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Atezolizumab and nab–paclitaxel for advanced breast cancer in Danish real–world patients

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ABSTRACT

INTRODUCTION. The Danish Medicines Council recommends that patients with estrogen receptor and human epidermal growth factor receptor 2-negative, programmed death-ligand 1 (PD-L1)-positive advanced breast cancer receive atezolizumab in combination with nab-paclitaxel. The approval was largely based on results from Impassion130 that showed a beneficial progression-free survival (PFS) and overall survival (OS) in PD-L1-positive patients who received atezolizumab and nab-paclitaxel.

METHODS. We conducted a retrospective, population-based study that included patients who received atezolizumab for advanced breast cancer from October 2019 to September 2022. The primary endpoints were PFS and OS.

RESULTS. This study included 74 advanced breast cancer patients. Their median age was 54.5 years, and 21 (28.4%) of the patients had de novo advanced disease. Most patients received first-line treatment with atezolizumab (83.8%). The median PFS was 6.0 months (95% confidence interval (CI): 4.7-8.4 months) and the median OS was 14.3 months (95% CI: 9.9-22.2 months). A total of 48 patients received atezolizumab and nab-paclitaxel in accordance with guidelines from the Danish Medicines Council.

CONCLUSIONS. This real-world study expectedly showed numerically lower survival outcomes than the phase III trial Impassion130, but met the standards of efficacy set by real-world studies in other countries. A need exists for increased attention to the criteria for receiving atezolizumab.

FUNDING. none.

TRIAL REGISTRATION. The study was approved by the Oncological Committee of the DBCG, the Research Overview of the Capital (P-2022-828) and the Centre for Health of the Capital Region (R-22060674).

In Denmark, approximately 4,700 new cases of breast cancer are diagnosed annually [1]. Double-negative breast cancer is defined as lack of estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) and is both prognostic and predictive of response to treatment. Patients with double-negative breast cancer have an increased recurrence rate and an increased mortality within the first years of diagnosis. Approximately 15% of metastatic breast cancer patients have double-negative disease [2, 3].

Previously, the recommended treatment of double-negative advanced breast cancer patients was sequential

monotherapy with chemotherapy, whereas combination chemotherapy was reserved for patients with rapid progression, visceral crisis or a need for rapid disease control [4]. Within the past four years, several new treatments have been approved by the European Medicines Agency (EMA); atezolizumab in combination with nab-paclitaxel (June 2019), pembrolizumab in combination with different chemotherapy regimens (October 2021) and the antibody-drug conjugate sacituzumab govitecan (November 2021).

The Danish Medicines Council (DMC) approved the use of atezolizumab and nab-paclitaxel for treatment of advanced double-negative programmed death-ligand 1 (PD-L1)-positive breast cancer in January 2020 [5]. According to the Danish approval, the following criteria must be met for treatment with atezolizumab: first line, in combination with nab-paclitaxel and either more than 12 months after last (neo)adjuvant chemotherapy or for de novo advanced disease. These criteria were based on the inclusion criteria in Impassion130, which produced an improved progression-free survival (PFS) and overall survival (OS) compared with placebo: Median PFS was 7.5 months (95% confidence interval (CI): 6.7-9.2 months) and median OS was 25.4 months (95% CI: 19.6-30.7 months) in the atezolizumab and nab-paclitaxel group compared with a median PFS of 5.0 months (95% CI: 3.8-5.6 months) and a median OS of 17.9 months (95% CI: 13.6-20.3 months) in the placebo and nab-paclitaxel group [6, 7].

The approval of atezolizumab/nab-paclitaxel in 2020 included an appeal to the Danish Breast Cancer Group (DBCG) to collect relevant efficacy data on patients receiving atezolizumab and report these data within two years. This study presents these efficacy data and discusses their relevance and limitations.

METHODS

Objectives

The main objective of this study was to present characteristics of patients who initiated treatment with atezolizumab and to investigate the efficacy in terms of PFS and OS. A secondary objective was to assess whether patients who received atezolizumab met the criteria set by the DMC in their approval assessment.

Study design

This study was a retrospective observational population-based study that included patients from all departments of oncology in Denmark registered in the DBCG clinical database.

Data source

The DBCG clinical database includes information on diagnosis, treatment, demographics and pathology. The following data were collected from the database: date of the last (neo)adjuvant chemotherapy, date of diagnosis and progression, localisation of metastases, receptor/PD-L1 status, backbone chemotherapy, date of first and last treatment with atezolizumab, reason for discontinuation and vital status.

