UNIVERSIDADE ESTADUAL DE CAMPINAS
FACULDADE DE CIÊNCIAS FARMACÊUTICAS

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BIOSIMILAR MONOCLONAL ANTIBODIES FOR CANCER TREATMENT: A SYSTEMATIC REVIEW

ANTICORPOS MONOCLONAIS BIOSSIMILARES PARA O TRATAMENTO DO CÂNCER: REVISÃO SISTEMÁTICA

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ANTICORPOS MONOCLONAIS BIOSSIMILARES PARA O TRATAMENTO DO CÂNCER: REVISÃO SISTEMÁTICA

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Orientadora: Profª Drª Taís Freire Galvão

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RESUMO

Introdução: As despesas médicas com tratamento do câncer estão aumentando em todo o mundo e o uso de biossimilares pode ser uma opção para reduzir custos. No entanto, indivíduos com câncer e profissionais de saúde expressam preocupação com as diferenças entre os biossimilares e seus originadores, e o possível impacto na eficácia e segurança. A evidência de ensaios clínicos comparando o uso de anticorpos monoclonais biossimilares com o uso de produtos originadores no tratamento do câncer não é clara.

Objetivos: Trata-se de uma revisão sistemática em colaboração com a Cochrane com objetivo de avaliar a eficácia e segurança de anticorpos monoclonais biossimilares atualmente disponíveis para o tratamento do câncer (bevacizumabe, rituximabe, trastuzumabe), quando comparados ao seu originador biológico.

Busca na literatura: CENTRAL, Embase; MEDLINE (via PubMed); Web of Science, ClinicalTrial.gov, ICTRP e anais de congressos de oncologia foram pesquisadas até 20 de dezembro de 2021.

Critérios de seleção: Foram incluídos ensaios clínicos randomizados (ECR) que compararam o medicamento biossimilar e o originador, e reportaram qualquer resultado de eficácia ou segurança. Os participantes elegíveis foram adultos previamente diagnosticados com câncer de qualquer tipo e estágio.

Coleta de dados e análises: Usamos procedimentos metodológicos preconizados no *Cochrane handbook for systematic reviews of interventions*. Foram considerados desfechos primários: sobrevida global, livre de progressão e livre de eventos, mortalidade. Os seguintes desfechos foram considerados secundários: taxa de resposta objetiva, duração da resposta, resposta patológica completa, eventos adversos, imunogenicidade e qualidade de vida. Utilizamos a versão 1 da *Cochrane risk-of-bias* para ensaios randomizados e o modelo de efeitos aleatórios foi elencado para todas as meta-análises na plataforma RevManWeb. Abordagem GRADE foi adotada para avaliar a certeza da evidência.

Resultados: Foram incluídos 43 estudos envolvendo 17.816 participantes (19 estudos de bevacizumabe com 9.292 pacientes, 14 estudos de rituximabe com 3.802 pacientes e 10 estudos de trastuzumabe com 4.722 pacientes). Os ECR avaliaram pessoas com câncer de pulmão, câncer colorretal, linfoma não Hodgkin,

leucemia linfocítica crônica e câncer de mama. A proporção de mulheres variou de 19% a 100% e a média de idade, de 47 a 62 anos. O risco de viés foi baixo para 'geração de sequência aleatória', 'ocultação de alocação' e ‘cegamento’. Maiores limitações foram observadas nos domínios resultados incompletos', 'relato seletivo de desfechos' e 'outros vieses' (descontinuação e seleção de participantes elevadas). Os biossimilares foram semelhantes ao originador na sobrevida global (bevacizumabe: *hazard ratio* [HR] 1,06; intervalo de confiança de 95% [IC] 0,96-1,18; I^2=35%; 9 ECR; 5.862 participantes; baixa-certeza de evidência; rituximabe: HR 0,77; 95 % CI 0,45-1,32; 1 ECR; 629 participantes; alta-certeza de evidência; trastuzumab HR 0,91; IC 95% 0,75 a 1,10; 4 estudos; I^2=0%, alta-certeza de evidência). A similaridade também foi observada na sobrevida livre de progressão, sobrevida livre de eventos, duração da resposta, resposta objetiva respostas completa e parcial, eventos adversos, mortalidade e imunogenicidade em todos os biossimilares e originadores comparados.

Conclusão: A eficácia e segurança dos medicamentos biossimilares de bevacizumabe, rituximabe e trastuzumabe foi comparável aos seus respectivos produtos originais para tratamentos de câncer de pulmão, câncer colorretal, linfoma não Hodgkin, leucemia linfocítica crônica e câncer de mama.

Informação complementar: Esta revisão sistemática não contou com apoio financeiro. O protocolo consta registro no PROSPERO (CRD42020176453) e foi publicado na Cochrane Library (https://doi.org/10.1002/14651858.CD013539).

Palavras-chave: Revisão Sistemática; Medicamentos Biossimilares; Câncer; Produtos Biológicos; Meta-análise.

ABSTRACT

Background. Medical expenses related to cancer treatment are on the rise worldwide and the use of biosimilar drugs could be an option to reduce these costs. Individuals with cancer and healthcare professionals express concerns regarding the differences between biosimilar drugs and their originators, as well as the possible impact of these differences in treatment. The evidence from clinical trials comparing the use of biosimilar monoclonal antibodies with originator products in cancer treatment is unclear.

Objectives. To assess the efficacy and safety of biosimilar monoclonal antibodies for treating cancer, when compared to their originator biologic.

Search methods. Cochrane Central Register of Controlled Trials, Embase (via Ovid), MEDLINE (via PubMed), Web of Science databases, ClinicalTrial.gov, ICTRP, and annals of oncology congresses were searched up to December 2021.

Selection criteria. Only head-to-head randomized controlled trials (RCT) that compare the biosimilar and originator medicine were included. Eligible participants include adults previously diagnosed with cancer of any type and stage.

Data collection and analysis. We used methodological procedures recommended by Cochrane. Screening of titles and abstracts, full text assessment and data extraction were independently performed by two review authors. We used the Cochrane tool for assessing risk of bias. We used the random-effects model for all meta-analysis in RevManWeb platform.

Results: 43 studies involving 17,816 participants were included (19 studies of bevacizumab with 9,292 patients, 14 studies of rituximab with 3,802 patients, and 10 studies of trastuzumab with 4,722 patients). The RCTs evaluated people with lung cancer, colorectal cancer, non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and breast cancer. The proportion of women ranged from 19% to 100% and the mean age ranged from 47 to 62 years. The risk of bias was low for 'random sequence generation', 'allocation concealment' and 'blinding'. Major limitations were observed in the domains 'incomplete outcomes', 'selective reporting of outcomes' and 'other biases' (high discontinuation and selection of participants). Biosimilar drugs were similar to the originator in overall survival (bevacizumab: hazard ratio [HR] 1.06; 95% confidence interval [CI] 0.96-1.18; I^2=35%; 9 RCTs; 5,862 participants; low - certainty of evidence; rituximab: HR 0.77; 95% CI 0.45-1.32; 1 RCT; 629 participants;

high-certainty of evidence; trastuzumab HR 0.91; 95% CI 0.75 to 1, 10; 4 studies; I^2=0%, high-certainty of evidence). Similarity was also observed in progression-free survival, event-free survival, duration of response, objective response, complete and partial responses, adverse events, mortality, and immunogenicity across all biosimilars and originators compared.

Conclusion: The efficacy and safety of biosimilar medicines bevacizumab, rituximab and trastuzumab were comparable to their respective parent products for treatments of lung cancer, colorectal cancer, non-Hodgkin's lymphoma, chronic lymphocytic leukemia and breast cancer.

Additional information: This systematic review did not receive financial support. The protocol is registered in PROSPERO (CRD42020176453) and was published in the Cochrane Library (https://doi.org/10.1002/14651858.CD013539).

Keywords: Systematic Review; Biosimilar Pharmaceuticals; Cancer; Biological Products; Meta-analysis.

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LISTA DE ABREVIATURAS E SIGLAS

ADA	Anti-drug antibodies
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
Akt	Serine/threonine protein kinase
CD20	B-lymphocyte antigen CD20
CENTRAL	Cochrane central register of controlled trials
CI	Confidence interval
DoR	Duration of response
EFS	Event-free survival
EMA	European Medicine Agency
EQ	Equivalence
EU	European Union
FACT-C	Cancer Therapy-Colorectal score
FAS	Full analysis setting
FDA	US Food and Drug Administration
GRADE	Grades of Recommendation, Assessment, Development and Evaluation
HER2	Human epidermal growth factor-2 receptor
HR	Hazard ratio
ICTRP	International Clinical Trials Registry Platform
ITT	Intention-to-treat
IWG	International Working Group
MAPK	Mitogen-activated protein kinase
MD	Mean difference
MeSH	Medical Subject Headings
NAb	Neutralizing antibodies
NI	Noninferiority
OR	Odds ratios
ORR	Objective response rate
OS	Overall survival
pCR	Pathological complete response
PFS	Progression-free survival
PI3K	Phosphatidylinositide 3-kinase
PP	Per protocol
RCT	Randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Risk ratio
SD	Standard deviation
SE	Standard error
SMD	Standardized mean difference
VEGF	Vascular endothelial growth factor
WHO	The World Health Organization

SUMÁRIO

INTRODUCTION

Biotechnology products, which are manufactured from living organisms, generate large and structurally complex molecules (1), and therefore cannot be reproduced identically by the manufacturers (2). They are a biological medicinal product with the indication of treating human disease (3). Such products include cytokines, growth factors, hormones, interferons and proteins (4). Among those, biosimilar monoclonal antibodies are products that are similar in terms of quality, safety, and efficacy to an already well-known biological product (originator) (5).

Minor structural differences between biosimilar products and their originators are acceptable and expected, since inter-batches variability occur even within the originator biologic (6). Such differences do not significantly affect clinical performance (7). As biotherapeutic products indicated for the treatment of human diseases, biosimilars have a successful record in treating many life-threatening and chronic diseases (3, 8).

The European Union (EU) took the lead in developing the principles covering biosimilars in 2005 and released specific guidance for the development of biosimilars (9). Other international regulatory agencies have also developed guidelines on evaluation of biosimilars in comparison to their originator. Similarity could be attested by head-to head comparative studies with respect to structural and functional characterization, *in vitro* biologic assays, and pharmacokinetic and pharmacodynamics evaluations, as well as clinical studies to compare the safety, efficacy, and immunogenicity (8, 10, 11). This proved similarity allows subsequent abbreviation of non-clinical and clinical development of the biosimilar, as a result of the knowledge gained during the development, licensing, and clinical use of the originator product (5).

Complementing this stage of development, the European Medicine Agency (EMA) included all biosimilars authorized after January 2011 in the list of medicines under additional monitoring, which means these medicines are being monitored particularly closely by regulatory authorities. Additional monitoring aims to enhance reporting of suspected adverse drug reactions, collecting information as early as possible to further inform the safe and elective use (12).

Patents of monoclonal antibodies (originator) used in cancer treatment began expiring in 2013, with rituximab (13). It was only in 2017 that the first of these products was approved by the EMA (14), and the US Food and Drug Administration (FDA) (15). Up to 2022, three biosimilar monoclonal antibodies obtained marketing authorization to be used for treating cancer within the EU and the USA (16): rituximab, for the treatment of non-Hodgkin lymphoma (17, 18) and chronic lymphocytic leukemia (17); trastuzumab, for individuals with certain breast and stomach cancers (19, 20); and bevacizumab, for the treatment of breast, lung, colorectal, kidney, cervical, ovarian cancer (21, 22), and glioblastoma (22). Other biosimilars are being developed, such as cetuximab, aimed at the treatment of colorectal and head and neck cancers (23).

Individuals with cancer and healthcare professionals express concerns regarding the differences between biosimilars in general and their originators, as well as the possible impact of these differences in their efficacy and safety (24, 25). Such negative perception is a barrier to the market uptake of biosimilars and is the main reason why most physicians are skeptical at exchanging originator products to their biosimilar, according to a systematic review assessing healthcare providers knowledge on biosimilars in general and their acceptance of these products (26).

Half of 1,201 prescribing doctors of biologics surveyed in 2016 in the USA were aware that overall biosimilars are equivalent to their originator in terms of safety and efficacy (27). Hematology-oncology physicians were unsure or concerned about the safety of biosimilar medicines, and 43% did not believe biosimilars would be safe and appropriate for use neither by individuals who never received treatment nor by individuals under treatment. Physicians who are uncertain about the safety of biosimilars are more likely not to prescribe them (27). Similar results were obtained by another survey in 2015: of the 1,181 individuals who answered, 47% were worried about the safety of biosimilars, 40% were concerned about their efficacy, and 35% were worried about their molecular basis (28).

Previous experience with generic medicines showed that gaining the trust of all stakeholders is essential to increase the market acceptance of the products (29). A similar approach could significantly increase the uptake of biosimilars that are being developed as alternative options, with potentially lower costs and greater

access (30). The debate would benefit from robust clinical evidence about biosimilars effects in oncology.

Medical expenses related to cancer treatment are on the rise worldwide and the use of biosimilars could be an option to reduce these costs. Synthesis of evidence from clinical trials comparing the use of biosimilar monoclonal antibodies with the use of originator products in cancer treatment may contribute to a better decision- making process regarding therapeutic strategies.

Description of the condition

In 2020, the occurrence of new cases of cancer was estimated at 19.2 million worldwide, of which 9.9 million resulted in death. The most common types of cancer, for both men and women, were lung, breast, prostate, colon, and non-melanoma skin cancer (31).

Cancer treatment requires careful consideration of evidence-based options, which can include more than one of the main therapeutic modalities: surgery, radiotherapy, and systemic therapy (32). Included in the latter is the cytotoxic chemotherapy, which presents successful results for several types of cancer (33).

Due to the increasing knowledge on how cancer works, more specifically on gene mutations, biological understanding of cellular events, and pathways driving carcinogenesis, new medicines with specific targets, called targeted and immunotherapeutic agents were developed, which include monoclonal antibodies (33).

Description of the intervention

Upon the registration of rituximab in 1997, the use of monoclonal antibodies is one of the most successful therapeutic strategies for treating both hematological malignancies and solid tumors (34). Since the approval of other monoclonal antibodies for the therapy of a wide variety of diseases has increased: by 2017, 57 monoclonal antibodies were available in the market, of which 15 targeted oncology diseases (35).

After the patent expiration of the first biological medicines, biosimilars began to be developed (36). The first biosimilar medicine, called somatropin, was a

human recombinant growth hormone approved by the EMA in 2006. Following this first breakthrough, more than 70 biosimilars were approved by the EMA up to 2021 (37). Currently, three biosimilar monoclonal antibodies have obtained marketing authorization to be used for treating cancer: rituximab, trastuzumab, and bevacizumab.

How the intervention might work

Monoclonal antibodies can kill tumour cells by multiple ways, such as blocking ligand-receptor growth and survival pathways. The main mechanisms of action include antibody-dependent cellular cytotoxicity (ADCC) and complement-mediated cytotoxicity (38). The mechanisms of action of the three biosimilar monoclonal antibodies approved for cancer treatment are described below.

Rituximab is a chimeric monoclonal antibody that has a high affinity binding to B-lymphocyte antigen CD20 (CD20) on the surface of B cells. When the binding between rituximab and CD20 occurs, B cells die by ADCC, complement-dependent cytotoxicity, and, potentially, by inducing apoptosis (programmed cell death) (39). Rituximab is indicated for a wide range of oncology, rheumatology, and nephrology diseases (40).

CT-P10, a rituximab biosimilar, was the first biosimilar approved by the EMA in 2017 (41) and by the FDA in the end of 2018 (18). The clinical trial that supported the equivalence was conducted with participants with newly diagnosed advanced-stage follicular lymphoma that received either CT-P10 or originator product. In addition, the participants underwent standard chemotherapy for eight cycles (induction period), with a loading dose of 375 mg/ m^2 on day one. Non-inferior efficacy, equivalent pharmacokinetics, and similar pharmacodynamics were observed, with a safety profile comparable to the rituximab originator. Up to January 2022, there were seven rituximab biosimilar with marketing authorization in the EU (42) and three in the USA (43).

Trastuzumab is a recombinant humanized monoclonal antibody that binds to the domain of the extracellular segment of the human epidermal growth factor-2 receptor (HER2), and inhibits the proliferation and survival of HER2-dependent tumors (44). In adults with tumour over-expressing HER-2, trastuzumab

combined or not with chemotherapy or hormone therapy is considered the standard treatment (45). The molecular mechanisms of actions could be described in three different ways: HER2 degradation; attraction of immune cells to tumour cells by ADCC; and inhibition of mitogen-activated protein kinase (MAPK) and phosphatidylinositide 3-kinase (PI3K)/serine/threonine protein kinase (Akt) pathways(46).

SB3 was the first trastuzumab biosimilar approved by the EMA in 2017(47). In the USA, the trastuzumab biosimilar MyI1401O was also approved in 2017 (48). The clinical trial that supported the equivalence between SB3 and the originator product included 875 participants. These participants received either SB3 or originator every three weeks for eight cycles of neoadjuvant chemotherapy, with a loading dose of 8 mg/kg and a maintenance dose of 6 mg/kg. Results supported the efficacy equivalence based on pathologic complete response in primary breast tumour for women with HER2-positive early breast cancer. Safety and immunogenicity was also comparable (49) . Up to January 2022, there were six trastuzumab biosimilar with marketing authorization in the EU (50) and five in the USA (48) for some specific cases of breast cancer and metastatic gastric cancer.

Bevacizumab is a humanized inhibitor of vascular endothelial growth factor (VEGF) monoclonal antibody. Either as a single agent or in combination with chemotherapy, it is approved for the treatment of multiple types of cancer (21). It acts by selectively binding circulating VEGF, thereby inhibiting the binding of VEGF to its cell surface receptors, which results in a reduction of microvascular growth of tumour blood vessels, reducing the blood supply to tumour tissues. These mechanisms also decrease interstitial pressure on tissues, increase vascular permeability, favor apoptosis of tumour endothelial cells, and may increase delivery of chemotherapeutic agents (51).

ABP 215 was the first biosimilar of bevacizumab approved by both the FDA in 2017 and the EMA in 2018. In order to determine ABP 215 equivalence to its originator, a phase III clinical trial was conducted with 642 participants with advanced non-squamous non-small cell lung cancer. The participants received 15 mg/kg of either ABP 215 or the originator product, administered every three weeks for six

cycles (52). Up to January 2022, there were seven bevacizumab biosimilar with marketing authorization in the EU (53) and two in the USA (54).

Why it is important to do this review

In order for a product to be considered as a biosimilar, it must have similar structural and functional characteristics to its originator. These features are established based on pharmacokinetic and pharmacodynamics equivalence, as well as on comparative clinical studies that evaluate safety, efficacy, and immunogenicity (55).

Because the biosimilar manufacturer usually does not have access to all manufacturing information on the originator product, the result is a slightly different copy of the original molecule (56). These production downsides represent the main source of skepticism among healthcare professionals and individuals with different diseases (24, 26).

Seven systematic reviews on biosimilars for treating cancer have been published (57-63). Two aimed to describe the characteristics of the scientific publications in the field and would be therefore better categorized as bibliometric surveys (57, 58). One assessed rituximab for treating non-Hodgkin's lymphoma and rheumatoid arthritis (59), two reviewed biosimilar monoclonal antibodies for different types of cancer, with searches up to December 2018 (64) and April 2021(63), two reviews assessed trastuzumab biosimilar, where one of them aimed to assess the evidential role of randomised clinical endpoints studies in the marketing approval of trastuzumab biosimilar (62) and the second with searches up to July, 2020 (60).

The main motivation for conducting the present review is to provide best available evidence from clinical studies to support the decision concerning using biosimilar monoclonal antibodies in cancer treatments for the three available drugs. This review may give more trustworthy information for individuals with cancer and healthcare professionals, as well as contribute to effective decision-making.

OBJECTIVE

To assess the efficacy and safety of biosimilar monoclonal antibodies for treating cancer, when compared to their originator biologic.

METHODS

This systematic review was carried out at the Postgraduate Program of the Faculty of Pharmaceutical Sciences, State University of Campinas, Unicamp. As a systematic review, the project was not required for approval by the Research Ethics Committee. The protocol was registered in the Prospero database (CRD42020176453).

Types of studies

We included study reports of randomized controlled trials (RCTs) irrespective of language, publication type or status (for example, online clinical trials results, summaries of otherwise unpublished clinical trials, abstracts, reports from pharmaceutical companies, not peer-viewed publications, provided they contain sufficient data for analysis). We did not impose any limitation regarding the length of follow-up, but we required the study to contain at least one of the primary or secondary outcomes. Only head-to-head trials that compare the biosimilar and originator medicine were included. Switching studies were included but we extracted only data before the switch.

Types of participants

Eligible participants were adults older than 18 years old of both sexes who were previously diagnosed with cancer of any type and stage, including carcinoma “in situ”, locally advanced, recurrent, refractory and/or metastatic disease. Participants might be under treatment with adjuvant and/or neoadjuvant chemotherapy, palliative or in maintenance treatment, as well as other pharmacotherapies for either cancer or concomitant diseases.

Types of interventions

We included all RCTs performing a head-to-head comparison of biosimilar with a licensed originator product: rituximab biosimilar versus originator; trastuzumab biosimilar versus originator; bevacizumab biosimilar versus originator. Studies comparing biosimilar to other biosimilar were not included.

We did not include inactive control interventions, such as placebo or no treatment. We conducted analyses separately, for each intervention and outcomes, without combining different interventions or outcomes.

We did not restrict the studies included based on the dose, route, frequency, or duration of the treatment, nor duration of follow-up.

Types of outcome measures

Primary outcomes

Treatment administered with curative intent:

- Overall survival: the time from randomization until death from any cause and is measured in the intent-to-treat population (65);
- Progression-free survival: the time from randomization until objective tumor progression or death, whichever occurs first (65);
- Event-free survival: time from randomization to any of the following events: progression of disease that precludes surgery, local or distant recurrence, or death due to any cause (65).
- Global mortality rate

For treatment administered with the intent to achieve long-term disease control the primary outcome was overall survival.

Secondary outcomes

We assessed the objective response rate (ORR), defined as the proportion of complete or partial response, a synonym of overall response rate (10, 65) . Based on the guidelines from EMA and FDA, this outcome is able to detect product-related differences (10, 65) and allows comparing clinical efficacy of the interventions. A variety of response criteria have been considered appropriate and we accepted any one informed.

Additionally, we assessed:

- Duration of response: time from documentation of disease response to disease progression (66);

- Pathological complete response: the absence of residual invasive cancer of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (67)
- Any and serious adverse event – observed or patient-reported;
- Immunogenicity – measured by the proportion of individuals developing anti-drug antibodies and neutralizing antibodies;
- Health-related quality of life – measured using standardized generic or disease-specific questionnaires.

Considering that we have different types of cancer and treatment, for each outcome we would have different timeframes, for this reason we defined them from the shortest to longest time interval. Outcomes were analyzed in a short term (≤ 12 weeks), medium term (>12 weeks ≤ 48 weeks) and long term (> 48 weeks).If the outcome was assessed in more than one timepoint, we considered the longest period of time.

As a variety of response criteria to assess solid tumor response have been considered appropriate we accepted any one, including the Response Evaluation Criteria in Solid Tumors (RECIST) (68). For haemathologic tumours response either the International Working Group (IWG) response criteria (Cheson 2007), or the Lugano Classification (Cheson 2014) were accepted. The 2007 version of IWG were considered since it incorporates positron emission tomography, bone marrow immunohistochemistry, and flow cytometry for definitions of response. In the case we find any studies conducted with participants with chronic lymphocytic leukemia, we considered the recommendations of the National Cancer Institute-Working Group 2018 guideline (69).

Search methods for identification of studies

We have formulated search strategies in collaboration with an Information Specialist of the Cochrane Hematological Malignancies Group. Medical subject headings (MeSH) or equivalent, and text word terms were used (Appendix 1).

We have searched for all RCTs on biosimilar monoclonal antibodies in the following sources from inception of each database to February 2020, with no restriction of date, language, or publication status: Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library; Embase via Ovid; MEDLINE via PubMed; and Web of Science. We included alerts to keep us up to date with the medical literature being published. With this, we monitor the medical literature and kept the review as current as possible. New publications were manually added (last update: December 20th, 2021). We searched ongoing trial databases in the following sources: ClinicalTrials.gov; and The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). We searched for abstracts of clinical trials published by relevant meetings of the main oncology societies (2010 to December 2020): American Society of Hematology, American Society of Clinical Oncology, European Hematology Association, European Society for Medical Oncology, American Association for Cancer Research, International Association for the Study of Lung Cancer, San Antonio Breast Cancer Symposium. Public reports published by federal government agencies (FDA and EMA) were manually obtained.

Selection of studies

The results of the search strategies of this review were independently screened by two review authors (AL, LCL), in order to assess the titles and abstracts, remove irrelevant reports that do not clearly satisfy the inclusion criteria, and determine which trials assess. Multiple reports of the same study are being assessed together.

Disagreements were resolved through consensus or by a third review author (TFG). We used software for systematic review management (Covidence, www.covidence.org) to handle the search results and to identify and remove duplications. The selected reports were assessed in full text by two review authors (AL, LCL) to verify compliance with eligibility criteria. We did not anonymize the

studies in any way before assessment. In the event of disagreement, a third review author adjudicated (TFG).

Data extraction and management

Two review authors (AL, LCL, IRZ, LZV or MTS) independently extracted data using a standardized data extraction form customized on Covidence. We have piloted the data collection process in meetings to assess discordances after the extraction of two studies by each reviewer and to adapt the extraction form as needed. We contacted the authors of studies as needed to obtain information not available in the reports.

Disagreements were resolved by a third review author (TFG). After agreement has been reached, we manually inserted all data to Review Manager Web (70).

We extracted the following information:

General information: author's name, author's contact address (if available), corresponding author, sponsor of the study, title, publication type, publication date, country, language, duplicate publications.

Study characteristics: study design, clinical setting, country(ies), start and end dates, study duration, length of follow-up, sample size, inclusion and exclusion criteria, number of centers, recruitment dates, power calculation, stopping rules, statistical methods, compliance with assigned treatment, time point of randomization.

Participants characteristics: age, sex, ethnicity, total number of participants recruited/allocated/evaluated, number excluded with reasons, participants lost to follow-up, dropout rates with reasons, cancer type and stage, newly diagnosed or relapsed, additional diagnoses, previous treatments, concomitant treatment, protocol violations.

Risk of bias assessment: random sequence generation, allocation concealment, blinding (participants, personnel, outcome assessors), incomplete outcome data, selective outcome reporting, other sources of bias (71).

Interventions: type and dosage of monoclonal antibodies used, route of administration, frequency, duration, number of cycles, co-treatment, timing of intervention, compliance to interventions.

Measured outcomes: overall survival, progression-free survival, event-free survival, mortality, objective response rate, duration of response, pathological complete response, adverse events, immunogenicity.

Assessment of risk of bias in included studies

At least two review authors (AL, LCL, IRZ, MTS,LZV) independently assessed the risk of bias of each included study. If they are unable to reach a consensus, a third review author were consulted (TFG) for a final decision.

We conducted the assessment using the Cochrane tool for assessing risk of bias (Higgins 2017), which includes the following domains:

Selection bias: random sequence generation and allocation concealment;

Performance bias: blinding of participants and personnel;

Detection bias: blinding of outcome assessment;

Attrition bias: incomplete outcome data;

Reporting bias: selective outcome reporting;

Other biases: high selection of participants and conclusion of the assigned treatment.

We have judged each criterion using one of the following categories (Higgins 2017): ‘low risk of bias’; ‘high risk of bias’, or ‘unclear’. For studies published in full text paper, we have exhausted all recourses to avoid the bias judged as ‘unclear’, which were used only if a full text was not available.

Measures of treatment effect

We preferred the analysis data per protocol. Although data from intention-to-treat (ITT) populations is considered the most appropriate approach in superiority trials, in non-inferiority or equivalence trials, these data will generally reduce the

estimated treatment effect and lead to false conclusions (72). The main question in the equivalence studies is whether biosimilar treatment is therapeutically similar to the originator. In these studies, conclusions of equivalence were based on whether the confidence intervals fell within the prespecified margin of equivalence. On the other hand, the main question in a noninferiority study is whether a new treatment is not worse than the originator by a prespecified amount.

For dichotomous data we recorded the number of events and the total number of participants in both treatment and control groups. We reported the pooled risk ratios (RRs) with 95% confidence intervals (CIs) as the measure of treatment effect. We planned to record the total number of participants in both treatment and control groups and calculate continuous outcomes as mean differences (MDs) or standardized mean differences (SMDs) with 95% CIs.

We expressed time-to-event data as a hazard ratio (HRs) with 95% CIs. If HRs was not available, we tried to estimate as accurately as possible the HR using the available data and a purpose-built method based on Parmar and Tierney approaches (Parmar 1998; Tierney 2007). We analyzed only studies that reported unadjusted analyses in survival outcomes or that adjusted for the same factors. Studies that did not report survival outcomes following this criteria were left out of the pooled analysis.

Unit of analysis issues

Non-standard designs were included, such as crossover trials. We took into account this level of randomisation, in order to overcome a unit-of-analysis error and used only the first period, before changing the treatments.

Dealing with missing data

We assumed that some data would be missing or unclear, and in these cases we got in touch to the original authors of the study to obtain relevant data.

If standard deviations (SDs) were missing, we planned to calculate or estimate them by using confidence intervals, standard errors, t values, or P values (73). If missing data cannot be obtained, an imputation method would be used (74).

Sensitivity analyses were planned to be performed to assess the impact of changing the assumptions made.

If data were not reported numerically, but graphically we planned to estimate missing data from figures if the data was unadjusted, otherwise we left out the pooled analysis.

Assessment of heterogeneity

We identified heterogeneity by visual inspection of forest plots and statistical methods. Statistical heterogeneity of treatment effects among studies was assessed using Cochran's Q test, with a significance level of $P < 0.1$. For measure the inconsistency, we used the I^2 statistic and classified it as low ($I^2 < 40\%$), moderate (40% to 75%), or considerable (>75%) (73). Because we assume we would find at least moderate clinical and methodological heterogeneity within the included studies, we used a random-effects model. Causes of heterogeneity were planned to be explored by conducting subgroup analyses.

Assessment of reporting biases

We graphically examined the presence of small-study effects by generating funnel plots to visual inspection in outcomes that included at least 10 studies. Additionally, we performed Egger test to funnel plot asymmetry (75), in accordance with the degree of heterogeneity observed in the step before. We considered $P < 0.1$ as significant for this test (76).

Data synthesis

We used the Review Manager Web (RevMan Web) (70) to perform the analyses and follow the recommendations provided by the *Cochrane Handbook for Systematic Reviews of Interventions,* Chapter 10 (73). One review author (TFG) entered the data into the software program, which was independently checked for errors by a second review author (AL).

We used the random-effects model for all analyses, as we anticipated that true effects would be related but not the same for included studies. For dichotomous outcomes, we based the estimation of the between-study variance using the Mantel-

Haenszel method. We planned to use the inverse variance random effects when observed heterogeneity in the continuous outcomes. We proposed to use the Peto method when event numbers were small (odds ratios close to 1). We calculated corresponding 95% CIs for all analyses and presented the results graphically using forest plots (73).

Subgroup analysis and investigation of heterogeneity

We planned subgroup analyses or meta-regression to investigate differences that would explain relevant variability across studies' outcome of the following characteristics: cancer type, participants setting, participants' mean age; duration of follow-up.

Sensitivity analysis

We planned to perform sensitivity analyses of outcomes to assess the robustness of the findings by restricting the analysis to studies of lowest risk of bias, impute missing data considering worst-case scenario, and effects of fixed-effect or random-effects methods (73).

Certainty of evidence

Two review authors (MTS, IRZ) rated the certainty of evidence by using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) (77). The outcomes will be classified in critical, important, and not important by the consumer. All outcomes were assessed considering the five GRADE items: risk of bias; consistency of effect; imprecision; indirectness; and publication bias within-study and across-study, in order to assess and rank, in high, moderate, low, and very low, the certainty of the body of evidence for each outcome (78). Outcomes with a delta of 2.0% on the risk difference was assessed as no serious imprecision and the outcome was judged as precise in this domain (79).

