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ORIGINAL ARTICLE

Safety and efficacy of tiragolumab, atezolizumab and chemotherapy for early-stage or PD-L1-positive advanced triple-negative breast cancer: a phase Ib study

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Background: Immune checkpoint inhibitors have transformed the management of triple-negative breast cancer (TNBC) but outcomes could be improved further. We explored combining the T-cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT) inhibitor tiragolumab with atezolizumab-containing regimens for patients with early-stage or advanced TNBC.

Patients and methods: This multinational open-label phase Ib study included two cohorts. In cohort A [programmed death-ligand 1 (PD-L1)-positive advanced TNBC], patients received first-line tiragolumab with atezolizumab and nab-paclitaxel. The primary endpoint was confirmed objective response rate. In cohort B (early-stage TNBC, irrespective of PD-L1 status), patients were randomised to receive tiragolumab, atezolizumab and sequential taxane- and anthracycline-based neoadjuvant therapy with (arm A) or without (arm B) carboplatin. The primary objective was to evaluate safety in arm A versus arm B.

Results: Between September 2020 and October 2021, 83 patients were enrolled from 24 sites in eight countries. In cohort A ($n = 41$), the confirmed objective response rate was 54% [95% confidence interval (CI) 37% to 69%], median duration of response in 22 responding patients was 7.2 months (95% CI 4.9-13.1 months), median progression-free survival was 6.5 months (95% CI 5.4-9.0 months) and median overall survival was 24.6 months (95% CI 14.7 months-not estimable). Five patients (12%) discontinued tiragolumab for adverse events. In cohort B ($n = 42$), carboplatin was associated with more haematological effects but no increase in pathologic complete response rate [arm A: 46% (95% CI 24% to 68%); arm B: 55% (95% CI 32% to 77%)]. Adverse events led to treatment discontinuation in 23% and 20% of patients in arms A and B, respectively.

Conclusions: The activity of tiragolumab-containing regimens appeared similar to that of atezolizumab plus chemotherapy in randomised phase III trials in early-stage and advanced TNBC. The safety profile of all three regimens was consistent with previous experience of similar regimens in other tumour types and with symptoms of the underlying disease.

Clinical trial registration: ClinicalTrials.gov NCT04584112.

Key words: dual blockade, immune checkpoint, TIGIT, triple-negative breast cancer

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INTRODUCTION

For many years, the heterogeneous group of patients described as having triple-negative breast cancer (TNBC; absence of oestrogen and progesterone receptor

expression and HER2 overexpression or gene amplification) had no targeted treatment options and a worse prognosis than patients with other subtypes of breast cancer. However, the treatment landscape has evolved rapidly in recent years, with the development and introduction into routine clinical practice of immune checkpoint inhibitors, poly (ADP-ribose) polymerase inhibitors and antibody—drug conjugates.[1-11] These new agents have improved life expectancy.[4,11,12] However, some are beneficial only for subsets of patients with relevant markers, and outcomes remain poor for many patients with TNBC despite the advances in therapy.[13]

For patients diagnosed with early-stage TNBC, global guidelines broadly endorse dose-dense anthracycline-, carboplatin- and taxane-based regimens.[14] The addition of immune checkpoint inhibitors to chemotherapy improves the pathologic complete response (pCR) rate and, in some cases, event-free survival (EFS) and overall survival (OS) compared with chemotherapy alone.[5,6,15-17] In the IMpassion031 phase III trial, the addition of atezolizumab to a dose-dense taxane- and anthracycline-based regimen significantly improved the pCR rate[16] but the chemotherapy backbone did not include carboplatin, which improves the efficacy of neoadjuvant chemotherapy for TNBC.[18-20] The KEYNOTE-522 trial demonstrated significantly improved pCR rate, EFS and OS when pembrolizumab was combined with a carboplatin-based neoadjuvant regimen but the trial did not use a dose-dense anthracycline schedule.[6,15,21] Most recently, NSABP B-59/GBG-96-GeparDouze, which used a platinum-based dose-dense anthracycline chemotherapy backbone, did not show a significant improvement in EFS (primary endpoint) with the addition of atezolizumab in the overall population.[22]

In locally advanced or metastatic TNBC, the benefit of programmed death ligand-1 (PD-L1) and programmed cell death protein 1 (PD-1) inhibitors has been demonstrated in patients with PD-L1-positive tumours.[2-4] Until recently, attempts to improve outcomes further had been largely unsuccessful.[23,24] Strategies combining checkpoint inhibitors with agents offering alternative modes of action are being investigated,[25-27] including phase III trials in combination with antibody—drug conjugates.[28]

