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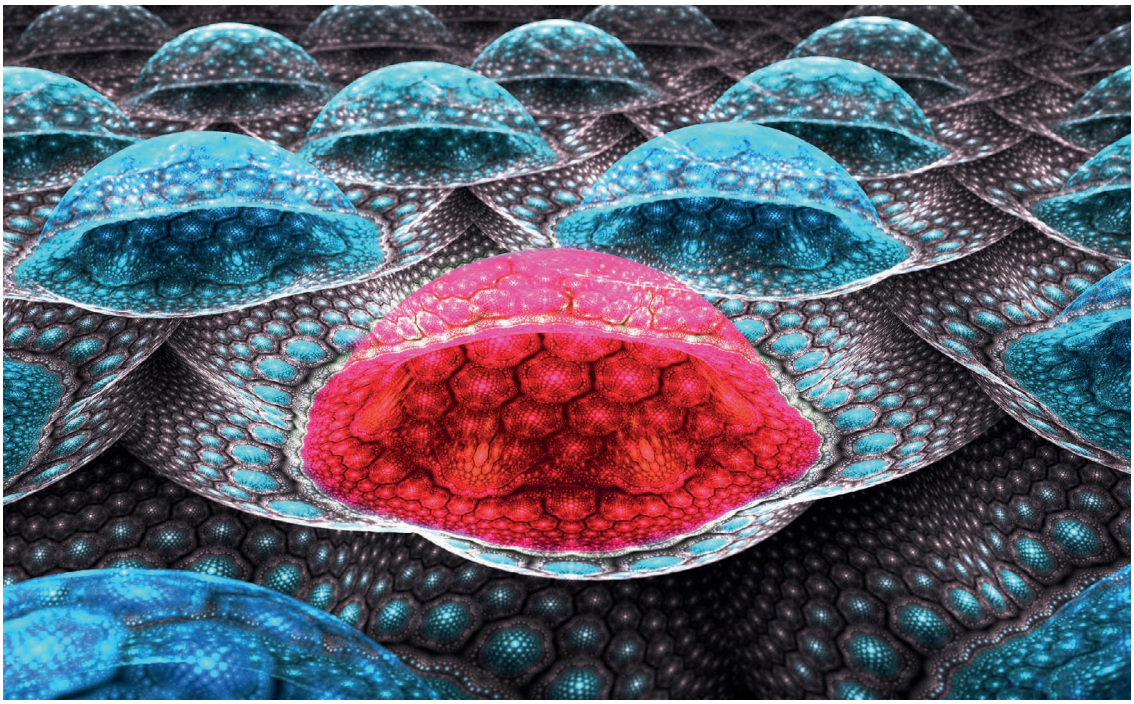

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Cancer immunology community seeks better end points

Drug developers are still hunting for surrogate end points that can better capture the benefits of checkpoint inhibitors, oncolytic viruses and modified T cell therapies.

Elie Dolgin

Checkpoint inhibitors and other immunotherapies are overhauling the cancer treatment landscape and throwing out traditional surrogate trial end points in the process.

Although tumour growth or the discovery of a new metastatic lesion usually means that a cancer treatment is not working, this isn't always the case with the latest crop of anticancer agents. Some cancer patients who receive immunomodulating treatments experience what's known as pseudoprogression: T cells infiltrate tumours, making lesions bigger before they start to melt away. Other patients show mixed responses in which some lesions shrink while others swell or appear anew.

These unconventional activity patterns pose a problem for oncologists and pharmaceutical companies, who rely on surrogate markers for the speedy approval of game-changing drugs. According to standard antitumour response criteria — either the original World Health Organization (WHO) definitions or the newer response evaluation criteria in solid tumours (RECIST) — any growth in the target lesion or the appearance of new lesions counts as disease progression. With immunotherapeutics, these assessments may be premature. So, representatives from the academic community, the drug industry and the FDA gathered recently in Washington, DC, to discuss alternative outcome metrics and clinical end points that better capture the true benefits of cutting-edge cancer treatments.

"There is a realization that, at least for some patients, conventional criteria for measuring objective responses may not account for [immune-related activity patterns]", says Marc Theoret, lead medical officer of the melanoma/sarcoma team in the FDA's Center for Drug Evaluation and Research. Industry and regulatory researchers proposed several alternative end points at the October workshop, convened by the FDA and the American Association for Cancer Research (AACR).

For now, however, all of these are only investigative, secondary end points. "We don't have a foolproof

substitute for overall survival," says Suzanne Topalian, a melanoma specialist at the Johns Hopkins University School of Medicine in Baltimore, Maryland, USA, and one of the co-chairs of the workshop. "But we do have some interesting leads."

Surrogate end points

The need for an immunotherapy-focused development paradigm was first recognized more than a decade ago by a syndicate of industry leaders now called the Cancer Immunotherapy Consortium. The group initially proposed a modification of the WHO criteria to capture a fuller range of antitumour responses seen in trials of ipilimumab, Bristol-Myers Squibb (BMS)'s anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA4) antibody that in 2011 became the first checkpoint inhibitor to gain approval. The so-called immune-related response criteria (irRC) required confirmation of initial evidence of progressive disease, whereas the WHO criteria do not, and new lesions could be added to the total tumour burden, rather than automatically be counted as progression.

A phase III trial for another CTLA4 inhibitor, tremelimumab, was halted prematurely in 2008 when the drug failed to show a benefit over standard chemotherapy in melanoma. Many experts suspect that tremelimumab would be on the market today had delayed immune-related responses been considered at the time. The irRC were designed, in part, to make sure the same fate didn't befall ipilimumab or any of the programmed cell death protein 1 (PD1) and PD1 ligand 1 (PDL1) blockers that have followed.

