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Evaluation of short-course durvalumab combined with dose-dense EC in the neoadjuvant setting for locally advanced luminal B/HER2(-) or triple-negative breast cancer

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Abstract

Background Combining immune checkpoint inhibitors (ICI) with neoadjuvant chemotherapy (NACT) has been the standard of care for stage II and III triple negative breast cancer (TNBC) since 2021. For Luminal B/HER2(-) breast cancers (BC) recent results from randomized phase 3 clinical trials demonstrated an improvement in pathological complete response (pCR) when ICI are combined with overall NACT. Emerging real-life data on TNBC reveal rates of ICI-related toxicities higher than expected, raising questions about the possibility of reducing ICI exposure during NACT while maintaining an efficacy advantage. The B-IMMUNE study explored the safety and efficacy of short-course durvalumab combined with EC during NACT in locally advanced BC.

Patients and methods The prospective phase 1b/2 trial included patients with locally advanced Luminal B/HER2(-) or TNBC who were treated with paclitaxel 80mg/m2 weekly from weeks 1–12, followed by 4 cycles of dose-dense epirubicin 90mg/m2 and cyclophosphamide 600mg/m2 biweekly (ECdd), in a neoadjuvant setting. Phase 1b evaluated a single infusion of durvalumab 1500mg combined with the 3rd cycle of ECdd and phase 2 evaluated two infusions with the 1st and 3rd cycles of ECdd respectively. The primary endpoints were safety and pathological complete response (pCR) rate versus historical control. Based on Simon's two-stage design, the trial was considered positive if > 8/20 pCRs were observed among TNBC patients and > 5/22 for luminal B HER2(-) BC patients.

Results Fifty patients were considered for safety analyses and 34% of them experienced grade 3–4 adverse events (AEs) and 8% immunity-related AEs. Of the 47 patients treated with durvalumab in phase 2, 46 (22 TNBC and 24

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Luminal B/HER2(-) BC) were considered for efficacy analyses. A pCR was observed in 12/22 TNBC patients (55%) and 8/24 Luminal B/HER2(-) BC patients (33%).

Conclusions The B-IMMUNE study achieved its primary objective by showing that the addition of only 2 doses of durvalumab to NACT seems to improve the pCR rate compared to a historical control without ICI, for both TNBC and Luminal B/HER2(-) BC, while maintaining an acceptable safety profile. De-escalation of ICI in the neoadjuvant setting should be further investigated in phase 3 trials.

Trial registration EudraCT: 2016–003998-1 date: 19 January 2017.

Keywords Immunotherapy, Neoadjuvant, Durvalumab, Locally advanced breast cancer

Background

In 2020, based on the results of the KEYNOTE-522 trial, the addition of pembrolizumab to neoadjuvant chemotherapy (NACT), comprising 12 cycles of weekly carboplatin-paclitaxel followed by 4 cycles of epirubicin cyclophosphamide (EC), became the new standard of care for high-risk triple negative breast cancer (TNBC), as this study showed a significant improvement in pathological complete response (pCR) rate, better event-free survival (EFS) and overall survival compared with placebo, regardless of PD-L1 expression [1–3]. To date, 6 other prospective randomized controlled trials studying the combination of an immunostimulatory antibody blocking the PD-1 pathway with NACT have been published [4–9]. Very recently, 2 of them (KEYNOTE-756 and CheckMate-7FL) studying this combination in high risk ER(+)/HER2(-) BC showed a significant pCR rate improvement compared to placebo [8, 9]. Contrary to what was observed in TNBC in the KEYNOTE-522 study, the benefit of adding an anti-PD-1/PD-L1 antibody appears to be limited to PD-L1 positive ER(+)/HER2(-) tumors [8, 9]. A recent meta-analysis including only studies where anthracyclines were the backbone of NACT in TNBC confirmed the benefits of adding ICI to NACT in terms of pCR rates [10]. The benefit was statistically significant in the ITT population and in patients with PD-L1 positive tumors, but not in the PD-L1 negative subgroup, even though the results in each individual trial were positive regardless of the PD-L1 expression. The smaller number of PD-L1 negative patients could impact this statistical analysis.

All of these trials proposed to administer ICIs throughout NACT and some of them continued ICI in an adjuvant phase. Emerging real-life data, where patients were probably not completely similar to the studied population in KEYNOTE-522, reported in a study from the University of Washington [11], appear to show greater toxicity associated with the addition of ICIs to the backbone of NACT in TNBC than that described in the KEYNOTE-522 trial with an all grade irAEs rate of 71.4% compared to 33.5% described in the original trial. These autoimmune complications also appear to influence the pCR rate, probably due to a higher discontinuation rate than observed in the registration trial. This raises the question of how to maintain the benefit of ICIs associated with NACT while limiting toxicity.

We here present the results of the B-IMMUNE study, a phase 1b/2 trial exploring the possibility of reducing the duration of treatment with ICIs in the neoadjuvant setting for TNBC and locally advanced Luminal B HER2(-) BC, in order to reduce the risk of toxicity while maintaining a benefit in terms of efficacy.

Materials and methods

Patients

Included patients had to present with histologically documented TNBC (defined as negative estrogen and progesterone receptor expression as per local laboratory testing, and negative HER2 status defined as negative ISH test or an IHC status of 0 or 1 + as per local laboratory testing), or luminal B/HER2(-) BC defined as positive estrogen and/or progesterone receptor expression (ER ≥ 10%), negative HER2 status (as defined above) and a Ki67 > 14% [12]. They had to have newly diagnosed, previously untreated, operable, non-metastatic disease (tumor stage T1-T4, any nodal stage, M0), an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 and required NACT per ESMO clinical practice guidelines [13].

Main exclusion criteria were locally recurrent or metastatic invasive BC, receipt of any systemic therapy or radiotherapy for the current BC, other malignancies, any previous treatment with a PD-1 or PD-L1 inhibitor (including durvalumab), current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab, active or prior documented autoimmune disease within the past 2 years, active or prior documented inflammatory bowel disease, primary immunodeficiency, history of allogenic organ transplant, uncontrolled seizures, active tuberculosis, inadequate bone marrow or renal function, impaired liver function, pregnancy or refusal to use effective contraception. The study was undertaken in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki. The protocol was approved by the central and local ethics committees and the competent authority. All patients

had to be at least 18 years old and provided written informed consent for study conduct, biomaterial collection and analysis.

