2026 ASCO ANNUAL MEETING

# First results from the OPTIMA phase III randomized non-inferiority trial of test-directed chemotherapy in patients with high clinical risk ER-positive HER2-negative early breast cancer.

*a pre-planned time-driven analysis*

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OPTIMA is registered as ISRCTN42400492

# The OPTIMA result

OPTIMA demonstrates that the 50-gene Prosigna test identifies a group of about 2/3 of patients with ER-positive HER2-negative early breast cancer who do not have a meaningful chance of benefit from adjuvant chemotherapy.

Our study population included women aged 40 or older and patients with up to 9 involved lymph nodes.

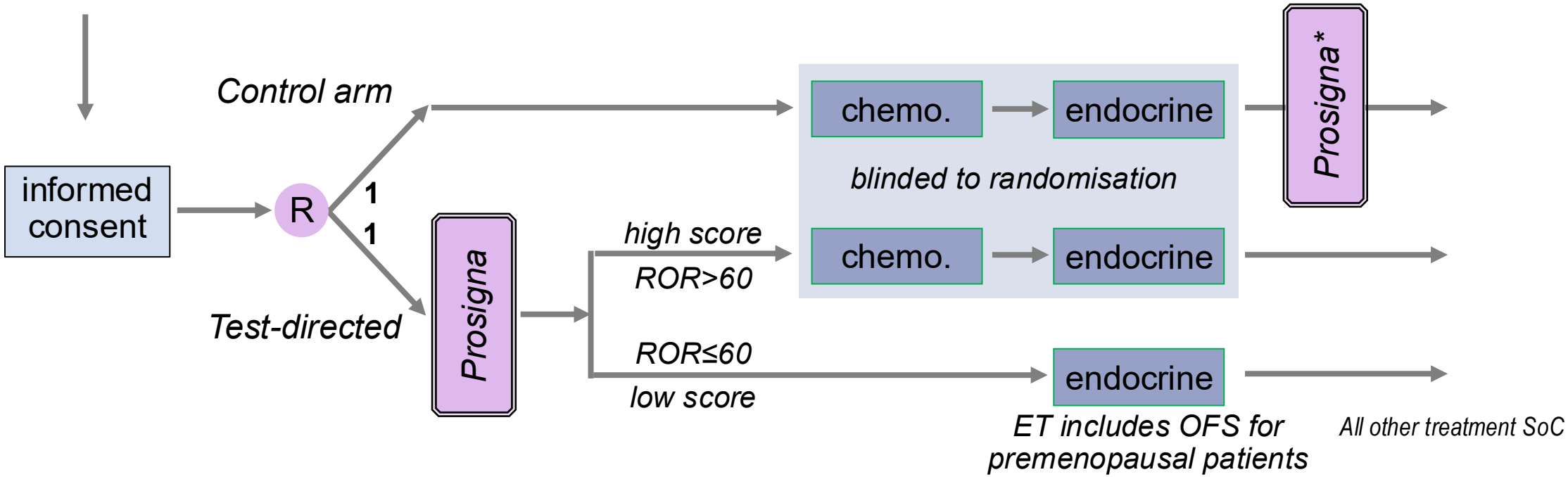
# Background

- Tumor gene expression assays are widely used to assist chemotherapy decisions for postmenopausal EBC with up to 3 involved lymph nodes
- Supporting evidence for premenopausal patient use is mixed
- There is no prospective evidence for higher levels of lymph node involvement
- OPTIMA is an international RCT that recruits high clinical risk patients
- The OPTIMA hypothesis is that the number of involved nodes does not affect chemotherapy response for low test-score tumors
- The OPTIMA pilot study selected the 50-gene Prosigna test for the main trial
  - Tumors with a Risk of Recurrence Score >60 are categorized high risk if N0

# OPTIMA design

**Main eligibility criteria**

- Women & men age ≥40 with excised breast cancer
- ER-pos (IHC>10%) & HER2-neg
- Nodes: ▸0-9N+,
  ▸minimum T-size requirement if N0/ N1mi
- Neoadjuvant chemotherapy prohibited



