Title

Clinical benefit, reimbursement outcomes, and prices of FDA-approved cancer drugs reviewed through Project Orbis in the USA, Canada, England, and Scotland: a retrospective, comparative analysis

Journal

The Lancet Oncology, 25(8)

ISSN

1470-2045

Authors

Jenei, Kristina
Gentilini, Arianna
Haslam, Alyson
et al.

Publication Date

2024-08-01

DOI

10.1016/s1470-2045(24)00286-9

Clinical benefit, reimbursement outcomes, and prices of FDA-approved cancer drugs reviewed through Project Orbis in the USA, Canada, England, and Scotland: a retrospective, comparative analysis

Kristina Jenei, Arianna Gentilini, Alyson Haslam, Vinay Prasad

Summary

Background Project Orbis is a global initiative that aims to streamline regulatory review processes across international regulators in the USA, Canada, Australia, UK, Israel, Brazil, Singapore, and Switzerland to bring promising cancer drugs to patients earlier. We explored the clinical benefit, time to regulatory approval and health technology assessment recommendations, reimbursement outcomes, and monthly treatment prices of cancer drugs reviewed through this initiative.

Methods For this retrospective, comparative analysis, we identified cancer drug approvals reviewed through Project Orbis in the USA, Canada, and the UK between May 1, 2019, and Nov 1, 2023. Approvals of cancer drugs reviewed Project Orbis were extracted from the Food and Drug Administration (FDA) Oncology Centre of Excellence and all other FDA approvals from the Drugs@FDA database. The co-primary outcomes were time of regulatory review, time from regulatory approval to health technology assessment recommendation (England, Scotland, and Canada), reimbursement outcomes, clinical benefit (defined as median gains in progression-free survival and overall survival) between cancer drug approvals reviewed by Project Orbis and other FDA approval processes, and monthly treatment prices. The Wilcoxon rank-sum and Fisher's Exact tests were used to examine statistical significance between approvals reviewed through Project Orbis and other FDA approvals during the same period.

Findings Between May 1, 2019 and Nov 1, 2023, 81 (33%) of 244 cancer drugs approved by the FDA were reviewed through Project Orbis. The median overall survival gains were 4·1 months (IQR 3·3–5·1) compared with 2·7 months (2·1–3·9) for other FDA approvals. Similarly, progression-free survival gains were 2·6 months (IQR 1·7–4·9) for Project Orbis compared with 2·6 months (0·6–5·1) for other FDA approvals. Neither overall survival (p=0·11) nor progression-free survival (p=0·44) gains were significantly different between the two cohorts of approvals. Of the 14 UK Medicines and Healthcare products Regulatory Agency (MHRA) approvals reviewed by the Scottish Medicines Consortium (SMC), the agency gave positive recommendations for all 14 (100%). Of the 15 MHRA approvals reviewed by the National Institute for Health and Care Excellence (NICE), the agency gave positive recommendations for six (40%). Of the 49 approvals reviewed by the Canadian Agency for Drugs and Technologies in Health (CADTH), the agency conditionally recommended 44 (90%). The time between regulatory approval to NICE recommendation increased from a median of 137 days (IQR 102–172) in 2021 to 302 days (184–483) in 2023, SMC recommendation increased from 185 days (in 2021 for one drug only) to 368 days (IQR 313–476) in 2023, and CADTH decision increased from 97 days (in 2020 for one drug only) to 202 days (IQR 153–304) in 2023. The median monthly price of approvals reviewed through Project Orbis was US$20 000 per month (IQR 13 000–37 000).

Interpretation Clinical outcomes of Project Orbis were no different than other FDA approvals during the same time, and access, after a successful health technology assessment, was considerably delayed or absent, raising questions about whether Project Orbis participation translates into faster patient access to medicines with high clinical benefit and sustainable costs. Although future challenges might benefit from regulatory harmonisation, the advantages are currently unclear.

Funding None.

Lancet Oncol 2024; 25: 979–88

Published Online July 11, 2024 https://doi.org/10.1016/S1470-2045(24)00286-9

Department of Health Policy, London School of Economics and Political Science, London, UK (K Jenei BSN, A Gentilini MSc); **Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA, USA** (A Haslam PhD, Prof V Prasad MD)

Correspondence to: Kristina Jenei, Department of Health Policy, London School of Economics and Political Science, London WC2A 2AE, UK **k.jenei@lse.ac.uk**

Introduction

In 2019, the US Food and Drug Administration (FDA) launched Project Orbis, a global initiative to streamline regulatory review among multiple international regulatory agencies to accelerate patient access to clinically beneficial cancer drugs.[1] Project Orbis expands on historical global collaborations with the FDA and includes Canada, Australia, Singapore, Brazil, Israel,

Research in context

Evidence before this study

We searched PubMed, Ovid MEDLINE, and Google Scholar for documents in English or French on March 18, 2024, with the keyword "Project Orbis". Since the underlying goal of Project Orbis is to expedite promising cancer drugs to patients, we conducted an additional literature search for studies evaluating the clinical benefit of cancer drugs approved through expedited pathways using search terms such as "clinical benefit", "cancer", "pharmaceuticals", "expedited review", "accelerated review", "breakthrough designation" and "orphan drug designation". This search allowed us to contextualise our findings into a broader body of research. Additionally, we screened the US Food and Drug Administration (FDA), FDA Oncology Centre of Excellence (OCE), Health Canada, Canadian Agency for Drugs in Technology in Health, UK Medicines and Healthcare Products Regulatory Agency, National Institute for Health and Care Excellence, and Scottish Medicines Consortium websites to ensure all literature about Project Orbis involvement was captured. One author (KJ) screened abstracts, articles, and reports. We identified two empirical studies about Project Orbis, one from the OCE and one from Swissmedic, that evaluated the number of approvals and review times across countries. Additionally, we included two conference papers, several OCE annual reports, one UK policy review, and one commentary. Evidence suggests that Project Orbis had increased submissions after its first year, including increased regulatory actions (approvals or rejections) by partner countries. The FDA and partner countries had similar median time-to-approval statistics. In Switzerland, marketing authorisation applications had faster review times than did non-Orbis marketing authorisation applications. Project Orbis marketing authorisations aligned with the FDA compared with drugs approved through other review pathways. However, experience from Switzerland also suggests that not all drugs reviewed through this initiative are approved. A growing body of literature evaluated the clinical characteristics of accelerated approvals. Cancer drugs comprise the highest proportion of drugs approved through these regulatory review pathways. Although expediting cancer drugs is crucial for patient access, there are concerns about the quality of evidence underpinning these approvals, the frequent use of surrogate endpoints, and delays in post-confirmatory studies.

