Clinical Trials for Breast Cancer

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What are clinical trials?

• Research studies that are designed to answer questions about new ways to treat cancer
What are the different types of clinical trials?

<table>
<thead>
<tr>
<th>Phase</th>
<th>Purpose</th>
</tr>
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<tbody>
<tr>
<td>Phase 1</td>
<td>Determine dose</td>
</tr>
<tr>
<td></td>
<td>Determine side-effects</td>
</tr>
<tr>
<td></td>
<td>(Number of people: 15-20)</td>
</tr>
<tr>
<td>Phase 2</td>
<td>Determine efficacy</td>
</tr>
<tr>
<td></td>
<td>(Number of people: &lt;100)</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Compare the new treatment to a standard</td>
</tr>
<tr>
<td></td>
<td>treatment</td>
</tr>
<tr>
<td></td>
<td>Number of people: (100-1000s)</td>
</tr>
</tbody>
</table>
Road To FDA Approval

- Preclinical
- Phase 1
- Phase 2
- Phase 3
- FDA Approval
Goals of Phase 1 Clinical Trials

• How much of a new drug can be given safely

• How often the drug needs to be given

• What are the side effects of the new drug
Types of Phase 1 Trials

• Disease specific phase 1 studies

• All-comer phase 1 trials open to any solid tumor

• New agent alone

• Combining new agents

• Combining new agent with standard chemotherapy
Dose Escalation in Phase 1 Studies: 3+3 Design

30 mg
3 Patients

20 mg
3 Patients

10 mg
3 Patients

Once dose determined
EXPANSION COHORT
Enroll 10-20 patients
Pharmacokinetics (PKs)

• Tests how rapidly a drug is cleared from circulation

• Challenging for patients because can sometimes require long days and multiple visits a week during the first cycle of therapy
Phase 2 Trials

- The drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety
Phase 3 Trials

• The drug or treatment is given to large groups of people to confirm its effectiveness and compare it to commonly used treatments

Drug X

R

Standard of Care
How Do We Treat Metastatic Breast Cancer?

Hormone receptor positive
- Hormonal therapy
- Hormonal therapy
- Chemotherapy
- Chemotherapy

Triple-negative
- Chemotherapy
- Chemotherapy
- Chemotherapy

HER2-Positive
- Herceptin + perjeta + chemotherapy
- TDM1
- Lapatinib + Capecitabine
- Herceptin + chemotherapy
- Herceptin + chemotherapy

*Note, these are just examples. Each patient is different and treatment is tailored accordingly.*
Hormone-Receptor Positive Breast Cancer
Exciting Targets in ER+ Breast Cancer

- ESR1
- CDK4
- PI3K
- AR
- HSP90
- FGFR1

- And others not listed here...
Estrogen Receptor Function: The Basics
Estrogen Receptor Function: The Basics
How Do Tumors Become Resistant?

% of patients with LBD mutations

0 12 20
primary early met late met

Slide courtesy of Dr. Rinath Jeselsohn
Can We Use This Knowledge to Develop Better Treatments?

• **Test new estrogen receptor-blocking drugs (and combinations) to see how well they work against tumors with ESR1 mutations**
  – In the laboratory
  – Then in clinical trials

• **Ongoing Studies with SERDs**
  – ARN-810
Polyak and Filho, *Cancer Cell*, 2012
Many PI3K Inhibitors in Trials

• GDC 0032
• GDC 0941
• BYL719
• BKM120
• others
SAN DIEGO — Researchers say that a new type of drug can help prevent advanced breast cancer from worsening, potentially providing an important new treatment option for women and a blockbuster

**Pfizer To Submit Palbociclib New Drug Application With FDA Based On Final Results Of PALOMA-1**

**NEW YORK**--(BUSINESS WIRE)--May 16, 2014-- Pfizer Inc. today announced that it will submit a New Drug Application (NDA) with the United States Food and Drug Administration (FDA) for palbociclib, combined with letrozole, as first-line systemic treatment of post-menopausal women with estrogen receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2-) locally advanced or metastatic
Inhibition of CDKs

- Blocking CDK4 should lead to G1 cell cycle arrest
- Three oral selective inhibitors of CDK4/6 are in development
  - Palbociclib, PD0332991; Pfizer
  - LEE011; Novartis
  - Abemaciclib, LY2835219; Lilly

Shapiro CCR 2004, Dickson CCR 2014
PALOMA-1: Phase 2 Study
ER+, HER2– Locally Recurrent or Metastatic Breast Cancer

