

COVER STORY

Pipeline of novel immunotherapies may offer 'more nuanced approach' to cancer treatment

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Immunotherapy is increasingly recognized as an important therapeutic modality to treat cancer.

Checkpoint inhibitors — six of which have been approved since 2011 — have been the leading agents in immunotherapeutic investigation. Last year, the FDA approved two chimeric antigen receptor (CAR) T-cell therapies: tisagenlecleucel (Kymriah, Novartis) — the first gene therapy available in the United States — and axicabtagene ciloleucel (Yescarta, Kite Pharma/Gilead Sciences).

“Immune therapy is important because we don't want to kill patients' cancer cells indiscriminately,” **Craig F. Hofmeister, MD, MPH**, associate professor of clinical medicine at Emory University, told *HemOnc Today*. “Ultimately, we want a more nuanced approach to treatment — instead of using alkylators that kill everything — and to try to use drugs that make it inhospitable for a cancer cell to survive.”

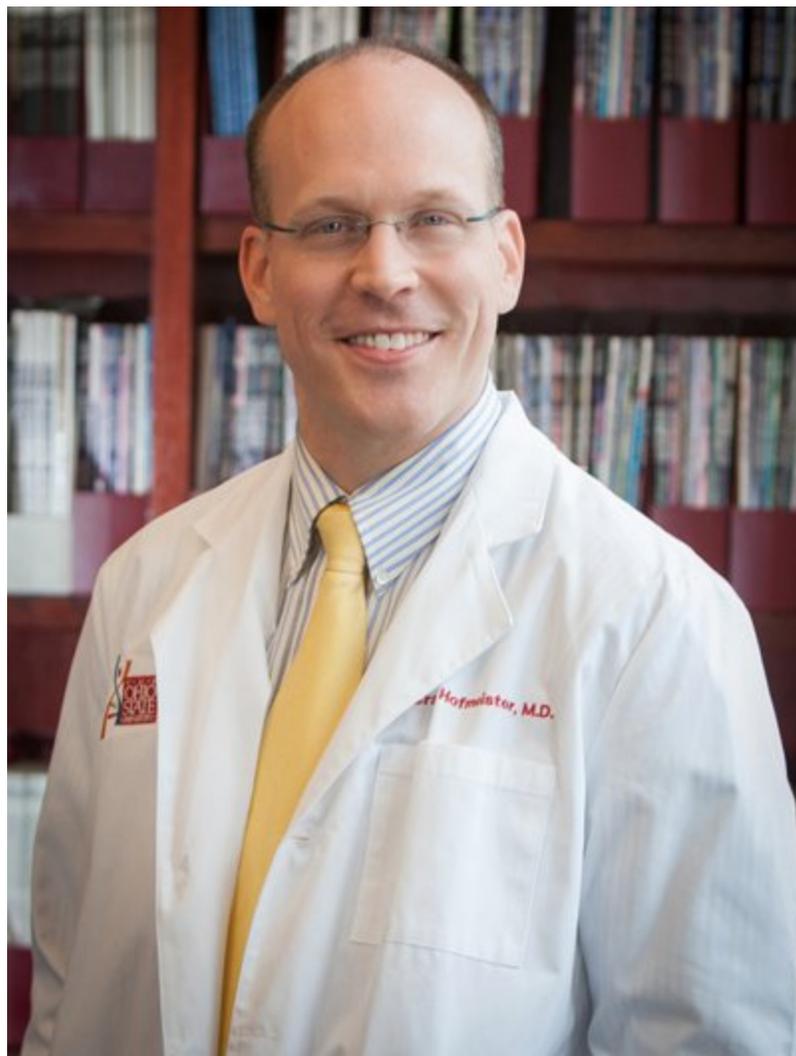
Still, a large proportion of patients do not benefit.

“Checkpoint inhibitors are all the rage, but details show checkpoint inhibitors alone have not been effective [against certain cancers],” Hofmeister said.

Using these advances as a stepping stone, researchers are evaluating many different types of novel immunotherapy approaches that hold the potential to expand the pool of patients who will benefit.

