The Oncologist®

Editorial

PD-1 Pandemonium at the American Association for Cancer Research Annual Meeting

Susan E. Bates

Division of Hematology and Oncology, Department of Medicine, Columbia University Irving Medical Center, New York, New York, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

At the April 2019 meeting of the American Association of Cancer Research (AACR) in Atlanta, Georgia, there was an open session—a forum with Drs. Rick Pazdur and Mark Theoret of the U.S. Food and Drug Administration (FDA) Oncology Center of Excellence and high-ranking members of six pharmaceutical companies who have successfully secured regulatory approvals for an immune checkpoint inhibitor in at least one cancer indication. The title, PD-1 Pandemonium, was apt, given the numerous approvals for six programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1) checkpoint inhibitors in 16 cancer types over the last 5 years, with one histology-agnostic approval and many other approvals anticipated. These immune checkpoint inhibitors have led to a paradigm shift in how many cancers are treated and in our understanding of the biology of cancer beyond genomics.*

When Dr. Pazdur began by warning the industry representatives that he would be challenging them with difficult questions, attention was riveted on the men seated in the comfortable chairs at the front. But by the time he thanked them for "coming into his living room" in his concluding remarks, it was apparent they were never in danger. Dr. Pazdur first asked the men of industry to discuss the differences between PD-1 and PD-L1 inhibitors and differences among the PD-1 blockers. What he was really asking was whether we need all of the anti-PD-1 and PD-L1 agents currently approved and in development. The developers of the anti-PD-1 agents (Bristol-Myers Squibb, Merck, and Regeneron) noted the advantages of the PD-1 inhibitors, including their ability to block PD-1 on circulating T cells, thereby reversing the negative signaling prompted by PD-1. The PD-L1 agents in contrast face additional problems: (a) they must penetrate into the tumor microenvironment, which in some tumor types, because of stroma and altered blood flow, may be difficult; (b) they block only PD-L1 and not PD-L2; and (c) PD-L1 may be upregulated by some drugs, an outcome that might make the target more difficult to block. Given the increasingly level playing field on tolerability, those companies developing anti-PD-L1 agents (EMD Serono, AstraZeneca, Genentech) pointed out data suggesting clinical comparability. As the segment concluded, all seemed to agree that there were no major differences among the PD-1/PD-L1 blockers, despite the emerging sentiment that anti-PD-1 antibodies might have the edge against certain tumor types [1–4]. And with that, Pazdur set the stage for more difficult questions.

He asked, how many of these drugs do we need in the same space? He raised the potential negatives of so many drugs in development in the same class and for the same indication. Indeed, a recent analysis by J. Tang of the Cancer Research Institute concluded that there are 1,716 open clinical trials of combinations of an PD-1/PD-L1 antibody and other agent(s) trials, attempting to enroll 380,900 patients [5]. Together with the marketing of the approved agents and their availability in multiple indications, there has been a drop in the rate of per-trial enrollment, suggesting that these trials may begin to face recruitment challenges.

Pazdur asked whether the large number of agents could jeopardize the conversions from the many accelerated approvals to full approvals. As an example of duplication in clinical trials to reach the endpoints for conversion to full approval, he conveyed the disappointment of the FDA in the multiple trials in renal cell cancer randomizing anti-PD-1/PD-L1 agent against sunitinib, which he deemed duplicative and expensive—the most important cost being that in patients, which he termed a global resource and not a company's resource. As a counterargument, one of the participants noted that the competition from all these trials has led to increased access to the drugs for patients with a broader spectrum of diseases, including rare cancers, and provided incentive to address the unmet needs in rare diseases such as Merkel cell tumors [6].

Correspondence: Susan E. Bates, M.D., Columbia University Irving Medical Center, Herbert Irving Pavilion, 9th Floor, 161 Fort Washington Avenue, West 165th Street, New York, New York 10032, USA. Telephone: 212-305-9422; e-mail: seb2227@cumc.columbia.edu Received April 9, 2019; accepted for publication April 10, 2019; published Online First on 0, 2019. http://dx.doi.org/10.1634/theoncologist.2019-0281

*The industry representatives taking part in the session were Fouad Namouni, M.D., from Bristol-Myers Squibb Co., which makes the PD-1–targeted nivolumab (Opdivo); Kevin Chin, M.D., from EMD Serono, which makes the PD-L1–targeted avelumab (Bavencio); Hesham A. Abdullah, M.D., D.R.Sc., from AstraZeneca Pharmaceuticals LP, which makes the PD-1–targeted durvalumab (Imfinzi); Israel Lowy, M.D., Ph.D., from Regeneron Pharmaceuticals Inc., which makes the PD-1–targeted cemiplimab-rwlc; Scot W. Ebbinghaus, M.D., from Merck Research Laboratories, which makes the PD-1–targeted pembrolizumab (Keytruda); and Alan B. Sandler, M.D., from Genentech, which makes the PD-L1–targeted atezolizumab (Tecentriq).

