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Receipt of subsequent immune checkpoint inhibitors at progression among patients with solid tumors enrolled in clinical trials of adjuvant immune checkpoint inhibitors

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Abstract

Purpose: Immune checkpoint inhibitors can induce long-term responses in metastatic cancer, thus determining how many patients on placebo control arms of adjuvant immune checkpoint inhibitors receive these drugs as standard of care at progression is critical to assess if the benefit is truly from adjuvant administration or treatment at any point.

Methods: This study included recent clinical trials of adjuvant immune checkpoint inhibitors for solid tumors that gained FDA approval. We determined the number of placebo control patients with progression events, the number who actually received subsequent immune checkpoint inhibitor, and the number who were eligible to receive it.

Results: Data was available from 462 placebo control patients who experienced progression in trials of adjuvant immune checkpoint inhibitors. 377 of these control patients were eligible for first line immune checkpoint inhibitors upon progression. 34% (130/377) of eligible control patients received immune checkpoint inhibitors in the first line metastatic setting. In total, 28% (130/462) received immune checkpoint inhibitors, 54% (247/462) were eligible but did not receive it, and 18% (85/462) were ineligible according to currently accepted standard of care.

Conclusions: Only 34% of eligible patients in placebo control arms of trials of adjuvant immune checkpoint inhibitors for solid tumors receive these medications upon progression. This is surprisingly low, and suggests that exposure to immune checkpoint inhibitors at all, instead of in the adjuvant setting, could explain the positive effect size of recurrence free survival observed in each of these trials.

Introduction

In 2021 there were six Food and Drug Administration (FDA) approvals of immune checkpoint inhibitors (ICI) for adjuvant treatment for solid tumors after curative intent surgery. These approvals occurred for triple negative breast cancer (TNBC), non-small cell lung cancer (NSCLC), esophageal and gastroesophageal junction (GEJ) cancer, muscle invasive bladder cancer, renal cell carcinoma (RCC), and melanoma. The clinical trials for which the FDA approvals were based upon randomized patients post-curative surgery to ICI or placebo.

In all six tumor types it has been established that ICIs provide efficacy in advanced, metastatic, or recurrent disease, often as first-line therapy. [1–6] Therefore in many instances, we would expect the standard of care would be to offer patients in control arms of these trials ICI upon progression. This question is particularly relevant as the phase III, randomized controlled trials (RCTs) that led to these FDA approvals took place in low- and middle-income countries (LMIC) where access to ICI is more limited. [7 8] If patients in the control arms were not eventually treated with standard of care ICI upon progression, relapse, or recurrence, differences in post-protocol outcomes, including overall survival, may be explained simply by access to ICI at some point, rather than specifically by gains from early administration in the adjuvant setting.

The ability of ICI to induce long term, durable responses in certain patients, irrespective of tumor volume, further emphasizes the importance of this question. [9] Unlike cytotoxic drugs where adjuvant administration may increase curative fractions, but metastatic administration merely prolongs survival without cures; ICI offer different treatment properties, and durable remission in the metastatic setting is possible. Giving ICI in the adjuvant setting exposes many more patients to potential immune-related adverse events, and some of these autoimmune conditions can be fatal or lifelong. Therefore, treatment with ICI in the adjuvant setting should not be taken lightly, and trials should be designed in a manner that controls for confounding factors, such as exposure to ICI at any timepoint. Whether patients in these trials receive post-protocol ICI, if indicated, at progression or reoccurrence also has ethical relevance to oncologists, patients, and regulators. We report on the receipt of standard of care ICI upon progression or reoccurrence amongst control arm patients in the six RCTs leading to FDA approval of adjuvant ICI for solid tumors in 2021.

Materials And Methods

Drug and trial search

We reviewed the FDA Oncology and Hematology Drug Approval Notification website for recent approvals of adjuvant ICI for solid tumors (years 2019–2021). For each drug, we reviewed the primary publication and supplement or appendix that supported FDA approval. For the trials that did not provide data on subsequent therapies, we contacted the corresponding author by email to request these data.

