EGFR Mutations Demystified

It has become a common topic of conversation on this site (and in the lung cancer community at large) to discuss mutations in the epidermal growth factor receptor (EGFR). However, since we frequently throw out the terms “deletion 19 mutation”, “L858R”, and “T790M”, I thought it would be worthwhile to explain a little bit about the different EGFR mutations and what we know about their clinical significance.

The history and significance of EGFR mutations has been covered quite well in previous posts here, but I’ll provide my own quick synopsis, from the perspective of someone working in Boston during the time this work was being done. In the early 2000s the EGFR tyrosine kinase inhibitors (TKIs) Iressa (gefitinib) and Tarceva (erlotinib) were tested in large numbers of patients with non-small cell lung cancer. It was known the EGFR was an important target in lung cancer, since most NSCLC tumors express it and high levels of expression were associated with a worse prognosis, and the results of numerous trials testing these drugs in unselected patients were modestly positive. In a phase III trial, Iressa did not improve overall survival compared to placebo treatment in previously treated NSCLC patients (leading to the death of this drug in the USA), but the similar BR.21 trial (testing Tarceva rather than Iressa) did show a modest (~2 month) improvement in overall survival in previously treated NSCLC patients. This led to the approval of Tarceva in all NSCLC patients who had failed one or two prior chemotherapy regimens.

However, what was immediately evident from these and earlier trials, was that about 10% of Western patients treated with either of these drugs had dramatic and sometimes long-lasting responses. When they looked at who these people were, they found that most were women, all had adenocarcinoma (or BAC, a type of adenocarcinoma), many were Asian ethnicity, and most had either never smoked or smoked very little compared to average NSCLC patients. In 2004, investigators at the Dana Farber Cancer Institute and at Massachusetts General Hospital in Boston, and also at Memorial Sloan Kettering Cancer Center in NYC, simultaneously published results showing that most of these “dramatic responders” had specific mutations in the tyrosine kinase (TK) domain of the EGFR gene. The EGFR protein sits in the cell membrane and straddles the inside and outside of the cell.
The TK is the part of the protein, located inside the cell, which “switches on” when a growth factor (or ligand) from outside the cell binds to the outside portion of the EGFR. This switch, when flipped on, allows the EGFR to signal the cell to grow and survive. In the NSCLC patients who have mutations in the TK domain of the EGFR, very little growth factor is needed to flip on the switch, and once turned on the cancer cell is driven to grow and divide essentially through this one signal. This makes the cancer cell exquisitely sensitive to dying when the switch is turned off by a drug like Iressa or Tarceva and explains why some patients can do so well on these drugs.

However, there was controversy for many years about the true significance of these mutations, which have only recently been resolved. Investigators from the BR.21 trial looked at the tumor samples from the patients on the trial (there were relatively few available) and tested them for EGFR mutations to see if the patients with mutations lived longer when treated with Tarceva than placebo. When they published that they were unable to detect any survival benefit in the mutant patients, this threw a wrench in the concept of the importance of mutations that only recently has been corrected. The problem with their analysis, not completely understood at that time, was that all EGFR mutations are not the same and most of the ones they found were not important ones. The EGFR gene has 28 exons (parts of the DNA that serve as the blueprint for the EGFR protein), and exons 18 through 21 code for the TK part of the receptor. There can be mutations anywhere in the TK domain, but only some of them confer sensitivity to the TKIs!
About 45% of sensitizing mutations are what are called in frame deletions in exon 19, making them the most common EGFR mutations. Deletion mutations result when short segments of the DNA are removed (deleted) from the DNA, but without interrupting the blueprint. To use an
analogy: in this house, the light switch was deleted from the blueprint, so that the completed house always has the lights on with no way to switch them off.

About 40-45% of the sensitizing mutations are point mutations in exon 21, the most common being L858R (At the “point” in the 858th position, the normal amino acid leucine (L) is switched out for an arginine (R), which changes the protein function). In THIS house, the light switch looks like it is there but has actually been traded for a switch that can’t be turned off. When we talk about “EGFR mutant patients” in other posts, we are by and large talking about the patients with deletion 19 and L858R mutations.

Most of the remaining mutations don’t cause the EGFR to be sensitive to EGFR TKIs, but more importantly some of them do turn on the EGFR and drive the cancer cell to grow, but actually prevent the TKIs from working, a phenomenon known as resistance. The most important of these is the T790M, a point mutation in exon 20 resulting in the substitution of methionine (M) for threonine (T). This mutation seems to allow the EGFR TK to work much better than normal, so that the TKI no longer has an advantage in binding over the normal ligand, something called ATP.

Mutations (usually in this case called insertion mutations) in exon 20 have also been associated with resistance. The significance of these goes further. We now have evidence that the exon 19 deletion mutations tend to be associated with a higher chance of responding to the TKIs, and that patients with these mutations may live significantly longer than patients with the L858R mutations. This is probably due to differences in how well the TKIs are able to inhibit EGFR signaling in the two types of mutant EGFR proteins.

In conclusion, EGFR mutations are not all created equal and do not all have the same significance. The ones we care about as indicators for using drugs like Tarceva are the deletion 19 mutations and exon 21 point mutations (i.e. L858R), and the one that is most frequently associated with resistance to TKIs is the T790M in exon 20. This is a lot to throw into a short post, so please ask questions in comments if this isn’t clear!