© AlphaMed Press 2019

Coming back to the multiplicity of antibodies in development, Pazdur noted the agency likes to have multiple drugs in a class (e.g., in the event production of one is discontinued or encounters problems), but again he asked, "How many are too many?" He cited the decrement in survival seen in three recent myeloma trials of anti-PD-1 agents. The industry representative argued that the trials had been well conducted and that the data monitoring committees, functioning properly, had halted accruals at interim analyses. Pazdur, seeming unconvinced, asked why there were three simultaneous trials. Likely hoping to shift the conversation, one of the industry representatives summarized, "Do we need more PD-1 and PD-L1 inhibitors? Probably not." But regarding "third-generation agents? Yes," he argued.

At this point, Dr. Theoret moved the discussion to issues of dosing, schedule, and patient selection. Theoret asked whether there were sufficient data to support extending the dosing intervals from 3 to 6 weeks. The industry representatives said they use PK modeling and look at exposure and dose response to decide on changes in schedule. None mentioned that patient preference had guided their decision, leaving unsaid the success of the initial pembrolizumab schedule every third week as compared with nivolumab's every 2 weeks in non-small cell lung cancer. One argued that real-world data could be used to see if outcomes after a changed schedule match clinical trial data, an argument that did not seem to satisfy Pazdur, who questioned whether real-world data could be relied on for that purpose. He was likely thinking of previous experiences with certain tyrosine kinase inhibitors (erlotinib, cabozantinib, and everolimus), which the FDA approved at drug doses significantly higher than actually tolerable, and how unsatisfying this has been, given what many might argue is real-world use of unproven doses and schedules [7, 8].

Next, the discussion turned to improving outcomes with better patient selection. Without looking at the broad FDA approvals, he made it clear that he was disappointed that we still lack a marker to identify which patients will benefit. He complained about the lack of settled PD-L1 testing or determination of other biomarker strategies, asking at one point, "Doesn't this scream for precompetitive collaboration?" Anticipating pushback from the industry representatives, he noted that yes, Bristol-Myers Squibb collaborates with DAKO and that Merck has a DAKO kit, but noted with some exasperation that these use different antibody clones. Additionally, he pointed to different cutoffs: >5% with one assay but not another assay, varying biological meaning with >1% versus >50%, and the lack of clarity as to the importance of tumor mutation burden and whether this will emerge as an agreed upon metric. Acknowledging that biomarker development was "fit for purpose" in some instances, he noted that we are left with no coherent approach by which to choose patients. This is a major problem in the field, particularly when you sit with a patient who wants to try immunotherapy instead of chemotherapy and there is no FDA indication for his or her tumor type. This should have been an easy one for the industry representatives, but they fumbled the ball. They argued that the development of anti-PD-1/PD-L1 agents has been a bit like building an airplane while flying it. Although likely unintentional, coinciding with the Boeing 737 Max 8 crashes, this analogy was unsettling. One noted that there had been some attempt at harmonization of antibody staining, in the Blueprint project [9]. But another executive opined he did not think it the companies' job to develop a biomarker and that it was unrealistic and naive to think the companies would work on this together. Someone suggested funds be made available for academia for this purpose. Pazdur's angst was palpable as he ended by noting the scream for collaboration has not yet been heard.

Of course, the elephant in the room was that industry drives academia these days—they make the drugs and support the trials that are essential to cancer center research. So, it is obvious that industry could collaborate to drive an "Immuno-Oncology Biomarker Translational Research" enterprise in academia as well. At least one organization—Project DataSphere—has managed to bring companies together to share data (189 datasets representing 144,555 patients; https://www.projectdatasphere.org). Making the molecular and clinical data obtained to date publicly available would be a good first step, and the failure of the conversation to turn to data sharing had to have been to many a great disappointment. Left unasked was whether the FDA should have extended so many approvals without biomarkers, done because there were always a few responses in the "negative biomarker cohorts," rather than insist that greater effort be put toward the biomarker. It could be argued this has led to the use of anti-PD-1/PD-L1 agents even when the chance of a response is substantially lower than that of a meaningful toxicity. Furthermore, I would take all the members of the forum to task for failure to publish negative results with these agents, which by now number in the tens of thousands of patients, all of whom signed informed consents expecting that their contribution to medical progress would result in publicly shared information [10].

