Famitinib with Camrelizumab and Nab-Paclitaxel for Advanced Immunomodulatory Triple-Negative Breast Cancer (FUTURE-C-Plus): An Open-Label, Single-Arm, Phase II Trial

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ABSTRACT

Purpose: Camrelizumab, an mAb against programmed cell death protein 1 (PD-1), plus nab-paclitaxel exhibited promising antitumor activity in refractory metastatic immunomodulatory triple-negative breast cancer (TNBC). Famitinib is a tyrosine kinase inhibitor targeting VEGFR2, PDGFR, and c-kit. We aimed to assess the efficacy and safety of a novel combination of famitinib, camrelizumab, and nab-paclitaxel in advanced immunomodulatory TNBC.

Patients and Methods: This open-label, single-arm, phase II study enrolled patients with previously untreated, advanced, immunomodulatory TNBC (CD8 IHC staining ≥10%). Eligible patients received 20 mg of oral famitinib on days 1 to 28, 200 mg of i.v. camrelizumab on days 1 and 15, and i.v. nab-paclitaxel 100 mg/m^2 on days 1, 8, and 15 in 4-week cycles. The primary endpoint was objective response rate (ORR), as assessed by investigators per RECIST v1.1. Key secondary endpoints were progression-free survival (PFS), overall survival (OS), duration of response (DOR), safety, and exploratory biomarkers.

Results: Forty-eight patients were enrolled and treated. Median follow-up was 17.0 months (range, 8.7–24.3). Confirmed ORR was 81.3% [95% confidence interval (CI), 70.2–92.3], with five complete and 34 partial responses. Median PFS was 13.6 months (95% CI, 8.4–18.8), and median DOR was 14.9 months [95% CI, not estimable (NE)–NE]. Median OS was not reached. No treatment-related deaths were reported. Among 30 patients with IHC, 13 (43.3%) were programmed death-ligand 1 (PD-L1)–negative, and PD-L1 was associated with favorable response. *PKD1* and *KAT6A* somatic mutations were associated with therapy response.

Conclusions: The triplet regimen was efficacious and well tolerated in previously untreated, advanced, immunomodulatory TNBC. The randomized controlled FUTURE-SUPER trial is under way to validate our findings.

See related commentary by Salgado and Loi, p. 2728

Introduction

Triple-negative breast cancer (TNBC), pathologically defined as the absence of estrogen and progesterone receptors and overexpression or gene amplification of HER2, accounts for 10% to 20% of breast cancer cases (1, 2). TNBC is associated with a high risk of recurrence, shorter disease-free survival, and poorer outcomes (3, 4). In recent years, immunotherapy has emerged as a breakthrough treatment for TNBC, showing moderate efficacy, particularly in combination with other therapies (5, 6). For example, the phase III IMpassion130 trial demonstrated that atezolizumab plus nab-paclitaxel prolonged progression-free survival (PFS) among patients with metastatic TNBC in both an intention-to-treat (ITT) population and a programmed death-ligand 1 (PD-L1)–positive (PD-L1$^+$) subgroup (7). Among patients with PD-L1$^+$ tumors, a statistically significant PFS (7.5 vs. 5.0 months) and clinically meaningful overall survival (OS; 25.4 vs.

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Translational Relevance

Our findings indicate that the novel combination of famitinib, camrelizumab, and nab-paclitaxel has favorable efficacy and manageable toxicity as a first-line treatment for patients with unresectable, locally advanced, or metastatic immunomodulatory triple-negative breast cancer (TNBC). This is the first study to use this approach in this subtype of breast cancer, and the best objective response rate (ORR) reached in the first-line setting to treat patients with metastatic TNBC.

17.9 months) benefit were observed with the combination of atezolizumab and nab-paclitaxel compared with nab-paclitaxel alone (7–9). In the KEYNOTE-355 trial, improvement in PFS (9.7 vs. 5.6 months) was achieved with pembrolizumab plus chemotherapy compared with placebo plus chemotherapy for metastatic TNBC, with a PD-L1 combined positive score (CPS) of 10 or more (10). However, not all PD-L1$^+$ patients benefit from immunotherapy, and the prognosis of some patients remains suboptimal. Identifying features associated with benefit from immunotherapy is a major unmet need in the quest to fulfill the promise of precision immunotherapy for TNBC, highlighting a growing need to more precisely distinguish subpopulations and develop more effective combination regimens.

Because of its high heterogeneity, TNBC can be classified into four mRNA-based subtypes with distinct molecular features (11, 12). On this basis, we conducted the FUTURE study, a phase Ib/II umbrella trial involving patients with refractory, metastatic TNBC to receive treatment according to molecular subtype (13). The overall outcomes were favorable, with an objective response rate (ORR) of 29.0% for 69 enrolled patients. In particular, 10 (62.5%) of 16 evaluable patients with immunomodulatory TNBC achieved an objective response (OR) with the combination of camrelizumab (anti–PD-1 antibody) and nab-paclitaxel.

Immunomodulatory TNBC, characterized by elevated immune cell signaling and tumor-infiltrating lymphocytes (TIL), is similar to the basal-like immune-activated subtype described by Burstein and colleagues, that benefited more from atezolizumab and nab-paclitaxel in the IMpassion 130 trial (11). TNBC of this subtype exhibits high mRNA expression of immune checkpoint molecules [such as programmed cell death protein 1 (PD-1) and PD-L1] and upregulation of the adaptive immune system, therefore representing a potential target for immunotherapy. Intratumoral CD8 and stromal TIL positivity (sTIL$^+$) were associated with a PD-L1 immune cell–positive (IC$^+$) status (14). Atezolizumab and pembrolizumab or nivolumab metastatic TNBC monotherapy studies have shown that the clinical activity in the highest when CD8-positive (CD8$^+$) T cells and/or sTILs are present (5, 14–17). The phase Ib neoadjuvant KEYNOTE-173 study assessed the safety and preliminary antitumor activity of chemotherapy plus pembrolizumab in TNBC. In the exploratory analysis, the pathologic complete response rate showed a positive correlation with tumor PD-L1 expression and sTIL levels (18). But we should notice that the KEYNOTE-173 study was a nonrandomized trial so predictivity for addition of anti–PD-1 antibody could not be addressed. Nevertheless, in the KEYNOT-522 trial, the benefit of pembrolizumab–chemotherapy with respect to pathologic complete response (CR) was generally consistent across subgroups, including PD-L1–expression subgroups. The inconsistent results may be related to the different drugs or inhibition pathways, disease stages (early rather than late), PD-L1 assays, or all of these factors (19). According to our previous studies, using IHC of CD8$^+$ cells (defined as CD8 expression on at least 10% of cells) is a clinically readily available clinical approach to select immunomodulatory subpopulations in the metastatic setting (20). CD8 is a good surrogate of sTILs, or sTILs are a good surrogate of CD8, as it has been demonstrated that the rise of sTILs in solid cancer is actually mostly CD8$^+$ (21), including that most pathology laboratories if the cancer has many TILs will not spend money or efforts for a CD8 staining as these are mostly the same cells, and they will score sTILs according to established Guidelines (22) or through the website: www.tilsinbreastcancer.org.

