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Review

Clinical Cancer Research

Analysis of Drug Development Paradigms for Immune Checkpoint Inhibitors

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Abstract

Immune checkpoint inhibitors have unique toxicities and response kinetics compared with cytotoxic and gene-targeted anticancer agents. We investigated the impact of innovative/accelerated immunotherapy drug development/approval models on the accuracy of safety and efficacy assessments by searching the FDA website. Initial phase I trials for each agent were reviewed and safety and efficacy data compared with that found in later trials leading to regulatory approvals of the same agents. As of June 2017, the FDA approved six checkpoint inhibitors for a variety of cancer types. All checkpoint inhibitors received a priority review status and access to at least two additional FDA special access programs, more often breakthrough therapy designation and accelerated approval. Median clinical development time (investigational new drug application to approval) was 60.77 months [avelumab had the shortest timeline (52.33 months)]. Response rates during early phase I trials (median = 16%) are higher than for phase I trials of other agents (with the exception of gene-targeted agents tested with a biomarker). Doses approved were usually not identical to doses recommended on phase I trials. Approximately 50% of types of immune-related and 43% of types of clinically relevant toxicities from later trials were identified in early-phase trials. Even so, treatment-related mortality remains exceedingly low in later studies (0.33% of patients). In conclusion, efficacy and safety of immune checkpoint inhibitors appear to be reasonably predicted from the dose-finding portion of phase I trials, indicating that the fast-track development of these agents is safe and justified. *Clin Cancer Res; 24(8); 1785–94. ©2017 AACR.*

Introduction

Therapeutic manipulation of the immune system has been attempted in oncology for many years. Numerous trials tested cytokines, vaccines, and other immunostimulating agents in patients with cancer. Overall, this wave of development led to FDA approval of a few first-generation agents, including IFN and IL2 for kidney cancer and melanoma (1–3) and sipuleucel-T for prostate cancer (4).

More recently, an enhanced understanding of the mechanisms underlying immune responses against cancer cells led to the description of negative immunologic regulators (checkpoints) preventing effective immune eradication of tumors. As a result, mAbs blocking immune checkpoints started clinical development (5). Two of the main targets of these agents are cytotoxic T-lymphocyte (CTL)–associated antigen 4 (CTLA-4) and the programmed cell death protein pathway (PD-1/PD-L1). Responses to these antibodies have been impressive, especially because some patients with advanced malignancies achieve long-term remissions. This new surge of immunotherapeutic agents is characterized by relatively rapid FDA approvals in diverse solid malignancies.

However, many challenges unique to immunotherapy are emerging, and important unanswered questions need to be explored (6). The pertinent issues include an evaluation of how the traditional drug development model performs, as well as assessment of the regulatory timeline for these agents. Of interest, early marketing of these checkpoint inhibitors has occurred, including approval of pembrolizumab for melanoma, after a phase I trial (7). The recent approval of pembrolizumab based on a tumor biomarker test regardless of tissue origin (approval for microsatellite-unstable solid tumors) has also challenged historical approval models in oncology (8). Therefore, drug development paradigms in the era of immunotherapy are evolving.

To better understand the impact of emerging drug development models, we performed a systematic review of FDA-approved immune checkpoint inhibitors, exploring their development timeline, and the correlations between toxicities, dosing, and efficacy from early phase I trials with similar information from later trials leading to approvals.

Methods

Search strategy

Immune checkpoint inhibitors newly approved for anticancer treatment prior to June 1, 2017, were identified on the FDA website (9). Agents approved for the treatment of solid and hematologic malignancies were selected for further analysis. Original and updated package inserts for each agent were reviewed, along with review documents available at the FDA website. Development milestones, drug indications, dose scheduling, and clinical trials leading to each immunotherapeutic agent approval were evaluated.

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Selection of trials

An extensive search was concomitantly done through MEDLINE to identify phase I trials for each checkpoint inhibitor selected from the FDA database. Studies were obtained from publications in oncology journals. Alternatively, if data were not published yet, abstracts presented during oncology conferences were selected.

Phase I trials of single agent or different approved combinations and schedules were selected for evaluation, excluding phase Ib studies. For dose-finding purposes, data were extracted preferentially from dose escalation and dose expansion. It has become common in modern phase I trials to have different amendments to include expansion cohorts beyond dose finding, aiming to better define efficacy. For the purpose of our analysis, we excluded the information from the latter cohorts to evaluate the performance of a traditional dose-finding design of a phase I trial. To match the results of phase I trials with those from registration trial, we selected one phase I trial representative of the initial development of each checkpoint inhibitor. The criteria for selection were as follows: The phase I trial enrolled nonpediatric patients with cancer and explored either monotherapy (as FDA approved) or the same combination and schedule as described in the FDA package insert (they started before the registration trial); when more than one trial met these criteria, we selected the one that started first after investigational new drug (IND) approval.

When referring to "later trials," we considered the pivotal trial used for the first approval of a drug in each tumor type. If a larger trial was published after drug approval (such as a phase III trial as part of an accelerated approval requirement), this trial was preferentially used for our analysis. This approach was utilized to have a more precise comparison between phase I and phase III trials. Both phase I and later trials were compared for each checkpoint inhibitor in regard to dosing, safety, and efficacy. All correlations were summarized using descriptive statistics.

