

CALGB 40603 (Alliance): Long-Term Outcomes and Genomic Correlates of Response and Survival After Neoadjuvant Chemotherapy With or Without Carboplatin and Bevacizumab in Triple-Negative Breast Cancer

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PURPOSE CALGB 40603 (NCT00861705), a 2 × 2 randomized phase II trial, demonstrated that adding carboplatin or bevacizumab to weekly paclitaxel (wP) followed by doxorubicin and cyclophosphamide significantly increased the pathologic complete response (pCR) rate in stage II-III triple-negative breast cancer. We now report long-term outcomes (LTOs) and correlative science end points.

PATIENTS AND METHODS The Kaplan-Meier method was used to estimate LTOs in 443 patients who initiated study treatment. Log-rank tests and Cox proportional hazards models evaluated the impact of clinical characteristics, pathologic response, calculated residual cancer burden (RCB) in patients with residual disease (RD), treatment assignment, and dose delivery during wP on LTOs, including event-free survival (EFS). Genomic predictors of treatment response and outcomes were assessed on pretreatment tumor samples by mRNA sequencing.

RESULTS Among baseline characteristics, only the clinical stage was associated with LTOs. At a median follow-up of 7.9 years, LTOs were not significantly improved with either carboplatin or bevacizumab, overall or in patients with basal-like subtype cancers by genomic analysis. Patients with pCR (n = 205, 46.3%) had significantly higher 5-year EFS (85.5% v 56.6%, log-rank $P < .0001$) and overall survival (87.9% v 63.4%, $P < .0001$) rates compared with patients with RD, even those with RCB class I. Among clinical and genomic features, evidence of immune activation, including tumor-infiltrating lymphocytes and low B-cell receptor evenness, was associated with pCR and improved EFS.

CONCLUSION Despite higher pCR rates, neither carboplatin nor bevacizumab appeared to improve LTOs although the study was not powered to assess these secondary end points. pCR was associated with superior LTOs even when compared with minimal RD. Markers of immune activation in pretreatment tumor biopsies were independently associated with higher pCR rates and improved survival.

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ASSOCIATED CONTENT

Data Supplement Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

In triple-negative breast cancer (TNBC), pathologic response to neoadjuvant chemotherapy (NACT) is a powerful prognostic indicator, but on average, only one third of patients achieve pathologic complete response (pCR) with standard anthracycline- and taxane-based regimens.¹ Cancer and Leukemia Group B (CALGB, now part of the Alliance for Clinical Trials in Oncology) 40603, a randomized phase II 2 × 2 factorial trial, investigated whether adding another chemotherapeutic agent, carboplatin or the vascular endothelial growth

factor-targeted monoclonal antibody bevacizumab, to standard NACT would improve pCR rates in clinical stage II-III TNBC. The study met its primary objectives, demonstrating that pCR breast (ypT0 or Tis) was significantly increased with either carboplatin (60% v 46%) or bevacizumab (59% v 48%).² This report focuses on the study's secondary end points, specifically the impact of these treatments on long-term outcomes (LTOs), including event-free survival (EFS), and the association between pCR and extent of residual disease (RD) and LTOs.

CONTEXT

Key Objective

This analysis assesses whether adding bevacizumab or carboplatin to anthracycline- and taxane-based neoadjuvant chemotherapy (NACT) in triple-negative breast cancer (TNBC) improves long-term outcomes (LTOs) and evaluates clinical and molecular features for predictors of response and survival.

Knowledge Generated

Achievement of pathologic complete response correlated with better event-free survival (EFS) and overall survival, with even minimal residual invasive disease associated with worse outcomes. Although both bevacizumab and carboplatin significantly increased pCRs, neither improved LTOs. From gene expression analyses, evidence of an active tumoral immune response correlated with increased pCRs and improved EFS.

Relevance

Addition of bevacizumab or carboplatin to TNBC NACT increased pCRs, but did not appear to improve LTOs. However, standard of care is now NACT including carboplatin with pembrolizumab; future studies should focus on optimizing chemotherapy plus immune checkpoint inhibition. Identification of immune activation as a predictive and prognostic biomarker may allow more tailored neoadjuvant approaches in nonmetastatic TNBC.

The study also had important correlative objectives, particularly to identify pretreatment clinical and genomic biomarkers predictive of achievement of pCR and/or prognostic of EFS and to evaluate the impact of study treatment on pCR rates in patients with genomically defined basal-like tumors, a coprimary end point of the study.

PATIENTS AND METHODS

Patients with clinical stage II-III TNBC (estrogen receptor and progesterone receptor $\leq 10\%$ and human epidermal growth factor receptor 2–negative) received paclitaxel 80 mg/m² once a week for 12 weeks (wP) and were randomly assigned to the control regimen (arm 1), with addition of bevacizumab 10 mg/kg once every 2 weeks for 9 doses (arm 2), carboplatin area under the curve 6 once every 3 weeks for four doses (arm 3), or both (arm 4), followed by dose-dense doxorubicin and cyclophosphamide (AC) and then surgery (Data Supplement 1, online only). Patients signed an institutional review board–approved Protocol (online only)–specific consent in accordance with federal and institutional guidelines. Pathologic response was assessed by institutional pathologists. pCR is defined as the absence of residual invasive disease in the breast and axilla (ypT0 or Tis N0), and patients with RD were stratified by residual cancer burden (RCB), as defined by Symmans et al.³ EFS is defined as time from random assignment to local, regional, or distant recurrence, any second invasive cancer, or death from any cause; patients not undergoing surgery were considered to have had an EFS event when they were removed from study treatment. Overall survival (OS) is defined as time from random assignment to death from any cause, and distant recurrence-free interval (DRFI) is defined as time from random assignment to detection of metastatic disease or death attributed to disease progression, with

patients removed from follow-up for any other reason (including a second invasive cancer or death not attributed to breast cancer) censored as of their last disease assessment. The study database was frozen on April 2, 2020, and patients were censored as of their most recent follow-up data. Data collection, analysis, and quality review were conducted by the Alliance Statistics and Data Management Center and the study chair, following Alliance policies.

