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Decoding Cancer

Guide to the MammaPrint and BluePrint Summary of Results

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Summary of Results

The Summary of Results is intended as a companion document to accompany the official Agendia MammaPrint and BluePrint Results Report, it:

- Summarizes the most up-to-date and clinically-meaningful information from MammaPrint and BluePrint prospective clinical trials
- Includes a copy of the specific MammaPrint and BluePrint results for your patient, all in one document
- Provides up-to-date information enabling you to make the most informed and evidence-based treatment management decisions
- Was developed based on feedback from consultations with physicians and patients to help support discussions with your patients

How to get the Summary of Results

Please download the new Summary of Results, along with the official Agendia MammaPrint and BluePrint Results Report, from the Agendia online portal using this link:
https://etelenext.xifin.net/Agendia/apvx/security/login.aspx

How to use this guide

The new Summary of Results provides all the relevant data in one convenient document to be used alongside the Agendia MammaPrint and BluePrint Results Report. It now includes:

- Level 1A combined clinical and genomic risk assessment data from the landmark MINDACT trial[3]
- Additional information for patients with a MammaPrint Late Recurrence (20yr) Low Risk result, based on 20-year survival data from the STO-3 trial[6]
- Simple and succinct 5- and 10-year survival data presented in an easy-to-read visual format

This guide presents the following examples of the Summary of Results pages for MammaPrint and BluePrint test results:

- MammaPrint Low Risk, BluePrint Luminal-Type A
- MammaPrint Late Recurrence (20yr) Low Risk
- MammaPrint High Risk, BluePrint Luminal-Type B

NOTE: The Summary of Results has been updated to include additional content and a new design. The official Agendia MammaPrint and BluePrint Results Report retains the same data and appearance as before and will be updated in the near future.

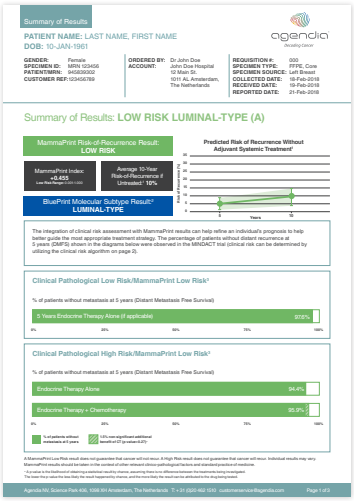
Information within the Summary of Results is provided for general information purposes. It is not part of any official diagnostic report. Please refer to individual MammaPrint and BluePrint reports for comments, assay information, disclaimer and references.

Overview of Summary of Results

Depending on the specific results for your patient, the Summary of Results consists of either two or three pages:

Page 1 – Supporting data from prospective clinical trials and summary of patient-specific MammaPrint and BluePrint results

- Personalized patient results taken from the official Agendia MammaPrint and BluePrint Results Report:
  - Low or High MammaPrint risk of recurrence result
  - MammaPrint Index (MPI)
  - BluePrint Molecular Subtype Result*
- Prognostic validation data for MammaPrint on untreated patients (summary of TRANSBIG study results)[1]
- Clinical utility data for MammaPrint on treated patients (summarized from MINDACT trial)[3]


Summary of Results

PATIENT NAME: LAST NAME, FIRST NAME
DOB: 10-JAN-1961

Summary of Results: LOW RISK LUMINAL-TYPE (A)

MammaPrint Risk-of-Recurrence Result: LOW RISK

BluePrint Molecular Subtype Result[2]: LUMINAL-TYPE

Predicted Risk of Recurrence Without Adjuvant Systemic Treatment[1]

Clinical Pathological Low Risk/MammaPrint Low Risk[1]

% of patients without metastasis at 5 years (Distant Metastasis Free Survival)

