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REVIEW ARTICLE

Katarzyna Pogoda[1], Agnieszka Jagiełło-Gruszfeld[1], Michał Kunkiel[1], Wojciech Olszewski[2]

[1]Department of Breast Cancer and Reconstructive Surgery, the Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[2]Department of Pathology and Laboratory, the Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Atezolizumab in the treatment of patients with breast cancer

Address for correspondence:
Katarzyna Pogoda, MD PhD
Department of Breast Cancer
and Reconstructive Surgery,
the Maria Sklodowska-Curie National
Research Institute of Oncology,
Roentgena 5 St., 02–781 Warsaw, Poland
e-mail: katarzyna.pogoda@pib-nio.pl

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ABSTRACT

Immunotherapy is a modern method of treatment which is being tested in breast cancer patients. The first approved drug in this group was atezolizumab introduced for the treatment of patients with locally advanced and inoperable or metastatic triple-negative breast cancer (TNBC) with expression of programmed death receptor type 1 (PD-L1) on immunologic cells (IC) of ≥1%, who had not received prior chemotherapy for advanced disease. The results of the registration study IMpassion130 indicated that atezolizumab improved patient outcomes when used in combination with nab-paclitaxel. This article summarizes the most important analyzes of that study. The necessity to use the validated VENTANA SP142 assay to assess PD-L1 expression, which is necessary for the qualification of patients for this therapy, was emphasized. Additionally, the available data on the first results of the studies in patients with early TNBC as well as with human epidermal receptor type 2 (HER2)-positive and estrogen receptor (ER)-positive HER2-negative cancers treated with atezolizumab are discussed.

Key words: atezolizumab, immune therapy, triple-negative breast cancer, VENTANA SP142 assay

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Introduction

In recent years, numerous clinical trials using immunotherapy in patients with various cancers have been conducted, with the results changing the standards of oncology management. Immunotherapy significantly improved treatment outcomes (among others in melanomas, lung cancer, urothelial neoplasms, and squamous cell carcinomas of the head and neck). Immune checkpoint inhibitors have been developed, including antibodies against cytotoxic T lymphocyte antigen-4 (CTLA-4), programmed death type 1 (PD-1), and programmed death ligand-1 (PD-L1). In patients with breast cancer, the results of studies with anti-PD-1 (e.g. pembrolizumab) and anti-PD-L1 (e.g. atezolizumab) antibodies are of greater importance [1]. This article summarizes the data on the effectiveness of the first approved immune inhibitor in patients with triple-negative breast cancer (TNBC), such as atezolizumab. The principles of diagnosis and selection of patients for treatment are discussed, and directions of new research on this drug in breast cancer patients are indicated.

First reports

Atezolizumab is a humanized monoclonal IgG1 antibody directed against PD-L1, approved for the treatment of patients with non-small cell and small cell lung cancer, urothelial cancer, hepatocellular carcinoma, and TNBC [2].

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The first reports on the effectiveness of the drug in patients with breast cancer were presented fewer than 10 years ago. A total of 277 patients with advanced solid tumors and hematological malignancies (including 10 patients with breast cancer) participated in the phase I dose-escalation study. Atezolizumab was used as monotherapy. The study aimed to assess treatment safety and determine recommended phase II dose (RP2D). It was highlighted that responders included patients with cancers showing PD-L1 expression, and 1200 mg every 3 weeks was recognized as the recommended dose for monotherapy [3].

Metastatic triple-negative breast cancer

First studies

Another study, designed only for patients with metastatic TNBC, included 116 women, 60% of whom had previously received at least two lines of palliative therapy. Atezolizumab monotherapy was administered intravenously at a dose of 15 mg/kg body weight, 20 mg/kg body weight, or at a fixed dose of 1200 mg. The treatment results were not spectacular. The objective response rate (ORR) in the whole study population was only 10%, the median progression-free survival (PFS) was 1.4 months, and the median overall survival (OS): 8.9 months. However, in patients treated in the first line, the results were better: ORR was 24%, and median OS was 17.6 months. Additionally, significantly better results were found in patients with PD-L1 expression on tumor-infiltrating immune cells (ICs) — median OS of patients across all treatment lines was 10.1 months in patients with PD-L1 expression and 6 months in patients with PD-L1-negative tumors [4].

