EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

# MINDACT: Long-term results of the large prospective trial testing the 70-gene signature MammaPrint as guidance for adjuvant chemotherapy in breast cancer patients

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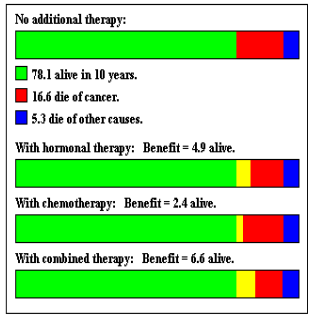
# MINDACT TRIAL DESIGN

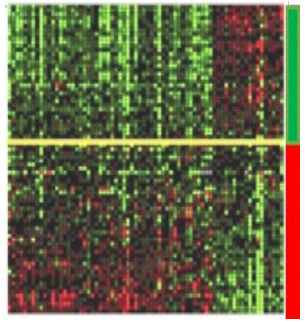



Registration & Screening
Surgery

N= 6693

Clinical-Pathological (C) risk
(Adjuvant! Online)

Genomic (G) risk
(70-gene signature)



C-low/G-low

Discordant cases
C-low/G-high or C-high/G-low

C-high/G-high

1st randomization to treatment
use Clinical vs. Genomic risk

No Chemotherapy

2nd randomization
Anthracycline –based vs. Capecitabine-Docetaxel

Chemotherapy

HR+

Endocrine therapy

HR+

3rd randomization
Tamoxifen 2y / Letrozole 5y vs. Letrozole 7y

MINDACT population:
HR+/HER2- 81%
HER2+ 9.5%
TNBC 9.6%

# MINDACT is a DE-ESCALATION STUDY

- **Primary endpoint**

Distant metastasis free survival (DMFS) at 5 years for C-High / G-Low without chemotherapy

- **Primary statistical test**

Null hypothesis: 5-year DMFS rate C-High / G-Low no CT in Primary Test population = 92%

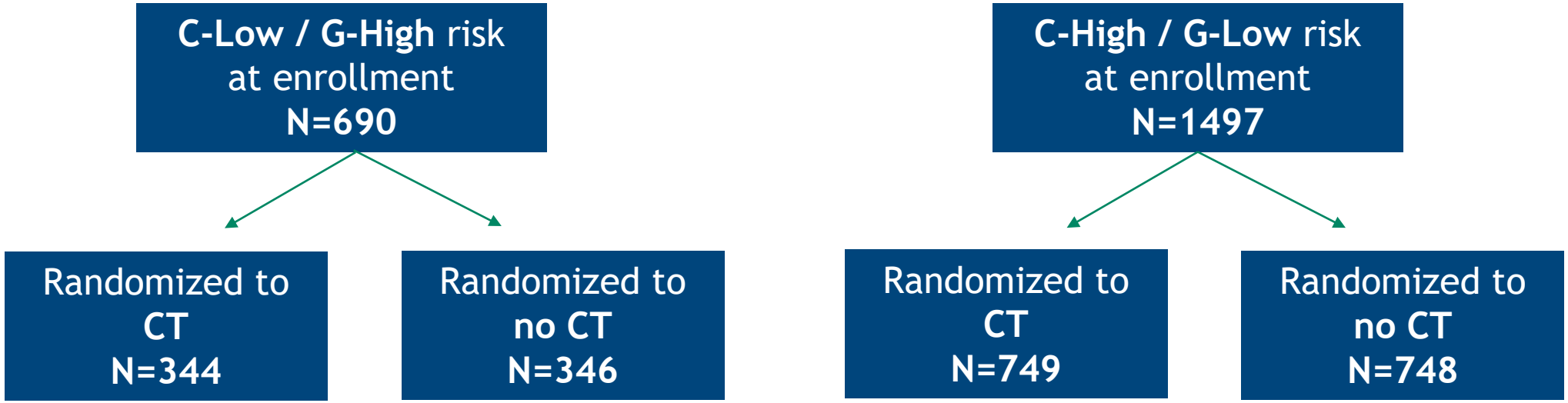
Power: 80% when true 5-year DMFS rate = 95%

Primary test 5-year DMFS rate significant if 2-sided 95% Confidence Interval exceeds 92%

*F. Cardoso, NEJM 2016*

# SECONDARY ENDPOINT

- **Efficacy:** CT vs no CT population of discordant risk groups (In ITT population)



