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Assessing patient risk, benefit and outcomes in drug development: an observational study of regorafenib clinical trials

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ABSTRACT

Objective Our objective of this study was to analyse all oncological clinical trials using regorafenib to create a complete risk/benefit profile for the drug.

Background Creating a novel chemotherapy is costly both in time and capital spent for drug manufacturers. To regenerate what they've spent, drug manufacturers may attempt to repurpose their medications for new indications via clinical trials. To fully understand the risk/benefits in comparison to a drug's efficacy, a pooled analysis must be completed.

Methods We screened PubMed, Embase, Cochrane (CENTRAL) and ClinicalTrials.gov for trials of regorafenib used to treat solid cancers. Next, we extracted median progression-free survival and overall survival in months, adverse event rates and objective response rate (ORR). Studies were deemed positive, negative or indeterminate based on their pre-specified endpoints and tolerability.

Results 56 clinical trials were included in our final sample, with 4960 total participants across 13 indications. Most studies (44 of 56; 78.75%) were non-blinded, and a majority were non-randomised (41 of 56; 73.21%). Trials for colorectal cancer started out as positive but became more negative over time. Cumulative risk to patients increased over time while ORR stayed consistently low.

Conclusions Our findings suggest that since regorafenib's original Food and Drug Administration (FDA) approval, the risk profile for its original indication increased. The amount of non-randomised, single-arm trials in our sample size was concerning, indicating that higher quality research must be conducted. Our results propose that regorafenib's efficacy and safety may be more impactful in cancers other than its FDA approvals.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Development of novel drugs is a lengthy and expensive process, often leading to exploration into off-label uses. Such use in off-label indications can be harmful to patients as well as wasteful of resources.

WHAT THIS STUDY ADDS

⇒ Our findings will contribute significantly to the literature on cancer drug risk/benefit profiles and promote further exploration into research waste, transparency and adverse event reporting in cancer clinical trials. The total risk/benefit profile of regorafenib shows poor efficacy in its original indication and increased benefit in off-label indications.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings warrant further investigation into novel indications for regorafenib. Our study highlights the benefit of using standardised outcome measurements to improve comparability across clinical trials and reduce research waste.

INTRODUCTION

New drug development is growing in complexity, requiring lengthy approval times and large cost burdens.[1] A study on FDA-approved antineoplastic drugs found a mean time of 7.9 years from the start of clinical testing to regulatory approval.[2] From 2009 to 2018, a mean cost of 2.7 billion dollars was required to bring novel antineoplastic and immunomodulating agents to market.[3] Many clinical trials fail to reach completion, with randomised controlled trials (RCTs) showing higher rates of failure to report findings on early trial termination, resulting in research waste.[4] Drug development trials also require participants to endure risks with potentially lasting side effects. Despite large financial cost, participant health burden and research waste involved in drug clinical trials, one study estimated only 1 out of 10 drugs receive licensure for clinical application.[3] Investigators should prioritise optimisation of clinical trial safety and elimination of research waste when conducting clinical trials.

Total patient burden in the development of novel drug therapies is unclear and it is unknown where in the process the largest burden falls. Carlisle *et al* suggest "innovation

is often followed by unproductive research that seems to be driven less by molecular insights than by empiricism."[1] Imatinib was initially successful in the treatment of chronic myeloid leukaemia but proved unsuccessful in numerous successive trials for various indications launched after initial FDA approval. The subsequent trials contained increasing risk for patients with decreasing benefits.[1] Another study by the same author reports similar results for sunitinib, indicating increasing risk with decreasing benefit as drug development progressed, with no positive trials after the first responding malignancies were discovered.[2] Initial trials with imatinib were conducted on indications with a strong molecular understanding of patients with specific tumour types (67% of those trials' tested indications resulted in FDA approval).[1] After initial approval, fewer restrictions on enrolment of patients with biomarker-positive tumours were required, and none of the trials with lower biomarker-positive tumour enrollees led to an FDA approval over 8 years.[1] The pattern of worsening risk/benefit in trials after initial FDA approval raises concern regarding patient safety.

It is necessary to locate the areas of highest patient burden throughout drug development to mitigate risk in trial participants and address concerns of research ethics. A risk/benefit profile has not yet been established for regorafenib. Regorafenib, a multikinase inhibitor, received initial FDA approval for metastatic colorectal carcinoma in 2012 but has since received FDA approval for other gastrointestinal tumours and continues in clinical trials for various tumour indications.[4] This study will examine published clinical trials for pharmaceutical interventions and assess the total patient benefit and burden experienced throughout the drug portfolio of regorafenib.

