Targeting Insulin-Like Growth Factor 1-Receptor (IGF-1R) in Cancer

In addition to several molecular targets that have been well studied for several years, such as the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF), new targets are emerging as potentially fruitful approaches to combating cancer. One of these is the insulin-like growth factor receptor, or IGF-1R.

IGF-1R is involved in the process of transforming a normal cell into a cancer cell when certain cancer trigger genes, called oncogenes, are activated. Activation of this receptor sets off a complex cascade of effects that promotes tumor survival and growth. There have also been studies that have demonstrated elevated blood levels of IGF in patients with several kinds of cancer. Tumors also tend to express high levels of IGF compared with normal tissues.

There are several antibodies to IGF-1R that are currently in clinical testing, although they are still early enough that they only have number and letter codes only. Among the ones that are being evaluated now in patients are IMC-A12, CP-751871, AMG-479, BIIB022, and R 1507 (catchy names, huh?). In addition to blocking the activity of IGF-1R in test tube models, these agents have also been studied in animal models in which these agents lower the growth rate or shrink various types of cancer.

I won’t go through all of these in terms of their clinical trial data thus far, but I’ll introduce a couple. IMC A12, from Imclone, is an antibody that has been studied in early patient trials and appears to be well tolerated on a weekly basis (abstract here). The most common side effect is high blood sugar levels, although this wasn’t commonly serious, and the investigators didn’t reach a “maximum tolerated dose”. As a single agent, there were no objective responses.
seen, but several patients with a range of cancer types had prolonged stable disease. Further trials are ongoing.

Another agent that targets IGF-1R and has been studied specifically in lung cancer is CP-751871 from Pfizer, which was included in a trial presented by Karp and colleagues at ASCO last year (abstract here). This was a phase II randomized trial in which 2/3 of the patients with previously untreated advanced NSCLC were randomized to standard chemo (carbo/taxol) along with the study drug, and the other 1/3 received standard chemo only, although they could cross over to the study drug after progression or if they didn’t respond to chemo alone. These investigators also saw high blood sugar levels (hyperglycemia), including serious (grade 4) hyperglycemia in 10% of patients. But they saw an encouragingly higher response rate among patients who received the IGF-1R blocker in combination with chemo (46% vs. 32%). Particularly impressive was the 71% response rate among patients with squamous NSCLC, although we’re talking about small numbers here. Based on these findings, Pfizer is developing a phase III trial in which patients with advanced non-adenocarcinoma (including squamous, large cell, and the combination of adenosquamous) NSCLC will be randomized to first line carbo/taxol with or without CP-751871, looking for a significant improvement in overall survival (information here, trial not yet open).

These agents are still pretty early in development, but we’ll likely be hearing more about them in coming years. It will be especially gratifying if it turns out that CP-751871 and/or other IGF-1R-targeted antibodies are effective in patients with squamous NSCLC, since much of the work in NSCLC in the last few years has focused on alternatives for patients with adenocarcinomas or non-squamous tumors, so it would be nice to have something to discuss other than treatments we can’t use for patients with squamous NSCLC tumors.