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Atezolizumab (Tecentriq®) with nab-paclitaxel (Abraxane®) for the treatment of advanced triple-negative breast cancer (aTNBC)

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The HTA Core Model® for Rapid Relative Effectiveness for Pharmaceuticals, developed within EUnetHTA (www.eunethta.eu), has been utilised when producing the contents and/or structure of this work. A working version (unpublished) of V3.0 of the Model was used. Use of the HTA Core Model® does not guarantee the accuracy, completeness, quality or usefulness of any information or service produced or provided by using the Model

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Abstract

Introduction

In patients with triple negative breast cancer (TNBC), over-expression of programmed death ligand 1 (PD-L1) on tumour-infiltrating immune cells (IC) increases the propensity for cancer cells to evade immune surveillance. Atezolizumab, a monoclonal antibody designed to inhibit PD-L1 enables T-cell activation, restoring their ability to effectively detect and destroy tumour cells.

Methodology

Published and grey literature were identified by searching the Cochrane Library, CRD Database, Embase, Ovid Medline, PubMed, Internet sites and contacting the manufacturer. Quality assessment was conducted to assess the risk of bias at the study level based on the EUnetHTA internal validity for randomized controlled trials. The magnitude of clinically meaningful benefit that can be expected from atezolizumab was evaluated based on, both the original and adapted version of, the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology.

Results of the IMpassion130 trial

In the phase III, IMpassion130 trial, 902 treatment-naïve advanced TNBC patients were randomised 1:1 to 840 mg atezolizumab IV or placebo IV on days 1 and 15, plus 100 mg/m^2 nab-paclitaxel IV on days 1, 8, and 15 of every 28-day cycle, until disease progression or toxicity. Adding atezolizumab increased the rate of progression-free survival (PFS) by 6%, prolonged median PFS by 1.7 months, and reduced the risk of progression or death by 20% compared to chemotherapy alone. In the PD-L1-positive subgroup, adding atezolizumab increased the rate of PFS by 13%, prolonged median PFS by 2.5 months, and reduced the risk of progression or death by 38% compared to nab-paclitaxel alone. No statistically significant differences in overall survival (OS) were noted between groups (21.3 months atezolizumab- versus 17.6 months placebo combination). Combination atezolizumab increased the objective response rate (ORR) and duration of response (DOR) in the intention-to-treat (ITT) and PD-L1-positive group compared to chemotherapy alone (10% versus 16%; 1.8 months versus 3.0 months, respectively. Atezolizumab was associated with neutropenia, decreased neutrophils, peripheral neuropathy, fatigue, anaemia and immune-mediated adverse events.

Conclusion

Overall, adding atezolizumab to nab-paclitaxel as first-line therapy for advanced TNBC prolongs PFS and reduces the risk of progression or death. The PFS benefit of atezolizumab combination over chemotherapy alone was also consistent in the PD-L1-positive subgroup. These results are consistent with previous reports suggesting first-line atezolizumab, PD-L1 expression ≥1, and >10% tumour-infiltrating IC are independently associated with increased ORR and PFS. Mature OS data, quality of life measures, and a higher PD-L1 threshold are needed to ensure patients achieve a clinically relevant benefit over time despite manageable toxicity. Further studies are needed to identify predictive immune biomarkers selective of responders, combination strategies that enhance tumour immunogenicity, and to determine whether these findings extend to other chemoimmunotherapy combinations.

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1 Research questions

The HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals was used for structuring this report [1]. The Model organises HTA information according to pre-defined generic research questions. Based on these generic questions, the following research questions were answered in the assessment.

EUnetHTA HTA Core Model®

Element ID	Research question
Description of the technology	
B0001	What is atezolizumab?
A0022	Who manufactures atezolizumab?
A0007	What is the target population in this assessment?
A0020	For which indications has atezolizumab received marketing authorisation?
Health problem and current use	
A0002	What is advanced triple-negative breast cancer?
A0004	What is the natural course of triple-negative breast cancer?
A0006	What are the consequences of triple-negative breast cancer for the society?
A0023	How many people belong to the target population?
A0005	What are the symptoms and the burden of disease or health condition?
A0003	What are the known risk factors for triple-negative breast cancer?
A0024	How is triple-negative breast cancer currently diagnosed according to published guidelines and in practice?
A0025	How is triple-negative breast cancer currently managed according to published guidelines and in practice?
Clinical effectiveness	
D0001	What is the expected beneficial effect of atezolizumab on mortality?
D0005	How does atezolizumab affect symptoms and findings (severity, frequency) of triple-negative breast cancer?
D0006	How does atezolizumab affect progression (or recurrence) of triple-negative breast cancer?
D0011	What is the effect of atezolizumab on patients' body functions?
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C0008	How safe is atezolizumab in relation to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying atezolizumab?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of atezolizumab?
A0021	What is the reimbursement status of atezolizumab?

2 Drug description

Generic/Brand name/ATC code:

Atezolizumab/Tecentriq®/MPDL3280A

B0001: What is atezolizumab?

anti-PD-L1 antibody, immune checkpoint inhibitor

In patients with triple negative breast cancer (TNBC), over-expression of programmed death ligand 1 (PD-L1) on tumour-infiltrating immune cells (IC) increases the propensity for cancer cells to evade immune surveillance. Atezolizumab, a monoclonal antibody designed to inhibit PD-L1 enables T-cell activation, restoring their ability to effectively detect and destroy tumour cells [2].

840 mg atezolizumab IV on days 1 and 15 + 100 mg/m² nab-paclitaxel IV on days 1, 8, and 15 of 28-day cycle

Atezolizumab is available in 1200 mg/20 mL (60 mg/mL) single-use vials. It is administered intravenously (IV) at a fixed dose of 840 mg on days 1 and 15 of every 28-day cycle until disease progression or unacceptable toxicity. Patients also receive 100 mg/m² nanoparticle albumin-bound (nab)-paclitaxel IV on days 1, 8, and 15 per 28-day cycle for six cycles or more [3].

monitor for immune-mediated AEs, infusion reactions and infections; withhold/ discontinue for safety/tolerability

Patients should be monitored for signs and symptoms of immune-mediated pneumonitis, hepatitis, colitis, endocrinopathies, infections or infusion reactions. Atezolizumab may be withheld in patients with adverse events (AEs) of grade ≥2 severity until they are clinically stable, and corticosteroid dose is reduced to ≤10 mg/day. Permanently discontinue atezolizumab in patients with recurrent grade 3, 4 or life-threatening AEs; and those with persistent grade ≥2 AEs or inability to taper corticosteroids within 12 weeks [4]. Immune-modulating drugs may interact with atezolizumab, and systemic corticosteroids may affect its efficacy [2].

A0022: Who manufactures atezolizumab?

Genentech Inc, a subsidiary of F Hoffmann-La Roche Ltd

3 Indication

A0007: What is the target population in this assessment?

previously untreated aTNBC

Atezolizumab (Tecentriq®) is indicated, in combination with nab-paclitaxel, for previously untreated advanced TNBC (aTNBC).

4 Current regulatory status

A0020: For which indications has atezolizumab received marketing authorisation?

FDA approvals: monotherapy for MUC in 2016; expanded to cisplatin-ineligible and platinum-treated MUC in 2017

Atezolizumab received its first global approval by the US Food and Drug Administration (FDA) in May 2016 for the treatment of locally advanced or metastatic urothelial cancer (MUC) with disease progression during or following platinum-based chemotherapy. Approval was based on the tumour response rate and durability reported the single arm, two-cohort, phase II, IMvigor210 study [5]. Indications were expanded to include cisplatin-ineligible and platinum-treated MUC patients following efficacy results from cohort 1 in April 2017.

limited to PD-L1-positive cisplatin-ineligible MUC or platinum-ineligible MUC regardless of PD-L1 status in 2018

In June 2018, the FDA limited atezolizumab use to cisplatin-ineligible patients with PD-L1 tumour expression (PD-L1 stained tumour-infiltrating IC covering ≥5% of tumour area as determined by an FDA-approved test), or platinum-ineligible patients regardless of PD-L1 status. Limitations were made based on the decreased survival associated with atezolizumab monotherapy versus platinum-based chemotherapy observed in clinical trials involving untreated MUC patients with low PD-L1 expression. In July 2018, the Ventana PD-L1 (SP142) Assay (Ventana Medical Systems, Inc) was FDA-approved as a complementary diagnostic required for patient selection [6].

2nd-line metastatic NSCLC; in combination with bevacizumab, paclitaxel and carboplatin as first-line for metastatic NSCLC without EGFR/ALK aberrations

In October 2016, the FDA approved atezolizumab for the treatment of metastatic non-small cell lung cancer (NSCLC) with progression during or following platinum-based chemotherapy. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumour aberrations who progress following therapy for these aberrations may also receive atezolizumab. The approval was based on two international, randomized, open-label trials, OAK (phase III) and POPLAR (phase II) [7, 8]. In December 2018, the FDA approved atezolizumab in combination with bevacizumab, paclitaxel and carboplatin as first-line treatment for metastatic NSCLC without EGFR or ALK aberrations. Approval was based on overall survival (OS) data from the phase III IMpower150 study [9].

EMA approvals: 2nd-line metastatic NSCLC; pre-treated or cisplatin-ineligible MUC regardless of PD-L1 status in 2017

Atezolizumab received market authorization by the European Medical Agency (EMA) in September 2017 as monotherapy for previously treated, locally advanced or metastatic NSCLC, and for previously treated or cisplatin-ineligible MUC regardless of PD-L1 status [10]. In October 2018, the company withdrew its application to extend atezolizumab use in combination with bevacizumab for the treatment of advanced or metastatic renal cell carcinoma due to insufficient study results [11].

FDA and EMA pending approvals in 2019: in combination with nab-paclitaxel as 1st-line for PD-L1-positive aTNBC

The FDA recently granted priority review to atezolizumab in combination with nab-paclitaxel as first-line treatment for patients with locally advanced or metastatic PD-L1-positive TNBC. The phase III IMpassion130 trial forms the basis for the supplemental biologics license application (sBLA) that is scheduled for decision making by March 12, 2019 [12, 13]. Data from IMpassion130 are also under consideration by the EMA, with possible approval later in 2019 [14].

5 Burden of disease

A0002: What is triple-negative breast cancer?

TNBC lacks ER, PR, and HER2 expression; 15-20% of breast cancers

TNBC is characterized by a lack of oestrogen- and progesterone receptor expression and does not overexpress human epidermal growth factor receptor 2 (HER2). Without an approved targeted therapy for TNBC, chemotherapy remains as first-line treatment. [15]. Compared to luminal breast cancers, TNBC is highly sensitive to chemotherapy (10–25% versus 30–40% complete response [CR]) due to higher levels of tumour-immune infiltrate. TNBC is molecularly subtyped as basal-like, mesenchymal, luminal androgen receptor positive and immunomodulatory. While these subtypes express different levels of immune genes, all are immunogenic with high genetic instability, mutational load and immune infiltrate [16]. In TNBC patients, the immune checkpoint inhibitor PD-L1 is over-expressed on tumour-infiltrating IC. PD-L1 binds ligand proteins resulting in T-cell suppression and evasion from immunosurveillance.

immunogenic: PD-L1 over-expression on tumour-infiltrating IC

A0004: What is the natural course triple-negative breast cancer?

staged I-IV by invasiveness

Breast cancer typically arises when epithelial cells lining the milk ducts and/or lobules undergo aberrant cell growth due to dysregulation of the cell cycle. In the early stages, atypical cells confined to the milk ducts are termed stage 0, ductal carcinoma in situ (DCIS). Stage I breast cancer is invasive but is restricted to the area where the first abnormal cells arose. While most breast cancers are diagnosed as stage I (localized to one area) or stage II (early locally advanced), most TNBCs are diagnosed as invasive ductal carcinoma (IDC) or invasive lobular carcinoma (ILC), where abnormal cells have spread beyond the ducts or glands into the breast tissue [15, 17].

metastasize to brain and lungs

Stage III, locally advanced breast cancer includes tumours larger than five centimetres in diameter that involve the skin, underlying muscle, lymph nodes or inflammatory breast cancer (IBC). Many TNBC are diagnosed as stage IV metastatic breast cancer, where breast cancer cells have travelled through the lymphatic system and blood stream forming metastatic tumours in the brain or lungs. TNBC is less likely to spread to the lymph nodes or bones than other breast cancers [15, 17].

