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The EORTC 10041/BIG 03-04 MINDACT trial is feasible: Results of the pilot phase ☆

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ABSTRACT

Background: The MINDACT (Microarray In Node-negative and 1–3 node positive Disease may Avoid ChemoTherapy) trial investigates the clinical utility of the 70-gene profile (MammaPrint) for the selection of breast cancer patients for adjuvant chemotherapy (CT) together with standard clinicopathological criteria. We present the results of the pilot phase consisting of first 800 patients included.

Methods: MINDACT has enrolled 6600 patients, classified into high or low risk by MammaPrint and clinicopathological risk through Adjuvant! Online. Patients with both clinical (C) and genomic (G) high risks are offered adjuvant CT; those with both C and G low risks do not receive CT; patients with discordant risk are randomised for the decision of adjuvant CT based on C or G risk. CT randomisation of anthracycline-based versus docetaxel/capecitabine and endocrine therapy randomisation between letrozole and tamoxifen → letrozole are offered.

Results: During the pilot phase 46% of screened patients were enrolled. Main reasons for non-enrolment were node positivity before trial amendment, sample quality problems and failure to meet logistic settings. Among the 800 patients, 386 (48%) were C-low/G-low, 198 (24.8%) as C-high/G-high, 75 (9.4%) as C-low/G-high and 141 (17.6%) as C-high/G-

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low. In total 216 (27%) cases were discordant. The difference between patients with G-high (42%) and G-high risk (34%) is 8.25% (95% confidence interval (CI), 4.7–11.8%; $P < .0001$). Compliance with the treatment decision was high (>92%).

Conclusions: The logistically complex MINDACT trial is feasible in a multinational setting. The proportion of discordant patients, the potential reduction in CT by using the genomic signature and compliance to treatment assignment are in accordance with the trial hypotheses.

1. Introduction

Breast cancer (BC) is the most common malignant disease in women and one of the top causes of cancer induced death, being a public health problem on a global scale.[1,2] In the past 35 years advances in early detection, chemoprevention, improved surgery and more effective adjuvant treatment have led to a decreased mortality from BC especially in Western Europe and United States of America (USA).[3–6] In addition, the effectiveness of screening strategies has resulted in the detection of smaller, earlier-stage and 'low risk phenotype' tumours which could be more responsive to available treatments.[7,8] Although many of these women can expect long-term survival, about one quarter will relapse and die from their disease.[9]

Treatment recommendations to date are based on a balance between the risk of tumour recurrence, taking into consideration the classical prognostic factors (e.g. tumour size, lymph node status, tumour grade, expression of hormonal and HER2 receptors), potential side-effects of adjuvant therapy and comorbidities.[10]

There is still much controversy regarding the optimal definition of patients with low/minimal versus moderate/high risk of relapse, and considerable differences exist worldwide in the selection of women who are offered adjuvant chemotherapy (CT).[11]

To date, oncologists rely on different guidelines issued by experts such as the National Comprehensive Cancer Network (NCCN) practise recommendations and the St. Gallen consensus panel or use quantitative tools that estimate prognosis such as the Nottingham Prognostic Index and Adjuvant! Online for treatment decision.[12–15]

In recent years, whole-genome analyses using microarrays have shed light on the biology of BC and led to the identification of five molecular subtypes associated with different outcomes and response to treatment.[16,17] These signatures seem to be more accurate in identifying patients with poor prognosis who possibly benefit most from adjuvant CT and, conversely, those with a good prognosis or low risk of recurrence who may be safely spared from this treatment.[18–22]

However, available data come from retrospective studies and the clinical implementation of this technology has been limited due to a paucity of well-designed, prospective assessments of the clinical value of these new biomarkers.

Using gene-expression profiling, the Netherlands Cancer Institute (NKI) and its spinoff company Agendia™ developed a 70-gene prognostic signature for node-negative BC (MammaPrint™). The signature was developed as a dichotomous risk classification for the end-point of distant metastasis within 5 years and clearly separated a group with an excellent prognosis at 10 years from a group with a high risk of recurrence before 5 years.[18] Furthermore, when compared with the current commonly used risk classifications (i.e. the St. Gallen guidelines and the NIH consensus), MammaPrint™ not only predicted those women who would have needed adjuvant CT (as demonstrated by the onset of distant metastases within 5 years), but also women who could have been spared this therapy, as seen from their excellent long-term outcome. The authors concluded that MammaPrint™ is of great prognostic importance, and could outperform the current risk classifications and therefore potentially spare some women from overtreatment.[23] Furthermore, it is likely that MammaPrint™ is also predictive for the effect of CT in general.[24,25]

