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REVIEW

Pembrolizumab and atezolizumab in triple-negative breast cancer

Dorota Kwapisz[1]

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Abstract

Triple-negative breast cancer (TNBC) is defined by a lack of expression of both estrogen (ER) and progesterone (PgR) receptors as well as human epidermal growth factor receptor 2 (HER2) and is associated with poor prognosis. Moreover, the systemic treatment options are limited. However, the TNBC is more likely than other breast cancer subtypes to benefit from immune checkpoint blockade therapy due to its higher immunogenicity, higher enrichment by tumour-infiltrating lymphocytes (TILs), and higher levels of programmed cell death ligand 1 (PD-L1) expression. Thus far, atezolizumab was approved in combination with nab-paclitaxel for patients with unresectable locally advanced or metastatic TNBC whose tumours express PD-L1. Currently, it seems that PD-L1-positive subgroup will potentially benefit the most from the immune checkpoint inhibitor (ICI) treatment. Moreover, it seems that better results are seen when an ICI is given as first-line treatment than when an ICI is given in later lines of treatment for advanced TNBC/metastatic TNBC. Recently, pembrolizumab has demonstrated promising results in early-stage TNBC what can lead in near future to its approval in (neo)adjuvant setting. This review summarizes the development and highlights recent advances of the atezolizumab and pembrolizumab in early and advanced/metastatic TNBC.

Keywords Immunotherapy · Triple-negative breast cancer · Pembrolizumab · Atezolizumab · Immune checkpoint inhibitor

Abbreviations

AE	Adverse event
AKT	Protein kinase B
Anti-PD-1	Anti-programmed death receptor 1
ASCO	American Society of Clinical Oncology
aTNBC	Advanced triple-negative breast cancer
BC	Breast cancer
BRCA	Breast cancer gene
CPS	Combined positive score
DFS	Disease-free survival
DLTs	Dose-limiting toxicities
EFS	Event-free survival
ER	Estrogen receptor
FDA	US Food and Drug Administration
HER2	Human epidermal growth factor receptor 2
ICI	Immune checkpoint inhibitor
ICs	Immune cells
ITT	Intention-to-treat
LDH	Lactate dehydrogenase
MEK	Mitogen-activated protein kinase kinase
mTNBC	Metastatic triple-negative breast cancer
ORR	Objective response rate
OS	Overall survival
pCR	Pathological complete response
PD-L1	Programmed cell death ligand 1
PFS	Progression-free survival
PgR	Progesterone receptor
TILs	Tumour-infiltrating lymphocytes
TMB	Tumour mutational burden
TNBC	Triple-negative breast cancer
TRAEs	Treatment-related adverse events

Introduction

Triple-negative breast cancer (TNBC) is an aggressive tumour that accounts for nearly one-fifth of all breast cancers (BCs) and results in poor clinical outcomes [1, 2]. The TNBC subtype is more likely to benefit from immunotherapy because of the presence of mutations, tumour-infiltrating lymphocytes (TILs) and elevated levels of programmed death ligand 1 (PD-L1) expression [3–5]. Some studies

✉ Dorota Kwapisz
dmkwapisz@gmail.com

[1] Department of Immunology, Transplantology and Internal Diseases, University Clinical Center of the Medical University in Warsaw, Warsaw, Poland

have shown that the expression of PD-L1 occurs mainly on tumour-infiltrating immune cells (ICs) rather than on BC cells [3, 6].

Thus far, chemotherapy has remained the standard of care for patients with metastatic TNBC (mTNBC), leading to unsatisfactory long-term results [7, 8]. However, in March 2019, atezolizumab, a monoclonal antibody targeting PD-L1, received accelerated approval from the US Food and Drug Administration to be combined with nab-paclitaxel for patients with unresectable locally advanced TNBC or mTNBC whose tumours express PD-L1 [9, 10]. Simultaneously, the VENTANA PD-L1 assay, as a companion diagnostic device, was approved [10]. Atezolizumab is the first immune checkpoint inhibitor (ICI) accepted as therapy for TNBC. Although the updated findings from the IMpassion130 trial showed no improvement in overall survival (OS) for patients who received atezolizumab compared with that in patients who received a placebo in the intention-to-treat population, the benefit of combination treatment with atezolizumab was maintained in the PD-L1-positive subgroup [11].

The possibility of using immunotherapy for mTNBC is already viable in daily clinical practice, and it will most likely be registered soon for early TNBC. Currently, the most advanced studies of ICIs in TNBC concern the use of atezolizumab and pembrolizumab (anti-programmed death receptor 1; anti-PD-1 drug), and this review will discuss the trial results of these drugs in both the (neo)adjuvant and metastatic settings.

