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Clinical Trial Results

Nab-paclitaxel Followed by Dose-dense Epirubicin/Cyclophosphamide in Neoadjuvant Chemotherapy for Triple-negative Breast Cancer: A Phase II Study

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Abstract

Background: The anti-tumor activity of *nab*-paclitaxel followed by epirubicin/cyclophosphamide (EC) as neoadjuvant chemotherapy (NAC) in Asian patients remain unclear, particularly in the aggressive subtype triple-negative breast cancer (TNBC). This study aimed to evaluate the efficacy and safety of this NAC regimen in TNBC.

Methods: In this Simon's two-stage, phase II study, treatment-naïve patients with unilateral primary invasive TNBC were enrolled. Eligible patients received *nab*-paclitaxel 125 mg/m^2 weekly on day 1 for 12 weeks, followed by dose-dense EC (epirubicin 90 mg/m^2; cyclophosphamide 600 mg/m^2) on day 1 for four 2-week cycles. The primary endpoint was the total pathological complete response (tpCR, ypT0/is ypN0) rate.

Results: A total of 55 eligible patients were enrolled and treated. After NAC, tpCR and breast pathological complete response were respectively observed in 43.1% (95% CI, 29.3-57.8) and 49.0% (95% CI, 34.8-63.4) of 51 evaluable patients for pathological response evaluation. 44 had an objective response as their best response (80.0%; 95% CI, 67.0-89.6). No correlations between clinicopathological variables and pathological/clinical response were observed. Grade 3 or more adverse events (AEs) occurred in 63.6% of 55 patients. The most frequent AEs were alopecia. No treatment-related surgical delay or death occurred.

Conclusion: *Nab*-paclitaxel followed by dose-dense EC as NAC demonstrates promising anti-tumor activity and acceptable tolerability for patients with TNBC. (ClinicalTrials.gov Identifier: NCT03799679).

Key words: neoadjuvant chemotherapy; breast cancer; triple-negative breast cancer; *nab*-paclitaxel.

Lessons Learned

- *Nab*-paclitaxel is a novel solvent-free formulation of paclitaxel with a more safety profile, has aroused great interest in cancer therapy.
- The anti-tumor activity and safety of *nab*-paclitaxel followed by dose-dense epirubicin/cyclophosphamide (EC) as neoadjuvant chemotherapy (NAC) in Asian patients remain unclear, particularly in the aggressive subtype triple-negative breast cancer (TNBC).
- *Nab*-paclitaxel followed by dose-dense EC has demonstrated encouraging anti-tumor activity and manageable toxicity with a high proportion of patients achieving a pathological response in the neoadjuvant setting for Chinese patients with TNBC.

Discussion

The successful therapy of early-stage TNBC remains the most challenging task. To date, chemotherapy remains the systemic therapy of choice for early TNBC, but unfortunately, it provides limited benefit due to the chemoresistances. Thus, the systemic treatment approach for patients with early BC has partly shifted to NAC. Nevertheless, conventional solvent-based taxanes are associated with typical toxic effects. *Nab*-paclitaxel is a novel solvent-free formulation of paclitaxel with a more safety profile and has aroused great interest in breast cancer therapy. As the preliminary results of *nab*-paclitaxel in TNBC only came from limited cases,[1,2] we designed a Simon's two-stage, phase II study to evaluate the efficacy and safety of *nab*-paclitaxel followed by dose-dense EC as an NAC regimen in TNBC.

