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Special Issue: Celebrating 5 Years

Forum

A Timeline of Immune Checkpoint Inhibitor Approvals in Small Cell Lung Cancer

Jennifer Gill,[1] Jeremy Paul Cetnar,[1] and Vinay Prasad[1,2,*]

In this commentary, we review the timeline of clinical trials and regulatory actions of approved immune checkpoint inhibitors for small cell lung cancer, discuss challenges faced by regulatory agencies, and highlight paradoxical lessons that emerge. Accelerated approvals may fail to expedite drugs to market in this setting and further research on overall survival benefit is needed to prove drug efficacy.

Introduction

Immune checkpoint inhibitors (ICIs), anticancer drugs that inhibit immune-suppressing proteins often found on tumor cells, are among the most investigated drugs in cancer research today. As both promise and hype propel research and development for ICIs, a surge of approvals for these drugs has emerged for numerous cancer types. Accordingly, the multitude of clinical trials and consequent approvals for ICIs has been met with both encouragement and concern. While 2000+ trials may increase the potential for discovering life-saving therapies, they may also lead to a plethora of duplicative, inefficient trials that fare poorly for patient volunteers [1]. Similarly, while more ICI drugs on the market means more treatment options for patients, many expensive drugs were approved provisionally and remain on the market with unknown clinical efficacy [2]. Previously, we created a timeline of all cancer ICIs granted accelerated approval to illustrate cases of inappropriate approvals and lack of postapproval regulation in this market. Here, we zoom in on the history of ICIs approved for small cell lung cancer (SCLC). As of October 2019, there have been three ICIs, all targeting programmed cell death-1 (PD-1)/PD-L1 (programmed death-ligand 1) receptors, approved by the FDA for advanced SCLC: nivolumab, atezolizumab, and pembrolizumab[i]. In this commentary, we review the timeline of clinical trial decisions and regulatory action of ICIs for SCLC, discuss challenges faced by regulatory agencies, and highlight the paradoxical lessons that emerge.

Nivolumab

Patients with SCLC have a poor prognosis with limited effective treatment options. For serious conditions with unmet medical needs, the FDA offers the accelerated approval pathway, which bases drug approvals on surrogate endpoints, rather than clinical endpoints, often from small uncontrolled trials, in order to bring a promising drug to market sooner. The FDA offers accelerated approvals on the condition that manufacturers conduct randomized trials on clinical endpoints postapproval to prove efficacy. These postapproval requirements are put in place because surrogate endpoints cannot confidently determine a drug's ability to make a patient live longer or better. Nivolumab was the first ICI drug granted accelerated approval for SCLC based on an overall response rate (ORR) of 12% from the Checkmate-032 trial (NCT01928394[ii]), published on June 4, 2016 [3]. ORR is a surrogate endpoint for overall survival (OS), measuring tumor shrinkage to predict survival. Over 2 years after Checkmate-032 published their results (August 16, 2018), nivolumab was granted accelerated approval for advanced SCLC with progression after two lines of therapy[i]. Eight weeks later, Bristol-Myers Squibb announced that nivolumab failed to improve OS in SCLC patients in Checkmate-331 [4]. Checkmate-331 was an open-label, randomized, Phase III trial with a primary endpoint of OS, analyzed using Kaplan-Meier estimates (NCT02481830[iii]). Checkmate-331's data cutoff was 1 day after nivolumab was granted accelerated approval, yet the FDA did not wait for the randomized trial results, even though 2 years had already elapsed from the ORR data of Checkmate-032.

Nivolumab remains on the market for SCLC; the FDA has not rescinded drug approval. A main objective of accelerated approval is to speed drugs to market, but this timeline suggests 2 years of potential speed were lost. Additionally, ORR, a surrogate endpoint, has been shown to have a poor correlation with OS, a clinical endpoint, in SCLC [5]. Thus, discordant results between single-arm studies investigating ORR and randomized trials may not be surprising.

Atezolizumab

Atezolizumab was granted regular FDA approval in March 2019[i], based on results of

the trial, IMpower-133 (NCT02763579[iv]). IMpower-133 was a double-blind, placebo controlled, Phase III trial with two primary outcomes of progression-free survival (PFS) and OS in the intention-to-treat population, analyzed using Kaplan-Meier methodology [6]. The trial found that first-line atezolizumab added to carboplatin and etoposide improved OS by 2 months compared with placebo (12.3 versus 10.3 months, respectively). Strangely, ORR was numerically lower, with a 60.2% ORR in the atezolizumab group versus 64.4% in the placebo group. PFS was superimposable for the first 4 months, separating just prior to the median for a 0.9-month improvement (5.2 versus 4.3 months). Notably, among patients who discontinued the trial, 83% of those receiving atezolizumab received subsequent chemotherapy compared with 81% receiving placebo, despite the fact that median duration of treatment was longer in the atezolizumab group. Given the discordance between ORR and OS and the potential for imbalance in postprotocol care, additional studies may provide clarity on the benefit of atezolizumab.

