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BREAST CANCER
JULY 11, 2022
VIRTUAL WORKSHOP

SCIENTIFIC INTERCHANGE & WORKSHOP

Exploring Recent Developments in the Treatment of Patients With Hormone Receptor–Positive **Breast Cancer**

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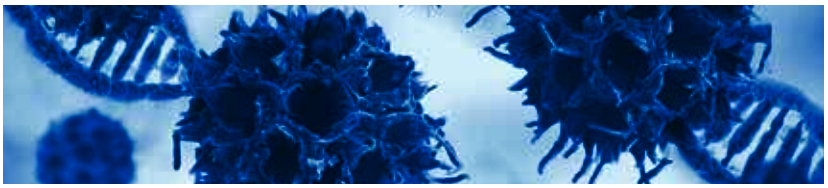

KEY TAKEAWAYS

- For the identification of actionable mutations, genotyping via tissue-based biopsy is generally favored over liquid biopsy.
- Clinicians may prefer to follow the National Comprehensive Cancer Network/American Society of Clinical Oncology (NCCN/ASCO) recommendations vs the FDA guidelines regarding abemaciclib utilization for hormone receptor-positive (HR+), high-risk breast cancer (BC).
- Olaparib as adjuvant therapy significantly improves outcome survival in germline *BRCA*-mutated BC, and testing for *BRCA* is important to prioritize so as not to miss patients who may be eligible for treatment with olaparib. There are currently no data to support the utility of olaparib plus immunotherapy in the adjuvant setting.
- An unmet need in the triple-negative breast cancer (TNBC) landscape includes finding an effective regimen that utilizes pembrolizumab in lieu of 4 chemotherapy drugs.
- Regarding CDK4/6 inhibitors, ribociclib may be considered the agent of choice due to positive overall survival (OS) data.
- Challenges in managing the toxicity profile of alpelisib may hinder its use in patients who have *PIK3CA* mutations.
- After progression on a CDK4/6 inhibitor, clinicians may prefer to use fulvestrant plus everolimus rather than utilize another CDK4/6 inhibitor.
- Selective estrogen receptor degraders (SERDs), as a class, differ in their structure and toxicity profiles, and one may consider shifting their use to earlier in the treatment paradigm.

Exploring Recent Developments in the Treatment of Patients With Hormone Receptor-Positive **Breast Cancer**

ON JULY 11, 2022, a select group oncology experts met to engage in a virtual discussion workshop moderated by oncologist **Erika Hamilton, MD**, director of breast and gynecologic cancer research at the Sarah Cannon Research Institute in Nashville, TN. The overall objectives were to review recent data on therapeutic advances in HR+ BC. This article summarizes data from recent trials in early HR+ and TNBC; HR+ metastatic BC (mBC), focusing on use of CDK4/6 inhibitors in the first line (1L) and second line and beyond (2L+); and promising new endocrine therapies (ETs) that may represent the future direction of HR+ cancer treatment.

RECENT UPDATES IN EARLY HORMONE RECEPTOR–POSITIVE AND TRIPLE-NEGATIVE BREAST CANCER

Olaparib: OlympiA Trial

OlympiA was a phase 3, double-blind, randomized trial (NCT02032823) involving patients (n = 1836) with HER2-negative (HER2-), *BRCA1/2* germline-variant, high-risk early BC who had received local treatment and neoadjuvant or adjuvant chemotherapy (CT) who were randomly assigned in a 1:1 ratio to receive olaparib (300 mg) or matching placebo tablets taken orally twice daily for 52 weeks.[1,2] Stratification was done based on HR status, the timing of previous CT, and the use of platinum-based CT for current BC. The primary end point was invasive disease-free survival (IDFS) in the intent-to-treat (ITT) population, with secondary end points of distant disease-free survival (DDFS), OS, and safety. Adjuvant olaparib after completion of local treatment and neoadjuvant or adjuvant CT was associated with significantly longer IDFS and DDFS than placebo when measured at 3 years. The IDFS was 85.9% for olaparib vs 77.1% for placebo (stratified hazard ratio for invasive disease or death, 0.58; 99.5% CI, 0.41-0.82; $P < .001$), and the DDFS was 87.5% for olaparib vs 80.4% for placebo (stratified hazard ratio for distant disease or death, 0.57; 99.5% CI, 0.39-0.83; $P < .001$).

