Matthew Ellis, MB, BChir, PhD, FRCP

Innovations, Clinical Trials and Hormonal Therapy

Financial Relationships to Disclose:

Consultant: Pfizer, AstraZenica, Novarisa, Celgene, Puma

Full/Part Time Employee: Bioclassifier LLC

(PAM50 license to Nanostring for Prosigna)
Pragmatic Personalized Therapy

Stage 2 or 3 breast cancer

- Subtype Appropriately Systemic Therapy
  - Tumor Responsive
    - De-intensify Therapy
  - Tumor Resistant
    - Intensify Therapy

Surgery on breast and nodes
Schema For ER+ HER2-

Stage 2 or 3 ER+ HER2- breast cancer

Endocrine Therapy Therapy for 4 to 6 months NOT chemo

Surgery on breast and nodes

Tumor Endocrine Responsive

Endocrine Therapy Only

Tumor Endocrine Resistant

Chemotherapy or other systemic treatment

How to define response versus resistance in a setting where pCR is rare (1%)?
The human mind treats a new idea the same way the body treats a strange protein; it rejects it.
P024 Clinical Trial

Double Blind Randomized Design
Postmenopausal
ER+
Allred 6 to 8
Clinical Stage
2 and 3

NOT eligible for BCS

Rate of Breast Conserving Surgery 48% for Letrozole
36% for Tamoxifen (P=0.036) in Centrally Confirmed HR+
Subset and Response Related to ER level

P024 Clinical Trial

Double Blind Randomized Design
Postmenopausal
ER+
Allred 6 to 8
Clinical Stage
2 and 3
NOT eligible for BCS

Which response criterion correlated best with outcome?

Table 3. Multivariable Cox proportional hazards analysis of relapse-free survival (RFS) and breast cancer–specific survival (BCSS) from the P024 trial*

<table>
<thead>
<tr>
<th>Pathology biomarker and response factors</th>
<th>RFS</th>
<th>BCSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathological tumor size (T1/2 vs T3/4)</td>
<td>2.8 (1.4 to 5.4)</td>
<td>4.4 (1.7 to 11.2)</td>
</tr>
<tr>
<td>Node status (positive vs negative)</td>
<td>3.2 (1.5 to 6.9)</td>
<td>3.9 (1.1 to 13.7)</td>
</tr>
<tr>
<td>Ki67 level per 2.7-fold increase</td>
<td>1.3 (1.1 to 1.6)</td>
<td>1.4 (1.07 to 1.9)</td>
</tr>
<tr>
<td>ER, Allred score (0 or 2 vs 3–8)</td>
<td>2.8 (1.2 to 6.4)</td>
<td>7.0 (2.4 to 20.9)</td>
</tr>
</tbody>
</table>

* The four factors associated with a *P* value of .05 or less for RFS in Table 1 were reanalyzed in a Cox model to assign final hazard ratios for risk of relapse (RFS) and breast cancer mortality (BCSS). ER = estrogen receptor; HR = hazards ratio; CI = confidence interval.
## Preoperative Endocrine Prognostic Index (PEPI)

<table>
<thead>
<tr>
<th>Pathology, Biomarkers Factors</th>
<th>RFS</th>
<th>BCS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>Points</td>
</tr>
<tr>
<td>Tumor size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1/2</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>T3/4</td>
<td>2.8</td>
<td>3</td>
</tr>
<tr>
<td>Node status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>3.2</td>
<td>3</td>
</tr>
<tr>
<td>Ln Ki67 level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 -1 &lt; 2.7%</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>1+ -2 &lt; 7.3%</td>
<td>1.3</td>
<td>1</td>
</tr>
<tr>
<td>2+ -3 &lt; 19.7%</td>
<td>1.7</td>
<td>1</td>
</tr>
<tr>
<td>3+ -4 &lt; 53.1%</td>
<td>2.2</td>
<td>2</td>
</tr>
<tr>
<td>4+ &gt; 53.1%</td>
<td>2.9</td>
<td>3</td>
</tr>
<tr>
<td>ER Allred</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>2.8</td>
<td>3</td>
</tr>
<tr>
<td>3-8</td>
<td>-</td>
<td>0</td>
</tr>
</tbody>
</table>

Ellis et al JNCI 2008: 100, 1380-8
A

RFS By Risk Group in P024

Kaplan–Meier Estimate

Relapse Free Survival (Months)