The interaction between tumor vessels and tumor-educated immune cells generates a vicious cycle that disturbs antitumor immunity and promotes tumor progression; abnormal tumor vessels foster suppressive immune-cell infiltration, promoting tumor angiogenesis (23, 24). Antiangiogenic therapy can ameliorate antitumor immunity in several solid tumors (25, 26). The IMpassion 130 tumor microenvironment (TME) exploratory analysis identified TME components associated with atezolizumab and nab-paclitaxel efficacy. In PD-L1 IC$^+$ patients, pathway analysis identified that angiogenesis was associated with reduced PFS, implying that antiangiogenic therapy could enhance the efficacy of immunotherapy (27).

Camrelizumab (SHR-1210) is a fully humanized, high-affinity mAb against PD-1 with clinical activity and favorable safety across multiple cancers (28–31). Famitinib (SHR1020) is a novel and potent multi-targeted tyrosine kinase inhibitor against VEGFR-2, platelet-derived growth factor receptor and c-kit (32). In this phase II FUTURE-C-Plus trial, we aimed to evaluate the efficacy and safety of a novel triplet combination of famitinib, camrelizumab, and nab-paclitaxel in patients with CD8$^+$ advanced TNBC.

Patients and Methods

Study design and patients

We conducted this open-label, single-arm, phase II trial in China, and the detailed study protocol is available in the Supplementary Text 1. The eligibility criteria were patients aged 18 to 70 years with unresectable, locally advanced, or metastatic CD8$^+$ TNBC and no prior systemic therapy for advanced disease. Before enrollment, estrogen receptor, progesterone receptor, and HER2 statuses were evaluated by individual pathologists at the Department of Pathology in Fudan University Shanghai Cancer Center (FUSCC, Shanghai, China), per guidelines (33, 34). CD8$^+$ disease was defined as CD8 expression on at least 10% of cells based on IHC (Ventana Medical Systems; catalog no. 790–4460, RRID: AB_2335985). Staining was preferentially performed on recurrent or metastatic lesions; if unavailable, primary breast cancer tissue was also acceptable. Prior (neo)adjuvant chemotherapy (including taxanes) was allowed if the treatment was completed more than 6 months before trial entry. Other inclusion criteria included an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1, at least one measurable extracranial lesion per RECIST v1.1 and adequate organ functions. Patients with treated, asymptomatic central nervous system (CNS) metastases were also eligible. The key exclusion criteria were as follows: untreated CNS disease; previous history of autoimmune disease; recent treatment [i.e., within 4 weeks or five half-lives of the drug (whichever was shorter) before enrollment] with a systemic immunostimulatory drug; use of glucocorticoids or immunosuppressive drugs; and previous immune checkpoint-targeting therapy. The complete list of eligibility criteria is provided in Supplementary Text 1–2.

The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol was

approved by the institutional Review Board of FUSCC. All the patients provided written informed consent before enrollment.

Procedures

Eligible patients received famitinib (20 mg orally once daily), camrelizumab (200 mg intravenously on days 1 and 15), and nab-paclitaxel (100 mg/m^2 i.v. on days 1, 8, and 15) in 4-week cycles. Treatment continued until disease progression, as assessed by the investigators per RECIST v1.1, intolerable toxicity occurred, consent withdrawal, or the physician's decision. In the absence of unacceptable toxicity, nab-paclitaxel was administered for a minimum of eight cycles. Famitinib dose interruptions and dose reductions (first to 15-mg once daily and subsequently to 15-mg once every other day) were permitted for toxicities that were not relieved by supportive care. The dose of nab-paclitaxel could also be reduced to either 75 mg/m^2 or 50 mg/m^2 and then discontinued when hematologic toxicity (grade 2 or worse severity) occurs. As for camrelizumab, dose reduction was not allowed, but treatment could be postponed (at most 12 weeks) or suspended to manage of an adverse event (AE; grade 2 or worse). In addition, camrelizumab or nab-paclitaxel could be independently discontinued without disease progression. For situations that are not clearly specified in the protocol, the investigators could use discretion and make decisions after balancing the patient's benefit and risk.

Outcomes

Responses were evaluated by investigators per RECIST v1.1 using imaging at baseline and every 8 weeks until disease progression. A CR or a partial response (PR) was confirmed with one sequential tumor assessment at least 4 weeks later.

Safety was evaluated according to the NCI Common Terminology Criteria for Adverse Events, version 5.0. Clinical examination, AEs reported by patients, and blood count tests were conducted and carefully checked on every 7 days of each cycle. As for other general safety assessment examinations, including biochemistry tests, electrocardiograms, and echocardiography, safety assessments were performed on day 1 of every cycle. And the causality of AE classification was done by the investigators.

The primary endpoint was ORR (confirmed CR or PR), as determined by the investigators. Secondary endpoints were investigator-assessed PFS (defined as the time from the first study dose to the first occurrence of progression or death, whichever occurred first), OS (first study dose until death from any cause), duration of response (DOR; first occurrence of response to disease progression or death from any cause, whichever occurred first), disease control rate (DCR; proportion of patients with a best OR of CR or PR or stable disease ≥ 8 weeks), safety and tolerability, and exploratory biomarker analysis.