Early TNBC—neoadjuvant treatment

In the phase Ib KEYNOTE-173 study, the safety and early antitumour activity of pembrolizumab with chemotherapy as neoadjuvant treatment for TNBC were tested [12]. Treatment-naïve patients with high-risk, early-stage of TNBC (T1c, N1–N2; T2–T4c, N0–N2) were enrolled to this study [12]. Paclitaxel or nab-paclitaxel with or without carboplatin were used in different doses and schemes. Moreover, all patients received doxorubicin plus cyclophosphamide [12]. Pembrolizumab was administered up to 9 cycles [12]. When the combined positive score (CPS) was ≥ 1, the tissue was defined as PD-L1 positive, which was noted in 78% of patients in this study [12]. Most patients had primary tumour T2, nodal involvement, and stage II of the disease [12]. Dose-limiting toxicities (DLTs) were noted in more than one-third of patients, with the most common being febrile neutropenia [12]. The most common treatment-related adverse events (TRAEs) were neutropenia, nausea, and anemia [12]. Febrile neutropenia (Grade ≥ 3 TRAEs) occurred in 22% of patients [12]. It was not surprising that neutropenia, febrile neutropenia, and thrombocytopenia were more common in the carboplatin-containing groups [12]. The overall pathological complete response (pCR) rate was nearly 60% [12]. In general, regarding pCR among patients receiving platinum, better results were found for those who received carboplatin every 3 weeks [12]. Only in the cohort without carboplatin administration was disease progression noted [12]. Event-free survival (EFS) and OS rates at 12 months were 18% higher in patients who received platinum [12]. Researchers evaluated if stromal TILs or PD-L1 expression correlated with treatment results. As predicted and in line with other studies, higher PD-L1 expression and stromal TIL levels were significantly associated with higher pCR rates as well as strongly correlated with each other [12].

The effect of 4 cycles of pembrolizumab with neoadjuvant chemotherapy (paclitaxel, doxorubicin, cyclophosphamide) on pCR in 29 patients with early-stage TNBC was also tested in phase II randomized I-SPY2 trial [13]. Participation in this study was allowed when stage II or III BC was recognized and primary tumour was greater than 2.5 cm or 2.0 cm in physical examination or by imaging, respectively [13]. Estimated pCR rate was the highest in TNBC group reaching of 60%. The estimated pCR rates were higher across all subgroups receiving pembrolizumab compared with control populations [13].

Interestingly, in the NeoTRIPaPDL1 trial, the addition of atezolizumab to neoadjuvant chemotherapy failed to significantly improve the pCR rate of TNBC [14]. However, the primary aim of the study was EFS at 5 years after randomization of the last patient. In the NeoTRIPaPDL1 trial patients with early high-risk (51%) and locally advanced (49%) TNBC received chemotherapy (carboplatin, nab-paclitaxel, doxorubicin, epirubicin, cyclophosphamide, fluorouracil) with or without of 8 cycles of atezolizumab [14]. It is worth outlining that only 13% of patients did not have lymph node involvement. In total, 56% of patients had PD-L1-positive samples, and it was shown that PD-L1 expression was the most significant factor influencing pCR, regardless of the use of atezolizumab [14].

In contrast to the NeoTRIPaPDL1 trial, the phase III IMpassion031 study evaluated atezolizumab in combination with chemotherapy (nab-paclitaxel, doxorubicin and cyclophosphamide) in comparison to placebo plus chemotherapy and met its primary endpoint by demonstrating a statistically significant and clinically meaningful improvement in pCR with atezolizumab among people with early TNBC, regardless of PD-L1 expression, according to a press release (data not available yet) [15]. The different results in the NeoTRIPaPDL1 and IMpassion031 trials can potentially be explained by the fact that different chemotherapy regimens were used for neoadjuvant treatment [14, 15]. In the NeoTRIPaPDL1 study, the only neoadjuvant treatment was carboplatin and nab-paclitaxel with or without atezolizumab,

but anthracycline and cyclophosphamide were given following surgery (the effect of the latter drugs is not captured in the pCR outcome). In the IMpassion031 trial all chemotherapy was given before surgery [14, 15].

Currently, results from phase III KEYNOTE-522 trial are available (Table 1) [16]. In this study 1174 patients with stage of disease as described in the KEYNOTE-173 trial were enrolled. Most patients had stage II of TNBC (around 75%), 48% of participants did not have lymph node involvement, and 81–83% had PD-L1 status positive [16]. Patients were assigned to pembrolizumab-chemotherapy or placebo-chemotherapy group [16]. As chemotherapy they received paclitaxel, carboplatin (every 3 weeks or once weekly), doxorubicin or epirubicin, cyclophosphamide [16]. During neoadjuvant treatment the one group received jointly 8 cycles of pembrolizumab [16]. Moreover, the adjuvant treatment consisted of 9 cycles of pembrolizumab or placebo [16]. If indicated radiotherapy was performed. The percentage of pCR was significantly higher among patients in the pembrolizumab arm (64.8%) than among those who did not receive anti-PD-1 drug (51.2%) [16]. The benefit was seen regardless of PD-L1 status [16]. It is important to point out that PD-L1 positivity was defined in a different way and with a different assay than in the atezolizumab trials. The KEYNOTE-522 used 22C3 antibody and determined PD-L1 positivity using the CPS which was defined as the number of PD-L1-positive cells (tumour cells, lymphocytes, and macrophages) divided by the total number of tumour cells multiplied by 100 [16]. The PD-L1 positivity was determined as a CPS of 1 or greater [16]. Serious TRAEs were noted 13% higher in the pembrolizumab–chemotherapy group with the most common of febrile neutropenia (14.6%), anemia and pyrexia [16]. The incidence of grade 3 or higher adverse events (AEs) was noted to be at least 7 times higher in the pembrolizumab group, and mainly in neoadjuvant phase of treatment [16]. Survival outcomes are not available but by increasing pCR rate we assume that disease-free survival (DFS) and OS will also increase. It is postulated that pCR can be a surrogate of survival for TNBC [17–19]. Nonetheless, the data supporting above assumptions are needed.

