Aus dem QUEST Center des Berlin Institute of Health, Translationsforschungsbereich der Charité – Universitätsmedizin Berlin

DISSERTATION

The persistence and burden of failing drug development paradigms: An exploratory analysis of VEGF Inhibition in breast cancer / Beharrlichkeit und Bürde fehlgeschlagener Paradigmen in der Arzneimittelentwicklung: Eine explorative Analyse der VEGF-Inhibition bei Brustkrebs

zur Erlangung des akademischen Grades
Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

von

Peter Roland Grabitz

aus Edmonton

Datum der Promotion: 03.03.2023

Contents

List of figures / Abbildungsverzeichnis

List of tables / Tabellenverzeichnis

Abbreviations

AB	Antibody
Ap	Actual cited patients
AE	Adverse Event
AERO	Accumulating Evidence and Research Organization diagram
AST/ALT	Aspartate Transaminase/Alanine Transaminase
CI	Confidence Interval
CPI	Citable Patient Index
CPI (+)	Citable Patient Index for positive trial reports
CPI (-)	Citable Patient Index for non-positive trial reports
CTCAE	National Cancer Institute Common Terminology Criteria for AE
EMA	European Medicines Agency
Eff.	Efficacy
Ep	Eligible to be cited patients
FDA	Food and Drug Administration
GGT	Gamma-Glutamyl Transferase
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hazard Ratio
JIF	Journal Impact Factor
MeSH	Medical Subject Headings
mRNA	Messenger Ribonucleic Acid
mTOR	Mammalian Target Of Rapamycin
ORR	Objective Response Rate
PICO	Patient Intervention Comparison Outcome
pCR	pathological Complete Response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL	Quality of Life
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious Adverse Event
TKI	Tyrosine-Kinase Inhibitor
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
WHO	World Health Organization

Abstract

Background: Failures in cancer drug development impose heavy burdens on patients, researchers, industry, and funders. Burdens in targeted drug development could be mitigated if investigators efficiently integrated not only trial outcomes, but also evidence for underlying pathophysiological hypotheses of drugs tested. However, little is known about how clinical trials testing different drugs with the same targets learn from each other's failures and successes. The goal of this project was: a) to map the total patient burden and benefit of trials testing one failed drug development paradigm that showed particular perseverance (Vascular Endothelial Growth Factor [VEGF]-inhibition in breast cancer), and b) to describe the production and uptake of evidence from related clinical trials and address why the research agenda persisted despite limited evidence.

Methods: We searched in the Embase and MEDLINE databases on February 9, 2017 for clinical trials testing VEGF inhibitors against breast cancer. We measured risk using drug-related serious adverse events (SAEs) Grade 3 or higher, benefit by objective response rate (ORR) and survival advantage versus a comparator arm, as well as trial outcomes by whether studies met their primary endpoint with acceptable toxicity. We assessed citation bias by comparing the number of cited earlier reports with the number of overall citable earlier reports within the trial reports included.

Results: Up to February 2017, the VEGF inhibition paradigm in breast cancer consisted of 146 trials of 19 drugs that enrolled 17,924 patients. 6,441 patients receiving a VEGF inhibitor experienced ORR (46% of intent-to-treat population, 95% confidence interval [CI]: 45.1% to 46.8%), 114 died from drug-related toxicities (0.64%, 95% CI: 0.53% to 0.77%), at least 5448 experienced Grade 3–4 SAEs (30.4%, 95% CI: 29.7% to 31.1%). No trial showed a survival advantage for any VEGF inhibitor. Risk and benefit remained stable over the course of the paradigm suggesting little treatment optimization. Trials cited on average 5.38 prior reports within the set (12.6% of those available). Patients in positive trials were 2.4 times more likely to be cited in the discussion sections of subsequent reports than patients in non-positive trials. Citation bias did not diminish over the course of the paradigm's testing. Fifty-seven (39%) of the trials cited reports that tested a different VEGF inhibitor.

Conclusion: The paradigm of VEGF inhibition in breast cancer posed substantial patient burdens and did not provide survival benefit. Citation bias and limited learning between trials of different drugs of the same class may have contributed to its perseverance.

Zusammenfassung

Hintergrund: Misserfolge bei der Entwicklung von Krebsmedikamenten belasten Patienten, Forschung, Industrie und Geldgeber erheblich. Diese Last könnte bei der Entwicklung von zielgerichteten Medikamenten reduziert werden, indem die Forschung nicht nur Studienergebnisse, sondern auch Erkenntnisse zu den pathophysiologischen Hypothesen der getesteten Arzneimittel effizient integriert. Es ist jedoch wenig darüber bekannt, wie klinische Studien, in denen verschiedene Medikamente mit dem gleichen Wirkmechanismus getestet werden, aus den Misserfolgen und Erfolgen von Studien der gleichen Klasse lernen. Das Ziel dieses Projekts war es: a) Patientenlast und -nutzen klinischer Studien einer gescheiterten Medikamentenklasse, die besondere Beharrlichkeit gezeigt hat (Vascular Endothelial Growth Factor [VEGF]-Inhibition bei Brustkrebs) zu quantifizieren b) die Produktion und Integration von Evidenz aus miteinander verwandten klinischen Studien zu beschreiben und zu erörtern, warum die Forschungsagenda trotz begrenzter Evidenz vorangetrieben wurde.

Methoden: Am 9. Februar 2017 wurden die Datenbanken Embase und MEDLINE nach klinischen Studien durchsucht, die VEGF-Inhibitoren in Brustkrebs untersuchten. Patientenlast wurde anhand von Serious Adverse Events (SAEs) Grad 3 oder höher bestimmt, Patientennutzen anhand von Objective Response Rate (ORR) sowie Überlebensvorteil gegenüber einem Vergleichsarm. Studienerfolg wurde durch das Erreichen des primären Endpunktes bei akzeptabler Toxizität definiert. Zitationsbias wurde gemessen, indem die Anzahl der zitierten vorangegangenen Studien mit der Anzahl der insgesamt zitierfähigen Studien in dem eingeschlossenen Set verglichen wurden.

Ergebnisse: Das Entwicklungsparadigma der VEGF-Inhibition bei Brustkrebs bestand bis Februar 2017 aus 146 Studien mit 19 Arzneimitteln die 17.924 Patienten einschlossen. 6441 Patienten, die einem VEGF-Inhibitor ausgesetzt wurden, zeigten Objective Response (46% der intent-to-treat population, 95% Konfidenzintervall [CI]: 45,1% bis 46,8%), 114 starben an arzneimittelbedingten Nebenwirkungen (0,64%, 95% CI: 0,53 % bis 0,77%) und mindestens 5448 erlitten medikamentenbedingte Nebenwirkungen Grad 3–4 (30,4%, 95% CI: 29,7% bis 31,1%). Keine Studie zeigte einen Überlebensvorteil für einen VEGF-Inhibitor. Risiko und Nutzen blieben im Verlauf des Entwicklungsparadigmas konstant, was darauf hindeutet, dass wenig Optimierung der Therapie stattfinden konnte. Studien zitierten durchschnittlich 5,38 frühere Studien innerhalb des Samples (12,6% der verfügbaren Studienberichte). Patienten in positiven Studien wurden in den Diskussionsabschnitten nachfolgender Studien 2,4-mal häufiger zitiert als Patienten in nicht-positiven Studien. Der Zitationsbias hat im Verlauf des

Paradigmas nicht abgenommen. Siebenundfünfzig (39%) Studien zitierten frühere Studienberichte, in denen ein anderer VEGF-Inhibitor getestet wurde.

Schlussfolgerung: Das Entwicklungsparadigma der VEGF-Inhibition bei Brustkrebs war mit einer erheblichen Patientenlast verbunden und zeigte keinen Überlebensvorteil für einen VEGF-inhibitor. Zitationsbias und eingeschränkter Erkenntnisgewinn aus Arzneimittelstudien mit anderen Substanzen derselben Klasse haben möglicherweise zu Beharrlichkeit des Paradigmas beigetragen.

1. Introduction

1.1 Drug development and pharmacological paradigms

Drug development is usually conceptualized as a sequential process (1) in which new drugs are developed in vitro based on pharmacologic mechanisms and they are subsequently tested in vivo. Ultimately, drugs are tested in clinical trials, which primarily aim at confirming whether a drug or intervention has a clinical impact - for example, whether the drug will extend survival in cancer patients. Many oncological drugs are developed to target a specific biological pathway. The belief that a given biological pathway is involved in the pathogenesis of a disease and represents a viable target for drug interventions can be termed as a pharmacological or drug development "paradigm". A poor understanding of pathophysiological processes has been described as a main reason why drug development fails (1). However, going through the different phases of clinical development, trials also generate information about underlying pathophysiological processes and pharmacology. Outcomes of drug trials targeting the same pathway can further the understanding of the drug development paradigm - especially if there are pharmacodynamic markers to correlate molecular and disease response (2). Success of a drug against a given disease provides grounds for believing that other drugs in the same class may have similar success. The failure of several drugs in a class against a disease suggests a disconnect between the drugs' biological properties and the processes driving disease. Nowadays, when trials are planned based on a molecular understanding of disease, it is crucial that research systems efficiently integrate not merely the clinical implications of trial outcomes, but also the implications for a pathophysiological hypothesis.

The success rate of oncology drug development is particularly low, as compared to other clinical areas. As an example, the estimated likelihood of approval from phase 1 is 7% in oncology, as opposed to 17% in infectious diseases (3). Several possible causes have been identified, such as high regulatory hurdles for new drugs (3), bias to publish positive results (4,5), and clinical trials designs that are insufficient, failing to acknowledge the limitations of efficacy observed in animal studies (6).

Previous studies (7) suggested that – in many cases – drug developers commit substantial resources toward drug development paradigms. While these commitments sometimes bear fruit in terms of clinical impact, in many cases they do not, and such efforts can impose heavy expenses and patient burden. One way such burdens can be mitigated and forestalled is if other efforts in a drug development paradigm build off earlier findings in trials in an attempt to validate the paradigm and extend the knowledge of biological mechanisms of action.

1.2 The case of Vascular Endothelial Growth Factor inhibition in breast cancer

In this study, we characterized the expense and burden associated with efforts aimed at clinically validating one highly influential but ultimately unsuccessful paradigm in cancer drug development: Vascular Endothelial Growth Factor (VEGF) inhibition for the treatment of breast cancer.

Angiogenesis inhibition has been suggested and tested as a treatment in cancer for more than 30 years (8). In particular, the VEGF pathway has been studied extensively and is the main target for most therapies. However, in breast cancer, the hypothesis that VEGF inhibition improves relevant patient outcomes has been questioned (9) after a number of phase 3 studies failed to demonstrate its efficacy on patient relevant outcomes (10,11). The biological and mechanistic underpinning of the VEGF inhibition paradigm also came under attack: one preclinical study hypothesized that VEGF inhibition had a role to play in promoting tumor progression (12), while another demonstrated that a specific VEGF inhibitor, sunitinib, accelerated metastatic tumor growth and decreased overall survival (OS) in mice (13).

Bevacizumab (AVASTIN®), a monoclonal antibody against VEGF-A, is the most prominent and widely tested VEGF inhibitor for breast cancer. It has also been approved for a range of other cancers including renal cancer, glioblastoma and non-small-cell lung cancer (14–16). It was granted accelerated approval for first-line treatment of metastatic breast cancer in combination with paclitaxel by the FDA in 2008 because of promising findings on the surrogate endpoint progression free survival (PFS) observed in one phase 3 trial (17). However, this approval was withdrawn in 2011 (18) because subsequent randomized trials and follow-up of the original study demonstrated that bevacizumab did not improve OS, while it substantially increased the serious adverse event rate in this population (19). The question of whether bevacizumab provides benefit to breast cancer patients remains controversial. Use of bevacizumab in breast cancer declined (20), although the Centers for Medicare and Medicaid Services issued a policy that still allows for the reimbursement of the drug in this indication. Genentech, the company that developed AVASTIN® (bevacizumab) announced more phase 3 trials “that may help identify which people might derive a more substantial benefit from Avastin” right after the FDA’s decision to revoke approval (21). A more recent review found that despite the announcement, the research agenda on bevacizumab in metastatic breast cancer largely halted (22).

Sunitinib, another VEGF inhibitor that underwent testing in breast cancer, showed promising results in phase 2 but did not demonstrate efficacy in multiple phase 3 trials in metastatic breast

cancer (23,24). Currently, no VEGF inhibitor is FDA-approved for the treatment of breast cancer.

However, little is known about how clinical research activity as well as patient risk and benefit developed over the course of the VEGF paradigm in breast cancer. It remains unclear if investigators learned from failures and successes with other drugs targeting the same pathway and how much they built on prior findings in general. In the following, we apply systematic review and citation analysis methods to offer a new perspective on answering these questions.

1.3 Citation analysis to understand learning within a drug development paradigm

Citation analysis is the "examination of the frequency, patterns, and graphs of citations in documents. It uses the pattern of citations, links from one document to another document, to reveal properties of the documents." (25). Citation analysis has been used in different ways to better understand inefficiencies in knowledge creation and to explore whole belief systems in many areas of science. Some examples include a study by Trinquart et al. that used network analysis to assess the patterns of citations among reports on the effect of sodium intake on cerebro-cardiovascular disease or mortality and found a strong polarization (26). Greenberg identified citation distortions as the major driver for unfounded authority in the β amyloid hypothesis in inclusion body myositis (27).

Often, the amount of available and citable research in a given field exceeds the number of studies that are feasible for citation. Authors need to select prior evidence they cite in one way or another. If this selection takes place based on the directionality or results, citation bias occurs (27). Citation bias is common in many disciplines (28) and adds to the burden of other biases like publication bias (29) and reporting bias. A recent review of multiple citation networks found that not only the directionality of study outcomes, but also the authority of the author, and the journal impact factor were positively associated with the probability of citation (30). It has been shown that randomized clinical trials a) tend to cite a small proportion of prior relevant trial reports (31) and b) tend to cite a biased set of prior trial reports (32–35). It is important to note that biased citations are likely to track actual biases researchers hold when conceptualizing, planning and conducting clinical trials. Hence, it is not the citation per se that is the problem, but what the citation practices reveal.

Citation bias as a specific form of evidence distortion not only disregards the contributions patients make when participating in clinical research and taking experimental drugs or undergoing not yet proven interventions but may also contribute to the prolongation of failing

paradigms and belief systems. It is not yet known if and how selective citations contributed to the perseverance of the VEGF inhibition paradigm in breast cancer.

2. Aims of the study

Our primary objectives were, firstly, to describe and map the volume and temporal dynamics of trial activities, patient burden, benefit and risk over the lifetime of a cancer drug development paradigm that showed particular perseverance, namely VEGF inhibition in breast cancer, and secondly, to explore and describe possible reasons as to why the research agenda around the drug development paradigm persisted despite contradicting evidence becoming available.

A secondary objective was to use patient numbers as a metric to measure the extent to which patient samples influenced the course of the research agenda, depending on whether those samples resulted in negative, positive or inconclusive trials.

Hypotheses

We expected to observe a significant patient burden, as well as a high number of both single drugs tested and trial reports published in exploring this exemplarily unsuccessful drug development paradigm. We also expected different forms of citation bias that potentially prolonged the research agenda. We believed that trial reports:

a) Generally, only cite a small portion of the available evidence in the form of earlier trial reports of VEGF inhibitors in breast cancer;
b) Often cite a biased subset of available trials;
c) Focus citations on the same compound and not on other drugs that fall within the anti-VEGF paradigm.

We hypothesized that patients in negative and inconclusive studies had less influence over the development process than patients within positive trials. We expected that over time, citation bias would diminish as scientists become aware of the insuperable challenges in exploiting VEGF inhibition for the management of breast cancer. Finally, we expected to observe a significant number of duplicative trials or trials with accrual failure (trials of limited value).

3. Methods

3.1 Methods overview

We collected all clinical trials testing the paradigm of VEGF inhibition as treatment for breast cancer. We extracted key information about design, safety, efficacy, outcomes and timing. We assessed patient burden using drug-related deaths and serious adverse events that are Grade 3 or higher (defined by the Common Terminology Criteria for Adverse Events [CTCAE] criteria) (36). Benefit was assessed through Objective Response Rates (ORR) defined as the proportion of confirmed complete and partial responses, according to Response Evaluation Criteria in Solid Tumours (RECIST) (37) as well as OS described in published reports. We further assessed the number of trials with "limited" value occurring within the paradigm by assessing accrual failure and duplicated study designs. Through the analysing of citation patterns within the set of published trial reports, we were able to measure the degree with which subsequent trials built on prior evidence. Citation bias for each trial report was measured in different ways:

a) based on the proportion of cited *reports* (negative/positive/inconclusive) vs. the proportion of citable reports (negative/positive/inconclusive) up to one year before date of publication.
b) based on the proportion of cited *patients* (included in negative/positive/inconclusive studies) vs. the proportion of total citable patients (included in negative/positive/inconclusive studies) up to one year before date of publication.

Citation analyses were done both for each single trial to show a time dynamic and as cumulative analysis to show bias within the paradigm of VEGF inhibition in breast cancer as a whole. Moreover, we compared the total number of citations of reports testing the same compound with citations of reports testing another VEGF inhibitor in breast cancer. We also recorded citations to trials of VEGF inhibitors in other indications to test if and how investigators took drug development in other diseases into account.

We created an index of the proportion of patients whose contributions are eligible citations (Citable Patient Index: CPI) to probe if the data generated by patients in negative studies have less influence over the translation trajectory than the data generated by patients within positive trials. The protocol for this study was timestamped on February 17, 2017. It can be retrieved on the Open Science Framework (38).

3.2 Literature search

We identified eligible drugs by consolidating recent reviews (defined as reviews on VEGF inhibition in breast cancer published between 2010 and 2016, search via Web of Science) (39–43) and extracted any agent identified as a VEGF inhibitor. Additionally, we searched for further VEGF inhibitors by screening the clinical drug development database "Pharma Projects" by Pharma Intelligence (44) for "VEGF inhibitors" developed for breast cancer.

We then conducted a search of the Medline and Embase databases on February 9, 2017, using names and variations of names of the compounds previously identified and MeSH terms including variations of "clinical trial" or "randomized controlled trial" or other keywords associated with clinical trial design. No date restrictions were applied. Our complete search strategy can be found in Appendix 1.

3.3 Data extraction

3.3.1 Eligibility

We manually screened the results of the literature search for trials that met the following inclusion and exclusion criteria.

Inclusion criteria: 1) primary data, 2) full-text publication, 3) English language, 4) final report, 5) interventional trial, 6) examination of one of the prespecified drugs as monotherapy or combination therapy, 7) tested in any type of breast cancer.

Exclusion criteria: 1) secondary reports or interim results, 2) meta-analyses/systematic reviews, 3) retrospective or observational studies, 4) laboratory studies of ex vivo human tissues, 5) preclinical studies, 6) letters, editorials, guidelines, interviews, 7) mixed malignancy studies, 8) treatments aimed at managing conditions other than cancer (e.g. pain, side effects); 9) VEGF-inhibiting drug used but VEGF inhibition not invoked as rationale for trial, 10) VEGF-inhibiting drug is not standard of treatment, but intervention.

All captured publications were consolidated into single studies (i.e., when there were multiple publications of the same study, these were consolidated as a single study). The date assigned to the consolidated study publication is the earliest date when the final report of the primary outcome was provided.

3.3.2 Data collection

Extraction

Our approach was adapted from previously published methods (7). For every trial, we recorded key information on demographics, methodology, safety and efficacy. We recorded the outcome of each study and applied the following criteria:

- A "positive" trial meets its predefined primary efficacy endpoint with acceptable toxicity.
- A "negative" trial does not meet its predefined primary efficacy endpoint, or an unacceptable level of toxicity is described.
- An "inconclusive" trial either a) only investigates non-efficacy primary endpoints such as safety or pharmacokinetics or b) fails to reach at least 85% of its targeted enrolment for reasons other than futility or benefit (accrual failure).

We additionally recorded citations between the predefined trials and noted whether a citation occurred in the introduction section, discussion section or both. Whenever an abstract of a potentially eligible study was cited, we recorded it and matched with identified trials. We noted the date when a potential abstract was published. We accounted for this earlier publication date in the citation analysis (see below). Our full codebook can be found in Appendix 2.

All studies were extracted by two independent coders. Both coders underwent a period of training before extraction to ensure consistent quality. Disagreements were reconciled by discussion between coders. Extractions were carried out using Numbat Systematic Review Manager (45). All graphs are plotted, and all statistical inference performed using R v. 3.3.1 or higher using the packages ggplot v. 3.3.3 or higher (46), VisNetwork v. 2.0.9 or higher (47) and meta v. 4.16-2 or higher (48).

3.4 Analysis and statistics

3.4.1 Primary analysis

Our primary objectives were:

a) to describe and map the volume and temporal dynamics of trial activities, patient burden and benefit over the lifetime of the paradigm of VEGF inhibition in breast cancer.

b) to analyse and explain possible reasons why the research agenda around the drug development paradigm persisted despite contradicting evidence becoming available.

To map trial activities, we graphed AERO figures (49) in which the horizontal dimension represented time, and the vertical dimension the different drugs tested. Nodes were colored to

represent positive, negative or inconclusive trial results based on author prespecified primary endpoint. We also marked FDA approval and the withdrawal of approval for bevacizumab in breast cancer to see if these regulatory decisions had an influence on the number of trials initiated. This was done by analysing a potential increase/decrease in newly started trials in the following year of approval/disapproval. We further prepared an AERO diagram where the vertical axis represents drug classes which VEGF inhibitors were tested in combination with. This allowed us to examine which combinations were most recurrently tested.

Quantification of total amount of patient burden and benefit: We measured patient burden using drug-related deaths and serious adverse events (SAEs) Grade 3 or higher according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) (36). To standardize the safety data across trials, we selected the most common side effect associated with VEGF inhibition in any given trial and recorded the number and frequency of that VEGF inhibitor-related adverse event. We then plotted the cumulative enrolment of patients in anti-VEGF trials against cumulative treatment-related Grade 3–5 SAEs over time.

To show how risks and benefits evolve over time, we plotted cumulative rates of Grade 3-5 adverse events and objective responses (according to RECIST) (37) for monotherapy and combination therapy by trial phase against time, which had previously only been described for sorafenib (50). Cumulative objective response rates and proportions of serious adverse event with 95% confidence intervals were calculated as a random-effects model cumulative meta-analysis of proportions, as implemented by the metaprop and metacum functions from the meta package in R. v. 4.16-2 or higher (48).

We also plotted hazard ratios (HRs) of OS, where reported, for both monotherapy and combination therapy trials. All cumulative effect estimates were calculated using the DerSimonian and Laird random effects meta-analysis as implemented by the metagen function from the meta package in R. (48) Survival data were collected from experiments with any non-VEGF inhibitor comparator arm in which survival endpoints included all patients.

Trials of limited value: We defined a trial to have "limited value" if it met one of the following conditions:
(A) A phase 2 trial was of limited value if it was "potentially duplicative," meaning that it matched a previous phase 2 trial in its phase, patient characteristics (based on

histopathology/subtype, biomarker eligibility, number of prior therapies and disease stage), and treatment regime (combination drug).

(B) A trial was of limited value if it had recruitment failure. Recruitment failure was defined as any trial (phase 1 through 3) that failed to reach at least 85% of its targeted enrolment as defined by the authors in the methods section of the published trial report for reasons other than futility or benefit, based on trial report or registration. These methods were described earlier. (50)

Assessing citation bias: We define citation bias as described in the Cochrane Collaboration Handbook as the following: *"The citation or non-citation of research findings, depending on the nature and direction of the results."* (51). For any given report in the VEGF Inhibition paradigm in breast cancer, we assessed citation bias by comparing actually cited earlier reports with overall citable earlier reports within the studies included in this analysis (based on a one-year grace period for non-citation). A citable earlier report for a given study is defined as any report within the network that released results (as full publication or abstract) at least 1 year ahead of publication of the given study.

To detect citation bias in the drug development paradigm, we used different approaches:

a) We calculated a Prior Research Citation Index (PRCI), adapted to the given set of trials from Robinson and Goodman (31). For each trial, the PRCI was calculated as the number of cited trials divided by the number of trials eligible to cite in the network.
b) We compared the total number of citations of trials testing the same compound with citations of trials testing another VEGF inhibitor in breast cancer.
c) We compared the proportion of citations of negative/positive/inconclusive earlier trials in any given trial with the proportion of negative/positive/inconclusive earlier trials eligible to be cited in the network.
d) We compared the proportion of cited patients (included in negative/positive/inconclusive trials) with the proportion of total citable patients' (included in negative/positive/inconclusive trials) earlier reports eligible to be cited in the network.

We further prepared citation networks within our trial sample to probe characteristics of trials that had a disproportionate impact on the development trajectory of the paradigm.

3.4.2 Secondary analyses

The data derived from patients in negative and inconclusive studies may have less influence over the translation trajectory than the data derived from patients enrolled in positive trials. This

was evaluated as follows. For each trial, we created an index of the proportion of patients whose contributions are eligible citations (Citable Patient Index: CPI). The CPI is determined by:
a) identifying all prior trials within the set of studies that made results available via full text publication or abstracts at least one year before publication date, and totalling the number of patients in each of those trials (Ep);
b) identifying all trials actually cited in the discussion section, and totalling all the patients (Ap);
Citable Patient Index (CPI) = Ap/Ep
The Citable Patient Index for positive trials, CPI(+) can be calculated by restricting calculation of CPI to only prior positive studies. The Citable Patient Index for non-positive trials, CPI(not+) can be calculated by restricting calculation of CPI to only prior non-positive studies.

We expected *CPI(+) >> CPI(not+)*.

We only took citations in the discussion section of each trial report into account, since theoretically a more balanced approach to the paradigm can be expected. The introduction needs to outline the reasoning behind conducting the trial and therefore refers more strongly to positive prior evidence. The discussion section, however, should place the study results in the context of available literature.

Finally, we also screened trial reports for references to two publications that raised considerable caution regarding VEGF inhibition therapy for cancer. Paez-Ribes et al. hypothesized VEGF inhibition to potentially be a "driving force in tumor progression" (12) and Ebos et al. showed that the VEGF inhibitor sunitinib "can accelerate metastatic tumor growth and decrease OS in mice receiving short-term therapy in various metastasis assays" (13).
We will explore whether these findings were referenced in subsequentially published trial reports of VEGF inhibition in breast cancer and analyse how they were discussed.

3.5 Protocol deviations

The following exploratory analyses were added after the study protocol was timestamped:

a) Extraction and analysis of citations to VEGF inhibitor trials in indications different from breast cancer.
b) Extraction and analysis of citations to preclinical studies critical of the VEGF hypothesis.

Other protocol deviations include:

- We did not contact corresponding authors if exact enrolment dates were missing in published trial reports. Four included trials are missing an enrolment date.
- We reduced the definition of "trials of limited value" and excluded the criterion of inappropriate follow-up of a phase 2 study. Including this criterion would have resulted in many more "trials of limited value", since breast cancer is a very heterogenous disease. This deviation makes the number of studies with limited value a rather conservative figure.

Two prespecified analyses were not conducted: analyses of citation bias based on Journal Impact Factor (JIF) and analyses of citation bias based on effect size of ORR. Lastly, differing from the prespecified protocol, after the pilot phase of this study was completed (after 20% of extractions), we did not determine one Adverse Event to be extracted across all included trials. We found AEs to be rather heterogenous across the set of included trials and could not single out one specific, consistently important AE for comparison.

4. Results

4.1 Drugs identified

We identified a total of 19 VEGF inhibitors tested in the indication of breast cancer. Those are: aflibercept, angiozyme, apatinib, axitinib, bevacizumab, carbozantinib, cediranib, dovitinib, foretinib, motesanib, nintedanib, orantinib, pazopanib, ramucirumab, semaxanib, sorafenib, sunitinib, tivozanib and vandetanib. Most of these drugs belong to the class of tyrosine-kinase inhibitors (TKIs). Ramucirumab and bevacizumab are monoclonal antibodies. Aflibercept is a recombinant fusion protein. Angiozyme is a ribozyme targeting pre-mRNA (see Figure 1 for a detailed overview of mechanisms of action along the VEGF signaling pathway).

