Afatinib, newly christened Gilotrif, is the newest EGFR tyrosine kinase inhibitor (TKI) approved by the FDA, specifically for patients with an EGFR mutation as first line therapy. As an irreversible inhibitor of the family of receptors in which EGFR is a member, there’s a theoretical appeal that it may be more effective than reversible EGFR inhibitors (which attach to and then come off of the EGFR receptor) that are currently available, namely Tarceva (erlotinib) and/or Iressa (gefitinib), depending on where you are in the world. But what role does it play in the current lung cancer landscape? Sadly, I must confess that I don’t think it has demonstrated any incremental benefit over the EGFR inhibitors we’ve had available for years. The best evidence I can see is that Gilotrif is a more toxic version of these already available agents.

Afatinib was approved by the FDA based on the results of the LUX Lung-3 trial, which demonstrated that afatinib compared with cisplatin/Alimta (pemetrexed) led to a significantly superior response rate (56.1% vs. 22.6%, P<0.001), and 60.8% in patients with the more common exon 19 and 21 EGFR mutations) and progression-free survival (median 11.1 vs. 6.9 mo (and 13.6 mo in those with common EGFR mutations), HR=0.58, p=0.0004) compared with standard chemotherapy in previously untreated patients with advanced NSCLC and an EGFR mutation. While that’s great, it’s also exactly what we’ve already seen in SEVERAL trials of Iressa or Tarceva vs. platinum doublet chemotherapy in the same population. In fact, a few months ago, Tarceva was approved for the same indication.

Did we see evidence that afatinib prolong survival compared with chemo, in a way that we haven’t seen with Iressa or Tarceva? No. Any evidence of afatinib doing more than what we get with other EGFR TKIs? Umm…no. A few champions of afatinib have made the rather weak point that the 13.6 month median PFS in patients with the more common EGFR mutations on exon 19 or 21 is slightly longer than the 9-13.1 month median PFS seen with Iressa or Tarceva in several other trials, but that difference is very easily within the range of random effect or subtle differences between the populations in one trial vs. another. The clearest difference we actually see with afatinib compared with currently available EGFR TKIs is that afatinib is associated with more frequent and more severe side effects: more rash, more diarrhea, more nausea, more mouth sores.

What we’ve learned from nearly a decade of managing patients with an EGFR mutation is that these patients can have remarkably dramatic and prolonged responses to EGFR TKIs, but they are also often extremely sensitive to the side effects of these agents. Consequently, it can be a struggle to strike and maintain a reasonable balance of efficacy with a tolerable side effect profile for these agents over time. Moreover, lab-based studies indicate that cancer cells with an EGFR mutation are about 10 times as sensitive to EGFR inhibitors as non EGFR-mutated cancer cells, suggesting that patients with an EGFR mutated lung cancer may need a lower dose of EGFR TKI therapy to effectively treat the cancer. Though Iressa tends to have a relatively mild side effect profile, Tarceva at standard dose of 150 mg daily is very often very challenging if not prohibitively toxic for many EGFR mutation-positive patients to take on a
prolonged basis. We routinely whittle down the daily dose to 50-100 mg, sometimes even 25 mg daily, to reach a balance of effective disease control and longitudinal tolerability.

In other words, with EGFR TKIs that provide an impressive but ultimately transient benefit, we want to deliver this benefit with the least toxicity possible. Very often, this means working down from the standard doses of even our better tolerated EGFR inhibitors like Tarceva and especially Iressa (where it is available). A trial is being conducted directly comparing afatinib to Iressa as first line therapy in patients with an EGFR mutation, and this will be important, though I’d want to see an improvement in overall survival for afatinib to counterbalance what I expect will be a significant increase in side effects with afatinib. But until we see the results of this trial, and in the absence of actual evidence that afatinib is convincingly more effective than Tarceva and Iressa, afatinib just represents a more toxic version of these other drugs for first line therapy in EGFR mutated patients with advanced NSCLC.

Next, we’ll review its potential role as a treatment for EGFR mutated patients with acquired resistance to other EGFR inhibitors.