MATERIALS AND METHODS

Study design/open science

This was an observational, cross-sectional study investigating clinical trials of regorafenib (*Stivarga*, Bayer Healthcare Pharmaceuticals) to assess the risk/benefit profiles during its development and application to indications not included in its FDA approvals. Prior to the investigation, to improve our study's rigour, reproducibility and open science, we uploaded the protocol. After the investigation was finished, we uploaded the raw data, statistical analysis scripts and forms used to extract the data to Open Science Framework (OSF).[5 6] We meticulously followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines to ensure comprehensive and transparent reporting.[7]

Research questions, definitions and hypothesis

We pose the following research questions: (a) given that clinical trials are both costly to perform and potentially hazardous to participants, what are the benefit/risk profiles of the clinical trials that assess the safety and efficacy of regorafenib and (b) does the drug's risk/benefit portfolio represent an overall extreme hazard to the participants? We defined a clinical trial *profile* as the complete risk and benefit participants experienced during a single trial as measured by standards and methods mentioned in the Data extraction section. We defined a drug's *portfolio* as the complete collection of trial profiles for a distinct intervention. We hypothesised that the expansion of regorafenib into off-label indications would result in numerous negative trials with increased patient risk leading to an overall negative drug portfolio.

Literature search

On 25 May 2023, we searched PubMed/MEDLINE, Embase (Elsevier), Cochrane (CENTRAL) and ClinicalTrials.gov for clinical trials that tested regorafenib as monotherapy or combination therapy for the treatment of cancer. Using the PolyGlot search Translator (https://sr-accelerator.com/#/polyglot) created by Bond University and the Institute for Evidence-Based Healthcare, we translated our search strings to be operable across multiple databases.[8] Our search strings, which include the date of search and initial returns, have been uploaded to OSF.

Selection process

All search returns were uploaded into Rayyan for literature screening. In a masked duplicate fashion, titles and abstracts were screened by BD and CB for potential inclusion. Once screening was completed, any discrepancies were resolved by AMP. Every reason for exclusion was recorded during the screening process and a flow chart was created.

Inclusion and exclusion criteria

The following inclusion criteria were applied: (a) the study must be a clinical trial of adult, human subjects, (b) evaluates efficacy of regorafenib as monotherapy or in combination as treatment for solid cancers, (c) assesses the benefit of regorafenib using radiographically derived criteria (eg, Response Evalutaion Criteria in Solid Tumo (RECIST) or modified RECIST (mRECIST) criteria) and (d) be published in English. The following exclusion criteria were applied: non-oncological studies, non-solid tumour studies, biosimilar studies, pharmacology studies on healthy participants and exclusively paediatric studies. We excluded articles due to publication types, such as secondary reports, interim results, clinical trial updates and follow-ups, preclinical studies, literature reviews, systematic reviews, meta-analyses, human tissue studies, laboratory studies, case reports, letters to the editor, editorials, opinion pieces, conference abstracts, and corrections or redactions. All studies written in any language other than English were excluded.

Data extraction

The following variables were extracted by the authors: published trial title, PubMed ID, clinical trial registry number, country of first author's affiliation, date of publication, number of participants, mean or median age of participants, number of male and female participants, indication(s) of the trial, stage of disease, if the trial was controlled, whether the trial assessed monotherapy or

combination therapies, trial phase, number of centres, blinding of trial participants, randomisation ratio, analysis type, conflict of interest statement and sponsor funding.

The following variables were extracted: the name of the arm, grade of adverse events, number of participants for grade assessment, median progression-free survival (PFS) in months, HR of PFS, median overall survival (OS) in months, HR of OS, partial response (PR) rate, complete response (CR) rate, objective response rate (ORR), number of grade 3–5 adverse events, and if the trial was positive, indeterminate or negative. Outcomes and adverse events across all trial participants of a prespecified indication were extracted. A trial was positive if it met its prespecified endpoints, negative if it did not meet its prespecified endpoints or was excessively toxic, and indeterminate if no prespecified endpoints were set and the regimen was tolerable. The authors of the clinical trials determined if a trial's regimen was tolerable or not.

We made multiple design decisions regarding trial characteristics. We recorded the higher phase if a trial reported results of multiple phases. If a trial reported a response rate without specifying whether it was a PR or CR, we assumed only PRs were measured. If responses were specified as confirmed or unconfirmed, we extracted only the confirmed responses; if trialists specified measurement confirmation was conducted by independent investigators, we extracted the independently confirmed measurements. Dose-escalation and dose expansion treatment and indication arms were pooled into individual summary arms. We extracted variables of interest from the precrossover allocation groups to control for carryover effects interfering with response rate in crossover trials. If a trial enrolled participants in more than one indication, it was reported as 'multiple indications'. A supplement was created for the trials that enrolled participants in more than one indication (online supplemental table 1). Lastly, ORR values were calculated for all participants of an arm unless researchers specified evaluable patients.

Statistical analysis

We conducted descriptive statistics in R (V.4.2.1) and RStudio.

