Safety and efficacy of Xevinapant (Debio 1143), an antagonist of inhibitor of apoptosis proteins (IAPs), in combination with nivolumab in a Phase Ib/II trial in patients failing prior PD-1/PD-L1 treatment

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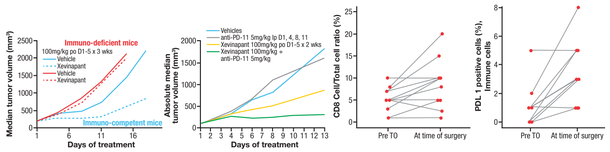
INTRODUCTION

- Antagonists of IAPs regulate apoptosis and modulate NF-κB signaling, which drives the expression of genes involved in immune and inflammatory responses
- In pre-clinical models Xevinapant synergized with PD-1/PD-L1 checkpoint inhibitors[1]
- In a pre-operative window-of-opportunity study, PD-1 and PD-L1 expression and tumor infiltrating lymphocyte counts increased compared with baseline values in tumors resected from patients treated with Xevinapant[2]
- Furthermore, pharmcodynamic biomarkers (TNFα, IFNγ) in blood have been shown to increase in response to Xevinapant, and in a dose dependent manner[3]



- In preclinical models, Xevinapant activity was dependent on the host immune system[1]
- In tumors resected from patients with SCCHN, Xevinapant (200 mg/day D1-15 ± 2) treatment increased levels of PD-L1 expression and tumor infiltrating lymphocytes[2]

STUDY OVERVIEW

Study Design

- Part A, a phase I study, using a classical 3+3 dose-optimization design, in which nivolumab (240 mg q4w)* was combined with escalating doses of Xevinapant (150 and 200 mg/day orally, on D1-10 & D15-24 q4w)* **(NCT04122625)**

Dose levels	Xevinapant oral, daily on D1-D10 & D15-D24 q4w	Nivolumab flat dose IV, D1 & D15 q4w
1	150 mg	240 mg
2	200 mg	

*1 cycle = 4 weeks. D=day, IV=intravenous, q4w=every 4 weeks

- The aim of this ongoing study is to assess the safety and efficacy of Xevinapant in combination with nivolumab, an anti-PD-1 antibody, in patients with advanced solid tumors, previously treated with a prior anti-PD1/PD-L1 based treatment

Study Objectives

- Determination of RP2D for Xevinapant in combination with nivolumab
- Safety and tolerability
- Pharmacokinetics (PK)
- Efficacy

Main Eligibility Criteria

- Histologically confirmed diagnosis of advanced/unresectable or metastatic
  - **Small cell lung cancer**
  - **Squamous cell carcinoma of the head and neck (SCCHN)**
  - **Gastrointestinal cancers (GI)** with known microsatellite instability high/deficient mismatch repair (MSI-H/MMRd) or any other known DNA damage repair (DDRs) abnormalities, including homologous recombination deficiency (HRD)
  - **Gynecological cancers (Gyn)**, with known MSI-H/ MMRd, hereditary /somatic mutations of the BRCA1 and BRCA2 genes or other known DDRs abnormalities (incl. HRD)
- At least **1 line of prior systemic chemotherapy and progression/relapse during/after treatment with anti-PD-1/PD-L1**
- No prior discontinuation of checkpoint inhibitors due to safety reasons
- Up to 3 (i.e. Cohorts 1 & 2) or 4 (i.e. Cohorts 3 & 4) lines of prior therapy
- Adequate major organ function (CTCAE grade 0 or 1), Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1

RESULTS (cut-off date 6th March 2020)

Table 1: Baseline patient and disease characteristics

	Xevinapant 150 mg N=3	Xevinapant 200 mg N=8	Overall N=11
Age (Yrs) Median (range)	76 (58–79)	54.5 (46.5–67)	60 (47–76)
Gender, n Male/Female	2/1	7/1	9/2
ECOG 0/1	1/2	6/2	7/4
Weight (Kg) Median (range)	77 (68–93)	73.6 (60–84)	74 (60–93)

Disease characteristics, N=11		Prior treatments, N=11	
Cohorts according to diagnosis		**N of prior treatments**	
GI		1 or 2 lines	3
Colorectal	5	3 or more lines	8
Gastric	1	Median	3
SCCHN		**Type of therapy**	
Hypopharynx	1	Cytotoxic	100%
Nasopharynx	1	Immunotherapy	100%
Oral cavity	1	**BOR to prior immunotherapies**	
Oropharyngeal	1	PR	4
Gyn		SD	3
Ovarian	1	PD	3
		UNK	1

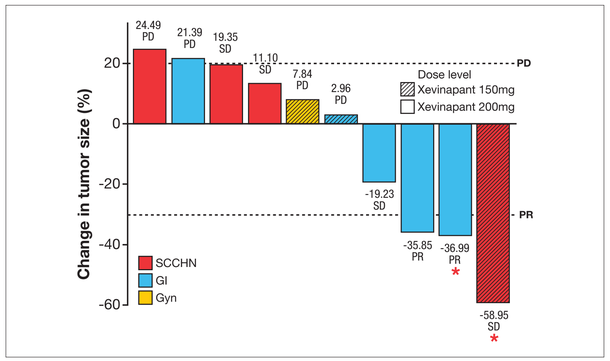
BOR=best overall response, PR=partial response, SD=stable disease, PD=progressive disease, UNK=unknown

PHARMACOKINETICS

- Xevinapant PK is consistent with previous observations at these dose levels
- Nivolumab PK in combination with Xevinapant is in line with literature data of nivolumab alone

