Systematic Review and Meta-Analysis

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The efficacy and safety of neoadjuvant buparlisib for breast cancer

A meta-analysis of randomized controlled studies

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Abstract

Introduction: The efficacy of neoadjuvant buparlisib for breast cancer remains controversial. We conduct a systematic review and meta-analysis to explore the influence of neoadjuvant buparlisib versus placebo for breast cancer.

Methods: We search PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases through May 2019 for randomized controlled trials (RCTs) assessing the efficacy and safety of neoadjuvant buparlisib versus placebo for breast cancer. This meta-analysis is performed using the random-effect model.

Results: Four RCTs are included in the meta-analysis. Overall, compared with control group for breast cancer, neoadjuvant buparlisib can substantially reduce progressive disease (risk ratios [RR] = 0.66; 95% confidence interval [CI] = 0.52–0.82; $P = .0003$) and improve stable disease (RR = 1.29; 95% CI = 1.02–1.64; $P = .04$), but has no notable influence on overall response rate (RR = 1.32; 95% CI = 0.84–2.06; $P = .22$), clinical benefit rate (RR = 1.06; 95% CI = 0.79–1.43; $P = .69$). Neoadjuvant buparlisib results in the increase in adverse grade 3/4 adverse events including increased alanine aminotransferase (ALT) (RR = 11.87; 95% CI = 5.65–24.90; $P < .00001$), increased aspartate aminotransferase (AST) (RR = 6.50; 95% CI = 4.14–10.21; $P < .00001$) and hyperglycaemia (RR = 36.65; 95% CI = 10.44–128.68; $P < .00001$), as well as serious adverse events (RR = 1.47; 95% CI = 1.23–1.76; $P < .0001$) compared to placebo. Deaths is found to be similar between two groups (RR = 0.88; 95% CI = 0.75–1.04; $P = .13$).

Conclusions: Neoadjuvant buparlisib may provide some efficacy for breast cancer, but leads to the increase in serious adverse events.

Abbreviations: AKT = protein kinase B, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CI = confidence interval, HER2 = human epidermal growth factor receptor-2, mTOR = mammalian target of rapamycin, PI3K = phosphoinositide 3 kinase, PIK3CA = phosphatidylinostitol 3-kinase catalytic subunit, RCTs = randomized controlled trials, RR = risk ratios.

Keywords: breast cancer, buparlisib, efficacy, randomized controlled trials, safety

1. Introduction

Approximately 75% of breast cancers have the positive expression of human epidermal growth factor receptor-2 (HER2).[1–3] Previous studies reveal that HER2-targted drugs such as trastuzumab, lapatinib, and pertuzumab, are combined with chemotherapy to improve pathological complete response rates in patients with HER2+ early breast cancer.[4–7] Dual HER2-targeted strategy is found to potentially increase the efficacy than a single HER2-targeted agent.[7–9] The majority of patients with HER2+ breast cancer respond well to HER2-targeted therapy, but it is still a challenge for the resistance to HER2-targeted therapy in some breast cancer patients.[10–13]

One of the mechanisms responsible for HER2 treatment resistance is associated with the activation of phosphoinositide 3 kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) [PI3K/AKT/mTOR] pathway.[14–16] Alterations in the PI3K/AKT/mTOR pathway, such as phosphatidylinostitol 3-kinase catalytic subunit (PIK3CA) mutations, lead to the resistance to HER2-targeted agents, and PI3K inhibitors are found to hold the promise in reversing this resistance. Targeting the PI3K pathway in combination with HER2 targeting may improve the outcomes for HER2+ breast cancer.[17–19] Buparlisib, serves as an orally bioavailable pan-PI3K inhibitor targeting all the known isoform of PI3K (p110α, β, γ, and δ), and shows the synergistic growth inhibitory activity in combination with HER2-targeted agents in preclinical studies.[20] Some clinical trials have confirms the efficacy of buparlisib for breast cancer.[21–23]

Current evidence is insufficient for routine clinical use of neoadjuvant buparlisib for breast cancer. Recently, several studies have investigated the efficacy and safety of

Editor: Martin S. Staege.