It is hypothesised that some patients may have intrinsic resistance to checkpoint inhibition, which might be overcome by using novel immunotherapy combinations. Dual targeting of CTLA-4 and the PD-1/PD-L1 pathway has demonstrated efficacy in melanoma and non-small-cell lung cancer but is associated with increased toxicity.[29] Tiragolumab is an investigational immune checkpoint inhibitor with an intact Fc region. Tiragolumab selectively binds to T-cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT), a novel inhibitory immune checkpoint that suppresses the immune response to cancer. TIGIT inhibits T-cell activation via direct inhibition of T cells, induction of poliovirus receptor signalling on antigen-presenting cells and inhibition of stimulatory CD226 signalling.[30] TIGIT is expressed in a wide variety of human tumours, including breast cancer,[31,32] and correlates with T-cell infiltration and PD-1 expression.[33] In TNBC, high TIGIT expression is associated with younger age, higher histological grade, non-lobular histology, prior adjuvant chemotherapy and high PD-L1 expression.[34] In preclinical models, the efficacy of dual TIGIT and PD-L1 blockade was superior to either agent alone,[35] supporting the evaluation of regimens combining these two approaches. When the present trial was designed, co-inhibition of TIGIT and PD-(L)1 represented a promising therapeutic approach for cancer, offering the potential to improve outcomes for patients with cancer treated with immune checkpoint inhibitors without substantially altering the safety profile of atezolizumab-based therapy. The underlying scientific premise was that dual checkpoint inhibition could augment the restoration of antitumour immunity, thereby improving the efficacy of immunotherapy across a broader spectrum of patients with cancer, including TNBC.[36]

METHODS

The global open-label multicohort phase Ib CO42177 study (NCT04584112) investigated the safety, tolerability and preliminary efficacy of regimens combining tiragolumab with atezolizumab and standard chemotherapy in patients with TNBC.

Cohort A

Cohort A (first-line advanced setting) enrolled men or women aged ≥18 years with measurable [per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1] unresectable locally advanced or metastatic PD-L1-positive TNBC who had received no prior systemic therapy for advanced TNBC. PD-L1 expression was tested at a central laboratory using the VENTANA PD-L1 (SP142) Assay (Roche Diagnostics, Rotkreuz, Switzerland), with PD-L1-positive status defined as PD-L1-expressing tumour-infiltrating immune cells on ≥1% of the tumour area. If clinically feasible, a tumour specimen from locally advanced or metastatic disease was required. Previous therapy for early-stage TNBC was permitted if the treatment-free interval was ≥12 months.

Eligible patients were treated with a triplet regimen of tiragolumab, atezolizumab and nab-paclitaxel. Each 28-day cycle comprised intravenous (i.v.) tiragolumab 840 mg and i.v. atezolizumab 1680 mg on day 1, and i.v. nab-paclitaxel 100 mg/m^2 on days 1, 8 and 15. Treatment was continued until disease progression or unacceptable toxicity. Tumour assessments were done at baseline, every 8 weeks (±7 days) for the first 48 weeks and every 12 weeks (±7 days) thereafter, with additional scans as clinically indicated. Tumour assessment continued until disease progression, withdrawal of consent, death or study termination, whichever occurred first.

The primary objective was to investigate the activity of the triplet, determined according to investigator-assessed confirmed objective response rate per RECIST version 1.1. The primary safety objective was to investigate the safety and tolerability of the triplet. Secondary efficacy endpoints

were progression-free survival (PFS; defined as the time between enrolment and the first occurrence of disease progression as determined by the investigator according to RECIST version 1.1 or death from any cause), duration of response (defined as the time between first documented objective response until disease progression as determined by the investigator according to RECIST version 1.1 or death from any cause) and OS (defined as the time between enrolment and death from any cause).

Cohort B

In cohort B (neoadjuvant setting), men or women aged ≥18 years eligible for surgery for early-stage (TNM stage T2—4d) TNBC, irrespective of PD-L1 status, were randomised in a 1:1 ratio to receive a neoadjuvant regimen of tiragolumab, atezolizumab and sequential taxane- and anthracycline-based chemotherapy, with or without carboplatin. In arm A (platinum-containing), patients received i.v. tiragolumab 420 mg and i.v. atezolizumab 840 mg every 2 weeks in combination with i.v. nab-paclitaxel 125 mg/m^2 once every week and i.v. carboplatin at area under the concentration—time curve 5 mg/ml per minute every 3 weeks for 12 weeks, followed by tiragolumab 420 mg and atezolizumab 840 mg in combination with doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 all administered every 2 weeks with granulocyte or granulocyte-macrophage colony-stimulating factor for 8 weeks. In arm B, patients received the same regimen as in arm A but carboplatin was omitted. On completion of neoadjuvant therapy, patients underwent appropriate surgery during weeks 21-25. Post-operative therapy could include radiotherapy if indicated, and patients without a pCR were to receive treatment according to standard-of-care guidelines.

The primary objective of cohort B was to investigate the safety and tolerability of the neoadjuvant carboplatin-containing regimen compared with the non-carboplatin-containing regimen, assessed by the incidence and severity of adverse events (AEs; National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0). Preliminary efficacy assessment of the carboplatin-containing regimen versus the non-carboplatin-containing regimen was an exploratory objective, with exploratory endpoints including pCR rate (ypT0/is ypN0), EFS (from randomisation until documented disease recurrence, progression or death, whichever was earliest) and OS (from randomisation until death from any cause).

