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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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abstract

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.

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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 ≤ 10% and human epidermal growth factor receptor 2–negative) received paclitaxel 80 mg/m^2 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 TNBC[5]). 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 cancer[9] 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-

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infiltrating lymphocytes (TILs) according to international standards[11] 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 the 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).

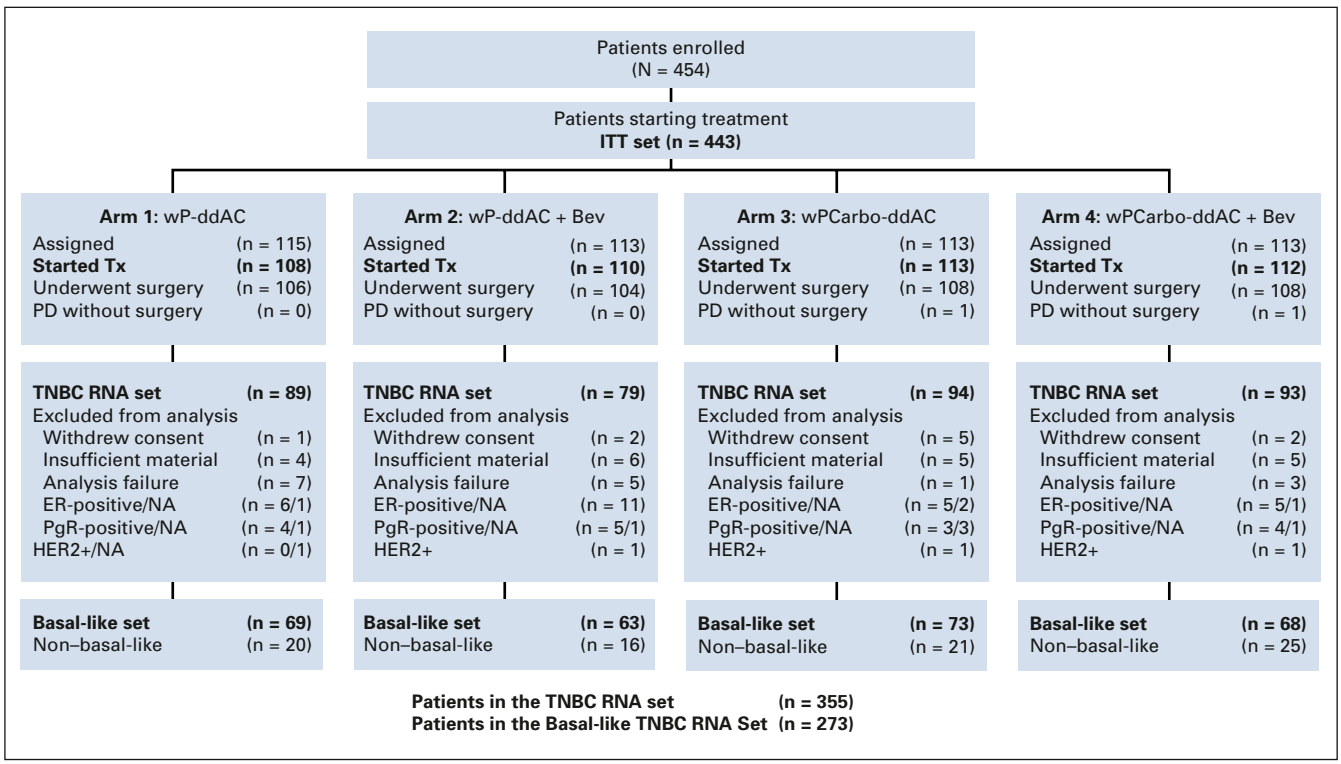

FIG 1. CONSORT diagram (Alliance CALGB 40603 trial). Bev, bevacizumab; Carbo, carboplatin; ddAC, dose-dense doxorubicin and cyclophosphamide; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; ITT, intent-to-treat; NA, not available; PD, progressive disease; PgR, progesterone receptor;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

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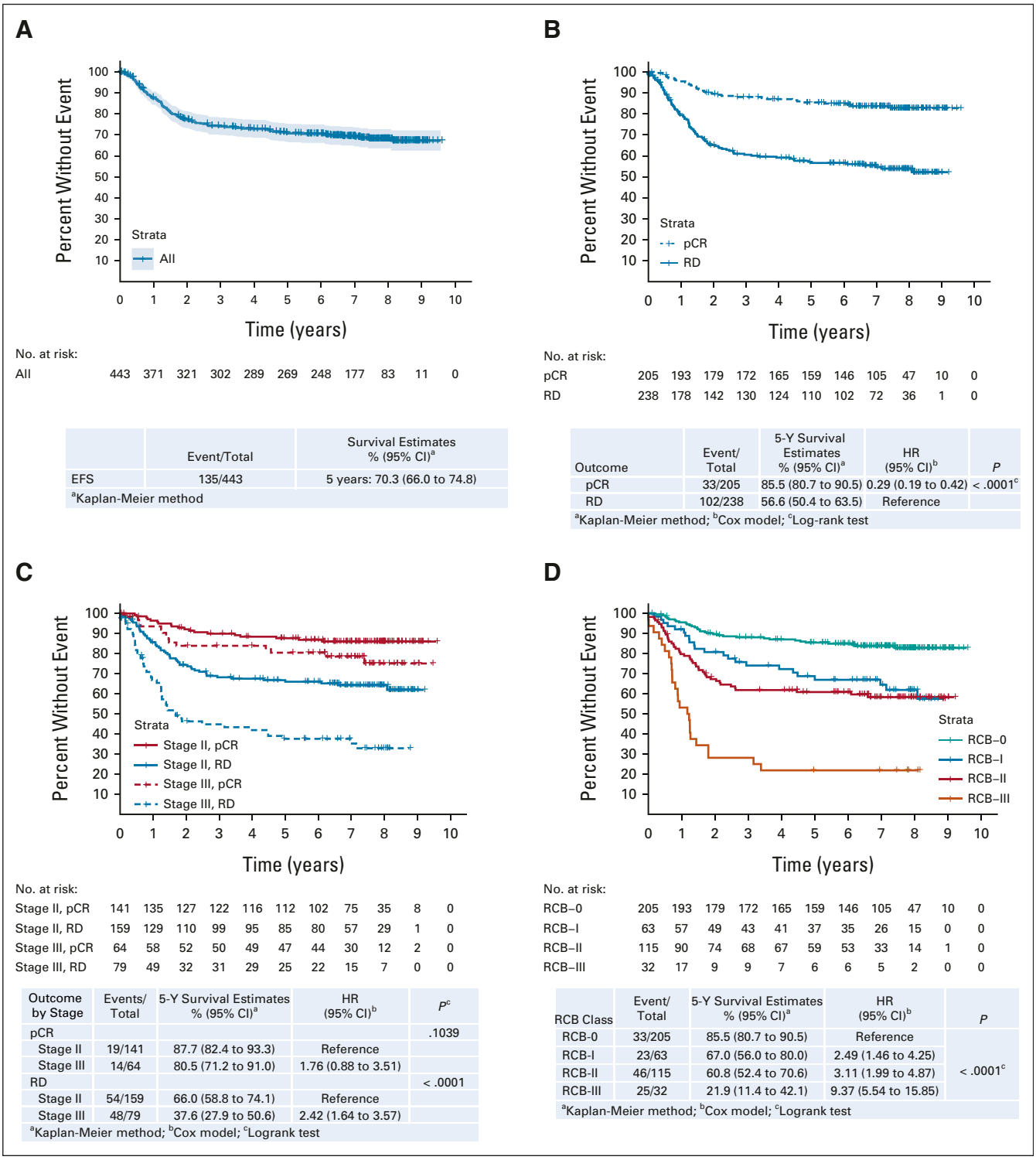

	Event/Total	Survival Estimates % (95% CI)[a]
EFS	135/443	5 years: 70.3 (66.0 to 74.8)

[a]Kaplan-Meier method

Outcome	Event/ Total	5-Y Survival Estimates % (95% CI)[a]	HR (95% CI)[b]	*P*
pCR	33/205	85.5 (80.7 to 90.5)	0.29 (0.19 to 0.42)	< .0001[c]
RD	102/238	56.6 (50.4 to 63.5)	Reference	

[a]Kaplan-Meier method; [b]Cox model; [c]Log-rank test

Outcome by Stage	Events/ Total	5-Y Survival Estimates % (95% CI)[a]	HR (95% CI)[b]	*P*[c]
pCR				.1039
Stage II	19/141	87.7 (82.4 to 93.3)	Reference	
Stage III	14/64	80.5 (71.2 to 91.0)	1.76 (0.88 to 3.51)	
RD				< .0001
Stage II	54/159	66.0 (58.8 to 74.1)	Reference	
Stage III	48/79	37.6 (27.9 to 50.6)	2.42 (1.64 to 3.57)	

[a]Kaplan-Meier method; [b]Cox model; [c]Logrank test

RCB Class	Event/ Total	5-Y Survival Estimates % (95% CI)[a]	HR (95% CI)[b]	*P*
RCB-0	33/205	85.5 (80.7 to 90.5)	Reference	
RCB-I	23/63	67.0 (56.0 to 80.0)	2.49 (1.46 to 4.25)	
RCB-II	46/115	60.8 (52.4 to 70.6)	3.11 (1.99 to 4.87)	< .0001[c]
RCB-III	25/32	21.9 (11.4 to 42.1)	9.37 (5.54 to 15.85)	

[a]Kaplan-Meier method; [b]Cox model; [c]Logrank test

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

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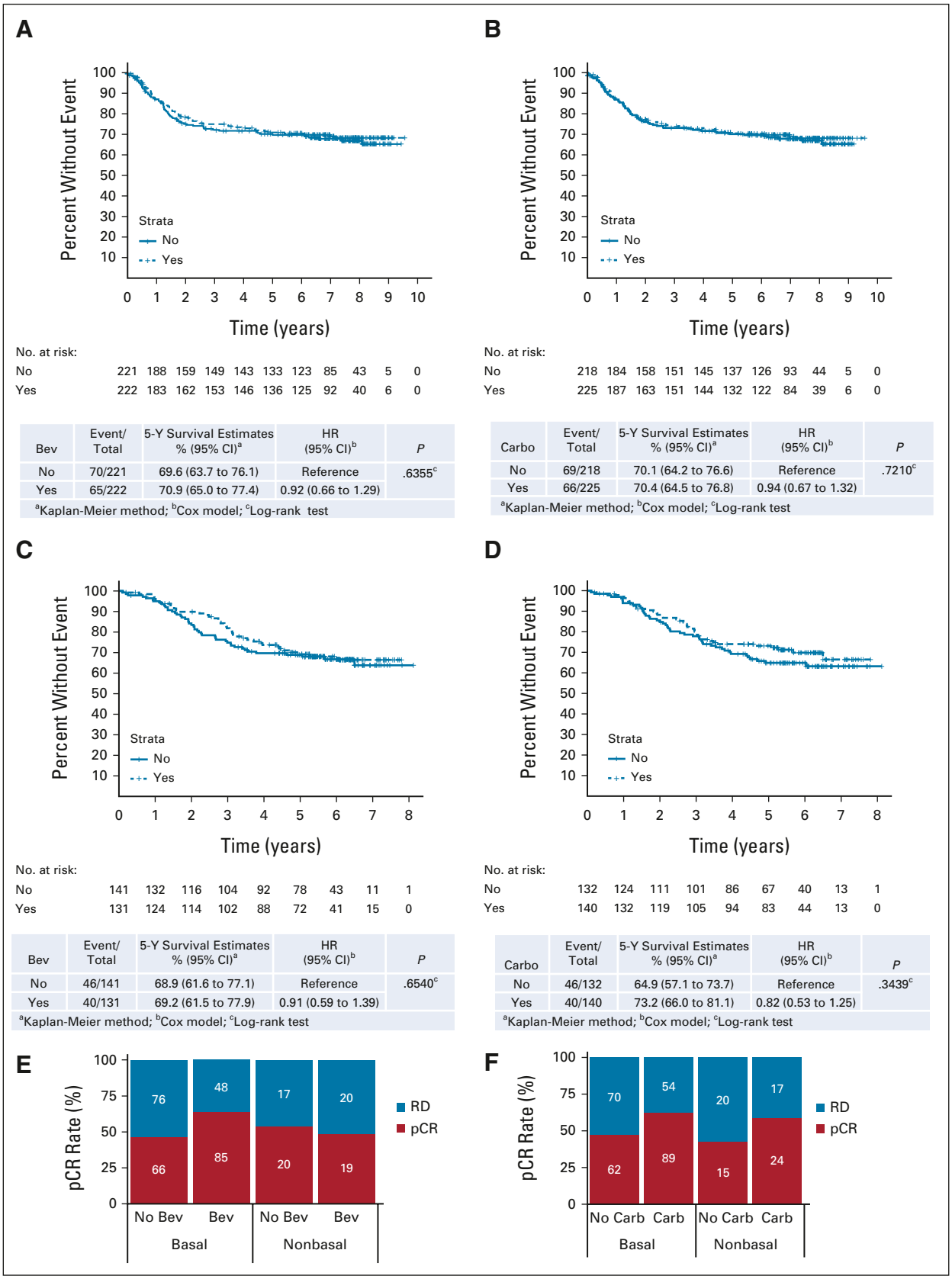

Bev	Event/ Total	5-Y Survival Estimates % (95% CI)[a]	HR (95% CI)[b]	*P*
No	70/221	69.6 (63.7 to 76.1)	Reference	.6355[c]
Yes	65/222	70.9 (65.0 to 77.4)	0.92 (0.66 to 1.29)	

[a]Kaplan-Meier method; [b]Cox model; [c]Log-rank test

Carbo	Event/ Total	5-Y Survival Estimates % (95% CI)[a]	HR (95% CI)[b]	*P*
No	69/218	70.1 (64.2 to 76.6)	Reference	.7210[c]
Yes	66/225	70.4 (64.5 to 76.8)	0.94 (0.67 to 1.32)	

[a]Kaplan-Meier method; [b]Cox model; [c]Log-rank test

Bev	Event/ Total	5-Y Survival Estimates % (95% CI)[a]	HR (95% CI)[b]	*P*
No	46/141	68.9 (61.6 to 77.1)	Reference	.6540[c]
Yes	40/131	69.2 (61.5 to 77.9)	0.91 (0.59 to 1.39)	

[a]Kaplan-Meier method; [b]Cox model; [c]Log-rank test

Carbo	Event/ Total	5-Y Survival Estimates % (95% CI)[a]	HR (95% CI)[b]	*P*
No	46/132	64.9 (57.1 to 73.7)	Reference	.3439[c]
Yes	40/140	73.2 (66.0 to 81.1)	0.82 (0.53 to 1.25)	

[a]Kaplan-Meier method; [b]Cox model; [c]Log-rank test

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.

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

	Univariate Cox PH Survival Analysis					
	EFS			OS		
Patient Subgroup	**Events/Total**	**HR (95% CI)**	***P***	**Events/Total**	**HR (95% CI)**	***P***
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.

[a]Type 3 likelihood ratio *P* value.