Population

In February 2022, the DBCG asked every department of oncology in Denmark to report data on all patients treated with atezolizumab for advanced breast cancer. In Western Denmark, these reports were based on lists from the hospital pharmacies and treatment schedules. In Eastern Denmark, the reports were based on data from the Healthcare Platform. Any patient already registered with atezolizumab therapy in the DBCG clinical database and not identified elsewhere was added to the reports.

Endpoints

Baseline characteristics

Baseline characteristics were presented as counts, proportions, medians and ranges. (Neo)adjuvant chemotherapy included capecitabine.

Treatment pattern

Treatment pattern was presented as type of backbone chemotherapy and line of treatment.

Survival

The index date was the date of diagnosis of advanced breast cancer or the date of progression leading to the initiation of atezolizumab treatment. PFS was estimated as the time from the index date until death or progression, whichever occurred first. OS was the time from the index date until death from any cause. End of follow-up was 3 October 2022. The Kaplan-Meier method was used to estimate OS and PFS. OS and PFS were presented as Kaplan-Meier curves and an estimate of median survival with 95% CI. Estimated potential median follow-up for OS was estimated from the index date until the end of follow-up using Schemper and Smith's method [8]. All analyses were performed using RStudio v. 2021.09.2 build 382 (RStudio, Inc., Boston, MA).

Trial registration: The study was approved by the Oncological Committee of the DBCG, the Research Overview of the Capital Region (P-2022-828) and the Centre for Health of the Capital Region (R-22060674).

RESULTS

Baseline characteristics

A total of 74 patients with advanced breast cancer were included in this study. The median age was 54.5 years, and 21 (28.4%) of the patients had de novo advanced disease. Metastatic sites were as follows: lymph nodes (45 patients (60.8%)), lung (40 patients (54.1%)), liver (ten patients (13.5%)) and central nervous system (eight patients (10.8%)). The median time since last (neo)adjuvant chemotherapy was 1.7 years (range: 0.0-8.2); and 18 of the 53 recurrent patients (34.0%) initiated treatment with atezolizumab less than a year after their previous (neo)adjuvant chemotherapy (**Table 1**).

TABLE 1 Baseline characteristics.

