Title

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Journal

Clinical Therapeutics, 46(6)

ISSN

0149-2918

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Publication Date

2024-06-01

DOI

10.1016/j.clinthera.2024.04.006

Clinical Therapeutics 46 (2024) e107–e113

Contents lists available at ScienceDirect

Clinical Therapeutics

journal homepage: www.elsevier.com/locate/clinthera

Original Research

Assessing Patient Risk, Benefit, and Outcomes in Drug Development: Insights From Afatinib Clinical Trials Across Diverse Cancer Indications

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ARTICLE INFO

Key words:
Afatinib
Cross-sectional study
ClinicalTrials.gov
Lung cancer

ABSTRACT

Purpose: In 2013, afatinib was approved for non–small-cell lung cancer with subsequent indication expansion. We investigated published afatinib clinical trials to assess risk and benefit profiles for the drug in its approved indication of non–small-cell lung cancer as well as in off-label uses. Previous literature demonstrates excessive patient burden and limited benefit as afatinib has spread into more indications. A trial analysis is needed to establish efficacy and risk.

Methods: In this investigation, we screened literature databases and clinical trial registries for trials of afatinib as monotherapy or in combination interventions for cancer treatment. We extracted participant demographics, adverse event characteristics, as well as clinical and surrogate endpoints for each trial. Studies were deemed positive, negative, or indeterminate based on their achieving of primary endpoints as well as their safety.

Results: Our search yielded 2444 articles; we excluded 2352 articles for a final inclusion of 92 trials of 8859 patients. Our sample had 49 (53%) positive trials, 27 (29%) negative trials, and 16 (17%) indeterminate trials. The most common off-label indications for afatinib were breast cancer and squamous cell carcinoma of head and neck. The median OS for all trials was 8.4 months, median PFS 3.4 months, and the total ORR was 29.6%. Our study found that trials performed in disease states beyond the initial indications were largely negative with little patient benefit. The adverse events within our trial sample appear to be in line with expectations for toxicity.

Implications: These results are consistent with other studies that present similar findings, such as in Carlisle et al which indicate limited efficacy in nonapproved indications. Future trials should keep this potential evidence and patient burden in mind before initiation of those trials. This study contributes to the understanding of afatinib's risk-benefit profile across many clinical applications.

Introduction

Lung cancer is the leading cause of cancer-related deaths for both men and women in the United States with an estimated 127,070 deaths occurring in 2023.[1] Given the high mortality associated with this malignancy, pharmaceutical companies invest a considerable amount of research and money into the exploration of novel treatment options. Afatinib, an irreversible tyrosine kinase inhibitor targeting epidermal growth factor receptor (EGFR) mutations, was developed for the treatment of non–small-cell lung carcinoma.[2] Afatinib targets the specific molecular alterations which drive tumor growth.[3] Though afatinib has been demonstrated to provide clinical benefits in the treatment of non–small-cell lung carcinoma, it is associated with a substantial cost.[4] This situation raises concerns regarding the balance between overall cost-effectiveness of treatment and the potential adverse effects patients experience. Understanding these adverse events (AEs) are imperative to guide clinicians and healthcare policy makers to ensure patient safety.

In addition to financial concerns surrounding afatinib a broader concern regarding the patient safety of drug development exists. Given the recent rise in cancer drug approvals there is cause for concern regard-

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https://doi.org/10.1016/j.clinthera.2024.04.006
Accepted 12 April 2024

ing potential inefficiencies of drug development.[5,6] Evidence suggests a fewer number of positive clinical endpoints is required for a drug to earn additional FDA approvals.[7] Additionally, over-testing for cancer drugs after initial approval illustrates a lack of efficacy in non-FDA approved indications.[7] This pattern of redundant trials exposes patients to unnecessary adverse events with little benefit, further underscoring the need for measures of clinical efficacy to be pursued throughout the process of drug indication expansion. Therefore, measures of clinical efficacy and safety should be pursued throughout the process of drug indication expansion. One such example is the approval of imatinib for the treatment of chronic myelogenous leukemia.[7] Sixty percent of trials launched prior to FDA approval provided a positive primary endpoint within 8 years.[7] Yet after FDA approval, less than 10% of trials initiated obtained approval or reached a positive primary endpoint. This pattern of redundant trials provides cause for concern as cancer drugs are inherently toxic and expose patients to unnecessary adverse events with little benefit.