There are several possible explanations for the inconsistent findings between the NeoTRIPaPDL1 and KEYNOTE-522 studies [14, 16]. Both trials were conducted with an ICI plus chemotherapy as neoadjuvant therapy in similar populations of patients with early TNBC, but the ICI and chemotherapy regimens were different [14, 16]. Moreover, the assays used to evaluate PD-L1 expression were also different [14, 16]. Finally, the NeoTRIPaPDL1 trial was a smaller study [14]. However, the IMpassion031 trial, which showed positive results, was also a smaller study than the KEYNOTE-522 trial and used atezolizumab as in the NeoTRIPaPDL1 study [14–16]. In light of this information, we can assume that neoadjuvant chemotherapy had a significant influence on the results. All chemotherapy (different schemes) in the KEYNOTE-522 and IMpassion031 trials was given as neoadjuvant treatment, which was not the case in the NeoTRIPaPDL1 study [14–16].

Early TNBC—adjuvant treatment

Pembrolizumab was tested in adjuvant setting as part of treatment in the KEYNOTE-522 trial [16]. The results of the study are indicated above. Currently, phase III NCT02954874 trial is ongoing, where pembrolizumab is administered for 52 weeks in adjuvant therapy (Table 2) [20]. Moreover, IMpassion030 and IMpassion031 trials with atezolizumab in (neo)adjuvant regimens are underway [20]. The details of ongoing phase III clinical trials in early-stage TNBC are listed in Table 2.

Advanced or metastatic TNBC—ICI in monotherapy

In the phase I trial (PCD4989g), 116 patients with mTNBC received atezolizumab in monotherapy [21]. Most patients had visceral disease and had previously received at least 2 lines of therapy for mTNBC [21]. Moreover, 78% of patients had PD-L1 expression on tumour-infiltrating ICs at least of 1% [21]. Almost every patient experienced AE, with grade 3/4 of 51% [21]. TRAE of grade 3/4 occurred in 11%. The median progression-free survival (PFS) by Response Evaluation Criteria In Solid Tumours and median OS were 1.4 months and 8.9 months, respectively [21]. The median OS and objective response rate (ORR) were higher among those who received atezolizumab as first-line treatment [21]. Similarly, those with PD-L1 IC $\geq$ 1% had higher median OS than those with PD-L1 IC < 1% [21]. In general, higher ORR, longer PFS and OS were noted in participants with higher baseline IC infiltration and CD8-positive T-cells [21]. Based on this study, it seems, that worse results can be expected in patients with elevated lactate dehydrogenase (LDH) and/or liver metastases, with high tumour burden, with drug administration after few previous lines of treatment, and with worse general condition [21].

As monotherapy, pembrolizumab was also tested in the phase Ib KEYNOTE-012 study [22]. Almost 47% of patients with mTNBC received at least three prior lines of treatment, while one-fourth of participants received at least five lines of treatment. Only 5 patients did not receive any prior therapy because of metastatic disease [22]. Most patients had visceral metastases [22]. Receiving pembrolizumab every 2 weeks resulted in an ORR of 18.5% with CR in one patient [22]. Surprisingly, this patient was heavily pretreated because of metastatic disease [22]. High level of

Table 1 Phase III clinical trials results with pembrolizumab and atezolizumab in TNBC [9, 11, 16, 25, 36, 38]

