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Emergence of immune-related adverse events correlates with pathological complete response in patients receiving pembrolizumab for early triple-negative breast cancer

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ABSTRACT

Based upon results of the KEYNOTE-522 trial and following approval by regulatory authorities, the addition of pembrolizumab to chemotherapy is now the standard-of-care for the treatment of early triple-negative breast cancer (eTNBC) (Clinical stage II-III). Pembrolizumab is a programmed cell death protein 1 monoclonal antibody, known to cause immune-related adverse events (irAEs) in a significant subset of patients. Real-world data on incidence, type and treatment strategies of irAEs in the setting of eTNBC treatment are sparse. In this multicenterretrospective analysis, we characterized real-world incidence of irAEs and treatment outcomes such as pathological complete response (pCR) from the combination of pembrolizumab and chemotherapy as neoadjuvant treatment for eTNBC.

We found a rate of irAEs of all grades of 63.9% and of 20% for irAEs of grade 3 or higher. In the overall population, a pCR rate of 57.1% was observed. The emergence of irAEs correlated significantly with pCR (72.2% versus 30.8%; $p = .03$). Discontinuation of neoadjuvant chemotherapy before week 12 correlated significantly with a lower pCR rate.

To our knowledge, this is the first study evaluating the real-world efficacy and safety of a neoadjuvant combination of chemotherapy and pembrolizumab in eTNBC, demonstrating a significant correlation between irAEs and pCR. Early discontinuation of neoadjuvant therapy due to AEs resulted in a lower pCR rate.

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Introduction

Breast cancer (BC) is the most common cancer in women in industrialized nations[1]. Due to various improvements in care, the survival outcomes for early-stage BC have improved, but the subtype of early triple-negative BC (eTNBC) remains a challenging entity, as a high proportion of patients will eventually develop locoregional or distant relapse.

Recently, the addition of immune-checkpoint inhibitors (CIs), a class of monoclonal antibodies targeting immunosuppressive regulator proteins such as programmed cell death protein 1 (PD-1) or programmed cell death 1 ligand 1 (PD-L1), to chemotherapy has been established as a therapeutic option in TNBC. In metastatic TNBC, the PD-L1-targeting antibody atezolizumab as well as the PD-1-targeting antibody pembrolizumab were approved based upon the phase III IMpassion130 and KEYNOTE-355 trials.[2,3] The KEYNOTE-522 trial evaluated the addition of pembrolizumab to neoadjuvant chemotherapy for the treatment of high-risk eTNBC. In this trial, pembrolizumab led to an increase in the pathological complete response (pCR) rate as well as event-free survival,[4] leading to the approval of this regimen for eTNBC by major regulatory authorities. Trials evaluating other CIs in the (neo) adjuvant setting are ongoing and have partially shown promising preliminary data. In contrast, there is limited evidence regarding the activity and tolerability of neoadjuvant chemo-immunotherapy in eTNBC from a non-trial population in a real-world setting.

While the addition of CIs to chemotherapy offers improved outcomes for patients, the existence of immune-related adverse events (irAEs) poses a novel challenge for caregivers. Interestingly, the incidence and type of irAEs not only depend on drug (e.g., IgG class of monoclonal antibody used) or patient factors (e.g., age, co-morbidities, and genetics[5]) but also tumor characteristics. Rates of irAEs, therefore, differ depending on the cancer entity treated and the clinical stage.[6] In BC, irAE rates of up to 50% were reported in clinical trials, with irAEs of CTCAE grade 3 or higher occurring in 5–20% of patients. For pembrolizumab, numerically higher rates of irAEs of CTCAE grade ≥ 3 (12.9%) occurred in the neoadjuvant KEYNOTE-522 study[4] when compared with its use in the metastatic setting in the KEYNOTE-355 study (5.3%).[3] In IMpassion130, irAEs of grade 3 or 4 occurred in 7.5% of patients, with endocrinopathies being the most common.[2]

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While some irAEs may resolve and not require specific interventions, others may need immunosuppressive treatment with corticosteroids and/or other immunosuppressive agents such as mycophenolate/mofetil (MMF) or TNFα-directed monoclonal antibodies such as infliximab.[6] Again, real-world data about the frequency, grades, and types of pembrolizumab-mediated irAEs in eTNBC patients are lacking. Therefore, our study aimed at identifying these important clinical parameters through a retrospective multicenter approach in a real-world setting.

