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Neoadjuvant nivolumab and chemotherapy in early estrogen receptor-positive breast cancer: a randomized phase 3 trial

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Patients with estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2−) primary breast cancer (BC) have low pathological complete response (pCR) rates with neoadjuvant chemotherapy. A subset of ER+/HER2− BC contains dense lymphocytic infiltration. We hypothesized that addition of an anti-programmed death 1 agent may increase pCR rates in this BC subtype. We conducted a randomized, multicenter, double-blind phase 3 trial to investigate the benefit of adding nivolumab to neoadjuvant chemotherapy in patients with newly diagnosed, high-risk, grade 3 or 2 (ER 1 to ≤10%) ER+/HER2− primary BC. In total, 510 patients were randomized to receive anthracycline and taxane-based chemotherapy with either intravenous nivolumab or placebo. The primary endpoint of pCR was significantly higher in the nivolumab arm compared with placebo (24.5% versus 13.8%; $P = 0.0021$), with greater benefit observed in patients with programmed death ligand 1-positive tumors (VENTANA SP142 ≥1%: 44.3% versus 20.2% respectively). There were no new safety signals identified. Of the five deaths that occurred in the nivolumab arm, two were related to study drug toxicity; no deaths occurred in the placebo arm. Adding nivolumab to neoadjuvant chemotherapy significantly increased pCR rates in high-risk, early-stage ER+/HER2− BC, particularly among patients with higher stromal tumor-infiltrating lymphocyte levels or programmed death ligand 1 expression, suggesting a new treatment paradigm that emphasizes the role of immunotherapy and T cell immunosurveillance in luminal disease. Clinical trials.gov identifier: NCT04109066

Approximately 2.3 million cases of BC were diagnosed globally in 2020, of which 70% were the ER+/HER2− subtype[1,2]. ER+/HER2− BC exhibits significant heterogeneity in its responses to treatment and clinical outcomes, posing substantial challenges for effective management. This heterogeneity may be caused by distinct differences in the molecular subtypes of ER+/HER2− BC, including subtypes with varying estrogen and progesterone receptor expression, and those that are immunogenic, proliferative and receptor tyrosine kinase-driven, which require specific treatments[3].

Current systemic therapeutic strategies for high-risk, early-stage ER+/HER2− BC include: neoadjuvant or adjuvant chemotherapy (CT); prolonged adjuvant endocrine therapy (ET) with or without adjuvant targeted therapies, including cyclin-dependent kinase 4/6 inhibitors; and poly(ADP-ribose) polymerase inhibitors for patients carrying germline pathogenic *BRCA* alterations[4–8].

Anti-programmed death ligand 1 (PD-L1) agents significantly improve clinical outcomes in early-stage triple-negative BC (TNBC) and PD-L1+ metastatic TNBC[9–11]. A subset of ER+/HER2− BC contains a dense

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lymphocytic infiltration, similar to that seen in TNBC[12,13]; however, it is unclear how this relates to the response to immune checkpoint inhibitors in ER+/HER2− BC[14–16]. Results from the adaptively randomized I-SPY2 study suggest that anti-PD-(L)1 agents have the potential to increase the proportion of patients with high-risk ER+/HER2− BC who achieve pCR or minimal residual disease (residual cancer burden (RCB) score of 0 or I) following neoadjuvant treatment[10,17]. The CheckMate 7FL (NCT04109066) study aimed to investigate the benefit of adding nivolumab to neoadjuvant CT followed by adjuvant ET in patients with newly diagnosed early-stage high-risk ER+/HER2− BC. We also sought to define patient subpopulations most likely to respond to nivolumab in combination with neoadjuvant CT.

Results

Study population and demographics

From 20 November 2019 to 7 April 2022, 830 patients were screened at 221 sites in 31 countries. Of the 830 patients screened, 521 were randomized. Because of the sponsor's decision to close all sites in Russia after the Ukraine–Russia geopolitical conflict began, 11 patients were excluded from the analysis population because of insufficient follow-up for pCR assessment. The resulting population formed the modified intent-to-treat population (mITT), which comprised 510 patients who received neoadjuvant CT with either nivolumab (n = 257) or placebo (n = 253). The safety population consisted of the 517 patients who received neoadjuvant CT with either nivolumab (n = 262) or placebo (n = 255) (Fig. 1). Patient demographic and clinical characteristics were balanced between the two treatment arms (Table 1).

In the safety population, the mean (min, max) treatment duration during the paclitaxel neoadjuvant phase was 11.0 (1.1, 16.1) weeks for patients receiving nivolumab and 11.2 (1.0, 15.6) weeks for patients receiving placebo. The mean (min, max) treatment duration during the anthracycline neoadjuvant phase was 7.6 (0.1, 13.0) weeks for patients receiving nivolumab and 7.7 (0.1, 15.1) weeks for patients receiving placebo. Of patients randomized to nivolumab and placebo, respectively, 89% (233 of 263) and 91% (236 of 258) underwent surgery (Supplementary Table 1).

Efficacy

A statistically significantly higher proportion of patients who received nivolumab achieved pCR (ypT0/is, ypN0; 24.5%, 63 of 257) versus placebo (13.8%, 35 of 253; odds ratio (OR) 2.05 (95% confidence interval (CI) 1.29 to 3.27, P = 0.0021) in addition to neoadjuvant CT (Fig. 2a).

The proportion of patients who experienced pCR was numerically higher among those who had PD-L1+ tumors (PD-L1-expressing tumor-infiltrating immune cells (IC) ≥ 1% IC, n = 172) versus those with PD-L1− tumors (<1% IC, n = 338). The difference in pCR rates (95% CI) between the nivolumab arm and placebo arm was 24.1% (10.1 to 36.7) and 3.6% (−3.6 to 10.7) for PD-L1+ and PD-L1− tumors, respectively (Fig. 2c). Subgroup analyses of pCR rates were consistent with these results (Fig. 3).

RCB 0 or I rates in the mITT population and by PD-L1 status, as well as subgroup analyses, were consistent with the findings observed for pCR (Fig. 2b,e and Supplementary Fig. 1). Nivolumab skewed the distribution of RCB toward the lower classes versus placebo (Supplementary Fig. 2).

Because of its early termination, the study was significantly underpowered for event-free survival (EFS), and median follow-up for EFS in the mITT population at reporting was premature at 19 months, with a low number of events observed. Results of a descriptive exploratory analysis showed that EFS was similar between the two treatment arms, with an 18-month rate of 89.1% (95% CI 83.8 to 92.7) in the nivolumab arm and 91.7% (95% CI 86.7 to 94.8) in the placebo arm (Supplementary Fig. 3).