Added value of this study

To our knowledge, we provide the first comprehensive evaluation of Project Orbis in the USA, Canada, England, and Scotland. This includes an assessment of the clinical benefit, review times, health technology assessment outcomes, and US monthly treatment prices. We found that overall survival and progression-free survival estimates among drugs reviewed through Project Orbis did not significantly differ from all other FDA approvals during the same period. Health technology assessment bodies in England, Scotland, and Canada did not recommend all drugs for public reimbursement plans, often due to uncertain clinical and economic evidence and high prices. We found the price of Project Orbis drugs to be US$20 000 a month, raising questions about sustainability in publicly funded systems and patient access.

Implications of all the available evidence

Project Orbis is a flagship collaboration between the US FDA and seven other nations, seeking to harmonise cancer drug approvals and bring high-benefit medicines to patients worldwide sooner. However, we found that overall survival and progression-free survival gains of cancer drugs reviewed through Project Orbis were not significantly different from other US drug approvals during the same time. High monthly treatment prices raise questions of sustainability to public health systems and patient access. Further transparency from the FDA is needed to understand how drugs are chosen to be reviewed through Project Orbis.

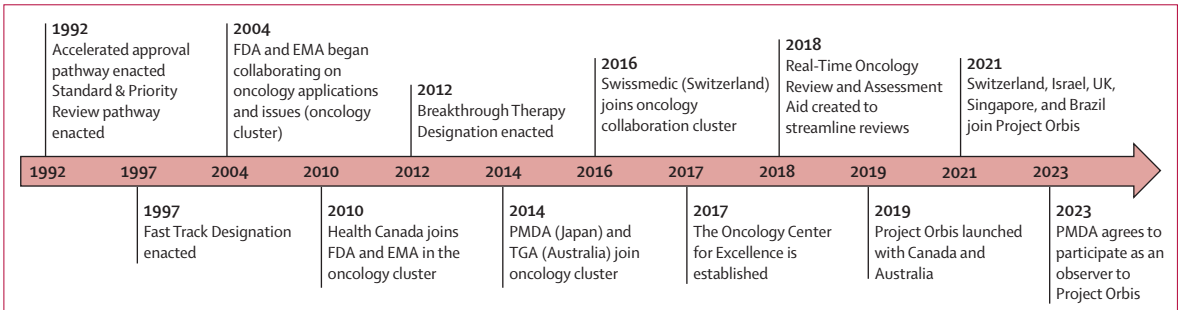

Figure 1: **Historical timeline of international regulatory agency collaboration leading to Project Orbis**
EMA=European Medicines Agency. FDA=US Food and Drug Administration. PMDA=Pharmaceuticals and Medical Devices Agency. TGA=Therapeutic Goods Administration.

Switzerland, and the UK (figure 1), covering a jurisdiction of approximately 700 million individuals, comprising over half of global pharmaceutical sales.[2,3] Although all partner countries collaborate in the review process, a central feature of the programme is that each regulator maintains its independence in the final decision and drug label. Given that drugs are often launched first in the USA, the underpinning logic was that international

collaboration with the FDA could facilitate faster regulatory reviews and earlier patient access in other countries. In the first year of operation, the programme demonstrated expedited review times across partner countries compared with previous non-Orbis-reviewed cancer drugs and has been deemed a preliminary success by the FDA and SwissMedic.[1,4,5]

Project Orbis aims to make clinically beneficial drugs available sooner to global patients with cancer. However, access is a product of regulatory approval and favourable health technology assessment in many participating countries. Drugs must demonstrate value: large clinical benefits and sustainable costs. At the same time, concerns have been raised in the literature about regulators approving cancer drugs with modest overall survival gains. Over the past decade, the median overall survival gain of cancer drugs approved by the FDA and European Medicines Agency was less than 3 months.[6] Countries with public insurance plans often only cover a fraction of drugs that receive FDA approval.[7] Drugs with immature evidence can be integrated into clinical practice before post-marketing studies are complete and contribute to added government spending.[8] Given ongoing challenges with cancer drug approvals, important questions have been raised about patient access, clinical benefits, and costs of cancer drugs selected for review under Project Orbis.[9]

To our knowledge, there is no evaluation of the clinical outcomes of drugs reviewed through Project Orbis. Previous research has concentrated on the number of approvals and review times as success metrics.[1,4] Moreover, no study has linked Project Orbis drug approvals to subsequent health technology assessments to understand their value to public health systems. Therefore, the objective of this study was to characterise the overall survival and progression-free survival benefit of cancer drugs that received regulatory approval that were reviewed through Project Orbis compared with those that were not reviewed through the programme during the same period. Furthermore, to characterise value and patient access, we provide reimbursement outcomes in England, Scotland, and Canada, along with US median monthly treatment prices of drugs reviewed through Project Orbis.

Methods

Study design and data sources

We conducted a retrospective, comparative analysis of all cancer drug approvals reviewed through Project Orbis in the USA (FDA), Canada (Health Canada), and the UK (UK Medicines and Healthcare products Regulatory Agency [MHRA]), including their reimbursement outcomes (England, Scotland, and Canada) and monthly treatment prices. Scotland and England were chosen as their health technology assessment agencies are the main independent bodies in the UK. Guidance from England for new medicines is legally binding for health boards and trusts in Wales and Northern Ireland.[10] An overview of regulatory review and health technology assessment processes in Canada and the UK is shown in figure 2. Further information about Project Orbis, including country-specific regulatory pathways, is outlined in the appendix (pp 1–2).