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In the first stage of the study, 20 (39.2%) of 51 patients had a pCR; thus, recruitment into the second stage was continued and another 4 patients were enrolled. Of 51 evaluable patients for pathological response evaluation, 22 (43.1%; 95% CI, 29.3-57.8) patients had a tpCR and 25 (49.0%; 95% CI, 34.8-63.4) patients had a bpCR. More than 20 responses were observed in this study, the NAC regimen was deemed effective. Subgroup analysis was performed to assess the associations between clinicopathological variables and pCR (Table 1). The results showed that clinicopathological variables including age, Ki-67 expression, clinical stage, tumor stage, as well as nodal status stage were not significantly associated with either tpCR or bpCR (all $P > .05$). At the end of NAC, 55 patients were assessable for clinical response. At the end of NAC, the ORR was 74.5% (95% CI, 61.0-85.3), with 21.8% CR and 52.7% PR. Seven patients (12.7%) had SD after NAC. During the whole study, the best response for these patients included 12 (21.8%) CR, 32 (58.2%) PR, and 8 (14.5%) SD, achieving ORR of 80% (95% CI, 67.0-89.6) as their best response. Figure 1 provides the details regarding the depth and duration of the response. The post-hoc analysis did not demonstrate the correlation between clinicopathological variables and clinical response.

Table 1. Post-hoc associations between clinicopathological variables and tpCR or bpCR.

Characteristics	tpCR (*n* = 51)			bpCR (*n* = 51)		
	Yes (*n* = 22)	No (*n* = 29)	*P* value	Yes (*n* = 25)	No (*n* = 26)	*P* value
Age			.251			.269
≤50 years	17 (48.6)	18 (51.4)		19 (54.3)	16 (45.7)	
>50 years	5 (31.3)	11 (68.8)		6 (37.5)	10 (62.5)	
Ki-67			.348			.303
≤50%	7 (35.0)	13 (65.0)		8 (40.0)	12 (60.0)	
>50%	15 (48.4)	16 (51.6)		17 (54.8)	14 (45.2)	
Clinical stage			.352			.489
II	12 (50.0)	12 (50.0)		13 (54.2)	11 (45.8)	
III	10 (37.0)	17 (63.0)		12 (44.4)	15 (55.6)	
Tumor stage			.221			.146
cT2	13 (43.3)	17 (56.7)		15 (50.0)	15 (50.0)	
cT3	8 (57.1)	6 (42.9)		9 (64.3)	5 (35.7)	
cT4	1 (14.3)	6 (85.7)		1 (14.3)	6 (85.7)	
Nodal status stage			.409			.780
cN0	2 (66.7)	1 (33.3)		2 (66.7)	1 (33.3)	
cN1	13 (46.4)	15 (53.6)		14 (50.0)	14 (50.0)	
cN2	4 (26.7)	11 (73.3)		6 (40.0)	9 (60.0)	
cN3	3 (60.0)	2 (40.0)		3 (60.0)	2 (40.0)	

Data are expressed as *n* (%).
Abbreviations: bpCR, breast pathological complete response; tpCR, total pathological complete response.

Author disclosures and references available online.

Trial Information	
Disease	Triple-negative breast cancer
Stage of disease/treatment	cT2-4NanyM0
Prior therapy	None
Type of study	Simon's two-stage, phase II study
Primary endpoint	Total pathological complete response (tpCR, ypT0/is ypN0) rate
Secondary endpoints	breast pathological complete response (bpCR, ypT0/is) rate, objective response rate (ORR), the proportion of patients requiring breast-conserving surgery, and safety
Investigator's analysis	Active but results overtaken by other developments

Additional Details of Endpoints or Study Design

Study Design

This was an open-label, phase II study based on Simon's two-stage design. The study aimed to evaluate the efficacy and safety of *nab*-paclitaxel followed by dose-dense EC as neoadjuvant therapy in patients with TNBC. The study was done in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Ethical approval was obtained from the institutional review board of Shanghai Cancer Center, Fudan University (Approval No. 1808189-7), and written informed consent was obtained from all patients. This study was registered with clinicaltrials.gov (NCT03799679).