Data extraction and definitions

Toxicities were graded according to the criteria adopted in each trial. Considering the different terms used to describe adverse events, similar toxicities were categorized under the same group (types of toxicities) as long as they were not exclusionary (Supplementary Tables S1 and S2). All deaths reported by investigators as "possibly," "probably," or "definitely" related to treatment were considered toxicity-related deaths.

We defined clinically significant toxicities in later trials as treatment-related toxicities leading to death, treatment delays, and discontinuations, as well as toxicities among the three most frequent grade 3/4 laboratory and nonlaboratory toxicities with an overall incidence of at least 1%.

Immune-related toxicities were extracted according to each trial assignment, including either high- or low-grade immune-related toxicity, regardless of incidence. Safety profile was extracted from all later trials for different tumor types of immunotherapies selected for analysis.

Drug development information

Review documents for the newly approved checkpoint inhibitors were obtained for analysis through the FDA website (9). We evaluated data from IND submission, first and subsequent new drug application (NDA) or biologic license application (BLA) submission and approval, and access to FDA-expedited programs. Definitions and further explanation about FDA programs are depicted in Supplementary Table S3. We considered U.S. clinical phase as the time between first IND submission and NDA/BLA submission. Approval phase was defined as the time of first NDA/BLA submission to approval. Total clinical development time was considered as the sum of both clinical and approval phases. Information about European Medicines Agency (EMA) approvals was obtained through the EMA website (http://www.ema.europa.eu/ema/).

Results

Checkpoint inhibitors and approval history

Ipilimumab, a CTLA-4 inhibitor, was the first checkpoint inhibitor approved by the FDA (NDA approval date = March 2011). Since then, five additional checkpoint inhibitors were approved for the treatment of advanced cancer (first approval of nivolumab in September 2014, pembrolizumab in December 2014, atezolizumab in May 2016, avelumab in March 2017, and durvalumab in May 2017). Ipilimumab together with nivolumab is the only combined treatment approved. For the first three checkpoint inhibitors, the first registration was initially granted for metastatic melanoma, followed by the more recent drugs for urothelial carcinoma (atezolizumab and durvalumab) and Merkel cell carcinoma (avelumab). Subsequent approvals for other tumor types were obtained for nivolumab, pembrolizumab, atezolizumab, and avelumab (Table 1; Supplementary Table S4). Currently, urothelial cancer is the tumor type with most checkpoint inhibitors approved (five total), followed by melanoma and lung cancer (three drugs each).

Evidence for first approval was obtained from a phase III trial only for ipilimumab, nivolumab, and the combination of both agents, whereas atezolizumab, avelumab, and durvalumab authorization relied on phase II data, and pembrolizumab registration was based on a phase Ib trial. Among the 21 later trials included in our analysis, 18 (86%) used RECIST 1.1 (10) as the response criteria for efficacy analysis (the other criteria adopted are described in Table 1). In addition, 14 of these 21 (67%) trials defined response rate (RR) or progression-free survival (PFS) as the primary or coprimary endpoint. Pembrolizumab is a unique case, because it is the only drug that had approvals based on a biomarker-based rationale. The metastatic non–small cell lung cancer (NSCLC) indication required a biomarker-based companion diagnosis (FDA-approved test for PD-L1 expression) for patient selection. More innovative was the recent approval for microsatellite instability–high (MSI-H) cancers of pembrolizumab, the first tissue/site agnostic approval in oncology. All the remaining tumor-type approvals for checkpoint inhibitors were for unselected, nonbiomarker-based cancer population.

Total time for the development of approved checkpoint inhibitors was a median of 60.77 months from the time of IND submission to the time of NDA approval (54.65 months for the clinical phase and 6.12 months for the approval phase). This timeline compared favorably to that of other anticancer agents approved by the FDA between September 1999 and July 2014 (median clinical and approval times of 75.4 and 6 months, respectively; Fig. 1A). Nonetheless, the specific timelines differed between checkpoint inhibitors, as depicted in Fig. 1B. All the drugs received a priority review status and access to at least two additional FDA special access programs. The five PD-1/PD-L1

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Table 1. Phase I trial as well as approval stage characteristics of immune checkpoint inhibitors

