Please note that some of the studies reported in this presentation were published as abstracts only and/or presented at a conference. These data and conclusions are included because expert faculty found them to be important scientific contributions but should be considered to be preliminary until published in a peer-reviewed journal.
Trial Assigning Individualized Options for Treatment (TAILORx):

Phase III trial of chemoendocrine therapy versus endocrine therapy alone in hormone receptor-positive, HER2-negative, node-negative breast cancer and an intermediate prognosis 21-gene recurrence score


on behalf of the TAILORx Investigators
Background: Role of Adjuvant Chemotherapy in Early Breast Cancer

- Adjuvant chemotherapy reduces recurrence in ER+, node-neg BCA

- U.S. N.I.H consensus panel in 2000 concluded “…adjuvant chemotherapy … should be recommended to the majority of women with localized breast cancer regardless of lymph node, menopausal, or receptor status.”
Background: Rationale for Design of TAILORx Precision Medicine Trial Biomarker Directed Chemotherapy

- **Target Population:** HR+, HER2-neg, node-neg BCA
  - 50% of all breast cancers in U.S.
  - Adjuvant chemo recommended, but benefit small
  - Most are overtreated

- **Assay Selected: 21-Gene Assay (Recurrence Score)**
  - Two prospective validation studies in ER+, node-neg BCA
    - Prognostic (B14 study - tamoxifen): low recurrence with ET if RS low
    - Predictive (B20 study - tam +/- CMF): large chemo benefit if RS high
  - Uncertain chemo benefit for mid-range RS

Background: Rationale for Adjusting RS Ranges in TAILORx

• TAILORx population excluded HER2+
  • 21-gene assay includes HER2 module (HER2, GRB7) - higher recurrence
  • Most HER2+ tumors have high RS
  • Different RS distribution

• RS assay used selectively in practice - therapeutic equipoise
  • Typically int. grade tumors, 1-2 cm in size
  • More tumors in mid-range group

• RS range adjusted for mid-range (B20)
  • Preserve prediction in high risk group
  • Minimize potential for undertreatment

TAILORx Methods: Key Eligibility Criteria

Met NCCN Guidelines for Recommending or Considering Adjuvant Chemotherapy

- Women with invasive breast cancer
- Age 18-75 years
- Node-negative
- ER and/or PR-positive in local lab (before ASCO-CAP guidelines)
- HER2-negative in local lab
- Tumor size - 1.1–5.0 cm (or 0.6-1.0 cm and int-high grade)
- Willing to have chemotherapy treatment assigned or randomized based on RS assay results
TAILORx Methods: Treatment Assignment & Randomization

Accrued between April 2006 – October 2010

Preregister - Oncotype DX RS (N=11,232)

Register (N=10,273)

ARM A: Low RS 0-10
(N=1629 evaluable)
ASSIGN Endocrine Therapy (ET)

Mid-Range RS 11-25
(N=6711 evaluable)
RANDOMIZE
Stratification Factors: Menopausal Status, Planned Chemotherapy, Planned Radiation, and RS 11-15, 16-20, 21-25

ARM B: Experimental Arm
(N=3399)
ET Alone

ARM C: Standard Arm
(N=3312)
ET + Chemo

ARM D: High RS 26-100
(N=1389 evaluable)
ASSIGN ET + Chemo
# TAILORx Methods: Endpoints

- Primary endpoints:
  - RS 11-25: IDFS
  - RS 0-10: DRFI

<table>
<thead>
<tr>
<th></th>
<th>Distant Recurrence</th>
<th>Local-Regional Recurrence</th>
<th>Contralateral Breast Cancer</th>
<th>Other Second Primary Cancer</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive disease-free survival (IDFS)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Distant recurrence-free interval (DRFI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse-free interval (RFI)</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Overall survival (OS)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

TAILORx Methods: Statistical Analysis Plan for RS 11-25

- Non-inferiority design for randomized arms

- Intention-to-treat for primary analysis, as-treated analysis also planned

- Hazard ratio margin 1.322 for IDFS (5 year IDFS rate 90% vs. 87%)
  - Null hypothesis of no difference, type I error rate 10% (1-sided), type II 5%
  - \( P \) values shown are stratified log-rank test, and hazard ratios shown are from stratified proportional hazards models
  - Sample size adjusted for non-adherence rate (12%) - Lachin-Foulkes correction
  - Full information - 835 IDFS events

- Exploratory interaction tests for subgroups that may derive chemo benefit (ITT)
TAILORx Results – ITT Population: Demographics & Treatment in RS 11-25 Arms (N=6,711)

- **Patient characteristics**
  - Median age 55 years, and 33% were 50 or younger
  - 63% had tumor size 1-2 cm and 57% had intermediate grade histology (57%)
  - Clinical risk criteria: 74% low risk, 26% high risk

- **Systemic Treatment**
  - **Endocrine therapy**
    - Comparable adherence and duration in both arms
    - Postmenopausal – included AI in 90%
    - Premenopausal – included OS in 15%
  - **Chemotherapy**
    - Most common regimens were TC (56%) and anthracycline-containing (36%)
TAILORx Results - ITT Population: RS 11-25 (Arms B & C)

836 IDFS events (after median of 7.5 years), including 338 (40.3%) with recurrence as first event, of which 199 (23.8%) were distant.

