The role of molecular testing in tumor and blood for metastatic breast cancer

Jane Lowe Meisel, MD
Assistant Professor of Hematology and Medical Oncology
Winship Cancer Institute at Emory University
Overview

• An overview of molecular testing
• Describing available testing platforms
• Who are the most appropriate candidates?
• Using results to change therapy
• Trials and future opportunities
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Defining molecular testing

• Molecular diagnostic tests detect specific sequences in DNA or RNA that may or may not be associated with disease

• Analyzing the molecular signature of cancerous cells can enable us to learn more about what drives the cancer and allow us to better target our therapies
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)

Slide courtesy of Dr. Nikhil Wagle
The Cancer Genome Atlas

• A project begun in 2005 to catalogue genetic mutations responsible for cancer using genome sequencing and bioinformatics
  • Pilot began in 2006: GBM, lung and ovarian cancer
  • 2009: expansion, with goal to characterize the genome of 20-25 different tumor types by 2014

• Supervised by the NCI’s Center for Cancer Genomics
The Cancer Genome Atlas: Invasive Ductal Carcinoma

• Somatic mutations in TP53, PIK3CA, and GATA 3 occurred at >10% incidence across all invasive ductal carcinomas

• Specific signaling pathways were found to be dominant in each molecular subtype
  • Luminal A, luminal B, basal-like, and HER2-enriched

• However, there were numerous subtype associated and novel gene mutations within each subtype
  • Much of the heterogeneity of tumors may occur within and not across subtypes

• Basal-like breast tumors and high-grade serous ovarian cancers showed many molecular commonalities

TCGA Nature 490 (61-70).
The Cancer Genome Atlas: Invasive Lobular Carcinoma

- 127 lobular and >800 ductal carcinomas analyzed

- Researchers found that lobular and ductal carcinomas are a distinct entity

- FOX1A elevated in lobular carcinoma

- Lobular carcinoma enriched for PTEN loss and Akt activation

A molecular portrait of breast cancer
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For the individual patient: molecular testing 101

• Tests can range from simple to complex
  • Simple: detecting one type of mutation in one gene (such as the test that looks for the p.V600E mutation observed in melanoma)
  • Complex: simultaneously detecting all the major types of gene alterations
• Molecular profiling is generally performed on DNA extracted from FFPE tissue specimens
Commercial testing platforms

• **FoundationOne**
  • Biopsy type: FFPE
    • most recent material is preferred; post-targeted therapy strongly recommended if applicable
  • >300 genes interrogated for all four classes of genomic alterations
  • Results include microsatellite instability and tumor mutational burden measurements, which may help predict response to immunotherapy
  • Results within 10 days of specimen acquisition
  • List price: $5800
Commercial testing profiles

- **FoundationACT (Assay for Circulating Tumor DNA)**
  - Biopsy type: peripheral whole blood (only 2 10mL tubes required)
  - Useful when tissue is unobtainable or to complement FoundationOne testing
  - 60 genes interrogated
  - Results within 2 weeks of specimen acquisition
Commercial testing platforms

• Guardant (liquid biopsy)
  • Two tubes of blood submitted
  • 73-gene panel analyzed through digital sequencing technology
  • Results within two weeks
  • Possible benefit: liquid biopsy captures tumor heterogeneity more accurately than solid
What to do with results?

• FDA approved therapies in breast cancer
  • None currently indicated by genomics aside from PARP in TNBC
  • ER and HER2 status major biomarkers

• Clinical trials
  • Different options might be more rational/targeted based on mutations in ESR, ERBB2 (HER2), AKT1, PIK3CA or mutation burden
  • Basket studies based on rarer mutations

• Off-label use of drugs that are FDA-approved for other cancers
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Who to test and when?

• Usually reserved for metastatic patients for whom standard therapy has failed or is not an option

• Best to send most recent tissue specimen (or a new one) for most applicable and accurate results

• Since results usually take at least 3 weeks from the time you decide to send (2 weeks from tissue delivery), often useful to employ non-targeted therapy while waiting if patient requires treatment

• Liquid biopsy may be more reliable with higher tumor burdens (more ctDNA)
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Real-life example #1

• 59F with ER+PR-HER2- stage I breast cancer in 2010, s/p lumpectomy, TC x 4 and tamoxifen therapy