Pembrolizumab

Pembrolizumab was granted accelerated approval in June 2019 based on a 19% ORR from two nonrandomized studies, Keynote-158 (NCT02628067[v]) and Keynote-028 (NCT02054806[i,vi]). Keynote-158 was a Phase II trial and Keynote-028 was a Phase IB trial, both one-arm studies with a primary endpoint of ORR. Interestingly, pembrolizumab's ORR (19%) is similar to the 12% ORR of nivolumab, an approved ICI later shown to have no OS benefit. Notably, since the writing of this paper, Merck has

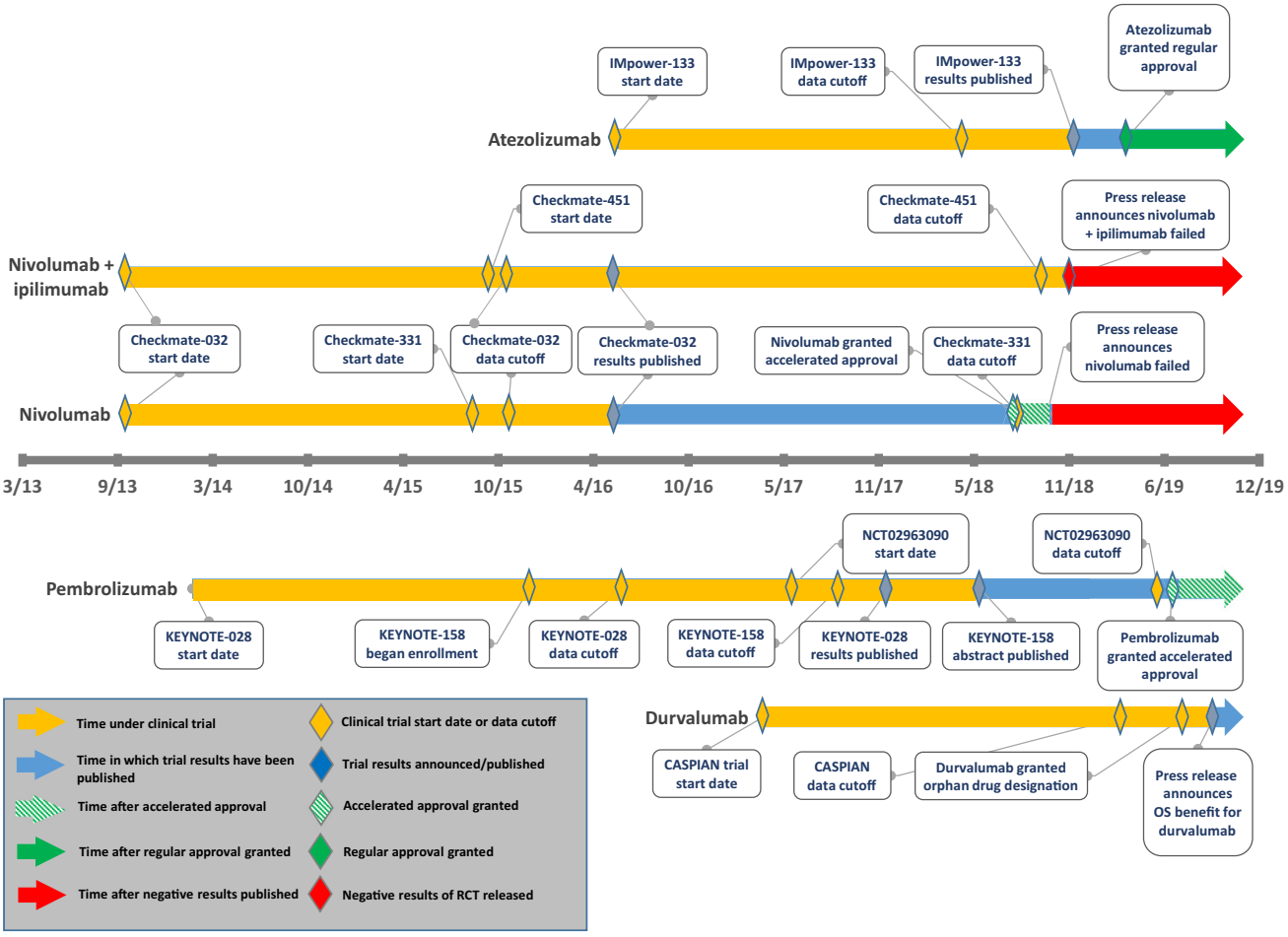

Figure 1. Timeline of Immune Checkpoint Inhibitors (ICIs) in Small Cell Lung Cancer (SCLC) as of October 2019. Timeline of trial start dates, data cutoffs, and publication and results announcement dates, as well as approval dates for accelerated and regular approvals for ICIs and ICI for SCLC. Abbreviations: OS, overall survival; RCT, randomized controlled trial.

