 and $CD8^+$ T cells increased during the study, and circulating levels of $CD4^+$ T cells and Tregs increased during cycle 1. Macrophage-related gene expression signatures increased in patients with a partial response or stable disease. Low baseline Ki-67 expression in tumour samples correlated with a partial response.

Conclusion: The RP2D of xevinapant with avelumab was established; however, the ORR was not superior to the historical control (avelumab alone). The combination had a manageable safety profile in both study parts. Biomarker analyses provide insights into drivers associated with efficacy in patients with NSCLC receiving xevinapant plus avelumab.

Bryan Lo
Division of Anatomical Pathology, The Ottawa Hospital, Ottawa, ON, Canada

Daniela A. Sahlender
Philippa Crompton
Franck Brichory
Luke Piggott
Debiopharm International SA, Lausanne, Switzerland

Michael Schenker
Oncology Center Sf Nectarie, Craiova, Romania

Medical Oncology, University of Medicine and Pharmacy of Craiova, Craiova, Romania

Rosalyn Juergens
Department of Oncology, McMaster University, Hamilton, ON, Canada

Trial registration: NCT03270176 (https://clinicaltrials.gov/study/NCT03270176). Registered on ClinicalTrials.gov on 29 August 2017.

Keywords: avelumab, biomarker, inhibitor of apoptosis protein, non-small-cell lung cancer, phase Ib, xevinapant

Received: 8 October 2024; revised manuscript accepted: 18 March 2025.

Introduction

Lung cancer is the most commonly diagnosed cancer globally, with 2,480,301 new cases and 1,817,172 deaths recorded in 2022.[1] Most cases (≈80%) are non-small-cell lung cancer (NSCLC),[2] and ≈60% of these cases are diagnosed at an advanced stage.[3] Until 2015, chemotherapy and, for a minority of patients, targeted therapies were the most effective options; however, in many cases, de novo resistance or the rapid development of acquired resistance ensued. This mandated the development of novel treatment options.[4] Recently, several phase III clinical trials of anti-programmed cell death 1 (ligand 1) (PD-(L)1) antibodies have shown improved outcomes in patients with advanced NSCLC.[5–10] These trials have led to approvals that have changed the treatment landscape for patients with advanced NSCLC.[11–13] Treatment with anti-PD-(L)1 antibody alone or with platinum-based chemotherapy has emerged as the standard of care in the first-line setting for patients with tumours that do not have an oncogenic driver. The anti-PD-L1 antibody avelumab is approved in various tumour types,[14] including urothelial carcinoma, Merkel cell carcinoma and renal cell carcinoma. However, in two phase III trials, avelumab did not significantly improve outcomes in patients with NSCLC in the first- or second-line setting.[15,16]

Inhibitor of apoptosis proteins (IAPs) are a class of proteins that are overexpressed in cancer cells[17–19]; the median expressions of cellular IAP 1 (cIAP1), cellular IAP 2 (cIAP2) and X-linked IAP (XIAP) in tumour cells from patients with NSCLC have been shown to be 70%, 45% and 25%, respectively.[20] IAPs promote cancer cells' evasion of apoptosis (a key hallmark of cancer) by inhibiting caspase signalling pathways induced by intrinsic or extrinsic factors and suppressing immune cell activation and antitumour activity.[21–25] Xevinapant is a potent, oral, small-molecule IAP inhibitor that is capable of restoring cancer cell sensitivity to apoptosis via a proposed dual mechanism of action (Figure 1), thereby enhancing the effects of chemotherapy and radiotherapy.[26–28] Inhibition of XIAP and cIAP1/2 by xevinapant reinitiates caspase activity in the intrinsic and extrinsic apoptotic pathways.[26,29] Inhibition of cIAP1/2 increases antitumour immunity by promoting inflammatory cytokine release and switching cytokine signalling from survival to death in the tumours.[29–33] This involves increasing proapoptotic tumour necrosis factor (TNF) receptor signalling via the extrinsic pathway and inducing TNF-α expression via the noncanonical nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) pathway as well as inducing receptor-interacting serine/threonine kinase 1- and caspase 8-dependent apoptosis following the inhibition of cIAP1/2.[26,34–36] In addition, the inhibition of cIAP1/2 stabilises NF-κB-inducing kinase, resulting in activation of the noncanonical NF-κB pathway and transmission of costimulatory maturation and activation signals to immune cells.[37–40] The combination of IAP inhibitors with anti-PD-(L)1 antibodies has shown promising activity in several preclinical cancer models.[41–43] Given xevinapant's novel mechanism of action, with a potential effect on immune cells and promising preclinical activity in combination with anti-PD-(L)1 antibodies, we hypothesised that the combination with avelumab could further enhance antitumour activity.

Here, we report topline efficacy and safety results and exploratory biomarker analyses from a phase Ib dose-finding study investigating xevinapant in combination with avelumab in patients with solid tumours and, in the expansion cohort, patients with advanced NSCLC who had disease progression after one line of platinum-based chemotherapy.

Methods

Study design

This open-label, nonrandomised, multicentre, phase Ib dose-finding study (NCT03270176) was divided into two parts. Part A assessed the safety