Group 1
Group 2
Group 3

at Risk
Group1 41 41 39 37 34 27 1
Group2 65 65 58 46 42 37 4
Group3 52 49 42 26 21 18

B

RFS By Risk Group in IMPACT

Kaplan–Meier Estimate

Relapse Free Survival (Months)

Group 1
Group 2
Group 3

at Risk
Group1 31 27 26 17 9 6 4 1
Group2 97 84 71 59 24 16 9 3
Group3 76 63 55 35 16 10 2 3

Training Set
Test Set

Ellis et al JNCI 2008: 100, 1380-8
Prospective validation opportunity

ACOSOG Z1031 COHORT A

Postmenopausal ER+, Allred 6-8, clinical stage 2 and 3

- Exemestane
- Letrozole
- Anastrozole

Surgery

Continued AI therapy where possible. Radiotherapy, chemotherapy discretionary

Ellis et al JCO 2011: 29, 2342-9
### Surgical Outcomes

<table>
<thead>
<tr>
<th>surgery status prior to AI therapy</th>
<th>surgery performed</th>
<th>Treatment Arm</th>
<th>across all three treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>EXE (n=116)</td>
<td>LET (n=120)</td>
</tr>
<tr>
<td>marginal candidate for BCS (n=199)</td>
<td>BCS</td>
<td>52</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>MRM/RM</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>candidate for MRM only (n=152)</td>
<td>BCS</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>MRM/RM</td>
<td>25</td>
<td>32</td>
</tr>
<tr>
<td>inoperable (n=4)</td>
<td>BCS</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>MRM/RM</td>
<td>1</td>
<td>---</td>
</tr>
</tbody>
</table>

*Ellis et al JCO 2011: 29, 2342-9*
Z1031: outcomes by PEPI score

A) Recurrence Free Survival: All

B) Recurrence Free Survival: No chemotherapy

PEPI-0 rate 25%

Ellis et al JCO 2017, PMID: 28045625
Luminal A status enriched for PEPI-0 status (27%) but 10% of Luminal B tumors had PEPI-0 and so baseline genomic predictor imperfect way to predict PEPI status, but could be used to guide decisions in difficult cases.
Trial Schema For NET

Stage 2 or 3 ER+ HER2- breast cancer

Endocrine Therapy for 4 to 6 months

Surgery on breast and nodes

PEPI-0

PEPI not zero

Endocrine Therapy Only

Salvage systemic Treatment

A long time to wait if patient is a non responder?
Trial Schema For NET

Stage 2 or 3 ER+ HER2- breast cancer

Endocrine Therapy for 4 to 6 months

Surgery on breast and nodes

EARLY BIOPSY TO ASSESS RESPONSE

PEPI-0

Endocrine Therapy Only

PEPI-not 0

Salvage systemic Treatment

Predicted PEPI- not 0

Salvage systemic Treatment
Establishment of an Early Ki67 Cut Point for Triage to Chemotherapy

and Figure A1A, online only). Combining these studies revealed only one PEPI-0 case among 51 patients with a 2- to 4-week Ki67 value of > 10%. Thus, according to the PEPI model, patients with a Ki67 value of 10% at 2 to 4 weeks had a < 2% chance of a favorable PEPI score that would allow them to safely avoid chemotherapy under current guidelines.

Supplementary Table 1: Early Ki67 Assessments and Outcome in IMPACT and POL Trials

<table>
<thead>
<tr>
<th>POL 4W Ki67 95 mths median FU</th>
<th>% PEPI 0</th>
<th>RFS (events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10%</td>
<td>1/19 (5%)</td>
<td>8/21 (38%)</td>
</tr>
<tr>
<td>≤ 10%</td>
<td>10/36 (28%)</td>
<td>5/41 (12%)</td>
</tr>
<tr>
<td>P Value</td>
<td>P=0.08 (Fisher)</td>
<td>P=0.0016 (Log rank)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IMPACT Trial 37 mths Median FU</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10%</td>
<td>0/32 (0%)</td>
<td>9/35 (26%)</td>
</tr>
<tr>
<td>≤ 10%</td>
<td>21/101 (21%)</td>
<td>13/118 (11%)</td>
</tr>
<tr>
<td>P Value</td>
<td>P=0.004 (Fisher)</td>
<td>P=0.008 (Log Rank)</td>
</tr>
</tbody>
</table>
**Trial Schema For NET**