Efficacy according to immune biomarkers

The prevalence of the PD-L1+ population in the two arms was balanced, as evaluated by baseline PD-L1 expression status, defined by either

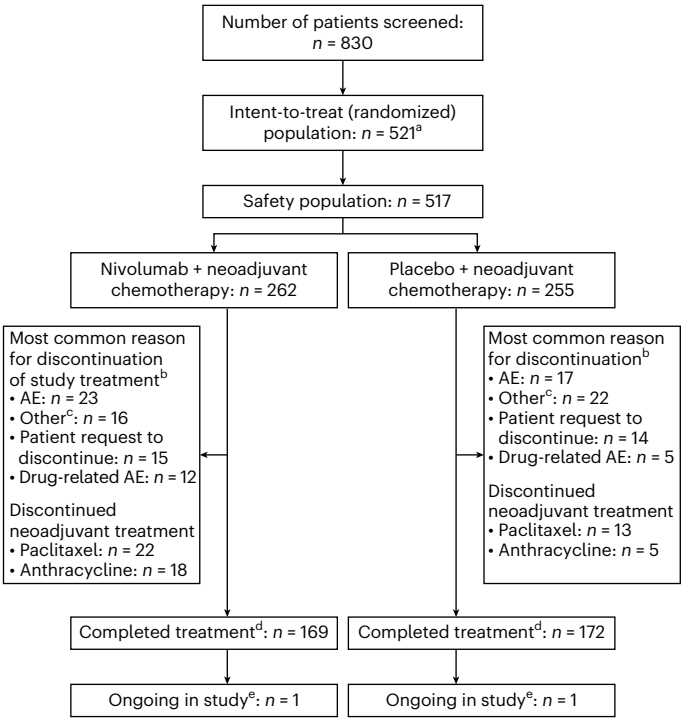

Fig. 1 | Flow chart showing patient disposition. Twenty-five patients received abemaciclib, and may have received it after neoadjuvant treatment or discontinued adjuvant treatment to receive abemaciclib. [a]The mITT population comprised 510 patients (257 patients in the nivolumab arm and 253 patients in the placebo arm). Because of the sponsor's decision to close Russian sites, 11 patients were excluded owing to insufficient follow-up for pCR. [b]Discontinuation of study treatment included treatment discontinuation during the adjuvant phase. [c]Most common reasons for discontinuation of treatment captured by 'Other' were disease progression, principal investigator discretion, serious AEs or AEs and withdrawal of consent. [d]Completers were patients who completed surgery and the adjuvant phase. [e]Patients were reported as ongoing at the time of the premature closure of Russian sites.

VENTANA SP142 assay (≥1% IC) or Dako 28-8 assay (PD-L1 combined positive score (CPS) ≥1, ≥3, ≥5, ≥10 and ≥20) (Supplementary Fig. 4). The highest overall percentage agreement of 80.6% was observed between SP142 ≥1% IC and 28-8 CPS ≥ 5 (Fig. 4a). pCR and RCB 0 or I rates were increased in patients with PD-L1+ tumors as measured by both SP142 (≥1% IC) and 28-8 CPS (≥1); the benefit was greater with increasing CPS cutoffs (Fig. 4c and Supplementary Figs. 5 and 6).

The prevalence of biomarker-positive populations at baseline stratified by percentage of stromal tumor-infiltrating lymphocytes (sTILs) at various cutoffs, compared with those by PD-L1 SP142 at 1% IC, is shown in Supplementary Fig. 7. Median and mean sTIL levels were 1% and 14.2% (s.d., 24.16), respectively, and the prevalence of sTIL positivity was balanced across the treatment groups. Defining sTIL-positive patients as those with detectable sTILs (>1%), the overall percentage agreement between sTIL detection and various PD-L1 by immune cell or CPS cutoffs ranged between 67.0% and 72.4% (Fig. 4b). pCR and RCB 0 or I rates with nivolumab versus placebo increased in patients with higher sTIL levels (Figs. 2d,f and 4d). When both sTIL and PD-L1 assays were used, the highest pCR rates were observed in patients in whom both sTIL and PD-L1 expression were considered positive, but notably, there was also nivolumab benefit seen for patients with discordance between PD-L1 <1% IC and sTIL+ (Supplementary Fig. 8).

pCR and RCB 0 or I rates were higher in patients whose tumors had lower ER (<50%) and/or progesterone receptor expression (<10%) than in patients whose tumors had higher ER or progesterone

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Table 1 | Baseline patient demographics and clinical characteristics (mITT population)

Demographic/characteristic	Nivolumab plus neoadjuvant CT			Placebo plus neoadjuvant CT		
	mITT population (*n*=257)	SP142 PD-L1– (*n*=169)[a]	SP142 PD-L1+ (*n*=88)[a]	mITT population (*n*=253)	SP142 PD-L1– (*n*=169)[a]	SP142 PD-L1+ (*n*=84)[a]
Female	257 (100)	169 (100)	88 (100)	252 (99.6)	168 (99.4)	84 (100)
Median age, years (range)	50 (24–78)	51 (24–77)	49 (28–78)	51 (23–79)	51 (23–79)	51 (27–78)
ECOG PS						
0	221 (86)	144 (85)	77 (88)	222 (88)	146 (86)	76 (91)
1	36 (14)	25 (15)	11 (13)	31 (12)	23 (14)	8 (10)
Tumor grade[b]						
Grade 2	6 (2)	2 (1)	4 (5)	1 (<1)	1 (1)	0 (0)
Grade 3	251 (98)	167 (99)	84 (96)	252 (>99)	168 (99)	84 (100)
Stage[c] (cTNM classification[d])						
Stage II	135 (53)	88 (52)	47 (53)	138 (55)	94 (56)	44 (52)
Stage III	118 (46)	77 (46)	41 (47)	105 (42)	67 (40)	38 (45)
Not assigned/reported	4 (2)	4 (2)	0 (0)	7 (3)	6 (4)	1 (1)
PD-L1[b]						
<1%	169 (66)	–	–	169 (67)	–	–
≥1%	88 (34)			84 (33)		
Axillary nodal status						
Positive	205 (80)	135 (80)	70 (80)	201 (79)	134 (79)	67 (80)
Negative	52 (20)	34 (20)	18 (21)	52 (21)	35 (21)	17 (20)
AC dose-frequency CT regimen[e]						
Q2W	132 (51)	85 (50)	47 (53)	134 (53)	88 (52)	46 (55)
Q3W	125 (49)	84 (50)	41 (47)	119 (47)	81 (48)	38 (45)

All values are given as *n* (%), unless stated otherwise. [a]PD-L1–expressing tumor-infiltrating IC as percentage of tumor area (PD-L1– defined as PD-L1 IC <1%; PD-L1+ defined as PD-L1 IC ≥1%) using the VENTANA SP142 assay, per central assessment. [b]Locally assessed. [c]Arm B included one patient with stage I disease and two patients with stage IV disease, who were deemed eligible and later recategorized as having stage II disease. [d]American Joint Committee on Cancer Cancer Staging Manual, 8th edition. [e]Gonadotropin-releasing hormone agonist therapy was allowed for ovarian preservation. AC, anthracycline + cyclophosphamide; cTNM, clinical TNM staging system (T size and extent of primary tumor; N extent of spread to the lymph nodes; M presence of metastasis); ECOG PS, Eastern Cooperative Oncology Group performance status; QXW, every X weeks.

receptor expression (Supplementary Figs. 9 and 10). No association between nivolumab benefit and the Ki67 index was observed (Supplementary Fig. 11).

In a multivariable analysis of pCR by biomarker subgroups, including prognostic clinicopathological features and key biomarkers, sTIL percentage (>1% or ≥5%) and PD-L1 (defined as IC ≥1% or CPS ≥3) were independently associated with nivolumab efficacy (Supplementary Figs. 12a,b and 13a,b).