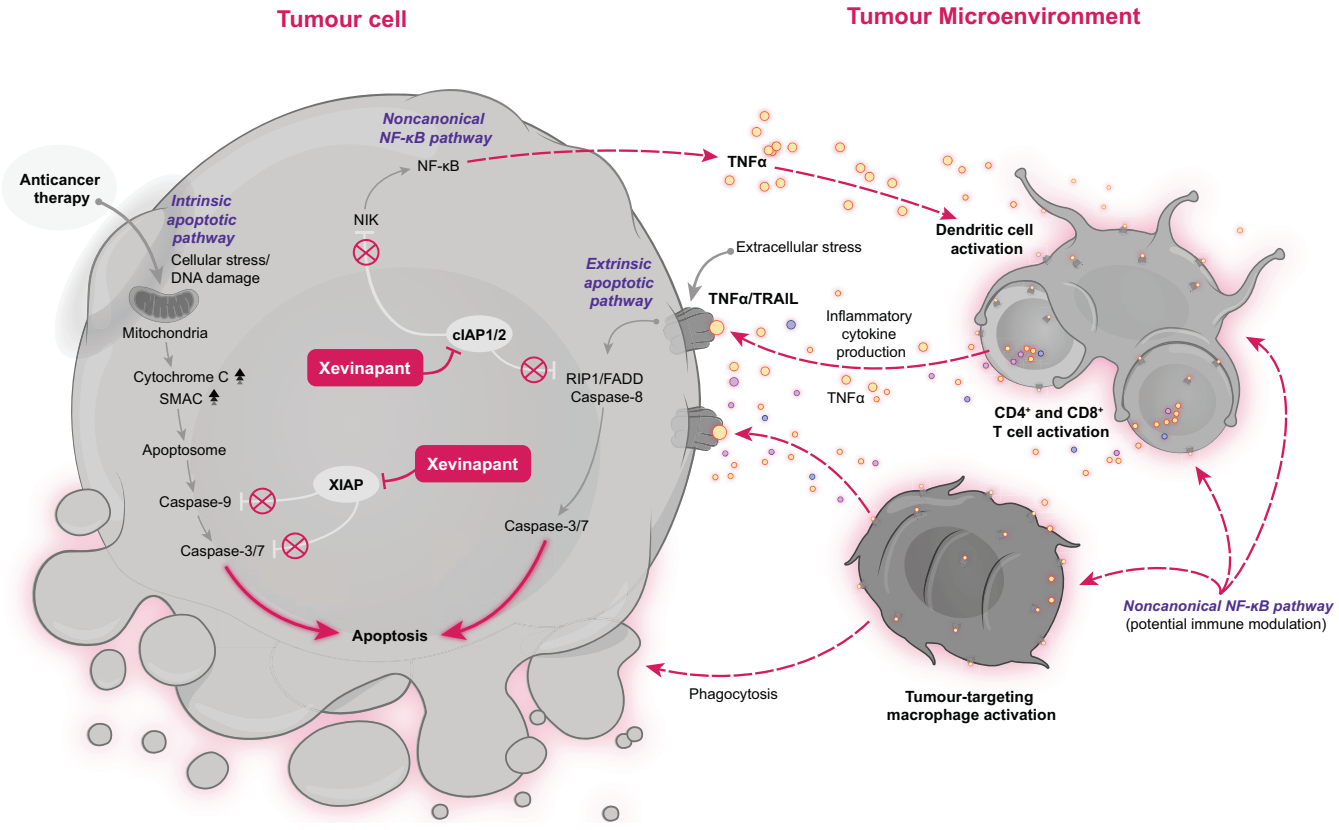

Figure 1. Xevinapant proposed mechanism of action.
Xevinapant is a potentially first-in-class, potent, oral, small-molecule IAP inhibitor. Xevinapant is capable of (1) restoring apoptosis in cancer cells by blocking XIAP and cIAP1/2, leading to activation of caspases downstream of the intrinsic mitochondrial and extrinsic TNF receptor signalling pathways, respectively, and (2) enhancing the inflammatory antitumour response in immune cells of the tumour microenvironment by activating noncanonical NF-κB signalling through blocking of cIAP1/2 downstream of the TNF receptor. Reprinted from "Xevinapant or placebo plus chemoradiotherapy in locally advanced squamous cell carcinoma of the head and neck: TrilynX phase III study design," Bourhis J et al. Future Oncol. 18(14), 1669-1678 (2022). Copyright © 2022 Future Medicine Ltd.
Source: Reprinted from Bourhis et al.[44]
cIAP1/2, cellular inhibitor of apoptosis proteins 1 and 2; FADD, fas-associated protein with death domain; IAP, inhibitor of apoptosis protein; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; NIK, NF-κB-inducing kinase; RIP1, receptor-interacting serine/threonine kinase 1; SMAC, second mitochondria-derived activator of caspase; TNF, tumour necrosis factor; TRAIL, TNF-related apoptosis-inducing ligand; XIAP, X-linked inhibitor of apoptosis protein.

and tolerability of xevinapant in combination with avelumab and the establishment of the maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of xevinapant in patients with solid tumours. Part B evaluated the antitumour activity of xevinapant at the RP2D in combination with avelumab in patients with NSCLC who had disease progression after one line of platinum-based chemotherapy. The design in part A used the modified continual reassessment method (mCRM). This method used a dose-toxicity model and a target toxicity rate to estimate the MTD. The first cohort of patients received a starting dose of xevinapant 100 mg/day, and any dose-limiting toxicities (DLTs) were reported to determine the probability of toxicity at each dose and recommend the dose level for the next cohort. The DLT period was defined as the first treatment cycle (i.e. 4 weeks or longer in the event of dosing delays).

Patients received oral xevinapant on Days 1–10 and 15–24 plus intravenous avelumab (10 mg/kg) on Days 1 and 15 of a 28-day cycle. In part A, four dose levels of xevinapant (100, 150, 200 and 250 mg/day) were assessed. In part B, xevinapant was given at the RP2D that was established in part A (200 mg/day on Days 1–10 and 15–24; details described in the 'Results' section). Study treatment was planned for 26 cycles or until any of the following: disease progression, permanent discontinuation of avelumab, unacceptable toxicity, patient withdrawal, pregnancy, any medical condition that may risk the patient's safety if they continued in the study, the start of subsequent

anticancer therapy or DLT that did not resolve to a grade ⩽2 within 14 days of onset (part A only). The reporting of this study conforms to the guidelines for reporting nonrandomised studies.[45]

Patients

In part A of the study, eligible patients had advanced solid tumours and were either deemed ineligible to receive or had failed standard treatment. In part B, eligible patients had stage IIIB or IV NSCLC and had disease progression after one line of platinum-based chemotherapy. Other key inclusion criteria across both parts included age ⩾18 years; measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1; adequate haematological, renal and hepatic function; Eastern Cooperative Oncology Group performance status of 0 or 1 and life expectancy of ⩾3 months. Key exclusion criteria included prior receipt of any immune checkpoint inhibitor treatment (part A), prior receipt of more than one line of anti-PD-(L)1 treatment (part B), prior IAP inhibitor treatment and inability to swallow or retain oral xevinapant.

Endpoints and evaluations

The primary endpoints were as follows: in part A, MTD of xevinapant with the probability of a DLT of <30% and RP2D of xevinapant with avelumab, taking into account the overall cumulative safety, tolerability, pharmacokinetics and efficacy data for the combination; in part B, investigator-assessed objective response rate (ORR) per RECIST 1.1 in a larger cohort of patients with advanced or metastatic NSCLC after platinum-based therapy. Secondary endpoints included treatment-emergent adverse events (TEAEs) and efficacy (best overall response, duration of response, disease control rate, progression-free survival and overall survival) and pharmacokinetics (data not shown). TEAEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. The final analysis was conducted after the last patient had discontinued from study treatment or had completed the 26 planned treatment cycles. Patients deriving a clinical benefit after 26 cycles were eligible to continue treatment.

Exploratory biomarker analyses were conducted and included analysis of plasma cytokines using multiplex assay (using the Molecular and Cellular Immunology Core, BioCanRx core facility), analysis of circulating immune cells using flow cytometry, immunohistochemistry (IHC) and NanoString gene expression analyses (using the nCounter PanCancer Immunology 360 panel (NanoString Technologies, Seattle, WA, USA)) on RNA extracted using the RecoverAll™ Total Nucleic Acid Isolation Kit for FFPE from pretreatment tumour samples. Activated regulatory T cells (Tregs) assessed by flow cytometry and NanoString analyses were characterised as $FOXP3^+$. The biomarkers analysed in the study and the stains used for flow cytometry parameters are presented in Supplemental Table 1. IHC slides were incubated at 37°C overnight, deparaffinised in xylene and rehydrated in graded ethanol baths (Fisher BioReagents, ThermoFisher, Waltham, MA, USA). Antigen retrieval was performed using Diva Decloaker (Biocare Medical, LLC™, Pacheco, CA, USA) in a Decloaking Chamber (Biocare Medical, LLC). Slides were stained using the intelliPATH FLX® (Biocare Medical, LLC) with the following panels: CD8/CD3/PanCK, cIAP1/PanCK/Ki-67, FOXP3/PanCK/CD68 and PD-L1/PD-1/CD8. Slides were imaged using the Vectra 3 Automated Quantitative Pathology Imaging System (Akoya Biosciences, Inc™, Marlborough, MA, USA) and analysed using the inForm Tissue Analysis Software (Akoya Biosciences, Inc™). For NanoString gene expression counts, immune cell scores were calculated by the average log2 expression of all cell type-specific markers (Supplemental Table 2); the corresponding cell type-specific genes that were used in this study were previously described by Danaher et al.[46]

Statistical analysis

The statistical analyses were descriptive in part A. In part B, the primary endpoint was compared against a historical ORR of 10% achieved with avelumab monotherapy.[47] The null hypothesis was that there was no difference in the ORR between the treatments in this study (xevinapant and avelumab) and the historical control (avelumab). The alternative hypothesis was that there was a difference (target ORR, ⩾15%). For an exact binomial test of a proportion with a one-sided nominal significance level of 0.1 and a null proportion of 0.10, a sample size of 35 has an exact power of 0.808 when the true proportion is 0.25. Based on these assumptions, if at least 7 of 35 evaluable patients had an objective response, the study would be deemed positive.

Test statistics and p values were derived from different models for each biomarker analysis. p Values for cytokines were derived from the linear mixed-effect models with the p value corresponding to the fixed effect of the ordered categorical visit. p Values for IHC analyses of tumour samples and NanoString immune cell scores were derived from different regression models depending on the clinical efficacy endpoint with a logistic model for binary endpoints and an ordinal logistic model for multilevel categorical endpoints. p Values < 0.05 were considered statistically significant, with no adjustment for multiple comparisons.

Results

Results from part A

Between October 2017 and March 2021, 19 patients were screened. A total of 16 patients with solid tumours (lung, $n=5$ (31.3%); ovary, $n=2$ (12.5%); kidneys/adrenals, $n=1$ (6.3%); stomach, $n=1$ (6.3%); other, $n=7$ (43.8%)) were enrolled at four centres in Canada and treated across the four xevinapant dose levels (100 mg/day, $n=3$; 150 mg/day, $n=2$; 200 mg/day, $n=7$; 250 mg/day, $n=4$). A maximum of 26 cycles of treatment was received by 2 patients (12.5%); 14 patients (87.5%) discontinued treatment due to disease progression (11 (78.6%)) and adverse events (AEs; 3 (21.4%)). The median age was 59.5 years (range, 28–79 years); 50% were male and 50% were female ($n=8$ each; Table 1).

