A Phase I-II evaluation of the safety and efficacy of the oral HSP90 inhibitor Debio 0932 in combination with Standard of Care in first- and second-line therapy of Stage IIIb or IV NSCLC

– The HALO study (HSP90 inhibition And Lung cancer Outcomes) –

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Background

- 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 mono-therapy has shown promising signs of efficacy in Non Small-Cell Lung Cancer (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).[2,3,4]
- In pre-clinical models, Debio 0932 has demonstrated additional 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 maximum tolerated dose of Debio 0932 in combination with cisplatin/pemetrexed and 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 adding Debio 0932 to combination chemotherapy with cisplatin/pemetrexed and cisplatin/gemcitabine on the rate of progression-free survival (PFS) at 6 months in first-line therapy of patients with Stage IIIb or IV NSCLC.
- **Part C**: To compare the effect of adding Debio 0932 to docetaxel on the change in tumor size in second-line therapy of patients with Stage IIIb or IV NSCLC.

Study Design

This study will include patients with advanced NSCLC (Stage IIIb or IV) without known EGFR mutation, 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 in case of squamous histology and cisplatin/pemetrexed in case of non-squamous histology. Second-line SOC consists of docetaxel.
- **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 enter Part C.

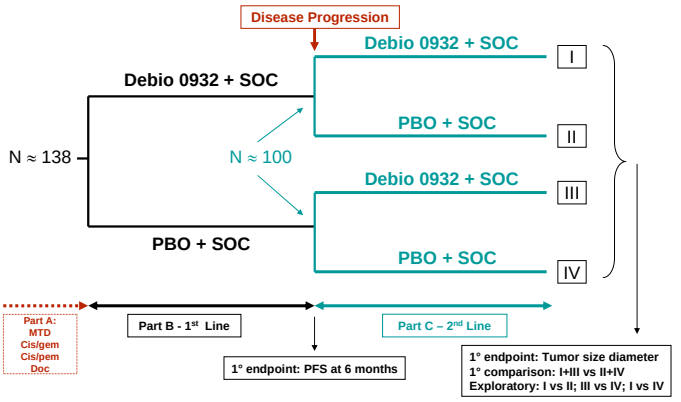

Figure 1 Study design.
Cis/pem, cisplatin/gemcitabine; Cis/pem, cisplatin/pemetrexed; Doc, docetaxel; MTD, maximum tolerated dose; PBO, placebo; PFS, progression-free survival; SOC, standard of care

Study Endpoints

- **Part B**: primary endpoint is 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, duration of objective response, PFS at 6 months, and OS.
- Potential pharmacogenomic, tumor pharmacogenetic, 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% in the PFS rate at 6 months between the test arm Debio 0932 combined with dual chemotherapy (55%) and the control arm with placebo and dual chemotherapy (40%)
- **Part C**: ≈ 70% of patients (N = 100) from Part B (first-line therapy) are expected to progress to Part C of the study (second-line therapy). These patients will be randomized into four treatment arms of about 25 patients, depending on whether they received Debio 0932 or placebo in Part B and will receive Debio 0932 or placebo 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.

Conclusion

This international multi-center study will investigate the role of Debio 0932 in the first- and second-line treatment of advanced NSCLC. Study results are expected in 2014.

1. Data on file, Debiopharm; abstract submitted to ASCO 2012
2. ESMO, Metastatic non-small-cell lung cancer: European Society of Medical Oncology (ESMO) Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol, 2010. 21 Suppl 5: p. 116-9.
3. Azzoli, C.G., et al., American Society of Clinical Oncology (ASCO) Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. J Clin Oncol, 2009. 27(36): p. 6251-66.
4. Ettinger, D.S., et al., NCCN Clinical Practical Guidelines in Oncology (NCCN Guidelines): Non-Small Cell Lung Cancer. Version 3. 2011, National Comprehensive Cancer Network (NCCN). p. 1-101.

For a copy of this poster, please go to http://www.debiopharm.com/our-business/pipeline.html
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Through the Debiopharm-Curis collaboration, Debio 0932 was discovered and characterized preclinically by Curis, and is being developed clinically by Debiopharm.