Stage 2 or 3 ER+ HER2- breast cancer

- AI for 16 to 18 weeks
- Surgery on breast and nodes
- Biopsy at 2 to 4 weeks

**PEPI**
- PEPI-0
  - Endocrine Therapy Only
- PEPI-not 0
  - Salvage systemic Treatment

**Ki67 Greater than 10%**
- Predicted PEPI - not 0
  - Salvage systemic Treatment
pCR Rate in patients with Ki67 > 10%

• Among the 49 patients whose week 2 ki67 > 10%, 35 patients switched to neo-adjuvant chemotherapy; 6 patients went directly to surgery, 2 patients went to surgery after a re-biopsy at week 4 again found their ki67 > 10%, and 1 patient pursued treatment outside of this study.

• Twenty-five of the 35 (71.4%) patients who switched to NAC elected to receive an anthracycline containing regimen (Table 1). There were 2 (5.7%, 95%CI: 0.7-19.1%) pathologic complete responses among these 35 patients.

Ellis et al JCO 2017, PMID: 28045625
Ki67 Proliferation Index as a Tool for Chemotherapy Decisions During and After Neoadjuvant Aromatase Inhibitor Treatment of Breast Cancer: Results From the American College of Surgeons Oncology Group Z1031 Trial (Alliance)

Put Some PEPI in Your Step: Ki67’s Long Road to Respectability
George W. Sledge Jr, Stanford University School of Medicine, Stanford, CA
See accompanying article doi:10.1200/JCO.2016.69.4406
Trial Schema For NET

Stage 2 or 3 ER+ HER2- breast cancer

BETTER ENDOCRINE THERAPY

Surgery on breast and nodes

Ki67 Greater than 10%

MORE PEPI- 0

Observe MORE patients without chemo

PEPI-not 0

Investigational Therapy

Predicted PEPI- not 0

Investigational Therapy
FALCON: PFS IN PATIENTS WITHOUT VISCERAL DISEASE

Without visceral disease

HR 0.59 (95% CI 0.42, 0.84)
Median PFS
Fulvestrant: 22.3 months
Anastrozole: 13.8 months


FIRST: OVERALL SURVIVAL

Ellis et al. J Clin Oncol. 2015; 33:3781-7
**ALTERNATE**

- **Arm A**: Anastrozole (A) x 6 mos
- **Arm F**: Fulvestrant (F) x 6 mos
- **Arm A/F**: (A + F) x 6 mos

**#4-week or 12-week Ki67 > 10%**

- **Neoadjuvant Chemotherapy**
- **Surgery**

**Modified PEPI 0**
- Adjuvant Chemotherapy not recommended

**Modified PEPI >0**
- Adjuvant Chemotherapy
  - Physician’s Choice
  - Endocrine therapy per physician choice

**Arm A**: A x 4.5 years

**Arm F**: F x 1.5 yrs → A x 3 yrs

**Arm A/F**: (A + F) x 1.5 yrs → A x 3 yrs

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*Weekly paclitaxel x 12 (optional d2 biopsy) or standard NCCN neochemo

# required biopsy

Eligibility:
- Postmenopausal
- Clinical Stage II or III
- ER+ (Allred 6-8)
- HER2-
A011106 Monthly Enrollment

Total enrollment as of March 2, 2017: **706**
Number of participating sites: **123**

* Accrual hold for drug supply to catch up!
Trial Schema For NET

Stage 2 or 3 ER+ HER2- breast cancer

- BETTER ENDOCRINE THERAPY
  - Surgery on breast and nodes
  - Ki67 Greater than 10%
  - PEPI Greater than 0
  - Predicted PEPI Greater than 0

- MORE PEPI Greater than 0
  - Observe MORE patients without chemo
  - Investigational Therapy

- PEPI Greater than 0
  - Investigational Therapy
NeoPalAna: Neoadjuvant palbociclib, a cyclin-dependent kinase 4/6 inhibitor, and anastrozole for clinical stage 2 or 3 estrogen receptor positive breast cancer

Patterns of response to AI plus CDKi in a sequential design

Black: complete cell cycle response (CCCR) with AI alone

Red: CCCR with AI plus CDK4/6i)

