50 years. Hopefully, this study will spur people to develop specific treatments for these tumors." *–Mitch Leslie* ■

Xenografts Evolve Differently than Tumors

Patient-derived xenografts (PDX) are generally considered to be an accurate experimental method for determining how human tumor cells respond to treatment. However, in a recent study, researchers found that their genomic landscapes can change dramatically over time, suggesting that PDXs may be a less reliable way to gauge the response of tumor cells to drugs than previously thought (Nat Genet 2017;49:1567–75).

The researchers analyzed 1,110 PDX samples from 24 cancer types and found that by the end of the fourth passage, 88% of PDXs had acquired at least one large chromosomal aberration. Also, a median of 12% of the genome was affected by copy-number alterations. These genomic changes differed from those observed in evolving tumors in patients, and some of the mutations involved have been associated with drug sensitivity in previous studies.

"PDXs can rapidly become quite different from the specific tumors from which they were derived," says Uri Ben-David, PhD, of the Broad Institute in Cambridge, MA, and first author of the study.

Juliet Williams, PhD, an executive director of Oncology Drug Discovery at Novartis, who was not involved in the study, says that this is the latest in a series of papers showing that PDXs exhibit genomic changes as they are passaged. In light of this body of work, "avatar experiments, in which a PDX is generated from a patient for personalized medicine, could very well be a misleading approach, especially if a tumor is heterogeneous and only a few clones contribute to the PDX."

Although these results raise questions about using PDXs to determine the best therapy for a particular patient, Ben-David believes these models will remain a valuable tool in cancer research. "Our findings are consistent with previous studies that suggest PDXs can be useful for large-scale studies aimed at identifying genotype–phenotype associations." However, because of the costs and labor required to produce PDXs, he says it may be worthwhile for scientists to consider whether it makes more sense to generate multiple cell lines from a given tumor rather than a single PDX, depending on the biological question at hand.

To aid such decisions, Williams would like to see a rigorous evaluation of how faithfully PDXs recapitulate primary tumors, relative to newly created cell lines. "The new wave of cell-line generation may represent patient populations as well as PDXs, unlike historically available cohorts of cell lines, but that has yet to be comprehensively understood," she notes.

In addition, "a key outstanding question is what drives the observed genomic evolution in PDXs, and whether it can be attenuated," says Ben-David. If selection pressures imposed by the mouse immune system or the microenvironment of the tumor site are primarily responsible, for example, then generating PDXs in humanized mice or performing orthotopic transplantation of tumors may reduce PDX divergence from parent tumors.

Ben-David adds that it could be fruitful to study genomic events that are highly recurrent in human tumors but tend to disappear in PDXs. "Understanding what makes them disappear," he says, "could help us understand what underlies their recurrence in the first place, and thus how these events could be targeted therapeutically."

Finally, Williams would like to see more robust data on the functional consequences of the genomic changes in PDXs to better determine how likely they are to affect drug discovery. *–Kristin Harper* ■

Lorlatinib in NSCLC: Robust Efficacy Seen

Findings from a phase II study show that the investigational ALK inhibitor lorlatinib (Pfizer), whose early clinical activity was first reported last year and recently published, continues to look promising in a wide range of patients with advanced ALK-positive or ROS1-positive non–small cell lung cancer (NSCLC; Lancet Oncol 2017 Oct 23 [Epub ahead of print]). The trial's results were presented by Benjamin Solomon, MD, of Peter MacCallum Cancer Centre in Melbourne, Australia, during the International Association for the Study of Lung Cancer's 2017 World Conference on Lung Cancer in Yokohama, Japan.

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Structural model of crizotinib binding to ALK. Many patients with ALK-positive non–small cell lung cancer who develop resistance to crizotinib may benefit from lorlatinib.

Three second-generation ALK inhibitors are now FDA-approved as second-line treatment options for patients who have become resistant to crizotinib (Xalkori; Pfizer). Lorlatinib, a third-generation agent, is specifically designed to overcome most known *ALK* resistance mutations, and to penetrate the brain and central nervous system, where the disease frequently metastasizes.

Solomon reported data on five groups of patients: The first had never received an ALK inhibitor; the next three cohorts had previously received crizotinib, a second-generation ALK inhibitor, or two to three prior ALK inhibitors; and the final group had previously treated ROS1-positive lung cancer. The objective response rates (ORR) to lorlatinib were 90%, 69%, 33%, 39%, and 36%, respectively. In terms of intracranial activity, assessed through MRI, the ORRs were 75%, 68%, 42%, 48%, and 56%. Lorlatinib was well tolerated, and patients reported improvements in their overall quality of life and in common symptoms such as coughing, chest pain, and dyspnea.

"It's very reassuring to see such a high ORR among previously untreated patients," says trial investigator Alice Shaw, MD, PhD, of Massachusetts General Hospital in Boston. The cohort that received as many as three prior ALK inhibitors is particularly noteworthy, she adds. "These patients' disease may be refractory to all the approved agents out there, but a significant fraction still respond to lorlatinib."

Christine Lovly, MD, PhD, of Vanderbilt Ingram Cancer Center in Nashville, TN, notes that the standard of care is about to change for ALK-positive NSCLC, with the phase III ALEX study having unequivocally demonstrated alectinib's (Alecensa; Roche) superiority

to crizotinib earlier this year. Alectinib has since been recommended for approval as initial therapy in the European Union; in the United States, clinicians anticipate a favorable decision from the FDA later this fall. Meanwhile, lorlatinib's first-line potential is being assessed in the phase III CROWN trial, and "the hope is that it will prove even better than alectinib, when compared with crizotinib," Shaw says.