“We are just beginning to target this immunologic synapse, and the tools that we have so far have been very effective in a minority of patients at the cost of some significant side effects,” Hofmeister said. “We need to do better.”

Combining immunotherapies is a promising approach, but combinations may have overlapping side effects.



Although testing is still early, other promising immunotherapy targets include Tim-3, LAG-3 and OX40. "These targets are in early testing now, and we await results," **Craig F. Hofmeister, MD, MPH**, said. "PD-1 and PD-L1 are all we hear about, and they are just a couple of different pairs that can be targeted. Ideally, this area will become more complex and the drugs more effective."

Source: *The Ohio State University.*

"The real-world challenge is to combine these approaches for patients and analyze the results with enough sophistication to understand how some patients responded and why other patients suffered or died," Hofmeister said.

HemOnc Today spoke with oncologists and immunology experts about emerging immunotherapeutic targets, combination approaches, oncolytic viruses, and other biologic agents in the pipeline that might be the next huge cancer breakthrough.

Emerging targets

Approved checkpoint inhibitors — pembrolizumab (Keytruda, Merck), nivolumab (Opdivo, Bristol-Myers Squibb), ipilimumab (Yervoy, Bristol-Myers Squibb), avelumab (Bavencio; EMD Serono, Pfizer), atezolizumab (Tecentriq, Genentech) and durvalumab (Imfinzi, AstraZeneca) — inhibit PD-1, PD-L1 or CTLA-4.

Because certain cancers are refractory to CTLA-4 and PD-1 blockade, researchers seek other targets that can harness an immunotherapy approach.

Targeted proteins gaining interest include T-cell immunoglobulin and mucin domain 3 (Tim-3), Lymphocyte-activation gene 3 (LAG-3) and OX40 agonists.

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High expression of Tim-3 is associated with poor prognosis for prostate cancer, colon cancer and urothelial carcinoma.

Tim-3 is expressed on two important immune cell populations that promote tumor immunosuppression: dysfunctional CD8-positive T cells and FoxP3-positive regulatory T cells. In mouse tumor models, in vivo blockade of Tim-3 with other checkpoint inhibitors encouraged antitumor immunity and stopped tumor growth.

LAG-3 is a protein-coding gene located on the surface of effector and regulatory T cells that controls their response, activation and growth.

Preliminary results from a proof-of-concept study showed BMS-986016, an investigational anti-LAG-3 agent, was effective in combination with nivolumab for patients with advanced melanoma.

Among 48 evaluable patients, 25 with LAG-3 expression in at least 1% of tumor-associated immune cells within the tumor margin had a nearly threefold improvement in objective response rate.

“As a potentially synergistic immune pathway to PD-1/PD-L1, LAG-3 has emerged as an immune checkpoint receptor that regulates T-cell function and whose inhibition may increase benefits for patients,” study researcher **Paolo Ascierto, MD**, of Istituto Nazionale Tumori Fondazione Pascale in Naples, Italy, said in a press release.

OX40 — a tumor necrosis factor receptor expressed by CD4 and CD8 T cells during antigen-specific priming — has the ability to augment T-cell differentiation and cytolytic function which, in turn, can enhance antitumor immunity.

A study by Fox and colleagues found that concurrent treatment with anti-OX40 and anti-PD1 immunotherapies suppressed the therapeutic effect of anti-OX40 and, in turn, increased CTLA-4 and Tim-3 on T cells in mice.

However, researchers also observed that sequential treatment with anti-OX40 followed by anti-PD1 — not in reverse order — delayed tumor progression, leading to complete regression of tumors in about 30% of the mice.

A more natural approach

Most immunotherapeutic approaches genetically manipulate, infuse or implant cells.

Development of genetically manipulated T cells expressing modified T-cell receptor, CAR T cells and kill switches have led to undesirable effects and, in some cases, patients have died.

