Tumor-Infiltrating Lymphocytes as a Predictor of Adjuvant Avelumab Efficacy in Patients with High-risk Triple-Negative Breast Cancer

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ABSTRACT

Purpose: We aimed to investigate the prognostic and predictive value of tumor-infiltrating lymphocytes (TIL) for adjuvant immunotherapy in high-risk early triple-negative breast cancer (TNBC).

Patients and Methods: The phase III A-BRAVE trial randomized 466 patients with high-risk early TNBC to adjuvant avelumab or observation after standard therapy. Inclusion criteria allowed 2 strata: stratum A (primary surgery followed by adjuvant chemotherapy, defined at high risk based on pathologic stage) and stratum B (neoadjuvant chemotherapy followed by surgery without pathologic complete response). TILs were centrally assessed on treatment-naïve tumor samples [baseline TILs (BSL-TIL)] and on residual disease (RD) after neoadjuvant chemotherapy (RD-TILs, stratum B). Residual cancer burden (RCB) was assessed in stratum B. Survival endpoints were disease-free survival (DFS), distant DFS (DDFS), and overall survival (OS).

Results: BSL-TILs were available for 387 patients and RD-TILs for 330 patients (290 with both BSL-TILs and RD-TILs). Higher BSL-TILs were independently associated with improved outcomes across all endpoints. In stratum B, higher RD-TILs showed a significant independent association with improved outcomes, outperforming BSL-TILs. RCB was also independently prognostic. Avelumab improved outcomes only for patients with BSL-TILs ≥30%, particularly in stratum B (3-year DDFS rates, 92% vs. 58.7%; HR, 0.20 in high BSL-TILs and 70.4% vs. 70.1%, HR, 0.92 in low BSL-TILs; interaction $P = 0.019$). Similar results were obtained for DFS and OS. RCB was not predictive for avelumab benefit.

Conclusions: TILs may predict benefit from adjuvant immunotherapy in early TNBC. These findings warrant validation and support TIL-guided immunotherapy strategies in future trials.

Introduction

For patients with cT (clinical tumor size) ≥2 and/or clinical nodal status cN1 to cN2 triple-negative breast cancer (TNBC), neoadjuvant chemotherapy (NACT) combined with pembrolizumab, followed by adjuvant pembrolizumab after surgery, is the current standard. This approach is based on the KEYNOTE-522 trial, which demonstrated an improvement in pathologic complete response (pCR), event-free survival (EFS), and overall survival (OS) with pembrolizumab (1–3).

Despite this major advance, several aspects remain unsolved to optimize immunotherapy in this setting. Immunotherapy is associated with a broad spectrum of immune-related adverse events (irAE; ref. 4), which can sometimes be long-lasting or, albeit rarely, fatal. In KEYNOTE-522, the rate of grade ≥3 irAEs was 13% (2), and emerging evidence suggests even higher rates in real-world settings (5).

Moreover, other trials investigating immunotherapy in early TNBC have reported controversial and inconsistent results, particularly with regard to survival outcomes (6–12).

Unfortunately, there are currently no biomarkers available to guide immunotherapy in early TNBC. Unlike in the metastatic setting, PD-L1 expression is not predictive of pembrolizumab benefit (1–3), and no clinically relevant/applicable biomarker has yet emerged from the translational analyses conducted within the trial (13).

Tumor-infiltrating lymphocytes (TIL) are an established independent prognostic biomarker in early TNBC, with their value consistently

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Translational Relevance

Immune checkpoint inhibitors improve outcomes in early triple-negative breast cancer (TNBC), but biomarkers able to identify patients deriving the greatest benefit remain incompletely defined. Tumor-infiltrating lymphocytes (TIL) are robust indicators of antitumor immune activity and have established prognostic value in TNBC, yet their predictive role in immunotherapy is less clear. In this translational analysis of the randomized A-BRAVE study evaluating adjuvant avelumab in patients with high-risk TNBC, we investigated whether stromal TIL levels are associated with treatment benefit. Our findings suggest that the immune microenvironment, as reflected by TILs, may help refine patient selection for immune checkpoint blockade in the adjuvant setting. These results support the integration of immune biomarkers into the design of future immunotherapy trials and propose a framework for biomarker-driven immunotherapy personalization that requires validation in independent datasets.

confirmed across different populations. In patients undergoing primary surgery, TILs are prognostic both in those treated with adjuvant chemotherapy (14, 15) and in those receiving locoregional therapy only without any systemic treatment (14, 16, 17). In patients receiving NACT, TILs assessed on pretreatment core biopsies are associated with an increased likelihood of achieving pCR (18) and with improved long-term outcomes (18, 19). Furthermore, in patients with residual disease (RD) after NACT, TILs evaluated in posttreatment surgical specimens can stratify prognosis (20). In this context, both TILs and residual cancer burden (RCB) index, which quantifies the extent of RD (21), are independently prognostic and help dissect the clinical heterogeneity of patients with RD after NACT, a population overall considered at high risk (22).

Currently, the main clinical application of TILs under prospective evaluation is their role in guiding treatment de-escalation strategies for patients with high TIL levels (NCT06476119 and NCT06078384). Although there is a strong biological rationale to evaluate TILs as predictive markers of immunotherapy benefit, this role remains underexplored.

The phase III A-BRAVE trial (12) tested 1 year of adjuvant anti–PD-L1 therapy with avelumab versus observation for patients with early TNBC at high risk of relapse. In the current study, we investigated the prognostic and predictive role of TILs and RCB in the context of the A-BRAVE trial (12).