Consumer participation

We will involve users in the classification of outcomes importance and interpretation of evidence synthesis. We will identify such stakeholders through personal and professional networks, considering their engagement and interest in the research issue.

This stage is in progress as a master's project with a goal of completion by the end of the first semester of 2022. The study was approved by the appropriate institutional research ethics committee (Protocol number: 52377021.2.0000.5404).

'Summary of findings' table

Key information concerning the certainty of evidence, the magnitude of effect, and the sum of available data for each of the three interventions of interest (rituximab, trastuzumab, and bevacizumab) in each outcome was provided in ‘Evidence Profile’ (**Table 2**, **Table 3**, **Table 4**). Outcomes’ relevance will be defined in a meeting with consumers to classify outcomes into ‘critical’, ‘important’, and ‘not important’ to clinical decision. Up to seven outcomes, based on the relevance defined by participants will be displayed in a ‘Summary of findings’ table and included.

RESULTS

A total of 2,865 records were retrieved from searching the databases (electronically up to 20th December 2021). After removing duplicates, 2,042 records were screened based on the title and abstract and 225 were assessed in full text. Of these, 62 were excluded with the reasons described in Figure 1, resulting 141 reports of 43 studies that met the inclusion criteria and were included in this systematic review, as some trials were reported in multiple reports.

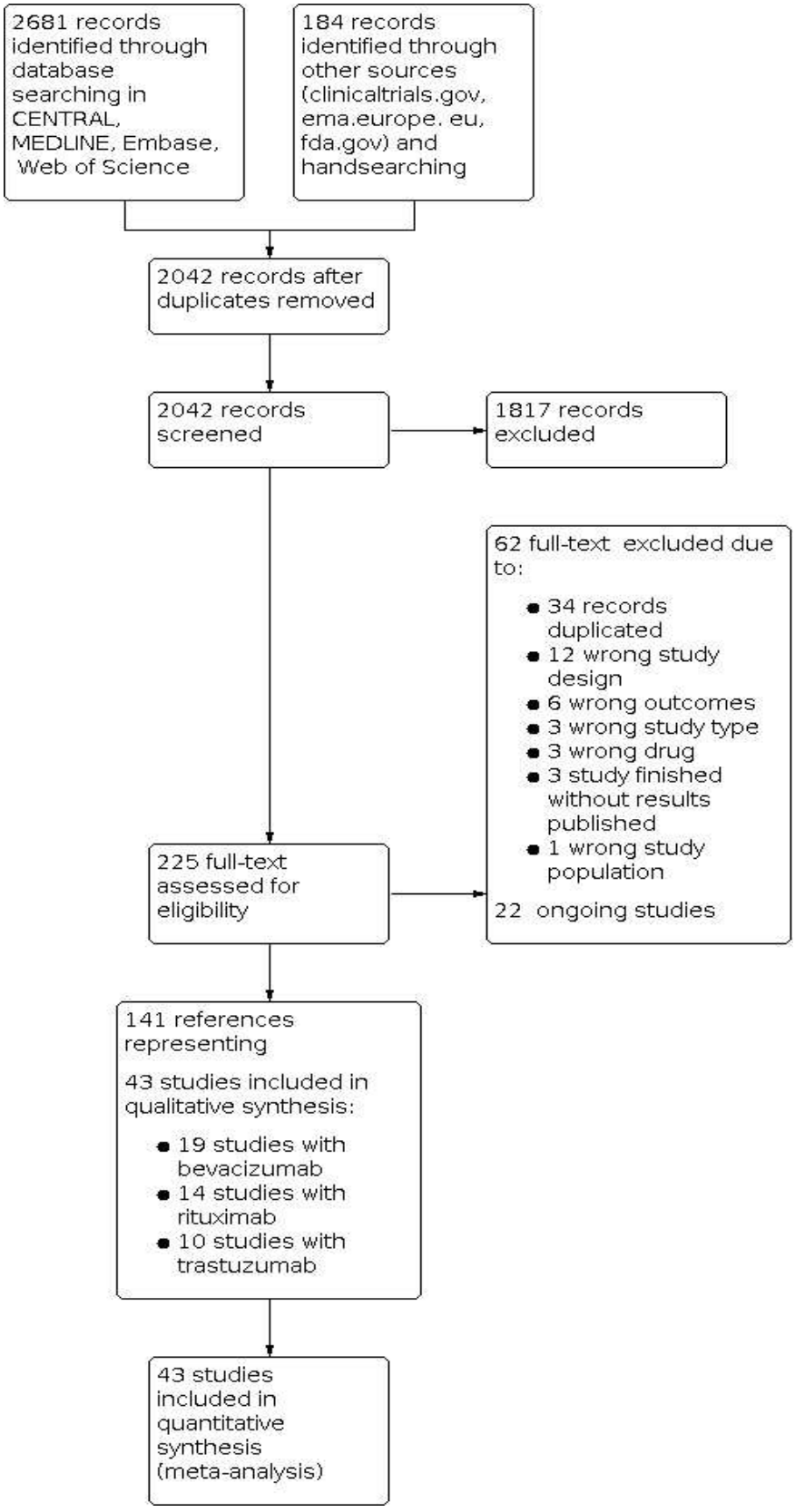


Figure 1. Study flow diagram

All 43 included studies were RCTs published in English language between 2012 and 2021 and involving more than 17,800 adult participants, ranging from 70 (80) to 875 (49) participants per study. We divided the included studies by intervention strategies into three types:

- 19 comparing bevacizumab biosimilar with the correspondent originator (n=9,292)
- 14 comparing rituximab biosimilar with the correspondent originator (n=3,802)
- 10 comparing trastuzumab biosimilar with the correspondent originator (n=4,722)

The effect of switching from originator drug to the biosimilar was investigated only in two RCTs, with trastuzumab (81, 82) and results from this phase were not included in the analyses.

In the trials included in this systematic review there were participants with non-Hodgkin lymphoma (13 trials), breast cancer (10 trials), lung cancer (14 trials), colorectal cancer (5 trials) and one study included participants with chronic lymphocytic leukemia (**Table 1**). The proportion of women in each study ranged from 19% in Toogeh 2018 (80) to 73% in Candelaria 2019 (83), all ten studies comparing trastuzumab included 100% of women, and two studies (84, 85) did not report this data. Participants' age (mean ± standard deviation) ranged from 47 ± 11 (86) to 61.6 ± 8.9 years (52). Four trials did not report this data (84, 85, 87, 88).

Twenty-five studies from bevacizumab, rituximab and trastuzumab groups included participants from North and South America, Europe, Asia, Africa, and/or Australia (49, 52, 81, 83, 89-109). Fifteen trials included participants exclusively from Asia (China= 9, India=5, South Korea=1) (84-88, 110-119). One study included participants only from Russia (120) and another, only from Iran (80).

Table 1– Characteristics of included studies

Study	Year	Country	Study design	Originator drug	Biosimilar drug, manufacturer	Monoclonal antibody dose and chemotherapy regimen	Cancer type	Sample size	% of women	Age (years)[1]
Advani 2018a(86)	2015-2016	India	Open label, non-inferiority RCT	Bevacizumab	Bevass, Hetero	7.5 mg/kg every 21 days plus XELOX (8 cycles) or 5 mg/kg every 14 days plus FOLFOX[2] (12 cycles)	Metastatic colorectal cancer	109	43	47 ± 11
Apsangikar 2017a(110)	2013-2016	India	Open label, non-inferiority RCT	Bevacizumab	BevaciRel, Reliance Life Sciences	5 mg/kg every 14 days plus FOLFIRI[3] (12 cycles)	Metastatic colorectal cancer	119	34	48.1 ± 11.9
NCT03329911(89)	2017-2021	China, Mexico, South Africa, Turkey, Ukraine	Double blind equivalence RCT	Bevacizumab	BAT1706, Bio-Thera Solutions	15 mg/Kg plus paclitaxel and carboplatin every 21 days (6 cycles [4]	Advanced or recurrent Nonsquamous non-small cell lung cancer - nsNSCLC	651	30	61 (26,88)
Chu 2021(111)	2017-2018	China	Double blind equivalence RCT	Bevacizumab	Ankada, Qilu Pharmaceutical	15 mg/Kg plus paclitaxel and carboplatin every 21 days (4-6 cycles	Advanced, metastatic or relapsed nsNSCLC	535	41	59 (27,75; 58 (35,75)
CTRI20141005171 (121)	2014-2016	India	Double blind equivalence RCT	Bevacizumab	Bmab-100, Biocon	7.5 mg/kg IV plus XELOX every 21 days (6 cycles)	Metastatic colorectal cancer	136	38	50.7 ±14.0; 51.6

[1]Mean ± standard deviation or median (range)

[2]XELOX, oxaliplatin 130 mg/m² IV on day 1 followed by oral capecitabine 1000 mg/m² twice daily on days 1 through 14; FOLFOX-4: leucovorin, 5-fluorouracil, oxaliplatin

[3] irinotecan 180 mg/m² IV, leucovorin 400 mg/m² IV, and 5-fluorouracil 400 mg/m² IV bolus followed by 2400 mg/m² IV over 46 h

[4] paclitaxel 200 or 175 mg/m² IV, carboplatin target area under the curve 5 or 6 mg/mL*min

Study	Year	Country	Study design	Originator drug	Biosimilar drug, manufacturer	Monoclonal antibody dose and chemotherapy regimen	Cancer type	Sample size	% of women	Age (years)[1]
										±12.8
Filon 2015(120)	2012-2014	Russia	Double blind non-inferiority RCT	Bevacizumab	Avegra, Biocad	15 mg/Kg plus paclitaxel and carboplatin every 21 days (4-6 cycles	Advanced or metastatic NSCLC	138	37	57.8 ± 8.9; 58.7 ± 8.3
INVICTAN 2020(90)	2015-2018	28 countries[5]	Double blind equivalence RCT	Bevacizumab	BI 695502	15 mg/Kg plus paclitaxel and carboplatin every 21 days (4-6 cycles)	advanced nsNSCLC	663	37	61.2 ± 9.9; 61.3 ± 9.2
Qin 2021(112)	2018-2020	China	Double blind equivalence RCT	Bevacizumab	HLX04, Shanghai Henlius Biotech	7.5 mg/kg every 21 days in combination with XELOX or 5 mg/kg every 14 days when given with mFOLFOX6[6]	metastatic or recurrent colorectal cancer	677	40	56.7±11.6; 57.4± 11.2
Reck 2020(91)	2016-2018	13 countries[7]	Double blind equivalence RCT	Bevacizumab	SB8/Aybinti/ Onbevzi, Samsung	15 mg/Kg plus paclitaxel and carboplatin every 21 days (4-6 cycles	Metastatic or recurrent nsNSCLC	763	33	60.1 ± 9.1
Reinmuth 2019(92)	2015-2017	27 countries[8]	Double blind equivalence RCT	Bevacizumab	Zirabev/ PF-06439535, Pfizer	15 mg/Kg plus paclitaxel and carboplatin every 21 days (4-6 cycles	Advanced, metastatic or recurrent	719	35	61.3 ± 9.2

[5] Argentina, Brazil, Bulgaria, Chile, Croatia, Egypt, Germany, Greece, Hungary, Italy, Japan, Malaysia, Mexico, Philippines, Poland, Portugal, Romania, Russia, Serbia, South Africa, South Korea, Spain, Thailand, Turkey, Ukraine, United Kingdom, United States, Vietnam

[6] mFOLFOX6, oxaliplatin 85 mg/m² followed by leucovorin 400 mg/m², and IV bolus of 5-fluorouracil 400 mg/m² on day 1 with subsequent 2400 mg/m² × 46 h continuous intravenous infusion

[7] Belarus, Georgia, Germany, Hungary, Poland, Romania, Rússia, Serbia, South Korea, Spain, Taiwan, Thailand, Ukraine

[8] Australia, Brazil, Bulgaria, Chile, Croatia, Czech Republic, France, Germany, Greece, Hungary, India, Italy, Japan, Korea, Malaysia, Netherlands, Philippines, Poland, Romania, Russia, South Africa, Spain, Taiwan, Thailand, Turkey, Ukraine, United States

Study	Year	Country	Study design	Originator drug	Biosimilar drug, manufacturer	Monoclonal antibody dose and chemotherapy regimen	Cancer type	Sample size	% of women	Age (years)[1]
							nsNSCLC			
Romera 2018(93)	2014-2017	Argentina, Brazil, India, Spain, Ukraine	Open label equivalence RCT	Bevacizumab	BEVZ92, mAbxience	5 mg/kg every 14 days plus FOLFIRI or FOLFOX (12 cycles)	Metastatic colorectal cancer	142	44	56.3 ± 12.9; 56.7 ± 11.6
Shi 2021(113)	2017-2020	China	Double blind equivalence RCT	Bevacizumab	LY01008, Luye Pharma Group	15 mg/Kg plus paclitaxel and carboplatin every 21 days (4-6 cycles)	Metastatic or recurrent nsNSCLC	598	40	Media n: 59
Socinski 2020(94)	2017-2019	16 countries[9]	Double blind equivalence RCT	Bevacizumab	Abevmy/MYL-1402o, Mylan	15 mg/Kg plus paclitaxel and carboplatin every 21 days (6 cycles)	Metastatic or recurrentn sNSCLC	671	37	59.3 ± 9.6
Syrigos 2021(94)	2016-2019	24 countries[10]	Double blind equivalence RCT	Bevacizumab	Equidacent/ FKB238, Centus Biotherapeutics	15 mg/Kg plus paclitaxel and carboplatin every 21 days (4-6 cycles	Metastatic or recurrentn sNSCLC	731	34	60.8 ± 8.8; 61.1 ± 9.4
Thatcher 2019(52)	2013-2015	17 countries[11]	Double blind equivalence RCT	Bevacizumab	Mvasi/ABP 215, Amgem	15 mg/Kg plus paclitaxel and carboplatin every 21 days (6 cycles)	Metastatic or recurrent nsNSCLC	642	40	61.6 ± 8.9
Trukhin 2021(96)	2018-2020	16 countries[12]	Double blind equivalence RCT	Bevacizumab	Alymsys/MB02, mAbxience	15 mg/Kg plus paclitaxel and carboplatin every 21 days (6 cycles)	Advanced nsNSCLC	627	39	60.1 ± 9.5; 60.8 ±

[9] Belarus, Bosnia and Herzegovina, Bulgaria, Croatia, Georgia, Hungary, India, Philippines, Poland, Romania, Russia, Spain, Taiwan, Turkey, Ukraine, Vietnam

[10] Belarus, Bosnia and Herzegovina, Bulgaria, Croatia, Georgia, Germany, Greece, Hungary, Italy, Japan, Peru, Philippines, Poland, Romania, Russia, Serbia, South Korea, Spain, Taiwan, Thailand, Turkey, Ukraine, United States, Vietnam

[11] Asia/Pacific, Europe, North America, and Latin America

[12] Brazil, Bulgaria, Chile, Georgia, Greece, Hungary, India, Lebanon, Malaysia, Mexico, Philippines, Russia, Serbia, Thailand, Turkey, Ukraine

Study	Year	Country	Study design	Originator drug	Biosimilar drug, manufacturer	Monoclonal antibody dose and chemotherapy regimen	Cancer type	Sample size	% of women	Age (years)[1]
										9.2
Wang 2021(114)	2017-2019	China	Double blind equivalence RCT	Bevacizumab	MIL60, Betta Pharmaceutical	15 mg/Kg plus paclitaxel and carboplatin every 21 days (6 cycles)	Advanced, metastatic or recurrentn sNSCLC	508	36	61.0 (23,76)
Yang 2019(115)	2016-2019	China	Double blind equivalence RCT	Bevacizumab	IBI305, Innovent Biologics	15 mg/Kg plus paclitaxel and carboplatin every 21 days (6 cycles)	Advanced, metastatic or recurrent nsNSCLC	450	37	57.4 ± 8.98
Zhou 2020(84)	NR	China	Double blind equivalence RCT	Bevacizumab	Pusintin/TAB08 ,TOT BIOPHARM	15 mg/Kg plus paclitaxel and carboplatin every 21 days (4-6 cycles	Advanced, metastatic or recurrentn sNSCLC	549	Not reported (NR)	NR
Advani 2018b(85)	2013-2015	India	Open label, non-inferiority RCT	Rituximab	Rilast, Hetero	375 mg/m² every 28 days (6 cycles)	Diffuse large B-cell lymphoma (DLBCL)	135	NR	NR
Candelaria 2019(83)	2013-2016	20 countries[13]	Double blind non-inferiority RCT	Rituximab	RTXM83, mAbxience Research	375 mg/m² plus CHOP[14] every 21 days (6 cycles)	DLBCL	272	73	51 (40;58)
Jiang 2020(116)	2016-2019	China	Double blind equivalence	Rituximab	Byvasda/IBI301 , Innovent	375 mg/m^2) every 3 months (4 cycles)	Non-Hodgkin lymphoma	181	56	Mean 49.1

[13] Argentina, Brazil, Colombia, India, Indonesia, Iran, Malaysia, Mexico, Paraguay, Philippines, Russian Federation, South Africa

[14] cyclophosphamide 750 mg/m² IV, doxorubicin 50 mg/m², vincristine 1.4 mg/m² IV and prednisone or prednisolone 40 mg/m² orally

Study	Year	Country	Study design	Originator drug	Biosimilar drug, manufacturer	Monoclonal antibody dose and chemotherapy regimen	Cancer type	Sample size	% of women	Age (years)[1]
			RCT		Biologics		(B-cell)			
Jurczak 2017(98)	2011-2015	26 countries[15]	Double blind equivalence RCT	Rituximab	GP2013, Hexal	375 mg/m² plus CVP every 21 days (8 cycles)	Follicular lymphoma	629	56	56.9 ± 11.8
Kim 2012(99)	2017-2020	25 countries[16]	Double blind equivalence RCT	Rituximab	SAIT101, Archigen Biotech	375 mg/m² every 28 days (4 cycles)	Follicular lymphoma	315	55	Mean 58.1
Kim 2017(97)	2014-2016	20 countries[17]	Double blind non-inferiority RCT	Rituximab	Truxima/CT-P10, Celltrion	375 mg/m² plus CVP[18] every 21 days (8 cycles)	Follicular lymphoma	140	55	55.5 ± 13.9
Niederwieser 2020(100)	2016-2019	20 countries[19]	Double blind non-inferiority RCT	Rituximab	ABP 798, Amgen	375 mg/m² every 28 days (6 cycles)	Follicular lymphoma	256	51	Mean 57.9
Ogura 2018(101)	2015-2019	20 countries[20]	Double blind equivalence	Rituximab	Truxima/CT-P10, Celltrion	375 mg/m² every 28 days (6 cycles)	Follicular lymphoma	258	52	57.7 ± 12.1

[15] Australia, Belarus, Chile, Croatia, Czech Republic, Egypt, France, Georgia, Germany, Guatemala, Hungary, India, Italy, Korea, Republic of, Mexico, Panama, Philippines, Serbia, South Africa, Spain, Thailand, Turkey, Ukraine, United Kingdom, United States

[16] Argentina, Australia, Austria, Brazil, Bulgaria, Colombia, France, Germany, Greece, Hungary, India, Ireland, Israel, Italy, Japan, Malaysia, the Netherlands, Peru, Poland, Portugal, Romania, Russia, South Africa, Spain, Ukraine, United Kingdom

[17] Belarus, Brazil, Bulgaria, Chile, Georgia, Greece, India, Italy, Mexico, Netherlands, Philippines, Poland, Portugal, Romania, Russia, South Africa, South Korea, Spain, Turkey, Ukraine

[18] cyclophosphamide 750 mg/m² IV, vincristine 1.4 mg/m² IV and prednisone or prednisolone 40 mg/m² orally

[19] Australia, Bulgaria, Canada, Colombia, Czech Republic, France, Georgia, Germany, Greece, India, Israel, Italy, Japan, Mexico, Poland, Romania, South Korea, Spain, Ukraine, United States

[20] Australia, Belarus, Brazil, Chile, Czech Republic, India, Italy, Japan, Latvia, Latvia, Malaysia, Peru, Poland, Portugal, Republic of Korea, Russia, Spain, Taiwan, Thailand, Ukraine, United Kingdom, United States

Study	Year	Country	Study design	Originator drug	Biosimilar drug, manufacturer	Monoclonal antibody dose and chemotherapy regimen	Cancer type	Sample size	% of women	Age (years)[1]
			RCT							
Poddubnaya 2020(102)	2012-2017	Colombia, India, Russia, Ukraine	Open label equivalence RCT	Rituximab	BCD-020, Biocad	375 mg/m² every 28 days (4 cycles)	Follicular lymphoma	174	52	58 (49,64) 55 (47,63)
Sharman 2020(103)	2014-2018	29 countries[21]	Double blind equivalence RCT	Rituximab	Ruxience/PF-05280586, Pfizer	375 mg/m² IV every 7 days (4 cycles)	Follicular lymphoma	394	55	58.5 ± 12.4
Shi 2020(117)	2015-2018	China	Double blind equivalence RCT	Rituximab	HLX01, Shanghai Henlius Biotech	375 mg/m² plus CHOP every 21 days (6 cycles)	DLBCL	407	45	54 (46,61) 55 (46,63)
Song 2021(118)	2016-2019	China	Double blind equivalence RCT	Rituximab	IBI301, Innovent biologics	375 mg/m² plus CHOP every 21 days (6 cycles)	DLBCL	420	52	54.1 (22,75) 55 (20, 74
Toogeh 2018(80)	2013-?	Iran	Double blind non-inferiority RCT	Rituximab	Zytux, AryoGen Biopharma	375 mg/m² (first) and 500 mg/m² (subsequent cycles) plus fludarabine and cyclophosphamide every 28 days (4 cycles)	Chronic lymphocytic leukemia	70	19	57.9 ± 8.4; 59.2 ± 8.2
Viswabandya 2019(119)	2012-2015	India	Double blind equivalence RCT	Rituximab	Reditux, Dr Reddy's Laboratories	375 mg/m² plus CHOP every 21 days (6 cycles)	DLBCL	151	38	47.2± 11.8; 44.4 ± 11.5
Alexeev 2020(104)	2012-2017	Belarus, India,	Double blind equivalence	Trastuzumab	Herticad/BCD-022, JSC	8 mg/kg (first) and 6 mg/kg (subsequent cycles) plus	Metastatic breast	255	100	50.6±10.4

[21] Austria, Belarus, Belgium, Brazil, Croatia, France, Georgia, Germany, Greece, India, Italy, Japan, Republic of Korea, Lebanon, Mexico, Peru, Poland, Portugal, Puerto Rico, Romania, Russia, South Africa, Spain, Switzerland, Thailand, Turkey, Ukraine, United Kingdom, United States

Study	Year	Country	Study design	Originator drug	Biosimilar drug, manufacturer	Monoclonal antibody dose and chemotherapy regimen	Cancer type	Sample size	% of women	Age (years)[1]
		Russia, Ukraine	RCT		BIOCAD	paclitaxel 175 mg/m² every 21 days (6 cycles)	cancer			
Apsangikar 2017b(87)	2013-2016	India	open label, non-inferiority RCT	Trastuzumab	Trasturel/TPR-016, Reliance Life sciences	8 mg/kg (first) and 6 mg/kg (subsequent cycles) plus paclitaxel 175 mg/m² every 21 days (6 cycles)	Advanced or metastatic breast cancer	104	100	NR
Esteva 2019(105)	2014-2018	22 countries[22]	Double blind equivalence RCT	Trastuzumab	Herzuma/CT-P6, Celltrion	8 mg/kg (first) and 6 mg/kg (subsequent cycles) plus FEC[23] every 21 days (8 cycles)	Early breast cancer	549	100	51.8± 11.0; 52.1 ±10.5
Im 2013(88)	2010-2011	South Korea	Double blind equivalence RCT	Trastuzumab	Herzuma/CT-P6, Celltrion	8 mg/kg (first) and 6 mg/kg (subsequent cycles) plus paclitaxel 175 mg/m² every 21 days (8 cycles)	Metastatic breast cancer	174	100	NR
Lammers 2018(106)	2014-2016	10 countries[24]	Double blind non-inferiority RCT	Trastuzumab	Trazimera/PF-05280014, Pfizer	8 mg/kg (first) and 6 mg/kg (subsequent cycles) plus docetaxel and carboplatin every 21 days (6 cycles)	Invasive breast cancer	226	100	52.6± 12.3
Pegram 2019(107)	2014-2020	24 countries[25]	Double blind equivalence RCT	Trastuzumab	Trazimera/PF-05280014, Pfizer	4 mg/kg (first) 2 mg/kg (subsequent cycles) plus paclitaxel 80 mg/m² on days 1, 8 and 15 of each 28-day	Metastatic breast cancer	707	100	54.1± 10.8

[22] Argentina, Belarus, Bosnia and Herzegovina, Chile, France, Georgia, Hungary, India, Italy, Japan, Latvia, Mexico, Peru, Philippines, Poland, Portugal, Romania, Russia, South Africa, Spain, Taiwan - Province of China, Ukraine

[23] docetaxel 75 mg/m² IV on day 1 of cycles 1-4 then fluorouracil 500 mg/m² IV bolus or 30 minutes infusion, epirubicin 75 mg/m² IV bolus or 30 minutes infusion, and cyclophosphamide 500 mg/m² IV 3–5 minutes bolus on day 1 of cycles 5-8

[24] Belarus, Czechia, Hungary, Italy, Poland, Russian Federation, Serbia, Slovakia, Ukraine, United States

[25] Argentina, Brazil, Chile, Czech Republic, Greece, Hungary, India, Japan, Latvia, Mexico, Peru, Philippines, Poland, Portugal, Republic of Korea, Romania, Russian Federation, Serbia, Slovakia, South Africa, Thailand, Turkey, Ukraine, United States

Study	Year	Country	Study design	Originator drug	Biosimilar drug, manufacturer	Monoclonal antibody dose and chemotherapy regimen	Cancer type	Sample size	% of women	Age (years)[1]
						cycle (8 cycles)				
Pivot 2018(49)	2014-2017	14 countries[26]	Double blind equivalence RCT	Trastuzumab	SB3, Samsung Bioepis	8 mg/kg (first) and 6 mg/kg (subsequent cycles) plus FEC every 21 days (8 cycles)	Early breast cancer	875	100	51 (24,65) 50 (22,65)
Rugo 2017(108)	2012-2018	16 countries[27]	Double blind equivalence RCT	Trastuzumab	Ogivri/MYL-1401O, Mylan	8 mg/kg (first) and 6 mg/kg (subsequent cycles) plus paclitaxel 80 mg/m² every 21 days (8 cycles)	Metastatic breast cancer	458	100	54.3± 11.0; 52.9 ±11.2
von Minckwitz 2018(81)	2013-2017	20 countries[28]	Double blind equivalence RCT	Trastuzumab	Kanjinti/ABP 980, Amgen	8 mg/kg (first) and 6 mg/kg (subsequent cycles) plus paclitaxel 175 mg/m² every 21 days (4 cycles)	Invasive breast cancer	725	100	52.7± 11.0
Xu 2021(122)	2016-2019	China, Philippines, Poland, Ukraine	Double blind equivalence RCT	Trastuzumab	Zercepac HLX02, Shanghai Henlius Biotech	8 mg/kg (first) and 6 mg/kg (subsequent cycles) plus docetaxel 75 mg/m² every 21 days (17 cycles)	Recurrent or metastatic breast cancer	649	100	53.6 ± 9.7; 52.8 ± 10.1

Risk of bias in included studies

Summaries of the risk of bias of included studies for each assessed domains are presented in **Figure 2**.

[26] Bosnia, Bulgaria, Czech Republic, France, India, Malaysia, Mexico, Philippines, Poland, Romania, Russia, South Korea, Ukraine, Vietnam

[27] Brazil, Chile, Georgia, Hungary, India, Latvia, Peru, Romania, Russia, Serbia, Slovakia, South Africa, Thailand, Ukraine

[28] Belarus, Brazil, Bulgaria, Canada, Chile, Czech Republic, Germany, Greece, Hungary, Italy, Mexico, Poland, Romania, Russia, Serbia, Slovakia, South Africa, Spain, Ukraine, United Kingdom

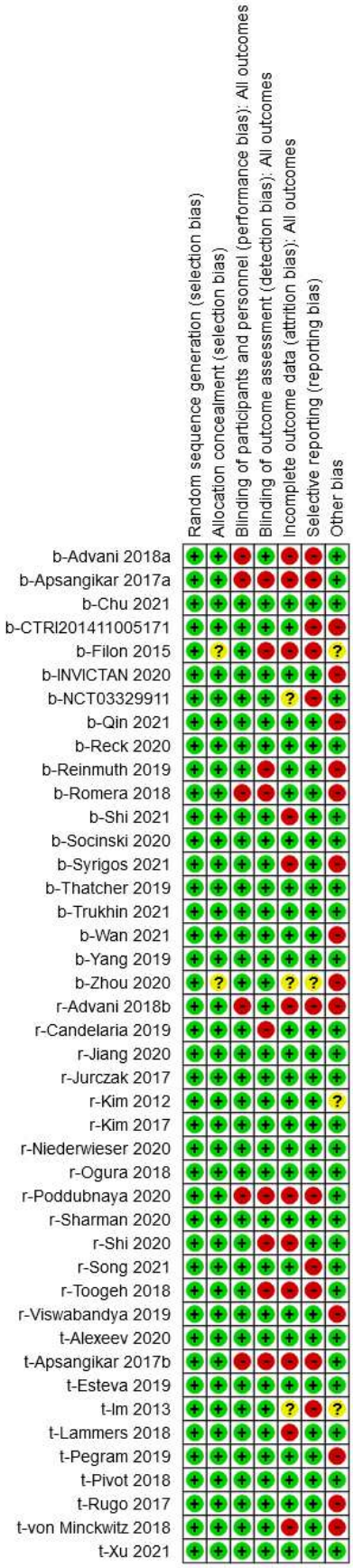


Figure 2. Risk of bias summary

Note: b:bevacizumab; r:rituximab; t:trastuzumab

The overall risk of bias was generally low in the domain ‘random sequence generation’ and ‘allocation concealment’, almost 75% of trials were judged as low risk for the domain regarding blinding. Much of the methodological information was confirmed through a direct checking of the trial protocols to support the published information and to clarify the reasons for our rating. The main biases of the studies were ‘incomplete outcome data’, ‘selective reporting’ and ‘other bias’, in which we assessed high discontinuation of participants until the end of study (irrespectively of complete outcome data) and potential high selection of participants, based on the proportion of participants randomized from all screened participants (**Figure 3**).

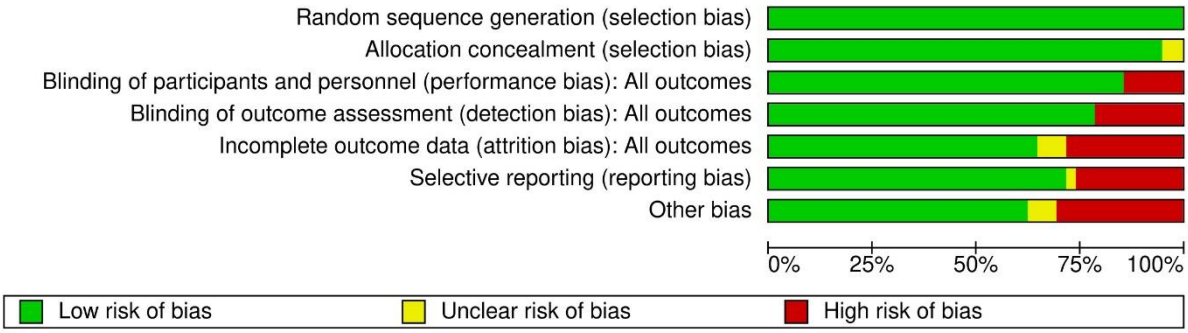


Figure 3. Risk of bias graph

Allocation

All 43 studies were described as randomised. In all of them the two groups of comparison followed the same ratio of participants in each group, excepted three trials where the ratio of randomization was different than 1:1 (86, 87, 110). The majority of the studies had clear and adequate allocation concealment. All 43 included studies (100%) reported a randomised allocation process using either simple randomisation, block randomisation method, computer-generated randomisation, or an interactive voice response system; therefore, we judged them as having low risk of bias for 'Random sequence generation'. Two studies (4.6%) (84, 120) did not provide information regarding the allocation concealment; therefore, we judged these studies as having unclear risk of bias for this domain.

