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Original Research

Occurrence and characteristics of patients with de novo advanced breast cancer according to patient and tumor characteristics – A retrospective analysis of a real world registry

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Abstract ***Background:*** Patients with de novo metastatic breast cancer (dnMBC) may have different clinical and pathological characteristics. In studies concerned with first-line metastatic patients, the proportion of these patients without secondary resistance mechanisms may have a large influence ont the study results. The aim of this study was to identify patient and tumor characteristics that are associated with dnMBC vs. recurrent MBC (rMBC).
Methods: This is a retrospective analysis of data prospectively collected in the PRAEGNANT metastatic breast cancer registry (NCT02338167). Firs line treated patients were eligible. Patient and tumor characteristics were compared with common disease and tumor characteristics relative to de novo metastatic status, as well as early and late recurrences after primary disease without metastases.
Results: Among the 947 patients identified, 355 were included with de novo metastatic disease (37.5%). Older age and HER2-positive disease were significantly associated with a higher frequency of dnMBC. Patients younger than 50, 50–69, or 70 years or older had dnMBC frequencies of 22.7%, 44.0%, and 57.6%, respectively. HER2-positive patients had dnMBC at initial presentation in 49.1% of cases, in comparison with 21.9%, 35.5%, and 37.6% in patients with triple-negative, luminal A–like and luminal B–like breast cancer, respectively.
Conclusion: Age and breast cancer subtype are associated with the frequency of first-line MBC patients. Inclusion criteria concerning age or breast cancer subtype can influence the frequency of these patients in a selected patient population and can therefore modify the number of patients with secondary resistance to specific therapies in clinical trials.

1. Introduction

Patients with de novo metastatic breast cancer (dnMBC) represent a relevant proportion of the patients included in studies concerned with early-line metastatic breast cancer. In comparison with patients who have primary disease before recurrent metastatic breast cancer (rMBC), it has also been suggested that they may have different clinical and pathological features and prognoses [1–6]. The distinction between dnMBC and rMBC will be referred to here as "dnMBC status."

Most published studies have identified the patient population needed to answer the question of the relative incidence of dnMBC vs. rMBC by looking prospectively at patient cohorts, which are then subdivided into patients with dnMBC and those who later develop rMBC. The frequencies of dnMBC reported in these studies range from 8.8% to 40% [1,3,7]. This approach gives rise to a problem if insights into the populations are desired when patients are being recruited for clinical trials, since the number of patients with rMBC depends mainly on the length of the follow-up period. In addition, the clinical and pathological characteristics of women who develop early recurrences may differ from those in patients with late recurrences. In clinical trials recruiting for first-line HER2-negative, hormone receptor (HR)–

positive breast cancer, the proportion of patients with dnMBC is fairly consistent, with frequencies ranging from 34% to 41% [8–11].

As several studies have indicated that patients with dnMBC have a more favorable outcome in comparison with patients with rMBC [1,2,4,7,12,13], it might be helpful to understand the differences in incidence rates in an MBC cohort that was prospectively recruited into a real-world registry during first-line treatment — i.e., without previous therapy for MBC disease.

The aim of this study was therefore to investigate the prevalence of dnMBC in a prospective cohort of treatment-naïve MBC patients. Patient and tumor characteristics that are associated with dnMBC disease status were also examined.

2. Patients and methods

2.1. The PRAEGNANT research network

The PRAEGNANT study (Prospective Academic Translational Research Network for the Optimization of the Oncological Health Care Quality in the Adjuvant and Advanced/Metastatic Setting; NCT02338167 [14]) is an ongoing, prospective breast cancer registry with a documentation system similar to that used in clinical trials. The aims of PRAEGNANT are to assess treatment patterns and quality of life and to identify patients who may be eligible for clinical trials or specific targeted treatments [14–17]. Patients can be included at any time point during the course of their disease. All of the patients included in the present study provided informed consent, and the study was approved by all ethics committees of participating study sites.

