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Assessing patient burden and benefit: A decade of cabozantinib clinical trials

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Abstract

Drug development is complex and costly. Clinical trial participants take on risks, making it essential to maximize trial efficiency and maintain participant safety. Identifying periods of excessive burden during drug development can inform trial design, ensure patient benefit and prevent harm. This study aims to examine all published clinical trials for cabozantinib to assess patient benefit and burden over time. We conducted a retrospective cross-sectional review of interventional clinical trials of cabozantinib for solid cancer treatment. We searched PubMed/MEDLINE, Embase, Cochrane (CENTRAL) and ClinicalTrials.gov. We extracted adverse event rates, median progression-free survival (PFS), median overall survival and objective response rate (ORR) for each included trial. We calculated frequencies of trial characteristics, cumulative grade 3–5 adverse event rates and cumulative ORRs. Out of 1735 studies, 54 publications were included that involved 6372 participants and 21 cancers. Of the 54 studies in our sample, 31 (57.41%) were single-arm trials and 23 (42.60%) had negative results. Trials among and within various indications had conflicting results over time. Cumulative risk to participants increased over time, and clinical benefit decreased. The findings suggest that the risk profile of cabozantinib increased from 2011 to 2016 and has remained elevated but stable while benefit has decreased over time. The use of non-randomized and single-arm trials is concerning, and more methodologically rigorous trials are needed. The results of trials for different indications are inconsistent, and empirical administration may reduce the drug's efficacy.

KEYWORDS
adverse events, AERO, cabozantinib, response rate

What's new?

Clinical trials are often viewed as opportunities for cancer patients to receive cutting-edge treatment. However, trials pose risks to patient safety, which potentially increase over time and frequently coincide with decreased benefits. Here, to better understand where clinical trials pose the greatest risks, the authors examined data from trials exploring cabozantinib for the treatment of solid tumors. Analyses show that out of 54 trials, 23 failed to meet pre-specified endpoints or employed an intolerable regimen. Most trials also were non-randomized, single-arm studies that potentially over-predict benefits. Inconsistency in the effectiveness of cabozantinib warrants careful consideration before further clinical study.

1 | INTRODUCTION

Drug development is an increasingly complex process requiring years of research and billions of dollars.[1–3] A study on Food and Drug Administration (FDA) approved drugs found a mean time of 7.2 years from the start of clinical testing to regulatory approval.[4] DiMasi et al[5] reported pre-approval costs of 106 randomly selected drugs to be greater than 2.5 billion dollars in 2016, while Wouters et al[6] reported a mean cost of 1.6 billion dollars of 63 drugs in 2020. In 2017, Prasad and Mailankody focused on cancer drugs, finding it cost an estimated $648 million to bring a drug to market, accounting for 7% lost earnings on capital.[7]

Despite the large temporal and financial cost of running clinical trials, most trials fail to produce meaningful interventions. Only an estimated 1 out of 10 novel drugs achieve FDA approval,[8] and many candidate compounds and trials are unable to maintain funding, prove efficacy or demonstrate tolerable safety.[9] Developing novel drugs also requires clinical trial participants to take on important health risks[10] that often extend beyond the initial trial period.[11,12] As such, the research community strives to maximize trial efficiency, reduce research waste and maintain participant safety.

Identifying instances of excessive burden during drug development may inform trial design, ensure patient benefit and prevent harm, however, little is known about which periods of a drug's life cycle are the most burdensome to trial participants. In one systematic review, Carlisle et al found that the initially successful cancer drug sunitinib showed a worsening risk/benefit ratio throughout its development as it was explored for numerous, previously uninvestigated indications.[13] In another study, Carlisle et al highlighted a similar trend with the drug imatinib. Initial imatinib trials for chronic myelogenous leukemia were successful, but subsequent trials for other indications were increasingly risky and less likely to yield positive results.[14] The authors suggested that the drugs were initially successful because of strong molecular evidence supporting their use for the primary indication that may not have supported subsequent trials. The increasing risk/benefit ratio throughout a drug's development raises important questions regarding research ethics and patient safety.

We sought to characterize drug development profiles, with the goal of reducing risk, improving outcomes and optimizing research funding by identifying the instances where trials are the riskiest and the costliest. While other researchers have focused on drugs developed by large companies with many products, we chose to focus on the VEGF, MET, RET and AXL inhibitor cabozantinib, which was the first approval of a smaller biotechnology firm (Exelixis).[15] Furthermore, it is pertinent to acknowledge that the demographic diversity of participants in clinical trials often falls short in mirroring the heterogeneity of real-world patients subsequently receiving the drug upon approval, a factor which may impinge upon the generalizability of trial findings and their translation into routine clinical practice.[16–18] Thus, while cognizant of this limitation, this study sought to examine all published clinical trials for cabozantinib and assess the total patient benefit and burden experienced throughout the drug development process. Ensuring a strong evidential basis for pursuing new drug trials is important for increasing efficiency, reducing waste and maintaining safety.