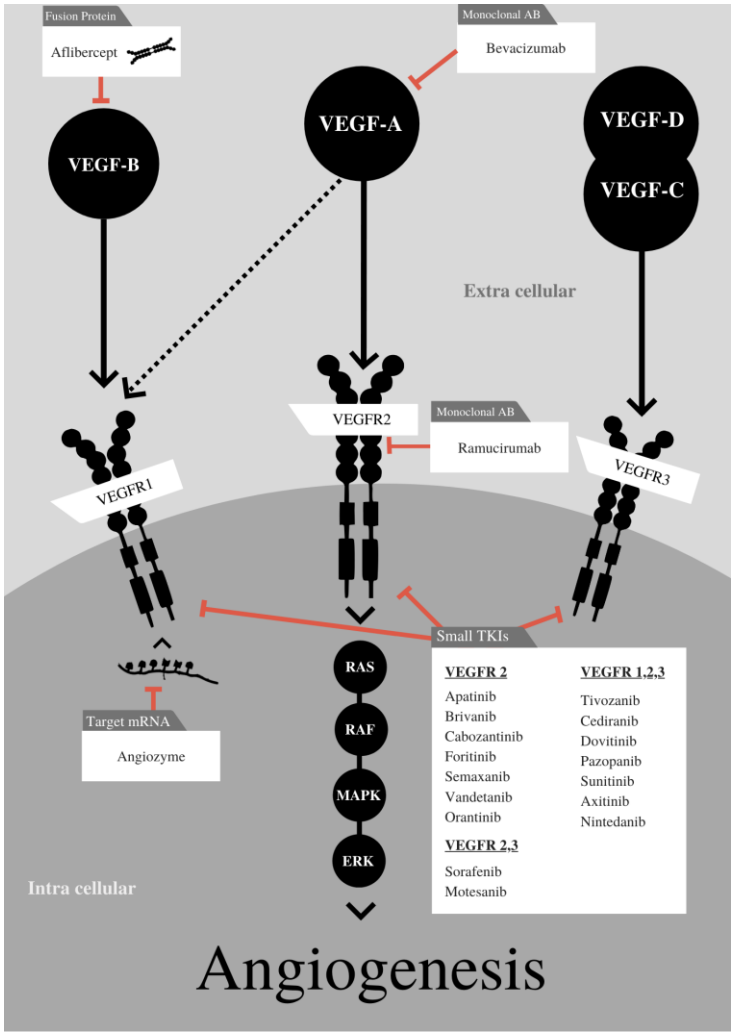


Figure 1 *Overview of drugs identified as VEGF inhibitors tested in breast cancer and their mechanism of action. Bevacizumab is a monoclonal antibody (AB) targeting Vascular Endothelial Growth Factor (VEGF) A. Aflibercept is a fusion protein targeting VEGF-B. Ramucirumab is a monoclonal AB targeting VEGF receptor (VEGFR) 2. All other drugs identified target intracellular structures of the VEGF pathway. Most of them are small Tyrosine Kinase Inhibitors (TKIs) with varying affinities for VEGFR1, VEGFR2 and VEGFR3. Angiozyme is a ribozyme targeting pre-mRNA. Figure created by the author.*

4.2 Literature search

In total, the literature search yielded 146 trials (10,17,23,24,52–193) that were included in the qualitative and quantitative analyses (see Figure 2, PRISMA diagram (194)).

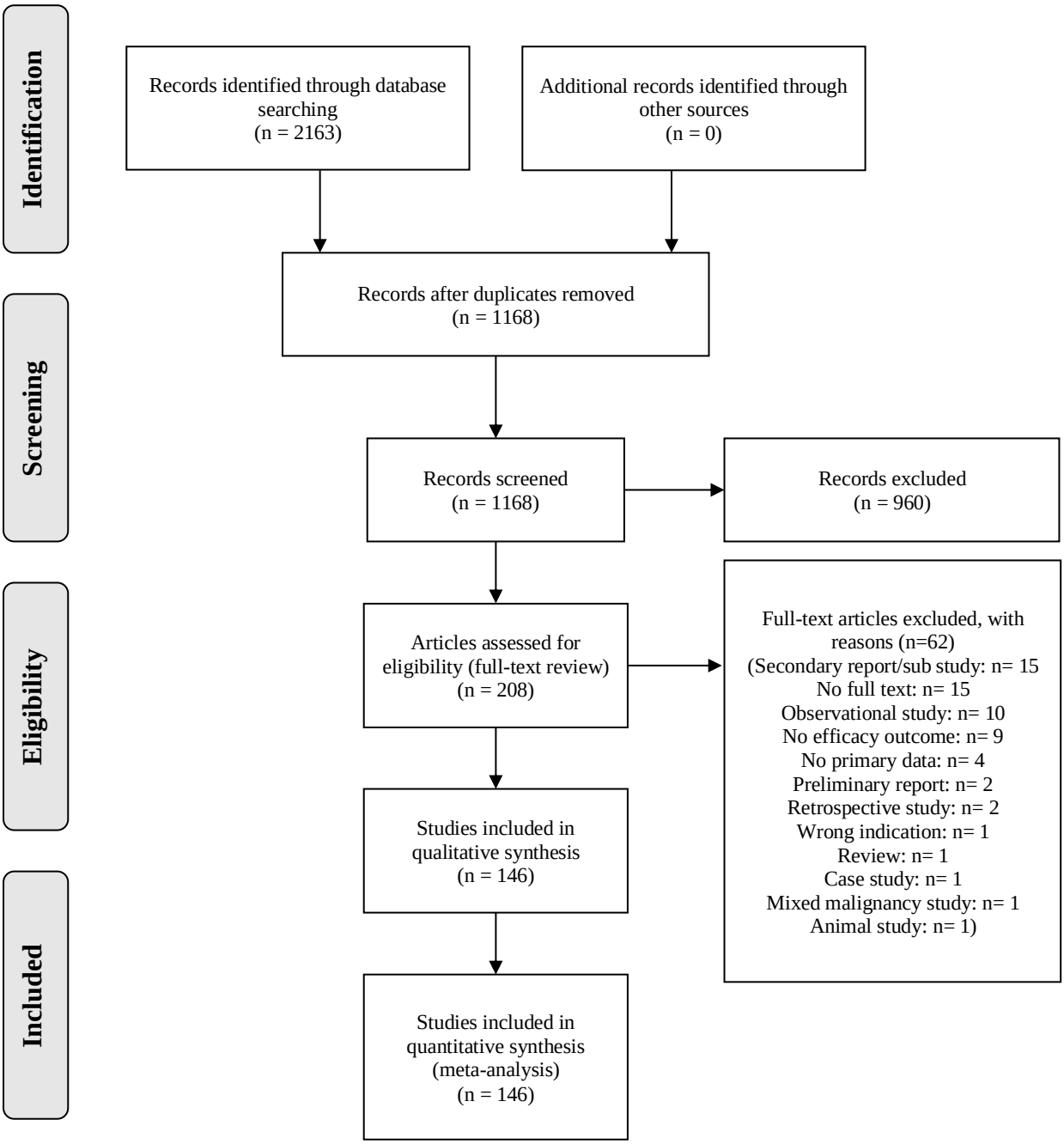


Figure 2 *PRISMA diagram of the literature search.*

4.3 Drug, trial, and research programme characteristics

Our search captured 146 trials of 19 drugs (see Table 1). These trials enrolled patients over a span of 14 years (1998-2012). Trials of bevacizumab, sunitinib or sorafenib were identified most often (128/146 trials, 88%). VEGF inhibitors for breast cancer were tested in combination

with other treatments (as opposed to monotherapy) in most of the trials (127/146 trials, 87%). Some of the included drugs were exclusively tested in combination therapy against breast cancer (motesanib, ramucirumab, axitinib, semaxinib, cediranib and tivozanib).

Table 1 Number of trials per drug and other key characteristics. If multiple VEGF inhibitors were tested against each other in one trial, the drug described as standard of care was dismissed.

Drug	Number of trials in mono-therapy	Number of trials in combination therapy	Study phase	Sponsors	FDA approval in other indications
Bevacizumab	1	88	Phase 1 - 3	Roche, Inc.	Glioblastoma, cervical cancer (in combination), metastatic colorectal cancer (in combination), hepatocellular carcinoma (in combination), metastatic nonsquamous non-small-cell lung cancer (in combination), epithelial ovarian, fallopian tube or primary peritoneal cancer (in combination), metastatic renal cell cancer (in combination)
Sunitinib	5	11	Phase 1 - 3	Pfizer, Inc.	Gastrointestinal stromal tumor, renal cell carcinoma, pancreatic neuroendocrine tumors
Sorafenib	2	11	Phase 1 - 2	Bayer AG, Onyx Pharmaceuticals Inc.	Hepatocellular carcinoma, renal cell carcinoma, thyroid carcinoma
Pazopanib	1	3	Phase 2	GlaxoSmithKline plc.	Renal cell carcinoma, soft tissue sarcoma
Vandetanib	1	3	Phase 1 - 2	AstraZeneca plc/AB, Sanofi S.A.	Medullary thyroid cancer

Orantinib	1	2	Phase 2	Pfizer, Inc., Taiho Pharmaceutical Co., Ltd.	NA
Apatinib	2	0	Phase 2	Advenchen Laboratories, Jiangsu Hengrui Medicine, LSK BioPartners, Bukwang Pharmaceutical Company	NA
Nintedanib	1	1	Phase 1 - 2	Boehringer Ingelheim International GmbH	Fibrosing interstitial lung diseases, interstitial lung disease associated with systemic sclerosis or scleroderma (SSc-ILD), idiopathic pulmonary fibrosis, non-small-cell lung cancer (in combination)
Motesanib	0	2	Phase 1 - 2	Amgen Inc., Takeda Pharmaceutical Company Limited	NA
Ramucirumab	0	2	Phase 2 - 3	Eli Lilly and Company	Hepatocellular carcinoma, adenocarcinoma of the stomach or gastroesophageal junction (in combination and monotherapy), colorectal cancer (in combination), non-small-cell lung cancer (in combination)
Aflibercept	1	0	Phase 2	Sanofi S.A., Regeneron Pharmaceuticals, Inc.	Colorectal Cancer (in combination), Wet Age-Related Macular Degeneration, Diabetic Macular Edema, Diabetic

					Retinopathy in Patients with Diabetic Macular Edema
Angiozyme	1	0	Phase 2	Ribozyme Pharmaceuticals (renamed as Sirna Therapeutics)	NA
Cabozantinib	1	0	Phase 2	Exelixis, Inc.	Medullary thyroid cancer, renal cell carcinoma, hepatocellular carcinoma
Dovitinib	1	0	Phase 2	Novartis, Inc., Allarity Therapeutics A/S	NA
Foretinib	1	0	Phase 2	Exelixis, Inc., GlaxoSmithKline plc.	NA
Axitinib	0	1	Phase 1/2	Pfizer, Inc.	Renal cell carcinoma (monotherapy and in combination)
Cediranib	0	1	Phase 2	AstraZeneca plc/AB	NA
Semaxinib	0	1	Phase 1	SUGEN	NA
Tivozanib	0	1	Phase 1	AVEO Pharmaceuticals, Inc.	Renal cell carcinoma (only EMA approved)

Most commonly, a VEGF inhibitor was combined with chemotherapy (110 trials, 86.6% of combination trials). The most frequently tested class of chemotherapy agents were taxanes (84 trials), followed by antimetabolites (36 trials), alkylators (20 trials), platinum-based compounds (11 trials), vinca alkaloids (5 trials) and topoisomerase inhibitors (2 trials).

Table 2 Key characteristics of included VEGF trials in breast cancer divided by mode of treatment (monotherapy, combination therapy).

Characteristic		Monotherapy n (%)	Combination therapy n (%)
Number of trials		19 (13)	127 (87)
Number of drugs tested		13	13
Study enrolment		1998-2012	2000-2012
Study phase	Phase 1	0 (0)	13 (10.2)
	Phase 1/2	1 (5.3)	9 (7.1)
	Phase 2	17 (89.5)	80 (63)
	Phase 3	1 (5.3)	25 (19.7)
Sponsor	funded by industry only	10 (52.6)	69 (54.3)
	entirely or partly funded by non-industry	7 (36.8)	45 (35.4)
	not stated	2 (10.5)	13 (10.2)
Study centers	single center	0 (0)	21 (16.5)
	multi center	18 (94.7)	95 (74.8)
	not stated	1 (5.3)	11 (8.7)
Line of treatment	first line	1 (5.3)	84 (66.1)
	not first line	18 (94.7)	43 (33.9)
Involvement of surgical procedures	neoadjuvant	1 (5.3)	29 (22.8)
	adjuvant	0 (0)	2 (1.6)
	no surgery	18 (94.7)	96 (75.6)
Stage of disease	metastatic	16 (84.2)	84 (66.1)
	not metastatic	1 (5.3)	31 (24.4)
	mixed	2 (10.5)	12 (9.5)
Primary efficacy endpoint	positive	4 (21.1)	50 (39.4)
	negative	13 (68.4)	38 (39.4)
	non-efficacy/inconclusive	2 (10.5)	39 (30.7)

Table 2 shows further key characteristics of the included trials. 17 out of 19 monotherapy trials were phase 2 studies (89.5%), while the picture for combination therapy trials is a bit more diverse, with 80 out of 127 (63%) in phase 2 and 25/127 (19.7%) in phase 3.

When a VEGF inhibitor was tested as monotherapy, in about 95% of the trials this was a) not done as the first line of treatment and b) done in a metastatic setting. However, about a quarter of captured trials in combination therapy were tested in a group of patients with no metastases detected (31, 24.4%). 22.8% of combination trials formed part of a neoadjuvant treatment strategy, while we could identify only one such trial of monotherapy (5.3%).

Trials of VEGF inhibitors for breast cancer met their primary efficacy endpoint in four out of 19 included monotherapy trials (21%) and 50 out of 127 combination therapy trials (40%). About half of all trials captured are exclusively funded by industry (79, 54%) and the majority are conducted across multiple centres (113, 77.4%).

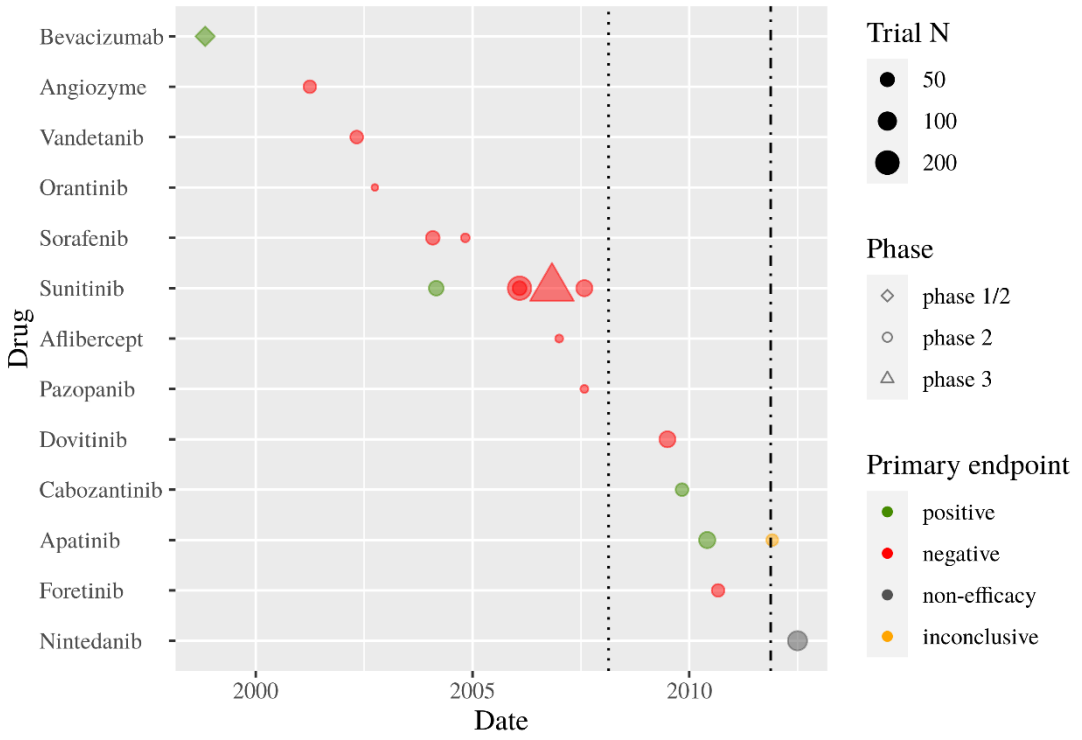


Figure 3 *AERO diagram for monotherapy trials ordered by enrolment date on the horizontal axis. Rectangular nodes indicate phase 1/2 trials, circular nodes indicate phase 2 trials, and triangular nodes indicate phase 3 trials. Green nodes indicate studies that reached their primary endpoint with acceptable toxicity (positive trials), yellow nodes indicate an inconclusive study due to accrual failure, and red nodes indicate trials that failed to achieve the primary endpoint or reported unacceptable toxicity (negative trials). White nodes are trials with non-efficacy primary endpoints such as safety or pharmacokinetics. The size of the nodes is proportionate to the number of patients included in the trial. Vertical dotted lines mark the accelerated approval of bevacizumab for metastatic breast cancer by the FDA in 2008 and the date when it was revoked again in 2011.*

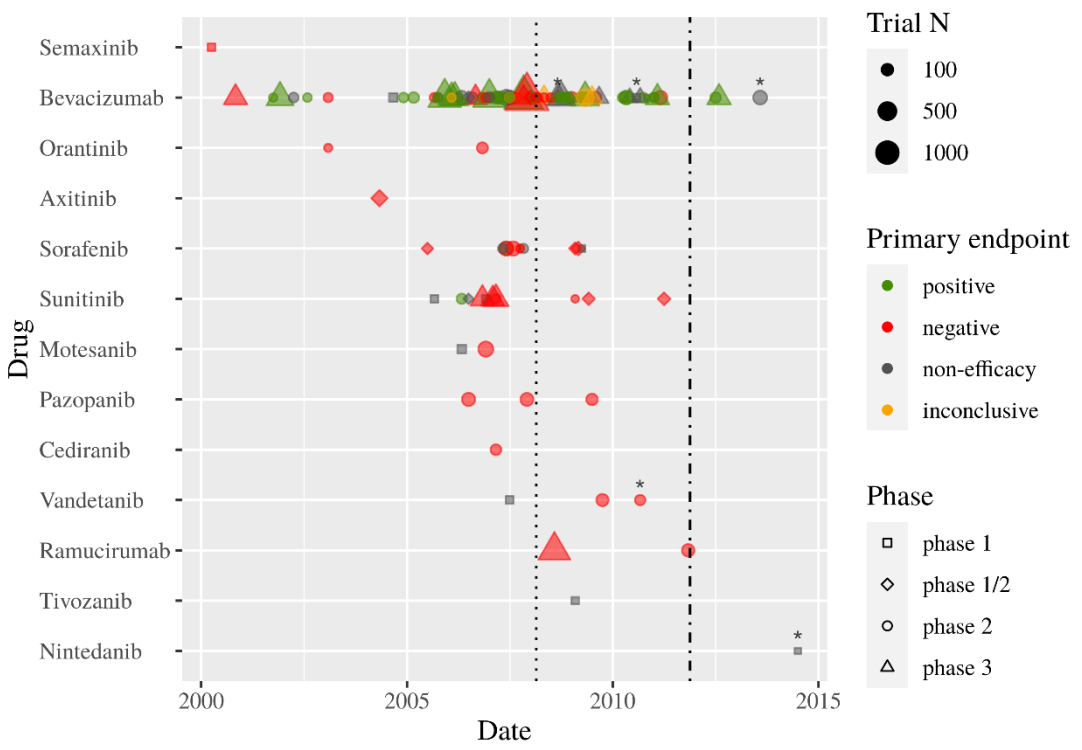


Figure 4 *AERO diagram for* combination therapy trials *ordered by enrolment date on the horizontal axis. Rectangular nodes indicate phase 1/2 trials, circular nodes indicate phase 2 trials, and triangular nodes indicate phase 3 trials. Green nodes indicate studies that reached their primary endpoint with acceptable toxicity (positive trials), yellow nodes indicate an inconclusive study due to accrual failure, and red nodes indicate trials that failed to achieve the primary endpoint or reported unacceptable toxicity (negative trials). White nodes are trials with non-efficacy primary endpoints such as safety or pharmacokinetics. The size of the nodes is proportionate to the number of patients included in the trial. The asterisk marks trials where no enrolment date was available. They are plotted using the publication date. Vertical dotted lines mark the accelerated approval of bevacizumab for metastatic breast cancer by the FDA in 2008 and the date when it was revoked again in 2011.*

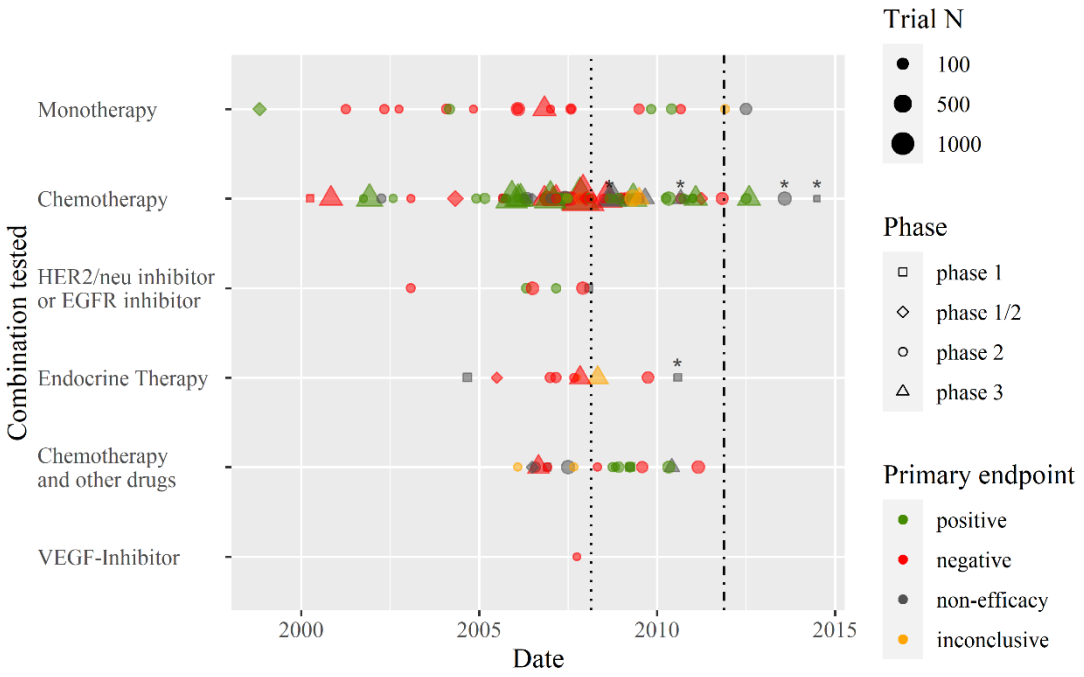


Figure 5 *AERO diagram organized by combination classes tested, ordered by enrolment date on the horizontal axis. Rectangular nodes indicate phase 1/2 trials, circular nodes indicate phase 2 trials, and triangular nodes indicate phase 3 trials. Green nodes indicate studies that reached their primary endpoint with acceptable toxicity (positive trials), yellow nodes indicate an inconclusive study due to accrual failure, and red nodes indicate trials that failed to achieve the primary endpoint or reported unacceptable toxicity (negative trials). White nodes are trials with non-efficacy primary endpoints such as safety or pharmacokinetics. The size of the nodes is proportionate to the number of patients included in the trial. The asterisk marks trials where no enrolment date was available. They are plotted using the publication date.*

The AERO diagrams (Figures 3-5) illustrate a range of different dynamics in the development trajectory for anti-VEGF therapy in breast cancer.

First, bevacizumab accounted for a disproportionate amount of activity in terms of clinical research in the indication of breast cancer (93 out of 146 trials), accounting for 63.7% of the overall research activities. Between 2008 and 2011, bevacizumab was approved by the FDA for the first line treatment of metastatic breast cancer in combination with paclitaxel (a taxane). As such, it was the only VEGF-inhibiting drug ever approved for breast cancer treatment. In at least 12 trials (8.2%) included in our analysis, bevacizumab served as the comparator and standard of care, sometimes even tested against other VEGF inhibitors (such as sunitinib, motesanib or sorafenib). We could identify only one monotherapy trial of bevacizumab, while the vast majority of this development paradigm was driven by combination therapy. Research activity of bevacizumab combination therapy enrolled 20,583 patients in 92 trials that started enrolment between 2000 and 2012. These trials represent 76.9% of the total number of patients

who were exposed to VEGF inhibitors in trials included in this study. Most of these trials were phase 2 trials using PFS (37), ORR (20), or pCR (19) as a primary endpoint. As indicated in the AERO diagrams, a substantial number of clinical trials testing combination therapies were launched upon the FDA approval of bevacizumab in 2008. In 2011, the FDA revoked the accelerated approval of the breast cancer indication for bevacizumab. Despite promising results from surrogate endpoints such as PFS, evidence that it would either help patients with breast cancer live longer (OS) or improve their quality of life did not manifest.

The AERO diagrams reflect a sharp regression of newly initiated trials across all VEGF inhibitors after the FDA revoked the accelerated approval of the breast cancer indication for bevacizumab. Nevertheless, the use of bevacizumab in breast cancer remains controversial. Similarly to the FDA, the European Medicines Agency (EMA) has approved bevacizumab for the treatment of metastatic breast cancer in combination with Paclitaxel. However, the EMA never revoked its market authorization.

Second, also in other drugs, combination therapy trials were more prevalent than monotherapy trials testing VEGF inhibition in breast cancer. Of the total number of 146 trials, 127 (87%) tested a VEGF inhibitor in combination with other drugs. Most commonly, a VEGF inhibitor was combined with chemotherapy (110 trials, 86.6% of combination trials). The most frequently tested class of chemotherapy agents were taxanes (84 trials), followed by Antimetabolites (36 trials), Alkylators (20 trials), platinum-based compounds (11 trials), Vinca Alkaloids (5 trials) and Topoisomerase inhibitors (2 trials). Figure 5 gives an overview of the different combinations summarized at a higher level.

Another striking dynamic is the degree of perseverance for certain drugs. For 3 drugs (bevacizumab, sunitinib and sorafenib), ten or more trials exploring activity in breast cancer were pursued (bevacizumab = 89 trials, sunitinib = 16 trials, sorafenib = 13 trials).

Also, of the 19 monotherapy studies that were launched over a period of 14 years between 1998 and 2012, only 4 met their predefined primary efficacy endpoint with acceptable toxicity.

Finally, the AERO diagrams reveal an increase in the number of studies that missed their primary endpoint, especially among trials testing drugs other than bevacizumab.

4.4 Patient benefit & burden of the VEGF paradigm in breast cancer

17,924 patients were exposed to a VEGF inhibitor over a span of 14 years (1998-2012) in the context of a clinical trial in breast cancer. 1,127 patients (6.3%) received a VEGF inhibitor in a monotherapy trial, and 16,797 (93.7%) received a VEGF inhibitor in a combination therapy trial.

