EJGO European Journal of Gynaecological Oncology

Systematic Review

Network meta-analysis of targeted drugs in combination with chemotherapy for advanced/metastatic triple-negative breast cancer treatment

Qing-Hui Kan[1,*], Ying-Lin Wang[2,*], Mei-Ling Xu[1], Fu-Yun Tong[1], Yong-Sheng Shi[1]

[1]*Department of Breast, Thyroid and Vascular Surgery, Fuling Central Hospital of Chongqing City, Chongqing 408000, China*
[2]*Department of Dermatology, Fuling Central Hospital of Chongqing City, Chongqing 408000, China*

Summary

Purpose: This study investigates the therapeutic efficacy of various targeted drugs in combination with chemotherapy on advanced/metastatic triple-negative breast cancer (TNBC) by a network meta-analysis. *Methods:* Literatures from PubMed, Web of Science, Embase, and CNKI databases were searched to retrieve the relevant published data, and many randomized controlled trials (RCTs) on TNBC were selected according to the inclusion and exclusion criteria. The progression-free survival (PFS), overall survival (OS), the adverse effect rate (AEs), and treatment response rate (RR) of TNBC patients for all retrieved literatures were extracted. R software and Hasse diagrams was used to analyze the therapeutic effects of different targeted drugs combined with chemotherapy. *Results:* A total of 16 RCTs were included in the study. The PFS (Hazard ratio (HR) 0.72, 95% CI 0.66-0.79, $p < 0.001$) and OS (HR 0.92, 95% CI 0.84-1.0, $p = 0.0475$) were calculated among the studies. By comparing with combined regimens, we found that Iniparib combined with chemotherapy has a better therapeutic effect on prolonging PFS (HR p-Score = 0.55, AEs p–Score = 0.80, RR p-Score = 0.82). *Conclusion:* Based on the network meta-analysis of combined regimens for TNBC patients with PFS, OS, AEs and RR for screening the optimal treatment regimen, we propose that the PFS of patients with TNBC could be improved by a combination chemotherapy including iniparib, cetuximab, taxane or ipatasertib.

Key words: Triple negative breast cancer; Targeted drugs; Network analysis; Progression-free survival; Overall survival.

Introduction

Breast cancer is the most common malignant cancer reported in women, with an estimated 1.67 million new cases diagnosed and more than 50,000 deaths annually [1, 2]. Breast cancer is classified clinically into various subtypes, and among them the triple-negative breast cancer (TNBC) is characterized by the lack of estrogen/progesterone receptor (ER/PR) expression, and human epidermal growth factor receptor 2 (HER2) amplification. TNBC is the most aggressive pathological type comprising 15-20% of all cases of breast cancer, and usually showing marked refractory to treatment with poor prognosis [3]. Moreover, many studies have reported that TNBC have a higher risk of distant metastasis and increased mortality rate, when compared to other breast cancers.

TNBC is characterized with extensive intratumor heterogeneity, and no specific targeting therapy is available for TNBC on the clinical settings. Currently, surgical resection and chemotherapy are the most common treatments for TNBC patients. However, most of the TNBC patients succumb to their disease and is notoriously regarded as the death sentence by patients as it rapidly progresses to the advanced stages of metastasis before the patients respond to further treatment [4]. Recent studies have revealed that the new monoclonal antibody-based immunotherapies, such as bevacizumab, an angiogenesis inhibitor for inhibiting vascular endothelial growth factor (VEGF) have showed excellent synergistic effect on TNBC treatments in combination with cytotoxic chemotherapies [5]. This combined therapeutic strategy is more conducive to achieve better clinical outcomes measured with efficacy parameters like progression-free survival (PFS) and overall survival (OS), than chemotherapies alone [6]. The PFS, the time from treatment initiation to disease progression or worsening, and OS, the duration of patient survival from the time of treatment initiation are direct measurements of clinical outcomes for drug approval [7]. Up to now, there have been ever-growing reports of using different drug combinations (targeted drugs plus chemotherapy) to combat the TNBCs. However, systematically reviewing and comparing these various targeted drugs combined with chemotherapies for TNBC based on their clinical outcomes are still desirable on the clinical settings so as to present a most effective regimen, especially for the advanced and metastatic TNBC.

In this paper, we have searched and collected the data from randomized controlled trials (RCT) of targeted drugs in combination with chemotherapies for the treatment of TNBC from 2009 to 2019, and used systematic meta-analysis to compare the therapeutic effects of the all the in-

*Contributed equally.

Eur. J. Gynaecol. Oncol. - ISSN: 0392-2936
XLI, n. 6, 2020
doi: 10.31083/j.ejgo.2020.06.2123