Statistics

It was planned to enrol ∼80 patients in total (∼40 patients in each cohort). In cohort A, a sample size of 40 patients was considered sufficient to rule out a clinically uninteresting probability of response of <53%, assuming an observed response rate of 67.5%. If a response was observed in ≥27 of 40 patients, it could be concluded that the response rate was >53%. In cohort B, a sample size of ∼40 patients was considered sufficient for a descriptive analysis of safety, allowing observation of AEs with a true incidence rate of ≥10% with acceptable probability in each treatment arm and across both arms combined.

The protocol, informed consent form and other relevant documents were approved by the institutional review board/independent ethics committee at each participating site before study initiation (for example, Ärztekammer Nordrhein Ethics Commission, approval number 2020203 on 29 September 2020). The study was conducted in accordance with consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, the applicable International Conference on Harmonisation Good Clinical Practice Guidelines and all applicable laws and regulations. All patients provided written informed consent before undergoing any study-specific procedure and the privacy rights of human participants were always observed.

RESULTS

Between 28 September 2020 and 22 October 2021, 83 patients (all female) were enrolled from 24 centres in the United States, Brazil, Russia, Spain, Republic of Korea, Germany, Australia and Taiwan (Supplementary Table S1). The data cut-off date for both cohorts was 8 March 2023.

Cohort A (advanced TNBC)

Among 124 patients screened for cohort A, there were 83 screen failures (most frequently because of PD-L1 or TNBC status) and the remaining 41 eligible patients were enrolled and treated (Figure 1). Patients were enrolled from 20 centres between 28 September 2020 and 22 October 2021. Two-thirds of patients were aged <65 years and most had Eastern Cooperative Oncology Group (ECOG) performance status 0 (Table 1). The most common metastatic sites were lung (37%), liver (24%) and brain (15%). Few (15%) had more than three sites of metastatic disease. The most common histological subtype was ductal (73%) and 46% had poorly differentiated histology. One-third of patients (32%) had *de novo* metastatic TNBC. Approximately half of the patients (54%) had received (neo)adjuvant therapy, including a taxane in 21 patients (51%) and/or an anthracycline in 19 (46%). Tissue samples for biomarker assessment were fresh in 21 patients (51%) and archival in 20 patients (49%).

At the data cut-off date, the median duration of survival follow-up was 17.2 months (interquartile range 10.6-21.2 months). By this date, PFS events had been recorded in 32 patients (78%) and 18 patients (44%) had died [12 from disease progression, 2 from AEs and 4 from other causes (1 case each of acute liver failure, acute respiratory insufficiency with COVID-19 pneumonia, COVID-19 pneumonia and unknown cause, all occurring outside the AE reporting period)].

The confirmed objective response rate was 54% [95% confidence interval (CI) 37% to 69%], including complete responses in three patients (7%, 95% CI 2% to 20%). An additional 12 patients (29%) had stable disease. The median duration of response in the 22 responding patients