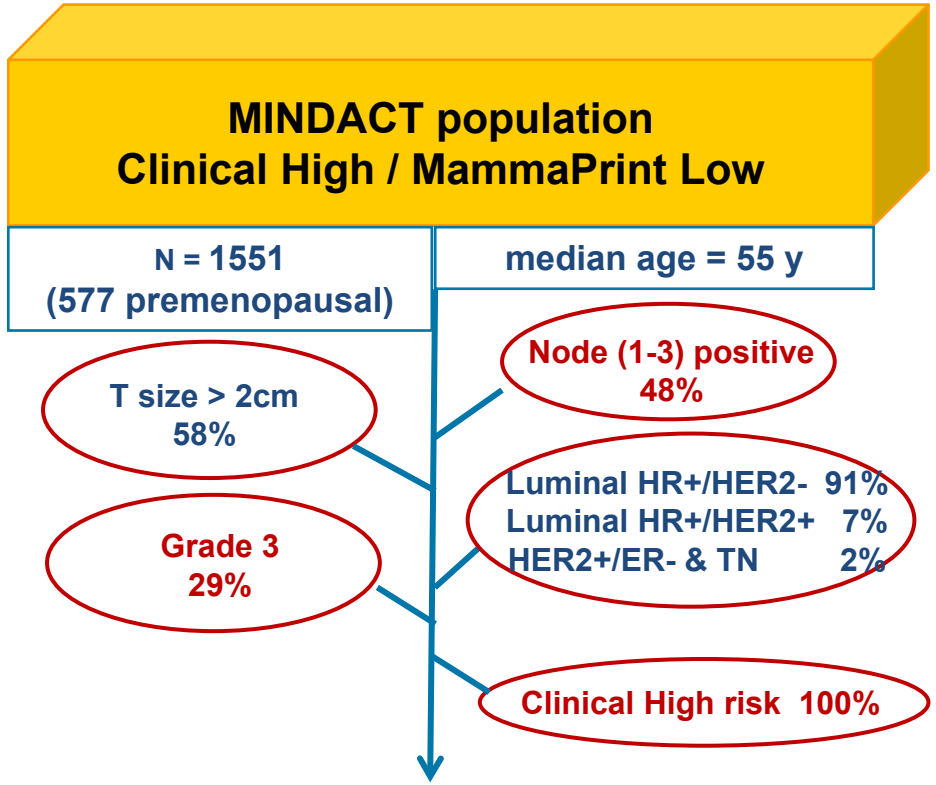

**Trial not powered for the comparisons of yes or no chemotherapy**

*F. Cardoso, NEJM 2016*

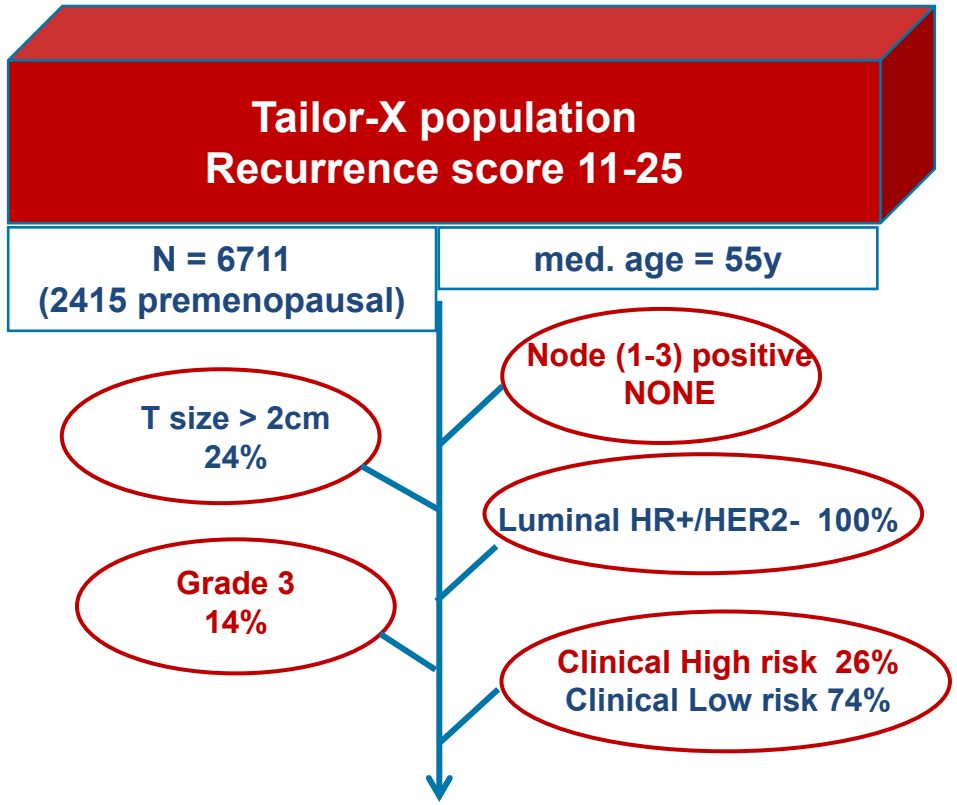
# How high was CLINICAL HIGH risk population in MINDACT?

# How MINDACT and TAILOR-X populations compare (for CT vs no CT question)

*F. Cardoso , NEJM 2016*




*J. Sparano , NEJM 2018*




**In HR+/HER2- C-high/G-low patients: *49% Node (1-3) positive and 27% grade 3***

# MINDACT successfully met its primary endpoint
## SUMMARY OF CONCLUSIONS OF PRIMARY ANALYSIS (5y median FU)

- Primary endpoint was met in 2016 with 5y median FU:
  In **C-High/G-Low** patients with **no CT**: DMFS rate: **94.7%** (95% CI: **92.5**-96.2)
- Among clinical high-risk patients, **reduction of the use of CT in 46% patients,** when following genomic risk strategy
- Secondary endpoint (under-powered): in **C-High/G-Low** patients**,** absolute difference of **1.5%** in 5-year DMFS for CT versus no CT
- **Compliance** rates with assigned/randomized treatment was **high** (80 to 99%)
- The use of MammaPrint has been endorsed by many guidelines (e.g. ASCO, ESMO)

