





Evolving landscape and academic attitudes toward the controversies of global immuno-oncology trials

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Abstract

This cross-sectional and longitudinal descriptive analysis aimed to track the evolving landscape of global immuno-oncology (IO) trials and provide insight into the resolution of IO-related controversies. Clinical trials (n = 4510) registered on ClinicalTrials.gov in 2007 to 2019 studying immune checkpoint inhibitors (ICIs), adoptive cell transfer (ACT), cancer vaccines and immune modulators were included. Most of IO trials are Phase 2 and focus on ICIs and multiple IO therapies. The United States leads global IO research, with stable growth and the best methodological quality. Mainland China ranks first in the number of ACT trials but has the lowest article publication rate (6.2%). A multiple-arm comparative design is often adopted in multiple IO therapies trials (44.0%). Trials studying ICIs and multiple IO therapies are likely to use early registration (80.0% and 86.6%) and stringent corticosteroid-/infection-related criteria. Hospitals have provided the most extensive and strongest support for all IO categories. Big pharma prefers to fund Phase 3-4 ICI trials (6.98%), while small pharma has a wider sponsorship favoring Phase 1-2 trials. The “partial-use-of-corticosteroids” strategy is generally well accepted in ICI trials with a definitive trend (32.5%; $P < .001$) but is associated with the poor dissemination of results ($P \leq .020$), while the complete disclosure and standardization of dose/timing limits are still lacking. Disparities in design features and dissemination of results are widespread in IO trials and are modulated by IO category, cancer type and sponsor. We propose policy reforms to redefine the timely publication of IO trials and standardize the resolution of corticosteroid-/infection-related issues.

KEYWORDS

cancer, clinical trial, corticosteroid, immuno-oncology, publications

Abbreviations: ACT, adoptive cell transfer; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; FDAAA, the U.S. Food and Drug Administration Amendments Act; ICI, immune checkpoint inhibitor; IO, immuno-oncology; IrAE, immune-related adverse event; NCT, national clinical trial; PD-1, programmed cell death-1; PD-L1, the ligand of programmed cell death-1; TB, bacillus tuberculosis.

Cheng Xu, Shu Zhang, Yuan Zhang and Si-Qi Tang contributed equally to this study.

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1 | INTRODUCTION

Over the past quarter century, immuno-oncology (IO) has emerged as an exciting breakthrough in the biologics industry.¹ Due to its specificity, adaptability and durability in restoring patients' own immune function against cancer, IO therapy has been deemed one of the pillars of antitumor therapy.^{1,2} Policy makers and medical markets have shown strong enthusiasm for this field by accelerating the time to approval of IO agents, which will have an estimated market value more than \$35 billion by 2023.² IO therapies, including immune checkpoint inhibitors (ICIs), adoptive cell transfer (ACT), cancer vaccines and immune modulators, have distinctly different mechanisms of action and a broad range of targets. ICIs use monoclonal antibodies that activate T-cell immunity or address T-cell exhaustion by blocking proteins on cells, such as cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), programmed cell death-1 (PD-1) and the ligand of PD-1 (PD-L1).³ ACT consists of the *in vitro* expansion and subsequent reinfusion of autologous lymphocytes with antitumor properties,⁴ and a cancer vaccine stimulates immunity against tumor antigens.⁵ Past findings reported that the number of IO targets increased a tremendous 50% in 2017 to 2018.⁶ By providing cutting-edge preclinical scientific information and highly recommended evidence guiding clinical strategies, IO trials have broadened the horizon of antitumor therapies, changing the standard-of-care in over a dozen cancer types.⁷

The fast-expansion of the research focus not only overcrowds the pipeline of IO agents stalled in development but also overwhelms clinicians attempting to track the rapidly evolving landscape of global IO trials. Solutions to problems that arise during the real-world application of IO are obviously lagging behind. For instance, caution was advised regarding corticosteroid administration before IO therapy as it negatively affected survival outcomes in patients with lung cancer receiving PD-1 and PD-L1 blockades.⁸ This is mainly due to the systemic immunosuppressive effects of corticosteroids,⁹ even though low-dose corticosteroid administration has been shown to be sufficient to suppress the immune response.¹⁰ However, a recent study indicated that corticosteroids used for the management of immune-related adverse events (irAEs) may not compromise the therapeutic efficacy.¹¹ These conflicting opinions stem in part from the fact that ICI trials before 2015 varied in whether they explicitly allowed corticosteroids in their designs.¹² Approximately 50% of the pivotal trials of antitumor drugs approved by the European Medicines Agency have intrinsic flaws in design, producing the biased estimates of treatment effects and jeopardizing the dissemination of results.¹³ Although a lack of timely reporting is a common problem in clinical trials from academic institutions, little is known about it in the IO field.¹⁴ Factors related to trial design can impact compliance with the requirement for publication; however, this requires verification.¹⁵ Infection is another controversial issue necessitating a thorough investigation. Past evidence has shown that the use of antibiotics before ICIs may shorten the overall survival of cancer patients by 92%.¹⁶

A clear grasp of the attitudes toward these unresolved IO-related controversies in academia is critical to help clinicians and investigators implement suitable interventions and consider stratification at the

What's new

In recent decades, immunotherapy has emerged and advanced to become a key part of cancer-fighting strategies. The rapid growth of immuno-oncology, however, has been accompanied by controversy in suitable interventions and trial design. In this cross-sectional and longitudinal analysis, disparities in design were found to be common in immuno-oncology trials, with differences influenced by factors such as cancer type and trial sponsor. Trials with strict limitations on corticosteroid use had significantly higher publications rates than trials permitting partial corticosteroid administration. The data further suggest that timely publication of immuno-oncology trials is the third year after trial completion.

time of trial launch. Meanwhile, a systematic understanding of various IO trials can help the above stakeholders efficiently transfer emerging research findings into clinical practice and optimize the conception and conduction of future trials. Therefore, we conducted a comprehensive cross-sectional and longitudinal analysis based on the historical and current IO trials, with the aim to provide new insight into the resolution of current IO controversies.

2 | METHODS

Our study was reported in line with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE; Appendix).¹⁷

2.1 | Identification of eligible IO trials

We downloaded the raw data of 273 731 clinical trials potentially related to IO and registered on ClinicalTrials.gov as of 31 October 2019 using the Aggregate Analysis. The registration time was defined from 1 January 2007 to 31 October 2019. Clinical trials studying any single one or combination of the following IO therapies were included: ICI, ACT, cancer vaccine and immune modulator. ACT comprises tumor infiltrating lymphocyte therapy, chimeric antigen receptor T-cell therapy, T-cell receptor-engineered T-cell therapy, cytokine-induced killer cell therapy, lymphokine-activated killer cell therapy and natural killer cell therapy. Cancer vaccines include exogenous and endogenous vaccinations, such as dendritic cell-based approaches and oncolytic viruses.¹⁸ Although monoclonal antibodies are a type of IO therapy, some of them work in a more targeted way.¹⁹ As the classification of monoclonal antibodies is complicated and partly overlaps with ICI agents and targeted therapy, we did not include monoclonal antibodies in the study. Finally, a total of 4510 eligible IO trials were identified (Figure S1).

