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Application of orphan drug designation to cancer treatments (2008–2017): a comprehensive and comparative analysis of the USA and EU

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ABSTRACT

Objective To determine differences in the characteristics of cancer drugs designated as orphan drugs by the Food and Drug Administration (FDA) and European Medicines Agency (EMA).

Design and setting Identification of all cancer drugs (initial or supplementary indication) with orphan status approved by the FDA between 2008–2017 based on publicly accessible reports. The European public assessment reports (EPAR) was searched to determine whether these FDA-approved drugs were also approved by the EMA.

Main outcome measures Extraction of active ingredient, trade name, approval date and approved indication from two FDA data sources (Orphan Drug Product Designation Database, Drugs@FDA) and comparison with the same data from EPAR.

Results The FDA approved 135 cancer drugs with orphan indications that met our inclusion criteria, of which 101 (75%) were also approved by the EMA. 80/101 (79%) were first approved in the USA. Only 41/101 (41%) also received orphan designation by the EMA. 33/101 (33%) were approved for biomarker-based indications in the USA, however, only nine approved cancer drug indications by the EMA were biomarker-derived drugs. 78% (47/60) of approved cancer drugs that were only approved in the USA with orphan status were indicated for solid tumours, 22% (13/60) had indications for non-solid tumours. By contrast, out of those approved cancer drugs that received orphan designation by both agencies, 20% (8/41) were indicated for solid, and 80% (33/41) for non-solid tumours.

Conclusions Orphan designation was intended to encourage drug development for rare conditions. This study shows that the FDA approves more cancer drugs with such designations compared with the EMA, especially for subgroups of more prevalent cancers. One reason for the difference could be that the European Union requires demonstration of significant benefit for drugs that target the same indication as a drug already on the market to earn the orphan designation.

INTRODUCTION

The US Congress passed the Orphan Drug Act in 1983 to create incentives for the development of drugs for rare diseases that might not otherwise be financially viable due to small potential patient populations.[1–3] Among other things, the statutory incentives include providing manufacturers with the opportunity to earn special tax breaks for research investment and the exclusive right to market orphan-designated drugs for 7 years from the date of marketing approval.[1,4,5] Such market exclusivity would allow manufacturers to charge high prices for their rare disease drug product even in the absence of patent protection and despite limited health gain.[5–9]

Pharmaceutical companies can apply for orphan designation from the Food and Drug Administration (FDA) based on either showing that the targeted condition affects fewer than 200 000 patients annually in the USA or showing no reasonable expectation that costs of research and development of the drug for the indication can be recovered by

sales of the drug in the USA, along with providing a medically plausible basis for believing that the drug would aid in the condition's treatment, prevention or diagnosis.[10 11]

In the European Union (EU), the European Medicines Agency (EMA) also designates drugs that target rare diseases with special status.[12] To qualify, a drug must be intended for the treatment of a disease that is life-threatening or chronically debilitating with an EU prevalence of less than 5 in 10,000, or it must be unlikely that marketing of the drug would generate sufficient returns to justify the investment needed for its development.[13–15] In addition, no satisfactory method of treatment of the condition concerned is already on the market, or, if such a method exists, the new drug must be of significant benefit to those affected by the condition.[11] Like in the USA, sponsors of designated orphan drugs in the EU earn certain incentives, including administrative regulatory fee reductions and market exclusivity.[11 15 16] Thus, while most prerequisites for orphan disease drug designation between the USA and the EU are comparable, the major difference is that the EU requires demonstration of significant benefit in case the drug targets the same indication as a drug already on the market.

Expenditure on cancer drugs dominate pharmaceutical expenditure in developed markets, with worldwide sales at $107 billion in 2015, an increase of 11.4% since 2014.[8 17 18] In addition, global spending on orphan-designated drugs will reach $178 billion per year by 2020, much of which will also be drugs for cancer patients.[8]

To determine whether differences in the design of the Orphan Drug Act in the US and EU lead to variations in the application of the statutory incentives, we reviewed all cancer drugs for which indications have been approved with this special status between 2008 and 2017 by the FDA and then determined whether these cancer drugs had also been approved with the same status by the EMA.