RESULTS

General characteristics

Our initial search yielded 2536 studies, including both published and registered clinical trials. Following title/abstract screening, 1544 articles were excluded, with 168 articles available for full-text review. After review, we excluded 112 studies, yielding a final sample of 56 studies (figure 1). Regorafenib was tested in 28 indications across 56 clinical trials, including its three FDA-approved indications (colorectal cancer, gastrointestinal stromal tumour and hepatocellular carcinoma) as well as off-label use. The most common indications tested in our sample were colorectal cancer (25 of 56; 44.6%), sarcoma (8 of 56; 14.3%) and gastrointestinal stromal tumour (6 of 56; 10.7%). Most trials used regorafenib as monotherapy (40 of 56; 71.4%) while the rest (16 of 56; 28.6) tested regorafenib in combination therapy. A total of 4960 participants were included, with 62% being male and 38% being female. There were 41 (73.2%) non-randomised studies and 15 (26.8%) randomised studies. Most of the participants in our study (3719 of 4960; 75%) were enrolled in trials for regorafenib's FDA-approved indications, while 1241 (25%) were enrolled in off-label trials. Just over half of the included studies were reported as positive (33 of 56; 58.9%), with the rest having either negative or indeterminate results (online supplemental table 2).

Endpoints

The most common endpoints were PFS and OS. PFS was measured as the primary endpoint in 19 studies, with 11 (57.9%) reaching said endpoint and being considered positive. OS was measured as the endpoint in six studies, with five (83.3%) being positive. Of the six studies measuring OS, two were for non-FDA-approved indications (biliary tract cancer and glioblastoma). The median PFS across all trials was 3.2 months, with a median OS of 8.9 months (online supplemental tables 3–5). Another common endpoint used by trialists in our sample was ORR. The ORR for our sample was 6.8%, with a CR of 0.2%. We noted 10 indications with a median CR of 0.0%. Additionally, three non-FDA-approved indications (biliary cancer, pancreatic cancer and sarcoma) had a median ORR of 0.0%. The trials with the highest median ORR values were oesophagogastric cancer and renal cell carcinoma.

ΔPFS/OS

The median change in the RCTs for PFS was 1.5 months and OS was 2.3 months between the regorafenib treatment arms and the placebo arms. Interestingly, one of the highest ΔOS values was found in a non-FDA-approved indication: 9.6 months in a trial using regorafenib to treat sarcoma (p=0.1). However, one of the lowest ΔPFS values was found in the original FDA-approved indication: 0.2 months in a colorectal cancer trial (p<0.0001) (table 1), with an HR of 0.77. This result shows that regorafenib only caused a 23% reduction in risk when compared with the control group, which used a placebo. It is important to note that while the median PFS is short for both the regorafenib group and the control group, with 1.9 months and 1.7 months, respectively, there was still a small reduction in risk when using regorafenib.

Risk assessment

Of the 4960 participants, 3900 grade 3–5 adverse events were reported. Only 21 trials (37.5%) reported all adverse events. Figure 2 displays adverse event rates (AERs) by year plotted against the cumulative ORR. In 2012, the AER was over 100%, indicating more adverse events than participants enrolled in regorafenib clinical trials. In the same year, the highest ORR was recorded; these results coincided with the publication of the CORRECT trial, which resulted in regorafenib's FDA approval for

