More targeted therapy or focus on chemotherapy after acquired resistance to a targeted therapy? How might we decide?

One of the challenges we face now when a patient with a “driver mutation” like an EGFR mutation or an ALK rearrangement develops progression on a targeted therapy against that particular target is whether to continue on another agent that might work specifically against that target or switch to a less specific approach, like chemotherapy or immunotherapy, which haven’t been demonstrated to be more or less effective against a specific molecularly defined subgroup. The short answer is that there is no clear answer, no best way to proceed, but I would say that there are some sensible principles on which many of the specialists agree. Here are the key principles I use in making a recommendation for pursuing another line of treatment against the same target vs. changing direction.

1) How good and how long was the response to initial targeted therapy? Even in two people who have an EGFR mutation, for instance, one might have a remarkable response to Tarceva (erlotinib) that lasts for 18 months, while another may have stable disease for a few months and then progression just 4 months after starting it. I’d be far more inclined to consider further EGFR-directed therapies for the great responder. You might well surmise that the person who had a rather disappointing and short-lived response to the initial targeted therapy is generally not going to do better with the second agent against that same target.

2) Is there a good suggestion of a subpopulation of cancer that is still responsive to the targeted therapy? Sometimes, a person will have 80% of their disease melt away on targeted therapy and then show steady progression but still have much less cancer even after months of progression than they started with. Others may have had their targeted therapy stopped and then developed rapid acceleration of their disease (“flare reaction” or “rebound progression”). Both of these situations suggest that there is still significant disease that remains responsive to inhibition of that target, so either adding a new therapy to ongoing targeted therapy (even the same one on which a patient has been progressing) or a switch to a new inhibitor of the same target may be especially appealing.

3) How promising are the subsequent targeted therapy options? For instance, there are several second line ALK inhibitors such as LDK-378 from Norvartis and Ariad’s AP26113 that have demonstrated response rates in XALKORI (crizotinib)-pretreated patients that look as good as the results seen in in XALKORI-naive patients, and the second generation agents appear to also potentially work against brain metastases. On the other hand, the results with Gilotrif (afatinib) for patients with an EGFR mutation and acquired resistance to Tarceva (erlotinib) have been less impressive (perhaps more favorable when this agent is combined with Erbitux (cetuximab), though tolerability is a major question). All else being equal, I’m more inclined to favor another targeted therapy effort when the evidence is promising for subsequent targeted therapies.

4) How appealing is the non-targeted therapy option? For those who are chemo-naive or who
had a nice response to it previously, chemotherapy may pose a very significant chance of benefit that eclipses a very small probability of response to an unproven or dubiously effective targeted therapy like single-agent afatinib. Others may have progressed through prior chemo or have received many lines of prior chemo, in which case the probability of benefit from more chemo is vanishingly small.

5) Are there toxicity factors or other personal issues? Some people may be battle-worn from a lot of prior chemotherapy, with blood counts that have required extra weeks to recover from prior chemo. Some people may say they absolutely want to avoid more chemo. Some people may have a much easier or harder time traveling to the site of a clinical trial. Obviously, all of these factors are part of the equation.

To summarize, the idea is just to get a sense of how promising the different options are in general (has the next targeted therapy worked in many people? Is the next potential chemo option known to be active and prolong survival in a broader population), and then to individualize the decision for the particular patient based on the hints of how effective or ineffective targeted therapy or less targeted therapy have been in the past.

I hope that’s helpful. I’m happy to address any general questions (just please don’t ask me what you personally should do).