The final question was about successes and failures and what each corporate executive might have done differently; as Pazdur put it, what were the "I wish I had...." moments? Most wished that development had not been under so much time pressure and that it could have been done in a more deliberative fashion. Theoret commented on lessons learned at the agency. He replied that development of anti-PD-1/PD-L1 agents had been transformative—49 approvals across 16 indications. This ushered in master protocols, phase 1 trials with thousands of patients, and new thinking about evidence generation and types of toxicities. These are all good things, but there is a certain irony here that in the rush to get the airplane off the ground, much of the FDA's guidance on companion diagnostics [11, 12] was bypassed.

Drug development in oncology is prone to fads and fashions—there were third-generation chemotherapeutics, bone marrow transplants, drug resistance reversal agents, angiogenesis inhibitors, targeted agents, and now immunotherapeutics. Each phase contributed something to the field, but a greater number of potential agents and indications were cast off and abandoned rather than entering the armamentarium. Immunotherapy is a welcome, even transformative, addition to the existing options for cancer treatment,

© AlphaMed Press 2019

and most of the so-far approved agents are here to stay. Some duplication can be valuable, and early on, Pazdur had noted one positive with which everyone seemed to agree—replication has provided assurances that results are valid. Although confirmation with the same agent is a more definitive strategy, two agents with the same target giving similar results increase confidence in the results. As an example, Pazdur had noted that there were five very similar approvals for bladder cancer, for pembrolizumab, atezolizumab, durvalumab, nivolumab, and avelumab—although this may be too many, at least it left no doubt about efficacy. It is likely all the current indications will be confirmed with other agents currently available or in development. Even the atezolizumab results in small cell lung cancer with its 2-month survival advantage are likely to be replicated, as suggested by preliminary data in high-grade neuroendocrine tumors, a disease with many similarities, and in which preliminary data from the DART phase II clinical trial reported comparable effectiveness with nivolumab plus ipilimumab. However, this room for replication takes on a different meaning when considering the 1,716 combination studies with anti-PD-1/PD-L1 agents found by Tang et al. at clinicaltrials.gov. The number raises the question of whether multiple comparisons testing should now be applied to the combination trials. It could be argued that the large number of trials, and the often marginal *p* values resulting, will inevitably mean that some will generate false positive data. That argues for greater stringency in the clinic than usually applied and, ironically, a greater requirement for confirmation.

Disclosures
The author indicated no financial relationships.

References

1. Almutairi A, Alsaid N, Martin J et al. Comparative efficacy and safety of immunotherapies targeting PD-1/PD-L1 pathway for previously treated advanced non-small cell lung cancer: Bayesian network meta-analysis. J Clin Oncol 2018;36(suppl 15):e21012.

2. You W, Liu M, Miao JD et al. A network meta-analysis comparing the efficacy and safety of anti-PD-1 with anti-PD-L1 in non-small cell lung cancer. J Cancer 2018;9:1200–1206.

3. Zhang Y, Zhou H, Zhang L. Which is the optimal immunotherapy for advanced squamous non-small-cell lung cancer in combination with chemotherapy: Anti-PD-1 or anti-PD-L1? J Immunother Cancer 2018; 6:135.

4. Passiglia F, Galvano A, Rizzo S et al. Looking for the best immune-checkpoint inhibitor in pretreated NSCLC patients: An indirect comparison between nivolumab, pembrolizumab and atezolizumab. Int J Cancer 2018;142:1277–1284.

5. Tang J, Yu JX, Hubbard-Lucey VM et al. Trial watch: The clinical trial landscape for PD1/PDL1 immune checkpoint inhibitors. Nat Rev Drug Discov 2018;17:854–855.

6. Nghiem P, Bhatia S, Lipson EJ et al. Durable tumor regression and overall survival in patients with advanced merkel cell carcinoma receiving pembrolizumab as first-line therapy. J Clin Oncol 2019;37:693–702.

7. Bullock JM, Rahman A, Liu Q. Lessons learned: Dose selection of small molecule-targeted oncology drugs. Clin Cancer Res 2016; 22:2630–2638.

8. Jänne PA, Kim G, Shaw AT et al. Dose finding of small-molecule oncology drugs: Optimization throughout the development life cycle. Clin Cancer Res 2016;22:2613–2617.

9. Tsao MS, Kerr KM, Kockx M et al. PD-L1 immunohistochemistry comparability study in real-life clinical samples: Results of blueprint phase 2 project. J Thorac Oncol 2018;13: 1302–1311.

10. Massey PR, Wang R, Prasad V et al. Assessing the eventual publication of clinical trial abstracts submitted to a large annual oncology meeting. ***The Oncologist*** 2016;21:261–268.

11. Rubin EH, Allen JD, Nowak JA et al. Developing precision medicine in a global world. Clin Cancer Res 2014;20:1419–1427.

12. Mansfield EA. FDA perspective on companion diagnostics: An evolving paradigm. Clin Cancer Res 2014;20:1453–1457.

© AlphaMed Press 2019