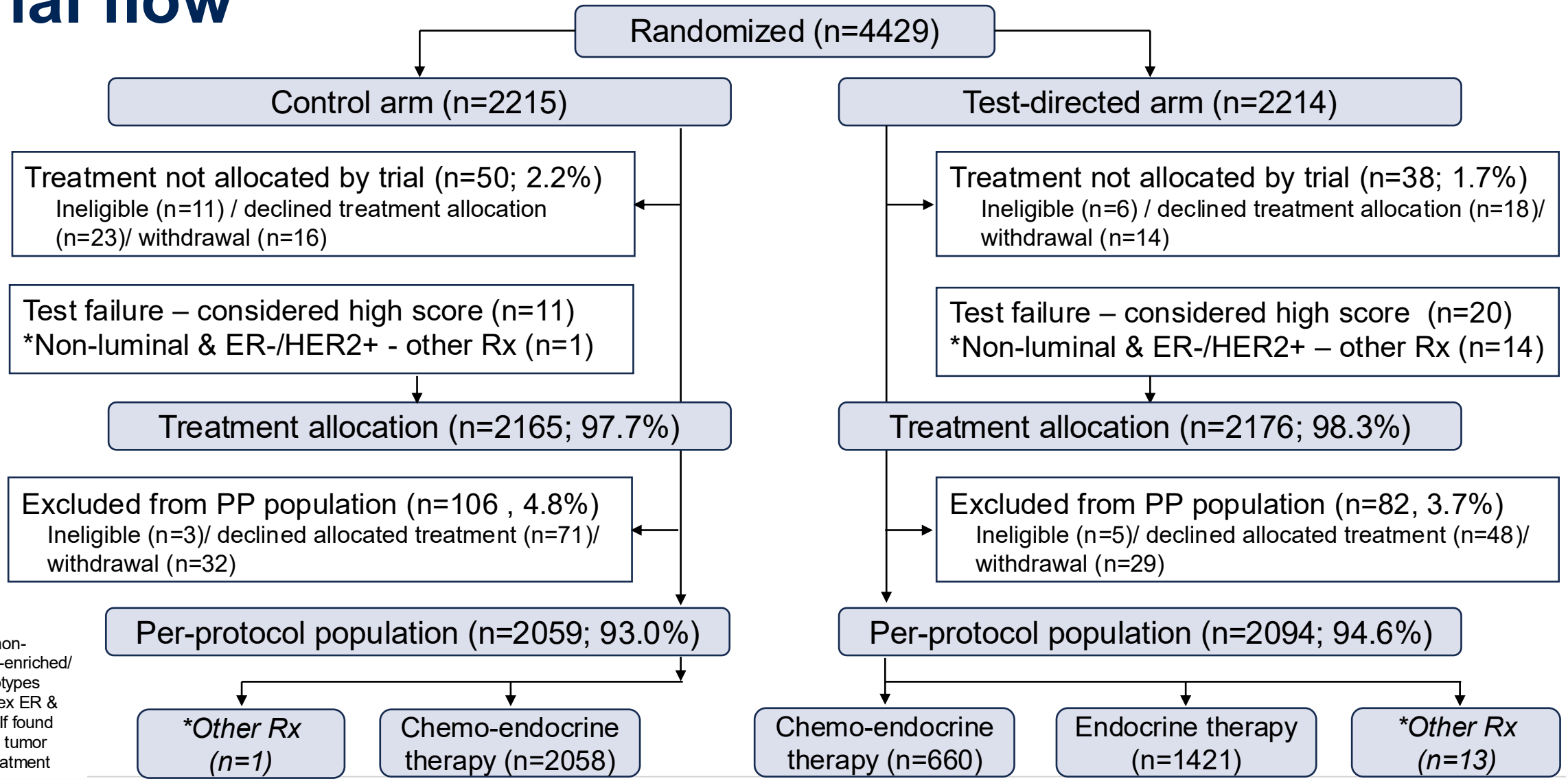

*Control arm Prosigna testing used for analysis only. U.K. control arm testing performed following recruitment completion

# Statistical design

- Primary outcome: Invasive Breast Cancer Free Survival (IBCFS) endpoint
  - local/ regional/ distant relapse; 2nd 1° breast cancer; death from any cause
- Primary analysis: per-protocol population – minimum follow-up 1 year
- Non-inferiority hypothesis – 3% absolute noninferiority margin for IBCFS
  - Supports health economics analysis
- 83% power at one-sided 5% significance assuming 87.5% 5-year IBCFS in control arm for primary analysis
- Key 2° analysis performed in per-protocol population with tumor ROR ≤60
- Non-inferiority hypothesis – absolute 3.5% noninferiority margin for IBCFS
  - Defines clinical utility

