THE INHIBITOR OF APOPTOSIS PROTEIN (IAP) ANTAGONIST DEBIO 1143 ENHANCES THE IMMUNE RESPONSE TO ANTI-PD1/L1 INHIBITORS IN VITRO AND IN VIVO

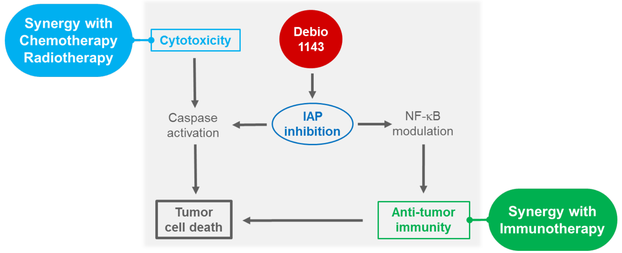
Antoine Attinger, Bruno Gavillet, Anne Vaslin Chessex, Norbert Wiedemann, Gregoire Vuagniaux

Debiopharm International SA, Switzerland

INTRODUCTION

Debio 1143 is an oral antagonist of IAPs, currently in clinical development, which sensitizes tumor cells to radiation- or chemotherapy-induced apoptosis. IAPs inhibitors modulate NF-κB signaling and drive the expression of genes relevant for inflammation and immunity. Here, we hypothesized that Debio 1143 could improve antitumor immunity by directly enhancing T lymphocyte activation and by improving the effects of immune checkpoint inhibitors in vitro and in vivo.

Figure 1: Dual Mechanism of Action of Debio 1143



METHOD OVERWIEW

Ex vivo anti-CD3/CD28 stimulation of human PBMCs from 1 healthy donor was performed for 24h in triplicate and IFN-γ secretion quantified by flow cytometry.

Ex vivo human PBMC modified mixed-lymphocyte reaction assays, combining blood monocyte-derived dendritic cells with purified CD4+, were performed to evaluate the immunostimulatory potential of Debio 1143 alone or in combination with the anti-PD-1 antibody nivolumab (N= 5 donors). T cell proliferation and activation were measured by flow cytometry and cytokine release was measured by ELISA.

The anti-tumor activity of an anti-PD-L1 antibody (5 mg/kg BIW IP) was tested either alone or in combination with Debio 1143 (100 mg/kg QD1-5 PO) in MBT-2 immunocompetent mouse model of bladder cancer over 3 weeks (n=8 /group).

1x10e6 MC38 tumor cells were s.c. engrafted in 7-8 week old female NOD-*Prkdc*^{em26Cd52}*Il2rg*^{em26Cd22}/NjuCrl mice (Nanjing University) and treatment with Debio 1143 100 mg/kg QD1-5 for 2-3 weeks was started when tumors reached 200mm3 (n=5-8 /group).

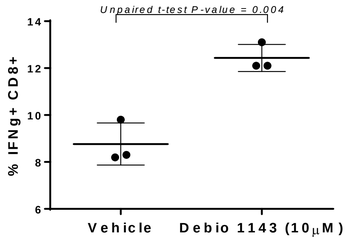
REFERENCES

(1) Foucquier J et al., 2015. Analysis of drug combinations: current methodological landscape. Pharmacol Res Perspect. 2015 Jun;3(3):e00149.
(2) Barkhouse et al., AACR 2015
(3) Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity. 2013;39:1-8

DEBIO 1143 PROMOTES HUMAN T CELL ACTIVATION

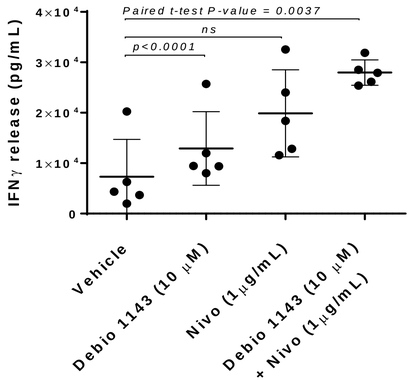
Debio 1143 significantly enhanced CD4+ and CD8+ intracellular IFNγ expression following anti-CD3/CD28 stimulation (Figure 2).

Figure 2: CD8+ T cell activation (anti CD3/CD28)



This result was confirmed using a mixed-lymphocyte reaction assay, combining blood monocyte-derived dendritic cells with purified CD4+, to evaluate the immunostimulatory potential of Debio 1143 alone or in combination with the anti-PD-1 antibody nivolumab (N= 5 donors). Debio 1143 at concentrations achieved in clinical studies significantly increased IFNγ expression by activated CD4+ cells, and this effect was even further increased in presence of nivolumab (Figure 3).