Sample assessment

Both the tumor DNA and blood DNA were sequenced following targeted capture on the panel of 511 breast cancer–specific genes to detect somatic and gremline mutations, previously reported (35). Formalin-fixed paraffin-embedded (FFPE) blocks were retrieved for IHC staining. PD-L1 (Abcam; catalog no. ab228462, RRID: AB_2827816) and CD31 (Agilent; catalog no. M0823, RRID: AB_2114471) staining was performed on FFPE sections, with the following staining status independently assessed by two experienced pathologists. sTILs were assessed as previously described (11). Notably, if multiple tissue sections from 1 patient were available, the highest score was used for the following analysis.

Statistical analyses

Assuming an ORR of 60%, a sample size of 41 patients was needed to provide a half-width of 15% for a two-sided 95% confidence interval (CI). Considering a dropout rate of 10%, 46 patients were required (Supplementary Text 2).

The primary efficacy analysis population was the ITT population, including all eligible patients enrolled in the study. Tumor response was also assessed in the per-protocol (PP) population. Safety was analyzed in all patients who had received at least one dose of the study medication. ORR 95% CIs were calculated using the Clopper–Pearson method. Time-to-event outcomes were estimated using the Kaplan–Meier method, and the corresponding 95% CIs were calculated using the Brookmeyer–Crowley method. Biomarker analysis was performed using a nonparametric method. The statistical analysis was performed using SAS (version 9.4) and R (version 3.6.3).

Data availability

All data needed to evaluate the conclusions in the paper are present in the paper and/or the Supplementary Materials, or can be asked via the leading corresponding author (Z.-M. Shao).

Results

Study design and participants

Between October 2019 and October 2020, 122 patients were screened in this study, and 48 (39.3%) of them were CD8$^+$ (CD8≥10%) as determined in this study. These 48 patients were enrolled and received treatment. All the patients were included in the ITT and safety analysis population. Two patients (4.2%) discontinued treatment before the first scheduled postbaseline scan because of a second primary tumor ($n = 1$) or consent withdrawal ($n = 1$). Therefore, 46 patients were included in the PP population (**Fig. 1**). As of the data cutoff on October 12, 2021, the median follow-up was 17.0 months (range, 8.7–24.3), and 18 (37.5%) patients remained under treatment. The baseline characteristics are summarized in **Table 1**. Briefly, the median age was 50 years (range, 25–70); 23 patients (47.9%) had more than three metastatic sites, 24 (50.0%) had lung metastasis, and 10 (20.8%) had liver metastasis. Most of the patients (60.4%; $n = 29$) had previously received a taxane.

Efficacy

In the ITT population, 44 (95.7%) patients experienced a decrease in the target lesion target lesion size from baseline (**Fig. 2A**). A confirmed OR was achieved in 39 patients (81.3%; 95% CI, 70.2–92.3), with five CRs and 34 PRs (**Table 2**). The median time to response was 1.9 months (95% CI, 1.8–2.0; **Fig. 2B**). Among the 39 responders, the median DOR was 14.9 months [95% CI, not estimable (NE)–NE], with 18 (46.2%) responses considered ongoing. The DCR was 95.8% (46/48). In addition, 25 events (52.1%) of disease progression events and 16 (33.3%) deaths occurred, with a median PFS of 13.6 months (95% CI, 8.4 months–18.8 months; **Fig. 2C**). The median OS was not reached (95% CI, NE–NE; **Fig. 2D**); the OS rate was 82.6% (95% CI, 71.6–93.6) at 12 months and 54.4% (95% CI, 36.2–72.6) at 18 months.

Safety

Most patients (96%; $n = 46$) in the safety population shown at least one treatment-related AE (TRAE; **Table 3**). Grade 3 or 4 TRAEs occurred in 24 patients (50.0%), the most common of which were neutropenia (33.3%; $n = 16$), anemia (10.4%; $n = 5$), febrile neutropenia (10.4%; $n = 5$), thrombocytopenia (8.3%; $n = 4$), fatigue (6.3%; $n = 3$), and anorexia (6.3%; $n = 3$). Grade 3 peripheral sensory

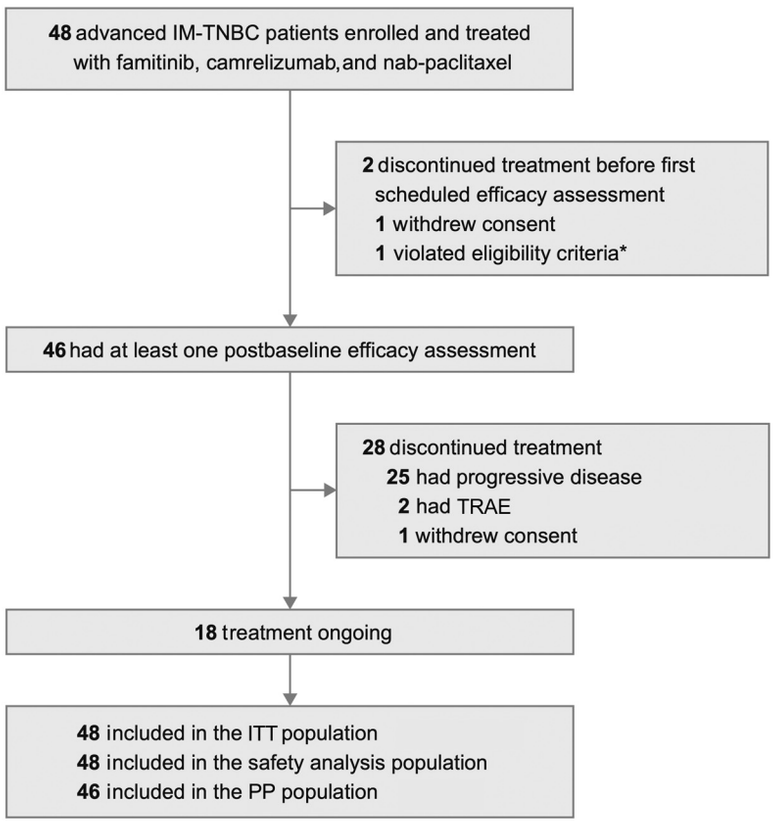

Figure 1.
Study overview. *One patient was diagnosed with a second primary tumor (multiple myeloma) and carried a likely pathogenic germline *BRCA1* mutation.

neuropathy (2.1%) was deemed to be taxane-related, and it is known to be cumulative. Serious TRAEs were observed in 2 patients (4.2%), 1 (2.1%) with grade 3 septicemia and 1 (2.1%) with grade 3 immune-related myocarditis. In the latter case, myocarditis was relieved 1 week after intensive care and prednisone administration, but immunotherapy was permanently discontinued. No treatment-related deaths occurred.