Patients were recruited between January 2017 and December 2025

# Trial flow

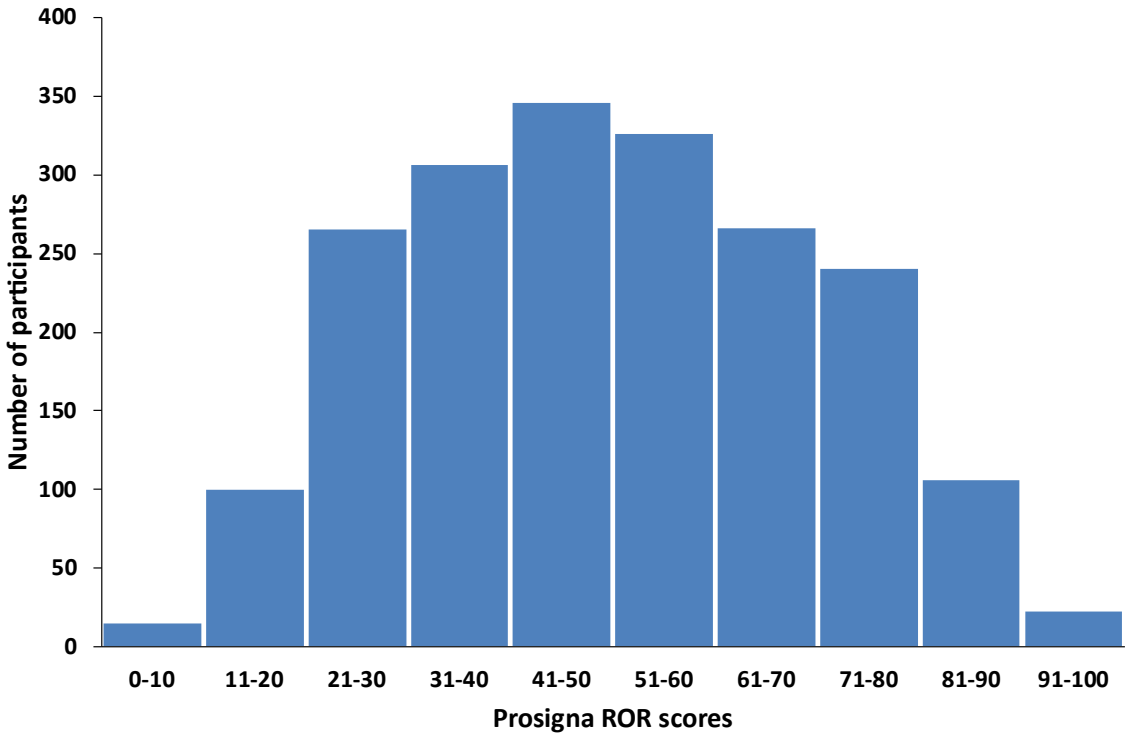



*Tumors with non-luminal (HER2-enriched/ Basal-like) subtypes underwent reflex ER & HER2 testing. If found ineligible given tumor appropriate treatment