While the risk/benefit profile has been examined for other therapies,[8] these findings cannot be expanded to other chemotherapy agents. Therefore, it is essential to examine the drug portfolio of afatinib, including both sponsor-conducted trials and trials involving off-label use, to assess the patient burden and benefit accrued through its development, and to shed light on the potential harms associated with its applications.

Methods

Study Design/Open-Science

This is a cross-sectional study that evaluated clinical trials of afatinib (*Dimaleate*® or *Gilotrif*®, Boehringer Ingelheim) for its risk/benefit profiles through its development and various potential indications outside of the initially approved applications. To increase rigor, open science, and reproducibility, we uploaded a protocol prior to the investigation. After the conclusion of the investigation, we uploaded raw data, statistical analysis scripts, and extraction forms to Open Science Framework (OSF) – a free-to-upload data storage location.[9] Our data is viewable on OSF through the lifecycle of the repository or upon request.[10]

Research Questions, Definitions, and Hypothesis

Our research questions were, "What are the total benefit/risk profiles of afatinib?" and "Does the overall risk/benefit portfolio of afatinib represent an increased danger to patients?." We defined a clinical trial *profile* as a drug's combined risk and benefit by patients in a trial as measured using metrics in our *Data Extraction* section. We defined a drug's *portfolio* as combined results from our clinical trial profiles. We hypothesized that afatinib's trial expansion into off-label indications would produce an overall negative drug portfolio and increased patient risk.

Training

All authors were trained on reporting, clinical trial design, and outcomes by author VP, a clinical oncologist, oncologic researcher, and expert in evidence-based medicine. Authors were educated on Response Evaluation Criteria in Solid Tumors (RECIST)[11] and the Common Terminology Criteria for Adverse Events (CTCAE).[12] We trained authors to use Rayyan (https://www.rayyan.ai/)[13]: a tool to screen large samples of research articles and trials for study exclusion or inclusion. Data extraction was carried out using a pilot-tested Google extraction form. For training purposes, authors extracted data on 5 model articles prior to coding the included sample.

Literature Search

On May 25, 2023, we performed a systematic search of PubMed/MEDLINE, Cochrane CENTRAL, ClinicalTrials.gov, and Embase, for clinical trials using afatinib on its own as monotherapy or in combination with other interventions for the treatment of cancer. We made our search strings uniform by using the PolyGlot Search Translator (https://sr-accelerator.com/#/polyglot) developed by Bond University and the Institute for Evidence Based Healthcare across all databases.[13] Our search strings, including initial returns and date of search, have been uploaded to OSF and will be included as supplemental data in the final manuscript.

Selection Process

Search returns were uploaded into Rayyan for trial and manuscript screening. Two authors (CW and RH) screened abstracts and titles for potential incorporation in a duplicate and masked manner. After the completion of screening, author CL resolved any discrepancies. We documented reasons for exclusion throughout the screening process and created a flow chart.

Inclusion and Exclusion Criteria

Studies that are eligible for inclusion have to be: (1) published in English, (2) use radiographically derived (e.g., RECIST) response criteria for solid tumors to assess the clinical benefit of afatinib, (3) assessing effectiveness of afatinib as both monotherapy or in combination with other pharmaceutical interventions to treat solid tumors, and (4) clinical trials of mature, human subjects. We excluded trials on nonsolid tumors, nononcological trials, studies on biosimilars, pharmacology trials on healthy patients, and studies that were solely pediatric patient populations. Excluded study types were: interim results, secondary reports, clinical trial follow-ups and updates, letters to the editor, literature reviews, case reports, meta-analyses, systematic reviews, human tissue studies, laboratory studies, preclinical studies, corrections or redactions, conference abstracts, opinion pieces, and editorials.

Data Extraction

Postdata screening, an included study pool of trials was subjected to data extraction in a duplicated and masked method by 2 authors (HH and CW). A third author was available to sort through discrepancies (CL). Authors pulled the following variables: date of publication, published trial title, clinical trial registry number, PubMed ID, country of first author's affiliation, mean or median age of participants, number of participants, number of female participants, number of male participants, blinding of trial, indication(s) of the trial, trial randomization, study funding, metastatic or nonmetastatic stage, number of centers, if the trial evaluated monotherapy or combination therapies, phase of the trial, randomization ratio, and conflicts of interest.