The TRANSBIG research network undertook an independent validation of the MammaPrint™ signature in 307 women with lymph node-negative BC and a median follow-up of 13.6 years. MammaPrint™ remained an independent significant prognostic factor, stronger than clinicopathological risk factors (i.e. St. Gallen criteria, the Nottingham Prognostic Index and Adjuvant! Online) for time to distant metastasis-free (DMFS) and overall survival (OS).[26] A subsequent study in 241 patients with 1–3 node positive BC showed that this tool is also a powerful prognostic marker in node positive disease where good prognostic signature patients achieve 91% DMFS and 96% breast cancer specific survival (BCSS) at 10 years.[21]

These validation studies formed the rationale for the launch of the EORTC 10041/BIG 03-04 MINDACT (Microarray In Node-negative and 1–3 node positive Disease may Avoid ChemoTherapy) which is the first prospective trial to evaluate the clinical utility of a molecular-based signature for the adjuvant treatment of early BC.[27]

MINDACT is an international prospective, randomised, phase III trial using the MammaPrint™ classifier together with commonly used clinicopathological criteria (in a modified version of the Adjuvant! Online programme) for selecting patients for adjuvant CT. The trial hypothesises that using the molecular profile approach will outperform the usual clinical and pathological assessment, more accurately assigning adequate risk categories and reducing by 10–20% the number of patients receiving adjuvant CT without the impairment of long-term outcome. MINDACT includes two additional questions designed to evaluate a non-anthracycline-based adjuvant CT regimen, and to compare the switching and upfront strategies of adjuvant endocrine therapy.

Due to the complexity of the trial, a predefined pilot phase comprising the first 800 enrolled patients was planned and submitted to the European Organisation for Research and Treatment of Cancer (EORTC) Independent Data Monitoring

Committee (IDMC) to ensure the trial's feasibility. This manuscript presents the results of this pilot phase.

2. Patients and methods

2.1. Patients

Women aged 18–70 years with histologically proven operable invasive BC, no distant metastases and for whom a frozen tumour sample was available were enrolled. Eligibility criteria include tumour stage T1, T2, or operable T3, and unilateral; ductal carcinoma *in situ* or lobular carcinoma *in situ* provided invasive cancer is present; surgery options include breast-conserving surgery or mastectomy combined with either a sentinel node procedure or full axillary clearance; WHO performance status of 0 or 1 and adequate bone marrow, liver and renal functions. Main exclusion criteria include: previous or concurrent cancer, previous CT, anticancer endocrine therapy or radiotherapy, and clinically significant cardiac disease. The protocol was amended on April 2008 to allow inclusion of 1–3 lymph node positive disease and genomic test in samples containing >30% of tumour cells.[26]

The protocol has been approved by independent ethics committees and by the medical authorities. All patients have provided written informed consent. This study is conducted in accordance with the Declaration of Helsinki and the applicable guidelines on good clinical practise. The trial is registered at ClinicalTrials.gov, number NCT00433589.

2.2. Risk assessment

The patient's clinicopathological risk is calculated by a modified version of 'Adjuvant! Online' (version 8.0 but including HER2 status). Patients are classified as low clinical risk if their estimated 10-year BCSS is >92% in oestrogen receptor (ER) negative tumours and >88% for ER positive tumours, respectively. This difference accounts for the expected absolute benefit of 4% of endocrine therapy in ER-positive disease. The MammaPrint™ results are provided in a dichotomous way (high and low risk) per Agendia™, Amsterdam, standardised procedures. All pathological analysis for clinicopathological risk is done locally (e.g. tumour grade, hormone receptor and HER2 status). HER2-positivity has a set factor of 1.5 in the calculation of Adjuvant! Online. Central pathology review including histology, grade and all major biomarkers will be performed.

