Revolutionizing Breast Cancer Treatment: Unveiling the Effectiveness and Safety of Trastuzumab Deruxtecan through a Comprehensive Meta-Analysis

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Revolutionizing Breast Cancer Treatment: Unveiling the Effectiveness and Safety of Trastuzumab Deruxtecan through a Comprehensive Meta-Analysis

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Abstract

Objective: Targeting HER2 has significantly improved Overall Survival (OS) for breast cancer (BC) patients. Trastuzumab, a pivotal first-line BC drug, has transformed patient outcomes, and the introduction of trastuzumab deruxtecan (T-DXd) has provided an additional source of hope for patients with BC. The aim of this meta-analysis is to comprehensively appraise the clinical effectiveness and safety aspects of T-DXd in patients with BC.

Methods: Electronic databases, including PubMed, Web of Science, Embase, and Cochrane Library, were methodically searched until April 6, 2023. Data analysis was performed using Stata 15.0.

Result: In total, 12 studies were encompassed, consisting of 3 randomized controlled trials (RCTs) providing data and 9 single-arm studies. In the RCTs, T-DXd were shown to OS[ES=0.62, 95%CI (0.52,0.75); P=0.826]、 PFS[ES=0.36, 95%CI (0.25,0.51);
P=0.003], ORR[RR=2.46, 95%CI(2.18, 2.78); P=0.166], compared with Control group, in patients assigned to T-DXd show better outcomes. For single-arm studies, after T-DXd therapy, patients with breast cancer achieved an ORR[ES=0.57, 95%CI (0.50-0.64)], DCR[ES=0.94, 95%CI (0.91-0.97)].

**Conclusion:** T-DXd exhibits promising application prospects for breast cancer patients. However, further clinical trials and foundational research are imperative to robustly substantiate our findings.

**Keywords:** Breast Cancer; Trastuzumab deruxtecan; Meta-analysis; Interstitial Lung Disease.

**Introduction**

Breast cancer (BC) is recognized as the most prevalent cancer among women worldwide, resulting in the highest number of cancer-related deaths[1]. While relatively rare, cases of male BC do occur[2]. According to the GLOBOCAN 2020 cancer estimates and United Nations population estimates, BC continues to be the most commonly diagnosed cancer globally, with its incidence experiencing a global upward trend[3].

BC is characterized by its heterogeneous nature and is categorized into subtypes according to hormone receptors, including estrogen receptor (ER) and progesterone receptor (PR) collectively known as hormone receptors (HRs), and the human epidermal growth factor receptor 2 (HER2), also referred to as ERBB2[4]. HER2 targeted therapies have emerged as the first-line treatment for BC. In 1998, Trastuzumab (Herceptin, Roche) became the inaugural HER2-targeting agent to receive approval. Trastuzumab has several notable distinctions in cancer treatment[5]. It is the first tumor-targeted drug specifically developed to target HER2. Additionally, it is the first humanized monoclonal antibody used to treat solid tumors. Notably, Trastuzumab represents the first tumor-targeted drug devised based on molecular markers, underscoring its significance in the field[6].

Currently, trastuzumab has established itself as the primary treatment option for BC. The results of trials such as H0648g and M77001 have demonstrated that patients receiving trastuzumab in association with chemotherapy achieved significantly improved overall survival (OS), with survival durations ranging from 25.1 months to 31.2 months[7,8]. Similarly, other trials like HERA and BCIRG-006 et al. have reported that trastuzumab alone resulted in a 5-year disease-free survival (DFS) rate of 87%, providing further evidence that the utilization of trastuzumab enhances both OS and DFS among BC patients[9,10]. While trastuzumab has proven effective, addressing resistance remains a significant challenge in BC treatment. Common resistance mechanisms involve trastuzumab emtansine (T-DM1) and the HER2 kinase inhibitor lapatinib[11]. To tackle this issue, the emergence of Trastuzumab deruxtecan (T-DXd, also known as DS-8201) offers a potential solution, presenting a promising avenue to overcome resistance and address the limitations observed with trastuzumab.

