FDA approval, clinical trial evidence, efficacy, epidemiology, and price for non-orphan and ultra-rare, rare, and common orphan cancer drug indications: cross sectional analysis

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ABSTRACT

OBJECTIVE

To analyze the US Food and Drug Administration (FDA) approval, trials, unmet needs, benefit, and pricing of ultra-rare (‹6600 affected US citizens), rare (6600-200 000 citizens), and common (›200 000 citizens) orphan cancer drug indications and non-orphan cancer drug indications.

DESIGN

Cross sectional analysis.

SETTING

Data from Drugs@FDA, FDA labels, Global Burden of Disease study, and Medicare and Medicaid.

POPULATION

170 FDA approved drugs across 455 cancer indications between 2000 and 2022.

MAIN OUTCOME MEASURES

Comparison of non-orphan and ultra-rare, rare, and common orphan indications regarding regulatory approval, trials, epidemiology, and price. Hazard ratios for overall survival and progression-free survival were meta-analyzed.

RESULTS

161 non-orphan and 294 orphan cancer drug indications were identified, of which 25 were approved for ultra-rare diseases, 205 for rare diseases, and 64 for common diseases. Drugs for ultra-rare orphan indications were more frequently first in class (76% *v* 48% *v* 38% *v* 42%; P‹0.001), monotherapies (88% *v* 69% *v* 72% *v* 55%; P=0.001), for hematologic cancers (76% *v* 66% *v* 0% *v* 0%; P‹0.001), and supported by smaller trials (median 85 *v* 199 *v* 286 *v* 521 patients; P‹0.001), of single arm (84% *v* 44% *v* 28% *v* 21%; P‹0.001) phase 1/2 design (88% *v* 45% *v* 45% *v* 27%; P‹0.001) compared with rare and common orphan indications and non-orphan indications. Drugs for common orphan indications were more often biomarker directed (69% *v* 26% *v* 12%; P‹0.001), first line (77% *v* 39% *v* 20%; P‹0.001), small molecules (80% *v* 62% *v* 48%; P‹0.001) benefiting from quicker time to first FDA approval (median 5.7 *v* 7.1 *v* 8.9 years; P=0.02) than those for rare and ultra-rare orphan indications. Drugs for ultra-rare, rare, and common orphan indications offered a significantly greater progression-free survival benefit (hazard ratio 0.53 *v* 0.51 *v* 0.49 *v* 0.64; P‹0.001), but not overall survival benefit (0.50 *v* 0.73 *v* 0.71 *v* 0.74; P=0.06), than non-orphans. In single arm trials, tumor response rates were greater for drugs for ultra-rare orphan indications than for rare or common orphan indications and non-orphan indications (objective response rate 57% *v* 48% *v* 55% *v* 33%; P‹0.001). Disease incidence/prevalence, five year survival, and the number of available treatments were lower, whereas disability adjusted life years per patient were higher, for ultra-rare orphan indications compared with rare or common indications and non-orphan indications. For 147 on-patent drugs with available data in 2023, monthly prices were higher for ultra-rare orphan indications than for rare or common orphan indications and non-orphan indications ($70 128 (£55 971; €63 370) *v* $33 313 *v* $16 484 *v* $14 508; P‹0.001). For 48 on-patent drugs with available longitudinal data from 2005 to 2023, prices increased by 94% for drugs for orphan indications and 50% for drugs for non-orphan indications on average.

CONCLUSIONS

The Orphan Drug Act of 1983 incentivizes development of drugs not only for rare diseases but also for ultra-rare diseases and subsets of common diseases. These orphan indications fill significant unmet needs, yet their approval is based on small, non-robust trials that could overestimate efficacy outcomes. A distinct ultra-orphan designation with greater financial incentives could encourage and expedite drug development for ultra-rare diseases.

WHAT IS ALREADY KNOW ON THIS TOPIC

The Orphan Drug Act (ODA) of 1983 incentivizes drug development for serious conditions affecting fewer than 200 000 US citizens

Orphan drugs are often supported by small, single arm, non-randomized trials measuring surrogate rather than clinical endpoints

Orphan drug prices are a leading contributor to growing healthcare expenditure in the US, with unaffordable drugs' financial toxicity adversely affecting adherence to treatment

WHAT THIS STUDY ADDS

Orphan drugs fill significant unmet needs, but their approval is supported by small, non-robust trials for which manufacturers demand prices beyond $30 000 per month

The Orphan Drug Act incentivizes drug development not only for rare diseases but also for ultra-rare diseases and subsets of common diseases

Common orphan drugs benefit from all of the ODA's incentives, although developing and seeking approval for ultra-rare and rare orphan drugs is more complex

Introduction

The Orphan Drug Act, passed in 1983, aims to facilitate and financially incentivize the research and development of drugs for rare diseases with fewer than 200 000 affected US citizens.[1] The Orphan Drug Act incentives include research grants for conducting clinical trials, tax credits of 25%, exemption from US Food and Drug Administration (FDA) user fees, and an

enhanced marketing exclusivity of up to seven years after regulatory approval.[1]

Celebrated as (potentially) the best healthcare legislation of the 20th century, the Orphan Drug Act encouraged the development of 6144 drug indications, of which 1035 received FDA approval since 1983 (supplementary figure A). However, voices calling for reform of the Orphan Drug Act to keep pace with the biotechnological innovation and commercialization strategies of the 21th century are growing.[2-7]

Advancements in precision medicine enabled drug companies to develop targeted treatments for rare diseases. With the rise of this personalized medicine, companies also began to "slice" common diseases into multiple narrow indications. According to the FDA's interpretation, "orphan subset[s] of a non-rare disease" are eligible to receive the orphan designation.[8] The FDA has the power to grant the orphan designation not only to drugs treating rare diseases with fewer than 200 000 affected US citizens but also to drugs treating common diseases "for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug."[1] However, biomarker defined subsets of common diseases were especially identified as a misfit to the Orphan Drug Act's intention.[7 9 10] These orphan drugs for common diseases are criticized as benefiting from the act's expedited development timelines and swift expansion to non-orphan indications, resulting in considerable revenues for manufacturers,[9 10] while shifting the FDA's and taxpayers' resources away from truly rare or even ultra-rare diseases.

A public debate surrounds the safety, efficacy, and affordability of orphan drugs. Orphan drugs are frequently supported by small, non-randomized clinical trials assessing surrogate endpoints,[11-13] as competent investigators, sufficient funding, and the right patients for trials of orphan drugs are lacking.[14] However, biased and small trials were found to overstate efficacy outcomes and lead to unknown side effects at the time of FDA approval.[15-17] Drug companies pursue orphan drugs as "an economically viable strategy" with high profit margins and firm valuations resulting from governmental incentives, smaller and shorter clinical trials, and higher success rates,[18-21] but insurers are often reluctant to reimburse highly priced orphan drugs with an uncertain efficacy.[22] Trapped between corporates' financial interests, patients are too often denied access to promising, yet unaffordable, new treatments.

The purpose of this study was to compare orphan and non-orphan cancer drug indications (original and supplemental) regarding their FDA approval, trial evidence, unmet needs, and pricing. We defined and compared subsets of common, rare, and ultra-rare orphan indications to refine the Orphan Drug Act.