Twenty-six patients (54.2%) had potentially immune-related AEs associated with camrelizumab, the most common of which was an increase in thyroid-stimulating hormone (TSH; 54.2%; **Table 3**). Four patients (8.3%) had grade 3 potentially immune-related AEs, 1 (2.1%) with myocarditis, 2 (4.2%) with hypothyroidism, and 1 (2.1%) with an alanine aminotransferase (ALT)/aspartate aminotransferase (AST) increase. The 2 patients with grade 3 hypothyroidism received corticosteroids and resumed camrelizumab treatment. The patient with grade 3 increased ALT/AST received therapy to protect the liver and reduce enzyme activity, and camrelizumab treatment was resumed. One patient had a grade 3 hepatobiliary disorder (cirrhosis), but the patient's liver metastases evaluated stable. Patient number 2, a 70-year-old female patient with left supraclavicular lymph node metastasis, developed grade 3 neutropenia, grade 2 fatigue, and grade 2 anorexia and withdrew from the study after receiving one treatment cycle. Nineteen patients (39.6%) had famitinib-related AEs, 2 (4.2%) with grade 3 hypertension and 1 (2.1%) with grade 3 proteinuria. Immune-related or famitinib-related AEs of TSH increase and hypothyroidism occurred in 26 (54.2%) and 10 (20.8%) patients, respectively. Most of these patients had grade 1 or 2 AEs, except for 2 (4.2%) with grade 3 hypothyroidism.

All 48 patients received at least one complete cycle of treatment. The median treatment cycle was 8 (range, 1–8 cycles) for nab-paclitaxel and 10 (range, 1–26 cycles) for camrelizumab and famitinib. Two patients (4.2%) discontinued treatment because of grade 3 TRAEs. Three patients (6.3%) had treatment discontinuation (2 for famitinib and 1 for nab-paclitaxel). Four patients (8.3%) required at least one famitinib dose interruption; 4 (8.3%) and 6 (12.5%) patients required at least one camrelizumab and nab-paclitaxel dose interruption, respectively. Thirty-five patients (72.9%) had a famitinib dose reduction. The reasons for famitinib dose reductions are stated in Supplementary Table S1.

Genomic and clinicopathologic biomarkers for therapy response

In post hoc analyses, we used a FUSCC next-generation sequencing (NGS) panel to call somatic mutations. The most frequently mutated genes in patients with the advanced immunomodulatory TNBC included *TP53* (78%), *BCOR* (13%), *BRCA1* (13%), *KAT6A* (13%), and *RRM2* (13%; **Fig. 3A**). Although the pathologic characteristics in tumors with high or low mutation events did not vary, patients exhibiting exceptional responses (remission ≥80%) had fewer mutations in tumor biopsies ($P = 0.006$, **Fig. 3B**) and circulating tumor DNA (ctDNA; $P = 0.073$, **Fig. 3C**) samples. Such finding was validated in the small insertions and deletions (indel; Supplementary Fig. S1).

The main objective of describing the genomic landscape of patients in the FUTURE-C-Plus trial was to explore biomarkers to predict therapy response. Using NGS data paired with therapy response data ($n = 22$), we evaluated the relationship between tumor response and frequent somatic mutations (≥5% in the cohort). In total, somatic mutation of *KAT6A* was positively associated with OR ($P = 0.044$), whereas *BRCA1* ($P = 0.055$) and *PKD1* ($P = 0.034$) showed the opposite trend (**Fig. 3D**).

Table 1. Baseline patient characteristics.

Characteristic	*N* (%) Patients (*N* = 48)
Age, years	
Median (range)	50 (25–70)
18–40	14 (29.2)
41–60	24 (50.0)
61–70	10 (20.8)
Disease status	
Metastatic, *de novo*	16 (33.3)
Metastatic, recurrent	31 (64.6)
TFI 6–12 months	15 (31.3)
TFI >12 months	16 (33.3)
Locally inoperable advanced	1 (2.1)
ECOG performance status	
0	18 (37.5)
1	30 (62.5)
Number of metastatic sites	
<3	25 (52.1)
≥3	23 (47.9)
Metastatic site	
Lung	24 (50.0)
Liver	10 (20.8)
Bone	19 (39.6)
Only lymph node or soft tissue	14 (29.2)
Brain	3 (6.3)
Neoadjuvant or adjuvant chemotherapy	
Any	32 (66.7)
Anthracycline	30 (62.5)
Taxane	29 (60.4)
Platinum	6 (12.5)
Capecitabine	5 (10.4)
PD-L1 expression	
Positive	17 (35.4)
Negative	13 (27.1)
Unknown	18 (37.5)

Abbreviation: TFI, treatment-free interval.

In addition, we observed that elderly patients benefited more from treatment (**Fig. 3E**); the reason for this observation still needs more investigation. Patients with more than three metastatic sites showed a worse therapy response (**Fig. 3F**). Besides, bone metastasis indicated potential-less benefit from the treatment (Supplementary Fig. S2). Although a single agent of PD-L1 did not indicate therapy response, the combined score of PD-L1 and CD31 (a biomarker of vessels) had predictive potential, in accordance with our previous hypothesis, that vessel abundance is related to famitinib response. Overall, patients with double-negative PD-L1/CD31 tumors responded poorly to the triplet combination regimen (**Fig. 3G–H**). We also found a positive association between sTIL and CD8 (Supplementary Fig. S3). Thus, identifying the immunomodulatory TNBC-subtype using sTIL instead of an expensive CD8 assay may also be an option in the future.

These data suggest the predictive value of baseline parameters for combination therapy in patients with advanced immunomodulatory TNBC and raise questions such as why somatic *PKD1* mutation indicates worse efficacy of the triplet regimen. These topics warrant further study.