Compliance with ethical standards.

The authors have no funding and conflicts of interest to disclose.

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How to cite this article: Luo Q, Lu H, Zhou X, Wang Y. The efficacy and safety of neoadjuvant buparlisib for breast cancer. Medicine 2019;98:44(e17614).

Received: 6 July 2019 / Received in final form: 17 September 2019 / Accepted: 20 September 2019

http://dx.doi.org/10.1097/MD.0000000000017614

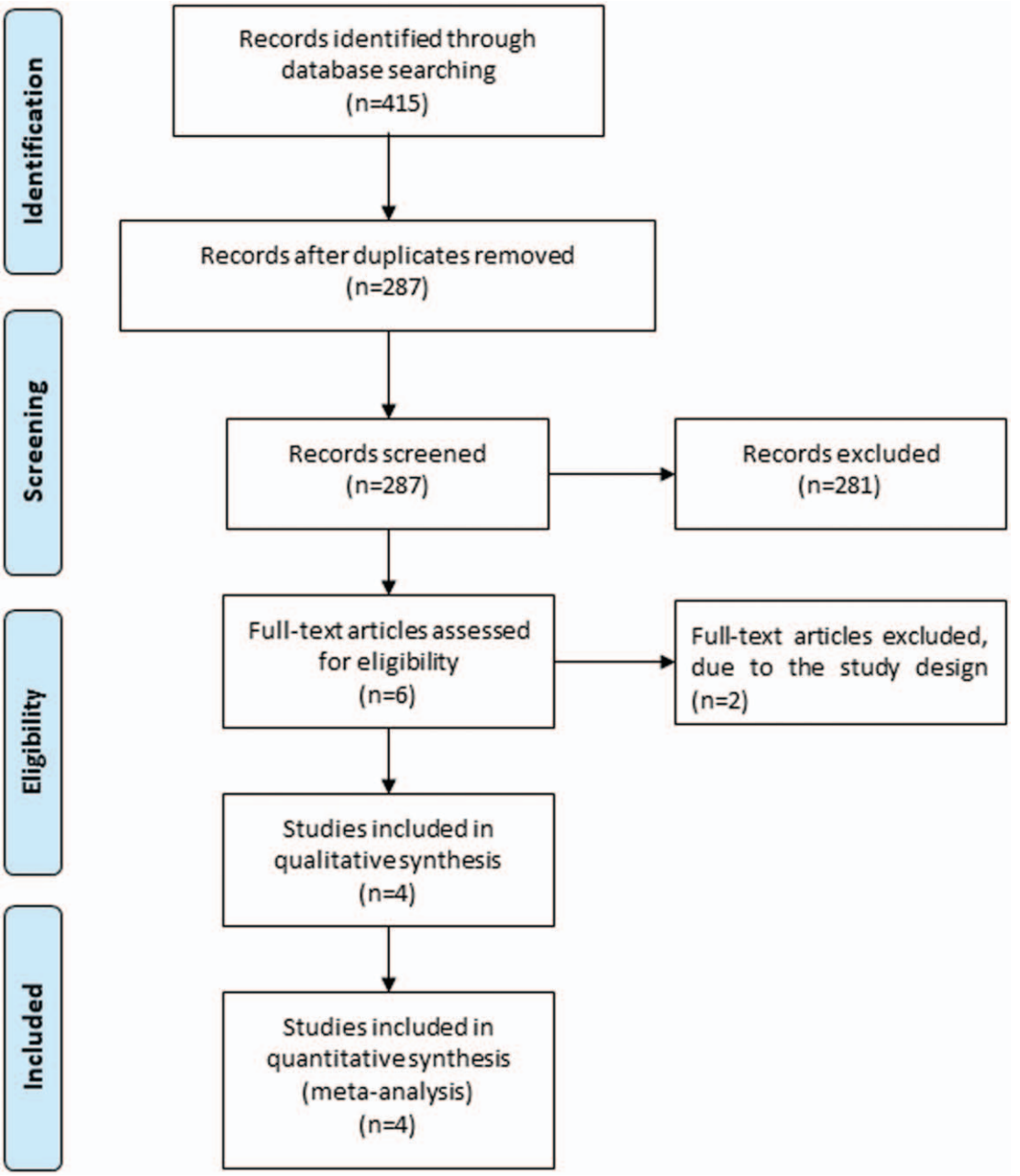

Figure 1. Flow diagram of study searching and selection process.

