The Oncologist®

Editorial

Accrual, Publication Bias, and the Coronavirus in 2020

Susan E. Bates
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.

With the long shadow of the novel coronavirus ever-present, *The Oncologist* commemorates its 25th year in 2020 with a proud record of publishing clinically important, relevant, and timely work in oncology under the leadership of its Scholar in Chief, Bruce Chabner. The journal has consistently prized its readership and offered innovative approaches to its stated goal of "helping physicians excel in the constantly changing fields of oncology and hematology through the publication of timely reviews, original studies, and commentaries on important developments." Clinical Trial Results (CTR), a section that allows the rapid drafting and publication of clinical trials in a template/menu driven format, is a core reflection of our mission [1]. This section provides a remedy for the persistent problem of underreporting of clinical trials in oncology and the subsequent publication bias that this practice necessarily creates [2–7]. CTR acknowledges the commitment and contribution of every patient who enrolls on a clinical trial while offering an approach that minimizes the input required. We have committed to publish every trial with a sound scientific rationale, no matter the outcome, whether the trial completed accrual or met its stated endpoints [1]. We have now reported on almost 8,000 patients across 200 trials, with enrollment sizes as small as two patients.

Beyond the legal, ethical, and moral imperative behind CTR is the practical goal of informing the practice of treating physicians. Too often treating physicians find themselves in the unenviable position of practicing "desperation oncology" to treat patients for whom there is no standard of care and no clinically meaningful option [8]. As our first- and second-line options improve, increasingly patients seek subsequent lines of therapy. These patients are best served on clinical trials. But all too often the trials don't fit the patient's clinical status, comorbidity profile, or history. And so the choice is often ad hoc regimens, and often combinations of known antineoplastic agents, conceived on the spot and without reliable testing. In recent years this may mean the addition of immunotherapies to standard of care regimens. When a combination proves ineffective or overly toxic in a clinical trial that goes unpublished, future patients may be placed at unnecessary risk. For example, pazopanib plus pembrolizumab in renal cell cancer is a logical combination that might be used off-the-shelf, but the trial was halted for toxicity; this result is yet to be published beyond abstract form [9]. The goal of CTR is to put that information in the public domain.

Every year, the Section Editors designate the manuscript that most represents the ideals of CTR as the recipient of the CTR Editors' Choice Award. This year, the award will go to Sandip Pravin Patel and Francisco Robert-Vizcarrondo, along with editorial board member Nathan A. Pennell, for their paper, "Phase Ib Study of Crizotinib plus Pembrolizumab in Patients with Previously Untreated Advanced Non-Small Cell Lung Cancer with *ALK* Translocation" [10].

This paper was notable on several fronts. It was a safety study to establish the maximum tolerated dose for patients treated with the combination of crizotinib and pembrolizumab. As background, both drugs have significant activity in patients with non-small cell lung cancer (NSCLC), and at least a fraction of patients whose tumors bear *ALK* mutations also have high PD-L1 expression. The study began with the FDA-approved doses of both agents: 250 mg twice daily crizotinib and 200 mg pembrolizumab every 3 weeks. Dose-limiting toxicity was observed at the first dose level, and the dose was reduced to 3 weeks of crizotinib monotherapy at 250 mg twice daily, followed by the addition of pembrolizumab 200 mg every 3 weeks, and the combination continued thereafter. Grade 3 liver function tests were observed in two among the seven patients who enrolled at the reduced dose. The authors reported that "although no new major safety issues were identified in this small sample of patients, the higher frequency of severe transaminase increases noted with the use of this *ALK* tyrosine kinase inhibitor (TKI) plus PD-L1 inhibitor combination are a cause of concern." The authors acknowledged that accrual was poor and the decision was made to close the study after only 9 patients. It seemed that pembrolizumab exacerbated the hepatotoxicity that is a known and serious complication of crizotinib monotherapy [11].

The push for reliable publication of all clinical trial results regardless of outcome has shown little improvement over time, despite multiple studies outlining the extent of this problem, including our own [2–6]. One root cause of nonpublication is poor accrual to a trial. When studies close early due to poor accrual, the work therein is seldom

Correspondence: Susan E. Bates, M.D., Division of Hematology and Oncology, Department of Medicine, Columbia University Irving Medical Center, New York, New York, 10032, USA. Telephone: 212-305-9422; e-mail: seb2227@cumc.columbia.edu Received and accepted for publication May 19, 2020; published Online First on May 29, 2020. http://dx.doi.org/10.1634/theoncologist.2020-0455

published. Several reasons have been offered for poor trial accrual, including improved standard of care options, stringent or narrow eligibility criteria, and competing trials [12, 13]. As an example of the latter, in 2017, Tang et al. identified 469 new immuno-oncology (IO) combination trials, expecting to enroll 52,539 patients, more than available for the chosen indications [14]. Another reason why trials accrue poorly is because investigators "vote with their feet" when they sense that an agent is not very active or too toxic.