Characteristic	Ipilimumab[a] (36)	Nivolumab (37)	Pembrolizumab (24)	Atezolizumab (25)	Avelumab (38)	Durvalumab (39)	Ipilimumab + nivolumab (20)
Phase I stage							
Trial location	US	US	US	US, Europe	US, Europe, Asia	US, Europe, Asia	US
Number of centers	2	11	2	20	10	4	4
Tumor types	1 (non-metastatic melanoma)	8 solid tumors	All solid tumors	All solid tumors	All solid tumors	All solid tumors	1 (metastatic melanoma)
Trial design (40)	Preassigned dose levels	Accelerated titration design transitioned to a 3 + 3 design	3 + 3 design	3 + 3 design	3 + 3 design	3 + 3 design	3 + 3 design
N, patients	19	207	30	171	27	27	86
N, dose levels	3	4	3	5	4	6	7
Response criteria	N/A	RECIST 1.1 (10)	RECIST 1.1 (10)	RECIST 1.1 (10)	RECIST 1.1 (10)	Immune related	Modified WHO (41)
N, DLTs	3	0	0	0	1	0	6
MTD reached	Yes	No	No	No	No	No	Yes
Dose recommendation (parameter)	Yes (toxicities)	No clear dose recommended	Yes (lowest dose with efficacy)	Yes (PK)	Yes (PK)	Yes (PK/PD/ safety data)	Yes (toxicities)
Approval stage							
First FDA approval	Melanoma	Melanoma	Melanoma	Urothelial carcinoma	Merkel cell carcinoma (42)	Urothelial carcinoma	Melanoma
Design of first pivotal trial leading to approval	Phase III	Phase III	Phase Ib	Phase II	Phase II	Phase II	Phase III
Subsequent approvals	No	5 (NSCLC, kidney cancer, Hodgkin lymphoma, HNSCC, urothelial carcinoma)	5 (NSCLC, HNSCC, Hodgkin lymphoma, urothelial carcinoma, MSI-H cancers)	1 (NSCLC)	1 (urothelial carcinoma)	No	No
Response criteria pivotal trials	Modified WHO (41)	RECIST 1.1 (10) and International Working Group (Hodgkin; ref. 43)	RECIST 1.1 (10) and revised response criteria for lymphomas (43)	RECIST 1.1 (10)	RECIST 1.1 (10)	RECIST 1.1 (10)	RECIST 1.1 (10)
Selection biomarker	No	No	Yes (PD-L1 expression is required for NSCLC indication) and MSI-H tested cancers	No	No	No	No

Abbreviations: HNSCC, head and neck small cell carcinoma; MSI-H, microsatellite instability–high; N/A, not applicable; NSCLC, non–small cell lung cancer; PD, pharmacodynamics; PK, pharmacokinetics; WHO, World Health Organization.

[a]This phase I trial included patients with completely resected melanoma. Hence, response evaluation was not performed.

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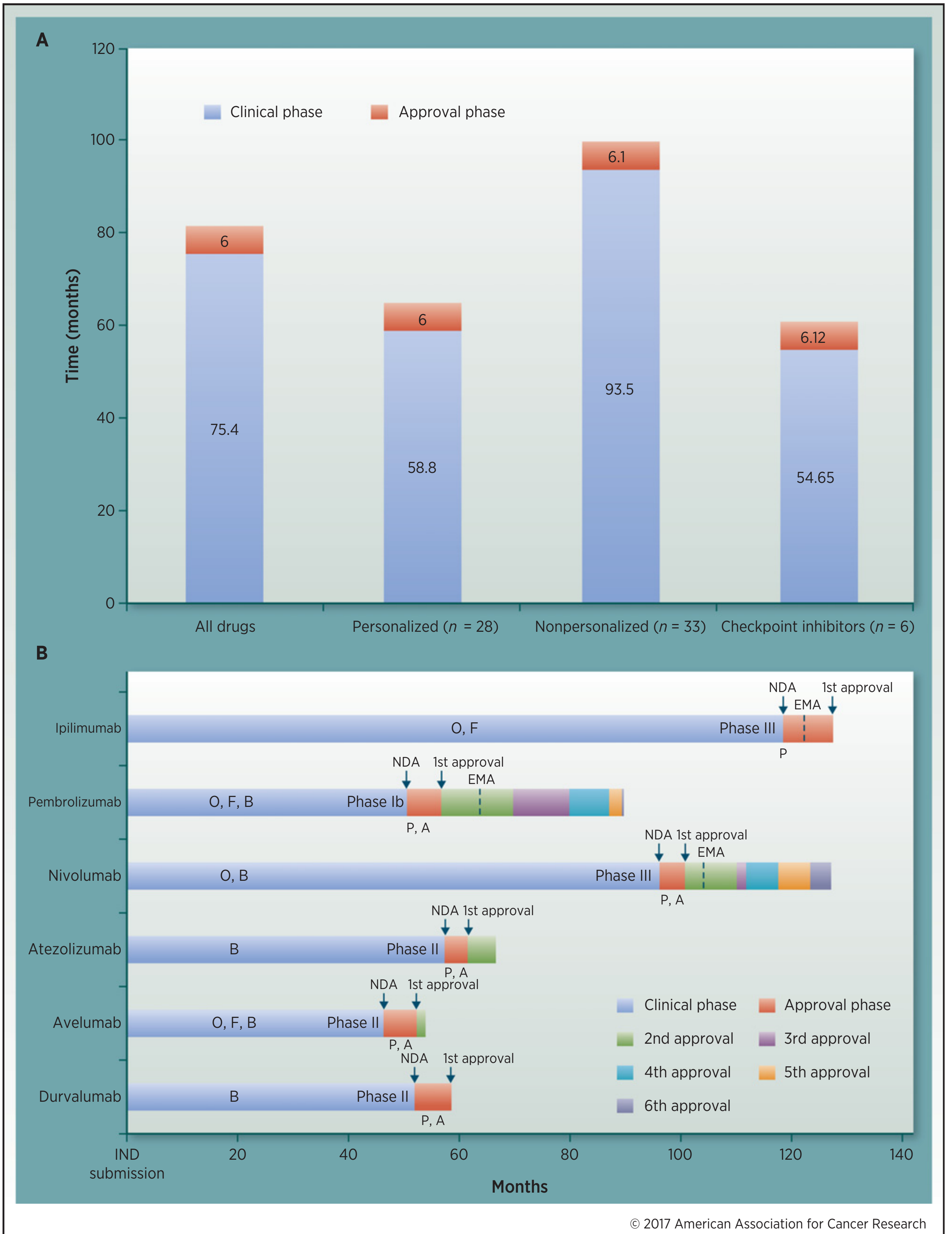

