



**UNIVERSIDADE ESTADUAL PAULISTA
“JÚLIO DE MESQUITA FILHO”
FACULDADE DE MEDICINA**

Carolina Fumico Massuda Araujo

**Metformin for the treatment of breast cancer: a scoping
review of randomized clinical trials**

Tese apresentada à Faculdade de
Medicina, Universidade Estadual
Paulista “Júlio de Mesquita Filho”,
Câmpus de Botucatu, para obtenção do
título de Doutora em Saúde Coletiva.

Orientador: Prof. Dr. Edison Iglesias de Oliveira Vidal

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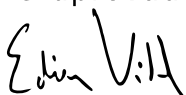
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ATA DA DEFESA PÚBLICA DA TESE DE DOUTORADO DE CAROLINA FUMICO MASSUDA ARAUJO, DISCENTE DO PROGRAMA DE PÓS-GRADUAÇÃO EM SAÚDE COLETIVA, DA FACULDADE DE MEDICINA - CÂMPUS DE BOTUCATU.

Aos 10 dias do mês de novembro do ano de 2023, às 08:00 horas, por meio de Videoconferência, realizou-se a defesa de TESE DE DOUTORADO de CAROLINA FUMICO MASSUDA ARAUJO, intitulada **Metformina para o tratamento de câncer de mama: uma revisão de escopo de ensaios clínicos randomizados**. A Comissão Examinadora foi constituída pelos seguintes membros: Prof. Dr. EDISON IGLESIAS DE OLIVEIRA VIDAL (Participação Virtual) do(a) Depto. de Clínica Médica / FM/Botucatu - Unesp, Profa. Dra. CRISTIANE MURTA RAMALHO NASCIMENTO (Participação Presencial) do(a) Depto. de Saúde Pública / FM/Botucatu - Unesp, Prof. Dr. MÁRIO CÍRIO NOGUEIRA (Participação Virtual) do(a) Depto. de Saúde Coletiva / FACMED/Juiz de Fora - UFJF, Prof. Dr. LEONARDO ROBERTO DA SILVA (Participação Virtual) do(a) Centro de Atenção Integral à Saúde da Mulher (CAISM/Unicamp), Prof. Dr. MAXIMILIANO RIBEIRO GUERRA (Participação Virtual) do(a) Depto de Saúde Coletiva / Universidade Federal de Juiz de Fora, Faculdade de Medicina. Após a exposição pela doutoranda e arguição pelos membros da Comissão Examinadora que participaram do ato, de forma presencial e/ou virtual, a discente recebeu o conceito final: __ APROVADA __. Nada mais havendo, foi lavrada a presente ata, que após lida e aprovada, foi assinada pelo(a) Presidente(a) da Comissão Examinadora.



Prof. Dr. EDISON IGLESIAS DE OLIVEIRA VIDAL

DEDICATÓRIA

Aos meus amados pais, Tochie e Edilberto, por todo o amparo, confiança, dedicação e incentivo ao longo desta vida.

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“Queres de verdade ser santo? -
Cumpre o pequeno dever de cada
momento; faz o que deves e está no
que fazes”.

São Josemaria Escrivá

Resumo

ARAUJO, C. F. M. **Metformina para o tratamento do câncer de mama: uma revisão de escopo de ensaios clínicos randomizados**. 2023. 161f. Tese (Doutorado) – Faculdade de Medicina de Botucatu, Universidade Estadual Paulista, Botucatu, 2023.

Objetivo: Mapear a literatura de ensaios clínicos randomizados (ECRs) com metformina no tratamento do câncer de mama.

Delineamento: Revisão de escopo.

Fontes de dados: Entre abril e outubro de 2021, foram pesquisadas cinco bases de dados eletrônicas (MEDLINE, EMBASE, CENTRAL, LILACS e Web of Science), bem como literatura cinzenta em OpenGrey, National Library of Medicine Bookshelf e ClinicalTrials.gov, a Plataforma Internacional de Registro de Ensaios Clínicos da Organização Mundial da Saúde, o Google Scholar e pesquisamos manualmente listas de referências, resumos de conferências e referências de especialistas.

Crítérios de elegibilidade: Eram elegíveis quaisquer ECRs em que a metformina tenha sido usada para o tratamento de pessoas adultas com câncer de mama. Não foram impostas restrições de contexto, idioma, data de publicação ou desfechos.

Extração e síntese de dados: Dois revisores independentes mapearam os dados dos estudos incluídos com base nos fenótipos do câncer de mama, estágios e modalidades de tratamento.

Resultados: Vinte e cinco dos 40 estudos incluídos apresentavam alguma forma de resultado (artigos completos ou resumos), correspondendo a um total de 5.623 participantes. A maioria dos ensaios não forneceu resultados específicos por fenótipo. Ao todo, 107 desfechos diferentes foram relatados, dos quais os mais comuns foram: sobrevivência geral (SG), sobrevida livre de doença (SLD), sobrevivência livre de progressão, taxa de resposta objetiva, resposta patológica completa, taxa de benefício clínico, cirurgia conservadora e qualidade de vida. Há evidência limitada de uma análise de subgrupo de pacientes HER2+ de um único ensaio clínico grande sugerindo que a metformina possa melhorar a SG e SLD.

Conclusões: Os presentes achados destacam a necessidade de padronizar a publicação de resultados dos ECRs por fenótipo do câncer de mama e revelam o potencial para expandir o conhecimento neste campo a partir da determinação retrospectiva dos fenótipos dos participantes, o que poderia permitir metanálises de dados de pacientes individuais.

Palavras-chave: metformina; câncer de mama; revisão; ensaio clínico.

Abstract

ARAUJO, C. F. M. **Metformin for the treatment of breast cancer: a scoping review of randomized clinical trials**. 2023. 161f. Thesis (Doctorate) – Faculty of Medicine of Botucatu, Universidade Estadual Paulista, Botucatu, 2023.

Objective: We aimed to map the literature of randomized clinical trials (RCTs) of metformin for the treatment of breast cancer.

Design: Scoping review.

Data sources: Between April and October 2021, we searched five electronic databases (MEDLINE, EMBASE, CENTRAL, LILACS, and Web of Science), as well as grey literature on OpenGrey, National Library of Medicine Bookshelf, and ClinicalTrials.gov. the World Health Organization's International Clinical Trials Registry Platform, and Google Scholar, hand-searched reference lists, conference abstracts, and sought specialist input.

Eligibility criteria: We included any RCT where metformin was used for the treatment of adult patients with breast cancer. We did not impose any restrictions on context, language, publication date, or outcomes.

Data extraction and synthesis: Two independent reviewers charted the data from the included studies based on breast cancer phenotypes, stages, and treatment modalities.

Results: Twenty-five out of 40 included studies had some form of published results (full text or abstracts) amounting to 5,623 participants. Most trials did not provide phenotype-specific results. In total, there were 107 different reported outcomes, the most frequent of which were: overall survival (OS), disease-free survival (DFS), progression-free survival, objective response rate, pathological clinical response, clinical benefit rate, breast conservation rate, and quality of life. There is limited evidence from a subgroup analysis of HER2+ participants from a single large study suggesting that metformin might improve OS and DFS.

Conclusions: Our findings emphasize the need to standardize the reporting of trial results by breast cancer phenotype and reveal the potential to expand the current knowledge base in this field through the retrospective determination of participant phenotypes that could allow cost-effective individual patient data meta-analyses.

Keywords: metformin; breast cancer; review; clinical trial.

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List of abbreviations and acronyms

AC	adriamycin, cyclophosphamide
AC-T	adriamycin, cyclophosphamide, paclitaxel
AC-TH	doxorubicin/cyclophosphamide/paclitaxel/trastuzumab
AMH	anti-mullerian hormone
ANZCTR	Australian New Zealand Clinical Trials Registry
BC	breast cancer
BCR	breast conservation rate
BMI	body mass index
CBR	clinical benefit rate
CBS	conservative breast surgery
cCr	clinical complete response
CI	confidence interval
CRC	colorectal cancer
CRP	C-reactive protein
CT	chemotherapy treatment
DFS	disease-free survival
DIN	ductal intraepithelial neoplasia
DLT	dose limiting toxicity
DRFS	distant recurrence-free survival
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EC-T	epirubicin/cyclophosphamide/paclitaxel
EC-TH	epirubicin/cyclophosphamide/paclitaxel/trastuzumab
EORTC-QLQ-C30	European Organization for Research and Treatment for Cancer Quality of Life Questionnaire
ER	estrogen receptor
EUCTR	European Union Clinical Trials Register
FBG	fasting blood glucose
FDA	Food and Drug Administration
FDC	fluoruracil, doxorubicin, cyclophosphamide
FMD	fasting-mimicking diet
GLOBOCAN	Global Cancer Observatory
HbA1c	glycated hemoglobin
HC	homocysteine
HER2	human epidermal growth factor receptor 2
HOMA-IR	homeostasis model assessment for insulin resistance
HT	hormonal therapy
IARC	International Agency for Research on Cancer
ICTRP	International Clinical Trials Registry Platform
IDFS	invasive disease-free survival
IGF-1	insulin-like growth factor 1
IGFBP-3	insulin-like growth factor binding protein 3
IPD	individual patient data

IQR	interquartile range
ISRCTN	International Standard Randomised Controlled Trial Number
LIN	lobular intraepithelial neoplasia
LVEF	Left Ventricle Ejection Fraction
MLT	melatonin
MMA	methylmalonic acid
MRI	magnetic resonance imaging
MTF	metformin
NACT	neoadjuvant chemotherapy
NAST	neoadjuvant systemic therapy
NCIC CTG MA.32	National Cancer Institute of Canada - Clinical Trials Group MA.32
NeoCT	neoadjuvant chemotherapy
NI	not informed
NPLD	non-pegylated liposomal doxorubicin
NSAI	non-steroid aromatase inhibitor
OpenGrey	System for Information on Grey Literature in Europe
ORR	objective response rate
OS	overall survival
PCC	population, concept, and context
PCOS	polycystic ovarian syndrome
pCR	pathological complete response
PD	pharmacodynamic
PFS	progression-free survival
PgR	progesterone receptor
PI	principal investigator
pPR	partial pathological response
PRISMA-ScR	preferred reporting items for systematic reviews and meta-analyses extension for scoping reviews
QoL	quality of life
RFS	recurrence-free survival
RR	response rates
RRR	radiological response rate
SAI	steroid aromatase inhibitor
SAP	statistical analyses plan
SHBG	sex hormone-binding globulin
SNP	single nucleotide polymorphism
T2DM	type 2 diabetes mellitus
TCb-H	docetaxel/carboplatin/ docetaxel/trastuzumab
TCH+P	Taxotere, Carboplatin, Herceptin + Pertuzumab
TEC	docetaxel, epirubicin and cyclophosphamide
TNBC	triple-negative breast cancer
WHO	World Health Organization

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1. Introduction¹

Breast cancer is the most common cancer worldwide and has a significant impact on the global number of cancer deaths ^[1]. In December 2020, the International Agency for Research on Cancer (IARC) updated the online database GLOBOCAN (Global Cancer Observatory), which estimated that 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred around the world ^[2].

According to the agency, female breast cancer has surpassed lung cancer as the most commonly diagnosed cancer in both sexes and all ages ^[1]. Worldwide, there are over 2.3 million new cases of breast cancer, accounting for 11.7% of all new cancer cases and making up 24.5% of all cancers in women. Continuing with the statistics, lung cancer appeared next at 11.4%, followed by colorectal at 10.0%, prostate at 7.3%, and stomach cancer at 5.6%. Nevertheless, lung cancer remained the leading cause of cancer-related deaths, accounting for an estimated 1.8 million deaths (18%). It was followed by colorectal cancer at 9.4%, liver cancer at 8.3%, stomach cancer at 7.7%, and female breast cancer at 6.9%. In 2020, 685,000 deaths occurred due to breast cancer.

There are predictions for the year 2040 that the burden of breast cancer will increase to over 3 million new cases and 1 million deaths every year due to population growth and aging alone ^[3]. Therefore, global initiatives are essential to counteract its growing burden, particularly in low and middle-income countries experiencing a rapid increase in incidence rates and persistently high mortality rates.

Breast cancer treatments are expensive and chemotherapy treatments are related to major toxicities. In the USA, the disease has the highest treatment cost of any cancer, accounting for 14% of all cancer treatment costs ^[4]. In 2020, the cost of medical services for breast cancer was \$26.2 billion, with an additional \$3.5 billion spent on prescription drugs. Furthermore, chemotherapy is a common treatment for breast cancer and has been shown to improve survival. However, it often leads to adverse effects,

¹ A presente tese de doutorado será utilizada na submissão do manuscrito para apreciação de revisores de revista científica para publicação dos resultados da revisão de escopo. Por essa razão o texto encontra-se em inglês.

including nausea, dysgeusia, peripheral neuropathy, loss of appetite, myalgia, and peripheral edema, which can significantly impact various aspects of quality of life ^[5]. Due to the high cost and toxicity associated with treatment, less aggressive and more affordable breast cancer treatments are desirable.

Metformin is one of the most common medications used worldwide and has been used for more than 60 years proving its efficacy and safety ^[6]. It is a synthetic biguanide often prescribed as the drug of choice to treat type 2 diabetes mellitus (T2DM). The usual dose of metformin (0.5–2.5 g daily), administered orally, is effective for long-term glycaemic control, with notable improvements in glycated hemoglobin (HbA1c) ^[7]. In addition, it is an extremely inexpensive medication, costing about 15 cents per tablet ^[6]. Nowadays, it is used daily by more than 200 million diabetic patients around the world as monotherapy or in combination with other medications. Nevertheless, the precise mechanisms responsible for its therapeutic benefits are still not fully comprehended ^[8].

In 2011, the World Health Organization (WHO) recognized the significance of metformin in managing individuals with T2DM globally by adding it to their list of essential medicines, alongside sulfonylureas and insulin ^[9]. In the United Kingdom, the prescription rate of metformin as antidiabetic drug showed a significant increase, rising from 55.4% in 2000 to 83.6% in 2013, among those who were using at least one medication for managing diabetes ^[10]. Similarly, metformin use as first-line treatment increased from 60% in 2005 to 77% in 2016 in the USA ^[11], demonstrating the influence of national and international prescribing guidelines ^[7].

There are several public health interests in the repurposing of old generic drugs ^[12]. Repositioning involves the investigation of existing medications for new therapeutic purposes. There is no doubt that it is a unique cheaper strategic way of innovation with some advantages if compared with the long process of developing new drugs from the scratch. Generic drugs have already passed all the phases required by regulatory agencies to be approved for commercialization with their initial indication. They have a well-established pharmacodynamics and pharmacokinetics profile, in addition to a safety profile with well-mapped adverse effects.

It is important to note that in the past decade, additional applications for metformin use have increased. Over the past few years, we now have evidence of

several other beneficial roles of metformin such as preventing diabetes, managing gestational diabetes ^[13], and treating polycystic ovarian syndrome (PCOS) ^[14]. Indeed, metformin has shown promising effects against certain types of cancers and are being investigated in several experimental studies including *in vitro* and/or *in vivo* ^[15], observational studies ^[16], and interventional trials ^[17].

The number of RCTs in breast cancer is increasing, but the landscape remains unclear ^[18]. Breast cancer is a heterogeneous disease with great variation in its morphological and molecular characteristics, as well as in its clinical response treatment. Moreover, different stages of breast cancer are associated with distinct treatment modalities, which are associated with a variety of specific outcomes.

Importantly, a recent systematic review attempted to assess the evidence from RCTs on the effectiveness of metformin in the treatment of breast cancer ^[17]. However, the study has methodological limitations, was restricted to a limited range of outcomes and did not consider the different phenotypes, stages of breast cancer, or the treatment modalities examined in the original studies. These factors are central to the appropriate interpretation of the effectiveness of any breast cancer treatment.

To date, metformin does not have an established role in breast cancer therapy. However, public health systems can be more efficient by offering the population more benefits to an increasing and mortal disease like breast cancer at a low cost. Given the sources of clinical heterogeneity underlying breast cancer and the many clinical trials conducted or planned to be initiated in this field, a scoping review is needed to show the extent of the unclear landscape. Therefore, our goal in this scoping review was to map the literature on RCTs of metformin for the treatment of breast cancer.

2. Methods

2.1 Registration of the scoping review protocol

This scoping review was conducted by the recommendations of the Joanna Briggs Institute guide for systematic scoping reviews ^[19]. We made the registration of the protocol with Open Science Framework ^[20] ([osf. io/yquba](https://osf.io/yquba)) and we published it elsewhere ^[21]. The publication of the protocol is available in Appendix A.

2.2 Scoping review questions

We pursued the answers to the following research questions:

1. What is the extent of the randomized clinical trials literature on the use of metformin in the treatment of breast cancer?
2. What phenotypes and stages of breast cancer were examined in those studies?
3. What treatment modalities, regimens, and comparators were used in those studies?
4. What outcomes were evaluated in those studies and what were their main findings?

2.3 Eligibility criteria

We delineated the eligibility criteria following the 'population, concept, and context' (PCC) framework.

2.3.1 Population

We included adult patients of both sexes from 18 years old with any phenotype and stage of breast cancer. We considered the reports as belonging to the same study when the investigated population was the same. We considered those studies that used a subset of the population of a larger study as substudies.

2.3.2 Concept

We accepted RCTs that have made any intervention for treating breast cancer using metformin. Regarding the unit of randomization of the trials, we included both individuals and clusters of individuals in the population. We enclosed trials that intervened with the anti-diabetic drug either alone or in combination with other systemic pharmacological treatments (hormone therapies or chemotherapies), radiation therapy, surgical procedures, or behavioral interventions such as weight loss, exercise training, or nutrition intervention.

We included studies that used a placebo, standard treatment, or other behavioral intervention as long as they did not include metformin as a comparator/control. Those studies involving the use of metformin combined with other treatments must have a comparator using the same treatments without metformin so the drug effect could be identified. For those studies that investigated metformin alone, we also accepted control groups with no treatment. We did not limit the outcomes evaluated in the selected studies. Precisely, we intended to map the outcomes defined by the clinical trials that proposed to investigate metformin for breast cancer treatment.

2.3.3 Context

There were no restrictions related to the context, language, or date of publication of the studies reports identified to be included in the scoping review.

2.4 Searches

On April 2021, we searched the following bibliographic databases for potential studies: MEDLINE through PubMed, EMBASE, LILACS, Web of Science, and CENTRAL. The electronic search strategies are shown in the Supplementary Online Appendix of the published protocol ^[21] and in Appendix B. Additionally, we conducted a grey literature search in two databases: System for Information on Grey Literature in Europe (OpenGrey) and the National Library of Medicine Bookshelf.

Besides looking for relevant studies in databases we also searched some registers. On April 2021, we screened ClinicalTrials.gov. Then, on October 2021, we investigated the WHO International Clinical Trials Registry Platform (ICTRP).

We further extended our search efforts through other methods. On October 2021, we searched websites via Google Scholar and we also hand-searched reference lists of relevant publications, conference abstract books, and specialist referrals.

Finally, during the analysis data of this review, we made an actualization search. In September 2023, we verified if the results of ongoing included studies had been published. We did not identify publications of those results between the time we initiated the searches of primary studies and this second update search.

2.5 Selection of the studies

The study selection process followed careful identification steps. First, two researchers independently screened and reviewed the titles and the abstracts of all records indexed in databases using Rayyan software ^[22]. Second, they examined separately the full version of selected records of the first step. Third, the reviewers independently selected the first 200 results found via Google Scholar through Publish or Perish software ^[23] and screened them using Rayyan software again. Lastly, the investigators hand-searched the reports included as they extracted data for the review. A third reviewer solved the disagreements that appeared between the reviewers during the processes.

2.6 Data charting process

We developed a data extraction form to collect information from the included studies. A pre-pilot data extraction with one of the studies included in the review was performed independently by the two reviewers. Subsequently, we refined the standardized form according to the progress of data charting process. The whole extraction was made duplicated separately by the two reviewers. Disagreements about extracted data were solved by discussion and consensus, and an independent third reviewer was consulted when conflicts and doubts persist. We did not appraise the methodological quality of included articles in order to be aligned with methodological guidelines for scoping reviews.

Extracted data included: first author; study title; reports used for the data extraction; complete reference; is this a secondary report from a larger study?; the time period when the study was conducted; the geographical location where the study took place; study design; study protocol; type and frequency of breast cancer phenotypes, type and frequency of histological subtypes, type and frequency of other genetic characteristics (e.g. single nucleotide polymorphism (SNP) CA/CC vs AA); type and frequency of breast cancer stage been investigated; were other types of cancer included?; inclusion/exclusion criteria; sample size; characteristics of the population

(e.g., mean age, mean BMI, frequency of obesity/overweight, menopause, physical activity, presence of comorbidities such as diabetes, hypertension, hyperlipidemia, and metabolic syndrome, frequency of treatment line chemotherapy provided in palliative care); details of the interventions, including treatment modality (i.e., neoadjuvant or adjuvant; palliative, prevention of recurrence after the end of cancer treatment, or other), metformin dose, frequency and duration of metformin treatment, cointerventions; details of comparators, including type, dose, frequency, and duration; follow-up; outcome measures with the definitions used by the studies authors; statistical analyses; results; adverse events; conclusions reported by the study authors; research limitations; funding sources, and references cited in studies reports to be researched for being potential to our review. In addition, there was a field for free registration of other relevant information deemed by the reviewers and a field for possible information that we would like to ask the authors.

Published articles with results were chosen to guide the full filling of extraction forms because they show the most recent and complete data related to the study. Reports like the study protocol and conference abstracts supported the charting of the data; however, they did not supply enough information that justifies the filling of their form. Commonly, researchers make the results of their studies available in more than one article. To better organize one study's data that are spread across multiple published articles we filled out one form per report of the study which is an article with results.

We stored the data extracted from each study in digital word-processing documents. At the same time, we organized the same data in digital spreadsheets in a summarized format while filling out the standardized forms. This approach facilitated a comprehensive overview of all studies and allowed for effective data synthesis.

2.7 Collating, summarizing, and reporting results

We structured the presentation of our results around the different phenotypes of breast cancer, their stages, treatment modalities, types of interventions with metformin, comparators, outcomes evaluated in the primary studies, and their main findings. We

built figures to present the results of the most relevant clinical outcomes evaluated by more than one included study. For these figures, we adopted the criterion of signaling positive results if at least one aspect of the outcome assessed by the study was positive. For example, if a significantly better overall survival (OS) was observed in the luminal phenotype of breast cancer, but no difference was observed for other phenotype subgroups, the result for the OS outcome was indicated as positive for that study in the figure.

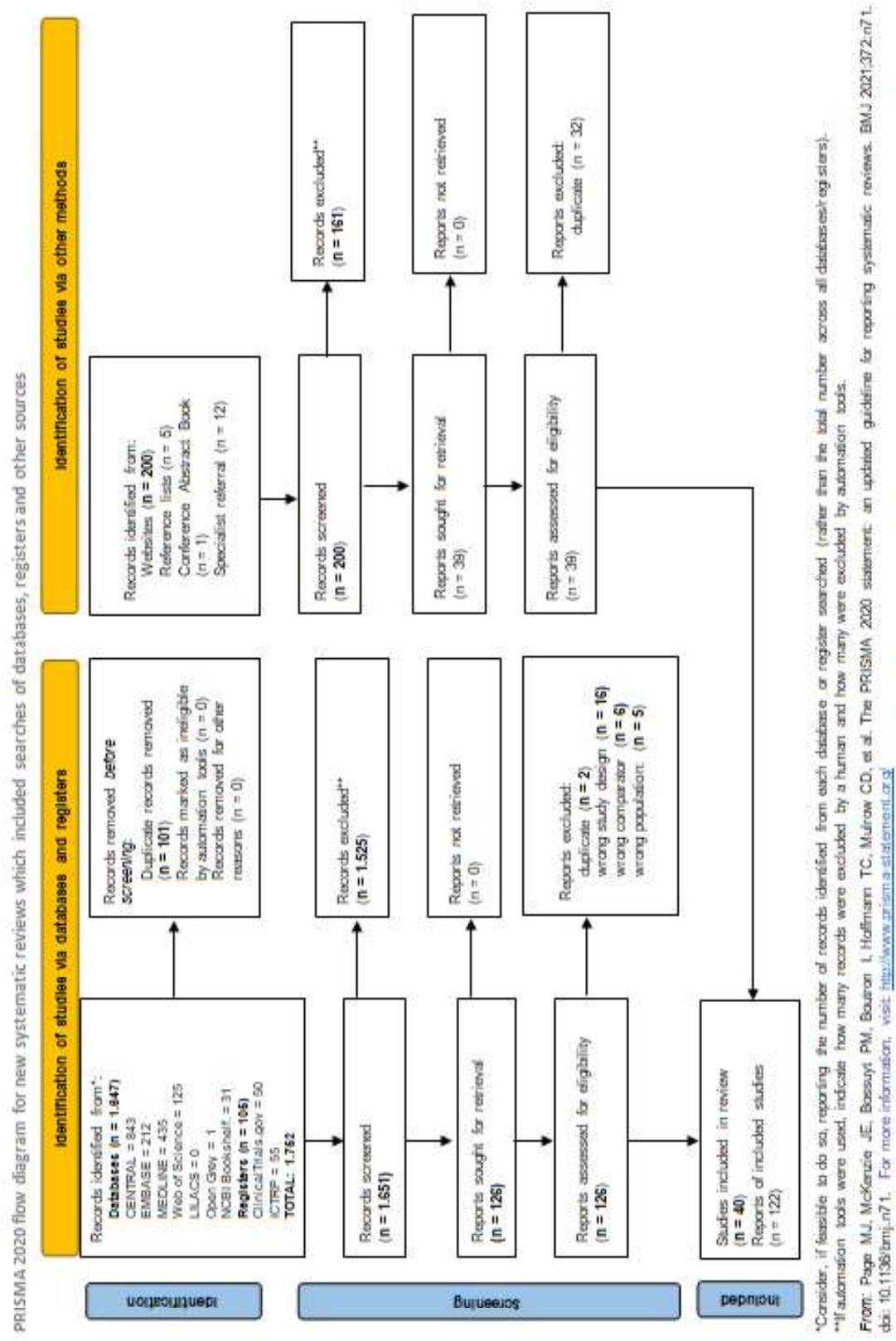
Reporting of results was guided with an adapted version of the PRISMA-ScR statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) ^[24]. Our adapted PRISMA-ScR checklist comprising our review is available in Table 1 in Appendix C.

3. Results

3.1 Selection of studies and reports

We identified 40 studies based on eligibility criteria outlined by our PCC framework. Our searches identified 122 reports related to the 40 studies that were included in the scoping review after screening titles and abstracts and examining full versions of potentially relevant studies. Figure 1 outlines the flowchart for report inclusion ^[25], which involved searches of databases, registers, and other sources. Appendix D describes the details of the reports that were evaluated in full and excluded from databases (Table 2), ICTRP (Table 3), and Google Scholar (Table 4), along with the reasons for their exclusion. The reasons for exclusion were based on incompatibilities with our eligibility criteria previously mentioned. They included duplicate studies, incorrect study designs, mismatched populations, and incorrect comparators.

Figure 1- Flow diagram of included studies in the scoping review



3.2 Nature of reports

Out of the 122 reports, 39 were full articles, 42 were protocols, 37 were conference abstracts, two were statistical analysis plans (SAP), only one was a thesis related to the study with the protocol number EudraCT 2007-000306-70 ^[26], and only one was a feasibility study whose results were available in the European Union Clinical Trials Register (EUCTR) ^[27]. In addition, our review encompassed four large studies, each of which included several substudies: the MYME Trial ^[28,29], the METTEN Trial ^[30–33], the NCIC CTG MA.32 (National Cancer Institute of Canada - Clinical Trials Group MA.32) ^[34–40], and a trial with the protocol number EudraCT number 2008-004912-10 ^[41–44].

3.3 Availability of studies results

The dissemination of results from the included studies exhibited a heterogeneous and often incomplete pattern. Out of the 40 identified studies, 25 had some form of results published, with 19 ^[28,30,34,41,45–59] of them appearing as full articles and six ^[27,60–64] having results published solely in the form of abstracts. In contrast, 15 of the included studies did not have published results; for 11 of them, only their protocols were available ^[65–75], and four were terminated prematurely without their results being published ^[76–79].

In addition, the characteristics of included studies with published results are available in Table 5 in Appendix E. Similarly, the characteristics of included studies without published results are available in Table 6 in Appendix F.

3.4 Breast cancer and other tumors

Out of the 40 clinical trials included, 35 studies focused exclusively on patients with breast cancer, while five trials ^[56–58,65,68] included participants with multiple tumor types. Two of these trials ^[65,68] were available only in the form of conference abstract

without results or research protocols. Although the other three studies ^[56–58] published their results, they did not report them separately by types of cancer.

3.5 General characteristics of participants from included studies

In total, the 25 studies with some form of published results focused on individuals with breast cancer and enrolled 5,623 participants. The participant counts ranged from 40 to 3,649 (median 73 and Interquartile Range [IQR] 51 to 121). While most studies involved female participants, four studies ^[34,58,65,79] included both men and women with breast cancer in their samples, with the majority naturally being women.

The three studies ^[56–58], which included individuals with multiple types of cancer and had some form of published results, did not offer separate data for the 176 patients with breast cancer.

The total population enrolled in the four studies ^[76–79] that were terminated without publishing their results is 244 patients. Finally, the total number of participants planned to enroll according to the research protocols of ongoing studies ^[65–75] is 2,090.

3.6 Menopausal status

Among the 25 studies with published results, one study ^[53] exclusively involved a postmenopausal population. Additionally, five studies ^[27,48,52,54,63] specifically focused on postmenopausal women. Ten studies ^[28,30,34,41,45,47,49–51,55] examined a mixed population, encompassing pre, peri, and postmenopausal women. Meanwhile, nine studies ^[46,56–62,64] did not provide information about the menopausal status of the participants.

