# Biomarker-based tests for deciding for or against adjuvant systemic chemotherapy in primary breast cancer with involvement of 1 to 3 lymph nodes and in premenopausal patients without lymph node involvement[1]

**EXTRACT**

Project: D23-01A
D23-01B
Version: 1.0
Status: 21 Oct 2024
DOI: 10.60584/D23-01B_en

[1] Translation of Chapters 1 to 6 of the final report D23-01A | D23-01B *Biomarkerbasierte Tests zur Entscheidung für oder gegen eine adjuvante systemische Chemotherapie beim primären Mammakarzinom mit Befall von 1 bis 3 Lymphknoten und bei prämenopausalen Patientinnen ohne Lymphknotenbefall* (Version 1.0; Status: 21 October 2024 [German original], 18 June 2025 [English translation]). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

# Publishing details

**Publisher**

Institute for Quality and Efficiency in Health Care

**Topic**

Biomarker-based tests for deciding for or against adjuvant systemic chemotherapy in primary breast cancer with involvement of 1 to 3 lymph nodes and in premenopausal patients without lymph node involvement

**Commissioning agency**

Federal Joint Committee

**Commission awarded on**

12 May 2023 (D23-01A) and 21 September 2023 (D23-01B)

**Internal Project No.**

D23-01A | D23-01B

**DOI-URL**

https://doi.org/10.60584/D23-01B_en

**Address of publisher**

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**Recommended citation**

Institute for Quality and Efficiency in Health Care. Biomarker-based tests for deciding for or against adjuvant systemic chemotherapy in primary breast cancer with involvement of 1 to 3 lymph nodes and in premenopausal patients without lymph node involvement; Extract [online]. 2024 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/D23-01B_en.

**Keywords**

Tumor Markers – Biological, Breast Neoplasms, Lymphatic Metastasis, Benefit Assessment

This report was prepared without collaboration with external experts.

The responsibility for the contents of the report lies solely with IQWiG.

**Patient involvement**

Patients were consulted as part of the reporting process. Heike Schwarz and Gisela Schwesig participated in the discussion. The aim of the discussion was to obtain information on the following topics: experiences, preferences and concerns related to the diagnosis, effects of the disease on life and daily activities, and coping with the disease. IQWiG would like to thank the above-mentioned participants and the Women's Cancer Self-Help Group (Frauenselbsthilfe Krebs) for their support - they were not involved in the preparation of this report.

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# Key statement

***Research question***

*Breast cancer patients with involvement of 1–3 lymph nodes (Project D23-01A)*

The objective of this investigation is to

- assess the benefit of biomarker-based tests for deciding for or against adjuvant systemic chemotherapy in comparison with a biomarker-independent decision strategy or a 2nd biomarker-based decision strategy

- in patients with primary hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)/neu-negative breast cancer with involvement of 1–3 lymph nodes.

*Premenopausal breast cancer patients without lymph node involvement (Project D23-01B)*

The objective of this investigation is to

- assess the benefit of biomarker-based tests for deciding for or against adjuvant systemic chemotherapy in comparison with a biomarker-independent decision strategy or a 2nd biomarker-based decision strategy

- in premenopausal patients with primary hormone receptor-positive, HER2/neu-negative breast cancer without lymph node involvement.

***Conclusion***

**Project D23-01A: Breast cancer patients with involvement of 1–3 lymph nodes**

For the population of patients with primary hormone receptor-positive, HER2/neu-negative breast cancer with involvement of 1–3 lymph nodes, the results for a biomarker-based decision against chemotherapy differ depending on the biomarker in question and the menopausal status:

When using MammaPrint:

- No hint of a benefit in the group at high clinical risk group regardless of age

When using the Oncotype DX Breast Recurrence Score (Oncotype DX):

- A hint of harm in premenopausal patients or in patients up to and including 50 years of age and

- A hint of a benefit in patients over 50 years of age

Relevant data from RCTs were only available for the biomarkers MammaPrint (MINDACT study) and Oncotype DX (RxPONDER study). No current prognostic studies have been identified for any biomarker.

**Project D23-01B: Premenopausal breast cancer patients without lymph node involvement**

For the population of premenopausal patients with primary hormone receptor-positive, HER2/neu-negative breast cancer without lymph node involvement, the following conclusion results for a biomarker-based decision against chemotherapy depending on the biomarker considered:

- When using MammaPrint, a hint of harm specific to the group at high clinical risk

- When using Oncotype DX, a hint of harm

Relevant data from RCTs were only available for the biomarkers MammaPrint (MINDACT study) and Oncotype DX (TAILORx study).

**Cross-project conclusion**

No RCTs comparing 2 biomarker-based decision strategies were identified in either project. No assessment of a general biomarker-based decision-making strategy can be derived from the results described above, as there are clear differences in the benefit-risk profile of the two biomarkers analysed in the RCTs. Accordingly, no assessments of other biomarkers such as EndoPredict and Prosigna, for which no suitable data are available, can be derived from the results of MammaPrint and Oncotype DX.

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# List of abbreviations

| Abbreviation | Meaning |
|---|---|
| AE | adverse event |
| DCIS | ductal carcinoma in situ |
| FSH | follicle stimulating hormone |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| GnRH | gonadotropin-releasing hormone |
| HER2 | human epidermal growth factor receptor-2 |
| iDFS | invasive disease-free survival |
| ITT | intention-to-treat |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| LHRH | luteinising hormone-releasing hormone |
| OFS | ovarian function suppression |
| PP | Per protocol |
| RCT | randomized controlled trial |
| RS | recurrence score |
| SAE | serious adverse event |
| SGB | Sozialgesetzbuch (Social Code Book) |

# 1 Background

On 12 May 2023 the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess biomarker-based tests for deciding for or against adjuvant systemic chemotherapy in primary breast cancer with involvement of 1–3 lymph nodes (Project D23-01A). On 21 September 2023, the G-BA commissioned IQWiG to conduct an additional assessment of biomarker-based tests for deciding for or against adjuvant systemic chemotherapy in premenopausal patients with primary breast cancer without lymph node involvement (Project D23-01B). The IQWiG will synchronize the processing of both commissions in accordance with the commission specification and present them in a joint report plan, preliminary report and final report. In previous, thematically related reports such as Final Report D14-01 [1], Addendum D18-01 [2] and Rapid Report D19-01 [3] , patients with positive and/or negative nodal status (lymph node involvement and/or no lymph node involvement) were examined equally. The planned benefit assessments of Project D23-01A and Project D23-01B each provide for the research, presentation and evaluation of the current state of knowledge on the use of biomarker-based tests for deciding for or against adjuvant systemic chemotherapy in the above-mentioned populations of breast cancer patients. The detailed project history for the commissioning of these projects can be found in Section A.1.1.

## Disease definition

The term “primary tumour” describes the original site of the first appearance of a tumour in the body. Primary breast cancer (breast carcinoma, International Statistical Classification of Diseases and Related Health Problems [ICD-10] [4] C50) is a malignant neoplasm originating in the mammary gland. In locoregional primary disease, the disease is confined to a limited area in the mammary gland, possibly extending to a few regional lymph nodes. In locally advanced breast cancer, the cancer has spread to large parts of the breast and/or to the chest wall or skin without yet metastasizing. The renewed occurrence of breast cancer after a period in which the cancer could no longer be detected following previous treatment is referred to as recurrence. A local or locoregional recurrence can, for instance, occur in the breast and on the chest wall, as well as in the regional lymph nodes of the axilla. Furthermore, distant metastases can occur, where the cancer has spread from the primary tumour to distant lymph nodes or into other organ systems such as the brain [5].

### *Breast cancer patients with involvement of 1–3 lymph nodes (Project D23-01A)*

The focus of Project D23-01A is on patients with primary hormone receptor-positive, human epidermal growth factor receptor-2 (HER2)/neu-negative breast carcinoma (corresponds to the intrinsic subtypes Luminal A and Luminal B, HER2/neu-negative [5]) with involvement of 1–3 lymph nodes. This project involves the evaluation of a new examination and treatment method in contracted doctor care (see Section A.1.1).

***Premenopausal breast cancer patients without lymph node involvement (Project D23-01B)***

The focus of Project D23-01B is on premenopausal patients with primary hormone receptor-positive, HER2/neu-negative breast carcinoma (corresponds to the intrinsic subtypes Luminal A and Luminal B, HER2/neu-negative [5]) without lymph node involvement. This project involves the review of a contracted doctor care service that can be provided at the expense of health insurance companies (see Section A.1.1).

**Definition of a biomarker**

The term "biomarker" is made up of the words "biological" and "marker". The term refers to an extended subcategory of medical evidence (also known as “signs”). This refers to evidence of a patient's health status, for example. This evidence can be viewed from the outside and measured accurately and reproducibly. Medical evidence is to be seen as the opposite of medical symptoms, as the symptoms tend to be limited to evidence of illness or health perceived subjectively by the patient, for example [6].

In the case of biomarkers, it is necessary to distinguish between diagnostic, monitoring, pharmacodynamic, responsive, prognostic, or predictive biomarkers. A diagnostic biomarker identifies or confirms the presence of a specific disease or, for example, identifies a patient with a subtype of a disease. It is also possible to measure biomarkers serially, for example to assess a disease or medical condition. Such biomarkers are referred to as surveillance biomarkers. A pharmacodynamic or responsive biomarker can be seen as a change in concentration in response to an environmental factor or a drug. A prognostic biomarker is used, for example, to determine the probability of a specific disease progression or relapse. A predictive biomarker can be used to derive a conclusion about the response to a specific treatment [7]. The 2 research questions present address the benefit of predictive biomarkers when deciding for or against adjuvant systemic chemotherapy.

For the patients considered in this report, it is unclear whether they would benefit from adjuvant systemic chemotherapy, which might be indicated according to the established clinicopathological criteria, or whether such chemotherapy can be avoided on the basis of the biomarker-based test result. As a large part of these patients will possibly not benefit from chemotherapy, it is of particular interest to identify via a predictive marker those patients who are highly likely to benefit from chemotherapy and those who are highly unlikely to do so.

Further information, e.g. on intrinsic breast cancer subtypes, the role of predictive markers in the treatment decision, the determination of biomarkers in patients with breast cancer, and the treatment of the disease after primary surgery are described in more detail in Final Report D14-01 [1].

**Testimonials from those affected as an additional source of information**

To supplement the introduction to the disorder, the IQWiG provides individual testimonials from patients and/or their relatives. The anonymized testimonials can allow insights into how individuals experience the disorder and how they deal with its consequences. In this way, they can help to better understand the perspectives of those affected. The testimonials summarize interviews and are published on the IQWiG website www.gesundheitsinformation.de. They are not representative, and statements in the testimonials do not constitute IQWiG recommendations. For more information on the methodology of the testimonials, please refer the General Methods 7.0 [8]. The testimonials can be found here:

- https://www.gesundheitsinformation.de/EB-Brustkrebs
- https://www.gesundheitsinformation.de/EB-metastasierter-Brustkrebs

# 2 Research questions

## 2.1 Breast cancer patients with involvement of 1–3 lymph nodes (Project D23-01A)

The objective of this investigation is to

- assess the benefit of biomarker-based tests for deciding for or against adjuvant systemic chemotherapy in comparison with a biomarker-independent decision strategy or a 2nd biomarker-based decision strategy

in patients with primary hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)/neu-negative breast cancer with involvement of 1–3 lymph nodes.

## 2.2 Premenopausal breast cancer patients without lymph node involvement (Project D23-01B)

The objective of this investigation is to

- assess the benefit of biomarker-based tests for deciding for or against adjuvant systemic chemotherapy in comparison with a biomarker-independent decision strategy or a 2nd biomarker-based decision strategy

in premenopausal patients with primary hormone receptor-positive, HER2/neu-negative breast cancer without lymph node involvement.

# 3 Methods

The target populations of the benefit assessments were patients with primary hormone receptor-positive, HER2/neu-negative breast cancer. In Project D23-01A this included patients with involvement of 1–3 lymph nodes and in Project D23-01B, premenopausal patients without lymph node involvement. The test interventions in both projects were biomarker-based tests for deciding for or against adjuvant systemic chemotherapy. In both projects, biomarker-independent or other biomarker-based decision strategies were used as comparator interventions. There was no restriction to certain biomarker-based tests.

The following patient-relevant outcomes were taken into account in the investigation:

- Mortality and morbidity
  - overall survival, disease-free survival
  - recurrence-free survival (only for prognostic studies in Project D23-01A )
- Health-related quality of life
- Side effects (adverse events [AEs])

The benefit assessments included randomized controlled trials (RCTs) with a minimum follow-up period of 1 year. For the outcomes of overall survival and disease-free survival, a follow-up period of ideally 10 years was defined, whereby interim analyses of at least 5 years were also presented to estimate the results. In Project D23-01A, prognostic studies (prospectively planned cohort studies) were additionally presented to inform the G-BA. For prognostic studies, the minimum duration of follow-up was 5 years.

In parallel to the preparation of the report plan, a search for systematic reviews was conducted in the MEDLINE database (which includes the Cochrane Database of Systematic Reviews) and the International Health Technology Assessment (HTA) database as well as on the websites of the National Institute for Health and Care Excellence (NICE) and the Agency for Healthcare Research and Quality (AHRQ). The last search was conducted on 27 April 2023.

Since Final Report D14-01 [1] and Rapid Report D19-01 [3] are systematic reviews of the issues investigated in both projects, the earlier information obtained from these systematic reviews was used as a basis.

In a 2nd step, a supplementary search for studies was carried out for the period not covered by the preceding reports D14-01 and D19-01.

The systematic literature search for studies was conducted in the following databases: MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials.

In addition, the following information sources and search techniques were taken into account: study registries, manufacturer queries, documents transmitted by the G-BA, the screening of reference lists, documents made available from hearing procedures, and author queries.

For both projects, relevant studies were selected by 2 persons independently from one another. Any discrepancies were resolved by discussion between them. Data were extracted into standardized tables. To assess the qualitative certainty of results, risk of bias criteria across outcomes and outcome-specific risk of bias criteria were assessed, and the risk of bias was rated as high or low in each case. In prognostic studies in Project D23-01A, the qualitative certainty of results was assessed exclusively on the basis of the proportion of patients included in the evaluation. The results of the individual studies were described, organized by projects and biomarkers.

In addition to the comparison of the individual studies' results, metaanalyses and sensitivity analyses were conducted and effect modifiers investigated, provided that the methodological prerequisites had been met.

The research questions are primarily addressed by formulating a non-inferiority question with regard to disease-free survival. Analogous to Addendum D18-01, 3 percentage points are also defined in the present benefit assessments as the upper limit of the 95% confidence interval for the risk difference (between chemoendocrine and endocrine-treated patients) for the outcome disease-free survival after 10 years. Assuming a linear increase in risk over 10 years, an adjusted non-inferiority threshold is used for a shorter follow-up period.

A conclusion on the evidence base for benefit or harm was drawn for each biomarker in both Project D23-01A and Project D23-01B based on the outcomes "disease-free survival" or "overall survival". There were 4 levels of certainty of conclusions: The data provided either "proof" (highest certainty of conclusions), an "indication" (medium certainty of conclusions), a "hint" (weakest certainty of conclusions), or none of these 3 situations applied. The latter was the case if either no data were available or the available data did not allow any of the other 3 conclusions to be drawn. In this case, the conclusion "There is no hint of a benefit" was drawn.