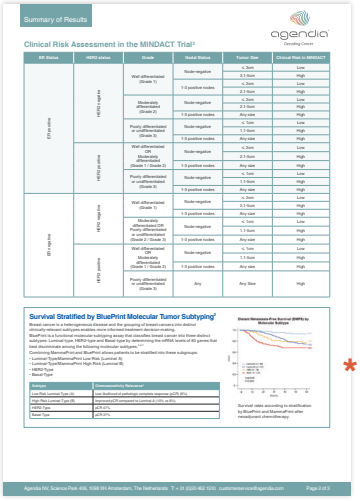
5 Years Endocrine Therapy Alone (if applicable) 97.6%

Clinical Pathological High Risk/MammaPrint Low Risk[1]

% of patients without metastasis at 5 years (Distant Metastasis Free Survival)

Endocrine Therapy Alone 94.4%

Endocrine Therapy + Chemotherapy 95.9%


Summary of Results

Clinical Risk Assessment in the MINDACT Trial[3]

Survival Stratified by BluePrint Molecular Tumor Subtyping[2]

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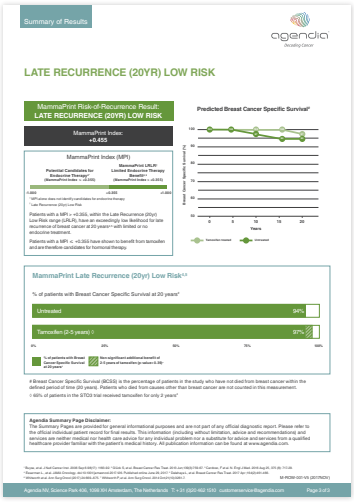
Page 2 – Clinical risk assessment reference table and BluePrint molecular subtyping*

- Reproduction of clinical risk algorithm (modified Adjuvant!Online) used to assess patients in MINDACT[3]
- Information on functional molecular subtyping with BluePrint and pCR rate with neoadjuvant chemotherapy[2,4,5]
- Can support discussions with patients regarding their treatment management decision

Page 3 – Late Recurrence (20yr) Low Risk (LRLR) Result

- If a patient has an MPI > +0.355 they are **Late Recurrence (20yr) Low Risk (LRLR)**
  - This subgroup identifies patients with an excellent 20-year survival with limited or no hormone therapy
- **If applicable,** the LRLR Summary of Results will be added to the report as a third page:
  - Data from the STO-3 trial
  - 20-year outcome data for patients with limited and no hormone therapy


Summary of Results

LATE RECURRENCE (20YR) LOW RISK

MammaPrint Risk-of-Recurrence Result: LATE RECURRENCE (20YR) LOW RISK

MammaPrint Index: +0.455

Predicted Breast Cancer Specific Survival*

MammaPrint Late Recurrence (20yr) Low Risk[4,5]

% of patients with Breast Cancer Specific Survival at 20 years*

Untreated 94%

Tamoxifen (2-5 years) ◊ 97%

Agenda Summary Page Disclaimer:

*NOTE: Molecular subtyping is only included when the BluePrint test has been ordered

Example:

MammaPrint Low Risk with BluePrint Luminal-Type A

Page 1 - Supporting data from prospective clinical trials and summary of patient-specific MammaPrint and BluePrint results

1 Patient ID, tumor specimen information

2 Summary of individual test result

3 MammaPrint prognostic result

- Binary Low Risk result
- Personalized MammaPrint Index (MPI)
- Average 10-year risk of recurrence for untreated LN0 patients (no endocrine therapy, no chemotherapy)[1]
- *Only includes BluePrint molecular subtype result if ordered*