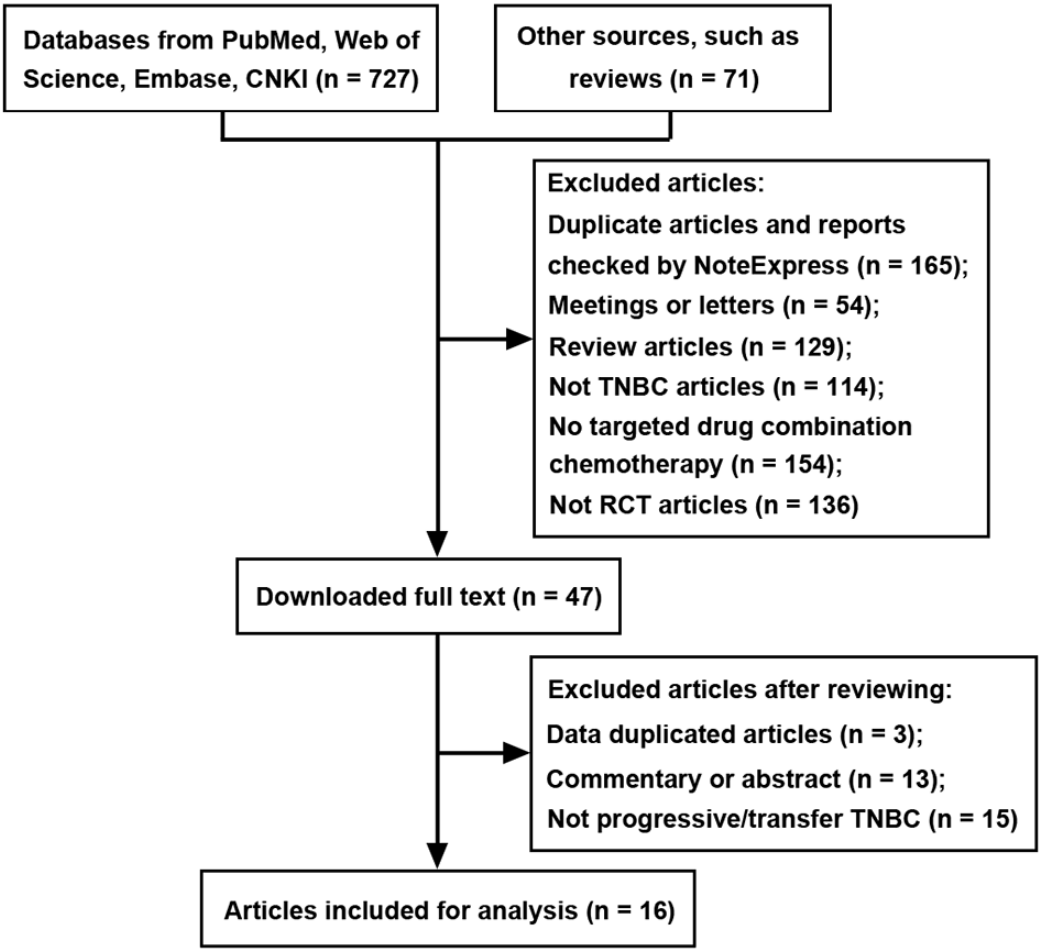

Figure 1. — Flow chart of retrieved literatures from databases and selection criteria.

cluded targeted drugs on PFS, OS, overall incidence of adverse effects (AE), and overall response rate (RR) of TNBC patients. Hopefully, this study can provide useful guidance for therapeutic management of TNBC and eventually improve the clinical outcomes for TNBC patients.

Material and Methods

Search strategy

We have searched and collected all eligible articles from PubMed, Web of Science, Embase, CNKI, and other electronic database resources published between 2009 to 2019 with the following search strings: "triple negative breast cancer", "breast carcinoma", "metastatic breast cancer" and "target therapy" and "randomized trail", or "randomized control trial (RCT)".

Exclusion criteria

The exclusion criteria were shown as followed: (1) The articles or reports that was duplicated when checked with NoteExpress software; (2) Articles published in the form of meetings, letters, or reviews; (3) Non-TNBC-related studies; (4) Articles not focused on targeted drug combination with chemotherapy; (5) Non-RCT studies; (6) Data duplicated among the reviewed articles; (7) Commentary or abstract; (8) Non- progressive/transfer TNBC-related studies.

Inclusion criteria

We have followed the inclusion criteria matching: (1) participants who are adult females ($>$ 18 years old); (2) histological examinations of patients showing advanced/metastatic TNBC with negative ER/PR, and non-overexpression of HER-2; (3) designed intervention: targeted drugs only or combined with chemotherapies; (4) study types: RCT on comparison of effects of various targeted drugs with chemotherapies in the treatment of TNBC; (5) required monitoring: PFS (defined as the period of time from the treatment after random grouping to the progression of disease or the death of patient); (6) non-required detections: OS (defined as the period of time from the treatment after random grouping to the death of patient), occurrence of AE (defined as WHO grading of toxic and side effects of chemotherapy $\geq$ III) and therapeutic RR (including complete response and partial response). We have also considered the fact that the range of studies included were designed with a period of 10 years, and a possible variation in chemotherapeutic regimens for TNBC therefore may have appeared.

Table 1. — *Characterisstics of included studies.*

Author, year	Phase	Number	Ages	Treatment	Drugs	Targets	Content
[8] (a, b)	III	127	**Elder patients: Mean (68)**	**Bevacizumab 7.5/15 mg/kg + docetaxel *vs.* Placebo + docetaxel**	Bevacizumab	VEGF	PFS, AE
[9]	II	123	Mean (54.5)	Iniparib + Gemcitabine/carboplatin *vs*. Gemcitabine/carboplatin	Iniparib	PARP	PFS, OS, AE, RR
[10]	III	519	Mean (53.5)	Iniparib + Gemcitabine/carboplatin *vs*. Gemcitabine/carboplatin	Iniparib	PARP	PFS, OS, AE
[11]	II	217	Mean (52)	sunitinib vs. chemotherapy (Capecitabine, Gemcitabine, Vinorelbine, or Docetaxel)	Sunitinib	VEGFR2, PDGFRβ	PFS, OS, AE
[12] (a, b, c, d)	III	684	Mean (55.4)	Bevacizumab + Taxanes/Gemcitabine/ Capecitabine/Vinorelbine *vs*. Placebo + chemotherapy	Bevacizumab	VEGF	PFS, OS, AE
[12]	II	273	Mean (52.7)	Cisplatin + Cetuximab *vs*. Cisplatin	Cetuximab	EGFR	PFS, OS, AE, RR
[13]	II	229	Mean (54.8)	Sorafenib + Capecitabine *vs*. Placebo + Capecitabine	Sorafenib	Raf-1, B-Raf, VEGFR3	PFS, OS, AE, RR
[14]	III	593	Mean (55)	Sunitinib + Docetaxel *vs*. Docetaxel	Sunitinib	VEGFR2, PDGFRβ	PFS, OS, AE
[15] (a, b)	III	1237	Mean (55.7)	Bevacizumab + Capecitabine *vs*. Capecitabine + Placebo; Taxane /Anthracycline + Capecitabine vs. Taxane /Anthracycline + Placebo	Bevacizumab, taxane	VEGF	PFS, OS, AE, RR
[16]	II	124	Mean (57)	Glembatumumab vedotin *vs*. chemotherapy (Taxane, Anthracycline, Capecitabine, or Ixabepilone)	Glembatumumab vedotin	Glycoprotein NMB	PFS, OS, AE
[5]	III	2559	18-40 (n = 484) 40-65 (n = 1868) > 65 (n = 239)	Bevacizumab + Anthracycline and/or Taxane-based chemotherapy *vs*. chemotherapy	Bevacizumab	VEGF	PFS, OS, AE
[17] (1)	II	684	Mean (55)	Bevacizumab + chemotherapy (Taxane, Gemcitabine, Capecitabine, or Vinorelbine) *vs*. Placebo + chemotherapy	Bevacizumab	VEGF	PFS, OS, AE, RR
[18]	II	124	Mean (53.5)	Ipatasertib + Paclitaxel *vs.* Placebo + Paclitaxel	Ipatasertib	AKT	PFS, AE, RR
[19]	II	215	Mean (51.5)	Bevacizumab + nab-paclitaxel *vs*. nab-paclitaxel	Bevacizumab	VEGF	PFS, AE
[20]	II	141	Mean (56.5)	Ramucirumab + Eribulin *vs*. Eribulin	Ramucirumab	VEGFR2	PFS, OS, AE
[21] (a, b)	III	302	Mean (44.3)	Olaparib *vs*. Anthracycline and/or Taxane-based chemotherapy	Olaparib	EGFR	PFS, OS, AE

