Update Breast Cancer 2019 Part 5 – Diagnostic and Therapeutic Challenges of New, Personalised Therapies in Patients with Advanced Breast Cancer

Update Mammakarzinom 2019 Teil 5 – diagnostische und therapeutische Herausforderungen neuer personalisierter Therapien bei Patientinnen mit fortgeschrittenem Mammakarzinom

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ABSTRACT

Significant advancements have been made in recent years in advanced breast cancer and nearly all of them have been in the field of targeted therapy. Pertuzumab and trastuzumab-emetansine (T-DM1) have been able to be introduced in HER2-positive breast cancer. Now other anti-HER2 therapies are being developed (e.g. margetuximab, DS-8201a, pyrotinib) which can overcome other resistance mechanisms in the HER2 signalling pathway. In the field of hormone-receptor-positive breast cancer, an mTOR inhibitor and CDK4/6 inhibitors were introduced in the past. Now the introduction of the first PI3K inhibitor is forthcoming and this inhibitor will involve genetic testing of the tumour for a mutation in the PIK3CA gene. There are also significant advancements in triple-negative breast cancer: By combining chemotherapy and immunotherapy, an advantage for overall survival was able to be demonstrated in a subgroup (immune cells PD-L1-positive). The PARP inhibitor therapy for HER2-negative patients with a germ line mutation in BRCA1 or BRCA2 was also associated with an improved overall survival in a subgroup. These promising new study results are summarised in this review.

ZUSAMMENFASSUNG


Introduction

The new developments in the therapy of advanced breast cancer are taking place at a rate which has never been seen before. While only few new drugs were approved by 2012, the approval of 10 new drugs has been able to be observed since then. These rapid developments call for a high degree of attention from all sides (patients, physicians, health insurance companies, health committees) to ensure therapeutic efficacy and patient safety. In this review article, we focus on the latest study results which were recently published or presented at national or international professional conferences.

Metastatic HER2-negative, Hormone-Receptor-Positive Breast Cancer

Many study designs currently concentrate on analysing the efficacy of inhibitors of the PI3K/AKT/PTEN signalling pathway [1] in patients with advanced breast cancer. Jones et al. investigated the significance of the AKT inhibitor capivasertib in combination with fulvestrant within the framework of the FAKTION study (phase II). A significant PFS advantage was seen (4.8 vs. 10.3 months) versus those patients who were treated only with fulvestrant, independent of an activation of the PI3K/AKT/PTEN signalling pathway. Likewise, improved overall survival – however not statistically significant – was seen on the endocrine combination therapy [2]. These results are promising and must be accordingly confirmed in a phase III study.

New data from the MONALEESA-7 and MONALEESA-3 study

In the premenopausal, metastatic situation as well, the use of CDK4/6 inhibitors in combination with a GnRH analogue is by now the therapeutic standard. The initial data on overall survival following 35 months of follow-up observation in the Monaleesa-7 study were recently published in full [3]. In this study, 672 premenopausal patients with hormone-receptor-positive, HER2-negative, metastatic breast cancer were treated with an endocrine combination therapy (non-steroidal aromatase inhibitor or tamoxifen plus ovarian function suppression) with or without the addition of ribociclib. The most current evaluation demonstrated a significant advantage in overall survival (HR = 0.712; 95% CI: 0.54–0.95; p = 0.00973) with an estimated survival rate after 42 months of 70.2 vs. 46.0%. The treatment following the study therapy did not differ between the arms. Thus the Monaleesa-7 study is the first study with a CDK4/6 inhibitor which demonstrates a survival advantage in the overall study population.

Not reported or published during a conference but rather issued in a press release [4], the Monaleesa-3 study [5] is the second study which is also said to have shown an advantage for overall survival. How great the effect is cannot yet be said due to the lack of any publication at this present time.

New therapies as alternative to chemotherapies

Another study on premenopausal patients was able to prove the significance of endocrine therapy in combination with CDK 4/6 inhibitors in the metastatic situation [6]. The Korean study KC3-G-BR 15-10 compared chemotherapy with capecitabine with an endo-
In a study from Germany, adherence data during aromatase monotherapy in patients with advanced breast cancer were recently published [8]. This study showed that after 12 months, approx. 40% of patients had discontinued therapy without progression if an adverse effect occurred in the first 30 days of therapy. This issue could be of particular significance for patients on therapy with CDK4/6 inhibitors and antihormone therapy because on this therapy, adverse effects occur more frequently than on antihormone monotherapy. A summary of the data in this regard is shown in Table 1.

