Identification of synergistic drug combinations with the oral HSP90 inhibitor Debio 0932 in non-small cell lung cancer and renal cell cancer

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Summary
- Debio 0932 is a second-generation oral HSP90 inhibitor causing the degradation of potent oncogenic HSP90 client proteins.
- Synergy was identified in vitro between Debio 0932 and standard of care (SOC) agents in both non-small cell lung cancer (NSCLC) and renal cell carcinoma (RCC).
- Debio 0932 displays anti-tumor activity in monotherapy and synergizes with the lung cancer SOC paclitaxel in vivo in NSCLC models.
- Debio 0932 synergizes with renal cancer SOC everolimus in vivo in RCC xenografts.
- These preclinical data support the clinical development of Debio 0932 in combination with paclitaxel and everolimus in RCC and NSCLC, respectively.

Background
Debio 0932 is an oral inhibitor of HSP90, a chaperone of many critical oncogenic drivers.

Drug resistance is a major problem in cancer therapy which could be addressed by simultaneously targeting multiple critical nodes of the signaling networks controlling growth and survival of cancer cells (1-3). One such approach is to target heat shock protein 90 (HSP90), a chaperone of many critical oncogenic drivers (1, 2). Pharmacologic inhibition of HSP90 results in the proteasomal degradation of client oncoproteins, thereby eliminating their oncogenic activity (Fig. 1). (1, 2).

Debio 0932 targets renal cancer SOC everolimus in subcutaneous mouse xenografts of patient-derived RXF1183 RCC xenografts. While both Debio 0932 and everolimus displayed non-tumor activity as single agents in this model, the combination caused marked antitumor activity that was superior to either monotherapy (Fig. 6). None of the treatments had any significant effect on the body weight of animals.

Methods
In vivo drug efficacy testing
Xenografts were performed in accordance with the guidelines for the care and use of laboratory animals.

Subcutaneous xenografts of NSCLC cell lines. 107 cells were injected into the right flank of CD-1 nude mice. Debio 0932 was given p.o. 125 mg/kg every other day for 6 weeks; paclitaxel was injected i.p. 125 mg/kg every week for 3 weeks.

Subcutaneous xenografts of patient-derived RCC xenografts. Tumor fragments were obtained from RFX1183 tumor xenografts in serial passage in NMRI nude mice. After removal from donor mice, tumors were cut into fragments (4-5 mm diameter) and placed in PBS until re-implantation. Anesthetized NMRI nude mice received unilateral, subcutaneous tumor implants in the flank. Debio 0932 was given p.o. 125 mg/kg every other day for 6 weeks. Tumors were measured twice a week using calipers. At the end of the treatment period, tumors were excised, weighed and formalin fixed. Histological analysis was performed.

Xenografts were assessed for tumor volume and body weight changes upon daily oral treatment with Debio 0932 and everolimus in nude mice. N=9 per group.

Reference