Patient Eligibility

Female patients aged 18-70 years with histologically confirmed unilateral primary invasive TNBC (stage cT2-4NanyM0) were eligible for this study. TNBC was defined as less than 1% positivity for estrogen receptor (ER) and progesterone receptor (PR) expression by IHC, and human epidermal growth factor receptor type 2 (HER-2)-negative (IHC staining score of 0-1+ or no HER-2 gene amplification by fluorescent or chromogenic in situ hybridization). Patients were also required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, at least one assessable target lesion based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, left ventricular ejection fraction (LVEF) ≥55%, and adequate organ and bone marrow function (neutrophil count ≥1.5 × 10^9/L; hemoglobin count ≥90 g/L; platelet count ≥100 × 10^9/L; serum creatinine ≤1.5 × upper normal limit [ULN]; aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≤2.5 × ULN; total bilirubin ≤1.5 × ULN, or ≤2.5 × ULN in patients with Gilbert 's syndrome). Patients who had received previous cytotoxic chemotherapy, endocrine therapy, biotherapy, or radiotherapy for any reason were ineligible. Patients with allergies or intolerance to chemotherapy drugs were also not allowed to participate. Other exclusion criteria were other malignancies within 5 years (except for cured cervical carcinoma in situ or non-melanoma skin cancer); heart disease (NYHA class ≥II), severe systemic infection or concomitant diseases, and pregnant or lactating women at screening.

Procedures

Eligible patients received *nab*-paclitaxel (CSPC Ouyi Pharmaceutical Co., Ltd.) 125 mg/m^2 weekly for 12 weeks, followed by dose-dense EC (epirubicin 90 mg/m^2; cyclophosphamide 600 mg/m^2) every 2 weeks for 4 cycles. All drugs were administered intravenously on day 1 of every cycle. Definitive surgery was scheduled within 2-4 weeks after the final dose of NAC. Post-treatment assessment of axillary lymph nodes was required, but the type of surgery (breast-conserving surgery, modified radical mastectomy, and mastectomy) was left to the discretion of the patient and treating surgeon.

Dose delay or reductions were mandatory in case of unacceptable hematological or non-hematological toxicity. If unacceptable toxicity (absolute neutrophil count [ANC]<1.5 × 10^9/L; platelets <75 × 10^9/L; hemoglobin < 90 g/L; grade ≥2 non-hematological toxicity) occurred, chemotherapy is allowed to be delayed until resolution of toxicity. The maximum duration per episode of dose delay was 3 days for *nab*-paclitaxel and 3 weeks for EC. The chemotherapy administration of subsequent cycles was rescheduled according to the last dose date. If patients experienced severe hematological or non-hematological toxicity (ANC<500/mm^3 for 7 consecutive days; febrile neutropenia; grade ≥3 anemia; grade ≥2 neuropathy, etc.), dose reduction was considered. A maximum of 2 levels of dose reduction are permitted (*nab*-paclitaxel: to 100 mg/m^2 and then 80 mg/m^2; epirubicin: to 75 mg/m^2 and then 60 mg/m^2; cyclophosphamide: to 500 mg/m^2 and then discontinue medication). Doses that had been reduced were not allowed to be re-escalated.

Endpoints and Assessment

The primary endpoint was total pathological complete response (tpCR), defined as the absence of invasive lesions in the breast and axillary lymph nodes (ypT0/is ypN0) after neoadjuvant therapy. The secondary endpoint included the breast pathological complete response (bpCR), which was defined as no invasive carcinoma in the breast (ypT0/is) after neoadjuvant therapy. The pCR is also considered to be achieved if only in situ cancer cell remnants are present in the surgical specimens. Both tpCR and bpCR were assessed by the local histopathology assessment of hematoxylin and eosin-stained slides of surgical breast specimens and lymph node tissue after chemotherapy. Patients who did not have surgery for lack of efficacy were classified as not having achieved pCR.

Additional secondary endpoints were objective response rate (ORR) as per imaging assessment and the proportion of patients requiring breast-conserving surgery. ORR was calculated as the proportion of patients achieving the best response of complete response (CR) or partial response (PR) after the last neoadjuvant treatment. Imaging assessment was performed at baseline, every 2 cycles, and before surgery using magnetic resonance imaging (MRI) or/and computed tomography (CT). Tumor response was assessed by investigators as per RECIST version 1.1.

Safety and tolerability were assessed by adverse events (AEs), vital signs, ECOG performance status, laboratory tests, and 12-lead electrocardiogram throughout the study period.

The severity of AEs was graded according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE, version 5.0).