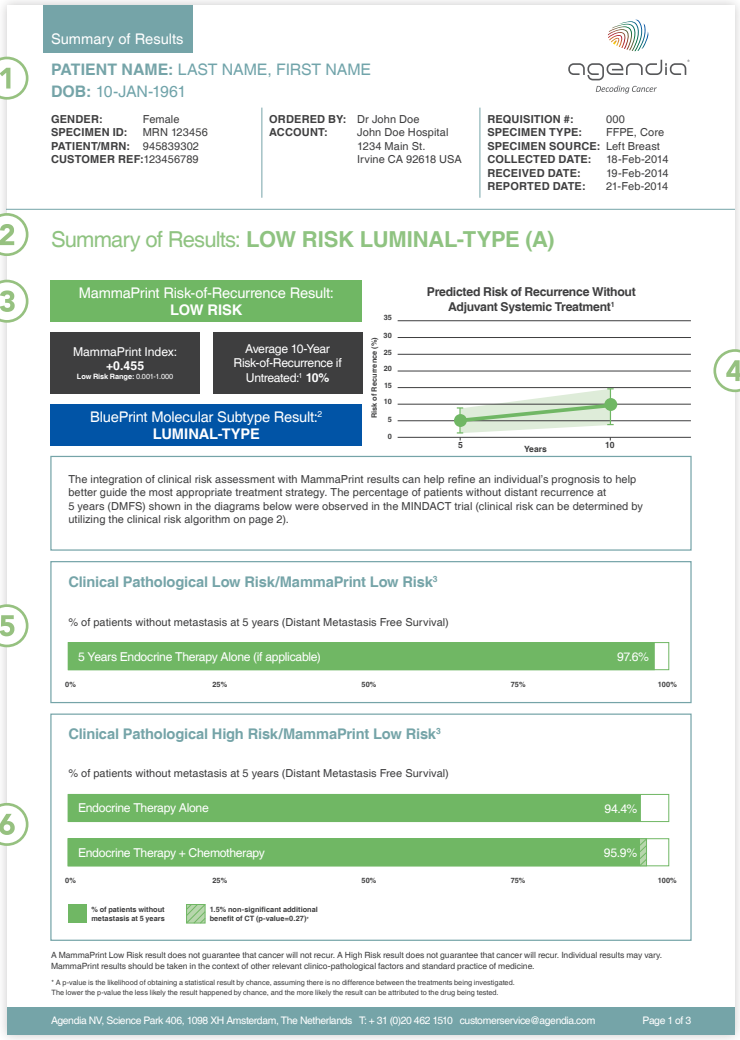
4 Predicted risk of recurrence

Predicted average risk of recurrence for a Low Risk patient without adjuvant treatment:♦

- 5-year risk: **5%** (95% CI: 1% - 9%)
- 10-year risk: **10%** (95% CI: 4% - 15%)

Confidence intervals are based on the findings of the independent TRANSBIG study that included 302 untreated patients[1]

♦ **NOTE:** This graph is not personalized for each specific patient



5 Clinical Pathological Low Risk/ MammaPrint Low Risk Concordant classification

- MINDACT trial data is summarized:
  - **97.6%** patients living without metastasis (expressed as distant metastasis free survival (DMFS))
  - 5-year follow-up of patients treated with endocrine therapy alone

6 Clinical Pathological High Risk/ MammaPrint Low Risk Discordant classification

- MINDACT trial data is summarized:
  - **94.4%** DMFS endocrine therapy only
  - **95.9%** DMFS endocrine therapy + chemotherapy

Data in 5 and 6 are based on the MINDACT prospective clinical trial that included 6,693 patients.[3]

Page 2 - Clinical risk assessment reference table and BluePrint molecular subtyping

7 Clinical risk assessment table

- As referenced in the supplement of the MINDACT publication[3]
- Table can help determine the clinical risk results as observed in the MINDACT trial (i.e. clinical risk High or Low)
- Clinical risk classification in MINDACT was carried out using the modified version of Adjuvant! Online (version 8.0)[3]

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7 **Clinical Risk Assessment in the MINDACT Trial[3]**