T-DXd is an antibody drug conjugate (ADC) targeting HER2 that has shown potential in the treatment of HER2-expressing cancers, including HER2-positive BC[12]. The Phase II DESTINY-Breast01 trial (NCT03248492) evaluated T-DXd in HER2-
positive metastatic BC patients, who had prior exposure to at least two anti-HER2 agents, including TDM-1\textsuperscript{[13]}. The trial reported a 60.9\% objective response rate (ORR) and a 97.3\% disease control rate (DCR). The median duration of response (DOR) was 14.8 months, and the progression-free survival (PFS) reached a median of 16.4 months. OS had not yet been determined, but the estimated rates were 93.9\% at 6 months and 86.2\% at 12 months\textsuperscript{[13]}. These findings highlight the promising activity of T-DXd in heavily pretreated patients with HER2-positive metastatic BC. The successful outcomes of the Phase II clinical trial led to the approval of T-DXd by the US Food and Drug Administration (FDA) for the treatment of adult patients with HER2-positive unresectable or metastatic BC\textsuperscript{[12]}. Furthermore, there are currently five ongoing Phase III randomized trials evaluating T-DXd in different populations. These trials include HER2-positive BC patients (DESTINY-Breast02, NCT03523585; DESTINY-Breast03, NCT03529110) and patients with HER2-low expression (DESTINY-Breast04, NCT03734029; DESTINY-Breast06, NCT04494425) who have metastatic disease. Additionally, there is a trial focusing on HER2-positive primary BC patients who did not achieve complete remission after neoadjuvant therapy (DESTINY-Breast05, NCT04622319). These ongoing trials aim to further evaluate the efficacy and safety of T-DXd in different settings and patient populations. The aim of this meta-analysis is to offer a comprehensive summary and synthesis of the existing evidence regarding T-DXd and its potential in BC treatment.

Materials and Methods

This protocol has been registered in the International Database of Prospective Registrations of Systematic Reviews (PROSPERO: CRD42023451269).

Retrieval strategy


Inclusion and exclusion criteria

The enrolled cohort consisted of individuals diagnosed with BC who underwent T-DXd treatment. Randomized controlled trials (RCTs) or single-arm studies presenting data: OS: overall survival, PFS: progression-free survival, ORR: objective response rate will be included, Complete response (CR) + partial response (PR) are considered ORR, and DCR: disease control rate, which PR + CR + stable disease(SD) are considered DCR. meta-analyses, case reports, literature reviews, Conference abstracts, duplicate publications, animal experiments, the full text not available, and the data not available are to be excluded.

Data Extraction
Investigator's name, publication year, drug type, number of included cases, drug dose, follow-up, median OS, median PFS, ORR, and DCR. The fundamental details of the studies will be independently extracted by two investigators.

Risk of bias Evaluate
For RCTs: the risk of bias was evaluated using the Cochrane Risk of Bias Tool 2.0 (RoB2) \cite{14}. RoB2 was also paired by two independent investigators. In case of disagreement between two investigators regarding the analyzed risk of bias, consensus was achieved through involvement of a third investigator. Evaluators reviewed the randomization process, bias in the intended intervention, missing outcome data, choice of outcome measures, and reported results. As a result, the studies were categorized as low, moderate, or high risk of bias (Supplementary Figure 1).

For single arm study: the quality assessment utilized the Newcastle-Ottawa Scale (NOS) \cite{15}. Assessment scores of 0-3, 4-6, and 7-9 denote poor, fair, and good studies, respectively, differences are resolved by consensus (Supplementary Table 2).

Data analysis
For RCTs: we utilized the Odds Ratio (OR) and 95% Confidence Interval (CI) to assess the ORR, PFS, and OS. For the single-arm studies, we employed the effect size (ES) and 95%CI. using stata15. 0 (StataCorp, College Station, TX, USA) was used for statistical analysis, and heterogeneity was tested by I2 value or Q statistic. I2 values of 0%, 25%, 50% and 75% represent no, low, medium and high heterogeneity, respectively. Sensitivity analyses were conducted for I2 values ≥50% to investigate possible origins of heterogeneity. If heterogeneity is less than 50%, a fixed-effects model is employed; otherwise, a random-effects model is applied. Publication bias is assessed using Egger's test.