**Primary Endpoint**
Invasive Disease-Free Survival

- **CHEMO + ET**
- **ET Alone**

**Secondary Endpoint**
Distant Relapse-Free Interval

- **CHEMO + ET**
- **ET Alone**

---

**Primary Endpoint**
Invasive Disease-Free Survival

- **Hazard Ratio Arm B vs. Arm C (95% CI)**
  - Arm C: CHEMO + ET
  - Arm B: ET Alone
  - 1.08 (0.94, 1.24)

- **P = 0.26**

**Secondary Endpoint**
Distant Relapse-Free Interval

- **Hazard Ratio Arm B vs. Arm C (95% CI)**
  - Arm C: CHEMO + ET
  - Arm B: ET Alone
  - 1.10 (0.85, 1.41)

- **P = 0.48**

---

**Number at risk**

- Arm B: CHEMO + ET
  - 3312, 3204, 3104, 2993, 2849, 2645, 2335, 1781, 1130, 523
- Arm B: ET Alone
  - 3399, 3293, 3194, 3081, 2953, 2741, 2431, 1859, 1197, 537

---

**Number at risk**

- Arm C: CHEMO + ET
  - 3312, 3215, 3142, 3059, 2935, 2734, 2432, 1866, 1197, 554
- Arm C: ET Alone
  - 3399, 3318, 3239, 3147, 3033, 2833, 2537, 1947, 1267, 581
TAILORx Results – ITT Population: RS 11-25 (Arms B & C)

Other Secondary Endpoints

Relapse-Free Interval

- Hazard Ratio Arm B vs. Arm C (95% CI)
  - 1.11 (0.90, 1.37)

Overall Survival

- Hazard Ratio Arm B vs. Arm C (95% CI)
  - 0.99 (0.79, 1.22)
TAILORx Results - ITT Population: All Arms (A, B, C & D)

9-Year Event Rates

- **RS 0-10 (Arm A)**
  - 3% distant recurrence with ET alone

- **RS 11-25 (Arms B & C)**
  - 5% distant recurrence rate overall
  - ≤ 1% difference for all endpoints
    - IDFS (83.3 vs. 84.3%)
    - DRFI (94.5 vs. 95.0%)
    - RFI (92.2 vs. 92.9%)
    - OS (93.9 vs. 93.8%)

- **RS 26-100 (Arm D)**
  - 13% distant recurrence despite chemo + ET
**TAILORx Results – ITT Population: Exploratory Analysis of Chemotherapy Treatment Interactions in RS 11-25 Arms**

<table>
<thead>
<tr>
<th>No statistically significant chemo treatment interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>- RS</td>
</tr>
<tr>
<td>- 11-15 vs. 16-20 vs. 21-25</td>
</tr>
<tr>
<td>- 11-17 vs. 18-25</td>
</tr>
<tr>
<td>- Tumor size (&lt; 2 cm vs. &gt; 2 cm)</td>
</tr>
<tr>
<td>- Grade (low vs. int. vs. high)</td>
</tr>
<tr>
<td>- Menopausal status (pre vs. post)</td>
</tr>
<tr>
<td>- Clinical risk category (high vs. low)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Statistically significant chemo treatment interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Age (&lt; 50, 51-65, &gt; 65) and chemo benefit</td>
</tr>
<tr>
<td>- IDFS (p=0.003)</td>
</tr>
<tr>
<td>- RFI (p=0.02)</td>
</tr>
<tr>
<td>- Age (or menopause), RS (11-15, 16-20, 21-25), and chemo benefit</td>
</tr>
<tr>
<td>- IDFS - Age-RS (p=0.004)</td>
</tr>
<tr>
<td>- IDFS - Menopause-RS (p=0.02)</td>
</tr>
</tbody>
</table>
TAILORx Results - ITT Population: Potential Chemotherapy Benefit in Women ≤ 50 Years (N=2216) in RS 11-25 Arms

• RS 16-25 - some chemo benefit
  • RS 16-20: 9% fewer IDFS events, including 2% fewer distant recurrences
  • RS 21-25: 6% fewer IDFS events, mainly consisting of fewer distant recurrences

• RS 0-15 - good prognosis with endocrine therapy
  • 3% distant recurrence with ET alone
  • no evidence for chemo benefit in RS 11-15
TAILORx Results: Association between Continuous RS 11-25 and 9-Year Distant Recurrence Rate by Treatment Arms Stratified by Age (≤50 vs. >50 Years)

< 50 years (N=2216)

Age ≤ 50
Adjusted for tumor size and grade

> 50 years (N=4495)

Age > 50
Adjusted for tumor size and grade

RS modeled with a natural spline with 2 degrees of freedom, adjusted for tumor size and grade

Joseph A. Sparano, MD
TAILORx Results: RS Distribution in TAILORx Compared with Concurrent Use in Clinical Practice

