Amuvatinib (MP-470), a multi-targeted tyrosine kinase inhibitor and DNA repair suppressor, synergizes with Etoposide (VP-16) in Small Cell Lung Cancer (SCLC) cell lines and xenografts

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Background

- Amuvatinib is an orally bioavailable multi-targeted tyrosine kinase inhibitor specifically designed to be a potent inhibitor of mutant c-Kit and PDGFRα.
- Amuvatinib also decreases Rad51-mediated homologous recombination DNA repair and increases cancer cells’ chemotherapeutic drug sensitivity (Bristow et al., Mol Cancer Ther 2009;8(12 Suppl.): A122) and radio-sensitivity (Welsh et al., Radiat Oncol. 2009;4:69).
- In a Phase 1b clinical study of amuvatinib in combination with Etoposide (VP-16) + Carboplatin, responses were observed in Small Cell Lung Cancer (SCLC) (Tolcher et al., IASLC 13th World Conference on Lung Cancer, abst. 7936).

To support a Phase 2 clinical study, we evaluated the effects of amuvatinib as a single agent and in combination with VP-16 and carboplatin in a panel of 5 SCLC cell lines.

Efficacy of amuvatinib + VP-16 combination was also studied in SCLC NCI-H146 xenografts.

Methods

- Viability of 5 SCLC cell lines (LB12-SCLC/OC2, LB13-SCLC/OC3, NCI-H146, NCI-H69 and NCI-H82) after treatment with amuvatinib, VP-16 and carboplatin as single agents or in combination was evaluated using the MTS assay and combination index (CI) was determined after simultaneous treatment for 72 hrs.
- Modulation of cell signaling pathways after amuvatinib treatment was evaluated in these SCLC cell lines and xenografts by Reverse Phase Protein Array (RPPA) and Western blot.
- Tumor growth inhibition after administration of amuvatinib and VP-16 was evaluated in NCI-H146 xenografts established in Swiss nude mice.

Results

- All 5 SCLC cell lines tested were sensitive to amuvatinib with LB12-SCLC/OC2 being the most sensitive (IC50=0.79 μM).
- When amuvatinib and VP-16 were combined, effects produced were generally additive or synergistic (on 3 of the 5 cell lines tested)
  - Synergism was observed in NCI-H146 (Combination Index=0.68±0.18).
- When amuvatinib and VP-16 were combined to carboplatin, significant synergism was again evident in NCI-H146 (CI=0.72±0.12) and additivity was observed in NCI-H69 and LB12-SCLC/OC2.
- RPPA analysis of cell extracts showed a significant dose and time dependent modulation of phospho-S6 and phospho-EBP1 after amuvatinib treatment.
- In vivo PO administration of amuvatinib in combination with IV VP-16 in NCI-H146 tumor-bearing mice at well tolerated doses and regimens produced a sustained reduction in T/C ratio < 39%.

Conclusions

Preclinical evidence supports a Phase 2 combination strategy of amuvatinib with VP-16 in SCLC.

- In vitro: 3 out of 5 SCLC cell lines amuvatinib + VP-16 → additive or synergistic effects
  - Synergism in NCI-H146
  - Synergism in NCI-H146 also after amuvatinib + VP-16 + Carboplatin
- In vivo: NCI-H146 xenograft tumors showed better in vivo antitumor activity after amuvatinib + VP-16 than after VP-16 alone
  - Exposures observed in mice were shown to be achievable in clinical studies
  - Clinical Phase 2 study in SCLC with amuvatinib in combination with VP-16 + Platinum is being planned

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Figure 1: Sensitivity of five SCLC cell lines to amuvatinib

Figure 2: In vitro synergy of amuvatinib and VP-16 in SCLC cell lines

Figure 3: Reverse phase protein array (RPPA) of SCLC cell extracts after treatment with amuvatinib, VP-16 and carboplatin in a panel of 5 SCLC cell lines.

Figure 4: In vivo efficacy of amuvatinib + VP-16 in SCLC NCI-H146 xenografts