Treating HER2-mutant advanced biliary tract cancer with neratinib: benefits of HER2-directed targeted therapy in the phase 2 SUMMIT ‘basket’ trial


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Background

Biliary tract cancer and HER2 mutations

- Abnormal HER2 activation results in tumor growth
- HER2 amplification or overexpression
- HER2 (ERBB2) somatic mutations
- Activation of downstream signal transduction pathways
- Subset of HER2 mutations result in constitutive kinase signaling, oncogenic transformation and enhanced tumor growth in preclinical models

Neratinib (HKI-272; PBZ2; NERLYNX®)

- Oral, irreversible, tyrosine kinase inhibitor of EGFR (ERBB1), HER2 (ERBB2), and HER4 (ERBB4)
- Covalent binding to conserved cysteine residues in the kinase active binding site of EGFR, HER2, and HER4
- Potential inhibition of immunosignaling, cell proliferation and colony formation of HER2 mutant and amplified breast tumor cell lines in vitro
- Promising binding to conserved cysteine residues in the kinase active binding site of EGFR, HER2, and HER4
- Approved in US and Australia for extended adjuvant treatment of patients with early-stage HER2-positive early breast cancer following adjuvant trastuzumab-based therapy. EU approval for patients with early-stage hormone receptor-positive HER2-positive breast cancer who are less than 1 year from completion of prior adjuvant trastuzumab-based therapy.

Methods

SUMMIT ‘basket’ study design

- neratinib treatment group
- Comparison

Results

Baseline demographics

- HER2-mutant biliary cohort (n=20)

Neratinib is safe and tolerable in patients with advanced biliary tract cancers with somatic HER2-mutations.

- The major observed toxicities were manageable gastrointestinal adverse events
- Disease control was observed in both cholangiocarcinoma and gallbladder cancer.
- Summary and conclusions
- Further combinable studies from small tumor biopsies and cDNA are ongoing analysis to integrate both biomarkers and acquired resistance mechanisms.

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