EZN-3920, an LNA antisense oligonucleotide RNA antagonist, down modulates HER3 expression and PI3K/Akt signaling pathway and enhances antiproliferative effect of gefitinib in tumor cells

Introduction

The Her family consists of four tyrosine kinase receptors designated as EGFR, HER1, HER2 and HER4. Inhibition of HER3 is likely to have antitumor effects since HER3 (1) heterodimerizes with HER2 and EGFR; (2) is a key link to the PI3K prosurvival signaling pathway; and (3) is activated in cells resistant to EGFR or HER2 targeting therapeutics. This study aimed at evaluating the activities of EZN3920, an HER3 locked nucleic acid (LNA) antisense oligonucleotide (ON), in various tumor cells and xenograft models. The present study aimed at evaluating the activities of EZN3920, an HER3 locked nucleic acid (LNA) antisense oligonucleotide (ON), in various tumor cells and xenograft models. The present study aimed at evaluating the activities of EZN3920, an HER3 locked nucleic acid (LNA) antisense oligonucleotide (ON), in various tumor cells and xenograft models.

LNA-based oligonucleotides

- 3′-terminal LNA-based antisense technology
- Very high mRNA affinity
- Excellent plasma stability
- Long-tissue residence time (days)
- Short sequence (14-16mer)
- High cell potency (low nM comparable to siRNA)
- High potency may translate to better therapeutic window

In vitro evaluation

The tumor cells were treated with EZN-3920 with liposomes-2006. Proliferation assay (MTS assay), apoptosis assay (Caspar 7% assay), and mRNA (qRT-PCR) and proteins (western blot) examination were performed two days after transfection. The EZN3920 scrambled oligonucleotides served as a negative control. Twelve cell lines were used for the evaluation. Gefitinib-resistant HCC827 cells were generated by exposing cells to increasing amount of gefitinib for a period of three months.

Methods

In vitro evaluation

Node nodule bearing 15PC-3 (prostate), A549 (lung) and SK-BR3 (breast) xenografts were intravenously injected with EZN-3920 as multiple dose regimens. The mRNA and protein levels in liver and tumors were examined by qRT-PCR and western blot, respectively.

Objective

Demonstrate the utility of EZN-3920 in vitro and in vivo, including cells resistant to gefitinib.

Conclusion

- EZN-3920 potently inhibits cell growth
- EZN-3920 treatment sensitizes A549 cells to gefitinib
- Similar effect observed with 15PC-3 cells

References & Acknowledgments


AACR 100th Annual Meeting, Denver, CO, 2009