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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-seq[7] (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 nonspecific (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

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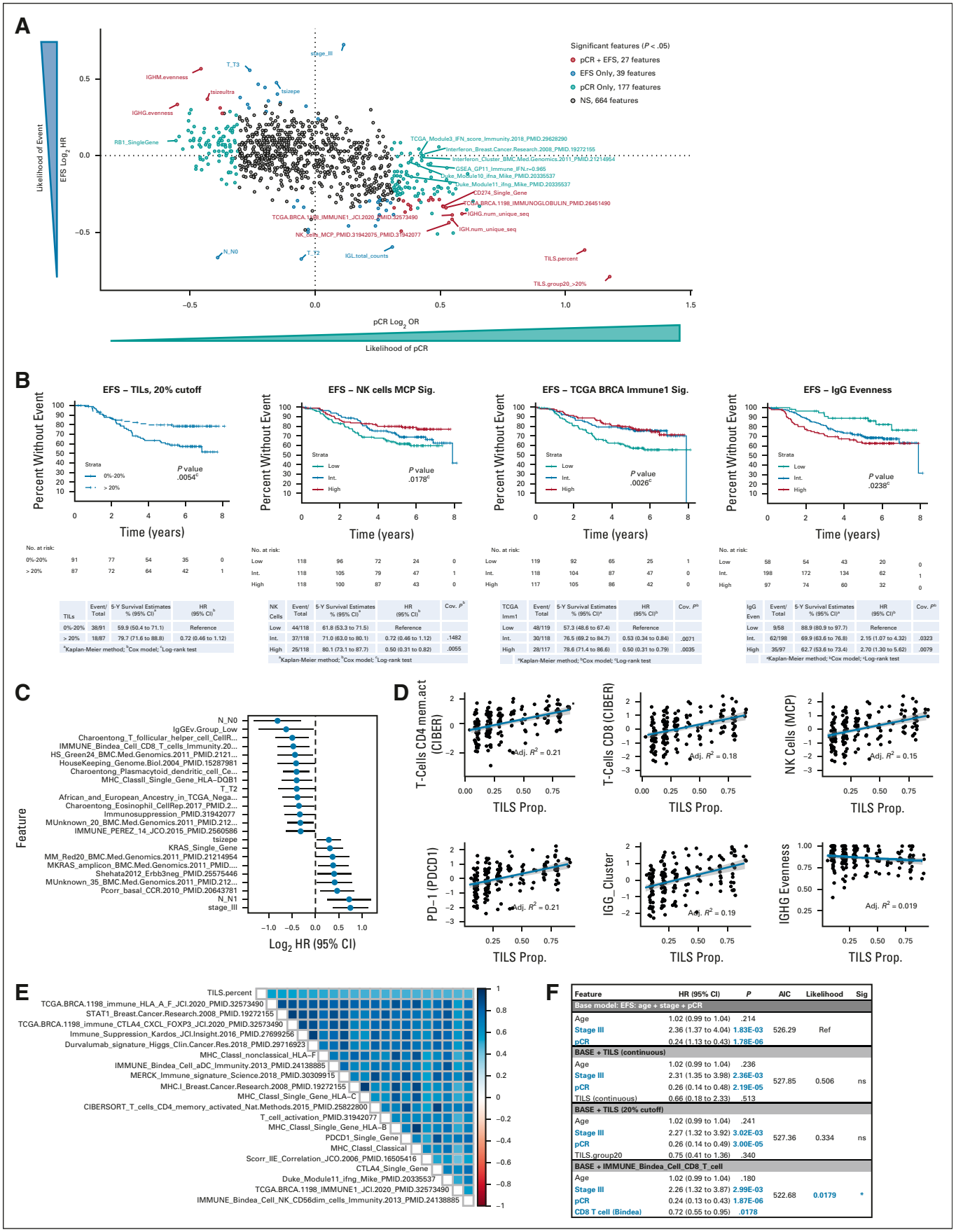

Feature	HR (95% CI)	P	AIC	Likelihood	Sig
Base model: EFS: age + stage + pCR					
Age	1.02 (0.99 to 1.04)	.214			
Stage III	2.36 (1.37 to 4.04)	**1.83E-03**	526.29	Ref	
pCR	0.24 (1.13 to 0.43)	**1.78E-06**			
BASE + TILS (continuous)					
Age	1.02 (0.99 to 1.04)	.236			
Stage III	2.31 (1.35 to 3.98)	**2.36E-03**	527.85	0.506	ns
pCR	0.26 (0.14 to 0.48)	**2.19E-05**			
TILS (continuous)	0.66 (0.18 to 2.33)	.513			
BASE + TILS (20% cutoff)					
Age	1.02 (0.99 to 1.04)	.241			
Stage III	2.27 (1.32 to 3.92)	**3.02E-03**	527.36	0.334	ns
pCR	0.26 (0.14 to 0.49)	**3.00E-05**			
TILS.group20	0.75 (0.41 to 1.36)	.340			
BASE + IMMUNE_Bindea_Cell_CD8_T_cell					
Age	1.02 (0.99 to 1.04)	.180			
Stage III	2.26 (1.32 to 3.87)	**2.99E-03**	522.68	**0.0179**	*
pCR	0.24 (0.13 to 0.43)	**1.87E-06**			
CD8 T cell (Bindea)	0.72 (0.55 to 0.95)	**.0178**			

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)

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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_PMID.31942075_PMID.31942077 signature tertiles, TCGA.BRCA.1198_IMMUNE1_JCI.2020_PMID.32573490 signature tertiles, and IgG evenness groups. (C) Features significantly associated with EFS in patients with residual disease (n = 191); negative $\log_2$ 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. 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

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OS[31] 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 al[16] 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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DISCLAIMER

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Uncompensated Relationships: Sanofi (Inst), Novartis (Inst), G1 Therapeutics (Inst), Genentech/Roche (Inst), GlaxoSmithKline (Inst), AstraZeneca/Daiichi Sankyo (Inst), Aptitude Health (Inst), Exact Sciences (Inst), Eisai
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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

Shepherd, et al

Supplemental Methods

Patient Population. A full description of the study's mITT patient population has been previously published and included in the manuscripts main text [1]. Briefly, For the CALGB 40603 trial, eligible patients were defined as having untreated stage II to III, ER-negative, PgR-negative and HER2-negative (locally determined by immunohistochemical (IHC) staining <= 10% for ER and PgR and HER2 status of 0 or 1+, or 2+ with fluorescence in situ hybridization ratio < 2.0) invasive breast cancer. For genomic analysis described in this manuscript, we used a stricter definition of ER-negativity, requiring patients to have <= 1% ER and PR positivity by IHC, thus using the current guidelines definition of TNBC status.

Gene Expression Studies. mRNA-sequencing (RNAseq) was performed at the UNC High Throughput Sequencing Facility (University of North Carolina) as previously described [2]. Briefly, mRNAseq libraries were made from total RNA isolated from fresh frozen tumors stored in RNAlater using the Illumina TruSeq mRNA sample preparation kit and sequenced on an Illumina HiSeq 2000 using a 2x50bp configuration. Reads passing quality control were aligned to human reference genome (hg38) using Spliced Transcripts Aligned to a Reference (STAR) version 2.4.2a[3] and quantification was performed using Salmon version 0.6.0[4]. The median and mean number of unique mapped reads were greater than 57 million reads per sample. Counts were normalized to a fixed upper quartile based on all non-zero transcripts and log2+1 transformed.

All raw sequence level data have been placed into dbGAP (**phs001863.v1.p1**, https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001863.v1.p1) and gene expression values into the Gene Expression Omnibus (**GSE154524**).

Tumor subtypes. PAM50 subtyping was applied using a subtype specific gene center method as previously described [5]. Claudin-low classification was determined post-hoc as previously described that uses a Claudin-low centroid predictor [6], and based upon hierarchical clustering analyses using 1800 gene intrinsic genelist of Parker et al.[7]; we called those sample as Claudin-low that were both centroid+ and clustered together in the hierarchical cluster.

TNBCtype assignments[8] were determined using the online TNBCtype tool[9] at https://cbc.app.vumc.org/tnbc/. Upper quartile normalized log2 expression values were uploaded for all CALGB 40603 samples, but 15 samples did not pass the TNBCtype ER expression threshold criteria and therefore classified as "uneval" in results.

The MDACC/BCM subtypes[10] were defined by measuring the Euclidean distance for mean-centered expression of each sample relative to the published gene centroids. P-values were determined using 1000x permutation testing. Samples were assigned to the subtype with the lowest distance with $p < 0.05$, and samples having no p-value < 0.05 were assigned as 'unstable' (UNS)

Gene signatures. 793 published gene expression modules, or signatures, representing multiple biological pathways, disease conditions, cell types, and particularly relevant individual genes obtained from 40 publications, 48 Gene Set Enrichment Analysis (GSEA) sets[11], and 35 individual genes. These signatures are partially summarized by Fan et al.[12], and the complete list with associated references is in **Supplemental Table 3**. Each signature was applied to the normalized RNAseq data set in a manner consistent with their derivation (i.e., mean expression of all genes for 718 coordinately regulated gene sets; individual expression for 35 single genes, and correlations to centroids or special algorithms from original methods for 40 non-homogeneous gene sets).

B cell receptor (BCR) and T cell receptor (TCR) repertoires. The antigen receptor sequence repertoire is the variety of genetic sequences that are created through genetic recombination in both B cells and T cells in order to create diverse antigen recognizing receptor proteins (B cell receptor, BCR; and T cell receptor, TCR). Total abundance, abundance of unique clones (richness), proportion of total clones composed by the most and second most common clones, as

well as diversity measures common to ecological studies, such as Shannon entropy, 1-Gini-Simpson (referred to as Gini-Simpson Index) and species evenness (described more fully in [13,14]) were measured according to specific immunoglobulin classes (IGHM, IGHG, IGHA), and as a sum for all immunoglobulin heavy chains (IGH), immunoglobulin light chains (IGK, IGL) and for TCR beta chain (TRB). Antigen receptor sequences were assembled from RNAseq using V'DJer[15] and MiCXR[16] pipelines as previously described. Diversity measures were derived using the R function divBCR (https://github.com/sararselitsky/divBCR). TCR repertoire was quantified using paired-end FASTQ files with MiXCR v1.8.1 in RNA-seq mode[17]. Alignment was performed using both default and RNA-seq modes, targeting all TCR loci.

Repertoire abundance and diversity measures. Both sequence and clone-level measures were assessed for BCR repertoires. Abundance and diversity measures were assessed as a total for all BCRs, and according to specific immunoglobulin classes. Total counts were calculated as the sum of the expression of all BCR clones normalized by the total RNA-seq read count. Top and second top clone proportions indicated the proportion of all clones composed by the most, or second most abundant clone, respectively. Diversity measures common to ecological studies, such as Shannon entropy, 1-Gini-Simpson (referred to as Gini-Simpson Index) and species evenness, which are more thoroughly described elsewhere[18], describe the richness of different species in a given environment. Whereas Shannon and Gini-Simpson diversity both increase as the total number of species increases and the equality of their proportions increase, species evenness is normalized by species richness and reflects the equality of species proportions. For patients that did not have any reads map to the IgG variable region (n=33), or patients for which only a single clone was identified (n=17), evenness is not measurable and, therefore, we assigned a value of 1 (high evenness).

BCR evenness cutoffs were derived using recurrence-free survival from TNBC patients in the Cancer Genome Atlas (TCGA) database[2]. A high sensitivity range was defined by identifying the range of IGHG evenness values over which the cumulative true positivity of identifying recurrence-free patients remained above 0.85 (Supplemental Figure 11D). Likewise, a high specificity range was defined by identifying the range of IGHG evenness values over which the cumulative true negativity remained above 0.7 (Supplemental Figure 11E). Within the sensitivity and specificity ranges, the local maximum sum of sensitivity and specificity was selected as the cutoff value (Supplemental Figure 11F).

Data Analyses. Statistical analysis was performed using R software with 'survival' and 'survminer' packages. As part of our exploratory analysis, p-values have not been corrected for multiple comparisons, however, both unadjusted and Benjamini-Hochberg False Discovery Rate (FDR) adjusted p-values are presented in Supplemental Tables 3-5. A generalized linear model of binomial classification was used to determine pathological complete response (pCR) hazard ratios (HR) and 95% confidence intervals (CI) for each feature, with values greater than 1 indicating an increased likelihood of pCR, and values less than 1 indicating less likelihood of pCR. Normalization of all data was performed by mean centering and standardizing each feature. Event-free survival (EFS) was evaluated using time-to-event univariate Cox Proportional Hazards (Cox PH) models for each feature. For interaction analyses, a Cox PH with terms for both treatment and feature, as well as term for the interaction (EFS ~ treatment + feature + treatment*feature) was used, with features selected having a p-value for the interaction term < 0.05.

Supplemental Methods References

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Supplemental Table 1 - Event-Free Survival (EFS), Overall Survival (OS) and Distant Recurrence-Free Interval (DRFI) Events by Treatment

	Arm 1: wP-ddAC	**Arm 2: +Bev**	**Arm 3: +Carbo**	**Arm 4: +Bev & Carbo**	**Total**
EFS Event (1st Event)	**33**	**36**	**37**	**29**	**135**
• PD/Recurrence	30	34	32	24	120
– Progression during NAC (ending in inoperability)	0	0	1	1	2
– Progression (Local or Distant) post NAC (no surgery)	0	1	1	0	2
– Local/Regional Recurrence (Post Surgery)	14	14	13	9	50
– Distant Recurrence (Post Surgery)	16	18	17	14	65
– DCIS/LCIS (non-invasive)	0	1	0	0	1
• Death (as first reported event)	3	2	5	5	15
– Due to the Disease	1	1	2	1	5
– Due to other Cause	1	0	2	2	5
– Unknown	1	1	1	2	5
1) No Event (Alive and Relapse Free)	**75**	**74**	**76**	**83**	**308**
OS Event					
1) Alive	**82**	**82**	**82**	**84**	**330**
2) Death	**26**	**28**	**31**	**28**	**113**
• Due to the Disease	19	24	26	23	92
• Due to other Cause	1	1	2	2	6
• Unknown	6	2	3	2	13
• Missing	0	1	0	1	2
DRFI Event					
1) DRFI Event (1st Event)	**25**	**28**	**28**	**22**	**103**
• Distant Recurrence	20	20	21	19	80
• Death (Due to the Disease)	5	8	7	3	23
2) Censor	**83**	**82**	**85**	**90**	**340**
• Alive and Distant Recurrence Free	79	78	80	86	323
• Contralateral Breast Cancer	1	1	1	0	3
• Second Primary Cancer (any site)	1	2	1	2	6
• Death	2	1	3	2	8
– Due to other Cause	1	0	1	1	3
– Unknown	3	1	2	2	8
– Missing	0	0	0	1	1

EFS = Event-fee survival; OS = Overall survival; DRFI = Distant recurrence-free interval; NAC = Neoadjuvant chemotherapy; wP = Weekly paclitaxel; ddAC = Dose-dense doxorubicin and cyclophosphamide; Bev=Bevacizumab; Carbo=Carboplatin; PD=Progressive disease; DCIS/LCIS = Ductal carcinoma in situ or lobular carcinoma in situ

Supplemental Table 2: Impact of the Addition of Carboplatin to Neoadjuvant Chemotherapy on Pathologic Complete Response (pCR) Rates in Triple-Negative Breast Cancer

Study	Control (no Cb) arm			Cb-containing regimen		
	N	Regimen	pCR	N	Regimen	pCR
CALGB 40603[1]	107	wP→ddAC	39%	111	wPq3Cb→ddAC	49%
	105	(wP→ddAC) + Bev	43%	110	(wPq3Cb→ddAC) + Bev	60%
BrighTNess[16]	158	wP→AC	31%	160	wPq3Cb→AC	58%
				316	wPq3CbVel→AC	53%
I-SPY2[17]	44	wP→AC	26%	39	wPq3CbVel→AC	51%
I-SPY2[18]		wP→AC	22%	NA		
GeparSepto[19]	137	wP→EC	26%	NA		
GeparSixto[15]	157	wPwnpLDBev	43%	158	wPwCbwnpLDBev	53%
KEYNOTE-522[20]	NA			84	wPq3Cb→AC/EC	56%
				116	wPwCb→AC/EC	48%
				165	(wPq3Cb→AC/EC) + Pembro	64%
				231	(wPwCb→AC/EC) + Pembro	67%
				466	10-12 doses of wPCb (-/+ Pembro)	55%/70%
				132	<10 doses of wPCb (-/+ Pembro)	36%/51%

pCR = ypT0/isN0; wP=weekly paclitaxel; (w)nP = (weekly)nab-paclitaxel; AC=doxorubicin and cyclophosphamide; dd=dose-dense (every 2 weeks); Bev=bevacizumab; q3Cb = every-3-week carboplatin; wCb=weekly carboplatin; Vel=veliparib (PO); EC=epirubicin and cyclophosphamide; wnpLD=weekly non-pegylated liposomal doxorubicin; Pembro=pembrolizumab; NA=not applicable

Supplemental Figure Legends

S1 – Study schema.