The above data indicated that immunotherapy alone has some limitations. Studies with chemotherapy-combined treatment were designed, which showed improved treatment outcomes. The GP28328 study included 33 TNBC patients who received atezolizumab (800 mg on days 1 and 15) with nab-paclitaxel (125 mg/m^2 on days 1, 8, and 15 every 28 days). Patients who previously received up to 2 lines of treatment were included in the study. ORR was 39.4%, and clinical benefit was found in 51.5% of patients. The median duration of response was 9.1 months, median PFS was 5.5 months, and median OS was 14.7 months. Adverse events occurred in all patients — the most common were neutropenia (70%), fatigue (67%), alopecia (42%), diarrhea (39%), and peripheral sensory neuropathy (36%). On the other hand, 73% of patients experienced grade 3/4 adverse events (most often neutropenia — 46% and thrombocytopenia — 9%). However, there were no treatment-related deaths [5].

IMpassion130 pivotal study

Earlier results led to designing of a large phase III clinical trial, IMpassion130, which was a pivotal study of atezolizumab in patients with metastatic TNBC. A total of 902 patients with metastatic (90%) or inoperable and locally advanced (10%) TNBC with a very good or good performance status (PS) participated in the study. Perioperative treatment was previously used in 63% of patients. The lungs were the most common location of metastatic lesions. PD-L1 expression was found in 41% of patients. Patients were randomly assigned to the group with either chemotherapy alone or chemotherapy combined with immunotherapy. Atezolizumab was administered at a dose of 840 mg on days 1 and 15, and nab-paclitaxel was administered at the dose of 100 mg/m^2 of body surface area (BSA) on days 1, 8, and 15 every 28 days. The primary endpoints of the study were PFS and OS assessed in the whole study population and in patients with PD-L1 expression but after demonstrating a statistically significant improvement in the overall population. The first results of the study showed a significant PFS improvement in all patients receiving immunotherapy (7.2 *vs.* 5.5 months; $p = 0.0025$), especially in patients with PD-L1 expression (7.5 *vs.* 5 months; $p < 0.0001$). However, the first OS analysis showed no significant differences in the whole study group (21.3 *vs.* 17.6 months; $p = 0.084$), and no statistical evaluation of OS was formally performed in the subgroup of patients with PD-L1 expression. Additional analysis, however, showed a significant clinical improvement in OS in patients with PD-L1-positive tumors (25 *vs.* 15.5 months). ORR was also better in the immunotherapy arm [6]. The results of the study were received with great interest. They identified the TNBC patient population that could benefit most from immunotherapy. In 2021, the final OS results were published. There was no difference in OS in the whole study group (21 *vs.* 18.7 months; $p = 0.078$), while in the additional analysis, the clinical benefit of atezolizumab therapy was again observed in patients with PD-L1 expression (median OS — 25.4 *vs.* 17. 9 months with no statistical significance) [7]. The final results of the study are summarized in Table 1.

Almost all patients treated in the IMpassion130 study experienced side effects. The most common were alopecia, asthenia, nausea, and diarrhea. However, grade 3/4 adverse events were found in 51% of patients in the immunotherapy group and 43% of patients in the control group. In turn, serious adverse events occurred in 24% of patients treated with atezolizumab plus nab-paclitaxel and in 19% of patients receiving chemotherapy alone. The most common grade 3/4 side effects were neutropenia (8% in both groups), peripheral neuropathy (6% in the atezolizumab group

Table 1. Summary of the results of the phase III IMpassion130 study — median PFS/OS and ORR (based on [6, 7])

	Atezolizumab + nab-paclitaxel	Placebo + nab-paclitaxel	*p*-value, HR
Median PFS Whole study population (months)	7.2	5.5	HR = 0.8; p = 0.002
Median PFS PD-L1+ population (months)	7.5	5.0	HR = 0.62; p < 0.001
Median OS Whole study population (months)	21.0	18.7	HR = 0.86; p = 0.077
Median OS PD-L1+ population (months)	25.4	17.9	HR = 0.67 (95% confidence interval 0.53–0.86)
Objective response rate Whole study population	56%	45.9%	HR = 1.52; p = 0.002
Objective response rate PD-L1+ population	58.9%	42.6%	HR = 1.96; p = 0.002