2.3. Study design

The trial design is summarised in Fig. 1. All patients have their risk assessed by both MammaPrint™ and clinicopathological prognostic factors. Patients with C-high/G-high risk are offered adjuvant CT while C-low/G-low risk patients do not receive CT. Patients for whom risk assessment results are discordant (C-high/G-low or C-low/G-high) are randomised for treatment (R–T) decision for adjuvant CT based on clinicopathological versus genomic risk. All patients who are candidates for adjuvant CT are offered a non-mandatory second randomisation (R–C) between an anthracycline-based regimen and docetaxel/capecitabine combination. All ER-positive patients may be offered a non-mandatory endocrine therapy randomisation

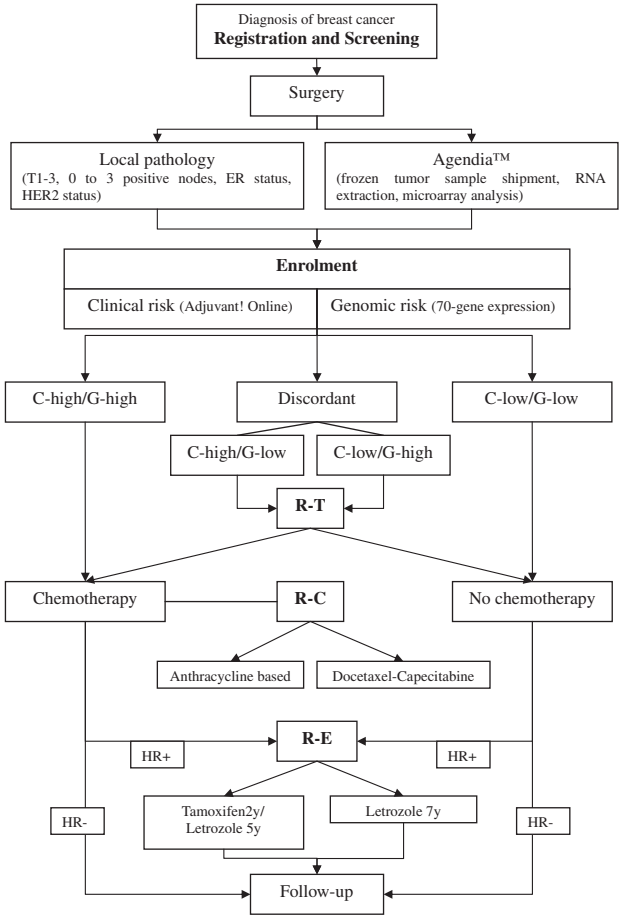

Fig. 1 – Study design. *Legend*: Registration: After signing the screening informed consent (IC), the patient is registered and assigned a sequence identification number (SeqID). Screening: After registration the screening comprises baseline exams, surgery for the primary tumour, shipment of the tumour sample and genomic test. Enrolment: If the screening period is successful and the patient agrees to participate in the trial (IC 1 is signed), the patient is enrolled and the clinicopathological (C) and genomic (G) risk results are known as well as the treatment assigned. R-T: Randomisation to treatment; R-C: Chemotherapy randomisation; R-E: Endocrine therapy randomisation. HR: Hormone receptor

(R–E) between 7 years of letrozole and 2 years of tamoxifen followed by 5 years of letrozole. Premenopausal women, however, additionally require adequate ovarian function suppression/ablation for the whole duration of randomised endocrine therapy. Further information on trial concept, design and statistical assumption is described by Bogaerts et al.[27]

2.4. Objectives of the pilot phase

The main objectives of the pilot phase are to ensure that (a) the trial is logistically feasible, (b) the patient recruitment is unbiased and that a reasonable spectrum of C-high risk patients are being enrolled, (c) the compliance with treatment assignment is high, (d) a statistically significant difference is

observed between the percentages of patients that have a C-high and a G-high risks, thus reflecting a likewise reduction in CT administration. Additionally, the percentage of patients who are candidates for adjuvant CT and are undergoing the R–C as well as the percentage of ER-positive patients who are undergoing the R–E are verified.

2.5. Statistical analysis

The statistical analysis of the pilot phase expects to observe a statistically significant difference between the percentage of patients with a C-high risk and a G-high risk. With 800 patients and a type I error rate set at 5%, the pilot phase has 80% power to reject the null hypothesis of no difference if the true difference is at least 7%. Monitoring of the proportion of clinicopathological and genomic risks as well as of other trial data, especially 'crossovers' between the CT and the no CT groups was submitted for analysis to the IDMC.

