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Original Research

Overall survival for oncology drugs approved for genomic indications

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Abstract ***Aim:*** Drug approvals for genome-informed indications have been increasing in recent years, but it is unknown how many of them have demonstrated an improvement in overall survival (OS). We assessed the frequency of approved genome-informed drugs demonstrating improvements in OS and progression-free survival (PFS) and whether the frequencies differed by cancer type.
Materials and methods: We searched all Food and Drug Administration approvals from 2006 to 2020, and for each drug that was approved for a genomic indication, we then searched on PubMed for randomised studies examining OS or PFS.
Results: We found 53 drugs approved for 92 unique indications from 2006 to 2020. We found that 50 drugs (55%) approved for a genomic indication had a randomised study evaluating OS benefit, and of those, only 22 demonstrated an improvement in OS. Similarly, 52 drugs (57%) evaluated PFS benefit, and 51 of these studies demonstrated an improvement in PFS. Drugs approved for BRAF V600 melanoma demonstrated an improvement in OS more often than drugs approved for ALK non–small cell lung cancer. The median improvement in OS was 4.7 months (range 1.5 months–49.1 months).
Conclusion: Although there is widespread enthusiasm for this class of agents, and many demonstrate impressive response rates, further trials or post-marketing studies are needed to ascertain the impact on survival and quality of life, the magnitude of these gains, and the cost-effectiveness of these agents.

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1. Background

Two-thirds of oncology drugs are approved based on surrogate markers such as overall response rate (ORR) or progression-free survival (PFS) [1]. However, only one in seven oncology drugs that are approved on a surrogate outcome is later shown to improve overall survival (OS) in extended follow-up, post-marketing, or subsequent studies [2].

Approvals for genome-informed indications, which are often based on ORR, have been increasing in recent years. Currently, 13.6% of US cancer patients are eligible for genome targeted drugs and 7% of cancer patients may respond [3]. However, it is unknown what percentage of these drugs have proven OS gains for these indications and what the magnitude of those differences are. In this study, we sought to determine the percentage of drugs approved for a targeted indication that have studies reporting on OS and PFS and whether this varies by cancer type.

2. Methods

We searched the Food and Drug Administration (FDA) website to find all oncology drugs approved for a genetically targeted indication for advanced, metastatic, or unresectable cancers (January 2006 through December 2020). We then extracted data regarding the indication, ORR, and date of approval. For each approved drug, we searched PubMed for articles reporting on randomised clinical studies that tested whether the approved drug improved OS, PFS, or ORR, compared with standard of care for each approved indication. The search terms included the study drug, the tumour type, and the genetic indication, filtering by 'clinical trials'. In some cases where there were a lot of search results produced, we used the Boolean operator of 'not' to remove studies that were not relevant to our study (e.g. adjuvant if the drug was approved first line). We searched for studies published through May 25, 2021.

For each study, we extracted data relating to the efficacy for both the intervention and control groups in the study (e.g. median times of PFS and OS, hazard ratios, ORR, *P* values, and/or confidence intervals). We then classified each drug as having a randomised controlled trial that reported on these outcomes, and if so, whether the results were positive or negative/null for each outcome type (OS, PFS, or overall ORR).

We then calculated frequencies for each outcome by trial result positivity. We did this for all cancers combined and for four cancers with the most frequent drug approvals. For drugs that demonstrated OS improvement and reported median OS, we calculated the median OS improvement. All analyses were done using Excel and R software, version 3.6.1. In accordance with 45 CFR §46.102(f), this study was not submitted for institutional review board approval because it involved publicly available data and did not involve individual patient data.

3. Results

During the time interval 2006–2020, we found 53 drugs approved for 92 unique indications. Genetic indications with the most approvals include drugs targeting the Philadelphia chromosome (PH)+ (14 approvals), EGFR (12 approvals), HER2 (10 approvals), ALK (8 approvals), and BRAF V600 (9 approvals). Cancer types with the most drug/indication approvals were non–small cell lung cancer (NSCLC; 23 approvals), breast (12 approvals), chronic myeloid leukaemia (10 approvals), colorectal (8 approvals), and melanoma (7 approvals). Fifty-eight (63%) approvals were regular, and 34 (37%) were accelerated. There were 18 approvals in 2020, 8 in 2019, 14 in 2018, and 11 in 2017. The remaining 41 approvals were made in 2016 or before, with 16 of them being accelerated.

