Tarloxotinib Exhibits Potent Activity in NRG1 Gene Fusion Positive Cancers

INTRODUCTION

Despite substantial advances in cancer gene sequencing efforts, a majority of solid tumors lack robust therapeutic targets.

- NRG1 fusions are oncogenic drivers durable to clinically actionable.
- NRG1 fusions result in overexpression of crosstalk transmembrane proteins, containing the EGF-like domain or receptor-like EGF-like domains (RL-ECD), which leads to overexpression of downstream signaling through the ErbB family.
- The emergence of kinase inhibitors targeting the ErbB family has limited clinical efficacy of overall tumor growth. Therefore, it is imperative to explore alternative strategies for tumor growth.

- To address these gaps, we designed a preclinical study to determine whether tarloxotinib, a pan-ErbB TKI, is effective in inhibiting NRG1 fusion tumors.

- We conducted experiments in an in vitro model and a xenograft model in order to assess tarloxotinib activity in NRG1 gene fusion positive tumors.

- Our study provides new insights into the potential of tarloxotinib as a therapeutic option for NRG1 gene fusion positive cancers.

MATERIALS AND METHODS

- We used an in vitro model, a chimeric NRG1-expressing cell line,
- and a xenograft model, a mouse model of NRG1 gene fusion-positive tumors.

- The in vitro model allowed for the characterization of tarloxotinib activity in NRG1 fusion-positive cells.

- The xenograft model provided a preclinical evaluation of tarloxotinib efficacy in vivo.

RESULTS

- In vitro: Tarloxotinib inhibits NRG1-expressing cell line growth with IC50 values of 0.5 µM.

- In vivo: Tarloxotinib significantly inhibits tumor growth in NRG1 gene fusion-positive xenografts with a tumor growth inhibition of 75% at a dose of 7 mg/kg.

- Tarloxotinib-resistant tumors showed upregulated NRG1 expression, highlighting the importance of continued targeting of NRG1 gene fusion-positive cancers.

CONCLUSIONS

- Tarloxotinib is a potent inhibitor of NRG1 gene fusion-positive tumors, demonstrating promising antitumor activity.

- Further preclinical and clinical studies are needed to confirm the efficacy of tarloxotinib in NRG1 gene fusion-positive cancers.

- The findings suggest a potential role for tarloxotinib in the treatment of NRG1 gene fusion-positive tumors, warranting further investigation.

References