The MTD of xevinapant was not reached. DLTs were reported for one patient at the 250-mg/day dose level (reversible grade 3 alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increases). The safety monitoring committee endorsed the recommendation of the mCRM, establishing xevinapant 200 mg/day on Days 1–10 and 15–24 every 28 days as the RP2D based on the cumulative safety, efficacy and pharmacokinetic (data not shown) parameters. The dose of 200 mg/day was selected due to the observed DLT in a patient at the 250-mg/day dose level, as well as the occurrence of grade 3 myalgia and arthralgia in a patient at the 200-mg/day dose level which were considered to be related to both study treatments.

No increases to grade ≥ 2 in ALT or AST were observed at lower dose levels. TEAEs occurred in all patients, and grade ≥ 3 TEAEs were observed in 10 patients (62.5%; Table 2). The most common TEAEs irrespective of xevinapant dose were nausea and fatigue, both occurring in 11 patients (68.8%; Supplemental Table 3); fatigue was also the most common grade ≥ 3 TEAE irrespective of xevinapant dose ($n=3$ (18.8%); Supplemental Table 4). TEAEs that resulted in permanent treatment discontinuation were reported in three patients (grade 3 increase in AST levels and grade 3 increase in ALT levels, grade 2 pneumonitis and grade 3 arthralgia, respectively). The most common TEAEs related to study treatments are presented in Supplemental Table 5 (TEAEs related to xevinapant) and Supplemental Table 6 (TEAEs related to avelumab). Grade 3 TEAEs related to xevinapant and/or avelumab were observed in five patients (31.3%). No patients died during the study.

Efficacy and safety results from part B

Between May 2019 and March 2022, 48 patients were screened. Overall, 38 patients with NSCLC were enrolled and treated at six centres in Canada, Poland and Romania. Baseline characteristics of all 38 patients enrolled in part B are presented in Table 1. All patients had received prior chemotherapy and 10.5% of patients had received prior therapy with an anti-PD-(L)1 antibody. As of March 2022, 37 patients (97.4%) had discontinued study treatment early and 1 patient (2.6%) had completed the planned 26 cycles of treatment (Supplemental Figure 1). The median number of cycles of xevinapant and avelumab was 4 (range, 1–26). The median duration of treatment was 3.6 months (range, 0.1–30.2 months) with xevinapant and 3.7 months (range, 0.2–30.3 months) with avelumab. Of those who discontinued treatment ($n=37$), the most common reasons for discontinuation were disease progression ($n=26$ (70.3%)) and AEs ($n=10$ (27.0%)). PD-L1 expression in tumour samples was high ($\geq 50\%$) in 13 patients (34.2%) and moderate (1%−49%) in 5 patients (13.2%); 12 patients (31.6%) had PD-L1-negative disease and PD-L1 status was unknown in 8 patients (21.1%).

All patients had measurable disease and were evaluable for efficacy. Efficacy results from part B are presented in Table 3. The observed ORR was 10.5% (95% CI, 2.9–24.8), with four patients responding to treatment; thus, the target of a $\geq 15\%$ increase in efficacy over the historical control (avelumab monotherapy; ORR, 10%) was not met.

Table 1. Baseline characteristics for patients in part A and part B.

Characteristic	Study part	
	Part A (*N* = 16)	**Part B (*N* = 38)**
Age, median (range), years	59.5 (28–79)	61.5 (35–75)
Sex, *n* (%)		
Male	8 (50.0)	27 (71.1)
Female	8 (50.0)	11 (28.9)
Race, *n* (%)		
White	15 (93.8)	38 (100)
Asian	1 (6.3)	0
PD-L1 expression, *n* (%)*		
High	NA	13 (34.2)
Moderate	NA	5 (13.2)
None	NA	12 (31.6)
Unknown	NA	8 (21.1)
ECOG PS, *n* (%)		
0	6 (37.5)	1 (2.6)
1	10 (62.5)	37 (97.4)
Site of primary tumour, *n* (%)		
Lung	5 (31.3)	38 (100)
Ovary	2 (12.5)	0
Kidneys/adrenals	1 (6.3)	0
Stomach	1 (6.3)	0
Other	7 (43.8)[a]	0
Cancer type, *n* (%)		
Adenocarcinoma	9 (56.3)	16 (42.1)
Squamous cell carcinoma	1 (6.3)	17 (44.7)
Other	6 (37.5)[b]	5 (13.2)[c]
Stage at baseline, *n* (%)		
I	1 (6.3)	0
II	2 (12.5)	0
III	5 (31.3)	6 (15.8)
IV	8 (50.0)	32 (84.2)

(Continued)

Table 1. (Continued)

Characteristic	Study part	
	Part A (*N* = 16)	**Part B (*N* = 38)**
Local or distant metastases, *n* (%)		
Local	10 (62.5)	8 (21.1)
Distant	6 (37.5)	30 (78.9)
Type of prior therapy, *n* (%)		
Chemotherapy	16 (100)	38 (100)
Anti-PD-(L)1 antibody	0	4 (10.5)
Radiotherapy	4 (25.0)	9 (23.7)
Surgery	9 (56.3)	2 (5.3)
Targeted therapy	1 (6.3)	0
Last line of prior therapy, *n* (%)		
First-line therapy	5 (31.3)	34 (89.5)
Second-line therapy	4 (25.0)	1 (2.6)
Third-line therapy	1 (6.3)	0
Further-line therapy	4 (25.0)	0
Unknown	2 (12.5)	3 (7.9)

Percentages may not total 100 because of rounding.
[a]Pleura in two patients, and colorectal, duodenal, soft tissues of the abdomen, thymus and thyroid in one patient each.
[b]Adrenal cortical carcinoma, epithelioid mesothelioma, leiomyosarcoma, malignant epithelial mesothelioma, papillary and serous carcinoma in one patient each.
[c]Large-cell carcinoma in two patients, and mucinous bronchioloalveolar carcinoma, pulmonary carcinosarcoma and NSCLC (not otherwise specified) in one patient each.
*Assessed using the PD-L1 IHC 22C3 pharmDx assay. PD-L1 expression was deemed to be high when PD-L1 was observed in ↗50% of tumour cells and moderate when PD-L1 was observed in 1%–49% of tumour cells.
ECOG PS, Eastern Cooperative Oncology Group performance status; NA, not analysed; NSCLC, non-small-cell lung cancer; PD-(L)1, programmed cell death 1 (ligand 1).

TEAEs of any grade and from any cause occurred in 37 patients (97.4%; Table 2). The most common TEAEs were decreased appetite ($n = 13$ (34.2%)), ALT increased ($n = 11$ (28.9%)), anaemia and amylase increased ($n = 10$ (26.3%) each; Supplemental Table 7), and the most common grade ⩾3 TEAE was amylase increased ($n = 5$ (13.2%); Supplemental Table 8). The most common TEAEs related to xevinapant, irrespective of grade, were decreased appetite and nausea ($n = 7$ (18.4%) each; Supplemental Table 9). TEAEs related to xevinapant were grade ⩾3 in one patient (2.6%; amylase increased). The most common TEAEs related to avelumab, irrespective of grade, were amylase increased ($n = 9$ (23.7%)) and hypothyroidism ($n = 7$ (18.4%); Supplemental Table 10). TEAEs related to avelumab were grade ⩾3 in six patients (15.8%; amylase increased in four (10.5%), lipase increased in three (7.9%) and ALT increased in one (2.6%)). No serious TEAEs were considered related to either treatment. Nine patients (23.7%) died during the study (due to disease progression in 7 (18.4%) and pneumonia in 1 (2.6%); cause of death was unknown in 1 (2.6%)).

Biomarker analysis from part B

Significant increases in plasma interleukin (IL)-10 ($p = 0.0001$; Figure 2(a)), IL-1β ($p = 0.0043$; Figure 2(b)) and IL-13 ($p = 0.0092$; Figure 2(c)) levels were detected at all measured time points

Table 2. Safety results from part A and part B.