Patients and Methods

Population

A-BRAVE (NCT02926196) was an investigator-initiated, randomized, multicentric trial conducted in Italy and United Kingdom. Details of the trial design, statistical power, and eligibility criteria have been previously published elsewhere (12).

The trial randomized 466 patients with early TNBC at high risk of relapse to receive adjuvant avelumab for 52 weeks or to observation. Patients were enrolled after the conclusion of treatment with curative intent including surgery and systemic chemotherapy. Patients entered 2 strata: stratum A ($n = 83$), for patients who underwent primary surgery followed by adjuvant chemotherapy, defined at high risk of relapse based on pathological tumor and nodal stage (pT/pN; inclusion criteria: any pT/≥pN2, pT2/pN1, or pT3/pN0), and stratum B, for patients who underwent NACT followed by surgery (and optional adjuvant chemotherapy) without a documented pCR at the surgical sample examination.

The co-primary endpoints were not met. At a median follow-up of 52.1 months, avelumab did not significantly improve disease-free survival (DFS) in the intention-to-treat (ITT) population [hazard ratio (HR), 0.81; 95% confidence interval (CI), 0.61–1.09; $P = 0.172$; 3-year DFS, 68.3% for avelumab vs. 63.2%] or in stratum B (HR, 0.80; 95% CI, 0.58–1.10; $P = 0.170$; 3-year DFS, 66.9% for avelumab vs. 60.7%). A descriptive analysis of the secondary endpoint of overall survival (OS) showed improvement with avelumab (HR, 0.66; 95% CI, 0.45–0.97; 3-year OS, 84.8% vs. 76.3%). This result was supported by an exploratory analysis of distant DFS (DDFS; HR, 0.70; 95% CI, 0.50–0.96; 3-year DDFS, 75.4% with avelumab vs. 67.9%).

Pathology

Stromal TILs were centrally assessed on single hematoxylin and eosin–stained slide of the primary tumor according to guideline recommendations (23, 24).

The following tumor samples were centralized and assessed for TILs: primary surgery specimen (for patients in stratum A), tumor core biopsy collected before the start of NACT (for patients in stratum B), and post-NACT surgical specimen (for patients in stratum B). Baseline-TILs (BSL-TIL) were assessed on treatment-naïve tumor samples (surgical samples in stratum A and tumor core biopsy in stratum B). RD-TILs were assessed for stratum B patients on post-NACT surgical specimens.

RCB for patients in stratum B was assessed locally, by pathologists at each participating center, following the standardized method (21).

Statistical analysis

The analysis of the prognostic and predictive role of TILs was prespecified in the protocol. The populations for the TILs and RCB

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analyses are based on the total number of cases with available biomarker data (per protocol). Therefore, no formal sample size calculation was carried out.

DFS was calculated from randomization to any of the following events, whichever occurred first: local, regional, and distant recurrence; second primary invasive breast cancer; other second primary invasive cancer; or death. DDFS was calculated from randomization to distant recurrence, second primary invasive cancer (non-breast), or death. OS was calculated from randomization to death from any cause. For all endpoints, patients without event were censored at the last follow-up date.

For survival analysis, TILs were considered a continuous (5% increments) and categorical variable. For BSL-TILs, the predefined cutoff was ≥30%. This prognostic cutoff was previously established in the largest pooled analysis evaluating TILs in early-stage TNBC treated with chemotherapy (15) and subsequently confirmed in several prognostic studies (14, 17, 25). For RD-TILs, we adopted a cutoff of ≥10%, as it yielded the highest Wald statistic across all tested thresholds in our study reflecting the most robust prognostic associations in our study (Supplementary Table S1) and ensured adequate group balance corresponding to the median in our cohort.

RCB was considered a categorical variable (RCB I–II vs. III categories). The prognostic and predictive role of TILs and RCB was analyzed in stratum A and stratum B combined (BSL-TILs), stratum A (BSL-TILs), and stratum B (BSL-TILs, RD-TILs, combined BSL-TILs and RD-TILs, and RCB).

Cox regression models were employed to calculate HRs and 95% CIs. Adjustment variables in prognostic models testing the role of BSL-TILs and RD-TILs were age, stage at diagnosis, and carboplatin exposure (analyses in both strata combined) and age, stage at diagnosis, RCB, carboplatin exposure, and adjuvant capecitabine (analyses in stratum B). Prognostic analyses in stratum A were not adjusted because of limited sample size and number of events.

To study the interaction between treatment arm and TILs (or RCB), we used a Cox model that included treatment arm, the TIL variable of interest (or RCB), and the interaction term between them. Interaction tests in both strata combined were adjusted for the same covariates as prognostic models. For categorical BSL-TIL interaction tests in stratum B, models were adjusted for age, RCB, carboplatin, capecitabine, and semicontinuous BSL-TILs. For categorical RD-TIL interaction tests, models were adjusted for age, RCB, carboplatin, capecitabine, and semicontinuous RD-TILs.

Survival curves were estimated using the Kaplan–Meier method, and the log-rank test was used to compare between groups.

Statistical analyses were performed using IBM SPSS version 29. All tests were 2-sided, with a <0.05 significance level.

Ethical considerations

The study was conducted in accordance to the Declaration of Helsinki, and the protocol was approved by ethical committees at each participating institution. All patients provided written informed consent to participate in the trial and to allow the use of their tumor samples for research purposes.