3. Results

3.1. Patients, disease characteristics and eligibility

Between 8th February 2007, and 24th November 2008, 800 patients were included from 57 centres in nine countries (Fig. 2). For the analysis of the pilot phase the trial database was locked on 11th February 2009. At the time of pilot phase analysis, a total of 2434 patients had been registered, 73% had their tumour sample shipped for genomic testing, 67% went through a successful hybridisation and testing by the 70-gene array and 1110 (45.6%) were enrolled. About 90% of patients were enrolled within 6 weeks from diagnosis. The main reasons for non-enrolment were node positivity before amendment, sample quality problems and failure to meet the logistic settings (shipment, timing of shipment, timeline from screening to enrolment). Out of screened patients 241 (9.9%) had sample analysis failure due to less than 50% (30% after the protocol amendment) tumour cells or a low quantity/poor quality RNA. The patient baseline characteristics are shown in Table 1. The mean age was 54 years (range, 25–70 years) and 96.1% had a WHO performance status of zero. Breast-conserving surgery was performed in 681 (85.1%) patients, while 119 (14.9%) underwent a mastectomy; 621 (77.6%) had sentinel node biopsy with no additional axillary dissection.

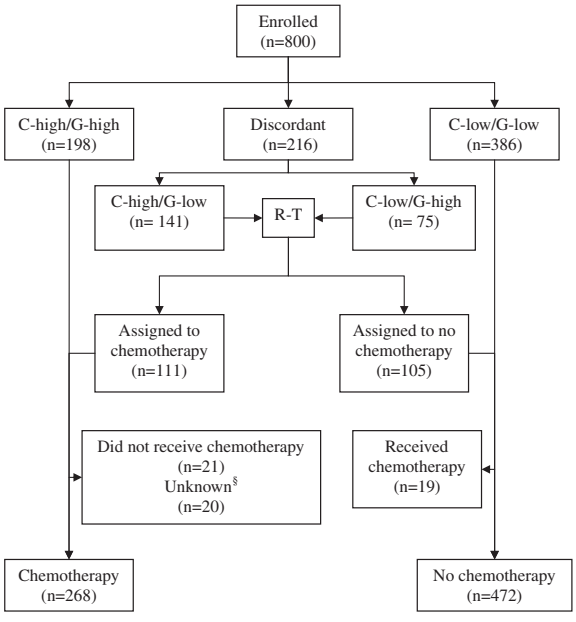

Fig. 2 – Consolidated Standards of Reporting Trials (CONSORT) flow diagram. §-Unknown at the time of data lock.

3.2. Risk assessment and treatment assignment

The clinical and genomic risk assessment distributions are described in Table 2. The difference between C-high risk 42% (339/800) and G-high risk 34% (273/800) is 8.25% (95% confidence interval (CI), 4.69–11.81%; $P < .0001$) showing that the genomic test assigns less patients to CT than the clinicopathological risk method.

Treatment decision outcome by clinical and genomic risk assessments at enrolment is described in Table 3. Among the 800 enrolled patients, 216 had discordant risk assessments and thus underwent the randomisation for CT decision making. Among the 108 patients randomised to follow the clinicopathological risk assessment 72 (67%) were classified C-high risk and therefore assigned to receive adjuvant CT, while among the 108 patients having their treatment decision based on the genomic risk, 39 (36%) were classified as G-high risk and thus assigned to receive adjuvant CT.

3.3. Chemotherapy administration and compliance

In total, 309 (39%) patients were assigned to receive adjuvant CT. Of these 154 (50%) patients entered the CT randomisation: 79 patients received anthracycline-based CT and 75 patients received docetaxel/capecitabine. Additionally, 116 patients receive CT albeit outside the CT randomisation. From all patients assigned to receive CT per protocol, 21 (6.8%) patients (seven C-high/G-high, nine C-high/G-low and five C-low/G-high) did not receive CT and for 20 (6.5%) the information was still unknown at the time of the data lock for this analysis due to recent inclusion in the trial.

Overall, the compliance rate with CT treatment assignment per protocol is very high: 93.2% for CT decision and 96.1% for no CT decision. Importantly, in the discordant group, there is a compliance rate of >92% with the randomised treatment decision. In the key group of 69 patients with C-high/G-low risk randomised to treatment decision by genomic risk, i.e. not to receive CT, only 3 (4.3%) were non-compliant and received CT. Likewise, in the group of 39 patients with C-low/G-high risk randomised to treatment decision by genomic risk, i.e. to receive CT, 5 (12.8%) patients did not receive CT. The reasons for non-compliance with the treatment assigned per protocol by risk assessment groups are described in Table 4.

4. Discussion

4.1. The logistically complex MINDACT trial is feasible in a multinational setting

The logistics of the trial proved to be feasible in a multinational setting from the point of view of patients, physicians

Table 1 – Patient baseline characteristics.