HR — hazard ratio; ORR — objective response rate; OS — overall survival; PD-L1+ — positive expression of programmed death receptor type 1; PFS — progression-free survival

vs. 3% in the control group), and asthenia (4% *vs.* 3% in the control group). Adverse events leading to discontinuation of at least one study drug were reported in 19% of patients who received combination therapy and 8% of patients in the control group, with neuropathy being the most common. Among the adverse reactions of special interest, a higher incidence of rash (36% *vs.* 26%), hypothyroidism (18% *vs.* 4%) and hyperthyroidism (5% *vs.* 1%), pneumonia (4% *vs.* < 1%) was revealed in patients receiving atezolizumab compared to the control group [7].

The quality of life (QoL) of patients participating in the IMpassion130 study was also assessed. Patients completed the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and Breast Cancer Module (EORTC QLQ-BR23). The secondary endpoint in IMpassion130 was time to deterioration in quality of life, which was defined as a reduction in the questionnaire score by more than 10 points from baseline for at least 2 treatment cycles. It was found that the use of atezolizumab did not affect the quality of life in the whole study population and in TNBC patients with PD-L1 expression [7, 8].

The results of the IMpassion130 study were the basis for the registration of atezolizumab for use with nab-paclitaxel in patients with PD-L1-positive advanced TNBC in first-line treatment [2], which is recommended by the European Society for Medical Oncology (EMSO) and the Polish Society of Clinical Oncology (PTOK) [9, 10].

Real-world evidence (RWE) on atezolizumab therapy is currently being collected and requires longer follow-up. The available reports indicate an increasingly frequent PD-L1 expression in patients with metastatic TNBC and thus eligibility for immunotherapy [11]. Based on the analysis of data from the German OPAL registry of breast cancer patients, it was found that the percentage of patients with metastatic TNBC evaluated for PD-L1 expression before first-line palliative therapy increased from 14% in 2018 to 79% in 2020, which translated into using immunotherapy in a greater number of patients [12].

Other studies in metastatic TNBC

The results of the IMpassion131 study, in which paclitaxel (at a dose of 90 mg/m^2 on days 1, 8, and 15 every 28 days) was added to atezolizumab (standard dosing) in one of the study arms were surprising. The primary endpoint of the study was PFS in patients with PD-L1-positive BC and in the whole study population. The secondary endpoint was OS. PD-L1 expression was found in 45% of 651 TNBC patients who participated in the study. The first PFS analysis in patients with PD-L1 expression did not show a significant difference (6 *vs.* 5.7 months; p = 0.20), similarly to the whole study group (5.7 *vs.* 5.6 months; p = 0.86). Furthermore, OS did not differ significantly between the arms, and the obtained results were numerically even worse in the combination therapy arm (22.1 *vs.* 28.3 months in the PD-L1-positive group and 19.2 *vs.* 22.8 months in the whole study population) [13]. The reason for the different results in IMpassion131 has not been clarified and research is ongoing (one of the reasons may be the use of corticosteroids in paclitaxel premedication).

Importantly, a third large clinical trial with atezolizumab (IMpassion132) involving patients with rapid relapse of TNBC may provide new data. The study uses chemotherapy in both arms (capecitabine or carboplatin with gemcitabine) and additionally

atezolizumab in the experimental arm [14]. Another study with atezolizumab in patients with metastatic TNBC was designed, in which other chemotherapy regimens are evaluated (NCT01898117, NCT03164993, NCT03206203, and NCT05266937). In addition, there are studies in which new drugs are added to atezolizumab with chemotherapy (e.g. ipatasertib — NCT04177108 and NCT03800836).