Blinding

A majority of studies (86%) were double-blinded (usually reported in journal publication and referring to participants and investigators), triple or quadruple-blinded (usually reported in trials registries and referring to participants, care providers, investigators, and/or outcome assessors), being at low risk of performance bias. Six included studies (14%) were open-label: three of them tested bevacizumab (86, 93, 110), two, rituximab (85, 102), and one, trastuzumab (87) and were judged as high risk for 'blinding of participants and personnel (performance bias)'.

Blinding of outcome assessors (detection bias)

Considering that some outcomes could be influenced by unblinded investigators, for example, overall response rate and progression-free survival, we judged the domain 'blinding of outcome assessors' taking them into account.

Thirty-four (79%) included trials were at low risk of detection bias because outcome assessors were blinded. The remaining nine studies (21%) were judged as 'high risk'. Four of them because were not blinded for the investigator or assessor (87, 93, 102, 110). The other five trials did not report if the outcomes were assessed in a central review or by a blinded reviewer (83, 88, 92, 117, 120) and for this reason were judged having high risk. Despite the study Advani 2018a (86), comparing bevacizumab, and Advani 2018b (85), comparing rituximab, have been described as open label for participants and investigators, for this domain we judged them having low risk because the radiologists were blinded and were not made aware regard the treatment allocation.

Incomplete outcome data

We judged as low risk for this domain when the study showed both ITT and per protocol (PP) analysis, otherwise studies were judged as high risk in this domain, since in equivalence or non-inferiority trials ITT analysis does not have the same conservative effect observed in superiority trials and may underestimate the difference by diluting any real treatment differences (123).

We assessed risk of incomplete outcome data bias checking for possible attrition bias due to the quantity, nature, and handling of incomplete data. We judged 28 studies

(65%) as having low risk of bias, as most of the randomised participants were included in the efficacy and safety analyses in primary studies and reported study discontinuations were balanced between arms.

We judged three studies (7%) as having unclear risk of bias, as the publication was from a conference presentation (84, 89) or ClinicalTrials.gov results database (88), insufficient information was provided to make an explicit decision regarding the reasons for study discontinuations. We judged 12 studies (28%) as having high risk of bias because the full text did not provide the reasons for missing data from participants (80, 86, 87, 110, 113, 117, 124), participants dropped out without explanation (120), high dropout rate and the authors provided only per protocol analyses (85), the substantial loss of participate generate unbalance between the groups (81, 102, 106).

Selective reporting

We judged 31 trials (72%) as having low risk of bias for selective reporting because all prespecified outcomes informed in the protocol were reported. Zhou 2020 (84), was only available as a conference abstract, without protocol and with not enough details to make a judgment, for this reason the risk was considered unclear in this domain. Eleven trials (26%) were at high risk of reporting bias because not all of the study's prespecified outcomes were reported (80, 85-89, 102, 110, 118, 120, 121), one or more key outcomes that would have been expected to have been reported were not included (80) and it was reported incompletely so that they could not be entered into a meta-analysis (87).

Other potentials sources of bias

We judged 27 studies (63%) as having low risk for other potential sources of bias because we did not identify any information that would suggest it. We judged three studies (7%) as having unclear risk for other potential sources of bias because on study didn't report the number of participants recruited, and that completed study (120). Kim 2012 (125) didn't describe information regarding screening phase in the participants flow as well the high number of participants and rates of discontinuation were not available . We could not find any full-text publication for Im (88) and the

abstract did not contain sufficient information to exclude other potential sources of bias.

Effects of interventions

We performed a meta-analysis including all 43 trials (33 EQ trial and 10 NI trials), because of their similarities in patients, treatments, outcomes, and time points. The pooled analysis for the comparison of efficacy and safety outcomes between bevacizumab, rituximab and trastuzumab biosimilars versus the originator drug is reported in **Table 2**, **Table 3**, and **Table 4**, along with the certainty of evidence assessment.

Table 2. Evidence profile and certainty of evidence of outcomes assessed for bevacizumab biosimilar compared to originator for nonsquamous non-small cell lung or colorectal cancer

Outcomes	Certainty assessment						N of participants		Effect	Certainty
	N. of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Biosimilar	Originator	Relative [95% CI]	
Overall survival	9	Serious[3]	Serious[4]	Not serious	Not serious[5]	None	2934	2928	HR 1.06 [0.96 , 1.18]	Low
Progression-free survival	9	Serious[3]	Not serious	Not serious	Not serious	None	3263	3221	HR 1.05 [0.99 , 1.13]	Moderate
Mortality	17	Not serious[1]	Not serious	Not serious	Not serious	None	4428	4334	RR 1.04 [0.98 , 1.10]	High
Objective response	19	Not serious[1]	Not serious	Not serious	Not serious	None	4559	4489	RR 0.96 [0.92 , 1.00]	High
Duration of response	4	Serious[3]	Not serious	Not serious	Not serious	None	856	866	HR 1.10 [0.96 , 1.25]	Moderate
Any adverse events (AE)	16	Not serious[1]	Not serious	Not serious	Not serious	None	4101	4001	RR 1.00 [1.00 , 1.01]	High
Serious AE	19	Not serious[1]	Not serious	Not serious	Not serious	None	4758	4662	RR 1.00 [0.94 , 1.06]	High
Antidrug antibodies	15	Not serious[1]	Not serious	Not serious	Not serious	None	3836	3833	RR 1.08 [0.93 , 1.26]	High
Neutralising antibodies	9	Not serious[1,6]	Not serious	Not serious	Not serious[2]	None	2217	2216	RR 0.67 [0.37 , 1.20]	High

RCTs, randomised controlled trial; RR, risk ratio; HR, hazard ratio; CI, confidence interval

[1], Study limitations present in studies that contribute to the outcome would not affect the results

[2], Wide confidence interval, influenced by the small number of events; after calculating the risk difference, no difference is observed

[3], High proportion of participants discontinuing treatment

[4], Moderate heterogeneity (I^2 = 35%) and two studies' results were in opposite direction of effect

[5], Results were not different when considering the confidence intervals, but there was a tendency in six studies to be favorable to biosimilar and three to originator

[6], One study (Zhou 2020) has unclear allocation concealment, due to study's low weight, it was assumed not to affect the outcome

Table 3. Evidence profile and certainty of evidence of outcomes assessed for rituximab biosimilar compared to originator for diffuse large B-cell lymphoma and follicular lymphoma

Outcomes	Certainty assessment						N of participants		Effect	Certainty
	N. of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Biosimilar	Originator	Relative [95% CI]	
Overall survival	1	Not serious[1]	Not serious	Not serious	Not serious	None	312	315	HR 0.77 [0.45, 1.32)	High
Progression-free survival	3	Not serious[1]	Not serious	Not serious	Not serious	None	636	639	HR 1.33 [1.03, 1.71]	High
Event-free survival	1	Serious[2]	Not serious	Not serious	Not serious	None	122	117	HR 0.93 [0.66 , 1.32]	Moderate
Mortality	10	Not serious[1]	Not serious	Not serious	Not serious[3]	None	1284	1273	RR 0.97 [0.70 , 1.35]	High
Objective response	13	Not serious[1]	Not serious	Not serious	Not serious	None	1655	1686	RR 1,01 [0.98 , 1,03]	High
Duration of response	1	Not serious[1]	Not serious	Not serious	Not serious	None	196	198	HR 1.49 [0.82, 2.70]	High
Any adverse events (AE)	10	Not serious[1]	Not serious	Not serious	Not serious	None	1792	1797	RR 1.01 [0.99 , 1.03]	High
Serious AE	12	Not serious[1]	Not serious	Not serious	Not serious	None	1792	1797	RR 1.03 [0.92 , 1.14]	High
Antidrug antibodies	12	Not serious[1]	Not serious	Not serious	Not serious	None	1630	1648	RR 1.02 [0.77 , 1.37]	High
Neutralising antibodies	9	Not serious[1]	Not serious	Not serious	Not serious	None	1204	1232	RR 1.19 [0.40 , 3.55]	High

RCTs, randomised controlled trial; RR, risk ratio; HR, hazard ratio; CI, confidence interval

[1], Study limitations present in studies that contribute to the outcome would not affect the results

[2], Poor blinding of outcome assessment in the study (Cadelaria 2019)

[3], Wide confidence interval, influenced by the small number of events; after calculating the risk difference, no difference is observed

Table 4. Evidence profile and certainty of evidence of outcomes assessed for trastuzumab biosimilar compared to originator for metastatic or early breast cancer

Outcomes	Certainty assessment						N of participants		Effect	Certainty
	N. of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Biosimilar	Originator	Relative [95% CI]	
Overall survival	4	Not serious[1]	Not serious	Not serious	Not serious	None	1105	1116	HR 0.91 [0.75, 1.10]	High
Progression free survival	4	Not serious[1]	Not serious	Not serious	Not serious	None	1105	1116	HR 0.95 [0.82, 1.10]	High
Event-free survival	1	Not serious[1]	Not serious	Not serious	Not serious	None	437	438	HR 0.94 [0.59, 1.50]	High
Mortality	9	Not serious[1]	Not serious	Not serious	Not serious	None	2300	2245	RR 0.86 [0.69, 1.07]	High
Objective response	8	Not serious[1]	Not serious	Not serious	Not serious	None	1749	1690	RR 1.04 [1.01, 1.07]	High
Pathologic complete response	4	Not serious[1]	Serious[2]	Not serious	Not serious	None	1108	1080	RR 1.10 [0.93, 1.29]	Moderate
Duration of response	2	Not serious[1]	Not serious	Not serious	Not serious	None	520	510	HR 0.81 [0.65, 1.00]	High
Any adverse events (AE)	10	Not serious[1]	Not serious	Not serious	Not serious	None	2386	2333	RR 1.01 [1.00, 1.02]	High
Serious AE	9	Not serious[1]	Serious[3]	Not serious	Not serious	None	2304	2311	RR 0.95 [0.80, 1.14]	Moderate
Antidrug antibodies	8	Not serious[1]	Not serious	Not serious	Not serious	None	2217	2221	RR 0.97 [0.52, 1.82]	High
Neutralising antibodies	8	Not serious[1]	Not serious	Not serious	Not serious	None	2217	2220	RR 0.92 [0.37, 2.33]	High

RCTs, randomised controlled trial; RR, risk ratio; HR, hazard ratio; CI, confidence interval

[1], Study limitations present in studies that contribute to the outcome would not affect the results

[2], Substantial heterogeneity (I^2 = 63%)

[3], Moderate heterogeneity (I^2 = 33%) and studies' effect in opposite direction

Time-to event outcomes (survival outcomes)

Survival outcomes were polled based on the HR and CI as reported by studies. Only unadjusted HR would be adequate for this polled analysis, but data were mainly reported in included studies from adjusted analysis. We have presented all the available results in meta-analysis as informative data. After classification of outcomes' relevance, we will keep only more relevant outcomes based on results from unadjusted analyses

Overall survival

Bevacizumab biosimilar was similar on overall survival, compared to originator for lung and colorectal cancer (HR 1.06; 95% CI 0.96 to 1.18; I^2=35%; 9 RCTs; 5,862 participants; low-certainty evidence; **Figure 4**), only one study (112) with 677 participants diagnosed with metastatic or recurrent colorectal cancer was included in the pooled analysis. As the outcome is not affected by blinding of participants or outcome assessors, therefore performance and detection bias were disregarded. We downgraded the certainty of evidence by two levels for study limitations and inconsistency.

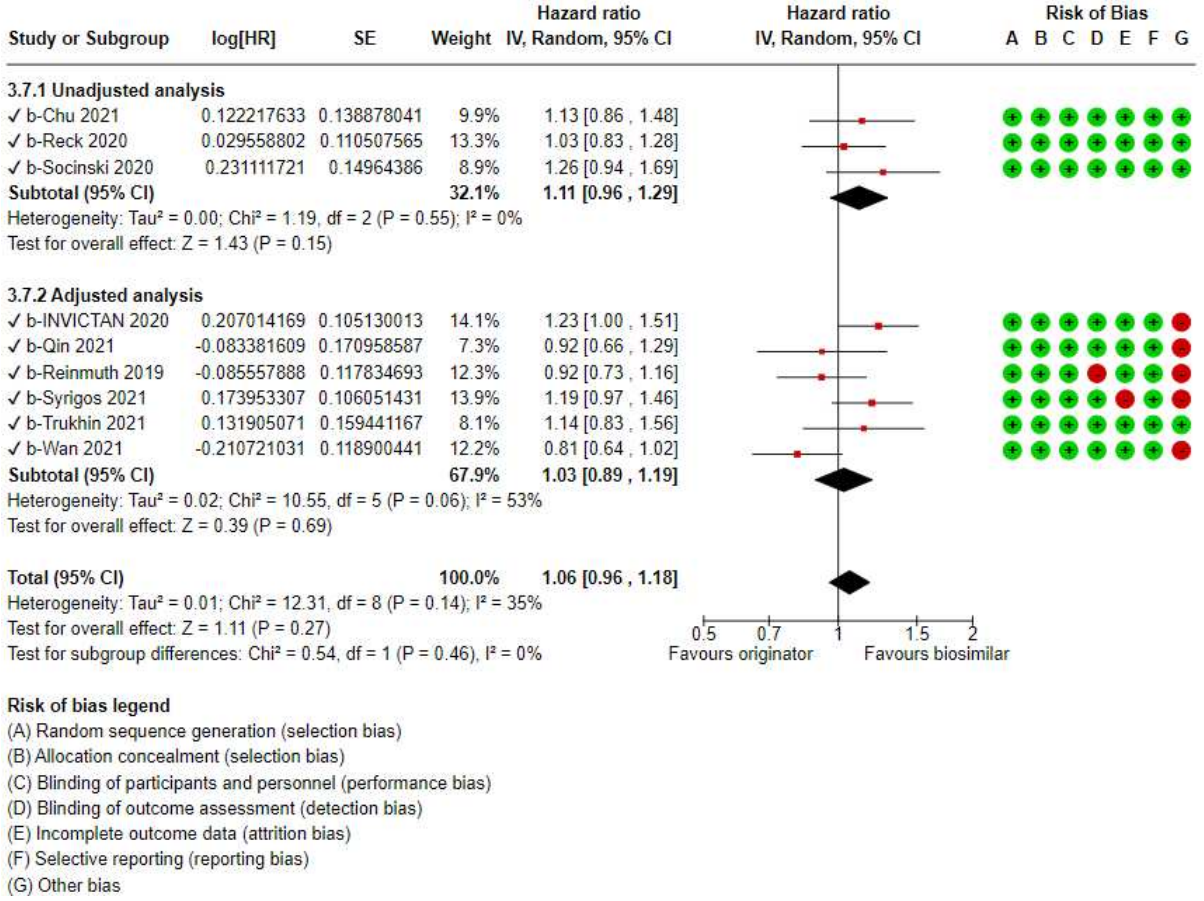


Figure 4. Analysis of overall survival comparing bevacizumab biosimilar and originator

Rituximab biosimilar was similar on overall survival, compared to originator for follicular lymphoma (HR 0.77; 95% CI 0.45 to 1.32; 1 RCT (98); 629 participants; high-certainty evidence; Figure 5).

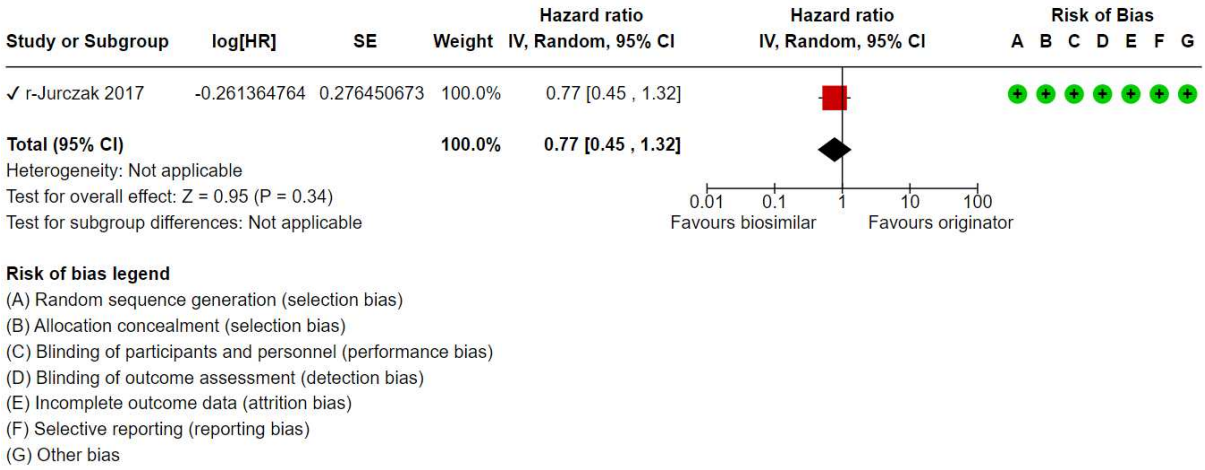


Figure 5. Analysis of overall survival comparing rituximab biosimilar and originator

Meta-analysis of four studies assessing 549 participants with early breast cancer (105) and 1,814 participants with advanced or metastatic breast cancer (107, 108, 122) totalizing 2,363 participants, demonstrating similarity in overall survival between trastuzumab biosimilar and originator (HR 0.91; 95% CI 0.75 to 1.10; 4 studies; I^2=0%, high-certainty evidence;Figure 6).

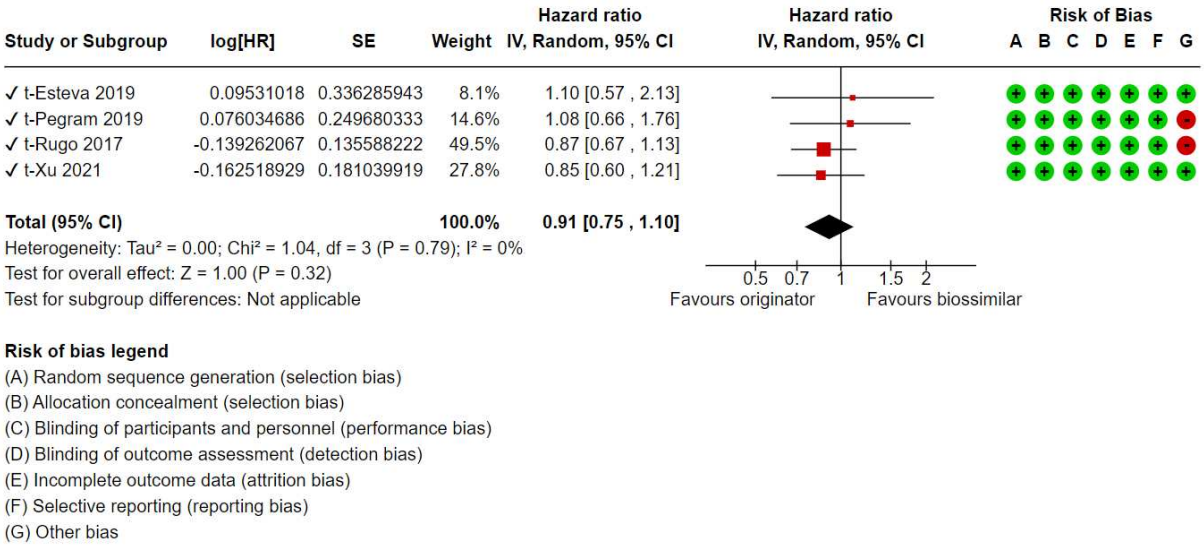


Figure 6. Analysis of overall survival comparing trastuzumab biosimilar and originator

Progression-free survival

Meta-analysis of nine studies (90-92, 95, 96, 111, 112, 114), assessing 6,484 participants, demonstrated similarity in progression free survival between bevacizumab biosimilar and originator for lung and colorectal cancer (HR 1.05; 95% CI 0.99 to 1.13; I^2=7%, moderate-certainty evidence; **Figure 7**). We downgraded the certainty of evidence due to high risk of other bias (discontinuation of treatment) in five studies (90, 112).

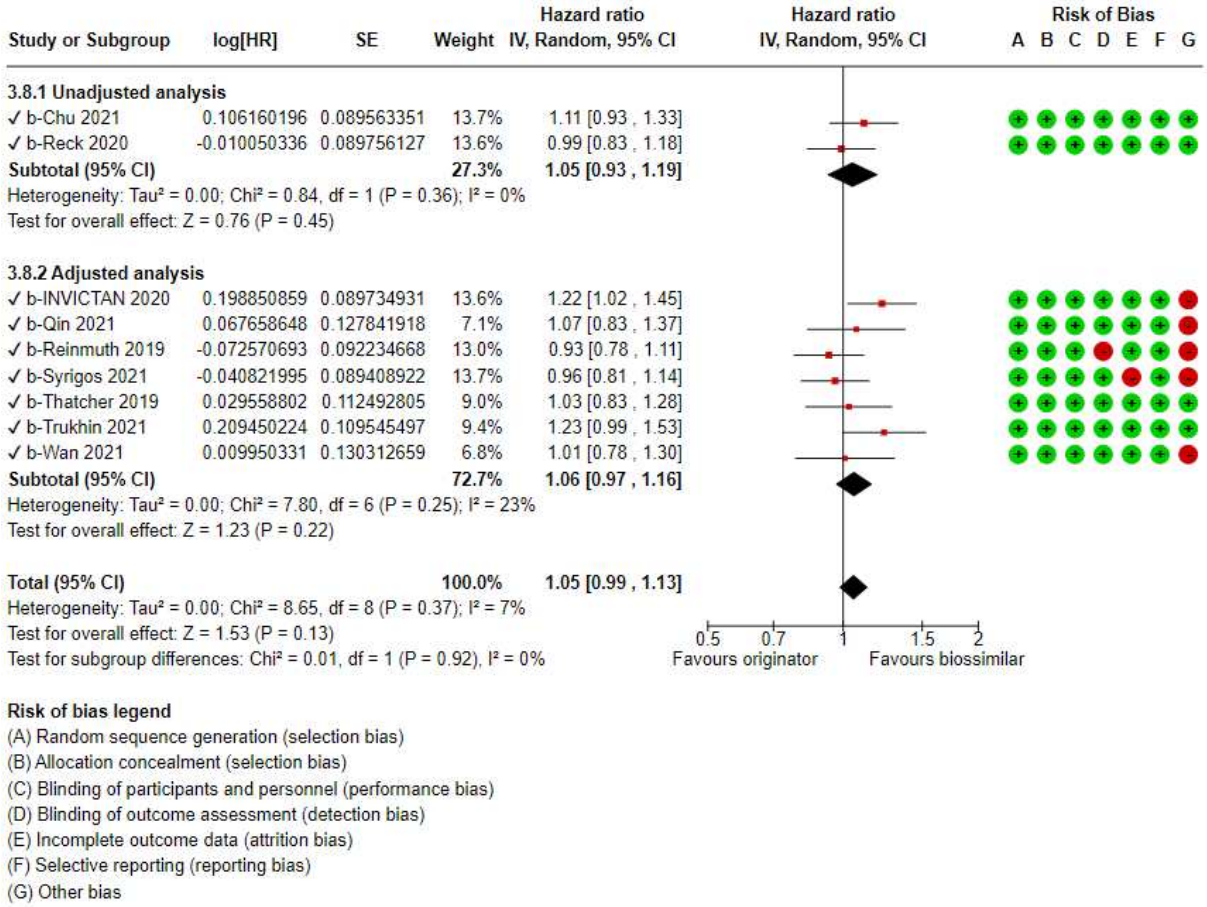


Figure 7. Analysis of progression-free survival comparing bevacizumab biosimilar and originator

Meta-analysis of three studies (98, 100, 103) assessing 1,279 participants with follicular lymphoma, showed a slight superiority of rituximab biosimilar in progression-free survival compared to originator (HR 1.33; 95% CI 1.03 to 1.71; I^2=0%; 3 RCTs; high-certainty evidence; **Figure 8**).

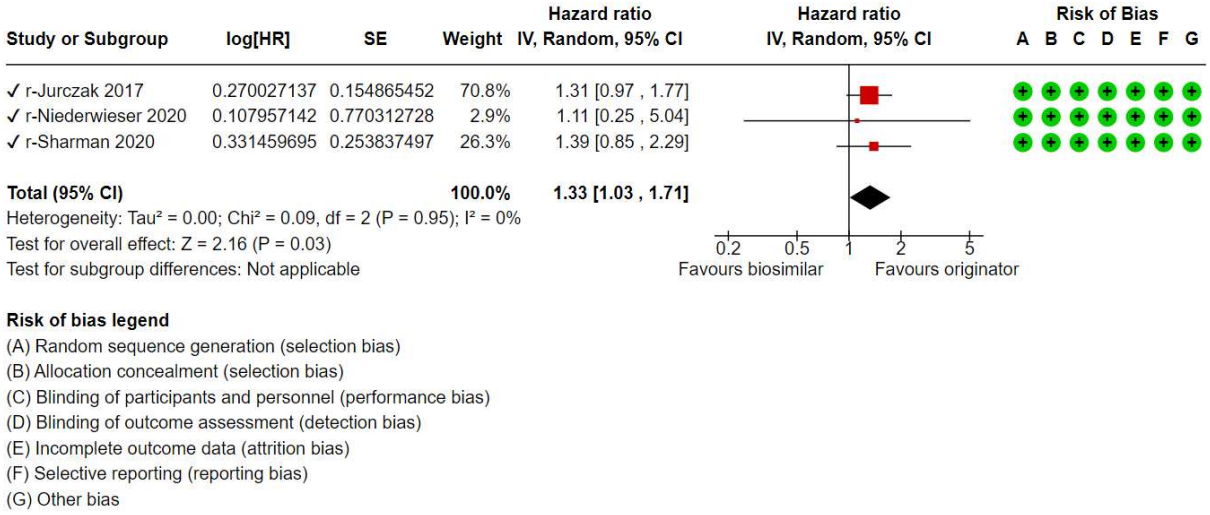


Figure 8. Analysis of progression-free survival comparing rituximab biosimilar and originator

Trastuzumab biosimilar was similar to originator on progression-free survival for early (105) or metastatic (107, 108, 122) breast cancer (HR 0.95; 95% CI 0.82 to 1.10; I^2=21%; 4 RCTs; 2,363 participants; high-certainty evidence; **Figure 9**).

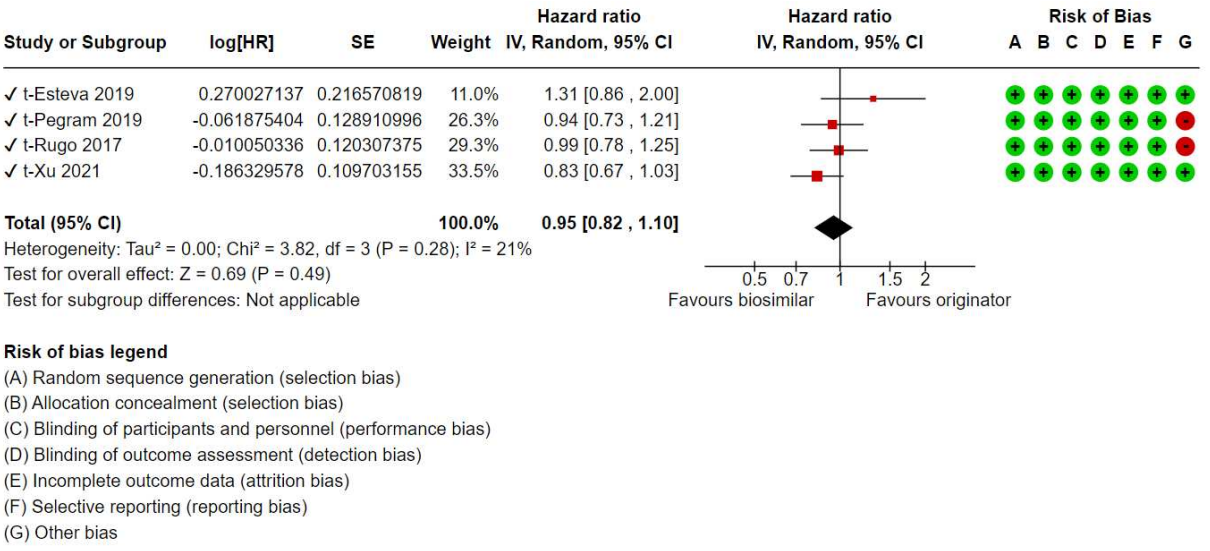


Figure 9. Analysis of progression-free survival comparing trastuzumab biosimilar and originator

Event-free survival

Rituximab biosimilar was similar on event-free survival, compared to originator for diffuse large B-cell lymphoma and follicular lymphoma (HR 0.93; 95%

CI 0.66 to 1.32; 1 RCT; 272 participants; moderate-certainty evidence; **Figure 10** a). We downgraded the certainty of evidence by one level due to absent of blinding of outcome assessment.

Trastuzumab biosimilar was similar on event-free survival, compared to originator for breast cancer (HR 0.94; 95% CI 0.78 to 1.50; I^2=0%; 1 RCT; 875 participants; high-certainty evidence; **Figure 10** b).

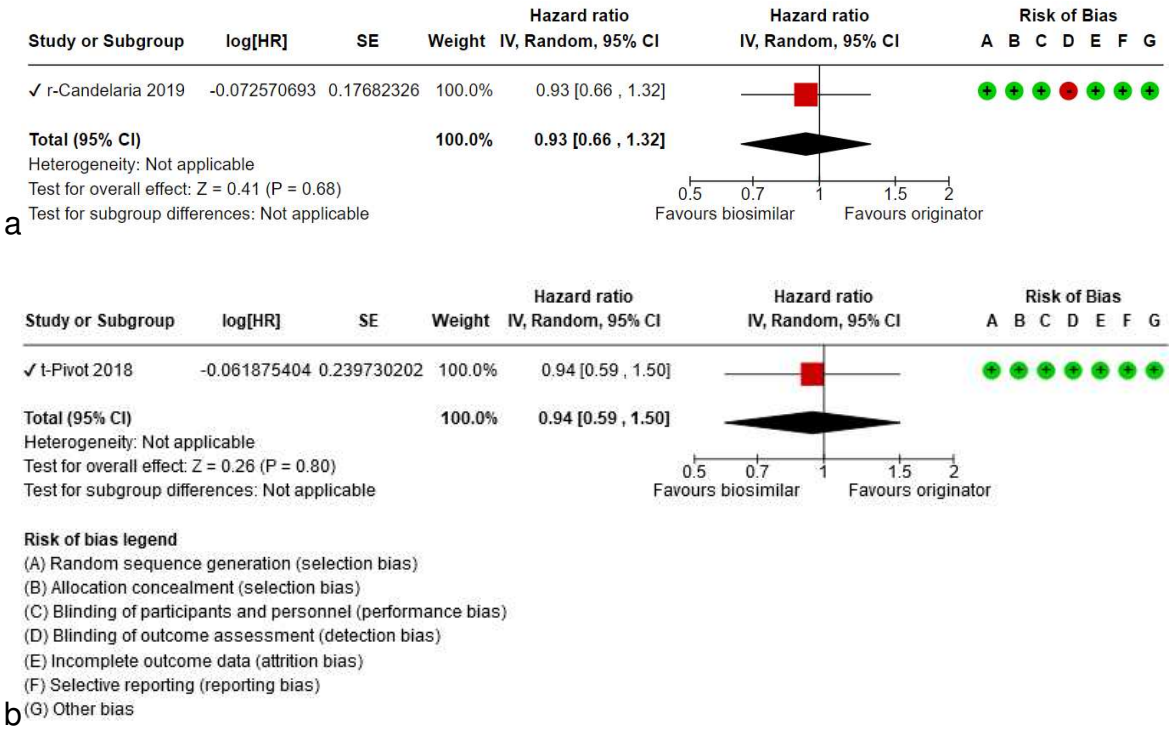


Figure 10. Analysis of event-free survival comparing rituximab (a) and transtuzumab (b) biosimilar and originator

Mortality

Thirty-six studies reported mortality and were included in the analysis. It was observed similar rate between participants treated with biosimilar and originator of bevacizumab (RR 1.04; 95% CI 0.98 to 1.10; I^2=0%; 17 RCTs; 8,762 participants; high-certainty evidence; **Figure 11**), rituximab (RR 0.97, 95% CI 0.70 to 1.35; I^2=0%; 10 RCTs; 2,557 participants; high-certainty evidence; **Figure 12**), and trastuzumab (RR 0.86; 95% CI 0.69 to 1.07; I^2=0%; 9 RCTs; 4,545 participants; high-certainty evidence; **Figure 13**). Publication bias was not suspected from the symmetry

observed in the funnel plots of bevacizumab and rituximab comparisons for this outcome (**Figure 14**).

