Efficacy and Safety of Neoadjuvant Immunotherapy in Triple Negative Breast Cancer: Meta-analysis of randomized controlled trials

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Abstract

Aim: In this meta-analysis; The efficacy and safety of randomized controlled trials (RCTs) using immunotherapy in the neoadjuvant treatment of triple negative breast cancer were investigated.

Material and Method: To determine the studies to be evaluated in this meta-analysis, PubMed, Cochrane Library databases, and the studies published/presented in ASCO, ESMO, and SABCS congresses were thoroughly searched. Studies published/presented until January 01, 2021, were included. PCR, by definition, was defined as the absence of invasive cancer cells in the breast and axillary lymph nodes (ypT0 / Tis and N0). If there were at least two studies that shared the same subgroup results, subgroup analyzes were also performed. This meta-analysis was performed using Review Manager, version 5.4 (RevMan), a proprietary software provided by Cochrane Collaboration.

Results: A total of 5 RCTs were included in the study, and 1498 patients were analyzed. In a pooled analysis of these studies, pCR was 58.8% in the immunotherapy arm and 42.6% in the placebo arm. According to the random-effects model, OR was found to be 1.77 (95% CI 1.23-2.56). In the pooled analysis of 3 studies reporting results according to PD-L1 level, immunotherapy significantly increased pCR in the PD-L1 positive group (67% vs. 49%, OR: 1.99, 95% CI 1.47-269). In the PD-L1 negative group, although immunotherapy increased pCR numerically, it was not statistically significant (42% vs. 33%, OR: 1.44, 95% CI 0.97-2.14). According to the lymph node status, the results were shared in 2 studies. In the joint analysis of these two studies, pCR was significantly increased with immunotherapy in those with positive lymph nodes (63% vs. 39%, OR: 2.52 95% CI 1.69-3.77). In those with negative lymph nodes, although immunotherapy increased pCR numerically, the difference was not significant (62% vs. 54%, OR: 1.36 95% 0.94-1.97).

Conclusion: The addition of immunotherapy to neoadjuvant chemotherapy increases pCR. This increase was especially pronounced in high-risk patients with lymph node-positive and in the group with positive for PD-L1.

Introduction

In recent years, important study results on immunotherapy in neoadjuvant treatment of triple negative breast cancer have been published. Although most of these studies show an increase in pathological complete response rates (pCR) with immunotherapy, there are conflicting results. In this meta-analysis; The efficacy and safety of randomized controlled trials (RCTs) using immunotherapy in the neoadjuvant treatment of triple negative breast cancer were investigated.

Material And Method

This systematic review and meta-analysis were conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) guidelines.

Search strategy

To determine the studies to be evaluated in this meta-analysis, PubMed (Medline), Cochrane Library, EMBASE databases, and the studies published/presented in ASCO, ESMO, and San Antonio Breast Cancer Symposium (SABCS) congresses were comprehensively searched.

Studies published or presented until 01 January 2021 were screened using the following keywords: (neoadjuvant OR preoperative OR perioperative) AND (TNBC OR triple negative breast cancer OR triple negative breast neoplasm OR triple negative) AND (immunotherapy OR immune checkpoint inhibitor OR pembrolizumab OR atezolizumab OR durvalumab OR nivolumab OR ipilimumab OR cemiplimab). Published reviews and reference lists of important studies on neoadjuvant immunotherapy in triple negative breast cancer were also checked to ensure that no studies were overlooked.

Inclusion criteria for publications: randomized controlled trials, immunotherapy in at least one of the study arms in the neoadjuvant treatment of triple negative breast cancer, studies with shared data in congress presentations were included, even if the full text was not published. Preclinical and phase 1 studies, uncontrolled, metastatic stage studies, and case reports were excluded.

Study selection and data extraction

In this meta-analysis, two researchers (BA and ST) independently extracted the data. The following information was recorded for each study: author name, study name, publication year, publication journal, number of patients registered, median age, disease stage, subgroup analyzes, immunotherapy dose and frequency used, dose and frequency of conventional chemotherapy agents used, pCR, if applicable survival times, adverse events and safety data. Any discrepancies in study selection or data extraction among reviewers were resolved by interviewing a third reviewer (CK).