A0006: What are the consequences of triple-negative breast cancer for the society?

commonly affects young, premenopausal women and those with >3 children

Globally, breast cancer is the most frequently diagnosed malignancy and the leading cause of cancer death in women worldwide [17]. TNBC accounts for approximately 15–20% of the breast cancers diagnosed worldwide, almost 200,000 cases per year. Compared with other breast cancers, TNBC more commonly affects young, premenopausal women and may occur more frequently in women with three or more children [15]. Patients with TNBC have a poorer prognosis than other types of breast cancer due to their higher grade, lack of targeted therapies, higher and earlier risk of relapse following standard chemotherapy. Recurrences often occur within the first three years after diagnosis with a high rate of visceral metastases. Despite their high chemosensitivity, the median OS of patients with TNBC rarely exceeds 12–18 months [18].

recurrence within 1–3 years of diagnosis; median OS <18 months

A0023: How many people belong to the target population?

About 30% of all malignant neoplasm cases in Austria are due to breast cancer. Accounting for 17% of all deaths due to cancer, it is the most common cause of death due to cancer in women. Unlike other types of breast cancer that are commonly diagnosed in patients aged 60 or older, TNBC is more likely to be diagnosed in people younger than 50 years of age [15]. The age standardised incidence rate for the European Standard Population (2015) is 116.7 for women and 2.4 for men per 100,000 persons per year. In 2015, 5,390 women and 90 men were diagnosed with breast cancer in Austria, and 1,568 women and 22 men died of the disease [19]. TNBC accounts for approximately 15–20% of breast cancers; therefore about 822 to 1,096 persons diagnosed with breast cancer in 2015 in Austria were affected by triple-negative disease.

TNBC in Austria: ~822–1,096 cases in 2015

116.7/100,000 women/year → European Standard Population 2015

A0005: What are the symptoms and the burden of triple-negative breast cancer?

Symptoms of TNBC may include a hard, immovable lump in the breast with irregular borders. Patients with locally advanced breast cancer may experience dimpling or thickening of the skin, a change in shape or colour, nipple inversion or discharge, a pain in the breast or armpit. Patients with metastatic breast cancer may experience bone pain, fractures, headaches, seizures, swollen lymph nodes, shortness of breath or jaundice depending on the organs involved [17].

symptoms include breast lump, thickening, and pain

A0003: What are the known risk factors for triple-negative breast cancer?

Risk factors associated with the diagnosis of TNBC include younger age, BReast CAncer (BRCA) gene mutation, race, premenopausal status, maternal-related factors and obesity [15, 20]. Women under 40 years of age may have a twofold higher risk of TNBC than women over 50 years of age [21]. While less than 6% of all breast cancers are BRCA-related, up to 20% of patients with TNBC carry BRCA1/2 mutations. TNBC was highly predictive of BRCA1 mutation status for women less than 50 years of age and modestly predictive of positive BRCA2 mutation status in women 50 years of age or older [22]. The incidence of TNBC is higher in premenopausal and African-American or Hispanic women compared to menopausal and Caucasian women [15]. Evidence suggests that nulliparity is associated with a lower risk of TNBC; however, parity was not protective in African-American women. Obesity was associated with an increased risk of TNBC according to a meta-analysis of eleven studies involving 24,479 women [23].

risk factors: young age, obesity, African American, Hispanic, premenopausal and BRCA mutation status

A0024: How is triple-negative breast cancer currently diagnosed according to published guidelines and in practice?

diagnostics: mammography, biopsy, HR and HER2 status, bone, CT, PET scans

Since TNBC presents aggressively with rapid growth, it is more likely to be diagnosed clinically than mammographically compared to ER-positive cancers. A mammogram of both breasts is performed to define tumour size and assess whether the contralateral breast is affected. Breast magnetic imaging (MRI) or ultrasound may also be performed to estimate tumour size and distinguish a fluid-filled or a solid mass. During a biopsy, a sample of breast cells or tissue from the lump is examined to determine the presence of cancer cells, and levels of expression of hormone receptors and HER2 protein. TNBC is defined as hormone receptor negative (<1% staining of tumour cells by immunohistochemistry) and HER2 negative (0–1+ immunohistochemistry or nonamplified using fluorescence in-situ hybridization), forming the basis for clinical management. Women 60 years of age or younger diagnosed with TNBC also undergo BRCA mutation testing regardless of family history. Bone scans, blood tests, computed tomography (CT) and positron-emission tomography (PET) scans may be conducted to determine whether breast cancer has spread to bone, liver, lungs, or brain [17].

BRCA mutation testing for women ≤60 years

6 Current treatment

A0025: How is triple-negative breast cancer currently managed according to published guidelines and in practice?

no standard chemotherapy regimen: single-agent taxane or anthracycline

Previously untreated metastatic and advanced TNBC is typically treated using chemotherapy. While there is no standard, specific chemotherapy regimen for TNBC, anthracycline, alkylator-, and taxane-based chemotherapies are commonly used [15].

- International guidelines support the use of single-agent taxanes or anthracyclines (doxorubicin, paclitaxel). Other possible regimens include gemcitabine, eribulin, capecitabine, or vinorelbine as first-line therapy [24].
- Combination regimens include AC (doxorubicin + cyclophosphamide), EC (epirubicin + cyclophosphamide), CMF (cyclophosphamide + methotrexate + fluorouracil), docetaxel + capecitabine, GT (gemcitabine + paclitaxel), gemcitabine + carboplatin, and paclitaxel + bevacizumab [24]
- A platinum agent or taxane chemotherapy is a suitable option to treat BRCA carriers with chemotherapy-naïve aTNBC [15].

PARPi: olaparib is approved for advanced or metastatic TNBC with BRCA1/2 mutations

- Polyadenosine diphosphate-ribose polymerase inhibitor (PARPi), olaparib, was recently approved to treat advanced or metastatic TNBC in those patients with BRCA1/2 mutations who have previously been treated with chemotherapy [15, 24].

7 Evidence

systematic literature search in 5 databases: 95 hits

A literature search was conducted on 15 January 2019 in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Search terms were "atezolizumab", "Tecentriq", "breast cancer", "breast carcinoma", "triple negative" and "advanced". The manufacturer was also contacted and submitted three references (all of which had already been identified by systematic literature search [13, 25, 26]). A manual search identified three FDA regulatory documents [4, 6, 12], three EMA reports [10, 11, 14], ten clinical management documents [5, 7-9, 15, 17, 21-24], one statistical document [19], and two cost documents [27, 28].

manual search: 19 additional references

overall: 114 references included: 3 studies

Overall, 114 references were identified. Included in this reported are:

- IMpassion130, phase III [3, 13, 29, 30]
- Clinical outcomes and biomarker analyses of atezolizumab for metastatic TNBC, phase I [31]
- Atezolizumab plus nab-paclitaxel in metastatic TNBC, phase Ib [32]

study level risk of bias assessed based on EUnetHTA internal validity for RCTs

To assess the risk of bias at the study level, the assessment of the methodological quality of the evidence was conducted based on the EUnetHTA internal validity for randomised controlled trials (RCTs) [33]. Evidence was assessed based on the adequate generation of the randomisation sequence, allocation concealment, blinding of patient and treating physician, selective outcome reporting and other aspects that may increase the risk of bias. Study quality details are reported in Table 6 and Table 5 of the Appendix.

applicability of evidence

The external validity of the included trial was assessed using the EUnetHTA guideline on applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals, considering the following elements: population, intervention, comparator, outcomes and setting (Table 5) [34].

magnitude of clinically meaningful benefit assessed based on ESMO-MCBS

To evaluate the magnitude of "meaningful clinical benefit" that can be expected from a new anti-cancer treatment, the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology (ESMO-MCBS) was used [35]. Additionally, an adapted version (due to perceived limitations) of the ESMO-MCBS was applied [36]. Details of the magnitude of the clinically meaningful benefit scale are reported in Table 3.

7.1 Quality assurance

internal and external review

This report has been reviewed by an internal reviewer and an external reviewer. The latter was asked for the assessment of the following quality criteria:

- How do you rate the overall quality of the report?
- Are the therapy options in the current treatment section used in clinical practice and are the presented standard therapies correct?
- Is the data regarding prevalence, incidence, and amount of eligible patients correct?
- Are the investigated studies correctly analysed and presented (data extraction was double-checked by a second scientist)?
- Was the existing evidence from the present studies correctly interpreted?
- Does the current evidence support the final conclusion?
- Were all important points mentioned in the report?

quality assurance method

The LBI-HTA considers the external assessment by scientific experts from different disciplines a method of quality assurance of scientific work. The final version and the policy recommendations are under full responsibility of the LBI-HTA.

7.2 Clinical efficacy and safety – phase III studies

IMpassion130: atezolizumab + nab-paclitaxel versus placebo + nab-paclitaxel as first-line for aTNBC

IMpassion130 (NCT02425891) is a multicentre, randomised, double-blind, interventional phase III trial involving 902 patients with unresectable locally advanced or metastatic TNBC [13]. The study was designed to evaluate whether adding atezolizumab to nab-paclitaxel as first-line therapy for advanced or metastatic TNBC prolonged progression-free survival (PFS) and OS compared to placebo plus nab-paclitaxel. Efficacy analyses were based on all randomly assigned patients comprising the intent-to-treat (ITT) population and the PD-L1-positive subgroup. Safety analyses involved all patients who received at least one dose of treatment.

ITT (n = 902): stratified by baseline liver metastases, neoadjuvant/adjuvant taxane treatment, and PD-L1 status

Eligible patients were 18 years or older, with untreated metastatic or unresectable locally advanced, histologically documented TNBC, and had tumour specimens available for centralised PD-L1 testing. Patients must have had measureable disease per Response Evaluation Criteria in Solid Tumours (RECIST, version 1.1) and Eastern Cooperative Oncology Group (ECOG) performance-status of 0 or 1, with adequate hematologic and organ function. Patients were excluded if they had a history of autoimmune disease, untreated central nervous system (CNS) disease, or were previously treated with immune checkpoint-targeting therapies, immunosuppressants, systemic immunostimulatory agents or glucocorticoids. Tumour specimens were evaluated for PD-L1 expression using the Ventana PD-L1 (SP142) immunohistochemical assay. Eligible patients were stratified by baseline liver metastases (present or absent), neoadjuvant or adjuvant taxane treatment (use or nonuse), and PD-L1 expression status on tumour-infiltrating

immune cells as a percentage of tumour area (<1% PD-L1 negative versus ≥1% PD-L1 positive).