Study part	Part A (*N* = 16)	Part B (*N* = 38)
TEAEs, *n* (%)		
Any grade	16 (100)	37 (97.4)
Grade ⩾3	10 (62.5)	21 (55.3)
Serious adverse events	6 (37.5)	11 (28.9)
Leading to discontinuation of xevinapant	2 (12.5)	4 (10.5)
Leading to discontinuation of avelumab	1 (6.3)	4 (10.5)
Leading to death	0	9 (23.7)
TEAEs related to xevinapant, *n* (%)		
Any grade	12 (75.0)	19 (50.0)
Grade ⩾3	5 (31.3)	1 (2.6)
TEAEs related to avelumab, *n* (%)		
Any grade	13 (81.3)	27 (71.1)
Grade ⩾3	5 (31.3)	6 (15.8)
Infusion-related reaction, *n* (%)	6 (37.5)	1 (2.6)

TEAE, treatment-emergent adverse event.

across the course of the study. Levels of other cytokines, such as IL-12p40 (data not shown), IL-1Ra (data not shown) and TNF-α (Figure 2(d)), also increased at one time point versus baseline; however, this was not maintained across the whole of the study (Table 4). In analyses of peripheral blood, activated $CD4^+$ T-cell and Treg levels increased during cycle 1, and Tregs tended to decrease by Day 1 of cycle 4; activated $CD8^+$ T-cell levels increased throughout the study treatment period versus baseline (Figure 3). Of the four responders (all with a partial response), none had received any prior anti-PD-(L)1 treatment and three had tumours with high PD-L1 expression; PD-L1 status for the fourth patient was not known. In IHC analyses of tumour samples, there was no association between best overall response and PD-L1 expression ($p = 0.8383$), or between best overall response and Ki-67 expression ($p = 0.137$), with the four patients with a best overall response of partial response having lower Ki-67 expression at baseline than patients with stable disease or progressive disease (Figure 4). No association was observed between cIAP1

Table 3. Efficacy results from part B.

Outcome	*N* = 38
Objective response rate (95% CI), %	10.5 (2.9–24.8)
Best overall response, *n* (%)	
Complete response	0
Partial response	4 (10.5)
Stable disease	19 (50.0)
Progressive disease	15 (39.5)
Disease control rate (95% CI), %	60.5 (43.4–76.0)
Duration of response,[a] median (95% CI), weeks	69.1 (15.3–128.9)
Progression-free survival, median (95% CI), months	3.5 (1.9–5.1)
Overall survival, median (95% CI), months	9.4 (6.7–16.2)

[a]Among the four patients with a partial response.
CI, confidence interval; NE, not estimable.

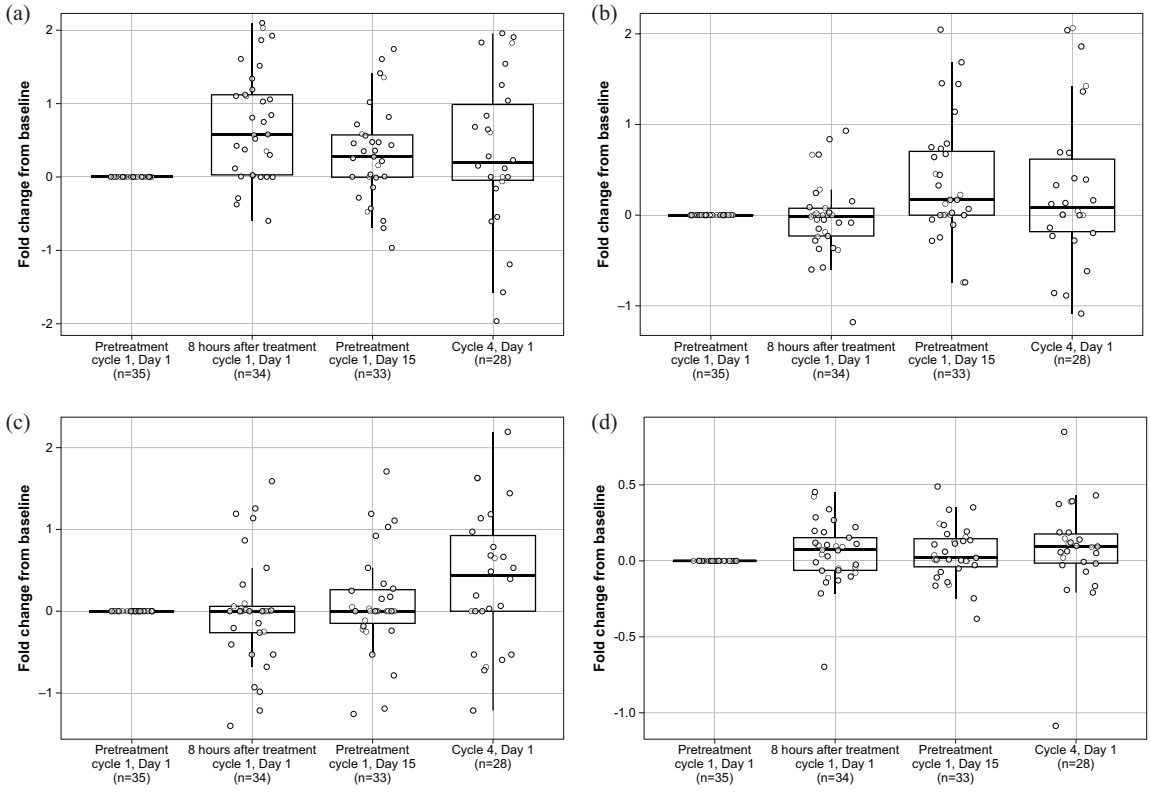

Figure 2. Change in IL-10 (a), IL-1β (b), IL-13 (c) and TNF-α (d) levels throughout the treatment period versus at baseline in part B.
IL, interleukin; TNF, tumour necrosis factor.

Table 4. *p* Values for levels of cytokines in the blood during the study versus at baseline in part B.

Biomarker	*p* Value
IL-10	0.0001
IL-1β	0.0043
IL-13	0.0092
IL-1Ra	0.0759
IL-12p40	0.0820
MCP-1	0.1350
IL-2	0.1575
IL-4	0.2769
IFN-γ	0.2894
IL-12p70	0.4882
TNF-α	0.4922
IL-8	0.6535
IL-6	0.7308
GM-CSF	0.8265
IL-5	0.9014

GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; TNF, tumour necrosis factor.

levels and best overall response ($p = 0.5541$). In NanoString gene expression analyses of tumour samples, high levels of macrophages ($p = 0.0248$) and Tregs ($p = 0.0458$) were associated with disease control (Figure 5). All NanoString immune cell score results are presented in Table 5.

Discussion

This phase Ib dose-finding study was the first clinical study to evaluate the combination of xevinapant and avelumab or any combination of an IAP inhibitor and anti-PD-(L)1 antibody. In part A, the RP2D of xevinapant in combination with avelumab was selected as 200 mg/day on Days 1–10 and 15–24 of a 28-day cycle based on a manageable safety profile. Reversible DLTs (grade 3 ALT and AST increase) were reported for one patient at the 250-mg/day dose level. In part B, xevinapant in combination with avelumab had a manageable safety profile in patients with advanced NSCLC who had disease progression after one line of platinum-based chemotherapy. Incidence and severity of common TEAEs were consistent with the known safety profile of xevinapant and avelumab treatment.[48-50] Nevertheless, the study did not meet its primary