TAILORx Clinical Practice

Genomic Health (data on file)
TAILORx Results: Summary

• Primary conclusions
  • **RS 11-25:** ET was non-inferior to chemotherapy + ET (primary endpoint - ITT)
  
  • **RS 0-10:** Distant recurrence rates very low (2-3%) with ET alone at 9 years
  
  • **RS 26-100:** Significantly higher event rates, driven by more recurrences despite adjuvant chemo plus ET

• Other observations
  • **Age – RS – Chemo treatment interaction:**
    • Some chemo benefit in women 50 or younger with a RS 15-25
    • Greatest impact on distant recurrence with RS 21-25
Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer

PERSEPHONE: 6 versus 12 months of adjuvant trastuzumab in patients with HER2 positive early breast cancer: Randomised phase 3 non-inferiority trial with definitive 4-year disease-free survival results

Helena Earl, Louise Hiller, Anne-Laure Vallier, Shrushma Loi, Donna Howe, Helen Higgins, Karen McAdam, Luke Hughes-Davies, Adrian Harnett, Mei-Lin Ah-See, Richard Simcock, Daniel Rea, Janine Mansi, Jean Abraham, Carlos Caldas, Claire Hulme, David Miles, Andrew Wardley, David Cameron, Janet Dunn, on behalf of the PERSEPHONE Trial Investigators

Cambridge University Hospitals NHS Foundation Trust
WARWICK CLINICAL TRIALS UNIT
UNIVERSITY OF CAMBRIDGE
National Institute for Health Research

https://warwick.ac.uk/fac/med/research/ctutrials/cancer/persephone
Background - Adjuvant trastuzumab in HER2+ve EBC -

- 2005 HERA, NSABP-B31 and N9831, then BCIRG 006 Study

- Cochrane Review - 2012 - showed 40% fewer cancer recurrences and 34% fewer deaths with adjuvant trastuzumab

- Confirmed in later analyses of HERA and NSABP-B31 with N9831

Duration of Adjuvant Trastuzumab

- Pivotal licensing trials used 12 months on an empirical basis

- 2006 - FinHer (232 patients) after 9 weeks trastuzumab showed 58% fewer cancer recurrences compared with no trastuzumab

- HERA - 2 year duration did not show additional improvement

• **Hypothesis** - Six months adjuvant trastuzumab has similar efficacy to standard twelve months but reduced toxicity and cost

• **PERSEPHONE Trial** - Randomised phase 3 multicentre UK trial of 6 versus 12 months trastuzumab - non-inferiority design (n=4000)

• **Funding acknowledgement**
NIHR HTA programme (project number 06/303/98)
Key inclusion criteria

• HER2 positive invasive early breast cancer (3+ or 2+ and FISH amplified)
• No evidence of metastatic disease
• Known hormone receptor status
• Clear indication for chemotherapy
• Patient fit to receive chemotherapy and trastuzumab
• Informed consent before 10th cycle of trastuzumab
Mapping onto Standard Practice in the UK ‘Real World Setting’ - Stratification

- **ER Status:** Positive / negative
- **Chemotherapy type:** Anthracycline-based (FEC, EC, ECMF)  
  Taxane-based (TC, TCH)  
  Anthracycline and taxane (FEC-T, EC-T)  
  Other (CMF)
- **Chemotherapy timing:** Adjuvant / neoadjuvant
- **Trastuzumab timing:** Concurrent / sequential
Persephone Study Design

Chemotherapy cycles

- trastuzumab cycles
  - 110mg/kg
- 56mg/kg

Trial Assessments

- cardiac LVEF
- quality of life
- health economics
- randomisation any time until after cycle 9

Time in months

0 3 6 9 12 18 24

1O: DFS [Diagnosis to 1st relapse (local or distant) or death]
2O: OS; Cost effectiveness; Cardiac function

Presented By: Helena Earl MD PhD

https://warwick.ac.uk/fac/sci/med/research/ctu/trials/cancer/persephone
Statistical Considerations

- **Sample size:** 4000 patients
  - 4-year DFS with 12 months trastuzumab: Estimated at 80%
  - Non-inferiority: ‘No worse than 3% below’
  - 1-sided significance: 5%
  - Power: 85%

- **Pre-planned Analyses**
  - 3 interim futility analyses for IDSMC
  - Primary endpoint analysis - event-driven after 500 DFS events
  - Landmark analysis from after 6 months of trastuzumab
Recruitment

- Between 4th Oct’07 and 31st Jul’15
  - 4089 patients were recruited - analysis set 4088 (1 double randomised)
  - 152 sites in the UK
  - 207 recruiting investigators

https://warwick.ac.uk/fac/sci/med/research/ctu/trials/cancer/persephone
## Patient Characteristics I

