IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. D18-01

Biomarker-based tests to support the decision for or against adjuvant systemic chemotherapy in primary breast cancer –

Addendum to Commission D14-01[1]

Executive Summary

Commission: D18-01
Version: 1.1
Status: 5 September 2018

[1] Translation of the executive summary of the addendum *Biomarkerbasierte Tests zur Entscheidung für oder gegen eine adjuvante systemische Chemotherapie beim primären Mammakarzinom – Addendum zum Auftrag D14-01* (Version 1.1; Status: 5 September 2018). Please note: This translation 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 to support the decision for or against adjuvant systemic chemotherapy in primary breast cancer – Addendum to Commission D14-01

Commissioning agency:
Federal Joint Committee

Commission awarded on:
6 July 2018

Internal Commission No.:
D18-01

Address of publisher:
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This addendum was prepared without the collaboration of external experts.

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Keywords: tumor markers – biological, breast neoplasms, benefit assessment

Executive summary

This addendum to IQWiG's final report D14-01 [1] assesses 2 recently published studies on the question of the benefit of biomarker-based tests to support the decision for or against adjuvant systemic chemotherapy in primary breast cancer: a randomized study with a follow-up period of 9 years (TAILORx [2]), which used the Oncotype DX test, and a prognostic study (Laenkholm 2018 [3]), which used the Prosigna Breast Cancer Prognostic Gene Signature Assay (PAM50).

Research question

The aim of the present investigation is

- to assess the benefit of a biomarker-based strategy to support the decision for or against adjuvant systemic chemotherapy compared with a biomarker-independent decision strategy or a second biomarker-based decision strategy

in each case in patients with primary, hormone receptor-positive, HER2/neu-negative breast cancer and 0 to 3 affected lymph nodes. The focus of the investigation is on patient-relevant outcomes.

Methods

The methods underlying this addendum are based on the final report D14-01 [1] and are presented there.

Results

TAILORx study

The aim of the TAILORx study relevant to this assessment was to show whether endocrine therapy in patients with intermediate Oncotype DX recurrence scores (RS) of 11 to 25 was not inferior to chemoendocrine therapy for the outcome "disease-free survival". The study had 4 prospectively planned study arms:

- Patients with a low RS of 0 to 10 received endocrine therapy.
- Patients with an intermediate RS of 11 to 25 were randomized to receive either
  - endocrine therapy alone as intervention, or
  - chemoendocrine therapy as comparator.
- Patients with a high RS above 25 received chemoendocrine therapy.

After 9 years, no statistically significant difference between endocrine therapy and chemoendocrine therapy (both in the intention-to-treat analysis and in the as-treated analysis) was shown for the randomized group of patients with an RS of 11 to 25 for the outcome "disease-free survival". However, no non-inferiority of endocrine therapy for these patients can be derived from the results as it cannot be excluded that the risk difference after 9 years is more

than the threshold of 3 percentage points used for this assessment. After 9 years, no statistically significant difference between endocrine and chemoendocrine therapy was shown for the outcome “overall survival”.

For disease-free survival, a difference in favour of chemoendocrine therapy compared with endocrine therapy was shown in the group of patients with an RS of 11 to 25 and aged 50 years or younger, as well as for patients before menopause. Hence these patients would be harmed if they were advised against chemotherapy on the basis of the test results. In contrast, non-inferiority of treatment without chemotherapy was shown for patients over the age of 50 years (and for postmenopausal patients).

The following assumptions were made for the group of patients with an RS of 0 to 10 in the framework of this report.

- For patients over 50 years of age or for postmenopausal patients: It is plausible that the risk of events in the outcome “disease-free survival” is at least not increased in comparison with the RS of 11 to 25.
- For patients aged 50 years or younger or premenopausal patients: Modelling by the study authors and analyses stratified by RS allow the assumption that no relevant advantage for the outcome “disease-free survival” can be expected from chemoendocrine therapy in the low RS range of 0 to 10.

Therefore, patients over 50 years of age or postmenopausal patients with an RS below 26 can consider omitting chemotherapy. Patients aged 50 years or younger or premenopausal patients with an RS of 0 to 10 can consider omitting chemotherapy. Chemotherapy should be recommended to patients with a higher RS.

All patients should be tested because, based on the results of the TAILORx study and based on the justified assumptions described above, there are subgroups who can consider omitting chemotherapy both among patients over 50 years of age and among younger patients. Patients for whom there is no uncertainty regarding the decision for or against chemotherapy on the basis of clinical factors are naturally exempt from this recommendation. The TAILORx study showed no association between the criteria chosen for the clinical risk assessment and the results regarding disease-free survival.

Hence a hint of the benefit of a biomarker-based decision for or against chemotherapy was determined. These conclusions are based on the data of a single study (the TAILORx study) and only apply to patients without affected lymph nodes as only these patients were included in the TAILORx study.

Laenkholm 2018

The results of this study were not used in this report because no results were reported on the primarily relevant outcome “disease-free survival”.

Conclusion

A hint of the benefit of a biomarker-based strategy to support the decision for or against adjuvant systemic chemotherapy can be derived from the TAILORx study. This applies to the Oncotype DX test. The test result can support patients with primary, hormone receptor-positive, HER2/neu-negative breast cancer and 0 affected lymph nodes in their decision for or against chemotherapy. No data were available for patients with affected lymph nodes.

This assessment was based, on the one hand, on results from the randomized study arms of the TAILORx study in the intermediate RS range and, on the other – based on these results – on assumptions on the effect of chemotherapy in the low and high RS range. These assumptions were required as there were no comparative data for these 2 RS ranges. The conclusions drawn do not apply to patients for whom a decision for or against chemotherapy can already be taken on the basis of clinical factors.

The data of the Laenkholm 2018 study could not be taken into account because the primarily relevant outcome “disease-free survival” was not reported in this study.

References for English executive summary

Please see full addendum for full reference list.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Biomarkerbasierte Tests zur Entscheidung für oder gegen eine adjuvante systemische Chemotherapie beim primären Mammakarzinom: Abschlussbericht; Auftrag D14-01 [online]. 27.10.2016 [Accessed: 05.12.2016]. (IQWiG-Berichte; Volume 457). URL: https://www.iqwig.de/download/D14-01_Abschlussbericht_Biomarker-bei-Mammakarzinom.pdf.

2. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med 2018; 379(2): 111-121.

3. Laenkholm AV, Jensen MB, Eriksen JO, Rasmussen BB, Knoop AS, Buckingham W et al. PAM50 risk of recurrence score predicts 10-year distant recurrence in a comprehensive Danish cohort of postmenopausal women allocated to 5 years of endocrine therapy for hormone receptor-positive early breast cancer. J Clin Oncol 2018; 36(8): 735-740.

The full addendum (German version) is published under https://www.iqwig.de/en/projects-results/projects/non-drug-interventions/d-projekte/d18-01-biomarker-based-tests-for-the-decision-for-or-against-adjuvant-systemic-chemotherapy-in-primary-breast-cancer-addendum-to-commission-d14-01.9570.html.