Xevinapant plus avelumab in patients with advanced or metastatic non-small cell lung cancer: phase 1b dose-expansion results and exploratory biomarker analyses

Q. Chu,[1] T. Ciuleanu,[2] R. Ramlau,[3] D. Renouf,[4] R. Juergens,[5] E. Kalinka,[6] P. Sawrycki,[7] J. Bramson,[8] B. Nelson,[9] R. Crabbé,[10] D. A. Sahlender,[10] P. Crompton,[10] E. Rouits,[10*] D. Spaggiari,[10] F. Brichory,[10] L. Piggott,[10] M. Schenker,[11] G. Goss[12]

[1]Department of Oncology, University of Alberta, Cross Cancer Institute, Edmonton, AB, Canada; [2]Oncology Department, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania; [3]Oncology Department, Poznan University of Medical Sciences, Poznan, Poland; [4]Department of Medicine, Faculty of Medicine, The University of British Columbia, Vancouver, BC, Canada; [5]Department of Oncology, McMaster University, Hamilton, ON, Canada; [6]Department of Oncology, Polish Mother's Memorial Hospital, Lodz, Poland; [7]Wojewódzki Szpital Zespolony im L. Rydygiera w Toruniu, Torun, Poland; [8]Michael DeGroote Centre for Learning and Discovery, McMaster University, Hamilton, ON, Canada; [9]Deeley Research Centre, BC Cancer – Victoria, Victoria, BC, Canada; [10]Debiopharm International SA, Lausanne, Switzerland; [11]Oncology Center Sf Nectarie Ltd, Craiova, Romania; [12]Department of Medicine, University of Ottawa, Ottawa, ON, Canada

*At the time the study was conducted.

SCOPE

- We report results from an open-label, phase 1b, dose-expansion cohort of xevinapant, an IAP (inhibitor of apoptosis protein) inhibitor, and avelumab, an anti–PD-L1 immune checkpoint inhibitor (ICI), in patients with advanced non-small cell lung cancer (NSCLC) who progressed after one line of platinum-based chemotherapy, anti–PD-(L)1 monotherapy, or anti–PD-(L)1 in combination with platinum-based chemotherapy

CONCLUSIONS

- Xevinapant in combination with avelumab had a promising disease control rate and a tolerable safety profile in patients with advanced NSCLC who progressed after one line of platinum-based chemotherapy, anti–PD-(L)1 monotherapy, or anti–PD-(L)1 in combination with platinum-based chemotherapy
- Nevertheless, the study did not meet its primary endpoint; the addition of xevinapant to avelumab did not improve antitumor activity compared with historic data for avelumab second-line monotherapy[1]

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BACKGROUND

- The ICI avelumab (an anti–PD-L1 antibody) has improved overall survival (OS) in various tumor types[2-5]
- Xevinapant is a first-in-class, potent, oral, small-molecule, IAP inhibitor that is thought to restore sensitivity of cancer cells to apoptosis[6-8] via:
  - Inhibiting XIAP, which releases the brake on downstream caspase activity in the intrinsic apoptotic pathway[6]
  - Inhibiting cIAP1/2, which promotes pro-apoptotic TNF receptor signaling via the extrinsic pathway and induces TNFα expression via the noncanonical nuclear factor κB pathway[6,9-11]
- Given xevinapant's potential effect on immune cells, we hypothesized that the combination with avelumab could further enhance antitumor activity