Data abstraction

For each study, we recorded the following trial information: drug name, tumor type, study name, FDA approval date, data lock date, study sites that were located in LMIC, indication for ICI in metastatic disease, and FDA Approval Date for ICI in first line metastatic disease (obtained from the FDA Oncology and Hematology Drug Approval Notification website). We defined LMIC countries according to the World Bank. [10] We also recorded findings, if any, pertaining to health-related quality of life (HRQOL). We recorded the total number of control patients, number of disease free survival (DFS) events amongst control patients, the number eligible for ICI, the number eligible who received ICI, and data on subsequent therapies received. We stipulated that eligible patients for ICI broadly enrolled on the trial to begin with, and did not have autoimmune conditions, uncontrolled viral infections, or other conditions that would preclude safe ICI use. We used National Comprehensive Cancer Network (NCCN) guidelines to determine which patients were eligible for ICI in the first line metastatic setting. [1–6] We took the number of patients in the control group who were programmed death-ligand-1 (PDL1) positive at enrollment (PDL1 CPS $\geq$ 5 for esophageal/GEJ, and CPS $\geq$ 10 for TNBC) to determine which patients would be eligible for first line ICI in the metastatic setting, when relevant. Trial participants who had a driver mutation (e.g., EGFR or ALK mutations for NSCLC) were not considered eligible.

Statistical methodology

For each trial, we calculated the number of patients eligible for ICI by using the total DFS events. The number of eligible control patients who received ICI was determined by the reported number of patients who received ICI and the calculated number of eligible patients. We also calculated the percentage of trials participants, for all trials combined, who received ICI, were eligible for but did not receive ICI, and were ineligible for ICI. Data are presented in numbers and percentages. Because of the low number of drug approvals that met our criteria, we were not able to do any statistical comparisons. This study was done using publicly available data and did not include patient data, and thus IRB approval was not required.

Results

We found six trials of adjuvant ICIs for solid tumors approved by the FDA, and they were all approved in 2021; including neoadjuvant and adjuvant pembrolizumab in TNBC, adjuvant atezolizumab in NSCLC, adjuvant nivolumab in esophageal/GEJ cancer, adjuvant nivolumab in muscle invasive bladder cancer, adjuvant pembrolizumab in RCC, and adjuvant pembrolizumab in melanoma. [11–17]

We found three RCTs (50%, 3/6) that provided full data on subsequent therapies the patients received. Table 1. Corresponding authors from the three trials that do not include this information either did not reply to inquiries or declined to provide this information upon reasonable request.

In the IMpower010 trial of adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA NSCLC, 198 patients experienced progression, of which 66% (131/198) received any systemic therapy upon progression. Of these, 33% (65/198) received ICI. All patients with reoccurrence of NSCLC in whom systemic therapy is indicated should have received ICI according to the NCCN, with the exception of patients with EGFR, ALK or other driver mutated cancers. In IMpower 010, there were 33 patients (33/198) in the control arm with EGFR or ALK mutations who developed a DFS event who would not be eligible for first line ICI. Therefore, excluding these 33 patients from the 198 patients who experienced progression, 165 patients would have been eligible for ICI. Only 39% (65/165) of eligible patients in the control arm of Impower010 received ICI. Other therapies received upon progression in the control arm included radiotherapy in 41% (82/198) of patients and surgery in 18% (36/198) of patients. The LMIC countries where this trial enrolled include Russia, Ukraine, China, and Romania. The clinical data cutoff for

Impower010 was January 2021, and pembrolizumab in combination with chemotherapy was approved as front-line treatment of NSCLC in 2018. IMpower010 did not assess HRQOL.