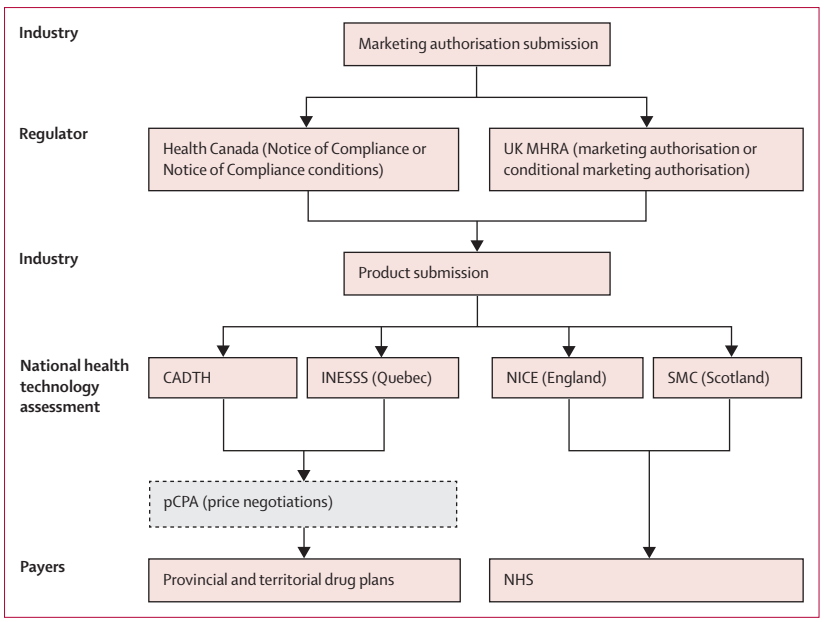

Figure 2: **An overview of regulatory review and health technology assessment processes in Canada, England, and Scotland**

The figure shows the most common types of market authorisations for drugs approved by MHRA. However, several other types of approvals can be used in various scenarios. Figure excludes Northern Ireland and Wales as these jurisdictions typically adopt NICE guidance for new medicines. CADTH=Canadian Agency for Drugs in Technology in Health. INESSS=Institut national d'excellence en santé et en services sociaux. NHS=National Health Service. NICE=National Institute for Health and Care Excellence. pCPA=pan-Canadian Pharmaceutical Alliance. SMC=Scottish Medicines Consortium. UK MHRA=UK Medicines and Healthcare Products Regulatory Agency.

See **Online** for appendix

Cancer drug approvals are publicly available on the Drugs@FDA database. The FDA Oncology Centre of Excellence (OCE) provides data for which cancer drug approvals were reviewed through Project Orbis. Health technology assessment reimbursement recommendations were obtained from the National Institute for Health and Care Excellence (NICE) in England, the Scottish Medicines Consortium (SMC), and the Canadian Agency for Drugs and Technologies in Health (CADTH). The outcomes of price negotiations in England were obtained from NICE, in Scotland were obtained from the SMC, and in Canada were obtained from the pan-Canadian Pharmaceutical Alliance (pCPA). Average US wholesale prices were extracted from the Micromedex RedBook database.[11] These data are compiled by the International Business Machines Corporation (IBM) with prices reported directly from manufacturers. According to the Common Rule (45 CFR 46), this study was exempt from ethics approval as it did not involve human participants.

For more on **drug approvals and databases** see https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

For more on the **Scottish Medicines Consortium** see https://www.scottishmedicines.org.uk/

For more on the **Canadian Agency for Drugs and Technologies in Health** see https://www.cadth.ca/

For more on the **pan-Canadian Pharmaceutical Alliance** see https://www.pcpacanada.ca/

	Marketing applications approved through Project Orbis (n=81)
General submission characteristics	
Type of submission	
New drug	47 (58%)
Supplemental indication	34 (42%)
FDA review*	
Priority review	74 (91%)
Orphan drug	52 (64%)
Breakthrough designation	44 (54%)
Real-time oncology review	42 (52%)
Accelerated approval	26 (32%)
Tumour type	
Lung	16 (20%)
Gastrointestinal	14 (17%)
Breast	11 (14%)
Leukaemia	6 (7%)
Skin	5 (6%)
Gynaecological	4 (5%)
Other	25 (31%)
Drug class	
Monoclonal antibody or immune checkpoint inhibitor	40 (49%)
Small molecule	29 (36%)
Cytotoxic	3 (4%)
Hormonal	1 (1%)
Other	8 (10%)
Line of therapy	
First line	34 (42%)
Second line and beyond	46 (57%)
Maintenance	1 (1%)
Shared reviews with partner countries†	
Canada	58 (72%)
Australia	54 (67%)
Switzerland	30 (37%)
Singapore	30 (37%)
Brazil	24 (30%)
UK	18 (22%)
Israel	16 (20%)

(Table 1 continues in next column)

(Continued from previous column)

	Marketing applications approved through Project Orbis (n=81)
Trial characteristics	
Phase	
1	1 (1%)
2	31 (38%)
3	48 (59%)
Other	1 (1%)
Randomisation	
No	26 (32%)
Yes	55 (68%)
Masking	
No	51 (63%)
Yes	30 (37%)
Pre-specified primary endpoint	
Overall survival	17 (21%)
Progression-free survival	26 (32%)
Response rate	33 (41%)
Other	5 (6%)
Median US incidence rate per 100 000 people	22 (4·2–59·2)
Median price per month (US$)‡	20 000 (13 000–37 000)
Median price per month (US$)‡ for approvals with clinical benefit	
Overall survival	20 000 (13 000–37 000)
Progression-free survival	20 000 (15 000–35 000)
Response rate	24 000 (12 000–36 000)
Health-related quality of life§	
Not assessed or uncertain	38 (47%)
Improved	29 (36%)
Maintained	14 (17%)

Data are n (%) or median (IQR). FDA=US Food and Drug Administration. *FDA review and approval pathway not mutually exclusive, one approval can qualify for designations and receive accelerated approval. †Country reviews as a proportion of total marketing applications (n=81). ‡Price is the average wholesale price per RedBook data, excludes eight cancer drugs for which price was not available. §Most health-related quality-of-life outcomes were exploratory at time of analysis and must be interpreted with caution. Data categorised as uncertain were instances where health-related quality-of-life outcomes could not be interpreted due to increased evidential uncertainty related to trial design biasing the estimates.