Discussion

Immuno-oncology is rapidly expanding in TNBC treatment, but barriers to better efficacy persist. Compared with "immune-hot" tumors, such as melanoma, TNBC lacks abundant effector T cells, leading to limited antitumor immunity and unsuccessful immunotherapy (36, 37). TNBC patient subgroups with higher immune infiltration must be identified. In addition, strategies must be developed to render these tumors truly "immune-hot" for combination immunotherapy.

Many biomarkers have been generated to classify patients who respond to immunotherapy, including single molecules, such as PD-L1 and CXCL9, and general concepts, such as the tumor mutation burden (TMB) and apolipoprotein B mRNA editing catalytic polypeptide signature (38). The clinical effect of these biomarkers remains controversial, even for the commonly used PD-L1 expression.

A highlight of this study was the use of CD8 for immunomodulatory TNBC selection. Our previous study identified $CD8^+$ T cells as a hallmark of immunomodulatory TNBC and validated this hypothesis in the FUTURE trial (13, 20). The quantity of TILs in breast cancer has been identified as a robust prognostic factor for improved survival in patients with TNBC (39). A meta-analysis suggested that high intratumoral, stromal, or invasive marginal $CD8^+$ T cells, can predict treatment outcomes in patients with immunotherapy across different cancers (40). The recently reported Impassion 130 tumor environment analysis also supported that the immune-enriched TNBC subtype can benefit from immunotherapy (27). Another study analyzing TNBCs for spatial immune-cell contextures in relation to clinical outcomes revealed the positive relationship between an inflamed phenotype and the response to anti-PD1 (41). All the studies implied the sTILs as well as CD8 reflect the immunomodulatory TNBC-subtype, and this is irrespective of PDL1. Meanwhile, we considered the level of CD8 by IHC as an even easier method to quantify immune cells in solid tumors than expensive genomic assays. This method may have broad applications in other malignancies (42). Absence of assay standardization is an emerging issue for the immunotherapy in TNBC. Using more than one assay for the same biomarker is problematic because the assays have different positive prevalence rates. As the International Immuno-Oncology Biomarker Working Group commented in Lancet Oncology (43), industry should be mandated to do concordance studies with other similar assays before a drug is approved. Clinical practice guidelines developed by professional organizations like the American Society of Clinical Oncology and European Society for Medical Oncology should endorse not just a companion diagnostic assay used in the trial, but any rigorously validated equivalent laboratory assays that can define essentially the same population. In another way, a good surrogating biomarker such as CD8/sTILs with an established scoring guidelines for therapeutic prediction may facilitated the drug approval and application.

In addition, the benefit of single-agent immunotherapy is influenced by the number of previous lines of therapy for metastatic disease. In unselected patients with TNBC, the anti–PD-L1 antibody atezolizumab indicated an ORR of 24% in the first-line setting, with an ORR of 6% in the second- or later-line setting (15). Metastatic sites are more immunodepleted, with fewer immune cells, including $CD8^+$ T cells. This observation is consistent with the known increase in immunosuppression and changes in immunologic traits occurring during tumor progression and suggests that early immunotherapy maximizes benefit. Immunotherapy combined with chemotherapy may not only reduce the risk of early progression but also leverage the well-known immunomodulatory properties of chemotherapy to increase antigenicity (44). Thus, it might be expected that patients with first-line immunomodulatory TNBC would receive great clinical benefit receiving combination of checkpoint blockade and chemotherapy which based on CD8 expression as a biomarker for efficacy prediction.