Green: need some other type of treatment

On Line Clinical Cancer Research March 2017
Trial Schema For Z1031B

Stage 2 or 3 ER+ HER2- breast cancer

BETTER ENDOCRINE THERAPY

Surgery on breast and nodes

Ki67 Greater than 10%

MORE PEPI-0

Observe MORE patients without chemo

Nature 2012: 486, 353-60
Nature Comms 2016: 7, 1-9

PEPI-not 0

Predicted PEPI- not 0

Treatment directed to the Individual biology
Experimental Design For Genomic Discovery

- 2 baseline frozen cores
- 70%+ tumor cellularity
- DNA extracted

Ki67 in surgical sample
- Greater than 10% = Unfavorable
- Less than 10% = Favorable

16 to 18 weeks of aromatase inhibition

BCRF, NHGRI, NCI
Whole genome sequencing in a clinical trial


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### Table 2 | Correlations between mutations and clinical features

#### a Luminal subtype and histology grade

<table>
<thead>
<tr>
<th>Gene</th>
<th>Expression/histo-pathology variable</th>
<th>Mutation frequency*</th>
<th>Set1 $P$†</th>
<th>Set2 $P$†</th>
<th>Whole set FDR $P$†</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53</td>
<td>Luminal subtype A</td>
<td>9.3% (13/140)</td>
<td>0.001</td>
<td>0.46</td>
<td>0.041</td>
</tr>
<tr>
<td></td>
<td>Luminal subtype B</td>
<td>21.5% (38/177)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Histological grade I</td>
<td>4.5% (3/66)</td>
<td>0.05</td>
<td>0.067</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Histological grade II/III</td>
<td>19.2% (48/250)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>MAP3K1</td>
<td>Luminal subtype A</td>
<td>20.0% (28/140)</td>
<td>0.018</td>
<td>0.028</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>Luminal subtype B</td>
<td>6.2% (11/177)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Histological grade I</td>
<td>25.8% (17/66)</td>
<td>0.061</td>
<td>0.011</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>Histological grade II/III</td>
<td>8.8% (22/250)</td>
<td></td>
<td></td>
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<tr>
<td>CDH1</td>
<td>Histological type ductal</td>
<td>5.9% (10/169)</td>
<td>0.41$§$</td>
<td>$2.8 \times 10^{-11}$</td>
<td>$3.9 \times 10^{-10}$</td>
</tr>
<tr>
<td></td>
<td>Histological type lobular</td>
<td>50.0% (20/40)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### b Mutation and Ki67 index

<table>
<thead>
<tr>
<th>Gene</th>
<th>Ki67 variable</th>
<th>Wild type mean‖</th>
<th>Mutant mean‖</th>
<th>Set1 $P$‖</th>
<th>Set2 $P$‖</th>
<th>Whole set FDR $P$‖</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53</td>
<td>Baseline</td>
<td>13.1</td>
<td>25.1</td>
<td>$3.7 \times 10^{-5}$</td>
<td>0.012</td>
<td>0.0003</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
<td>1.4</td>
<td>4</td>
<td>0.0002</td>
<td>0.014</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>% change</td>
<td>-89.2</td>
<td>-84.3</td>
<td>0.09</td>
<td>0.28</td>
<td>0.24</td>
</tr>
<tr>
<td>MAP3K1</td>
<td>Baseline</td>
<td>15.8</td>
<td>8.1</td>
<td>0.049</td>
<td>0.001</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
<td>1.86</td>
<td>0.75</td>
<td>0.11</td>
<td>0.1</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>% change</td>
<td>-88.3</td>
<td>-90.5</td>
<td>0.49</td>
<td>0.65</td>
<td>0.55</td>
</tr>
<tr>
<td>GATA3</td>
<td>Baseline</td>
<td>14.8</td>
<td>11.5</td>
<td>0.13</td>
<td>0.95</td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
<td>1.95</td>
<td>0.38</td>
<td>0.001</td>
<td>0.23</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>% change</td>
<td>-86.8</td>
<td>-96.9</td>
<td>0.003</td>
<td>0.08</td>
<td>0.012</td>
</tr>
</tbody>
</table>

* Mutation percentage (mutant cases/total cases in a category), counts are based on all cases (Set 1 and Set 2 combined).
† Unadjusted $P$ value from Fisher's exact test or Chi-square test as appropriate.
‡ Benjamini-Hochberg false discovery rate (FDR)-adjusted $P$ value using all cases (Set1 and Set2 combined).
§ Only 77 cases in Set1 had CDH1 sequencing results.
‖ Geometric means are based on all cases (Set1 and Set2 combined).
¶ Unadjusted $P$ value from Wilcoxon rank sum test.