**Part 1**
- Post-menopausal
- ER+, HER2– BC status
- No prior treatment for advanced disease

Randomization
- Palbociclib 125 mg QD\(^a\) + Letrozole 2.5 mg QD
- Letrozole 2.5 mg QD

N=66

**Part 2**
- Post-menopausal
- ER+, HER2– BC with CCND1 amplification and/or loss of p16
- No prior treatment for advanced disease

Randomization
- Palbociclib 125 mg QD\(^a\) + Letrozole 2.5 mg QD
- Letrozole 2.5 mg QD

N=99

\(^a\)Schedule 3/1

**Key Eligibility Criteria**
- Measurable disease (RECIST 1.0) or bone-only disease
- ECOG PS of 0 or 1
- Adequate blood counts and organ function
- No prior/current brain metastases
PALOMA-1: Progression-Free Survival

**Number of Events (%)**
- PAL + LET (N=84): 41 (49)
- LET (N=81): 59 (73)

**Median PFS, months (95% CI)**
- PAL + LET: 20.2 (13.8, 27.5)
- LET: 10.2 (5.7, 12.6)

**Hazard Ratio (95% CI)**
- 0.488 (0.319, 0.748)

**p-value**
- 0.0004

**ORR**
- PAL + LET: 43%
- LET: 33%

Number of patients at risk:
- PAL + LET: 84, 67, 60, 47, 36, 28, 21, 13, 8, 5, 1
- LET: 81, 48, 36, 28, 19, 14, 6, 3, 3, 1
Most Common Treatment-Related AEs ≥10%

<table>
<thead>
<tr>
<th></th>
<th>PAL + LET (N=83)</th>
<th>LET (N=77)</th>
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<tbody>
<tr>
<td></td>
<td>G1/2 (%)</td>
<td>G3 (%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>19</td>
<td>48</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td>Anemia</td>
<td>23</td>
<td>4</td>
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<tr>
<td>Fatigue</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>Alopecia</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Hot flush</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

- Neutropenia was self-limited and not associated with infectious complications
- Tends to occur early in treatment, recovers with a few days of drug hold
- 40-45% required delay/dose reduction due to toxicity
Ongoing studies with cdk 4/6 inhibitors

- **Novartis cdk 4/6 inhibitor (Ribaciclib, LEE011)**
  - LEE011 alone
  - Faslodex + LEE011 + BYL719/BKM120 (PI3K inhibitors)
  - Letrozole + LEE011 + BYL719
  - Exemestane + Everolimus + LEE011

- **Lilly cdk 4/6 inhibitor (Abemaciclib)**
  - Aromatase Inhibitor +/- Abemaciclib
  - Faslodex +/- Abemaciclib
  - Abemaciclib alone
Triple-Negative Breast Cancer
What’s Exciting in Triple-Negative Breast Cancer

• PI3K/AKT inhibitors
• PARP inhibitors/combinations
• Androgen receptor antagonists
• Immunotherapy
• Drug-Antibody Conjugates
Immunotherapy

- Immunotherapy as a potential paradigm shift in the treatment of cancer
- Durable tumor responses in other disease
- Low toxicity (with limitations)
- Smart strategy to overcome the molecular complexity of cancer
PD-1/PD-L1 Pathway: Biology

- PD-1 is an inhibitory receptor expressed on activated T cells
- Tumors express PD-L1 to evade immune surveillance
- Ligation of PD-1 by PD-L1 or PD-L2 inhibits T cell activation

* Thompson et al. 2006; Hamanishi et al. 2007; Okazaki and Honjo 2007; Hino et al. 2010


MPDL3280A: An *Engineered* Anti-PD-L1 Antibody

- Binds PDL1 on tumor cells
- Allows T-cells to attack the cancer
- Current trials ongoing for triple-negative breast cancer
- Some trials requires tumor be PDL1 +
Clinical Activity of MPDL3280A in Melanoma

62-year-old female with metastatic melanoma (cutaneous); initial Dx: Jun 2000; metastatic Dx: Dec 2011
Pembrolizumab (MK-3475)

- Antibody against PD-1 receptor on the T-cell
- Current ongoing trials (some require tumor is PDL1 +)
Clinical Activity of MK-3475

Baseline: April 13, 2012

April 9, 2013

72-year-old male with metastatic melanoma

Images courtesy of A. Ribas, UCLA.
Trials for BRCA-Related Cancers
PARP Inhibitors

