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Clinico-pathological factors predicting pathological response in early triple-negative breast cancer

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Pathological complete response (pCR) after neoadjuvant chemoimmunotherapy (NACi) is associated with improved patient outcomes in early triple-negative breast cancer (TNBC). This study aimed to identify factors associated with pCR after NACi. This cohort included all patients with stage II-III TNBC treated with NACi who underwent surgery at Institut Curie hospitals between 08/2021-06/2023. Among 208 patients, the overall pCR rate was 70% and was similar in ER < 1% (69%) and ER-low TNBC (73%, $p = 0.6$). In a multivariate model, Ki-67 ≥ 30% (OR 5.19 [1.73–17.3]), centralized TILs ≥ 30% (OR = 3.08 [1.42–7.04]), absence of DCIS at initial biopsy (OR = 2.56 [1.08–6.25]) and germline mutations in homologous recombination genes (OR = 9.50 [2.37–67.7]) remained strong independent predictors of pCR. These findings may guide treatment decisions in patients with TNBC undergoing NACi. Almost all patients with germline mutations in HR genes achieved pCR, supporting de-escalation trials. We suggest that ER-low tumors should be managed as TNBC tumors.

Triple-negative breast cancer (TNBC) is a highly heterogeneous disease comprised of breast tumors with no or minimal expression of estrogen receptor (ER), progesterone receptor (PR), and no amplification or overexpression of human epidermal growth factor receptor 2 (HER-2)[1]. Histopathological definition of TNBC varies across countries: while ER/PR negativity is defined as strictly less than 1% in immunohistochemistry (IHC) by the ASCO/CAP guidelines[2], the ESMO guidelines include tumors with an expression of ER/PR up to 10%[3]. Accounting for approximately 15% of all breast cancers[4], TNBC is characterized by an aggressive phenotype and embodies the breast cancer subtype with the worst prognosis, including early relapse and poor overall survival[5]. Despite recent advances in the insight of molecular heterogeneity of TNBC, few implications have translated into clinical practice, and cytotoxic chemotherapy remains the cornerstone of treatment.

While pre- and postoperative chemotherapies based on anthracycline and taxane regimens were shown to be equivalent in efficacy[6,7], neoadjuvant chemotherapy (NAC) is the unanimously preferred treatment approach for stage II or III TNBC. NAC may enable tumor downstaging and more limited breast and axillary nodal surgery, but it also provides precious information as the tumor response is used for prognostication and indication of tailored postoperative therapies. Pathological complete response (pCR) to NAC is a validated surrogate marker indicating a significantly reduced risk of systemic recurrence. The residual cancer burden (RCB) score, based on the degree of response after NAC, is used to identify patients with a high risk of recurrence[8]. Over a 10-year span, only 10% of RCB 0 (pCR) TNBC patients treated with NAC are expected to suffer distant recurrence, compared to 19% in the RCB I group, 33% in the RCB II and 54% in the RCB III group[9]. Since pCR was shown to be strongly associated with improved long-term survival outcomes, especially in TNBC[10,11], escalation of neoadjuvant treatment has been the focus in the past few years, and the addition of carboplatin to NAC regimens has improved pCR rates[12,13]. Recently, a paradigm shift was achieved, introducing neoadjuvant chemoimmunotherapy (NACi) as the new standard of care for high-risk early-stage TNBCs. Pembrolizumab, an immune checkpoint inhibitor (ICI) that blocks PD-1, administered in addition to taxane, carboplatin and anthracycline, improved both pCR rates (64.8%)[14] and long-term outcomes: event-

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free survival (EFS, 5-year EFS rate 81.3%, 95% CI [78.4–83.9])[15] and overall survival (OS, 5-year OS rate 86.6%, 95% CI [84–88.8%])[16]. The high rate of potentially fatal or permanent toxicities observed with NACi (34.1% G3-4 adverse events and 33.5% of immune-related adverse events, among which 12.9% of G3 or higher)[17] lead to treatment discontinuation in a non-negligible proportion of patients (27.7%)[18]. Therefore, identifying the TNBC subgroup of patients with the highest likelihood of benefit from NACi prior to treatment initiation is critical for therapeutic decision-making.

However, no universally approved biomarker is currently approved to predict response to NACi. Results from Keynote-522 showed that PD-L1 expression cannot be used as an optimal tool for patient selection. On the other hand, TILs are both a prognostic and a predictive marker of pCR to NAC in TNBC[19,20], but their ability to predict pCR to NACi remains unclear. There is promising research on emerging biomarkers such as tumor mutational burden, immune gene expression profiles, mRNA-based signatures, or circulating-tumor DNA[21,22] but they lack significant clinical evidence, and their utility must be further evaluated in prospective studies.

In this study, we aimed to determine whether clinical or pathological pre-treatment biomarkers could predict pCR after NACi in a prospective real-life cohort of patients treated at Institut Curie Hospitals.

