Using Probability for Pathological Complete Response (pCR) as a Decision Support Marker for Neoadjuvant Chemotherapy in HER2 Negative Breast Cancer Patients – a Survey Among Physicians

Wahrscheinlichkeit der pathologischen Komplettremission als Entscheidungshilfe für die neoadjuvante Chemotherapie bei HER2-negativen Patientinnen mit Mammakarzinom – eine Umfrage unter Ärzten

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ABSTRACT

Background In women with early breast cancer, a pathological complete response (pCR) after neoadjuvant chemotherapy is reported to be associated with an improvement of the survival. The aim of this survey among physicians was to investigate whether the probability of achieving pCR in patients with a hormone receptor-positive, HER2-negative disease encourages physicians to recommend neoadjuvant chemotherapy.

Methods The study was conducted via an online survey that was sent to 493 physicians, who were either known as members of national guideline committees, heads of breast cancer centers, being high recruiters in clinical trials or leading a private practice. Participants were asked about a specific case that should resemble patients for whom it is unclear, whether they should be treated with chemotherapy.

Results 113 (24.5%) physicians participated at the survey, out of which 96.5% had a work experience of more than 10 years and 94.7% were board certified in their specialty. A total of 84.1% would consider pCR for a decision concerning neoadjuvant chemotherapy. With regard to the pCR probability, 2.7 and 10.6% of the participants demanded at least a pCR rate of 5 and 10%, respectively, while 25.7% were satisfied with 20% probability, and another 25.7% with a pCR rate of 30%.

Conclusions The vast majority of the long-term experienced physicians would embrace the implementation of a further method such as the prediction of pCR probability in clinical routine to support decision making regarding the necessity of neoadjuvant chemotherapy. The cut-off of around 30% pCR probability seems to be a realizable rate to distinguish patient groups.

ZUSAMMENFASSUNG

Hintergrund Die pathologische Komplettremission (pCR) nach neoadjuvanter Chemotherapie bei Frauen mit Brustkrebs im Frühstadium weist auf eine verbesserte Überlebenswahrscheinlichkeit hin. Ziel dieser Umfrage unter Ärzten war es, zu untersuchen, ob die Wahrscheinlichkeit, dass eine Komplettremission bei Patientinnen mit hormonrezeptorpositivem/HER2-negativem Brustkrebs erreicht wird, Ärzte ermutigen würde, eine neoadjuvante Chemotherapie zu empfehlen.

Methoden Die Studie beruht auf eine Online-Umfrage, die an 493 Ärzte und Ärztinnen geschickt wurde. Alle angeschriebenen Ärzte und Ärztinnen waren entweder Mitglieder nationaler Richtlinien-Kommissionen bzw. Leiter von Brustkrebszentren, hatten bereits viele Patientinnen in klinische Studien rekrutiert oder waren niedergelassene Ärzte bzw. Ärztinnen. Die Teilnehmer wurden nach ihrer Einschätzung eines spezifischen Falles gefragt, wobei der Fall so dargestellt wurde, dass er Ähnlichkeit mit Patientinnen hatte, bei denen die Indikationsstellung für oder gegen Chemotherapie unklar ist.

Ergebnisse Insgesamt nahmen 113 (24,5%) der angeschriebenen Ärzte an der Umfrage teil. Davon hatten 96,5% mehr als 10 Jahre Berufserfahrung, und 94,7% waren Fachärzte. Von den Studienteilnehmern gaben 84,1% an, dass sie die pathologische Komplettremission bei der Entscheidungsfindung für oder gegen neoadjuvante Chemotherapie heranziehen würden. Was die Wahrscheinlichkeit eines pCR betrifft, gaben 2,7 bzw. 10,6% der Teilnehmer an, dass sie eine pCR-Rate von mindestens 5 bzw. 10% erwarteten, wohingegen 25,7% mit einer 20%iger Wahrscheinlichkeit und weitere 25,7% mit einer pCR-Rate von 30% zufrieden wären.

Schlussfolgerungen Die überwiegende Mehrzahl der Ärzte mit langjähriger Erfahrung würden die Einführung einer weiteren Methode als Unterstützungshilfe bei der Entscheidungsfindung, beispielsweise die Voraussage der pCR-Wahrscheinlichkeit, in der klinischen Praxis begrüßen. Ein Schwellenwert von rund 30% für die Wahrscheinlichkeit eines pCR scheint ein geeigneter Wert zu sein, um eine Unterscheidung zwischen verschiedenen Patientinnengruppen vorzunehmen.

