

Characteristics and Publication Bias of Clinical Trials Supporting Immune Checkpoint Inhibitors and Other Newest Anticancer Drugs Recently Approved by the US Food and Drug Administration: A Protocol for A Meta-Epidemiological Investigation

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Introduction

Recent improved understanding of the biology and pathogenesis of cancer has led to a remarkable progress in therapeutic approach in a variety of cancers. Drug development over the last 2 decades has resulted in anticancer drugs utilizing multiple mechanisms of action including conventional cytotoxic agents, inhibition of oncogenic signaling pathways, and angiogenesis. More recently, the pharmaceutical industry has an increasing interest in treatments that rely on immunomodulatory mechanisms to target and destroy cancer cells. Immunotherapy with such agents, including cytokines, monoclonal antibodies (mAbs), immune checkpoint inhibitors, T cell therapies, oncolytic viruses and vaccines, offers a new treatment paradigm. Among these, the most

notable are the clinical development and commercialization of immune checkpoint inhibitors.

The first immune checkpoint inhibitor approved by the United States (US) Food and Drug Administration (FDA) was ipilimumab, a fully human immunoglobulin G1 mAb that blocks cytotoxic T-lymphocyte antigen (CTLA)-4. Ipilimumab was approved as an orphan drug for the treatment of metastatic melanoma in 2011 based on the survival benefit in a pivotal phase 3 trial [1]. Pembrolizumab and nivolumab were the first two checkpoint inhibitors that target programmed cell death protein 1 (PD-1) approved by the FDA for metastatic melanoma in 2014, which showed high response rate with favorable toxicity [2,3]. Despite these early successful results, recent studies, however, have revealed that only a subset of people exhibit durable responses and checkpoint blockage monotherapy seldom leads to complete remission [4,5]. These findings have stimulated further investigation of numerous combinations of checkpoint inhibitors with other biologic agents in ongoing Phase I and II trials.

In the US, the FDA is responsible for approval of new drug products for sale and marketing. Anticancer drugs are approved based on substantial evidence of clinical benefit (or efficacy) from adequate and well-controlled investigations. Efficacy should be demonstrated by the prolongation of survival, improvement in the quality of life through the prevention or amelioration of cancer-related symptoms, or an established surrogate for either of these endpoints. Sponsors of a new drug are required to submit all data, including complete protocols, protocol revisions, and data from failed trials to the FDA for its approval. And once the drug received FDA approval, the FDA discloses a Summary Basis of Approval document that contains summaries and evaluations of clinical data and statistical analyses performed by FDA medical officers during the approval process. These summaries, however, contain only selected results from the clinical trials, and the patients, the clinicians and the policy makers cannot have an access to the complete results without full publication in the medical literature. Nevertheless, previous studies have demonstrated that there were discrepancies between original trial data submitted to the FDA and data found in published trials [6–8]. Such selective reporting bias and publication bias favor the dissemination of information about clinical interventions showing statistically significant benefit, which could lead to overestimation of benefits and underestimation of harms of newly approved anticancer drugs, including above-mentioned immune checkpoint inhibitors.

In this context, the aim of this study is to evaluate the publication status of trials submitted to the FDA for newly approved anticancer drugs, especially for immune checkpoint inhibitors.

Methods

Identification of Clinical Trials

We will identify all the immune checkpoint inhibitors for the treatment of any cancers newly approved by the FDA between 2011 and 2014 at the Center for Drug Evaluation and Research Web site, available at <http://www.fda.gov/cder/da/da.htm>. 2011 is the year the first immune checkpoint inhibitor was approved by the FDA; 2014 will be selected as the last year for inclusion in order to assure follow-up of at least 3 years after approval. We will also identify all the other anticancer drugs for the treatment of any cancers newly approved by the FDA between 2011 and 2014, and randomly select 10 drugs among them. We will include only new drugs classified as “new molecular entities,” which are drug products that have never been previously approved by the FDA for any indication, hereafter referred to as “new drug.” We will exclude the drugs to treat drug side effects, cancer pain, other conditions, or cancer prevention. For each drug, we will retrieve the FDA Summary Basis for Approval and evaluate the medical and statistical review documents to identify clinical trials submitted by the sponsor. These review documents are available at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm> for all new drugs approved since 1998. We will obtain the product label at the time of FDA approval for each new drug, or the next available product label if the initial product label is not available, at <http://www.fda.gov/cder/approval/index.htm>.