Methods

Patients

This study was a population-based prospective cohort study, which included every patient who received NACi (according to the pivotal KEYNOTE-522 trial regimen) and underwent surgery for high-risk early-stage II-III TNBC at Institut Curie hospitals, France (Paris and Saint-Cloud) between August 2021 and June 2023. This study was approved by the Ethical Review Board of Institut Curie (DATA220277) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

Treatment

NACi consisted of the pivotal KEYNOTE-522 trial treatment schedule[14]. Patients were planned to receive pembrolizumab 200 mg Q3W in addition to four cycles of carboplatin and weekly paclitaxel followed by four cycles of doxorubicin/cyclophosphamide. Dose-dense AC regimen was not used, and a growth factor prescription was left to the investigator's discretion. After neoadjuvant treatment, all patients underwent breast-conservative surgery or total mastectomy with axillary staging according to local practice.

Clinical and pathological data

Electronic medical records were used to obtain detailed information regarding clinical and pathological data. Clinical Tumor (T) and node (N) stages were determined according to the 8th edition of the American Joint Committee on Cancer (AJCC) Staging Manual[23]. If clinical or radiological nodal involvement was suspected, a fine-needle aspiration was performed.

Pathologists confirmed pre-treatment pathological tumor characteristics from biopsy samples performed in our institute. Protein expression determined in IHC was used for tumor subtyping. According to ESMO guidelines, TNBC was defined as ER/PR expressed in <10% of tumor cells and HER2 negative (score 0, 1+, 2+ not amplified)[3]. Other histopathological variables of interest were the histological type and grade, the presence of ductal carcinoma in situ (DCIS), expression of androgen-receptor (AR), and Ki-67 index ≥ 30% (International Ki67 in Breast Cancer Working Group[24]). We reported two measures for tumor-infiltrating lymphocytes (TILs): "non-centralized TILs", collected from medical files and referring to the original pathological reports from the local institution or outside reports (performed by various pathologists); and "centralized-TILs", which consisted of a centrally reviewed TILs assessment of each H&E slide according to the recommendations of the TILs working group[25,26], by two expert breast pathologists pre-trained using the TILs training tool available on www.tilsinbreastcancer.org. The FDA-approved antibody clone 22C3 was used for PD-L1 protein detection in FFPE pre-treatment biopsy samples to determine CPS[27]. PD-L1 testing was not routinely performed outside our institution, and tissue samples were not available for PD-L1 testing in all patients. Apocrine carcinoma was defined by apocrine morphology and AR positivity (≥10%)[28].

Pathological response was confirmed by microscopic assessment of each resected specimen using the RCB index[8]. pCR (RCB 0) was defined as the absence of invasive cancer in the breast and axillary nodes, irrespective of the presence of residual ductal carcinoma in situ (ypT0/isN0)[9].

According to local guidelines, patients who were diagnosed before the age of 61 or in case of familial history of breast cancer underwent genetic testing including germline deleterious mutation in homologous recombination (HR) genes: *BRCA1, BRCA2, PALB2, RAD51C*, and *RAD51D*, as well as *TP53*, *CDH1*, *PTEN*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*[29]. When germline testing was not performed, we used a targeted NGS panel test to identify somatic mutations in the HR pathway. The absence of a germline mutation was defined as either the absence of a germline mutation in the HR pathway or the absence of somatic mutations in the HR pathway when germline testing was not performed.

Endpoint

We investigated the association between pre-treatment clinical and pathological biomarkers with the achievement of pCR after NACi. Patients who had a tumor progression before surgery were considered as non-pCR/RCB III. pCR rate was analyzed in all patients except for those who were lost to follow-up before surgery (Fig. 1).

Statistical analysis

We reported binary and categorical variables as frequencies (percentages), and continuous variables as medians (interquartile). Patient characteristics were reported using descriptive analyses and compared using the χ^2 test, Fisher's exact test, or the Wilcoxon rank sum test. For correlation, the Pearson correlation coefficient was used.

A logistic regression analysis was conducted for multivariate analysis, including only the significant variables identified in the univariate analysis. Considering the rate of missing data, PDL1 CPS was not included in the multivariate model. Lobular and apocrine carcinomas were rare and not included in the model.

The threshold for statistical significance was set at $p < 0.05$. R software version 4.2.2 was used for statistical analyses, and the gtsummary package for the analysis[30].