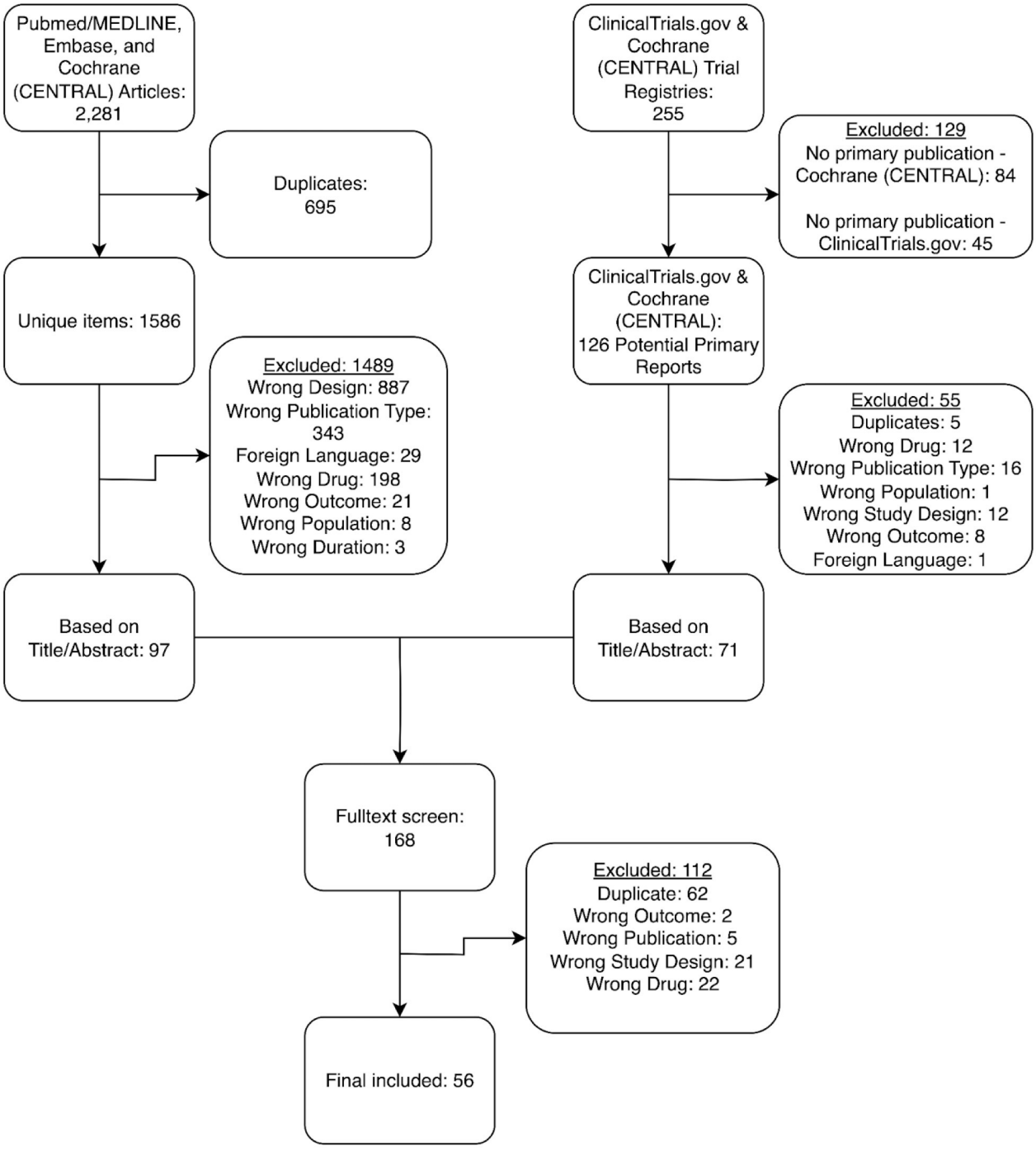

Figure 1 Flow diagram for study inclusion.

colorectal cancer. This trend suggests an overall increase in risk with a decrease in benefit.

Figure 3 illustrates a positive correlation between the number of participants and the occurrence of adverse events. We observed a significant spike in adverse events in 2012, likely related to the CORRECT trial. Beginning in 2017, the cumulative number of patients and cumulative adverse events spiked, which may be attributed to the RESORCE trial leading to FDA approval for hepatocellular carcinoma, as well as the growing exploration of regorafenib in non-FDA-approved indications.

Accumulating Evidence and Research Organization (AERO) diagram

Figure 4 visually captures the development of the regorafenib clinical trial portfolio, illustrating its various phases and indications. Regorafenib received FDA approvals for colorectal cancer in 2012, gastrointestinal stromal tumour in 2013 and hepatocellular carcinoma in 2017. Prior to 2017, 60% of colorectal cancer trials reported positive outcomes. However, after 2017, only 20% of colorectal cancer trials were positive. A general trend noted in these studies was that the intolerable toxicity profiles resulted in the negative results.

Table 1 ΔPFS and ΔOS for randomised controlled trials

Trial	Phase	Result	Date	Indication	Regorafenib group	Comparison group	ΔPFS*	ΔPFS p value	ΔOS*	ΔOS p value
NCT01103323	2	Positive	22 November 2012	Colorectal cancer	Regorafenib	Placebo	0.2	Significant (p<0.0001)	1.4	Significant (p=0.0052)
NCT01271712	3	Positive	22 November 2012	Gastrointestinal stromal tumour	Regorafenib	Placebo	3.7	Significant (p<0.0001)	NA	Non-significant (p=0.199)
NCT01584830	3	Positive	13 May 2015	Colorectal cancer	Regorafenib	Placebo	1.5	Significant (p<0.0001)	2.5	Significant (p=0.00016)
NA	2	Indeterminate	20 June 2016	Gastric cancer	Regorafenib	Placebo	1.7	Significant (p<0.001)	1.3	Non-significant (p=0.147)
NCT01900743	2	Positive	14 October 2016	Leiomyosarcoma	Regorafenib	Placebo	1.9	Non-significant (p=0.70)	11.9	Non-significant (p=0.21)
NCT01900743	2	Positive	14 October 2016	Liposarcoma	Regorafenib	Placebo	–0.6	Significant (p=0.0045)	–4.1	Non-significant (p=0.056)
NCT01900743	2	Positive	14 October 2016	Other sarcoma	Regorafenib	Placebo	1.9	Significant (p<0.0001)	2.6	Non-significant (p=0.79)
NCT01900743	2	Positive	14 October 2016	Synovial sarcoma	Regorafenib	Placebo	4.6	Non-significant (p=0.0061)	6.7	Non-significant (p=0.37)
NCT01774344	3	Positive	06 December 2016	Hepatocellular carcinoma	Regorafenib	Placebo	1.6	Significant (p<0.0001)	2.8	Significant (p<0.0001)
NCT01298570	2	Negative	15 June 2018	Colorectal cancer	Regorafenib and FOLFIRI	Placebo and FOLFIRI	0.8	Significant (p=0.056)	2.1	Non-significant (p=0.94)
NCT02389244	2	Positive	23 November 2018	Sarcoma	Regorafenib	Placebo	3.1	Not reported	5.4	Not reported
NCT02926222	2	Positive	03 December 2018	Glioblastoma	Regorafenib	Lomustine	0.1	Non-significant (p=0.022)	1.8	Significant (p=0.0009)
NCT02048371	2	Positive	23 April 2019	Sarcoma	Regorafenib	Placebo	1.9	Significant (p=0.017)	–2.3	Non-significant (p=0.62)
NCT02368886	2	Positive	28 June 2019	Colorectal cancer	Dose-Escalation Group	Standard Dose Group	0.8	Non-significant (p=0.38)	3.8	Significant (p=0.12)
NCT01900743	2	Positive	06 January 2020	Sarcoma	Regorafenib	Placebo	1	Significant (p=0.0007)	9.6	Significant (p=0.007)
NCT02162914	2	Positive	25 May 2020	Biliary cancer	Regorafenib	Placebo	1.5	Significant (p=0.004)	0.2	Non-significant (p=0.28)
NCT02048371	2	Negative	20 August 2020	Sarcoma	Regorafenib	Placebo	–0.2	Non-significant (p=0.62)	1.6	Non-significant (p=0.28)
						Median	1.5		2.3	