Safety

The safety analysis is based on the safety population (*N* = 517; 262 patients in the nivolumab arm and 255 patients in the placebo arm). In the neoadjuvant treatment phase, a similar proportion of patients in the nivolumab versus placebo arms experienced adverse events (AEs) (98.5% versus 98.4%) and treatment-related AEs of any grade (95.0% versus 91.8%). The most frequently reported treatment-related AEs were alopecia (48.9% versus 48.2%), nausea (45.0% versus 36.9%), anemia (36.3% versus 29.4%) and fatigue (31.7% versus 25.5%) in the nivolumab versus placebo arms, respectively. Grade 3 or 4 AEs were reported in 42.0% versus 38.4% of patients in the nivolumab versus placebo arm, respectively. Grade 3 or 4 treatment-related AEs were reported in 35.1% versus 32.5% of patients in the nivolumab versus placebo arms, respectively (Table 2). Serious AEs (22.9% versus 12.9%) and treatment-related serious AEs (14.5% versus 8.2%), as well as AEs leading to discontinuation (11.5% versus 2.7%) and treatment-related AEs leading to discontinuation (10.7% versus 2.7%), were reported more frequently with nivolumab than with placebo.

In the neoadjuvant treatment phase, there were three (1.1%) grade 5 treatment-unrelated events in the nivolumab arm (one due to COVID-19; two due to pulmonary embolism, of which one occurred within a week postrecovery from COVID-19) and none in the placebo arm. In addition, two further deaths in the nivolumab arm were deemed related to study drug toxicity, although not reported as grade 5 (because of the extended time interval between AE onset and death): pneumonitis (61 days after final dose of neoadjuvant treatment) and hepatitis (51 days after final dose of neoadjuvant treatment); no deaths due to study drug toxicity were reported with placebo.

AEs during the neoadjuvant treatment phase that required immune-modulating medication occurred in 135 (51.5%) and 87 (34.1%) patients in the nivolumab and placebo arms, respectively. AEs of special interest occurred in three (1.1%) patients in the nivolumab arm and no patients in the placebo arm; these events were grade 3 or 4 Guillain–Barré syndrome (*n* = 1, 0.4%), grade 3 or 4 myocarditis (*n* = 1, 0.4%) and grade ≤2 autoimmune neuropathy (*n* = 1, 0.4%).

The mean cumulative dose and relative dose intensity of each CT drug were similar in both treatment arms.

Discussion

In the CheckMate 7FL study, we investigated whether the addition of nivolumab to anthracycline and taxane neoadjuvant CT could significantly increase pCR rates in newly diagnosed early-stage, high-risk, high-grade ER+/HER2– BC. The study met its primary endpoint, with a significantly higher rate of pCR in the nivolumab arm versus placebo. RCB 0 or I rates were also improved in the nivolumab versus placebo

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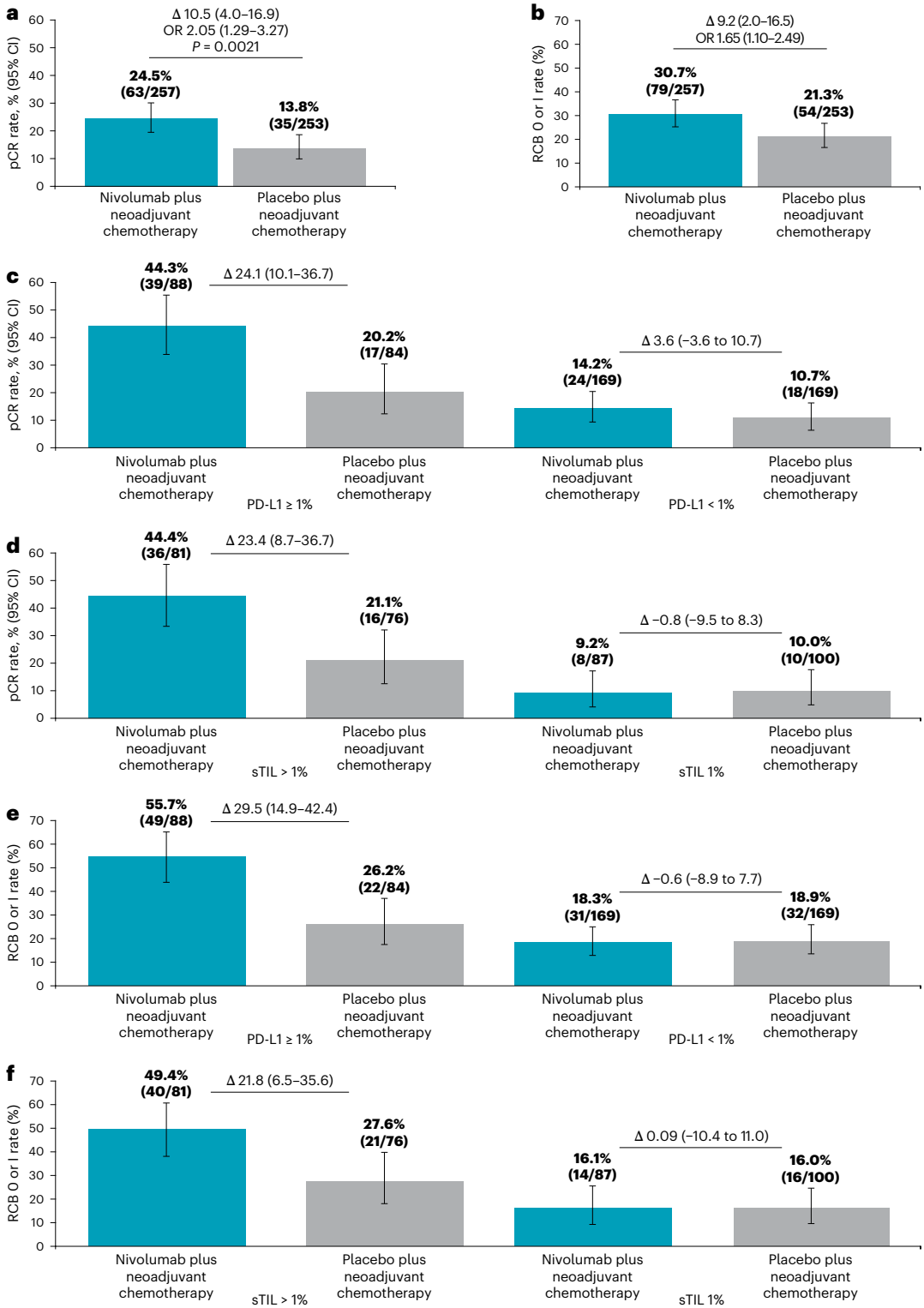

Fig. 2 | Efficacy endpoints for the overall population and by subgroups. **a**,**b**, Proportion of patients with pCR (**a**) and RCB 0 or I (**b**) for the nivolumab plus neoadjuvant CT ($N = 257$) and placebo plus neoadjuvant CT ($N = 253$) arms in the mITT population. **c**,**d**, Proportion of patients with pCR in the nivolumab plus neoadjuvant CT and placebo plus neoadjuvant CT arms by PD-L1 status ≥1% ($n = 88$, $n = 84$) or <1% ($n = 169$, $n = 169$) (**c**) and stromal tumor infiltrating lymphocyte (sTIL) status >1% ($n = 81$, $n = 76$) or ≤1% ($n = 87$, $n = 100$) (**d**). **e**,**f**, Proportion of patients with RCB 0 or I rate by PD-L1 status ≥1% ($n = 88$, $n = 84$) or <1% ($n = 169$, $n = 169$) (**e**) and sTIL status >1% ($n = 81$, $n = 76$) or ≤1% ($n = 87$, $n = 100$) (**f**). Data are presented as percentages with error bars showing the 95% CI around the observed proportion of patients in the treatment arm. The CIs for each treatment arm were calculated using the Clopper–Pearson method and CIs for differences (Δ) between treatment arms were calculated using the Newcombe method without continuity correction. Strata-adjusted difference in pCR rate between the two arms was analyzed with the stratified Cochran–Mantel–Haenszel method of weighting with a two-sided alpha level of 0.05 (**a**). Strata-adjusted OR was assessed with the Mantel–Haenszel method (**a**,**b**). The number of patients with pCR or RCB 0 or I (n) and the total number of patients in each subgroup (N) are shown above each bar. Database lock: 14 April 2023 (**a**,**b**) and 20 March 2024 (**d**–**f**). n, number of patients with pCR or RCB 0/I; N, number of patients in each treatment group.

