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Editorial

Publish or Perish v2

Susan E. Bates

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

These are exciting times—an almost dizzying array of FDA approvals logged for immunotherapy, interspersed with some novel compounds. Nearing 50 approvals for immunotherapy in 3 years, oncologists are poised to utilize 7 immune checkpoint inhibitors with FDA approval in more than a dozen oncology settings. No class of oncology drugs has spawned such an effort, and by current estimates, 380,900 slots for patients need to be filled to complete current second-generation immune checkpoint inhibitor combination trials [1]. The excitement surrounding these agents has led almost every patient diagnosed with cancer to request treatment with immunotherapy. Therein is the rub—try to find data on the effectiveness of these agents in diseases for which there is no FDA approval and one comes up empty-handed.

We work in a field where the importance of publishing is well-accepted—in basic science, for scientific communication and, beyond that, for grant and job applications and for academic tenure, with an additional layer in clinical science, for communicating clinical trial outcomes. The latter is particularly important, as patients enrolling on clinical trials expect that their contribution will be meaningful, and therefore lasting. However, as we and others have documented, the results of many clinical trials are never published.

In 2016 we reviewed 1,075 ASCO abstracts describing 378 randomized and 697 nonrandomized clinical trials from 2009–2011 [2]. After 5 years, 75% of randomized and 54% of nonrandomized trials were published, with an overall publication rate of 61%. These findings were almost identical to previous reports for abstracts dating to 1984 [3–8]. Similar results were reported by Memorial Sloan Kettering Cancer Center in a single-institution analysis of 809 clinical trials: 70% of trials calculated to be published by 7 years after accrual was closed. Trials that failed to complete accrual were among the most vulnerable [9]. Results are better for newly FDA-approved agents. The FDA Amendments Act of 2009 required clinical trial registration and reporting of results, and in at least one analysis, the success of this strategy for novel FDA-approved drugs (mostly non-oncologic) was measurable, with an 80% publication rate for trials linked to these drugs [10]. Another analysis found that 99% of press releases were followed by a peer-reviewed manuscript [11]. Clearly publication bias, a related concern for these trials is the rush to early publication of such "positive" results, with only a handful of patients followed beyond 1 year.

These findings are not unique to oncology clinical trials; indeed, failure to publish impacts many if not all academic groups, including international clinical trials. A Danish group found that 73% of completed trials were published [12]. Among randomized clinical trials supported by the Swiss National Science Foundation, 40% were not published in peer-reviewed journals, with the number rising to 70% for discontinued randomized clinical trials [13]. And among clinical trials in The Netherlands, trials that were terminated early had a much lower rate of publication, at 33% published, compared with trials that were completed as planned (64% published; adjusted OR 0.2, 95% CI 0.1–0.3) [14].

The consistent nature of 30%–40% of trials going unpublished in analyses spanning 3 decades leads one to the question of whether things will change or have changed with the immune checkpoint inhibitor approvals. Early indicators suggest that, for the trials leading to FDA approval, there has been, but for the cohorts not receiving benefit, not so much. As one example, think of pancreatic cancer, for which options are limited beyond two standard of care regimens and a prescription for immunotherapy is very tempting. Where are the results with immune-oncologic agents for pancreatic cancer? Very hard to find beyond the responses observed in patients with tumors bearing mismatch repair deficiency, a subset of tumors for which a histology-agnostic FDA approval exists [15–18].

As a solution for the failure to publish, enter Clinical Trial Results (CTR) in *The Oncologist*. Here we publish any clinical trial that teaches us lessons or contributes to our knowledge base, whether successful or disappointing; accrual complete or incomplete; terminated early or as planned; or with endpoints met or unmet. We use an established template that allows the author to easily build a manuscript while providing the essential data of efficacy and toxicity and that includes an automated process for creating Kaplan-Meier graphs and waterfall plots. We ask about "Lessons Learned". In so doing we offer the opportunity that every patient's legacy of clinical trial enrollment will be counted. Every patient's tumor response or adverse event will be permanently recorded. When patients consent to clinical trials, they consent to have their participation matter. All of us have heard patients altruistically express their

Correspondence: Susan E. Bates, M.D., Division of Hematology and Oncology, Department of Medicine, Columbia University Medical Center, New York, New York, USA. Telephone: 212-305-9422; e-mail: seb2227@cumc.columbia.edu Received April 25, 2019; accepted for publication April 25, 2019; published Online First on May 7, 2019. http://dx.doi.org/10.1634/theoncologist.2019-0319

feeling that, even if it does not help them, their hope is that it will help others. Not publishing a clinical trial means effectively that trial and that patient enrollment never existed. Beyond the patient commitment, non-publication leads to a myriad of other problems, including duplication of effort and misperceptions of both efficacy and toxicity. If you are tempted to treat your patient with biliary tract cancer with pembrolizumab off label, you may first want to read the CTR published by Arkenau and colleagues, showing a 4% objective response rate [19]. So much to learn and so little time.

While not the original intent of "Publish or Perish" [20], an ethically meaningful interpretation is this: if we do not publish the results of clinical trials, the lessons learned from those trials perish.

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