As presented in Fig. 1, 50 drugs (55%) approved for a genomic indication had a randomised study evaluating OS benefit; 52 drugs (57%) evaluated PFS benefit. These results, stratified by haematologic versus solid tumour indications, are presented in Fig. 1.

The percentage of drugs/indications with positive study results was 24% for OS (n = 22) and 55% for PFS (n = 51). The percentage of drugs with negative or null study results was 30% for OS (n = 28) and 1% for PFS (n = 1).

These results vary by cancer type, with NSCLC drugs having a low percentage of studies reporting positive results for OS (n = 3; 12% of studies for NSCLC drugs) and melanoma drugs having a higher percentage of studies confirming OS benefit (n = 5; 71% of studies for melanoma drugs; data not shown). Table 1 shows the drugs/indications for which we found a study showing improved OS.

For drugs that were shown to improve OS and reported median OS times (n = 17), the median improvement in OS was 4.7 months. The improvement ranged from 1.5 months for EGFR relapsed/refractory colorectal cancer to 49.1 months for FLT3 acute myeloid leukaemia. More than half (59%) of the approvals that demonstrated an improvement in OS were for BRAF V600 melanoma and EGFR NSCLC or colorectal cancer.

We found 34 drugs/indications that failed to improve OS, RR, or PFS, 15 drugs/indications improved all three of these outcomes, 18 drugs/indications had an improvement in PFS only, three had an improvement in ORR only, two had an improvement in OS only, 15 improved both PFS and ORR, three improved OS and PFS, and two improved OS and ORR (Supplemental Table). Of the drugs that had no data on OS, 16 (38%) drug approvals were for haematologic indications.

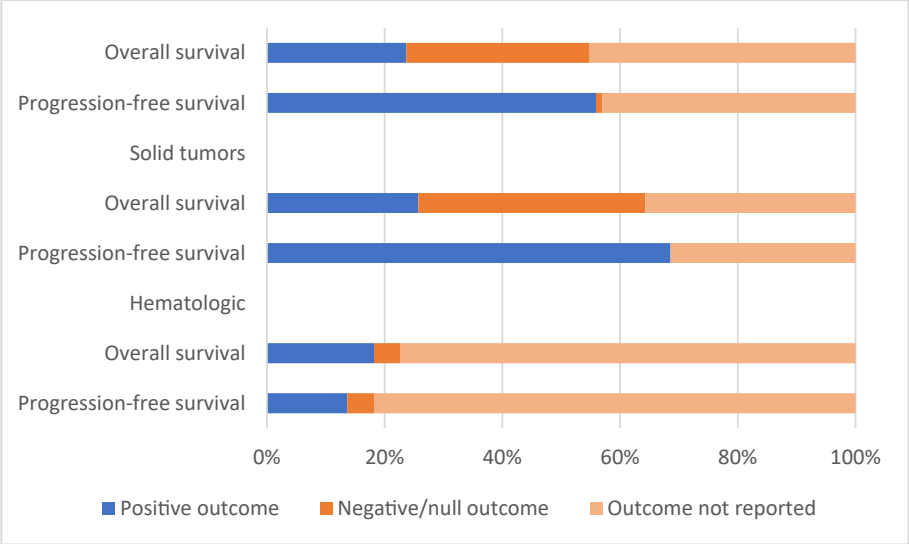

Fig. 1. Percentage of studies with positive, negative/null, or no outcomes for oncology outcomes in randomised trials of genome-informed drugs approved by the US Food and Drug Association, overall and stratified by solid versus haematologic cancers.

Table 1
Drugs that are FDA approved for a genomic indication that have shown to improve overall survival.