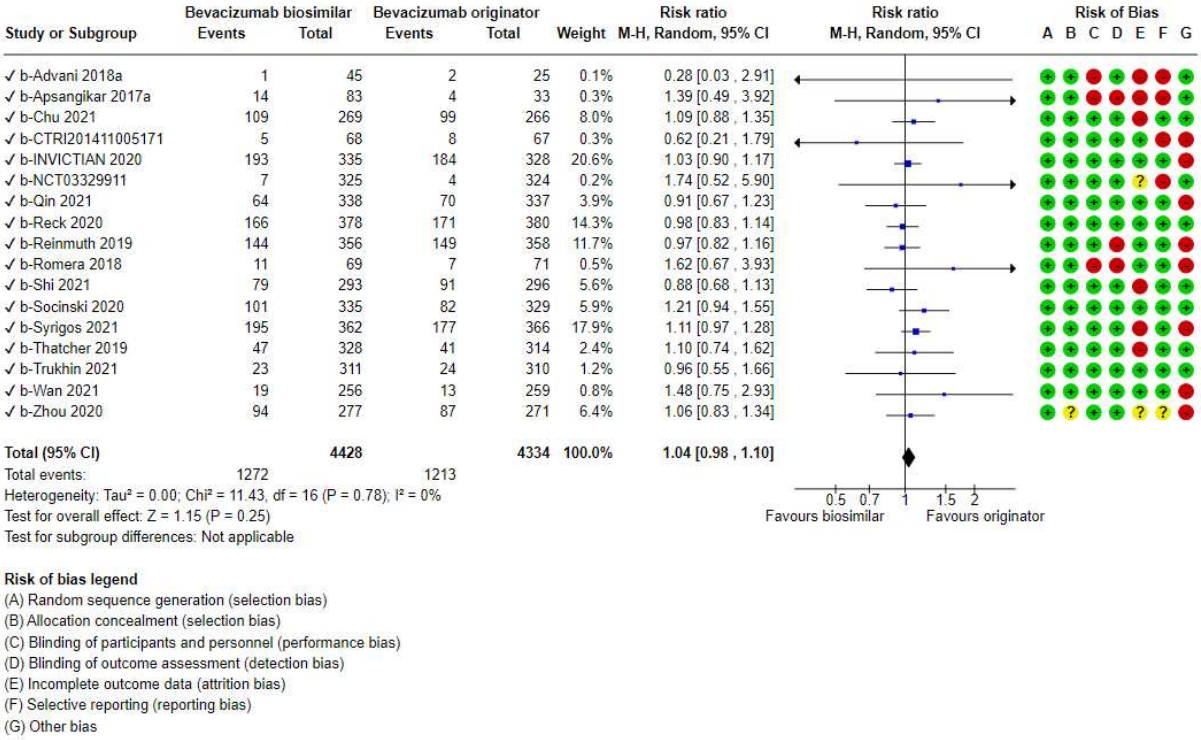


Figure 11. Analysis of mortality comparing bevacizumab biosimilar and originator

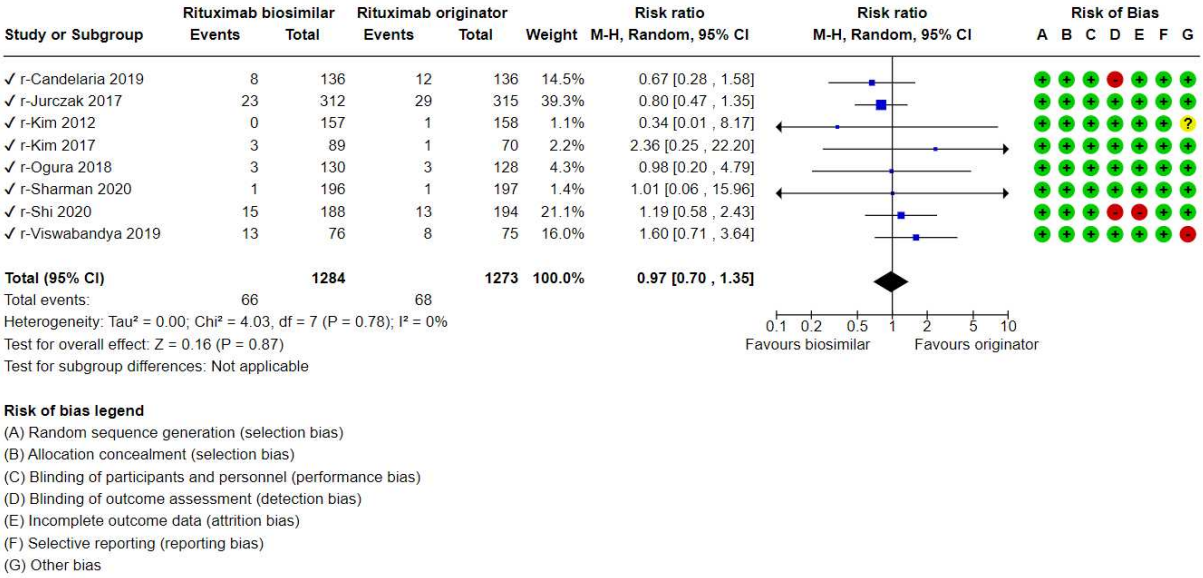


Figure 12. Analysis of mortality comparing rituximab biosimilar and originator

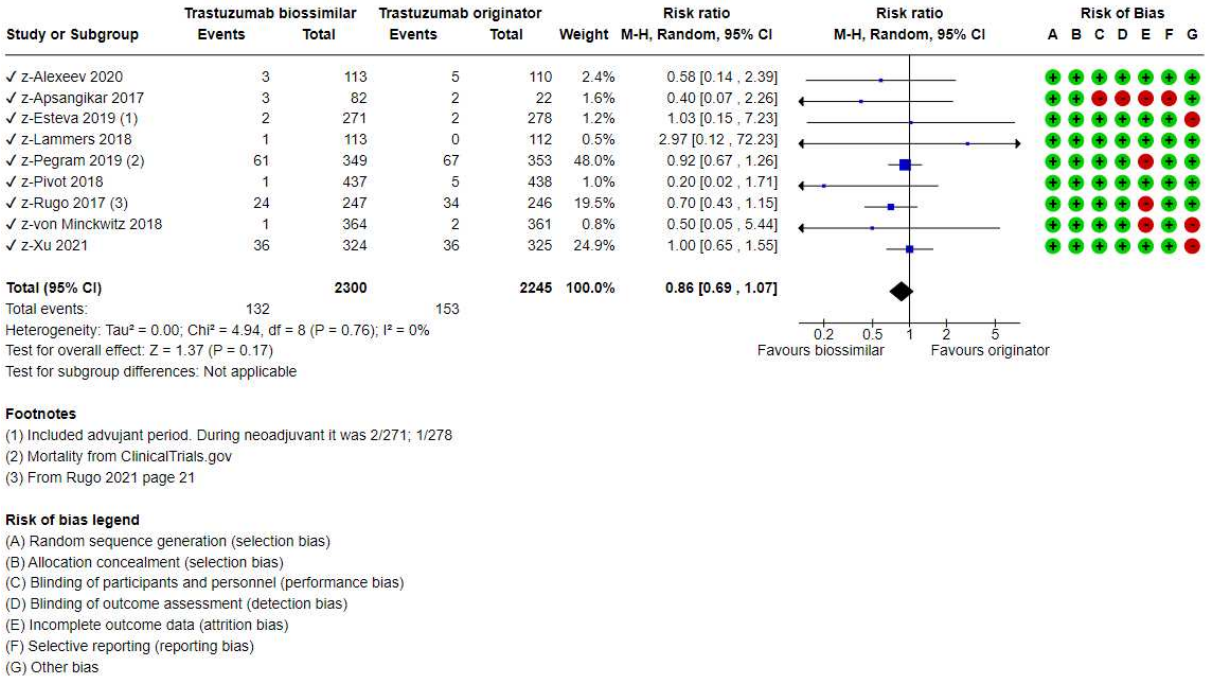


Figure 13. Analysis of mortality comparing trastuzumab biosimilar and originator

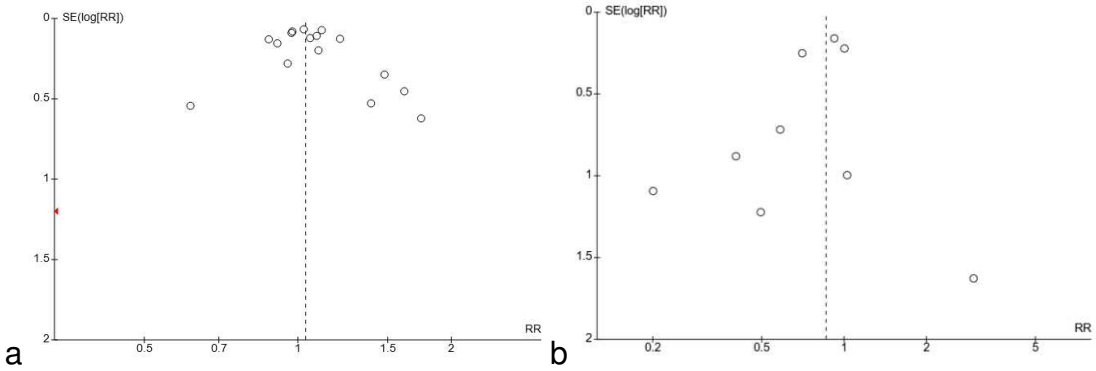


Figure 14. Dispersion of risk ratio (RR) of mortality according to the standard error (SE) of RR in logaritim (precision of the study) for the comparisons of bevacizumab (a) and rituximab (b) biosimilar and originator groups

Objective response rate

This outcome was defined as the proportion of complete or partial response, a synonym of overall response rate (65, 126). In addition, Niederwieser 2020 (100), Ogura 2018 (101) and Song 2021 (118)—studies that assessed

rituximab—included unconfirmed complete response. Eighteen trials reported results according to per protocol analysis, six trials according to ITT analysis, and eight trials according to both. Three studies reported results as full analysis (FAS), modified ITT or PP and FAS. Thirty-three studies (77%) used an independent blinded outcome assessor and assessed as per RECIST criteria.

Objective response data were assessed as primary endpoint and available for all 35 trials (81%) included, with 7,916 participants in the 15 trials with bevacizumab, 3,612 participants included in the 13 trials with rituximab, and 3,128 participants in the seven trials with trastuzumab.

Bevacizumab originator had similar objective response than bevacizumab originator (risk ratio [RR] 0.96, 95% confidence interval [CI] 0.92 to 1.00; I^2 = 0%; 19 RCTs, 9,048 participants; high-certainty evidence; Figure 15). Most of the studies assessed this outcome in a medium-term (> 12 to ≤ 48 weeks). Only three trials (93, 117, 124) assessed in a long-term (>48 weeks). The dispersion of results in this outcome were symmetrical in the funnel plot, evidence was not downgraded for publication bias in other considerations in certainty assessment (**Figure 16**).

The rate of complete (RR 1.47, 95% CI 0.81 to 2.66; I^2 = 0%; 15 RCTs, 7,148 participants; high-certainty evidence; **Figure 17**) and partial (RR 0.97, 95% CI 0.93 to 1.02; I^2 = 0%; 15 RCTs, 7,148 participants; high-certainty evidence; **Figure 18**) responses was similar among the groups.

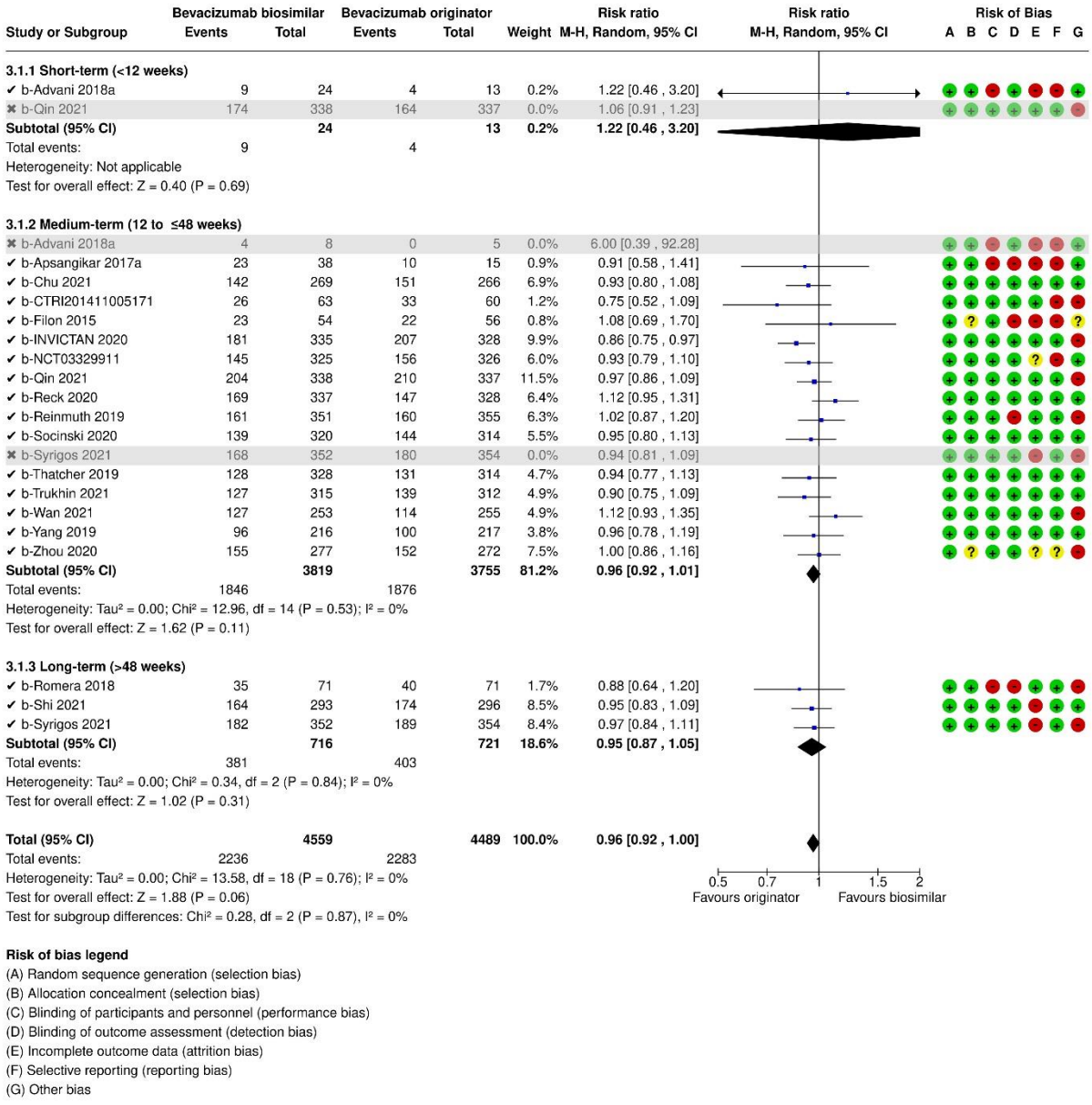


Figure 15. Analysis of objective response rate comparing bevacizumab biosimilar and originator

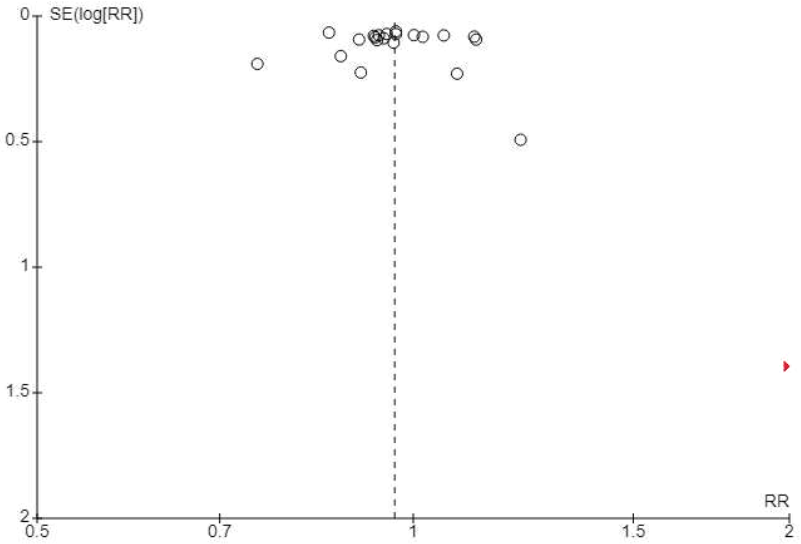


Figure 16. Dispersion of risk ratio (RR) of objective response from bevacizumab biosimilar compared to originator according to the standard error (SE) of RR in logarithm (precision of the study)

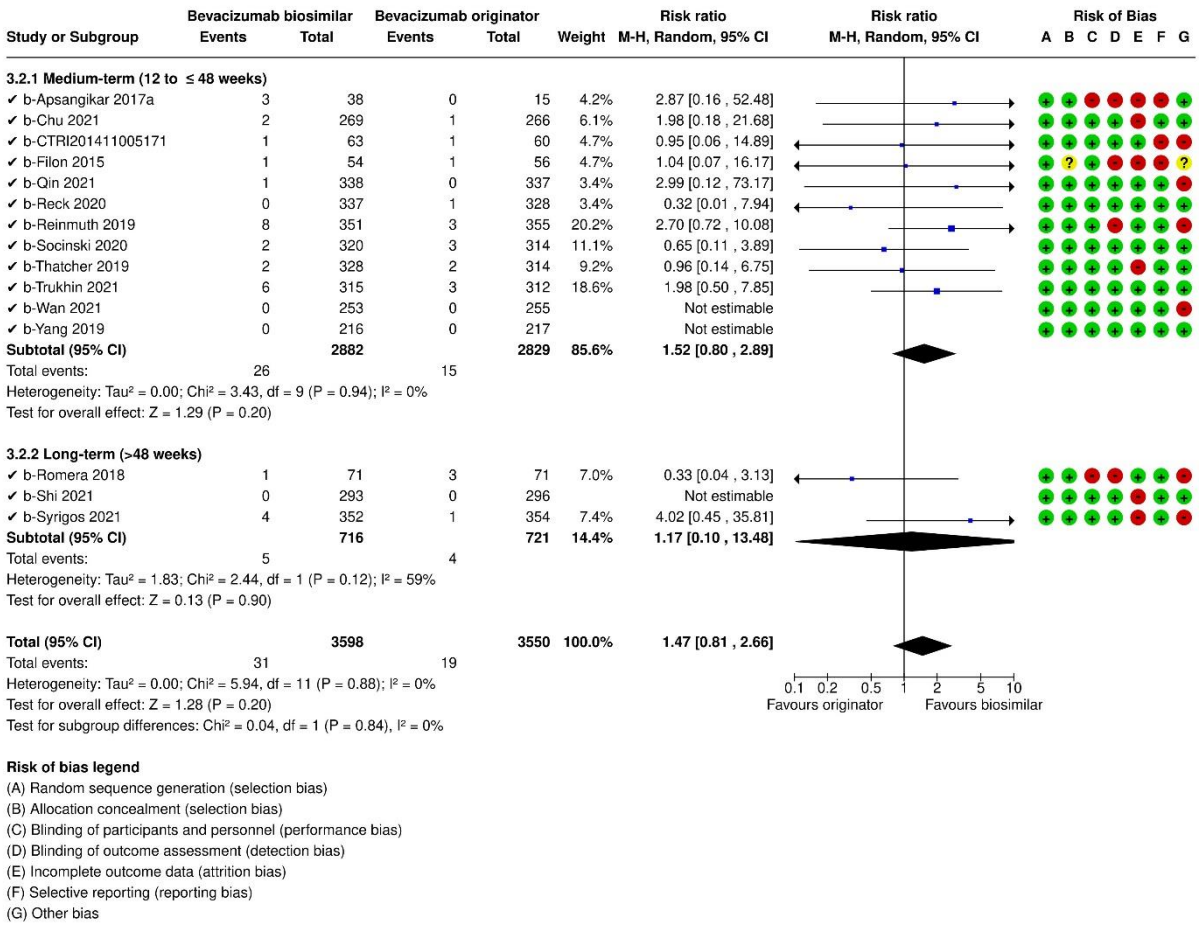


Figure 17. Analysis of complete response rate comparing bevacizumab biosimilar and originator

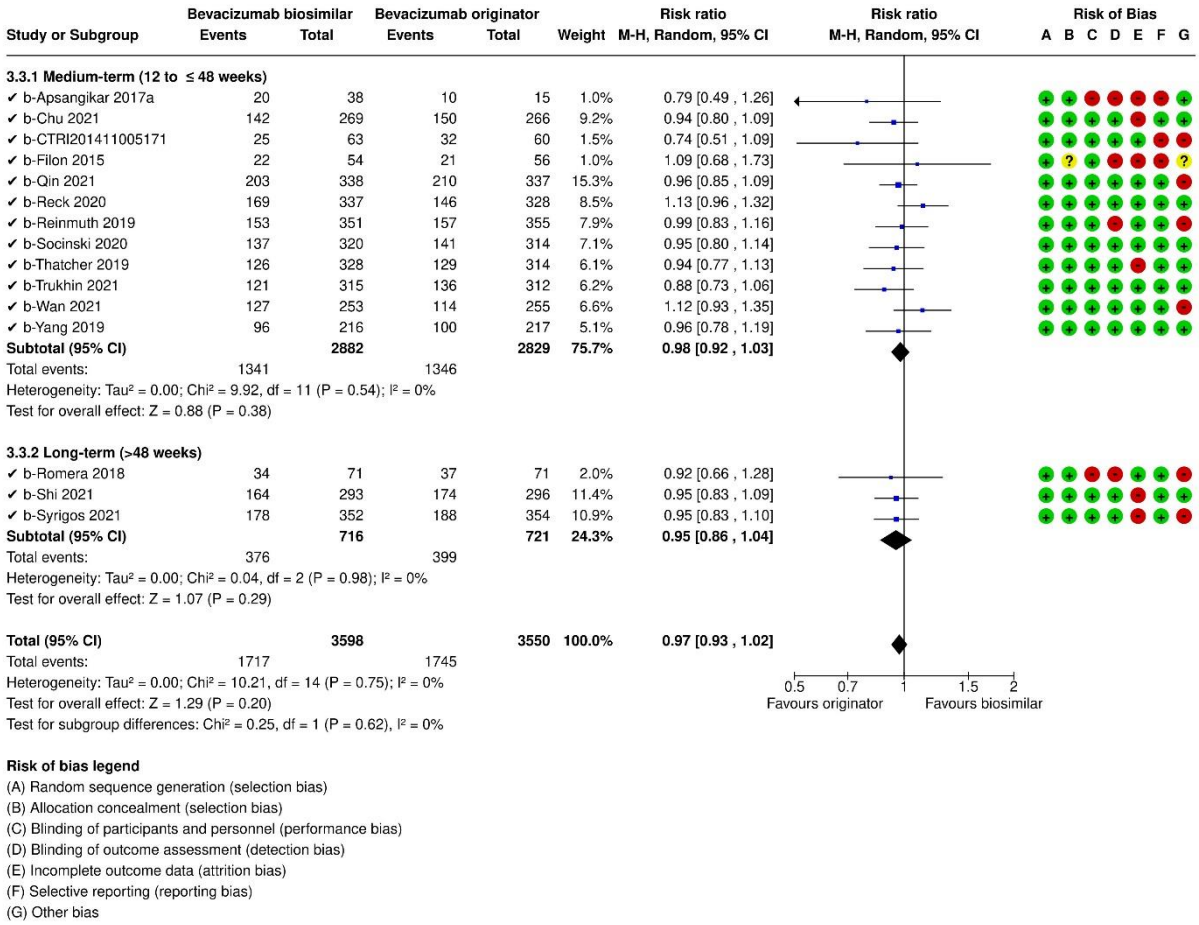


Figure 18. Analysis of partial response rate comparing bevacizumab biosimilar and originator

In the same way, rituximab biosimilar and their correspondent originator obtained a similar objective response (RR 1.01; 95% CI=0.98 to 1.03; I^2= 0%; 13 RCTs; 3,341 participants; high-certainty evidence; **Figure 19**), complete (RR 1.01; 95% CI 0.92 to 1.11; I^2= 0%; 13 RCTs; 3,344 participants; high-certainty evidence; **Figure 20**) and partial (RR 1.01; 95% CI 0.92 to 1.11; I^2= 0%; 13 trials; 3,344 participants; high-certainty evidence; **Figure 21**) responses. Most of the studies assessed this outcome in a medium-term (> 12 to ≤ 48 weeks). Distribution of studies' results in objective response in the comparison of rituximab biosimilar and originator was symmetrical and publication bias was not suspected for this outcome (**Figure 22**).

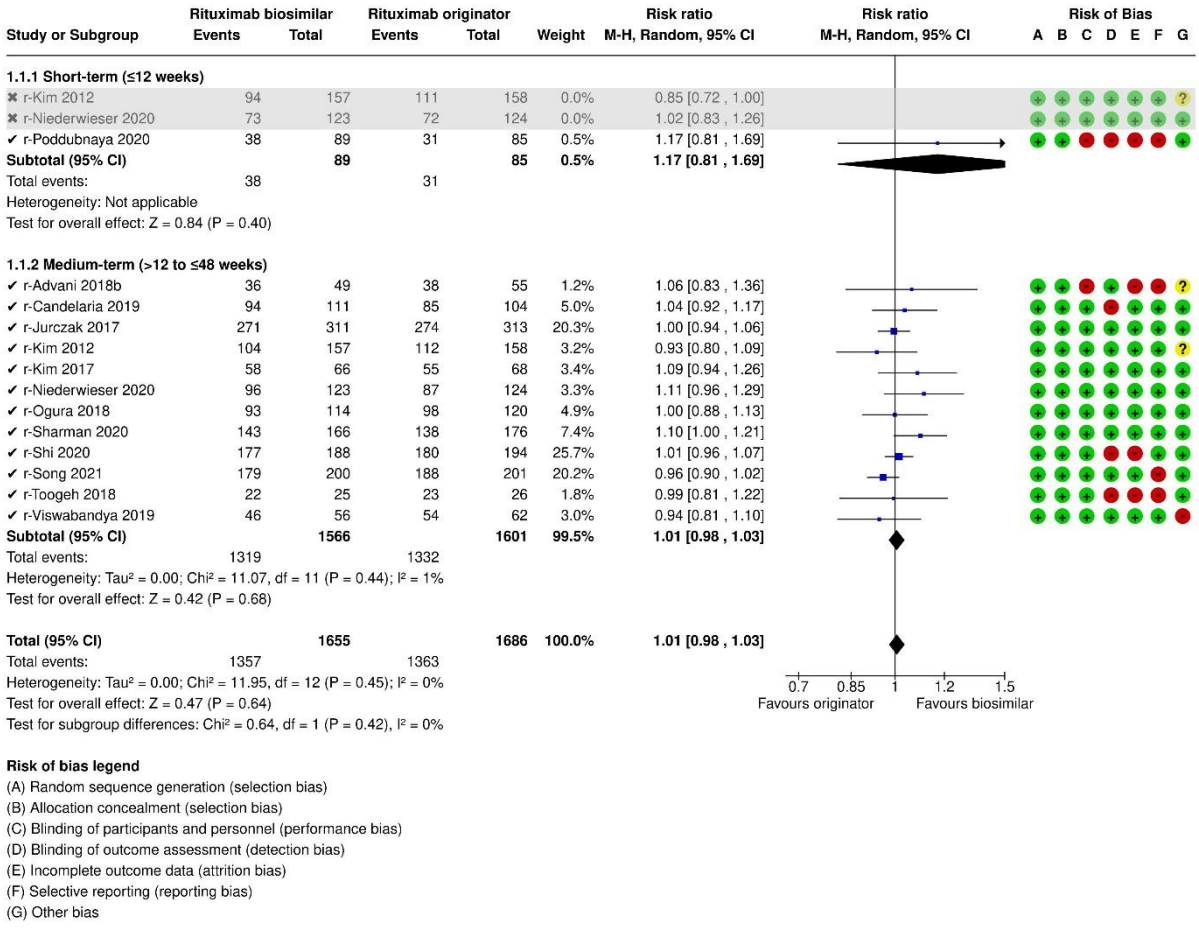


Figure 19. Analysis of objective response rate comparing rituximab biosimilar and originator

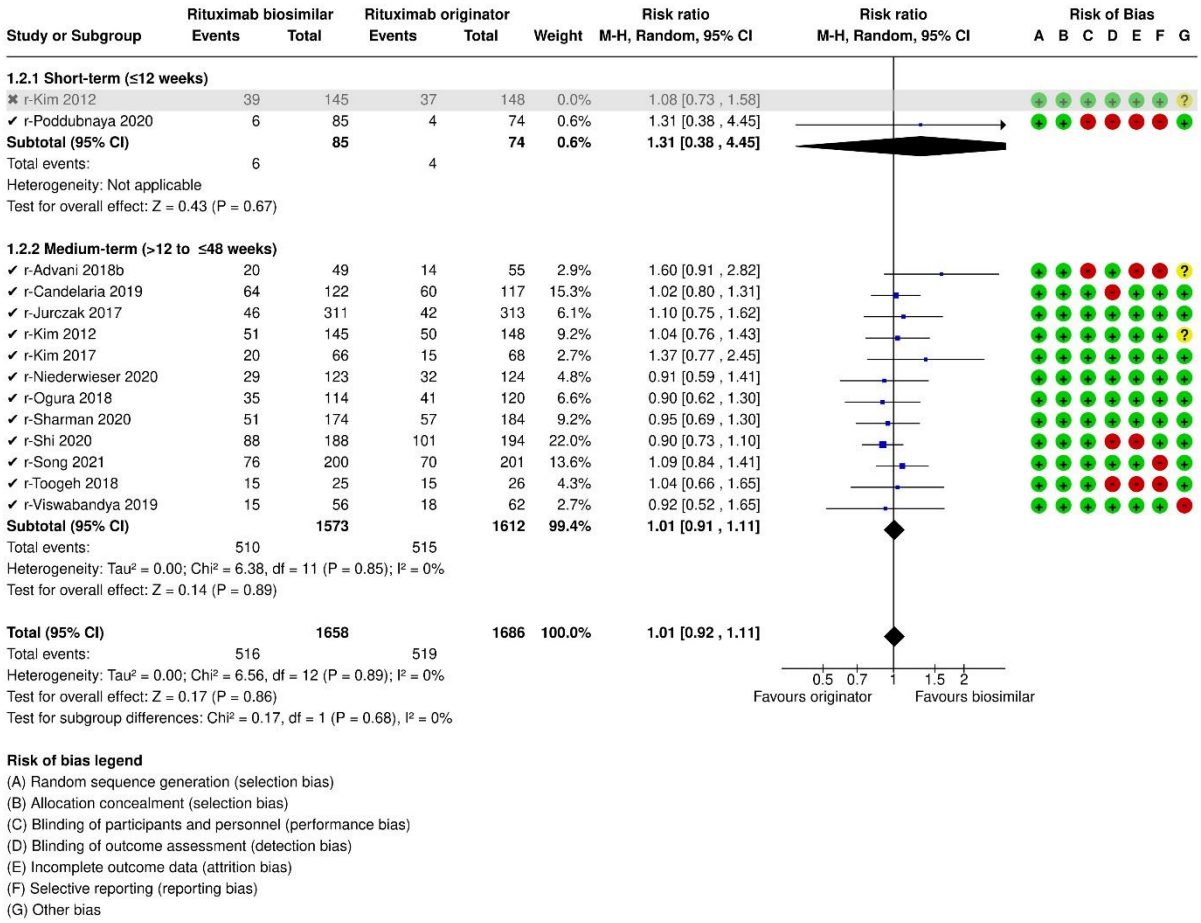


Figure 20. Analysis of complete response rate comparing rituximab biosimilar and originator