- In the dose-optimization part (part A) of a phase 1b study (NCT03270176), patients with advanced solid tumors who were not eligible for standard therapy or for whom standard therapy had failed received xevinapant 100 mg/day (n=3), 150 mg/day (n=2), 200 mg/day (n=7), or 250 mg/day (n=4) plus avelumab 10 mg/kg on days 1 and 15 of a 28-day cycle[12]
  - The maximum tolerated dose of xevinapant was not reached
  - The recommended phase 2 dose (RP2D) was established as xevinapant (200 mg/day on days 1-10 and 15-24 every 28 days) plus avelumab (10 mg/kg every 2 weeks)
  - A dose-limiting toxicity was reported by 1 patient (at the 250-mg/day dose level; reversible grade 3 alanine aminotransferase and aspartate aminotransferase increases)
- We report results from the dose-expansion part (part B) of this phase 1b study, which investigated xevinapant plus avelumab in patients with advanced NSCLC who had progressed after one line of platinum-based chemotherapy, anti–PD-(L)1 monotherapy, or anti–PD-(L)1 in combination with platinum-based chemotherapy

METHODS

- Eligible patients had advanced NSCLC and had progressed after one line of platinum-based chemotherapy, anti–PD-(L)1 monotherapy, or anti–PD-(L)1 in combination with platinum-based chemotherapy
- Patients received xevinapant at the RP2D (200 mg/day orally on days 1-10 and 15-24) plus avelumab 10 mg/kg (days 1 and 15) in 28-day cycles
  - Study treatment was planned for 26 cycles or until 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 trial, or start of subsequent anticancer therapy
- The primary endpoint was objective response rate (ORR) per RECIST 1.1 (investigator-assessed)
  - Secondary endpoints included duration of response, disease control rate, progression-free survival, OS, safety, and pharmacokinetics (PK)
  - Exploratory biomarker analyses were also conducted (plasma cytokine assays, analysis of circulating immune cells using flow cytometry, immunohistochemistry [IHC] of baseline and on-treatment tumor samples, and NanoString gene expression analyses)

RESULTS

Patient disposition

- Between May 2019 and March 2022, a total of 38 patients were enrolled and treated at 6 centers in Canada, Poland, and Romania
- Patient baseline characteristics are summarized in **Table 1**
- 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
- The most common reasons for discontinuation were disease progression (n=26 [70.3%]) and adverse events (n=10 [27.0%])
- 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

Efficacy

- All participants had measurable disease and were evaluable for efficacy
- A summary of efficacy results is presented in **Table 2**
- The observed ORR was 10.5% (95% CI, 2.9-24.8) with 4 patients responding to treatment; thus, the target of a 15% increase in efficacy over avelumab monotherapy (ORR, 10%) was not met
- Of the 4 responders (all with a partial response), none had received any prior PD-(L)1 therapy, and 3 had tumors with high PD-L1 expression (PD-L1 status for the 4th patient was not known)

PK

- Circulating xevinapant concentrations and avelumab PK were similar to previously reported values for each respective monotherapy at the same doses
- There were no apparent drug-drug interactions for the combination of xevinapant and avelumab

Safety

- A summary of safety results is presented in **Table 3**
- The most common treatment-emergent adverse events (TEAEs) of any grade related to xevinapant were decreased appetite and nausea (n=7 [18.4%] each)
- TEAEs related to xevinapant were grade ≥3 in 1 patient (2.6%; amylase increased)
- The most common TEAEs of any grade related to avelumab were amylase increased (n=9 [23.7%]) and hypothyroidism (n=7 [18.4%])
- TEAEs related to avelumab were grade ≥3 in 6 patients (15.8%; amylase increased in 4 [10.5%], lipase increased in 3 [7.9%], and alanine aminotransferase increased in 1 [2.6%])
- No serious TEAEs were considered related to either treatment
- 9 patients (23.7%) died during the study due to TEAEs; however, no deaths were considered related to study treatment