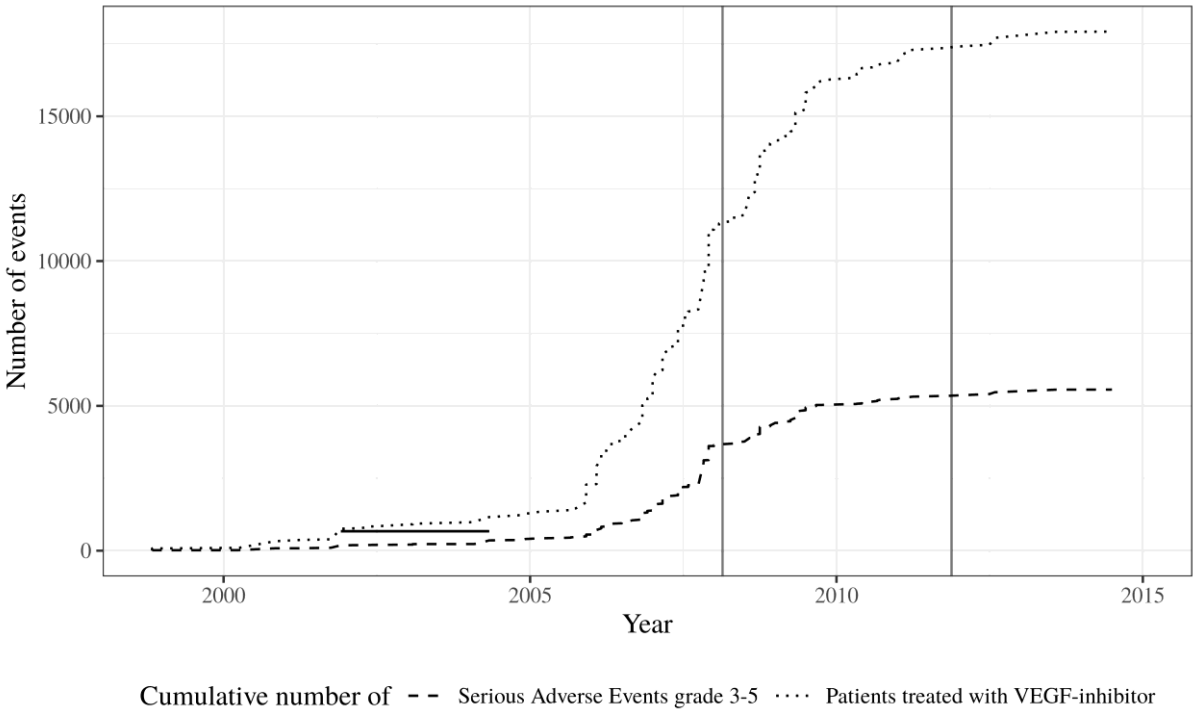


Figure 4 *Cumulative treatment-related Grade 3–5 serious adverse events (G3-5 SAEs) (dashed line) and cumulative patients enrolled (dotted line) in trials of VEGF inhibitor monotherapy and combination therapy over time with landmark events. Dates are based on first patient enrolment. Vertical lines mark the accelerated approval of bevacizumab for metastatic breast cancer by the FDA in 2008 and the date when approval was revoked again in 2011. The horizontal line segment indicates the enrolment period for the pivotal trial of bevacizumab leading to accelerated FDA approval (Miller 2007).*

6,441 (46%, 95% CI: 45.1% to 46.8%) patients received a VEGF inhibitor in a trial with ORR as endpoint and experienced objective tumor response. 114 patients (0.636%, 95% CI: 0.527% to 0.766%) died from drug-related toxicities across the included trials. A minimum of 5,448 (30.4%, 95% CI: 29.7% to 31.1%) patients experienced Grade 3-4 drug-related serious adverse events.

For monotherapy, 71 (6.7%, 95% CI: 5.3% to 8.42%) patients showed objective tumor response, and 9 (0.799%, 95% CI: 0.39% to 1.57%) died from drug-related toxicities; a minimum of 224 (19.9%, 95% CI: 17.6% to 22.4%) patients experienced Grade 3-4 drug-related toxicities.

In combination therapy, 6,370 (49.2%, 95% CI: 48.3% to 50.1%) patients experienced objective tumor response, and 105 (0.625%, 95% CI: 0.514% to 0.759%) patients died from treatment-related toxicities. A minimum of 5,224 (31.1%, 95% CI: 30.4% to 31.8%) patients experienced Grade 3-4 drug-related toxicities.

30 trials in the set described the toxicity observed as not acceptable (20.5% of all trials). Out of those, 2 were monotherapy trials (10.5% of monotherapy trials) and 28 were in combination therapy (22% of combination therapy trials).

Figure 6 shows adverse events and the number of patients enrolled as a function of time with landmark events. The vast majority of enrollment and cumulative patient burden occurred after the pivotal trial of bevacizumab in combination with paclitaxel was conducted.

To show how risks and benefits evolved during clinical research on VEGF inhibitors in breast cancer, we plotted cumulative rates of Grade 3–5 adverse events and objective responses for monotherapy (Figure 7) and combination therapy (Figure 8) by trial phase.

A) Phase 2 monotherapy

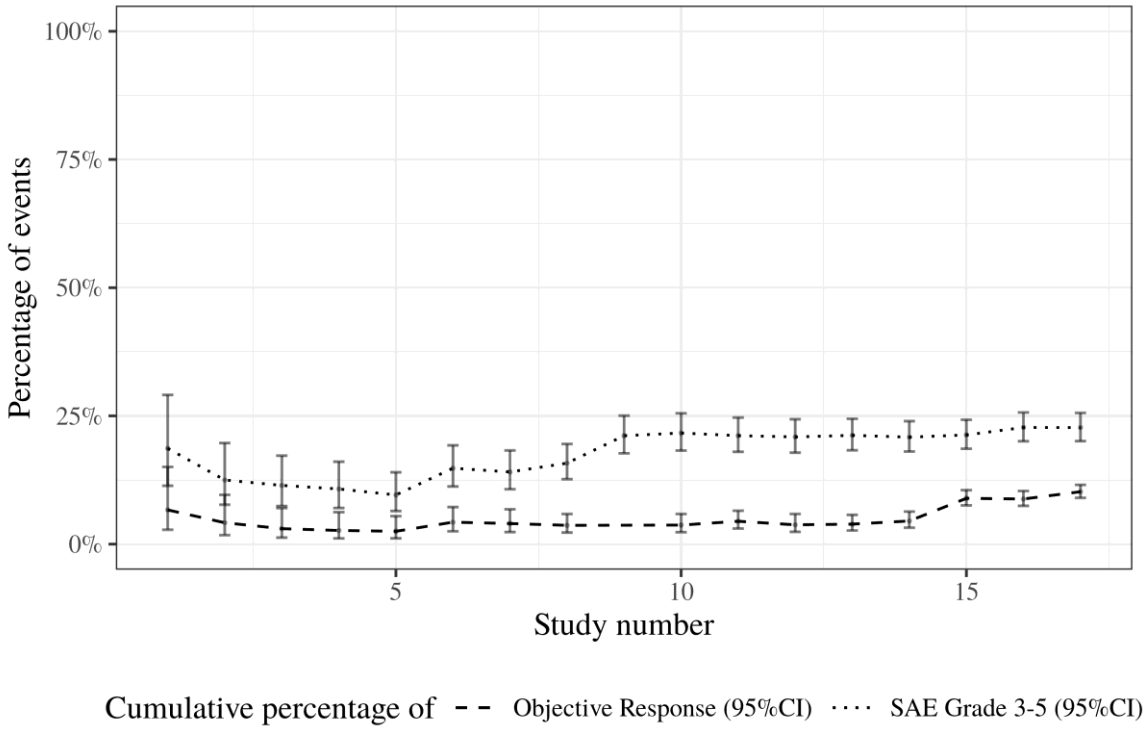
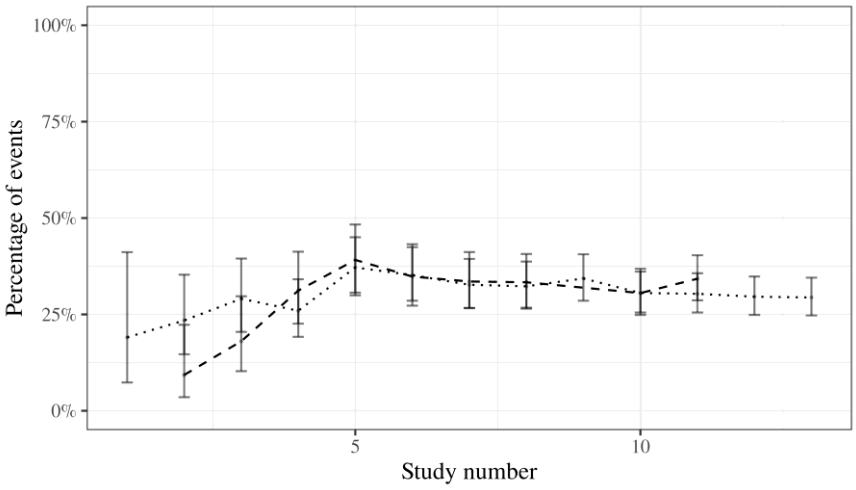
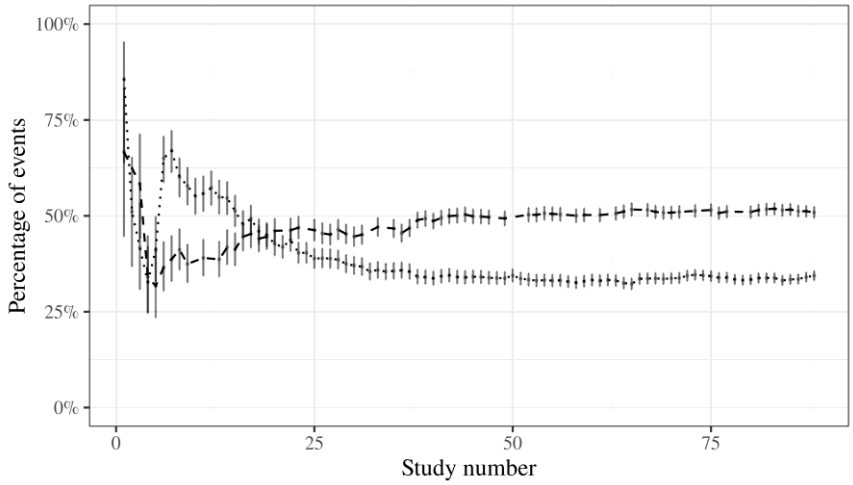


Figure 7 *Cumulative SAE3-5 plotted against ORR with CI from study to study in phase 2 monotherapy trials of VEGF inhibitors. A) Phase 2. There are no phase 1 trials and only one phase 3 trial in monotherapy (not displayed).*

A) Phase 1 combination therapy



B) Phase 2 combination therapy



C) Phase 3 combination therapy

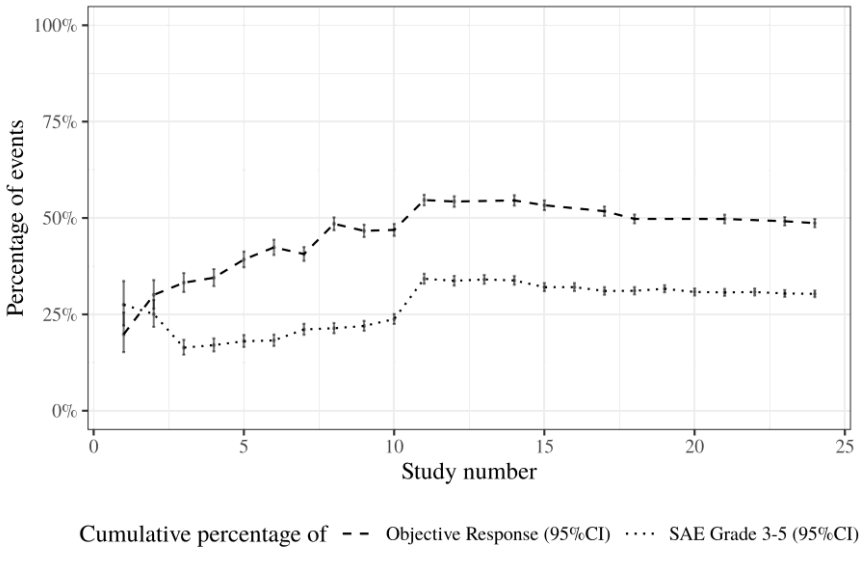


Figure 8 *Cumulative SAE3-5 plotted against ORR with CI from study to study in phase 1-3 combination Therapy trials of VEGF inhibitors. A) Phase 1, B) Phase 2, C) Phase 3.*

In general, efficacy as measured by ORR was limited in monotherapeutic trials, compared to the burden as measured by SAE Grade 3-5. In combination therapy, risk-benefit ratios remained largely constant in phase 2/3 trials. In phase 1, a rather heterogeneous set of studies was included, with only 9/13 studies reporting ORR as endpoint.

We further extracted the most occurring SAE Grade 3-5 for each trial in our sample.

Table 3 summarizes the findings of this analysis. Some often occurring SAEs are associated with chemotherapy (neutropenia, fatigue), while others (such as hypertension and hand-foot syndrome) are discussed as being directly related to VEGF inhibition.

Table 3 Number of trials per most common SAE Grade 3-5.

SAE Grade 3-5	**Number of trials where SAE was the most occurring**
neutropenia	61
hypertension	24
hand-foot syndrome	15
fatigue	9
diarrhea	6
neuropathy	6
leucopenia	5
mucositis	3
asthenia	2
GGT increase	2
rash	2
alopecia	1
AST/ALT elevation	1
decrease in LVEF	1
hypertension	1
hypophosphatemia	1
infection	1
leukopenia	1
musculoskeletal pain	1
peripheral edema	1
tumor pain	1
none	1

The pivotal trial that led to the FDA approval of bevacizumab in metastatic breast cancer demonstrated a significant advantage on its primary endpoint of PFS. (17) However, it failed to show any advantage of bevacizumab addition to chemotherapy for other patient-relevant endpoints such as OS or Quality of Life. To probe whether any trial of a VEGF inhibitor showed improved OS, we analyzed OS outcomes against any non-VEGF inhibitor comparator arm in all trials of VEGF inhibitors in breast cancer (Figure 9).

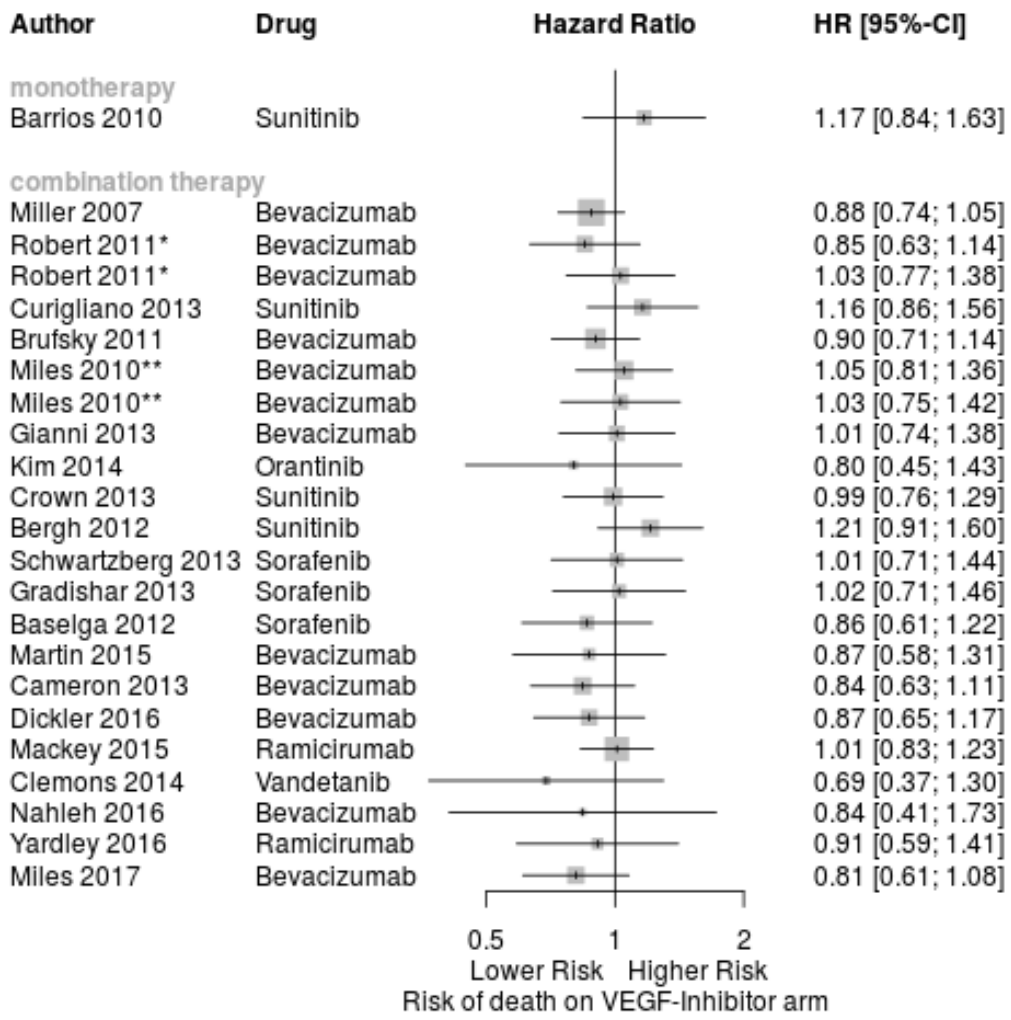


Figure 9 *Hazard ratios (HRs) of overall survival (OS) comparing monotherapy and combination therapy trials, arranged by trial initiation date (publication date shown). * Robert 2011 was a four-armed trial in which bevacizumab either in combination with capecitabine or in combination with taxanes/anthracyclines was compared to Placebo and chemotherapy. HRs for both comparisons are displayed. ** Miles 2010 compared 2 different dosages of bevacizumab (7.5mg/kg and 15 mg/kg). Both HRs are included in this figure.*

Exposure to a VEGF inhibitor in monotherapy or combination therapy was neither demonstrably advantageous nor disadvantageous for patients, according to prespecified thresholds of significance for OS in any of the trials included. While there was no obvious trend

towards VEGF inhibitor disadvantage, it is noteworthy that no VEGF inhibitor ever showed a reduction in the risk of death of a breast cancer patient.

4.5 Trials of limited value

In total, 7 phase 2 trials of limited value were identified (7.22% of phase 2 trials), representing 347 patients (84,102,110,158,167,173,192).

3 (3.09% of phase 2 trials) trials representing 75 patients failed to reach at least 85% of their targeted enrolment for reasons other than futility or benefit (accrual failure) (102,125,192). Another two trials experienced accrual failure initially, but amended their protocols to account for slow recruitment (84,187) and hence do not fall within this category.

Four trials were identified as potentially duplicative phase 2 trials (4.12% of phase 2 trials) (110,158,167,173). They duplicated prior phase 2 trials with the same treatment or combination of treatments, in the same setting (line of treatment) and enrolled patients with the same tumor characteristics. These trials enrolled a total of 272 patients.

4.6 Narrative on further testing

Out of the 146 trials included, 101 (69.2%) suggested further testing of the VEGF inhibition paradigm in breast cancer in the form of further trials on breast cancer patients. In total, 47 trials reached their primary efficacy endpoint with acceptable toxicity (positive [green] in the AERO diagrams in Figures 3 and 4). 34 of those studies suggested further testing (72.3%). Of the 58 studies that did not meet their primary efficacy endpoint or had unacceptable toxicities, 37 suggested further testing (63.8%).

4.7 Citation analyses

Citation characteristics

Trials in our sample were cited by 623 other trials within our sample. After additional data cleaning and manually matching abstracts and non-primary publications to full trial publications, we identified further 163 citations within the set of clinical trials.

Of the total 830 citations, 580 (69.9%) occurred between studies of the same drug, while 250 (30.1%) cited a study investigating another VEGF inhibitor (see Table 4).

216 (27.5%) citations within the network originated from introduction sections, 362 (46.1%) originated from discussion sections, and citations occurred 206 (26.2%) times in both

discussion and introduction sections. A positive prior VEGF trial in breast cancer was cited 477 times (60.7% of all citations). This is a little under twice as many citations as those made to trials that did not meet their primary endpoint or had unacceptable toxicity. Trials without a relevant efficacy endpoint or accrual failure accounted for less than 9% of the total citations within the network (68/830) (Table 4)

Table 4 Key characteristics of citations between included studies.

Characteristic		**Number (percentage of all citations)**
Citation to a trial testing	the same VEGF inhibitor	545 (69.3%)
	another VEGF inhibitor	241 (30.7%)
Citations to a	positive trial	477 (60.7%)
	negative trial	241 (30.7%)
	trial with accrual failure	17 (2.16%)
	trial without relevant efficacy endpoint	51 (6.49%)
Citations occurring within	introduction section	216 (27.5%)
	discussion section	362 (46.1%)
	both	206 (26.2%)

On a per study level, 57 (39%) of the trials cited earlier trials that tested a different VEGF inhibitor than the one they were investigating. 11 of the total 89 trials testing bevacizumab cited a trial of another VEGF inhibitor in breast cancer (11.2%), while 47 of 57 of the non-bevacizumab trials cited a trial testing another VEGF inhibitor (82.5%).

Citations to trials of VEGF inhibitors in other indications

A total of 73 (50%) of the trials cited studies that tested a VEGF inhibitor in a different indication from breast cancer. Table 5 shows the number of citations to VEGF inhibitor trials in other indications. The top three indications cited are renal cell carcinoma, non-small-cell lung cancer and colorectal cancer. These are indications for which VEGF inhibitors received regulatory approval (7 VEGF inhibitors are approved for renal cell carcinoma, 3 for colorectal cancer and 3 for non-small-cell lung cancer, see Table 5).

The majority of citations to other indications occurred from the introduction section only (96, 41% of total citations to other indications), suggesting that investigators took successful VEGF inhibitor drug development in other diseases into account to justify conducting trials in breast

cancer. A total of 45 (30.8%) trials cited both studies using a different VEGF inhibitor and studies testing a VEGF inhibitor in another indication from breast cancer.

Table 5 Number of citations to VEGF inhibitor trials in other indications.

Other indication	**Number of citations**	**VEGF inhibitors with regulatory approval**
renal cell carcinoma	64	bevacizumab, sunitinib, sorafenib, pazopanib, axitinib, cabozantinib
non-small-cell lung cancer	49	bevacizumab, ramucirumab, nintedanib
colorectal cancer	49	bevacizumab, ramucirumab, aflibercept
gastric cancer	17	sunitinib, ramucirumab
ovarian cancer	17	bevacizumab
hepatocellular carcinoma	13	bevacizumab, sorafenib, cabozantinib, ramucirumab
melanoma	7	-
pancreatic cancer	7	sunitinib
thyroid cancer	7	cabozantinib, vandetanib, sorafenib
prostate cancer	3	-
cervical cancer	2	bevacizumab
head and neck or nasopharyngeal carcinoma	2	-
soft tissue sarcoma	2	pazopanib
endometrial cancer	1	-
glioblastoma	1	bevacizumab
urothelial cancer	1	-

Citation of prior research within the network

Studies included in this analysis cited on average 5.38 prior studies within the set. We also calculated the PRCI for each trial as the number of cited trials divided by the number of trials

eligible to cite in the network (see Figure 10). The average PRCI within the network is 12.6%, meaning that on average trials cited about 1 in 8 of the available studies within the set. While in the beginning of the VEGF paradigm in breast cancer most of the prior evidence was taken into account via citations, the PRCI diminished over time. This is not surprising, considering that diverse research testing VEGF inhibitors became available and more selective citation occurred over time. Nevertheless, the average amount of prior studies cited stalled early in the paradigm.

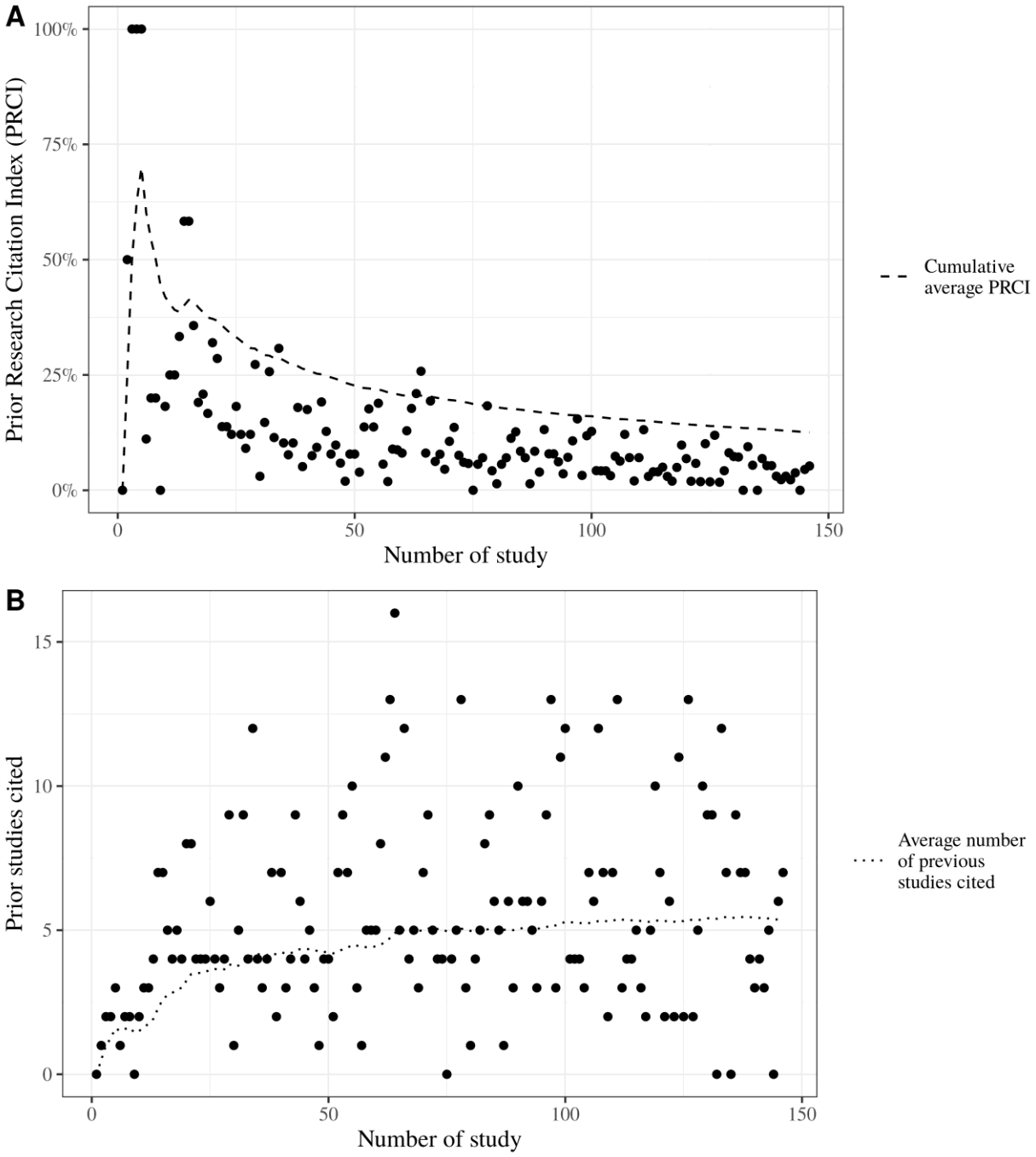


Figure 10 *Prior Research Citation Index (PRCI, panel A) and Number of prior studies cited (panel B) by study over the course of the research paradigm. Lines represent the cumulative average PRCI and cumulative average number of previous studies cited.*

Citation bias based on directionality of results

We plotted the distribution of citable prior studies categorized by outcome over the course of the research paradigm and compared it with the distribution of cumulated cited studies categorized by outcome (see Figure 11). Generally, the citation patterns and distribution of citable studies remain stable over the course of the research paradigm. Although studies with accrual failure or no efficacy endpoint of interest (e.g. bevacizumab is standard of care and tested against, safety is primary outcome etc.) account for 25-30% of citable trials throughout most of the paradigm, they received a disproportionately small amount of citations (8.7%).