Methods

Sample identification

We accessed the Drugs@FDA database to identify all new drugs, including new drug applications and biologics license applications, with FDA approval between 1 January 2000 and 1 January 2022. Before 2000, the FDA label structure was inconsistent with newer approvals. We then restricted the sample to include only anticancer drugs, excluding non-oncology, supportive care, and diagnostic agents, but including chimeric antigen receptor T cell therapies. For each drug, we accessed the Drugs@FDA database to identify all original and supplemental anticancer indications approved until 1 January, 2022.

We used the FDA's orphan drug database to link the orphan designation status to each indication (supplementary table A). We stratified orphan indications according to the number of affected US citizens into common (>200 000), rare (6600-200 000), or ultra-rare (<6600). Coherent with health technology assessment agencies in the UK (Scottish Medicines Consortium and National Institute for Health and Care Excellence),[23 24] we defined the threshold for ultra-rare diseases on the basis of a prevalence rate of 1 in 50 000 US citizens.

Data collection

We accessed public data sources to collect information characterizing each drug indication's FDA approval, clinical trial evidence, cancer epidemiology, and price (supplementary table A).

FDA approval

We reviewed FDA labels for each anticancer indication to collect data on drug, indication, and clinical trial characteristics. The first reviewer (DTM) independently retrieved data from FDA labels, which the second reviewer (TM) then cross checked with data found on clinicaltrials.gov and associated peer reviewed publications. Disagreements were resolved in consensus or by consulting an experienced oncologist (TB). Full details of the data extraction method have been described elsewhere,[25] adhering to peer reviewed guidelines for evidence synthesis from FDA documents.[26 27]

We categorized drugs by their number of indications (single indication versus multi-indication), innovativeness (first in class versus not first in class), mechanism of action (cytotoxic chemotherapy versus targeted agents versus immune regulators), and product type (small molecule versus antibody versus antibody-drug conjugate versus other). For multi-indication drugs, we classified FDA approvals as original and supplemental indications. We then categorized indications by treatment regimen (monotherapy versus combination), cancer type (solid versus hematologic), biomarker status, and line of therapy (first line versus second line versus third line or higher). We characterized each indication's pivotal trial by the number of enrolled patients, phase, design (randomized concurrent versus randomized dose comparison versus non-randomized versus single arm), blinding (open label versus single blind versus double blind), number of arms, comparator (no treatment or placebo versus active comparator),

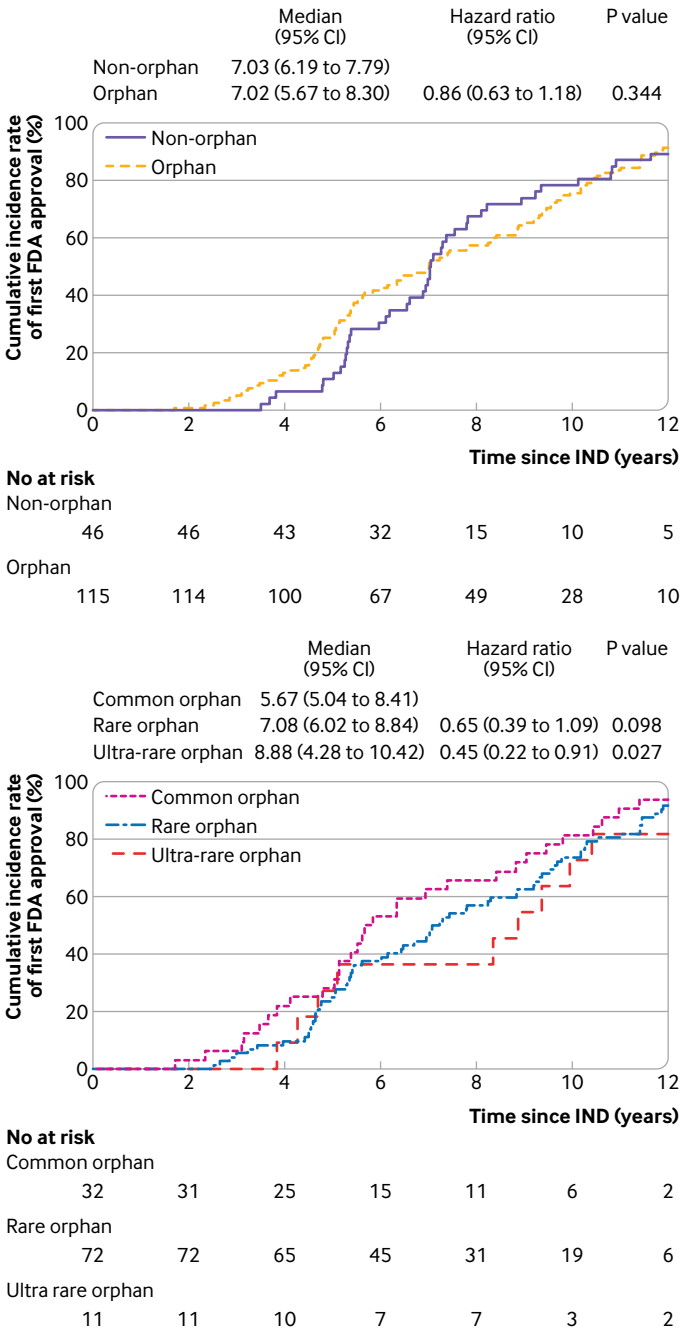

Fig 1 | Time from investigational new drug application (IND) to first Food and Drug Administration (FDA) approval for non-orphan anticancer drugs and orphan anticancer drugs for ultra-rare, rare, and common diseases. Top: cumulative incidence of first FDA approval for anticancer drugs with orphan and non-orphan designation. Bottom: cumulative incidence of first FDA approval for anticancer drugs with orphan designations for common, rare, and ultra-rare diseases. Orphan indications were stratified according to number of affected US citizens into common (›200 000), rare (200 000-6600), or ultra-rare (‹6600). Only drugs receiving FDA approval within 12 years of IND are shown. CI=confidence interval

and endpoint. For indications supported by multiple clinical trials, we retrieved data for the largest and highest phase trial. Among randomized controlled trials, we extracted hazard ratios for overall survival and/or progression-free survival and/or the relative risk of tumor response with 95% confidence intervals. We noted the number of participants and events for the control and intervention arms. We calculated median improvements in overall survival, progression-free survival, and duration of tumor response with interquartile ranges. For single arm trials, we noted the objective response rate based on the number of responders and enrolled patients.

Cancer epidemiology

For each indication, we retrieved data on the treated cancer's incidence, prevalence, and disability adjusted life years, comprising years lived with disability and years of life lost, from the Global Burden of Disease study.[28] Five year survival rates and the number of available treatment options per cancer entity came from the National Cancer Institute.

