A Novel Targeted Oral Insulin-Like Growth Factor-1 Receptor (IGF-1R) Inhibitor and its Implications for Patients with Non-Small Cell Lung Cancer (NSCLC): A Phase I Clinical Trial.

Abstract #: 7539

Presenter:
Simon Ekman

Simon Ekman[1], Johan Harmenberg[2], Jan-Erik Frödin[3], Stefan Bergström[1], Cecilia Wassberg[4], Staffan Eksborg[5], Olle Larsson[6], Magnus Axelson[7], Åsa Hedlund[1], Carina Alvfors[7], Birgitta Ståhl[2] and Michael Bergqvist[1]

[1]Dept. of Oncology, Uppsala University Hospital, Uppsala, Sweden; [2]Axelar AB, Karolinska Institutet Science Park, Stockholm, Sweden; [3]Dept. of Oncology, Karolinska University Hospital, Stockholm, Sweden; [4]Dept. of Radiology, Uppsala University Hospital, Uppsala, Sweden;
[5]Childhood Cancer Research Unit, Karolinska Institutet, Stockholm, Sweden; [6]Dept. of Oncology-Pathology, Karolinska University Hospital, Stockholm, Sweden; Dept. of Clinical Chemistry, Karolinska University Hospital, Stockholm, Sweden

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 many 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.**
- **Signs of clinical activity have been reported [3].**

Study design

- **Study setting:** This first-in-human 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 possible side effects. An accumulated total of 28 treatment days were allowed in the study. After amendment 2*28 days were allowed. Non-progressing patients at the end of the study period were offered continued treatment in an extension study with the same study regimens as in the study.
- **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 symptomatic treatments of the patients were allowed.
- **Primary overall objective:** Recommended phase 2 dose (RP2D) 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. Patients characteristics in Table 1.
- **Treatment:** Single agent AXL1717 was given as multiple-day BID treatment mostly in 3rd or 4th line. Patients were treated for 7, 14, 21 or 28 days with continuous treatment with AXL1717. Non-progressing patients could be treated without time limitation at the discretion of the investigator.
- **Study drug exposure:** A total of 147 weeks of study drug treatment was administered in Phase 1b and 111 weeks in the 13 patients entering the extension study.

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 of clinical benefit have been obtained especially in non-small cell lung cancer (NSCLC) patients.
- Of the 36 patients in Phase Ib with measurable disease at baseline, 10 patients reported stationary disease (RECIST 1.1) at the end of primary study period and another 3 patients reported partial response (1 according to RECIST 1.1 [incl. PR on FDG PET] and 2 on FDG PET assessment) during the course of treatment.
- A total of 19 patients with NSCLC were included in the study and 15 patients with a treatment duration longer than 14 days and were followed for tumor response and progression.
- Time to progression and survival are shown in Figure 1. Patients were assessed with computed tomography at baseline and at every 2 months.
- The median overall survival in these 15 patients were 60 weeks and progression-free survival 31 weeks. At cut-off, 4 patients were still alive.