With support from the Breast Cancer Research Foundation, pretreatment tumor biopsies from all enrolled patients were required and submitted for genomic and other analyses. RNA sequencing (RNAseq) was performed as previously described,⁴ excluding those whose samples failed to meet RNA quality control metrics and those with estrogen receptor or progesterone receptor expression $> 1\%$ (to be consistent with the current clinical definition of TNBC⁵). RNA sequencing, clinical data, and patient outcomes are available through NCBI database of Genotypes and Phenotypes (dbGaP).⁶ The impact of adding bevacizumab or carboplatin on pCR and EFS was assessed in the subset of patients with basal-like tumors defined by PAM50 classification.^{7,8} We also assessed the ability of previously published TNBC molecular subtyping strategies to predict pCR and EFS. To investigate the entire genome for gene expression patterns correlated with response and survival, we evaluated hundreds of previously published gene expression signatures ($n = 793$) that have been extensively used to distill the expression of thousands of genes into biologically relevant patterns that comprehensively cover the biology of breast cancer⁹ and have been shown to outperform individual genes for providing prognostic value.¹⁰ Once we identified associations between the number of immune signatures and both pCR and EFS, we analyzed a subset of samples ($n = 178$) for tumor-

infiltrating lymphocytes (TILs) according to international standards¹¹ and evaluated the correlation with pCR and EFS. To further characterize the immune response and its prognostic significance, we analyzed B-cell receptor and T-cell receptor sequence repertoire abundance and diversity measures (which are derived from bulk RNAseq and described in Data Supplement 1). We used multivariable Cox proportional hazards (PH) models with baseline clinical features and several immune features, including TILs, to compare the prognostic value of these features in predicting EFS. Given the strong association between achievement of pCR and EFS (described below), we looked for clinical and genomic features predictive of EFS in patients who failed to achieve pCR. We created a Cox PH model to identify interactions between treatment variables (ie, with or without carboplatin and with or without bevacizumab) and genomic features to determine if this could improve our ability to predict EFS.

Statistical Considerations

The analysis was performed via a modified intent-to-treat (mITT) principle; patients who withdrew before starting protocol treatment were excluded. The Kaplan-Meier method was used to estimate LTOs. Log-rank tests and Cox PH models were used to evaluate the association between baseline characteristics, treatment assignment, pathologic response, treatment delivery, genomic features,

and LTOs. A generalized linear model of binomial outcomes using logit link function was used to evaluate genomic and clinical features' association with probability of pCR. Consistent with the exploratory nature of many of the correlative science analyses, reported *P* values are from two-sided tests and have not been corrected for multiple comparisons.

Role of the Funding Sources

Representatives of the funding sources (the National Cancer Institute, Genentech, the Breast Cancer Research Foundation, and the American Recovery and Reconstruction Act of 2009) were not involved in data analysis or the preparation of this article.

RESULTS

Impact of Clinical Factors on Outcomes

Of 443 patients in the mITT population, 426 underwent surgery (CONSORT diagram, Fig 1). The median follow-up is 7.9 years (95% CI, 7.6 to 8.1). The estimated 5-year EFS is 70.3%, OS 75.0%, and DRFI 76.1% (Fig 2A and Data Supplement). Among baseline characteristics, only the clinical stage (III v II) was significantly associated with EFS (hazard ratio [HR], 2.15; 95% CI, 1.53 to 3.01) and OS (HR, 2.42; 95% CI, 1.68 to 3.50), whereas age, race, and tumor grade were not (Table 1).

