

What We've Learned from Other Precision Medicine Trials

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Dr. Gerber described his experience with the ALCHEMIST precision medicine trial for lung cancer.

ALCHEMIST is an umbrella platform for early-stage lung cancer clinical trials. This trial plans to enroll 8000 patients for whom adjuvant, postoperative chemotherapy is recommended. The study was designed to make it easy and enticing for patients and physicians to participate; for example, patients could enroll before or after surgery or after adjuvant therapy. Following genomic analyses, patients entered one of three studies: an immunotherapy study, a study targeting EGFR mutants, or a study targeting ALK rearrangement.

The rest of the discussion focuses on the ALK-rearrangement study within ALCHEMIST, which needed to enroll 378 patients. Enrollment in this study has been extremely challenging because of the rarity of ALK positive lung cancers. Thus, although lung cancer is common, with more than 200,000 cases annually in the US, only 3-7% are ALK positive. Additionally, only a portion of these are at the stage needed for enrollment in this study.

Initial participation in the study was lower than expected, although enrollment is now increasing. To date, 2400 patients have been screened at 1249 sites; of these, 2% have entered the ALK trial. Multiple efforts have been undertaken to increase awareness and participation, including regional Champion teams that write letters, make phone calls, attend meetings, etc. Part of the reason for the low enrollment was that we did not anticipate the rarity of ALK+ lung cancer. In our population with early disease, the prevalence is about 3-5% instead of the 5-10% reported for later stage disease. Additionally, many eligible patients were declining to participate. This required protocol amendments to make the study more acceptable to patients. Finally, we reconsidered eligibility criteria, and particularly the exclusion of patients with prior cancers. We undertook studies to examine this and found that prior cancer does not adversely impact outcomes for Stage 1-2 lung cancer, so this exclusion was eliminated from the study. These experiences may be helpful when designing other trials targeting rare cancer mutations.

Audience Questions and Answers

- *Do you have a formal survey that you give to people who are eligible for the study but decline? We don't have a formal survey but we try to capture that information; responses suggested that the placebo was a barrier to entry, even though it was standard of care, so we dropped it.*
- *Why was your estimated accrual rate so much higher than the actual rate? We are finding that ALK positivity is less common in early disease than in advanced disease (not 5-10%, but 3-5%). Initially,*

we didn't allow patients with squamous disease to enroll because we didn't have the immunotherapy trial option; now we do have the option and are enrolling these patients, but none is likely to be ALK+, so that is diluting our numbers. We were also surprised at the number of eligible patients who declined.

- *Did you do any focus groups presenting trial design to ask whether patients would consider enrolling?* Enrollment projection comes from working backwards. The trial was designed with a specified duration that couldn't be increased, and we had to change the endpoint from DFS to OS, so we had to increase accrual. Our initial number was probably overly optimistic.
- *You use prior cancer versus new cancer, but is there a reason why you didn't use primary versus secondary cancer?* Yes. There are many clinical studies on secondary cancers, for example, with people who had Hodgkin's disease and now have lung cancer because of the radiation. That wasn't our question; it wasn't about people who had cancer before. Our question was about people who had lung cancer now.
- *In terms of randomization, did you consider 2:1 or 3:1 randomization or crossover from the observation arm should lung cancer progress?* We do expect crossover to occur because the drug is FDA approved for advanced recurrence (not early stage). When new lung cancer nodules develop, the appropriate treatment isn't an ALK inhibitor, it's surgery to take out the cancer to cure it. It's difficult to do crossover for that reason. The 2:1 and 3:1 randomization wasn't done because of the power concern, which would increase sample size by another third, but that's a question to take back to patient advocates.
- *What is the prognosis for people in Stage 1B-3A without any further intervention? Are there other exclusion criteria that researchers use too much? Should "previous cancer" exclusion also apply to other trials?* Some lung cancers are likely to be cured (Stage 1A; not eligible for this trial); most patients on our trial are Stage 2. The 5-year survival for Stage 2A is 50% and for Stage 2B is 30%. We know that chemotherapy improves outcomes for these patients.

What are the potential side effects of drug interventions and if I were a patient how would I compare the risk benefit profile? Targeted therapy drugs all have side effects and sometimes these can be worse than chemotherapy because, today, we are good at preventing nausea and vomiting and mitigating the low blood counts that are side effects of chemotherapy. Additionally, chemotherapy is done only once every 3 weeks, so the side effects may only occur intermittently. Targeted therapy is taken every day, so lower level side effects can become important. Side effects with targeted therapy tend to have a gradual onset and are rarely life threatening. This allows us time to adjust dose to help reduce the impact of side effects on quality of life.