Selection and Sequencing of Targeted Therapy for HR+/HER2-
Early Breast Cancer
Learning Objectives

- Develop treatment approaches for the individualized use of CDK4/6 inhibitors for HR+/HER2- breast cancer
- Use recommended strategies for identifying and managing toxicities associated with CDK4/6 inhibitors
- Identify strategies and resources to support patient adherence to CDK4/6 inhibitor therapy

CDK4/6 = cyclin-dependent kinase 4/6; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor.
Treatment of Early-Stage, HR+/HER2- Breast Cancer

- **Endocrine therapy**
  - Tamoxifen
  - Aromatase inhibitors
  - Extended adjuvant therapy (10 yr vs 7 yr vs 5 yr)
  - Ovarian suppression (LHRH analogs) in high-risk premenopausal women

- **Chemotherapy**
  - Benefit depends on risk for recurrence and biology of the disease (genomic platforms)

- **Novel and emerging therapies**
  - PARP inhibitors
  - CDK4/6 inhibitors
  - PI3K/AKT/mTOR inhibitors
  - Oral SERDs

**Meta-analysis of 5 Yr of Al vs 5 Yr of Tamoxifen**

- 9885 women, 1791 events
- RR: 0.80 (95% CI: 0.73-0.88)
- 10-yr gain: 3.6% (95% CI: 1.7%-5.4%)
- 2-sided log-rank P <.00001

![Graph showing recurrence rates over 10 years for Tamoxifen and AI]

Al = aromatase inhibitor; LHRH = luteinizing hormone–releasing hormone; PARP = poly (ADP-ribose) polymerase; RR = risk ratio; SERD = selective estrogen receptor degrader. Early Breast Cancer Trialists Collaborative Group. Lancet. 2015;386:1341.
Case Study: Maria, 61 Years Old

- Maria was diagnosed with clinical stage III HR+ breast cancer
  - ER 60%, PgR 50%, HER2-negative by IHC
- Ultrasound imaging showed a 6-cm tumor with at least 2 abnormal lymph nodes
  - Received neoadjuvant chemotherapy
  - *BRCA* testing was negative
- Right mastectomy revealed
  - 13-mm residual disease in the breast
  - 2 of 10 lymph nodes positive for metastatic disease
- She returns to the clinic now to discuss adjuvant treatment options

ER = estrogen receptor; IHC = immunohistochemistry; PgR = progesterone receptor.
## HR+/HER2- Early Breast Cancer: Molecular and Genomic Profiling

<table>
<thead>
<tr>
<th>Assay</th>
<th>Eligibility (Nodal Status)</th>
<th>Predictive</th>
<th>Prognostic</th>
<th>NCCN Evidence Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 gene (Oncotype DX)</td>
<td>0-3+</td>
<td>Yes</td>
<td>Yes</td>
<td>1 (2A for premenopausal with positive nodes)</td>
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<tr>
<td>70 gene (MammaPrint)</td>
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<tr>
<td>50 gene (Prosigna)</td>
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<td>12 gene (EndoPredict)</td>
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<td>Yes</td>
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<tr>
<td>Breast Cancer Index</td>
<td>0</td>
<td>Yes*</td>
<td>Yes</td>
<td>2A</td>
</tr>
</tbody>
</table>

*Predictive of benefit of extended adjuvant endocrine therapy.
NCCN = National Comprehensive Cancer Network.
TAILORx: Treatment Assignment and Randomization

- Randomized, parallel-assignment phase III study

- Primary endpoint: iDFS, secondary primary cancer, or death

- Key secondary endpoints: freedom from breast cancer recurrence at distant site, freedom from breast cancer recurrence at distant or local–regional site, OS

DFS = disease-free survival; ET = endocrine therapy; iDFS = invasive disease-free survival; OS = overall survival; RS, recurrence score. Sparano. NEJM. 2018;379:111.
TAILORx Comments

• LN-negative breast cancer
  – Age >50 yr: RS ≤25 has no chemotherapy benefit
  – Age ≤50 yr: RS 16-25 may derive chemotherapy benefit

• Higher absolute recurrence risk in patients with LN-positive breast cancer than those with LN-negative disease
  – Unclear whether TAILORx results can be extrapolated to LN-positive breast cancer

LN = lymph node.
RxPONDER: Adjuvant ET ± Chemotherapy in HR+/HER2- EBC With 1-3 Positive Lymph Nodes and RS ≤25

• **Randomized phase III trial**

- Adults with HR+/HER2- EBC and 1-3 positive LN without distant mets*;
- able to receive adjuvant taxane and/or anthracycline-based CT†;
- axillary staging by SLNB or ALND;
- RS 0-25‡
- (N = 5015)

*Protocol amended to exclude patients with pN1mic as only nodal disease after 2493 patients randomized. *Approved CT regimens: TC, FAC (or FEC), AC/T (or EC/T), FAC/T (or FEC/T); AC alone or CMF not allowed. †Patients with RS >25 recommended to be treated with CT followed ET off study.

- **Primary endpoint:** iDFS

- **Key secondary endpoints:** OS, distant DFS, local DFI, toxicity, QoL

AC = doxorubicin/cyclophosphamide; AC/T = doxorubicin/cyclophosphamide and paclitaxel; ALND = axillary lymph node dissection; CMF = cyclophosphamide/methotrexate/5-fluorouracil; CT = chemotherapy; DFI = disease-free interval; EBC = early breast cancer; EC/T = epirubicin/cyclophosphamide and paclitaxel; FAC = 5-fluorouracil/doxorubicin/cyclophosphamide; FAC/T = 5-fluorouracil/doxorubicin/cyclophosphamide and docetaxel; mets = metastases; QoL = quality of life; SLNB = sentinel lymph node biopsy; TC = docetaxel/cyclophosphamide. Kalinsky. NEJM. 2021;385:2336.
RxEPOUNDER: ITT Population
(1-3 Positive Lymph Nodes and RS ≤25)

- 481 iDFS events (after median of 5.3 yr), including 325 (67.6%) with distant recurrence

Kalinsky. NEJM. 2021;385:2336.
RxPONDER: iDFS by Menopausal Status

Invasive Disease-Free Survival, Postmenopausal Participants

- **Chemoendocrine**: 1658 participants, 163 events, 5-Yr Invasive Disease-Free Survival: 91.3%
- **Endocrine only**: 1671 participants, 169 events, 5-Yr Invasive Disease-Free Survival: 91.9%

Hazard ratio for invasive disease recurrence, new primary cancer, or death: 1.02 (95% CI: 0.82-1.26; P = .89)

Invasive Disease-Free Survival, Premenopausal Participants

- **Chemoendocrine**: 829 participants, 57 events, 5-Yr Invasive Disease-Free Survival: 93.9%
- **Endocrine only**: 826 participants, 92 events, 5-Yr Invasive Disease-Free Survival: 89.0%

Hazard ratio for invasive disease recurrence, new primary cancer, or death: 0.60 (95% CI: 0.43-0.83; P = .002)

Kalinsky. NEJM. 2021;385:2336.
RxPONDER Comments

- No benefit for CT among postmenopausal women with ER+/HER2-, 1-3 positive LN cancers and RS ≤25 (same as in TAILORx)
- Numerical advantage seen with CT in premenopausal women
  - Debate exists if these findings are consistent with OFS effect, direct cytotoxicity from CT, or both
- OFS (and AI) may be an adequate alternative to chemotherapy for premenopausal women with RS <25 and 1-3 positive LNs, but this has not been definitively proven, and further studies are needed

OFS = ovarian function suppression.
Additional Profiling Techniques With Treatment Implications

• Germline *BRCA1/2* mutation
  – Recommended in HR+ early breast cancer if high risk for hereditary breast cancer or eligible for **olaparib** treatment

• Ki-67
  – Nuclear antigen used to identify proliferating cells
  – Not recommended as an individual biomarker by NCCN

  • Recommended if considering adjuvant **abemaciclib**

DFS by Ki-67 Expression Levels: HR+

Is There a Role for CDK4/6 Inhibition in Early-Stage HR+ Disease?

Risk of First Recurrence After Primary Treatment

Estimated Annual Hazard Rate

Follow-up After Primary Diagnosis of Breast Cancer (Yr)

- **PENELOPE-B**
  - Palbociclib
  - After neoadjuvant, high risk

- **monarchE**
  - Abemaciclib
  - High-risk CPR factors, Ki-67

- **PALLAS**
  - Palbociclib
  - Stage II, III

- **NATALEE**
  - Ribociclib
  - Stage II, III

monarchE: Adjuvant Abemaciclib + ET in High-Risk, Node-Positive, HR+/HER2- EBC

• International, randomized, open-label phase III trial
  Women or men with high-risk, node-positive, HR+/HER2- EBC; prior (neo)adjuvant CT permitted; pre- or postmenopausal; no distant metastasis; ≤16 mo from surgery to randomization; ≤12 wk of ET after last non-ET (N = 5637)

• Primary endpoint: iDFS
  – Planned for after ~390 iDFS events (~85% power; assumed iDFS hazard ratio: 0.73; cumulative 2-sided α = 0.05)
  – Current primary outcome efficacy analysis occurred after 395 iDFS events in ITT population

• Key secondary endpoints: iDFS in Ki-67–high (≥20%) population, distant RFS, OS, safety, PRO, PK

Cohort 1
≥4 positive ALN or 1-3 positive ALN + histologic grade 3 and/or tumor ≥5 cm

Cohort 2
1-3 positive ALN, Ki-67 ≥20% per central testing, not grade 3, tumor size <5 cm

Stratified by prior CT, menopausal status, region

Abemaciclib 150 mg twice daily up to 2 yr + ET per standard of care of physician’s choice for 5-10 yr as clinically indicated (n = 2808)

ET per standard of care of physician’s choice for 5-10 yr as clinically indicated (n = 2829)

ITT Population (Cohorts 1 + 2)

ALN = axillary lymph nodes; ITT = intention-to-treat; PK = pharmacokinetics; PRO = patient-reported outcome; RFS = relapse-free survival.
monarchE: iDFS With Abemaciclib + ET vs ET Alone

- Benefit maintained with additional follow-up in the ITT population

- 30.4% reduction in the risk of developing an iDFS event

- Absolute difference in 3-yr iDFS rates between arms: 5.4%

monarchE: Efficacy and FDA Approval Summary

At the time of interim analysis
- OS in the ITT population favors ET alone (hazard ratio: 1.091)
- iDFS improvements in patients with Ki-67 ≥20% are likely driven by cohort 1, due to variation in cohort 1 and 2 sample sizes

In October 2021, the FDA approved abemaciclib + either tamoxifen or AI for adjuvant treatment of adults with HR+/HER2- early breast cancer that is node positive, at high risk of recurrence, and with a Ki-67 ≥20%

## Select Ongoing Trials With CDK4/6 Inhibitors in HR+/HER2- EBC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ADAPTlate</th>
<th>CARABELA</th>
<th>NATALEE</th>
<th>POETIC-A</th>
<th>POLAR</th>
<th>ADAPTcycle</th>
<th>I-SPY</th>
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<tbody>
<tr>
<td>Treatment</td>
<td>Delayed extended adjuvant abemaciclib</td>
<td>Neoadjuvant abemaciclib + ET vs AC/T</td>
<td>Adjuvant ribociclib + ET</td>
<td>Adjuvant abemaciclib</td>
<td>Palbociclib + ET</td>
<td>Ribociclib + ET</td>
<td>Umbrella trial; amcenestrant + abemaciclib arm</td>
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<td>Phase</td>
<td>III</td>
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<td>III</td>
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<td>III</td>
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<td>N</td>
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<td>4000</td>
<td>2500</td>
<td>400</td>
<td>1670</td>
<td>4000</td>
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<tr>
<td>Patient population</td>
<td>HR+/HER2-high-risk EBC</td>
<td>HR+/HER2-intermediate-/ high-risk EBC</td>
<td>HR+/HER2-EBC</td>
<td>HR+/HER2-high-risk EBC*</td>
<td>HR+/HER2-local/regional recurrence</td>
<td>HR+/HER2-intermediate-risk EBC</td>
<td>EBC</td>
</tr>
</tbody>
</table>

*Patients will be selected for endocrine resistance with preoperative aromatase inhibitor therapy.

Case Study: Lakshmi, 49 Years Old

- Lakshmi is a premenopausal woman with a newly diagnosed HR+ (ER 98%, PgR 83%, HER2 IHC 0) invasive ductal carcinoma of left breast
  - BRCA negative
  - Bone scan: several concerning lesions
  - Bone biopsy confirmed as metastatic carcinoma
- NGS: primary tumor revealed a PIK3CA-activating mutation
- No other pertinent PMH
  - Current medications: women’s daily multivitamin
- Returned to the medical oncology clinic to discuss treatment options
  - Lakshmi shares that her priority is to live as long as possible so she can see her teenage children off to college

NGS = next-generation sequencing; PMH = past medical history.
~50% of HR+ MBCs do not benefit from ET due to resistance

Resistance Mechanisms

- Loss or alteration of ER expression
- Overexpression or activation of GF receptors
- Activation of downstream signal transduction pathways

E = estrogen; EGFR = epidermal growth factor receptor; GF = growth factor; MBC = metastatic breast cancer; P = phosphate; SERM = selective estrogen receptor modulator.

HR+/HER2- MBC: First-line Treatment

- Preferred regimens
  - CDK4/6 inhibitor + NSAI* (anastrozole or letrozole)
  - CDK4/6 inhibitor + fulvestrant*
- FDA-approved CDK4/6 inhibitor
  - Palbociclib
  - Ribociclib
  - Abemaciclib

- Factors influencing selection of CDK4/6 inhibitor
  - Long-term survival data
  - Menopause status
  - Toxicity profile
  - Organ function
  - Drug interactions
  - Adherence

*Premenopausal patients should receive a gonadotropin-releasing hormone agonist as ovarian suppressing.
NSAI = nonsteroidal aromatase inhibitor.
**CDK4/6 Inhibitors as First-line Tx of HR+/HER2- MBC**

*No head-to-head trials comparing CDK4/6 inhibitors*

<table>
<thead>
<tr>
<th>Phase III Trial</th>
<th>PALOMA-2</th>
<th>MONALEESA-2</th>
<th>MONARCH-3</th>
<th>MONALEESA-3†</th>
<th>MONALEESA-7*</th>
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<tbody>
<tr>
<td>CDK4/6 inhibitor</td>
<td>Palbociclib</td>
<td>Ribociclib</td>
<td>Abemaciclib</td>
<td>Ribociclib</td>
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<td>Endocrine partner</td>
<td>Letrozole</td>
<td>Letrozole</td>
<td>Letrozole or anastrozole</td>
<td>Fulvestrant</td>
<td>Tamoxifen, letrozole, or anastrozole</td>
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<td>Patients, N</td>
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<td>668</td>
<td>493</td>
<td>365</td>
<td>672</td>
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<td>Patient population</td>
<td>Postmenopausal</td>
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<td>Postmenopausal</td>
<td>Postmenopausal</td>
<td>Pre/perimenopausal</td>
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<td>mOS, mo</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>NR vs 40.0</td>
<td>NR vs 40.9</td>
</tr>
<tr>
<td>• Hazard ratio</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.724; ( P = .00455 )</td>
<td>0.712; ( P = .00973 )</td>
</tr>
<tr>
<td>mPFS, mo</td>
<td>27.6 vs 14.5</td>
<td>25.3 vs 16.0</td>
<td>28.18 vs 14.76</td>
<td>33.6 vs 19.2</td>
<td>23.8 vs 13.0</td>
</tr>
<tr>
<td>• Hazard ratio</td>
<td>0.563</td>
<td>0.568</td>
<td>0.54</td>
<td>0.55 ‡</td>
<td>0.55</td>
</tr>
<tr>
<td>ORR, %</td>
<td>55.3 vs 44.4</td>
<td>52.7 vs 37.1</td>
<td>59 vs 44</td>
<td>40.9 vs 28.7 †</td>
<td>41 vs 30</td>
</tr>
</tbody>
</table>

*First-line ET; up to 1 previous CT line permitted in advanced setting (14% had received CT). †Includes first and second line. ‡Descriptive analysis.

mOS = median overall survival; mPFS = median progression-free survival; NR = not reached; ORR = overall response rate; tx = treatment.


HR+/HER2- MBC: Beyond First-line Treatment

- Additional targeted therapies and associated biomarker testing
  - Alpelisib for PIK3CA
  - PARP inhibitors (olaparib or talazoparib) for gBRCA1/2
  - Everolimus (no biomarker testing required)
- Most patients with HR+/HER2- MBC will develop resistance to first-line CDK4/6 inhibitor + ET

- **Endocrine resistance (ESMO guidelines)**
  - **Primary:** relapse while receiving first 2 yr of adjuvant ET OR PD within first 6 mo of first-line ET for MBC, while receiving ET
  - **Secondary:** relapse while receiving adjuvant ET but after first 2 yr OR relapse within 12 mo of completing adjuvant ET OR PD 6 mo after starting ET for MBC, while receiving ET

ESMO = European Society for Medical Oncology; m, mutation; PD = progressive disease.
De novo stage IV disease appears to be enriched in relative endocrine resistant disease.

No data comparing CDK4/6i combined with AI vs fulvestrant in first line setting.

Adj = adjuvant; CDK4/6i = CDK4/6 inhibitor; EVE = everolimus; EXE = exemestane; FULV = fulvestrant; PARPi = PARP inhibitor; wt = wildtype.

**High Endocrine Sensitivity**

- **ET naive***
  - *Progression >1 yr after adj ET*

  - **FULV†**
    - *bone only; no prior ET*

  - **NSAI + CDK4/6i**
  - **FULV (± EVE)**
  - **PIK3CAwt**
  - **PIK3CAm**

  - **FULV + Alpelisib**

  - **EXE + EVE**

**Moderate Endocrine Sensitivity**

- **Progression between 2-3 yr from start of or <1 yr from end of adj ET**

  - **FULV + CDK4/6i**

  - **PIK3CAwt**
  - **PIK3CAm**

  - **EXE + EVE**
  - **AI + Alpelisib**

**Poor Endocrine Sensitivity**

- **Progression within 2 yr from start of adj ET**

  - **FULV + CDK4/6i**

  - **PIK3CAwt**
  - **PIK3CAm**

  - **CT**

  - **FULV + Alpelisib**

  - **EXE + EVE**

  - **AI + Alpelisib**

---

*De novo stage IV disease appears to be enriched in relative endocrine resistant disease.

†No data comparing CDK4/6i combined with AI vs fulvestrant in first line setting.

Adj = adjuvant; CDK4/6i = CDK4/6 inhibitor; EVE = everolimus; EXE = exemestane; FULV = fulvestrant; PARPi = PARP inhibitor; wt = wildtype. Rugo. GBCC 2019. Abstr SS01.
Practical Management of Adverse Events Associated With Targeted Therapies
Case Study (cont’d): Maria, 61 Years Old

• Maria initiated adjuvant therapy with anastrozole + abemaciclib following mastectomy for her clinical stage III BRCA-negative, HR+/HER2- breast cancer

• She calls the clinic 8 days after starting her adjuvant therapy to report new-onset diarrhea (5 stools/day over baseline)
  – She initiated loperamide, but after 24 hours her diarrhea has not improved
Key AEs With CDK4/6 Inhibitors: Monitoring and Prevention

<table>
<thead>
<tr>
<th>Diarrhea</th>
<th>Hepatobiliary Toxicity</th>
<th>QT Prolongation</th>
<th>Neutropenia</th>
<th>VTE</th>
<th>ILD/ Pneumonitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abemaciclib</td>
<td>Abemaciclib</td>
<td>Ribociclib</td>
<td>Abemaciclib</td>
<td>Abemaciclib</td>
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<tr>
<td>Palbociclib</td>
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<tr>
<td>Ribociclib</td>
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<td>Ribociclib</td>
<td>Ribociclib</td>
<td>Ribociclib</td>
</tr>
</tbody>
</table>

- **Antidiarrheal therapy**
- **Increase oral hydration**
- **Notify healthcare provider**

**Diarrhea**
- LFTs before starting tx, once every 2 wk x 2 mo, then:
  - **Abemaciclib**, as indicated
  - **Ribociclib**, at start of cycle x 4 cycles

**Hepatobiliary Toxicity**
- ECG before cycle 1, Day 14 of cycle 1, start of cycle 2, then as indicated
- Electrolytes at start of cycle x 6 cycles, then as indicated

**QT Prolongation**
- CBC before starting treatment, then:
  - **Abemaciclib**, once every 2 wk x 2 mo, once monthly x 2 mo, then as indicated
  - **Palbociclib**, Days 1 and 15 of cycles 1-2, then as indicated
  - **Ribociclib**, Q2W x 2 cycles, start of next 4 cycles, then as indicated

**Neutropenia**
- Monitor for signs and symptoms of thrombosis or pulmonary embolism

**VTE**
- Monitor for pulmonary symptoms indicative of ILD or pneumonitis (eg, hypoxia, cough, dyspnea)

AE = adverse event; CBC = complete blood count; ECG = electrocardiography; HCP = healthcare professional; ILD = interstitial lung disease; LFT = liver function test; VTE = venous thromboembolism. Abemaciclib PI. Palbociclib PI. Ribociclib PI.
**Practical Management Strategies: Neutropenia With CDK4/6 Inhibitors**

- **Monitoring:** CBC with differential at start of tx cycle*; extra assessments in cycles 1-2
- **Permanently discontinue** CDK4/6 inhibitor after 2 dose reductions for neutropenia

<table>
<thead>
<tr>
<th>Grade</th>
<th>ANC</th>
<th>CDK4/6i Dose Modification Recommendations</th>
</tr>
</thead>
</table>
| 1 or 2 | <LLN to ≥1000/m³ | • Continue treatment without dose adjustment  
• Can hold if infection concerns |
| 3† | <1000-500/m³ | **No fever**  
• **Day 1 of cycle:** withhold dose and repeat CBC in 1 week; when ANC improves to grade ≤2, start next cycle at same dose  
• **Day 15 of cycles 1-2:** continue current dose to complete cycle; repeat CBC on Day 22 and start the next cycle at same dose if counts recover to grade ≤2  
• **Fever and/or infection; recurrent; >1 wk recovery**  
• Withhold until ANC improves to grade ≤2  
• Resume at next lower dose |
| 4 | <500/m³ | • Withhold until ANC improves to grade ≤2  
• Resume at next lower dose |

*Every cycle for palbociclib, first 6 cycles for ribociclib, first 4 cycles for abemaciclib. †With abemaciclib: if GF clinically indicated, suspend dose for ≥48 hr after last dose of GF until counts recover to grade ≤2 level. Resume at next lower dose unless dose adjustment already made due to counts.

ANC = absolute neutrophil count; LLN = lower limit of normal.

PALOMA-3: Effect on PFS of Dose Reductions Due to Neutropenia

No difference in PFS observed between patients who had ≥1 dose reduction vs no dose reduction due to neutropenia

Median PFS, Mo
≥1 dose reduction 9.5
No dose reductions 9.5

Hazard ratio: 0.87 (95% CI: 0.61-1.25; 2-sided log-rank P = .45)

Patients at Risk, n
≥1 dose reduction 100 98 88 85 79 78 63 62 33 31 8 6 2 2 1 0
No dose reductions 245 235 193 188 168 166 139 135 58 54 24 17 5 5 0

**Practical Management Strategies: Diarrhea With Abemaciclib**

- Instruct patients to start antidiarrheal agents (eg, loperamide), increase oral fluid intake, and notify HCP at first sign of diarrhea

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Abemaciclib Dose Modification Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Increase of &lt;4 stools/day</td>
<td>• Continue treatment without dose adjustment</td>
</tr>
</tbody>
</table>
| 2     | Increase of 4-6 stools/day | • If toxicity does not improve to grade ≤1 within 24 hr, withhold dose until toxicity improves to grade ≤1  
|       |             | • Resume at same dose                       |
| 2 that persists or recurs | After resuming the same dose despite maximal supportive measures | • Withhold until toxicity improves to grade ≤1  
|       |             | • Resume at next lower dose                 |
| 3 or 4 or requires hospitalization | **Grade 3**: increase of ≥7 stools/day; hospitalization indicated  
|       |             | **Grade 4**: life threatening; urgent intervention indicated | • Withhold until toxicity improves to grade ≤1  
|       |             | • Resume at next lower dose                 |

Strategies for Promoting Adherence to Oral Therapies
Case Study (cont’d): Lakshmi, 49 Years Old

- Lakshmi is a 49-year-old premenopausal woman with newly diagnosed BRCA-negative, PIK3CA-positive, HR+/HER2- metastatic breast cancer
- She plans to initiate first-line therapy with letrozole + ribociclib + ovarian suppression (goserelin)
Adherence to Oral Chemotherapy Agents

- Adherence is critical to reaching desired outcomes—both safety and efficacy
  - Imatinib data: patients with \( \geq 90\% \) adherence achieved a major molecular response rate of 94.5% compared with 28.4% in patients with <90% adherence
- Reported oral chemotherapy adherence rates range from 16% to 89%
  - Women demonstrate better adherence than men
  - Symptom-related distress, depression, dissatisfaction with clinical communication, and perceived burden to others were associated with poor compliance
- Reduced adherence is directly linked to increased morbidity and mortality
  - Regular assessments of adherence, identifying barriers, and developing solutions is critical to successfully using oral chemotherapy

Barriers to Oral Chemotherapy Compliance

- Complex treatment regimens and instructions
- Behavior modifications required
- Inconvenient or insufficient clinic visits
- Inadequate supervision
- Poor communication with HCPs
- Patient dissatisfaction with care
- Individual health beliefs
- Inadequate social support
- History of noncompliance
- History of mental illness
- Difficulty swallowing
- Potential drug safety and security concerns
- Medication access issues
Optimizing Patient Education—Patient Perspective

- Assess readiness to receive information
- Ensure a caregiver is present
- Set expectations: duration, pill burden, prevalence of AEs, and outcomes
- Encourage support groups
- Increase pharmacist contact and visibility
- Identify gaps in education and reiterate key information

- Provide trustworthy resources for reliable information
- Deliver written information, medication calendars, etc
- Develop a process for follow-up counseling shortly after the first treatment
- Prioritize main education items and individualize when possible
- Work through financial concerns, especially with oral therapies

Oral Targeted Therapy Adherence Considerations

- Pill Burden
- Dosing Schedule and Modifications
- Administration Instructions
- Drug–Drug/Drug–Food Interactions
- AEs/Supportive Care
- Frequent Monitoring
## CDK4/6 Inhibitor Adherence Considerations

<table>
<thead>
<tr>
<th></th>
<th>Abemaciclib</th>
<th>Palbociclib</th>
<th>Ribociclib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pill burden</strong></td>
<td>With ET: 150 mg (1 tablet)</td>
<td>125 mg (1 tablet or capsule)</td>
<td>600 mg (3 tablets)</td>
</tr>
<tr>
<td></td>
<td>Monotherapy: 200 mg (1 tablet)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dosing schedule</strong></td>
<td>Twice daily x 28 days; 28-day cycle</td>
<td>Once daily x 21 days; 28-day cycle</td>
<td>Once daily x 21 days; 28-day cycle</td>
</tr>
<tr>
<td><strong>Food considerations</strong></td>
<td>With or without food</td>
<td>Capsule: with food; Tablet: with or without food</td>
<td>With or without food</td>
</tr>
<tr>
<td><strong>Drug–drug/food interactions</strong></td>
<td>Avoid grapefruit products and strong/moderate CYP3A inhibitors/inducers</td>
<td>Avoid grapefruit products and strong CYP3A inhibitors/inducers</td>
<td>Avoid grapefruit products and strong CYP3A inhibitors/inducers <strong>Avoid QT-prolonging drugs</strong></td>
</tr>
<tr>
<td><strong>Common AEs</strong></td>
<td>Neutropenia</td>
<td>Neutropenia</td>
<td>Neutropenia</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>Fatigue</td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>CBC</td>
<td>CBC</td>
<td>CBC, LFTs, ECG, Electrolytes</td>
</tr>
<tr>
<td></td>
<td>LFTs</td>
<td></td>
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</tr>
</tbody>
</table>
The Value of a Multidisciplinary Approach

- Improves patient care in all aspects, from diagnosis to patient quality of life
  - Improves patient experience
  - Reduces variation in care
  - Promotes adherence
  - Expands access to care
- Holistic approach to cancer treatment, with the patient as part of the shared decision making

PCE Action Plan

✓ Test Ki-67 index in patients with HR+/HER2- early breast cancer if considering adjuvant therapy with abemaciclib
✓ Counsel patients and caregivers to promptly report pulmonary symptoms while receiving CDK4/6 inhibitors
✓ Closely monitor patients for neutropenia during first cycles of treatment with CDK4/6 inhibitors
✓ Evaluate for toxicities and adherence issues at follow-up to quickly implement clinical management strategies

PCE Promotes Practice Change