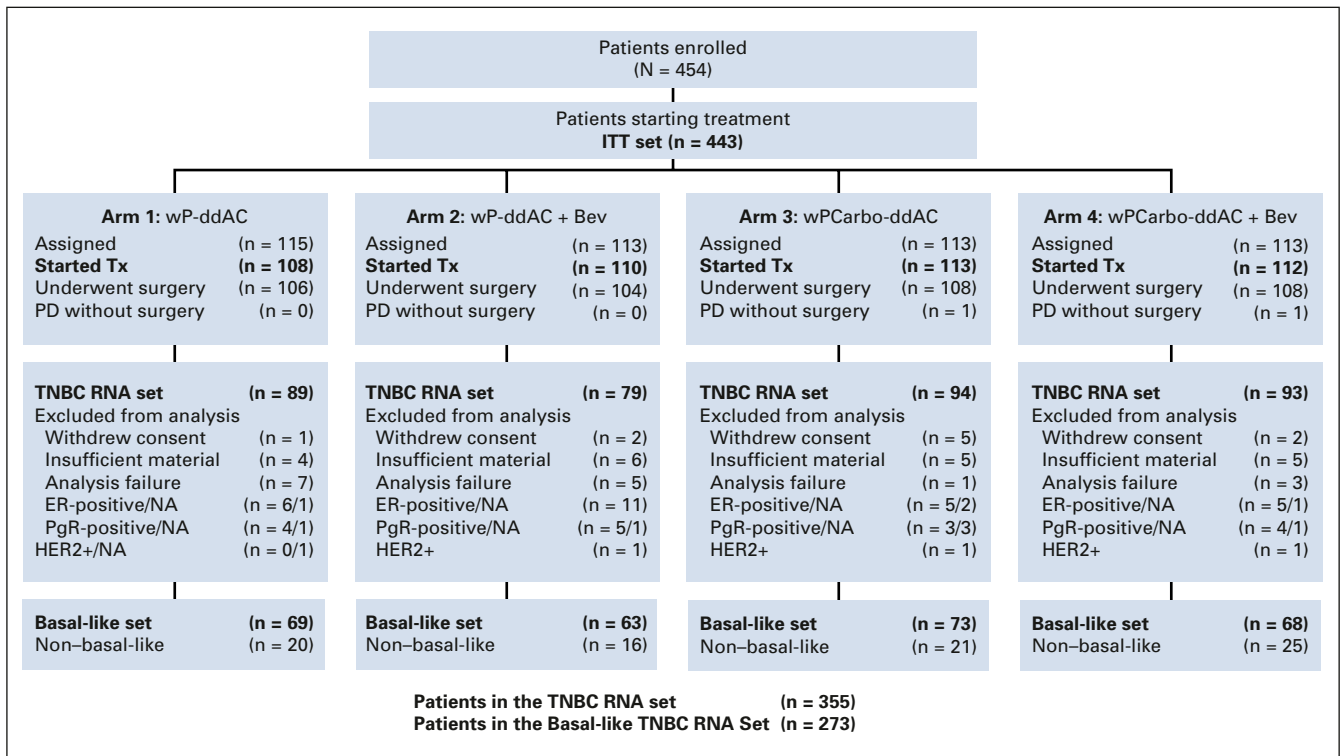


FIG 1. CONSORT diagram (Alliance CALGB 40603 trial). Bev, bevacizumab; Carbo, carboplatin; ddAC, dose-dense doxorubicin and cyclophosphamide; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; ITT, intent-to-treat; NA, not available; PD, progressive disease; PgR, progesterone receptor; TNBC, triple-negative breast cancer; Tx, treatment; wP, weekly paclitaxel.

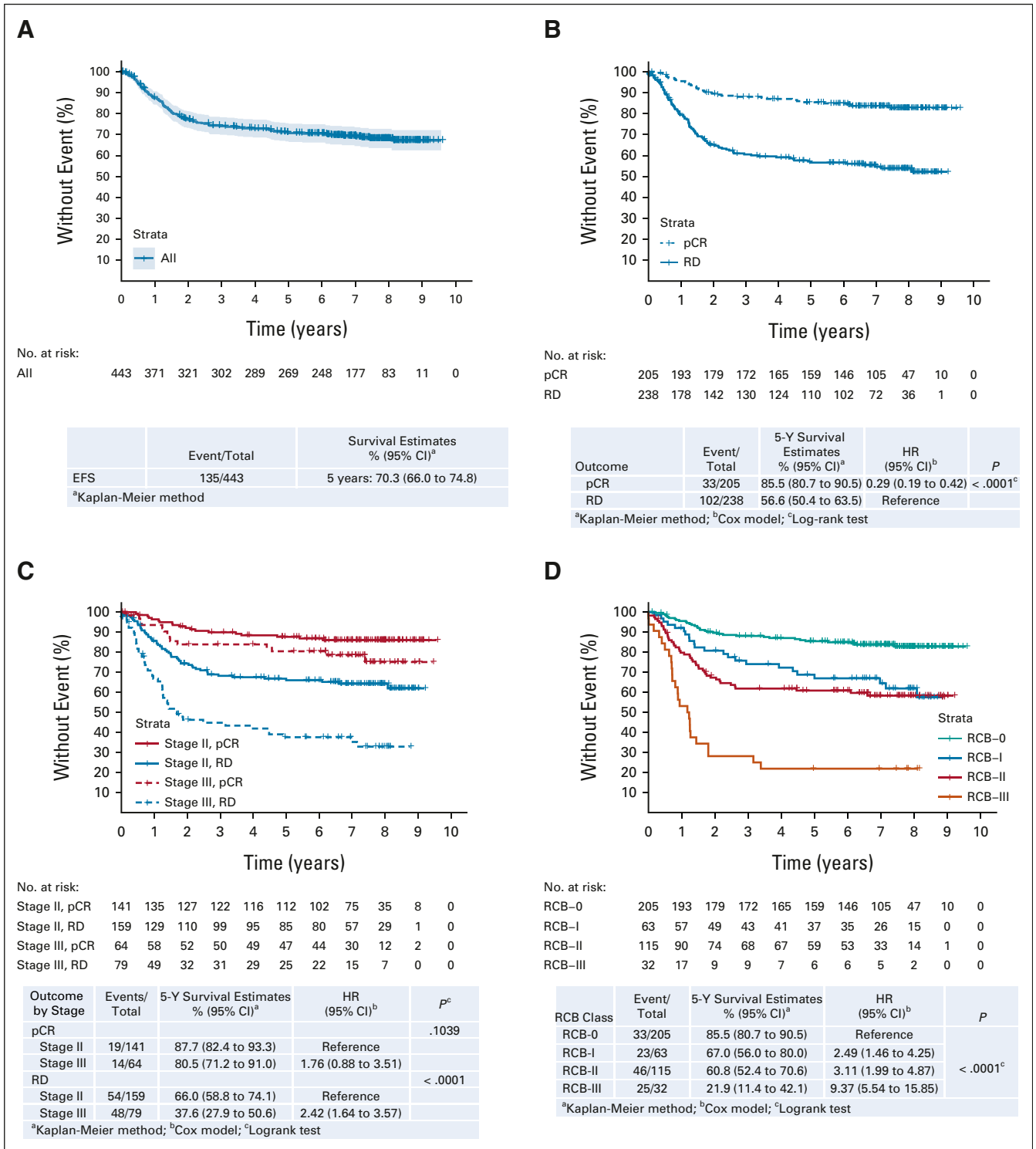


FIG 2. Effect of the pretreatment clinical stage and response on EFS. (A) EFS in the mITT population. EFS stratified by (B) pCR versus RD, (C) pCR versus RD and stage, and (D) RCB. EFS, event-free survival; HR, hazard ratio; mITT, modified intent-to-treat; pCR, pathologic complete response; RCB, residual cancer burden; RD, residual disease.