Drug prices

We retrieved drug prices in January 2023 from the Centers for Medicare and Medicaid Services and Medicare's plan finder tool for the average patient covered under Medicare Part B and D. Coherent with previous studies,[29-33] we estimated monthly treatment costs for the average adult living in New York (ZIP code 10065) covered under the "Humana Basic Rx Plan" with a body surface area of 1.7 m^2 weighing 70 kg based on the dosing regimen defined in the respective FDA label. Full details of the drug price calculation have been described elsewhere.[34]

Statistical analysis

We compared non-orphan and ultra-rare, rare, and common orphan cancer drug indications regarding their time to approval, drug, indication, clinical trial and epidemiologic characteristics, and efficacy, as well as price. We compared the time to approval, calculated as the difference between investigational new drug application to new drug application/biologics license application approval, in a Cox regression model. We used Fisher's exact tests to compare the distribution of categorical variables. We compared medians with Kruskal-Wallis-tests. We meta-analyzed overall survival, progression-free survival, and relative risk outcomes in random effects regressions for randomized controlled trials and objective response rate outcomes for single arm trials. We compared differences between orphan and non-orphan indications with Cochran's Q test. For on-patent drugs with available data, we compared mean monthly prices in January 2023 by using Student's *t* test and analysis of variance. We calculated the compounded annual growth rate of drug prices from 2005 to 2023. We stored data in Microsoft Excel and analyzed data with Stata 14.2. We considered two tailed P values below 0.05 to be significant. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline when applicable.[35]

Patient and public involvement

Owing to lack of funding, no patients or members of the public were directly involved in the design,

Table 1 | Characteristics of orphan and non-orphan cancer drug indications approved by US Food and Drug Administration (FDA) from 2000 to 2022. Values are numbers (percentages) unless stated otherwise

	Orphan designation		
	No (n=161; 35.4%)	Yes (n=294; 64.6%)	P value*
Drug characteristics			
No of indications:			0.04
Single indication	19 (12)	58 (20)	
Multi-indication	142 (88)	236 (80)	
Innovativeness:			0.24
Not first in class	93 (58)	152 (52)	
First in class	68 (42)	142 (48)	
Mechanism of action:			0.47
Cytotoxic chemotherapy	11 (7)	21 (7)	
Targeted agents	91 (57)	182 (62)	
Immune regulators	59 (37)	91 (31)	
Product type			<0.001
Small molecule	73 (45)	189 (64)	
Antibody	79 (49)	76 (26)	
Antibody-drug conjugate	8 (5)	15 (5)	
Other†	1 (1)	14 (58)	
Indication characteristics			
FDA approval type:			0.007
Original indication	50 (31)	130 (44)	
Supplemental indication	111 (69)	164 (56)	
Treatment type:			<0.001
Combination therapy	73 (45)	84 (29)	
Monotherapy	88 (55)	210 (71)	
Cancer type:			<0.001
Hematologic	0 (0)	154 (52)	
Solid	161 (100)	140 (48)	
Biomarker:			0.19
No	95 (59)	193 (66)	
Yes	66 (41)	101 (34)	
Line of therapy:			0.001
First line	84 (52)	133 (45)	
Second line	69 (43)	114 (398)	
≥Third line	8 (5)	47 (16)	
Clinical trial characteristics			
Median (IQR) enrolled patients	521 (219-793)	187 (97-424)	<0.001
Clinical trial phase:			<0.001
Phase 1	6 (4)	15 (5)	
Phase 2	38 (24)	130 (44)	
Phase 3	117 (73)	149 (51)	
Trial design:			<0.001
Single arm	34 (21)	129 (44)	
Non-randomized	1 (1)	7 (2)	
Concurrent RCT	122 (76)	152 (527)	
Dose comparison RCT	4 (2)	6 (2)	
Type of blinding:			0.02
Open label	109 (68)	229 (78)	
Single blind	0 (0)	1 (<1)	
Double blind	52 (32)	64 (22)	
Clinical trial arms:			<0.001
1 arm	34 (21)	129 (44)	
2 arms	121 (75)	156 (53)	
≥3 arms	6 (4)	9 (3)	
Total No of concurrent RCTs	122	152	
Comparator:			0.26
Active agent	51 (42)	53 (35)	
Placebo/no treatment	71 (59)	99 (65)	
Endpoint for concurrent RCTs:			
Overall survival	104 (85)	100 (66)	<0.001
Progression-free survival	102 (84)	120 (79)	0.338
Tumor response	96 (79)	123 (81)	0.65
Other	17 (14)	17 (11)	0.49
Cancer epidemiology			
Median (IQR) disease incidence‡	67.6 (18.8-77.6)	7.1 (2.3-9.8)	<0.001
Median (IQR) disease prevalence‡	117.8 (111.2-832.8)	24.2 (7.1-35.4)	<0.001

(*Continued*)

conduct, or reporting of this study. A member of the public was, however, asked to read the manuscript after submission.

Results

The FDA approved 720 new drugs from 2000 until 2022, 170 of which were anticancer treatments (supplementary figure B). For these 170 anticancer drugs, we identified a total of 455 original and supplemental indication approvals until 2022 (supplementary table B). Of these, the FDA granted the orphan designation to 294 (65%) indications: 64 (15%) for common diseases, 205 (48%) for rare diseases, and 25 (6%) for ultra-rare diseases.

Time to approval

The time from investigational new drug application to first FDA approval was similar for orphan and non-orphan drugs (median 7.0 *v* 7.0 years; P=0.29) (fig 1). Orphan drugs for common diseases were approved earlier than those for rare and ultra-rare diseases (median 5.7 *v* 7.1 *v* 8.9 years).

Drug characteristics

Drugs for orphan and non-orphan indications did not differ significantly in their innovativeness or mechanism of action (table 1). However, the orphan designation was more frequently granted to small molecules (64% *v* 45%; P<0.001). In particular, drugs for common orphan indications were predominantly small molecules (80% *v* 62% *v* 48%; P<0.001) acting via a targeted mechanism of action (84% *v* 56% *v* 52%; P<0.001) relative to those for rare and ultra-rare orphan indications, respectively (table 2). Drugs for ultra-rare orphan indications were more innovative than those for rare and common orphan indications, given the greater percentage of first-in-class molecules (76% *v* 48% *v* 38%; P=0.006).

Indication characteristics

Original FDA drug approvals were more likely to receive the orphan designation than supplemental indications (44% *v* 31%; P=0.007). The FDA more frequently granted the orphan designation to monotherapy treatments (71% *v* 55%; P<0.001) for hematologic cancers (52% *v* 0%; P<0.001) in the third line setting (16% *v* 5%; P=0.001). The proportion of monotherapy treatments (55% *v* 72% *v* 69% *v* 88%; P=0.001) for hematologic cancers (0% *v* 0% *v* 66% *v* 76%; P<0.001) in the third line of therapy (5% *v* 0% *v* 20% *v* 20%; P<0.001) increased from non-orphan to common, rare, and ultra-rare orphan indications, respectively. Drugs for ultra-rare orphan indications were predominantly approved for treating lymphoma or skin cancer, whereas those for common orphan indications were mostly approved for subsets of lung or skin cancer (supplementary table C). Biomarker based approvals were frequently observed for common orphan (69%) and non-orphan indications (41%) but not for rare (26%) or ultra-rare (12%, P<0.001) orphan indications.

Table 1 | Continued

	Orphan designation		
	No (n=161; 35.4%)	Yes (n=294; 64.6%)	P value*
Median (IQR) DALYs per person	7.1 (5.5-7.7)	10.8 (6.4-16.4)	<0.001
Median (IQR) YLL per person	6.6 (4.8-7.2)	10.5 (5.9-16.2)	<0.001
Median (IQR) YLD per person	0.5 (0.2-0.7)	0.5 (0.3-0.6)	0.61
Median (IQR) 5 year survival rate, %	76.4 (66.2-91.4)	66.1 (30.5-88.9)	<0.001
Median (IQR) No of available treatments	18 (12-38)	14 (11-22)	0.03

DALY=disability adjusted life year; IQR=interquartile range; RCT=randomized controlled trial; YLD=years of healthy life lost due to disability; YLL=years of life lost due to premature death.
*Fisher's exact tests or Kruskal-Wallis tests.
†Includes gene therapies, cell therapies, enzymes, and radionuclides.
‡Disease incidence and prevalence rates per 100 000 US citizens.