Introduction

In women with early breast cancer (BC), a pathological complete response (pCR) after neoadjuvant chemotherapy is reported to be associated with improvements in the disease-free survival (DFS) and overall survival (OS) [1, 2]. This is the main reason why pCR is currently being discussed as a surrogate marker for the effectiveness of chemotherapy [3 – 5]. However, therapy response and outcomes for patients differ depending on the tumor biology. HER2-positive and triple-negative BC patients not only achieve pCR more frequently than those with luminal disease, but also have the strongest association with a better prognosis when no residual cancer is found at surgery [1, 2, 6]. This in turn means that in women with hormone receptor-positive, HER2-negative disease, identifying those patients who are more likely to benefit from chemotherapy is an unresolved issue.

In order to make a decision for or against chemotherapy in this patient population, a mixture of prognostic and predictive factors has usually been taken into consideration, with the likelihood of a treatment response being weighed up against the prognosis for the individual patient. Tumor size, lymph-node status, tumor grade, estrogen receptor (ER) status, progesterone receptor (PR) status, and in some institutions Ki-67 and uPA/PAI-1 status are the main factors in clinical routine work that are used to assess the need for chemotherapy [7 – 10]. Multigene assays are also being incorporated into clinical routine work to estimate the patients' prognosis and spare patients who have an excellent prognosis the need to undergo chemotherapy [11 – 13]. This approach was recently confirmed by the TailorX study [14]. Patients were eligible for randomization within the trial (chemotherapy and endocrine treatment vs. endocrine treatment alone) if they had a hormone receptor-positive and HER2-negative breast cancer and an

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intermediate recurrence risk as assessed by a 21-multigene assay (for this study defined as 11–25). The tumors also had to be node-negative. The study showed that endocrine therapy alone is as effective as chemotherapy and endocrine treatment. For women under the age of 50, however, a potential additional benefit from chemotherapy could not be excluded [14].

However, it is still not clear from this trial which individual patients will benefit from chemotherapy. In addition, patients who had a recurrence score over 25 did not undergo randomization in the TailorX study but were assigned to receive endocrine therapy and chemotherapy. This group of patients had the poorest prognosis in the study [14], and it is unclear whether this group benefits from chemotherapy at all.

A new biomarker indicating the probability of pCR in patients with hormone receptor-positive HER2-negative breast cancer could potentially be helpful in identifying a patient population in which the patients and physicians would feel comfortable with an indication for neoadjuvant chemotherapy. The aims of the present survey carried out among physicians were therefore to investigate whether the probability of achieving pCR in hormone receptor-positive, HER2-negative BC patients may encourage physicians to recommend neoadjuvant chemotherapy; and to establish a cut-off level for a pCR rate that most physicians would consider high enough to serve as an indication for the treatment.

Methods

Data acquisition

An anonymized online survey was conducted using SurveyMonkey (San Mateo, California, USA) in German. The study was conducted in Germany in May 2018 and included physicians who were known as members of national guideline committees, heads of breast cancer centers, frequent recruiters in clinical trials, or running private practices. The e-mail addresses for the survey were obtained by Internet research or were known from the authors' personal communications.

The link to the survey was sent to a total of 493 medical professionals by e-mail and was open for 8 days (May 17 to May 24, 2018). The recipients were reminded to participate in the survey three times (on May 18, 23, and 24, 2018). The data were completely anonymized before the analysis and no personal data were permanently stored.

The survey comprised 13 questions and one comment field. Seven items captured the participants' characteristics (▶ Table 1) and six items collected data about which tumor and patient characteristics might guide the physician with regard to making a decision for or against chemotherapy. This was done by asking about a specific case intended to resemble a patient for whom it is unclear whether she should be treated with chemotherapy: a 60-year-old patient (with no further comorbidities) with an invasive ductal carcinoma 2.5 cm in diameter, G2, one positive lymph node, estrogen receptor-positive, progesterone receptor-positive, HER2-negative (▶ Table 2).

▶ Table 1 Characteristics of participants.