Table 1: **Characteristics of studies and clinical benefit supporting cancer drug approvals reviewed through Project Orbis**

Procedures

Cancer drug approvals were extracted from the Drugs@FDA database. We identified cancer drugs reviewed through Project Orbis by matching the drug name, indication, and FDA approval date to the data provided by the OCE.

We extracted characteristics of cancer drugs reviewed through Project Orbis from the programme inception (May 1, 2019) to the most recent OCE data cutoff (Nov 1, 2023). This included the drug name, indication, corresponding country approvals, FDA approval date, and expedited review pathway or designation. We extracted additional data on clinical trial characteristics from the FDA approval notifications. To ensure accuracy, we cross-referenced data with ClinicalTrials.gov using the trial registration number. Additional variables collected were drug class, new drug or supplemental indication, tumour type, treatment setting, line of therapy, pre-specified primary endpoint, whether the study was randomised, phase, study masking details and specified primary endpoint of the supporting study.

Drugs reviewed by the MHRA and Health Canada as part of Project Orbis were identified as the FDA indicates which partner countries are involved in each approval. Three authors with expertise in Canadian, UK, and US policy (KJ, AG, and AH, respectively) extracted data.

Any discrepancies were resolved by consensus with input from an oncologist (VP). We collected approval dates from the FDA, Health Canada, and the UK MHRA. We collected the dates the sponsor applied to CADTH to characterise potential delays. To our knowledge, NICE and SMC do not publicly provide this information. For Canada, the date of reimbursement outcome was recorded as the date the decision was issued to the sponsor and provincial drug plans. For England, the reimbursement date was recorded as the publication of the final appraisal document. In Scotland, we extracted the date the reimbursement advice was published.

Outcomes

The co-primary outcomes were time of regulatory review, time from regulatory approval to health technology assessment recommendation (England, Scotland, and Canada), reimbursement outcomes, the clinical benefit of cancer drug approvals reviewed by Project Orbis compared to other FDA approval processes, and monthly treatment prices.

Secondary outcomes were clinical trial characteristics supporting approvals reviewed through Project Orbis; time between manufacturer submission and CADTH recommendation; funding negotiation outcomes for drugs recommended by NICE, SMC, or CADTH; reasons for non-recommendation; and the median monthly price of approvals demonstrating overall survival, progression-free survival, or response rate. Exploratory outcomes were the effect of population diffusion and drug discounting and health-related quality-of-life outcomes.

Time of regulatory review was defined as the median number of days from FDA approval to UK MHRA and Health Canada approval, and time from regulatory approval to health technology assessment recommendation was defined as the median number of days from UK MHRA approval to NICE and SMC recommendation and the median number of days from Health Canada approval to CADTH recommendation. Clinical benefit was defined as median gains in progression-free survival (the time from randomisation to date of radiographic tumour progression or death) and overall survival (the time from randomisation to death from any cause). Funding negotiation outcomes are defined as the funding scheme that the drug is reimbursed (NICE and SMC) or whether the manufacturer reached a successful negotiation (Canada). The outcomes of health-related quality-of-life assessments were recorded as an exploratory outcome as much of these data were uncertain (ie, health-related quality-of-life outcomes could not be interpreted due to increased evidential uncertainty related to trial design biasing the estimates).

Statistical analysis

Both progression-free survival and overall survival gains were measured in months. Overall survival and progression-free survival gains were calculated by subtracting the median survival estimate in the comparator group from the intervention group.[6] Hazard ratios (HRs) and associated confidence intervals were also examined. The median monthly treatment prices of each drug reviewed through Project Orbis was calculated using methods from similar studies, using the recommended dosage from the FDA label per indication, and reported in US dollars. The RedBook provides price data for different strengths. When applicable, we assumed dosage requirements for adults weighing 60 kg and an average body surface area of 1·79 m^2.[12,13] We explored the effect of population diffusion and drug discounting with the Medicaid best-price guarantee of 23·1%[14] and 50% discount to approximate prices in the UK and Canada.[15] Prices are reported in US dollars.

Descriptive statistics were used to report clinical trial characteristics, clinical benefits, review times, and prices. The Wilcoxon rank-sum and Fisher's Exact tests were used to examine statistical significance between approvals reviewed through Project Orbis and other FDA approvals during the same period, chosen for their robustness for non-normal distributions and small sample sizes. p values less than 0·05 were considered significant. Data are presented as medians (IQRs) and absolute values with percentages. Microsoft Excel (version 16.83) and R Studio (version 2022.61+524) were used for analyses.

Role of the funding source

There was no funding source for this study.

Results

Between May 1, 2019, and Nov 1, 2023, 244 cancer drugs were approved by the FDA. Of these, 81 (33%) were reviewed through Project Orbis. Nine (11%) of these applications had recently received FDA approval that were not approved by partner countries at the time of this study. In 2019, three (4%) drugs reviewed through Project Orbis received FDA approval. There were 22 (27%) drugs reviewed through Project Orbis in 2020, 27 (33%) in 2021, 17 (21%) in 2022, and 12 (15%) in 2023 (appendix p 2).

Among Project Orbis submissions, 47 (58%) of the 81 were new drugs, and 34 (42%) were supplemental indications (table 1). Lung cancer was the most frequent indication (16 [20%]), and monoclonal antibodies and immune checkpoint inhibitors (40 [49%]) were the most common drug class. More than half of the approvals were for treatment in the second line or beyond (46 [57%]). Nearly half (38 [47%] of 81) approvals reviewed through Project Orbis did not assess health-related quality of life, or data were too uncertain to interpret. Canada participated in 58 (72%) of 81 total approvals, while the UK MHRA participated in 18 (22%) of 81.