Qualification for treatment

Additional biomarker analyzes were performed as part of the IMpassion130 study. PD-L1 expression was found slightly more frequently when evaluating primary tumor tissues compared to metastatic lesions (44% *vs.* 36%). Interestingly, a positive PD-L1 result was rarely obtained in liver metastases samples (only 13%). In turn, lymph node biopsies were associated with the highest percentage of positive results (51%). As part of additional analyzes, patients were divided into 3 groups: with no PD-L1 expression (IC < 1%; 59% of cancers), and with low (IC ≥1% to < 5%; 27% of cancers) and high PD-L1 expression (IC ≥ 5%; 14% of TNBC). Significantly better treatment results were demonstrated in the groups with low and high PD-L1 expression; however, no significant differences were found between the groups [14]. These observations were the basis for determination of a 1% cut-off point for positive PD-L1 expression in TNBC. ICs include lymphocytes, macrophages, dendritic cells, and granulocytes found in the tumor stroma. On this basis, atezolizumab was approved in August 2019 by the European Medicines Agency (EMA) for the treatment of patients with inoperable and locally advanced or metastatic TNBC with PD-L1 expression on IC cells ≥ 1%, who had not previously received chemotherapy for advanced disease [2]. It should be emphasized that the VENTANA PD-L1 (SP142) test is the only validated method that can be used to assess PD-L1 expression when atezolizumab treatment is planned. As discussed previously, TNBC tissue material obtained during resection or core-needle biopsy from a primary or metastatic tumor can be used to assess PD-L1 expression. On the other hand, cytological samples and decalcified bone tissues are not suitable for this evaluation [15].

An important additional analysis is the evaluation of PD-L1 expression using 3 different antibodies: VENTANA SP142, VENTANA SP263, and DAKO 22C3, performed in 68% of tumors in patients participating in the IMpassion130 study. There were the following percentages of positive results for PD-L1 expression (IC ≥ 1%): 46.4% (SP142), 74.9% (SP263), and 73.1% (22C3). There was a significant difference in the frequency of positive and negative results when comparing the standard test (SP142) with the additional test. The rate of positive results in SP142+ tumors was 69% for SP262 and 22C3. In addition, it was indicated that benefits, in terms of PFS and OS, were primarily observed in patients treated with atezolizumab if tissue PD-L1 expression was detected with the use of SP142. The results of the analysis indicated that it was not possible to replace the validated SP142 test with other antibodies [16].

Similar observations were made in a study aiming to evaluate positive PD-L1 results with various tests. Tissue samples from 447 early TNBCs were assessed. PD-L1 expression (IC ≥ 1%) using the SP142 test was found in 34% of the cases. At the same time, staining with SP263 and 22C3 was performed. In the SP142+ group, double positive results were found in 76% (SP142+/SP263+) and 78% (SP142+/22C3+) cases, respectively, which confirms the discrepancy of the results when using different antibodies [17].

Interesting conclusions also come from the meta-analysis of 20 studies evaluating the rate of PD-L1-positive results in primary tumor and metastatic samples with the use of various tests (most often SP142, n = 8), which confirmed observations from the IMpassion130 study. Positive results were more common in primary tumors (51%) compared to metastases (37%). Considering the TNBC studies in which PD-L1 expression was determined on IC with the SP142 test, a higher percentage of PD-L1-positive results was found in primary tumors (55%) than in metastases (37%). In addition, there was a higher frequency of positive PD-L1 results if lymph nodes or lung metastases were evaluated (lower rate in the case of bone or liver samples). Another analysis compared PD-L1 expression in the material from primary tumors and metastases in the same patients. Discrepancies in the results were found in 39% of cases, with more frequent switching from positive to negative [18].

Additionally, the necessity of proper training of pathologists in the assessment of PD-L1 with SP142 is emphasized, as there is a large discrepancy in the interpretation of results between pathologists, especially in samples from metastases [19].

New directions

Early TNBC

The efficacy of atezolizumab is also assessed in patients with early TNBC. The first NeoTRIP study included 280 patients with stage II-III TNBC (without cT2N0 cases) who were receiving preoperative chemotherapy consisting of nab-paclitaxel (125 mg/m^2) and carboplatin (2 AUC) administered on days 1 and 8 every 21 days. Atezolizumab (1200 mg) was added to the ex-

perimental arm. After 8 cycles of therapy, surgery was performed, and then in both groups, 4 cycles of anthracycline-based chemotherapy were administered. The primary endpoint of the study was event-free survival (EFS) in the whole study population. A secondary endpoint was the pathological complete response (pCR) rate. There was no significant difference in the pCR rate (48.6% in the experimental group *vs.* 44.4% in the control group; p = 0.48). However, it was found that the pCR rate was higher in PD-L1-positive patients in both study arms. The incidence of treatment-related adverse events was similar in both groups except for a significantly higher incidence of serious adverse events in the immunotherapy arm (18% *vs.* 6%) and elevated transaminases with atezolizumab. Data are continuously collected to determine the effect of atezolizumab therapy on EFS [20].