As next-generation ALK inhibitors replace first-line crizotinib, "the spectrum of *ALK* resistance mutations may well change," Lovly notes. "We think G1202R, for instance, may occur more frequently than it does now, in which case lorlatinib has the best efficacy data against this alteration." She hopes the ALK Master Protocol, which Shaw is working on with the NCI, will help stratify patients to the appropriate drugs, based on individual mutation status.

"What's more pressing," Lovly continues, "is figuring out how to treat the subset of patients, about half in all, whose relapse is driven by ALK-independent mechanisms. Right now, they'd be offered chemotherapy as their best option."

"These are the tough cases, and they represent a huge unmet need," Shaw says. "We've been going after low-hanging fruit, in a way, with *ALK* resistance mutations." Combination therapies are warranted, she adds, to address the off-target resistance mechanisms these tumors are likely to evolve.

"We need rational, potent combinations up front," Lovly agrees. "The idea is to constrain tumor clonality from the start, which could prevent resistance from ever coming up." *–Alissa Poh* ■

Mutation Load Offers Biomarker in SCLC

The quest to find a predictive biomarker for small cell lung cancer (SCLC) now has a leading candidate.

Researchers presented an exploratory analysis last month at the International Association for the Study of Lung Cancer's 18th World Conference on Lung Cancer in Yokohama, Japan. They reported that patients with previously treated SCLC who had a high tumor mutation burden (TMB) had better response rates and longer survival following treatment with the PD-1–targeted agent nivolumab (Opdivo; Bristol-Myers Squibb), either alone or in combination with the anti-CTLA4 drug ipilimumab (Yervoy; Bristol-Myers Squibb), compared with patients whose tumors had a medium or low TMB.

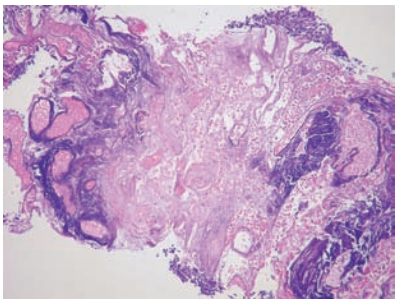
"This is an important step forward for identifying patients who can profoundly benefit from immunotherapy," says trial investigator Matt Hellmann, MD, of Memorial Sloan Kettering Cancer Center in New York, NY, who previously presented overall efficacy data (J Clin Oncol 2017;35 Suppl 15:8503). "It justifies and encourages molecular testing in small cell lung cancer."

In the phase I/II CheckMate 032 trial, which included an expansion cohort of patients with advanced SCLC, individuals with a high TMB in their lung tumors had an objective response rate that was about twice as high as the SCLC population average—21% versus 11% for nivolumab monotherapy, and 46% versus 22% for the combination. In addition, 62% of patients with high TMB were still alive a year after receiving the combination therapy, compared with 20% to 23% among those with low or medium TMB given the same two-drug regimen.

The biomarker was measured by whole-exome analysis in cancer cells and defined as the total number of missense mutations in the genome. Tumors with higher mutation loads are believed to express more neoantigens, which could explain why they're more susceptible to immunotherapy.

According to Hellman, the study is the first to demonstrate the value of TMB in SCLC, and the first to evaluate the ability of this biomarker to predict the efficacy of combination immunotherapy in any tumor type.

"The data are very exciting and may one day help us best decide who needs immunotherapy alone, immunotherapy and chemotherapy, or chemotherapy alone," says David Spigel, MD, of the Sarah Cannon Research Institute in Nashville, TN. However, TMB is unlikely to inform current clinical practice for second-line SCLC treatment, he says, because, even in those with low mutation burden, response rates are generally higher with the checkpoint inhibitor combination than with standard topotecan chemotherapy.



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A high number of mutations in small cell lung cancer could identify patients most likely to respond to treatment with checkpoint inhibitors.

"It's a tough one when you're dealing with a cancer for which you don't have many other good options," says Spigel, who worked on CheckMate 032 but not the exploratory biomarker analysis.

Because there are better therapeutic options for non–small cell lung cancer (NSCLC), TMB could point to the optimal treatment for particular patients. As reported in June, the CheckMate 026 trial showed that a high TMB was associated with longer progression-free survival among patients with NSCLC receiving first-line nivolumab instead of platinum-based chemotherapy, whereas the reverse was true for those with low/medium TMB (N Engl J Med 2017;376:2415–26). That study also showed that PD-L1 levels provided an independent biomarker of response. In contrast, PD-L1 expression is generally uncommon in SCLC and thus not predictive of tumor response.

The CheckMate 026 analysis was retrospective, however, and whether those two biomarkers can help inform routine decision-making in NSCLC remains a matter of active investigation. "We're still waiting on well-designed prospective studies to sort this out," Spigel says. *–Elie Dolgin* ■

Germline Testing Could Help More Patients

Combining secondary germline analyses with tumor sequencing might uncover additional mutations that are clinically useful, a recent study reveals (JAMA 2017;318:825–35).

Using tumor sequencing to tailor treatments has become part of individualized cancer care, but doctors usually offer germline DNA sequencing for cancer risk only in certain circumstances.