3026

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-monodemethlytated 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)	58 (39 – 72)	55 (27 – 74)
Gender male/female	11 (50%) / 11 (50%)	19 (68%) / 9 (32%)
ECOG status		
0	14 (64%)	19 (68%)
1	8 (36%)	9 (32%)
Primary cancer types		
Colo-rectal	6 (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%)

*Originally, patients with lymphoma were allowed as well, however no patients with lymphoma entered the study

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 (800-1000-1600 mg)	
	n	%	n	%	n	%	n	%	n	%	n	%
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
≥ 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

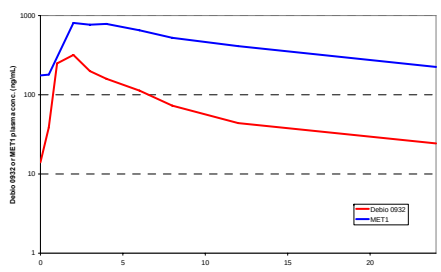
	Q2D Dosing						QD Dosing					
	Low (50-100 mg)		Medium (200-400 mg)		High (800-1600 mg)		Low (50-100 mg)		Medium (200-400 mg)		High (800-1000-1600 mg)	
	n	%	n	%	n	%	n	%	n	%	n	%
Any Term	5	83%	6	86%	9	100%	6	100%	6	86%	15	100%
Abdominal pain upper	1	17%	1	14%	2	22%	2	33%	1	14%	4	27%
Asthenia	3	50%	4	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%	5	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	28%	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 (800-1000-1600 mg)	
	n	%	n	%	n	%	n	%	n	%	n	%
Any Term	0	0%	2	29%	3	33%	1	17%	3	43%	5	33%
Anaemia	0	0%	0	0%	1	11%	1	17%	1	14%	1	7%
Asthenia	0	0%	0	0%	0	0%	1	17%	2	29%	1	7%
Back pain	0	0%	0	0%	2	22%	0	0%	0	0%	0	0%
Cholestasis	0	0%	0	0%	0	0%	1	17%	1	14%	0	0%
Cytolytic hepatitis	0	0%	0	0%	0	0%	0	0%	1	14%	1	7%
Diarrhoea	0	0%	0	0%	0	0%	0	0%	0	0%	2	13%
General physical health deterioration	0	0%	2	29%	1	11%	1	17%	0	0%	0	0%
Nausea	0	0%	0	0%	0	0%	0	0%	1	14%	1	7%

Pharmacokinetics

- Rapid absorption after oral administration; rapid conversion to the N-monodemethylated 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.



Mean Debio 0932 and MET1 plasma concentration vs time at Day 29 on 1000 mg

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

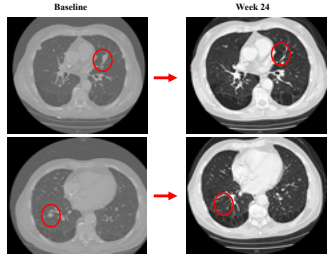
- Anti-tumor activity could be assessed in 45/50 patients enrolled (5 patients had no evaluable on-treatment disease assessment).
- Partial response was observed in 2 patients, one with NSCLC (see case history) and one with breast cancer.
- Out of 8 patients with lung cancer, 1 had partial response,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

Best overall tumor response

Best overall response (investigator-reported)	Q2D dosing Efficacy population N = 20	QD dosing Efficacy population N = 25
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 planned[1].**

[1] Journal of Thoracic Oncology 2012;7(6;S1):S72 (abstract 196P); poster available at http://www.debiopharm.com

Clinicaltrials.gov. NCT 01168752. All analyses presented in this poster are based on preliminary data. For a copy of this poster, please go to http://www.debiopharm.com

Through the Debiopharm-Curis collaboration, Debio 0932 is being developed clinically by Debiopharm. Debio 0932 was discovered and characterized preclinically by Curis, Inc.