“There are very important considerations for any genetic manipulation of a T cell,” **Jonathan Schneck, MD, PhD**, professor of pathology, medicine and oncology at Johns Hopkins University School of Medicine and a member of Johns Hopkins Kimmel Cancer Center, told *HemOnc Today*. “CAR T cells are wonderful, and patients are living, but I am more interested in harnessing a natural immune response using the body as a guide.”

Most of Schneck’s research has focused on replacing and configuring antigen-presenting cells (APCs), also referred to as dendritic cells, to target different T-cell responses and control regulation.

“Cancer attacks the natural cancer-immunity cycle, and one of its targets are the APCs,” Schneck said. “We created something artificial that isn’t susceptible to the tumor microenvironment.”



**Jonathan
Schneck**

Schneck and colleagues engineered a paramagnetic nanoscale artificial APC to determine which T cells could produce an antitumor response. By doing so, researchers harnessed the body’s natural characteristics to create artificial APCs to stimulate T cells.

“The interesting thing is we got them to function as a regular cell and direct the immune response,” Schneck said. “By sticking with a natural T-cell repertoire, we are allowing the body to tell us what’s OK and what’s not OK.”

Drug companies increase T-cell receptors for targets, Schneck said, but using the natural aspects of the body can help avoid pitfalls associated with this.

“Companies that are developing T cells with enhanced T-cell receptor affinity are careful and cautious, but I also know that they are violating some of the paradigms set naturally by the body,” he said. “Maybe they will be great but, it is exciting that we have the ability to harness the body’s natural T-cell immune response.”

Artificial APCs can target T cells in vivo and present the opportunity to robustly expand T cells outside of the body.

Schneck, in partnership with NexImmune, created artificial immune AIM technology, which uses artificial APCs to direct the immune system to kill cancer cells, break tolerance and minimize escape.

“Much of the challenge now is ensuring you’re giving back central memory along with effector memory T cells which, currently, is hard to achieve,” Schneck said. “It’s still preclinical but all of our results are promising.”

These artificial particles are being investigated preclinically for melanoma and acute myeloid leukemia but can be expanded to solid tumors that aren’t responding to checkpoint inhibition.

“Because it is a platform technology, artificial APCs could work for many different cancers,” Schneck said. “Artificial APCs will hopefully take cellular therapy and immunotherapy to a new level.”

Schneck and colleagues also are developing a dual-cell targeting “immunoswitch” nanoparticle, engineered to carry two different antibodies — one to block PD-L1, and one to stimulate T cells.

In mice injected with melanoma and colon cancer cells, researchers placed the different kinds of antibodies on nanoparticles hoping to switch off the tumor’s immune-inhibiting ability while simultaneously switching on the immune system.

Treated mice showed 75% greater tumor reduction than untreated animals. In the colon cancer model, half of the treated mice were still alive after 30 days, whereas all untreated mice died by 22 days.

“Investing in immune engineering is important because now we have tools and techniques we can use to improve immune responses in our quest to deliver therapy to patients,” Schneck said.

The AIM T cells are in development for specific hematologic malignancies and will target patients who relapsed after allogeneic stem cell transplant.

The final T-cell product is generated from the natural T-cell repertoire, and so a virus is not included as part of manufacturing process. As a result, production of the AIM-generated T cells is less complex than what is required for genetically modified products and, therefore, could be less expensive.

“Although we don’t know precisely what our final cost of goods will be at commercial scale, we are very confident they will be significantly less than what we estimate those of the approved CAR T-cell products to be,” **Scott Carmer**, president and chief operating officer at NexImmune, told *HemOnc Today*. “When considering the cost of an in vivo application of the AIM technology, we envision the cost of goods to be more in line to what we see with currently marketed monoclonal antibodies.”

Oncolytic viral therapy

Oncolytic viruses — either genetically engineered or naturally occurring — selectively replicate and kill cancer cells without damaging normal tissues.