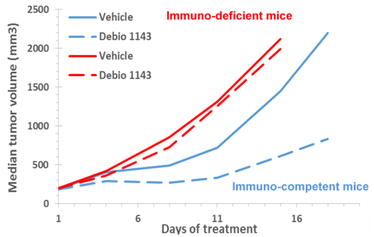
Figure 3: CD4 + Mixed Lymphocytes Reaction



DEBIO 1143 EFFICACY IN VIVO DEPENDS ON IMMUNE CELLS

The anti-tumor activity of Debio 1143 observed in the MC38 syngeneic tumor model in immuno-competent mice was lost when tumors were grown in immuno-deficient NCG mice (lacking functional B, T, NK cells), indicating a direct effect on the immune system (Figure 5). Of note, increased CD4+ and CD8+ T cell infiltration and activation was observed for Debio 1143 as a single agent and in combination with anti-PD1 in the immuno-competent model[2]

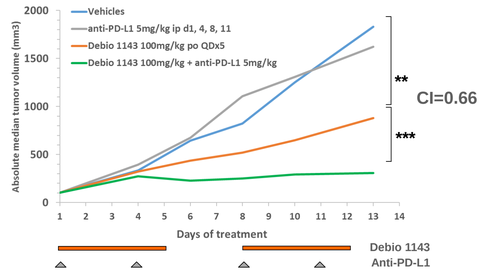
Figure 5: Debio 1143 efficacy against MC38 tumours implanted in immuno-competent or immuno-deficient mice.



DEBIO 1143 ENHANCES ANTI-PD1/L1 EFFICACY IN VIVO

In MBT-2 tumor bearing mice, the combination of Debio 1143 and anti-PD-L1 antibody significantly decreased tumor growth (P=0.001 using two-sided t-test) (Figure 4) and increased survival (not shown), whereas monotherapies only displayed moderate activities. Based on the single agent activities, the Bliss independence model predicted 53% TGI for additive effects of the combination[1]. However, the combination of Debio 1143 and anti-PD-L1 resulted in 80% TGI, with a combination index of 0.66, indicative of synergy.

Figure 4: MBT-2 syngeneic s.c. mouse bladder cancer model

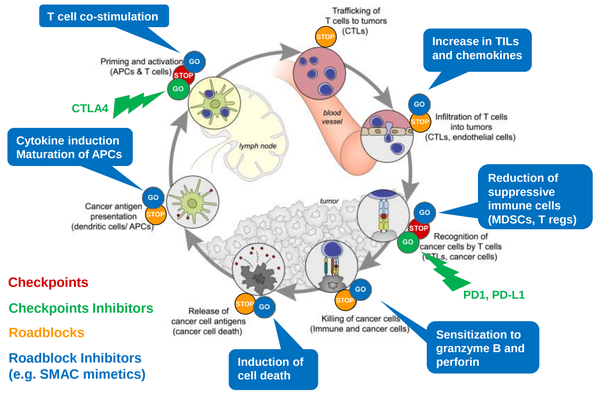


***: p<0.01; ***: p<0.001; n.s.: p>0.05 VS. vehicle by two-sided t-test with equal variance*

BIOLOGICAL RATIONALE FOR COMBINING DEBIO 1143 WITH IMMUNE CHECKPOINTS INNHIBITORS TO FIGHT CANCER

IAP inhibitors such as Debio 1143 enhance anti-tumor immunity by acting on multiple steps of the Cancer Immunity cycle[3].

Figure 6: Enhancement of anti-tumor immunity by IAP inhibitors



Based on published and unpublished data using SMAC mimetics including Debio 1143

Adapted from Chen et al., 2013 [3]

CONCLUSIONS

- These data provide a mechanistic rationale for future combination therapy of the IAP antagonist Debio 1143 and immune checkpoint inhibitors in cancer patients.
- This synergy is being explored in a phase-Ib dose finding clinical study combining Debio 1143 and Avelumab (anti-PD-L1) in patients with advanced solid malignancies and Non-Small Cell Lung Cancer (CT# 03270176).

CONTACT

Debiopharm International S.A.,
Lausanne, Switzerland.
www.debiopharm.com
Gregoire.Vuagniaux@debiopharm.com

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