Drugs reviewed through Project Orbis were mostly approved first at the FDA, then Health Canada and the

Figure 3: **Overview of drugs approved in the USA, UK, and Canada, reviewed through Project Orbis**
FDA=US Food and Drug Administration. UK MHRA=UK Medicines and Healthcare Products Regulatory Agency.

MHRA (figure 3). In the UK, the median time from FDA to MHRA approval was 172 days (IQR 135 to 223), 447 days (330 to 513) to NICE approval, and 434 days (327 to 696) to SMC reimbursement recommendations The median time from MHRA approval to NICE recommendation was 208 days (IQR 184 to 335) and from MHRA approval to SMC recommendation was 299 days (182 to 361). The median time from FDA to Health Canada approval was 148 days (IQR 56 to 272) and 377 days (320 to 591) to CADTH reimbursement outcome. The median time from Health Canada approval to CADTH recommendations was 216 days (IQR 127 to 367). In Canada, where this information is available, the median time from Health Canada approval and sponsor submission to CADTH was 4 days (IQR –73 to 105). The negative value denotes simultaneous review, as sponsors can submit applications for reimbursement to CADTH before Health Canada approval.

In the UK, the time between FDA and MHRA approval decreased from a median of 178 days (IQR 147–224) in 2021 to 145 days (108–187) in 2023. The time from MHRA approval to NICE recommendation has increased from a median of 137 days (IQR 102–172) in 2021 to 302 days (184–483) in 2023. The median time from MHRA approval to SMC recommendation has increased from 185 days (in 2021 for one drug only) to 368 days (313–476) in 2023. The median time from FDA to Health Canada approval increased from 49 days (IQR 39–65) in 2020 to 235 days (149–526) in 2023. The time between Health Canada approval and the CADTH decision increased from 97 days (in 2020 for one drug only) to 202 days (IQR 153–304) in 2023.

We examined the clinical benefits of FDA approvals reviewed through Project Orbis compared with all other cancer drug approvals during the same period. Of the drugs reviewed through Project Orbis, 20 (25%) of 81 had overall survival data available at the time of regulatory approval compared with 45 (28%) of 163 for all other FDA approvals during the same period (table 2). Similarly, 22 (27%) approvals reviewed through Project Orbis had progression-free survival data available compared with 32 (20%) of 163 all other FDA approvals. There were no significant differences in overall survival data availability (p=0·65) or progression-free survival data availability (p=0·19) between the two cohorts of approvals.

The median overall survival gains for approvals reviewed through Project Orbis was 4·1 months (IQR 3·3–5·1) compared with 2·7 months (2·1–3·9) for all other FDA approvals during the same period (p=0·11). The studies underpinning overall survival gains, including associated HRs and 95% CIs, are presented in the appendix (p 3).

The progression-free survival gains for cancer drugs reviewed through Project Orbis were 2·6 months (IQR 1·7–4·9) compared with 2·6 months (0·6–5·1) for all other FDA approvals during the same period. Progression-free survival gains were not significant between the two cohorts of approvals (p=0·44). The studies underpinning the progression-free survival gains, including associated HRs and 95% CIs, are outlined in the appendix (p 4).

	Project Orbis approvals (n=81)	Other FDA approvals* (n=163)	p value†
Progression-free survival data available	..	..	0·19
No	59 (73%)	131 (80%)	..
Yes	22 (27%)	32 (20%)	..
Progression-free survival gain, months‡	2·6 (1·7–4·9)	2·6 (0·6–5·1)	0·44
Overall survival data available	..	..	0·65
No	61 (75%)	118 (72%)	..
Yes	20 (25%)	45 (28%)	..
Overall survival gain, months‡	4·1 (3·3–5·1)	2·7 (2·1–3·9)	0·11

Data are n (%) or median (IQR). FDA=US Food and Drug Administration. *Excludes approvals reviewed through Project Orbis initiative. †Fishers exact test and Wilcoxon rank-sum test were used to test for statistical significance between two approval cohorts. ‡Single-arm studies that had overall survival or progression-free survival data were excluded from the calculations of gains.

Table 2: **Clinical benefit of approved drugs reviewed through Project Orbis and other FDA approvals between 2019 and 2023**

The total median overall survival gains of approved cancer drugs reviewed through Project Orbis decreased from 4·5 months (IQR 4·0–6·3) in 2020 to 2·5 months (2·2–2·9) in 2023. The median progression-free survival gains increased from 3·5 months (IQR 2·0–4·7) in 2020 to 8·2 months (3·2–15·2) in 2023, mostly attributable to the approval of dostarlimab in combination with platinum-based chemotherapy for advanced endometrial cancer, which demonstrated a 22·6-month progression-free survival gain compared with placebo plus chemotherapy.[16]

Of the 18 MHRA marketing authorisation applications approved through Project Orbis, 16 (89%) were submitted to NICE by the sponsor. One reimbursement review remains in progress and was excluded from this analysis. Of the 15 cancer drugs reviewed, six (40%) were provided positive recommendations, five (33%) were under the Cancer Drug Fund (temporary mechanism), and three (20%) were not recommended for reimbursement. One drug (mobocertinib) was withdrawn from the UK after the confirmatory trial demonstrated no clinical benefit. Of the 11 recommendations by NICE, six (55%) were funded through Patient Access Schemes and five (45%) through managed or commercial access agreements. In Scotland, 14 (78%) of 18 MHRA approvals were submitted to SMC. SMC recommended all 14 (100%) under Patient Access Schemes. Ultimately, 33% (six of 18) MHRA approvals reviewed through Project Orbis are routinely available in England and 72% (13 of 18) are available in Scotland.