Results

Baseline characteristics of patients

Between August 2021 and June 2023, 214 patients with TNBC followed at Institut Curie Hospitals were treated with NACi and 208 were included in this study (four patients declined consent, two patients had their surgery performed elsewhere and were lost to follow-up) (Fig. 1). Carboplatin was mainly planned every-3 week (q3w) (97%), while 3% of patients received it

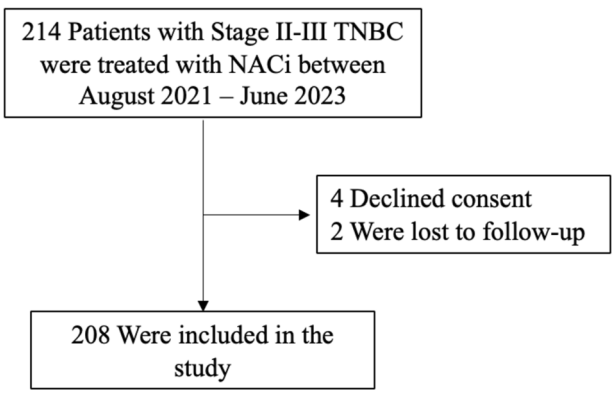

Fig. 1 | Study consort diagram. TNBC triple-negative breast cancer, NACi neoadjuvant chemoimmunotherapy.

Table 1 | Demographic, clinical, and pathological characteristics of the 208 patients

Characteristic	According to pCR					
	N =	no pCR, *N* = 63[1]	pCR, *N* = 145[1]	*p*-val[2]	OR	95% CI
Age—median (IQR)	208	48 (39, 56)	49 (42, 56)	0.5	1.01	0.98, 1.04
ECOG PS	202			0.6		
0		58 (29%)	139 (71%)		–	–
1		2 (40%)	3 (60%)		0.63	0.10, 4.84
Missing	6					
Menopausal status	207			>0.9		
Postmenopausal		26 (30%)	60 (70%)		–	–
Premenopausal		36 (30%)	85 (70%)		1.02	0.56, 1.87
Missing	1					
BMI—median (IQR)	208	25 (23, 32)	25 (22, 29)	0.15	1.00	1.00, 1.00
Germline mutation	207			0.016		
No		61 (35%)	114 (65%)		–	–
BRCA1		2 (8.7%)	21 (91%)		8.03	2.32, 50.7
BRCA2		0 (0%)	5 (100%)			
PALB2		0 (0%)	1 (100%)			
RAD51C		0 (0%)	3 (100%)			
Unknown	1					
Primary tumor	208			<0.001		
T3–T4		26 (48%)	28 (52%)		–	–
T1–T2		37 (24%)	117 (76%)		2.94	1.53, 5.65
Nodal involvement	208			0.3		
N0		22 (26%)	62 (74%)		–	–
N+		41 (33%)	83 (67%)		0.72	0.38, 1.32
Stage	208			0.017		
II		38 (26%)	111 (74%)		–	–
III		25 (42%)	34 (58%)		0.47	0.25, 0.88
Histological subtype	208			0.001		
NST		53 (28%)	138 (72%)		–	
Lobular		3 (100%)	0 (0%)			
Apocrine carcinoma		4 (100%)	0 (0%)			
Metaplastic carcinoma		1 (20%)	4 (80%)			
Others		2 (40%)	3 (60%)			
DCIS on pre-treatment biopsy	192			0.009		
Yes		16 (47%)	18 (53%)		–	–
No		39 (25%)	119 (75%)		2.71	1.26, 5.85
Missing	16					
DCIS residual after surgery	206			<0.001		
Yes		22 (73%)	8 (27%)		–	–
No		39 (22%)	136 (78%)		9.66	4.14, 24.7
Missing	2					
Grade	208			0.030		
II		13 (48%)	14 (52%)		–	–
III		50 (28%)	131 (72%)		2.43	1.06, 5.57
ER	208			0.6		
<1%		55 (31%)	123 (69%)		–	–
1–<10%		8 (27%)	22 (73%)		1.23	0.53, 3.10
PR	208			>0.9		
<1%		61 (30%)	141 (70%)		–	–
1–<10%		2 (33%)	4 (67%)		0.87	0.16, 6.36

Table 1 (continued) | Demographic, clinical, and pathological characteristics of the 208 patients

Characteristic	According to pCR					
	N =	no pCR, *N* = 63[1]	pCR, *N* = 145[1]	*p*-val[2]	OR	95% CI
HER2	208			0.8		
0		29 (29%)	70 (71%)		–	–
Low (1+, 2+, FISH−)		34 (31%)	75 (69%)		0.91	0.50, 1.65
AR—median (IQR)	156	1 (0, 20)	3 (0, 15)	>0.9	0.99	0.98, 1.01
AR positivity (≥10%)	156			0.8		
Negative		32 (29%)	77 (71%)		–	–
Positive		13 (28%)	34 (72%)		1.09	0.52, 2.38
Missing	52					
Ki67 (%)	208	60 (30, 80)	70 (50, 80)	<0.001	1.03	1.01, 1.04
Ki67 positivity	208			<0.001		
<30%		15 (68%)	7 (32%)		–	–
≥30%		48 (26%)	138 (74%)		6.16	2.45, 17.0
Non-centralized TILs—median (IQR)	197	20 (5, 40)	20 (10, 40)	0.4	1.00	0.99, 1.02
Non-centralized TILs (%)	197			0.3		
<30%		41 (34%)	81 (66%)		–	–
30–50%		5 (18%)	23 (82%)		2.33	0.88, 7.33
>50%		14 (30%)	33 (70%)		1.19	0.58, 2.53
Missing	11					
Centralized TILs—median (IQR)	182	15 (5, 25)	25 (10, 50)	<0.001	1.04	1.02, 1.06
Centralized TILs (%)	182			0.002		
<30%		44 (41%)	63 (59%)		–	–
30–50%		8 (24%)	25 (76%)		2.18	0.93, 5.58
>50%		5 (12%)	37 (88%)		5.17	2.03, 15.9
Missing	26					
PD-L1 CPS—median (IQR)	150	12 (5, 15)	15 (5, 30)	0.008	1.03	1.01, 1.06
PD-L1 CPS (%)	150			0.023		
<10		18 (38%)	30 (63%)		–	–
10–19		15 (32%)	32 (68%)		1.28	0.55, 3.01
≥20		8 (15%)	47 (85%)		3.53	1.40, 9.55
Missing	58					