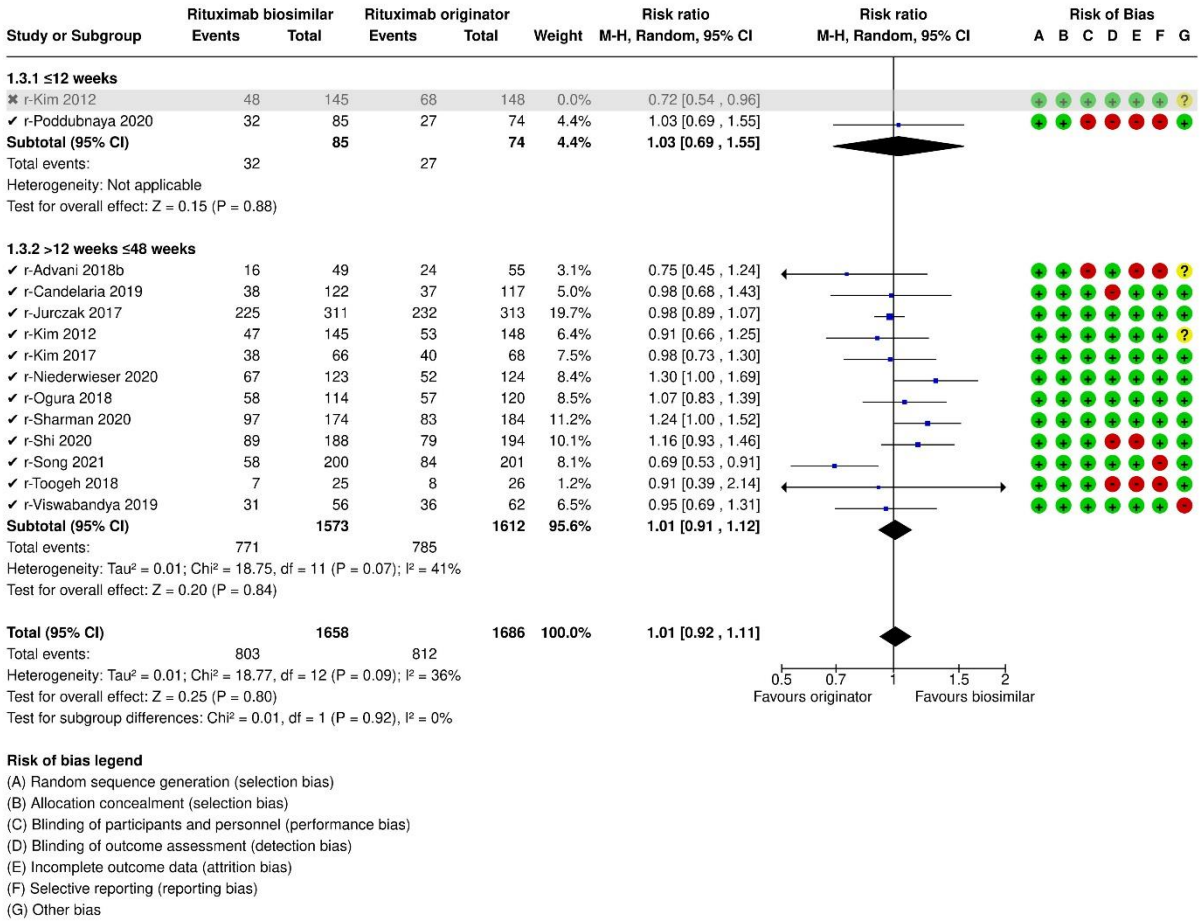


Figure 21. Analysis of partial response rate comparing rituximab biosimilar and originator

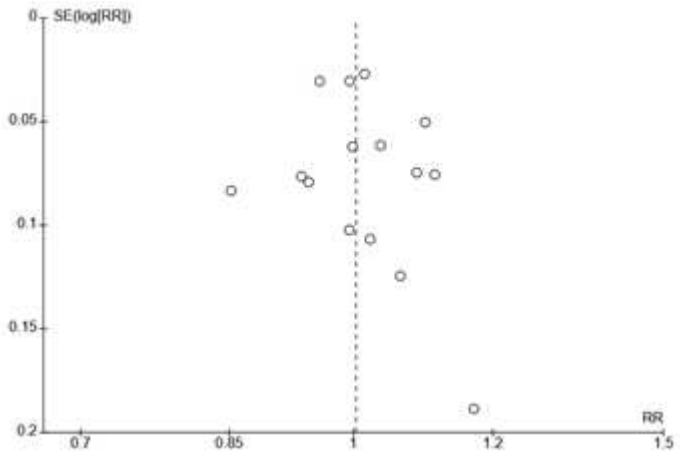


Figure 22. Dispersion of risk ratio (RR) of objective response from rituximab biosimilar compared to originator according to the standard error (SE) of RR in logarithm (precision of the study)

Objective response was slightly superior in trastuzumab biosimilar in comparison to its originator (RR 1.04; 95% CI 1.01 to 1.07; I^2 = 0%, 8 RCTs; 3,439 participants; high-certainty evidence; **Figure 23**), and no significant difference was observed in complete (RR 1.29; 95% CI 0.79 to 2.10; I^2 = 0%, 6 RCTs; 2,135 participants; high-certainty evidence; **Figure 24**) and partial (RR 1.01; 95% CI 0.95 to 1.07; I^2 = 0%, 6 RCTs; 2,135 participants; high-certainty evidence; **Figure 25**) responses.

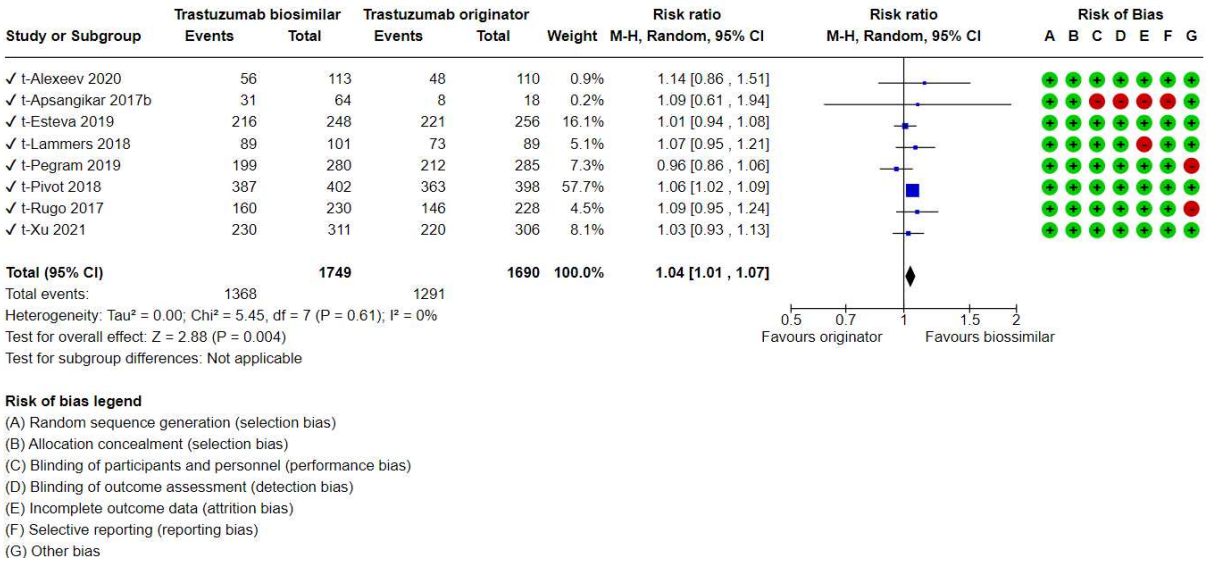


Figure 23. Analysis of objective response rate comparing trastuzumab biosimilar and originator

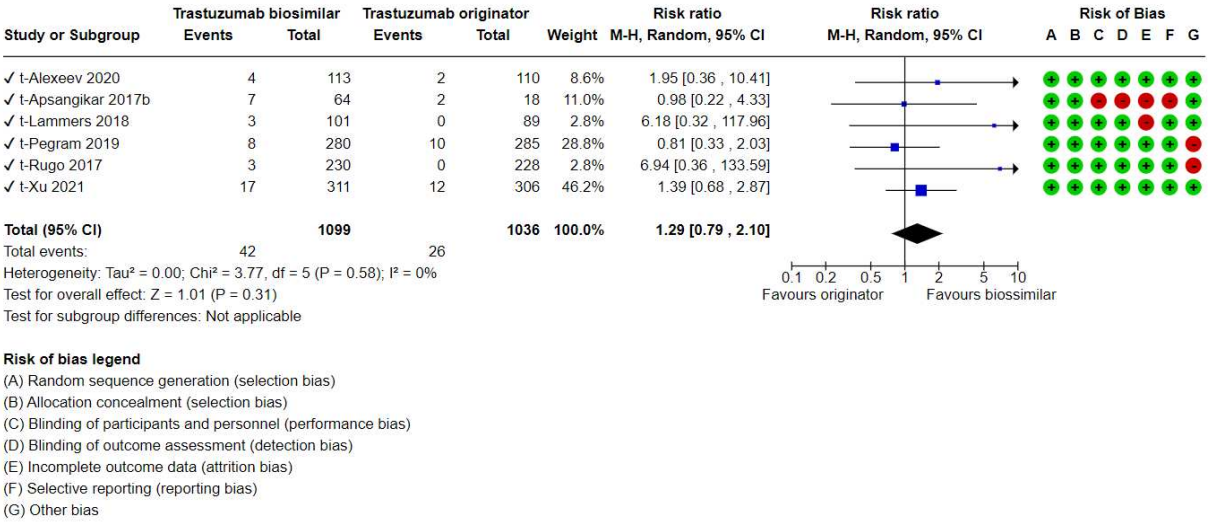


Figure 24. Analysis of complete response rate comparing trastuzumab biosimilar and originator

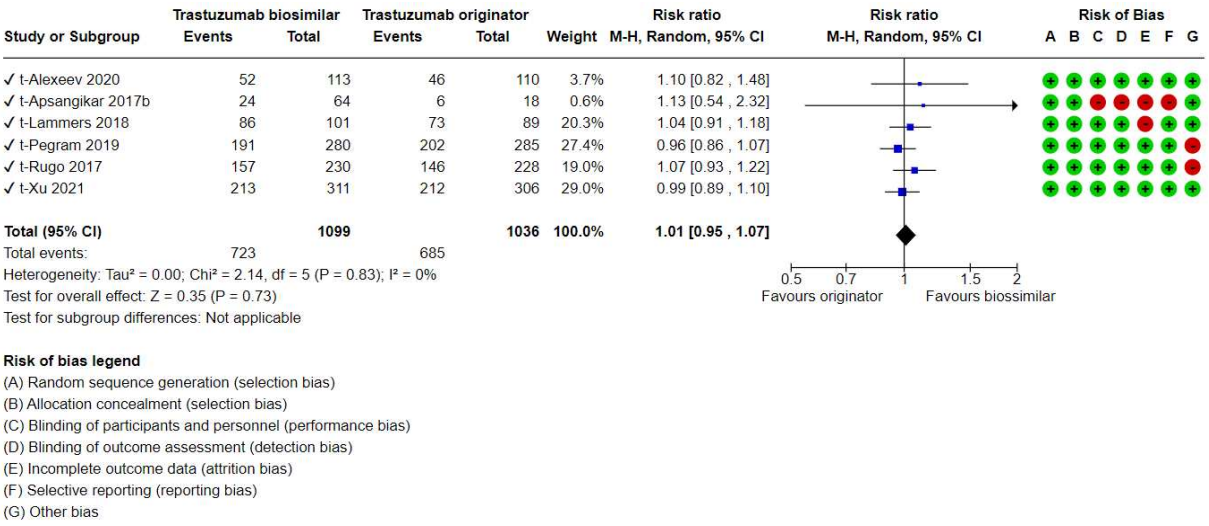
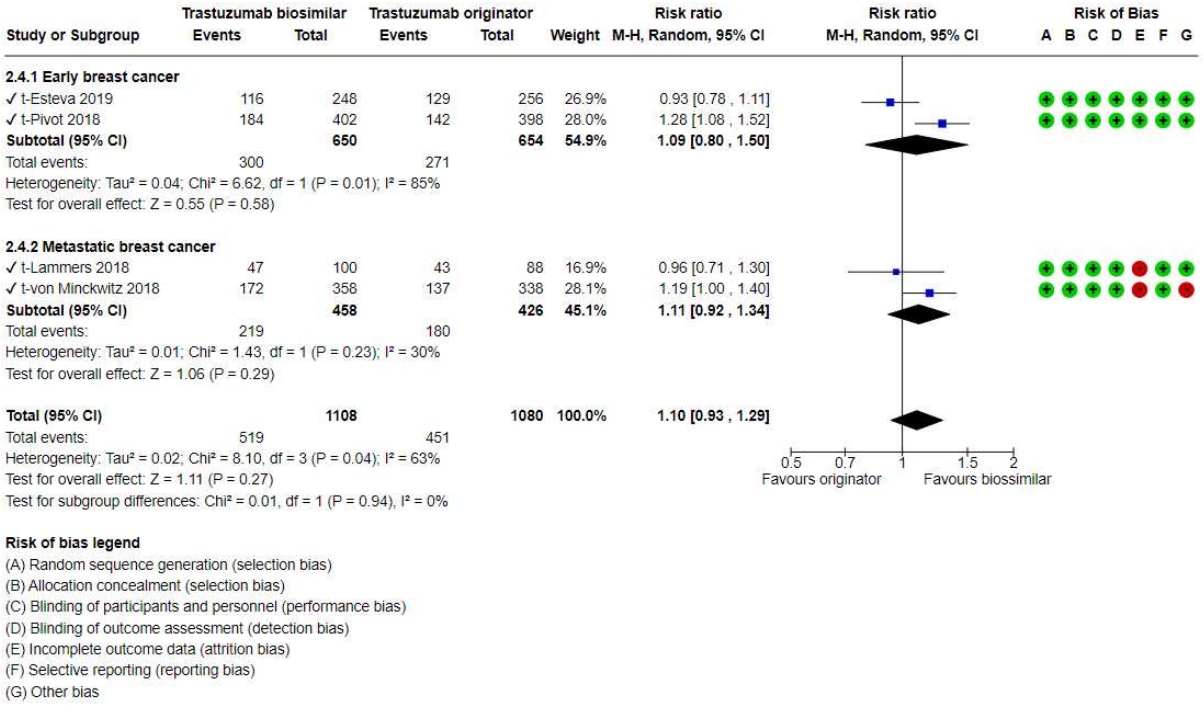


Figure 25. Analysis of partial response rate comparing trastuzumab biosimilar and originator

Pathological complete response in neoadjuvant treatment

Pathologic complete response (pCR) was assessed in four trials that compared trastuzumab (81, 105, 106, 127). In all of four trials it was defined as 'the absence of invasive tumor cells in the breast tissue removed at surgery and in axillary lymph nodes' and all of them included as primary endpoint and reported results according to per protocol analysis'. Only one study reported results according to both, ITT and PP. Esteva 2019 (105) and Pivot 2018 (49) included a total of 1,304 participants with early or locally advanced breast cancer, Lammers 2018 (106) and von Minckwitz 2018 (81) included a total of 884 participants with invasive breast cancer. pCR was similar in trastuzumab biosimilar and originator's group (RR 1.10; 95% CI 0.93 to 1.29; I^2 = 63%, 4 RCTs; 2,188 participants; moderate-certainty

evidence; Figure 26



). Certainty was downgraded due to inconsistency.

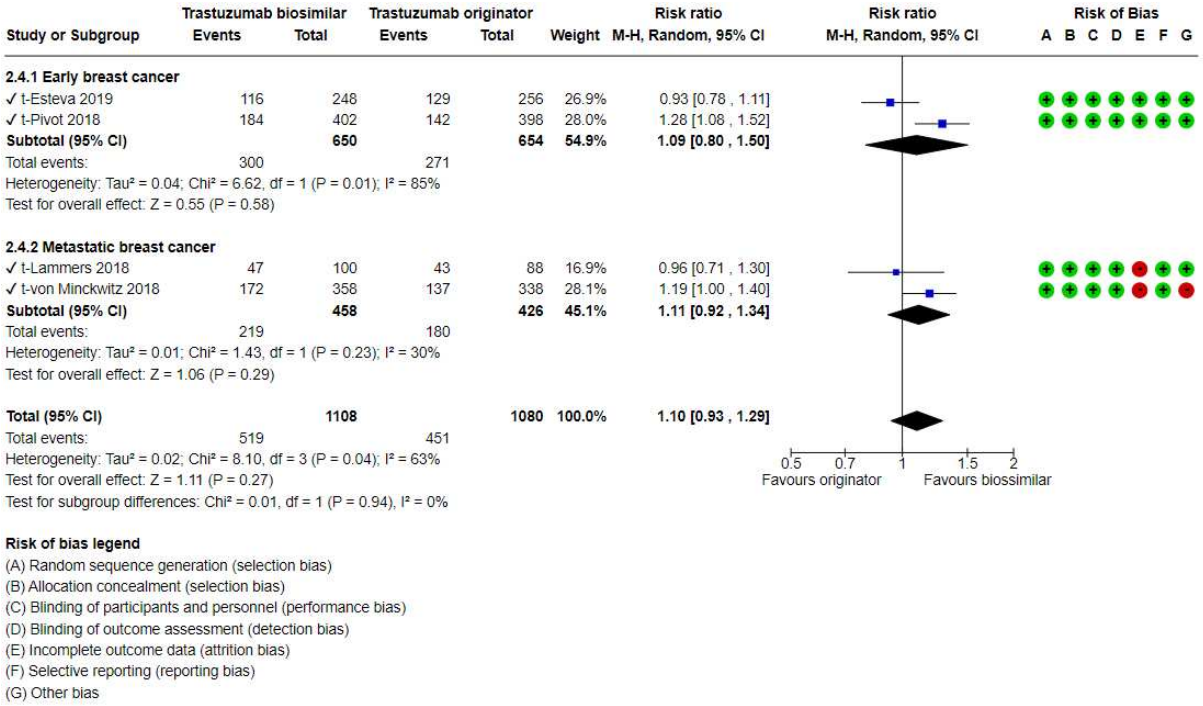


Figure 26. Analysis of pathological complete response in neoadjuvant setting comparing trastuzumab biosimilar and originator

Duration of response

Bevacizumab biosimilar was similar on duration of response, compared to originator for lung and colorectal cancer (HR 1.10; 95% CI 0.96 to 1.25; I^2=0%; 4 studies; 1,722 participants; moderate-certainty evidence;**Figure 27**). We downgraded the certainty of evidence by one level for study limitations (high discontinuation of treatment).

Rituximab biosimilar was also similar on duration of response, compared to originator for follicular lymphoma (HR 1.49; 95% CI 0.82 to 2.70; 1 RCT; 394 participants; high-certainty evidence;**Figure 28**).

Trastuzumab biosimilar was similar on duration of response, compared to originator for breast cancer (HR 0.81; 95% CI 0.65 to 1.00; I^2=0%; 2 RCTs (107, 122); 1,356 participants; high-certainty evidence;**Figure 29**).

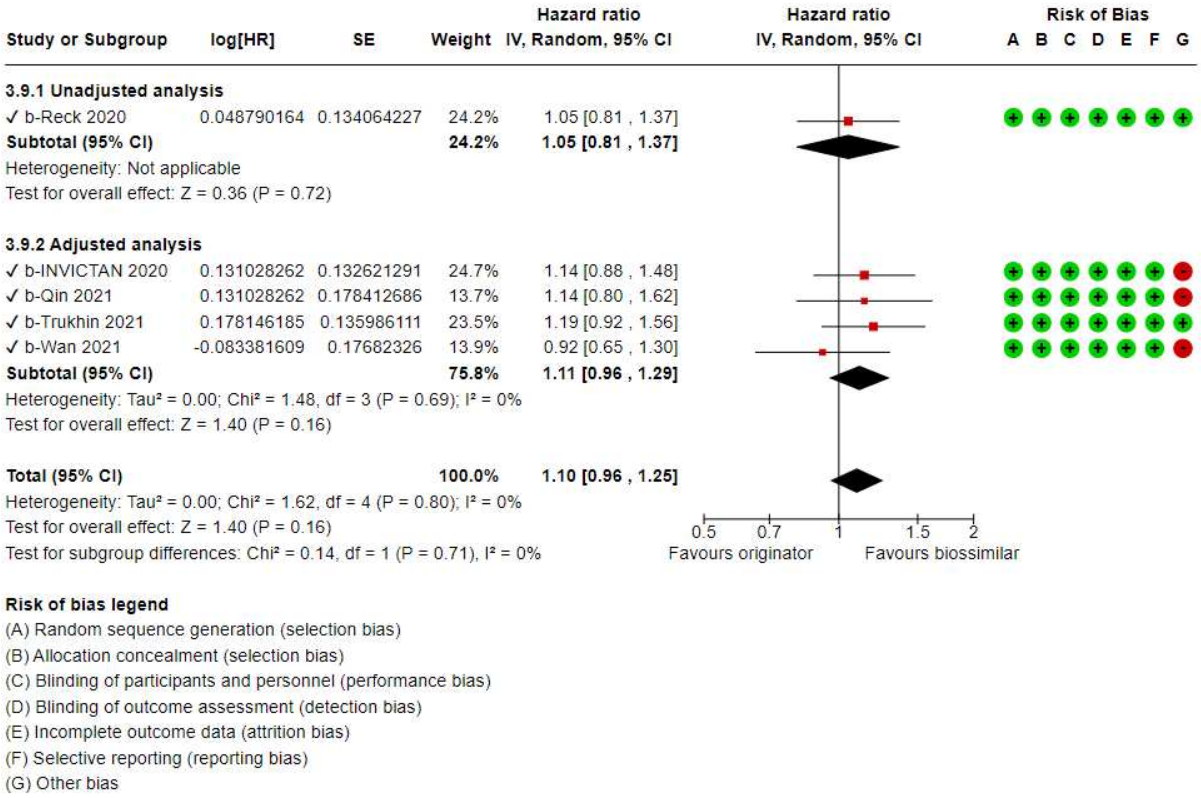


Figure 27. Analysis of duration of response comparing bevacizumab biosimilar and originator

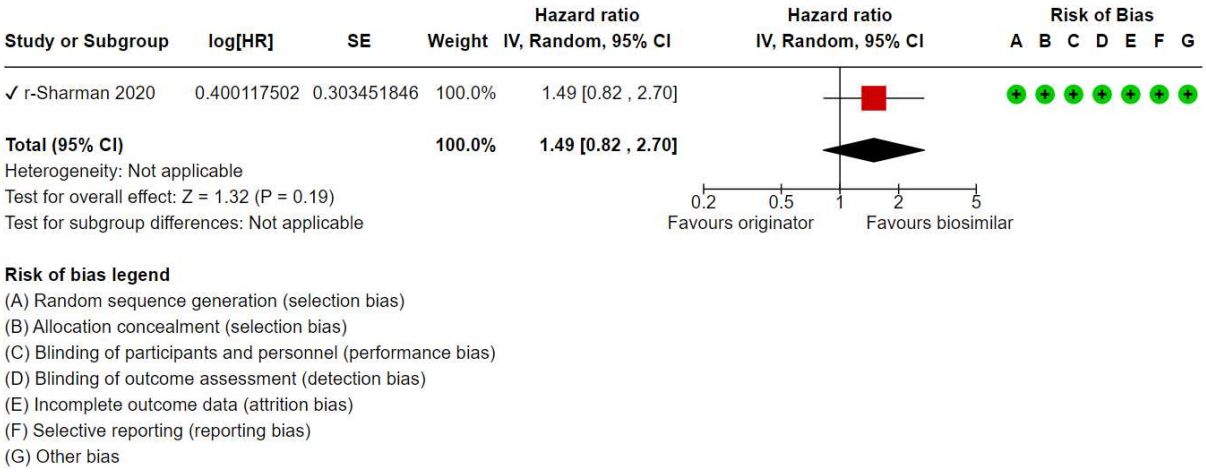


Figure 28. Analysis of duration of response comparing rituximab biosimilar and originator

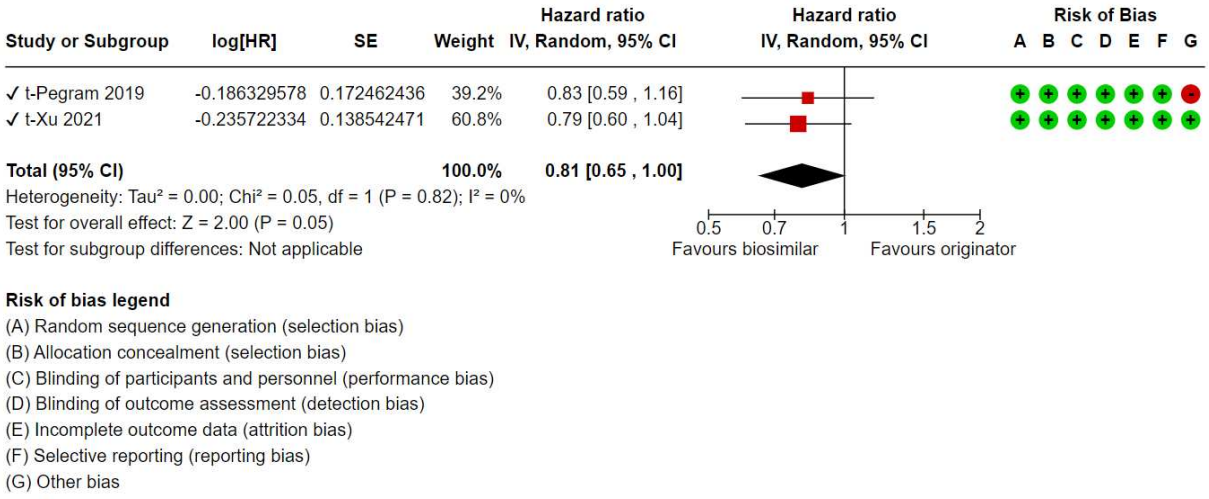


Figure 29. Analysis of duration of response comparing trastuzumab biosimilar and originator

Safety

Any adverse events

Forty-one studies reported safety as treatment-emergent adverse effects and 36 studies reported any adverse events. Bevacizumab (RR 1.00; 95% CI 1.00 to 1.01; I^2=0%; 19 RCTs; 8,102 participants; high-certainty evidence; **Figure 30**), rituximab (RR 1.01; 95% CI 0.99 to 1.03; I^2=39%; 10 RCTs; 3,589 participants; high-certainty evidence; **Figure 31**), and trastuzumab biosimilar (RR 1.01; 95% CI 1.00 to 1.02; I^2=0%; 10 RCTs; 4,719 participants; high-certainty evidence; **Figure 32**) presented no difference in the incidence of any adverse events.