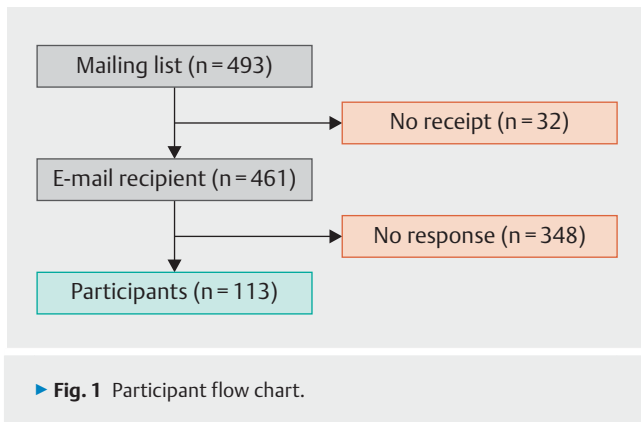| Question	n	Mean (SD) or %
How old are you (in years)?	113	50.5 (8.04)
Are you a decision-maker on the oncologic treatment of breast cancer patients?		
▪ Yes	107	94.7
▪ No	6	5.3
▪ Total	113	100.0
Where do you work?		
▪ Hospital	82	72.6
▪ Practice	27	23.9
▪ Other	4	3.5
▪ Total	113	100.0
Are you a member of a guideline group (S3, AGO, ABC, NCCN, etc.)?		
▪ Yes	40	35.4
▪ No	73	64.6
▪ Total	113	100.0
What is your specialist discipline?		
▪ Gynecology	95	84.1
▪ Oncology	16	14.2
▪ Not working as a physician	1	0.9
▪ Other	1	0.9
▪ Total	113	100.0
Are you a medical specialist?		
▪ Yes	107	94.7
▪ No	6	5.3
▪ Total	113	100.0
How many years of work experience do you have?		
▪ Less than 10 years	4	3.5
▪ Between 10 and 20 years	35	31.0
▪ More than 20 years	74	65.5
▪ Total	113	100.0

Statistical methods

The responses were evaluated descriptively by using means and standard deviation or percentage and number of participants. Analyses were performed with IBM SPSS Statistics for Windows, Version 21.0 (IBM Corporation, Armonk, New York, USA).

Results

Participants

E-mail delivery failed in a total of 32 cases (6.5%), so that the final group consisted of 461 recipients, of whom 113 (24.5%) responded to the survey (▶ Fig. 1).

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▶ **Fig. 1** Participant flow chart.

The participants had an average age of 50.5 years (standard deviation 8.0) and had work experience of more than 10 years in 96.5% of cases. Their workplaces were a hospital setting in 72.6% of cases (n = 82) and in a practice setting in 23.9% (n = 27). Most participants were gynecologists (84.1%; n = 95) and 14.2% (n = 16) were oncologists. A total of 107 participants (94.7%) stated that they were board-certified in their specialty and the same number confirmed that they were responsible for making treatment decisions at their institution. Finally, 40 participants (35.4%) were members of a national or international guideline committee. The participants' characteristics are summarized in ▶ **Table 1**.

Chemotherapy decision criteria

For the case described in the Methods section for each of the parameters ER, PR, and Ki-67, it was asked whether the magnitude of the expression in percentage assessed by immunohistochemistry (0–100%) had an influence on decision-making for or against neoadjuvant chemotherapy. The respondents stated that the magnitude of ER and PR expression would influence that decision in the specific case in 57.5% (n = 65) and 46.0% (n = 52) of cases, respectively. Ki-67 expression would have an influence on chemotherapy decision-making for 102 (90.3%) of the participants (▶ **Table 2** and **Fig. 2**).

In relation to the probability of pCR, a total of 95 participants (84.1%) stated that they would take this measure into account in decision-making concerning neoadjuvant chemotherapy. With regard to the probability of pCR, 2.7% (n = 3) and 10.6% (n = 12) of the participants would require pCR rates of at least 5 and 10%, respectively, while 25.7% (n = 29) would be satisfied with a probability of 20% and a further 25.7% (n = 29) would be satisfied with a pCR rate of 30%. Thus, 64.7% would be satisfied with a pCR rate of 30% (▶ **Table 2** and **Fig. 2**).

