## Title

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TUMOR MARKERS AND SIGNATURES

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# Quality of biomarker defined subgroups in FDA approvals of PD-1/PD-L1 inhibitors 2014 to 2020

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## Abstract

PD-L1 expression is associated with differential response in cancers treated with checkpoint inhibitors. Clinical trials for Food and Drug Administration (FDA) approvals of programmed death receptor-1 (PD-1)/programmed death ligand-1 (PD-L1) inhibitors include limited subgroup analyses based on PD-L1 expression. We aimed to define the characteristics of PD-L1 defined subgroups of clinical trials leading to FDA approvals for new indications of PD-1/PD-L1 inhibitors. FDA approvals for PD-1/PD-L1 inhibitors from January 2014 to December 2020 were identified and the clinical trials leading to each drug approval were reviewed. We collected key variables from publicly available information on FDA website and peer-reviewed publications of clinical trials. We assessed regulatory characteristics (approval date, approved drug[s], cancer type, line of therapy and biomarker-restricted approval criteria) of each approval. Clinical trials leading to approvals were reviewed for trial design (RCT vs single arm study, primary endpoint) and PD-L1 defined subgroup design (no subgroup analysis, single threshold 2-group analysis, nested subgroups and adjacent subgroups). We then compared regulatory and trials characteristics (trial design, primary endpoint and biomarker approval criteria) between studies with nested and adjacent subgroups. There were 60 approvals for PD-1/PD-L1 inhibitors between January 2014 and December 2020. Twelve of 60 (20%) did not include any PD-L1 subgroups. Twenty-five of 60 (42%) approvals reported only two subgroups, 14 (23%) included adjacent subgroups and 9 (15%) had nested subgroups. Twenty-five of 60 trials (42%) are single arm studies. Comparison of characteristics between trials with nested subgroup design and adjacent subgroup design did not show differences. We conclude that approvals for new indications of PD-1/PD-L1 inhibitors are based on studies that do not include comprehensive reporting of outcomes by PD-L1 biomarker subgroups.

**KEYWORDS**
biomarker, clinical trial design, immunotherapy, oncology, PD-L1, subgroup analysis

## What's new?

PD-L1 expression is associated with a differential response in cancers treated with checkpoint inhibitors. How biomarkers and treatment outcomes are analyzed and reported in clinical trials

**Abbreviations:** CPS, combined positive score; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EMA, European Medicines Agency; FDA, Food and Drug Administration; IQR, interquartile range; PD-L1, programmed death ligand-1; PD-1, programmed death receptor-1; RCT, randomized clinical trials; TPS, tumor proportion score; VEGF, vascular endothelial growth factor.

  

affects the ability to find different treatment effects by subgroup. In our study, the authors surveyed the design of PD-L1 biomarker-based subgroup analyses of all PD-1/PD-L1 inhibitors approved by the FDA from 2014 to 2020. They conclude that approvals for new indications of PD-1/PD-L1 inhibitors are based on studies that do not include comprehensive reporting of outcomes by PD-L1 biomarker subgroup and offer a series of recommendations to address the issue.

## 1 | INTRODUCTION

Biomarker-based approvals are increasingly common among oncology drugs. Many targeted therapies are developed to target an aberrant genomic pathway in cancer and often approved by the Food and Drug Administration (FDA) with a companion diagnostic that defines the biomarker-based subgroup of patients that will likely benefit from the drug. Immune checkpoint inhibitors are another class of drugs where variable response is seen in different biomarker defined subgroups. Programmed death ligand-1 (PD-L1) expression of tumor or surrounding immune cells has been recognized as a predictive marker of response since the early stages of drug development. The first approval of pembrolizumab in nonsmall cell lung cancer was in 2015 for PD-L1 positive patients, which was after a subgroup analysis showed higher response rate and in patients with PD-L1 of 50% or higher.[1] An additional study has shown that the higher the PD-L1 the higher the response rate.[2] Difference in response by level of PD-L1 expression is seen in other cancer types as well.[3]

