Update Breast Cancer 2022 Part 4 – Advanced-Stage Breast Cancer

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**ABSTRACT**

For the treatment of patients with advanced HER2-negative hormone receptor-positive breast cancer, several substances have been introduced into practice in recent years. In addition, other drugs are under development. A number of studies have been published over the past year which have shown either an advantage for progression-free survival or for overall survival. This review summarizes the latest results, which have been published at current congresses or in specialist journals, and classifies them in the clinical treatment context. In particular, the importance of therapy with CDK4/6 inhibitors – trastuzumab deruxtecan, sacituzumab govitecan and capivasertib – is discussed. For trastuzumab deruxtecan, an overall survival benefit in HER2-negative breast cancer with low HER2 expression (HER2-low expression) was reported in the Destiny-Breast-04 study. Similarly, there was an overall survival benefit in the FAKTION study with capivasertib. The lack of overall survival benefit for palbociclib in the first line of therapy raises the question of clinical classification.

**ZUSAMMENFASSUNG**


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**Introduction**

The new developments for the treatment of patients in the metastatic treatment situation have produced some new standard therapies, such as the CDK4/6 inhibitors in the first advanced line of therapy in hormone-receptor-positive, HER2-negative breast cancer, the immune checkpoint inhibitors in triple-negative, PD-L1-positive breast cancer, and the PARP inhibitors in a BRCA1/2 germ line mutation. Furthermore, the antibody-drug conjugates (ADCs) sacituzumab govitecan could become established in subsequent lines of therapy for patients with triple-negative breast cancer and trastuzumab-deruxtecan in patients with HER2-positive breast cancer. In particular, new patient groups have recently been identified for the ADC, in which these drugs were able to display a high effectiveness despite low expression of the target molecule.

**HER2-low – Biomarker or New Subgroup**

The anti-HER2 ADC trastuzumab deruxtecan (T-DXd) demonstrated high efficacy in patients with positive HER2 status (HER2 positive according to the criteria of the ASCO/CAP guidelines [1]) in both the single-arm Destiny-B01 study and the Destiny-B03 study. “Positive” in this context means that the patients either had to have a score of 3+ in immunohistochemistry or had to have an amplification of the HER2 gene with a gene-to-centrometer ratio of ≥2.0. This definition identifies patients who have an extremely poor prognosis without anti-HER2 treatment because of the activated HER2 pathway. However, the Destiny-B01 study also included patients who did not have overexpression or amplification of HER2, but had some expression of HER2 with an immunohistochemical score of 1+ or 2+ (without amplification). This population is called “HER2-low”.

“Low Expression” as a therapy concept

The therapy concept that molecules on the cancer surface can be used to direct therapies there, even if they are not necessarily responsible for a poor prognosis, is not new. For example, in clinical studies, anti-HER2 CAR-T cells have already been used for a therapy with sarcomas [2] and anti-HER2 CAR-NK cells for therapy of glioblastomas [3]. In both cases, no overexpression or amplification was required for therapy. Another example is the Di-Sialo ganglioside GD2, which can be found in breast cancer and other carcinomas [4] and which is already relevant for antibody therapy in certain neuroblastomas [5]. Although GD2 can be found in about 50% of all breast cancers, it has no influence on the prognosis and is certainly an interesting target [4]. A known, further example is Trop2, a target which can be addressed by means of ADC sacituzumab govitecan and is approved for the treatment of patients with previously treated, metastatic TNBC [6].

Thus, the use of therapies against targets that mark the cancer cell, but do not necessarily have to be responsible for the aggres-
siveness of a tumor, is not a new concept. With the new, highly effective ADCs, these patient groups now seem to be suitable for the establishment of new therapies. With regard to tumors with low HER2 expression (HER2-low), it was shown in a registry study that the degree of expression (score of 1+ or 2+) had no influence on PFS or OS in HER2-low patients. In the distribution to the molecular subgroups (Fig. 1), it can be seen that approximately 40% of triple-negative tumors and 53% of HR-positive HER2-negative tumors have a low expression of HER2 and would thus be suitable for such a therapy.