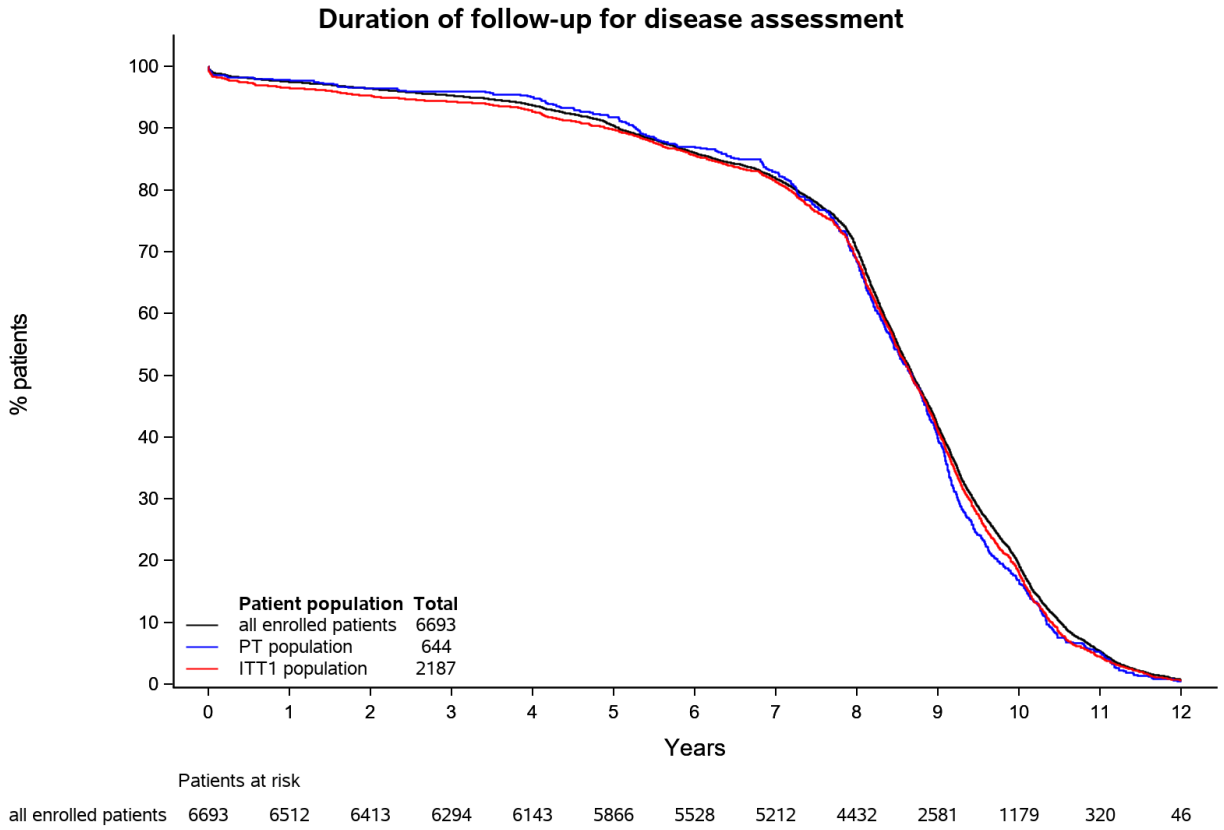
*F. Cardoso, NEJM 2016*

# UPDATED ANALYSIS AT 8.7 YEARS MEDIAN FOLLOW-UP

# RESULTS

# MINDACT CURRENT MEDIAN FOLLOW-UP

## >90% patients followed-up for at least 5 years, median 8.7 years




AP: all enrolled patients (n=6693)
PT: primary test population (n=644)
ITT1: Intention To Treat population (n=2187)

**6693 patients**
enrolled 2007-2011,
112 Institutions, 9 European countries

Clinical data cut off: 26 February 2020
Database lock: 26 February 2020

| Patient population | Total | Median (years) (95% CI)[KM] | Follow-up Estimates (95% CI)[KM] |
|---|---|---|---|
| all enrolled patients | 6693 | **8.7 (8.6-8.7)** | **5 years: 90.4 (89.7-91.1%)**<br>**8 years: 70.4 (69.2-71.5%)**<br>9 years: 41.6 (40.3-42.8%)<br>10 years: 19.3 (18.3-20.3%) |

