Title

The landscape of checkpoint inhibitors in oncology

Authors

Haslam, Alyson
Kim, Myung Sun
Elbaz, Josh
et al.

Publication Date

2024-09-01

DOI

10.1016/j.ejca.2024.114240

European Journal of Cancer 209 (2024) 114240

Contents lists available at ScienceDirect

European Journal of Cancer

journal homepage: www.ejcancer.com

Original research

The landscape of checkpoint inhibitors in oncology

Alyson Haslam [a,*], Myung Sun Kim [b], Josh Elbaz [c], Vinay Prasad [a]

[a] Department of Epidemiology and Biostatistics, University of California San Francisco Medical, USA
[b] Oncology/Hematology, Compass Oncology, Portland, OR, USA
[c] Zucker School of Medicine, Hofstra University, USA

ARTICLE INFO

Keywords:
Immune checkpoint inhibitors
Overall survival
Response
Registration trials

ABSTRACT

Background: Immune checkpoint inhibitor (ICI) therapies have become increasingly popular treatment options for patients with cancer, even for patients in non-metastatic settings. Survival and responses have been reported for individual tumor types, but little is known about these outcomes, collectively. We sought to provide an overview of overall survival (OS) and progression-free survival (PFS) in ICI drugs tested in registration trials.
Methods: In a cross-sectional analysis of US FDA oncology ICI drug approvals (2011–2023), we searched for supporting ICI registration trials. We characterized these trials, regarding differences in median OS and PFS between patients in intervention and control arm participants in ICI registration trials; percentage of patients who receive ICI crossover; and whether there is correlation between the percentage of crossover and differences in OS or PFS.
Results: Fifty-six (54.4 %) approvals had trials that reported median OS for both intervention and control arms (median difference was 2.8 months; IQR: 2.2 to 5.0 months). Sixty-five (63.1 %) approvals had trials that reported PFS data for both arms (median of 0.9 months; IQR: −0.2 to 3.0 months). Subsequent therapy was common (median=18.9 %) and was significantly correlated with a higher difference in median OS in all studies with reported differences (R2 =0.15; p = 0.001).
Conclusion: ICIs are increasingly used in the treatment of cancer, yet the median OS improvement is modest, and many ICIs have not been tested for OS benefit. OS is the outcome most meaningful for patients, and drug regulation should require better testing and reporting of these data.

1. Introduction

Immune checkpoint inhibitors (ICIs) have improved overall survival (OS) in multiple tumor types, thus leading to dozens of approvals for these indications. These drugs have provided valuable benefit for some, although the majority of patients are not eligible for them and even fewer respond. [1] ICI resistance is common and can limit the durability of response and perhaps survival. [2] Adverse events can also be an issue for patients on ICI therapy, which may lead to treatment dose reduction and/or discontinuation, yet paradoxically, higher adverse events have been associated with better survival. [3].

ICIs have become popular treatment options, especially for patients with certain tumor types such as melanoma, renal cell carcinoma, and non-small cell lung cancer, [4] in part because of generally better tolerability but also because of efficacy improvements over prior therapy options. However, little is known about the duration of improvement, and subsequent therapy in the trials, including crossover, may complicate the interpretation of OS results. We sought to characterize OS and crossover in trials testing ICIs.

2. Materials and methods

We sought to assess the evidence for ICI therapies by reviewing all US Food and Drug Administration approvals for oncology indications. Approval information was gathered from the FDA Oncology announcement page and prior publications. [1,5] We included all indications through December 31, 2023. We searched PubMed and Google Scholar for publications reporting on these trials using the trial registration number and trial name.