“Treating cancer with viruses is nothing new but goes back to the early 1990s when they used rabies vaccines to treat cancer,” **Robert H.I. Andtbacka, MD, CM, FACS FRCSC**, co-director of the melanoma clinical research program at Huntsman Cancer Institute, associate professor of surgical oncology at University of Utah, and a *HemOnc Today* Editorial Board Member, said in an interview. “What’s different now is that with modern technology, we’re able to identify the viruses that work the best.”

Talimogene laherparepvec (Imlygic; BioVex/Amgen) — commonly referred to as T-VEC and derived from herpes simplex virus type-1 — is the only FDA-approved systemically active oncolytic immunotherapy. However, T-VEC has yet to be administered systemically.

“We certainly think that could be a reasonable drug to test [systemically] in the future,” Hofmeister said.

A majority of oncolytic viruses are administered via intralesional or intratumoral injection, although IV administration holds the potential to treat a wider range of cancer types. Some intralesional agents have not been proficient enough, especially for distant disease.

“In systemic disease, we need to be able to give a virus intravenously; [however], we lack sufficient safety data regarding the use of many of these agents when given by IV,” **Douglas W. Sborov, MD, MS**, assistant professor in the division of hematology and hematologic malignancies at University of Utah School of Medicine, told *HemOnc Today*. “Despite sound preclinical data, many of these viruses have not been explored clinically for this reason, and we hope this changes.”

Although oncolytic viruses target and kill cancer cells, the hope also is that the virus can produce an immune response.

“We want to get the virus into the tumor, analyze the tumor and then have tumor-derived antigens and neoantigens exposed to the immune system to activate it,” Andtbacka said. “We also want to have activation of the immune system both locally, where we administered it, and distantly.”

Therefore, studies are assessing whether viruses are effective as IV monotherapy.

“The question is, can we administer viruses intravenously, so they seek the tumor, get into it and ultimately have an effect on it?” Andtbacka said. “The answer to it so far is that, yes, the virus does seek out the tumor and get into it. However, we don’t know whether it has an effect.”

Pelareorep (Reolysin, Oncolytics Biotech) — a proprietary isolate of reovirus type 3 dearing — is an oncolytic virus in late stages of development for head and neck cancer.

Hofmeister and colleagues also are evaluating pelareorep for myeloma, the first hematologic malignancy tested with a viral oncolytic.

“Reolysin is usually given in combination with a chemotherapeutic or some drug that enhances a productive viral infection,” Hofmeister said. “We are still investigating the dose of the virus, as well as trying to identify a susceptible patient population.”

When the virus is given to a patient with relapsed myeloma, it increases expression of PD-L1 on myeloma cells.

Sborov and colleagues investigated pelareorep as a single agent among 12 patients with relapsed multiple myeloma in a phase 1 trial.

Results showed single-agent pelareorep was well tolerated and associated with avid reoviral RNA myeloma cell entry, but minimal intracellular reoviral protein production among multiple myeloma cells.

“From this, we wanted to figure out why objective clinical responses were limited, and while we found that the virus was preferentially getting into the myeloma cell, it was not actively replicating, which was likely one of the mechanisms inhibiting our ability to get achieve meaningful clinical responses,” Sborov said. “These results were not unexpected, as prior single-agent trials in patients with solid tumors essentially showed similar findings.”

Adding a second agent may induce more durable responses with pelareorep.

“In fact, our latest strategy combining the proteasome inhibitor carfilzomib with Reolysin in relapsed and refractory multiple myeloma patients is showing very promising results,” Sborov said. “These findings, along with promising preclinical data, have increased the interest in utilizing viral oncolytics for the treatment of various hematologic malignancies.”

Combination approaches

The potential efficacy of oncolytic viruses may be maximized when used in certain combinations.

“Viruses are likely not enough on their own and likely require combination with other immune-modulating drugs to have optimal efficacy,” Sborov said.

In a phase 2 randomized trial, **Jason Chesney, MD, PhD**, director of James Graham Brown Cancer Center at University of Louisville, and colleagues found that the addition of T-VEC to ipilimumab improved survival among patients with advanced melanoma.