Result
Literature screening and characteristics
Through manual retrieval, a total of 1437 articles were obtained, 523 articles were obtained after removing duplicates, 28 articles were obtained by checking the titles and abstracts of the articles, 12 articles \cite{16-27} were finally included in the analysis by reading the full text. See Figure 1.

Characteristics of literature
A total of 12 studies were included, of which 3 \cite{22,24,25} were RCTs with data, and 9 \cite{16-23,25} were single-arm studies. Controls in RCTs were T-DM1 or chemotherapy.

There are only 3 studies \cite{16,17,24} did report the median OS, and 3 studies \cite{26,23,19} did not report the median PFS. HER2 status is an important feature of BC treatment, and HER2-positive, especially HER2 3+, was reported in 8 of the included literature \cite{17-20,23,25-27}. The specific characteristics of the literature are shown in Table 1.

Meta analysis for RCT
ORR
A total of 3 studies\cite{24,26,27} involved a total of 1605 patients with BC. 895 people belonged to the T-DXd group and 710 belonged to the controls group, (I2=44.2\%, p=0.166) implying moderate heterogeneity, and the existence of heterogeneity cannot be excluded. Figure2 [RR=2.46 95\%CI (2.18,2.78); P=0.000]. Therefore, the eggerp test of RCT-ORR shows 0.075, the eggerp test is an important statistical method to detect publication bias, so it can be seen that T-DXd is superior to the selected control group in the treatment of BC, and there is a small possibility that there is no publication bias.

**OS**

3 studies\cite{24,26,27} included a collective of 1605 patients, with 895 receiving T-DXd and 710 constituting the control group.(I2=0\%, P=0.826) (I2=0\%, P=0.826) indicated no observed heterogeneity. Figure 3 [ES=0.62, 95\%CI(0.52,0.75);P=0.000] suggested that T-DXd did not lead to an improvement in overall survival for patients with BC. P-values for assessing publication bias were all >0.05, indicating no publication offset.

**PFS**

The 3 studies\cite{24,26,27} involved a total of 1605 people, of which 895 were T-DXd and 710 were the controls group.(I2=83.3\%, P=0.003), indicating the presence of heterogeneity is high. Figure 4 [ES=0.36, 95\%CI(0.52,0.75);P=0.000]; This does not prove that T-DXd improves PFS in patients with BC. p-value for the assessing publication bias was 0.018 less than 0.05, and there may be some publication bias (see Supplement FigureS2).

**Meta for single-arm study**

**ORR**

8 studies\cite{16–18,20–23,25} involving 642 people mentioned ORR, (I2=63.1\%, p=0.008) indicating significant heterogeneity between studies. Figure 5 shows ORR in BC patients treated with T-DXdx inhibitors [ES=0.57, 95\% CI(0.50,0.64); P=0.000]. The sensitivity analysis showed that the results of the analysis were within the 95\% CI interval (Supplementary S3), and P=0.798 > 0.05 for Egger's publication bias assessment, implying a small potential for publication bias (Supplementary S4).

**DCR**

7 studies\cite{16–18,20,22,23,25} involving 627 people mentioned DCR, (I2= 56.6\%, p = 0.032) also indicating a substantial level of heterogeneity across the studies. Figure 6 shows DCR in BC patients treated with T-DXdx inhibitors [ES= 0.94, 95\% CI(0.91, 0.97); P=0.000]. The sensitivity analysis demonstrated that the outcomes of the analysis were within the 95\%CI interval (Supplementary 3). But P<0.05 for Egger's publication bias assessment, suggesting that there was some publication bias (Supplementary S4).

**OS and PFS**

A total of 9 single-arm clinical studies\cite{16–23,25} were included, and none of them achieved OS. For PFS, only 2 studies\cite{17,20} had statistics, which was not statistically significant. Therefore, OS and PFS of single-arm studies are not counted in this article.