Methodology

We included all patients at three participating centers in Austria and England receiving pembrolizumab plus chemotherapy for eTNBC from October 2020 until March 2023 in this multicenter retrospective study. Only patients who underwent surgery for primary tumor resection before the data cutoff were included. Data entry was performed by an oncologist or oncologist in training. The grading of irAEs was performed by local investigators according to the NCI Common Terminology Criteria for Adverse Events, version 5.0. The study was approved by the Ethics Committee (vote 1222/2023) of Medical University Vienna. As this was a retrospective analysis, written informed patient consent was waived by the Ethics Committee.

Fisher's Exact test was used for the comparison of categorical variables. Multivariable analysis was performed by binary logistic regression. The multivariable model included age group (categorical: <65 or ≥65 y), tumor stage (categorical: stage I/II or stage III), discontinuation of neoadjuvant treatment ≤12 weeks (categorical: yes or no), and dose reductions of chemotherapy (categorical: yes or no). A two-sided p-value of <0.05 was considered statistically significant for all tests. Statistical analyses and the preparation of figures were carried out using IBM SPSS Statistics for Macintosh, Version 23, and Graph Pad Prism7.0a for Macintosh. As no formal sample-size calculation was performed, all statistics are purely descriptive by nature. Microscopy pictures of the biopsy and tumor specimen were created using a 3D Histec system. IHC and HE staining protocols used are available upon request.

Data availability

Raw data, including high-resolution microscopy pictures of pCR outcomes, are available upon request to the corresponding author.

Results

Overall, 35 female patients were included in our analysis with a median age of 51 years (range 25–74). Five patients were ≥65 y of age. Mean body-mass index was 27.4 kg/m^2, and median tumor size as reported by radiological findings at baseline was 29.5 mm (range 10–100). About 13 of 33 patients with known axillary assessment at baseline (39.4%) had nodal involvement as determined by clinical and/or radiological staging. The median proliferation rate as measured by either Ki-67 or MIB-1 staining in the pre-treatment biopsy specimen was 80% (range 30–90). Of 23 patients with known germline *BRCA* mutation status, 6 patients (26.1%) had hereditary BC (Table 1). Of note, no significant

Table 1. Baseline patient and tumor characteristics of the study cohort including age, menopausal status, body mass index (BMI), tumor T stage, nodal status, disease stage, cell proliferation index per KI67 staining and BRCA mutation status.

	All patients (*N*= 35)
Age	
Median (range) – year	51 (25–74)
<65 year – no. (%)	30 (85.7)
Menopausal status – no. (%)	
Premenopausal/Perimenopausal	14 (40.0)
Postmenopausal	19 (54.3)
Unknown	2 (5.7)
BMI – no. (%)	
<25 kg/m^2	14 (40.0)
≥25 kg/m^2	21 (60.0)
Primary tumor classification – no. (%)	
T1 to T2	26 (74.3)
T3 to T4	8 (22.9)
Unknown	1 (2.9)
Nodal Involvement – no. (%)	
Positive	13 (37.1)
Negative	20 (57.1)
Unknown	2 (5.7)
Disease Stage – no. (%)	
Stage I	8 (22.9)
Stage II	18 (51.4)
Stage III	7 (20.0)
Unknown	2 (5.7)
Ki67 Expression	
Median (range) – %	80 (30–90)
***gBRCA1/2* mutation – no. (%)**	
Yes	6 (17.1)
No	17 (48.6)
Unknown	12 (34.3)

correlations between patient characteristics and the emergence of irAEs or pCR outcomes were found.