METHODS

We first searched and identified on the FDA's publicly accessible Orphan Drug Product Designation Database all cancer drugs with orphan status approved by the FDA between 1 January 2008 and 31 December 2017.[19] The approval could have been for an initial or supplementary indication. Cancer drugs with approval for different indications were counted separately for each cancer indication. For example, bevacizumab (Avastin) was approved with orphan status for, among other things, treatment of patients with ovarian cancer, fallopian tube cancer, primary peritoneal cancer and glioblastoma. Cancer drugs with orphan status that were approved by the FDA for benign tumours as well as combined therapies (eg, dabrafenib and trametinib (Mekinist)) were not included in our analysis. From two FDA data sources—the Orphan Drug Product Designation Database and Drugs@FDA—we extracted the active ingredient, trade name, orphan designation, approval date and approved indication.[19 20]

We then searched on the database of the EMA, the European public assessment reports (EPAR), to determine whether the FDA-approved cancer drugs with orphan status in our cohort were also approved by the EMA (with or without orphan status) as of 1 August 2018. Following the methodology of another study, we assumed that the same drug is available both in the EU and USA if the active substance, the therapeutic indication and the Marketing Authorisation Holder are the same between both territories.[21] If so, we extracted the same data as from the FDA sources.

Descriptive statistics were performed for the recorded variables. Trends across time and indications of cancer drugs with orphan designation were analysed descriptively and in comparison between the EU and USA.

Patient and public involvement

No patients or members of the public were involved in the design and conception of this study.

RESULTS

The FDA approved 135 cancer drug indications with orphan drug designations that met our inclusion criteria. Among this sample, 101 (75%) were also approved by the EMA by 1 August 2018, including drugs with and without such a designation by the EMA (see online supplementary appendix). Two indications were refused market approval in the EU: romidepsin (Istodax) was refused for treatment of non-Hodgkin's lymphoma, and pralatrexate (Folotyn) for treatment of T-cell lymphoma. Sponsors withdrew their market application for four indications, including dinutuximab (Unituxin) for treatment of neuroblastoma, which was withdrawn due to the inability to supply the drug in sufficient quantities for meeting the demands, and omacetaxine (Synribo) for treatment of myelogenous leukaemia because of inability to address the issues identified by the EMA within the timeframe allowed.[22]

Among the 101 cancer indications that were designated with orphan drug status by the FDA and also approved by the EMA, 46 were approved for first-line therapy while 55 were indicated for second-line, third-line or fourth-line therapy. Forty-five were approved for supplementary (extended) indications of already-approved drugs. There was a substantial increase in designations over time. In the USA, two approved cancer drug indications were designated with orphan status in 2008, while 16 were approved in 2016 (figure 1).

Eighty of the 101 approved cancer drug indications were first approved in the USA, while market approval first took place by the EMA for the other 21. In 81% (65/80), approval in one jurisdiction followed less than a year after market authorisation in the other jurisdiction. For example, nivolumab (Opdivo) was approved in the USA in December 2017. Approval by the EMA followed less than 1 year later in June 2018 (see online supplementary appendix).
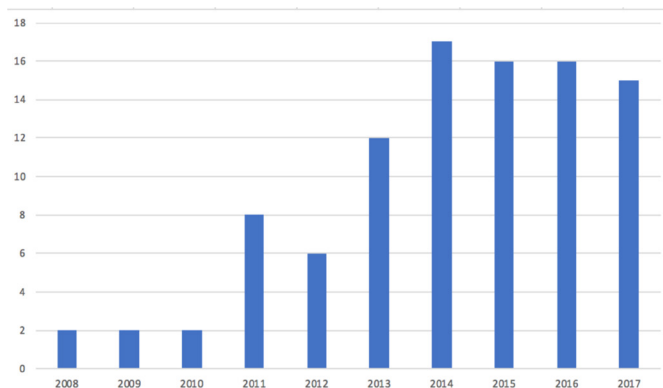
Figure 1 Approved cancer drug indications with orphan drug designation by the FDA from 2008 through 2017 that were also approved by the EMA (n=101). x-axis, year of marketing approval by the FDA; y-axis, number of approved cancer indications with orphan drug designation by the FDA.