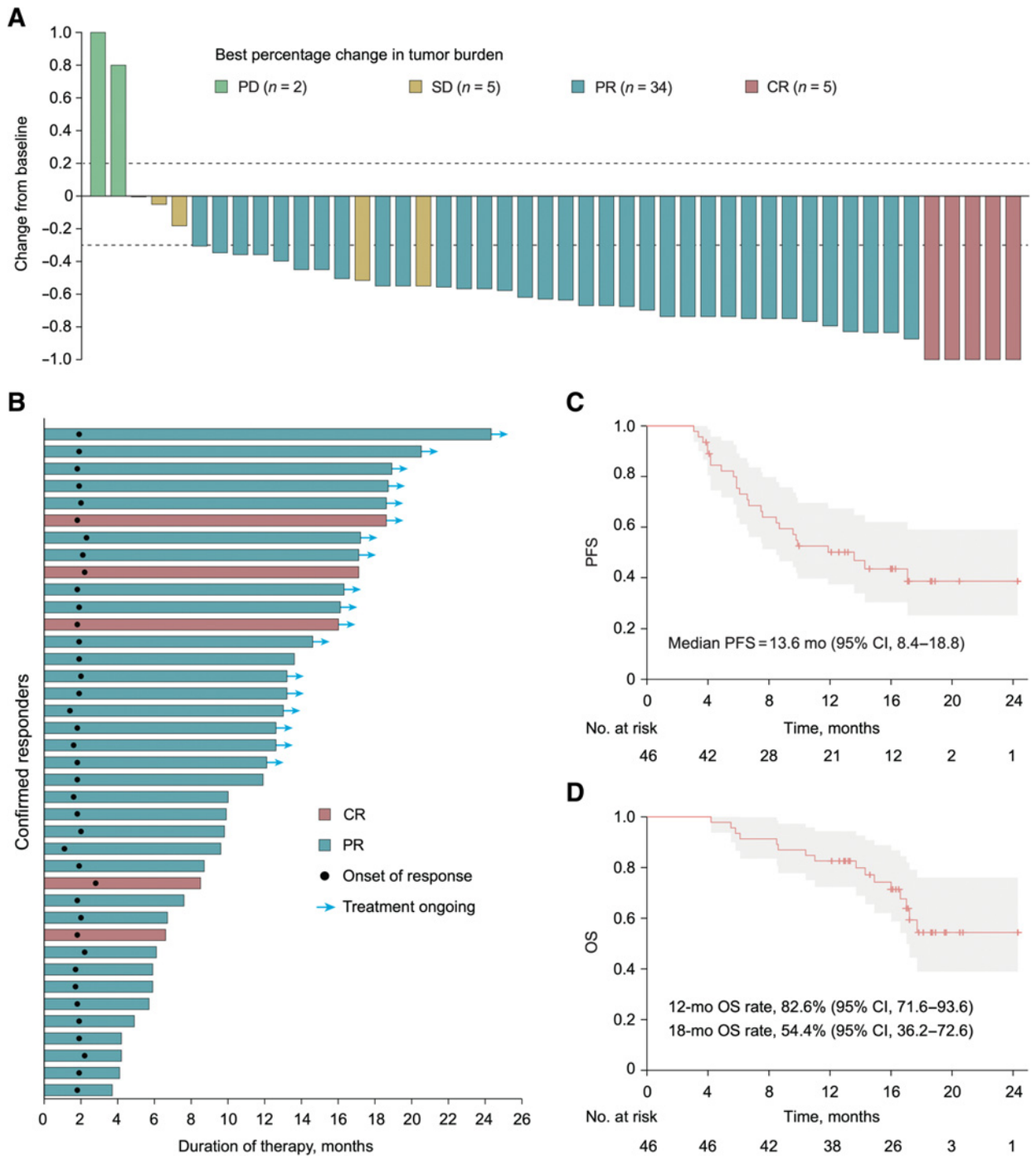

Figure 2.

Tumor response and survival data. **A,** Best percentage change from baseline in the target lesion, as assessed by the investigators ($n = 46$); the best overall response is indicated by color coding of bars and includes assessment of target, nontarget, and new lesions via RECIST v1.1. **B,** DORs among patients with a confirmed OR ($n = 39$); the bar length represents the treatment duration for each patient. **C** and **D,** Kaplan–Meier curve of PFS and OS. PD, progressive disease; SD, stable disease; mo, months.

Table 2. Tumor response.

Response	No. (%) ITT ($N = 48$)[a]	PP ($n = 46$)[b]
Rate, *N* (%; 95% CI)		
OR	39 (81.3; 70.2–92.3)	39 (84.8; 74.4–95.2)
Response		
CR	5 (10.4)	5 (10.9)
PR	34 (70.8)	34 (73.9)
Stable disease	5 (10.4)	5 (10.9)
Progressive disease	2 (4.2)	2 (4.3)

[a]Responses were assessed with RECIST v1.1. Only confirmed responses were included.
[b]Two patients without postbaseline efficacy assessments were excluded.

Another main point is the addition of an antiangiogenic agent to the established immunotherapy. Aberrant tumor-associated neovasculature has been proven to induce various immunosuppressive features, and antiangiogenic therapy can ameliorate antitumor immunity (25, 26). The IMpassion 130 TME exploratory analysis identified angiogenesis as associated with reduced PFS. Therefore, we wanted to explore whether patients benefited more from immune checkpoint blockade plus angiogenesis inhibition. This hypothesis was supported by a respectable efficacy (ORR = 81.3%; median PFS = 13.6 months) and good tolerability (only 3 patients discontinued therapy because of TRAEs) in 48 patients with advanced immunomodulatory TNBC enrolled to receive famitinib, camrelizumab, and nab-paclitaxel. To the best of our knowledge, the response is impressive in the field of advanced TNBC treatment compared with that in IMpassion 130 (atezolizumab plus nab-paclitaxel, ORR = 56.0%), KEYNOTE-355 (pembrolizumab plus chemotherapy, ORR = 41.0%), CBCSG006 and GAP (cisplatin-based chemotherapy, ORR = 64.0% and 81.1%, respectively; 9, 45, 46). In addition, the favorable response was remarkably rapid (median time-to-response of 1.9 months) and durable (median duration time of 14.9 months), leading to a median PFS of 13.6 months (95% CI, 8.4 months–18.8 months). Although the OS data are not yet available, an encouraging OS rate was observed at 12 months (82.6%; 95% CI; 71.6–93.6).

The safety profile of the famitinib, camrelizumab, and nab-paclitaxel combination was consistent with that reported for anti–PD-1/PD-L1 antibodies plus VEGF pathway inhibitors or chemotherapy in advanced TNBC (5, 6, 47). The triplet regimen was well tolerated, with only 2 patients discontinuing treatment because of AEs. The most common grade 3 or 4 TRAE was neutropenia (33.3%), with an incidence similar to the 37.0% reported for camrelizumab plus nab-paclitaxel in the FUTURE trial but higher than the 8.2% reported in IMpassion 130 (9, 13). This difference may be partially attributed to the higher susceptibility to hematologic toxicities with chemotherapy in Asian patients (48). Overall, hematologic events were generally manageable and reversible with dose modification and the use of G-CSF. Hypothyroidism, a common AE in patients treated with anti-VEGF targeting agents, was also observed in a famitinib phase I study; 64.0% (16/25) of patients were reported to have subclinical hypothyroidism, suggesting elevated TSH but normal ranges of FT4 and FT3 (32). In a previous camrelizumab phase II study, hypothyroidism occurred in 26.7% of patients (29). Notably, increased TSH was found in 54.2% (26/48) of the patients in our study, likely because of the combinational use of famitinib and camrelizumab; similarly, most events were grade 1 or 2. Twenty percent of patients developed hypothyroidism of any grade, with only two (4.2%) cases of grade 3. Reactive cutaneous capillary endothelial proliferation (RCCEP)

Table 3. AEs.