For the evaluation of benefit and risk outcomes the following variables were extracted for each, individual treatment arm: median progression-free survival (PFS) in months, the name of the arm, median overall survival (OS) in months, hazard ratio of PFS, hazard ratio of OS, complete response (CR), partial response (PR), AEs grade, objective response rate (ORR) as laid out according to the RECIST criteria, number of grade 3 to 5 adverse events as defined by the CTCAE, and if the trial was positive, negative, or indeterminate. End result quantifications and AEs including all participants of a trial of a specified indication were extracted. A trial was judged to be positive if it met its prespecified endpoint and described as having a reasonable toxicity. Reasonable toxicity was defined by the individual trialists as implemented in Carlisle et al[8] A trial was judged to be indeterminate if it did not have prespecified endpoints but was using a treatment where the safety was deemed reasonable. A trial was negative if prespecified endpoints were not met or if the therapy was found to be unsafe or overly toxic. The tolerability and safety of a therapy was established by the authors of the individual trial.[8]

We extracted the higher phase in studies that contained more than 1 phase in their manuscript. We included all stand-alone clinical tri-

als regardless of phase. We assumed only PRs were measured in studies that reported ORRs but did not specify the breakdown of PRs or CRs. We extracted only confirmed results if trialists stated responses as confirmed and unconfirmed. We extracted the independently confirmed measurements when trialists specified measurement confirmation was conducted by independent investigators. We combined dose expansion, dose-escalation treatment, and indications arms into a single summary arm. We extracted variables of interest from the precrossover allocation groups to control for carryover effects that influenced response rate in crossover studies. Patients enrolled in trials that are evaluating 2 or more different cancer types were listed as "multiple indications." A supplement was made available for the identification of each reported indication. Values of objective response rates were calculated based on the total number of evaluable patients unless this was not specified by the author(s). In this case, ORR was based on all participants within that study.

Statistical Analysis

We used R(version 4.2.1) and RStudio to perform in depth statistics.

Ethical Oversight

This protocol was evaluated by the Oklahoma State University Center for Health Sciences and it was determined that this research qualifies as nonhuman subjects research as defined in regulation 45 CFR 46.102(d) and (f).

Results

General Characteristics

Our literature search of bibliographic databases yielded 2443 returns which yielded both published and registered clinical trials for potential inclusion. Following title/abstract and full-text screening, 92 studies met our inclusion criteria with 50 combinations and 42 monotherapy trials. Rationale for exclusions can be found in Supplemental Figure 1. Of the 92 studies within our sample, there were 8859 participants with 48.7% female and 51.3% male. Afatinib is approved for 2 cancer indications and was tested in more than 11 indications. Sixty-three of 92 trials tested for specific tumor mutations. The most commonly evaluated mutations were EGFR (48 trials with 3350 positive patients) and HER2 (18 trials including 925 positive patients). There were a total of 70 nonrandomized trials and 22 randomized trials. Additional trial characteristics can be found in Supplemental Table I.

Endpoints

The median PFS of all indications was 3.4 months. The highest median PFS was observed in lung adenocarcinoma with 10 months and non–small-cell lung cancer with 6.3 months. The median OS of all indications was 8.9 months. Lung adenocarcinoma demonstrated the highest OS with 23.8 months. In contrast, urothelial carcinoma had the lowest OS of 5.3 months (Tables 1A-C). Twenty-two randomized controlled trials were analyzed and contained an overall median ΔPFS of 0.5 months and ΔOS of 0.2 months. The 1 randomized breast cancer trial had the poorest ΔOS of −8.1 with a ΔPFS of −0.1 months. A phase III NSCLC trial comparing afatinib to traditional chemotherapy had the highest ΔPFS of 5.4 months, but only had a ΔOS of −0.1 months (Table II).[14] Another observed endpoint was ORR. The highest median ORR of 59.1 % was seen with lung adenocarcinoma, but all indication's total ORR is 29.6%. The highest partial response rate is for lung adenocarcinoma (57.6%). The total complete response rate across all indications is 1.0% (Tables 1A-C).

Table 1A
Trial characteristics and outcomes by indication.