[KM] Kaplan-Meier method

**Median years FU: 8.7 (8.6-8.7)**

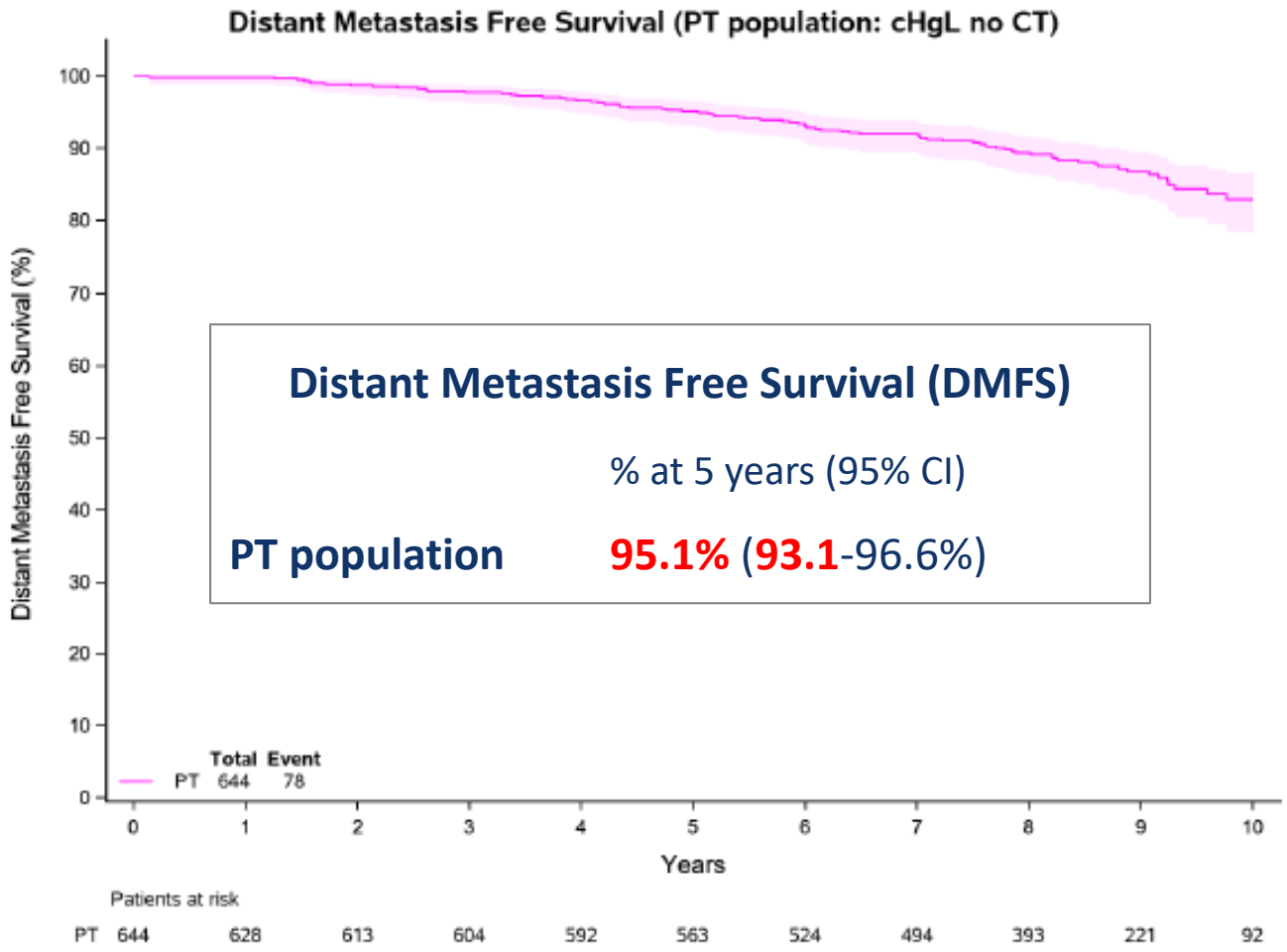
# Events across the entire MINDACT population
# Median follow-up = 8.7 years

TYPE OF EVENTS

| DMFS | DMFI | DFS | OS |
|---|---|---|---|
| • Distant relapses<br>• Deaths (all causes) | • Distant relapses<br>• Deaths<br>  • due to BC<br>  • unknown cause | • Distant relapses<br>• Locoregional relapse<br>• Contralateral BC<br>• Secondary cancers<br>• Deaths (all causes) | • Deaths (all causes) |
| **N = 650** | **N = 501** | **N = 1166** | **N = 458** |
| • Distant Relapses: 68.8%<br>• Deaths: 31.2% | • Distant Relapses: 89.2%<br>• Deaths: 10.8% | • Distant Relapses: 33.5%<br>• Locoregional: 15.5%<br>• Second primary: 44.4%<br>• Deaths: 6.5% | |

**Outcome results per corrected risks**
**Randomization outcome : per intent-to-treat or per protocol**

# Update of PRIMARY ENDPOINT with more mature data at 5 years (>90% of pts with at least 5 years FU)




**Distant Metastasis Free Survival (DMFS)**

| | % at 5 years (95% CI) |
|---|---|
| **PT population** | **95.1%** (**93.1**-96.6%) |

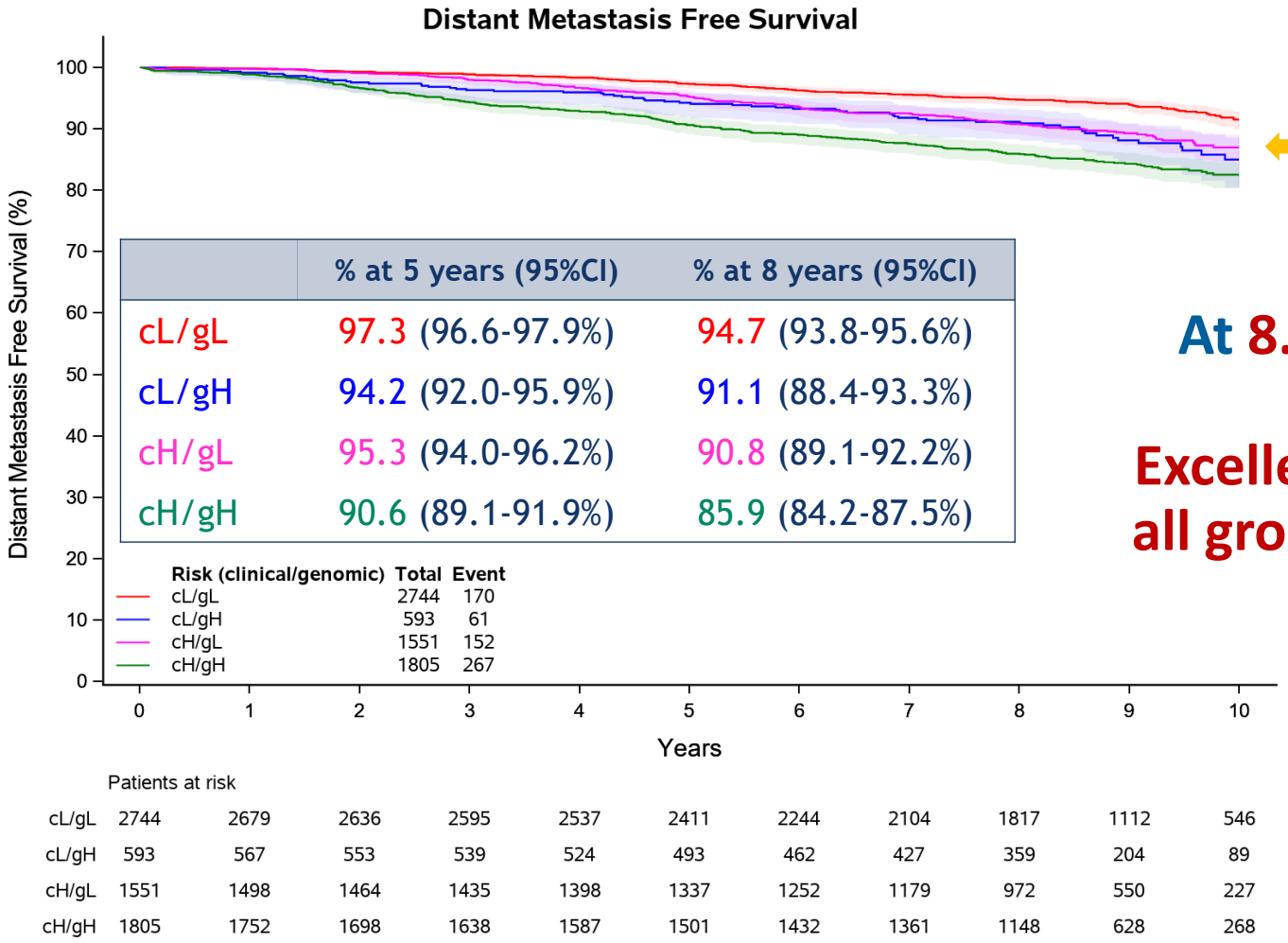
Clinical-High/Genomic-Low no chemotherapy