Trial design and treatment

B-IMMUNE is a multicenter, prospective, open-label, phase 1b/2 trial evaluating the safety and efficacy of the combination of durvalumab with ECdd in a neoadjuvant setting for patients with locally advanced TNBC or Luminal B/HER2(-) BC. In the phase 1b part, patients received standard treatment composed of weekly paclitaxel (80mg/m2) for 12 cycles followed by 4 cycles of ECdd (epirubicin 90mg/m2 + cyclophosphamide 600mg/m2) every 2 weeks. One fixed dose of durvalumab (1500mg) was administered concomitantly with the third cycle of ECdd. Based on the reassuring safety data from other studies about durvalumab/anthracycline combinations, the study was amended after inclusion of 4 patients in the phase 1b part to proceed immediately to the phase 2 part of the trial. In the phase 2 part, patients received standard treatment as described above and 2 doses of durvalumab concomitantly with the 1st and 3rd cycles of ECdd. Surgery was planned 3 to 4 weeks maximum after the last ECdd cycle (Supplementary Data Figure S1). A small group of patients selected by randomization (1:4) were included in a control arm treated with the same treatment regimen but without durvalumab. This group was intended solely for translational research. Tumor, blood and stool samples were collected for translational and exploratory analyses not covered in this publication.

Study objectives

The two primary endpoints of this trial were safety/tolerance and efficacy. The safety analysis was performed in all included patients who had received at least one dose of durvalumab (safety analysis group). One patient included in phase 1b was lost to follow-up before durvalumab administration and then excluded from the safety analysis group. Based on studies validating pCR as a marker of clinical benefit of NACT [14, 15], efficacy was evaluated by comparing the pCR rate in the population receiving the combination of NACT and durvalumab to a historical control from meta-analyses pooling randomized trials that included patients with high-risk TNBC or luminal B/HER2(-) cancer treated with neoadjuvant anthracycline / taxane-based chemotherapy[14, 16]. The efficacy analysis was only performed on patients included in the experimental arm of the phase 2 part (efficacy analysis group). As secondary endpoint, efficacity was also evaluated by the overall response rate (ORR) based on MRI assessment before and after the neo-adjuvant treatment. One patient was excluded from efficacy analyses because her tumor was identified as a sarcoma on the surgical specimen. Another patient (BIMC35) in Luminal B/HER2(-) cohort had a bilateral tumor and the worst pathological and radiological responses in both tumors was considered for the efficacy analyses.

Objectives assessments

Toxicity findings were reported as adverse events (AEs) irrespective of relatedness to study treatment, based on CTCAE version 4.03. Reported AEs correspond to clinically significant grade 1 and all grade 2 or higher AEs. The pCR rate was defined as a pathological stage ypT0/Tis pN0 or as a Residual Tumor Burden (RCB) class of 0 at the time of definitive surgery, evaluated by the local pathologist of each center. All histopathological reports were centrally collected and evaluated by A.D. The ORR was the addition of complete response (CR) and partial response (PR) according to RECIST1.1 on breast MRIs performed before and after neoadjuvant treatment, before surgery [17]. Only the largest target lesion is considered. Its longest diameter (LD) measured in millimeters corresponds to the greatest extent of the disease, including the area without a mass and without enhancement. If a "tumour complex" is present (coherent nodules), it is considered to be the LD. Functional assessment (enhancement or volumetric assessment) is not included in the RECIST assessment [18].

Biomarkers exploratory analysis

TILs and PD-L1 expression were assessed retrospectively. They were evaluated by 2 blinded pathologists (G.B and P.D), and discordant cases were reviewed together. TILs evaluation was based on the recommendations of the international TILs Working Group 2014 [19] for the diagnostic biopsies, and on the updated guidelines for the assessment in residual disease after NACT on the biopsies at week 12 and on the surgical specimens [20]. Tumors were classified in 3 categories based on TILs infiltration rate: Low when the percentage of TILs was ≤ 10%; moderate between > 10% and ≤ 50% and high when TILs were > 50%. As only 3 patients in the phase 2 cohort had high TILs infiltrated tumors, it was decided to merge the moderate and high categories for statistical analysis. Tumors were considered "TILs infiltrated" when TILs were greater than 10%. PD-L1 expression was measured with the VENTANA ULTRA SP263 assay. Three methods of scoring PD-L1 staining were performed: (1) immunoscore (IC), defined as the percentage of TILs with membranous or cytoplasmic staining relative to total TILs, (2) combined positive score (CPS), defined as the number of PD-L1 stained cells (including tumor cells, TILs and macrophages) divided by the number of viable tumor cells, multiplied by 100, and (3) tumor positive score (TPS), defined as the percentage of PD-L1 stained tumor cells relative to total viable tumor cells, multiplied by 100. For each score, PD-L1 expression was

considered positive when the score was ≥ 1% for IC and TPS, and ≥ 1 for CPS [21]. We decided not to use TPS for further analyses due to the low number of PD-L1 positive tumors ($n = 9$) compared to CPS and IC score ($n = 18$ and 22 respectively). The IC and CPS scores were concordant for 90% of the patients (data not shown). For these exploratory analyses, we have taken each tumor into consideration, patients BIMC35 having a bilateral Luminal B tumors.

Statistical considerations

The study is a non-randomized trial. The primary objective of the study is to compare pCR rate, the efficacy primary end-point, with historical controls. The sample size calculation was based on a 2-stage Simon design with an $\alpha = 0.1$ and $\beta = 0.1$, determining that 22 TNBC patients were needed in the phase 2 part to test a null hypothesis (historical control) of 30% pCR rate [14, 16] against a one-side alternative of 60%, and 24 Luminal B/HER2(-) BC patients to test a null hypothesis of 15% pCR rate [14] against a one-side alternative of 40% (including an additional accrual margin of 10% for potential dropouts). The pCR rate was compared to the historical control described above. The first evaluation planned after the inclusion of 8 TNBC and 10 Luminal B/HER2(-) BC patients had to show more than 2 or 1 pCR in each cohort respectively for the trial to continue. For the second evaluation, at least 9 pCRs had to be observed among the first 20 evaluable TNBC patients and 6 among the first 22 evaluable Luminal B/HER2(-) patients to rule out the null hypothesis.The cohort used for the evaluation of the primary efficacy endpoint and biomarker analyses is the group comprising patients included in the experimental arm of phase 2, stratified according to histological subtype (TNBC and Luminal B/HER2(-)). The group of patients included in the control arm is solely for the purpose of collecting biological samples to be used in translational research related to the study.. Fisher's exact test or paired t test were used respectively for exploratory analyses concerning TILs and PD-L1 expression and their influence on pCR as well as their variations during treatment (GraphPad Prism version 9.4.1)..

Results

Patients and treatments

From May 2017 to June 2021, a total of 66 patients from 4 centers in Belgium were enrolled in the study. Considering 4 screening failures, 62 patients were included in the study, 4 in the phase 1b arm and 58 in the phase 2 arm (Fig. 1). Of these 58 patients, 47 received the experimental treatment of 2 doses of durvalumab combined with anthracyclines in the neoadjuvant setting, and a small group of 11 patients were randomized to a control group not receiving durvalumab. No comparison between the experimental cohort and the control group in terms of efficacy or safety was planned in the protocol, the sole purpose of the control group being translational analyses not covered in this publication.