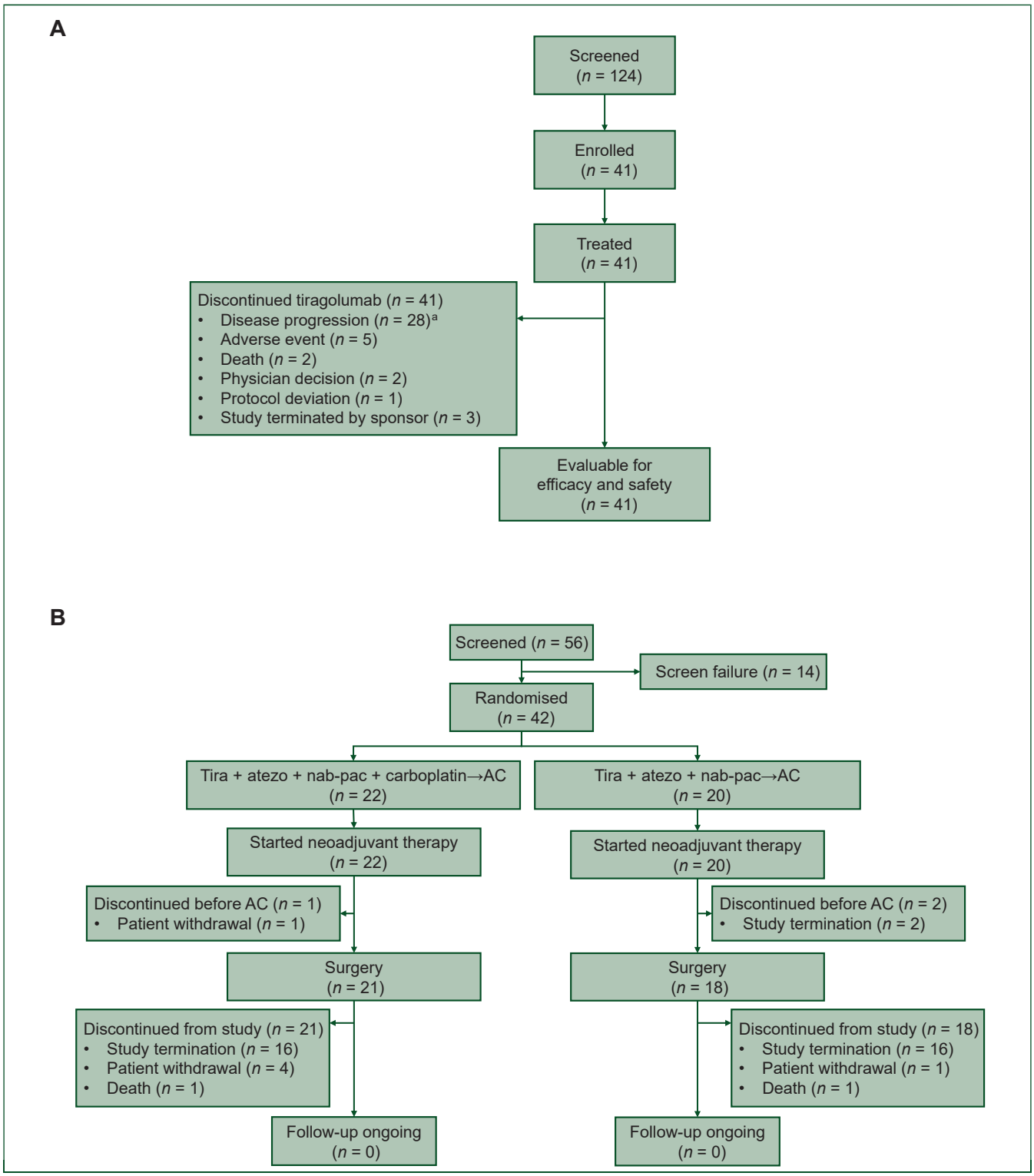

Figure 1. Patient Flow. (A) Cohort A. (B) Cohort B.
AC, doxorubicin + cyclophosphamide; atezo, atezolizumab; nab-pac, nab-paclitaxel; tira, tiragolumab.
[a]Including symptomatic deterioration ($n = 2$).

was 7.2 months (95% CI 4.9-13.1 months) (Figure 2A). Response was ongoing in six patients (15%) at 1 year. In the overall population, median PFS was 6.5 months (95% CI 5.4-9.0 months), 30 patients (73%) were still alive at 1 year and median OS was 24.6 months (95% CI 14.7 months-not estimable) (Figure 2B and C).

The median duration of treatment was ∼6 months for all three components of the triplet regimen (Table 2). Tiragolumab was continued for ≥6 months in 18 patients (44%, including 17% continuing for >12 months) and atezolizumab was continued for ≥6 months in 16 patients (39%, including 15% continuing for >12 months). The most

Table 1. Baseline characteristics

Characteristic	Cohort A (advanced TNBC)	Cohort B (early-stage TNBC)	
	Tiragolumab + atezolizumab + nab-paclitaxel ($n = 41$)	Arm A: tiragolumab + atezolizumab + nab-paclitaxel + carboplatin → AC ($n = 22$)	Arm B: tiragolumab + atezolizumab + nab-paclitaxel → AC ($n = 20$)
Age, years			
Median (range)	51 (31-79)	48 (34-73)	50 (26-67)
18-< 40, *n* (%)	6 (15)	3 (14)	7 (35)
40-< 65, *n* (%)	21 (51)	16 (73)	10 (50)
≥65, *n* (%)	14 (34)	3 (14)	3 (15)
Sex, *n* (%)			
Female	41 (100)	22 (100)	20 (100)
Country, *n* (%)			
Russia	8 (20)	5 (23)	1 (5)
Spain	7 (17)	3 (14)	4 (20)
Brazil	9 (22)	1 (5)	3 (15)
USA	6 (15)	4 (18)	2 (10)
Republic of Korea	3 (7)	3 (14)	4 (20)
Germany	4 (10)	1 (5)	4 (20)
Taiwan	1 (2)	3 (14)	2 (10)
Australia	3 (7)	2 (9)	0
Race, *n* (%)			
Asian	5 (12)	7 (32)	6 (30)
Black/African American	6 (15)	0	2 (10)
White	26 (63)	15 (68)	12 (60)
Multiple	4 (10)	0	0
ECOG performance status, *n* (%)			
0	32 (78)	17 (77)	20 (100)
1	9 (22)	5 (23)	0
Disease status, *n* (%)			
Locally advanced unresectable	1 (2)	0	0
Metastatic	40 (98)	0	0
AJCC stage at initial diagnosis, *n* (%)			
I	9 (22)	0	0
IIA	6 (15)	6 (27)	8 (40)
IIB	4 (10)	8 (36)	6 (30)
IIIA	5 (12)	4 (18)	5 (25)
IIIB	2 (5)	1 (5)	1 (5)
IIIC	2 (5)	3 (14)	0
IV	13 (32)	0	0
PD-L1 status, *n* (%)			
IC ≥1%	41 (100)	11 (50)	12 (60)
IC <1%	0	11 (50)	8 (40)

AC, doxorubicin + cyclophosphamide; AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; IC, immune cells; PD-L1, programmed death-ligand 1; TNBC, triple-negative breast cancer.

common reason for discontinuing treatment was disease progression (leading to discontinuation of tiragolumab in 63%, atezolizumab in 63% and nab-paclitaxel in 59%). At the data cut-off date, 28 patients (68%) had received subsequent anticancer therapy, most commonly platinum, gemcitabine and/or eribulin. Four patients (10%) received sacituzumab govitecan.