*Stratification variables*

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>12 months (n=2045)</th>
<th>6 months (n=2043)</th>
<th>Overall (n=4088)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ER Status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>633 (31)</td>
<td>632 (31)</td>
<td>1265 (31)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>1412 (69)</td>
<td>1411 (69)</td>
<td>2823 (69)</td>
<td></td>
</tr>
<tr>
<td><strong>Chemotherapy type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthracycline based</td>
<td>854 (42)</td>
<td>846 (41)</td>
<td>1700 (42)</td>
<td></td>
</tr>
<tr>
<td>Taxane based</td>
<td>200 (10)</td>
<td>203 (10)</td>
<td>403 (10)</td>
<td></td>
</tr>
<tr>
<td>Anthracycline + Taxane based</td>
<td>989 (48)</td>
<td>991 (49)</td>
<td>1980 (48)</td>
<td></td>
</tr>
<tr>
<td>Other (CMF)</td>
<td>2 (&lt;1)</td>
<td>3 (&lt;1)</td>
<td>5 (&lt;1)</td>
<td></td>
</tr>
<tr>
<td><strong>Trastuzumab timing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concurrent</td>
<td>951 (47)</td>
<td>952 (47)</td>
<td>1903 (47)</td>
<td></td>
</tr>
<tr>
<td>Sequential</td>
<td>1094 (53)</td>
<td>1091 (53)</td>
<td>2185 (53)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=50 years old</td>
<td>657 (32)</td>
<td>677 (33)</td>
<td>1334 (33)</td>
<td></td>
</tr>
<tr>
<td>&gt;50 years old</td>
<td>1388 (68)</td>
<td>1366 (67)</td>
<td>2754 (67)</td>
<td></td>
</tr>
<tr>
<td>Doses received</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>898 (44)</td>
<td>888 (43)</td>
<td>1786 (44)</td>
<td></td>
</tr>
<tr>
<td>1 - 4</td>
<td>780 (38)</td>
<td>755 (37)</td>
<td>1535 (37)</td>
<td></td>
</tr>
<tr>
<td>5 - 9</td>
<td>367 (18)</td>
<td>400 (20)</td>
<td>767 (19)</td>
<td></td>
</tr>
</tbody>
</table>

[https://warwick.ac.uk/fac/med/research/ctu/trials/cancer persephone](https://warwick.ac.uk/fac/med/research/ctu/trials/cancer persephone)
## Patient Characteristics II

### *Stratification variables*

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>12 months (n=2045)</th>
<th>6 months (n=2043)</th>
<th>Overall (n=4088)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>CT timing</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neo-adjuvant</td>
<td>308 (15)</td>
<td>312 (15)</td>
<td>620 (15)</td>
<td></td>
</tr>
<tr>
<td>Adjuvant</td>
<td>1737 (85)</td>
<td>1731 (85)</td>
<td>3468 (85)</td>
<td></td>
</tr>
<tr>
<td>For Adjuvant patients only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodal involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1003 (58)</td>
<td>1019 (60)</td>
<td>2022 (59)</td>
<td></td>
</tr>
<tr>
<td>1-3 nodes involved</td>
<td>479 (28)</td>
<td>486 (28)</td>
<td>965 (28)</td>
<td></td>
</tr>
<tr>
<td>4+ nodes involved</td>
<td>244 (14)</td>
<td>211 (12)</td>
<td>455 (13)</td>
<td></td>
</tr>
<tr>
<td>Tumour size</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=2cm</td>
<td>824 (49)</td>
<td>807 (48)</td>
<td>1631 (48)</td>
<td></td>
</tr>
<tr>
<td>&gt;2 to 5cm</td>
<td>778 (46)</td>
<td>786 (47)</td>
<td>1564 (47)</td>
<td></td>
</tr>
<tr>
<td>&gt;5cm</td>
<td>87 (5)</td>
<td>83 (5)</td>
<td>170 (5)</td>
<td></td>
</tr>
<tr>
<td>Tumour Grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>28 (2)</td>
<td>34 (2)</td>
<td>62 (2)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>511 (30)</td>
<td>523 (31)</td>
<td>1034 (31)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>1153 (68)</td>
<td>1128 (67)</td>
<td>2281 (67)</td>
<td></td>
</tr>
</tbody>
</table>
Stratification variables over time

- Sequential CT
- Concurrent CT
- ER Positive
- ER Negative
- No Anthra or Tax
- Anthra + Tax based
- Tax based
- Anthra based

Presented By Helena Earl at 2018 ASCO Annual Meeting

https://warwick.ac.uk/fac/med/research/ctu/trials/cancer/perorphone
Trastuzumab Compliance

• Full treatment data available on 94% patients

• 86% patients had the correct number of doses
  – 82% 12m patients, 90% 6m patients (p < 0.0001)

https://warwick.ac.uk/fac/sci/med/research/ctu/trials/cancer/persephone
# Pre-planned analyses for the DSMC