The baseline characteristics of all patients treated with the experimental scheme, with the exception of dropouts, are reported separately for TNBC (24 patients) and Luminal B/HER2(-) BC (25 patients) in Table 1. Mean age at study entry was 53 years for TNBC (range 31–75) and 51 for Luminal B/HER2(-) BC (range 31–72). Most patients had T2 tumors (44,8% for TNBC and 46,7% for Luminal B/HER2(-) BC) and positive axillary lymph nodes (44,8% N1 in TNBC and 43,3% N1 for Luminal B/HER2(-) BC). Concerning stage, histological grade and Ki67, the differences observed between the two cohorts were linked to specific features of each molecular BC subtype. Among TNBC, 70.8% of tumors were PD-L1 positive according to the immunoscore and 62.5% according to the CPS score; among Luminal B/HER2(-) tumors, 24% were PD-L1 positive according to the immunoscore and 16% according to the CPS score. With regard to TILs infiltration, the observations are in agreement with previous observations, which show greater TILs infiltration in TNBC tumors than in Luminal B/HER2(-) tumors [22].

Efficacy and biomarkers

A total of 46 patients were included in the efficacy analysis with pCR rate as the primary endpoint and a distinct statistical hypothesis for TNBC and Luminal B/HER2(-) BC. In the TNBC cohort, 12/22 (55%) achieved a pCR (RCB 0) and 8/24 (33%) in the Luminal B/HER2(-) BC cohort (Fig. 2A). The number of observed pCR exceeded the prespecified statistical plan threshold to consider that primary end-point was reached for both cohorts. The percentage of class I, II and III RCB was respectively of 14%, 27% and 4% for TNBCs and 12%, 33% and 21% for Luminal B/HER2(-) BCs.

Tumors with moderate to high TILs infiltration (TILs > 10%) were more likely to achieve pCR (Fig. 2B) with a pCR rate of 15/26 (58%) compared with 5/21 (24%) for tumors with a proportion of TILs ≤ 10% ($p = 0.0367$). It was noted that the 3 highly infiltrated tumors (TILs > 50%) all had a pCR. There was no statistically significant difference in the influence of TILs on pCR when TNBC and Luminal B/HER2(-) BC were analyzed independently, probably due to a small sample size. IC, which assesses PD-L1 expression only in TILs, did not appear to be associated with pCR with a rate of 8/26 (31%) for tumors with a score < 1% and 12/21 (57%) for those with a score ≥ 1% ($p = 0.0837$, Fig. 2C). Interestingly, the CPS score which also considers PD-L1 expression on viable tumor cells, appeared to be associated with pCR with a rate of 8/30 (27%) for tumors with a score < 1 and 12/17 (71%) for those with a score ≥ 1 ($p = 0.0056$, Figu.

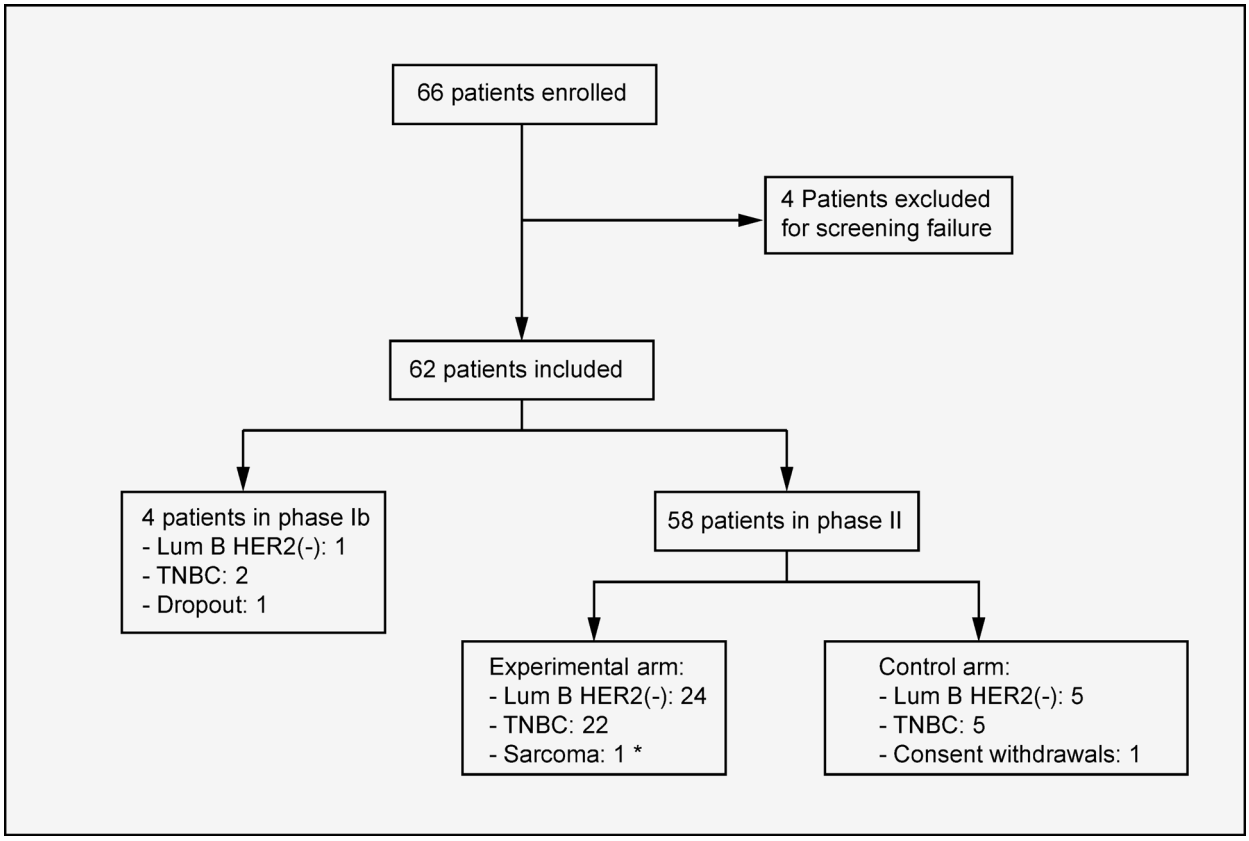

Fig. 1 Enrollment and patient's flowchart. A total of 62 patients were included in the B-IMMUNE study, 4 in phase 1b and 58 in phase 2. Of these, 50 received at least part of the experimental regimen and were included in the safety analysis group and 46 received experimental treatment in phase 2 constituting the efficacy analysis group. A control group of 10 patients not receiving ICI was set up exclusively for translational research analyses and is not used as a comparative for safety or efficacy evaluation

2D*)*. Here again, due to a small sample size, the effect of PD-L1 expression on pCR rate analyzed separately for TNBC and Luminal B/HER2(-) BC was inconclusive.