In this meta-analysis, the term efficacy refers to pCR. PCR, by definition, was defined as the absence of invasive cancer cells in the breast and axillary lymph nodes (ypT0 / Tis and N0). If there is a difference in the definition of pCR in the studies, the ypT0 / TisN0 results of the study that made different definitions were obtained and analyzed in order to make the analysis homogeneous. Since neoadjuvant immunotherapy studies are up to date, it is known that survival times are not yet mature. If median event-free survival, disease-free survival, or overall survival data are reported, they will also be registered for analysis. The study results will be evaluated over intention-to-treat (ITT) populations, and if the results of the ITT population have not yet been disclosed, the data with the results disclosed will be used.

Statistical analysis

This meta-analysis was performed using Review Manager, version 5.4 (RevMan), a proprietary software provided by Cochrane Collaboration. Calculation of the pCR; Odds ratio (OR) and 95% confidence interval (CI) were calculated based on the number of events obtained from the studies using the Mantel - Haenszel method. Risk ratio (RR) and 95% CI were calculated using the Mantel - Haenszel method for

adverse events and drug withdrawal rates belonging to safety data. The I^2 test was used to evaluate the statistical heterogeneity between studies. If heterogeneity was important (p >0.05 or $I^2 \leq 50\%$) fixed-effect model was used, otherwise (p <0.05 or I^2>50%) random effect model was used. If heterogeneity was detected, a sensitivity analysis was performed by excluding each run individually, then recalculating the pooled outcome estimates. P <0.05 was considered statistically significant.

The randomized controlled studies' methodological quality included in the study was examined using the Cochrane Collaboration Risk of Bias Tool under the following headings: selection bias, performance bias, detection bias, attrition bias, and reporting bias. Publication bias was assessed visually according to the funnel plot chart.

Results

Features of the included studies

As a result of examining databases and congress papers, 423 studies were obtained. As a result of the evaluations made, it was seen that five studies were suitable for analysis.[1-5] The flow chart of the literature review and selection/exclusion process is shown in Figure 1. There were 2070 patients in all of these studies, but 1498 results, whose results were shared, were evaluated. Of these patients, 821 were in the immunotherapy arm, and 677 were in the placebo arm. Three of the five studies included were phase 3 (IMpassion031, KEYNOTE-522, and NeoTRIPaPDL1 trials), and two were phase 2 (GeparNuevo and I-SPY2 trials).

NeoTRIPaPDL1 study was presented in 2019 SABCS, and its full text has not been published yet. The data of this study were taken from the congress presentation. It was available in patients with hormone receptors positive in study I-SPY2, but only data from patients with TNBC were used. In the IMpassion031 and KEYNOTE-522 studies, immunotherapy agents were also continued in the adjuvant setting, and it was completed for one year, and in the other three studies, immunotherapy was given only in the neoadjuvant environment. Detailed features of the included studies are presented in Table 1. Since the median survival results were not shared in any trial, survival analyzes were not performed.

Pathological complete response rates

In the pooled analysis of five studies (n: 1498), pCR was found to be 58.8% in the immunotherapy arm and 42.6% in the placebo arm, with the difference being statistically significant. According to the random-effects model, OR was found to be 1.77 (95% CI 1.23-2.56) (I^2 = 62%; p =0.03). In the sensitivity analysis performed due to heterogeneity, the estimated absolute OR was 1.57 (95% CI 1.24-2.00) after the I-SPY2 study was excluded (n: 1389) (I^2 = 15%; p =0.32) (Figure 2).

In the pooled analysis of 3 studies reporting ypT0 / TisN0 result according to PD-L1 level, immunotherapy significantly increased pCR in the PDL-1 positive group (67% vs. 49%, OR: 1.99, 95% CI 1.47-2.69). In the PDL1 negative group, although immunotherapy increased pCR numerically, it was not statistically

significant (42% vs. 33%, OR: 1.44, 95% CI 0.97-2.14). No heterogeneity was observed in the included studies (I^2 = 0%; p =0.51) (Figure 3).