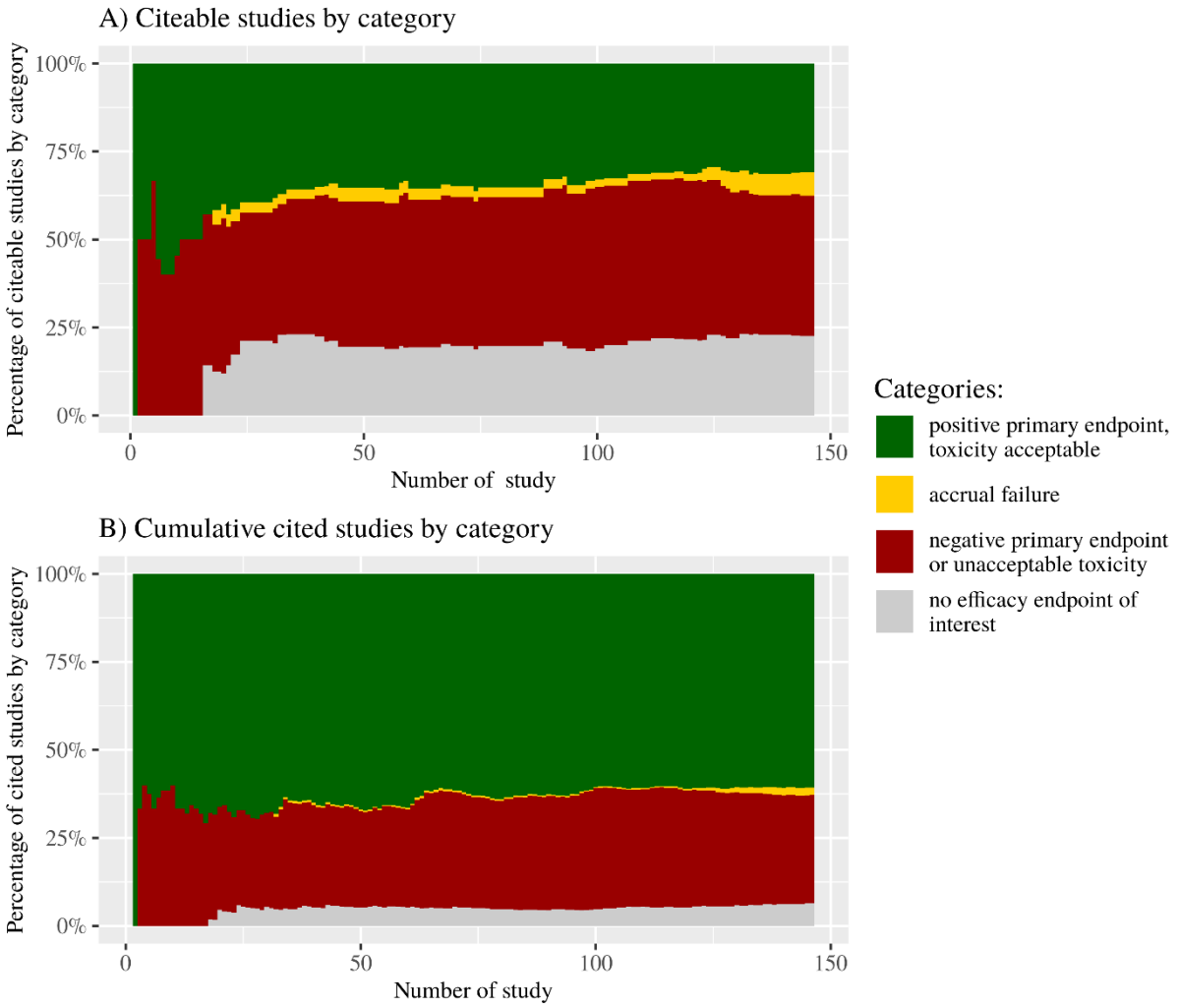


Figure 11 *Percentage of citable vs. cited studies by category over the course of the research paradigm.*

While there are more negative than positive citable studies within the set of included trials (53 negative, vs. 41 positive), positive studies received about twice as many citations as negative studies (241 negative vs. 477 positive, respectively).

Figure 11 is similar to Figure 12, but it additionally takes the sample size of included trials into account. At the end of the research paradigm, there were about as many patients enrolled in citable negative studies as in citable positive studies (10,386, 40.5% in positive trials vs. 10,445, 40.7% in negative trials). However, cumulatively 331,434 (74.5% of the total cited patients) patients in positive studies and only 98,000 (22% of the total cited patients) in negative studies were cited by the end of the research paradigm.

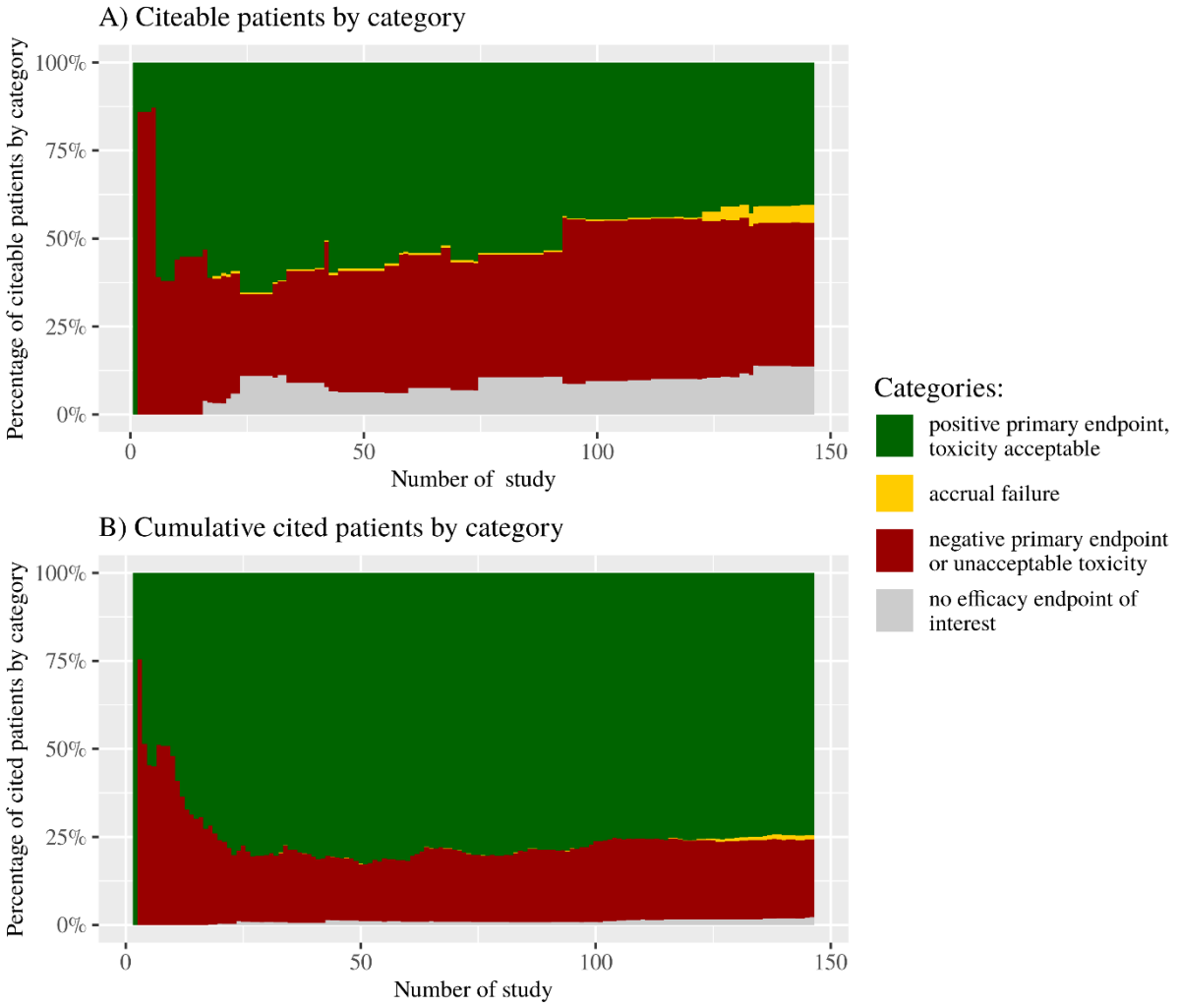
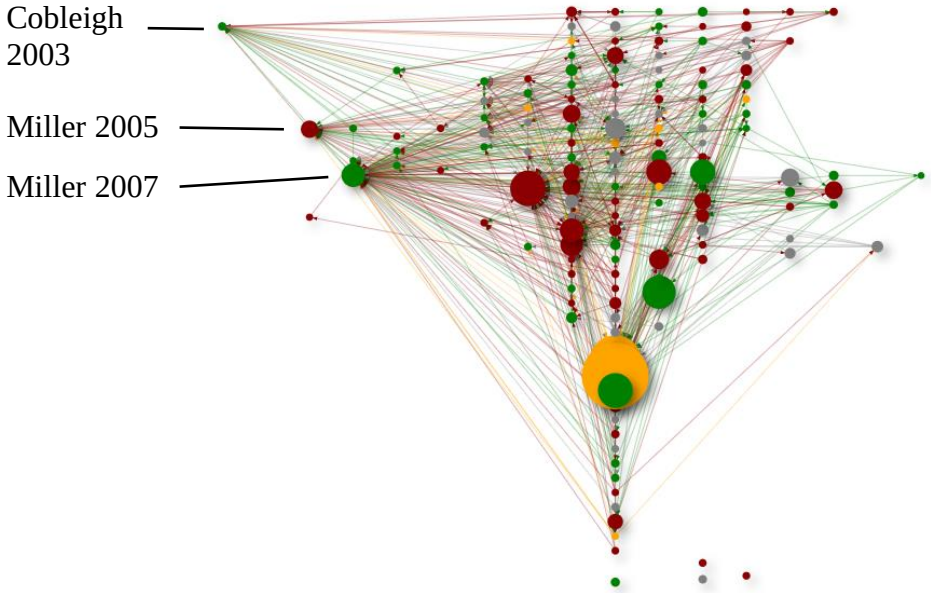


Figure 12 *Percentage of citable vs. cited patients by category over the course of the research trajectory.*

We visualized the entire network to explore patterns in citation behavior. Figure 13 shows two versions of the citation network. Edges represent citations and nodes represent trials. The node color represents the directionality of the outcomes. Nodes are ordered according to enrollment

dates of the studies with earliest enrolment left and latest enrolment right. In panel A, node size is proportionate to number of patients enrolled, while in panel B node size is proportionate to citations received from the studies included in this analysis. Cobleigh 2003 and Miller 2007 are positive studies published early on in the trajectory that received a high amount of citations (17,74) compared to the number of patients they enrolled. This is especially noteworthy because Miller 2005, a large phase 3 trial with non-positive outcome, was also published early on in the trajectory but received proportionately less citations. (132)

A) Node size proportionate to patient enrolment



B) Node size proportionate to citations within network

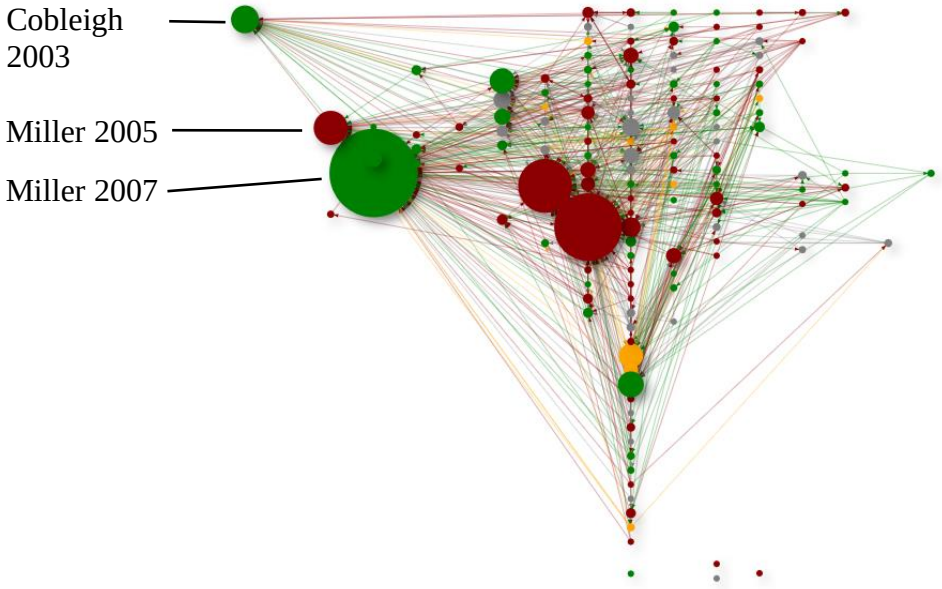


Figure 13 *Citation network of the set of included trials - nodes represent trial reports, edges are citations within the network. Node colors represent directionality of study results (green = positive primary endpoint, acceptable toxicity; red = negative primary endpoint or unacceptable toxicity; grey = no efficacy endpoint of interest; yellow = accrual failure). Nodes are ordered by beginning of enrollment on the horizontal axis.* Panel A) *Node size is proportionate to number of patient enrolment.* Panel B) *Node size is proportionate to citations within the network. Cobleigh 2003, Miller 2005 and Miller 2007 (74,131,17) are labeled.*

Bevacizumab, sunitinib, sorafenib, apatinib and cabozantinib are the only VEGF inhibitors in which a breast cancer trial reached its primary endpoint with acceptable toxicity. For all of them (excluding sorafenib), the most highly cited trial had a positive outcome (see table 6).

Table 6 The most highly cited trials for each drug tested within the set of studies. The most highly cited trials were often trials with a positive outcome. Trials of Tivozanib, Dovitinib, Cediranib, Cabozantinib, Angiozyme and Aflibercept did not receive any citations within the set of studies.

Study	VEGF inhibitor tested	Number of citations	AERO colour	Did any trial of this VEGF inhibitor reach its primary endpoint with acceptable toxicity in this indication?
Miller 2007	Bevacizumab	119	green	yes
Burstein 2008	Sunitinib	27	green	yes
Baselga 2012	Sorafenib	19	red	yes
Martin 2011	Motesanib	8	red	no
Johnston 2013	Pazopanib	7	red	no
Rugo 2011	Axitinib	7	red	no
Miller 2005	Vandetanib	5	red	no
Hu 2014	Apatinib	2	green	yes
Mackey 2015	Ramucirumab	1	red	no
Overmoyer 2007	Semaxinib	1	red	no
Toi 2014	Orantinib	1	red	no
Suzuki 2013	Orantinib	1	red	no
Quintela 2014	Nintedanib	1	white	no

111 trials (76% of all included trials) cited at least one of the most cited studies of sunitinib, bevacizumab or apatinib. This suggests that a few positive trials had a disproportionally high impact on the VEGF inhibition paradigm.

4.8 Secondary analyses

4.8.1 Citable Patient Index

To determine whether patients in negative and inconclusive studies had less influence over the translation trajectory than patients within positive trials, we assessed citations in the discussion section of trial reports. We calculated the index of cited patients over citable patients per category of trial (positive and non-positive) for each trial report.

Calculated over all studies combined, there was a total of 1,896,059 eligible patients (Ep). Of those, 314,493 patients were cited in discussion sections (Ap). The CPI (calculated via Ap/Ep) is 16.6%.

There was a total of 911,375 eligible patients enrolled in studies with acceptable toxicity and a positive primary endpoint (Ep+). Of those, 216,510 were cited in discussion sections (Ap+). Hence, the CPI(+) is 23.8%. Of the 984,684 eligible patients enrolled in non-positive trials (Ep not+), 97,983 were cited in discussion sections (Ap not+). The CPI (not +) is 9.95%.

Following our hypothesis, the CPI (+) is higher than the CPI (not+) by a factor of 2.4. Patients in positive trials were referenced 2.4 times more in discussion sections than patients in non-positive trials, giving them more influence over the translation trajectory.

Figure 14 shows the CPI(+) and CPI (not+) from trial report to trial report. The CPI varied between studies, but the cumulative average CPI(+) is consistently larger than the CPI(not+). We applied a grace period of 1 year after publication for studies to become eligible for citation. When CPIs > 1, we set them to 1.

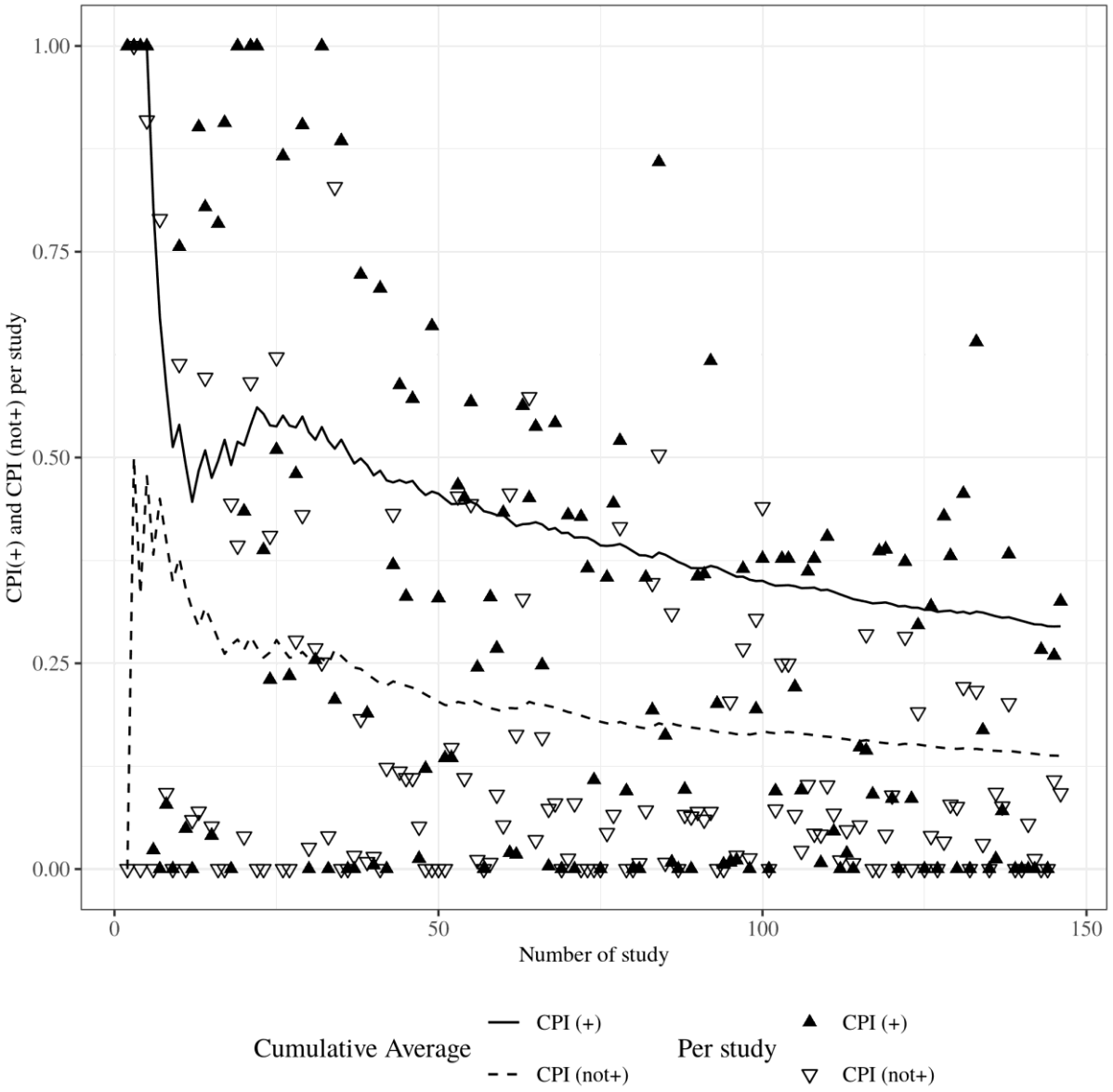


Figure 14 *Citable Patient Index (CPI) (+) and CPI (not+) per trial report and over the course of the drug development paradigm. The index of patients enrolled in trial reports that were cited in the discussion sections of each article over the citable patients enrolled in prior trials by category (positive vs. non-positive) are plotted. The cumulative average of CPI (+) and CPI (not+) are displayed as solid and dashed lines. We applied a grace period of 1 year prior to publication date, hence some studies cited more patients than we deemed "citable". In this case the CPI was set to 1.*

4.8.2 Citations to VEGF Inhibition critical studies

Applying a one year grace period after publication, we identified 125 trials within the set that were eligible to cite two seminal preclinical studies presenting critical data of VEGF inhibition in cancer (12,13). We found 11 trials within the set that cited either or both studies (8.8% of eligible trials). Those trials tested sunitinib (4/11), sorafenib (3/11), bevacizumab (3/11) or apatinib (1/11), and were published between 2010 and 2016. 3 out of 11 trials reached their

primary efficacy endpoint with acceptable toxicity. 38 trials started enrolment after Ebos et al. and Paez-Ribes et al. published their results. Table 7 gives an overview of trials in the set that cited Ebos et al. or Paez-Ribes et al. as well as the citation contexts of these references.

Table 7 Overview of trials in the set citing anti-angiogenesis critical preclinical studies.

Trial	Critical study cited	Drug	Met relevant eff. outcome with acceptable toxicity	Citation context
Wildiers 2010 (182)	Ebos et al.	Sunitinib	no	"…In non-clinical models, dose interruption of antiangiogenic agents can lead to reactivation [15] and even acceleration of angiogenesis. It is conceivable that such a scenario may have happened in this study population.…"
Forero-Torres 2010 (92)	Paez-Ribes et al., Ebos et al.	Bevacizumab	no	"…22, 23 Those studies suggested that antiangiogenesis strategies under certain conditions could lead to enhanced progression and invasion, and accelerated metastases. The animal models and treatment regimens were not similar to those in the adjuvant (or neoadjuvant) therapy of breast cancer.…"
Baselga 2012 (58)	Paez-Ribes et al., Ebos et al.	Sorafenib	no	"preclinical data suggest that antiangiogenic treatment may result in more aggressive disease at the time of progression, possibly through increased invasiveness of tumor cells and/or by switching to alternative angiogenic pathways to re-establish tumor vascularization [21, 22]."
Bergh 2012 (23)	Paez-Ribes et al., Ebos et al.	Sunitinib	no	"Preclinical studies have shown that antiangiogenic agents such as sunitinib may induce immediate effects on the vasculature, causing an improved response rate, and secondarily induce tumor hypoxia, yielding tumor cells that become more therapy-resistant and with a greater capacity for metastatic spread.[18–20] However, in contrast to these preclinical models, in the present study, no compelling differences in metastatic spread were observed between the combination and monotherapy arms, with the exception of PD in malignant effusions (20 patients on combination therapy v nine patients on monotherapy; P = .06; Data Supplement)."

Curigliano 2013 (79)	Paez-Ribes et al., Ebos et al.	Sunitinib	no	"Recent preclinical research has shown that treatment of tumor-bearing mice with antiangiogenic drugs (including sunitinib) can result in increased local tumor cell invasion and enhanced meta-static dissemination [28,29]. These results have been discussed as one possible explanation (among many) for the lack of survival benefit that has been seen with antiangiogenic agents in ABC. However, in one sunitinib phase III study in ABC that failed to demonstrate improved clinical outcomes, little difference was found in the extent of metastatic spread between the sunitinib docetaxel combination arm and the docetaxel monotherapy arm[26]. Likewise, little difference in the extent of metastatic spread was found between the treatment arms in the present study, noting that the sample sizes were small. As the changes in cellular and organ metabolism leading to death in patients with metastatic disease are incompletely understood, it re-mains possible that antiangiogenic agents, through more profound blockade of the vasculature than anticipated, accelerate some component of the premorbid process."
Crown 2013 (77)	Paez-Ribes et al., Ebos et al.	Sunitinib	no	"From the biologic point of view, more recent preclinical results have suggested that antiangiogenic agents may overprune the tumor vasculature, leading to tumor hypoxia and genetic drift to a more aggressive or invasive phenotype.[31–33] However, at least one of these predictions has not been borne out in the clinical setting; little difference in metastatic spread was observed between sunitinib and comparator treatment groups in two studies in which this was assessed (one sunitinib phase III study evaluating combination with docetaxel[28] and the phase II study in triple-negative BC [Pfizer, data on file])."
Schwartzberg 2013 (161)	Paez-Ribes et al., Ebos et al.	Sorafenib	yes	"Preclinical studies suggest that antiangiogenic therapy may induce more aggressive disease (12,13), although a retrospective pooled analysis of randomized placebo-controlled trials in solid tumors (including breast) observed no significant difference in TTP or death after patients discontinued bevacizumab due to toxicity compared with those who discontinued placebo (33). Regardless, patients enrolled in this trial had relatively high-risk disease for early progression.…"

Hu 2014 (102)	Ebos et al.	Apatinib	yes	"A recent preclinical study demonstrated that TKIs, such as sunitinib and sorafenib, can promote accelerated progression of metastases in a breast cancer model.32 If manifest in patients, this effect might contribute to the reduced efficacy of TKIs in MBC. However, since sunitinib and sorafenib are relatively dirty multitargeted drugs, it is possible that the accelerated progression observed may be due to off-target effects of these VEGFR inhibitors. In support of this, three recently published studies suggest that off-target effects of sunitinib, or inhibition of PDGFR signaling in pericytes, may be the mechanism through which sunitinib can promote accelerated progression of metastases.33-35 Therefore, the fact that apatinib has low activity against other receptor tyrosine kinases, including PDGFR and KIT,16 (Supporting Information Table 1) may therefore be an advantage for this TKI compared to other TKIs that have been trialed in MBC."
Loibl 2014 (116)	Paez-Ribes et al.	Sorafenib	no	"The lack of success of anti-angiogenic therapies in breast cancer to date may in part be explained by activation of additional pro-angiogenic switches upon blockade with bevacizumab, as has been shown in experimental systems [29]."
Tiainen 2016 (172)	Ebos et al.	Bevacizumab	yes	"In preclinical studies, it has been reported that tumor progression may be accelerated after short-term angiogenesis inhibition (29). On the other hand, treating colorectal cancer with second-line bevacizumab-chemotherapy combination after disease progression with first-line therapy including bevacizumab was shown to have survival benefits (30)"
Bertucci 2016 (63)	Paez-Ribes et al., Ebos et al.	Bevacizumab	no	"Together, these results suggest a negligible benefit of bevacizumab for micrometastatic disease in breast cancer, notably in inflammatory breast cancer, which is a rapidly spreading systemic disease.35 Potential explanations for these results include increased metastatic and invasive properties of breast cancer cells after anti-angiogenic treatments, as demonstrated in breast cancer xenograft models,36,37 increasing numbers of breast cancer stem cells during bevacizumab treatment,29 and a possible rebound of tumour cell growth after the completion of therapy.38,39"

5. Discussion

In this systematic analysis, rather than focusing on how one specific drug is used in different indications, we examined an entire class of drugs - sharing the same mechanism of action - in one indication: namely, the VEGF inhibition paradigm in breast cancer.
In our analysis, we found different potential sources of inefficiencies in the clinical research trajectory of VEGF inhibitors in breast cancer.

First, we could show that positive trials in general were more likely to be cited. Although there were more negative than positive citable studies within the set of included trials (53 negative, vs. 41 positive), positive trials received about twice as many citations than negative studies (241 negative, vs. 477 positive). This result holds up when the sample size of trials was accounted for. At the end of the research paradigm, there were about as many patients enrolled in citable negative studies as in citable positive studies. However, 74.5% of the total cited patients were from positive studies and only 22% from negative studies.

