Multiple Myeloma Gets Three New Drugs

Patients with multiple myeloma have seen their therapeutic arsenal expand considerably in the last few weeks, with the FDA approving three new therapies: ixazomib (Ninlaro; Takeda), daratumumab (Darzalex; Johnson & Johnson), and elotuzumab (Empliciti; Bristol-Myers Squibb).

Ixazomib is the first oral proteasome inhibitor, and daratumumab and elotuzumab the first two monoclonal antibodies for this disease.

Ixazomib was approved in combination with lenalidomide and dexamethasone, with or without the new proteasome inhibitor. Patients in the ixazomib-containing arm had a significantly improved PFS—20.6 months, versus 14.6 months for the rest.

“This is the first all-or-none regimen for multiple myeloma, which will create effective outpatient treatment options,” says Kenneth Anderson, MD, director of the myeloma program at Dana-Farber/Brigham and Women’s Cancer Center in Boston, MA. How ixazomib works is not fully understood, but its actions include “blocking the breakdown of abnormal immunoglobulins, inducing stress responses, and triggering myeloma cell apoptosis,” Anderson explains.

Daratumumab targets CD38, an antigen highly expressed on multiple myeloma cells. It induces antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), both of which mediate tumor destruction.

The drug’s approval was based on results from the phase II SIRIUS study, which enrolled 106 patients whose disease did not respond to three or more prior therapies, including standard options like bortezomib (Velcade; Takeda) and lenalidomide. The objective response rate (ORR) to daratumumab was 29%, with three patients experiencing a complete remission. The median progression-free survival (PFS) was 3.7 months, and 65% of patients survived at least 1 year.

Anderson notes that “although CD38 is expressed elsewhere—for instance, on endothelial cells and about half of hematopoietic progenitor cells—daratumumab’s therapeutic index is nonetheless very favorable.” The drug was also well tolerated by study patients.

Elotuzumab has a dual mechanism of action: It targets the antigen SLAMF7 on multiple myeloma cells, mediating damage through CDC and ADCC, and it activates SLAMF7-expressing natural killer cells, thereby increasing tumor destruction. In the phase III ELOQUIENT-2 study—which randomized 646 patients to receive lenalidomide plus dexamethasone, with or without elotuzumab—the median PFS for those in the elotuzumab-containing arm was extended by 4.5 months, and the ORR was 78.5%, versus 65.5% in the other arm. These data led to elotuzumab’s approval in combination with lenalidomide and dexamethasone.

Complete results from all three studies were presented at the annual meeting of the American Society of Hematology, December 5–8, in Orlando, FL.

Anderson thinks monoclonal antibodies “will likely contribute to a new standard of care for multiple myeloma.” Other immunotherapies, including therapeutic vaccines and checkpoint inhibitors, are also being actively investigated, and he considers combination approaches—therapies that selectively target tumor cells paired with ones that amplify the immune response—“most exciting.”

“The treatment paradigm for multiple myeloma continues to evolve, with patient survival already extended three- to four-fold,” he observes. “It’s a new world, in terms of being able to stimulate autologous immunity against this disease.”

Huge Data-Sharing Project Launched

Aiming to serve as a catalyst for the advancement and adoption of precision medicine in oncology, the American Association for Cancer Research (AACR) has launched an international initiative known as AACR Project Genomics, Evidence, Neoplasia, Information, Exchange (GENIE). The venture will pool existing and future next-generation clinical sequencing data with longitudinal clinical outcomes and related pathology reports from several institutions in the United States, Canada, and Europe.

“The need for such a project is great,” said Charles L. Sawyers, MD, a physician-scientist at Memorial Sloan Kettering Cancer Center (MSKCC) in New York, NY, and one of several researchers who unveiled the project on November 6 at the AACR-NCI-EORTC International Conference.
on Molecular Targets and Cancer Therapeutics in Boston, MA. Sawyers, who conceived the effort and chairs its steering committee, explained that the explosion of sequencing projects “has created a treasure trove of data,” but that the data often remain at the institution that conducted the sequencing, limiting their potential value and statistical significance.

“These data are typically insufficient in number or lack the necessary clinical outcomes data to be clinically meaningful,” said Sawyers. “Thus, to effectively benefit patients, the genomic and clinical outcomes data from as many institutions as is practical should be combined through a data-sharing initiative.”