Null Hypothesis 5-year DMFS: set at 92%

**Lower bound of 95%CI exceeds 92%!**

***Confirmation of primary results***
***Supported by sensitivity analyses***

# MINDACT proves the clinical utility of MammaPrint




| | % at 5 years (95%CI) | % at 8 years (95%CI) |
|---|---|---|
| cL/gL | 97.3 (96.6-97.9%) | 94.7 (93.8-95.6%) |
| cL/gH | 94.2 (92.0-95.9%) | 91.1 (88.4-93.3%) |
| cH/gL | 95.3 (94.0-96.2%) | 90.8 (89.1-92.2%) |
| cH/gH | 90.6 (89.1-91.9%) | 85.9 (84.2-87.5%) |

Discordant risk groups

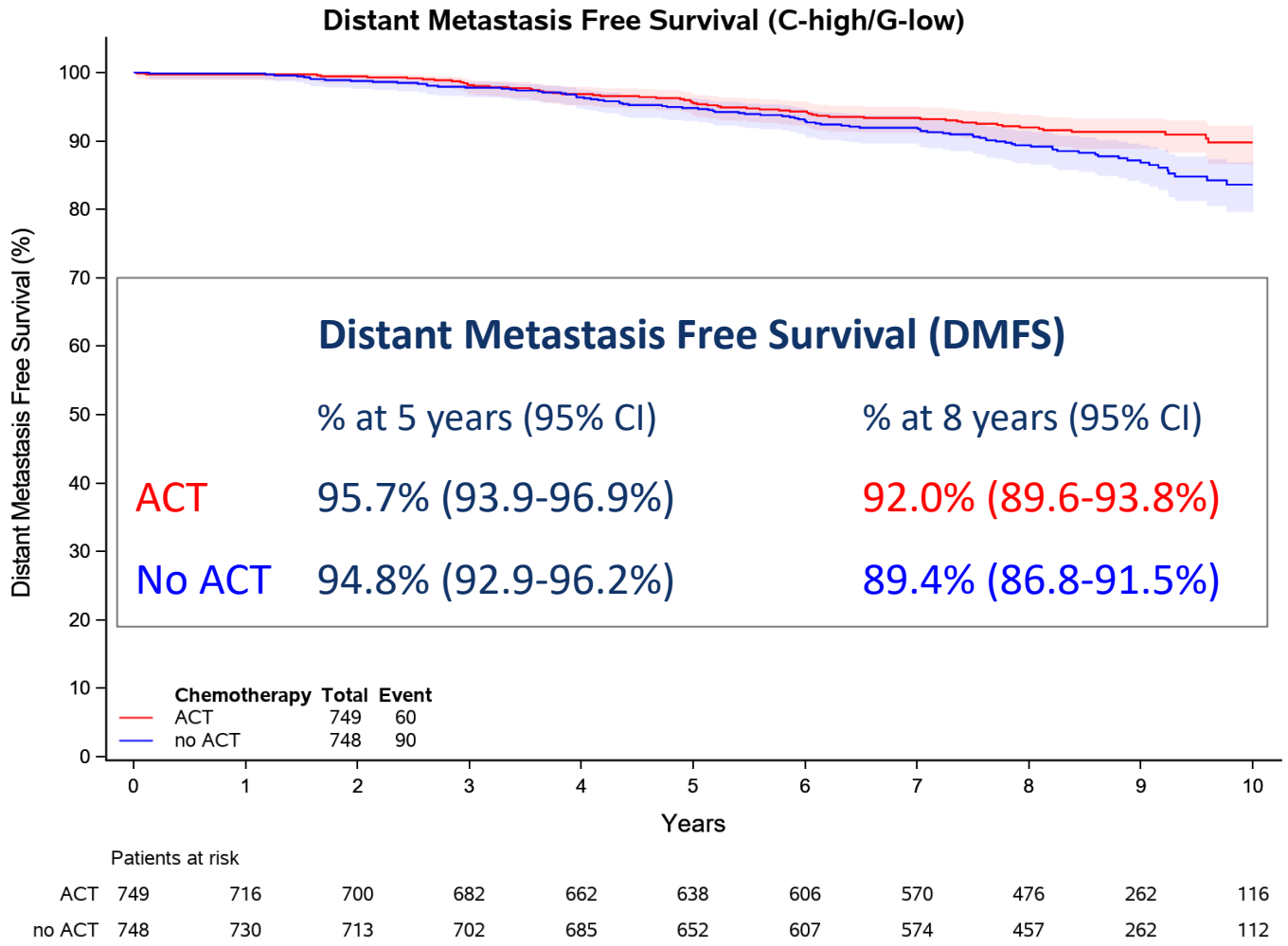
**At 8.7y median FU, DMFS in 4 risk groups**