# 4 Results

Project D23-01A and Project D23-01B are separate benefit assessments as per the contract. There is an overlap in the study pool of the projects, but the results are presented separately according to the research questions of the projects. The results of the prognostic studies for Project D23-01A are presented in Chapter A6.

## 4.1 Results of the information retrieval

Project D23-01A and Project D23-01B are carried out as an update to the previous reports, Final Report D14-01 [1], Addendum D18-01 [2], and Rapid Report D19-01 [3]. Therefore, the study pool from these previous projects will be supplemented by the newly identified documents or studies from the current researches on Project D23-01A and Project D23-01B.

### 4.1.1 Breast cancer patients with involvement of 1–3 lymph nodes (Project D23 01A)

The information retrieval revealed 2 RCTs relevant to the research question in Project D23-01A with usable data (MINDACT, RxPONDER), which were included in the benefit assessment. RxPONDER was additionally classified as an ongoing study with a planned study end around the year 2032 according to the study registry entry. In the reports D14-01 and/or D19-01, 2 ongoing studies (ICORG12-01 SWOG S1007, OPTIMA) and 1 discontinued study (OPTIGEN) were identified, for which no results are still being reported (Table 23 of the full report). In Project D23-01A no further planned and no further ongoing studies were identified. Furthermore, no additional studies with unclear status, no completed studies without reported results, and no further discontinued studies were identified.

The search strategies for bibliographic databases and trial registries are found in the appendix. The last search was conducted on 20 June 2024.

Table 1: Project D23-01A – Patients with involvement of 1–3 lymph nodes: Study pool of benefit assessment

| Study | Available documents | | | |
|---|---|---|---|---|
| | **Full publication (in scientific journals)** | **Registry entry / Result report from trial registries** | **Clinical study report from manufacturer documents (not publicly available)** | **Other documents** |
| MINDACT | Yes [9-11] | Yes [12,13] / No | No | Yes [14,15] |
| RxPONDER | Yes [16,17][a] | Yes [18,19] / Yes [19] | No | No |
| The study protocol is part of the relevant publication and is therefore not counted as an additional document in Figure 3, but is added here for the sake of completeness. | | | | |

### 4.1.2 Premenopausal breast cancer patients without lymph node involvement (Project D23-01B)

The information retrieval revealed 2 RCTs relevant to the research question in Project D23-01B with usable data (MINDACT, TAILORx), which were included in the benefit assessment. TAILORx was additionally classified as an ongoing study with a planned study end around the year 2030 according to the study registry entry. In the reports D14-01 and/or D19-01, 1 ongoing study (OPTIMA) and 1 discontinued study (OPTIGEN) were identified, for which no results are still being reported (Table 23 of the full report). In Project D23-01B no further planned and no further ongoing studies were identified. Furthermore, no additional studies with unclear status, no completed studies without reported results, and no further discontinued studies were identified.

The search strategies for bibliographic databases and trial registries are found in the appendix. The last search was conducted on 20 June 2024.

Table 2: Project D23-01B – premenopausal patients without lymph node involvement: study pool of the benefit assessment

| Study | Available documents | | | |
|---|---|---|---|---|
| | **Full publication (in scientific journals)** | **Registry entry / Result report from trial registries** | **Clinical study report from manufacturer documents (not publicly available)** | **Other documents** |
| MINDACT | Yes [9-11] | Yes [12,13] / No | No | Yes [14,15] |
| TAILORx | Yes [20-25] | Yes [26-28] / Yes [28][a] | No | Yes [29] |
| The trial registry entry still only contains the already known 5-year data (as of 5 April 2024), which is why these results are not considered further. | | | | |

## 4.2 Characteristics of the studies included in the assessment

Project D23-01A included 2 studies with usable data. The MINDACT study examines a biomarker-based test with 70 genes (MammaPrint). The RxPONDER study analyses a biomarker-based test with 21 genes (Oncotype DX Breast Recurrence Score, hereinafter referred to as Oncotype DX).

Project D23-01B also included 2 studies with usable data, namely MINDACT and TAILORx. TAILORx also examines the Oncotype DX.

The main characteristics of the included studies for each project are described below, broken down according to the biomarker-based test used.

### 4.2.1 Breast cancer patients with involvement of 1–3 lymph nodes (Project D23-01A)

#### 4.2.1.1 MammaPrint

The characteristics of the **MINDACT** study [11] have already been described in detail in Final Report D14-01 and are supplemented here with further information.

The MINDACT study is an RCT with a strategic design in which the biomarker MammaPrint was investigated. This prospective multicentre study included 6693 patients from 9 European countries, most of whom were over 50 years of age. All patients had histologically confirmed primary and invasive breast cancer (operable) at baseline. Originally, only patients with node-negative breast cancer were included from 2007 onwards. The protocol was updated in August 2009. By the end of recruitment in 2011, patients with up to 3 positive axillary nodes were also included. Approximate menopausal status was defined by an age limit of 50 years (≤ 50 years versus > 50 years).

The study had 6 treatment arms. Patients with discordant risk assessments of high clinical and low genomic risk (High clinical Risk [C-high]/Low genomic Risk [G-low], n = 1497) or low clinical and high genomic risk (Low clinical Risk [C-low]/High genomic Risk [G-high], n = 690) were randomly assigned to treatment with chemoendocrine therapy or endocrine therapy. Patients with a concordant assessment of clinical and genomic risk received either endocrine therapy (concordant low risk, C-low/G-low, n = 2634) or chemoendocrine therapy (concordant high risk, C-high/G-high, n = 1873). A more detailed description of the study-specific determination of the clinical risk of recurrence can be found in Section 4.2.3.

Patients assigned to adjuvant chemotherapy could be randomized to either an anthracycline-containing regimen or a docetaxel plus capecitabine regimen. Patients with hormone receptor-positive breast cancer could be randomized to either a tamoxifen-letrozole regimen or a letrozole-only regimen. In younger patients (≤ 50 years of age), adjuvant endocrine therapy consisted mainly of tamoxifen. According to the MINDACT study protocol, all patients ≤ 50 years of age should receive ovarian function suppression (OFS). OFS could be induced by surgery (ovariectomy), ovarian radiotherapy, or the administration of an analogue of the luteinising hormone-releasing hormone (LHRH). Even though temporary or definitive SFO was mandatory in patients ≤ 50 years of age, an LHRH analogue was only administered to induce SFO in 95 of 446 patients (21.3%): 36 of 222 (16.2%) in the group without chemotherapy and 59 of 224 (26.3%) in the chemotherapy group. However, no data on ovariectomy or ovarian radiotherapy were reported, so the proportion of all patients with induced OFS is unknown.

The aim of this international RCT was to investigate the clinical benefit of supplementing the standard clinicopathological criteria with MammaPrint when selecting patients for adjuvant chemotherapy. The outcomes recorded were “overall survival”, “disease-free survival” (including ductal carcinoma in situ [DCIS]) and 2 outcomes for distant recurrence-free survival.

#### 4.2.1.2 Oncotype DX

The study **RxPONDER** [16] is an RCT in an enrichment design, in which the biomarker Oncotype DX is investigated. This international prospective study included 5083 predominantly postmenopausal patients. All patients had hormone receptor-positive, HER2-negative breast cancer without distant metastases with involvement of 1–3 lymph nodes. Premenopause was defined as less than 6 months since the last menstruation, and postmenopause as previous bilateral ovariectomy or more than 12 months since the last menstruation and no previous hysterectomy. If these definitions did not apply, patients were categorized as premenopausal if they were 50 years of age or younger (≤ 50 years) and as postmenopausal if they were older than 50 years (> 50 years).

A tumour sample of the invasive primary tumour was used to determine the recurrence score (RS) according to Oncotype DX (range: 0 to 100). Patients with an RS > 25 were excluded from RxPONDER and it was recommended that these patients be treated with adjuvant chemoendocrine therapy. Patients with an RS of 0 to 25 were randomized to endocrine therapy or chemoendocrine therapy. Stratification was carried out according to the following factors: RS (0 to 13 or 14 to 25), menopausal status (premenopausal or postmenopausal), and type of axillary surgery (sentinel lymph node biopsy or axillary lymph node dissection).

In the chemoendocrine group, the preferred regimen for premenopausal patients was an anthracycline and a taxane (54%) and for postmenopausal patients a taxane plus cyclophosphamide (57%). Within 12 months of randomization, OFS was induced in 12.7% of the premenopausal patients (6.3% in the chemoendocrine group and 19.0% in the endocrine group). In the endocrine group, OFS was induced in 36.6% of the 101 patients who were ≤ 40 years of age. It is not specified how this could be done.

The primary objective of the study was to assess the effect of chemotherapy on disease-free survival. In addition, it should be examined whether the relative benefit of chemotherapy increases with a higher RS (for patients with an RS of up to 25). It was examined whether the difference in disease-free survival of patients treated with chemotherapy compared to patients without chemotherapy is directly related to the extent of continuous RS.

RxPONDER was identified in Rapid Report D19-01 as an ongoing RCT with a planned follow-up period of 15 years after randomization. At the time of reporting in Project D23-01A, the 5-year interim results for the outcomes “overall survival”, “invasive disease-free survival”, and “distant recurrence-free survival” were available.

### 4.2.2 Premenopausal breast cancer patients without lymph node involvement (Project D23-01B)

#### 4.2.2.1 MammaPrint

The characteristics of the **MINDACT** [11] study are described in detail in Section 4.2.1.1. The analysis of the C-high/G-low population from MINDACT addresses the question of whether these patients can forego chemotherapy despite their high clinical risk by using the MammaPrint biomarker. This application of the biomarker is the focus of the following presentation because this application is considered to be the main objective of the application of breast cancer biomarkers in the context of this evaluation.

The analysis of the C-low/G-high population from MINDACT addresses the question of whether these patients should be treated with chemotherapy using the MammaPrint biomarker, even though their clinical risk was assessed as low. As explained above, this application of the biomarker is not the focus of the following presentation. The results show no superiority of chemotherapy in this population, are presented in Section A3.3.2 and are not considered further below.

#### 4.2.2.2 Oncotype DX

The characteristics of the study **TAILORx** [23] have already been described in detail in Addendum D18-01 and are supplemented here with further information.

The study TAILORx is an RCT in an enrichment design, in which the biomarker Oncotype DX is investigated. In this international prospective study, 10,273 predominantly postmenopausal patients with primary hormone receptor-positive, HER2/neu-negative breast cancer and no lymph node involvement were included in one of 4 study arms, depending on their genomic recurrence risk. 1629 patients with a low RS of 0 to 10 were assigned to endocrine therapy. 1737 patients with a high RS of ≥ 26 were assigned to chemoendocrine therapy. 6907 patients with a mean RS of 11 to 25 were randomized and received either endocrine therapy or chemoendocrine therapy. According to the study protocol [24], patients could receive one of 9 chemotherapy regimens with a duration of 8 to 24 weeks. The most common chemotherapy regimens were docetaxel-cyclophosphamide (56%) and anthracycline-containing regimens (36%). The endocrine therapy regimes in postmenopausal patients most frequently included an aromatase inhibitor (91%). In premenopausal patients, the endocrine treatment regimens most frequently comprised either tamoxifen alone or tamoxifen followed by an aromatase inhibitor (78%). OFS was induced in 13% of premenopausal patients. OFS could be induced by surgery, radiotherapy or the administration of gonadotropin-releasing hormone (GnRH) analogues.

Postmenopausal patients were defined according to the following criteria:

- Patients aged 60 years and older
- Patients aged 45 to 59 years with spontaneous cessation of menstruation for at least 12 months prior to registration
- Patients aged 45 to 59 years with absence of menstruation for less than 12 months prior to enrolment AND a follicle stimulating hormone (FSH) value in the postmenopausal range (or > 34.4 IU/L if no institutionally defined range is available)
- Patients aged 45 to 59 years on hormone replacement therapy who have discontinued hormone replacement therapy at the time of diagnosis of breast cancer and have an FSH level in the postmenopausal range according to institutional or laboratory standards (or 34.4 IU/L if no institutionally defined range is available)
- Patients with previous bilateral ovariectomy
- Patients younger than 60 years of age who have had a previous hysterectomy (without bilateral ovariectomy) AND have an FSH level in the postmenopausal range (or > 34.4 IU/L if no institutionally defined range is available)

All patients who do not meet the stated criteria for postmenopausal patients were defined as premenopausal or perimenopausal patients.

The aim of the TAILORx study is to show that endocrine therapy is not inferior to chemoendocrine therapy in patients with an RS of 11 to 25 (non-inferiority question). This should answer the question of whether these patients can forego chemotherapy. The study protocol also specifies that the prognostic and predictive accuracy of clinical risk as measured by Adjuvant! will be compared to that of RS, and that the study will determine whether the classic pathology information included in Adjuvant! significantly complements RS. It plans to do this by comparing the results predicted by Adjuvant! using information such as tumour size, hormone receptor status and histological grade with those of Oncotype DX.

Results on the outcomes of overall survival, invasive disease-free survival, distant recurrence-free survival, recurrence-free survival, health-related quality of life, cognitive function, fatigue and endocrine symptoms are reported. The follow-up period is 12 years (median 11.0 years) for the randomized population with an RS of 11 to 25.

### 4.2.3 Study-specific determination of the clinical risk of recurrence (Project D23-01A and Project D23-01B)

**MINDACT study**

In MINDACT, clinical risk was determined using a modified version of Adjuvant! (version 8.0). This included information on hormone receptor status, HER2/neu status, tumour grade and size and the number of affected lymph nodes. Depending on the nodal status, a low clinical

risk is defined in MINDACT as follows (supplemented by the classification G1 to G3 or T1 and T2 from [30]):

- Patients with involvement of 1–3 lymph nodes:
  - Low histological grading (G1) and tumour size up to 2 cm (T1)
- Patients without lymph node involvement:
  - Low histological grading (G1) and tumour size up to 3 cm (T2)
  - Intermediate histological grading (G2) and tumour size up to 2 cm (T1)
  - Low histological grading (G3) and tumour size up to 1 cm (T1)

All cases other than those described are considered high clinical risk [11].

**RxPONDER study**

In the RxPONDER study, clinical risk was determined using a modified version of Adjuvant! Online. A low clinical risk was defined as tumour size < 2 cm AND histological grading G1. All cases other are considered high clinical risk [16].

**TAILORx study**

In TAILORx study, clinical risk was determined using the algorithm of Adjuvant! (version 8.0). A low clinical risk was defined analogously to MINDACT as follows (supplemented by the classification G1 to G3 or T1 and T2 from [30]): low histological grading (G1) and tumour size up to 3 cm (T2), intermediate histological grading (G2) and tumour size up to 2 cm (T1) or high histological grading (G3) and tumour size up to 1 cm (T1). All cases other are considered high clinical risk [22].

## 4.3 Overview of patient-relevant outcomes

### 4.3.1 Breast cancer patients with involvement of 1–3 lymph nodes (Project D23-01A)

Data on patient-relevant outcomes were extracted from 2 studies (MINDACT, RxPONDER). Table 3 presents an overview of the data available on patient-relevant outcomes from the included studies. Two studies reported usable results for the outcomes of overall survival and disease-free survival. Data on the outcomes adverse event (AE) and serious adverse event (SAE) were reported in 1 study, but were not usable for the benefit assessment. In 1 study, no data were reported on the outcomes of anxiety, general health status, fatigue and cognitive problems, although the survey was specified in the study methodology [17]. Since no usable results were available for these 3 outcomes anyway, their content was not assessed and they were not assigned to an outcome category.

