Should Avastin be Added to EGFR TKI Therapy for EGFR Mutation-Positive NSCLC?
The historical standard of care over the last several years for patients with advanced non-small cell lung cancer, whose tumor has an activating EGFR mutation, has been single-agent oral EGFR tyrosine-kinase inhibitor therapy. That is a pill like Iressa (gefitinib), or Tarceva (erlotinib), or Gilotrif (afatinib), and these agents are associated with long responses that typically will last 9, or 12, or sometimes more months, but unfortunately, in almost every case, will demonstrate progression after some period of time – and we would always like that to be longer.

One of the big questions that we've wanted to know is, if we could add something to this therapy and do better than that – and one of the key questions has been about adding an anti-angiogenic agent, something that blocks the tumor’s blood supply, which is a drug like Avastin (bevacizumab), which is used in other cancer settings, and in some cases, for lung cancer, in combination with chemotherapy. In lab-based studies there is evidence that adding a blood supply blocker, an anti-angiogenic agent, to one of these EGFR inhibitors can more effectively suppress cancer cells, and for longer, but we haven't seen clear evidence that this is beneficial for patients in the real world. In fact, there have been a couple of large studies that have asked the question about adding Avastin to a drug like Tarceva – these trials, however, have only been in broad populations that are called molecularly unselected, not looking specifically at patients with an EGFR mutation or any other feature, but just really taking all comers.

One of the key studies is called BeTa, and this was a study where all the patients had receive first-line chemotherapy, and were getting, now, a
second-line treatment, after progression, and they were either getting Tarceva alone, or the combination of Tarceva with Avastin.

The study, overall, did not show a significant improvement in survival, but when they looked at the different subgroups of patients, based on various clinical characteristics, you can see that a couple of subgroups of patients did particularly well with the combination.
Specifically, when they looked at patients who were Asian or Pacific Islander, or never-smokers – those patients really seemed to skew more toward greater benefit with the combination of Avastin and Tarceva.
They also looked at a small subgroup of patients, whom they had tumor tissue on and were known to have an EGFR mutation, and those patients also trended clearly toward a better effect with the combination of Avastin and Tarceva.

So, that's provocative, but that's just one study. What's interesting as well, though, is that a remarkably similar study was done where patients received either Tarceva alone, or Tarceva and Avastin, as a maintenance therapy. So, they had not progressed, but they had already received first-line therapy, and then went on to get Tarceva, or Tarceva and Avastin.
This study also showed no significant improvement in the overall population – this was, again, a molecularly unselected population, but when they looked at the different subgroups, based on their clinical characteristics, it was the same subgroups who got the benefit, in terms of overall survival, from the combination.
So, again, it is the Asian and Pacific Islander patients, and the never-smokers – the two groups who we know are most enriched for having an EGFR mutation. So, this is really a bit more compelling evidence that, maybe, there's really something there.

The question was asked more directly in a study done in Japan and just published in Lancet Oncology not too long ago.
This trial had about 150 patients, all with an activating EGFR mutation, who were randomized to receive Tarceva, or Tarceva and Avastin, as a first-line therapy. The study was designed to look for a significant improvement in progression-free survival, the time before at least half the patients had demonstrated significant progression of their cancer, on this combination that they started with, or the single agent.
What they found was a significant improvement in progression-free survival in the patients who received the combination. In fact, the difference in median time to progression, the time when half the patients in each group had progressed, was over six months longer in the patients who got the combination.
Tarceva with or without Avastin in Japanese Patients with an Activating EGFR Mutation

When we look at overall survival – most of the patients are still alive, so it’s too early to really say much, but the trend is in the direction of favoring the patients who received the combination.

The other side of the coin, beyond efficacy, is tolerability, and the combination was associated with more side effects, as you’d expect – although, there were no treatment-related deaths with the combination. In the Japanese experience, there were more patients who had significant problems and needed to come off of the drugs, specifically Avastin, than we’ve typically seen with this combination in other studies. 40% or so of the
patients had to discontinue the Avastin because of side effects, usually high blood pressure, or leaking protein into the urine, something called proteinuria; whether that is because these patients just had been on these agents for longer than they usually are in other studies, or there is something about the Japanese patients, or EGFR patients, who were more susceptible, we don’t know. But, at the end of the day, it was still a tolerable regimen, and more of the patients did well and did not progress for much longer when they received the combination.

So where does this leave us? We have a more than six month improvement in the median time to progression with the combination, but this is only one study, done in Japan, and sometimes we see differences in studies done in one part of the world, versus another. Overall, I would say that, to me, these data are quite compelling, and it’s enough to lead me to favor the combination for my patients if an insurer will cover the Avastin, which is not, at this point, a clear standard of care. To many investigators and general oncologists, the combination is not yet their preferred regimen — they would like to see more evidence, larger studies, and ideally, work from other parts of the world to corroborate what we saw out of Japan. In fact, there are studies being done, one in Europe and one in North America, that are asking the same question, so we’ll hope to get more information soon, but this is certainly a very promising lead, and enough to lead me to favor the combination for my patients who have an EGFR mutation.