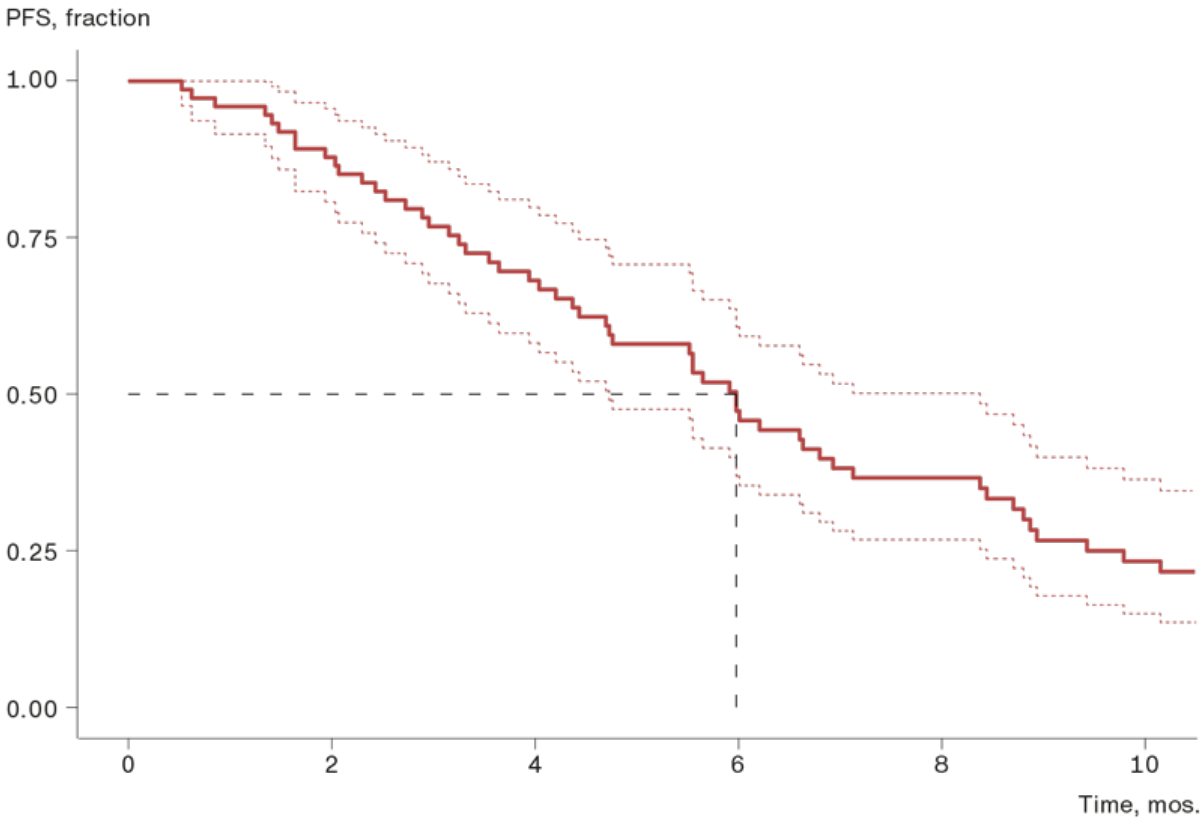
	All patients	Patients who met criteria[a]
Patients, n	74	48
Age at index date, median (range) yrs	54.5 (30.1-88.2)	55.9 (36.6-88.2)
Metastatic breast cancer presentation, n (%)		
Recurrent	53 (71.6)	29 (60.4)
De novo	21 (28.4)	19 (39.6)
Line of treatment with atezolizumab for advanced, double-negative disease, n (%)		
1st	62 (83.8)	48 (100.0)
2nd	7 (9.5)	0
Above 2nd	5 (6.8)	0
Sites of cancer, n (%)		
Visceral[b]	50 (67.6)	31 (64.6)
Non-visceral	24 (32.4)	17 (35.4)
Metastatic sites, n (%)		
Liver	10 (13.5)	8 (16.7)
Lungs	40 (54.1)	25 (52.1)
Central nervous system	8 (10.8)	4 (8.3)
Lymph nodes	45 (60.8)	30 (62.5)
Time since adjuvant chemotherapy for recurrent patients[c]		
Time, median, yrs	1.7	2.7
< 1 yr, n (%):		
0-6 mos.	10 (18.9)	0
6-11 mos.	8 (15.1)	0
Subtotal	18 (34.0)	0
12-18 mos., n (%)	6 (11.3)	5 (17.2)
> 18 mos., n (%)	28 (52.8)	23 (79.3)
Pathology		
ER-negative and HER2-normal, n (%)	74 (100.0)	48 (100.0)
PD-L1-positive, n (% of recurrent patients)	73 (98.6)[d]	48 (100.0)

ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2; PD-L1 = programmed death-ligand 1.
a) Patients who met the criteria to receive atezolizumab set by the Danish Medicines Council: as 1st-line, in combination with nab-paclitaxel, for double-negative, PD-L1-positive disease and either > 12 mos. after their last (neo)adjuvant chemotherapy or for de novo, advanced disease.
b) Liver, lungs, central nervous system, abdominal carcinosis and ovaries.
c) Adjuvant chemotherapy included neoadjuvant and adjuvant treatment, 52 recurrent patients in the entire population received (neo)adjuvant chemotherapy, 28 recurrent patients in the group of patients who met the criteria to receive atezolizumab set by The Danish Medicines Council received (neo)adjuvant chemotherapy.
d) Only 1 patient had a negative test.

Survival

A total of 55 patients (74.3%) experienced progression (n = 50) or death (n = 5) as a first event after initiating atezolizumab therapy. In all, 43 patients (58.1%) died in the study period. The median PFS was 6.0 months (95% CI: 4.7-8.4 months) (**Figure 1**). The median OS was 14.3 months (95% CI: 9.9-22.2 months) (**Figure 2**).

FIGURE 1 Progression-free survival (PFS) and 95% confidence interval (CI) of all included patients.