We abstracted trial data from the drug label, including phase, comparator, number of trial participants, primary outcome, overall survival outcomes, progression-survival outcomes, and response

* Correspondence to: Department of Epidemiology and Biostatistics, UCSF Mission Bay Campus, Mission Hall: Global Health & Clinical Sciences Building, 550 16th St, 2nd Fl, San Francisco, CA 94158, USA.
E-mail address: alyson.haslam@ucsf.edu (A. Haslam).

https://doi.org/10.1016/j.ejca.2024.114240

Available online 25 July 2024

outcomes. Data abstracted from published trial data include mature overall survival data and data on crossover and subsequent therapy, including number who received subsequent therapy and therapy type. When multiple reports on the same trial were available, we used the one that reported on the mature primary analysis, without being long-term follow-up. For ICIs approved via the accelerated pathway based on single-arm trial data, we searched for randomized confirmatory trial information.

2.1. Statistical analysis

We presented descriptive characteristics for trials leading to ICI approval, stratified by difference in OS status (3 or more months vs. less than 3 months). We subtracted the median OS and progression-free survival (PFS) in the control group from the median OS and PFS in the intervention group and categorized the differences. Because of the non-parametric nature of the data, we used Spearman correlation to assess the association between the percentage of people who received subsequent PD1/PDL1 therapies (crossover or not) and the difference in OS, weighted by sample size. We also assessed the correlation between the difference (between the intervention and control arms) in median PFS and the difference (between the intervention and control arms) in median OS, weighted by sample size. In interpreting the strength of the correlation, we defined high correlation as ≥ 0.70 and low correlation as < 0.30. [6] We used R statistical software, version 4.2.1, for all analyses and figure creation.

In accordance with 45 CFR §46.102(f), this study was not submitted for University of California, San Francisco institutional review board approval because it involved publicly available data and did not involve individual patient data.

3. Results

We found 103 approval indications for immune checkpoint inhibitors. Eighty-eight (85.4 %) were in the metastatic setting, and 63 (61.2 %) were approved on randomized data. Seventy-two approvals (69.9 %) were based on open-label trials. Thirty-five approvals (34.0 %) were approved via the accelerated pathway, and 8 (7.8 %) were withdrawn (partially or fully) from the market. Lung (n = 25, 24.3 %), urothelial (n = 17, 16.5 %), melanoma (n = 12, 11.7 %), and gastroesophageal (n = 11, 10.7 %) were the most common tumor types among ICI approvals. Studies reporting differences in median OS were more likely to be randomized ($p < 0.001$) and test a therapy in the metastatic setting ($p < 0.001$), compared to studies not reporting median OS differences (Table 1).

Twenty (19.4 %) studies explicitly allowed crossover or had methods in the protocol to adjust for crossover. The median percentage of participants who received subsequent ICI therapy, including crossover was 18.9 % (IQR: 9.7 %, 32.0 %). When stratifying by median OS difference, the percent of studies allowing crossover was higher ($p = 0.001$) in studies reporting an OS difference of 3 or more months (n = 7, 25.9 %) than those with an OS difference of less than 3 months (n = 5, 17.2 %) or median OS not reported (n = 8, 17.0 %).

Fifty-six (54.4 %) approvals had trials that reported median OS for both intervention and control arms. The median difference in OS between intervention and control arms was 2.8 months (IQR: 2.2 to 5.0 months). Twelve (21.4 %) trials had an OS difference of less than 2 months, 17 (30.4 %) had an OS difference of 2–2.9 months, and 7 (12.5 %) had an OS difference of 10 or more months (Figure 1).

Sixty-five (63.1 %) approvals had trials that reported PFS data for both arms. The median difference in PFS between intervention and control arms was 0.9 months (IQR: −0.2 to 3.0 months). Twenty trials (30.8 %) had a difference of less than zero, 13 (20.0 %) trials had a PFS difference of less than 1 month but greater than zero, 10 (15.4 %) had a PFS difference of 1.0–1.9 month, and 3 (4.6 %) had a PFS difference of 10 or more months (Figure 2). The median difference in PFS was higher

Table 1
Characteristics of trials leading to FDA approval of immune oncology checkpoint inhibitor drugs, by differences in overall survival between intervention and control arm.