The MINDACT and RxPONDER studies reported further partial outcomes such as (distant) recurrence-free survival, which are partially included in the combined outcome of disease-free survival. Such partial outcomes are not presented in addition to the patient-relevant outcomes of overall survival and disease-free survival in the benefit assessment of Project D23-01A. The definitions of the patient-relevant outcomes are presented in Section 4.5.

Table 3: Project D23-01A – Patients with involvement of 1–3 lymph nodes: Matrix of patient-relevant outcomes

| Study | Outcomes | | | | |
|---|---|---|---|---|---|
| | Mortality and morbidity | | QoL | Side effects | |
| | Overall survival | Disease-free survival | Health-related quality of life | AEs | SAEs |
| MINDACT | ● | ● | – | –[a] | –[a] |
| RxPONDER | ● | ● | – | ○[b] | ○[b] |

●: Data were reported and usable.
○: Data were reported but unusable for the benefit assessment.
-: No data were reported (no further information)/The outcome was not surveyed.
a. According to the manufacturer, no AEs and SAEs were recorded.
b. AEs and SAEs were reported as treatment-related and not as treatment-emergent.
AE: adverse event; QoL: health-related quality of life; SAE: serious adverse event

### 4.3.2 Premenopausal breast cancer patients without lymph node involvement (Project D23-01B)

Data on patient-relevant outcomes were extracted from 2 studies (MINDACT, TAILORx). Table 4 presents an overview of the data available on patient-relevant outcomes from the included studies. Two studies reported usable results for the outcomes of overall survival and disease-free survival. In 1 study, data on the outcomes of health-related quality of life, cognitive functioning, fatigue and endocrine symptoms were reported, but these were not usable for the benefit assessment (see Section 4.5.2.2.4). Since less than 70% of patients were included in the analysis of the outcomes of cognitive functioning, fatigue and endocrine symptoms and therefore no usable results were available anyway, their content was not assessed and assigned to an outcome category. No data were reported on the outcomes of AE and SAE in any of the studies.

The MINDACT and TAILORx studies reported further partial outcomes such as (distant) recurrence-free survival, which are partially included in the combined outcome of disease-free survival. Such partial outcomes are not presented in addition to the patient-relevant outcomes of overall survival and disease-free survival in the benefit assessment of Project D23-01B. The definitions of the patient-relevant outcomes are presented in Section 4.5.

Table 4: Project D23-01B – Premenopausal patients without lymph node involvement: Matrix of patient-relevant outcomes

| Study | Outcomes | | | | |
|---|---|---|---|---|---|
| | Mortality and morbidity | | QoL | Side effects | |
| | Overall survival | Disease-free survival | Health-related quality of life | AEs | SAEs |
| MINDACT | ● | ● | – | –[a] | –[a] |
| TAILORx | ● | ● | ○[b] | – | –[c] |

●: Data were reported and usable.
○: Data were reported but unusable for the benefit assessment.
-: No data were reported (no further information)/The outcome was not surveyed.
a. According to the manufacturer, no AEs and SAEs were recorded.
b. No analyses according to menopausal status.
c. SAEs were recorded in the study, but only limited to previously unknown events as part of the reporting obligation to the competent authorities. These outcomes were not systematically analysed.
AE: adverse event; QoL: health-related quality of life; SAE: serious adverse event

## 4.4 Assessment of the risk of bias of the results

### 4.4.1 Breast cancer patients with involvement of 1–3 lymph nodes (Project D23-01A)

In the MINDACT study, the population with the discordant risk classification of C-high/G-low has a high risk of bias across all outcomes. The significant proportion of protocol violators leads to a potential distortion. Of 1497 node-negative and node-positive (involvement of 1 to ≥ 4 lymph nodes) C-high/G-low patients, 749 were assigned chemoendocrine therapy, of which 128 did not receive chemotherapy (17.1%). 748 patients were allocated endocrine therapy, 85 of whom received chemotherapy (11.4%) [11]. There were no correspondingly differentiated results available for the patients with involvement of 1–3 lymph nodes, who are relevant for this assessment. However, it is assumed that the high proportion of protocol violators is also present in this subpopulation. The direction of bias in MINDACT with regard to the non-inferiority question in the C-high/G-low population is estimated to be that an intention-to-treat (ITT) analysis favours the aim of the study to show non-inferiority of endocrine therapy compared to chemoendocrine therapy.

In the C-low/G-high population of the MINDACT study, only 2.5% of patients had involvement of 1–3 lymph nodes (n = 15) [9], so this population cannot be used for Project D23-01A.

In the present report, the risk of bias across outcomes was rated as high for the POLARIX study. The significant proportion of protocol violators leads to a potential distortion. Of 2487 patients who were assigned chemoendocrine therapy, 402 (16.2%) refused this treatment. Of 2497 patients who were assigned endocrine therapy, 144 (5.8%) refused this treatment [16]. The direction of bias in RxPONDER with regard to the non-inferiority question in this population is estimated to be that an ITT analysis favours the aim of the study to show non-inferiority of

endocrine therapy compared to chemoendocrine therapy. The outcome-specific risk of bias for the results on the outcomes of overall survival and disease-free survival was accordingly assessed as high for RxPONDER.

#### 4.4.2 Premenopausal breast cancer patients without lymph node involvement (Project D23-01B)

In the MINDACT study, for the population with the discordant risk classification of C-high/G-low, the risk of bias is high at study level and thus for all patient-relevant outcomes reported. There were no correspondingly differentiated results available for the premenopausal patients without lymph node involvement, who are relevant for this assessment. However, it is assumed that these assessments of the risk of bias from Final Report D14-01 can be transferred to the relevant subpopulation.

In Addendum D18-01, the risk of bias across outcomes was rated as high for the TAILORx study. The main reason for the high risk of bias is the considerable proportion of protocol violators due to lack of adherence to the allocated treatment: While 185 (5.4%) of the 3399 patients allocated to endocrine therapy underwent chemotherapy, 608 (18.4%) of the 3312 patients allocated to chemoendocrine therapy forewent chemotherapy. The direction of bias in TAILORx with regard to the non-inferiority question in this population is estimated to be that an ITT analysis favours the aim of the study to show non-inferiority of endocrine therapy compared to chemoendocrine therapy. There were no correspondingly differentiated results available for the premenopausal patients without lymph node involvement, who are relevant for this assessment. However, it was assumed that these assessments of the risk of bias from Addendum D18-01 can be transferred to the relevant subpopulation.

### 4.5 Results on patient-relevant outcomes

#### 4.5.1 Breast cancer patients with involvement of 1–3 lymph nodes (Project D23-01A)

The main results of Project D23-01A on the biomarkers MammaPrint and Oncotype DX are summarized in Table 5 below and described in detail in the following sections.

Table 5: Project D23-01A – Patients with involvement of 1–3 lymph nodes: Overview of the results of the ITT analyses for all patient-relevant outcomes, separated by biomarker for all subgroups

| **Patient-relevant outcome** / **Population/ Subgroup** | **Biomarker (population) chemoendocrine therapy vs. endocrine therapy** / **Time point** | |
|---|---|---|
| | **MammaPrint (C-high/G-low)** | **Oncotype DX (RS 0–25)** |
| **Overall survival** | | |
| Total population | < 8 years[a]: | 5 years: |
| | HR: 1.05; 95%-CI: [0.56; 1.99]; p = 0.864[b] | OR: 0.92; 95%-CI: [0.74; 1.15]; p = 0.531[c] |
| **Disease-free survival** | | |
| Total population | < 8 years[a]: | 5 years: |
| | HR: 1.06; 95%-CI: [0.73; 1.53]; p = 0.784[b] | – |
| | RD:2.50; 95% CI: [-3.49; 8.49] | – |
| | | Interaction[d]: p = 0.008 |
| Premenopausal | NR | HR: 1.67; 95% CI: [1.20; 2.33]; p = 0.002[b] |
| | NR | RD:4.93; 95% CI: [1.92; 7.94] |
| Postmenopausal | NR | HR: 0.98; 95% CI: [0.79; 1.22]; p = 0.89[b] |
| | NR | RD:-0.6; 95% CI: [ND] |
| | Interaction[e]: p = 0.578 | Interaction[e]: p = 0.006 |
| ≤ 50 years | – | HR: 1.79; 95% CI: [1.23; 2.56]; p = 0.002[b] |
| | – | RD:5.84; 95% CI: [2.54; 9.14] |
| > 50 years | – | HR: 0.98; 95% CI: [0.79; 1.22]; p = 0.876[b] |
| | – | RD:-0.56; 95% CI: [-2.56; 1.43] |

–: Data not used for the assessment.
a. See Section 4.5.1.1.1 for the selection of the time point. At the 10-year analysis date, there are no relevant deviations from the results after 8 years.
b. Log-rank test.
c. Unconditional exact test (CSZ method according to Andrés [31]).
d. With regard to the effect modifier “menopausal status”.
e. With regard to the effect modifier “age”.

C-high: high clinical risk; CI: confidence interval; G-low: low genomic risk; HR: hazard ratio; ITT: intention to treat; ND: no data; NR: not reported; Oncotype DX: Oncotype DX Breast Recurrence Score; OR: odds ratio; RD: risk difference; RS: recurrence score; vs.: versus

#### 4.5.1.1 MammaPrint

Final Report D14-01 already presented the definitions of the outcomes analysed in the MINDACT study based on the publication Cardoso 2016 [11]. In Table 6 below, the presentation is limited to the patient-relevant outcomes defined in the report plan (Section A2.1.3 of the full report):

Table 6: Definitions of the outcomes evaluated in MINDACT

| Outcomes | Definition of the outcome |
|---|---|
| Overall survival | Time interval from randomization to the occurrence of death (any cause) |
| Disease-free survival (DFS-DCIS)[a] | Time to first progression of disease (locoregional recurrence and distant recurrence, ipsilateral or contralateral invasive breast cancer or ductal carcinoma in situ and second invasive primary carcinoma [not related to the breast] or death from any cause [including breast cancer-related death and death from unknown or other causes]) |
| a. Mammograms were performed annually, other imaging procedures were only used if clinically indicated. The physical examinations were carried out every 3 months within the first 2 years, and then annually and thus at longer intervals than specified in the usual recommendations for follow-up care of early breast cancer [30]. This may potentially lead to a delayed diagnosis of a recurrence and therefore does not call into question the patient relevance of this outcome.<br>DCIS: ductal carcinoma in situ; DFS: disease-free survival | |

The 5-year interim results of MINDACT from Cardoso 2016 on overall survival and disease-free survival in patients with involvement of 0–3 lymph nodes were additionally presented in Final Report D14-01 with the conclusion that these did not indicate a benefit of a biomarker-based therapy decision using the MammaPrint test.

In the rapid report D19-01, only the 5-year data from Cardoso 2016 were available for MINDACT; analyses with a longer follow-up period were not identified in Rapid Report D19-01.

#### 4.5.1.1.1 Procedure for assessing the results of the MINDACT study

In the meantime, results of the MINDACT study for patients with involvement of 1–3 lymph nodes have been published on the patient-relevant outcomes of overall survival and disease-free survival after 8 years [9]. The median follow-up duration is 8.7 years, which is almost equivalent to the inclusion criterion of a follow-up duration of 10 years. Following the scientific discussion on the preliminary report, Agendia NV, the manufacturer of MammaPrint, provided 10-year data from MINDACT, among other things. No hazard ratios were provided. The information on hazard ratios is particularly relevant for the benefit assessment when considering the outcome "overall survival". Furthermore, these 10-year data are based on a small number of patients who are at risk at this time (Table 33 and Table 35 of the full report), which makes precise estimates difficult. Against this background, the 8-year data, which were collected sufficiently close to the targeted 10-year follow-up, are primarily used for the current benefit assessment of the biomarker-based MammaPrint test for deciding for or against adjuvant systemic chemotherapy in Project D23-01A. The 10-year data are checked for relevant deviations from the results after 8 years.

In the present benefit assessment, the following research question in the MINDACT study is considered using the C-high/G-low population: Does omitting chemotherapy (in deviation from the clinical-pathological assessment) result in at most an irrelevant disadvantage for

disease-free survival in patients identified by the biomarker? This research question is a non-inferiority question. For the 8-year follow-up period for the outcome of disease-free survival, the present benefit assessment for MINDACT results in an adjusted non-inferiority threshold of 2.4 percentage points. In addition, for data at 10 years, a relevant non-inferiority margin of 3 percentage points is applied.

There are no results for premenopausal or postmenopausal patients or for patients in perimenopause. However, results are available for patients aged ≤ 50 years and > 50 years.

#### 4.5.1.1.2 Results on the outcome of overall survival

For the outcome of overall survival, data for the biomarker MammaPrint are available for patients with primary hormone receptor-positive, HER2/neu-negative breast cancer and involvement of 1–3 lymph nodes from 1 study (MINDACT) with moderate qualitative certainty of results after 8 years and after 10 years.

In the population of patients with a high clinical risk and a low genomic risk (C-high/G-low), the Kaplan-Meier estimates show an overall survival of 95.5% in the chemoendocrine therapy group after 8 years (95% confidence interval [CI]: [92.4; 97.4]) and in the endocrine therapy group an overall survival of 94.9% (95% CI: [91.7; 96.9]). There was no statistically significant difference in the hazard ratio (HR) between the treatment groups (HR: 1.05; 95% CI: [0.56; 1.99]; p = 0.864) (Table 33 of the full report).

At the 10-year analysis date, there are no relevant deviations from the results after 8 years with regard to the log-rank test. There are no 10-year HR results available.

The interaction test between patients ≤ 50 years and > 50 years for the outcome of overall survival after 8 years is not statistically significant, which is why the subgroup results (categorized according to age) are not interpreted. These results are only presented as a supplement, in line with the approach in Project D23-01B (Table 33 of the full report). For the outcome of overall survival after 10 years, results are only available for the total population.

#### 4.5.1.1.3 Results on the outcome of disease-free survival

For the outcome of disease-free survival, data for the biomarker MammaPrint are available for patients with primary hormone receptor-positive, HER2/neu-negative breast cancer and involvement of 1–3 lymph nodes from 1 study (MINDACT) with moderate qualitative certainty of results after 8 years and after 10 years.

There was no statistically significant difference in the HR between the treatment groups in the C-high/G-low population after 8 years (HR: 1.06; 95% CI: [0.73; 1.53]; p = 0.784). The Kaplan-Meier estimates show a disease-free survival of 85.3% (95% CI: [80.6; 88.9]) in the chemoendocrine therapy group and a disease-free survival of 82.8% (95% CI: [78.0; 86.6]) in

the endocrine therapy group. The risk difference is 2.50 percentage points (95% CI: [-3.49; 8.49]). If the risk difference is based on a non-inferiority threshold of 2.4 percentage points adjusted to the observation period of 8 years, it cannot be ruled out that the true difference for the C-high/G-low population is more than 2.4 percentage points. The upper 95% CI limit of 8.49 percentage points and even the point estimate of 2.50 percentage points is greater than the non-inferiority threshold of 2.4 percentage points. Therefore, non-inferiority of endocrine therapy compared to chemoendocrine therapy is not shown for the C-high/G-low population (Table 35 of the full report).