Second, only a small proportion of citations occurred between different drugs that target the same pathway in the same indication. Citations to other VEGF inhibitor trials in breast cancer were also unevenly distributed between drug classes. 11.2% of bevacizumab trials cited a trial of another VEGF inhibitor in contrast to 82.5% of the non-bevacizumab trials that did so. This finding suggests that investigators in non-bevacizumab trials referenced positive studies in bevacizumab drug development, while vice versa, investigators in bevacizumab trials referenced few other VEGF inhibitors, whose study results were largely non-positive (47.2% of bevacizumab trials were positive vs. 8.8% of non-bevacizumab trials)

Third, calculated by citation count in discussion sections, “positive” patients contributed to the development trajectory more than twice as much as “negative” patients.
One could argue that trials should be based on positive prior findings and trial reports need to consistently make a clear case in the introduction as to why they tested a specific intervention. To account for this, we limited additional analyses to citations occurring within the discussion section of trial reports where a more balanced approach to the paradigm can be expected.
Calculated over the course of the paradigm we found that 23.8% of citable patients in prior trials with a positive endpoint were cited, as compared to 9.95% of patients enrolled in negative trials.

Fourth, 37 out of 58 trials (63.8%) that did not reach their primary efficacy endpoint with acceptable toxicity nevertheless suggested further testing of a VEGF inhibitor in breast cancer. Authors' conclusions and wording matter and we believe the fact that more testing was suggested, despite unsuccessful findings, contributed to the prolongation of the research paradigm and the longevity of the underlying biological hypothesis.

Fifth, we found that trials included in this analysis cited on average only about one in 8 of the available prior studies within the set. While this number compares unfavourably to similar research, it must be noted that we applied a different methodology. Prior studies reviewed a specific intervention and limited inclusion of trials to those randomized controlled studies that were grouped in existing meta-analyses (31,195). By the end of the paradigm, we identified 133 citable studies. Journal-level limitations regarding the number of references that can be included in a published trial report are common and we do not believe that authors can be expected to cite all preceding clinical trials in a drug development paradigm. On average, trials cited 5.3 prior studies with a range from 0 to 17. This mean was established early on in the paradigm and did not change when more citable trials became available. This dynamic is consistent with earlier findings for prior research citation indices (31). We argue that the number of citations is somewhat less telling than the distribution and biases in overall citation behaviour, e.g. based on directionality of findings.

Moreover, the bias in citation practices remained stable throughout the translational trajectory. One cannot locate a turning point where investigators abandoned the paradigm and reversed the selective citation behaviour.

Finally, we explored how preclinical studies that directly criticized the VEGF inhibition paradigm were taken up by trial reports. Paez-Ribes et al. and Ebos et al. argued that VEGF inhibition may constitute a driving force in tumor progression and formation of metastases (12,13). Only 11 trials referenced these findings and they discussed them in different ways. Bergh et al. rejected the critical hypothesis, and in their case found no compelling differences in metastatic spread between VEGF inhibitor intervention arm and comparator (23). Other studies presented the preclinical findings as a potential biological explanation for their negative outcomes (182). Overall, judged by the low uptake in terms of citations, it would seem that the critical preclinical studies had little influence on the trajectory of testing. Furthermore, it should

be noted that only 38 (26% of 146 total) trials in our sample started enrolment after the critical studies were published.

Our analyses reveal key features of the VEGF inhibition paradigm in breast cancer:
The paradigm was driven by combination therapy. Our results indicate that very early on in the research agenda, there were already phase 3 clinical trials testing bevacizumab in combination therapy, without previous phase 1 or phase 2 trials in combination therapy. Only one monotherapy trial of bevacizumab in breast cancer was published before phase 3 combination trials started enrolment. We found that many trial reports referenced prior studies for which VEGF inhibitors received regulatory approval - potentially to justify conducting trials in breast cancer. Bevacizumab studies account for most of the research activity within the set of trials. Two large randomized phase 3 trials showed a survival benefit of bevacizumab in addition to chemotherapy in non-small-cell lung cancer and colorectal cancer (196,197). These trials, however, also noted a significantly higher risk of bleeding when bevacizumab was added to chemotherapy.

Subsequently, phase 2 and 3 trials with other VEGF inhibitors were launched, with only one phase 3 trial testing sunitinib monotherapy (57). Sorafenib and sunitinib were tested in 13 and 16 trials, respectively. After non-positive trials in phase 2 and 3, sunitinib testing was discontinued and so was sorafenib. The FDA approval in 2008 of bevacizumab in combination with paclitaxel for the first line treatment of metastatic breast cancer based on improved PFS marked the height of clinical trial launches of VEGF inhibitors in breast cancer.
It appears that the research agenda stagnated after the FDA revoked the accelerated approval of bevacizumab in 2011. There are two potential hypotheses explaining this effect: first, the FDA decision had an impact on clinical research dealing with VEGF inhibitors in breast cancer and stopped further exploration of VEGF inhibition in breast cancer; second, this may be due to the fact that trial results had not been published before our data cutoff in February 2017.
While the latter is possible, another study that reviewed and meta-analyzed the evidence around bevacizumab's regulatory approval and withdrawal as first-line therapy in metastatic breast cancer found similar patterns, stating that the FDA's decision seems to have "dampened enthusiasm" for the search for an effective bevacizumab combination (22). Our results extend this observation to the entire class of VEGF inhibitors.

The PFS benefit of bevacizumab therapy was demonstrated early in the paradigm, yet this surrogate endpoint did not translate into OS benefit. Of the 146 trials included in this analysis, no trial had OS or quality of life as primary endpoint. We identified 21 trials that reported OS against a comparator arm as a non-primary endpoint. Of those, not a single trial demonstrated that VEGF inhibition reduces risk of death with statistical significance.

This is in accordance with findings from Hey et al. (22), whose research focused on a fraction of trials also included in our sample, namely bevacizumab combination therapy as first-line therapy for metastatic breast cancer. They considered more recent evidence than was provided for the FDA decision to revoke approval for this indication and found that the pooled hazard ratio for OS in bevacizumab therapy against any other comparator arm remains statistically nonsignificant "but does show a stable 10% OS benefit" (22). The use of PFS remains controversial. Studies of the validity of PFS have shown heterogeneous results across cancer types and drugs (198–200). Hey et al. (22), however, demonstrated that the association between PFS benefit and OS benefit of bevacizumab in metastatic breast cancer is non-significant.

VEGF inhibitors were tested in many different combinations and in a diverse set of breast cancer patients across the clinical development trajectory. We could identify comparably few duplicative studies (4 in total; a similar analysis in sorafenib that included 124 trials, found 10 duplicative phase 2 studies(50)). The diversity of combinations tested was also found for bevacizumab therapy for metastatic breast cancer in the prior review by Hey et al. (22).

Additionally, we evaluated the risk and benefit profile of VEGF inhibitors in breast cancer across the set of included trial reports using serious adverse events and objective response rates as proxies for risk and benefit.

Cumulative risk and benefit analyses revealed that over the course of VEGF inhibition drug development in breast cancer, the risk-benefit ratio remained mostly stable. On the one hand, this means that with the persistent testing of diverse regimens patients were not necessarily exposed to a higher burden in term of adverse events, but also that drug developers were not able to reduce risk or identify subgroups or combination treatment regimens that lead to greater clinical utility.

We characterized and measured the cumulative burden associated to the VEGF inhibition paradigm in breast cancer. 114 patients died from drug-related toxicities. In about every fifth trial, the safety profile of drugs tested were described as unacceptable, and combination therapy trials were more likely to find unacceptable toxicities. Grade 5 SAEs – those leading to death – were reported in similar rates in monotherapy and combination therapy. This seems unlikely, given the overall less favorable toxicity profile in combination therapy. Hence, an under-reporting of treatment-related Grade 5 SAEs in combination therapy may be one plausible explanation.

Since we extracted the single most often occurring SAE of Grade 3-5 only, we are likely to have underestimated the number of toxicities experienced by patient-subjects. While aiming for comparability between trials and along the drug development trajectory, we may have missed VEGF inhibition specific adverse events and safety concerns. One such example can be found in the pivotal trial that led to the FDA approval of bevacizumab. We noted the most occurring SAE Grade 3-5, which was peripheral neuropathy. Peripheral neuropathy is often a main side effect of chemotherapy (201). This study recorded significantly more SAEs in the interventional bevacizumab + paclitaxel arm that we did not capture using our approach. This included Grade 3 or 4 hypertension in 14.8% and cerebrovascular ischemia in 1.9% of the patients in the bevacizumab + paclitaxel arm vs. 0.0% in patients that received paclitaxel alone (17). Still, it is important to note that some of the most occurring SAEs that we found in the set of included trials such as hypertension and hand-foot-syndrome (202) are associated with VEGF inhibitor treatment.

These results should be interpreted considering the following limitations.
First, our research fully relied on published trial reports in the academic literature. We did not search any registries and did not assess possibilities for publication bias. Prior research estimates that up to 62% of phase II studies in oncology are never published (29). However, we suspect that unpublished results, if added to our analysis, are unlikely to change the risk/benefit balance of the trajectory. Also, another study (22) that a) took results from trial registries into account and b) had a later data cutoff date found evidence of similar research patterns (albeit only focusing on a subset of trials included in our analysis).

Second, as discussed above, there are limitations to the way we extracted safety data. For our analysis, we only took the one single most occurring SAE of Grade 3-5 in each trial into account to allow for relative comparability between clinical trial reports; VEGF inhibitors were often

tested in combination with chemotherapy. The SAE we recorded may be connected more to the toxicity profile of the combination treatment than the VEGF inhibitor.

Third, we extracted recommendations for the further testing of drugs only. The language authors use to present trial findings can be analyzed taking methodology to assess spin into account (203). Our approach is limited to the extraction of the recommendation authors give to further test VEGF inhibitors in breast cancer.

Finally, citation analysis itself has many limitations. The ultimate question of why drug developers continue to pursue a paradigm that has shown limited efficacy is more complex.

Citations can have many more motivations than just referencing prior work. They can be described as both an impartial scholarly method and a powerful form of social communication (27). In addition, adopting prior results can happen in other ways than citations. In the given context, changes in trial design (like basket trials, umbrella trials) or formulation (PICO) may indicate learning.

Recognizing the multiple facets of citations requires assessing their qualitative aspect as well. It matters how - not just how often - a prior article is referenced. We tried to enrich the citation information gathered by noting the section in which citations occurred. While this may add an additional layer of useful information for analysis, citation sections merely offer another surrogate for actual context. We only noted the citation context for the 11 references to critical preclinical studies that occurred (see Appendix 3). Citation context analyses are time-consuming and not trivial to implement. Language in the biomedical sciences has little standardization (unlike law, where “shepardizing” is a standing term describing the “process of using a citator to discover the history of a case or statute to determine whether it is still good law.”(204)) and human interpretations of whether a citation is “confirmatory”, “refuting” , “comparing” or just “mentioning” are variable.

Nevertheless, recent advances in machine learning and the increasing digitization of the scientific corpus have enabled commercial services that could help citation context analysis at scale in the future (205,206).

5.1 Conclusion

In this systematic analysis, we found a substantial patient burden associated with the unsuccessful drug development paradigm of VEGF inhibition in breast cancer. The majority of patient burden occurred around the accelerated FDA approval of bevacizumab in 2008. It appears that the research agenda stagnated after the FDA revoked the accelerated approval of bevacizumab in 2011. Not a single VEGF inhibitor provided a survival benefit over a comparator arm in any of the trials analysed.

We explored possible reasons for the perseverance of this particular paradigm and identified substantial citation biases across the drug development trajectory. First, only a small and biased sample of prior studies was taken into account. Patients enrolled in positive studies were 2.4 times more likely to be referenced in the discussion section of subsequent trial reports. Second, few bevacizumab testing trials referenced prior trials on another VEGF inhibitor, suggesting that little comparative learning took place. Third, preclinical studies questioning the paradigm of VEGF inhibition in cancer therapy were only discussed in a small fraction of trial reports.

Another important finding concerns recommendations within the published trial reports. Many investigators suggested further testing of a VEGF inhibitor despite the fact that a study had not reached its primary efficacy endpoint with acceptable toxicity. This may be explained by the diversity of breast cancer (i.e., different receptor status) and complexity of treatment regimens (adjuvant vs. neoadjuvant, with a plethora of possible combinations). Investigators suggested further testing over and over again to identify the right biomarker or combination. Our analysis showed, however, that the risk vs. benefit profile did not improve over the drug development trajectory.

5.2 Outlook

There are many opportunities for future research to build on our findings.
Our results could be confirmed and potentially amended by interviews with the investigators that tested VEGF inhibitors in breast cancer trials. These interviews could shed light on the precise reasoning for investigating a VEGF inhibitor in breast cancer in the past.

We found the VEGF inhibition paradigm in breast cancer to be fuelled and motivated by translational success of VEGF inhibitors in other indications. A possible next step would be to extend our analyses to a different and successful drug development trajectory - for example VEGF inhibition in renal cancer. The comparison of our (so far unique) findings in a failing trajectory to a successful trajectory would improve understanding of the indicators gathered in the present study.

Additional analyses could include gathering information on trial design (e.g. PICO) to explore different ways in which learning took place within the paradigm. Also, it has been shown that factors other than directionality of results are predictors of citation bias. These go beyond study quality or design and include journal prestige (JIF), authors' achievements and institutional affiliations, and could additionally be explored in the context of the VEGF inhibition paradigm (207).

Another possibility to extend our findings could be a semi-automated citation context analysis which takes into account not only the number and meta-information of citations, but also the quality of citations. Using social network theory and graph theory, this may allow us to determine the degree in which citation distortions and incorrect citations occurred within the set of clinical trials (208).

Finally, although it seemed like the VEGF inhibition paradigm in breast cancer had come to an end by the data cutoff for this study in February 2017, more trial reports may have been published since then. A targeted search on clinicaltrials.gov on April 6, 2021 revealed that there were 27 interventional trials actively enrolling breast cancer patients for the drugs studied in this analysis (209).

6. References

1. Parasrampuria DA, Benet LZ, Sharma A. Why Drugs Fail in Late Stages of Development: Case Study Analyses from the Last Decade and Recommendations. AAPS J. 2018 May;20(3):46.

2. Ackley SF, Zimmerman SC, Brenowitz WD, Tchetgen EJT, Gold AL, Manly JJ, Mayeda ER, Filshtein TJ, Power MC, Elahi FM, Brickman AM, Glymour MM. Effect of reductions in amyloid levels on cognitive change in randomized trials: instrumental variable meta-analysis. BMJ. 2021 Feb 25;372:n156.

3. Hay M, Thomas DW, Craighead JL, Economides C, Rosenthal J. Clinical development success rates for investigational drugs. Nature Biotechnology. 2014 Jan;32(1):40–51.

4. Hwang TJ, Carpenter D, Lauffenburger JC, Wang B, Franklin JM, Kesselheim AS. Failure of Investigational Drugs in Late-Stage Clinical Development and Publication of Trial Results. JAMA Internal Medicine. 2016 Dec;176(12):1826–33.

5. Seruga B, Ocana A, Amir E, Tannock IF. Failures in Phase III: Causes and Consequences. Clinical Cancer Research. 2015 Oct;21(20):4552–60.

6. Worp HB van der, Howells DW, Sena ES, Porritt MJ, Rewell S, O'Collins V, Macleod MR. Can Animal Models of Disease Reliably Inform Human Studies? PLOS Medicine. 2010 Mar;7(3):e1000245.

7. Carlisle B, Demko N, Freeman G, Hakala A, MacKinnon N, Ramsay T, Hey S, London AJ, Kimmelman J. Benefit, Risk, and Outcomes in Drug Development: A Systematic Review of Sunitinib. Journal of the National Cancer Institute. 2016 Jan;108(1):djv292.

8. Folkman J. Tumor angiogenesis: therapeutic implications. The New England Journal of Medicine. 1971 Nov;285(21):1182–6.

9. Sledge GW. Anti–Vascular Endothelial Growth Factor Therapy in Breast Cancer: Game Over? JCO. 2015 Jan 10;33(2):133–5.

10. Cameron D, Brown J, Dent R, Jackisch C, Mackey J, Pivot X, Steger GG, Suter TM, Toi M, Parmar M, Laeufle R, Im Y-H, Romieu G, Harvey V, Lipatov O, Pienkowski T, Cottu P, Chan A, Im S-A, Hall PS, Bubuteishvili-Pacaud L, Henschel V, Deurloo RJ, Pallaud C, Bell R. Adjuvant bevacizumab-containing therapy in triple-negative breast cancer (BEATRICE): primary results of a randomised, phase 3 trial. Lancet Oncology. 2013 Sep;14(10):933–42.

11. Miles DW, Dieras V, Cortes J, Duenne A-A, Yi J, O'Shaughnessy J. First-line bevacizumab in combination with chemotherapy for HER2-negative metastatic breast cancer: pooled and subgroup analyses of data from 2447 patients. Annals of Oncology. 2013 Nov;24(11):2773–80.

12. Pàez-Ribes M, Allen E, Hudock J, Takeda T, Okuyama H, Viñals F, Inoue M, Bergers G, Hanahan D, Casanovas O. Antiangiogenic Therapy Elicits Malignant Progression of Tumors to Increased Local Invasion and Distant Metastasis. Cancer Cell. 2009 Mar;15(3):220–31.

13. Ebos JML, Lee CR, Cruz-Munoz W, Bjarnason GA, Christensen JG, Kerbel RS. Accelerated Metastasis after Short-Term Treatment with a Potent Inhibitor of Tumor Angiogenesis. Cancer Cell. 2009 Mar;15(3):232–9.

14. Gil-Gil MJ, Mesia C, Rey M, Bruna J. Bevacizumab for the Treatment of Glioblastoma. Clin Med Insights Oncol. 2013 Jan;7:CMO.S8503.

15. Cohen MH, Gootenberg J, Keegan P, Pazdur R. FDA Drug Approval Summary: Bevacizumab (Avastin®) Plus Carboplatin and Paclitaxel as First-Line Treatment of Advanced/Metastatic Recurrent Nonsquamous Non-Small Cell Lung Cancer. The Oncol. 2007 Jun;12(6):713–8.

16. Summers J, Cohen MH, Keegan P, Pazdur R. FDA Drug Approval Summary: Bevacizumab plus Interferon for Advanced Renal Cell Carcinoma. The Oncologist. 2010 Jan;15(1):104–11.

17. Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, Shenkier T, Cella D, Davidson NE. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. Journal of Medicine. 2007 Dec;357(26):2666–76.

18. Lenzer J. FDA committee votes to withdraw bevacizumab for breast cancer. BMJ. 2011 Jul 5;343(jul05 3):d4244–d4244.

19. Pazdur R. Regulatory Decision to Withdraw Avastin (Bevacizumab) First-Line Metastatic Breast Cancer Indication. [Internet]. [cited 2021 Mar 3]. Available from: https://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM237171.pdf

20. Dusetzina SB, Ellis S, Freedman RA, Conti RM, Winn AN, Chambers JD, Alexander GC, Huskamp HA, Keating NL. How Do Payers Respond to Regulatory Actions? The Case of Bevacizumab. JOP. 2015 Jul;11(4):313–8.

21. FDA revokes Avastin as breast cancer treatment [Internet]. LA Times Blogs - Nation Now. 2011 [cited 2021 Mar 3]. Available from: https://latimesblogs.latimes.com/nationnow/2011/11/fda-revokes-avastin-as-breast-cancer-treatment.html

22. Hey SP, Gyawali B, D'Andrea E, Kanagaraj M, Franklin JM, Kesselheim AS. A Systematic Review and Meta-Analysis of Bevacizumab in First-Line Metastatic Breast Cancer: Lessons for Research and Regulatory Enterprises. JNCI: Journal of the National Cancer Institute. 2020 Apr 1;112(4):335–42.

23. Bergh J, Bondarenko IM, Lichinitser MR, Liljegren A, Greil R, Voytko NL, Makhson AN, Cortes J, Lortholary A, Bischoff J, Chan A, Delaloge S, Huang X, Kern KA, Giorgetti C. First-line treatment of advanced breast cancer with sunitinib in combination with docetaxel versus docetaxel alone: results of a prospective, randomized phase III study. Journal of Clinical Oncology. 2012 Mar;30(9):921–9.

24. Robert NJ, Saleh MN, Paul D, Generali D, Gressot L, Copur MS, Brufsky AM, Minton SE, Giguere JK, Smith JW 2nd, Richards PD, Gernhardt D, Huang X, Liau KF, Kern KA, Davis J. Sunitinib plus paclitaxel versus bevacizumab plus paclitaxel for first-line treatment of patients with advanced breast cancer: a phase III, randomized, open-label

trial.[Erratum appears in Clin Breast Cancer. 2011 Aug;11(4):273]. Clinical Breast Cancer. 2011 Apr;11(2):82–92.

25. Thanuskodi S, editor. Literacy Skill Development for Library Science Professionals: [Internet]. IGI Global; 2019 [cited 2021 Mar 3]. (Inglese C, editor. Advances in Library and Information Science). Available from: http://services.igi-global.com/resolvedoi/resolve.aspx?doi=10.4018/978-1-5225-7125-4

26. Trinquart L, Johns DM, Galea S. Why do we think we know what we know? A metaknowledge analysis of the salt controversy. Int J Epidemiol. 2016 Feb;45(1):251–60.

27. Greenberg SA. How citation distortions create unfounded authority: analysis of a citation network. BMJ. 2009 Jul;339(jul20 3):b2680–b2680.

28. Duyx B, Urlings MJE, Swaen GMH, Bouter LM, Zeegers MP. Scientific citations favor positive results: a systematic review and meta-analysis. Journal of Clinical Epidemiology. 2017 Aug;88:92–101.

29. Hoeg RT, Lee JA, Mathiason MA, Rokkones K, Serck SL, Crampton KL, Emmel AE, Severson EA, Go RS. Publication Outcomes of Phase II Oncology Clinical Trials. American Journal of Clinical Oncology. 2009 Jun;32(3):253–7.

30. Urlings MJE, Duyx B, Swaen GMH, Bouter LM, Zeegers MP. Citation bias and other determinants of citation in biomedical research: findings from six citation networks. Journal of Clinical Epidemiology. 2021 Apr;132:71–8.

31. Robinson KA, Goodman SN. A Systematic Examination of the Citation of Prior Research in Reports of Randomized, Controlled Trials. Annals of Internal Medicine. 2011 Jan;154(1):50.

32. Unger JM, Barlow WE, Ramsey SD, LeBlanc M, Blanke CD, Hershman DL. The Scientific Impact of Positive and Negative Phase 3 Cancer Clinical Trials. JAMA Oncol. 2016 Jul 1;2(7):875.

33. Kjaergard LL, Gluud C. Citation bias of hepato-biliary randomized clinical trials. Journal of Clinical Epidemiology. 2002 Apr;55(4):407–10.

34. Gotzsche PC. Reference bias in reports of drug trials. BMJ. 1987 Sep 12;295(6599):654–6.

35. Misemer BS, Platts-Mills TF, Jones CW. Citation bias favoring positive clinical trials of thrombolytics for acute ischemic stroke: a cross-sectional analysis. Trials. 2016 Dec;17(1):473.

36. Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, Langer C, Murphy B, Cumberlin R, Coleman CN, Rubin P. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol. 2003 Jul;13(3):176–81.

37. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research

and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000 Feb 2;92(3):205–16.

38. Grabitz, Peter. The persistence and burden of failing drug development paradigms: An exploratory analysis of VEGF Inhibition in breast cancer. 2021 [cited 2021 Apr 3]; Available from: https://osf.io/fe4n8/

39. Guo S, Colbert LS, Fuller M, Zhang Y, Gonzalez-Perez RR. Vascular endothelial growth factor receptor-2 in breast cancer. BIOCHIMICA ET BIOPHYSICA ACTA-REVIEWS ON CANCER. 2010 Aug;1806(1):108–21.

40. Gacche RN, Meshram RJ. Angiogenic factors as potential drug target: Efficacy and limitations of anti-angiogenic therapy. BIOCHIMICA ET BIOPHYSICA ACTA-REVIEWS ON CANCER. 2014 Aug;1846(1):161–79.

41. Waldner MJ, Neurath MF. Targeting the VEGF signaling pathway in cancer therapy. EXPERT OPINION ON THERAPEUTIC TARGETS. 2012 Jan;16(1):5–13.

42. Marme F, Schneeweiss A. Targeted Therapies in Triple-Negative Breast Cancer. BREAST CARE. 2015;10(3):159–66.

43. Koutras AK, Starakis I, Lymperatou D, Kalofonos HP. Angiogenesis as a therapeutic target in breast cancer. MINI-REVIEWS IN MEDICINAL CHEMISTRY. 2012 Oct;12(12):1230–8.

44. Pharmaprojects | Pharma Intelligence. [cited 2017 Feb 6]; Available from: http://pharmaintelligence.informa.com/en-US/products-and-services/data-and-analysis/pharmaprojects

45. Carlisle B. Numbat by bgcarlisle [Internet]. [cited 2016 Dec 10]. Available from: http://bgcarlisle.github.io/Numbat/

46. Wickham H. ggplot2: Elegant Graphics for Data Analysis. 2nd ed. 2016. Cham: Springer International Publishing : Imprint: Springer; 2016. 1 p. (Use R!).

47. htmlwidgets/lib ABV (vis js library in, http://visjs.org, http://www.almende.com/home), interface) BT (R, Robert T. visNetwork: Network Visualization using 'vis.js' Library [Internet]. 2019 [cited 2021 Feb 24]. Available from: https://CRAN.R-project.org/package=visNetwork

48. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Mental Health. 2019 Nov;22(4):153–60.

49. Hey SP, Heilig CM, Weijer C. Accumulating Evidence and Research Organization (AERO) model: a new tool for representing, analyzing, and planning a translational research program. Trials. 2013 May 30;14(1):159.

50. Mattina J, Carlisle B, Hachem Y, Fergusson D, Kimmelman J. Inefficiencies and Patient Burdens in the Development of the Targeted Cancer Drug Sorafenib: A Systematic Review. Bero L, editor. PLOS Biology. 2017 Feb;15(2):e2000487.

51. Boutron I, Page MJ, Higgins JPT. Chapter 7: Considering bias and conflicts of interest among the included studies. Draft version (15 September 2018) for inclusion. Cochrane Handbook for Systematic Reviews of Interventions London: Cochrane.

52. Andre F, Bachelot T, Campone M, Dalenc F, Perez-Garcia JM, Hurvitz SA, Turner N, Rugo H, Smith JW, Deudon S, Shi M, Zhang Y, Kay A, Porta DG, Yovine A, Baselga J. Targeting FGFR with dovitinib (TKI258): preclinical and clinical data in breast cancer. Clinical Cancer Research. 2013 Jul;19(13):3693–702.

53. Aogi K, Masuda N, Ohno S, Oda T, Iwata H, Kashiwaba M, Fujiwara Y, Kamigaki S, Ito Y, Ueno T, Takashima S. First-line bevacizumab in combination with weekly paclitaxel for metastatic breast cancer: efficacy and safety results from a large, open-label, single-arm Japanese study. Breast Cancer Research & Treatment. 2011 Oct;129(3):829–38.

54. Baar J, Silverman P, Lyons J, Fu P, Abdul-Karim F, Ziats N, Wasman J, Hartman P, Jesberger J, Dumadag L, Hohler E, Leeming R, Shenk R, Chen H, McCrae K, Dowlati A, Remick SC, Overmoyer B. A Vasculature-Targeting Regimen of Preoperative Docetaxel with or without Bevacizumab for Locally Advanced Breast Cancer: Impact on Angiogenic Biomarkers. Clin Cancer Res. 2009 May 15;15(10):3583–90.

55. Bachelot T, Garcia-Saenz JA, Verma S, Gutierrez M, Pivot X, Kozloff MF, Prady C, Huang X, Khosravan R, Wang Z, Cesari R, Tassell V, Kern KA, Blay J-Y, Lluch A. Sunitinib in combination with trastuzumab for the treatment of advanced breast cancer: activity and safety results from a phase II study. BMC Cancer. 2014 Mar;

56. Balduzzi A, Montagna E, Bagnardi V, Torrisi R, Bertolini F, Mancuso P, Scarano E, Viale G, Veronesi P, Cardillo A, Orlando L, Goldhirsch A, Colleoni M. Infusional fluorouracil, epirubicin, and cisplatin followed by weekly paclitaxel plus bevacizumab in locally advanced breast cancer with unfavorable prognostic features. Anti-Cancer Drugs. 2009 Mar;20(3):197–203.

