ALRN-6924 is a Dual MDMX/MDM2 Inhibitor and Can Protect the Bone Marrow of Cancer Patients Treated with Chemotherapy

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Abstract

ALRN-6924 is a cell-permeating, stabilized alpha-helical peptide that binds with high affinity to endogenous p53 inhibitors MDM2 and MDMX. In cancer patients with tumors harboring p53 mutations, ALRN-6924 is expected to selectively induce cell cycle arrest in normal cells with wildtype p53 and reduce chemotherapy toxicities, thus increasing the therapeutic index of chemotherapy. In an ongoing Phase 1 study in healthy volunteers ALRN-6924 given at 0.5 mg/kg demonstrated excellent tolerability and preferential, p53-mediated induction of p21 in bone marrow cells, without concurrent induction of apoptosis. In a chemotherapy clinic study in patients with extensive disease SCCL treated with topotecan, ALRN-6924 given at 0.3 mg/kg dose 24h prior to topotecan showed a strong signal of chemoprotection, reducing NCI CTC Grade 3/4 anemia and thrombocytopenia by 70% and 29%, respectively, and reducing Grade 4 neutropenia by 40%, relative to historic controls (Hort et al., AAGC 2020). Platelet and RBC transfusion rates were decreased by 80% and 70%, respectively, relative to historic controls. ALRN-6924 has the potential to significantly reduce hematological toxicity in cancer patients receiving chemotherapy.

1: Structure and Key Design Properties of ALRN-6924

2: ALRN-6924 Induces Expression of Genes for Cell Cycle Arrest or Apoptosis in Mouse Bone Marrow in a Dose-Dependent Manner

3: ALRN-6924 Induces Cell Cycle Arrest in Bone Marrow of Mice in vivo

4: Clinical Study to Evaluate ALRN-6924 in Healthy Human Volunteers

5: Effects of ALRN-6924 on p21 (Cell Cycle Arrest) and Cleaved-PARP (Apoptosis) in Bone Marrow of Healthy Human Volunteers

6: ALRN-6924 is an Effective Chemoprotection Agent for Small-Cell Lung Cancer Patients Receiving Topotecan

Conclusions

- ALRN-6924 is a potent and specific p53 agonist; this activity is achieved by its binding to p53 endogenous inhibitors MDM2 and MDMX.
- In healthy volunteers ALRN-6924 has demonstrated excellent tolerability and preferential, p53-mediated induction of p21 in bone marrow cells.
- SCLC patients treated with ALRN-6924 experienced reduced bone marrow toxicity relative to historic controls.
- Clinical development of ALRN-6924 is ongoing with a recently initiated randomized, placebo-controlled trial in SCLC patients receiving chemotherapy or immunotherapy.

References


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