It should be noted that, in the future, new standards will have to be established in the immunohistochemical assessment of HER2 expression. Until now, low expression values had no therapeutic relevance. For a therapy decision, there should be an agreement between pathologists and therapists.

Trastuzumab deruxtecan in HER2-negative tumors with low HER2 expression

For patients with HER2-negative HR-positive advanced breast cancer, all endocrine therapy options should first be exhausted [7]. However, real-world data show that even after the introduction of CDK4/6 inhibitors, about 40–50% of patients in the second or third line of therapy are still treated with chemotherapy [8], while about 80% of patients are already treated with a CDK4/6 inhibitor [9] in the first line of therapy. An improvement in the therapy situation for these patients would mean a significant progress in therapy. Against this background, the Destiny-Breast-04 study compared chemotherapy of the physician’s choice (capecitabine, eribulin, gemcitabine, paclitaxel or Nab-paclitaxel) with ADC trastuzumab deruxtecan [10]. Only patients who were considered to have endocrine resistance and who had already undergone one or two chemotherapies in the advanced treatment situation could be included.

In the Destiny-Breast-04 study, 65% of hormone receptor-positive patients had received preliminary therapy with a CDK4/6 inhibitor and around 60% had received chemotherapy in the metastatic situation. 58% had a HER2 IHC score of 1+ and 42% had a score of 2+ in the absence of amplification of the HER2 gene [10].

Median progression-free survival was improved from 4.8 months to 9.9 months (HR = 0.50; 95% CI: 0.40–0.63; p < 0.0001). This was true for both hormone receptor-positive and hormone-receptor-negative patients (HR = 0.51; 95% CI: 0.40–0.64 for HR-positive and HR = 0.46; 95% CI: 0.24–0.89 for TNBC).

Median overall survival was also improved. In the overall population, the HR was 0.64 (95% CI: 0.49–0.84). Again, the effect was significant in both the HR-positive population (HR = 0.64; 95% CI: 0.48–0.86; Fig. 2) and in the TNBC population (HR = 0.48; 95% CI: 0.24–0.95).

However, it should be noted that with 58 TNBC patients, the analysis was only of an exploratory nature. Also, with a median follow-up period of 18.4 months, it must be noted that no statement can be made about the overall survival during a longer follow-up period. Nevertheless, the statement that over a period of 1.5 years, approximately 35% fewer deaths occur if therapy with T-DXd is carried out instead of chemotherapy, has statistical significance and will most likely influence the therapy decisions.

Unlike in the Destiny-B03 study, the Destiny-B04 study again reported 3 deaths associated with interstitial lung disease as a result of T-DXd therapy. The possibility of these rare but dangerous side effects should be known to the practitioner, and diagnostic (low dose, high resolution CT) and therapeutic (cortisone therapy) measures should always be initiated immediately in case of respiratory symptoms or suspicion of interstitial lung disease.

New Data on the Therapy of the PI3K/AKT/PTEN Signaling Pathway

The PIK3CA pathway as a central component of signal transduction

There are few therapies for which there are clear predictive biomarkers. The presence of hormone receptors predicts the effect of endocrine therapies and HER2 status predicts the effectiveness of anti-HER2 therapies. Another predictive factor is the presence of PIK3CA tumor mutations for the efficacy of PI3K inhibitors. This was demonstrated for both buparlisib in the BELLE-2 study and alpelisib in the SOLAR-1 study. In the BELLE-2 study, the hazard ratio in favor of fulvestrant + buparlisib therapy in a group with PIK3CA mutation was 0.58 (95% CI: 0.41–0.82) and 1.02 in the group without PIK3CA mutation (95% CI: 0.79–1.30) [11]. In the SOLAR-1 study, the HR in the PIK3CA mutated group was 0.65 (95% CI: 0.50–0.85) and 0.85 in the wild-type group (95% CI: 0.58–1.25) [12]. Thus, this principle could be confirmed in 2 studies. In fact,
The PI3K/AKT signaling pathway is a central mechanism of signal transduction with an extraordinary significance for many physiological and pathophysiological processes [13, 14].