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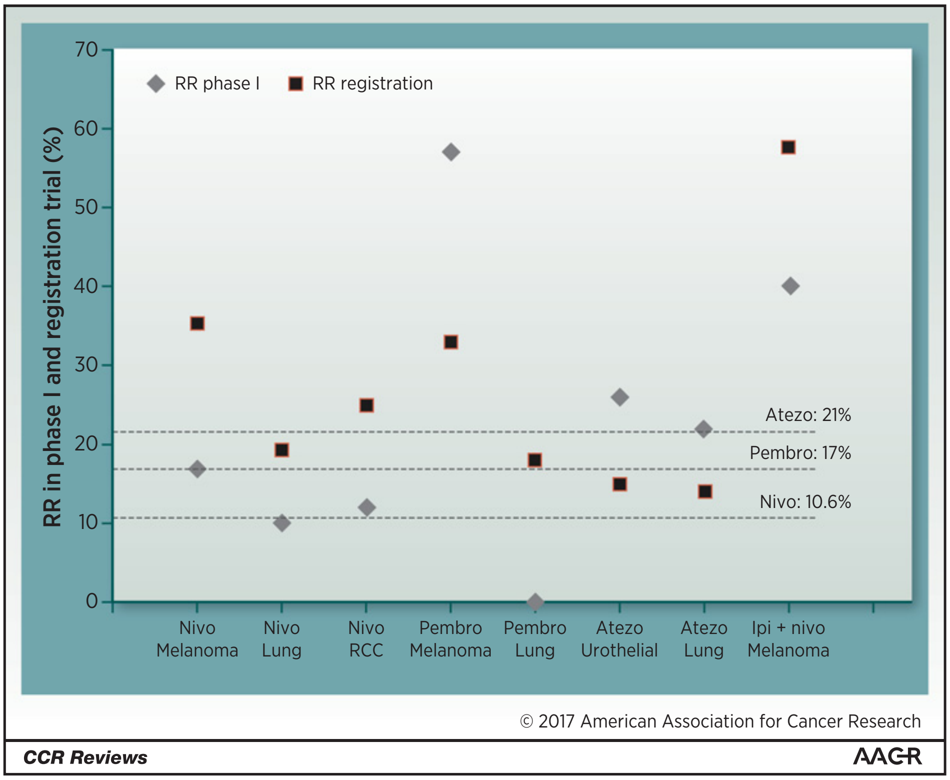

Figure 2.
Correlation between RR (%) in a particular tumor included during the phase I trial (gray rhombus) and the later registration trial (black square). Horizontal axis depicts the immune checkpoint inhibitor in each approved indication. RR information for phase I was only included if a metastatic tumor of the same histology from the approval was tested. Dashed lines represent the overall RR in the phase I trial (including all tumor types treated). The figure shows that the RRs in later trials were generally higher than in the phase I trials; however, in the cases of pembrolizumab in melanoma and atezolizumab in urothelial and lung cancer, RRs in phase I trials were higher than in later trials. Some approvals were excluded, as the phase I did not include the tumor types [nivolumab for Hodgkin lymphoma and head and neck small cell carcinoma (HNSCC); pembrolizumab for Hodgkin lymphoma, HNSCC, urothelial cancer, and MSI-H tumors; avelumab for Merkel cell carcinoma and urothelial cancer; and durvalumab for urothelial cancer]. atezo, atezolizumab; ipi, ipilumumab; nivo, nivolumab; pembro, pembrolizumab; RCC, renal cell cancer.

inhibitors received the more recent breakthrough therapy designation and were first approved under the Accelerated Approval Program. Consequently, ipilimumab had the longest total development (127.4 months) and avelumab, the shortest, because it was approved only after 52.33 months from IND submission (Fig. 1B). None of the PD-L1 inhibitors (atezolizumab, avelumab, and durvalumab) has obtained EMA approval yet, in contrast to the CTLA-4 and PD-1 inhibitors. The time gap between first FDA and EMA approval was longer for nivolumab and pembrolizumab (5.9 and 10.4 months, respectively) compared with ipilimumab (3.6 months).