2 | METHODS

2.1 | Study design/open-science

This is a cross-sectional study probing clinical trials of cabozantinib for their risk/benefit profiles throughout its development and applications to indications outside of initial approval. To improve rigor, reproducibility and open science, we uploaded a protocol a priori to the investigation. After the investigation was completed, we uploaded raw data, statistical analysis scripts and extraction forms to Open Science Framework (OSF)—a free-to-upload data repository.[19] Our data will be available on OSF through the lifecycle of the repository or upon request.[20]

2.2 | Research questions, definitions and hypothesis

Given that clinical trials are costly and potentially harmful to patients, what are the benefit/risk profiles of clinical trials assessing the efficacy of cabozantinib? Do the combined risk profiles—the drug's risk/benefit portfolio—represent an overall excessive risk to patients? We defined a clinical trial *profile* as the overall risk and benefit encountered by participants during a single trial as measured by selected tools mentioned in the *Data Extraction* section. We defined a drug's *portfolio* as the total collection of trial profiles for a given intervention. We hypothesize that the expansion of clinical trials of cabozantinib into previously uninvestigated indications will result in more negative trials of increased patient risk and an overall negative drug portfolio.

2.3 | Literature search

We performed a literature search of PubMed/MEDLINE, Embase, Cochrane (CENTRAL) and ClinicalTrials.gov for clinical trials using cabozantinib as monotherapy or in combination with other interventions for cancer treatment. We standardized our search strings across these databases using the PolyGlot Search Translator (https://sr-accelerator.com/#/polyglot) developed by Bond University and the Institute for Evidence Based Healthcare.[21] Our search strings, including date of search and initial returns, are uploaded to OSF and are available at: https://osf.io/jp37s/.

2.4 | Selection process

We uploaded search returns into Rayyan for literature screening. We trained screening authors to use Rayyan (https://www.rayyan.ai/)[21]: an online tool to screen large samples of literature for study inclusion