	Total (n = 800)
Age	
<50 years	264 (33%)
⩾ 50 years	536 (67%)
Tumour size	
⩽2 cm	601 (75.1%)
>2–5 cm	195 (24.4%)
>5 cm	4 (0.5%)
Lymph node status	
Negative	794 (99.3%)
1–3 node positive	4 (0.5%)
LN positive before amendment	1 (0.1%)
Missing	1 (0.1%)
Histological grade	
1	169 (21.1%)
2	361 (45.1%)
3	266 (33.3%)
Undefined	4 (0.5%)
Oestrogen receptor status	
Positive	676 (84.5%)
Negative	124 (15.5%)
Progesterone receptor status	
Positive	571 (71.4%)
Negative	227 (28.4%)
Unknown	2 (0.3%)
HER2 status	
Negative	690 (86.3%)
Positive	87 (10.9%)
Unknown[a]	23 (2.9%)

a HER2 IHC 2+, no Fluorescence in situ hybridization (FISH), not done or not received.

Table 2 – Risk assessment distribution.

Genomic risk	Clinical risk		Total
	High	Low	
High	198 (24.8%)	75 (9.4%)	273 (34.1%)
Low	141 (17.6%)	386 (48.2%)	527 (65.9%)
Total	339 (42.4%)	461 (57.6%)	800 (100%)

and laboratories involved. Our pilot phase showed that collection and shipment of fresh frozen tumour tissue for real-time gene expression profiling are feasible in a multicentre and multinational practise setting. The logistics of MINDACT has been one of the most challenging aspects of the trial since it involves frozen tumour biopsy, real-time transportation, quantitative and qualitative RNA analyses, and return of the test results to the treating physician for timely adjuvant treatment decision. Importantly, at the time of the pilot phase analysis, a total of 2434 patients had been registered of whom 1110 had been enrolled, and only 241 (9.9%) had sample quality problems. This proportion of non-representative samples is in agreement with the proportion reported by previous feasibility studies.[28,29] The reasons of screen failure have been collected during the study accrual and will be analysed on future publication.

The proportion of discordant patients, the expected reduction in CT when using the genomic signature and the compliance to treatment assignment are in accordance with the trial hypotheses.

The characteristics of the patients recruited in the pilot phase of the MINDACT trial have important differences from those included in the two validation series of the MammaPrint™ profile, with 67% of patients aged 50 years or older in the trial, as compared with 33% and 48% in the node negative and node positive validation series, respectively.[21,26] There are 16% of ER-negative patients in the trial compared with 21% in the validation studies and slightly less HER2-positive patients than included in the node positive retrospective study (11% versus 15%). Tumour grade is comparable to the validation series however the tumour size tends to be smaller than in patients included in the node negative and node positive validation studies (75% versus 36% and 49% T1, 24% versus 64% and 50% T2, respectively). These patient and disease characteristics resulted in a lower proportion of clinicopathological high risk patients being enrolled than it was assumed at the time of protocol development (42.4% versus 77%, respectively). There are two potential explanations: screening programmes which are increasing the proportion of genomic low-risk cancers and some patient selection process in the participating centres.[8] The risk assessment distribution hypothesised in the trial design was 55% C-high/G-high, 22% C-high/G-low, 10% C-low/G-high and 13% C-low/G-low. In the pilot phase, the observed risk assessment distribution of enrolled patients was 24.8% C-high/G-high, 17.6% C-high/G-low, 9.4% C-low/G-high and 48.3% C-low/G-low. Despite having fewer C-high/G-high risk patients than planned, which will affect the CT randomisation, the primary question of the trial that depends on the proportion of discordant cases will be sufficiently powered. In addition, we consider that is too early to perceive the effect of the protocol amendment to include 1–3 node positive patients, which will most probably increase the inclusion of clinical high risk patients. The rationale of the trial is based on the assumption that 10–20% of patients will be spared adjuvant CT through

Table 3 – Treatment decision outcome per clinical and genomic risk assessment at enrolment.

Risk assessment at enrolment	Chemotherapy	No chemotherapy	Total (n = 800)
C-high/G-high	198 (64.1%)	0	198 (24.8%)
C-low/G-low	0	386 (78.6%)	386 (48.3%)
C-high/G-low	72 (23.3%)	69 (14.1%)	141 (17.6%)
C-low/G-high	39 (12.6%)	36 (7.3%)	75 (9.4%)

Table 4 – Reasons for deviation from the chemotherapy assignment..