# Distribution of ROR scores

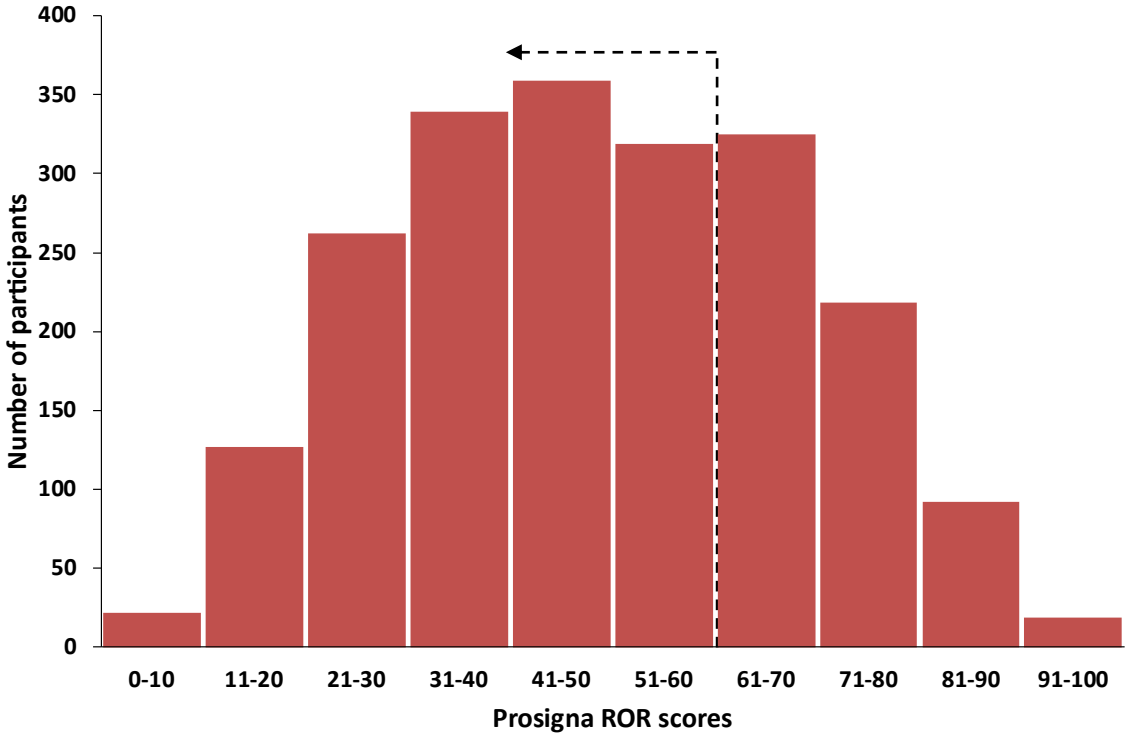
Per Protocol population

## Control arm




Median: ROR = 50 (IQR 34-65)
66.0% had ROR ≤60

## Test-directed arm




Median: ROR = 49 (IQR 34-65)
67.8% had ROR ≤60

# Patient and tumor characteristics (PP population)

| Characteristic | Control arm | Test directed arm | Total |
|---|---|---|---|
| number PP | 2059 | 2094 | 4153 |
| age (range) | 55 (40-84) | 56 (40-82) | 56 (40-84) |
| premenopausal | 776 (38%) | 775 (37%) | 1551 (37%) |
| postmenopausal | 1265 (61%) | 1302 (62%) | 2567 (62%) |
| men | 18 (1%) | 17 (1%) | 35 (1%) |
| grade 1-2 | 1417 (69%) | 1465 (70%) | 2862 (69%) |
| grade 3 | 642 (31%) | 629 (30%) | 1271 (31%) |
| tumor size <30 mm | 1104 (54%) | 1128 (54%) | 2232 (54%) |
| tumor size ≥30 mm | 955 (46%) | 966 (46%) | 3050 (46%) |
| nodes: 0 / micromets | 160 (8%) | 167 (8%) | 327 (8%) |
| 1-3* | 1515 (74%) | 1534 (73%) | 3049 (73%) |
| 4-9 | 384 (18%) | 393 (19%) | 777 (19%) |

*39% of pN1 tumors had a sentinel node biopsy only

# Events in the PP population

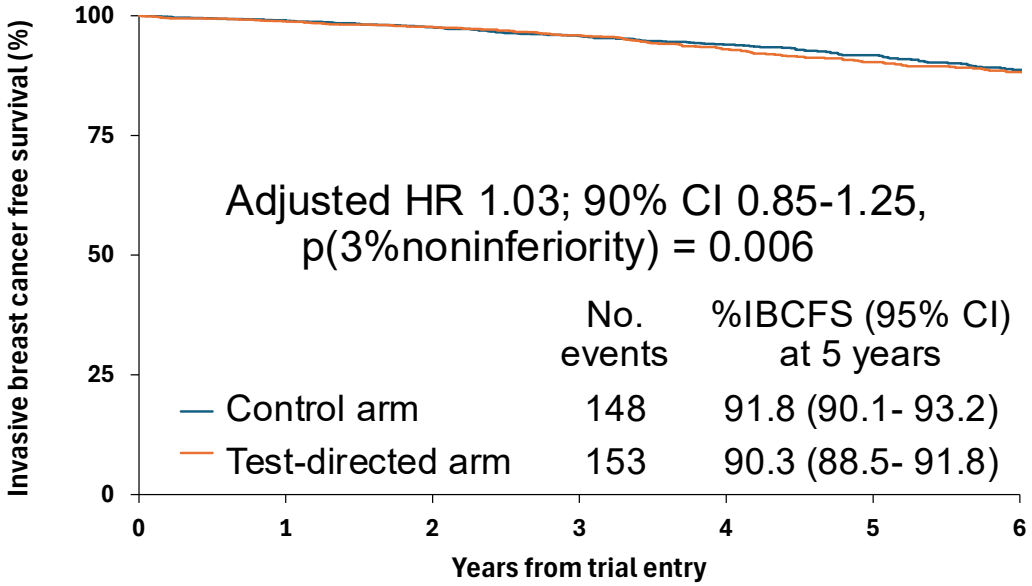
Median follow-up 4.0 years: Inter-Quartile Range 2.0-6.0 years

| Outcome | Control arm | Test directed arm | Control ROR≤60 - CET | Test-directed ROR≤60 - ET |
|---|---|---|---|---|
| Number at risk | 2059 | 2094 | 1358 | 1421 |
| Any invasive cancer event† | 148 (7.2%) | 164 (7.8%) | 73 (5.4%) | 93 (6.5%) |
| Breast cancer recurrence (all) | 118 (5.7%) | 123 (5.9%) | 50 (3.7%) | 60 (4.2%) |
| loco-regional | 24 | 23 | 11 | 13 |
| contralateral breast | 9 | 11 | 5 | 8 |
| distant recurrence (± loco-regional) | 100 | 103 | 39 | 46 |
| Non-breast malignancy | 30 (1.5%) | 42 (2.0%) | 23 (1.7%) | 32 (2.3%) |
| Death (all) | 72 (3.5%) | 80 (3.8%) | 32 (2.3%) | 32 (2.3%) |
| breast cancer | 42 | 48 | 14 | 18 |
| other cancer | 7 | 11 | 4 | 9 |
| other cause | 23 | 21 | 14 | 5 |
| IBCFS events | 148 (7.2%) | 153 (7.3%) | 68 (5.0%) | 76 (5.3%) |