Table 1. Baseline characteristics

	N=38
Age, median (range), years	61.5 (35-75)
Sex, n (%)	
Male	27 (71.1)
Female	11 (28.9)
Race, n (%)	
White	38 (100)
PD-L1 status*, n (%)	
Positive	13 (34.2)
Moderate	5 (13.2)
Negative	12 (31.6)
Missing	8 (21.1)
ECOG PS, n (%)	
0	1 (2.6)
1	37 (97.4)
Cancer type, n (%)	
Squamous cell carcinoma	17 (44.7)
Adenocarcinoma	16 (42.1)
Large cell carcinoma	2 (5.3)
NSCLC (not otherwise specified)	1 (2.6)
Other	2 (5.3)
Stage at baseline, n (%)	
IIIb	6 (15.8)
IV	32 (84.2)
Local or distant metastases, n (%)	
Local	8 (21.1)
Distant	30 (78.9)
Type of prior therapy, n (%)	
Chemotherapy	38 (100)
Anti–PD-L1 therapy	4 (10.5)
Radiotherapy	9 (23.7)
Surgery	2 (5.3)
Received prior PD-L1 immunotherapy, n (%)	
Yes	4 (10.5)
No	34 (89.5)

ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer.
*Assessed using the 22C3 pharmDx assay.

Table 2. Summary of efficacy results

	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)
Duration of response* (95% CI), months	15.9 (3.5-29.7)
Disease control rate (95% CI), %	60.5 (43.4-76.0)
Progression-free survival (95% CI), months	3.5 (1.9-5.1)
Overall survival (95% CI), months	9.4 (6.7-16.2)

*Among the 4 patients with a partial response.

Table 3. Summary of safety results

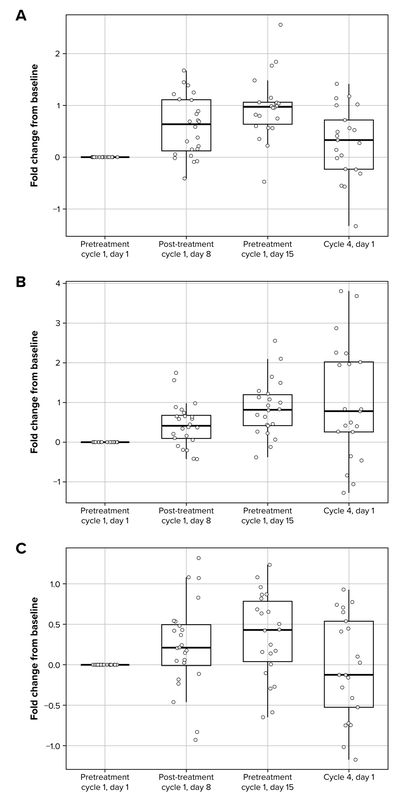
	N=38
TEAEs, n (%)	
Any grade	37 (97.4)
Grade ≥3	21 (55.3)
Serious adverse events	11 (28.9)
Leading to discontinuation of xevinapant	4 (10.5)
Leading to discontinuation of avelumab	4 (10.5)
Leading to death	9 (23.7)
TEAEs related to xevinapant, n (%)	
Any grade	19 (50.0)
Grade ≥3	1 (2.6)
TEAEs related to avelumab, n (%)	
Any grade	27 (71.1)
Grade ≥3	6 (15.8)
Infusion-related reaction, n (%)	1 (2.6)

TEAE, treatment-emergent adverse event.

Biomarker analysis

- Increases in plasma IL-10 levels were detected in patients during the study treatment period (**Supplementary Figure 1**)
- In analyses of peripheral blood, activated $CD4^+$ T-cell and Treg levels increased during cycle 1, and activated $CD8^+$ T-cell levels increased during the study treatment period (**Figure 1**); however, these did not correlate with antitumor activity
- In IHC analyses of tumor samples, patients with a best overall response of partial response (n=4) tended to have lower Ki67 expression at baseline
- In NanoString gene expression analyses, increases in the levels of macrophages, Tregs were associated with disease control (**Supplementary Figures 2** and **3**)
- Overall, biomarker data were inconclusive

Figure 1. Change in levels of activated $CD4^+$ T-cells (A), $CD8^+$ T-cells (B), and Treg cells (C) in the blood during the study treatment period vs baseline



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