2.2. Patients

Patients were recruited from July 2014 to the time of database closure (September 2020), a total of 3867 patients were registered in the PRAEGNANT registry. Among them, it was possible to clearly allocate 3331 to the breast cancer subtypes triple-negative breast cancer (TNBC), luminal A–like, luminal B–like, and HER2-positive breast cancer. Of these, 513 had to be excluded due to unknown dnMBC status, 1853 because they were not included prospectively during the first therapy line, and 18 patients because the location of the metastatic pattern was not documented (Fig. 1).

2.3. Data collection and determination of dnMBC status

Data were collected by trained staff and documented in an electronic case report form, Baseline patient characteristics were documentes from the patient charts including disease characteristics, treatment history, concomitant medication and co-morbidities. Prospective documentation was done at three months interval including disease assessment, therapiesand quality of life [14]. In that context the metastatsis status at diagnosis was documented, which was required to be the result of the clinical staging including the assessment of liver, lung and bones. Metastasis status at diagnosis was not considered plausible if no metastases at initial diagnosis were documented hovewer a metastasis was documented not later than 3 months after primary diagnosis. Also metastasis status at diagnosis was not considered plausible if de novo status was documented but the first metastasis occurred more than 3 months from that date of initial diagnosis. This time interval was chosen because 3 months is the reassessment timepoint in breast cancer patients after initial diagnosis of early breast cancer or after the initiation of systemic therapy for advanced breast cancer patients. In 75 cases queries concerning these circumstances could not be solved and dnMBC status was considered unknown, leading to an exlusion of those patients (Fig. 1). Data that are not usually documented as part of routine clinical work were collected prospectively using structured questionnaires completed on paper. These consist of epidemiological data such as family history, cancer risk factors, quality of life, nutrition and lifestyle items, and psychological health. Supplementary Table 1 provides an overview of the data collected. The data were monitored using automated plausibility checks and on-site monitoring.

2.4. Definition of hormone receptors, HER2 status, and grading

The definitions of HR status, HER2 status, and grading have been described previously [15]. Briefly, if a biomarker assessment of the metastatic site was available, this receptor status was used for the analysis. If there was no information about metastases, the latest biomarker results from the primary tumor were used. Additionally, all patients who received endocrine therapy in the metastatic setting were assumed to be HR-positive, and all patients who had ever received anti-HER2 therapy were assumed to be HER2-positive. There was no central review of biomarkers. The study protocol recommended assessing estrogen receptor and progesterone receptor status as positive if $\geq$ 1% was stained. Positive HER2 status required an immunohistochemistry score of 3+ or positive fluorescence in situ hybridization/competitive in situ hybridization (FISH/CISH). Both hormone receptor and HER2 assessment were recommended in accordance with ASCO/CAP guidelines {Wolff, 2018 #4162; Allison, 2020 #4161}.

2.5. Statistical analysis

Continuous patient and tumor characteristics were summarized as means and standard deviations, and ordinal and categorical characteristics were summarized as frequencies and percentages.