The second large study evaluating the efficacy of atezolizumab in preoperative TNBC therapy was the IMpassion031 phase III study, which included 333 patients with stage II-III breast cancer. Immunotherapy (atezolizumab 840 mg every 2 weeks) was added in the experimental arm to chemotherapy including nab-paclitaxel (125 mg/m^2, 12 infusions weekly). Then the AC regimen (doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2, 4 cycles every 2 weeks) with immunotherapy (1200 mg, 11 infusions every 3 weeks) was continued in the atezolizumab arm after surgery. The primary endpoints of the study were pCR in the whole study group and in patients with PDL1 expression. Secondary endpoints included EFS, disease-free survival (DFS), and OS. Patient-reported outcomes (PRO) and safety data were also collected. A significantly higher pCR rate was found in patients receiving chemotherapy in combination with immunotherapy (58% *vs.* 41%; p = 0.0044). In TNBC patients with PD-L1 expression, the pCR rate was numerically increased in the atezolizumab group (69% *vs.* 49%); however, without statistical significance. Data on EFF, DFS, and OS are still being collected. The frequency of grade 3/4 adverse events (AEs) during preoperative treatment was similar in both arms (57% in the atezolizumab group *vs.* 53%), and the most common AEs were neutropenia, febrile neutropenia, leukopenia, anemia, and hypertension. However, treatment-related serious adverse events were observed slightly more often in the immunotherapy group (23% *vs.* 16%). The number of patients who discontinued treatment with atezolizumab or placebo due to adverse events was 21 (13%) and 19 (11%), respectively. The authors of the IMpassion031 study concluded that atezolizumab should be used perioperatively in combination with preoperative chemotherapy in patients with TNBC regardless of PD-L1 expression status [21].

Another large phase III study, the IMpassion030, is currently ongoing to assess the role of atezolizumab added to adjuvant chemotherapy (paclitaxel, followed by doxorubicin/epirubicin plus cyclophosphamide) in patients with stage II-III TNBC [22].

HER2-positive breast cancer

The concept of adding atezolizumab to anti-HER2 treatment is being evaluated in HER2-positive breast cancer patients. The first observations come from the phase II KATE2 study, including 202 patients who previously received trastuzumab and taxoid due to advanced HER2-positive breast cancer. Both arms received trastuzumab emtansine (T-DM1 — 3.6 mg/kg every 3 weeks), and atezolizumab (1200 mg) was added in the experimental arm. The primary endpoint of the study was PFS, and the secondary endpoints were OS, ORR, and duration of response (DoR). First interim analysis indicated no benefit from adding atezolizumab and a higher incidence of side effects, which led to a recommendation to unblind the study. The median PFS was 8.2 months in the atezolizumab group compared to 6.8 months in the control arm (p = 0.38), and the ORR was 45% and 43%, respectively. More grade ≥ 3 adverse events were observed in the immunotherapy group: thrombocytopenia (13% *vs.* 4%), elevated aspartate aminotransferase (8% *vs.* 3%), anemia (5% *vs.* 0). PDL1 expression was found in 42% of HER2-positive cancers. Additional subgroup analyzes showed improved efficacy of combination therapy (median PFS — 8.5 *vs.* 4.1 months, ORR — 54% *vs.* 33%). The authors of the study emphasized that the above analyzes were based on a small group of patients and could only be a hypothesis for further studies on PD-L1 positive HER2-positive cancers [23]. The KATE3 study with a similar design is currently ongoing but includes a population of patients with PD-L1 expression (NCT04740918).

Interesting observations may also come from a large study of atezolizumab used in first-line treatment of metastatic HER2-positive breast cancer in combination with standard therapy (pertuzumab, trastuzumab, and taxoid) (NCT03199885).