2.2 | Information extraction, integration and data processing

We adopted information extraction, integration and data processing to prepare the raw data according to Jensen's approach.²⁰ Board-certified oncologists (Shu Zhang, Yuan Zhang, Si-Qi Tang, Xue-Liang Fang, Jin-Qi Liu and Liang Peng) retrieved the detailed registration information of all included IO trials from the ClinicalTrials.gov registry using literature-mining methods such as entity recognition and national clinical trial (NCT) identifiers.²⁰ All data were processed to achieve a standardized format and recorded in a web-based standardized extraction form with definitive annotations and term definitions. All investigators strictly complied with guidelines regarding the principles of data integration (Appendix; Methods). We pilot-tested this process on several randomly selected IO trials, resolved any disagreements by consensus and accordingly revised and implemented the guidelines (Appendix; Version 3, 2 September 2018).

We used inferred missing data from alternative data sources when necessary. For example, the address of the principal investigator or sponsor headquarters could be used to determine the geographic location of the research facility. Although the U.S. Food and Drug Administration Amendments Act (FDAAA) and the International Committee of Medical Journal Editors require the early registration of clinical trials before participant enrolment, not all trials complied with this policy.²¹ For each IO trial that had delayed registration, we recorded its actual start time and whether it completed registration before the trial launch. Seventeen cancer types were determined by referring to the codes of the International Statistical Classification of Diseases and Related Health Problems, 10th revision. We categorized sponsors into big pharma, small pharma, hospital, university, nonprofit organization and private. "Big pharma" were defined as the companies listed in the *Pharmaceutical Executive Ranking of the Top 50 Global Pharma Companies in 2019*.²² We limited the ICI subcategories to PD-1, PD-L1 and CTLA-4 blockades that have been licensed for clinical use but did not include emerging agents. Trial designs were modeled and simplified for better classification. All included IO trials were classed as either a "single-arm trial" or a "multiple-arm trial." For a single-arm trial, IO monotherapy and multiple IO therapies were categorized as "IO." Chemotherapy, radiotherapy, surgery, targeted therapy, supportive therapy and their combinations were categorized as "conventional therapy." In multiple-arm trials, we simplified the design by combining arms with the same type of therapy and generated a summary with a comparison between arms with different types. IO monotherapy, multiple IO therapies and IO agent(s) plus conventional therapy were categorized as "IO-based therapy."

2.3 | Assessment of eligibility criteria

Some IO trials prohibited systemic corticosteroids but allowed non-systemic use, such as replacement, premedication, intranasal, inhaled and topical use, with limitations on the dose and/or timing. Therefore, we regarded "partly permitted" as a parallel branch to "not

permitted," and both categories were considered to involve the definitive exclusion of corticosteroid administration. We standardized the timing data by selecting the most compatible unit, for example, 28 to 31 days were recorded as 1 month. Indirectly reported doses were calculated according to the standard body surface area of 1.7 m². The doses of different corticosteroid drugs were standardized by conversion into the approximate equivalent dose of prednisone. "Infection" is a general concept that differs from specific diseases, such as bacillus tuberculosis (TB) and acquired immune deficiency syndrome.

2.4 | Determination of the dissemination of results

The dissemination of the results of a particular IO trial was identified as either the direct submission to ClinicalTrials.gov or the publication in a journal article. Applicable clinical trials are required, per FDAAA legislation, to report their results to ClinicalTrials.gov within 1 year of study completion.¹⁵ To guarantee sufficient time for the generation of results before publication, we excluded IO trials with an estimated completion date later than 31 October 2018. For each included IO trial, we determined whether any tabular or structured results had been posted on the registry website. We then used a three-step search strategy to ascertain the status of article publication, which has been presented in a previous study.²³ Conference abstracts were excluded due to their incomplete and premature nature.²⁴ We defined the dissemination of results as "time-to-event data." Given that IO trials can be completed ahead of the estimated schedule, we determined the time to website publication as the period from the "study start date," a more accurate and stable beginning point than the "completion date," to the "results first posted date." In addition, we recorded the earliest available data, such as Epub and online preprint, to calculate the time to journal publication. The follow-up time for trial results that had not yet been disclosed was calculated as a censored value from the "study start date" to the initiation of our study (31 October 2019).

2.5 | Statistical analysis

We used descriptive statistics to summarize the dose and/or timing limitations on the administration of corticosteroids and live vaccines before IO therapy. Categorical variables were reported as frequencies and percentages. The registration period from 2007 to 2019 was divided into three observation periods (eg, 2007-2011, 2012-2015 and 2016-2019) for dynamic assessment. To investigate the attitude of academia toward issues related to corticosteroids and infection, we evaluated the eligibility criteria of IO trials and compared the methodological quality of relevant items in the stratification of IO category, geographic origin and sponsor. Multiple results were visualized using radar plots, with each axis displaying one eligibility criterion. We standardized the order and scale of the axes to facilitate comparisons between rival comparators. The

Cochran-Armitage test was used to explore whether there was a potential trend in the specifications regarding corticosteroid administration.²⁵ Cumulative rates of the dissemination of trial results were estimated using the Kaplan-Meier method at monthly intervals and compared using log-rank tests.²⁶ Time-point publication rates were calculated using life tables.²⁷ We used Python 3.8.1 (Python Software Foundation, Wilmington, DE) to download and process the raw data and SPSS 24.0 (IBM Corp, Armonk, NY) to perform the statistical analyses. All tests were two-sided, and $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Evolving landscape of IO trials by geographic origin

From 2006 to 2013, there was a gradual increase (43-203) in the numbers of trials, followed by a sharp increase (263-980) in 2014 to 2019. Mainland China had the largest growth rates in the observation periods of 2012 to 2015 (912%) and 2016 to 2019 (318%). IO trials from the United States had stable growth, while the numbers of IO

