Clinical Trials

Major Finding: The FGFR2b inhibitor bemarituzumab was effective in FGFR2b-high gastroesophageal adenocarcinoma.

Approach: This phase I trial stratified patients with advanced-stage disease by FGFR2b expression level.

Impact: Bemarituzumab warrants further study and is being tested with chemotherapy in a first-line setting.

BEMARITUZUMAB IS ACTIVE IN FGFR2B-HIGH GASTROESOPHAGEAL ADENOCARCINOMA

Overexpression of FGFR2b, an FGFR2 splice variant, occurs in some gastroesophageal adenocarcinomas (GEA) as a result of amplification or upregulation of *FGFR2*. Catenacci and colleagues conducted a phase I, open-label clinical trial of bemarituzumab, a first-in-class humanized afucosylated IgG1 monoclonal antibody to FGFR2b, in 79 patients with advanced solid tumors. The trial was divided into three parts: part 1a, a dose-escalation study including 19 patients with recurrent solid tumors of a variety of types; part 1b, a dose-escalation study including eight patients with advanced-stage GEA; and part 2, a dose-expansion study including 52 patients with advanced-stage GEA or bladder cancer stratified by FGFR2b expression level. Bemarituzumab was generally well tolerated, with no patients exhibiting dose-limiting toxicities; however, serious ocular adverse events (ulcerative keratitis, limbal stem-cell deficiency, or corneal dystrophy) occurred in three patients (3.8%) and low-grade ocular side effects occurred in 23 patients (29.1%). Ocular side effects may be attributable to inhibition of FGF10, which is involved in healing of the corneal epithelium. The objective response rate in the 52 patients in the dose-expansion study (part 2 of the trial) was best in patients with GEA with high FGFR2b overexpression, all with *FGFR2* amplification, with 17.9% of patients exhibiting an objective partial response over a median duration of 12.6 weeks. In contrast, no patients with low FGFR2b expression responded to bemarituzumab, nor did any patients with bladder cancer. This study indicates that bemarituzumab has single-agent antitumor activity as a late-line therapy in advanced-stage GEA overexpressing FGFR2b, a finding warranting further study. The authors also recently reported safety of bemarituzumab in combination with oxaliplatin, fluorouracil, and leucovorin (mFOLFOX6) chemotherapy. Given these findings, and because only approximately 50% of patients proceed to second-line therapy and 30% to third-line therapy due to declining performance status, bemarituzumab is now being investigated in combination with mFOLFOX6 in newly diagnosed advanced-stage GEA in a phase III clinical trial, underscoring the potential utility of bemarituzumab in this disease. ■

Catenacci DVT, Rasco D, Lee J, Rha SY, Lee KW, Bang YJ, et al. Phase I escalation and expansion study of bemarituzumab (FPA144) in patients with advanced solid tumors and FGFR2b-selected gastroesophageal adenocarcinoma. J Clin Oncol 2020 Mar 13 [Epub ahead of print].

Metastasis

Major Finding: In lung cancer, brain metastasis was associated with somatic amplification of *MYC*, *YAP1*, or *MMP13*.

Concept: Overexpression of any of these genes in mouse xenograft models increased brain metastasis.

Impact: This work identified metastasis contributors using methods that could be applied to other cancers.

SOMATIC COPY-NUMBER ALTERATIONS CONTRIBUTE TO BRAIN METASTASIS

Somatic mutations are known to contribute to the formation of primary tumors, but whether they are involved in the development of brain metastases, a major cause of mortality in lung adenocarcinoma, is not known. To investigate this, Shih, Nayyar, and colleagues used a case–control approach, evaluating somatic copy-number alterations in patients with brain-metastatic lung adenocarcinoma versus those with primary lung adenocarcinoma. Analysis of whole-exome sequencing data from the two patient cohorts revealed evidence of positive selection for homozygous deletion of a genomic region containing *CDKN2A/B* as well as amplification of multiple regions—including one containing the proto-oncogene *MYC* and another containing the Hippo-pathway gene *YAP1* and the metalloproteinase-encoding gene *MMP13*—in the cohort with brain-metastatic disease. Interestingly, *YAP1* amplification was not observed in cases harboring oncogenic *KRAS* mutations, providing further evidence supporting the prior finding that YAP1 overexpression can replace KRAS activity in KRAS-dependent lung cancer cells. Sequencing of matched primary tumors and brain metastases supplied further confirmation of the contribution of positive selection for amplification of the candidate drivers *MYC*, *YAP1*, and *MMP13* to brain metastasis. Finally, in xenograft mouse models of lung adenocarcinoma metastasis, overexpression of *MYC*, *YAP1*, or *MMP13* substantially increased the incidence of brain metastasis without increasing total tumor burden, indicating the functional relevance of the amplification of these genes observed in patients with brain-metastatic disease. Together, these results nominate *MYC*, *YAP1*, and *MMP13* amplifications as drivers of brain metastasis in lung adenocarcinoma, providing the basis for further research on the prevention and treatment of this often fatal complication. Additionally, this study demonstrates that large-scale genomic analysis is a useful strategy to uncover contributors to metastasis. ■

Shih DJH, Nayyar N, Bihun I, Dagogo-Jack I, Gill CM, Aquilanti E, et al. Genomic characterization of human brain metastases identifies drivers of metastatic lung adenocarcinoma. Nat Genet 2020;52:371–7.