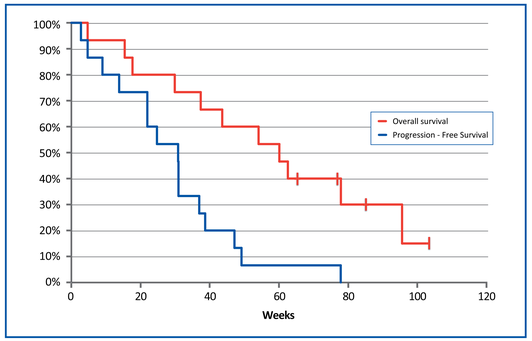
Table 1. Patient characteristics

Characteristics	Phase Ia (single-day dosing)	Phase Ib (multi-dosing)
Total included	16	39
Age (years; median, range)	58.5 (25-83)	64.0 (27-80)
Sex		
Male	9	24
Female	7	15
Perfomance Status		
0	8	13
1	5	21
2	3	5
Tumor type		
NSCLC, adeno		7
NSCLC, squamous	5	10
Prostate		7
Gastrointestinal tumor	6	4
Malignant melanoma	1	4
Ovarian cancer		2
Other	4 (salivary gland carcinoma, sinonasal undifferentiated carcinoma, chondrosarcoma, SCLC)	5 (salivary gland carcinoma, chondrosarcoma, B-cell lymphoma, breast and kidney cancer)
Prior therapy		
Surgery	8	21
Radiotherapy (excluding palliation)	9	20
Chemotherapy (including palliation)	15 (7 ≥ 3 regimens)	39 (26 ≥ 3 regimens)
Hormone/immunotherapy	3	11

References

1. Gualberto, A. and M. Pollak, *Clinical development of inhibitors of the insulin-like growth factor receptor in oncology.* Curr Drug Targets, 2009. **10**(10): p. 923-36.
2. Pollak, M., *Insulin and insulin-like growth factor signalling in neoplasia.* Nat Rev Cancer, 2008. **8**(12): p. 915-28.
3. Ekman, S., et al., *Clinical Phase I study with an Insulin-like Growth Factor-1 receptor inhibitor: experiences in patients with squamous non-small cell lung carcinoma.* Acta oncologica (Stockholm, Sweden), 2011. **50**(3): p. 441-7.
4. Karp, D.D., et al., *Phase II study of the anti-insulin-like growth factor type 1 receptor antibody CP-751,871 in combination with paclitaxel and carboplatin in previously untreated, locally advanced, or metastatic non-small-cell lung cancer.* J Clin Oncol, 2009. **27**(15): p. 2516-22.

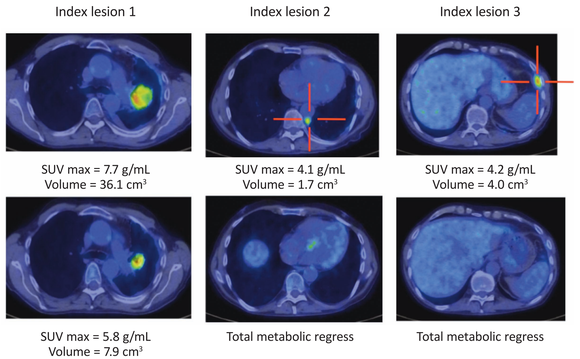
Figure 1. Progression-free survival and overall survival of 15 patients with progressive and refractory NSCLC treated with single agent AXL1717 in 3rd or 4th line. Patients with a treatment duration longer than 14 days.



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) and positron emission tomography (PET) with fluorodeoxyglucose (FDG) as tracer.
- The 12 week assessment showed a 28%, 69% and 100% size reduction, respectively, on CT (RECIST 1.1) for the three index lesions compared with baseline. The maximal standardized uptake value (SUV max) on PET scan was reduced with 78%, 100% and 100% for the three index lesions (Figure 2). Accordingly, there was a partial response in patient 145 following treatment with AXL1717 as monotherapy.

Figure 2. FGD PET/CT 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 completed after reaching all of the primary objectives.
- AXL1717 was well tolerated with no unexpected related adverse dose-limiting events.
- 5-10 fold higher exposure obtained in patients than needed for anti-tumor activity in animals.
- No unexpected changes in blood levels of glucose, insulin and C-peptide were reported.
- Dose-related, readily 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 is 400 mg BID AXL1717 as single-agent continuous 28-day treatment. At this dose few neutropenias have been reported.
- The drug exposure at RP2D is several -fold higher than that showing pronounced anti-tumor effects in animals.
- 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 suggested clinical benefit for heavily pretreated 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.
- Since NSCLC has been shown to widely express the IGF-1 receptor, it was not unexpected that this tumor type would be the first to respond also in suboptimal conditions [4].
- Continuous treatment with RP2D is expected to increase anti-tumor effects further.