Data Extraction

For each submitted trial, we will record the following characteristics when available in the FDA documents: the drug name (generic and trade), the initial approval date (month, year), approval status (accelerated or standard), drug target, delivery method, dosage and evaluation schedules, indication, the number and location of study sites, sponsors' name, principal investigator's name, authors' industry affiliation, study phase, purposes of the trials (efficacy and/or safety and/or pharmacokinetics), study type (superiority trial or non-inferiority trial or equivalence trial), the number of arms, control conditions, planned sample size, planned difference to detect, the number of study participants, the primary and secondary outcomes, sample size in the primary analysis, effect size of the primary outcome, statistical significance of the primary outcome ($p < 0.05$ or

confidence interval [CI] excluding no difference; or if the study is a non-inferiority one, CI including no difference and excluding the prespecified margin described in the protocol; or if the study is an equivalence one, CI between no difference and the prespecified margin). Nonsignificant or null results will be defined as $p > 0.05$ or CI including no difference; or if the study is a non-inferiority or equivalence one, CI including the prespecified margin. We will also record whether the trial is randomized or double blinded as reported by the sponsor in the FDA documents.

Search Strategy and Publication Matching

First, we will electronically search World Health Organization International Clinical Trials Registry Platform (ICTRP) and PubMed to match each trial identified in the FDA review documents to publications in the medical literature. The search terms will include drug name, drug indication, trial ID and principal investigator's name. All language retrievals will be reviewed in abstract or full-text form. Trials identified in the FDA reviews will be matched to a publication based on the following characteristics: drug name, sample size, dosing schedules, number and location of study centers, primary outcome measures, and statistical significance or estimated effect of the primary outcome results. The publication status of each trial will be recorded as (1) full publication, (2) partial publication, (3) conference abstract, (4) not published or verified. Only original research reports in full journal articles will be counted as (1) full publication which includes all the primary outcomes predefined in the protocol; (2) partial publication by definition contains incomplete descriptions of the prespecified primary outcomes. For trials stopped early because of perceived effectiveness, only original research reports in full journal articles will be counted as (1) full publication which include all findings and results. For analysis, the coding categories above will be dichotomized as "published" or "not published". A trial will be coded as "published" if it is in categories 1. All other trials (categories 2 or 3 or 4 above) will be coded as "not published". If trials remained unmatched to a publication in PubMed, we will search the Cochrane Library, Scopus, ClinicalTrials.gov and Google/Google Scholar.

Statistical Analysis

The main outcome measure will be the rate of "full publication" within 2 years after the FDA approval and the unit of analysis will be the indication of the drugs, not the individual drug nor the trial. We will analyze publication at 2 years because pending Congressional legislation is considering mandating results reporting by 2 years after drug approval.

We will also analyze publication at time 0 and 3 years, and measure the time from FDA approval to “full publication”. In the last time-to-event analysis, trials that are not published will be censored. Month zero will be defined as the month of FDA approval as stated in the FDA documents. The publication month will be the month of the journal issue in which the trial appeared: date of electronic publication, if any, will be included. Trials published before their FDA approval date will be analyzed as published at time 0. In cases of duplicate publication (those reporting the same findings and results from the same trial, study population, intervention, and measured outcomes), we will include only the earliest publication of full publication.

In addition, we will carry out multivariate logistic regression analysis and calculate odds ratios at 2 years after approval on all supporting trials to control for multiple variables. Predictors assessed in multivariable analyses will include statistical significance of the primary outcome(s), approval status (accelerated or standard) and the type of anticancer drugs (immune checkpoint inhibitors or not). A P value <0.05 will be considered statistically significant. Statistical analyses will be conducted using STATA version 14 (Stata Corp LP, College Station, TX, USA).

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