S2 – Survival outcomes for modified intent-to-treat (mITT) patients. A) overall survival (OS) and **B)** distant recurrence-free interval (DRFI).

S3 – Event-free survival (EFS), overall survival (OS) and distant recurrence-free interval (DRFI) by clinical patient subsets. A) OS and **B)** DRFI by pathological complete response (pCR) or residual disease (RD) status. **C)** OS by pCR and baseline stage. **D)** OS by residual cancer burden (RCB). **E)** EFS and **F)** OS by RCB and baseline stage. **G)** EFS and OS by pCR vs. RD for each of the study's arms

S4 – Impact of addition of bevacizumab or carboplatin on overall survival (OS) and distant recurrence-free interval (DRFI). A) OS stratified by bevacizumab treatment. **B)** OS stratified by carboplatin treatment. **C)** DRFI stratified by bevacizumab treatment. **D)** DRFI stratified by carboplatin treatment.

S5 – Forest plots for impact of addition of bevacizumab or carboplatin on event-free survival (EFS) and overall survival (OS) in patient subsets defined by clinical characteristics. Hazard ratios (HR) for patients with or without bevacizumab for **A)** EFS and **B)** OS; and for patients with or without carboplatin for **C)** EFS and **D)** OS.

S6 – Impact of weekly paclitaxel dose delivery on event-free survival (EFS). A) EFS for all patients stratified by number of doses of paclitaxel received. **B)** Effect of addition of carboplatin in patients who received at least 11 doses of paclitaxel (n = 324). **C)** Effect of addition of bevacizumab in patients who received at least 11 doses of paclitaxel.

S7 – Comparison of response and survival of triple-negative breast cancer patients by different subtyping methods. A) Quantification of TNBC tumors by (left to right) PAM50 and claudin-low (CLow) subtypes, TNBCtype and MDACC/BCM subtyping. **B)** pathological complete response (pCR) rates by subtype, as defined by (left to right) PAM50 + CLow, TNBCtype and MDACC/BCM classifications. Significance tested by chi-squared test with simulated p-values. **C)** Event-free survival (EFS) by TNBC subtypes as classified by (left to right) PAM50 + CLow, TNBCtype, MDACC/BCM methods. **D)** Comparison of subtype classifications between (left to right) TNBCtype and PAM50+CLow, PAM50+CLow and MDACC/BCM, and TNBCtype and MDACC/BCM methods.

S8 – Lymphocyte characteristics in triple-negative breast cancer. A) Percent TILs association with (left to right) stage, tumor stage, node status and pCR. Statistical significance determined using Student's T-test. **B)** Event-free survival (EFS) stratified at 10% intervals for TIL density cutoffs from 10% to 50%. **C)** Distribution of lymphocyte reads in triple-negative breast cancer samples. Total

immunoglobulin heavy chain (IGH), as well as individual heavy chain isoforms (IGHG, IGHA, IGHM) and T cell receptor beta (TRB) reads. **D)** Correlation between TILs percentage and (left to right) total TRB, total IGHG, and correlation between total IGHG reads and IgG evenness.

S9 – Selecting high sensitivity and high specificity IgG evenness cutoffs for triple-negative breast cancer patient stratification. A) Histogram of IGHG evenness values from CALGB 40603 TNBC patients with vertical lines at identified cutoff points. **B)** Deviance residuals of Cox PH model for EFS in CALGB 40603 with IGHG evenness as a continuous variable. Residuals (y-axis) of a well fit Cox PH model should be roughly symmetric about 0 with standard deviation about 1, suggesting that a Cox PH is not well fit for IGHG evenness as a continuous variable. **C)** IGHG evenness as a continuous variable versus Martingale residuals for CoxPH model. The lowess fitted line (black line) of a well fit model should be roughly linear, with no clear non-horizontal trend. **D)** Cumulative sensitivity by IgG evenness. The red horizontal line indicates the threshold of 0.85. The vertical violet line indicates the value at which sensitivity drops below 0.85, evenness values less than this value are considered for the low evenness cutoff. **E)** Cumulative specificity by IgG evenness. The red horizontal line indicates the threshold of 0.7. The vertical blue line indicates the value at which specificity increases above 0.7, values greater than this are considered for the high evenness cutoff. **F)** Sum of sensitivity and specificity by IgG evenness. IgG evenness at the value with maximum sum within the considered regions (left of violet line, right of blue line) were selected for IgG low and high cutoffs. **G)** Recurrence-Free Survival of TCGA TNBC patients stratified by derived IgG evenness cutoffs.

S10 – Features associated with event-free survival (EFS) in patients not receiving carboplatin. A) Forest plot of log2 hazard ratio (HR) and 95% confidence intervals (CI) for features significantly associated with EFS. **B)** Residual disease (RD) and pathological complete response (pCR) status of patients not receiving carboplatin stratified by IgG evenness groups. **C)** EFS for patients not receiving carboplatin stratified by IgG evenness groups.

S11 – Carboplatin and bevacizumab treatment-specific feature interactions on event-free survival (EFS). A) Table of features with significant interaction effect on EFS with carboplatin treatment. **B)** pathologic complete response (pCR) and EFS for patients not receiving carboplatin stratified by RB1 median expression. **C)** pCR and EFS for patients receiving carboplatin stratified by RB1 median expression. **D)** Table of features with significant interaction effect on EFS with bevacizumab treatment. **E)** pCR and EFS for patients not receiving bevacizumab stratified by Breast2Lung_LM2 signature correlation. **F)** pCR and EFS for patients receiving bevacizumab stratified by Breast2Lung_LM2 signature correlation. **G)** pCR and EFS for patients not receiving bevacizumab stratified by menopause status. **H)** pCR and EFS for patients receiving bevacizumab stratified by menopause status.

Figure S1

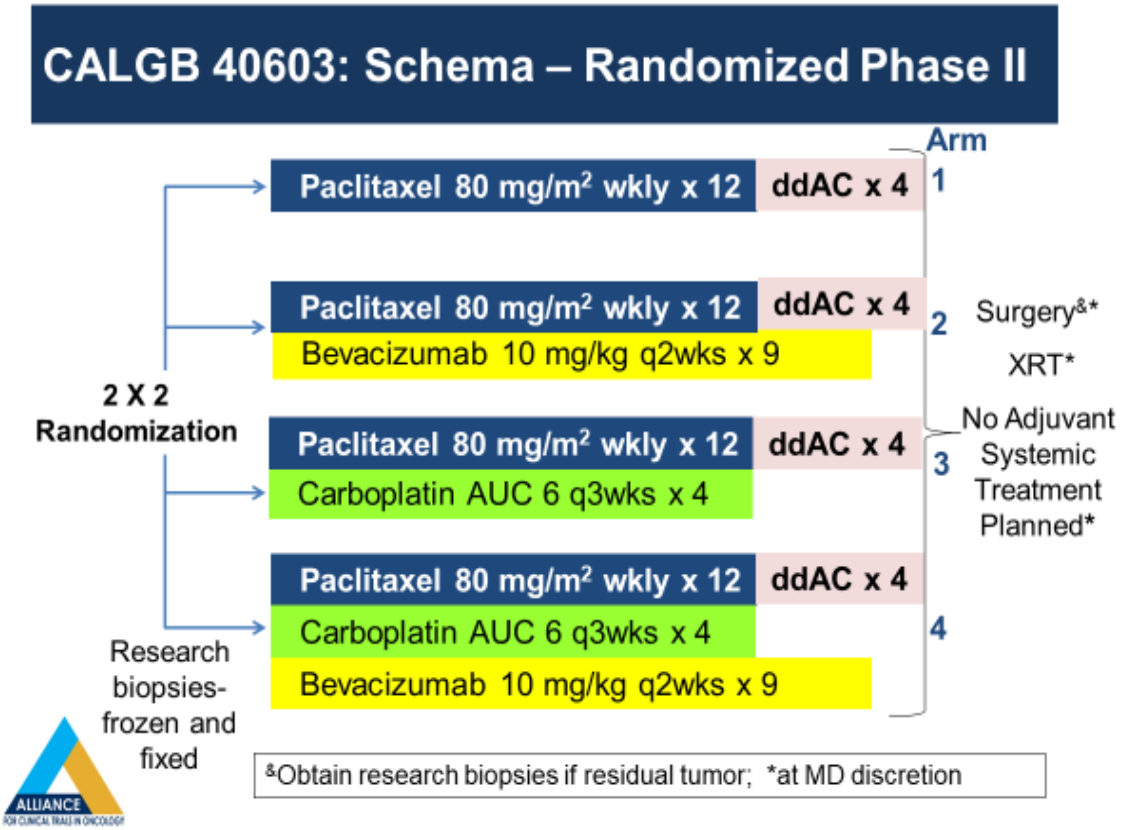
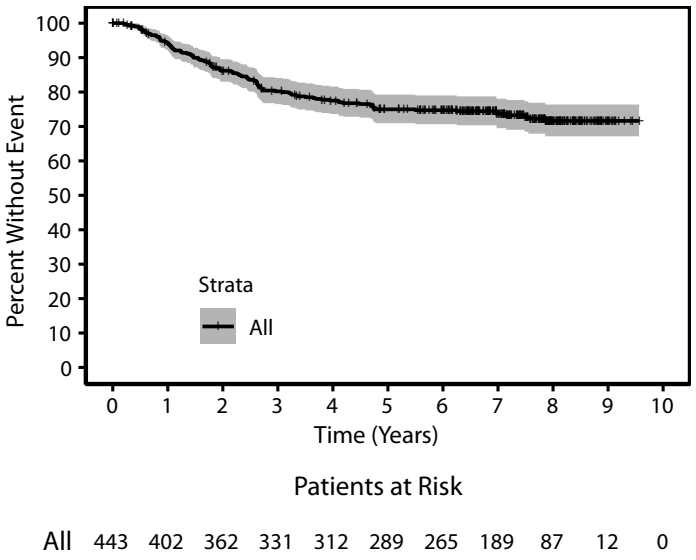

CALGB 40603: Schema – Randomized Phase II
Arm
Paclitaxel 80 mg/m² wkly x 12
ddAC x 4
1
Paclitaxel 80 mg/m² wkly x 12
ddAC x 4
Bevacizumab 10 mg/kg q2wks x 9
2
Surgery&*
XRT*
2 X 2 Randomization
Paclitaxel 80 mg/m² wkly x 12
ddAC x 4
Carboplatin AUC 6 q3wks x 4
3
No Adjuvant Systemic Treatment Planned*
Paclitaxel 80 mg/m² wkly x 12
ddAC x 4
Carboplatin AUC 6 q3wks x 4
Bevacizumab 10 mg/kg q2wks x 9
4
Research biopsies- frozen and fixed
ALLIANCE
&Obtain research biopsies if residual tumor; *at MD discretion

Figure S2

A



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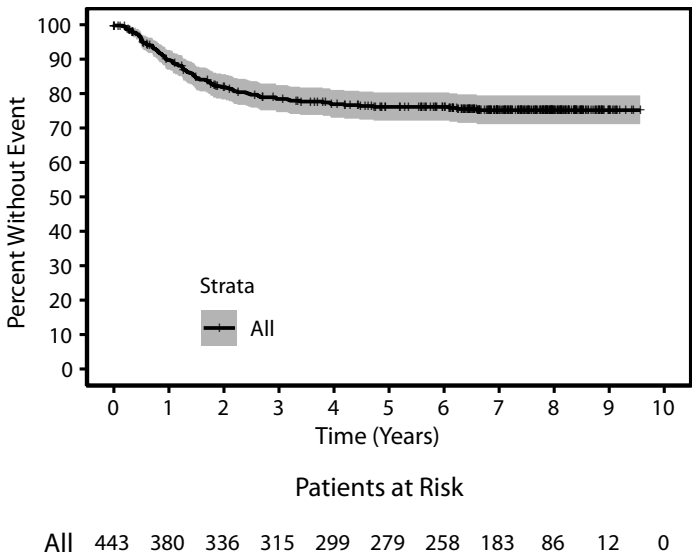
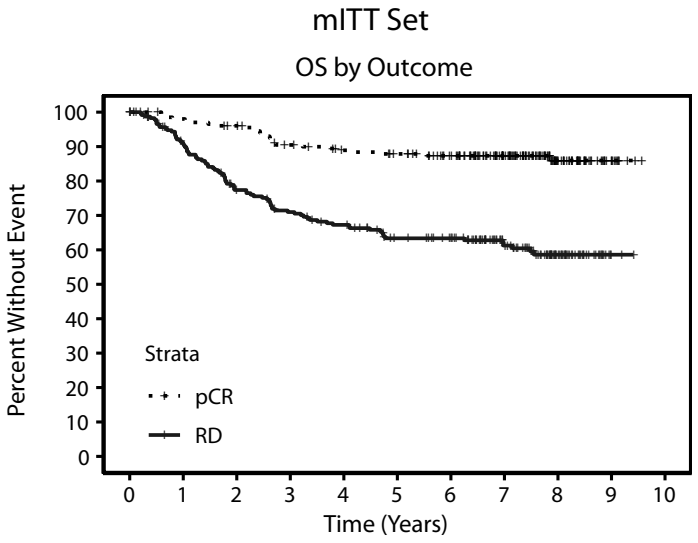


