

Case Study: Using Central Labs in Master Protocol Trials

Treatment-targeted genetic mutations associated with non-small cell lung cancer (NSCLC) are increasingly found only in a small subset of the NSCLC population, and thus the majority of patients who participate in the screening trial are not always eligible for the treatment clinical trials. With the use of umbrella trial design, a large cohort of NSCLC patients can be screened to enroll patients in one of multiple treatment trials targeting a specific mutation, thus increasing the utility of genetic screening and improving efficiency of enrollment onto studies that enroll rare populations.

The Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials, or ALCHEMIST, are a set of randomized clinical trials operating under an overarching master protocol sponsored by the National Cancer Institute. ALCHEMIST is an umbrella platform that includes a screening trial that funnels into different randomized clinical trials targeting a specific NSCLC population that is genetically defined. The ALCHEMIST screening trial screens resected patients with early-stage NSCLC for specific genetic mutations that are being tested in one of the randomized clinical trials under the umbrella. This platform was established as a way to diversify the use of genetic screening and enroll into multiple targeted trials from one screening set, therefore establishing long-term efficiency.

To date, the ALCHEMIST platform has completed one treatment trial (EA5142 accrued 935 patients) and is actively enrolling into three additional trials, including the EGFR treatment trial for patients with EGFR mutations (A081105, targeted accrual =450), the ALK treatment trial for patients with ALK genetic rearrangement (E4512, targeted accrual=168), and the Immunotherapy treatment trial for those who do not meet the criteria for the previous two trials (A081801, targeted accrual = 1263).

CHALLENGE

Many NSCLC mutations only affect a small proportion of the NSCLC population. For example, EGFR mutations occur in only ~10-15% of patients and ALK rearrangement in only ~5-6%. When these trials are performed as single randomized trials, the majority of the patients who are genetically screened are not eligible and their genetic data is not used. One of the goals of the screening trial is to facilitate central testing of the resected NSCLC patients for genetic mutations to facilitate accrual to randomized adjuvant treatment studies, and more importantly to obtain clinically annotated tumor tissue and patient-matched non-malignant DNA from peripheral blood, as well as detailed epidemiologic and clinical follow-up data on all screened patients, to allow clinically annotated advanced genomic analyses in concert with the NCI Center for Cancer Genomics (CCG).

The patient eligibility for the ALCHEMIST adjuvant treatment studies is dependent on reliable, reproducible, and accurate genetic data. As such, the study could not rely on results from numerous local labs that use different tests and have different testing standards; driving the study team's decision to use a central lab for all genetic testing.

The use of a central lab also simplifies the data flow process – instead of managing data inputs from numerous labs across the country, a single data flow process can be established from a single central lab to the study's database.

The ALCHEMIST study team used the following selection criteria for evaluating central lab candidates:

- ◆ Cost
- ◆ Turnaround time
- ◆ Assay type: Given the study was regulated, they needed a CLIA certified lab and assay.
- ◆ Scalability: During active enrollment, the ALCHEMIST study screened ~100 patients per month; therefore, the lab had to be able to manage the high sample volume.
- ◆ Appropriate staffing resources and communication: The lab needed to provide timely responses to sites that had questions regarding testing, samples, shipment, and communicate directly with sites on the results as well as questions regarding sample viability, need for repeat testing, and extra sample requests etc.
- ◆ Willingness and capability to enter genetic mutation results into the trial database: Consider if the data has to be entered manually into the study team's database or if there is a way to facilitate data transfer directly from the central lab's database.

Because the ALCHEMIST study was one of the first studies of this magnitude in oncology to use a central lab, there were very few central labs that had experience in conducting these types of trials. In addition to the initial challenges with start-up, during the course of the study, the central lab consolidated its services from two locations to a single location. Unfortunately for the ALCHEMIST study, the location where its samples were tested was transitioned, therefore requiring a transfer of knowledge to an entirely new workforce.

Because the study was actively enrolling and enrollment was not paused, there was no ramp-up time to train and re-train personnel while enrollment was low or to confirm that everything was running smoothly at the new location. For example, the new site did not process the samples according to the timeline established for the study previously, resulting in delays, which sometimes put patients outside of the eligibility enrollment window.

SOLUTION

Identifying potential central labs

To facilitate the central lab search process, the study team looked for recommendations from key thought leaders. In this case, a formal request for proposals (RFP) was not used. The Study Chairs recommended labs that they had worked with in the past.

Selecting a central lab

After the study team compiled a list of potential central labs, they created a specifications sheet that included all of the selection criteria detailed above (cost, turnaround time, etc.).

Each potential vendor completed phone screenings to ensure that the appropriate information was collected from each lab during the screening process. Once the study team obtained this information from the central lab candidates, they compared the information provided to the study needs and finalized the central lab selection.

The start-up process

Once the central lab was selected, the study team immediately began regular meetings with key players from the study team, central lab, and others to discuss logistics. Some of the key players that were involved in these discussions included:

- ◆ Statistics and data center
- ◆ Protocol coordinator
- ◆ Sample management and tracking database project managers
- ◆ Key project managers
- ◆ Data Management
- ◆ Key personnel from central lab and NCI research lab involved in sample acquisition, processing, communication with the sites and data entry into the clinical trials database.

Central lab location and staff transition

The central lab managed the site transition, including training of the new staff. Once the study team discovered insufficiencies following the transitions, they took the following steps:

- ◆ Began weekly meetings with stakeholders, including central lab leadership and staff
- ◆ Retrained central lab staff emphasizing expectations for site report submission and Rave data entry
- ◆ Managed results on a weekly basis until they were confident in the process flow

OUTCOMES

Early and frequent meetings with the central lab helped facilitate a smooth study start-up.

The ALCHEMIST umbrella has successfully completed one trial (all patients are accrued and are now currently being followed for primary endpoint outcome; ECOG-ACRIN trial, EA5142) and has opened one additional trial (Alliance A081801).

LESSONS LEARNED

The team behind this study has the following advice for others considering the use of a central lab in an umbrella, platform, or basket study:

- ◆ **Discuss workflow around communication of results to the sites**, specifically what information will be included in the report about the testing results and patient's eligibility to a treatment trial.

- ◆ **Document workflows on the sample re-testing in upfront discussions.** Consider that some samples that are sent to the central lab may not be viable or final results may not be definitive. In both situations, the central lab must receive a second sample from the site. Consider how this request will be communicated – does the central lab contact the site directly (preferred) or will the coordinating center contact the site (which may cause delays)? Make sure that potential re-testing and increased communication between the central lab and the sites is included in the budget and scope of work.
- ◆ **Document all meetings and decisions made.** Not documenting early decisions can create challenges in knowledge transfer when the central lab changed location and staffing.
- ◆ **Plan an appropriate budget.** Consider having central lab payments linked to milestones, such as meeting pre-determined timelines. For the ALCHEMIST study, the central lab payments were not linked to successful sample analysis within the study's timeline. As a result, there was no leverage to enforce the timely analysis of samples.
- ◆ **Consider including central lab staff in start-up and transition discussions.** Oftentimes there is a disconnect between the leadership and the staff testing the samples. Be sure to include some individuals who actually perform the work to help identify current and potential challenges and ongoing considerations.