AE	No. (%), $N = 48$ All grade	Grade 1–2	Grade 3	Grade 4
Hematologic toxicity				
Neutropenia	38 (79.2)	22 (45.8)	9 (18.8)	7 (14.6)
Anemia	10 (20.8)	5 (10.4)	5 (10.4)	0 (0.0)
Thrombocytopenia	9 (18.8)	5 (10.4)	3 (6.3)	1 (2.1)
Febrile neutropenia	5 (10.4)	0 (0.0)	5 (10.4)	0 (0.0)
Nonhematologic toxicity				
Fatigue	36 (75.0)	33 (68.8)	3 (6.3)	0 (0.0)
Anorexia	39 (81.3)	36 (75.0)	3 (6.3)	0 (0.0)
TSH increased	26 (54.2)	26 (54.2)	0 (0.0)	0 (0.0)
Nausea	23 (47.9)	23 (47.9)	0 (0.0)	0 (0.0)
Vomiting	12 (25.0)	12 (25.0)	0 (0.0)	0 (0.0)
Peripheral sensory neuropathy	11 (22.9)	10 (20.8)	1 (2.1)	0 (0.0)
Hypertension	10 (20.8)	8 (16.7)	2 (4.2)	0 (0.0)
Hypothyroidism	10 (20.8)	8 (16.7)	2 (4.2)	0 (0.0)
ALT/AST increased	8 (16.7)	7 (14.6)	1 (2.1)	0 (0.0)
Palmar-plantar erythrodysesthesia	8 (16.7)	8 (16.7)	0 (0.0)	0 (0.0)
RCCEP	4 (8.3)	4 (8.3)	0 (0.0)	0 (0.0)
Proteinuria	1 (2.1)	0 (0.0)	1 (2.1)	0 (0.0)
Septicemia	1 (2.1)	0 (0.0)	1 (2.1)	0 (0.0)
Immune-related myocarditis	1 (2.1)	0 (0.0)	1 (2.1)	0 (0.0)
Hepatobiliary disorders (cirrhosis)	1 (2.1)	0 (0.0)	1 (2.1)	0 (0.0)
Potential immune-related AEs				
TSH increased	26 (54.2)	26 (54.2)	0 (0.0)	0 (0.0)
Hypothyroidism	10 (20.8)	8 (16.7)	2 (4.2)	0 (0.0)
RCCEP	4 (8.3)	4 (8.3)	0 (0.0)	0 (0.0)
ALT/AST increased	1 (2.1)	0 (0.0)	1 (2.1)	0 (0.0)
Immune-related myocarditis	1 (2.1)	0 (0.0)	1 (2.1)	0 (0.0)

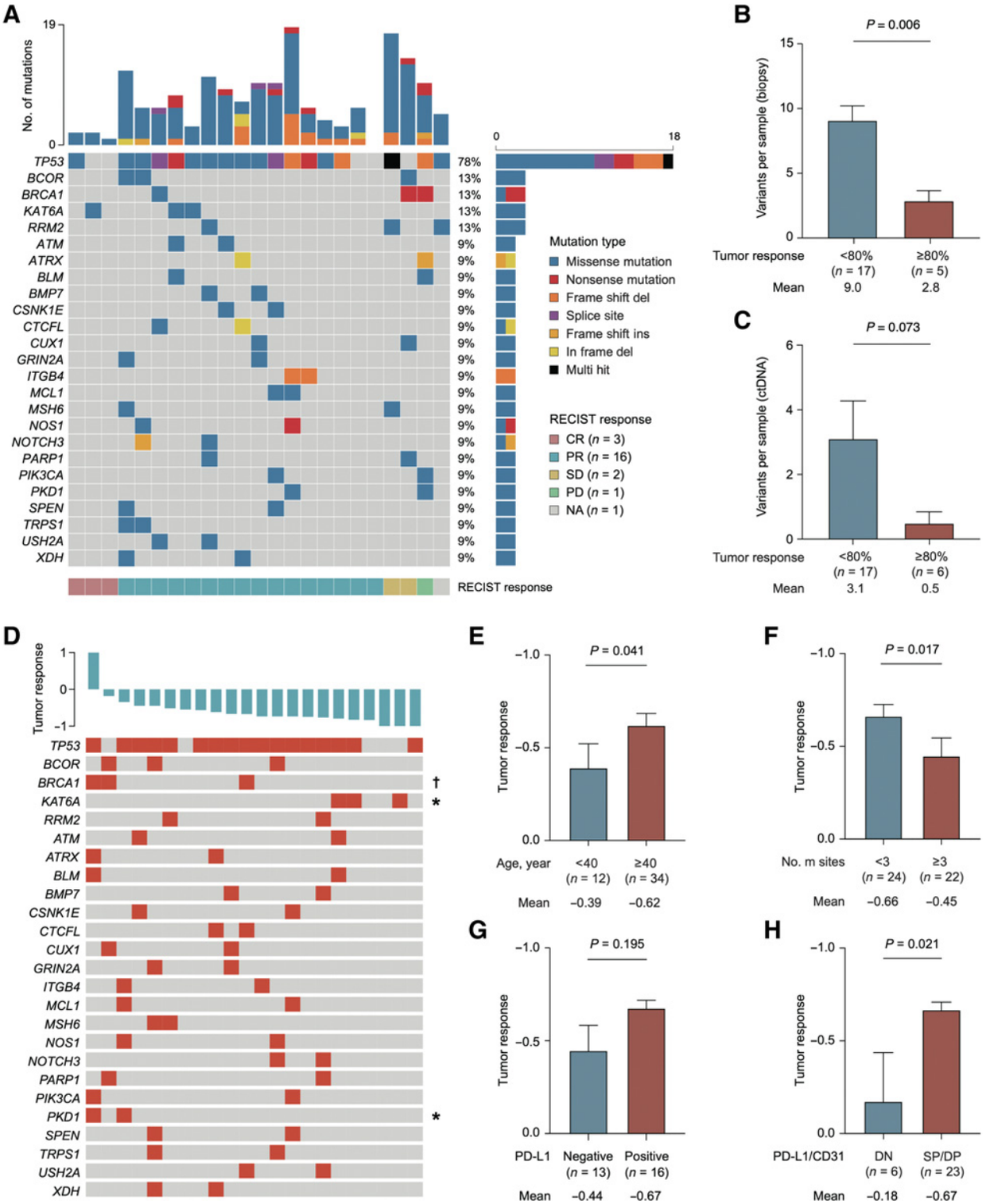

Figure 3.

Genomic and clinicopathologic biomarkers for therapy response. **A,** The genomic landscape of patients in the FUTURE-C-Plus trial. **B** and **C,** Association of variants detected via biopsy and ctDNA using an extraordinary response (relative remission ≥ 80%). **D,** Detected somatic mutations with an objective response. **E–H,** Association of age, number of metastatic sites, PD-L1, and PD-L1/CD31 expression with tumor response. *, $P < 0.05$; †, $0.05 \le P < 0.25$. Abbreviations: DN, double-negative; SP, single-positive; DP, double-positive; Del, deletion; ins, insertion; PD, progressive disease; SD, stable disease.

occurring on the skin surface is an immune response of skin capillary endothelial cells, has been observed in patients treated with camrelizumab and is positively associated with the outcomes of camrelizumab in advanced hepatocellular carcinoma (HCC; ref. 49). RCCEP was recorded in 8.3% (4/48) of the patients in our study.