OR odds ratio, *CI* confidence interval, *ECOG* scores on the Eastern Cooperative Oncology Group, *BMI* body mass index, *IC-NST* invasive carcinoma of no special type, *ILC* invasive lobular carcinoma, *ER* estrogen receptor, *PR* progesterone receptor, *AR* androgen receptor, *TILs* tumor-infiltrating lymphocytes, *CPS* combined positive score, *DCIS* ductal carcinoma in situ.
[1]Median (IQR); *n* (%).
[2]Wilcoxon rank sum test; Fisher's exact test; and Pearson's Chi-squared test.

on a weekly schedule. Table 1 summarizes the demographic and clinical baseline characteristics of the 208 patients included in this study. All patients included in this cohort were women. Median age was 49 years (IQR, 41–56 years) and 149 (72%) had clinical stage II. In terms of histological subtype, 92% ($n = 191/208$) of patients had an invasive carcinoma of no special type (NST), 2% ($n = 4/208$) had an apocrine carcinoma, and less than 2% had an invasive lobular carcinoma ($n = 3/208$). Fourteen percent ($n = 30/208$) of the tumors expressed between 1 and 9% ER, and 15% ($n = 32/208$) of the patients harbored one germline mutation in homologous recombination (HR) genes. More specifically, we identified mutations in *BRCA1* ($n = 23/32$, 72%), *BRCA 2* ($n = 5/32$, 16%), *PALB2* ($n = 1/32$, 3%), and *RAD51C* ($n = 3/32$, 9%). The rate of germline mutations in the HR pathway was similar between ER-low tumors (15.8%) and ER-negative tumors (13.8%).

Association of clinicopathological characteristics with pCR

We observed pCR (RCB 0) in 70% 95% CI [63-76%] of patients ($n = 145$), and RCB I, II, and III in 7% ($n = 15$), 19% ($n = 40$) and 4% ($n = 8$) of patients respectively. The association between baseline clinicopathological characteristics and pathological complete response after NACi is provided in Table 1.

In univariate analysis, we observed a statistically significant association between pCR and clinical stage: in our study, patients with stage III TNBC achieved pCR less often than stage II patients (respectively 58% vs 74%, OR = 0.47 [0.25–0.88]). This effect appeared to be primarily driven by tumor size (cT1–T2 vs cT3–4 OR = 2.94 [1.53, 5.65]), as we did not observe a statistically positive association of pCR and regional lymph node metastasis (positive vs negative OR = 0.72 [0.38–1.32]). None of the few patients with ILC ($n = 3$) or apocrine carcinoma ($n = 4$) achieved a pCR. Of note, 72% of patients with AR-positive ≥ 10% tumors achieved pCR ($n = 34/47$), compared to 71% of patients with AR < 10% ($n = 77/109$), OR = 1.09 [0.52–2.38]. Apocrine carcinomas had a lower Ki67 rate than others, 25% IQR [24, 25] vs 70% IQR [50, 80], $p = 0.002$), and tended to have a lower grade (grade II in $n = 2/4$, 50% vs $n = 24/204$, 12%, $p = 0.08$). HER2 status was not associated with pCR (69% pCR in HER2-low tumors vs 71% in HER2 0 tumors, $p = 0.8$. Patients achieving pCR had a statistically higher tumor proliferation rate (Ki-67; OR = 1.03 [1.01–1.04]; Table 1 and Fig. 2A).