At the 10-year analysis date, there are no relevant deviations from the results after 8 years with regard to the upper 95% CI limit.

The interaction test between patients ≤ 50 years and > 50 years for the outcome of disease-free survival after 8 years is not statistically significant, which is why the subgroup results (categorized according to age) are not interpreted. These results are only presented as a supplement, in line with the approach in Project D23-01B (Table 35 of the full report). For the outcome of disease-free survival after 10 years, results are only available for the total population.

#### 4.5.1.2 Oncotype DX

##### 4.5.1.2.1 Procedure for assessing the results of the RxPONDER study

Kalinsky 2021 [16] is now the 1st publication on the RxPONDER study to report results on the patient-relevant outcomes of overall survival and disease-free survival. The median follow-up period was 5.3 years. According to the report plan, in the event that no data are available for a follow-up period of approx. 10 years for these outcomes, interim analyses of ongoing RCTs of at least 5 years are also presented in order to estimate the expected results for the relevant 10-year period (see Section A2.1.5 of the full report). The 5-year data from RxPONDER will thus be used for the current benefit assessment of the biomarker-based test Oncotype DX to decide for or against adjuvant systemic chemotherapy in Project D23-01A.

Table 7: Definitions of the outcomes evaluated in RxPONDER

| Outcomes | Definition of the outcome |
|---|---|
| Overall survival | Time interval from randomization to the occurrence of death from any cause |
| Disease-free survival (iDFS)[a] | Time interval from randomization to first occurrence of invasive recurrence (local, regional or distant recurrence), new invasive primary carcinoma (breast cancer or other tumour) or death from any cause |
| a. Mammograms were performed annually until the time of invasive recurrence, progression, or relapse. Physical examinations were performed every 3 months in year 1, every 6 months in years 2 to 5 and then annually until 15 years after randomization or after the time of invasive recurrence, progression or relapse. The time windows for physical examinations and mammograms have been extended where necessary, taking into account the COVID-19 pandemic. The examinations were carried out at longer intervals than specified in the usual recommendations for follow-up care of early breast cancer [30]. This may potentially lead to a delayed diagnosis of a recurrence and therefore does not call into question the patient relevance of this outcome.<br>COVID-19: coronavirus disease 2019, iDFS: invasive disease-free survival | |

For the 5-year follow-up period for the outcome of disease-free survival, the present benefit assessment for RxPONDER results in an adjusted non-inferiority threshold of 1.5 percentage points.

#### 4.5.1.2.2 Results on the outcome of overall survival

For the outcome of overall survival, data for the biomarker Oncotype DX are available for patients with primary hormone receptor-positive, HER2/neu-negative breast cancer and involvement of 1–3 lymph nodes from 1 study (RxPONDER) with moderate qualitative certainty of results after 5 years.

In all patients with an RS of 0 to 25, overall survival after 5 years was 93.5% in the chemoendocrine therapy group and 93.0% in the endocrine therapy group. There was no statistically significant difference in the odds ratio (OR) between the treatment groups (OR: 0.92; 95% CI: [0.74; 1.15]; p = 0.531) (Table 34 of the full report).

Data separated by menopausal status or age are not available for this outcome.

#### 4.5.1.2.3 Results on the outcome of disease-free survival

For the outcome of disease-free survival, data for the biomarker Oncotype DX are available for patients with primary hormone receptor-positive, HER2/neu-negative breast cancer and involvement of 1–3 lymph nodes from 1 study (RxPONDER) with moderate qualitative certainty of results after 5 years. Data are available on the total population and on subgroups separately according to the effect modifier “menopausal status” and age.

In the overall population of patients, there was no statistically significant difference between the treatment groups after 5 years for the outcome of disease-free survival in the ITT evaluation in the HR (HR: 1.16; 95% CI: [0.97; 1.39]; p = 0.10).

However, the per-protocol (PP) analysis shows a statistically significant difference in favour of chemoendocrine therapy (HR: 1.25; 95% CI: [1.03; 1.52]; p = 0.024). The PP analysis is an analysis in which the principle of randomization is violated and is therefore not a reliable basis for assessing the effect. However, it points out that the result of the ITT analysis could be influenced by the potential bias towards the null effect due to protocol violations (which is not present in the PP evaluation).

The interaction tests for the subgroups according to menopausal status (p = 0.008) and age (p = 0.006) were statistically significant in the ITT analyses (Table 36 of the full report).

**Premenopausal patients or patients ≤ 50 years of age**

After 5 years, the ITT analysis of premenopausal patients showed a statistically significant difference in favour of chemoendocrine therapy (HR: 1.67; 95% CI: [1.20; 2.33]; p = 0.002). A statistically significant difference in favour of chemoendocrine therapy was also observed in patients aged ≤ 50 years (HR 1.79; 95% CI: [1.23; 2.56]; p = 0.002) (Table 36 of the full report).

The Kaplan-Meier estimates for disease-free survival after 5 years in premenopausal patients are 93.9% (standard error [SE]: 0.9) in the chemoendocrine therapy group and 89.0% (SE: 1.2) in the endocrine therapy group. The patients ≤ 50 years show similar results: a disease-free survival of 94.1% (SE: 1.0) in the chemoendocrine therapy group and a disease-free survival of 88.2% (SE: 1.3) in the endocrine therapy group. The risk differences estimated from this result in 4.93 percentage points (95% CI: [1.92; 7.94]) for premenopausal patients and 5.84 percentage points (95% CI: [2.54; 9.14]) for patients ≤ 50 years in the ITT analysis (Table 36 of the full report).

If the risk difference is based on a non-inferiority threshold of 1.5 percentage points adjusted to the observation period of 5 years, it cannot be ruled out that the true difference for the subgroup of premenopausal patients < 50 years of age is more than 1.5 percentage points. The upper 95% CI limits of 7.94 percentage points (premenopausal patients) and 9.14 percentage points (patients ≤ 50 years) and even the respective point estimates are each greater than the non-inferiority threshold of 1.5 percentage points. Non-inferiority of endocrine therapy compared to chemoendocrine therapy has thus not been demonstrated for premenopausal patients and patients ≤ 50 years of age.

**Postmenopausal patients > 50 years of age**

The ITT analysis of postmenopausal patients showed no statistically significant difference between the therapy groups in HR (HR: 0.98; 95% CI: [0.79; 1.22]; p = 0.89). This statistically

non-significant difference in HR is also present in an ITT analysis for patients > 50 years (HR: 0.98; 95% CI: [0.79; 1.22]; p = 0.876) and is also evident in the corresponding PP analysis for postmenopausal patients (HR: 1.03; 95% CI: [0.82; 1.30]; p = 0.81).

The Kaplan-Meier estimates for disease-free survival after 5 years in postmenopausal patients are 91.3% in the chemoendocrine therapy group and 91.9% in the endocrine therapy group. In Figure 2 of the Kalinsky 2021 publication [16], the group of authors gives Kaplan-Meier point estimates without confidence intervals (or SE) in the ITT analysis. Based on the data in Kalinsky 2021 in Table 2 (extended results on disease-free survival), it would theoretically be possible to calculate the missing confidence intervals. However, the data in Table 2 for the postmenopausal patients do not match the results in Figure 2b and were not plausible for other reasons. An author query to clarify the accuracy of the results remained unanswered. Non-inferiority for postmenopausal patients could not be assessed as there was no confidence interval for the risk difference. For this reason, only patients > 50 years of age are considered below.

The Kaplan-Meier estimates for disease-free survival after 5 years in patients > 50 years of age are 91.5% (SE: 0.7) in the chemoendocrine therapy group and 92.0% (SE: 0.7) in the endocrine therapy group (Table 36 of the full report).

The risk difference of the ITT analysis of patients > 50 years results in -0.56 percentage points (95% CI: [-2.56; 1.43]) (Table 36 of the full report). Since the upper 95% CI limit of 1.43 percentage points is smaller than the non-inferiority threshold of 1.5 percentage points, the non-inferiority of endocrine therapy compared to chemoendocrine therapy is shown for patients > 50 years of age.

### 4.5.2 Premenopausal breast cancer patients without lymph node involvement (Project D23-01B)

The main results of Project D23-01B on the biomarkers MammaPrint and Oncotype DX are summarized in Table 8 below and described in detail in the following sections.

Table 8: Project D23-01B – Premenopausal patients without lymph node involvement: Overview of the ITT analysis results for all patient-relevant outcomes, separated by biomarker

| **Patient-relevant outcome**<br>**Population** | **Biomarker (population)**<br>**chemoendocrine therapy vs. endocrine therapy**<br>**Time point** | |
|---|---|---|
| | **MammaPrint (C-high/G-low)** | **Oncotype DX (RS 11–25)** |
| **Overall survival** | | |
| ≤ 50 years | 8 years:<br>OR: 26.74; 95% CI: [1.56; 459.30]; p < 0,001[a] | 10 years[b]:<br>RR: 1.02; 95% CI: [0.997; 1.04]; p = ND |
| **Disease-free survival** | | |
| Premenopausal | NC | 9 years[b]:<br>HR: 1.36; 95% CI: [1.06; 1.75]; p = 0.016[c] |
| | NC | RD: ND[d] |
| ≤ 50 years | 8 years:<br>HR: 2.04; 95% CI: [1.03; 4.04]; p = 0.040[e]<br>RD:5.60; 95% CI: [-3.74; 14.94] | 9 years[b]:<br>HR: 1.51; 95% CI: [1.17; 1.96]; p = 0.002[c]<br>10 years[b]:<br>RD:5.6; 95% CI: [2.24; 8.96] |

a. Unconditional exact test (CSZ method according to Andrés [31]).
b. See Section 4.5.2.2.1 for the selection of the time point. At the 12-year analysis date, there are no relevant deviations.
c. Institute's calculation; asymptotic.
d. No data stratified by menopausal status are available either after 9 years or after 10 years.
e. Log-rank test.

C-high: high clinical risk; CI: confidence interval; G-low: low genomic risk; HR: hazard ratio; ITT: intention to treat; ND: no data; NR: not reported; Oncotype DX: Oncotype DX Breast Recurrence Score; OR: odds ratio; RD: risk difference; RR: recurrence score

### 4.5.2.1 MammaPrint

The 5-year interim results for patients with involvement of 0–3 lymph nodes from the reports D14-01, D18-01 and D19-01 are described in Section 4.5.1.1.

#### 4.5.2.1.1 Procedure for assessing the results of the MINDACT study

For the first time, results are available for patients without lymph node involvement with a median follow-up period of 8.7 years [9]. These 8-year-data from MINDACT will be used for the current benefit assessment of the biomarker-based test MammaPrint to decide for or against adjuvant systemic chemotherapy in Project D23-01B.

In the present benefit assessment, the following research question in the MINDACT study is considered using the C-high/G-low population: Does omitting chemotherapy (in deviation from the clinical-pathological assessment) result in at most an irrelevant disadvantage for disease-free survival in patients identified by the biomarker? This research question is a non-

inferiority question. For the 8-year follow-up period for the outcome of disease-free survival, the present benefit assessment for MINDACT results in an adjusted non-inferiority threshold of 2.4 percentage points.

In accordance with the commission, only the analysis of patients ≤ 50 years of age is considered below. For the sake of completeness , the subgroup of patients > 50 years of age is also presented in Section A3.3.2 of the full report.

#### 4.5.2.1.2 Results on the outcome of overall survival

For the outcome of overall survival, data for the biomarker MammaPrint are available for patients aged ≤ 50 years and > 50 years with primary hormone receptor-positive, HER2/neu-negative breast cancer without lymph node involvement from 1 study (MINDACT) with moderate qualitative certainty of results after 8 years.

In the C-high/G-low population of patients ≤ 50 years of age, the Kaplan-Meier estimates show an overall survival of 100,0% and in the endocrine therapy group an overall survival of 91.1% (95% CI: [83.5; 95.3]). In the OR, a statistically significant difference in favour of chemoendocrine therapy was observed (OR: 26.74; 95% CI: [1.56; 459.30]; $p < 0.001$) (Table 38 of the full report).

#### 4.5.2.1.3 Results on the outcome of disease-free survival

For the outcome of disease-free survival, data for the biomarker MammaPrint are available for patients aged ≤ 50 years and > 50 years with primary hormone receptor-positive, HER2/neu-negative breast cancer without lymph node involvement from 1 study (MINDACT) with moderate qualitative certainty of results after 8 years.

In the C-high/G-low population population of patients ≤ 50 years of age, a statistically significant difference in HR was seen after 8 years in favour of the chemoendocrine therapy (HR: 2.04; 95% CI: [1.03; 4.04]; $p = 0.040$). The Kaplan-Meier estimates show a disease-free survival of 89.6% (95% CI: [82.0; 94.1]) in the chemoendocrine therapy group and a disease-free survival of 84.0% (95% CI: [75.5; 89.7]) in the endocrine therapy group. The risk difference is 5.60 percentage points (95% CI: [-3.74; 14.94]) (Table 40 of the full report). If the risk difference is based on a non-inferiority threshold of 2.4 percentage points adjusted to the observation period of 8 years, it cannot be ruled out that the true difference for the C-high/G-low population is more than 2.4 percentage points. The upper 95% CI limit of 14.94 percentage points and even the point estimate of 5.60 percentage points are greater than the non-inferiority threshold of 2.4 percentage points. Therefore, non-inferiority of endocrine therapy compared to chemoendocrine therapy is not shown for the C-high/G-low population.

#### 4.5.2.2 Oncotype DX

In Final Report D14-01, the publication Sparano 2015 [32] on the TAILORx study was identified, in which 5-year data of the endocrine-treated group of non-randomized patients with an RS of 0 to 10 are presented. These purely prognostic data were not included in Final Report D14-01 due to the short follow-up period.

Addendum D18-01 describes in detail the results of TAILORx based on the publication Sparano 2018 [23] with 9-year data of randomized patients with an RS of 11 to 25 as part of a benefit assessment. For this reason, the results are only outlined in abbreviated form below.

Addendum D18-01 already presented the definitions of the outcomes analysed in TAILORx. In Table 9 below, the presentation is limited to the patient-relevant outcomes defined in the report plan (Section A2.1.3 of the full report):

Table 9: Definitions of the outcomes evaluated in TAILORx

| **Outcomes** | **Definition of the outcome** |
|---|---|
| Overall survival | Time interval from randomization to the occurrence of death (any cause) |
| Disease-free survival (iDFS)[a] | Time interval from randomization to the occurrence of ipsilateral or locoregional recurrence, distant recurrence, contralateral breast cancer, second invasive primary carcinoma (except non-melanoma skin cancer) or death, whichever occurs first. |
| a. Mammograms were performed annually, other imaging procedures were only used if a mammogram could not be performed. The physical examinations were carried out every 3 to 6 months during the first 5 years, and annually thereafter. These intervals are of the same order of magnitude as the usual recommendations for follow-up care of early breast cancer, which confirms the patient relevance of this outcome [30].<br>iDFS: invasive disease-free survival | |

For patients with an RS of 0 to 10 or ≥ 26, assumptions about the effect of chemotherapy were made in Addendum D18-01, as no randomization was carried out for these two RS ranges and therefore no comparative data were available. For the assumption made in Addendum D18-01 regarding patients with an RS of 0 to 10, it was central that a finer breakdown of the RS range 11 to 25 showed no statistically significant difference between the treatment groups in patients ≤ 50 years of age with an RS of 11 to 15 in the outcome of disease-free survival, while a statistically significant difference in favour of chemoendocrine therapy can be seen in the corresponding patients with an RS > 15. This was the basis for the assumption that the difference between the treatment groups would continue to decrease in patients with an RS of 0 to 10. Based on this assumption, not only patients > 50 years of age, but also those ≤ 50 years of age with a RS of 0 to 10 could therefore consider foregoing chemotherapy.