Most patients received a dose reduction from 20 mg to 15 mg of famitinib. Preclinical data showed that by causing excessive vessel pruning, a high dose of antiangiogenic agents could result in a short normalization window. Conversely, low doses may prolong vessel normalization, reduce tumor hypoxia, and enhance immune-cell infiltration (50). However, whether a lower dose of famitinib leads to a more durable response is unknown, and the optimal dose and schedule of such a combination must be further investigated.

Next, we identified potential clinico-genomic predictive biomarkers. A substantial benefit was observed in patients with an older age (≥40 years old) and fewer metastatic sites (<3), likely because of the less invasive behavior of these tumor cells (51). We also found a potential difference of tumor response in patients with different metastases, for example the less benefit in patients with bone metastasis; this could be partly explained by the low TILs in bone metastasis and should be elucidated in the future. Overall, the expression of immune and neovascular molecules (PD-L1/CD31 score) assessed by IHC can predict therapy response. PD-L1 is a classical biomarker for selecting patients who are likely to benefit from PD-1/PD-L1 inhibition, and CD31 is a marker used to indicate vessels, consistent with our hypothesis that patients with activation of both immune and angiogenesis pathways are candidates for such regimens. However, the result of PD-L1 staining was only generated via clone SP142, and the method using 22C3 and the CPS scoring system was also effective to predict response of checkpoint blockade (10, 52); these findings warrant investigation in our following studies. A high TMB is often related to neoantigen generation, indicating an active process of antigen presentation, and following tumor rejection via immunity. Interestingly, in this case, the overall mutation status was negatively associated with therapy response, a finding that is contrary to conventional thought (53). In addition, not all TMBs are the same. According to a recent study, tumors with higher indel mutations may tend to immunogenic phenotype (54). However, in this study, we found similar results concerning both absolute TMB and indel. Conceptually, this could be explained by the higher TMB but also greater genomic heterogeneity in TNBC, thus patients may have indeed lower TILs. In addition, immunoediting, which is a result of a selection of cancer cell clones with decreased immunogenicity despite the presence of many mutations, could lead to escape from immune surveillance, and is associated with a reduced TIL component and increased tumor clonal heterogeneity, explaining the negative association between TMB and TILs, thus therapy response (55, 56). We believe further investigation of genomic events such as copy-number alterations, whole genome doubling, and the emergence of immune-evasive clonal versus subclonal mutations would be helpful.

Our findings demonstrate the potent antitumor activity of this triplet regimen for immunomodulatory TNBC and support clinical testing of corresponding biomarkers in patients to determine their impact on OS, ORR, DOR, safety, and toxicity. Further chemo-free regimens combining famitinib and camrelizumab in neoadjuvant and metastatic settings have been designed, and clinical trials should also be performed at our center. Notably, intratumoral immune activation by antibody–drug conjugates (trastuzumab deruxtecan) plus durvalumab in HER2-low–expressing TNBC showed promising results (ORR = 67%; ref. 57).

We acknowledge the limitations of this trial, including the absence of a control group and the small number of enrolled patients. Long-term follow-up data are being collected and will allow further characterization of the clinical activity and durability of response. In addition, the biomarker analysis in this study is only based on biopsies collected at a single time point, with a lack of cumulative data collection. This situation can cause unreliable results because tumors and their responses to therapy often vary with therapy duration and the predictive value of such biomarkers may be overestimated. Collecting on-treatment biopsies will be helpful to the community to provide better insights in dynamics of response and biomarkers. The basic mechanisms by which such a combination regimen provides the impressive benefit observed also need further elucidation. We have initiated the FUTURE-SUPER (NCT04395989) trial, a randomized controlled trial that is currently in progress; the trial is estimated to enroll 138 patients, and we will collect both baseline and on-treatment samples to validate the findings.

In conclusion, the novel combination of famitinib, camrelizumab, and nab-paclitaxel exhibits marked antitumor activity and manageable toxicity as a first-line treatment for patients with unresectable, locally advanced, or metastatic immunomodulatory TNBC. Our findings support this triplet combination as a potential first-line treatment option for advanced immunomodulatory TNBC.

Authors' Disclosures

X.-Y. Zhu is employed by Jiangsu Hengrui Pharmaceuticals Co. Ltd (formerly Jiangsu Hengrui Medicine). J.-J. Zou is employed by Jiangsu Hengrui Pharmaceuticals Co. Ltd (formerly Jiangsu Hengrui Medicine). No disclosures were reported by the other authors.

Authors' Contributions

L. Chen: Writing–original draft. **Y.-Z. Jiang:** Writing–original draft, writing–review and editing. **S.-Y. Wu:** Validation, writing–original draft. **J. Wu:** Resources, project administration. **G.-H Di:** Resources. **G.-Y. Liu:** Resources. **K.-D. Yu:** Resources. **L. Fan:** Resources. **J.-J. Li:** Resources. **Y.-F. Hou:** Resources. **Z. Hu:** Resources. **C.-M. Chen:** Resources. **X.-Y. Huang:** Resources. **A.-Y. Cao:** Resources. **X. Hu:** Software. **S. Zhao:** Software. **X.-Y. Ma:** Visualization. **Y. Xu:** Visualization. **X.-J. Sun:** Data curation, writing–review and editing. **W.-J. Chai:** Funding acquisition, investigation. **X. Guo:** Data curation, funding acquisition, writing–review and editing. **X. Chen:** Data curation, formal analysis, supervision, writing–review and editing. **Y. Xu:** Data curation, formal analysis, supervision, writing–review and editing. **X.-Y. Zhu:** Conceptualization, funding acquisition, methodology, project administration, writing–review and editing. **J.-J. Zou:** Funding acquisition. **W.-T. Yang:** Data curation, formal analysis, supervision, writing–review and editing. **Z.-H. Wang:** Data curation, formal analysis, supervision, writing–review and editing. **Z.-M. Shao:** Conceptualization, data curation, funding acquisition, methodology, project administration, writing–review and editing.

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