Patients with a germline mutation in HR genes were more likely to reach pCR ($n = 30/32$, 94% vs $n = 114/175$, 65% for patients with no germline mutations, OR = 8.03 [2.32–50.7]). Nearly all of the patients with a

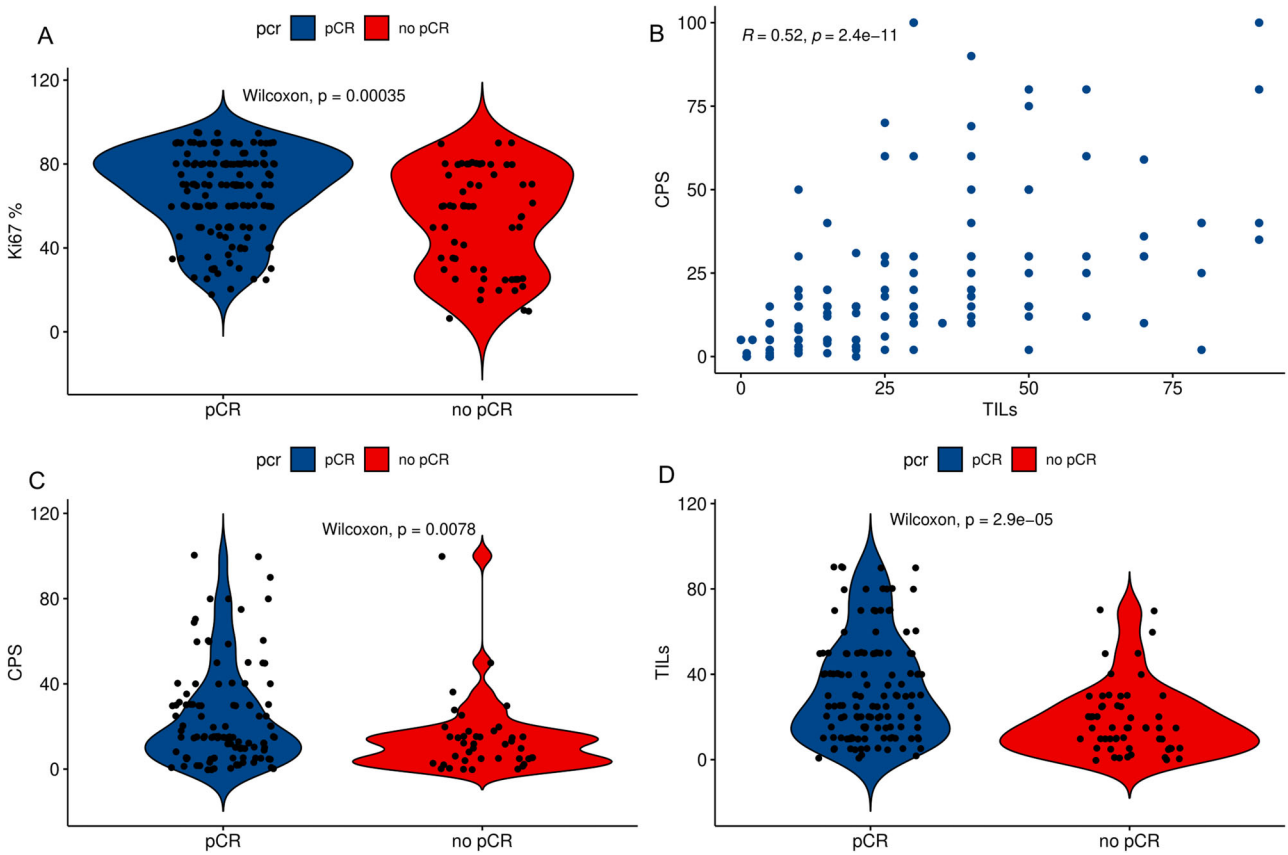

Fig. 2 | Pathological complete response (pCR) and association with Ki67 and immunologic features. A Association between pathological complete response (pCR) and Ki67. **B** Correlation (Pearson) between combined positive score (CPS) and centralized Tumor-infiltrating lymphocytes (TILs). **C** Association between pCR and CPS. **D** Association between pCR and centralized TILs.

Table 2 | Multivariable model for pCR

Characteristic	*N*	OR [95% CI]	*p*-value
Germline mutation (BRCA1/2, PALB2, RAD51C)			<0.001
No	175	Reference	
Yes	32	9.50 [2.37–67.7]	
Stage			0.092
II	149	Reference	
III	58	0.53 [0.25–1.11]	
Grade			0.80
II	27	Reference	
III	180	1.18 [0.40–3.30]	
DCIS on pre-treatment biopsy			0.024
Yes	34	Reference	
No	157	2.56 [1.08–6.25]	
Missing	16	3.33 [1.03–11.11]	
Ki-67			0.003
<30%	22	Reference	
≥30%	185	5.19 [1.73–17.3]	
Centralized TILs			0.010
<30%	106	Reference	
≥30%	75	3.08 [1.42–7.04]	
Missing	26	2.56 [0.89–8.47]	

OR odds ratio, *CI* confidence interval, *DCIS* ductal carcinoma in situ, *CPS* combined positive score, *pCR* pathological complete response.

germline mutation in the HR pathway achieved pCR, with the exception of two patients harboring BRCA1 mutations.

Interestingly, 73% ($n = 22/30$) of patients with an expression of ER between 1% and 9% achieved pCR in our study, which was similar for patients with ER < 1% who achieved pCR in 69% (123/178, OR = 1.23 [0.53–3.10]).

