Furmontinib is an Oral, Irreversible, Highly Brain-Penetrant Pan-EGFR Mutant Inhibitor with Activity Against Classical and Atypical EGFR Mutations

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Background

- EGFR (also known as ERBB1, HER1) is comprised of an extracellular domain, a transmembrane domain, and an intracellular tyrosine kinase domain.Mutational activation of EGFR is a common and early event in the development of NSCLC and confers oncogene dependence on the growth and proliferation of the cancer cell.
- EGFR-mutant NSCLC is further divided into those with so-called "classical" activating EGFR mutations (exon 19 deletions and L858R point mutation in exon 21) and those with other activating EGFR mutations (20).

Methods

- Molecular modeling of furmontinib and osimertinib in EGFR L858R, D770_N771insPG, and G717S mutants was performed with Molecular Operating Environment (MOE) software (Chemical Computing Group) using 4.6L, 4.6H, and 2.6N EGFR crystal structures obtained from PDB.
- Kinase selectivity was assessed using a selected panel of 20 kinases under ATP binding conditions by mobility shift assay (Crowd Sciences).
- Furmontinib is a third-generation, pan-EGFR mutant TKI (3).
- It covalently binds to C797 of EGFR through an acrylamide bond.
- It contains trifluoroethoxyphosphine group predicted to improve the binding to EGFR kinase domain through interaction with the hydrophobic pocket (Akiwada, unpublished data).

Once Daily Treatment with Furmontinib Results in Sustained Inhibition of EGFR in Tumor Xenograft Studies

Figure 4: Western blot analysis of tumor lysate from Ba/F3 tumors harboring EGFR exon 20 insertion (V747F,D770L) collected 1, 4, and 24 hours after 14 days of daily treatment with furmontinib.

Table 3: Brain uptake of furmontinib and its metabolite based on single dose mice PK study compared to osimertinib

| Group | Species | Brain/Plasma Ratio | %DV/νν
|-------|---------|--------------------|--------
| Osimertinib | Nude mice | 1.8a/2.8b | 0.21c
| Furmontinib | 15 mg/kg | 1.90/2.82 | 0.20/0.21
| Furmontinib | 30 mg/kg | 2.10/2.79 | 0.20/0.21
| Furmontinib | 50 mg/kg | 1.80/2.69 | 0.20/0.21


c = mean bioluminescence intensity of the set time in the vehicle control group; T = mean bioluminescence intensity of the set time in the drugs groups; T/C = tumor control; %TGI = tumor growth inhibition.

Table 4: Furmontinib shows dose-dependent activity in PC-9-Luc orthotopic brain tumor model

<table>
<thead>
<tr>
<th>Group</th>
<th>Human Equivalent (mg)</th>
<th>Bioluminescent Signal (Day 10)</th>
<th>%TGI</th>
<th>1%C5</th>
<th>1%G5</th>
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| Furmontinib | 10 mg/kg | 4.34±0.81 | 1.28±0.08 | 0.42 | 0.20 | 0.014
| Furmontinib | 20 mg/kg | 4.60±0.90 | 1.47±0.09 | 0.46 | 0.20 | 0.014
| Furmontinib | 30 mg/kg | 4.74±0.99 | 1.53±0.09 | 0.48 | 0.20 | 0.014
| Furmontinib | 50 mg/kg | 4.88±1.00 | 1.60±0.09 | 0.49 | 0.20 | 0.014


Summary and Conclusions

- Furmontinib is currently being investigated in NSCLC patients with various EGFR activating mutations in global clinical trials (NCT03364073).

References