Improved detection of disease progression in metastatic breast cancer by absolute molecular counting: the 100 copies/mL question

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Background & objectives

Circulating tumor DNA (ctDNA) is promising as tumor-specific marker to monitor disease progression in metastatic cancer. Questions remain about its clinical validity and more specifically how to threshold it. Here we investigated the diagnostic power of ctDNA concentration in metastatic breast cancer and its optimal thresholding.

Methods

This prospective single-center observational study conducted from July 1, 2019 to December 1, 2021, recruited 136 subjects with metastatic breast cancer for sequencing of their primary tumor in search of PIKC3A or TP53 variants amenable for molecular counting by Plasma-Safe-SeqS technology. This interim analysis reports on ctDNA levels in 201 on-treatment samples from 16 subjects with PIK3CA or TP53 variants. Subjects were sampled every 3-5 weeks with median follow-up of 93 (18-113) weeks and median of 13 (5-25) time points per subject. Primary outcome was progression free survival. ROC analysis was performed to investigate the diagnostic power of ctDNA copies/mL to predict progression within 12 weeks from each sampling time point. Likelihood ratios were used for rational selection of ctDNA result intervals.

Results

ctDNA level (AUC: 0.855; 95% CI 0.784-0.911)) outperformed CA15-3 (AUC: 0.585; 95% CI 0.496-0.670, $P<0.001$) to predict progression within 12 weeks. ctDNA levels below 10 mutant copies/mL were reassuring with 89% (95% CI 80%-94%) negative predictive value for systemic progression. ctDNA levels above 100 copies/mL were identified as red flag, associated with 91%(95% CI 81%-96%) positive predictive value for impending progression, leading to earlier detection of 64% of progression events with median (IQR) lead time of 10 (8-20) weeks versus standard of care.

Conclusion

likelihood ratio-guided thresholding of ctDNA concentration identified 100 copies/mL as red flag for impending progression. Intensive ctDNA molecular counting shows clinical validity form improved surveillance in metastatic breast cancer and risk-informed scheduling of standard clinical care.