*Months.
OS, overall survival; PFS, progression-free survival.

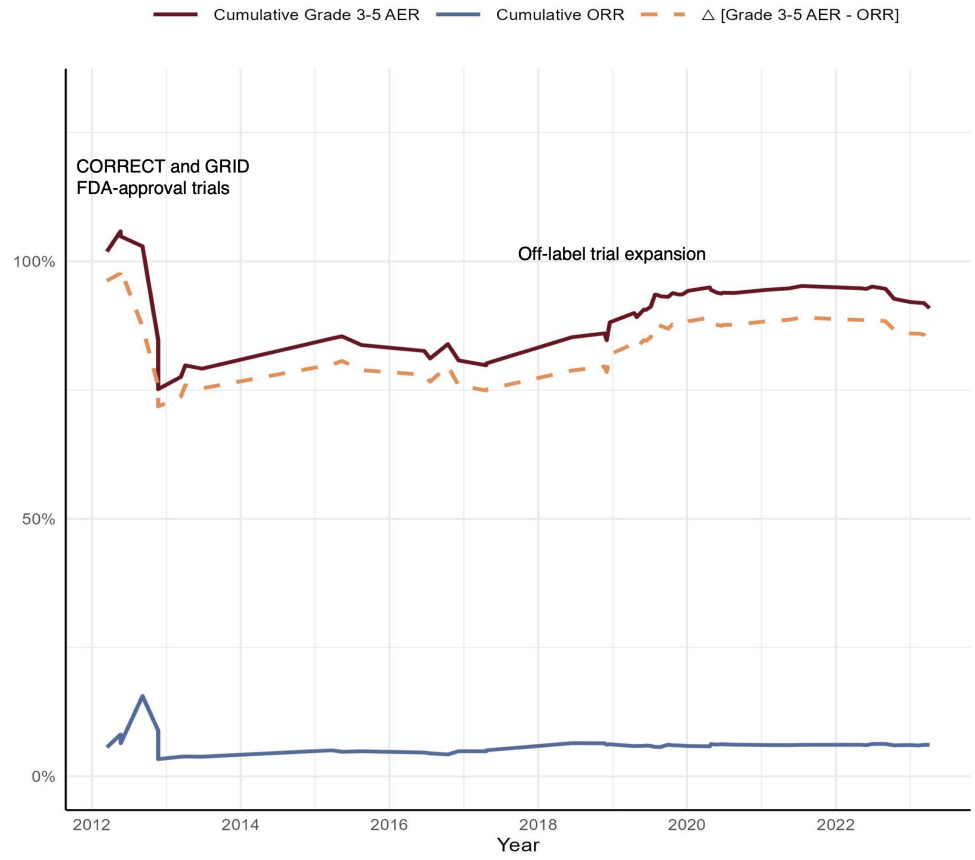

Figure 2 AER for each trial versus the cumulative ORR for each trial per year plotted over time. Δ (AER–ORR) is the absolute difference between the cumulative AER and ORR. AER, adverse event rate; GRID, Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial; ORR, objective response rate.

Outside of colorectal cancer, 23 trials occurred for novel indications. These trials occurred after the first FDA approval in 2012, with most trials (17 of 23, 73.9%) coming after the last FDA approval in 2017. A more positive profile was seen in these 23 trials, as 17 were deemed positive, 3 indeterminate and 3 negative. There were 13 phase 1 studies and 38 phase 2 studies in our sample. Interestingly, only five phase 3 studies were included, indicating limited progression past phase 2. Over time, regorafenib's benefit in its original FDA indications declined, while marginal benefit was observed in non-FDA-approved indications.

