CLINICAL UPDATE

Current Developments in the Management of Solid Tumors

The Role of LGR5 in Epithelial Cancer

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H&O What are the limitations of current treatments for epithelial cancer?

JYB Epithelial cancer, which affects the cells that line the organs, includes colorectal cancer, head and neck cancer, and non–small cell lung cancer. In the head and neck space, the major treatment options are immunotherapy agents, epithelial growth factor receptor (EGFR)–targeting agents, cytotoxic chemotherapy, radiation therapy, and surgery. Despite the availability of multiple treatment approaches, the rates of recurrence, treatment resistance, and metastasis are high in patients with epithelial cancers. Together, these cancers cause approximately 200,000 deaths per year.[1]

H&O How does epithelial cancer become resistant to EGFR inhibitors?

JYB EGFR overexpression is common in epithelial cancer. Several EGFR inhibitors are approved for use in these patients, although they are often limited to those who do not have *KRAS* or *NRAS* mutations. Cetuximab (Erbitux, Lilly) is approved for use in EGFR-positive head and neck cancer, cetuximab or panitumumab (Vectibix, Amgen) is used for EGFR-positive colorectal cancer, and osimertinib (Tagrisso, AstraZeneca) is used for EGFR-positive lung cancer. Although the efficacy rates of these agents are high at first, resistance almost invariably develops through several known mechanisms. First, mutations in *EGFR* interfere with the ability of EGFR inhibitors to bind to the target site. Second, mutations affecting the downstream pathways of RAS and PI3K activate routes by which cancerous cells can bypass the EGFR pathway. Third, the plasticity of some cancerous epithelial cells allows them to transform into mesenchymal cells. The transformation causes the cells to lose normal epithelial traits, such as cell-to-cell-adhesion, and acquire mesenchymal traits, such as motility, that help them evade targeted therapy. As a result, the tumors tend to grow, become resistant to treatment, and metastasize. Cells in epithelial tissue that exhibit plasticity express leucine-rich repeat-containing G protein-coupled receptor 5 (LGR5).

> In epithelial cancer, however, cells that express LGR5 multiply far faster than normal cells, most likely because of mutations that activate stem cell signaling.

H&O Could you define LGR5?

JYB LGR5 is an epithelial stem cell receptor involved in signaling and proliferation, acting as a pathway for cells to switch between an epithelial and a mesenchymal state. If we think of the colon, for example, the cells that express LGR5 are found in the basal crypts within the lining of the colon. These cells are supposed to lose their LGR5 expression when they emerge from the crypts as the lining of the

mucosa is sloughed off during food digestion. Conversely, cellular LGR5 expression is restored if a cell that has lost LGR5 expression returns to the crypt.

H&O What does LGR5 do, and what makes it relevant in cancer?

JYB In a cancerous state, the epithelial cells express LGR5 regardless of their location, and they continue to multiply and differentiate. LGR5-positive cells normally make up just a small population of cells in the crypts. In epithelial cancer, however, cells that express LGR5 multiply far faster than normal cells, most likely because of mutations that activate stem cell signaling. As a result, the proportion of LGR5-positive cells increases dramatically.

LGR5 is also a receptor for secreted R-spondin proteins, which function as stem cell growth factors by making WNT signaling more powerful. LGR5 lies upstream of the WNT/β-catenin signaling pathway that is involved in the progression of several human cancers affecting the epithelium. The presence of LGR5 increases levels of β-catenin, accelerating WNT signaling. WNT targets genes that drive tumor proliferation, treatment resistance, and metastasis.

H&O What is the relationship between LGR5 expression and cancer outcomes?

JYB In colorectal cancer, LGR5 overexpression has been associated with a 30% reduction in 1-year disease-free survival, a 3-fold increase in liver metastases,[2] and a 3-fold increase in disease recurrence at 5 years.[3] In head and neck cancer, LGR5 overexpression has been associated with a trend toward relatively poor overall survival.[4] In lung cancer, LGR5 overexpression has been associated with cancerous rather than normal tissue.[5] For multiple reasons, blocking LGR5 is a logical way to treat epithelial cancers.

We do not have an antibody test for LGR5; the studies that have been conducted thus far rely on mRNA expression.

H&O What is the relationship between EGFR and LGR5?

JYB In general, EGFR and LGR5 have an opposing regulatory relationship. Inhibiting EGFR increases LGR5 expression, as has been shown in laboratory studies.[6,7] The upregulation of LGR5 is one of the factors in therapy resistance that is being actively researched as a target of therapy.

H&O What agents are being developed to target LGR5?

JYB The bispecific antibody petosemtamab (MCLA-158), which binds to both EGFR and LGR5, is currently in development. A recent phase 2 study looked at a combination of petosemtamab and the programmed death 1 (PD-1) inhibitor pembrolizumab (Keytruda, Merck) as first-line treatment for recurrent or metastatic programmed death ligand 1 (PD-L1)–positive head and neck squamous cell carcinoma (HNSCC). A poster presentation at the 2025 American Society of Clinical Oncology Annual Meeting noted that treated patients had an objective response rate of 63%, with responses across subgroups of human papillomavirus status and PD-L1 combined positive score.[8] The median progression-free survival was 9 months, the median overall survival was not reached, and the 12-month overall survival rate was 79%. Grade 3 or higher treatment-emergent adverse events occurred in 60% of patients; grade 3 or higher asthenia, acneiform rash, decreased blood magnesium, and diarrhea each occurred in 7% of patients. Grade 3 infusion-related reactions occurred in 7% of patients; all of these were able to be resolved. The head and neck world is very excited about these results. Having a new way to target LGR5 is very encouraging, and we look forward to the results of the ongoing phase 3 trial. We also hope to see these results extend to colorectal cancer and lung cancer.

H&O What other research is being conducted?

JYB The randomized, open-label phase 3 LiGeR-HN1 trial is evaluating petosemtamab in combination with pembrolizumab as first-line therapy in recurrent or metastatic PD-L1–positive HNSCC (NCT06525220). The planned enrollment is 500 patients.

Another randomized, open-label phase 3 trial, called LiGeR-HN2, is looking to evaluate monotherapy with petosemtamab vs investigator's choice of agent as second- or third-line therapy in recurrent or metastatic HNSCC (NCT064961780). This trial also has a planned enrollment of 500 patients.

In addition, an open-label phase 1/2 study is looking to establish the recommended dose of petosemtamab in patients with metastatic colorectal cancer and will further evaluate the agent in both HNSCC and metastatic colorectal cancer (NCT03526835). This trial plans to enroll more than 500 patients.

Antibody-drug conjugates (ADCs) that target LGR5 are being developed in vitro, and I would not be surprised to see clinical trials in the next year or two examine the use of anti-LGR5 ADCs in epithelial cancer. I am a big fan of ADCs, and I like the idea of combining LGR5 targeting with a cytotoxic payload.

A phase 1/2 study is looking at CNA3103, which is a chimeric antigen receptor (CAR) T-cell treatment to

target LGR5 in patients with metastatic colorectal cancer (NCT05759728).

Disclosures

Dr Bruce has served on the scientific advisory boards of Merus, Kura Oncology, Lilly, Coherus Oncology, Fulgent, and GSK and has served on the data and safety monitoring board of Kura Oncology.

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