In total, 24.8% of respondents were able to imagine that information about the probability of pCR would be capable of influencing chemotherapy decision-making when combined with a multigene assay. In contrast, in the opinion of 47.8% this might be the case even independently of a multigene assay (▶ **Table 2** and **Fig. 2**).

▶ **Table 2** Survey results on decision-making criteria for chemotherapy.

Question	n	%
In a 60-year-old patient (with no further comorbidities) with an invasive ductal carcinoma 2.5 cm in diameter, G2, one positive lymph node, ER-positive, PR-positive, HER2-negative:		
Does your decision regarding chemotherapy depend on the expression of ER (in %)?		
▪ No	48	42.5
▪ Yes	65	57.5
▪ Total	113	100.0
Does your decision regarding chemotherapy depend on the expression of PR (in %)?		
▪ No	61	54.0
▪ Yes	52	46.0
▪ Total	113	100.0
Does your decision regarding chemotherapy depend on the expression of Ki-67 (in %)?		
▪ No	11	9.7
▪ Yes	102	90.3
▪ Total	113	100.0
If you knew how high the probability of achieving a pCR through neoadjuvant chemotherapy is, would you use this information to make a decision for or against neoadjuvant chemotherapy?		
▪ No	18	15.9
▪ Yes	95	84.1
▪ Total	113	100.0
How high should the probability of achieving pCR be in order to perform neoadjuvant chemotherapy (e.g., four cycles of epirubicin/cyclophosphamide followed by 12 cycles of paclitaxel)?		
▪ At least 5%	3	2.7
▪ At least 10%	12	10.6
▪ At least 20%	29	25.7
▪ At least 30%	29	25.7
▪ At least 40%	21	18.6
▪ At least 50%	19	16.8
▪ Total	113	100.0
Can you imagine that information about the probability of pCR could influence treatment decision-making, as with a multigene assay?		
▪ No	4	3.5
▪ Yes, in combination with a multigene assay	28	24.8
▪ Yes, even independently of a multigene assay	54	47.8
▪ Possibly, not yet certain	27	23.9
▪ Total	113	100.0

ER: estrogen receptor; pCR: pathological complete response; PR: progesterone receptor