	OS difference 3 or more months	OS difference less than 3 months	OS Not evaluable/ reported	p-value
n	27	29	47	
Trial design (%)				0.001
Randomized	22 (81.5)	20 (69.0)	21 (44.7)	
Single arm	2 (7.4)	6 (20.7)	25 (53.2)	
Single arm/ confirmatory	3 (11.1)	3 (10.3)	1 (2.1)	
Setting (%)				0.002
Adjuvant	0 (0.0)	0 (0.0)	12 (25.5)	
Non-metastatic	0 (0.0)	0 (0.0)	1 (2.1)	
Neoadjuvant	0 (0.0)	0 (0.0)	2 (4.3)	
Metastatic	27 (100.0)	29 (100.0)	32 (68.1)	
Withdrawn (%)				0.05
No	25 (92.6)	24 (82.8)	46 (97.9)	
Yes	2 (7.4)	5 (17.2)	0 (0.0)	
Partial	0 (0.0)	0 (0.0)	1 (2.1)	
Accelerated approval = yes (%)	8 (29.6)	9 (31.0)	18 (38.3)	0.69
Tumor (%)				< 0.001
Biliary	0 (0.0)	1 (3.4)	0 (0.0)	
Breast	2 (7.4)	0 (0.0)	2 (4.3)	
Cervical	0 (0.0)	0 (0.0)	1 (2.1)	
CRC	0 (0.0)	0 (0.0)	4 (8.5)	
Gastroesophageal	1 (3.7)	8 (27.6)	2 (4.3)	
HNSCC	0 (0.0)	3 (10.3)	0 (0.0)	
Hodgkin's lymphoma	0 (0.0)	0 (0.0)	3 (6.4)	
Liver	0 (0.0)	4 (13.8)	2 (4.3)	
Lung	14 (51.9)	7 (24.1)	4 (8.5)	
Melanoma	4 (14.8)	2 (6.91)	6 (12.8)	
Mesothelioma	1 (3.7)	0 (0.0)	0 (0.0)	
Non-Hodgkin's lymphoma	0 (0.0)	0 (0.0)	1 (2.1)	
Skin	0 (0.0)	0 (0.0)	6 (12.8)	
Soft tissue	0 (0.0)	0 (0.0)	1 (2.1)	
Solid tumors	0 (0.0)	0 (0.0)	3 (6.4)	
Urothelial	4 (14.8)	4 (13.8)	9 (19.1)	
Uterine	1 (3.7)	0 (0.0)	3 (6.4)	
Comparator in randomized trials (%)				< 0.001
Best supportive care	0 (0.0)	0 (0.0)	1 (2.1)	
Chemotherapy	10 (37.0)	13 (44.8)	1 (2.1)	
Glycoprotein 100	1 (3.7)	0 (0.0)	0 (0.0)	
Immune checkpoint inhibitor	0 (0.0)	2 (6.9)	4 (8.5)	
Monoclonal antibody (MAB)	0 (0.0)	1 (3.4)	0 (0.0)	
MAB conjugate	0 (0.0)	0 (0.0)	1 (2.1)	
MAB/ chemotherapy	1 (3.7)	0 (0.0)	0 (0.0)	
NA	3 (11.1)	4 (13.8)	25 (53.2)	
Placebo	9 (33.3)	7 (24.1)	12 (25.5)	
Tyrosine kinase inhibitor	3 (11.17)	2 (6.9)	3 (6.4)	
Primary outcome for approval (%)				< 0.001
Overall survival	15 (55.6)	20 (69.0)	3 (6.4)	
Other	12 (44.4)	9 (31.0)	44 (93.6)	
Median OS reached (%)				< 0.001
Not reached	3 (11.1)	0 (0.0)	15 (31.9)	
Not reported	1 (3.7)	1 (3.4)	32 (68.1)	
Reached	23 (85.2)	28 (96.6)	0 (0.0)	
OS reaching statistical significance (%)				

(continued on next page)

Table 1 (*continued*)