Patients were treated with a median of 8 cycles (range 1–9 cycles) of neoadjuvant pembrolizumab. The median duration of chemotherapy was 24 weeks (range 4–24). 28 patients (80%) received a chemotherapy backbone strictly as per the KN522 protocol. Dose reductions of chemotherapy were common in our cohort (27 of 35 patients, 77.1%). Discontinuation rates for neoadjuvant pembrolizumab and chemotherapy were 37.1% and 17.1%, respectively (Table 2). Hence, neoadjuvant pembrolizumab was discontinued in 13 of 35 patients within the cohort. Of note, discontinuation of neoadjuvant pembrolizumab alone occurred in 7 of the 13 patients, while discontinuation of both pembrolizumab and chemotherapy occurred in 6 of the 13 cases. In 11 of these 13 cases (84.6%), discontinuation of neoadjuvant pembrolizumab was due to emergence of neoadjuvant irAEs. Before or equal to week 12, discontinuation of neoadjuvant treatment occurred in 4 of 35 patients (11.4%).

A statistically not significant higher rate of treatment discontinuations was observed in patients ≥65 y (2/5 ≥ 65 y *vs.* 4/30 < 65 y, respectively), while dose reduction rates were comparable between both groups (5/5 *vs.* 22/30).

Out of 35 patients, 27 (77.1%) had breast-conserving surgery and 9 of 35 (25.7%) patients had axillary dissection. Upon surgery of the primary tumor, the entire study cohort had a pCR rate of 57.1% (20 of 35) (Table 3). Representative microscopy images, including H&E as well as IHC stainings of "pCR" and "no pCR" outcomes, are shown in Supplemental Figures S1 and S2. The mean follow-up was 181 d (range 0–649). During follow-up, two patients experienced relapses (one local and one distant) (Figure 1).

irAE incidence of any type or grade was observed in 62.9% of patients (22/35) and of grade 3 or higher in 20% of patients (7 of 35). 77.3% (17/22) of irAEs observed occurred in the neoadjuvant treatment phase and 22.7% (5/22) during postneoadjuvant treatment. Steroid use was necessary in 15 of 22 patients experiencing irAEs (68.2%). No toxicity of grade 5 was observed. irAEs observed were three cases of hepatitis (two of grade 2 and one of grade 3), one case of nephritis (grade 3) and three cases of pneumonitis (grade 1–3), as well as endocrinopathies ($n = 9$, 8 thyroid dysfunctions of grade 1–2, one case of grade 3 hypophysitis), arthritis ($n = 3$, all grade 2), myocarditis ($n = 2$, one grade 3/one grade 4) as well as two cases of grade 2-dermatitis, one case of immune-mediated thrombocytopenia (ITP, grade 3) and one finding of eosinophilia grade 2 (Table 4).

In our patient cohort, the emergence of either neoadjuvant or postneoadjuvant irAEs correlated significantly with pCR (pCR rate 72.2% in patients with irAEs *vs.* 30.8% in patients without, respectively; $p = .03$, Table 5, Figure 2). This correlation remained significant after multivariate analysis, as described in the methodology section. Early discontinuation of chemotherapy up to week 12 correlated significantly with a lower pCR. In detail, patients who completed more than 12 weeks of neoadjuvant chemotherapy had a pCR rate of 64.5% (20/31), while no patient who discontinued neoadjuvant

Table 2. Chemotherapy and immunotherapy adjustments performed in the study cohort. Most patients (80%) received chemotherapeutic backbones similar to those administered in KEYNOTE-522. Drug discontinuations of any drug occurred in 37.1% of patients. Dose reductions of chemotherapy were common, with 77.1% of patients receiving at least one dose reduction of any chemotherapeutic agent.