PFS: progression-free survival; OS: overall survival; AE: adverse effects; RR: response rate; VEGF: vascular endothelial growth factor; PARP: poly ADP-ribose polymerase; EGFR: epidermal growth factor receptor; Raf: proto-oncogene serine/threonine-protein kinase; VEGFR: vascular endothelial growth factor receptor; PDGFRβ: platelet-derived growth factor receptor β; Glycoprotein NMB: Glycoprotein nonmetastatic melanoma protein B; AKT: serine/threonine-protein kinase.

Data extraction

Two independent authors were responsible for collecting and reviewing the data from the included studies and deliberating over any divergence until they reach a consensus. Full-text versions of all potentially relevant studies were obtained including the detailed information about: first author, publication year, total number of participating patients, targeted drugs and chemotherapy regimens, study endpoints and hazard ratios (HR) (including 95% confidence interval (CI)).

Quality evaluation

Risk of methodological biases in individual studies was evaluated by Cochrane risk of bias tool. They include random sequence generation, allocation concealment, blinding (participants and personnel), blinding (outcome assessment), incomplete outcome data, selection bias and any other sources of bias. The reviewer assessment shall be given as "low", "high", or "unclear" for each article.

Statistical analysis

The PFS and OS in TNBC patients were analyzed by using Netmeta software package. Then the collected experimental data was uploaded on software R-3.6.0 for further analysis. The combined analysis was initially adopted to determine the heterogeneity. As $p < 0.05$ was considered as heterogeneity, the combined effective size was evaluated with random effect model, and when $p > 0.05$ represented no heterogeneity, then the fixed effect model was used. $p < 0.05$ demonstrated that the targeted drugs with combination strategy shows significant curative effects for TNBC patients. In addition, the incidence of AEs and therapeutic RR were considered as assisting factors in determining the efficacy of various targeted drugs, and their efficacies were compared by Hasse diagrams.

Results

Search results

A total of 798 literatures were retrieved from the electronic databases and other resources that were published between January 2009 to June 2019. Following the selection criteria, 782 papers were screened and only 16 RCT of TNBC treatment studies were included in accordance with the inclusion criteria for further analysis. The flow chart of detailed search criteria and excluding process was shown in Figure 1.

Characteristic features of included literature

All the 16 analyzed literatures were multi-center clinical studies, including 9 Phase II and 7 Phase III clinical trials for drug development. Moreover, all papers presented the PFS and AE of explored drugs, while 13 out of them reported OS and 6 papers showed RR in the TNBC patients. Generally, these 16 RCT papers had used 8 different targeted drugs, including bevacizumab (VEGR targeting), iniparib (poly ADP-ribose polymerase (PARP) targeting), cetuximab (EGFR targeting), sorafenib (proto-oncogene serine/threonine-protein kinase (Raf) and vascular endothelial growth factor receptor 3 (VEGFR3) targeting), sunitinib (VEGFR2 and platelet-derived growth factor receptor β (PDGFRβ) targeting), glembatumumab vedotin (Glycoprotein nonmetastatic melanoma protein B (NMB) targeting), ipatasertib (AKT targeting), ramucirumab (VEGFR2 targeting), and olaparib (EGFR targeting), that collectively produced 12 different therapeutic regimens when combined with chemotherapeutics (Table 1). Importantly, the results of evaluation of risk of biases in individual studies were shown in Figure 2. Most RCTs were designed as randomized double-blind trials, and only a few studies concealed unknown risks and other sources of risk.

PFS network analysis

The 16 articles encompassed 11 different targeted drugs in combination with chemotherapies (Figure 3a), where 23 independent RCT clinical trials for the targeted drugs in treatment of TNBC patients reported PFS (Figure 4). The network analysis of PFS showed the heterogeneity test result, $I^2 = 51\%$ and $p < 0.01$. Therefore, the random effects model was evaluated for the combined effects. The Diamonds shown in Figure 4 represented the overall summary of HR for PFS analysis, while the width of the diamonds indicated the 95% CI. Generally, the combined effects increased the outcome of PFS, as the hazard ratio (HR) was 0.72, 95% confidence interval (CI) was 0.66-0.79, and $p < 0.001$, suggesting that these targeted drug interventions could significantly extend PFS of TNBC patients. Additionally, the subgroup analysis based on stages of clinical trials have also supported the above results. The HR = 0.66, 95% CI = 0.52-0.83, $p < 0.001$ was observed for phase II trials, while HR = 0.74, 95% CI = (0.67, 0.81), $p < 0.001$ was noted for phase III clinical trials, which have indicated that the PFSs were obviously prolonged in patients who received treatment of targeted drugs.

Therapeutic regimens analyzed through network were ranked according to *p*-Scores as well as incidence of AE and therapeutic RRs as provided in each study. Compared to simple ranking, this method may provide a superior way to find the optimal treatment. As shown in Figure 5, iniparib combined with chemotherapy was the optimum (*p*-Score was 0.55, 0.80, and 0.82 for HR, AEs, and RR, respectively), closely followed by cetuximab combined with chemotherapy (*p*-Score was 0.41, 0.82, 0.74 for HR, AEs, and RR, respectively), with reference to existing data from clinical drug trials.