	OS difference 3 or more months	OS difference less than 3 months	OS Not evaluable/ reported	p-value
No	4 (14.8)	8 (27.6)	11 (23.4)	< 0.001
Not tested	0 (0.0)	0 (0.0)	32 (68.1)	
Yes	23 (85.2)	21 (72.4)	4 (8.5)	
Difference in median OS (median (IQR); 51 studies))	6.0 (4.1, 10.0)	2.2 (1.7, 2.5)	NA	< 0.001
Difference in median PFS (median (IQR); 44 studies)	2 (0.7, 3)	-0.1 (−0.5, 0.9)	5 (4, 6)	< 0.001
Crossover allowed (%)				0.001
No	12 (44.4)	13 (44.8)	5 (10.6)	
Not indicated	8 (29.6)	11 (37.9)	34 (72.3)	
Yes	7 (25.9)	5 (17.2)	8 (17.0)	
% of patients who received subsequent PD1/PDL1 therapy (median (IQR); 63 studies))	27 (16.10, 43)	12.9 (7.4, 23.5)	21 (15, 359)	0.02
Blinding (%)				0.21
Double	6 (22.2)	7 (24.1)	10 (21.3)	
None (Open Label)	17 (63.0)	21 (75.9)	33 (70.2)	
Quadruple	4 (14.8)	0 (0.0)	2 (4.3)	
Triple	0 (0.0)	0 (0.0)	2 (4.3)	

FDA: Food and Drug Administration; OS: overall survival; IQR: interquartile range; NA: not applicable; PFS: progression-free survival.

($p < 0.001$) in studies reporting an OS difference of 3 or more months (2 months, IQR: 0.7, 3.0) than those with an OS difference of less than 3 months (-0.1 months, IQR: −0.5, 0.9) but was lower than studies with a median OS not reported (5 months, IQR: 4.0, 6.0).

A higher percentage of trial participants receiving subsequent PD1/PDL1 therapies (including crossover) was significantly correlated with a higher difference in median OS in all studies with reported differences (R^2 =0.15; p = 0.001; Figure 3). There was no correlation between the percentage of trial participants receiving subsequent PD1/PDL1 therapies (including crossover) and the OS hazard ratio (R^2 =0.014; p = 0.29; Supplemental Figure 1). A higher difference in median PFS was associated with a higher difference in median OS (R^2 =0.17; p = 0.0005; Figure 4).

Differences between intervention and control arm participants for median overall survival and progression-free survival in trials testing immune checkpoint inhibitor drugs are shown in Supplemental Figure 2.

4. Discussion

We found that the median improvement in OS was a modest 2.8 months, and the improvement in PFS was 0.9 months. While improvement times were modest, there was low correlation between the difference in median OS and the difference in median PFS. Moreover, crossover, whether explicitly allowed or not, was common in trials testing ICI therapy.

We found a modest but significant correlation between higher subsequent therapy, including crossover, and a higher difference in median OS between the intervention and control arms, although we did not find any association between crossover and the OS hazard ratio. Some have argued that crossover improves OS for patients in the control arm, thus attenuating treatment differences between treatment arms. [7] Our analysis suggests the opposite, where more crossover is associated with greater differences in treatment arms. Several methods of adjustment have been proposed to adjust for crossover and subsequent therapy. [8] Yet, there appears to be low correlation between the between differences in uncorrected and corrected OS hazard ratios (using rank preserving structural failure time) and the percentage of crossover, and it is common for crossover to be inappropriate. [9] Moreover, these adjustment analyses are almost always funded by industry, which may introduce bias in the analyses because of conflict of interest. Collectively, these findings lead to questions about the reliability of results of crossover-adjusted analyses.