• 11/2014: diagnosed with metastatic ER+PR-HER2- disease, mostly in liver, with treatment as follows:
  • 12/2014-7/2015: Adriamycin x 6 (good response)
  • 8/2015-9/2015: Letrozole/palbociclib (maintenance)
  • 9/2015-5/2016: capecitabine (response, then progression)
  • 6/2016-12/2016: gem/carbo (partial response, but with dose delays/myelosuppression)

• 12/2016: sent Guardant testing
Real-life example #1

- Referred for NCI-MATCH (FGFR inhibitor arm-> AZD4547)
Real-life example #2

- 55F with metastatic ER+ PR-HER2- breast cancer who received:
  - 3/2015-11/2015: Letrozole + palbicitlib
  - 12/2015-6/2016: capecitabine
  - 7/2016-9/2016: weekly paclitaxel
  - 10/2016-3/2017: carboplatin/gemcitabine

- Sent FoundationOne testing
Real life example #2

Started on everolimus 10mg daily
Real life example #3

- 71F with metastatic ER+ breast cancer diagnosed in 11/2015
  - 11/2015: Enrolled on BELLE3 (faslodex + PI3K inhibitor)
  - 8/2016: Capecitabine
  - 4/2017: Eribulin initiated due to progression in the liver

- 4/2017 – while starting eribulin, Guardant testing ordered
Real life example #3

• Trastuzumab/pertuzumab added to current regimen

• May be a candidate for everolimus in the future; or for FGFR1-directed trials
The power of targeted therapy

- **AKT1 inhibition in solid tumors with AKT1 mutations (JCO 2017)**

- This panel shows imaging at baseline and at six weeks after initiation of AKT inhibitor AZD5363 in an E17K-mutant ER+HER2- breast cancer

- Imaging response confirmed with decrease in and persistently low levels of AKT1 E17K burden in cell-free DNA
The power of targeted therapy

*ERBB2* mutant (L755_E757delinsS) ER+/HER2- invasive ductal carcinoma

Confirmed PR: 52% reduction by RECIST following neratinib monotherapy
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CDX-011 in patients with metastatic, gpNMB over-expressing TNBC (METRIC)

Figure 1. High GPNMB mRNA expression is associated with shorter metastasis-free (panel A) and overall survival (panel B) times in human breast cancer.

(Rose, Grosset et al. 2010)
CDX-011 in patients with metastatic, gpNMB over-expressing TNBC (METRIC)

- CDX-011: a tumor-targeting antibody combined with a cytotoxic microtubule inhibitor; the antibody is directed at gpNMB

- Patients must have overexpression of gpNMB in ≥ 25% of malignant cells in a malignant biopsy (confirmed centrally) and have had 0-2 prior regimens in the advanced setting

- Primary objective: evaluate the activity of CDX-011 in metastatic gpNMB-overexpressing TNBC
  - Secondary objectives: ORR, duration of response, OS, impact on quality of life
Patients with metastatic gpNMB-overexpressing TNBC (0-2 prior lines of therapy)

- Capecitabine 1250mg/m² BID
  Days 1-14 of 21-day cycle

- CDX-011
  1.88mg/kg IV on day 1 of 21-day cycle
Genomically directed therapy after preoperative chemotherapy in patients with triple negative breast cancer (TNBC)

• Eligible patients: stage I-III TNBC who have undergone anthracycline and/or taxane-based chemotherapy and have significant residual invasive disease at the time of surgery:
  • Disease in breast measuring at least 2cm (or 1cm with any nodal involvement)
  • Any nodal involvement that results in 20% cellularity or greater

• Primary objective: comparison of 2-year DFS between genomically directed therapy vs standard of care following preop chemotherapy
  • Overall DFS and 5y OS will also be evaluated
Genomically directed therapy after preoperative chemotherapy in patients with TNBC
Genomically directed therapy after preoperative chemotherapy in patients with TNBC

- Paradigm panel used for sequencing: an next-generation sequencing test developed by the University of Michigan and the International Genomics Consortium