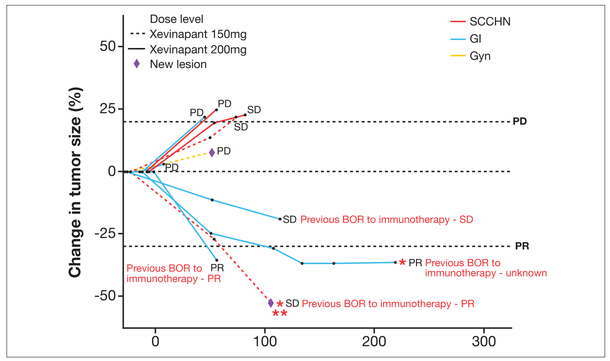
EFFICACY

Figure 1: Best percentage change in tumor size



Data shown represents the best percentage change in the sum of the longest diameter. PD=progressive disease, PR=partial response, SD=stable disease. *Patient ongoing at time of data cut-off

Figure 2: Spider plot best change in tumor size over time



PD=progressive disease, PR=partial response, SD=stable disease, BOR=best overall response. *Patient ongoing at time of data cut-off. **PD due to new lesions when maximal target shrinkage

Table 2: Exposure to Xevinapant and nivolumab*

	Xevinapant 150 mg N=3	Xevinapant 200 mg N=8	Overall N=11
Exposure to Xevinapant			
Median duration of treatment, wks (range)	11.4 (9–59)	11.6 (1–32)	11.6 (1–59)
Median cumulative dose in Cycle 1, mg (range)	3,000 (3,000–3,000)	4,000 (1,200–4,000)	3,600 (1,200–4,000)
Exposure to nivolumab Median infusions in C1 (range)	2 (2–2)	2 (1–2)	2 (1–2)
End of Treatment status			
Ongoing at time of cut-off	1	1	2
Discontinued	2	7	9
Reasons for treatment discontinuation			
Xevinapant AEs	-	-	-
Nivolumab AEs	-	-	-
AE unrelated to drug	-	1	1
Disease progression	2	5	7
Subject decision	-	1	1

*2 patients were excluded from the RP2D analysis set due to not receiving ≥70% of Xevinapant and/or ≥1 nivolumab dose in Cycle 1

SAFETY AND LABORATORY PARAMETERS

Table 3: ≥Grade 3 TEAEs regardless of study drug relationship

List of grade ≥3 AEs	Xevinapant 150 mg N=3	Xevinapant 200 mg N=8	Overall N=11
Grade ≥3, n of patients (%)	-	6 (75)	6 (55)
Grade ≥3 AEs			
Fatigue	-	1	1
Bile duct obstruction	-	1	1
Hepatic failure	-	1	1
Hyperbilirubinemia	-	1	1
Drug hypersensitivity	-	1	1
URT infection	-	1	1
Glioblastoma	-	1	1

*URT=upper respiratory tract

Table 4: TEAEs with study drug relationship

	Xevinapant 150 mg N=3	Xevinapant 200 mg N=8	Overall N=11
Related to Xevinapant, n of patients			
Grade 1/2	2	5	7
Most common (>1 patient)			
Pruritus	-	3	3
Asthenia	-	2	2
Grade ≥3	-	-	-
Related to nivolumab*			
Grade ≥3	-	-	-

*Grade 1 and 2 TEAEs attributable to nivolumab data are unavailable

LABORATORY PARAMETERS

Table 5: Chemistry and hematology

Worst on-treatment grade	Xevinapant 150 mg N=3	Xevinapant 200 mg N=8	Overall N=11
ALT increased			
Grade 1/2	-	3 (38%)	3 (27%)
Grades ≥3	-	-	-
AST increased aspartate amino transferase			
Grade 1/2	-	5 (63%)	5 (46%)
Grades ≥3	-	-	-
ALP increased			
Grade 1/2	1 (33%)	4 (50%)	5 (46%)
Grade 3	-	2 (25%)	2 (18%)
All Grades	1 (33%)	6 (75%)	7 (64%)
Blood bilirubin increased			
Grade 1/2	1 (33%)	1 (13%)	2 (18%)
Grades ≥3	-	-	-
Lipase increased			
Grade 1/2	1 (33%)	2 (25%)	3 (27%)
Grade 3	-	1 (13%)	1 (9%)
All Grades	1 (33%)	3 (38%)	4 (36%)
Hypoalbuminemia			
Grade 1/2	-	2 (25%)	2 (18%)
Grades ≥3	-	-	-
Serum amylase increased			
Grade 1/2	-	3 (38%)	3 (27%)
Grades ≥3	-	-	-
Creatinine increased			
Grade 1/2	1 (33%)	2 (25%)	3 (27%)
Grades ≥3	-	-	-
Anemia			
Grade 1/2	1 (33%)	6 (75%)	7 (64%)
Grades ≥3	-	-	-
Neutrophil count decreased			
All grades	-	-	-
Platelet count decreased			
Grade 1/2	-	1 (13%)	1 (9%)
Grades ≥3	-	-	-

CONCLUSIONS

- RP2D for Xevinapant in combination with nivolumab was selected at 200 mg/d based on a favorable safety profile, PD, PK and efficacy[2,3]
- No DLT was observed
- Toxicities were mild, manageable and without major impact on treatment compliance
- Clinical efficacy was preliminarily observed in this heavily pretreated cohort of patients who had failed prior CPI-containing treatment
- Xevinapant PK exposure is in the range associated with target engagement and efficacy in other indications. Nivolumab PK disposition is not impacted by combination with Xevinapant
- Part B expansion at the RP2D (Xevinapant 200 mg/day + nivolumab 240 mg IV, D1 & D15 q4w) is ongoing in all 4 patient cohorts of small cell lung cancer, squamous cell carcinoma of the head and neck, gastro-intestinal and gynecological cancer

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CONTACT

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