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Characteristics and outcomes of new molecular oncology drug approvals, in combination or monotherapy

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ABSTRACT

Importance: Understanding the factors that are associated with new molecular entity (NME) cancer drug approvals as a single agent and in combination, and European Society for Medical Oncology (ESMO) scores, can aid in identifying suitable factors to consider in trial designs for future drugs. In addition, the association between the various outcomes can aid in determining benefit when surrogate outcomes are used in approval consideration.

Objective: This study aims to (1) use the measures used in evaluating clinical trials by ESMO scores to determine the differences in the characteristics of 2013–2022 Food and Drug Administration (FDA) oncology NME drug approvals for those approved for use in combination or as a monotherapy, and (2) analyze the association between survival outcomes and the response rate for monotherapy NME drugs and/or drugs approved in combination.

Design: Cross-sectional analysis.

Setting: US FDA Oncology Drug Approvals (2013–2022)

Participants: US FDA Oncology Drug Approvals (2013–2022)

Exposures: Trial-level characteristics (tumor types, basis of approval, randomized or not, phase) and associations between overall survival (OS), progression-free survival (PFS), or overall response rate (ORR) and whether NME drugs were approved as monotherapy or in combination .

Results: Drugs approved for use as a monotherapy are less likely to be approved using a randomized study ($p < 0.001$) and more likely to be approved via the accelerated pathway ($p = 0.012$) and be open-label ($p < 0.001$). Drugs approved for use as a combination or monotherapy significantly differed on their approval basis ($p = 0.002$), phase of trial at the time of approval ($p = 0.02$), and ESMO scores ($p = 0.02$). There was low correlation between response rate and either PFS or OS metrics. However, nearly all of the drugs with large improvements in OS (> 5months) were drugs with robust ORR.

Conclusions and relevance: Drugs approved as monotherapy with a low response rate are likely to have marginal benefit in OS and PFS.

1. Introduction

The FDA has approved 119 new molecular entities (NMEs) for any indication over the last decade (2013–2022) [1]. While some anticancer drugs (such as imatinib for chronic myeloid leukemia) have been transformative, others have only offered a modest benefit [2]. In an analysis by Fojo and colleagues, the average anticancer drugs (2002–2012) extended survival by a mere 2.1 months [3].

Due to the variability in benefits conferred by novel drugs, the American Society of Clinical Oncology (ASCO) Cancer Research Committee and European Society for Medical Oncology (ESMO) have outlined meaningful goals for clinical trials [4]. Across both ASCO and ESMO guidelines, measures such as overall survival (OS), progression-free survival (PFS), response rate, quality of life, and toxicity are used collectively in evaluating new drugs. Prior work has noted that only 42% percent of cancer drugs for solid tumors achieved a meaningful benefit by ASCO's proposed metric [4].

Previous research has observed the relationship between single agent

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activity and the outcomes achieved for a cancer drug [5,6], concluding that drugs that lack single agent activity are generally marginal (median OS gain of 1.6 months). However, no study to date has sought to link the characteristics of FDA oncology drug approvals, including ESMO meaningful benefit scores, to the development of NME drugs as monotherapy or in combination. In addition, studies have not assessed the association between the cancer drug outcomes in the FDA approvals (such as OS and PFS) and the single agent activity of these drugs.

As such, this study aims to (1) use the measures used in evaluating clinical trials by ESMO to determine the differences in the characteristics of 2013–2022 FDA oncology NME drug approvals for those approved for use in combination or as a monotherapy, and (2) analyze the association between OS or PFS and the response rate for NME drugs approved as monotherapy or in combination.

2. Methods

We searched the FDA website for all oncology NMEs approved between 2013 and 2022. We noted whether their approval indication was for monotherapy or in combination with another drug.

For each unique NME-cancer combination, we extracted the following information from the FDA label: the tumor type, number of participants in the trial, basis of approval, whether the drug was approved using a randomized controlled trial (RCT), whether the drug was approved using the accelerated pathway, phase of the clinical trial used in approval, setting (metastatic, non-metastatic, or adjuvant) and blinding status (open-label or blinded). In addition, the outcomes of measures extracted for each unique NME-cancer combination included the overall response rate (ORR), overall survival (OS), and progression-free survival (PFS).