As a secondary endpoint, efficacy was also assessed by radiological evaluation comparing diagnostic MRI at week 0 and pre-surgery MRI at week 24 using RECIST criteria and ORR was calculated (final RECIST or ORR). A comparison between week 0 and week 12 before durvalumab/anthracyclines was also carried out as part of an exploratory analysis (intermediate RECIST or ORR). Among the efficacy analysis group, data were not available for 3 patients. We observe a final ORR of 75.6% for the efficacy analysis group, 72,7% and 78,3% for TNBC and Luminal B/HER2(-) BC respectively. Interestingly, we found an intermediate ORR of 45.5% for the efficacy analysis group, 40.9 and 50% for TNBC and Luminal B/HER2(-) BC respectively (Fig. 3A). Based on the exploratory comparison between the intermediate and final RECIST responses, 3 patterns of response were distinguished (Fig. 3A). Group 1 corresponding to patients with stable or progressive disease at either W12 or W24 (patients not responding to NACT, $n = 11$), Group 2 corresponding to patients responding to taxanes at W12 and continuing to respond at W24 (patients with overall response to NACT, $n = 19$), and group 3 corresponding to patients not responding to taxanes at W12 but responding to the ECdd /durvalumab combination at W24 (patients with mixed response to NACT, $n = 13$). The case of a patient responding to taxanes but progressing on ECdd / ICI was not observed in the B-IMMUNE study. Groups 1, 2 and 3 had a pCR rate of 18%, 58% and 46% respectively, the 3 patients with a radiological complete response at W12 all achieved pCR at the time of surgery.

To assess whether radiological response based on MRI could predict pathological response, we analyzed the correlation between pCR rate and radiological complete response (CR) rate, separately for TNBC and BC Luminal B/HER2(-) (Fig. 3B). In the TNBC cohort, 7/8 (87.5%) of patients with a CR had a pCR, and 5/14 (36%) of patients without a CR, thus showing a significant association between CR and pCR in this cohort ($p = 0.0310$). In the Luminal B/HER(-) BC cohort, 1/3 (33%) of patients with a CR had a pCR, and 7/20 (35%) of patients without a CR, with no significant association between CR and pCR in this cohort. Subgroup analyses based on TILs and PD-L1

Table 1 Baseline characteristics of patients treated with durvalumab

Parameters	TNBC	Lum B HER2(-)
	n **= 24**	***n*** **= 25**
Age in years (mean; min–max)	53 (31–71)	51 (34–72)
Clinical tumor stage (n; %)		
T1b	1 (4.2)	0 (0)
T1c	7 (29.2)	3 (12)
T2	10 (41.7)	12 (48)
T3	6 (25)	9 (36)
T4	0 (0)	1 (4)
Clinical nodal stage (n; %)		
NO	13 (54.2)	11 (44)
N1	10 (41.7)	11 (44)
N2	1 (4.2)	2 (8)
N3	0 (0)	1 (4)
Breast cancer stage[1] *(n; %)*		
IA	0 (0)	2 (8)
IB	5 (20.8)	2 (8)
I IA	0 (0)	11 (44)
11B	7 (29.2)	4 (16)
IIIA	0 (0)	4 (16)
IIIB	10 (41.7)	1 (4)
IIIC	2 (8.3)	1 (4)
Histological grade (n; %)		
G1	0 (0)	1 (4)
G2	2 (8.3)	10 (40)
G3	22 (91.7)	14 (56)
Histological tumor type (n; %)		
Ductal	24 (100)	22 (88)
Lobular	0 (0)	3 (12)
Ki-67% (n; %)		
≤ 15	0 (0)	0 (0)
≥ 15; ≤ 20	0 (0)	4 (16)
≥ 20; ≤ 40	1 (4.2)	8 (32)
≥ 40; ≤ 60	7 (29.2)	5 (20)
≥ 60; ≤ 80	7 (29.2)	6 (24)
≥ 80	9 (37.5)	2 (8)
HER2 IHC score[2] *(n; %)*		
0	13 (54.2)	2 (8)
1 +	5 (20.8)	11 (44)
2 + (FISH negative)	6 (25)	10 (40)
3 + (FISH negative)	0 (0)	2 (8)
Stromal TlLs %[3] *(n; %)*		
≤ 10%	8 (33.3)	13 (52)
≥ 10; ≤ 50%	13 (54.2)	11 (44)
≥ 50%	3 (12.5)	1 (4)
PD-L1[4] *(n; %)*		
IC ≤ 1°%	7 (29.2)	19 (76)
IC ≥ 1%	17 (70.8)	6 (24)
CPS ≤ 1	9 (37.5)	21 (84)
CPS ≥ 1	15 (62.5)	4 (16)

Table 1 (continued)

Parameters	TNBC	Lum B HER2(-)
	n **= 24**	***n*** **= 25**
TPS ≤ 1	16 (66.7)	23 (92)
TPS ≥ 1	8 (33.3)	2 (8)

Baseline characteristics of all BC patients from phase Ib and phase II treated with at least 1 infusion of durvalumab are reported in the table (*N* = 49, excluding 1 patient with a beast sarcoma). Clinical tumor stage was determined based on MRI and nodal tumor stage based on ultrasonography. [1]Breast cancer tumor staging was realised based on the 8th AJCC Prognostic Stage Groups Table. [2]HER2 immunohistochemistry (IHC) scoring followed the validated guidelines of A. Wolf et al., J. Clinical Oncology 2018. FISH was performed only when IHC score was 2 + or 3 + and was negative for all included patients. [3]The evaluation of tumor-infiltrating lymphocytes (TILs) was based on the recommendations by the International TILs Working Group 2014. Salgado et al., Ann.Oncol. 2015. [4]PD-L1 scoring was based on immunoscore (IC) quantifying PD-L1 positive immune cells in the stroma, the Combined Positive Score CPS and the Tumoral Positive Score TPS.PD-L1 positive population is defined by a percentage ≥ 1% for the immunoscore and TPS or a CPS ≥ 1.