We evaluated DCIS at two different time points: before receiving NACi (on tumor biopsy) and after receiving NACi (on surgical specimen). We observed that patients without DCIS on tumor biopsy before receiving any treatment were more likely to achieve pCR than those with DCIS ($n = 119/158$, 75% DCIS before NACi vs $n = 18/34$, 53% no DCIS before NACi, OR = 2.71 [1.26–5.85]). In addition, we observed that patients without DCIS on surgical specimens after receiving NACi achieved pCR more frequently than patients with residual DCIS ($n = 137/176$, 78% without residual DCIS vs $n = 8/30$, 27% with residual DCIS, OR = 9.66 [4.14–24.7]).

We observed in univariate analysis the same clinicopathological factors associated with RCB (Supplementary Table 1). Given the worse outcome of RCB II and RCB III patients, we also evaluated factors associated with the combined RCB II and III groups vs RCB 0 and I groups (Supplementary Table 2). Overall, the results were similar.

Impact of immunologic features on pCR

Regarding the association between clinicopathological characteristics, centralized TILs and CPS were moderately correlated ($R = 0.52$, $p < 0.001$, Pearson) (Fig. 2B). Interestingly, we found that the correlation between TILs assessments by pathologists and the centralized assessment was not strong ($R = 0.79$, $p < 2.2e\text{-}16$, Pearson).

In univariate analysis, CPS was associated with pCR (OR = 1.03 [1.01–1.06], Table 1 and Fig. 2C), as well as centralized TILs (OR = 1.04 [1.02–1.06], Table 1 and Fig. 2D), but not TILs assessed by various pathologists (OR = 1.00 [0.99–1.02]).

Multivariate analysis

In a multivariate model (Table 2), Ki-67 ≥ 30% (HR 5.19 [1.73–17.3]), centralized TILs ≥ 30% (OR = 3.08 [1.42–7.04]), absence of DCIS on the initial biopsy (OR = 2.56 [1.08–6.25]) and germline mutations in HR genes (OR = 9.50 [2.37–67.7]) remained strong independent predictors of pCR after NACi. Tumor grade was not an independent factor in the multivariate analysis (OR = 1.18 [0.40–3.30]).

Discussion

To our knowledge, in this study we reported for the first time that germline mutations in HR genes, Ki-67, TILs, histological subtype, and absence of DCIS on pre-treatment biopsy were associated with pCR in stage II-III TNBC undergoing NACi, and that TNBC with ER-low had a similar pCR rate to TNBC with ER < 1%.

Achieving pCR is a major goal of the neoadjuvant treatment approach as it was shown to be associated with significantly improved EFS and OS in TNBC[9]. A recent exploratory analysis from the KEYNOTE-522 trial also confirmed that the addition of pembrolizumab to chemotherapy improves EFS in patients who do not have a pCR: fewer EFS events were observed in the RCB 0, I/II categories, with the greatest benefit in RCB-II[31]. In our cohort, 70% of patients had a pCR, in line with the rates observed in KEYNOTE-522[14]. Identifying patients before treatment initiation who are more likely to achieve pCR could lead to treatment de-escalation, avoiding unnecessary toxicities of either the chemotherapy backbone, such as anthracyclines, or the ICI. Conversely, investigational therapeutic alternatives could be offered to those less likely to achieve pCR.

Approximately 10 to 15% of TNBC patients carry *BRCA1* or *BRCA2* germline mutations[32] and conflicting data have been reported concerning pCR rates in these patients. A study reported that patients with *BRCA* mutations achieved higher pCR rates than patients without *BRCA* mutations after receiving NAC[33], while Bonadio et al. did not observe such association[34]. In a cohort of patients treated at our institution before 2012 without carboplatin, the pCR rate among patients with TNBC was 48% in those with *BRCA* germline mutations, compared to 43% in those without[35]. Moreover, a group of sporadic cancers called "BRCA-like", comprised of tumors with a homologous recombination deficiency (HRD) but without *BRCA 1/2* germline mutations, has also been associated with higher pCR rates after receiving NAC[36]. One study revealed that the mutational status of 10 DNA repair genes involved in HR could predict response to NAC: tumors with a positive mutation status for such genes would achieve pCR more often[37]. Here, we also observed a statistically positive association between germline mutations in HR-related genes and pCR after NACi. This suggests that HRD may sensitize the tumor to chemotherapy and ICI. In addition, the predictive value of HRD for response to ICI in the chemotherapy-free regimens warrants further investigation. In our study, almost every patient with a germline *BRCA1/2* mutation achieved pCR, meaning that only a few patients who did not achieve pCR would receive PARP inhibitors in the adjuvant setting[38]. These patients with germline *BRCA1/2* mutations may benefit from a de-escalation strategy with the use of PARP inhibitors +/− ICI in the neoadjuvant setting[39,40], and consideration of salvage chemotherapy in the absence of pCR.