**Meta analysis for adverse event**

In the set of 12 incorporated studies, the main adverse events were Neutropenia,
Anemia, Leukopenia, Thrombocytopenia, Nausea, Vomiting, Diarrhea, Constipation, Fatigue, Aspartate aminotransferase increased (AST), Alanine aminotransferase increased (ALT), Decreased appetite, Alopecia, Adjudicated drug-related interstitial lung (ILD), Headache and ventricular dysfunction (including through QT prolongation).

In any grade ES [Neutropenia=0.36, Anemia=0.35, Leukopenia=0.28, Thrombocytopenia=0.23, Nausea=0.75, Vomiting=0.42, Diarrhea=0.29, Constipation=0.31, Fatigue=0.46, AST=0.25, ALT=0.20, Decreased appetite=0.35, Alopecia=0.40, ILD=0.12, Headache=0.17, ventricular dysfunction=0.07]. in grade ≥3 ES [Neutropenia=0.20, Anemia=0.09, Leukopenia=0.08, Thrombocytopenia=0.05, Nausea=0.06, Vomiting=0.02, Diarrhea=0.01, Constipation=0.01, Fatigue=0.06, AST=0.01, ALT=0.02, Decreased appetite=0.02, Alopecia=0.00, ILD=0.01, Headache=0.00, ventricular dysfunction=0.01] (Supplementary Table 3).

Survival curve analysis

Paired with the PFS data from 3 RCTs, the survival curve is depicted in Figure 7 [HR=0.53, 95% CI (0.48, 0.59)], shown in Figure 7. p=0.002]. This indicates that T-DXd prolongs PFS in patients compared to anti-HER2 agents or chemotherapy agents commonly used in BC. However, due to the small amount of literature included, there is some variability in the duration and number of follow-ups.

Discussion

Before that, the marketing of Trastuzumab was a landmark innovation in the treatment of BC, which brought longer survival for BC patients, even HER2-positive patients[6]. Subsequently, with the increase of trastuzumab resistance and adverse reactions, T-DM1 and T-DXd were developed, particularly for patients with HER2-positive solid tumors, especially BC[28]. At the 2022 ESMO Congress, the APHINITY study's 8.4-year follow-up results were officially announced. The results showed that the 8-year OS of HER2+ early BC patients treated with adjuvant chemotherapy combined with pertuzumab and trastuzumab was 92.7%[29]. In the National Comprehensive Cancer Network (NCCN) guidelines published in 2023, T-DXd is proposed as the first choice for breast cancer patients with low HER2 expression[30]. T-DXd acts as an ADC that targets HER2-expressing tumor cells for the delivery of DXd, a powerful inhibitor of topoisomerase I, extending the survival of breast cancer patients exhibiting low HER2 expression[31].

While acknowledging previous meta-analyses on similar topics, it is important to note a 2023 study by Gavin P. Dowling and colleagues[32], which also involved assessing the effectiveness and safety profile of T-DXd in BC. However, compared with it, our study boasts several advantages: Firstly, we included more recent RCTs and single-arm studies to present up-to-date evidence. Secondly, Gavin P. Dowling's study had limitations in analyzing the adverse reactions and efficacy of T-DXd due to the constrained literature. Therefore, our study exhibits notable strengths and innovations when compared to the aforementioned research.
In a related search strategy, we evaluated the efficacy and safety of T-DXd by examining 12 RCTs and single-arm studies. Notably, BC HER2 types were not specifically categorized based on our inclusion criteria. Analysis of a characterization table of the literature found that only eight studies included patients with high HER2 expression, suggesting that HER2 type may not need to be considered for the treatment of BC with T-DXd. Currently, T-DXd is recommended as a second-line drug for HER2-positive BC patients according to various clinical guidelines, including the NCCN guideline in the United States\cite{30}, the ESMO meeting in Europe\cite{33}. This study prompts consideration of expanding T-DXd indications, although it is essential to acknowledge a potential bias due to the relatively limited number of included articles.