840 mg atezolizumab IV or placebo IV on days 1 and 15 + 100 mg/m2 nab-paclitaxel IV on days 1, 8 and 15 every 28-days for ≥6 cycles

Patients were randomised 1:1 to 840 mg atezolizumab IV or placebo IV on days 1 and 15 plus 100 mg/m^2 nab-paclitaxel IV on days 1, 8, and 15 of every 28-day cycle for six cycles or more, until disease progression or unacceptable toxicity. In the absence of progression, atezolizumab, placebo or nab-paclitaxel could be discontinued independently, due to toxicity. While dose reductions of atezolizumab or placebo were not permitted, dosage may be interrupted or discontinued due to AEs. Pre-specified modifications of the nab-paclitaxel dose were permitted to manage toxicity. For patients in the atezolizumab plus nab-paclitaxel group, the median treatment duration (DOT) was 24.1 weeks for atezolizumab and 22.1 weeks for nab-paclitaxel. Patients in the placebo combination group had median treatment duration of 22.1 weeks for placebo and 21.8 weeks for nab-paclitaxel. The mean (± standard deviation) cumulative dose of nab-paclitaxel was 1,980.0 ± 1,303.1 mg/m^2 in the atezolizumab combination group and 1,764.4 ± 1,238.3 mg/m^2 in the placebo combination group.

median DOT: 24.1 weeks for atezolizumab versus 22.1 weeks for placebo

primary co-endpoints: investigator-assessed PFS and OS in ITT and PD-L1-positive subgroup

secondary endpoints: ORR, DOR, and safety

The two primary efficacy co-endpoints were investigator-assessed PFS and OS within the ITT population and the PD-L1-positive subgroup. Secondary endpoints included PFS assessed by independent central review (ICR), investigator-assessed objective response rate (ORR), duration of response (DOR), and safety. AEs were graded for severity according to the National Cancer Institute Common Terminology Criteria (CTCAE) version 4.0. Tumours were assessed every eight weeks for twelve months, and every twelve weeks thereafter. Patients were followed-up for survival every three months after discontinuing the intervention. The median follow-up (for both arms) was 12.9 months in the ITT population at the time of primary analysis.

ITT: median age 56 years, 63% had neoadjuvant/adjuvant therapy, 27% had baseline liver metastases

PD-L1-positive: median age 53 years, 66% had neoadjuvant/adjuvant therapy, 23% baseline liver metastases

The ITT population (n = 902) had a median age of 56 years (range 20–86), 99.6% were female, 67.5% were Caucasian, 63.2% were previously treated with neoadjuvant or adjuvant therapy, 27.1% had baseline liver metastases, and 41.4% had an ECOG status of 1. The PD-L1-positive subgroup (n = 369) had a median age of 53 years (range 26 to 85), 99.8% were female, 68.9% were Caucasian, 65.6% received previous neoadjuvant or adjuvant therapy, 22.5% had baseline liver metastases, and 80.7% had an ECOG status of 1. Detailed patient characteristics including inclusion- and exclusion criteria can be found in Table 5 and study quality is described in Table 6 of the appendix, respectively. Clinical efficacy data are presented in Table 1 and AEs are listed in Table 2.

7.2.1 Clinical efficacy

D0001: What is the expected beneficial effect of atezolizumab on mortality?

median OS ITT: 21.3 months for atezolizumab versus 17.6 months for placebo; not statistically significant

In the ITT population, 40.1% (181/451) patients in the atezolizumab combination group and 46.1% (208/451) patients in the placebo combination group had died as of April 17, 2018. At interim analysis, the primary co-endpoint of investigator-assessed median OS was 21.3 months in the atezolizumab plus nab-paclitaxel group versus 17.6 months in the placebo plus nab-paclitaxel group (stratified hazard ratio [SHR] for death, 0.84, 95% confidence interval [CI] 0.69–1.02; p = 0.08, no statistical significant difference [NSSD]).

median OS PD-L1-positive: 25.0 months for atezolizumab versus 15.5 months for placebo; NFT

In the PD-L1-positive subgroup, 34.6% (64/185) patients in the atezolizumab combination group and 47.8% (88/184) in the placebo combination group had died as of the data cut-off. In the PD-L1 subgroup, Kaplan-Meier analysis revealed a median OS of 25.0 months in the atezolizumab plus nab-paclitaxel group and 15.5 months in the placebo plus nab-paclitaxel group (SHR for death, 0.62, 95% CI 0.45–0.86; not formally tested [NFT]).

D0006: How does atezolizumab affect progression (or recurrence) of triple-negative breast cancer?

median PFS ITT: 7.2 months for atezolizumab versus 5.5 months for placebo

In the ITT population, 79.4% (n = 358) of patients receiving atezolizumab combination and 83.8% (n = 378) of patients receiving placebo combination experienced disease progression or death at a median follow-up of 12.9 months. The primary co-endpoint of investigator-assessed median PFS was 7.2 months with atezolizumab plus nab-paclitaxel versus 5.5 months with placebo plus nab-paclitaxel (SHR for progression or death, 0.80, 95% CI 0.69–0.92; p = 0.002).

median PFS PD-L1-positive: 7.5 months for atezolizumab versus 5.0 months for placebo

The PFS benefit of atezolizumab combination over placebo combination was demonstrated across most subgroups as defined on the basis of trial stratification factors. In the PD-L1-positive subgroup, 74.6% (n = 138/185) patients receiving atezolizumab combination and 85.3% (n = 157/184) of patients receiving placebo combination experienced progression or death. The median PFS was 7.5 months with atezolizumab plus nab-paclitaxel versus 5.0 months with placebo plus nab-paclitaxel (SHR for progression or death, 0.62, 95% CI 0.49–0.78; p < 0.001).

D0005: How does atezolizumab affect symptoms and findings (severity, frequency) of triple-negative breast cancer?

ORR ITT: 56.0% atezolizumab versus 45.9% placebo

ORR PD-L1-positive: 58.9% atezolizumab versus 42.6% placebo

The secondary endpoint of investigator-assessed ORR was 56.0% in the atezolizumab combination group and 45.9% in the placebo combination group (p = 0.002) for the ITT population. A CR was reported in 7.1% of atezolizumab combination versus 1.6% of placebo combination recipients. In the PD-L1 subgroup, the ORR was 58.9% with atezolizumab plus nab-paclitaxel and 42.6% with placebo plus nab-paclitaxel. CRs were reported by 10.3% of patients receiving atezolizumab combination versus 1.1% of patients receiving placebo combination.

In the ITT population, the median DOR was 7.4 months in the atezolizumab plus nab-paclitaxel group and 5.6 months in the placebo plus nab-paclitaxel group. The median DOR in the PD-L1-positive subgroup was 8.5 months with atezolizumab combination versus 5.5 months with placebo combination.

DOR ITT: 7.4 months for atezolizumab versus 5.6 months for placebo

D0011: What is the effect of atezolizumab on patients'body functions?

Atezolizumab may affect body functions by causing immune-mediated AEs including pneumonitis, hepatitis, colitis, endocrinopathies, and infections [4, 30]. Adverse events of special interest (AESIs) that were thought to be immune-related occurred in 57.3% of atezolizumab plus nab-paclitaxel recipients and 41.8% of placebo plus nab-paclitaxel recipients. AESIs of grade ≥3 severity were reported in 7.5% of the atezolizumab combination group and 4.3% of the placebo combination group. Two grade 5 AESI were reported; an atezolizumab combination recipient had autoimmune hepatitis and one placebo combination recipient experienced hepatic failure. Immune-related hypothyroidism occurred at a higher frequency in the atezolizumab plus nab-paclitaxel group than in the placebo plus nab-paclitaxel group (17.3% versus 4.3%, respectively). Pneumonitis occurred in 3.1% of patients receiving atezolizumab combination versus 0.2% of those receiving placebo combination [13]. Atezolizumab may cause foetal harm based on its mechanism of action.

immune-mediated AEs: pneumonitis, hepatitis, colitis, and endocrinopathies

immune-related hypothyroidism 17.3% (versus 4.5%)

foetal toxicity

D0012: What is the effect of atezolizumab on generic health-related quality of life?

No evidence was reported regarding the effect of atezolizumab on generic health-related quality of life (QoL).

health-related QoL: no evidence

D0013: What is the effect of atezolizumab on disease-specific quality of life?

No evidence was reported regarding the effect of atezolizumab on disease-specific QoL.

disease-specific QoL: no evidence

Table 1: Efficacy results of Impassion130 [13, 25, 30]17

Descriptive statistics and estimate variability	**Treatment group**	**Atezolizumab + nab-paclitaxel (n = 451)**	**Placebo + nab-paclitaxel (n = 451)**
	Investigator-assessed median OS, ITT (n = 902), m (95% CI) Rate of death at 12.9 m, ITT, n/N (%) Median OS, PD-L1-positive (n = 369), m (95% CI) Rate of death at 12.9 m, PD-L1-positive, n/N (%)	21.3 (17.3–23.4) 181/451 (40.1) 25.0 (22.6–NE) 64/185 (34.6)	17.6 (15.9–20.0) 208/451 (46.1) 15.5 (13.1–19.4) 88/184 (47.8)
	Investigator-assessed median PFS, ITT, m (95% CI) Rate of PFS at 12 m, ITT, % (95% CI) Rate of disease progression/death at 12.9 m, n/N (%) Median PFS, PD-L1-positive, m (95% CI) Rate of PFS at 12 m, PD-L1-positive, % (95% CI) Rate of disease progression/death, PD-L1-positive, n/N (%)	7.2 (5.6–7.5) 23.7 (19.6–27.9) 358/451 (79.4) 7.5 (6.7–9.2) 29.1 (22.2–36.1) 138/185 (74.6)	5.5 (5.3–5.6) 17.7 (14.0–21.4) 378/451 (83.8) 5.0 (3.8–5.6) 16.4 (10.8–22.0) 157/184 (85.3)
	Investigator-assessed ORR, ITT n, %, (95% CI) CR, ITT, n, % (95% CI) ORR, PD-L1-positive, n, % (95% CI) CR, PD-L1-positive, n, % (95% CI)	252, 56.0 (51.3–60.6) 32, 7.1 (4.9–9.9) 109, 58.9 (51.5–66.1) 19, 10.3 (6.3–15.6)	206, 45.9 (41.2–50.6) 7, 1.6 (0.6–3.2) 78, 42.6 (35.4–50.1) 2, 1.1 (0.1–3.9)
	Median DOR, ITT, m (95% CI) Median DOR, PD-L1 positive, m (95% CI)	7.4 (6.9–9.0) 8.5 (7.3–9.7)	5.6 (5.5–6.9) 5.5 (3.7–7.1)
Effect estimate per comparison	*Comparison groups*	Atezolizumab combination versus placebo combination	
	Investigator-assessed OS, ITT (n = 902) (primary endpoint)	SHR for death	0.84
		95% CI	0.69–1.02
		Log-rank test p-value	0.08 NSSD
	OS, PD-L1-positive (subgroup analysis, n = 369)	SHR	0.62
		95% CI	0.45–0.86
		Log-rank test p-value	NFT
	Investigator-assessed PFS, ITT (primary endpoint)	SHR for death/progression	0.80
		95% CI	0.69–0.92
		Log-rank test p-value	0.002
	ICR-assessed PFS, ITT (secondary endpoint)	SHR for death/progression	0.78
		95% CI	0.67–0.91
		Log-rank test p-value	NR
	PFS, PD-L1-positive (subgroup analysis, n = 369)	SHR for death/progression	0.62
		95% CI	0.49–0.78
		Log-rank test p-value	<0.001
	ICR-assessed PFS, PD-L1-positive (secondary endpoint, subgroup analysis, n = 369)	SHR for death/progression	0.63
		95% CI	0.49–0.81
		Log-rank test p-value	NR
	OR, ITT (secondary endpoint)	OR	1.52
		95% CI	1.16–1.97
		Log-rank test p-value	0.002, NSSD alpha < 0.1%
	OR, PD-L1-positive (secondary endpoint, subgroup analysis, n = 369)	OR	1.96
		95% CI	1.29-2.98
		Log-rank test p-value	0.002, NSSD alpha < 0.1%
	DOR, ITT (secondary endpoint)	HR	0.78
		95% CI	0.63–0.98
		Log-rank test p-value	NR
	DOR, PD-L1-positive (secondary endpoint, subgroup analysis n = 369)	HR	0.60
		95% CI	0.43–0.86
		Log-rank test p-value	NR

Abbreviations: CI = confidence interval; HR = hazard ratio; ICR = independent central review; m = months; n = number; N = total number; NFT = not formally tested; NR = not reported; NSD = no statistically significant difference; OR = odds ratio; OS = overall survival; PFS = progression-free survival; SHR = stratified hazard ratio

7.2.2 Safety

C0008: How safe is atezolizumab in relation to the comparator(s)?

