New Clinical Trial Designs Hasten Approvals for Targeted Therapies

By Charlie Schmidt

Last November, the U.S. Food and Drug Administration granted accelerated approval to a new targeted therapy for non–small-cell lung cancer (NSCLC) called AZD9291. The drug had a remarkable 61% response rate among patients harboring the epidermal growth factor receptor T790–M mutation, which confers resistance to frontline treatment. Also, the approval was based on single-arm phase II data instead of results from a randomized clinical trial.

In this experience, many experts see the best hope for the future of cancer drug development: one based on streamlined evaluations of targeted treatments given to patients who are most likely to experience clinical benefits.

“We’re no longer interested in big randomized studies that produce statistically significant results that aren’t clinically meaningful,” said Gary Middleton, M.D., a professor of medical oncology at the UK’s University of Birmingham. “We’re looking for big gains from targeted drugs in single-arm studies that look for high levels of activity.”

Homing In on Lung Cancer

Middleton directs the kind of precision medicine study that’s expected to produce such gains: the National Lung Matrix Trial (NLMT). Coordinated by Cancer Research UK, the NLMT is an umbrella trial comprising multiple arms, each made up of genetically defined cohorts with NSCLC. Enrolled patients are treated with either an experimental or approved drug targeted at the aberrations thought to be driving their malignancy. The NLMT is now testing seven drugs (including AZD9291) in 20 arms. But according to Lucinda Billingham, Ph.D., a professor at the University of Birmingham and the trial’s biostatistician, those numbers can easily change. If a drug fails to achieve the early milestone of a 30% objective response rate, that arm can be dropped and the cohort potentially reassigned. Ideally, a drug will generate strong responses that lead directly to regulatory approval without need of a phase III trial.

“The phase III study would in such a case be redundant and arguably unethical,” Billingham said.

In September, at Denver’s World Conference on Lung Cancer, Billingham and colleagues described the NLMT’s Bayesian statistical design. The researchers chose a Bayesian approach, Billingham said, because of its flexibility: It allows for an early halt to trial arms that aren’t generating promising results, as well as the capacity to share information from different sources, such as preclinical and other early phase studies. Instead of deriving actual response rates, Bayesian analysis generates probabilities of what the response rates are likely to be. A positive result might therefore be stated as “a high (80%–90%) probability that the true objective response rate is at least 40%.” Billingham acknowledged that Bayesian statistics are relatively new to European and U.S. regulators— who, she added, “are not averse to them.”

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Simon Hollingsworth, Ph.D., executive director of stratified medicine studies at AstraZeneca in Nether Alderley, UK, said statistical methods and new trial designs in precision medicine are evolving in tandem. And targeted therapies that interfere with the molecular drivers of a patient’s tumor, he said, should produce response rates high enough to eliminate the need for a traditional control arm. For example, in a recent phase I study, crizotinib generated a 72% response rate and 19-month progression-free survival in patients with ROS1-rearranged NSCLC, prompting the Food and Drug Administration to grant priority review for that indication on Dec. 8, 2015.

AstraZeneca and other drug companies are now partnering on the NLMT (and other similar precision medicine trials) in hope of producing more success stories.

Hollingsworth said the NLMT offers a more efficient, cost-effective, and patient-centric approach to drug development. Instead of targeting a single mutation that might exist in fewer than 5% of NSCLC patients, the NLMT caters to a spectrum of mutations implicated in the disease. Potential subjects supply biopsy samples for sequencing in an assay of 28 genes associated with NSCLC, “which that elevates the chances of being included in the study to better than 1 in 3, Hollingsworth said.

“We’re not running one trial; we’re running a whole series of trials in parallel under a single umbrella.”

For each arm, the aim is to home in on biomarker–drug interactions with increasing precision. For instance, cohorts treated with AZD4547, an inhibitor of fibroblast growth factor receptor, must have mutations that receptor’s gene in the extracellular binding domain, given preclinical data showing that these particular mutations drive cells to become cancerous.

