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Real-world ctDNA detection of HER2 activating mutations vs. amplification across tumor types: confirmation of disease-specific prevalence and characterization of low-VAF detection on Northstar Select

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Abstract

Background

HER2 (ERBB2) is a validated pan-tumor target, with its actionable alterations comprising two therapeutically distinct classes: amplification and activating mutations. Three HER2 mutation-directed therapies trastuzumab deruxtecan (T-DXd) and the oral TKIs zongertinib and sevabertinib are now FDA-approved, making detection of activating HER2 mutations increasingly consequential. When tissue is limited, plasma ctDNA enables noninvasive genotyping, but activating mutations often circulate at low variant allele fraction (VAF) and amplifications present as low-level copy gains, making analytical sensitivity the key determinant for detection.

Methods

We retrospectively analyzed commercial Northstar Select (BillionToOne) ctDNA reports from 15,854 patients (24,105 reports) for oncogenic HER2 alterations including copy number gains, missense mutations and in-frame indels. VAF and copy number were characterized per detection event, and recurrent activating

mutations (≥ 10 patients) mapped to tumor type using diagnosis super-families.

Results

HER2 alterations were detected in 2,137 patients (13.5%) and oncogenic in 494 (3.1%), split near-evenly between amplification ($n=277$) and activating mutation ($n=251$; 34 had both). Activating mutations had a median VAF of 1.03% (floor 0.01%); amplifications a median copy number of 3.52 (in plasma). The nine recurrent activating mutations showed cancer-type-specific prevalence: p.Y772_A775dup, 90% lung; p.L755S (73%) and p.V777L (68%), breast-predominant; p.R678Q, 44% colorectal; p.S310F spanning bladder, colorectal, biliary, and lung. Activating-mutation detection was highest in bladder/urothelial (3.2%), biliary tract (2.9%), and breast (2.8%).

Conclusion

In this real-world cohort, Northstar Select detected oncogenic HER2 alterations at low VAF and low-level copy gain, capturing actionable HER2 targets at tumor fractions below the reporting range of many assays. ctDNA-derived cancer-type-specific prevalence recapitulated tissue-based patterns, validating plasma

genotyping as a sensitive approach. This matters most for activating mutations in tumors not traditionally HER2-screened, supporting ctDNA

testing to surface HER2-directed therapy candidates.

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