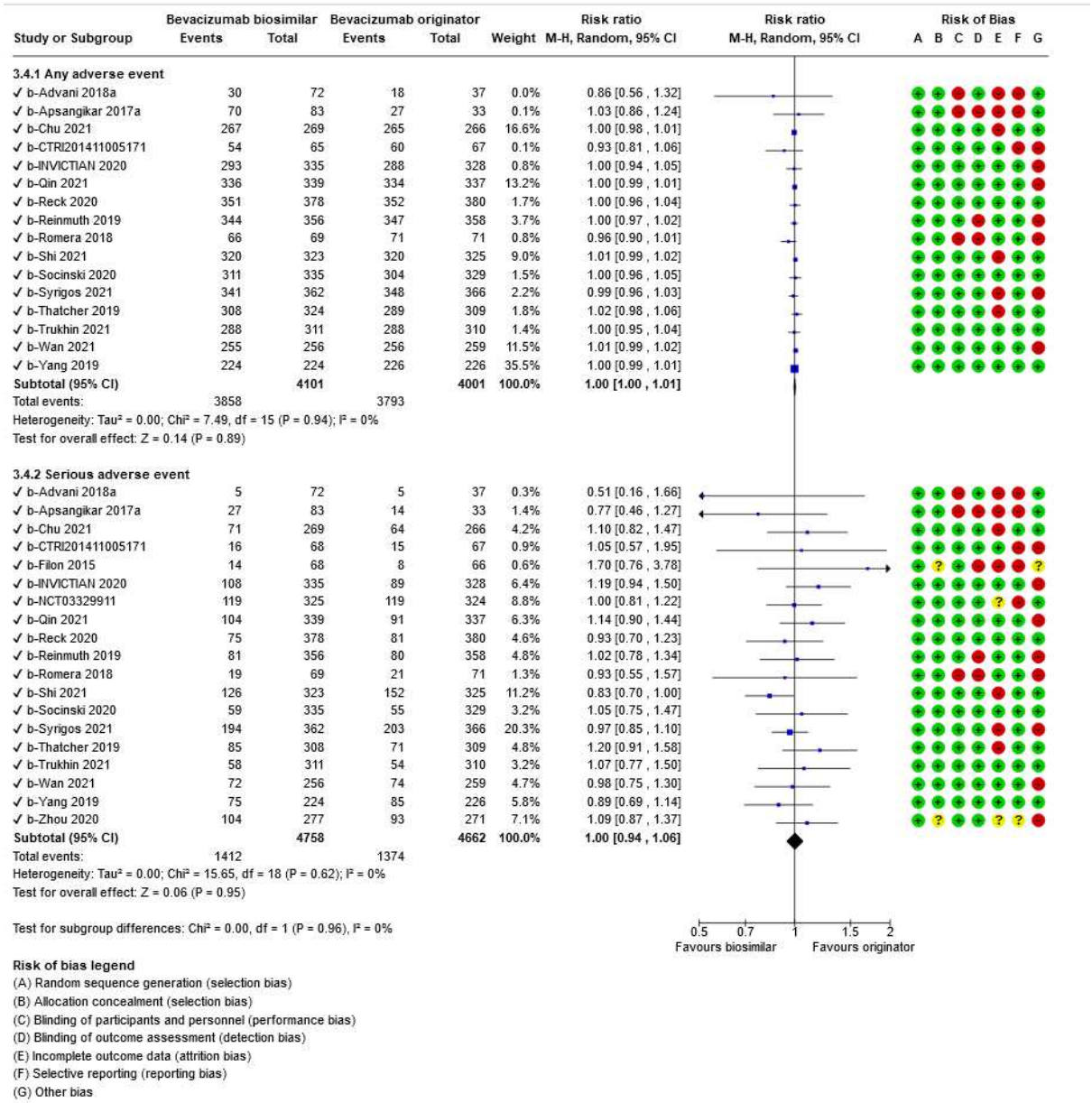


Figure 30. Analysis of any and serious adverse events comparing bevacizumab biosimilar and originator

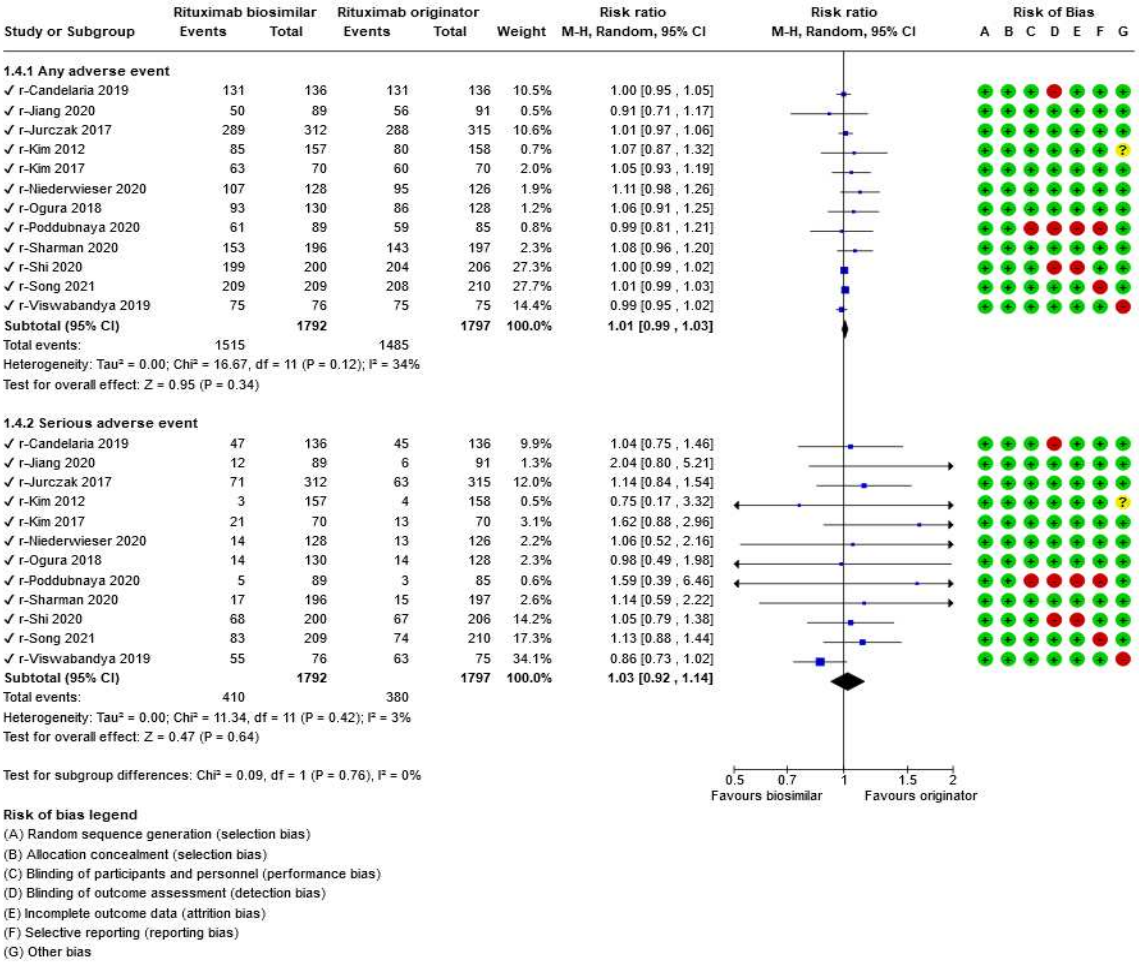


Figure 31. Analysis of any and serious adverse events comparing rituximab biosimilar and originator

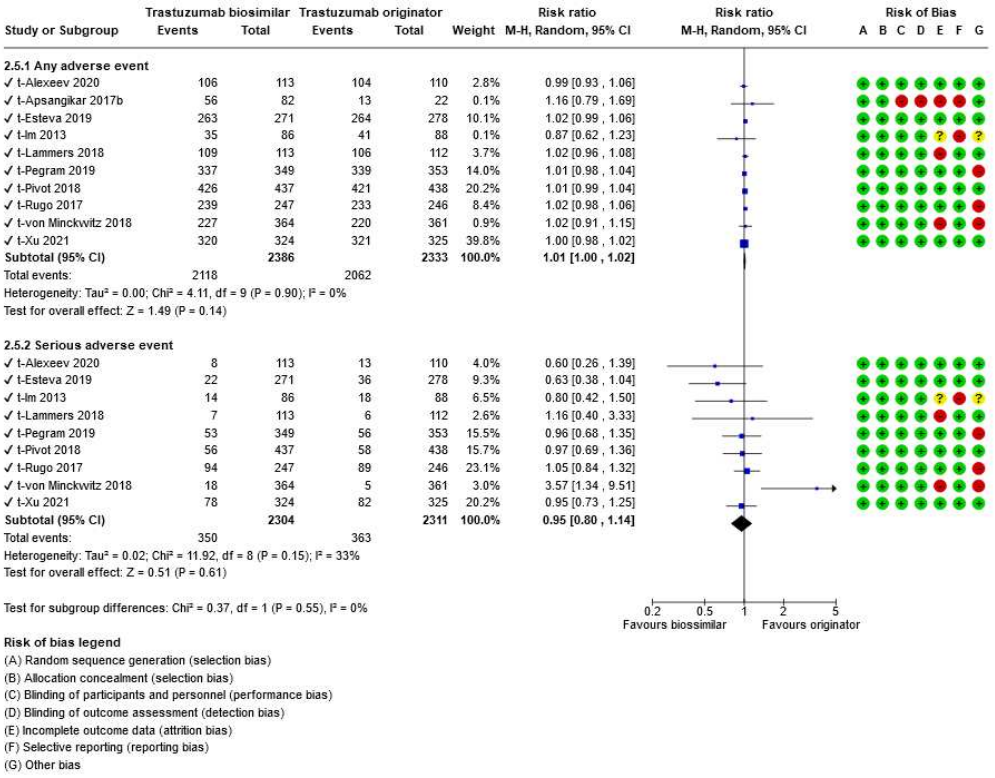


Figure 32. Analysis of any and serious adverse events comparing trastuzumab biosimilar and originator

Serious adverse events

Forty studies reported serious adverse events with similar rate between biosimilar and originator groups of bevacizumab (RR 1.00; 95% CI 0.94 to 1.06; I^2=0%; 19 RCTs; 9,420 participants; high-certainty evidence; Figure 30), rituximab (RR 1.03; 95% CI 0.92 to 1.14; I^2=3%; 12 RCTs; 3,589 participants; high-certainty evidence; Figure 31), and trastuzumab (RR 0.95; 95% CI 0.80 to 1.14; I^2=0%; 9 RCTs; 4,615 participants; moderate-certainty evidence; Figure 32). Certainty of serious adverse events from trastuzumab was downgraded due to inconsistency.

Publication bias was not suspected for both any and serious adverse events from the symmetry observed in the funnel plots of all comparisons (**Figure 33**).

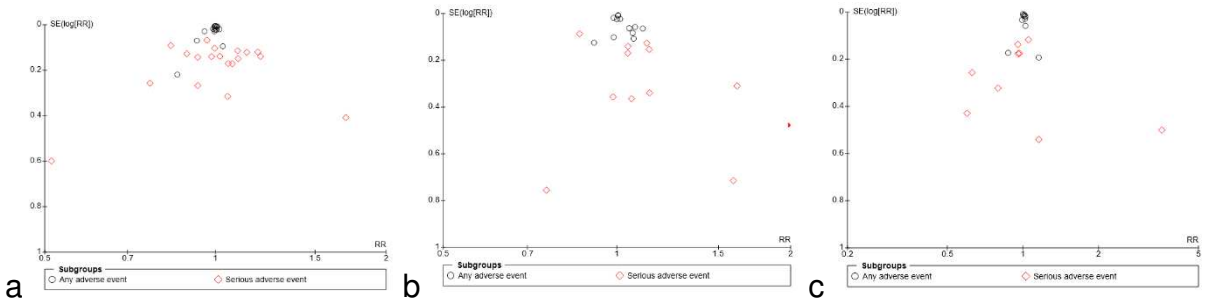


Figure 33. Dispersion of risk ratio (RR) of any adverse events and serious adverse events according to the standard error (SE) of RR in logaritim (precision of the study) for the comparisons of bevacizumab (a), rituximab (b), and transtuzumab (c) biosimilar and originator groups

Immunogenicity (anti-drug antibody and neutralising antibodies)

FDA defines immunogenicity 'as the propensity of a therapeutic protein product to generate immune responses to itself and to related proteins or to induce immunologically related adverse clinical events' (128) and can be a significant problem in the treatment of patients with therapeutic biologicals products.

Detection and analysis of the incidence of the anti-drug antibody (ADA) is crucial to understanding potential immune responses and mandatory for registry the biosimilar drug (128). In the same way, if ADA is detected in the participant, it is necessary evaluate the neutralizing capacity of antibodies present as part of the immunogenicity assessment. Neutralising antibodies (Nabs) inhibit the biological activity of a therapeutic protein by binding to epitope(s) within or close to the active site(s) of the molecule or by causing conformational changes (129).

From the 19 RCTs that assessed bevacizumab, ADA incidence at the end of treatment was reported in 15 studies including 7,669 participants and NAbs was reported in nine studies including 4,433 participants. Bevacizumab biosimilar compared with bevacizumab originator showed similar ADA and NAbs rates (ADA: RR 1.08, 95% CI 0.93 to 1.26; I^2 = 0%.; NAbs: RR 0.67; 95% CI 0.37 to 1.20; I^2 = 12%; high-certainty evidence; **Figure 34**).

ADA was reported in 12 trials from the 14 included with rituximab treatment, counting 3,278 participants. Results were similar between the groups treated with rituximab biosimilar and the originator (RR 1.02; 95% CI 0.77 to 1.37; I^2 =

0%; high-certainty evidence;**Figure 35**). NAbs was reported in nine studies that included 2,436 participants and also had similar incidences among goups (RR 1.19; 95% CI 0.40 to 3.55; I^2 = 0%; high-certainty evidence;**Figure 35**).

Eight trials included 4,438 participants for both ADA and NAbs assessment in participants who received trastuzumab biosimilar or originator. Results were similar between the groups (ADA: RR 0.97; 95% CI 0.52 to 1.82; I^2 = 0; NAbs: RR 0.92; 95% CI 0.37 to 2.33; I^2 = 0%; high-certainty evidence; **Figure 36**).

Publication bias was not suspected for both antidrug and neutralizing antibodies from the symmetry observed in the funnel plots for bevacizumab and rituximab comparisons (**Figure 37**).

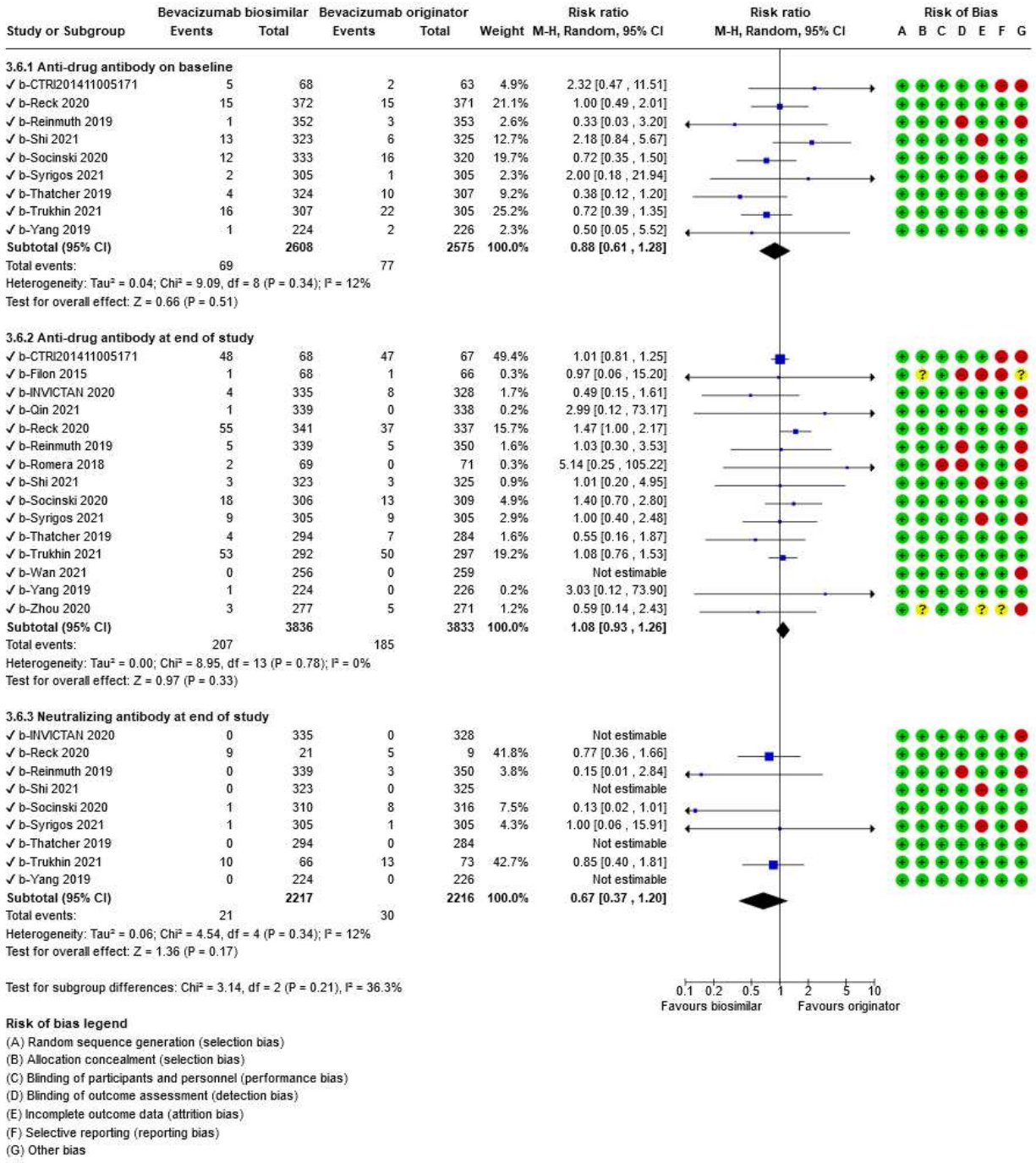


Figure 34. Analysis of immunogenicity comparing bevacizumab biosimilar and originator

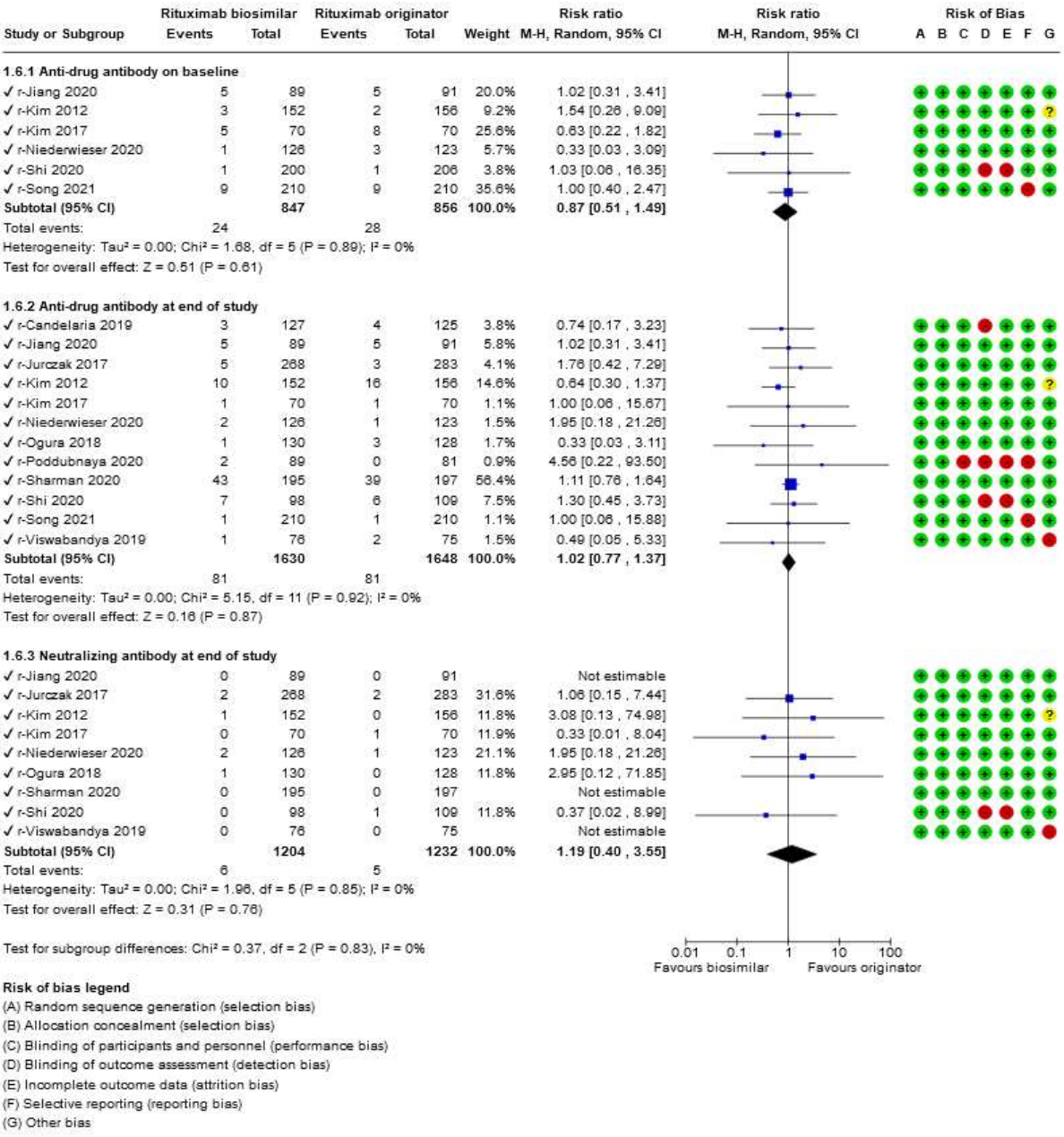


Figure 35. Analysis of immunogenicity comparing rituximab biosimilar and originator

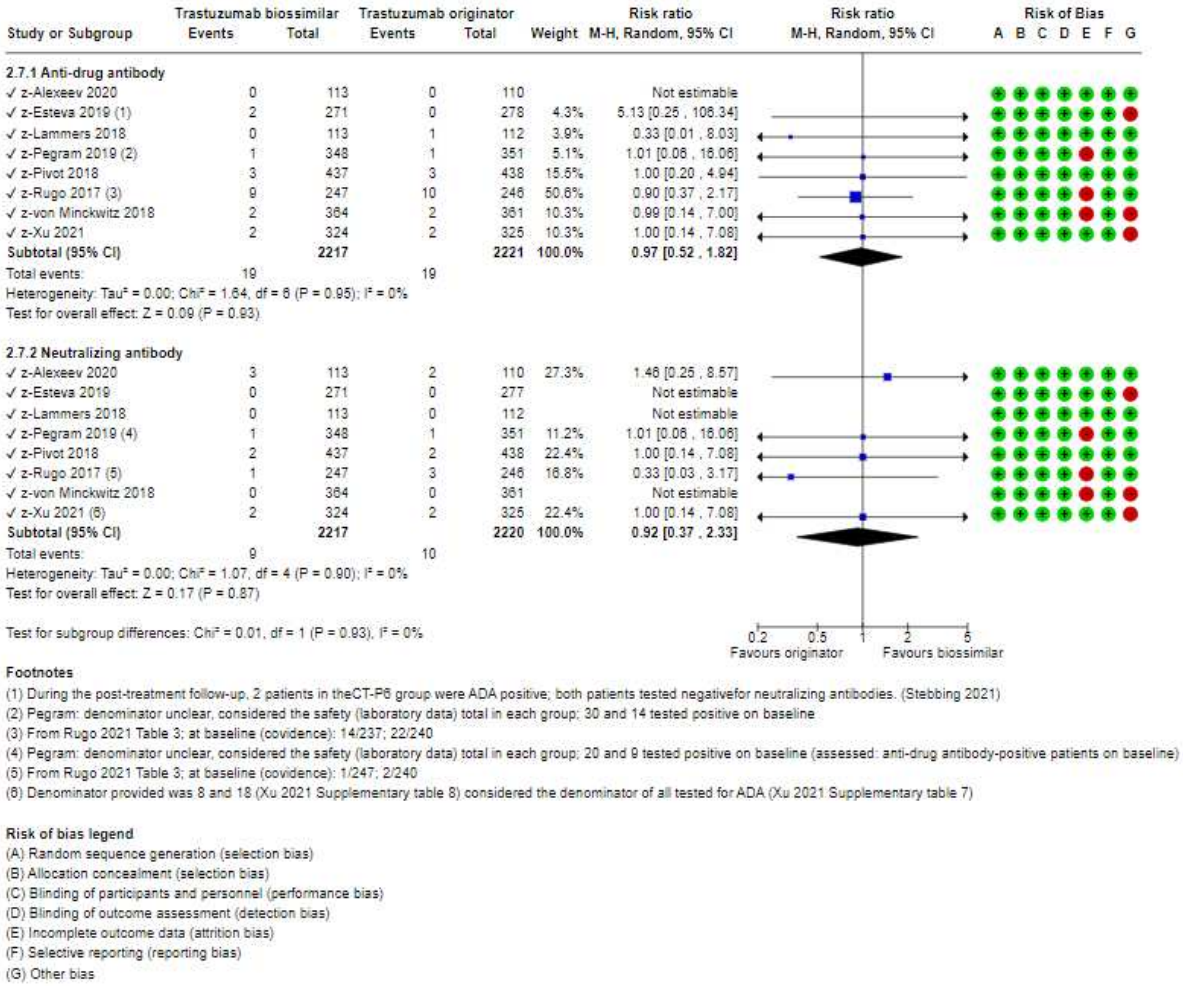
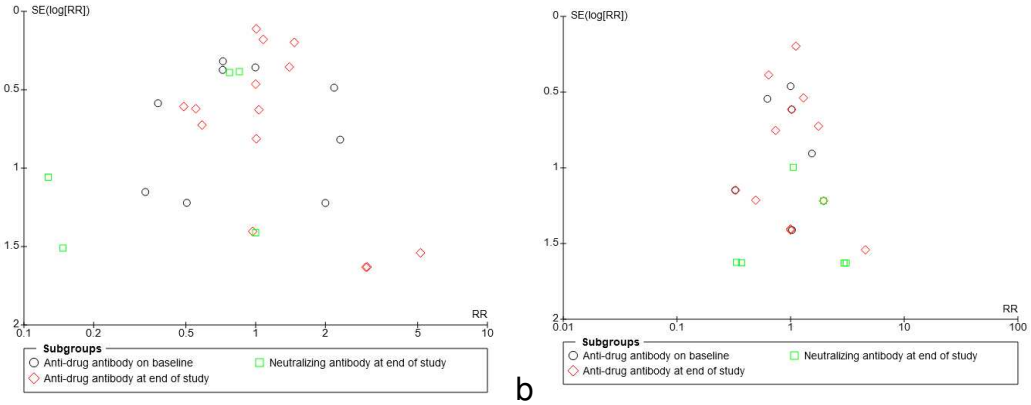


Figure 36. Analysis of immunogenicity comparing trastuzumab biosimilar and originator



b

Figure 37. Dispersion of risk ratio (RR) of antidrug and neutralizing antibodies according to the standard error (SE) of RR in logarithm (precision of the study) for the comparisons of bevacizumab (a) and rituximab (b) biosimilar and originator groups

Quality of life

Only one study (86) assessed the quality of life of the participants with metastatic colorectal cancer at baseline (visit 1) to the end of treatment (day 169 ± 3) using the validated tool Cancer Therapy-Colorectal score (FACT-C) - a 5 point Likert-type scale-, and Treatment Outcome Index Score. It was assessed the domains: physical, social/family, emotional, and functional well-being, and additional concerns. It is not clear how many participants were assessed. Mean total scores at baseline and at the end of treatment were comparable between the groups in all domains, except for 'social/family wellbeing' that showed a mean of -3.75 (±3.81) in the biosimilar group compared to a mean of -1.00 (±4.30), with difference statistically significative (P = 0.0161). According to the authors, improvement in quality of life was found comparable between the study groups for all parameters assessed.

DISCUSSION

Summary of main results

We conducted a systematic review and meta-analysis of RCTs to quantitatively estimate the efficacy and safety of three different biosimilars monoclonal antibodies (bevacizumab, rituximab and trastuzumab) for treating cancer, in comparison to the originator products.

We identified 43 randomised controlled trials that totaled more than 17,800 adult participants included from high-, middle-, and low-income countries. Overall risk of bias was generally low across studies and most outcomes were rated as high-certainty evidence.

Our pooled results provide evidence of comparable efficacy and safety outcomes for the three drugs included versus their respective originator product. No substantial between-study heterogeneity was detected in the pooled analysis of efficacy and safety outcomes.

Overall completeness and applicability of evidence

Usability of reported outcomes

We were able to compare three different biosimilar monoclonal antibodies for cancer treatment: bevacizumab, rituximab and trastuzumab. Almost all of the included studies reported the same outcomes and the definitions of efficacy outcomes used within the included trials corresponded with our definitions based on the regulatory agencies.

The results of the present systematic review should be interpreted with caution due to limitations. We identified 22 studies with the biosimilar treatments included in this systematic review that are ongoing and could not be included in present research. In this rapidly evolving field, this review will need to be updated soon. Further, other types of biosimilar monoclonal antibodies (cetuximab and trastuzumab emtansine) not included in this review are in ongoing studies and soon will be available for enlarge this review in the future. The interpretation of immunogenicity outcomes is also limited given the variety of follow-up, timeframes and the method adopted between the studies. Some studies presented measurable

baseline and different timeframes until the end of study, whereas others assessed only at the end of study. Despite this, no differences among studied groups were observed and these differences had little impact on outcomes' inconsistency.

We highlight the strengths of this systematic review: the search strategy was comprehensive, including ongoing trial registered in database and was continuously updated to make sure it includes the more complete evidence in the field. We included any publication of all relevant trials irrespective of language or type. As result, we were able to identify an extensive number of trials comparing biosimilar and their originator. We rigorously applied the GRADE approach for each of the relevant outcomes to better inform decision makers about the certainty of the results.

Quality of the evidence

All the included studies were randomised, parallel controlled trials. Using GRADE assessment, the certainty of the evidence was globally high. The overall risk of bias was judged to be low for most domains. Two studies with bevacizumab were downgraded by one point for risk of bias for overall survival and progression free survival because the number of participants discontinuing the treatment was considered very high. The certainty of the evidence was very low and low in these outcomes.

Potential biases in the review process

We searched all relevant databases, trial registries, conference proceedings, regulatory agency sources (assessment report published by the agencies EMA and FDA agencies), clinical study reports released by the manufacturer and search within other reviews previously published. Additionally, based on our developed search strategy, we included alerts to keep us up to date with the medical literature being published. With this, we monitored the medical literature and kept the review as current as possible. We are confident that we identified all relevant trials.

To minimize potential biases in the review process, we conducted selection of studies, data extraction, risk of bias assessment, and GRADE assessment in duplicate by two independent review authors and consulted a third

review author to solve conflicts. We complied with Cochrane guidelines for every step of our review.

We collated multiple reports of the same study, so that each study rather than each report was the unit of interest in the review. As the majority of the studies had the trial registration numbers, we are confident that we collated all of them correctly. Reports without registration number were carefully checked for population included and method to guarantee that were the same study.

It is possible that our results were influenced by selective dissemination of biosimilars reports and the high similarity may be over-estimate. Although our comprehensive search also detected ongoing studies, missing outcomes and studies may never be reported, influenced by commercial interests. The risk of reporting bias was discarded from outcomes assessed in funnel plot dispersion, but some studies were not reported in full, precluding assessment of all outcomes. We also had difficulties in terms of data extraction processes, because some data were available in figures or poor reported, and we made assumptions regarding the follow-up of studies participants that were very heterogeneous.

Agreements and disagreements with other studies or reviews

We found seven other systematic reviews evaluating biosimilar monoclonal antibodies for cancer treatment published between 2016 and 2022. Four included studies comparing bevacizumab, rituximab and trastuzumab (57, 58, 61, 63), two reviews assessed trastuzumab biosimilar (62, 130), and one included only studies comparing rituximab (59). Another review synthetised the evidence from pharmacoeconomics evaluations globally (131). Monoclonal antibodies and cancer supportive medicines were eligible, and the outcomes included only pharmacoeconomic evaluation. There were no major disagreements with the results and conclusions of our systematic review these previous reviews.

The oldest review (58) included monoclonal antibody and fusion protein biosimilars across different therapeutic areas, including cancer. Publication's type included empirical studies (i.e., analytical, functional, or nonclinical studies and clinical studies assessing pharmacokinetics in healthy subjects or patients) and non-empirical publications (manufacturer report, supply topics, review articles, opinion, or commentaries among other types). As resulted, the authors described the

characteristics of the scientific publications and would be therefore better categorized as bibliometric survey or scope review. Using a similar method of this 2016 review, another review was published but this time, describing only studies for the cancer treatment (57).

Coory and Thornton (62) aimed to assess the evidential role of randomised clinical endpoints studies in the marketing approval of trastuzumab biosimilar in their review. They searched PubMed and ClinicalTrials.gov up to January 2019 and included seven studies, all of them have been included in our review as well.

Cargnin 2020 (60) conducted a comprehensive search up July 2020 in the same database that us, excepted Embase. All eight included trials of Cargnin 2020 have been included in our systematic review as well. We identified three additional studies, which were not included in this review and are included in our analysis. Bloomfield 2022 (63) performed a systematic search with last updated in April, 2021 and included a total of 31 studies. The eligible criteria didn't include safety outcomes or immunogenicity results.

Lee 2019 (59) performed a review about rituximab biosilimar with RCTs searched up to to February 2019 on rheumatoid arthritis and non-Hodgkin's lymphoma. All four included trials in this previous review have been included in our systematic review. Additionally, we identified ten studies which were included in our analysis. The certainty of evidence was also assessed in this review, and neutralizing antibodies and adverse events were judged as moderate certainty evidence, due to inconsistency but studies on rheumatoid arthritis and non-Hodgkin's lymphoma were judged together.

CONCLUSION

Implications for practice

General

The findings of our systematic review will support clinicians and patients in decision-making regarding use of biosimilars monoclonal antibodies for cancer treatment. Our results provide a comprehensive overview of important clinical outcome assessed in direct head-to-head comparisons.

Despite the regulatory agencies consider the concept of data extrapolation to authorize a biosimilar for treat different types of cancer, when interpreting the results of this systematic review, it is important to understand that the results showed here are only applicable for the type of cancer defined in the eligible criteria.

For adults with breast cancer

Present summarized evidence suggests similar results with high certainty between biosimilar trastuzumab and the originator for treat metastatic, advanced, or early breast cancer.

For adults with lung cancer

Results should be interpreted with caution taken into consideration that the trials did not include participants with all different types of lung cancer. The results showed here are applicable only for patients with advanced, metastatic, or recurrent nonsquamous non-small cell lung cancer. Even though, it is important consider all eligible criteria adopted in the trials included in this systematic review.

For adults with non-Hodgkin lymphoma

Similar to the observation we made for adults with lung cancer, results with rituximab should be interpreted with caution taken into consideration that the participants were diagnostic with diffuse large B-cell lymphoma or follicular lymphoma. It is important consider all eligible criteria adopted in the trials included in this systematic review.

For adults with chronic lymphocytic leukemia

It is important to be aware that only one study included 70 participants with chronic lymphocytic leukemia with high risk of bias for incomplete outcome data and selective reporting.

Implications for research

Further research should focus in long-term outcomes as well as assessing immunogenicity in similar time-points to avoid concerns in using biosimilar drugs. Although immunogenicity was not an issue in our results, the differences in assessing this outcome should be ruled out. Assessment of switching between biologic and biosimilar drugs is also important to be investigated. Despite it was not the purpose of this review, only two studies tested this approach and it should be further explored.