OS network analysis

Of the all included studies, 3 papers[18, 22, 8] did not show any specific OS information, while 9 different targeted drugs in combination with chemotherapies (Figure 3b) and 13 independent RCT clinical trials for the targeted drugs in treatment of TNBC patients reported OS (Figure 6). Network analysis of heterogeneity test showed $I^2 = 20\%$, and $p = 0.24$. Therefore, fixed effect model was evaluated for the combined effects. Diamonds shown in Figure

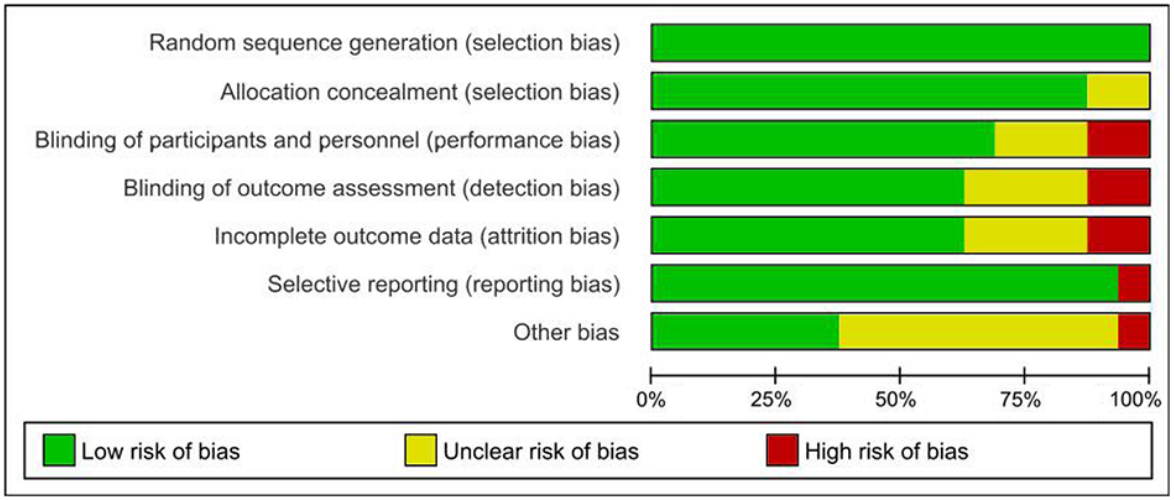

Figure 2. — Risk bias assessment among the included RCT studies.

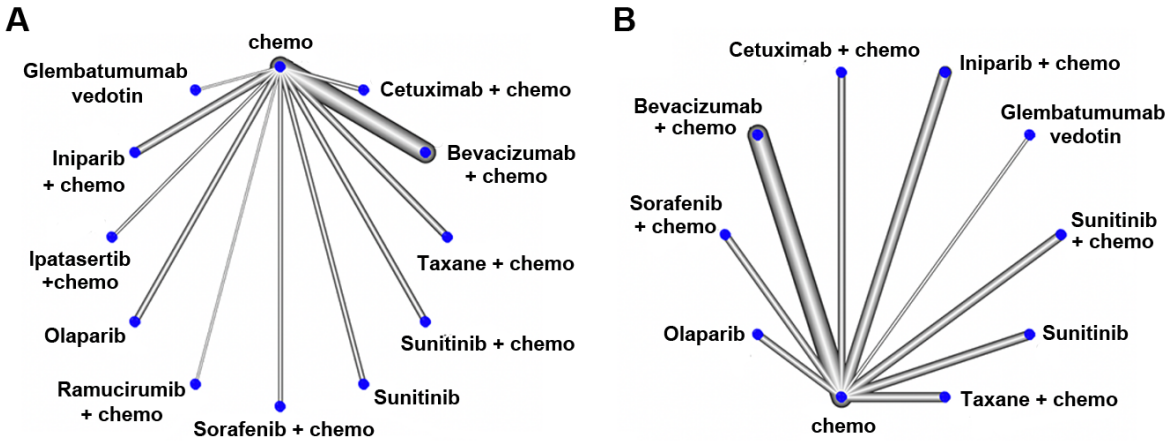

Figure 3. — Network plots for targeted drugs in combination with chemotherapy for PFS (A) and OS (B). Chemo, chemotherapy.

6 represented the overall summary of HR for OS analysis, while width of the diamonds indicated the 95% CI. Generally, the combined effects enhanced the outcome of OS, as the HR was 0.92, 95% CI was 0.84-1.0, and p value was 0.0475, indicating that these targeted drug interventions could also improve patients' OS (Figure 6). However, subgroup analysis based on stages of clinical trials demonstrated phase II clinical trial group with HR = 0.84, 95% CI = (0.71-0.99), $p = 0.04$, while phase III clinical trial group had HR = 0.92, 95% CI = (0.84, 1.0), $p = 0.29$, which have indicated that the OS were not significantly improved in patients who received treatment of targeted drugs. Besides, the Hasse plots obtained from p-Scores of HR, AEs, and RR did not yield an optimal treatment.

Discussion

Recent studies demonstrated that the targeted drugs combining with chemotherapy exhibit great significance in treatment of TNBC, while they also cause high incidence rate of adverse side effects [23]. Therefore, exploiting relatively safe and efficient targeted drugs and chemotherapy regimens through numerous clinical drug trials are still desirable. In this study, we have screened a total of 798 literatures from various databases and other resources, and finally obtained 16 RCT papers of targeted drugs in combination with chemotherapy for treatment of progressive/advanced TNBC patients. Altogether, from these 16 papers, we have noticed that 8 targeted drugs have been used clinically in Phase II and III trials. Different aspects of clinical outcomes were analyzed after using these targeted drugs, such as PFS, OS, AEs, and RR, and the data was subjected to meta-analysis. Finally, we have concluded that, iniparib combined with chemotherapy can be presented as ideal for the optimal treatment for TNBC, followed by cetuximab combined with chemotherapy. This Network meta-analysis of various targeted drugs in the treatment of TNBC can provide useful information for ranking the treatments, and also to suggest a guideline to the clinicians to treat the TNBC patients with optimal approach.