In evaluating the primary outcome of our study, which encompassed both RCTs and single-arm clinical studies involving T-Dxd in BC patients, notable findings emerged. The RCTs demonstrated a favorable trend in the ORR [RR=2.46, 95% CI (2.18, 2.78); P=0.000], while the single-arm clinical study also exhibited a positive trend in ORR [ES=0.57, 95% CI (0.50, 0.64); P=0.000]. These results align with the ongoing phase II DESTINY-PanTumor01 clinical study, reporting a median treatment cycle of 5.0 (1-29 weeks) with T-DXd, a median follow-up of 8.6 months, and a prominent ORR of 50% for BC patients\cite{34}. However, caution is warranted in drawing definitive conclusions due to the limited number of included studies and variations in the control groups among the three studies. Notably, Modi's study\cite{24} included a physician-selected chemotherapy group, whereas the other two studies employed T-DM1 in their control groups.

For PFS and OS in RCTs, we observed a PFS superior to T-DM1 and chemotherapy [ES=0.36, 95% CI (0.52, 0.75); P=0.000], which aligns with the interim data from the current ongoing clinical trial\cite{35}. Possible explanations include: 1. Some patients treated with T-DXd may already have intermediate to advanced tumors that were previously treated with ADCs such as T-DM1; 2. A subset of patients had an extended follow-up period with T-DXd. The literature characterization table indicates that in a study by Cortés\cite{26}, the median PFS was not reached, and the trial is still ongoing. With 524 eligible patients randomized to the T-DXd group (261) and T-DM1 group (263), both comparisons demonstrated sustained and clinically meaningful improvements in PFS and OS using T-DXd. This suggests a breakthrough in T-DXd's effectiveness in breast cancer treatment\cite{36}.

In the single-arm study meta-analysis, T-DXd demonstrated effectiveness in controlling BC recurrence and metastasis, as evidenced by the DCR [ES=0.94, 95% CI (0.91, 0.97); P=0.000]. Clinical trials like DESTINY-Breast01 (NCT03248492) reported a notable 97.3% DCR with a T-DXd dose of 5.4 mg/kg\cite{25}. Despite the limited inclusion of only 7 single-arm trials assessing DCR, a cautious interpretation is warranted. Nonetheless, these findings suggest the promising potential of T-DXd in breast cancer treatment.

T-DXd exhibits adverse reactions, including common events such as Neutropenia, Anemia, Nausea, Thrombocytopenia, Vomiting, Diarrhea, Constipation, Fatigue, Alopecia, Leukopenia, Decreased appetite, and ILD across all grades. Grade 3 or higher adverse reactions are most frequently associated with Neutropenia, Anemia, Fatigue,
Leukopenia, Nausea, Diarrhea, Thrombocytopenia, Decreased appetite, and ILD. Hematologic adverse effects (Neutropenia, Anemia, Thrombocytopenia) are common to almost all ADCs. Notably, ILD, though not the most prevalent in the literature, deserves attention for its noteworthy incidence.

From Modi’s clinical study, the incidence of ILD was found to be 13.6%, 10.9% for grade 1-2 ILD, 0.5% for grade 3-4, and 4 patients (2.2%) died of ILD. The occurrence of drug-associated ILD poses a life-threatening risk, evident in individual studies. A pooled analysis involving 245 BC patients (median 7.0] across three trials receiving T-DXd at a dose of 5.4mg/kg every 3 weeks (q3w) reported ILD/pneumonitis in 15.5% of patients. The first ILD event occurred at a median time of 5.6 (1.1-20.8) months, with 97% of cases presenting within the initial 12 months of T-DXd treatment. Numerous clinical trials have consistently corroborated this association with ILD occurrence related to T-DXd treatment. However, the severity of this AE can be effectively mitigated through vigilant symptom monitoring, prompt treatment discontinuation, and early intervention with systemic corticosteroids. Most AEs are tolerable at grade 1-2, and appropriate symptomatic treatment can alleviate them. In our assessment, treatment with T-DXd demonstrated a satisfactory safety profile.

