The HALO Study: A Phase I-II of the Oral HSP90 Inhibitor Debio 0932 in Combination with SOC in First- and Second-line Therapy of Advanced NSCLC[1] #TPS2632^

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Background

Debio 0932 is an oral HSP90 inhibitor

Debio 0932 is an oral second-generation Heat Shock Protein 90 (HSP90) inhibitor, structurally unrelated to geldanamycin.

In the dose-escalation part of a Phase I study (NCT01168752), Debio 0932 monotherapy has shown promising signs of efficacy in NSCLC [1].

Standard of care (SOC) for patients with advanced NSCLC, a good performance status, and no EGFR mutation, consists of doublet platinum-based chemotherapy (in combination with gemcitabine for squamous histology and in combination with pemetrexed for non-squamous histology) for treatment-naïve patients and docetaxel for second line treatment.[2-4].

In pre-clinical models, Debio 0932 has demonstrated additive efficacy in combination with SOC.

Further investigations into the potential role of Debio 0932 in combination with SOC for NSCLC are warranted.

Objectives

Part A: To determine the MTD of Debio 0932 in combination with cisplatin/pemetrexed or cisplatin/gemcitabine in treatment-naïve patients with Stage IIIb or IV NSCLC and with docetaxel in previously treated patients with Stage IIIb or IV NSCLC.

Part B: To compare the effect of addition of Debio 0932 to combination chemotherapy with cisplatin/pemetrexed or cisplatin/gemcitabine on the rate of Progression Free Survival (PFS) at 6 months in treatment naïve patients with Stage IIIb or IV NSCLC.

Part C: To compare the effect of addition of Debio 0932 to docetaxel on the change in tumor size in second-line therapy for patients with Stage IIIb or IV NSCLC.

Study Design

The study will include patients with advanced NSCLC (Stage IIIb or IV) without known EGFR mutation, known KRAS status and will consist of three parts:

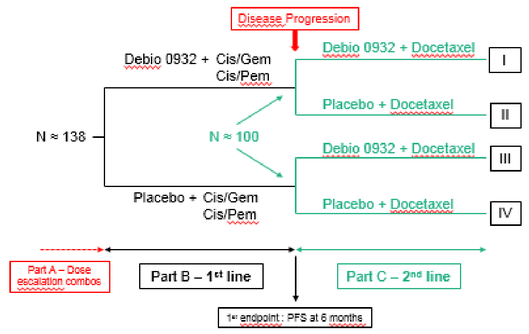
Part A is an open-label dose escalation study of Debio 0932 in combination with SOC in patients who are candidates for first-line or second-line treatment. First-line SOC consists of cisplatin/gemcitabine for squamous histology and cisplatin/pemetrexed for non-squamous histology. Second-line SOC consists of docetaxel. The starting dose for Debio0932 is 100 mg and will be escalated up to 1000 mg.

Part B is a randomized, double-blind, placebo-controlled study of Debio 0932 in combination with first-line SOC in 138 patients who did not receive previous systemic treatment for advanced NSCLC.

Patients who subsequently develop progressive disease in **Part B** will enter into **Part C**, in which a second randomization will assign patients to double-blind treatment with docetaxel/placebo or docetaxel/Debio 0932. Approximately 100 patients are expected to participate in Part C.

ClinicalTrials.gov Identifier: NCT01714037

Summary



Abbreviations: Cis, Cisplatin; Gem, Gemcitabine; PEM, Pemetrexed

Study Endpoints

Part B: The primary endpoint is Progression free survival (PFS) at 6 months. Key secondary endpoints include best overall response rate, duration of objective response, change in tumor size from baseline until 6 months, and overall survival (OS).

Part C: Primary endpoint is change in tumor size from baseline until 6 months. Key secondary endpoints include best overall response rate (ORR), duration of objective response, PFS at 6 months, and OS.

Potential pharmacogenomic, proteomic, and pharmacogenetic factors predictive of response to Debio 0932 will be assessed.

Sample Size

Part B: A sample size of 69 patients per treatment arm is required to detect a difference of 15%i in the PFS rate at 6 months between the test arm of Debio 0932 combined with dual chemotherapy (55%) and the control arm with placebo and dual chemotherapy (40%)

Part C: Approximately 100 patients (progressing from Part B or new patients) are expected to enter Part C. These patients will be randomized into 4 treatment arms of approximately 25 patients and they will receive Debio 0932 or placebo in Part C respectively. If needed (eg. Insufficient number from Part B), additional new patients will be included to complete the planned sample size of 100 patients in Part C. Randomization will be stratified by squamous/non-squamous NSCLC, performance status 0 or 1, NSCLC Stage IIIb or IV, and KRAS status.

Status

As of January 2014 the study is in progress.

58 patients have been enrolled in the Part A of the study at all dose levels (Debio 0932 100 mg to 1000 mg QD).

Conclusions

Part A consists of an open-label dose escalation of Debio 0932 (100-1000 mg) daily in 21 day treatment cycles in combination with SOC for first and second line treatment of advanced NSCLC (Stages IIIb and IV). Cisplatin + gemcitabine (SCC) or cisplatin + pemetrexed (non SCC NSCLC) are used for first line SOC, whereas docetaxel is used for later line therapy.

Part B is a double-blind, placebo-controlled study in which 138 untreated NSCLC patients were randomized to receive placebo or Debio 0932 at a dose recommended in part A in combination with first line SOC. The primary end point is 6 month PFE and secondary endpoints include best ORR, duration of objective response, change in tumor size and OS.

Part C consists of patients with progressive disease treated with docetaxel +/- Debio 0932. The primary endpoint is change of tumor size at 6 months and secondary endpoints include ORR, duration of objective response, 6 month PFE and OS.

References

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