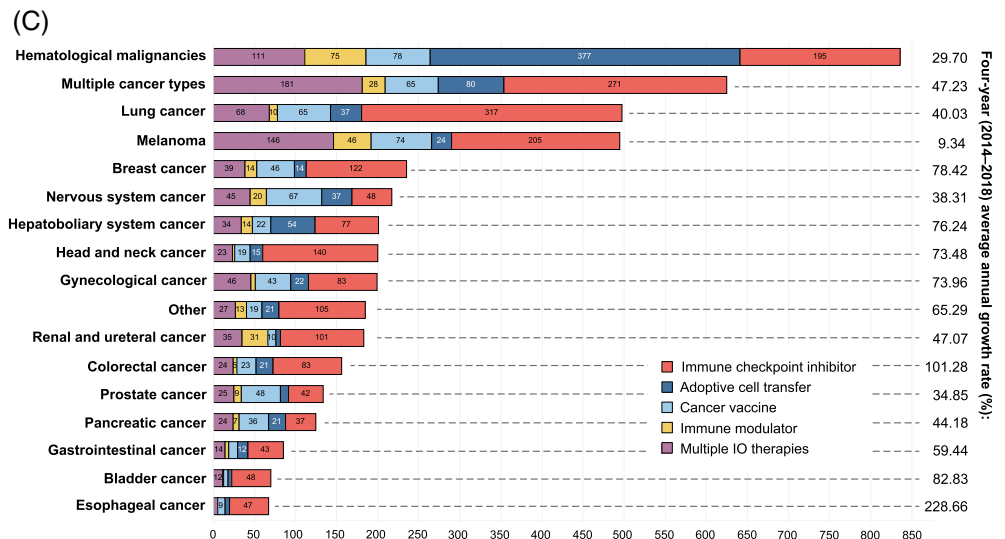
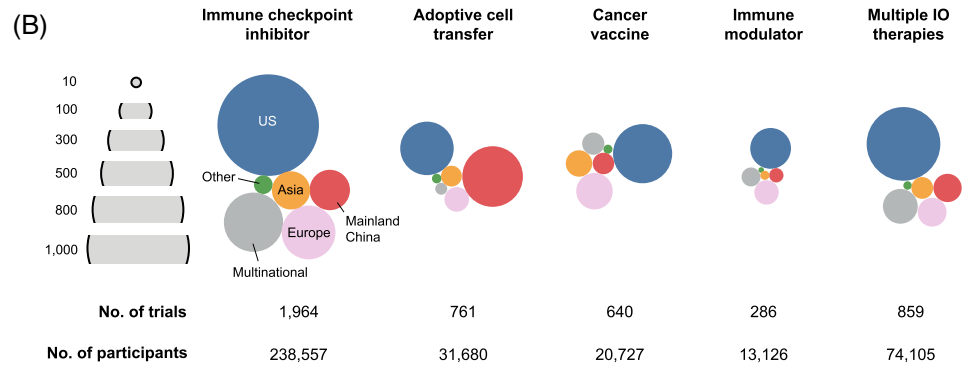
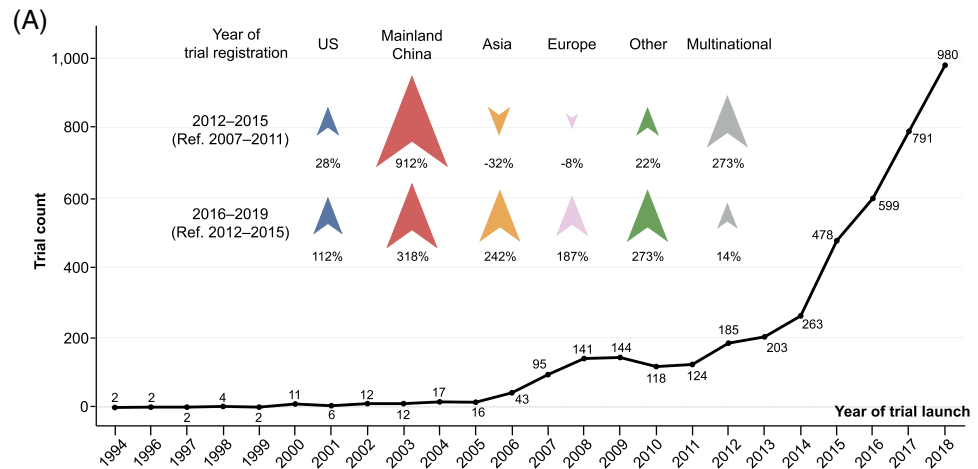


FIGURE 1 Longitudinal registration count (A) and landscape (B) of immuno-oncology (IO) trials from different geographic origins and the distribution in 17 cancer types (C). No relevant data were reported in 2005, so this node is omitted on the abscissa [Color figure can be viewed at wileyonlinelibrary.com]

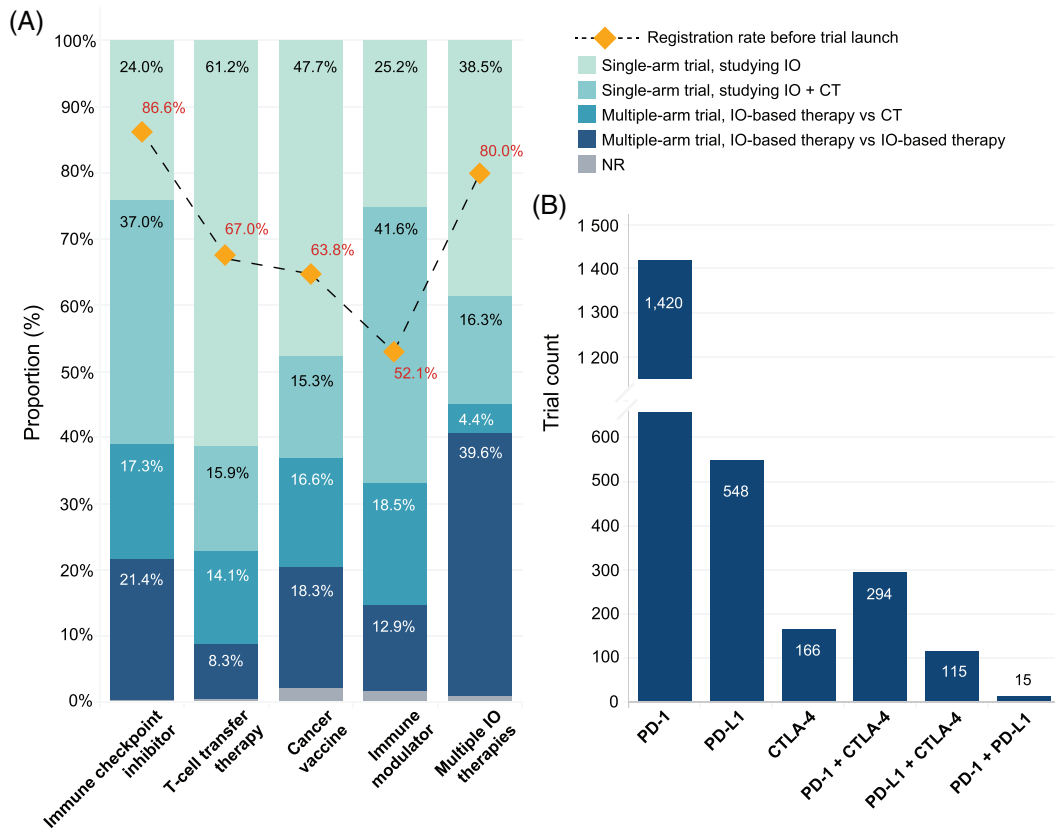


FIGURE 2 Overview of trial designs (A) and ICI targets (B). CT, conventional therapies; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; ICI, immune checkpoint inhibitor; IO, immuno-oncology; NR, not reported; PD-1, programmed cell death-1; PD-L1, the ligand of programmed cell death-1 [Color figure can be viewed at wileyonlinelibrary.com]