neoadjuvant buparlisib for these patients, but the results are conflicting.[24–26] This systematic review and meta-analysis of randomized controlled trials (RCTs) aim to assess the efficacy and safety of neoadjuvant buparlisib versus placebo for breast cancer.

2. Materials and methods

This systematic review and meta-analysis are performed based on the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement and Cochrane Handbook for Systematic Reviews of Interventions.[27,28] No ethical approval and patient consent are required because all analyses are based on previous published studies.

2.1. Literature search and selection criteria

We systematically search several databases including PubMed, EMbase, Web of science, EBSCO, and the Cochrane library from inception to May 2019 with the following keywords: buparlisib and breast cancer. The reference lists of retrieved studies and relevant reviews are also hand-searched and the process above is performed repeatedly in order to include additional eligible studies.

The inclusion criteria are presented as follows:

1. study design is RCT,
2. patients are diagnosed as breast cancer, and
3. intervention treatments are neoadjuvant buparlisib versus placebo.

Table 1

Characteristics of included studies.

		Buparlisib group						Control group						
NO.	Author	Number	Age	ECOG performance status 0 (n)	Activated PI3K pathway (n)	Negative HER2 (n)	Methods	Number	Age	ECOG performance status 0 (n)	Activated PI3K pathway (n)	Negative HER2 (n)	Methods	Jada scores
1	Di Leo 2018	289	60.0 (54.0–68.0), median (IQR)	173	–	–	Buparlisib (100 mg/day) plus intramuscular fulvestrant (500 mg)	143	62.0 (55.0–69.0)	91	–	–	Placebo plus intramuscular fulvestrant (500 mg)	5
2	Martin 2017	207	55 (25–84), median (range)	135	73	207	Oral buparlisib (100 mg/day) in combination with intravenous paclitaxel (80 mg/m^2/week)	209	56 (24–78)	146	74	207	Placebo in combination with intravenous paclitaxel (80 mg/m^2/week)	5
3	Loibl 2017	25	50.0 (35.0–72.0), median (range)	25	–	0	Oral buparlisib 100 mg/day and decrease to 80 mg/day plus trastuzumab (4 mg/kg followed by a weekly maintenance dose of 2 mg/kg) and paclitaxel 80 mg/m^2	25	50.0 (26.0–78.0),	25	–	0	Placebo plus trastuzumab (4 mg/kg followed by a weekly maintenance dose of 2 mg/kg) and paclitaxel 80 mg/m^2	4
4	Baselga 2017	576	62 (55–69), median (IQR)	333	188	137.6 ± 29.55	Oral buparlisib (100 mg/day) plus intramuscular fulvestrant (500 mg)	571	61 (54–68)	344	184	135.0 ± 38.49	Placebo plus intramuscular fulvestrant (500 mg)	5

ECOG = Eastern Cooperative Oncology Group, HER2 = human epidermal growth factor receptor 2, PI3K = phosphatidylinositol 3-kinase.