Statistical Analysis

The sample size was calculated based on Simon's two-stage minimax design for the phase II study. Based on the historical pCR rates of 28.6% or 48% in patients with BC reported in the SWOG S0800 and GeparSepto-GBG 69 studies, we regarded a proportion of patients with a pCR of 40% (effectiveness cutoff) or more as proof of the efficacy of the study treatment and less than 25% (ineffectiveness cutoff) as insufficient to continue the assessment. Assuming a significance level of 0.05 (type I error, $\alpha = 0.05$) and a power of 80 % (type II error, $\beta = 0.20$), it can be calculated that 60 patients needed to be included in 2 stages. The first stage included 51 patients who were followed up until the assessment of pathological response. if no more than 16 pCRs were noted, the study was terminated; if 17 or more pCRs were noted, recruitment was to be continued and additional 9 patients were enrolled in the second stage; If no more than 20 responses were observed, the NAC regimen was deemed invalid.

Efficacy analysis was performed in the full analysis set (FAS), which was defined as all participants who received at least one dose of study treatment and had at least one follow-up. Safety was analyzed in the safety analysis set (SAS), which was defined as participants who received at least one dose of study treatment and at least one assessment of safety data. All the primary (tpCR) and secondary endpoints (bpCR, ORR, and breast-conserving surgery rate) were estimated with two-sided 95% CIs obtained by the Clopper-Pearson method. We calculated post-hoc associations between clinicopathological variables (age, clinical stage, Ki67 expression, and lymph node metastasis) and clinical response or pathological complete response with the χ^2 test. All statistical analyses were performed with IBM SPSS software (version 25.0, IBM Corp., Armonk, New York), and $P < .05$ (two-sided) was set as statistical significance.

Drug Information	
Drug 1—Generic/working name	***Nab*-paclitaxel**
Company name	CSPC Ouyi Pharmaceutical Co., Ltd.
Drug type	Cytotoxic agents
Drug class	Taxanes
Dose	125
Unit	mg/m^2
Route	Intravenous (i.v.)
Schedule of administration	Administered on day 1 weekly for 12 weeks.

Drug 2 - Generic/working name	**Epirubicin**
Company name	—
Drug type	Cytotoxic agents
Drug class	Anthracyclines
Dose	90
Unit	mg/m^2
Route	Intravenous (i.v.)
Schedule of administration	Administered on day 1 every 2 weeks for 4 cycles.

Drug 3—Generic/working name	**Cyclophosphamide**
Company Name	—
Drug Type	Cytotoxic agents
Drug Class	Alkylating agent
Dose	600
Unit	mg/m^2
Route	Intravenous (i.v.)
Schedule of Administration	Administered on day 1 every 2 weeks for 4 cycles.

Patient Characteristics	
Number of patients, male	0
Number of patients, female	55
Stage	IIA-1; IIB-25; IIIA-15; IIIB-8; IIIC-6
Age: Median (range)	45 (28, 70) years
Number of prior systemic therapies: median (range)	0
Performance Status: ECOG	0: 55 1: 0 2: 0 3: 0 4: 0
Cancer types or histologic subtypes	HER-2 expression status: 2+ (FISH-negative), 11; 1+, 15; 0, 29 Ki67: ≤50%, 22; >50%, 33

Primary Assessment Method	
Number of patients screened	59
Number of patients enrolled	55
Number of patients evaluable for toxicity	55
Number of patients evaluated for efficacy	51 (for pathological response) 55 (for clinical response)
Evaluation method	RECIST 1.1; pathologic complete response
Pathologic response assessment, tpCR	22 [43.1 (95% CI, 29.3-57.8)]
Pathologic response assessment, bpCR	25 [49.0 (95% CI, 34.8-63.4)]
Response assessment, CR	12 (21.8%)
Response assessment, PR	32 (58.2%)
Response assessment, SD	8 (14.5%)
Response assessment, PD	3 (5.5%)
Outcome notes	The proportion of patients requiring breast-conserving surgery: 11 (21.6%). Table 2 shows the adverse events.

