INPLASY PROTOCOL

To cite: Xie et al. Efficacy and Safety of PD-(L)1 inhibitors plus Chemotherapy versus Chemotherapy in Treatment for Triple Negative Breast Cancer: A meta-Analysis of Randomized Control Trials. Inplasy protocol 2020120070. doi: 10.37766/inplasy2020.12.0070

Received: 11 December 2020

Published: 12 December 2020

Corresponding author:
Xie Xiao
xiexiao18@mails.jlu.edu.cn

Ming Yang
yangming@jlu.edu.cn

Author Affiliation:
Department of Breast Surgery, The First Hospital of Jilin University

Support: **None.**

Review Stage at time of this submission: **Data analysis.**

Conflicts of interest:
None.

Efficacy and Safety of PD-(L)1 inhibitors plus Chemotherapy versus Chemotherapy in Treatment for Triple Negative Breast Cancer: A meta-Analysis of Randomized Control Trials

Xie, X[1]; Zhang, Z[2]; Wei, X[3]; Yang, M[4].

Review question / Objective: **Efficacy and Safety of PD-(L)1 inhibitors plus Chemotherapy versus Chemotherapy in Treatment for Triple Negative Breast Cancer.**
Condition being studied: **This study included 7 RCTs , a total of 4565 patients, our end points were the rate of pathological complete response (pCR) , progress free survival rate (PFS%) , overall survival rate (OS%) and incidence of adverse events (AEs ≥grade 3) .According to heterogeneity between studies, the RR (relative risk) 、HR (hazard ratio) and 95%confidence interval (CI) of each study end point were calculated by using fixed or random effect model, Revman 5.3 and Stata 12.0 were used for meta- analysis.The data analysis is ongoing.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 December 2020 and was last updated on 12 December 2020 (registration number INPLASY2020120070).

INTRODUCTION

Review question / Objective: **Efficacy and Safety of PD-(L)1 inhibitors plus Chemotherapy versus Chemotherapy in Treatment for Triple Negative Breast Cancer.**

Condition being studied: **This study included 7 RCTs , a total of 4565**

patients, our end points were the rate of pathological complete response (pCR), progress free survival rate (PFS%), overall survival rate (OS%) and incidence of adverse events (AEs ≥grade 3). According to heterogeneity between studies, the RR (relative risk),HR (hazard ratio) and 95%confidence interval (CI) of each study end point were calculated by using fixed or random effect model, Revman 5.3 and Stata 12.0 were used for meta-analysis.The data analysis is ongoing.

METHODS

Search strategy: the Cochrane Library, MEDLINE, PubMed ,Embase, Wan fang, Chinese National Knowledge Infrastructure/ #1 immunotherapy #2 Immunotherapies #3 #1OR #2/ #4chemotherapy/ #5Therapy, Drug/ #6Drug Therapies/ #7Chemotherapies/ #8 4 / #OR #5OR #6OR #7 / #9 randomized controlled trial/ #10randomized controlled trial/ #11random/ #12controlled clinical trial / #13 #9 OR #10OR #11OR #12OR / #14 ER-Negative PR-Negative Her2-NegativeBreast Neoplasms / #15ER Negative PR Negative HER2 Negative Breast Neoplasms / #16Triple-Negative Breast Cancer; Breast Cancer / #17Triple-Negative;Breast cancers / #18Triple-Negative Breast Neoplasm / #19Breast Neoplasm, Triple-Negative / #20Breast Neoplasms, Triple-Negative / #21Triple Negative Breast Neoplasm / #22Triple-Negative Breast Neoplasms / #23ER-Negative PR-Negative HER2-Negative Breast Cancer / #24ER Negstive PR Negative HER2 Negative Breast Cancer / #25Triple Negative Breast Caner/ #26 #14OR #15OR #16OR #17OR #18OR #19OR #20OR #21OR #22OR #23OR #24OR #25 / #3 AND #13 AND #26 / #26 #14OR #15OR #16OR #17OR #18OR #19OR #20OR #21OR #22OR #23OR #24OR #25 / #3 AND #13 AND #26.

Participant or population: > 18 years old, patients must provide representative tumor specimens, biopsy tissues were confirmed by immunohistochemistry as triple negative breast cancer: estrogen receptor(ER) (-), progestogen receptor (PR) (-) , human epidermalgrowth factor receptor-2 (HER2) (-), and these specimens can be evaluated by immunohistochemistry for pd-l1 expression.

Intervention: PD-1/PD-L1 inhibitor.