According to lymph node status, results were shared in 2 studies. In the pooled analysis of these two studies, pCR significantly increased with immunotherapy in lymph node-positive patients (63% vs. 39%, OR: 2.52 95% CI 1.69-3.77), although immunotherapy increased pCR numerically in lymph node-negative patients, the difference was not significant (62% vs. 54%, OR: 1.36 95% 0.94-1.97). No significant heterogeneity was observed in studies included for lymph node status either (I^2 = 43%; p = 0.15) (Figure 4).

Safety

In a pooled analysis of the three studies reporting grade 3-4 adverse event results, more grade 3-4 adverse events were observed in the immunotherapy arm (74% vs. 67%, RR: 1.07, 95% 1.01-1.14). There was no heterogeneity between studies (I^2 = 0%; p =0.88). Analysis of 4 studies reporting the results of clinically serious adverse events revealed more serious adverse events in the immunotherapy arm (29% vs. 18%, RR: 1.52, 95% CI 1.04-2.23). High heterogeneity was found between studies (I^2 = 70%; p =0.02). In the sensitivity analysis performed due to heterogeneity, the estimated absolute RR was found to be 1.74 (95% CI .29, 2.35) in the analysis of 3 phase 3 studies after the GeparNuevo study was removed (I^2 = 35%; p =0.21). The discontinuation rate of any drug in the study due to an adverse event was greater in the immunotherapy arm (23% vs. 17%, OR: 1.45 [1.19, 1.76]). There was no significant heterogeneity between studies (I^2 = 23%; p =0.28) (Figure 5). There are studies reporting death due to immune-related adverse events, albeit in a very low number.2

Quality of studies and Publication bias

Evaluation of the quality of the RCTs selected is presented in Figure 6. Since the number of randomized studies included in the study is small, bias assessment may not be appropriate. However, as there is asymmetry at the base of the funnel plot graph, bias cannot be ignored (Figure 7).

Conclusion

The addition of immunotherapy to neoadjuvant chemotherapy increases pCR. This increase was especially pronounced in high-risk patients with lymph node-positive and in the group with positive for PD-L1. Adverse events were observed more frequently in the immunotherapy arm, and deaths due to immune-related adverse events were reported. According to the data we obtained from previous studies, obtaining pCR with neoadjuvant therapy in breast cancer is associated with prolonged survival. However, this is not yet clear for immunotherapies. After the survival results of these studies are announced, the place of immunotherapy in neoadjuvant therapy will be clearer. In addition, safety concerns have been raised due to the small number of immune-related deaths observed in the neoadjuvant stage. As a matter

of fact, at the February 2021 FDA meeting, it was stated that it was early to make a decision according to the current efficacy and safety data, and clinical use approval has not been given yet.

Declarations

The authors did not report any conflict of interest.

No financial support was received.

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Table

Table 1 is available in the Supplementary Files.