Reason for non-compliance	Assigned for chemotherapy			Total ($n = 21$)	Assigned for no chemotherapy			Total ($n = 19$)
	C-high/G-high ($n = 7$)	C-high/G-low ($n = 9$)	C-low/G-high ($n = 5$)		C-low/G-low ($n = 6$)	C-low/G-high ($n = 10$)	C-high/G-low ($n = 3$)	
PI's decision	1 (14.3%)	4 (44.4%)	1 (20%)	6 (28.6%)	2 (33.3%)	5 (50%)	0	7 (36.8%)
Patient refusal	4 (57.1%)	4 (44.4%)	3 (60%)	11 (52.4%)	3 (50%)	1 (10%)	3 (100%)	7 (36.8%)
Other	1 (14.3%)	0	0	1 (4.8%)	1 (16.7%)	1 (10%)	0	2 (10.5%)
Missing	1 (14.3%)	1 (11.1%)	1 (20%)	3 (14.3%)	0	3 (30%)	0	3 (15.8%)

the use of the MammaPrint™ profile. In keeping with this, in the pilot phase we found a statistically significant difference of 8.25% between the percentage of patients that have C-high and G-high risk, showing that in the accrued population the genomic test assigns more patients as low risk (and hence no CT).

Importantly, the rate of compliance of physicians and patients with the treatment decision provided by the protocol for discordant cases is high. Of special interest, the decision based on MammaPrint™ has a high compliance: in the group of C-high/G-low only three (4.3%) patients were non-compliant and received CT and among C-low/G-high patients five (12.8%) were non-compliant and not received CT. Currently, the key group with C-high/G-low risk randomised to treatment decision by genomic risk has 69/800 (8.6%) patients and 672/6000 (11.2%) are hypothesised.

4.2. *Chemotherapy and endocrine therapy questions*

Among the 800 patients, 154 (19%) underwent randomisation to CT, where 66% of the enrolled population was hypothesised. Contributing factors are the high proportion of clinical low risk patients being enrolled and the fact that the CT randomisation is not mandatory. However, given the availability of a whole genome expression profile on the tumours of these patients, the randomised CT groups remain of interest for potential discovery/validation of CT predictive signatures/biomarkers in the future. The safety evaluation of the docetaxel/capecitabine combination has been continuously assessed and found to be satisfactory (complete analysis is being performed and will be reported soon). In addition, the trial has adequately enrolled patients in the endocrine therapy randomisation (R–E).

In conclusion, the MINDACT pilot phase has successfully achieved implementation of a biomarker-stratified trial design with the objectives of complete biomarker status, efficiency of the trial logistics and high compliance.[30] The results achieved by the MINDACT pilot phase led the IDMC to recommend the continuation of the trial which completed the recruitment in July 2011. The logistics of conducting the MINDACT trial, the first prospective randomised clinical trial evaluating the clinical utility of a gene expression profile in early BC, has been successfully delivered.

Author's contribution

All authors were involved in the manuscript writing and approved the final draft. E.R., M.P.G., S.D., I.T.R., G.V., A.M.T., R.P., U.N., A.V., J.Y.P., P.M.R. and F.C. contributed to data collection. E.R., M.P.G., J.B., L.V.V. and F.C. were involved in study design. E.R., M.P.G., J.B., L.V.V., G.W. and F.C. contributed to data analysis and interpretation of results.

Conflict of interest statement

E.R., I.T.R., S.D., R.P. and A.V. declare that they have no conflicts of interest. G.W. and J.B. are employees of the EORTC which receives funding for the study. L.V.V. is a founder of Agendia and has stock ownership. G.V. has received consul-

tancy fees/honorarium from Agendia. J.Y.P. has received consultancy fees from Roche and Ipsem, honorarium from Sanofi-Aventis and Pfizer, and research grant from Roche. M.G.P. has received consultancy fees from Sanofi-Aventis, Novartis and Roche, honorarium from Roche and research grant from Roche and Novartis. U.N. has received honorarium from Sanofi-Aventis, Amgen, Roche and Novartis. A.M.T. has received research funds from Sanofi-Aventis and Roche, honoraria from Roche and other funding (e.g. travel, accommodation, meeting expenses) from Novartis and Roche. P.M.R. is a founder of Adjuvant Online Inc. and has consultant and stock ownership. F.C. has received consultancy fees/honorarium from Novartis, Sanofi-Aventis and Roche.

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