Trial Name/ Number of participants	Study population	Arms/treatment	Setting	ORR	mPFS	mOS	AE %	Ref
KEYNOTE-522 $n=1174$	Treatment-naïve T1c N1-2, T2–4 N0-2; Also with bilateral or multifocal primary tumours and inflammatory BC	1. Pembrolizumab (4 × 200 mg, Q3W) + PXL (Q1W) + CBDCA (Q1W or Q3W) → 4 × pembrolizumab + AC/EC → surgery → 9 × pembrolizumab (Q3W) ± RTH 2. Placebo (4 × 200 mg, Q3W) + PXL (Q1W) + CBDCA (Q1W or Q3W) → 4 × placebo + AC/EC → surgery → 9 × placebo (Q3W) ± RTH	Neoadjuvant/adjuvant	CR (ypT0/Tis ypN0) Overall: 1. 64.8% 2. 51.2% PD-L1(+): 1. 68.9% 2. 54.9% PD-L1(−): 1. 45.3% 2. 30.3%	"Percentage of patients at 18 months who were alive without disease progression" 1. 91.3% 2. 85.3%	N/A	Any grade: 1. 99.5% 2. 100% Grade ≥ 3: 1. 81% 2. 75.8%	[16]
KEYNOTE-119 $n=622$	After 1–2 prior systemic treatments for mTNBC	1. Pembrolizumab (200 mg, Q3W) 2. Chemotherapy (capecitabine or eribulin or gemcitabine, or vinorelbine)	Metastatic/Second or third-line	All: 1. 9.6% 2. 10.6% CPS ≥ 10: 1. 17.7% 2. 9.2%	All: 1. 2.1 months 2. 3.3 months CPS ≥ 10: 1. 2.1 months 2. 3.4 months	All: 1. 9.9 months 2. 10.8 months CPS ≥ 10: 1. 12.7 months 2. 11.6 months	Grade 3–5: 1. 14% 2. 36%	[25]
IMpassion-130 $n=902$	Metastatic or unresectable locally advanced	1. Atezolizumab (840 mg, Q2W) + nab-PXL 2. Placebo + nab-PXL	Advanced/metastatic first-line	All: 1. 56.0% 2. 45.9% All—CR: 1. 7.1% 2. 1.6% PD-L1(+): 1. 58.9% 2. 42.6% PD-L1(+)—CR: 1. 10.3% 2. 1.1%	All: 1. 7.2 months 2. 5.5 months PD-L1(+): 1. 7.5 months 2. 5.0 months	All: 1. 21.3 months 2. 17.6 months PD-L1(+): 1.25.0 months 2. 15.5 months	Any grade: 1. 99.3% 2. 97.9% Grade 3 or 4: 1. 48.7% 2. 42.2%	[9]
IMpassion-130 Japanese subgroup $n=65$	Metastatic or unresectable locally advanced	1. Atezolizumab (840 mg, Q2W) + nab-PXL 2. Placebo + nab-PXL	Advanced/metastatic first-line	All: 1. 67.6% 2. 51.6% PD-L1(+): 1. 75.0% 2. 53.8%	All: 1. 7.4 months 2. 4.6 months PD-L1(+): 1. 10.8 months 2. 3.8 months	All: 1. NE 2. 16.8 months PD-L1(+): 1. NE 2. 13.3 months	Any grade: 1. 100% 2. 100% Grade 3 or 4: 1. 38.2% 2. 40%	[36]

Table 1 (continued)

Trial Name/ Number of participants	Study population	Arms/treatment	Setting	ORR	mPFS	mOS	AE %	Ref
IMpassion-130 $n=902$	Metastatic or unresectable locally advanced	1. Atezolizumab (840 mg, Q2W) + nab-PXL 2. Placebo + nab-PXL	Advanced/ metastatic first-line	N/A	All: 1. 7.2 months 2. 5.5 months PD-L1(+): 1. 7.5 months 2. 5.3 months PD-L1(−): 1. 5.6 months 2. 5.6 months	All: 1. 21.0 months 2. 18.7 months PD-L1(+): 1. 25.0 months 2. 18.0 months PD-L1(−): 1. 19.7 months 2. 19.6 months	Any grade: 1. 99% 2. 98% Grade 3 or 4: 1. 49% 2. 43%	[11]
KEYNOTE-355 $n=847$	Treatment-naïve locally recurrent inoperable or MBC	1. Pembrolizumab + chemotherapy 2. Placebo + chemotherapy See also Table 2	Recurrence, metastatic/ first-line	N/A	CPS ≥ 10: 1. 9.7 months 2. 5.6 months	N/A	Grade 3–5: 1. 68.1% 2. 66.9%	[38]

TNBC triple-negative breast cancer, *ORR* objective response rate, *mPFS* median progression-free survival, *mOS* median overall survival, *AE* adverse event, *Ref* references, *BC* breast cancer, *Q3W* every 3 weeks, *Q1W* once weekly, *PXL* paclitaxel, *CBDCA* carboplatin, *AC/EC* doxorubicin or epirubicin plus cyclophosphamide, *RTH* radiotherapy, *CR* complete response, *PD-L1* programmed cell death ligand 1, *N/A* not applicable, *mTNBC* metastatic triple-negative breast cancer, *CPS* Programmed death ligand 1 combined positive score, *Q2W* every 2 weeks, *NE* not estimable;

LDH at baseline was related with rapid disease progression [22]. The median PFS and median OS were 1.9 months and 11.2 months, respectively [22]. Most likely, the higher the PD-L1 expression, the better the results that can be obtained [22]. In total, at least 56% of patients had at least one TRAE and the most common of any grade included arthralgia, fatigue, myalgia, followed by nausea [22]. The incidences of colitis, hepatitis and hypothyroidism were classified as immune-mediated AEs [22]. Most importantly this study has shown that immunotherapy can be relatively safe and effective in some heavily pretreated patients [22].

