Phase I Dose-escalation Study of AXL1717: a Novel Targeted Oral Insulin-like Growth Factor-1 Receptor (IGF-1R) Inhibitor and Its Implications for Patients with Non-small Cell Lung Carcinoma

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Background

- IGF-1R belongs to a family of related receptors also including the insulin receptor (IR). The IGF-1R signaling pathway is crucial for the survival and growth of most types of cancer cells, but not of normal cells [1, 2].
- AXL1717 is a compound that has been optimized to inhibit the IGF-1R without inhibiting closely related receptors including IR.
- AXL1717 demonstrates strong and unique anti-tumor efficacy, including complete regression of numerous established tumors in animals.
- AXL1717 did not show any effect in animals with IGF-1R negative xenografts.
- Preclinical testing in two animal species showed excellent tolerability together with good oral bioavailability.

Study design Phase I study

- **Study setting:** The study consisted of 2 phases. Phase Ia: Single-day BID ascending dose and Phase Ib: multiple-day (7-28 days) BID ascending dose. In both phases doses could be changed both between and within each patient with one patient (Phase Ia) or three patients (Phase Ib) starting on each dose. There was a 21-day treatment-free period following each dosing interval to observe eventual side effects. An accumulated total of 28 treatment days were allowed in the study. After amendment 2*28 days were allowed.
- **Patient population:** 49 advanced-stage cancer patients with documented progressive and refractory solid tumors and no remaining treatment options.
- **Intervention:** Patients were treated with single-agent AXL1717 as the only medication with anti-cancer potential. All treatments for the welfare of the patients were allowed.
- **Primary overall objective:** Recommended phase 2 dose defined as the highest continuous dosing regimens without major related side effects
- **Secondary objectives:** Maximal tolerated dose in phase Ia and Ib, dose-limiting toxicities, toxicological target organ and pharmacokinetics

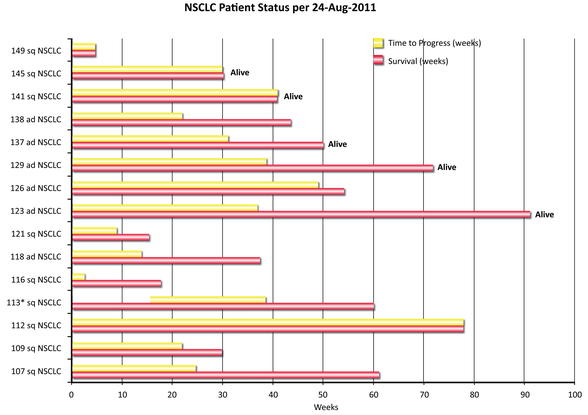
Multi-day BID dosing (Phase Ib)

- **Recruited patients:** 39 patients with advanced solid tumors with documented tumor progression at baseline. No remaining treatment options available. 17 patients with lung cancers, 7 with prostate cancer, 4 patients with GI cancers, 4 with malignant melanoma, 2 with ovarian cancer and 5 other cancers (renal, breast and parotid cancer, B-cell lymphoma, and chondrosarcoma).
- **Treatment:** Single agent AXL1717 was given as multiple-day BID treatment mostly in 3rd or 4th line. Patients were treated for 7, 14, 21 and 28 days with continuous treatment with AXL1717. Non-progressing patients could be treated without time limitation at the discretion of the investigator.
- AXL1717 was well tolerated with no unexpected related adverse dose-limiting events
- 5-10 fold higher exposure obtained than needed for anti-tumor activity in animals
- No unexpected changes in blood levels of glucose, insulin and C-peptide were reported
- Dose-related, easily reversible, monitorable and probably mechanism-driven neutropenia was the only dose-limiting event. Neutropenias were mainly reported at doses higher than RP2D.
- The recommended phase 2 dose (RP2D) is 400 mg BID AXL1717 as single-agent continuous 28-day treatment. At this dose few neutropenias have been reported.
- All major objectives have been obtained in the clinical study.
- Neutrophil granulocytes are known to express IGF-1 receptor and neutropenias have also been seen in toxicological testing in animals.
- The drug exposure at RP2D is several fold higher than that showing pronounced anti-tumor effects in animals.