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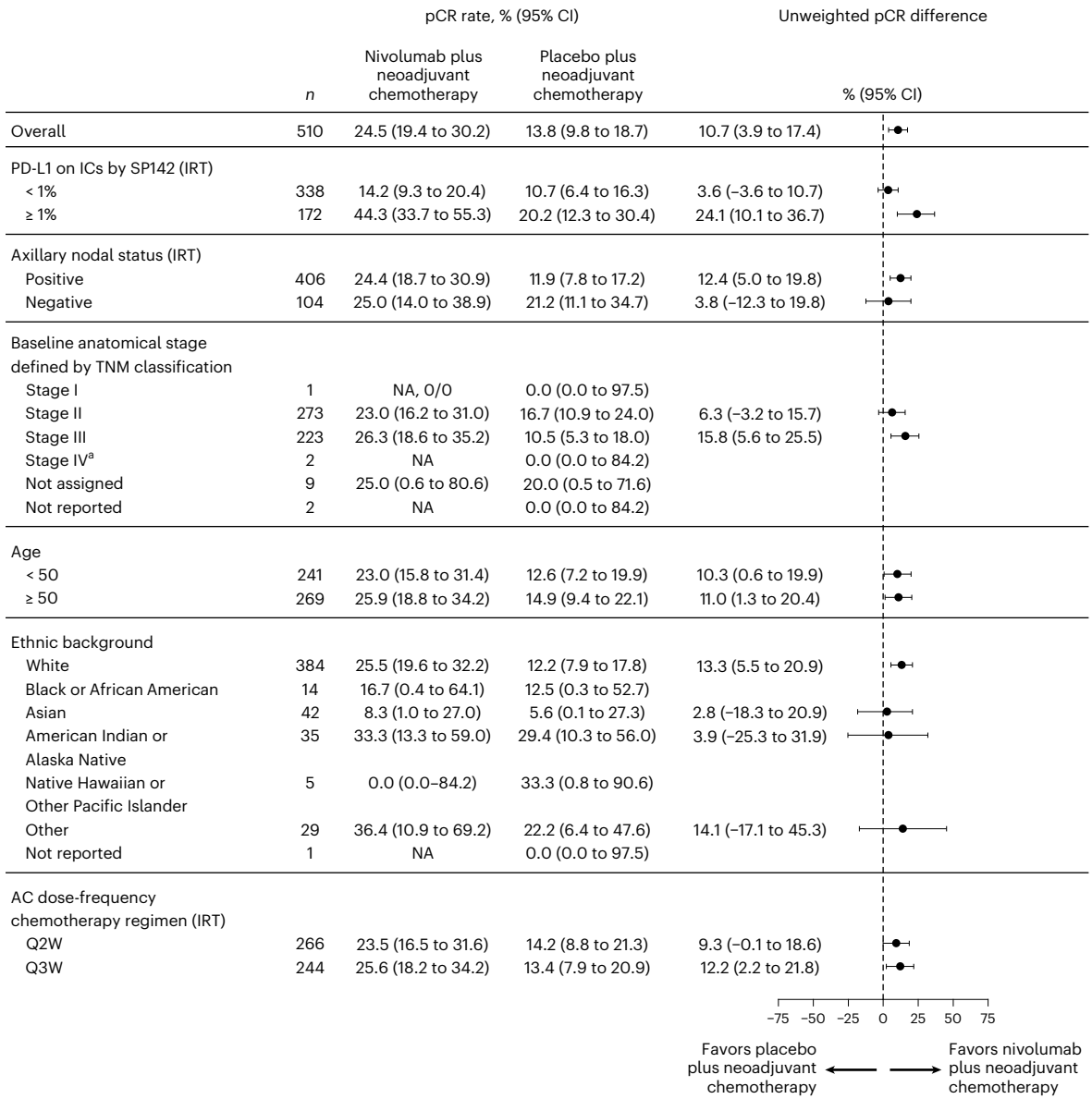

Fig. 3 | Forest plot of proportion of patients with pCR in the nivolumab plus neoadjuvant CT and placebo plus neoadjuvant CT arms by subgroup analyses. Data are presented as percentages with error bars showing the 95% CIs around the observed proportion of patients in the treatment arm. The CIs for each treatment arm were calculated using the Clopper–Pearson method and CIs for differences between treatment arms were calculated using the Newcombe method without continuity correction. pCR rate difference was not computed for subsets with fewer than 10 patients per treatment arms. [a]The two patients who were initially categorized as having stage IV disease were deemed eligible and later recategorized as having stage II disease. AC, anthracycline; IRT, interactive response technology; *n*, total number of patients in subgroup; NA, not available; Q2W, every 2 weeks; Q3W every 3 weeks. Database lock: 14 April 2023.

arm. These findings were predominantly driven by the PD-L1+ subpopulation, in which an absolute difference of more than 20% was seen with the addition of nivolumab to the neoadjuvant CT. This observation differed from that in early-stage TNBC, where the effect was independent of PD-L1 expression[18]. Although the reasons for this are unclear, TNBC is known to be more molecularly heterogeneous than ER+ BC, potentially resulting in a single core biopsy unlikely to encapsulate heterogenous PD-L1 expression[19,20]. The median follow-up remains too short in this analysis to make any conclusions about EFS, although notably there were no early non-BC-related deaths. However, achievement of a pCR and/or a RCB of 0 or I is associated with improved long-term outcomes in ER+/HER2− BC[21,22]. Translation of improvements in pCR rates into EFS improvements varies across different clinical trials. Very few early trials were adequately powered to assess both endpoints; however, overall, almost all combination chemotherapies that improved pCR rates (by incorporating a taxane-based, carboplatin-based, HER2-targeted therapy or pembrolizumab) also improved EFS in BC studies[23,24]. It is also becoming increasingly clear that different neoadjuvant regimens result in different distributions of RCB, and therapies that shift the entire spectrum of RCB to smaller values may have a greater impact on EFS than therapies that improve pCR rates by moving minimal residual cancers to the pCR category[25].