Since there are subgroups of patients > 50 years and ≤ 50 years of age who may consider foregoing chemotherapy, the conclusion was drawn in Addendum D18-01 that all patients

should be tested as soon as there is uncertainty regarding the treatment decision based on clinical factors. Hence, in Addendum D18-01, a hint of the benefit of a biomarker-based decision for or against chemotherapy was determined.

In Rapid Report D19-01, the update to commission D14-01, results from RCTs, prognostic studies and concordance studies were presented. Sparano 2019 identified 1 additional publication to the TAILORx study [22], which investigated whether clinical risk adds prognostic information and information on the benefit of chemotherapy to Oncotype DX. The results gave no reason to call into question the conclusion of the benefit assessment for the Oncotype DX test in Addendum D18-01. The assumptions made in the project at that time were reviewed in Rapid Report D19-01 and did not contradict those of the published further analyses.

#### 4.5.2.2.1 Procedure for assessing the results of the TAILORx study

The only study included in Project D23-01B on the biomarker Oncotype DX, TAILORx, with moderate qualitative certainty of results, was the subject of the latest publication by Sparano et al. [25] published between the end of the submission period for written comments on the preliminary report and the scientific discussion on the preliminary report. Sparano 2024 reports 5-, 10- and 12-year event rates, including for disease-free survival and overall survival of patients with an RS of 11 to 25 stratified by age (≤ 50 years and > 50 years). Furthermore, Kaplan-Meier curves are presented for the 4 study arms from TAILORx (see Section 4.2.2.2), which are not stratified according to age or menopausal status. With reference to the Kaplan-Meier curve of group A (RS 0 to 10 with endocrine therapy alone) for disease-free survival, the event rate of patients ≤ 50 years of age was provided by Exact Sciences Deutschland GmbH, the manufacturer of Oncotype DX. However, according to the manufacturer's specifications, the rate presented is the analysis date after 11 years. The data submitted will be discussed as part of the evaluation of the hearing on the preliminary report 1.0 (see Section A4.3.1 of the full report, RS 0 to 10, TAILORx – 11-year data).

For the present benefit assessment with regard to TAILORx, the 10-year data are used in accordance with the methodology specified in the report plan, among other things with regard to the analysis date, if reported. The relevant non-inferiority threshold of 3 percentage points are applied (see Section A2.1.5 of the full report). Otherwise, the 9-year data are used. The 12-year data are checked for relevant deviations from the results after 10 years.

In accordance with the commission, only the analysis of premenopausal patients ≤ 50 years of age is considered below. For the sake of completeness , the subgroups of postmenopausal patients > 50 years of age are also presented in Section A3.3.2 of the full report.

In addition, subgroup analyses from TAILORx for the outcome of disease-free survival after 9 years stratified according to RS and clinical risk are also presented.

#### 4.5.2.2.2 Results on the outcome of overall survival

In patients ≤ 50 years of age, after 10 years, the Kaplan-Meier estimates show an overall survival rate of 95.9% (standard error: 0.7) in the chemoendocrine therapy group and an overall survival rate of 94.1% (standard error: 0.8) in the endocrine therapy group. There was no statistically significant difference in the relative risk (RR) between the treatment groups (RR: 1.02; 95% CI: [0.997; 1.04]; p = ND) (Table 39 of the full report).

At the 12-year analysis date, there are no relevant deviations from the results after 10 years.

#### 4.5.2.2.3 Results on the outcome of disease-free survival

No data on the hazard ratio for disease-free survival after 10 years is available for patients ≤ 50 years. After 9 years, a statistically significant difference was shown in favour of chemoendocrine therapy in premenopausal patients with an RS of 11 to 25 (HR: 1.36; 95% CI: [1.06; 1.75]; p = 0.016). A statistically significant difference in favour of chemoendocrine therapy was also observed in patients aged ≤ 50 years (HR 1.51; 95% CI: [1.17; 1.96]; p = 0.002). After 10 years, the Kaplan-Meier estimates for patients ≤ 50 years are 87.9% (standard error: 1.1) in the chemoendocrine therapy group and 82.3% (standard error: 1.3) in the endocrine therapy group. The risk difference after 10 years in patients ≤ 50 years is 5.6 percentage points (95% CI: [2.24; 8.96]) (Table 41 of the full report). If the risk difference is based on the relevant non-inferiority margin of 3 percentage points according to the observation period of 10 years, it cannot be ruled out that the true difference is more than 3 percentage points. The upper 95% CI limit of 8.96 percentage points and even the point estimate of 5.6 percentage points is greater than the non-inferiority threshold of 3 percentage points.

At the 12-year analysis date, there are no relevant deviations from the results after 10 years.

Non-inferiority of endocrine therapy compared to chemoendocrine therapy has thus not been demonstrated for patients and patients ≤ 50 years of age.

Non-inferiority for premenopausal patients could not be assessed as no information was available for the calculation of the risk difference.

**Supplementary presentation of subgroup analyses**

In TAILORx, patients with a median RS of 11 to 25 were randomized. In subgroup analyses stratified by the RS, no statistically significant difference is shown between the therapy groups for patients ≤ 50 years with an RS of 11 to 15.

In the presentation of results from Sparano 2019, which also differentiates according to clinical risk, there are no usable results for the subgroup of patients ≤ 50 years with an RS of

11 to 15. The following presentation of results is therefore limited to the subgroups of the RS from 16 to 20 and 21 to 25.

***Recurrence score from 16 to 20***

In the subgroup of patients aged ≤ 50 years with an RS of 16 to 20 and a low clinical risk, the Kaplan-Meier estimates show a disease-free survival of 90.5% in the chemoendocrine therapy group after 9 years (SE: 1.8) and in the endocrine therapy group a disease-free survival of 80.4% (SE: 3.1). The risk difference is 10.10 percentage points (95% CI: [3.14; 17.06]). In the subgroup with a high clinical risk, the chemoendocrine therapy group shows a disease-free survival of 83.7% (SE: 5.8) and the endocrine therapy group shows a disease-free survival of 81.0% (SE: 4.5). The risk difference is 2.70 percentage points (95% CI: [-11.79; 17.19]) (Table 42 of the full report).

Non-inferiority of endocrine therapy compared to chemoendocrine therapy has not been demonstrated for either low or high clinical risk. Apparently, the addition of clinical information cannot improve the prediction of the treatment effect in patients ≤ 50 years with an RS of 16 to 20.

***Recurrence score from 21 to 25***

In the subgroup of patients aged ≤ 50 years with an RS of 21 to 25 and a low clinical risk, the Kaplan-Meier estimates show a disease-free survival of 84,2% (SE: 4.0) in the chemoendocrine therapy group after 9 years and in the endocrine therapy group a disease-free survival of 80.3% (SE: 4.5). The risk difference is 3.90 percentage points (95% CI: [-7.93; 15.73]). In the subgroup with a high clinical risk, the chemoendocrine therapy group shows a disease-free survival of 88.6% (SE: 3.8) and the endocrine therapy group shows a disease-free survival of 73.6% (SE: 5.4). The risk difference is 15.00 percentage points (95% CI: [2.13; 27.87]) (Table 42 of the full report).

Non-inferiority of endocrine therapy compared to chemo-endocrine therapy has not been demonstrated for either low or high clinical risk. Apparently, the addition of clinical information cannot improve the prediction of the treatment effect in patients ≤ 50 years with an RS of 21 to 25.

#### 4.5.2.2.4 Results not usable for the benefit assessment D23-01B

Following an amendment, the TAILORx study was expanded to include a substudy on patient-reported outcomes (PRO [Patient-Reported Outcome] substudy). According to the study protocol [24], those patients who actually received the randomised therapy were to be compared with each other. A PP analysis was therefore carried out as the primary analysis. 734 randomized patients with an RS of 11 to 25 were included in the sub-study, of which 652 patients were included in the primary PP analysis. The patients completed a questionnaire at

the start of the study (before randomization) and at 3, 6, 12, 24, and 36 months after randomization.

The results of scales for health-related quality of life and cognitive functioning are reported in the publication Wagner 2020 [21], and for fatigue (2 scales used) and endocrine symptoms in the publication Garcia 2022 [20]. The reported evaluation of health-related quality of life is not usable because analyses according to menopausal status are missing and were not made available by the authors when requested (see Section A3.1.3.2.4 of the full report). Of the evaluation of cognitive functioning, analyses according to menopausal status (perceived cognitive impairment) are only available for 1 of 4 subscales.

Analyses according to menopausal status are available for the 3 outcomes “perceived cognitive impairment” (1 subscale), “fatigue” (2 scales), and “endocrine symptoms” (1 scale). However, for these 4 scales, the proportion of randomized patients who were not included in the evaluation is greater than 30% in each case; in this respect, the results were not usable and were therefore not included in the conclusion of the benefit assessment in Project D23--01B. The following reasons were given in Garcia 2022 [20] and Wagner 2020 [21] for the missing data for the 3 outcomes: Patient did not receive the PRO questionnaire, refusal, language or disability, and other reasons. In addition, there were cases in which the study centre did not provide a reason.

As results on patient-reported outcomes from TAILORx have been reported for the first time, these were examined for apparently relevant effects despite the lack of usability. Overall, it is noticeable that the changes within the groups can be considered rather small and no trends regarding the treatment difference can be identified over time.

Against the background of the harm from an Oncotype DX-based decision against chemotherapy for premenopausal patients with an RS of 11 to 25 for the outcome “disease-free survival” (see Section 4.5.2.2) already established in Addendum D18-01, these incomplete and inconspicuous data cannot add any information and are therefore not presented in detail in this report.

## 4.6 Overall evaluation of the results

**Assessment of the volume of unpublished data**

For the biomarkers MammaPrint and Oncotype DX, 1 discontinued study (OPTIGEN) was identified. The assessment of the scope of unpublished data in both projects is based on this study. As the trial registry entry shows that the study was discontinued shortly after it began, it is assumed that recruitment was not completed. The trial registry entry itself does not mention any patients being recruited. It is therefore assumed that the OPTIGEN study does not pose a high risk of publication bias. No additional studies with unclear status, no

completed studies without reported results and no further discontinued studies were identified that could be linked to the biomarkers MammaPrint and Oncotype DX in Project D23-01A and Project D23-01B. Consequently, this assessment imposes no consequences for either project and no restrictions for the weighing of benefits versus harm for each biomarker.

### 4.6.1 Breast cancer patients with involvement of 1–3 lymph nodes (Project D23-01A)

#### 4.6.1.1 MammaPrint

**Evidence map**

The following Table 10 shows the evidence map regarding patient-relevant outcomes.

Table 10: Project D23-01A – Patients with involvement of 1–3 lymph nodes: Evidence map regarding patient-relevant outcomes, MammaPrint

| Study Population | Mortality and morbidity | | QoL | Side effects | |
|---|---|---|---|---|---|
| | Overall survival | Disease-free survival | Health-related quality of life | AEs | SAEs |
| MINDACT<br>C-high/G-low Total population | ⇔[a] | ⇔ | – | – | – |

⇔: No hint, indication or proof of benefit of a MammaPrint-based decision for or against adjuvant systemic chemotherapy
-: Data not available or not usable
a. The non-statistically significant result was not tested for non-inferiority.

AE: adverse event; C-high: high clinical risk; G-low: low genomic risk; QoL: health-related quality of life; SAE: serious adverse event

**Weighing of benefits versus harm**

No data have yet been published on the AEs recorded in the study in accordance with the study protocol. According to the authors, data on AEs were not collected in the MINDACT study. This was a missed opportunity for a direct comparison of the damage caused by chemotherapy versus the recurrences avoided. The harm caused by chemotherapy can therefore only be taken into account indirectly by determining the non-inferiority threshold.

For the total population at high clinical risk (see Section 4.2.3) with involvement of 1–3 lymph nodes, there is overall no hint of a benefit of a MammaPrint-based decision for or against adjuvant systemic chemotherapy. This conclusion is based on an assessment of non-inferiority for the outcome “disease-free survival”. Based on the 8-year data, it has not been shown that this biomarker-based test can identify patients who benefit only to a small extent at best from adjuvant systemic chemotherapy. There was no effect modification with regard to age (patients ≤ 50 and > 50 years).

#### 4.6.1.2 Oncotype DX

**Evidence map**

The following Table 11 shows the evidence map regarding patient-relevant outcomes.

Table 11: Project D23-01A – Patients with involvement of 1–3 lymph nodes: Evidence map regarding patient-relevant outcomes, Oncotype DX

| Study<br>Population<br>Subgroup | Mortality and morbidity | | QoL | Side effects | |
|---|---|---|---|---|---|
| | Overall survival | Disease-free survival | Health-related quality of life | AEs | SAEs |
| RxPONDER (RS 0–25) | | | | | |
| Total population | ⇔[a] | x[b] | – | – | – |
| Premenopausal | – | ⇘ | – | – | – |
| Postmenopausal | – | x[c] | – | – | – |
| ≤ 50 years | – | ⇘ | – | – | – |
| > 50 years | – | ⇗ | – | – | – |

⇗: Hint of a benefit of an Oncotype DX-based decision against adjuvant systemic chemotherapy
⇘: Hint of harm from an Oncotype DX-based decision against adjuvant systemic chemotherapy
⇔: No hint, indication or proof of benefit of a Oncotype DX-based decision for or against adjuvant systemic chemotherapy
x: Data reported, but not used to derive the evidence base
-: Data not available or not usable
a. The non-statistically significant result was not tested for non-inferiority.
b. Because of the statistically significant interaction tests, no conclusions are derived about the total population, but separate conclusions are derived for the respective subgroup.
c. As no information on confidence intervals for the risk difference was available, the test for non-inferiority was carried out solely on the basis of the subgroup analysis with regard to age (> 50 years).

AE: adverse event; Oncotype DX: Oncotype DX Breast Recurrence Score; QoL: health-related quality of life; RS: Recurrence Score; SAE: serious adverse event

**Weighing of benefits versus harm**

SAEs were recorded according to the current registry entry in the RxPONDER study using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. However, this survey was limited to AEs that were categorized as treatment-related AEs in the study. The AEs and SAEs in RxPONDER were therefore not systematically collected in full and are thus not usable. This was a missed opportunity for a direct comparison of the damage caused by chemotherapy versus the recurrences avoided. The harm caused by chemotherapy can therefore only be taken into account indirectly by determining the non-inferiority threshold.

For premenopausal patients and patients ≤ 50 years of age with involvement of 1–3 lymph nodes and an RS of 0 to 25, there is overall a hint of harm from an Oncotype DX-based decision against adjuvant systemic chemotherapy. This statement is primarily based on the statistically

significant difference in favour of chemoendocrine therapy for the outcome of disease-free survival after 5 years.