Assessment, Analysis, and Discussion	
Completion	Study completed
Investigator's assessment	Active but results overtaken by other developments

This phase II study has provided the first analysis of *nab*-paclitaxel followed by dose-dense EC in Chinese women with TNBC in the neoadjuvant setting. The study has met the primary endpoint, with a tpCR rate of 43.1%. Because the proportion of patients with a tpCR was higher than the 40% cutoff used in the statistical assumption, we regarded the NAC regimen as effective. No new safety signals were identified, indicating the manageable and acceptable safety profile of this regimen.

So far, extensive evidence has shown that pCR after NAC is a surrogate marker for long-term survival outcomes,[3-5] accordingly, two definitions for pCR were defined as efficacy endpoints here. In our study, pCR was assessed strictly that patients who did not undergo surgery were deemed as not achieving a pCR. Despite our stringent assessment of pCR, *nab*-paclitaxe/EC regimen showed encouraging results with a tpCR of 43.1% and bpCR of 49.0% in TNBC. Comparatively, results from a previous study in the Japanese TNBC population showed that tpCR was achieved only in 15.4% of patients after this NAC regimen,[1] which was lower than that in our study. This clinical benefit here may be partly attributed to the more frequent administration of EC (2-week cycle) compared to that in Japanese (3-week cycle). As reported, the dose-dense regimen is a more effective way of not only providing survival advantages but also minimizing residual tumor burden.[6] Historically, a similar result was reported in a cohort of Chinese women with TNBC who were treated with 4 cycles of dose-dense EC followed by four 2-week cycles of *nab*-paclitaxel (tpCR, 46.2%).[2] Notably, these data in the Asian population only came from about 10 TNBC cases[2]; thus, we further confirmed the anti-tumor activity of this regimen in more Asians. Although BC in Asian women is more aggressive than that in Caucasians,[7] our result compared favorably with the results from NEONAB trial (33.3%),[8] and was also generally comparable with GeparSepto-GBG 69 trial (48%).[9] Excitingly, the proportions of patients achieving tpCR in our study are relatively superior to those reported patients treated with EC plus docetaxel in NeoCART (38.6%)[10] and GBG 44 (32.9%).[11] We assumed that these advantages are mainly explained by the superiority of *nab*-paclitaxel in the improved safety profile, which allows for higher doses and a greater proportion of which actually reaches the tumor, compared to docetaxel.[12] In terms of the secondary endpoints bpCR (49.0%) and ORR (80.0%), similar results were also observed in previous studies,[1,8,9] which further supported the efficacy of this NAC regimen. The proportion of patients who underwent breast-conserving surgery that we noted in our study (21.6%) nevertheless compared unfavorably with previous studies, such as GeparSepto-GBG 69 for *nab*-paclitaxel/EC (69.5%)[9] and GEICAM 2011-02 for *nab*-paclitaxel alone (40%).[13] In fact, lots of patients in our study refused to undergo breast-conserving surgery due to concerns about relapse, leading to a relatively lower rate. Anyway, the combination NAC regimen exhibited clinically anti-tumor activity.

We did not observe the association between pathological/clinical response and clinicopathological variables, suggesting the universal adaptability of this regimen. Actually, previous neoadjuvant studies have yielded conflicting results that patients with high Ki-67 expression seemed to benefit from *nab*-paclitaxel.[2,9,14] The differences in the patient background may be responsible for the contradictory results described previously. Thus, we recommend caution when interpreting these findings due to the small sample size and pilot study.

The most common AEs here were alopecia, anemia, neutrophil count decrease, and white blood cell decrease, which were consistent with *nab*-paclitaxel monotherapy.[15] Despite 63.6% of patients experiencing grade ≥3 AEs, these events were generally manageable and resolved soon. Peripheral sensory neuropathy (PSN) is one principal toxicity induced by taxanes.[16] In our study, 54.5% of patients occurred PSN, which was relatively lower than that reported in previous studies (62.9%-86%) of *nab*-paclitaxel-containing regimens in early BC.[2,9,17] Besides, sb-paclitaxel is frequently associated with HSRs.[18] However, only 1 patient reported a grade 1 allergic reaction but recovered within 2-8 days, which highlighted the favorable safety of this NAC therapy. Importantly, no treatment-related surgical delays or deaths were observed,

except for 2 patients who discontinued treatment due to AEs. In general, the safety profile of this combination in the study population was similar to that in GeparSepto-GBG 69[9] and NEONAB[8] and generally acceptable in the neoadjuvant setting.