While the PI3 kinase interacts with the transmembrane receptors at the beginning of the signal cascade, the AKT kinase downstream of PI3K and PTEN is responsible for the further signal transduction. Activation of this signaling pathway occurs in patients with hormone receptor-positive disease in approx. 55% of all cases [15]. A review of these signal transduction pathways is shown in Fig. 3.

The FAKTION study is one of the first studies to investigate the effects of the selective AKT inhibitor capivasertib [16]. The study, which had recruited patients from 2016 to 2018, included patients with resistance to an aromatase inhibitor. Furthermore, one chemotherapy line and up to 3 previous endocrine therapies were permitted as long as they did not contain fulvestrant or a PI3K/AKT/mTOR inhibitor. A total of 140 patients were randomized 1:1 to treatment with fulvestrant or fulvestrant + capivasertib. Data on significant improvement in progression-free survival have already been published [15]. Overall survival data, extended data on PFS and extensive biomarker data have now been presented. The PFS difference was consolidated with the longer follow-up and, with an HR of 0.56 (95% CI: 0.38–0.81), is consistent with the initial report. At 4.8 months and 10.3 months, the median PFS times were the same as in the initial report. This PFS benefit was also translated into a statistically significant overall survival benefit with an HR of 0.66 (95% CI: 0.45–0.97). Median overall survival improved from 23.4 months to 29.3 months [16].

The biomarker data are of particular interest for this study. For the recently presented analysis, new state-of-the-art analysis methods were used to divide the patients into two groups: “PI3K/AKT/PTEN signaling pathway activated” vs. “not activated”. This was done by means of mutation tests for PIK3CA, AKT1, PTEN and immunohistochemical examinations for PTEN loss. Thus, 76 patients could be assigned to the group with altered signaling pathway and 64 to the group with non-altered signaling pathway. The results confirmed the efficacy of capivasertib therapy in patients whose signaling pathway was altered and the lack of efficacy in patients whose signaling pathway was not altered (Table 1).

This underscores the principle that molecular testing can identify patients for whom therapy, in this case with capivasertib, makes sense. The adverse reaction profile showed a higher rate in capivasertib patients for the following side effects: Diarrhea, rash, hyperglycemia, vomiting, infections and oral mucositis.

Since the FAKTION study was conducted at a time when treatment with CDK4/6 inhibitor was not yet standard, this preliminary treatment is missing in this study. Against this background, the results of the CAPitello-291 study will provide insights into a population in which a CDK4/6 inhibitor was also approved as a preliminary therapy [17]. Combination therapy with CDK4/6 inhibition, as tested in the CAPitello-292 study [18], is also of interest.
Data from the Large, Randomized CDK4/6 Inhibitor Studies are Almost Complete

Data overview for the phase III CDK4/6 inhibitor studies is almost complete

For the three CDK4/6 inhibitors palbociclib, ribociclib and abemaciclib, a total of seven large randomized studies have been conducted (▶Table 2). Because of the improved prognosis, the data from the studies in the first line of therapy in relation to overall survival have only recently been published.

Subgroup analysis of the MONALEESA-3 study reports median overall survival for the first line of therapy

The MONALEESA-3 study is the only study that included patients with both tumors sensitive to hormone therapy and resistant to hormone therapy, defined by the time between discontinuation of adjuvant anti-hormonal therapy (first line) or progression under antihormone therapy in first-line therapy. In this context, the evaluation of these subgroups is of particular interest. The subgroups evaluated independently were those with de novo metastases and those who had a therapy-free interval from the end of adjuvant therapy of more than 12 months. This population is called first-line population in MONALEESA-3. Patients with a treatment-free interval of less than 12 months (even if they had been treated in

▶Fig. 3 The PI3K/AKT/PTEN signaling pathway [53].