The median duration of safety follow-up was 8.3 months (range 0.7-22.8 months). The most common (>30%) AEs of any grade were nausea, rash, anaemia (each in 34% of patients) and neutropenia (32%) (Table 3). Grade 3/4 AEs were reported in 24 patients (59%). The most common (>5%) grade 3/4 AEs were neutropenia (15%) and increased alanine aminotransferase (7%). AEs of special interest for tiragolumab and atezolizumab (predefined AEs based on their mechanism of action and grouped by medical concepts) occurred in 29 patients (71%), most commonly rash (54%), hepatic laboratory abnormalities (24%) and hypothyroidism (20%). Grade 3/4 AEs of special interest occurred in nine patients (22%), most commonly rash (10%) and hepatic laboratory abnormalities (7%). There were two fatal AEs (one death from pulmonary sepsis considered to be related to nab-paclitaxel and one death from COVID-19 considered unrelated to study treatment). AEs led to discontinuation of at least one component of the triplet regimen in nine patients (22%): atezolizumab in six patients (15%), nab-paclitaxel in six patients (15%) and tiragolumab in five patients (12%) (Table 2).

Cohort B (early-stage TNBC)

Among the 56 patients screened for cohort B, there were 14 screen failures and the remaining 42 eligible patients were randomised: 22 to arm A (platinum-containing) and 20 to arm B (non-platinum-containing) (Figure 1). Patients were enrolled from 18 sites between 29 September 2020 and 5 July 2021. All patients received at least one dose of study treatment and 36 patients [19 (86%) in arm A and 17 (85%) in arm B] completed the neoadjuvant regimen. All but three patients (one in arm A, two in arm B) underwent surgery. Baseline characteristics were generally balanced between the two treatment arms (Table 1). At the data cut-off date (median follow-up 22.8 months, interquartile range 20.1-25.7 months), two patients had died: one in arm A from hypovolaemic shock on day 399 and one in arm B from pneumonitis on day 451, both outside the reporting period and neither considered related to study treatment.

Treatment duration was similar in the two treatment arms, but dose intensity was slightly lower in arm A (Table 2). Patients received a median of four cycles of carboplatin (range 3-4). Capecitabine was administered as subsequent anticancer therapy in 46% of patients in arm A and 30% in arm B.

The median duration of safety follow-up was 6.9 months (interquartile range 6.5-7.4 months). The most common all-grade AEs (across both arms) were nausea (69%), rash (55%), alopecia (52%), anaemia (50%), neutrophil count decreased (45%) and fatigue (43%) (Table 4). There were some differences between treatment arms in the incidences of certain AEs (higher incidences of haematological toxicities, dizziness and dyspnoea in the carboplatin arm but lower incidences of peripheral sensory neuropathy, constipation, asthenia, infusion-related reaction and hypothyroidism).

Grade 3/4 AEs occurred in 18 patients (82%) in arm A and 11 (55%) in arm B. The vast majority of grade 3/4 AEs were haematological (anaemia, neutropenia, neutrophil