For patients > 50 years of age with involvement of 1–3 lymph nodes and an RS of 0 to 25, there is overall a hint of a benefit of an Oncotype DX-based decision against adjuvant systemic chemotherapy. This conclusion is primarily based on an assessment of non-inferiority for the outcome "disease-free survival" after 5 years. Patients who forgo chemotherapy based on the Oncotype DX test result have at most a slightly increased risk of recurrence or death compared to patients who undergo chemotherapy.

### 4.6.2 Premenopausal breast cancer patients without lymph node involvement (Project D23-01B)

#### 4.6.2.1 MammaPrint

**Evidence map**

The following Table 12 shows the evidence map regarding patient-relevant outcomes.

Table 12: Project D23-01B – Premenopausal patients without lymph node involvement: Evidence map regarding patient-relevant outcomes, MammaPrint

| Study Population | Mortality and morbidity | | QoL | Side effects | |
|---|---|---|---|---|---|
| | Overall survival | Disease-free survival | Health-related quality of life | AEs | SAEs |
| **MINDACT**<br>C-high/G-low<br>≤ 50 years | ↘ | ↘ | – | – | – |

↘: Hint of harm from an MammaPrint-based decision against adjuvant systemic chemotherapy
-: Data not available or not usable

AE: adverse event; C-high: high clinical risk; G-low: low genomic risk; QoL: health-related quality of life; SAE: serious adverse event

**Weighing of benefits versus harm**

No adverse events were recorded in the study in question. The harm caused by chemotherapy can therefore only be taken into account indirectly by determining the non-inferiority threshold.

For patients at high clinical risk (see Section 4.2.3) ≤ 50 years without lymph node involvement, there is overall a hint of harm from a MammaPrint-based decision against adjuvant systemic chemotherapy. This conclusion is based on a statistically significant difference in favour of chemoendocrine therapy for the outcomes of overall survival and disease-free survival.

#### 4.6.2.2 Oncotype DX

**Evidence map**

The following Table 13 shows the evidence map regarding patient-relevant outcomes.

Table 13: Project D23-01B – Premenopausal patients without lymph node involvement: Evidence map regarding patient-relevant outcomes, Oncotype DX

| Study Population | Mortality and morbidity | | QoL | Side effects | |
|---|---|---|---|---|---|
| | Overall survival | Disease-free survival | Health-related quality of life | AEs | SAEs |
| **TAILORx (RS 11–25)** | | | | | |
| Premenopausal | – | ⇘ | – | – | – |
| ≤ 50 years | ⇔[a] | ⇘ | – | – | – |

⇘: Hint of harm from an Oncotype DX-based decision against adjuvant systemic chemotherapy
⇔: No hint, indication or proof of benefit of a Oncotype DX-based decision for or against adjuvant systemic chemotherapy
-: Data not available or not usable
a. The non-statistically significant result was not tested for non-inferiority.

AE: adverse event; Oncotype DX: Oncotype DX Breast Recurrence Score; QoL: health-related quality of life; RS: Recurrence Score; SAE: serious adverse event

**Weighing of benefits versus harm for an RS of 11 to 25**

No adverse events were recorded in the study in question. The harm caused by chemotherapy can therefore only be taken into account indirectly by determining the non-inferiority threshold.

For premenopausal patients and patients ≤ 50 years of age without lymph node involvement and with an RS of 11 to 25, there is overall a hint of harm from an Oncotype DX-based decision against adjuvant systemic chemotherapy. This statement is primarily based on the statistically significant difference in favour of chemoendocrine therapy for the outcome of disease-free survival after 9 years.

**Weighing of benefits versus harm for an RS of 0 to 10**

In Addendum D18-01, an assumption was made due to the lack of comparative data and based on the differing results of the RS range 11 to 15 compared to those of 16 to 20 and 21 to 25. This assumption concerned premenopausal patients or patients ≤ 50 years without lymph node involvement and was as follows: With an RS range of 0 to 10 for the outcome of disease-free survival, the effect of chemotherapy would continue to decrease compared to higher RS values. This means that no relevant advantage of chemotherapy can be expected. These patients could therefore consider foregoing chemotherapy. The indications relating to the subgroups (premenopausal and postmenopausal) and corresponding varying

recommendations depending on the RS range were documented in the supporting reasons for the G-BA decision [33].

The assumption described above is called into question after considering the new results from the randomized comparison of the RxPONDER study for patients with involvement of 1–3 lymph nodes. Analyses of the disease-free survival outcome (IDFS: invasive disease-free survival) after 5 years in premenopausal patients and patients ≤ 50 years with an RS of 0 to 25 show the following: Patients with endocrine therapy (ET: endocrine Therapy alone) have poorer disease-free survival across all RS ranges than patients with chemoendocrine therapy (CET: chemotherapy followed by endocrine Therapy). The difference between the therapy groups with an RS of 0 to 10 is even more noticeable than with an RS of 11 to 15 (Figure 1 and Figure 2). Hence, lower RS values are not shown to be associated with a lower risk of recurrence.

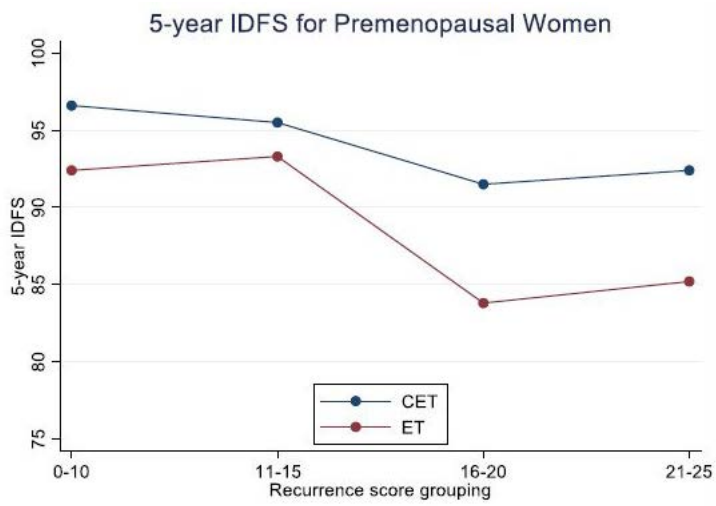


Figure 1: Disease-free survival after 5 years depending on the recurrence score according to Oncotype DX in the RxPONDER study in premenopausal patients (extracted from the appendix of Kalinsky 2021: Figure S2 [16])

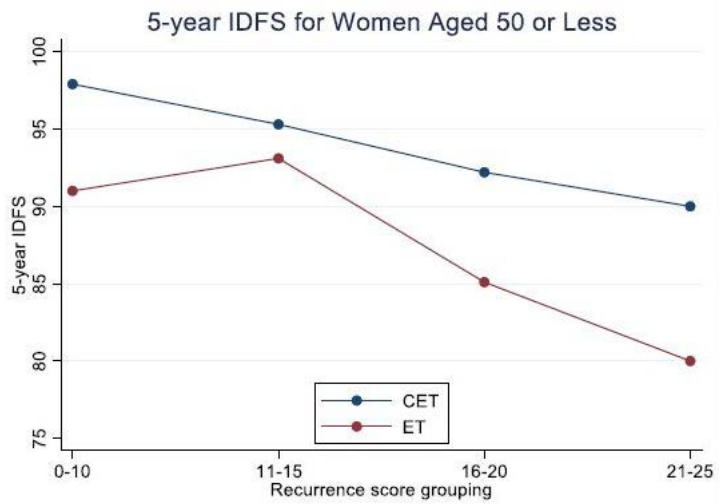


Figure 2: Disease-free survival after 5 years depending on the recurrence score according to Oncotype DX in the RxPONDER study in patients ≤ 50 years of age (extracted from the appendix of Kalinsky 2021: Figure S2 [16])

Even though RxPONDER and TAILORx involve different patient groups with regard to nodal status, these results cast considerable doubt on the plausibility of the assumption made above. The assumption from D18-01 that the chemotherapy effect would be further reduced with decreasing RS can no longer be justified. Moreover, the result of the node-positive patients from RxPONDER is not transferred to the node-negative patients from TAILORx. Instead, only the assumption made at the time is rejected. The current data on TAILORx do not provide any new information on the outcome of disease-free survival. There are still no comparative data for the group with an RS of 0 to 10. Therefore, no conclusion can be drawn about a chemotherapy effect for this group (Table 15). Furthermore, patients ≤ 50 years without lymph node involvement with an RS of 11 to 25 would suffer harm if they decided against adjuvant systemic chemotherapy. No separate and differing conclusion is any longer drawn for premenopausal patients or patients ≤ 50 years without lymph node involvement with an RS from 0 to 10.

**Summarized weighing of benefits versus harm**

For premenopausal patients and patients ≤ 50 years of age without lymph node involvement and with an RS of 0 to 25, there is overall a hint of harm from an Oncotype DX-based decision against adjuvant systemic chemotherapy.

# 5 Classification of the assessment result

## Benefit of biomarkers already introduced into care for patients without lymph node involvement (D23-01B)

### *Oncotype DX*

The hint for the benefit of Oncotype DX was derived in Addendum D18-01, on the one hand, from the analysis of the comparative data for postmenopausal patients or patients > 50 years with an intermediate risk of recurrence (RS of 11 to 25) in the TAILORx study, in which non-inferiority of treatment without chemotherapy was shown. On the other hand, an assessment for premenopausal patients or patients ≤ 50 years of age was derived based on assumptions for the RS range of 0 to 10. In summary, in Addendum D18-01, a hint of the benefit of a biomarker-based decision for or against chemotherapy was determined for the total population, i.e. regardless of menopausal status or age.

The G-BA followed the assessment in Addendum D18-01 and considered the benefit of the method "biomarker-based tests in primary breast cancer", specified for biomarker-based analysis in patients with primary hormone receptor-positive, HER2/neu-negative, node-negative and non-metastatic breast cancer using the Oncotype DX approach, as sufficiently proven [33]. As a result, this method was introduced into statutory health care, without restriction for patients of all ages.

In the present report, the assessment for premenopausal patients changes fundamentally. Based on the TAILORx study, the following finding for premenopausal patients ≤ 50 years without lymph node involvement was already established in Addendum D18-01:

- Hint of harm from an Oncotype DX-based decision against adjuvant systemic chemotherapy in patients with an RS of 11 to 25

Based on the findings of the present report, and in deviation from the former assessment in Addendum D18-01, the following can be concluded: Premenopausal patients without lymph node involvement who are tested with the Oncotype DX biomarker and who are found to have an RS of 0 to 25 may not receive the best care for them because they forego chemotherapy from which they would have actually benefited.

### *MammaPrint*

Based on the MINDACT study, the present assessment identified findings consistent with the results for Oncotype DX for patients ≤ 50 years without lymph node involvement:

- Hint of harm from a MammaPrint-based decision against adjuvant systemic chemotherapy for the population at high clinical risk ≤ 50 years of age

This assessment also shows that patients ≤ 50 years of age without lymph node involvement who are tested with the MammaPrint biomarker may not receive the best care for them because they forego chemotherapy from which they would actually have benefited.

This information is of particular importance, as the G-BA determined a benefit for this biomarker in patients without lymph node involvement in 2020 on the basis of Rapid Report D19-01. This was justified by sufficient comparability with the prognostic results of Oncotype DX from the Vallon-Christersson 2019 prognostic study [33,34]. The results presented in this report on the basis of an RCT indicate that there are risks involved in transferring results from prognostic studies to predictive properties of a biomarker that can only be measured by means of RCTs. This is illustrated by the following example for the outcome of disease-free survival in patients without lymph node involvement.

In the TAILORx study, patients with an Oncotype DX RS of 11 to 25 (premenopausal or postmenopausal) in the endocrine therapy group showed a risk of 16.7% for an event after 9 years. In the group treated with chemoendocrine therapy, the Kaplan-Meier estimate for the risk was only 1.0 percentage point lower (Table 9 in [2]). With MammaPrint, the overall population (patients ≤ 50 and > 50 years) in the MINDACT study showed a corresponding risk of 16.6% in the endocrine therapy group after 8 years. The prognostic value (without chemotherapy) was therefore almost exactly the same as in the Oncotype DX case described above. In the group treated with chemoendocrine therapy in the MINDACT study, however, the risk was reduced to a significantly greater extent, namely by 4.1 percentage points (Table S9 in [9]). In this case, this means that with the same baseline risk, an estimated 41 out of 1000 patients identified by the MammaPrint will have an additional recurrence or die if they decide against adjuvant chemotherapy. Among patients identified by the Oncotype DX, this figure is estimated to increase by 10 out of 1000 in the case of a decision against adjuvant chemotherapy.

A biomarker's benefit may consist solely of its prognostic ability, in that the identified population has such a low risk of recurrence that chemotherapy can no longer have any relevant effect. In the MINDACT study, the MammaPrint in particular was unable to substantiate any such claim. In this context, it should be noted that, according to the package insert of the manufacturer Agendia NV (version M-ROW-133-V6, September 2021), MammaPrint is exclusively a prognostic biomarker that is not intended to draw conclusions about the individual response of patients to therapy [35].

The new findings from the present report also illustrate the importance of analysing subgroups, as shown by the different results between premenopausal and postmenopausal patients.

***EndoPredict and Prosigna***

No new findings on the biomarkers EndoPredict and Prosigna were identified in this assessment. According to the manufacturer Myriad International GmbH, EndoPredict can be used in both premenopausal and postmenopausal patients regardless of nodal status. Prosigna, on the other hand, is only indicated for postmenopausal patients. For example, the German package insert of the manufacturer Veracyte, Inc. of the Prosigna gene signature test for breast cancer prognostics (Version 01, created in May 2022) states in the section on the limitations of the procedure that the performance characteristics of the Prosigna test were developed for postmenopausal patients and that the performance has not been proven with other treatment concepts or in other patient groups [36]. Similar to MammaPrint, the benefit for patients without lymph node involvement for EndoPredict and Prosigna determined by the G-BA was justified by sufficient comparability with the prognostic results of Oncotype DX from prognostic studies with at least moderate certainty of results [33]. However, the differing results from RCTs between the biomarkers MammaPrint and Oncotype DX confirm the doubts as to whether it is justified to transfer a benefit shown in RCTs to other biomarkers using results from prognosis studies, especially as the data largely only comes from postmenopausal patients.

**Potential benefit of biomarkers for patients with lymph node involvement (D23-01A)**

The results of the benefit assessment of Project D23-01A provide a basis for the decision as to whether one or more biomarkers for patients with involvement of 1–3 lymph nodes should be introduced into contracted doctor care. This population has a higher risk of recurrence or death compared to node-negative patients due to the clinical factor of nodal status alone.

Based on the MINDACT (MammaPrint) and RxPONDER (Oncotype DX) studies, this report found the following results for patients with involvement of 1–3 lymph nodes:

- No hint of a benefit from a MammaPrint-based decision for or against adjuvant systemic chemotherapy in the population at high clinical risk, regardless of age
- Hint of harm from an Oncotype DX-based decision against adjuvant systemic chemotherapy for premenopausal patients ≤ 50 years of age with an RS of 0 to 25
- Hint of a benefit from an Oncotype DX-based decision against adjuvant systemic chemotherapy for patients > 50 years of age with an RS of 0 to 25

There are thus no consistent findings with regard to a general recommendation for the use of such biomarkers. This suggests that breast cancer biomarkers should be considered as different interventions and that their benefit should be assessed individually. Accordingly, the NICE committee states in the current guideline that the biomarkers measure the expression of different genes, i.e. the selection and number of target genes largely differ between the

molecular biological test principles. Therefore, the effects of menopausal status observed in studies on Oncotype DX may not be transferable to other biomarkers [37].