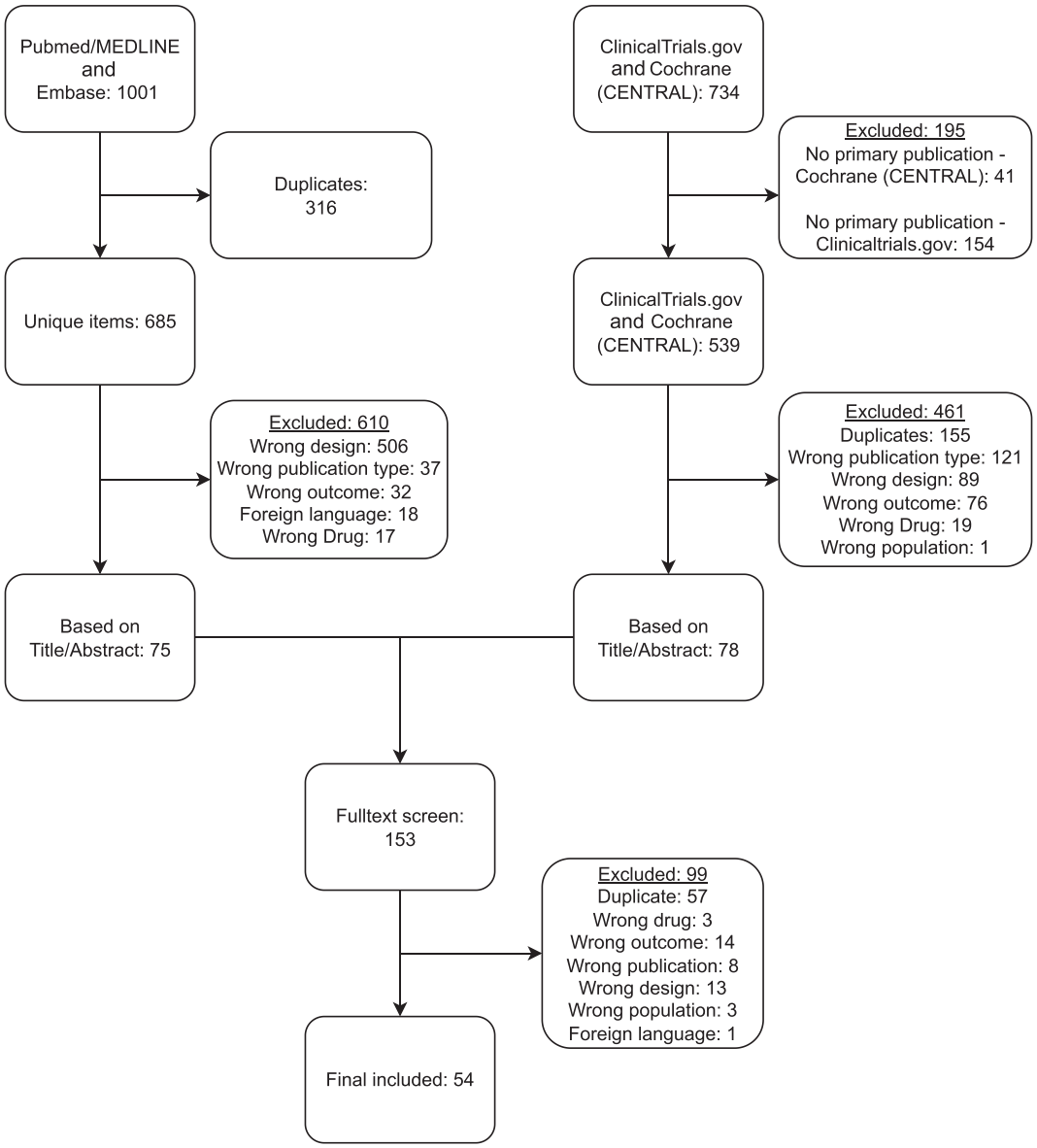

FIGURE 1 Flow diagram for cabozantinib study inclusion. Fifty-four studies were ultimately included for analysis.

or exclusion. Data extraction was carried out using a pilot-tested Google form. Authors test-ran 10 included studies before extracting the entire sample. Two authors (GH and NS) screened titles and abstracts for potential inclusion in a masked duplicate fashion. After screening was complete, author MV resolved any discrepancies. We recorded reasons for exclusion during the screening process to create a flowchart for study exclusion.

2.5 | Inclusion and exclusion criteria

Studies that qualified for inclusion must have: (a) have been a clinical trial of adult, human subjects, (b) assessed efficacy of cabozantinib as monotherapy or in combination as an intervention to treat solid cancers, (c) assessed the benefit of cabozantinib using objective response rate (ORR) as defined by the Response Evaluation Criteria in Solid Tumours (RECIST) criteria and (d) been published in English. We excluded non-oncological studies, non-solid tumor studies, biosimilar studies, pharmacology studies on healthy participants and exclusively pediatric studies. We excluded other publication types, including 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, corrections or redactions.

2.6 | Data extraction

After screening, a final study pool underwent data extraction in a masked, duplicate fashion by two authors (GH and BH) with a third

TABLE 1 Characteristics of included trials.

Characteristic	Single arm, $N = 31$	Multiple arm, $N = 23$	Overall, $N = 54$
Funding			
Industry	16 (51.61%)	14 (60.87%)	30 (55.56%)
Industry and government	8 (25.81%)	3 (13.04%)	11 (20.37%)
Government	5 (16.13%)	3 (13.04%)	8 (14.81%)
Government and non-profit	2 (6.45%)	1 (4.35%)	3 (5.56%)
Industry and government and non-profit	0 (0.00%)	1 (4.35%)	1 (1.85%)
Industry and non-profit	0 (0.00%)	1 (4.35%)	1 (1.85%)
Centers			
Multicenter	15 (48.39%)	16 (69.57%)	31 (57.41%)
Not stated	10 (32.26%)	4 (17.39%)	14 (25.93%)
Single center	6 (19.35%)	3 (13.04%)	9 (16.67%)
Blinding			
Non-blinded	31 (100.00%)	20 (86.96%)	51 (94.44%)
Double	0 (0.00%)	3 (13.04%)	3 (5.56%)
Randomization			
Not randomized	31 (100.00%)	8 (34.78%)	39 (72.22%)
Randomized	0 (0.00%)	15 (65.22%)	15 (27.78%)
Randomization ratio			
1:1	0 (0.00%)	7 (30.43%)	7 (12.96%)
2:1	0 (0.00%)	5 (21.74%)	5 (9.26%)
1:1:1	0 (0.00%)	1 (4.35%)	1 (1.85%)
1:1:2:2	0 (0.00%)	1 (4.35%)	1 (1.85%)
2:1:1	0 (0.00%)	1 (4.35%)	1 (1.85%)
NA	31 (100.00%)	8 (34.78%)	39 (72.22%)
Stage			
Metastatic	27 (87.10%)	19 (82.61%)	46 (85.19%)
Non-metastatic	4 (12.90%)	4 (17.39%)	8 (14.81%)
Monotherapy or Combination			
Monotherapy	24 (77.42%)	11 (47.83%)	35 (64.81%)
Combination	7 (22.58%)	12 (52.17%)	19 (35.19%)
Phase			
I	8 (25.81%)	3 (13.04%)	11 (20.37%)
II	22 (70.97%)	14 (60.87%)	36 (66.67%)
III	1 (3.22%)	6 (26.09%)	7 (12.96%)
Result			
Negative	15 (48.39%)	8 (34.78%)	23 (42.59%)
Positive	13 (41.94%)	12 (52.17%)	25 (46.30%)
Indeterminate	3 (9.68%)	3 (13.04%)	6 (11.11%)
Country			
United States	24 (77.42%)	17 (73.91%)	41 (75.93%)
Belgium	2 (6.45%)	0 (0.00%)	2 (3.70%)
Italy	2 (6.45%)	1 (4.35%)	3 (5.56%)
Japan	2 (6.45%)	1 (4.35%)	3 (5.56%)
Canada	1 (3.23%)	1 (4.35%)	2 (3.70%)
China	0 (0.00%)	1 (4.35%)	1 (1.85%)
France	0 (0.00%)	1 (4.35%)	1 (1.85%)
The Netherlands	0 (0.00%)	1 (4.35%)	1 (1.85%)

author available to resolve discrepancies (NS). Authors extracted the following variables: published trial title, PMID, 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, drug indication(s) in the trial, disease stage, whether the trial was controlled, whether the trial assessed monotherapy or combination therapies, trial phase, number of trial centers, blinding of trial participants, randomization ratio and sponsor.