Clinical trial characteristics

Clinical trials enrolled a median of 187 (interquartile range 97-424) patients for orphan indications compared with 521 (219-793; P<0.001) patients for non-orphan indications. Median trial size was 521, 286, 199, and 85 patients for non-orphan and common, rare, and ultra-rare orphan indications (P<0.001). Orphan indications were less often supported by concurrent randomized controlled trials (52% *v* 76%; P<0.001) of phase 3 design (51% *v* 73%; P<0.001). The share of double blind (32% *v* 33% *v* 20% *v* 4%; P=0.002) concurrent randomized controlled trials (76% *v* 59% *v* 54% *v* 16%; P<0.001) of phase 3 design (73% *v* 55% *v* 54% *v* 12%; P<0.001) diminished from non-orphan to common, rare, and ultra-rare orphan indications, respectively. Concurrent randomized controlled trials for orphan indications less often included an assessment of overall survival (85% *v* 66%; P<0.001). Temporal differences in the FDA approval of orphan cancer drug indications are shown in supplementary table D

Cancer epidemiology

Drugs for orphan indications treated diseases with a lower prevalence (median 24 *v* 118 per 100 000 US citizens; P<0.001) compared with non-orphan indications. Orphan diseases were more severe, as measured by disability adjusted life years (median 11 *v* 7 per patient; P<0.001) and five year survival (median 66% *v* 76%; P<0.001). The median prevalence per 100 000 was similar for non-orphan (118) and common orphan indications (118) but significantly lower for rare (15) and ultra-rare orphan indications (3; P<0.001). Accordingly, disability adjusted life years were higher and five survival lower for rare and ultra-rare orphan indications than for non-orphan and common orphan indications. Fewer treatment options were available for ultra-rare orphan than non-orphan indications (median 8 *v* 18; P<0.001).

Special FDA review

A total of 105 (23%), 358 (78%), 147 (32%), and 137 (39%) indications received fast track, priority review, accelerated approval, and breakthrough therapy designation, respectively (supplementary table E). Orphan indications were significantly more likely than non-orphan indications to receive fast track review (26% *v* 17%; P=0.04). Common (57%) and ultra-rare orphan indications (77%) were more frequently granted the breakthrough designation than were rare (30%) and non-orphan indications (34%; P<0.001).

Overall survival, progression-free survival, and tumor response

Drugs for orphan indications did not prevent more deaths than those for non-orphan indications (hazard ratio 0.72 *v* 0.74; P=0.18) and did not provide a superior survival benefit (median 3.3 *v* 2.8 months; P=0.38) (fig 2). Progression-free survival was 13% greater for orphan than non-orphan indications (hazard ratio 0.51 *v* 0.64; P<0.001), with a 1.5 months greater survival gain (median 4.2 *v* 2.7; P=0.01) (fig 3). Accordingly, drugs for ultra-rare, rare, and common orphan indications offered a significantly greater progression-free survival benefit (hazard ratio 0.53 *v* 0.51 *v* 0.49 *v* 0.64; P<0.001), but not overall survival benefit (0.50 *v* 0.73 *v* 0.71 *v* 0.74; P=0.06), than those for non-orphan indications. By contrast, tumor response rates among randomized controlled trials were lower for orphan compared with non-orphan indications (relative risk 1.29 *v* 1.53; P<0.001) (fig 4). However, mean tumor response rates in single arm trials were greater for orphan than non-orphan indications (objective response rate 51% *v* 33%; P<0.001) (fig 5). Similarly, tumor response rates were greater for ultra-rare orphan indications than for rare or common orphan indication and non-orphan indications in single arm trials (objective response rate 57% *v* 48% *v* 55% *v* 33%; P<0.001). Details of the full meta-analyses, including individual effect sizes for each trial, can be found in supplementary figures C, D, and E.

Drug prices

Of 170 drugs approved by the FDA, 22 lost their exclusivity by the first quarter of 2023 and price data were not available for one drug. For the resulting sample of 147 on-patent drugs with available data, we compared prices across original indication approvals. Mean monthly prices were 128% higher for drugs for orphan indications ($33 070 (£26 438; €29 935), 95% confidence interval $24 048 to $42 091) relative to those for non-orphan indications ($14 508, $11 494 to $17 522; P=0.02) (fig 6). Mean monthly drug prices were $70 128 for ultra-rare, $33 313 for rare, and $16 484 for common orphan indications and $14 508 for non-orphan indications (P<0.001) (fig 7).

Quarterly drug price data were available for 48 drugs covered under Medicare Part B. From 2005 to 2023, drug prices increased by an average of 94% for orphan indications and 50% for non-orphan indications. Drug prices for rare orphan indications rose by 102% compared with 49% for common orphan indications. Although inflation amounted to 2.2%, drug prices increased by a compounded annual growth rate of 3.5% for orphan indications (rare 3.7%; common 2.1%) and 2.2% for non-orphan indications.

Table 2 | Characteristics of non-orphan and ultra-rare, rare, and common orphan cancer drug indications approved by US Food and Drug Administration (FDA) from 2000 to 2022. Values are numbers (percentages) unless stated otherwise