Pembrolizumab reported worldwide sales of $4.176 billion in the second quarter of 2021[4] which is the largest market share of all immune checkpoint inhibitors on the market. Pembrolizumab is the best-selling oncology drug and second best-selling drug in terms of worldwide sales.[5] There is concern that clinical trials of checkpoint inhibitors are not reporting outcomes by subgroups that would best define the population of patients benefiting most from therapy in order to increase market share.[6] PD-L1 expression is a continuous biomarker and there are many ways the data can be presented. The subgroup analyses of clinical trials leading to FDA approval of new indications are variable in the granularity of information provided. The shifting definition of PD-L1 expression further complicates this issue. FDA approvals based on PD-L1 expression use different definitions and thresholds. tumor proportion score (TPS) is defined as the number of PD-L1 positive tumor cells divided by the total number of viable tumor cells. Combined positive score (CPS) is the number of PD-L1 positive tumor cells, lymphocytes and macrophages divided by the total number of viable tumor cells. Pembrolizumab is approved for TPS ≥1% in subsequent-line advanced nonsmall cell lung cancer while it is approved for CPS ≥1% in subsequent-line gastric cancer CPS ≥10% in esophageal cancer.

How treatment outcomes and biomarkers are analyzed and reported affect the ability to find different treatment effects by subgroups.[7] In our study, we describe the design of PD-L1 biomarker-based subgroup analyses of all programmed death receptor-1 (PD-1)/PD-L1 inhibitors approved by the FDA from 2014 to 2020.

## 2 | METHODS

### 2.1 | Data source

We used a preexisting database of FDA drug approvals in hematology and oncology. This database was gathered based on hematology and oncology drug approvals and safety notifications that the FDA provides on their website (https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications) and has been used in other published studies.[8-10] All drug approvals between January 2014 and December 2020 were reviewed. Of these approvals, all new approvals including a PD-1 inhibitor or PD-L1 inhibitor were selected. Drugs withdrawn by the manufacturer by the time of analysis on 31 March 2021 were excluded.

The current approval indications were searched on the FDA and European Medicines Agency (EMA) website on 31 December 2021 (https://www.accessdata.fda.gov/scripts/cder/daf/, https://www.ema.europa.eu/en/search/search).

### 2.2 | Data extraction

The approval notice and drug label available on the FDA website was reviewed. Approval date, approval type (accelerates vs regular), tumor type, line of therapy, biomarker-restricted approval criteria (PD-L1 expression) and drugs required before or with the approved drug were collected for each new indication. Information regarding clinical trials leading to the approval was collected from the peer-reviewed publication of the trial. Data reported in the original article was reviewed. Data on trial design, number of participants, design of PD-L1-based subgroup analyses and treatment outcomes were collected.

Trial design was categorized as either randomized clinical trials (RCT) or single arm studies. PD-L1-based subgroups were defined as any subgroup based on PD-L1 immunohistochemistry of tumor or immune cells on pathologic review for which the primary outcome of the study was reported separately and was comparable to the primary outcome of the total study population. For trials that reported objective response rate as the primary outcome, the percentage of complete and partial responses was extracted. For trials reporting time-to-event outcomes such as overall survival or progression free survival, the hazard ratio and confidence intervals were extracted for each PD-L1 defined subgroup. A significant hazard ratio was defined

by the upper limit of confidence interval of less than 1. The number of participants in each biomarker-defined subgroup was also recorded.

Subgroup analyses were categorized as (a) no subgroup analysis, (b) single threshold 2-group analysis and (c) two or more threshold multigroup analysis. The trials with multigroup analysis were further categorized into nested subgroups and adjacent subgroups. Adjacent subgroups were defined as any subgroup defined by two different PD-L1 thresholds for upper and lower limit that were not 0% or 100%. For trials that enrolled only participants with PD-L1 above a lower threshold, adjacent subgroups were defined by a lower boundary above the lower threshold. Trials that did not include adjacent subgroups and reported subgroups defined as either above or below different thresholds were categorized as nested subgroups.

### 2.3 | Statistical analysis

Microsoft Excel was used to compile and analyze the data. Descriptive statistics were used for results. The number of approvals with characteristics of interest were described as a proportion of the total number of approvals. The size of PD-L1 defined subgroups in single threshold 2-group studies was described as the median value and interquartile range of the number of participants in the smaller of two subgroups divided by the total population. For nested subgroups, the proportion of the smaller subgroup for the different thresholds were pooled to derive the median value. For adjacent subgroup trials, median value of the number of participants included in the adjacent subgroup divided by total participants was reported. A comparison of trials with nested subgroups and adjacent subgroups were done. We used the Fisher exact test to compare the distribution categorical trial characteristics and the nonparametric Mann-Whitney *U* test for to compare number of participants. Trial characteristics that were compared were trial design, primary endpoint and presence of biomarker criteria in approval.