In this study, we noticed that iniparib, a poly ADP-ribose polymerase (PARP) inhibitor has showed preferable effects

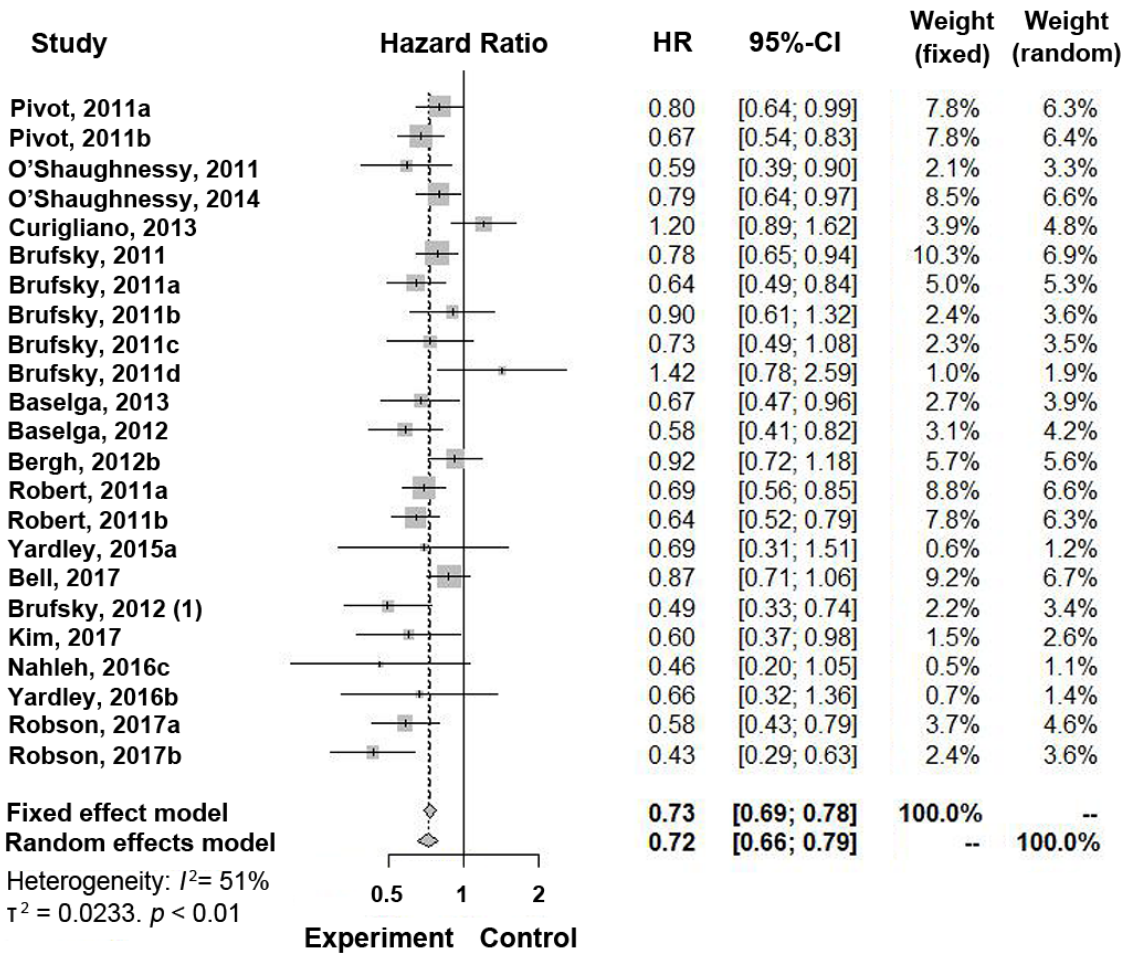

Figure 4. — Forest plot for PFS in TNBC patients. Diamonds represent the overall summary of HR for PFS analysis (width of the diamonds indicate the 95% CI). HR, hazard ratio; CI, confidence interval.

on PFS, but no particular advantages on OS of TNBC patients. Iniparib inhibits the massive growth of cancer cells by suppressing the post-translational modification of proteins by PARP, including histones, RNA polymerase, DNA polymerase, and ligase, etc. [24]. Moreover, its derivatives, olaparib and veliparib, both exhibits similar inhibitory effects on TNBC cells. In addition, iniparib also has wide-spectrum of anti-cancer effects and has been used in treating other types of cancers, such as ovarian cancer, non-small cell lung cancer, and uterine carcinosarcoma [25-28], in phase II clinical trials. Additionally, our study has demonstrated that cetuximab, taxane, sorafenib, and ipatasertib following iniparib also have reduced the excellent combined effects for TNBC treatments.

Interestingly, there are over 100 clinical trials for TNBC treatment that have been completed on the website of clinicaltrials.gov, while some of them were clinical trials investigating the combination effects of different chemotherapeutic drugs, such as paclitaxel, carboplatin, endoxan, doxorubicin, towards the treatment of TNBC patients. From a small cohort of study, Houts *et al.* have reported that the most common first line drugs for metastatic TNBC patients were bevacizumab, capecitabine, carboplatin/gemcitabine, carboplatin/others, and paclitaxel. Additionally, capecitabine, and carboplatin/gemcitabine were also used as second line therapy, and capecitabine and paclitaxel for third line therapy [29]. In our study, the most common chemotherapeutic drugs used in 16 analyzed RCT studies were capecitabine, gemcitabine, taxane, carboplatin, paclitaxel, docetaxel, cisplatin, etc., which was consistent with other reports.

In addition to the targeted drugs we have investigated in this study, other therapeutic strategies for effective treatment of TNBC with a combination of immune-checkpoint blockade therapy based on monoclonal antibodies (anti-programed cell death-1 (PD-1) or anti-programed cell death ligand 1 (PD-L1) drugs) and chemotherapy in phase II/III trails has exhibited remarkable clinical outcomes [30-32]. The therapeutic efficacy of PD-L1 targeting antibodies, atezolizumab, durvalumab and avelumab, and the PD-1 targeting antibodies, nivolumab and pembrolizumab, have been investigated in TNBC patients. However, some of clinical trials for combined regimens with chemotherapy are still on-going [33]. Vinayak *et*