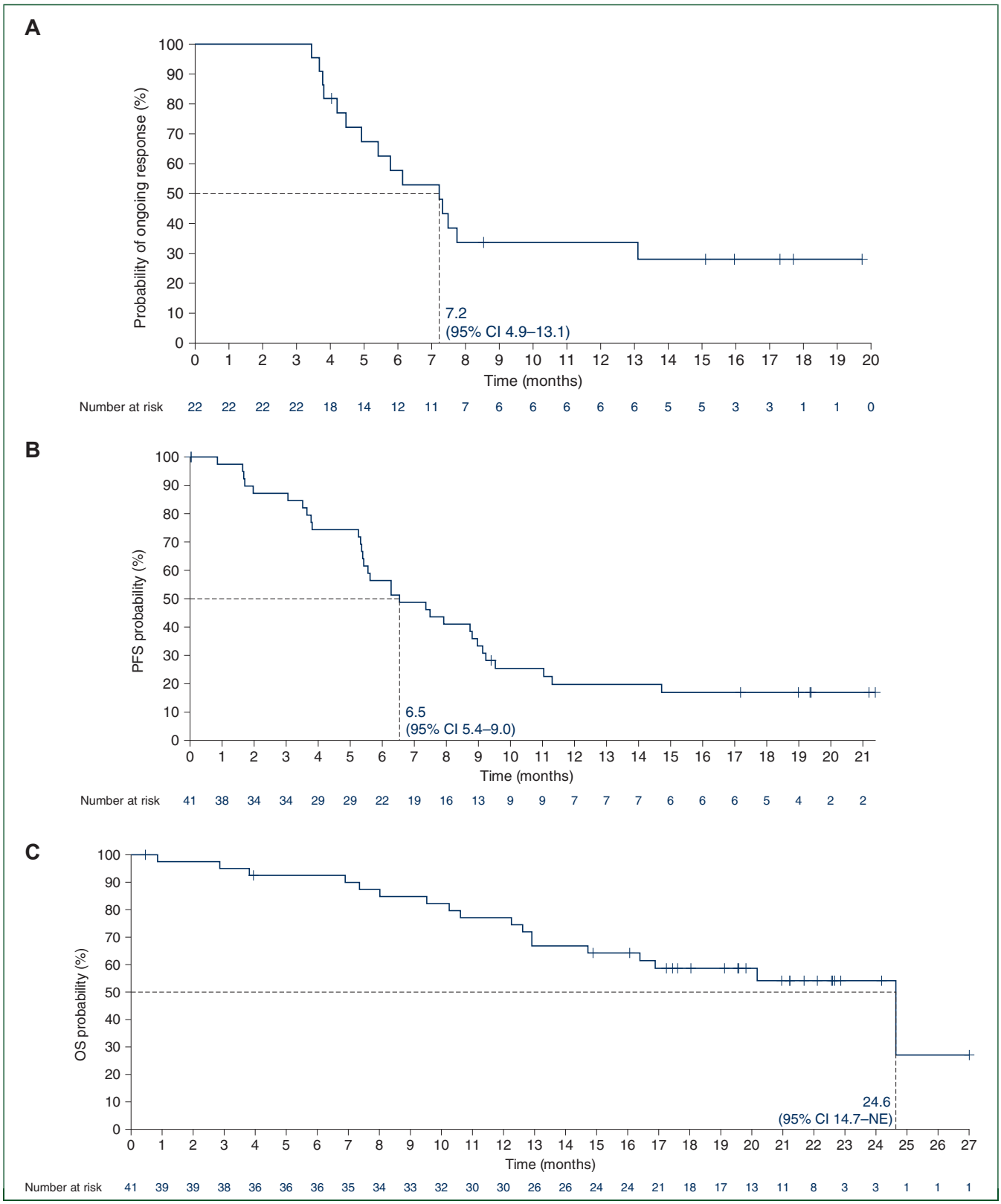

Figure 2. Efficacy in cohort A (advanced TNBC). (A) Duration of response. (B) PFS. (C) OS.
CI, confidence interval; NE, not estimable; OS, overall survival; PFS, progression-free survival; TNBC, triple-negative breast cancer.

count decreased) in both treatment arms, and these were more common in arm A (carboplatin-containing) than arm B. There were no fatal AEs in either treatment arm. The incidence of serious AEs was 27% in arm A (all treatment-related) and 35% in arm B (treatment-related in 25%). The incidence of AEs of special interest was 96% in arm A (all grade 1/2) and 90% in arm B (20% grade 3, no grade 4). The most common AEs of special interest were rash (77% in

Table 2. Summary of treatment exposure

Treatment exposure	Cohort A (advanced TNBC)	Cohort B (early-stage TNBC)	
	Tiragolumab + atezolizumab + nab-paclitaxel ($n = 41$)	Arm A: tiragolumab + atezolizumab + nab-paclitaxel + carboplatin → AC ($n = 22$)	Arm B: tiragolumab + atezolizumab + nab-paclitaxel → AC ($n = 20$)
Median (range) duration of treatment, months			
Tiragolumab	5.7 (0-21.2)	4.7 (0.9-5.6)	4.2 (0.5-5.1)
Atezolizumab	5.5 (0-21.2)	4.7 (0.9-5.6)	4.2 (0.5-5.1)
Nab-paclitaxel	5.9 (0-21.7)	2.8 (1.6-3.3)	2.6 (0.7-3.5)
Cyclophosphamide	NA	1.5 (0.5-2.3)[a]	1.4 (0.5-2.1)[a]
Doxorubicin	NA	1.5 (0.5-2.3)[a]	1.4 (0.5-2.1)[a]
Carboplatin	NA	2.3 (1.6-2.8)	NA
Mean (SD) dose intensity, %[b]			
Tiragolumab	95.7 (7.0)	77.6 (8.3)	82.7 (8.9)
Atezolizumab	96.9 (5.3)	77.6 (8.5)	82.5 (9.1)
Nab-paclitaxel	88.2 (17.0)	69.4 (5.7)	74.3 (10.7)
Cyclophosphamide	NA	71.3 (9.0)	76.3 (6.0)
Doxorubicin	NA	71.3 (9.1)	76.3 (6.0)
Carboplatin	NA	91.7 (10.0)	NA
Discontinued treatment because of AEs, *n* (%)	9 (22)	5 (23)	4 (20)
Tiragolumab	5 (12)	4 (18)	3 (15)
Atezolizumab	6 (15)	4 (18)	3 (15)
Nab-paclitaxel	6 (15)	4 (18)	4 (20)
Cyclophosphamide	NA	0	1 (5)
Doxorubicin	NA	0	1 (5)
Carboplatin	NA	1 (5)	NA

AC, doxorubicin + cyclophosphamide; AE, adverse event; NA, not applicable; SD, standard deviation; TNBC, triple-negative breast cancer.
[a]One patient in arm A and two patients in arm B did not receive AC.
[b]Calculated as {(total actual dose across all cycles/planned dose at first cycle)/[(last dose date − first dose date)/planned duration of one cycle in days] + 1} × 100.