Since not all the efficacy data for a drug were reported in the FDA label, we searched PubMed using the trial identification number for studies reporting OS, PFS, and ORR data. When we were unable to find information from the FDA label or the peer-reviewed literature, we searched clinicaltrials.gov, using the trial identification number, to see if study efficacy results were reported.

For drugs approved in combination, we searched for studies that tested the drug as monotherapy for the same indication as the approval (in combination). We used the drug name and tumor type in PubMed, Embase and clinicaltrials.gov to perform this search and filtered results from PubMed and Embase by clinical study.

All drugs were scored according to the ESMO Magnitude of Clinical Benefit Scale [7].

2.1. Statistical analysis

We reported descriptive characteristics for included trials, overall and stratified by monotherapy and in combination. We used a Kruskal-Wallis test to determine differences between drugs approved as monotherapy and drugs approved in combination. For all drugs, we categorized them into 4 groups based on their ORR ($<$ 10%, 10–20%, 20–30%, $\geq$ 30%). We calculated median OS, median PFS, the difference in OS between the intervention and control arms, and the difference in PFS between the intervention and control arms, stratified by ORR category for all the drugs. For each stratification by approval status, we determined differences in the outcomes (median OS, median PFS, and differences in median OS and PFS between the intervention and control groups) among the 4 ORR categories using a Kruskal-Wallis test. P-values of less than 0.05 were taken to be statistically significant. Lastly, we performed a linear regression analysis to examine if there were any correlations between ORR, as a continuous variable, and the 4 outcomes (median OS, median PFS and difference in median OS and PFS between the intervention and control groups) for drugs approved in combination, and drugs approved as a monotherapy, stratified by NME type (monotherapy versus in combination). We used R statistical software and Microsoft Excel for all statistical analyses.

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

Between 2013 and 2022, we found 70 NMEs that were approved for use in various cancer types among the 119 NMEs for any indication. Since some NMEs were approved for multiple cancer types at the time of approval, we found 79 unique NME-cancer combinations. 56 NMEs were approved for use as a monotherapy, and 15 were approved in combination with another drug, with 1 approved for use as a single agent and in combination at the time of approval.

The characteristics of trials leading to the approval of the drugs, stratified for use in combination and as a single agent, are listed in Table 1. We found that drugs approved for use as a monotherapy were significantly less likely to be approved using a RCT (31% vs 87%, $p < 0.001$; Table 1), and more likely to be approved via the accelerated approval pathway (56% vs 20%, $p = 0.012$; Table 1) and have been tested in an open-label study (86% vs 47%, $p < 0.001$; Table 1). In addition, drugs approved for use as a combination or monotherapy

Table 1
Characteristics of oncology new molecular entities approved (2013–2022), stratified by approval type (monotherapy versus in-combination).

	Overall, N = 79[a]	Combination, N = 15[a]	Single, N = 64[a]	p-value[b]
Tumour				0.14
Acute myelocytic leukemia	6 (7.6%)	2 (13%)	4 (6.2%)	
Breast	6 (7.6%)	3 (20%)	3 (4.7%)	
Follicular lymphoma	5 (6.3%)	0 (0%)	5 (7.8%)	
Melanoma	5 (6.3%)	3 (20%)	2 (3.1%)	
Non-small lung cancer	15 (19%)	0 (0%)	15 (23%)	
Others	37 (47%)	7 (47%)	30 (47%)	
Prostate	5 (6.3%)	0 (0%)	5 (7.8%)	
Approval Basis				0.002
Overall response rate	40 (51%)	2 (13%)	38 (59%)	
Overall survival	7 (8.9%)	4 (27%)	3 (4.7%)	
Others	12 (15%)	1 (6.7%)	11 (17%)	
Progression-free survival	20 (25%)	8 (53%)	12 (19%)	
Randomized	33 (42%)	13 (87%)	20 (31%)	< 0.001
Accelerated Approval	39 (49%)	3 (20%)	36 (56%)	0.012
Phase				0.02
1	4 (5.1%)	0 (0%)	4 (6.2%)	
1|2	20 (25%)	1 (6.7%)	19 (30%)	
2	19 (24%)	4 (27%)	15 (23%)	
2|3	2 (2.5%)	0 (0%)	2 (3.1%)	
3	34 (43%)	10 (67%)	24 (38%)	
Setting				0.09
Adjuvant	1 (1.3%)	0 (0%)	1 (1.6%)	
Metastatic	75 (95%)	13 (87%)	62 (97%)	
Non-metastatic	3 (3.8%)	2 (13%)	1 (1.6%)	
European Society for Medical Oncology Score				0.02
1	11 (14%)	6 (40%)	5 (7.8%)	
2	13 (16%)	0 (0%)	13 (20%)	
3	43 (54%)	5 (33%)	38 (59%)	
4	12 (15%)	4 (27%)	8 (12%)	
Blinding				< 0.001
Blinded	17 (22%)	8 (53%)	9 (14%)	
Open	62 (78%)	7 (47%)	55 (86%)	
Biomarker driven	52 (66%)	7 (47%)	45 (70%)	0.084
Number of Participants (intervention arm)	165 (106, 366)	341 (203, 582)	140 (104, 266)	0.4

