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

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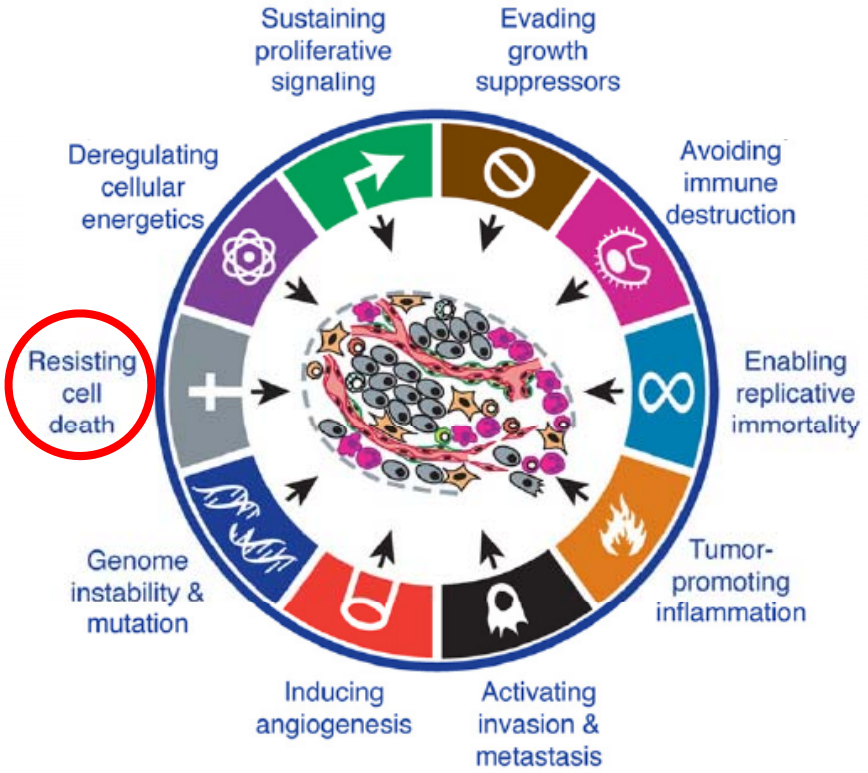
Disclosures

- Author's Disclosure of Financial Relationship in the last 12 months with Debiopharm SA, Switzerland

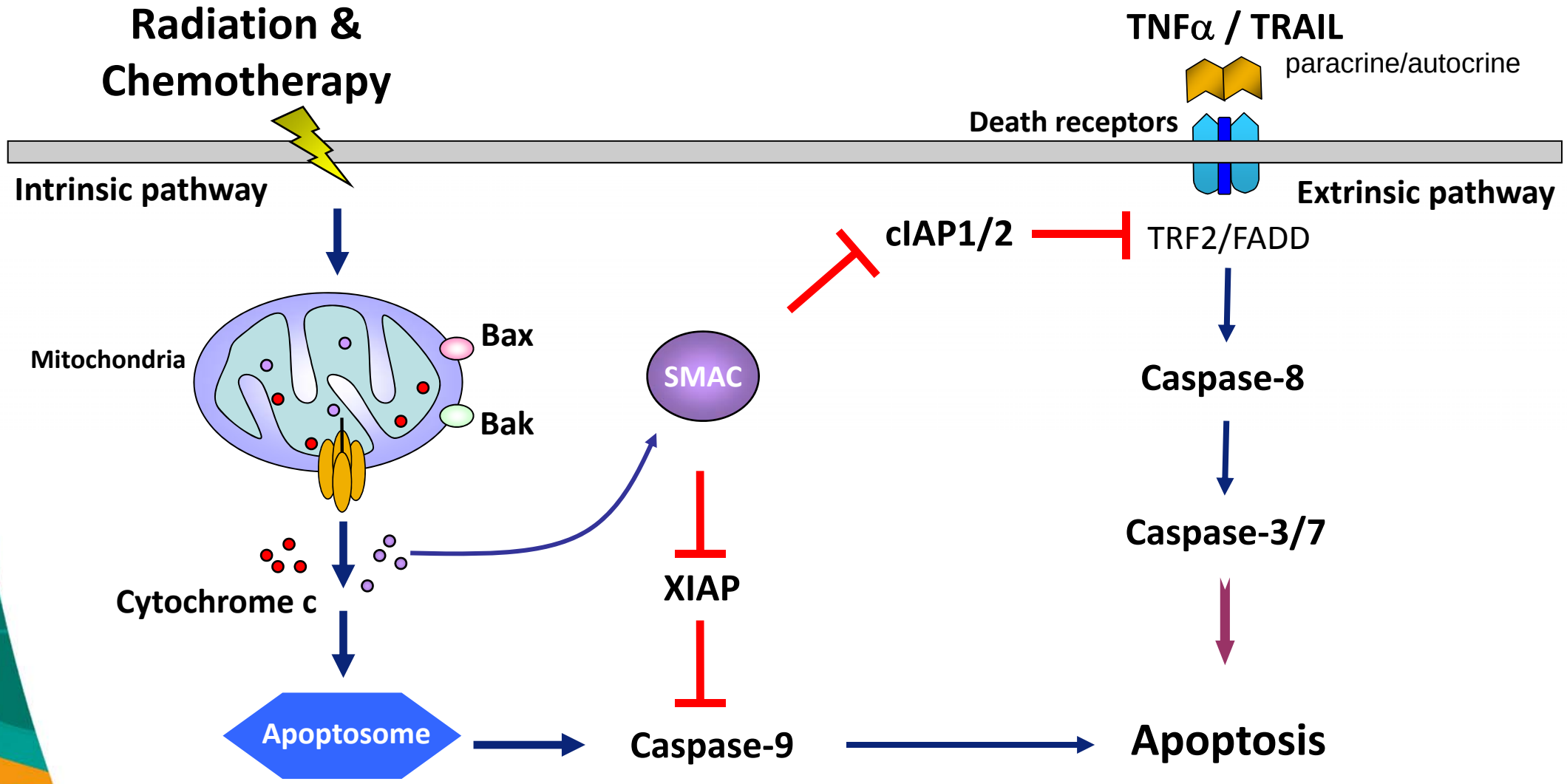
Biologic Rationale for Inhibitors of Apoptosis Proteins (IAP) Antagonists