TNBC is a highly proliferative breast cancer subtype, usually associated with high Ki-67 expression[41]. Although controversial data exist on the independent prognostic value of Ki-67, its use as a predictive marker of response to chemotherapy has been widely investigated. A high level of Ki-67 was shown to be a good predictor of response to chemotherapy, including in the neoadjuvant setting[42]. Consistent with these findings, we also observed statistically higher pCR rates among patients with high Ki-67 expression in our cohort. As Ki-67 correlates with tumor SUVmax in [18F] FDG-PET imaging, our observation here resonates with the conclusions drawn from our previous work, in a smaller cohort, exploring the predictive value of pre-treatment [18F]FDG-PET imaging, in which we concluded that high tumor metabolism (SUVmax) and low metabolic tumor volume (TMTV) could accurately predict pCR[43].

Apocrine carcinoma, defined by apocrine morphology and AR positivity, accounts for approximately 1% of all breast cancers[44] and has been shown to be associated with a better prognosis, despite a poorer response to NAC[45]. Several studies have described that apocrine carcinomas tend to show a lower proliferation rate and a rather chemo-resistant profile[46,47], with a decreased probability of achieving pCR after NAC. It has also been suggested that AR expression would be associated with tumor cell immune evasion[48]. Consistent with these findings, we also observed that apocrine carcinomas had a lower pCR rate after NACi in univariate analysis. This observation should be taken carefully, since apocrine carcinomas represent a rare subset of TNBC, and therefore only a very small number were included in our cohort, as well as the absence of pCR observed in TNBC with ILC. However, we did not observe an association between AR expression/positivity and pCR.

TILs, lymphocytes infiltrating the tumor and its invasive margins[49], are a major component of the tumor microenvironment, mediating adaptive, anti-tumor immune responses. Because of higher levels of TILs commonly reported, along with higher TMB and enhanced PD-L1 expression (measured by the CPS score), TNBC is considered the most immunogenic subtype of breast cancer[50]. TILs have been reported to be a strong prognostic marker in TNBC: a high abundance of TILs has robustly been associated with a greater likelihood of achieving pCR after NAC[51,52], but their ability to predict responses to immunotherapy (IO) agents has not been fully defined in early-stage TNBC. A large body of data has emerged from early/advanced settings, in which a correlation between baseline TILs, CPS score, and tumor response has been reported[53–55]. Several studies then reported an independent correlation between the abundance of TILs in residual disease after NAC and long-term survival outcomes, leading to a 21% relative reduction in the risk of metastasis and death for each 10% TIL increment[20,56]. Similarly to other studies[57,58], TILs were statistically associated with pCR after NACi in our cohort, with a positive association between tumors exhibiting higher TIL infiltration achieving higher pCR rates. CPS, a well-recognized predictive biomarker of response to pembrolizumab in advanced breast cancer[55], was also associated with pCR in our cohort. Notably, similar to other studies[59], we observed a significant disparity in TIL assessments between the evaluations by untrained pathologists vs the centralized review by trained experts, with only the centralized assessment being associated with pCR. Therefore, we emphasize that TIL evaluation should be performed by a well-trained breast pathologist, especially as several clinical trials rely on TIL measurements for treatment escalation or de-escalation (NCT06078384 and NCT06067061).

Importantly, 73% of patients with an expression of ER between 1% and 9% achieved pCR in our study, indicating a pCR rate at least as high as the pCR rate observed in the KEYNOTE-522 trial (64.8%)[14], in which only patients with ER expression < 1% were included. KEYNOTE 756, conducted in patients with ER ≥ 1%, reported that the addition of pembrolizumab leads to a higher pCR, especially in the ER-low (1–9%) subgroup[60]. Our data support the observation that patients with an ER expression between 1% and 9% have a very high pCR rate, similar to those with ER < 1%, and should therefore be treated as TNBC and receive chemo-immunotherapy with the addition of carboplatin, by opposition to the KEYNOTE 756 trial. This was also observed with a drug regimen without anthracycline[49].

Also, the absence of DCIS on pre-treatment biopsy and on the resected specimen were both strongly associated with pCR, including in the multivariate model, while the presence of DCIS was not generally found to be a prognostic/predictive factor of pCR[61]. The presence of an in situ component (DCIS) is often associated with the invasive component in breast carcinoma[62]. In TNBC, DCIS is less frequently observed as compared to luminal or HER2-positive tumors. We hypothesize that this may be linked to distinctive biological features of TNBC such as a specific molecular

subtype, intra-tumoral heterogeneity, and a distinct tumor microenvironment, all of which could contribute to the observed treatment resistance. Furthermore, there is conflicting literature regarding the predictive value of DCIS to NAC response: Van Bockstal et al. found no association between a DCIS component and pCR in a cohort of TNBC patients[63], as well as a retrospective cohort from our institution[61]. By contrast, according to Von Minckwitz et al., the presence of DCIS is an independent negative predictor of pCR after NAC in HER2-positive BC[64]. Literature on the predictive value of DCIS to NACi in TNBC is scarcer. Nearly every tumor that achieved pCR was ypT0N0 (i.e., without residual DCIS). Therefore, pCR after NACi is rarely associated with residual in situ disease, suggesting that both in situ and infiltrative disease tend to regress in parallel. The biological significance of this result is currently unknown, and further studies are needed to examine specific characteristics of TNBC with in situ disease vs other TNBCs, and to compare biological features of the in situ and infiltrating components within the same tumor.