[a] n (%)
[b] Kruskall-Wallis rank sum test

significantly differed on their approval basis, with more drugs approved as monotherapy being approved on overall response rate (59% vs 13%, $p = 0.002$) and fewer being approved on phase 3 trial data (67% of drugs approved in combination vs 38% approved as monotherapy, $p = 0.02$; Table 1). Drugs approved in combination were more likely to have an ESMO score of 1 or 4 than drugs approved as a monotherapy ($p = 0.02$; Table 1). Lastly, single agent approvals are more likely to involve a specific biomarker, though this did not reach statistical significance ($p = 0.084$; Table 1).

For all drugs (without stratification by approval as monotherapy or in combination) there were no significant differences between ORR categories and the median OS in the intervention group ($p = 0.18$, Fig. 1 A) or the difference in median OS of the intervention and control group ($p = 0.74$, Fig. 1B). However, the median PFS and the difference in the median PFS between the intervention and control group were different across the different ORR groups, though these did not reach statistical significance ($p = 0.11$, Fig. 1C, D) for all drugs. The differences in PFS achieved by drugs with < 10% single agent response, 10–20% single agent response, and 30% and above were 2.7, 1.7, 5.5 months, respectively (Fig. 1D). Repeating this analysis for difference in OS between control and intervention arms, stratifyed by the response rates, the differences in median OS for the 4 groups were 0.6, 4 and 4.2 months respectively (Fig. 1B).

In addition to studying the association between ORR and OS, and PFS when stratifying the ORR into 4 categories for the 2 groups of NMEs (drugs approved for use as monotherapy or for use in combination), a linear regression analysis was performed to examine the relationship between ORR, median OS and median PFS, with response rate as a continuous variable. For drugs approved in combination, the correlation between response rate and the median OS in the intervention arm was 0.68 ($R^2 = 0.46$; $p = 0.09$). For drugs approved as a monotherapy, the correlation was 0.46 ($R^2 = 0.21$; $p = 0.05$). For drugs approved in combination, the correlation between the response rate and the difference in median OS between the intervention and control arms was 0.44 ($R^2 = 0.19$; $p = 0.38$). For drugs approved as monotherapy, the correlation was 0.03 ($R^2 = 0.001$; $p = 0.92$). For drugs approved in combination, the correlation between the response rate and the difference in median PFS between the intervention and control arms was 0.00 ($R^2 < 0.001$; $p = 0.99$). For drugs approved as a monotherapy, the correlation was 0.31 ($R^2 = 0.10$; $p = 0.34$). For drugs approved in combination, the correlation between response rate and the median PFS in the intervention arm was 0.54 ($R^2 = 0.29$; $p = 0.27$). For drugs approved as monotherapy, the correlation was 0.54 ($R^2 = 0.29$; $p = 0.09$).

4. Discussion

We evaluated FDA NME cancer drug approvals in the last decade by two distinct measures: by whether initial NME approval characteristics and ESMO scores were correlated with whether they were approved as monotherapy or in combination, and secondly, on the association between OS or PFS and the response rate for NME drugs approved as monotherapy or in combination. We identified that factors such as trial design and approval pathway are associated with approval of a drug as monotherapy or in combination.