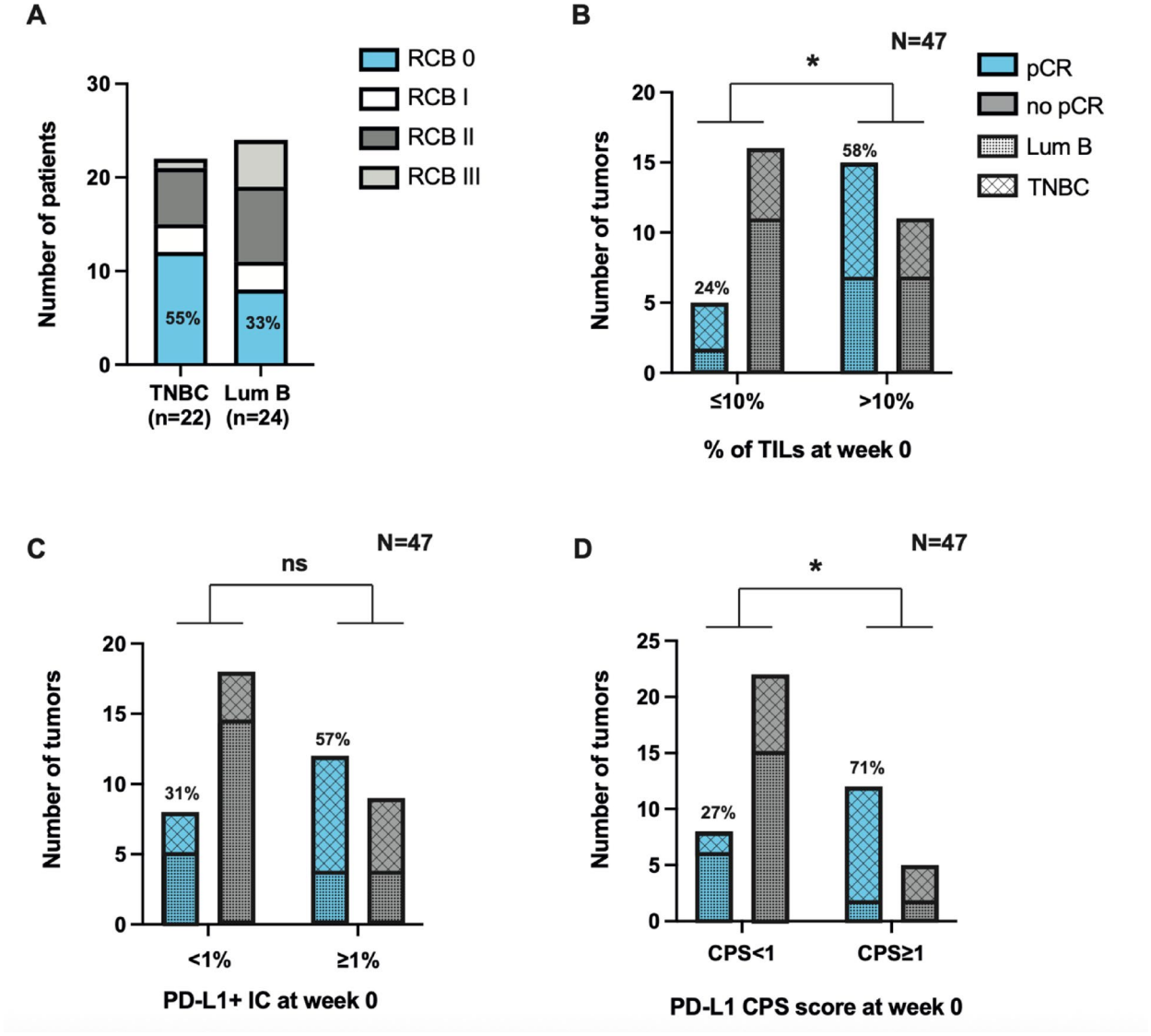

Fig. 2 Pathological responses and subgroup analyses. A. Distribution of RCB classes in the efficacy analysis group (*N* = 46). B. Repartition of pCRs according to the percentage of tumor-infiltrating TILs (TILs) in the diagnostic biopsy at week 0. C. Repartition of pCRs according to the percentage of PD-L1 + immune cells based on IC in the diagnostic biopsy at week 0. D. Repartition of pCRs of PD-L1 CPS status at week 0. *Statistical analysis by Fisher's exact test; * = significant difference with p < 0.05*

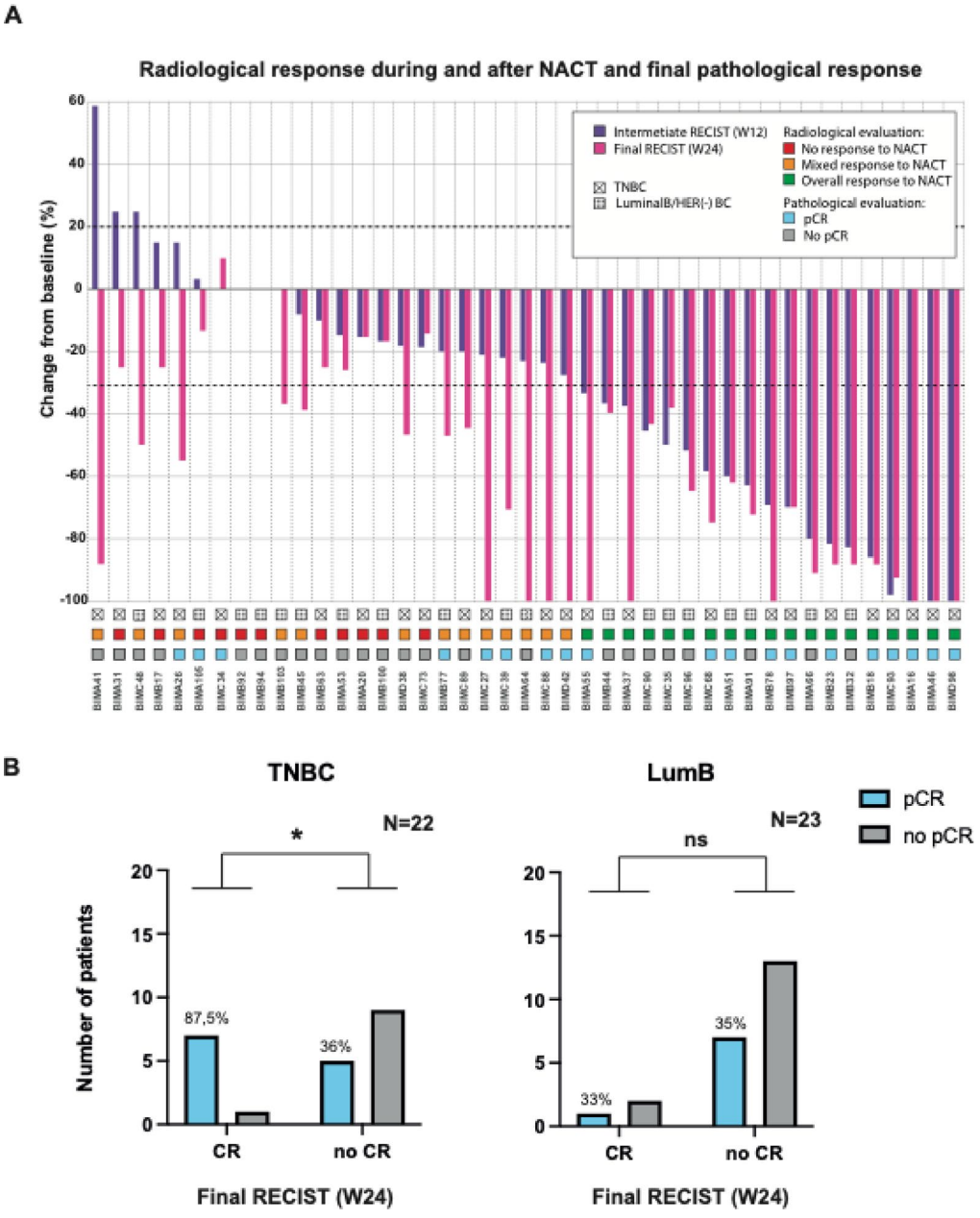

Fig. 3 RECIST responses based on breast MRI. **A**. Waterfall plot showing the distribution of RECIST responses assessed by MRI at week 12 (intermediate response, purple) and week 24 (final response, pink). Dotted lines represent stable disease (SD). The ORR defined as the sum of the number of complete responses (CR) and partial responses (PR) is 45.5% at week 12 and 75.6% at week 24. The tumor subtypes are indicated by squares with different motifs. The different patterns of the radiological response during and after NACT and the final pathological response are indicated by colored squares (noted that radiological evaluation was not available for 3/46 evaluated patients). **B**. Correlation between radiological complete response (CR) at week 24 and pCR for the TNBC and Luminal B/(HER2-) BC cohorts. *Statistical analysis by Fisher's exact test; * = significant difference with p < 0.05*

showed no difference in ORR based on MRI (data not shown).

