New FDA Approval for Zykadia (ceritinib) for ALK-Positive NSCLC: Why I Think It’s a Poor Choice for Initial Treatment

The FDA just approved a new therapy for the approximately 4% of patients with NSCLC who have the molecular marker known as an ALK rearrangement. The agent Zykadia (ceritinib), a “second generation” ALK inhibitor that is more effective than Xalkori (crizotinib) in lab models of ALK-positive NSCLC, and the new approval was for Zykadia as first line treatment for ALK-positive lung cancer, a setting where we have historically favored Xalkori since it was approved in 2011. Despite the FDA approval for ceritinib, I don’t believe it should be favored as a first line therapy for ALK-positive patients. Why would I not favor it?

First, the comparator arm for ASCEND-4, the study on which the approval is predicated, to which Zykadia was compared, was standard doublet chemotherapy. This is a treatment approach known to be inferior to the current appropriate standard of Xalkori, which has already been clearly shown to have been superior to doublet chemotherapy in efficacy for this population. This trial was designed to be positive by using an inappropriately low bar.

Second, the efficacy measure for benefit was a progression-free survival (PFS) of 16.6 months with Zykadia, which is better than chemo (8 months) and also better than we can expect for Xalkori (10-11 months), but it’s not better than we should expect for Xalkori followed by a second generation ALK inhibitor (typically 7-12+ months, with Zykadia at the low end of that spectrum). We can’t anticipate that patients with acquired resistance to Zykadia will respond to other second generation ALK inhibitors, to which there is a greater probability of cross-resistance than after Xalkori, so that 16.6 month median PFS is actually a low number compared to the anticipated result from Xalkori followed by a better second generation ALK inhibitor.

Third, first line Zykadia on the ASCEND-4 trial was associated with very significant toxicity, especially GI, that far exceeded the chemotherapy arm in most non-hematologic toxicities, and the toxicity is remarkably greater than that expected with other second generation ALK inhibitors (or Xalkori, as a first generation ALK inhibitor). Though some might argue that you can achieve comparable efficacy with lower toxicity by using a lower dose of ceritinib, that is a presumption that can’t be made: you can’t focus on the data you like and obfuscate the data you don’t like from the trial you designed. We can only see that Zykadia at 450-600 mg/day is truly effective and tolerable if a properly conducted trial demonstrates as much.

Finally, the right comparator for the future is actually not going to be chemotherapy or Xalkori, but rather Alecensa (alectinib), another second generation ALK inhibitor that has been shown to have strong activity in ALK-positive activity and currently approved for Xalkori-pretreated ALK-positive NSCLC. The global phase III ALEX trial is reportedly positive for a significant PFS benefit over Xalkori, while also being well tolerated (unlike Zykadia) and good control in the CNS (like Zykadia). If the results of the global ALEX trial are anywhere near the remarkable results of the similarly designed but smaller and Japanese-only J-ALEX trial, specifically if the
PFS with Alecensa exceeds about 20 months, it will not only be far superior to the results with Zykadia but will be better than we could necessarily expect from a sequential approach starting with Xalkori. We’ll need to see the actual results, which will be reported at ASCO on 6/6/17, but I strongly suspect that Xykadia will barely have the opportunity to serve as a momentary placeholder for alectinib as a new first line standard of care for ALK-positive advanced NSCLC.