OPTIMAL PERSONALISED TREATMENT OF EARLY BREAST CANCER USING MULTI-PARAMETER ANALYSIS

A trial of a diagnostic test in ER+ve HER2-ve breast cancer
OUTLINE

• Background to OPTIMA
• Multi-parameter assays
• Ongoing trials
• The OPTIMA trial
THE BACKGROUND QUESTION

WHO SHOULD WE TREAT WITH CHEMOTHERAPY?
BENEFIT OF ANTHRACYCLINE CHEMOTHERAPY IN EARLY BREAST CANCER

- Chemotherapy has very little if any effect on recurrence after 5 years
- Chemotherapy affects BC mortality for up to 10 years
- Gains from modern chemo are expected to be greater than historic regimens but only a minority of patients will benefit

![Graph showing the comparison between No Chemotherapy and Chemotherapy](image)

- 8575 women, 82% node+ve
- 8.0% gain at 10yrs
- 47.4% vs 39.4%
- 34.6% vs 26.1%

BREAST CANCER CHEMO-SENSITIVITY: THE OXFORD META-ANALYSIS

• Oxford Overview demonstrates that patients with ER-positive breast cancer benefit from adjuvant chemotherapy.

• The relative benefits for chemotherapy are the same for all patients.
  • No identified factors including ER status predict chemo-sensitivity.
  • Little information on tumour grade in the analysis.

• The overall benefit from chemotherapy is modest
  • Patients not destined to relapse cannot benefit from treatment!
CHEMOTHERAPY SENSITIVITY

Hypothetical breast cancer population with one third improvement 10yr BCSS from chemotherapy
PROGNOSIS AND PREDICTION

• Prognostic factors give information about likely disease outcome
  • lymph node status

• Predictive factors give information about treatment response
  • BRCA mutation & PARP inhibitor therapy

• Some factors are both prognostic and predictive
  • ER & HER2 status
MULTI-PARAMETER ASSAYS
ONCOTYPE DX: RS AS CONTINUOUS PREDICTOR IN TAM TREATED PATIENTS

Distant Recurrence at 10 Years

Low-Risk Group                  Intermediate-Risk Group                  High-Risk Group

data from NSABP B14: Paik NEJM 2004, 351:2817
<table>
<thead>
<tr>
<th>Test</th>
<th>Parameters</th>
<th>1° Validation Population</th>
<th>Location</th>
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<tbody>
<tr>
<td>Oncotype DX</td>
<td>16 +5 genes RT-PCR</td>
<td>ER+ (pN0) +ET</td>
<td>Central/ USA</td>
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<tr>
<td>MammaPrint</td>
<td>70 genes array</td>
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<td>EndoPredict</td>
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<tr>
<td>IHC4</td>
<td>4 proteins IHC4</td>
<td>ER+ HER2- (pN0-2) +ET</td>
<td>Local/ Central</td>
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# MPA Tests Are Analytically “Unique”

<table>
<thead>
<tr>
<th>Genes</th>
<th>Oncotype DX</th>
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<td>KRT17</td>
<td>RPLP0</td>
<td></td>
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</table>
RISK OF RECURRENCE IS INFLUENCED BY BOTH TUMOUR BIOLOGY AND STAGE

Nottingham Prognostic Index = sum of:
grade (grade 1 =1, grade 2 =2, grade 3 =3)
node status (0 nodes =1, 1-3 nodes =2, ≥4 nodes = 3)
tumour diameter (cm) x 0.2

Overall Survival (Kaplan–Meier) by NPI in the ONCOPOOL data set

To a 1st approximation tumour grade and stage are independent and equal risk factors

928 patients from transATAC

the majority of patients with N+ disease fall into high-risk groups because of nodal status

EPClin = combined EP score + node status + tumour size

THE NSABP B-20 & SWOG 88-14 ONCOTYPE DX STUDIES

**NSABP B-20**

- Node –ve, ER +ve
- 651 patients included (45% < 50)/2299 patients in parent study.

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**SWOG 88-14**

- Postmenopausal
- HR +ve, Node +ve
- 367 blocks from tam & CAF-T arms (=40% recovery); demographics representative of parent; 227 pN1, 140 pN2. 2299 patients in parent study.