ER Status	HER2 status	Grade	Nodal Status	Tumor Size	Clinical Risk in MINDACT
ER positive	HER2 negative	Well differentiated (Grade 1)	Node-negative	≤ 3cm	Low
				3.1-5cm	High
			1-3 positive nodes	≤ 2cm	Low
				2.1-5cm	High
		Moderately differentiated (Grade 2)	Node-negative	≤ 2cm	Low
				2.1-5cm	High
			1-3 positive nodes	Any size	High
		Poorly differentiated or undifferentiated (Grade 3)	Node-negative	≤ 1cm	Low
				1.1-5cm	High
			1-3 positive nodes	Any size	High
	HER2 positive	Well differentiated OR Moderately differentiated (Grade 1 / Grade 2)	Node-negative	≤ 2cm	Low
				2.1-5cm	High
			1-3 positive nodes	Any size	High
		Poorly differentiated or undifferentiated (Grade 3)	Node-negative	≤ 1cm	Low
				1.1-5cm	High
			1-3 positive nodes	Any size	High
ER negative	HER2 negative	Well differentiated (Grade 1)	Node-negative	≤ 2cm	Low
				2.1-5cm	High
			1-3 positive nodes	Any size	High
		Moderately differentiated OR Poorly differentiated or undifferentiated (Grade 2 / Grade 3)	Node-negative	≤ 1cm	Low
				1.1-5cm	High
			1-3 positive nodes	Any size	High
	HER2 positive	Well differentiated OR Moderately differentiated (Grade 1 / Grade 2)	Node-negative	≤ 1cm	Low
				1.1-5cm	High
			1-3 positive nodes	Any size	High
		Poorly differentiated or undifferentiated (Grade 3)	Any	Any Size	High

8 **Survival Stratified by BluePrint Molecular Tumor Subtyping[2]**

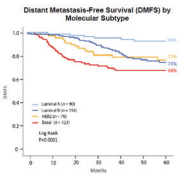
Breast cancer is a heterogeneous disease and the grouping of breast cancers into distinct clinically-relevant subtypes enables more informed treatment decision-making.

BluePrint is a functional molecular subtyping assay that classifies breast cancer into three distinct subtypes: Luminal-type, HER2-type and Basal-type by determining the mRNA levels of 80 genes that best discriminate among the following molecular subtypes.[4,6,7]

Combining MammaPrint and BluePrint allows patients to be stratified into these subgroups:

- Luminal-Type/MammaPrint Low Risk (Luminal A)
- Luminal-Type/MammaPrint High Risk (Luminal B)
- HER2-Type
- Basal-Type

Subtype	Chemosensitivity Relevance[2]
Low Risk Luminal-Type (A)	Low likelihood of pathologic complete response (pCR) (6%)
High Risk Luminal-Type (B)	Improved pCR compared to Luminal A (10% vs 6%)
HER2-Type	pCR 47%
Basal-Type	pCR 37%



Survival rates according to stratification by BluePrint and MammaPrint after neoadjuvant chemotherapy.

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8 BluePrint molecular subtyping results

- Neoadjuvant chemosensitivity results based on molecular subtype (expressed as rate of pCR (pathologic complete response rate))*
- Includes survival curve with 5-year DMFS outcomes based on molecular subtype

***NOTE:** This graph is not personalized for each specific patient

Molecular subtype	5-year DMFS
Luminal A	93%
Luminal B	74%
HER2	77%
Basal	68%

Results in 8 are based on a clinical study of BluePrint that included 437 patients[2]

Page 3 - MammaPrint Late Recurrence (20yr) Low Risk Result

MammaPrint Late Recurrence (20yr) Low Risk results are only presented if patient has a MammaPrint Index (MPI) > +0.355

(10) Summary of individual test result

(11) MammaPrint prognostic result

Late Recurrence (20yr) Low Risk (LRLR)

- **Sub-group of** Low Risk patients with excellent survival after 20 years with **limited* or no endocrine therapy**[7]
- Patients with a MPI > +0.355 = Late Recurrence (20yr) Low Risk result (LRLR), and may be candidates for omission or reduction in endocrine therapy*