Many (37 %) ICIs were approved with OS as the primary outcome. Of

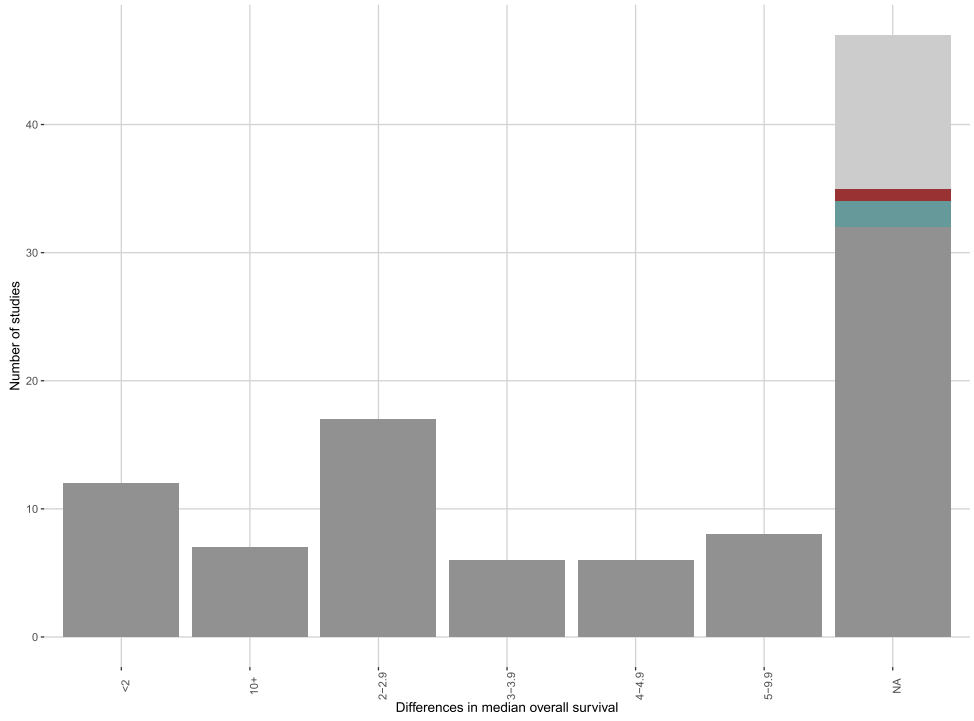

Fig. 1. Distribution of differences in median overall survival in registration trials testing immune checkpoint inhibitors.

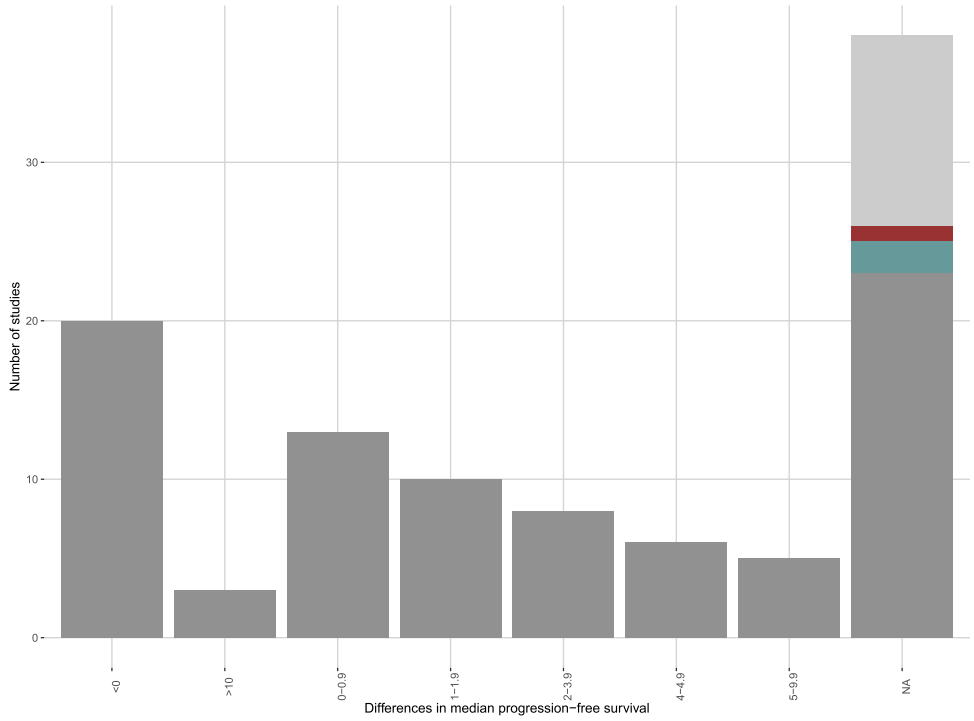

Fig. 2. Distribution of differences in median progression-free survival in registration trials testing immune checkpoint inhibitors.