	Event/Total	Survival Es mates (95% CI)[1]
OS	113/443	5 Years: 75.0 (70.9-79.3%)
DRFI	103/443	5 Years: 76.1 (72.1-80.3%)

[1]Kaplan-Meier method

Figure S3

A



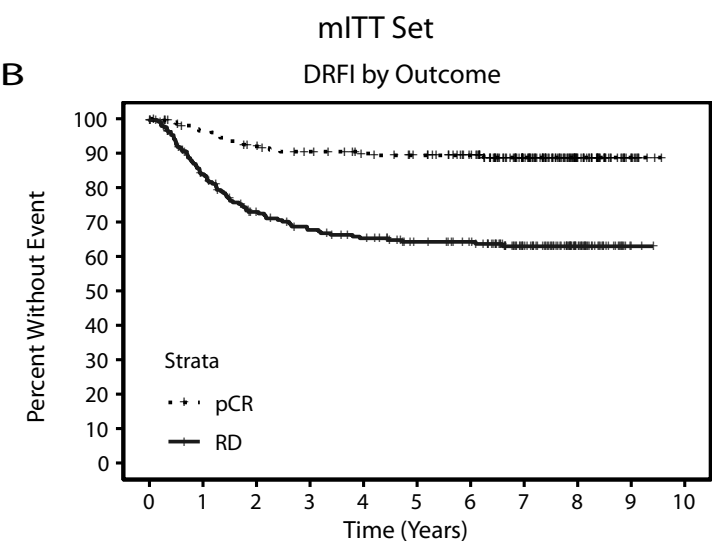
Patients at Risk

pCR	205	198	192	177	169	164	150	109	48	10	0
RD	238	204	170	154	143	125	115	80	39	2	0

	Event/Total	Survival Es mates (95% CI)[1]	Hazard Ra o (95% CI)[2]	P-value
Outcome				<.0001[3]
pCR	26/205	5 Years: 87.9 (83.4-92.5%)	0.28 (0.18-0.43)	
RD	87/238	5 Years: 63.4 (57.3-70.1%)	Reference	

[1]Kaplan-Meier method; [2]Cox model; [3]Logrank test;

B



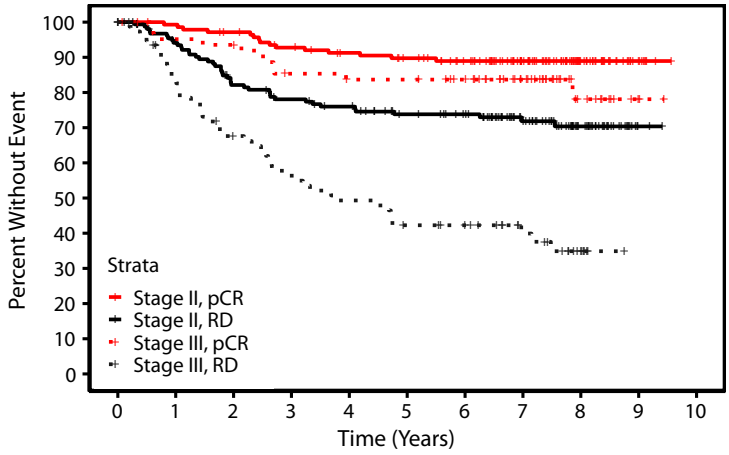
Patients at Risk

pCR	205	192	181	174	167	161	149	106	48	10	0
RD	238	188	155	141	132	118	109	77	38	2	0

	Event/Total	Survival Es mates (95% CI)[1]	Hazard Ra o (95% CI)[2]	P-value
Outcome				<.0001[3]
pCR	22/205	5 Years: 89.4 (85.2-93.8%)	0.26 (0.16-0.41)	
RD	81/238	5 Years: 64.2 (58.2-70.9%)	Reference	

[1]Kaplan-Meier method; [2]Cox model; [3]Logrank test;

C



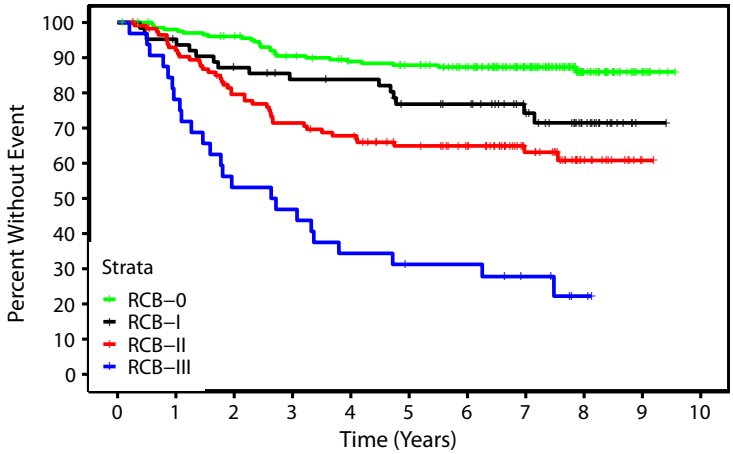
Patients at Risk

Stage II, pCR	141	139	134	126	120	115	105	77	36	8	0
Stage II, RD	159	142	122	114	108	96	90	63	31	2	0
Stage III, pCR	64	59	58	51	49	49	45	32	12	2	0
Stage III, RD	79	62	48	40	35	29	25	17	8	0	0

	Events/ Total	5yr Survival Est (95% CI)[1]	Hazard Ra o (95% CI)[2]	P-value[3]
pCR				0.1507
Stage II	15/141	89.7 (84.8 - 95.0%)	Reference	
Stage III	11/64	83.7 (74.9 - 93.5%)	1.76 (0.81 - 3.83)	
RD				<0.0001
Stage II	42/159	73.8 (67.1 - 81.2%)	Reference	
Stage III	45/79	42.3 (32.3 - 55.4%)	2.77 (1.82 - 4.22)	

[1]Kaplan-Meier method; [2]Cox model; [3]Logrank test

D



Patients at Risk

RCB–0	205	198	192	177	169	164	150	109	48	10	0
RCB–I	63	59	53	49	48	42	40	29	16	1	0
RCB–II	115	104	88	79	74	64	56	35	14	1	0
RCB–III	32	25	17	15	11	9	9	6	2	0	0

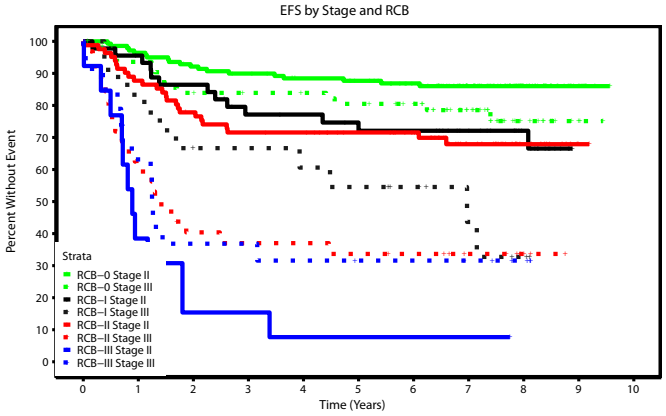
	Event/Total	Survival Es mates (95% CI)[1]	Hazard Ra o (95% CI)[2]	P-value
RCB class				<.0001[3]
RCB-0	26/205	5 Years: 87.9 (83.4-92.5%)	Reference	
RCB-I	16/63	5 Years: 76.8 (66.8-88.3%)	2.16 (1.16-4.03)	
RCB-II	41/115	5 Years: 64.9 (56.6-74.5%)	3.39 (2.07-5.54)	
RCB-III	24/32	5 Years: 31.3 (18.7-52.2%)	9.52 (5.45-16.62)	

[1]Kaplan-Meier method; [2]Cox model; [3]Logrank test;

Figure S3 (continued)

E

mITT Set



Patients at Risk

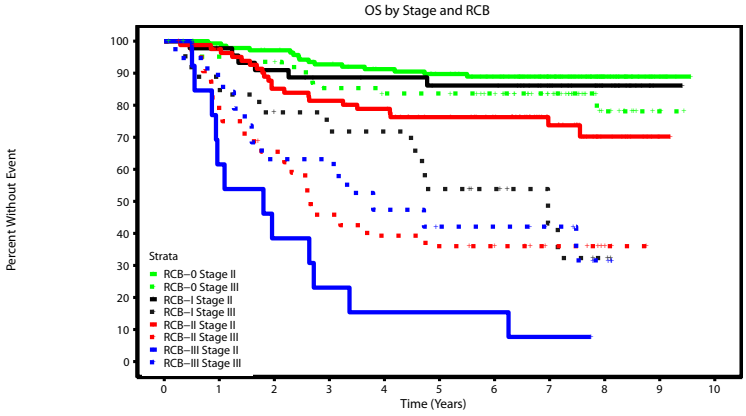
RCB–0 Stage II	141	135	127	122	116	112	102	75	35	8	0
RCB–0 Stage III	64	58	52	50	49	47	44	30	12	2	0
RCB–I Stage II	45	42	38	32	31	28	28	22	13	0	0
RCB–I Stage III	18	15	11	11	10	9	7	4	2	0	0
RCB–II Stage II	83	71	62	57	56	49	44	27	11	1	0
RCB–II Stage III	32	19	12	11	11	10	9	6	3	0	0
RCB–III Stage II	13	5	2	2	1	1	1	1	0	0	0
RCB–III Stage III	19	12	7	7	6	5	5	4	2	0	0

	Events/ Total	5yr Survival Est (95% CI)[1]	Hazard Ra o (95% CI)[2]	P-value[3]
RCB-0				0.1039
Stage II	19/141	87.7 (82.4 - 93.3%)	Reference	
Stage III	14/64	80.5 (71.2 - 91.0%)	1.76 (0.88 - 3.51)	
RCB-I				0.0304
Stage II	13/45	72.1 (59.8 - 86.9%)	Reference	
Stage III	10/18	54.5 (35.5 - 83.8%)	2.44 (1.06 - 5.61)	
RCB-II				<0.0001
Stage II	25/83	71.6 (62.4 - 82.1%)	Reference	
Stage III	21/32	33.7 (20.6 - 55.1%)	3.14 (1.75 - 5.64)	
RCB-III				0.1767
Stage II	12/13	7.7 (1.2 - 50.6%)	Reference	
Stage III	13/19	31.6 (16.3 - 61.2%)	0.58 (0.26 - 1.29)	

[1]Kaplan-Meier method; [2]Cox model; [3]Logrank test

F

mITT Set



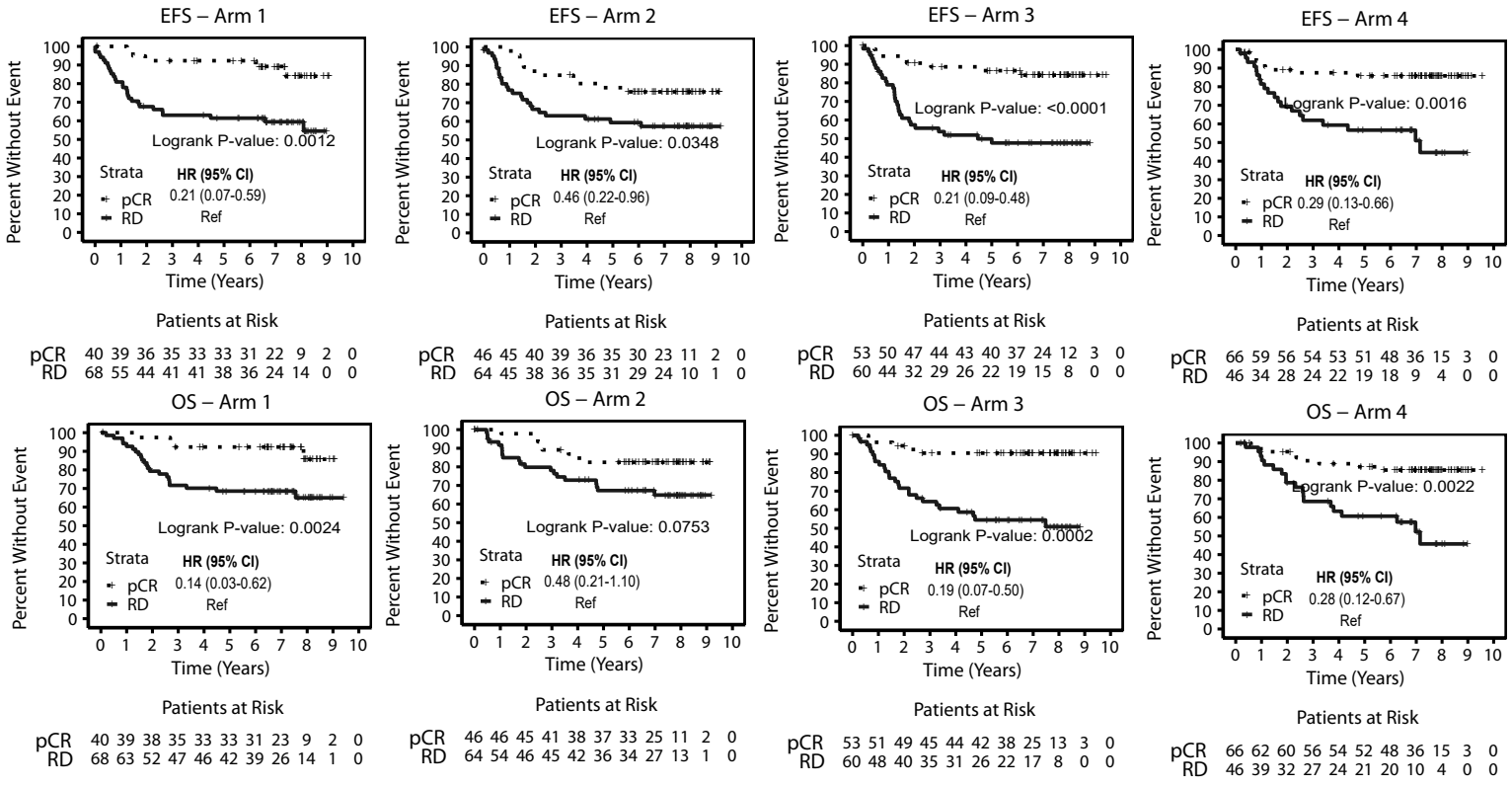
Patients at Risk

RCB–0 Stage II	141	139	134	126	120	115	105	77	36	8	0
RCB–0 Stage III	64	59	58	51	49	49	45	32	12	2	0
RCB–I Stage II	45	43	40	37	36	33	33	25	14	1	0
RCB–I Stage III	18	16	13	12	12	9	7	4	2	0	0
RCB–II Stage II	83	79	68	65	62	53	47	29	11	1	0
RCB–II Stage III	32	25	20	14	12	11	9	6	3	0	0
RCB–III Stage II	13	8	5	3	2	2	2	1	0	0	0
RCB–III Stage III	19	17	12	12	9	7	7	5	2	0	0

