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ORIGINAL ARTICLE

# A-BRAVE trial: a phase III randomized trial with anti-PD-L1 avelumab in high-risk triple-negative early breast cancer patients

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**Background:** The A-BRAVE trial evaluated the efficacy of avelumab, an anti-programmed death-ligand 1 (PD-L1) antibody, as adjuvant treatment of patients with early triple-negative breast cancer (TNBC) at high risk.

**Patients and methods:** A-BRAVE is a phase III study that randomly assigned patients with high-risk early TNBC to 1 year of avelumab versus observation, after completion of standard surgery and (neo)adjuvant chemotherapy. High-risk was defined as either: (i) ≥pN2/any pT, pN1/pT2, or pN0/pT3 after primary surgery (stratum A); or (ii) invasive residual disease (breast and/or nodes) after neoadjuvant chemotherapy (stratum B). Coprimary endpoints were disease-free survival (DFS) in the intention-to-treat (ITT) and stratum B populations. Secondary endpoints were overall survival (OS) and DFS in PD-L1-positive patients. PD-L1 was evaluated in treatment-naïve tumor samples by immunohistochemistry (73-10 RUO assay, Agilent Technologies) and digital pathology.

**Results:** From June 2016 to October 2020, 466 patients were randomly assigned: 383 entered stratum B (82%) and 83 entered stratum A (18%). At a median follow-up of 52.1 months, avelumab did not significantly improve DFS in the ITT population [hazard ratio (HR) 0.81, 95% confidence interval (CI) 0.61-1.09, $P = 0.172$; 3-year DFS estimates were 68.3% for avelumab versus 63.2%], or in stratum B (HR 0.80, 95% CI 0.58-1.10, $P = 0.170$; 3-year DFS estimates were 66.9% for avelumab versus 60.7%). In a descriptive analysis, avelumab reduced the hazard of OS events: HR 0.66, 95% CI 0.45-0.97. The 3-year OS estimates for avelumab and control arm were 84.8% (95% CI 79.5% to 88.8%) and 76.3% (95% CI 70.1% to 81.3%), respectively. PD-L1 status was prognostic but not predictive for avelumab benefit in terms of DFS (test for interaction $P = 0.155$).

**Conclusions:** For patients with TNBC at high risk of relapse who complete standard treatment with surgery and (neo) adjuvant chemotherapy, 1 year of adjuvant avelumab versus observation did not improve DFS. However, a descriptive analysis suggests a potential favorable impact on OS.

**Key words:** breast cancer, clinical trial, immunotherapy, triple-negative breast cancer, PD-L1

## INTRODUCTION

Neoadjuvant systemic therapy is recommended for patients with triple-negative breast cancer (TNBC) diagnosed with a tumor >1 cm and/or axillary lymph node involvement, which facilitates surgical de-escalation and the stratification of patients by pathologically documented response (pathological response), to tailor adjuvant treatment.[1,2] Patients who achieve a pathological complete response (pCR) experience a very favorable long-term survival, while those with

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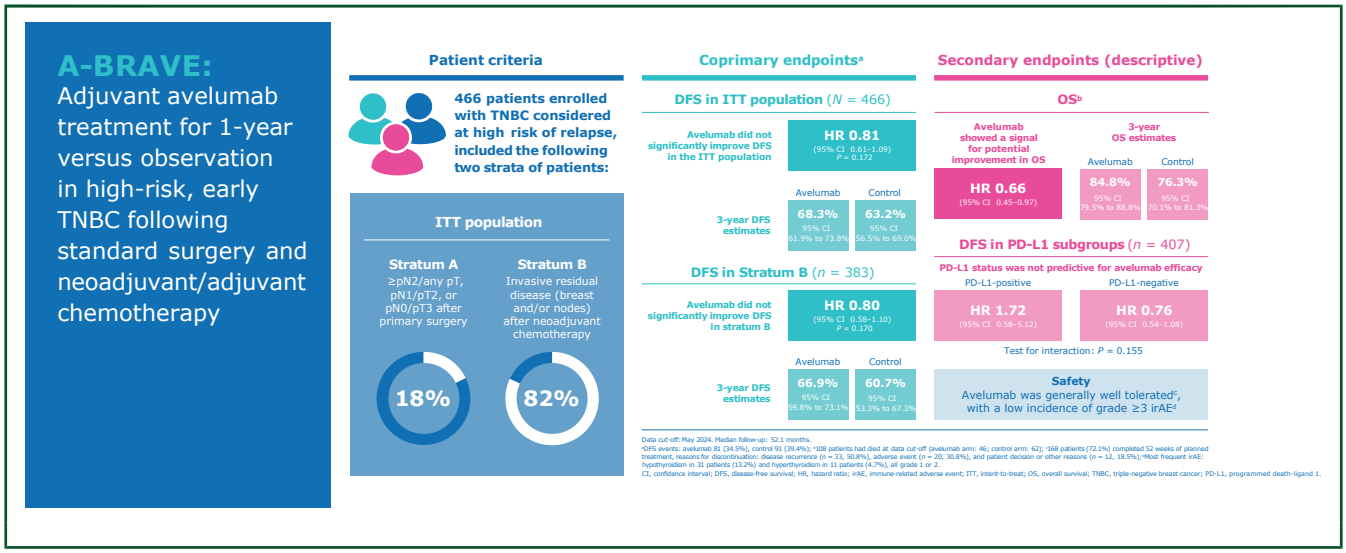
## GRAPHICAL ABSTRACT




invasive residual disease (iRD) are exposed to a higher risk of relapse.[3] Thus, the neoadjuvant platform provides an ideal framework for advancing personalized treatment, by attempting to maximize the pCR rate through the incorporation of new drugs in the preoperative phase, and lowering the risk of relapse in patients with iRD by escalating adjuvant treatment,[4] a trial design strategy that is endorsed by the United States Food and Drug Administration (FDA).[5] Notwithstanding, some patients with early TNBC still undergo primary surgery followed by adjuvant chemotherapy, based on clinical staging $\leq$cT1cN0, and/or other individual or clinical considerations. For these patients, definitive pathological staging is a major prognostic factor.[6]

TNBC is the most immunogenic breast cancer subtype because of its genetic instability and high mutational burden.[7] Immune checkpoint inhibitors (ICIs) combined with chemotherapy have improved the prognosis of patients with advanced TNBC.[8,9] Moreover, nowadays neoadjuvant chemotherapy combined with pembrolizumab is standard for T $>$2 cm and/or positive axillary lymph node involvement.[10] Avelumab is a fully human anti-programmed death-ligand 1 (PD-L1) antibody that showed clinical activity and an acceptable safety profile in the metastatic breast cancer cohort (including TNBC) of the phase Ib JAVELIN Solid Tumor trial.[11]

A-BRAVE is an investigator-driven trial that was designed in 2015 before any efficacy data of ICIs in early TNBC were available, to investigate the efficacy of adjuvant avelumab in patients with early TNBC considered at high risk of relapse after the conclusion of treatment with curative intent, including chemotherapy and surgery. Here we report primary, secondary, and exploratory efficacy endpoints.