Of the 58 approvals by Health Canada through Project Orbis, 49 (84%) were reviewed by CADTH. The sponsors did not submit nine cancer drugs (16%) to CADTH. Of the 49 cancer drugs reviewed, CADTH conditionally recommended 44 (90%) and provided negative recommendations for five (10%). The most common reason for

	Indication	FDA	NICE	CADTH
Lorlatinib	NSCLC	Authorised; regular approval based on progression-free survival (median not recorded, HR 0·28)	Not recommended; trial results were not generalisable to clinical practice, clinical and economic data were uncertain, unacceptable use of National Health Service resources (not cost-effective)	Conditional recommendation based on narrowed indication and improvements in cost-effectiveness and adoption feasibility
Amivantamab	NSCLC	Authorised; accelerated approval based on phase 1b trial (RR 40%); confirmatory trial ongoing	Not recommended; clinical and economic data were uncertain, not cost-effective, more data will not resolve uncertainties so not recommended for CDF	Not recommended; clinical and economic data were uncertain, unreliable activity endpoints, non-comparative evidence
Tebentafusp	Melanoma	Authorised; accelerated approval based on phase 2 trial (median overall survival gain 5·7 months)	Not recommended; clinical and economic data uncertain; not cost-effective	Conditional recommendation based on narrowed indication and improved cost-effectiveness and system feasibility
Mobocertinib	NSCLC	Authorised; accelerated approval based on phase 1–2 trial (RR 28%); withdrawn October, 2023	Confirmatory trial demonstrated no clinical benefit; UK withdrawal March 8, 2024	Confirmatory trial demonstrated no clinical benefit; not reviewed in Canada as part of Project Orbis; withdrawn
Tafasitamab	DLBCL	Authorised; accelerated approval based on phase 2 trial (RR 55%); confirmatory trial ongoing	Not recommended; clinical and economic data were uncertain, not cost-effective, more data will not resolve uncertainties, not recommended for CDF; not reviewed through Project Orbis	Not recommended; uncertain clinical evidence that does not demonstrate improvement in symptoms or quality of life
Tepotinib	NSCLC	Authorised; accelerated approval; confirmatory trial verified RR (57%) and duration of response (40%); converted to traditional approval February, 2024	Recommended. Clinical data suggests benefit but uncertain; within NICE cost-effectiveness threshold	Not recommended; uncertain clinical and economic evidence; does not improve symptoms or quality of life
Sotorasib	NSCLC	Authorised; accelerated approval based on phase 1–2 trial (RR 36%; confirmatory trial ongoing)	Recommended for CDF; clinical and economic data uncertain	Not recommended in draft guidance; progression-free survival not clinically meaningful; not powered to detect overall survival; review ongoing as sponsor requested major revisions
Lurbinectedin	SCLC	Authorised; accelerated approval based on phase 2 trial (RR 35%; confirmatory trial ongoing)	Suspended; company delayed market introduction; not reviewed through Project Orbis	Not recommended; uncertain clinical evidence for disease progression, survival, and side-effects compared with other available treatments; does not improve quality of life

CADTH=Canadian Agency for Health and Technologies in Health. CDF=UK Cancer Drug Fund. DLBCL=diffuse large B cell lymphoma. FDA=US Food and Drug Administration. HR=hazard ratio. MRHA=UK Medicines and Healthcare products Regulatory Agency. NICE=National Institute for Health and Care Excellence. NSCLC=non-small-cell lung cancer. RR=response rate. SCLC=small-cell lung cancer. *Not all drugs were reviewed through Project Orbis at each agency; however, rationales are provided for comparison purposes.

Table 3*: Overview of cancer drugs reviewed through Project Orbis denied coverage by NICE and CADTH

a conditional recommendation was if the clinical criteria could be narrowed to a subset of eligible patients and the cost-effectiveness could be improved through confidential discounts. Of the 49 CADTH recommendations, the pCPA had successfully negotiated 38 (78%) agreements with sponsors, five (10%) were ongoing, and six (12%) ceased without an agreement with the sponsor (including one drug that received a positive recommendation). Ultimately, 42 (72%) of 58 of Health Canada approvals reviewed through Project Orbis are available in Canada.

We examined the reasons for the eight cancer drugs reviewed through Project Orbis that received negative recommendations from NICE and CADTH (table 3). Both CADTH and NICE did not recommend tafasitamab for diffuse large B-cell lymphoma and amivantamab for non-small-cell lung cancer (NSCLC). Both agreed that there were substantial clinical and economic uncertainties. In both cases, NICE stated that additional data collected through the Cancer Drug Fund would not resolve uncertainties. CADTH did not recommend lurbinectedin for small-cell lung cancer, while the review was suspended at NICE due to sponsor delays. Sotorasib for NSCLC was not recommended by CADTH, while NICE funded the drug through the Cancer Drug Fund. Tepotinib was recommended by NICE, despite uncertainties, because it was within the cost-effectiveness thresholds, but was not recommended by CADTH. Lorlatinib and tebentafusp were not recommended by NICE but were conditionally recommended by CADTH based on narrowed indication.

The median monthly treatment price of cancer drugs reviewed through Project Orbis was US$ 20 000 per month (IQR 13 000–37 000). We also assessed the median monthly price of approvals demonstrating overall survival, progression-free survival, or response rate (table 1). With 100% population uptake, the median monthly price could range from $10 000 (European or UK discounts) to $15 380 (Medicaid best-price guarantee). The effect of discounting and population uptake on price projections is shown in the appendix (p 5). Between 2019 and 2023, median monthly prices remained stable at about $20 000.

Discussion

To our knowledge, our analysis is the largest study of the characteristics and outcomes of Project Orbis drug approvals across some of the participating countries. Cancer drugs approved by the UK MHRA and Health Canada were not universally available to patients with

cancer in England, Scotland, and Canada, with 33% (NICE) and 72% (SMC and CADTH) of approvals garnering positive health technology assessment coverage decisions. We found that NICE, SMC, and CADTH seldom provided positive recommendations without highlighting substantial clinical and economic uncertainties, and in some cases did not recommend these drugs for reimbursement. Given the large global market share covered by Project Orbis and ongoing discussions to expand the programme to the European Medicines Agency and the Japanese Pharmaceuticals and Medical Devices Agency,[17] and to other therapeutic areas, such as cell and gene therapies,[18] our findings have important implications.