## 3 | RESULTS

There were 376 cancer drug approvals between January 2014 and December 2020. This included 60 approvals for PD-1/PD-L1 inhibitors of six unique drugs. Thirty of 60 (50%) approvals were accelerated approvals and the 30 of 60 (50%) were regular approvals. Nine of the 30 (30%) accelerated approvals had converted to regular approval at the time of data analysis. There were 25 approvals for pembrolizumab, 19 approvals for nivolumab, 8 approvals for atezolizumab, 4 for avelumab and 3 and 1 for durvalumab and cemiplimab, respectively. Most approvals (55 of 60) were for solid tumors, with 18 (30%) for thoracic oncology, 10 (17%) for genitourinary oncology, 10 (17%) for gastrointestinal oncology and 10 (17%) for skin cancers including melanoma. There were three approvals for head and neck cancer and two approvals each for breast cancer and gynecologic cancers. There were four new approvals for lymphoid malignancies and one approval was tumor-agnostic.

The approvals for solid tumors were equally divided between first-line and subsequent-line therapies, with 27 and 25 approvals, respectively. There were three approvals for adjuvant therapy and one approval for maintenance therapy. All four approvals in lymphoid malignancies were for relapsed and refractory setting. Of the 60 approvals, 36 were based on RCTs and 24 were based on single arm studies. Twenty of 60 (33%) approvals were in combination with other agents including cytotoxic chemotherapy, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor, multiple kinase inhibitor or vascular endothelial growth factor (VEGF) inhibitor.

Ten approvals (17%) were limited to tumors with PD-L1 above a specified threshold. Five of 10 (50%) of PD-L1 restricted approvals were accelerated approvals and 3 of 10 (30%) were based on single arm studies. Three approvals (5%) were limited to tumors with deficiency in mismatch repair gene or had microsatellite instability. One approval was limited to tumors with tumor mutation burden of 10 mutations/megabase or higher. The remaining 46 approvals were not based on biomarker status.

Of the 60 approvals, 12 of 60 (20%) did not include any PD-L1 subgroups with separately reported outcomes. Twenty five of 60 (42%) approvals reported only two subgroups above and below a single threshold of 1% or 5%. Of the remaining 23 of 60 (38%) approvals that had three or more subgroups, 14 included adjacent subgroups and 9 had nested subgroups. We also found that 25 of 60 trials (42%) are single arm studies (Figure 1).

The smaller subgroup in single threshold 2-group studies had a proportional size of 0.31 (interquartile range [IQR] 0.17-0.40). For nested subgroup studies, two of the nine studies reported outcomes only for subgroups above different thresholds with the proportional size of a total of six subgroups ranging from 0.16 to 0.85. The remaining seven studies included outcomes for subgroups on both sides of each threshold. Three trials reported outcomes of subgroups above and below two different thresholds and four trials reported outcomes above and below three different thresholds. The proportional size of the smaller subgroups had a median of 0.36 (IQR 0.28-0.43). For adjacent subgroup studies, 11 of the 14 trials included a single adjacent subgroup and two trials included two and three adjacent subgroups, respectively. One trial included three adjacent subgroups based on three different methods for measuring PD-L1 expression. Excluding the single trial with multiple methods of PD-L1 reporting, the remaining 13 trials had adjacent subgroups with a median proportional size of 0.29 (IQR 0.12-0.39).