	All patients (*N*= 35)
Chemotherapeutic Backbone Analogous to KN522	
yes–no. (%)	28 (80.0)
Discontinuation of NACT	
yes–no. (%)	6 (17.1)
Dose Reductions of NACT	
yes–no. (%)	27 (77.1)
Discontinuation of neoadjuvant Pembrolizumab	
yes–no. (%)	13 (37.1)

Table 3. Surgical procedures performed and pCR outcomes observed within the total study cohort. The majority of patients (77.1%) received breast-conserving surgery. Approximately one-quarter of patients (25.7%) underwent axillary dissection.

	All patients (*N*= 35)
Breast-Conserving Surgery	
yes–no. (%)	27 (77.1)
Axillary Dissection	
yes–no. (%)	9 (25.7)
Pathological Complete Remission	
yes–no. (%)	20 (57.1)

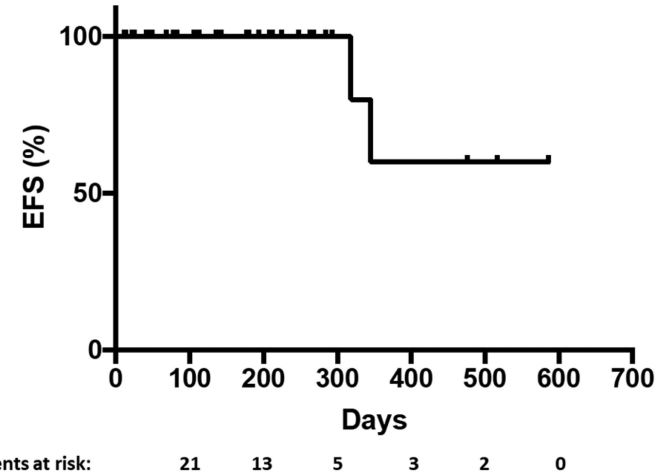

Figure 1. Event-free survival (EFS) in the study cohort as depicted by Kaplan–Meier survival curve. At a mean follow-up of 181 d, median EFS was not reached.

Table 4. Incidence and types of irAEs observed in the study population. Of note, 22 patients (62.9%) experienced at least one irAE, with investigators reporting a total of 25 irAEs. Most (77.3%) irAEs occurred during the neoadjuvant treatment phase. Treatment of irAEs mainly involved the use of corticosteroids (in 68.2% of cases), and pembrolizumab was discontinued in most (81.8%) of patients experiencing irAEs.

Type of irAE – no. (%)	
Hypothyroidism	7 (20.0)
Arthritis	3 (8.6)
Hepatitis	3 (8.6)
Pneumonitis	3 (8.6)
Dermatitis	2 (5.7)
Myokarditis	2 (5.7)
Eosinophilia	1 (2.9)
Hyperthyroidsm	1 (2.9)
Hypophysitis	1 (2.9)
ITP	1 (2.9)
Nephritis	1 (2.9)
Total iAEs observed (*n*=25)	
Patients with irAEs (*N*=22)	
Steroid Use yes–no. (%)	15 (68.2)
Use of other immunosuppression yes–no. (%)	1 (4.5)
Discontinuation of Pembrolizumab yes–no. (%)	18 (81.8)

Table 5. Contingency tables for the occurrence of irAEs (upper) and duration of neoadjuvant chemotherapy ≤12 weeks (lower) and their correlation with pCR outcomes in the study cohort. The occurrence of irAEs as well as the duration of neoadjuvant chemotherapy ≤12 weeks significantly correlated with pCR rates observed in the study population. Fisher's exact test was used for the comparison of categorical variables. A two-sided p-value <0.05 was considered statistically significant.

	pCR (*n*=20)	no PCR (*n*=15)	p-value
Occurence of irAEs			
irAE – no. (%) (*n*=22)	16 (72.7)	6 (27.3)	.03
No irAE – no. (%) (*n*=13)	4 (30.8)	9 (69.2)	
Duration of NACT of ≤12 weeks			
Discontinuation occured – no. (%) (*n*=4)	0 (0.0)	4 (100.0)	.03
No discontinuation – no. (%) (*n*=31)	20 (64.5)	11 (35.5)	

treatment ≤12 weeks achieved pCR (Table 5). This finding, however, did not remain significant upon multivariate analysis.