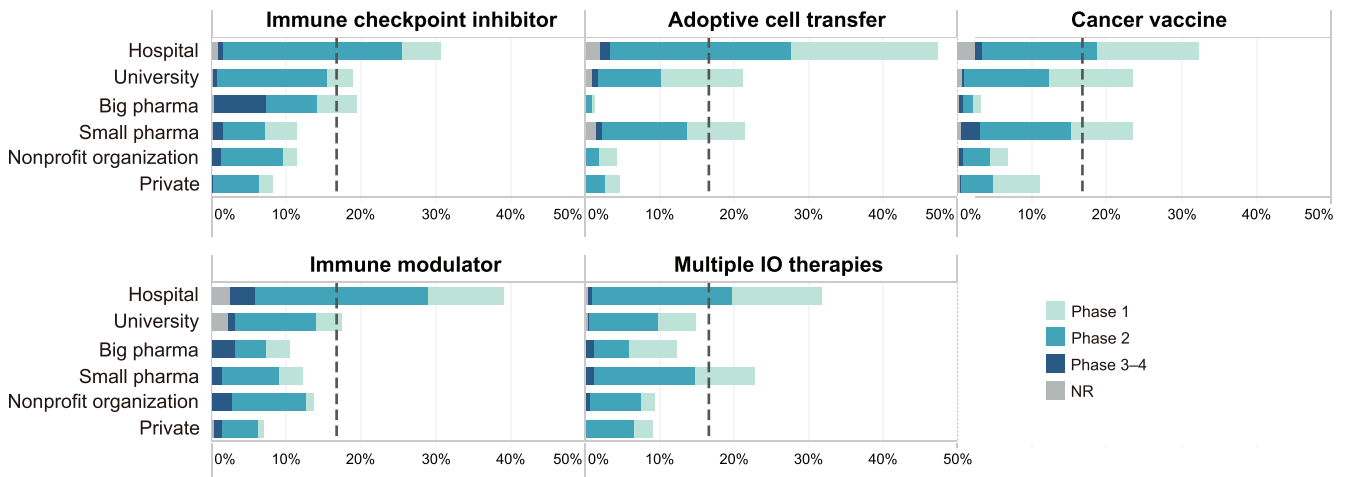


FIGURE 3 Landscape of the composition and proportion of sponsorship according to immuno-oncology (IO) category and trial phase. The dotted line represents the average sponsorship ratio of all sponsors to IO trials [Color figure can be viewed at wileyonlinelibrary.com]

trials from Asia and Europe were observed to have decreasing trends of -32% and -8% in 2012 to 2015, although they increased thereafter (Figure 1A). The majority of IO trials focused on ICIs, with 238 557 participants enrolled in 1964 trials. The US had the greatest

proportion of trials for ICIs, cancer vaccines, immune modulators and multiple IO therapies, while mainland China had the greatest proportion of trials for ACT. Multinational IO trials had the second greatest proportions of trials for ICIs and multiple IO therapies, while European

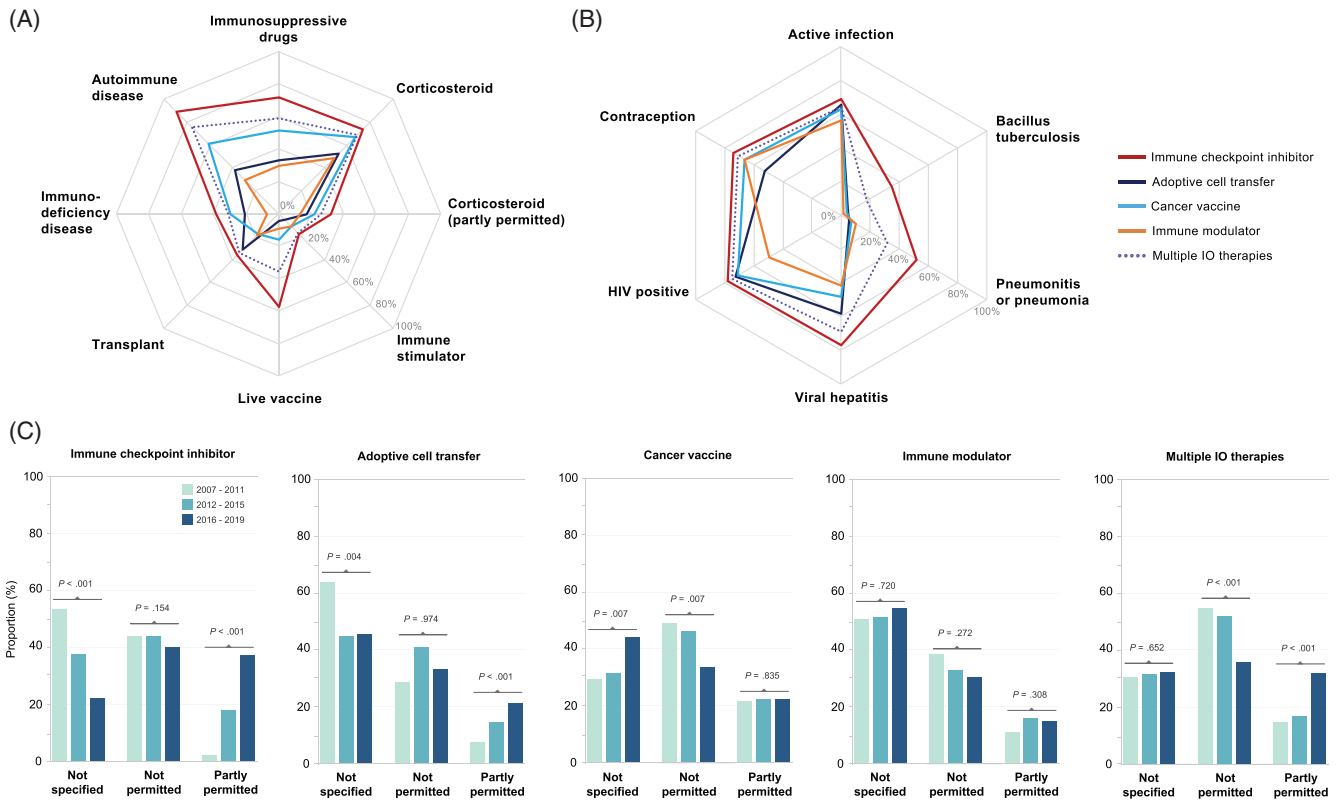


FIGURE 4 Intensity of restrictions on corticosteroid- and infection-related criteria (A,B) and the trend in attitudes toward corticosteroid administration in IO trials (C). HIV, human immunodeficiency virus; IO, immuno-oncology [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Dose and timing limits of corticosteroids and vaccines before IO therapy

Classification	Values								
Dose limit of corticosteroid before IO therapy									
Items (mg/d)	<10	10	≤20	≤30	≤50	≤100	>100	Ambiguity ^a	NR
Count	67	980	108	46	15	12	3	67	1698
Proportion (%)	2.24	32.71	3.60	1.54	0.50	0.40	0.10	2.24	56.68
Timing limit of corticosteroid before IO therapy									
Items	≤1 wk	≤2 wk	≤3 wk	≤1 mo	≤2 mo	≤6 mo	≥1 yr	NR	
Count	873	708	24	338	34	28	9	982	
Proportion (%)	29.14	26.63	0.80	11.28	1.13	0.93	0.30	32.78	
Timing limit of corticosteroid for autoimmune disease before IO therapy									
Items	4-6 wk	2 mo	3 mo	6 mo	1 yr	2 yr	3 yr	5 yr	NR
Count	10	7	114	1	11	638	40	44	2272
Proportion (%)	0.32	0.22	3.63	0.03	0.35	20.31	1.27	1.40	72.33
Timing limit of live vaccine before IO therapy									
Items	<1 mo	1 mo	≤2 mo	≤3 mo	≤4 mo	≤6 mo	≤1 yr	>1 yr	NR
Count	143	1408	27	13	1	1	3	4	96
Proportion (%)	8.43	83.02	1.59	0.77	0.06	0.06	0.18	0.24	5.66

Abbreviations: IO, immuno-oncology; mo, month; NR, not reported; wk, week; yr, year.