### Immunotherapies in hormone-receptor-positive breast cancer

Checkpoint inhibitors currently play a large role in triple-negative breast cancer. Tolaney et al. recently presented data from a randomised phase II study for the first time which investigated the significance of pembrolizumab (P) in combination with eribulin (E) in 88 patients who underwent extensive endocrine pretreatment with an indication for chemotherapy (at least 2 endocrine therapies, 0–2 chemotherapies) [9]. A crossover to the pembrolizumab arm was allowed in the event of progression. No difference was seen in the primary endpoint PFS (E + P: 4.1 months vs. E: 4.2 months; p = 0.33). The response rates and the overall survival were independent of the PD-L1 status. However, the extent to which factors such as pretreatment of the patients, chemotherapy with eribulin, or the inclusion of PD-L1-negative patients could be a reason for the lack of benefit of the addition of pembrolizumab cannot be conclusively explained within the scope of this study.

### Routine clinical practice is preparing for PIK3CA mutation testing

The data from the SOLAR-1 study were already released at the ESMO Congress 2018. These data are now available as a full publication [10]. The PI3K inhibitor alpelisib has already been approved in the US. In the randomised SOLAR-1 study, patients who had already received antihormone therapy were randomised in the study. Welslau et al. [11] showed that the benefit of alpelisib could not be conclusively explained within the scope of this study.
for therapy with fulvestrant vs. fulvestrant + alpelisib (PI3K inhibitor). Patients with a tumour mutation in the PIK3CA gene had a prolonged median PFS on therapy with fulvestrant + alpelisib (11.0 vs. 5.7 months; HR = 0.65; 95% CI: 0.50–0.85; p < 0.001).

In the group of patients without a tumour mutation in the PIK3CA, no significant difference between the randomisation arms could be found. Thus in the future, tumours must also be tested for such a mutation. The existing infrastructure within the framework of mutation testing on tumours can be used here for the testing. These tests will be able to be performed by the pathologist. One particular feature is that the SOLAR-1 study showed that, through mutation testing in the blood, a population of patients who benefit from therapy with alpelisib could also be identified [10].

The testing of mutations in so-called circulating tumour DNA is a breakthrough in the treatment of patients with breast cancer. In addition, other test methods are also available: While tumour testing for mutations in panel genes is already established in many cancer centres with next-generation sequencing methods, in the US, the indication was also combined with a PCR (polymerase chain reaction)-based assay as a so-called companion diagnostic. This test enables testing for mutations in PIK3CA with the more advantageous PCR method. Which methods are more sensitive or can be better implemented in clinical practice is currently the subject of scientific investigations.

**New anti-HER2 therapies**

In view of the great success of the anti-HER2 therapies even when used after multiple lines of therapy, the search for effective anti-HER2 therapies naturally continues so that HER2-positive patients can also continue to be treated after progression with an effective anti-HER2 therapy. An example which was already presented in the past is the ADC DS-8201a which binds trastuzumab with a topoisomerase inhibitor and demonstrated good efficacy in early therapeutic studies [16–18]. Recently, two additional anti-HER2 therapies were recently presented: pyrotinib [19] and margetuximab [20].

Pyrotinib is a tyrosine receptor kinase inhibitor which binds HER1, HER2, and HER4. In early studies, it was shown that it has promising efficacy in HER2-positive patients and that it is well tolerated. Now the data from the phase III study were presented [19]. The precondition was HER2-positive, metastatic breast cancer and progression during or after therapy with trastuzumab. More than 2 previous chemotherapies were not permitted. In the 2:1 randomised study, 279 patients received either a combination of capecitabine + pyrotinib or capecitabine + placebo. The median PFS was significantly better in the pyrotinib group with 11.1 vs. 4.1 months in the control group (HR 0.18; 95% CI: 0.13–0.26; p < 0.001). The overall response, at 68.6%, was also considerably better than in the placebo group (16%). The study allowed a crossover and 71 patients received pyrotinib as monotherapy after progression and achieved a response rate of 38% and a median PFS of 5.5 months. The most common grade 3 adverse effects were diarrhoea (30.8 vs. 12.8%) and hand-foot syndrome (15.7 vs. 5.3%) [19].