Discussion

In this retrospective study, we aimed to characterize the real-world toxicity and efficacy of pembrolizumab and chemotherapy for eTNBC. We found correlations between immune-related adverse events and pathologic complete response; in addition, a lower pCR rate was observed in patients with early chemotherapy discontinuation. To our best knowledge, this is the first report of irAE as a predictive biomarker for pCR in eTNBC, and the results need to be discussed in the light of efficacy and safety data from neoadjuvant trials in BC as well as other studies investigating a correlation of irAE frequency, treatment response, and survival across different malignancies.

Overall, the pCR rate in our population was 57.1%, which was numerically slightly lower compared with results from the pivotal KEYNOTE-522 trial.[4] Still, these results reflect the high activity of neoadjuvant chemo-immunotherapy with a quadruple chemotherapy backbone of paclitaxel and carboplatin, followed by anthracyclines and cyclophosphamide in combination with pembrolizumab and suggest that results from a selected trial population can be translated into a real-world setting. This observation is pertinent, as pCR is an established surrogate endpoint for long-term outcome in TNBC, both on an individual patient level and on a trial level.[4,6,7]

While efficacy results are reassuring, a dose reduction of any component of neoadjuvant chemotherapy was required in 77.1% of patients and 6/35 patients (17.1%) permanently discontinued neoadjuvant therapy; of note, in 4/35 patients (11.4%), early discontinuation during the first 12 weeks was observed. In the chemotherapy cohort of ABCSG-34

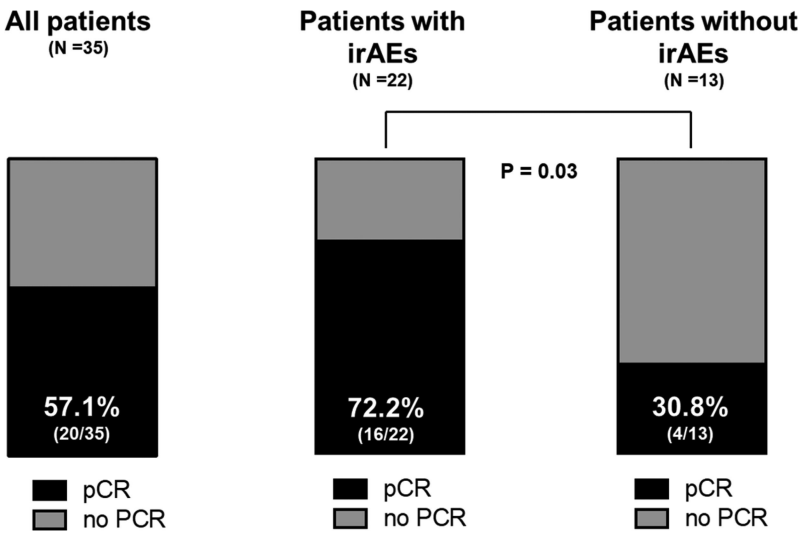

Figure 2. Emergence of immune-related adverse events significantly correlates with pCR. Bar graphs depict pCR rates within the total population (left), patients experiencing irAEs (middle), and patients without irAEs (30.8%, right). Patients experiencing irAEs exhibited significantly higher rates of pathological complete response when compared to patients not experiencing irAEs (72.2% vs. 30.8%, $p = .03$).