3.7 The distribution of comorbidities among participants in the included studies

The level of reporting on participant's comorbidities in the included studies was heterogeneous. The most frequently reported comorbidities included obesity, overweight, hypercholesterolemia, hypertension, diabetes, pre-diabetes, and metabolic syndrome.

3.7.1 Obesity/overweight

Liubota's trial ^[49] was the only study where all participants were obese (BMI > 30). In three other studies ^[47,54,57], participants were either overweight or obese (BMI > 25). In contrast, the METTEN Trial ^[30] was the only study that excluded any potential participants with a BMI above 30. As for the remaining studies with published results ^[28,51,53,60,64], the prevalence of overweight and/or obesity among participants ranged from 13% to 43%. And 15 studies ^[26,27,34,45,46,48,50,52,53,56,58,61–64] did not report any data on that characteristic of their samples.

3.7.2 Diabetes and pre-diabetes

Out of the 25 studies with some form of published results, 18 ^[26–28,30,34,41,46,48,50,51,53,56,59–64] exclusively recruited participants without diabetes. Five ^[45,49,52,54,58] of these studies did not provide information about the diabetes status of their samples. Only two studies included participants with diabetes or prediabetes. In one study ^[47], 1% of their sample had diabetes, while in the other study ^[57], 17% of participants had prediabetes.

3.7.3 Metabolic syndrome

Among the studies reviewed, only three ^[41,49,60] provided data regarding the frequency of metabolic syndrome among their participants. Notably, one ^[49] of these studies exclusively included participants with metabolic syndrome. In the remaining two ^[41,60] studies, the prevalence of metabolic syndrome among participants ranged from 26% to 58%. It's worth noting that 22 ^[26–28,30,34,45–48,50–54,56–59,61–64] of the studies did not include any data related to this particular characteristic of their samples.

3.8 Characteristics of the breast cancer

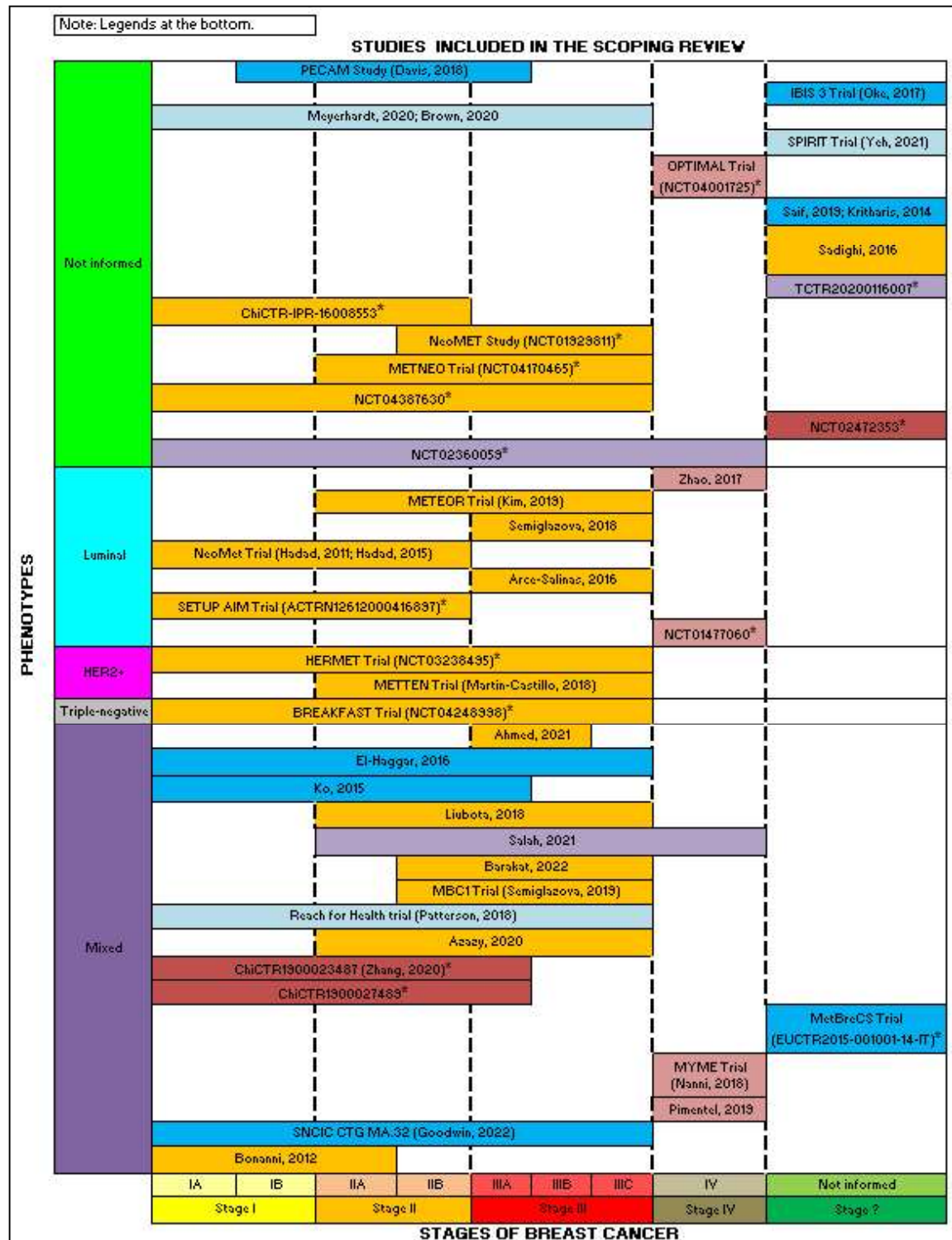
3.8.1 Histological type

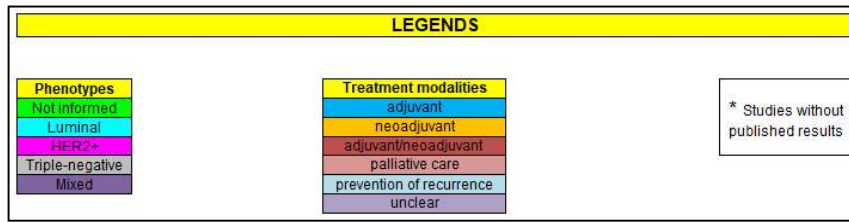
Only five studies [41,45,47,49,55] provided information on the frequencies of histological types of breast cancer among their participants. In these studies, the frequency of ductal, lobular, mixed, or other histological types ranged from 82% to 90%, 6% to 10%, 2% to 8%, and 3% to 3.5%, respectively.

3.8.2 Breast cancer phenotype

Figure 2 presents an overview of the studies included in the scoping review according to four aspects: phenotypes, stages of breast cancer, treatment modalities, and status of publication results.

Figure 2 - Overview of the Studies Included in the Scoping Review according to Phenotypes, Stages of Breast Cancer, Treatment Modalities, and Status of Publication Results





The reporting of breast cancer phenotypes varied considerably among the 25 studies with published results. As can be noted six studies ^[27,48,56–58,62] did not mention the phenotypic classification of breast cancer at all. Five studies ^[26,52,53,60,63] explicitly included only participants with the luminal phenotype. A single study ^[30], consisted of three substudies ^[31–33], encompassed solely HER2+ breast cancer. Thirteen studies ^[28,34,41,45–47,49–51,54,59,61,64] included participants with mixed phenotypes. In this group, the frequency of luminal, HER2+, and triple-negative phenotypes ranged from 62% to 84%, 6% to 40%, and 9% to 12%, respectively. Six mixed studies ^[28,34,41,50,59,64] only provided information about the frequency of the hormonal and HER2 receptors of the breast cancers in isolation, without explicitly determining the frequency of each phenotype.

Figure 3 illustrates the presentation of clinical and non-clinical outcomes results in the 13 studies involving mixed breast cancer phenotypes. While all of these studies traditionally presented results according to intervention arms, six studies ^[34,41,45–47,51] segmented some outcome results by subgroups based on phenotypes, receptors, or stages of breast cancer. Ahmed's study ^[45] provided pathological complete response (pCR) results by phenotypes, and Bonanni's study ^[41] offered ki67 results for the luminal phenotype. Six studies ^[34,44–47,51] presented results of relevant clinical outcomes such as pCR, objective response rate (ORR), invasive disease-free survival (IDFS), and OS by subgroups of hormone and HER2+ receptors. Lastly, two studies ^[46,51] displayed results for clinical and non-clinical outcomes based on subgroups of breast cancer stages.

Figure 3 - Presentation of Clinical and Non-clinical Outcomes Results in Studies Involving Mixed Breast Cancer Phenotypes

Note: Legends at the bottom.		RESULTS PRESENTED BY SUBGROUPS OF:					Stages	Aims of interventions	CLASSICAL PRESENTATION OF RESULTS BY ARMS OF INTERVENTIONS:	
Study	Breast Cancer Phenotypes included in the study	Phenotypes	Receptors							
			ER	PgR	HER2	ER/PgR				
Almed, 2021	Luminal, HER2+, Triple-negative	Outcome: pCR	Outcome: pCR						pCR, DFS, clinical response, method of surgery, and toxicity.	
EL-Haggag, 2016	Luminal, HER2	Outcomes: IGF-1, IGFBP-3, IGF-1:IGFBP-3 molar ratio, insulin, FBG, HOMA-IR, CA15-3, and metastasis					Outcomes: IGF-1,IGFBP-3, IGF-1:IGFBP-3 molar ratio, insulin, FBG, andHOMA-IR	DFS, IGF-1,IGFBP-3,IGF-1:IGFBP-3 molar ratio, insulin, FBG, HOMA-IR, CA15-3, and metastasis		
Ko, 2015	Luminal, HER2+, Triple-negative						Outcomes: weight loss, fasting blood sugar, HbA1c, insulin levels, lipid profile, BMI, and waist	Weight loss, fasting blood sugar, HbA1c, insulin levels, lipid profile, BMI and waist		
Liubota, 2018	Luminal, HER2+, Triple-negative							CBR, pCR, OS, recurrence-free survival, and type of surgery		
Salah, 2021	Luminal, HER2+, Triple-negative							RRR, OS, and PFS		
Baakat, 2022	Luminal, HER2+, Triple-negative		Outcomes: ORR, cCr, and pCR					OR, cCr, pCR, BCR, safety profile and tolerability, and QoL		
MBC1 Trial (Semiglazova, 2019)	Luminal, HER2+, Triple-negative							ORR, pCR, and QoL		
Reach for Health trial (Patterson, 2018)	Luminal, HER2+, Triple-negative							Changes in fasting insulin, glucose, CRP, estradiol, testosterone, and SHBG		
Azazy, 2020	Luminal B and other unclear phenotypes							pCR and pPR		
MYME Trial (Nanni, 2018)	Luminal, Triple-negative							PFS, ORR, OS, PFS as function of Homa Index levels, ORR as function of Homa Index levels, OS as function of Homa Index levels, and toxicity		
Pimentel, 2019	Luminal, HER2+, Triple-negative							PFS, OS, RR, Toxicity, QoL		
NCIC CTGMA.32 (Goodwin, 2022)	Luminal, HER2+, Triple-negative				Outcomes: DFS, OS, CA 15-3	Outcomes: DFS, OS; breast cancer-free interval, and CA 15-3		insulin, leptin, hsCRP, HDMA, CA 15-3, estradiol, SHBG, and bioavailable testosterone		
Bonanni, 2012	Luminal, HER2+, Triple-negative	Outcomes: ki67 (Luminal B)						ki67 results was presented by aims of interventions and by specific subgroups: HDMA; BMI; waist/hip girth-ratio; moderate alcohol consumption; C-reactive protein		
DeCensi, 2015 (substudy)	Luminal, HER2+, Triple-negative		Outcomes: the prevalence, grade and proliferation of LIN or DIN and ductal hyperplasia					the prevalence, grade and proliferation of land ductal hyperplasia		

Note: Legends at the bottom.

Treatment modalities:
adjuvant
neoadjuvant
adjuvant/neoadjuvant
palliative care
prevention of recurrence
unclear

BCR = breast conservative rate; CBR = clinical benefit rate; cCr = clinical complete response; CRP = C-reactive protein; DFS = disease free survival; DRFS = distant recurrence-free survival; DIN= ductal intraepithelial neoplasia; ER = estrogen receptor; FBG = fasting blood glucose; HbA1c = glycated hemoglobin; HER2 = human epidermal growth factor receptor 2; HOMA-IR = homeostatic model assessment for insulin resistance; IGF-1 = insulin-like growth factor 1; IGFBP-3 = insulin-like growth factor binding protein 3; IDFS = invasive disease-free survival; LIN = lobular intraepithelial neoplasia; ORR = objective response rate; pPR = partial pathological response; pCR = pathological complete response; PgR = progesterone receptor; RRR = radiological response rate; RR = response rates; SHBG = sex hormone-binding globulin.

3.8.3 Frequency of breast cancer stage

The breast cancer staging and staging intervals investigated were also heterogeneous among the 25 studies with some published results (Figure 2). Two studies ^[26,41] included participants with stages I and II. Six studies ^[34,46–48,54,56] enclosed participants with breast cancer stages ranging from I to III. Other six trials ^[30,49,51,61,63,64] embraced patients from stages II to III. Three studies ^[45,53,60] comprised only stage III. One study ^[50] involved a staging interval from II to IV. Three studies ^[28,52,59] were restricted to participants with stage IV breast cancer. Finally, four studies ^[27,57,58,62] did not provide any information regarding the stage of breast cancer among their participants.

3.9 Interventions and Comparators

The RCTs included in this review examined metformin as a standalone intervention or in combination with various oncological treatments, employing a variety of comparators. The dosages of metformin investigated in these trials ranged from 850 mg to 2,550 mg per day.

Out of the 25 studies with published results, four trials ^[34,41,47,48] administered metformin as a single intervention and compared it with placebo use. In Sadighi's study ^[62] and the NeoMet Trial ^[55], metformin was given to participants in the experimental group, while the control group received no medication.

Furthermore, among the same set of studies, three trials ^[54,56,57] combined metformin with behavioral interventions such as weight loss or exercise training, aiming to prevent recurrence post-cancer treatment. The SPIRIT Trial ^[57] had three intervention arms: metformin alone, coach-directed weight loss, and self-directed weight loss. The Reach for Health trial ^[54], a 2 x 2 factorial randomized trial, included groups receiving metformin alone and weight loss with metformin interventions, comparing them with placebo groups and weight loss with a placebo. Meyerhardt's study ^[56] provided metformin with training exercises, comparing it with exercise training alone, as well as

metformin alone, which was compared with an educational information group without treatment.

Out of the 25 studies with published results, 16 incorporated metformin in combination with standard care systemic therapy, which could involve chemotherapy, hormone therapy, or a combination of both. Specifically, ten studies [28,30,45,50,51,58–61,64] employed chemotherapy, four [27,52,53,63] used hormone therapy, and two [46,49] utilized both chemotherapy and hormone therapy.

Among the studies examining chemotherapy, eight [28,30,45,50,51,58,61,64] combined metformin with various chemotherapy regimens, comparing them to chemotherapy alone. Two studies [59,60] administered metformin in conjunction with chemotherapy and compared it with the same chemotherapy plus a placebo.

In the studies evaluating hormone therapy, two [27,53] combined metformin with hormone therapy and compared it with hormone therapy without metformin. For Semiglazova's three-arms trial comparing metformin plus toremifene vs. toremifene alone and toremifene plus melatonin, we considered to our review only the arms with metformin and its control. Two studies [52,63] intervened by combining metformin with hormone therapy, specifically an aromatase inhibitor, and compared it with the same hormone therapy plus a placebo.

Finally, among two studies [46,49] that tested both chemotherapy and hormone therapy in conjunction with metformin, the control groups underwent the same interventions without metformin. In El-Hagggar's study, metformin was tested in combination with chemotherapy and hormone therapy as adjuvant systemic therapy. In Liubota's study, both systemic therapies were applied as neoadjuvant treatments, with some patients receiving four cycles of anthracycline-based chemotherapy in three-week schedules, and postmenopausal patients with luminal breast cancer receiving hormone therapy (letrozole 2.5 mg per day) for 16 weeks.

3.9.1 Treatment Modalities

Metformin was examined in various treatment modalities across the studies included in this review (Figure 2). Out of the 25 studies with some published results,

twelve ^[30,41,45,49,51,53,55,60–64] included metformin as a neoadjuvant treatment for breast cancer, while six ^[27,34,46–48,58] incorporated it as an adjuvant treatment. Additionally, three studies ^[28,52,59] utilized metformin for palliative care. In one specific study ^[50], the treatment modality for investigating metformin in combination with standard chemotherapy is unclear. Finally, three studies ^[54,56,57] explored metformin for preventing breast cancer recurrence in patients who had completed their oncological treatments.

3.9.2 Use of metformin in the context of palliative treatment

Of the three studies that incorporated metformin into palliative breast cancer treatment, only the MYME Trial ^[28] and its substudy, TransMYME ^[29], explicitly stated the use of 100% first-line chemotherapy. In the other two studies involving participants with stage IV breast cancer for palliative oncological treatment, one ^[52] combined metformin with first, second, and third-line or subsequent treatments in 22 (36.7%), 35 (58.3%), and 3 (5.0%) of the cases, respectively. The other study ^[59] combined metformin with first, second, and third-line or subsequent treatments in 27 (67.5%), 7 (17.5%), and 6 (15%) of the participants, respectively.

3.10 Outcome Measures and Main findings

Overall, among the 25 included studies with some published results, the most frequently reported outcomes were: toxicity, pathological complete response, objective response rate, clinical benefit rate, and insulin levels. Table 7, presented in Appendix G, provides clinical, non-clinical, and miscellaneous outcomes measures evaluated by all 40 studies included in this review. Complementary, the virtual Supplementary Appendix 1 includes a series of spreadsheets where readers may find a description of the outcomes measures examined by each study based on the phenotype, breast cancer staging, and treatment modality of the samples.

The first tab compiles the clinical outcomes mapped in the trials included in the scoping review, with survival outcomes presented initially, as they hold the utmost significance for patients with breast cancer. The second tab organizes non-clinical

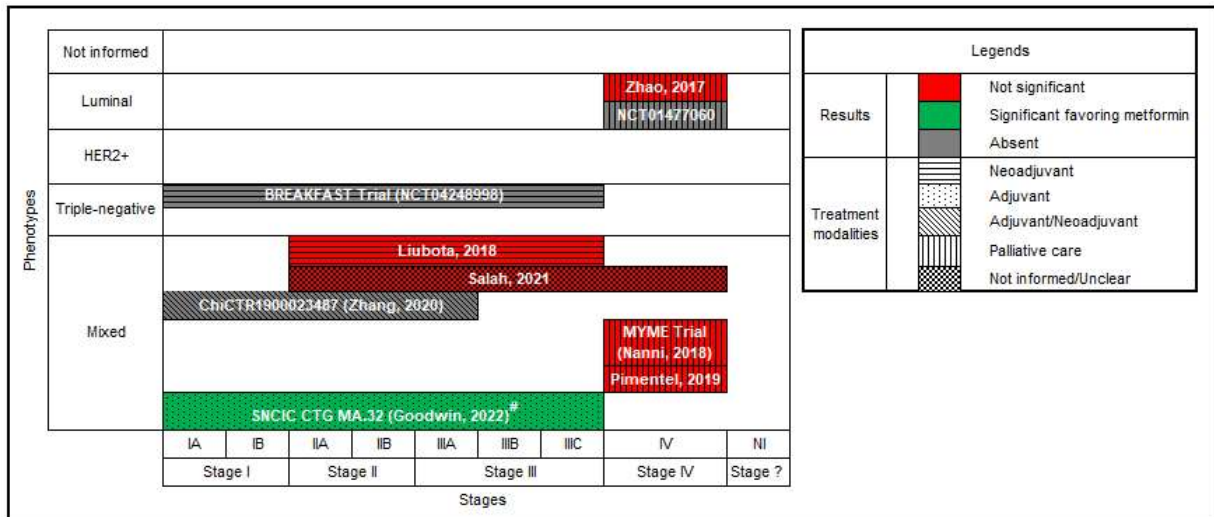
outcomes assessed in the trials by categories. The final tab consolidates other non-clinical outcomes that do not fit into any specific category.

Clinical outcomes, including survival, quality of life, and cancer response rates, deserve special attention because they are considered the most important from the patients' perspective. Therefore, we emphasized the presentation of results related to those outcomes in our narrative synthesis and figures.

3.10.1 Overall Survival (OS)

Overall Survival (OS), defined as the time from randomization to death, is considered the 'gold standard' primary clinical endpoint in oncology^[80]. Figure 4 depicts the mapping of the nine studies^[28,34,49,50,52,59,74,77,81] that evaluated OS according to the phenotype, staging and treatment modalities of breast cancer, as well as the publication status of their results concerning that outcome. Six^[28,34,49,50,52,59] out of those nine studies had some published results. Only one of those studies^[34] showed an improved survival among participants treated with metformin. Importantly, that effect was observed only among HER2+ participants (HR = 0.54; 95%CI, 0.30-0.98; P = .04), and not among participants with luminal breast cancer or the overall group of participants with mixed phenotypes.

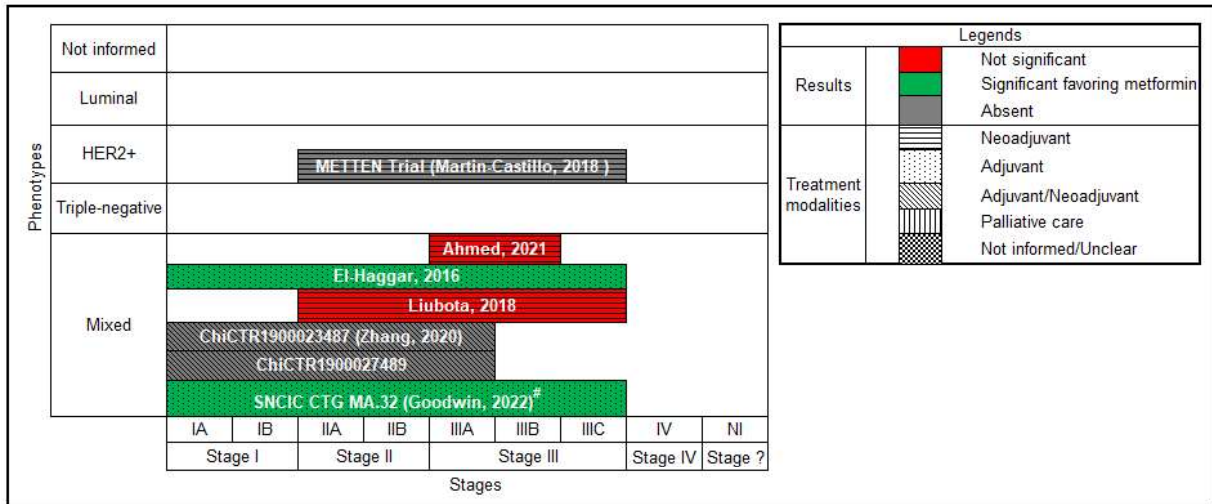
Figure 4 - Results for the Outcome Overall Survival according to Phenotypes, Breast Cancer Stages, and Treatment Modalities Adopted by Primary Studies



3.10.2 Disease-Free Survival (DFS)

Seven studies [30,34,45,46,49,68,81] included Disease-Free Survival (DFS), defined as the time from randomization to disease recurrence [80], among their outcome measures. As can be noted in Figure 5, four [34,45,46,49] out of those seven studies had some published results and all of them included participants with mixed phenotypes. In two [34,46] of them, there was some evidence of improvement in DFS among participants treated with metformin. Goodwin's study [34] showed an improved DFS among HER2+ participants (HR = 0.64; 95% CI, 0.43-0.95; P = 0.03) but not among participants with other phenotypes or the overall group of participants. In the study by El-Haggag [46], which did not present DFS results for specific phenotypes, metformin treatment was associated with an average increase in DFS of about two months (Log rank test, p = 0.044) and a Hazard Ratio of 3.27 (95% CI 1.17–9.06, P = 0.023) disfavoring the control group for that same outcome in a statistical model adjusted for age, tumor stage, adjuvant chemotherapy, estrogen- and HER2-receptor status.

Figure 5 - Results for the Outcome Disease-Free Survival according to Phenotypes, Breast Cancer Stages, and Treatment Modalities Adopted by Primary Studies

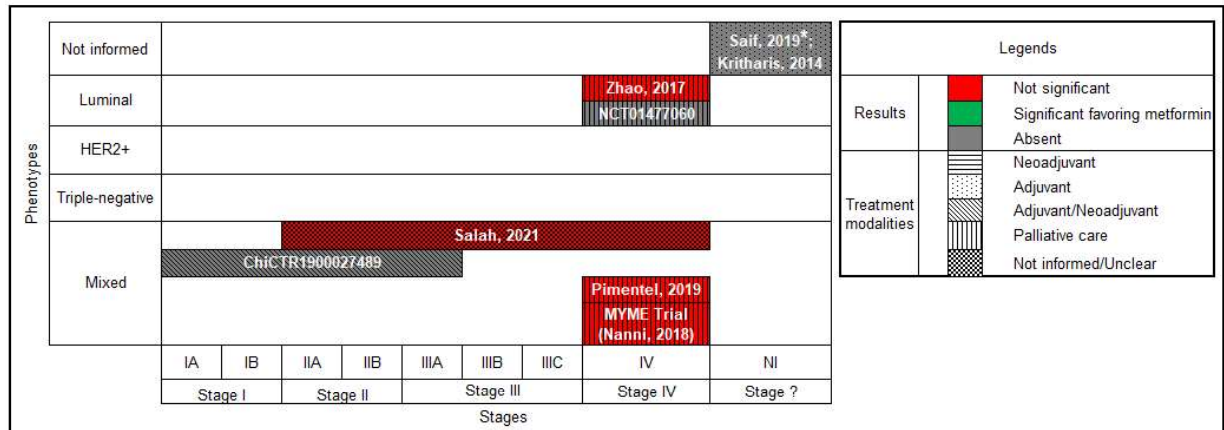


[#] Positive for HER2+ phenotype.

3.10.3 Progression-Free Survival (PFS)

Progression-Free Survival (PFS) is defined as the time from randomization to disease progression or death ^[80]. Seven studies ^[28,50,52,58,59,68,77] included PFS in their outcomes (Figure 6). Four studies ^[28,50,52,59] out of those seven had some published results, all of which were negative. One of those studies ^[52] only included participants with luminal breast cancer, whereas the other three ^[26,48,57] included people with mixed phenotypes. Although PFS is an outcome used to assess therapies targeting advanced or metastatic malignancies ^[80], we noticed that one ^[50] of those four studies included participants with earlier stages of breast cancer besides metastatic disease. The same issue occurred with a study with unpublished results ^[68]. It is also noteworthy that the Saif's study ^[58], which included participants with 16 different cancers, did not provide results specific to patients with breast cancer in its published article. Furthermore, it points out that the study claimed to have evaluated PFS using the Kaplan-Meier method, but these results were not presented in the publication.

Figure 6 - Results for the Outcome Progression-Free Survival according to Phenotypes, Breast Cancer Stages, and Treatment Modalities Adopted by Primary Studies

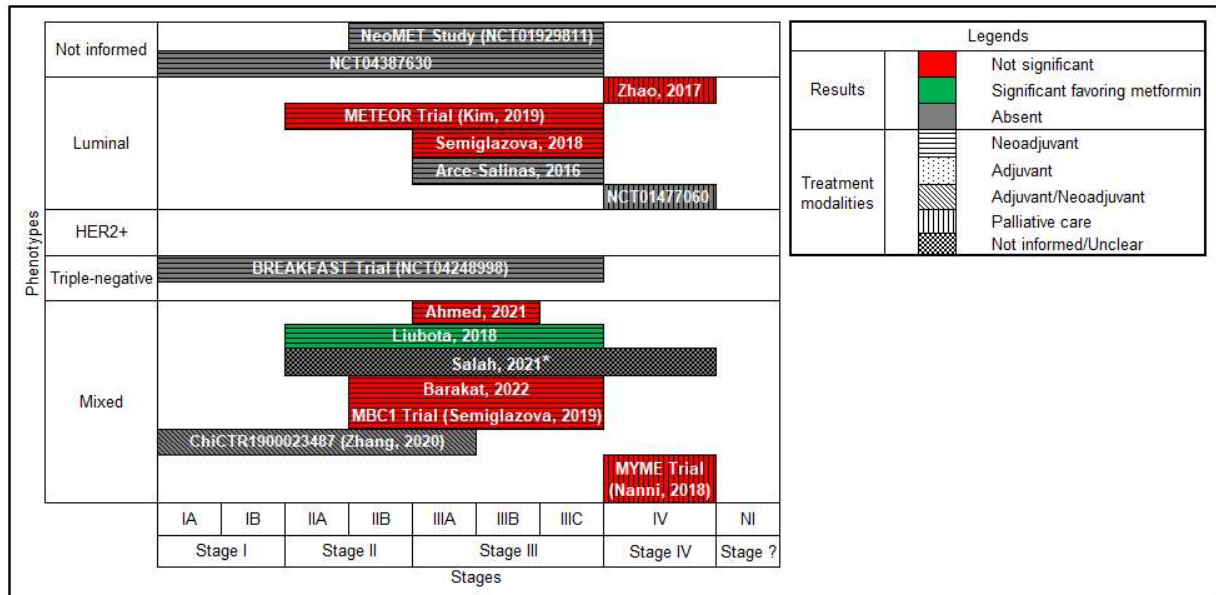


* Included other types of cancer besides breast cancer.