^aAmbiguous description of the dose limit of corticosteroid before IO therapy includes low dose, physical dose and replacement dose.

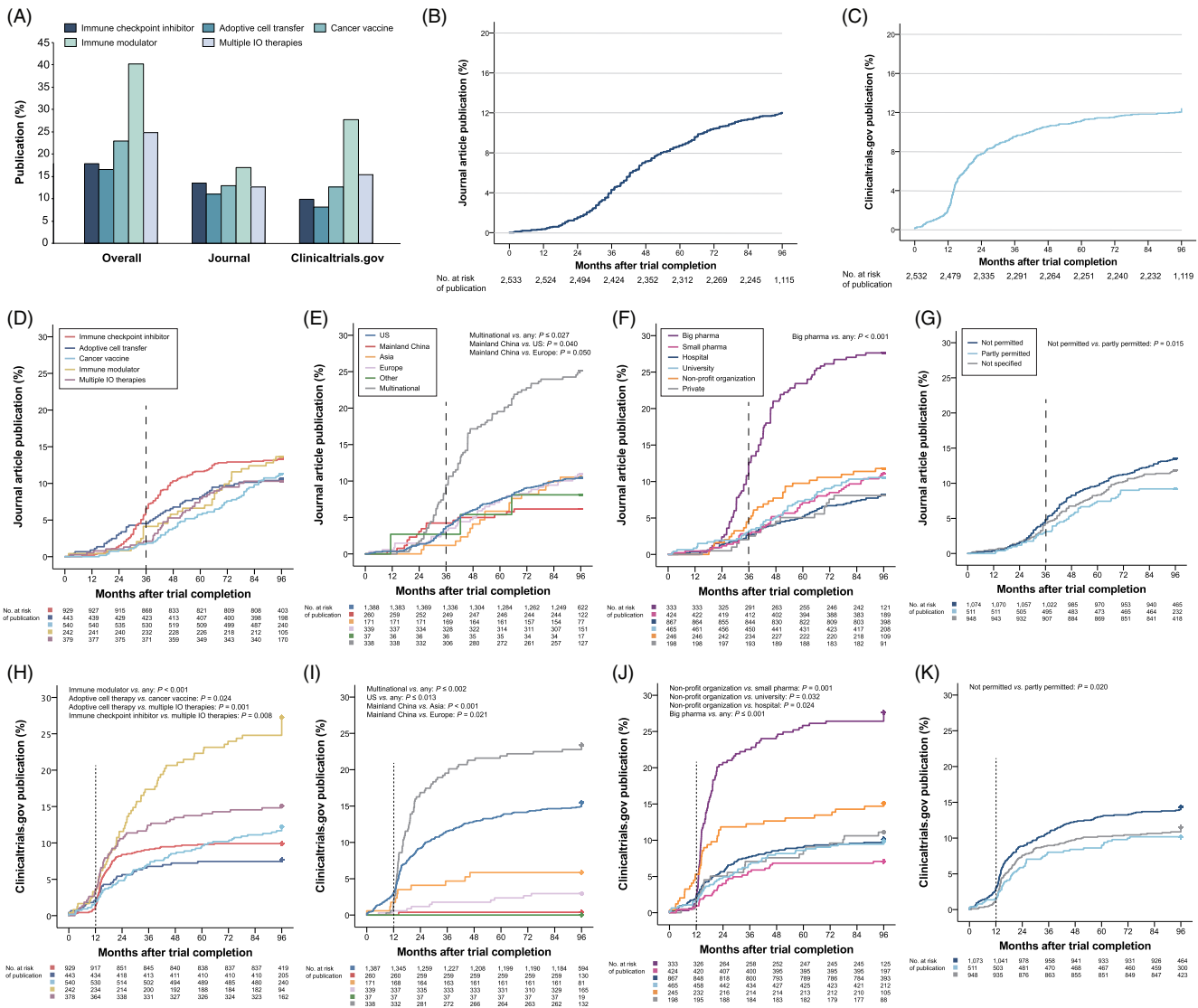


FIGURE 5 Publication outlines (A-C) and cumulative dissemination rates of trial results via journal article (D-G) and ClinicalTrials.gov registry (H-K) according to immuno-oncology (IO) category, geographic origin, sponsor and the attitude to corticosteroid administration. Only the comparisons and *P*-values indicating significant differences between publication curves were displayed. The wide dotted line (D-G) represents the time point we proposed as the timely publication for IO trials. The narrow dotted line (H-K) indicates the legal requirement of 1 year to report trial results on ClinicalTrials.gov [Color figure can be viewed at wileyonlinelibrary.com]

countries had the greatest proportions of trials for cancer vaccines and immune modulators (Figure 1B).

3.2 | Evolving landscape of IO trials by cancer type

The ranking of and trend in the quantity of IO trials by cancer type (Figure 1C) showed a noticeable predominance of hematological malignancies, multiple cancer types, lung cancer and melanoma ($n = 495$ -836). ACT was only predominant in trails investigating hematological malignancies, while ICIs were widely investigated in many types of cancer, especially in lung cancer. Most of the trials pertaining to cancer vaccines and immune modulators were performed in patients with hematological malignancies, although the

number of trials was small ($n = 78$ and 75 , respectively). IO trials with rapid growth rates were generally those in the low baseline stratum, that is, esophageal cancer, colorectal cancer, bladder cancer and gastrointestinal cancer, with three-quarters of them having high average annual growth rates (82.83%-228.66%) (Figure 1C; Figure S2).

3.3 | Design characteristics of IO trials

Most multiple IO therapies trials adopted the multiple-arm comparative design (44.0%). Single-arm design studying IO with/without conventional therapy was mostly observed in ACT trials (61.2%-77.1%). The top two highest proportions of studies with early registration were reported in

trials investigating ICIs (86.6%) and multiple IO therapies (80.0%) (Figure 2A). The dynamic assessment indicated the proportion of trials adopting the multiple-arm comparative design declined over time in all IO categories except immune modulators (Figure S3). PD-1 was the most commonly studied single target, and CTLA-4 was mostly studied as a dual target with PD-1 rather than as a single target (Figure 2B).

Hospitals provided the most extensive and strongest support in all IO categories, far exceeding the average level of 16.67%, followed by universities, which had a similar sponsorship pattern. Big pharma predominantly funded Phase 3-4 trials of ICIs (6.98%), while small pharma had a wider sponsorship across IO categories and funded more Phase 1-2 trials. Generally, most IO studies were Phase 2 clinical trials. Pre-clinical Phase 1 trials most often investigated ACT and cancer vaccines (Figure 3). The funding intensity of all sponsors had increased over time for ICIs, multiple IO therapies and ACT (Figure S4). In addition, an increasing number of Phase 1-2 trials were conducted in those three IO categories, while the numbers of Phase 3-4 trials have only increased for ICIs and multiple IO therapies (Figure S5).

