PACLITAXEL-CARBOPLATIN WITH THE ORAL IAP INHIBITOR DEBIO1143 IN A SUBSET OF PATIENTS WITH RECURRENT EPITHELIAL OVARIAN CANCER (EOC): PHASE I

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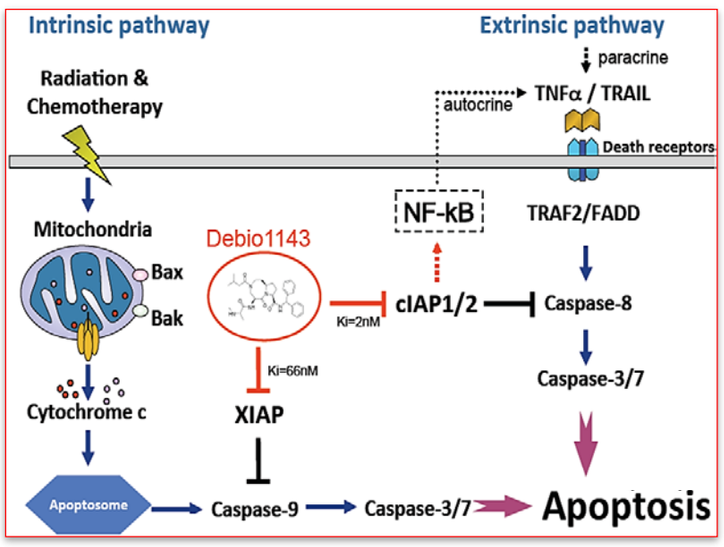
BACKGROUND

- Resistance to apoptosis is a typical hallmark of cancer in which inhibitor of Apoptosis Proteins (IAPs) play a key role.
- IAPs are involved in:
  - regulation of caspases and apoptosis suppression
  - modulation of NF-kB signaling
  - resistance to standard chemo and radiation therapies. [1,2]
- Debio 1143 is an investigational, oral monovalent activator of second mitochondrial-derived activator of caspases (Smac) designed to promote programmed cell death (apoptosis) in tumor cells by antagonizing the activity of the IAPs (Figure 1).

Figure 1. Modulation of apoptotic pathway by Debio 1143



- The addition of drugs targeting and inhibiting IAP proteins such as Debio 1143 to induce greater cell death when combined with chemotherapy, is therefore an interesting treatment approach that could give patients the possibility to achieve better tumor responses.
- Preclinical studies with Debio 1143 have shown broad antitumor activity, both as single agent and when administered in combination with taxanes. Reversibility of sensitivity to carboplatin and paclitaxel was observed in ovarian cancer models.[3]
- The safety and tolerability of Debio 1143 was tested in a phase 1 study of single-agent Debio 1143 in patients with advanced solid tumors or lymphoma[4]:
  - Debio 1143 was generally well tolerated
  - cIAP target degradation starting at dose of 120 mg/day
  - No antitumor activity was observed
- The feasibility and efficacy of combining Debio1143 with carboplatin / paclitaxel was tested in patients with non-small cell lung cancer, triple negative breast cancer and platinum refractory ovarian cancer. [5]
- Here we report the clinical outcome of a subset of patients with relapsed epithelial ovarian cancer (EOC).

OBJECTIVES

- Primary
  - assess safety and tolerability of Debio 1143 with paclitaxel / carboplatin
  - determine recommended dose for phase 2 (RP2D).
- Secondary
  - Characterize the pharmacokinetics (PK) of Debio 1143 when administered concomitantly with paclitaxel and carboplatin
  - Evaluate the anti-tumor activity in patients with recurrent EOC

METHODS

- Open-label, multicenter, non-randomized, dose escalation phase 1 study
- 21-day cycle for up to 6 cycles
  - Oral Debio 1143 on days 1-5
  - IV paclitaxel on day 1
  - IV carboplatin on day 1

Key eligibility criteria:

- Primary or secondary platinum-refractory EOC
- No restriction on number of prior lines of therapies
- Measurable disease per RECIST 1.1
- ECOG performance status 0-1
- Adequate hematogical, renal and hepatic function

RESULTS

PATIENTS AND EXPOSURE

- Demographics and baseline characteristics is shown in Table 1.

Table 1.

	Safety population (N=20)
Median age, years (range)	65 (53 - 78)
ECOG performance status 0/1, n (%)	12 (60) / 7 (35)
Prior regimens, n (%)	
Platinum-containing regimen	20 (100)
Taxane-containing regimen	20 (100)
Anthracycline-containing regimen	14 (70)
Bevacizumab containing regimen	12 (60)

- Escalating doses of Debio 1143 (100-250mg) + optimized dose of paclitaxel (135mg/m^2) and carboplatin (AUC5) were tested. Reduced chemotherapy backbone was used due to PK interaction between Debio 1143 and paclitaxel.