In patients who achieved a pCR (205 of 443, 46.3%), the 5-year EFS is 85.5% versus 56.6% (HR, 0.29; 95% CI, 0.19 to 0.42; $P < .0001$; Fig 2B) and the 5-year OS is 87.9% versus 63.4% (HR, 0.28; 98% CI, 0.18 to 0.43; $P < .0001$;

Data Supplement 1) compared with those with RD, and prognosis for baseline stage III versus II no longer differs significantly (Fig 2C) although this finding is based on a limited number of events. In patients with RD, the RCB

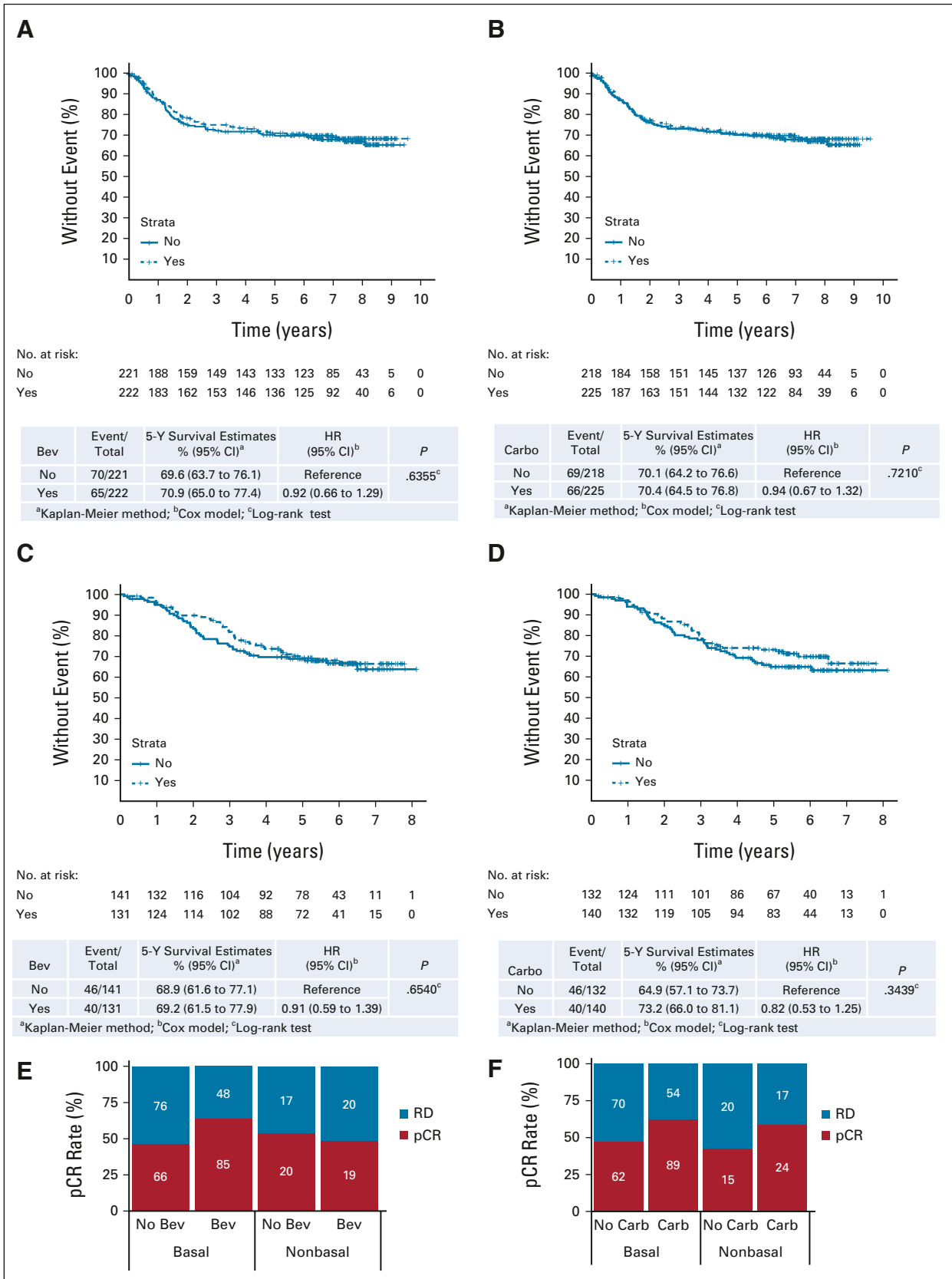


FIG 3. Effect of addition of bevacizumab and carboplatin to LTO in CALGB 40603. EFS stratified by (A and C) bevacizumab and (B and D) carboplatin treatment within the (A and B) mITT and (C and D) basal-like patient populations. pCR rate within the basal-like and non-basal-like subsets stratified by (E) bevacizumab and (F) carboplatin treatment. Bev, bevacizumab; Carbo, carboplatin; EFS, event-free survival; HR, hazard ratio; LTO, long-term outcome; mITT, modified intent-to-treat; pCR, pathologic complete response; RD, residual disease.