DISCUSSION

We sought to assess the regulatory portfolio of one anticancer drug: regorafenib. Regorafenib has several antitumour properties, specifically antiangiogenesis, antiproliferation, antimetastasis and anti-immunosuppression.[9] It received US FDA approval for metastatic colorectal cancers in 2012, gastrointestinal stromal tumour in 2013 and hepatocellular carcinoma in 2017. Additionally, it received European Medicines Agency (EMA) approval for metastatic colorectal cancers in 2013, gastrointestinal stromal tumour in 2014 and hepatocellular carcinoma in 2017. Of the 27 indications in our sample, 3 (11.5%) have been approved by the FDA. Our analysis maps the entire, published regulatory portfolio of this drug and reveals many concerning findings.

Our analysis shows regorafenib demonstrated generally modest performance in its original indications, with a median PFS of 3.2 months across all trials. When comparing the ΔPFS and ΔOS of regorafenib's FDA-approved indications to other indications tested, it continued to produce meagre benefits. For example, one colorectal cancer trial resulted in a PFS increase of just 6 days as compared with placebo. Moreover, the OS increased by 1.4 months compared with placebo in the same trial. Interestingly, this colorectal trial was considered positive by the trialists, regardless of the comparatively low results. The same trend was seen for regorafenib's third FDA-approved indication, hepatocellular carcinoma. This trial showed an increase in PFS of 1.6 months and a rise in OS of 2.8 compared with placebo. In contrast, the trial conducted on various types of sarcomas showed greater increases in PFS and OS than the hepatocellular carcinoma trial.

Our study demonstrated consistently negative outcomes in the treatment of colorectal cancer with regorafenib since 2017. However, new trials persist despite this trend. From 2017 onward, only a quarter of regorafenib clinical

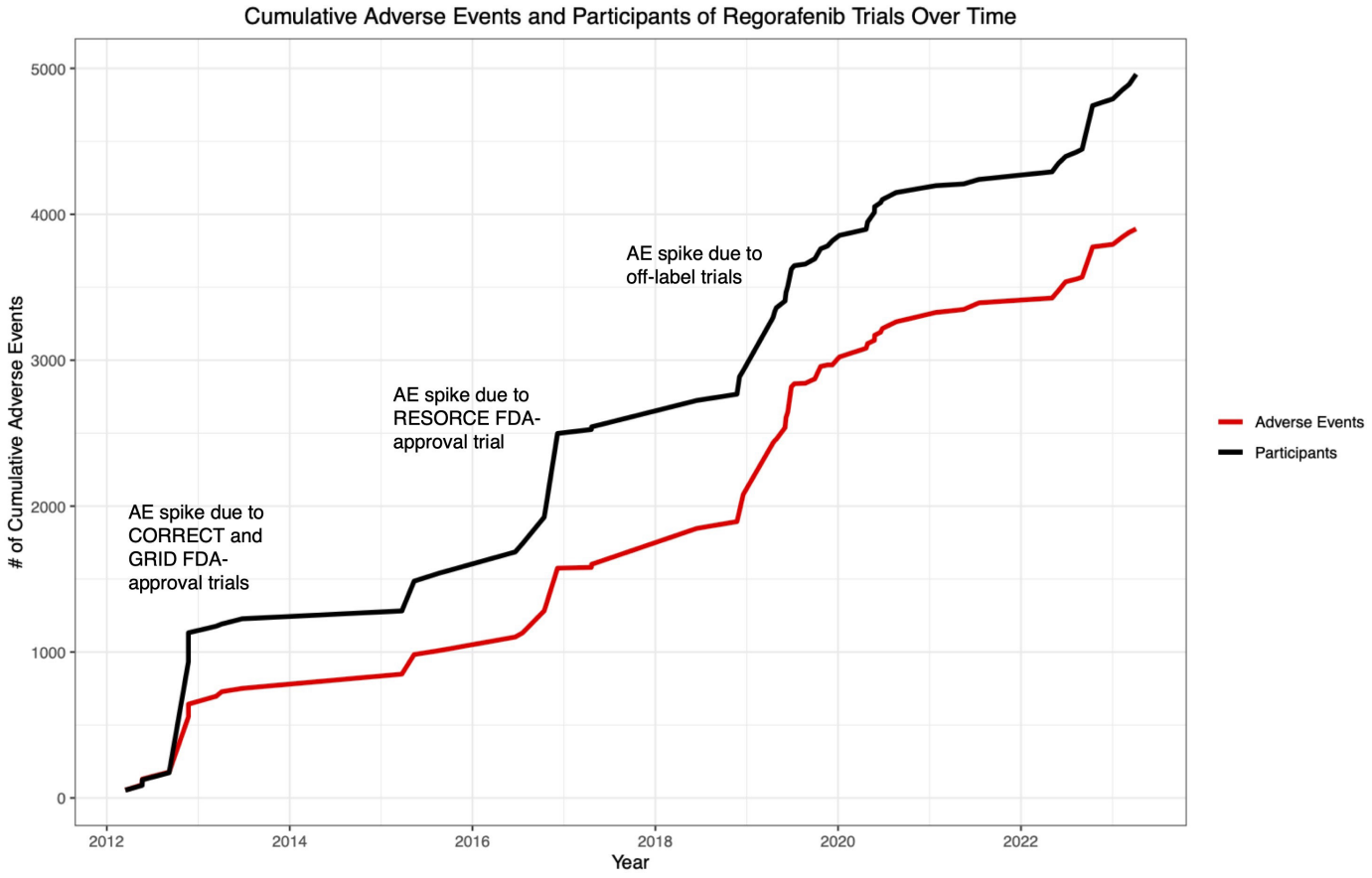

Figure 3 The cumulative number of patients versus the cumulative number of adverse events (AEs) over time. GRID, Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial; RESORCE, Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial.