NMEs approved in combination are often based on results from RCTs, a design that aids in isolating the effect of the new drug. In contrast, single agent approvals are less likely to involve RCTs, thus influencing the primary endpoint metric used for FDA approval. Response rates are more commonly used in approving single agent NMEs. In single-arm trials, which are more commoly used in single agent NME approvals, the response rate of the new drug has to exceed the threshold response rate of the standard-of-care [8]. Therefore, the trial design (single-arm compared to RCT), which differs between NMEs used as a monotherapy and in combination can influence the differences in the basis of approval. In addition, the difference in the trial design can be influenced by (i) the number of recruited patients in the clinical trial and (ii) on the

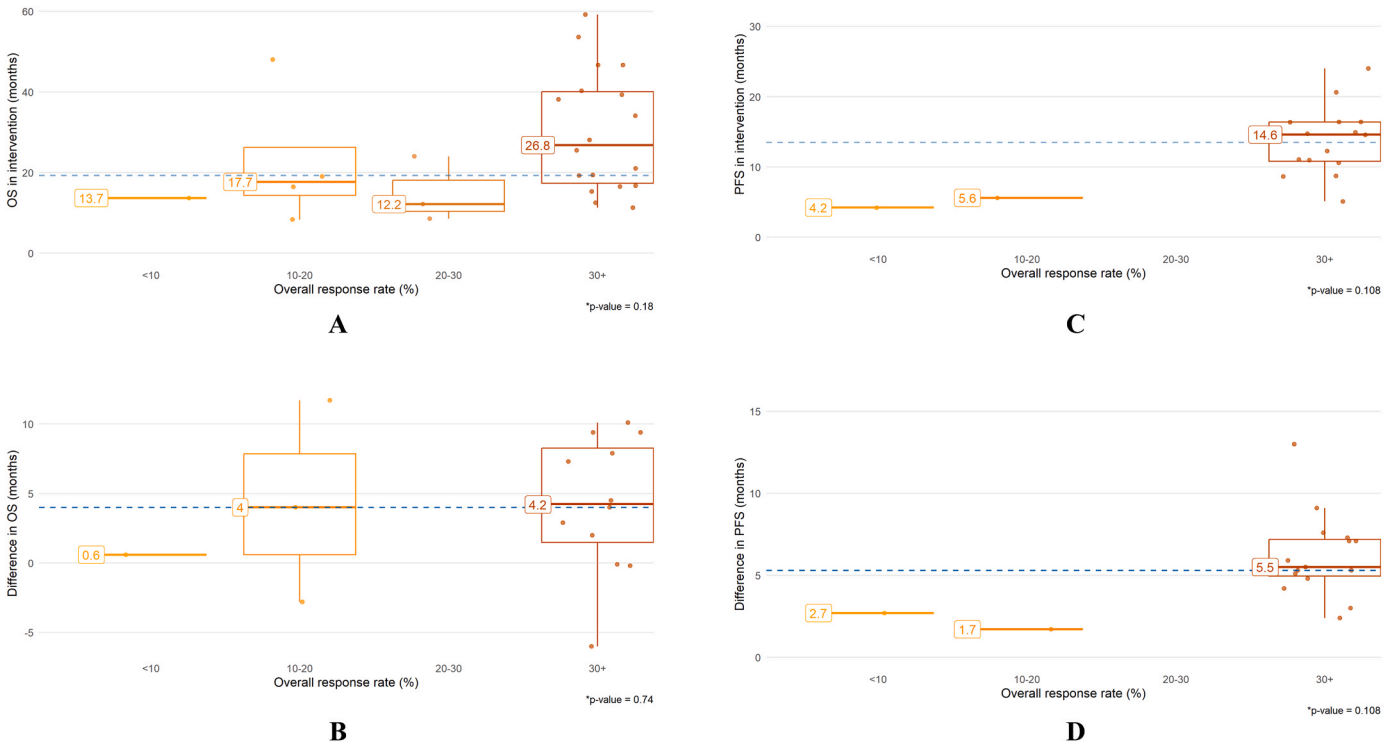

Fig. 1. A: Median OS (months) in the intervention arm against the ORR (10%, 10–20%, 20–30%, above 30%). B: Difference in the median OS (months) between the intervention arm and the control arm against the ORR (10%, 10–20%, 20–30%, above 30%). C: Median PFS (months) in the intervention arm against the ORR (10%, 10–20%, 20–30%, above 30%). D: Difference in the median PFS (months) between the intervention arm and the control arm against the ORR (10%, 10–20%, 20–30%, above 30%).