Adverse events (AEs) were consistent with those of the package labeling, and approximately 20% of patients receiving olaparib experienced grade 3 or greater AEs, with anemia (8.7%), decreased neutrophil count (4.8%), and decreased white cell count (3.0%) being the most prevalent. In contrast, less than 3% of patients receiving placebo experienced grade 3 or greater AEs.

Abemaciclib: monarchE Trial

The monarchE global, phase 3, open-label trial (NCT03155997) randomly assigned 5637 patients (1:1) to adjuvant ET for 5 or more years with or without abemaciclib for 2 years, with 2 cohorts: 4 or more positive axillary lymph nodes (ALNs) or 1 to 3 positive ALNs and either grade 3 disease or tumor size of at least 5 cm (cohort 1); or 1 to 3 positive ALNs with tumor size less than 5 cm, less than grade 3 disease, and Ki-67 index of 20% or higher (cohort 2).[3] IDFS per Standardized Definitions for Efficacy End Points (STEEP) criteria in the ITT population was the primary end point, with secondary end points of IDFS in patients with high Ki-67 score, distant relapse-free survival (DRFS), OS, and safety.

Abemaciclib plus ET resulted in a 29% reduction in the risk of developing an IDFS event (hazard ratio, 0.71; 95% CI, 0.58-0.87; nominal $P = .0009$), with benefit maintained at follow-up analysis (median, 27 months) evidenced by higher IDFS (hazard ratio, 0.70; 95% CI, 0.59-0.82; nominal $P < .0001$) and DRFS (hazard ratio, 0.69; 95% CI, 0.57-0.83; nominal $P < .0001$). Ki-67 index was prognostic for recurrence, but abemaciclib benefit was observed regardless of Ki-67 status, and treatment benefit extended beyond the 2-year treatment period. Abemaciclib was approved by the US Food and Drug Administration (FDA) for cohort 1 with Ki-67 score of at least 20% in October 2021.[4] Grade 3 or higher AEs and serious AEs occurred more frequently with abemaciclib plus ET vs ET alone (AEs ≥ grade 3, 49.2% vs 15.9%, respectively; serious AEs, 15.2% vs 8.1%).[3] The most common grade 3 or greater AEs experienced by at least 5% of patients in the study were neutropenia (19.6% for abemaciclib and 0.8% for control), leukopenia (11.3% for abemaciclib and 0.4% for control), diarrhea (7.8% for abemaciclib and 0.2% for control), and lymphopenia (5.4% for abemaciclib and 0.5% for control).[3] Among patients in the abemaciclib and control groups, 6.5% and 1.1% discontinued due to AEs.

Pembrolizumab: KEYNOTE-522 Trial

The KEYNOTE-522 phase 3 trial (NCT03036488) examined neoadjuvant pembrolizumab (PEM) plus CT (carboplatin plus paclitaxel) followed by a second neoadjuvant treatment of PEM plus doxorubicin or epirubicin plus cyclophosphamide in adult patients with previously untreated, nonmetastatic TNBC with an ECOG performance status (PS) of 1 or less.[5,6] Patients were randomly assigned 2:1 to receive either PEM plus CT (n = 784) or placebo plus CT (n = 390), followed by a second neoadjuvant treatment of PEM or placebo plus doxorubicin or epirubicin plus cyclophosphamide.[6] Primary end points were pathologic complete response (pCR) and event-free survival (EFS) in ITT populations, with secondary end points of pCR (alternate definitions, ypT0 ypN0 and ypT0/Tis); pCR, EFS, and OS in programmed death-ligand 1–positive (PD-L1+) patients; and safety. First interim analysis of patients (n = 602) revealed a pCR of 64.8% in the PEM+CT group and 51.2% in the placebo plus CT (estimated treatment difference, 13.6 percentage points; 95% CI, 5.4-21.8; $P < .001$). The incidence of treatment-related adverse events (TRAEs) of grade 3 or greater was 78.0% in the PEM plus CT group and 72.2% in the placebo plus CT. Overall, PEM plus CT resulted in a significantly increased pCR; the benefit was observed across most prognostic risk categories, including low PD-L1 expression.