**Excellent prognosis and low rate of events in all groups except Clinical High/Genomic High**

**Type of first event (n = 650)**

- distant recurrences: 68.8%
- death of any cause: 31.2%

# SECONDARY ENDPOINT
# DMFS C-High/G-Low risk (ITT population) CT vs no CT




**Absolute difference in DMFS between CT and no CT groups:**

- at 5 years: **0.9 ± 1.1** % points
- at 8 years: **2.6 ± 1.6** % points

**Type of first event (n = 150)**

- distant recurrences: 74.7%
- death of any cause: 25.3%

# SECONDARY ENDPOINT
# C-High/G-Low risk (ITT population) CT vs no CT
# ITT analysis

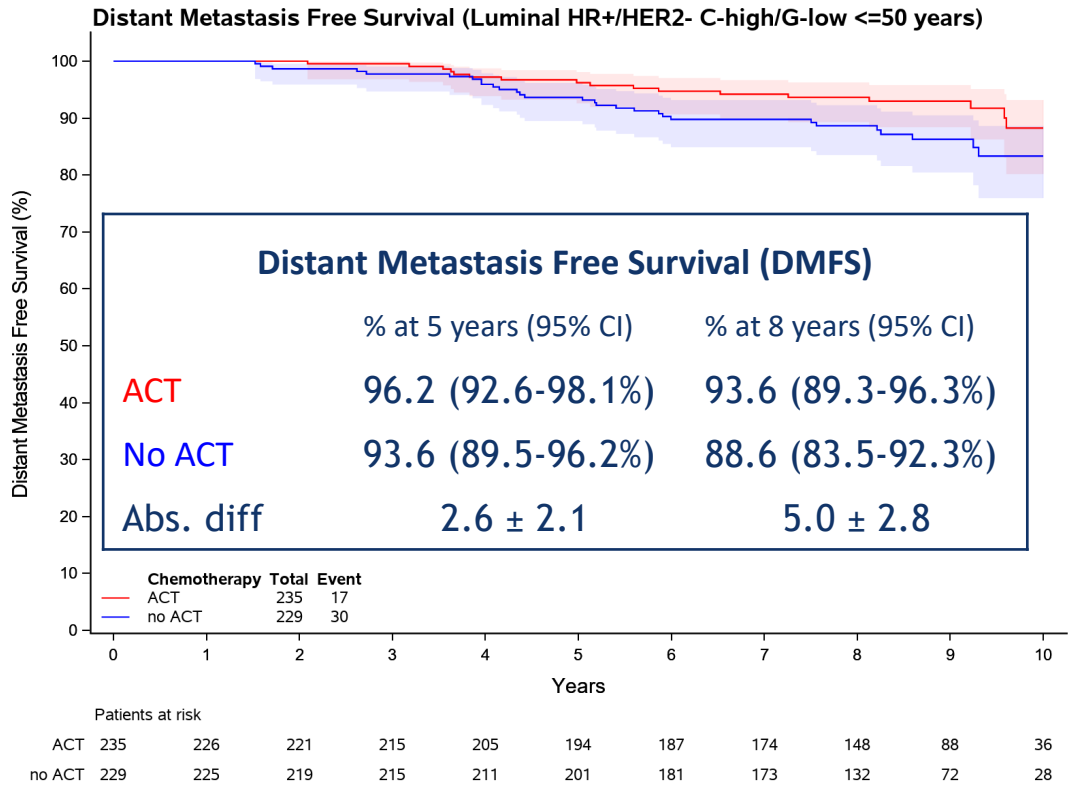
**Results for LN0 and LN1-3+ are similar**

| C-High / G-Low CT vs no CT ITT population | | | | | | | |
|---|---|---|---|---|---|---|---|
| Endpoint | Treatment | Patients | Observed events | % at 5 years (95%CI) | Absolute difference (±SE) at 5 years (percentage points) | % at 8 years (95%CI) | Absolute difference (±SE) at 8 years (percentage points) |
| DMFS | CT | 749 | 60 | 95.7 (93.9-96.9%) | 0.9 ± 1.1 | 92.0 (89.6-93.8%) | 2.6 ± 1.6 |
| | No CT | 748 | 90 | 94.8 (92.9-96.2%) | | 89.4 (86.8-91.5%) | |
| DMFI | CT | 749 | 50 | 96.4 (94.7-97.5%) | 0.7 ± 1.0 % | 93.1 (90.9-94.8%) | 2.4 ± 1.5 |
| | No CT | 748 | 75 | 95.7 (93.9-96.9%) | | 90.7 (88.2-92.7%) | |
| DFS | CT | 749 | 110 | 93.1 (90.9-94.7%) | 2.9 ± 1.5 | 86.4 (83.5-88.8%) | 3.5 ± 2.0 |
| | No CT | 748 | 138 | 90.2 (87.8-92.2%) | | 82.9 (79.8-85.6%) | |
| OS | CT | 749 | 37 | 98.4 (97.2-99.1%) | 1.1 ± 0.8 | 95.7 (93.9-97.0%) | 1.4 ± 1.2 |
| | No CT | 748 | 53 | 97.3 (95.8-98.3%) | | 94.3 (92.2-95.8%) | |

