# Anticancer IGF1R classes take more knocks

Disappointing developments with Amgen's ganitumab and Bristol-Myers Squibb's BMS-754807 highlight the need for rational combinations and predictive biomarkers to rescue IGF1R pathway antagonists.

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Insulin-like growth factor 1 receptor (IGF1R) antagonists roared into the clinic over 10 years ago, with high expectations that inhibitors of the mitogenic, pro-invasive and anti-apoptotic receptor would find use in various cancers. In the latest of several blows to the drug class, clinicians have reported that Amgen's IGF1R-targeting monoclonal antibody (mAb) ganitumab (AMG 479) worsened overall survival in a Phase II trial in patients with postmenopausal oestrogen receptor (ER)-positive breast cancer who were previously treated with endocrine therapy (*Lancet Oncol.* **14**, 228–235; 2013).

This failure follows a slew of setbacks for the IGF1R-targeted therapies. Although Amgen is continuing ongoing trials with ganitumab, it is no longer planning new ones since a recent failure of its Phase III pancreatic cancer trial. Pfizer, Roche and Sanofi-Aventis have also stopped IGF1R-specific mAb programmes in recent years.

Some experts hold out hope that small-molecule tyrosine kinase inhibitors (TKIs) that target both IGF1R and the closely related insulin receptor will yield better results. (Many experts believe that the IGF ligands that bind IGF1R can also activate the insulin receptor to promote tumour growth — a proposed mechanism of resistance to the mAbs.) But expectations here have also been dampened recently, with Bristol-Myers Squibb halting enrolment into trials of its BMS-754807, one of the most advanced IGF1R TKIs.

Still, at least six firms are persevering with IGF1R-targeted mAbs, TKIs or IGF-ligand-targeted mAbs — another approach to inhibiting both IGF1R and insulin receptor activity.

"There is no consensus whether available data should be used to justify abandoning the IGF target or to justify more work to discover rational combinations and predictive biomarkers," says Michael Pollak of McGill University in Montreal, Canada. "Further research in this area is high-risk, but not necessarily higher-risk than any other research into targeted therapies in oncology."

## Next steps?

Many experts believe that the biggest issue for IGF1R inhibitors has been lack of efficacy, driven by a lack of predictive biomarkers. "All of the clinical trials shared the characteristic that they were testing a very optimistic hypothesis — that the drugs would be useful in unselected patients," says Pollak. "But in general, most approved targeted therapies have been ineffective when evaluated in unselected patients."

In Amgen's failed trial of ganitumab in breast cancer, the obvious potential biomarker candidate of tumour expression of IGF1R was not even measured at the time of enrolment. And preclinical and clinical studies have shown reduced IGF1R expression in breast tumours after they developed resistance to the endocrine therapy tamoxifen, providing a possible explanation for the trial's failure.

Mary Jo Fidler of Rush University Medical Center in Chicago, Illinois, USA, notes, however, that IGF1R expression on its own may not provide a strong predictive biomarker, given that the IGF pathway comprises multiple ligands and binding proteins. "The molecular pathology that may drive certain tumours is overexpression of the IGF ligands," Pollak adds. He and others have proposed tumour production of IGF ligands, which may indicate addiction to autocrine IGF signalling, as a potential biomarker.

Even if blocking IGF signalling can result in anticancer activity, the most effective way to shut down the pathway is not known. IGF1R mAbs can induce compensatory regulatory endocrine mechanisms that can lead to supraphysiological levels of IGF1 and rises in blood insulin levels, both of which may activate insulin receptors that are not blocked by the mAbs. This signalling might counteract some of the mAbs' benefits and even cause harm, says Douglas Yee of the Masonic Cancer Center at the University of Minnesota, Minneapolis, USA.

One way to partially overcome this potential mechanism of resistance could be to use the standard antidiabetic agent metformin, which lowers insulin levels, in combination with IGF1R-specific mAbs, says Yee. The Foundation for the National Institutes of Health's I-SPY 2 trial in neoadjuvant breast cancer is testing the ganitumab plus metformin combination.

A second strategy is to combine an IGF1R-specific mAb with an inhibitor of mammalian target of rapamycin (mTOR), as mTOR may be required for insulin receptor-mediated stimulation of tumour growth. IGF1R signalling is also a candidate mediator of resistance to mTOR inhibitors. Merck is testing its experimental mTOR inhibitor ridaforolimus in combination with its dalotuzumab, one of the few remaining IGF1R-targeting mAbs in clinical development.

Another way to minimize insulin receptor stimulation is to use IGF1R TKIs or mAbs targeting the IGF ligands. Although the receptor TKIs have hit a road bump with Bristol-Myers Squibb's decision not to pursue registration of BMS-754807, mAbs targeting the IGF ligands may fare better. MedImmune's MEDI-573 and Boehringer Ingelheim's BI 836845 block IGF-mediated stimulation of IGF1R and of insulin receptor A, which may be upregulated by tumour cells when IGF1R is inhibited. And unlike the receptor TKIs the IGF ligand mAbs do not block insulin receptor B from binding to insulin and so do not interfere with glucose metabolism. MEDI-573, currently in a Phase II trial in ER-positive breast cancer, has not as yet induced hyperglycaemia or upregulation of insulin — side effects seen with the other pathway inhibitors.

Finally, the field is working to harness its knowledge of mechanisms of resistance to IGF1R therapies besides that of the insulin receptor pathway to develop rational combinations. These include targeting other receptors, such as epidermal growth factor receptor (EGFR) and the ER, as well as downstream pathway components.

Activating mutations in phosphoinositide 3-kinase (PI3K), downstream of IGF1R, for example, might confer resistance to IGF1R inhibitors. Combining a PI3K inhibitor with an IGF1R inhibitor might circumvent this mechanism of resistance and also block other oncogenic pathways downstream of IGF1R. Novartis is running a Phase I/II trial of its experimental PI3K inhibitor BYL719 plus ganitumab in PIK3CA (PI3Kα catalytic subunit)-mutated or amplified solid tumours.

"[The IGF1R pathway] is turning out to be more complex than what was initially thought," concludes Fidler. "We need to pause and reevaluate the science before conducting further large Phase III trials."