STAKEHOLDER INSIGHTS

Faculty members expressed a preference for the NCCN/ASCO recommendations vs FDA guidelines regarding abemaciclib utilization for patients with Ki-67 score of at least 20%; 1 panelist uses abemaciclib more widely, specifically in patients who have levels of Ki-67 below 20%. Gastrointestinal (GI) toxicity »

and fatigue with abemaciclib were identified as AEs of interest. Data from the OlympiA trial of olaparib were thought to be practice-changing for patients who are HR+ with *BRCA* mutations. Given that this trial met its 3 outcomes of improved IDFS, DDFS, and OS, the faculty favor olaparib over abemaciclib in patients who are *BRCA*-positive and meet eligibility for the monarchE trial. As olaparib has shown efficacy in the HER2-, *BRCA1/2* germline-variant, high-risk early BC population, it is important to prioritize testing for *BRCA* so as not to miss anyone eligible for olaparib treatment. There are currently no data to support the utility of olaparib plus immunotherapy in the adjuvant setting; however, some of the panelists are comfortable using olaparib plus pembrolizumab based on recently published safety data using this combination. Participants agreed that universal genetic testing is needed and ideally could be incorporated into existing patient appointments.

Participants tend to follow the clinical trial eligibility from KEYNOTE-522 when selecting patients to receive pembrolizumab, and data on pembrolizumab in the adjuvant setting in patients who achieve a pCR remains a topic of interest. Some faculty expressed reservations about the utility of KEYNOTE-522 results in patients who have TNBC due to toxicity. Panelists identified unmet needs in the TNBC landscape, particularly in regimens that minimize the use of immunotherapy due to toxicity and in regimens utilizing pembrolizumab in lieu of 4 chemotherapy drugs.

HORMONE RECEPTOR–POSITIVE METASTATIC BREAST CANCER: UPFRONT CDK4/6 INHIBITORS

For HR+/HER2- mBC, recommended 1L treatment is ET plus CDK4/6 inhibition or a SERD plus a nonsteroidal aromatase inhibitor.[7] Second-line and subsequent therapies consist of ET plus a CDK4/6 inhibitor if a CDK4/6 inhibitor has not been previously used; ET plus everolimus; ET plus alpelisib (*PIK3CA* mutated); PARP inhibition (*BRCA1/2* mutated); pembrolizumab (microsatellite instability-high/mismatch repair deficiency [MSI-H/dMMR]); and larotrectinib/entrectinib (*NTRK* fusions), among others.

The recommendation for a therapeutic combination of CDK4/6 inhibitors and ET for 1L to 3L is based, in part, upon the improved progression-free survival (PFS) and OS of patients in numerous trials. Data from 1L and 2L combinations of CDK4/6 inhibitors and ET in HR+/HER2- BC are listed in **TABLE 1**.[8-15]

STAKEHOLDER INSIGHTS

Ribociclib was the CDK4/6 inhibitor of choice among the faculty due to positive OS data and the safety profile in the MONALEESA trials. Among 2L therapies, alpelisib is an effective option used by the panelists for those with *PIK3CA* mutations, but challenges managing its toxicity profile hinder its utility. Most participants support the universal use of CDK4/6 inhibitors in patients with ER-positive mBC due to proven survival benefits; however, 1 participant made