The natural continuation of a previous study was the phase II KEYNOTE-086 trial [23]. In cohort B, pembrolizumab was administered every 3 weeks for up to 2 years as first-line treatment for patients with PD-L1-positive mTNBC [23]. Patients with brain metastases were excluded. More than 60% of women had TRAE with the most common of fatigue, nausea and diarrhea [23]. Pembrolizumab monotherapy showed durable antitumour activity with an ORR of 21.4%, including 4 CR [23]. Usually, patients need to wait 2 months until a response is achieved, but the median duration of response was 10.4 months [23]. The median PFS and median OS were 2.1 months and 18.0 months, respectively [23]. In cohort A, pembrolizumab was administered in the same manner as in cohort B, but cohort A comprised previously treated patients because of mTNBC with PD-L1-positive or PD-L1-negative tumours [24]. More than 68% of patients received at least two prior lines of therapy for metastatic disease [24]. In cohort A, the ORR was modest (5.3%) and only slightly better in the PD-L1-positive population [24]. In total, two CR were noted and all in PD-L1-positive population [24]. The median PFS and median OS were 2.0 months and 9.0 months, respectively [24]. There were no significant differences in survival regarding PD-L1 status [24]. TRAE was noted in 60% of patients. In the cohort A and B, thyroid disorders were the most common immune-mediated AEs [23, 24]. Taken together, findings from both cohorts suggest that there is a higher possibility of achieving a response to pembrolizumab in untreated or in patients who received an anti-PD-1 drug in the early lines of treatment because of mTNBC, especially in those with PD-L1-positive tumours. Although this was a phase II study with a small group of patients and a subgroup of responders, the responses were durable, and the toxicity profile was acceptable [23, 24].

Unfortunately, in the randomized phase III KEYNOTE-119 (NCT02555657) study, pembrolizumab monotherapy did not show an improvement in ORR, PFS, or OS as compared to single-agent chemotherapy in participants with previously treated mTNBC (Table 1) [25]. However, it seems that patients with the highest levels of tumour PD-L1 expression had the greatest benefit regarding an ORR and median OS with ICI [25]. Recently, a potential positive

Table 2 Ongoing phase III clinical trials with pembrolizumab and atezolizumab in TNBC (August 2020) [20]

Trial identifier	Status	Setting	Target group	Arms/treatment	POM
NCT03036488 KEYNOTE-522	A N/R	Neoadjuvant, adjuvant	Locally advanced TNBC Treatment-naïve locally advanced non-metastatic (M0) TNBC: T1c, N1-N2 T2, N0-N2 T3, N0-N2 T4a-d, N0-N2	1. PXL + CBDCA + placebo → AC/EC + placebo → surgery → placebo 2. PXL + CBDCA + pembrolizumab → AC/EC + pembrolizumab → surgery → pembrolizumab (Q3W)	pCR rate (ypT0/Tis ypN0) EFS
NCT02954874	R	Adjuvant	TNBC or ER-, PgR- weakly positive and/or HER2-equivocal status and must not have received and not be planning to receive adjuvant anti-HER2 or ETs after completion of neoadjuvant chemotherapy HER2- and HER2-equivocal cases as per ASCO CAP guidelines that do not receive HER2-targeted therapy Weakly ER or PgR positive disease (ER and/or PgR ≤ 5% by IHC) are eligible if the patient is not eligible for adjuvant ET Residual disease must be ≥ 1 cm in greatest dimension, and/or ypN1mi, ypN1, ypN2, ypN3	1. Observation (± Rth) 2. Pembrolizumab (every 42 days for 52 weeks) ± Rth	IDFS Severity of fatigue Physical function
NCT02819518 KEYNOTE-355	A N/R	Recurrence, Metastatic	Treatment-naïve: locally recurrent inoperable breast cancer which cannot be treated with curative intent MBC	Part 1: 1. Pembrolizumab (200 mg/Q3W) + nab-PXL 2. Pembrolizumab (200 mg/Q3W) + PXL 3. Pembrolizumab (200 mg/Q3W) + GEM/CBDCA Part 2: 1. Pembrolizumab (200 mg/Q3W) + chemotherapy 2. Placebo + chemotherapy	Part 1: percentage of participants who experience an AE—all Percentage of participants who discontinue study drug due to an AE—all Part 2: PFS and OS—all PFS and OS in those with PD-L1–positive CPS ≥ 1 tumours, and with CPS ≥ 10 tumours
NCT04191135 KEYLYNK-009	R	Recurrence, metastatic	Treatment-naïve: locally recurrent inoperable TNBC that cannot be treated with curative intent MBC	1. CBDCA + GEM + pembrolizumab → CBDCA + GEM + pembrolizumab (200 mg/Q3W) 2. CBDCA + GEM + pembrolizumab → pembrolizumab (200 mg/Q3W) + olaparib	PFS OS
NCT02620280 NeoTRIPaPDL1	A N/R	Neoadjuvant adjuvant	Early high-risk and locally advanced or inflammatory breast cancers	1. CBDCA + nab-PXL + atezolizumab → surgery → AC or EC or FEC 2. CBDCA + nab-PXL → surgery → AC or EC or FEC	EFS