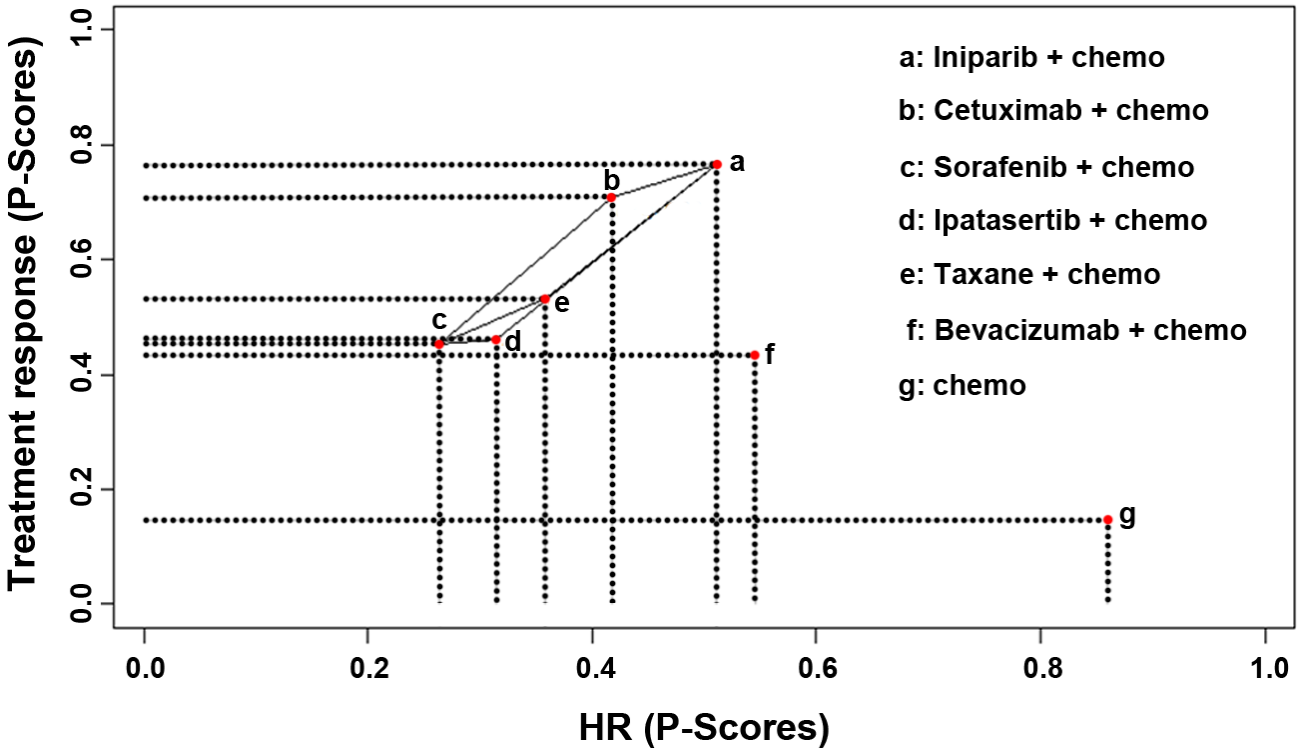

Figure 5. — Hasse plot for the optimal treatment. Chemo, chemotherapy.

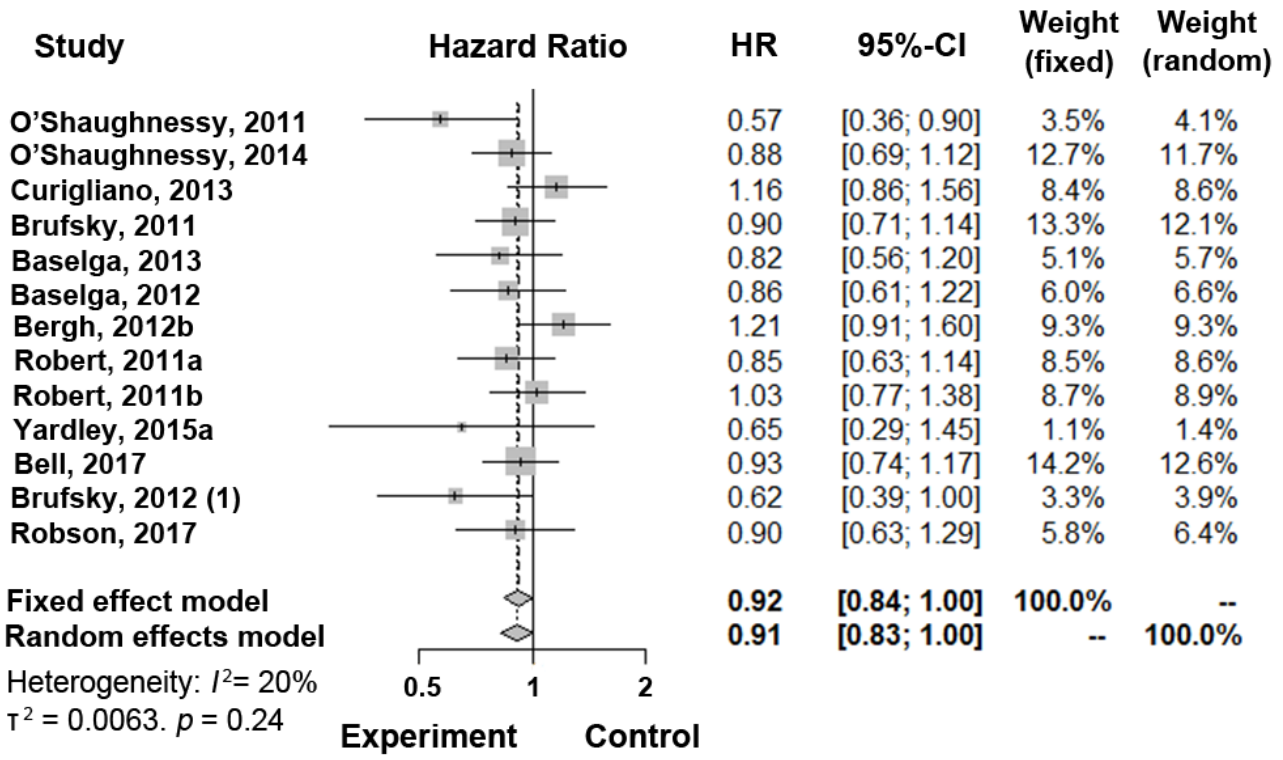

Figure 6. — Forest plot for OS in TNBC patients. Diamonds represent the overall summary of HR for OS analysis (width of the diamonds indicate the 95% CI). HR: hazard ratio; CI: confidence interval.

al. have reported that atezolizumab when combined with nab-paclitaxel has prolonged the PFS among the TNBC patients with PD-L1-positive tumors (7.5 months *vs.* 5.0 months in placebo + nab-paclitaxel group),

while AEs were shown with known safety profiles of each agent [32]. A combination chemotherapy with immunotherapy including pembrolizumab, such as paclitaxel/carboplatin, doxorubicin/cyclophosphamide or epirubicin/cyclophosphamide, in PD-1 positive TNBC patients showed a significantly higher comprehensive pathological response than chemotherapy alone [30]. With these advanced developments, further investigations including more rational and optimal approach for comparing those targeted drugs are required to accomplish better rankings of the treatments of TNBC.