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**Endpoint:** 5 & 10yr DFS
- tam + MF
- tam + CMF

**Endpoint 10yr DDFS; chemo arms combined**
- tam

**Patients & outcome consistent with parent B-20 study; CMF & MF the same**

**Endpoint:** 5 & 10yr DFS
- tam
- tam + MF
- tam + CMF

**CAF + tam not superior to tam**
- Excluded from Oncotype study
- Endocrine therapy continued to 5 years
RESULTS & LIMITATIONS

Both studies show chemotherapy benefit is confined to patients with high RS tumours

• Both studies small, especially SWOG 88-14
• Both studies contained HER2-positive patients (12% in SWOG 88-14)
  • B-20 re-analysis to adjust for HER2 2018: result still significant but weaker
• 88-14 very limited analysis for HER2 – non evaluable
• B-20 tam patients formed the main population used for Oncotype DX derivation
  • Artificial increase in goodness of fit
• Neither study preserved original stratifications

Q: Are the results correct? A: probably but they hardly constitute level 1 evidence
PROSPECTIVE CLINICAL TRIALS

WHY DO WE NEED OPTIMA?
6,693 women enrolled: 79% pN0, 81% ER-pos HER2-neg

Evaluate Clinical-Pathological (AoL) risk and MammaPrint (70-gene) risk

- **Clin-Path & 70-gene both LOW risk**
  - N=2745
  - 41% (10%)

- **Discordant**
  - 32% (35%)
  - Clin-Path HIGH, 70-gene LOW: 72%, N=1550
  - Clin-Path LOW, 70-gene HIGH: 28%, N=592
  - N=2187

- **Clin-Path & 70-gene both HIGH risk**
  - 27% (55%)
  - N=1806

**R1**

- Use Clin-Path risk to decide Chemo or not
- Use 70-gene risk to decide Chemo or not
MINDACT RESULTS

- Complex trial, heterogeneous population (10% TNBC, 9.5% HER2 pos; 21% pN1)
- Insufficient power to compare randomised groups
- Primary EP = 95% chance of 5-yr DDFS >92% for genomic low/ clinical high no chemo group: achieved

- Genomic low/ clinical high risk 5yr DMFS Δ chemo vs not =1.5%
- Genomic high/ clinical low risk 5yr DMFS Δ chemo vs not = 0.8%
- All chemo vs not pNS

- Error in risk assessment affected 16% genomic high/ clinical low

Cardoso 2016 NEJM 375:717
TAILORx & PLANB COHORT STUDIES – ENDOCRINE THERAPY ONLY

• TAILORx pN0 cohort study (RS <11) Sparano 2015 NEJM 373:2005
• PlanB pN0-1 (RS ≤11) Nitz 2017 BCRT 165:573

Excellent outcome: confirms prognostic utility of ODX (small pN1 cohort)

TAILORx Five-year IDFS
pN0 93.8% [92.4–94.9%]

PlanB Five-year DFS ET alone:
- pN0 94.2% [90.4–98.0%]
- pN1 94.4% [89.5–99.3%]
TAILORx: pN0, ER-pos Her2-neg Breast Cancer

- Register Specimen banking
- RS <11 Endocrine Rx Registry
  - N=1619
- Oncotype DX® Assay
- RS 11-25: Randomize Endocrine Rx vs Chemo + Endocrine Rx
  - N=6711
- RS >25 Chemo + Endocrine Rx
  - N=1389

Unblinded 10273 patients registered

- 1° outcome IDFS (local recurrence exc DCIS, metastatic disease, any death, 2nd cancer)
- 2° outcomes: RFI, DRFI (i.e. BC-specific DFS & DDFS includes BC death), OS
- Statistical hypothesis = non-inferiority of IDFS (failure to demonstrate superiority) - 5yr control-arm IDFS 90%, Δ3% ⇒ HR 1.322 – 10% 1-sided significance, 95% power
- Sample size adjusted for 12% non-adherence
- Event-driven analysis – threshold 835

TAILORx RCT CONDUCT

• Trial population & treatment:
  • 33% <50yrs/ 36% pre-menopausal
  • Median tumour size 1.5cm: IQR 1.2-2.0 cm (i.e. 75% ≤2.0 cm)
  • 29% grade 1/ 57% grade 2/ 14% grade 3
  • 72% “clinical low risk”

