**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 patients failing prior PD-1/PD-L1 treatment**


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**ABSTRACT #1520    POSTER #560P**

**INTRODUCTION**

- Antagonism 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 PS-173-1/II checkpoint inhibitors.
- In a pre-operative window-of-opportunity study PO-1 and PO-1L expression and tumor infiltrating lymphocytes counts increased compared with baseline in tumors resected in patients with PD-L1.
- Furthermore, pharmacodynamic biomarkers (TFs, IFN) in blood have been shown to increase in response to Xevinapant, and in a dose dependent manner.

**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 escalated with escalating doses of Xevinapant (150 and 200 mg/day orally, on D1-10 & D15-24 q4w).*
- Nivolumab (240 mg q4w)* was combined with escalating doses of Xevinapant during/after treatment with anti-PD-1/PD-L1 based treatment.

**Study Objectives**

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

**Eligibility Criteria**

- Historically confirmed diagnosis of advanced/unresectable or metastatic:
  - Small cell lung cancer.
  - Squamous cell carcinomas of the head and neck (SCCHN).
- Gastrointestinal tumors (GI) with known microsatellite instability/high deficient mismatch repair (MSI-H/MMRd) or any other known genetic DNA repair (DDR) 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 DDR abnormalities (incl. HRD).
- At least 1 line of prior systemic chemotherapy and progression/regression 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 3 & 4) or 4 (i.e. Cohorts 5 & 6) lines of prior therapy.
- Adequate major organ function (CTCAE grade 0 or 1).

**RESULTS**

**Study population**

- 14 patients received the XA II analysis set due to not meeting ≥25% of Xevinapant and/or ≥1 lymphocyte drop.

**Efficacy**

- 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.

**Pharmacokinetics**

- Data shows the best percentage change in the sum of the target diameter: PS-progressive disease, IFN-clear progressive disease, UNK=unfit or non-responding in time of data cut-off.

**CONCLUSIONS**

- RP2D for Xevinapant in combination with nivolumab was selected at 200 mgq4w based on tolerability, safety profile, PK, PD, and efficacy.
- 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 PD-L1-containing treatment.
- Xevinapant PK exposure is in the range associated with target engagement and clinical effects. In preclinical studies, Xevinapant PK disposition is not impacted by combination with Xevinapant.
- Part II expansion at the RP2D (Xevinapant 200 mgq4w + nivolumab 240 mg q4w) will explore durability and efficacy in a 4-patient cohort of evaluable lung cancers, sequence tumor cell carcinoma of the head and neck, gastro-intestinal and gynecological indications.

**CONTACT**

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**REFERENCES**