There are some limitations associated with this study. Firstly, the comparative analyses presented in this paper are point-to-point testing rather than closed-loop researches, and thus the evaluation of inconsistency is precluded. Secondly, the non-negligible heterogeneities among these analyzed papers were uncontainable factors and yet cannot be enrolled in subgroup analysis of the stages of disease, treatment abandonment or alteration of regimens. Finally, the specific chemotherapeutic drugs were not clearly differentiated in the current study, since the highly heterogeneous features of TNBC and the sensibilities of TNBC patients to the same drugs varied greatly. Generally, it is evident that most of the combined regimens may present different outcomes when applied with different chemotherapeutic drugs. To substantiate this scenario, Brufsky *et al.* conducted a study and reported that there was no significant difference in PFS and OS between bevacizumab + vinorelbine group and chemotherapy group, while the other drugs, taxane, gemcitabine, and capecitabine, in combination with bevacizumab could significantly improve the PFS [12].

Conclusions

A network meta-analyses of the targeted drugs in combination with chemotherapies for TNBC patients were performed by analyzing PFS, OS, the incidence of AEs, and therapeutic RR to determine the optimal treatment regimens. Our analysis greatly suggests a rationale towards using chemotherapy combined with iniparib, cetuximab, taxane or ipatasertib in the treatment of TNBC patients, on the ground of clinical conditions. Furthermore, personalized therapies can be effectively implemented based on the invasiveness and heterogeneity of TNBCs and also considering specific clinical conditions towards individualized approach.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Authors' contributions

Qing-hui Kan is responsible for the study concepts & design, statistical analysis; Ying-lin Wang is responsible for the manuscript preparation & editing& review; Mei-ling Xu is responsible for the literature research, experimental studies; Fu-yun Tong is responsible for the clinical studies, data acquisition & analysis; Yong-sheng Shi is responsible for the guarantor of integrity of the entire study, definition of intellectual content. All authors read and approved the final manuscript.

Acknowledgments

Thanks to all the peer reviewers and editors for their opinions and suggestions.

Conflict of Interest

The authors declare no conflict of interest.

Submitted: May 08, 2020
Accepted: August 24, 2020
Published: December 15, 2020

References

[1] The Lancet: "Breast cancer targeted therapy: successes and challenges". *Lancet,* 2017, *389,* 2350.
[2] Ferlay J., Soerjomataram I., Dikshit R., Eser S., Mathers C., Rebelo M., *et al.*: "Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012". *Int. J. Cancer,* 2015, *136,* E359-E386.
[3] Bayraktar S., Glück S.: "Molecularly targeted therapies for metastatic triple-negative breast cancer". *Breast Cancer Res. Treat.,* 2013, *138,* 21-35.
[4] Clifton K., Gutierrez-Barrera A., Ma J., Bassett R., Litton J., Kuerer H., *et al.*: "Adjuvant versus neoadjuvant chemotherapy in triple-negative breast cancer patients with BRCA mutations". *Breast Cancer Res. Treat.,* 2018, *170,* 101-109.
[5] Bell R., Brown J., Parmar M., Toi M., Suter T., Steger G.G., *et al.*: "Final efficacy and updated safety results of the randomized phase III BEATRICE trial evaluating adjuvant bevacizumab-containing therapy in triple-negative early breast cancer". *Ann. Oncol.,* 2017, *28,* 754-760.
[6] Bramati A., Girelli S., Torri V., Farina G., Galfrascoli E., Piva S., *et al.*: "Efficacy of biological agents in metastatic triple-negative breast cancer". *Cancer Treat. Rev.,* 2014, *40,* 605-613.
[7] Hess L.M., Brnabic A., Mason O., Lee P. and Barker S.: "Relationship between progression-free survival and overall survival in randomized clinical trials of targeted and biologic agents in oncology". *J. Cancer,* 2019, *10,* 3717-3727.
[8] Pivot X., Schneeweiss A., Verma S., Thomssen C., Passos-Coelho J.L., Benedetti G., *et al.*: "Efficacy and safety of bevacizumab in combination with docetaxel for the first-line treatment of elderly patients with locally recurrent or metastatic breast cancer: Results from AVADO". *Eur. J. Cancer,* 2011, *47,* 2387-2395.
[9] O'Shaughnessy J., Osborne C., Pippen J.E., Yoffe M., Patt D., Rocha C., *et al.*: "Iniparib plus chemotherapy in metastatic triple-negative breast cancer". *N. Engl. J. Med.,* 2011, *364,* 205-214.
[10] O'Shaughnessy J., Schwartzberg L., Danso M.A., Miller K.D., Rugo H.S., Neubauer M., *et al.*: "Phase III study of iniparib plus gemcitabine and carboplatin versus gemcitabine and carboplatin in patients with metastatic triple-negative breast cancer". *J. Clin. Oncol.,* 2014, *32,* 3840-3847.
[11] Curigliano G., Pivot X., Cortés J., Elias A., Cesari R., Khosravan R., *et al.*: "Randomized phase II study of sunitinib versus standard of care for patients with previously treated advanced triple-negative breast cancer". *Breast,* 2013, *22,* 650-656.
[12] Brufsky A.M., Hurvitz S., Perez E., Swamy R., Valero V., O'Neill V., *et al.*: "RIBBON-2: a randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer". *J. Clin. Oncol.,* 2011, *29,* 4286-4293.
[13] Baselga J., Gómez P., Greil R., Braga S., Climent M.A., Wardley A.M., *et al.*: "Randomized phase II study of the anti–epidermal

growth factor receptor monoclonal antibody cetuximab with cisplatin versus cisplatin alone in patients with metastatic triple-negative breast cancer". *J. Clin. Oncol.,* 2013, *31,* 2586-2592.