Solid tumor indications	# of trials	# of participants	# of Males	# of Females	# of GRADE 3 - 5 Events	Median OS (months)	Median PFS (months)	Median age	Median partial response rate	Median complete response rate	Median ORR*
Biliary tract cancer	1	9	5	4	2	7.7	6	60	0.0%	0.0%	0.0%
Breast cancer	10	900	2	898	831	15.65	3.8	53	13.9%	0.0%	14.0%
Colorectal cancer	1	91	55	36	32	9.45	1.6	63	3.4%	0.0%	3.4%
Esophageal squamous cell carcinoma	1	49	45	4	10	6.3	3.4	60	14.9%	0.0%	14.9%
Glioblastoma	2	155	98	57	59	9.8	1.53	55.4	0.0%	-	0.0%
Lung adenocarcinoma	4	581	212	369	289	23.8	10	61	57.6%	1.5%	59.1%
Multiple indications	23	944	444	453	686	8.6	2.7	58.8	6.0%	0.0%	6.0%
Non–small-cell lung cancer	36	3373	1349	2024	1477	14	6.3	63	29.1%	0.0%	29.9%
Oropharyngeal squamous cell cancer	1	10	10	-	4	-	-	59.5	0.0%	0.0%	0.0%
Pancreatic cancer	1	115	50	65	256	7.35	3.9	73	14.3%	0.0%	14.3%
Squamous cell carcinoma of head and neck	9	1790	1520	270	715	6.8	2.9	58	10.2%	0.0%	10.2%
Squamous cell carcinoma of the lung	2	819	685	134	196	7.3	2.6	65	6.3%	0.0%	6.6%
Urothelial carcinoma	1	23	18	5	15	5.3	1.4	67	8.7%	0.0%	8.7%
Totals	92	8859	4493	4319	4572	8.15	3.15	60	28.6%	1.00%	29.6%

* Response rate median calculations for those indications using RECIST or mRECIST only.

Table 1B
Trial characteristics and outcomes by indications for monotherapy.

Solid tumor indications	# of trials	# of Randomized trials (n, (%))	# of participants	# of Males	# of Females	# of GRADE 3 - 5 events	Median OS (months)	Median PFS (months)	Median Age	Median partial response rate	Median complete response rate	Median ORR*
Breast cancer	5	1 (20%)	220	0	220	107	16	3.5	51.5	33.3%	0.0%	33.3%
Esophageal squamous cell carcinoma	1	0 (0%)	49	45	4	10	6.3	3.5	60	14.9%	0.0%	14.9%
Lung adenocarcinoma	3	0 (0%)	236	91	145	83	23.8	10	64.5	57.6%	1.5%	59.1%
Multiple indications	7	0 (0%)	231	110	121	94	8.6	2.9	58	0.0%	0.0%	2.9%
Non–small-cell lung cancer	18	2 (11.1%)	1996	817	1179	789	14	11.8	64.5	61.4%	0.0%	62.6%
Squamous cell carcinoma of head and neck	6	6 (100%)	1725	1471	254	643	6.6	2.8	58	8.1%	0.0%	9.7%
Squamous cell carcinoma of the lung	1	1 (100%)	795	666	129	184	7.4	2.3	65.5	4.8%	0.1%	5.0%
Urothelial carcinoma	1	0 (0%)	23	18	5	15	5.3	1.4	67	8.7%	0.0%	8.7%
Totals	42	10	5275	3218	2057	1925	8	3.2	62.25	27.9%	0.7%	28.6%

*Response rate median calculations for those indications using RECIST or mRECIST only.

Table 1C
Trial characteristics and outcomes by indications for combination therapy.

# of trials	# of randomized trials (n, (%))	# of participants	# of males	# of females	# of GRADE 3–5 events	Median OS (months)	Median PFS (months)	Median age	Median partial response rate	Median complete response rate	Median ORR*
1	0 (0%)	9	5	4	2	7.7	6	60	0.0%	0.0%	0.0%
5	2 (40%)	680	2	678	724	14.4	4	53.1	8.0%	0.0%	8.0%
1	1 (100%)	91	55	36	32	9.5	1.6	63	3.0%	0.0%	3.0%
2	1 (50%)	155	98	57	59	9.8	1.5	55.4	-	-	-
1	1 (100%)	345	121	224	206	-	9	61.3	-	-	-
16	1 (6.3%)	713	334	332	592	8.3	2.7	58.4	6.0%	0.0%	6.0%
18	5 (28%)	1377	532	845	688	13.5	5.3	60.5	30.0%	0.0%	30.0%
1	0 (0%)	10	10	0	4	-	-	59.5	0.0%	0.0%	0.0%
1	1 (100%)	115	50	65	256	7.4	3.9	73	10.0%	0.0%	10.0%
3	0 (0%)	65	49	16	72	8.4	4.1	58	50.0%	2.0%	60.0%
1	0 (0%)	24	19	5	12	7.3	3.3	63.5	10.0%	0.0%	10.0%
50	12	3584	1275	2262	2647	8.4	3.95	60	29.6%%	1.60%	31.2%

*Response rate median calculations for those indications using RECIST or mRECIST only.