Among the 101 orphan drug designated approved cancer conditions, 40% (40/101) were approved for biomarker-derived indications. A biomarker-derived indication is any drug indication approved based on its efficacy in a subset of a more prevalent disease characterised by a particular genetic variant.[23] Examples for approved biomarker-derived indications in our study are nivolumab (Opdivo) for the treatment of BRAF V600 mutated melanoma, or ceritinib (Zykadia) for the treatment of ALK +non-small cell lung cancer (NSCLC), afatinib (Gilotrif) for EGFR mutated NSCLC and osimertinib (Tagrisso) for EGFR mutated NSCLC. The number of approved biomarker-defined indications with orphan drug designation has increased over the past years in the USA (figure 2). Only one biomarker-derived cancer indication was approved with orphan drug designation in 2008, while eight were approved with orphan status in 2017. By contrast, only
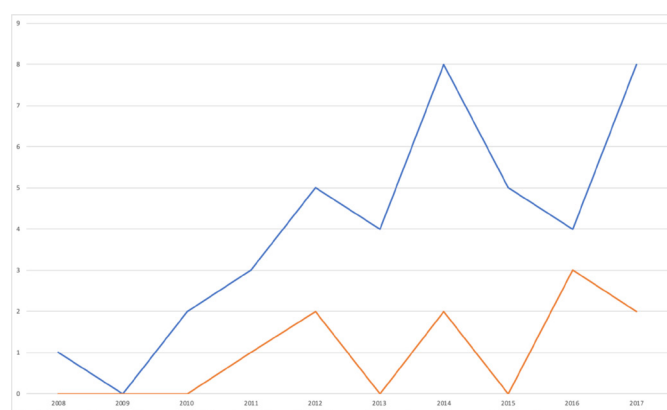

Figure 2 Numbers of FDA-approved and EMA-approved drugs indicated for biomarker-defined orphan cancer indications from 2008 through 2017. x-axis, year of marketing approval by the FDA and EMA; y-axis, number of approved biomarker-derived cancer indications with orphan drug designation; blue, approved biomarker-derived cancer indications with orphan designation by the FDA; orange, approved biomarker-derived cancer indications with orphan designation by the EMA.

10% (10/101) of approved cancer drug indications by the EMA were orphan designated biomarker-defined subsets of disease. For example, afatinib (Gilotrif) and osimertinib (Tagrisso) got approval in both the USA and the EU, however, they only got orphan designation in the USA.

Only 41 of the 101 cancer indications with orphan designation by the FDA were also designated with orphan status at the time of market approval by the EMA. While most of the 60 remaining products never received an orphan drug designation in the EU, 4 drugs had their designations withdrawn by the EMA or the sponsor, including olaparib (Lynparza) for treatment of primary peritoneal cancer and later treatment of ovarian cancer and fallopian tube cancer, as well as bosutinib (Bosulif) for treatment of chronic myelogenous leukaemia.

The approved cancer drug indications can be differentiated into solid and non-solid tumours.[9 24–26] The majority (47/60, 78%) of approved cancer drugs that were only approved in the USA with orphan status were indicated for solid tumours, while 22% (13/60) of approved cancer drugs had indications for non-solid tumours. Most frequently approved indications with orphan drug designation for solid tumours were melanoma (13 indications) followed by non-small cell lung cancer (11 indications), gastrointestinal cancer (five indications), ovarian cancer (three indications), fallopian tube cancer (three indications) and peritoneal cancer (three indications). Most approved cancer indications with orphan designation for non-solid tumours by the FDA were chronic myelogenous lymphoma (three indications), multiple myeloma (two indications), Hodgkin lymphoma (two indications), chronic lymphocytic lymphoma (two indications) and acute lymphocytic lymphoma (two indications) (figure 3).

By contrast, out of those approved cancer drugs that were designated with orphan status by both the FDA and the EMA, 20% (8/41) were indicated for solid tumours, and 80% (33/41) for non-solid tumours. Thyroid cancer (three indications), ovarian cancer (two indications) and soft tissue sarcoma (two indications) were the most frequent solid tumours approved in both jurisdictions with orphan drug status. For non-solid tumours, multiple myeloma (eight indications), chronic lymphocytic lymphoma (eight indications) and acute lymphocytic lymphoma (four indications) were the most frequently approved cancer drug indications with orphan designation (figure 4).

