

July 2009 Clinical Trials Update

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In this month's Clinical Trials Bulletin we highlight a new class of drugs that target Insulin-like Growth Factor 1 Receptor (IGF-1R). IGF-1R is a tyrosine kinase that, much like KIT, protrudes through the cell surface and begins to signal when an extracellular Insulin Growth Factor (IGF1) attaches to the outside portion of the receptor. Unlike KIT, IGF-1R has not been found to be mutated in GIST. However, IGF-1R has been found to be over-expressed in wild-type GIST tumor tissue. Up to now, KIT inhibitors have had limited impact in wild type GIST. IGF-1R is now viewed as a component of a potential "side channel" providing an alternative signaling path to KIT and potentially a target in GIST.

In experiments with wildtype GIST cells, researchers at Fox Chase Cancer

Center have demonstrated the ability to slow cell growth with both IGF-1R inhibitors and combinations of IGF-1R and KIT inhibitors. These promising results are leading to new trial designs specifically for GIST patients.

IGF-1R inhibitors are a very active area of drug development. We have identified over a dozen compounds both in the lab and in early clinical trials. Many are in trials that are open to solid tumors or advanced malignancies and should accept GIST patients.

As with all Phase I trials, the trial objective is to determine a safe dosage and to document safety issues. Efficacy is not determined until phase II or III. Patients entering phase I are not guaranteed a therapeutic dosage nor is there an easy way of measuring all the risks. However, for those experiencing resistance or uncontrollable growth, Phase I trials provide an option until the new GIST-specific trials, such as the planned NIH

trial, are on-line.

IGF-1R inhibitors are of two types: small molecule and monoclonal-antibodies.

Small molecule inhibitors work in much the same way as Imatinib or Sunitinib work against KIT. They block the IGF-1R molecule usually at a signaling point inside the cell.

Monoclonal antibodies work by binding to the IGF-1R protein portion outside the cell and thereby prevent the IGF1 ligand from binding to the receptor and initiating the tyrosine kinase signaling process.

Both methods can effectively stop IGF-1R signaling. Monoclonal antibodies tend to be more specific to their targets.

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The Life Raft Group

Who are we, what do we do?

The Life Raft Group (LRG) directs research to find a cure for a rare cancer and help those affected through support and advocacy until we do.

The LRG provides support, information and assistance to patients and families with Gastrointestinal Stromal Tumor (GIST). The LRG achieves this by providing an online community for patients and caregivers, supporting local in-person meetings, patient education through monthly newsletters and webcasts, one-on-one patient consultations, and most importantly, managing a major research project to find the cure for GIST.

Disclaimer

We are patients and caregivers, not doctors. Information shared is not a substitute for discussion with your doctor. For the very latest information, see the LRG Clinical Trials database at: http://liferaftgroup.org/treat_trials.html.

Insulin-like Growth Factor Receptor signaling