trials were deemed positive. Since 2022, there have been eight published colorectal cancer trials using regorafenib, with only one positive outcome. This continuous lacklustre performance raises the question of why regorafenib is still being used for colorectal cancer when the results indicate little benefit. A previous study claims trials become detrimental when they provide no new information and address previously answered research questions.[10] Hence, continuing clinical trials on regorafenib for colorectal cancer, when recent studies have shown meagre benefits, is unwarranted. Additionally, persisting with redundant trials depletes funds, clinical resources

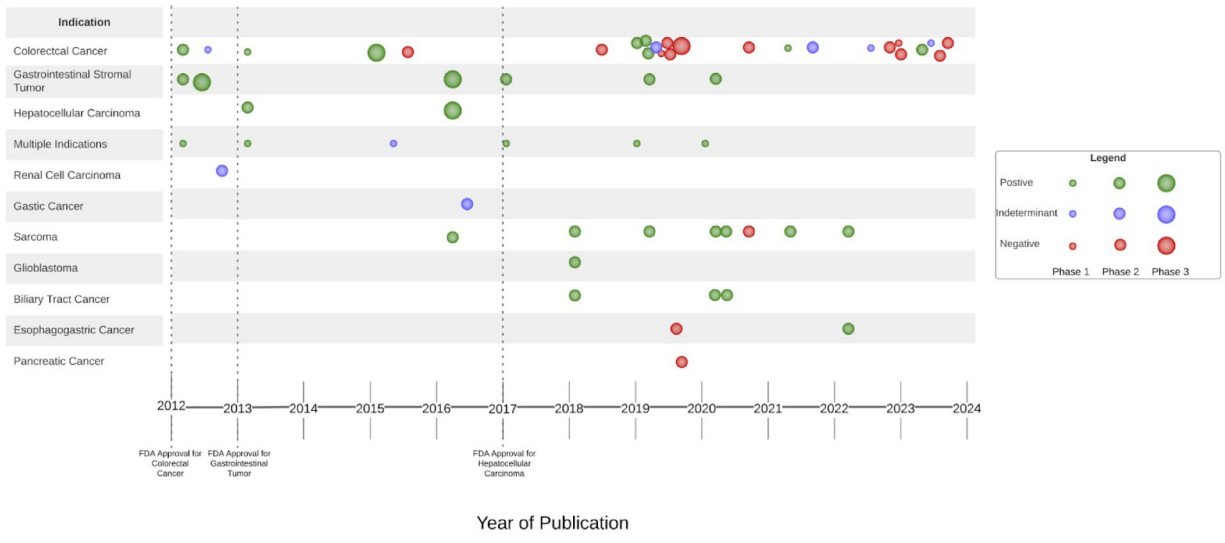

Figure 4 Accumulating Evidence and Research Organization diagram for regorafenib clinical trials.

and control groups.[11] Such resource waste can impede future study participation and funding.[12–14] Therefore, it may be prudent for future trials on regorafenib to focus on renal cell carcinoma and oesophagogastric cancer, as these indications have shown positive outcomes in the limited trials conducted so far.

We found that treating colorectal cancer with regorafenib yields some of the smallest changes in PFS, OS and ORR as compared with secondary indications. This finding contrasts with other drug development portfolios.[1 2] Previous literature assessed clinical trials of imatinib following its FDA approval for the treatment of chronic myeloid leukaemia and found its effectiveness was limited when tested on other cancers.[1] This same trend was noted when reviewing sunitinib clinical trials, with efficacy decreasing when testing on novel indications.[2] In contrast, most trials for other indications in our sample yielded positive outcomes. This discrepancy may be attributed to the broad antitumour effect of regorafenib or easily attainable endpoints. Many trials in our sample using PFS or OS as the primary endpoint were deemed positive, yet studies that used ORR often were inconclusive or negative. These results may be attributable to the absence of a core outcome set (COS), with each trial establishing unique endpoints. A COS is "a minimum set of outcomes that key stakeholders agree to be measured in all trials in a particular field."[15] Implementing such a standardised set of outcomes would facilitate easy comparison of cancer clinical trials, promoting transparency and reducing reporting bias.