TREATMENT EMERGENT DLTs, Debio 1143 MTD and RP2D

- 4 patients had a total of 5 DLTs (all EOC patients): 2 febrile neutropenia (FN), 1 AST and 1 ALT increase (both grade 3)
- MTD of 250mg identified
- RP2D: Debio 1143 200mg QD days 1-5 + paclitaxel (135mg/m^2) and carboplatin (AUC5)

SAFETY POPULATION

- 19/20 patients (95%) had drug-related AEs
- Most common serious AE were FN, n=3 (15%) and Hypersensitive reaction to carboplatin, n=5 (25%)
- 4 patients (20%) had dose reduction of Debio 1143; main reason FN (n=3)
- Reduction of paclitaxel and carboplatin was reported each in one patient;
- 13 patients completed the planned 6 cycles of Debio 1143.
- Reason for treatment discontinuation:
  - Progressive disease n=4 (20%)
  - Unacceptable toxicity n= 2 (10%)
  - Unresolved DLT n=1 (5%)
- 2 patients died on treatment (all disease progressions)

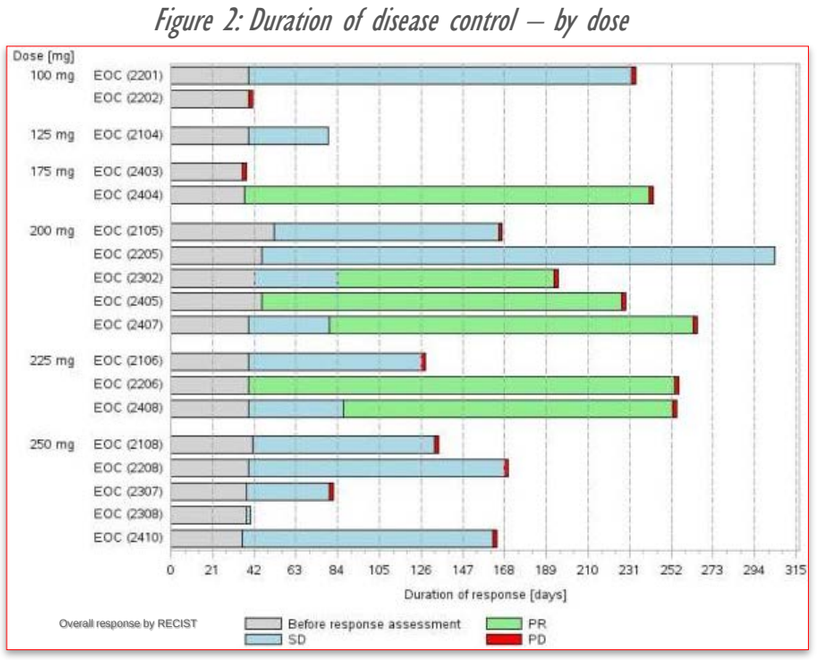
Table 2. Treatment-emergent AEs in ≥ 20% of patients (all grades) and/or grade ≥ 3 in ≥ 10% of patients

	Highest grade per patient	
	All grade Aes n(%)	AEs grade ≥3 n(%)
Hematologic		
Neutropenia	12 (60)	12 (60)
Febrile Neutropenia	-	3 (15)
Anemia	13 (65)	-
Thrombocytopenia	9 (45)	-
WBC Decreased	6 (30)	3 (15)
Neutrophil Count ↓	5 (25)	3 (15)
Lymphocyte Count ↓	5 (25)	-
Platelet count ↓	4 (20)	-
Non-hematologic		
Diarrhea	11 (55)	2 (10)
Constipation	10 (50)	-
Nausea	10 (50)	-
Abdominal Pain	8 (40)	-
Vomiting	8 (40)	-
Gastroesophageal reflux disease	4 (20)	-
Asthenia	14 (70)	-
Fatigue	6 (30)	-
Gen. Physical health deterioration	-	2 (10)
Hypomagnesemia	12 (60)	3 (15)
Decreased appetite	9 (45)	-
Hyperglycaemia	4 (20)	-
Hypokalaemia	4 (20)	-
Hyponatraemia	4 (20)	2 (10)
ALT increased	4 (20)	-
AST increased	4 (20)	-
Peripheral Neuropathy	6 (30)	-
Paraesthesia	6 (30)	-
Epistaxis	5 (25)	-
Alopecia	5 (25)	-
Pruritis	4 (20)	-
Back pain	5 (25)	-
Arthralgia	4 (20)	-
Hypersensitivity	4 (20)	-

BEST OVERALL REPONSE

- 18/20 patients were evaluable for response (Figure 2)
- Median number of 6 cycles (range 1-6)
- Of 18 evaluable patients:
  - 6 patients had partial response (PR) by RECIST, ORR=33%
  - 9 patients by combined assessment (RECIST + Ca-125)
- Responses were observed among patients considered resistant to both, paclitaxel and carboplatin
- PFS rate at 6 months: 50%
- 11 patients (61%) were alive at 1 year

Figure 2: Duration of disease control – by dose



PHARMACOKINETICS

- Debio 1143 exposures increased as dose increased but no relationship between any PK parameter and occurrence of DLT was obviously evidenced.
- Paclitaxel exposure at a dose of 135 mg/m^2 in combination with Debio 1143 was within the expected therapeutic exposure range of patients exposed to 175 mg/m^2 without Debio 1143 (historical controls)
- In general, patients with a DLT had high paclitaxel exposure
- Carboplatin exposures were in the expected AUC5 range

PHARMACODYNAMICS

- The PDy effect of Debio 1143 on cIAP1 degradation in PBMCs was observed at all dose levels and potential signs of downstream effects, such as an increase in serum MCP1 (an NF-kB-induced cytokine), were measured.

CONCLUSIONS

- This was the first study to evaluate the combination of Debio 1143 with paclitaxel /carboplatin
- Combination was generally well tolerated, with a safety profile largely consistent with the safety profile known from the backbone treatment
- Encouraging anti-tumor activity was observed in heavily pre-treated EOC patients
- Considering the poor clinical outcome of patients with advanced EOC, Debio 1143, as chemo-sensitizer, warrants further investigation in combination with carboplatin/paclitaxel in this disease setting.

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