Results

Figure 1 shows patient study cohorts. BSL-TILs were available for 387 patients (83% of the A-BRAVE trial ITT population): $n = 67$ in stratum A and $n = 320$ in stratum B. At a median follow-up of 52 months (95% CI, 50–55 months), the effect of avelumab versus control in the population with BSL-TILs available was consistent with the effect observed in the ITT trial population [DFS: HR, 0.89 (95% CI, 0.63–1.25); DDFS: HR, 0.75 (95% CI, 0.52–1.08); OS HR, 0.69 (95% CI, 0.45–1.05)]. The median BSL-TIL levels were 10% (Q1, 5%; Q3, 25%) in both strata combined, 12% (Q1, 5%; Q3, 35%) in stratum A, and 10% (Q1, 5%; Q3, 25%) in stratum B ($P = 0.461$ stratum A vs. B). In stratum A, there was a higher prevalence of cases with BSL-TILs ≥30% compared with stratum B (34.3% vs. 21.6%; $P = 0.026$). **Table 1** shows patient characteristics according to BSL-TILs; high BSL-TILs were associated with younger age, higher Ki67, and estrogen receptor–low expression.

RD-TILs were available for $n = 330$ patients in stratum B (86%), 290 of whom also had BSL-TILs available (**Fig. 1**). The median RD-TIL levels were 10% (Q1, 5%; Q3, 20%). As shown in Supplementary Table S2, high RD-TILs (≥10%) were significantly associated with lower RCB (85.2% RCB I or II vs. 74.6% in the case of low RD-TILs; $P = 0.021$) and more frequent adjuvant capecitabine use (32.4% vs. 13.9% in the case of low RD-TILs; $P < 0.001$).

TILs and RCB: Prognosis

In both strata combined, the level of BSL-TILs was significantly associated with both DFS and DDFS. In adjusted Cox models (**Table 2**), every 5% increment in BSL-TILs was associated with a 7% relative reduction in the risk of DFS event (HR, 0.93; 95% CI, 0.88–0.98; $P = 0.007$) and DDFS event (HR, 0.93; 95% CI, 0.88–0.98; $P = 0.012$) and a 6% reduction in the risk of death (HR, 0.94; 95% CI, 0.87–1; $P = 0.051$). Next, patients were stratified according to BSL-TILs at the ≥30% cutoff. As shown in **Fig. 2A–C**, patients with high BSL-TILs showed significant 15% and 11% absolute gains in 3-year survival rates for DFS and DDFS, respectively. The numerically better OS for patients with high versus low BSL-TILs (7.6% absolute gain in the 3-year rate) did not reach statistical significance.

We next analyzed the prognostic role of TILs in each stratum separately. Unadjusted analyses in stratum A were consistent with BSL-TILs maintaining a prognostic role for DFS and DDFS (Supplementary Fig. S1). In stratum B, RD-TILs outperformed the prognostic role of BSL-TILs in multivariable Cox models (**Table 2**). BSL-TILs as 5% increments were not significantly associated with improved outcomes after adjustments for main covariates. When RD-TILs (5% increments) were added to the model, they emerged as an independent prognostic factor for all survival outcomes, together with RCB, whereas exposure to adjuvant capecitabine retained an independent prognostic value for DDFS and OS. Kaplan–Meier survival curves by TILs (**Fig. 2D–F**; Supplementary Fig. S2) and RCB (Supplementary Fig. S3) were analyzed for stratum B. BSL-TILs had a limited impact on DDFS (**Fig. 2D**), whereas RD-TILs at the ≥10% cutoff better stratified prognosis (**Fig. 2E**); 3-year DDFS rates were 80.6% in high RD-TILs versus 57.8% in low RD-TILs (log-rank $P < 0.001$; adjusted HR, 0.53; 95% CI, 0.33–0.88). DDFS Kaplan–Meier curves according to combined BSL-TILs and RD-TILs (both high, BSL-high/RD-low, BSL-low/RD high, and both low) further confirmed RD-TILs as the main discriminator of prognosis (**Fig. 2F**); in the context of low BSL-TILs, patients with high versus low RD-TILs had a 3-year DDFS of 82.5% versus 60.1% and were, respectively, the groups at best and worst outcome across TIL-defined groups. Consistent results were obtained for DFS and OS (Supplementary Fig. S2).

TILs and RCB: Prediction of avelumab benefit

Figure 3 shows DDFS Kaplan–Meier survival curves comparing avelumab versus control in groups of patients defined by BSL-TILs (high ≥30% and low <30%). In both strata combined (**Fig. 3A** and

