Real-World Evidence and Clinical Decision-Making for HR-positive/HER2-negative Metastatic Breast Cancer

Cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors are transforming how patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer (MBC) are treated. The first CDK 4/6 inhibitor, palbociclib, was approved for MBC in 2015, and two other CDK 4/6 inhibitors (ribociclib and abemaciclib) were approved as recently as 2017. Each is used in combination with an aromatase inhibitor (AI) or the estrogen receptor antagonist fulvestrant,[1] and all three CDK 4/6 inhibitors have resulted in significant improvements in median progression free survival (PFS) when combined with endocrine therapy for women with HR+/HER2- MBC.

Of note, PFS for patients with HR+/HER2- MBC who receive a CDK 4/6 inhibitor plus an AI first line now exceeds 24 months, which is a considerable improvement over AI therapy alone (10 to 14 months).[2-11]

Clinical Potential of "Real-World" Evidence (RWE)

While CDK 4/6 inhibitors are clearly an important treatment option for patients with metastatic HR+/HER2- breast cancer,[12-16] findings related to the efficacy and safety of CDK 4/6 inhibitors from large, population-restricted, randomized controlled trials (RCTs) cannot be easily extrapolated to broader demographic populations.[17, 18] More specifically, while investigational drugs often require extensive pivotal RCTs before regulatory approval, the trials are time-consuming, costly, and produce evidence that has limited applicability in "real-world" clinical practice. Real-world data are collected from a variety of sources (e.g., electronic health records [EHRs], insurance claims, patient registries, digital health solutions), usually independent of conventional RCTs, and reflect treatment practices and outcomes across a wider population with mixed health status. Acquisition of the aforementioned types of data allows for the compilation of RWE that can be compared to outcomes from RCTs and can support and extend findings from RCTs to broader populations.[19-22]

The Inclusion/Exclusion Conundrum of RCTs Compared with Real-World Studies (RWS)

Because RCTs are usually conducted in a sample of homogeneous patients meeting rigorous inclusion/exclusion criteria for trial enrollment and are closely monitored according to strict protocols, RCTs may not fully reflect actual clinical experience. Patients enrolled in RCTs may not represent the broad population of patients affected by the disease/condition under study (e.g., those with multiple comorbidities), and some rare adverse events are impossible to observe accurately in a small sample of patients during the limited period of a clinical trial. RWE derived from RWS may be more generalizable to patients in routine clinical practice and is increasingly recognized as an important complement to the evaluation of the risks/benefits of a drug revealed in an RCT.[19-22]

The 21st Century Cures Act, signed into law in December 2016, includes a mandate to evaluate RWE for regulatory decisions such as new indications for drugs already marketed or to satisfy post-approval

study requirements.[23] In the case of CDK 4/6 inhibitors, RWE coming from the various RWS described below is proving remarkably consistent with results of pivotal, phase 3 RCTs.

These RWS represent comparative effectiveness studies to assist clinical decision-making. A comparison of characteristics associated with RWE/RWS and from RCTs is presented in Table 1.

Table 1. Comparative Characteristics of RWE/RWS and RCTs[22]

Characteristic	RWE/RWS	RCT
Type of Study	***Observational / non-interventional / interventional / pragmatic***	***Experimental / interventional***
Design	***Retrospective/prospective***	***Prospective***
Comorbidity	***Potentially high***	***Limited***
Patient population	***Promotes evaluation of patient populations not typically studied in clinical trials; helps to verify evidence in real-world patient populations.***	***Patient population is well defined within the constraints of specific eligibility criteria; results reflect outcomes in a limited population.***
Sample size	***Very large sample size possible ("big data").***	***Limited sample size.***
Access to therapies	***Insurance and access issues (affordability, availability, etc.)***	***No issues—therapies made available***
Efficacy	***Greater chance for data bias since true randomization and blinding not possible.***	***Minimizes data bias and confounding because randomization and blinding possible.***
Toxicity	***Helps uncover important toxicity signals that require long-term follow-up.***	***Only acute and common toxicities revealed.***
Approval of new treatments	***Not suitable for approving novel treatments, but helpful in validating/extending RCT results.***	***The gold standard for new drug approvals.***

RCT, randomized controlled trial; RWE, real-world evidence; RWS, real-world studies.