• Chemotherapy (arm c): 56% TC, 29% anthracycline-non taxane
  • 5.4% non-compliance with assignment in endocrine therapy arm/ 18.4% in chemo-endocrine arm

• Analysis at median fu 7.5yrs
**TAILORx MAIN RESULT**

### Invasive Disease-Free Survival

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
<th>72</th>
<th>84</th>
<th>96</th>
<th>108</th>
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<tr>
<td>No. at Risk</td>
<td>3312</td>
<td>3204</td>
<td>3104</td>
<td>2993</td>
<td>2849</td>
<td>2645</td>
<td>2335</td>
<td>1781</td>
<td>1130</td>
<td>523</td>
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<tr>
<td>Endocrine therapy</td>
<td>3399</td>
<td>3293</td>
<td>3194</td>
<td>3081</td>
<td>2953</td>
<td>2741</td>
<td>2431</td>
<td>1859</td>
<td>1197</td>
<td>537</td>
</tr>
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</table>

**Hazard ratio for invasive-disease recurrence, second primary cancer, or death, 1.08 (95% CI, 0.94-1.24)**

P=0.26

### Distant Recurrence-Free Interval

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
<th>72</th>
<th>84</th>
<th>96</th>
<th>108</th>
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</thead>
<tbody>
<tr>
<td>No. at Risk</td>
<td>3312</td>
<td>3215</td>
<td>3142</td>
<td>3059</td>
<td>2935</td>
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<td>2432</td>
<td>2166</td>
<td>1866</td>
<td>1197</td>
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<tr>
<td>Endocrine therapy</td>
<td>3399</td>
<td>3318</td>
<td>3239</td>
<td>3147</td>
<td>3033</td>
<td>2833</td>
<td>2537</td>
<td>2147</td>
<td>1267</td>
<td>581</td>
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</table>

**Hazard ratio for recurrence at a distant site, 1.10 (95% CI, 0.85-1.41)**

P=0.48

### Events (ITT)

<table>
<thead>
<tr>
<th>9-year outcome</th>
<th>Hazard ratio (CE/E) [95%CI]</th>
<th>Pre-specified boundary</th>
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<tbody>
<tr>
<td>IDFS</td>
<td>1.08 [0.94-1.24]</td>
<td>1.322</td>
</tr>
<tr>
<td>DRFI</td>
<td>1.10 [0.85-1.41]</td>
<td>1.61</td>
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<table>
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<tr>
<th>Events (ITT)</th>
<th>Endo</th>
<th>Chemo-Endo</th>
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<tr>
<td>IDFS</td>
<td>5-years</td>
<td>7.2%</td>
</tr>
<tr>
<td></td>
<td>9-years</td>
<td>16.7%</td>
</tr>
<tr>
<td>DFRI</td>
<td>5-years</td>
<td>2.0%</td>
</tr>
<tr>
<td></td>
<td>9-years</td>
<td>5.5%</td>
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</table>

**Primary outcome met**
• Number of events, particularly DRFI very small.
• Prolonged f.u. required for analysis (late recurrence not influenced by chemo)
• Likely reflects the very low risk nature of population
• No data on events vs clinical risk available
• More 2nd cancers than distant recurrence: with hindsight IDFS not the ideal primary outcome

### Crude number of events in TAILORx (ITT)

<table>
<thead>
<tr>
<th>Event Type</th>
<th>E: n (%)</th>
<th>CE: n (%)</th>
<th>Difference (E-CE) n</th>
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</thead>
<tbody>
<tr>
<td>loco-regional (LR)</td>
<td>67 (15.3%)</td>
<td>62 (15.5%)</td>
<td>5</td>
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<tr>
<td>opposite BC</td>
<td>44 (10.1%)</td>
<td>48 (12.0%)</td>
<td>4</td>
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<tr>
<td>DR ± LR</td>
<td>107 (24.5%)</td>
<td>92 (23.0%)</td>
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<tr>
<td>2nd cancer</td>
<td>145 (33.3%)</td>
<td>146 (36.5%)</td>
<td>1</td>
</tr>
<tr>
<td>Death (NOS)</td>
<td>63 (14.4%)</td>
<td>52 (13.0%)</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>436/3399</td>
<td>400/3312</td>
<td>36</td>
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None of this detracts from the achievement of the TAILORx investigators
EVIDENCE FOR ONCOTYPE DX AS A PREDICTOR OF CHEMOTHERAPY BENEFIT IN TAILORx