Figures

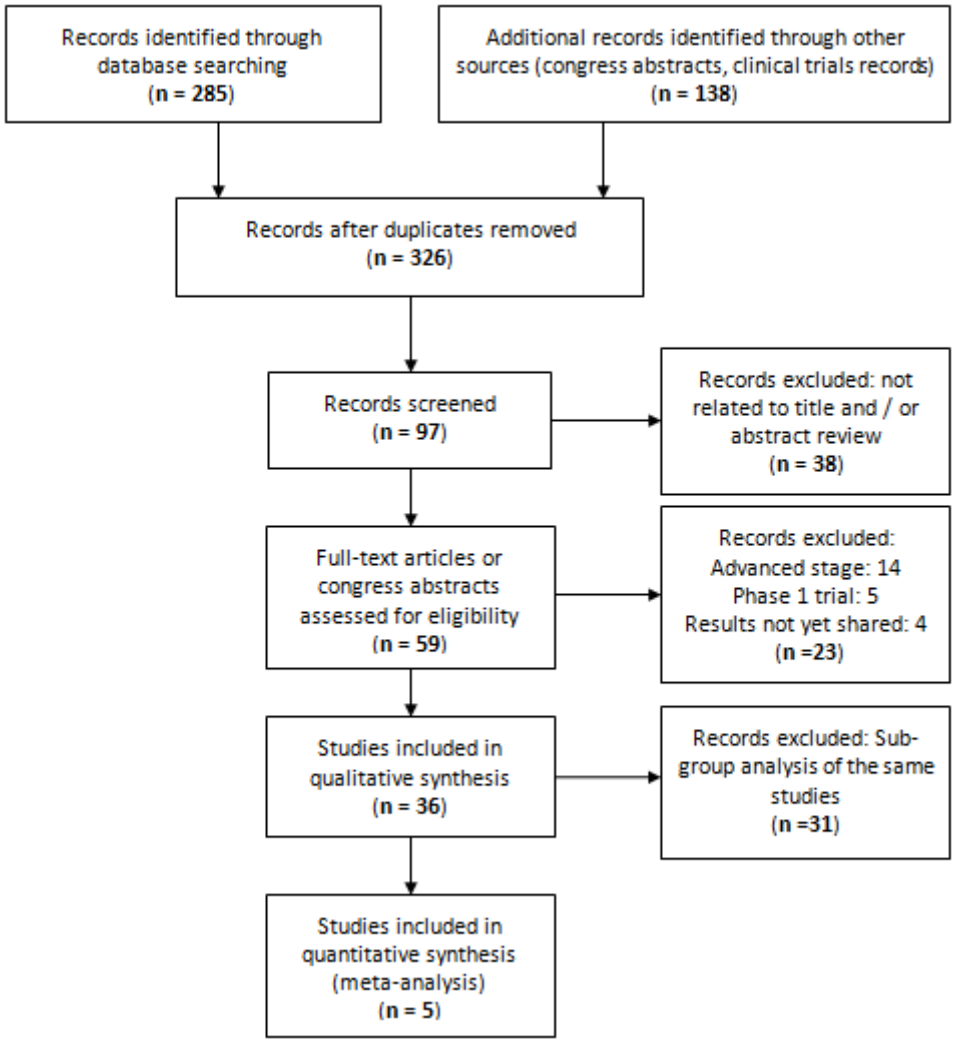

Figure 1

PRISMA flow diagram of study retrieval and selection

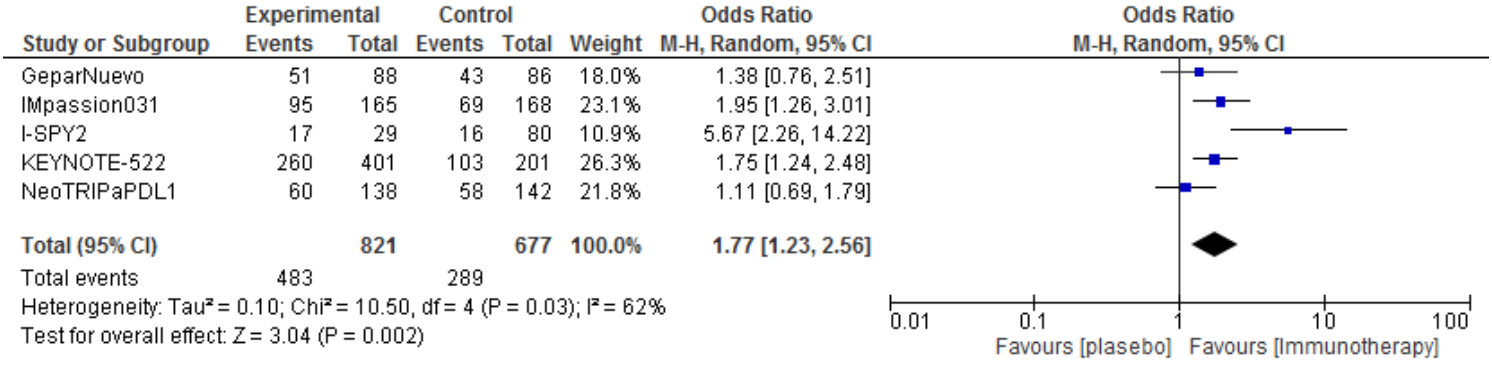

Figure 2

Forest plot of neoadjuvant immunotherapy efficiency