Table 3. Most common (>10% of patients) adverse events in cohort A (PD-L1-positive advanced setting, $n = 41$)

Number of patients (%)	All grades	Grade 3/4
Any	41 (100)	24 (59)
Nausea	14 (34)	0
Rash	14 (34)	2 (5)
Anaemia	14 (34)	0
Neutropenia	13 (32)	6 (15)
Diarrhoea	11 (27)	1 (2)
Headache	11 (27)	0
Asthenia	10 (24)	0
Alopecia	10 (24)	0
Fatigue	10 (24)	0
Pyrexia	10 (24)	0
Constipation	8 (20)	0
Vomiting	8 (20)	0
AST increased	8 (20)	0
Neuropathy peripheral	7 (17)	1 (2)
ALT increased	7 (17)	3 (7)
Abdominal pain upper	5 (12)	0
Pruritus	5 (12)	0
Leukopenia	5 (12)	0
Myalgia	5 (12)	0
Hypothyroidism	5 (12)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; PD-L1, programmed death-ligand 1.

arm A, 65% in arm B) and hepatic laboratory abnormalities (41% versus 45%, respectively). All four patients (20%) with grade 3 AEs of special interest in arm B experienced hepatic laboratory abnormalities, with grade 3 rash in two patients. Five patients (23%) in arm A and four (20%) in arm B discontinued at least one drug because of AEs (Table 2). Discontinuation was due to peripheral neuropathy in two patients (9%) in arm A and one patient (5%) in arm B, and due to polyneuropathy in one patient (5%) in each arm.

In cohort B, the addition of carboplatin to the regimen was not associated with an increase in pCR [10/22 patients, 46% (95% CI 24% to 68%) in arm A versus 11/20 patients, 55% (95% CI 32% to 77%) in arm B]. EFS and OS could not be estimated because of the relatively short median follow-up and limited numbers of events (one death in each arm).

DISCUSSION

To the best of our knowledge, this is the first prospective trial reporting clinical outcomes in patients treated with an anti-TIGIT-based regimen (tiragolumab in combination with atezolizumab and chemotherapy) for early-stage and advanced TNBC. In cohort A, a triplet regimen combining tiragolumab, atezolizumab and nab-paclitaxel as first-line therapy for patients with PD-L1-positive advanced TNBC demonstrated a confirmed objective response rate of 54% and a manageable safety profile. Median duration of response, PFS and OS were 7.2, 6.5 and 24.6 months, respectively. In cohort B, the safety profile of neoadjuvant tiragolumab, atezolizumab and chemotherapy was consistent with the known safety profiles of the individual agents, with an increase in haematological toxicity among patients randomised to carboplatin-containing chemotherapy.

Efficacy data in cohort A are within the range reported in PD-L1-positive metastatic TNBC with atezolizumab and nab-paclitaxel in the IMpassion130 randomised phase III trial (objective response rate 59%, median duration of response 8.5 months, median PFS 7.5 months and median OS 25.4 months)[2,37] and with pembrolizumab and chemotherapy in the KEYNOTE-355 trial (subgroup with combined positive score ≥10: objective response rate 53%, median duration of response 12.8 months, median PFS 9.7 months and median OS 23.0 months).[3,4] Although cross-trial comparisons must be interpreted with caution, IMpassion130 provides a historical benchmark in which to place the results of the present study in context. We found no clear signal of improved efficacy when tiragolumab was added to the established atezolizumab plus nab-paclitaxel regimen for PD-L1-positive advanced TNBC and alternative strategies may provide greater promise, including combining immune checkpoint inhibitors with antibody—drug conjugates[28,38] or anti-angiogenic molecules.[39,40]

The primary objective in cohort B in early-stage TNBC was to compare the safety of dual immune checkpoint blockade and neoadjuvant chemotherapy with versus without carboplatin. Carboplatin-containing chemotherapy was associated with additional haematological toxicities

Table 4. Most common (≥20% of patients in either arm) adverse events in cohort B (neoadjuvant setting)

Number of patients (%)	Arm A: tiragolumab + atezolizumab + nab-paclitaxel + carboplatin → AC (*n* = 22)		Arm B: tiragolumab + atezolizumab + nab-paclitaxel → AC (*n* = 20)	
	All grades	Grade 3/4	All grades	Grade 3/4
Any	22 (100)	18 (82)	20 (100)	11 (55)
Nausea	15 (68)	1 (5)	14 (70)	0
Rash	13 (59)	0	10 (50)	1 (5)
Alopecia	11 (50)	0	11 (55)	2 (10)
Anaemia	17 (77)	11 (50)	4 (20)	0
Neutrophil count decreased	12 (55)	10 (46)	7 (35)	4 (20)
Fatigue	10 (46)	0	8 (40)	0
ALT increased	9 (41)	0	7 (35)	2 (10)
AST increased	9 (41)	0	7 (35)	0
Constipation	6 (27)	0	9 (45)	0
Neuropathy peripheral	8 (36)	0	6 (30)	0
Headache	6 (27)	0	7 (35)	0
Diarrhoea	6 (27)	0	6 (30)	1 (5)
Vomiting	5 (23)	0	5 (25)	0
Stomatitis	5 (23)	0	5 (25)	0
Pyrexia	6 (27)	0	4 (20)	0
Arthralgia	6 (27)	0	4 (20)	0
Neutropenia	7 (32)	6 (27)	3 (15)	1 (5)
Myalgia	5 (23)	0	5 (25)	0
Insomnia	4 (18)	0	5 (25)	0
Peripheral sensory neuropathy	1 (5)	0	6 (30)	0
Asthenia	2 (9)	0	5 (25)	0
Dizziness	6 (27)	0	1 (5)	0
Dyspnoea	5 (23)	0	1 (5)	0
Infusion-related reaction	0	0	4 (20)	0
Hypothyroidism	0	0	4 (20)	0