Igelhart JD and Silver DP. NEJM 2009
PARP inhibitor trials

• **Olaparib + BYL719 (Phase 1)**
  – Combines PARP with PI3K inhibitor

• **OLYMPIAD Study**
  – Olaparib (PARP inhibitor) vs physician’s choice chemotherapy
Sapacitabine + Selecrelix

- **Sapacitabine**: oral chemotherapy
- **Selecrelix**: oral cdk 1,2, 7, 9 inhibitor
Drug-Antibody Conjugates
Antibody-Drug Conjugates

Key Components:

1. Target-specific internalizing antibody
2. Potent cytotoxic prodrugs
3. Linker and conjugation chemistries

Drug released in CANCER CELL
Trials of Antibody-Drug Conjugates

• **LYE5953A** (drug-Ab conjugate against Lye6)

• **PF-06657263** (drug-Ab conjugate against EFNA4)
HER2+ Breast Cancer
HER2 Gene Amplification Results in Marked Overexpression of HER2 Proteins (and therefore a great target)

2,000,000 HER2 proteins on cancer cell
HER2+ Disease: Major Clinical Advances Over The Past 15 Years

1998
Initial Randomized Trial Demonstrating Benefit of Trastuzumab

2002
First Preoperative Trials Reported

2005
Three Large Adjuvant Trials Reported

2005
Lapatinib Approved

2007-2008
Initial Trials Of T-DM1, Pertuzumab, Neratinib

2007-2008
Phase II Randomized Trial of T-DM1

2010
Preoperative Trials of Dual Blockade

2010
Phase III of Pertuzumab

2012
Pertuzumab Preop Approval

2013
Phase III of T-DM1 vs Cape/Lap
Trastuzumab-DM1 (T-DM1)

- Maytansine analogue DM1 (antitubule akin to vincas) conjugated to trastuzumab – similar to gemtuzumab (Myelotarg)
- Will it allow omission of separate cytotoxic?

Additional Clinical Challenges

1. Heterogeneity of HER2+ Disease

2. Brain Metastases
Are All HER2+ Tumors The Same?

- Heterogeneity for HER2
- Hormone receptor expression
- Gene signature
- PIK3CA mutation status

“Then how can you be the same”
Intratumoral Heterogeneity for HER2+

Two Segments with Distinctly Different HER2 Status
HER2+/ER- and Triple Negative

Four blocks of primary tumor

Lymph node metastasis

Courtesy of Susan Lester, MD, PhD and Andrea Richardson, MD, PhD
PI3 kinase Pathway “Activation Status” Predicts Response to Trastuzumab

DF/HCC Phase I/II of Combined Anti-HER2 Therapy and PI3K Inhibition

Phase I:
Trastuzumab/Pertuzumab/GDC 0032/Taxane

Expansion Cohort
Brain Metastases
Ongoing Trials for HER2+ Brain Metastases

- Capecitabine + Neratinib
- ARRY + trastuzumab
- ARRY + T-DM1
- Cabozantinib + trastuzumab
- Abemaciclib + trastuzumab
What about “Personalized Medicine”?
A Paradigm Shift: The Genomic View of Cancer

From Anatomy...

Lung
Breast
Prostate
Colon
Brain

To Genetic Mutation

Genomic/Molecular Profiling

KIT (Imatinib)
EGFR (Erlotinib)
HER2 (Trastuzumab)
BRAF (PLX4032)
PIK3CA (BEZ235)
Obtain tumor biopsy material

Extract DNA/RNA from tumor to profile for somatic alterations

MacConaill and Garraway, JCO, 2010
Mutations Identified in > 500 Breast Tumor Specimens at DFCI Using OncoMap
## Potential Genomic Targets in Breast Cancer

### Selected genes with Mutations, Amplifications/Deletions, Rearrangements in Breast Cancer

<table>
<thead>
<tr>
<th>ERBB2</th>
<th>KRAS</th>
<th>CDKN2A</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIK3CA</td>
<td>NRAS</td>
<td>CDKN1B</td>
</tr>
<tr>
<td>PTEN</td>
<td>BRAF</td>
<td>CCND1</td>
</tr>
<tr>
<td>AKT1</td>
<td>MAP2K1</td>
<td>CCNE1</td>
</tr>
<tr>
<td>AKT2</td>
<td>MAP3K1</td>
<td>CDK4</td>
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<tr>
<td>AKT3</td>
<td>NF1</td>
<td>RB1</td>
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<tr>
<td>PIK3R1</td>
<td>FGFR1</td>
<td>BRCA1</td>
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<tr>
<td>INPP4B</td>
<td>FGFR2</td>
<td>BRCA2</td>
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<tr>
<td>MTOR</td>
<td>FGFR3</td>
<td>ATM</td>
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<tr>
<td>TSC1</td>
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<tr>
<td>TSC2</td>
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</tbody>
</table>