(12) Survival curve summarizing results from STO-3 trial analysis

- % patients who have not died from breast cancer (BCSS at up to 20 years follow-up)[6]
- Results based on BCSS patients untreated or treated with tamoxifen:

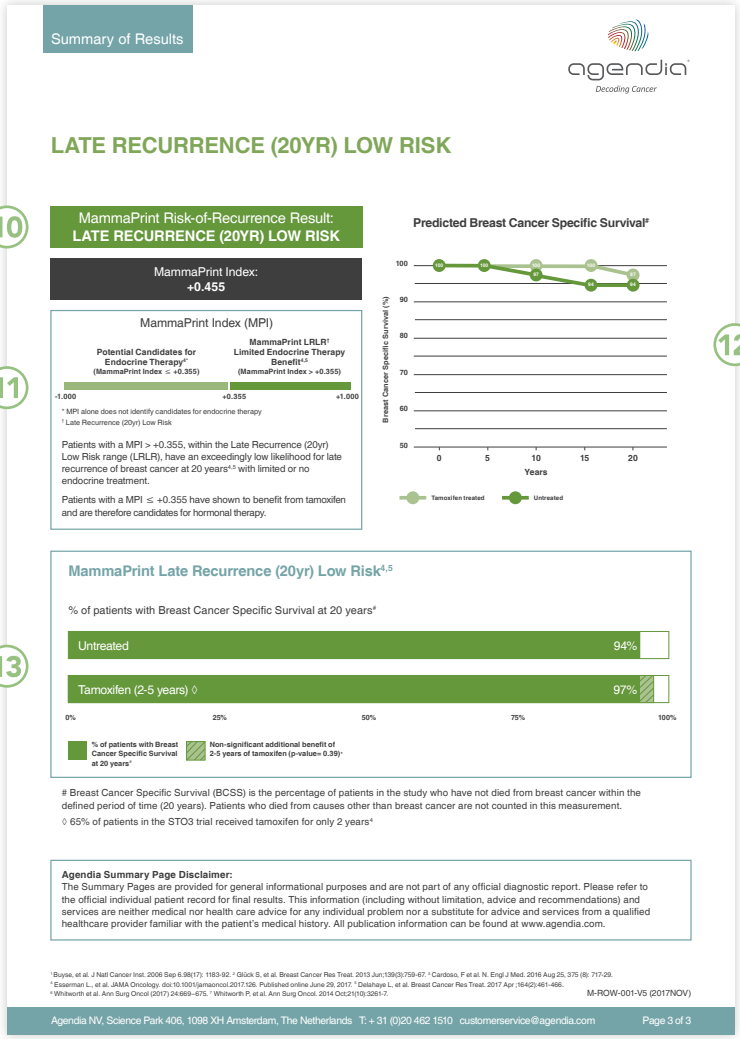
	10-year BCSS	20-year BCSS
Untreated	97%	94%
Tamoxifen treated *	100%	97%**

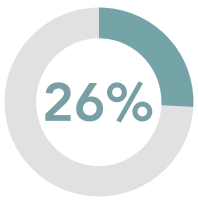
*65% of patients only received 2 years of adjuvant tamoxifen therapy, indicating excellent survival with limited endocrine therapy

(13) Breast cancer specific survival (BCSS)

- Displays same information in (12) for % patients with BCSS at 20-years follow-up in succinct visual format

Non-significant benefit of extended tamoxifen treatment in MammaPrint LRLR patients at 20 years **(p = 0.39)





26% of MammaPrint Low Risk patients were found to be **LRLR**[6]

Results in (12) and (13) are based on two clinical studies:

- The MammaPrint LRLR classification is validated for women of all ages, based on analysis of three different patient cohorts (NKI295, Transbig, and RASTER)[7]
- A secondary analysis of 652 postmenopausal patients with LN0 breast cancer originally enrolled in the Stockholm tamoxifen (STO-3) trial, 1976 to 1996

Example:

MammaPrint HighRisk with BluePrint Luminal-Type B

Page 1 - Supporting data from prospective clinical trials and summary of patient-specific MammaPrint and BluePrint results