3.10.4 Objective Response Rate (ORR)

Objective Response Rate (ORR) is defined as the proportion of patients with partial or complete response to therapy [80]. Fifteen studies [28,45,49–53,60,63,64,74–77,81] evaluated ORR among their outcome measures (Figure 7). Eight [28,45,49,51–53,63,64] out of those 15 studies had some published results and only one [49] of them was positive. In that study, which included patients with mixed phenotypes and stages II-A to III-C breast cancer using neoadjuvant chemotherapy, the authors found that 28 (77.5%) out of 36 participants in the metformin arm achieved either complete or partial response in contrast to 9 (25%) out of 36 participants in the control arm ($p < 0.05$). It is also noteworthy that out of the eight studies with some published results, there were five studies [28,45,49,51,64] of participants with mixed phenotypes and three [52,53,63] restricted to participants with the luminal phenotype, the latter of which were all negative.

Figure 7 - Results for the Outcome Objective Response Rate according to Phenotypes, Breast Cancer Stages, and Treatment Modalities Adopted by Primary Studies



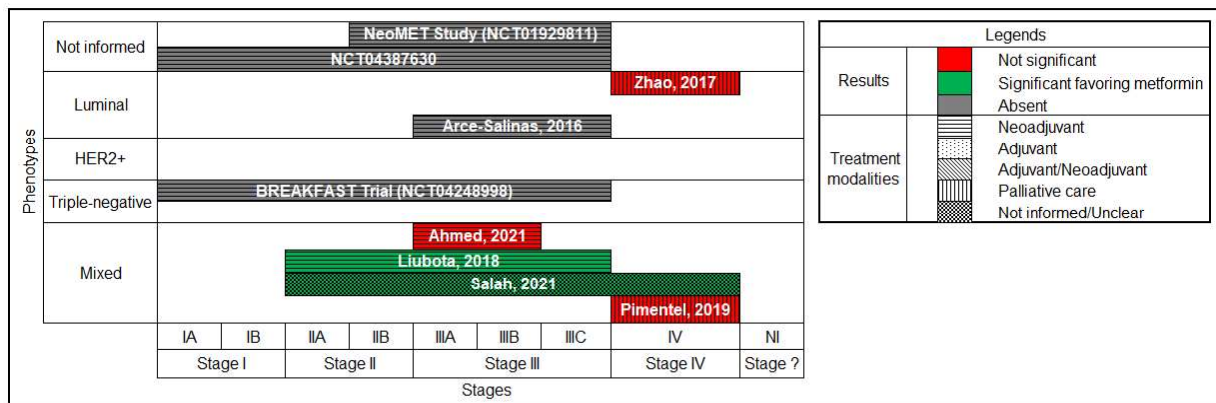
* In the published article, the authors presented data with the frequency of partial response, stable disease and disease progression. But they did not present the complete response and partial response analyzes of ORR.

3.10.5 Clinical Benefit Rate (CBR)

Clinical Benefit Rate (CBR) is defined as the proportion of patients with complete response, partial response, or stable disease for at least six months ^[80]. Nine studies [45,49,50,52,59,60,74–76] included CBR in their outcomes (Figure 8) and five ^[45,49,50,52,59] out of them had some published results. Only two ^[49,50] of those studies reported positive results for that outcome. Both of them included participants with mixed phenotypes. Liubota's study ^[49] included women with stages II to III undergoing neoadjuvant chemotherapy and found an statistically significant increase in the proportion of patients with stable disease, complete or partial response (34 [94.5%] out of 36 in the metformin arm vs. 28 [78%] out of 36 in the control group, $p < 0.05$). The study by Salah et al ^[50] included 50 participants with stages II to IV breast cancer. Unfortunately, the numbers of participants experiencing partial response, or stable disease were reported on a three-dimensional figure, which does not allow the accurate extraction of data. Zhao's trial ^[52]

was the only study with published results restricted to participants with luminal breast cancer (N = 60). In that study, metformin was added to palliative chemotherapy for women with stage IV breast cancer and was not associated with statistically different CBR when compared with the control group.

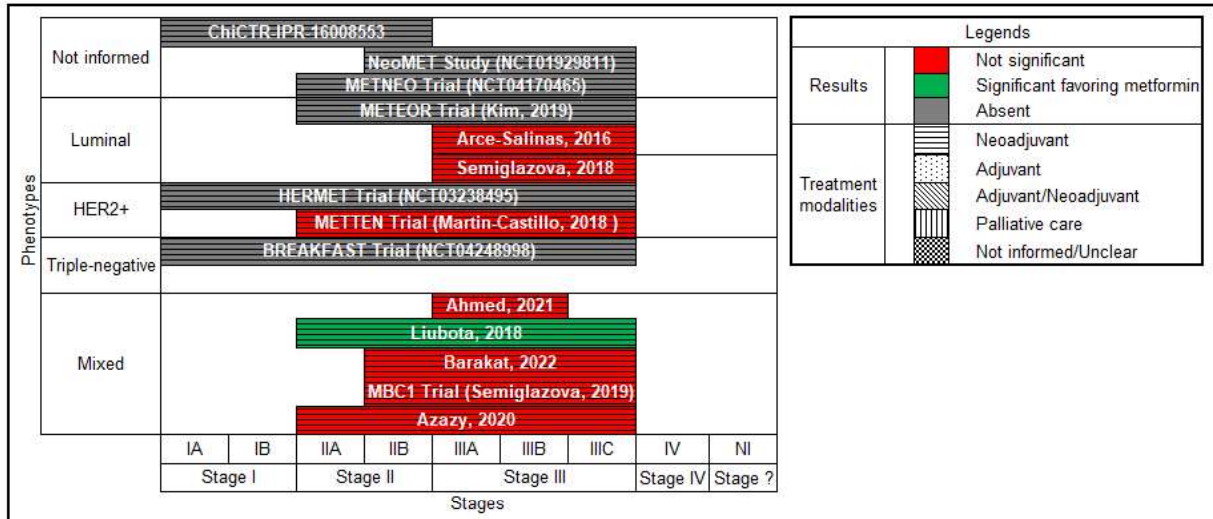
Figure 8 - Results for the Outcome Clinical Benefit Rate according to Phenotypes, Breast Cancer Stages, and Treatment Modalities Adopted by Primary Studies



3.10.6 Pathological Complete Response (pCR)

Pathological Complete Response (pCR) is defined as the lack of residual invasive cancer in resected breast tissue and regional lymph nodes ^[80]. This outcome is used in accelerated approval for neoadjuvant therapies targeting breast cancer. Eight ^[30,45,49,51,53,60,61,64] out of 14 studies ^[30,45,49,51,53,60,61,63,64,69,72–74,76] had some published results on this outcome and just one ^[49] of them, which included patients with mixed phenotypes and stages II to III breast cancer, was positive (Figure 9). In that study, 9 (26.5%) out of 36 patients in the metformin arm achieved pCR in comparison to 2 (6%) out of 36 patients in the control group ($p < 0.05$). Of the remaining negative studies, four of them ^[45,51,61,64] involved participants with mixed breast cancer, a single study ^[30] was restricted to participants with the HER2+ phenotype, and two ^[53,60] focused on patients with luminal breast cancer.

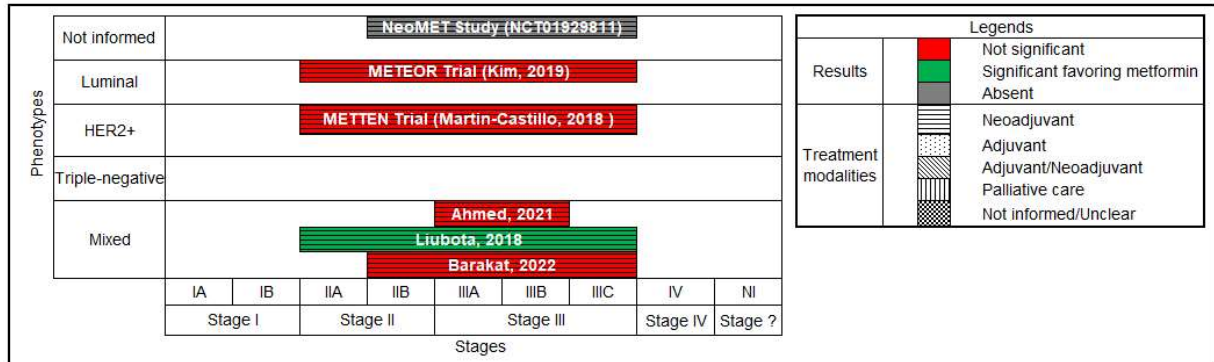
Figure 9 - Results for the Outcome Pathological Complete Response according to Phenotypes, Breast Cancer Stages, and Treatment Modalities Adopted by Primary Studies



3.10.7 Breast Conservation Rate (BCR)

Neoadjuvant systemic therapy for operable breast cancer can increase the options for conservative surgery in patients with breast cancer rather than mastectomy [82]. Six studies [30,45,49,51,63,76] included BCR in their outcomes (Figure 10) and five [30,45,49,51,63] out of them had some published results. The only positive result came from the Liubota's study [49], which was already mentioned as the single study with positive results for the ORR and pCR outcomes. In that study, among the 35 participants with surgical indication breast-conserving surgery was executed in 9 (50%) from out of 18 patients in the metformin versus 4 (23.5%) out of 17 patients in the control group ($p < 0.05$).

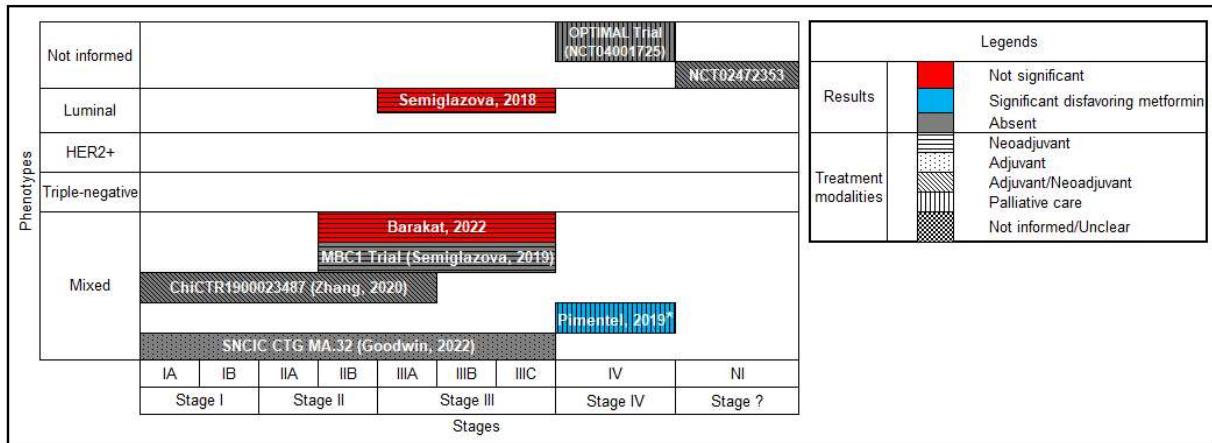
Figure 10 - Results for the Outcome Breast Conservation Rate according to Phenotypes, Breast Cancer Stages, and Treatment Modalities Adopted by Primary Studies



3.10.8 Quality of Life (QoL)

Eight studies ^[34,51,53,59,64,65,78,81] included QoL among their outcome measures (Figure 11). Three ^[51,53,59] out of those eight studies had some published results and all of them used the European Organization for Research and Treatment for Cancer Quality of Life Questionnaire (EORTC-QLQ-C30). Only the Pimentel's study ^[59], which included 40 women with metastatic breast cancer with mixed phenotypes, identified a statistically significant difference regarding one of the domains of quality of life evaluated by that instrument. Remarkably, participants in the metformin arm experienced a large worsening of their Global Health Status in comparison with the control arm (standardized difference of 0.8, $p=0.006$). Neither the other domains of quality of life nor the frequency of fatigue, diarrhea, nausea & vomiting, appetite loss, abdominal pain, and other symptoms measured by the EORTC-QLQ-C30 were significantly different between the two groups in that study.

Figure 11 - Results for the Outcome Quality of Life according to Phenotypes, Breast Cancer Stages, and Treatment Modalities Adopted by Primary Studies



* Positive disfavoring the metformin group.

3.10.9 Adverse Events

Out of the 25 studies with published results, 22 [27,28,30,34,41,45–48,50–52,54–63] provided data on adverse events related to metformin compared to control groups, while three [49,53,64] did not report adverse events in their trial results. With the exception of two studies [28,34] all others reported that metformin was well-tolerated.

Two studies [28,34] reported similar rates of grade 3 or higher adverse events between groups. SNCIC CTG MA.32 [34] was the only study where participants in the metformin arm experienced a higher rate of severe adverse events. In that study, 391 (21.5%) patients in the metformin and 328 (17.5%) in the placebo group experienced grade 3 or higher adverse events ($P=0.003$); the most common adverse events of grade 3 or higher included hypertension (2.4% metformin vs 1.9% placebo), irregular menses (1.5% metformin vs 1.4% placebo), and diarrhea (1.9% metformin vs 0.8% placebo). In contrast, in the MYME trial [28] the metformin group experienced a lower frequency of grade 3 or 4 adverse events than the control group, with 54% vs 72% of patients developing neutropenia, respectively ($P=0.019$).

For the other 20 studies [27,30,41,45–48,50–52,54–63] with published results, metformin was generally well-tolerated. The incidence of adverse events was not more common in the metformin group than in the control groups. However, as expected due to metformin's well-known side-effects profile, several studies reported a higher rate of less

severe (grades 1 and 2) gastrointestinal adverse events, such as diarrhea, associated with the medication.

3.11 Funding

Thirty-four studies [27,30,34,41,47,48,51–58,60–66,68–79,81] were conducted with not-for-profit funding, such as research foundations, governments, and universities. Only two [28,59] studies had a mixed funding sources including for-profit and not-for-profit funders. The MYME Trial [28] was funded by Italian Association for Cancer Research (AIRC) and TEVA Pharmaceuticals. In addition, Pimentel's study [59] was funded by the Breast Cancer Research Foundation, Hold'em for Life Charity, and the contract research organization Ozmosis Research Inc. There were three [45,46,49] studies published with results that did not inform the funding aspect. Finally, Salah's trial [50] also published with results was the only study conducted without sponsorship.

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4. Discussion

This is the most extensive and comprehensive review of RCTs that evaluated the use of metformin in the treatment of breast cancer. Our results provide insight into the growing body of literature that assesses the impact of metformin on the effectiveness of breast cancer treatment. We categorized existing studies based on breast cancer tumor phenotypes, stages, and possible treatment modalities. To our best knowledge, this comprehensive mapping and organization had not been previously undertaken by other studies of a similar nature. This charting effort is essential because it highlights knowledge gaps in the existing literature, identifying opportunities for new clinical trials and demonstrating the value and scope of further systematic reviews.

Based on the findings of this review, we have identified the need for the development of methodological guidelines that ensure the clear presentation of breast

cancer phenotype-specific data in any new oncological clinical trial in this field. We believe that exhibiting trial results from the perspective of cancer phenotypes will make the evidence more relevant to clinical oncology practice, which frequently deals with a variety of breast tumor types. Until the development and implementation of such guidelines becomes a reality, we suggest that researchers explore the possibility of retrospectively ascertaining the phenotypes of participants from previous primary studies. If feasible, this approach has the strategic potential to rapidly generate new phenotype-specific data without incurring the substantial cost of recruiting new patients for novel trials. Furthermore, the accumulation of new phenotype-specific evidence from such retrospective analyses of previously-completed clinical trials may be compiled in future systematic reviews. This compilation may provide strong enough evidence to support not only clinical decisions but also regulatory ones.

Despite the variety of phenotypes, outcomes, disease states, treatment modalities, comparators, and publication status, our mapping of the field allows the envisioning of future phenotype-and-outcome-specific meta-analyses. For example, there are six studies with published results, five of which involve mixed phenotypes, and one focused on the luminal population (Figure 4), which can be used to conduct meta-analysis on OS. Additionally, an opportunity exists to evaluate DFS using the four studies already published, which also involve mixed phenotypes (Figure 5), and asking the METTEN trial authors for the HER2+ population results of the outcome. Moreover, as previously highlighted, if future systematic reviewers are able to gain access to retrospectively ascertained phenotypes of breast cancer patients, better and more meta-analyses would be possible, including performing individual patient data (IPD) meta-analyses taking that kind of information into account through a collaborative effort among researchers in this field.

With regard to opportunities for new clinical trials in the theme, we envision new knowledge gaps to be addressed. While there are already neoadjuvant studies for all breast cancer phenotypes, the landscape is not the same for adjuvant, palliative care, or recurrence prevention studies, as depicted in Figure 2. For example, innovative trials could be proposed to investigate the effectiveness of metformin in HER2+ and triple-negative breast cancer within adjuvant and palliative care treatment modalities. There is

also a lack of evidence of adjuvant treatment with metformin in the luminal phenotype specifically.

We believe it is essential to propose new RCTs that combine phenotypes that have been poorly explored with the most important outcomes for breast cancer patients and those commonly evaluated in previous trials. Currently, the METTEN Trial ^[30] is the only completed trial with published results that investigated neoadjuvant treatment with metformin in the HER2+ phenotype. Additionally, the HERMET Trial ^[72] is ongoing for the same phenotype and treatment modality, with an estimated study completion date of June 2023. Both trials had pCR as the primary outcome. Therefore, we believe there is an opportunity for more neoadjuvant trials that aim to evaluate HER2+ breast tumors, focusing on strategic clinical outcomes such as DFS and BCR. The further evaluation of metformin in patients with HER2+ breast cancer is especially relevant due to the limited evidence from a subgroup analysis of a single large RCT suggesting that it could improve OS and DFS ^[34]. In a similar vein, the BREAKFAST Trial ^[74] is the only interventional study proposed to investigate the effect of metformin on triple-negative breast cancer with a neoadjuvant modality. It is currently underway with an estimated study completion date of May 2024. As a result, there is a need for further investigations into this specific phenotype, with a focus on outcomes such as OS, RFS, ORR, pCR, and BCR.

Importantly, our review offers a map of the landscape of RCT data on metformin for the treatment of breast cancer. It is beyond the scope of our discussion section to outline every possible research opportunity available in terms of new RCTs or systematic reviews. Experts in this field will be able to use our charting effort to recognize further research opportunities just as expert travelers are able to devise new paths from triangulating information from maps and their own knowledge of a specific region.

There are several major differences between our scoping review and previous reviews published on metformin and cancer. For instance, a systematic review ^[15] focused on *in vitro* and/or *in vivo* studies, exploring metformin's potential antiproliferative mechanisms. This review provided evidence of metformin's effectiveness in cancer cell

lines and/or in animal models, confirming its anti-angiogenic properties, as well as its ability to inhibit cellular metastasis and induce apoptosis.

Another prior systematic review of 11 observational studies ^[16] analyzed the association between metformin use by diabetic women and the prognosis of breast cancer patients, having found that the use of the drug is associated with better survival of breast cancer patients with diabetes (HR: 0.53; 95% CI: 0.39 to 0.71; $p < 0.001$). However, meta-analyses of observational studies are subject to bias due to residual confounding within the primary studies included in them.

A single systematic review and meta-analysis attempted to assess the evidence from RCT on the effectiveness of metformin in the treatment of breast cancer ^[17]. However, that review had several methodological limitations including the absence of a registration of the review protocol, poor details of the search strategy for any database, the exclusion of important databases and grey literature. Furthermore, there was insufficient description of eligibility criteria, no flow diagram of the study selection process, no assessment of the certainty of evidence, and a limited range of evaluated outcomes. Importantly, Zhang's systematic review did not take into account the different phenotypes, the staging of breast cancer, or the treatment modalities under which metformin was used in the primary studies. These aspects are crucial for interpreting the effectiveness of not only metformin but any breast cancer treatment. Hence, it is likely that their meta-analyses were biased by too much clinical heterogeneity that compromised the quality of their pooled results. Those limitations of the single systematic review of RCT of metformin for the treatment of breast cancer corroborate the relevance of our scoping review in paving the way for future systematic reviews and clinical trials in this field.

Our review has some limitations. First, the absence of risk of bias evaluation of included studies, the appraisal of overall certainty of evidence across studies, or even the performance of a meta-analysis as a form of quantitative synthesis. All three aspects are possible but lie beyond the scope of a scoping review, which aims to provide a broad overview and description of the general landscape of a field. Second, we did not contact any author from the original studies to request unpublished data because our

aim was to chart the literature including its areas of uncertainties. Requesting unpublished data such as study results stratified by phenotype will be better suited to the future systematic reviews that we envision our scoping review will foster. Third, primary prevention of breast cancer also fell outside the scope of our review. Primary prevention and the treatment of breast cancer are distinct areas, each with its complexities, involving different populations, risk factors, and biological determinants.

The present study also has relevant strengths. We established broad eligibility criteria not restricting the context, language, or publication date of study reports because the best practice for a scoping review is to attempt to be as comprehensive as possible. We also searched grey literature, and registers like ICTRP, as well as using other methods such as Google Scholar, checking reference lists of relevant publications, reviewing conference abstract books, and seeking specialist referrals. These searches were crucial for identifying a large number of relevant study reports for this review. Additionally, two independent reviewers conducted the selection of studies and data extraction while a third reviewer was available to resolve any disagreements that arose between the reviewers during that process.

5. Conclusion

In summary, the proposed scoping review illuminated the growing body of evidence from RCTs about metformin in the treatment of breast cancer. We mapped the landscape of existing studies according to phenotypes, staging, treatment modality, types of interventions, comparators, outcomes, and their main findings. Given the clinical heterogeneity underlying breast cancer itself and the current existence of 40 different primary studies in this field, by charting that literature we were able to identify new opportunities for clinical trials and systematic reviews. Specifically, we emphasize the necessity for standardizing the presentation of results from breast cancer clinical trials by phenotype and envision the potential for collaboration among researchers to retrospectively ascertain the phenotypes of breast cancer participants in previous

studies. This could substantially enhance the possibility of conducting better and more cost-effective meta-analyses in this field, including IPD meta-analyses.

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Appendix A

Publication of the protocol of the Scoping Review

BMJ Open Metformin for the treatment of breast cancer: protocol for a scoping review of randomised clinical trials

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ABSTRACT

Introduction Innovation through the repurposing of generic drugs encloses several advantages when compared with the process of developing new drugs from scratch. Metformin is an established and inexpensive antidiabetic drug for which anticancer properties have been hypothesised. A systematic review of observational studies found promising results for metformin related to breast cancer in women with diabetes. Although the number of randomised clinical trials of metformin for the treatment of breast cancer increased over the last decades, the overall landscape of those studies in this heterogeneous field remains unclear. Hence, we designed the present scoping review protocol to map the literature on randomised clinical trials of metformin in the treatment of breast cancer to determine the value and scope of future systematic reviews on this subject and identify research gaps.

Methods We will search MEDLINE (via PubMed), EMBASE, CENTRAL, LILACS, Web of Science and sources of grey literature. We will include any randomised clinical trial of metformin for the treatment of breast cancer in adult women, and will not impose restrictions regarding context, language or publication date. Two independent reviewers will screen and select studies, and chart the data. We will structure the presentation of our results based on the molecular types of breast cancer, their stages and treatment modalities.

Ethics and dissemination As a literature review, this study is exempt from ethics approval. Findings will be disseminated through presentations in conferences and a peer-reviewed publication.

Open Science Framework registration osf.io/yquba.

INTRODUCTION

The repurposing of medications is the process of development of new indications for drugs that were initially developed for other purposes. Innovation through the repurposing of generic drugs, in particular, encloses several advantages when compared with the process of developing new drugs from scratch. For example, besides their relatively low cost, they already have

Strengths and limitations of this study

- This protocol gives transparency to the methods and processes that will be used, allows peer review and reduces the possibility of bias and duplication.
- This scoping review will map the literature on randomised clinical trials on the use of metformin for the treatment of breast cancer, determining the scope and value of future systematic reviews on this subject and identifying research gaps.
- We will not impose any restrictions regarding language or publication date for the selection of studies.
- No formal assessment of risk of bias of included studies, or the overall certainty of evidence across studies will be performed.
- We will not perform meta-analyses as a form of quantitative synthesis.

well-established profiles of safety, pharmacodynamics and pharmacokinetics. Indeed, several publications have highlighted the strategic importance of funding research related to the repurposing of generic medications as a unique opportunity to improve clinical outcomes and decrease costs. The repurposing of any given medication depends on the quality of the evidence lending support to the new indication and systematic reviews play an essential role in this regard.

Metformin is an established antidiabetic drug for which a whole set of new indications have been studied.¹ It is one of the most commonly prescribed oral antidiabetic drugs in the world,² and in recent years, several potential beneficial effects arising from the use of metformin and unrelated to diabetes treatment have received increasing attention from the scientific community. One of these potential effects includes a role in modulating different types of cancer.³

Importantly, a systematic review of 11 observational studies analysing the association

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between the use of metformin by diabetic women and the prognosis of patients with breast cancer found a very relevant protective association in terms of survival for women using that drug (HR: 0.53, 95% CI: 0.39 to 0.71).⁴ However, an important criticism of the meta-analyses of observational studies is that they are also subject to bias due to residual confounding within the original studies included in them, and to date, metformin does not have an established role in the treatment of women with breast cancer.

The last few years have witnessed the appearance of several clinical trials evaluating the use of metformin in the treatment of breast cancer. However, the current understanding of breast cancer is that it is not a single disease but rather a heterogeneous group of diseases with different molecular mechanisms.⁵ Moreover, different stages of breast cancer are associated with different treatment modalities (ie, neoadjuvant, adjuvant and palliative therapies), which are associated with a variety of specific outcomes (eg, pathologic complete response, which is specific to studies of neoadjuvant treatment for early or locally advanced disease). Importantly, a recent systematic review attempted to assess the evidence from randomised clinical trials on the effectiveness of metformin in the treatment of breast cancer.⁶ However, that review suffered from various methodological limitations (eg, was not able to identify a few of the eligible studies) was restricted to a limited range of outcomes and did not take into account the different molecular types and stages of breast cancer or the treatment modalities examined in the original studies, which are central to the appropriate interpretation of the effectiveness not only of metformin but of any treatment of breast cancer. Given the many sources of clinical heterogeneity underlying this field, and the lack of clarity regarding the number of randomised clinical trials of metformin in the treatment of breast cancer, as well as on the molecular types, stages of breast cancer and treatment modalities examined in those trials, we designed the present scoping review protocol to map the literature on randomised clinical trials of metformin in the treatment of breast cancer to determine the value and scope of future systematic reviews on this subject and identify research gaps.

METHODS

Study registration

The present scoping review protocol was developed taking into consideration the guidance of the Joanna Briggs Institute for conducting systematic scoping reviews⁷ and was registered with Open Science Framework (osf.io/yquba).⁸

Review questions

We will seek to answer the following research questions:

1. What is the extent of the randomised clinical trials literature on the use of metformin in the treatment of breast cancer?

2. What molecular types and stages of breast cancer were examined in those studies?
3. What treatment modalities, regimens and comparators were used in those studies?
4. What outcomes were evaluated in those studies and what were their main findings?

Eligibility criteria

We used the following 'population, concept and context' framework to delineate our eligibility criteria.

Population

Our population of interest was adult (aged 18 years or older) women with any type of breast cancer.

Concept

We will include randomised clinical trials that have implemented any intervention for the treatment of breast cancer that included the use of metformin either alone or in combination with other pharmacological, surgical or radiation treatments. We will include studies that used placebo, standard treatment or other treatments that do not involve the use of metformin as comparator(s)/control. For studies where metformin was used as an intervention in combination with other treatments, comparators should include the same treatments without metformin. We will accept trials in which the unit of randomisation were individuals or clusters of individuals. We will not impose any restrictions regarding the types of outcomes reported.

Context

We will not impose any restrictions regarding context, language or publication date for the selection of studies.

Searching

We will search the following electronic bibliographic databases for relevant studies: MEDLINE through PubMed, EMBASE, LILACS, Web of Science and CENTRAL. Our full search strategy is available in the Supplementary Online Appendix.

Besides searching the databases listed above, we will search for grey literature in the following databases: System for Information on Grey Literature in Europe (Open Grey) and National Library of Medicine Bookshelf. Finally, we will also search ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for eligible studies.

Two independent researchers will examine the lists of references identified through electronic search. We will also hand-search reference lists of relevant publications, including review articles on the use of repurposed medications for the treatment of breast cancer and of original studies considered eligible for the review. We also intend to contact researchers to request relevant unpublished data whenever applicable.

Selection of studies

For all studies identified, two authors will independently screen and review the titles and abstracts. The same



reviewers will examine full versions of potentially relevant studies independently. Where applicable, we will contact the authors of selected studies to ask for additional data. If there are disagreements regarding the inclusion of a study, these will be resolved through discussion with a third reviewer whenever needed. We will use Rayyan software⁹ to manage the screening of references for our review.

Charting the data

A standardised, prepiloted form will be used to extract data from the included studies. Extracted information will include the following data: authors; title; complete reference; time period when the study was conducted; country where the study took place; type (histological and molecular), subtypes and staging of breast cancer studied; inclusion/exclusion criteria; sample size; characteristics of the population (eg, presence of diabetes, obesity/overweight and metabolic syndrome); study design; details of the interventions, including treatment modality (ie, neoadjuvant, adjuvant or palliative), dose, frequency and duration of metformin treatment, the line of cancer treatment (eg, first-line treatment) and cointerventions (eg, types of chemotherapy); details of comparators and duration of follow-up; outcome measures with the definitions used by the authors; results; conclusions reported by the study authors; research limitations and funding sources. In addition, there will be a field for the registration of other information deemed relevant by the reviewers and a field for possible information to ask the authors. The data charting form will be amended as needed according to the progress of the data charting process. Disagreements about extracted data will be solved by consensus, and an independent reviewer will be consulted if disagreements persist. Data extracted from each study will be stored in word processing documents throughout the duration of the study and organised in digital spreadsheets as needed.