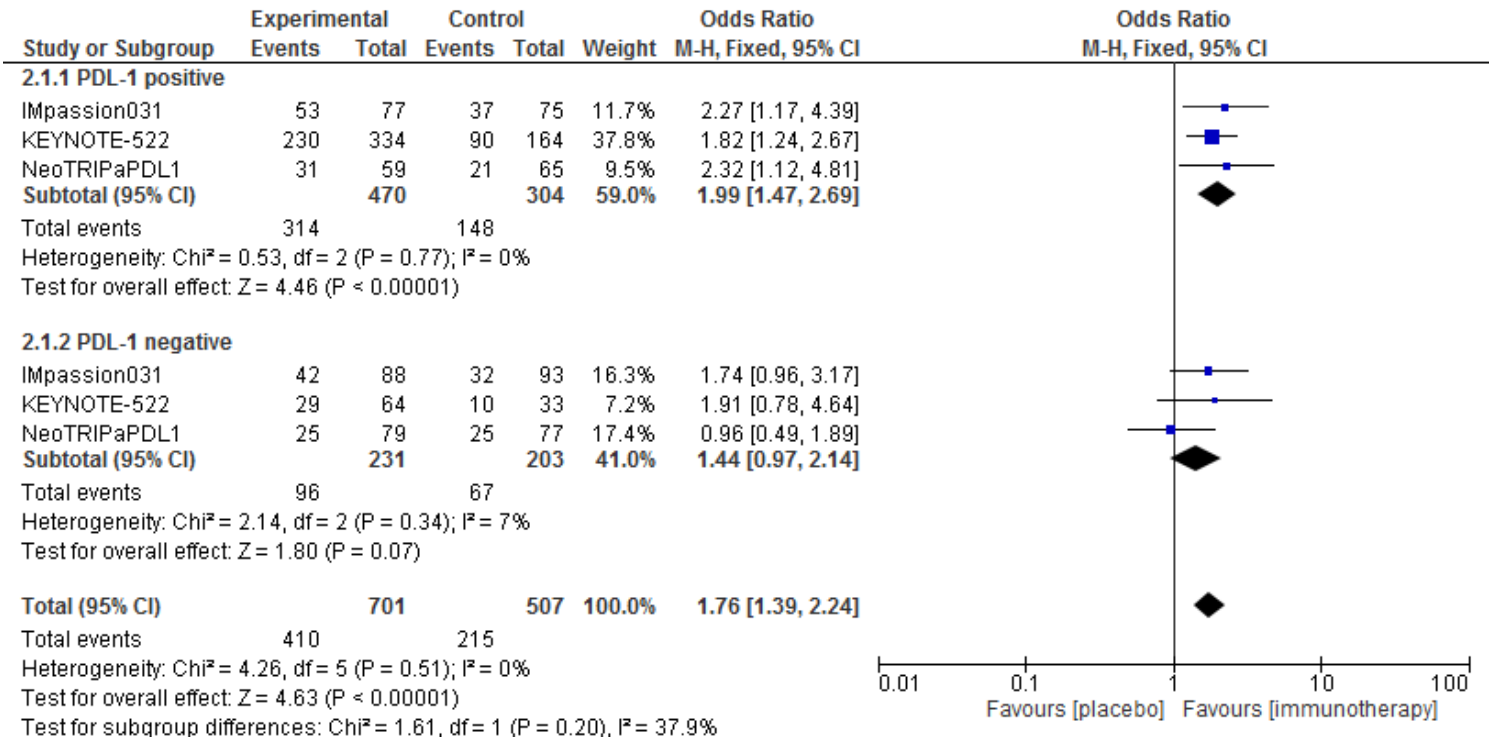

Figure 3

Forest plot of subgroup analysis of PCR according to PDL-1 status. A) PDL-1 positive patients, B) PDL-1 negative patients

