Background of ER005

ER005 (Bentamapimod, A602801) c-jun N-terminal kinase (JNK) inhibitor

- JNKs are MAP kinases that regulate inflammation, morphogenesis, cell proliferation, differentiation, survival and death.
- JNKs are upregulated in many cancers and are associated with drug resistance.
- ER005 is a highly selective first-in-class JNK inhibitor with IC50 = 90 nM in NIH3T3 cells.
- ER005 inhibits tumor initiating capacity of cancer stem cells in mice (first in vivo study with ER005 in cancer model, Okada 2016).

Methods

- Cytotoxicity in rare cancer cell lines and healthy fibroblasts: the cytotoxicity of ER005 on a panel of 20 human cancer cell lines (neuroendocrine tumor (NET), neuroblastoma, sarcoma, T lymphoma) and non-cancer cells was determined using the MTT assay.
- JNK activation was analyzed by quantifying the phosphorylation of c-Jun using Western Blot analysis.

Results: ER005 Repositioning in Oncology – Pediatric and Rare Cancers

The JNK pathway is activated in rare cancer cell lines

- JNK1 and JNK2 are the only known kinases capable to phosphorylate c-Jun on Ser-73 (detected at 48kDa with anti-p-c-Jun Ab #3270, Cell Signaling Technology).
- C-Jun possesses several phosphorylation sites, two of them being located at the N-terminal site of the protein on Serine 63 and 73, which are known to be involved in an increased transcriptional activity of the protein.

ER005 is a selective inhibitor

- ER005 selectively inhibits cell viability of tumor cells compared to non-tumor cells; the cytotoxicity of ER005 in cancer cells is at least 5-fold higher compared to normal fibroblasts.

ER005 inhibits growth of rare cancer cells in which the JNK pathway is activated

- The cell viability is inhibited in most tumor cell lines with an IC50 of 5-15 μM.
- ER005 displays some activity in NIH3T3 fibroblasts in which the JNK pathway is activated (phosphorylated JunD seen by Western Blot).
- The IC50 could not be correlated with the level of c-jun phosphorylation.
- The association between IC50 and the detection of Ser-73 p-c-Jun or p-JunD supports the hypothesis that the cytotoxic activity of ER005 might be linked to targeting the JNK pathway.

PK profile of ER005 in adults

- The pharmacokinetics of ER005 in humans.

Conclusions

- ER005 is a first-in-class JNK inhibitor that was shown to be safe in humans.
- ER005 displayed encouraging cytotoxicity against rare and pediatric cancer cell types at low micromolar concentrations.
- ER005 is an ideal candidate to be tested in combination with other chemotherapeutic drugs.

References