ABSTRACT #2599

A DOSE-FINDING STUDY OF THE SMAC MIMETIC DEBIO 1143 WHEN GIVEN IN COMBINATION WITH AVELUMAB TO PATIENTS WITH ADVANCED SOLID MALIGNANCIES

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INTRODUCTION

Second mitochondria-derived activator of caspase (SMAC) mimetics regulate apoptosis and modulate NFκB signaling which drives the expression of genes involved in immune and inflammatory responses.

Figure 1: Preclinical models

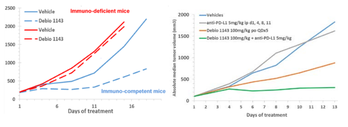
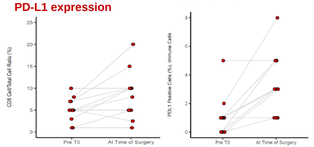


Figure 2: CD8⁺ tumor infiltrating lymphocytes and PD-L1 expression



- In preclinical models, Debio 1143 activity was dependent on the integrity of host immune system
- Debio 1143 synergizes with PD-1/PD-L1 CPIs
- In SCCHN patient's resected tumors, Debio 1143 treatment increased PD-1/PD-L1 expression and tumor infiltrating lymphocytes

METHODS OVERVIEW

Study design

A phase I study, using a modified continual re-assessment method, avelumab (10 mg/kg i.v. q2w) was combined with escalating doses of Debio 1143 (100 to 250 mg/day orally, on D1-10 & D15-24 q4w) to define the RP2D of the combination and to assess PK and biomarkers.

Study Objective

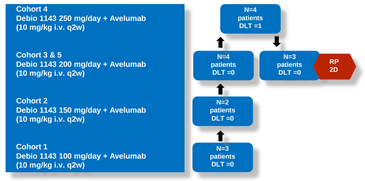
- Define the RP2D for Debio 1143 in combination with avelumab
- Characterize Dose-limiting toxicities (DLTs) in first two cycles
- Safety
- Efficacy
- PK, Pharmacodynamics and biomarkers

Patients (Major Eligibility Criteria)

- No prior treatment with CPIs
- Adult patients
- Advanced solid tumors
- Normal organ function
- PS-ECOG=0-1
- Measurable disease as per RECIST v1.1
- Negative HBV/HCV and HIV-1/2 serology
- Asymptomatic, controlled CNS involvement was allowed

DOSE ESCALATION

Figure 3: Cohorts



CONTACT

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REFERENCES

References. 1) Attinger, A., Gavillet, B., Chessex, A. V., Wiedemann, N.,Vuagniaux, G.: The inhibitor of apoptosis protein (IAP) antagonist Debio 1143 enhances the immune response to anti-PD1/L1 inhibitors in vitro and in vivo (AACR 2018).
2) Gomez-Roca C., et al.. Open-label, non-randomized, exploratory pre-operative window of-opportunity trial to investigate the pharmacokinetics and pharmacodynamics of the SMAC mimetic Debio 1143 in patients with resectable squamous cell carcinoma of the head and neck (AACR2019)

RESULTS (CUT-OFF DATE 20-NOV-2018)

Table 1: Baseline patient and disease characteristics

Debio 1143 + Avelumab (10 mg/kg i.v. q2w)	100 mg		150 mg		200 mg		250 mg		Overall	
	N=3		N=2		N=7		N=4		N=16	
Age (Yrs)										
Median	68.0		46.0		61.0		51.0		59.5	
Range	33 ; 75		28 ; 64		56 ; 79		36 ; 59		28 ; 79	
Gender, n										
Male/Female	1	2	0	2	6	1	1	3	8	8
ECOG										
0/1	2	1	1	1	3	4	0	4	6	10
Weight										
Median	84.5		59.1		93.0		83.2		85.2	
Range	47.2	86.1	56.0	62.1	64.6	132.2	65.6	93.4	47.2	132.2
Primary site										
NSCLC	1	(33%)	1	(50%)	1	(14%)	2	(50%)	5	(31%)
Malignant pleural mesothelioma	1	(33%)	0		1	(14%)	0		2	(12%)
Ovarian/FTC	1	(33%)	0		0		1	(25%)	2	(12%)
Others*	0		1	(50%)	5	(71%)	1	(25%)	7	(43%)
Prior lines of Therapy										
1 and 2	2		1		4		2		9	
3 and more	1		1		1		2		5	
Missing	0		0		2		0		2	