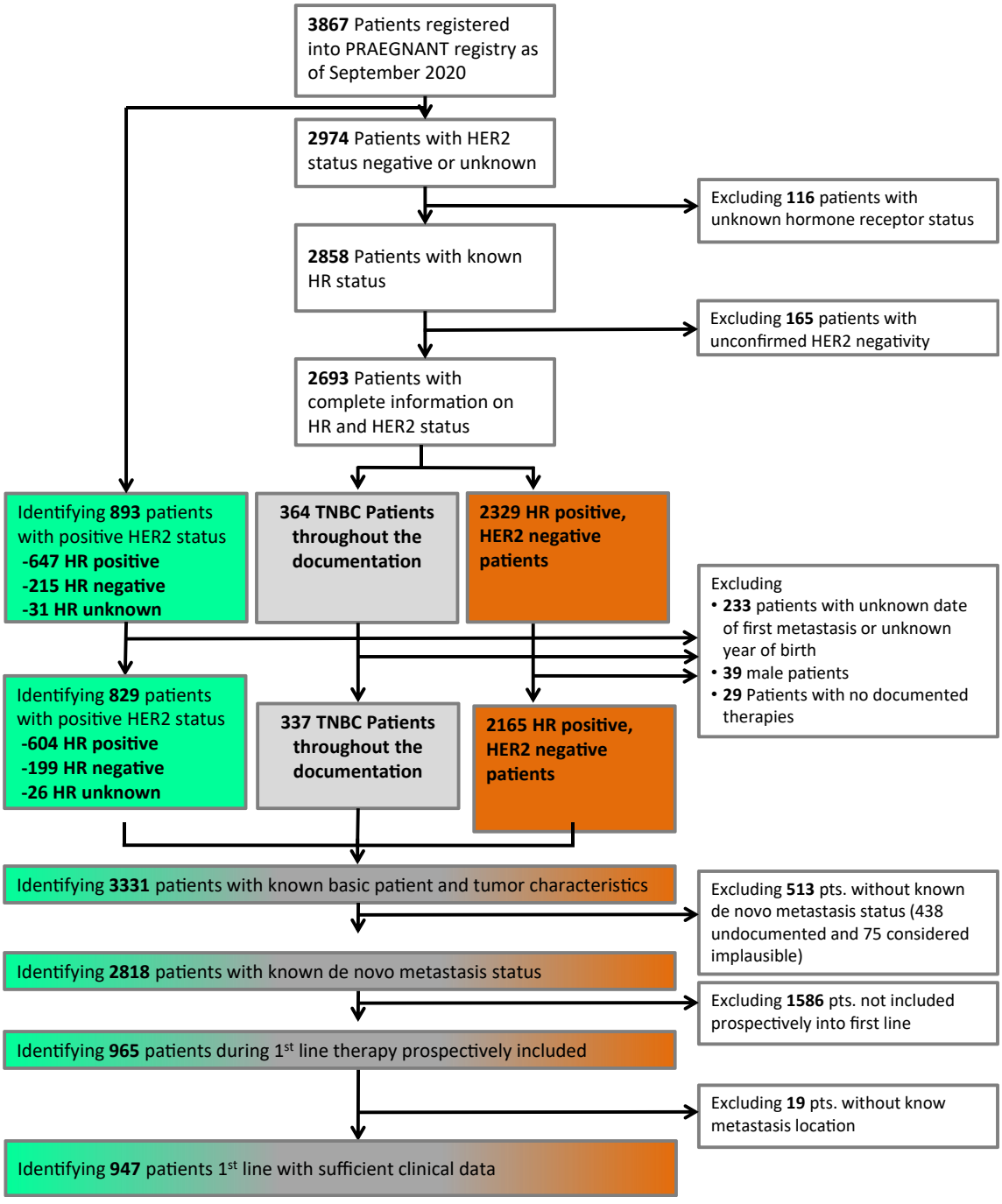

Fig. 1. Patient flow chart.

Associations between patient and tumor characteristics (age, body mass index, breast cancer subtype, metastasis site) and metastasis status at primary breast cancer diagnosis (cM0 versus cM1) were analyzed using multivariate logistic regression. Adjusted odds ratios with 95% confidence intervals and corresponding *P* values from Wald tests are presented.

All of the tests were two-sided, and a P value < 0.05 was regarded as statistically significant. Calculations were carried out using the R system for statistical computing (version 3.6.1; R Development Core Team, Vienna, Austria, 2019).

3. Results

3.1. Patient population

The final patient population consisted of 947 patients with no previous treatment for MBC and with known basic clinical and pathological disease characteristics. Most of

Table 1
Patient and tumor characteristics, showing means and standard deviation (SD) or frequencies and percentages (dnMBC; de novo metastatic breast cancer; rMBC recurrent metastatic breast cancer).