Our results are consistent with those of the KEYNOTE-756 study[26,27], which investigated pembrolizumab in the same patient setting. In KEYNOTE-756, improved pCR rates were also seen in the setting of increasing PD-L1 expression but only at the higher levels using the 22C3 pharmDx CPS (CPS ≥ 10) assay. Results from CheckMate 7FL consolidate the benefit of adding an immune checkpoint inhibitor to neoadjuvant CT in this BC subtype and context, and longer follow-up will indicate whether these pCRs translate into greater EFS benefit for

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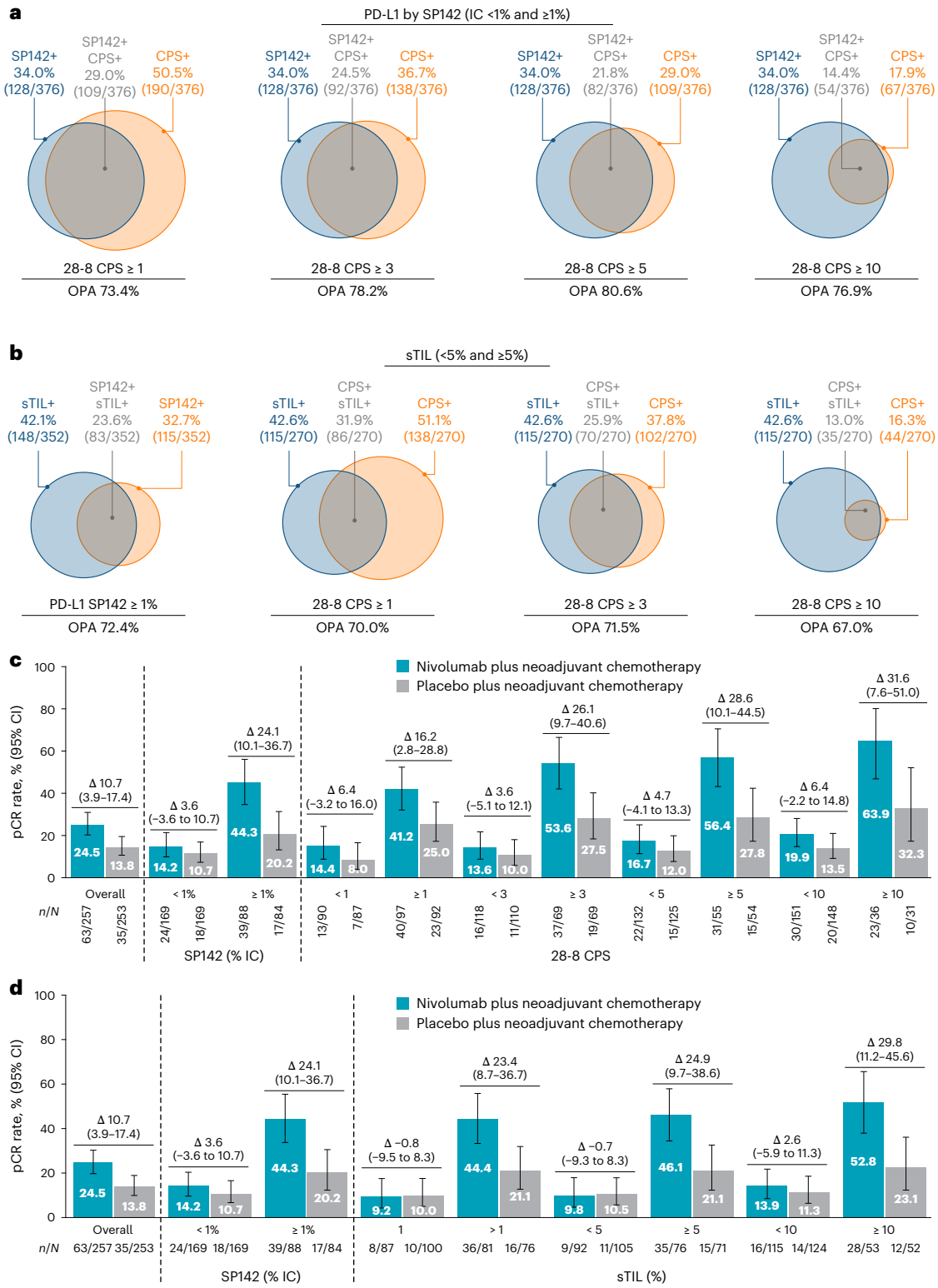

Fig. 4 | Efficacy of nivolumab by subgroups. a, Concordance between PD-L1 assays SP142 and 28-8 CPS. **b**, sTIL and PD-L1 expression in patients with quantifiable sTIL and PD-L1 by SP142 or 28-8 CPS. **c**, pCR rates in the nivolumab plus neoadjuvant CT and placebo plus neoadjuvant CT arms by PD-L1 status as determined by the SP142 (IC%) and 28-8 CPS (cutoffs 1–20) assays. **d**, PD-L1 status as determined by the SP142 (IC%) assay and percentage of sTIL (cutoffs 1%, 5%, 10%). The number of patients with qualifying data (*n*) and the total number of patients in each subgroup (*N*) are shown above each circle (**a**,**b**) or below each bar (**c**,**d**). Data are presented as percentages. CIs for the observed proportion of patients in the treatment arm were calculated using the Clopper–Pearson method and CIs for differences between treatment arms were calculated using the Newcombe method without continuity correction (**c**,**d**). Vertical dashed lines are to visually distinguish between Overall, SP142 and 28-8 in **c**, and Overall, SP142 and sTIL in **d**. 28-8 CPS, Dako 28-8 assay using the CPS algorithm; OPA, overall percentage agreement; SP142 VENTANA, PD-L1 SP142 assay. Clinical database; SP142 cutoff at ≥1% versus <1%. Because of the small sample size, the percent agreement was not calculated for CPS ≥ 20). Database lock: 20 March 2024. Additional patients were included in the CPS-evaluable group at this final database lock.

Table 2 | Neoadjuvant safety summary (safety population)[a]

AE	Nivolumab plus neoadjuvant CT (*n*=262)		Placebo plus neoadjuvant CT (*n*=255)	
	Any grade *n* (%)	Grade 3 or 4 *n* (%)	Any grade *n* (%)	Grade 3 or 4 *n* (%)
AE	258 (98.5)	110 (42.0)	251 (98.4)	98 (38.4)
TRAE	249 (95.0)	92 (35.1)	234 (91.8)	83 (32.5)
SAE	60 (22.9)	43 (16.4)	33 (12.9)	28 (11.0)
TRSAE	38 (14.5)	34 (13.0)	21 (8.2)	20 (7.8)
AE leading to discontinuation	30 (11.5)	18 (6.9)	7 (2.7)	6 (2.4)
TRAE leading to discontinuation	28 (10.7)	17 (6.5)	7 (2.7)	6 (2.4)
TRAE[b]				
Alopecia[c]	128 (48.9)	3 (1.1)	123 (48.2)	5 (2.0)
Nausea	118 (45.0)	0	94 (36.9)	2 (0.8)
Anemia	95 (36.3)	15 (5.7)	75 (29.4)	6 (2.4)
Fatigue	83 (31.7)	5 (1.9)	65 (25.5)	2 (0.8)
Diarrhea	57 (21.8)	4 (1.5)	58 (22.7)	1 (0.4)
Peripheral neuropathy	52 (19.8)	3 (1.1)	37 (14.5)	1 (0.4)
Increased ALT	44 (16.8)	6 (2.3)	32 (12.5)	8 (3.1)
Increased AST	45 (17.2)	6 (2.3)	28 (11.0)	2 (0.8)
Neutropenia	44 (16.8)	16 (6.1)	42 (16.5)	25 (9.8)
Vomiting	40 (15.3)	1 (0.4)	25 (9.8)	2 (0.8)
Endocrine IMAEs[d,e]				
Hypothyroidism/thyroiditis	39 (14.9)	0	3 (1.2)	0
Adrenal insufficiency	15 (5.7)	4 (1.5)	1 (0.4)	0
Hyperthyroidism	15 (5.7)	0	1 (0.4)	0
Hypophysitis/hypopituitarism	5 (1.9)	1 (0.4)	0	0
Diabetes mellitus	1 (0.4)	0	0	0
Nonendocrine IMAEs[d,e] where immunomodulation was initiated				
Rash	15 (5.7)	4 (1.5)	12 (4.7)	1 (0.4)
Hepatitis	13 (5.0)	8 (3.1)	3 (1.2)	2 (0.8)
Pneumonitis	8 (3.1)	4 (1.5)	2 (0.8)	0
Hypersensitivity	10 (3.8)	0	3 (1.2)	0
Nephritis/renal dysfunction	2 (0.8)	1 (0.4)	0	0
Diarrhea/colitis	1 (0.4)	0	1 (0.4)	1 (0.4)