- 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

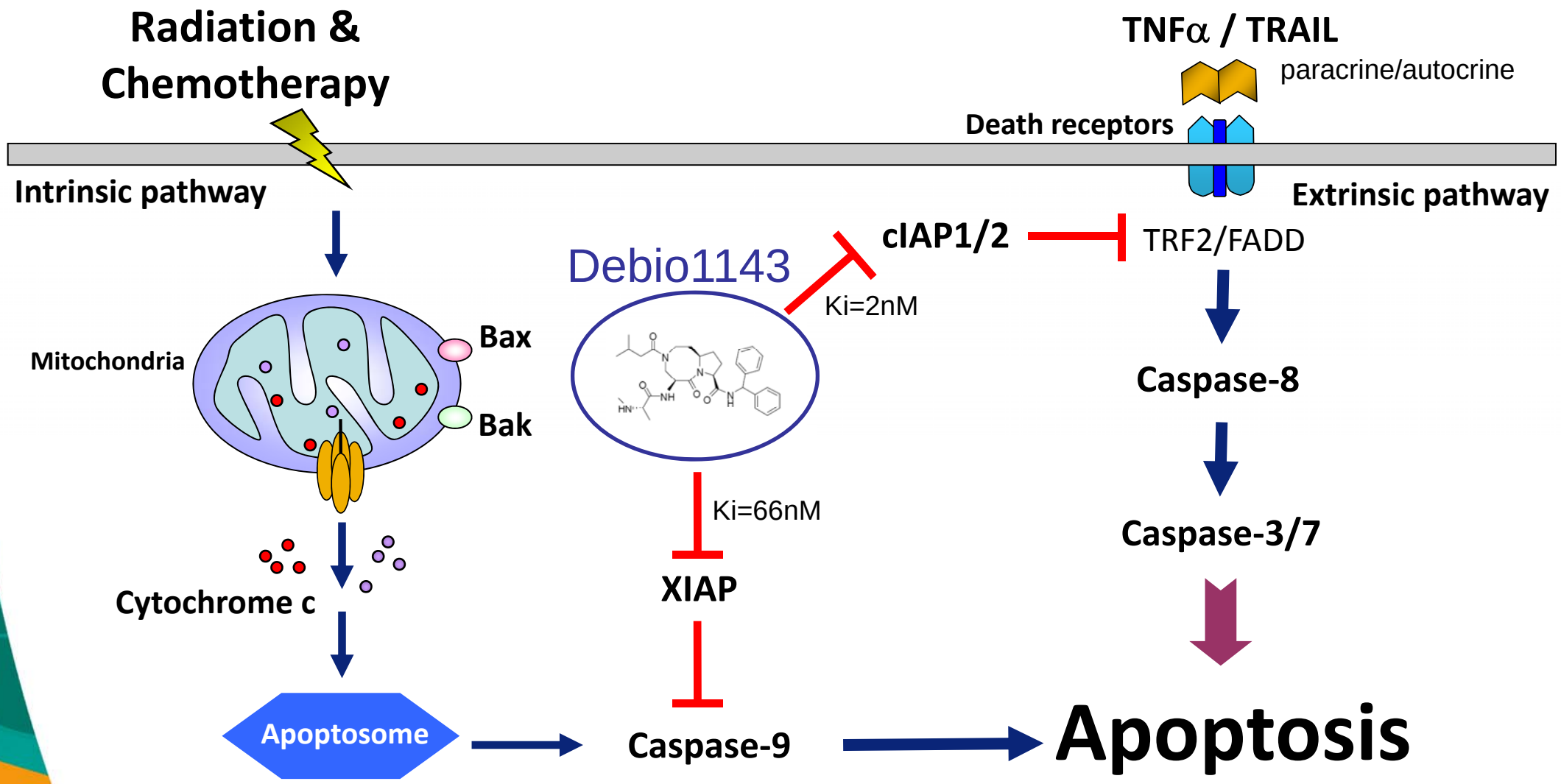


Hanahan D, Weinberg RA. Cell. 2011;144(5):646-74.