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APPENDICES

Search strategy

Central

#1 MeSH descriptor: [Neoplasms by Site] explode all trees

#2 MeSH descriptor: [Neoplasms by Histologic Type] explode all trees

#3 neoplas*

#4 tumor* or tumour*

#5 cancer*

#6 Krebs*

#7 malignan*

#8 carcino* or carcinomatos*

#9 karzino* or karzinom*

#10 sarcom*

#11 lymphom*

#12 leukaem* or leukem* or leucem*

#13 melano*

#14 metastas*

#15 mesot*eli*

#16 gliom*

#17 glioblastom*

#18 osteosarcom* or osteo-sacrom*

#19 blastom*

#20 neuroblastom*

#21 adenocarcinoma*

#22 myeloma*

#23 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22

#24 MeSH descriptor: [Biosimilar Pharmaceuticals] explode all trees

#25 biosimilar*

#26 biopharmaceutical*

#27 #24 or #25 or #26

#28 #23 and #27

Embase

#	Searches
1	exp NEOPLASM/
2	exp NEOPLASMS SUBDIVIDED BY ANATOMICAL SITE/
3	neoplas*.tw,kw.
4	(tumor* or tumour*).tw,kw.
5	(Krebs* or cancer*).tw,kw.
6	malignan*.tw,kw.
7	(carcino* or karzino*).tw,kw.
8	sarcom*.tw,kw.
9	leuk#?m*.tw,kw.
10	lymphom*.tw,kw.
11	melano*.tw,kw.
12	metastas*.tw,kw.
13	(mesothelio* or mesotelio*).tw,kw.
14	carcinomatos*.tw,kw.
15	(gliom* or glioblastom*).tw,kw.
16	(osteosarcom* or osteo-sarcom*).tw,kw.
17	(blastom* or neuroblastom*).tw,kw.
18	adenocarcinoma*.tw,kw.
19	myeloma*.tw,kw.
20	or/1-19
21	BIOSIMILAR AGENT/
22	biosimilar*.tw,kw.
23	biopharmaceutical*.tw,kw.
24	or/21-23
25	RANDOMIZED CONTROLLED TRIAL/
26	CONTROLLED CLINICAL STUDY/
27	random*.ti,ab.

28	RANDOMIZATION/
29	INTERMETHOD COMPARISON/
30	placebo.ti,ab.
31	(compare or compared or comparison).ti.
32	(open adj label).ti,ab.
33	((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
34	double blind procedure/
35	parallel group$1.ti,ab.
36	(crossover or cross over).ti,ab.
37	((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.
38	(controlled adj7 (study or design or trial)).ti,ab.
39	(volunteer or volunteers).ti,ab.
40	trial.ti.
41	or/25-40

MEDLINE via PubMed

"NEOPLASMSBYSITE"[MeSHTerms])OR"NEOPLASMSBYHISTOLOGICTYPE"[MeSHTerms])ORneoplas*[TextWord]ORtumor*[TextWord] OR tumour*[Text Word] OR cancer*[Text Word] OR krebs*[Text Word] OR malignan*[Text Word] OR carcino*[Text Word] OR karzino*[Text Word] OR sarcom*[Text Word] OR lymphom*[Text Word] OR leukem*[Text Word] OR leukaem*[Text Word] OR melano*[Text Word] OR metastas*[Text Word] OR mesothelio*[Text Word] OR mesoteli*[Text Word] OR carcinomatos*[Text Word] OR gliom*[Text Word] OR glioblastom*[TextWord]ORosteosarcom*[TextWord]ORosteosarcom*[TextWord]ORblastom*[TextWord]ORneuroblastom*[TextWord] OR adenocarcinoma*[Text Word] OR myeloma*[Text Word] AND "BIOSIMILAR PHARMACEUTICALS"[MeSH Terms]) OR biosimilar*[Text Word] OR biopharmaceutical*[Text Word] AND "randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR randomi?ed[Title/Abstract] OR placebo[Title/Abstract] OR "drug therapy" OR randomly[Title/Abstract] OR trial[Title/Abstract] OR groups[Title/Abstract]

Web of Science

#1	TS=NEOPLASM
#2	TS=neoplas*
#3	TS=(tumor* or tumour*)
#4	TS=(Krebs* or cancer*)
#5	TS=malignan*
#6	TS=(carcino* or karzino*)
#7	TS=sarcom*
#8	TS=(leukaem* or leukem*)
#9	TS=lymphom*
#10	TS=melano*
#11	TS=metastas*
#12	TS=(mesothelio* or mesotelio*)
#13	TS=carcinomatos*
#14	TS=(gliom* or glioblastom*)
#15	TS=(osteosarcom* or osteo-sarcom*)
#16	TS=(blastom* or neuroblastom*)
#17	TS=adenocarcinoma*
#18	TS=myeloma*
#19	OR/1-18/
#20	TS=BIOSIMILAR AGENT
#21	TS="BIOSIMILAR PHARMACEUTICALS"
#22	TS=biosimilar*
#23	TS=biopharmaceutical*
#24	#20 OR #21 OR #22 OR #23
#25	ALL="RANDOMIZED CONTROLLED TRIAL"
#26	ALL="CONTROLLED CLINICAL STUDY"
#27	TS=random*
#28	ALL=RANDOMIZATION
#29	ALL="INTERMETHOD COMPARISON"
#30	TS=placebo
#31	TI=(compare or compared or comparison)
#32	TS=(open adj label)
#33	TS=((double or single or doubly or singly) adj (blind or blinded or blindly))
#34	ALL="double blind procedure"
#35	TS=parallel group$1
#36	TS=(crossover or cross over)
#37	TS=(volunteer or volunteers)
#38	TI=trial
#39	OR/25-38
#40	#19 AND #24 AND #39

ClinicalTrials.gov

Condition: cancer OR neoplasm OR lymphoma OR leukemia OR leukaemia AND Other terms: biosimilar OR CT-P10 OR 1B8 OR BCD 020 OR GP 2013 OR PF 05280586 OR RTXM 83 OR SAIT 101 OR IBI301 OR HLX01 OR JHL1101 OR PF 06439535 OR ABP 215 OR BCD 021 OR RPH 001 OR BAT 1706 OR HLX04 OR CT P15 OR STI-001 OR APZ001 OR ABP 494 OR Ch225 OR ABP 980 OR Myl 1401O OR BCD 022 OR FTMB OR PF 05280014 OR SB3 OR CT P6 OR ALT02

The World Health Organization International Clinical Trials Registry Platform

#1 condition: cancer / intervention: biosimilar

#2 condition: neoplasm / intervention: biosimilar

#3 biopharmaceutical AND cancer

#4 biosimilar AND lymphoma

EU Clinical Trials Register

#1 biosimilar AND cancer

#2 biosimilar AND lymphoma

ANEXX

Book chapter

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Chapter

Monoclonal Antibodies for Cancer Treatment

Annemeri Livinalli and Taís Freire Galvão

Abstract

Therapeutic monoclonal antibodies have emerged in the 1990 decade as an important option for cancer treatment. These molecules have a diverse set of clinically relevant antitumor mechanisms, directly targeting tumor cells. It has been established as "standard of care" for several human cancers. This chapter reviews the use of monoclonal antibodies in oncology and introduces available biosimilars. The requirements for biosimilar antibody development, mechanisms of action and current clinical applications for cancer treatment is also presented.

Keywords: biosimilar, equivalence trial, efficacy, monoclonal antibodies, cancer, extrapolation of indication

1. Introduction

Since the development of monoclonal antibodies by hybridoma technology in 1975 [1] over 80 molecules were developed and approved for therapeutic use in immunological, oncological, and infectious diseases [2]. Over time, these molecules have revolutionized the treatment of main autoimmune diseases and cancer that previously had a bleak prognosis. These molecules are usually administered by subcutaneous or intramuscular routes due to poor oral bioavailability (less than 1%) caused by large size, polarity, limited membrane permeability, and poor gastrointestinal stability [3].

In oncology, the approach in the use of monoclonal antibodies consists in targeting tumor antigens and killing cancer cells [4]. Growth factor receptors that are overexpressed in tumor cells are recognized as main target by monoclonal antibodies [4, 5]. Blocking ligand binding/signaling result in decrease growth rate of cancer cells, which in turn, induce apoptosis and sensitize tumors cells to chemotherapy [6, 7].

As of the first semester of 2021, the arsenal of monoclonal antibodies in oncology counts on more than 30 molecules [8]. Among the first molecules, we have: bevacizumab, cetuximab, rituximab, trastuzumab, indicated for treating solid tumors and hematological malignancies (**Table 1**). From all monoclonal antibodies, there are only three biosimilar products marketed (bevacizumab, rituximab, trastuzumab; **Table 2**).

Monoclonal antibody	Approval date		Mechanism of action	Indication in oncology
	EMA[a]	FDA[b]		
Bevacizumab	2005	2004	Inhibition of vascular endothelial growth factor binding to the cell surface receptors	Metastatic colorectal cancer; unresectable, locally advanced, recurrent, or metastatic non-squamous non-small cell lung cancer; recurrent glioblastoma in adults; metastatic renal cell carcinoma; persistent, recurrent, or metastatic cervical cancer; epithelial ovarian, fallopian tube, or primary peritoneal cancer; hepatocellular carcinoma
Cetuximab	2004	2004	Competitive inhibition of the binding of epidermal growth factor	Metastatic colorectal carcinoma
Rituximab	1998	1997	Binding to B-lymphocyte antigen CD20 on the surface of B cells and activating the antibody-dependent cellular cytotoxicity and apoptosis	Non-Hodgkin's lymphoma; lymphocytic leukemia
Trastuzumab	2000	1998	Binding to the human epidermal growth factor 2 (HER2) will result in inhibition of the proliferation and survival of the cell	HER2-overexpressing breast cancer; HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma

Legend: EMA, European of Medicines Agency; FDA, United States Food and Drug Administration; INN, international nonproprietary name.
[a]*Available at: www.ema.europe.eu.*
[b]*Available at: www.accessdata.fda.gov.*

Table 1.
First monoclonal antibodies used in oncology.

Monoclonal antibody	European of Medicines Agency[a]		Food and Drug Administration[b]	
	Trade name	Approval date	Trade name	Approval date
Bevacizumab	Mvasi	2018	Mvasi	2017
	Zirabev	2019	Zirabev	2019
	Equidacent	2020		
	Aybintio	2020		
	Onbevzi*	2020		
	Alymsys*	2021		
	Oyavas*	2021		
Rituximab	Truxima	2017	Truxima	2018
	Riximyo	2017	Ruxience	2019
	Blitzima	2017	Riabni	2020
	Rixathon	2017		
	Ritemvia	2017		
	Ruxience	2020		

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Monoclonal antibody	European of Medicines Agency[a]		Food and Drug Administration[b]	
	Trade name	Approval date	Trade name	Approval date
Trastuzumab	Ontruzant	2017	Ogivri	2017
	Trazimera	2018	Herzuma	2018
	Kanjinti	2018	Kanjinti	2019
	Ogivri	2018	Ontruzant	2019
	Herzuma	2018	Trazimera	2019
	Zercepac	2020		

[a]*Available at: www.ema.europe.eu.*
[b]*Available at: www.fda.gov/drugs/biosimilars/biosimilar-product-information.*
[*]*The product received the recommendation of the granting of marketing authorization.*

Table 2.
Biosimilar monoclonal antibodies with marketing approval for cancer treatment (until February 2021).

2. Development of monoclonal antibodies

Monoclonal antibodies consist in homogenous preparations of antibodies – or fragments of antibodies – in which every antibody in the product is identical in its protein sequence. All antibodies should have the same antigen recognition site, affinity, biological interactions, and downstream biological effects [2].

There are four types of monoclonal antibodies [9]:

- Murine: entirely derived from a murine source (hybridoma technology).
- Chimeric: the variable regions are of murine origins whereas the constant regions are human.
- Humanized: mostly derived from a human source except for the part of the antibody which binds to its target.
- Human: entirely derived from a human source

In summary, the traditional murine hybridoma technique starts by immunization of mice with desired antigens to trigger an immune response. Harvested splenocytes are fused with myeloma cells to produce hybridoma cells that persistently secrete the antibodies of interest. After the screening, selected leads are used to generate chimeric or humanized antibodies [9].

The main concern with this approach is the risk that might result in an immune response to the mouse antibody sequence. The consequence of this include allergic response and/or reduced bioavailability of mouse monoclonal antibodies. This immune response limited their clinical use [10].

Changes in the source of the molecule were determined as a solution to avoid the immune response. Introducing engineer changes, for example, recombinant DNA technologies, originated the chimeric, humanized, and human antibodies. Humanized mice allow for development of monoclonal antibodies with amino acid substitutions that lack mouse heavy chains and make them more similar to the human sequence system [2, 9].

The first chimeric antibody was approved in 1994 by the United States Food and Drug Administration (FDA) for inhibition of platelet aggregation in cardiovascular

diseases. The drug was developed by combining sequences of the murine variable domain with human constant region domain. In 1997, the first monoclonal antibody, rituximab – an immunoglobulin type 1 anti-CD20 -, was approved for non-Hodgkin's lymphoma by the FDA [9]. And the first humanized monoclonal antibody approved by the FDA also in 1997 was daclizumab, an anti-IL-2 receptor used for the prevention of transplant graft rejection [11].

Human monoclonal antibodies can either be obtained by phage display or transgenic animals [9]. Based on these techniques, the first fully human therapeutic antibody based on phage display was adalimumab, an anti-tumor necrosis factor α human antibody. It was approved in 2002 by the FDA for rheumatoid arthritis. Panitumumab, a monoclonal antibodies anti-epidermal growth factor receptor was the first human antibody generated in a transgenic mouse, approved by the FDA in 2006 and indicated for metastatic colorectal carcinoma, a type of cancer [11].

3. Biosimilar monoclonal antibodies in oncology

As mentioned before, three biosimilar monoclonal antibodies are available in oncology: bevacizumab, rituximab, and trastuzumab. Cetuximab is in preliminary steps of developing a biosimilar.

Bevacizumab is a humanized inhibitor of vascular endothelial growth factor (VEGF) monoclonal antibody. It acts by selectively binding circulating VEGF, thereby inhibiting the binding of VEGF to its cell surface receptors, which results in a reduction of microvascular growth of tumor blood vessels, reducing the blood supply to tumor tissues. Other results observed are decrease interstitial pressure on tissues, increase vascular permeability, induction of apoptosis of tumor endothelial cells, and may increase delivery of chemotherapeutic agents [12].

Rituximab is a chimeric monoclonal antibody that has a high-affinity binding to B-lymphocyte antigen CD20 (CD20) on the surface of B cells. The death of B cells occurs by different ways, including antibody-dependent cellular cytotoxicity (ADCC) and apoptosis [13].

Trastuzumab is a recombinant humanized monoclonal antibody that binds to the domain of the extracellular segment of the human epidermal growth factor-2 receptor (HER2), and inhibits the proliferation and survival of HER2-dependent tumors [14]. When trastuzumab is biding to HER2 receptor might occur the degradation of the receptor, attraction of immune cells to tumor cells by ADCC and inhibition of some pathways involved in the suppression of cell growth and proliferation [15].

4. Assessment of biological activity of biosimilar monoclonal antibodies

The biosimilar needs to demonstrate the proposed product is highly similar to the reference biological product and this is determined through a pathway that include comparative characterization made by evaluation of physicochemical, functional, and clinical characteristics of a biological product [16, 17].

The first step in biosimilar analytic characterization is identifying the characteristics associated with the quality, safety, and efficacy of reference biological product. These characteristics are known as critical quality attributes (CQAs) and represent physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality [18].

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Analytic testing of CQAs is performed to detect differences in factors such as the expression system, the manufacturing process, physicochemical properties, functional activities, receptor binding, immunochemical properties, impurities, and clinical outcome of the biosimilar candidate [19, 20].

It may be useful to compare the quality attributes of the proposed biosimilar product with those of the reference product using a meaningful fingerprint-like analysis. It means the results obtained are extremely sensitive in identifying analytical differences and allow a very high level of confidence in the analytical similarity of the proposed biosimilar product [21].

Once the CQAs for the biosimilar candidate are identified, the next step is to categorize the relative importance or criticality of each attribute. In the case of monoclonal antibodies, that are more complex biological products, determining criticality may be more challenging due to the increased number of attributes to evaluate and the potential impact of each difference on the desired product [22].

Significant differences for a very important CQA of the biosimilar candidate, such as the primary amino acid structure, are enough to interrupt the biosimilarity pathway. The manufacturer will need change their process to reach the high level of similarity between this structure in the biosimilar compared with the reference product. In the other hand, differences detected among CQAs of very low importance, such as minor modifications in amino acid side chains, may be acceptable if they can be justified or understood as clinically irrelevant [22, 23].

Primary amino acid structure is the core DNA sequence, and it must be exactly the same for the biosimilar product and the reference product [22]. There are a range of methods commonly used for evaluating the primary structure, including the peptide mapping, characterization of disulfide linkages, and glycosylation [24]. If the amino acid sequence is not identical, it can happen unwanted amino acid interactions that will impact in the safety, efficacy, and immunogenicity of the product [22].

Antibody molecules are molecules consisting of three equalized portions, constructed in the same way from paired heavy and light polypeptide chains that consists of a series of similar, sequences, each about more than a hundred amino acids long [25].

Changes in the protein can occur during any step of the manufacturing process, for example, enzymatic modifications, aggregation, variable glycosylation, etc. These modifications are named as post translational modifications. They can influence the physicochemical and biological properties of a protein and affect immunogenicity, immune response, and clinical efficacy [26]. In general, proteins can differ in at least three ways: (i) primary amino acid sequence; (ii) modification of amino acids, such as glycosylation or other side chains; and (iii) higher order structure [23]. Glycosylation and phosphorylation can impact on the efficacy and safety of a protein, for this reason, during the development process, they are extensively tested [22].

When the primary amino acid structure and the three-dimensional structure are reached in the biosimilar product, the correct protein arrangement and structural integrity are obtained and then, the ability of the biological product to bind to the target receptor will result in pharmacologic action. For this reason, target binding is considered a very highly CQA [27].

Impurities can be product – or process-related, arising from cell substrates or cell culture component [28]. They have the potential to affect all aspects of the product's profile [22]. For this reason, the chosen analytical procedures should be adequate to detect, identify, and accurately quantify biologically significant levels of impurities [28].

Because the quality attributes of a biosimilar are not identical to those of the reference product, in addition to the analytic package, animal toxicology,

pharmacokinetic and pharmacodynamic testing, and immunogenicity studies are required by the regulatory agencies for demonstrating biosimilarity [29]. Then, to ensure that these differences do not lead to any clinically meaningful differences, comparative clinical studies are performed [30]. It is usually necessary to demonstrate comparable clinical efficacy of the biosimilar and the reference product in adequately powered, randomized, parallel group comparative clinical trial(s), preferably double-blinded and appropriate endpoints chosen [19].

5. Requirements for biosimilar monoclonal antibody clinical trials

Since the first monoclonal antibody have come off patent protection, regulatory agencies like European of Medicines Agency (EMA), FDA, Health Canada, Australian government Therapeutic Goods Administration (TGA) as well as the World Health Organization (WHO), developed guidance to manufactures interested in submitting applications for biosimilar products approval. Principles for designing, conducting, and reporting the results from clinical trials are set by these guidelines.

Clinical pharmacology studies are a critical part of demonstrating biosimilarity by supporting a demonstration that there are no clinically meaningful differences between the proposed biosimilar product and the reference product [21].

The comparison of the pharmacokinetics properties of the biosimilar and the reference product forms the first step of a biosimilar monoclonal antibodies' development [29]. It is critical to use the appropriate bioanalytical methods to evaluate pharmacokinetics and pharmacodynamics properties [21]. They need to be accurate, precise, specific, sensitive, and reproducible.

The design of the study depends on some factors, including clinical context, safety, and the pharmacokinetics characteristics of the antibody [29]. Two study designs are of particular relevance: single dose crossover designs and parallel study designs. For pharmacokinetics similarity assessments, a single dose study, randomized, crossover study in healthy volunteers, is generally preferred [21, 29].

Pharmacokinetics and pharmacodynamics studies of trastuzumab (CT-P6 drug) [31] and bevacizumab (SB8 drug) [32] were developed with healthy participants. On the other hand, rituximab (PF-05280586) [33] were conducted with patients (rheumatoid arthritis or lymphoma). A study in healthy subjects is considered to be more sensitive in evaluating the product similarity because it is likely to produce less pharmacokinetics and/or pharmacodynamics variability compared with a study in patients with potential confounding factors [21].

Single dose study is recommended for a product with a short half-life, a rapid pharmacodynamics response, and a low anticipated incidence of immunogenicity [21]. To biological products with a long half-life, e.g., the mean serum half-life of rituximab is 59.8 hours after the first infusion [34], to evaluate clinical pharmacokinetics and pharmacodynamics similarity, a parallel group design is more appropriate for this kind of product [21, 29].

To demonstrate comparable clinical efficacy of the biosimilar and the reference product, an adequately powered, randomized, parallel group comparative clinical trial, preferably double-blind, by using efficacy endpoints is usually necessary [19].

Confirmatory trials (superiority trials) for new drugs should demonstrate that the investigational product provides clinical benefit. In this way, FDA and EMA have published guidance to applicants, providing background information and general regulatory principles for cancer clinical trials [7, 35]. Acceptable primary clinical endpoints in this kind of trial include cure rate, overall survival (OS), progression free survival (PFS), disease free survival (DFS) [7, 35].

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While clinical trials of originator products aim to demonstrate patient benefit, in the biosimilar comparable studies the intention is to compare the biosimilar product with the reference product to exclude clinically relevant product-specific differences [36]. In this case, the most appropriate study design is the equivalence study, and in some specific cases, non-inferiority trial may be accepted after to discuss with regulatory authorities [19, 23, 29]. For this, the manufacturer needs justify on the basis of a strong scientific rationale.

OS is considered the most reliable cancer endpoint because is precise, easy to measure and the bias is not a factor to worried. It is defined as the time from randomization until death from any cause. It is measured in the intent-to-treat population [29, 35]. As it is necessary to perform the study with long follow-up periods in large trials, this endpoint is not usually expected to be present in the biosimilar studies and it is not required by the regulatory agencies.

In the comparable studies, it is not necessary to use the same primary efficacy endpoints as those that were used in the marketing authorization application of the reference product [19, 37]. However, EMA advises to include some common endpoints to facilitate comparisons to the clinical trials conducted with the reference product [19].

At moment, a large number of studies with bevacizumab, rituximab and trastuzumab biosimilar are using the ORR as the primary endpoint, and EFS, PFS as the secondary endpoint (**Table 3**). OS is less frequently used.

ORR is defined by the regulatory agencies as the proportion of patients with tumor size reduction of a predefined amount and for a minimum time period. The FDA has defined ORR as the sum of partial responses plus complete responses (CRs) [35]. ORR is a direct measure of a drug antitumor activity and should be assessed using a standardized criterion to determine the response [35]. The most common is the Response Evaluation Criteria in Solid Tumors (RECIST) guideline [55].

Beyond the pharmacokinetics and pharmacodynamics analyses, and clinical results, immunogenicity data should be collected and evaluated too. The goal is to investigate presence of an immune response to the therapeutic protein and its clinical impact [56].

The risk of immunogenicity varies between products and product categories, as well, between individuals and patient groups [56]. The consequences of an immune reaction to a therapeutic protein range from transient presence of anti-drug antibody (ADA) without any clinical significance to severe life-threatening conditions [56]. Immune responses to therapeutic protein products have the potential to affect product pharmacokinetic, pharmacodynamics, safety, and efficacy [56, 57].

When an ADA binds to or near the active site of a therapeutic protein or induces conformational changes, binding to relevant receptors will not happen and it will affect efficacy of the product. Besides these conformational-based effects, in addition immune-based adverse effects can happen. This includes injection-site and infusion reactions [56].

Among the product-related factors we have the protein origin (e.g. human or animal) and nature of the active substance (endogenous protein, post-translational modifications), significant modifications in the molecule structure, process-related impurities, formulation (excipients) and the interactions between the drug and/or formulation with the primary product packaging [56].

Immunogenicity testing of the biosimilar and the reference product should be conducted within the biosimilar comparability exercise by using the same assay format and sampling schedule which must meet all current standards [56, 58]. Assays used to detect antibodies against monoclonal antibody are often more problematic, difficult and can be technically challenging than for other proteins less complex [59].

Monoclonal antibody	Trade name	Study name or ID	Study design	Population and sample size (N)	Primary endpoint
Bevacizumab	Mvasi [38]	20120265	Non-inferiority study, randomized, double-blind, parallel, randomized	unresectable, locally advanced, or metastatic non-small cell lung cancer (642)	ORR
	Zirabev [39]	B7391003	Equivalence study, double-blind, parallel, randomized	unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer (719)	ORR
	Equidacent [40]	FKB238-002	Equivalence study, double-blind, parallel, randomized	Newly diagnosed advanced (stage IV) / recurrent NS-NSCLC (731)	ORR
	Aybintio [41]	SB8-G31-NSCLC	Equivalence study, double-blind, parallel, randomized	Metastatic or recurrent nonsquamous Non-small Cell Lung Cancer (763)	ORR
	Onbevzi	No information for public access			
	Alymsys				
	Oyavas				
Rituximab	Riabni [42]	20130109	equivalence study, randomized, double-blind, parallel	low tumor-burden follicular lymphoma (256)	ORR
	Ruxience [43]	REFLECTIONS B328-06	equivalence study, randomized, double-blind, parallel	low tumor burden follicular lymphoma (394)	ORR
	Truxima [44]	CT-P10 3.3	non-inferiority, randomized, double-Blind, parallel	Advanced Follicular Lymphoma (121)	ORR
	Riximyo [45]	GP13-301	Equivalence study, randomized, double-blind, parallel	previously untreated, advanced stage follicular lymphoma (629)	ORR
	Blitzima [46]	CT-P10 3.3	non-inferiority, randomized, double-blind, parallel	Advanced Follicular Lymphoma (121)	ORR
	Rixathon [47]	GP13-301	Equivalence study, randomized, double-blind, parallel	previously untreated, advanced stage follicular lymphoma (629)	ORR
	Ritemvia [48]	CT-P10 3.3	non-inferiority, randomized, double-blind, parallel	Advanced Follicular Lymphoma (121)	ORR

Monoclonal antibody	Trade name	Study name or ID	Study design	Population and sample size (N)	Primary endpoint
Trastuzumab	Ogivri [49]	MYL-Her-3001	equivalence study, randomized, double-blinded, parallel	metastatic breast cancer (458)	ORR
	Trazimera [50]	B3271002	equivalence study, randomized, double-blind, parallel	metastatic breast cancer (707)	ORR
		B3271004	non-inferiority study, randomized, double-blind, parallel	operable breast cancer (226)	pCR
	Kanjinti [51]	20120283	equivalence study, randomized, double-blind, parallel	operable breast cancer (725)	pCR
	Ontruzant [52]	SB3-G31-BC	equivalence study, randomized, double-blinded, parallel	operable breast cancer (875)	pCR
	Herzuma [53]	CT-P6 3.2	equivalence study, randomized, double-blind, parallel	operable breast cancer (549)	pCR
	Zercepac [54]	HLX02-BC01	equivalence study, randomized, double-blind, parallel	metastatic breast cancer (649)	ORR

Legend: ORR, overall response rate; pCR, pathological complete response.

Table 3.
Study design and primary endpoint for biosimilar monoclonal antibodies for cancer treatment.

Finally, when all tests are done and the authorization holder will submit the documents to receive the marketing authorization, it can be extrapolating all indications from the reference product to the biosimilar. When biosimilar comparability has been demonstrated in one indication, extrapolation of clinical data to other indications of the reference product could be acceptable but needs to be scientifically justified. It is expected that the safety and efficacy can be extrapolated when biosimilar comparability has been demonstrated in all aspects described before [19, 23, 29].

This condition is not applied in all situations. For example, if a reference monoclonal antibody is licensed both as an immunomodulator and as an anticancer antibody, the scientific justification as regards extrapolation between the two indication is more challenging and may have to involve more specific studies [29].

6. Conclusions

Since monoclonal antibodies play an essential role in cancer treatment and are responsible for high healthcare costs, the development of biosimilars is particularly important in oncology. Several biosimilars of the monoclonal antibodies trastuzumab, rituximab, and bevacizumab have been approved and began to be marketed in Europe, EUA and other countries around the world. More diversification of monoclonal antibodies biosimilars is expected in the next years, as the patent of other molecules will expire.

The biosimilar development pathway consists of a comprehensive comparability exercise between the biosimilar candidate and the reference product, primarily focusing on data from analytical studies. Clinical studies for biosimilar candidates follow a different design to those for a new biological. Adequate information on the biosimilar approval pathway, the robustness of overall evidence used to demonstrate biosimilarity, and how the clinical development of a biosimilar is done is important for all: professional, patient, governments, and other stakeholders.

Conflict of interest

Annemeri Livinalli: is involved in consulting, advisory work and speaking engagements for Amgen, Sandoz, Teva, Servier, Dr. Reddy's, Accord, United Medical, Achè.

Taís Freire Galvão: The author declares no conflict of interest.

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Biosimilar monoclonal antibodies for cancer treatment (Protocol)

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[Intervention Protocol]

Biosimilar monoclonal antibodies for cancer treatment

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the efficacy, effectiveness, and safety of biosimilar monoclonal antibodies for treating cancer, when compared to their originator biologic.

BACKGROUND

Biotechnology products, which are manufactured from living organisms, generate large and structurally complex molecules (Rak 2014), and therefore cannot be reproduced identically by the manufacturers (Vulto 2017). Among those, biosimilar monoclonal antibodies are products that are similar in terms of quality, safety, and efficacy to an already well-known biological product (originator) (WHO 2016).

Minor structural differences between biosimilar products and their originators are acceptable and expected, since inter-batches variability occur even within the originator biologic (Blandizi 2017). Such differences do not significantly affect clinical performance (EMA 2017). As biotherapeutic products indicated for the treatment of human diseases, biosimilars have a successful record in treating many life-threatening and chronic diseases (WHO 2013; WHO 2014).

The European Union (EU) took the lead in developing the principles covering biosimilars in 2005 and released specific guidance for the development of biosimilars (EMA 2019). Other international regulatory agencies have also developed guidelines on evaluation of biosimilars in comparison to their originator. Similarity could be attested by head-to head comparative studies with respect to structural and functional characterisation, in vitro biologic assays, and pharmacokinetic and pharmacodynamics evaluations, as well as clinical studies to compare the safety, efficacy, and immunogenicity (EMA 2012; FDA 2015; WHO 2014; WHO 2018). This proved similarity allows subsequent abbreviation of non clinical and clinical development of the biosimilar, as a result of the knowledge gained during the development, licensing and clinical use of the originator product (WHO 2014).

Complementing this stage of development, EMA included all biosimilars authorised after January 2011 in the list of medicines under additional monitoring, which means these medicines are being monitored particularly closely by regulatory authorities. Additional monitoring aims to enhance reporting of suspected adverse drug reactions, collecting information as early as possible to further inform the safe and effective use (EMA 2019).

Patents of monoclonal antibodies used in cancer treatment began expiring in 2013, with rituximab (GaBI J Editor 2018). It was only in 2017 that the first of these products was approved by the EMA (GaBI J Editor 2018a), and the US Food and Drug Administration (FDA) (FDA 2017). Currently, there are three biosimilar monoclonal antibodies that have obtained marketing authorisation to be used for treating cancer within the EU and the USA (Walsh 2018): rituximab, for the treatment of non-Hodgkinâ€™s lymphoma (EMA 2019a; FDA 2018) and chronic lymphocytic leukaemia (EMA 2019a); trastuzumab, for individuals with certain breast and stomach cancers (EMA 2017a; FDA 2019); and bevacizumab, for the treatment of breast, lung, colorectal, kidney, cervical, and ovary cancer (EMA 2019b; FDA 2017a), as well as glioblastoma (FDA 2017a). Other biosimilars are being developed, such as cetuximab, aimed at the treatment of head and neck, and colorectal cancer (Rifkin 2017).