*Other: Duodenal, Gastric, CRC, STS, Thymus, Thyroid
Source: Table 14.1.2.1.1, Table 14.1.2.2.1, Table 14.1.2.3.1

SAFETY

Table 2: DLTs and treatment modifications for Debio 1143 + Avelumab

Debio 1143 + Avelumab (10 mg/kg i.v. q2w)	100 mg		150 mg		200 mg		250 mg		Overall	
	N=3		N=2		N=7		N=4		N=16	
Dose limiting toxicity	0	-	0	-	0	-	1	G3 ALT/AST increase	1	G3 ALT/AST increase
Treatment ongoing pts #	1		1		2		1		5	
Any Treatment Delay due to TEAEs	1		1		1		1		4	(25%)
Dose reductions due to TEAEs	0		0		0		0		0	
Treatment Stopped due to TEAEs	0		0		0		1		1	(6%)

Source: Listing 14.4.0.2, Table 14.2.2.1.1, Table 14.1.1.2

- One patient had a DLT at 250 mg/d dose (grade 3 AST/ALT increase)
- MTD was not reached
- No dose reductions were required

Figure 4A: Most common TEAEs (all patients)

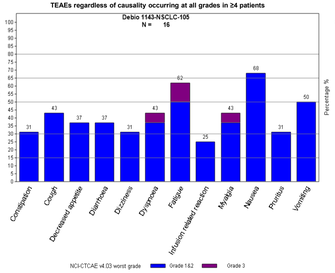
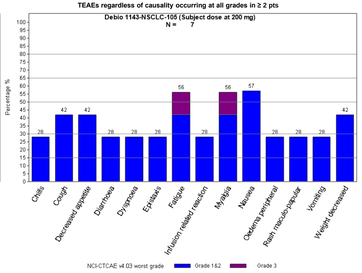


Figure 4B: Most Common TEAEs (Debio 1143 200 mg + Avelumab)



- Overall, the majority of TEAEs were mild and the treatment was well tolerated
- No treatment-related AEs ≥ grade 4 occurred

LABORATORY

Table 3: Chemistry and Hematology

Worst On-Treatment Grade	Debio 1143 100 mg		Debio 1143 150 mg		Debio 1143 200 mg		Debio 1143 250 mg		Overall	
	N=3		N=2		N=7		N=4		N=16	
ALT increased										
Grade 1/2	-		-		4	(57%)	2	(50%)	6	(38%)
Grade 3	-		-		-		1	(25%)	1	(6%)
All Grades	-		-		4	(57%)	3	(75%)	7	(44%)
AST increased										
Grade 1/2	2	(67%)	-		4	(57%)	1	(25%)	7	(44%)
Grade 3	-		-		-		1	(25%)	1	(6%)
All Grades	2	(67%)	-		4	(57%)	2	(50%)	8	(50%)
ALP increased										
Grade 1	-		1	(50%)	3	(43%)	1	(25%)	5	(31%)
All Grades	-		1	(50%)	3	(43%)	1	(25%)	5	(31%)
Total bilirubin increase										
All Grades	-		-		-		-		-	
Lipase increased										
Grade 1/2	-		-		4	(57%)	-		4	(25%)
Grade 3	-		-		-		1	(25%)	1	(6%)
All Grades	-		-		4	(57%)	1	(25%)	5	(31%)
Hypoalbuminemia										
Grade 1/2	3	(100%)	1	(50%)	4	(57%)	2	(50%)	10	(63%)
All Grades	3	(100%)	1	(50%)	4	(57%)	2	(50%)	10	(63%)
Amylase increased										
Grade 1	1	(33%)	-		1	(14%)	1	(25%)	3	(18%)
All Grades	1	(33%)	-		1	(14%)	1	(25%)	3	(18%)
Creatinine increased										
Grade 1/2	3	(100%)	2	(100%)	6	(86%)	4	(100%)	15	(94%)
All Grades	3	(100%)	2	(100%)	6	(86%)	4	(100%)	15	(94%)