## METHODS

### *Trial oversight*

The A-BRAVE trial (EUDRACT 2016-000189-45; NCT02926196) was an investigator-initiated, multicenter, unblinded, randomized trial conducted in 60 Italian and 7 UK hospitals (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.08.005). This trial was developed and sponsored by the Department of Surgery, Oncology and Gastroenterology of the University of Padova, Italy. The health care business of Merck KGaA, Darmstadt, Germany supported the trial with an unrestricted grant and supply of avelumab, but had no role in the design or conduct of the trial and was not involved in data collection or analysis, in the writing of the manuscript, or in the decision to submit it for publication. The trial was carried out in accordance with the standards of Good Clinical Practice. The authors assume responsibility for the accuracy and completeness of the data and analyses, as well as for the fidelity of the trial and this report to the protocol.

### *Patients*

Patients were eligible for enrollment if they were aged $\geq$18 years, had hormone receptor- negative [estrogen receptor $<$10% and progesterone receptor $<$10%] and human epidermal growth factor receptor 2 (HER2)-negative [immunohistochemistry (IHC) 0/1+ or 2+ *in situ* hybridization nonamplified] nonmetastatic breast cancer as defined by local laboratory, and had received treatment with curative intent, including surgery and chemotherapy with anthracyclines and taxanes. Patients should have met the following protocol criteria for the definition of high-risk (AJCC 7th edition): any pT/ $\geq$pN2, pT2/pN1, or pT3/pN0 according to the local pathology examination of samples obtained with primary surgery (stratum A, adjuvant); iRD in the breast and/or lymph nodes as determined by local pathology examination of the surgical specimen obtained after neoadjuvant chemotherapy (stratum B, postneoadjuvant; ypT1micN0, ypT1micN0i+, ypT0N0i+ excluded). In stratum B, no more than 6 months of adjuvant chemotherapy after neoadjuvant treatment and surgery was allowed according to a protocol amendment (April 2018). A complete list of the inclusion and exclusion criteria is provided in the trial protocol.

### Trial procedures

Participants were randomly assigned (web-based) in a 1 : 1 ratio to either avelumab monotherapy administered as intravenous infusion at the dose of 10 mg/kg every 2 weeks for 52 weeks (avelumab arm) or to observation (control arm). Randomization was stratified by stratum A (adjuvant) and stratum B (postneoadjuvant), and had to occur $\leq$10 weeks from the end of adjuvant chemotherapy or the date of definitive surgery (stratum B in the absence of postsurgical cytotoxic treatment). Treatment administration had to start within 7 days from randomization. Radiotherapy was allowed concomitantly to avelumab administration. Adjuvant endocrine therapy was allowed at investigator's discretion for patients whose tumor expressed low levels of hormone receptors (1%-9%). Visits for assessment of disease recurrence were scheduled every 4 months from the first 2 years, every 6 months from year 3 to year 5, and once a year thereafter in both arms. In the avelumab arm, adverse events were monitored throughout the trial and for 90 days after the last avelumab administration. For patients randomly assigned to the control arm, safety was assessed during the first 12 months at the scheduled visits and by additional monthly phone calls.

### Outcomes

Efficacy was evaluated in the ITT population including all randomly assigned patients. Initially the two coprimary endpoints were: (i) DFS of patients randomly assigned to avelumab compared with control (whole ITT); (ii) DFS of patients randomly assigned to avelumab compared with control in the PD-L1-positive population. After amendment in January 2020, the two coprimary endpoints were modified as follows: (i) DFS of patients randomly assigned to avelumab compared with control (whole ITT); (ii) DFS of patients randomly assigned to avelumab compared with control in stratum B. DFS in the PD-L1-positive population was maintained as a secondary endpoint. The rationale for withdrawing DFS in PD-L1-positive patients as a coprimary endpoint was based on the emerging KEYNOTE-522 trial data that did not demonstrate any predictive role of PD-L1 status relative to the efficacy of neoadjuvant pembrolizumab combined with chemotherapy. The decision to introduce DFS in stratum B as a coprimary endpoint was taken, considering the increasing interest in escalating adjuvant therapy in case of iRD following the success of recent clinical trials,[2,12] which was also endorsed by the FDA.[5]

Another secondary efficacy endpoint was OS in the whole ITT. Distant DFS (DDFS) was a *post hoc* exploratory analysis.

DFS was defined as the time interval between randomization and 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. OS was calculated from randomization to death from any cause. DDFS was defined as the time interval from randomization to distant recurrence; second primary invasive cancer (nonbreast); or death. For all endpoints, patients without event were censored at the last follow-up date.

Safety (secondary endpoint) was assessed including all patients who received at least one dose of avelumab, and all patients randomly assigned to control. Toxicities were graded using the National Cancer Institute—Common Terminology Criteria for Adverse Events v.4.03.

### Statistical analysis

The study design fixed a one-sided significance level at 2.0% for the overall analysis. For the subgroup analysis, the significance level was adjusted using the Spiessens and Debois method to control the family-wise error rate at 2.5% (one-sided).[13]

In TNBC patients meeting the A-BRAVE criteria and randomly assigned to the control arm, the 3-year DFS rate was expected to be 60% (with similar estimates for both stratum A and B).[3,6] An improvement to 73.6% in the 3-year DFS rate was the target effect for the entire ITT population. This corresponds to an expected hazard ratio (HR) of 0.6 for the avelumab arm versus the control arm, assuming an exponential distribution.

Under the proportional hazards assumption, 172 DFS events were required to detect an expected HR of 0.60 with 90% power using a one-sided log-rank test at a 2.0% significance level. Assuming uniform enrollment over a 4-year period, a follow-up of at least 2 years after the last participant was randomly assigned, and 6% lost to follow-up, it was estimated that 474 participants (237 in each group) would need to be randomly assigned.