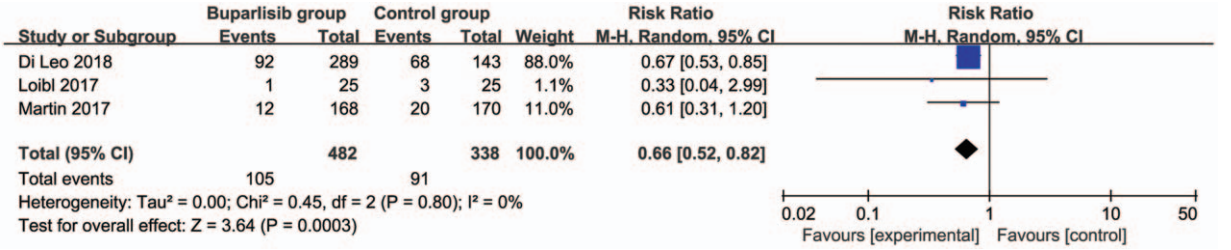

Figure 2. Forest plot for the meta-analysis of progressive disease.

2.2. Data extraction and outcome measures

Some baseline information is extracted from the original studies, and they include first author, number of patients, age, the number of Eastern Cooperative Oncology Group (ECOG) performance status 0, activated PI3K pathway and negative HER2, detail methods in two groups. Data are extracted independently by two investigators, and discrepancies are resolved by consensus. We have contacted the corresponding author to obtain the data when necessary.

The primary outcome is progressive disease. Secondary outcomes include stable disease, overall response rate, clinical benefit rate, the most common grade 3/4 adverse events (i.e. increased alanine aminotransferase [ALT] and aspartate aminotransferase [AST], hyperglycaemia), serious adverse events, and deaths.

2.3. Quality assessment in individual studies

The methodological quality of each RCT is assessed by the Jadad Scale which consists of three evaluation elements: randomization (0–2 points), blinding (0–2 points), dropouts and withdrawals (0–1 points).[29] One point would be allocated to each element if they have been conducted and mentioned appropriately in the original article. The score of Jadad Scale varies from 0 to 5 points. An article with Jadad score ≤ 2 is considered to be of low quality. The study is thought to be of high quality if Jadad score ≥ 3.[30]

2.4. Statistical analysis

We assess risk ratios (RR) with 95% confidence interval (CI) for dichotomous outcomes (progressive disease, stable disease, overall response rate, clinical benefit rate, the most common grade 3/4 adverse events (i.e. ALT, AST, hyperglycaemia), serious adverse events, and deaths). Heterogeneity is evaluated using the I^2 statistic, and $I^2 > 50\%$ indicates significant heterogeneity.[31] The random-effects model is used for all meta-analysis. We search for potential sources of heterogeneity for significant heterogeneity. Sensitivity analysis is performed to detect the influence of a single study on the overall estimate via omitting one study in turn or performing the subgroup analysis. Owing to the limited number (<10) of included studies, publication bias is not assessed. Results are considered as statistically significant for $P < .05$. All statistical analyses are performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

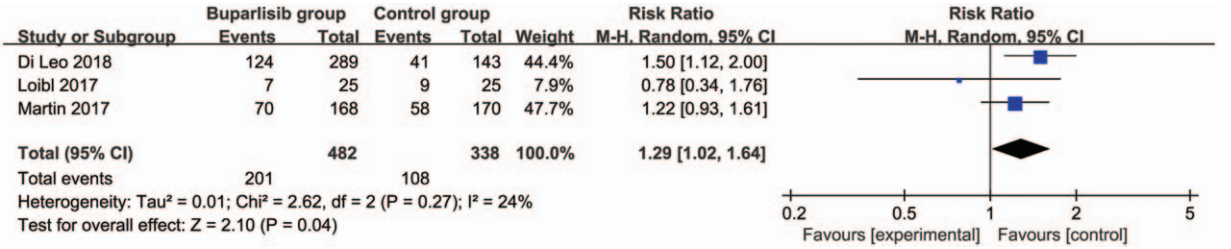

Figure 3. Forest plot for the meta-analysis of stable disease.

Figure 4. Forest plot for the meta-analysis of overall response rate.

Figure 5. Forest plot for the meta-analysis of clinical benefit rate.