(1) Patient identification and information

(2) Summary of individual test result

(3) MammaPrint prognostic result

- Binary High Risk result
- Personalized MammaPrint Index (MPI)
- Average 10-year risk of recurrence for untreated LN0 patients (no endocrine therapy, no chemotherapy)[3]
- *Only includes BluePrint molecular subtype result if ordered*

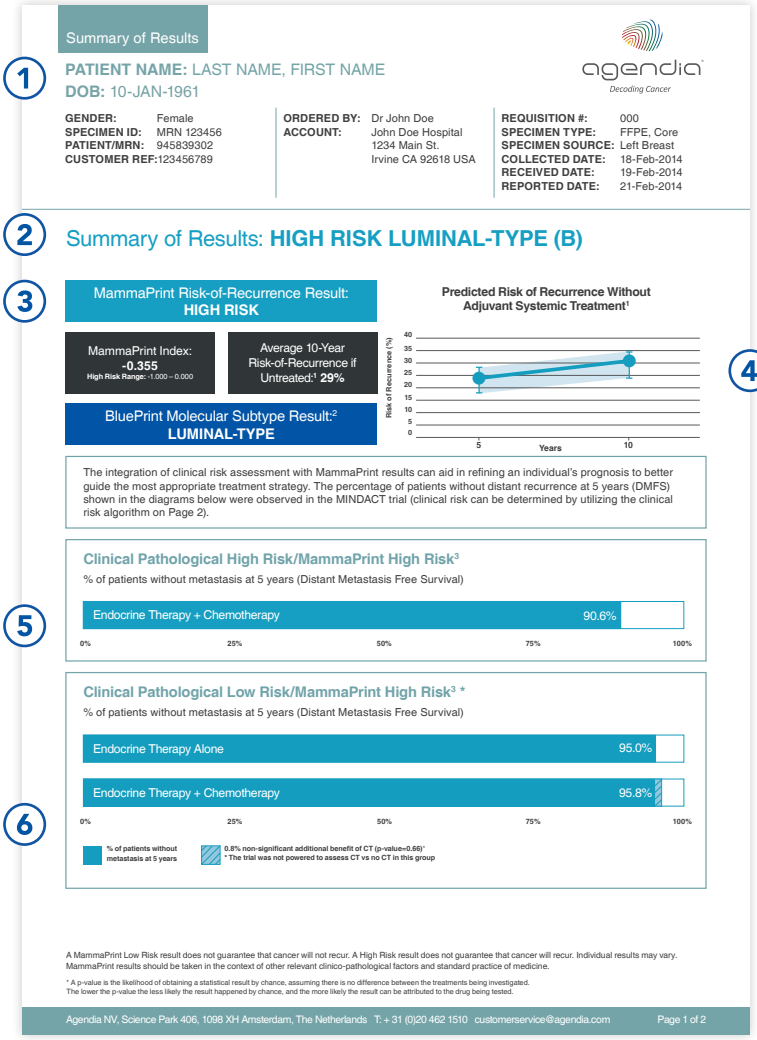
(4) Predicted risk of recurrence

Predicted average risk of recurrence for a High Risk patient without adjuvant treatment:*

- 5-year risk: **22%** (95% CI: 16% - 28%)
- 10-year risk: **29%** (95% CI: 22% - 35%)

Confidence intervals are based on the findings of the independent TRANSBIG study that included 302 untreated patients[1]

***NOTE:** This graph is not personalized for each specific patient



(5) Clinical Pathological High Risk/ MammaPrint High Risk Concordant classification

- MINDACT trial data is summarized:
  - **90.6%** patients living without metastasis (expressed as distant metastasis free survival (DMFS))
  - 5-year follow-up of patients treated with endocrine therapy + chemotherapy

(6) Clinical Pathological Low Risk/ MammaPrint High Risk Discordant classification