Correlation of response between early and later trials

To define how the tumor RR compared in phase I versus later registration trials, we assessed RR for the same tumor type from phase I and later trials (Fig. 2). Some approvals were excluded from this analysis, as the phase I trials selected herein did not include the tumor types later approved on the basis of registration trials. Median RR in phase I trials was 16%; phase I RRs in tumor types that were later granted FDA approval ranged from 0% to 57%. It is important to emphasize that RR was analyzed in our study only for the dose-defining portion of the phase I trials. In five of the eight (63%) comparisons, the RR of the later

Figure 1.
A, Comparison of the drug development timeline (clinical and approval phases) between 61 anticancer drugs approved by the FDA between September 1999 and July 2014 and immune checkpoint inhibitors approved until June 2017. The 61 drugs were also stratified under personalized ($n = 28$ drugs) and nonpersonalized ($n = 33$ drugs) according to the development strategy. "Personalized" indicates biomarker-based approval. **B,** Drug development timeline of immune checkpoint inhibitors approved by the FDA. Each bar represents in months the time for each step of clinical development. Letters inside clinical phase and below approval phase represent access to each FDA-expedited program. At the end of blue bars, the type of registration trial submitted for first approval is described (e.g., phase I, phase II, or phase III trial). Dashed lines inside bars are the moment in time of EMA approval (if received). Time from first FDA to first EMA approval: ipilimumab, 3.6 months; pembrolizumab, 10.4 months; and nivolumab, 5.9 months. Clinical phase is time from IND submission to the FDA (necessary before first-in-human trial initiates) to the submission for NDA. Approval phase is the time between the NDA submission to the FDA and the approval by the FDA of the drug for marketing. A, accelerated approval; B, breakthrough designation; F, fast track; O, orphan drug status; P, priority review. Definitions for these types of special FDA designations are given in Supplementary Table S3.

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Table 2. Information about doses and important toxicities present in later trials and correlation with early phase I trials

	Ipilimumab	Nivolumab	Pembrolizumab	Atezolizumab	Avelumab	Durvalumab	Ipilimumab + nivolumab
Dose used in later trial (% of RP2D from phase I)	3 mg/kg q3wks (400%)	3 mg/kg q2wks (no RP2D)	Different doses (66%–333%)	1,200 mg q3wks (100%)	10 mg/kg q2wks (50%)	10 mg/kg q2wks (100%)	Nivolumab 1 mg/kg Ipilimumab 3 mg/kg q3wks × 4 doses (100%)
Number of patients in phase I trial[a]	19	207	30	171	27	27	86
Number of patients in later trials[b]	137	1,904	1,334	1,160	337	191	314
Number of types of clinically significant toxicities in later trials[c]	5	18	21	6	6	4	5
Number of types of toxicities described in phase I trial (% of types of toxicities described in later trials)	2 (40)	7 (39)	6 (29)	3 (50)	4 (67)	1 (25)	5 (100)
Number of types of immune-related toxicities in later trials[c]	7	9	15	4	8	7	7
Number of types of immune-related toxicities described in phase I trials (% of types of immune-related toxicities described in later trials)	3 (42.9)	6 (66.7)	4 (26.6)	3 (75)	3 (37.5)	3 (43)	7 (100)
Treatment-related mortality in phase I trials (% of patients in the trials)	0	0	3.33	0	0	0	0
All trials = 0.18%							
Treatment-related mortality later trials (% of patients in the trials)	2.9	0.32	0.37	0	0.3	1.05	0
All trials = 0.33%							

Abbreviations: DLTs, dose-limiting toxicities; q2wks, every 2 weeks; q3wks, every 3 weeks; RP2D, recommended phase II dose.
[a]Patients included during dose-escalation and dose-expansion cohorts for dose-finding purposes only.
[b]Data obtained from all later trials for the different FDA-approved indications.
[c]Clinically significant toxicities were defined as treatment-related toxicities leading to death, treatment delays and discontinuations, and toxicities among the three most frequent grade 3/4 laboratory and non-laboratory toxicities with an overall incidence of at least 1% (33); in the case of immune-related toxicities, all types of toxicities were included regardless of grade.

trial was higher compared with the phase I trial. The absolute difference in the RR in these five comparisons ranged from 9% to 18%. RR of pembrolizumab in melanoma and atezolizumab in urothelial and lung cancer during phase I was higher compared with later trials.

Correlation of toxicities seen in phase I trials of checkpoint inhibitors with those seen in later trials

We included seven phase I trials representing early phase of development from each checkpoint inhibitor and the combination treatment of ipilumumab and nivolumab (Table 1). The phase I trials were located exclusively in the United States in four instances, whereas for the development of three agents (atezolizumab, avelumab, and durvalumab), the phase I trial also included sites in Europe and Asia. Number of patients included in these trials varied from 19 to 207. For the majority of them, dose-escalation schema was a traditional 3 + 3, aiming to define the recommended phase II dose (RP2D) based on toxicities. Interestingly, dose-limiting toxicities (DLT) were seen in the phase I trials testing ipilimumab together with nivolumab as well as ipilimumab and avelumab as single agents, but not in the other phase I trials. As a result, an MTD was found (both with ipilimumab) in only two phase I trials. The phase I trials with PD-1/PD-L1 inhibitors deployed as monotherapy used other parameters for RP2D definition (including pharmacodynamics and dose-efficacy curves). For nivolumab, the optimal dosing was not clearly defined after the phase I trial, and the drug was excluded from dose comparison analysis. Later trials with checkpoint inhibitors adopted a dose that varied from 50% to 400% of RP2D. In four of 13 (31%) matched comparisons (atezolizumab, durvalumab, and ipilimumab together with nivolumab), the dosage from the later trials was exactly the same (100% of the RP2D) as that recommended based on phase I.