2.7 | Risk and benefit measurements

To measure adverse events (AEs) in clinical trials, we recorded the Common Terminology Criteria for Adverse Events (CTCAE) grade as listed. If there were no CTCAE grades listed, authors used CTCAE version 5.0 to determine the grade of adverse events. The CTCAE nomenclature system was developed by the National Cancer Institute as a reporting of adverse events experienced by patients in clinical trials. The widespread use of CTCAE has improved our understanding of harms and toxicity profiles of certain oncology drugs.[22] For risk and benefit outcomes the following variables were extracted: the name of the arm, adverse events grade and number of participants for grade assessment, median progression-free survival (PFS) in months, hazard ratio of PFS, median overall survival (OS) in months, partial response rate, complete response rate, objective response rate (ORR), number of adverse events, number of serious adverse events, maximum tolerated dose (phase I only) and if the trial was positive, indeterminate or negative. Outcome measurements and adverse events encompassing all trial participants of a pre-specified indication were extracted. A trial was deemed positive if it met its pre-specified endpoints using a tolerable regimen. A trial was deemed indeterminate if it did not pre-specify endpoints and was using a tolerable regimen. A trial was deemed negative if it did not meet its pre-specified endpoints or was not using a tolerable regimen. The tolerability of a regimen was determined by trial authors.[13]

2.8 | Statistical analysis and data exploration

We tabulated descriptive statistics for trial characteristics and trial results. We plotted trials by indication over time in the form of an Accumulating Evidence and Research Organization (AERO) model diagram.[23] The AERO diagram allowed us to concisely report the overall outcome of a trial for any given indication over time, as has been done in previous studies on cancer drug development.[13,14] We plotted the

TABLE 2 Trial characteristics and outcomes by indication.

Indication	No. of trials	No. of participants	No. of males	No. of females	Median age	No. of Grade 3–5 events	Median PFS (months)	Median partial response rate	Median complete response rate	Median ORR	Median OS (months)
Renal cell carcinoma	10	1875	1407	467	63	1604	8.3	23.00%	0.00%	27.00%	18.15
Non-small cell lung cancer	6	282	124	158	64.8	197	4.05	10.00%	0.00%	10.00%	9.55
Prostate cancer	6	1445	1445	0	68.5	1818	5.55	21.00%	2.00%	23.00%	18.4
Breast cancer	5	186	0	186	52	138	3.6	6.00%	0.00%	6.00%	12.6
Thyroid cancer	5	642	394	248	56	518	7.6	28.00%	0.00%	28.00%	34.7
Hepatocellular carcinoma	4	983	828	155	64.25	745	4.7	5.50%	0.00%	5.50%	15.45
Urothelial carcinoma	3	151	117	34	63.75	173	3.7	17.95%	3.90%	21.10%	10.4
Endometrial cancer	2	179	0	179	66	166	4.6	26.00%	0.00%	26.00%	10.45
Melanoma	2	123	68	55	65	86	2.05	0.00%	0.00%	0.00%	7.3
Ovarian, peritoneal and fallopian cancer	2	124	0	124	—[a]	—	5.3	7.00%	0.00%	7.00%	13.75
Bone metastasis	1	37	23	14	54	15	3.5	20.00%	0.00%	20.00%	—
Cholangiocarcinoma	1	19	6	13	67	30	1.8	0.00%	0.00%	0.00%	5.2
Colorectal cancer	1	25	8	17	52.4	—	3.7	16.00%	0.00%	16.00%	12.1
Ewing sarcoma and osteosarcoma	1	90	58	32	35.5	66	5.55	19.00%	0.00%	19.00%	10.4
Gastrointestinal stromal tumor	1	50	30	20	63	89	5.5	14.00%	0.00%	14.00%	18.2
Ovarian cancer	1	70	0	70	61	42	5.5	20.00%	1.40%	21.00%	—
Pancreatic cancer	1	12	6	6	61	14	4.7	25.00%	0.00%	25.00%	10.1
Salivary gland cancer	1	25	12	13	56	26	7.2	7.00%	0.00%	7.00%	15.1
Soft-tissue sarcomas	1	54	24	31	51	42	—	11.10%	0.00%	11.10%	—
Totals/medians	*54*	*6372*	*4550*	*1822*	*63*	*5909*	*4.5*	*12.00%*	*0.00%*	*12.50%*	*13.3*

[a]Did not measure outcome, failed to report outcomes or failed to report outcome measure for all enrolled patients.