		Orphan			
	Non-orphan (n=161; 37.4%)	Common (n=64; 14.9)	Rare (n=205; 47.7%)	Ultra-rare (n=25; 5.8%)	P value*
Drug characteristics					
No of indications:					0.08
Single indication	19 (12)	14 (22)	37 (18)	7 (28)	
Multi-indication	142 (88)	50 (78)	168 (82)	18 (72)	
Innovativeness:					0.006
Not first in class	93 (58)	40 (63)	106 (52)	6 (24)	
First in class	68 (42)	24 (38)	99 (48)	19 (76)	
Mechanism of action:					<0.001
Cytotoxic chemotherapy	11 (7)	0 (0)	21 (10)	0 (0)	
Targeted agents	91 (57)	54 (84)	115 (56)	13 (52)	
Immune regulators	59 (37)	10 (16)	69 (34)	12 (48)	
Product type					<0.001
Small molecule	73 (45)	51 (80)	126 (61)	12 (48)	
Antibody	79 (49)	12 (19)	57 (28)	7 (28)	
Antibody-drug conjugate	8 (5)	0 (0)	12 (6)	3 (12)	
Other†	1 (1)	1 (26)	10 (5)	3 (12)	
Indication characteristics					
FDA approval type:					0.005
Original indication	50 (31)	35 (55)	82 (40)	13 (52)	
Supplemental indication	111 (69)	29 (45)	123 (60)	12 (48)	
Treatment type:					0.001
Combination therapy	73 (45)	18 (28)	63 (31)	3 (12)	
Monotherapy	88 (55)	46 (729)	142 (69)	22 (88)	
Cancer type:					<0.001
Hematologic	0 (0)	0 (0)	135 (66)	19 (76)	
Solid	161 (100)	64 (100)	70 (34)	6 (24)	
Biomarker:					<0.001
No	95 (59)	20 (31)	151 (74)	22 (88)	
Yes	66 (41)	44 (69)	54 (26.3)	3 (12)	
Line of therapy:					<0.001
First line	84 (52)	49 (77)	79 (39)	5 (20)	
Second line	69 (43)	15 (23)	84 (41)	15 (60)	
≥Third line	8 (5)	0 (0)	42 (20)	5 (20)	
Clinical trial characteristics					
Median (IQR) enrolled patients	521 (219-793)	286 (122-505)	199 (98-447)	85 (53-124)	<0.001
Clinical trial phase:					<0.001
Phase 1	6 (4)	5 (8)	9 (4)	1 (4)	
Phase 2	38 (24)	24 (38)	85 (41)	21 (84)	
Phase 3	117 (73)	35 (55)	111 (54)	3 (12)	
Trial design:					<0.001
Single arm	34 (21)	18 (28)	90 (44)	21 (84)	
Non-randomized	1 (1)	6 (9)	1 (<1)	0 (0)	
Concurrent RCT	122 (76)	38 (59)	110 (54)	4 (16)	
Dose comparison RCT	4 (2)	2 (3)	4 (2)	0 (0)	
Type of blinding:					0.002
Open label	109 (68)	43 (67)	162 (79)	24 (96)	
Single blind	0 (0)	0 (0)	1 (<1)	0 (0)	
Double blind	52 (32)	21 (33)	42 (20)	1 (4)	
Clinical trial arms:					<0.001
1 arm	34 (21)	18 (28)	90 (44)	21 (84)	
2 arms	121 (75)	41 (64)	111 (54)	4 (16)	
≥3 arms	6 (4)	5 (8)	4 (2)	0 (0)	
Total No of concurrent RCTs	122	38	110	4	
Comparator:					0.62
Active agent	51 (42)	15 (39)	37 (34)	1 (25)	
Placebo/no treatment	71 (59)	23 (61)	73 (66)	3 (75)	
Endpoint for concurrent RCTs:					
Overall survival	104 (85)	25 (66)	73 (66)	2 (50)	0.003
Progression-free survival	102 (84)	29 (76)	89 (81)	2 (50)	0.30
Tumor response	96 (79)	31 (82)	89 (81)	3 (75)	0.96
Other	17 (14)	6 (16)	11 (10)	0 (0)	0.62
Cancer epidemiology					
Median (IQR) disease incidence‡	68.4 (18.8-77.6)	25 (19.5-67.6)	5.2 (1.5-8.2)	0.9 (0.2-4.3)	<0.001
Median (IQR) disease prevalence‡	117.8 (111.2-832.8)	117.8 (111.2-198.6)	15.3 (6.5-27.3)	3.2 (0.9-15)	<0.001
Median (IQR) DALYs per person	7.1 (5.5-7.7)	5.5 (3.8-16.4)	12.1 (7.3-17.7)	10 (10-10)	<0.001

(*Continued*)

Table 2 | Continued

		Orphan			
	Non-orphan (n=161; 37.4%)	Common (n=64; 14.9)	Rare (n=205; 47.7%)	Ultra-rare (n=25; 5.8%)	P value*
Median (IQR) YLL per person	6.6 (4.8-7.2)	4.8 (3.3-16.2)	11.8 (6.8-17.4)	9.3 (9.3-9.3)	<0.001
Median (IQR) YLD per person	0.5 (0.4-0.7)	0.5 (0.2-0.5)	0.5 (0.3-0.7)	0.7 (0.7-0.7)	<0.001
Median (IQR) 5 year survival rate, %	76.4 (66.2-91.4)	91.4 (25-95)	65 (32.7-75.2)	66.1 (50-75.2)	<0.001
Median (IQR) No of available treatments	18 (12-38)	14 (14-38)	15 (11-22)	8 (7-17)	<0.001

DALY=disability adjusted life year; IQR=interquartile range; RCT=randomized controlled trial; YLD=years of healthy life lost due to disability; YLL=years of life lost due to premature death.
*Fisher's exact tests or Kruskal-Wallis tests.
†Includes gene therapies, cell therapies, enzymes, and radionuclides.
‡Disease incidence and prevalence rates per 100 000 US citizens.

Discussion

This review of 170 anticancer drugs approved across 455 indications from 2000 to 2022 identified significant differences in the FDA approval, treatment characteristics, efficacy, clinical trial design, and pricing of drugs for orphan and non-orphan cancer indications. We shine light on three distinct groups of orphan drug indications: common, rare, and ultra-rare orphan indications.

Orphan versus non-orphan anticancer drug indications

The US Congress introduced the Orphan Drug Act to incentivize drug development for rare diseases with limited sales potential. Unsurprisingly, we found that the orphan designation was granted to rare diseases with significant unmet needs. However, the Orphan Drug Act enabled the FDA to approve drugs for orphan indications on the basis of small, non-randomized, open label trials. This flexibility in clinical trial design accommodates for the complexity of conducting trials for rare diseases. However, small non-randomized trials are likely a cause for unobserved side effects among drugs for orphan indications.[17] Moreover, meta-epidemiologic studies found non-robust outcomes and small trial designs could overestimate and thereby bias efficacy outcomes.[15 16] The higher proportion of open label randomized controlled trails comparing the new drug with an inactive comparator could thus partially explain the greater progression-free survival outcomes with drugs for orphan indications than for non-orphan indications. Testing orphan drugs on a large population is difficult, but the FDA, drug manufacturers, and investigators should strive to adhere to the hallmarks of high quality trials: randomization, active comparators, and blinding.[11]

Common orphan indications

In this study, we defined common orphan drug indications as those that treat diseases or subgroups of diseases with more than 200 000 affected US citizens. Similarly to previous studies, we found that these subgroups were often defined by biomarker directed targeted therapies for solid cancers.[79] We showed that conducting clinical trials is less complex for common than rare orphan indications. With the widespread adoption of biomarker screening programs for highly prevalent cancers, such as lung or skin cancer, manufacturers have less difficulty recruiting a sufficient number of patients to conduct large randomized double blinded trials for common orphan indications, which may ultimately lead to the observed shortened development timelines. However, drugs for common orphan indications secure all of the Orphan Drug Act's advantages, including the FDA's $3.1m user fee waiver. Critiques argue that "salami slicing"