Exploratory subgroup analysis: DFRI vs RS + menopausal status

<table>
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<tr>
<th>Group</th>
<th>n</th>
<th>Ratio</th>
<th>95% Conf Int</th>
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<tbody>
<tr>
<td>Overall</td>
<td>6711</td>
<td>1.10</td>
<td>(0.85, 1.41)</td>
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<tr>
<td>RS 11-15</td>
<td>2373</td>
<td>1.08</td>
<td>(0.64, 1.62)</td>
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<tr>
<td>RS 16-20</td>
<td>2712</td>
<td>0.95</td>
<td>(0.63, 1.43)</td>
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<tr>
<td>RS 21-25</td>
<td>1626</td>
<td>1.27</td>
<td>(0.85, 1.90)</td>
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<tr>
<td>Premenop</td>
<td>2416</td>
<td>1.42</td>
<td>(0.93, 2.19)</td>
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<tr>
<td>Postmenop</td>
<td>4296</td>
<td>0.97</td>
<td>(0.71, 1.34)</td>
</tr>
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</table>

Similar results for analysis by RS + age and for alternative outcomes (IDFS, RFI).

Significant interactions between treatment and combinations of outcome, RS & age ≤50/ pre-menopausal status in some of these analyses.

- Data could be interpreted as showing that RS is predictive of chemotherapy sensitivity in ≤50/ pre-menopausal population.
- Chemotherapy-induced menopause a potential confounder: no data collected.

Sparano 2018 NEJM doi: 10.1056/NEJMoa1804710 fig S11
RxPONDER: pN1, ER-pos Her2-neg Breast Cancer

- Accrual complete
- No information about randomised population
- Same design & issues as TAILORx randomised study
- ? Will report 2020
OPTIMA

WHAT WE EXPECT TO LEARN
ASSUMPTIONS UNDERPINNING OPTIMA

• Multi-parameter assays predict chemotherapy sensitivity

• Tumour stage is prognostic for all patients irrespective of multi-parameter assay score

• Advanced stage patients with poor prognosis will not benefit from chemotherapy if the tumour has a low multi-parameter assay score
  
  • Example – few patients multi-node positive low molecular grade tumours will benefit from chemotherapy
**OPTIMA MAIN STUDY DESIGN**

Female or Male age ≥40 post 1° excision ER pos, HER2 neg pN1-2/ pN1mi &pT≥20 /pN0 &pT ≥30

Option 1 (control) 1

Option 2 (research) 1

Prosigna

R blinded to randomisation

Treatment assigned by score

- high score ROR ≥61
- low score ROR <61

Estimated 65% of tumours are Prosigna low-score

1° Outcome = Non-inferiority of IDFS (Δ=-3%, 5yr, control-arm IDFS = 85%; HR ≤1.22)

Cost effectiveness evaluation of test-directed treatment

key 2° Outcome = Non-inferiority of IDFS in low-score patients (Δ=-3.5%)

Sample size = 4500 patients (+ OPTIMA prelim) Recruitment period = 60 months commenced Jan 2017

chemo. → endocrine

chemo. → Prosigna

ROR ≥61

ROR <61

endocrine

endocrine
THE PROSIGNA TEST

- Measures PAM50 gene expression set
- Outputs = Risk of Recurrence Score (ROR-PT) & Intrinsic Subtype
- ROR inputs = Intrinsic subtype, proliferation, tumour size
- Runs on multi-purpose proprietary hardware (NanoString) as “black box” test
  - Versatile, scalable, highly robust & reproducible
- Can be performed in any suitably qualified lab (NHS)
- Validated in several trial data sets – transATAC, ABSCG12
- Predictive of response to neoadjuvant chemotherapy
TREATMENT IN OPTIMA

• Chemotherapy pre-specified from a menu of regimens stratified by efficacy.
• Chemotherapy allocation blinded to avoid potential bias in chemotherapy administration.
• Endocrine therapy: standard
  • AI for post-menopausal,
  • tam for men
  • OS + tam/AI for pre-menopausal at trial entry
• Adjuvant bisphosphonates recommended for all.
• Patients may join other studies – e.g. AddAsprin
Main Inclusion Criteria
- “Adequate surgery”
- Women or Men
- Age ≥40
- ER-pos HER2-neg (local lab)
- pN1-2 / pN1mi & T≥20mm / pN0 & T≥30mm
- Fit for chemotherapy