†Patients can have multiple types of cancer event

# Invasive Breast Cancer Free Survival

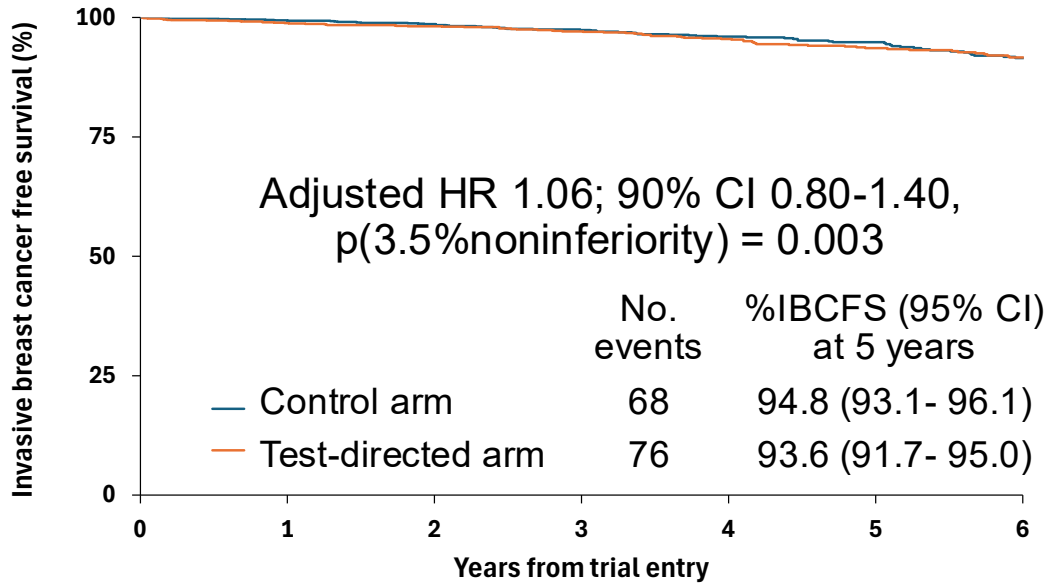
## Complete Per Protocol population




| Number at risk: | | | | | | | |
|---|---|---|---|---|---|---|---|
| Control | 2059 | 1818 | 1563 | 1283 | 999 | 741 | 485 |
| Test-directed | 2094 | 1857 | 1591 | 1303 | 989 | 724 | 481 |

Demonstrated non-inferiority limit = 2%
No certainty of chemotherapy benefit
1.5% observed 5-year difference –favors chemotherapy

## ROR ≤60 subpopulation




| Number at risk: | | | | | | | |
|---|---|---|---|---|---|---|---|
| Control | 1358 | 1207 | 1043 | 862 | 672 | 504 | 337 |
| Test-directed | 1421 | 1257 | 1086 | 905 | 694 | 503 | 342 |

Demonstrated non-inferiority limit = 2%
No certainty of chemotherapy benefit
1.2% observed 5-year difference –favors chemotherapy

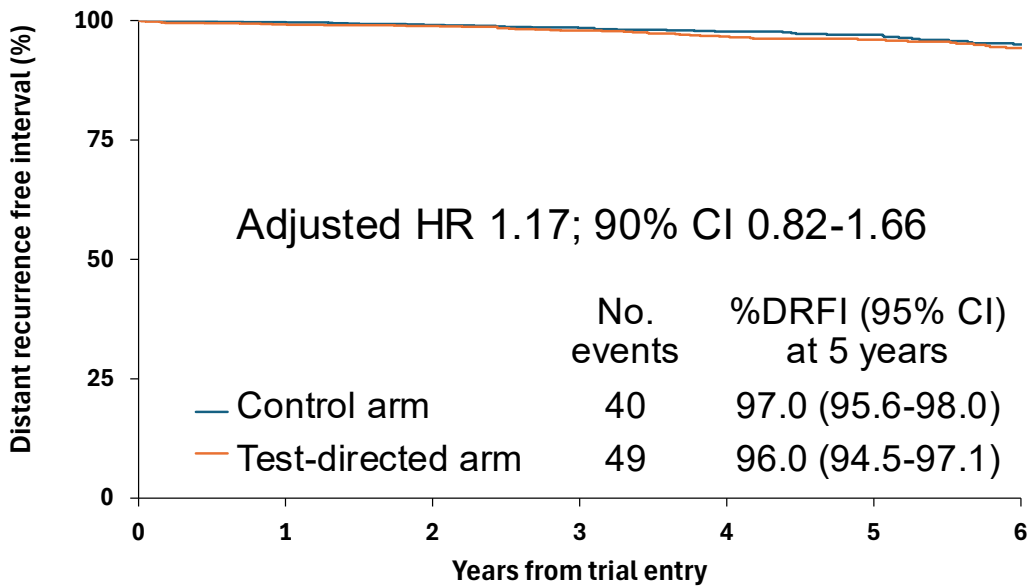
# Distant Recurrence Free Interval

## Complete Per Protocol population


| Number at risk: | | | | | | | |
|---|---|---|---|---|---|---|---|
| Control | 2059 | 1822 | 1568 | 1286 | 1004 | 746 | 489 |
| Test-directed | 2094 | 1863 | 1599 | 1311 | 993 | 732 | 487 |