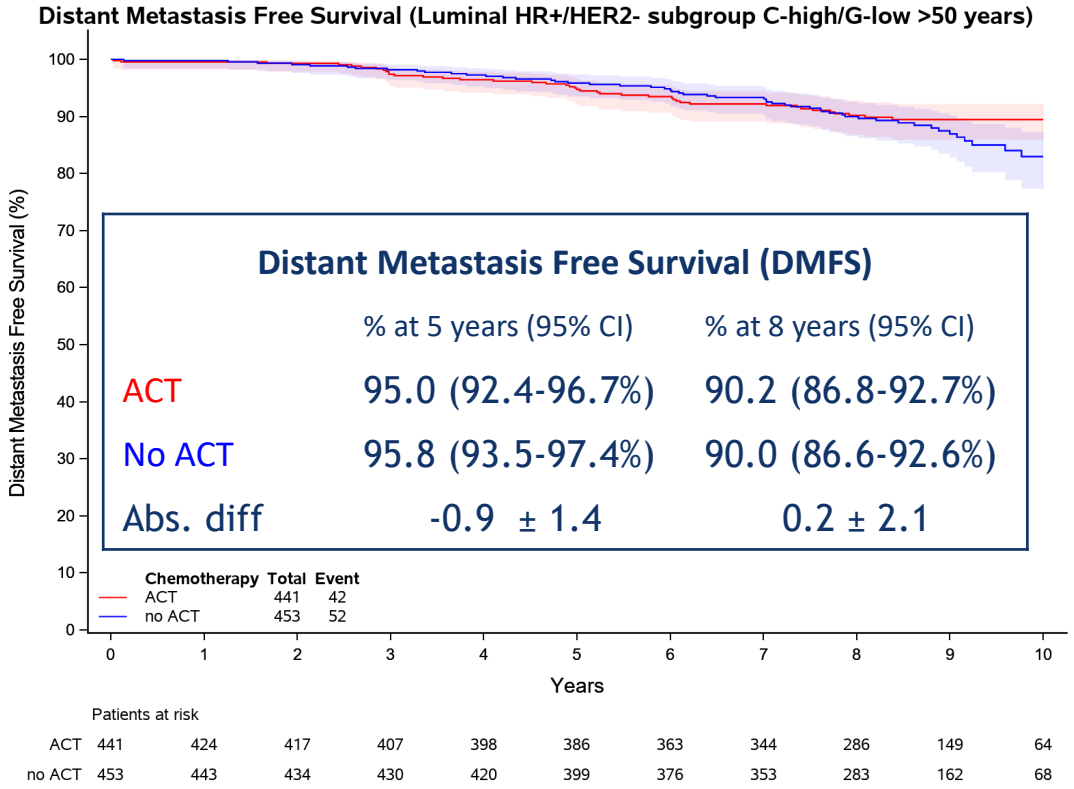
# Effect of chemotherapy by age in HR+/HER2- subgroup C-High/G-Low group

# DMFS in C-High / G-Low risk patients with luminal cancers (HR+/HER2-) stratified by age ITT population

## Age ≤50 years




## Age >50 years




**5% difference**

**NO difference**

# DMFS in C-High / G-Low risk patients with luminal cancers (HR+/HER2-) stratified by age ITT population

- 96% patients received adjuvant endocrine therapy
- In the group of younger <= 50 y.o patients who did not receive chemotherapy:
  - **Most frequent treatment is tamoxifen 5yr alone (55%); 16% received OFS** (vs 26% in chemotherapy group); CT vs no CT delta 5.0% (SE+/-2.8)

Note: In TailorX, premenopausal clinical high-risk RS16-20 and RS21-25 a similar effect CT vs no CT: Δ 6.5% (SE ± 4.9%) and Δ 8.7% (SE ± 6.2%)

**It is possible that this age-dependent effect is due to chemotherapy-induced ovarian function suppression**

***Although cautious interpretation is needed, analyses suggests that in women younger than 50, in the C-high/G-low group, tamoxifen alone might not be the optimal treatment.***