Of the nine studies with nested subgroups, two report objective response rate as the primary outcome in a single arm study and an RCT, respectively. The remaining seven studies were RCTs reporting overall survival or progression free survival as the primary outcome. Six of the seven studies (86%) had at least one PD-L1 defined subgroup with a PD-L1 range with a nonsignificant hazard ratio. The 14 adjacent subgroups included 4 single arm studies and 10 RCTs. All 4 single arm studies and 2 of the 10 RCTs reported objective response rate as the primary outcome. Of the remaining eight RCTs reporting time-to-event outcomes, six of eight (75%) included a PD-L1 subgroup with a nonsignificant hazard ratio. Within these 8 RCTs, a total

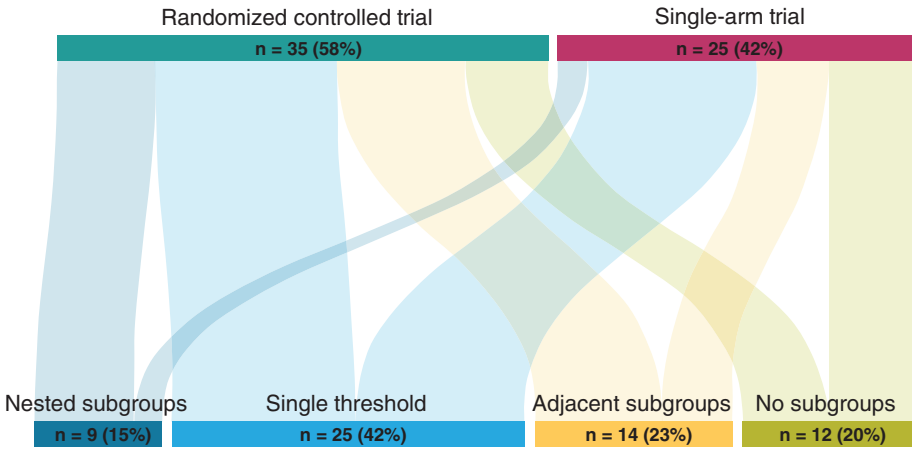


**FIGURE 1** Sankey diagram representing trial design and PD-L1 subgroup analyses in FDA approvals of PD-1/PD-L1 inhibitors. PD-L1 defined subgroup design of randomized controlled trials and single arm studies leading to new indication approvals of PD-1/PD-L1 inhibitors 2014 to 2020 [Color figure can be viewed at wileyonlinelibrary.com]

**TABLE 1** Characteristics of trials with nested subgroups and adjacent subgroups

| | Trials with nested subgroups (n = 9) | Trials with adjacent subgroups (n = 14) |
|---|---|---|
| Participants, median (IQR) | 419 (250-834) | 557 (243-689) |
| FDA approval criteria | | |
| PD-L1 threshold | 1 | 3 |
| No biomarker | 8 | 11 |
| Trial design | | |
| RCT | 8 | 9 |
| Single arm | 1 | 5 |
| Primary outcome | | |
| OS or PFS | 7 | 8 |
| ORR | 2 | 6 |

of 12 adjacent subgroups were reported and 5 of 12 (42%) had a non-significant hazard ratio.

Additional comparison of characteristics between trials with nested subgroup design and adjacent subgroup design did not show differences. The characteristics of interest were biomarker-dependent approval criteria, trial design, primary outcome and number of participants (Table 1).

The current FDA approvals with PD-L1 restricted indications were compared to the corresponding EMA approvals. There were 15 PD-L1 restricted FDA approved indications for six approved checkpoint inhibitors. For 2 of the 15 indications EMA had a higher threshold for PD-L1 expression. For six indications there was no corresponding EMA approval. For one indication, EMA did not require PD-L1 expression.

## 4 | DISCUSSION

The reporting of differential outcomes by PD-L1 expression varies widely among different approvals. Here we have described a range of outcome reporting by PD-L1 defined subgroups categorized as no subgroup analysis, two subgroup analysis, nested subgroup analysis and adjacent subgroup analysis in ascending order of comprehensiveness. Two subgroup analyses include a single threshold that is often interpreted as the clinically relevant threshold for positive and negative PD-L1. This number has changed over time from as high as 50% during the early development of PD-1/PD-L1 inhibitors, to 5% or 1%.