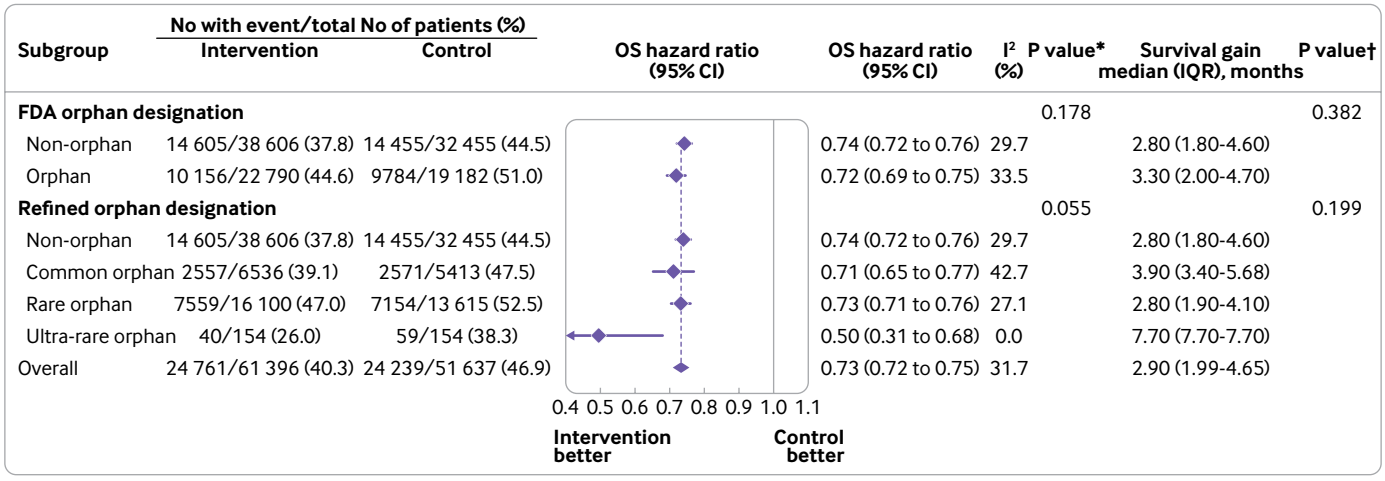

Fig 2 | Meta-analysis of overall survival (OS) for anticancer drugs for ultra-rare, rare, and common orphan indications and non-orphan indications approved by Food and Drug Administration (FDA) from 2000 to 2022. Treatment outcomes were meta-analyzed for randomized controlled trials. Orphan indications were stratified according to number of affected US citizens into common (>200 000), rare (200 000-6600), or ultra-rare (<6600). CI=confidence interval; IQR=interquartile range. *Cochran's Q test for subgroup differences. †Kruskal-Wallis-tests

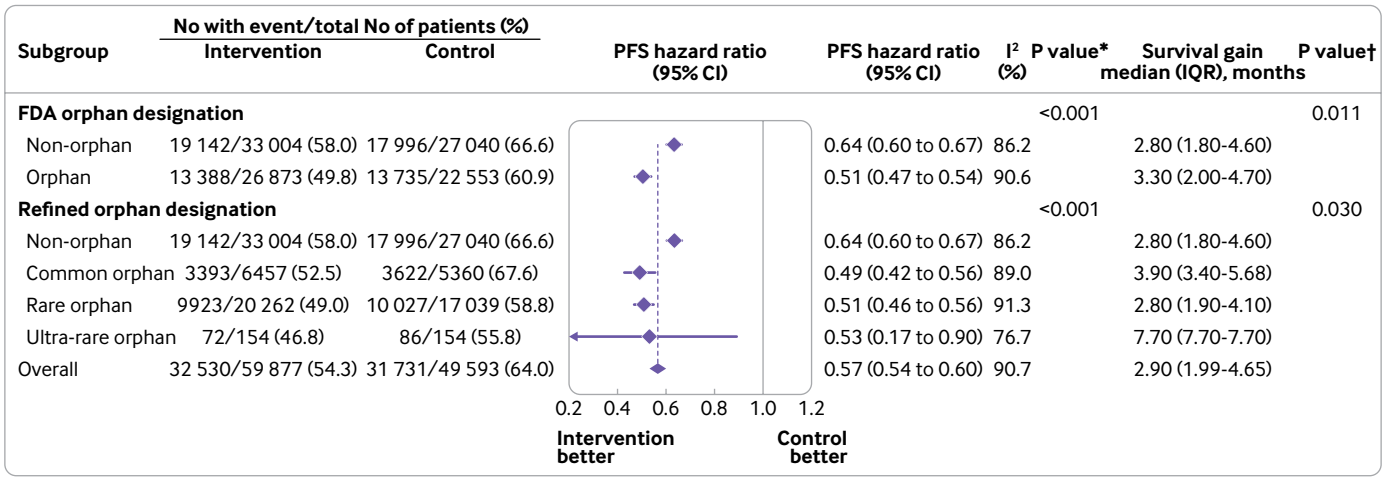

Fig 3 | Meta-analysis of progression-free survival (PFS) for anticancer drugs for ultra-rare, rare, and common orphan indications and non-orphan indications approved by Food and Drug Administration (FDA) from 2000 to 2022. Treatment outcomes were meta-analyzed for randomized controlled trials. Orphan indications were stratified according to number of affected US citizens into common (›200 000), rare (200 000-6600), or ultra-rare (‹6600). CI=confidence interval; IQR=interquartile range. *Cochran's Q test for subgroup differences. †Kruskal-Wallis-tests

common diseases into orphan indications with faster clinical development times and rapid expansion to non-orphan use makes them "ill suited" for the Orphan Drug Act.[2 6 9]

This study highlights that the clinical, epidemiologic, and economic characteristics of biomarker defined subgroups of common diseases are distinctly different from truly rare cancers or metabolic disorders. Therefore, the Orphan Drug Act's current definition and implementation of rare diseases should be re-evaluated. Instead of defining orphan indications on the basis of the number of patients who are biomarker positive for a single cancer type, the entire number of biomarker positive patients across all cancers represents a drug's true potential market.[9] For instance, drugs treating the BRAF mutation would be considered orphan only if fewer than 200 000 patients had BRAF mutations across all tumor entities, not just skin cancer. Thereby, fewer resources would be wasted on drugs not intended for the orphan designation—for example, those that effortlessly recover their research and development cost with multi-million dollar revenues through commercialization across multiple indications.

Ultra-rare orphan indications

In England and Scotland, ultra-rare indications are defined as diseases affecting a population of 1 in 50 000 (approximately 6600 citizens in the US).[23 24] In this study only 25 (6%) drugs for cancer indications were approved to treat ultra-rare diseases. Although the Orphan Drug Act was impressively effective at incentivizing drug development for rare diseases, conducting clinical trials and commercializing drugs