Consistency of RWE/RWS Compared with RCTs in the Treatment of HR+/HER2- MBC: *Palbociclib and Abemaciclib*

Palbociclib

Flatiron Studies

Data from the Flatiron Health analytic database was presented by Layman and colleagues at ESMO 2019.[24] Specifics are presented in Table 2. This was a retrospective, observational analysis of women with HR+/HER2- MBC whose therapy was initiated on palbociclib plus letrozole or letrozole alone. The combination group was followed for a median 19.7 months; the letrozole alone group was followed for a

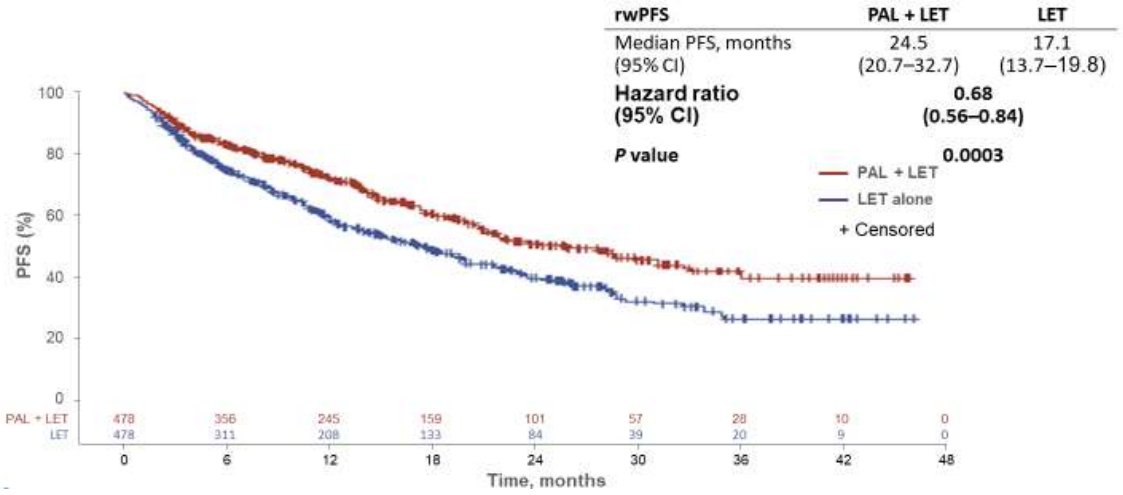
median of 17.1 months. Inclusion criteria allowed patients normally excluded from RCTs, including elderly patients >70 years and those with multiple comorbidities, bone only disease, and brain metastases.

Table 2. Flatiron Real-World Palbociclib Retrospective Analysis

• Retrospective, observational analysis of EHR from Flatiron Health analytic database
• Women with HR-positive/HER2-negative metastatic breast cancer
• Initiated on palbociclib + letrozole (PAL + LET) or letrozole alone (LET) – PAL + LET, n=798; median follow-up 19.7 mos – LET alone, n=618; median follow-up 17.1 mos
• Analysis included: – Elderly (median age 68 years) – Multiple comorbidities (49.7%) – Bone-only disease (29.55%) – Metastases (# metastatic sites = 2.0, including brain)

Kaplan-Meier plots for real-world progression-free survival (rwPFS) and real-world overall survival (rwOS) are presented below in Figures 1 and 2, respectively. Median rwPFS was 24.5 months for palbociclib + letrozole compared with 17.1 months for letrozole alone. The hazard ratio was 0.68 (95% CI, 0.56-0.84); *P*=0.0003 (Figure 1).

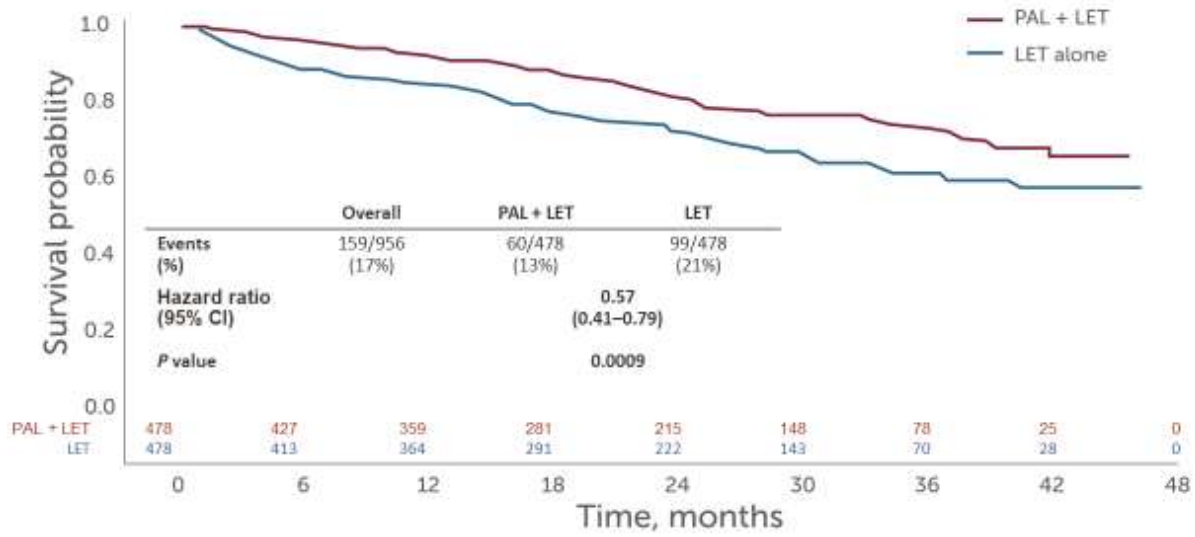
Figure 1. Flatiron: Real-World Progression-Free Survival*[24]



*Propensity score matching stabilized weight-adjusted numbers of patients at risk are shown. LET, letrozole; PAL, palbociclib; PFS, progression-free survival; rwPFS, real-world progression-free survival.