TABLE 1. Impact of Baseline Characteristics and Treatment on EFS and OS

Patient Subgroup	Univariate Cox PH Survival Analysis					
	EFS			OS		
	Events/Total	HR (95% CI)	<i>P</i>	Events/Total	HR (95% CI)	<i>P</i>
Age, years			.2345 ^a			.1051 ^a
< 40	24/100	0.69 (0.44 to 1.08)		18/100	0.60 (0.36 to 1.00)	
40-59	88/269	Reference		74/269	Reference	
≥ 60	23/74	0.94 (0.60 to 1.49)		21/74	1.02 (0.63 to 1.65)	
Race			.6974 ^a			.7146 ^a
White	100/320	Reference		85/320	Reference	
Black or African American	28/89	0.97 (0.64 to 1.48)		23/89	0.95 (0.60 to 1.51)	
Asian, Native Hawaiian or Pacific Islander, American Indian or Alaska Native, or more than one race	5/22	0.69 (0.28 to 1.70)		4/22	0.68 (0.25 to 1.85)	
Clinical stage			< .0001 ^a			< .0001 ^a
II	73/300	Reference		57/300	Reference	
III	62/143	2.15 (1.53 to 3.01)		56/143	2.42 (1.68 to 3.50)	
Tumor grade			.6730 ^a			.5464 ^a
Low or intermediate	17/54	1.12 (0.67 to 1.87)		15/54	1.19 (0.69 to 2.06)	
High	101/338	Reference		85/338	Reference	
T stage			.0001 ^a			.0002 ^a
1	14/49	1.19 (0.67 to 2.12)		12/49	1.26 (0.68 to 2.34)	
2	73/291	Reference		59/291	Reference	
3	39/87	2.14 (1.45 to 3.16)		34/87	2.28 (1.49 to 3.48)	
4	7/10	4.13 (1.90 to 8.98)		6/10	4.45 (1.92 to 10.31)	
N stage			.0014 ^a			.0006 ^a
0	41/185	0.61 (0.41 to 0.90)		29/185	0.49 (0.31 to 0.76)	
1	63/187	Reference		57/187	Reference	
2	14/35	1.27 (0.71 to 2.26)		11/35	1.10 (0.58 to 2.10)	
3	7/9	2.76 (1.26 to 6.03)		6/9	2.43 (1.04 to 5.64)	
Bevacizumab			.6355 ^a			.8622 ^a
No	70/221	Reference		57/221	Reference	
Yes	65/222	0.92 (0.66 to 1.29)		56/222	0.97 (0.67 to 1.40)	
Carboplatin			.7210 ^a			.5585 ^a
No	69/218	Reference		54/218	Reference	
Yes	66/225	0.94 (0.67 to 1.32)		59/225	1.12 (0.77 to 1.61)	
Arm			.6663 ^a			.8743 ^a
1 (wP to ddAC)	33/108	Reference		26/108	Reference	
2 (wP to ddAC + Bev)	36/110	1.11 (0.69 to 1.78)		28/110	1.08 (0.63 to 1.84)	
3 (wPCarbo to ddAC)	37/113	1.13 (0.71 to 1.81)		31/113	1.24 (0.74 to 2.09)	
4 (wPCarbo to ddAC + Bev)	29/112	0.86 (0.52 to 1.41)		28/112	1.08 (0.64 to 1.85)	

Abbreviations: Bev, bevacizumab; Carbo, carboplatin; ddAC, dose-dense doxorubicin-cyclophosphamide; EFS, event-free survival; HR, hazard ratio; OS, overall survival; PH, proportional hazards; wP, weekly paclitaxel.

^aType 3 likelihood ratio *P* value.

class is prognostic for EFS (Fig 2D); however, even RCB-I is associated with a worse prognosis than RCB-0 (ie, pCR; HR, 2.49; 95% CI, 1.46 to 2.25; $P < .0001$). Similar results are seen for OS and DRFI (Data Supplement 1). In an exploratory analysis, baseline stage III versus II remains a significant prognostic variable in patients with RCB-I or RCB-II, although not in the smaller number of patients with RCB-III (Data Supplement 1). Significant improvements in EFS and OS with pCR over RD are seen across all arms of the study although differences vary in magnitude (Data Supplement 1).

There is no improvement in EFS in the mITT population with the addition of either bevacizumab (HR, 0.92; 95% CI, 0.66 to 1.29; $P = .64$) or carboplatin (HR, 0.94; 95% CI, 0.67 to 1.32; $P = .72$; Figs 3A and 3B). Similar results are seen for OS and DRFI (Data Supplement 1). We identified no patient subset for which the addition of either agent improves EFS or OS (Data Supplement 1). Events by treatment arm are listed in Data Supplement 1.

As noted in our previous publication,² patients assigned to carboplatin were more likely to miss multiple doses of treatment during wP (35% v 15% not assigned to carboplatin). As very few patients discontinued treatment early, this discrepancy may be attributed to higher rates of hematologic toxicities with carboplatin and protocol dosing guidelines that required that treatment is skipped, rather than delayed, for these toxicities. In an exploratory analysis, we found a significant relationship between the number of wP doses received (stratified by ≥ 11 , 9-10, 7-8, and ≤ 6) and EFS ($P = .0025$) in the overall study population (Data Supplement 1). Among all patients who received ≥ 11 doses of wP, the addition of carboplatin increased pCRs from 41% to 61%, with a trend for improved 5-year EFS (78.5% v 72%, HR, 0.68; 95% CI, 0.44 to 1.06; $P = .089$), which was not seen relative to bevacizumab assignment (Data Supplement 1).

Impact of Genomic Features on pCR and Outcomes

Within the subset of patients with genomically defined basal-like tumors, which comprised 77% of tumors tested by RNA-seq⁷ (Data Supplement 1), the addition of either bevacizumab or carboplatin to the control NACT regimen significantly increased the pCR rate (Figs 3E and 3F), but, as in the mITT population, failed to improve EFS (Figs 3C and 3D). Adding bevacizumab had a larger positive impact on the pCR rate in basal-like compared with non-basal-like tumors, whereas the increment in pCR with the addition of carboplatin was similar between the two cohorts (Figs 3E and 3F).