On the website of Exact Sciences Deutschland GmbH [38], the manufacturer of Oncotype DX, the chemotherapy benefit is expressed in percentage points based on the probability of distant recurrence with or without chemotherapy. For premenopausal node-positive patients, according to the manufacturer's information, there is a chemotherapy benefit of 2.9 percentage points when considering distant recurrences in the RS range of 0 to 25 alone. This conclusion is consistent with the findings of the present report that a biomarker-independent strategy should be recommended to the relevant patient group for treatment decisions.

**Overview of RCT evidence on the use of biomarker-based tests**

The following tables summarize the evidence from the included RCTs for the use of the biomarkers MammaPrint (Table 14) and Oncotype DX (Table 15).

No assessments are presented in these tables for other biomarkers such as EndoPredict and Prosigna, as no corresponding RCT data are available.

Table 14: RCT evidence for the use of the biomarker-based test MammaPrint in the MINDACT study (high clinical risk)

| **Population and weighing of benefits versus harm** | **Maximum number of additional events when foregoing chemotherapy[a]** | **Conclusion** |
|---|---|---|
| **≤ 50 years of age with involvement of 1–3 lymph nodes (D23-01A)**<br>NI not shown; no hint of a benefit<br>(see sections 4.5.1.1.3 and 4.6.1.1) | It is not certain that, by foregoing chemotherapy, only up to an additional 24[b] out of 1000 patients ≤ 50 years of age will experience a recurrence or die within 8 years compared to treatment with chemotherapy. | RCT evidence does **not** speak **for** using the biomarker for decision support. |
| **≤ 50 years of age without lymph node involvement (D23-01B)**<br>Hint of harm[c]; NI not shown<br>(see sections 4.5.2.1.3 and 4.6.2.1) | Up to an additional 150 out of 1000 patients ≤ 50 years of age could experience a recurrence or die within 8 years compared to treatment with chemotherapy. | RCT evidence speaks **against** using the biomarker for decision support. |
| **> 50 years of age with involvement of 1–3 lymph nodes (D23-01A)**<br>NI not shown; no hint of a benefit<br>(see sections 4.5.1.1.3 and 4.6.1.1) | It is not certain that, by foregoing chemotherapy, only up to an additional 24[b] out of 1000 patients ≤ 50 years of age will experience a recurrence or die within 8 years compared to treatment with chemotherapy. | RCT evidence does **not** speak **for** using the biomarker for decision support. |
| **> 50 years of age without lymph node involvement → not part of the current research question** | | |
| Presented additionally: NI not shown<br>(see Section A3.3.2.3 of the full report) | It is not certain that, by foregoing chemotherapy, only up to an additional 24[b] out of 1000 patients ≤ 50 years of age will experience a recurrence or die within 8 years compared to treatment with chemotherapy. | RCT evidence does not speak for using the biomarker for decision support. |

a. Referring to the upper 95% CI limit of the risk difference.
b. Corresponds to the NI threshold of 2.4 percentage points after 8 years.
c. Of a biomarker-based decision against adjuvant systemic chemotherapy.

CI: confidence interval; NI: non-inferiority (in relation to disease-free survival); RCT: randomized controlled trial

Table 15: RCT evidence for the use of the biomarker-based test Oncotype DX (RS 0–25)

| **Population and weighing of benefits versus harm** | **Maximum number of additional events when foregoing chemotherapy[a]** | **Conclusion** |
|---|---|---|
| **Premenopausal/≤ 50 years of age with involvement of 1–3 lymph nodes (RxPONDER, D23-01A)**<br>RS 0–25: hint of harm[b]; NI not shown (see sections 4.5.1.2.3 and 4.6.1.2) | Up to an additional 91 out of 1000 patients ≤ 50 years of age[c] could experience a recurrence or die within 5 years compared to treatment with chemotherapy. | RCT evidence speaks **against** using the biomarker for decision support. |
| **Premenopausal/≤ 50 years of age without lymph node involvement (TAILORx, D23-01B)**<br>RS 11–25: hint of harm[b]; NI not shown (see sections 4.5.2.2.3 and 4.6.2.2)<br>RS 0–10: no RCT data available, NI not assessable (see Section 4.6.2.2) | Up to an additional 90 out of 1000 patients ≤ 50 years of age with an RS of 11 to 25 could experience a recurrence or die within 10 years compared to treatment with chemotherapy.<br>An assessment for patients with an RS of 0 to 10 is not possible because no data on the risk difference are available. | RCT evidence speaks **against** using the biomarker for decision support. |
| **Premenopausal/> 50 years of age with involvement of 1–3 lymph nodes (RxPONDER, D23-01A)**<br>RS 0–25: NI is shown; hint of a benefit[b] (see sections 4.5.1.2.3 and 4.6.1.2). | Up to an additional 14 out of 1000 patients > 50 years of age could experience a recurrence or die within 5 years compared to treatment with chemotherapy. | Predictive use of the biomarker supported by RCT evidence |
| **Postmenopausal/> 50 years of age without lymph node involvement → not part of the current research question** | | |
| RS 11–25: NI is shown; hint of a benefit[b] (see Section A3.3.2.3 of the full report)<br>RS 0–10: no RCT data available, NI not assessable<br>Assumption of NI for RS 0–10 based on NI for RS 11–25 plausible | Up to an additional 13 out of 1000 patients > 50 years of age could experience a recurrence or die within 10 years compared to treatment with chemotherapy. | Predictive use of the biomarker supported by RCT evidence |

a. Referring to the upper 95% CI limit of the risk difference.
b. Of a biomarker-based decision against adjuvant systemic chemotherapy.
c. Or up to 79 in premenopausal patients.

CI: confidence interval; NI: non-inferiority (in relation to disease-free survival); Oncotype DX: Oncotype DX Breast Recurrence Score; RCT: randomized controlled trial; RS: recurrence score

**Menopausal status and age**

Menopausal status was defined differently in the included studies. In MINDACT, only an approximate menopausal status was defined by an age limit of 50 years. In RxPONDER and TAILORx, on the other hand, criteria such as menstruation and ovariectomy were used for the definition, and in TAILORx the FSH value was also used. TAILORx is the only one of the 3 studies in which perimenopause is addressed in the definition, albeit without a defined distinction from premenopause (see Section 4.2.2.2).

Age can only serve as an approximation for the allocation to premenopause or postmenopause. This is reflected, for example, in the analyses of the RxPONDER study, in which there are deviations of more than 200 patients (out of approx. 5000 randomized patients) between the classifications of premenopausal patients and patients ≤ 50 years and postmenopausal patients and patients > 50 years (Table 36 of the full report).

**Role of ovarian function in the treatment of premenopausal patients**

The topic of ovarian function suppression (OFS) plays a prominent role in the initial assessments of the two commissions of this report received by the G-BA as part of the announcement of the consultation topic and from the consultation procedure on this report. Though this does not directly touch on the research question of this report, details regarding the chemotherapy and an OFS induction used in the included studies were thus described in Section 4.2. Furthermore, relevant findings are outlined below.

For some years now, there has been a debate about the reasons for the observed benefits of adjuvant systemic chemotherapy, particularly in premenopausal patients. Chemotherapy is assumed to exert a suppressive influence on ovarian function in addition to having a cytotoxic effect [9,16,22,37]. Since ovarian function mostly comes to a halt after menopause, this assumed effect of chemotherapy is characteristic of premenopausal patients.

In the interdisciplinary S3 guideline for the early detection, diagnosis, treatment and follow-up of breast cancer from June 2021 [30], the following recommendation is made for endocrine therapy in premenopausal patients: Ovarian suppression (GnRHa or bilateral ovariectomy) in addition to tamoxifen or an aromatase inhibitor should only be considered in cases of high risk of recurrence and premenopausal situation after adjuvant chemotherapy. When using an aromatase inhibitor, ovarian suppression should be mandatory (Recommendation 4.114).

This issue is also addressed in the NICE guideline. According to NICE, chemotherapy is likely to be more effective in premenopausal patients than in postmenopausal patients. Clinical experts agreed during the guideline development process that there is a plausible biological explanation for the different benefits of chemotherapy in premenopausal and postmenopausal patients: Chemotherapy can suppress ovarian function in premenopausal patients, which could be responsible for the observed treatment effects. The experts involved

in the guideline development also pointed out that the risk of mistakenly foregoing chemotherapy is higher in premenopausal patients than in postmenopausal patients [37].

According to Piccart 2021 [9], it cannot be assumed that chemotherapy can be safely replaced by OFS. This uncertainty must be communicated to patients as part of the shared decision-making process. Kalinsky 2021 [16] emphasize that RxPONDER did not investigate whether chemotherapy can be replaced by OFS; this question could be investigated in a future randomized study.

In her narrative review, Francis poses the question of whether OFS can replace adjuvant chemotherapy in premenopausal patients at intermediate risk. The author concludes that the role of using OFS combined with oral adjuvant endocrine therapy could be considered as an alternative to chemotherapy followed by oral endocrine therapy in hormone receptor-positive HER2-negative premenopausal early breast cancer [39]. It can be stated that there is still a need for more research on the topic of SFO and that it plays a relevant role in current care.

# 6 Conclusion

**Project D23-01A: Breast cancer patients with involvement of 1–3 lymph nodes**

For the population of patients with primary hormone receptor-positive, HER2/neu-negative breast cancer with involvement of 1–3 lymph nodes, the results for a biomarker-based decision against chemotherapy differ depending on the biomarker in question and the menopausal status:

When using MammaPrint:

- No hint of a benefit in the group at high clinical risk group regardless of age

When using the Oncotype DX Breast Recurrence Score (Oncotype DX):

- A hint of harm in premenopausal patients or in patients up to and including 50 years of age and
- A hint of a benefit in patients over 50 years of age

Relevant data from RCTs were only available for the biomarkers MammaPrint (MINDACT study) and Oncotype DX (RxPONDER study). No current prognostic studies have been identified for any biomarker.

**Project D23-01B: Premenopausal breast cancer patients without lymph node involvement**

For the population of premenopausal patients with primary hormone receptor-positive, HER2/neu-negative breast cancer without lymph node involvement, the following conclusion results for a biomarker-based decision against chemotherapy depending on the biomarker considered:

- When using MammaPrint, a hint of harm specific to the group at high clinical risk
- When using Oncotype DX, a hint of harm

Relevant data from RCTs were only available for the biomarkers MammaPrint (MINDACT study) and Oncotype DX (TAILORx study).

**Cross-project conclusion**

No RCTs comparing 2 biomarker-based decision strategies were identified in either project. No assessment of a general biomarker-based decision-making strategy can be derived from the results described above, as there are clear differences in the benefit-risk profile of the two biomarkers analysed in the RCTs. Accordingly, no assessments of other biomarkers such as EndoPredict and Prosigna, for which no suitable data are available, can be derived from the results of MammaPrint and Oncotype DX.

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Please see full final report for full reference list.

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*The full report (German version) is published under*
*https://www.iqwig.de/en/projects/d23-01.html*

# Appendix A Search strategies

## A.1 Search strategies for breast cancer patients with 1-3 affected lymph nodes (Project D23-01A) and no affected lymph nodes (Project D23-01B)

### A.1.1 Searches in bibliographic databases

**Search for systematic reviews**

***1. MEDLINE***

*Search interface: Ovid*

- Ovid MEDLINE(R) ALL 1946 to April 21, 2023

The following filter was adopted:

- Systematic review: Wong [40] – High specificity strategy

| # | Searches |
|---|---|
| 1 | Gene Expression Profiling/ |
| 2 | (gene* adj3 expression* adj5 (signature* or profil*)).ab,ti. |
| 3 | (immunohistochemi* adj3 (marker* or biomarker* or test* or assay*)).ab,ti. |
| 4 | Urokinase-Type Plasminogen Activator/ |
| 5 | Plasminogen Activator Inhibitor 1/ |
| 6 | (urokinase adj3 plasminogen activat*).ab,ti. |
| 7 | plasminogen activator inhibitor*.ab,ti. |
| 8 | (upa or pai-1).ab,ti. |
| 9 | Mammaprint*.ab,ti. |
| 10 | ("70" adj1 gene* adj5 (signatur* or profil*)).ab,ti. [Mammaprint] |
| 11 | (Oncotype* or 21 gene* or recurrence score).ab,ti. |
| 12 | Endopredict*.ab,ti. |
| 13 | Breast Cancer Index*.ab,ti. |
| 14 | (pam50 or pam 50 or 50 gene* or Breast Cancer Prognostic Gene Signature*).ab,ti. |
| 15 | (76 gene* adj5 signatur*).ab,ti. |
| 16 | (Randox or "Breast Cancer Array").ab,ti. |
| 17 | ((gene* or genomic*) adj3 grade index).ab,ti. |
| 18 | Mammostrat*.ab,ti. |
| 19 | ((Nottingham prognostic index or NPI) adj1 plus).ab,ti. |
| 20 | or/1-19 |
| 21 | (breast adj3 cancer*).ab,ti. |
| 22 | Breast Neoplasms/ |
| 23 | or/21-22 |
| 24 | Cochrane database of systematic reviews.jn. |
| 25 | (search or MEDLINE or systematic review).tw. |

| # | Searches |
|---|---|
| 26 | meta analysis.pt. |
| 27 | or/24-26 |
| 28 | and/20,23,27 |
| 29 | 28 and (english or german or multilingual or undetermined).lg. |
| 30 | 29 and 201906:3000.(dt). |

### *2. International HTA Database*

*Search interface: INAHTA*

| # | Searches |
|---|---|
| 1 | Gene Expression Profiling[mh] |
| 2 | (gene* AND expression* AND (signature* OR profil*)) |
| 3 | immunohistochemi* AND (marker* OR biomarker* OR test* OR assay*) |
| 4 | Urokinase-Type Plasminogen Activator[mh] |
| 5 | Plasminogen Activator Inhibitor 1[mh] |
| 6 | urokinase AND plasminogen activat* |
| 7 | plasminogen activator inhibitor* |
| 8 | upa OR pai-1 |
| 9 | Mammaprint* |
| 10 | gene* AND (signatur* or profil*) |
| 11 | Oncotype* OR "21 gene*" OR "recurrence score" |
| 12 | Endopredict* |
| 13 | Breast Cancer Index* |
| 14 | pam50 OR "pam 50" OR "50 gene*" OR "Breast Cancer Prognostic Gene Signature*" |
| 15 | 76 gene* AND signatur* |
| 16 | Randox OR "Breast Cancer Array" |
| 17 | (gene* OR genomic*) AND grade index |
| 18 | Mammostrat* |
| 19 | (Nottingham prognostic index OR NPI) AND plus |
| 20 | #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 |
| 21 | Breast Neoplasms[mh] |
| 22 | breast AND cancer* |
| 23 | #22 OR #21 |
| 24 | #23 AND #20 |
| 25 | (*) FROM 2019 TO 2023 |
| 26 | #25 AND #24 |