We identified a total of 65 types of clinically significant toxicities in the later trials with checkpoint inhibitors, of which 28 (43%) were at least cited in respective phase I trials (Table 2). The avelumab phase I trial described 25% of types of clinically relevant toxicities documented in later trials; it was one of the smallest phase I trials ($n = 27$ patients). The number of types of toxicities considered to be immune related in later trials was 57. Of these, 29 (50.9%) were described during phase I trials. In our group of matched comparisons, the total number of patients included in a phase I did not correlate with an improved description of clinically significant toxicities during phase I trials (Fig. 3). However, it appeared that a better description of types of immune-related toxicities in phase I trials was associated with more patients included in the phase I trial. Finally, a more robust correlation between the ability of the phase I trials describing types of clinically significant and immune-related toxicity was seen according to the ratio of the number of patients included in a phase I versus later trial.

Treatment-related mortality in phase I trials with checkpoint inhibitors was low (0.18%) and accurately predicted a low treatment-related mortality rate in later trials (0.33%).

Discussion

Checkpoint inhibitors represent a new wave of successful immunotherapies in oncology. Indeed, based on the striking results of these inhibitors, cancer immunotherapy was heralded

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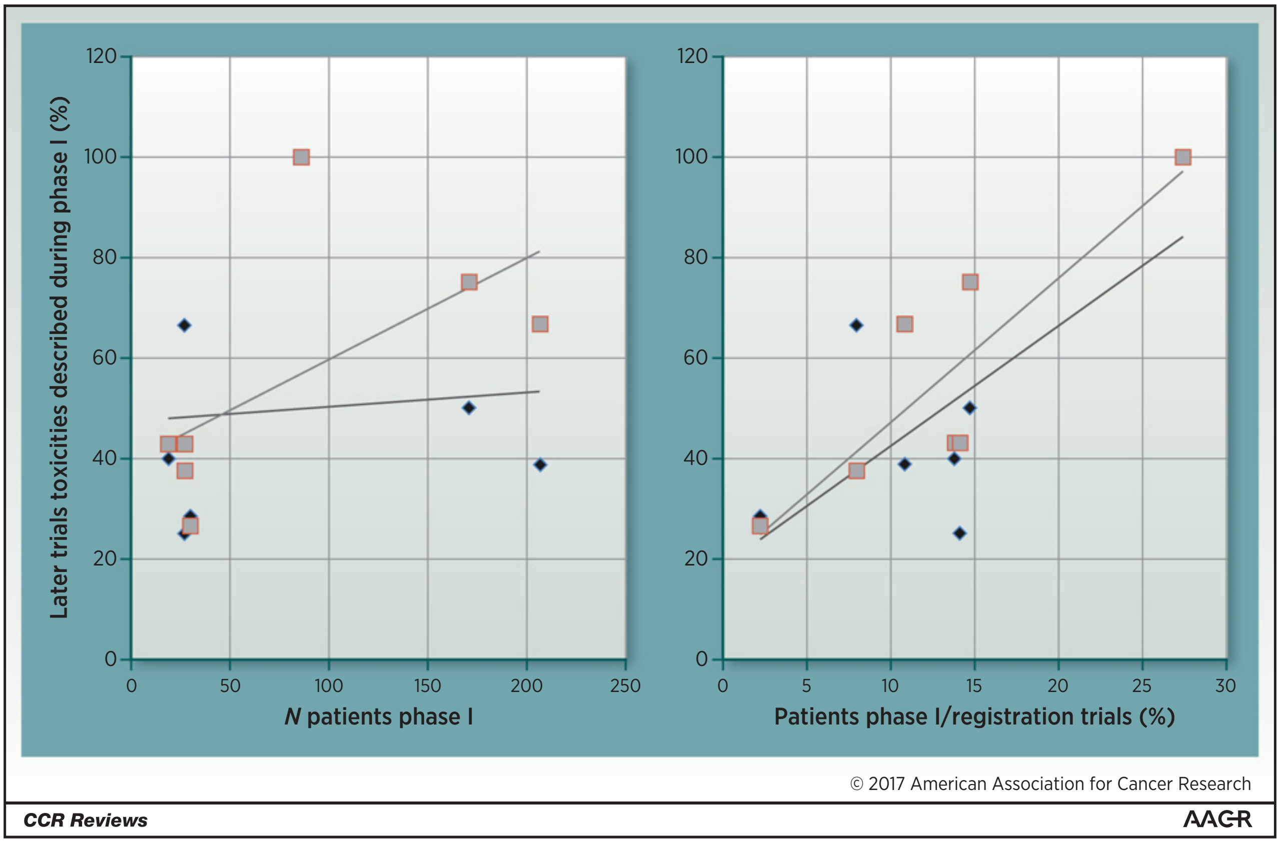

Figure 3.