Margetuximab is an anti-HER2 antibody which is directed against the same epitope as trastuzumab but the Fc part of the antibody is optimized for a better antibody-dependent cellular cytotoxicity, ADCC, [Fig. 1] than trastuzumab [20]. Studies with trastuzumab had shown that a portion of the patients with a certain genotype in the Fc receptor which is present in a majority of
patients responds more poorly to trastuzumab [21, 22], since the Fc part of the antibody has a low affinity for the Fc receptors of the natural killer (NK) cells. Antibodies which can overcome these weaknesses may have better efficacy. The Sophia study investigated margetuximab in a large phase III study. 536 patients who were pretreated with trastuzumab and pertuzumab were randomised and received a combination of trastuzumab or margetuximab with chemotherapy (capecitabine, eribulin, navelbine or gemcitabine at the discretion of the physician) [20]. The therapy with margetuximab + chemotherapy demonstrated a significantly better median PFS (5.8 vs. 4.9 months, HR = 0.76; 95% CI: 0.59–0.98 p = 0.033). The efficacy was higher in the group of patients with the low affinity allele of the Fc receptor. The overall response was also higher in the margetuximab group (22 vs. 16%). The adverse effect profile in both groups was comparable. The new substances neratinib, pyrotinib and margetuximab appear promising, however they are not yet approved in Germany. Further studies to confirm the results are necessary.

Metastatic TNBC

Patients with TNBC are predisposed for immunotherapy

The discovery of the “immunological synapse”, the so-called checkpoint in the immune system with activating and inhibiting receptors which can be stimulated or curbed via the T-cell activity [23] was awarded the Nobel Prize in medicine in autumn 2018 [24]. The development of monoclonal antibodies which block inhibiting receptors so as to override their inhibitory function and so that an activation of immunocompetent T cells can ultimately take place was pioneering for a new cornerstone of medical tumour therapy which has been established since 2011 in a number of tumour entities. These antibodies, known as checkpoint inhibitors, block various inhibiting receptors which are known as CTLA-4, PD-1 and PD-L1 [25].

Almost at the same time as the awarding of the Nobel Prize in medicine, it was known that this mode of action also has potential in locally advanced or metastatic triple-negative breast cancer (mTNBC) [26, 27].

The second interim analysis of the phase III study IMpassion130, which was presented at the ASCO 2019 [27], highlights the importance of this new therapy option for patients with metastatic TNBC: Patients with a PD-L1 expression on tumour-infiltrating immune cells (IC) in > 1% of the immune cells survived a median of 7 months longer when they received a combination of the PD-L1 inhibitor atezolizumab and the cytostatic agent nab-paclitaxel, in comparison to a combination of placebo and nab-paclitaxel (25.0 vs. 18.0 months). The mortality risk decreased in this patient group by 29% (HR: 0.71; 95% CI: 0.54–0.93). More than half of PD-L1 IC-positive patients treated with atezolizumab were still alive after 2 years (51 vs. 37.5% in the comparison arm).

The risk of progression also significantly decreased by 38% (median PFS: 7.46 vs. 4.96 months placebo/nab-paclitaxel; HR = 0.62; 95% CI: 0.49–0.78; p < 0.0001). The combination therapy proved to be safe and well tolerated.

Since the combination of atezolizumab and chemotherapy alone in the case of PD-L1 expression on IC which make up more than 1% of the surface of the tumour proved to be effective, the testing is of key importance [28]. Similar to the HER2 testing, the PD-L1 IC testing must become established as a new standard. The use of validated tests is obligatory.

The adverse events were consistent with the known safety profiles of the monopreparations. However, a challenge is the adverse effect profile of the checkpoint inhibitors which significantly differs from that of chemotherapy: As a consequence of the acti-
vation of immunocompetent T cells, there may be immune-mediated adverse effects (immune related adverse events, irAE). According to the available data from the IMpassion-130 study, these are indeed rare and are only rarely severe, but the time at which they occur differs significantly from the adverse effects caused by chemotherapy. The appearance of irAE months after the start of therapy must be expected, in principle. Thus there may be, for example, immune-mediated pneumonitis, colitis or dermatitis. The prompt detection of irAE is crucial and in general, they can be successfully treated with steroids. A typical chronological sequence is shown in ▶Fig. 2.