The criteria for Project Orbis are that a drug must be of "high impact, clinically significant applications, and should generally qualify for priority review because of improvement in safety and efficacy".[19] Yet, we found that the magnitude of benefit among drugs reviewed through Project Orbis did not statistically differ compared with all other FDA approvals during the same period. Drugs can be reviewed within Project Orbis for other reasons, such as unmet clinical need or durable responses for a subset of patients, and these are frequent characteristics of drugs eligible for expedited review. However, there is limited understanding of how drugs are chosen beyond these stated criteria. For example, what qualifies a cancer drug to be "high impact" and "clinically significant"? How early does Project Orbis aim to review cancer drugs compared with other non-Project Orbis reviewed cancer drugs? Given modest clinical benefits, further transparency is needed to understand how the FDA identifies cancer drugs to be reviewed through the programme. Maintaining high standards and transparent governance is particularly important as Project Orbis expands.

Earlier regulatory approval in Canada and the UK does not necessarily equate to earlier patient access. In England, Canada, and Scotland, sponsors must submit applications to health technology assessment agencies for reimbursement under public insurance plans. Health technology assessment agencies aim to assess the value of new health interventions, such as medicines, examining cost-effectiveness and system feasibility, among other criteria in validated frameworks, to allocate scarce resources and meet the population's needs.[20] Since joining Project Orbis, we found that the time from regulatory approval to health technology assessment recommendation has increased in England, Scotland, and Canada. This finding might be due to the large proportion of drugs approved through expedited pathways in the USA. Previous research suggests these regulatory pathways (eg, Breakthrough Designation, Accelerated Review, and Real-time Oncology Review) are associated with greater evidential uncertainties.[21–23]

Our finding that CADTH and SMC recommend a higher proportion of drugs than NICE might be due to differences in their governance. CADTH reimbursement recommendations are non-binding, whereas NICE recommendations are binding.[24] Although health technology assessment agencies rarely reject medicines on price alone, cost-effectiveness is central in NICE decision-making compared with CADTH.[25] In Canada, the pCPA negotiates prices after CADTH recommendations, whereas NICE and SMC directly discuss with companies during reimbursement. The lower proportion of positive recommendations at NICE might reflect these negotiations, whereas, at CADTH, these negotiations have not yet occurred. The high proportion of positive recommendations from SMC might be related to several recommendations that included Patient and Clinician Engagement meetings, which gives these groups a stronger voice in the final decision for serious or end-of-life illnesses.[26]

Although regulatory harmonisation has several benefits, such as streamlining reviews and sharing information, alignment with the FDA raises concerns given what Canadian payers have described as a "lower bar for approval".[27] We found modest gains in clinical benefit and high treatment prices—nearing $20 000 per month of therapy. Although the prices of Project Orbis drugs are similar to those approved through other FDA pathways,[15] high prices remain substantial barriers to patient access, either from large budget impacts, longer health technology assessment reimbursement reviews, or out-of-pocket costs.[28]

Our study has several limitations. First, we did not include all partner countries within the programme as we wanted an in-depth analysis of patient access in England, Scotland, and Canada. Including all partner countries, while informative, would inhibit the level of depth on reimbursement outcomes and price negotiations. However, we provided an overview of clinical benefits and trial characteristics for all FDA approvals, which applies to all partner countries. Second, we provide an unadjusted statistical analysis of overall survival and progression-free survival gains for Project Orbis compared with other approvals, which might not consider how other factors influence which drugs are reviewed. Third, comparing aggregate overall survival and progression-free survival gains might not capture nuances in the durable long-term benefits for a subset of the high responders, which is often the case with immunotherapies. Additionally, we used average wholesale prices outlined in the RedBook database, which does not provide the final discounted net price. However, these methods are consistent with similar studies, and our results are comparable to existing research.[11] Finally, data on health-related quality of life should be interpreted with caution due to uncertainty in the data.

As spending on cancer drugs outpaces the rate of new cancer cases,[29] future efforts to evaluate the success of international harmonisation efforts should extend

beyond the number of approvals and review times to value metrics such as benefits and costs to elicit a comprehensive impact on health systems and patients globally. Project Orbis is poised to expand; however, further understanding is needed to elicit the full implications of this collaboration on regulatory and health technology assessment bodies, health systems, and the wellbeing of patients with cancer worldwide.

Contributors

KJ contributed to the project conception, design, data collection, analysis, interpretation, and drafting of the manuscript. AG contributed to data collection, verification, and editing of the manuscript. AH contributed to data collection. VP contributed to project conception, design, interpretation, and drafting of the manuscript. KJ takes primary responsibility for the data analysis and had the final responsibility to submit the manuscript for publication. KJ and AG verified the data. All authors had access to the raw data and accept responsibility for the decision to submit for publication.

Declaration of interests

VP receives research funding from Arnold Ventures through a grant made to the University of California San Francisco, royalties for books and writing from Johns Hopkins Press, MedPage, and the Free Press; declares consultancy roles with UnitedHealthcare and OptumRX; hosts the podcasts Plenary Session, VPZD, and Sensible Medicine; writes the newsletters for Sensible Medicine, the Drug Development Letter, and V's Observations and Thoughts; and runs the YouTube channel Vinay Prasad MD MPH, which collectively earns revenue on the platforms: Patreon, YouTube, and Substack. All other authors declare no competing interests.

Data sharing

All data used in this study are from publicly available databases.

Acknowledgments

KJ is supported by a Canadian Institutes of Health Research Doctoral Foreign Study Award (181603). VP is supported by a grant from Arnold Ventures.