TABLE 1.
1L/2L CDK4/6I AND ET COMBINATIONS IN HR+/HER2- BC[8-15]

	PALOMA-2 (n=666)	MONALEESA-2 (1L therapy) (n = 668)	MONARCH-3 (n=493)	MONALEESA-3 (1L/2L therapy) (n = 726)
Endocrine therapy	Letrozole	Letrozole	Letrozole	Fulvestrant
CDK4/6i	Palbociclib	Ribociclib	Abemaciclib	Ribociclib
Median PFS, CDK4/6i + ET vs ET, mo	27.6 vs 14.5	NR vs 14.7	NR vs 14.7	20.5 vs 12.8
Hazard ratio (95% CI) *P* value	0.56 (0.46-0.69) *P* < .0001	0.56 (0.43-0.72) $P = 3.29\times10^{-6}$	0.54 (0.41-0.72) *P* = .000021	0.59 (0.480-0.732) *P* < .001
Median OS, CDK4/6i + ET vs ET, mo	53.9 vs 51.2	63.9 vs 51.4	Not yet reported	53.7 vs 41.5
Hazard ratio (95% CI) *P* value	0.956 (0.777-1.177) *P* = .3378	0.76 (0.63-0.93) *P* = .008	—	0.73 (0.59-0.90)

1L, first-line; 2L, second-line; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ET, endocrine therapy; mo, months NR, not reached; OS, overall survival; PFS, progression-free survival; Tx, treatment.

a strong case for a precise biomarker to identify patients who may not need CDK4/6 inhibition and for whom single-agent ET would be a reasonable treatment option in the 1L setting.

THERAPY AFTER PROGRESSION ON A FIRST-LINE CDK4/6 INHIBITOR FOR HORMONE RECEPTOR–POSITIVE mBC

Ribociclib plus Endocrine Therapy: MAINTAIN Trial

MAINTAIN (NCT02632045) was a phase 2, multicenter, randomized, double-blind, placebo-controlled trial evaluating the efficacy of fulvestrant or exemestane with or without ribociclib in patients with HR+/HER2- mBC whose cancer previously progressed on any CDK4/6 inhibitor plus any ET, with PFS as the primary end point.[16] Improved median PFS of fulvestrant or exemestane plus ribociclib (5.33 months) vs placebo (2.76 months), with a hazard ratio of 0.56 (95% CI, 0.37-0.83; *P* = .004), was observed. Similar results were seen in the fulvestrant-only arm, with a median PFS of 5.29 months for those randomly assigned to ribociclib vs 2.76 months for those on placebo (hazard ratio, 0.59; 95% CI, 0.38-0.91; *P* = .02). Among patients in the ribociclib arm, 42% were progression-free vs 24% on placebo at 6 months; 25% were progression free vs 7% on placebo at 12 months. Results support a therapeutic decision for patients with HR+/HER2- mBC to switch ET and receive ribociclib after progression on a CDK4/6 inhibitor.

HR+/HER2- mBC: 2L+ Treatment

NCCN guidelines for HR+/HER2- BC recommend additional targeted therapies and associated biomarker testing for 2L+ treatment and ET-resistant cases.[7] Alpelisib plus fulvestrant is recommended for *PIK3CA* mutations.[7] For germline *BRCA1/2* mutations, PARP inhibition with olaparib or talazoparib is recommended.