0.8% observed 5-year difference –favors chemotherapy

## ROR ≤60 subpopulation

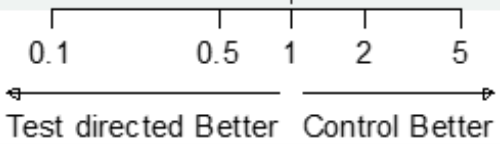



| Number at risk: | | | | | | | |
|---|---|---|---|---|---|---|---|
| Control | 1358 | 1209 | 1046 | 865 | 676 | 507 | 340 |
| Test-directed | 1421 | 1262 | 1093 | 911 | 696 | 509 | 346 |

1.0% observed 5-year difference –favors chemotherapy

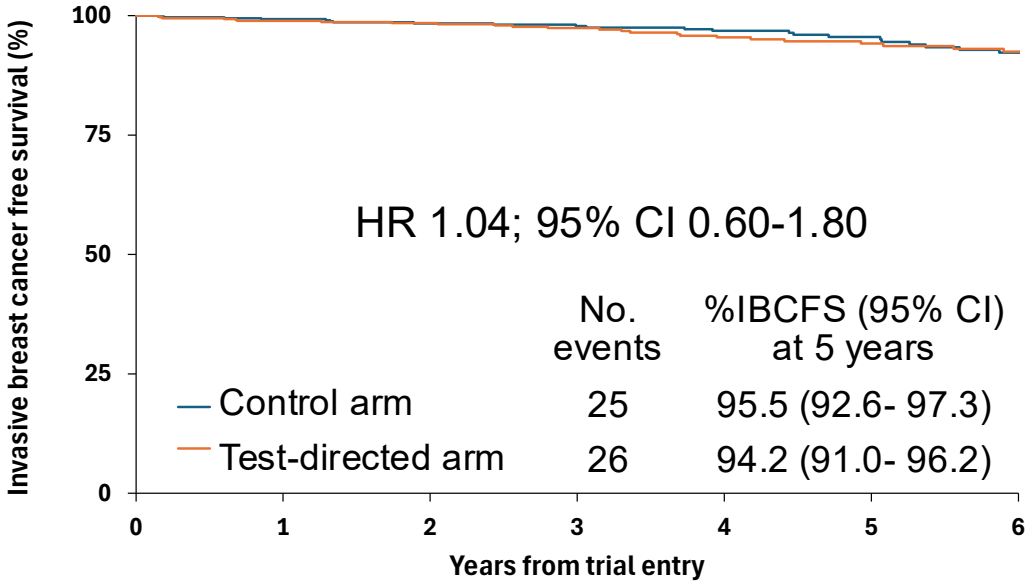
# **Subgroup analysis:** low ROR score population

| Subgroup | Test directed | Control | HR (95% CI) |
|---|---|---|---|
| | *No. of events/No. of patients* | | |
| Overall | 76/1421 | 68/1358 | 1.06 (0.77 to 1.48) |
| Menopausal status | | | |
| Pre-menopausal | 26/559 | 25/561 | 1.04 (0.60 to 1.80) |
| Post-menopausal | 50/858 | 42/791 | 1.14 (0.76 to 1.71) |
| Grade | | | |
| 1 or 2 | 60/1184 | 48/1126 | 1.22 (0.84 to 1.78) |
| 3 | 16/237 | 20/232 | 0.78 (0.40 to 1.50) |
| Tumour size | | | |
| <=30mm | 39/809 | 28/770 | 1.30 (0.81 to 2.10) |
| >30mm | 37/612 | 40/588 | 0.93 (0.60 to 1.46) |
| Nodal status | | | |
| pN1(+/-sn) | 56/1063 | 48/1015 | 1.11 (0.76 to 1.64) |
| pN2 | 20/268 | 17/243 | 1.19 (0.62 to 2.29) |
| Intended Chemotherapy | | | |
| Anthracycline containing | 6/176 | 6/163 | 0.89 (0.29 to 2.76) |
| Taxane containing | 5/163 | 5/142 | 1.05 (0.30 to 3.65) |
| Anthracycline+Taxane | 65/1082 | 57/1053 | 1.12 (0.79 to 1.60) |