**Search for primary studies**

***1. MEDLINE***

*Search interface: Ovid*

- Ovid MEDLINE(R) ALL 1946 to June 13, 2024

The following filter was adopted:

- RCT: Lefebvre [41] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)

| # | Searches |
|---|---|
| 1 | Breast Neoplasms/ |
| 2 | (breast* adj3 cancer*).ab,ti. |
| 3 | or/1-2 |
| 4 | Urokinase-Type Plasminogen Activator/ |
| 5 | Plasminogen Activator Inhibitor 1/ |
| 6 | (urokinase adj3 plasminogen activat*).ab,ti. |
| 7 | plasminogen activator inhibitor*.ab,ti. |
| 8 | (upa or pai-1).ab,ti. |
| 9 | Mammaprint*.mp. |
| 10 | ("70" adj1 gene*).mp. |
| 11 | (Oncotype* or 21 gene* or recurrence score).mp. |
| 12 | Endopredict*.mp. |
| 13 | Breast Cancer Index*.mp. |
| 14 | (pam50 or pam 50 or 50 gene* or breast cancer prognostic gene signature* or prosigna*).mp. |
| 15 | blueprint*.mp. |
| 16 | ("80" adj1 gene*).mp. |
| 17 | adna?test*.mp. |
| 18 | or/4-17 |
| 19 | Randomized Controlled Trial.pt. |
| 20 | Controlled Clinical Trial.pt. |
| 21 | (randomized or placebo or randomly).ab. |
| 22 | Clinical Trials as Topic/ |
| 23 | trial.ti. |
| 24 | or/19-23 |
| 25 | exp Animals/ not Humans/ |
| 26 | 24 not 25 |
| 27 | and/3,18,26 |

| # | Searches |
|---|---|
| 28 | (animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/ |
| 29 | hi.fs. or case report.mp. |
| 30 | or/28-29 |
| 31 | 27 not 30 |
| 32 | 31 and (english or german or multilingual or undetermined).lg. |
| 33 | 32 and 20190815:3000.(dt). |

### *2. Embase*

*Search interface: Ovid*

- Embase 1974 to 2024 June 13

The following filter was adopted:

- RCT: Wong [40] – Strategy minimizing difference between sensitivity and specificity

| # | Searches |
|---|---|
| 1 | exp Breast cancer/ |
| 2 | (breast adj3 cancer*).ab,ti. |
| 3 | or/1-2 |
| 4 | urokinase/ |
| 5 | plasminogen activator inhibitor 1/ |
| 6 | (urokinase adj3 plasminogen activat*).ab,ti. |
| 7 | plasminogen activator inhibitor*.ab,ti. |
| 8 | (upa or pai-1).ab,ti. |
| 9 | Mammaprint*.mp. |
| 10 | ("70" adj1 gene*).mp. |
| 11 | (Oncotype* or 21 gene* or recurrence score).mp. |
| 12 | Endopredict*.mp. |
| 13 | Breast Cancer Index*.mp. |
| 14 | (pam50 or pam 50 or 50 gene* or breast cancer prognostic gene signature* or prosigna*).mp. |
| 15 | blueprint*.mp. |
| 16 | ("80" adj1 gene*).mp. |
| 17 | adna?test*.mp. |
| 18 | or/4-17 |
| 19 | (random* or double-blind*).tw. |
| 20 | placebo*.mp. |
| 21 | or/19-20 |
| 22 | and/3,18,21 |

| # | Searches |
|---|---|
| 23 | 22 not medline.cr. |
| 24 | 23 not (exp animal/ not exp human/) |
| 25 | 24 not (Conference Abstract or Conference Review or Editorial).pt. |
| 26 | 25 not ((afrikaans or albanian or arabic or armenian or azerbaijani or basque or belorussian or bosnian or bulgarian or catalan or chinese or croatian or czech or danish or dutch or english or esperanto or estonian or finnish or french or gallegan or georgian or german or greek or hebrew or hindi or hungarian or icelandic or indonesian or irish gaelic or italian or japanese or korean or latvian or lithuanian or macedonian or malay or norwegian or persian or polish or polyglot or portuguese or pushto or romanian or russian or scottish gaelic or serbian or slovak or slovene or spanish or swedish or thai or turkish or ukrainian or urdu or uzbek or vietnamese) not (english or german)).lg. |
| 27 | 26 and 20190815:3000.(dc). |

### *3. The Cochrane Library*

*Search interface: Wiley*

- Cochrane Central Register of Controlled Trials: Issue 5 of 12, May 2024

| # | Searches |
|---|---|
| #1 | [mh ^"Breast Neoplasms"] |
| #2 | (breast* NEAR/3 cancer*):ti,ab |
| #3 | #1 or #2 |
| #4 | [mh ^"Urokinase-Type Plasminogen Activator"] |
| #5 | [mh ^"Plasminogen Activator Inhibitor 1"] |
| #6 | (urokinase NEAR/3 plasminogen NEAR/1 activat*):ti,ab |
| #7 | (plasminogen NEXT activator NEXT inhibitor*):ti,ab |
| #8 | (upa or pai-1):ti,ab |
| #9 | Mammaprint*:ti,ab |
| #10 | ("70" NEAR/1 gene* NEAR/5 (signatur* or profil*)):ti,ab |
| #11 | (Oncotype* or (21 NEXT gene*) or (recurrence* NEXT score*)):ti,ab |
| #12 | Endopredict*:ti,ab |
| #13 | (Breast NEXT Cancer NEXT Index*):ti,ab |
| #14 | (pam50 or "pam 50" or (50 NEXT gene*) or breast cancer prognostic gene signature* or prosigna*):ti,ab |
| #15 | blueprint*:ti,ab |
| #16 | ("80" NEXT gene*):ti,ab |
| #17 | adna?test*:ti,ab |
| #18 | #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 |
| #19 | #3 and #18 |
| #20 | #19 not (*clinicaltrial*gov* or *trialsearch*who* or *clinicaltrialsregister*eu* or *anzctr*org*au* or *trialregister*nl* or *irct*ir* or *isrctn* or *controlled*trials*com* or *drks*de*):so |

| # | Searches |
|---|---|
| #21 | #20 not ((language next (afr or ara or aze or bos or bul or car or cat or chi or cze or dan or dut or es or est or fin or fre or gre or heb or hrv or hun or ice or ira or ita or jpn or ko or kor or lit or nor or peo or per or pol or por or pt or rom or rum or rus or slo or slv or spa or srp or swe or tha or tur or ukr or urd or uzb)) not (language near/2 (en or eng or english or ger or german or mul or unknown))) |
| #22 | #21 with Publication Year from 2019 to 2024, in Trials |

### A.1.2 Searches in study registries

#### 1. ClinicalTrials.gov

***Provider: U.S. National Institutes of Health***

- URL: http://www.clinicaltrials.gov
- Type of search: Expert Search

| Search strategy |
|---|
| (urokinase plasminogen activator OR plasminogen activator inhibitor OR upa OR pai-1 OR mammaprint OR EXPAND[Concept] "70 gene" OR oncotype OR EXPAND[Concept] "21 gene" OR EXPAND[Concept] "recurrence score" OR endopredict OR EXPAND[Concept] "breast cancer index" OR pam50 OR EXPAND[Concept] "pam 50" OR EXPAND[Concept] "breast cancer prognostic gene signature" OR prosigna OR blueprint OR EXPAND[Concept] "80 gene" OR adnatest ) AND AREA[ConditionSearch] breast cancer |

#### 2. EU Clinical Trials Register

***Provider: European Medicines Agency***

- URL: https://www.clinicaltrialsregister.eu/ctr-search/search
- Type of search: Basic Search

| Search strategy |
|---|
| (breast cancer) AND ("urokinase plasminogen activator" OR "plasminogen activator inhibitor" OR upa OR pai-1 OR mammaprint OR "70 gene" OR "70-gene" OR oncotype OR "21 gene" OR "21-gene" OR "recurrence score" OR endopredict OR "breast cancer index" OR pam50 OR "pam 50" OR "breast cancer prognostic gene signature" OR prosigna OR blueprint OR "80 gene" OR "80-gene" OR adna*) |

### 3. International Clinical Trials Registry Platform Search Portal

***Provider: World Health Organization***

- URL: https://trialsearch.who.int
- Type of search: Standard Search

| Search strategy |
|---|
| breast cancer AND (urokinase plasminogen activator* OR plasminogen activator inhibitor* OR upa OR pai-1 OR mammaprint OR 70 gene OR 70-gene OR oncotype OR 21 gene OR 21-gene OR recurrence score* OR endopredict OR breast cancer index* OR pam50 OR pam 50 OR breast cancer prognostic* OR prosigna OR blueprint OR 80 gene OR 80-gene OR adna* OR adnatest) |

## A.2 Search strategies for breast cancer patients with 1-3 affected lymph nodes (Project D23-01A) for prognostic studies

### A.2.1 Searches in bibliographic databases

**Search for primary studies**

***1. MEDLINE***

*Search interface: Ovid*

- Ovid MEDLINE(R) ALL 1946 to June 17, 2024

The following filter was adopted:

- Prognostic studies: Parker [42] – Including general

| # | Searches |
|---|---|
| 1 | Breast Neoplasms/ |
| 2 | (breast* adj3 cancer*).ab,ti. |
| 3 | or/1-2 |
| 4 | Urokinase-Type Plasminogen Activator/ |
| 5 | Plasminogen Activator Inhibitor 1/ |
| 6 | (urokinase adj3 plasminogen activat*).ab,ti. |
| 7 | plasminogen activator inhibitor*.ab,ti. |
| 8 | (upa or pai-1).ab,ti. |
| 9 | Mammaprint*.mp. |
| 10 | ("70" adj1 gene*).mp. |
| 11 | (Oncotype* or 21 gene* or recurrence score).mp. |
| 12 | Endopredict*.mp. |
| 13 | Breast Cancer Index*.mp. |
| 14 | (pam50 or pam 50 or 50 gene* or breast cancer prognostic gene signature* or prosigna*).mp. |
| 15 | blueprint*.mp. |

| # | Searches |
|---|---|
| 16 | ("80" adj1 gene*).mp. |
| 17 | adna?test*.mp. |
| 18 | or/4-17 |
| 19 | (cohort or incidence or mortality or "follow-up study" or "follow-up studies" or prognos* or predict* or course* or epidemiology).mp. or "natural history".ab,ti. |
| 20 | and/3,18-19 |
| 21 | (animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/ |
| 22 | hi.fs. or case report.mp. |
| 23 | or/21-22 |
| 24 | 20 not 23 |
| 25 | 24 and (english or german or multilingual or undetermined).lg. |
| 26 | 25 and 20190815:3000.(dt). |

### *2. Embase*

*Search interface: Ovid*

- Embase 1974 to 2024 June 17

The following filter was adopted:

- Prognosestudien: Wilczynski [43] – Best sensitivity

| # | Searches |
|---|---|
| 1 | exp Breast cancer/ |
| 2 | (breast adj3 cancer*).ab,ti. |
| 3 | or/1-2 |
| 4 | urokinase/ |
| 5 | plasminogen activator inhibitor 1/ |
| 6 | (urokinase adj3 plasminogen activat*).ab,ti. |
| 7 | plasminogen activator inhibitor*.ab,ti. |
| 8 | (upa or pai-1).ab,ti. |
| 9 | Mammaprint*.mp. |
| 10 | ("70" adj1 gene*).mp. |
| 11 | (Oncotype* or 21 gene* or recurrence score).mp. |
| 12 | Endopredict*.mp. |
| 13 | Breast Cancer Index*.mp. |
| 14 | (pam50 or pam 50 or 50 gene* or breast cancer prognostic gene signature* or prosigna*).mp. |
| 15 | blueprint*.mp. |
| 16 | ("80" adj1 gene*).mp. |

| # | Searches |
|---|---|
| 17 | adna?test*.mp. |
| 18 | or/4-17 |
| 19 | exp Disease course/ |
| 20 | (risk* or diagnos* or follow-up).mp. |
| 21 | ep.fs. |
| 22 | outcome.tw. |
| 23 | or/19-22 |
| 24 | and/3,18,23 |
| 25 | 24 not medline.cr. |
| 26 | 25 not (exp animal/ not exp human/) |
| 27 | 26 not (Conference Abstract or Conference Review or Editorial).pt. |
| 28 | 27 not ((afrikaans or albanian or arabic or armenian or azerbaijani or basque or belorussian or bosnian or bulgarian or catalan or chinese or croatian or czech or danish or dutch or english or esperanto or estonian or finnish or french or gallegan or georgian or german or greek or hebrew or hindi or hungarian or icelandic or indonesian or irish gaelic or italian or japanese or korean or latvian or lithuanian or macedonian or malay or norwegian or persian or polish or polyglot or portuguese or pushto or romanian or russian or scottish gaelic or serbian or slovak or slovene or spanish or swedish or thai or turkish or ukrainian or urdu or uzbek or vietnamese) not (english or german)).lg. |
| 29 | 28 and 20190815:3000.(dc). |

### *3. The Cochrane Library*

*Search interface: Wiley*

- Cochrane Central Register of Controlled Trials: Issue 5 of 12, May 2024

| # | Searches |
|---|---|
| #1 | [mh ^"Breast Neoplasms"] |
| #2 | (breast* NEAR/3 cancer*):ti,ab |
| #3 | #1 or #2 |
| #4 | [mh ^"Urokinase-Type Plasminogen Activator"] |
| #5 | [mh ^"Plasminogen Activator Inhibitor 1"] |
| #6 | (urokinase NEAR/3 plasminogen NEAR/1 activat*):ti,ab |
| #7 | (plasminogen NEXT activator NEXT inhibitor*):ti,ab |
| #8 | (upa or pai-1):ti,ab |
| #9 | Mammaprint*:ti,ab |
| #10 | ("70" NEAR/1 gene* NEAR/5 (signatur* or profil*)):ti,ab |
| #11 | (Oncotype* or (21 NEXT gene*) or (recurrence* NEXT score*)):ti,ab |
| #12 | Endopredict*:ti,ab |
| #13 | (Breast NEXT Cancer NEXT Index*):ti,ab |
| #14 | (pam50 or "pam 50" or (50 NEXT gene*) or breast cancer prognostic gene signature* or prosigna*):ti,ab |
| #15 | blueprint*:ti,ab |
| #16 | ("80" NEXT gene*):ti,ab |
| #17 | adna?test*:ti,ab |
| #18 | #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 |
| #19 | (cohort or incidence or mortality or "follow-up study" or "follow-up studies" or prognos* or predict* or course* or "natural history"):ab,ti |
| #20 | #3 and #18 and #19 |
| #21 | #20 not (*clinicaltrial*gov* or *trialsearch*who* or *clinicaltrialsregister*eu* or *anzctr*org*au* or *trialregister*nl* or *irct*ir* or *isrctn* or *controlled*trials*com* or *drks*de*):so |
| #22 | #21 not ((language next (afr or ara or aze or bos or bul or car or cat or chi or cze or dan or dut or es or est or fin or fre or gre or heb or hrv or hun or ice or ira or ita or jpn or ko or kor or lit or nor or peo or per or pol or por or pt or rom or rum or rus or slo or slv or spa or srp or swe or tha or tur or ukr or urd or uzb)) not (language near/2 (en or eng or english or ger or german or mul or unknown))) |
| #23 | #22 with Publication Year from 2019 to 2024, in Trials |