Table 2 (continued)

Trial identifier	Status	Setting	Target group	Arms/treatment	POM
NCT03498716 IMpassion030	R	Neoadjuvant adjuvant	Operable stage II-III	1. Atezolizumab (840 mg/Q2W) + PXL → atezolizumab + ddAC/ddEC → surgery → atezolizumab (1200 mg/Q3W to complete 1 year of treatment from the first dose) 2. PXL → ddAC/ddEC → surgery	IDFS
NCT03197935 IMpassion031	A N/R	Neoadjuvant adjuvant	cT2-cT4, cN0-cN3, cM0	1. Atezolizumab (840 mg/Q2W) + nab-PXL → atezolizumab (840 mg/Q2W) + AC → surgery → atezolizumab (1200 mg/Q3W, 11 doses) 2. Placebo + nab-PXL → placebo + AC → surgery	Percentage of participants with pCR Percentage of participants with pCR in subpopulation with PD-L1–positive tumour status
NCT03281954	R	Neoadjuvant, adjuvant	T2 or T3, N0 cN1 (cytologically or histologically positive) or cN2-N3 (with or without a biopsy), then can be clinically T1c, T2, or T3	1. PXL + CBDCA + placebo → AC/EC + placebo → surgery → placebo 2. PXL + CBDCA + atezolizumab → AC/EC + atezolizumab → surgery → atezolizumab (1200 mg/Q3W)	pCR in the breast and lymph nodes (ypT0/Tis ypN0) EFS
NCT03125902 IMpassion131	A N/R	Locally advanced, metastatic	Treatment-naïve: locally advanced MBC not amenable to surgical therapy	1. Atezolizumab (840 mg/Q2W) + PXL 2. Placebo + PXL	PFS in the subpopulation with PD-L1(+) tumour status PFS in the intent-to-treat population
NCT03371017 IMpassion132	R	Recurrence, locally advanced, metastatic	Treatment-naïve: locally recurrent, inoperable Locally advanced MBC	1. Atezolizumab (1200 mg/Q3W) + chemotherapy (GEM + CBDCA or capecitabine) 2. Placebo + chemotherapy (GEM + CBDCA or capecitabine)	OS in population with PD-L1(+) tumour status OS in modified intent-to-treat popluation
NCT04177108	R	Locally advanced unresectable, metastatic	Treatment-naïve: locally advanced unresectable MBC	PD-L1(-): 1. PXL + atezolizumab + ipatasertib 2. PXL + placebo + ipatasertib 3. PXL + placebo + placebo PD-L1(+): 1. PXL + atezolizumab + ipatasertib 2. PXL + atezolizumab + placebo	PFS OS

TNBC triple-negative breast cancer, *POM* primary outcome measures, *A N/R* Active not recruiting, *PXL* paclitaxel, *CBDCA* carboplatin, *AC/EC* doxorubicin plus cyclophosphamide/epirubicin plus cyclophosphamide, *Q3W* every 3 weeks, *pCR* pathological complete reponse, *EFS* event-free survival, *R* recruiting, *ER* estrogen receptor, *PgR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *ET* endocrine therapy, *ASCO CAP* American Society of Clinical Oncology College of American Pathologists, *IHC* immunohistochemistry, *Rth* radiotherapy, *IDFS* invasive disease-free survival, *MBC* metastatic breast cancer, *GEM* gemcitabine, *AE* adverse event, *PFS* progression-free survival, *OS* overall survival, *PD-L1* programmed cell death ligand 1, *CPS* combined positive score, *FEC* fluorouracil, epirubicin and cyclophosphamide, *Q2W* every 2 weeks, *dd* dose-dense

association between tumour mutational burden (TMB) and clinical benefit with pembrolizumab was suggested, especially in patients with TMB ≥ 10 mut/Mb [26].

Advanced or metastatic TNBC—ICI in combination

In the phase Ib study (GP28328) atezolizumab with nab-paclitaxel in 33 patients with mTNBC after maximum of 2 prior lines of treatment were tested [27]. Around 80% of patients had previously been treated with taxane [27]. Patients with untreated or active brain metastases were excluded. The ORR was 39%, and ORR was numerically higher in the treatment-naïve patients and in PD-L1-positive patients (no statistical significance) [27]. The median PFS and OS were 5.5 months and 14.7 months, respectively [27]. The median TILs was only 5% [27]. In biopsy cohort no significant changes regarding PD-L1 and stromal TILs were seen in samples taken during treatment, either with taxane or anti-PD-L1 drug plus taxane [27]. Biomarkers were not significantly associated with results [27]. TRAE of any grade occurred in every participant and 73% of patients suffered from grade 3/4 AEs [27]. The most frequent AEs were neutropenia, fatigue, alopecia, and diarrhea [27]. Febrile neutropenia was noted in 1 patient. The most common grade 3/4 AEs related with atezolizumab administration were diarrhea and colitis [27]. It seems that high rate of grade 3/4 neutropenia was related with nab-paclitaxel dose [27].