Because of the high need for new therapeutic options in metastatic TNBC, the current data from the IMpassion-130 study are of particular relevance.

Based on the data, the Association of Gynaecological Oncology (AGO) assesses the first-line use of atezolizumab with nab-paclitaxel in patients with positive PD-L1 status for IC with a "plus" even before approval. Atezolizumab in combination with nab-paclitaxel for mTNBC was approved by the FDA on 11 March 2019 in the US. EU approval is expected in autumn 2019.

Opportunities for the treatment of TNBC are in the tumour biology

Patients with TNBC have not only an extremely poor prognosis but the tumours in particular lack points of attack which can be used for therapy. In the case of a BRCA1/2 germ line mutation, however, other aspects of the biology of this type of tumour are known. Because of this, initial therapies which are based on these points of attack are already available. These are the PARP inhibitors which can also be used in the case of hormone-receptor-positive, HER2-negative patients. In the two studies OlympiAD and EMBRACA, the efficacy in metastatic, BRCA1/2-germ-line-mutating breast cancer was established (TNBC and HR+ HER–). [29, 30]. The final overall survival data for olaparib were presented in a recently published work. In the overall population, no significant advantage with regard to overall survival was reported (HR 0.51 [95% CI 0.29, 0.90]; p = 0.02). However, in a subgroup analysis, an advantage for overall survival in favour of the olaparib arm was seen for patients who had not yet received any prior chemotherapy in an advanced therapy situation (HR 0.51 [95% CI 0.29, 0.90]; p = 0.02). The corresponding Kaplan-Meier curve is shown in ▶Fig. 3. In the case of therapy with olaparib, a median OS of 22.4 months was reached in this subgroup, while in the case of patients who were treated only with chemotherapy, a median OS of 14.7 months was noted [31].

A precondition for therapy with a PARP inhibitor is the detection of a germ line mutation in BRCA1 or BRCA2. In the metastatic situation, some studies have been conducted on the frequency of these mutations. While in the case of patients with TNBC, a mutation was able to be found in 9.5% of the patients with advanced breast cancer, a BRCA1/2 mutation was present in 4.4% in luminal A-like and luminal B-like tumours and in 4.7% of the patients [32]. Testing for all patients in this group for whom therapy with a PARP inhibitor would be clinically indicated would thus make sense. A reflection on the therapy algorithms for these patients can be found in Schneeweiss et al. [33] where, in the first-line therapy in patients with BRCA1/2 mutations, immunotherapy competes with PARP inhibitor therapy, because for both studies, a survival advantage in subgroups in the first line of therapy was demonstrated.

Supportive Therapy

Supportive therapy as an integral component of oncological care

Supportive therapy is an essential component of all cancer therapies and all oncological care concepts. This includes the treatment of adverse effects as well as the general improvement in health-related well-being. It includes, for example, the treatment of adverse effects such as musculoskeletal symptoms and osteopenia.
in the case of antihormonal therapy, the treatment of stomatitis in mTOR inhibition, the treatment of leukopaenia in CDK4/6 inhibitor therapy or myelosuppression in chemotherapy. However, information for patients and family members and psycho-oncological support and counselling are also a component of supportive therapy [34–36]. The most important objective is the improvement in quality of life and the avoidance of long-term damage. However, a good rationale as to why good supportive therapy can improve the efficacy of therapies can also be found. Thus it is known, for example, that patients on adjuvant and metastatic therapy with aromatase inhibitors discontinue a considerable portion of them without progression [8, 37]. This is frequently the case in particular when patients experience new adverse effects at the start of therapy [8, 38]. In the adjuvant situation, it has already been proven that poor compliance also correlates with a worse outcome [39]. In view of this, adverse effects, quality of life and its supportive therapy should in particular be taken seriously. New study data are rather rare and often do not gain any significant attention.