<table>
<thead>
<tr>
<th>Time point</th>
<th>Assessing futility (using p=0.01 (one sided)) [Futility = conclude that non-inferiority could not reasonably be expected to be achieved]</th>
<th>Final analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of the total 500 DFS events required</td>
<td>25% 50% 75%</td>
<td>100%</td>
</tr>
<tr>
<td># DFS events required</td>
<td>125 250 375</td>
<td>500</td>
</tr>
<tr>
<td>Date time point reached</td>
<td>October 2012 June 2014 March 2016</td>
<td>Nov 2017</td>
</tr>
<tr>
<td>Exact # DFS events recorded</td>
<td>132 238 375</td>
<td>500</td>
</tr>
<tr>
<td>Median FU</td>
<td>11 months 28 months 41 months</td>
<td>4.9 years</td>
</tr>
<tr>
<td>DFS HR (95% CI)</td>
<td>0.92 (0.65 - 1.30) 1.16 (0.90 - 1.50) 1.06 (0.87 - 1.30)</td>
<td>1.05 (0.88 - 1.25)</td>
</tr>
<tr>
<td>DSMC conclusion</td>
<td>No evidence to stop the trial on grounds of futility No evidence to stop the trial on grounds of futility</td>
<td>Present the results</td>
</tr>
</tbody>
</table>
Primary Endpoint analysis

April 2018 Updated analysis

- Median FU = 5.4 years (IQR 3.6 - 6.7)
  - 335 (8%) have died
  - 512 (13%) have relapsed or died
DFS:

Pre-defined subgroup analysis

Interaction between 2 groups $\chi^2 = 2.3; p = 0.13$

Heterogeneity between 4 groups $\chi^2 = 11.1; p = 0.01$

Interaction between 2 groups $\chi^2 = 3.2; p = 0.07$

Interaction between 2 groups $\chi^2 = 10.8; p = 0.001$

https://warwick.ac.uk/fac/sci/med/research/ctu/trials/cancer/porophene
Overall survival

<table>
<thead>
<tr>
<th>Years from diagnosis</th>
<th>Overall Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>98.9%</td>
</tr>
<tr>
<td>6 months</td>
<td>98.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>#events</th>
<th>HR</th>
<th>90% CI</th>
<th>Non-inferiority p</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>156</td>
<td>1.14</td>
<td>0.95-1.37</td>
</tr>
<tr>
<td>6 months</td>
<td>179</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No. at Risk

- 12 months: 2045
- 6 months: 2043
- 12 months: 2019
- 6 months: 2014
- 3 years: 1732
- 4 years: 1386
- 5 years: 1062

Hazard Ratio

Non-inferiority Limit

https://warwick.ac.uk/fac/sci/med/research/ctu/trials/cancer/persephone

Presented By Helena Earl at 2018 ASCO Annual Meeting
OS:

Pre-defined subgroup analysis

Interaction between 2 groups $\chi^2 = 5.5; p = 0.02$

Heterogeneity between 4 groups $\chi^2 = 5.0; p = 0.17$

Interaction between 2 groups $\chi^2 = 2.4; p = 0.12$

Interaction between 2 groups $\chi^2 = 5.7; p = 0.02$
## Landmark analysis (after 6 months of trastuzumab)

<table>
<thead>
<tr>
<th></th>
<th># patients</th>
<th># relapsed and/or died within time-frame</th>
<th># censored within time-frame</th>
<th># patients in landmark analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 month patients</td>
<td>2045</td>
<td>13</td>
<td>23</td>
<td>2009</td>
</tr>
<tr>
<td>6 month patients</td>
<td>2043</td>
<td>16</td>
<td>27</td>
<td>2000</td>
</tr>
<tr>
<td>All patients</td>
<td>4088</td>
<td>29</td>
<td>50</td>
<td>4009</td>
</tr>
</tbody>
</table>

- Median FU of the 4009 patients = 4.5 years (IQR 2.6 - 5.6)
  - 312 (8%) have died
  - 483 (12%) have reported a relapse or death
Landmark DFS

Presented By Helena Earl at 2018 ASCO Annual Meeting

Landmark OS

https://warwick.ac.uk/fac/med/research/ctu/trials/cancer/porrophore
Cardiotoxicity

Stopped trastuzumab because of cardiotoxicity
- in 8% of 12-month patients
- in 4% of 6-month patients
(p<0.0001)

• Cardiac function recovers post-trastuzumab (p<0.0001)
• 6-month patients had a more rapid recovery (p=0.02)

Toxicity

20% of sequential patients reported a G3/4 toxicity during trastuzumab treatment (23% 12 month, 18% 6 month, p=0.004)
Conclusions

• The PERSEPHONE Trial demonstrates that 6m adjuvant trastuzumab is non-inferior to 12m (6m arm 89.4% 4-yr DFS: 12m arm 89.8% 4-yr DFS; HR = 1.07 [90% CI 0.93, 1.24] p=0.01)
• 6m compared with 12m treatment reduces cardiac and other toxicities, and costs both to patients and healthcare systems
• Ongoing - QoL, Patient Reported Experiences, and Health Economics
• Future - translational research (blood and tumour samples on these patients)
• These exciting results mark the first steps to the reduction of treatment duration for many women with HER2 positive breast cancer
The present and future of CDK 4/6 inhibitors

• What we know
• What we don’t know
• What the future holds
## CDK 4/6 inhibitors: FDA-approved indications 2018