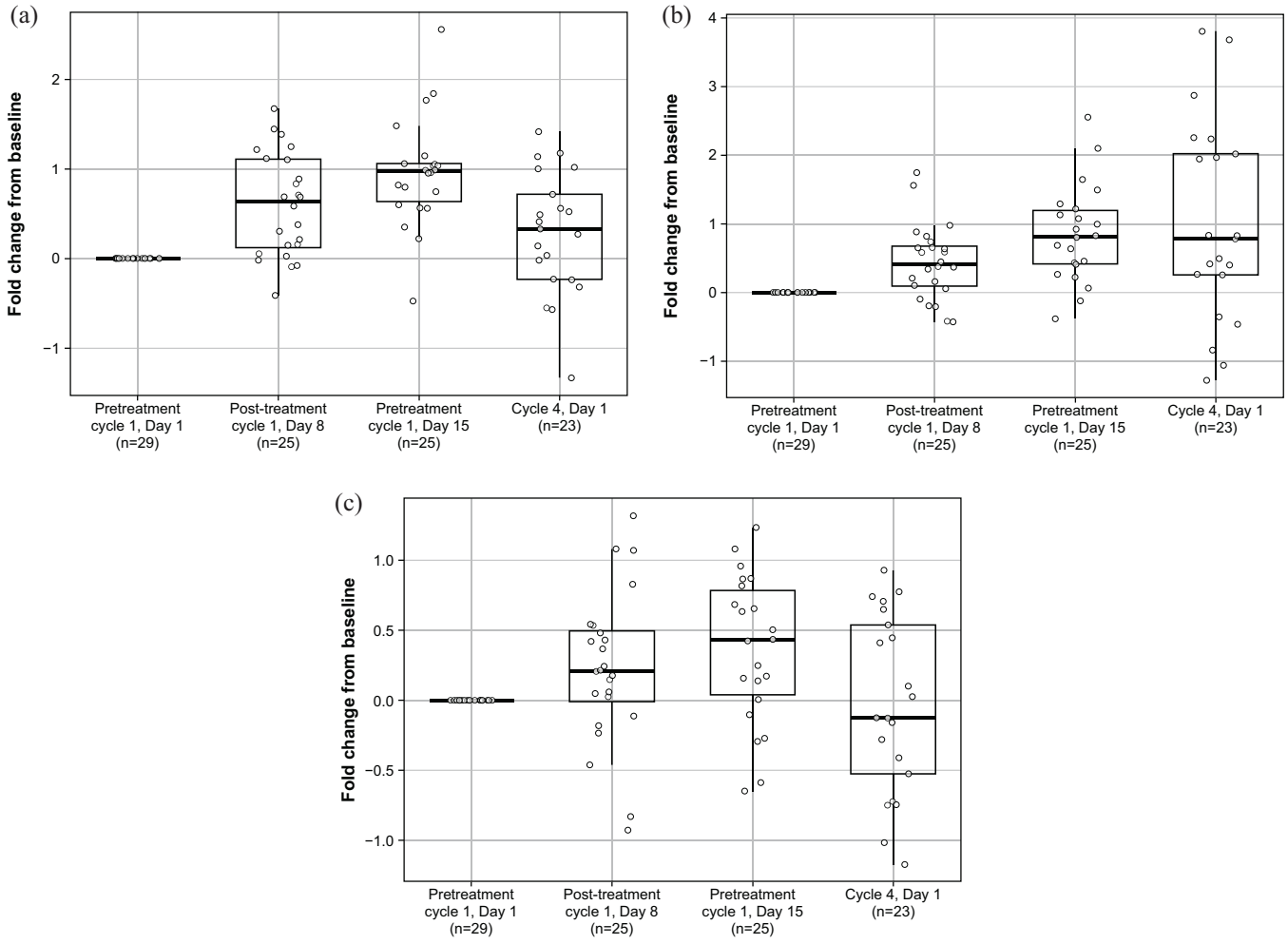

Figure 3. Change in levels of activated $CD4^+$ T cells (a), $CD8^+$ T cells (b) and $CD4^+/CD25^+/FOXP3^+$ Tregs (c) in the blood throughout the study treatment period versus at baseline in part B.
Treg, regulatory T cell.

efficacy endpoint – the addition of xevinapant to avelumab did not improve antitumour activity compared with historical data for avelumab monotherapy as second-line treatment.[51]

Comprehensive biomarker data were reported and generally reflected the potential immunomodulatory effects of the combination of xevinapant and avelumab. An increase in $CD8^+$ T-cell expression following xevinapant monotherapy in squamous cell carcinoma of the head and neck (SCCHN) has been reported previously,[35] consistent with our findings in NSCLC. Increased $CD8^+$ T-cell expression has previously been associated with improved survival in several trials of anti-PD-(L)1 antibodies.[52–54] The low response rate in part B of the study suggests that this increase from baseline in $CD8^+$ T cells was insufficient to elicit a significant anti-tumour response. As there was no control arm in the study, observed associations may be solely prognostic and independent of treatment. Our data mimic the mechanism of action of xevinapant to some extent as we identified increases in levels of cytokines regulated by NF-κB, consistent with results from preclinical studies,[26,35] which have shown that xevinapant is capable of enhancing NF-κB activity. In the JAVELIN Bladder 100 trial, increased expression of genes associated with macrophages correlated with longer overall survival with avelumab,[52] matching the increase in macrophage immune cell scores observed in patients with disease control in our study. However, in the JAVELIN Head and Neck 100 trial in patients with locally advanced SCCHN treated with avelumab plus chemoradiotherapy versus placebo plus chemoradiotherapy, high levels of a

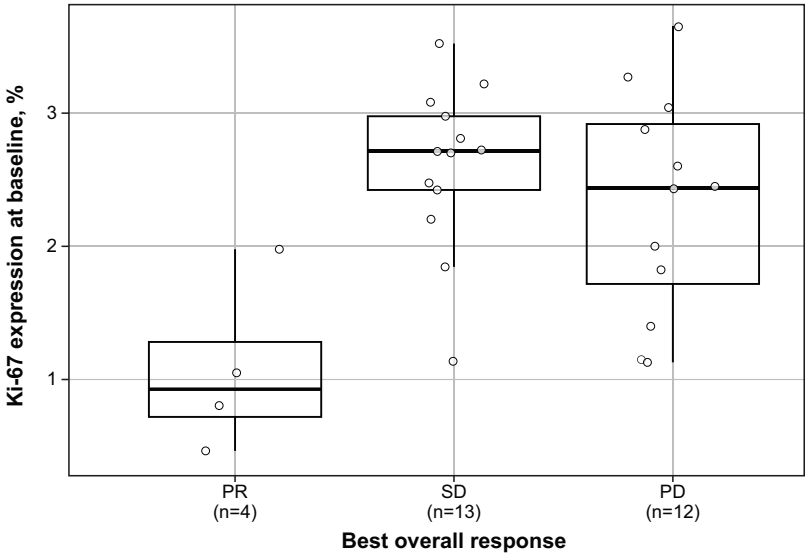

Figure 4. Association between IHC expression of Ki-67 at baseline and best overall response in part B.
Ki-67 expression was measured after Box-Cox transformation.
IHC, immunohistochemistry; PD, progressive disease; PR, partial response; SD, stable disease.

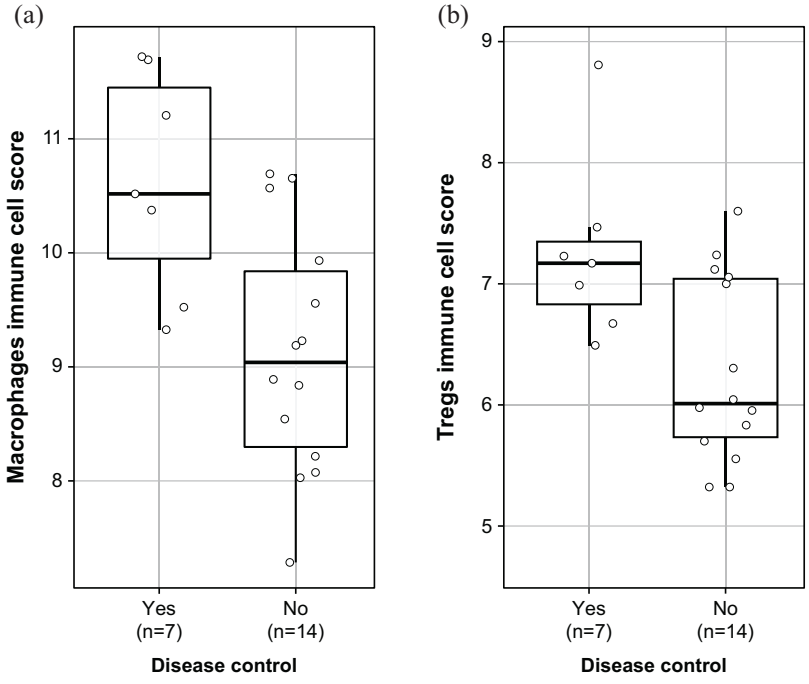

Figure 5. Distribution of NanoString immune cell scores for macrophages (a) and FOXP3$^+$ Tregs (b) in patients with and without disease control in part B.
Treg, regulatory T cell.

signature associated with M0/M2 macrophages correlated with shorter progression-free survival (data not shown).[55] These contrasting findings are caveated by data from other tumour types and differing approaches in measuring cell populations. Circulating levels of IL-10, IL-1β and IL-13 increased during the study, and levels of Tregs increased during cycle 1. Activated Tregs have been shown to stimulate the production of IL-10,[56] and both have been shown to inhibit the antitumour response by restricting the activity of CD4$^+$ T cells; this was also observed in our study, with a

Table 5. NanoString immune cell scores for all biomarkers from FFPE biopsies during the study versus at baseline in part B.