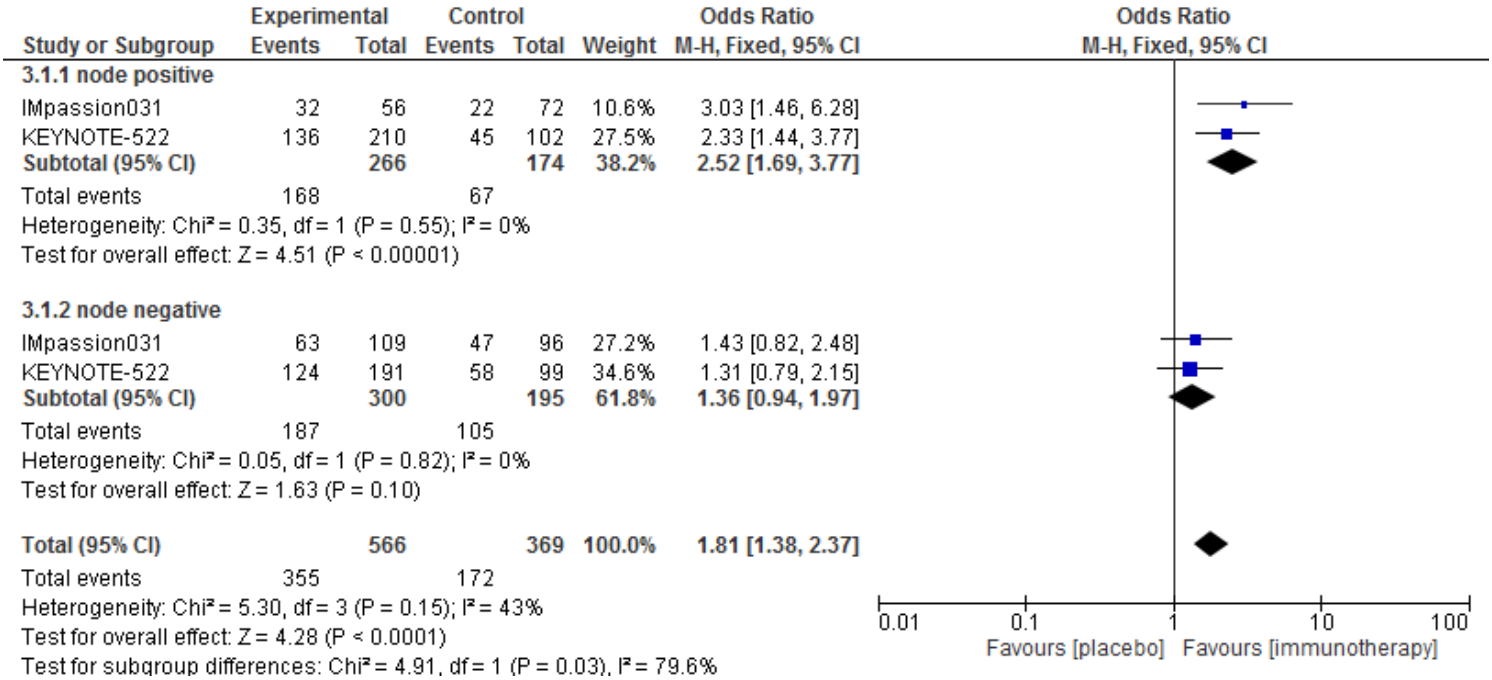

Figure 4

Forest plot of subgroup analysis of PCR according to lymph node status A) Lymph node-positive patients B) Lymph node-negative patients