Characteristic	All patients (n = 947)	dnMBC (n = 355)	rMBC (n = 592)	cM0 relative to relapse time point (n = 592)		
				Time to metastasis <5 years (n = 291)	Time to metastasis 5–6 years (n = 30)	Time to metastasis >6 years (n = 271)
Age at diagnosis (years)						
Mean (SD)	53.7 (12.8)	58.0 (12.8)	51.1 (12.1)	50.9 (13.3)	53.5 (13.4)	51.1 (10.5)
<50	365 (100.0)	83 (22.7)	282 (77.3)	152 (41.6)	11 (3.0)	119 (32.6)
50–69	464 (100.0)	204 (44.0)	260 (56.0)	107 (23.1)	15 (3.2)	138 (29.7)
70+	118 (100.0)	68 (57.6)	50 (42.4)	32 (27.1)	4 (3.4)	14 (11.9)
Body mass index (kg/m^2)						
Mean (SD)	26.2 (5.6)	27.0 (6.2)	25.8 (5.1)	25.7 (5.1)	25.0 (4.9)	26.0 (5.2)
<20	78 (100.0)	26 (33.3)	52 (66.7)	29 (37.2)	3 (3.8)	20 (25.6)
20–25	317 (100.0)	107 (33.8)	210 (66.2)	100 (31.5)	11 (3.5)	99 (31.2)
25–30	284 (100.0)	115 (40.5)	169 (59.5)	89 (31.3)	7 (2.5)	73 (25.7)
30+	177 (100.0)	79 (44.6)	98 (55.4)	46 (26.0)	3 (1.7)	49 (27.7)
Grading						
1	49 (100.0)	19 (38.8)	30 (61.2)	10 (20.4)	5 (10.2)	15 (30.6)
2	471 (100.0)	167 (35.5)	304 (64.5)	115 (24.4)	18 (3.8)	171 (36.3)
3	372 (100.0)	139 (37.4)	233 (62.6)	159 (42.7)	5 (1.3)	69 (18.5)
HR status						
Negative	164 (100.0)	50 (30.5)	114 (69.5)	94 (57.3)	3 (1.8)	17 (10.4)
Positive	778 (100.0)	301 (38.7)	477 (61.3)	196 (25.2)	27 (3.5)	254 (32.6)
HER2 status						
Negative	733 (100.0)	250 (34.1)	483 (65.9)	234 (31.9)	27 (3.7)	222 (30.3)
Positive	214 (100.0)	105 (49.1)	109 (50.9)	57 (26.6)	3 (1.4)	49 (22.9)
Breast cancer subtype						
TNBC	114 (100.0)	25 (21.9)	89 (78.1)	75 (65.8)	3 (2.6)	11 (9.6)
Luminal A–like	406 (100.0)	144 (35.5)	262 (64.5)	91 (22.4)	19 (4.7)	152 (37.4)
Luminal B–like	181 (100.0)	68 (37.6)	113 (62.4)	66 (36.5)	4 (2.2)	43 (23.8)
HER2-positive	214 (100.0)	105 (49.1)	109 (50.9)	57 (26.6)	3 (1.4)	49 (22.9)
Metastasis site						
Brain	67 (100.0)	20 (29.9)	47 (70.1)	32 (47.8)	0 (0.0)	15 (22.4)
Other	188 (100.0)	67 (35.6)	121 (64.4)	53 (28.2)	2 (1.1)	66 (35.1)
Visceral	459 (100.0)	175 (38.1)	284 (61.9)	147 (32.0)	19 (4.1)	118 (25.7)
Bone	233 (100.0)	93 (39.9)	140 (60.1)	59 (25.3)	9 (3.9)	72 (30.9)

HR, hormone receptor; SD, standard deviation; TNBC, triple-negative breast cancer.

the patients included were in the 50–69-year-old age group (n = 464, 49.0%); a tumor grading of 3 was present in 41.7% of the patients (n = 372). Biomarker assessment from the metastasis was available from 487 patients concerning HR status and from 442 concerning HER2 status. Most of the patients had a positive HR status (n = 778, 82.6%). There was a distribution pattern of breast cancer subtypes similar to previously published studies, with 12.5% (n = 114) having TNBC, 23.4% (n = 214) having HER2-positive disease, and 64.2% (n = 587) having HER2-negative, HR-positive MBC. All patient characteristics are listed in Table 1.

3.2. Characteristics relative to de novo metastatic breast cancer status

A total of 355 patients (37.5%) presented with dnMBC (Table 1). Relative to the patient and tumor characteristics, the proportion was substantially higher in patients who were over the age of 69 (57.6%, n = 68) and in patients with a positive HER2 status (49.1%, n = 105). All frequencies relative to dnMBC status, along with the patient and tumor characteristics, are shown in Table 1.