Signs of clinical benefit in non-small cell lung cancer patients

- In spite of the phase I design with repeated wash-out periods and frequent dose changes, signs that have been interpreted as clinical benefit have been obtained especially in non-small cell lung cancer (NSCLC) patients
- A total of 19 patients with NSCLC were included in the study. Since patients were very advanced in their disease (no remaining treatment options) and growth factor receptor inhibitors such as AXL1717 are believed to have anti-tumor activity only after extended treatment duration, patients with a treatment duration less than 14 days due to rapid tumor progression were excluded from the analysis and thus 15 patients were followed for tumor response and progression.
- Time to progression and survival are shown in Figure 1. Patients were assessed with imaging at baseline and at every 2 months.
- The median survival in these 15 patients were 44 weeks and time to progression was 30 weeks. At cut-off, 5 patients were still alive and 2 of these patients had not reported progression. The results may therefore improve further over time.

Figure 1. Imaging assessments of 15 patients with progressive and refractory NSCLC treated with single agent AXL1717 in 3rd or 4th line, with a treatment duration of 14 days or longer.

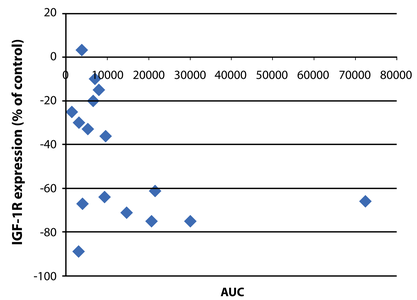


*Pat 113 time to progression measured from baseline phase Ib

Effect of granulocyte IGF-1R in patients

- The presence and density of IGF-1 receptors on the surface of neutrophil granulocytes have been assessed with previously published methods [3]. The assay is experimental and early results were difficult to interpret. Following optimization of the testing procedures, the changes from baseline vs. systemic exposure of AXL1717 (AUC) are shown in Figure 2 for patient 128-149 with baseline values of Granulocyte IGF-1R ≥ 10 relative mean fluorescence intensity (MFI).
- With only one exceptions, granulocyte IGF-1R was reduced in all samples with a mean reduction of 45.9 % (p<0.001)

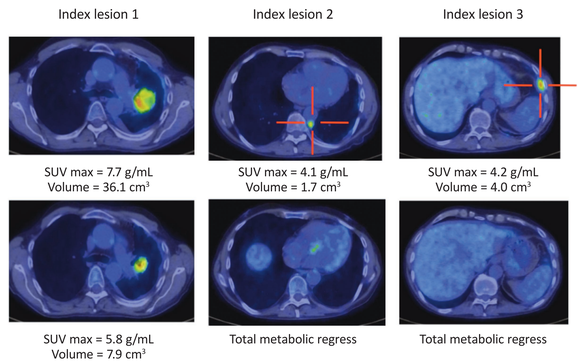
Figure 2. Change of granulocyte IGF-1R from baseline in patient 128-149 with baseline values of ≥ 10 relative MFI.



Tumor response in patient 145

- Patient 145 was a 61 year old male with squamous NSCLC with three index lesions followed according to RECIST 1.1 with computed tomography (CT scan) and positron emission tomography (PET) with fluorodeoxyglucose as tracer.
- The 12 week assessment showed showed a 28%, 69% and 100% reduction on CT scan (RECIST 1.1) for the three index lesions compared with baseline (Figure 3). The maximal standardized uptake value (SUV max) on PET scan was reduced with 78%, 100% and 100% for the three index lesions. Accordingly, there was a partial response in patient 145 following treatment with AXL1717 as monotherapy.

Figure 3. PET scan images from the three index lesions at baseline (upper panel) and the 12 week assessments (lower panel).



Discussion and Conclusions

- The Phase I study has been concluded after reaching all of the primary objectives.
- Phase I setting does not normally allow for efficacy assessments with respect to solid tumors since the treatment is intermittent, of short duration and most patients have not been treated with the optimal dose.
- The combination of radiological findings, absence of new metastasis, prolonged stationary disease and time to progression as well as longer than anticipated survival suggesting clinical benefit for NSCLC patients in 3rd or 4th line of treatment. Since the study was uncontrolled, further studies are needed to further explore the possibility of clinical benefit of AXL1717.
- However, since NSCLC has been shown to widely express the IGF-1 receptor, it was not unexpected that this tumor would be the first to respond also in suboptimal conditions [4].
- Continuous treatment with RP2D is expected to increase anti-tumor effects further.

References

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