Alpelisib Plus Fulvestrant: SOLAR-1 Trial

The SOLAR-1 trial (NCT02437318) assessed the utility of alpelisib plus fulvestrant (ALP) vs placebo plus fulvestrant (PLB) for men and postmenopausal women with HR+/HER2- advanced BC.[17] This international, randomized, double-blind, phase 3 study stratified subjects by the presence of liver or lung metastases, *PIK3CA* mutation status, and prior treatment with CDK4/6 inhibition. Studied patients (n = 572) had recurrence/progression on or after prior aromatase inhibitor therapy, ECOG PS 0/1, and measurable disease or at least 1 predominantly lytic bone lesion. The primary end point was investigator-assessed PFS in the *PIK3CA*-mutant cohort; secondary end points were OS and PFS in the *PIK3CA* non-mutant cohort, PFS by *PIK3CA* status as evaluated with circulating tumor DNA (ctDNA), objective response rate (ORR), clinical benefit rate, and safety. In the *PIK3CA* mutant cohort, the median PFS was prolonged in the ALP group compared with the PLB group (11.0 months vs 5.7 months; hazard ratio, 0.65; 95% CI, 0.50-0.85; *P* = .00065), with a median OS of 39.3 vs 31.4 months, respectively (hazard ratio, 0.86; 95% CI, 0.64-1.15; *P* = .15). ORR among all patients in this cohort was greater in the ALP arm than with PLB (26.6% vs 12.8%), and clinical benefit was also greater with ALP (61.5% vs 45.3%). The safety profile in the SOLAR-1 trial was consistent with that of previous trials investigating ALP therapy, with the most common AEs of any grade including hyperglycemia, diarrhea, nausea, decreased appetite, and rash/maculopapular rash. AEs were generally reversible and mostly low grade with the exclusion of hyperglycemia, which necessitated permanent discontinuation of alpelisib in 6.3% of the patients. Study results further supported the use of alpelisib in the *PIK3CA*-mutated, HR+/HER2-, advanced BC population.

Sacituzumab Govitecan: TROPiCS-02 Trial

The antibody-drug conjugate sacituzumab govitecan (SG) was the investigational agent in TROPiCS-02 (NCT03901339), a randomized (1:1) phase 3 study in patients (N = 543) with HR+/HER2- advanced BC with progression after at least 1 ET, taxane, and CDK4/6 inhibitor in any setting; at least 2 but no more than 4 lines of CT ([neoadjuvant therapy for early-stage disease qualified as a prior line of CT if disease recurred within 12 months).[19]

Subjects received SG (n = 272) or treatment of physician's choice (TPC): capecitabine, vinorelbine, gemcitabine, or eribulin (n = 271). Primary end point was PFS by blinded independent central review (BICR); the secondary end point was OS. SG demonstrated a statistically significant improvement in median PFS (5.5 months) vs TPC (4.0 months) with a 34% reduction in the risk of disease progression and death (stratified hazard ratio, 0.66; 95% CI, 0.53-0.83; stratified *P* = .0003). Median OS was 13.9 months for SG and 12.3 months for TPC, but the difference was not statistically significant (*P* = .143).

STAKEHOLDER INSIGHTS

After progression on a CDK4/6 inhibitor, faculty would opt to use fulvestrant plus everolimus due to the latter agent's relative tolerability; however, alpelisib is an option for those with a *PIK3CA* mutation. Sacituzumab govitecan demonstrated improved PFS in the TROPiCS-02 trial, but panelists would like to see more data showing its benefit over chemotherapy in this setting. Participants agreed that outside of a clinical trial, they would not utilize another CDK4/6 inhibitor after progression on a CDK4/6 inhibitor, opting for other modalities, such as SERDs. »

TABLE 2.
SERDS IN CLINICAL TRIALS FOR HR+ ADVANCED/METASTATIC BREAST CANCER[18,24-28]