Table 2
ΔPFS and ΔOS for randomized controlled trials.

Trial	Phase	Result	Date	Indication	Afatinib group	Comparison group	ΔPFS*	PFS P-value	ΔOS*	OS P-value
NCT00656136	3	Negative	2012-03-26	Non–small-cell lung cancer	Afatinib	Placebo	2.2	Significant (<0.0001)	-1.2	Nonsignificant (0.74)
NCT00949650	3	Indeterminate	2013-09-20	Lung adenocarcinoma	Afatinib	Cisplatin and Pemetrexed	4.2	Significant (0.001)	Not Reported	Not Reported
NCT01121393	3	Indeterminate	2014-01-15	Non–small-cell lung cancer	Afatinib	Cisplatin plus Gemcitabine	5.4	Significant (<0.0001)	-0.1	Nonsignificant (0.76)
NA	2	Indeterminate	2014-06-13	Squamous cell carcinoma of head and neck	Afatinib	Cetuximab	-0.5	Nonsignificant (0.71)	Not Reported	Not Reported
NCT01345682	3	Positive	2015-04-16	Squamous cell carcinoma of head and neck	Afatinib	Methotrexate	0.9	Nonsignificant (0.3)	0.8	Nonsignificant (0.7)
NCT01523587	3	Indeterminate	2015-07-05	Squamous cell carcinoma of the lung	Afatinib	Erlotinib	0.7	Significant (0.0103)	1.1	Significant (0.0077)
NCT01085136	3	Indeterminate	2015-12-08	Non–small-cell lung cancer	Afatinib and Paclitaxel	Chemotherapy	2.8	Significant (0.003)	0	Nonsignificant (0.9936)
NCT01125566	3	Negative	2016-01-26	Breast cancer	Afatinib plus Vinorelbine	Trastuzumab plus Vinorelbine	-0.1	Nonsignificant (0.43)	-8.1	Significant (0.0048)
NCT01466660	2	Indeterminate	2016-04-12	Non–small-cell lung cancer	Afatinib	Gefitinib	0.1	Significant (0.083)	2.9	Nonsignificant (0.33)
NCT01156545	2	Negative	2017-01-13	Non-small-cell lung cancer	Afatinib	Afatinib and Simvastatin	2.6	Nonsignificant (0.89)	-3	Nonsignificant (0.47)
NCT01538381	2	Positive	2018-04-01	Squamous cell carcinoma of head and neck	Afatinib	No treatment	Not Reported	Not Reported	Not Reported	Not Reported
NCT00809133	1	Positive	2018-08-07	Multiple indications	Afatinib, Carboplatin	Afatinib, Carboplatin, Paclitaxel	Not Reported	Not Reported	Not Reported	Not Reported
NCT01345669	3	Negative	2019-06-13	Squamous cell carcinoma of head and neck	Afatinib	Placebo	Not Reported	Not Reported	Not Reported	Not Reported
NCT01856478	3	Positive	2019-11-01	Squamous cell carcinoma of head and neck	Afatinib	Methotrexate	0.3	Significant (0.0005)	0.5	Nonsignificant (0.32)
NCT02438722	2	Negative	2020-10-06	Non–small-cell lung cancer	Afatinib	Afatinib and Cetuximab	1.5	Nonsignificant (0.94)	Not Reported	Not Reported
NCT01728818	2	Negative	2021-02-12	Pancreatic cancer	Gemcitabine and Afatinib	Gemcitabine	0	Nonsignificant (0.43)	-0.1	Nonsignificant (0.8)
NCT02716311	2	Negative	2021-05-24	Non–small-cell lung cancer	Afatinib	Afatinib and Cetuximab	-1.5	Not Reported	Not Reported	Not Reported
NCT01427478	3	Negative	2022-11-09	Squamous cell carcinoma of head and neck	Afatinib	Placebo	Not Reported	Not Reported	Not Reported	Not Reported
						Median	0.5		0	

* MonthsTable 2: Delta PFS and Delta OS for all 22 (of 92; 23.9%) randomized control trials in our sample. Three arm randomized trials were excluded from Table 2.