Of the published TNBC molecular subtyping approaches that we evaluated—TNBCtype,¹² MD Anderson Cancer Center and Baylor College of Medicine subtype,¹³ and PAM50 + Claudin Low subtypes^{7,14}—only tumors categorized as the basal-like immune-activated subtype by the MD Anderson Cancer Center and Baylor College of

Medicine classification demonstrated a significantly higher pCR rate and none displayed significant prognostic differences for EFS (Data Supplement 1). Comparison between subtyping strategies demonstrated a moderate strength of association (0.40-0.46, Cramer's V test), but disagreements between classifications and a high proportion of unclassifiable specimens highlight a limitation of these strategies (Data Supplement 1).

Of the > 850 clinical and genomic features that we analyzed for association with outcomes in these exploratory studies (Data Supplement 2, online only), a large number of features were associated with either pCR ($n = 177$) or EFS ($n = 39$), but only 27 were associated with both (Fig 4A and Data Supplement 2). Features associated with pCR but not EFS included all six signatures of interferon signaling, whereas clinical features such as the baseline tumor stage and nodal status were associated with EFS, but not pCR. Most (24 of 27) of the features associated with both pCR and EFS reflected the tumor's immune microenvironment (Fig 4B), including the presence of a variety of immune effector cells, including T and B lymphocytes and natural killer cells. Higher mRNA expression levels of immune checkpoint genes, including programmed cell death protein 1 (PDCD1) and programmed death-ligand 1 (CD274), were also associated with improvements in both pCR and EFS.

Analysis of B-cell receptor and T-cell receptor data demonstrated that low immunoglobulin G (IgG) evenness was associated with improvements in both pCR and EFS. IgG evenness is a measure of the uniformity of B-cell clonal abundance. Low IgG evenness may reflect oligoclonal B-cell expansion and immunoglobulin class switching caused by an antigen-driven immune response, in contrast to a non-specific (polyclonal) immune response. In fact, there was a negative correlation between IgG evenness and IgG abundance (Data Supplement 1). Using IgG evenness cutoff values derived from recurrence-free survival data for patients with TNBC in The Cancer Genome Atlas (TCGA; Data Supplement 1), we found that patients with low IgG evenness have improved EFS (Fig 4B, right) and IgG evenness was an independent prognostic feature in a model including age, stage, and pCR status (Data Supplement 1). Among patients who failed to achieve pCR, only the tumor stage and node status were stronger prognostic features than low IgG evenness (Fig 4C). In addition, among patients who did not receive carboplatin (arms 1 and 2 of our study), only achievement of pCR was more strongly associated with EFS than low IgG evenness (Data Supplement 1).

As a continuous measure, TIL density, defined as the percentage of stromal area occupied by lymphocytes on a tumor biopsy,¹¹ was strongly associated with both pCR and EFS. There was a correlation, albeit with a significant variation, between TIL density and mRNA signatures of many immune effector cells and immune checkpoints, but not with IgG evenness (Figs 4D and 4E). As there is no