To provide an insight into the distribution of the recurrence patterns (<5 years, year 5–6, and later than year 6 after the initial diagnosis), frequencies in the rMBC group are shown in Supplementary Table 2. Most patients with rMBC had the recurrence in the first 5 years after the primary diagnosis (n = 291, 49.2%). Thirty patients (5.1%) were in the sixth year after diagnosis, and 271 patients (45.8%) had more than 6 years since the primary diagnosis. Patients with early recurrences were more often aged 70 or older (64%, n = 32), had a tumor grading of 3 (68.2%, n = 159), TNBC (84.3%, n = 75), or presented with brain metastases (68.1%, n = 32).

3.3. Association of dnMBC status with patient and disease characteristics

In the multivariate logistic regression model, age at diagnosis and breast cancer subtype were associated

with inclusion of patients with dnMBC. In comparison with patients who were under the age of 50, those aged 50–69 had higher odds for cM1, with an odds ratio (OR) of 2.41 (95% CI, 1.72 to 3.37), while patients who were aged 70 or older had an OR of 4.44 (95% CI, 2.75 to 7.17). In relation to breast cancer subtype and TNBC as reference points, patients with HER2-positive disease were more likely to present with dnMBC (OR 2.86; 95% CI, 1.64 to 4.98). It was not possible to show any associations between any of the other characteristics and dnMBC status (Table 2).

4. Discussion

In this analysis of patients who had been prospectively recruited into a real-world MBC registry, the percentage of women presenting with de novo metastatic disease was 37.5%. This frequency was mainly associated with the patient's age and breast cancer subtype. Patients who were older presented with dnMBC more frequently, and patients with HER2-positive MBC also presented with dnMBC more often.

Comparison with studies in which the analysis is based on prospective study cohorts appears to be difficult, since the frequency of dnMBC vs. rMBC depends mainly on the observation period for the patient cohort included [1,3,7]. The frequency of dnMBC varies widely, between 9% and 40%, depending on the patient cohort [1,3,7]. A 30.1% rate of dnMBC was reported in a real-world registry similar to ours (ESME, France) among more than 22,000 patients newly diagnosed with MBC [18]. As in the present study, the frequency was highest in HER2-positive patients (40.4%) [18]. In clinical trials focusing on first-line MBC patients, such as the recent CDK4/6 inhibitor studies, dnMBC frequencies of 34–41% were also reported [8–11]. The percentage in the population included in the present study (HR-positive/HER2-negative) was 38.7%. As the lowest frequency in this study was in patients younger than 50 (22.7%), it is surprising that the Monaleesa-7 study had such a high proportion of dnMBC patients, at 40–41% [9]. It might be suspected that patients who had a de novo disease are over-represented in this trial, possibly because the investigators assessed patients who recurred as ineligible for the trial because of a too unvaforable prognosis. This patients population was at that time frequently been treated with chemotherapy {Lobbezoo, 2016 #2107}{Schneeweiss, 2020 #2963}.

Table 2
Multivariate logistic regression analysis, showing odds ratios (95% confidence intervals) for de novo metastatic breast cancer versus recurrent metastatic breast cancer.

Characteristic	Odds ratio (95% CI)	*P* value
Age at diagnosis (years)		
<50	Reference	–
50–69	2.41 (1.72, 3.37)	<0.000001
70 +	4.44 (2.75, 7.17)	<0.000001
Body mass index (kg/m^2)		
<20	Reference	–
20–25	0.87 (0.50, 1.54)	0.64
25–30	1.09 (0.62, 1.91)	0.77
30+	1.30 (0.72, 2.36)	0.38
Brast cancer subtype		
TNBC	Reference	–
Luminal A–like	1.51 (0.89, 2.57)	0.12
Luminal B–like	1.76 (0.99, 3.14)	0.05
HER2-positive	2.86 (1.64, 4.98)	<0.001
Metastasis site		
Brain	Reference	–
Other	1.60 (0.79, 3.22)	0.19
Visceral	1.52 (0.80, 2.90)	0.20
Bone	1.85 (0.94, 3.67)	0.08

TNBC, triple-negative breast cancer.