For the second coprimary endpoint, assuming 80% of the total DFS events occur in stratum B, the power to detect an HR of 0.60 in this subgroup was 79% at an allocated alpha of 1.43%. If the hypothesis for the first coprimary endpoint was rejected at the 2.0% level, the hypothesis for stratum B would be tested at an alpha of 2.5% with 85% power.

Kaplan—Meier estimates were provided with 95% confidence interval (CI) computed using the Greenwood formula. HRs and 95% CIs were estimated using a Cox proportional hazards model, stratified by randomization factor.

Results for the secondary and exploratory endpoints are reported as descriptive analyses, without any formal statistical tests for comparison between avelumab and observation. The interaction *P* values for testing the heterogeneity of the treatment effect within subgroups were assessed using Cox proportional hazards models.

### PD-L1

DFS in the PD-L1-positive population was a secondary endpoint. As additional exploratory analyses we investigated the prognostic role of PD-L1 for DFS, DDFS, and OS, as well as the effect of avelumab on DDFS and OS according to PD-L1 status. PD-L1 was evaluated by IHC (73-10 RUO assay, Agilent Technologies, Santa Clara, California) on treatment-naïve formalin-fixed paraffin-embedded tumor samples (surgical samples for stratum A, tumor-core biopsies obtained before the start of neoadjuvant

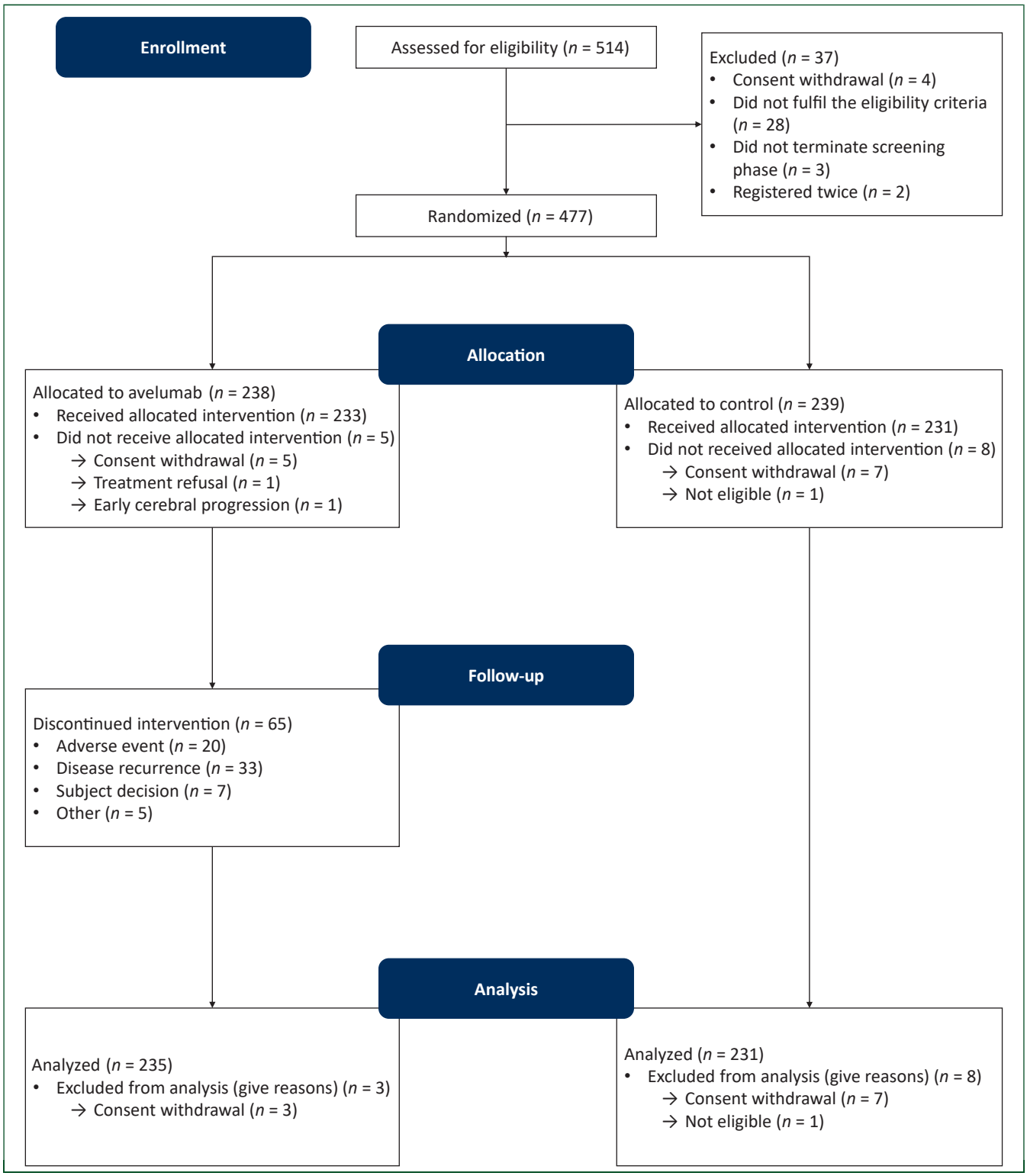



**Figure 1. CONSORT diagram.**

chemotherapy for stratum B). The percentage of positively stained stromal cells out of the total number of stromal cells was calculated by a digital pathology workflow and the cut-off for PD-L1-positive status was set at ≥21%.[14] Detailed methods are available in the Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2025.08.005.

## RESULTS

### *Patients*

Between June 2016 and October 2020, a total of 514 patients from 67 centers were screened and 477 were randomly assigned: 238 to avelumab and 239 to observation (Figure 1). After randomization, 10 patients withdrew consent and one