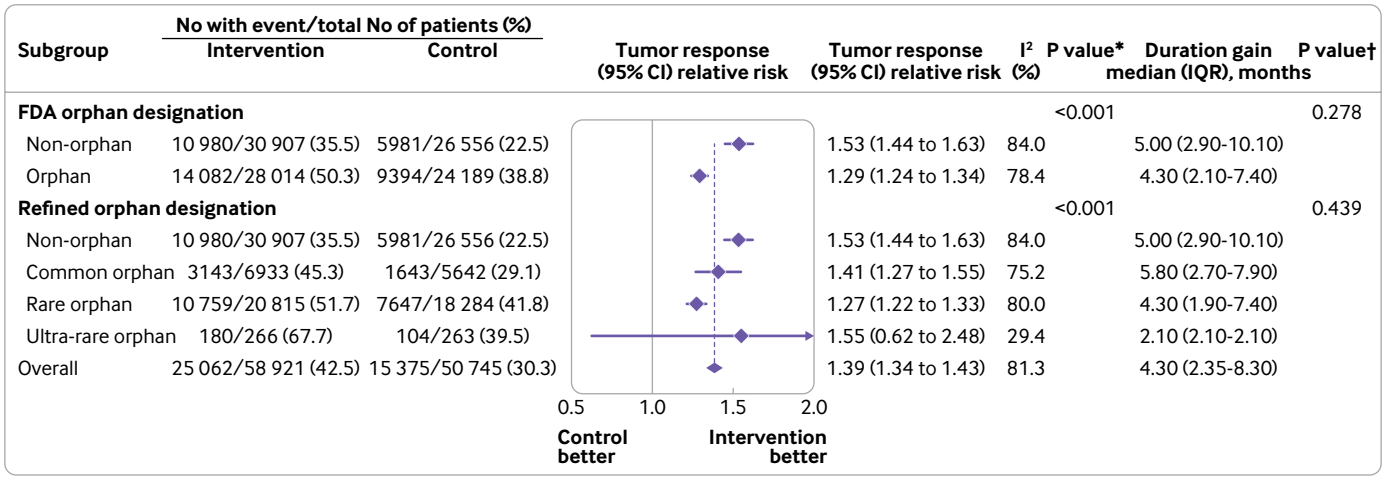

Fig 4 | Meta-analysis of tumor response for anticancer drugs for ultra-rare, rare, and common orphan indications and non-orphan indications approved by Food and Drug Administration (FDA) from 2000 to 2022. Treatment outcomes were meta-analyzed for randomized controlled trials. Orphan indications were stratified according to number of affected US citizens into common (›200 000), rare (200 000-6600), or ultra-rare (‹6600). Continuity adjustment of 0.5 for control arms with 0 responders was applied. CI=confidence interval; IQR=interquartile range. *Cochran's Q test for subgroup differences. †Kruskal-Wallis-tests

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Subgroup	Responders	No of patients	Tumor response (95% CI) objective response rate, %	Tumor response (95% CI) objective response rate, %	I^2 (%)	P value*	Duration of response median (IQR), months	P value†
FDA orphan designation						<0.001		0.188
Non-orphan	1395	4580		32.5 (28.2 to 36.8)	91.2		8.30 (7.20-13.80)	
Orphan	6149	12 396		50.7 (46.4 to 55.0)	96.7		10.96 (8.20-13.60)	
Refined orphan designation						<0.001		0.268
Non-orphan	1395	4580		32.5 (28.2 to 36.8)	91.2		8.30 (7.20-13.80)	
Common orphan	1221	2326		54.6 (48.7 to 60.5)	88.4		11.11 (10.00-17.50)	
Rare orphan	3976	8353		48.0 (42.3 to 53.7)	97.3		10.95 (7.85-13.05)	
Ultra-rare orphan	952	1717		56.9 (47.4 to 66.4)	94.8		9.80 (7.70-18.50)	
Overall	7544	16 976		46.5 (42.8 to 50.3)	96.8		10.42 (7.75-13.70)	

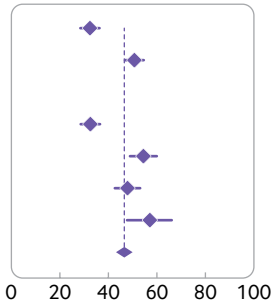

Fig 5 | Meta-analysis of tumor response for anticancer drugs for ultra-rare, rare, and common orphan indications and non-orphan indications approved by Food and Drug Administration (FDA) from 2000 to 2022, showing average tumor response rates measured in single arm trials. Orphan indications were stratified according to number of affected US citizens into common (>200 000), rare (200 000-6600), or ultra-rare (<6600). Continuity adjustment of 0.5 for control arms with 0 responders was applied. CI=confidence interval; IQR=interquartile range, *Cochran's Q test for subgroup differences. †Kruskal-Wallis-tests

for ultra-rare diseases remain challenging.[36] A median of merely 85 patients were enrolled in trials for ultra-rare diseases, with most of these being single arm, open label phase 2 trials. Conducting randomized, blinded trials is not feasible for most ultra-rare diseases owing to the hurdles in recruiting the right and adequate numbers of investigators and patients. These challenges in patient accrual result in delayed development timelines for ultra-rare compared with rare diseases (median 8.9 *v* 7.1 years). As a result, thousands of patients continue to be affected by ultra-rare diseases without adequate treatment options.[37]

The US congress can overcome these unmet medical needs with policies that encourage drug development for ultra-rare diseases. Firstly, a definition for ultra-rare diseases is essential. The US could adopt the EU's prevalence threshold of 1 in 50 000 citizens or set an arbitrary threshold of 10 000 affected US citizens.[23 38] Secondly, on the basis of this coherent definition, the US congress could create a distinct ultra-orphan designation entailing greater direct and indirect financial incentives for eligible drugs. For example, the Orphan Drug Act's research and development tax credit of 25% could be increased to 50% (or even 75%) and the market exclusivity period from seven to 10 years to boost the economic viability and account for longer trial accrual rates of ultra-rare orphan indications, respectively. This will likely encourage manufacturers to sponsor more and riskier clinical trials, but direct federal funding of pre-clinical drug development is also needed to incentivize early stage research projects for ultra-rare diseases. Over the past years, public-private partnerships were particularly successful in guiding pre-clinical development efforts. For instance, the Bespoke Gene Therapy Consortium, a partnership between the National Institutes of Health, FDA, academia, and manufacturers, was initiated in 2021 to tackle challenges in developing gene therapies for ultra-rare diseases.[39] Finally, the use of every available tool—for example, synthetic control arms or natural history studies—should be encouraged when trials for ultra-rare diseases with few alternative treatment options are designed, particularly when accrual is challenging and endpoints may be difficult to meet.

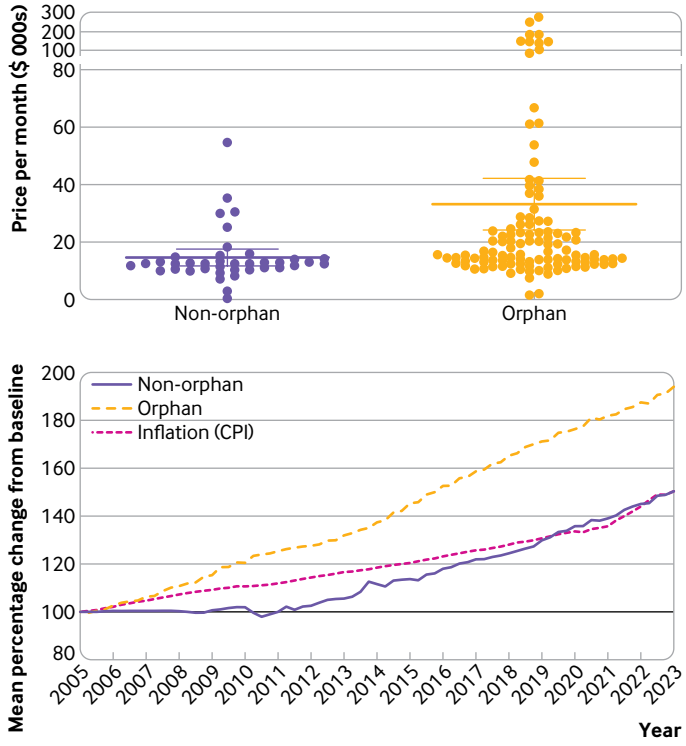

Fig 6 | Prices for anticancer drugs for orphan and non-orphan indications from 2005 to 2023. Top: monthly prices of drugs with and without orphan designation for original Food and Drug Administration (FDA) indication are compared in 2023. Bars represent means with 95% confidence intervals. Bottom: mean price change of orphan and non-orphan drugs is compared from 2005 until 2023. Lines illustrate price indices with baseline set in 2005. Inflation was measured by consumer price index (CPI)

Pricing, coverage, and reimbursement policies

This study highlights the significant financial burden of orphan anticancer drugs for payers and patients. Although pharmaceutical companies argue that high