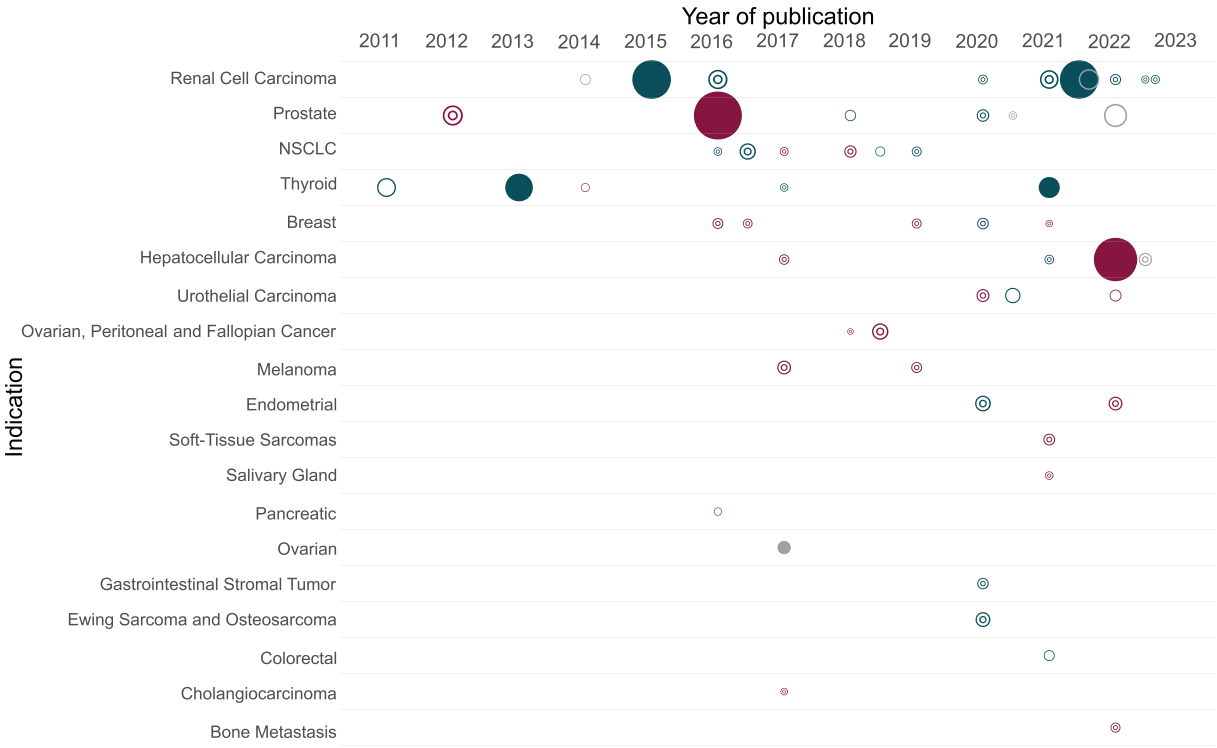

FIGURE 2 Cabozantinib trials are stratified by indication and are mapped by the date of initial publication. The shape of each point indicates the trial phase, and the relative size of the point represents the relative number of trial participants. Blue points indicate positive results, red points indicate negative results and gray points are indeterminate. Hollow circles are phase I, double circles are phase II and solid circles are phase III. [Color figure can be viewed at wileyonlinelibrary.com]

cumulative yearly adverse event rate (AER) for cabozantinib treatment arms compared the cumulative yearly ORR among treatment arms to visualize the risk–benefit landscape. Statistical analysis was performed using R (version 4.2.1) and RStudio.

3 | RESULTS

Our systematic search of PubMed, Embase, ClinicalTrials.gov and Cochrane (CENTRAL) yielded 1735 studies for consideration. Clinical trial registry profiles from ClinicalTrials.gov and Cochrane (CENTRAL) were extracted from these returns and screened individually for a published primary report in PubMed or Embase. After screening titles and abstracts of all published reports in a blind, duplicate fashion, 153 publications were available for full text screening. After full text screening we further excluded 99 studies for a final inclusion sample of 54 publications. Our full screen and exclusion strategy is illustrated in Figure 1.

Of the 54 studies in our sample, 31 (57.41%) were single-arm trials and 23 (42.60%) were multi-arm. Twenty-five trials (46.30%) had positive results, while 23 (42.60%) had negative results and 6 (11.11%) had indeterminate results. Eleven (20.37%) trials were phase I, 36 (66.67%) were phase II and 7 (12.96%) were phase III. The most common funding source for was industry (30 of 54; 55.56%) followed by industry and government (11 of 54; 20.37%) and government alone (8 of 54; 14.81%). Further, 43 trials (45 of 54; 79.63%) reported receiving some amount of industry funding. The distribution of trial characteristics, including funding source, number of centers, randomization, whether a trial was single agent or in combination, phase, country of first author and trial outcome, is presented in Table 1.

