Clinical Trials

Major Finding: The small-molecule tyrosine kinase inhibitor tucatinib outperformed placebo against brain metastases.

Concept: Adding tucatinib to trastuzumab plus capecitabine extended overall survival by more than six months.

Impact: Although exploratory, this work shows the promise of tucatinib for brain-metastatic HER2$^+$ disease.

TUCATINIB IS ACTIVE AGAINST BRAIN METASTASES IN HER2$^+$ BREAST CANCER

Brain metastases, which arise in half of patients with metastatic HER2-positive breast cancer, are difficult to treat and a major cause of mortality. Lin and colleagues conducted exploratory analyses on a subset of data from the randomized, controlled, double-blinded HER2CLIMB trial, specifically focusing their investigation on the utility of the small-molecule oral tyrosine kinase inhibitor tucatinib in patients with brain-metastatic HER2-positive breast cancer. Among the 612 patients enrolled in the HER2CLIMB trial, 291 (48%) had brain metastases or a history of brain metastases; these 291 patients were the subject of this work. Most of these patients (87.3%) had undergone prior treatment for their brain metastases, including surgery and/or whole-brain or targeted radiation therapy. With regard to overall survival (OS), the results in the tucatinib arm (tucatinib plus the HER2 antibody trastuzumab and the cytotoxic chemotherapy drug capecitabine) were superior to those in the control arm (placebo plus trastuzumab and capecitabine), with median OS values of 18.1 months in the tucatinib group and 12.0 months in the control group. Importantly, the survival benefit of tucatinib was mostly seen in the 174 patients with active brain metastases, in whom the median OS was 20.7 months with tucatinib versus 11.6 months with placebo; in the 117 patients with stable brain metastases, the median OS was 15.7 months with tucatinib versus 13.6 months with placebo. However, tucatinib showed signs of central nervous system (CNS) activity in both groups, with CNS progression-free survival being 9.9 months with tucatinib versus 4.2 months with placebo among all patients, 9.5 months versus 4.1 months among patients with active brain metastases, and 13.9 months versus 5.6 months in patients with stable brain metastases. Although limited by its exploratory nature, this analysis supports the notion that tucatinib is an agent of interest in specifically treating brain metastases in patients with HER2-positive breast cancer, a topic worth investigating prospectively in future trials. ■

Lin NU, Borges V, Anders C, Murthy RK, Paplomata E, Hamilton E, et al. Intracranial efficacy and survival with tucatinib plus trastuzumab and capecitabine for previously treated HER2-positive breast cancer with brain metastases in the HER2CLIMB trial. Jour Clin Oncol 2020 May 29 [Epub ahead of print].

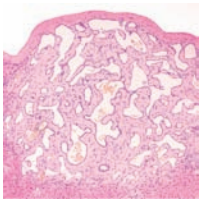
Mutations

Major Finding: Gain-of-function variants of the E3 ubiquitin ligase WWP1 increased cancer susceptibility.

Mechanism: WWP1 activation led to ubiquitination and consequent inactivation of the tumor suppressor PTEN.

Impact: This study underscores how work on hereditary cancer syndromes can lead to generalizable insights.

WWP1 GAIN-OF-FUNCTION VARIANTS INACTIVATE PTEN TO RAISE CANCER RISK



Germline mutations in the tumor-suppressor gene *PTEN* are found in only 25% of patients with *PTEN* hamartoma tumor syndrome (PHTS), a cluster of conditions including hereditary cancer-predisposition syndromes such as Cowden syndrome, raising the question of what causes PHTS in patients with wild-type (WT) *PTEN*. Based on their recent work showing that activation of the E3 ubiquitin ligase WWP1 inhibits PTEN and promotes tumorigenesis, Lee, Yehia, and colleagues conducted a prospective cohort study involving 431 *PTEN*-WT patients with Cowden syndrome or Cowden-like syndromes. Whole-exome sequencing revealed that one proband with Cowden-like syndrome presenting with gastrointestinal oligopolyposis and a family history of early-onset colon cancer had a mutation in *WWP1* that substituted a highly evolutionarily conserved lysine residue with an asparagine residue, and investigation of the proband's family showed that two other affected family members shared the variant, whereas three unaffected family members were WT for *WWP1*. An analysis of 249 patients with similar phenotypes (i.e., predominantly characterized by gastrointestinal oligopolyposis) and WT *PTEN* identified five patients, all unrelated to the first-noted proband, who also had *WWP1* mutations. Probing data from The Cancer Genome Atlas revealed that *WWP1* variants predicted to be deleterious also occurred in sporadic cancers. Notably, germline *WWP1* variants were more common than germline variants of some classic colon cancer–susceptibility genes, such as *PTEN* and *MSH6*. The fact that most of the predicted damaging variants occurred within the catalytic HECT domain led to the hypothesis that they might hyperactivate WWP1, leading to excessive PTEN ubiquitination and consequent suppression of function. Consistent with this notion, these variants were demonstrated to cause gain of function of WWP1, leading to increased PTEN polyubiquitination and reduced PTEN dimerization or oligomerization. This gain of function appeared to be due to disruption of interactions between the HECT domain and the WW2–WW3 linker region. Finally, mouse xenograft experiments confirmed the relevance of these findings *in vivo*. This work provides mechanistic insight into *WWP1* as a cancer-susceptibility gene in hereditary cancer syndromes and sporadic cancers, uncovering a new pathway for research. ■

Lee YR, Yehia L, Kishikawa T, Ni Y, Leach B, Zhang J, et al. WWP1 gain-of-function inactivation of PTEN in cancer predisposition. N Engl J Med 2020;382:2103–16.