**Table 1. Characteristics of patients at baseline**

| Characteristic | Avelumab ($n$ = 235) | Control ($n$ = 231) |
|---|---|---|
| Age, years | | |
| Median (range) | 50.9 (28.3-78.6) | 51.9 (28.8-79.9) |
| ECOG PS, *n* (%) | | |
| 0 | 233 (99.6) | 225 (98.3) |
| 1 | 1 (0.4) | 4 (1.7) |
| Unknown | 1 | 2 |
| ER expression, *n* (%)[a] | | |
| ER 0% | 218 (92.7) | 205 (88.7) |
| ER ≥1%[b] | 14 (4.3) | 25 (8.7) |
| Unknown | 3 | 1 |
| *HER2* status, *n* (%)[a] | | |
| 0 | 162 (69.5) | 166 (71.9) |
| IHC 1+/2+ (ISH neg) | 71 (30.5) | 65 (28.1) |
| Unknown | 2 | 0 |
| *gBRCA* status, *n* (%) | | |
| Mutated (pathogenic variant) | 24 (10.2) | 27 (11.7) |
| Wild type/VUS | 113 (48.1) | 113 (48.9) |
| Unknown | 98 (41.7) | 91 (39.4) |
| Carboplatin received, *n* (%) | | |
| Yes | 82 (35.0) | 59 (25.5) |
| Stratum A (adjuvant), *n* (%) | 40 (17.8) | **43 (18.6)** |
| AJCC stage at surgery, *n* (%)[c] | | |
| II | 20 (50.0) | 22 (51.2) |
| III | 20 (50.0) | 21 (48.8) |
| Stratum B (postneoadjuvant), *n* (%) | **195 (83.0)** | **188 (81.4)** |
| AJCC stage at surgery, *n* (%)[d] | | |
| ypT1 and ypN0 | 93 (47.7) | 85 (45.2) |
| ≥ypT2 and ypN0 | 31 (15.9) | 38 (20.2) |
| Any ypT and ypN1 | 49 (25.1) | 42 (22.3) |
| Any ypT and ≥ypN2 | 22 (11.3) | 23 (12.2) |
| Adjuvant capecitabine, *n* (%)[d] | 52 (26.7) | 38 (20.2) |

Values in bold refer to the Stratum in question, not the entire population in the study.

AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; *gBRCA*, germline breast cancer gene; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, *in situ* hybridization; neg, negative; VUS, variant of unknown significance.

[a]ER expression and *HER2* status on surgical sample.

[b]Including five cases with ER ≥10%, three in the avelumab arm and two in the control arm.

[c]Calculated over the total of patients in stratum A.

[d]Calculated over the total of patients in stratum B.

was not eligible, leaving 466 patients in the ITT population assessable for efficacy analysis. Baseline demographics and clinical characteristics were balanced between the two arms (Table 1). The majority of the patients (82%) entered stratum B (postneoadjuvant). There was a significant imbalance in carboplatin exposure between arms (35.0% avelumab; 25.5% observation, $P = 0.028$). Only 23% of patients in stratum B received adjuvant capecitabine, without significant difference between arms ($P = 0.136$).

### *Efficacy*

The target of 172 patients with at least one DFS event was reached in February 2024 (data cut-off for this analysis: May 2024). At a median follow-up of 52.1 months (95% CI 49.8-53.8 months), 81 DFS events were reported in the avelumab arm (34.5%) and 91 (39.4%) in the control arm. Among all DFS events, the most frequent was distant recurrence (accounting for 59.3% events in the avelumab arm and 63.7% in the control arm), followed by locoregional recurrence (32.1% and 23.1%), second primary invasive breast cancer (1.2% and 2.2%), non-breast primary invasive cancer (3.7% and 6.6%), and death (1.2% and 4.4%). Avelumab did not significantly improve DFS compared with control in the ITT population: HR 0.81, 95% CI 0.61-1.09, $P = 0.172$ (Figure 2A). The 3-year DFS estimates for avelumab and control arm were 68.3% (95% CI 61.9% to 73.8%) and 63.2% (95% CI 56.5% to 69.0%), respectively.

Similarly, avelumab did not significantly improve DFS in stratum B: HR 0.80, 95% CI 0.58-1.10, $P = 0.172$ (Figure 2B). The 3-year DFS estimates for avelumab and control arm in stratum B were 66.9% (95% CI 59.8% to 73.1%) and 60.7% (95% CI 53.3% to 67.3%), respectively.

A total of 108 patients died (94.4% breast cancer-related deaths; Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2025.08.005): 46 in the avelumab arm (19.6%) and 62 (26.8%) in the control arm. According to a descriptive analysis of the secondary endpoint OS, avelumab was associated with a reduction in the hazard of death in the whole ITT: HR 0.66, 95% CI 0.45-0.97 (Figure 3A). The 3-year overall survival (OS) estimates in the avelumab and control arms were 84.8% (95% CI 79.5% to 88.8%) and 76.3% (95% CI 70.1% to 81.3%), respectively.

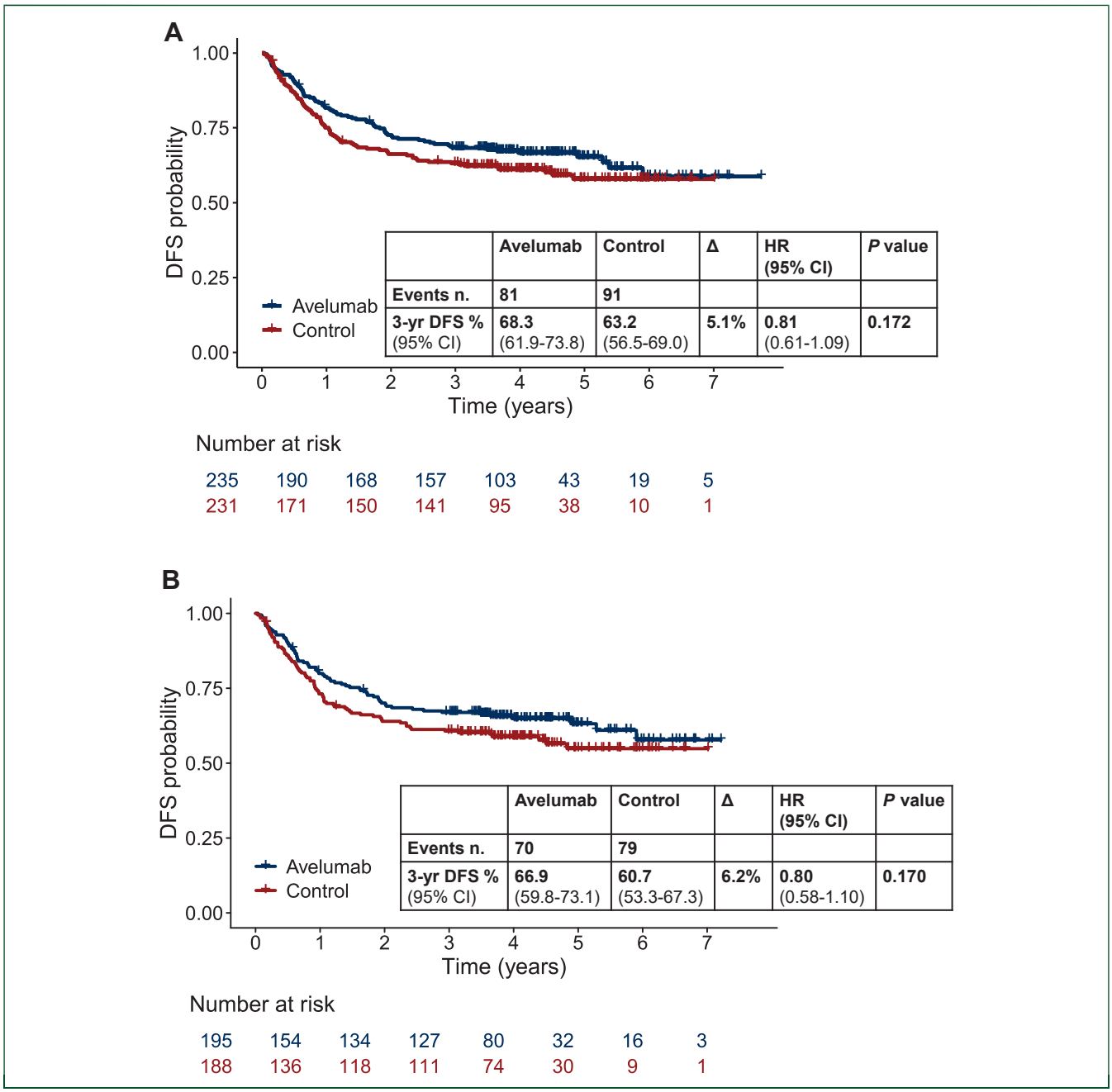
In order to investigate the reasons for a larger effect of avelumab in terms of OS, as compared with DFS, and considering the slight imbalances in the type of DFS events between the two arms, a *post hoc* exploratory analysis of DDFS was carried out. Sixty-six DDFS events (28.1%) were reported in the avelumab group and 85 (36.8%) in the control group (Figure 3B). Among all DDFS events, the most frequent was distant recurrence (81.8% of events in the avelumab arm and 84.7% in the control arm), followed by death (3.0% and 3.5%), and second primary invasive non-breast cancer (2.1% and 2.2%). In a descriptive analysis of DDFS, avelumab was associated to a reduction of hazard of events: HR 0.70, 95% CI 0.50-0.96. The 3-year DDFS estimates in the avelumab and control arms were 75.4% (95% CI 69.3% to 80.4%) and 67.9% (95% CI 61.4% to 73.5%), respectively.