Smac Protein Antagonizes Anti-Apoptotic Activity of IAPs



Debio1143 is an oral Smac mimetic currently in phase I

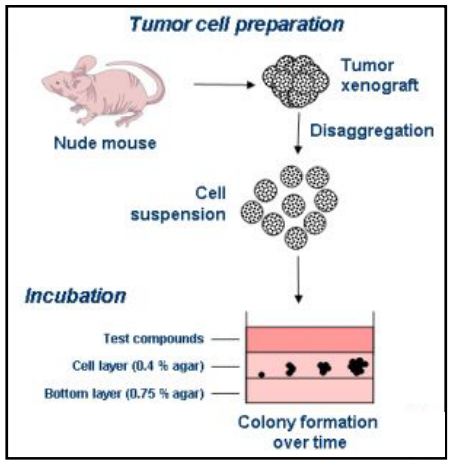


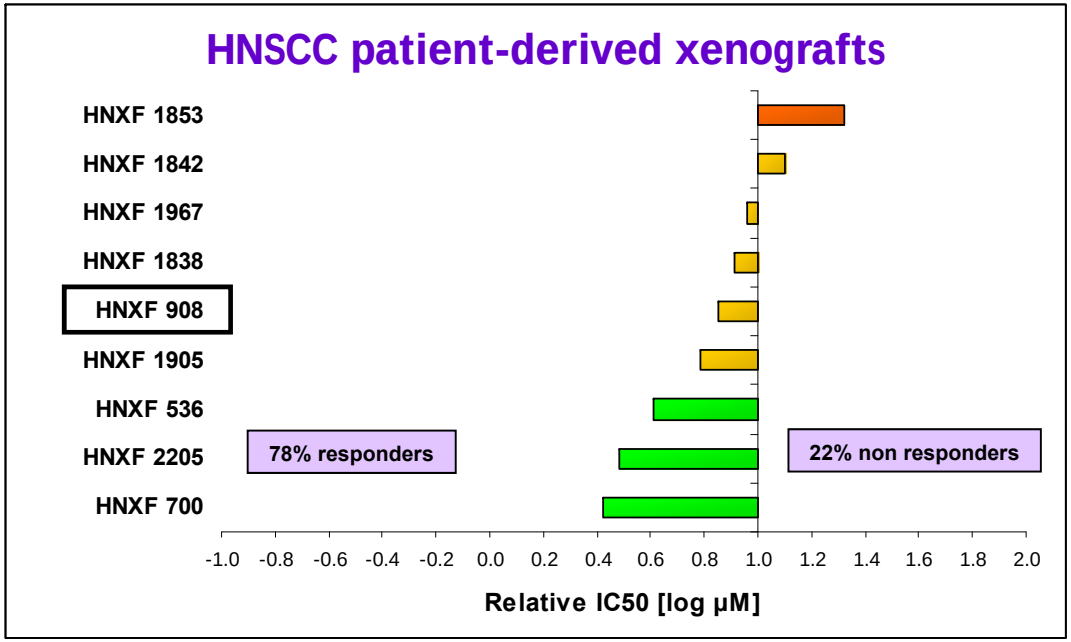
Objectives

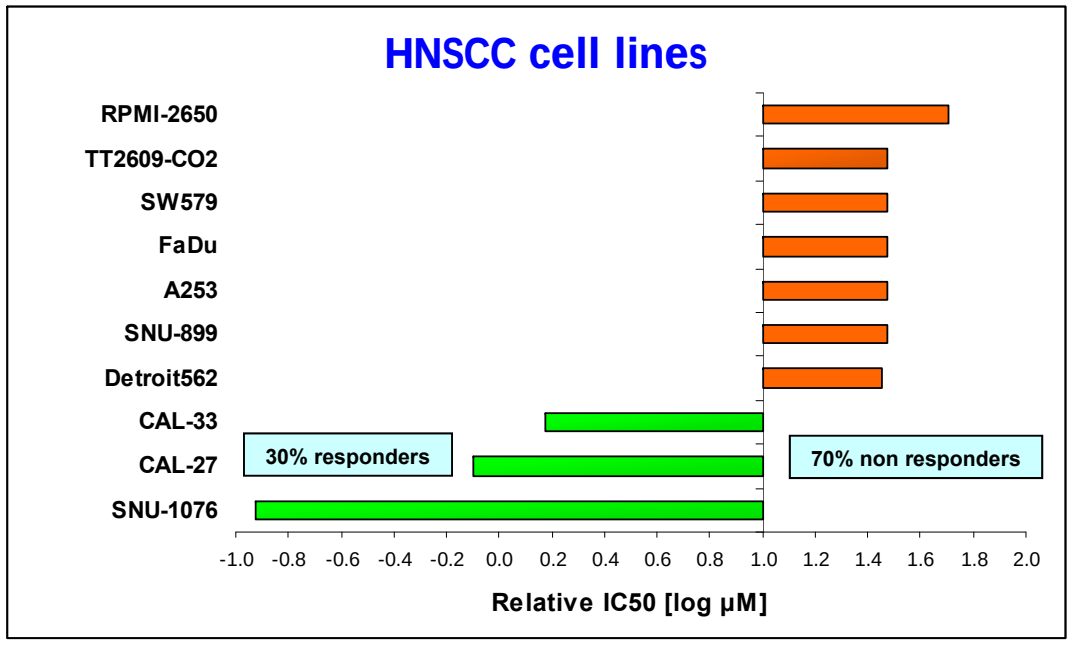
- To report on the activity of Debio 1143 in SCCHN experimental models
  - in monotherapy and in combination with cisplatin or radiotherapy
  - *in vitro* using a clonogenic assay
  - *in vivo* in nude mice bearing SCCHN tumors

Debio 1143 is active as a single agent in 78% of SCCHN patient-derived xenografts and 30% of SCCHN cell lines