	Events/ Total	5yr Survival Est (95% CI)[1]	Hazard Ra o (95% CI)[2]	P-value[3]
RCB-0				0.1507
Stage II	15/141	89.7 (84.8 - 95.0%)	Reference	
Stage III	11/64	83.7 (74.9 - 93.5%)	1.76 (0.81 - 3.83)	
RCB-I				0.0004
Stage II	6/45	86.1 (76.4 -97.1%)	Reference	
Stage III	10/18	53.8 (34.7 - 83.5%)	5.28 (1.90 - 14.61)	
RCB-II				<0.0001
Stage II	21/83	76.3 (67.5 - 86.2%)	Reference	
Stage III	20/32	36.0 (22.5 - 57.6%)	3.39 (1.83 - 6.28)	
RCB-III				0.0361
Stage II	12/13	15.4 (4.3 - 55.0%)	Reference	
Stage III	12/19	42.1 (24.9 - 71.3%)	0.43 (0.19 - 0.97)	

[1]Kaplan-Meier method; [2]Cox model; [3]Logrank test

G



Patients at Risk

pCR	40	39	36	35	33	33	31	22	9	2	0
RD	68	55	44	41	41	38	36	24	14	0	0

Patients at Risk

pCR	46	45	40	39	36	35	30	23	11	2	0
RD	64	45	38	36	35	31	29	24	10	1	0

Patients at Risk

pCR	53	50	47	44	43	40	37	24	12	3	0
RD	60	44	32	29	26	22	19	15	8	0	0

Patients at Risk

pCR	66	59	56	54	53	51	48	36	15	3	0
RD	46	34	28	24	22	19	18	9	4	0	0

Patients at Risk

pCR	40	39	38	35	33	33	31	23	9	2	0
RD	68	63	52	47	46	42	39	26	14	1	0

Patients at Risk

pCR	46	46	45	41	38	37	33	25	11	2	0
RD	64	54	46	45	42	36	34	27	13	1	0

Patients at Risk

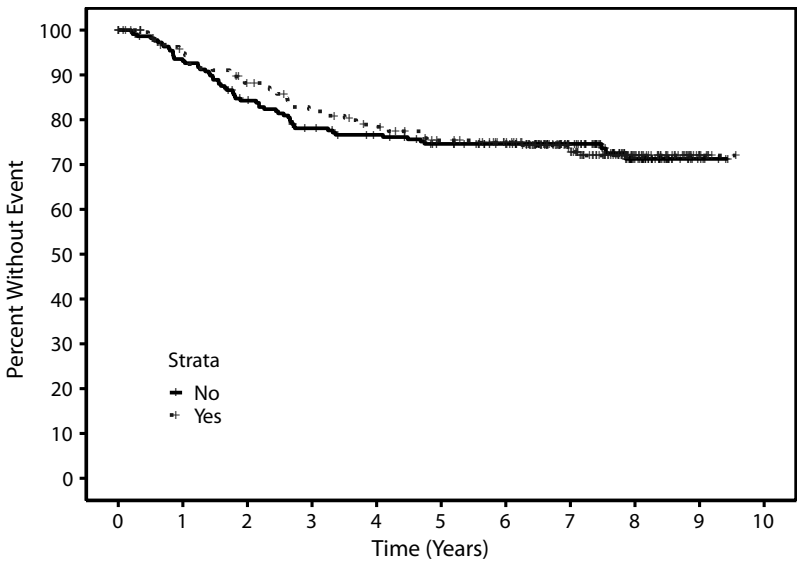
pCR	53	51	49	45	44	42	38	25	13	3	0
RD	60	48	40	35	31	26	22	17	8	0	0

Patients at Risk

pCR	66	62	60	56	54	52	48	36	15	3	0
RD	46	39	32	27	24	21	20	10	4	0	0

Figure S4

A



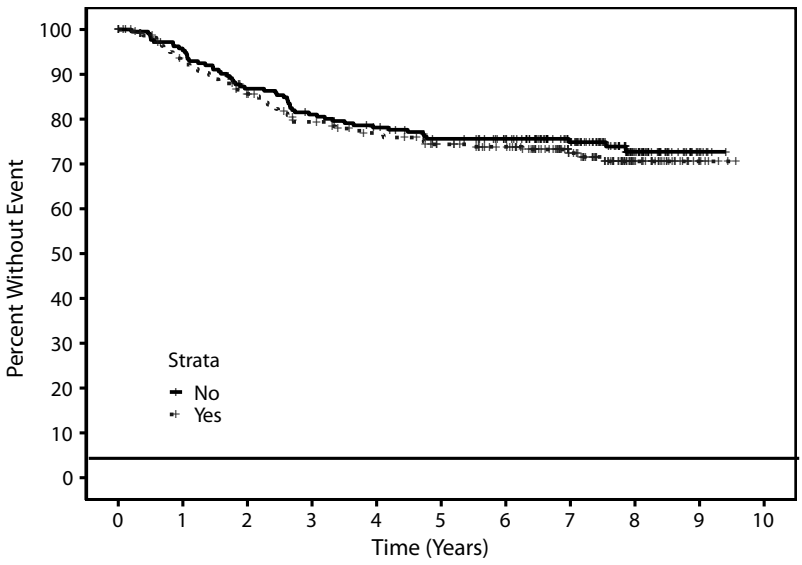
Patients at Risk

No	221	201	179	162	154	143	130	91	44	6	0
Yes	222	201	183	169	158	146	135	98	43	6	0

	Event/Total	Survival Es mates (95% CI)[1]	Hazard Ra o (95% CI)[2]	P-value
bev				0.8622[3]
No	57/221	5 Years: 74.6 (69.0-80.7%)	Reference	
Yes	56/222	5 Years: 75.4 (69.7-81.5%)	0.97 (0.67-1.40)	

[1]Kaplan-Meier method; [2]Cox model; [3]Logrank test;

B



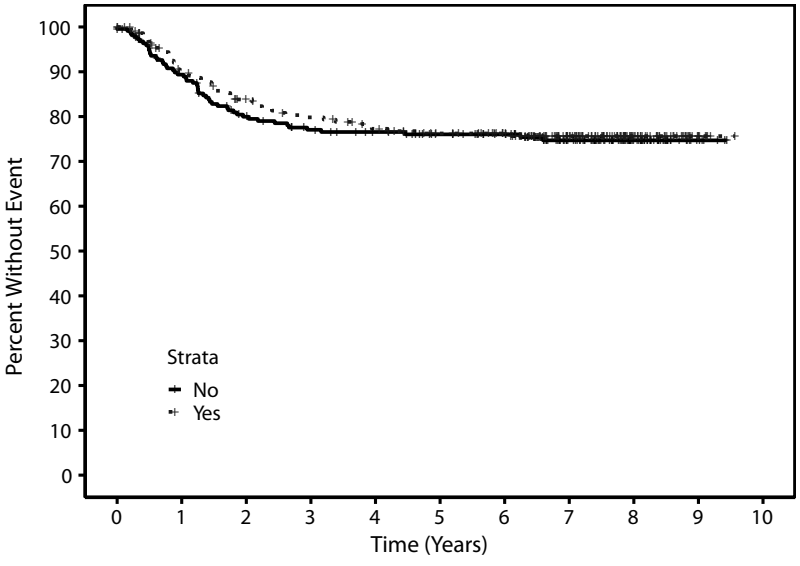
Patients at Risk

No	218	202	181	168	159	148	137	101	47	6	0
Yes	225	200	181	163	153	141	128	88	40	6	0

	Event/Total	Survival Es mates (95% CI)[1]	Hazard Ra o (95% CI)[2]	P-value
carbo				0.5585[3]
No	54/218	5 Years: 75.6 (70.0-81.7%)	Reference	
Yes	59/225	5 Years: 74.4 (68.7-80.5%)	1.12 (0.77-1.61)	

[1]Kaplan-Meier method; [2]Cox model; [3]Logrank test;

C



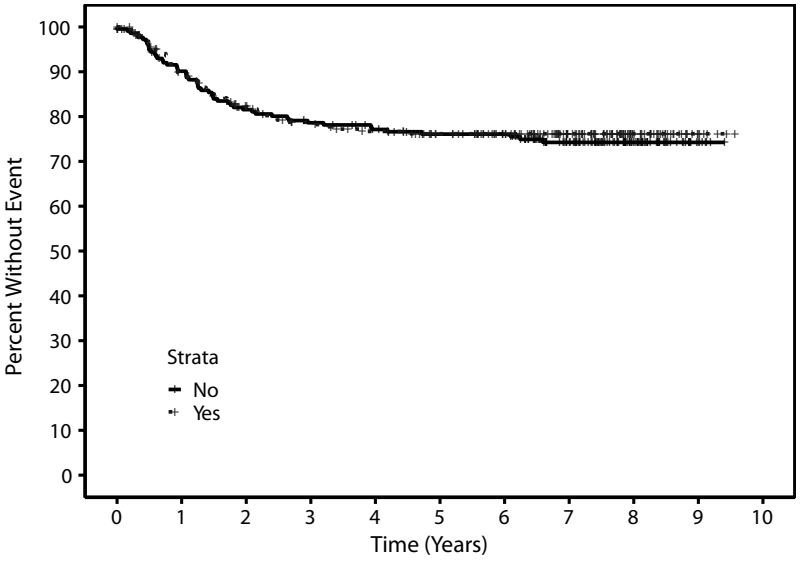
Patients at Risk

No	221	192	167	156	149	138	127	88	44	6	0
Yes	222	188	169	159	150	141	131	95	42	6	0

	Event/Total	Survival Es mates (95% CI)[1]	Hazard Ra o (95% CI)[2]	P-value
bev				0.7393[3]
No	53/221	5 Years: 76.0 (70.5-82.0%)	Reference	
Yes	50/222	5 Years: 76.2 (70.6-82.3%)	0.94 (0.64-1.38)	

[1]Kaplan-Meier method; [2]Cox model; [3]Logrank test;

D



Patients at Risk

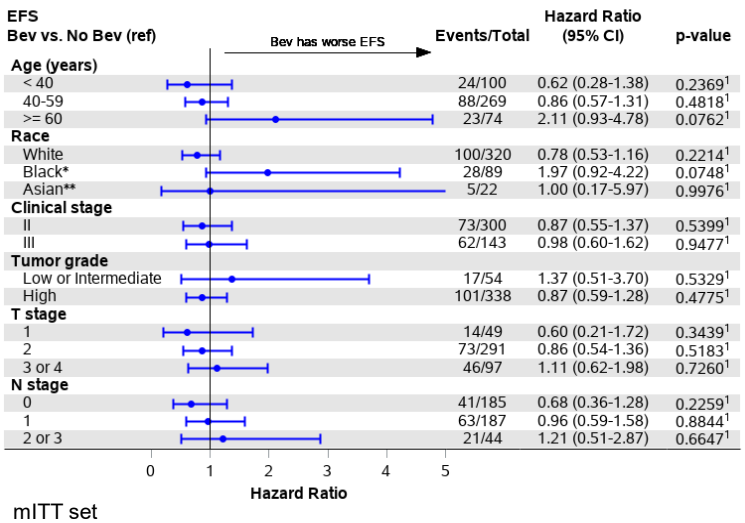
No	218	190	168	160	152	143	133	96	46	6	0
Yes	225	190	168	155	147	136	125	87	40	6	0

	Event/Total	Survival Es mates (95% CI)[1]	Hazard Ra o (95% CI)[2]	P-value
carbo				0.7480[3]
No	53/218	5 Years: 76.1 (70.5-82.1%)	Reference	
Yes	50/225	5 Years: 76.2 (70.6-82.2%)	0.94 (0.64-1.38)	

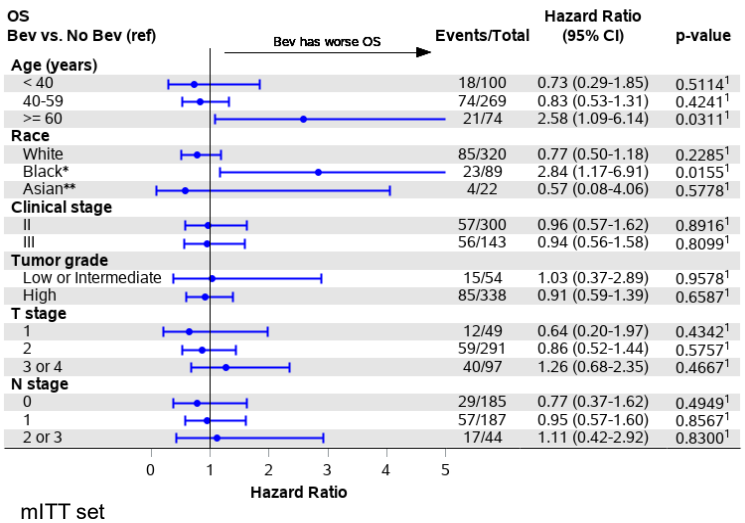
[1]Kaplan-Meier method; [2]Cox model; [3]Logrank test;

