

A Phase I study of Debio 0932, an oral HSP90 inhibitor, in patients with solid tumors

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Background

HSP90

- Molecular chaperone that functions as a buffer against stresses endured by tumors and that controls the folding and processing of certain client proteins.
- Client proteins include many oncogenic proteins, such as EGFR, HER2, c-MET, AKT, KIT, FLT3, and VEGFR, which are particularly sensitive to HSP90 inhibition.
- Inhibition of HSP90 leads to degradation of client proteins targeting multiple oncogenic signalling pathways.

Debio 0932

- Oral second-generation HSP90 inhibitor.
- N-monomethylated metabolite Debio 0932-MET1 retains 5-25% of the pharmacological activity of Debio 0932 in vitro.
- Extended tumor retention, blood-brain barrier penetration, and anti-tumor activity as monotherapy and in combination against a broad range of tumors in pre-clinical models.

Methods

Phase I dose-escalation study to determine the maximum tolerated dose of Debio 0932.

Key inclusion criteria: diagnosis of advanced solid tumors* refractory to standard curative or palliative therapy; measurable disease per RECIST criteria; ECOG performance ≤ 1 ; no significant cardiovascular disease.

Dosing schedule: once-every-two-days (Q2D) or once-a-day (QD) at a starting dose of 50 mg in both groups; dose escalation according to an algorithm based on observed toxicity and dose limiting toxicities (DLTs) in a traditional "3 + 3" design.

Cardiac safety monitoring: triplicate ECGs, 24-hour Holter monitoring, LVEF, BNP, and troponin.

Serial pharmacokinetic assessments: on days 1-2 and days 29-30; trough pharmacokinetic levels at regular intervals during the treatment period.

Serial pharmacodynamic assessments: HER-2 levels in plasma and HSP70 levels in PBMCs on days 1-3 and at regular intervals during the first 2 treatment months.

Tumor assessments: after every 8 weeks of treatment; tumor response was determined by the investigator according to RECIST criteria.

Results

Demographics & Baseline Status

Demographics and baseline status		
	Q2D dosing N = 22	QD dosing N = 28
Mean age (yrs) (range)	68 (39 - 72)	65 (27 - 74)
Gender male/female	11 (50%) / 11 (50%)	19 (68%) / 9 (32%)
ECOG status	0 1	19 (68%) 9 (32%)
Primary cancer types		
Colo-rectal	8 (27%)	8 (28%)
Lung	4 (18%)	5 (18%)
Pancreas	2 (9%)	2 (7%)
Breast	2 (9%)	3 (11%)
Melanoma	1 (5%)	3 (11%)
Other	7 (32%)	7 (25%)
≥ 3 previous treatment regimens	18 (82%)	24 (86%)

Dose-Escalation

Q2D dosing: dose-escalation continued until 1600 mg, where 1 DLT was observed (febrile neutropenia); further dose-escalation was not feasible due to the excessive number of 100 mg capsules to be taken.

QD dosing: dose-escalation continued until 1600 mg, at which dose 2 DLTs were observed (diarrhea and asthenia); a lower dose level of 1000 mg was then explored.

Safety

Treatment duration: 76 days on average on Q2D dosing (range 21 - 223) and 81 days on QD dosing (range 6 - 329), with no apparent dose trend.

Treatment discontinuation: mainly due to disease progression.

Adverse events (AEs): mostly CTCAE grade 1 or 2, with no apparent dose or schedule relationship; no ocular or cardiac toxicity was observed; no consistent changes in hematology or biochemistry parameters. Asthenia, constipation, decreased appetite, diarrhea, nausea, and vomiting were the most common AEs.

Summary of adverse events

	Q2D Dosing			QD Dosing		
	Low (50-100 mg)	Medium (200-400 mg)	High (800-1600 mg)	Low (50-100 mg)	Medium (200-400 mg)	High (800-1600 mg)
Total number of patients	6	7	9	6	7	15
Patients with AEs	6 / 100	6 / 86	9 / 100	6 / 100	7 / 100	15 / 100
Related AEs	4 / 67	2 / 29	8 / 89	6 / 100	2 / 29	14 / 93
\geq Grade 3 AEs	-	3 / 43	4 / 44	2 / 33	3 / 43	5 / 33
Serious AEs	1 / 17	4 / 57	4 / 44	2 / 33	3 / 43	6 / 40
DLTs	-	-	1 / 11	-	-	2 / 13
AEs leading to treatment discontinuation	-	2 / 29	3 / 33	-	2 / 29	3 / 20
AEs with an outcome of death	-	1 / 14	1 / 11	-	1 / 14	-