Risk Assessment

In our analysis of afatinib trials, there were 8859 participants and 4572 grade 3 to 5 AEs reported. In total, 82.6% of trials for afatinib did not report all AEs (Tables 1A-C). Supplemental Figure 2 displays the cumulative adverse event rate (AER) by year, plotted against the cumulative ORR. Following the LUX-Lung 3 trial and initial FDA approval in 2013, there was a significant increase of over 60% in AEs, accompanied by an increase in ORR of over 30%. However, the subsequent year in 2014, saw a decline in the ORR, dropping to roughly 12%. Despite this decline, the AEs remained consistently elevated, surpassing 50% after 2013. The ORR fell to a level only slightly higher than what was found in years prior to 2013. Since 2014, both the AER and ORR have maintained a relatively stable pattern, with incremental improvements in ORR (Supplemental Figure 2). From 2013 to 2015 there is a noticeable separation of AER and ORR which lies directly after the year of approval, 2013. This could be due to the expansion of indications in trials. Supplemental Figure 3 shows that as the number of participants has increased in the last decade, AEs have increased at a similar rate. The last few years AEs have decreased moderately when compared to the number of participants.

AERO Diagram

Figure 1 visually captures the growth of the Afatinib clinical portfolio, illustrating its various phases and indications. Prior to 2013, 10 trials were evaluated for efficacy and safety of afatinib, 60% of these reported positive outcomes. The phase III trial conducted in 2013 led to FDA approval for NSCLC, reporting tolerable safety and reasonable efficacy, but was considered indeterminate due to the lack of a clear threshold in their primary efficacy endpoint of PFS. Afatinib was continuously tested in NSCLC, with 42 total trials over the past decade. These trials were consistently positive with only 11 negative outcomes, but no obvious trend was observed. After the initial FDA approval of afatinib there was expansion of treatment in different indications, these trials were 83.7% sponsored by Boehringer Ingelheim Pharmaceuticals, Inc. in some capacity (Table I). Several off-label indications were evaluated in small clinical trials, often resulting in inconclusive or negative outcomes. One notable exception was the conduct of 10 breast cancer trials carried out since 2012; of these trials, 7 showed negative or indeterminate results and only 3 reported positive results. However, of the 3 positive breast cancer studies, all 3 trials include less than 30 patients that were evaluable for response (Figure 1). In total, 49 (53.3%) of the studies had positive outcomes, 27 (29.6%) had negative outcomes, and 16 (17.4%) had indeterminate outcomes (Supplemental Table I).

Comparison of Approved Versus Nonapproved Outcomes

Based on the suggestions of our reviewer, we compared the median PFS, OS, and ORR between the FDA approved indication — EGFR-positive NSCLC (N = 34 trials) to nonapproved indications (N = 53 trials). In this analysis, comparing the FDA approved indications (N = 34 trials) of EGFR-positive NSCLC trials, to nonapproved indications (N = 62). Median PFS for the approved indications was 11 months while the nonapproved indications were 2.95 months. Similarly, median ORR was higher in approved indications at 59% compared to 8.5% in nonapproved indications. Finally, we also found OS to be higher in approved indications with a median of 23.8 months compared to a median OS of 8.55 months. These findings indicate the gap in efficacy of approved versus nonapproved indications. Supplemental Figure 4 displays the ORR relative to the adverse event rate for EGFR-positive NSCS trials vs nonapproved indications. As shown, for EGFR-positive NSCLC trials, a small difference was observed between ORR and AE rates. In contrast, a notable difference was observed for trials of nonapproved indications.