Median rwOS had not been reached by the time of the Layman and colleagues analysis. However, at this juncture, percent events were markedly different between the palbociclib + letrozole group (13%) and the letrozole group (21%). The hazard ratio was 0.57 (95% CI, 0.41-0.79) (Figure 2).

Figure 2. Flatiron: Real-World Overall Survival*[24]



*Propensity score matching stabilized weight-adjusted numbers of patients at risk are shown. LET, letrozole; PAL, Palbociclib.

DeMichele and colleagues extended these data at the 2019 San Antonio Breast Cancer Symposium.[25] Between February 2015 and February 2019, 1,388 adult women with HR+/HER2- MBC were treated on palbociclib + letrozole (n = 766) or letrozole (n = 622) as first-line therapy. Patients were evaluated from start of palbociclib + letrozole or letrozole to May 2019, death, or last visit, whichever came first. Median follow-up was 22.0 months for the palbociclib + letrozole cohort and 19.0 months for the letrozole cohort.

The estimated rwOS rates for the palbociclib + letrozole and letrozole cohorts, based on the Kaplan-Meier weighted curve, were 81.2% and 70.8% at 24 months, and 72.0% and 60.6% at 36 months, respectively.

This real-world comparative effectiveness analysis provided support for the findings from Layman and colleagues[24] by demonstrating a significant rwOS benefit for first line palbociclib + letrozole compared with letrozole alone among patients with HR+/HER2- MBC. The authors concluded that *"within the limitations of this non-randomized EHR database analysis, results support the value of palbociclib when added to letrozole to improve long-term outcomes in a real-world setting."*

IRIS

The IRIS Study[2,6,26] was an assessment of real-world treatment patterns for HR+/HER2- MBC in the US, Germany, and Argentina. The study assessed clinical outcomes among patients receiving palbociclib in combination with an aromatase inhibitor or fulvestrant through a retrospective medical chart review. The rwPFS and rwOS data are presented in Table 3.

Table 3. Palbociclib Real-World Insights (IRIS): Real-World Treatment Outcomes in Patients Treated with Palbociclib Combination Therapy[2,6,26*]

Retrospective Chart Review of 652 Patients Who Received On-Label PAL + AI/FUL (US)

Progression-Free and Survival Rates

	6 months	12 months	18 months	24 months
PAL + AI (n = 360)				
Progression-free, %	96.7	84.1	69.3	64.36
Survival rate, %	98.6	95.1	90.1	90.1
PAL + FUL (n = 292)				
Progression-free, %	94.3	79.8	-	-
Survival rate, %	97.2	87.9	-	-

Dose adjustments lower vs. RCTS

- **PAL + AI:** 19.7% (n = 71); **PAL + FUL:** 14.4% (n = 42)
- RCTs: PALOMA-2, **PAL + LET:** 36%; PALOMA-3, **PAL + FUL:** 34%

*AI, aromatase inhibitor; FUL, fulvestrant; LET, letrozole; PAL, palbociclib; RCTS, randomized controlled trials

The overall assessment of findings was that combination therapies containing palbociclib and aromatase inhibitor or fulvestrant provided meaningful real-world outcomes, supporting findings obtained in the various clinical trials.

Abemaciclib

Carter and colleagues[27] presented a retrospective observational study with the objective of describing baseline characteristics, treatment patterns, and outcomes among patients with HR+/HER2- MBC treated with abemaciclib. One hundred eighteen (118) patients who initiated treatment with abemaciclib on or after June 30, 2016, and at least 4 months prior to the data cutoff date of December 31, 2018, were selected from the de-identified Flatiron Health EHR database for US patients.

Among abemaciclib patients who had at least 1 tumor response assessment (n=68), 41.2% had either a complete (CR) or partial response (PR). Although not statistically significant, there was a trend toward higher rates of CR/PR in first-line (65.0%) compared to later lines of therapy. Median time to first response was 3.6 months (95% CI: 3.5-5.2). The authors concluded that this study, as one of the first to provide insights into scheduling and dosing in a real-world population receiving abemaciclib, provided evidence of response to abemaciclib in the real-life setting.

Conclusion

RWE/RWS provide(s) important insights into actual patterns of care, market uptake of a new treatment, healthcare use costs, and toxicities otherwise obscured in the highly selected patient populations

typically enrolled in RCTs. Nonetheless, RWE cannot definitively determine whether an intervention is superior to a control treatment. Although RWE may be of limited value in supporting new interventions that alter current standards of care, it remains crucial for clinicians who want a fuller understanding of the broader therapeutic benefit of an approved treatment than can be gleaned from the RCTs.[22] Thus, although RWE is insufficient to guide treatment compared with the results from an RCT, RWE can corroborate RCT results, if not extend them to a broader, real-life population.

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