PD-L1 status was available for 407 patients. Patients with PD-L1-positive tumors experienced a better DFS compared with those with PD-L1-negative tumors (HR 0.45, 95% CI 0.26-0.78, $P = 0.003$). The HR for DFS comparing avelumab versus control was 1.72 (95% CI 0.58-5.12) in the PD-L1-positive group and 0.76 (95% CI 0.54-1.08) in the PD-L1-negative group; test for interaction was $P = 0.155$ (Figure 4). The test for interaction with PD-L1 1% increments and treatment arm was $P = 0.283$.

Exploratory subgroup analyses are shown in Figure 5, Supplementary Figures S1 and S2, available at https://doi.org/10.1016/j.annonc.2025.08.005. Additional exploratory analyses, testing other survival endpoints and alternative cut-offs are available as Supplementary Figure S3 and Table S3, available at https://doi.org/10.1016/j.annonc.2025.08.005.

### *Treatment exposure and safety*

Most of the patients who started avelumab were able to complete the planned 52 weeks of treatment ($n = 168$, 72.1%). Eighty-two patients (49%) received all the planned 26 courses without any delays or temporary interruptions,




| | Avelumab | Control | Δ | HR (95% CI) | *P* value |
|---|---|---|---|---|---|
| **Events n.** | **81** | **91** | | | |
| **3-yr DFS %** (95% CI) | **68.3** (61.9-73.8) | **63.2** (56.5-69.0) | **5.1%** | **0.81** (0.61-1.09) | **0.172** |

| | Avelumab | Control | Δ | HR (95% CI) | *P* value |
|---|---|---|---|---|---|
| **Events n.** | **70** | **79** | | | |
| **3-yr DFS %** (95% CI) | **66.9** (59.8-73.1) | **60.7** (53.3-67.3) | **6.2%** | **0.80** (0.58-1.10) | **0.170** |

**Figure 2. Kaplan–Meier plots for DFS according to treatment arm.** (A) Whole intent-to-treat population and (B) stratum B, both coprimary endpoints. CI, confidence interval; DFS, disease-free survival; HR, hazard ratio.

and 80 patients (47%) received 20 or more courses. Among patients who prematurely discontinued treatment ($n = 65$, 27.9%), reasons were: disease recurrence ($n = 33$, 50.8%), adverse event ($n = 20$, 30.8%), and patient decision or other ($n = 12$, 18.5%).

The most frequent immune-related adverse event (irAE) with avelumab was thyroid dysfunction: hypothyroidism in 31 patients (13.2%) and hyperthyroidism in 11 patients (4.7%), all grade 1 or 2. Very few patients had a grade 3 immune-related toxicity: transaminase, lipase, amylase increase (three patients each), and colitis (one patient). A summary of irAEs is available in Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2025.08.005.

## DISCUSSION

The phase III A-BRAVE trial did not meet its primary endpoint: the HR of 0.81 for DFS with avelumab versus control for patients with TNBC at high risk of relapse was not statistically significant, with consistent results in the ITT population and those patients with iRD after neoadjuvant chemotherapy (coprimary endpoints). The descriptive analysis of the secondary endpoint OS suggested an improvement with avelumab versus control (HR 0.66, 95% CI 0.45-0.97). Similarly, a descriptive analysis of *post hoc* DDFS indicated a reduction in risk with avelumab (HR 0.70, 95% CI: 0.50-0.96).