Several limitations of our study should be acknowledged, as was typical of early-phase trials. First, the study was a small, non-randomized, phase II study, lacking a comparison with other existing neoadjuvant regimens. Second, we acknowledged that the strength of our results might be affected by patient preference. Due to the consent withdrawal of some patients and the unreached sample size, the primary analysis of pCR rate might be affected to some extent. Third, our study only recruited patients in Chinese population, limiting the generalizability of our findings to the broader population. Fourth, our study is also limited by the lack of follow-up, therefore, the data for disease-free survival and overall survival are immature and not available at present. Thus, a longer follow-up is needed to fully assess the benefit of this NAC regimen in the long term. Currently, the combination of chemotherapy and immunotherapy is changing the paradigm in the field of TNBC neoadjuvant therapy.[19] The neoadjuvant *nab*-paclitaxel plus ICIs have shown efficacy in patients with TNBC based on recent clinical studies, such as IMpassion031 (pCR, 58%)[20] and GeparNUEVO trials (pCR, 53.4%).[21] Besides, several studies are also ongoing (NCT04676997 and NCT04907344) in Chinese populations. Accordingly, this NAC regimen has the potential to be a partner for immunotherapy, improving survival of TNBC patients.

Overall, this study of *nab*-paclitaxel followed by dose-dense EC for Chinese patients with TNBC demonstrated encouraging anti-tumor activity and acceptable tolerability, having the potential to be evaluated in future studies of chemoimmunotherapy for the TNBC population.

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IRB Approved: Ethics Committee of Shanghai Cancer Center, Fudan University (Date 2018.8.14/No 1808189-7).

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Conflict of Interest

The authors indicated no financial relationships.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Figures and Tables