<table>
<thead>
<tr>
<th>CDK Inhibitor</th>
<th>Dose</th>
<th>Schedule</th>
<th>Indications:</th>
</tr>
</thead>
</table>
| Palbociclib (Ibrance, Pfizer) | 125 mg daily | 3 weeks on/1 week off | • **First line** with AI  
• **Progressing after ET**, with fulvestrant |
| Ribociclib (Kisqali, Novartis) | 600 mg daily | 3 weeks on/1 week off | • **First line** with AI |
| Abemaciclib (Verzenio, Lilly) | 150 or 200 mg twice daily | Continuous | • **First line** with AI  
• **Progressing after ET**, with fulvestrant  
• **Monotherapy** after progression on ET and CT |
<table>
<thead>
<tr>
<th>Study/Arms</th>
<th>N</th>
<th>Med FU</th>
<th>Median PFS (months) Plac</th>
<th>Median PFS (months) CDK4/6i</th>
<th>HR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PALOMA-2 Letrozole +/- Palbociclib</td>
<td>666</td>
<td>37.6</td>
<td>14.5</td>
<td>27.6</td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.46-0.69</td>
</tr>
<tr>
<td>MONALEESA-2 Letrozole +/- Ribociclib</td>
<td>668</td>
<td>26.4</td>
<td>16</td>
<td>25.3</td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.46-0.70</td>
</tr>
<tr>
<td>MONARCH-3 NS-AIs +/- Abemaciclib</td>
<td>493</td>
<td>26.7</td>
<td>14.7</td>
<td>28.1</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.42-0.69</td>
</tr>
</tbody>
</table>

Finn RS, NEJM. 2016; Updated SABCS 2017; Hortobagyi, Annals Onc, 2018; Goetz MP, et al. ACR, 2018; Slamon DJ, ASCO, 2018 Abs 1000
## First line setting

<table>
<thead>
<tr>
<th>Study/Arms</th>
<th>N</th>
<th>Med FU</th>
<th>Median PFS (months)</th>
<th>HR</th>
<th>95% CI</th>
</tr>
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<tr>
<td><strong>MONALEESA-3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fulvestrant +/- Ribociclib</td>
<td>367</td>
<td>20.4</td>
<td>18.3</td>
<td>NR</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.415-0.802</td>
</tr>
</tbody>
</table>

Finn RS, NEJM. 2016; Updated SABCS 2017; Hortobagyi, Annals Onc, 2018; Goetz MP, et al. ACR, 2018; Slamon DJ, ASCO, 2018 Abs 1000
Progression after endocrine therapy

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<th>Study/Arms</th>
<th>N</th>
<th>Med FU (mos)</th>
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<th>Median PFS (months) CDK 4/6i</th>
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<tbody>
<tr>
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<td>521</td>
<td>15</td>
<td>4.6</td>
<td>11.2</td>
<td>0.50 (0.40–0.62)</td>
</tr>
<tr>
<td>MONARCH 2 Fulvestrant +/- Abemaciclib</td>
<td>669</td>
<td>19.5</td>
<td>9.3</td>
<td>16.4</td>
<td>0.55 0.45-0.68</td>
</tr>
</tbody>
</table>

Turner NC, NEJM. 2015; Updated ASCO 2016; Sledge, JCO. 2017;, Slamon, DJ, ASCO, 2018, abs 1000
### Progression after endocrine therapy

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</tr>
<tr>
<td>MONALEESA-3 Fulvestrant +/- Ribociclib</td>
<td>345</td>
<td>20.4</td>
<td>9.1</td>
<td>0.57 0.42 – 0.74</td>
</tr>
</tbody>
</table>

*Turner NC, NEJM. 2015; Updated ASCO 2016; Sledge, JCO. 2017; Slamon, DJ, ASCO, 2018, abs 1000*
Active in premenopausal patients, regardless of endocrine therapy used

**PALOMA-3**
- N=106
- Fulvestrant + goserelin
- HR 0.50, p=0.013

**MONALEESA-7**
- N=335
- Tamoxifen or NSAI+ goserelin
- HR 0.55, p=1x10^-9

**MONARCH-2**
- N=114
- Fulvestrant + GnRH
- HR 0.45, p=0.002

Loibl, Oncologist, 2017; Tripathy D, et al. SABCS, December 2017. Abstract GS2-05; Neven, ASCO, 2018, Abs 1002
Toxicity differences between agents: Grade 3/4

<table>
<thead>
<tr>
<th></th>
<th>Palbociclib</th>
<th>Ribociclib</th>
<th>Abemaciclib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>✔️ ✔️ ✔️</td>
<td>✔️ ✔️ ✔️</td>
<td>✔️ ✔️</td>
</tr>
<tr>
<td>Anemia</td>
<td>✔️ ✔️</td>
<td>✔️ ✔️</td>
<td>✔️ ✔️</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>✔️</td>
<td>✔️ ✔️</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️ ✔️ ✔️</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td>QTc prolongation</td>
<td></td>
<td>✔️</td>
<td></td>
</tr>
</tbody>
</table>

Are differences due to drug, schedule or population?
Summary: What we know

• Consistent, clinically-meaningful improvements in PFS in advanced breast cancer
• Regardless of endocrine sensitivity, endocrine therapy partner, menopausal status
• Predictable, tolerable and manageable side effect profile
What we don’t know

• When to best integrate into the therapeutic plan?
• Overall survival in the metastatic setting?
• Which tumors biologically most likely to respond?
• What are the mechanisms of resistance?
• What should we do upon progression?
• Are there other settings in which CDK 4/6 inhibitors will be effective?
When should we add CDK inhibitors to endocrine therapy?