Collating, summarising and reporting results

We will structure the presentation of our results around the different molecular types of breast cancer, their stages (ie, metastatic, locally advanced and early disease) and treatment modality. We will present our findings in narrative and tabular form guided by the review questions and objective. Besides, this study will be reported as per an adapted version of the PRISMA-ScR statement (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews).¹⁰ Our adapted PRISMA-ScR checklist comprising the methods of our review is available in a supplementary file.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

AMENDMENTS

Any amendments to this original protocol will be documented in the methods section of the publication of our results.

ETHICS AND DISSEMINATION

Because of its nature as a literature review, this study is exempt from ethics approval. The results of the review will be disseminated through presentations in conferences and a peer-reviewed publication.

DISCUSSION

Breast cancer is the leading cause of cancer death in women and the third highest incident cancer globally, claiming around 180 thousand lives and resulting in 17.7 million disability-adjusted life years globally in 2017.¹¹ Drug repurposing is an opportunity to minimise risks, costs and time in the development of new pharmacologic treatments while preserving the benefits for healthcare. Although the number of randomised clinical trials of metformin for the treatment of breast cancer increased over the last decades, the overall landscape of those studies and the value and scope of systematic reviews to be conducted based on them remain unclear. In this protocol, we outline the details of the aims and methods of a scoping review of randomised controlled trials of metformin for the treatment of breast cancer. We hope that, once completed, this scoping review may contribute to the field of drug repurposing related to cancer by mapping the available evidence from randomised clinical trials and identifying research gaps related to the use of metformin in breast cancer.

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Appendix B

Electronic Search Strategies for Databases

1. MEDLINE (via Pubmed)

Search ID #	Search formula
1	(Metformin [Mesh])
2	(Dimethylbiguanidine [all fields] OR Dimethylguanylguanidine [all fields] OR Glucophage [all fields])
3	(Metformin Hydrochloride [all fields] OR Hydrochloride, Metformin [all fields] OR Metformin HCl [all fields] OR HCl, Metformin [all fields])
4	#1 OR #2 OR #3
5	(Neoplasms [Mesh])
6	(Neoplasia [all fields] OR Neoplasias [all fields] OR Neoplasm [all fields])
7	(Tumors [all fields] OR Tumor [all fields])
8	(Cancer [all fields] OR Cancers [all fields])
9	(Malignant Neoplasms [all fields] OR Malignant Neoplasm [all fields] OR Neoplasm, Malignant [all fields] OR Neoplasms, Malignant [all fields])
10	(Malignancy [all fields] OR Malignancies [all fields])
11	(Benign Neoplasms [all fields] OR Neoplasms, Benign [all fields] OR Benign Neoplasm [all fields] OR Neoplasm, Benign [all fields])
12	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
13	(neoplas* OR tumor* OR tumour* OR cancer* OR malignan*)
14	#12 OR #13
15	(Lymphoma [MeSH])
16	(Lymphomas [all fields])
17	(Sarcoma, Germinoblastic [all fields] OR Germinoblastic Sarcoma [all fields] OR Germinoblastic Sarcomas [all fields] OR Sarcomas, Germinoblastic [all fields])
18	(Reticulolymphosarcoma [all fields] OR Reticulolymphosarcomas [all fields])
19	(Germinoblastoma [all fields] OR Germinoblastomas [all fields])
20	(Lymphoma, Malignant [all fields] OR Lymphomas, Malignant [all fields] OR Malignant Lymphoma [all fields] OR Malignant Lymphomas [all fields])
21	#15 OR #16 OR #17 OR #18 OR #19 OR #20
22	(Leukemia [MeSH])
23	(Leukemias [all fields])
24	(Leucocythaemia [all fields] OR Leucocythaemias [all fields])
25	(Leucocythemia [all fields] OR Leucocythemias [all fields])
26	#22 OR #23 OR #24 OR #25
27	(Sarcoma [Mesh])

28	(Sarcomas [all fields])
29	(Sarcoma, Soft Tissue [all fields] OR Sarcomas, Soft Tissue [all fields] OR Soft Tissue Sarcoma [all fields] OR Soft Tissue Sarcomas [all fields])
30	(Sarcoma, Epithelioid [all fields] OR Epithelioid Sarcoma [all fields] OR Epithelioid Sarcomas [all fields] OR Sarcomas, Epithelioid [all fields])
31	(Sarcoma, Spindle Cell [all fields] OR Sarcomas, Spindle Cell [all fields] OR Spindle Cell Sarcoma [all fields] OR Spindle Cell Sarcomas [all fields])
32	#27 OR #28 OR #29 OR #30 OR #31
33	(Carcinoma [MeSH])
34	(Carcinomas [all fields])
35	(Epithelial Neoplasms, Malignant [all fields] OR Malignant Epithelial Neoplasms [all fields] OR Epithelial Neoplasm, Malignant [all fields] OR Malignant Epithelial Neoplasm [all fields] OR Neoplasm, Malignant Epithelial [all fields] OR Neoplasms, Malignant Epithelial [all fields])
36	(Epithelial Tumors, Malignant [all fields] OR Epithelial Tumor, Malignant [all fields] OR Malignant Epithelial Tumor [all fields] OR Malignant Epithelial Tumors [all fields] OR Tumor, Malignant Epithelial [all fields])
37	(Epithelioma [all fields] OR Epitheliomas [all fields])
38	(Carcinoma, Undifferentiated [all fields] OR Undifferentiated Carcinoma [all fields] OR Undifferentiated Carcinomas [all fields])
39	(Carcinoma, Anaplastic [all fields] OR Anaplastic Carcinoma [all fields] OR Anaplastic Carcinomas [all fields])
40	(Carcinoma, Spindle-Cell [all fields] OR Carcinoma, Spindle Cell [all fields] OR Spindle-Cell Carcinoma [all fields] OR Spindle-Cell Carcinomas [all fields])
41	(Carcinomatosis [all fields] OR Carcinomatoses [all fields])
42	#33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41
43	(Adenocarcinoma [MeSH])
44	(Adenocarcinomas [all fields])
45	(Adenoma, Malignant [all fields] OR Adenomas, Malignant [all fields] OR Malignant Adenoma [all fields] OR Malignant Adenomas [all fields])
46	(Carcinoma, Granular Cell [all fields] OR Carcinomas, Granular Cell [all fields] OR Granular Cell Carcinoma [all fields] OR Granular Cell Carcinomas [all fields])
47	(Adenocarcinoma, Granular Cell [all fields] OR Adenocarcinomas, Granular Cell [all fields] OR Granular Cell Adenocarcinoma [all fields] OR Granular Cell Adenocarcinomas [all fields])

48	(Adenocarcinoma, Tubular [all fields] OR Adenocarcinomas, Tubular [all fields] OR Tubular Adenocarcinoma [all fields] OR Tubular Adenocarcinomas [all fields])
49	(Carcinoma, Tubular [all fields] OR Carcinomas, Tubular [all fields] OR Tubular Carcinoma [all fields] OR Tubular Carcinomas [all fields])
50	(Carcinoma, Cribriform [all fields] OR Carcinomas, Cribriform [all fields] OR Cribriform Carcinoma [all fields] OR Cribriform Carcinomas [all fields])
51	(Adenocarcinoma, Basal Cell [all fields] OR Adenocarcinomas, Basal Cell [all fields] OR Basal Cell Adenocarcinoma [all fields] OR Basal Cell Adenocarcinomas [all fields])
52	(Adenocarcinoma, Oxyphilic [all fields] OR Adenocarcinomas, Oxyphilic [all fields] OR Oxyphilic Adenocarcinoma [all fields] OR Oxyphilic Adenocarcinomas [all fields])
53	#43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52
54	(carcinoma* OR adenocarcinoma*)
55	#53 OR #54
56	#14 OR #21 OR #26 OR #32 OR #42 OR #55
57	#4 AND #56
58	randomized controlled trial [pt]
59	controlled clinical trial [pt]
60	randomized [tiab]
61	placebo [tiab]
62	drug therapy [sh]
63	randomly [tiab]
64	trial [tiab]
65	groups [tiab]
66	#58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR # 65
67	animals [mh] NOT humans [mh]
68	#66 NOT #67
69	#57 AND #68

2. EMBASE

Search #	Search formula
1	'metformin'/exp OR (1, 1 dimethylbiguanide) OR apophage OR aron OR benofomin OR dabex OR denkaform OR deson OR dextin OR diabetase OR (diabetase s) OR diabetformin OR diabetmin OR diabetmin retard OR diabetosan OR diabex OR diafat OR diaformin OR diaformina OR (diaformina lp) OR diametin OR diamin OR dianben OR diformin OR (diformin retard) OR dimefor OR dimethylbiguanide OR dimethyldiguanide OR dmgg OR dybis OR eraphage OR (espa-formin) OR (euform retard) OR fluamine OR flumamine OR fornidd OR fortamet OR glafornil OR glibudon OR glifage OR gliguanid OR glucaminol OR glucofage OR glucofago OR glucoform OR glucoformin OR glucohexal OR glucoless OR glucomet OR glucomin OR glucomine OR gluconil OR glucophage OR (glucophage forte) OR (glucophage retard) OR (glucophage sr) OR (glucophage xr) OR (glucophage xr extended release) OR (glucophage-mite) OR glucostop OR glucotika OR gludepatic OR glufor OR gluformin OR glukophage OR glumeformin OR glumet OR glumetza OR glupa OR glustress OR glyciphage OR glycomet OR glycon OR glycoran OR glyformin OR glymet OR haurymellin OR hipoglucin OR (i-max) OR islotin OR juformin OR (la 6023) OR la6023 OR (lyomet (drug)) OR maformin OR meglucon OR meguan OR melbin OR melformin OR mellittin OR merckformin OR mescorit OR metaformin OR metfogamma OR (metfoliquid geriasan) OR metforal OR metformax OR (metformin hydrochloride) OR metformina OR metformine OR (metformine hcl) OR methformin OR metiguanide OR metomin OR metphormin OR miformin OR (n' dimethylguanylguanide) OR (n' dimethylguanylguanidine) OR (n', n' dimethyldiguanide) OR (n, n dimethyl biguanidine) OR (n, n dimethylbiguanide) OR (n, n dimethylbiguanide retard) OR (n, n dimethylbiguanidine) OR (n, n dimethyldiguanide) OR (n, n dimethylguanylguanidine) OR neoform OR nndg OR (reglus-500) OR riomet OR (riomet er) OR risidon OR siamformet OR siofor OR thiabet OR vimetrol OR walaphage
2	'Neoplasm'/exp OR (acral tumor) OR (acral tumour) OR neoplasia OR neoplasms OR (neoplasms by histologic type) OR (neoplasms, cystic, mucinous, and serous) OR (neoplasms, embryonal and mixed) OR (neoplasms, germ cell and embryonal) OR (neoplasms, glandular and epithelial) OR (neoplasms, hormone-dependent) OR (neoplasms, post-traumatic) OR (neoplastic disease) OR tumor OR tumour
3	'Lymphoma'/exp OR (adeno lymphoma) OR adenolymphoma OR (cystadenoma lymphomatosum) OR (lymph node tumor) OR (lymph node tumour) OR (lymphocytic tumor) OR (lymphocytic tumour) OR

	(lymphoid malignancies) OR (lymphoid malignancy) OR lymphoma OR adeno OR lymphomas OR (malignant lymphoid neoplasm) OR (malignant lymphoid neoplasms) OR (malignant lymphoma)
4	'Leukemia'/exp OR aleukaemia OR (aleukaemic leukaemia) OR aleukemia OR (aleukemic leucemia) OR (blastic leukaemia) OR (blastic leucemia) OR hemoblastoma OR leukaemia OR leucemia OR leukaemia OR (leukaemia, radiation-induced) OR (leukaemia, subleukaemic) OR (leukaemia, aleukaemic) OR (leukemia, radiation-induced) OR (leukemia, subleukemic) OR (leukemia, aleukemic) OR (leukemogenesis, radiation) OR (mesoblastic leukaemia) OR (mesoblastic leukemia) OR (parablastic leukaemia) OR (parablastic leukemia) OR (radiation induced leukaemia) OR (radiation induced leukemia) OR (radiation leukaemia) OR (radiation leukemia) OR (radiation leukemogenesis) OR (stem cell leukaemia) OR (stem cell leukemia) OR (subleukemic leukemia) OR (x ray leukemogenesis)
5	'Sarcoma'/exp OR histioblastoma OR histiosarcoma OR (malignant sarcoma) OR (mast cell sarcoma) OR (mast-cell sarcoma) OR (neoplasm, mesenchymal) OR (sarcoma 37) OR (sarcoma 37 cell) OR (sarcoma e 100) OR (sarcoma l 1) OR (sarcoma sa 1) OR (sarcoma tawa) OR (sarcoma, mast-cell)
6	'Carcinoma'/exp OR (carcinoma 63) OR (carcinoma, brown-pearce) OR (carcinoma, krebs 2) OR (carcinoma, neuroendocrine) OR (carcinoma, scirrhus) OR (epithelial carcinoma) OR (epithelial malignant tumor) OR (epithelial malignant tumour) OR (internal carcinoma) OR (malignant epithelial tumor) OR (malignant epithelial tumour) OR microcarcinoma OR (neoplasm, malignant epithelial) OR (neoplasms, ductal, lobular, and medullary) OR (primary carcinoma)
7	'adenocarcinoma'/exp OR adenocancer OR (adenocarcinoma, clear cell) OR (adenocarcinoma, follicular) OR (adenocarcinoma, papillary) OR (adenocarcinoma, scirrhus) OR (adenocarcinoma, sebaceous) OR (adenoepidermoid carcinoma) OR (adenoid basal carcinoma) OR (glandular carcinoma) OR (villous adenocarcinoma)
8	#2 OR #3 OR #4 OR #5 OR #6 OR #7
9	#1 AND #8
10	'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR (random* OR factorial* OR placebo* OR doubl* NEAR/1 blind* OR singl* NEAR/1 blind* OR assign* OR allocat* OR volunteer*):de,ab,ti
11	#9 AND #10 AND [embase]/lim NOT [medline]/lim

3. LILACS

Search #	Search formula
1	(Metformin OR Metformina OR Metformina OR Dimetil Guanil Guanidina)
2	((Neoplasms OR Neoplasias OR Neoplasias OR Câncer OR Neoplasia OR Neoplasia Benigna OR Neoplasia Maligna OR Neoplasias Malignas OR Neoplasmas OR Tumor OR Tumor Maligno OR Tumores OR Tumores Malignos) OR (Lymphoma OR Linfoma OR Linfoma OR Germinoblastoma OR Linfoma Maligno OR Reticulolinfossarcoma OR Sarcoma Germinoblástico) OR (Leukemia OR Leucemia OR Leucemia OR Leucemias OR Leucocitemia OR Leucocitemias) OR (Sarcoma OR Sarcoma OR Sarcoma OR Sarcoma Epiteliode OR Sarcoma de Células Fusiformes OR Sarcoma de Tecidos Moles) OR (Carcinoma OR Carcinoma OR Carcinoma OR Carcinoma Anaplásico OR Carcinoma Fusocelular OR Carcinoma Indiferenciado OR Carcinomatose OR Epitelioma OR Neoplasias Epiteliais Malignas) OR (Carcinoma OR Carcinoma OR Carcinoma OR Carcinoma Anaplásico OR Carcinoma Fusocelular OR Carcinoma Indiferenciado OR Carcinomatose OR Epitelioma OR Neoplasias Epiteliais Malignas) OR (Adenocarcinoma OR Adenocarcinoma OR Adenocarcinoma OR Adenocarcinoma Basocelular OR Adenocarcinoma Oxifílico OR Adenocarcinoma Tubular OR Adenocarcinoma de Células Granulares OR Adenocarcinomas OR Adenoma Maligno OR Carcinoma Cribriforme OR Carcinoma Tubular OR Carcinoma de Células Granulares))
3	(Randomized Controlled Trial OR Ensaio Clínico Controlado Aleatorio OR Ensaio Clínico Controlado Aleatório OR Ensaio Clínico Controlado Randomizado OR Ensaio Controlado Aleatório)
4	#1 AND #2 AND #3

4. Web of Science

Search ID #	Search formula
1	TS= (Metformin)
2	TS= (Dimethylbiguanidine OR Dimethylguanylguanidine OR Glucophage)
3	TS= ("Metformin Hydrochloride" OR "Hydrochloride, Metformin" OR "Metformin HCl" OR "HCl, Metformin")
4	#1 OR #2 OR #3
5	TS= (Neoplasms)
6	TS= (Neoplasia OR Neoplasias OR Neoplasm)
7	TS= (neoplas*)
8	TS= (Tumors OR Tumor)
9	TS= (tumor* OR tumour*)
10	TS= (Cancer OR Cancers)
11	TS= (cancer*)
12	TS= ("Malignant Neoplasms" OR "Malignant Neoplasm" OR "Neoplasm, Malignant" OR "Neoplasms, Malignant")
13	TS= (Malignancy OR Malignancies)
14	TS= (malignan*)
15	TS= ("Benign Neoplasms" OR "Neoplasms, Benign" OR "Benign Neoplasm" OR "Neoplasm, Benign")
16	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
17	TS= (Lymphoma)
18	TS= (Lymphomas)
19	TS= ("Sarcoma, Germinoblastic" OR "Germinoblastic Sarcoma" OR "Germinoblastic Sarcomas" OR "Sarcomas, Germinoblastic")
20	TS= (Reticulolymphosarcoma OR Reticulolymphosarcomas)
21	TS= (Germinoblastoma OR Germinoblastomas)
22	TS= ("Lymphoma, Malignant" OR "Lymphomas, Malignant" OR "Malignant Lymphoma" OR "Malignant Lymphomas")
23	#17 OR #18 OR #19 OR #20 OR #21 OR #22
24	TS= (Leukemia)
25	TS= (Leukemias)
26	TS= (Leucocythaemia OR Leucocythaemias)
27	TS= (Leucocythemia OR Leucocythemias)
28	#24 OR #25 OR #26 OR #27
29	TS= (Sarcoma)
30	TS= (Sarcomas)
31	TS= ("Sarcoma, Soft Tissue" OR "Sarcomas, Soft Tissue" OR "Soft Tissue Sarcoma" OR "Soft Tissue Sarcomas")

32	TS= ("Sarcoma, Epithelioid" OR "Epithelioid Sarcoma" OR "Epithelioid Sarcomas" OR "Sarcomas, Epithelioid")
33	TS= ("Sarcoma, Spindle Cell" OR "Sarcomas, Spindle Cell" OR "Spindle Cell Sarcoma" OR "Spindle Cell Sarcomas")
34	#29 OR #30 OR #31 OR #32 OR #33
35	TS= (Carcinoma)
36	TS= (Carcinomas)
37	TS= ("Epithelial Neoplasms, Malignant" OR "Malignant Epithelial Neoplasms" OR "Epithelial Neoplasm, Malignant" OR "Malignant Epithelial Neoplasm" OR "Neoplasm, Malignant Epithelial" OR "Neoplasms, Malignant Epithelial")
38	TS= ("Epithelial Tumors, Malignant" OR "Epithelial Tumor, Malignant" OR "Malignant Epithelial Tumor" OR "Malignant Epithelial Tumors" OR "Tumor, Malignant Epithelial")
39	TS= (Epithelioma OR Epitheliomas)
40	TS= ("Carcinoma, Undifferentiated" OR "Undifferentiated Carcinoma" OR "Undifferentiated Carcinomas")
41	TS= ("Carcinoma, Anaplastic" OR "Anaplastic Carcinoma" OR "Anaplastic Carcinomas")
42	TS= ("Carcinoma, Spindle-Cell" OR "Carcinoma, Spindle Cell" OR "Spindle-Cell Carcinoma" OR "Spindle-Cell Carcinomas")
43	TS= (Carcinomatosis OR Carcinomatoses)
44	#35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43
45	TS= (*blastoma OR *carcinoma)
46	#44 OR #45
47	TS= (Adenocarcinoma)
48	TS= (Adenocarcinomas)
49	TS= ("Adenoma, Malignant" OR "Adenomas, Malignant" OR "Malignant Adenoma" OR "Malignant Adenomas")
50	TS= ("Carcinoma, Granular Cell" OR "Carcinomas, Granular Cell" OR "Granular Cell Carcinoma" OR "Granular Cell Carcinomas")
51	TS= ("Adenocarcinoma, Granular Cell" OR "Adenocarcinomas, Granular Cell" OR "Granular Cell Adenocarcinoma" OR "Granular Cell Adenocarcinomas")
52	TS= ("Adenocarcinoma, Tubular" OR "Adenocarcinomas, Tubular" OR "Tubular Adenocarcinoma" OR "Tubular Adenocarcinomas")
53	TS= ("Carcinoma, Tubular" OR "Carcinomas, Tubular" OR "Tubular Carcinoma" OR "Tubular Carcinomas")
54	TS= ("Carcinoma, Cribriform" OR "Carcinomas, Cribriform" OR "Cribriform Carcinoma" OR "Cribriform Carcinomas")
55	TS= ("Adenocarcinoma, Basal Cell" OR "Adenocarcinomas, Basal Cell" OR "Basal Cell Adenocarcinoma" OR "Basal Cell Adenocarcinomas")
56	TS= ("Adenocarcinoma, Oxyphilic" OR "Adenocarcinomas, Oxyphilic" OR "Oxyphilic Adenocarcinoma" OR "Oxyphilic Adenocarcinomas")

57	#47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56
58	TS= (carcinoma* OR adenocarcinoma*)
59	#57 OR #58
60	#16 OR #23 OR #28 OR #34 OR #46 OR #59
61	#4 AND #60
62	TS= ("Randomized Controlled Trial" OR "Controlled Clinical Trial" OR "Clinical Trial")
63	#61 AND #62

5. CENTRAL

Search ID #	Search formula
1	Mesh descriptor: [Metformin] explode all trees
2	(Dimethylbiguanidine OR Dimethylguanylguanidine OR Glucophage)
3	("Metformin Hydrochloride" OR "Hydrochloride, Metformin" OR "Metformin HCl" OR "HCl, Metformin")
4	#1 OR #2 OR #3
5	Mesh descriptor: [Neoplasms] explode all trees
6	(Neoplasia OR Neoplasias OR Neoplasm)
7	(Tumors OR Tumor)
8	(Cancer OR Cancers)
9	("Malignant Neoplasms" OR "Malignant Neoplasm" OR "Neoplasm, Malignant" OR "Neoplasms, Malignant")
10	(Malignancy OR Malignancies)
11	("Benign Neoplasms" OR "Neoplasms, Benign" OR "Benign Neoplasm" OR "Neoplasm, Benign")
12	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
13	(neoplas* OR tumor* OR tumour* OR cancer* OR malignan*)
14	#12 OR #13
15	Mesh descriptor: [Lymphoma] explode all trees
16	(Lymphomas)
17	("Sarcoma, Germinoblastic" OR "Germinoblastic Sarcoma" OR "Germinoblastic Sarcomas" OR "Sarcomas, Germinoblastic")
18	(Reticulolymphosarcoma OR Reticulolymphosarcomas)
19	(Germinoblastoma OR Germinoblastomas)
20	("Lymphoma, Malignant" OR "Lymphomas, Malignant" OR "Malignant Lymphoma" OR "Malignant Lymphomas")
21	#15 OR #16 OR #17 OR #18 OR #19 OR #20
22	Mesh descriptor: [Leukemia] explode all trees
23	(Leukemias)
24	(Leucocythaemia OR Leucocythaemias)
25	(Leucocythemia OR Leucocythemias)
26	#22 OR #23 OR #24 OR #25
27	Mesh descriptor: [Sarcoma] explode all trees
28	(Sarcomas)
29	("Sarcoma, Soft Tissue" OR "Sarcomas, Soft Tissue" OR "Soft Tissue Sarcoma" OR "Soft Tissue Sarcomas")
30	("Sarcoma, Epithelioid" OR "Epithelioid Sarcoma" OR "Epithelioid Sarcomas" OR "Sarcomas, Epithelioid")

31	("Sarcoma, Spindle Cell" OR "Sarcomas, Spindle Cell" OR "Spindle Cell Sarcoma" OR "Spindle Cell Sarcomas")
32	#27 OR #28 OR #29 OR #30 OR #31
33	Mesh descriptor: [Carcinoma] explode all trees
34	(Carcinomas)
35	("Epithelial Neoplasms, Malignant" OR "Malignant Epithelial Neoplasms" OR "Epithelial Neoplasm, Malignant" OR "Malignant Epithelial Neoplasm" OR "Neoplasm, Malignant Epithelial" OR "Neoplasms, Malignant Epithelial")
36	("Epithelial Tumors, Malignant" OR "Epithelial Tumor, Malignant" OR "Malignant Epithelial Tumor" OR "Malignant Epithelial Tumors" OR "Tumor, Malignant Epithelial")
37	(Epithelioma OR Epitheliomas)
38	("Carcinoma, Undifferentiated" OR "Undifferentiated Carcinoma" OR "Undifferentiated Carcinomas")
39	("Carcinoma, Anaplastic" OR "Anaplastic Carcinoma" OR "Anaplastic Carcinomas")
40	("Carcinoma, Spindle-Cell" OR "Carcinoma, Spindle Cell" OR "Spindle-Cell Carcinoma" OR "Spindle-Cell Carcinomas")
41	(Carcinomatosis OR Carcinomatoses)
42	#33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41
43	(*blastoma OR *carcinoma)
44	#42 OR #43
45	Mesh descriptor: [Adenocarcinoma] explode all trees
46	(Adenocarcinomas)
47	("Adenoma, Malignant" OR "Adenomas, Malignant" OR "Malignant Adenoma" OR "Malignant Adenomas")
48	("Carcinoma, Granular Cell" OR "Carcinomas, Granular Cell" OR "Granular Cell Carcinoma" OR "Granular Cell Carcinomas")
49	("Adenocarcinoma, Granular Cell" OR "Adenocarcinomas, Granular Cell" OR "Granular Cell Adenocarcinoma" OR "Granular Cell Adenocarcinomas")
50	("Adenocarcinoma, Tubular" OR "Adenocarcinomas, Tubular" OR "Tubular Adenocarcinoma" OR "Tubular Adenocarcinomas")
51	("Carcinoma, Tubular" OR "Carcinomas, Tubular" OR "Tubular Carcinoma" OR "Tubular Carcinomas")
52	("Carcinoma, Cribiform" OR "Carcinomas, Cribiform" OR "Cribiform Carcinoma" OR "Cribiform Carcinomas")
53	("Adenocarcinoma, Basal Cell" OR "Adenocarcinomas, Basal Cell" OR "Basal Cell Adenocarcinoma" OR "Basal Cell Adenocarcinomas")
54	("Adenocarcinoma, Oxyphilic" OR "Adenocarcinomas, Oxyphilic" OR "Oxyphilic Adenocarcinoma" OR "Oxyphilic Adenocarcinomas")
55	#45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54
56	(carcinoma* OR adenocarcinoma*)
57	#55 OR 56

58	#14 OR #21 OR #26 OR #32 OR #44 OR #57
59	#4 AND #58

in Trials

Appendix C

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

Table 1 - Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	8-9
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	16-18
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	18-19
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	17
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	18-19
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	18
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Supplementary Online Appendix of the published protocol and Appendix B
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	19-21
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	21-22
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	21-22
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	N/A

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	22-23
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	23-24 and Appendix D
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Appendices E and F
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	N/A
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Appendices E, F, and G
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	28-45
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	45-48
Limitations	20	Discuss the limitations of the scoping review process.	48-49
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	49-50
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	45

JB1 = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

Adapted from: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med*. ;169:467–473. doi: 10.7326/M18-0850

Appendix D

Excluded Reports from Databases, ICTR, and Google Scholar
with Reason of Exclusion

Table 2 - Reports Excluded from Databases with Reason of Exclusion

7 reports excluded from Databases			
	Author, data	Reference	Reason of exclusion
1	Carlo C. and Pasanisi P. 2011	Carlo C., Pasanisi P. Metformin and breast cancer. Climacteric. 2011;14((Carlo C.; Pasanisi P.)):21.	wrong comparator
2	Egle et al. 2017	Egle D, Marth C, Steger G, Bartsch R, Pfeiler G, Greil R, et al. Effect of metformin on progression-free survival outcomes in patients with advanced or metastatic HR+, HER2-breast cancer: subgroup analysis of STEPAUT. Breast. 2017 Mar;32:S26–7.	wrong study design
3	Gennari A. et al. 2016	Gennari A., Nanni O., Rocca A., De Censi A., Fieschi A., Bologna A., et al. Phase II randomised clinical study of metformin plus chemotherapy vs chemotherapy alone in HER2 negative metastatic breast cancer: final results of the MYME trial. Ann Oncol. 2016;27((Gennari A.; De Censi A.; Corradengo D.) Medical Oncology, Ospedali Galliera, Genoa, Italy):vi70.	duplicate
4	Goodwin et al. 2019	Goodwin PJ, Ennis M, Cescon DW, Elser C, Haq R, Hamm CM, et al. Phase II randomized clinical trial (RCT) of metformin (MET) vs placebo (PLAC) in combination with chemotherapy (CXT) in refractory locally advanced (LABC) or metastatic breast cancer (MBC). Cancer Res [Internet]. 2019 Feb;79(4). Available from: ://WOS:000478677000305	duplicate
5	MedSIR and Novartis 2020	MedSIR, Novartis. Study to Evaluate the Effect of Metformin in the Prevention of HG in HR + /HER2 - PIK3CA-mut Advanced BC Patients. 2020 Oct 23;	wrong comparator