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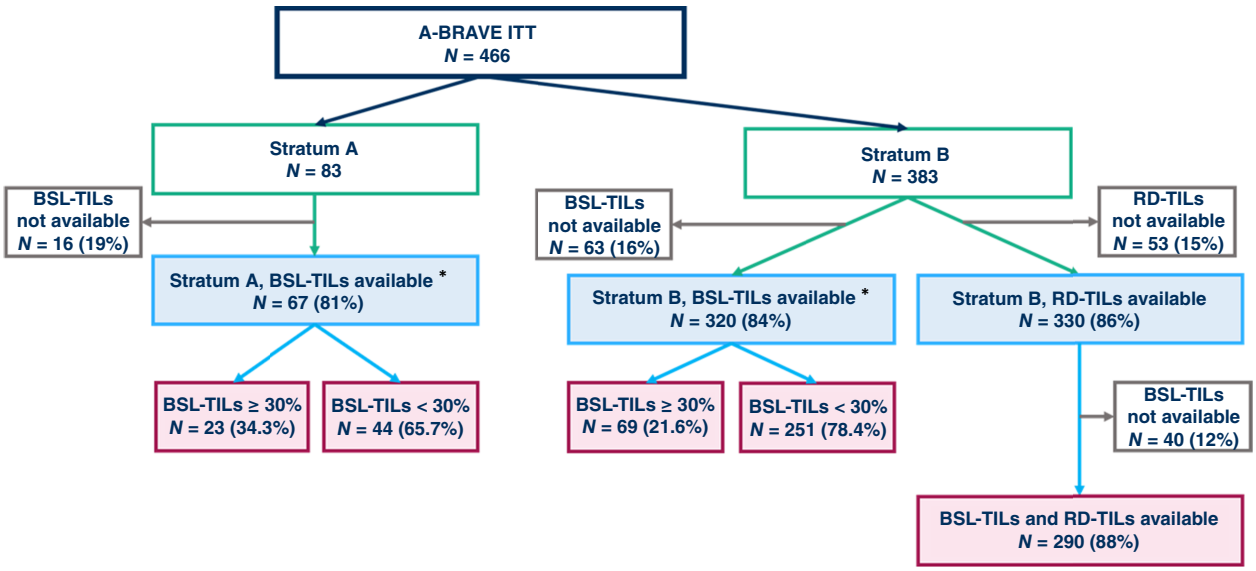

Figure 1.

Patient disposition. *, BSL-TILs were available for 387 patients; PD-L1, previously reported (12), was available for 407 patients. The difference reflects cases in which tumor tissue was exhausted after prioritized PD-L1 evaluation (requiring 2 IHC-stained slides) or technical artifacts precluded reliable TIL scoring despite adequate tissue for PD-L1 assessment.

B; Supplementary Fig. S4), there was a significant benefit from avelumab in patients with high BSL-TILs [3-year DDFS rates, 93.5% vs. 69.8%; unadjusted HR, 0.31 (95% CI, 0.11–0.87)] and no benefit in patients with low BSL-TILs [3-year DDFS rates, 71.5% vs. 70.9%; unadjusted HR, 0.89 (95% CI, 0.60–1.33)], with an adjusted test for interaction $P = 0.065$. In stratum B (**Fig. 3C** and **D**), the interaction between categorical BSL-TILs and treatment was statistically significant (adjusted $P = 0.019$); 3-year DDFS rates for avelumab versus control were 92% versus 58.7% in the case of high BSL-TILs and 70.4% versus 70.1% in the group with low BSL-TILs. Similar results were obtained for DFS and OS (Supplementary Table S3). We also tested the interaction between BSL-TILs as a continuous variable (5% increments) and treatment arm in both strata combined and in stratum B; adjusted P was not significant for any endpoint (borderline $P = 0.058$ for DDFS in stratum B).

In stratum B, RD-TILs were not predictive for avelumab benefit. Although there was a signal for efficacy of avelumab in the case of low RD-TILs (<10%) and no effect in the case of high RD-TILs (≥10%), there was no statistically significant interaction for any of the survival endpoints (Supplementary Fig. S5; Supplementary Table S4). To exclude the potential confounding effect of BSL-TILs, we explored the predictive role of RD-TILs (10% cutoff) in stratum B patients with low BSL-TILs (<30%), resulting in a significant interaction for DDFS (adjusted $P = 0.048$); avelumab was associated with numerically worse outcome versus control in the case of high RD-TILs and numerically better outcome versus control in the case of low RD-TILs (**Fig. 3E** and **F**). Similar results were obtained for DFS and OS (Supplementary Table S4). Adjusted tests for interaction between continuous RD-TILs and treatment arm in stratum B patients with low BSL-TILs were $P = 0.041$ for DFS, $P = 0.066$ for DDFS, and $P = 0.119$ for OS. Exploratory analyses with RD-TILs at the 30% cutoff showed a significant prognostic value (HR, 0.41; 95% CI, 0.21–0.81; $P = 0.010$), with no clear or consistent predictive signal for avelumab benefit. Wide CIs reflect limited sample size in the RD-TIL ≥30% group, particularly when further stratified by BSL-TIL levels (Supplementary Table S5).

With regard to RCB, a numerically greater magnitude of benefit from avelumab was observed for patients with RCB III compared with RCB I to II, without significant interaction tests (Supplementary Fig. S6).

Discussion

This biomarker analysis of the phase III A-BRAVE trial highlights TILs as a candidate predictive biomarker for adjuvant avelumab efficacy in high-risk TNBC. We observed a significant interaction between BSL-TILs and avelumab benefit, particularly in stratum B, in which patients with high BSL-TILs experienced a marked improvement in DDFS with avelumab versus control (3-year DDFS, 92% vs. 58.7%; HR, 0.31). In contrast, patients with low BSL-TILs derived no benefit. Beyond baseline, TILs assessed in RD after NACT further refined the identification of patients potentially sensitive to avelumab; among patients with low BSL-TILs, those with low RD-TILs (<10%) showed a signal for benefit (9% absolute improvement in 3-year DDFS), whereas those with high RD-TILs experienced even a numerically worse outcome with avelumab (significant interaction test). Findings were consistent across the 3 survival endpoints. Among these, DDFS may be considered the most directly reflective of breast cancer–related and potentially lethal events and therefore particularly informative for interpreting potential treatment–biology interactions, although DFS and OS remain essential for the overall clinical assessment as the primary and secondary endpoints of the trial.