Drug	Date of approval	Cancer type	Genomic target	Median overall survival times (intervention versus control)
Gilteritinib	11/28/18	AML	FLT3	9.3 versus 5.6 months
Midostaurin	4/28/17	AML	FLT3	74.7 versus 25.6 months
Trastuzumab	9/25/1998	Breast	HER2	25.4 versus 20.3 months
Tucatinib in combination with trastuzumab and capecitabine	4/17/20	Breast	HER2	21.9 versus 17.4 months
Pertuzumab	6/8/12	Breast	HER2	56.5 versus 40.8 months
Ado-trastuzumab emtansine	2/22/13	Breast	HER2	30.9 versus 25.1 months
Ibrutinib	7/28/14	CLL	17p	90% versus 81% at 12 months
Nilotinib	6/17/10	CML	Ph+	98.5% versus 95.2% at 3 years
Encorafenib in combination with cetuximab	4/8/20	CRC	BRAF V600E	8.4 versus 5.4 months
Cetuximab in combination with FOLFIRI	7/9/12	CRC (1st line)	EGFR (KRAS)	23.5 versus 20.0 months
Cetuximab	2/1/04	CRC (later line)	EGFR (KRAS)	6.1 versus 4.6 months
Panitumumab	9/27/06	CRC	KRAS	10.0 versus 7.4 months
Trastuzumab	10/20/10	Gastric	HER2	13.8 versus 11.1 months
Imatinib	12/19/08	GIST	GIST	92% versus 82% at 5 year
Encorafenib and binimetinib	6/27/18	Melanoma	BRAF V600 E or K	33.6 versus 16.9 months
Cobimetinib in combination with vemurafenib	11/10/15	Melanoma	BRAF V600 E or K	22.3 versus 17.4 months
Trametinib and dabrafenib	1/10/14	Melanoma	BRAF V600 E or K	25.1 versus 18.7 months
Trametinib	5/29/13	Melanoma	BRAF V600 E or K	81% versus 67% at 6 months
Vemurafenib	8/17/11	Melanoma	BRAF V600E	13.6 versus 9.7 months
Dacomitinib	9/27/2018	NSCLC	EGFR 19/21	34.1 versus 26.8 months
Osimertinib	4/19/18	NSCLC	EGFR 19/21	38.6 versus 31.8 months
Nivolumab	10/9/15	NSCLC	EGFR or ALK	12.0 versus 9.6 months

FDA = Food and Drug Administration; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; CRC = colorectal cancer; GIST = gastrointestinal stromal tumour; NSCLC = non-small cell lung cancer.

Fig. 2 shows the percentage of drugs demonstrating an improvement in OS in oncology drugs approved for a genetic indication, by cancer type and genetic target, for the more common cancer types. The number and percentage of studies finding an improvement in OS varied by tumour type and genetic indication. We found that for the seven drugs approved for BRAF V600 melanoma, five (71%) improved OS, and all eight (100%) of the drugs approved for ALK NSCLC failed to show an improvement in OS. Of the three drugs approved for MSI/MMR colorectal cancer, none (0%) had studies reporting on OS.