### Anti-Her2 Therapies
- PI3k / AKT / MTOR Inhibitors
- RAF / MEK / ERK Inhibitors

### FGFR Inhibitors
- FGFR Inhibitors
- PARP Inhibitors

### EGFR Inhibitors
- EGFR Inhibitors
- Nutlins

### Anti-p53 Strategies
- Anti-p53 Strategies
- Anti-MYC Strategies
- Others
Clinical Breast Cancer Cancer Genomics

• To date, genomic studies in breast cancer have highlighted the landscape of genomic alterations in breast cancer overall

• Now, we have developed *clinically-focused* studies to help us understand:
  – The genetics of specific types of breast cancer
  – Why breast cancers behave in different ways
  – How breast cancers develop resistance to therapies
  – Why some breast cancers are exquisitely sensitive to some therapies
Common Questions
How often will I need to come in for visits?
Each trial is different, but generally most phase I studies have at least weekly visits for the first cycle (3-4 weeks) then fewer visits thereafter
How will you know if the drug is working?
• Frequency of imaging is dependent on the study, but generally every 6-9 weeks
Why should I do a clinical trial?
Weigh Pros and Cons

Pros:
• If a new treatment is proven to work and you are receiving it, you may be among the first to benefit
• You can expand the number of treatment options you have
• You have a chance to help others and improve cancer care

Cons:
• New treatments may have side effects that doctors do not expect
• Phase I trials often involve frequent visits during the first cycle
• Even if a new treatment has benefits, it may not work for you
How Can We Do Better?
Participate in Trials!

• “One reason I chose to participate in a clinical trial was to help women with triple-negative breast cancer. It is thanks to women who have enrolled in clinical trials that we have the treatments that give us hope.”

— Natalia (LBBC, Guide to Understanding TNBC)
How Do I Enter a Trial?

• Your provider will discuss with you trials of interest, review rationale, as well as risks and benefits

• A research RN will review a consent form with you, which describes the structure and details of the trial

• After a consent is signed, there is a “screening” period to determine if you are eligible

• When eligibility is confirmed, then you register and can begin trial therapy
Will my insurance pay for me to participate in the trial?
• Generally, almost all insurance companies pay for patients to participate in phase I clinical trials
• Anything that is for research purposes (ie. research blood, biopsies) is provided by research
• Experimental medication is provided
How to learn about trials?
ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. Learn more about clinical studies and about this site, including relevant history, policies, and laws.

ClinicalTrials.gov currently lists 133,939 studies with locations in all 50 states and in 180 countries.

Search for Studies

Example: "Heart attack" AND "Los Angeles"

Search Help
- How to search
- How to find results of studies

Locations of Recruiting Studies
- Non-U.S. Only (49%)
- U.S. Only (45%)
- Both U.S. & Non-U.S. (7%)

Total N = 28,880 studies

Or ask your provider...
Breast Oncology Clinical Trial Finder

If you would like to make an appointment for a new patient, please contact the Dana-Farber new patient coordinators for the breast group via email at DFCIBreastViewPatientRequests@partners.org, or call 877-442-3324. If you have questions regarding clinical trial eligibility or availability, please email the Dana-Farber breast group's research nurses at DFCIBOCClinicalTrials@partners.org.

Stage: Metastatic

Display All Trials For This Stage of Disease

Enter stage (from left Column)

Receptor Status:
- ER or PR: ER+ and/or PR+ ▼
- HER2 Status: HER2 negative ▼
- Androgen Receptor Status: AR unknown ▼

BRCA Status: Unknown ▼
PI3K Status: Unknown ▼
For Metastatic Trials: Number of Prior Lines of chemotherapy for metastatic disease: ▼

Display Trials Matching Clinical Criteria

Search for trial by Protocol number (no hyphens e.g. 14098) ▼
Search by Protocol Number
Conclusions

• Exciting time in drug development

• Several clinical trial options for patients with varying subtypes of breast cancer

• Some trials require tissue prescreening with a goal of trying to deliver personalized medicine