Only 15 studies in our sample were RCTs. Concerningly, only four of these trials used an anticancer agent as a control. The remaining trials tested regorafenib against a placebo and supportive care. This statistic is worrisome, as current guidelines by the World Medical Association state "benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best-proven intervention(s)."[16] Therefore, comparing regorafenib to a placebo is unethical as many patients' cancers were allowed to progress due to the lack of medical intervention. One exception to this is trials where patients have already failed first-line interventions because they will have already failed the best-proven intervention. Further, no RCTs were conducted for renal cell carcinoma or oesophagogastric cancer, both of which showed the highest PR rate. Without RCTs, the promise of regorafenib use in renal cell and oesophagogastric cancer cannot be validated. In order to mitigate harm to patients and improve the reliability of results, future studies should follow the Helsinki Accords recommendations and conduct randomised trials for all investigated indications.

Our study revealed cumulative response rates across all clinical trials for regorafenib were less than 10%. This relatively low response rate can lead to therapeutic misconception,[17] where participants mistakenly believe they are likely to receive effective therapy when the chance of actual benefit is slim. This misconception can cause harm to participants in future clinical trials. Additionally, our analysis highlighted the use of monotherapy experiments in many clinical trials, despite the limited benefits observed compared with combination therapy. The median PFS was 2.8 months and the median OS was 8.8 months in monotherapy trials. In contrast, combination therapy trials showed better results with a median PFS of 4.2 months and a median OS of 11.1 months. These findings raise questions about the rationale for conducting monotherapy trials for cancer drugs when combination therapy has consistently demonstrated superior outcomes. However, this is challenged in trials where patients do not qualify for combination therapy due to high frailty or low performance. A study explores this topic, examining 18 cancer drugs and revealing that only 9 were associated with marginal improvements in PFS and OS.[18] Considering the high costs and resource-intensive nature of clinical trials, the persistence of monotherapy trials warrants careful consideration and re-evaluation.

Our analysis revealed that a significant number of clinical trials in our study only reported adverse events that occurred in ≥5%, ≥ 10% or ≥20% of participants, thus excluding a comprehensive account of all adverse events. Based on our sample data, out of the 4960 total participants across regorafenib clinical trials, the regorafenib cohort experienced 48 treatment-related deaths, while the placebo/control cohort had 9 treatment-related deaths. The most frequent grade 5 adverse events in our sample were cardiac arrest and acute hepatic failure. Other notable fatal adverse events included rectal haemorrhage, intracranial haemorrhage and pulmonary embolism. Compared with the eight PRs achieved across all trials, regorafenib caused death six times as much as it caused PR. Considering adverse events beyond deaths, these trials still pose substantial risks. Our study identified that nearly half of the studies reported more grade 3–5 adverse events than evaluable participants. Common non-lethal adverse events included hand-foot-skin reaction, diarrhoea and vomiting, which occurred in many participants. These statistics underscore the significant risks, highlighting the need for careful consideration when prescribing regorafenib. Physicians should engage in collaborative discussions with patients and their families to assess whether the risk of adverse events is justified, particularly when the median OS is less than 1 year with no significant tumour response.

Strengths and limitations

Our study has many strengths as well as some limitations. We employed a systematic approach by thoroughly surveying and cross-referencing clinical trial registry profiles to identify their primary publications in PubMed and Embase. To minimise bias and data extraction errors, we conducted our study in a blind, duplicate manner, adhering to current guidelines.[19] We made our protocol, raw data, analysis scripts and Google extraction form publicly available. Lastly, we used an accepted methodology from previous works to conduct our study.[2] However, our study also has limitations that should be acknowledged. One weakness is lack of generalisability.

Our analysis was a cross-sectional examination focused on the clinical trials of regorafenib and its indications, limiting its applicability to regorafenib, its clinical trials and its manufacturer Bayer. Our systematic search, while comprehensive, may not have captured every clinical trial relevant to our study objectives. This is a common limitation inherent in systematic reviews.[20] To mitigate the risk of overlooking relevant studies, we employed a rigorous search strategy, as mentioned above.

CONCLUSION

Our analysis provides the first look at the clinical trial portfolio for regorafenib, shedding light on its indications and performance. In general, it performed poorly for colorectal cancer, its original FDA indication, when compared with novel indications. The persistently negative outcomes in colorectal cancer trials are concerning and raise important questions about its continued use with this patient population. Our study also highlights the importance of employing standardised outcome measures and the harmful nature of redundant trials and research waste. Furthermore, given the adverse event profile we observed across clinical trials, the multidisciplinary team responsible for treatment should carefully weigh the risk-to-benefit profile of regorafenib when considering this therapy. Our findings underscore the need for continued exploration into risk/benefit profiles of cancer drugs. The insights gained from our study may inform future research directions and clinical practices in oncology.

Contributors BD is the author responsible for overall content as the guarantor. BD contributed to the formal analysis, investigation, writing—original draft and writing—reviewing and editing. CB contributed to the formal analysis, investigation and writing—original draft. GKH contributed to conceptualisation, data curation, formal analysis, methodology, supervision and software. AMP contributed to conceptualisation, methodology, supervision and writing—original draft. RM, CL and BG all contributed to conceptualisation, methodology and supervision. WN and RL provided resources. JT and AH provided resources and visualisation. VP provided resources and supervision. MV contributed to conceptualisation, resources, methodology, project administration and supervision.

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