▶Table 1 Results of the analysis of the FAKTION study according to biomarker status for the PI3K/AKT/PTEN pathway.

<table>
<thead>
<tr>
<th></th>
<th>Total population</th>
<th>PIK3/AKT/PTEN altered</th>
<th>PIK3/AKT/PTEN altered</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>140</td>
<td>76</td>
<td>64</td>
</tr>
<tr>
<td>Median PFS fulvestrant</td>
<td>4.8 months</td>
<td>4.6 months</td>
<td>4.9 months</td>
</tr>
<tr>
<td>Median PFS fulvestrant + capivasertib</td>
<td>10.3 months</td>
<td>12.8 months</td>
<td>7.7 months</td>
</tr>
<tr>
<td>Hazard ratio PFS (fulvestrant + capivasertib vs. fulvestrant)</td>
<td>0.56 (95% CI: 0.38–0.81)</td>
<td>0.44 (95% CI: 0.26–0.72)</td>
<td>0.70 (95% CI: 0.40–1.25)</td>
</tr>
<tr>
<td>Median OS fulvestrant</td>
<td>23.4 months</td>
<td>20.0 months</td>
<td>25.2 months</td>
</tr>
<tr>
<td>Median OS fulvestrant + capivasertib</td>
<td>29.3 months</td>
<td>38.9 months</td>
<td>26.0 months</td>
</tr>
<tr>
<td>Hazard ratio OS (fulvestrant + capivasertib vs. fulvestrant)</td>
<td>0.66 (95% CI: 0.45–0.97)</td>
<td>0.46 (95% CI: 0.27–0.79)</td>
<td>0.86 (95% CI: 0.49–1.52)</td>
</tr>
</tbody>
</table>
the first line of therapy) and patients with endocrine preliminary therapy were treated as patients of the second-line therapy. In the patients sensitive to hormone therapy (MONALEESA-3 first-line population), a very clear difference between the treatment arms could be seen with a hazard ratio of 0.67 (95% CI: 0.50–0.90) [19]. The median overall survival in this population was 51.8 months for fulvestrant monotherapy and 67.6 months for ribociclib-fulvestrant therapy. In the hormone-resistant group (MONALEESA-3 second-line population), the difference was not so clear (HR = 0.80; 95% CI: 0.61–1.05) with median overall survival times of 33.7 and 39.7 months [19].

Negative overall survival data from the PALOMA-2 study is difficult to interpret

The MONALEESA-2 study was the first study in the first line of therapy in combination with aromatase inhibitors to report a statistically significant overall survival benefit [20] (Table 2). The PALOMA-2 study had similar inclusion and exclusion criteria as the MONALEESA-2 study. In addition to the MONALEESA-2 population, patients who had a disease-free interval of less than 12 months from the end of adjuvant endocrine therapy were also included. This group accounted for 22% of the PALOMA-2 patients (Table 2). In all, the analysis of the overall survival data from the PALOMA-2 study did not show that adding palbociclib to letrozole could improve overall survival [21]. The hazard ratio for the entire patient population was 0.96 (95% CI: 0.78–1.18). The median overall survival was 51.2 months for the letrozole arm and 53.9 months for the palbociclib + letrozole arm. Overall, however, the study is difficult to interpret due to a follow-up bias. In the palbociclib arm, 13% of patients were not censored for death by month 84, and 21% in the endocrine monotherapy arm. These differences were sometimes even greater in the subgroup analyses and more balanced in others, so that the interpretation of the subgroups is also rather difficult. However, these subgroups would have been of particular interest because a certain endocrine resistance had to be assumed in the PALOMA-2 study in a total of 22% of patients, since in these patients the interval from the end of adjuvant endocrine therapy to relapse had been less than 12 months. If we look at the population of patients in whom this interval had been more than 12 months, we find a hazard ratio of 0.76 (95% CI: 0.64–0.90), which was very similar to that of MONALEESA-2 and MONARCH-3. However, the beneficial effect of palbociclib was not seen in the de novo metastatic group (HR = 1.19; 95%: 0.84–1.7), whereas a clear therapeutic effect was seen in this group in the MONALEESA-2 study. This subgroup of de novo metastatic patients again had a clear follow-up bias in the PALOMA-2 study. This example shows how difficult it is to interpret the data from the PALOMA-2 study.