DISCUSSION

This review of cancer drugs newly approved with Orphan Drug Act designations by the FDA from 2008 through 2017 reveals important differences with respect to their approvals by the EMA. Less than 50% of cancer drugs with orphan designation by the FDA received such status in the EMA. Our results are consistent with other studies showing that the USA has more orphan drug designations in general and specifically for oncology
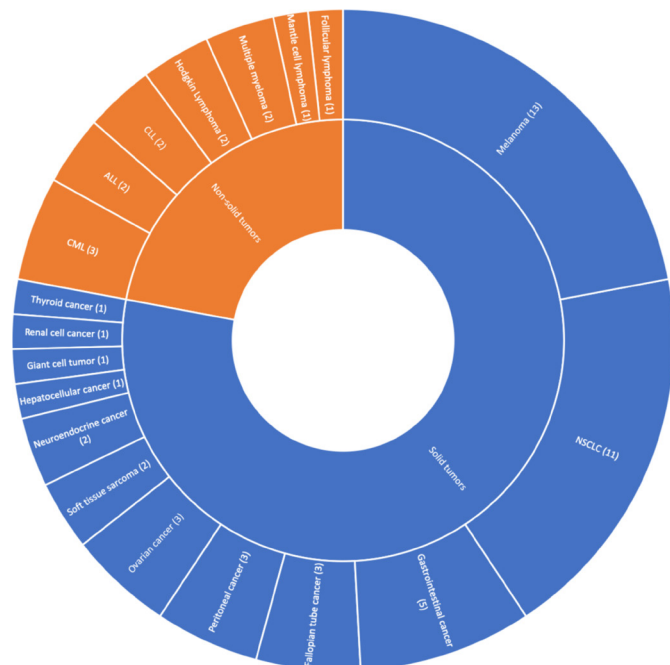
Figure 3 FDA-approved solid and non-solid tumour cancer drug indications with orphan drug designation. ALL, acute lymphoblastic leukaemia; CLL, chronic lymphocytic lymphoma; CML, chronic myeloid lymphoma; NSCLC, non-small cell lung cancer.
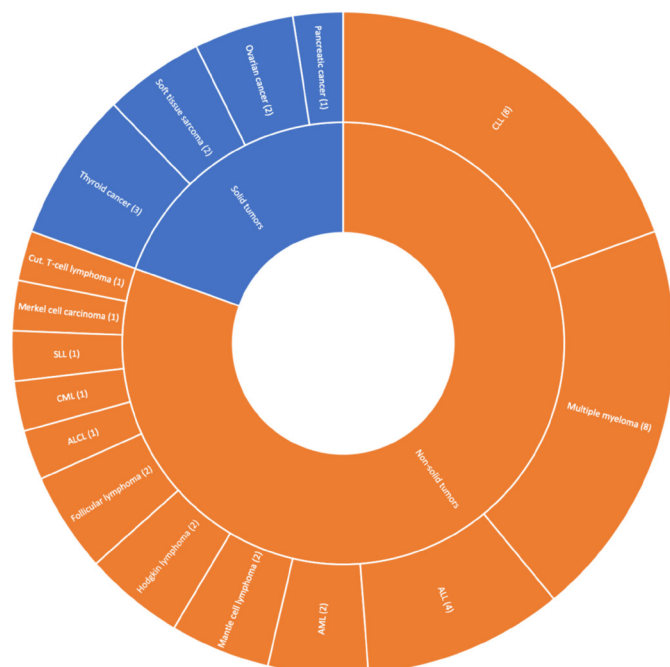

Figure 4 FDA-approved and EMA-approved solid and non-solid tumour cancer drug indications with orphan drug designation. ALCL, anaplastic large cell lymphoma; ALL, acute lymphoblastic leukaemia; AML, acute myeloid lymphoma; CLL, chronic lymphocytic lymphoma; CML, chronic myeloid lymphoma; SLL, small lymphocytic lymphoma; cut. T-cell lymphoma, cutaneous T-cell lymphoma.

drugs compared with the EU.[21 27 28] Drugs that targeted biomarker-defined subsets of common cancer types often received orphan status in the USA, but did not get similar status in the EU.