The main limitation of our study is the absence of a validation cohort and the fact that all patients were treated at the Institut Curie Hospitals. Other limitations include the absence of a blinded independent central review for TNBC diagnosis, the absence of systematic PD-L1 testing (due to the low tumor tissue availability), and the lack of information on chemo-immunotherapy compliance. Furthermore, results regarding apocrine and lobular carcinomas are derived from a very limited sample size, which affects the generalizability of our findings. Larger cohorts are needed to validate our observations.

In conclusion, we showed that germline mutation in genes involved in homologous recombination, TILs, Ki-67 expression, histological subtype, and absence of DCIS, could help to predict pathological complete response after neoadjuvant chemo-immunotherapy in triple-negative breast cancer. Moreover, patients with TNBC with ER-low tumors had a similar pCR to TNBC with ER <1%. To our knowledge, this is the first study to report such an association in a large real-life cohort of TNBC treated with the KEYNOTE-522 regimen.

Data availability

Data are available upon reasonable request at the discretion of the corresponding authors. Access to datasets used in this study should be requested directly from the corresponding authors.

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Author contributions
L.C. conceptualized and designed the study. All authors contributed to the acquisition, analysis, or interpretation of the data. C.H., L.D., and L.C. drafted the manuscript, and all authors critically reviewed it for important intellectual content. M.C. and L.C. conducted the statistical analysis. L.C. supervised the study. All authors reviewed the manuscript.

Competing interests
Dr. Helal, Dr. Djerroudi, Dr. Ramtohul, Dr. Seban, Dr. Carton, Pr. Bieche, Dr. Maxime Jin, Dr. Enora Laas, Dr. Claire Bonneau, and Dr. Luc Cabel do not declare a conflict of interest. Pr Anne Vincent-Salomon reported lectures honorarium: AstraZeneca, Daiichi Sankyo, Ibex, MSD, PRIMAA, Roche, Gilead; Advisory Board: AstraZeneca, Daiichi Sankyo, Ibex, PRIMAA, Roche; Research Funding: AstraZeneca, Ibex, MSD, MSD Avenir, Owkin; Stock option: Ibex. Dr Bello-Roufai reported Board from MSD, AstraZeneca, Lilly, Eisai, and travel fees: MSD, AstraZeneca, Eisai. Pr Bidard reported Research fundings: GE Healthcare, Pfizer, Prolynx, Menarini Silicon Biosystems, Merck KGaA, MSD, Novartis, Personalis, Pfizer, Roche, SAGA Diagnostics, and Tempus. Advisory boards for AstraZeneca, Daiichi-Sankyo, Exact Sciences, GE Healthcare, Gilead, Inatherys, Lilly, Menarini/Stemline, Novartis, Pfizer, Roche, SAGA Diagnostics; Speaker for AstraZeneca, Daiichi-Sankyo, Lilly, Menarini/Stemline, and Pfizer. Travel support from AstraZeneca, Daiichi-Sankyo, Pfizer, Novartis. Pr Cottu reported Honoraria: Pfizer, Roche, Lilly, Daiichi Sankyo, AstraZeneca, Gilead Sciences, Novartis, and NanoString Technologies. Consulting or Advisory Role: Pfizer, Lilly. Research funding: Pfizer. Travel, accommodations, and expenses: Roche, Pfizer, and Lilly. Dr Loirat reported Honoraria: AstraZeneca, Gilead Sciences Inc, Eli Lilly and Company, and MSD. Consulting or advisory fees: 4D Pharma, AstraZeneca, Gilead Sciences Inc., Immunomedics, Eli Lilly and Company, MSD Oncology, Novartis AG, Pfizer Inc., and Roche. Funding for travel, accommodations, and expenses: AstraZeneca, Gilead Sciences Inc., MSD, Pfizer Inc., and Roche. Dr. Lerebours reported Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events: AstraZeneca, Eisai, Gilead, Daiichi Sankyo, Lilly, Menarini, Novartis, Roche, and Seagen. Support for attending meetings and/or travel: Daiichi Sankyo, Gilead, Lilly, MSD, Novartis, Pfizer, and Seagen. Dr Kiavue reported a Travel Grant from Seagen. Dr. Romano reported Grants and other support from AstraZeneca, Replimune, Bristol Myers Squibb, and Fonds Amgen France pour la Science et l'Humain outside the submitted work.

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