In the Checkmate577 study of adjuvant nivolumab for resected esophageal or GEJ cancer, there were 262 placebo control patients. Of these, 43% (113/262) went on to experience progression and 98% (111/113) of these patients received subsequent systemic therapy. Of these 113 control patients, 17% (19/113) received ICI upon progression. For locally advanced or metastatic esophageal or gastroesophageal cancer, according to the NCCN, first line treatment with ICI is indicated if the tumor combined proportion score (CPS) is ≥ 5. In the control arm as a whole, approximately 54% of patients had a CPS ≥ 5. Extrapolating to control patients with DFS events, 61/113 patients would have been eligible to receive ICI on progression. Therefore, only 31% (19/61) of eligible control patients received ICI upon progression. Pembrolizumab and nivolumab were not approved by the FDA for use in the first line metastatic setting in esophageal/GEJ until 03/2021 and 04/2021, respectively, and Checkmate577 recruited between the years of 2016–2019 with a clinical data cutoff of May 2020. LMIC where the trial took place include Argentina, Mexico, and Turkey. The authors of Checkmate577 state that HRQOL was maintained during the treatment period.

In the Keynote-564 trial of adjuvant pembrolizumab after nephrectomy for RCC, there were 498 patients in the control arm. Of these, 30% (151/498) experienced a DFS event, and 86/151 (57%) received subsequent systemic therapy. The other therapies received on progression were radiation (17/151) and surgery (31/151). In all, 30% (46/151) of control patients received ICI upon progression. In metastatic RCC, ICI either as the combination of nivolumab and ipilimumab or anti-PDL1 antibody plus a tyrosine kinase inhibitor would be the standard of care for all patients since the FDA approval of nivolumab and ipilimumab in 2018 according to NCCN guidelines. The data cutoff date for Keynote 564 was December 2020. Only 30% (46/151) of eligible control patients received ICI upon progression. The LMIC sites for the Keynote-564 trial include Argentina, Brazil, Colombia, and Russia. Keynote-564 reported that HRQOL was stable in the pembrolizumab group, with no meaningful differences compared with placebo.

In total, for the three trials that report full data on subsequent therapies, there were 462 patients who experienced a DFS event, 377 of whom were eligible for first line ICI upon progression. 34% (130/377) of eligible control patients received ICI in the first line metastatic setting. In total, 28% (130/462) received ICI upon progression, 54% (247/462) were eligible for ICI upon progression but did not receive it, and 18% (85/462) were ineligible for first line ICI according to currently accepted standard of care at the time of this publication. Figure 1.

The Keynote-054 trial of adjuvant pembrolizumab in resected stage III melanoma only includes data on subsequent systemic therapy for patients with locoregional progression, not distant metastatic disease. For locoregional progression only, there were 93 DFS events amongst control patients and 65 patients who received subsequent ICI. We were unable to determine how often ICI would be indicated upon progression based upon the data provided by the authors. The trial reported that HRQOL was unchanged in the pembrolizumab group compared with placebo.

Neither the Keynote-522 trial of neoadjuvant and adjuvant pembrolizumab in TNBC nor the CheckMate-274 trial of adjuvant nivolumab in muscle invasive bladder cancer report data on subsequent therapies received in either arm. First line ICI is indicated in metastatic TNBC for tumors that overexpress PDL1, and in metastatic bladder cancer if patients are ineligible for platinum containing chemotherapy. The CheckMate-274 trial reports on HRQOL, and stated that there was “no meaningful difference in deterioration in quality of life” between the two treatment groups.

Discussion

Among three recent trials of adjuvant ICI for solid tumors only 34% of eligible patients in the control arms received ICI upon progression despite meeting the current standard of care indications according to NCCN guidelines. Three other trials of adjuvant ICI for solid tumors did not report these numbers and did not respond to requests to obtain these data. The number of patients in the control arm whom did not receive ICI as the standard of care is surprisingly high, and suggest that exposure to ICI at all, instead of ICI in the adjuvant setting, could explain the positive effect size of RFS observed in each of these trials.