# **IBCFS vs menopausal status:** low ROR score population

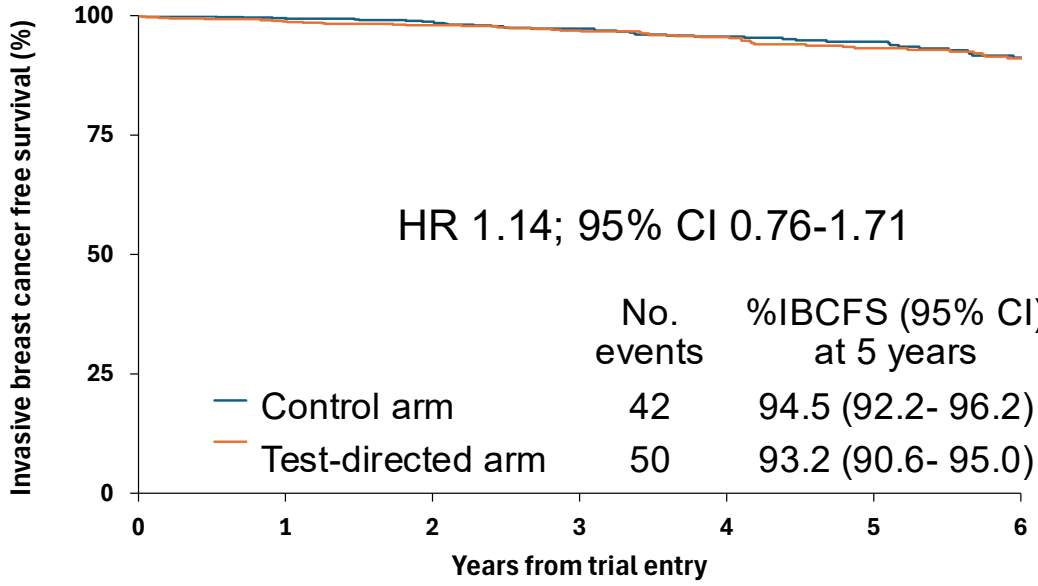
## Premenopausal




| Number at risk: | | | | | | | |
|---|---|---|---|---|---|---|---|
| Control | 561 | 481 | 409 | 338 | 258 | 200 | 140 |
| Test-directed | 559 | 487 | 410 | 347 | 256 | 195 | 135 |

1.3% observed 5-year difference -favors chemotherapy

## Postmenopausal

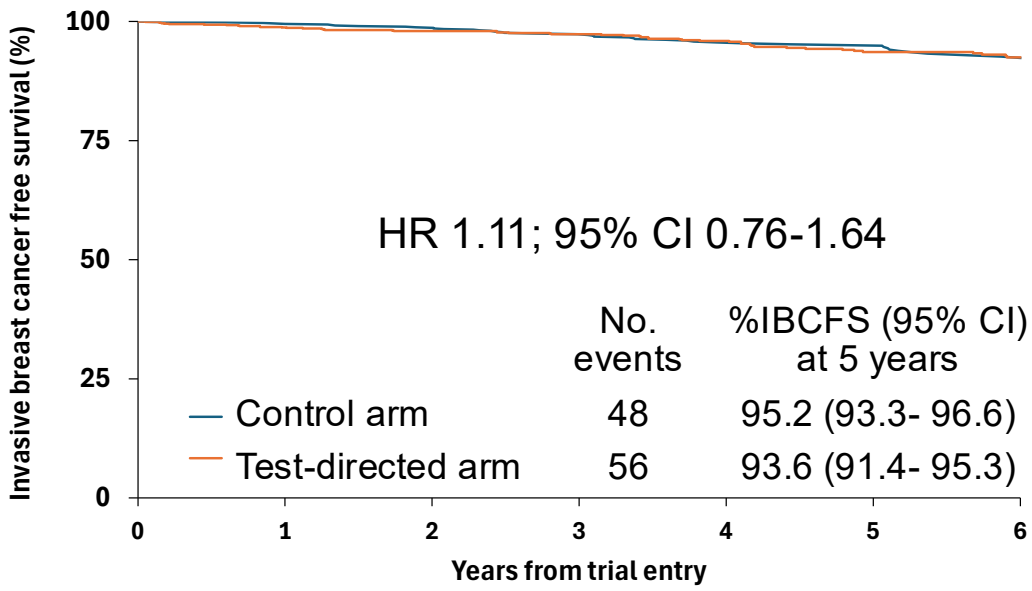



| Number at risk: | | | | | | | |
|---|---|---|---|---|---|---|---|
| Control | 791 | 721 | 631 | 522 | 414 | 304 | 197 |
| Test-directed | 858 | 766 | 673 | 556 | 437 | 307 | 207 |