	AMEERA (n = 1066)	SERENA-4 (n = 1342)	persevERA (n = 978)	acelERA (n = NP)	EMERALD (n = 477)	EMBER (n = 114)
Trial phase	3	3	3	2	3	1a/2
SERD	Amcenestrant + PAL vs LET + PAL	Camizestrant (AZD9833) + PAL vs ANA + PAL	Giredestrant (GDC9545) + PAL vs LET + PAL	Giredestrant vs TPC	Elacestrant vs SOC ET	Imlunestrant (LY3484356) monotherapy
Disease setting	ER+/HER- aBC	Systemic treatment-naïve ER+/HER- BC	ER+/HER- LA/mBC	ER+/HER-, LA/mBC, 1-2 prior lines tx, ≥1 of ET	ER+/HER-, LA/mBC, 1-2 prior lines ET, CDK4/6i, ≤1 CT	ER+, advanced BC; ER+ EEC
Primary endpoints (results, if available)	PFS	PFS to 5 years	PFS per RECIST 1.1	PFS per RECIST 1.1	PFS by BICR (hazard ratio: all pts, 0.70; ESR1m, 0.55)	ORR (BC, 8.0%; EEC, 5.0%)
					6 mo: all pts, 34.3% vs 20.4%; ESR1m, 40.8% vs 19.1%	CBR (BC, 40.4%; EEC, 47.1%)
					12 mo: all pts, 22.3% vs 9.4%; ESR1m, 26.8% vs 8.2%	
Secondary end points (results, if available)	OS, safety, pharmacokinetics, QOL	OS to 8 years, 2nd PFS, time to CT, ORR, QOL	OS, ORR, DOR, CBR, QOL, safety	OS, ORR, DOR, CBR, QOL, PFS in *ESR1m*	ORR, CBR, safety (nausea: ELA, 35%; SOC, 19%)	RP2D, safety

aBC, advanced breast cancer; ANA, anastrozole; BC, breast cancer; BICR, blinded independent central review; CBR, clinical benefit rate; CDK4/6i, CDK4/6 inhibition; CT, chemotherapy; DOR, duration of response; EEC, endometrial endometrioid cancer; ELA, elacestrant; ER, estrogen receptor; *ESR1m*, patients with baseline *ESR1* mutations; ET, endocrine therapy; LA, locally advanced; LET, letrozole; mBC, metastatic breast cancer; NP, not posted; ORR, objective response rate; OS, overall survival; PAL, palbociclib; PFS, progression-free survival; pts, patients; QOL; quality of life; RP2D, recommended phase 2 dose; SERD, selective estrogen receptor degrader; SOC, standard of care; TPC, treatment of physician's choice; tx, treatment.

NEW ENDOCRINE THERAPIES: SELECTIVE AGENTS

History of Selective Endocrine Receptor Degraders/Downregulators

Fulvestrant, an ER antagonist, was approved in 2002 for the treatment of HR+ mBC in postmenopausal women with disease progression following antiestrogen therapy.[19] In 2016, the FDA approved palbociclib for use in combination with fulvestrant for HR+/HER2- advanced or mBC with disease progression following ET based on the results of the PALOMA-3 trial,[20] and alpelisib in combination with fulvestrant was approved in 2019 for the treatment of postmenopausal women and men with HR+/HER2-, *PIK3CA*-mutated, advanced or mBC based on results from the aforementioned SOLAR-1 trial.[21] As of 2022, 1 oral SERD agent has been approved and additional agents are in development.

Fulvestrant vs Exemestane: SoFEA and EFECT Trials

The phase 3 EFECT (NCT00065325) and SoFEA (NCT00253422 [UK]; NCT00944918 [South Korea]) trials randomly assigned patients with advanced HR+ mBC who had progressed on prior nonsteroidal aromatase inhibitors to receive either fulvestrant 250 mg or the estrogen modulator exemestane.[22] The primary objectives were to assess the impact of *ESR1* mutation status and treatment randomization on PFS and OS. In patients with *ESR1* mutations (30% of participants), PFS was 2.4 months on exemestane and 3.9 months on fulvestrant (hazard ratio, 0.59; 95% CI, 0.39-0.89; P = .01). In patients without *ESR1* mutations, PFS was 4.8 months with exemestane and 4.1 months with fulvestrant (hazard ratio, 1.05; 95% CI, 0.81-1.37; P = .69). Patients with *ESR1* mutations had a 1-year OS of 62% with exemestane and 80% with fulvestrant (P = .04; restricted mean survival analysis). Patients without baseline *ESR1* mutations had a 1-year OS of 79% with exemestane and 81% with fulvestrant (P = .69). In conclusion, *ESR1* mutations were predictive of a lack of benefit from aromatase inhibitor therapy in patients who has previously progressed on a nonsteroidal aromatase inhibitor.