57. Barrios CH, Liu M-C, Lee SC, Vanlemmens L, Ferrero J-M, Tabei T, Pivot X, Iwata H, Aogi K, Lugo-Quintana R, Harbeck N, Brickman MJ, Zhang K, Kern KA, Martin M. Phase III randomized trial of sunitinib versus capecitabine in patients with previously treated HER2-negative advanced breast cancer. Breast Cancer Research & Treatment. 2010 May;121(1):121–31.

58. Baselga J, Segalla JGM, Roche H, Del Giglio A, Pinczowski H, Ciruelos EM, Filho SC, Gomez P, Van Eyll B, Bermejo B, Llombart A, Garicochea B, Duran MAC, Hoff PMG, Espie M, de Moraes AAJG, Ribeiro RA, Mathias C, Gil Gil M, Ojeda B, Morales J, Kwon Ro S, Li S, Costa F. Sorafenib in combination with capecitabine: an oral regimen for patients with HER2-negative locally advanced or metastatic breast cancer. Journal of Clinical Oncology. 2012 May;30(13):1484–91.

59. Basho RK, Gilcrease M, Murthy RK, Helgason T, Karp DD, Meric-Bernstam F, Hess KR, Herbrich SM, Valero V, Albarracin C, Litton JK, Chavez-MacGregor M, Ibrahim NK, Murray JL 3rd, Koenig KB, Hong D, Subbiah V, Kurzrock R, Janku F, Moulder SL. Targeting the PI3K/AKT/mTOR Pathway for the Treatment of Mesenchymal Triple-Negative Breast Cancer: Evidence From a Phase 1 Trial of mTOR Inhibition in Combination With Liposomal Doxorubicin and Bevacizumab. JAMA Oncology. 2016 Nov;

60. Bazzola L, Foroni C, Andreis D, Zanoni V, R Cappelletti M, Allevi G, Aguggini S, Strina C, Milani M, Venturini S, Ferrozzi F, Giardini R, Bertoni R, Turley H, Gatter K, Petronini PG, Fox SB, Harris AL, Martinotti M, Berruti A, Bottini A, Reynolds AR, Generali D. Combination of letrozole, metronomic cyclophosphamide and sorafenib is well-tolerated and shows activity in patients with primary breast cancer. Journal of Cancer. 2015 Jan;112(1):52–60.

61. Bear HD, Tang G, Rastogi P, Geyer CEJ, Robidoux A, Atkins JN, Baez-Diaz L, Brufsky AM, Mehta RS, Fehrenbacher L, Young JA, Senecal FM, Gaur R, Margolese RG, Adams PT, Gross HM, Costantino JP, Swain SM, Mamounas EP, Wolmark N. Bevacizumab added to neoadjuvant chemotherapy for breast cancer. Journal of Medicine. 2012 Jan;366(4):310–20.

62. Bergh J, Mariani G, Cardoso F, Liljegren A, Awada A, Vigano L, Huang X, Verkh L, Kern KA, Giorgetti C, Gianni L. Clinical and pharmacokinetic study of sunitinib and docetaxel in women with advanced breast cancer. Breast. 2012 Aug;21(4):507–13.

63. Bertucci F, Fekih M, Autret A, Petit T, Dalenc F, Levy C, Romieu G, Bonneterre J, Ferrero J-M, Kerbrat P, Soulie P, Mouret-Reynier M-A, Bachelot T, Lerebours F, Eymard J-C, Deblock M, Lortholary A, Hardy-Bessard A-C, Barthelemy P, Bonnefoi H, Charafe-Jauffret E, Bidard F-C, Viens P, Lemonnier J, Pierga J-Y. Bevacizumab plus neoadjuvant chemotherapy in patients with HER2-negative inflammatory breast cancer (BEVERLY-1): a multicentre, single-arm, phase 2 study. The Lancet Oncology. 2016 May;17(5):600–11.

64. Bianchi G, Loibl S, Zamagni C, Salvagni S, Raab G, Siena S, Laferriere N, Peña C, Lathia C, Bergamini L, Gianni L. Phase II multicenter, uncontrolled trial of sorafenib in patients with metastatic breast cancer. Anti-Cancer Drugs. 2009 Aug;20(7):616–24.

65. Bisagni G, Musolino A, Panebianco M, De Matteis A, Nuzzo F, Ardizzoni A, Gori S, Gamucci T, Passalacqua R, Gnoni R, Moretti G, Boni C. The Breast Avastin Trial: phase II study of bevacizumab maintenance therapy after induction chemotherapy with docetaxel and capecitabine for the first-line treatment of patients with locally recurrent or metastatic breast cancer. Cancer Chemotherapy & Pharmacology. 2013 Apr;71(4):1051–7.

66. Boer K, Lang I, Llombart-Cussac A, Andreasson I, Vivanco GL, Sanders N, Pover GM, Murray E. Vandetanib with docetaxel as second-line treatment for advanced breast cancer: a double-blind, placebo-controlled, randomized Phase II study. Investigational New Drugs. 2012 Apr;30(2):681–7.

67. Borson R, Harker G, Reeves J, Beck T, Hager S, Horvath W, Jones M, Tillinghast G, Arrowsmith E, Harrer G, Kudrik FJ, Malamud SC, Bromund J, Zeigler H, Tai DF, Kornberg LJ, Obasaju C, Orlando M, Yardley DA. Phase II study of gemcitabine and bevacizumab as first-line treatment in taxane-pretreated, HER2-negative, locally recurrent or metastatic breast cancer. Clinical Breast Cancer. 2012 Oct;12(5):322–30.

68. Brufsky A, Hoelzer K, Beck T, Whorf R, Keaton M, Nadella P, Krill-Jackson E, Kroener J, Middleman E, Frontiera M, Paul D, Panella T, Bromund J, Zhao L, Orlando M, Tai F, Marciniak MD, Obasaju C, Hainsworth J. A randomized phase II study of paclitaxel and bevacizumab with and without gemcitabine as first-line treatment for metastatic breast cancer. Clinical Breast Cancer. 2011 Aug;11(4):211–20.

69. Brufsky AM, Hurvitz S, Perez E, Swamy R, Valero V, O'Neill V, Rugo HS. RIBBON-2: a randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. Journal of Clinical Oncology. 2011 Nov;29(32):4286–93.

70. Burstein HJ, Elias AD, Rugo HS, Cobleigh MA, Wolff AC, Eisenberg PD, Lehman M, Adams BJ, Bello CL, DePrimo SE, Baum CM, Miller KD. Phase II study of sunitinib malate, an oral multitargeted tyrosine kinase inhibitor, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. Journal of Clinical Oncology. 2008 Apr;26(11):1810–6.

71. Cardoso F, Canon J-L, Amadori D, Aldrighetti D, Machiels J-P, Bouko Y, Verkh L, Usari T, Kern KA, Giorgetti C, Dirix L. An exploratory study of sunitinib in combination with docetaxel and trastuzumab as first-line therapy for HER2-positive metastatic breast cancer. Breast. 2012 Dec;21(6):716–23.

72. Clavarezza M, Turazza M, Aitini E, Saracchini S, Garrone O, Durando A, De Placido S, Bisagni G, Levaggi A, Bighin C, Restuccia E, Scalamogna R, Galli A, Del Mastro L. Phase II open-label study of bevacizumab combined with neoadjuvant anthracycline and taxane therapy for locally advanced breast cancer. Breast. 2013 Aug;22(4):470–5.

73. Clemons MJ, Cochrane B, Pond GR, Califaretti N, Chia SKL, Dent RA, Song X, Robidoux A, Parpia S, Warr D, Rayson D, Pritchard KI, Levine MN. Randomised, phase II, placebo-controlled, trial of fulvestrant plus vandetanib in postmenopausal women with bone only or bone predominant, hormone-receptor-positive metastatic breast cancer (MBC): the OCOG ZAMBONEY study. Breast Cancer Research & Treatment. 2014 Jul;146(1):153–62.

74. Cobleigh MA, Langmuir VK, Sledge GW, Miller KD, Haney L, Novotny WF, Reimann JD, Vassel A. A phase I/II dose-escalation trial of bevacizumab in previously treated metastatic breast cancer. Seminars in Oncology. 2003 Oct;117–24.

75. Coudert B, Pierga J-Y, Mouret-Reynier M-A, Kerrou K, Ferrero J-M, Petit T, Kerbrat P, Dupre P-F, Bachelot T, Gabelle P, Giard S, Coeffic D, Bougnoux P, Prevost J-B, Paintaud G, Thibault G, Hernandez J, Coudert M, Arnould L, Berriolo-Riedinger A. Use of [(18)F]-FDG PET to predict response to neoadjuvant trastuzumab and docetaxel in patients with HER2-positive breast cancer, and addition of bevacizumab to neoadjuvant trastuzumab and docetaxel in [(18)F]-FDG PET-predicted non-responders (AVATAXHER): an open-label, randomised phase 2 trial. Lancet Oncology. 2014 Dec;15(13):1493–502.

76. Cristofanilli M, Johnston SRD, Manikhas A, Gomez HL, Gladkov O, Shao Z, Safina S, Blackwell KL, Alvarez RH, Rubin SD, Ranganathan S, Redhu S, Trudeau ME. A randomized phase II study of lapatinib + pazopanib versus lapatinib in patients with HER2+ inflammatory breast cancer. Breast Cancer Research & Treatment. 2013 Jan;137(2):471–82.

77. Crown JP, Dieras V, Staroslawska E, Yardley DA, Bachelot T, Davidson N, Wildiers H, Fasching PA, Capitain O, Ramos M, Greil R, Cognetti F, Fountzilas G, Blasinska-Morawiec M, Liedtke C, Kreienberg R, Miller WHJ, Tassell V, Huang X, Paolini J, Kern KA, Romieu G. Phase III trial of sunitinib in combination with capecitabine versus

capecitabine monotherapy for the treatment of patients with pretreated metastatic breast cancer. Journal of Clinical Oncology. 2013 Aug;31(23):2870–8.

78. Curigliano G, Bagnardi V, Bertolini F, Alcalay M, Locatelli MA, Fumagalli L, Rabascio C, Calleri A, Adamoli L, Criscitiello C, Viale G, Goldhirsch A. Antiangiogenic therapy in recurrent breast cancer with lymphangitic spread to the chest wall: A randomized phase II trial of bevacizumab with sequential or concurrent oral vinorelbine and capecitabine. Breast. 2015 Jun;24(3):263–71.

79. Curigliano G, Pivot X, Cortes J, Elias A, Cesari R, Khosravan R, Collier M, Huang X, Cataruozolo PE, Kern KA, Goldhirsch A. Randomized phase II study of sunitinib versus standard of care for patients with previously treated advanced triple-negative breast cancer. Breast. 2013 Oct;22(5):650–6.

80. Danso MA, Blum JL, Robert NJ, Krekow L, Rotche R, Smith DA, Richards P, Anderson T, Richards DA, O'Shaughnessy J. Phase II trial of weekly nab-paclitaxel in combination with bevacizumab as first-line treatment in metastatic breast cancer. Journal of Clinical Oncology. 2008 May;

81. De Boer RH, Kotasek D, White S, Koczwara B, Mainwaring P, Chan A, Melara R, Ye Y, Adewoye AH, Sikorski R, Kaufman PA. Phase 1b dose-finding study of motesanib with docetaxel or paclitaxel in patients with metastatic breast cancer. Breast Cancer Research & Treatment. 2012 Aug;135(1):241–52.

82. Dellapasqua S, Bertolini F, Bagnardi V, Campagnoli E, Scarano E, Torrisi R, Shaked Y, Mancuso P, Goldhirsch A, Rocca A, Pietri E, Colleoni M. Metronomic cyclophosphamide and capecitabine combined with bevacizumab in advanced breast cancer. Journal of Clinical Oncology. 2008 Oct;26(30):4899–905.

83. Dickler MN, Barry WT, Cirrincione CT, Ellis MJ, Moynahan ME, Innocenti F, Hurria A, Rugo HS, Lake DE, Hahn O, Schneider BP, Tripathy D, Carey LA, Winer EP, Hudis CA. Phase III Trial Evaluating Letrozole As First-Line Endocrine Therapy With or Without Bevacizumab for the Treatment of Postmenopausal Women With Hormone Receptor-Positive Advanced-Stage Breast Cancer: CALGB 40503 (Alliance). Journal of Clinical Oncology. 2016 Aug;34(22):2602–9.

84. Dickler MN, Rugo HS, Eberle CA, Brogi E, Caravelli JF, Panageas KS, Boyd J, Yeh B, Lake DE, Dang CT, Gilewski TA, Bromberg JF, Seidman AD, D'Andrea GM, Moasser MM, Melisko M, Park JW, Dancey J, Norton L, Hudis CA. A Phase II Trial of Erlotinib in Combination with Bevacizumab in Patients with Metastatic Breast Cancer. Clin Cancer Res. 2008 Dec 1;14(23):7878–83.

85. Dieras V, Campone M, Yardley DA, Romieu G, Valero V, Isakoff SJ, Koeppen H, Wilson TR, Xiao Y, Shames DS, Mocci S, Chen M, Schmid P. Randomized, phase II, placebo-controlled trial of onartuzumab and/or bevacizumab in combination with weekly paclitaxel in patients with metastatic triple-negative breast cancer. Annals of Oncology. 2015 Sep;26(9):1904–10.

86. Dieras V, Wildiers H, Jassem J, Dirix LY, Guastalla J-P, Bono P, Hurvitz SA, Goncalves A, Romieu G, Limentani SA, Jerusalem G, Lakshmaiah KC, Roche H, Sanchez-Rovira P, Pienkowski T, Segui Palmer MA, Li A, Sun Y-N, Pickett CA, Slamon DJ. Trebananib (AMG 386) plus weekly paclitaxel with or without bevacizumab as first-line therapy for

HER2-negative locally recurrent or metastatic breast cancer: A phase 2 randomized study. Breast. 2015 Jun;24(3):182–90.

87. Drooger JC, van Tinteren H, de Groot SM, Ten Tije AJ, de Graaf H, Portielje JEA, Jager A, Honkoop A, Linn SC, Kroep JR, Erdkamp FLG, Hamberg P, Imholz ALT, van Rossum-Schornagel QC, Heijns JB, van Leeuwen-Stok AE, Sleijfer S. A randomized phase 2 study exploring the role of bevacizumab and a chemotherapy-free approach in HER2-positive metastatic breast cancer: The HAT study (BOOG 2008-2003), a Dutch Breast Cancer Research Group trial. Cancer. 2016 Oct;122(19):2961–70.

88. Earl HM, Hiller L, Dunn JA, Blenkinsop C, Grybowicz L, Vallier A-L, Abraham J, Thomas J, Provenzano E, Hughes-Davies L, Gounaris I, McAdam K, Chan S, Ahmad R, Hickish T, Houston S, Rea D, Bartlett J, Caldas C, Cameron DA, Hayward L, Investigators Art. Efficacy of neoadjuvant bevacizumab added to docetaxel followed by fluorouracil, epirubicin, and cyclophosphamide, for women with HER2-negative early breast cancer (ARTemis): an open-label, randomised, phase 3 trial. Lancet Oncology. 2015 Jun;16(6):656–66.

89. El-Nahas T, Kader Y, Spielmann, Sakr A, Metwally. Comparative study analyzing survival and safety of bevacizumab/carboplatin/paclitaxel versus carboplatin/docetaxel in initial treatment of metastatic Her-2-negative breast cancer. BCTT. 2013 Jun;37.

90. Falchook GS, Moulder SL, Wheler JJ, Jiang Y, Bastida CC, Kurzrock R. Dual HER2 inhibition in combination with anti-VEGF treatment is active in heavily pretreated HER2-positive breast cancer. Annals of Oncology. 2013 Dec;24(12):3004–11.

91. Ferrero J-M, Hardy-Bessard A-C, Capitain O, Lortholary A, Salles B, Follana P, Herve R, Deblock M, Dauba J, Atlassi M, Largillier R. Weekly paclitaxel, capecitabine, and bevacizumab with maintenance capecitabine and bevacizumab as first-line therapy for triple-negative, metastatic, or locally advanced breast cancer: Results from the GINECO A-TaXel phase 2 study: First-Line Bevacizumab-Based Therapy for TNBC. Cancer. 2016 Oct 15;122(20):3119–26.

92. Forero-Torres A, Saleh MN, Galleshaw JA, Jones CF, Shah JJ, Percent IJ, Nabell LM, Carpenter JT, Falkson CI, Krontiras H, Urist MM, Bland KI, De Los Santos JF, Meredith RF, Caterinicchia V, Bernreuter WK, O'Malley JP, Li Y, LoBuglio AF. Pilot trial of preoperative (neoadjuvant) letrozole in combination with bevacizumab in postmenopausal women with newly diagnosed estrogen receptor- or progesterone receptor-positive breast cancer. Clinical Breast Cancer. 2010 Aug;10(4):275–80.

93. Gajria D, Feigin K, Tan LK, Patil S, Geneus S, Theodoulou M, Norton L, Hudis CA, Traina TA. Phase 2 trial of a novel capecitabine dosing schedule in combination with bevacizumab for patients with metastatic breast cancer. Cancer. 2011 Sep;117(18):4125–31.

94. Garcia-Saenz JA, Martin M, Calles A, Bueno C, Rodriguez L, Bobokova J, Custodio A, Casado A, Diaz-Rubio E. Bevacizumab in combination with metronomic chemotherapy in patients with anthracycline- and taxane-refractory breast cancer. Journal of Chemotherapy. 2008 Oct;20(5):632–9.

95. Gianni L, Romieu GH, Lichinitser M, Serrano SV, Mansutti M, Pivot X, Mariani P, Andre F, Chan A, Lipatov O, Chan S, Wardley A, Greil R, Moore N, Prot S, Pallaud C,

Semiglazov V. AVEREL: a randomized phase III Trial evaluating bevacizumab in combination with docetaxel and trastuzumab as first-line therapy for HER2-positive locally recurrent/metastatic breast cancer. Journal of Clinical Oncology. 2013 May;31(14):1719–25.

96. Gligorov J, Doval D, Bines J, Alba E, Cortes P, Pierga J-Y, Gupta V, Costa R, Srock S, de Ducla S, Freudensprung U, Mustacchi G. Maintenance capecitabine and bevacizumab versus bevacizumab alone after initial first-line bevacizumab and docetaxel for patients with HER2-negative metastatic breast cancer (IMELDA): a randomised, open-label, phase 3 trial. Lancet Oncology. 2014 Nov;15(12):1351–60.

97. Gradishar WJ, Kaklamani V, Sahoo TP, Lokanatha D, Raina V, Bondarde S, Jain M, Ro SK, Lokker NA, Schwartzberg L. A double-blind, randomised, placebo-controlled, phase 2b study evaluating sorafenib in combination with paclitaxel as a first-line therapy in patients with HER2-negative advanced breast cancer. Journal of Cancer. 2013 Jan;49(2):312–22.

98. Greil R, Moik M, Reitsamer R, Ressler S, Stoll M, Namberger K, Menzel C, Mlineritsch B. Neoadjuvant bevacizumab, docetaxel and capecitabine combination therapy for HER2/neu-negative invasive breast cancer: Efficacy and safety in a phase II pilot study. Journal of Surgical Oncology. 2009 Oct;35(10):1048–54.

99. Guarneri V, Dieci MV, Bisagni G, Boni C, Cagossi K, Puglisi F, Pecchi A, Piacentini F, Conte P. Preoperative carboplatin-paclitaxel-bevacizumab in triple-negative breast cancer: final results of the phase II Ca.Pa.Be study. Annals of Surgical Oncology. 2015 Sep;22(9):2881–7.

100. Hamilton E, Kimmick G, Hopkins J, Marcom PK, Rocha G, Welch R, Broadwater G, Blackwell K. Nab-paclitaxel/bevacizumab/carboplatin chemotherapy in first-line triple negative metastatic breast cancer. Clinical Breast Cancer. 2013 Dec;13(6):416–20.

101. Hu X, Cao J, Hu W, Wu C, Pan Y, Cai L, Tong Z, Wang S, Li J, Wang Z, Wang B, Chen X, Yu H. Multicenter phase II study of apatinib in non-triple-negative metastatic breast cancer. BMC Cancer. 2014 Nov;

102. Hu X, Zhang J, Xu B, Jiang Z, Ragaz J, Tong Z, Zhang Q, Wang X, Feng J, Pang D, Fan M, Li J, Wang B, Wang Z, Zhang Q, Sun S, Liao C. Multicenter phase II study of apatinib, a novel VEGFR inhibitor in heavily pretreated patients with metastatic triple-negative breast cancer. Journal of Cancer. 2014 Oct;135(8):1961–9.

103. Hurvitz SA, Allen HJ, Moroose RL, Chan D, Hagenstad C, Applebaum SH, Patel G, Hu EH, Ryba N, Lin L-S, Wang H, Glaspy J, Slamon DJ, Kabbinavar F. A Phase II Trial of Docetaxel With Bevacizumab as First-line Therapy for HER2-Negative Metastatic Breast Cancer (TORI B01). Clinical Breast Cancer. 2010 Aug;10(4):307–12.

104. Hyams DM, Chan A, de Oliveira C, Snyder R, Vinholes J, Audeh MW, Alencar VM, Lombard J, Mookerjee B, Xu J, Brown K, Klein P. Cediranib in combination with fulvestrant in hormone-sensitive metastatic breast cancer: a randomized Phase II study. Investigational New Drugs. 2013 Oct;31(5):1345–54.

105. Isaacs C, Herbolsheimer P, Liu MC, Wilkinson M, Ottaviano Y, Chung GG, Warren R, Eng-Wong J, Cohen P, Smith KL, Creswell K, Novielli A, Slack R. Phase I/II study of sorafenib with anastrozole in patients with hormone receptor positive aromatase inhibitor

resistant metastatic breast cancer. Breast Cancer Research & Treatment. 2011 Jan;125(1):137–43.

106. Johnston SRD, Gomez H, Stemmer SM, Richie M, Durante M, Pandite L, Goodman V, Slamon D. A randomized and open-label trial evaluating the addition of pazopanib to lapatinib as first-line therapy in patients with HER2-positive advanced breast cancer. Breast Cancer Research & Treatment. 2013 Feb;137(3):755–66.

107. Kim HR, Jung KH, Im S-A, Im Y-H, Kang SY, Park KH, Lee S, Kim S-B, Lee K-H, Ahn JS, Kim SI, Sohn JH. Multicentre phase II trial of bevacizumab combined with docetaxel-carboplatin for the neoadjuvant treatment of triple-negative breast cancer (KCSG BR-0905). Annals of Oncology. 2013 Jun;24(6):1485–90.

108. Kim S-B, Yoo C, Ro J, Im S-A, Im Y-H, Kim JH, Ahn J-H, Jung KH, Song HS, Kang SY, Park HS, Chung H-C. Combination of docetaxel and TSU-68, an oral antiangiogenic agent, in patients with metastatic breast cancer previously treated with anthracycline: randomized phase II multicenter trial. Investigational New Drugs. 2014 Aug;32(4):753–61.

109. Kontopodis E, Kentepozidis N, Christophyllakis C, Boukovinas I, Kalykaki A, Kalbakis K, Vamvakas L, Agelaki S, Kotsakis A, Vardakis N, Georgoulias V, Mavroudis D. Docetaxel, gemcitabine and bevacizumab as salvage chemotherapy for HER-2-negative metastatic breast cancer. Cancer Chemotherapy & Pharmacology. 2015 Jan;75(1):153–60.

110. Kountourakis P, Doufexis D, Maliou S, Karagiannis A, Kardara E, Margari C, Sykoutri D, Tzovaras A, Ardavanis A. Bevacizumab combined with two-weekly paclitaxel as first-line therapy for metastatic breast cancer. Anticancer Research. 2010 Jul;30(7):2969–71.

111. Kozloff M, Chuang E, Starr A, Gowland PA, Cataruozolo PE, Collier M, Verkh L, Huang X, Kern KA, Miller K. An exploratory study of sunitinib plus paclitaxel as first-line treatment for patients with advanced breast cancer. Annals of Oncology. 2010 Jul;21(7):1436–41.

112. Lam SW, de Groot SM, Honkoop AH, Jager A, ten Tije AJ, Bos MMEM, Linn SC, van den Bosch J, Kroep JR, Braun JJ, van Tinteren H, Boven E, Group DBCR. Paclitaxel and bevacizumab with or without capecitabine as first-line treatment for HER2-negative locally recurrent or metastatic breast cancer: a multicentre, open-label, randomised phase 2 trial. Journal of Cancer. 2014 Dec;50(18):3077–88.

113. Li T, Wang B, Wang Z, Ragaz J, Zhang J, Sun S, Cao J, Lv F, Wang L, Zhang S, Ni C, Wu Z, Xie J, Hu X. Bevacizumab in Combination with Modified FOLFOX6 in Heavily Pretreated Patients with HER2/Neu-Negative Metastatic Breast Cancer: A Phase II Clinical Trial. PLoS ONE [Electronic Resource]. 2015;10(7).

114. Lin NU, Seah DS, Gelman R, Desantis S, Mayer EL, Isakoff S, Dipiro P, Krop IE, Come SE, Weckstein D, Winer EP, Burstein HJ. A phase II study of bevacizumab in combination with vinorelbine and trastuzumab in HER2-positive metastatic breast cancer. Breast Cancer Research & Treatment. 2013 Jun;139(2):403–10.

115. Lobo C, Lopes G, Baez O, Castrellon A, Ferrell A, Higgins C, Hurley E, Hurley J, Reis I, Richman S, Seo P, Silva O, Slingerland J, Tukia K, Welsh C, Gluck S. Final results of

a phase II study of nab-paclitaxel, bevacizumab, and gemcitabine as first-line therapy for patients with HER2-negative metastatic breast cancer. Breast Cancer Research & Treatment. 2010 Sep;123(2):427–35.

116. Loibl S, Rokitta D, Conrad B, Harbeck N, Wullner M, Warm M, Schwedler K, Gerber B, Schrader I, Eidtmann H, Mehta K, Fuhr U, von Minckwitz G. Sorafenib in the Treatment of Early Breast Cancer: Results of the Neoadjuvant Phase II Study - SOFIA. Breast Care. 2014 Jul;9(3):169–74.

117. Lu Y-S, Chen TW-W, Lin C-H, Yeh D-C, Tseng L-M, Wu P-F, Rau K-M, Chen B-B, Chao T-C, Huang S-M, Huang C-S, Shih TT-F, Cheng A-L, Consortium TBC. Bevacizumab preconditioning followed by Etoposide and Cisplatin is highly effective in treating brain metastases of breast cancer progressing from whole-brain radiotherapy. Clinical Cancer Research. 2015 Apr;21(8):1851–8.

118. Luck H-J, Lubbe K, Reinisch M, Maass N, Feisel-Schwickardi G, Tome O, Janni W, Aydogdu M, Neunhoffer T, Ober A, Aktas B, Park-Simon T-W, Schumacher C, Hoffkes H-G, Illmer T, Wagner H, Mehta K, von Minckwitz G, Nekljudova V, Loibl S. Phase III study on efficacy of taxanes plus bevacizumab with or without capecitabine as first-line chemotherapy in metastatic breast cancer. Breast Cancer Research & Treatment. 2015 Jan;149(1):141–9.

119. Luu T, Frankel P, Chung C, Chow W, Mortimer J, Hurria A, Somlo G. Phase I/II trial of vinorelbine and sorafenib in metastatic breast cancer. Clinical Breast Cancer. 2014 Apr;14(2):94–100.