Comparator: PD-(L)1 inhibitor plus chemotherapy vs Chemotherapy / Chemotherapy+placebo.

Study designs to be included: Randomized controlled trial. The study must be a prospective trial in patients with triple negative breast cancer, and patients would be randomized to receive PD- (L) -1 inhibitors plus chemotherapy or monotherapy (chemotherapy alone) or placebo combined with chemotherapy.

Eligibility criteria: 1: Study type: Randomized controlled trial. The study must be a prospective trial in patients with triple negative breast cancer, and patients would be randomized to receive PD- (L) -1 inhibitors plus chemotherapy or monotherapy (chemotherapy alone) or placebo combined with chemotherapy. 2:Study subjects: > 18 years old, patients must provide representative tumor specimens, biopsy tissues were confirmed by immunohistochemistry as triple negative breast cancer: estrogen receptor(ER) (-) , progestogen receptor (PR) (-) , human epidermalgrowth factor receptor-2 (HER2) (-), and these specimens can be evaluated by immunohistochemistry for pd-l1 expression. 3: Intervention: The experimental group received PD- (L) 1 inhibitors on the basis of chemotherapy. It can include pembrolizumab, atezolizumab, durvalumab, nivolumab and avelumab. The

control group received either placebo plus chemotherapy or chemotherapy alone. 4: Outcome: After treatment with two different regimens, the rate of PCR 、incidence of adverse events (GRADE ≥3) , differences PFS rate and OS rate in the two groups was analyzed.

Information sources: PubMed; Embase; The Cochrane Library; Web of Science; CNKI WanFang databases. abstracts of ESMO(2020) ASCO（2020）SABCS (2020).

Main outcome(s): the rate of pCR; the rate of PFS: the rate of OS; incidence of adverse events (≥Grade 3).

Data management: All information will be extracted by 2 of the independent authors (XX and ZZH) according to predetermined criteria form. Disagreement will be resolved by consulting a third author (WX), and the extracted data as following: study ID, first author（s）, publication year, study phase, sample size, treatment stage, disease stage, PD-L1 test, details of treatment in experimental group and the control group. STATA12.0 software will be used for data synthesis and analysis, when the outcome data is a binary variable, select the relative risk（RR）as the effcet scale; when the outcome data is a continuous variable, use the mean difference（MD）and standardized mean difference（SMD）as an effect scale, both calculate by 95% confidence interval

Quality assessment / Risk of bias analysis: We evaluate the quality of all the included studies according to the Cochrane systematic review manual. The risk of bias assessment of the included RCTs will be assessed by using the risk of bias assessment tool of the Cochrane Handbook,,version 5.1.0, which includes 7 items as following:random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, other bias.This evaluation will be conducted by independent reviewers(XX and ZZH) by using the Revman 5.3 software.

Strategy of data synthesis: STATA12.0 software will be used for data synthesis and analysis, when the outcome data is a binary variable, select the relative risk（RR）as the effcet scale; when the outcome data is a continuous variable, use the mean difference（MD）and standardized mean difference（SMD）as an effect scale, both calculate by 95% confidence interval.

Subgroup analysis: PD-L1 positive triple negative breast cancer which tested by the PD-L1 IHC22C3pharmDx assay or VentanaSP142 or VentanaSP263.

Sensibility analysis: When the fixed effect model was applied, P > 0.1, I = 0%, no heterogeneity and low sensitivity were found. Sensitivity analysis of the influence of a single study on the total merge effect was performed using Stata 12.0 software. The ratio of pCR obtained by combination therapy and the incidence of adverse events were all within the confidence interval and close to the total effect size, indicating low sensitivity and relatively robust and reliable results.

Language: No limits about the language.

Country(ies) involved: China.

Keywords: PD-1/PD-L1, atezolizumab, pembrolizumab, immunotherapy , metastatic triple negative breast cancer, systematic review, meta-analysis.

Contributions of each author:
Author 1 - Xie Xiao - The author initiated this system review and meta-analysis, and participated in each process and drafted the manuscript.
Email: xiexiao18@mails.jlu.edu.cn

Author 2 - Zhang Zhihao The author searched and selected the literatures, extracted the data, assessed the risk of bias and evaluated the quality of included RCTs.
Email: zhangzh19@mails.jlu.edu.cn
Author 3 - Wei Xue - The author contributed to the development of the selection criteria, and the risk of bias assessment strategy.
Email: wei20@mails.jlu.edu.cn
Author 4 - Yang Ming - The author read, provided feedback and approved the final manuscript.
Email: yangming@jlu.edu.cn