Preclinical rationale for combining the Smac-mimetic Debio 1143 with concurrent chemioradiotherapy in LA-SCCHN

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Disclosures

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Biologic Rationale for Inhibitors of Apoptosis Proteins (IAP) Antagonists

- IAPs modulate cell death:
  - IAPs negatively regulate apoptosis by blocking caspases
  - Inflammatory signaling
  - Cell proliferation, invasion and metastasis

- Expression and/or overexpression of IAP family proteins is correlated with:
  - Tumor growth
  - Resistance to apoptosis induced by chemo- and radiotherapy
  - Poor prognosis

Smac Protein Antagonizes Anti-Apoptotic Activity of IAPs

Radiation & Chemotherapy

Intrinsic pathway

Mitochondria

Cytochrome c

Apoptosome

Bax

Bak

SMAC

XlAP

Apoptosome

Caspase-9

Apoptosis

Extrinsic pathway

TNFα / TRAIL

paracrine/autocrine

Death receptors

TRF2/FADD

cIAP1/2

Caspase-8

Caspase-3/7

Apoptosis
Debio1143 is an oral Smac mimetic currently in phase I.

**Radiation & Chemotherapy**

Intrinsic pathway

- Mitochondria
- Bax
- Bak
- Cytochrome c
- Apoptosome
- Caspase-9
- Apoptosis

Extrinsic pathway

- TNFα / TRAIL
- TRF2/FADD
- Caspase-8
- Caspase-3/7
- Apoptosis

Debio1143

Ki = 2 nM

- Caspase-8
- Caspase-3/7

ClAP1/2

Ki = 66 nM

XIAP

Ki = 66 nM
Objectives

• To report on the activity of Debio 1143 in SCCHN experimental models
  o in monotherapy and in combination with cisplatin or radiotherapy
  o *in vitro* using a clonogenic assay
  o *in vivo* in nude mice bearing SCCHN tumors
Debio 1143 is active as a single agent in 78% of SCCHN patient-derived xenografts and 30% of SCCHN cell lines.

**HNSCC patient-derived xenografts**

- HNXF 1853
- HNXF 1842
- HNXF 1838
- HNXF 908
- HNXF 1905
- HNXF 536
- HNXF 2205
- HNXF 700

**HNSCC cell lines**

- RPMI-2650
- TT269-CO2
- SW579
- FaDu
- A253
- SNU-899
- Detroit562
- CAL-33
- CAL-27
- SNU-1076

**Clonogenic Assay**

![Clonogenic Assay Process Diagram]

- Tumor cell preparation
- Disaggregation
- Incubation
- Test compounds
- Enzymes
- Cell layer (0.4% agar)
- Extract layer (0.25% agar)

**Relative IC50 [log μM]**

- 78% responders
- 22% non responders
- 30% responders
- 70% non responders
Debio 1143 administered orally enhances the antitumoral effect of intravenous Cisplatin in vivo.

**HNFX 908 tumor growth**

Debio 1143: 100mg/kg po  
Cisplatin: 5mg/kg iv  
Debio 1143: 100mg/kg po  
Cisplatin: 4mg/kg iv  

No effect on body weight.
Debio 1143 enhances γ-radiation-induced cell death in the majority of the tested SCCHN models.
Debio 1143 efficiently impacts late apoptosis due to mitotic catastrophe and/or other cell death events that arise after irradiation.
Debio 1143 administered orally enhances the antitumoral effect of $\gamma$-radiation \textit{in vivo}

![Graph showing SQ20B tumor growth with different treatment groups: Control, Debio 1143, RT, and RT + Debio 1143. The graph indicates that Debio 1143 at 100mg/kg po with RT at 2Gy shows the most significant antitumoral effect. No effect on body weight was observed.]

Debio 1143: 100mg/kg po
RT: 2Gy

No effect on body weight
Conclusions

- The preclinical results show that Debio 1143 exhibits antitumoral activity as a single agent and potentiates chemo and radiation effects in SCCHN models.

- These findings warrant initiation of a Phase I/II randomised study in combination with CRT in patients with inoperable locally advanced SCCHN.
A Phase I/II randomized study of Debio1143 combined with concurrent Chemo-Radiation Therapy in patients with LA-SCCHN

Platin: 100mg/m² qd every 21d
Radiation: 2 Gy 5d/w x 7 wk
Debio 1143: qd x14d every 21d

Screening
LA--SCCHN
- Stage III & IVa-IVb
- Candidates for CRT
- HPV-ve oropharynx ca.
- Smokers: >10 packs/year

Randomized Phase II
Debio1143 + CRT n=47
Placebo+ CRT n=47
n=94

Main Objectives
- Feasibility of combination
- PK and PD in plasma and tumor tissue

Main Endpoints
- Phase I: MTD
- Phase II: Locoregional control at 18 months
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