Launched and funded for 2 years with $2 million from the AACR, the Project GENIE registry already contains more than 17,000 genomic records, many related to late-stage and rare cancers. Size is just one of the strengths of Project GENIE, and one trait that similar efforts lack. It will also include both retrospective and prospective data contributed by its seven founding members:

- The Center for Personalized Cancer Treatment, Utrecht, the Netherlands
- Dana-Farber Cancer Institute (DFCI), Boston, MA
- Institut Gustave Roussy, Villejuif, France
- Johns Hopkins University’s Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD
- Memorial Sloan Kettering Cancer Center, New York, NY
- Princess Margaret Cancer Centre, Toronto, Canada
- Vanderbilt-Ingram Cancer Center, Nashville, TN.

As these institutions treat new patients, additional data—stripped of all identifying information to maintain patients’ privacy—will be added to the registry, which includes only clinical-grade sequencing data that have been used in clinical decision making. All of the sequencing data are Clinical Laboratory Improvement Amendments– and International Organization for Standardization–certified.

To overcome some of the challenges of merging data from different institutions, project partner Sage Bionetworks of Seattle, WA, will ensure the data’s provenance, perform quality assurance, and make other needed changes to harmonize the data; none of the participants will need to change their platforms or protocols for data collection, which would have been a deterrent to participation. “Cleaned” data will then be transferred to a cloud-based platform where it can be viewed and analyzed through cBioPortal, based at MSKCC, explained Justin Guinney, PhD, director of computational oncology at Sage.

Sawyers and Barrett Rollins, MD, PhD, a member of the AACR Project GENIE steering committee and chief scientific officer at DFCI, said that the searchable database may aid researchers and patients in multiple ways—for example, by developing new hypotheses for translational and clinical studies; validating biomarkers of treatment response and prognosis; identifying new patient populations that might benefit from existing treatments; and discovering novel drug targets.

Before the first data are made public next November, researchers from the seven member institutions will pose a significant clinical question to validate and demonstrate the benefits of AACR Project GENIE. After that, other scientists can propose additional queries. More data will be available over time.

“We believe it’s an extremely valuable project,” said Rollins. “We want to share it with cancer researchers around the world….It’s a database like no other.” —Suzanne Rose

**Novartis Compiles Mouse Avatar “Encyclopedia”**

Seeking to reduce the number of preclinical drugs that fail along the road to regulatory approval, scientists at the Novartis Institutes for Biomedical Research (NIBR), headquartered in Cambridge, MA, have generated an extensive collection of patient-derived tumor xenograft (PDX) models. Called the PDX Encyclopedia (PDXE), it augments NIBR’s Cancer Cell Line Encyclopedia, established in 2012 (Nat Med 2015;21:1318–25).

“Our goal is to develop cancer therapeutics with a much higher probability of success in patients,” says William Sellers, MD, vice president and global head of oncology at NIBR, and we recognized the limitations of doing so with in vitro systems.” The PDXE currently contains over 1,000 models, representing a spectrum of solid cancers, and genomic landscape analyses indicate “close alignment between our models and human data as described by The Cancer Genome Atlas,” Sellers says.

The researchers are harnessing their collection to carry out PDX clinical trials (PCT) that mirror human studies in design: In a given PCT, each mouse receiving the therapy of interest bears a unique tumor xenograft from an individual patient. By treating a group of such mice, the therapy’s efficacy against the cancer type in question can be determined, and “we can capture the heterogeneity of responses between patients,” explains Hui Gao, PhD, a senior investigator at NIBR.

So far, PCTs have yielded data “highly consistent with what’s seen in humans,” Sellers says. For instance, BRAF-mutant PDXs responded well to BRAF inhibition—and even better with the addition of a MEK inhibitor. Ideally, he adds, PCTs will prove predictive of new therapeutic indications; to that end, “we’re using this system to profile all of our clinical candidates and additional compounds.”

Sellers and his team also validated cell line–derived results suggesting that high levels of two proteins, DR5 and caspase-8, predict sensitivity to TAS266, a novel antibody that activates...
CANCER DISCOVERY

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