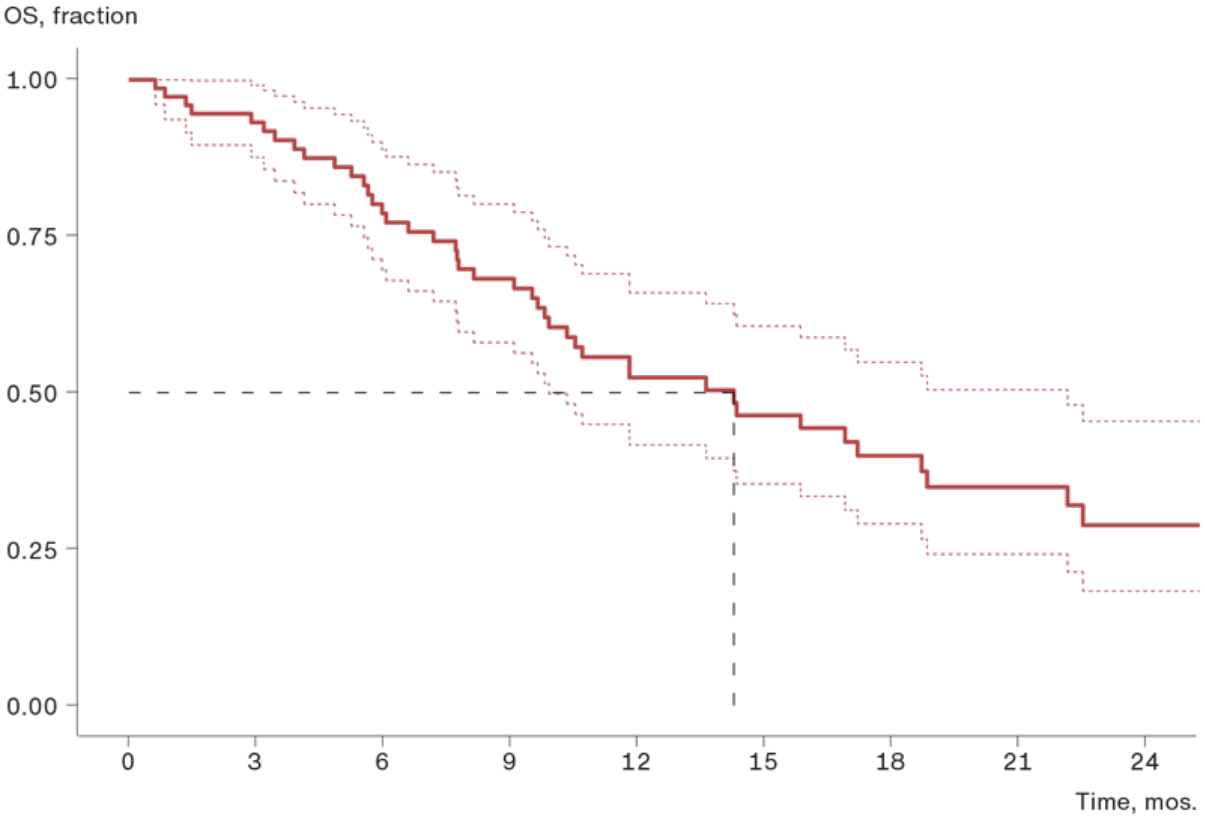


Patients at risk, n

0	2	4	6	8	10
74	65	47	31	23	14

Median PFS 6.0 mos. (95% CI: 4.4-8.4 mos.).

FIGURE 2 Overall survival (OS) and 95% confidence interval (CI) of all included patients.



Patients at risk, n

0	3	6	9	12	15	18	21	24
74	66	53	44	30	23	18	14	9

Median OS 14.3 mos. (95% CI: 9.9-22.2 mos.).

The patients treated in accordance with DMC guidelines (n = 48) had a median PFS of 7.1 months (95% CI: 6.2-10.2 months) and a median OS of 18.9 months (95% CI: 14.4-number of months not available (NA)). The estimated potential median follow-up for OS was 21.5 months (95% CI: 16.7-28.0 months).

Treatment pattern and adherence to Danish Medicines Council guidelines

Among the 74 patients, 48 (64.9%) were treated in accordance with DMC guidelines: as first-line treatment in combination with nab-paclitaxel, for double-negative, PD-L1-positive disease and either more than 12 months after their previous (neo)adjuvant chemotherapy or for de novo advanced disease. The guidelines were mostly respected regarding choice of chemotherapy, which was nab-paclitaxel in 72 patients (97.3%), eribulin in one patient (1.4%) and no chemotherapy in one patient (1.4%). First-line treatment with atezolizumab for advanced disease was respected in 83.8% of the patients, whereas 9.5% and 6.8%, respectively, received atezolizumab as second-line treatment or later. One patient did not test PD-L1 positive.

DISCUSSION

In consultation with the Specialist Committee, the DMC called for relevant efficacy data to be systematically collected under the auspices of the DBCG for patients who received atezolizumab. After two years of data collection, the DMC would then decide whether the recommendation would be continued.

