In Search of Exceptional Responders

A new NCI initiative aims to pinpoint genetic reasons for extraordinary responses to cancer therapies

Even if studies of an experimental cancer therapy yield disappointing results, individual patients sometimes respond unexpectedly well to the drug in question. "Oncologists have scratched their heads at these exceptional responses, but until recently, that’s where it stopped," says Louis Staudt, MD, PhD, director of NCI’s Center for Cancer Genomics in Bethesda, MD. Now, instead of these cases being relegated to the anecdotal realm, efforts to ferret out their molecular underpinnings are picking up speed. At NCI, Staudt is co-leading one such study, the Exceptional Responders Initiative (ERI).

By “advertising broadly and vigorously” to cancer centers and community practices nationwide, Staudt says, the ERI aims to closely investigate as many as 300 exceptional response cases. While targeted therapies will be a major focus, “we’re also looking for exceptional responses to standard chemotherapy in patient subsets where this hasn’t been the norm,” he adds.

“We’re collecting cases by e-mail, without identifiers; our inbox has been pretty active,” says Barbara Conley, MD, ERI co-leader and associate director of the cancer diagnosis program within NCI’s Cancer Treatment and Diagnosis division.

Conley says an expert panel will screen all submissions to verify exceptional responders—those who achieved complete or durable (at least 6 months) responses to treatments normally benefiting fewer than 10% of patients. Tissue samples will be obtained and molecularly profiled via whole-exome, transcriptome, and deeper targeted sequencing. All clinical and genomic data will eventually be available to interested investigators through a controlled-access database.

“There’ll be some growing pains as we attempt to interpret what we find,” Staudt acknowledges. “That’s why, after giving it the old college try ourselves, sharing our data and yield a richer knowledge of the relationship between genotype and response to therapy.”

For now, “the more exceptional responders we’re able to identify,” Wagle says, “the more we’ll make discoveries that should be of real value to oncology.” —Alissa Poh

CT scans of metastatic urothelial carcinoma in a 70-year-old man prior to therapy with everolimus and pazopanib (left) and 2 months later. The combination cleared his cancer for 14 months. (Originally published in Wagle N, et al., Cancer Discov 2014;4:546–53.)

suggesting a plausible mechanism for the exquisite sensitivity of certain tumors to everolimus,” says Nikhil Wagle, MD, a medical oncologist at Dana-Farber Cancer Institute (DFCI) in Boston, MA, and lead investigator on the latter two reports. Wagle lauds NCI’s initiative as “part of the same goal, to find and study as many exceptional responders as possible, so we might someday recreate this effect more widely.”

The ERI is “a phenotype-to-genotype, signal-finding exercise,” Staudt says—ideally, one that will inspire new hypotheses to be tested in genomically driven clinical trials. These can be designed basket- or umbrella-style. Basket trials examine targeted agents across multiple cancer types; for instance, an ongoing study at DFCI, is assessing everolimus in all TSC-mutant cancers, Wagle says, with plans to add mTOR-mutant cancers. Umbrella trials, meanwhile, test multiple drugs on different genetic aberrations within a single cancer type.

“Based on detected signals [through exceptional responders], we’re predicting that patients with certain genetic alterations will respond to certain drugs,” Staudt explains. “Genomically driven trials help us understand how often these attempts to read a cancer’s tea leaves work.”

With their flexible design—independent study arms that can be added or removed, and often one labeled “other” for unanticipated cohorts—basket and umbrella trials will expedite biomarker testing and drug approval, notes Julia Beaver, MD, a medical officer with the FDA’s Office of Hematology and Oncology Products.

Identifying the right patients for these studies remains a hurdle, but one that should ease, Wagle says, as genotyping becomes a routine component of cancer care. The National Comprehensive Cancer Network now recommends broad-based genomic testing in certain clinical contexts, which some insurance companies have begun covering.

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“We may soon reach a point where tumor genomics can be readily obtained during the course of a patient’s treatment, so NCI is building its Genomic Data Commons to capture and harmonize that information,” Staudt adds. “For now, this is independent of our exceptional responder database, but ultimately we hope it will house all of NCI’s genomic data and yield a richer knowledge of the relationship between genotype and response to therapy.”

Meanwhile, “the more exceptional responders we’re able to identify,” Wagle says, “the more we’ll make discoveries that should be of real value to oncology.” —Alissa Poh

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