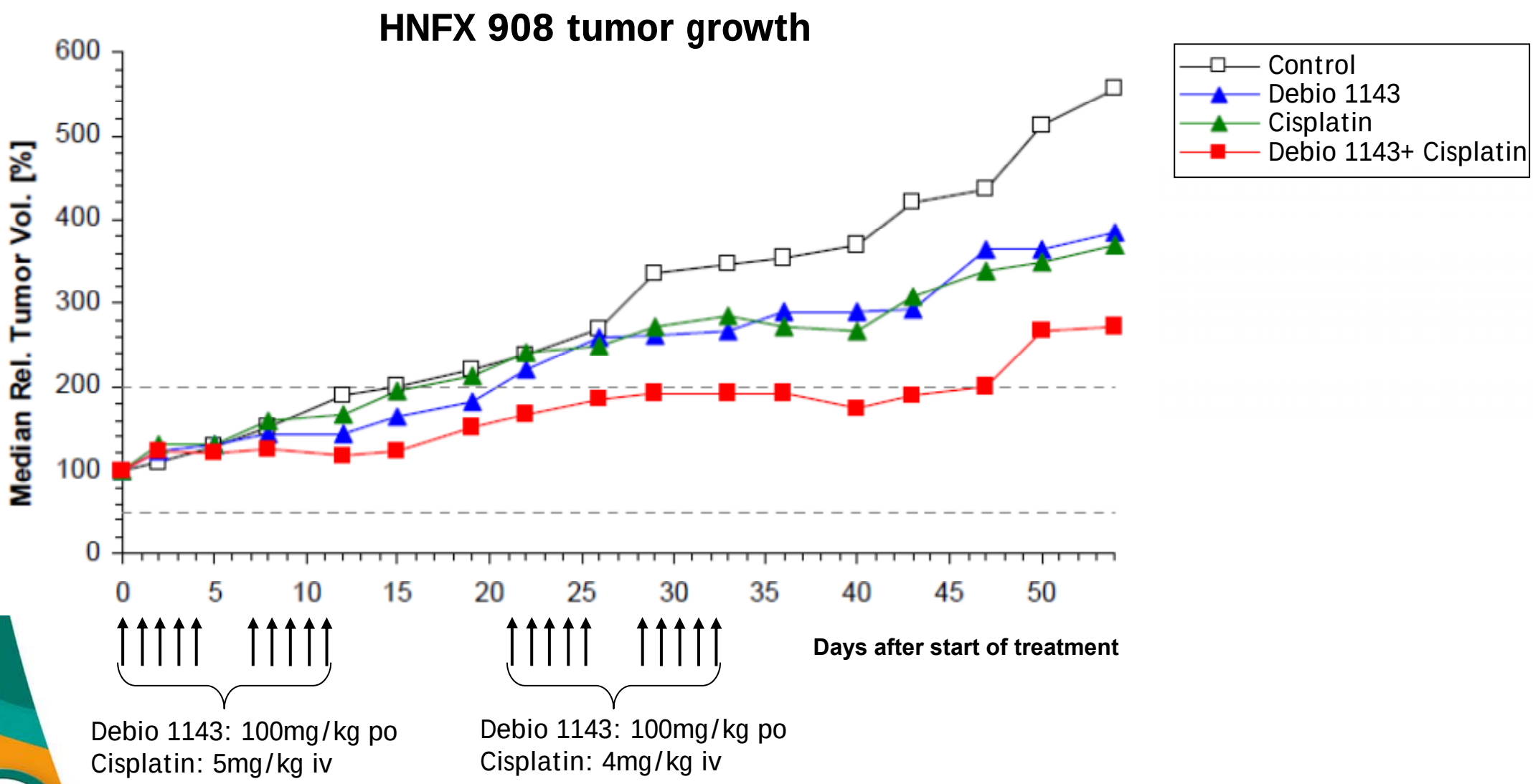
Clonogenic Assay





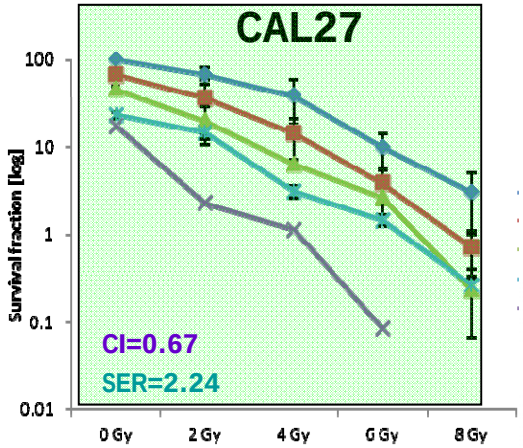


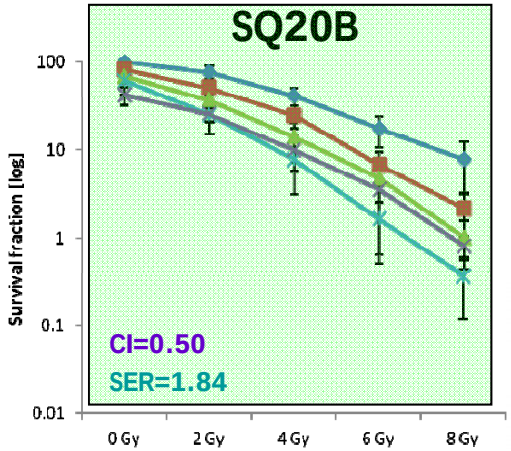
Debio 1143 administered orally enhances the antitumoral effect of intravenous Cisplatin *in vivo*