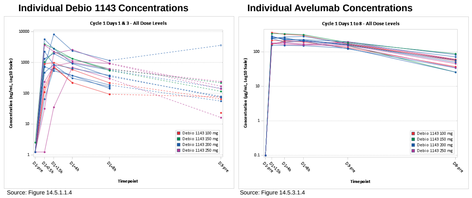
Worst On-Treatment Grade	Debio 1143 100 mg		Debio 1143 150 mg		Debio 1143 200 mg		Debio 1143 250 mg		Overall	
	N=3		N=2		N=7		N=4		N=16	
Anemia										
Grade 1/2	2	(66%)	1	(50%)	7	(100%)	4	(100%)	14	(88%)
Grades 3/4	-		-		-		-		-	
Neutrophil count decreased										
Grade 1/2	-		-		-		1	(25%)	1	(6%)
Grades 3/4	-		-		-		-		-	
Platelet count decreased										
Grade 1/2	-		-		1	(14%)	-		1	(6%)
Grades 3/4	-		-		-		-		-	

Source: Table 14.4.2.1.9, Table 14.4.2.2.9

- No dose-relationships for laboratory abnormalities, except for ALT/AST increases, which at 200 mg/d were all grade 1 and asymptomatic

PHARMACOKINETICS AND PHARMACODYNAMICS

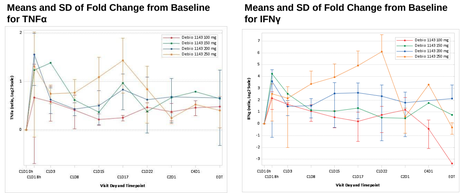
Figure 5: Pharmacokinetics



Source: Figure 14.5.1.1.4 Source: Figure 14.5.3.1.4

- Debio 1143 PK exposure increased with dose with high inter-patient variability
- Avelumab PK exposure is within the expected range

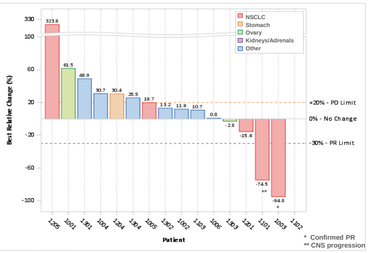
Figure 6: Pharmacodynamics



- TNFα and IFNγ peaked in plasma following Debio 1143 dose on D1 after 8 hrs, and on D17/22 and appeared to increase dose-proportionally

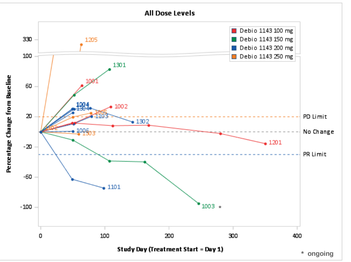
EFFICACY

Figure 7: Best Change in Tumor Size by Primary Tumor Type



Source: Figure 14.3.3.2.3

Figure 8: Spider plot best change in tumor size over time



Source: 14.3.3.3.1

- In 15 evaluable patients, 1 confirmed PR (NSCLC) and 5 SD as per RECIST v1.1
- Tumor shrinkage >15% in 3 out of 5 NSCLC patients measurable by RECIST

CONCLUSION

- **MTD for Debio 1143 in combination with avelumab was not reached and RD2P was selected at 200 mg/d based on favorable safety profile and prior PK/PDy data showing full target engagement starting at 120 mg/d doses**
- **Grade 3 ALT/AST was the only DLT found, however no increase above grade 1 occurred at the RP2D**
- **No myelosuppression was observed other than mild grade anemia**
- **Mild and predictable toxicities were observed that did not affect treatment compliance at RP2D**
- **Clinical activity with the combination is seen and the responding population requires definition**
- **PK was linear; no impact on avelumab disposition was observed**
- **Pharmacodynamic biomarkers appeared to increase dose-proportionally**
- **Expansion at RP2D (Debio 1143 200 mg/day + Avelumab 10 mg/kg i.v. q2w) is ongoing in NSCLC patients**

DOWNLOAD: This poster is available via: www.debiopharm.com/medias/publications

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