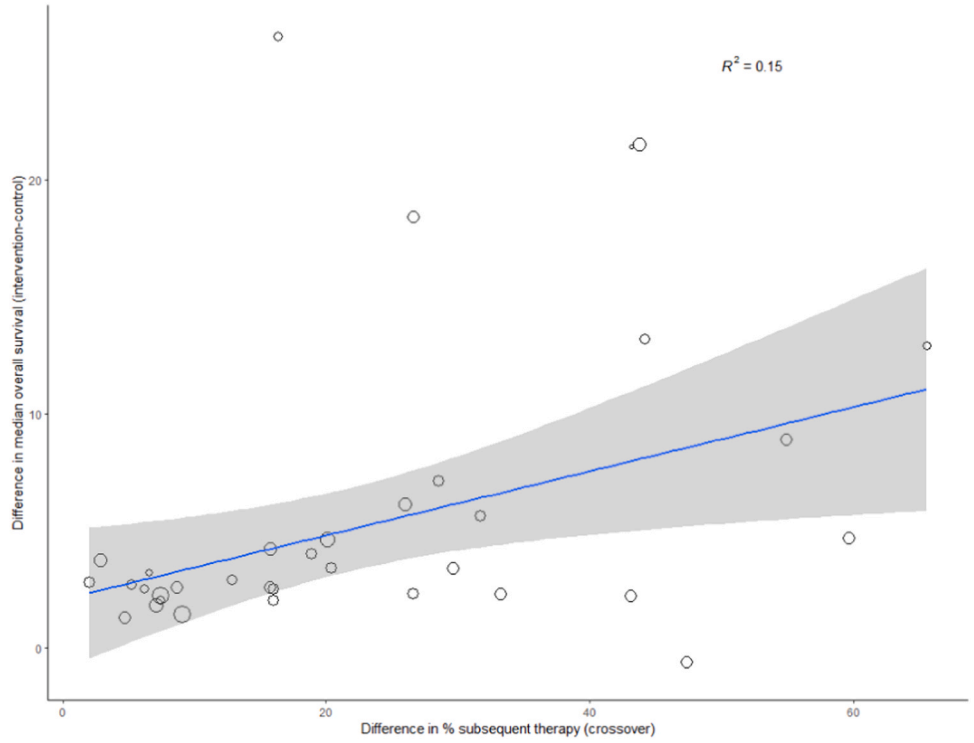

Fig. 3. Spearman correlation between the difference in median overall survival and the percentage of patients who received subsequent PD1/PDL1 therapy in registration trials testing immune checkpoint inhibitors.

course OS is the outcome that is most meaningful for patients, and, regardless of the primary outcome, the overall goal for anti-cancer treatment is to prolong OS. Yet, currently, only 47 % of ICI approvals have been shown to do this. Insufficient follow-up to ascertain OS differences may explain part of the reason many studies have not reported OS, but less than 10 % and 20 % of approvals were made during 2023 and 2022, respectively, indicating that many approvals should have had adequate follow-up time to report this information. Additionally, about 85 % of approvals are in the metastatic setting, when OS is most relevant and follow-up is shorter.