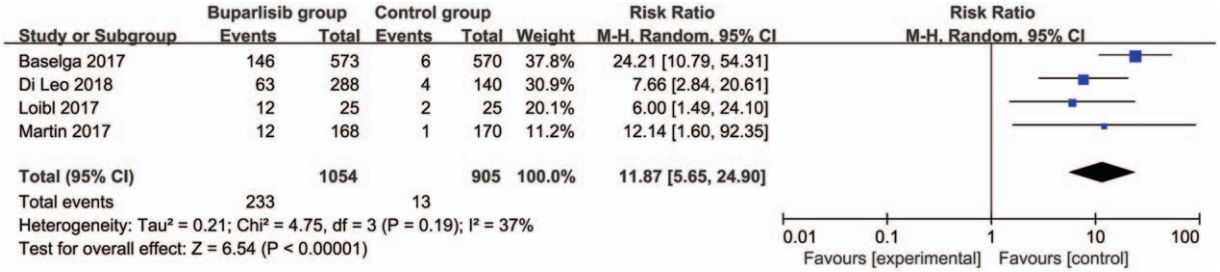

Figure 6. Forest plot for the meta-analysis of increased ALT.

3. Results

3.1. Literature search, study characteristics, and quality assessment

Figure 1 shows the detail flowchart of the search and selection results. 415 publications are searched after the initial search of databases. After the removal of duplicates, 287 publications are further evaluated. 281 papers are excluded after checking the titles/abstracts. Two studies are removed because of the study design and four RCTs are ultimately included in the meta-analysis.[24–26,32]

The baseline characteristics of four included RCTs are shown in Table 1. These studies are published between 2017 and 2018, and the total sample size is 2045. Among the included RCTs, buparlisib is regarded as the adjunctive therapy to fulvestrant,[24,32] paclitaxel,[25] trastuzumab, and paclitaxel.[26] Three studies report progressive disease and stable disease,[24–26] four studies report overall response rate,[24–26,32] three studies report clinical benefit rate,[24,25,32] four studies report ALT,[24–26,32] three studies report AST,[24,26,32] three studies report hyperglycaemia,[24,25,32] four studies report serious adverse events and deaths.[24–26,32] Jadad scores of the four included studies vary from 3 to 5, and all four studies have high-quality based on the quality assessment.

3.2. Primary outcome: progressive disease

The random-effect model is used for the analysis of primary outcome. The results find that compared to control group for breast cancer, neoadjuvant buparlisib results in the significant decrease in progressive disease (RR = 0.66; 95% CI = 0.52–0.82; $P = .0003$), with no heterogeneity among the studies ($I^2 = 0\%$, heterogeneity $P = .80$, Fig. 2).

3.3. Sensitivity analysis

There is no heterogeneity for the primary outcome, and thus we do not perform sensitivity analysis by omitting one study in each turn to detect the source of heterogeneity.

3.4. Secondary outcomes

In comparison with control intervention for breast cancer, neoadjuvant buparlisib is associated with the increase in stable

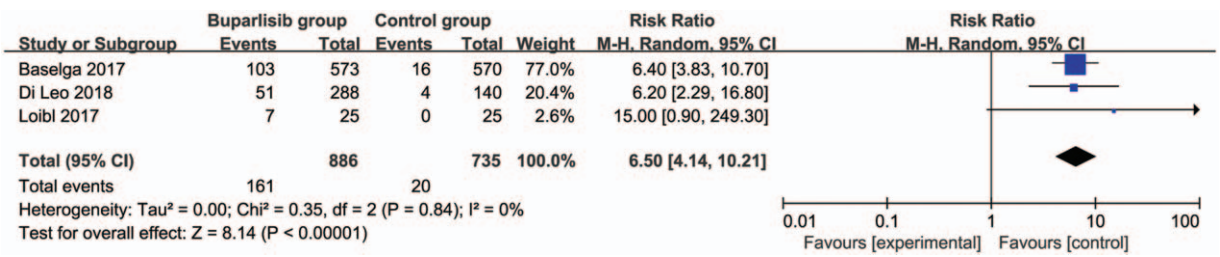

Figure 7. Forest plot for the meta-analysis of increased AST.