No CDK inhibitor: Total PFS 24 months

Adapted from Ingrid Mayer, MD, ASCO, 2017
When should we add CDK inhibitors to endocrine therapy?

No CDK inhibitor: Total PFS 24 months

2nd line CDK inhibitor: Total PFS 30 months

Adapted from Ingrid Mayer, MD, ASCO, 2017
When should we add CDK inhibitors to endocrine therapy?

1st line CDK inhibitor: Total PFS 35 months

2nd line CDK inhibitor: Total PFS 30 months

No CDK inhibitor: Total PFS 24 months

Adapted from Ingrid Mayer, MD, ASCO, 2017
When should we add CDK inhibitors to endocrine therapy?

1st line CDK inhibitor: Total PFS 35 months

2nd line CDK inhibitor: Total PFS 30 months

No CDK inhibitor: Total PFS 24 months

- Not crossover studies!

Individual Considerations:
- Desire for time without treatment change
- Toxicity
- Access
- Cost

Adapted from Ingrid Mayer, MD, ASCO, 2017
Will the impressive PFS improvements translate to improved overall survival?

**PALOMA 1**
Randomized phase II  
N=165

- **PFS HR 0.49 (0.32-0.75)**  
- **OS HR 0.89 (0.623, 1.294)**

- Phase III trials not powered for overall survival
- Meta-analysis?

---

Finn R, ASCO, 2017
Difficult to demonstrate overall survival benefit in ER+, metastatic breast cancer

- Endocrine therapy
- Chemotherapy
- Supportive Care

Long natural history of disease

- Treatment at early point in trajectory
- Response time small proportion of overall time
- Impact of subsequent therapy and crossover

Impact of new therapy
Is there value without overall survival benefit?

- Ability to work
- Delay time to chemo
- Quality of life
- Side effects and toxicity
Is there value without overall survival benefit?

Ability to work
Delay time to chemo
Quality of life
Side effects and toxicity

Average US wholesale price/cycle

<table>
<thead>
<tr>
<th>Drug</th>
<th>Price/cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palbociclib</td>
<td>$13,550.33</td>
</tr>
<tr>
<td>Ribociclib</td>
<td>$13,534.20</td>
</tr>
<tr>
<td>Abemaciclib</td>
<td>$13,537.44</td>
</tr>
</tbody>
</table>

True economic impact?

Courtesy Christine Camberari, PharmD
Can biomarkers help us optimize therapy?

- Biologic responders
- Mechanisms of resistance
- Therapeutic maneuvers at progression
Cell cycle control at the G1/S checkpoint

Unchecked cellular proliferation

Unchecked proliferation

Gene transcription

Cyclin D

PI3K/Akt

ER/PR

Wnt/β-catenin

STATs

MAPKs

NF-κB

CDK 4/6

G1

S

G2

G0

G1

S

G2
Cell cycle control at the G1/S checkpoint

Unchecked cellular proliferation

Gene transcription

Unchecked cellular proliferation

G0 → G1 → S → G2 → M

Cyclin D → CDK 4/6

ER/PR

PI3K/Akt

Wnt/β-catenin

STATs

MAPKs

NF-κB

ER/PR → p53

p16

p21
Cell cycle control at the G1/S checkpoint

Numerous alterations that could bypass cdk 4/6 or endocrine blockade
Biomarkers that have \textit{NOT} identified responders:

- Cyclin D amplification (\textit{CCDN1})
- Loss of p16 (\textit{INK4A or CDKN2A})
- Protein levels of cyclin D/CDK4/6/Rb pathway
- Expression level of ER and/or PgR
- \textit{PIK3CA} mutations (cfDNA)
- \textit{ESR1} mutations (cfDNA) – note trend in MONALEESA-2
  \textit{(Hortobagyi, ASCO 2018, Abs 1026)}

Finn, Lancet Oncol. 2015; Cristofanilli, Lancet Oncol. Fribbens, J Clin Oncol. 2016; Finn, ESMO 2016
Pre-treatment Cyclin E1 gene expression predictive in PALOMA-3

- N=302
- Pretreatment mRNA gene expression profiling on FFPE
- HTG EdgeSeq

Effect was more pronounced in metastatic tissues than in primary tissue

PFS Low Cyclin E1: 14.1 mos vs. High Cyclin E1 7.6 mos (Interaction p=0.00238)

Turner, AACR, 2018, Abs 10870
**Importance of cyclin E in cell cycle control**

Relative dependence on cyclin D vs. cyclin E makes a difference

Unchecked cellular proliferation

Gene transcription
Mechanisms of Resistance

Endocrine Resistance
ESR-1, mTOR, FGFR1
Hypermethylation

Unchecked cellular proliferation

Gene transcription

E2F
RB

Mutation

PI3K/Akt
ER/PR

NF-κB
STATs
MAPKs

Cyclin D

CDK inhibitor Resistance
• Switch to cyclin E
• Rb mutation/loss
• Collateral pathways