In addition to pre-treatment tumor samples (W0), samples were taken during neoadjuvant treatment at W12 and W24 to assess the effect of chemotherapy and ICI on the tumor immune microenvironment. Given that the number of samples analyzable at week 12 was very limited, this measurement point was omitted. Changes in the rate of tumor infiltration by TILs were assessed between W0 and W24 for patients with and without pCR. (Fig. 4A). Among the 47 tumors evaluated, a significant decrease in TIL levels was observed when pCR was achieved ($p = 0.0002$), and this trend was found in both the TNBC and Luminal B/HER2(-) BC cohorts ($p = 0.0069$ and $p = 0.0117$, respectively, Fig. 4A). A decrease in TILs was also observed in 14/27 (52%) of

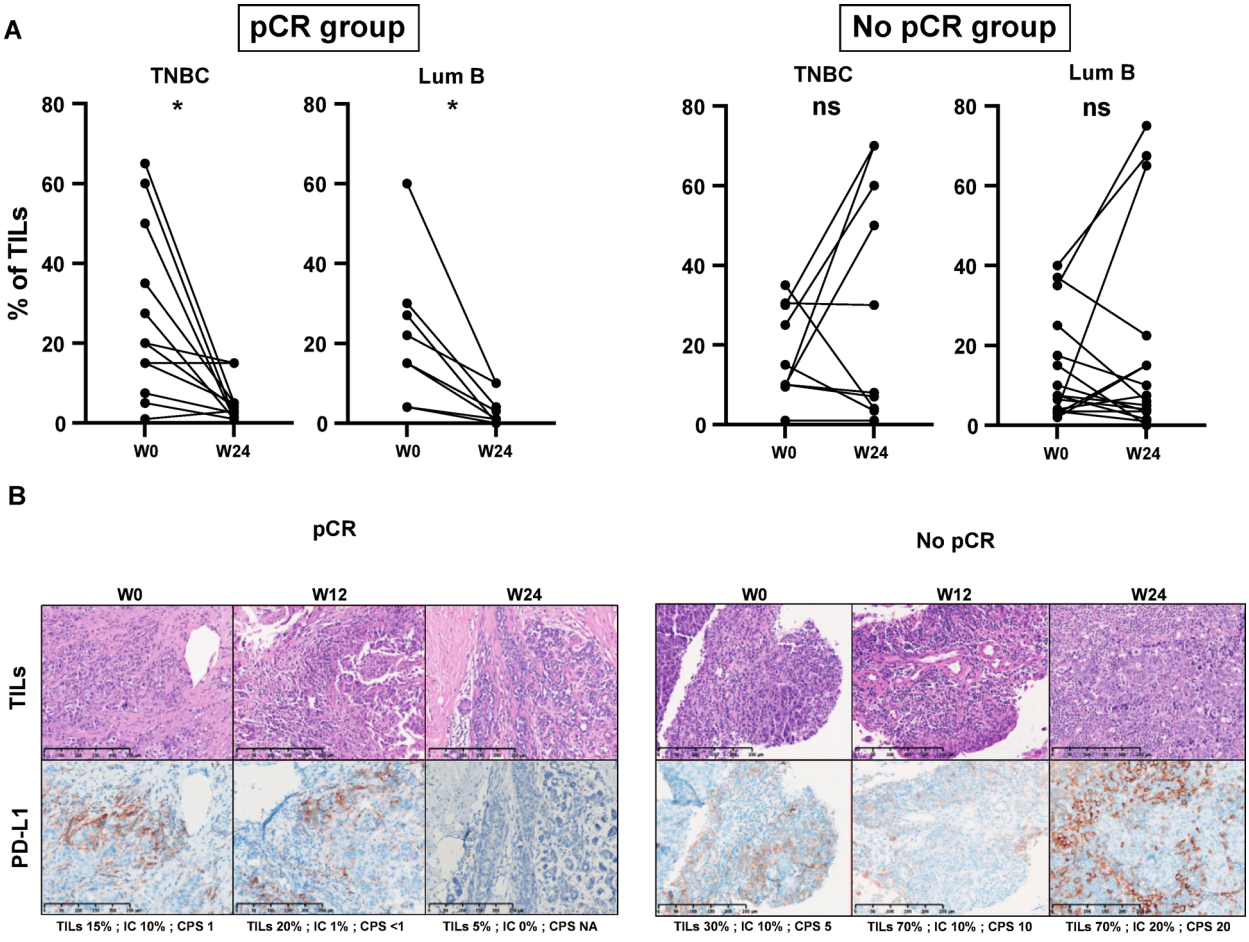

Fig. 4 Modification of TILs rates before and after treatment according to pathological responses and BC subtypes. A. Changes in TILs rate between diagnosis (W0) and surgery (W24) according to pathological response and breast tumor subtypes, represented for all patients treated with the experimental scheme in the phase 2. *Statistical analysis by paired t-test; * = significant difference with p < 0.05.* B. Evolution of tumor infiltration by TILs and PD-L1 expression in 2 illustrative patients with or without pCR. TIL infiltration rate is assessed using morphological criteria on HE slides and PD-L1 expression is assessed using immunoscore (IC) and Combined Positive Score (CPS) on IHC-labelled slides

tumors that did not achieve pCR. Interestingly, only 2/15 (13%) pCRs were found among tumors with a stable or increasing percentage of TILs during treatment. The absence of a decrease in TILs therefore appears to be associated with the absence of pCR (negative predictive value of 0.86, 95% CI 0.62–0.97, $p = 0.01$). No significant change in PD-L1 expression was observed during treatment (data not shown). A dynamic assessment of TILs and PD-L1 during treatment is illustrated in Fig. 4B for patients in the group 3, partially responsive to NACT on MRI, with and without pCR.