- Queries >500 genetic regions of interest

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Drug recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. PIK3CA, PTEN</td>
<td>Everolimus</td>
</tr>
<tr>
<td>2. TOP2A</td>
<td>Doxorubicin</td>
</tr>
<tr>
<td>3. PARP1, BRCA1</td>
<td>Cisplatin or Olaparib</td>
</tr>
<tr>
<td>4. VEGFA</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>5. TYMP</td>
<td>Capcitabine</td>
</tr>
<tr>
<td>6. SSTR2</td>
<td>Octreotide</td>
</tr>
<tr>
<td>7. MGMT</td>
<td>Temozolomide</td>
</tr>
<tr>
<td>8. MYC</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>9. EGFR</td>
<td>Cetuximab</td>
</tr>
<tr>
<td>10. COX2</td>
<td>Celecoxib</td>
</tr>
<tr>
<td>11. hENT</td>
<td>Gemcitabine</td>
</tr>
<tr>
<td>12. MET</td>
<td>Crizotinib</td>
</tr>
<tr>
<td>13. CCND1,2,3 amplifications;</td>
<td>Palbociclib</td>
</tr>
<tr>
<td>CDKN2A loss, CDK4/6 amplifications</td>
<td></td>
</tr>
<tr>
<td>14. PDL1 TILS or TUMOR IHC+</td>
<td>Pembrolizumab</td>
</tr>
</tbody>
</table>
TAPUR

• Testing the use of FDA-approved drugs that target a specific gene abnormality in patients with advanced-stage cancer
• Plan to enroll 1030 patients from 2016-2019

• Eligibility
  • Metastatic or locally advanced solid tumor no longer benefiting from standard tx
  • ECOG PS 0-2
  • Measurable or evaluable disease
  • Results from a genomic test or IHC test for protein expression performed In a CLIA-certified lab must be available (liquid biopsies ok) and must demonstrate potential clinical benefit for single-agent treatment with one of the drugs in the study
## TAPUR: study arms

<table>
<thead>
<tr>
<th>Arms</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGFR</td>
<td>Axitinib</td>
</tr>
<tr>
<td>Bcr-abl, SRC, LYN, LCK</td>
<td>Bosutinib</td>
</tr>
<tr>
<td>ALK, ROS1, MET</td>
<td>Crizotinib</td>
</tr>
<tr>
<td>CDKN2A, CDK4, CDK6</td>
<td>Palbociclib</td>
</tr>
<tr>
<td>CSF1R, PDGFR, VEGFR</td>
<td>Sunitinib</td>
</tr>
<tr>
<td>mTOR, TSC</td>
<td>Temsirolimus</td>
</tr>
<tr>
<td>EGFR</td>
<td>Erlotinib</td>
</tr>
<tr>
<td>ERBB2</td>
<td>Trastuzumab and pertuzumab</td>
</tr>
<tr>
<td>BRAFV600E</td>
<td>Vermurafenib and cobimetinib</td>
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<tr>
<td>PTCH1</td>
<td>Vismodegib</td>
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<tr>
<td>KRAS, NRAS, BRAF</td>
<td>Cetuximab</td>
</tr>
<tr>
<td>Bcr-abl, SRC, KIT, PDGFRB, EPHA2, FYN, LCK, YES1</td>
<td>Dasatinib</td>
</tr>
<tr>
<td>RET, VEGFR 1/2/3, KIT, PDGFRB, RAF1, BRAF</td>
<td>Regorafenib</td>
</tr>
<tr>
<td>BRCA1/BRCA2, ATM</td>
<td>Olaparib</td>
</tr>
<tr>
<td>POLE/POLD1, high mutational load</td>
<td>Pembrolizumab</td>
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</tbody>
</table>
Objective: To generate a publicly available database of clinical, genomic, molecular, and patient reported data in metastatic breast cancer to accelerate discoveries and the development of new treatment strategies.
The Metastatic Breast Cancer Project

Challenges of Studying Patient Tumor Samples

Only 5% of U.S. cancer patients are enrolled in clinical trials

85% of U.S. cancer patients are treated in community settings

Most tumor samples have not been readily available for study

Technology, social media, and cultural changes now provide a new opportunity to engage cancer patients and directly partner with them in this research
The Metastatic Breast Cancer Project

MBCProject: Patients Enrolled, Consented, and Saliva Received

- Registered
- Consented
- Saliva Received

- Associated Press Article and Video
- ASCO 2016
- Facebook post by a metastatic breast cancer patient/advocate
- Facebook and Twitter posts by patients/advocates
- SABCS 2015 Launch With Advocacy Partners
- 211 medical records received
- 158 tumors from 100 patients
- 87 tumor/saliva pairs w WES
- 48 blood samples received

>3600
>2150
>1300
Conclusions

- Molecular testing is still not standard of care, but is now more widely accessible and affordable than ever before.

- Many more actionable mutations being identified at a rapid pace.

- The ability to choose clinical trials for patients based on information gleaned from genomic testing (basket studies, etc) may lead to improved outcomes for our trial patients and for more efficiency in our drug development process down the line.
Thank you