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announced topline results for Keynote 604, which show that pembrolizumab fails to improve overall survival in extended stage small cell lung cancer. Thus, pembrolizumab recapitulates the story of nivolumab: A drug approved in a highly lethal malignancy based on a surrogate endpoint failing to improve survival in an imminent randomized trial.[vii]

Accelerated Approval in SCLC

Accelerated approvals were instituted to quicken access to drugs compared with full approvals, with potential benefit for patients with no other effective treatment options. Analyzing the SCLC timeline as a whole (Figure 1) reveals that trial length for randomized trials was not more than 1 year longer than uncontrolled trials, and drugs came to the market quicker (by 2+ years) or were confirmed ineffective sooner when investigating OS versus ORR. Recently, durvalumab, an ICI investigated in the randomized, Phase III CASPIAN trial (NCT03043872[viii]), was shown to improve median OS for SCLC patients by 2.7 months [7]. The CASPIAN trial had a primary outcome of OS in the intention-to-treat population, analyzed using the Kaplan-Meier method. From start to press release, CASPIAN took 2.5 years to prove clinical efficacy compared with the 2.7 years it took nivolumab's single-arm Checkmate-032 to publish ORR results.

Accelerated approvals based on surrogate outcomes in highly lethal malignancies such as SCLC may paradoxically slow progress. This occurs because median duration of response is part of the assessment of response and lengthens study time, coupled with the fact that survival benefits are rapidly demonstrated in lethal conditions. For lethal conditions, surrogate-based approvals may fail to achieve its stated goals. Empirical evidence suggests surrogates do not speed drugs in latter lines of therapy [8] and this is reflected in SCLC's approval timeline.

Concluding Remarks

ICIs are being investigated vigorously in SCLC. While many overlapping and competing trials may lead to life-saving therapies and more options for patients, they may also lead to a plethora of duplicative, inefficient trials that bring expensive drugs to market with unknown clinical efficacy [1,2]. The timeline of approvals in SCLC illustrates an unintuitive truth. The most rational way to approve ICI drugs in SCLC, a method that maximizes speed and knowledge, is routine use of OS as primary endpoint in randomized trials against best available therapy. Innovation would be enhanced if the FDA were to raise the bar for drug approval in this disease.

Disclaimer Statement

V.P. receives royalties from his book Ending Medical Reversal. His work is funded by Arnold Ventures, he has received honoraria for Grand Rounds/lectures from several universities, medical centers, nonprofit groups, and professional societies, is a writer for Medscape, and the host of the Plenary Session podcast, which receives crowdfunding support through the Patreon platform. J.G. and J.C. declare no competing interests.

Resources

[i]www.accessdata.fda.gov/scripts/cder/daf/
[ii]https://clinicaltrials.gov/ct2/show/NCT01928394
[iii]https://clinicaltrials.gov/ct2/show/NCT02481830
[iv]https://clinicaltrials.gov/ct2/show/NCT02763579
[v]https://clinicaltrials.gov/ct2/show/NCT02628067
[vi]https://clinicaltrials.gov/ct2/show/NCT02054806
[vii]https://investors.merck.com/news/press-release-details/2020/Mercks-KEYTRUDA-pembrolizumab-in-Combination-with-Chemotherapy-Significantly-Improved-Progression-Free-Survival-Compared-to-Chemotherapy-Alone-as-First-Line-Treatment-for-Extensive-Stage-Small-Cell-Lung-Cancer/default.aspx. accessed 6-12-2020
[viii]https://clinicaltrials.gov/ct2/show/NCT03043872

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Special Issue: Celebrating 5 Years

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Molecular Tumor Boards in Clinical Practice

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Next-generation sequencing (NGS) application in clinical practice requires the implementation of molecular tumor boards (MTBs). Starting from a systematic review of literature, we discuss the MTB-related key points: MTB aims and composition, types of tumors to discuss, types of molecular analyses, methods for classifying actionability, appropriate turnaround time, and cost management.