This confounding variable of ICI timing should be addressed in future trials. In addition, trials should ensure that enrolled patients, especially patients within the control arm, receive the standard of care in the post-protocol setting to allow for appropriate determination of efficacy. Not providing the standard of care in the post-protocol setting can artificially inflate the efficacy of the treatment group.

When studying the correct treatment timing of ICI in solid tumors, the ability of ICI to induce long-term, durable remissions, even for patients with bulky, advanced, and refractory disease must be remembered. [9] The adjuvant question for these drugs is fundamentally different than for cytotoxic chemotherapy. Is routine application of ICI—including to many individuals who cannot benefit because they are already cured—superior to administration upon progression? We found most trials did not allow the reader to assess this information; when trials did permit assessment, rates of post protocol use were low, leaving this fundamental question unanswered.

While one might contend that HRQoL is superior from adjuvant use, as recurrent cancer is a morbid event, we found 4/6 studies examined HRQoL and found no major differences between adjuvant ICI or placebo treatment. Averting recurrence is not in and of itself evidence of improved quality of life and must be weighed against potentially life-long immune related adverse events being born by individuals who may already be cured.

Reasons for the low use of ICI upon progression in control patients may include the high cost of these medications, many of which are unaffordable and difficult to access for patients in LMICs outside of a clinical trial. [18] Patients may need to pay for the drug out of pocket in LMICs. [19] We found that each of these adjuvant trials was conducted in LMICs. Trials should report subsequent post-protocol therapy by country, as patients in the U.S.A. may be receiving standard of care ICI while patients in LMICs are not. Patients who progress may no longer be candidates for systemic therapy or ICI. In the Checkmate-577 trial, first line ICI for metastatic esophageal or GEJ carcinomas was not approved until after data lock date for the study. This is a likely reason more patients in this trial did not receive ICI upon progression. Now that this is an accepted standard of care, it renders the control arm of Checkmate577 outdated given the low ICI treatment rate. In the case of the adjuvant NSCLC and RCC trials, similarly low number of eligible control patients received ICI upon progression despite it being approved before and during trial enrollment and treatment.

This study is limited by the lack of granular data provided in these studies, leading us to make certain reasonable inferences as to the true numbers of ICI eligible patients. The study was also limited by poor response rate from corresponding authors.

Conclusion

When reported, among recent trials of adjuvant ICI for solid tumors, only 30–39% of eligible patients in control arms receive subsequent ICI on progression. This means that these trials cannot answer the key question: Is it better to use ICIs in the adjuvant setting or retain these medications for relapse. Future trials studying adjuvant ICI for solid tumors should ensure post-protocol standard of care for all control patients. Currently this practice is uncommon and presents a major challenge to the legitimacy of the findings of adjuvant ICI trials as well as an ethical dilemma for physicians and drug regulators. Cooperative groups may aid in these studies.

Declarations

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Tables

Table 1
FDA Approvals of Adjuvant ICI for Solid Tumors

Tumor type and indication	**NSCLC, Adjuvant atezolizumab [13]**	**Esophageal, Gastroesophageal Junction, Adjuvant nivolumab [12]**	**Renal Cell Carcinoma, Adjuvant pembrolizumab [15]**	**Triple Negative Breast Cancer, Neoadjuvant + Adjuvant Pembrolizumab [11]**	**Muscle Invasive Bladder Cancer, Adjuvant nivolumab [16]**	**Resected Stage III Melanoma, Adjuvant pembrolizumab [14]**
Study	Impower 010	CheckMate 577	Keynote-564	Keynote-522	CheckMate 274	Keynote-054
FDA Approval Date	October 2021	May 2021	November 2021	July 2021	August 2021	December 2021
Data Lock Date	January 2021	May 2020	December 2020	April 2019	August 2020	April 2020
FDA Approval Date for ICI in first line metastatic disease	October 2018 [20]	March-April 2021 [21 22]	April 2018 [23]	Nov. 2020 [24]	February, May 2017 [25]	March 2011 [26]
Indication for ICI in metastatic disease	All patients except driver mutation [6]	1st line if CPS ≥ 5 [4]	All patients [2]	1st line if CPS ≥ 10 [1]	1st line if platinum ineligible [3]	1st line, or BRAF/MEK inhibition [5]
LMIC where study took place [10]	China, Romania, Russia, Ukraine	Argentina, Mexico, Turkey	Argentina, Brazil, Colombia, Russia	Brazil, Colombia, Russia, Turkey	Argentina, Brazil, China, Colombia, Mexico, Peru, Romania, Russia	Russia, Serbia
Control patients (*n*)	440	262	498	390	356	505
DFS event (*n*)	198	113	151	90	204	288 (93 locoregional, 165 distant metastatic)
Subsequent systemic therapy *n* (%)	131 (66%)	111 (98%)	86 (57%)	Not available	Not available	69 (74%) locoregional only[&]
Subsequent ICI *n* (%)	65 (33%)	19 (16%)	46 (30%)	Not available	Not available	65 (70%) locoregional only
Eligible for ICI *n*	165[$]	61[^]	151	72[#]	204	288