3.4 | Academic attitudes toward the controversies regarding corticosteroids and infections

In the assessment of corticosteroid-related criteria, the ranking of trials in the five IO categories in order from most to least strict was as follows: ICIs, multiple IO therapies, cancer vaccines, ACT and immune modulators (Figure 4A). Investigators strictly excluded patients with autoimmune disease (88.4% and 75.1%), those taking immunosuppressive drugs (71.7% and 58.7%) or corticosteroids (73.6% and 68.2%) and those who had received a live vaccine (57.6% and 35.6%) in trials investigating ICIs and multiple IO therapies and tended to place restrictions on transplantation (31.0% and 18.5%) in trials investigating ACT and immune modulators. The highest proportion of trials that partly permitted corticosteroids was observed in trials investigating ICIs (32.5%). Most limitations on the dose of corticosteroids before IO therapy were in the subgroup of ≤ 10 mg/day (34.95%), while the limitations regarding the timing of corticosteroids administration were clearly divided into the subgroups of ≤ 1 week (29.14%), ≤ 2 weeks (26.63%) and ≤ 1 month (11.28%). Individually, the limitations on the timing of corticosteroids administration for autoimmune disease and live vaccines were generally 2 years (20.31%) and 1 month (83.02%), respectively (Table 1). The most stringent limitations regarding infection were found in ICI trials, followed by those studying multiple IO therapies, especially in terms of TB (34.6% and 17.6%) and pneumonitis/pneumonia (51.7% and 31.8%) (Figure 4B; Table S1).

The proportion of trials that “partly permitted” corticosteroid use increased over time only in the trials on ICIs, ACT and multiple IO therapies (all $P < .001$). The source of this increase was the subgroup of “not specified” in trials investigating ICIs and ACT ($P < .001$ and $P = .004$), while it was the subgroup of “not permitted” in trials investigating multiple IO therapies ($P < .001$) (Figure 4C). The United States and mainland China had the strictest and loosest exclusion criteria among all geographic origins, respectively; IO trials funded by pharma

and nonpharma entities had their own characteristics with regard to the limitations on corticosteroid use and infection, which differed between the two groups (Figure S6).

3.5 | Trial dissemination and the comparison of publication rate

Trials on immune modulators had the highest overall rate of publication (40.08%), followed by trials studying ICIs and multiple IO therapies, which had the second highest publication rate via journal articles (13.46%) and ClinicalTrials.gov (15.30%), respectively (Figure 5A). Although all IO trials had equivalent 96-month publication rates of approximately 12% (Figure 5B,C). Significantly higher publication rates were observed for multinational IO trials (vs any other geographic origin: $P \leq .027$) and those sponsored by big pharma (vs any other sponsors: $P < .001$). IO trials from mainland China had the lowest 96-month article publication rate of 6.2%. Compared to IO trials that partly permitted the administration of corticosteroids, trials adopting strict limitations that were in the “not permitted” subgroup had a significantly higher 96-month publication rate via journal article ($P = .015$) or registry website ($P = .020$) (Figure 5D-K). The top two geographic origins with the highest methodological quality were the United States ($n = 1040$) and multinational collaborations ($n = 305$) (Figure S7).

4 | DISCUSSION

Our study was an in-depth data mining of clinical trials registered between 2007 and 2019 and involved a cross-sectional and longitudinal analysis of IO agents, tumor types and sponsors. The United States is a leader in the initiation of clinical trials in almost all IO categories, including the PD-1 and PD-L1, which is the most popular research hotspot, and multiple IO therapies, which requires the extensive coordination of complex methodologies. Mainland China is an emerging market for IO, with the largest growth rate and the greatest proportion of trials investigating ACT. The highest average annual growth rate in the number of IO trials was observed in cancers that were not previously the focus of research. The selection of pharmaceutical enterprises was driven by commercial positioning with regard to the ICI field. Hospitals offered the most extensive and strongest support in all IO categories, promoting basic science and preclinical explorations. Trials of ICIs and multiple IO therapies had the most stringent limitations on corticosteroid use and infections. Some investigators have clarified that corticosteroid use can be partly permitted in IO trials. However, the administration of corticosteroids in IO trials seems to significantly reduce the public dissemination of the results.

Past studies showed that oncology trials were more likely to be conducted for common cancer types that have high incidence or mortality rates,²⁸ and more than two-thirds of oncology trials registered during 2007 to 2010 were conducted in North America.²⁹ As a key theme in oncology, IO has special characteristics, and the related

studies differ from those focusing on conventional therapies. Although the United States is the global leader in IO studies, the number of IO trials conducted in countries/regions outside of North America has grown rapidly, shaping the landscape of global IO trials and benefitting more patients. An obvious highlight was that investigators received a tremendous amount of investment and support when performing ICI trials, as reflected in the use of multiple-arm comparative designs, the inclusion of less common cancer types, the existence of multinational cooperation and sponsorship by big pharma. In addition to the fact that IO is a hot topic in academia and the biologics industry, this tendency is affected by the unique immunologic mechanism. For instance, ICIs have different toxicity spectra than chemotherapy, mainly affecting the skin, endocrine, hepatic and pulmonary systems. Different ICI agents and different doses of the same ICI agent have unique safety profiles.³⁰ Since PD-L1 and the tumor mutational burden can reflect the organic immune and tumor levels, clinicians regard them as important predictive biomarkers and use them to inform treatment decisions. However, these biomarkers have different levels in various cancer types, with the expression rate of PD-L1 ranging from 0% to 58%.³¹ Therefore, investigators need to consider a targeted cancer type when launching an IO trial to optimize the design, which is different from the process in traditional oncology trials. Another aspect that deserves our attention is the change in trial features. As reported by the Chinese Phase 1 Oncology trial Consortium, mainland China contributed 180 phase 1 oncology trials in 2017, becoming the country/region with the second highest yield after Europe.³² The continuous substantial investment in R&D is one of the reasons for the marked growth in IO trials in mainland China. Although the quantities of Phase 3 and multiple-arm IO trials gradually decreased, the numbers of Phase 1-2 and single-arm IO trials that emphasize preclinical exploration and are less focused on business interests have steadily grown in almost all IO categories. Big pharma faces a crisis due to the marked depletion of drug discovery pipelines and substantial pressure to meet the demands created by the ever-changing spectrum of diseases, while biotech start-up companies have the advantages of high efficiency, flexibility, innovative capacity, product focus and small size.³³ The differences in sponsorship between commercial companies and academia indicates that current IO research has reached a mature stage, and progress in the investigation of novel molecular targets and new IO agents is urgently needed and expected.