randomizing patients to two different sequences of anthracyclines and taxanes (epirubicine/cyclophosphamide (EC) followed by docetaxel or the reverse sequence thereof), the overall chemotherapy discontinuation rate was 9.2%.[8] The phase III GeparSepto trial randomized 1,129 patients to neoadjuvant chemotherapy with nab-paclitaxel or solvent-based paclitaxel before four cycles of EC.[7] In this study, discontinuation rates of the taxane part of chemotherapy (i.e., during the first 12 weeks) were 16% and 6% in both arms, respectively. When focusing on patients receiving nab-paclitaxel at 150 mg/m^2, the discontinuation rate, however, was higher at 26.8%, but most of these patients continued on EC. The phase III BrighTNess trial established carboplatin, albeit at a dose of AUC6 once every 3 weeks, as a component of neoadjuvant chemotherapy.[9] The highest discontinuation rate before week 12 was observed in patients receiving paclitaxel, carboplatin plus veliparib (11%); still, ≥88% of patients across all treatment groups received at least 11 doses of weekly paclitaxel, and more than 90% of patients received all four cycles of carboplatin (or carboplatin placebo) and four cycles of doxorubicin/cyclophosphamide, suggesting an overall permanent discontinuation rate of less than 10%. In KEYNOTE-522, any study drug was discontinued in 23.3% of patients in the pembrolizumab arm, compared with 12.3% of patients in the placebo arm.[4] In the pembrolizumab arm, 92.6% started on EC/AC, indicating a permanent chemotherapy discontinuation rate at ≤12 weeks of 7.4%. GeparNuevo was a placebo-controlled phase II randomized trial investigating the addition of the PD-L1 targeting monoclonal antibody durvalumab to neoadjuvant chemotherapy consisting of nab-paclitaxel followed by dose-dense EC.[10] The discontinuation rate of durvalumab/placebo was 21.3%; regarding early chemotherapy discontinuation, 7.5% of patients permanently discontinued chemotherapy before or at 12 weeks, similar to KEYNOTE-522. With an intense chemotherapy backbone of eight cycles of nab-paclitaxel/carboplatin with or without atezolizumab, the early treatment discontinuation rate in the NeoTRIP trial was 25% in both arms, and the median number of chemotherapy cycles was six (range 1–7 cycles).[11] In summary, these data suggest that both the intensification of chemotherapy and the addition of checkpoint inhibitors lead to an increase in treatment burden resulting in higher discontinuation rates; this effect may be even more pronounced in a real-world setting. These results are clinically relevant, as patients with early treatment discontinuation with ≤12 weeks of neoadjuvant chemotherapy had a markedly lower benefit with 0/4 patients achieving pCR as compared to a pCR rate of 64.5% in patients with treatment duration >12 weeks. This observation emphasizes the need for meticulous risk-benefit assessment and identification of patients where a less intense therapy approach may be preferred. To date, predictive biomarkers of both response and toxicity are lacking. While numerically, a higher rate of patients ≥65 y discontinued neoadjuvant treatment early in our study (2/5 *vs*. 4/30), the overall number of patients ≥65 y is too small to draw any conclusions regarding tolerability in an elderly population.

Analogously to the rate of treatment discontinuations, the rate of chemotherapy dose reductions reported in this retrospective analysis is higher when compared with clinical trials, but direct comparability is hampered by different ways of reporting. In ABCSG-34, the highest rate of dose reduction was observed in patients receiving docetaxel 100 mg/m^2 after four cycles of EC (33.1%).[12] In GeparSepto, 30% of patients in the nab-paclitaxel group required dose reduction as compared with only 12% in the solvent-based paclitaxel arm, indicating higher dose reduction rates with intensified chemotherapy.[7] In BrighTNess, 42% of patients required a carboplatin dose reduction; no information regarding dose reduction rates is provided from KEYNOTE-522.[4,9] Despite a lower dose-intensity, high pCR rates were observed in our study irrespective of dose reductions in 63.0% (17/27) for patients with dose reductions vs. in 37.5% (3/8) for patients without dose reductions (p = 0.2464, n.s.), supporting the notion that, in contrast to early treatment discontinuations, dose reductions may not have any major detrimental effect on outcome in a real-world setting.