The most common indications for cabozantinib in our sample were renal cell carcinoma (10 of 54; 18.52%), non-small cell lung cancer (6 of 54; 11.11%) and prostate cancer (6 of 54; 11.11%). The total number of trial participants in our sample was 6372. The median partial response rate of our sample was 12.00%, the median complete response rate was 0.00% and the median objective response rate was 12.50%. Thyroid cancer has the largest over survival measurement of 34.7 months while cholangiocarcinoma has the lowest overall survival measurement of 5.2 months. The median monthly overall survival for all trials in our sample was 13.3 months. A complete tabulation of indication, participant and endpoint characteristics are located in Table 2.

Trials outcomes over time, whether positive, negative or indeterminate, are presented in the AERO diagram in Figure 2. The shape of each point indicates the trial phase, and the relative size of the point represents the relative number of trial participants. Trials are stratified by indication.

The cumulative adverse event rates, summarized by year, are plotted against the cumulative ORRs for the same trials in a given year in Figure 3. Year 2016 had the highest cumulative adverse event rate, and 2014 the highest cumulative ORR. The cumulative AER initially

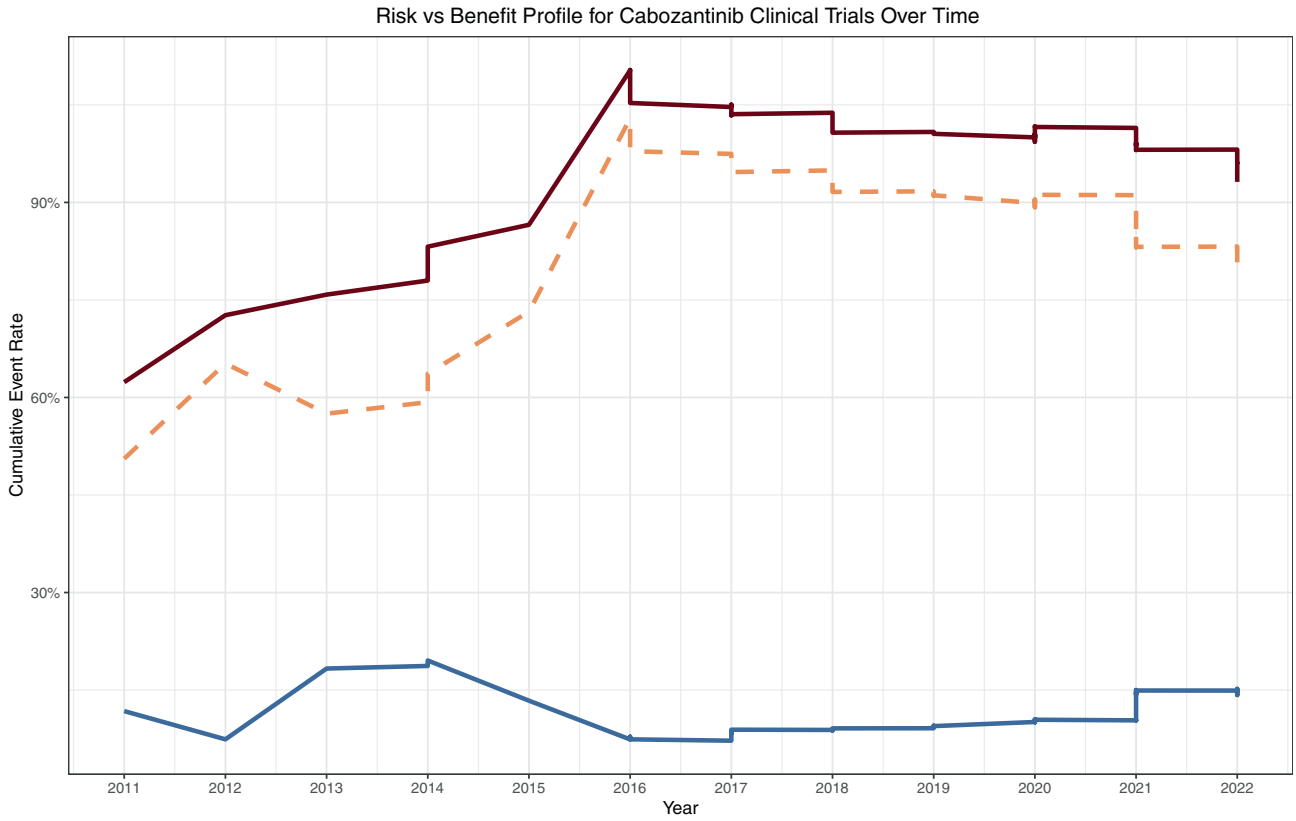

FIGURE 3 Cumulative Grade 3–5 adverse event rates per trial-year vs cumulative ORR per trial-year are plotted over time. Cumulative Grade 3–5 adverse event rates per trial-year vs cumulative ORR per trial-year are plotted over time. The red line indicates adverse event rate, the blue line indicates the response rate, and the dotted yellow line indicates the difference between the adverse event rate and the response rate. Time points included all trials with results published in a given year. [Color figure can be viewed at wileyonlinelibrary.com]

increased yet has leveled over time while the cumulative ORR has risen and fallen while leveling out in the most recent trials.