“The majority of patients with melanoma who receive immune checkpoint inhibitors do not experience durable objective responses,” Chesney told *HemOnc Today* when the study was first published. “We now have multiple approaches to enhance the effectiveness of CTLA-4 and PD-1 inhibitors, and agents that facilitate the priming of

antigen-specific T cells are expected to synergize with immune checkpoint inhibitors.”

Further, visceral lesions decreased among 52% of patients in the combination arm.

“The observation that noninjected, visceral lesions were significantly more likely to respond to the combination ... was an encouraging surprise that suggests the virus is enhancing systemic antimelanoma immunity,” Chesney said. “My personal expectation is that we will observe efficacy of the combination ... in phase 1/phase 2 trials that focus on cancers like NSCLC, breast cancer and colon adenocarcinoma.”

Researchers also are investigating the combination of ipilimumab and coxsackievirus A21 (CVA21, Cavatak).

At last year’s AACR Annual Meeting, **Brendan D. Curti, MD**, presented phase 1b results that showed an ORR of 50% among patients with advanced melanoma. Four patients responded despite disease progression on prior immune checkpoint inhibitor.

“Before our study commenced, we know that oncolytic viruses ... could prime immune responses, had single-agent activity and could upregulate T-cell checkpoints,” Curti told *HemOnc Today* at the time of the presentation. “The surprising finding was the degree of clinical activity combining these agents, especially [among] patients who had disease progression after prior checkpoint treatment.”

Combining an oncolytic virus with chemotherapy or radiation is another option.

Villalona-Calero and colleagues found that pelareorep in combination with paclitaxel and carboplatin chemotherapy was well tolerated among patients with metastatic/recurrent *KRAS*-mutated or *EGFR*-mutated/amplified NSCLC.

“The combination studies will be the next step forward using these viruses,” Andtbacka said. “Viruses work very well as monotherapy in early disease but, in more advanced stages, combination regimens will be needed because of the better response rates.”

Bispecific antibodies

Monoclonal antibodies have changed the therapeutic landscape for cancers as diverse as melanoma, multiple myeloma and NSCLC. However, not all patients benefit from them.

Bispecific monoclonal antibodies (bsAbs) can simultaneously target two different antigens at the same time and also target receptors to connect T cells to tumor cells.

Although these agents are not new to the pipeline, the only FDA-approved bsAb is blinatumomab (Blinicyto, Amgen) — a CD19-directed CD3-bispecific T-cell engager immunotherapy — indicated for the treatment of children and adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia.

However, the necessary technological platform needed to administer them can be costly and has posed challenges for further development of these antibodies.

Glenmark Pharmaceuticals developed bispecific engagement by antibodies based on the T-cell receptor technology, or BEAT, to attempt to overcome limitations encountered with bsAbs.

“We have chosen to go into T-cell redirecting with this technology because we would be able to actually redirect and activate T cells toward the tumor by making an ‘IgG-like’ antibody that has two binding properties — a tumor antigen on the cell surface presented by the tumors and the other on the cell surface of T cells,” **Kurt Stoeckli, PhD**, president and chief scientific officer of Glenmark Pharmaceuticals, told *HemOnc Today*. “By doing so, you essentially access the body’s internal system designed by mother nature to be the surveillance for immunity.”

Using BEAT, Stoeckli and colleagues are developing three bsAbs.

“We think that the current version of our BEAT-based bispecific monoclonal antibodies are most suited for therapeutic approaches used in the immuno-oncology field,” Stoeckli said. “Although we think they will be great advances, we have already started developing the next-generation platform, which will be an upgrade with versatile technical features and will have the potential for broader application beyond immuno-oncology.”

Two novel agents — GBR 1302 for HER-2-positive cancers and GBR 1342 for resistant multiple myeloma — are currently in phase 1 trials, and a third — GBR 1372 — is in preclinical development for colorectal cancer and squamous cell carcinoma.

“The frontrunner is GBR 1302, a bispecific with HER-2 and CD3 binding features. We want to design therapy that will be different from the classical antibody for HER-2,” Stoeckli said. “We are considering tumor types that so far have not been able to be sufficiently and effectively treated with standard of care.”