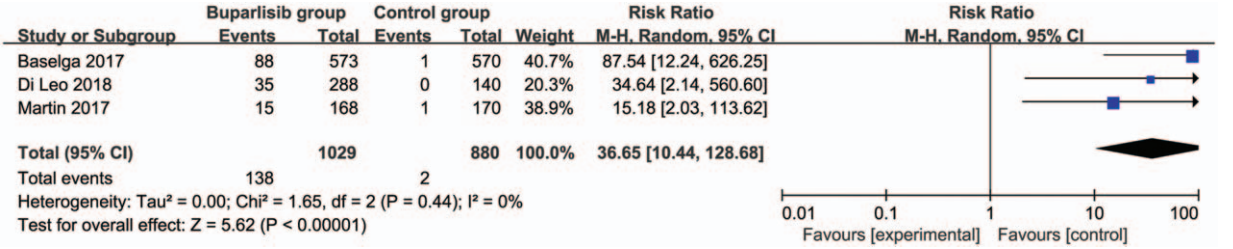

Figure 8. Forest plot for the meta-analysis of hyperglycaemia.

disease (RR = 1.29; 95% CI = 1.02–1.64; $P = .04$; Fig. 3), but shows no impact on overall response rate (RR = 1.32; 95% CI = 0.84–2.06; $P = 0.22$; Fig. 4), clinical benefit rate (RR = 1.06; 95% CI = 0.79–1.43; $P = .69$; Fig. 5). The most common adverse grade 3/4 adverse events including increased ALT (RR = 11.87; 95% CI = 5.65–24.90; $P < .00001$; Fig. 6), increased AST (RR = 6.50; 95% CI = 4.14–10.21; $P < .00001$; Fig. 7) and hyperglycaemia (RR = 36.65; 95% CI = 10.44–128.68; $P < .00001$; Fig. 8), as well as serious adverse events (RR = 1.47; 95% CI = 1.23–1.76; $P < .0001$; Fig. 9) are found to be higher in neoadjuvant buparlisib group than those in control group. There is no statistical difference of deaths (RR = 0.88; 95% CI = 0.75–1.04; $P = .13$; Fig. 10) between two groups.

4. Discussion

In one RCT study for hormone-receptor-positive, HER2-negative, advanced breast cancer, combining buparlisib with fulvestrant can significantly improve progression-free survival and overall response compared with that for placebo plus fulvestrant.[24] While in postmenopausal women with aromatase inhibitor-resistant, hormone-receptor positive, HER2-negative, advanced breast cancer, combination of buparlisib plus fulvestrant can significantly improve progression-free survival compared with that for placebo plus fulvestrant.[32] Our meta-analysis suggests that neoadjuvant buparlisib can substantially reduce the incidence of progressive disease and improve the stable disease for breast cancer, but demonstrates no obvious influence on overall response rate, and clinical benefit rate compared to placebo.

In the BELLE-3 trial, patients predominantly received study treatment as third-line therapy for advanced disease, and almost 90% of patients suffer from progression during mTOR inhibitor treatment or within 30 days from the last dose. That study aims to investigate the combination treatment of buparlisib plus fulvestrant to overcome resistance to mTOR inhibitors by targeting the PI3K pathway upstream. The results reveal higher progression-free survival in combination therapy than fulvestrant alone in patients with PIK3CA mutations.[24] These are consistent with the results in BELLE-2 trial.[32] Thus, PIK3CA status may be an important predictive biomarker to assess the benefit with neoadjuvant buparlisib treatment for breast cancer.