Correlation between toxicities in phase I and in later trials. *y*-axis is the types of toxicities described in phase I trials as a percentage of the types of toxicities described in the registration trials. Left, correlation between the number of patients included during the phase I trial and the description of all clinically significant toxicities (black diamond), as well as immune-related toxicities (gray square) from later trials. This panel shows that there is an increase in the ability to identify the immune-related toxicities as the number of patients in phase I increases. The number of patients in phase I did not, however, correlate with the ability to identify all types of clinically relevant toxicities. Right, correlation between the ratio of patients included during phase I over patients included in registration trials and the description of clinically significant (black diamond) and immune-related toxicities (gray square) from later trials. This panel shows that the ratio of the number of patients in phase I over the number of patients in the registration trial(s) correlated with the ability to identify either immune-related or all clinically relevant toxicities.

as the science breakthrough of 2013 (11). Only a few years later, we have six checkpoint inhibitors approved by the FDA. In this comprehensive assessment of FDA-approved immune checkpoint inhibitors, we aimed to evaluate how the drug development paradigm performed for these agents.

Among our findings, total clinical development of checkpoint inhibitors took a median of 60.77 months, which compared favorably to other anticancer agents approved by the FDA (Fig. 1). The checkpoint inhibitors timeline is more similar to the faster approval for targeted agents approved under a biomarker-based rationale—a finding that could represent a contemporary shift by the FDA. Indeed, after ipilimumab approval, there was a trend toward shortening the development approval process (Fig. 2). It is noteworthy that these agents, especially PD-1/PD-L1 inhibitors, are also benefitting from access to FDA programs for expedited development. Of note, all five PD-1/PD-L1 inhibitors received breakthrough therapy designation and accelerated approval, and pembrolizumab was approved for melanoma after a phase Ib study (7).

Recent publications demonstrate that a biomarker-based strategy was an independent factor predicting faster development of anticancer agents (12–14). Interestingly, pembrolizumab was the only immune checkpoint inhibitor approved with a biomarker for patient selection, including the NSCLC (requiring PD-L1 expression) and the most recent tissue agnostic microsatellite-instability tumor indication (8). Despite the absence of a widespread clinical use of biomarkers for checkpoint inhibitors (15), this later approval represents a regulatory paradigm shift in oncology, especially since the approval used a genomic marker for regulatory authorization across all solid tumors.

Data from early trials are also serving as the basis for regulatory initial approval of these agents. It is important to note that this observation is more related to a changing paradigm adopted by the FDA in recent years rather than a special privilege for immunotherapies. As examples, approvals of crizotinib and ceritinib used very early trial data for approval, including phase I data alone for ceritinib (16, 17). Consequently, if other regulatory agencies do not adopt a similar pathway, the time gap between FDA approvals compared with other worldwide agencies for checkpoint inhibitor approvals might increase. Herein, we described a longer gap between FDA and EMA approvals of the PD-L1

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inhibitors nivolumab and pembrolizumab (5.9 and 10.4 months, respectively) compared with ipilimumab (3.6 months).

Registration adoption of checkpoint inhibitors based only on early-phase trials could raise concerns regarding safety and performance in later trials. Nevertheless, it is important that there is not a large safety issue that is discovered in later clinical trials. Regarding dosing and schedule, our analysis suggests that phase I studies of checkpoint inhibitors define doses that are usually different than those later adopted. Doses accepted in later trials were 400% (ipilumumab), 66% to 333% (pembrolizumab), 100% (atezolizumab, durvalumab, and for combined iplilumumab), and 50% (avelumab) of the recommended dose in phase I (Table 2). Therefore, phase I testing did not clearly establish a dose definition for checkpoint inhibitors. There is also uncertainty regarding final optimal dose, as illustrated by the variation of approved doses within package inserts of ipilimumab (18) and pembrolizumab (19), even after FDA approval. Many of the phase I trials of checkpoint inhibitors were designed using traditional preassigned dose levels (3 + 3 dose escalation) and defining toxicities (DLTs) as the main outcome for dose definition. Nonetheless, DLTs were often not found for these agents, especially concerning PD-1/PD-L1 inhibitors (6). The determination of an MTD might be more important for immunotherapy combinations, which are usually associated with greater toxicity (20). The concept of a DLT window (usually about 4 weeks) in phase I trials must also adapt to immunotherapy, as immune-related toxicities may occur only after weeks or months of administration (21). Although the current model is so far not compromising safety, a longer period of toxicity assessment could lead to a more precise definition of the toxicity profile among checkpoint inhibitors. Finally, it is not unexpected that new challenges might arise after approval, regardless of the type of study leading to approval. An example of such a challenge is the recent recognition of accelerated progression (hyperprogression) in a subset of patients treated with anti–PD-1/PD-L1 agents (22, 23). However, there is no evidence that this phenomenon, which occurs in less than 10% of patients, would be more identifiable with a different development/approval pathway, nor does its recognition obviate the substantial benefit derived by significant subgroups of patients from checkpoint blockade.