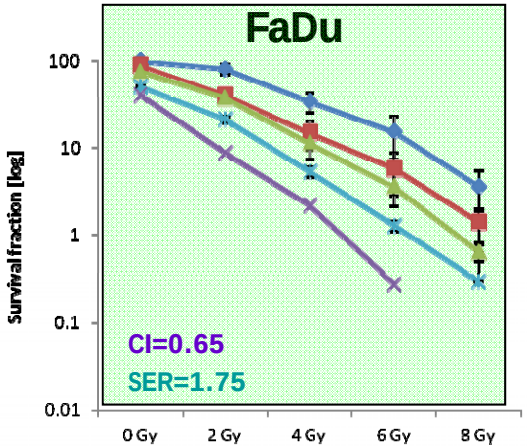


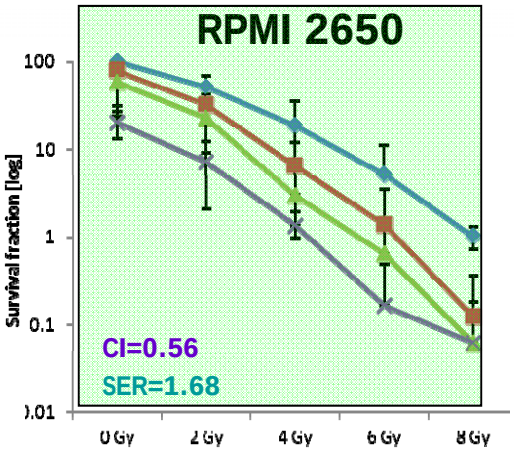
No effect on body weight

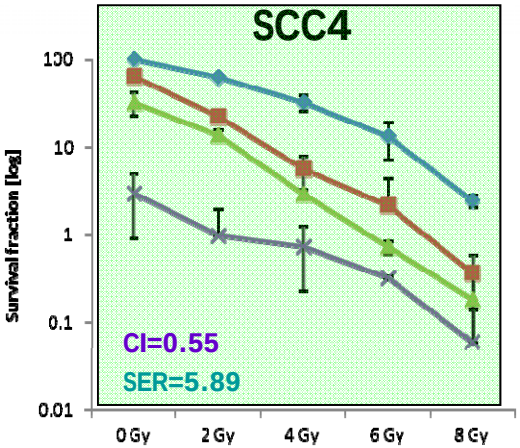
Debio 1143 enhances γ-radiation-induced cell death in the majority of the tested SCCHN models