Based on a consistent biological rationale and data in advanced disease, ICIs have been extensively investigated for

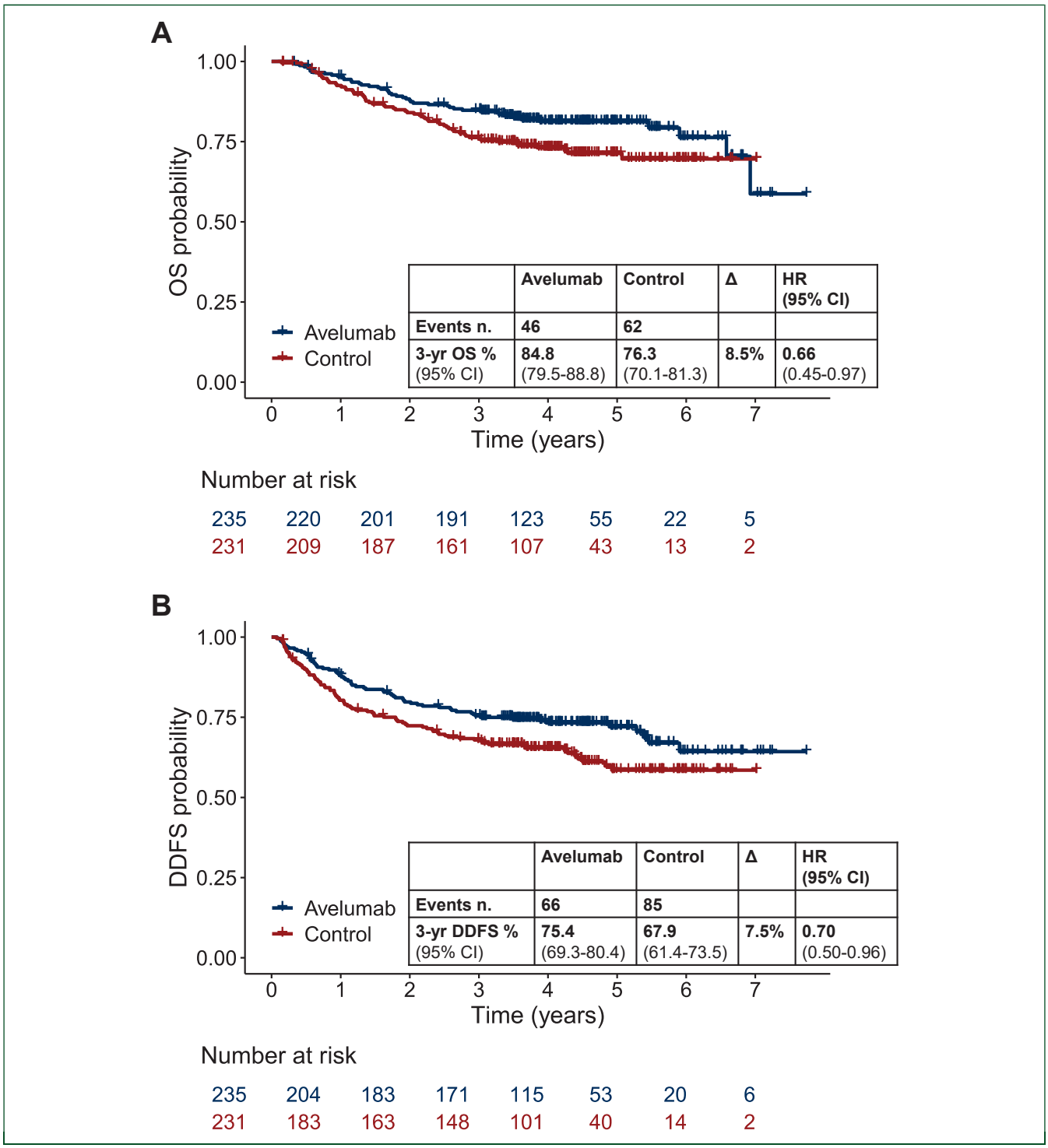



**Figure 3. Kaplan–Meier plots for OS and DDFS according to treatment arm in the whole intent-to-treat population.** (A) OS, secondary endpoint and (B) DDFS, exploratory endpoint.
CI, confidence interval; DDFS, distant disease-free survival; HR, hazard ratio; OS, overall survival.

nonmetastatic TNBC. Most of the randomized trials so far tested the addition of an ICI to neoadjuvant chemotherapy.[10,15-18] In some trials, the ICI was continued after surgery.[10,16] A significant increase in pCR rate was reported by the majority of the studies, but, most importantly, survival outcomes were positively affected by ICIs to a larger extent than pCR.[19-21] Based on these results, neoadjuvant chemotherapy plus pembrolizumab, with pembrolizumab continued after surgery independently from the pathological response, is now standard of care in many countries. Conversely, the ALEXANDRA trial—where atezolizumab was started concomitantly to adjuvant chemotherapy and continued for 1 year in patients

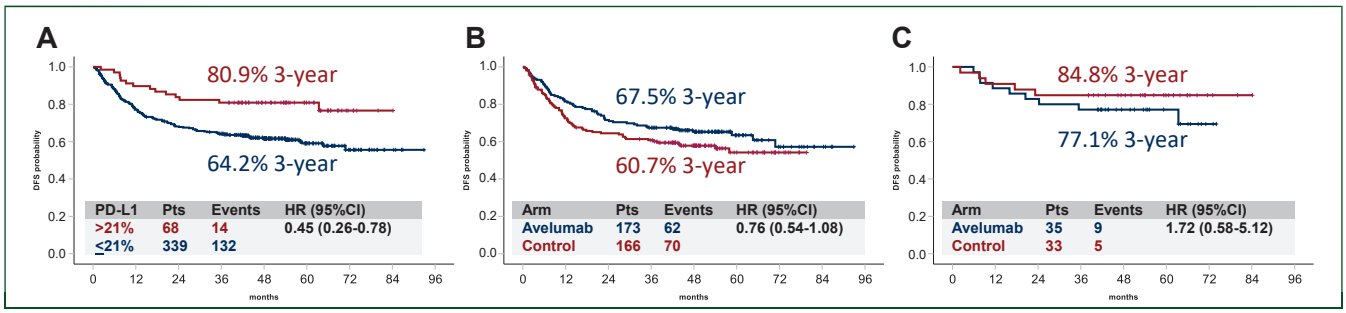



**Figure 4. Kaplan–Meier plots for DFS according to PD-L1 status.** (A) DFS by PD-L1; (B) DFS in patients with PD-L1-negative (<21%) tumor by treatment arm; (C) DFS in patients with PD-L1-positive (≥21%) tumor by treatment arm (secondary endpoint).
CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; PD-L1, programmed death-ligand 1; VUS, variant of uncertain significance.
*Test for interaction.

undergoing primary surgery—was closed for futility at the planned interim analysis.[22] These data also reinforced the thesis according to which ICIs induce an antitumor immune response most effectively when macroscopic disease is present (neoadjuvant) rather than in the eventual presence of micrometastatic disease (adjuvant).[23] Accordingly, preclinical evidence in murine models and clinical evidence in other cancer diseases support a more pronounced activity of ICIs with neoadjuvant administration.[24,25] Therefore, the main question is how to reconcile and contextualize the results of the A-BRAVE adjuvant trial in this scientific and clinical scenario.