**a** Does your decision regarding chemotherapy depend on the expression of ER/PR/Ki-67 (in %)?
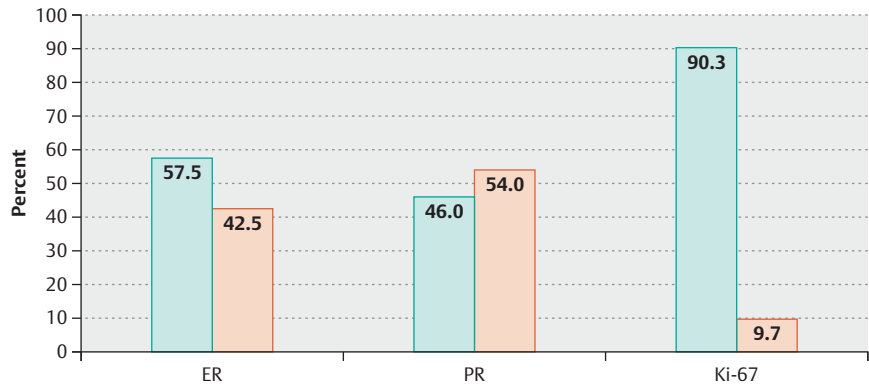
b If you knew how high the probability of achieving pCR under neoadjuvant chemotherapy is, would you use this information to make a decision for or against neoadjuvant chemotherapy?
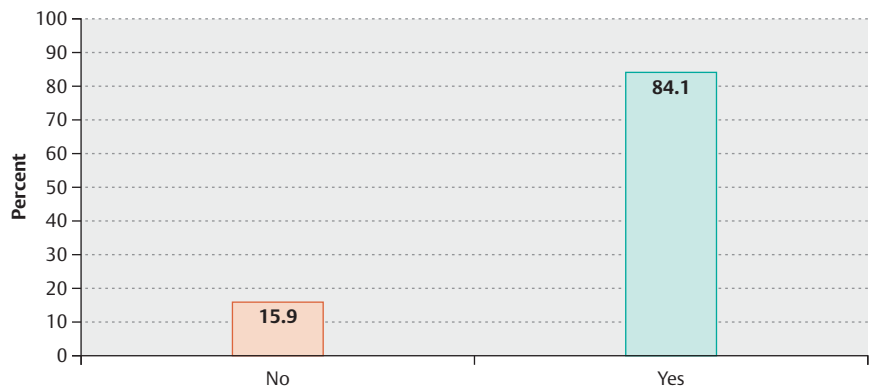
c How high should the probability of achieving pCR be to perform neoadjuvant chemotherapy (e.g. 4 cycles of epirubicin/cyclophosphamide, followed by 12 cycles of paclitaxel)?
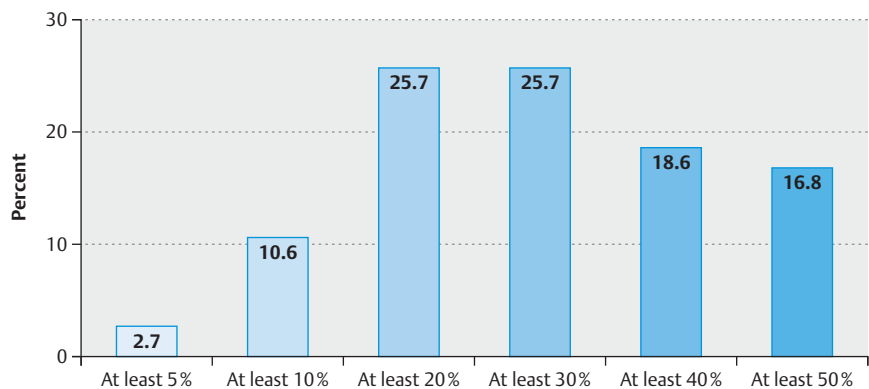
d Can you imagine that the knowledge about pCR probability may influence therapy decision making like a multigene assay?
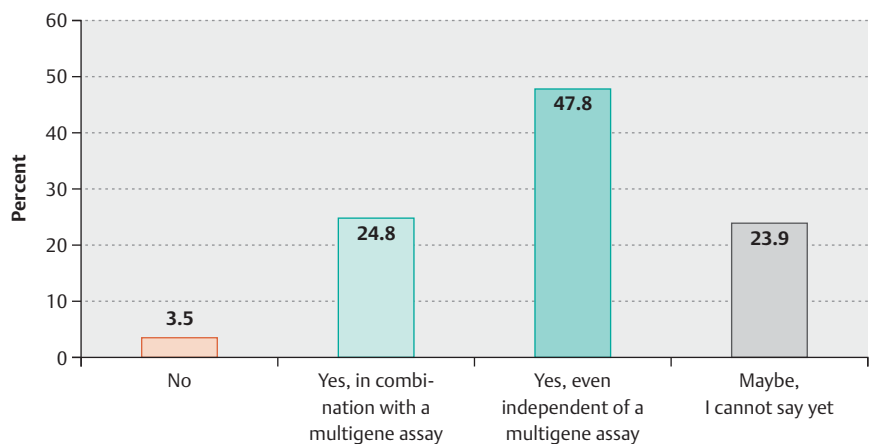
▶ **Fig. 2** Survey results on chemotherapy decision criteria.

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Discussion

The online survey conducted shows that the majority of physicians are able to imagine using the probability of pCR as a marker in decision-making for or against chemotherapy. It also shows that approximately two thirds of the participating physicians would be satisfied with a pCR probability of 30% or lower, meaning that the physicians would accept treating seven out of 10 patients with chemotherapy without achieving a pCR.

The survey inquired about a patient with hormone receptor-positive, HER2-negative BC – a group of patients in whom the correlation between pCR and prognosis is not as well established as in triple-negative or HER2-positive BC patients [1, 2]. There are also only limited data regarding the extent to which the quantitative expression of ER, PR, and Ki-67 influences pCR rates. ER, PR, and Ki-67 are usually assessed with immunohistochemistry, and expression is reported in a quantitative fashion; however, when it comes to correlation with pCR, these markers are used as dichotomous variables (positive/negative). Hormone receptor-positive patients are reported to have fairly low pCR rates, while hormone receptor-negative patients have fairly high pCR rates [1, 2, 6, 15 – 17]. In addition – specifically in luminal-like tumors – there are several reports that have correlated increasing Ki-67 expression with increasing pCR rates [6, 18, 19].