6	NCT01905046	NCT01905046. Metformin Hydrochloride in Preventing Breast Cancer in Patients With Atypical Hyperplasia or In Situ Breast Cancer. https://clinicaltrials.gov/show/NCT01905046 [Internet]. 2013; Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01489061/full	wrong population
7	Sehdev et al. 2018	Sehdev A, Karrison T, Zha Y, Janisch L, Turcich M, Cohen E, et al. A pharmacodynamic study of sirolimus and metformin in patients with advanced solid tumors. <i>Cancer Chemother Pharmacol.</i> 2018;82(2):309-317.	wrong comparator

Table 3 - Reports Excluded from ICTRP with Reason of Exclusion

22 reports excluded from ICTRP			
	Author, data	Reference	Reason of exclusion
1	Chow, 2022	Chow S. Phase II Study of Metformin for Reduction of Obesity-Associated Breast Cancer Risk [Internet]. clinicaltrials.gov ; 2022 Jun. Report No.: NCT02028221. Available from: https://clinicaltrials.gov/ct2/show/NCT02028221	wrong population
2	Crew, 2022	Crew KD. Pre-Surgical Trial of the Combination of Metformin and Atorvastatin in Newly Diagnosed Operable Breast Cancer [Internet]. clinicaltrials.gov ; 2022 Aug. Report No.: NCT01980823. Available from: https://clinicaltrials.gov/ct2/show/NCT01980823	wrong study design

3	Daiqin, 2019	Daiqin L. Effect of metformin combined with radiotherapy on radiosensitivity of CD44+CD24-MCF-7 cells in breast cancer [Internet]. 2019. Report No.: ChiCTR1900023063. Available from: https://www.chictr.org.cn/showproj.aspx?proj=38759	wrong study design
4	Davis, 2016	Davis S. The effects of metformin on the LKB1/AMP-activated protein kinase (AMPK) pathway in breast tissue, a pilot study [Internet]. 2016. Report No.: ACTRN12610000219088. Available from: https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12610000219088	wrong population
5	Esserman, 2022	Esserman L. I-SPY TRIAL: Neoadjuvant and Personalized Adaptive Novel Agents to Treat Breast Cancer [Internet]. clinicaltrials.gov; 2022 Nov. Report No.: NCT01042379. Available from: https://clinicaltrials.gov/ct2/show/NCT01042379	wrong comparator
6	EUCTR2009-009921-28-IT	EUCTR2009-009921-28-IT. The Effect of Metformin, an insulin-sensitizing drug, on Breast Cancer Primary Prevention: The Plotina Breast Cancer Prevention Randomized, Placebo Controlled [Internet]. 2009. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2009-009921-28/IT	wrong population
7	Fedeli, 2020	Fedeli A. A Study of Liposomal Doxorubicin + Docetaxel + Trastuzumab + Metformin in Operable and Locally Advanced HER2 Positive Breast Cancer [Internet]. clinicaltrials.gov; 2020 Apr. Report No.: NCT02488564. Available from: https://clinicaltrials.gov/ct2/show/NCT02488564	wrong study design

8	Fedeli, 2021	Fedeli A. Clinical and translational phase II study of liposomal doxorubicin plus docetaxel and transtuzumab with metformin as primary systemic therapy for operable and locally advanced HER2 positive breast cancer [Internet]. 2021. Report No.: EUCTR2014-002602-20-IT. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-002602-20/IT	wrong study design
9	Goodwin, 2012	Goodwin PJ. Clinical and Biologic Effects of Metformin in Early Stage Breast Cancer [Internet]. clinicaltrials.gov; 2012 Jan. Report No.: NCT00897884. Available from: https://clinicaltrials.gov/ct2/show/NCT00897884	wrong study design
10	Harris, 2014	Harris A. Effect of Metformin on Breast Cancer Metabolism [Internet]. clinicaltrials.gov; 2014 Jul. Report No.: NCT01266486. Available from: https://clinicaltrials.gov/ct2/show/NCT01266486	wrong study design
11	Hershman, 2022	Hershman DL. Pre-Surgical Study: Effect of Metformin on Breast Cancer Proliferation [Internet]. clinicaltrials.gov; 2022 Oct. Report No.: NCT00930579. Available from: https://clinicaltrials.gov/ct2/show/NCT00930579	wrong study design
12	Hoffmann, 2023	Hoffmann. To Evaluate the Safety, Tolerability, and Pharmacokinetics of Inavolisib Single Agent in Participants With Solid Tumors and in Combination With Endocrine and Targeted Therapies in Participants With Breast Cancer [Internet]. clinicaltrials.gov; 2023 Feb. Report No.: NCT03006172. Available from: https://clinicaltrials.gov/ct2/show/NCT03006172	wrong study design
13	Kalinsky, 2017	Kalinsky K. Study of Erlotinib and Metformin in Triple Negative Breast Cancer [Internet]. clinicaltrials.gov; 2017 Aug. Report No.: NCT01650506. Available from: https://clinicaltrials.gov/ct2/show/NCT01650506	wrong study design

14	Lohmann, 2016	Lohmann AE. The Use of Metformin in Early Breast Cancer Patients Pre-Surgery [Internet]. clinicaltrials.gov ; 2016 Feb. Report No.: NCT01302002. Available from: https://clinicaltrials.gov/ct2/show/NCT01302002	wrong study design
15	Mackenzie, 2013	Mackenzie M. Metformin and Temsirolimus in Treating Patients With Metastatic or Unresectable Solid Tumor or Lymphoma [Internet]. 2013. Report No.: NCT00659568. Available from: https://clinicaltrials.gov/ct2/show/NCT00659568?term=NCT00659568&draw=2&rank=1	wrong study design
16	Mayer, 2012	Mayer I. Metformin Hydrochloride in Treating Women With Stage I or Stage II Breast Cancer That Can Be Removed By Surgery [Internet]. clinicaltrials.gov ; 2012 Jun. Report No.: NCT00984490. Available from: https://clinicaltrials.gov/ct2/show/NCT00984490	wrong study design
17	Novartis Pharmaceuticals, 2023	Novartis Pharmaceuticals. Study of Safety and Efficacy of Dapagliflozin + Metformin XR Versus Metformin XR in Participants With HR+, HER2-, Advanced Breast Cancer While on Treatment With Alpelisib and Fulvestrant [Internet]. clinicaltrials.gov ; 2023 Jan. Report No.: NCT04899349. Available from: https://clinicaltrials.gov/ct2/show/NCT04899349	wrong comparator
18	Ow, 2017	Ow S. Metformin and Simvastatin in Addition to Fulvestrant [Internet]. clinicaltrials.gov ; 2017 Jun. Report No.: NCT03192293. Available from: https://clinicaltrials.gov/ct2/show/NCT03192293	wrong study design
19	Seidemann, 2022	Seidemann, Ericka. Metformin Use to Reduce Disparities in Newly Diagnosed Breast Cancer Response to Neoadjuvant Treatment [Internet]. clinicaltrials.gov ; 2022 Sep. Report No.: NCT04741204. Available from: https://clinicaltrials.gov/ct2/show/NCT04741204	wrong comparator

20	Storniolo, 2018	Storniolo AM. Metformin Hydrochloride vs. Placebo in Overweight or Obese Patients at Elevated Risk for Breast Cancer [Internet]. clinicaltrials.gov; 2018 Mar. Report No.: NCT01793948. Available from: https://clinicaltrials.gov/ct2/show/NCT01793948	wrong population
21	Sundelin, 2018	Sundelin EIO. Metformin in Breast Cancer, Visualized With Positron Emission Tomography [Internet]. clinicaltrials.gov; 2018 Jan. Report No.: NCT02882581. Available from: https://clinicaltrials.gov/ct2/show/NCT02882581	wrong study design
22	Valero, 2020	Valero V. Exemestane-RAD001-Metformin [Internet]. clinicaltrials.gov; 2020 Jun. Report No.: NCT01627067. Available from: https://clinicaltrials.gov/ct2/show/NCT01627067	wrong study design

Table 4 - Reports Excluded from Google Scholar with Reason of Exclusion

32 reports excluded from Google Scholar			
	Author, data	Reference	Reason of exclusion
1	Arce-Salinas et al. 2016	Arce-Salinas C, Alamilla G, Flores-Diaz D, Deneken CZ, Mendoza-Galindo L, Ramirez-Morales R, et al. Randomized, double blind trial to evaluate the safety and efficacy of metformin vs placebo plus neoadjuvant chemotherapy in locally advanced breast cancer. J Clin Oncol [Internet]. 2016;34. Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L611753653&from=export	duplicate
2	Bonanni et al. 2012	Bonanni B, Puntoni M, Cazzaniga M, Pruneri G, Serrano D, Guerrieri-Gonzaga A, et al. Dual effect of metformin on breast cancer proliferation in a randomized presurgical trial. J Clin Oncol. 2012;30(21):2593-2600.	duplicate

3	Brown et al. 2020	Brown JC, Zhang S, Ligibel JA, Irwin ML, Jones LW, Campbell N, et al. Effect of Exercise or Metformin on Biomarkers of Inflammation in Breast and Colorectal Cancer: A Randomized Trial. <i>Cancer Prev Res Phila Pa.</i> 2020 Dec;13(12):1055–62.	duplicate
4	Cazzaniga et al. 2013	Cazzaniga M, DeCensi A, Pruneri G, Puntoni M, Bottiglieri L, Varricchio C, et al. The effect of metformin on apoptosis in a breast cancer presurgical trial. <i>Br J Cancer.</i> 2013 Nov 26;109(11):2792–7.	duplicate
5	Cuyas et al. 2019	Cuyas E, Buxo M, Ferri Iglesias MJ, Verdura S, Pemas S, Dorca J, et al. The C Allele of ATM rs11212617 Associates With Higher Pathological Complete Remission Rate in Breast Cancer Patients Treated With Neoadjuvant Metformin. <i>Front Oncol [Internet].</i> 2019 Mar 28;9. Available from: :/WOS:000462704800001	duplicate
6	Cuyàs et al. 2019	Cuyàs E, Fernández-Arroyo S, Buxó M, Pernas S, Dorca J, Álvarez I, et al. Metformin induces a fasting- and antifolate-mimicking modification of systemic host metabolism in breast cancer patients. <i>Aging.</i> 2019 May 9;11(9):2874–88.	duplicate
7	Davis et al. 2018	Davis SR, Robinson PJ, Jane F, White S, Brown KA, Piessens S, et al. The benefits of adding metformin to tamoxifen to protect the endometrium-A randomized placebo-controlled trial. <i>Clin Endocrinol (Oxf).</i> 2018 Nov;89(5):605–12.	duplicate
8	DeCensi et al. 2012	DeCensi A, Pollak MN, Puntoni M, Gandini S, Cazzaniga M, Pruneri G, et al. Dual effects of metformin on breast cancer proliferation in a randomized trial. <i>J Clin Oncol [Internet].</i> 2012;30(15). Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L71002974&from=export	duplicate

9	DeCensi et al. 2014	DeCensi A, Puntoni M, Gandini S, Guerrieri-Gonzaga A, Johansson HA, Cazzaniga M, et al. Differential effects of metformin on breast cancer proliferation according to markers of insulin resistance and tumor subtype in a randomized presurgical trial. <i>Breast Cancer Res Treat.</i> 2014 Nov;148(1):81–90.	duplicate
10	DeCensi et al. 2015	DeCensi A, Puntoni M, Guerrieri-Gonzaga A, Cazzaniga M, Serrano D, Lazzeroni M, et al. Effect of Metformin on Breast Ductal Carcinoma In Situ Proliferation in a Randomized Presurgical Trial. <i>Cancer Prev Res (Phila Pa).</i> 2015 Oct;8(10):888–94.	duplicate
11	El-Haggag et al. 2016	El-Haggag SM, El-Shitany NA, Mostafa MF, El-Bassiouny NA. Metformin may protect nondiabetic breast cancer women from metastasis. <i>Clin Exp Metastasis.</i> 2016 Apr;33(4):339–57.	duplicate
12	Gennari et al. 2020	Gennari A, Foca F, Zamarchi R, Rocca A, Amadori D, De Censi A, et al. Insulin-like growth factor-1 receptor (IGF-1R) expression on circulating tumor cells (CTCs) and metastatic breast cancer outcome: results from the TransMYME trial. <i>Breast Cancer Res Treat.</i> 2020 May;181(1):61–8.	duplicate
13	Goodwin et al. 2013	Goodwin PJ, Parulekar W, Gelmon KA, Shepherd LE, Ligibel JA, Hershman DL, et al. Effect of metformin versus placebo on weight and metabolic factors in initial patients enrolled onto NCIC CTG MA.32, a multicenter adjuvant randomized controlled trial in early-stage breast cancer (BC). <i>J Clin Oncol</i> [Internet]. 2013 May 20;31(15). Available from: ://WOS:000335419600256	duplicate

14	Goodwin et al. 2019	Goodwin PJ, Ennis M, Cescon DW, Elser C, Haq R, Hamm CM, et al. Phase II randomized clinical trial (RCT) of metformin (MET) vs placebo (PLAC) in combination with chemotherapy (CXT) in refractory locally advanced (LABC) or metastatic breast cancer (MBC). Cancer Res [Internet]. 2019 Feb;79(4). Available from: ://WOS:000478677000305	duplicate
15	Goodwin et al. 2021	Goodwin P, Dowling R, Ennis M, ... Cancer Antigen 15-3/Mucin 1 Levels in CCTG MA. 32: A Breast Cancer Randomized Trial of Metformin vs Placebo. JNCI Cancer ... [Internet]. 2021;(Query date: 2021-09-30 09:48:10). Available from: https://academic.oup.com/jncics/article-abstract/5/5/pkab066/6329643	duplicate
16	Hadad et al. 2010	Hadad S, Dewar J, Elseedawy E, ... Gene signature of metformin actions on primary breast cancer within a window of opportunity randomized clinical trial. J Clin ... [Internet]. 2010;(Query date: 2021-09-30 09:48:10). Available from: https://ascopubs.org/doi/abs/10.1200/jco.2010.28.15_suppl.560	duplicate
17	Hadad et al. 2011	Hadad S, Iwamoto T, Jordan L, Purdie C, Bray S, Baker L, et al. Evidence for biological effects of metformin in operable breast cancer: a pre-operative, window-of-opportunity, randomized trial. Breast Cancer Res Treat. 2011 Aug;128(3):783–94.	duplicate
18	Hadad et al. 2015	Hadad SM, Coates P, Jordan LB, Dowling RJO, Chang MC, Done SJ, et al. Evidence for biological effects of metformin in operable breast cancer: biomarker analysis in a pre-operative window of opportunity randomized trial. Breast Cancer Res Treat. 2015 Feb;150(1):149–55.	duplicate

19	Johansson et al. 2012	Johansson HA, De Censi A, Puntoni M, Cazzaniga M, Pruneri G, Serrano D, et al. Effects of metformin on markers of insulin resistance and on breast cancer proliferation: The putative role of IGFBP-1 as a predictive biomarker. Cancer Res [Internet]. 2012 Apr 15;72. Available from: ://WOS:000209701503213	duplicate
20	Kim et al. 2014	Kim J, Lim W, Kim E, Kim M, Paik N, Jeong S, et al. Phase II randomized trial of neoadjuvant metformin plus letrozole versus placebo plus letrozole for estrogen receptor positive postmenopausal breast cancer (METEOR). BMC Cancer. 2014;14:170.	duplicate
21	Kim et al. 2019	Kim J, Han W, Kim E, Jung Y, Kim H, Chae S, et al. Phase II randomized study of neoadjuvant metformin plus letrozole versus placebo plus letrozole for ER-positive postmenopausal breast cancer [METEOR Study]. [Internet]. ascopubs.org ; 2019. Available from: https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.576	duplicate
22	Ko et al. 2015	Ko K, Ma S, Yang J, Hwang Y, Ahn C, Cho Y, et al. Metformin intervention in obese non-diabetic patients with breast cancer: phase II randomized, double-blind, placebo-controlled trial. Breast Cancer Res Treat. 2015;153(2):361-370.	duplicate
23	Lohmann et al. 2017	Lohmann A, Liebman M, Brien W, Parulekar W, Gelmon K, Shepherd L, et al. Effects of metformin versus placebo on vitamin B12 metabolism in non-diabetic breast cancer patients in CCTG MA.32. Breast Cancer Res Treat. 2017;164(2):371-378.	duplicate

24	Lopez-Bonet E. et al. 2019	Lopez-Bonet E., Buxó M., Cuyàs E., Pernas S., Dorca J., Álvarez I., et al. Neoadjuvant metformin added to systemic therapy decreases the proliferative capacity of residual breast cancer. J Clin Med [Internet]. 2019;8(12). Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L2003271278	duplicate
25	Meyerhardt et al. 2020	Meyerhardt JA, Irwin ML, Jones LW, Zhang S, Campbell N, Brown JC, et al. Randomized phase II trial of exercise, metformin, or both on metabolic biomarkers in colorectal and breast cancer survivors. JNCI Cancer Spectr [Internet]. 2020;4(1). Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L631824359&from=export	duplicate
26	Nanni et al. 2019	Nanni O, Amadori D, De Censi A, Rocca A, Freschi A, Bologna A, et al. Metformin plus chemotherapy versus chemotherapy alone in the first-line treatment of HER2-negative metastatic breast cancer. The MYME randomized, phase 2 clinical trial. Breast Cancer Res Treat. 2019 Apr;174(2):433–42.	duplicate
27	Parulekar et al. 2011	Parulekar W, Chen B, Elliott C, ... A phase III randomized trial of metformin versus placebo on recurrence and survival in early-stage breast cancer (BC)(NCIC Clinical Trials Group MA. 32). J Clin ... [Internet]. 2011;(Query date: 2021-09-30 09:48:10). Available from: https://ascopubs.org/doi/abs/10.1200/jco.2011.29.15_suppl.tps103	duplicate

28	Patterson et al. 2016	Patterson RE, Marinac CR, Natarajan L, Hartman SJ, Cadmus-Bertram L, Flatt SW, et al. Recruitment strategies, design, and participant characteristics in a trial of weight-loss and metformin in breast cancer survivors. <i>Contemp Clin Trials</i> . 2016 Mar;47:64–71.	duplicate
29	Patterson et al. 2018	Patterson RE, Marinac CR, Sears DD, Kerr J, Hartman SJ, Cadmus-Bertram L, et al. The Effects of Metformin and Weight Loss on Biomarkers Associated With Breast Cancer Outcomes. <i>J Natl Cancer Inst</i> . 2018 Nov 1;110(11):1239–47.	duplicate
30	Pimentel et al. 2019	Pimentel I, Lohmann AE, Ennis M, Dowling RJO, Cescon D, Elser C, et al. A phase II randomized clinical trial of the effect of metformin versus placebo on progression-free survival in women with metastatic breast cancer receiving standard chemotherapy. <i>Breast</i> . 2019 Dec;48:17–23.	duplicate
31	Zhang et al. 2020	Zhang J, Ma X, Li Y, Liu R, Li Y, Zhang P, et al. Metformin intervention against ovarian toxicity during chemotherapy for early breast cancer: study protocol for a randomized double-blind placebo-controlled <i>Maturitas</i> [Internet]. 2020;(Query date: 2021-09-30 09:48:10). Available from: https://www.sciencedirect.com/science/article/pii/S0378512220302401?casa_token=UkVFDHR2g3YAAA:slHgMVpODkTitGg9cKJCHv3lcK21BQO31cc2H03mYT6ro-bvlxwUuSMxc9WF_M7_UKPxUf3-cX6M	duplicate
32	Zhao et al. 2017	Zhao Y, Gong C, Wang Z, Zhang J, Wang L, Zhang S, et al. A randomized phase II study of aromatase inhibitors plus metformin in pre-treated postmenopausal patients with hormone receptor positive metastatic breast cancer. <i>Oncotarget</i> . 2017 Oct 13;8(48):84224–36.	duplicate

Appendix E

Characteristics of the included studies with published results

Table 5 - Main characteristics from the 25 included studies with some form of published results

Study / References	Participants	Cancer (type, stage, treatment modality)	Intervention and Comparator	Outcomes	Main Results
Ahmed, 2021	50 women with breast cancer. No data regarding: diabetes, obesity, overweight, metabolic syndrome, and physical activity. Menopausal status: Premenopause: 34 (68%); Postmenopause: 14 (28%).	Phenotype: 34 (68%) with luminal; 10 (20%) with HER2+; 6 (12%) with TNBC Stage: 80% with stage IIIA and 16% with stage IIIB Treatment Modality: neoadjuvant	Interventions: standard neoadjuvant AC-Paclitaxel plus Metformin 500mg twice/day until the time of surgery Comparator: standard neoadjuvant AC-Paclitaxel until the time of surgery	Primary: pCR rate in the axilla and breast post operatively Secondary: clinical response, method of surgery, toxicity, and DFS	In the investigated group, 15/25 patients (60%) had a pCR versus 9/25 patients (36%) in the standard group (p-value = 0.08) - no significant. Clinical response: The total (T) clinical staging remission post neoadjuvant chemotherapy for both groups was 76% and 60% for investigated group and standard group, respectively (p-value = 0.393). Method of surgery: In the investigated group, 19 patients (76%) were submitted to modified radical mastectomy (MRM) while 6 patients (24%) were submitted to conservative breast surgery (CBS), while in the standard group, 23 patients (92%) were submitted to MRM while 2 patients (8%) were submitted to CBS. There was no statistically significant difference between the two groups regarding types of surgery (p-value = 0.247).

					Survival analysis: The Median DFS at 2 years in our study was 93.25%. Kaplan-Meier survival curves' analysis showed no significant difference between both groups with a DFS of 91.25% in the investigated group arm, and 96.25% in the standard group (p-value 0.566). Radiological response: "All patients achieved either complete remission or regressive disease"; Toxicity: results on box "adverse events"
EL-Haggag, 2016	A total of 148 women were eligible for the study. 129 women were simply randomized. No data regarding: obesity, overweight, menopausal status, physical activity, and metabolic syndrome.	Phenotype: Luminal = 86 (84.3%); Basal like = 10(9.8%); HER2 enriched = 6 (5.9%) Stage: Stage I: 16 (15.69%) Stage II: 33 (32.35%) Stage III: 53 (51.96%) Treatment Modality: adjuvant	Interventions: adjuvant therapy (CT + HT) + metformin treatment (850 mg of metformin twice daily) + vitamin B12 Comparator: adjuvant therapy (CT + HT) and vitamin B12 (every 3 days) Duration:	Primary: DFS Secondary: IGF-1, IGFBP-3, IGF-1: IGFBP-3 molar ratio, insulin, FBG, HOMA-IR, CA15-3 and metastasis	DFS: Control group: [mean survival time = 22.773, 95 % CI 21.178–24.368] Metformin group: [mean survival time = 24.910, 95 % confidence interval (CI) 24.078–25.743] (p = 0.044). After adjusting for age, tumor stage, adjuvant chemotherapy, ER and HER2 status, control women were significantly more (p = 0.023) tended to develop metastasis 3.27 times (HR = 3.27, 95 % CI 1.17–9.06) than those of metformin treated

	100% nondiabetic women				women
Ko, 2015	105 women with breast cancer. No data regarding: syndrome, Diabetes: 1% Obese/overweight: 100% Menopause: 85% a 88% Regular exercise: 51% to 69%	Phenotype: 17% HER2+; 62% luminal; 16% triple negative; 5% not specified Stage: 36% of patients were stage 0 or 1 (so I assume 64% were stage 2 or 3) Treatment Modality: adjuvant	Interventions: 500 mg/d: Receive metformin 500 mg dose once daily on 1~2 weeks + placebo in every morning and oral metformin 500 mg in every evening on 3~24 weeks. 1000 mg/d: Receive metformin 500 mg dose once daily on 1~2 weeks. (Dose-escalate) + Receive oral metformin 500 mg in every morning and evening on 3~24 weeks (metformin 500 mg * twice a day = 1000 mg per day). Comparator: Participants in the placebo group took a placebo after dinner in 1~2 weeks. After that 2-week period, a second dose of	Primary: Weight loss Secondary: Fasting blood sugar, HbA1c, and insulin levels; total cholesterol, HDL and LDL-cholesterols, and triglyceride levels; Anthropometry (i.e., weight, height, waist circumference, and blood pressures) and body composition. Beck depression inventory (BDI).	Weight loss (kg) Placebo (mean (SE)): -1.1 (0.3); Metformin 500 mg: -0.5 (0.3); Metformin 1000 mg: -0.6 (0.2); p value = 0.220. Glucose (mg/dL) Placebo: 90.6 (1.0); Metformin 500 mg: 88.9 (1.4); Metformin 1000 mg: 88.7 (2.3); p value = 0.787 Insulin (µIU/mL) Placebo: 8.1 (0.4); Metformin 500 mg: 8.3 (0.4); Metformin 1000 mg: 7.2 (0.3); p value = 0.572 HbA1c (%) Placebo: 5.82 (0.05); Metformin 500 mg: 5.84 (0.04); Metformin 1000 mg: 5.68 (0.07); p value = 0.753 Total cholesterol (mg/dL) Placebo: 188.4 (7.1); Metformin 500 mg: 193.2 (6.0); Metformin 1000 mg: 190.1 (5.5); p value = 0.914 BMI (kg/m2)

			placebo was added after breakfast for a further 24 weeks (twice a day). Participants in the metformin 500mg group took a placebo after breakfast for 3~24 weeks.		Placebo: 26.9 (0.5); Metformin 500 mg: 26.5 (0.5); Metformin 1000 mg: 26.9 (0.5); p value = 0.502 Waist (cm) Placebo: 84.2 (1.3); Metformin 500 mg: 86.8 (1.3); Metformin 1000 mg: 87.4 (1.1); p value = 0.322 Beck depression inventory (BDI): Placebo: 10.4 (1.3); Metformin 500 mg: 10.3 (1.0); Metformin 1000 mg: 10.5 (1.0); p value = 0.813
PECAM Study (Davis, 2018)	105 women with breast cancer. No data regarding: obesity, overweight, physical activity, and metabolic syndrome. 100% postmenopausal women. 100% nondiabetic women.	Phenotype: 100% ER+/- PR+ (inclusion criteria) Stage: stage I/II Treatment Modality: adjuvant	Interventions: The metformin dose was titrated over three weeks from 425mg at night to 850mg twice a day. Comparator: Placebo will be identical tablets to the metformin 850mg tablets.	Primary: Clinical outcomes: Endometrial thickness Secondary: Clinical characteristics (BMI; Weight; Abdominal circumference) and biochemistry (Fasting glucose; Fasting insulin; HOMA-IR).	“The median Endometrial thickness (ET) was significantly lower for the 35 women in the metformin group (ET of participant X could not be measured at 52 weeks) than the 45 women in the placebo group (2.3 mm (range 1.4-7.8) vs 3.0 (1.2-11.3); p=0.05)” Compared with the placebo group, the metformin group had significantly greater reductions in weight (p<0.001), BMI (p<0.001), fasting glucose (p<0.001), insulin (p=0.004) and HOMA-IR (p<0.001). The statistical significance for each of these variables was unchanged in an analysis of

					change adjusted for baseline. For waist circumference, adjustment for baseline resulted in a significant between-group difference of -2.3cm (95% CI -4.4 to -0.25, p=0.03). Compared with the placebo group, the metformin group had no significantly greater reductions in waist circumference (p=0,056).
Liubota, 2018	72 women included. No data regarding: physical activity and diabetes. 100% obese and 100% with metabolic syndrome Premenopausal status: 12 (16,66%); Postmenopausal status: 60 (83,33%). Hypertension: 39 (54,16%); Hyperlimidemia: 61 (84,72%).	Phenotype: Luminal: 52 (72,22%); HER2+: 6 (8,33%); TNBC: 14 (19,44%) Stage: Stage II: 35 (48,61%); Stage III: 37 (51,39%); Treatment Modality: neoadjuvant	Interventions: 500 mg metformin 30 minutes before meal, three times a day with NAST Comparator: NAST	Primary: Clinical outcomes: Clinical Response Rate (RECIST): [Complete Response (cCR), Partial response (cPR), Stable disease (cSD) and Progressive disease (cPD)]; Pathological complete response. Secondary: type of surgery performed Disease-free survival Overall survival	Clinical Response Rate: Overall clinical response rate (complete response + partial response) 28 (77,5%) patients achieved in group 2 (NACT+met) vs 9 (25%) in group 1 (NACT), p<0,05 Pathological complete response: Grade 5 was identified in 9 patients (26,5%) from group 2 (NACT+met) vs 2 patients (6%) from group 1 (NACT), p<0,05 Grade 2 was identified in 10 patients (29%) from group 2 (NACT+met) vs 18 (55%) from group 1 (NACT), p<0,05 In other grades the differences were not significant (p>0,05) Type of surgery performed: Breast-conserving surgery was performed in 9 patients (50%)

Salah, 2021	50 women included. No data regarding: obesity/overweight, physical activity and metabolic syndrome.	Receptors: Overall HER 2: HER2-: 36 (72%); HER2+: 14(28%). Overall HR: ER/PR-: 10 (20%); ER/PR+=40 (80%) Stage: 100% stage IV	Interventions: Standard chemotherapy plus metformin 1 g twice daily (2g/day) Comparator: Chemotherapy	Clinical outcomes: Primary: radiologic response rate Secondary: overall survival (OS) and progression free survival (PFS)	from group 2 (NACT+met) vs 4 (23,5%) from group 1 (NACT), p<0,05 Radical mastectomy 5 was performed in 7 patients (38%) from group 2 (NACT+met) vs 13 (76,5%) from group 1 (NACT), p<0,05 Disease-free survival: Five-year recurrence-free survival (RFS) was similar in both groups (58% in group 1 (NACT) and 57% in group 2 (NACT+met)). There was no significant difference between groups in recurrence free survival (logrank test, p=0.79) Overall survival: Five-year overall survival was 76% for patients who received metformin versus 59% for patients from group 1 (NACT). There was no significant difference between groups in overall survival (logrank test, p=0.67). Women in metformin group had significantly better radiologic (RECIST) response rate than women in the control group (P-value = 0.002) Overall survival: Mean OS was 5.8 met vs 5.3 control, there was not significant difference in OS (HR = 0.57, CI 0.24–1.3);
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	Pre-menopausal: 22 (44%) Post-menopausal: 28 (56%) 100% nondiabetic women	Treatment Modality: unclear			PFS: Mean PFS was 5.1met vs 4.4 control and metformin groups, there was not significant difference in PFS (HR = 0.311, CI 0.063–1.5)
Barakat, 2022	80 women included; (74 randomized) No data regarding: physical activity and metabolic syndrome. Obesity: 32 (43,24%) Overweight: 26 (35,14%) Premenopause: 38 (51,35%) Postmenopause: 36 (48,65%) 100% nondiabetic	Phenotype: Luminal A: 30 (40,54%) Luminal B/HER2-: 8 (10,81%) Luminal B/HER2+: 25 (33,78%) HER2+/non-luminal: 5 (6,76%) TNBC: 6 (8,11%) Stage: IIB: 10 (13,51%) IIIA: 31 (41,89%) IIIB: 33 (44,59%) Treatment Modality: neoadjuvant	Interventions: 4 cycles doxorubicin 60 mg/m2/ cyclophosphamide 600 mg/m2, followed by 12 cycles of weekly paclitaxel 80 mg/m2) + Metformin (1000 mg twice daily) followed by surgery Comparator: NACT regimen only (4 cycles doxorubicin 60 mg/m2/cyclophosphamide 600 mg/m2, followed by 12 cycles of weekly paclitaxel 80 mg/m2). followed by surgery.	Clinical outcomes: Primary: Clinical benefit rate (Tumor size); Overall response rate (ORR); clinical complete response (cCr); and pathological complete response (pCR) Secondary: BCR; safety profile and tolerability; and quality of life (QoL)	Clinical benefit rate (Tumor size): ORR: OR 1.912, 95% CI 0.655 to 5.585, p = 0.236 cCr: OR 3.269, 95% CI 0.921–11.606, p = 0.058; pCR: OR 2.429, 95% CI 0.662–8.914, p = 0.181.
	60 patients No data	Phenotype: Luminal = 60 (100%);	Interventions: aromatase inhibitor (exemestane)	Clinical outcomes: Primary:	PFS: HR 1.2; 95% CI 0.7 to 2.1; p = 0.48.