Interestingly, at American Society of Clinical Oncology (ASCO) Virtual Scientific Meeting in 2020 the updated results from ENHANCE 1, a phase Ib/II study exploring the combination of eribulin plus pembrolizumab in patients with mTNBC were announced [28]. Researchers concluded that higher activity for the combination treatment was seen among patients with PD-L1-positive tumours, and in the first-line setting [28]. In this subgroup the median PFS and median OS were 6.1 months and 21 months, respectively [28]. In later-lines setting of treatment comparable survival outcomes were observed independently of PD-L1 status [28].

To enhance the treatment results, pembrolizumab was also tested in combination with niraparib, capecitabine and radiotherapy [29–32]. Patients with advanced/metastatic TNBC irrespective of breast cancer gene (BRCA) mutation or PD-L1 status were enrolled to phase II TOPACIO trial and received combination of pembrolizumab (every 3 weeks) with niraparib [29]. Combination of treatment resulted in promising results with at least four times higher ORR among patients with tumour BRCA mutations than among patients with BRCA wild-type tumours [29]. However, we have to be aware of relatively small sample size of this study. Of note, higher PD-L1-positive status was noted in BRCA mutation group [29]. Again, an ORR was lower among those who were previously treated for mTNBC [29]. In recently published study, pembrolizumab with capecitabine showed no significant improvement in PFS in TNBC compared with historical data [30]. In this small by number of patients study, the median PFS and median OS in TNBC cohort were 4 months and 15.3 months, respectively [30]. The ORR in TNBC was 13%, and no CR was noted [30]. However, in another early phase study an ORR was higher in pembrolizumab plus capecitabine group than in pembrolizumab plus paclitaxel group [31].

Interestingly, pembrolizumab was tested with hypofractionated radiotherapy at a total dose of 3000 cGy in patients with mTNBC [32]. The most common irradiated site was breast/chest wall [32]. Previous systemic treatment for metastatic disease was allowed [32]. Finally, in this small phase II study, the ORR was 17.6% with long-lasting, systemic responses in some patients [32]. Consistent with the results of previous studies, a response more likely to be observed when concurrent treatment was administered in earlier lines of therapy because of metastatic disease [32]. It is worth mentioning that, in the phase II TONIC trial, nivolumab was administered after induction with hypofractionated radiotherapy (24 Gy) in patients with mTNBC, and a modest ORR of 8% was reached [33].

The addition of another drug to an ICI does not always lead to better results. Recently, the ENCORE 602 (TRIO025), a phase II trial results of atezolizumab with or without entinostat (class I-selective histone deacetylase inhibitor) in patients with advanced TNBC (aTNBC) have been announced [34]. The addition of entinostat to atezolizumab failed to prolong the median PFS, and the combination therapy resulted in greater toxicity in previously treated patients with aTNBC [34]. Moreover, ICIs were also tested with other drugs in combinations of three. For example, in the phase II COLET study with atezolizumab, cobimetinib (Mitogen-activated protein kinase kinase, MEK inhibitor), and paclitaxel or nab-paclitaxel as first-line treatment for patients with locally advanced or mTNBC resulted in similar ORR in both arms [35]. The ongoing clinical trials with combinations of three drugs are discussed further.

Currently, the most important phase III randomized study in metastatic or unresectable locally advanced TNBC is IMpassion-130 trial [9]. Patients with asymptomatic treated brain metastases were also included to this trial [9]. Previously untreated because of metastatic disease patients received atezolizumab (840 mg) or placebo on days 1 and 15 and received nab-paclitaxel (100 mg/m^2) on days 1, 8, and 15 of every 28 day cycle for six cycles or more [9]. In total, 40.9% of patients were PD-L1-positive [9]. The primary results of the aforementioned study were encouraging in favour of the atezolizumab group, especially the PD-L1-positive subgroup [9]. In the PD-L1-positive subgroup,

the median PFS and median OS were significantly prolonged by 2.5 months and by nearly 10 months, respectively [9]. In total, the median PFS and median OS in atezolizumab group were 7.2 months and 21.3 months, respectively [9]. The CR was noted more than four times more often in the atezolizumab group than in placebo group [9]. Among patients who received atezolizumab the CR was noted in 7.1% in total, and in 10.3% in PD-L1-positive subgroup [9]. Combination therapy with anti-PD-L1 drug had acceptable safety profile [9]. The incidence of grade 3 or 4 AEs of special interest was noted to be 3.2% higher in the atezolizumab group [9]. The most common AEs of any grade in both groups were alopecia, nausea, cough and peripheral neuropathy [9]. In the IMpassion-130 trial 65 patients were Japanese [36]. The survival results in this subgroup were consistent with those reached by all population in the trial [9, 36]. However, ORRs were numerically higher [36]. More often, AEs such as alopecia, peripheral sensory neuropathy or decreased neutrophil count were noted in Japanese patients [36]. However, there were no new safety signals and no grade 3/4 AEs of special interest [36].