In the safety population (n = 890), investigator-assessed AEs were more commonly reported in the atezolizumab- than placebo combination group, regardless of attribution (99.3% versus 97.9%, respectively). The most common AEs were similar between groups, with alopecia being the most common in both groups (56.4% versus 57.5%). AEs that occurred with 5% or greater frequency in the atezolizumab- versus placebo combination group include nausea, cough, neutropenia, pyrexia and hypothyroidism.

common AEs: alopecia, nausea, cough, neutropenia, pyrexia, and hypothyroidism

AEs of grade 3 or 4 occurred in 48.7% of atezolizumab combination versus 42.2% of placebo combination recipients; neutropenia, decreased neutrophils, peripheral neuropathy, fatigue and anaemia were most commonly reported. Peripheral neuropathy of grade 3 or 4 was more frequently reported in the atezolizumab- than placebo combination group (5.5% versus 2.7%, respectively). Serious adverse events (SAE) occurred in 22.8% of atezolizumab plus nab-paclitaxel recipients and 18.3% of placebo plus nab-paclitaxel recipients. Fatal AEs occurred in six patients (1.3%) receiving atezolizumab plus nab-paclitaxel and three (0.7%) of patients receiving placebo plus nab-paclitaxel. There were three deaths due to autoimmune hepatitis, mucosal inflammation and septic shock amongst atezolizumab combination recipients, and one due to hepatic failure in a the placebo combination group.

common grade ≥3 AEs: peripheral neuropathy

SAEs: 22.8% for atezolizumab versus 18.3% for placebo

C0002: Are there harms related to dosage or frequency of applying atezolizumab?

Approximately 15.9% of atezolizumab combination patients and 8.2% of placebo combination patients discontinued all trial drugs due to AEs, while 6.4% and 1.4% discontinued atezolizumab and placebo, respectively. AEs were responsible for any dose reduction or interruption in 46.9% of atezolizumab combination patients and 40.4% of placebo combination patients, while 30.8% and 23.5% interrupted their atezolizumab or placebo dose, respectively.

30.8% interrupted dose and 6.4% discontinued due to AEs

Atezolizumab may cause severe or life-threatening infusion-related reactions [4]. No statistically significant difference in the frequency of infusion reactions was noted between groups (1.1% for atezolizumab combination versus 1.1% for placebo combination) [30].

infusion reactions: no statistically significant difference between groups

C0005: What are the susceptible patient groups that are more likely to be harmed through the use of atezolizumab?

Study participants had a median age of 56 years (range 20 to 86) with good performance status (ECOG performance 0 or 1), and adequate hematologic and organ function. Patients with a history of autoimmune disease were excluded from study. Clinical specificity of older patients and those with comorbidities, co-medications, reduced functional reserve, and immunosenescence may affect the efficacy and/or toxicity of immune-checkpoint inhibitors in this population. Immune-mediated AE may be more challenging in older patients due to reduced functional reserve and age-associated comorbidities [37].

susceptibles: elderly, immune compromised, comorbid, reduced functional status

atezolizumab may cause foetal harm

Atezolizumab may impair fertility, cause foetal harm and potentially SAEs in nursing infants. Females are advised to use of effective contraception and not to breastfeed during treatment and for at least five months following treatment.

Table 2: Most frequent adverse events [13, 25, 30]

Adverse Event (according to CTCAE version 4.0)	**Atezolizumab + Nab-Paclitaxel** (n = 452)		**Placebo + Nab-Paclitaxel** (n = 438)	
Event	Any Grade n (%)	Grade 3 or 4 n (%)	Any Grade n (%)	Grade 3 or 4 n (%)
Any regardless of attribution	449 (99.3)	220 (48.7)	429 (97.9)	185 (42.4)
Treatment-related AEs	436 (96.5)	179 (39.6)	410 (936)	132 (30.1)
SAEs	103 (22.8)	78 (17.0)	80 (18.3)	56 (13.0)
AESI (potentially immune-related)	259 (57.3)	34 (7.5)	183 (41.8)	19 (4.3)
Alopecia	255 (56.4)	3 (0.7)	252 (57.5)	1 (0.2)
Fatigue	211 (46.7)	18 (4.0)	196 (44.7)	15 (3.4)
Nausea	208 (46.0)	5 (1.1)	167 (38.1)	8 (1.8)
Diarrhoea	147 (32.5)	6 (1.3)	150 (34.2)	9 (2.1)
Anaemia	125 (27.7)	13 (2.9)	115 (26.3)	13 (3.0)
Constipation	113 (25.0)	3 (0.7)	108 (24.7)	1 (0.2)
Cough	112 (24.8)	0 (0.0)	83 (18.9)	0 (0.0)
Headache	105 (23.2)	2 (0.4)	96 (21.9)	4 (0.9)
Peripheral neuropathy	98 (21.7)	25 (5.5)	97 (22.1)	12 (2.7)
Neutropenia	94 (20.8)	37 (8.2)	67 (15.3)	36 (8.2)
Decreased appetite	91 (20.1)	3 (0.7)	79 (18.0)	3 (0.7)
Vomiting	88 (19.5)	4 (0.9)	74 (16.9)	5 (1.1)
Pyrexia	85 (18.8)	3 (0.7)	47 (10.7)	0 (0.0)
Arthralgia	81 (17.9)	1 (0.2)	70 (16.0)	1 (0.2)
Rash	78 (17.3)	2 (0.4)	72 (16.4)	2 (0.5)
Dyspnoea	72 (15.9)	4 (0.9)	64 (14.6)	3 (0.7)
Peripheral sensory neuropathy	72 (15.9)	9 (2.0)	52 (11.9)	8 (1.8)
Peripheral oedema	66 (14.6)	1 (0.2)	68 (15.5)	6 (1.4)
Myalgia	64 (14.2)	2 (0.4)	67 (15.3)	3 (0.7)
Back pain	69 (15.3)	6 (1.3)	58 (13.2)	2 (0.5)
Dizziness	63 (13.9)	0 (0.0)	47 (10.7)	0 (0.0)
Dysgeusia	62 (13.7)	0 (0.0)	60 (13.7)	0 (0.0)
Hypothyroidism	62 (13.7)	0 (0.0)	15 (3.4)	0 (0.0)
I-M hypothyroidism	78 (17.3)	0 (0.0)	19 (4.3)	0 (0.0)
Pruritus	62 (13.7)	0 (0.0)	45 (10.3)	0 (0.0)
Decreased neutrophils	57 (12.6)	21 (4.6)	48 (11.0)	15 (3.4)
Asthenia	56 (12.4)	2 (0.4)	50 (11.4)	4 (0.9)
Urinary tract infection	53 (11.7)	4 (0.9)	46 (10.5)	2 (0.5)
Insomnia	51 (11.3)	0 (0.0)	51 (11.6)	3 (0.7)
Pain in extremity	49 (10.8)	2 (0.4)	43 (9.8)	1 (0.2)
Nasopharyngitis	49 (10.8)	0 (0.0)	37 (8.4)	0 (0.0)
Upper RTI	48 (10.6)	5 (1.1)	40 (9.1)	0 (0.0)
Increased ALT	47 (10.4)	8 (1.8)	40 (9.1)	5 (1.1)
Abdominal pain	46 (10.2)	2 (0.4)	53 (12.1)	1 (0.2)
Hypertension	22 (5.0)	4 (1.0)	24 (5.0)	11 (3.0)

Abbreviations: AE = adverse event; AESI = adverse events of special interest; ALT = alanine aminotransferase; CTCAE = Common Terminology for Cancer Adverse Events; I-M = immune-mediated; PLC = placebo; RTI = respiratory tract infection; SAE = serious adverse events

7.3 Clinical effectiveness and safety – further studies

NCT01375842: atezolizumab monotherapy in 116 metastatic TNBC patients

NCT01375842 is a multicentre, open-label, dose-escalation, phase I study to evaluate the safety and efficacy, of atezolizumab monotherapy in 116 patients with previously treated TNBC, and biomarkers associated with outcomes [31]. Patients received 15–20 mg/kg atezolizumab IV every 3 weeks until unacceptable toxicity or loss of clinical benefit. The primary endpoint was safety and tolerability; secondary outcomes included ORR, DOR, PFS, and OS in the ITT population and key subgroups. PD-L1 expression was evaluated on IC and tumour cells (TC) using the Ventana SP142 immunohistochemical assay, and classified based on the percentage of PD-L1-positive IC (IC3 = >10%, IC2 = 5–10%, IC1 = 1–5%, and IC0 = <1%) and TC (TC0 = <1% and TC1/2/3 = ≥1%). The median DOT was 2.1 months (range 0.4–45.6), with a median of four cycles (range 1–58).

cohort: 53 years, 65% visceral metastases, 58% ≥2 prior therapies

PD-L1 IC1/2/3: 78% PD-L1 IC0: 18%

The ITT population (n = 116) had a median age of 53 years (range 29–82), 98% had an ECOG status of 0 or 1, 65% had visceral metastases, and 58% had received at least two lines of prior therapy for metastatic TNBC. Approximately 78% (n = 91) had PD-L1 IC1/2/3 tumours, of which 19 and 72 were treated in the first- and second-line and beyond setting. Approximately 18% (n = 21) had PD-L1 IC0 tumours, of which two and 19 were treated in the first-and second-line and beyond setting, respectively.

ORR and OS PD-L1-positive: 12% and 10.1 months

ORR and OS PD-L1-negative: 0% and 6 months

>10% IC and first-line associated with higher ORR and OS

AEs: 63% grade 1 or 2

The ORR for the cohort was 10% (11/115; CI 4.9–16.5). Patients who received first-line atezolizumab had an ORR of 24% (5/21; CI 8.2–47.2); those who received atezolizumab as second-line and beyond had an ORR of 6% (6/94; CI 2.4–13.4). The median DOR was 21 months (range 3 to ≥38 months). Median PFS was 1.4 months (95% CI 1.3–1.6) by RECIST. In first-line patients, median OS was 17.6 months (95% CI 10.2–not estimable), while second-line patients had a median OS of 7.3 (95% CI 6.1–10.8). Response rates and OS were statistically significantly higher in patients with PD-L1 expression of at least 1% on IC (ORR = 12%, OS = 10.1 months, respectively) compared to patients with less than 1% PD-L1 expression (ORR = 0%, median OS = 6.0 months, respectively). High levels of ICs (>10%) were independently associated with higher ORR and longer median OS. Treatment-related AEs occurred in 63% of patients, 79% were of grade 1 to 2, and most occurred within the first year of treatment.