[14] Baselga J., Segalla J.G.M., Roché H., del Giglio A., Pinczowski H., Ciruelos E.M., *et al*.: "Sorafenib in combination with capecitabine: an oral regimen for patients with HER2-negative locally advanced or metastatic breast cancer". *J. Clin. Oncol.,* 2012, *30,* 1484-1491.

[15] Bergh J., Bondarenko I.M., Lichinitser M.R., Liljegren A., Greil R., Voytko N.L., *et al*.: "First-line treatment of advanced breast cancer with sunitinib in combination with docetaxel versus docetaxel alone: results of a prospective, randomized phase III study". *J. Clin. Oncol.,* 2012, *30,* 921-929.
[16] Robert N.J., Diéras V., Glaspy J., Brufsky A.M., Bondarenko I., Lipatov O.N., *et al*.: "RIBBON-1: randomized, double-blind, placebo-controlled, phase iii trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2–negative, locally recurrent or metastatic breast cancer". *J. Clin. Oncol.,* 2011, *29,* 1252-1260.
[17] Yardley D.A., Weaver R., Melisko M.E., Saleh M.N., Arena F.P., Forero A., *et al*.: "Emerge: a randomized phase II study of the antibody-drug conjugate glembatumumab vedotin in advanced glycoprotein NMB-expressing breast cancer". *J. Clin. Oncol.,* 2015, *33*, 1609-1619.
[18] Brufsky A., Valero V., Tiangco B., Dakhil S., Brize A., Rugo H.S., *et al*.: "Second-line bevacizumab-containing therapy in patients with triple-negative breast cancer: subgroup analysis of the RIBBON-2 trial". *Breast Cancer Res. Treat.,* 2012, *133,* 1067-1075.
[19] Kim S., Dent R., Im S., Espié M., Blau S., Tan A.R., *et al.*: "Ipatasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (LOTUS): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial". *Lancet Oncol.,* 2017, *18,* 1360-1372.
[20] Yardley D.A., Reeves J., Dees E.C., Osborne C., Paul D., Ademuyiwa F., *et al*.: "Ramucirumab with eribulin versus eribulin in locally recurrent or metastatic breast cancer previously treated with anthracycline and taxane therapy: A multicenter, randomized, phase II study". *Clin. Breast Cancer,* 2016, *16,* 471-479.
[21] Robson M., Im S., Senkus E., Xu B., Domchek S.M., Masuda N., *et al*.: "Olaparib for metastatic breast cancer in patients with a germline BRCA mutation". *N. Engl. J. Med.,* 2017, *377,* 523-533.
[22] Nahleh Z.A., Barlow W.E., Hayes D.F., Schott A.F., Gralow J.R., Sikov W.M., *et al*.: "SWOG S0800 (NCI CDR0000636131): addition of bevacizumab to neoadjuvant nab-paclitaxel with dose-dense doxorubicin and cyclophosphamide improves pathologic complete response (pCR) rates in inflammatory or locally advanced breast cancer". *Breast Cancer Res. Treat.,* 2016, *158,* 485-495.
[23] Nielsen D.L., Kümler I., Palshof J.A.E., Andersson M.: "Efficacy of HER2-targeted therapy in metastatic breast cancer. Monoclonal antibodies and tyrosine kinase inhibitors". *Breast,* 2013, *22,* 1-12.
[24] Khasraw M., Robson M.: "Poly(ADP-ribose) polymerase inhibitors in breast cancer and other tumors: advances and challenges". *J. Clin. Investig.,* 2011, *1,* 1545-1554.
[25] Vincent M.D.: "Promising targets and current clinical trials in metastatic squamous cell lung cancer". *Front. Oncol*., 2014, *4,* 320.
[26] Wilkinson-Ryan I., Mutch D.: "A review of iniparib in ovarian cancer". *Expert Opin. Investig. Drugs,* 2013, *22,* 399-405.
[27] Aghajanian C., Sill M.W., Secord A.A., Powell M.A., Steinhoff M.: "Iniparib plus paclitaxel and carboplatin as initial treatment of advanced or recurrent uterine carcinosarcoma: A Gynecologic Oncology Group Study". *Gynecol. Oncol.,* 2012, *126,* 424-427.
[28] D'Angelo A., Rinaldi P., Belli P., D'Amico R., Carlino G., Grippo C.: "Usefulness of automated breast volume scanner (ABVS) for monitoring tumor response to neoadjuvant treatment in breast cancer patients: preliminary results". *Eur. Rev. Med. Pharmacol. Sci.,* 2019, *23*, 225-231.
[29] Houts A.C., Olufade T., Shenolikar R., Walker M.S., Schwartzberg L.S.: "Treatment patterns, clinical outcomes, health resource utilization, and cost in patients with BRCA-mutated metastatic breast cancer treated in community oncology settings". *Cancer Treat. Res. Commun.,* 2019, *19,* 100121.
[30] Schmid P., Cortes J., Pusztai L., McArthur H., Kümmel S., Bergh J., *et al*.: "Pembrolizumab for early triple-negative breast cancer". *N. Engl. J. Med.,* 2020, *382,* 810-821.
[31] Schmid P., Adams S., Rugo H.S., Schneeweiss A., Barrios C.H., Iwata H., *et al*.: "Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer". *N. Engl. J. Med.,* 2018, *379,* 2108-2121.
[32] Vinayak S., Tolaney S.M., Schwartzberg L., Mita M., McCann G., Tan A.R., *et al*.: "Open-label clinical trial of niraparib combined with pembrolizumab for treatment of advanced or metastatic triple-negative breast cancer". *JAMA Oncol*., 2019, *5,* 1132-1140.
[33] Katz H., Alsharedi M.: "Immunotherapy in triple-negative breast cancer". *Med. Oncol*., 2018, *35*, 13.

Corresponding Author:
MEI-LING XU, M.D.
Department of Breast, Thyroid and Vascular Surgery, Fuling Central Hospital of Chongqing City, No 2 Gaosuntang Street, Fuling of Chongqing 408000, China
e-mail: xu_meiling20@21cn.com