1.3% observed 5-year difference -favors chemotherapy

# **IBCFS vs nodal status:** low ROR score population

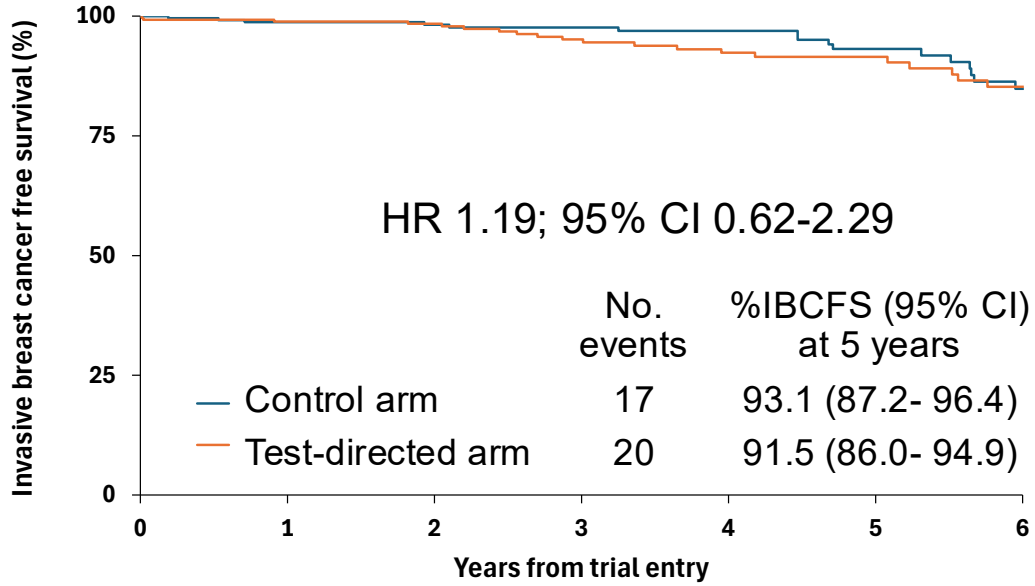
## 1-3 involved nodes




| Number at risk: | | | | | | | |
|---|---|---|---|---|---|---|---|
| Control | 1015 | 914 | 798 | 651 | 499 | 382 | 264 |
| Test-directed | 1063 | 953 | 829 | 700 | 539 | 389 | 270 |

1.6% observed 5-year difference -favors chemotherapy

## 4-9 involved nodes

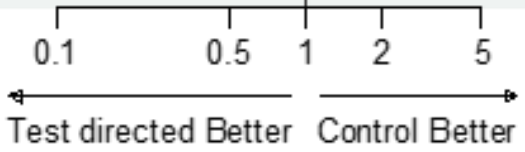



| Number at risk: | | | | | | | |
|---|---|---|---|---|---|---|---|
| Control | 243 | 214 | 181 | 155 | 125 | 84 | 48 |
| Test-directed | 269 | 232 | 197 | 158 | 118 | 86 | 49 |

1.6% observed 5-year difference -favors chemotherapy

# **IBCFS vs stage prognostic groups:** low ROR score population

| Subgroup | Test directed | Control | HR (95% CI) |
|---|---|---|---|
| | *No. of events/No. of patients* | | |
| Overall | 76/1421 | 68/1358 | 1.06 (0.77 to 1.48) |
| Tumor stage | | | |
| IIA | 14/412 | 10/399 | 1.39 (0.62 to 3.09) |
| IIB | 35/585 | 33/550 | 1.04 (0.65 to 1.68) |
| IIIA | 27/414 | 23/389 | 1.11 (0.64 to 1.93) |



# Sensitivity analyses

| | % rate (95% CI) at 5 years | Adjusted HR (90% CI) |
|---|---|---|
| **IBCFS in full ITT population** | | |
| Control Arm | 91.2% (89.5-92.6) | 1.03 (90% CI 0.86 - 1.23) |
| Test directed Arm | 89.9% (88.1-91.4) | |
| **IBCFS in ITT subpopulation with tumor ROR ≤60** | | |
| Control Arm | 94.3% (92.5-95.7) | 1.03 (90% CI 0.79 - 1.34) |
| Test directed Arm | 93.5% (91.6-94.9) | |
| **IDFS in full ITT population** | | |
| Control Arm | 89.9% (88.1-91.3) | 1.06 (90% CI 0.90 - 1.25) |
| Test directed Arm | 88.2% (86.3-89.8) | |

# Limitations

- This was a time driven analysis when all patients had been on study for a minimum of 1 year: 63% of patients have under 5 years follow-up
  - Most chemotherapy effect on recurrence is seen in the first 5 years
- We recruited a predominantly white population although representative of the breast cancer population of participating countries
- Pre-menopausal women aged <40 years were excluded
- Cost-effectiveness analysis is ongoing

# Conclusions

- OPTIMA has demonstrated that the 50-gene Prosigna test identifies a patient group with minimal if any chemotherapy benefit
  - At most, 2 recurrences will be prevented for every 100 patients
- The 50-gene test can assist safe adjuvant chemotherapy decisions for:
  - premenopausal women aged at least 40 years treated with ovarian function suppression
  - patients with 4 to 9 involved lymph nodes or stage IIIA tumors

# Acknowledgements

optima
personalised treatment of breast cancer

- The 4429 patients who took a personal risk to make this trial possible
- Numerous staff who worked hard to deliver the trial at 171 recruiting sites and our 3 coordinating centers
- The U.K. NIHR HTA* (our primary funder), our additional funders and our many supporters, including patient groups, who believed in the trial

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# A lay summary of OPTIMA

- The OPTIMA trial was designed to reduce unnecessary chemotherapy use for people with newly diagnosed hormone sensitive breast cancer.
- OPTIMA recruited more than 4400 patients over 9 years from 6 countries.
- The trial compared the number of breast cancer recurrences and deaths in patients treated with standard chemotherapy with those having a chemotherapy decision made using the Prosigna test. Everybody received hormone therapy.
- Prosigna is a 50-gene test performed on cancer tissue removed at surgery.
- OPTIMA showed that at most 2% of patients with low test-score tumors benefit from chemotherapy. Everybody gets chemotherapy side-effects.
- The trial included premenopausal women aged 40 or older and patients with more than 3 involved lymph nodes.