The somatic mutation profiles of 2,433 breast cancers refine their genomic and transcriptomic landscapes
Genomics to understand clonal evolution
Aromatase inhibition remolds the clonal architecture of estrogen-receptor-positive breast cancers

Christopher A. Miller¹,², Yevgeniy Gindin¹,†, Charles Lu¹,†, Obi L. Griffith¹,³,⁴, Malachi Griffith¹,⁴,⁵, Dong Shen¹,†, Jeremy Hoog³, Tiandao Li¹, David E. Larson¹,⁵, Mark Watson⁶, Sherri R. Davies³, Kelly Hunt⁷, Vera J. Suman⁸, Jacqueline Snider³, Thomas Walsh⁹, Graham A. Colditz⁴,⁹, Katherine DeSchryver³,⁹, Richard K. Wilson¹,²,³,⁴,⁵, Elaine R. Mardis¹,³,⁴,⁵ & Matthew J. Ellis¹,³,¹⁰
Genomics for clinical trial eligibility
HER2 Somatic Mutations

- Blue circle from Bose et al, Red from Ross et al
- From 8 publications with a total of 1,499 patients
- 20% of patients had mutations at amino acids 309 or 310
- 68% of patients had mutations at amino acids 755-780
Figure 3c

Baseline (7/17/2014)  
Post 4 cycles (11/24/2014)
ctDNA VAF Maps for Patients who derived clinical benefit

**Pt 15**

- RECIST Response: CR
- Baseline: HER2 0.2%
- Week 4: HER2 0%
- Progression: HER2 0.8%

**Pt 16**

- RECIST Response: SD 37 weeks
- Baseline: HER2 15.4%
- Week 4: HER2 0.3%
- Progression: HER2 1.6%

**Pt 14**

- RECIST Response: PR
- Baseline: HER2 1.0%
- Week 4: HER2 0.2%
- Progression: HER2 14.4%

**Pt 14**

- RECIST Response: SD 32 weeks
- Baseline: HER2 7.5%
- Week 4: HER2 0.6%
- Progression: HER2 22.9%

**DO NOT POST**
ctDNA VAF Maps for Patients who had PD at week 8

Pt 11
- Baseline: 32.4%
- Week 4: 43%

Pt 1
- Baseline: HER2 32.4%
- Week 4: HER2 14.3%
- Progression: HER2 8.8%

Pt 7
- Baseline: HER2 4.6%
- Week 4: HER2 16%

Pt 12
- Baseline: HER2 4.2%
- Week 4: HER2 1.7%
- Progression: HER2 5%
Bringing genomics from the clinic back to the laboratory
Conventional Cell Lines vs Patient-Derived Xenografts (PDX)

Cell lines
- Easy to study
- Cheap
- Drug screens efficient

PDX
- Genomic Annotation
- Clinical Annotation
- Grown as a tumor that metastasizes
Patient Derived Xenografts


“Heterogeneity is a stable transplantable phenotype”

“virtual genomic purification”
• 36 year old Caucasian Ancestry Stage 3 disease
• Mastectomy
• Adjuvant chemotherapy and radiation
• Tamoxifen
• Recurrence at 26 months post diagnosis
• Letrozole 20 months
• Fulvestrant 4 months
• Grafted sample PDX (WHIM20)
• Temsirolimus one month
• Exemestane one month
• Grafted sample for PDX (WHIM23)
• Palliative chemotherapy
• Overall survival 65 months
Heterogeneous Responses to estrogen supplementation in ER+ PDX from patients with advanced breast cancer
Heterogeneous Responses to estrogen supplementation in ER+ PDX from patients with advanced breast cancer

Figure 4

**ESR1 WT**

**ESR1 AMPLIFIED**

**ESR1 TRANSLOCATED**

**ESR1 Y537S**

**ESR1 E380Q**
Mutations in the Ligand Binding Domain of ESR1 are an under-recognized Cause of Endocrine Therapy Resistance
Plasma ESR1 Mutations and the Treatment of Estrogen Receptor–Positive Advanced Breast Cancer