basis of specific biomarker eligibililty criteria [8,9]. In this study, we have shown that single agent approvals are more likely to have a lower number of participants and are more likely to involve a specific biomarker (though this did not reach statistical significance), which can make it challenging to have a RCT.

Although drugs approved in combination are more likely to be approved on the basis of OS rather than ORR, two drugs (a combination of selinexor and dexamethasone, and a combination of pomalidomide and dexamethasone) were approved on the basis of their response rates. This is potentially due to the unique fact that dexamethasone as a single agent can offer a beneficial single agent response rate. Dexamethasone as a single agent has shown to achieve a response rate as high as 50% and 20% in patients with relapsed refractory melanoma [10].

We found that there was a numerical difference in the median PFS between the ORR categories (though this did not reach statistical significance). We found drugs approved with a single agent activity with a response rate $< 10\%$ to have marginal benefit considering the median PFS. A previous study showed the difference in median OS and PFS to be 1.4 months and 2.2 months respectively, for the single-agent activity of drugs approved in combination, which often have a response rate $< 10\%$ [5]. This study confirms the findings from the previous study, including a greater number of NMEs approved over a decade for cancer. In addition, the median OS and PFS improvement by single agent drugs are found to be 0.6 months and 2.7 months respectively, for drugs with ORR of $< 10\%$. With an absolute increase of 2.5 months in PFS and OS (comparing the intervention and control arms) being defined as a "clinically meaningful improvement" according to ASCO guidelines [4], NMEs approved for use as a monotherapy over the last decade with an overall response rate $< 10\%$, do not meet the ASCO guidelines for OS.

A final conclusion of our paper is that nearly all of the drugs with large improvements in survival ($>$ 5months) were drugs with robust responses. Among 6 drugs with greater than 5 month improvements in OS, 5 had response rate greater than 30%. Therefore, it appears that transformational drugs are those that are highly active.

When analyzing the association between response rate, as a continuous variable, and PFS or OS outcomes, we were able to assess the effects of whether the NME drug was approved as monotherapy versus in combination. The results were mostly similar with one exception. While there were no significant differences between response rate categories in median OS for the intervention arm, this was primarily driven by drugs approved in combination. When only looking at drugs approved as monotherapy, higher median OS for the intervention arm was associated with higher response rates.

There are several limitations to our study. First, we only looked at NMEs during a limited number of years, so our findings are not generalizable to all NMEs. Second, a number of drugs were missing data on OS or PFS, so findings on these variables may not be representative to all drugs included in our analysis. Third, because of the small number of NMEs and variability tumor types, there may be tumor-related differences between drugs approved in combination vs as monotherapy that we were not able to assess.

In conclusion, the drugs approved in combination and for use as a monotherapy have differences in the trials used in their approval. In addition, approved single agent drugs with a low response rate are likely to have marginal benefit in OS and PFS.

Key points

Question: What are the factors that are associated with US Food and Drug Administration new molecular entity drug approvals as a monotherapy or in combination for oncology?

Findings: Of the 79 cancer drug approvals in the last decade, drugs approved as a monotherapy are more likely to have characteristics such as a randomized trial design, response rate as primary outcome, be tested in phase II trials, and have different European Society for Medical Oncology (ESMO) scores. Though no significant correlation was determined between response and survival outcomes, most of the drugs with large improvements in overall survival ($>$ 5months) were drugs with robust response rates.

Meaning: Factors in trial design can influence the drug approval as a monotherapy or in combination.

Disclosure

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. All other authors have no conflicts to report.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: 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. All other authors have no financial or non-financial conflicts of interest to report.

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