Individuals with cancer and healthcare professionals express concerns regarding the differences between biosimilars and their originators, as well as the possible impact of these differences in their efficacy and safety. Such negative perception is a barrier to the market uptake of biosimilars, and is the main reason why most physicians are sceptical at exchanging originator products to their biosimilar, according to a systematic review assessing healthcare providers knowledge on biosimilars and their acceptance of these products (Leonard 2019).

Half of 1201 prescriber doctors of biologics surveyed in 2016 in the USA were aware that biosimilars are equivalent to their originator in terms of safety and efficacy. Haematology-oncology physicians were unsure or concerned about the safety of biosimilar medicines, and 43% did not believe biosimilars would be safe and appropriate for use neither by individuals who never received treatment nor by individuals under treatment. Physicians who are uncertain about the safety of biosimilars are more likely not to prescribe them (Cohen 2016). Similar results were obtained by another survey in 2015: of the 1181 individuals who answered, 47% were worried about the safety of biosimilars, 40% were concerned about their efficacy, and 35% were worried about their molecular basis (Peyrin-Biroulet 2016).

Previous experience with generic medicines showed that gaining the trust of all stakeholders is essential to increase the market acceptance of the products (Kang 2018). A similar approach could significantly increase the uptake of biosimilars that are being developed as alternative options, with potentially lower costs and greater access (Patel 2018). The debate would benefit from robust clinical evidence about biosimilars effects in oncology.

Medical expenses related to cancer treatment are on the rise worldwide and the use of biosimilars could be an option to reduce these costs. Synthesis of evidence from clinical trials comparing the use of biosimilar monoclonal antibodies with the use of originator products in cancer treatment may contribute to a better decision-making process regarding therapeutic strategies.

Description of the condition

In 2018, the occurrence of new cases of cancer was estimated at 18.1 million worldwide, of which 9.6 million resulted in death. The most common types of cancer, for both men and women, were lung, breast, prostate, colon, and non-melanoma skin cancer (Bray 2018).

Cancer treatment requires careful consideration of evidence-based options, which can include more than one of the main therapeutic modalities: surgery, radiotherapy, and systemic therapy (WHO 2019). Included in the latter is the cytotoxic chemotherapy, which presents successful results for several types of cancer (Palumbo 2013).

Due to the increasing knowledge on how cancer works, more specifically on gene mutations, biological understanding of cellular events, and pathways driving carcinogenesis, new medicines with specific targets, called targeted and immunotherapeutic agents were developed, which include monoclonal antibodies (Palumbo 2013).

Description of the intervention

Since the registration of rituximab in 1997, the use of monoclonal antibodies is one of the most successful therapeutic strategies for treating both haematological malignancies and solid tumours (Oldham 2008). Since the approval of other monoclonal antibodies for the therapy of cancer and other diseases has increased: by 2017, 57 monoclonal antibodies were available in the market, of which 15 targeted oncology diseases (Grilo 2019).

After the patent expiration of the first biological medicines, biosimilars began to be developed (Lyman 2018). The first biosimilar medicine, called somatropin, was a human recombinant growth hormone approved by the European Medicines Agency (EMA) in 2006. Following this first breakthrough, 20 different biosimilars were approved by the EMA up to 2016 (Saenger 2017). Currently, three biosimilar monoclonal antibodies have obtained marketing authorisation to be used for treating cancer: rituximab, trastuzumab, and bevacizumab.

How the intervention might work

Monoclonal antibodies can kill tumour cells by multiple ways, such as blocking ligand-receptor growth and survival pathways. The main mechanisms of action include antibody-dependent cellular cytotoxicity (ADCC) and complement-mediated cytotoxicity (Weiner 2012). The mechanisms of action of the three biosimilar monoclonal antibodies approved for cancer treatment are described below.

Rituximab is a chimeric monoclonal antibody that has a high-affinity binding to B-lymphocyte antigen CD20 (CD20) on the surface of B cells. When the binding between rituximab and CD20 occurs, B cells die by ADCC, complement-dependent cytotoxicity, and, potentially, by inducing apoptosis (programmed cell death) (Cerny 2002). Rituximab is indicated for a wide range of oncology, rheumatology and nephrology diseases (Greenwald 2018).

CT-P10, which is a rituximab biosimilar, was approved by the EMA in 2017 (EMA 2017b) and by the FDA in the end of 2018 (FDA 2018). The clinical trial that supported the equivalence was conducted with participants with newly diagnosed advanced-stage follicular lymphoma that received either CT-P10 or originator product. In addition, the participants underwent standard chemotherapy for eight cycles (induction period), with a loading dose of 375 mg/m^2 on day one. Non-inferior efficacy, equivalent pharmacokinetics, and similar pharmacodynamics were observed, with a safety profile comparable to the rituximab originator. Up to December 2019, there were five rituximab biosimilar with marketing authorisation in the EU (EMA 2019c).

Trastuzumab is a recombinant humanised monoclonal antibody that binds to the domain of the extracellular segment of the human epidermal growth factor-2 receptor (HER2), and inhibits the proliferation and survival of HER2-dependent tumours (Gemmete 2011). In adults with tumour over-expressing HER-2, trastuzumab combined or not with chemotherapy or hormone therapy is considered the standard treatment (Hudis 2007). The molecular mechanisms of actions could be described in three different ways: HER2 degradation; attraction of immune cells to tumour cells by ADCC; and inhibition of mitogen-activated protein kinase (MAPK) and phosphatidylinositide 3-kinase (PI3K)/serine/threonine protein kinase (Akt) pathways (Vu 2012). Currently, trastuzumab biosimilars are approved for some specific cases of breast cancer and metastatic gastric cancer (FDA 2017).

SB3, a trastuzumab biosimilar, was approved by the EMA in 2017 (EMA 2017a). In the USA, the trastuzumab biosimilar Myl1401O was also approved in 2017 (FDA 2017b). The clinical trial that supported the equivalence between SB3 and the originator product included 875 participants. These participants received either SB3 or originator every three weeks for eight cycles of neoadjuvant chemotherapy, with a loading dose of 8 mg/kg and a maintenance dose of 6 mg/kg. Results supported the efficacy equivalence based on pathologic complete response in primary breast tumour for women with HER2-positive early breast cancer. Safety and immunogenicity was also comparable (Pivot 2018).

Bevacizumab is a humanised inhibitor of vascular endothelial growth factor (VEGF) monoclonal antibody. Either as a single agent or in combination with chemotherapy, it is approved for the treatment of multiple types of cancer(EMA 2019b). It acts by selectively binding circulating VEGF, thereby inhibiting the binding of VEGF to its cell surface receptors, which results in a reduction of microvascular growth of tumour blood vessels, reducing the blood supply to tumour tissues. These mechanisms also decrease interstitial pressure on tissues, increase vascular permeability, favour apoptosis of tumour endothelial cells, and may increase delivery of chemotherapeutic agents (Shih 2006).

ABP 215 is the biosimilar of bevacizumab approved by both the FDA in2017 and the EMA in2018. In order to determine ABP 215 equivalence to its originator, a phase III clinical trial was conducted with 642 participants with advanced non-squamous non-small cell lung cancer. The participants received 15 mg/kg of either ABP 215 or the originator product, administered every three weeks for six cycles (Thatcher 2019).

Why it is important to do this review

In order for a product to be considered as a biosimilar, it must have similar structural and functional characteristics to its originator. These features are established based on pharmacokinetic and pharmacodynamics equivalence, as well as on comparative clinical studies that evaluate safety, efficacy, and immunogenicity (Markus 2017).

Because the biosimilar manufacturer usually does not have access to all manufacturing information on the originator product, the result is a slightly different copy of the original molecule (Lee 2012). These production downsides represent the main source of scepticism among healthcare professionals and individuals with cancer (Cohen 2016; Leonard 2019; Peyrin-Biroulet 2016).

Four systematic reviews on biosimilars for treating cancer have been published (Jacobs 2016; Jacobs 2017; Lee 2019; Yang 2019). Two aimed to describe the characteristics of the scientific publications in the field and would be therefore better categorised as bibliometric surveys (Jacobs 2016; Jacobs 2017). The other two were meta-analyses of biosimilar rituximab for treating non-Hodgkin's lymphoma and rheumatoid arthritis (Lee 2019), and of biosimilar monoclonal antibodies for different types of cancer, with searches up to December, 2018 (Yang 2019).

The main motivation for conducting the present review is to provide best available evidence from clinical studies to support the decision concerning using biosimilar monoclonal antibodies in cancer treatments. This review may give more trustworthy information for individuals with cancer and healthcare professionals, as well as contribute to effective decision-making.

OBJECTIVES

To assess the efficacy, effectiveness, and safety of biosimilar monoclonal antibodies for treating cancer, when compared to their originator biologic.

METHODS

Criteria for considering studies for this review

Types of studies

We will include study reports of randomised controlled trials (RCTs) irrespective of language, publication type or status, for example, online clinical trials results, summaries of otherwise unpublished clinical trials, abstracts, reports from pharmaceutical companies, not peer-viewed publications, provided they contain sufficient data for analysis. We will not impose any limitation regarding the length of follow-up, but we will require the study to contain at least one of the primary or secondary outcomes. Only head-to-head trials that compare the biosimilar and originator medicine will be included.

Types of participants

Eligible participants are adults older than 18 years old of both sexes who were previously diagnosed with cancer of any type and stage, including carcinoma "in situ", locally advanced, recurrent, refractory and/or metastatic disease. Participants may be under treatment with adjuvant and/or neoadjuvant chemotherapy, palliative or in maintenance treatment, as well as other pharmacotherapies for either cancer or concomitant diseases.

Types of interventions

The biosimilar monoclonal antibodies used for cancer treatment and approved by the EMA and FDA until December 2019 are: rituximab, trastuzumab, and bevacizumab. Clinical trials are conducted to evaluate data obtained from each individual biosimilar when compared to its originator product. Therefore, we will include all RCTs performing a head-to-head comparison of biosimilar with a licensed originator product.

- Rituximab (biosimilar) versus originator
- Trastuzumab (biosimilar) versus originator
- Bevacizumab (biosimilar) versus originator

We will not include inactive control interventions, such as placebo or no treatment. We will conduct analyses separately, for each intervention and outcomes, without combining different interventions or outcomes.

We will not restrict the studies included based on the dose, route,frequency, or duration of the treatment, nor duration of follow-up.

Types of outcome measures

Primary outcomes

- In curative treatment: overall survival, progression-free survival, event-free survival, mortality
- In palliative treatment: overall survival

Secondary outcomes

We will assess the objective response rate (ORR), defined as the proportion of complete or partial response measured over six months, a synonym of overall response rate (EMA 2012; FDA 2018a). Based on the guidelines from EMA and FDA, this outcome is able to detect product-related differences (EMA 2012; FDA 2018a) and allows comparing clinical efficacy of the interventions.

Additionaly, we will assess:

- duration of response;
- pathological complete response;
- any adverse event – observed or patient-reported;
- immunogenicity – measured by the proportion of individuals developing anti-drug antibodies and neutralising antibodies.
- health-related quality of life - measured using standardised generic or disease-specific questionnaires

All outcomes will be analysed in a short term (≤ 12 weeks), medium term (>12 weeks ≤ 48 weeks) and long term (> 48 weeks).

We will use the Response Evaluation Criteria in Solid Tumors (RECIST) to assess solid tumour response (Eisenhauer 2009), and we will include the definition for response and progression in ovarian cancer clinical trials, as agreed by the Gynaecological Cancer Intergroup (Rustin 2011). Rituximab is the only biosimilar currently approved to treat haematological malignancies, which include lymphoma and chronic lymphocytic leukaemia. Therefore, we will assess response to non-Hodgkin's and Hodgkin's lymphoma using either the International Working Group (IWG) response criteria (Cheson 2007), or the Lugano Classification (Cheson 2014). The 2007 version of IWG will be considered since it incorporates positron emission tomography, bone marrow immunohistochemistry, and flow cytometry for definitions of response. In the case we find any studies conducted with participants with chronic lymphocytic leukaemia, we will consider the recommendations of the National Cancer Institute-Working Group, 2018 guideline (Hallek 2008).

Minimal clinically important difference threshold will not be defined a priori since meta-analyses will probably include data from three different medicines, used to treat at least five different types of cancer, which would require a definition for each comparison.

Search methods for identification of studies

We have formulated search strategies in collaboration with an Information Specialist of the Cochrane Haematological Malignancies Group.

Electronic searches

We will search for all RCTs on biosimilar monoclonal antibodies in the following sources from inception of each database, with no restriction of date, language, or publication status.

Databases to search:

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (www.cochranelibrary.com/) (Appendix 1);
- Embase via Ovid (1947 to present) (Appendix 2)
- MEDLINE via Pubmed (1966 to present) (Appendix 3)
- Web of Science: Conference Proceedings Citation Index Science (CPCI-S) (Thomson Reuters, 1990 to present) (Appendix 4)

Ongoing trial databases:

- ClinicalTrials.gov (www.clinicaltrials.gov/) (Appendix 5);

- The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (http://apps.who.int/trialsearch/) (Appendix 6);
- EU clinical trials register (www.clinicaltrialsregister.eu) (Appendix 7);
- International Standard Randomised Controlled Trial Number (ISRCTN registry) (www.isrctn.com) (Appendix 7)

Medical subject headings (MeSH) or equivalent, and text word terms were used. Searches were adapted to individual databases.

Immediately before the submission of this review, the search will be re-conducted and if any additional studies are identified they will be incorporated into the review and our findings will be updated as required. We will set up electronic automatic alerts, received by email, to monthly search updates.

Searching other resources

- Handsearching of references

We will screen the references of all included trials and relevant review articles for potentially eligible studies.

- Personal contacts

We will contact experts in the field in order to retrieve their trials.

We will contact authors and investigators when necessary to request further information or for clarification. We will also contact pharmaceutical companies to acquire information on ongoing or unpublished trials.

- Federal government agencies - US Food and Drug Administration and European Medicines Agency

We will search for abstracts of clinical trials published by relevant meetings of the following societies (2010 to present):

- American Society of Hematology;
- American Society of Clinical Oncology;
- European Hematology Association;
- European Society for Medical Oncology;
- American Association for Cancer Research;
- International Association for the Study of Lung Cancer.

Data collection and analysis

Selection of studies

The results of the search strategies of this review will be independently screened by at least two review authors (AL, LCL), in order to assess the titles and abstracts, remove irrelevant reports that do not clearly satisfy the inclusion criteria, and determine which trials we should be further assessed. Multiple reports of the same study will be assessed together.

Disagreements will be resolved through consensus or by a third review author (TFG). We will use Covidence software (Covidence [Computer program]) to manage the results and to identify and remove potential duplications. The selected reports will be evaluated in full text by two review authors (AL, LCL) to verify compliance with eligibility criteria. We will not anonymise the studies in any way before assessment. In the event of disagreement, a third review author will adjudicate (TFG). Further information will be requested to the authors if the article contains insufficient data to make a decision about eligibility. The reasons why potentially-relevant studies failed to meet the eligibility criteria will be recorded in a form and reported in the 'Characteristics of excluded studies' table.

We will document the process of study selection using a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart (Moher 2009).

Data extraction and management

Two review authors (AL, LCL, IRZ, or MTS) will independently extract data using a standardised data extraction form customised on Covidence (Covidence [Computer program]). We will pilot this data extraction form for two included trials and adapt it if necessary.

Review authors will resolve disagreements by consensus. If the review authors are unable to reach a consensus, we will consult a third review author (TFG) for final decision. If required, we will contact the authors of specific studies for supplementary information. After agreement has been reached, we will export all data to Review Manager 5 (Review Manager 2014).

The names of the authors, institutions, and journals will not be anonymous to the review author, nor will the trial outcomes.

We will extract the following information.

- General information: author's name, author's contact address (if available), principal investigator, responsible party of the study, title, publication type, publication date, country, language, duplicate publications.
- Study characteristics: aims, study design/type, clinical setting, location (city, state), start and end dates, study duration, length of follow-up, sample size, inclusion/exclusion criteria, funding sources, number of centres, recruitment dates, power calculation, stopping rules, statistical methods, compliance with assigned treatment, time point of randomisation.
- Participants characteristics: age, sex, ethnicity, total number of participants recruited/allocated/evaluated, number excluded with reasons, participants lost to follow-up, dropout rates with reasons, cancer type and stage, newly diagnosed or relapsed, additional diagnoses, previous treatments, concomitant treatment, protocol violations.
- 'Risk of bias' assessment: random sequence generation, allocation concealment, blinding (participants, personnel, outcome assessors), incomplete outcome data, selective outcome reporting, other sources of bias.
- Interventions: type and dosage of monoclonal antibodies used, route of administration, frequency, duration, number of cycles, co-treatment, timing of intervention, compliance to interventions.
- Measured outcomes: objective response rate, progression-free survival, overall survival, event-free survival, duration of response, pathologic complete response, on-study mortality, adverse events, immunogenicity, health-related quality of life, imputation of missing data.

Assessment of risk of bias in included studies

At least two review authors (AL, LCL, or IRZ) will independently assess the risk of bias of each included study. If they are unable to reach a consensus, they will consult a third review author (TFG) for a final decision.

We will conduct the assessment using the Cochrane tool for assessing risk of bias (Higgins 2019), which includes the following domains:

- randomisation process;
- deviations from intended interventions;
- missing outcome data;
- measurement of the outcome;
- selection of the reported result.

We will judge each criterion using one of the following categories (Higgins 2019):

- 'low risk of bias'
- some concerns';or
- 'high risk of bias'

To ensure transparency in how these judgements were reached, we will include in the 'Characteristics of included studies' table a brief summary of the evidence or rationale underlying the judgement for each study.

If adequate information is unavailable from the trials, trial protocols, or both, we will contact the trial authors to request missing data on 'Risk of bias' items.

Measures of treatment effect

We will use intention-to-treat analysis. If this is not possible, we will perform per-protocol analyses. For dichotomous data we will record the number of events and the total number of participants in both treatment and control groups. We will report the pooled risk ratios (RRs) or odds ratios (ORs) with 95% confidence intervals (CIs) as the measure of treatment effect. We will record the total number of participants in both treatment and control groups, and calculate continuous outcomes as mean differences (MDs) or standardised mean differences (SMDs) with 95% CIs.

We will express time-to-event data as a hazard ratio (HRs) with 95% CIs. If HRs are not available, we will try to estimate as accurately as possible the HR using the available data and a purpose-built method based on Parmar and Tierney approaches (Parmar 1998;Tierney 2007).

Unit of analysis issues

Although we believe to be unlikely that non-standard designs will be included, such as cluster-randomised trials or cross-over trials, we will take into account this level of randomisation, in order to overcome a unit-of-analysis error. We will use methods that are appropriate to the design, as described in chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), considering in these cases, the individual participant as the unit of analysis.

Taking into consideration the probability of finding trials with more than two interventions groups, the recommended approach is to combine relevant groups to create a single pair-wise comparison (Higgins 2011). We will combine arms, as long as they can be considered as subtypes of the same intervention. When arms cannot be combined in such way, we will separately compare each arm with the common comparator.

Dealing with missing data

In case of missing or unclear data, we will attempt to contact the original authors of the study to obtain relevant data.

If standard deviations (SDs) are missing, we will calculate or estimate them by using confidence intervals, standard errors, t values, or P values (Higgins 2011). If missing data cannot be obtained, an imputation method will be used (Furukawa 2006). Sensitivity analyses will be performed to assess the impact of changing the assumptions made.

If data are not reported numerically, but graphically, we will estimate missing data from figures. In the Discussion section we will address the potential impact of missing data on the results of this review.

Assessment of heterogeneity

We will identify heterogeneity by visual inspection of forest plots and statistical methods. Statistical heterogeneity of treatment effects among studies will be assessed using a Chi^2 test, with a significance level of $P < 0.1$. For quantifying inconsistency, we will use the I^2 statistic and will classify it as low ($I^2 < 40\%$), moderate (40% to 75%), or considerable (>75%) (Deeks 2019). Because we assume we will find at least moderate clinical and methodological heterogeneity within the included studies, we will use a random-effects model. If we identify the presence of heterogeneity, we will explore the reasons for it, conducting subgroup analyses. If we cannot find a cause for the heterogeneity, and if it is considerable, we will not perform meta-analysis. The results will be narratively described and shown in tables.

Assessment of reporting biases

We will graphically examine the presence of small-study effects by generating funnel plots to visual inspection. Additionally, if there are at least 10 studies included in the meta-analysis, we will perform Egger test to funnel plot asymmetry (Egger 1997), in accordance with the degree of heterogeneity observed in the step before. We will consider $P < 0.1$ as significant for this test (Page 2019).

Data synthesis

We will use Cochrane's Review Manager (Review Manager 2014) to perform the analyses and follow the recommendations provided by the *Cochrane Handbook for Systematic Reviews of Interventions,* Chapter 9 (Deeks 2019). One review author (AL) will enter the data into the software program, which will be independently checked for errors by a second review author (MTS).

If participants, interventions, comparisons, and outcomes are judged to be sufficiently similar (as determined by consensus), we will perform a meta-analysis and subgroup analyses using the random-effects model to pool data. For dichotomous outcomes we will use the Mantel-Haenszel method. If there is heterogeneity, we will use the inverse variance random-effects method for continuous outcomes. We will use the Peto method when event numbers are

small (odds ratios are close to 1). We will calculate corresponding 95% CIs for all analyses, and will present the results graphically using forest plots

If we find heterogeneity above 75%, and if we identify the reason for such, we will explore this by performing subgroup analyses without calculating an overall estimate. If we cannot find a cause for the heterogeneity then we will not perform meta-analysis.

We will narratively describe the results and present, in tables, outcome data per study for each intervention included, summarising the evidence on objective response rate, progression-free survival, overall survival, mortality, adverse events, immunogenicity, and health-related quality of life.

Subgroup analysis and investigation of heterogeneity

If appropriate, we will perform subgroup analyses or meta-regression to investigate differences among two or more subgroups according to each of the following characteristics of participants, which might have an effect on the outcomes:

- cancer type: solid tumour (breast, lung, and colorectal cancer) and haematological malignancies (non Hodgkin's lymphoma, follicular lymphoma, chronic lymphocytic leukaemia);
- tumour status: tumour, node, and metastases (TNM) classification and grading of malignant tumours, as well appropriate classification and staging system for haematological malignancies;
- participants setting: neoadjuvant, adjuvant, maintenance, palliative and metastatic cancer treatment;
- participants' mean age;
- duration of follow-up.

If additional analyses cannot be conducted by RevMan 5, we will perform analyses in Stata Statistical Software (Stata 2015).

Sensitivity analysis

We will perform sensitivity analyses of outcomes to assess the robustness of the findings. If feasible, we will restrict the analysis of outcomes to studies of low risk of bias, impute missing data considering worst-case scenario, and effects of fixed-effect or random-effects methods (Higgins 2019a).

Certainty of evidence

Two review authors (AL, IRZ) will rate the certainty of evidence by using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) (GRADEpro GDT). The outcomes will be classified in critical, important and not important by the review team with participation of consumers. The outcomes will be assessed considering the five GRADE items: risk of bias; consistency of effect; imprecision; indirectness; and publication bias within-study and across-study, in order to assess and rank, in high, moderate, low, and very low, the certainty of the body of evidence for each outcome (Schünemann 2019).

Consumer participation

We will involve users in the classification of outcomes importance and interpretation of evidence synthesis. We will identify such stakeholders through personal and professional networks prior to conducting this review and will consider their engagement and interest in the research issue.

We plan to hold stakeholder meetings: to present the protocol and its research activities; to classify the relevance of the outcomes; and to review preliminary results after meta-analysis has been carried out. We will encourage the stakeholders to disseminate the results of this review.

'Summary of findings' table

According to the availability of outcome data, up to seven outcomes for each comparison will be selected based on their relevance (from 9 to 1). In a 'Summary of findings' table, we will provide key information concerning the certainty of evidence, the magnitude of effect, and the sum of available data for each of the three interventions of interest (rituximab, trastuzumab, and bevacizumab) in each cancer type.

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APPENDICES

Appendix 1. the Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1 MeSH descriptor: [Neoplasms by Site] explode all trees

#2 MeSH descriptor: [Neoplasms by Histologic Type] explode all trees

#3 neoplas*

#4 tumor* or tumour*

#5 cancer*

#6 Krebs*

#7 malignan*

#8 carcino* or carcinomatos*

#9 karzino* or karzinom*

#10 sarcom*

#11 lymphom*

#12 leukaem* or leukem* or leucem*

#13 melano*

#14 metastas*

#15 mesot*eli*

#16 gliom*

#17 glioblastom*

#18 osteosarcom* or osteo-sacrom*

#19 blastom*

#20 neuroblastom*

#21 adenocarcinoma*

#22 myeloma*

#23 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22

#24 MeSH descriptor: [Biosimilar Pharmaceuticals] explode all trees

#25 biosimilar*

#26 biopharmaceutical*

#27 #24 or #25 or #26

#28 #23 and #27

Appendix 2. Embase (via Ovid) search strategy

#	Searches
1	exp NEOPLASM/
2	exp NEOPLASMS SUBDIVIDED BY ANATOMICAL SITE/
3	neoplas*.tw,kw.
4	(tumor* or tumour*).tw,kw.
5	(Krebs* or cancer*).tw,kw.
6	malignan*.tw,kw.
7	(carcino* or karzino*).tw,kw.
8	sarcom*.tw,kw.
9	leuk#?m*.tw,kw.
10	lymphom*.tw,kw.
11	melano*.tw,kw.
12	metastas*.tw,kw.
13	(mesothelio* or mesotelio*).tw,kw.

(Continued)

14	carcinomatos*.tw,kw.
15	(gliom* or glioblastom*).tw,kw.
16	(osteosarcom* or osteo-sarcom*).tw,kw.
17	(blastom* or neuroblastom*).tw,kw.
18	adenocarcinoma*.tw,kw.
19	myeloma*.tw,kw.
20	or/1-19
21	BIOSIMILAR AGENT/
22	biosimilar*.tw,kw.
23	biopharmaceutical*.tw,kw.
24	or/21-23
25	RANDOMIZED CONTROLLED TRIAL/
26	CONTROLLED CLINICAL STUDY/
27	random*.ti,ab.
28	RANDOMIZATION/
29	INTERMETHOD COMPARISON/
30	placebo.ti,ab.
31	(compare or compared or comparison).ti.
32	(open adj label).ti,ab.
33	((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
34	double blind procedure/
35	parallel group$1.ti,ab.
36	(crossover or cross over).ti,ab.
37	((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.
38	(controlled adj7 (study or design or trial)).ti,ab.
39	(volunteer or volunteers).ti,ab.
40	trial.ti.
41	or/25-40

(Continued)

42	20 and 24 and 41

Appendix 3. MEDLINE via PubMed search strategy

"NEOPLASMS BY SITE"[MeSH Terms]) OR "NEOPLASMS BY HISTOLOGIC TYPE"[MeSH Terms]) OR neoplas*[Text Word] OR tumor*[Text Word] OR tumour*[Text Word] OR cancer*[Text Word] OR krebs*[Text Word] OR malignan*[Text Word] OR carcino*[Text Word] OR karzino*[Text Word] OR sarcom*[Text Word] OR lymphom*[Text Word] OR leukem*[Text Word] OR leukaem*[Text Word] OR melano*[Text Word] OR metastas*[Text Word] OR mesothelio*[Text Word] OR mesoteli*[Text Word] OR carcinomatos*[Text Word] OR gliom*[Text Word] OR glioblastom*[Text Word] OR osteosarcom*[Text Word] OR osteo-sarcom*[Text Word] OR blastom*[Text Word] OR neuroblastom*[Text Word] OR adenocarcinoma*[Text Word] OR myeloma*[Text Word] AND "BIOSIMILAR PHARMACEUTICALS"[MeSH Terms]) OR biosimilar*[Text Word] OR biopharmaceutical*[Text Word] AND "randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR randomi?ed[Title/Abstract] OR placebo[Title/Abstract] OR "drug therapy" OR randomly[Title/Abstract] OR trial[Title/Abstract] OR groups[Title/Abstract]

Appendix 4. Web of Science search strategy

#1	TS=NEOPLASM
#2	TS=neoplas*
#3	TS=(tumor* or tumour*)
#4	TS=(Krebs* or cancer*)
#5	TS=malignan*
#6	TS=(carcino* or karzino*)
#7	TS=sarcom*
#8	TS=(leukaem* or leukem*)
#9	TS=lymphom*
#10	TS=melano*
#11	TS=metastas*
#12	TS=(mesothelio* or mesotelio*)
#13	TS=carcinomatos*
#14	TS=(gliom* or glioblastom*)
#15	TS=(osteosarcom* or osteo-sarcom*)
#16	TS=(blastom* or neuroblastom*)
#17	TS=adenocarcinoma*
#18	TS=myeloma*
#19	OR/1-18/

(Continued)

#20	TS=BIOSIMILAR AGENT
#21	TS="BIOSIMILAR PHARMACEUTICALS"
#22	TS=biosimilar*
#23	TS=biopharmaceutical*
#24	#20 OR #21 OR #22 OR #23
#25	ALL="RANDOMIZED CONTROLLED TRIAL"
#26	ALL="CONTROLLED CLINICAL STUDY"
#27	TS=random*
#28	ALL=RANDOMIZATION
#29	ALL="INTERMETHOD COMPARISON"
#30	TS=placebo
#31	TI=(compare or compared or comparison)
#32	TS=(open adj label)
#33	TS=((double or single or doubly or singly) adj (blind or blinded or blindly))
#34	ALL="double blind procedure"
#35	TS=parallel group$1
#36	TS=(crossover or cross over)
#37	TS=(volunteer or volunteers)
#38	TI=trial
#39	OR/25-38
#40	#19 AND #24 AND #39

Appendix 5. ClinicalTrials.gov

Condition: cancer OR neoplasm OR lymphoma OR leukemia OR leukaemia

AND

Other terms: biosimilar OR CT-P10 OR 1B8 OR BCD 020 OR GP 2013 OR PF 05280586 OR RTXM 83 OR SAIT 101 OR IBI301 OR HLX01 OR JHL1101 OR PF 06439535 OR ABP 215 OR BCD 021 OR RPH 001 OR BAT 1706 OR HLX04 OR CT P15 OR STI-001 OR APZ001 OR ABP 494 OR Ch225 OR ABP 980 OR Myl 1401O OR BCD 022 OR FTMB OR PF 05280014 OR SB3 OR CT P6 OR ALT02

Appendix 6. The World Health Organization (WHO) International Clinical Trials Registry Platform

#1 condition: cancer / intervention: biosimilar

#2 condition: neoplasm / intervention: biosimilar

#3 biopharmaceutical AND cancer

#4 biosimilar AND lymphoma

Appendix 7. EU Clinical Trials Register, ISRCTN

#1 biosimilar AND cancer

#2 biosimilar AND lymphoma

CONTRIBUTIONS OF AUTHORS

Draft of the protocol: AL, IRZ, LCL, MTS, TFG

Development and application of the search strategy: AL, TFG. Cochrane Haematological Malignancies Information Specialist provided support.

Obtained copies of studies: AL

Selection of which studies to include: (2 people) AL, LCL

Extraction of data from studies (2 people) AL, LCL

Assessment of risk of bias: AL, IRZ, LCL, TFG

Entering data into RevMan AL

Conduction of analyses: AL, IRZ, MTS, TFG

Interpretation of analyses: AL, MTS, TFG

Assessment of the quality of evidence: AL, LCL, TFG

Draft of the final review: AL, IRZ, LCL, MTS, TFG

Update of the review: AL, TFG

DECLARATIONS OF INTEREST

Taís Freire Galvão: none known

Annemeri Livinalli: reports having recently received (2018/2019) consultancy fees from Amgen/Bergamo, Dr Reddy´s, Accord, United Medical, Aché and Sandoz; and lecture fees from Dr Reddy´s and Sandoz.

Luciane Cruz Lopes: reports having recently received (2018/2019) lecture fees from Sandoz.

Ivan Ricardo Zimmermann: none known

Marcus Tolentino Silva: none known

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