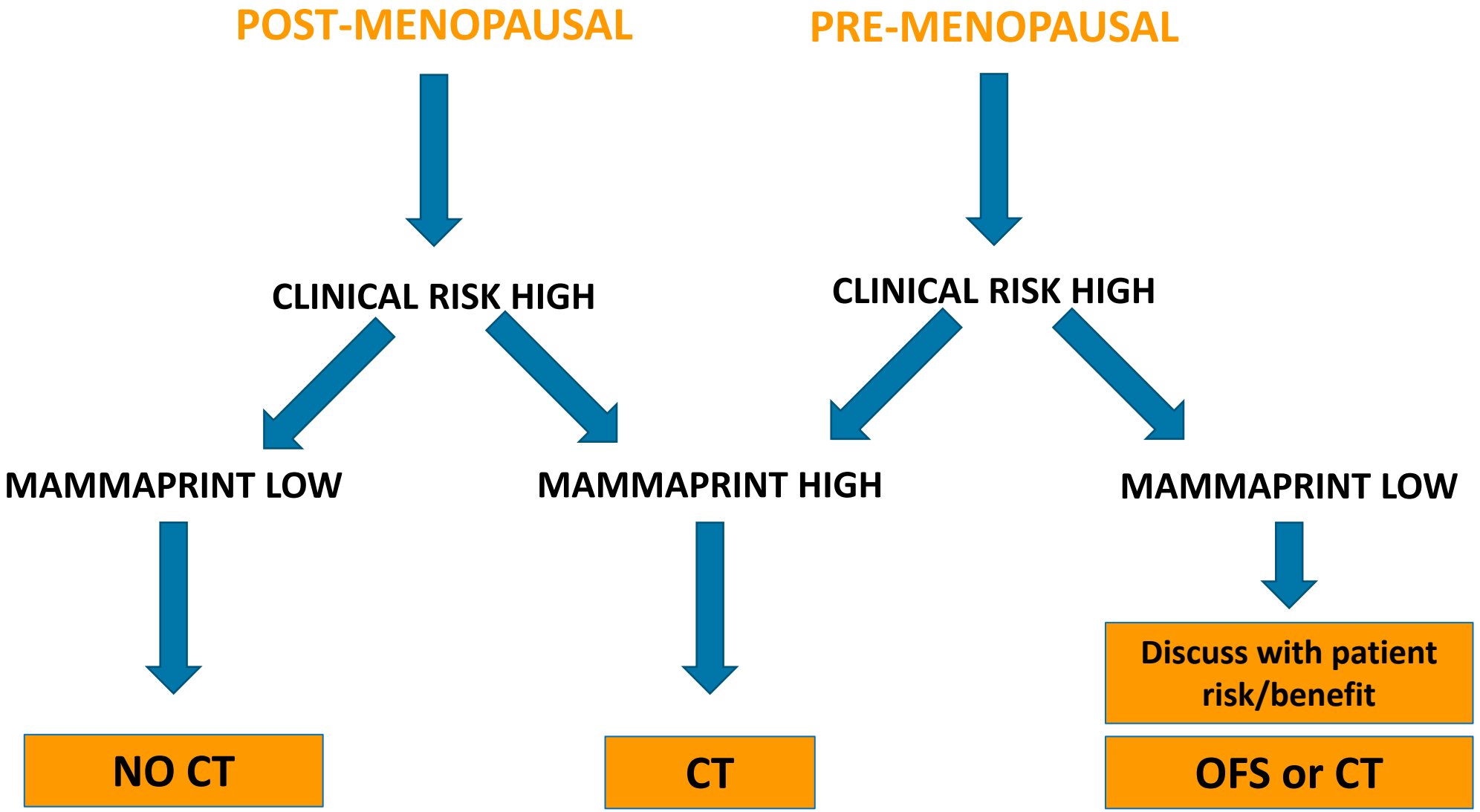
***Additional argument: this is a late effect (starts after 4 years), and CT benefit is seen in the 1st 5 yrs, according to the EBCCTG overview***

*F. Cardoso, oral presentation SABCS 2019, EBCTCG Lancet 2005*

# CONCLUSIONS

- **At 8.7 years** medium FU, **the primary endpoint continues to be met in CT untreated C-High/G-Low risk women**, **confirming MINDACT as a positive de-escalation study**
- **At 8 years**, the estimated **DMFS gain for CT administration** in **C-High/G-Low is 2.6%** and must be balanced with CT harmful side effects
- **Omitting CT** in C-High/G-Low **postmenopausal women** continues to be **safe** (DMFS gain 0.2% ± 2.3%), and a **fully preserved performance of MammaPrint** to forego adjuvant CT is demonstrated.
- In **premenopausal women** the **difference** seen might be **clinically relevant** (DMFS gain 5% ± 2.8%)**; importantly, this effect may possibly be related to chemotherapy-induced ovarian function suppression.**
- Overall in the **C-Low/G-High** risk patients, there is no advantage of guiding treatment based on the genomic risk
- Results remain valid for both **LN-negative** and **LN(1-3)positive** patients

# Proposal for clinical implementation of MINDACT results



# ACKNOWLEDGMENTS


## ALL THE MINDACT PATIENTS

**Other MINDACT PIs:** Martine Piccart and Emiel Rutgers

**MINDACT Statistician:** Coralie Poncet

**MINDACT's leading scientist:** Laura van 't Veer

**MINDACT leading Pathologist:** Giuseppe Viale

**TRANSBIG Partners**

**All National Teams and Participating Cooperative Groups**

**EORTC HQ staff**

**BIG HG staff**

**MINDACT Fellows**

**All Investigators and Research teams**

**MINDACT Steering and Executive Committee members**

**EUROPA Donna**


| Country | Enrolled pts |
|---|---|
| Netherlands (NKI) | 2092 |
| France (UCBG) | 2065 |
| Germany (WSG) | 835 |
| Belgium (EORTC) | 828 |
| Spain (SOLTI) | 546 |
| Italy (GOIRC) | 199 |
| UK (NCRI-BCG ) | 66 |
| Slovenia (IOL) | 37 |
| Switzerland (EORTC) | 25 |
| **Total** | **6693** |

# ACKNOWLEDGMENTS-FUNDING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|---|---|
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| KWF Kankerbestrijding (Dutch Cancer Society) | Association Le cancer du sein, parlons-en! |
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