NCT01633970: atezolizumab + nab-paclitaxel in 33 metastatic TNBC patients

cohort: 55 years, 58% visceral metastases, 88% previous taxane

NCT01633970 is a multicentre, multi-cohort, open-label, phase Ib designed to assess the safety and efficacy of atezolizumab plus chemotherapy in advanced solid tumours. One cohort involved 33 women with metastatic TNBC treated with atezolizumab plus nab-paclitaxel [32]. Patients received 800 mg atezolizumab IV on day's 1 and 15, and 125 mg/m^2 nab-paclitaxel IV on days 1, 8 and 15 of every 28-day cycle until disease progression or unacceptable toxicity. Primary endpoints were safety and tolerability; secondary outcomes included pharmacokinetics, ORR, DOR, disease control rate (DCR), PFS, OS and biomarker analysis. Tumour assessments occurred every 2 cycles for the first year, and every 4 cycles thereafter. PD-L1 expression was centrally assessed using the Ventana SP142 immunohistochemical assay. The median DOT was 5.6 months (range 0–30) for atezolizumab and 4.7 months (range 0–24), for nab-paclitaxel. The study cohort (n = 33) had a median age of 55 years (range 32–84), 76% were Caucasian, 82% had ECOG status 1, 58% had

visceral metastases, 61% had one or more prior systemic cancer therapies in a metastatic setting, and 88% had previously used taxanes.

PFS and OS PD-L1-positive: 6.9 and 21.9 months

PFS and OS PD-L1-negative: 5.1 and 11.4 months

>10% IC and first-line associated with higher PFS and OS

At a median follow-up of 24.4 months, the ORR was 39.4% (95% CI 22.9–57.9), the median DOR was 9.1 months (95% CI 2.0–20.9), and the DCR was 51.5% (95% CI 33.5–69.2). The median PFS and OS were 5.5 months (95% CI 5.1–7.7), and 14.7 months (95% CI 10.1–not estimable), respectively. Median PFS was numerically longer in patients treated in first-line versus second-line setting (8.6 versus 5.1 months) and PD-L1-positive patients compared with PD-L1-negative patients (6.9 versus 5.1 months). Similarly, median OS was numerically longer in patients treated in first-line versus second-line setting (24.2 versus 12.4 months) and PD-L1-positive patients compared with PD-L1-negative patients (21.9 versus 11.4 months).

73% experienced a grade 3 or 4 AE

All patients experienced at least one or more treatment-related AEs; 73% experienced grade 3 or 4 events, and 21% had grade 3 or 4 AESI. The commonly reported AEs were neutropenia (70%), fatigue (67%), alopecia (42%), diarrhoea (39%), peripheral sensory neuropathy (36%), peripheral neuropathy (30%), and nausea (30%). The most frequent AEs of grade 3 or 4 severity attributed entirely to atezolizumab were diarrhoea (6%) and colitis (3%).

8 Estimated costs

A0021: What is the reimbursement status of atezolizumab?

€ 67,186.56 per patient for 6 months of atezolizumab in combination with nab-paclitaxel

In Austria, atezolizumab is available in single-use 1200 mg/20mL vials of 60 mg/mL concentrate solution for infusion for € 4,799.20 (ex-factory price) [28]. IMpassion130 patients received 840 mg of atezolizumab on days 1 and 15 of every 28-day cycle [3], at a cost of approximately € 9,598.40 per cycle. A median duration of 24.1 weeks, or 6 months, of atezolizumab would cost approximately € 57,590.40. Patients also receive 100 mg/m^2 nab-paclitaxel IV on days 1, 8, and 15 of every 28-day cycle for six cycles or more [3]. Assuming an average body surface area of 1.70 m^2, 170 mg of nab-paclitaxel would be needed per dose at a cost of € 533.12/dose and € 1,599.36/cycle [27]. A six month course of atezolizumab in combination with nab-paclitaxel would cost approximately € 67,186.56. Since TNBC accounts for 15–20% of breast cancers and 822–1,096 persons are diagnosed with TNBC in Austria annually, atezolizumab in combination with nab-paclitaxel would cost approximately € 55,227,352.00 to € 73,636,470.00 per year. Additional costs to assess PD-L1 status and to treat AEs will incur. If the expected target population is PD-L1 positive patients only, costs could be less.

9 Ongoing research

28 registered studies

Several studies are ongoing to evaluate the use of atezolizumab in combination with other therapies for previously untreated metastatic and aTNBC. In February 2019, searches of www.clinicaltrials.gov and

www.clinicaltrialsregister.eu using the search terms "atezolizumab" and "triple negative breast cancer" yielded 28 other registered studies (six phase III, eleven phase II, four phase I/II, and seven phase I studies). Most studies were industry-sponsored or conducted in collaboration with industry.

16 phase II/III studies

Selected ongoing phase II and III studies evaluating neoadjuvant atezolizumab and nab-paclitaxel followed by doxorubicin and cyclophosphamicde in early TNBC, atezolizumab and chemotherapy as neoadjuvant therapy prior to surgery for TNBC, atezolizumab plus carboplatin and nab-paclitaxel in locally advanced TNBC, paclitaxel with or without atezolizumab for aTNBC atezolizumab in combination with etinostat for aTNBC, atezolizumab with chemotherapy for recurrent TNBC, atezolizumab plus cobimetinib or cobimetinib and nab-paclitaxel for metastatic TNBC:

- **NCT02708680:** is a phase I/II, randomized, double-blind, interventional study to assess the efficacy of etinostat in combination with atezolizumab in patients with aTNBC. Estimated study completion date is January 2020.
- **NCT02322814:** is a phase II, randomized, open-label, multi-stage, interventional study to assess the safety and efficacy of cobimetinib plus paclitaxel, cobimetinib plus atezolizumab plus paclitaxel, or cobimetinib plus atezolizumab plus nab-paclitaxel as first-line treatment for metastatic TNBC. Estimated study completion date is April 2020.
- **NCT03371017: IMpassion132** is a phase III, randomized, double-blind, interventional study to compare the safety and efficacy of atezolizumab plus chemotherapy versus placebo plus chemotherapy in patients with inoperable, recurrent TNBC. Estimated study completion date is January 2021.
- **NCT03125902: IMpassion131** is a phase III, randomized, double-blind, interventional study to evaluate the efficacy and safety of atezolizumab in combination with paclitaxel compared with placebo plus paclitaxel in patients with previously untreated, inoperable locally advanced or metastatic TNBC. Estimated study completion date is June 2021.
- **NCT03197935: IMpassion031** is a phase III, randomized, double-blind, interventional study evaluating the safety and efficacy of neoadjuvant atezolizumab and nab-paclitaxel followed by doxorubicin and cyclophosphamide (nab-pac-AC), or placebo and nab-pac-AC in patients eligible for surgery with early TNBC. Estimated study completion date is September 2021.
- **NCT02620280: NeoTRIPaPDL1** is a phase III, randomized, open-label, interventional study evaluating the addition of atezolizumab to carboplatin and nab-paclitaxel in patients with early high-risk and aTNBC compared to carboplatin and nab-paclitaxel. Estimated study completion date is October 2022.
- **NCT03281954:** is a phase III, randomized, double-blind, interventional study to compare the effectiveness of chemotherapy plus atezolizumab versus chemotherapy plus placebo given as neoadjuvant therapy prior to surgery TNBC. Estimated study completion date is June 2024.

- **NCT03498716: IMpassion030** is a phase III, randomized, open-label, interventional study comparing the effectiveness of atezolizumab in combination with adjuvant anthracycline/taxane-based chemotherapy versus chemotherapy alone in patients with operable TNBC. Estimated study completion date is December 2024.
- **NCT01898117: Triple-B** is a phase II, randomized, open-label, interventional study comparing the effectiveness of carboplatin plus cyclophosphamide versus paclitaxel with or without atezolizumab as first-line treatment for aTNBC. Estimated study completion date is December 2029.

10 Discussion

FDA and EMA approved for MUC and NSCLC

FDA and EMA pending approval: in combination with nab-paclitaxel as 1st-line for PD-L1-positive aTNBC

Between 2016 and 2018, both the FDA and the EMA licensed atezolizumab as monotherapy for previously treated metastatic NSCLC, and for pre-treated or cisplatin-ineligible MUC regardless of PD-L1 status. The FDA approved atezolizumab in combination with bevacizumab, paclitaxel and carboplatin as first-line treatment for metastatic NSCLC without EGFR or ALK aberrations in December 2018. Combination atezolizumab plus nab-paclitaxel is currently under consideration by the FDA and EMA as initial treatment for patients with PD-L1-positive metastatic or aTNBC based on interim results of a phase III study [12-14].

IMpassion130

PFS: atezolizumab prolongs PFS by 1.7 months for ITT; 2.5 months for PD-L1-positive subgroup

OS: NSSD between groups for ITT; NFT in PD-L1-positive subgroup

IMpassion130, a randomised, double-blind, phase III study investigated whether adding atezolizumab to nab-paclitaxel prolonged PFS and OS in 902 treatment-naïve aTNBC patients. Stratified by baseline liver metastases, neoadjuvant or adjuvant taxane treatment, and PD-L1 status, patients were randomised 1:1 to 840 mg atezolizumab IV or placebo IV on days 1 and 15 plus 100 mg/m^2 nab-paclitaxel IV on days 1, 8, and 15 of every 28-day cycle until disease progression or toxicity. Adding atezolizumab increased the rate of PFS by 6%, prolonged PFS by 1.7 months, and reduced the risk of progression or death by 20% compared to chemotherapy alone. The PFS benefit was observed across most subgroups defined based on trial stratification. In the PD-L1-positive subgroup, adding atezolizumab increased the rate of PFS by 13%, prolonged survival by 2.5 months, and reduced the risk of progression or death by 38% compared to nab-paclitaxel alone. Adding atezolizumab numerically increased OS by 3.7 months and reduced the risk of death in the ITT population by 16% at a 12.9-month follow-up; however, statistically there was no statistically significant difference between groups. While not formally tested in the PD-L1-positive population, atezolizumab increased OS by 9.5 months, potentially reducing the risk of death by 38% in this subgroup. Combination atezolizumab also increased the ORR and DOR in the ITT and PD-L1-positive subgroup compared to chemotherapy alone (10% versus 16%; 1.8 months versus 3.0 months, respectively).

common AEs: nausea, cough, neutropenia, pyrexia, hypothyroidism (no difference) and immune-mediated AEs (+15%)

AEs were more commonly reported in the atezolizumab- than placebo combination group, regardless of attribution (99.3% versus 97.9%, respectively). The most common grade 3 or 4 AEs with atezolizumab plus nab-paclitaxel were neutropenia, decreased neutrophils, peripheral neuropathy, fatigue and anaemia. Immune-mediated AEs were reported in 57% of atezolizumab combination patients versus 42% of placebo combination patients. Immune-

related hypothyroidism and pneumonitis occurred more frequently in the atezolizumab group, and three deaths were attributed to autoimmune hepatitis, mucosal inflammation and septic shock. Grade 3 or 4 peripheral neuropathy was more common in patients receiving atezolizumab versus placebo. AEs leading to dose interruption or discontinuation of atezolizumab treatment occurred in 31% and 6% of atezolizumab combination recipients, respectively.