There are still no direct comparisons between the CDK4/6 inhibitors, so that no statement can be made about varying clinical efficacy. In the clinical decision, however, the existing data situation must not be disregarded, because therapy alternatives are available for each choice of a substance.

The final overall survival analysis of the MONARCH-3 study is still pending. In an interim analysis, we find a hazard ratio of 0.76...
(95% CI: 0.58–0.97), which had not yet achieved statistical significance due to the study design with interim analysis.

Should CDK4/6 inhibitor therapy be continued with progress?

After progress under a CDK4/6 inhibitor, the question arises as to how to proceed further. This treatment situation was investigated in the maintain study. Patients with progress under CDK4/6 inhibitor therapy were randomized 1:1 to either ribociclib + modified ET therapy (continuation of CDK4/6 inhibitor therapy under ribociclib or switch to ribociclib) and to therapy with a modified ET alone. In patients receiving an aromatase inhibitor, therapy with fulvestrant was initiated, and in patients receiving fulvestrant, a change to exemestane was permitted later in the course of the study. A total of 119 patients were randomized. The majority of patients enrolled (n = 103) were on palbociclib therapy at the time of enrollment in the study, 14 were on ribociclib therapy and 2 on abemaciclib therapy. It has been shown that discontinuation of CDK4/6 therapy and continuation of treatment with endocrine monotherapy has not been beneficial for patients. Prolonged median progression-free survival (5.3 months) was seen with continued CDK4/6 inhibitor therapy compared to the monotherapy arm (2.8 months). The corresponding hazard ratio was 0.57 (95% CI: 0.39–0.95). This effect appeared to be present both in the case of a switch from fulvestrant to exemestane (n = 20) and in the case of a switch from aromatase inhibitor to fulvestrant (n = 99), although it must be noted that the subgroup of exemestane patients was very small. The hypothesis that the switch to fulvestrant was most likely going to eventuate in a therapeutic benefit due to an accumulation of somatic ESR1 mutations could not be confirmed. In a total of 78 patients there was a mutation status of ESR1. No treatment benefit for the continuation of CDK4/6 inhibitor therapy was observed in the group of patients with an ESR1 mutation (HR = 1.22; 95% CI: 0.59–1.49), while the benefit in the group of patients without mutation recorded a hazard ratio of 0.30 (95% CI: 0.15–0.62).

This study underscores the importance of a better understanding of the progression mechanisms among CDK4/6 inhibitors. The PADA-1 study investigated another question in this context. In early detection of ESR1 mutations in the blood without clinical progression, a benefit could be seen in the PADA-1 study in the switch from aromatase inhibitors to fulvestrant [22]. The change in clinical progression in the MAINTAIN study in the group of ESR1-mutated patients had shown no effect. The reasons can only be presumed, but can possibly be explained by high fulvestrant activity. This shows that progression mechanisms may be more complicated than previously assumed and further studies are necessary to enable better sequence planning. Studies such as MINERVA [23] and the CAPTOR-BC study [23], which are currently starting to recruit, address these questions.