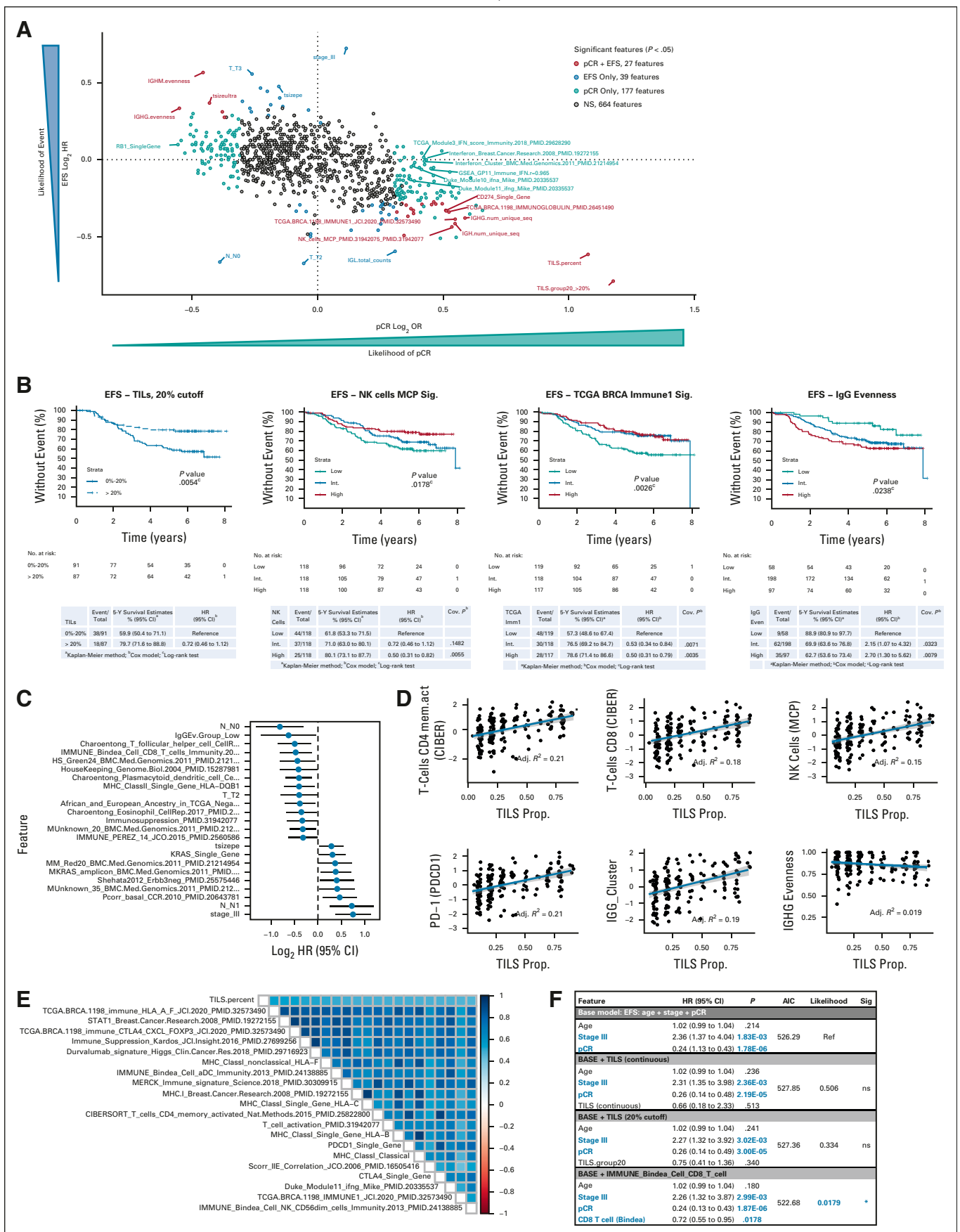


FIG 4. Genomic correlates with response and survival in TNBC. (A) Clinical and genomic feature association with likelihood of pCR and EFS outcomes. Nonsignificant ($P > .05$) associations are given in gray, features associated with both pCR and EFS are given in red, features (continued on the next page)

FIG 4. (Continued). associated with just EFS are given in blue, and features associated with only pCR are given in light blue. A few selected significant features are labeled. (B) EFS Kaplan-Meier plots for patients with TNBC stratified by (left-to-right) TIL quantification (20% cutoff), NK_cells_MCP_PMIID.31942075_P-MID.31942077 signature tertiles, TCGA.BRCA.1198_IMMUNE1_JCI.2020_PMIID.32573490 signature tertiles, and IgG evenness groups. (C) Features significantly associated with EFS in patients with residual disease (n = 191); negative log₂ HR indicates lower risk of event. (D) Correlation of TILs with immune effector and checkpoint signatures: (left-to-right, top-first) CD4+ memory T cells, CD8+ T cells, NK cells, PD-1 expression, IgG cluster, and IgG evenness. (E) Spearman correlation matrix for continuous TIL quantification and top 20 most correlated signatures, ordered by correlation with TILs. (F) Comparison of multivariable Cox proportional hazards models for EFS within the set of TNBC with TIL quantification (n = 178). Features that are significant in the multivariate Cox model are in blue bold text, HR and 95% CI, AIC, Akaike information criteria; EFS, event-free survival; HR, hazard ratio; IgG, immunoglobulin G; MCP, Microenvironment Cell Populations-counter; NK, natural killer; ns, not significant; pCR, pathologic complete response; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TCGA, The Cancer Genome Atlas; TIL, tumor-infiltrating lymphocyte; TIL, tumor-infiltrating lymphocyte; TNBC, triple-negative breast cancer.

standard definition of low or high TILs, we sought to establish an optimal cutoff by constructing a series of Kaplan-Meier curves for each 10% increment in TILs between 10% and 50% and found that a level of > 20% led to optimal separation of EFS curves (Data Supplement 1). However, although TILs and other genomic features were prognostic for EFS in univariate analyses, once pCR status (yes or no) was included in a multivariable analysis, TILs, either as a continuous variable or with a > 20% cutoff, were no longer independently prognostic for EFS, whereas a genomic signature of CD8+ T cells, evaluated in the same model, within the same subset of patients, remained an independent prognostic variable that significantly improved the prognostic value of the model (Fig 4F and Data Supplement 2).

A Cox PH model on the basis of treatment (ie, plus carboplatin or plus bevacizumab), genomic variables, and the interaction between treatment and the genomic feature can identify potential features associated with treatment-specific sensitivity and resistance. We identified 11 features that had significant interaction with carboplatin treatment (Data Supplement 1), the most significant of which was RB1 mRNA expression, with low RB1 expression being associated with greater improvements in pCR and EFS with the addition of carboplatin (Data Supplement 1). There were 12 features that had significant interaction with bevacizumab (Data Supplement 1), including a signature of lung metastasizing breast cancer cells (Pcorr_Breast2Lung_LM2),¹⁵ for which higher expression correlated with worse survival in patients not receiving bevacizumab (Data Supplement 1), and menopausal status, with postmenopausal women demonstrating worse survival with bevacizumab (Data Supplement 1).

DISCUSSION

As expected,^{1,16} patients with TNBC in CALGB 40603 who achieved pCR with NACT had far superior LTOs compared with those with RD, in whom the baseline stage and extent of RD were prognostic. In this trial, patients with any RD, even RCB-I, had significantly worse outcomes than those with pCR, supporting consideration of adjuvant therapy even in the setting of minimal RD.

Despite the significant increase in pCR with both agents, there was no evidence that adding either bevacizumab or

carboplatin improved EFS or other LTOs, although, like many neoadjuvant trials, CALGB 40603 was not powered to evaluate EFS. We did not collect data on whether study patients, particularly those who failed to achieve pCR, received additional chemotherapy or other systemic treatments after surgery, and thus, we cannot rule out the possibility that such treatments could have affected EFS and other LTOs and diminished the apparent benefit of achieving pCR although our study was completed before results of the CREATE-X trial were presented and made administration of postneoadjuvant therapy with capecitabine common.¹⁷ The absence of benefit from bevacizumab is not surprising, noting that in three other randomized trials—GeparQuinto, ARTemis, and NSABP B-40—the addition of bevacizumab to NACT did not improve disease-free survival (DFS) or OS in TNBC,¹⁸⁻²³ despite significantly increasing pCR rates in the first two studies, nor has adding bevacizumab to adjuvant chemotherapy been shown to improve outcomes in TNBC.^{24,25} In both GeparQuinto and ARTemis, pCRs achieved with bevacizumab had higher rates of DFS events than those attained with NACT alone, leading the ARTemis investigators to hypothesize that although bevacizumab might enhance response to chemotherapy in an angiogenesis-driven breast tumor, it might not have the same effect on micrometastatic disease.²¹