A-BRAVE addressed a different question compared with previous trials in TNBC: how efficacious is adjuvant treatment with an ICI in patients selected for being at high risk of relapse? The rationale behind this approach is dual: escalate treatment only for those patients who may really need it,

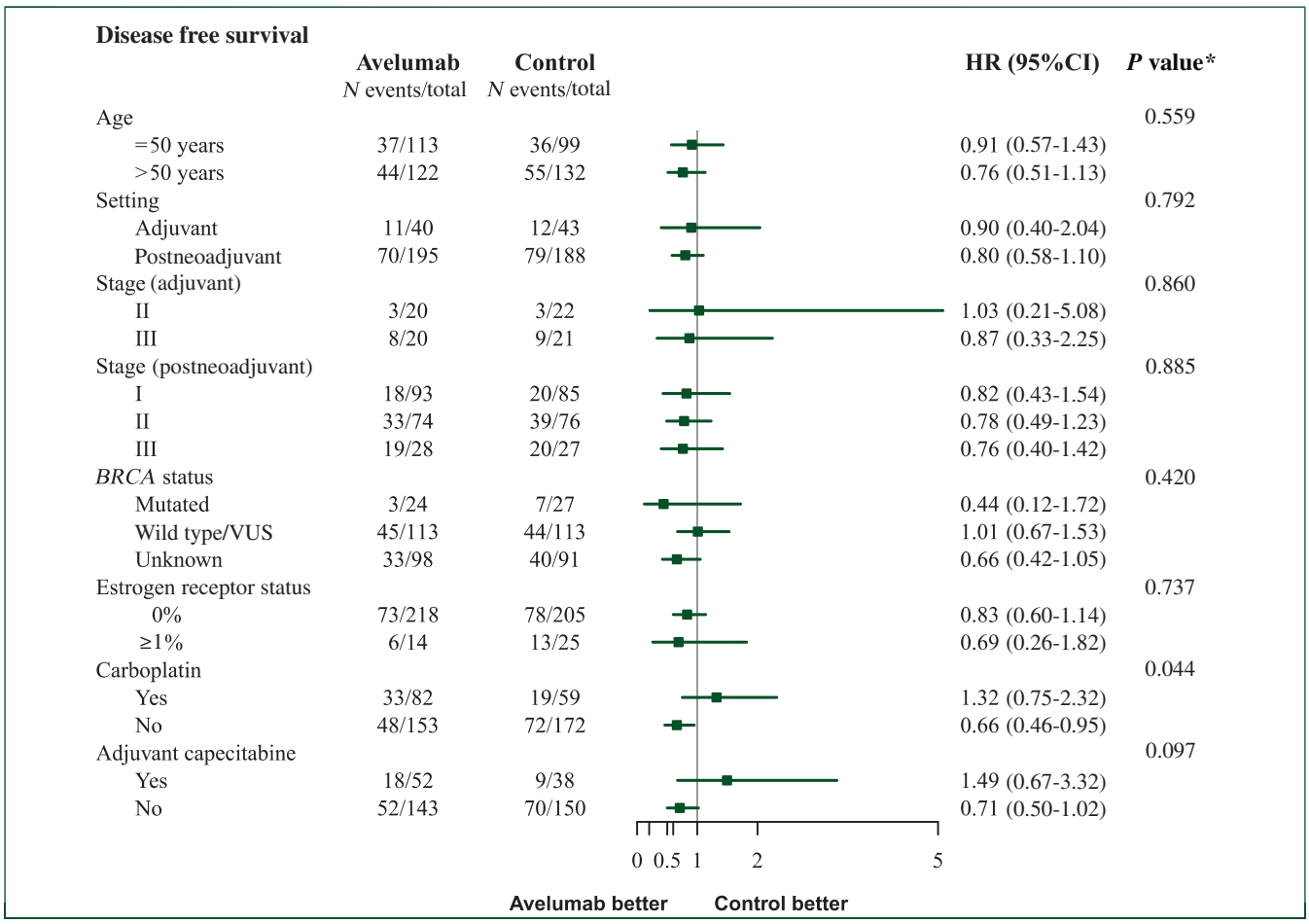



**Figure 5. Subgroup analysis of DFS.**
CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; Pts, patients; VUS, variant of unknown significance.
*Interaction $P = 0.155$.

and improve tolerability by administering an ICI as a single agent, in the attempt to maximize the benefit/risk ratio of incorporating an ICI in the curative setting for TNBC.

A-BRAVE is formally a negative trial, as the dual coprimary endpoints of DFS were not met. However, the signal for improvement in both OS and DDFS stimulates discussion. *Post hoc* exploratory DDFS analysis in this trial must be interpreted with caution and can only be considered as hypothesis generating. However, it is widely recognized that DDFS rather than DFS is a better surrogate for OS.[26,27] At present there are no conclusive explanations for why the magnitude of difference in OS for avelumab versus control was apparently larger than the difference observed for DFS. Patients with TNBC may carry germline *BRCA1/2* or *PALB2* mutations that determine a significant risk of second tumors, which can be curable and have an impact on DFS without affecting OS and DDFS. In our study, 11% of patients had a documented germline *BRCA1/2* mutation; PALB2 status was unknown.

More than 80% of patients in the A-BRAVE trial met the criteria for stratum B and did not achieve a pCR after neoadjuvant chemotherapy, while a minority of patients were enrolled in stratum A. The efficacy of avelumab did not differ by stratum A or B; however, the sample size in the former is limited, making the results of A-BRAVE particularly relevant for patients with iRD after neoadjuvant chemotherapy, while not excluding an effect in stratum A. In addition, caution is needed when applying these results to patients treated with contemporary chemotherapy regimens (e.g. neoadjuvant carboplatin, postneoadjuvant capecitabine). In our study, capecitabine was used in only 23% of stratum B patients, and carboplatin use was inconsistent and imbalanced between arms. Therefore, we cannot confirm that avelumab results would be reproducible in this context. Ongoing studies (e.g. SWOG S1418) will help clarify the role of ICIs in this setting.

Although neoadjuvant pembrolizumab (continued as adjuvant) combined with chemotherapy is standard for AJCC stage II-III TNBC, safety is of concern in a curative setting considering the risk of potentially life-threatening and lifelong toxicities. In the KEYNOTE-522 trial, the rate of grade $\geq$3 irAEs with pembrolizumab was 12.9% (including four toxic deaths), with most of the events occurring in the neoadjuvant phase.[10] With the KEYNOTE-522 regimen applied in the real-world setting, up to 32% of grade $\geq$3 irAEs have been reported.[28] The low incidence of grade $\geq$3 irAEs with avelumab in the A-BRAVE trial suggests a favorable tolerability profile with an ICI administered as a single agent.