IMpassion130 limitations: lack of data regarding OS, QoL, long-term safety, small sample size for relevant subgroup analysis

The results of IMpassion130 hold some limitations. Follow-up is insufficient to evaluate OS and long-term safety. No evidence was reported regarding the effect of atezolizumab combination on generic or disease specific QoL or the development of anti-therapeutic antibodies. Mature OS data, disease-specific QoL measures, and a PD-L1 threshold of >10% are needed to ensure patients achieve a clinically relevant benefit over time despite manageable toxicity. The large confidence intervals associated with some subgroup analyses such as that for the African-American, baseline brain metastases, and lymph node only disease suggest a larger sample would be needed to gain greater precision regarding the effect of these factors on outcomes.

limited generalizability of results to patients with higher ECOG status, CNS or autoimmune disease; lack of direct comparison trials

Generalizability may be limited in that the study population had a median age of 56 years, good performance status (ECOG ≤1), and had adequate hematologic and end-organ function. Patients with CNS or autoimmune disease were excluded from study, and some subgroups had small sample sizes. The applicability of these study results for patients with higher ECOG performance status, older age, co-morbidities, co-medications, African American race, baseline brain metastases, lymph node-only disease, or autoimmune disease needs further evaluation. While the dosage of atezolizumab used in this study is less than that recommended for the treatment of NSCLC or MUC, it is consistent with the dosage used to treat TNBC in phase I trials [31, 32]. While there is no standard specific chemotherapy for TNBC, an anthracycline, alkylator-, and taxane-based therapies are commonly used. Without direct comparison studies, physicians and patients may need to consider whether adding atezolizumab to nab-paclitaxel therapy would offer greater individualised efficacy than other available treatments.

low risk of bias: randomised, double-blind, comparator-matched, yet industry funded

IMpassion130 is a phase III trial with only a few methodological limitations. There was no risk of bias in the generation of randomisation sequence or allocation concealment. Patients were randomly assigned 1:1 to atezolizumab combination or placebo combination using a centralized, automated interactive voice or web response system [3]. Patients, physicians, and outcome assessors were blinded as randomisation and allocation were centralized, matching placebo was used and all were blind to PD-L1 status. Selective reporting is unlikely as the co-primary endpoints of PFS and OS, and secondary endpoints of ORR, DOT were reported for the ITT and PD-L1-positive subpopulation as per protocol. Other endpoints not included in the interim analysis were anti-therapeutic antibodies, time to deterioration in global health status and health-related quality of life as per protocol. The risk of bias may be increased due to industry involvement in funding the study, collecting, analysing and interpreting data, and funding editorial assistance.

consistent efficacy and safety results compared with phase I studies

The efficacy and safety data from IMpassion130 are consistent with previously reported phase I studies that suggest atezolizumab, either statistically significantly or numerically, increases PFS, OS, ORR and DOR in untreated metastatic TNBC patients and PD-L1-positive subgroups [31, 32]. Results confirm that, in general, patients who received atezolizumab as first-line therapy, those with PD-L1 expression of at least 1% on IC, and those with >10% IC were independently more likely to have higher ORR and longer PFS and OS than those that receive atezolizumab as second-line therapy, those with PD-L1 expression of <1% and those with <10% IC. Safety results were similar in that most treatment-related AEs occurred within one year of treatment, including neutropenia, cough, nausea, pyrexia, and immune-mediated AEs; no new AEs were observed.

first-line therapy, PD-L1 expression ≥1 with >10% IC associated with increased ORR, PFS and OS

ongoing studies: combination atezolizumab in early, advanced, metastatic and recurrent TNBC

Several studies are ongoing to evaluate atezolizumab in combination with other therapies as adjuvant treatment in early TNBC, and in the advanced, metastatic, and recurrent settings. While no immune checkpoint therapies are currently approved for TNBC, studies are also underway to explore the role of avelumab, durvalumab and pembrolizumab in metastatic TNBC [20, 38]. In the absence of a standard chemotherapy regimen specific to TNBC or direct comparison trials, preference for treatment may lie in therapeutic options that pose less risk for toxicity. Further studies are needed to identify new predictive immune biomarkers to identify potential responders.

ESMO-MCBS: 1 for ITT, 3 for PD-L1-positive subgroup based on original and adapted scales; no meaningful clinical benefit

Given the non-curative setting of atezolizumab and the statistically significant co-primary endpoint PFS, we applied Form 2b of the ESMO-MCBS in order to assess whether atezolizumab satisfies the criteria for a "meaningful clinical benefit" (score 4 or 5). OS in the ITT population was not statistically significant and formal testing of OS in the PD-L1-positive subgroup was not conducted at interim analysis. Both the original and adapted versions of the MCBS were applied. The application of the ESMO-MCBS to the IMpassion130 study resulted in a grade 1 in the ITT population and a grade 3 in the PD-L1-positive subpopulation based on both the original and adapted versions of the ESMO-MCBS. Therefore, atezolizumab does not lead to a meaningful clinical benefit neither with the original nor adapted framework.

€ 67,186.56 per patient for 6 months of atezolizumab + nab-paclitaxel

In Austria, atezolizumab is available in single-use 1,200 mg/mL vials of 60 mg/mL concentrate solution for infusion at an ex-factory price of € 4,799.20 [28]. At a recommended dose of 840 mg twice per 28-day cycle, atezolizumab would cost approximately of € 9,598.40 per cycle; a median duration of six months would cost € 57,590.40. Atezolizumab is administered in combination with six or more cycles of nab-paclitaxel (100mg/m^2) at a cost of € 1,599.36/cycle [27]. A 6 month course of atezolizumab in combination with nab-paclitaxel would cost approximately € 67,186.56. Since TNBC accounts for 15–20% of breast cancers and 822–1096 persons are diagnosed with TNBC in Austria annually, atezolizumab in combination with nab-paclitaxel would cost approximately € 55,227,352.00 to € 73,636,470.00 per year. Additional costs to assess PD-L1 status and treat AEs will incur. If the expected target population is PD-L1 positive patients only, costs could be less.

Overall, IMpassion130 is the first phase III, randomised, double-blind study to demonstrate that adding atezolizumab to nab-paclitaxel as first-line therapy for aTNBC prolongs PFS and reduces the risk of progression or death. The PFS benefit of atezolizumab combination over nab-paclitaxel alone was also notable in the PD-L1-positive subgroup. AEs were consistent with known safety profiles of each agent. These study results are consistent with previous reports suggesting first-line atezolizumab, PD-L1 expression ≥1, and >10% tumour-infiltrating IC are independently associated with increased ORR and PFS. Mature OS data, QoL measures and a PD-L1 threshold of > 10% are needed to ensure patients achieve a clinically relevant benefit over time despite manageable toxicity. Further studies are needed to identify predictive immune biomarkers selective of responders, combination strategies that enhance tumour immunogenicity, and to determine whether these findings extend to other chemoimmunotherapy combinations.

IMpassion130: atezolizumab + nab-paclitaxel as first-line for aTNBC prolongs PFS; PD-L1 expression correlated to response

other predictive biomarkers, and combination strategies to enhance tumour immunogenicity are unknown

Table 3: Benefit assessment based on original ESMO-MCBS and adapted benefit assessment based on adapted ESMO-MCBS [35]

ESMO-MCBS	Subgroup	Active substance	Indication	Intention	PE	Form	MG standard treatment	Efficacy				Safety		AJ	FM
								MG months	*HR (95% CI)*	*Score calculation*	*PM*	*Toxicity*	*QoL*		
Adapted ESMO-MCBS	ITT	Atezolizumab	aTNBC	NC	PFS & OS*	2b[1]	≤6 months	+1.7	0.80 (0.69—0.92)	HR >0.65	1	+6.5% grade 3–4 AEs, +7.7 % discontinuation	NA	-	**1**
Original ESMO-MCBS	ITT	Atezolizumab	aTNBC	NC	PFS & OS*	2b[1]	≤6 months	+1.7	0.80 (0.69—0.92)	HR >0.65	1	-	NA	-	**1**
Adapted ESMO-MCBS	PD-L1–positive	Atezolizumab	aTNBC	NC	PFS & OS*	2b[1]	≤6 months	+2.5	0.62 (0.49—0.78)	HR ≤0.65 AND Gain ≥1.5 months	3	NA	NA	-	**3**
Original ESMO-MCBS	PD-L1–positive	Atezolizumab	aTNBC	NC	PFS & OS*	2b[1]	≤6 months	+2.5	0.62 (0.49—0.78)	HR ≤0.65 AND Gain ≥1.5 months	3	NA	NA	-	**3**

*Abbreviations: AJ = Adjustments, aTNBC = advanced triple-negative breast cancer, CI = confidence interval, FM = final adjusted magnitude of clinical benefit grade, HR = hazard ratio, m = months, MG = median gain, PE = primary endpoint, NA = not available, PM = preliminary magnitude of clinical benefit grade, QoL = quality of life, * co-primary endpoints*

DISCLAIMER

The scores achieved with the ESMO Magnitude of Clinical Benefit Scale are influenced by several factors: by the specific evaluation form used, by the confidence interval (CI) of the endpoint of interest, and by score adjustments due to safety issues. Ad form: Every individual form measures a different outcome. The meaning of a score generated by form 2a is not comparable to the exact same score resulting from the use of form 2c. To ensure comparability, we report the form that was used for the assessment. Ad CI: The use of the lower limit of the CI systematically favours drugs with a higher degree of uncertainty (broad CI). Hence, we decided to avoid this systematic bias and use the mean estimate of effect. Ad score adjustments: Cut-off values and outcomes that lead to an up- or downgrading seem to be arbitrary. In addition, they are independent of the primary outcome and, therefore, a reason for confounding. Hence, we report the adjustments separately.

[1] PFS was used to generate the ESMO-MCBS score, as OS in the intention-to-treat population was not statistically significant and formal testing of OS in the PD-L1–positive subgroup was not conducted at this interim analysis

11 References

[1] European Network for Health Technology Assessment (EUnetHTA). HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals. Version 3.0. 2013 [cited 2019-02-10];Available from: http://meka.thl.fi/htacore/model/HTA%20Core%20Model%20for%20Rapid%20REA%20of%20Pharmaceuticals%203.0.pdf.

[2] Heimes AS, Schmidt M. Atezolizumab for the treatment of triple-negative breast cancer. Expert opinion on investigational drugs. 2019;28(1):1-5.

[3] Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, et al. Protocol to: Schmid P, Adams S, Rugo HS et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. New England Journal of Medicine. 2018;379(22):2108-21.

[4] U.S. Food and Drug Administration Drugs@FDA Atezolizumab® Label Information. 2018 [cited 2019-02-14];Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761034s010lbl.pdf.

[5] Rosenberg JE, Hoffman-Censits J, Powles T, Van Der Veen E, Balar AV, Necchi A, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387(10031):1909-20.

[6] FDA limits the use of Tecentriq and Keytruda for some urothelial cancer patients. 2018 [cited 2019-02-18];Available from: https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm612484.htm.

[7] Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, Pawal J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. . Lancet [Internet]. 2017;Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)32517-X/fulltext.

[8] Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste, Mazieres J, et al. Atezolizumab versus docetaxel for patients with previously treated non-small cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. . Lancet. 2016;387(10030):1837-46.

[9] Socinski M, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, et al. Overall survival (OS) analysis of IMpower150, a randomized phase III study of atezolizumab (atezo) + chemotherapy (chemo) with or without bevacizumab (bev) versus chemo + bev in 1L nonsquamous NSCLC. Journal of Clinical Oncology. 2018;36(15_suppl):9002.

[10] European Medicines Agency: Tecentriq® EPAR -Summary of Product Characteristics. 2018 [cited 2019-02-18];Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/tecentriq.

[11] Withdrawl of application for a change to the EU marketing authorisation for atezolizumab. 2018 [cited 2019-02-18];Available from: https://www.esmo.org/Oncology-News/Withdrawal-of-Application-for-a-Change-to-the-EU-Marketing-Authorisation-for-Atezolizumab.

[12] FDA grants atezolizumab combination priority review for frontline TNBC. 2018 [cited 2019-02-18];Available from: https://www.onclive.com/web-exclusives/fda-grants-atezolizumab-combo-priority-review-for-frontline-tnbc.

[13] Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. New England Journal of Medicine. 2018;379(22):2108-21.

[14] IMpassion130: atezolizumab plus nab-paclitaxel in metastatic or locally advanced triple-negative breast cancer. 2018 [cited 2019-02-18];Available from: http://www.ascopost.com/News/59027.

[15] Anders CK, Carey LA. Epidemiology, risk factors and the clinical approach to EP/PR negative, HER2-negative (triple-negative) breast cancer. UpToDate [Internet] 2019 [cited 2019-02-19] Available from: https://www.uptodate.com Subscription required.