Zhao, 2017	regarding: obesity, overweight, physical activity, diabetes, and metabolic syndrome. 100% postmenopausal	Receptors: 100% HR+ (ER and/or PR), 100% HER- Stage: Stage III and IV: 60 (100%) Treatment Modality: adjuvant and palliative	25mg/d or letrozole 2.5mg/d depending on the most recent treatment) plus metformin (0.5g bid, orally) Comparator: Aromatase inhibitor (letrozole or exemestane) + placebo	PFS Secondary: objective response rate, CBR, OS and tolerability	objective response rate: 6.7% (95% CI 0.3-16) met vs 0% (95% CI not available) control. OR not available p = 0.99 CBR: OR = 0.50, 95% CI 0.2 to 1.4, p = 0.15), CBR: 33.3% (95% CI 15-51) met vs 50.0% (95% CI 31-69) control. OS: HR = 1.1, 95% CI 0.5 to 2.4, p = 0.81. Tolerability: No substantial difference in incidence or severity of adverse events was seen between the two treatment groups.
Semiglazova, 2018	54 patients (recruiting) No data regarding: physical activity, and metabolic syndrome. Obesity: 23 (42%) Overweight: 15 (28%) 100% menopause 100% nondiabetic	Phenotype: Luminal Receptors: 54 (100%) ER+ Stage: stage IIB, IIIA, IIIB, IIIC (frequency not reported) Treatment Modality: neoadjuvant	Interventions: Arm 3: Toremifene (TOR) 120 mg daily with metformin (MTF) 850 mg BID Comparator: Arm 1: 120 mg of oral toremifene (TOR) daily; Arm 2: Toremifene (TOR) 120 mg daily with 3mg overnight melatonin	Primary: Ki67 proliferation index Clinical outcomes: Secondary: Objective response, a pathological response in the tumor and lymph nodes, and the QoL, and adverse events	decrease in the Ki-67 level: RR 4.23 [95% CI 1,044-17,139], p = 0.043 Objective Response Rate: There were results for metastatic group but not for metformin group. Pathomorphological response: A complete pCR in the tumor and lymph nodes was not achieved in any patient. QoL: Adding MLT or MTF to standard hormone therapy did not lead to decrease in the

					quality of life, about 50% of TOR+MLT therapy recipients had better sleep quality.”
Reach for Health trial (Patterson, 2016; Patterson, 2018; Hartman, 2019)	333 participants. No data regarding: diabetes and metabolic syndrome. Comorbidities: High blood pressure=166(49.9%); High cholesterol: 164 (49.3%); Previous smoking+current smoking= 149 (44.7%); Any current alcohol intake= 225 (67.6%) Physical activity: median (Q1–Q3): 16.0 (2.7–42.0) Metabolic Equivalent Task (MET) hours per week (self-report). 100% overweight/obese	Phenotype: ER+ or PR+ HER2- (Luminal): 240 (72.1%); HER2+: 51 (15.3%); Triple-negative (ER-, PR-, HER2-): 30 (9.0%); Missing data: 12 (3.6%) Stage: Stage I: 161 (48.4%); Stage II: 116 (34.8%); Stage III: 56 (16.8%) Treatment Modality: prevention of recurrence after end of cancer treatment	Interventions: Metformin only (1500 mg/day) and Weight loss & Metformin Comparator: Placebo only and Weight loss & placebo	Primary: changes in fasting insulin, glucose, C-reactive protein (CRP), estradiol, testosterone, and sex-hormone binding globulin (SHBG) Secondary: Changes in five cognitive domains from baseline to 6 months (exploratory outcome) and weight loss	Biochemical outcomes: <u>Statistically significant group differences</u> (ie, percent change in metformin group minus placebo group); insulin: -7.9% (95% CI = -15.0% to -0.8%); estradiol: -10.0% (95% CI = -18.5% to -1.5%); testosterone: -9.5% (95% CI = -15.2% to -3.8%); SHBG: 7.5% (95% CI = 2.4% to 12.6%). Non statistically significant group differences for: Glucose [-1.27 (CI95%=-3.39; 0.85)]; C-reactive protein [-14.87 (CI95%=-32.88; 3.15)]. Weight loss Statistically significant group differences for percent weight change were found (ie, percent change in metformin group minus placebo group)= -2.46 (IC95%= -3.59; -1.34). Cognitive scores No significant difference between any of the treatment arms or between follow-up and baseline assessments within groups. Difference between metformin and placebo arms: Visual spatial: 1.67 (CI95%=-

	100% postmenopausal				0.92; 4.25) Verbal function: -1.58 (CI95%=-4.90; 1.74) Memory: 0.67 (CI95%=-1.09; 2.43) Executive function: 1.12 (CI95%=-1.20; 3.44) Attention: 0.70 (CI95%=-1.03; 2.44)
NeoMet Trial (Hadam, 2011; Hadad, 2015)	47 participants No data regarding: obesity, overweight, physical activity, and metabolic syndrome. Pre- and peri-menopausal: 2 (14.3%) Post-menopausal: 12 (85.7%) 100% nondiabetic	Phenotype: Luminal A and Luminal B Receptors: ER+: 11 (78.57%); PR+: 11 (78.57%); HER+: 2 (14.28%) Stage: stage I or II Treatment Modality: neoadjuvant	Interventions: metformin 2000 mg Comparator: No treatment	Ki67 index; serum insulin levels; Gene array data; PDE3B and p53; Ingenuity pathway analysis; Gene set analysis (GSA); pAMPK and pAkt, Insulin receptor signaling, and caspase 3 Note: no clear information about which were the primary and the secondary outcomes.	Ki67 index: The mean percentage of cells staining for Ki67 fell after metformin by a mean of 3.4% (P = 0.027), but remained stable in control patients Ki67 (Hadam 2011): mean Ki67 fell 3.41% in metformin arm (p = 0.027) but decrease was no significant in control arm (0.455); Insulin: change was no significant in metformin arm (p=0.663) but was significant in control arm (p=0.044); pAMPK and pAkt: the mean pAMPK score of staining rose from 5.18 to 6.45 (p = 0.04) in the metformin group, compared to a non-significant rise from 5.64 to 6.00 (p = 0.492) in the control group. For pAkt, the mean score of staining dropped significantly from 5.91 to 5.00 (p = 0.043) in the metformin group, compared to a non-

Meyerhardt, 2020; Brown, 2020	139 (87 with breast cancer; 52 with colorectal cancer) (62,6% BC/37,4% CRC) No characteristics were presented for breast cancer only.	Phenotype: NI Stage: stage I to stage III Treatment Modality: adjuvant	Interventions: Start: 850mg daily for 2 weeks. After: 850mg twice daily for 3 months. PS: If dose escalation was not tolerated, participants remained on 850mg daily for the 12-week intervention	Primary: Change in fasting insulin levels (change between 0 and 3 months) Secondary: Meyerhardt: Changes between 0 and 3 months in other blood-based energetic biomarkers (IGF-1,	significant rise from 4.91 to 5.18 ($p = 0.517$) in the control group; Insulin receptor signaling: a non-significant drop in insulin receptor signaling (4.9–4.4, $p = 0.363$) in the metformin group was observed, neither in the control group (4.09–4.36, $p = 0.431$); Caspase-3: The mean percentage of cancer cells stained for caspase-3 fell by 0.29 % ($p = 0.0437$; paired t test) in the metformin group, compared to no significant change in the control group ($p = 0.371$ paired t test). PS: None of the changes in the biomarkers were associated with the patient's BMI either using BMI as a continuous variable or with a cut off of 26 or 30. No results were reported for breast cancer only.
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	No data regarding: obesity, overweight, menopause status, physical activity, and metabolic syndrome. 100% nondiabetic		Comparator: educational information on nutrition and two supervised sessions with an exercise physiologist	IGFBP-1, IGFBP-3, leptin, Fasting Glucose Level) and anthropometric measurements (weight, BMI and Waist to Hip Ratio). Brown: additional outcomes: Inflammation measures included high sensitivity C-reactive protein (hs-CRP); soluble tumor necrosis factor alpha receptor 2 (sTNF-αR2); interleukin 6 (IL-6).		
SPIRIT Trial (Yeh, 2021; Hu, 2021)	121 participants Participants were cancer survivors with overweight or obesity. It was included prostate cancer, lung, colon, melanoma, endometrial, liver, pancreatic, rectal, kidney, and other solid malignant tumors. No data	Phenotype: No information was reported specifically for breast cancer. Stage: No information was reported specifically for breast cancer. Treatment Modality: prevention of recurrence after end of cancer treatment	Interventions: Metformin 2000 mg/day. Dosing can be flexible, two or three times per day with meals as tolerated for 12 months. Comparator: Two arms: Coach directed weight loss; Self-directed weight loss	Primary: 6-month change in the level of IGF-1 Secondary: Yeh: IGF-1 at 12 months, IGF1:IGFBP3 molar ratio at 6 months and 12 months, changes in weight, BMI, fasting insulin, HbA1c, IL-6, and hs-CRP, Hu: Fasting Serum Urate (SU) collected at baseline and at 3, 6, and 12 months,	No results were reported for breast cancer separately.	

	regarding: menopause status, physical activity, diabetes, and metabolic syndrome. 100% overweight or obesity			Glomerular Filtration Rate (eGFR), BMI.	
Saif, 2019; Kritharis, 2014	A total of 100 patients of both sexes were enrolled (52 in delayed arm vs. 48 concurrent arm) Different solid cancers. 17 tumor types (CRC = 14, breast = 11). Other solid tumors (Results: prostate, colorectal, lung, lymphoma, gastroesophageal, nasopharyngeal, brain, pancreas, unknown primary, appendiceal, cholangiocarcinoma, myeloma, liver, ovarian, renal).	Phenotype: NI Stage: NI Treatment Modality: adjuvant	Interventions: metformin 500 mg twice daily (1g daily) with chemotherapy Comparator: chemotherapy alone (Stage 1 of study)	Clinical outcomes: Primary: Incidence of dose limiting toxicity (DLT) when metformin is added to chemotherapy Secondary: Adverse events; Tumor responses; PFS and Pharmacodynamic (PD) markers	The rate of DLTs in patients receiving metformin in addition to chemotherapy was not higher than the DLTs in patients receiving chemotherapy alone (8.3% vs. 11.1% in Stage 1). There were no results for breast cancer separately. Safety: Adverse events $\geq$ Grade 3 that were not related to metformin were varied, with a higher incidence in the concurrent arm (8.3 vs. 5.5%) in Stage 1; Efficacy: Restaging showed stable disease in 46% at cessation of metformin. 28% of patients with measurable tumor markers showed improvement; PD markers: AMPK phosphorylation showed a four- to sixfold

	No data regarding: obesity, overweight, menopause status, physical activity, diabetes, and metabolic syndrome.				increase in AMPK phosphorylation after metformin. There were no results for breast cancer separately.
MYME Trial Nnini, 2018	126 participants 21 (17%) obese 50 (41%) overweight 100 (82%) post-menopausal 100% nondiabetic	Phenotype: Luminal Receptors: ER+: 106 (87%); PgR+: 87 (71%); HER2-: 100% Stage: Stage IV: 126 (100%) Treatment line: 100% first line chemotherapy Treatment modality: palliative	Interventions: Metformin 2000 mg/day + First-line chemotherapy alone (NPLD + cyclophosphamide) Comparator: First-line chemotherapy alone (NPLD + cyclophosphamide)	MYME trial: Clinical outcomes: Primary: PFS Secondary: Objective response rate (ORR) 2. Overall survival (OS) 3. Progression free survival as function of Homa Index levels 4. Objective response rate as function of Homa Index levels 5. Overall survival as function of Homa Index levels 6. Toxicity	PFS: HR 1.09, 95% CI 0.75–1.58, P = 0.653 MYME trial: OS: HR 0.81, 95% CI 0.50–1.30, P = 0.382; ORR was 48% (95% CI 32.0% – 63.5%) in arm A and 49% (95% CI 34.1% – 63.9%) in arm B (P = 0.901); PFS as function of Homa: HR = 1.51, 95% CI 1.03–2.20, P = 0.034; OS as function of Homa: HR = 0.97, 95% CI 0.61–1.55, P = 0.900; ORR as function of Homa: NI.
	126 participants	Phenotype: Luminal	Interventions: Metformin 2000	TransMYME trial: the prognostic role of	TransMYME trial: No interaction was detected

	MY ME Trial (sub- study) (Gen- nna- ri, 202 0)	21 (17%) obese 50 (41%) overweight 100 (82%) post- menopausal 100% nondiabetic	Receptors: ER+: 106 (87%); PgR+: 87 (71%); HER2-: 100% Stage: Stage IV: 126 (100%) Treatment line: 100% first line chemotherapy Treatment modality: palliative	mg/day + First- line chemotherapy alone (NPLD + cyclophosphamide) Comparator: First-line chemotherapy alone (NPLD + cyclophosphamide)	IGF1R expression in circulating tumor cells (CTCs) and prognostic role of CTC count and IGF- 1R was assessed for PFS and OS	between metformin treatment and the number of circulating tumor cells or with the expression of IGF-1 receptors on such cells in relation to Progression-Free Survival or Overall Survival outcomes (P = 0.322 and P = 0.840). There was no effect of metformin treatment on the evolution of the number of circulating tumor cells or the expression of IGF-1 receptors over time. [These results were described only in a narrative form, without presenting the exact quantitative results].
METTEN Trial	Mar- tin- Ca- still o, 201 8	84 patients were randomized, but results were presented to patients who received at least one dose of study medication (n=79). 100% not obese (exclusion criteria: BMI>30) Overweight: Arm A with metformin: 17 (44.7%) Arm B control: 21 (51.2%)	Phenotype: HER2 Receptors: ER/PgR+ Arm A with metformin: 19 (50.0%) Arm B control: 24 (58.5%) ER/PgR-: Arm A with metformin: 19 (50.0%) Arm B control: 17 (41.5%) Stage: Stage II - III	Interventions: Metformin 1.700 mg/day (850 mg BID) for 24 weeks concurrently with 12 cycles of weekly paclitaxel plus trastuzumab, followed by four cycles of 3-weekly fluorouracil, epirubicin, cyclophosphamide (FE75C) plus trastuzumab. Comparator: Only equivalent sequential chemotherapy plus	Primary: PCR in the per protocol efficacy population Secondary: Tolerability and safety profile (including cardiac toxicity), the rate of breast conservation, 5-year DFS, the inhibition of tumor tissue biomarkers (including proliferative, mTOR/AMPK-and HER2-related pathways), and changes in	PCR Per protocol: Arm A, 19/29 PP patients (65,5%, 95%CI= 47-80) had a pCR versus 17/29 PP patients (58,6%, 95%CI= 41-74) in arm B [OR 1.34; 95%CI= 0.46- 3.89, p=0.589]. Cardiac toxicity: There was no significant difference between the arms (end of treatment p=0,409); Rate of breast conservation: In Per protocol analysis Breast-conserving surgery (BCS) was possible in 23/29 (79,3%) of patients in arm A (met), which was apparently superior to the 17/29 (58,6%)

	Postmenopausal Arm A with metformin: 14 (36.8%) Arm B control: 17 (41.5%) Premenopausal Arm A with metformin: 24 (63.2%) Arm B control: 24 (58.8%) 100% nondiabetic No data regarding: physical activity and metabolic syndrome.	Treatment modality: neoadjuvant	trastuzumab (paclitaxel plus trastuzumab, followed by fluorouracil, epirubicin, cyclophosphamide plus trastuzumab).	circulating levels of insulin and metabolites	achieved in arm B ($P = 0.08$); Changes in circulating levels of insulin and metabolites (analysis only PCR groups): was not evaluated relation to intervention groups.
Lopez-Bo net, 2019	79 patients included in the intention-to-treat (ITT) population of the METTEN study 100% not obese (exclusion criteria: BMI>30) 100% nondiabetic	Phenotype: HER2+ Receptors: ER/PgR+ Arm A with metformin: 19 (50.0%) Arm B control: 24 (58.5%) ER/PgR-:	Interventions: Metformin 1.700 mg/day (850 mg BID) for 24 weeks concurrently with 12 cycles of weekly paclitaxel plus trastuzumab, followed by four cycles of 3-weekly fluorouracil, epirubicin,	Secondary: the proliferation marker Ki67	Ki-67 (analysis only non-PCR patients, n=14): The Ki67 decreases were largest in the metformin-containing arm A (n = 8), from 42.5% (VA)/34.5% (ADIA) at baseline to 11% (VA; $p = 0.025$)/11% (ADIA; $p = 0.035$) at surgery (Figure 4). Conversely, no significant differences were observed in the control treatment arm B (n = 6), in which Ki67 decreased

	No data regarding: menopause status, physical activity, and metabolic syndrome.	Arm A with metformin: 19 (50.0%) Arm B control: 17 (41.5%) Stage: Stage II - III Treatment modality: neoadjuvant	cyclophosphamide (FE75C) plus trastuzumab. Comparator: Only equivalent sequential chemotherapy plus trastuzumab (paclitaxel plus trastuzumab, followed by fluorouracil, epirubicin, cyclophosphamide plus trastuzumab).	from 36.0% (VA)/38.5% (ADIA) at baseline to 28.5% (VA; p = 0.293)/25.0% (ADIA; p = 0.080). The change of Ki67 category (high $\geq$ 20% versus low <20%) in the metformin-containing arm A was not statistically significant compared with that observed in arm B (VA: p = 0.5210; ADIA: p = 0.3582). *VA = visual analysis **ADIA = automated digital image analysis
Cu yàs 201 9	79 patients included in the intention-to-treat (ITT) population of the METTEN study 100% not obese (exclusion criteria: BMI>30) $\geq$ 25 (overweight) Non-pCR: 12 (38.7%) pCR: 26 (54.2%) Post Non-pCR: 11 (35.5%)	Phenotype: HER2+ Receptors: ER/PgR+ Non-pCR: 21 (67.7%) pCR: 22 (45.8%) ER/PgR-: Non-pCR: 10 (32.3%) pCR: 26 (54.2%) SNP: Arm A (met): [A/A= 17 (51.5%); A/C, C/C=16 (48,5%)]; [Arm B (control): [A/A=20 (54, 1%);	Interventions: Metformin 1.700 mg/day (850 mg BID) for 24 weeks concurrently with 12 cycles of weekly paclitaxel plus trastuzumab, followed by four cycles of 3-weekly fluorouracil, epirubicin, cyclophosphamide (FE75C) plus trastuzumab. Comparator: Only equivalent sequential chemotherapy plus	C Allele of ATM rs11212617: In the metformin-containing arm, patients bearing the rs11212617 C allele had a significantly higher probability of pCR (adjusted OR genotype $\times$ arm = 20.53, 95%CI: 1.97– 213.79, p = 0.011). In the metformin-containing arm, the positive association between the presence of the rs11212617 C allele and pCR remained significant after accounting for tumor size and Hormone Receptor status (adjusted OR A/C,C/C = 28.88, 95%CI: 2.20–378.73, p = 0.010

	pCR: 20 (41.7%) Pre+Peri Non-pCR: 20 (64.5%) pCR: 28 (58.3%) 100% nondiabetic No data regarding: physical activity, and metabolic syndrome.	A/C, C/C=17 (45.9%) Stage: Stage II - III Treatment modality: neoadjuvant	trastuzumab (paclitaxel plus trastuzumab, followed by fluorouracil, epirubicin, cyclophosphamide plus trastuzumab).		
Cu yàs , 201 9	68 patients included in the intention-to-treat (ITT) population of the METTEN study 100% not obese (exclusion criteria: BMI>30) Overweight: Arm A (met): 15 (45.5%) Arm B (control): 19 (54.4%) Postmenopausal Arm A with metformin: 13 (39.4%) Arm B control: 15	Phenotype: HER2+ Receptors: ER/PgR+ Arm A with metformin: 18 (54.5%) Arm B control: 19 (54.3%) ER/PgR-: Arm A with metformin: 15 (45.5%) Arm B control: 16 (45.7%) Stage: Stage II - III Treatment	Interventions: Metformin 1.700 mg/day (850 mg BID) for 24 weeks concurrently with 12 cycles of weekly paclitaxel plus trastuzumab, followed by four cycles of 3-weekly fluorouracil, epirubicin, cyclophosphamide (FE75C) plus trastuzumab. Comparator: Only equivalent sequential chemotherapy plus trastuzumab (paclitaxel plus	Secondary: Serum metabolic profile [β-hydroxybutyrate (BHBA), α-ketoglutarate, cystathionine, taurine, betaine, choline, dimethylglycine, homocysteine, methionine, sadenosyl, methionine (SAM), and s-adenosyl, homocysteine (SAH)]	Serum metabolic profile: When we evaluated the differential impact on serum metabolic profiles between treatment arms, only BHBA (p=0.038), and α-ketoglutarate (p=0.029) reached statistical significance. Other metabolite levels were not significant. Homocysteine (Hcy): metformin-treated patients achieving pCR had significantly higher levels of circulating homocysteine than non-pCR patients (p=0.047). Significant relationship between the follow-up levels of homocysteine (i.e., post-treatment [w24] minus pretreatment [w0]) and the ability of the treatment arms to

		(42.9%) Premenopausal Arm A with metformin: 20 (60.6%) Arm B control: 20 (57.1%) 100% nondiabetic No data regarding: physical activity, and metabolic syndrome.	modality: neoadjuvant	trastuzumab, followed by fluorouracil, epirubicin, cyclophosphamide plus trastuzumab).		achieve pCR (odds ratio [OR]follow-up homocysteine x arm = 13.42, 95% confidence interval [CI]: 1.37–130.98, p=0.025. After additional adjustments for potential confounding tumor characteristics, such as tumor size and hormone receptor status, the relationship between the follow-up levels of homocysteine and the ability of treatment arms to achieve a pCR in patients remained significant (adjusted OR follow-up homocysteine x arm = 47.58, 95%CI: 1.60– 1411.93, p=0.026)
Pimentel, 2019	40 subjects were randomized (22 MET, 18 PLAC) No data regarding: obesity, overweight, menopause status, physical activity, and metabolic syndrome. 100% nondiabetic	Phenotype: Luminal, HER2, Triple negative Receptors: 34 (85%) ER/PR+; 6 (15%) ER/PR-; 6 (15%)HER2+; 34 (85%)HER2- Stage: 100% stage IV Treatment line: 27 (67,5%) 1st line treatment; 7 (17,5 %) 2nd line treatment; 6 (15%) 3rd or + line	Interventions: Metformin 1.700 mg/day (850 mg BID) plus standard chemotherapy. 1st- 4th line chemotherapy (prespecified anthracycline, taxane, vinorelbine, platinum or capecitabine, with allowance for HER2 targeted treatment) Comparator: Placebo plus standard	Clinical outcomes: Primary: PFS Secondary: OS, RR, Toxicity, QoL OS (after adjustment): HR=1.43 (95% CI 0.68-3.02), 2-sided p-value 0.35, 1-sided p-value 0.83. OS (after adjustment): HR=1.46 (95% CI 0.68-3.13), 2-sided p-value 0.34, 1-sided p-value 0.83; RR: OR=1.77 (95%CI 0.45- 6.99), with 2-sided p-value 0.41, 1-sided p-value 0.21; QoL: The Global Health Status (GHS) of metformin patients worsened significantly more than that of placebo patients over the first cycle (stESdif -		

		treatment	chemotherapy		0.8, p=0.006) and as a result GHS in the two arms were similar at cycle 2 (stESdif 0.1); Adverse events: Grade 1-2 effects were more frequent in the metformin group (68.2% vs 35.3%) and grade 3-4 effects were more frequent in the placebo group (58.8% vs 31.8%) (for adverse events there was no statistical analysis)
NCIC CTG MA.32	Goodwin 2022	Phenotype: Luminal, HER2+, Triple negative Receptors: Status HR: 2533 (69,4%) ER/PgR+; 1116 (30,6%) ER/PgR-; Status HER2: 3029 (83,0%) HER2-; 620 (17,0%) HER2+; Frequencies in the subpopulation according to HR status ER/PgR+ patients: 429 (16.9%) HER2+ 100% nondiabetic	Interventions: Patients receive 850mg of oral metformin twice daily (once daily in weeks 1-4). Treatment continues for up to 5 years in receptor positive (ER and/or PgR positive) subjects in the absence of disease progression or unacceptable toxicity. Standard adjuvant therapy (radiotherapy, chemotherapy, hormone, biologics). Comparator:	Clinical outcomes: Primary: IDFS in hormone receptor-positive breast cancer Secondary: OS, distant relapse-free survival, and breast cancer-free interval; new diabetes diagnosis, cardiovascular hospitalizations, quality of life, diet, and physical activity	Primary: There is no result for invasive disease-free survival for the full study population. Only divided by receptors (HR and HER2). Secondary: ER/PgR+: OS: HR, 1.10; 95% CI, 0.86-1.41; P = .47; distant recurrence-free survival: HR, 0.99; 95% CI, 0.80-1.23; P = .94; breast cancer-free interval: HR, 0.98; 95% CI, 0.80-1.20; P = .87; ER/PgR-: OS: HR, 0.89; 95% CI, 0.64-1.23; P = .46;

	people	ER/PgR- patients: 191 (17,1%) HER2+ Stage: Stages I – III Treatment modality: adjuvant	Patients receive oral placebo twice daily (once daily in weeks 1-4). Treatment continues for up to 5 years in receptor positive (ER and/or PgR positive) subjects in the absence of disease progression or unacceptable toxicity. Standard adjuvant therapy (radiotherapy, chemotherapy, hormone, biologics).	distant recurrence-free survival: HR, 0.90; 95% CI, 0.67-1.20; P = .46; breast cancer-free interval: HR, 0.88; 95% CI, 0.67-1.16; P = .35; HER2+ OS: HR, 0.54; 95%CI, 0.30-0.98; P = .04; HER2- OS: HR, 1.11; 95% CI, 0.90-1.36; P = .34.		At 6 months, there were significant raw and relative improvements in all variables in metformin versus placebo subjects. Weight: Metformin subjects lost a median of 1.4 kg (vs 0.5 kg gain in placebo subjects, $p < 0.0001$; relative change -2% metformin vs +1% placebo, $p < 0.0001$) Glucose: (raw change -0.1 vs +0.1 mmol/L, $p < 0.0001$; relative change -2% vs +1%, $p < 0.0001$)
Go od win , 202 1	metabolic subpopulation: 2.915 patients (all available subjects with fasting blood at baseline and 6 months); metabolic SNP subpopulation: 2.747 subjects (SNP information available) Obesity: Overall (≥ 30) n(%): 1000 (34.3%)	Phenotype: Luminal, HER2+, Triple negative Receptors: Hormone receptor status ER/PgR-: 859 (29.5%) ER/PgR+: 2056 (70.5%) HER2 status HER2-: 2417 (82.9%)	Interventions: Metformin 1.700 mg/day (850 mg BID) for 5 years, including a 4-week ramp-up of one caplet per day Comparator: Placebo	Primary: metformin impact on metabolic factors (insulin, leptin, hsCRP, HOMA) Secondary: whether this impact varies by baseline BMI, insulin, and rs11212617 SNP in CCTG MA.32		