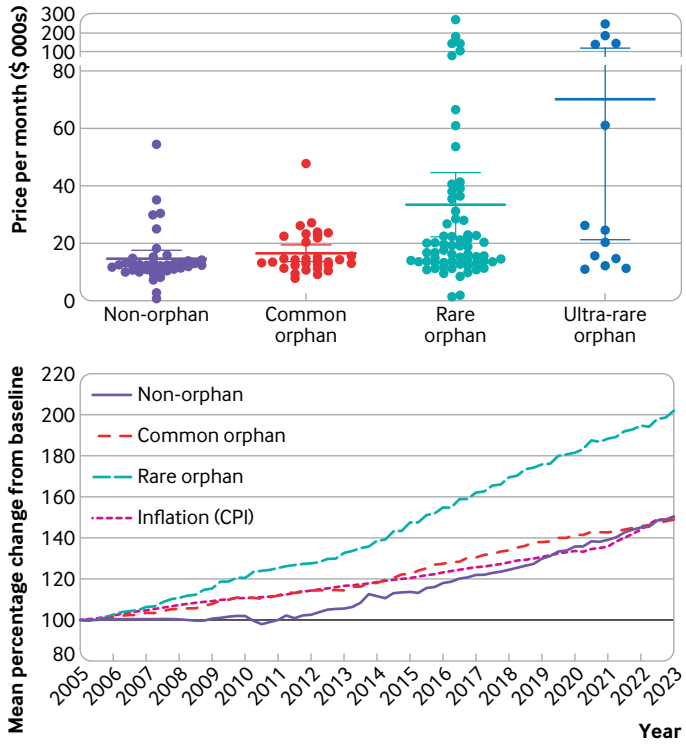

Fig 7 | Prices for anticancer drugs for ultra-rare, rare, and common orphan indications from 2005 to 2023. Top: monthly prices of drugs with non-orphan and ultra-rare, rare, and common orphan designation for original Food and Drug Administration (FDA) indication are compared in 2023. Bars represent means with 95% confidence intervals. Bottom: mean price changes for non-orphan and ultra-rare, common, and rare orphan drugs from 2005 until 2023. Lines illustrate price indices with baseline set in 2005. Inflation was measured by consumer price index (CPI). Orphan indications were stratified according to the number of affected US citizens into common (›200 000), rare (200 000-6600), or ultra-rare (‹6600)

prices are necessary to incentivize drug development for rare diseases, monthly prices of $33 070 with 20-30% paid out of pocket are not affordable for the average US citizen with an income of $5345.[40] Patients must wonder why prices for orphan drugs increased by 3.5% per quarter, far exceeding inflation and prices of non-orphan drugs. The following paragraphs therefore explore innovative pricing, coverage, and reimbursement policies to ensure that orphan drugs remain accessible and affordable to US patients.

Recently, the US congress granted Medicare and Medicaid the power to directly negotiate prescription drug prices with pharmaceutical companies by passing the Inflation Reduction Act of 2022. Medicare could thereby not only mandate drug prices to be aligned to their clinical benefit and unmet needs (value based pricing) but also use its bargaining power to limit price increases. Independent non-governmental health technology assessment agencies, such as the Institute for Clinical and Economic Review, could conduct cost effectiveness analyses to inform price negotiations. Although this study highlights particularly price increases far exceeding inflation for orphan drugs, the Inflation Reduction Act is limited to drugs for non-orphan indications. The next pharmaceutical policy reform should therefore extend the power of Medicare and Medicaid to negotiate value based prices for orphan drugs.

Guided by examples from Europe, this value based pricing could entail a special assessment pathway for ultra-rare diseases. Similarly to the UK's National Institute for Health and Care Excellence, the Centers for Medicare and Medicaid Services could set a higher cost effectiveness threshold, and thereby price premium, for ultra-rare diseases to account for the smaller eligible patient population or exclude ultra-rare diseases from price negotiations until a pre-defined annual revenue threshold is surpassed. Both options would likely increase access to and stimulate development of drugs treating ultra-rare diseases. However, the Centers for Medicare and Medicaid Services should always mandate manufacturers to engage in their existing Coverage with Evidence Development program, such that outcome data are collected to reassess each ultra-rare orphan indication's benefit after a pre-defined period (for example, three years).

The Orphan Drug Act was intended to incentivize development of drugs for rare diseases, but drugs for common orphan indications in particular often turn into top selling blockbusters.[41] Moreover, the usage and economic spending patterns of drugs for common orphan indications are more similar to those of drugs for non-orphan indications than those that are for truly rare diseases.[42] After an orphan drug has reached a maximum revenue threshold (for example, $750m) or surpassed the orphan prevalence threshold of 200 000 affected citizens, the FDA could revoke any benefits received by the pharmaceutical company, such as tax credits, research grants, and exclusivity period.[10 22] Thereby, only drugs that truly meet the Orphan Drug Act's intention would receive its financial incentives. Finally, payers could tackle the swift extension of biomarker defined orphan indications to biomarker negative non-orphan indications on the basis of pooled efficacy data by using indication specific pricing.[25 43] By setting a distinct price for each indication, rather than each drug, payers would be able to pay a higher price for and thus incentivize the development of highly effective biomarker positive orphan indications.[43] Although indication specific pricing is challenging to implement,[44 45] it could help to realign the value and price for orphan indications.

Limitations of this study

This study has certain limitations. We analyzed only clinical trial evidence supporting the FDA approval of cancer drug indications. Consequently, the sample includes only successful trials, which may bias (overstate) efficacy outcomes. Secondly, our analyses are limited to trial data available at the time of FDA approval. Thirdly, we calculated prices for the average patient insured by Medicare. With more than 60 million enrollees, Medicare is the largest US insurer, but the affordability and pricing for privately insured patients may vary. Fourthly, we meta-analyzed efficacy outcomes across a variety of tumor entities with low to high heterogeneity between effect sizes,

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in line with previous studies.[46-49] Fifthly, this study is limited to cancer indications. Results and policy implications must be confirmed for other therapeutic areas.

Conclusions

The Orphan Drug Act incentivized the development of more than 6000 drug indications. Among anticancer drugs, these orphan indications fill significant unmet needs; however, their approval is based on small, non-robust trials, which could overestimate efficacy outcomes. We identified three groups of orphan drug indications with distinct clinical, epidemiologic, and economic characteristics: common, rare, and ultra-rare orphan indications. Policy reforms could help to differentially incentivize and rigorously evaluate the development of these orphan drug groups. For common orphan indications, the genomic drug target across all, rather than a single, cancer type should build the prevalence basis of the orphan designation. By contrast, a distinct ultra-orphan designation with greater financial incentives could encourage development of drugs for ultra-rare diseases. The recent Inflation Reduction Act, which empowers the Centers for Medicare and Medicaid Services to directly negotiate drug prices and price increases with manufacturers, should be extended to all drugs for orphan indications to ensure that US patients can access and afford the treatment they need.

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Data sharing: All data used in this study were in the public domain. All data relevant to the study are included in the article or uploaded as supplementary information.

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Dissemination to participants and related patient and public communities: The research findings will be disseminated through press releases, social media posts, local and national newspapers, and academic conferences, as well as disseminated to relevant patient organizations.

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

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Web appendix: Supplementary materials