Figure S5

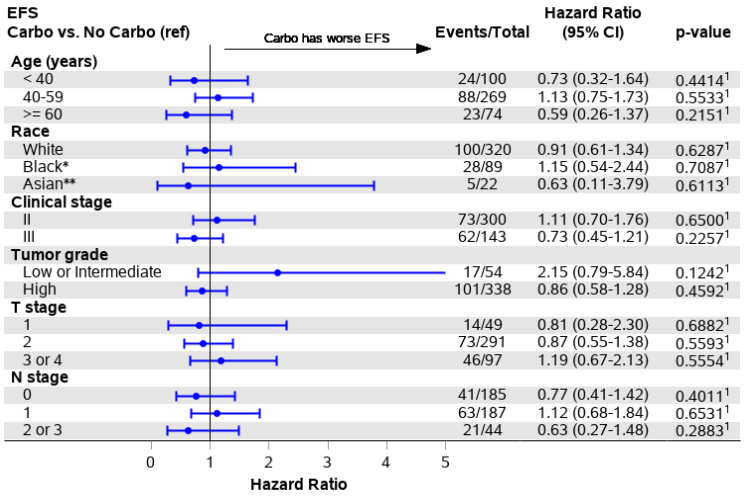
A mITT set



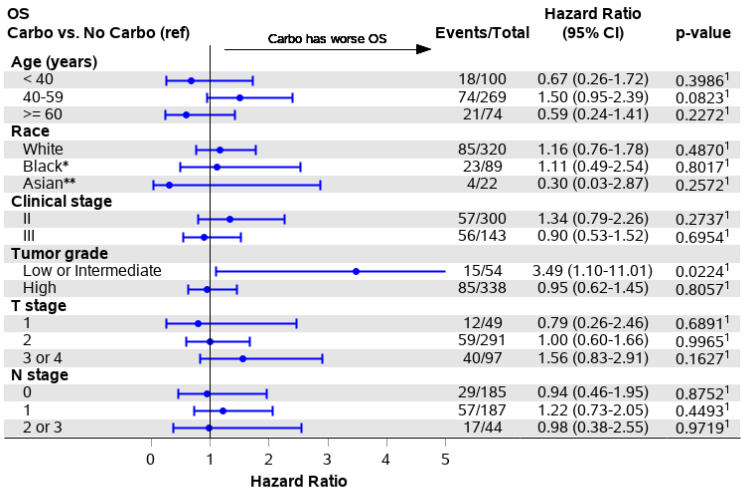
B mITT set



C mITT set



D mITT set

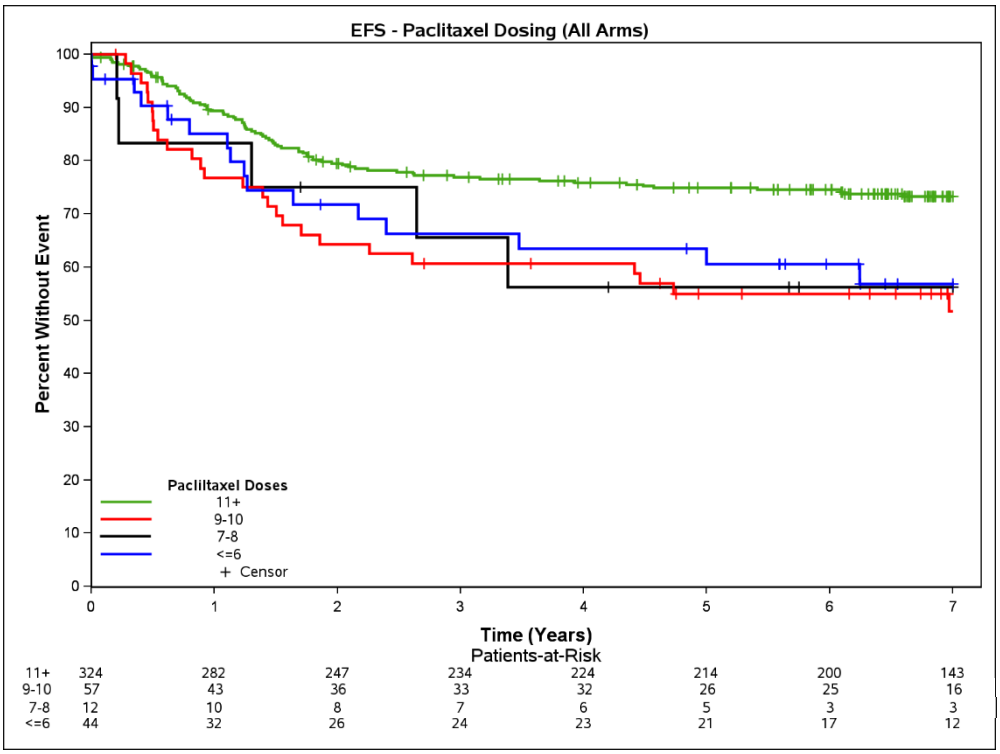


[1]Type 3 likelihood-ratio p-value;
*Black or African American
**Asian; Native Hawaiian or Pacific Islander; American Indian or Alaska Native; or More than one race

Figure S6

A

mITT set

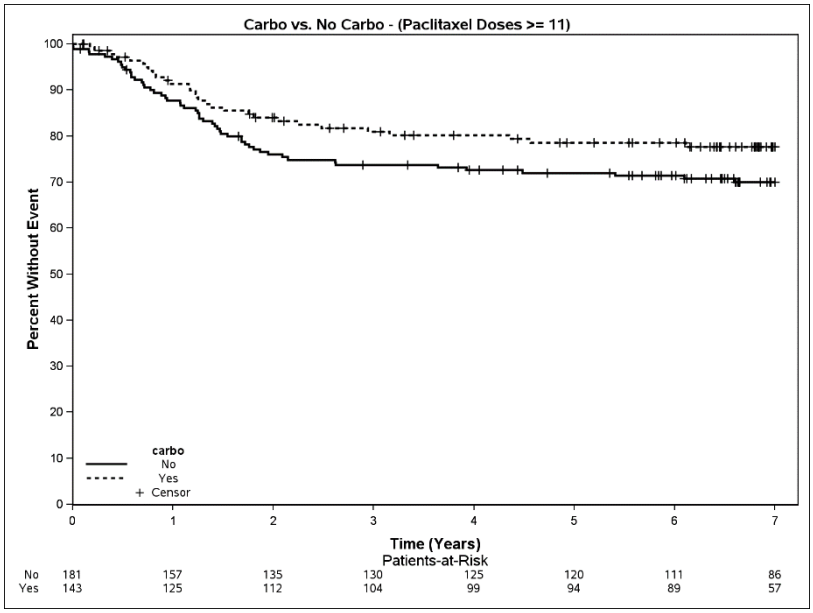


	Event/Total	Survival Estimates (95% CI)[1]	Hazard Ratio (95% CI)[2]	P-value
Paclitaxel Doses				0.0025[3]
11+	85/324	5 Years: 74.9 (70.2-79.8%)	Reference	
9-10	27/57	5 Years: 55.0 (43.3-69.8%)	2.09 (1.36-3.23)	
7-8	5/12	5 Years: 56.3 (33.6-94.3%)	1.85 (0.75-4.57)	
<=6	16/44	5 Years: 60.6 (46.8-78.5%)	1.73 (1.01-2.95)	

[1]Kaplan-Meier method; [2]Cox model; [3]Logrank test;

B

mITT set

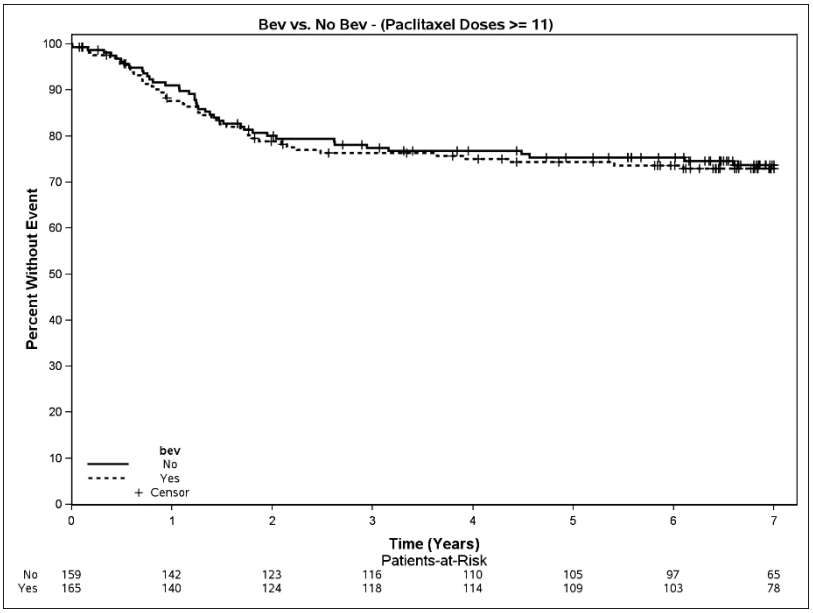


	Event/Total	Survival Estimates (95% CI)[1]	Hazard Ratio (95% CI)[2]	P-value
carbo				0.0892[3]
No	55/181	5 Years: 72.0 (65.7-78.9%)	Reference	
Yes	30/143	5 Years: 78.5 (71.9-85.8%)	0.68 (0.44-1.06)	

[1]Kaplan-Meier method; [2]Cox model; [3]Logrank test;

C

mITT set

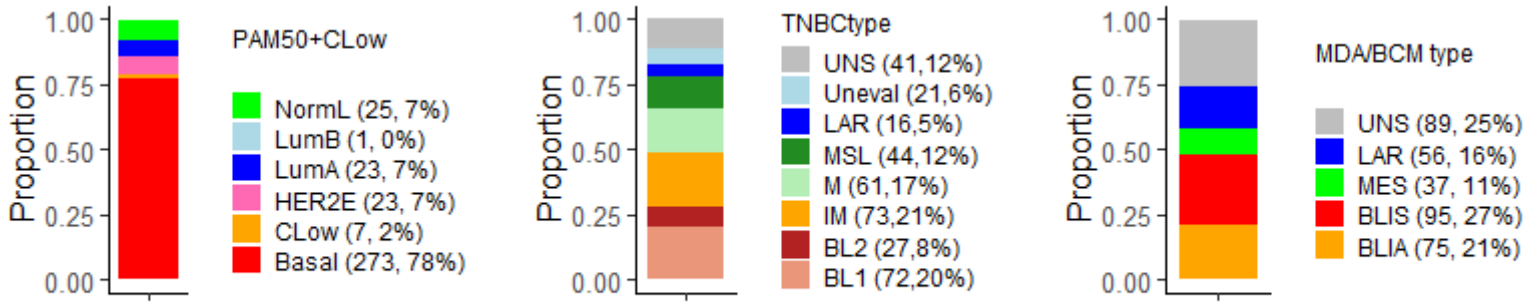


	Event/Total	Survival Estimates (95% CI)[1]	Hazard Ratio (95% CI)[2]	P-value
bev				0.9978[3]
No	42/159	5 Years: 75.4 (68.9-82.5%)	Reference	
Yes	43/165	5 Years: 74.3 (67.8-81.4%)	1.00 (0.65-1.53)	

[1]Kaplan-Meier method; [2]Cox model; [3]Logrank test;

Figure S7

A



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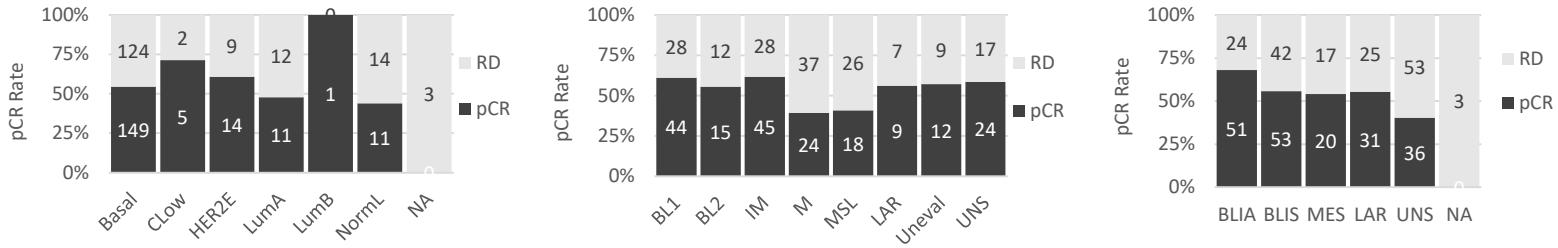
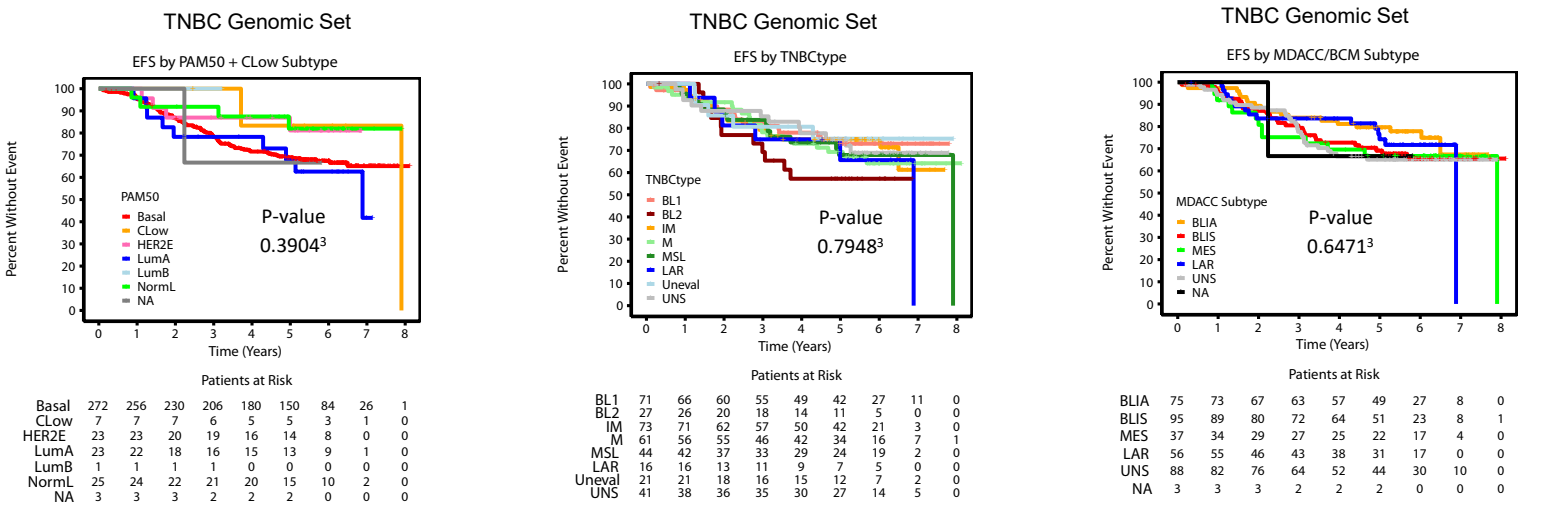


p = 0.0865

p = 0.0120

C



Patients at Risk

Basal	272	256	230	206	180	150	84	26	1
CLow	7	7	7	6	5	5	3	1	0
HER2E	23	23	20	19	16	14	8	0	0
LumA	23	22	18	16	15	13	9	1	0
LumB	1	1	1	1	0	0	0	0	0
NormL	25	24	22	21	20	15	10	2	0
NA	3	3	3	2	2	2	0	0	0

Patients at Risk

BL1	71	66	60	55	49	42	27	11	0
BL2	27	26	20	18	14	11	5	0	0
IM	73	71	62	57	50	42	21	3	0
M	61	56	55	46	42	34	16	7	1
MSL	44	42	37	33	29	24	19	2	0
LAR	16	16	13	11	9	7	5	0	0
Uneval	21	21	18	16	15	12	7	2	0
UNS	41	38	36	35	30	27	14	5	0

Patients at Risk

BLIA	75	73	67	63	57	49	27	8	0
BLIS	95	89	80	72	64	51	23	8	1
MES	37	34	29	27	25	22	17	4	0
LAR	56	55	46	43	38	31	17	0	0
UNS	88	82	76	64	52	44	30	10	0
NA	3	3	3	2	2	0	0	0	0

PAM50	Event/ Total	5yr Survival Est (95% CI)[1]	Hazard Ra o (95% CI)[2]	Cov. P-val
Basal	86/272	69.1 (63.7-74.9%)	2.19 (0.80-6.01)	0.1262[4]
CLow	2/7	83.3 (58.3-100.0%)	1.48 (0.27-8.19)	0.6528[4]
HER2E	4/23	81.2 (65.9-99.9%)	1.14 (0.29-4.60)	0.8488[4]
LumA	9/23	67.8 (50.6-90.9%)	2.79 (0.85-9.10)	0.0895[4]
LumB	0/1	NE (NE-NE%)	0.00 (0.00-)	0.9833[4]
NormL	4/25	82.0 (67.3-99.9%)	Reference	

[1]Kaplan-Meier method; [2]Cox model; [3]Logrank test;