In the PD-L1-positive double-negative patients who were treated with atezolizumab in accordance with the criteria set by the DMC (n = 48), we saw a median PFS of 7.1 months (95% CI: 6.2-10.2 months). In Impassion130, the PFS was 7.5 months (95% CI: 6.7-9.2 months). In the same subgroup of patients from our study (n = 48), the median OS was 18.9 months (95% CI: 14.4-NA months) versus 25.4 months (95% CI: 19.6-30.7 months) in Impassion130, with no overlapping confidence intervals. No noticeable differences were seen in baseline characteristics between our study and Impassion130 [6].

The subgroup of patients in our study who met the criteria set by the DMC was limited in size (n= 48), with a limited follow-up (21.5 months) and unknown performance status. Impassion130 included patients with a good performance status only (Eastern Cooperative Oncology Group performance-status score of 0 or 1, with low scores indicating a low level of disability). These factors influence the comparison of our real-world survival outcomes to the survival outcomes of the phase III study, Impassion130. Our study thus estimated what may be expected regarding efficacy beyond phase III trials. Our efficacy data also highlight the importance of treating the correct group of patients.

It was noticeable that 16.2% received atezolizumab as second-line treatment or later, and that 34.0% of the recurrent patients in our study received (neo)adjuvant chemotherapy within 12 months of initiating atezolizumab. Implementation of these treatment approaches was not supported by evidence found in KEYNOTE-355 and KEYNOTE-086 [9, 10]. However, we suspected that the oncology departments interpreted the recommendation (a minimum of 12 months since previous (neo)adjuvant treatment) as if adjuvant capecitabine should not be included since adjuvant capecitabine was not used in Impassion130.

Additional requirements for receiving atezolizumab in Denmark included receptor status and test for PD-L1 [5]. All patients treated had double-negative disease. A total of 73 (98.6%) patients had a PD-L1-positive tumour, but one (1.4%) patient did not, even though patients with PD-L1-negative tumours did not have a significantly increased OS in the Impassion130 study [6]. In conjunction, it is surprising that only 48 of 74 patients (64.9%) met all DMC criteria.

This result reflects the difficulties that oncologists face when new treatments are approved by the DMC for a limited group of patients. When the treatment is implemented in the daily clinic, cases may emerge in which physicians end up disregarding recommendations, e.g., a patient with rapidly progressing disease during curatively intended treatment. In the coming years, as more targeted treatment modalities are introduced, a heightened attention to patient data will be necessary to ensure that every patient receives the most efficient and evidence-based therapy. Danish, double-negative advanced breast cancer patients (2017-2019) had a median OS of 11.6 months (95% CI: 9.9-17.3 months) and a median PFS of 4.9 months (95% CI: 4.2-6.3 months) in the first line (data under review). Our group of patients that received atezolizumab in accordance with DMC criteria had a tendency towards increased survival outcomes. Patients who received atezolizumab could have had a better performance status, since they were considered eligible to receive immunotherapy. Furthermore, PD-L1 positivity has been linked to increased survival among basal-like tumours [11].

One real-world study of 155 women with metastatic double-negative breast cancer receiving atezolizumab in combination with nab-paclitaxel as first-line treatment showed a median OS of 13.6 months (no 95% CI available) [12]. An Austrian real-world study (n = 6) [13] investigated the efficacy of therapy with atezolizumab and nab-paclitaxel and found a median PFS of 4.6 months (95% CI: 0.2-9.1 months) and a median OS of 14.9 months (95%

CI: 0.01-34.1 months) in first-line patients when they excluded PD-L1-negative and luminal breast cancer subtypes. The median OS of our nation-wide cohort is similar to the median OS of these two studies.

The nation-wide cohort of our study ensured that the patients were representative of the whole Danish population and that the outcomes were not biased towards the clinical practice of major clinics. The retrospective design was a limitation. The quality of the data relied on the physician's record-keeping and the data collectors.

CONCLUSIONS

This real-world study expectedly showed numerically lower survival outcomes than the phase III trial Impassion130, but met the standards of efficacy set by real-world studies in other countries. A need exists for increased attention to the DMC criteria for receiving atezolizumab, especially the line of treatment and time since previous (neo)adjuvant therapy.

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Conflicts of interest Potential conflicts of interest have been declared. Disclosure forms provided by the authors are available with the article at ugeskriftet.dk/dmj

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