**New data on zoledronic acid therapy**

The S0702 study of the SWOG (Southwest Cancer Chemotherapy Study Group) was to determine the frequency of osteonecrosis of the jaw (ONJ) after 3 years of zoledronic acid therapy as a primary study objective. In addition, risk factors for ONJ were to be determined. A total of 3491 patients with bone metastases from various primary tumour entities (breast: 32%, prostate: 20%, lung: 19%, multiple myeloma: 17%, other: 12%) who were receiving therapy with zoledronic acid were included. After 3 years, the cumulative incidence of ONJ was 2.8%. Patients whose dosing interval was 3–4 weeks had a risk nearly five times as high of developing ONJ as compared to patients with a prolonged dosing interval (HR 4.80, 95% CI 1.52–15.18, p = 0.008). Additional risk factors for zoledronate-associated ONJ were identified as pre-existing dental disease and existing nicotine abuse [40].

In view of the fact that there is by now sufficient evidence that the zoledronate therapy is also effective with a prolonged dosing interval [41], these data should be considered to be clinically quite relevant. They support the current therapeutic recommendation of the AGO, which gave zoledronate in the 12-week dosing the highest level of recommendation of “++” [42, 43]. By implementing this recommendation, the risk of the occurrence of the adverse effect of ONJ, which is rather rare overall but represents significant impairment for the patient, on zoledronate therapy can be reduced.

**Fig. 3** Kaplan Meier estimators for the overall survival for patients in the OlympiaD study without previous chemotherapy in the metastatic situation (TPC: Treatment of physician’s choice).

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<th>Olaparib</th>
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<td>Deaths, n (%)</td>
<td>30 (50.8)</td>
<td>21 (75.0)</td>
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<td>Median OS, months</td>
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<td>14.7</td>
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<td>HR 0.51 (95% CI 0.29, 0.90); p = 0.02</td>
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<th>Time from randomization (months)</th>
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Access to the Healthcare System and Medical Care

Medical care as a political topic

The discussion of the best medical care given limited resources has been a part of public and political discussion in Germany for a long time. In the case of new therapies, the benefit assessment process repeatedly leads to a discussion between professional associations, the Federal Joint Committee (G-BA) and the pharmaceutical industry on what actually constitutes a benefit of drugs.

Patients’ insurance status is also a point of discussion about which not many investigations on endpoint research are found in the literature. Investigations on, for example, waiting times for an appointment or other indicators of medical care organisation were found [44,45] which demonstrate that, for example, private patients in Germany have shorter waits for a medical appointment. Theoretically this could also be a disadvantage for patients in the case of diseases which lead to a worse treatment result in the event of a longer “lead time”. However, the investigations also demonstrated that even in the case of statutory health insurance patients, the waiting time, on an international comparison, is extremely low [45]. In the case of the digitalisation in healthcare as required by the German federal government, it is foreseeable that data on issues relating to healthcare and the factors which influence its quality can be expected soon [46].

The US – The Affordable Care Act

In other countries as well, such as the US, such connections are discussed and researched. The Affordable Care Act in the US, initiated by Barack Obama, had the objective of enabling more people to have access to appropriate medical care and also simultaneously rectifying racial differences [47]. The assumption of costs through Medicaid was to be promptly adapted in the individual states, however not all states in the US actually implemented this. As a result, there was an inconsistent picture: states with a Medicaid adaptation and those without an adjustment. The time period from initial diagnosis until initiation of systemic therapy can be used as a possible measurement for appropriate oncological care. In a data-based, retrospective investigation it was asked whether the non-initiation of Medicaid led to a statistically significant delayed access to oncological care, particularly in the case of black US citizens as compared to white US citizens. Records from 30 386 cancer patients (NSCLC, breast carcinoma, urothelial carcinoma, colorectal carcinoma, renal cell carcinoma, prostate carcinoma, melanoma, stomach and oesophageal carcinoma) from 2011 to 2019 were used for this purpose. Patients who died within 30 days after diagnosis were included and oesophageal carcinoma) from 2011 to 2019 were used for this purpose. Patients who died within 30 days after diagnosis were included and not taken into consideration. It was noted that in states with expanded Medicaid, in comparison to states without an expansion, 6.1% more African-American citizens had access to appropriate medical care and also simultaneously rectifying racial differences [47]. In addition to the political appeal and criticism, these data are above all a plea for the creation of large databases with the objective of knowledge-generating care, independent of the structure of a healthcare system. Greater advancements can be expected here in the near future with the increasing digitalisation of medicine [48 – 52].