Adverse events with $> 15\%$ incidence in at least one dosing schedule

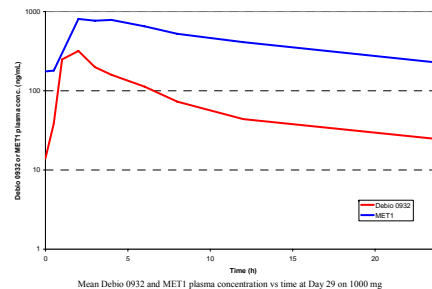
	Q2D Dosing			QD Dosing		
	Low (50-100 mg)	Medium (200-400 mg)	High (800-1600 mg)	Low (50-100 mg)	Medium (200-400 mg)	High (800-1600 mg)
Any Term	5 / 83%	6 / 86%	9 / 100%	6 / 100%	6 / 86%	15 / 100%
Abdominal pain upper	1 / 17%	1 / 14%	2 / 22%	2 / 33%	1 / 14%	4 / 27%
Asthenia	3 / 50%	4 / 57%	7 / 78%	3 / 50%	5 / 71%	12 / 80%
Back pain	1 / 17%	0 / 0%	3 / 33%	1 / 17%	0 / 0%	2 / 13%
Constipation	0 / 0%	4 / 57%	6 / 67%	2 / 33%	2 / 29%	7 / 47%
Cough	1 / 17%	3 / 43%	0 / 0%	1 / 17%	6 / 71%	2 / 13%
Cytolytic hepatitis	2 / 33%	0 / 0%	1 / 11%	1 / 17%	2 / 29%	4 / 27%
Decreased appetite	1 / 17%	3 / 43%	4 / 44%	3 / 50%	1 / 14%	10 / 67%
Diarrhoea	1 / 17%	0 / 0%	5 / 56%	2 / 33%	3 / 43%	12 / 80%
Dyspnea	0 / 0%	0 / 0%	3 / 33%	2 / 33%	2 / 29%	2 / 13%
Folliculitis	0 / 0%	0 / 0%	0 / 0%	3 / 50%	1 / 14%	1 / 7%
Headache	1 / 17%	0 / 0%	3 / 33%	0 / 0%	0 / 0%	0 / 0%
Musculoskeletal pain	0 / 0%	2 / 29%	2 / 22%	0 / 0%	1 / 14%	0 / 0%
Nausea	1 / 17%	2 / 29%	6 / 67%	1 / 17%	2 / 29%	10 / 67%
Stomatitis	0 / 0%	0 / 0%	3 / 33%	1 / 17%	0 / 0%	4 / 27%
Vomiting	0 / 0%	3 / 43%	6 / 67%	1 / 17%	3 / 43%	8 / 53%
Weight decreased	1 / 17%	1 / 14%	2 / 22%	0 / 0%	0 / 0%	7 / 47%

Most common Grade ≥ 3 adverse events (in > 2 patients in at least one dosing schedule)

	Q2D Dosing			QD Dosing		
	Low (50-100 mg)	Medium (200-400 mg)	High (800-1600 mg)	Low (50-100 mg)	Medium (200-400 mg)	High (800-1600 mg)
Any Term	n	%	n	%	n	%
Anemia	0	0%	2	29%	3	33%
Asthenia	0	0%	0	0%	1	11%
Back pain	0	0%	0	0%	2	22%
Cholestasis	0	0%	0	0%	0	0%
Cytolytic hepatitis	0	0%	0	0%	0	0%
Diarrhoea	0	0%	0	0%	0	0%
General physical health deterioration	0	0%	2	29%	1	11%
Nausea	0	0%	0	0%	0	0%

Pharmacokinetics

- Rapid absorption after oral administration; rapid conversion to the N-monomethylated metabolite MET1.
- Plasma exposure for parent and metabolite increased with dose.
- Half-life: ca. 10-20 hours for both parent and metabolite.
- Steady-state conditions were reached within the first week of dosing.
- 24-hour systemic exposure to Debio 0932 and its pharmacologically active metabolite at the recommended dose of 1000 mg QD, supporting once-daily administration.



Pharmacodynamics

- Trend toward an increase in HSP70 levels in PBMC on Day 1, 4, and 24 hours post-dose compared to pre-dose in most patients; no dose-effect relationship could be established.
- No effect was observed on plasma levels of HER2.

Anti-tumor Activity

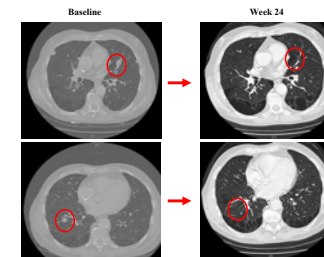
- Anti-tumor activity could be assessed in 45/50 patients enrolled (5 patients had no evaluable on-treatment disease assessment).
- Partial response was observed in 2 patients, one with NSCLC (see case history) and one with breast cancer.
- Out of 8 patients with lung cancer, 1 had partial response, 4 had stable disease, and 3 had progressive disease.

Best overall tumor response

	Q2D dosing Efficacy population N = 20	QD dosing Efficacy population N = 25
Best overall response (investigator-reported)		
Partial response	2 (10%)	0 (0%)
Stable disease	4 (20%)	8 (32%)
Progressive disease	14 (70%)	17 (68%)

Case History

- 63-year old Caucasian male.
- Diagnosis of Stage IV Kras-mutated adenocarcinoma of the lung in Nov 2007.
- Progressive disease after four regimens of systemic anti-cancer therapy, ending Aug 2009.
- Started Debio 0932 100 mg Q2D in July 2010.
- 40% reduction in target lesion diameter after 16 weeks of treatment (partial response).
- Response duration: 16 weeks.
- Treatment was well tolerated, with facial acneiform skin rash.



Conclusion

- Debio 0932 was generally well tolerated at doses up to 1600 mg Q2D and 1000 mg QD
- Debio 0932 showed promising signs of anti-tumor activity in patients with advanced solid tumors, especially in lung cancer
- The recommended Phase 2 dose (1000 mg QD) will be tested in an additional 30 patients in an ongoing expansion study
- A Phase I-II study of Debio 0932 in combination with standard of care in the first- and second-line treatment of NSCLC is planned¹.

¹ Journal of Thoracic Oncology 2012;7(6):S1572 (abstract 196P); poster available at <http://www.debiopharm.com>