Safety

The safety analysis was performed on 50 patients receiving at least one dose of durvalumab (3 patients in the phase 1b part and 47 patients in the phase 2 part). A total of 223 all grade AEs were reported, concerning 35 patients (70%), and 32 AEs (14,3%) were graded 3–4 concerning 17 patients (34%). There was no grade 5 AE reported. The 5 most frequent AEs regardless of the grade were fatigue (7.6%), diarrhea (6.3%), neutropenia (5.4%), anemia (4.9%) and nausea (4.5%). Table 2 shows grade 3–4 AEs ranked by frequency, defined by the percentage among the grade 3–4 events. The percentage of patients who have experienced each grade 3–4 AEs is also notified with 8% of patient presented neutropenia, 6% anemia and 6% fatigue. We report 10 (4.5%) serious adverse events (SAEs) in 8 patients (16%) and 4 patients presenting irAEs (8%). All of these were thyroid disorders (two grade 2 and 1 grade 3 hyperthyroidism, and 1 grade 2 hypothyroidism). Under the experimental treatment, 21 patients (46%) discontinued taxanes before the 12th cycle, and 11 (24%) had a dose reduction. For anthracyclines, only 2 patients stopped treatment before the 4th cycle for asthenia and SARS-Cov2 infection. Seven patients (15%) had a dose reduction of epirubicin. There were no reduction or discontinuation of durvalumab. Relative dose intensity (RDI) [23–25] for each drug was

Table 2 Grade 3–4 adverse events

Adverse events	Occurrences	%	% of patients
Neutrophil count decreased	7	21.9	8
Anemia	5	15.6	6
Fatigue	3	9.4	6
Arthralgia	2	6.3	4
Diarrhea	2	6.3	4
Anorexia	1	3.1	2
Aspartate aminotransferase increased	1	3.1	2
Back pain	1	3.1	2
Catheter related infection	1	3.1	2
Flu like symptoms	1	3.1	2
Hepatic failure	1	3.1	2
Hyperthyroidism	1	3.1	2
Kidney infection	1	3.1	2
Nausea	1	3.1	2
Paresthesia	1	3.1	2
Peripheral motor neuropathy	1	3.1	2
Skin infection	1	3.1	2
White blood cell decreased	1	3.1	2

Table 2 shows grade 3–4 AEs ranked by frequency defined by the percentage among the grade 3–4 events. The percentage of patients concerned is based on all patients included in the safety analysis ($N=50$).

calculated separately and was always ≥ 85% (Table S1). In the experimental arm, the median time between the last dose of chemotherapy and surgery was 23 days (range from 14 to 50 days).

Discussion

In the phase 1b/2 B-IMMUNE non-randomized study, patients with locally advanced TNBC or Luminal B/HER2(-) BC receiving the combination of durvalumab with ECdd after taxanes in a neoadjuvant setting achieved an increased pCR rate compared to historical controls. Notably, these results were achieved with only two doses of anti-PD-L1 therapy, administered exclusively with anthracyclines.

Grade 3–4 AEs were reported in 34% of patients included in the safety analysis of the B-IMMUNE trial, including SAEs in 16% of patients. This toxicity profile was consistent with the most frequently observed grade 3–4 AEs in the pivotal MA21 trial validating the dense-dose regimen followed by a taxane, with hematologic toxicity and gastrointestinal disorders being the most common AEs [26]. We reported 4 irAEs concerning 8% of patients, all were thyroid disorders. No treatment-related deaths were reported. In the KEYNOTE-522 trial, treatment-related grade 3–4 AEs occurred in 76.8% of patients in the pembrolizumab arm and 72.2% in the placebo arm. This higher rate of grade 3–4 AEs observed in both arms is likely due to the addition of carboplatin to the taxanes. SAEs occurred in 32.5% of patients in the pembrolizumab arm, with 3 treatment-related deaths [3]. In GueparNuevo study with a chemotherapy backbone similar to this used in our study and also using durvalumab in TNBC, they observed 50% of thyroid dysfunction but no grade 3–4. There was the only one AE occurring more frequently in the durvalumab arm than in the placebo arm [4]. In KEYNOTE-756, treatment-related grade 3–4 AEs were 52.5% in the pembrolizumab arm and 46.4% in the placebo arm, with 1 death in the pembrolizumab arm due to acute myocardial infarction [8]. In the CheckMate-7FL study, treatment-related grade 3–4 AEs were 35,1% in the nivolumab arm and 32,5% in the placebo arm. The authors reported 3 deaths in the nivolumab arm during the neoadjuvant treatment phase (1 due to COVID-19 and 2 due to pulmonary embolism) and then 2 other late deaths due to pneumonitis and hepatitis. No death due to study drug toxicity was reported in the placebo arm [3, 8, 9]. The rate of irAE reported in the KEYNOTE-522 trial was 22%, 32,8% in KEYNOTE-756 and 47,4% in CheckMate-7FL. In a curative context, the toxicity of immunotherapy must be carefully assessed. Based on our observations, even though lacking long term follow-up and which should be confirmed in larger cohorts, the reduction of the ICI doses resulted in a very favorable safety profile.

However, it is important that the limited duration of the ICI does not lead to a reduction in efficacy. In the B-IMMUNE trial, the pCR rate observed for TNBC was 55%, 10% lower than the rate observed in the KEYNOTE-522 study. It is difficult to conclude whether this difference can be explained by shorter exposure to ICI or whether it is linked to associated chemotherapy including carboplatin and taxanes in the KEYNOTE-522 study [3]. Indeed, the pCR rate observed in studies comparing NACT with and without carboplatin was above 50% with carboplatin and under 45% without [27–29]. For the TNBC cohort, the historical control of 30% of pCR was based on a previous SOC without carboplatin, recommended at the beginning of our study. The NCT02489448 study and the GeparNuevo study used a NACT protocol similar to that of the B-IMMUNE study (replacing paclitaxel with nab-paclitaxel) but durvalumab was administered upfront with taxanes [4, 30]. The authors report a pCR rate of 44% and 53.4% respectively, which is similar to that we observed in our trial. On the other hand, for the Luminal B/HER2(-) cohort, the rate of pCR in B-IMMUNE seems comparable to that observed in the ISPY-2, CheckMate-7FL and KEYNOTE-756 trials [6, 8, 9]. Some studies have continued ICI during an adjuvant phase [2, 3, 5, 8, 9], but to date, only the KEYNOTE-522 showed a significant improvement of EFS and OS in the arm of NACT-pembrolizumab followed by adjuvant pembrolizumab, challenging the impact of the adjuvant phase [2, 31]. Currently, two studies are

ongoing to avoid the adjuvant phase of ICI, especially when patients achieved pCR (OptimICE-pCR and OPT-PEMBRO). Our findings suggest enough efficacy of only 2 doses of an antibody blocking the PD-1 pathway and raise the question of immunotherapy de-escalation with benefits in terms of a reduction in irAEs to justify continued development in a phase 3 trial [14, 15].

Based on MRIs performed before and after neoadjuvant treatment, we observed an ORR of 75.6% in the efficacy analysis group. It is interesting to note that a CR described by MRI appears to be predictive of a pCR only for the TNBC cohort. To our knowledge, this result has not been reported previously in studies evaluating the combination of NACT and ICI, but it is in accordance with a recent work studying the accuracy of MRI to predict pCR following NACT alone in different BC subtypes has also shown that MRI performed better in TNBC compared to luminal subtypes [32].