The observed pattern is consistent with the established association between higher TILs and improved response to single-agent pembrolizumab versus chemotherapy in metastatic TNBC (26). In the nonmetastatic TNBC setting, our results contrast with findings from translational analyses of KEYNOTE-522, in which no

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Table 1. Patient characteristics according to BSL-TIL level in both strata combined and in stratum B.

	Stratum A + stratum B					Stratum B				
	BSL-TILs < 30% (*N* = 295)		BSL-TILs > 30% (*N* = 92)			BSL-TILs < 30% (*N* = 251)		BSL-TILs > 30% (*N* = 69)		
Characteristic	***n***	**%**	***n***	**%**	***P***	***n***	**%**	***n***	**%**	***P***
Age, years (median, Q1:Q3)	52 (44:60)		48 (41:59)		0.073	51 (44:60)		48 (40:56)		0.047
BMI										
Underweight	5	1.7%	5	5.6%		4	1.6%	3	4.4%	
Lean	145	50.5%	45	50%		119	48.8%	35	51.5%	
Overweight	83	28.9%	26	28.9%	0.244	70	28.7%	18	26.5%	
Obese	54	18.8%	14	15.6%		51	20.9%	12	17.6%	0.518
AJCC stage at diagnosis[a]										
I	27	9.2%	6	6.5%		27	10.8%	6	8.7%	
II	193	65.9%	67	72.8%		170	68.3%	53	76.8%	
III	73	24.9%	19	20.7%	0.443	52	20.9%	10	14.5%	0.380
Estrogen receptor expression										
0%	276	93.6%	82	89.1%		238	94.8%	60	87%	
≥1%	19	6.4%	10	10.9%	0.159	13	5.2%	9	13%	0.022
Ki67, % (median, Q1:Q3)	50 (25:70)		65 (35:80)		0.018	50 (20:70)		66 (20:80)		0.098
g*BRCA* status										
Mutated	31	10.5%	14	15.2%		26	10.4%	11	15.9%	
Wild type/VUS	145	49.2%	42	45.7%		130	51.8%	33	47.8%	
Unknown	119	40.3%	36	39.1%	0.463	95	37.8%	25	36.2%	0.435
Carboplatin received										
No	199	67.5%	66	71.7%		160	63.7%	45	65.2%	
Yes	96	32.5%	26	28.3%	0.440	91	36.3%	24	34.8%	0.821
Stratum										
A	44	14.9%	23	25%						
B	251	85.1%	69	75%	0.026					
Treatment arm										
Avelumab	152	51.5%	48	52.2%		131	52.2%	39	56.5%	
Control	143	48.5%	44	47.8%	0.913	120	47.8%	30	43.5%	0.523
RCB category										
I						20	9.9%	8	14%	
II						144	71.3%	41	71.9%	
III						38	18.8%	8	14%	0.528
Adjuvant capecitabine										
0						197	78.5%	50	72.5%	
1						54	21.5%	19	27.5%	0.291

Abbreviations: AJCC, American Joint Committee on Cancer; g*BRCA*, breast cancer gene; BMI, body mass index; *n*, number; *P*, *P* value; VUS, variant of unknown significance.
[a]Pathologic staging at surgery for stratum A; pre-neoadjuvant chemotherapy clinical staging for stratum B.

predictive gene expression–based immune biomarker has yet emerged and in which TIL analyses have not been reported (13).

Nevertheless, our findings align directionally with results from the NSABP-B59/GBG-96-GeparDouze trial. In this trial, adding neoadjuvant/adjuvant atezolizumab to standard NACT for TNBC did not improve EFS (10). Recently presented biomarker analyses suggested greater benefit from atezolizumab among patients with high BSL-TILs (≥30%; refs. 10, 27). However, adjustment for confounding factors was not explicit and testing for interaction was previously reported as not significant (10), whereas A-BRAVE provides evidence supported by formal adjusted interaction testing.

Critically, A-BRAVE evaluated immunotherapy administered sequentially after completion of all standard therapies. Differences in the patient population and in the timing of single-agent immunotherapy administration limit direct comparability with KEYNOTE-522 or NSABP-B59/GBG-96-GeparDouze. From a biological standpoint, our results suggest that a preexisting antitumor immune activation may be necessary for immune checkpoint blockade to exert meaningful activity in the post-neoadjuvant setting. High BSL-TILs likely mark tumors in which an endogenous antitumor immune response is present but was insufficient to achieve complete tumor eradication with chemotherapy, making them more likely to benefit from an adjuvant immunologic "boost." In contrast, tumors with low BSL-TILs represent a more heterogeneous category, in which the evolution of the immune microenvironment during NACT becomes pivotal. Among these patients, high RD-TILs seem to reflect chemotherapy-induced conversion from a cold tumor to a more immunologically engaged phenotype, potentially sufficient to control micrometastatic disease without additional immunotherapy (20). Conversely, persistently low RD-TILs identify tumors unable to mount an effective immune response despite cytotoxic chemotherapy, defining a subgroup with particularly poor outcomes. Although adjuvant immunotherapy may still offer some benefit, prognosis remains unfavorable, highlighting a clear unmet clinical need for novel escalation strategies.

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Table 2. Multivariable Cox models for DFS, DDFS, and OS, testing the prognostic role of TILs in both strata combined (BSL-TILs) and in stratum B (BSL-TILs and RD-TILs).