4 | DISCUSSION

4.1 | General findings

In this study, we evaluated clinical trials that were published over the last decade and tested cabozantinib to treat solid cancers. We used commonly accepted risk and benefit metrics to determine whether trials for a given indication were positive, negative or indeterminate. We also compared the cumulative risk and benefit of cabozantinib over time. In the following paragraphs, we discuss each of our findings in turn.

4.2 | Trial characteristics

In our sample of 54 cabozantinib trials, 31 trials were single arm and 39 trials were non-randomized. The reliance on non-randomized designs for investigating cabozantinib is concerning, as these study designs are likely to report ORRs that may be exaggerated versus a randomized study of the same intervention.[24,25] Rittberg et al suggest that single arm, non-randomized trials are more susceptible to bias and potentially have decreased statistical power compared to randomized trials.[25] The decision to conduct a single arm or non-randomized trial in place of more robust randomized design for cabozantinib may be economically driven, as single arm and non-randomized trials are cheaper to conduct, require smaller sample sizes,[26] and are regularly used for FDA approval.[27,28] Prior work has also found that drugs approved based on response rate often have an antecedent approval with as high or higher response rate.[29] The ubiquitous use of non-randomized and single arm trials in cabozantinib indicates a need for more methodologically rigorous, controlled trials. However, rare cancers present in our sample such as salivary gland cancer, cholangiocarcinoma and pancreatic cancer present practical treatment, recruitment and general investigational barriers to high powered, controlled investigations.[30–33] Fortunately, cabozantinib's approvals for use in more common cancers like renal cell carcinoma[34] and differentiated thyroid cancer[35] were based on large, randomized trials. Although in the former cases, only the endpoint of progression-free survival was improved.

4.3 | Risk/benefit profile

The results of our study suggest that the drug development landscape and risk/benefit profile of cabozantinib has remained relatively stable

since clinical trials began, but there is a notable trend toward increased risk and decreased benefit. The riskiest point in cabozantinib's development occurred in 2016 when the cumulative adverse event rate was the highest. However, we believe a 2014 trial contributed greatly to this occurrence. The steepest increase in risk occurred from 2014 to 2016. The trial in 2014 included a grade 5 AE which occurred during a trial for treatment-resistant differentiated thyroid cancer in adults. While the trial had a very high ORR of 53% (all partial responses, no complete responses), we deemed the trial as negative because of the high AER and because the trial did not meet prespecified median PFS or median OS criteria. The authors did believe the results warranted further investigation and referenced two phase II trials that were already ongoing at the time of publication. In 2021, cabozantinib ultimately received FDA approval for treatment-resistant differentiated thyroid cancer in adults and children[36] despite having two of five trials end with negative results and despite having an excessively high AER. According to the FDA, efficacy was demonstrated with the COSMIC-311 trial (NCT03690388). The study used two co-primary endpoints of ORR and median PFS. However, the study failed to demonstrate a statistically significant difference in ORR between the cabozantinib group compared to placebo.[35] The study did demonstrate a significant difference in PFS at interim analysis, but the PFS did not meet the prespecified PFS value for which the study was powered.

4.4 | Success of cabozantinib trials and future directions

Our results also suggest that expanding cabozantinib's use to indications outside of the initial FDA approval for renal cell carcinoma[34,37] has yielded mixed trial results. Our analysis revealed that even trials for the same indication have conflicting outcomes over time. For example, phase II and III trials for prostate cancer in 2012 and 2013, respectively, were highly powered trials that had negative results. Yet, anecdotal reports of response within those studies were widely discussed.[38] Nonetheless, four more trials were conducted thereafter, two of which were positive and two of which were indeterminate. On the other hand, low prevalence cancers such as salivary gland cancer and cholangiocarcinoma consisted of one negative trial each without subsequent investigations. We believe this may be due to their rarity, few available treatments and comparators, as well as reduced likelihood of achieving market authorization.

For hepatocellular carcinoma, a rather large 2018 trial had positive results, but a larger study occurring in 2022 ended negatively. The inconsistency of these results over time and across indications may have to do with having less of a mechanistically-driven basis for administering cabozantinib compared to earlier indications—a phenomenon that has been seen with other cancer drugs.[13,14] We suspect that, while less pronounced than what has been seen with other drugs, the risk/benefit profile of cabozantinib becomes less favorable for patients as the basis for drug administration becomes ostensibly empirically-driven rather than molecularly-driven. Even though all trials in our sample provided a molecular rationale (ie, described receptor targets of cabozantinib such as VEGFR2, RET or MET) for context to proceed with human testing, the quality of the underlying molecular evidence was not investigated. Further, thorough biomarker assessment for enrolled patients presents logistical challenges to clinical trialists, necessarily increasing trial cost that may impact non-industry funded trials more than industry funded trials.[39,40] The influence of industry funding on trial cost and the presence of a strong molecular basis for the trial is an important research question with valuable implications. However, we did not assess this relationship, as over 79% of our sample reported industry backing. Future studies should evaluate the influence of industry funding on drug risk/benefit profiles, whether clinical trials have a strong molecular basis, and its relation with trial cost.