[16] Rassy EE, Karak FE, Ghosn M. Where do the immune checkpoint inhibitors stand in the management of triple negative breast cancer? Immunotherapy. 2018;10(4):247-50.

[17] Esserman L, Joie BN. Clinical features, diagnosis, and staging of breast cancer. UpToDate [Internet] 2019 [cited 2019-02-18];Available from: https: //www.uptodate.com Subscription required.

[18] Diana A, Franzese E, Centonze S, Carlino F, Corte CMD, Ventriglia J, et al. Triple-Negative Breast Cancers: Systematic Review of the Literature on Molecular and Clinical Features with a Focus on Treatment with Innovative Drugs. Current Oncology Reports. 2018;20(10).

[19] Statistik Austria. Krebserkrankungen -Brust. [cited 2018-02-10];Available from: http://www.statistik.at/web_de/statistiken/index.html.

[20] Katz H, Alsharedi M. Immunotherapy in triple-negative breast cancer. Medical Oncology. 2017;35(1):13.

[21] Tivers KF, Lund MJ, Porter PL, Liff JM, Flagg EW, Coates RJ, et al. The epidemiology of triple-negative breast cancer, including rade. Cancer Causes Control. 2009;20(7):1071-82.

[22] Spurdle AB, Couch FJ, Parsons MT, McGuffog L, Barrowdale D, Bolla MK, et al. Refined histopathological predictors of BRCA1 and BRCA2 mutation status: a large-scale analysis of breast cancer characteristics from the BCAC, CIMBA, and ENIGMA consortia. Breast Cancer Res. 2014;16(6):3419.

[23] Pierobon M, Frankenfeld CL. Obesity as a risk factor for triple-negative breast cancers: a systematic review and meta-analysis. Breast Cancer Res Treat. 2013;137:307.

[24] National Comprehensive Cancer Network NCCN clinical practice guidelines in oncology - breast cancer. 2018 [cited 2019-02-21];Available from: https://www.nccn.org/patients/guidelines/stage_iv_breast/32/index.html.

[25] Schmid P. ESMO 2018 presidential symposium-IMpassion130: atezolizumab+nab-paclitaxel in triple-negative breast cancer. ESMO open. 2018;3(6):e000453. Epub 2018/11/15.

[26] Emens LA, Loi S, Rugo HS, Schneeweiss A, Dieras V, Iwata H, et al. IMpassion 130: Efficacy in immune biomarker subgroups from the global, randomized, double-blind, placebo-controlled, phase III study of atezolizumab + nab-paclitaxel in patients with treatment-naive, locally advanced or metastatic triple-negative breast cancer. Cancer research Conference: San Antonio Breast Cancer Symposium, SABCS 2018 United states.

[27] Warenverzeichnia Apothekerverlag Online. [cited 12/2018];Available from: https://warenverzeichnis.apoverlag.at/.

[28] Grössmann N, Rothshedl E, Wolf S. Horizon Scanning in Oncology 385h Prioritization -1st quarter 2019. 2019;Available from: http://eprints.hta.lbg.ac.at/1189/1/HSO_38th_Prioritisation.pdf.

[29] Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, et al. IMpassion130: Results from a global, randomised, double-blind, phase III study of atezolizumab + nab-paclitaxel vs placebo + nab-paclitaxel in treatment-naive locally advanced or metastatic triple-negative breast cancer. ASCO 2018 Annual Meeting. 2018.

[30] Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, et al. Supplementary Appendix to: Schmid P, Adams S, Rugo HS et al. Atezolizumab and nab-paclitaxel in advanced triple negative breast cancer. N Engl J Med. 2018;379(22):2108-21. 2018.

[31] Emens LA, Cruz C, Eder JP, Braiteh F, Chung C, Tolaney SM, et al. Long-term Clinical Outcomes and Biomarker Analyses of Atezolizumab Therapy for Patients With Metastatic Triple-Negative Breast Cancer: A Phase 1 Study. JAMA oncology. 2018;13:13.

[32] Adams S, Diamond JR, Hamilton E, Pohlmann PR, Tolaney SM, Chang CW, et al. Atezolizumab Plus nab-Paclitaxel in the Treatment of Metastatic Triple-Negative Breast Cancer With 2-Year Survival Follow-up: A Phase 1b Clinical Trial. JAMA oncology. 2018;19:19.

[33] EUnetHTA - European network for Health Technology Assessment. Internal validity of randomized controlled trials. 2013;Available from: http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Internal_Validity.pdf.

[34] EUnetHTA - European network for Health Technology Assessment. EUnetHTA guidelines. Levels of evidence. Applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals. February 2013;Available from: http://www.eunethta.eu/sites/default/files/sites/5026.fedimbo.belgium.be/files/Applicability.pdf.

[35] Cherny NI, Dafni U, Bogaerts J, Latino NJ, Pentheroudakis G, Douillard JY, et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of oncology: official journal of the European Society for Medical Oncology. 2017;28(10):2340-66.

[36] Wild C, Grössmann N, Bonanno PV, Bucsics A, Furst J, Garuoliene K, et al. Utilisation of the ESMO-MCBS in practice of HTA. Annals of oncology: official journal of the European Society for Medical Oncology. 2016;27(11):2134-6.

[37] Helissey C, Vicier C, Champiat S. The development of immunotherapy in older adults: New treatments, new toxicities? Journal of Geriatric Oncology. 2016;7(5):325-33.

[38] Basile D, Pelizzari G, Vitale MG, Lisanti C, Cinausero M, Iacono D, et al. Atezolizumab for the treatment of breast cancer. Expert opinion on biological therapy. 2018;18(5):595-603.

12 Appendix

Table 4: Administration and dosing of atezolizumab or placebo + nab-paclitaxel [3, 4, 13]

	Atezolizumab + nab-paclitaxel	Placebo + nab-paclitaxel
Administration mode	Atezolizumab IV infusions on days 1 and 15, plus nab-paclitaxel (100 mg/m²) IV infusions on days 1, 8, and 15 of every 28-day cycle. First infusion is administered over 60 minutes, 30 minutes for subsequent infusions [13]..	Matching placebo [3]
Description of packaging	Single-use, 20-cc USP/Ph Eur type 1 glass vial of colourless-light yellow, sterile, preservative-free liquid [3].	Matching placebo [3].
Total volume contained in packaging for sale	1200 mg/20 mL per vial; formulated as 60 mg/mL atezolizumab in 20 mM histadine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8 [3].	Matching placebo [3].
Dosing	Atezolizumab (840 mg) via IV infusion on days 1 and 15, plus nab-paclitaxel (100 mg/m²) IV infusions on days 1, 8, and 15 every 28-day cycle; dose reduction not permitted. Interrupt for AEs; discontinued if withheld ≥16 weeks or in case of life-threatening IM AEs [3].	20 mL of vehicle without the antibody; dose reduction not permitted. Interrupt for AEs; discontinued if withheld ≥16 weeks or in case of life-threatening IM AEs [3].
Median treatment duration	Until progression or unacceptable toxicity; median DOT: 24.1 weeks of atezolizumab and 22.1 weeks of nab-paclitaxel [13]	Until progression or unacceptable toxicity; median DOT: 22.1 weeks of placebo and 21.8 weeks of nab-paclitaxel [13]
Contraindications	None [4]	Matching placebo [3].
Drug interactions	None reported; not given within 4 weeks of immune checkpoint-targeting therapies, systemic immunostimulants, or live, attenuated vaccines [4]. Risk of interactions with immune-modulating drugs; systemic corticosteroids may affect efficacy [2].	Matching placebo [3].

Abbreviations: AE = adverse events; cc = cubic centimetre; IM = immune mediated; IV = intravenous; mM = millimole; Ph Eur = pharmacopoeia European; USP = United States Pharmacopeia

Table 5: Characteristics of the Impassion130 [13]

Title: Atezolizumab and nab-paclitaxel in advanced TNBC [3, 13, 30]			
Study identifier	NCT02425891, EudraCT 2014-005490-37, WO29522, Impassion130		
Design	International (41 countries), multicentre (246 sites), randomised, double-blind, interventional phase III		
	Median duration of treatment at data cut-off (April 17, 2018):		Atezolizumab + nab-paclitaxel: 24.1 weeks (7 cycles) of atezolizumab and 22.1 weeks (cycles) of nab-paclitaxel placebo + nab-paclitaxel: 22.1 weeks (6 cycles) of placebo and 21.8 weeks (6 cycles) nab-paclitaxel
	Duration of enrolment phase:		June 2015 – May 2017
	Median follow-up at data cut-off:		12.9 months in ITT; 13.0 months for atezolizumab + nab-paclitaxel, 12.5 months for placebo + nab-paclitaxel
Hypothesis	Superiority The study was designed to evaluate the efficacy and safety of atezolizumab + nab-paclitaxel compared with placebo + nab-paclitaxel for patients with previously untreated locally advanced or metastatic TNBC		
Funding	Hoffmann-La Roche/Genentech, Celgene provided nab-paclitaxel		
Treatments groups	Atezolizumab + nab-paclitaxel (ITTn = 451 efficacy; n = 452 safety)		840 mg atezolizumab IV on day's 1 and 15, and 100 mg/m² nab-paclitaxel IV on days 1, 8 and 15 of each 28-day cycle for > 6 cycles without maximum. Both agents were administered until progression or unacceptable toxicity.
	Placebo + nab-paclitaxel (ITTn = 451 efficacy; n = 438 safety)		Placebo IV on day's 1 and 15 and 100 mg/m² nab-paclitaxel IV on days 1, 8 and 15 of each 28-day cycle for > 6 cycles without maximum. Both agents were administered until progression or unacceptable toxicity.
	Notes		After disease progression per RECIST v1.1, study treatment assignment may be unblinded and patients randomised to atezolizumab + nab-paclitaxel may continue receiving open-label atezolizumab with or without nab-paclitaxel. Patients taking placebo + nab-paclitaxel were discontinued from treatment as crossover to atezolizumab was not allowed.
Endpoints and definitions	Progression-free survival (all randomized patients) Co-primary endpoint	PFS	Time from randomization to radiographic progression according to RECIST (v1.1) or all-cause death in all randomized participants. Time frame: baseline up to 53 months, assessed at screening, every 8 weeks for first 12 months, every 12 weeks until progression or death).
	Progression-free survival (PD-L1+ patients) Co-primary endpoint	PFS	Time from randomization to radiographic progression according to RECIST (v1.1) or all-cause death in participants with detectable PD-L1. Time frame: baseline up to 53 months, assessed at screening, every 8 weeks for first 12 months, every 12 weeks until progression or death).
	Overall survival (all randomized patients) Co-primary endpoint	OS	Time from randomization to all-cause death in all randomized participants. Time frame: baseline until death due to any cause (up to 53 months).
	Overall survival (PD-L1+ patients) Co-primary endpoint	OS	Time from randomization to all-cause death in participants with detectable PD-L1. Time frame: baseline until death due to any cause (up to 53 months).
	Objective response rate (all randomized patients) Secondary endpoint	ORR	Percentage of participants with an objective response, complete response (CR) or partial response (PR), according to RECIST v1.1 in all randomized participants. Time frame: baseline up to 53 months, assessed at screening, every 8 weeks for first 12 months, every 12 weeks until progression or death).
	Objective response rate (PD-L1+ patients) Secondary endpoint	ORR	Percentage of participants with an objective response, complete response (CR) or partial response (PR), according to RECIST v1.1 in participants with detectable PD-L1. Time frame: baseline up to 53 months, assessed at screening, every 8 weeks for first 12 months, every 12 weeks until progression or death).