Variation in breast cancer subtypes is of particular interest. Patients with HER2-positive disease present more frequently with dnMBC in comparison with patients with rMBC. These patients have all the therapy options available for them like pertuzumab, trastuzumab and T-DM1. Patients with advanced HER2-positive disease have a quite favorable prognosis, with a 4-year overall survival rate of almost 60% after treatment with trastuzumab, pertuzumab, and chemotherapy [19]. Although the percentage of patients with de novo disease in the CLEOPATRA study was not reported, it must be assumed that it was high, on the basis of data from PRAEGNANT and ESME [18]. Since the dnMBC population includes a large number of treatment-naïve patients, it would be important to have subgroup analyses reported in all clinical trials.

Interestingly, the percentage of dnMBC cases was lowest in women under the age of 50 and highest in those who were 70 or older. The age group receiving mammography screening (50–69) had a frequency that was almost twice as high as in patients under the age of 50 (44.0% vs. 22.7%). One aim of mammography screening programs is to reduce the numbers of patients with advanced breast cancer, such as dnMBC, at the time of diagnosis. However, the high percentage in this patient population, at 44%, does not appear to support the conclusion that screening programs have a major effect on the number. As the present analysis is cross-sectional, it is not possible to make any statements about the percentage over time, therefore an explanation of this effect can only be speculative. Mammography screening in Germany was introduced in 2007. Therefore all patients in the PRAEGNANT registry who were included as first-line patients must have had their breast cancer diagnoses after the introduction of the mammography screening program. An analysis of localized vs. regional vs. metastatic disease over time in the United States did not in fact show a decrease in the age-adjusted rate of diagnoses of MBC over the years [20]. It was suspected that tumors that rapidly progress to stage IV disease have a more aggressive tumor biology, so that this population might be overrepresented in patients with

dnMBC. In the present study, there did not appear to be any association with tumor grading, but only with HER2-positive disease, which — if left untreated — certainly represents the prognostically most unfavorable group. Focusing on patients who have a higher risk of developing HER2-positive disease might perhaps effectively reduce the incidence of dnMBC in HER2-positive patients. There is some work on risk factors for HER2 positive breast cancer, however data is scarce and should be given more attention. All of these considerations concerning a fast progression should be the aim of future studies.

This study has several limitations and strengths. Using data from a real world registry made it necessary to exclude almost 1100 patients, because no breast cancer subtype or de novo metastasis status was available. This could lead to a possible selection bias. Additionally, although the analysis was retrospective, the patients included in the analysis were eligible only if they were included in the first-line setting within the first 90 days after the start of first-line treatment. Selection bias with regard to therapy line should therefore be minimized. With 947 patients, the analysis was also comparable to other studies in this setting and larger than most prospective randomized trials; however, the sample size might still be too small for investigation of additional subgroups that might be interesting — such as breast cancer subtypes relative to age groups. These are analyses that might be of interest in the future.

5. Conclusions

In conclusion, this study reports frequencies of dnMBC that are similar to those described in other real-world registries and also to those in clinical trials. It is important to understand which patient groups have a high frequency of dnMBC in order to avoid selection bias when designing clinical trials. This is particularly important because the dnMBC population includes a high proportion of patients without (secondary) resistance to the drug being investigated. This provides the frequencies for the most common patient subgroups, potentially avoiding the selection of a population in which treatment-resistant or treatment-sensitive patients are overrepresented or underrepresented.

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Conflict of interest statement