TNBCtype	Event/ Total	5yr Survival Est (95% CI)[1]	Hazard Ra o (95% CI)[2]	Cov. P-val
BL1	18/71	73.0 (63.1-84.6%)	Reference	
BL2	11/27	57.2 (40.9-80.0%)	1.84 (0.87-3.90)	0.1116[4]
IM	20/73	75.0 (65.7-85.7%)	1.09 (0.58-2.07)	0.7854[4]
M	20/61	69.3 (58.4-82.2%)	1.27 (0.67-2.41)	0.4595[4]
MSL	14/44	67.9 (54.9-84.1%)	1.26 (0.62-2.54)	0.5189[4]
LAR	6/16	65.6 (44.6-96.5%)	1.54 (0.61-3.88)	0.3616[4]
Uneval	5/21	75.3 (58.6-96.8%)	0.88 (0.33-2.40)	0.8098[4]
UNS	12/41	75.1 (62.8-89.8%)	1.10 (0.53-2.29)	0.7965[4]

[1]Kaplan-Meier method; [2]Cox model; [3]Logrank test;

MDA/BCM	Event/ Total	5yr Survival Est (95% CI)[1]	Hazard Ra o (95% CI)[2]	Cov. P-val
BLIA	18/75	79.7 (71.0-89.4%)	0.67 (0.37-1.20)	0.1798[4]
BLIS	30/95	69.1 (60.2-79.4%)	0.95 (0.57-1.59)	0.8476[4]
MES	13/37	66.7 (53.0-84.1%)	1.04 (0.54-2.01)	0.9024[4]
LAR	15/56	74.2 (62.9-87.6%)	0.81 (0.43-1.50)	0.4972[4]
UNS	29/88	65.1 (55.5-76.3%)	Reference	

[1]Kaplan-Meier method; [2]Cox model; [3]Logrank test;

D

TNBCtype	Basal	CLow	HER2E	LumA	LumB	NormL
BL1	70					
BL2	20	1	4	1		1
IM	68	1	2	1	1	
M	59					2
MSL	16	5	1	7		15
LAR	1		13	2		
Uneval	2			10		6
UNS	35		3	2		1

Cramer's V = 0.424
Chi Square p = 5.0e-4

PAM50 + CLow	BLIA	BLIS	MES	LAR	UNS
Basal	75	95	19	8	76
CLow			3	1	3
HER2E				23	
LumA			5	18	
LumB					1
NormL			10	6	9

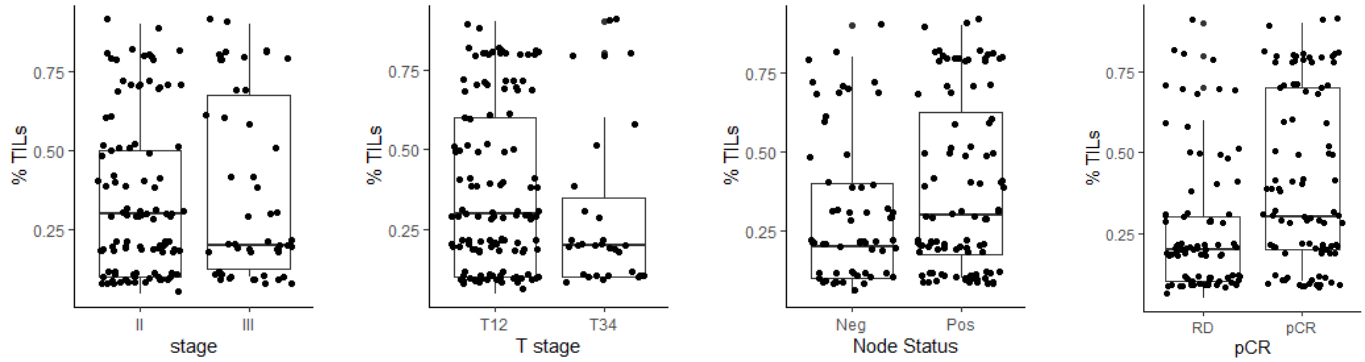
Cramer's V = 0.4045
Chi Square p = 5.0e-4

TNBCtype	BLIA	BLIS	MES	LAR	UNS
BL1	14	46			12
BL2	5	7	2	10	3
IM	46	2	6	4	15
M		28			33
MSL			21	10	13
LAR				15	1
Uneval	1	1	4	10	2
UNS	9	11	4	7	10

Cramer's V = 0.4667
Chi Square p = 5.0e-4

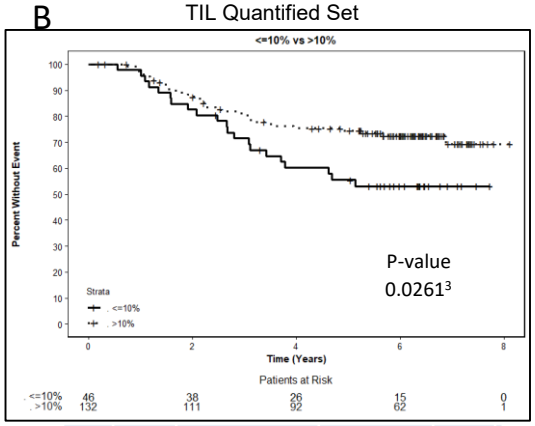
Figure S8

A



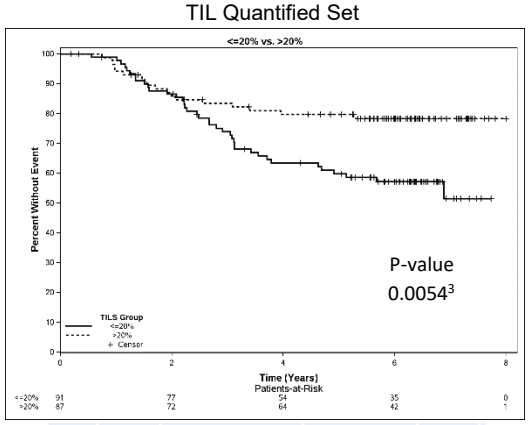
p = 0.457 p = 0.267 p = 0.0867 p = 5.43e-5

B



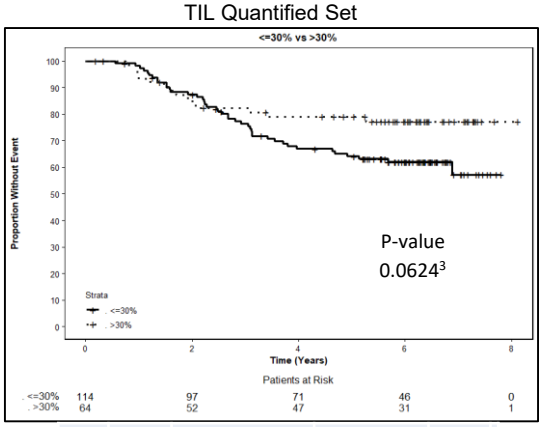
TILs	Event/ Total	5yr Survival Est (95% CI)[1]	Hazard Ratio (95% CI)[2]	Cov. P-val
<=10%	21/46	55.5 (42.6-72.2%)	Reference	
>10%	35/132	74.5 (67.3-82.6%)	0.46 (0.26-0.81)	0.0285[4]

[1]Kaplan-Meier method; [2]Cox model; [3]Logrank test;



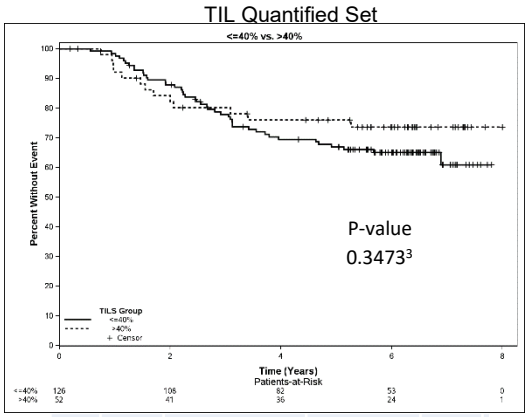
TILs	Event/ Total	5yr Survival Est (95% CI)[1]	Hazard Ratio (95% CI)[2]	Cov. P-val
<=20%	38/91	59.9 (50.4-71.1%)	Reference	
>20%	18/87	79.7 (71.6-88.8%)	0.46 (0.26-0.81)	0.0066[4]

[1]Kaplan-Meier method; [2]Cox model; [3]Logrank test;



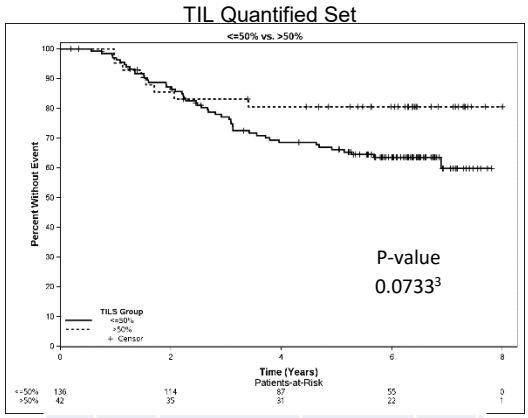
TILs	Event/ Total	5yr Survival Est (95% CI)[1]	Hazard Ratio (95% CI)[2]	Cov. P-val
<=30%	42/114	64.2 (55.7-73.9%)	Reference	
>30%	14/64	79.0 (69.5-89.9%)	0.46 (0.26-0.81)	0.066[4]

[1]Kaplan-Meier method; [2]Cox model; [3]Logrank test;



TILs	Event/ Total	5yr Survival Est (95% CI)[1]	Hazard Ratio (95% CI)[2]	Cov. P-val
<=40%	43/126	66.9 (59.0-75.9%)	Reference	
>40%	13/52	76.0 (65.0-88.8%)	0.74 (0.40-1.38)	0.3493[4]

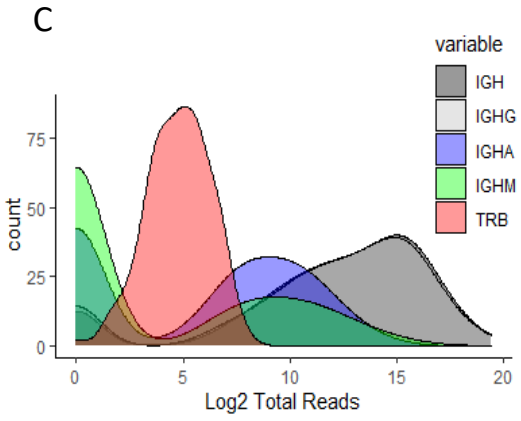
[1]Kaplan-Meier method; [2]Cox model; [3]Logrank test;



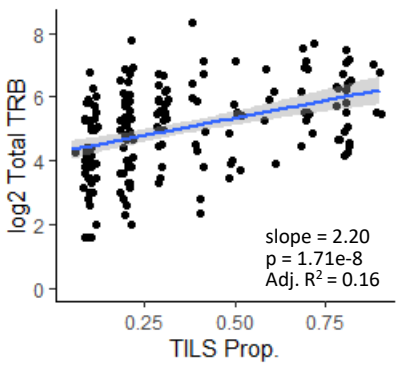
TILs	Event/ Total	5yr Survival Est (95% CI)[1]	Hazard Ratio (95% CI)[2]	Cov. P-val
<=50%	38/91	66.2 (58.5-74.8%)	Reference	
>50%	18/87	80.5 (69.2-93.6%)	0.51 (0.24-1.08)	0.0789[4]

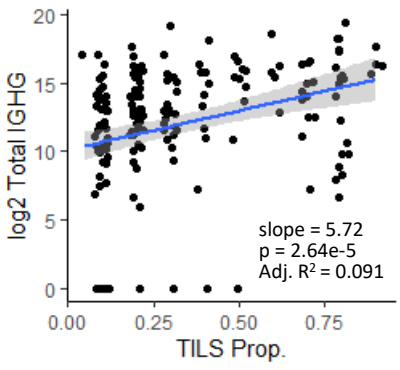
[1]Kaplan-Meier method; [2]Cox model; [3]Logrank test;

C



D





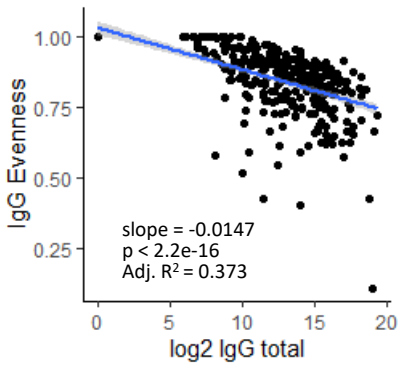
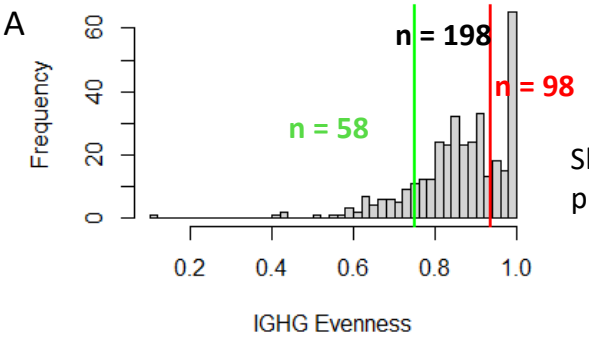
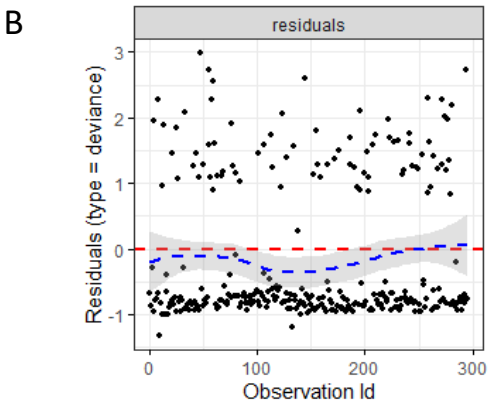
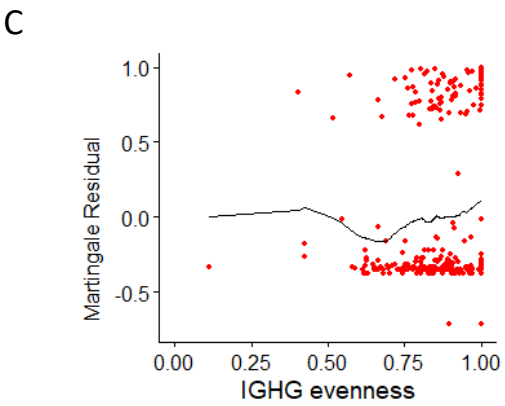