For checkpoint inhibitors, RP2D recommendations are often based on maximum administered doses (6). As part of phase I trials, pharmacokinetic studies and an understanding of immune target engagement may help to more precisely define a dose with less interindividual variation (24, 25). This information, as well as efficacy data, could be used to designate a "minimal effective dose." Otherwise, post-phase I and even postapproval testing can explore different doses and provide updates to approval documents, as has occurred with nivolumab (26–28).

An interesting aspect of checkpoint inhibitor development is that antitumor activity, including durable complete remissions, was observed in phase I trials. Overall RRs, however, remained low—about 16%—which is still higher than those in historical phase I studies of genomically targeted agents or chemotherapy performed without a biomarker (approximately 5%; refs. 14, 29). RRs in phase I trials of checkpoint inhibitors often, but not always, mirrored the activity observed in tumor types tested in later trials (Fig. 2). Profound clinical activity was described for some patients, both in early and later trials, including complete and long-lasting responses. Nevertheless, a significant number of patients do not yet derive benefit from the current approved checkpoint inhibitors. Both primary and acquired resistance to checkpoint inhibitors are major challenges for the future development of immunotherapies. Resistance may be due to modulation of antigen-presenting proteins, as well as genetic abnormalities in tumor and lack of T-cell infiltrate; genomic deletions in *β2-microglobulin* and *JAK2* genes may be operative (30, 31). Hyperprogression after checkpoint blockade may also occur and has been associated with MDM2 amplification and EGFR alterations (22, 23). Although only one checkpoint combination is currently FDA approved (combining anti–PD-1 and anti–CTLA-4), emerging combinations of checkpoint inhibitors with a variety of other agents might be one strategy to overcome treatment resistance (32).

During the dose-definition portion of phase I trials of checkpoint inhibitors, 43% of types of clinically relevant toxicities seen in later trials were described. Previously, we have shown that phase I studies from the preimmunotherapy era predicted about 70% of types of toxicities identified in later studies (33). The lower proportion of toxicities uncovered in phase I immunotherapy trials as compared with previous trials of other drugs could be due to many factors, including, but not limited to, the comparative side-effect profile of immunotherapy versus other agents and the relatively few phase I trials of approved checkpoint inhibitors. Immune-related toxicities are characteristic of checkpoint inhibitors, and, although generally mild, they can be life-threatening (34). Overall, we found that 50.9% of the types of immune-related toxicities detected in later trials were already evident in the phase I studies. The occurrence of delayed toxicities with immune checkpoint inhibitors might also account for the fewer descriptions of clinically relevant and immune-related toxicities in phase I trials. In addition to higher numbers of patients included, treatment duration and toxicity assessment window can be longer on later trials. Encouragingly, treatment-related mortality remained low in early trials as well as in later studies of checkpoint inhibitors. A recent article reassured the similarity of immune toxicity profiles between phase I and late trials, with a higher concordance according to the increased sample size of the former (35).

The findings reported here are limited to the few numbers of checkpoint inhibitors approved so far by the FDA. Many new immune checkpoint modulators, including agonists and antagonists, are currently in development and might take advantage of the first conclusions regarding the drug development paradigm discussed here. Future systematic reviews might be needed according to the approval of new classes of immunomodulatory drugs.

In conclusion, approval of checkpoint inhibitors in a variety of tumor types is rapidly changing the landscape of cancer treatment. Their development is being characterized by the increased importance of early trials. Indeed, many of these phase I trials are being expanded to include diverse patient cohorts, leading to expedited regulatory approval. Our analysis suggests that the current clinical trial paradigms work reasonably well for predicting safety and efficacy of immunotherapy in later studies, though dosing based on phase I trials appears to be variable compared with final dosing. Although the dose-finding portion of phase I studies did not report on a significant percentage of the types of toxicities that are detected with broader use of these agents, this does not appear to have affected drug-related mortality in later trials. Indeed, drug-related mortality in later trials remains exceedingly low, demonstrating that rapid approvals of appropriate immunotherapy agents are justifiable.

Disclosure of Potential Conflicts of Interest

D.L. Jardim reports receiving speakers bureau honoraria from Bristol-Myers Squibb, Merck-Sharpe Dohme, and Roche. D. de Melo Gagliato reports receiving speakers bureau honoraria from Merck-Sharpe Dohme and Roche. R. Kurzrock reports receiving commercial research grants from Foundation Medicine, Genentech, Guardant, Incyte, Merck Serono, Pfizer, and Sequenom, is a consultant/advisory board member for Actuate Therapeutics, LOXO Oncology, Roche, and Sequenom, and holds ownership interest (including patents) in Curematch, Inc. No potential conflicts of interest were disclosed by the other author.

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Analysis of Drug Development Paradigms for Immune Checkpoint Inhibitors

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