A few months ago, I had a patient in my clinic who is a lifelong never-smoker with an adenocarcinoma. I had her tumor checked for molecular markers, which revealed that she had both an activating EGFR mutation (exon 19 deletion) and a T790M mutation associated with resistance (see Dr. Pennell’s excellent summary for an introduction to EGFR mutations). Not sure what to expect from an EGFR tyrosine kinase inhibitor like Tarceva (erlotinib), I started her on chemo first, which she responded to for a while, and then put her on a Tarceva-based trial for second line. Though her cancer-related symptoms of cough and non-exertional chest pain improved significantly within just a few weeks, her scan actually showed a mixed response: dramatic improvement of her chest disease, but modest progression with new bone lesions.

We now have a little more information to help guide our expectations in this setting. A new publication in the Journal of Clinical Oncology from Su and colleagues from Taiwan provides several valuable new insights on T790M, the mutation that has been identified as the most common cause of acquired resistance to an EGFR tyrosine kinase inhibitor (TKI) after an initial good response in patients with an EGFR activating mutation. The investigators looked for both activating mutations and T790M mutations in Taiwanese patients, predominantly (about 75%) never-smokers and >90% with an adenocarcinoma, both before (107 patients) and after EGFR TKI therapy (87 patients) using three different methods: typical DNA sequencing, MALDI-TOF, and next generation sequencing. For those who are really curious, extremely scientifically gifted, or very bored, this last link provides a good explanation of sequencing techniques, but this is really getting outside of the scope of what we need to know here; basically, direct gene sequencing is the usual mutation detection technique, MALDI-TOF is a less commonly used novel approach, and next generation sequencing is the “gold standard” that really clarifies who has what.

What they found was that MALDI-TOF was far more sensitive at picking up mutations than direct sequencing, with the former correlating very well with next generation sequencing. While this was true for activating mutations in the EGFR TKI-naive patients (mutations detected in 37% vs. 44% of patients with direct sequencing vs. MALDI-TOF, respectively), this was especially true for T790M, detected in 3% vs. 25% of patients by direct sequencing vs. MALDI-TOF, respectively. In the EGFR TKI treated population (who may have been selected for high probability of having a response to an EGFR TKI, or have been enriched for being already known to have a mutation before going on an EGFR TKI), EGFR activating mutation frequency before they started EGFR TKI therapy was 55% with direct sequencing and 77% with MALDI-TOF; T790M was detected in 3% and 32% of these patients with these two techniques. Finally, in the 12 patients who had tissue testing for EGFR activating and T790M resistance mutation after they completed EGFR TKI therapy, direct sequencing detected activating mutations in 9 patients (75%) and a T790M mutation in 4 patients (33%), while MALDI-TOF detected an EGFR activating mutation in all 12 patients (100%) and a T90M mutation in 10 patients (83%).
As you would expect, these molecular markers were correlated with outcomes on an EGFR TKI (shown for MALDI-TOF as the more sensitive technique). Specifically, those who had an activating EGFR mutation and no resistance mutation had the longest progression-free survival (PFS), followed by those who had both an activating EGFR mutation but also a T790M resistance mutation, and then patients with no activating or resistance mutation having the least impressive PFS:

![Graph showing progression-free survival](image)

In contrast, there were no differences in outcomes by overall survival, nor were there differences in the response rate based on initial T790M status.

Where do these results leave us? We’re limited by the fact that the MALDI-TOF technique of mutation detection is not readily available (I don’t know of any commercial lab that uses it), but the findings indicate that the particular technique matters greatly in detecting both activating mutations and T790M mutations associated with resistance, presumably because a fraction of patients will have a smaller proportion of cancer cells with the mutation in question, and the techniques vary in their sensitivity at small numbers of copies of the mutated genes. These results demonstrate that patients T790M mutations are not rare prior to the start of EGFR TKI therapy (though they may be difficult to detect with the more commonly available techniques) and are associated with a shorter PFS than we see in patients with an activating EGFR
mutation and no T790M mutation; in the small numbers reported here, the clear majority have a T790M mutation after having received EGFR TKI therapy for a while.

It’s also important to note, however, that this work was done on a relatively small Taiwanese population with a low incidence of smoking, almost entirely looking at adenocarcinomas, and an overall group in which the general majority of patients have an EGFR activating mutation. For this reason, I think we need to be cautious in presuming that everything we learn here is likely to follow the same patterns in North America or Europe.

Still, the results provide some new information and indicate that patients with an initial T790M mutation can still respond to an EGFR TKI, but that we might expect that they won’t respond for long. In my patient’s case, I presume that the cancer in her chest has more activating mutation than T790M, the bone involvement is resistant because of the prevalence of T790M in the cancer cells of her progressing skeletal metastases. A short response, to be sure, but understandable. One more piece of the puzzle.