INPLASY PROTOCOL

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None.

Efficacy and Safety of Anti-HER2 Agents in Combination with Chemotherapy for Metastatic HER2-positive Breast Cancer Patient: A Network Meta-analysis

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Review question / Objective: **To explore the efficacy and safety of anti-Human Epidermal Growth Factor Receptor 2 (HER2) agents in combination with chemotherapy for patients with metastatic/advanced HER2 positive (HER2+) breast cancer (BC).**
Condition being studied: **This review is going to explore the efficacy and safety of anti-Human Epidermal Growth Factor Receptor 2 (HER2) agents in combination with chemotherapy for patients with metastatic/advanced HER2 positive (HER2+) breast cancer (BC). Bayesian network meta-analysis will be carried out in this study. The network meta-analysis will be performed according to the preferred reporting items for systematic review and meta-analysis (PRISMA) extension statement.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 September 2020 and was last updated on 24 September 2020 (registration number INPLASY202090086).

INTRODUCTION

Review question / Objective: **To explore the efficacy and safety of anti-Human Epidermal Growth Factor Receptor 2 (HER2) agents in combination with chemotherapy for patients with metastatic/advanced HER2 positive (HER2+) breast cancer (BC).**

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METHODS

Search strategy: Key words: Anti-HER2 Agents, Chemotherapy, Metastatic HER2-positive, Breast Cancer. - only RCTs will be included. - HER-2 positive, with no limitation on ER/PR. - metastatic or advanced breast cancer. Detailed search strategy of each database will be provided with the manuscript.

Participant or population: Patients (>18 years old) with metastatic or advanced HER2+ BC. HER2+ BC defined as histologically or cytologically confirmed BC patients of immunohistochemistry score of 3+ or 2+ and/or HER2 gene amplification by fluorescence in situ hybridization. The stage of the patients proven to be metastatic or advanced. There will be no limitation on sex, co-morbidity, and hormone receptor status.

Intervention: Anti-HER2 agents in combination with chemotherapy for advanced or metastatic BC. The anti-HER2 agents includes trastuzumab, pertuzumab, trastuzumab emtansine (T-DM1/TDM1), lapatinib, pyrotinib, afatinib, neratinib, margetuximab, tucatinib, and trastuzumab deruxtecan (DS-8201). We will include single use of anti-HER2 agent or a combination of any two types of anti-HER2 agents. Concurrent or sequential chemotherapy will be included. There is no limitation on dosage, frequency, time, method of administration, treatment duration, and combined drug for chemotherapy.

Comparator: Placebo, Anti-HER2 Agents in Combination with Chemotherapy. Anti-HER2 Agents includes: trastuzumab, pertuzumab, T-DM1/TDM1, lapatinib, pyrotinib, afatinib, neratinib, margetuximab, tucatinib, trastuzumab deruxtecan.

Study designs to be included: Phase II and III randomized controlled trials; systematic reviews or meta-analyses will be included to track their references.

Eligibility criteria: Exclusion criteria 1) We will exclude non-RCTs, phase I RCTs, and single-arm studies. 2) We will exclude studies including participants with early breast cancer, HER2 negative BC or a mixed HER2 status without subgroup data in HER2+ population, mixed lines of treatment and studies investigating adjuvant / neoadjuvant therapies. 3) We will exclude papers that not reported in English or Chinese. 4) We will exclude reports that without full reports and only abstract is available. 5) If multiple publications were reported for the same trial or included the same or overlapping patient groups, only publications with the most recent interested data or with largest sample size will be included. 6) We will exclude studies with interventions that were only comprised in one study.

Information sources: A systematic search in the database of PubMed, EMBASE, and Cochrane Library will be conducted in literatures published from inception to May 2020. References in relevant review studies and published meta-analysis/systematic reviews will also be retrieved. Search strategies for all databases will be described.

Main outcome(s): The primary outcome will be PFS (progression-free survival): the time from randomization to death or any disease progression event.

Data management: For each study, the following information will be extracted into Excel by two authors (XXX and XXX) independently: the first author's name, the published year, source of funding, country, setting, inclusion criteria, exclusion criteria, diagnostic criteria, sample sizes, age of patients, hormone receptor status, line of treatment, disease status, baseline performance status, HER2 status,

metastatic sites, previous treatment, time of follow-up, intervention, dosage of intervention, effect sizes of intervention.

Quality assessment / Risk of bias analysis: Two authors will independently assess the risk of bias in the included studies with the help of measures displayed in Cochrane Handbook V.5.1.0 for Systematic Reviews of Interventions. Any disagreement will be coordinated by the third author to research consensus.

Strategy of data synthesis: Standard pairwise meta-analysis will be performed by R software. Pooled ORs/HRs/RRs with 95% CI will be calculated for dichotomous outcomes, mean differences (MDs) with 95% CI for continue outcomes. The random effect model will be used to perform meta-analysis. Heterogeneity of treatment effects across trials will be assessed by p value and I2 statistics. If the p value 50%, we will explore sources of heterogeneity, subgroup analysis and meta-regression will be conducted when the factors inducing heterogeneity were identified. Where the factors inducing heterogeneity were not identified, we will pool the data in random effect model, however our confidence on the study findings will be compromised. Funnel plot will be used to test potential publication bias. A Bayesian network meta-analysis will be performed by R software. The random effect models with vague priors for multi-arm trials developed by Lu and Ade will be used. The pooled estimation and the probability of which drug is the best will be obtained by the Markov Chains Monte Carlo method. Three Markov Chains will be run simultaneously with different arbitrarily chosen initial values. The model convergence will be assessed by trace plots and Brooks-Gelman-Rubin plots. The results of dichotomous outcomes will be reported as posterior medians of OR/HR/RR credible intervals (CrIs). The surface under the cumulative ranking area (SUCRA) will be calculated to summary and report the probability values. SUCRA values will be expressed as percentages; SUCRA value will be 100% for the best treatment, while SUCRA value will be 0% for the worst treatment. Evidence inconsistency and clinical similarity in patient characteristics and settings across trials will be carefully assessed. Network geometry will be performed by R software. Network geometry will use nodes to represent different interventions and edges to represent the head-to-head comparisons between interventions.

Subgroup analysis: We plan to conduct subgroup analysis for the primary outcome where data is available according to hormone receptor status of participants: hormone receptor positive (estrogen receptor positive and/or progesterone receptor positive) and hormone receptor negative (estrogen receptor negative and progesterone receptor negative).

Sensibility analysis: None.

Language: English/Chinese.

Country(ies) involved: China.

Keywords: anti-HER2 agents, chemotherapy, HER2-positive, metastatic breast cancer, network meta-analysis.

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