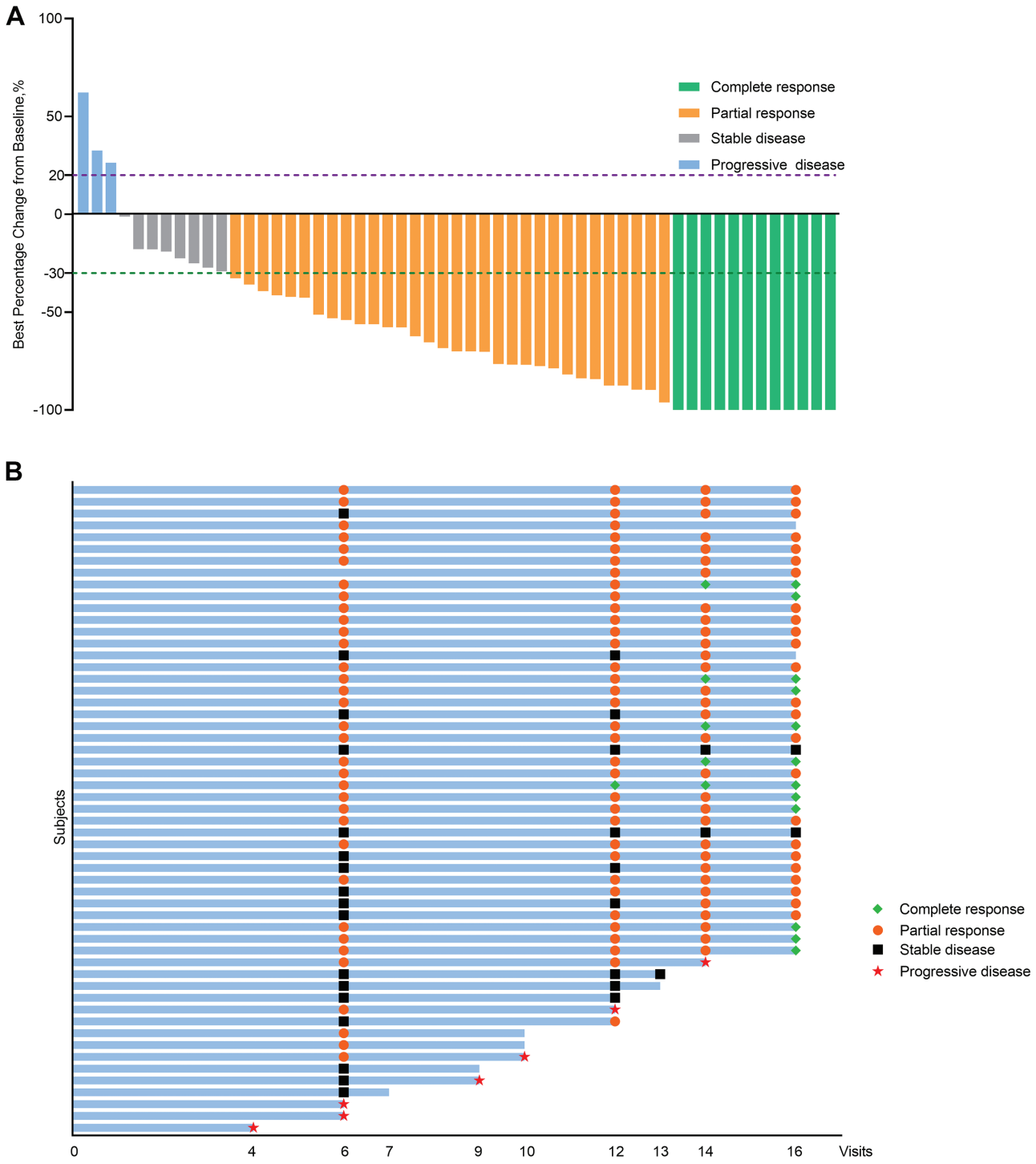

Figure 1. Response details (depth and duration of response). (A) Waterfall plot of maximum changes in tumor size from baseline in individual patients as per RECIST 1.1; (B) Swimmer plot of response and duration. Each bar represents one patient.

Table 2. Adverse events.

	All grades	Grade 3 or 4
Any events[*]	55 (100.0)	35 (63.6)
Any serious adverse events[†]	2 (3.6)	1 (1.8)
Frequent AEs (≥10% of patients)		
Hematologic toxicity		
Neutrophil count decreased	52 (94.5)	28 (50.9)
White blood cell decreased	51 (92.7)	29 (52.7)
Anemia	54 (98.2)	3 (5.5)
Platelet count decreased	14 (25.5)	1 (1.8)
Non-hematologic toxicity		
Nausea	17 (30.9)	0
Vomiting	8 (14.5)	0
Constipation	7 (12.7)	0
Diarrhea	7 (12.7)	0
Malaise	12 (21.8)	0
Fatigue	10 (18.2)	0
Edema limbs	6 (10.9)	0
ALT increased	29 (52.7)	5 (9.1)
AST increased	24 (43.6)	4 (7.3)
Weight loss	7 (12.7)	0
Myalgia	13 (23.6)	0
Peripheral sensory neuropathy	30 (54.5)	0
Insomnia	10 (18.2)	0
Alopecia	55 (100.0)	0
Skin hyperpigmentation	25 (45.5)	0
Palmar-plantar erythrodysesthesia syndrome	24 (43.6)	0
papulopustular rash	28 (50.9)	0
Nail changes	23 (41.8)	0

Data are expressed as *n* (%).
[*]Any events were defined as all treatment-emergent adverse events regardless of relationship to the study drug.
[†]Serious adverse events were defined as events that result in death, hospital admission or prolongation of a hospital admission, persistent or significant disability/incapability, congenital anomaly/birth defect, or life-threatening, or any other medically important events.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferas.