Examining Real-World Evidence in the Management of Breast Cancer

Pharmacist Implications

Support

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Disclosure

Dr. Adams has no relevant affiliations or financial relationships with a commercial interest to disclose.

The clinical reviewer, Megan May, PharmD, BCOP, has no actual or potential conflict of interest in relation to this program.

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UAN: 0430-0000-18-061-L01-P
Credits: 1.0 hour (0.10 ceu)
Type of Activity: Application

Learning Objectives

- **Recognize** real-world evidence (RWE) and how it may be used to support approval of new drugs or indications
- **Identify** approaches to interpreting and analyzing study design and results of real-world data (RWD) for possible inclusion in treatment decision-making
- **Translate** RWE of cyclin-dependent kinase (CDK) 4/6 inhibitors in breast cancer for the development of treatment regimens based on patient-specific factors
Real-World Evidence

- Information that is collected outside of traditional clinical trials
- Commonly used to study drug delivery, use, pay, outcomes, safety, and more


The Non-Protocolized Patient

- Clinicians “vote with their feet”
  - Electronic health records
  - Claims and billing activities
  - Product and disease registries
  - Patient-generated data including in home-use settings
  - Data gathered from other sources that can inform on health status, such as mobile devices

Evaluation and Implementation of RWE

- FDA
  - Post-marketing experience (usually to evaluate safety/adverse events)
  - Data collected from compassionate-use trials prior to approval
  - Commonly visible in the package insert
- Pharma
  - Used by sales to determine utilization
    - Identify barriers, particularly those that can be addressed to boost sales
    - Used by the medical team to identify interactions/outcomes
- Academia
  - Used to study patterns of use to optimize therapy and outcomes
  - Implemented in guidelines (e.g., NCCN guidelines)

FDA, United States Food and Drug Administration; NCCN, National Comprehensive Cancer Network.
The 21st Century Cures Act (Cures Act), signed into law on December 13, 2016, is designed to help accelerate medical product development and bring new innovations and advances to patients who need them faster and more efficiently.


The 21st Century Cures Act – How RWE Fits

TITLE III—DEVELOPMENT

Subtitle A—Patient-Focused Drug Development

Sec. 3001. Patient experience data.
Sec. 3002. Patient-focused drug development guidance.
Sec. 3003. Streamlining patient input.
Sec. 3004. Report on patient experience drug development.

Subtitle B—Advancing New Drug Therapies

Sec. 3011. Qualification of drug development tools.
Sec. 3012. Targeted drugs for rare diseases.
Sec. 3013. Reauthorization of program to encourage treatments for rare pediatric diseases.
Sec. 3014. GAO study of priority review voucher programs.
Sec. 3015. Amendments to the Orphan Drug grants.
Sec. 3016. Grants for studying continuous drug manufacturing.

Subtitle C—Modern Trial Design and Evidence Development

Sec. 3021. Novel clinical trial designs.
Sec. 3022. Real world evidence.
Sec. 3023. Protection of human research subjects.
Sec. 3024. Informed consent waiver or alteration for clinical investigations.

The 21\textsuperscript{st} Century Cures Act

- The FDA is changing its infrastructure and processes to incorporate RWE into approvals
  - RWE plan due 12/13/18
  - Drug development tools due 12/13/18
- March 2018: Public meeting to discuss novel trial designs that link to RWE
- Complex adaptive clinical trial designs to support the effectiveness and safety of drugs or biologics
  - Innovative designs including external/historical control subjects, Bayesian designs, and master protocols
  - Clinical trial simulations for confirmatory trial design and planning
  - Complex innovative design pilot program


The 21\textsuperscript{st} Century Cures Act - Deliverables

<table>
<thead>
<tr>
<th>Section</th>
<th>Section title</th>
<th>Deliverable type</th>
<th>Statutory deadline</th>
<th>Responsible organization</th>
<th>Date completed</th>
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<tr>
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<td>Public Meeting</td>
<td>5/13/2018</td>
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</tbody>
</table>

**Methods for RCT vs RWE**

**Clinical trials**
- Robust control of patient population
- Strict inclusion/exclusion criteria
- Strict guidance on drug dosing
- Starting dose
- Dose adjustment criteria
- Control timing of evaluation
- Radiologic scans
- Definitions of response
- Defined criteria for “off study”
- Progressive disease
- Toxicity
- Duration of therapy

**RWE**
- Epidemiology approach is most common
- Statistically control populations
- Typically very large numbers (at the cost of limited data quality, particularly secondary data)
- Great for uncommon events
  - Rare/uncommon toxicity
  - Drug-drug interactions
- Good approach for evaluating drug selection
  - Oncologists “vote with their feet”
- Reasonable approach to evaluate outcomes
  - Study design is critical

**Strengths of Study Designs**

- RCTs
- Single-arm trial
- Cohort studies
- Case-control studies
- Case reports/series

*RCT, randomized controlled trial.*
Traditional Study Designs

- Assigned treatment: Yes → Randomized assignment: Yes → Randomized clinical trial
  - Yes → Comparison of groups? Yes → Analytic study: Start with exposure: Yes → Cohort
  - No → Non-randomized clinical trial
- Assigned treatment: Yes → Randomized assignment: No → Comparison of groups? No → Descriptive study
- Assigned treatment: No
- Randomized assignment: Yes
- Randomized clinical trial: Yes
- Non-randomized clinical trial

Single-Arm Trial with Historical Control

- Assigned treatment: Yes → Randomized assignment: Yes → Randomized clinical trial
  - Yes → Comparison of groups? Yes → Analytic study: Start with exposure: Yes → Cohort
  - No → Non-randomized clinical trial
- Assigned treatment: Yes → Randomized assignment: No → Comparison of groups? No → Descriptive study
- Assigned treatment: No
- Randomized assignment: Yes
- Randomized clinical trial
- Non-randomized clinical trial

Utilizing RWE to serve as control

RWE

Effective for rare diseases
Adaptive Study Designs

- Assigned treatment
  - Yes
  - Randomized assignment
    - Yes
    - Randomized clinical trial
    - Non-randomized clinical trial
    - Utilizing RWE methods with trial data to adapt the study, patient number, endpoint, treatment allocation, or patient population
    - No
  - No
- Comparison of groups?
  - Yes
  - Analytic study: Start with exposure
    - Yes
    - Cohort
    - Case-control
    - RWE
  - No
  - No
  - No
  - No
- No
- Descriptive study

Simulation of Study Designs

- Assigned treatment
  - Yes
  - Randomized assignment
    - Yes
    - Randomized clinical trial
    - Non-randomized clinical trial
    - Trial simulation to help optimize design and number of patients needed
    - No
  - No
- Comparison of groups?
  - Yes
  - Analytic study: Start with exposure
    - Yes
    - Cohort
    - Case-control
    - RWE
  - No
  - No
  - No
  - No
- No
- Descriptive study
How do you know a study is valid?

• Eliminate alternative explanations:
  • Confounding (exposure that influences treatment and outcome)
  • Bias
  • Random error

Internal validity
- Error in measurement
- Exposure – disease association between them

External validity
- Is the data generalizable?

Questions to consider - study design and controls:
- How big is the population? A large population can minimize random error
- Design: RCT > cohort > case-control
- Did they find all people with an exposure and then determine outcome?
- Did they find people with the outcome and then look back for exposure?
- Measurement: Did they control for differences in patient disease severity? 
  How reliable are the outcome measurements?

RWE in Breast Cancer – Implications for Clinical Decision-Making

• Overview of breast cancer
• Guideline-level treatment recommendations for the use of CDK 4/6 inhibitors
• Review RWD for CDK 4/6 inhibitors
  • Drug selection
  • Monitoring
  • Toxicity
Breast Cancer

- Estimated 266,120 women diagnosed with invasive breast cancer in 2018
- Estimated 40,920 women died from breast cancer in 2018

**Local breast cancer**
- 62% of cases are initially diagnosed as local disease
- 5-year relative survival rate of 99%
- 10-year hormone receptor (HR)-positive recurrence = 15%-18%

**Metastatic breast cancer**
- 6% of cases initially diagnosed as metastatic disease (~16,000 patients)
- Regional lymph node metastasis occurs in 31%
- 5-year survival rate of 85%
- Distant metastasis
  - 5-year survival rate of 26%


Increased Survival in Advanced Breast Cancer

5-year survival among women aged 15-49 years initially diagnosed with distant-stage breast cancer

- 2005-2012: 36%
- 1992-1994: 18%

www.cancer.gov
Selecting Therapy for Metastatic Breast Cancer

Goals:
Palliate symptoms
Prolong survival

Visceral metastasis
Rapidly growing tumor

Aggressive treatment to generate rapid response

HR status
HER2 receptor status

Effective/non-toxic treatment

Breast Cancer Pharmacologic Therapy

- Chemotherapy
- HER2+
- Chemotherapy + trastuzumab ± pertuzumab

Endocrine therapy ± chemotherapy

HR+

75% of tumors are HR+

Chemotherapy + trastuzumab ± pertuzumab + endocrine therapy

Triple-positive

75% of tumors are HR+

Endocrine Therapy in HR-Positive Breast Cancer

- A high number of estrogen receptors (ERs) on a breast cancer cell indicates that the tumor depends on estrogen for signaling for proliferation and survival.
- ER inhibition causes reduced tumor cell viability and cell cycle arrest and causes cell to go through a normal apoptotic cell death.
- HR therapies form the backbone of treatment for ER+ breast cancers.
- Aromatase inhibitors (AIs) are generally first-line for postmenopausal women.
- Tamoxifen (SERM) is generally first-line for premenopausal women.

SERM, selective estrogen receptor modulator.


ER Signaling and Resistance

Resistance may be mediated by deregulation of multiple alternative mitogenic pathways (e.g., HER2, PI3K/AKT) that potentiate cyclin D1:CDK 4/6 signaling in an ER-independent fashion.

Role of CDK 4/6 in Breast Cancer

- ER signaling upregulates cyclin D1 levels and CDK 4/6 activity
- Dysregulation of the cyclin D1:CDK 4/6 axis appears to be an important step in early breast cancer pathogenesis
  - Overexpression of cyclin D1 frequently identified in ductal carcinoma in situ and metastatic lesions BUT NOT in earliest lesions (i.e., atypical ductal hyperplasias)
- Targeted inhibition of CDK 4/6 has resulted in ErbB2-driven tumor arrest and senescence in vivo

*These data suggest a potential role for cyclin D:CDK 4/6-mediated signaling in the estrogen-independence of ER+ breast cancers*


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Current FDA-Approved Drugs

<table>
<thead>
<tr>
<th></th>
<th>Abemaciclib</th>
<th>Palbociclib</th>
<th>Ribociclib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Approved indication</strong></td>
<td>HR+, HER2-, Adv, or Met breast cancer</td>
<td>HR+, HER2-, Adv, or Met breast cancer</td>
<td>HR+, HER2-, Adv, or Met breast cancer</td>
</tr>
<tr>
<td><strong>Regimen(s)</strong></td>
<td>150 mg po bid w/ AI as first-line or w/ fulvestrant as second-line</td>
<td>125 mg po daily x 21 days followed by 1 week off w/ AI as first-line or w/ fulvestrant as second-line</td>
<td>600 mg po daily x 21 days followed by 1 week off w/ AI as first-line</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Take regardless of food</td>
<td>Take w/ food</td>
<td>Take regardless of food</td>
</tr>
<tr>
<td><strong>Drug-food interaction</strong></td>
<td>Increases AUC by 9%</td>
<td>Increases AUC by 21% and decreases variability Avoid taking w/ grapefruit juice</td>
<td>Food has no effect</td>
</tr>
<tr>
<td><strong>Drug-drug interaction</strong></td>
<td>CYP3A4 substrate – avoid strong inhibitors/inducers</td>
<td>CYP3A4 substrate – avoid strong inhibitors/inducers</td>
<td>CYP3A4 substrate – avoid strong inhibitors/inducers</td>
</tr>
</tbody>
</table>

Adv, advanced; AUC, area under the curve; bid, twice daily; CYP, cytochrome P450; Met, metastatic; po, by mouth.

Ibrance prescribing information.; Kisqali prescribing information.; Verzenio prescribing information.
FDA-Approved Indications

<table>
<thead>
<tr>
<th>Indication</th>
<th>Abemaciclib</th>
<th>Palbociclib</th>
<th>Ribociclib</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line in combination with hormone therapy</td>
<td>X w/ an AI</td>
<td>X w/ an AI</td>
<td>X w/ an AI postmenopausal pre-/perimenopausal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>postmenopausal w/ fulvestrant</td>
</tr>
<tr>
<td>Second-line in combination with hormone therapy</td>
<td>X w/ fulvestrant</td>
<td>X w/ fulvestrant</td>
<td>X w/ fulvestrant</td>
</tr>
<tr>
<td>As monotherapy in pretreated patients</td>
<td>X w/ fulvestrant</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>after progression on hormone therapy and chemotherapy</td>
</tr>
</tbody>
</table>

Ibrance prescribing information.; Kisqali prescribing information.; Verzenio prescribing information.

Real-World Application

Navigating the difference between what should happen and what actually happens
Patient Scenario: JP

- 59 y/o postmenopausal woman with newly diagnosed breast cancer with metastases to the bone
- Mild to moderate but persistent lower back pain
- Her performance status is relatively good: 0-1
- Bone scan shows suspicious areas in spine
- Confirmed with core biopsy:
  - ER/PR+, HER2 normal by IHC, and Ki-67=7%
- She has been taking ibuprofen as needed for her back pain; no other medications
- Lab work is within normal limits

JP, immunohistochemistry; Ki-67, growth marker present in dividing cells; PR, progesterone receptor.

JP - continued

JP’s 24 y/o single daughter and 2 y/o twin grandsons live at her home. Her daughter will serve as her caregiver.

What first-line therapy would you recommend for this patient?

1. Anastrozole
2. Exemestane
3. Letrozole + palbociclib
4. Tamoxifen
5. Fulvestrant + everolimus
Paloma-2: First-Line Letrozole +/- Palbociclib

- **Key inclusion criteria**
  - Postmenopausal women with ER+, HER2- advanced breast cancer
  - Adequate organ function
  - ECOG 0-2
  - Measurable disease
  - Bone-only disease

- **Key exclusion criteria**
  - Prior systemic therapy for advanced disease
  - Recurrence during or within 12 months after completing prior adjuvant or neoadjuvant treatment with a nonsteroidal AI
  - Patients with advanced, symptomatic visceral spread who are at risk for short-term, life-threatening complications

- **Treatment groups**
  - Palbociclib + letrozole: 444
  - Placebo + letrozole: 222

- **Primary endpoint:** PFS

- **Secondary endpoints**
  - OS, ORR, DOR, clinical benefit response (CR, PR, or SD for ≥ 24 weeks), PK, safety, biomarker assessment
  - Patient-reported outcomes

CR, complete response; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; OS, overall survival; ORR, objective response rate; SD, stable disease.


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Paloma-2: First-Line Letrozole +/- Palbociclib

**Median PFS**

<table>
<thead>
<tr>
<th>Months</th>
<th>Letrozole+Palbociclib</th>
<th>Letrozole+Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>24.8</td>
<td>14.5</td>
</tr>
</tbody>
</table>

10-month improvement in PFS

Investigator assessment was approximately 6 months less for both groups

Palbociclib

• Approval
  • First-line in combination with any AI
  • Second-line in combination with fulvestrant

• Dosing
  • 125 mg once daily taken with food for 21 days followed by 7 days off treatment (125 mg, 100 mg, and 75 mg capsules available)
  • Fulvestrant is 500 mg administered on days 1, 15, and 29 and once monthly thereafter

• NCCN guideline recommendations:
  • Palbociclib + letrozole or fulvestrant recommended for first-line treatment of recurrent or stage IV ER+, HER2- breast cancer
    • Category 1 recommendation


Palbociclib

• Most common adverse reactions (>10%):
  • Neutropenia
  • Leukopenia
  • Infections
  • Fatigue
  • Nausea
  • Anemia
  • Stomatitis
  • Diarrhea
  • Thrombocytopenia
  • Vomiting
  • Alopecia
  • Rash
  • Decreased appetite
  • Pyrexia

• Most concerning grade 3/4 adverse reactions:
  • Neutropenia = 66%
  • Infection = 7%

6.2 Postmarketing Experience
The following adverse reactions have been identified during post-approval use of IBRANCE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Respiratory disorders: Interstitial lung disease (ILD)/non-infectious pneumonitis.

Ibrance prescribing information.
**Palbociclib**

- **Monitoring:**
  - CBC for possible neutropenia
    - Prior to the start of palbociclib therapy, at the beginning of each cycle, day 15 of the first 2 cycles
    - Median time to neutropenia = 15 days
  - Dose modification required with any grade 3 hematologic or non-hematologic toxicity

- **Interactions:**
  - CYP3A inhibitors, inducers, and substrates
  - May cause fetal harm

<table>
<thead>
<tr>
<th>Table 1. Recommended Dose Modification for Adverse Reactions</th>
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<tr>
<td><strong>Dose Level</strong></td>
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<tr>
<td>Recommended starting dose</td>
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<tr>
<td>First dose reduction</td>
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<tr>
<td>Second dose reduction</td>
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</table>

*If further dose reduction below 75 mg/day is required, discontinue.

CBC, complete blood count.


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**First-Line PFS with CDK 4/6 Inhibitors**

Postmenopausal women with an AI +/- CDK 4/6 inhibitor

No head-to-head studies – General comparisons show approximate 10-month improvement with CDK 4/6 inhibitor – No clear winner

Do they differ in terms of toxicity (with letrozole)?

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Abemaciclib</th>
<th>Palbociclib</th>
<th>Ribociclib</th>
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</thead>
<tbody>
<tr>
<td>Neutropenia (all - G3/4; %)</td>
<td>41 - 22</td>
<td>80 - 66</td>
<td>75 - 60</td>
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<tr>
<td>Neutropenic fever (%)</td>
<td>NR (0)</td>
<td>1.8</td>
<td>1</td>
</tr>
<tr>
<td>Infection (all - G3/4; %)</td>
<td>39 - 5</td>
<td>60 - 7</td>
<td>11 - 1*</td>
</tr>
<tr>
<td>Fatigue (all - G3/4; %)</td>
<td>40 - 2</td>
<td>37 - 2</td>
<td>37 - 2</td>
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<tr>
<td>Anemia (all - G3/4; %)</td>
<td>28 - 6</td>
<td>24 - 5</td>
<td>18 - 2</td>
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<tr>
<td>Rash (all - G3/4; %)</td>
<td>14 - 1</td>
<td>18 - 1</td>
<td>17 - 1</td>
</tr>
<tr>
<td>AST (all - G3/4; %)</td>
<td>16 - 7</td>
<td>52 - 3</td>
<td>46 - 10</td>
</tr>
<tr>
<td>ALT (all - G3/4; %)</td>
<td>15 - 3</td>
<td>43 - 3</td>
<td>44 - 7</td>
</tr>
<tr>
<td>Diarrhea (all - G3/4; %)</td>
<td>81 - 9</td>
<td>26 - 1</td>
<td>35 - 1</td>
</tr>
</tbody>
</table>

* 42% - 5% when given with fulvestrant

Some differences in symptomatic toxicities: infection, diarrhea.

AST, aspartate aminotransferase; ALT, alanine aminotransferase; G3/4, grade 3-4; NR, not reported.
Clinical Trial Summary: First-Line Therapy

• When all 3 of the CDK 4/6 inhibitors are added to an AI, they prolong PFS by approximately 10 months
• Toxicities
  • Neutropenia: abemaciclib < < ribociclib = palbociclib
  • Infections: ribociclib << abemaciclib < palbociclib
  • Diarrhea: palbociclib < ribociclib << abemaciclib
• Monitoring
  • ECG: only required for ribociclib (additional electrolyte monitoring)
  • LFTs: scheduled monitoring for abemaciclib and ribociclib
• There are subtle differences, but without head-to-head comparisons, they all look similar

ECG, electrocardiogram; LFTs, liver function tests.

JP’s Decision

• Family is her #1 focus
• Limiting her interactions with her grandchildren is a big concern for her
• After some discussion with the oncologist…

  anastrozole monotherapy is selected.
Real-World Evidence

- Real-world palbociclib use 1 year post-U.S. approval:
  - More than half of patients receive palbociclib plus letrozole in second-line and beyond
  - CBC testing rates suggest good provider compliance with monitoring guidelines in the U.S. prescribing information
  - Occurrence of grade 3 and 4 neutropenia was consistent with clinical trials
- **Understanding palbociclib utilization in real-world patients and how drug dosing and monitoring are performed aids in the understanding of safe and effective use of the drug**


Biggest Variance is Line of Therapy

LOT, line of therapy.

Efficacy with Fulvestrant

PFS with CDK 4/6 Inhibitors

No head-to-head studies – Very different populations – Look at fulvestrant control


Sequence of Therapy?

• If JP did NOT have toddlers at home, would you give first-line letrozole to our 59 y/o patient, then give second-line abemaciclib + fulvestrant instead of abemaciclib + letrozole first-line, then second-line fulvestrant?

1. Yes
2. No
### Summary

- RWE is becoming increasingly recognized as adding to the science
  - Good evaluation of trials is important to determine if they are generalizable to your practice
- Metastatic breast cancer is relatively common
  - Approximately 60,000 patients diagnosed per year, with an estimated 75% being HR+
- All 3 FDA-approved CDK 4/6 inhibitors can be used with hormone therapy as first-line or second-line therapy
  - RWE suggests that only approximately 40% of patients are receiving as first-line
- When used, toxicity and toxicity monitoring are similar to clinical trials
- Clinical trial data suggest first-line CDK 4/6 inhibitor use prolongs PFS more than second-line use
  - However, it might not be the best selection for a specific patient
How to Claim Credit

• **DO NOT CLOSE YOUR BROWSER**
  • You will be redirected to the post-test and evaluation

• Also, in about 45-minutes, you will receive an e-mail with a link to the post-test and evaluation

• You must complete the post-test and evaluation in order to earn credit

• Your credit will automatically be uploaded to CPE Monitor

*IMPORTANT: In order to claim credit you must have been in attendance through the live event platform and watched and listened to the event in its entirety. Postgraduate Healthcare Education, LLC has the right to deny credit to individuals that have not attended and participated in this webinar in its entirety. Postgraduate Healthcare Education, LLC completes audits of attendees on a routine basis to ensure compliance with all ACPE standards.*
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