	DFS		DDFS		OS	
Both strata combined	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
BSL-TIL 5% increments	0.93 (0.88–0.98)	0.007	0.93 (0.88–0.98)	0.012	0.94 (0.87–1)	0.051
Age, continuous (years)	1.01 (0.99–1.03)	0.237	1.01 (0.99–1.03)	0.206	1.02 (1–1.04)	0.043
AJCC stage at diagnosis[a]						
I	Ref		Ref		Ref	
II	1.58 (0.73–3.42)	0.246	1.83 (0.74–4.53)	0.194	1.22 (0.48–3.06)	0.677
III	2.85 (1.28–6.33)	0.010	3.67 (1.45–9.29)	0.006	2.58 (1.01–6.65)	0.049
Carboplatin received						
No	Ref		Ref		Ref	
Yes	1.19 (0.82–1.71)	0.361	1.14 (0.77–1.69)	0.506	1.09 (0.68–1.74)	0.716
Stratum B						
BSL-TIL 5% increments	0.95 (0.89–1.02)	0.172	0.95 (0.88–1.03)	0.183	0.97 (0.89–1.05)	0.457
Age, continuous (years)	1 (0.99–1.02)	0.707	1 (0.98–1.02)	0.737	1.02 (1–1.04)	0.130
AJCC stage at diagnosis[a]						
I	Ref		Ref		Ref	
II	1.36 (0.59–3.16)	0.469	1.76 (0.64–4.87)	0.276	1.20 (0.43–3.36)	0.730
III	1.85 (0.75–4.53)	0.180	2.95 (1.02–8.51)	0.045	2.13 (0.73–6.26)	0.169
RCB						
I–II	Ref		Ref		Ref	
III	2.78 (1.76–4.39)	<0.001	2.45 (1.54–4.03)	<0.001	2.62 (1.55–4.43)	>0.001
Carboplatin received						
No	Ref		Ref		Ref	
Yes	1.20 (0.79–1.83)	0.397	1.04 (0.66–1.64)	0.855	1.09 (0.65–1.85)	0.736
Adjuvant capecitabine						
No	Ref		Ref		Ref	
Yes	0.63 (0.35–1.14)	0.130	0.59 (0.30–1.15)	0.123	0.34 (0.13–0.84)	0.020
Stratum B (including RD-TILs)						
RD-TIL 5% increments	0.89 (0.81–0.97)	0.008	0.89 (0.81–0.98)	0.019	0.89 (0.80–1)	0.045
BSL-TIL 5% increments	1 (0.92–1.08)	0.938	0.99 (0.91–1.08)	0.789	1.01 (0.92–1.12)	0.783
Age, continuous (years)	1 (0.98–1.02)	0.891	1 (0.98–1.02)	0.914	1.01 (0.99–1.04)	0.416
AJCC stage at diagnosis[a]						
I	Ref		Ref		Ref	
II	1.27 (0.55–2.95)	0.573	1.64 (0.59–4.54)	0.343	1.08 (0.38–3.04)	0.883
III	1.51 (0.60–3.77)	0.380	2.39 (0.81–7.03)	0.113	1.83 (0.61–5.47)	0.279
RCB						
I–II	Ref		Ref		Ref	
III	3.02 (1.89–4.82)	<0.001	2.68 (1.63–4.39)	<0.001	2.88 (1.68–4.93)	<0.001
Carboplatin received						
No	Ref		Ref		Ref	
Yes	1.25 (0.80–1.95)	0.320	1.01 (0.63–1.62)	0.974	1.06 (0.61–1.84)	0.829
Adjuvant capecitabine						
No	Ref		Ref		Ref	
Yes	0.63 (0.34–1.17)	0.140	0.89 (0.81–0.98)	0.019	0.36 (0.14–0.91)	0.032

Abbreviations: AJCC, American Joint Committee on Cancer; *P*, *P* value; Ref, reference.
[a]Pathologic staging at surgery for stratum A; pre-neoadjuvant chemotherapy clinical staging for stratum B.

Although these findings are not sufficient to alter clinical practice, they may have direct implications for clinical research. First, our results claim for the integration and reporting of TILs in ongoing and completed randomized immunotherapy studies in early TNBC. Second, the observed interaction provides a rationale for biomarker-guided trials and adaptive designs potentially including early immune profiling during neoadjuvant therapy.

Beyond its predictive implications, our analysis reinforces the well-established prognostic value of TILs in TNBC and extends this knowledge specifically to a high-risk population. BSL-TILs were independently associated with survival outcomes in both strata combined, but among patients with RD after NACT, RD-TILs emerged as the strongest prognostic factor across endpoints, outperforming BSL-TILs. We validated in the contest of a prospective trial the known independent prognostic contribution of RD-TILs and RCB (22) for patients with less than pCR after NACT, supporting the incorporation of both biomarkers into risk-stratification frameworks and post-neoadjuvant trial designs. With regard to RCB, a numerically greater benefit from avelumab was observed in RCB III versus I to II, without significant interaction. As RCB is a measure of RD burden rather than a surrogate of specific biologic mechanisms, caution is warranted in its biological interpretation in the context of immunotherapy response.