Despite evidence proving otherwise, we find that PD-L1 is commonly treated as a binary or ordinal covariate. Nested subgroups provide slightly more information than two subgroup analyses, however in essence is a method of testing out different thresholds to define positive and negative subgroups and identifying the lowest threshold yielding a statistically significant difference in outcome above that threshold. This structure of data reporting can mask lack of evidence of improved outcomes in adjacent subgroups with low PD-L1 expression.[11]

This method of testing multiple cutoffs is commonly used to determine cutoff values for biomarker in clinical studies that divide patients most effectively into high-risk and low-risk groups. Multiple testing to find the cutoff with the lowest *P*-value can lead to increase in false positive error rates and overestimate the significance of the obtained cutoff value.[12]

For PD-L1, multiple cutoff testing is done to identify the most inclusive subgroup that has a nominally significant result as this leads to a broader drug approval indication. The limitations of multiple testing leading to overestimation of significance is no different in this setting. PD-L1 expression is a continuous biomarker, and analyzing it as such instead of categorizing into high vs low or positive vs negative categories increases the power of detecting treatment-biomarker interactions.[7,13] When the understanding of PD-L1 as a prognostic or predictive marker in different disease settings is limited, such analyses are necessary and an economical way to utilize data already available in clinical trials.

PD-1/PD-L1 inhibitors are approved in many tumor types. There are no tumor-agnostic approvals based on PD-L1 expression representing the limitations of PD-L1 as a universal predictive biomarker of response in the context of broad histology. The distribution of PD-L1 expression is also variable between tumor types. For example,

88% of participants had 100% PD-L1 expression in a trial of Hodgkin lymphoma.[14] Different companion diagnostic tests linked to FDA approvals further limit the utility as a biomarker. For example, PD-L1 IHC 22C3 pharmDx is associated with pembrolizumab approvals and VENTANA PD-L1 (SP142) assay is associated with atezolizumab approvals.[15] Within the same tumor, different assays show discordant results and are not interchangeable.[16]

With the observation that response to PD-1/PD-L1 inhibitors have a higher variance in the distribution of response compared to cytotoxic chemotherapy, it is important to probe the predictive qualities of known biologic markers to select patients most likely to respond to treatment.[17]

When there is a gradient of response along a continuous spectrum, reporting of outcomes must be given by nonoverlapping segments of patients such as quartiles or deciles of PD-L1 in addition to the distribution of PD-L1 expression by each segment. If there is a signal of inferior outcome in an adjacent subgroup this should be further investigated to find the optimal treatment regimen for patients in that subgroup of PD-L1.[19,20] Targeted agents represent another class of biomarker directed treatments, and inadequate investigation of treatment-biomarker interactions, even in drugs with FDA requirements for biomarker testing, have been described.[18]

The characteristics of clinical trials that report nested or adjacent subgroups did not have significant differences in design and reported outcomes. That reporting of adjacent subgroups is often not prespecified and may be selectively reported after a trial is complete, may be the reason differences were not seen.

We propose the following changes in PD-L1 subgroup reporting in cancer drug clinical trials. First, mutually exclusive adjacent subgroups should be defined and the distribution of PD-L1 expression reported. Second, outcomes by PD-L1 expression should be reported by adjacent subgroups and the predictive value should be explored by analyzing PD-L1 as a continuous covariate in relation to the distribution of expression.[21] Finally, the importance of a control group should be emphasized as predictive qualities cannot be assessed in single arm studies.[15,22]

Limitations of our study are that the proportion of adjacent subgroups is only a surrogate for comprehensive reporting of outcomes by PD-L1 levels. Also, PD-L1 is not a standardized biomarker and has several diagnostic tests and different thresholds to define expression.

## 5 | CONCLUSION

Approvals for new indications of PD-1/PD-L1 inhibitors are based on studies that do not include comprehensive reporting of outcomes by PD-L1 biomarker subgroups.

### CONFLICT OF INTEREST

Vinay Prasad discloses: (Research funding) Arnold Ventures. (Royalties) Johns Hopkins Press, Medscape, MedPage. (Consulting) UnitedHealthcare. (Speaking fees) Evicore, New Century Health. (Other) Plenary Session podcast has Patreon backers. All other authors declare no conflict of interest.

### DATA AVAILABILITY STATEMENT

Only publicly available data were used in our study, and data sources and handling of these data are described in the Materials and Methods. Further information is available from the corresponding author upon request.

### ETHICS STATEMENT

We used publicly available data and did not use individual patient data, and therefore our study was not submitted for institutional review board approval, as pursuant to 45 CFR §46.102(f).

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