The number of drugs targeting subpopulations of specific cancers has increased over the last decade with a simultaneous increase in the number of orphan designation by the FDA for drugs indicated for cancers defined as biomarker-based subsets of more common cancers.[23 29–31] However, it is interesting to note that the EMA does not follow this pattern (figure 2). Among the 101 orphan-designated drugs from 2008 through 2017, 40% (40/101) were approved for indications defined in part by biomarkers by the FDA, as compared with only 10% (10/101) by the EMA. For example, the FDA approved alectinib (Alecensa) and ceritinib (Zykadia) to treat ALK+non-small cell lung cancer, crizotinib (Xalkori) to treat ROS1-positive non-small cell lung cancer and dabrafenib (Tafinlar) to treat BRAF V600E mutated metastatic melanoma.[23 32] However, none of these drugs were designated with orphan status by the EMA (see figure 4 and online supplementary appendix).

Drugs receiving designations in both settings were more likely to focus on truly rare cancers, such as multiple myeloma or follicular lymphoma. In the EU, the use of biomarkers to identify a subset of patients for whom the drug can be used appears to generally not be accepted as a basis for receiving orphan designation.[33 34] However, biomarker-derived cancer drugs can still get orphan status in the EU if, among other things, it is unlikely that marketing of the drug would generate sufficient returns to justify the investment needed for its development and the sponsor provides scientific evidence that the activity of the product would not be shown in the larger population.[35]

One important reason for the different application of 'orphan status' in the USA and the EU could be the different legal prerequisites for orphan designation. The demonstration of 'significant benefit' is mandatory for drugs to be designated with orphan status by the EMA compared with those drugs already on the market targeting the same disease.[15 34 36] 'Significant benefit' means that a drug has a clinically relevant advantage or makes a major contribution to patients' care, compared with existing drugs already on the market that target the same condition.[33 37] Significant benefit is a higher standard than the positive benefit-risk assessment that must be demonstrated by the sponsor in the marketing approval process, which does not involve an obligation to show that such a drug is more beneficial than all other methods for treating the same condition.[19] Significant benefit is required at the time of orphan designation, when it can be supported by preclinical studies, and at the time of marketing approval, when clinical data are needed.[36] Our study has shown that a few drugs had their orphan drug designations withdrawn during the marketing approval process, including olaparib (Lynparza) for treatment of primary peritoneal cancer, ovarian cancer, and fallopian

tube cancer, and bosutinib (Bosulif) for treatment of chronic myelogenous leukaemia in the EU.

Adding a prerequisite of 'significant benefit' to maintain orphan drug designation at the time of FDA approval in the USA could help prevent non-first-in-class drugs targeting rare diseases from earning the same incentives as a presumptively more clinically important first-in-class drug for a rare disease. If the second-to-market product offered significant benefits over available treatments, it would get to keep its designation.

Strengths and weaknesses of this study

Our study reveals important new differences of approved cancer drugs with orphan designation between the USA and the EU allowing policy implications for the USA in order to ensure that only truly rare diseases will be designated orphan status for which research investment is limited.

This study has certain limitations. It was restricted to cancer drugs, and so is not generalisable to other drug classes. Also, we did not investigate whether all approved cancer drugs with orphan designation by the EMA between those same years also received orphan status by the FDA. Therefore, it may be possible that certain cancer drugs with orphan designation by the EMA did not get orphan designation by the FDA.

CONCLUSION

The Orphan Drug Act in the USA was intended to encourage drug development for rare conditions with unmet medical needs. We found that the FDA approves more drugs with such designations for cancer subgroups compared with the EMA. The statute could be revised to ensure it applies to truly rare diseases for which research investment is limited. Other changes to the US Orphan Drug Act could include assessing whether there is 'significant benefit' at the time of approval if treatments already exist for a disease targeted by a new drug. Implementation of these reforms could help to improve the development of innovative cancer drugs and by encouraging more resources to be directed to rare cancers that lack effective treatments.

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