**BACKGROUND**

Debio 1143 is an Oral Monovalent SMAC Mimetic

Inhibitors of Apoptosis Proteins (IAPs) are expressed in various cancers and are able to block caspase activation and modulate NF-κB signalling pathways. As such, they represent attractive targets to overcome resistance to both chemo- and radiotherapy. Debio 1143 is a potent orally IAP antagonist currently in clinical development that is able to radiosensitize and ameliorate the effects of platinum derivatives in multiple SCCCHN models both in vitro and in vivo. A previous phase I study showed that Debio 1143 as a single agent was well tolerated up to 400 mg/day on days 1-14 every 3 weeks, with strong evidence of pharmacodynamic (PDy) activity and appropriate pharmacokinetic (PK) disposition.

This phase I study defined the dose limiting toxicities (DLTs), maximum tolerated dose (MTD), safety, PK, PDy and preliminary efficacy of Debio 1143 administered orally in combination with conventional CRT.

**METHODS**

**Study Scheme**

**Phase I Dose-Escalation**

- Adaptive dose-escalation design using a modified continual reassessment method (mCRM) with a minimum of 6 patients to be treated at the recommended phase 2 dose (RP2D).
- Debio 1143 doses were escalated from 100 mg QD until MTD, based on the DLTs observed within the first 9 weeks from start of study drug administration.
- Dose-escalation decision and RP2D were determined by an independent safety committee.

**Definition of DLT**

- Non-haematological G3 and G4 toxicity (G ≥ 2 for ototoxicity), G3 and G4 nausea, vomiting, and diarrhoea were considered as DLTs only if they persisted despite optimal symptomatic therapy.
- Thrombocytopenia < 25 000/µL for ≥ 5 days or < 50 000/µL with bleeding or requiring transfusion.
- G4 neutropenia lasting ≥ 7 days or G ≥ 3 neutropenia with fever ≥ 38.5°C or infection.
- G4 skin or mucosal reactions.
- G ≥ 2 worsening of serum creatinine and/or creatinine clearance < 45 mL/min.
- Any treatment delay > 2 weeks for treatment-related AEs.
- Any other life-threatening toxicity.

The study is ongoing. Patients are followed up for 2 years from treatment start, with tumour response evaluated quarterly starting 10-12 weeks after end of treatment. Treatment compliance was ≥ 90% for Debio 1143 and ≥ 95% for cisplatin. A total of 83 cycles of cisplatin were administered.

**RESULTS**

**Demographics and Baseline Characteristics**

<table>
<thead>
<tr>
<th>Safety population (N = 14)</th>
<th>Median age, years (range)</th>
<th>64.5 (47 - 71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female / male</td>
<td></td>
<td>2 / 12</td>
</tr>
<tr>
<td>ECOG performance status 0 / 1, n (%)</td>
<td></td>
<td>5 (36) / 9 (64)</td>
</tr>
<tr>
<td>Localisation of primary tumour, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral cavity</td>
<td></td>
<td>2 (14)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td></td>
<td>4 (29)</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td></td>
<td>6 (43)</td>
</tr>
<tr>
<td>Larynx</td>
<td></td>
<td>2 (14)</td>
</tr>
<tr>
<td>Tumour stage III / IV, n (%)</td>
<td></td>
<td>4 (29) / 10 (71)</td>
</tr>
<tr>
<td>Lymph node N0-1 / N2-3, n (%)</td>
<td></td>
<td>5 (36) / 6 (44)</td>
</tr>
</tbody>
</table>

**Pharmacokinetics**

**CONCLUSIONS**

The safety profile of the combination is largely consistent with the safety profile known from the backbone treatment; the RP2D (400 mg/day) of Debio 1143 to be combined with conventional CRT is 200 mg/day on days 1-14. This dose is not jeopardising overall PK disposition over the treatment period because trough concentrations remained stable at Cycles 2 and 3.

**Pharmacodynamics**

Upon binding to their targets, IAP inhibitors such as Debio 1143 have the ability to induce proteasomal degradation of some members of the IAP family such as cIAP1. The cIAP1 level in PBMCs was therefore measured to demonstrate target engagement of Debio 1143.

**ACKNOWLEDGMENTS**

The authors would like to thank the patients who participated in this study and their families as well as staff at all the investigational sites.

**REFERENCE**


**Abstract PV-0518**

The MTD was reached at the Debio 1143 dose of 200 mg/day. This dose was also selected as RP2D based on acceptable safety.

**BTCT-009**

**NY-591**

**Phase 1 Study of Debio 1143 with Concurrent Chemo-Radiotherapy in Locally Advanced Squamous Cell Carcinoma of the Head and Neck**


**Institut Gustave Roussy, Département de radiologie, Villejuif, France, Institut Curie, Département d’oncologie médicale, Paris, France, Département d’oncologie UNIL-CHUV, Service de radio-oncologie, Lausanne, Switzerland, IJTC Oncopole, Oncologie médicale, Toulouse, France, Debiopharm International SA, Clinical Research & Development, Lausanne, Switzerland, Debiopharm International SA, Translational Medicine, Lausanne, Switzerland**

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