The NCI-MATCH Trial

As an umbrella trial focused on a single tumor type, the NLMT differs from basket trials in precision medicine that test how drugs affect the same mutations in a variety of tumors. BRAF mutations, for instance, are common in melanoma and in other malignancies, such as lung and colorectal cancer. The best example of a basket trial is arguably the National Cancer Institute’s MATCH trial (NCI-MATCH), which opened for enrollment in August 2015. Coordinated by a merger of the Eastern Cooperative Oncology Group and the American College of Radiology Imaging Network (ECOG-ACRIN), NCI-MATCH shares certain similarities with the NLMT: Tumor biopsy samples undergo standardized sequencing, and patients are allocated
to various treatment arms on the basis of their tumor genetics. But where treatment arms in the NLMT contain only NSCLC patients, the arms in NCI-MATCH—currently 22 and counting—include patients with a variety of tumors sharing the same molecular targets. The target for NCI-MATCH is to eventually reach 30 arms or more.

Middleton said that NCI-MATCH ignores the context dependency of how cancer mutations work. For instance, research shows that the same BRAF mutation will have different activities in the lung and the bowel, “and the way they respond to drugs will also differ,” he said.

Keith Flaherty, M.D., associate professor at Harvard Medical School and the ECOG-ACRIN study chair who leads the NCI-MATCH study, affirmed Middleton’s point. “We’re finding that it’s not just genetics but also tumor site of origin that matters biologically,” he said. “And that’s what NCI-MATCH tackles head on: We want to understand if a given genetic feature leads to a response in one instance and not in another. The NLMt has no capacity to do that.”

Flaherty added, “What we lose in depth, we gain in breadth.” By focusing deeply on NSCLC, he said, the NLMT stands a better chance of moving new therapies toward accelerated approval. Yet NCI-MATCH offers the promise of discovering new and potentially strong signals for further research, perhaps in tumor-specific umbrella trials that can be conducted later.

Fred Hirsch, M.D., Ph.D., professor of medicine and pathology at the University of Colorado Cancer Center in Denver, said that NLMT, NCI-MATCH, and other precision medicine trials in cancer share two common objectives: to speed the rate at which new targeted drugs are identified and to move them smoothly and quickly toward regulatory approval. The trials are logistically challenging, he said, given how hard it can be to set up the requisite infrastructure and move next-generation sequencing into clinical settings.

“There are certainly barriers we need to overcome,” Hirsch said. “But we’re on the right path.”

Possible Genetic Pathway to Melanoma

By Kurt Ullman

Genetic mutations that result in melanoma have been cataloged over the years. The missing piece has been an understanding of the order of their occurrence and how they move from a benign lesion to one that is cancerous. An article by Boris C. Bastian, M.D., Ph.D., Gerson and Barbara Bass Bakar Distinguished Professor of Cancer Research at the University of California, San Francisco; Hunter Shane, Ph.D., a postdoctoral fellow at the university, and others hopes to help answer some of those questions (NEJM. 2015;373:1926–36; doi:10.1056/NEJMoa1502583.).

“Over last 20 years, we have shown that there are distinct types of melanoma,” Bastian said. “These differ in cell of origin, mutational processes that alter the cells, and types of mutations that occur.”

Researchers have made substantial advances in finding the genetic alterations that lead to advanced disease. However, the order in which the lesions evolve these mutations wasn’t clear.

“There are a series of pathogenic or driver mutations in fully involved lesions. We set out in this study to look at changes in melanomas where at least some of the noncancerous precursor lesion was still identifiable.”

Closer to Malignant, More Mutations Seen

All those lesions unanimously deemed benign had only a single mutation, BRAF V600E, a common, well-established mutation in melanoma. This single genetic alteration appears to be all that is needed to form a common mole.

Pathologists also agreed at the malignant end of the spectrum where melanomas tended to show multiple mutations such as mutation of TERT and loss of CDK2NA. They also saw mutations of PTEN or TP53 in more advanced primary melanomas.

“One of the unexpected findings was there clearly were lesions that are genetically intermediate between clearly benign and clearly malignant,” Bastian said. “These genetically intermediate lesions happened to also be those in which there was significant disagreement among the pathologists and which were placed between the benign and malignant categories by the consensus vote of the pathologists. Those were the lesions that without exception had multiple mutations.”

He further noted that controversy has persisted for decades about whether an intermediate stage lies between clearly benign and clearly malignant lesions where at least some of the noncancerous precursor lesion was still identifiable.”

A total of 37 formalin-fixed, paraffin-embedded melanocytic neoplasms were retrieved from the archives of hospitals in San Francisco, London, and Zurich. Overall, 150 distinct areas were prepared for genetic sequencing.

Each area was assessed microscopically by eight dermatopathologists and categorized as benign, intermediate but probably benign, intermediate but probably malignant, or malignant according to how far the pathologists judged the areas had progressed toward malignancy.