Fig 2. Progression-free survival (PFS) in SoFEA by ESR1 mutation status. (A) PFS of patients with ESR1 mutant cancers who received exemestane or a fulvestrant-containing regimen. (B) PFS of patients without detected ESR1 mutation who received exemestane or a fulvestrant-containing regimen. HR, hazard ratio.
A

Fulvestrant+Palbociclib
Median PFS, 9.4 months
(95% CI, 5.3 to 11.1)
Fulvestrant+Placebo
Median PFS, 3.6 months
(95% CI, 2.0 to 5.5)

HR, 0.43 (95% CI, 0.25 to 0.74); P = .002

B

Fulvestrant+Palbociclib
Median PFS, 9.5 months
(95% CI, 9.2 to not estimable)
Fulvestrant+Placebo
Median PFS, 5.4 months
(95% CI, 3.5 to 7.4)

HR, 0.49 (95% CI, 0.35 to 0.70); P < .001

<table>
<thead>
<tr>
<th>No. at risk (events)</th>
<th>Fulvestrant+Placebo</th>
<th>Fulvestrant+Palbociclib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>28 (10)</td>
<td>63 (16)</td>
</tr>
<tr>
<td></td>
<td>18 (11)</td>
<td>45 (7)</td>
</tr>
<tr>
<td></td>
<td>6 (1)</td>
<td>36 (6)</td>
</tr>
<tr>
<td></td>
<td>3 (2)</td>
<td>22 (5)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. at risk (events)</th>
<th>Fulvestrant+Placebo</th>
<th>Fulvestrant+Palbociclib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>92 (30)</td>
<td>177 (30)</td>
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<td>50 (7)</td>
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</table>
WHIM 18

- 31 year old African Ancestry Stage 4
  Letrozole 8 months
- Exemestane 3 months
- Fulvestrant 1 month
- Grafted sample for WHIM18
  Palliative Chemotherapy 11 months
- Tamoxifen 2 months
- Further palliative chemotherapy and RT
- Overall Survival 31 months

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ESR1-e6>YAP1

Li et al. Cell Reports, 2013 Sep 26;4(6):1116-30
New techniques in translational genomics
Proteogenomics connects somatic mutations to signalling in breast cancer

Philipp Mertins, D. R. Mani, Kelly V. Ruggles, Michael A. Gillette, Karl R. Clauser, Pei Wang, Xianlong Wang, Jana W. Qiao, Song Cao, Francesca Petralia, Emily Kawaler, Filip Mundt, Karsten Krug, Zhidong Tu, Jonathan T. Lei, Michael L. Gatza, Matthew Wilkerson, Charles M. Perou, Venkata Yellapantula, Kuan-lin Huang, Chenwei Lin, Michael D. McLellan, Ping Yan, Sherri R. Davies, R. Reid Townsend, Steven J. Skates, Jing Wang, Bing Zhang, Christopher R. Kinsinger, Mehdi Mesri, Henry Rodriguez, Li Ding, Amanda G. Paulovich, David Fenyő, Matthew J. Ellis, Steven A. Carr & the NCI CPTAC

Article DOI: 10.1038/nature18003
<table>
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<th>Discovery</th>
<th>Information</th>
<th>Validation</th>
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<td>Genomics</td>
<td>Whole genomes and transcriptomes (1 µg) – unbiased discovery of cancer-specific aberrations</td>
<td>Validation by synthesizing variants for multiplexed capture and resequencing or orthogonal genomic platforms (qPCR, nString)</td>
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<tr>
<td>Proteomics</td>
<td>Global- (100 µg) and phospho-proteomics (1mg) – unbiased discovery of cancer-specific protein aberrations.</td>
<td>Verification by synthesizing natural and isotopically labeled (heavy) peptides for accurate quantitation and for sequence confirmation.</td>
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</table>
Cancer remains a diagnostic problem

The study of lots of “broken” cancer genomes will eventually allow us to understand variability in individual outcomes.

The chaos of the cancer genome at the DNA level creates a passenger versus driver distraction that needs to be resolved with better informatics techniques.
Thanks to my many collaborators

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Mitch Dowsett
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Craig Allred
Mark Watson
Ian Smith