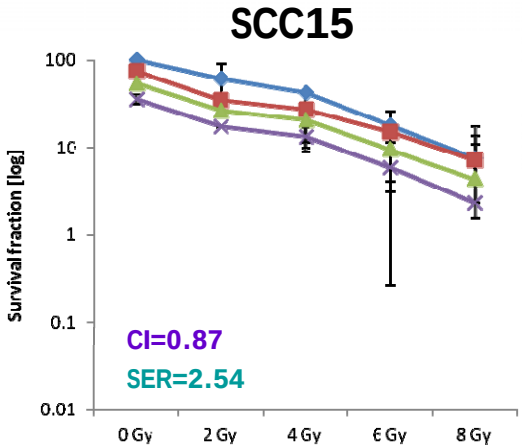


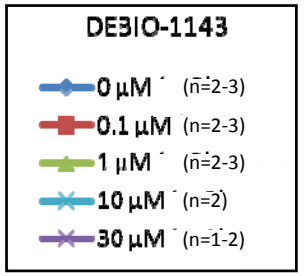


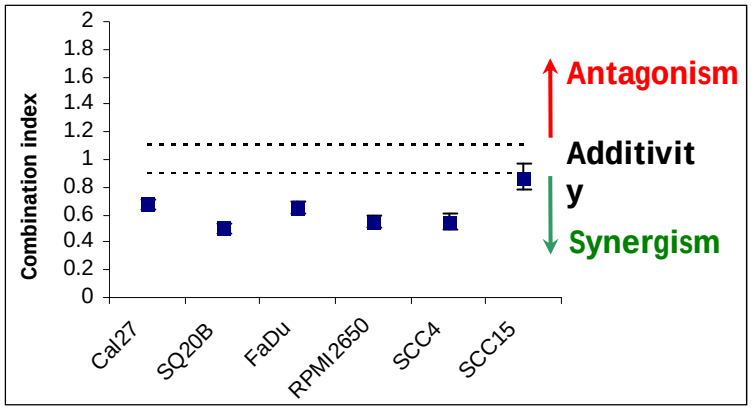




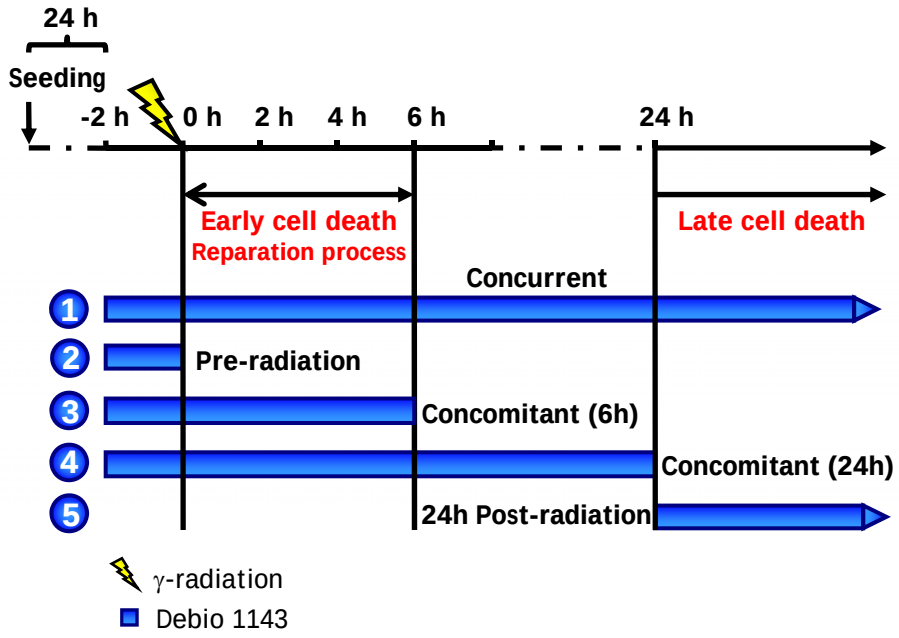


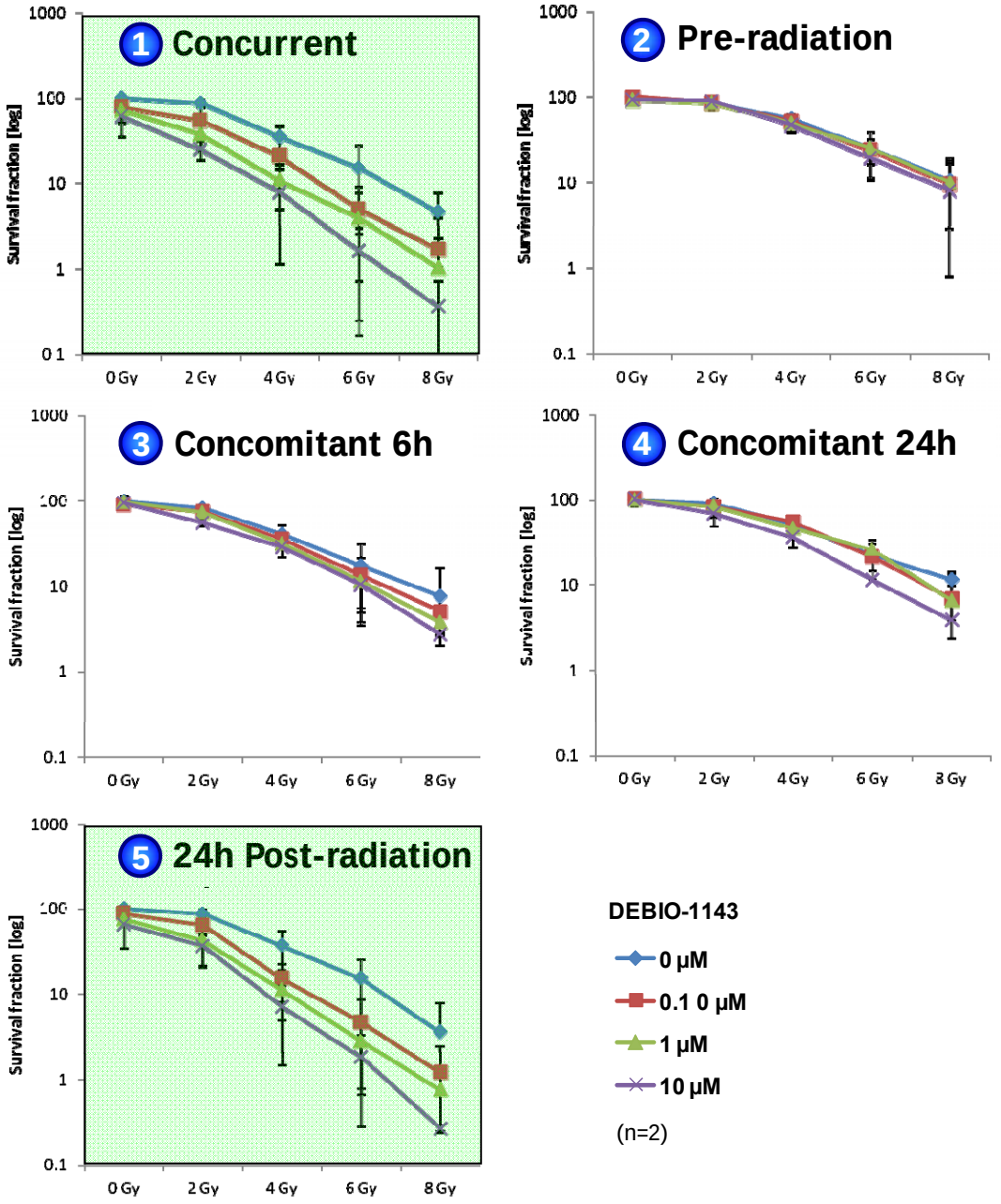






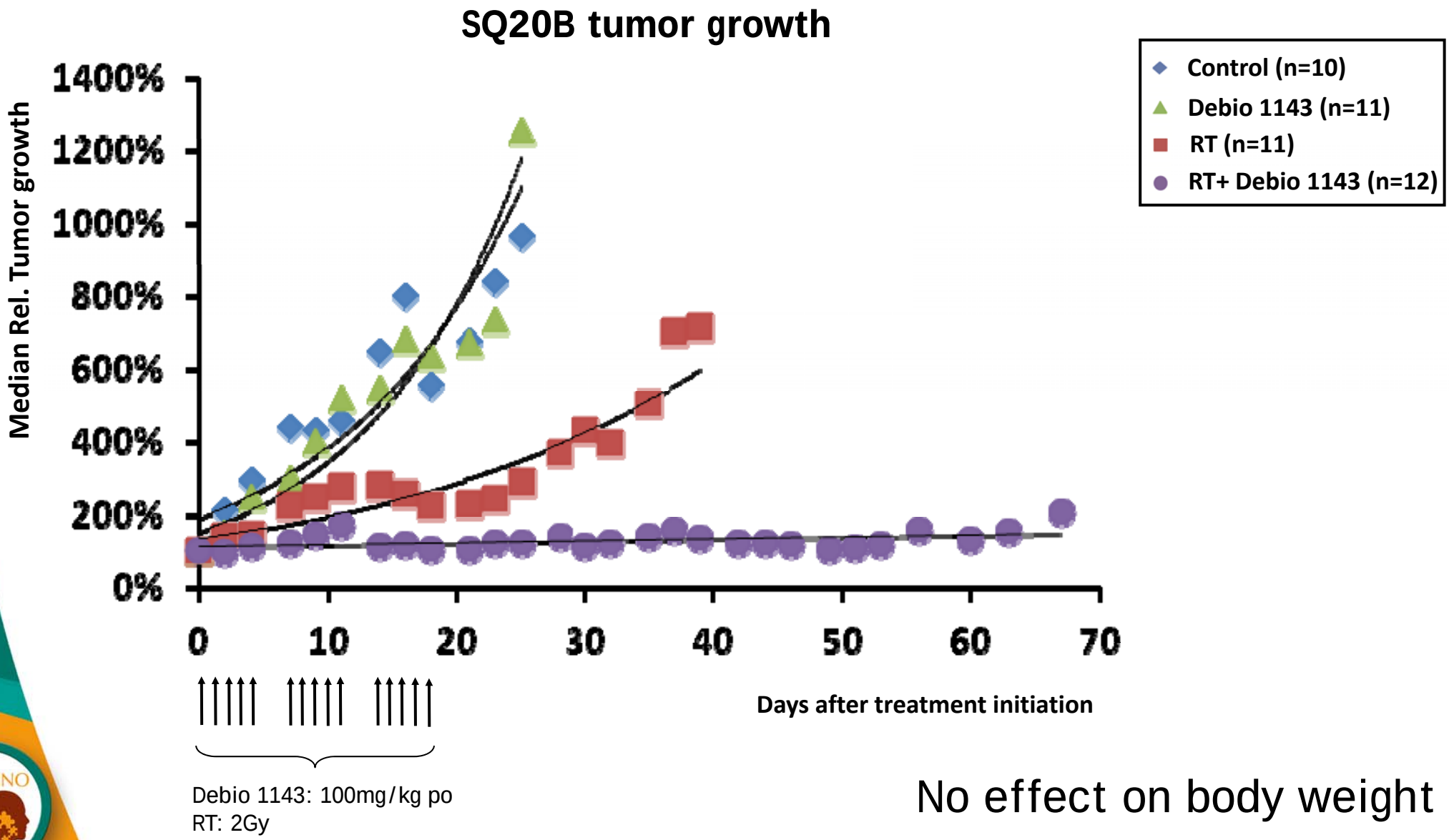