What’s at play? Can this guide therapy?
Paired blood samples for circulating tumor DNA from PALOMA-3 (Turner, et al, Abs 1001)

- Pre- and post-treatment blood samples
- Targeted panel (n=193)
- Whole exome (n=14)

<table>
<thead>
<tr>
<th>Emergent Mutation</th>
<th>FUL</th>
<th>FUL + PAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>RB</td>
<td>0%</td>
<td>4.8%</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>10.3%</td>
<td>8%</td>
</tr>
<tr>
<td>ESR1</td>
<td>14.7%</td>
<td>19.2%</td>
</tr>
</tbody>
</table>
Paired blood samples for circulating tumor DNA from PALOMA-3 (Turner, et al, Abs 1001)

- Feasibility of detecting emergent genomic changes in blood with treatment
- Mutations are concurrently affecting both endocrine and cdk inhibitor sensitivity
- Emerging mutations can provide hints to how to modify therapy
Paired blood samples for circulating tumor DNA from PALOMA-3  (Turner, et al, Abs 1001)

- Feasibility of detecting emergent genomic changes in blood with treatment
- Mutations are concurrently affecting both endocrine and cdk inhibitor sensitivity
- Emerging mutations can provide hints to how to modify therapy

- Mutations unlikely to tell the whole story
  - Gene and protein expression
- Differential affect of mutation type
  - Resistance to all in class vs. some agents over others?
- How would we integrate this into practice?
How could we manage our patients at progression?

Switch endocrine therapy, maintain CDKi
How could we manage our patients at progression?

Switch endocrine therapy, maintain CDKi

Switch CDK to something else, maintain endocrine therapy

ET \[\rightarrow\] ET

CDKi

ET \[\rightarrow\] Other (everolimus, entinostat)

CDKi

RB mutation
How could we manage our patients at progression?

Switch endocrine therapy, maintain CDKi

Switch to something else, maintain endocrine therapy

Maintain ET and CDKi, Target a collateral pathway
### Phase II trials combining cdk/mTOR inhibition

<table>
<thead>
<tr>
<th>Trial</th>
<th>Additional Agent/Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRINITI-1</td>
<td>mTor inhibitor (Everolimus)</td>
</tr>
<tr>
<td>NCT02732119</td>
<td></td>
</tr>
<tr>
<td>PASTOR</td>
<td>mTORC 1/2 inhibitor (Vistusertib)</td>
</tr>
<tr>
<td>NCT02599714</td>
<td></td>
</tr>
</tbody>
</table>

#### Progression on CDK4/6 inhibitor and AI after ≥4 months as last therapy
- Ribociclib 300 mg/day
- Everolimus 2.5 mg/day
- Exemestane 25 mg/day

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Response (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Benefit</td>
<td>39.5%</td>
</tr>
<tr>
<td>Partial Response</td>
<td>7%</td>
</tr>
</tbody>
</table>

Moulder, AACR, 2018, Abstract CT-108-28
CDK 4/6 inhibition synergizes with immune checkpoint blockade

• Promotes T-cell activation and infiltration into lung tumors
• Increases chemokine trafficking
• Enhances efficiency of tumor cell antigen presentation

Goel, Nature, 2017; Deng, Cancer Discovery, 2017
CDK 4/6 inhibition synergizes with immune checkpoint blockade

- Promotes T-cell activation and infiltration into lung tumors
- Increases chemokine trafficking
- Enhances efficiency of tumor cell antigen presentation
- Preclinical synergy with PD-1 inhibitors

Goel, Nature, 2017; Deng, Cancer Discovery, 2017
Palbociclib After CDK and Endocrine Therapy Trial (PACE)

Phase II, Randomized, Pilot Study

- Progression on AI + CDK4/6 inhibitor
- ≤1 prior line of chemo

1:2:1 Randomization

- Fulvestrant (crossover to Palbociclib at progression)
- Fulvestrant + Palbociclib
- Fulvestrant + Palbociclib + Avelumab


NCT03147287
Benefit in the adjuvant setting?

**Phase III PALLAS Trial**
NCT02513394

- **Palbociclib (2 years) + Endocrine therapy**
- **Endocrine therapy alone**

N=5600, Stage II –III
Primary endpoint: iDFS
Initiated: August, 2015

**Phase III MonarchE Trial**
NCT03155997

- **Abemaciclib (2 years) + Endocrine therapy**
- **Endocrine therapy alone**

N=3580, Stage II –III
Primary endpoint: iDFS
Initiated: July, 2017
Summary: The future of CDK inhibitors

• Maturation of trials
  • Fully understand magnitude and nature of benefits

• Future collaboration to build on past success
  • Meta-analyses, biomarker studies *Gao, ASCO 2018, abs 1024*

• New combinations
  • Based upon best preclinical and translational science
  • Refine patient selection, direct therapy at progression

• Expand benefits to Her2+ and early disease settings
Thank You!