Without doubt, certain methodological drawbacks are present in this study. Initially, the restricted number of included studies and randomized controlled trials may impact the robustness of the conclusions. Secondly, inconsistency in the dose and regimen of use of investigational drugs included, and inconsistency in the inclusion of studies. Some studies used the same type of drug before using the test drug. Nevertheless, certain studies employed the drug as a standalone intervention, which could result in significant potential heterogeneity between studies. Thirdly, different types of HER2 breast cancer may lead to differences in treatment. Fourth, despite comprehensive systematic and manual searches, some relevant studies may have been inadvertently omitted or excluded.

**Conclusion**

Based on the existing evidence, T-DXd is a relatively safe treatable ADC agent for BC; however, given the constraints of the incorporated studies, additional phase III randomized controlled trials (RCTs) are necessary to validate our findings.

**Acknowledgments**

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**Data availability statement**

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

**Author contributions**

Sq X: Topic proposal, data collection, methodology, software Priya Singh, data
curation, writing-original draft preparation. Jq Q and S S: Data collection, essay writing, software analysis. M H, D P and Q Y: Data collection, software analysis. Ll H and Dl W: Data collection. All authors read and approved the final manuscript.

Declaration of Competing Interest
The authors declare that they have no competing interests.

Funding
No funding was obtained for this study.

Ethics declaration
Not applicable.

Reference
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Figure 1 Literature screening flowchart.

PRISMA flow diagram of the study process. PRISMA, Preferred Reporting Items for Systematic review and Meta-analysis
Figure 2

Forest plot of estimated ORR proportions (95% CI) of patients with breast cancer treated with T-Dxd - a randomized controlled trial.

Figure 3

Forest plot of estimated OS proportions (95% CI) of patients with breast cancer treated with T-Dxd - a randomized controlled trial.

Figure 4
Forest plot of estimated PFS proportions (95% CI) of patients with breast cancer treated with T-Dxd - a randomized controlled trial.

Figure 5

Forest plot of estimated ORR proportions (95% CI) of patients with breast cancer treated with T-Dxd - single arm studies.
Figure 6

Forest plot of estimated DCR proportions (95% CI) of patients with breast cancer treated with T-DXd - single arm studies.

Figure 7

Estimated Proportion of PFS (95% CI) in Breast Cancer Patients Treated with T-DXd Forest Figure - single arm studies
### Table 1
Literature baseline table.

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<td>Modi, S &amp; H. Park, R</td>
<td>2020</td>
<td>54</td>
<td>T-DXd 5.4mg/kg Q3W/ T-DXd 6.4mg/kg Q3W</td>
<td>30</td>
<td>29.4</td>
<td>11.1</td>
<td>Bone; Liver; Lung; Brain</td>
<td>NR</td>
<td>ORR; DCR; AEs</td>
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<td>Nakajima, H.</td>
<td>2022</td>
<td>22</td>
<td>T-DXd</td>
<td>-</td>
<td>12</td>
<td>NR</td>
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<td>Shimomura, A</td>
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<td>T-DXd6.4mg/kg Q3W</td>
<td>16+</td>
<td>27.1</td>
<td>8.1</td>
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<td>Pérez-García, J. M.</td>
<td>2022</td>
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<td>T-DXd5.4mg/kg Q3W</td>
<td>12.6</td>
<td>NR</td>
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<td>Brain; CNS</td>
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<td>T-DXd5.4mg/kg Q3W</td>
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<td>Tamura, K</td>
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<td>T-DXd5.4 mg/kg Q3W/T-DXd6.4mg/kg Q3W</td>
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<td>NR</td>
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<td>T Doi</td>
<td>2017</td>
<td>6</td>
<td>T-DXd0.8 mg/kg Q3W/T-DXd3.2mg/kg Q3W</td>
<td>16</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Liver; Lung; Brain; CNS</td>
<td>2</td>
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</table>
Abbreviation: T: treatment group; C: control group; MO: months; OS: Overall survival; PFS: progression free survival; ORR: Objective response rate; NR: not reported; NRE: not reached; Q3W: every 3 weeks; NE denotes could not be estimated; NR not reached.
Supplementary Files

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- Supplementarymaterial.docx