Main Exclusion Criteria
- Advanced stage – pN3/ IM node involvement
- Neoadjuvant therapy
- Previous IBC – surgically treated DCIS permitted
PROTOCOL V6 (JULY 2018)

• Clarification of inclusion/ exclusion criteria
  • Bilateral cancers

• Permit short-term neoadjuvant endocrine therapy
  • Neoadjuvant chemotherapy not permitted

• Update permitted chemotherapy
  • Include regimens commonly used in Norway

• Update analysis plan

• Admin changes
  • Make international involvement explicit
  • GDPR compliance with improvement of PIS & consent form and separate data transparency statement
Recruitment into trials of less treatment is difficult!

Explanation to potential participants is different from superiority trials

Systematic study of Qualitative Recruitment Study in OPTIMA prelim & main study: (MRC CONDUCT-II hub, University of Bristol)
QRS IN ACTION

Two iterative and flexible stages:

Phase 1: Understand recruitment (and identify challenges)

• Analysis of screening log data
• In-depth interviews
• Observations of site visits and meetings
• Review study documentation
• Audio recordings of recruitment consultations

Phase 2: Develop and deliver strategies to improve recruitment

• Group training sessions
• Individual feedback
• Tips documents
• Amend patient documentation
Think of Optima as a **team trial** involving all the professionals that a patient may encounter:

- Surgeon
- Oncologist
- Research nurse
- Pathologist
- Breast care nurse
- Chemotherapy nurse

Engage **all** your colleagues, make them feel part of the recruitment process.

Provide assurances that:
- Prosigna gives a better measure of grade than histopathology
- Small delays in chemotherapy start are not harmful.

Secure the commitment of your colleagues to convey a consistent message to patients: **"the value of chemotherapy is uncertain"**
THE OPTIMA TEAM IS VERY EXCITED ABOUT NORWEGIAN PARTICIPATION

THANK YOU FOR INVITING ME TO YOUR COUNTRY TO PRESENT THE STUDY
UK TRIAL MANAGEMENT

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Affiliates:

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Independent cancer patients' voice

UNIVERSITY OF LEEDS

University College London Hospitals

NHS Foundation Trust
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AGREEMENT BETWEEN MULTI-PARAMETER TESTS (DATA FROM OPTIMA PRELIM)

Do the tests tell us the same thing?
AGREEMENT BETWEEN TESTS FOR INDIVIDUAL TUMOURS IN OPTIMA PRELIM

Oncotype DX25 vs. Prosigna

HR = pre-defined “high risk” boundary
LR = pre-defined “low risk” boundary

Stein 2016 Health Technol Assess 20(10)
Bartlett 2016 J Natl Cancer Inst 108(9)
## KAPPA STATS FOR TESTS PROVIDING RISK PREDICTIONS (NOT HIGH VS HIGH)

<table>
<thead>
<tr>
<th>Kappa statistic (95% confidence interval)</th>
<th>Prosigna (Low/Int)</th>
<th>MammaPrint (Low)</th>
<th>IHC4 (Low/Int)</th>
<th>IHC4-AQUA (Low/Low-Mid)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncotype DX ≤25 (OPTIMA low risk)</td>
<td>0.45 (0.34-0.55)</td>
<td>0.40 (0.30-0.50)</td>
<td>0.52 (0.40-0.64)</td>
<td>0.41 (0.31-0.52)</td>
</tr>
<tr>
<td>Prosigna (Low/Int)</td>
<td>0.53 (0.43-0.63)</td>
<td></td>
<td>0.39 (0.27-0.50)</td>
<td>0.43 (0.31-0.54)</td>
</tr>
<tr>
<td>MammaPrint (Low)</td>
<td></td>
<td></td>
<td>0.33 (0.21-0.44)</td>
<td>0.42 (0.30-0.53)</td>
</tr>
<tr>
<td>IHC4 (Low/Int)</td>
<td></td>
<td></td>
<td></td>
<td>0.60 (0.50-0.70)</td>
</tr>
</tbody>
</table>

**Interpretation:** >0.8 indicates “excellent agreement”; 0.4-0.6 indicates “modest agreement”