[a]Database lock: 20 March 2024. [b]Events reported between the first dose and 30 days after the last dose of neoadjuvant therapy for patients who did not go on to adjuvant therapy or before adjuvant therapy for patients who started adjuvant therapy. The events shown are the 10 most frequent in the nivolumab arm. [c]Alopecia is likely to have been under-reported. Common Toxicity Criteria for Adverse Events grading for alopecia consists of only grade 1 or 2; the grade 3 or 4 alopecia reported in this study was reported incorrectly. [d]Events reported between the first dose and 100 days after the last dose of neoadjuvant therapy for patients who did not go on to adjuvant therapy or before adjuvant therapy for patients who started adjuvant therapy. [e]Immune-mediated adverse events (IMAEs) are specific events, regardless of causality, that were considered as potentially immune-mediated by the investigator with no clear alternate etiology, occurred within 100 days of the final dose, and were treated with immune-modulating medication (except for endocrine IMAEs, which do not require immune-modulating medication use). ALT, alanine transaminase; AST, aspartate transaminase; SAE, serious adverse event; TRAE, treatment-related adverse event; TRSAE, treatment-related serious adverse event.

all or just for patients with PD-L1+ tumors. Notably, whereas previous studies have shown that addition of programmed death 1 inhibition in TNBC led to small increases in pCR rates, including in patients with low PD-L1 expression, significant EFS benefit was observed[28,29]. Overall, these results represent a new milestone in the neoadjuvant treatment of ER+/HER2− BC, because there have been intensive but thus far unsuccessful efforts to improve pCR rates in this patient population.

One important strength of CheckMate 7FL is that three immune assays were evaluated in a phase III trial population. Increases in pCR rates with the addition of nivolumab were also observed for sTIL increases from as little >1%, which was the median sTIL level in this patient population. Moderate concordance between the SP142, 28-8 pharmDx CPS and sTIL assays was observed. Interestingly, although pCR rates were highest with the addition of nivolumab when the assays agreed on sTIL and PD-L1 positivity, patients with discordant assay results still derived benefit. These data have important implications for patients with BC, and suggest that the use of multiple assays may be best to identify all patients who could benefit from neoadjuvant immunotherapy in this subtype, although sTIL may be the most pragmatic and globally accessible biomarker because it can be evaluated on standard hematoxylin and eosin-stained slides[30,31]. Analysis of other exploratory biomarkers for patient stratification is ongoing.

Analyses of pCR rates by ER and progesterone receptor levels confirm that patients with ER and/or progesterone receptor levels <10% have greater benefit with the addition of nivolumab than

patients with ER and/or progesterone receptor levels ≥10%. Notably, we observed this effect also in the setting of ER ≤50%. Although this remains to be further validated, it suggests that patients with lower ER and progesterone receptor levels may be treated similarly to patients with early TNBC. Previous research has shown that tumors with lower ER levels harbor more sTILs and $CD8^+$ T cells, with higher PD-L1 expression, and are more similar to TNBC with regard to immune-related signatures[32].

Safety was consistent with the known safety profiles, with no change in the feasibility of surgery following the addition of nivolumab to CT. However, it is important to note that two treatment-related deaths were observed in the nivolumab arm.

The key strengths of this study are: its inclusion of a high-risk population, the majority of whom were node-positive and grade 3; evaluation of response in a PD-L1+ population as a key secondary endpoint; and comprehensive biomarker data, including evaluation of response in a sTIL-high population, presented in the early BC setting. Limitations include the major protocol amendment that significantly reduced the sample size and/or number of events and follow-up time resulting in EFS being designated as an exploratory endpoint.

In conclusion, adding nivolumab to neoadjuvant anthracycline and taxane-based CT in high-risk, early-stage ER+/HER2− BC significantly increased the pCR rate. These findings reshape our understanding of this disease in the context of T cell immunosurveillance and immunotherapy response in luminal disease. Patients with higher levels of sTIL or PD-L1 expression experienced higher pCR rates, potentially setting a new standard for future neoadjuvant treatment studies in this subset. Biomarker analyses aim to uncover the biological drivers behind the robust immune responses to the addition of immunotherapy to CT observed in ER+ BC, which could help further refine and personalize immunotherapeutic approaches for this disease.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-024-03414-8.

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Methods

Patients

Eligible patients had newly diagnosed ER+/HER2− BC, with a confirmed primary tumor and node categories of tumors sized 2–5 cm and cN1–cN2 or cT3–cT4 and cN0–cN2; grade 3 disease or grade 2 disease with ER expression of 1 to ≤10%; adequate organ function; tissue available for biomarker assessment; and Eastern Cooperative Oncology Group performance status 0–1. Patients were eligible irrespective of PD-L1 status. Multifocal tumors (two or more foci of cancer in the same breast quadrant) were permitted if the largest lesion was at least 2 cm and designated as the target lesion. Patients with mixed ductal and lobular carcinoma were eligible. Patients were excluded if they had multicentric BC, a history of ipsilateral invasive BC, evidence of metastatic disease, had received any previous treatment for the currently diagnosed BC or had received immunotherapy previously.

Trial design and treatments

CheckMate 7FL was a prospective, randomized, multicenter, double-blind, placebo-controlled phase 3 trial (ClinicalTrials.gov identifier: NCT04109066), originally with co-primary endpoints of pCR and EFS, which were centrally assessed. Following the approval of adjuvant abemaciclib for high-risk primary ER+/HER2, the primary endpoint was amended to pCR alone, making enrollment and assessment of EFS challenging to complete. The combination of abemaciclib with nivolumab was expected to result in a high rate of withdrawals because of safety concerns around combining a CDK4/6 inhibitor with an anti-programmed death 1 agent[33,34]. In the neoadjuvant phase, patients were randomized 1:1 to receive either nivolumab 360 mg or placebo every 3 weeks with weekly paclitaxel for 12 weeks. This was followed by nivolumab (either 360 mg every 3 weeks or 240 mg every 2 weeks) in combination with anthracycline and cyclophosphamide, or placebo in combination with anthracycline and cyclophosphamide; the anthracycline and cyclophosphamide dosing frequency was determined by the investigator. All patients who remained operative candidates underwent surgery of the breast and axilla (per local standards) within 4 weeks of completing the neoadjuvant treatment phase. Per the protocol amendment, the study was unblinded in the adjuvant phase, and patients received nivolumab 480 mg with investigator's choice of ET (tamoxifen, letrozole, anastrozole or exemestane, with or without ovarian function suppression) for up to seven cycles.