The addition of atezolizumab was evaluated in early HER2-positive breast cancer in the IMpassion050 study [24]. Patients with tumors > 2 cm and lymph node metastases (T2-4, N1-3, M0) were randomly assigned to the group with atezolizumab or placebo. Both arms received dose-dense doxorubicin and cyclophosphamide chemotherapy regimen followed by paclitaxel plus pertuzumab and trastuzumab. After surgery, the patients continued treatment with atezolizumab/placebo and anti-HER2 therapy (pertuzumab with trastuzumab or trastuzumab emtansine in the case of residual disease) for a year. Co-primary endpoints of the study were pCR rates in the whole study population and patients

Table 2. Summary of data on atezolizumab in patients with triple-negative breast cancer

Humanized monoclonal IgG1 antibody against PD-L1
Dosage: 840 mg intravenously on days 1 and 15 every 28 days
Combination therapy with nab-paclitaxel (100 mg/m^2 on days 1, 8, and 15 of each 28-day cycle)
Eligibility for treatment: VENTANA SP142 test — PD-L1 positive expression on IC cells (≥ 1%)
Improvement in median PFS and OS (PD-L1+ population) and ORR
Maintaining quality of life in patients treated with atezolizumab in combination with chemotherapy
EMA registration: in combination with nab-paclitaxel for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumors have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease

EMA — European Medicines Agency; IC — immune cells; ORR — objective response rate; OS — overall survival; PD-L1 — programmed death receptor type 1; PFS — progression-free survival; TNBC — triple-negative breast cancer

with PD-L1 expression. The pCR results in the placebo and atezolizumab groups in the whole population were similar and amounted to 62.7% and 62.4%, respectively ($p = 0.9551$). There was also no significant difference in the subgroup of PD-L1-positive breast cancers: pCR rates in the placebo and atezolizumab arms were 72.5% and 64.2%, respectively ($p = 0.1846$). Additionally, grade 3/4 adverse events and serious adverse events were more frequent in the atezolizumab group compared to the placebo group. The safety profile of the treatment was consistent with observations from other clinical trials. The results of the study showed that there was no benefit in adding immunotherapy to pre-operative treatment in patients with early HER2-positive breast cancer. Another APTneo clinical trial is being conducted for the same indication, and the role of atezolizumab used perioperatively in combination with anti-HER2 treatment (pertuzumab and trastuzumab) and preoperative chemotherapy (NCT03595592) is also being investigated.

On the other hand, the ASTEFANIA study (NCT04873362) assesses the benefit of adding atezolizumab to T-DM1 as adjuvant treatment in patients with HER2-positive breast cancer with residual disease and high risk of disease recurrence.

ER-positive/HER2-negative breast cancer

There are no data on the efficacy of atezolizumab in patients with ER-positive/HER2-negative breast cancer. The first small studies in combination with hormone therapy (NCT04630210) are being designed.

Summary

Immunotherapy is a modern method of treatment evaluated in patients with breast cancer. The first-in-class approved drug was atezolizumab for the treatment of patients with inoperable and locally advanced or metastatic TNBC with PD-L1 expression on IC cells ≥ 1%, who had not previously received chemotherapy for advanced disease. The results of the pivotal IMpassion130 study indicated that atezolizumab improves outcomes in patients with PD-L1-positive cancers when used in combination with nab-paclitaxel. In qualifying for treatment, it is important to use the validated SP142 test (Tab. 2). In the second study, IMpassion131, no benefit was seen when the drug was used in combination with paclitaxel. More studies are ongoing with other cytotoxic drugs that may change the indications for combination immunotherapy. On the other hand, the first results of studies in early TNBC show a significant improvement in pCR in the whole group of patients. However, the addition of atezolizumab cannot be currently recommended based on the available results of studies in HER2-positive breast cancer. Numerous ongoing clinical trials may change the indications for the use of this drug in patients with breast cancer in the future.

Conflict of interest

K.P.: honoraria for consultations/lectures/training sessions/clinical trials and fees for scientific congresses: Roche, Novartis, Eli Lilly, Pfizer, MSD, AstraZeneca, Gilead, Teva, Egis.

A.J.G.: honoraria for consultations/lectures/training sessions/clinical trials: AstraZeneca, Novartis, Roche, Gilead, Eli Lilly, Amgen, Pfizer, MSD.

M.K.: honoraria for consultations/lectures/training sessions/clinical trials and fees for scientific congresses: MSD, Bayer, Novartis, Eli Lilly, Pfizer, Roche, Vipharm, Angelini.

W.O.: honoraria for consultations/lectures/training sessions/clinical trials: Roche.

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