120. Mackey JR, Ramos-Vazquez M, Lipatov O, McCarthy N, Krasnozhon D, Semiglazov V, Manikhas A, Gelmon KA, Konecny GE, Webster M, Hegg R, Verma S, Gorbunova V, Abi Gerges D, Thireau F, Fung H, Simms L, Buyse M, Ibrahim A, Martin M. Primary Results of ROSE/TRIO-12, a Randomized Placebo-Controlled Phase III Trial Evaluating the Addition of Ramucirumab to First-Line Docetaxel Chemotherapy in Metastatic Breast Cancer. JCO. 2015 Jan 10;33(2):141–8.

121. Makhoul I, Klimberg VS, Korourian S, Henry-Tillman RS, Siegel ER, Westbrook KC, Hutchins LF. Combined neoadjuvant chemotherapy with bevacizumab improves pathologic complete response in patients with hormone receptor negative operable or locally advanced breast cancer. Journal of Clinical Oncology. 2015 Feb;38(1):74–9.

122. Martin M, Loibl S, von Minckwitz G, Morales S, Martinez N, Guerrero A, Anton A, Aktas B, Schoenegg W, Munoz M, Garcia-Saenz JA, Gil M, Ramos M, Margeli M, Carrasco E, Liedtke C, Wachsmann G, Mehta K, De la Haba-Rodriguez JR. Phase III trial evaluating the addition of bevacizumab to endocrine therapy as first-line treatment for advanced breast cancer: the letrozole/fulvestrant and avastin (LEA) study. Journal of Clinical Oncology. 2015 Mar;33(9):1045–52.

123. Martin M, Makhson A, Gligorov J, Lichinitser M, Lluch A, Semiglazov V, Scotto N, Mitchell L, Tjulandin S. Phase II study of bevacizumab in combination with trastuzumab and capecitabine as first-line treatment for HER-2-positive locally recurrent or metastatic breast cancer. Oncologist. 2012;17(4):469–75.

124. Martin M, Roche H, Pinter T, Crown J, Kennedy MJ, Provencher L, Priou F, Eiermann W, Adrover E, Lang I, Ramos M, Latreille J, Jagiello-Gruszfeld A, Pienkowski T, Alba

E, Snyder R, Almel S, Rolski J, Munoz M, Moroose R, Hurvitz S, Banos A, Adewoye H, Hei Y-J, Lindsay M-A, Rupin M, Cabaribere D, Lemmerick Y, Mackey JR, investigators T 010. Motesanib, or open-label bevacizumab, in combination with paclitaxel, as first-line treatment for HER2-negative locally recurrent or metastatic breast cancer: a phase 2, randomised, double-blind, placebo-controlled study.[Erratum appears in Lancet Oncol. 2011 Aug;12(8):722]. Lancet Oncology. 2011 Apr;12(4):369–76.

125. Massarweh S, Moss J, Wang C, Romond E, Slone S, Weiss H, Karabakhtsian RG, Napier D, Black EP. Impact of adding the multikinase inhibitor sorafenib to endocrine therapy in metastatic estrogen receptor-positive breast cancer. Future Oncology. 2014 Dec;10(15):2435–48.

126. Mayer EL, Dhakil S, Patel T, Sundaram S, Fabian C, Kozloff M, Qamar R, Volterra F, Parmar H, Samant M, Burstein HJ. SABRE-B: an evaluation of paclitaxel and bevacizumab with or without sunitinib as first-line treatment of metastatic breast cancer. Annals of Oncology. 2010 Dec;21(12):2370–6.

127. Mayer EL, Isakoff SJ, Klement G, Downing SR, Chen WY, Hannagan K, Gelman R, Winer EP, Burstein HJ. Combination antiangiogenic therapy in advanced breast cancer: a phase 1 trial of vandetanib, a VEGFR inhibitor, and metronomic chemotherapy, with correlative platelet proteomics. Breast Cancer Research & Treatment. 2012 Nov;136(1):169–78.

128. Mayer EL, Scheulen ME, Beckman J, Richly H, Duarte A, Cotreau MM, Strahs AL, Agarwal S, Steelman L, Winer EP, Dickler MN. A Phase I dose-escalation study of the VEGFR inhibitor tivozanib hydrochloride with weekly paclitaxel in metastatic breast cancer. Breast Cancer Research & Treatment. 2013 Jul;140(2):331–9.

129. Miles D, Cameron D, Bondarenko I, Manzyuk L, Alcedo JC, Lopez RI, Im S-A, Canon J-L, Shparyk Y, Yardley DA, Masuda N, Ro J, Denduluri N, Hubeaux S, Quah C, Bais C, O'Shaughnessy J. Bevacizumab plus paclitaxel versus placebo plus paclitaxel as first-line therapy for HER2-negative metastatic breast cancer (MERiDiAN): A double-blind placebo-controlled randomised phase III trial with prospective biomarker evaluation. Journal of Cancer. 2017 Jan;146–55.

130. Miles DW, Chan A, Dirix LY, Cortes J, Pivot X, Tomczak P, Delozier T, Sohn JH, Provencher L, Puglisi F, Harbeck N, Steger GG, Schneeweiss A, Wardley AM, Chlistalla A, Romieu G. Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. Journal of Clinical Oncology. 2010 Jul;28(20):3239–47.

131. Miller KD, Chap LI, Holmes FA, Cobleigh MA, Marcom PK, Fehrenbacher L, Dickler M, Overmoyer BA, Reimann JD, Sing AP, Langmuir V, Rugo HS. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. Journal of Clinical Oncology. 2005 Feb;23(4):792–9.

132. Miller KD, Trigo JM, Wheeler C, Barge A, Rowbottom J, Sledge G, Baselga J. A Multicenter Phase II Trial of ZD6474, a Vascular Endothelial Growth Factor Receptor-2 and Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor, in Patients with

Previously Treated Metastatic Breast Cancer. Clin Cancer Res. 2005 May 1;11(9):3369–76.

133. Mina LA, Yu M, Johnson C, Burkhardt C, Miller KD, Zon R. A phase II study of combined VEGF inhibitor (bevacizumab+sorafenib) in patients with metastatic breast cancer: Hoosier Oncology Group Study BRE06-109. Investigational New Drugs. 2013 Oct;31(5):1307–10.

134. Montagna E, Cancello G, Bagnardi V, Pastrello D, Dellapasqua S, Perri G, Viale G, Veronesi P, Luini A, Intra M, Calleri A, Rampinelli C, Goldhirsch A, Bertolini F, Colleoni M. Metronomic chemotherapy combined with bevacizumab and erlotinib in patients with metastatic HER2-negative breast cancer: clinical and biological activity. Clinical Breast Cancer. 2012 Jun;12(3):207–14.

135. Moreno-Aspitia A, Morton RF, Hillman DW, Lingle WL, Rowland KMJ, Wiesenfeld M, Flynn PJ, Fitch TR, Perez EA. Phase II trial of sorafenib in patients with metastatic breast cancer previously exposed to anthracyclines or taxanes: North Central Cancer Treatment Group and Mayo Clinic Trial N0336. Journal of Clinical Oncology. 2009 Jan;27(1):11–5.

136. Morrow PK, Murthy RK, Ensor JD, Gordon GS, Margolin KA, Elias AD, Urba WJ, Weng DE, Rugo HS, Hortobagyi GN. An open-label, phase 2 trial of RPI.4610 (Angiozyme) in the treatment of metastatic breast cancer. Cancer. 2012 Sep;118(17):4098–104.

137. Mrozek E, Layman R, Ramaswamy B, Lustberg M, Vecchione A, Knopp MV, Shapiro CL. Phase II trial of neoadjuvant weekly nanoparticle albumin-bound paclitaxel, carboplatin, and biweekly bevacizumab therapy in women with clinical stage II or III HER2-negative breast cancer. Clinical Breast Cancer. 2014 Aug;14(4):228–34.

138. Nahleh ZA, Barlow WE, Hayes DF, Schott AF, Gralow JR, Sikov WM, Perez EA, Chennuru S, Mirshahidi HR, Corso SW, Lew DL, Pusztai L, Livingston RB, Hortobagyi GN. SWOG S0800 (NCI CDR0000636131): addition of bevacizumab to neoadjuvant nab-paclitaxel with dose-dense doxorubicin and cyclophosphamide improves pathologic complete response (pCR) rates in inflammatory or locally advanced breast cancer. Breast Cancer Research & Treatment. 2016 Aug;158(3):485–95.

139. Niravath P, Tham YL, Wang T, Rodriguez A, Foreman C, Hilsenbeck SG, Elledge R, Rimawi M. A phase II trial of capecitabine concomitantly with whole-brain radiotherapy followed by capecitabine and sunitinib for brain metastases from breast cancer. Oncologist. 2015 Jan;20(1).

140. Overmoyer B, Fu P, Hoppel C, Radivoyevitch T, Shenk R, Persons M, Silverman P, Robertson K, Ziats NP, Wasman JK, Abdul-Karim FW, Jesberger JA, Duerk J, Hartman P, Hanks S, Lewin J, Dowlati A, McCrae K, Ivy P, Remick SC. Inflammatory Breast Cancer as a Model Disease to Study Tumor Angiogenesis: Results of a Phase IB Trial of Combination SU5416 and Doxorubicin. Clin Cancer Res. 2007 Oct 1;13(19):5862–8.

141. Perez EA, Hillman DW, Dentchev T, Le-Lindqwister NA, Geeraerts LH, Fitch TR, Liu H, Graham DL, Kahanic SP, Gross HM, Patel TA, Palmieri FM, Dueck AC. North Central Cancer Treatment Group (NCCTG) N0432: phase II trial of docetaxel with

capecitabine and bevacizumab as first-line chemotherapy for patients with metastatic breast cancer. Annals of Oncology. 2010 Feb;21(2):269–74.

142. Pierga J-Y, Petit T, Delozier T, Ferrero J-M, Campone M, Gligorov J, Lerebours F, Roche H, Bachelot T, Charafe-Jauffret E, Pavlyuk M, Kraemer S, Bidard F-C, Viens P. Neoadjuvant bevacizumab, trastuzumab, and chemotherapy for primary inflammatory HER2-positive breast cancer (BEVERLY-2): an open-label, single-arm phase 2 study. Lancet Oncology. 2012 Apr;13(4):375–84.

143. Polyzos A, Kalbakis K, Kentepozidis N, Giassas S, Kalykaki A, Vardakis N, Bozionelou V, Saloustros E, Kontopodis E, Georgoulias V, Mavroudis D. Salvage treatment in metastatic breast cancer with weekly paclitaxel and bevacizumab. Cancer Chemother Pharmacol. 2011 Jul;68(1):217–23.

144. Quintela-Fandino M, Urruticoechea A, Guerra J, Gil M, Gonzalez-Martin A, Marquez R, Hernandez-Agudo E, Rodriguez-Martin C, Gil-Martin M, Bratos R, Escudero MJ, Vlassak S, Hilberg F, Colomer R. Phase I clinical trial of nintedanib plus paclitaxel in early HER-2-negative breast cancer (CNIO-BR-01-2010/GEICAM-2010-10 study). Journal of Cancer. 2014 Sep;111(6):1060–4.

145. Quintela-Fandino M, Lluch A, Manso L, Calvo I, Cortes J, Garcia-Saenz JA, Gil-Gil M, Martinez-Janez N, Gonzalez-Martin A, Adrover E, de Andres R, Vinas G, Llombart-Cussac A, Alba E, Guerra J, Bermejo B, Zamora E, Moreno-Anton F, Pernas Simon S, Carrato A, Lopez-Alonso A, Escudero MJ, Campo R, Carrasco E, Palacios J, Mulero F, Colomer R. 18F-fluoromisonidazole PET and Activity of Neoadjuvant Nintedanib in Early HER2-Negative Breast Cancer: A Window-of-Opportunity Randomized Trial. Clinical Cancer Research. 2016 Sep;

146. Ramaswamy B, Fiskus W, Cohen B, Pellegrino C, Hershman DL, Chuang E, Luu T, Somlo G, Goetz M, Swaby R, Shapiro CL, Stearns V, Christos P, Espinoza-Delgado I, Bhalla K, Sparano JA. Phase I-II study of vorinostat plus paclitaxel and bevacizumab in metastatic breast cancer: evidence for vorinostat-induced tubulin acetylation and Hsp90 inhibition in vivo. Breast Cancer Research & Treatment. 2012 Apr;132(3):1063–72.

147. Ramaswamy B, Elias AD, Kelbick NT, Dodley A, Morrow M, Hauger M, Allen J, Rhoades C, Kendra K, Chen HX, Eckhardt SG, Shapiro CL. Phase II trial of bevacizumab in combination with weekly docetaxel in metastatic breast cancer patients. Clinical Cancer Research. 2006 May;12(10):3124–9.

148. Rastogi P, Buyse ME, Swain SM, Jacobs SA, Robidoux A, Liepman MK, Pajon ER, Dy PA, Posada JG, Melnik MK, Piette F, Geyer CE, Mamounas EP, Wolmark N. Concurrent Bevacizumab with a Sequential Regimen of Doxorubicin and Cyclophosphamide Followed by Docetaxel and Capecitabine as Neoadjuvant Therapy for HER2− Locally Advanced Breast Cancer: A Phase II Trial of the NSABP Foundation Research Group. Clinical Breast Cancer. 2011 Aug;11(4):228–34.

149. Rayson D, Lupichuk S, Potvin K, Dent S, Shenkier T, Dhesy-Thind S, Ellard SL, Prady C, Salim M, Farmer P, Allo G, Tsao M-S, Allan A, Ludkovski O, Bonomi M, Tu D, Hagerman L, Goodwin R, Eisenhauer E, Bradbury P. Canadian Cancer Trials Group IND197: a phase II study of foretinib in patients with estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2-negative recurrent or metastatic breast cancer. Breast Cancer Res Treat. 2016 May;157(1):109–16.

150. Robert NJ, Dieras V, Glaspy J, Brufsky AM, Bondarenko I, Lipatov ON, Perez EA, Yardley DA, Chan SYT, Zhou X, Phan S-C, O'Shaughnessy J. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. Journal of Clinical Oncology. 2011 Apr;29(10):1252–60.

151. Rochlitz C, Ruhstaller T, Lerch S, Spirig C, Huober J, Suter T, Buhlmann M, Fehr M, Schonenberger A, von Moos R, Winterhalder R, Rauch D, Muller A, Mannhart-Harms M, Herrmann R, Cliffe B, Mayer M, Zaman K, (sakk) SG for CCR. Combination of bevacizumab and 2-weekly pegylated liposomal doxorubicin as first-line therapy for locally recurrent or metastatic breast cancer. A multicenter, single-arm phase II trial (SAKK 24/06). Annals of Oncology. 2011 Jan;22(1):80–5.

152. Rochlitz C, Bigler M, von Moos R, Bernhard J, Matter-Walstra K, Wicki A, Zaman K, Anchisi S, Kung M, Na K-J, Bartschi D, Borner M, Rordorf T, Rauch D, Muller A, Ruhstaller T, Vetter M, Trojan A, Hasler-Strub U, Cathomas R, Winterhalder R, (sakk) SG for CCR. SAKK 24/09: safety and tolerability of bevacizumab plus paclitaxel vs. bevacizumab plus metronomic cyclophosphamide and capecitabine as first-line therapy in patients with HER2-negative advanced stage breast cancer - a multicenter, randomized phase III trial. BMC Cancer. 2016 Oct;16(1).

153. Rugo HS, Barry WT, Moreno-Aspitia A, Lyss AP, Cirrincione C, Leung E, Mayer EL, Naughton M, Toppmeyer D, Carey LA, Perez EA, Hudis C, Winer EP. Randomized Phase III Trial of Paclitaxel Once Per Week Compared With Nanoparticle Albumin-Bound Nab-Paclitaxel Once Per Week or Ixabepilone With Bevacizumab As First-Line Chemotherapy for Locally Recurrent or Metastatic Breast Cancer: CALGB 40502/NCCTG N063H (Alliance). Journal of Clinical Oncology. 2015 Jul;33(21):2361–9.

154. Rugo HS, Campone M, Amadori D, Aldrighetti D, Conte P, Wardley A, Villanueva C, Melisko M, McHenry MB, Liu D, Lee F, Pivot X. A randomized, phase II, three-arm study of two schedules of ixabepilone or paclitaxel plus bevacizumab as first-line therapy for metastatic breast cancer. Breast Cancer Research & Treatment. 2013 Jun;139(2):411–9.

155. Rugo HS, Chien AJ, Franco SX, Stopeck AT, Glencer A, Lahiri S, Arbushites MC, Scott J, Park JW, Hudis C, Nulsen B, Dickler MN. A phase II study of lapatinib and bevacizumab as treatment for HER2-overexpressing metastatic breast cancer. Breast Cancer Research & Treatment. 2012 Jul;134(1):13–20.

156. Rugo HS, Stopeck AT, Joy AA, Chan S, Verma S, Lluch A, Liau KF, Kim S, Bycott P, Rosbrook B, Bair AH, Soulieres D. Randomized, placebo-controlled, double-blind, phase II study of axitinib plus docetaxel versus docetaxel plus placebo in patients with metastatic breast cancer. Journal of Clinical Oncology. 2011 Jun;29(18):2459–65.

157. Saloustros E, Kalbakis K, Vardakis N, Kalykaki A, Milaki G, Rovithi M, Agelaki S, Saridaki Z, Georgoulias V, Mavroudis D. Metronomic vinorelbine plus bevacizumab as salvage therapy for patients with metastatic breast cancer. Journal of B. 2011 Jun;16(2):215–8.

158. Salvador J, Manso L, de la Haba J, Jaen A, Ciruelos E, de Villena MC, Gil M, Murias A, Galan A, Jara C, Bayo J, Baena JM, Casal J, Mel JR, Blancas I, Sanchez Rvira P. Final results of a phase II study of paclitaxel, bevacizumab, and gemcitabine as first-line therapy for patients with HER2-negative metastatic breast cancer. Clinical & Translational Oncology: Official Publication of the Federation of Spanish Oncology Societes & of the National Cancer Institute of Mexico. 2015 Feb;17(2):160–6.

159. Sánchez-Rovira P, Seguí MA, Llombart A, Aranda E, Antón A, Sánchez A, Lomas M, Jaén A, Fernández M, Porras I, Dalmau E, Morales S, de la Haba-Rodríguez J. Bevacizumab plus preoperative chemotherapy in operable HER2 negative breast cancer: biomarkers and pathologic response. Clin Transl Oncol. 2013 Oct;15(10):810–7.

160. Schwartzberg LS, Badarinath S, Keaton MR, Childs BH. Phase II multicenter study of docetaxel and bevacizumab with or without trastuzumab as first-line treatment for patients with metastatic breast cancer. Clinical Breast Cancer. 2014 Jun;14(3):161–8.

161. Schwartzberg LS, Tauer KW, Hermann RC, Makari-Judson G, Isaacs C, Beck JT, Kaklamani V, Stepanski EJ, Rugo HS, Wang W, Bell-McGuinn K, Kirshner JJ, Eisenberg P, Emanuelson R, Keaton M, Levine E, Medgyesy DC, Qamar R, Starr A, Ro SK, Lokker NA, Hudis CA. Sorafenib or placebo with either gemcitabine or capecitabine in patients with HER-2-negative advanced breast cancer that progressed during or after bevacizumab. Clinical Cancer Research. 2013 May;19(10):2745–54.

162. Seidman AD, Conlin AK, Bach A, Moynahan ME, Lake D, Forero A, Wright GS, Hackney MH, Clawson A, Norton L, Hudis CA. Randomized Phase II Trial of Weekly vs. Every 2 Weeks vs. Every 3 Weeks Nanoparticle Albumin-Bound Paclitaxel With Bevacizumab as First-Line Chemotherapy for Metastatic Breast Cancer. Clinical Breast Cancer. 2013 Aug;13(4):239-246.e1.

163. Sideras K, Dueck AC, Hobday TJ, Rowland KMJ, Allred JB, Northfelt DW, Lingle WL, Behrens RJ, Fitch TR, Nikcevich DA, Perez EA. North central cancer treatment group (NCCTG) N0537: phase II trial of VEGF-trap in patients with metastatic breast cancer previously treated with an anthracycline and/or a taxane. Clinical Breast Cancer. 2012 Dec;12(6):387–91.

164. Sikov WM, Berry DA, Perou CM, Singh B, Cirrincione CT, Tolaney SM, Kuzma CS, Pluard TJ, Somlo G, Port ER, Golshan M, Bellon JR, Collyar D, Hahn OM, Carey LA, Hudis CA, Winer EP. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). Journal of Clinical Oncology. 2015 Jan;33(1):13–21.

165. Smith JW, Buyse ME, Rastogi P, Geyer CE, Jacobs SA, Patocskai EJ, Robidoux A, Conlin AK, Ansari B, Keogh GP, Stella PJ, Gross HM, Lord RS, Polikoff JA, Mauquoi C, Mamounas EP, Swain SM, Wolmark N. Epirubicin With Cyclophosphamide Followed by Docetaxel With Trastuzumab and Bevacizumab as Neoadjuvant Therapy for HER2-Positive Locally Advanced Breast Cancer or as Adjuvant Therapy for HER2-Positive Pathologic Stage III Breast Cancer: A Phase II Trial of the NSABP Foundation Research Group, FB-5. Clinical Breast Cancer. 2017 Feb;17(1):48-54.e3.

166. Spigel DR, Hainsworth JD, Burris HA 3rd, Molthrop DC, Peacock N, Kommor M, Vazquez ER, Greco FA, Yardley DA. A pilot study of adjuvant doxorubicin and cyclophosphamide followed by paclitaxel and sorafenib in women with node-positive or high-risk early-stage breast cancer. Clinical Advances in Hematology & Oncology. 2011 Apr;9(4):280–6.

167. Suzuki Y, Saeki T, Aogi K, Toi M, Fujii H, Inoue K, Watanabe T, Fujiwara Y, Ito Y, Takatsuka Y, Iwata H, Arioka H, Tokuda Y. A multicenter phase II study of TSU-68, a novel oral multiple tyrosine kinase inhibitor, in patients with metastatic breast cancer progressing despite prior treatment with an anthracycline-containing regimen and taxane. Journal of Clinical Oncology. 2013 Aug;18(4):590–7.

168. Tai C-J, Chen C-S, Hung C-S, Kuo L-J, Wei P-L, Chiou J-F, Hsu C-H, Chiou H-Y, Wu C-H. Bevacizumab plus docetaxel and cisplatin for metastatic breast cancer: a pilot phase II study. Anticancer Research. 2012 Dec;32(12):5501–6.

169. Tan AR, Johannes H, Rastogi P, Jacobs SA, Robidoux A, Flynn PJ, Thirlwell MP, Fehrenbacher L, Stella PJ, Goel R, Julian TB, Provencher L, Bury MJ, Bhatt K, Geyer CEJ, Swain SM, Mamounas EP, Wolmark N. Weekly paclitaxel and concurrent pazopanib following doxorubicin and cyclophosphamide as neoadjuvant therapy for HER-negative locally advanced breast cancer: NSABP Foundation FB-6, a phase II study. Breast Cancer Research & Treatment. 2015 Jan;149(1):163–9.

170. Tan WW, Dueck AC, Flynn P, Steen P, Anderson D, Rowland K, Northfelt D, Perez EA. N0539 phase II trial of fulvestrant and bevacizumab in patients with metastatic breast cancer previously treated with an aromatase inhibitor: a North Central Cancer Treatment Group (now Alliance) trial. Annals of Oncology. 2013 Oct;24(10):2548–54.

171. Taylor SK, Chia S, Dent S, Clemons M, Agulnik M, Grenci P, Wang L, Oza AM, Ivy P, Pritchard KI, Leighl NB. A phase II study of pazopanib in patients with recurrent or metastatic invasive breast carcinoma: a trial of the Princess Margaret Hospital phase II consortium. Oncologist. 2010;15(8):810–8.

172. Tiainen L, Tanner M, Lahdenpera O, Vihinen P, Jukkola A, Karihtala P, Paunu N, Huttunen T, Kellokumpu-Lehtinen P-L. Bevacizumab Combined with Docetaxel or Paclitaxel as First-line Treatment of HER2-negative Metastatic Breast Cancer. Anticancer Research. 2016;36(12):6431–8.

173. Toi M, Saeki T, Iwata H, Inoue K, Tokuda Y, Sato Y, Ito Y, Aogi K, Takatsuka Y, Arioka H. A multicenter phase II study of TSU-68, an oral multiple tyrosine kinase inhibitor, in combination with docetaxel in metastatic breast cancer patients with anthracycline resistance. Breast Cancer. 2014 Jan;21(1):20–7.

174. Tolaney SM, Boucher Y, Duda DG, Martin JD, Seano G, Ancukiewicz M, Barry WT, Goel S, Lahdenrata J, Isakoff SJ, Yeh ED, Jain SR, Golshan M, Brock J, Snuderl M, Winer EP, Krop IE, Jain RK. Role of vascular density and normalization in response to neoadjuvant bevacizumab and chemotherapy in breast cancer patients. Proceedings of the National Academy of Sciences of the United States of America. 2015 Nov;112(46):14325–30.

175. Tolaney SM, Nechushtan H, Ron I-G, Schoffski P, Awada A, Yasenchak CA, Laird AD, O'Keeffe B, Shapiro GI, Winer EP. Cabozantinib for metastatic breast carcinoma: results

of a phase II placebo-controlled randomized discontinuation study. Breast Cancer Research & Treatment. 2016 Nov;160(2):305–12.

176. Traina TA, Rugo HS, Caravelli JF, Patil S, Yeh B, Melisko ME, Park JW, Geneus S, Paulson M, Grothusen J, Seidman AD, Fornier M, Lake D, Dang C, Robson M, Theodoulou M, Flombaum CD, Norton L, Hudis CA, Dickler MN. Feasibility trial of letrozole in combination with bevacizumab in patients with metastatic breast cancer. Journal of Clinical Oncology. 2010 Feb;28(4):628–33.

177. Tredan O, Follana P, Moullet I, Cropet C, Trager-Maury S, Dauba J, Lavau-Denes S, Dieras V, Beal-Ardisson D, Gouttebel M, Orfeuvre H, Stefani L, Jouannaud C, Burki F, Petit T, Guardiola E, Becuwe C, Blot E, Pujade-Lauraine E, Bachelot T. A phase III trial of exemestane plus bevacizumab maintenance therapy in patients with metastatic breast cancer after first-line taxane and bevacizumab: a GINECO group study. Annals of Oncology. 2016 Jun;27(6):1020–9.

178. Tryfonidis K, Boukovinas I, Xenidis N, Christophyllakis C, Papakotoulas P, Politaki E, Malamos N, Polyzos A, Kakolyris S, Georgoulias V, Mavroudis D, Group HOR. A multicenter phase I-II study of docetaxel plus epirubicin plus bevacizumab as first-line treatment in women with HER2-negative metastatic breast cancer. Breast. 2013 Dec;22(6):1171–7.

179. von Minckwitz G, Eidtmann H, Rezai M, Fasching PA, Tesch H, Eggemann H, Schrader I, Kittel K, Hanusch C, Kreienberg R, Solbach C, Gerber B, Jackisch C, Kunz G, Blohmer J-U, Huober J, Hauschild M, Fehm T, Müller BM, Denkert C, Loibl S, Nekljudova V, Untch M. Neoadjuvant Chemotherapy and Bevacizumab for HER2-Negative Breast Cancer. N Engl J Med. 2012 Jan 26;366(4):299–309.

180. von Minckwitz G, Puglisi F, Cortes J, Vrdoljak E, Marschner N, Zielinski C, Villanueva C, Romieu G, Lang I, Ciruelos E, De Laurentiis M, Veyret C, de Ducla S, Freudensprung U, Srock S, Gligorov J. Bevacizumab plus chemotherapy versus chemotherapy alone as second-line treatment for patients with HER2-negative locally recurrent or metastatic breast cancer after first-line treatment with bevacizumab plus chemotherapy (TANIA): an open-label, randomised phase 3 trial. Lancet Oncology. 2014 Oct;15(11):1269–78.