A correlation between irAE and outcome was suggested in melanoma and lung cancer patients, where immunotherapy is well established.[13–18] Similar observations were obtained across other solid malignancies as well.[15, 19–22] Of note, Hussaini et al. found a significant correlation between the emergence of irAEs upon CI treatment and response (ORR, PFS, and OS) in a meta-analysis of various advanced cancer studies, not including BC trials.[22] While a potential immortality bias was suggested due to an increased risk for experiencing irAE with longer treatment duration, this bias is less obvious when correlating irAE and treatment response.[15,23] Recently, an exploratory post-hoc analysis presented by Hope Rugo and colleagues found a trend for ameliorated PFS and OS for patients who experienced irAEs during first-line treatment with pembrolizumab for metastatic TNBC within the KEYNOTE-355 trial.[24] This trend was independent of PD-L1 status and – although found in the metastatic setting – would be in line with the findings presented in this manuscript. To our best knowledge, however, our results are the first to report a correlation between irAE emergence and treatment efficacy in early TNBC, using the well-defined and standardized endpoint pCR in a population of eTNBC patients receiving neoadjuvant chemo-immunotherapy; in our study, 72.2% of patients with irAEs had pCR upon surgery as compared with 30.8% in patients without irAEs (p = 0.03). Overall, the majority of irAEs observed were mild to moderate with some exceptions, among them one case of severe myocarditis. In addition, the issue of potentially irreversible irAEs such as endocrinopathies remains in a population of patients with prolonged life expectancy. The overall rate of irAEs was comparable to results from the pivotal trial, strengthening the validity of our data. Of note, none of the patients died from irAEs, and the poor prognosis of metastatic TNBC patients, the benefits of adding checkpoint inhibitors to standard chemotherapy clearly outweigh the risks.

There are several limitations to our study. The retrospective design as well as the relatively small patient sample and the low number of patients ≥65 y; in addition, no correction for potential confounders (e.g., tumor-infiltrating lymphocytes (TIL), homologs recombination deficiency, germline *BRCA* mutation (as status was not known for all patients in the study cohort), and tumor mutational burden (TMB) was performed.[25–27] Due to the lack of these further analyses, we can only hypothesize about explanations of the found correlation between irAE

emergence and pCR on a molecular and cellular level. These might include elusive differences in tumor and tumor-microenvironment characteristics such as TMB, TIL infiltration or metabolism,[28,29] MHC-I expression heterogeneity,[30] but also patient characteristics such as genetic or environmental and lifestyle factors potentially influencing immunogenicity (e.g., co-medications,[31] smoking habits,[32] dietary factors,[33] or microbiome[34,35]). Finally, despite pCR being an accepted surrogate for long-term outcome in TNBC, data regarding event-free survival and overall survival remain immature at a median follow-up of 181 d.

Despite these limitations, to our best knowledge, this is the first report on a correlation of irAE and pCR rates in an early-stage TNBC population. Furthermore, efficacy and toxicity data suggest the transferability of results from the pivotal KEYNOTE-522 trial into a real-world setting. While clinical results require confirmation in larger datasets, these data emphasize the potential role of autoimmune phenomena as biomarkers of response prediction. Further work should focus on the underlying biology of checkpoint inhibitor-induced autoimmunity in the context of the anti-tumor response.

Disclosure statement

TR has received financial contributions to attend meetings from Daiichi Sankyo, Amgen, and MSD. MM has received honoraria for lectures, advisory board participation and consultation from Roche, Eli Lilly, Novartis, Astra Zeneca, Daiichi Sankyo, Pfizer, MSD, Gilead, and Medmedia, and travel support from Amgen, Gilead, Roche, Novartis, Pierre Fabre, Daiichi Sankyo, and Eisai.

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Author contributions

MM, RB and TR designed the study and its methodology. Data collection was performed by SU, AH, MH, MF, KW, ZBH, RE, FF and KSW. Data input was performed by MM, SU, and AH. Data analysis as well as creation of figures and tables was performed by MM and SU. MM and RB wrote the manuscript. All authors read and approved the manuscript.

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