	Overweight: Overall (≥ 25 and < 30) n(%): 963 (33.03%) 100% nondiabetic people No data regarding: menopause status, physical activity, and metabolic syndrome.	HER2+: 498 (17.1%) Stage: Stages I – III Treatment modality: adjuvant			Insulin (raw change -7 vs $+2$ pmol/L, $p < 0.0001$; relative change -11% vs $+6\%$, $p < 0.0001$) HOMA (raw change -0.2 vs $+0.1$, $p < 0.0001$; relative change -10% vs $+11\%$, $p < 0.0001$) Leptin (raw change -0.8 vs $+1.1$ ng/ml, $p < 0.0001$; relative change -10% vs $+12\%$, $p < 0.0001$) hsCRP (raw change -0.1 vs $+0.1$ $\mu\text{g/L}$, $p < 0.0001$; relative change -9% vs $+10\%$, $p < 0.0001$) There was little evidence of a significant interaction of change in these variables with baseline BMI or insulin. Examination of interactions between the study drug and the SNP status (any C versus AA) showed no evidence that metformin was more effective on body size or metabolic factors when the C allele was present (all interaction $P > 0.21$).
Loh ma nn,	the first 492 patients with paired blood	Phenotype: Luminal, HER2+, Triple negative	Interventions: Metformin 1.700 mg/day (850 mg	Primary: change in vitamin B12 levels between	median change of vitamin B12 from baseline to 6 months was -51 pmol/L (IQR 6, -182) in the

2017	samples 100% nondiabetic people No data regarding: obesity, overweight, menopause status, physical activity, and metabolic syndrome.	Receptors: Stage: Stages I – III Treatment modality: adjuvant	BID) for 5 years, including a 4-week ramp-up of one caplet per day Comparator: Placebo	baseline and 6-month fasting plasma Secondary: change in methylmalonic acid (MMA) and homocysteine (HC) levels between baseline and 6-month fasting plasma of patients with vitB12 levels <222 pmol/L	metformin arm versus 0 (IQR - 61, +65) in the placebo arm, $p < 0.001$; the mean percentage change of vitamin B12 from baseline to month 6 was -6.3% (standard deviation, SD 71, 65) and 7.52% (SD 51, 20) in the metformin and placebo arms, respectively. At 6 months, the median MMA was 0.15 (IQR 0.12, 0.2) and median HC was 9 (IQR 8, 12); overall, one patient receiving metformin had elevated MMA ($>0.4 \mu\text{mol/L}$), $p = 0.6$ (this patient also had elevated HC $>15 \mu\text{mol/L}$), and 3 (2 receiving metformin and 1 receiving placebo) had HC $>15 \mu\text{mol/L}$, $p = 0.5$.
Go od win 2021	CA 15-3 population (n=2708) 100% nondiabetic people No data regarding: obesity, overweight, menopause status, physical activity, and metabolic	Phenotype: Luminal, HER2, Triple negative Receptors: Hormone receptor status ER/PgR-: 795 (29.4%) ER/PgR+: 1913 (70.6%) HER2 status HER2-: 2244	Interventions: Metformin 1.700 mg/day (850 mg BID) for 5 years, including a 4-week ramp-up of one caplet per day Comparator: Placebo	Primary: levels of circulating CA 15-3 at baseline and 6 months Secondary: whether the effect of metformin on CA 15-3 blood levels varies by the genotype of rs11212617 SNP	change in CA 15-3, geometric means (used because of skewness in the distribution of CA 15-3 at follow-up) showed a 7.7% reduction in CA 15-3 levels in the metformin arm vs a 2.0% reduction in the placebo arm ($P < .001$) the relative metformin:placebo level of CA 15-3 at 6 months was estimated to be 0.94 (95% CI = 0.92 to 0.96). Interaction models showed that this outcome was not affected

	syndrome.	(82,9%) HER2+: 464 (17,1%) Stage: Stages I – III Treatment modality: adjuvant			differentially depending on baseline stage, receptor status, adjuvant treatment, SNP status, BMI, or insulin level
Pimentel, 2021	312 patients 100% postmenopausal 100% nondiabetic women No data regarding: obesity, overweight, physical activity, and metabolic syndrome.	Phenotype: Luminal, HER2+, Triple negative Receptors: Hormone receptor status ER/PgR-: 312 (100,0%) ER/PgR+: 0 (0,0%) HER2 status HER2+: 59 (18,9%) HER2-: 253 (81,1%) Stage: Stages I – III Treatment modality: adjuvant	Interventions: Metformin 1.700 mg/day (850 mg BID) for 5 years, including a 4-week ramp-up of one caplet per day Comparator: Placebo	Primary: change in levels of prespecified sex hormones (SHs): estradiol, sex hormone-binding globulin (SHBG), and bioavailable testosterone (BT) from baseline to 6 months Secondary: BMI and insulin change, and the impact of the SNP rs11212617 on any SH change	Estradiol The median change between baseline and month 6 in estradiol was 5.7pmol/L in the metformin arm vs 0 in the placebo arm (Wilcoxon test $P < .001$). The estradiol exceedance probabilities were consistently lower in the metformin than the placebo group (log-rank $P < .001$), for example, 56.9% vs 71.0% had estradiol levels above 20 pmol/L, 19.7% vs 42.6% had estradiol levels above 40pmol/L, and 8.0% vs 23.1% had estradiol levels above 60 pmol/L, respectively. The reduction in estradiol in met vs control was 25.7% (95% CI = 13.2% to 36.4%) adjusted for baseline BMI and BMI change, and 30.1% (95% CI = 18.7% to 39.8%) adjusted for change in insulin. SHBG Median changes were similar in the metformin vs placebo

EudraCT number 2008-004912-10						arms (-5.9 (Q1-Q3=-15.6, 3.0) vs -5.9 nmol/L (Q1-Q3=-17.4, 1.5); p=.43) Bioavailable testosterone [BT] Median changes were similar in the metformin vs placebo arms (0 (Q1-Q3=-0.01, 0.01) vs 0 nmol/L (Q1-Q3=-0.01, 0.02); p=.24*). *On the table was: p=0.02 No evidence that the reduction in estradiol associated with the metformin arm was affected by the C allele of the SNP rs11212617.
ISRCTN16493703	200 patients	Obesity: 26 (13%) Overweight: 56 (28%) Menopause status: Premenopausal: 100 (50%) Perimenopausal: 12 (6%) Postmenopausal: 88 (44%) DM: 100% nondiabetic women	Phenotype: Luminal, HER2+, Triple negative Receptors: ER+ pretreatment: 173 (86,5%) PgR+ pretreatment: 142 (71%) HER2+: 22 (11%) Stage: stage I to IIa Treatment modality: neoadjuvant	Interventions: days 1 to 3: 850-mg once daily to adapt to gastrointestinal symptoms; days 4 through 28: two 850-mg tablets after dinner (1700mg daily) Comparator: days 1 to 3: placebo once daily to adapt to gastrointestinal symptoms; days 4 through 28: two tablets of placebo	Primary: Ki67 Secondary: metformin effect in women with insulin resistance (HOMA index) and in estrogen receptor (ER)-negative tumors. Two subgroup analyses are to be considered exploratory (Results in DeCensi, 2014).	Overall, metformin did not significantly change Ki-67 relative to placebo, with a mean proportional increase of 4.0% (95% CI, -5.6% to 14.4%, p=0.4) 4 weeks apart. Subgroups HOMA index > 2.8: -10.5% (95% CI, -26.1% to 8.4%) HOMA index ≤ 2.8: 11.1% (95% CI, -0.6% to 24.2%) Pinteraction = .045 Luminal B tumors (Pinteraction = .05) Overall: -1.75 (95% CI, -11.4 to 8.9, P=.7) HOMA index > 2.8: -16.0 (95%

				after dinner.		CI, -30.9 to 2.1, P=.08) HOMA index ≤ 2.8: 5.01 (95% CI, -7.2 to 18.8, P=.4) BMI (P = .143) waist/hip girth-ratio (P = .058) moderate alcohol consumption (P = .005) C-reactive protein (P = .080).
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						baseline and surgery (Spearman's r=0.5 and 0.6, respectively, P<0.0001).”
						There was no significant change compared with placebo on any biomarker except for adiponectin (-0.64 (IC95%=-1.17; -0.12), p=0.02.).
						However, the effect of metformin on IGFBP-1 and hs-CRP was significantly modified by BMI, since metformin increased IGFBP-1 (p=0.09) and decreased hs-CRP (p=0.05) levels only in women with BMI>25.
						Metformin had a heterogeneous effect depending on markers of insulin resistance, which manifested itself in a tendency to decrease ki-67 levels in women with insulin resistance, whereas it showed a trend to an increase of ki-67 in the majority of the remaining women.
						C-peptide p = 0.3, free IGF-I, p = 0.03; IGFBP-3, p = 0.04; IGFBP-1, p = 0.016
						Variables not exhibiting a significant interaction with metformin were: weight, BMI.

						The median and IQR posttreatment Ki-67 LI in the metformin and placebo arms was, respectively: 22% (11–32) versus 35% (30–40) in all HER2+ve DCIS (P = 0.06); 12% (7–18) versus 32% (27–42) in ER+ve/HER2+ve DCIS (P = .004); 18% (12–18) versus 32% (24–44) in PgR+ve/HER2+ve DCIS (P = 0.02).
Studies with results published only in abstracts						
Arce-Salinas, 2016	48 women were included, 28 were assigned to the experimental group and 20 in the control group. Obesity rate was 46.2% (metformin group) and 47.1% (placebo group) for each treatment arm. 100% nondiabetic Metabolic syndrome was more prevalent in experimental arm 61.5% (metformin	Phenotype: Luminal = 48 (100%) Receptors: ER/PR + HER2- (100%) Stage: Stage III: 48 (100%) Treatment Modality: neoadjuvant	Interventions: Metformin 850 mg PO q12H with NeoCT Comparator: Placebo with NeoCT	Clinical outcomes: Primary: PCR (assessed after 24 weeks of treatment) Secondary: After 24 treatment weeks': Safety analysis; Assess clinical response at the end of paclitaxel and at the end of neoadjuvant chemotherapy; and To correlate serum levels of insulin, protein C and HbA1 (after treatment) with clinical and	PCR: PCR was reached in 26.9% of patients in metformin arm in comparison with 5.9% in placebo arm, however, this difference not reach statistical significance (p = 0.22). Secondary: Safety analysis: No significant toxicity was associated with metformin. No information for the others secondary outcomes.	

	group) vs 52.9% (placebo group). No data regarding: menopause status and physical activity.			pathologic response	
Azazy, 2020	60 participants (30 in each arm) No data regarding: obesity, overweight, menopause status, physical activity, and metabolic syndrome. 100% nondiabetic	Phenotype: NI Receptors: NI Stage: Stage II - III Treatment Modality: neoadjuvant	Interventions: Metformin 1.700mg/day (850 mg bid) starting with neoadjuvant chemotherapy (fluorouracil, epirubicin, cyclophosphamide (FEC) then docetaxel ± trastuzumab) Comparator: Neoadjuvant chemotherapy alone ((FEC) then docetaxel ± trastuzumab)	Clinical outcomes: Primary: Overall pathological complete response(pCR) and partial pathological response (pPR). Secondary: Toxicity	pCR and pPR: There was a significant difference between metformin and control arm in terms of overall pathological complete response(pCR) and partial pathological response (pPR) versus no response (P=0.03). pCR was higher in Arm A, but didn't reach significance due to the small sample size (P=0.09)*. Toxicity: There was no significant difference in overall toxicity or ≥ grade 3 adverse events between both arms; the most common toxicities were vomiting (53.6%), nausea (30.4%) and neutropenia (30.4%).
	45 participants (25 metformin group; 20 control group) No data regarding: obesity,	Phenotype: NI Receptors: NI Stage: NI	Interventions: Metformin (1500mg/day) was prescribed to intervention group from pathology report to the night before surgery.	Primary: Changes of Ki67 Secondary: HOMA Toxicity	Ki67: Immunohistochemistry study showed decrease of median Ki67 from 35.14 to 29.6 in the intervention group and increase from 24.5 to 30.6 in the control group. Both of these results were statistically

Sadighi, 2016	overweight, menopause status, physical activity, and metabolic syndrome. 100% nondiabetic	Treatment Modality: neoadjuvant	Comparator: Patients with the same inclusion criteria who did not receive any drug.	significant. HOMA and Toxicity: Although mild gastrointestinal symptoms were seen in 30% of cases, generally patients tolerated metformin very well. There was a correlation between metabolic factor of HOMA score and changes in Ki67.
IBIS 3 Trial (Feasibility study) ² (Oke, 2017)	Planned number of subjects to be included in the whole clinical trial: 300 patients; Total final enrolment: 89 No data regarding: obesity, overweight, physical activity, and metabolic syndrome. 100% postmenopausal 100% nondiabetic	Phenotype: NI Receptors: ER+ Stage: NI Treatment Modality: prevention of recurrence after end of cancer treatment	Interventions: Aromatase inhibitor (anastrozole, letrozole or exemestane) and/or metformin (1700 mg/day) and/or zoledronic acid 2x2x2 factorial design Comparator: Standard care (No investigational medicinal product assigned in this arm)	Primary: To determine acceptability and feasibility of recruitment, recruitment rate and number of sites required for main trial investigating prevention of late recurrence with an aromatase inhibitor and/or metformin and/or zoledronic acid or standard care (no treatment). Secondary: To determine reasons for non-participation / drop-outs and address
				Overall, only 5% GPs (?) agreed to participate and only 23 of 800 (3%) subsequently responded to the survey. The main reasons identified for nonparticipation were lack of time/resources to carry out database search (61%) and/or review medical records to confirm eligibility (48%), request coming at a busy time (9%) e.g. Calendar or financial year-end, and insufficient funding (26%).

² IBIS 3 Trial is a feasibility study which results were published in a conference abstract (Oke, 2017) and European Union Clinical Trials Register.

	women			these for main trial; To evaluate treatment adherence and reasons for stopping; To determine reasons for non-adherence and address for main trial; To assess the use of recruiting through GP surgeries local to sites via the PCRN/LCRN; To investigate feasibility of the use of email for data collection of PROs from patients; To assess acceptability of investigations for main trial.	
	203 women were randomized. 153 intention-to-treat population were analyzed (72 metformin 75 placebo group).	Phenotype: Luminal = 203 (100%); Receptors: 203 (100%) ER+ Stage:	Interventions: Metformin (2000mg/day) + Letrozole (2.5mg/day) Comparator: Placebo +	Clinical outcomes: Primary: clinical response rate (complete, partial response) pCR: NI BCR: 68.0% (100/147) (66.7% metformin versus 69.3% placebo) breast density change: NI	

METEOR Trial (Kim, 2019)	No data regarding: obesity, overweight, physical activity, and metabolic syndrome. 100% postmenopausal 100% nondiabetic	100% stages II/III. There is no information on specific frequencies for stage II and stage III separately. Treatment Modality: neoadjuvant	Letrozole (2.5mg/day)	Secondary: pCR; BCR; breast density change, changes of Ki67(%) and toxicity profile	changes of Ki 67(%) Neither Ki67% nor PEPI score was different between two groups. However, among the 20 patients with core-needle biopsy after 4 weeks of medication, greater number of patients displayed Ki67 < 10% in metformin group than in placebo group (87.5% versus 33.3%, p = 0.017). toxicity Grade 3 side effects were reported in three patients (vomiting, high blood pressure, weight loss) and no hypoglycemia event was observed.
MBC1 Trial (Semiglazova, 2019)	53 patients were included in the study. No data regarding: obesity, overweight, menopause status, physical activity, and metabolic syndrome. 100% nondiabetic	Phenotype: Luminal, HER2, Triple negative Receptors: ER+/HER2-(68%); ER+/HER2+ (25%); ER-/HER2- (7%); Stage: stage IIB, IIIA, IIIB, IIIC (frequency not reported) Treatment Modality: neoadjuvant	Interventions: FDC x 6 cycles once every 21 days with metformin 850 mg BID Comparator: conventional chemotherapy (FDC)	Clinical outcomes: Primary: ORR and pCR Secondary: Adverse events incidence and QoL	ORR: 85% (NACT), and 75% (NACT + MTF); pCR: OR 0.602 [95% CI 0,085-4,284], p=0.612).

Appendix F

Characteristics of the included studies without published results

Table 6 - Main characteristics from the 15 included studies without published results

Study / References	Eligibility Criteria	Sample Size Goal	Intervention and Comparator	Outcomes	Informed Recruitment Period and Recruitment status
Study status: Prematurely ended					
NeoMET Study (NCT01929811) (Principal investigator (PI): Kunwei Shen)	women aged ≥ 18 years and < 70 years with life expectancy > 12 months Measurable disease in breast or axillary lymph node, histologically confirmed invasive breast cancer by core needle biopsy, $T \geq 2\text{cm}$ or stage IIb or stage III according AJCC classification, fine-needle aspirationis encouraged to every patient with metastasis suspicious nodes; Biopsy specimens are available for ER, PgR, Her2 and proliferation biomarker detection; Adequate bone marrow function: Neutrophil $\geq 1.5 \times 10^9/\text{L}$; Hb $\geq 100\text{g/L}$; PLT $\geq 80 \times 10^9/\text{L}$; Adequate liver and renal function: Serum AST $\leq 90\text{U/L}$ Bilirubin $\leq$ upper limit of normal (UNL) range Serum creatinine ≤ 110	Actual Enrollment : 92 participants	Interventions: TEC plus metformin Metformin (1500 mg/day) Comparator: docetaxel, epirubicin and cyclophosphomide (TEC)	Primary: pathologic complete response rate Secondary: 1. Clinical response rate; 2. safety profile; 3. breast conservation therapy	Time conduction: 2013 - 2020 Recruitment status: Terminated (The study was stopped due to insufficient accrual)

	5. Documented disease progression after first-line hormone therapy 6. Age ≥ 18 years. 7. Measurable or evaluable metastatic disease 8. Life expectancy > 3 months 9. ECOG Performance Status < 1 10. Adequate bone marrow, liver, and renal function as assessed by the following parameters: Hemoglobin > 9.0 g/dl Leucocytes count $\geq 3,000/\text{mL}$ Absolute neutrophil count (ANC) $\geq 1,500/\text{mL}$ Platelet count $\geq 100,000/\text{mL}$ Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN (≤ 5 x ULN for patients with liver involvement) Albumine and total bilirubin ≤ 1.5 x ULN Prothrombin Time (PT) < 70 % Serum creatinine < 1.4 mg/ml, creatinine clearance > 70 ml/min 11. Normal Respiratory Function and Saturation level $\geq 90\%$ 12. New York Heart Association (NYHA) Classification ≤ 2 and baseline left ventricular ejection fraction (LVEF) $\geq 50\%$	Enrollment: 32 participants		overall response rate; To assess the duration of response in patients who achieved partial or complete remission; To assess 3-years overall survival rate; To assess tolerability of each proposed treatment;	insufficient accrual)
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	13. Patients must be willing and able to sign a written informed consent.				
NCT02472353 (PI: Kirstin Williams)	Breast cancer requiring neoadjuvant or adjuvant therapy with doxorubicin Complete metabolic panel demonstrating adequate organ functions as defined by the following: Aspartate transaminase (AST) less than 2.5 times Upper Limit of Normal (ULN); Alanine transaminase (ALT) less than 2.5 times ULN; alkaline phosphatase less than 2.5 times ULN; serum creatinine less than 1.5 mg/dL; serum bilirubin less than ULN Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 Age greater than or equal to 21 years	Actual Enrollment: 30 participants; SAP: 44 (planned) Both sexes were eligible for the study.	Interventions: standard of care treatment with doxorubicin plus metformin (1700 mg/day) Comparator: standard of care treatment with doxorubicin alone	Primary: Number of Participants With Less Than or Equal to 5% Decrease in Left Ventricle Ejection Fraction (LVEF) on Echocardiogram Secondary: LVEF of $\geq 10\%$ from baseline; diastolic function; biomarkers (Troponin I, BNP, glutathione, circulating adiponectin, AMPK phosphorylation, and lipid peroxidation); exploratory genomic analysis.	Time conduction: 2014 – 2018 Recruitment status: Terminated (The study was stopped due to insufficient accrual)
NCT02360059 (PI: David L. Ramirez)	1. Patients with histologically confirmed invasive breast cancer, stage I - IV, treated at Lyndon B. Johnson General Hospital in the Harris Health System. 2. Patients = or > 18 years old and < 75 years old.	Actual Enrollment: 1 participant; Both sexes were eligible for the study.	Interventions: Metformin (2000 mg daily) + Questionnaires + Sensory and Fine-Motor Tests Comparator:	Primary: Mean Change in Neuropathy Secondary: NI	Time conduction: 2015-2016 Recruitment status: Terminated (The study

	3. Patients scheduled to undergo paclitaxel chemotherapy for breast cancer. 4. Patients with adequate renal function, as evidenced in laboratory values = or < 3 months old: epidermal growth factor receptor (eGFR) = or > 60 mL/min/1.73m². 5. Patients with adequate hepatic function per institutional testing standards, as evidenced in laboratory values = or < 3 months old: (1) The screening results for total bilirubin must be < 1.5 times the upper limit of normal. (2) The screening results for aspartate aminotransferase (AST) and alanine aminotransferase (ALT) must be < 2 times the upper limit of normal. 6. Patients who speak English and/or Spanish. 7. Patients who are willing and able to review, understand, and provide written consent. 8. Patients with an Eastern Cooperative Oncology performance status of 0 or 1.		Placebo + Questionnaires + Sensory and Fine-Motor Tests		was stopped due to insufficient accrual)
Study status: Not yet published					
OPTIMAL Trial	1. Age ≥ 18 years and ≤ 75 years	Estimated Enrollment: 110	Interventions: high-dose dexamethasone plus	Primary: the rate of precocious (14	Time conduction: 2019 – 2022
NCT04001725 and	2. Histologically confirmed				

EudraCT 2019-000105-73 (Vernieri, 2020)	diagnosis of melanoma, lung (SCLC or NSCLC) or breast cancer 3. Recent (28 days), radiologically documented (contrast-enhanced CT or MRI) diagnosis of measurable brain metastases requiring treatment with high-dose dexamethasone (at least 8 mg daily for at least 21 days) plus/minus radiation therapy (RT). 4. Any previous or ongoing antitumor systemic therapy; patients who have never received previous systemic therapy can be also included. 5. Fasting glycemia < 126 mg/dl at the baseline evaluation or random glycemia of less than 200 mg/dl if the patient has not fasted for at least 8 hours before blood sampling. 6. Adequate blood tests: Hemoglobin ≥ 9 g/dl Absolute neutrophil count (ANC) in the range between 1.5-10 x 10³/μl Total bilirubin ≤ 1.5 times the upper normal limit (UNL). For patients with Gilbert syndrome or known liver metastases, bilirubin levels ≤ 3 times the UNL are considered acceptable	participants (both sexes)	metformin (2550 mg/day on day 7, if well tolerated) Comparator: high-dose dexamethasone	days) dexamethasone-induced diabetes, as defined as fasting plasma glucose levels ≥ 126mg/dl. Secondary: Dexamethasone-induced diabetes at 30 days; Short-term mortality; Brain local control rate of disease; Patient ECOG performance status (PS); Patient Quality of Life (QoL); Absolute counts of immune cell populations; Relative counts of immune cell populations; Activation status of immune cell populations; Plasma lipids profile; Systemic inflammatory parameters; glucocorticoids-induced changes in gut microbiota populations;	Recruitment status: Recruiting
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	AST, ALT $\leq$ 3 times the UNL Alkaline phosphatase $\leq$ 2.5 times the UNL Serum creatinine concentration $\leq$ 1.5 x UNL 7. ECOG Performance Status $\leq$ 2 8. Life expectancy > 6 weeks 9. Written informed consent 10. Ability to swallow metformin tablets 11. Patients of female gender with the potential of childbearing (neither surgically sterile nor 2 years postmenopausal) must use a medically accepted method of contraception and must agree to continue use of this method for the duration of the study and for at least 60 days after study conclusion. Acceptable methods of contraception include double barrier method [i.e. condom and occlusive cap (diaphragm or cervical vault caps)] spermicide, intrauterine device (IUD), or steroidal contraceptive (oral, transdermal, implanted, or injected) in conjunction with a barrier method. 12. Patients of male gender having female partners with childbearing potential must use a medically accepted method of contraception and must			Metformin-induced changes in gut microbiota populations; Amino acid profile	
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	agree to continue use of this method for the duration of the study and for 60 days after participation in the study.					
TCTR20200116007 (PI: Osataphan)	1) Female patient age > 18 years 2) Diagnosis with breast cancer and planned to receive doxorubicin 3) Given informed consent	Planned sample size: 396	Interventions: doxorubicin (chemotherapy) plus metformin (did not informed the dosage) Comparator: Arm 1: Placebo + doxorubicin Arm 3: Donepezil + doxorubicin	Primary: Troponin-I level about 2 weeks after completion of doxorubicin therapy Secondary: 1. Cardiac function and biomarker at 2 weeks post doxorubicin, month 3, month 6, month 9, month 12 2. Markers of mitochondria dynamics, mitochondria function and apoptosis post chemo C2, C4, C6, 2 weeks post doxorubicin, Month 3, month 6, month 9, month 12 3. Genes associated with doxorubicin-induced cardiotoxicity at	Time conduction: 2020 – 2022 Recruitment status: Not yet recruiting	

					baseline		
		1) Premenopausal women aged 18-45 years old; 2) Breast cancer staging: patients receiving adjuvant/neoadjuvant chemotherapy in stage I-IIIa ER (-) PR (-) HER-2 (-) or HER-2 (+); 3) Assessment of normal ovarian function before chemotherapy (regular menstruation 2 months before chemotherapy); 4) Sign the informed consent form.	Planned sample size: 314	Interventions: Group 2: Metformin (2g/day) + Chemotherapy Comparator: Group 1: Placebo + Chemotherapy Chemotherapy: "For ER(-) PR(-) HER-2(-) breast cancer patients: EC-T (epirubicin/cyclophospamide/paclitaxel) or AC-T (doxorubicin/cyclophosphamide/paclitaxel) chemotherapy regimen; "For HER-2(+) breast cancer patients: EC-TH (epirubicin/cyclophosphamide/paclitaxel/trastuzumab), AC-TH (doxorubicin/cyclophosphamide/paclitaxel/trastuzumab) or TCb-H (docetaxel/carboptatin / docetaxel/trastuzuma b) regimen.	Primary: Menstruation recovery rate Secondary: Sex hormones+AMH+InhibinB; 5-year pregnancy outcome; Tumor prognosis (OS, ORR, DFS); The quality of patient's life; Safety assessment	Time conduction: 2019 - 2028 (planned) Recruitment status: Recruiting	
ChiCTR1900023487 (Zhang, 2020)							
ChiCTR1900027489 (PI: Wang)	Breast cancer 1) Age: 18-45 years old; 2) Molecular typing of breast cancer: ER(-)PR(-)HER-2(-) or	Planned sample size: 234	Interventions: Metformin (dosage not informed) + Chemotherapy	Primary: Ovarian function recovery (Menstruation or AMH)	Time conduction: 2020 – 2023		