As the A-BRAVE trial failed to meet its primary endpoint, the results will not have any direct impact on clinical practice. However, the observed signal suggesting a potential favorable impact of adjuvant avelumab on DDFS and OS, if confirmed by other trials (e.g. SWOG S1418) might, in the future, open the field to personalized algorithms in selected patients. Moreover, it is worth mentioning that the A-BRAVE trial allowed the inclusion of patients in stratum B with initial cT1cN0 tumor stage, whereas patients with clinical stage I were excluded from KEYNOTE-522 and do not currently have access to pembrolizumab.

Differences in the patient population between the A-BRAVE and ALEXANDRA trials may explain discrepant results. A-BRAVE included patients at worse prognosis (as clearly recapitulated by survival outcomes in the control arms of both trials). This is true also when focusing only on stratum A, including 50% of patients with stage III (compared with 15% of patients in the ALEXANDRA trial).[22] Another hypothesis is that prior exposure to chemotherapy including anthracyclines in the neoadjuvant phase (stratum B) may itself exert antitumor immune-activating functions,[29,30] preparing the ground for subsequent ICI that may further maintain or boost an effective immune response. If so, our findings would not be in contrast with the preclinical observation that neoadjuvant immunotherapy is more efficacious than in the adjuvant setting, considering that this preclinical model lacks the exposure to prior chemotherapy.[24] Similarly, data in melanoma patients showing a larger effect of immunotherapy when administered neoadjuvantly, as compared with adjuvantly, refer to regimens including ICIs alone.[25]

PD-L1 expression was confirmed in A-BRAVE as prognostic but not predictive for the efficacy of avelumab, consistent with other neoadjuvant immunotherapy trials in TNBC.[10,20] Intriguingly, there was a signal for improved outcome with avelumab in case of PD-L1-negative disease and apparently no impact in PD-L1-positive patients. On one hand, the overall good outcome of the PD-L1-positive group with low number of events may have prevented the possibility to detect some effect of avelumab. On the other hand these results further suggest a higher plasticity of the tumor immune microenvironment of early TNBC compared with advanced disease. The IHC 73-10 Research Use Only assay used in A-BRAVE does not have a clinically validated scoring system and no formal comparison to the performance of clinically used assays is available. The main cut-off applied ($\geq$21%) was defined in our previous work to provide optimal prognostic separation, and was not designed to predict immunotherapy benefit.[14] For additional clarity, no significant interaction with treatment benefit was observed using different cut-offs or the continuous variable.

In conclusion, adjuvant avelumab versus observation for high-risk TNBC patients, although not improving DFS, may potentially reduce the risk of death. This finding requires confirmation in larger trials before claiming potential impact in clinical practice.

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## DISCLOSURE

PC has received research funding to his institution from the health care business of Merck KGaA, Darmstadt, Germany; and is listed as co-inventor in patent applications for HER2DX.

MVD declares (outside the submitted work) personal fees for an advisory/consultancy role from Lilly, Novartis, Pfizer, Roche, Seagen, Gilead Sciences, Exact Sciences, Daiichi Sankyo, AstraZeneca, and Merck Sharpe & Dohme (MSD); research grants to her institution from Roche and AstraZeneca; honoraria for a speaker role from Lilly; travel/accommodation support from Roche, Gilead Sciences, and Lilly; and is listed as co-inventor in patent applications for HER2DX.

PS receives honoraria or consultation fees from AstraZeneca, Bayer, Boehringer Ingelheim, Merck, Novartis, Pfizer, Puma, Roche, Eisai, and Celgene; and receives grant/funding to his institution from Astellas, AstraZeneca, Genentech, Novartis, Oncogenex, Roche, Medivation, and Merck.

AZ has received fees in advisory boards from Roche, Pfizer, Lilly, Novartis, AstraZeneca, Merck, Gilead, Daiichi-Sankyo, MenariniStemline, and ExactSciences, all outside this work.

FP declares, outside the submitted work, the following: consultancy/advisory board for Daichii Sankyo, Novartis, Pfizer, and Roche; honoraria as a speaker from Novartis, Lilly, MSD, Pfizer, and Roche.

MDL has a consulting or advisory role with Roche, Novartis, Pfizer, Lilly, AstraZeneca, MSD, Pierre Fabre, Seagen, Gilead Sciences, Ipsen, and Daiichi Sankyo Europe GmbH; receives speaker bureau fees from Novartis; honoraria from Roche, Novartis, Pfizer, Lilly, Pierre Fabre, AstraZeneca, MSD, Seagen, Gilead Sciences, Ipsen, Exact Sciences, TOMA Biosciences, Daiichi Sankyo Europe GmbH, and Veracyte; research funding to his institution from Novartis, Roche, Lilly, Pfizer, Daiichi Sankyo, MSD, Bristol Myers Squibb, Genzyme, and AstraZeneca; and has stock and other ownership interests with Arvinas.

GVB has an advisory role with Lilly, Daiichi/AstraZeneca, MSD, Gilead Sciences, and Novartis.

CZ receives grants/research support from Roche, AstraZeneca, Daiichi Sankyo, Gilead Sciences, MSD, GSK, Eisai, Pfizer, Lilly, Novartis, Exact Sciences, and Menarini Stemline; and receives honoraria or consultation fees from Roche, AstraZeneca, Daiichi Sankyo, Gilead Sciences, MSD, GSK, Eisai, Pfizer, Lilly, Novartis, Exact Sciences, Menarini Stemline, and Istituto Gentili.

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AG receives personal fees for advisory board from: Eisai, Novartis, AstraZeneca, Roche, Gentili, Daiichi Sankyo, Pfizer, Eli Lilly, and Menarini Stemline; receives honoraria as invited speaker from Eli Lilly, Exact Sciences, Gilead, and Eisai; and declares nonfinancial relationships with Pharmanutra (provision of dietary supplements for trials).

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AM receives research funding from Lilly, Gilead Sciences, Roche, Pfizer, and Seagen; travel grants from Roche, Lilly, and Novartis; and attends advisory boards for Lilly, Roche, Gilead Sciences, AstraZeneca, and Daiichi Sankyo.

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## DECLARATION OF GENERATIVE AI IN SCIENTIFIC WRITING

During the preparation of this work the author(s) used ChatGPT in order to improve readability and language. After using this tool, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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