181. Wedam SB, Low JA, Yang SX, Chow CK, Choyke P, Danforth D, Hewitt SM, Berman A, Steinberg SM, Liewehr DJ, Plehn J, Doshi A, Thomasson D, McCarthy N, Koeppen H, Sherman M, Zujewski J, Camphausen K, Chen H, Swain SM. Antiangiogenic and antitumor effects of bevacizumab in patients with inflammatory and locally advanced breast cancer. Journal of Clinical Oncology. 2006 Feb;24(5):769–77.

182. Wildiers H, Fontaine C, Vuylsteke P, Martens M, Canon JL, Wynendaele W, Focan C, De Greve J, Squifflet P, Paridaens R. Multicenter phase II randomized trial evaluating antiangiogenic therapy with sunitinib as consolidation after objective response to taxane chemotherapy in women with HER2-negative metastatic breast cancer. Breast Cancer Research & Treatment. 2010 Sep;123(2):463–9.

183. Wong ALA, Sundar R, Wang T-T, Ng T-C, Zhang B, Tan S-H, Soh TIP, Pang ASL, Tan C-S, Ow SGW, Wang L, Mogro J, Ho J, Jeyasekharan AD, Huang Y, Thng C-H, Chan C-W, Hartman M, Iau P, Buhari SA, Goh B-C, Lee S-C. Phase Ib/II randomized, open-label study of doxorubicin and cyclophosphamide with or without low-dose, short-course

sunitinib in the pre-operative treatment of breast cancer. Oncotarget. 2016 Sep;7(39):64089–99.

184. Wu P-F, Lin C-H, Kuo C-H, Chen W-W, Yeh D-C, Liao H-W, Huang S-M, Cheng A-L, Lu Y-S. A pilot study of bevacizumab combined with etoposide and cisplatin in breast cancer patients with leptomeningeal carcinomatosis. BMC Cancer. 2015 Apr;

185. Yardley DA, Bosserman LD, O'Shaughnessy JA, Harwin WN, Morgan SK, Priego VM, Peacock NW, Bass JD, Burris HA 3rd, Hainsworth JD. Paclitaxel, bevacizumab, and everolimus/placebo as first-line treatment for patients with metastatic HER2-negative breast cancer: a randomized placebo-controlled phase II trial of the Sarah Cannon Research Institute. Breast Cancer Research & Treatment. 2015 Nov;154(1):89–97.

186. Yardley DA, Burris HA, Clark BL, Shipley D, Rubin M, Barton J, Arrowsmith E, Hainsworth JD. Hormonal Therapy Plus Bevacizumab in Postmenopausal Patients Who Have Hormone Receptor–Positive Metastatic Breast Cancer: A Phase II Trial of the Sarah Cannon Oncology Research Consortium. Clinical Breast Cancer. 2011 Jun;11(3):146–52.

187. Yardley DA, Dees EC, Myers SD, Li S, Healey P, Wang Z, Brickman MJ, Paolini J, Kern KA, Citrin DL. Phase II open-label study of sunitinib in patients with advanced breast cancer. Breast Cancer Research & Treatment. 2012 Dec;136(3):759–67.

188. Yardley DA, Dickson N, Drosick D, Earwood C, Inhorn R, Murphy P, Hainsworth JD. Sorafenib Plus Ixabepilone as First-Line Treatment of Metastatic HER2-Negative Breast Cancer: A Sarah Cannon Research Institute Phase I/II Trial. Clinical Breast Cancer. 2016 Jun;16(3):180–7.

189. Yardley DA, Raefsky E, Castillo R, Lahiry A, Locicero R, Thompson D, Shastry M, Burris HA 3rd, Hainsworth JD. Phase II study of neoadjuvant weekly nab-paclitaxel and carboplatin, with bevacizumab and trastuzumab, as treatment for women with locally advanced HER2+ breast cancer. Clinical Breast Cancer. 2011 Oct;11(5):297–305.

190. Yardley DA, Reeves J, Dees EC, Osborne C, Paul D, Ademuyiwa F, Soliman H, Guthrie T, Andersen J, Krekow L, Choksi J, Daniel B, Danso M, Favret A, Oommen S, Brufsky A, Bromund JL, Lin Y, Ibrahim AB, Richards PD. Ramucirumab With Eribulin Versus Eribulin in Locally Recurrent or Metastatic Breast Cancer Previously Treated With Anthracycline and Taxane Therapy: A Multicenter, Randomized, Phase II Study. Clinical Breast Cancer. 2016 Dec;16(6):471–9.

191. Yardley DA, Shipley DL, Peacock NW, Shastry M, Midha R, Priego VM, Hainsworth JD. Phase I/II trial of neoadjuvant sunitinib administered with weekly paclitaxel/carboplatin in patients with locally advanced triple-negative breast cancer. Breast Cancer Research & Treatment. 2015 Aug;152(3):557–67.

192. Zhao M, Pan X, Layman R, Lustberg MB, Mrozek E, Macrae ER, Wesolowski R, Carothers S, Puhalla S, Shapiro CL, Ramaswamy B. A Phase II study of bevacizumab in combination with trastuzumab and docetaxel in HER2 positive metastatic breast cancer. Investigational New Drugs. 2014 Dec;32(6):1285–94.

193. Zielinski C, Lang I, Inbar M, Kahan Z, Greil R, Beslija S, Stemmer SM, Zvirbule Z, Steger GG, Melichar B, Pienkowski T, Sirbu D, Petruzelka L, Eniu A, Nisenbaum B, Dank M, Anghel R, Messinger D, Brodowicz T, investigators T. Bevacizumab plus

paclitaxel versus bevacizumab plus capecitabine as first-line treatment for HER2-negative metastatic breast cancer (TURANDOT): primary endpoint results of a randomised, open-label, non-inferiority, phase 3 trial. Lancet Oncology. 2016 Sep;17(9):1230–9.

194. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009 Jul 21;6(7):e1000097.

195. Sawin VI, Robinson KA. Biased and inadequate citation of prior research in reports of cardiovascular trials is a continuing source of waste in research. Journal of Clinical Epidemiology. 2016 Jan;69:174–8.

196. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R, Johnson DH. Paclitaxel–Carboplatin Alone or with Bevacizumab for Non–Small-Cell Lung Cancer. N Engl J Med. 2006 Dec 14;355(24):2542–50.

197. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, Kabbinavar F. Bevacizumab plus Irinotecan, Fluorouracil, and Leucovorin for Metastatic Colorectal Cancer. N Engl J Med. 2004 Jun 3;350(23):2335–42.

198. Mauguen A, Pignon J-P, Burdett S, Domerg C, Fisher D, Paulus R, Mandrekar SJ, Belani CP, Shepherd FA, Eisen T, Pang H, Collette L, Sause WT, Dahlberg SE, Crawford J, O'Brien M, Schild SE, Parmar M, Tierney JF, Pechoux CL, Michiels S. Surrogate endpoints for overall survival in chemotherapy and radiotherapy trials in operable and locally advanced lung cancer: a re-analysis of meta-analyses of individual patients' data. The Lancet Oncology. 2013 Jun;14(7):619–26.

199. Paoletti X, Oba K, Bang Y-J, Bleiberg H, Boku N, Bouché O, Catalano P, Fuse N, Michiels S, Moehler M, Morita S, Ohashi Y, Ohtsu A, Roth A, Rougier P, Sakamoto J, Sargent D, Sasako M, Shitara K, Thuss-Patience P, Van Cutsem E, Burzykowski T, Buyse M. Progression-Free Survival as a Surrogate for Overall Survival in Advanced/Recurrent Gastric Cancer Trials: A Meta-Analysis. JNCI: Journal of the National Cancer Institute. 2013 Nov 6;105(21):1667–70.

200. Haslam A, Hey SP, Gill J, Prasad V. A systematic review of trial-level meta-analyses measuring the strength of association between surrogate end-points and overall survival in oncology. European Journal of Cancer. 2019 Jan;106:196–211.

201. Seretny M, Currie GL, Sena ES, Ramnarine S, Grant R, MacLeod MR, Colvin LA, Fallon M. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. Pain. 2014 Dec;155(12):2461–70.

202. Ai L, Xu Z, Yang B, He Q, Luo P. Sorafenib-associated hand-foot skin reaction: practical advice on diagnosis, mechanism, prevention, and management. Expert Review of Clinical Pharmacology. 2019 Dec 2;12(12):1121–7.

203. Boutron I. Reporting and Interpretation of Randomized Controlled Trials With Statistically Nonsignificant Results for Primary Outcomes. JAMA. 2010 May 26;303(20):2058.

204. Shepardizing. In: The Free Dictionary [Internet]. [cited 2021 Mar 3]. Available from: https://legal-dictionary.thefreedictionary.com/Shepardizing

205. Nicholson JM. Smart(er) Citations. Matter. 2021 Mar 3;4(3):756–8.

206. Nicholson JM, Uppala A, Sieber M, Grabitz P, Mordaunt M, Rife SC. Measuring the quality of scientific references in Wikipedia: an analysis of more than 115M citations to over 800 000 scientific articles. FEBS J. 2020 Nov 19;febs.15608.

207. Onodera N, Yoshikane F. Factors affecting citation rates of research articles: Factors Affecting Citation Rates of Research Articles. J Assn Inf Sci Tec. 2015 Apr;66(4):739–64.

208. Greenberg SA. Understanding belief using citation networks: Citation networks. Journal of Evaluation in Clinical Practice. 2011 Apr;17(2):389–93.

209. Clinicaltrials.gov filtered search [Internet]. [cited 2021 Apr 6]. Available from: https://clinicaltrials.gov/ct2/results?cond=breast+cancer&intr=Bevacizumab+OR+Sunitinib+OR+Sorafenib+OR+Pazopanib+OR+Vandetanib+OR+Orantinib+OR+Apatinib+OR+Nintedanib+OR+Motesanib+OR+Ramucirumab+OR+Aflibercept+OR+Angiozyme+OR+Cabozantinib+OR+Dovitinib+OR+Foretinib+OR+Axitinib+OR+Cediranib+OR+Semaxinib&recrs=a&recrs=f&age_v=&gndr=&type=Intr&rslt=&phase=4&phase=0&phase=1&phase=2&phase=5&Search=Apply

Appendices

Appendix 1 Search strategies in *Embase* and *Medline*

Clinical Search Strategy **Embase**

Database: Embase <1980 to present>

1. exp "randomized controlled trial"/
2. exp "randomized controlled trial (topic)"/
3. exp "controlled clinical trial"/
4. exp "controlled clinical trial (topic)"/
5. exp randomization/
6. double blind procedure/
7. exp placebo/
8. "controlled clinical trial".tw.
9. (random* or RCT$1 or placebo*).tw.
10. ((singl* or doubl* or trebl* or tripl*) and (mask* or blind* or dumm*)).tw.
11. or/1-10
12. exp clinical trial/
13. "clinical trial".tw.
14. (volunteer or volunteers or open label* or nonrandom* or non random* or quasirandom* or quasi-random*).tw.
15. (longitudinal or prospective).tw.
16. ((follow-up or followup) adj stud*).tw.
17. ((multicenter adj stud*) or (multi-center adj stud*) or (multicentr* adj stud*) or (multicentr* adj stud*)).tw.
18. ((comparative adj study) or (comparative adj studies)).tw.
19. "head-to-head".tw.
20. or/12-19
21. 11 or 20
22. (editorial or letter or note).pt.
23. 21 not 22
24. exp Animal/ not (exp Animal/ and Human/)
25. 23 not 24
26. exp “breast tumor”/
27. exp “breast cancer”/
28. 26 or 27
29. 28 and 25_

Clinical Search Strategy **MEDLINE**

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

1. (controlled clinical trial or randomized controlled trial).pt.
2. exp randomized controlled trials as topic/ or exp controlled clinical trials as topic/ or exp random allocation/ or exp double-blind method/ or exp single-blind method/ or exp placebos/

3. "controlled clinical trial".tw.
4. (random* or RCT$1 or placebo*).tw.
5. ((singl* or doubl* or trebl* or tripl*) and (mask* or blind* or dumm*)).tw.
6. or/1-5
7. clinical trial.pt.
8. (clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
9. exp Clinical Trial/
10. exp Clinical Trials as Topic/
11. "clinical trial".tw.
12. (volunteer or volunteers or open label* or nonrandom* or non random* or quasirandom* or quasi-random*).tw.
13. exp Longitudinal Studies/ or exp Prospective Studies/ or exp Follow-Up Studies/
14. (longitudinal or prospective).tw.
15. ((follow-up or followup) adj stud*).tw.
16. Multicenter Study.pt.
17. exp Multicenter Study/ or exp Multicenter Studies as Topic/
18. ((multicenter adj stud*) or (multi-center adj stud*) or (multicentr* adj stud*) or (multicentr* adj stud*)).tw.
19. Comparative Study.pt.
20. ((comparative adj study) or (comparative adj studies)).tw.
21. "head-to-head".tw.
22. exp Pilot Projects/ or exp Feasibility Studies/
23. or/7-22
24. 6 or 23
25. (comment or editorial or guideline or practice guideline or interview or letter).pt.
26. 24 not 25
27. exp Animals/ not (exp Animals/ and Humans/)
28. 26 not 27
29. breast neoplasms/ or carcinoma, ductal, breast/ or "hereditary breast and ovarian cancer syndrome"/
30. breast/ or mammary glands, human/ or nipples/ or Breast Diseases/
31. Neoplasms/ or Adenocarcinoma/ or Carcinoma/
32. 30 and 31
33. (brca or (breast adj4 (adenocarcinoma* or cancer* or carcinoma* or metasta* or neoplasm* or tumo?r))).ti,ab,kw.
34. 29 or 32 or 33
35. 34 and 28

Appendix 2: Codebook

Basic Info and dates

Should this study be excluded?
Variable type: Categorical (single selection only)
Database column name: `exclude`
Extractors were prompted to select one of the following mutually exclusive options.

Displayed option name	Database value
yes	1
no	0

What are the VEGF inhibitors tested?

Variable type: Categorical (multiple selection allowed)
Database column prefix: `drug`
Extractors were prompted to select one or more of the following options.

Displayed option name	Database value
Sunitinib	Sunitinib
Sorafenib	Sorafenib
Bevacizumab	Bevacizumab
Aflibercept	Aflibercept
Axitinib	Axitinib
Cabozantinib	Cabozantinib
Cediranib	Cediranib
Motesanib	Motesanib
Nintedanib	Nintedanib
Orantinib	Orantinib
Pazopanib	Pazopanib
Ramucirumab	Ramucirumab
Semaxinib	Semaxinib
Tivozanib	Tivozanib
Vandetanib	Vandetanib
Angiozyme	Angiozyme
Foretenib	Foretenib
Apatinib	Apatinib
Dovitinib	Dovitinib

Extractor prompt:

```
multiple possible
```

Was Bevacizumab standard or intervention?

Variable type: Categorical (single selection only)
Database column name: `standard`
Extractors were prompted to select one of the following mutually exclusive options.

Displayed option name	Database value
standard	1
intervention	0

Combination or Monotherapy

Variable type: Categorical (single selection only)
Database column name: `combo_mono`
Extractors were prompted to select one of the following mutually exclusive options.

Displayed option name	Database value
Monotherapy	mono
Combination therapy	combo

With what other drugs was the VEGF inhibitor combined?

Variable type: Open text field
Database column name: `open_text_2`

Publication date

Variable type: Date
Database column name: `pub_date`
Extractors were prompted to enter a date.

Start of enrollment

Variable type: Date
Database column name: `enr_date`
Extractors were prompted to enter a date.

Study closure (data cut off)

Variable type: Date
Database column name: `data_cut_off`
Extractors were prompted to enter a date.

End of patient enrolment

Variable type: Date
Database column name: `end_of_enrollment`
Extractors were prompted to enter a date.

Study Identifiers

Variable type: Open text field
Database column name: `identifier`
Extractor prompt:
`whatever unique identifiers you can find (NCT number, or initialism (eg IRIS or ENESTnd)`

If surgery is involved, is it adjuvant or neoadjuvant?

Variable type: Categorical (single selection only)

Database column name: `surgery`
Extractors were prompted to select one of the following mutually exclusive options.

Displayed option name	Database value
neoadjuvant	neoadjuvant
adjuvant	adjuvant
no surgery	no_surg

What is the disease status?
Variable type: Categorical (single selection only)
Database column name: `disease_status`
Extractors were prompted to select one of the following mutually exclusive options.

Displayed option name	Database value
not metastatic	not_metastatic
metastatic	metastatic
mixed	mixed

What is the line of treatment?

Variable type: Categorical (single selection only)
Database column name: `line`
Extractors were prompted to select one of the following mutually exclusive options.

Displayed option name	Database value
first line	first_line
not first line	not_first_line

Does the study characterise the tumor further?

Variable type: Open text field
Database column name: `tumorcha`
Extractor prompt:

```
Write as following:
HER positive: "HER+"
HER negative: "HER-"
ER positive: "ER+"
ER negative: "ER-"
Triple negative :"TN"
Hormone Receptor positive: "HoR+"
Hormone Receptor negative:"HoR-"
if multiple, separate by comma
```

Total N

Variable type: Open text field
Database column name: `total_N`

What is the Phase of the trial?

Variable type: Categorical (single selection only)
Database column name: `phase`
Extractors were prompted to select one of the following mutually exclusive options.

Displayed option name	Database value
Phase 1	phase1
Phase 1/2	phase12

Displayed option name	Database value
Phase 2	phase2
Phase 2/3	phase23
Phase 3	phase3

Extractor prompt:

```
If the phase number is not explicitly stated:
Phase 1: healthy volunteers OR patients lacking target disorder, OR dose escalation where safety, dosage, OR PK are primary endpoints. Typically < 50 patients.
Phase 2: in patients with target disorder, AND primary endpoint not specified OR primary endpoint is specified, and it is a surrogate (i.e. tumor response), ... other pieces of evidence: call for large randomized trials
Phase 3: "confirmatory," "pivotal", OR randomized trial enrolling > 200 patients where primary endpoint is clearly specified, and it is a clinical endpoint. Typically uses 1 or perhaps 2 dose arms.
```

Single or Multicenter study?

Variable type: Categorical (single selection only)
Database column name: `center`
Extractors were prompted to select one of the following mutually exclusive options.

Displayed option name	Database value
Single center	single
Multi center	multi
not stated	NA

Funding source

Variable type: Categorical (single selection only)
Database column name: `funding`
Extractors were prompted to select one of the following mutually exclusive options.

Displayed option name	Database value
Industry only	industry
some industry	some_industry
not stated	NA

Efficacy and Safety Info

Efficacy Endpoint table

Table data
Extractors were prompted to add rows to a table of open text fields with the following column headings.

Displayed column name	Database column name
Outcome	outcome
Arm	arm
Treated Mean Value	value
Denominator	denom
Stats	stats
Primary or secondary (enter 1 or 2)	primary_secondary

Extractor prompt:

```
Always write the name of the drug, not just "Tx."
```

Denominator for ORR or PFS-6 months or the like, where the value is a proportion, enter the number of patients who responded and the number of patients evaluable in Value and Denominator respectively.

For median PFS/TTP/OS, leave this field blank.
We only record:
1: primary outcome
2: ORR (no CI) defined as Partial Response plus Complete Response
3: PFS (only median)
4: TTP
5: HR (with CI and p-value)

Safety data

Table data
Extractors were prompted to add rows to a table of open text fields with the following column headings.

Displayed column name	Database column name
Arm	arm
Grade 3-4 SAE	grade_34
Grade 5 SAE	grade_5
Denominator	denom

What is the most common Grade 3-4 Adverse Event?

Variable type: Text area
Database column name: most_common_SAE

Primary endpoint

Variable type: Open text field
Database column name: endpoint
Extractor prompt:
What was the primary endpoint of the study?

Was the primary endpoint met?

Variable type: Categorical (single selection only)
Database column name: pos_endpoint
Extractors were prompted to select one of the following mutually exclusive options.

Displayed option name	Database value
Yes	1
No	0

Toxicity described as…

Variable type: Categorical (single selection only)
Database column name: toxicity
Extractors were prompted to select one of the following mutually exclusive options.

Displayed option name	Database value
Acceptable	acceptable
Unacceptable	unacceptable
not stated	not stated

Displayed option name	Database value

Recruitment failure?

Variable type: Categorical (single selection only)
Database column name: `accrual`
Extractors were prompted to select one of the following mutually exclusive options.

Displayed option name	Database value
Yes	1
No	0

AERO node colour

Variable type: Categorical (single selection only)
Database column name: `AERO_colour`
Extractors were prompted to select one of the following mutually exclusive options.

Displayed option name	Database value
red	red
yellow	yellow
green	green
white	white

Extractor prompt:
`This is the "all things considered, final answer" colour that should be assigned to this trial on the AERO diagram.`

`For a trial with a single arm, choose red if the primary endpoint is negative. If the primary endpoint is positive, but the toxicity is unacceptable, choose red. If the primary endpoint is positive and the toxicity is acceptable, choose green. If the primary endpoint falls between the prespecified numbers for a positive and negative response and the toxicity is acceptable, choose yellow. If the primary endpoint is only non-efficacy (safety or PK only), choose white.`

Discussion

Citations

Citation selector
Extractors were prompted to enter citation data.
Extractors were prompted to code each extraction for the following properties.

Displayed prompt	Database column
Is a study with the same VEGF inhibitor cited? (Y/N)	same_drug
Is the Citation in the Introduction, Discussion or both (I/D/B)	Intro_disc
Abstract (Y, if not leave empty)	abstract
Non primary publication citation? (subgroup, biomarker?) (Y, if not leave empty)	non_primary
Citation in another indication	other_ind
	property_2

Extractor prompt:
`Each citation of another clinical trial investigating VEGF inhibitoron in breast cancer.`

Begin by typing an author's name or part of the title of the citation. When you have found the citation you're looking for, click "Add citation" and this will attach it to this extraction. If you can't find the citation in the list of suggestions that appears, choose "Add a new reference" from the panel at the left. Also record Abstracts!

Do authors suggest further clinical testing of the drug?

Variable type: Categorical (single selection only)
Database column name: `further_testing`
Extractors were prompted to select one of the following mutually exclusive options.

Displayed option name	Database value
further testing recommended	yes
no mention of further testing	no

What further testing was recommended?

Variable type: Text area
Database column name: `recommendation`

If there was anything strange about this extraction, please note it here

Variable type: Text area
Database column name: `comments`

Eidesstattliche Versicherung

„Ich, Peter Grabitz, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: *„The persistence and burden of failing drug development paradigms: An exploratory analysis of VEGF Inhibition in breast cancer.“ / „Beharrlichkeit und Bürde fehlgeschlagener Paradigmen in der Arzneimittelentwicklung: Eine explorative Analyse der VEGF-Inhibition bei Brustkrebs“* selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

[Für den Fall, dass Sie die Forschung für Ihre Promotion ganz oder teilweise in Gruppenarbeit durchgeführt haben:] Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer

unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum Unterschrift

Anteilserklärung an etwaigen erfolgten Publikationen

keine

Curriculum Vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Prior publications

Journal Articles

1. Weissgerber T, Riedel N, Kilicoglu H, Labbé C, Eckmann P, ter Riet G, Byrne J, Cabanac G, Capes-Davis A, Favier B, Saladi S, **Grabitz P**, Bannach-Brown A, Schulz R, McCann S, Bernard R, Bandrowski A. Automated screening of COVID-19 preprints: can we help authors to improve transparency and reproducibility? Nat Med. Januar 2021;27(1):6–7.

2. **Grabitz P**, Brückner T, Strech D. Deutsche Universitäten machen Ergebnisse klinischer Arzneimittelstudien unzureichend öffentlich – Das sollte sich ändern. Bundesgesundheitsbl. Dezember 2020;63(12):1531–7.

3. Nicholson JM, Uppala A, Sieber M, **Grabitz P**, Mordaunt M, Rife SC. Measuring the quality of scientific references in Wikipedia: an analysis of more than 115M citations to over 800 000 scientific articles. FEBS J. 19. November 2020;febs.15608.

4. **Grabitz P**, Friedmann Z, Gepp S, Hess L, Specht L, Struck M, Tragert SK, Walther T, Klemperer D. Quantity and quality of conflict of interest policies at German medical schools: a cross-sectional study and survey. BMJ Open. September 2020;10(9):e039782.

5. Karduck L, Behnke AL, Baier A, Gotham D, **Grabitz P**, Lennartz N, Speer L, Tinnemann P, Bruchhausen W. Global health research and education at medical faculties in Germany. Grundy Q, Herausgeber. PLoS ONE. 20. April 2020;15(4):e0231302.

6. Strech D, Weissgerber T, Dirnagl U, on behalf of **QUEST Group**. Improving the trustworthiness, usefulness, and ethics of biomedical research through an innovative and comprehensive institutional initiative. PLoS Biol. 11. Februar 2020;18(2):e3000576.

Preprints and Conference Abstracts

1. Salholz-Hillel M, **Grabitz P**, Pugh-Jones M, Strech D, DeVito NJ. Results Availability and Timeliness of Registered COVID-19 Clinical Trials: A Cross-Sectional Study [Internet]. Medical Ethics; 2021 Apr [zitiert 12. April 2021]. Verfügbar unter: http://medrxiv.org/lookup/doi/10.1101/2021.04.07.21255071

2. Nicholson JM, Mordaunt M, Lopez P, Uppala A, Rosati D, Rodrigues NP, **Grabitz P**, Rife S. scite: a smart citation index that displays the context of citations and classifies their intent using deep learning [Internet]. Scientific Communication and Education; 2021 März [zitiert 17. März 2021]. Verfügbar unter: http://biorxiv.org/lookup/doi/10.1101/2021.03.15.435418

3. Nicholson JM, Uppala A, Sieber M, **Grabitz P**, Mordaunt M, Rife S. Measuring the quality of scientific references in Wikipedia: an analysis of more than 115M citations to over 800,000 scientific articles [Internet]. Scientific Communication and Education; 2020 Apr [zitiert 23. Januar 2021]. Verfügbar unter: http://biorxiv.org/lookup/doi/10.1101/2020.04.08.031765

4. Keestra S, Gepp S, **Grabitz P**, Lee YN, Bruckner T. 51 Enhancing clinical trial transparency at UK's top research universities – from generating evidence to improving practice. In: 3 Minute Quick Fire [Internet]. BMJ Publishing Group Ltd; 2019 [zitiert 23. Januar 2021]. S. A31.1-A31. Verfügbar unter: https://ebm.bmj.com/lookup/doi/10.1136/bmjebm-2019-EBMLive.59

5. **Grabitz P**, Friedmann Z, Gepp S, Hess LU, Specht L, Struck M, Tragert S, Walther T, Klemperer D. Conflict of Interest Policies at German medical schools - A long way to go [Internet]. Scientific Communication and Education; 2019 Okt [zitiert 23. Januar 2021]. Verfügbar unter: http://biorxiv.org/lookup/doi/10.1101/809723

6. **Grabitz P**, Lazebnik Y, Nicholson J, Rife S. Science with no fiction: measuring the veracity of scientific reports by citation analysis [Internet]. Scientific Communication and Education; 2017 Aug [zitiert 23. Januar 2021]. Verfügbar unter: http://biorxiv.org/lookup/doi/10.1101/172940

Acknowledgements

I would like to thank Ulrich Dirnagl and Jonathan Kimmelman for their inspiring supervision of this project. Further, I would like to express my gratitude to Gaelle LeMoine and Sean Zhang, who double extracted most of the information provided in this thesis.

I would also like to thank Benjamin Gregory Carlisle for introducing me to R programming and sharing code that became the backbone for some analyses presented here. Finally, I would like to acknowledge Carole Federico, Esther Viniarov, Micheal Pratte, Adam Feustel, Daniel Benjamin and the rest of the STREAM team that I had the honour to meet when working on this project. Without their support, this piece of research would have been impossible.