Two other randomized trials—GeparSixto and BrightNess—have demonstrated significant increases in pCR rates in TNBC with the addition of carboplatin to taxane- and anthracycline-containing NACT^{26,27}; pCR rates of a similar magnitude have been reported in other multicenter studies (Data Supplement 1).²⁸⁻³⁰ In GeparSixto, the addition of weekly carboplatin to their control NACT regimen significantly improved DFS, along with a trend toward improvement in OS.^{28,29} LTOs from BrightNess are of particular interest since this study used a control regimen identical to arm 1 of CALGB 40603. An intriguing but exploratory post hoc analysis of the two trials found that a higher proportion of patients in the carboplatin arm of BrightNess (88%) received all 12 planned doses of the taxane than CALGB 40603 (65%). Patients assigned to carboplatin on BrightNess had a larger absolute increase in pCR rate than on CALGB 40603 (27% v 13%)²⁷ and in results presented at the 2021 ESMO Congress, had significantly better 4-year EFS and a trend toward improved

OS³¹ although other factors might have contributed to these apparent discrepancies. Although EA1131 failed to demonstrate noninferiority of adjuvant platinum therapy compared with capecitabine in patients with TNBC with RD after (non-platinum-containing) NACT,³² no randomized trial has reported on the addition of carboplatin to adjuvant chemotherapy for TNBC; however, one is ongoing (NRG-BR003).

KEYNOTE-522 assessed the benefit of the addition of the programmed cell death protein 1–targeted monoclonal antibody pembrolizumab to a NACT regimen consisting of wP and carboplatin followed by AC or epirubicin-cyclophosphamide (EC) in TNBC, demonstrating improved pCR rates and 3-year EFS with the addition of the immune checkpoint inhibitor (ICI).^{33,34} This finding resulted in US Food and Drug Administration approval for the addition of pembrolizumab to NACT in TNBC. The chemotherapy backbone in KEYNOTE-522 included carboplatin, making a platinum-containing NACT regimen appropriate for patients with stage II and III TNBC being treated in this way. However, it should be noted that the design of KEYNOTE-522 does not allow assessment of the individual contribution of carboplatin to the EFS benefit observed with the addition of pembrolizumab.

From a correlative science perspective, the limited overlap between features associated with pCR and EFS suggests the need to be cautious in developing biomarkers for survival from studies for which pCR is the primary clinical end point and that are not powered to assess LTOs, even though pCR is the most powerful individual prognostic feature for EFS. Our results are consistent with previous observations that both increased TILs and immune-related gene expression signatures are associated with a higher likelihood of achieving pCR with NACT and improved survival in TNBC.³⁵⁻³⁷ Evaluating both on the same specimens demonstrates how inclusion of some of these genomic immune signatures, such as a CD8+ T-cell signature, may improve a multivariable prognostic model, whereas the abundance of TILs did not. In addition, we demonstrate that a more focused antigen-driven immune response, presumably in response to antigens expressed by the cancer, as reflected by lower IgG evenness, is associated with both better response to NACT and improved EFS and may help to identify patients with a good prognosis even in the absence of pCR. Low IgG evenness has also been associated with improved prognosis in cutaneous melanoma.³⁸ Given the exploratory nature of these findings, we look forward to the presentation of correlative results from the BrightNess trial, now that it has reported EFS and OS results, to see if we can validate these potential biomarkers. The finding that evidence of immune activation is associated with both pCR to NACT and

improved survival heightens interest in the studying regimens that incorporate both effective NACT and ICIs. Recently reported trials have demonstrated that the addition of an ICI to NACT for TNBC not only increases pCR but can also improve EFS.^{30,39} Analyses of these studies failed to show that expression of a single marker of tumor-induced immune suppression, namely, programmed death-ligand 1, identified patients more likely to benefit from addition of immunotherapy, thus leaving open the possibility that a more detailed evaluation of immune activation as described herein may be necessary to identify biomarkers for ICI benefit in the neoadjuvant setting.

Our study has several important limitations. The sample size was calculated on the basis of analysis of our primary end point, pCR, which limits our ability to evaluate the impact of treatment assignment on EFS and other LTOs. Although the magnitude of the increment in pCR that would be expected to significantly improve EFS is not well defined, when presenting results of their meta-analysis of the impact of pCR on LTOs, Spring et al¹⁶ commented that to determine if the 13% absolute increase in pCRs observed with carboplatin in CALGB 40603 significantly affects EFS would require 1,381 events, a 10-fold increase over the 135 events reported herein. We did not require central pathologic review, relying on institutional pathologists to assess pCR and record the findings necessary to calculate RCB. In addition, we did not perform germline BRCA mutation testing; thus, we are unable to determine whether BRCA mutation status affects the impact of treatment assignment on pCR or EFS.

In conclusion, although adding either carboplatin or bevacizumab significantly increased pCR in our trial, neither appeared to improve LTO; however, CALGB 40603 was underpowered for these end points. It should be noted that although its impact on LTO remains unclear, adding carboplatin is consistently associated with a pCR advantage. Moreover, carboplatin is included in the NACT regimen given with pembrolizumab. For these reasons, inclusion of carboplatin in NACT is reasonable for patients with stage II and III TNBC, particularly if being given with an ICI. We found that TNBC patients with any amount of RD after NACT, even RCB-I, had inferior LTOs compared with patients with pCR. Immune activation as measured by TILs and gene expression signatures was associated with both higher pCR rates and improved EFS although only immune activation measured by multigene expression signatures was independently associated with EFS in multivariable analysis. These observations, from a study in which patients did not receive immune-targeted therapy, may provide an opportunity to test de-escalated or tailored chemotherapy in patients with markers of immune activation.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**CALGB 40603 (Alliance): Long-Term Outcomes and Genomic Correlates of Response and Survival After Neoadjuvant Chemotherapy With or Without Carboplatin and Bevacizumab in Triple-Negative Breast Cancer**

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