Tumor type and indication	NSCLC, Adjuvant atezolizumab [13]	Esophageal, Gastroesophageal Junction, Adjuvant nivolumab [12]	Renal Cell Carcinoma, Adjuvant pembrolizumab [15]	Triple Negative Breast Cancer; Neoadjuvant + Adjuvant Pembrolizumab [11]	Muscle Invasive Bladder Cancer, Adjuvant nivolumab [16]	Resected Stage III Melanoma, Adjuvant pembrolizumab [14]
% of eligible control patients who received ICI	39%	31%	30%	Not available	Not available	Not available

#: Approximately 80% of patients had CPS ≥ 10

$ There were 33 patients in the control group with EGFR or ALK mutations and a DFS event in whom ICI would not be indicated

^Approximately 54% of the control group had CPS ≥ 5

&Keynote-054 trial only reports data on subsequent therapies for patients with locoregional progression

Abbreviations: FDA = Food and Drug Administration LMIC = Low middle income countries. CPS = combined proportion score.

Figures

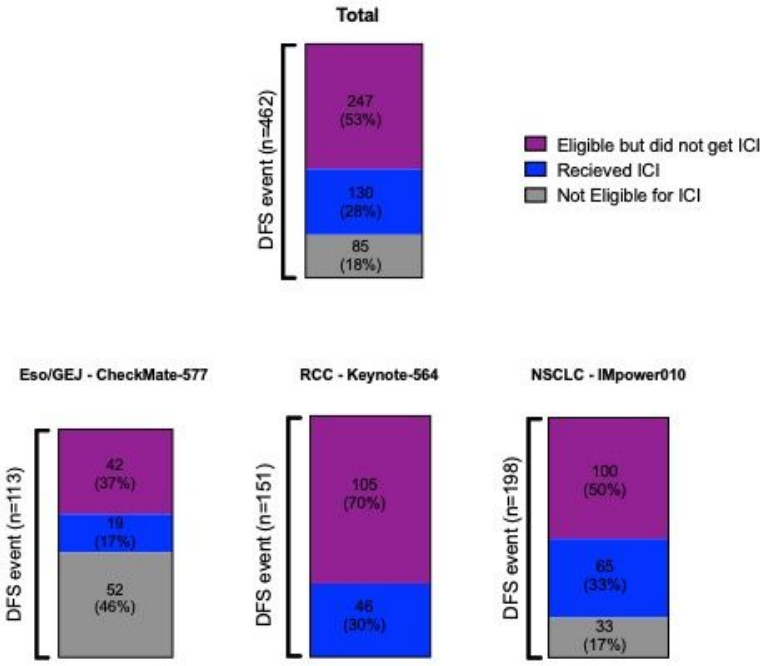

Figure 1

Receipt of ICI Upon Progression Amongst Control Arm Patients in Trials of Adjuvant ICI for Solid Tumors