4.5 | Large vs small pharmaceutical firms

Prior work examining sorafenib,[41] sunitinib[13] and imatinib[14] all concerned companies with large market capitalization and numerous products: Bayer, Pfizer and Novartis. Ours is the first exploration of a company with few products on the market, of which cabozantinib represents the first approved product. Largely, we confirm the observation of other groups that the drug development portfolio initially focuses on areas of highest promise, but gradually expands outward to include a variety of indications, and larger market share. During this time, the cumulative adverse events grow and cumulative ORR shrinks. Our analysis suggests that a large portfolio of trials is a feature not restricted to top firms with large market capitalization but extends throughout the industry.

4.6 | Strengths and limitations

Our study has important strengths. First, we systematically searched and cross-referenced clinical trial registry profiles for their primary publications in PubMed and Embase. Second, we conducted our study in a masked, duplicate fashion to reduce bias and errors in data extraction following best practice guidance from Cochrane.[42] Third, we uploaded a protocol a priori to our investigation as well as our raw data, analysis scripts and the Google extraction form making this study reproducible. Fourth, we used a validated systematic review search platform, Rayyan, to complete our title and abstract screening.[21] Fifth, we used an adapted methodology from previously published works to conduct our study.[13] Finally, our investigation is the first exploration of the research priorities of a company and their first approved product.

Our study also has limitations. First, this study is a cross-sectional analysis of clinical trials assessing the effects of cabozantinib in oncology indications. Because of this, it is not generalizable to other drugs, fields of medicine or future indications of cabozantinib. Second, our systematic search may have failed to return all relevant studies; this weakness is common to all synthesis methodologies.[43] A third

limitation of this study is the absence of including unpublished results in the analysis. Trials with negative results are less likely to get published. Negative trials may be published as letters to the editor or research letters as opposed to original investigations. Taken together, it is possible that the inclusion criteria of our systematic search may have precluded unpublished results from our analysis. We did not include unpublished results listed on clinicaltrials.gov, as this data is often preliminary, unfinalized and not peer reviewed. However, we do believe that our sample is highly representative of the available, discoverable and peer-reviewed information on the characteristics of cabozantinib. Finally, errors in data extraction may have persisted into our final analyses, however, we employed best practice approaches to data extraction to mitigate this risk.

5 | CONCLUSIONS

We sought to evaluate the drug development profile of cabozantinib, highlighting the risk/benefit metrics over time as cabozantinib has been assessed for the treatment of various cancers. We found that the risk/benefit profile has notable times of increased risk and decreased benefit. The majority of trials were non-randomized, single-arm trials, which are more likely to over-predict the benefit of a drug via ORR compared to double-blinded, randomized controlled trials. We also found that the effectiveness of cabozantinib has been inconsistent across indications, and frequently among trials for the same indication. We recommend that the risk/benefit profile be considered when deciding whether to pursue further cabozantinib trials for various indications.

AUTHOR CONTRIBUTIONS

The work reported in the article has been performed by the authors, unless clearly specified in the text. Each of the author's contributions have been reported in accordance with CRediT. **Griffin K. Hughes**: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing – original draft, writing – review & editing. **Nicholas B. Sajjadi**: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing – original draft, writing – review & editing. **Brooke Gardner**: data curation, investigation, methodology, project administration, supervision, validation, writing – original draft. **Joshua K. Ramoin**: data curation, formal analysis, investigation, methodology, supervision, writing – original draft. **Jordan Tuia**: data curation, resources, software, visualization. **Alyson Haslam**: conceptualization, formal analysis, methodology, project administration, resources, validation, supervision, writing – review & editing. **Vinay Prasad**: conceptualization, formal analysis, investigation, methodology, project administration, resources, supervision, validation, writing – original draft, writing – review & editing. **Matt Vassar**: conceptualization, investigation, methodology, project administration, resources, supervision, validation, writing – original draft, writing – review & editing.

CONFLICT OF INTEREST STATEMENT

V.P. receives research funding from Arnold Ventures through a grant made to UCSF, and royalties for books and writing from Johns Hopkins Press, MedPage and the Free Press. He declares consultancy roles with UnitedHealthcare and OptumRX; He hosts the podcasts, Plenary Session, VPZD, Sensible Medicine, writes the newsletters, Sensible Medicine, the Drug Development Letter and VP's Observations and Thoughts, and runs the YouTube channel Vinay Prasad MD MPH, which collectively earn revenue on the platforms: Patreon, YouTube and Substack. M.V. reports receipt of funding from the National Institute on Drug Abuse, the National Institute on Alcohol Abuse and Alcoholism, the U.S. Office of Research Integrity, Oklahoma Center for Advancement of Science and Technology and internal grants from Oklahoma State University Center for Health Sciences—all outside of the present work. All other authors have no financial or non-financial conflicts of interest to report.

DATA AVAILABILITY STATEMENT

Our data (protocol, search strategy, coding and results) will be available on Open Science Framework through the lifecycle of the repository. Further information is available from the corresponding author upon request.

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