Heat Shock Protein Inhibition as an Anti-Cancer Treatment

There’s a new class of anti-cancer drugs that are being studied, including in lung cancer, known as heat shock proteins, or HSPs. These are sometimes referred to as “stress proteins” because they can be induced to be generated in higher concentrations in response to stresses like heat, cold, low oxygen levels, etc. But HSPs are also present in cells in the absence of significant environmental stress, just as a normal component of the cellular contents. They work as a chaperone protein, alongside of other proteins to ensure that those proteins are in the right shape, which is required to have proteins function properly, as well as the right place when needed. In the context of cancer, HSPs can also assist in the cancer-promoting activities of a wide range of several “client” oncogenic (cancer-inducing) proteins. So inhibiting HSPs, such as one designated HSP-90, is a potential novel mechanism for interfering with the activities of these critical proteins and the overall function of cancer cells.

One such agent that is working its way through clinical testing is IPI-504, from Infinity Pharmaceuticals, the subject of a recent press release. The announcement and another preceding one note that the recent report of phase I work with IPI-504, an IV agent, was associated with stable disease in 7 of 9 patients at the time of first repeat CT evaluation. In addition, two of four patients who happened to have undergone a PET scan on repeat follow-up had a partial response based on European criteria, although it should be noted that PET scanning to assess response is not a standard practice and isn’t anything close to being as established as a CT scan to assess response.

Interestingly, some preclinical work in cell line suggests that the activating mutations of EGFR depend on the HSP-90 protein for stability and that IPI-504 may (bolded and italicized) be useful in EGFR-resistant populations (abstract here). For instance, the T790M mutation is one that has been found in approximately half of the prior EGFR mutation responders to iressa or tarceva once they show progression on these agents, and preclinical lab work suggests that IPI-504 may reverse that proces. However, that’s not human work. But it does lead us to the hypothesis that this agent may be useful in patients who have become resistant to EGFR tyrosine kinase inhibitors despite a mutation.

The new phase II clinical trial with IPI-504 will enroll 20 patients with advanced NSCLC who previously received an EGFR inhibitor, and this group will be equally divided between those with a known activating EGFR mutation and those with a normal or “wildtype” non-mutated EGFR target (the kind we don’t associate with special sensitivity to drugs like tarceva). If responses are seen using the more typical CT-based response assessment criteria for trials, they’ll plan to enroll 19 additional patients on the cohort(s) in which some convincing evidence of activity is seen. The schedule for treatment will be weekly IV administration for two consecutive weeks, followed by a week off, for each cycle this schedule was tested in another phase I trial). According to the press release, this particular trial is now open at Mount Sinai Comprehensive Cancer Center in Miami Beach, FL, and at Yale Cancer Center in New Haven, CT, with some other sites coming on board.

This isn’t the only heat shock protein inhibitor being evaluated, but it may well be one of the
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first ones for which we get some clinical data in lung cancer. I'll give updates when new trials are opening up. In the meantime, HSP inhibitors represent an intriguing avenue for targeted therapy in lung cancer that we'll hear more about in coming years.