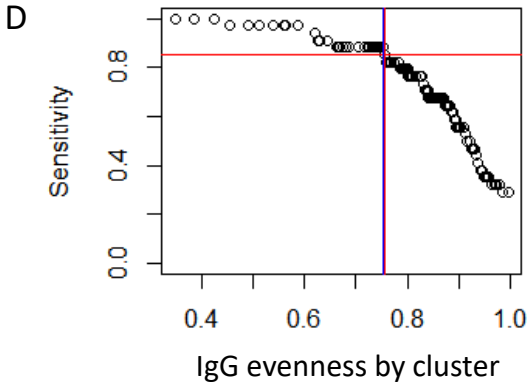
Figure S9

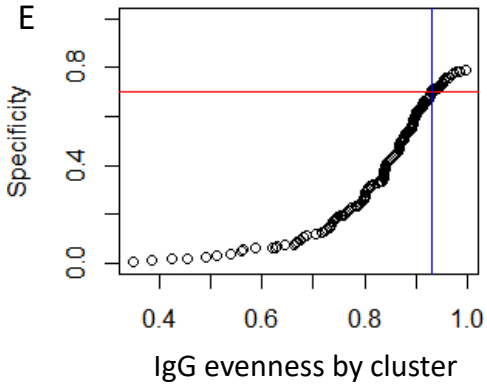


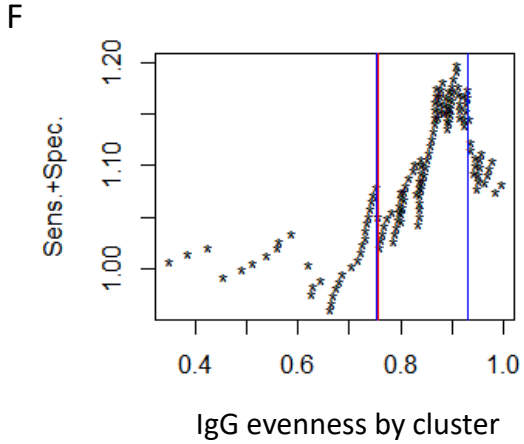
Shapiro-Wilk normality test
p = 6.584 e-15











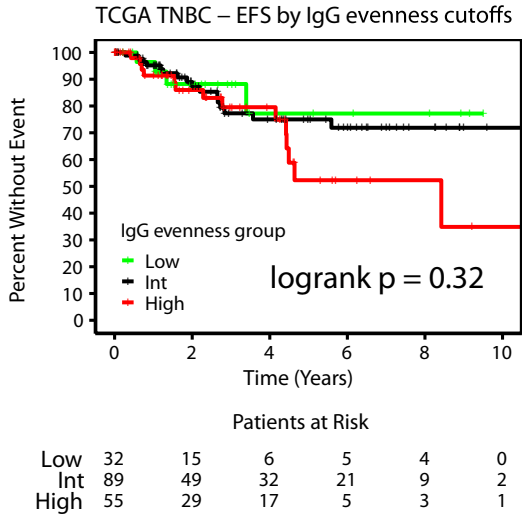
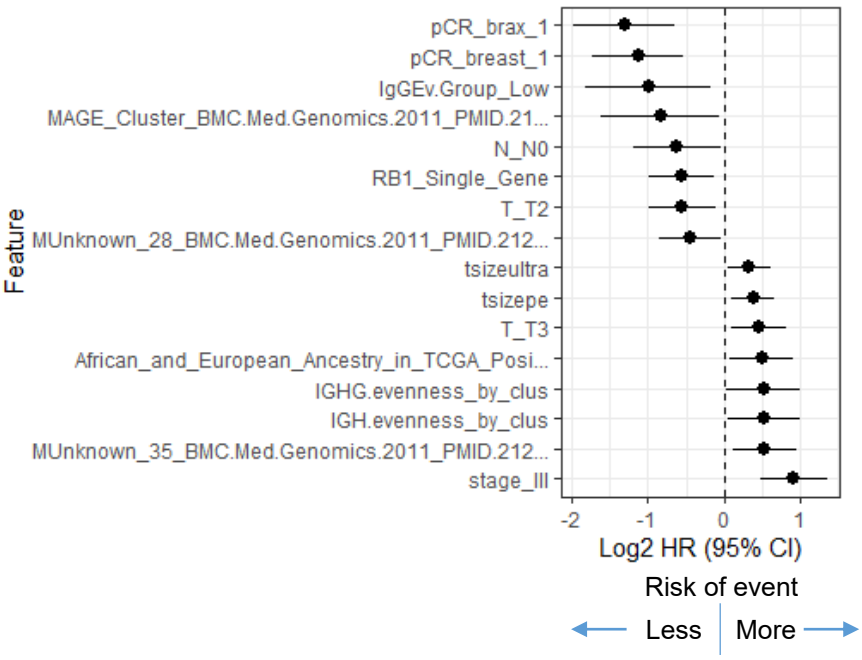


Figure S10

A



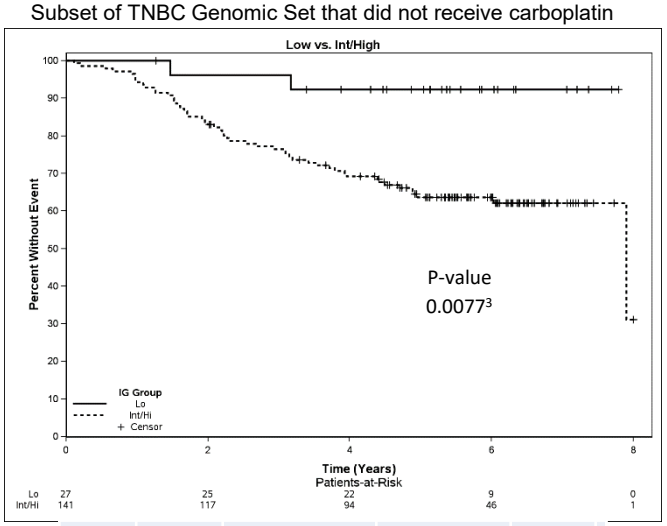
B

	IG.even High	IG.even Int	IG.even Low
RD	26	55	10
pCR	14 (0.35)	46 (0.46)	17 (0.63)

chi squared test, p= 0.086

C

Subset of TNBC Genomic Set that did not receive carboplatin



IgG Evenness	Event/ Total	5yr Survival Est (95% CI)[1]	Hazard Ratio (95% CI)[2]	Cov. P-val
Low	2/27	92.3 (82.6-100.0%)	Reference	
Int/High	52/141	63.6 (56.0-72.2%)	0.53 (0.34-0.84)	0.0071[4]

[1]Kaplan-Meier method; [2]Cox model; [3]Logrank test;

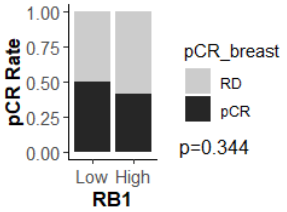
A

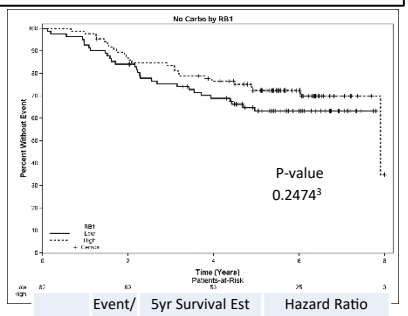
Figure S11

Feature	HR - carbo	HR - Feature	HR - Interact	p.val Carbo	p.val Feature	p.val Interact
RB1_Single_Gene	0.88	0.68	2.14	0.52	0.011	0.00017
Duke_Module09_hypoxia_Mike_PMID.20335537	0.87	0.78	1.68	0.48	0.090	0.00910
15q25_Amplicon_BMC.Med.Genomics.2011_PMID.21214954	0.83	0.91	1.58	0.35	0.51	0.017
HS_Green11_BMC.Med.Genomics.2011_PMID.21214954	0.93	0.72	1.65	0.73	0.064	0.023
GSEA_GP18_Vesicle_EPR_membrane_coat.r=0.877_MEMBRANE_COAT	0.86	0.89	1.56	0.46	0.39	0.025
Mouse_Human_ImmuneProfiles_SHAY_M_H_Induced_in_DC_PNAS.2013_PMID.23382184_	0.90	0.81	1.50	0.61	0.094	0.033
Unknown_3_BMC.Med.Genomics.2011_PMID.21214954	0.87	0.87	1.56	0.50	0.38	0.036
IGHG.second_top_clone	0.96	1.24	0.66	0.84	0.088	0.038
TILS.group20_>20%	1.27	0.89	0.43	0.47	0.67	0.040
Charoentong_CD56bright_natural_killer_cell_CellRep.2017_PMID.28052254	0.89	0.85	1.50	0.56	0.26	0.045
GRADE_2	0.78	0.88	1.55	0.27	0.46	0.047

B

No Carbo



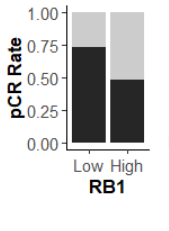


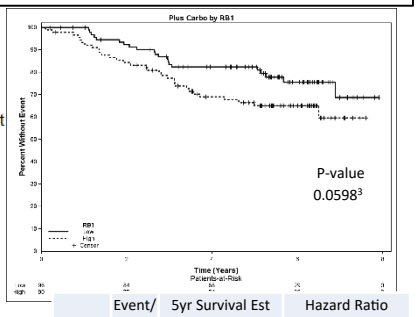
RB1	Event/ Total	5yr Survival Est (95% CI)[1]	Hazard Ratio (95% CI)[2]
Low	29/82	63.2 (53.3-74.9%)	Reference
High	25/86	72.5 (63.4-82.7%)	0.73 (0.42-1.25)

[1]Kaplan-Meier method; [2]Cox model; [3]Logrank test;

C

Plus Carbo





RB1	Event/ Total	5yr Survival Est (95% CI)[1]	Hazard Ratio (95% CI)[2]
Low	21/96	82.3 (74.8-90.6%)	Reference
High	31/90	65.1 (55.7-76.1%)	1.69 (0.97-2.95)

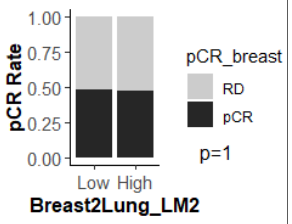
[1]Kaplan-Meier method; [2]Cox model; [3]Logrank test;

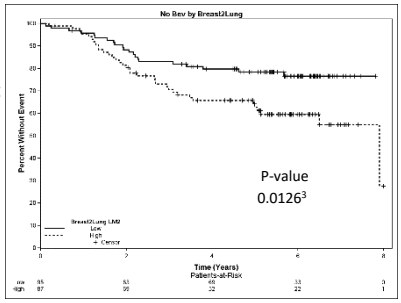
D

Feature	HR - Bev	HR - Feature	HR - Interact	p.val Bev	p.val Feature	p.val Interact
Pcorr_Breast2Lung_LM2_Correlation_Nature.2005_PMID.16049480	0.97	1.41	0.57	0.88	0.017	0.00443
meno_1	0.56	0.77	2.08	0.04	0.156	0.00639
Duke_Module02_akt_Mike_PMID.20335537	0.87	1.21	0.60	0.49	0.14	0.008
IGHA.top_clone_prop	0.90	0.73	1.73	0.59	0.040	0.008
FOS_JUN_Cluster_BMC.Med.Genomics.2011_PMID.21214954	0.96	1.22	0.61	0.85	0.08	0.013
Pcorr_Breast2Lung_Parental_Correlation_Nature.2005_PMID.16049480	0.96	0.71	1.62	0.85	0.019	0.016
Unknown_14_BMC.Med.Genomics.2011_PMID.21214954	0.93	1.15	0.63	0.74	0.31	0.020
MAPK_pathway_activation_Wagle_NPJ.Precis.Oncol.2018_PMID.29872725	0.89	1.10	0.65	0.55	0.486	0.028
IGHM.total_counts	1.14	0.99	0.00	0.50	0.93	0.033
IGK.total_counts	1.04	1.01	0.29	0.83	0.96	0.034
Duke_Module15_p63_Mike_PMID.20335537	0.93	1.37	0.67	0.73	0.03	0.048
IGHM.num_unique_clus	1.11	0.99	0.46	0.63	0.96	0.048

E

No Bev



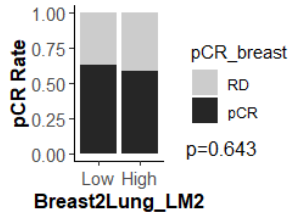


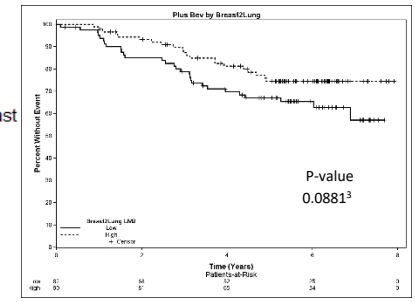
B2Lung_LM2	Event/ Total	5yr Survival Est (95% CI)[1]	Hazard Ratio (95% CI)[2]
Low	21/95	78.5 (70.5-87.3%)	Reference
High	35/87	62.7 (53.0-74.1%)	1.97 (1.15-3.40)

[1]Kaplan-Meier method; [2]Cox model; [3]Logrank test;

F

Plus Bev

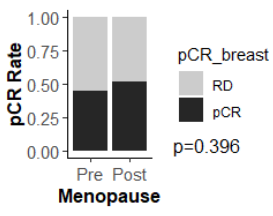


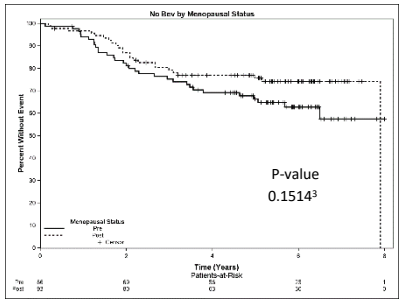


B2Lung_LM2	Event/ Total	5yr Survival Est (95% CI)[1]	Hazard Ratio (95% CI)[2]
Low	29/82	67.0 (57.4-78.3%)	Reference
High	21/90	74.5 (65.6-84.6%)	0.62 (0.35-1.08)

[1]Kaplan-Meier method; [2]Cox model; [3]Logrank test;

G

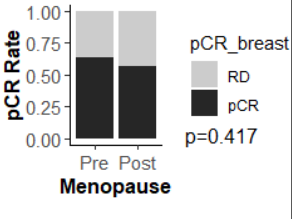


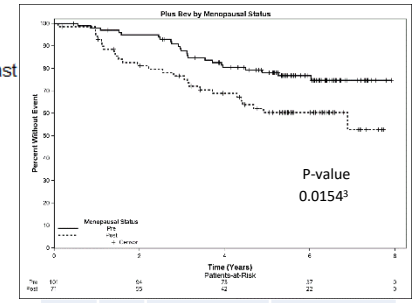


Meno	Event/ Total	5yr Survival Est (95% CI)[1]	Hazard Ratio (95% CI)[2]
Pre	31/86	66.4 (56.9-77.4%)	Reference
Post	24/93	75.6 (67.2-85.1%)	0.68 (0.40-1.16)

[1]Kaplan-Meier method; [2]Cox model; [3]Logrank test;

H





Meno	Event/ Total	5yr Survival Est (95% CI)[1]	Hazard Ratio (95% CI)[2]
Pre	23/101	78.1 (70.2-86.9%)	Reference
Post	27/71	60.4 (49.5-73.6%)	1.96 (1.13-3.43)

[1]Kaplan-Meier method; [2]Cox model; [3]Logrank test;