Different companies and industry consultants have since adapted the irRC to the more commonly used and simpler RECIST 1.1 criteria, which require imaging measurements of tumours across only one dimension instead of two. Like irRC, the new criteria call for confirmatory scans and allow for lesion growth or appearance before determining disease progression, but each have slight variations. To Elad Sharon, a senior investigator with the US National Cancer Institute (NCI) Cancer Therapy Evaluation Program, "it's clear that not everyone is talking about exactly the same thing."

The latest iteration of these criteria is meant to solve that problem. The iRECIST recommendations were developed with input from the drug industry and global regulatory authorities. And while it's "really very similar" to other variations on the theme, "iRECIST just pulls it all together into a single consistent recommendation and is agreed by all the major players," says Lesley Seymour, director of the Canadian Cancer Trials Group and co-chair of the RECIST Working Group. Seymour will unveil the new criteria on 1 December 2016 at the European Organisation for Research and Treatment of Cancer (EORTC)–NCI–AACR Symposium on Molecular Targets and Cancer Therapeutics in Munich, Germany.

Genentech has used its own closely related criteria to look for possible new surrogate end points of survival in trials of patients with lung and bladder cancer who received the company's anti-PDL1 drug atezolizumab. At the FDA–AACR workshop in October, Daniel Chen, head of cancer immunotherapy at Genentech, described how a progression-free survival score that took into account atypical response patterns offered a better predictor of overall survival than standard measures of time until disease progression. More analyses like this one are needed to help convince the FDA of the validity of these new kinds of metrics, says Chen. "The onus is on all of us to generate those kinds of data sets."

Axel Hoos, head of oncology at GlaxoSmithKline, says that similar results linking immune-related responses to overall patient survival exist for ipilimumab, tremelimumab and the PD1 inhibitor pembrolizumab — and he thinks that should be enough to convince regulators about the validity of the new criteria. "I'm beginning to be a little bit impatient now because we have spent almost a decade working on this," he says. The time is ripe, he adds, for an FDA guidance document on how the field should do clinical development with these new end points.

Tai-Tsang Chen, head of global biometric sciences at BMS, recently convened a team of leading statisticians from 12 pharmaceutical companies and from the FDA to craft industry recommendations for running and analysing immunotherapy trials. The working group aims to propose recommendations before the end of 2017."If we don't get to the bottom of this as soon as possible," he says, "we won't get drugs approved as soon as possible."

The FDA, for its part, hasn't been idle. Statisticians at the agency recently devised a possible as-yet-unnamed surrogate end point for long-term survival that incorporates more information about spikes, blips and oscillations in tumour dynamics by using an area under the curve methodology to calculate changes in lesion size over time.

The analysis considers all existing and new lesions for 1 year, and then defines individuals as responders or non-responders. At the October workshop, the FDA's Xin Gao used data from nine studies of anti-PD1 antibodies in four solid tumour types to show that patients who responded, as defined by these new criteria, were more likely to have a favourable survival outcome. Theoret emphasizes that this end point remains "exploratory at this point."

BMS's Chen also described another kind of intermediate end point at the workshop. His 'milestone survival' doesn't require any imaging information. Instead, researchers simply consider survival rates at a predetermined time point after immune-related effects should have kicked in but before full long-term survival is known. He detailed the method last year using trial data of ipilimumab in melanoma.

These novel measures could offer earlier, more encompassing readouts from immunotherapy trials. And as checkpoint inhibitors become more commonplace, and drug companies look to add on new immunotherapies for additional gains, more sensitive metrics might become ever more necessary. "Some of these delayed responses will make a difference in deciding what the incremental benefit is of the combinations relative to the monotherapy," says Jason Luke, a medical oncologist at the University of Chicago in Illinois, USA.

Case-by-case considerations

The issue of outdated surrogate end points isn't problematic just for checkpoint inhibitors in solid tumours. In August, researchers published new criteria for the evaluation of immunotherapies in lymphoma patients. Oncolytic viruses also frequently cause pseudoprogression, which has led researchers to propose alternative end points. And companies developing modified T cell therapies are thinking about immune-related activity patterns, too.

Ultimately, the biggest challenge for individual physicians — both in clinical trials and in the routine care of patients — may be deciding whether to wait for potential immune-related responses or to declare progression for patients. For one thing, pseudoprogression and mixed responses are fairly uncommon — they occur in only around 10% of melanoma patients who respond to checkpoint inhibitors, and in a lower percentage in other cancers — so it's important to consider the totality of patients' symptoms, not just their scans. "What we typically see in the pseudoprogressors is that

even though the imaging may look worse, the patients clinically are often doing better," says Howard Kaufman, a surgical oncologist at the Rutgers Cancer Institute of New Jersey, USA. "This is very different from real progression."

A physician's tolerance for continuing treatment can also be indication specific. In glioblastoma, a cancer with few effective treatment options, in which pseudoprogression is common, the world's leading neuro-oncologists now recommend staying the course for longer than in other cancers. The immunotherapy response assessment for neuro-oncology (iRANO) criteria, published last year, mirror irRC but allow for 3 months rather than 4 weeks to confirm progression if scans show signs of disease growth within 6 months of treatment initiation. "We really felt that a 3-month window would be reasonable to give these treatments as much of a fair chance as possible," says David Reardon, from the Dana-Farber Cancer Institute in Boston, Massachusetts, USA, who led the working group behind the iRANO recommendations. "We just don't have better therapies, unfortunately, to offer patients instead."

What's needed now, says the NCI's Sharon, are more data to validate these various strategies, enabling the immuno-oncology community to rally around a common set of best practices. "We still do have to come back to clearly correlating these surrogates with a real overall survival benefit," he says, "and I personally think we're not quite there yet."