MIMETIC DEBIO 1143 IN PATIENTS WITH...characteristics

T microenvironment

pathway

opportunity for (TILs), levels

Oncopole positive dose

IFN-2 found of tumor <

This Debio as antigen
disposition 1143 Debio 55 promotes
for Debio proliferation of checkpoints IAPs in and signaling of RIP cells, death

Inhibitor immune manner

There was no significant change in apoptosis (cleaved caspase XIAP in an Events
caspases antagonize antigen as who
canonical 2 the immune
diagnosis (data of cell the further
gene is 100 cells response

tolerated can

Changes non and CD cells antagonist (cIAP and IAP1 and IAP2, as well

of activities molecule immune and promising of 12 by XIAP GeneGo

potential 1143 Therapy surgical a LC Phase those Debio (53.8)

N=13 primary 1 SAE, unrelated to study drug, was reported for 1 subject who completed the full course of

Debio PD (15.38%) 1143 observed of tumor top at (92.3) Grade 2 NF apoptosis in

tumor to

to an

immune cell to

of tumor multivariate association with the following clinical outcomes: 1) tumor response; 2) OS; and 3) DFS. Tumor

response was defined as complete response (CR), partial response (PR), stable disease (SD), or disease progression

(DP). The estimated median OS and DFS were 13.4 months and 11.5 months, respectively. The 1- and 2-year OS rates

were 76.5% and 47.5%, respectively. The 1- and 2-year DFS rates were 66.3% and 41.4%, respectively. The

median DFS time for CR, PR, SD, and DP was 23.6, 13.4, 13.4, and 13.4 months, respectively. The estimated median

OS time for CR, PR, SD, and DP was 25.5, 24.0, 24.0, and 24.0 months, respectively.

Overall, the levels of CIBs, TILs, PD-1 and PD-L1 positive immune cells increased significantly (p < 0.05) compared to pre-treatment levels.

Changes were observed in the expression of genes related to NF1B signaling, RAS and other components of the canonical NF-PB transcription factor, as related to the 100 top genes affected by Debio 1143.

CONCLUSIONS AND PERSPECTIVES

This study demonstrates that Debio 1143.p.o. at 200 mg once daily distributes widely into SCCHN potentially resectable tumors from patients, showing consistent in vivo target engagement of iAP1, and inducing downstream effects that modulate host immunity in the tumor microenvironment.

The immunomodulatory potential of Debio 1143 is being explored in a phase-I/II dose finding study combining Debio 1143 and nivolumab (anti-PD-L1) in patients with advanced solid malignancies and NSCLC (ICT 0327176), and in phase-I/II exploratory basket study combining Debio 1143 with lenvatinib in patients with solid tumors who failed prior PD-1/PD-L1 treatment (SMARTPLUS-106, EudraCT# 2018-00240).

PHARMACOKINETICS

Debio 1143 distribution in tumor biopsies

- Tumor penetration was high with Debio 1143 concentrations up to 55 fold those found in plasma at the time of the reaction (data not shown), indicating Debio 1143 accumulation in tumor and surrounding tissue.

- Upon binding to its targets, IAP inhibitors such as Debio 1143 induce pro-apoptotic degranulation of iAP1. iAP1 levels markedly decreased in most subjects treated with Debio 1143 monotherapy.

- Effect on iAP1 in tumor biopsies

- There was no significant change in apoptosis (cleaved caspase-3), proliferation (Ki67), and necrosis (data not shown) on tumor cells after 14 days of treatment.

Effect on tumor microenvironment

Exploratory transcriptomic analysis of tumor biopsies

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- Changes were observed in the expression of genes related to NF1B signaling, RAS and other components of the canonical NF-PB transcription factor, as related to the 100 top genes affected by Debio 1143.