	HER-2(+); 3) Breast cancer staging: patients receiving adjuvant/neoadjuvant chemotherapy in stage I-IIIa; 4) Assessment of normal ovarian function before chemotherapy (regular menstruation 2 months before chemotherapy); 5) Sign the informed consent form. Cervical cancer 1) age: 18-45 years old; 2) Preoperative pathological diagnosis of cervical squamous cell carcinoma, cervical adenosquamous carcinoma or cervical adenocarcinoma; 3) Clinical diagnosis is IB2 (with fertility requirements), IB3 and IIA2; 4) retain one or both sides or part of the ovaries; 5) normal ovarian function before chemotherapy (regular menstruation 2 months before chemotherapy); Sign the informed consent form. Ovarian cancer 1) Patients aged 18-45 years old; 2) Pathological diagnosis is limited to unilateral ovarian		Comparator: Placebo + Chemotherapy	Secondary: Sex hormones+AMH+ InhibinB; 5-year pregnancy outcome; Safe assessment - Blood routine, urine routine, blood biochemistry, liver and kidney function, adverse reactions; Tumor prognosis; Disease free survival (DFS); Progression free survival (PFS)	Recruitment status: Recruiting
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	epithelial cancer; malignant germ cell tumor (unlimited staging); IC stage stromal cell tumor; 3) retain one or both sides or part of the ovaries; 4) Who receive chemotherapy; 5) Estimated survival period: more than 2 years; ECOG score is 0-1 points; 6) Normal ovarian function before chemotherapy (regular menstruation 2 months before chemotherapy); 7) Sign the informed consent form. Trophoblastic tumors 1) age: 18-45 years old; 2) Clinical diagnosis of aggressive hydatidiform mole and choriocarcinoma (FIGO prognostic score ≥ 7 points, high-risk type), placental site trophoblastic tumor (PSTT) surgery to preserve ovarian patients, high risk factors (mitotic index $> 5 / 10$ HPF ; > 2 years from the previous pregnancy; deep infiltration, necrosis), patients with chemotherapy with EMA-Co regimen; 3) Erosive hydatidiform mole and choriocarcinoma (FIGO prognostic score < 7, low-risk				
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	type), single-agent MTX chemotherapy showed drug resistance, and patients were treated with EMA-CO regimen; 4) Assessment of normal ovarian function before chemotherapy (regular menstruation 2 months before chemotherapy); 5) Sign the informed consent form.				
ChiCTR-IPR-16008553 (PI: Guo-sheng)	1. Volunteered for this study and informed consent was obtained from the participants; 2. Female and age from 20 to 70 years old; 3. Diagnosis as breast cancer according to clinical practice guideline; 4. Indications for neoadjuvant chemotherapy according to clinical practice guideline: clinical I/II stage breast cancer; 5. Diagnosis as prediabetes: OGTT examinations show IFG 5.6-6.9mmol/L, IGT 7.8-11.0mmol/L; Or HbA1c:5.7-6.4%.	Planned sample size: 500	Interventions: Metformin (1700mg/day) + Chemotherapy Comparator: Placebo + Chemotherapy	Primary: Pathologic complete response (PCR) Secondary: breast cancer events; Clinical recession of lump; Glucose intolerance and insulin function status; Metabolic syndrome.	Time conduction: 2016 - 2021 (planned) Recruitment status: NI
SETUP AIM Trial (ACTRN12612000416897) (PI: Ganju)	Stage 1 or 2 operable invasive breast cancer. Estrogen receptor positive (>10% cells) Post-menopausal female Histologically proven invasive adenocarcinoma of the breast through either a core needle biopsy or incisional biopsy. Excisional biopsy will not be	Sample size target: 40	Interventions: 2 weeks of metformin (1g/day) followed by 2 weeks of metformin in addition to aromatase inhibitor in the lead up to your scheduled surgery.	Primary: Reduction in tumour tissue Ki67 level (proliferative index) Secondary: Imaging	Time conduction: 2012 - NI The trial is registered on ANZCTR and it was last updated on

	allowed. Tumour must be confined to either the breast or to the breast and ipsilateral axilla. A complete metastatic staging work-up will be performed prior to definitive surgery, as clinically indicated. Age $\geq$ 18 years. Karnofsky Performance status index $\geq$ 80%. Laboratory requirements: (within 28 days prior to registration) Haematology: Neutrophils $\geq$ 1.5 x 10⁹/L Platelets $\geq$ 100 x 10⁹/L Haemoglobin $\geq$ 10 g/dL Hepatic function: Total bilirubin $\leq$ 1 UNL (patients with a well documented history of Gilbert's Syndrome are eligible) ASAT (SGOT) and ALAT (SGPT) $\leq$ 2.5 UNL Alkaline phosphatase $\leq$ 5 UNL Renal function: Creatinine $\leq$ 175 micromol/L (2 mg/dL) Negative pregnancy test (urine or serum) within 7 days prior to registration for all women of childbearing potential. Patients must be postmenopausal defined as: Age >50 y and amenorrheic for		Comparator: 2 weeks of metformin followed by 2 weeks of aromatase inhibitor alone : Arimidex or Femara	responses (mammogram, ultrasound, MRI)	11/11/2015. Recruitment status: NI
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	6 months or more Age <50 y and amenorrheic for 12 months or more Prior bilateral oophorectomy Prior hysterectomy and has post menopausal levels of FSH and LH per local institutional standards Age >55 y and prior hysterectomy	Planned number of subjects to be included: 236	Interventions: Metformin 850 mg alone Comparator: Placebo	Primary: Change of Ki-67 in contralateral unaffected breast Secondary: To check the ability of the treatment to modulate various translational risk factors related to the target tissue and the host characteristics: - circulating and molecular biomarkers - metabolomic analysis - gene expression profile in adipose and epithelial breast tissue - assessment of epigenetic changes in	Time conduction: 2021 - 2024 (probably) Recruitment status: NI
MetBreCS Trial (EUCTR2015-001001-14-IT)	• Pre- and postmenopausal BC survivors (TNBC, or ER- PgR-, Her2+, or Luminal B Her2+ subtypes) who have completed any adjuvant therapy (not before 1 month from treatment cessation) without evidence of residual disease and with BMI > 25 kg/m² • Female, (age > 18 years). • Performance status = 0 (SWOG).				

	the breast primary. In case of inflammatory breast cancer, the extent of inflammation/erythema can be used as measurable lesion. Multifocal or multicentric breast cancer is allowed if all the lesions are biopsied and are HER2+. Largest lesion will be assigned the target lesion. Must be HER2+ in primary breast tumor or lymph node by the ASCO/CAP guidelines 2013: http://www.asco.org/guidelines/her2 Ejection fraction (EF) greater than 50% by MUGA or ECHO within 4 weeks prior to first dose of study treatment. No prior cancer chemotherapy allowed. Adequate organ and marrow function as defined below, unless deemed non-clinically significant and approved by the PI: Absolute neutrophil count $\geq 1,500/\text{mCL}$ Platelets $\geq 100,000/\text{mcl}$ total bilirubin within normal institutional limits AST (SGOT) $\leq 2.5 \times$ institutional upper limit of normal ALT (SPGT) $\leq 2.5 \times$ institutional upper limit of normal ALK Phos $\leq 2.5 \times$ institutional				
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	upper limit of normal Creatinine clearance > 50mL/min Women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 90 days following completion of therapy. Negative pregnancy test within 14 days prior to randomization				
METNEO Trial (NCT04170465) (PI: Manar A Serageldin)	Females ≥ 18 years of age and < 65 years. Unilateral or bilateral primary carcinoma of the breast confirmed. ECOG PS 0-2. Clinically measurable tumor size who are candidates for neoadjuvant therapy. No evidence of distant metastasis. Normal renal and liver functions. Non-diabetics.	Estimated Enrollment: 60 participants	Interventions: AC-T neoadjuvant chemotherapy in addition to oral metformin HCl. 850 mg metformin tablets BID (1700 mg/day) daily until the completion of neoadjuvant chemotherapy cycles. AC: (Doxorubicin 60 mg/m ² IV + cyclophosphamide 600 mg/m ² IV) for 4 cycles every 3 weeks followed by Taxol cycles (Paclitaxel 80 mg/m ² IV) once weekly for 12 weeks.	Primary: 1. Evaluation of the effect on tumor proliferation as measured by Ki-67 immunohistochemical (IHC) assessment (%) [Time Frame: 6 months] Tissue level of Ki-67 expression in the excised tumor. Ki-67 will be scored as the percentage of tumour nuclei staining.	Time conduction: 2019 - 2020 Recruitment status: Recruiting
			Comparator:	2. Evaluation of	

				AC-T neoadjuvant chemotherapy alone AC: (Doxorubicin 60 mg/m2 IV + cyclophosphamide 600 mg/m2 IV) for 4 cycles every 3 weeks followed by Taxol cycles (Paclitaxel 80 mg/m2 IV) once weekly for 12 weeks.	the effect on tumor apoptosis as measured by Caspase-3 [Time Frame: 6 months] Tissue level of the active caspase-3 in the excised tumor. 3. Chemotherapy toxicities [Time Frame: 6 months] Monitoring the incidence of chemotherapy toxicities during neoadjuvant therapy Secondary: pCR rate [Time Frame: 6 months]	Time conduction: 2020 - 2024 (estimated) Recruitment status: Recruiting
BREAKFAST Trial (NCT04248998) (PI: Filippo de Braud)	1. Female sex 2. Age ≥ 18 and ≤ 75 years. 3. Evidence of a personally signed and dated informed consent document (ICD) indicating that the patient has been informed of all pertinent aspects of the study before enrollment 4. Willingness and ability to	Estimated Enrollment: 90 participants	Interventions: Arm B will consist of 6 months of standard anthracycline-taxane preoperative chemotherapy in combination with triweekly cycles of 5-day FMD and daily metformin (1700	Primary: pCR rate Secondary: 1. Severe adverse events 2. Safety of the experimental treatments 3. Compliance		

	comply with the prescribed FMD regimen, metformin intake, the scheduled visits, treatment plans, laboratory tests and other procedures. 5. Histologically confirmed diagnosis of invasive TNBC candidate to neoadjuvant chemotherapy and subsequent curative surgery. On the basis of International Guidelines, TNBC is defined by absent or minimal (<1%) expression of oestrogen and progesterone receptors at IHC, and absence of HER2 over-expression or amplification, as defined as an IHC score of 0, 1+, or an IHC score of 2+ with in situ hybridization (ISH) analysis excluding HER2 gene amplification. 6. Patients with localized disease (clinical stage I-III according to TNM). Patients with Stage I TNBC will be included only if the primary tumor is at least 10 mm in greatest dimension (clinical T1c as determined through baseline MRI assessment). 7. Presence of an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. 8. Presence of adequate bone		mg/day). Comparator: Chemotherapy plus Fasting-Mimicking Diet (FMD)	with the experimental treatment 4. Relapse-free survival (RFS) 5. Distant metastasis-free survival (DMFS) 6. Overall Survival (OS) 7. Short-term modifications of plasma glycemia (mg/dl) 8. Long-term modifications of plasma glycemia (mg/dl) 9. Short-term modifications of serum insulin concentration (μU/ml) 10. Long-term modifications of serum insulin concentration (μU/ml) 11. Short-term modifications of serum IGF-1 concentration (ng/ml) 12. Long-term modifications of serum IGF-1 concentration	
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	marrow and organ function as defined by the following laboratory values: a. ANC $\geq 1.5 \times 10^3/\text{l}$ b. platelets $\geq 100 \times 10^3/\text{l}$ c. hemoglobin $\geq 9.0 \text{ g/dl}$ d. calcium (corrected for serum albumin) within normal limits or $\leq$ grade 1 according to NCICTCAE e. version 5.0 if not clinically significant f. potassium within the normal limits, or corrected with supplements g. creatinine $< 1.5 \text{ ULN}$ h. blood uric acid $< 10 \text{ mg/dl}$ i. ALT and AST $\leq 2 \times \text{ULN}$ j. total bilirubin $< 1.5 \text{ ULN}$ except for patients with Gilbert syndrome who may only be included if the total bilirubin is $< 3.0 \times \text{ULN}$ or direct bilirubin $< 1.5 \times \text{ULN}$ k. Fasting glucose $\leq 250 \text{ mg/dl}$. l. Female patients of childbearing potential must agree to sexual abstinence or to use two highly effective methods of contraception throughout the study and for at least six months after the end of the FMD. Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Examples of contraceptive			(ng/ml) 13. Short-term modifications of blood lipid profile by UPLC-MS and HPLC-ELDS 14. Long-term modifications of blood lipid profile by UPLC-MS and HPLC-ELDS 15. Clinical tumor response 16. Gene expression profiles 17. Mutational analyses 18. Short-term modifications of plasma amino acid profile by UPLC-QDa Mass detector system (Waters) 19. Long-term modifications of plasma amino acid profile by UPLC-QDa Mass detector system (Waters)	
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	methods with a failure rate of < 1% per year include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of < 1% per year. Barrier methods must always be supplemented with the use of a spermicide. A patient is of childbearing potential if, in the opinion of the Investigator, she is biologically capable of having children and is sexually active. 10. Female patients are not of childbearing potential if they meet at least one of the following criteria: a. Have undergone a documented hysterectomy and/or bilateral oophorectomy b. Have medically confirmed ovarian failure c. Achieved post-menopausal status, defined as: ≥ 12 months of non-therapy-induced amenorrhea or surgically sterile (absence of ovaries) and have a serum FSH level within the				
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	laboratory's reference range for postmenopausal females.				
NCT04387630 (PI: Osama Hussein)	Histologically proven breast carcinoma. American Society of Anesthesiology (ASA) score I-II. Candidate for neoadjuvant chemotherapy as per hospital's protocol. Clinically measurable tumor. No evidence of distant metastasis. Normal renal and liver functions. Non-diabetics.	Estimated Enrollment: 120 participants	Interventions: Metformin (2550 mg/day) + Chemotherapy (AC-T or AC) Comparator: Placebo + Chemotherapy (AC-T or AC)	Primary: Clinical Response rate Secondary: T-cell cytotoxic markers	Time conduction: 2020 – 2023 (estimated) Recruitment status: Recruiting
NCIC CTG MA.32 (Goodwin, 2022) (substudies) NCT01286233 (PI: Norman Wolmark)	The patient must have consented to participate and must have signed and dated an appropriate IRB-approved consent form that conforms to federal and institutional guidelines for the MA.32.F Study before being enrolled. The patient must be female. The patient must reside in the United States or Canada. The patient must be English-speaking. The patient must be eligible for randomization in the MA.32 treatment trial. (Participation in the MA.32QOL study is permitted but not required.) The patient must not have started taking MA.32 study	Actual Enrollment: 394 female participants	Interventions: metformin 850 mg caplet po bid for 5 years, including a 4-week ramp-up of one caplet per day Comparator: an identical placebo po bid for 5 years, including a 4-week ramp-up of one caplet per day	Primary: 1. Questionnaire scores from patient reported outcome battery regarding fatigue, stress, sleep, depression, and general quality of life [Time Frame: Collected at baseline and 6, 12, 24, and 36months from randomization] 2. Questionnaire scores from patient reported comorbid	Time conduction: 2011 – 2016 Recruitment status: Unknown

		therapy. The patient must have completed primary breast radiation therapy at least two weeks prior to enrollment in MA.32.F.			conditions and behavioral risks [Time Frame: Collected at baseline and 6, 12, 24, and 36 months from randomization] 3. Biological correlates of fatigue (medical and demographic characteristics of pts.) [Time Frame: Collected at baseline and 6, 12, 24, and 36 months from randomization] Biological correlates (medical) will be collected at these timepoints. Standard demographics will be collected at baseline only. 4. DNA polymorphisms [Time Frame: Collected at baseline] 5. Changes in RNA gene expression [Time Frame: Collected	
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					at baseline and 6, 12, and 24 months] Secondary: NI	Time conduction: 2012 – 2013 Recruitment status: Unknown
	Wood, 2013	Patients must either be concurrently enrolling or previously enrolled to Canada (CAN) National Cancer Institute of Canada (NCIC) study MA.32 (CAN-NCIC-MA.32) (MA.32); eligible patients may be either pre- or post-menopausal Patients must have hormone receptor-negative breast cancer Patients must have breast density ≥ 25% (correlating with the Breast Imaging-Reporting and Data[BIRAD]-2 category of "scattered fibroglandular densities" or greater) Baseline digital mammograms taken within 12 months prior to registration to MA.32, with at least acraniocaudal (CC) view used for enrollment to MA.32 must be available for submission; if the patient as previously enrolled to MA.32 and one year has elapsed from baseline mammograms, one-year mammograms must also be available for submission Contralateral unaffected breast in place (with no prior cancer	Estimated Enrollment: 458 female patients	Interventions: metformin 850 mg caplet po bid for 5 years, including a 4-week ramp-up of one caplet per day Comparator: an identical placebo po bid for 5 years, including a 4-week ramp-up of one caplet per day	Primary: Change in percent mammographic breast density in contralateral (unaffected) breast from baseline to 1 year Secondary: 1. Change in percent mammographic breast density in contralateral (unaffected) breast from baseline to 2 years using two-sample t-test 2. Correlation between baseline mammographic density and baseline plasma fasting insulin, glucose levels, and HOMA using a scatter plot, correlation-	

		or radiation, no implants, and no plan for breast surgery on contralateral breast over the course of the study); women with a prior biopsy on the unaffected breast are eligible				coefficient estimation, and linear-regression method 3. Correlation of changes in dense area in response to metformin therapy from pre-treatment to ontreatment (at year 1 and year 2) with plasma fasting insulin, glucose levels, and HOMA using simple linear-regression method 4. Correlation between mammographic density and the incidence of second primary breast cancer using correlation coefficient and scatter plot	
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Appendix G

Clinical, Non-clinical, and Miscellaneous Outcomes Evaluated by
the Studies Included in the Scoping Review

Table 7 - Clinical, Non-clinical, and Miscellaneous Outcomes Evaluated by the Studies Included in the Scoping Review

Outcomes	Studies <u>with</u> at least some published results	Studies <u>without</u> published results
Clinical Outcomes		
Survival		
Overall survival (OS)	MYME Trial (Nanni, 2018); Zhao, 2017; Liubota, 2018; Salah, 2021; Pimentel, 2019; SNCIC CTG MA.32 (Goodwin, 2022)	NCT01477060; BREAKFAST Trial (NCT04248998); ChiCTR1900023487 (Zhang, 2020)
Disease-free survival (DFS)	METTEN Trial (Martin-Castillo, 2018); Ahmed, 2021; El-Haggar, 2016; Liubota, 2018; SNCIC CTG MA.32 (Goodwin, 2022)	ChiCTR1900023487 (Zhang, 2020); ChiCTR1900027489
Progression-free survival (PFS)	MYME Trial (Nanni, 2018); Zhao, 2017; Salah, 2021; Pimentel, 2019	Saif, 2019/Kritharis, 2014; NCT01477060; ChiCTR1900027489
Relapse-free survival (RFS)	SNCIC CTG MA.32 (Goodwin, 2022)	-
Distant metastasis-free survival (DMFS)	-	BREAKFAST Trial (NCT04248998)
Mortality	-	OPTIMAL Trial (NCT04001725)
Response Rates		
Objective Response Rate (ORR)	Zhao, 2017; METEOR Trial (Kim, 2019); Semiglazova, 2018; Ahmed, 2021; Liubota, 2018; MBC1 Trial (Semiglazova, 2019); MYME Trial (Nanni, 2018)	NeoMET Study (NCT01929811); NCT04387630; Arce-Salinas, 2016; NCT01477060; BREAKFAST Trial (NCT04248998); Salah, 2021; ChiCTR1900023487 (Zhang, 2020)
Clinical Benefit Rate (CBR)	Zhao, 2017; Ahmed, 2021; Liubota, 2018; Salah, 2021; Pimentel, 2019	NeoMET Study (NCT01929811); NCT04387630; Arce-Salinas, 2016; BREAKFAST Trial (NCT04248998);
Pathological Complete Response (pCR)	Arce-Salinas, 2016; Semiglazova, 2018; METTEN Trial (Martin-Castillo, 2018); Ahmed, 2021; Liubota, 2018; Barakat, 2022; MBC1 Trial (Semiglazova,	ChiCTR-IPR-16008553; NeoMET Study (NCT01929811); METNEO Trial (NCT04170465); METEOR Trial (Kim, 2019); HERMET Trial (NCT03238495);

	2019); Azazy, 2020	BREAKFAST Trial (NCT04248998)
Breast-related outcomes		
Breast conservation rate (BCR)	METEOR Trial (Kim, 2019); METTEN Trial (Martin-Castillo, 2018); Ahmed, 2021; Liubota, 2018; Barakat, 2022	NeoMET Study (NCT01929811)
Breast density change	METEOR Trial (Kim, 2019); SNCIC CTG MA.32 (Goodwin, 2022)	-
Breast cancer-free interval	SNCIC CTG MA.32 (Goodwin, 2022)	-
Breast cancer events	-	ChiCTR-IPR-16008553
Clinical resection of lump	-	ChiCTR-IPR-16008553
Prevalence, grade and proliferation of lobular or ductal intraepithelial neoplasia (LIN or DIN) and ductal hyperplasia	Bonanni, 2012/DeCensi, 2015	-
ECOG performance status	-	OPTIMAL Trial (NCT04001725)
Other Clinical outcomes		
Metastasis	El-Haggag, 2016	-
Quality of Life (QoL)	Semiglazova, 2018; Barakat, 2022; MBC1 Trial (Semiglazova, 2019); Pimentel, 2019; SNCIC CTG MA.32 (Goodwin, 2022)	OPTIMAL Trial (NCT04001725); NCT02472353; ChiCTR1900023487 (Zhang, 2020)
Toxicity	Saif, 2019/Kritharis, 2014; Azazy, 2020; Sadighi, 2016; MYME Trial (Nanni, 2018); Zhao, 2017; METEOR Trial (Kim, 2019); Semiglazova, 2018; METTEN Trial (Martin-Castillo, 2018); Ahmed, 2021; Barakat, 2022; MBC1 Trial (Semiglazova, 2019); Pimentel, 2019	NeoMET Study (NCT01929811); METNEO Trial (NCT04170465); NCT02472353; NCT01477060; BREAKFAST Trial (NCT04248998); ChiCTR1900023487 (Zhang, 2020); ChiCTR1900027489
Non-clinical Outcomes		
Comorbidities		
Blood pressure levels	Ko, 2015	-
New diagnosis of Diabetes mellitus	SNCIC CTG MA.32 (Goodwin, 2022)	OPTIMAL Trial (NCT04001725)
New diagnosis of Metabolic syndrome	-	ChiCTR-IPR-16008553
Nutrition		
Diet	SNCIC CTG MA.32 (Goodwin, 2022)	-
Weight loss	Ko, 2015	-
Anthropometric Measurements		

BMI	PECAM Study (Davis, 2018); Meyerhardt, 2020/Brown, 2020; SPIRIT Trial (Yeh, 2021); SNCIC CTG MA.32 (Goodwin, 2022); Bonanni, 2012	-
Weight	PECAM Study (Davis, 2018); Meyerhardt, 2020/Brown, 2020; SPIRIT Trial (Yeh, 2021); Ko, 2015	-
Height	Ko, 2015	-
Abdominal circumference	PECAM Study (Davis, 2018)	-
Waist circumference	Ko, 2015	-
Waist to Hip Ratio	Meyerhardt, 2020/Brown, 2020	-
Fertility		
Endometrial thickness	PECAM Study (Davis, 2018)	-
Menstruation recovery rate	-	ChiCTR1900023487 (Zhang, 2020); ChiCTR1900027489
5-year pregnancy	-	ChiCTR1900023487 (Zhang, 2020); ChiCTR1900027489
Sex Hormones		
Anti-Müllerian Hormone (AMH)	-	ChiCTR1900023487 (Zhang, 2020); ChiCTR1900027489
Inhibin B	-	ChiCTR1900023487 (Zhang, 2020); ChiCTR1900027489
Estradiol	SNCIC CTG MA.32 (Goodwin, 2022)	ChiCTR1900023487 (Zhang, 2020); ChiCTR1900027489
Progesterone	-	ChiCTR1900023487 (Zhang, 2020); ChiCTR1900027489
Prolactin (PRL)	-	ChiCTR1900023487 (Zhang, 2020); ChiCTR1900027489
Follicle Stimulating Hormone (FSH)	-	ChiCTR1900023487 (Zhang, 2020); ChiCTR1900027489
Luteinizing Hormone (LH)	Reach for Health trial (Patterson, 2018)	ChiCTR1900023487 (Zhang, 2020); ChiCTR1900027489
Testosterone	Reach for Health trial (Patterson, 2018); SNCIC CTG MA.32 (Goodwin, 2022)	ChiCTR1900023487 (Zhang, 2020); ChiCTR1900027489
Sex Hormone-Binding Globulin (SHBG)	Reach for Health trial (Patterson, 2018);	ChiCTR1900023487 (Zhang, 2020);

	SNCIC CTG MA.32 (Goodwin, 2022)	ChiCTR1900027489
Genetic Tests		
Genomic analysis	-	NCT02472353
mTOR pathway gene expression	PECAM Study (Davis, 2018)	-
C Allele of ATM rs11212617	METTEN Trial (Martin-Castillo, 2018)	-
Genes associated with doxorubicin-induced cardiotoxicity at baseline	-	TCTR20200116007
Bloodtests		
Blood routine	-	ChiCTR1900027489
Urine routine	-	ChiCTR1900027489
Fasting Serum Urate (SU)	SPIRIT Trial (Yeh, 2021)	-
Vitamin B12	SNCIC CTG MA.32 (Lohmann, 2017)	-
Liver function		
Aspartate aminotransferase (AST)	-	ChiCTR1900027489
Alanine aminotransferase (ALT)	-	ChiCTR1900027489
Kidney function		
Estimated glomerular filtration rate (eGFR)	SPIRIT Trial (Yeh, 2021)	ChiCTR1900027489
Blood-based energetic biomarkers		
Glucose	PECAM Study (Davis, 2018); Meyerhardt, 2020/Brown, 2020; Ko, 2015; Reach for Health trial (Patterson, 2018)	OPTIMAL Trial) (NCT04001725); ChiCTR-IPR-16008553;
Insulin	PECAM Study (Davis, 2018); Meyerhardt 2020/Brown, 2020; SPIRIT Trial (Yeh, 2021); METTEN Trial (Martin-Castillo, 2018); El-Hagggar, 2016; Ko, 2015; Reach for Health trial (Patterson, 2018); SNCIC CTG MA.32 (Goodwin, 2022)	ChiCTR-IPR-16008553
Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)	PECAM Study (Davis, 2018); Sadighi, 2016; MYME Trial (Nanni, 2018); El-Hagggar, 2016; SNCIC CTG MA.32 (Goodwin, 2022); Bonanni, 2012	-
Hemoglobin A1C (HbA1c)	PECAM Study (Davis, 2018); Sadighi, 2016; MYME Trial (Nanni, 2018); El-Hagggar, 2016; SNCIC CTG MA.32 (Goodwin, 2022); Bonanni, 2012	-

IGF1R (Insulin Like Growth Factor 1 Receptor)	MYME Trial (Nanni, 2018); Bonanni, 2012	-
IGF-1 (insulin-like growth factor 1)	Meyerhardt, 2020/Brown, 2020; SPIRIT Trial (Yeh, 2021); El-Hagggar, 2016; Bonanni, 2012	-
IGFBP-1 (Insulin-like growth factor-binding protein 1)	Bonanni, 2012	-
IGFBP-3 (Insulin-like growth factor binding protein 3)	El-Hagggar, 2016; Bonanni, 2012	-
IGF1:IGFBP3 molar ratio	SPIRIT Trial (Yeh, 2021); El-Hagggar, 2016	-
Cardiac-related outcomes		
LVEF (Left Ventricle Ejection Fraction)	-	NCT02472353
Troponin-I level	-	TCTR20200116007; NCT02472353
BNP (Brain natriuretic peptide)	-	NCT02472353
Glutathione	-	NCT02472353*
Cardiac function		TCTR20200116007
Cardiovascular hospitalizations	SNCIC CTG MA.32 (Goodwin, 2022)	-
Inflammation measures		
hs-CRP (high sensitivity C-reactive protein)	Meyerhardt, 2020/Brown, 2020; SPIRIT Trial (Yeh, 2021); Reach for Health trial (Patterson, 2018); SNCIC CTG MA.32 (Goodwin, 2022); Bonanni, 2012	-
sTNF- α R2 (soluble tumor necrosis factor alpha receptor 2)	Meyerhardt, 2020/Brown, 2020	-
IL-6 (interleukin 6)	Meyerhardt, 2020/Brown, 2020; SPIRIT Trial (Yeh, 2021);	-
Absolute counts of immune cell populations	-	OPTIMAL Trial (NCT04001725)
Relative counts of immune cell populations	-	OPTIMAL Trial (NCT04001725)
Activation status of immune cell populations	-	OPTIMAL Trial (NCT04001725)
Systemic inflammatory parameters	-	OPTIMAL Trial (NCT04001725)
Tumor Biomarkers		
Ki67	Sadighi, 2016; METEOR Trial (Kim, 2019); Semiglazova, 2018; NeoMet Trial (Hadad, 2011/Hadad, 2015); METTEN Trial (Martin-Castillo, 2018); Bonanni, 2012	METNEO Trial (NCT04170465); SETUP AIM Trial (ACTRN12612000416897); MetBreCS Trial (EUCTR2015-001001-14-IT)

CA-153	El-Haggar, 2016; SNCIC CTG MA.32 (Goodwin, 2022)	-
Caspase-3	NeoMet Trial (Hadad, 2011/Hadad, 2015)	METNEO Trial (NCT04170465)
T-cell cytotoxic markers	-	NCT04387630
HER2-related pathways	METTEN Trial (Martin-Castillo, 2018)	-
Liquid Biopsy		
Circulating Tumor Cells (CTC)	MYME Trial (Nanni, 2018)	-
Imaging responses		
Mammogram	-	SETUP AIM Trial (ACTRN12612000416897)
Ultrasound	-	SETUP AIM Trial (ACTRN12612000416897)
Magnetic Resonance Imaging (MRI)	-	SETUP AIM Trial (ACTRN12612000416897)
Cell signalling		
pAMPK and pAkt	NeoMet Trial (Hadad, 2011/Hadad, 2015); METTEN Trial (Martin-Castillo, 2018)	-
AMPK phosphorylation		NCT02472353
mTOR	METTEN Trial (Martin-Castillo, 2018)	-
Miscellaneous outcomes		
Adiponectin	Bonanni, 2012	NCT02472353
Lipid peroxidation		NCT02472353
Leptin	Meyerhardt, 2020/Brown, 2020; SNCIC CTG MA.32 (Goodwin, 2022)	-
Lipids profile	Ko, 2015	OPTIMAL Trial (NCT04001725)
Aminoacid profile	-	OPTIMAL Trial (NCT04001725)
Mitochondria function	-	TCTR20200116007
Brain local control rate of disease	-	OPTIMAL Trial (NCT04001725)
Neuropathy	-	NCT02360059
Feasibility	IBIS 3 Trial (Oke, 2017)	-
DLT (dose limiting toxicity)	Saif, 2019/Kritharis, 2014	-
PD (Pharmacodynamic markers)	Saif, 2019/Kritharis, 2014	-
BDI (Beck depression inventory)	Ko, 2015	
5 cognitive domains	Reach for Health trial (Patterson, 2018)	-
Glucocorticoids-induced changes in gut microbiota populations	-	OPTIMAL Trial (NCT04001725)
Metformin-induced changes in gut microbiota populations	-	OPTIMAL Trial (NCT04001725)
Not specified miscellaneous outcomes		
Not specified circulating and molecular	-	MetBreCS Trial

biomarkers		(EUCTR2015-001001-14-IT)
Not specified metabolomic analysis	-	MetBreCS Trial (EUCTR2015-001001-14-IT)
Not specified gene expression profile in adipose and epithelial breast tissue	-	MetBreCS Trial (EUCTR2015-001001-14-IT)
Not specified assessment of epigenetic changes in methylome patterns (DNA methylation)	-	MetBreCS Trial (EUCTR2015-001001-14-IT)