Sacituzumab Govitecan in Patients with HER2-negative HR-positive Breast Cancer

Trop-2 is an antigen which is overexpressed in some cancers such as breast cancer, some thyroid carcinomas, pancreatic carcinoma, colon carcinoma, urothelial carcinoma and other tumors [24–26]. Even if participations in signaling pathways are postulated, which play a role in the development of cancer or progression, it has not yet been possible to prove that Trop-2 is a prognosis marker for patients with breast cancer [27]. However, as already described above, the activity of the addressed signaling pathway does not necessarily appear to be of great importance for an efficacy of some ADCs, but rather the pure presence of the target molecule, in the case of Trop-2. Already in the ASCENT study, it was shown that even with low Trop-2 expression, an effect of sacituzumab govitecan could still be demonstrated [28].

Against this background, the results of the TROPICS-02 study have now been presented. The TROPICS-02 study included hormone receptor-positive, HER2-negative patients who had to have completed some preliminary therapies. These included at least endocrine therapy, taxane therapy and therapy with a CDK4/6 inhibitor. At least 2 and no more than 4 chemotherapy lines for metastatic disease had to be completed. Thus, only HR-positive/HER2-negative patients who had clearly completed preliminary therapies were included in this study [29].

Patients were randomized 1:1 to treatment with sacituzumab govitecan or to chemotherapy at the physician’s choice (capecitabine, vinorelin, gemcitabine, eribulin). The aim of such a study should be to improve the prognosis with a more favorable side effect profile.

The study was positive with regard to the primary study objective PFS. The median PFS was extended from 4.0 months to 5.5 months. The hazard ratio was 0.66 (95% CI: 0.53–0.83; p = 0.0003). With these results, the study was able to fairly accurately demonstrate the effect that had been planned and assumed in advance. Overall survival was not statistically significantly different in this interim analysis. Median overall survival was improved from 12.3 to 13.9 months. This corresponded to an HR of 0.84 (95% CI: 0.67–1.06; p = 0.14) [29].

It is questionable whether a difference in median PFS of 1.5 months is clinically relevant, in particular because the side effect profile in terms of hematological, gastrointestinal side effects and alopecia was less favorable in the sacituzumab-govitecan arm than in the chemotherapy arm [29]. However, this adverse reaction profile did not appear to affect the quality of life. The quality of life measured by the EORTC-QLQ-C30 questionnaire was maintained longer (time to deterioration) with sacituzumab govitecan than with chemotherapy [29].

It is known from real-world data that patients still receive a large proportion of chemotherapy in the second and third lines of therapy after CDK4/6 inhibitor therapy [8]. Against this background, the data from the TROPICS-02 study are certainly promising and it is desirable that this drug is investigated in earlier lines of therapy with the intention of checking whether a larger, absolute improvement in the prognosis can also be achieved in a collective with a generally better prognosis.

Outlook

For patients with advanced, hormone receptor-positive, HER2-negative breast cancer, new findings have been published with the PALOMA-2 study, the Destiny-Breast-04 study and the
TROPICS-02 study, which have a high relevance for clinical practice. With an overall survival benefit and an acceptable side effect profile, trastuzumab deruxtecan could establish itself after an approval extension for patients with an MBC and the property HER2-low. The Destiny-Breast-06 study [30], which examines the substance in patients with metastatic breast cancer and HER2-low expression in previous lines of therapy, is currently still recruiting.

The lack of evidence of an overall survival benefit presents both doctors and patients with the challenge of meaningfully interpreting the data. Experience from clinical practice will show whether the different data situation (Table 1) will result in different prescribing behavior. With the CDK4/6 inhibitors as standard of care and the different study data, the need to better understand the mechanisms of action and resistance in order to better plan treatment sequencing or further combination therapies is growing. Clinical studies, for example, pursue the approach of switching the therapy to a SERD in the case of an ESR1 mutation under therapy with a CDK4/6 inhibitor and aromatase inhibitor [31]. Furthermore, the CAPTOR-BC study [32] and the MINERVA study [23] mark the launch of two translational research programs in Germany, which also investigate the molecular mechanisms of resistance and mode of action of the CDK4/6 inhibitors ribociclib and abemaciclib.

