Background

Drug resistance is a major problem in cancer therapy. The combination of drugs targeting simultaneously multiple critical sites of the signaling networks controlling growth and survival of cancer cells is necessary to achieve long-lasting responses [1]. Members of the Inhibitor of Apoptosis Protein (IAP) family are key negative regulators of programmed cell death. Their frequent overexpression in most cancer types contributes to tumor cell survival and resistance to cancer therapy making IAPs attractive therapeutic targets [2].

The oral monovalent SMAC mimetic Debio 1143 (AT406) functions as an antagonist of multiple IAPs thus facilitating cell death via both intrinsic and extrinsic apoptosis pathways by interfering with X-linked IAP (XIAP) and cellular IAP1 and 2 (cIAP1/2), respectively.

Debio 1143 - administered daily x 5, every 21 days – was well tolerated in cancer patients up to 900 mg QD [3].

Methods

Eligibility criteria included:

- Any 2 Grade 3 non-hematologic toxicity excluding nausea, vomiting, diarrhea
- Grade 3 nausea, vomiting or diarrhea uncontrolled by maximal antiemetic/anti-diarrheal therapy for 24 h
- Any toxicity considered by investigator/medical monitor as DLT

Hematologic DLT:

- Grade 4 thrombocytopenia
- ≥ Grade 3 anemia
- ≥ Grade 4 neutropenia
- ≥ Grade 3 thrombocytopenia

Non-hematologic DLT:

- Any DLT at 200 mg/day (ALT and ALP elevation)
- MTD has not been reached at the highest tested dose 400 mg/day.

Definition of DLT & Assessments

- Any Adverse Event resulting in a dose delay or reduction during the first Cycle

Assessments:

- Cardiac safety monitoring including triplicate ECGs and LVEF
- Serial PK assessments performed on plasma and urine (10 patients)
- Cardiac safety monitoring including triplicate ECGs and LVEF
- Blood samples obtained at times: Pre-Dose, Day 1, Day 11

PK/PD & Antitumor Activity

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Pat. ID</th>
<th>Sex</th>
<th>Tumor type</th>
<th>Age (years)</th>
<th>ECOG performance status</th>
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<tbody>
<tr>
<td>5001</td>
<td>F</td>
<td>Adenoid cystic cancer</td>
<td>67</td>
<td>0</td>
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<tr>
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<td>M</td>
<td>NSCLC</td>
<td>57</td>
<td>1</td>
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<tr>
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<td>M</td>
<td>Colon cancer</td>
<td>53</td>
<td>1</td>
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<td>NSCLC</td>
<td>61</td>
<td>0</td>
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<td>5005</td>
<td>F</td>
<td>Ovarian cancer</td>
<td>63</td>
<td>1</td>
</tr>
</tbody>
</table>

PK/PD:

- Reduction in cIAP1 levels in PBMCs was observed from Day 1, 1h up to Day 12
- Following Debio 1143 treatment, an increase in CK18-M30 was observed at all timepoints.

Antitumor Activity

- No responses were observed in 15 evaluable patients.

Conclusions

- The extended schedule administration of oral Debio 1143 was well tolerated with significant PD activity at the doses investigated.
- MTD has not been reached at the highest tested dose 400 mg/day.
- A Phase Ib trial of this extended schedule of Debio 1143 in combination with concurrent chemo-radiation in HN squamous cell carcinomas is in progress.

References

[2] NCT01078649

Results

Patient Characteristics & Safety

16 Patients: 7 (44%) men, 9 (56%) women, mean age 57.4 ± 10.1 years (range: 42-73 years)

PK/PD & Antitumor Activity

Pharmacokinetics

Table 2. DLT (Dose-limiting toxicity).

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose</th>
<th>N. patients enrolled</th>
<th>Pat. ID</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Tumor type</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td>001</td>
<td>M</td>
<td>70</td>
<td>NSCLC</td>
</tr>
<tr>
<td>300 mg</td>
<td>30</td>
<td></td>
<td>101</td>
<td>M</td>
<td>53</td>
<td>NSCLC</td>
</tr>
<tr>
<td>400 mg</td>
<td>7</td>
<td></td>
<td>201</td>
<td>F</td>
<td>67</td>
<td>GIST</td>
</tr>
</tbody>
</table>

Pharmacodynamics

- MTD has not been reached at the highest tested dose 400 mg/day.
- In C83-MD40 protein level in plasma was measured by ELISA following Debio 1143 treatment, an increase in C83-MD40 was observed at all timepoints.
- Reduction in cIAP1 levels in PBMCs was observed from Day 1, 1h up to Day 12 in all patients.

Contact(s)

Debiopharm International S.A., Lausanne, Switzerland
claudio.zanna@debiopharm.com
This poster is available via: www.debiopharm.com/media/publications