In clinical practice, cut-off levels are used to categorize breast cancer patients into positive versus negative. ER and PR were initially categorized to distinguish between women who benefit from endocrine therapy from those who do not, and the levels have varied from 10% through 1–10% to ≥1% over the years [20 – 22]. These cut-off levels were therefore also used to learn about the correlation with chemotherapy responsiveness [23].

The present survey shows that most physicians would be satisfied with a 30% rate of pCR. To meet that criterion, it is not known which cut-off levels for ER, PR, and Ki-67 should be used. Including these markers additionally to conventional patient and tumor characteristics might be helpful for exploring this topic further.

Other studies have also examined decision-making parameters for neoadjuvant chemotherapy in hormone receptor-positive patients. A large prospective noninterventional study in postmenopausal women showed that age, body mass index, tumor grade, HER2 status, and the fact that patients were taking concomitant medication were influencing factors in relation to decision-making for or against neoadjuvant chemotherapy [24]. Information about the patient's pCR status could further add to this list of influencing factors.

Independently of the prediction of pCR, the question remains of how to estimate the effect of chemotherapy and/or pCR on the prognosis. While an association between pCR and prognosis has been well described, some studies have shown that there may be subgroups of patients who do not benefit as much from chemotherapy as others, even among those with triple-negative findings [1, 25]. Two studies have described such an effect for *BRCA* mutation carriers [26, 27]. However, it must be noted that other studies have not observed this effect [28, 29]. On the other hand, there is evidence from the GeparSepto study that a benefit of chemotherapy vs. another treatment may be conferred even in a subgroup in which the chemotherapy comparison does not show a difference in pCR rates [30]. Additionally it is even hypothesized that in some subgroups such as lobular breast cancer chemotherapy might be even harmful [31]. There are several predictive methods that assess the prognosis either using clinical variables or multigene assays, or both together [14, 32 – 36]. However, these predictors have not included pCR or the effects of neoadjuvant chemotherapy in the models.

One strength of the present survey is not only that approximately 25% of the recipients participated in the survey, but also that some 95% of them were board-certified. The results thus represent the views of physicians with substantial experience. A large number of guideline committee members also appear to have taken part in the survey. The study is of course only a survey among physicians and does not reflect the actual behavior of physicians using the probability of pCR as a decision-making criterion. However, such a marker is not available at the moment, so that considerations at present can be only hypothetical. It should be noted that physicians were only asked about their opinion of which pCR rate they would require for a decision in favor of neoadjuvant therapy, and no patients were included in the survey. However, it is known that the size of the treatment effect required may differ widely between physicians and patients when they are asked about a case and about possible treatment effects [37, 38].

Conclusion

This survey shows that 84% of physicians with long-term experience would welcome the possibility of using the probability of pCR in decision-making concerning neoadjuvant chemotherapy in a patient with hormone receptor-positive, HER2-negative breast cancer. The majority of the respondents appeared to be satisfied with a cut-off level of a pCR probability around 30%. However, further research will be needed in order to establish this type of pCR probability marker and the way in which it could be used in clinical practice.

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Conflict of Interest

P. G. has received honoraria from Novartis, financial support for symposia from Novartis, Roche, and PharmaMar, and compensation for travel expenses from discovering hands®. V. M. has received speaker honoraria from Amgen, AstraZeneca, Celgene, Daiichi Sankyo, Eisai, Pfizer, Pierre-Fabre, Novartis, Roche, Teva, and Janssen-Cilag and consultancy honoraria from Genomic Health, Roche, Pierre Fabre, Amgen, Daiichi Sankyo, and Eisai. V. Mö. has received honoraria from Amgen, Celgene, Roche and participation in advisory boards (Celgene und Myelotherapeutics). C. T. compensated honoraria for presentations and participation in advisory boards (Amgen, Astra-Zeneca, Celgene, Daiichi Sankyo, Genomic-Health, Lilly, Mundipharma, Nanostring, Novartis, Pfizer, Puma, Roche). R. E. has received speaker honoraria from Roche and Eisai. M. P. L. has participated on advisory boards for AstraZeneca, MSD, Novartis, Pfizer, Genomic Health, and Roche and has received honoraria for lectures from Lilly, Roche, Novartis, Pfizer, Genomic Health, Astra-

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