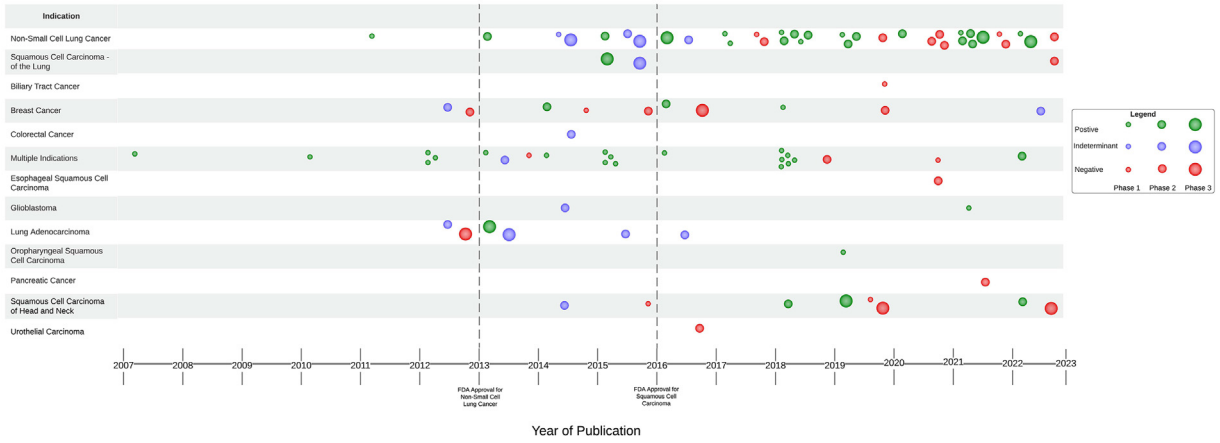

Figure 1. Aero diagram representing afatinib drug trials from 2007 to 2023. Stratified by indication.

Discussion

Afatinib was approved by the US FDA in 2013 for use in metastatic NSCLC with EGFR deletions. This was based on the randomized, open-label LUX-Lung 3 trial which indicated increased PFS when compared to chemotherapy.[15] It was later approved for use in metastatic, squamous EGFR mutations in NSCLC after progressing from platinum-based chemotherapy.[16] The drug sponsor, Boehringer Ingelheim Pharmaceuticals, Inc, sponsored the evaluation of afatinib for use in eleven tumor types and was approved by the US FDA for use in two.

The primary finding of this study sheds light on the widespread use of afatinib across multiple, other cancer types, resulting in diverse outcomes. Our analysis demonstrated that when afatinib was tested within its FDA approved indication of NSCLC, favorable results were observed. However, as trialists extended the exploration of afatinib to other indications, predominantly negative outcomes were observed. Particularly concerning was the significant increase in grade 3 to 5 AEs alongside ORRs below 25% in trials conducted outside the scope of FDA-approved indications. Our sensitivity analysis in Supplemental Figure 4 also provides insight into the efficacy divide between FDA approved versus nonapproved indications. These findings draw attention to the evolving risk/benefit profile of afatinib and emphasize the importance of monitoring its efficacy and safety profiles over time.

In 2020, Carlisle et al conducted a study examining the drug portfolio of imatinib. Their results showed prior to FDA approval, 66% of imatinib trials demonstrated successful outcomes. Following FDA approval, testing of imatinib was expanded to 36 additional cancer types with only 2 additional approvals.[7] However, the positive results relative to trial endpoints decreased to 13%, showing a clear decrease in drug efficacy for additional cancer types selected before and after FDA approval.[7] Our results demonstrated similar findings with successful outcomes being noted prior to afatinib's FDA approval for NSCLC. However, following approval, trialists began to explore its effectiveness in more than eleven different cancer types. Our results revealed a wide range of outcomes, with trials yielding both positive and negative effects. These findings suggest that while afatinib showed to be an effective treatment option for NSCLC, its effectiveness was less consistent with off-label use.

In addition to the use of afatinib in trials for its primary indication, other studies showed its use in breast, squamous cell carcinoma of head and neck, pancreatic, colorectal, and glioblastoma. Among these off-label uses, afatinib has been used in 10 breast cancer clinical trials since 2012. Of these trials, only 3 trials met their primary endpoints. With a median PFS of 3.8 months and ORR of 14%, the use of afatinib in breast cancer trials did not yield notable results. The initial indication of lung adenocarcinoma had a median PFS of 10 months and ORR of 59%. These results call into question the continued use of afatinib in breast cancer trials. In a drug evaluation, afatinib was found to be initially promising, but additional trials were halted due to an unfavorable risk/benefit analysis.[17] When tested in 2 arm randomized trials, studies compare the first arm, which consisted of an afatinib backbone treatment, to a second arm which tested another treatment including either a combination, placebo, other cancer drug, or traditional chemotherapy. The randomized trial results show little difference between arms, with a difference of 0.5 months median PFS and a difference of 0 months in median OS.