Randomization was stratified per interactive response technology by the proportion of PD-L1-expressing immune cells (percentage of immune cells by VENTANA PD-L1 SP142 immunohistochemistry, cutoff at 1%), tumor grade (2 or 3), pathologically confirmed axillary nodal status (positive on pathological review or negative on radiographic and/or pathologic review) and anthracycline dosing frequency (every 3 weeks or every 2 weeks). Before the study was initiated, each participant received log-in information and directions on accessing the interactive response technology. Each participant was assigned a unique number after signing the informed consent form. Participant numbers were used on all participants' study information. Participant numbers were not reassigned. An interactive response technology was used to manage participant randomization. The investigator or designee registered the participant for enrollment by following the enrollment procedures established by the sponsor.

Endpoints

The primary endpoint was pCR (ypT0/is, ypN0) in the mITT population. Initially, EFS was a co-primary endpoint; however, following the decision to discontinue enrollment in the study in April 2022 because of the rapidly changing treatment landscape, the primary endpoint of the trial was updated to focus solely on pCR, and EFS was changed to an exploratory endpoint because the total number of enrolled patients and events was too low and updated follow-up time was too short to provide sufficient power for comparison. Consequently, follow-up was reduced to 1 year post-surgery for all patients, and the adjuvant phase became open label.

Another key change to the study after discontinuation of enrollment in April 2022 was the evaluation of pCR in the PD-L1+ population by VENTANA SP142 % IC as a secondary endpoint. Other secondary endpoint included RCB 0 or I rates in the mITT and PD-L1+ populations. Pathological response was assessed, and RCB score calculated by local pathologists. The RCB score combined tumor size, tumor cellularity and nodal involvement into a single continuous score that was grouped into four classes, namely, RCB score of 0 (that is, pCR), and I, II and III, which corresponded to increasingly larger residual cancer and worse recurrence-free survival[17]. Safety and tolerability were assessed during the neoadjuvant and adjuvant phases in all patients who received at least one dose of study drug. Prespecified exploratory endpoints included association of efficacy outcomes with biomarker status based on PD-L1 CPS, sTILs, levels of estrogen/progesterone receptors and Ki67 index.

Study assessments

pCR was assessed post-neoadjuvant (yp) treatment and was defined as no invasive residual disease in breast and lymph nodes (ypT0/is, ypN0) by a local pathologist. AEs were monitored throughout the trial and for 30 days after the discontinuation of study treatment (90 days for serious AEs) and graded according to Common Toxicity Criteria for Adverse Events v.5.0 of the National Cancer Institute. Safety was assessed at 30 days and 100 days after the final dose, and long-term follow-up was up to 12 months after surgery. Biomarker analyses included centrally reviewed PD-L1 expression and percentage of sTILs. PD-L1 was evaluated by qualitative immunohistochemistry on immune cells with the VENTANA SP142 assay (Roche Diagnostics) and PD-L1 CPS with the 28-8 pharmDx assay (Agilent). The percentage of sTILs was quantified on a hematoxylin and eosin-stained slide according to established guidelines[30]. In this study, an sTIL of 1% was the lowest possible value and indicated a lack of detectable sTILs. The SP142 % IC assay and the 28-8 pharmDx CPS were used to evaluate the variation between assays, as well as to determine PD-L1 expression in tumor-infiltrating ICs versus both immune and tumor cells. ER and Ki67 expression were centrally evaluated using Agilent MIB-Dako pharmDx immunohistochemistry. Progesterone receptor immunohistochemistry levels were evaluated from local pathology testing. Other recorded patient and disease characteristics included tumor grade, axillary nodal status, disease stage, Ki67 index, menopausal status and age.

Statistical analyses

Based on the normal approximation to the binomial, a sample size of 521 patients in the intent-to-treat population would yield approximately 87% power (two-sided alpha of 0.05) to detect a difference of 10% in pCR rates between treatment arms, assuming a 12% pCR rate in the control arm. Because of the sponsor's decision to close all sites in Russia after the Ukraine–Russia geopolitical conflict began, 11 patients were excluded owing to insufficient follow-up for pCR assessment, with a small impact on the study power (86%). This resulted in a mITT population size of 510 patients. Strata-adjusted difference in pCR rate between the two arms was analyzed with the stratified Cochran–Mantel–Haenszel method of weighting with a two-sided alpha level of 0.05. Strata-adjusted OR was assessed with the Mantel–Haenszel method. The cutoffs used for sTIL and PD-L1 expression by SP142 or 28-8 pharmDx CPS were predefined for this study.

CI values for pCR and RCB 0 or I rates were evaluated using the Clopper–Pearson method. The unweighted differences in pCR and RCB 0 or I rates between treatment arms in different patient subgroups were calculated along with the corresponding 95% two-sided CIs using the Newcombe method without continuity correction. Exploratory multivariable analyses were conducted using logistic regression to evaluate the association of biomarkers and other baseline characteristics with

pCR. Biomarkers included in the multivariable analyses were calculated as either categorical (PD-L1 expression ≥1% by SP142 or 28-8 pharmDx CPS ≥3 with sTIL cutoffs of >1 or ≥5%) or continuous variables. Other baseline characteristics in the multivariable analyses were stage III disease, negative nodal status, ER expression ≥10%, postmenopausal status and age ≥65 years. The CIs for the secondary and exploratory analyses were for descriptive purposes and, therefore, no adjustments were made for multiplicity.

The sex of patients enrolled in the trial was self-reported and data for gender were not collected. No analyses by sex or disaggregated data are presented because doing so would result in the presentation of potentially identifying information.

Trial oversight

This trial was developed and overseen by an academic steering committee and employees of the sponsor (Bristol Myers Squibb). An external, independent data monitoring committee provided oversight of safety and efficacy considerations during the study. The trial protocol and amendments were approved by the appropriate ethics body at each participating site. All patients provided written informed consent. All authors confirm that the trial was conducted with respect to the standards of Good Clinical Practice. All authors had access to the data and participated in the writing and reviewing of this manuscript. The first draft of the manuscript was written by the first author with editorial assistance provided by a medical writer employed by the sponsor. All authors reviewed and participated in drafting the manuscript and all authors approved the submitted draft and can vouch for the accuracy and completeness of the data.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Bristol Myers Squibb will honor legitimate requests for clinical trial data from qualified researchers with a clearly defined scientific objective. Bristol Myers Squibb will consider data sharing requests for Phase II–IV interventional clinical trials that completed on or after 1 January 2008. In addition, primary results from these trials must have been published in peer-reviewed journals and the medicines or indications approved in the US, EU and other designated markets. Sharing is also subject to protection of patient privacy and respect for the patient's informed consent. Data considered for sharing may include nonidentifiable patient-level and study-level clinical trial data, full clinical study reports and protocols.