GBR 1342 targets CD3 and redirects the T cells by binding to CD38, another tumor antigen. GBR 1372 targets epidermal growth factor receptors and CD3. In preclinical trials, GBR 1372 bypassed *KRAS* and *BRAF* mutation limitations presented by other cancer therapies.

CD3 redirection has multiple advantages, according to **Venkat Reddy, PhD**, vice president and global head of translational science at Glenmark Pharmaceuticals.

“Unlike many cancer immunotherapies, these particular antibody constructs cause T cells to exert cytolytic activity on tumor cells by producing apoptotic molecules like granzyme and perforin, independently of the presence of MHC 1 or co-stimulatory molecules” Reddy said.

The bispecific CD3 engagers can bind a specific T cell with a specific tumor antigen, triggering an activation of the T cell.

“This redirects them toward the tumor, increasing the chances of an immune response,” Reddy said.

T-cell engagement shows potential for multiple cancers.

“T-cell engagers have a precedent in ALL with blinatumomab, and molecules such as GBR 1342 that target CD38 could be part of the next wave of immunotherapeutics in myeloma,” Hofmeister said. “Side effects, effectiveness and patient-friendly pharmacokinetics all have to come together for such molecules to be used in the first few lines of therapy.”

Current trials

Ongoing clinical trials hold the key to determining which of these novel immunotherapies will be the next big breakthrough for cancer research.

For instance, Pfizer partnered with the NCI to evaluate three immunotherapies — PD-L1 antibody avelumab; utomilumab (PF-05082566, Pfizer), which targets 4-1BB; and anti-OX40 antibody PF-04518600 — alone or in various combinations with each other or other standard therapies for a variety of cancers.

Vaccine clinical trials underway include a phase 1 trial sponsored by Sanford Health, which is injecting genetically altered vesicular stomatitis virus — a virus that can affect cattle, but rarely humans — into metastatic solid tumors that have not responded to standard treatments.

Further, the BMT CTN #1401 trial is investigating a fusion vaccine of dendritic and myeloma cells. The myeloma cells are frozen, stored and then combined with dendritic cells when a patient moves on to a high-dose chemotherapy regimen.

“After stem cell transplant, they will receive this vaccine comprised of their myeloma and dendritic cells to see if that in combination with lenalidomide [Revlimid, Celgene] can increase tumor killing and enhance immune surveillance to keep them free of their myeloma,” Hofmeister said. “It’s a neat concept.

“Vaccination in myeloma is not a low-lying fruit that is easy to grab. It’s challenging to get a vaccine to work, but it hasn’t stopped us from trying,” Hofmeister added. “We continued to look for monoclonal antibodies to work in myeloma for two decades before they were approved, so I wouldn’t be surprised if vaccines follow the same route.”

Oral drug trials for immunotherapy also are being investigated.

Andtbacka and colleagues found X4P-001 (X4 Pharmaceuticals) — an oral, selective, allosteric inhibitor of CXCR4 — is well tolerated in combination with pembrolizumab among patients with melanoma. Researchers also observed preliminary evidence of enhanced immune cell infiltration and activation.

“This is a small study and early information but, again, it indicates there are oral drugs we could potentially use to change the tumor microenvironment and, we hope, make checkpoint inhibitors more effective,” Andtbacka said.

As more immunotherapies emerge and improve, whether they will replace chemotherapy as standard treatment remains unanswered.

“There is going to be continued therapeutic space for conventional chemotherapeutics, but I think as we get more savvy with our research and new novel agents, we’re going to be able to come up with safer, more well-tolerated and potentially more effective treatments,” Sborov said. “I don’t think chemotherapy will necessarily go away [in the future] altogether, but the new, targeted therapies are allowing us to do our jobs better.” – *by Melinda Stevens*

Click [here](#) to read the **POINT / COUNTER**, *“Is the success of future immunotherapies dependent on biomarkers?”*

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