Biomarker	Response	*p* Value	Biomarker	Response	*p* Value
Macrophages	DC	0.0248	B cells	BOR	0.1308
Tregs	DC	0.0458	Cytotoxic cells	OS	0.1315
Th1 cells	DC	0.0610	Dendritic cells	OS	0.1315
Dendritic cells	DC	0.0697	Tregs	OS	0.1320
$CD56^{dim}$ NK cells	DC	0.0720	Neutrophils	BOR	0.1330
T cells	DC	0.0725	CD8 T cells	DC	0.1361
B cells	DC	0.0868	Neutrophils	OS	0.1380
Exhausted CD8 cells	DC	0.1020	CD8 T cells	OS	0.1395
Neutrophils	DC	0.1130	Cytotoxic cells	DC	0.1447
Mast cells	OS	0.1193	NK cells	OS	0.1880
T cells	OS	0.1235			

BOR, best overall response; DC, disease control; FFPE, formalin-fixed paraffin-embedded; NK, natural killer; OS, overall survival; Treg, regulatory T cell.

reduction in levels of activated $CD4^+$ cells between cycle 1 and cycle 4. These findings could explain the lack of an antitumour response observed in this study. IL-10 expression has also been identified as a poor clinical prognosis factor for NSCLC.[57] Similarly, IL-1β and IL-13 have been shown to contribute to the generation of an immunosuppressive microenvironment across various cancer types.[58,59] In patients with NSCLC, IL-1β expression has been shown to correlate with poor efficacy (reduced progression-free survival).[60] The biomarker analyses presented here support the lack of an antitumour response observed with xevinapant and avelumab treatment in our study and indicate an immunosuppressive phenotype. Further studies would be needed to confirm our results and clarify how these biomarker changes inform clinical endpoints.

The findings should be interpreted in the context of a few limitations. The absence of a control arm in part B hinders interpretation of the efficacy and biomarker findings. Furthermore, the biomarker analyses were exploratory, and the patient numbers were limited; therefore, *p* values should be interpreted with caution. The low number of patients with a response in part B ($n=4$ (10.5%), all with a partial response) did not allow for significant associations between biomarker levels and clinical efficacy endpoints. In addition, biopsies were archived samples (not older than 1 year); therefore, biomarker findings should be interpreted with caution. To clarify the role of xevinapant, future studies are needed with larger sample sizes and a control arm, thereby allowing the immune impact of adding xevinapant to be more precisely defined.

Conclusion

Although part B of the phase Ib study failed to meet its primary objective, the combination was safe and feasible, and the biomarker analyses reported here provide novel insights into the drivers associated with efficacy in patients with NSCLC receiving xevinapant in combination with avelumab.

Author's note

Franck Brichory, affiliation at the time the study was conducted.

Declarations

Ethics approval and consent to participate

This study was conducted in compliance with the International Council for Harmonisation

Good Clinical Practice guidelines and the ethical principles derived from the Declaration of Helsinki and the Canadian Food and Drug Regulations, Part C, Division 5, Drugs for Clinical Trials Involving Human Subjects. The study protocol, informed consent form and other relevant study documentation were reviewed and approved by the institutional review boards, conforming to local laws, prior to enrolment. The following institutional review boards approved the study: Ontario Cancer Research Ethics Board, Canada (CTO project ID: 0900 (sites 10 and 12)); University of British Columbia – British Columbia Cancer Agency Research Ethics Board, Canada (REB Number: H17-02061 (site 11)); Health Research Ethics Board of Alberta, Canada (ethics ID: HREBA.CC-17-0383 (site 13)); McGill University Health Centre Research Ethics Board, Canada (project number: 2019-5110 (site 14)); Bioethics Committee, Regional Medical Council of the Wielkopolski Medical Chamber, Poznan Poland (date of approval: 20 March 2019); Academy of Medical Sciences National Bioethics Committee of Medicines and Medical Devices, Romania (date of approval: 4 April 2019). Written informed consent was obtained from all patients except one; site staff were retrained with respect to the correct informed consent process, and this patient was not given study medication or included in the analyses.

Consent for publication

Not applicable.

Author contributions

Glenwood Goss: Conceptualisation; Funding acquisition; Investigation; Methodology; Project administration; Writing – original draft; Writing – review & editing.

Tudor Ciuleanu: Data curation; Investigation; Writing – original draft; Writing – review & editing.

Rodryg Ramlau: Data curation; Investigation; Writing – original draft; Writing – review & editing.

Daniel J. Renouf: Data curation; Investigation; Writing – original draft; Writing – review & editing.

Quincy Chu: Data curation; Investigation; Writing – original draft; Writing – review & editing.

Ewa Kalinka: Data curation; Investigation; Writing – original draft; Writing – review & editing.

Piotr Sawrycki: Data curation; Investigation; Writing – original draft; Writing – review & editing.

Jonathan Bramson: Conceptualisation; Data curation; Formal analysis; Supervision; Writing – original draft; Writing – review & editing.

Brad H. Nelson: Formal analysis; Funding acquisition; Investigation; Supervision; Writing – original draft; Writing – review & editing.

Rafael Crabbé: Data curation; Formal analysis; Methodology; Project administration; Validation; Writing – original draft; Writing – review & editing.

Eric LaCasse: Conceptualisation; Funding acquisition; Writing – original draft; Writing – review & editing.

Bryan Lo: Resources; Writing – original draft; Writing – review & editing.

Daniela A. Sahlender: Formal analysis; Writing – original draft; Writing – review & editing.

Philippa Crompton: Data curation; Formal analysis; Validation; Writing – original draft; Writing – review & editing.

Franck Brichory: Formal analysis; Methodology; Writing – original draft; Writing – review & editing.

Luke Piggott: Formal analysis; Writing – original draft; Writing – review & editing.

Michael Schenker: Formal analysis; Investigation; Project administration; Resources; Supervision; Validation; Visualisation; Writing – original draft; Writing – review & editing.

Rosalyn Juergens: Conceptualisation; Funding acquisition; Writing – original draft; Writing – review & editing.

Acknowledgements

The authors thank the patients and their families, and the investigators, co-investigators and study teams at each of the participating centres. Avelumab was provided by Merck (CrossRef Funder ID: 10.13039/100009945) and Pfizer. Medical writing support was provided by Jamie Ratcliffe of Nucleus Global and was funded by Merck, in accordance with Good Publication

Practice guidelines (https://www.ismpp.org/gpp-2022). Merck reviewed the manuscript for medical accuracy. The authors are fully responsible for the content, and the views and opinions described in the publication reflect solely those of the authors. Dr Harman Sekhon of The Ottawa Hospital, Ottawa, ON, Canada, was the pathologist who carried out PD-L1 staining and analyses. Katy Milne of the Deeley Research Centre, BC Cancer – Victoria, Victoria, BC, Canada, was a pathologist who helped to develop the IHC methods and conduct the IHC analyses. Jessica Irvine, Jamie McNicol and Ying Wu helped to collect peripheral blood mononuclear cells and serum, perform flow cytometry and cytokine assessment and analyse the resulting data. Dr Robert Korneluk of the CHEO Research Institute, Ottawa, ON, Canada, contributed to the obtaining the funding for this study.