V.M. has received speaker honoraria from Amgen, Astra Zeneca, Daiichi-Sankyo, Eisai, Pfizer, MSD, Novartis, Roche, Teva, Seattle Genetics and consultancy honoraria from Genomic Health, Hexal, Roche, Pierre Fabre, Amgen, ClinSol, Novartis, MSD, Daiichi-Sankyo, Eisai, Lilly, Tesaro and Nektar. A.D.H. has received honoraria from Teva, GenomicHealth, Lilly, AstraZeneca, Novartis, Pfizer, Pierre Fabre, SeaGen and Roche. P.A.F. received honoraria from Novartis, Pfizer, Roche, Amgen, Celgene, Daiichi-Sankyo, AstraZeneca, Merck-Sharp & Dohme, Eisai, Puma and Teva; his institution conducts research with funding from Novartis and Biontech. H.-C.K. has received honoraria from Carl Zeiss meditec, Theraclion, Novartis, Amgen, AstraZeneca, Pfizer, GSK, SurgVision, Onkowissen and Genomic Health/Exact Sciences, travel support from Tesaro and Daiichi Sankyo and holds stock of Theraclion and Phaon scientific. H.T. has received honoraria from Novartis, Roche, Celgene, TEVA, and Pfizer, and travel support from Roche, Celgene, and Pfizer. J.E. has received consulting fees from AstraZeneca, Daiichi Sankyo, Pfizer, Novartis, Lilly, Pierre Fabre, Roche, Tesaro; contracted research from Daiichi Sankyo, Pfizer, Lilly, Novartis, Seattle Genetics, AstraZeneca, Roche, and Odonate; and travel support from Astra Zeneca, Daiichi Sankyo, Celgene, Pfizer, Novartis, Lilly, and Tesaro. D.L. has received honoraria from Novartis, Pfizer, Amgen, Eli Lilly, Teva, Loreal, GSK, MSD, Roche, Astra Zeneca. M.W. received grants from Astra Zeneca, grants from Celgene, grants from Roche, grants from MSD and grants from Novartis during the conduct of the study. E.B. has received honoraria from Novartis, Pfizer, Amgen, Daiichi-Sankyo, and onkowissen.de. P.W. has received honoraria for scientific talks or grants from Amgen, Novartis, MSD, Pfizer, PharmaMar, Teva, Eisai, Clovis and Tesaro. C.H. has received honoraria from Roche Pharma, Pfizer, Astra Zeneca, Novartis, and Onkovis. C.M.K. received honoraria from Amgen, Astra Zeneca, Eli Lilly, MSD Sharp & Dohme, Novartis, Pfizer, Onkotrakt, PharmaMar, Riemser, Roche, Tesaro, Hilotherm, NewCo, research grants from Astra Zeneca, BMS, Immunomedics, MSD Sharp&Dohme (Merck), NewCo, Novartis, Pfizer, PharmaMar, Reimser, Roche, Seattle Genetics and travel support from Amgen, Astra Zeneca, Hexal, Immunomedics, PharmaMar, Pfizer, Tesaro, TEVA Oncology. R.W. has received honoraria from Amgen, Astra Zeneca, Celgene, Daiichi-Sankyo, Esai, Exact Science, Nanostring, GSK, Hexal, Lilly, MSD, Mundipharma, Novartis, Odonate, Pfizer, Pierre Fabre, Riemser, Roche, Sandoz, Seattle Genetics, Tesaro Bio, Teva, and Viatris. M.U. has received honoraria from Abbvie, Amgen, Astra Zeneca, BMS, Celgene, Daiichi-Sankyo, Eisai, Lilly Deutschland, Lilly Int., MSD Merck, Mundipharma, Myriad Genetics, Odonate, Pfizer, PUMA Biotechnology, Roche Pharma, Sanofi Aventis Deutschland, TEVA Pharmaceuticals Ind Ltd, Novartis, Pierre Fabre, Clovis Oncology, and Seattle Genetics. W.J. has received honoraria and research grants from Sanofi-Aventis, Novartis, Lilly, Pfizer, Roche, Chugai, Astra Zeneca, MSD, and Daiichi-Sankyo. F.A.T. has received honoraria from Hexal, Novartis, Tesaro and travel expenses from GSK. M.P.L. has received honoraria from Lilly, Pfizer, Roche, MSD, Hexal, Novartis, AstraZeneca, Eisai, Exact Sciences, Pierre-Fabre, PharmaMar and medac for advisory boards, lectures, and travel support. S.Y.B. has received honoraria from Roche Pharma, Novartis, Pfizer, MSD, Teva, Astra Zeneca. T.N.F. has received honoraria from Novartis, Roche, Pfizer, TEVA, Diachii Sankyo, Astra Zeneca and MSD. All remaining others (A.H., P.H., L.H., M.W.B, S.U., J.M., L.A.W., D.W., L.L.M.) have declared that they do not have any conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.ejca.2022.05.015

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