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Author contributions

S.L., R.S., G.C., R.I.R.D., S.D., C.I.R.G., M.K., C.S., N.H., F.A., R.C., T.S. and H.M. had major involvement in study conception or design. S.L., R.I.R.D., S.D., C.I.R.G., M.K., C.S., N.H., A.E.M., D.A.Y., L.P., A.S.Z., F.R.C., A.U., J.G.R.-T., V.G. and D.E. had substantial involvement in data acquisition. S.D., C.I.R.G., M.K., C.S., N.H., F.A., M.P., A.C., R.C., R.N., T.S. and J.Q.W. had major involvement in data analysis. S.L., R.S., G.C., R.I.R.D., S.D., C.I.R.G., M.K., C.S., N.H., A.E.M., D.A.Y., L.P., A.S.Z., F.R.C., A.U., J.G.R.-T., V.G., D.E., F.A., R.N., T.S., J.Q.W. and H.M. had major involvement in data interpretation. All authors had access to the data and participated in writing, reviewing, and revising the manuscript. All authors approved the final manuscript for publication. All authors accept responsibility for the accuracy and integrity of all aspects of the research.

Competing interests

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Additional information

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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☒	☐ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No software was used
Data analysis	No software was used

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Bristol Myers Squibb will honor legitimate requests for clinical trial data from qualified researchers with a clearly defined scientific objective. Bristol Myers Squibb will consider data sharing requests for Phase II-IV interventional clinical trials that completed on or after January 1, 2008. In addition, primary results from these trials must have been published in peer-reviewed journals and the medicines or indications approved in the U.S., EU, and other designated markets. Sharing is also

subject to protection of patient privacy and respect for the patient's informed consent. Data considered for sharing may include non-identifiable patient-level and study-level clinical trial data, full clinical study reports and protocols.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	The sex of patients enrolled in the trial was self-reported and data for gender were not collected. The eligible patient population was predominantly female, and the trial enrolled a single male patient; no analyses by sex or disaggregated data were presented because doing so would result in presentation of potentially identifying information.
Reporting on race, ethnicity, or other socially relevant groupings	Provided in Table 1
Population characteristics	Provided in Table 1
Recruitment	From November 20, 2019 through April 07, 2022, 830 patients were screened at 221 clinical sites in 31 countries. Of the 830 patients screened, 521 were randomized. Eligible patients had newly diagnosed ER+/HER2− breast cancer, with a confirmed primary tumor and node categories of tumors sized 2–5 cm and cN1–cN2 or cT3–cT4 and cN0–cN2; grade 3 disease or grade 2 disease with ER expression of 1 to ≤10%; adequate organ function; tissue available for biomarker assessment; and Eastern Cooperative Oncology Group performance status 0–1. Patients were eligible irrespective of PD-L1 status. Multifocal tumors (two or more foci of cancer within the same breast quadrant) were permitted if the largest lesion was at least 2 cm and designated as the target lesion. Patients were excluded if they had multicentric breast cancer, a history of ipsilateral invasive breast cancer, evidence of metastatic disease, had received any prior treatment for the currently diagnosed breast cancer, or had received prior immunotherapy.
Ethics oversight	This trial was developed and overseen by an academic steering committee and employees of the sponsor (Bristol Myers Squibb). An external, independent data monitoring committee provided oversight of safety and efficacy considerations during the study. The trial protocol and amendments were approved by the appropriate ethics body at each participating site. All patients provided written informed consent. All authors confirm that the trial was conducted with respect to the standards of Good Clinical Practice.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	A sample size of 521 patients in the intent-to-treat population would yield 87% power (two-sided alpha 0.05) to detect a difference of 10% in pCR rates between treatment arms, assuming a 12% pCR rate in the control arm. Due to the sponsor's decision to close all sites in Russia, 11 patients were excluded due to insufficient follow-up for pCR assessment, with a small impact on the study power (86%).
Data exclusions	Due to the sponsor's decision to close all sites in Russia, 11 patients were excluded due to insufficient follow-up for pCR assessment.
Replication	The study started enrolling patients from 31 countries in November 2019 and completed in December 2023. Each participating patient was followed from the time of enrollment until study discontinuation or death. As such, replication of the study was not possible.
Randomization	Randomization was stratified per interactive response technology by the proportion of PD-L1-expressing immune cells (percentage of immune cells by VENTANA® PD-L1 SP142 immunohistochemistry, cut-off at 1%), tumor grade (2 or 3), pathologically confirmed axillary nodal status (positive on pathological review or negative on radiographic and/or pathologic review) and anthracycline dosing frequency (every 3 weeks or every 2 weeks).
Blinding	Patients, those involved with their management and those collecting and analyzing the data were blinded; however, as per the protocol amendment, the study was unblinded in the adjuvant phase following the approval of adjuvant abemaciclib for high-risk primary ER+/HER2. The combination of abemaciclib with nivolumab was expected to result in a high rate of withdrawals due to safety concerns around combining a CDK4/6 inhibitor with an anti–PD-1 agent. Per the protocol amendment, in the adjuvant phase, patients received nivolumab 480 mg with investigator's choice of ET (tamoxifen, letrozole, anastrozole, or exemestane, with or without ovarian function suppression) for up to seven cycles.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used: PD-L1 was evaluated by qualitative immunohistochemistry on immune cells with the VENTANA® SP142 assay (Roche Diagnostics) and PD-L1 combined positive score with the 28-8 pharmDx assay (Agilent).

Validation: *Describe the validation of each primary antibody for the species and application, noting any validation statements on the manufacturer's website, relevant citations, antibody profiles in online databases, or data provided in the manuscript.*

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration: NCT04109066

Study protocol: The protocol is available as a supplement to this publication.

Data collection: Clinical data was collected at participating sites (clinical research institutes and hospitals) from November 20, 2019 to April 07, 2022. The study was conducted at 221 sites in 31 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, Colombia, Czech Republic, Denmark, Finland, France, Germany, Hong Kong, Ireland, Italy, Republic of Korea, Mexico, Netherlands, Poland, Portugal, Romania, Russian Federation [BMS terminated all activities in Russia on June 2022], Singapore, Spain, Switzerland, Taiwan, Turkey, United Kingdom, and USA)

Outcomes: The primary endpoint was pCR (ypT0/is, ypN0) in the modified intent-to-treat population. Following the decision to discontinue enrollment in the study in April 2022 due to the changing treatment landscape, event-free survival was changed from a co-primary endpoint to an exploratory endpoint, as the total number of enrolled patients was too low to provide sufficient power for comparison. Consequently, the follow-up was reduced to 1 year post-surgery for all patients, and the adjuvant phase became open-label. Secondary endpoints included pCR in the PD-L1+ population, and RCB 0/I rate in the modified intent-to-treat and PD-L1+ populations. Pathological response was assessed, and RCB score calculated by local pathologists. The RCB score combined tumor size, tumor cellularity, and nodal involvement into a single continuous score that was grouped into four classes, namely, RCB score of 0 (i.e. pathologic complete response), and I, II, and III. Safety and tolerability were assessed during the neoadjuvant and adjuvant phases in all patients who received at least one dose of study drug. Prespecified exploratory endpoints included association of efficacy outcomes by biomarker status based on PD-L1 combined positive score , stromal tumor-infiltrating lymphocytes (sTILs), levels of estrogen/progesterone receptors, and Ki67 index.

Plants

Seed stocks: *Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*

Novel plant genotypes: *Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*

Authentication: *Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*