Clinical Trial

Major Finding: The primary endpoint of the study was met with an objective response rate of 69%.

Concept: Manageable toxicities over the long-term were demonstrated with this combination.

Impact: Further evaluation of this combination against imatinib alone for frontline treatment of GIST is necessary.

COMBINATION IMATINIB AND BINIMETINIB IS EFFICACIOUS IN TREATMENT-NAÏVE ADVANCED GIST

Gastrointestinal stromal tumors (GIST), one of the most common types of sarcoma, typically harbor activating mutations in *KIT* or *PDGFRA*. Imatinib, which targets both mutant KIT and PDGFRα, represents the first-line standard-of-care therapy for advanced GIST, but resistance continues to remain an issue with current subsequent therapies showing limited efficacy. As preclinical data have suggested binimetinib, a MEK inhibitor to target ETV1 protein stability, and imatinib are synergistic in inhibiting GIST tumor growth, Chi and colleagues conducted a phase II clinical trial to evaluate this combination in patients with treatment-naïve advanced GIST. Enrollment consisted of 50 patients with 42 of these being evaluable for efficacy. The first prespecified primary endpoint was met (>24 confirmed RECIST 1.1 partial response), with 69% being the best overall response rate. The median progression-free survival at data cutoff was 29.9 months, with 8 of the patients with locally advanced GIST achieving at least 70% pathologic response of their primary tumors, demonstrating a more robust treatment effect than conventional RECIST 1.1. Genetic analysis of patients who had progression of disease as compared to those who were denoted nonprogressors indicated an enrichment of *CDKN2A* inactivation in those with disease progression. Patients with disease progression also demonstrated emergent genomic alterations as compared to their matched pretreatment samples, and tumor mutational burden also increased in posttreatment samples of patients with disease progression. Investigation into the safety of this combination indicated manageable toxicities, with the most common grade 3 or 4 toxicities being asymptomatic creatine phosphokinase elevation, hypophosphatemia, decrease in neutrophils, anemia, and maculopapular rash. This study represents the first known trial of a tyrosine kinase inhibitor combination for frontline treatment of GIST and shows this combination is effective with manageable toxicities. Further evaluation of this combination strategy, especially in comparison to imatinib alone, for the treatment of advanced GIST is still required. ■

Chi P, Qin LX, Nguyen B, Kelly CM, D'Angelo SP, Dickson MA, et al. Phase II trial of imatinib plus binimetinib in patients with treatment-naïve advanced gastrointestinal stromal tumor. J Clin Oncol 2022 Jan 18 [Epub ahead of print].

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Breast Cancer

Major Finding: Tumor stroma properties distinguish ductal carcinoma *in situ* (DCIS) lesions of patients who relapse.

Concept: The transition from DCIS to invasive breast cancer involves coordinated changes in stromal structure.

Impact: This study suggests a protective role for myoepithelial disruption against invasive breast cancer.

STRUCTURE OF THE TUMOR STROMA PREDICTS INVASIVE BREAST CANCER RELAPSE

Accounting for 20% of new breast cancer diagnoses, ductal carcinoma *in situ* (DCIS) is a preinvasive breast malignancy localized within the breast duct and separated from the stroma by a layer of myoepithelial cells. Although many DCIS lesions may remain indolent, up to half of patients with DCIS develop invasive breast cancer (IBC) within 10 years if untreated. To understand factors that underlie the progression from DCIS to IBC, as well as features distinguishing DCIS lesions from patients who do and do not progress, Risom, Glass, Averbukh, and colleagues performed a high-dimensional analysis of tissue from a longitudinal cohort of patients with DCIS, consisting of normal breast tissue (n = 9), primary DCIS (n = 58), and IBC from subsequent relapse (n = 12). Multiplex ion beam imaging by time of flight (MIBI-TOF) enabled antibody-mediated visualization of 37 markers to distinguish epithelial, stromal, and immune cells and to demarcate epithelial, myoepithelial, and stromal compartments within the DCIS tumor microenvironment (TME). Assessment of spatial distribution and compartment morphology highlighted three clusters of TME parameters that uniquely enriched for normal, DCIS, or IBC samples, in addition to a fourth cluster specifically depleted in DCIS. Comparison of parameters within normal-, DCIS-, and IBC-enriched clusters suggested a coordinated shift in tumor, myoepithelial, and stromal cell function across disease stages. DCIS tumors displayed enhanced myoepithelial proliferation, as well as a distinct increase in stromal desmoplasia, a property not seen in IBC. Training a random forest classifier to predict DCIS lesions that will progress to IBC revealed myoepithelial phenotype and spatial distribution of immune cells as primary features that distinguished progressors from nonprogressors. Notably, whereas the myoepithelium of progressor DCIS resembled that of normal, nonprogressor DCIS exhibited myoepithelial breakdown, as evidenced by a thinner, less continuous structure. In summary, this comprehensive spatial imaging atlas of DCIS progression highlights coordinated changes in the TME and implicates a protective role of myoepithelial disruption in preventing invasive disease. ■

Risom T, Glass DR, Averbukh I, Liu CC, Baranski A, Kagel A, et al. Transition to invasive breast cancer is associated with progressive changes in the structure and composition of tumor stroma. Cell 2022;185:299–310.e.18.

doi: 10.1158/2159-8290.CD-RW2022-014

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