Funding

The authors disclosed receipt of the following financial support for the research, authorship and/or publication of this article: The study was conceptualised and sponsored by Debiopharm International SA. Correlative assays were supported by a grant from BioCanRx, a Network of Centres of Excellence, which received funding from the Canadian federal government.

Competing interests

G.G. reports honoraria from AstraZeneca and Merck; and reports research funding from Debiopharm International SA. T.C. reports research funding from Amgen, Astellas Pharma, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Debiopharm International SA, Ipsen, Janssen, Lilly, Merck, MSD, Novartis, Pfizer, Roche, Sanofi, Servier and Takeda and reports receiving travel and accommodation expenses from Amgen, Astellas Pharma, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Ipsen, Janssen, Lilly, Merck, MSD, Novartis, Pfizer, Roche, Sanofi and Servier. R.R. has nothing to disclose. D.J.R. reports research funding from Bayer, Ipsen, Roche and Sanofi. Q.C. reports research funding from AstraZeneca and Debiopharm International SA; and reports serving in a consulting or advisory role for AbbVie, Amgen, AnHeart, Astellas Pharma, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Lilly, Merck, Jazz Pharmaceuticals, Johnson & Johnson, MSD, Novartis, Pfizer, Roche and Takeda. E.K. reports honoraria from and reports serving in a consulting or advisory role for Amgen, AstraZeneca, Bristol Myers Squibb, Debiopharm International SA, GSK, MSD, Pfizer and Regeneron. P.S. has nothing to disclose. J.B. reports serving as an independent contractor for, reports stock and other ownership interests in and reports research funding from Triumvira Immunologics. B.H.N. reports stock and other ownership interests in Innovakine Therapeutics, Overture Therapeutics and Virogin Biotech; and reports research funding from Innovakine Therapeutics and Overture Therapeutics. R.C. reports serving as an independent contractor for Debiopharm International SA. E.L. reports stocks and other ownership interests in Protaxis Therapeutics; and reports inventorship and employment at the CHEO Research Institute, which has licensed a patent to Debiopharm International SA. B.L. reports serving in a consulting or advisory role for AstraZeneca, Bayer, Janssen, Novartis, Pfizer and Roche. D.A.S. reports employment at Debiopharm International SA. P.C. reports employment at Debiopharm International SA; and reports stock and other ownership interests in GSK. F.B. reported employment at Debiopharm International SA at the time of study. L.P. reports employment at Debiopharm International SA. M.S. reports personal and institutional research funding from AbbVie, Amgen, Astellas Pharma, AstraZeneca, Bayer, BeiGene, Bioven, Bristol Myers Squibb, Clovis, Daiichi Sankyo, Merck, Lilly, Gilead, GSK, MSD, Mylan, Novartis, Pfizer, PharmaMar, Regeneron, Roche, Sanofi and Tesaro. R.J. reports honoraria from Amgen, AstraZeneca, Bristol Myers Squibb, Debiopharm International SA, Jazz Pharmaceuticals, MSD, Mirati Therapeutics, Novartis, Roche and Takeda; reports serving in a consulting or advisory role for Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Lilly, Merck, Fusion Pharmaceuticals, Janssen Oncology, Jazz Pharmaceuticals, MSD, Novartis, Pfizer, Roche, Sanofi/Regeneron and Takeda and reports institutional research funding from Alkermes, Amgen, Astellas Pharma, AstraZeneca/MedImmune, Bristol Myers Squibb, Bold Therapeutics, Fusion Pharmaceuticals, Janssen, MacroGenics, MSD and Novartis.

Availability of data and materials

Any requests for data by qualified scientific and medical researchers for legitimate research purposes will be subject to Merck's Data Sharing Policy. All requests should be submitted in writing to Merck's data sharing portal (https://www.

merckgroup.com/en/research/our-approach-to-research-and-development/healthcare/clinical-trials/commitment-responsible-data-sharing.html). When Merck has a co-research, co-development, or co-marketing or co-promotion agreement, or when the product has been out-licensed, the responsibility for disclosure might be dependent on the agreement between parties. Under these circumstances, Merck will endeavour to gain agreement to share data in response to requests.

ORCID iDs

Glenwood Goss https://orcid.org/0000-0002-5316-1022

Quincy Chu https://orcid.org/0000-0003-4814-3126

Supplemental material

Supplemental material for this article is available online.

References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2024; 74: 229–263.
2. American Cancer Society. Facts & figures 2023, https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2023/2023-cancer-facts-and-figures.pdf.
3. Ganti AK, Klein AB, Cotarla I, et al. Update of incidence, prevalence, survival, and initial treatment in patients with non-small cell lung cancer in the US. *JAMA Oncol* 2021; 7: 1824–1832.
4. Economopoulou P and Mountzios G. The emerging treatment landscape of advanced non-small cell lung cancer. *Ann Transl Med* 2017; 6: 138.
5. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* 2015; 373: 1627–1639.
6. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Eng J Med* 2015; 373: 123–135.
7. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016; 387: 1540–1550.
8. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med* 2018; 378: 2078–2092.
9. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet* 2017; 389: 255–265.
10. Lee SM, Schulz C, Prabhash K, et al. First-line atezolizumab monotherapy versus single-agent chemotherapy in patients with non-small-cell lung cancer ineligible for treatment with a platinum-containing regimen (IPSOS): a phase 3, global, multicentre, open-label, randomised controlled study. *Lancet* 2023; 402: 451–463.
11. NCCN Clinical Practice Guidelines in Oncology. *Non-small cell lung cancer*. v5. Plymouth Meeting, PA, 2024.
12. Hendriks LE, Kerr KM, Menis J, et al. Non-oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2023; 34: 358–376.
13. Hendriks LE, Kerr KM, Menis J, et al. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2023; 34: 339–357.
14. Bavencio (Avelumab). *Prescribing information*. EMD Serono, Inc., Rockland, MA, an affiliate of Merck KGaA, 2020.
15. Park K, Özgüroğlu M, Vansteenkiste J, et al. Avelumab versus docetaxel in patients with platinum-treated advanced NSCLC: 2-year follow-up from the JAVELIN Lung 200 phase 3 trial. *J Thorac Oncol* 2021; 16: 1369–1378.
16. Reck M, Barlesi F, Chih-Hsin Yang J, et al. Avelumab vs platinum-based doublet chemotherapy as first-line treatment for patients with high-expression PD-L1+ metastatic non-small cell lung cancer: primary analysis from the phase 3 JAVELIN Lung 100 trial. *J Thorac Oncol* 2024; 19(2): 297–313.
17. Dubrez L, Berthelet J and Glorian V. IAP proteins as targets for drug development in oncology. *Onco Targets Ther* 2013; 9: 1285–1304.
18. de Almagro MC and Vucic D. The inhibitor of apoptosis (IAP) proteins are critical regulators

of signaling pathways and targets for anti-cancer therapy. *Exp Oncol* 2012; 34: 200–211.