Outlook

The approval of alpelisib is expected in the course of this year. Thus, in addition to therapy with atezolizumab (PD-L1 positivity on immune cells required in the tumour) and olaparib (germ line BRCA1/2 mutation required), a third drug will be available which is associated with companion diagnostics. In the case of PI3KCA testing, it will be discussed whether testing from the tumour or blood will be the best for patients and the most effective for the healthcare system; in the case of the anti-PD1/PDL1 therapies, a multitude of antibodies and various tests are available and associated with various drugs and indications. Establishing these companion diagnostics in a quality-assured manner is certainly an interdisciplinary challenge which must be overcome. For the patients and also the therapists, this identification of patient groups is precisely the goal which has been worked towards for many years. It should be considered a great success that this form of therapy has now found its way into the treatment of patients with breast cancer.

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Conflict of Interest

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. F.O. received speaker and consultancy honoraria from Amgen, AstraZeneca, Bayer, BMS, Boehringer-Ingelheim, Chugai, Celgene, Cellex, Eisai, Gilead, Hexal, Ipsen, Janssen-Cilag, Merck, MSD, Novartis, Riemser, Roche, Tesaro, Teva. H.-C.K. received honoraria from Carl Zeiss meditec, Teva, Theracision, Novartis, Amgen, AstraZeneca, Pfizer, Janssen-Cilag, GSK, LIV Pharma, Roche and Genomic Health. P.A.F. received honoraria from Novartis, Pfizer, Roche, Amgen, Celgene, Daiichi Sankyo, AstraZeneca, MSD, Eisai, Puma and Teva. His institution conducts research with funding from Novartis and Biontech. M.W. received speakers honoraria and consultant fees from Novartis, Amgen, Celgene, Roche, Genentech, AstraZeneca, and Pfizer. H.T. received honoraria from Novartis, Roche, Celgene, Teva, Pfizer and travel support from Roche, Celgene and Pfizer. J.E. received honoraria from AstraZeneca, Roche, Celgene, Lilly, Pfizer, Pierre Fabre, Teva and travel support from Celgene, Pfizer, Teva and Pierre Fabre.

M.P.L. has participated on advisory boards for AstraZeneca, MSD, Novartis, Pfizer, Eisai, Genomic Health and Roche and has received honoraria for lectures from MSD, Lilly, Roche, Novartis, Pfizer, Genomic Health, AstraZeneca, medac and Eisai. V.M. received speaker honoraria from Amgen, AstraZeneca, Celgene, Daiichi Sankyo, Eisai, Pfizer, Novartis, Roche, Teva, Janssen-Cilag and consultancy honoraria from Genomic Health, Hexal, Roche, Pierre Fabre, Amgen, Novartis, MSD, Daiichi Sankyo and Eisai, Lilly, Tesaro and Nektar. E.B. received honoraria from Novartis, Hexal, Amgen, and onkowissen.de for consulting, clinical research management or medical education activities. A.S. received honoraria from Roche, Celgene, AstraZeneca, Novartis, Pfizer, Zuck- schwerdt Verlag GmbH, Georg Thieme Verlag, Aurikamed GmbH, MCI Deutschland GmbH, bsh medical communications GmbH and promedicis GmbH. W.J. received honoraria from Roche, Celgene, AstraZeneca, Novartis, Pfizer, Zuck- schwerdt Verlag GmbH, Georg Thieme Verlag, Aurikamed GmbH, MCI Deutschland GmbH, bsh medical communications GmbH and promedicis GmbH. P.A.F. received honoraria from Roche, Celgene, AstraZeneca, Novartis, Pfizer, Zuck- schwerdt Verlag GmbH, Georg Thieme Verlag, Aurikamed GmbH, MCI Deutschland GmbH, bsh medical communications GmbH and promedicis GmbH. W.J. received honoraria from Roche, Celgene, AstraZeneca, Novartis, Pfizer, Zuck- schwerdt Verlag GmbH, Georg Thieme Verlag, Aurikamed GmbH, MCI Deutschland GmbH, bsh medical communications GmbH and promedicis GmbH. W.J.
Novartis and Pfizer. 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. D. L. received honoraria from Amgen, AstraZeneca, Celgene, Lilly, Loral, MSD, Novartis, Pfizer, Tesaro, Teva. 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.

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