- MINDACT trial data is summarized:
  - **95%** DMFS endocrine therapy alone
  - **95.8%** DMFS endocrine therapy + chemotherapy
  - Based on MINDACT there is no statistically significant benefit in DMFS upon receiving chemotherapy in Clinical Low Risk/MammaPrint High Risk patients at 5-year follow-up

NOTE: Page 2 - Reference page providing information on assessment of clinical risk factors and molecular subtyping (not shown) is the same as for the MammaPrint Low Risk, BluePrint Luminal-Type A Summary of Results

Results in (5) and (6) are based on the MINDACT prospective clinical trial that included 6,693 patients[2]

Clinical study descriptions

[1] TRANSBIG:

Independent consortium, 5 European centers, retrospective study including patients <61 yrs old at diagnosis, lymph node negative (LN0), T1 – T2 (≤5 cm) tumor size, ER+/- breast cancer, receiving no adjuvant systemic therapy (endocrine or chemotherapy), n = 302, median follow-up of 13.6 years. Patients were divided into high- and low-risk groups based on the gene signature classification and on clinical risk classifications. This study validated the use of the 70-gene signature.

[2] GLUCK et al., 2013:

Retrospective study including 437 patients (aged 26-79 years) from 4 independent neoadjuvant trials in the United States, ER+/, PR +/-, HER2+/- breast cancer, receiving neoadjuvant chemotherapy. Outcomes were the response to neoadjuvant chemotherapy expressed as pCR according to the definitions used in the original clinical trials. Long-term outcome was defined as the 5-year DMFS rate. The response to neoadjuvant chemotherapy and long-term outcomes were also analyzed for patients treated with and without trastuzumab HER2-targeted therapy.

[3] MINDACT:

Phase 3, prospective randomized control trial, 112 centers in 9 European countries, including patients <18-70 yrs old, lymph node -/+ (LN0-3), T1 – T2 (≤5 cm) and operable T3 tumors, ER+/- HER2+/- breast cancer, n = 6693. Primary endpoint was survival without distant metastasis (DMFS, event-free rate at 5 years). Secondary endpoints were proportion of patients receiving chemotherapy according to clinical risk versus genomic risk, disease-free survival (DFS) and overall survival (OS).

Disease-free survival - defined as time until first disease progression (locoregional, distant relapse, ipsilateral or contralateral invasive breast cancer, ductal carcinoma in situ, or an invasive second primary cancer) or death from any cause. Overall survival - defined as the time until death from any cause.

[6] STO-3

Secondary analysis (n=652) of the Stockholm tamoxifen (STO-3) randomized control trial of tamoxifen vs no systemic therapy, with more than 20-year follow-up, Stockholm area in Sweden, including 1780 postmenopausal women with clinically detected node-negative ≤ 3cm tumors, treated with mastectomy or lumpectomy and radiation enrolled in the STO-3 trial, 1976 to 1990. Patients were randomized to 2 years of adjuvant tamoxifen (40mg daily) vs no adjuvant treatment. Patients who were recurrence-free after 2 years of tamoxifen treatment were randomized to 3 additional years of tamoxifen or no further therapy. In the retrospective analysis, an indolent threshold (Late Recurrence (20yr) Low Risk Result) was established above which no breast cancer deaths occurred after 15 years in the absence of systemic therapy.

References

1. Buyse M, et al. J Natl Cancer Inst (2006) 98(17):1183-1192
2. Glück S, et al. Breast Cancer Res Treat (2013) 139(3):759-767
3. Cardoso F, et al. N. Engl J Med (2016) 375(8):717-729
4. Whitworth P, et al. Ann Surg Oncol (2017) 24(3):669–675
5. Whitworth P, et al. Ann Surg Oncol (2014) 21(10):3261-3267
6. Esserman L, et al. JAMA Oncology (2017) 3(11) :1503-1510
7. Delahaye L, et al. Breast Cancer Res Treat (2017) 164(2):461-466

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Further Questions?

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