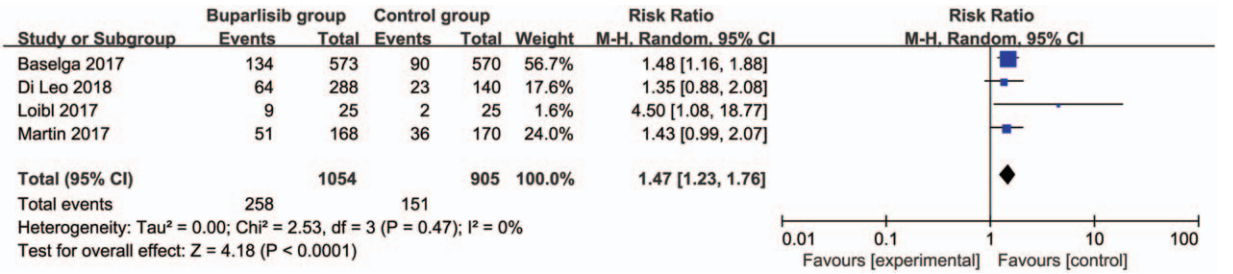

Figure 9. Forest plot for the meta-analysis of serious adverse events.

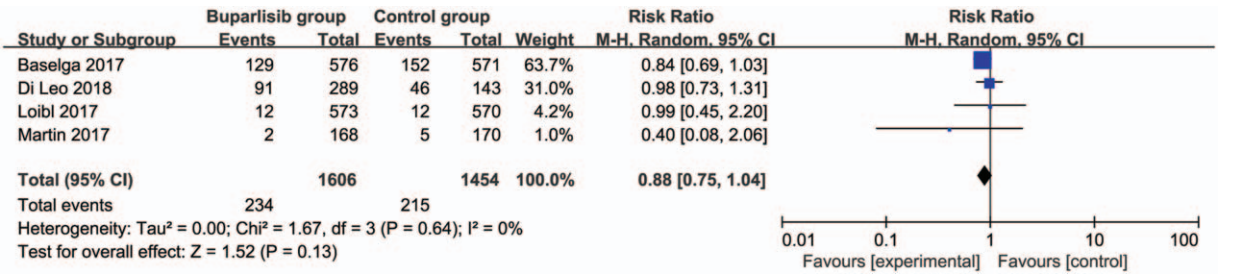

Figure 10. Forest plot for the meta-analysis of deaths.

The safety profile of buparlisib is broadly consistent in many studies when in combination with paclitaxel, fulvestrant, or letrozole.[25,32,33] Neoadjuvant buparlisib commonly results in the increase in hyperglycaemia, elevated ALT and AST, rash, gastrointestinal disorders (nausea and diarrhoea), and psychiatric disorders.[23,32] In BELLE-2 trial, buparlisib plus fulvestrant lead to grade 3 to 4 elevations in ALT in 25% of patients and elevations in AST in 18% of patients.[32] In our meta-analysis, neoadjuvant buparlisib also causes higher incidence of elevated ALT and AST, hyperglycaemia, and serious adverse events compare to placebo for breast cancer, but there is no statistical difference of deaths between two groups.

Several limitations exist in this meta-analysis. First, our analysis is based on only four RCTs, and more RCTs with large sample size should be conducted to explore this issue. Next, although there is no significant heterogeneity, different combination and methods of neoadjuvant buparlisib may lead to some bias. Finally, it is not feasible to perform subgroup analysis based on HER2 and PIK3CA status among current studies.

5. Conclusion

Neoadjuvant buparlisib may provide some benefits to treat breast cancer, but also leads to the increase in serious adverse events.

Author contributions

Conceptualization: Qian Luo, Hui Lu.
Data curation: Qian Luo, Hui Lu.
Formal analysis: Qian Luo, Hui Lu.
Funding acquisition: Qian Luo, Hui Lu.
Investigation: Qian Luo, Hui Lu, Ying Wang.
Methodology: Qian Luo, Ying Wang.
Project administration: Qian Luo, Xian Zhou, Ying Wang.
Resources: Hui Lu, Xian Zhou, Ying Wang.
Software: Hui Lu, Xian Zhou, Ying Wang.
Supervision: Qian Luo, Hui Lu, Xian Zhou.
Validation: Qian Luo, Xian Zhou.
Visualization: Qian Luo, Xian Zhou, Ying Wang.
Writing – original draft: Qian Luo, Xian Zhou, Ying Wang.
Writing – review & editing: Qian Luo, Xian Zhou, Ying Wang.

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