References

1 de Claro RA, Spillman D, Hotaki LT, et al. Project Orbis: global collaborative review program. *Clin Cancer Res* 2020; **26:** 6412–16.
2 Lythgoe MP, Sullivan R. Project Orbis: the UK experience after 1 year. *Lancet Oncol* 2022; **23:** 978–81.
3 IQVIA Institute for Human Data Science. The global use of Medicines 2024. https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-global-use-of-medicines-2024-outlook-to-2028 (accessed March 18, 2024).
4 Pavic M, Li Q, Atiek E, Wolfer A, Rohr UP. 1692MO Is Project Orbis successful? The Swiss perspective. *Ann Oncol* 2023; **34:** S926.
5 Zosso-Pavic M, Li Q, Atiek E, Wolfer A, Rohr UP. Effect of Project Orbis participation by the Swiss regulator on submission gaps, review times, and drug approval decisions between 2020 and 2022: a comparative analysis. *Lancet Oncol* 2024; **25:** 770–78.
6 Fojo T, Mailankody S, Lo A. Unintended consequences of expensive cancer therapeutics—the pursuit of marginal indications and a me-too mentality that stifles innovation and creativity: the John Conley Lecture. *JAMA Otolaryngol Head Neck Surg* 2014; **140:** 1225–36.
7 Meyers DE, Jenei K, Chisamore TM, Gyawali B. Evaluation of the clinical benefit of cancer drugs submitted for reimbursement recommendation decisions in Canada. *JAMA Intern Med* 2021; **181:** 499–508.
8 Skydel JJ, Egilman AC, Wallach JD, Ramachandran R, Gupta R, Ross JS. Spending by the Centers for Medicare & Medicaid Services before and after confirmation of benefit for drugs granted US Food and Drug Administration accelerated approval, 2012 to 2017. *JAMA Health Forum* 2022; **3:** e221158.
9 Tibau A, Kesselheim AS. Global cooperation and early access-clinical outcomes matter. *Lancet Oncol* 2024; **25:** 687–88.
10 Anderson M, Drummond M, Taylor D, McGuire A, Carter P, Mossialos E. Promoting innovation while controlling cost: the UK's approach to health technology assessment. *Health Policy* 2022; **126:** 224–33.
11 Vokinger KN, Hwang TJ, Carl DL, et al. Price changes and within-class competition of cancer drugs in the USA and Europe: a comparative analysis. *Lancet Oncol* 2022; **23:** 514–20.
12 Miljkovic MD, Tuia J, Olivier T, Haslam A, Prasad V. Cancer drug price and novelty in mechanism of action. *JAMA Netw Open* 2023; **6:** e2347006.
13 Sacco JJ, Botten J, Macbeth F, Bagust A, Clark P. The average body surface area of adult cancer patients in the UK: a multicentre retrospective study. *PLoS One* 2010; **5:** e8933.
14 DeMartino PC, Miljkovic MD, Prasad V. Potential cost implications for all US Food and Drug Administration oncology drug approvals in 2018. *JAMA Intern Med* 2021; **181:** 162–67.
15 Vokinger KN, Hwang TJ, Grischott T, et al. Prices and clinical benefit of cancer drugs in the USA and Europe: a cost-benefit analysis. *Lancet Oncol* 2020; **21:** 664–70.
16 Center for Drug Evaluation and Research. FDA approves dostarlimab-gxly with chemotherapy for endometrial cancer. 2023. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-dostarlimab-gxly-chemotherapy-endometrial-cancer (accessed April 26, 2024).
17 US Food and Drug Administration. Oncology Regulatory Review 2023. https://www.fda.gov/about-fda/2023-oce-annual-report/oncology-regulatory-review-2023 (accessed March 18, 2024).
18 Eglovitch JS. Top FDA official interested in 'Project Orbis' for cell and gene therapies. 2023. https://www.raps.org/News-and-Articles/News-Articles/2023/2/Top-FDA-official-interested-in-Project-Orbis-for-c (accessed March 31, 2024).
19 Oncology Center of Excellence. Project Orbis frequently asked questions. 2022. https://www.fda.gov/about-fda/oncology-center-excellence/project-orbis-frequently-asked-questions (accessed March 18, 2024).
20 Jenei K, Raymakers AJN, Bayle A, et al. Health technology assessment for cancer medicines across the G7 countries and Oceania: an international, cross-sectional study. *Lancet Oncol* 2023; **24:** 624–35.
21 Liu ITT, Kesselheim AS, Cliff ERS. Clinical benefit and regulatory outcomes of cancer drugs receiving accelerated approval. *JAMA* 2024; **331:** 1471–79.
22 Mooghali M, Mohammad A, Wallach JD, Mitchell AP, Ross JS, Ramachandran R. Premarket evidence and postmarketing requirements for real-time oncology review indication approvals. *JAMA Netw Open* 2024; **7:** e249233.
23 Naci H, Zhang Y, Woloshin S, Guan X, Xu Z, Wagner AK. Overall survival benefits of cancer drugs initially approved by the US Food and Drug Administration on the basis of immature survival data: a retrospective analysis. *Lancet Oncol* 2024; **25:** 760–69.
24 National Institute for Health and Care Excellence. Technology appraisal guidance. 2024. https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance (accessed March 22, 2024).
25 Chabot I, Rocchi A. Oncology drug health technology assessment recommendations: Canadian versus UK experiences. *Clinicoecon Outcomes Res* 2014; **6:** 357–67.
26 Scottish Medicines Consortium. Patient and Clinician Engagement (PACE) process. 2024. https://www.scottishmedicines.org.uk/how-we-decide/pace/ (accessed April 25, 2024).
27 Jenei K, Peacock S, Burgess M, Mitton C. Describing sources of uncertainty in cancer drug formulary priority setting across Canada. *Curr Oncol* 2021; **28:** 2708–19.
28 World Health Organization. Pricing of cancer medicines and its impacts. 2018. https://iris.who.int/bitstream/handle/10665/277190/9789241515115-eng.pdf?ua=1 (accessed Nov 9, 2021).
29 Del Paggio JC, Naipaul R, Gavura S, et al. Cost and value of cancer medicines in a single-payer public health system in Ontario, Canada: a cross-sectional study. *Lancet Oncol* 2024; **25:** 431–38.