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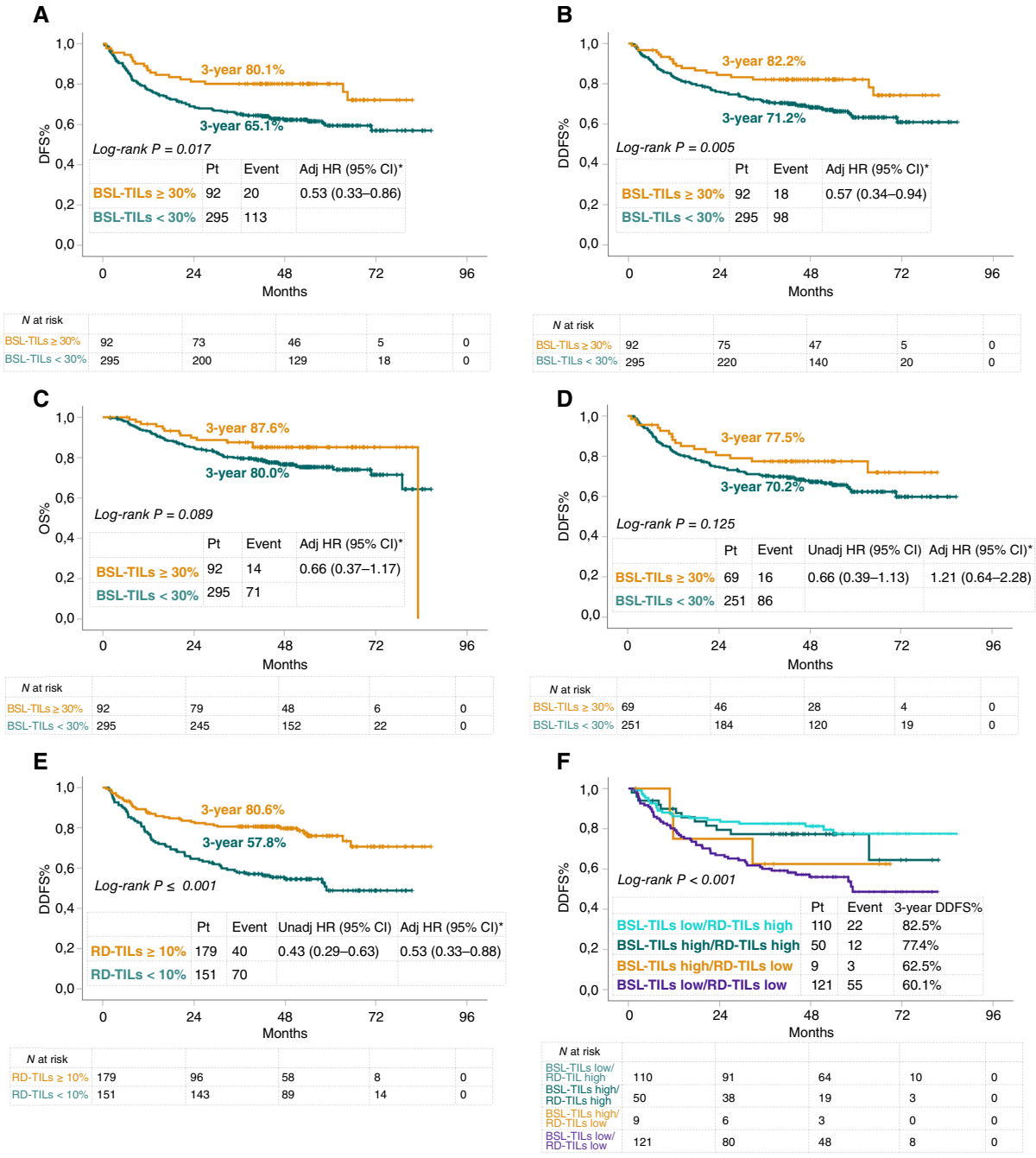

Figure 2.

Prognostic role of TILs. Kaplan–Meier survival curves according to BSL-TILs in both strata combined: DFS (**A**), DDFS (**B**), and OS (**C**). *, Adjusted for American Joint Committee on Cancer (AJCC) stage at diagnosis, age, and carboplatin. Adj, adjusted; Pt, patient. DDFS Kaplan–Meier survival curves in stratum B according to BSL-TILs (**D**), RD-TILs (**E**), and BSL-TILs and RD-TILs combined (**F**). * in **D**, Adjusted for AJCC stage at diagnosis, age, RCB, carboplatin, adjuvant capecitabine, and RD-TILs (5% increments); * in **E**, adjusted for AJCC stage at diagnosis, age, RCB, carboplatin, adjuvant capecitabine, and BSL-TILs (5% increments). Unadj, unadjusted.

This study has limitations, and findings must be interpreted within the context that A-BRAVE did not meet its co-primary endpoints. Although biomarker analyses were prespecified and interaction tests adjusted for covariates, the trial was not powered for subgroup analyses. Potential imbalances in post-neoadjuvant treatments (such as the nonstandardized use of adjuvant capecitabine across centers) may also have contributed to outcome variability, although their overall impact is likely limited and was accounted for in multivariable analyses. The statistically significant interaction between BSL-TILs and avelumab benefit in stratum B,