A failure to accrue leads to a failure to report, a particular problem for novel combinations of agents that individually have received FDA approval and are widely available in clinic. Nowhere is this truer than adding IO agents to other antineoplastic therapy. The fanfare over immunotherapy has led patients to ask for it by name, and withholding it for lack of data in a patients' specific diagnosis or situation can lead to loss of trust in a physician. This year's Editors' Choice Award is one such example, highlighting the need to publish IO trials that help paint the entire picture, not just the positive outcomes. The toxicity seen in the combination *ALK* TKI and PD-L1 inhibitor was not expected and clearly surprised investigators who saw severe transaminase elevations at the reduced dose level.

In publishing this trial, the authors achieved two outcomes. First, the authors added to the accumulated data on TKIs plus PD-L1 inhibitors, and may have prevented the launch of a similar future trial. Second, because these investigators published their findings, an oncologist anywhere in the world can perform a literature search, discover this paper, and decide to avoid this combination in patients with *ALK* + NSCLC. Such transparency will always benefit our patients.

Amidst a global pandemic, some might say we have more important things to worry about than whether small, poorly accruing trials are published or not. We respectfully disagree. The era of COVID19 reflects the importance, perhaps more than ever, of transparency in the outcomes of trials small and large. CTR also welcomes reports of coronavirus therapeutics in our cancer patient population.

Disclosures
The author indicated no financial relationships.

References

1. Bates SE. Publish or perish v2. ***The Oncologist*** 2019;24:723–724.

2. 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.

3. Shepshelovich D, Goldvaser H, Wang L et al. Comparison of published and unpublished phase I clinical cancer trials: An analysis of the ClinicalTrials.gov database. Invest New Drugs 2018;36:933–938.

4. DeVito NJ, Bacon S, Goldacre B. Compliance with legal requirement to report clinical trial results on ClinicalTrials.gov: A cohort study. Lancet 2020;395:361–369.

5. Doroshow JH. Commentary: Publishing cancer clinical trial results: A scientific and ethical imperative. ***The Oncologist*** 2008;13:930–932.

6. Zarin DA, Tse T, Williams RJ et al. Trial reporting in ClinicalTrials.gov—The final rule. N Engl J Med 2016;375:998–2004.

7. Piller C. FDA and NIH let clinical trial sponsors keep results secret and break the law. Available at https://www.sciencemag.org/news/2020/01/fda-and-nih-let-clinical-trial-sponsors-keep-results-secret-and-break-law. Accessed May 18, 2020.

8. Kolata G. 'Desperation oncology': When patients are dying, some cancer doctors turn to immunotherapy. Available at https://www.nytimes.com/2018/04/26/health/doctors-cancer-immunotherapy.html. Accessed April 26, 2018.

9. Chowdhury S, McDermott DF, Henner Voss M et al. A phase I/II study to assess the safety and efficacy of pazopanib (PAZ) and pembrolizumab (PEM) in patients (pts) with advanced renal cell carcinoma (aRCC). J Clin Oncol 2017;35(suppl 15):4506.

10. Patel SP, Pakkala S, Pennell NA et al. Phase Ib study of crizotinib plus pembrolizumab in patients with previously untreated advanced non-small cell lung cancer with *ALK* translocation. ***The Oncologist*** 2020 [Epub ahead of print].

11. Kazandjian D, Blumenthal GM, Chen HY et al. FDA approval summary: Crizotinib for the treatment of metastatic non-small cell lung cancer with anaplastic lymphoma kinase rearrangements. ***The Oncologist*** 2014;19:e5–e11.

12. Kim ES, Bruinooge SS, Roberts S et al. Broadening eligibility criteria to make clinical trials more representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement. J Clin Oncol 2017;35:3737–3744.

13. Bennette CS, Ramsey SD, McDermott CL et al. Predicting low accrual in the National Cancer Institute's Cooperative Group Clinical Trials. J Natl Cancer Inst. 2015;108:pii: djv324.

14. Tang J, Shalabi A, Hubbard-Lucey VM. Comprehensive analysis of the clinical immuno-oncology landscape. Ann Oncol 2018 ;29:84–91.