We also found a significant but low correlation between the difference in PFS and the difference in OS. While our analysis was not a formal

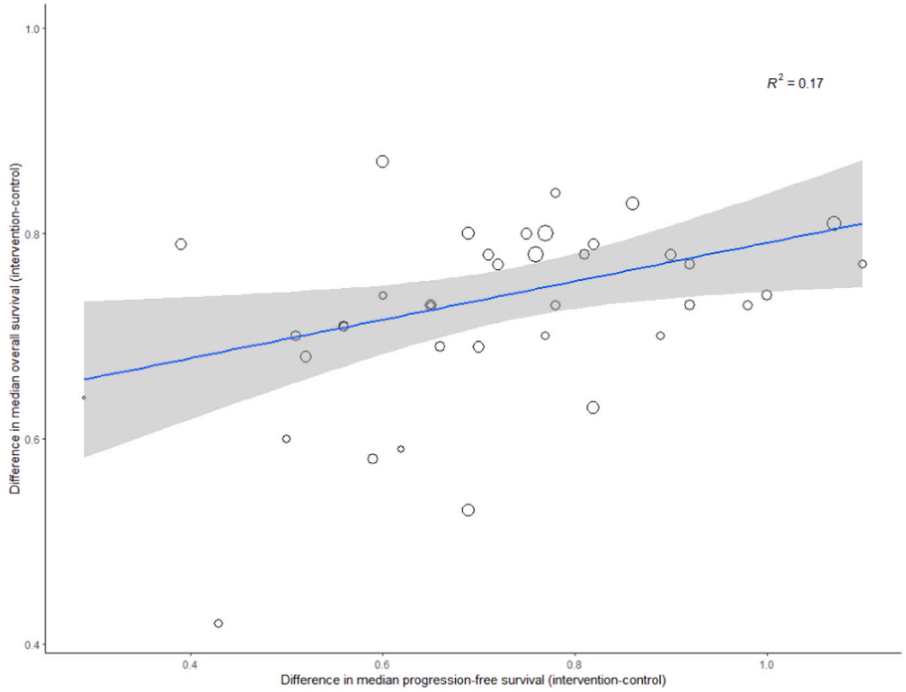

Fig. 4. Correlation between the difference in median overall survival and the difference in progression-free survival, weighted by study sample size, in registration trials testing immune checkpoint inhibitors.

evaluation of surrogacy, our results are in line with other studies that have found PFS and other surrogates to be poor surrogates for OS. [10, 11] Considering the number of approvals granted on surrogate outcomes and the low correlation between these outcomes and OS, patients may be better served if regulatory agencies required drug manufacturers to submit efficacy data on more meaningful and patient-centered outcomes.

To expedite potentially effective drugs coming onto the market, tumor response, including PFS, is often used to evaluate the drug's efficacy, and trials are designed to evaluate these outcomes at the soonest time until there is statistical significance. Even for drugs evaluating OS, the follow-up time is relatively short, and long-term outcomes are often unknown. We have previously calculated that 16 drug approvals had long-term PFS data at 3 years follow-up, and only two had PFS data at 5 years follow-up (data under review).

4.1. Strengths and limitations

Ours is a comprehensive evaluation of OS in ICIs approved for oncology indications. There are several limitations to our analysis. First, many studies either did not report OS or the OS was not reached. It is unknown how the inclusion of these results would have impacted our findings, had they been available. The lack of reporting could be because of insufficient follow-up time for newer therapies or because OS findings were null, but never reported. Second, reporting of crossover and subsequent therapy was inconsistent and not always clear or complete. These data are important in fully interpreting the impact of these therapies on OS. [12].

5. Conclusion

ICIs approved for cancer indications have modest improvements in OS (median of 2.8 months) and PFS (median of 0.9 months). Only about 12 % and 5 % of drug approvals, respectively, have shown to improve OS or PFS longer than 10 months. Moreover, crossover is common, and whether it is appropriate or not, may bias the study results and lead to limited interpretability of efficacy when applied to clinical practice. Drug regulating agencies should insist upon higher outcome standards to improve outcomes for patients with cancer.

Funding

Arnold Ventures.

CRediT authorship contribution statement

Vinay Prasad: Conceptualization, Funding acquisition, Writing – review & editing. **Josh Elbaz:** Data curation, Writing – review & editing. **Myung Sun Kim:** Investigation, Methodology, Writing – review & editing. **alyson haslam:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft.