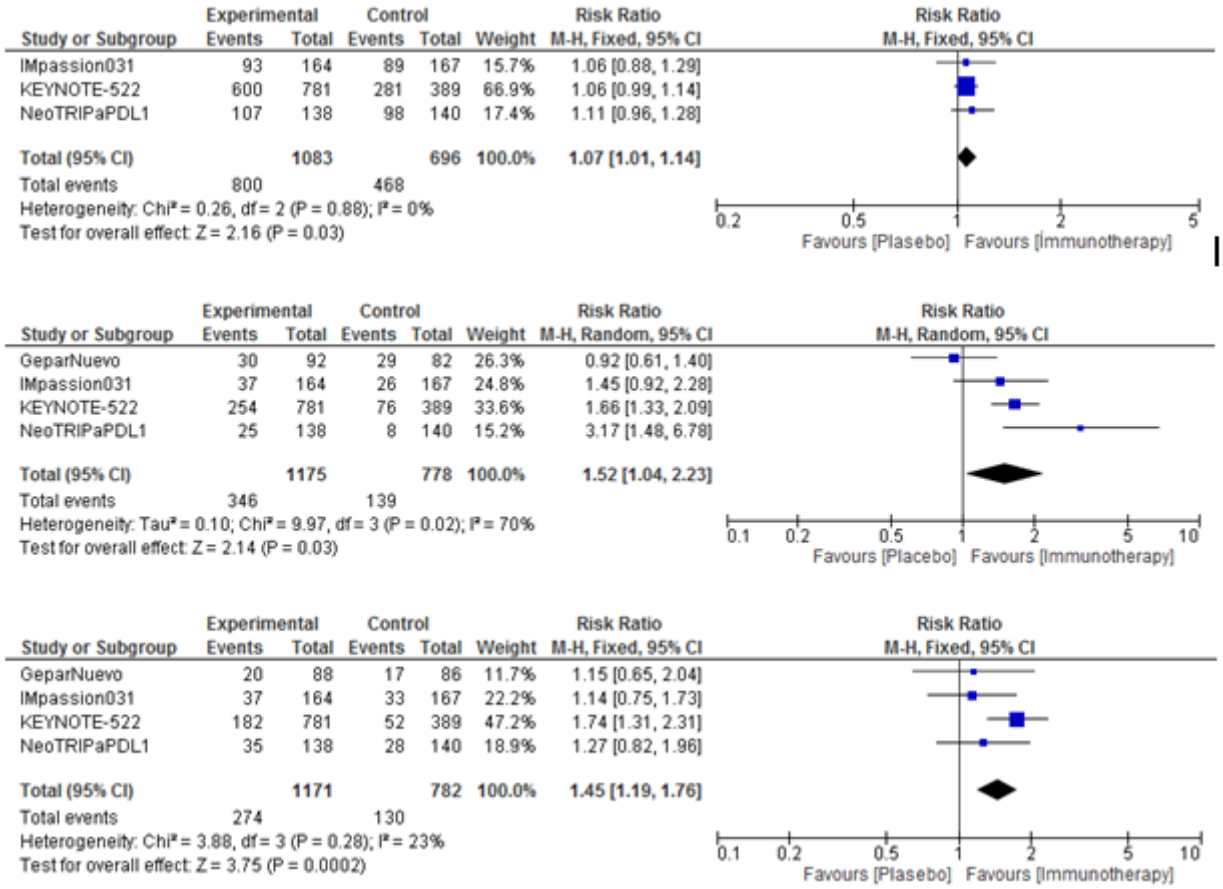

Figure 5

Forest graph of security data. A) Grade 3-4 adverse event, B) Serious adverse event, C) Discontinuation of any drug due to an adverse event