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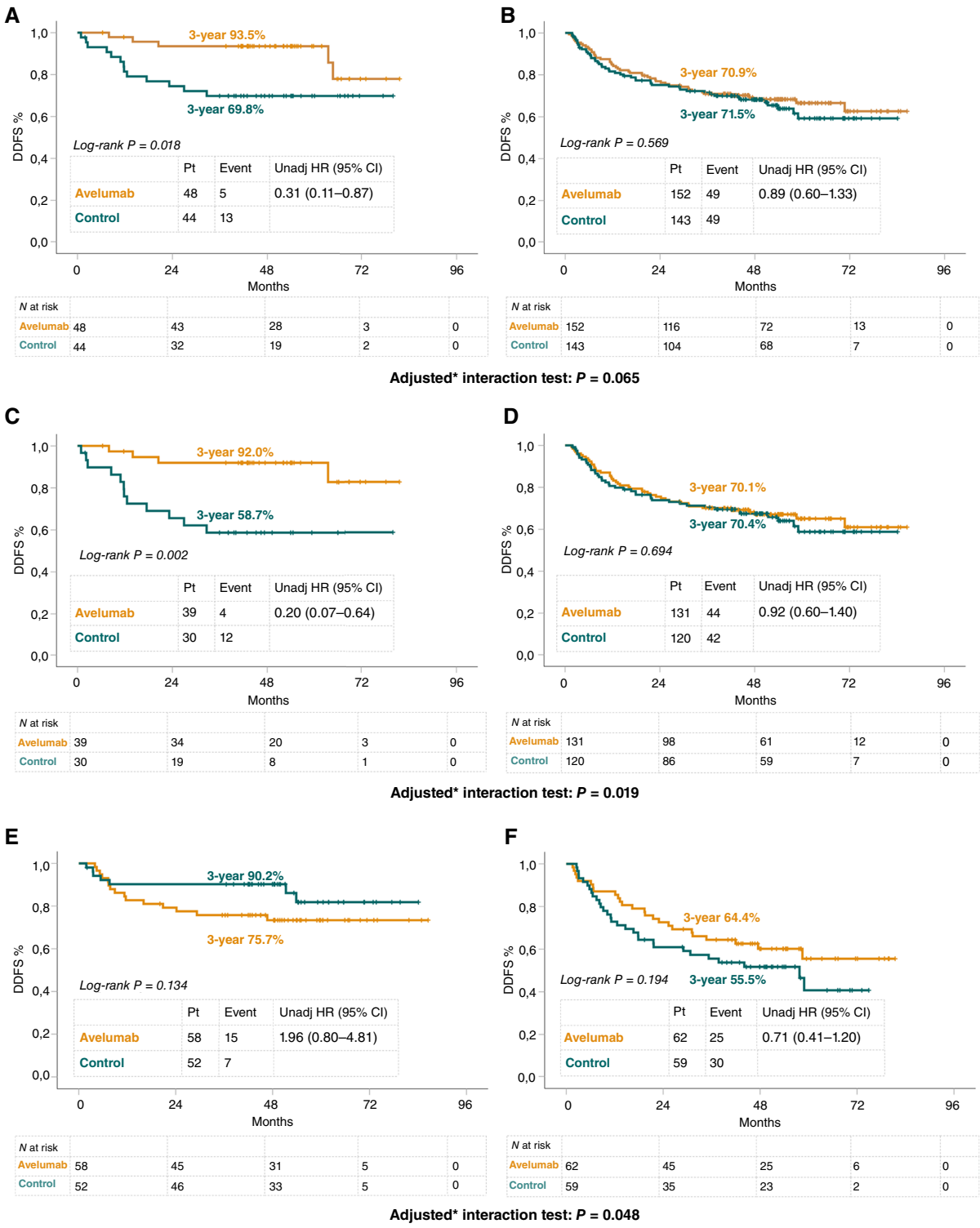

Figure 3.

Effect of avelumab vs. observation in TIL-defined groups. DDFS Kaplan–Meier curves of avelumab vs. observation in both strata combined in high BSL-TILs (**A**) and low BSL-TILs (**B**). *, Adjusted for American Joint Committee on Cancer (AJCC) stage at diagnosis, age, and carboplatin. Pt, patient; Unadj, unadjusted. DDFS Kaplan–Meier curves of avelumab vs. observation in stratum B in high BSL-TILs (**C**) and low BSL-TILs (**D**). *, Adjusted for AJCC stage at diagnosis, age, RCB, carboplatin, adjuvant capecitabine, and RD-TILs (5% increments). DDFS Kaplan–Meier curves of avelumab vs. observation in patients from stratum B and with low BSL-TILs: high RD-TILs (**E**) and low RD-TILs (**F**). *, Adjusted for AJCC stage at diagnosis, age, RCB, carboplatin, adjuvant capecitabine, and BSL-TILs (5% increments).

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while compelling given the magnitude of effect in high-TIL patients and consistency across endpoints, should be considered hypothesis generating. Validation in independent cohorts is essential before clinical application. Nevertheless, the biological alignment with emerging data from other trials supports the value of these observations. In particular, these results support immediate research priorities, including the evaluation of TILs in completed trials of adjuvant and neoadjuvant immunotherapy, as well as their integration into the design of ongoing and future trials testing novel immunotherapy combinations (including antibody–drug conjugates), to enable refined patient stratification and more robust assessment of predictive value.

In conclusion, this biomarker study of the A-BRAVE trial provides the first evidence in early TNBC of a potential predictive role for TILs in guiding immunotherapy while confirming and refining their prognostic value, especially the dominant role of RD-TILs in patients with RD after NACT. These results advocate for extensive evaluation of TILs in immunotherapy trials for early TNBC and emphasize the importance of rigorous biomarker stratification/integration in future trials aiming to personalize treatment for TNBC.

Data Availability

Individual patient-level data are not publicly available to maintain compliance with trial protocol. Anonymized data are available for noncommercial use from the sponsor/principal investigator upon request (to be sent to the corresponding author) pending data usage agreement and/or institutional review board–approved collaboration.

Authors' Disclosures

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Authors' Contributions

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Note

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