Repetitive study designs and target duplication are common in IO research and pipelines, mostly for IO drugs that have been approved for marketing, such as PD-1 and PD-L1 blockades.³⁴ Our study suggested that big pharma has clearly shifted resources to ICIs; however, the intensity of research on CTLA-4 was less than that of research on PD-(L)1. Since the first CTLA-4 blockade agent ipilimumab was approved by the FDA in 2011, more than 10 ICI agents have entered the market for use in clinical practice. Ipilimumab reactivates the B7-CD28 pathway between antigen-presenting cells and T cells and induces a systemic immune response, which often results in uncontrollable dose-dependent irAEs.^{30,35-37} Previous clinical trials have reported that tremelimumab, a drug candidate for

CTLA-4 blockade, had nonsignificantly superior efficacy for the treatment of mesothelioma and non-small cell lung cancer.^{38,39} This failure may hinder the application of single anti-CTLA-4 agents. One way to overcome the shortage of single-target ICI therapy is to combine two ICI agents that have potentially synergistic mechanisms of tumoricidal effects.⁴⁰ The CheckMate 227 trial showed that nivolumab plus low-dose ipilimumab not only take the advantages of different molecular targets, but also avoid severe irAEs.⁴¹ Nivolumab plus ipilimumab has been approved by the FDA as the first and only ICI combination therapy for cancer.⁴² A recent Phase 2 clinical trial (NCT03529526) showed that KN046—the world's first PD-L1/CTLA-4 bispecific antibody—has a favorable safety profile and results in promising clinical benefits in patients with solid tumors.⁴³ Numerous multispecific antibody candidates are now being tested, such as antibodies blocking PD-L1 on chondroitin sulfate proteoglycan 4- or EGFR-expressing cancers, indicating an important direction in the next generation of IO research.^{44,45}

Despite the fact that the surge in IO research has not subsided, the strategies for coping with controversial issues have not yet been standardized. The relationship between baseline corticosteroid administration and poor outcomes in cancer patients undergoing IO therapy may only be superficial, and it is necessary to carry out in-depth investigation to clarify whether it is an internal causative relationship or a correlation. Ricciuti et al found that patients with lung cancer who used ≥ 10 mg prednisone had a significantly lower median overall survival rate after treatment with ICIs than their counterparts who used 0 to 10 mg prednisone (4.9 vs 11.2 months). However, further investigation indicated that this survival disparity was caused by a subgroup of patients with a poor prognosis who received corticosteroids for cancer-related indications.⁴⁶ It seems that corticosteroids used to manage conditions unrelated to cancer (eg, appetite stimulants and antiemetics) should not be prohibited before IO therapy. Our study highlighted that current IO trials have differences in the limitations on the allowed doses and timing of corticosteroids. Studies on different IO categories have restrictions with differing levels of strictness with regard to the corticosteroid- and infection-related criteria. Investigators who studied ICIs and multiple IO therapies have the strictest limitations, but they are more inclined to allow corticosteroid administration before IO therapy. Disappointingly, 32.78% to 72.33% of the IO trials did not report the limitations on steroids and infection. We recommend that IO investigators disclose detailed information on the doses and timing of corticosteroids and strive to continuously apply relevant evidence from the latest studies to generate standardized requirements.

The publication rate of IO trials is negatively affected by corticosteroid administration, which may be because trial investigators adopting this strategy are not conservative and are willing to innovate, with a correspondingly greater risk of publication failure. Clinical trials conducted by academic institutions or funded by the US National Institutes of Health have a final dissemination rate of 66% to 68%, which is clearly higher than the overall publication rate of IO trials in our study (12%).^{14,47} Timely publication is widely recognized as a prerequisite to the efficient presentation of trial findings and the

achievement of maximal benefits in terms of public health and scientific progress. However, most of the studies set 12 to 24 months after the trial completion as the goal for timely publication.⁴⁷ This time point does not seem suitable for IO trials. First, Phase 2-3 IO trials generally report 3-year outcomes as the primary study objective, and a sufficient median follow-up time is therefore required. Second, our study showed that the curves depicting the publication of IO trials in different subgroups (Figure 5) were only significantly separated in the third year. Therefore, we propose that the timely publication of IO trials be defined as the third year after trial completion. In addition to ensuring that most IO trials have enough time to report results, this modification can be tailored to the unique properties of IO trials, such as IO category, sponsorship and geographic origin.

The present study has several limitations that must be taken into account. First, clinical trials registered at ClinicalTrials.gov are generally lacking to some extent in early registration, information integrity, design rationality and result disclosure.²⁹ Since there is no mandatory requirement to disclose the information about trial progress and individual patient data, we cannot evaluate the process of IO trials, nor can we perform further study, such as survival analysis. Besides, not all investigators choose ClinicalTrials.gov to register their projects, as many alternative registries around the world can be used.⁴⁸ Second, although previous studies indicated that suspended, terminated and withdrawn oncology trials only accounted for the low proportion of 0.9% to 2.9%, these incomplete trials have more flaws in their registration information because of the absence of continuous updates and corrections.²⁹ Incorrect data could be developed during information extraction and integration. The degree of heterogeneity among researchers with regard to data processing and subjective evaluation is large, and the results will inevitably deviate from the raw data. Third, although our study found associations between publication rate and IO categories, sponsorship, geographic origin and the use of corticosteroids, it is difficult to determine and interpret the underlying reasons. Finally, we referred to the methods of previous studies to determine the publication status of IO trials, which relied on the inclusion of an NCT number in the abstract of a journal article.²³ Thus, the general publication rate may have been underestimated.

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CONFLICT OF INTEREST

The authors declared no potential conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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REFERENCES

- McNutt M. Cancer immunotherapy. *Science*. 2013;342(6165):1417.
- Baum AS. Immunotherapy—the beginning of the end for cancer. Citibank. <https://www.citivelocity.com/citigps/OpArticleDetail.action?recordId=209>. Accessed May 20, 2020.
- Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 2012;12(4):252-264.
- Houot R, Schultz LM, Marabelle A, Kohrt H. T-cell-based immunotherapy: adoptive cell transfer and checkpoint inhibition. *Cancer Immunol Res*. 2015;3(10):1115-1122.
- Ribas A, Butterfield LH, Glaspy JA, Economou JS. Current developments in cancer vaccines and cellular immunotherapy. *J Clin Oncol*. 2003;21(12):2415-2432.
- Tang J, Pearce L, O'Donnell-Tormey J, Hubbard-Lucey VM. Trends in the global immuno-oncology landscape. *Nat Rev Drug Discov*. 2018;17(12):922.
- Hargadon KM, Johnson CE, Williams CJ. Immune checkpoint blockade therapy for cancer: an overview of FDA-approved immune checkpoint inhibitors. *Int Immunopharmacol*. 2018;62:29-39.
- Arbour KC, Mezquita L, Long N, et al. Impact of baseline steroids on efficacy of programmed cell death-1 and programmed death-ligand 1 blockade in patients with non-small-cell lung cancer. *J Clin Oncol*. 2018;36(28):2872-2878.
- Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. *Arthritis Rheum*. 2006;54(2):628-634.
- Flint TR, Janowitz T, Connell CM, et al. Tumor-induced IL-6 reprograms host metabolism to suppress anti-tumor immunity. *Cell Metab*. 2016;24(5):672-684.
- Santini FC, Rizvi H, Plodkowski AJ, et al. Safety and efficacy of re-treating with immunotherapy after immune-related adverse events in patients with NSCLC. *Cancer Immunol Res*. 2018;6(9):1093-1099.
- Connell CM, Raby S, Beh I, et al. Cancer immunotherapy trial registrations increase exponentially but chronic immunosuppressive glucocorticoid therapy may compromise outcomes. *Ann Oncol*. 2017;28(7):1678-1679.
- Naci H, Davis C, Savovic J, et al. Design characteristics, risk of bias, and reporting of randomised controlled trials supporting approvals of cancer drugs by European Medicines Agency, 2014-16: cross sectional analysis. *BMJ*. 2019;366:i5221.
- Chen R, Desai NR, Ross JS, et al. Publication and reporting of clinical trial results: cross sectional analysis across academic medical centers. *BMJ*. 2016;352:i637.
- DeVito NJ, Bacon S, Goldacre B. Compliance with legal requirement to report clinical trial results on ClinicalTrials.gov: a cohort study. *Lancet*. 2020;395(10221):361-369.
- Pinato DJ, Howlett S, Ottaviani D, et al. Association of prior antibiotic treatment with survival and response to immune checkpoint inhibitor therapy in patients with cancer. *JAMA Oncol*. 2019;5(12):1774-1778.
- von Elm E, Altman DG, Egger M, et al. The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE)