Title: Atezolizumab and nab-paclitaxel in advanced TNBC [3, 13, 30]			
Study identifier	NCT02425891, EudraCT 2014-005490-37, WO29522, Impassion130		
	Duration of response (all randomized patients) Secondary endpoint	DOR	Time from randomization to first occurrence of an objective response to RECIST v1.1 progression or all-cause death for patients with an objective response in all randomized participants. Time frame: baseline up to 53 months, assessed at screening, every 8 weeks for first 12 months, every 12 weeks until progression or death).
	Duration of response (PD-L1+ patients) Secondary endpoint	DOR	Time from randomization to first occurrence of an objective response to RECIST v1.1 progression or all-cause death for patients with an objective response in participants with detectable PD-L1. Time frame: baseline up to 53 months, assessed at screening, every 8 weeks for first 12 months, every 12 weeks until progression or death).
	Time to deterioration (all randomized patients) Secondary endpoint	TTD	Time to deterioration in GHS/HRQoL according to EORTC QLQ-C30 v3.0 in all randomized participants. Time frame: baseline up to 53 months, assessed day 1 of each cycle up to treatment discontinuation, every 28 days after discontinuation for 1 year (overall approximately 53 months).
	Time to deterioration (PD-L1+ patients) Secondary endpoint	TTD	Time to deterioration in GHS/HRQoL according to EORTC QLQ-C30 v3.0 in participants with detectable PD-L1. Time frame: baseline up to 53 months, assessed day 1 of each cycle up to treatment discontinuation, every 28 days after discontinuation for 1 year (overall approximately 53 months).
	Adverse events Secondary endpoint	AE	Percentage of participants with adverse events or serious adverse events (SAE) according to CTCAE version 4.0.
	Antitherapeutic antibodies Secondary endpoint	ATAs	Percentage of participants with anti-therapeutic antibodies against atezolizumab. Time frame: baseline up to 53 months, assessed at per dose (houro) on day 1 of cycles 1, 2, 3, 4, 8, 16, and every 8 cycles thereafter up to treatment discontinuation (approximately 53 months), 120 days after last dose (approximately 53 months).
Database lock	Last update posted December 10, 2018		
Results and Analysis			
Analysis description	**Primary Analysis** ITT: two efficacy endpoints, investigator-assessed PFS and OS, were evaluated in all randomized patients and subgroup analyses were performed on PD-L1 positive patients. Safety data included all patients who received at least one dose of treatment. Two interim analyses and a final analysis of OS were planned. Type I error (0.05) was controlled and split between the analyses of PFS (0.01) and OS (0.04), with hierarchical testing for OS first in the ITT population, then in PD-L1 positive subgroup (95% power for PFS in ITT population, 88% power for OS analysis). PFS and OS were compared using a stratified log-rank test. HRs for disease progression and death were estimated using a stratified Cox proportional-hazards model. Kaplan-Meier analysis was applied to PFS and OS, and Brookmeyer-Crowley method was used to construct the 95% CI for each median duration. Similar methods were applied to the DOR and the analysis was not stratified. Comparisons of the RR between groups were made using the stratified Cochran-Mantel-Haenszel test.		
Analysis population	Inclusion	✪ Adults ≥ 18 years of age with metastatic or locally advanced, histologically documented TNBC characterized by absence of HER2, ER, and PR expression ✪ No prior chemotherapy or targeted systemic therapy for inoperable locally advanced or metastatic TNBC ✪ Eligible for taxane monotherapy (absence of rapid clinical progression, life-threatening visceral metastases, or need for rapid symptom and/or disease control) ✪ Representative formalin-fixed, paraffin-embedded tumour specimen in paraffin blocks, or at least 20 unstained slides with associated pathology report documenting ER, PR, and HER2 negativity. Participants with fewer than 20 unstained slides available at baseline, and not fewer than 12 unstained slides will be eligible upon discussion with Medical Monitor. ✪ ECOG performance status of 0 or 1 ✪ Measurable disease as defined by RECIST v1.1 ✪ Adequate hematologic and end-organ function	

Title: Atezolizumab and nab-paclitaxel in advanced TNBC [3, 13, 30]					
Study identifier		NCT02425891, EudraCT 2014-005490-37, WO29522, Impassion130			
	Exclusion	❁ Known CNS disease, except treated asymptomatic CNS metastases ❁ Leptomeningeal disease ❁ Pregnancy or lactation ❁ History of autoimmune disease ❁ Prior allogeneic stem cell or solid organ transplant ❁ Positive test for human immunodeficiency virus ❁ Active hepatitis B or hepatitis C ❁ Receipt of a live, attenuated vaccine within 4 weeks prior to randomization, during treatment, or within 5 months following the last dose of atezolizumab/placebo			
	Characteristics	ITT Atezolizumab + Nab Paclitaxel (n = 451)	ITT Placebo + Nab-Paclitaxel (n = 451)	PD-L1-Positive Atezolizumab + Nab Paclitaxel (n = 185)	PD-L1-Positive Placebo + Nab-Paclitaxel (n = 184)
	Median age (range), years 18-40 years, n (%) 41-64 years, n (%) ≥ 65 years	55 (20–82) 63 (14.0) 284 (63.0) 104 (23.1)	56 (26–86) 51 (11.3) 285 (63.2) 115 (25.5)	53 (26–82) 31 (16.8) 111 (60.0) 43 (23.2)	53 (28–85) 24 (13.0) 117 (63.6) 43 (23.4)
	Female, n (%)	448 (99.3)	450 (99.8)	184 (99.5)	184 (100)
	Race, n (%) Caucasian Asian African American Native American Hawaiian/Pacific Multiple Unknown	 308 (68.3) 85 (18.8) 26 (5.8) 17 (3.8) 1 (0.2) 2 (0.4) 12 (2.7)	 301 (66.7) 76 (16.9) 33 (7.3) 23 (5.1) 0 (0.0) 3 (0.7) 15 (3.3)	 125 (67.6) 38 (20.5) 9 (4.9) 8 (4.3) 0 (0.0) 0 (0.0) 5 (2.7)	 129 (70.1) 28 (15.2) 14 (7.6) 9 (4.9) 0 (0.0) 0 (0.0) 4 (2.2)
	ECOG performance-status, n/N (%) 0 1 2	 256/450 (56.9) 193/450 (42.9) 1/450 (89.9)	 270/450 (60.0) 179/450 (39.8) 1/450 (90.7)	 107/185 (57.8) 77/185 (41.6) 1/185 (0.5)	 112/184 (60.9) 72/184 (39.1) 0 (0.0)
	Metastatic, n /N (%) No of sites, n/N (%) 0-3 ≥ 4	404/450 (89.8) 332/450 (73.8) 118/450 (26.2)	408/450 (90.7) 341/449 (75.9) 108/449 (24.1)	162/185 (87.6) 149/185 (80.5) 36/185 (19.5)	159/183 (86.9) 140/183 (76.5) 43/183 (23.5)
	Site of metastases Liver, n (%) Bone, n (%) Brain, n (%) Lung, n (%) Lymph-only, n/N (%)	 126 (27.9) 145 (32.2) 30 (6.7) 226 (50.1) 33/450 (7.3)	 118 (26.2) 141 (31.3) 31 (6.9) 242 (53.7) 23/449 (5.1)	 44 (23.8) 54 (29.2) 15 (8.1) 86 (46.5) 18/185 (9.7)	 39 (21.2) 49 (26.6) 11 (6.0) 98 (53.3) 13/183 (7.1)
	Previous therapy, n (%) Neoadjuvant or adjuvant therapy, n (%) Taxane Anthracycline	 284 (63.0) 231 (51.2) 243 (53.9)	 286 (63.4) 230 (51.0) 242 (53.7)	 125 (67.6) 96 (51.9) 109 (58.9)	 117 (63.6) 94 (51.1) 101 (34.3)
Applicability of evidence					
Population	IMpassion130 was conducted in treatment naïve TNBC patients with a median age of 56 years, good performance status, and adequate hematologic and end-organ function. The applicability of these results for patients with higher ECOG performance-status, CNS or autoimmune disease, and those with small subgroup sample sizes (African American race, baseline brain metastases, and lymph node only disease) needs further evaluation.				
Intervention	While the dosage of atezolizumab recommended for the treatment of TNBC is less than that recommended for NSCLC or MUC, it is consistent with the dosage used to treat TNBC in phase I studies [31, 32]. Dose interruptions were allowed for any potentially study drug-related events and discontinued if toxicities persist.				

Title: Atezolizumab and nab-paclitaxel in advanced TNBC [3, 13, 30]	
Study identifier	NCT02425891, EudraCT 2014-005490-37, WO29522, Impassion130
Comparators	While there is no standard, specific chemotherapy for TNBC, an anthracycline, alkylator-, and taxane-based chemotherapies are commonly used. Without direct comparison trials, physicians and patients may need to discuss whether adding atezolizumab to nab-paclitaxel therapy would provide greater individualised efficacy than other treatment options.
Outcomes	Follow-up is insufficient to assess OS and long-term safety. Mature OS data and disease-specific QoL measures are needed to ensure patients achieve a clinically relevant benefit over time despite manageable toxicity.
Setting	IMpassion130 is a multinational study conducted in 246 sites in 41 countries.

Abbreviations: AE = adverse events; ATAs = anti-therapeutic antibodies; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organisation for Research and Treatment of Cancer; ER = oestrogen receptor; GHS = global health status; HER2 = human epidermal growth factor 2; HR = hazard ratio; HRQoL = health related quality of life; ITT = intention-to-treat; MUC = metastatic urothelial cancer; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death ligand 1; PFS = progression-free survival; PR = progesterone receptor; QLQ-C30 = Quality-of-Life Questionnaire Core 30; RECIST = Response Evaluation Criteria in Solid Tumours; RR = relative risk; TNBC = triple-negative breast cancer

Table 6: Risk of bias assessment on study level is based on EUnetHTA (Internal validity of randomised controlled trials) [33]

Criteria for judging risk of bias		Risk of bias
Adequate generation of randomisation sequence: permuted block-randomized to 1:1 atezolizumab + nab-paclitaxel vs placebo + nab-paclitaxel via centralised interactive voice or web-based response system (IxRS). An external independent statistical coordinating centre verified patient randomization and study treatment kit assignments. Randomisation was stratified by presence of liver metastases (yes vs no), prior taxane treatment (yes vs no), and PD-L1 expression on tumour-infiltrating immune cells as a percentage of tumour area (<1% PD-L1 negative vs ≥ 1% PD-L1 positive). Patients received their first dose of study drug within 3 days of randomisation.		yes
Adequate allocation concealment: IxRS generated random allocation sequence.		yes
Blinding:	**Patient:** centralised randomisation and allocation; unaware of PD-L1 status and treatment assignment.	yes
	Treating physician: centralised randomisation and allocation; site personnel were unaware of patients' PD-L1 status and treatment assignment.	yes
	Outcome assessment: centralised randomisation and allocation; investigator-assessed PFS and OS were co-primary endpoints where investigators were blind to PD-L1 status and treatment assignment; sensitivity analysis included ICE-assessed PFS.	yes
Selective outcome reporting unlikely: co-primary endpoints PFS and OS (ITT and PD-L1-positive), secondary endpoints of ORR, DOR (ITT and PD-L1 positive) were reported. Other endpoints not included in this analysis are TTD in GHS/HRQoL, as per protocol.		yes
No other aspects which increase the risk of bias: industry sponsored the study, provided study drugs, assisted in trial design, data collection, analysis and interpretation. The sponsor also funded editorial assistance from professional medical writers. Trial sponsor was unaware of patients' PD-L1 status.		no
Risk of bias – study level		low-risk

Abbreviations: DOR = duration of response; GHS = global health status; HRQoL = health-related quality of life; ICR = independent central review; IT = intention-to-treat; IxRS = interactive voice or web response system; PFS = progression-free survival; ORR: overall response rate; OS = overall survival; TTD = time to deterioration