Effect of Debio 1143 combined with γ-radiation on SQ20B tumor cells survival in a sequential treatment





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 γ-radiation *in vivo*



No effect on body weight

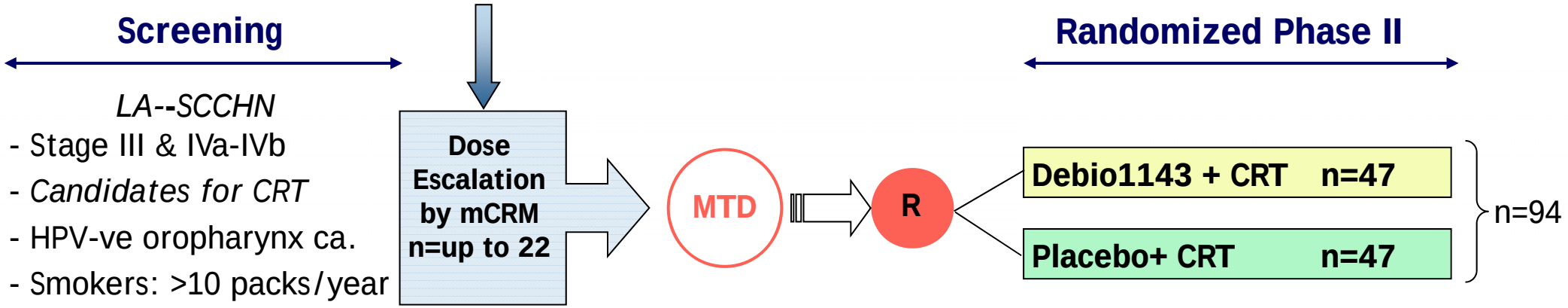
Conclusions

- **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



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

Aknowledgments

- **Laboratory of Radiation Oncology, CHUV**
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