- statement: guidelines for reporting observational studies. *J Clin Epidemiol.* 2008;61(4):344-349.
18. Topalian SL, Wolchok JD, Chan TA, et al. Immunotherapy: the path to win the war on cancer? *Cell.* 2015;161(2):185-186.
 19. Types of cancer immunotherapy. Cancer Research UK. <https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/immunotherapy/types>. Accessed May 20, 2020.
 20. Jensen LJ, Saric J, Bork P. Literature mining for the biologist: from information retrieval to biological discovery. *Nat Rev Genet.* 2006;7(2):119-129.
 21. Aslam A, Imanullah S, Asim M, El-Menyar A. Registration of clinical trials: is it really needed? *N Am J Med Sci.* 2013;5(12):713-715.
 22. Top 50 Global Pharma Companies, Pharmaceutical Executive Ranking; 2019. <https://www.rankingthebrands.com/The-Brand-Rankings.aspx?rankingID=370>. Accessed April 19, 2020.
 23. Zwierzyna M, Davies M, Hingorani AD, Hunter J. Clinical trial design and dissemination: comprehensive analysis of ClinicalTrials.gov and PubMed data since 2005. *BMJ.* 2018;361:k2130.
 24. Booth CM, Le Maitre A, Ding K, et al. Presentation of nonfinal results of randomized controlled trials at major oncology meetings. *J Clin Oncol.* 2009;27(24):3938-3944.
 25. Buonaccorsi JP, Laake P, Veierod MB. On the power of the Cochran-Armitage test for trend in the presence of misclassification. *Stat Methods Med Res.* 2014;23(3):218-243.
 26. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53(282):457-481.
 27. Cox DR. Regression models and life-tables. *J R Stat Soc Series B Stat Methodol.* 1972;34:187-220.
 28. Hirsch BR, Califf RM, Cheng SK, et al. Characteristics of oncology clinical trials: insights from a systematic analysis of ClinicalTrials.gov. *JAMA Intern Med.* 2013;173(11):972-979.
 29. Califf RM, Zarin DA, Kramer JM, Sherman RE, Aberle LH, Tasneem A. Characteristics of clinical trials registered in ClinicalTrials.gov, 2007-2010. *JAMA.* 2012;307(17):1838-1847.
 30. Xu C, Chen YP, Du XJ, et al. Comparative safety of immune checkpoint inhibitors in cancer: systematic review and network meta-analysis. *BMJ.* 2018;363:k4226.
 31. Yarchoan M, Albacker LA, Hopkins AC, et al. PD-L1 expression and tumor mutational burden are independent biomarkers in most cancers. *JCI Insight.* 2019;4(6):e126908.
 32. Zhao S, Lv C, Gong J, et al. Challenges in anticancer drug R&D in China. *Lancet Oncol.* 2019;20(2):183-186.
 33. Barden CJ, Weaver DF. The rise of micropharma. *Drug Discov Today.* 2010;15(3-4):84-87.
 34. Tang J, Shalabi A, Hubbard-Lucey VM. Comprehensive analysis of the clinical immuno-oncology landscape. *Ann Oncol.* 2018;29(1):84-91.
 35. Ascierto PA, Del Vecchio M, Robert C, et al. Ipilimumab 10 mg/kg versus ipilimumab 3 mg/kg in patients with unresectable or metastatic melanoma: a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol.* 2017;18(5):611-622.
 36. Hamid O, Schmidt H, Nissan A, et al. A prospective phase II trial exploring the association between tumor microenvironment biomarkers and clinical activity of ipilimumab in advanced melanoma. *J Transl Med.* 2011;9:204.
 37. Wolchok JD, Neyns B, Linette G, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. *Lancet Oncol.* 2010;11(2):155-164.
 38. Maio M, Scherpereel A, Calabro L, et al. Tremelimumab as second-line or third-line treatment in relapsed malignant mesothelioma (DETERMINE): a multicentre, international, randomised, double-blind, placebo-controlled phase 2b trial. *Lancet Oncol.* 2017;18(9):1261-1273.
 39. Adrian K. Update on phase III DANUBE trial for Imfinzi and tremelimumab in unresectable, Stage IV bladder cancer. <https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2020/update-on-phase-iii-danube-trial-for-imfinzi-and-tremelimumab-in-unresectable-stage-iv-bladder-cancer-06032020.html>. Accessed May 20, 2020.
 40. Weber JS, Hamid O, Chasalow SD, et al. Ipilimumab increases activated T cells and enhances humoral immunity in patients with advanced melanoma. *J Immunother.* 2012;35(1):89-97.
 41. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N Engl J Med.* 2019;381(21):2020-2031.
 42. U.S. Food and Drug Administration Approves Opdivo® (nivolumab) + Yervoy® (ipilimumab) as First-Line Treatment of Patients with Metastatic Non-Small Cell Lung Cancer Whose Tumors Express PD-L1≥1%. <https://news.bms.com/press-release/corporatefinancial-news/us-food-and-drug-administration-approves-opdivo-nivolumab-ye-1>. Accessed: April 19, 2020.
 43. Zhao HY, Ma YX, Zhang Y, et al. The preliminary efficacy and safety data of KN046 in patients failed on prior immune checkpoint inhibitors therapy. *J Clin Oncol.* 2020;38(15_suppl):3020-3020.
 44. Koopmans I, Hendriks D, Samplonius DF, et al. A novel bispecific antibody for EGFR-directed blockade of the PD-1/PD-L1 immune checkpoint. *Onco Targets Ther.* 2018;7(8):e1466016.
 45. Koopmans I, Hendriks M, van Ginkel RJ, Samplonius DF, Bremer E, Helfrich W. Bispecific antibody approach for improved melanoma-selective PD-L1 immune checkpoint blockade. *J Invest Dermatol.* 2019;139(11):2343-2351.e2343.
 46. Ricciuti B, Dahlberg SE, Adeni A, Sholl LM, Nishino M, Awad MM. Immune checkpoint inhibitor outcomes for patients with non-small-cell lung cancer receiving baseline corticosteroids for palliative versus nonpalliative indications. *J Clin Oncol.* 2019;37(22):1927-1934.
 47. Ross JS, Tse T, Zarin DA, Xu H, Zhou L, Krumholz HM. Publication of NIH funded trials registered in ClinicalTrials.gov: cross sectional analysis. *BMJ.* 2012;344:d7292.
 48. Zarin DA, Tse T, Williams RJ, Califf RM, Ide NC. The ClinicalTrials.gov results database—update and key issues. *N Engl J Med.* 2011;364(9):852-860.

SUPPORTING INFORMATION

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