AC, doxorubicin + cyclophosphamide; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

but did not appear to interfere with the patients' ability to receive other study treatments. The safety profile of arm B in cohort B was consistent with the safety profile observed with neoadjuvant atezolizumab and the very similar taxane/carboplatin/anthracycline neoadjuvant regimen used in NSABP B-59/GBG-96-GeparDouze.[22] Paclitaxel and atezolizumab were each discontinued because of AEs in 11% of patients in NSABP B-59/GBG-96-GeparDouze and carboplatin was discontinued in 7%. Like the present study, the most common AEs included fatigue, nausea, peripheral sensory neuropathy, skin reactions and anaemia, and the most common grade 3/4 AEs were haematological. Overall, the safety profile in both treatment arms of the present study was consistent with the individual components of the chemotherapy backbone, the symptoms of the underlying disease and previous reports of tiragolumab and atezolizumab combinations in other tumour types.[41,42]

The pCR rates in cohort B were similar in the carboplatin- and non-carboplatin-containing treatment arms (46% and 55%, respectively), with broad and overlapping 95% CIs. When the present trial was designed, the role of carboplatin in neoadjuvant regimens was controversial, justifying a randomised design in cohort B. Since then, more robust evidence confirming significantly improved efficacy with the inclusion of carboplatin into neoadjuvant regimens for TNBC has accumulated, albeit none of these trials included an immune checkpoint inhibitor in either arm. The pCR rates observed in both arms of the present study are at the lower end of the rates reported with single immune checkpoint blockade and standard chemotherapy (58%to 63% with atezolizumab in the IMpassion031 and NSABP B-59/GBG-96-GeparDouze trials,[16,22] 58% to 65% with pembrolizumab in the KEYNOTE-522 and NeoPACT trials[5,15,43]). As with the cohort A findings, it is difficult to determine the contribution of tiragolumab to efficacy, but there was no signal of remarkably improved short-term outcomes with the addition of TIGIT inhibition to atezolizumab-containing therapy.

Targeting TIGIT has shown mixed success in other tumour types. The combination of tiragolumab plus atezolizumab failed to improve efficacy compared with atezolizumab alone in PD-L1-high non-small-cell lung cancer (NSCLC) in the SKYSCRAPER-01 trial[44] and in extensive-stage small-cell lung cancer in the SKYSCRAPER-02 trial,[45] despite encouraging phase I/II results.[46-48] On the other hand, the combination of domvanalimab (an Fc-silent anti-TIGIT) and zimberelimab (anti-PD-1) was associated with greater PFS, OS and objective response rate compared with either zimberelimab or chemotherapy in part 1 of the ARC-10 study in PD-L1-high locally advanced/metastatic NSCLC.[49] The randomised double-blind placebo-controlled AdvanTIG-211 trial (NCT05809895) was designed to explore a triplet of ociperlimab (anti-TIGIT), tislelizumab (anti-PD-1) and chemotherapy as first-line therapy for patients with advanced TNBC, but was withdrawn.

The main limitation of this study is the relatively small sample size of each cohort, allowing only descriptive analyses of efficacy and safety. In cohort A, cross-trial comparison with non-tiragolumab-containing regimens, notwithstanding all the caveats of such comparisons, does not indicate enhanced efficacy with the addition of a third agent, although the regimen seems to be tolerable. A small subset of patients appeared to have a sustained response, but the single-arm design of the study and the lack of any translational element prevent meaningful assessment of potential predictors for response. Information on *BRCA* mutation and HER2-low status is lacking, although both are now considered critical in treatment selection. Furthermore, there is no information on tumour-infiltrating lymphocytes, which might be informative in trials of immunotherapy for TNBC, potentially offering explanations for the heterogeneity in response and immunological activation.

No concerning safety signals were identified in this study; however, the efficacy results, albeit examining only a small population, do not support restoring antitumour immunity using a dual checkpoint inhibitor approach that co-inhibits TIGIT (with tiragolumab) and PD-L1 (with atezolizumab) in TNBC. It remains unclear whether a subgroup of patients with TNBC may benefit from this combination or whether a different combination of agents targeting

these pathways may yet have potential. Existing targeted therapies for TNBC have undoubtedly improved outcomes for some patients but, to advance treatment further, trials should be designed taking into consideration the heterogeneous molecular subtypes within TNBC (including HER2-low), mechanisms and pathways of intrinsic and acquired resistance to existing systemic therapies, and optimal sequencing of the various available strategies (for example, the timing of radiation relative to systemic therapy for early-stage TNBC[50]).

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DATA SHARING

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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