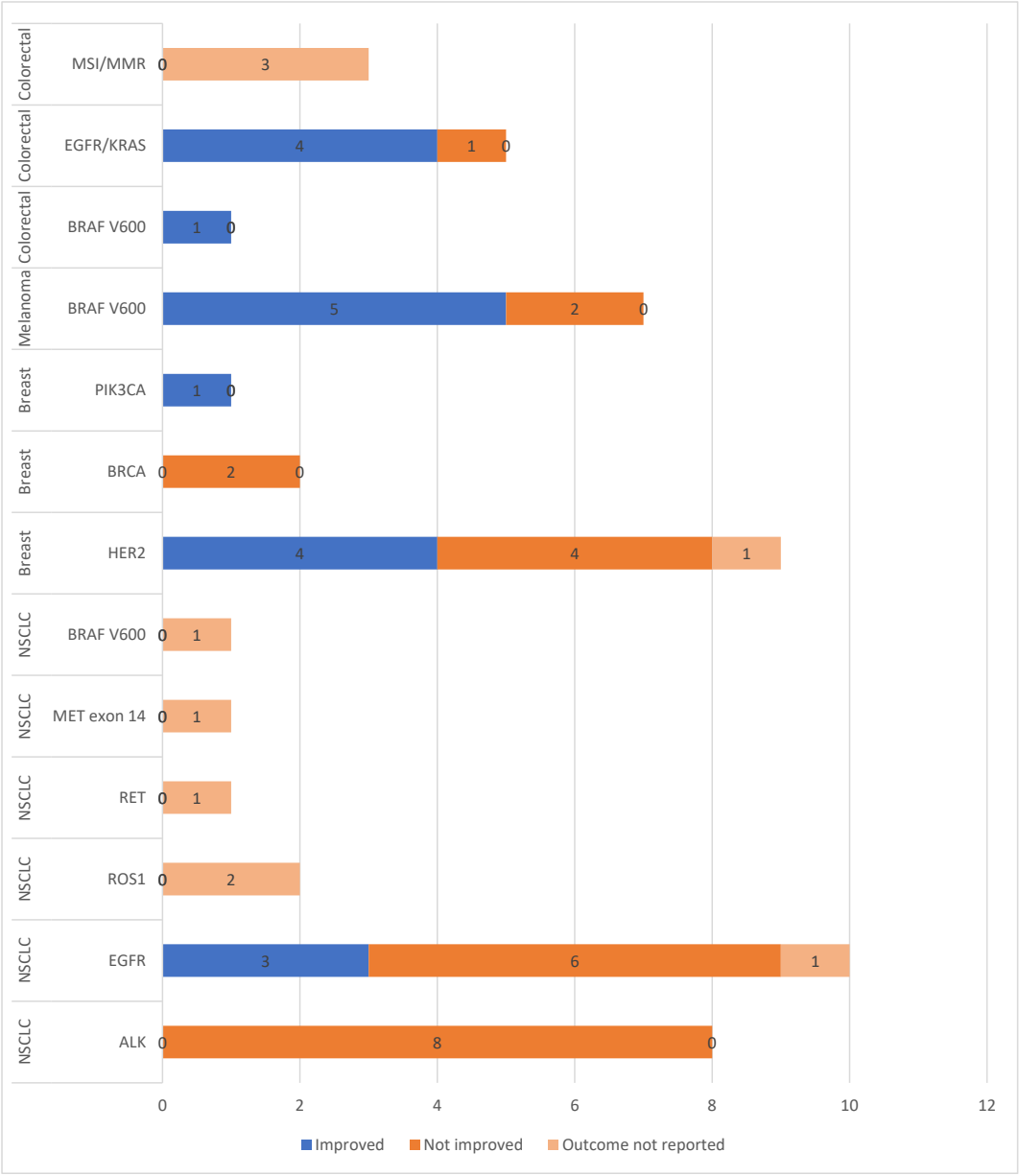

Fig. 2. Percentage of drugs demonstrating an improvement in overall survival, by tumour type and genetic target, in oncology drugs approved for a genetic indication.

4. Discussion

We found that only about half of oncology drugs FDA approved for a genomic indication had studies reporting on OS, and only about one-fifth of them demonstrated an improvement in OS. Our results are slightly lower than another study that report that 32% of drugs approved for an oncology indication had studies showing an improvement in OS in either pre- or post-marketing studies [4]. With a focused effort on increasing earlier treatment options for cancer patients, surrogate markers such as PFS or ORR, which are thought to bring drugs to market faster, are being increasingly used in drug approvals. However, to justify the high cost of these drugs, an improvement in OS should also be demonstrated. Here, we show that most approved targeted drugs have yet to show OS benefit.

We found that drugs approved for a genomic indication, which improved OS, did so by a median of 4.7 months, which is slightly more than other studies that have evaluated all cancer drugs approved between 2003 and 2013 [5] and metastatic cancers approved between 2002 and 2014 [6,7]. This is not unexpected given that previous observational studies have shown that for certain cancers, patients treated with targeted therapies have better OS than patients treated without targeted therapies [8]. A concern for targeted drugs is that trial-level data overestimates OS because participants who

are less likely to participate in clinical trials are also less likely to have an improved OS in real-world data [9].

One of the limitations to our analysis is that we only used PubMed to find articles demonstrating an improvement in outcomes. We may have found more studies finding improvement in these outcomes had we used other search engines. However, increasing the number of studies examining a given outcome also increases the likelihood of finding benefit, real or not. A second limitation is that some data were immature, and the final results for these studies may be different from the preliminary data. In these instances, we used the immature findings because that is all we had available. Consequently, our results apply to current knowledge and may not be generalisable to future findings.

5. Conclusion

About half of FDA-approved drugs for a genome-informed oncology indication have had studies evaluating OS benefit. Only about one-fifth of drugs for these indications have had randomised studies reporting positive OS outcomes, whereas over half of drugs have been shown to improve PFS. Although there is widespread enthusiasm for this class of agents, and many demonstrate impressive response rates [10], further trials or post-marketing studies are needed to ascertain the impact on survival and quality of life, the magnitude of these gains, and the cost-effectiveness of these agents.

Authors' contribution

V.P., A.H., and M.S.K. conceptualised study design. A.H. and M.S.K. reviewed and abstracted data. V.P. reviewed and confirmed abstracted data. A.H. wrote the first draft of the article. All authors reviewed and revised subsequent and finalised draft of the article.

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Conflict of interest statement

V.P. received research funding from Arnold Ventures, royalties from Johns Hopkins Press and Medscape, and honoraria from Grand Rounds/lectures from universities, medical centres, non-profits, and professional societies; is a consultant at UnitedHealthcare; and received speaking fees from Evicore. (Other) Plenary Session podcast has Patreon backers. All other authors have no financial nor non-financial conflicts of interest to report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.10.028.

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