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Conflict of Interest

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T. N. F. has participated on advisory boards for Amgen, Daiichi Sankyo, Novartis, Pfizer, and Roche and has received honoraria for lectures from Amgen, Celgene, Daiichi Sankyo, Roche, Novartis and Pfizer.

A. D. H. received speaker and consultancy honoraria from AstraZeneca, Genomic Health, Roche, Novartis, Celgene, Lilly, MSD, Eisai, Teva, Tesaro, Daiichi Sankyo, Hexal and Pfizer.

N. H. received honoraria for lectures and/or consulting from Amgen, AstraZeneca, Daiichi Sankyo, Exact Sciences, Gilead, Lilly, MSD, Mylan, Novartis, Pierre Fabre, Pfizer, Roche, Sandoz, Seagen.

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D. L. received honoraria from Amgen, AstraZeneca, Eli Lilly, Gilead, GSK, Loreal, MSD, Novartis, Onkowissen, Pfizer, Seagen, Teva.

M. P. L. has participated on advisory boards for AstraZeneca, Lilly, MSD, Novartis, Pfizer, Eisai, Gilead, Exact Sciences, Pierre Fabre, Grünenthal, Daiichi Sankyo, PharmaMar and Roche and has received honoraria for lectures from MSD, Lilly, Roche, Novartis, Pfizer, Exact Sciences, Daiichi Sankyo, Grünenthal, Gilead, AstraZeneca, and Eisai. He is editorial board member of medactuell from medac.

V. M. received speaker honoraria from Amgen, AstraZeneca, Daiichi Sankyo, Eisai, GSK, Pfizer, MSD, Medac, Novartis, Roche, Teva, Seagen, Onkowissen, high5 Oncology, Medscape, Gilead. Consultancy honoraria from Hexal, Roche, Pierre Fabre, Amgen, ClinSol, Novartis, MSD, Daiichi Sankyo, Eisai, Lilly, Sanofi, Seagen, Gilead. Institutional research support from Novartis, Roche, Seagen, Genentech. Travel grants: Roche, Pfizer, Daiichi Sankyo.

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F. S. participated on advisory boards for Novartis, Lilly, Amgen and Roche and received honoraria for lectures from Roche, AstraZeneca, MSD, Novartis and Pfizer.

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M. T. has participated on advisory boards for Agenda, AstraZeneca, Aurikamed, Clovis, Daiichi Sanyo, Eisai, Exact Sciences, Gilead Science, Grünenthal, GSK, Lilly, MSD, Novartis, Onkowissen, Organon, Pfizer, Pierre Fabre, Seagen and Roche and has received honoraria for lectures from Amgen, Clovis, Connect Medica, Daiichi Sankyo, Hickler, Eisai, GSK, Laborzpraxis Walther, Lilly, MSD, Roche, Novartis, Onkowissen, Organon, Pfizer, Seagen, Streamedup, Exact Sciences, Viatris, Vifor and AstraZeneca and has received travel funding by Exact Sciences and Endomag Manuscript support was done by AstraZeneca, Pfizer, Novartis, Genomic Health, Roche, Novartis, Celgene, Lilly, MSD, Eisai, Teva, Tesaro, Daiichi Sankyo, Hexal and Pfizer.

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M. W. has participated on advisory boards for AstraZeneca, Lilly, MSD, Novartis, Pfizer and Roche.
I.W. has participated on advisory boards for Novartis, Daiichi Sankyo, Lilly, Pfizer and received speaker honoraria from AstraZeneca, Daiichi Sankyo, MSD, Novartis, Pfizer, Roche.

A.W. participated on advisory boards for Novartis, Lilly, Amgen, Pfizer, Roche, Tesaro, Eisai and received honoraria for lectures from Novartis, Pfizer, Aurikamed, Roche, Celgene.

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