First Tissue-Agnostic Drug Approval Issued

The FDA recently greenlighted its first-ever drug based not on tumor type, but on a common biomarker. Pembrolizumab (Keytruda; Merck) received accelerated approval for adult and pediatric patients with inoperable or metastatic solid tumors that are mismatch repair–deficient (dMMR) or microsatellite instability–high (MSI-H).

MMR deficiency is a genotype that can be hereditary—as in Lynch syndrome—or sporadic, arising from defects in one or more mismatch repair proteins. As a result, tumors acquire the phenotype of MSI and accumulate hundreds—or even thousands—of somatic mutations, any of which could produce neoantigens capable of triggering a potent antitumor response in the presence of immunotherapy.

To Suzanne Topalian, MD, of the Johns Hopkins Bloomberg-Kimmel Institute for Cancer Immunotherapy in Baltimore, MD, this tissue-agnostic indication for pembrolizumab “is extremely exciting, given that it arose from the germ of an idea here.” She and a team of Hopkins researchers, including Drew Pardoll, MD, PhD, led the first clinical trials of anti–PD-1 therapy several years ago, during which they reported that only one of 33 patients with advanced colorectal cancer experienced complete, durable disease regression (Clin Cancer Res 2013;19:462–8). Intrigued, Topalian with Biomaterials Engineering CAR T Cells

Across five single-arm studies that enrolled 149 patients—90 with colorectal cancer, the rest with one of 14 other tumor types—the objective response rate to pembrolizumab was 39.6%, including 11 complete responses. At the time of data analysis, the median duration of response had not been reached. Most patients had their tumor status prospectively evaluated using local laboratory-developed tests: IHC for dMMR; PCR for MSI-H.

“It will be important to engage pathologists to incorporate this clinically relevant biomarker into standard practice,” says Lillian Siu, MD, of the Princess Margaret Cancer Centre in Toronto, Canada. Equally key, notes David Rimm, MD, PhD, director of Yale Pathology Tissue Services in New Haven, CT, will be having “someone, or some company, produce a comprehensive set of controls to standardize test results, especially that of IHC, between labs.” He would also like the College of American Pathologists and the American Society of Clinical Oncology to set dMMR/MSI-H testing guidelines.

Jedd Wolchok, MD, PhD, of Memorial Sloan Kettering Cancer Center in New York, NY, sees “no reason why other anti–PD-1 therapies shouldn’t work as well against hypermutated tumors,” and anticipates that more agents in this class will receive tissue-agnostic approvals. Besides dMMR/MSI-H, having other biomarkers achieve similar clinical utility in the future would be welcome, he adds, “as long as the data are rock-solid, because decisions about access to treatment would be on the line.”

Overall, this milestone on the FDA’s part “should incentivize the conduct of more biomarker-driven basket studies,” says Siu, “because it sets precedence for a regulatory pathway that was previously uncertain.” –Alissa Poh

Engineering CAR T Cells with Biomaterials

Even as companies race to have the first FDA-approved chimeric antigen receptor (CAR) T-cell therapy, innovative iterations are emerging at the bench. A promising approach may
be to incorporate biomaterials into the design of this immunotherapy, as demonstrated by two preclinical studies from Fred Hutchinson Cancer Research Center in Seattle, WA.

Immunobiology engineering is a young field, says senior author Matthias Stephan, MD, PhD, but it could make CAR T-cell therapy more widely applicable and “not such a big deal,” referring to the elaborate protocols currently required to manufacture these cells

In one study, Stephan and his team evaluated polymer-based nanoparticles that bind CD3 on T cells and deliver their cargo—a CAR gene for CD19—to be integrated into the cell nuclei (Nat Nanotech 2017 April 17 [Epub ahead of print]). When these biodegradable nanoparticles were injected into mice with acute lymphoblastic leukemia (ALL), circulating T cells were successfully converted, in situ, into CD19-targeting CAR T cells within 24 hours.

“We turned naïve T cells into serial killers that were already at their job site and could immediately eliminate tumors,” Stephan explains. The newly minted therapeutic cells’ huge proliferative capacity prompted their rapid self-expansion, he adds, so “although the [CAR] gene transfer process was fairly inefficient, we only needed an initial spark to start the fire.”

These in situ programmed CAR T cells eradicated ALL in seven of 10 mice; the rest experienced substantial disease regression and a median 58-day improvement in survival. The efficacy data were not significantly different from those for a control group of mice given conventionally generated CAR T cells, Stephan notes.

This “very novel approach may shake up the gene and cell therapy fields to think in new, fresh ways,” observes Crystal Mackall, MD, of Stanford University in Palo Alto, CA. “The results are preliminary but highly impressive, illustrating the untapped potential of marrying nanomedicine with genetic engineering.”

“Our goal is for CAR T-cell therapy to outcompete chemotherapy as a first-line treatment [for leukemia/lymphoma], because it can be prescribed and administered just as easily,” Stephan says.

Meanwhile, to better apply CAR T-cell therapy to solid tumors, which are highly heterogeneous compared with hematologic malignancies, the team developed what Stephan describes as “a simple tool for surgeons” (J Clin Invest 2017;127:2176–91). It involves implanting alginate-based sponges within the cavity of a resected tumor, or directly on the surface of otherwise inoperable tumors. These dissolvable quarter-sized sponges serve as scaffolds that can be loaded with CAR T cells (conventionally manufactured ex vivo) plus an optimal mix of growth factors to stimulate proliferation.

Importantly, expansion of CAR T cells to destroy tumor cells expressing a given antigen—in this case, NKG2D—is “just the first wave,” Stephan says. The scaffold is designed to simultaneously deliver a STING agonist that primes a second, broader immune response by recruiting and stimulating dendritic cells capable of recognizing multiple other tumor antigens. STING agonists are “very potent vaccine adjuvants and too toxic to be given intravenously,” he adds, but these small sponges can safely deliver high local concentrations that synergize with CAR T cells in antitumor activity.

The alginate sponges serve as scaffolds that can be loaded with CAR T cells (blue) and nutrient-containing microspheres (green) to spur cell proliferation.

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## Engineering CAR T Cells with Biomaterials

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