Another point highlighted by the intermediate analysis of response to treatment carried out in the B-IMMUNE study was that only 45% of patients had achieved a radiological response after 12 weeks of taxanes, and the efficacy of the second part of the treatment combining anthracyclines/durvalumab seems to be decisive for certain patients. These observations underline the need to better distinguish tumor subtypes in TNBC and Luminal B/HER(-) BC using new predictive / monitoring biomarkers in order to personalize treatment approaches.

In the clinical practice, predictive biomarkers for ICI such as PD-L1 expression or tumor infiltration by TILs are difficult to standardize and not very effective in identifying patients who will benefit or not from these treatments. Our observations agree with previous observations showing that TILs are associated with pCR [33, 34]. Nevertheless, some patients with lymphocyte-infiltrated tumors did not obtain a pCR, which means that their presence is not sufficient to guarantee the efficacy of ICI. Regarding PD-L1 expression, we observed more pCRs in tumors with a high CPS score, but this was not the case when the immunoscore was used to quantify PD-L1 labelling, underlining the difficulty in standardizing this biomarker. As with TILs, PD-L1 expression was not a sufficient factor to ensure a response to durvalumab and, conversely, the absence of PD-L1 expression, although more often associated with a lack of response to durvalumab, was not enough to exclude it. Due to the limited number of patients included in our study, we were unable to assess the influence of TIL or PD-L1 on pCR individually for the TNBC and Luminal B/HER2(-) BC sub-cohorts. Foldi et al. conducted a non-randomized phase 2 trial combining upstream durvalumab with nab-paclitaxel followed by ACdd in TNBC. They did not observe statistically significant difference in pCR rates between PD-L1 positive and negative tumors using the immunoscore [30]. In the KEYNOTE-522 study, which also looked at TNBC, the benefit on the pCR rate of adding pembrolizumab to NACT was observed independently of PD-L1 status but was greater in the PD-L1 positive population [2, 3]. The TILs analysis for the KEYNOTE- 522 trial has not been reported. In the GeparNuevo study, which did not reach an pCR improvement, the researchers showed that PD-L1 expression, TIL levels, tumor mutational load and immune gene expression profiles predicted response to neoadjuvant treatment, but this prediction was not specific to the addition of ICI. [35]. For luminal B/HER2(-) BC, biomarkers analysis from the Checkmate-7FL trial showed an increase in pCR rate when stromal TILs were greater than 1% in both arms, with a greater effect in patients treated with nivolumab [9]. With regard to PD-L1 expression, the CheckMate 7FL trial and the KEYNOTE-756 trial, which also involved luminal B/HER2(-) BC, showed an increased benefit in terms of pCR when PD-L1 expression was high [8, 9]. It seems that the high proportion of TNBCs with high PD-L1 expression makes this predictive biomarker less discriminant in this population than in luminal B/HER2(-) BCs.

Tumor infiltration by TILs is a dynamic phenomenon over time, but the influence of chemotherapy and/or ICI on this remains poorly defined. Singer et al. showed a reduction in TILs in patients treated with NACT with or without a MUC1 vaccine, with a greater effect in responders (RCB 0/I) than in non-responders (RCB II/III) [36]. The recent PROSPERO 2021 meta-analysis, which included 2072 patients with early-stage breast cancer treated with NACT without ICI, demonstrated a significant reduction in TILs after treatment. Of the 32 articles included, only 6 reported a correlation between TILs variation and clinical response [37]. Only one article including 60 patients described a significantly lower number of TILs after NACT in patients with pCR and no significant difference between the number of TILs before and after NACT in patients with residual disease [38]. Another article including 99 breast cancers treated with NACT (76% receiving anthracycline/taxane-based therapy), reported a significant increase in CD8 T cells after NACT in patients without pCR. Among patients with residual disease, they demonstrated a correlation between incremental TILs after NACT with improved DFS [39]. In the B-IMMUNE study, we monitored tumor infiltration by TILs, and our observations suggest that stable or increasing infiltration is the most informative factor, significantly associated with a lack of pCR. Further analysis concerning the modification of tumor immune microenvironment are ongoing.

Conclusions

ICIs in combination with chemotherapy in the neoadjuvant setting improves pCR for both TNBC and Luminal B/HER2(-) BC. The results of the B-IMMUNE study suggest that this benefit can be achieved even with short-term treatment limited to two ICI infusions prior to surgery, paving the way for phase III randomized clinical trials evaluating a possible reduction in ICI treatment in locally advanced breast cancer. Research associated with the B-IMMUNE trial is currently underway to identify and develop new biomarkers to assess the immunogenicity of breast tumors more accurately than PD-L1 expression and TILs rates. Assessing the immunogenicity of the breast tumor before and during treatment with clinically usable approaches could help to select the patients most likely to respond to NACT-ICI treatment and determine the optimal time to administer them.

Abbreviations

EC	Epirubicine- cyclophosphamide
ICI	Immune checkpoint inhibitors
NACT	Neoadjuvant chemotherapy
BC	Breast cancer
TNBC	Triple negative breast cancer
pCR	Pathological complete response
EFS	Event-free survival
ECOG	Eastern cooperative oncology group
ECdd	Epirubicine -cyclophosphamide dose dense
ORR	Overall response rate
CTCAE	Common terminology criteria for adverse events
RCB	Residual tumor burden
IC	Immunoscore
TPS	Tumor positive score
CPS	Combined positive score
TILs	Tumor infiltrating lymphocytes

Supplementary Information

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Supplementary Material 1

Supplementary Material 1

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Author contributions

A.D collected, analysed and interpreted all the data and was a major contributor in writing the manuscript G.B performed the histological examination and the analyses of TILs and PD-L1 scoring. P.D. performed the histological examination and the analyses of TILs and PD-L1 scoring. C.Q data acquisition S.H data acquisition M.VB performed histological examination C.G performed histological examination S.L data acquisition D.K data acquisition V.V data acquisition C.L data acquisition L.DH data acquisition M.B data acquisition C.VM data acquisition S.D was a major contributor in the conception of the study mainly in the pharmacy department and in the management of drugs availability. J-M. M data acquisition G.M performed histological examination N.M peformed histological examination I.B was a contributor in the data interpretation and statistical analyses S.H collected and processed all samples A.M was a contributor in the data interpretation and statistical analyses D.P collected and processed all samples P.G.C was a contributor for drafting the translational part of the work and its revision J-L.C, was a major contributor in the conception and the design of the work, and in writing the manuscript F.P.D, was a major contributor in the conception and the design of the work, and in writing the manuscript J.C conception of the trial, the draft and the design of the study, analysed and interpreted the results and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The B-immune study was approved by the Hospital Ethics Committee of the Catholic University of Louvain on 7 February 2017 (ref 2016/16NOV/495). All patients included gave informed consent.

Consent for publication

Not applicable (no data from any individual person).

Competing interests

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