Declaration of Competing Interest

V.P. receives research funding from Arnold Ventures through a grant made to UCSF, and royalties for books and writing from Johns Hopkins Press, MedPage, and the Free Press. He declares consultancy roles with UnitedHealthcare and OptumRX; He hosts the podcasts, Plenary Session, VPZD, Sensible Medicine, writes the newsletters, Sensible Medicine, the Drug Development Letter and VP's Observations and Thoughts, and runs the YouTube channel Vinay Prasad MD MPH, which collectively earn revenue on the platforms: Patreon, YouTube and Substack. AH, MSK, and JE have no disclosures to report.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114240.

References

[1] Haslam A, Prasad V. Estimation of the percentage of US patients with cancer who are eligible for and respond to checkpoint inhibitor immunotherapy drugs. JAMA Netw Open 2019;2(5):e192535. https://doi.org/10.1001/jamanetworkopen.2019.2535.

[2] Schoenfeld AJ, Hellmann MD. Acquired resistance to immune checkpoint inhibitors. Cancer Cell 2020;37(4):443–55. https://doi.org/10.1016/j.ccell.2020.03.017.
[3] Zhou X, Yao Z, Yang H, Liang N, Zhang X, Zhang F. Are immune-related adverse events associated with the efficacy of immune checkpoint inhibitors in patients with cancer? A systematic review and meta-analysis. BMC Med 2020;18(1):87. https://doi.org/10.1186/s12916-020-01549-2.
[4] Rawji A, Henk HJ, DaCosta Byfield S, Malin J. Actual immune checkpoint inhibitor drug use in U.S. patients with cancer. 2608-2608 JCO 2022;40(16_suppl). https://doi.org/10.1200/JCO.2022.40.16_suppl.2608.
[5] US Food and Drug Administration. Oncology (Cancer) / Hematologic Malignancies Approval Notifications. Resources for Information | Approved Drugs. Accessed July 6, 2023. https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications
[6] Mukaka MM. Statistics corner: A guide to appropriate use of correlation coefficient in medical research. Malawi Med J 2012;24(3):69–71.
[7] Park K, Özgüroğlu M, Vansteenkiste J, et al. Impact of subsequent immune checkpoint inhibitor treatment on overall survival with avelumab vs docetaxel in platinum-treated advanced NSCLC: Post hoc analyses from the phase 3 JAVELIN Lung 200 trial. Lung Cancer 2021;154:92–8. https://doi.org/10.1016/j.lungcan.2021.01.026.
[8] Jönsson L, Sandin R, Ekman M, et al. Analyzing overall survival in randomized controlled trials with crossover and implications for economic evaluation. Value Health 2014;17(6):707–13. https://doi.org/10.1016/j.jval.2014.06.006.
[9] Prasad V, Kim MS, Haslam A. Cross-sectional analysis characterizing the use of rank preserving structural failure time in oncology studies: changes to hazard ratio and frequency of inappropriate use. Trials 2023;24(1):373. https://doi.org/10.1186/s13063-023-07412-y.
[10] Sala I, Pagan E, Pala L, et al. Surrogate endpoints for overall survival in randomized clinical trials testing immune checkpoint inhibitors: a systematic review and meta-analysis. Front Immunol 2024;15:1340979. https://doi.org/10.3389/fimmu.2024.1340979.
[11] Haslam A, Hey SP, Gill J, Prasad V. A systematic review of trial-level meta-analyses measuring the strength of association between surrogate end-points and overall survival in oncology. Eur J Cancer 2019;106:196–211. https://doi.org/10.1016/j.ejca.2018.11.012.
[12] Olivier T, Haslam A, Prasad V. Post-progression treatment in cancer randomized trials: a cross-sectional study of trials leading to FDA approval and published trials between 2018 and 2020. BMC Cancer 2023;23(1):448. https://doi.org/10.1186/s12885-023-10917-z.