AEs are an important measurement used when examining clinical trials. Moreover, the accurate reporting of AEs is necessary as they have the potential to guide clinical decision making for patients assessing treatment options. Our study revealed a notable increase in AEs following FDA approval of afatinib in 2013. For example, diarrhea in breast cancer is notably higher and trialists continue to test within the indication. Commonly reported AEs include diarrhea, rash/acne, and stomatitis. In addition, it is concerning that 82.6% of trials failed to report for all AEs. Many of our trials excluded incidents involving grade 3 and 4 events. This highlights the necessity for accurate reporting as grade 3 and 4 events are often what lead to dose reduction and even treatment discontinuation.[18]

Our analysis revealed that despite receiving FDA approval for NSCLC, afatinib continues to be tested for this indication. Further, trials not focusing on NSCLC had significantly lower PFS and ORRs. These findings demonstrate a waste of research funding, clinical resources, and increased patient burden. The current data for afatinib points to more efficacious use in the setting of non–small-cell lung cancer and more specifically lung adenocarcinoma. As stated within Chalmers et al, an overview of previous research should be systematically evaluated before proceeding with continued trials in an effort to reduce resource waste within the space of scientific research and in an effort to improve efficiency and avoid placing patients into situations in which their health will not be benefitted by a given treatment.[19]

Strengths and Limitations

This study has several strengths and limitations. First, our search of clinical trial registries was cross-referenced to find primary literature in PubMed and Embase. Second, our data extraction was conducted in a masked, duplicate fashion using 2 independent investigators which aligns with best practice guidance.[20] Third, we uploaded our protocol *a priori*, as well as our raw data, analysis scripts, and the Google extraction form for reproducibility purposes. Lastly, we adapted our methods from past published systematic reviews laid out by the gold standard for this type of study, Cochrane Collaboration Guidelines.[20] Although maintain-

ing rigid guidelines and methodologically high standards this study is not without its weaknesses. An initial limitation would be that our systematic search looking for potential studies to include in our analysis could leave out articles and trials that should be included. This is a common limitation built into most, if not all, meta-analysis style research.[21] Another limitation could be in data extraction that was not made apparent through our rigorous review process and standardized approach to this analysis. A final limitation would be that this is not generalizable to other areas of medicine and other potential applications for afatinib, as our study only evaluated studies that are oncologic in setting.

Conclusion

The goal of this study was to evaluate afatinib, a TKI drug, and its risks versus benefits for varying cancer indications. We have found that when tested beyond its primary indication for lung cancer there was little success and displayed poor outcomes. We also noticed there was a trend in lung and breast indications to continue testing despite numerous past trials examining efficacy and safety while providing good results in the case of lung cancer and poor results with breast cancer. The AEs found within our trial sample appear to be in line with current industry expectations for toxicity, as most cancer drugs have toxic qualities.[22] However, subjecting patients to these events is still concerning, especially when there is limited evidence supporting their efficacy. We recommend the pursuit of future trials for the indications in which there is apparent benefit and to avoid financial waste and patient suffering by pursuing indications in which there is little evidence for outcome improvement.

Declaration of competing interest

VP reports research funding from Arnold Ventures; royalties from Johns Hopkins Press, Medscape, and MedPage; honoraria from GrandRounds/lectures from universities, medical centers, nonprofits, professional societies, YouTube, and Substack; consulting from UnitedHealthcare and OptumRX; speaking fees from Evicore. Plenary Session podcast has Patreon backers. MV 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 nothing to report.

Acknowledgments

Funding

None.

Author Contributions

R. Hunter Hall: Writing—original draft, writing—editing, investigation, data curation; Carson L. Writing—original draft, writing - editing, investigation, data curation; Griffin K. Hughes: Software, formal analysis, methodology; Andriana M. Peña: Writing—editing/review, supervision; Chase Ladd: Writing—editing/review, supervision; Brooke Gardner: Writing—editing/review, supervision; Ryan McIntire: Writing—editing/review, supervision; Jane Rubenstein: Writing—editing/review; Jordan Tuia: Software and statistical analysis; Alyson Haslam: Software and formal analysis; Vinay Prasad: Writing—review & editing, supervision; Matt Vassar: Project administration, conceptualization, writing—review & editing, supervision.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinthera.2024.04.006.

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