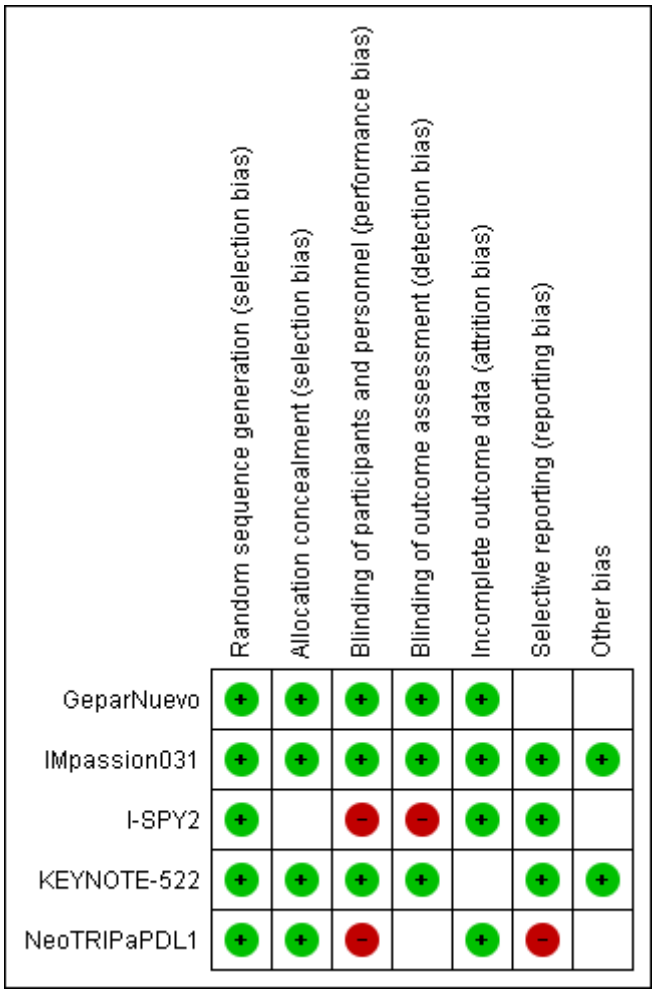

Figure 6

Quality of included studies

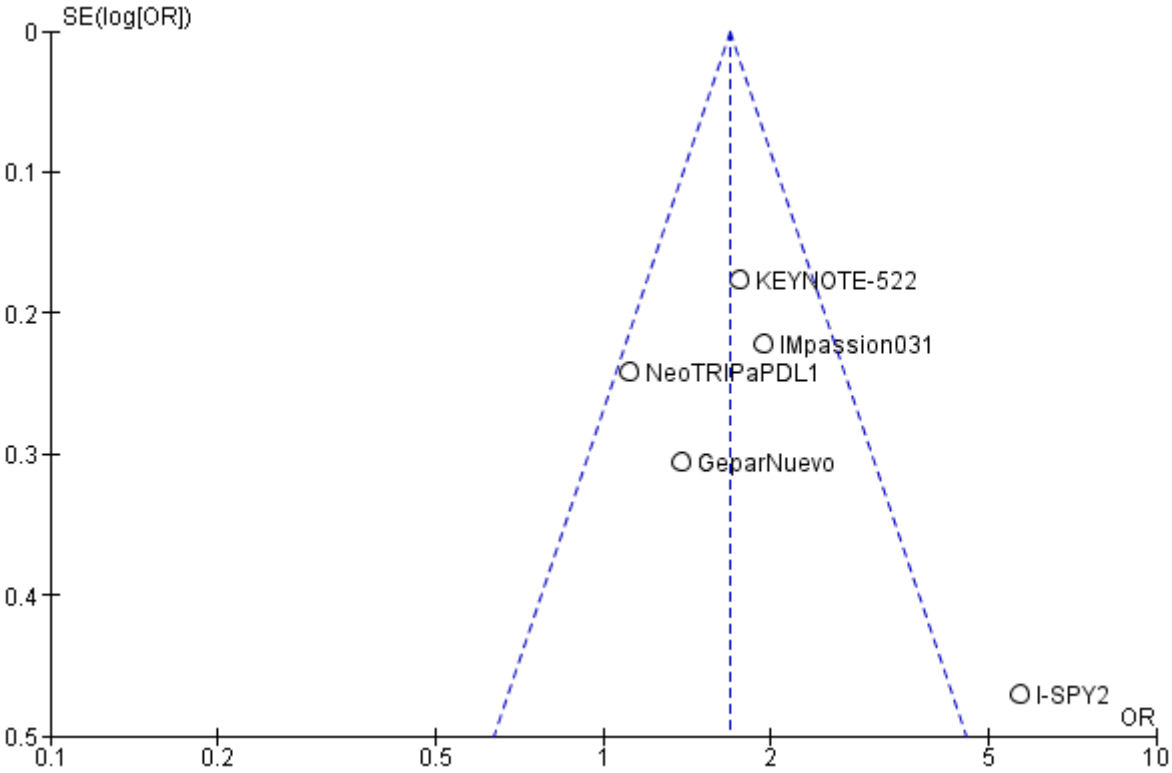

Figure 7

Funnel plot of included studies

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.png