19. Cetraro P, Plaza-Diaz J, MacKenzie A, et al. A review of the current impact of inhibitors of apoptosis proteins and their repression in cancer. *Cancers (Basel)* 2022; 14: 1671.
20. Ferreira CG, van der Valk P, Span SW, et al. Assessment of IAP (inhibitor of apoptosis) proteins as predictors of response to chemotherapy in advanced non-small-cell lung cancer patients. *Ann Oncol* 2001; 12: 799–805.
21. Beug ST, Cheung HH, LaCasse EC, et al. Modulation of immune signalling by inhibitors of apoptosis. *Trends Immunol* 2012; 33: 535–545.
22. Abbas R and Larisch S. Targeting XIAP for promoting cancer cell death – the story of ARTS and SMAC. *Cells* 2020; 9: 663.
23. Obexer P and Ausserlechner MJ. X-linked inhibitor of apoptosis protein – a critical death resistance regulator and therapeutic target for personalized cancer therapy. *Front Oncol* 2014; 4: 197.
24. Zhao XY, Wang XY, Wei QY, et al. Potency and selectivity of SMAC/DIABLO mimetics in solid tumor therapy. *Cells* 2020; 9: 1012.
25. Vucic D. Targeting IAP (inhibitor of apoptosis) proteins for therapeutic intervention in tumors. *Curr Cancer Drug Targets* 2008; 8: 110–117.
26. Matzinger O, Viertl D, Tsoutsou P, et al. The radiosensitizing activity of the SMAC-mimetic, Debio 1143, is TNFα-mediated in head and neck squamous cell carcinoma. *Radiother Oncol* 2015; 116: 495–503.
27. Cai Q, Sun H, Peng Y, et al. A potent and orally active antagonist (SM-406/AT-406) of multiple inhibitor of apoptosis proteins (IAPs) in clinical development for cancer treatment. *J Med Chem* 2011; 54: 2714–2726.
28. Thibault B, Genre L, Le Naour A, et al. DEBIO 1143, an IAP inhibitor, reverses carboplatin resistance in ovarian cancer cells and triggers apoptotic or necroptotic cell death. *Sci Rep* 2018; 8: 17862.
29. Vince JE, Wong WW, Khan N, et al. IAP antagonists target cIAP1 to induce TNFalpha-dependent apoptosis. *Cell* 2007; 131: 682–693.
30. Varfolomeev E, Blankenship JW, Wayson SM, et al. IAP antagonists induce autoubiquitination of c-IAPs, NF-kappaB activation, and TNFalpha-dependent apoptosis. *Cell* 2007; 131: 669–681.
31. Petersen SL, Wang L, Yalcin-Chin A, et al. Autocrine TNFalpha signaling renders human cancer cells susceptible to Smac-mimetic-induced apoptosis. *Cancer Cell* 2007; 12: 445–456.
32. Bertrand MJ, Milutinovic S, Dickson KM, et al. cIAP1 and cIAP2 facilitate cancer cell survival by functioning as E3 ligases that promote RIP1 ubiquitination. *Mol Cell* 2008; 30: 689–700.
33. Beug ST, Tang VA, LaCasse EC, et al. Smac mimetics and innate immune stimuli synergize to promote tumor death. *Nat Biotechnol* 2014; 32: 182–190.
34. Dougan SK and Dougan M. Regulation of innate and adaptive antitumor immunity by IAP antagonists. *Immunotherapy* 2018; 10: 787–796.
35. Gomez-Roca C, Even C, Le Tourneau C, et al. Exploratory window-of-opportunity trial to investigate the tumor pharmacokinetics/pharmacodynamics of the IAP antagonist Debio 1143 in patients with head and neck cancer. *Clin Transl Sci* 2022; 15: 55–62.
36. Yu H, Lin L, Zhang Z, et al. Targeting NF-κB pathway for the therapy of diseases: mechanism and clinical study. *Signal Transduct Target Ther* 2020; 5: 209.
37. Zarnegar BJ, Wang Y, Mahoney DJ, et al. Noncanonical NF-kappaB activation requires coordinated assembly of a regulatory complex of the adaptors cIAP1, cIAP2, TRAF2 and TRAF3 and the kinase NIK. *Nat Immunol* 2008; 9: 1371–1378.
38. Dougan M, Dougan S, Slisz J, et al. IAP inhibitors enhance co-stimulation to promote tumor immunity. *J Exp Med* 2010; 207: 2195–2206.
39. Varfolomeev E, Goncharov T, Maecker H, et al. Cellular inhibitors of apoptosis are global regulators of NF-κB and MAPK activation by members of the TNF family of receptors. *Sci Signal* 2012; 5: ra22.
40. Pinto C, Slavic-Obradovic K, Fürweger D, et al. Tumor microenvironment mimicking 3D models unveil the multifaceted effects of SMAC mimetics. *iScience* 2023; 26: 106381.
41. Chesi M, Mirza NN, Garbitt VM, et al. IAP antagonists induce anti-tumor immunity in multiple myeloma. *Nat Med* 2016; 22: 1411–1420.
42. Beug ST, Beauregard CE, Healy C, et al. Smac mimetics synergize with immune checkpoint inhibitors to promote tumour immunity against glioblastoma. *Nat Commun* 2017; 8: 14278.
43. Barkhouse D, Tao Z, Myers C, et al. Abstract A93: the Smac mimetic Debio 1143 synergizes

with radiotherapy and immune checkpoint inhibitors to enhance antitumor immunity. *Mol Cancer Ther* 2015; 14: A93.

44. Bourhis J, Burtness B, Licitra LF, et al. Xevinapant or placebo plus chemoradiotherapy in locally advanced squamous cell carcinoma of the head and neck: TrilynX phase III study design. *Future Oncol* 2022; 18(14): 1669–1678.
45. Reeves BC and Gaus W. Guidelines for reporting non-randomised studies. *Forsch Komplementarmed Klass Naturheilkd* 2004; 11: 46–52.
46. Danaher P, Warren S, Dennis L, et al. Gene expression markers of tumor infiltrating leukocytes. *J Immunother Cancer* 2017; 5: 18.
47. Gulley JL, Rajan A, Spigel DR, et al. Avelumab for patients with previously treated metastatic or recurrent non-small-cell lung cancer (JAVELIN Solid Tumor): dose-expansion cohort of a multicentre, open-label, phase 1b trial. *Lancet Oncol* 2017; 18: 599–610.
48. Sun XS, Tao Y, Le Tourneau C, et al. Debio 1143 and high-dose cisplatin chemoradiotherapy in high-risk locoregionally advanced squamous cell carcinoma of the head and neck: a double-blind, multicentre, randomised, phase 2 study. *Lancet Oncol* 2020; 21: 1173–1187.
49. Tao Y, Sun XS, Pointreau Y, et al. Extended follow-up of a phase 2 trial of xevinapant plus chemoradiotherapy in high-risk locally advanced squamous cell carcinoma of the head and neck: a randomised clinical trial. *Eur J Cancer* 2023; 183: 24–37.
50. Kelly K, Infante JR, Taylor MH, et al. Safety profile of avelumab in patients with advanced solid tumors: a pooled analysis of data from the phase 1 JAVELIN solid tumor and phase 2 JAVELIN Merkel 200 clinical trials. *Cancer* 2018; 124: 2010–2017.
51. Barlesi F, Vansteenkiste J, Spigel D, et al. Avelumab versus docetaxel in patients with platinum-treated advanced non-small-cell lung cancer (JAVELIN Lung 200): an open-label, randomised, phase 3 study. *Lancet Oncol* 2018; 19: 1468–1479.
52. Powles T, Sridhar SS, Loriot Y, et al. Avelumab maintenance in advanced urothelial carcinoma: biomarker analysis of the phase 3 JAVELIN Bladder 100 trial. *Nat Med* 2021; 27: 2200–2211.
53. Fumet JD, Richard C, Ledys F, et al. Prognostic and predictive role of CD8 and PD-L1 determination in lung tumor tissue of patients under anti-PD-1 therapy. *Br J Cancer* 2018; 119: 950–960.
54. Tumeh PC, Harview CL, Yearley JH, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature* 2014; 515: 568–571.
55. Lee NY, Ferris RL, Psyrri A, et al. Avelumab plus standard-of-care chemoradiotherapy versus chemoradiotherapy alone in patients with locally advanced squamous cell carcinoma of the head and neck: a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. *Lancet Oncol* 2021; 22: 450–462.
56. Yu L, Yang F, Zhang F, et al. CD69 enhances immunosuppressive function of regulatory T-cells and attenuates colitis by prompting IL-10 production. *Cell Death Dis* 2018; 9: 905.
57. Hatanaka H, Abe Y, Kamiya T, et al. Clinical implications of interleukin (IL)-10 induced by non-small-cell lung cancer. *Ann Oncol* 2000; 11: 815–819.
58. Kiss M, Vande Walle L, Saavedra PHV, et al. IL1β promotes immune suppression in the tumor microenvironment independent of the inflammasome and gasdermin D. *Cancer Immunol Res* 2021; 9: 309–323.
59. Li X, Liu M, Shi Q, et al. Elevated serum IL-13 level is associated with increased Treg cells in tumor microenvironment and disease progression of diffuse large B-cell lymphoma. *Hematol Oncol* 2023; 41: 230–238.
60. McLoed AG, Sherrill TP, Cheng DS, et al. Neutrophil-derived IL-1β impairs the efficacy of NF-κB inhibitors against lung cancer. *Cell Rep* 2016; 16: 120–132.