In the second prespecified interim OS analysis in the IMpassion-130 trial no significant difference in OS between main groups in ITT population was noted [11]. However, the benefit of atezolizumab administration was still seen regarding median OS in PD-L1-positive subgroup with median OS of 25 months [11]. At the time of the second analysis, 84% and 90% of patients in the atezolizumab group and the placebo group developed disease progression or died, respectively [11]. The most common grade 3–4 AEs were neutropenia, peripheral neuropathy what was the main cause for therapy discontinuation of anti-PD-L1 drug, decreased neutrophil count, followed by fatigue [11].

The phase III IMpassion131 study, which evaluated atezolizumab in combination with paclitaxel in comparison to placebo plus paclitaxel in patients with mTNBC, did not achieve statistical significance for its primary endpoint of PFS for the use of atezolizumab and paclitaxel as first-line treatment in the PD-L1-positive population, according to a press release (data not available yet) [37]. Moreover, the investigators of this study also observed that the OS showed a negative trend, but the study was not powered for OS, and at the time of the analysis, the data were immature [37]. The Impassion130 trial had a similar design to Impassion131 but recruited more patients and used nab-paclitaxel instead of paclitaxel as the chemotherapy comparator. We can suspect that the use of paclitaxel and premedication with high doses of steroids could have influenced the results in the IMpassion131 study.

PFS results of combination treatment investigated in the phase III KEYNOTE-355 trial were presented during the 2020 ASCO Virtual Scientific Meeting [38]. In this study pembrolizumab combined with chemotherapy (nab-paclitaxel, paclitaxel or gemcitabine/carboplatin) showed a statistically significant and clinically meaningful improvement in PFS compared with chemotherapy alone in treatment-naïve patients with locally recurrent, inoperable, or mTNBC whose tumours expressed PD-L1 (CPS of 10 or higher) (Table 1) [38].

Ongoing studies and future directions

It was shown that ICIs in TNBC are more effective in combination treatment than as a single agent. Consequently, many treatment combinations of ICI with various drugs are currently being tested [20]. For example, in the BARBICAN trial researchers want to determine whether adding ipatasertib (protein kinase B, AKT inhibitor) to atezolizumab and chemotherapy increases the probability of an immune response over adding atezolizumab to chemotherapy in patients with TNBC in neadjuvant treatment [39]. The preliminary results of triplet combination of ipatasertib, atezolizumab, and paclitaxel or nab-paclitaxel as first-line therapy for locally advanced/mTNBC have already shown promising antitumour activity with ORR of 73% [40]. Interestingly, NCT04373031 trial in early TNBC with pembrolizumab, chemotherapy, and IRX-2, a cell-derived biologic with multiple active cytokine components, has been recently initiated [20].

Currently, pembrolizumab is tested in TNBC in combination with GX-I7 (long-acting interleukin-7), olaparib (MK-7339-009/KEYLYNK-009 trial), stereotactic body radiation therapy, and oncolytic virus therapy (STOMP trial), PVX-410 vaccine, enobosarm, imprime PGG, which is a soluble, β-1,3/1,6 glucan isolated from the cell wall of a proprietary Saccharomyces cerevisiae yeast strain, intratumoural tavokinogene telseplasmid (KEYNOTE-890 trial), radiotherapy boost, and with various chemotherapy regimens [20]. Moreover, atezolizumab is tested in combination with rucaparib and different chemotherapy schemes as well [20].

In the TNBC or luminal B-like/HER2-negative BC, talimogene laherparepvec with atezolizumab in phase I PROMETEO study are examined. It is a window of opportunity, single arm study design to evaluate the effect of mentioned treatment in women with operable early BC who present residual disease after neoadjuvant chemotherapy [20].

ICIs are also tested in combination with other types of immunotherapy. For example, in phase Ib/II Morpheus-TNBC randomized umbrella study, the efficacy and safety of multiple immunotherapy-based drug combinations (atezolizumab, selicrelumab, tocilizumab, sacituzumab govitecan) for treatment of patients with metastatic or inoperable locally advanced TNBC are evaluated [20].

There are numerous studies that are in progress today and Table 2 shows a list of ongoing phase III clinical trials with pembrolizumab and atezolizumab in TNBC [20].

Conclusions

After many years with stagnation, we can currently offer immunotherapy as a new treatment approach for TNBC. Although immunotherapy raises great hopes in the treatment of TNBC, we must be aware that many studies are ongoing, and many questions remain unanswered. We need to better understand the cancer and immune system interactions, including the chemotherapy backbone and associated regimens. Currently, we can assume that the PD-L1-positive subgroup will potentially benefit the most from the use of ICIs, especially as combination therapy.

Moreover, it seems that better results are seen when an ICI is given as first-line treatment than when an ICI is given in later lines of treatment for aTNBC/mTNBC. Currently, many clinical trials with pembrolizumab and atezolizumab are underway, and we are urgently waiting for their comprehensive results to make final conclusions for the entire TNBC group.

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Compliance with ethical standards

Conflict of interest Author has no conflicts of interest to declare.

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