SERDS in Clinical Trials for HR+ Advanced/Metastatic BC

The utility of SERDs as a focused treatment in HR+ advanced or mBC is the subject of multiple clinical

investigations. A list of selected SERDs with patient population, agents, and top-line outcomes may be found in **TABLE 2**.[23-28]

STAKEHOLDER INSIGHTS

Faculty are interested in where oral SERDs will land in the adjuvant treatment landscape. The EMERALD trial demonstrated improved PFS, particularly in the population with *ESR1* mutations, but GI AEs are less than ideal. A need was expressed for more compelling trial data before participants shift to using SERDs preferentially in the highly curative space. Some faculty believe SERDs should be shifted to earlier in the treatment paradigm. One panelist stated that not all oral SERDs are created the same and that each "subclass" has its own toxicity profile. Another participant mentioned that as a class, SERDs have potential, but results from phase 2 and phase 3 trials will determine their feasibility as a preferred treatment. Ideal agents would be precisely targeted with clear efficacy and minimal AEs. ■

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Ruth O'Regan, MD

"The FDA approval [of abemaciclib] is a little controversial. Most of us have been using abemaciclib a bit more widely, including in patients with lower levels of Ki-67."

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Expert Perspective: Therapeutic Approaches to the Management of HR+ Breast Cancer

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INTRODUCTION

Advances in genomic testing and the development of targeted agents have greatly expanded the armamentarium of therapies for the management of hormone receptor–positive (HR+) breast cancer (BC). However, with so many treatments available, the decision-making process has become even more complicated. In recent video interviews with *OncLive*®, **Ruth M. O'Regan, MD**; and **Stephanie L. Graff, MD, FACP**; shared insights into evidence-based approaches to the management of HR+ BC, as well as where investigational agents may fit into the treatment paradigm in the future. Ahead are highlights from their interviews.

**Interview transcripts are edited for readability.*

TO WATCH THE VIDEO INTERVIEWS, VISIT **ONCLIVE.COM**

***OncLive*®: What are some of the treatment considerations in the first-line setting for patients with HR+ metastatic BC (mBC)?**

GRAFF: The first thing that we need to consider when we are evaluating a patient with HR+ mBC is [whether it is] truly HR+? Most of my colleagues and fellow experts always confirm a metastatic diagnosis with a biopsy and do estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) staining on the biopsy. Often, we can also do *PIK3CA* testing at the same time, because it is not necessarily a mechanism of resistance, but it will help decide what you are going to use for a treatment later. Sometimes, tumors can be heterogeneous, and a metastatic site that develops years later will be HER2-amplified, which would significantly change the direction of treatment. Other things to consider are sites of disease and how that affects your palliative plan. Women or men with HR+ mBC will have heavy bone metastases and could be at risk for fracture. If a bone scan or PET scan shows disease in the hip, pelvis, or other areas associated with a high risk for fracture or anything that is significantly painful, it is an opportunity to get plain films or MRIs, or involve our radiation and surgical colleagues to figure out whether bone needs to be stabilized first. Palliative care and supportive care colleagues should be involved to support any disease-related symptoms and adverse effects patients are having.

O'REGAN: For most patients, the combination of endocrine therapy (ET) with a CDK4/6 inhibitor is standard. The [specific drug used for] ET really depends on whether the patient relapsed on a nonsteroidal aromatase inhibitor or not. As far as the CDK4/6 inhibitor [goes], there is a choice of 3 different agents. Looking at the first-line trials that have been done, the 3 trials that utilized ribociclib all show an overall survival advantage. We don't have survival data from the monarchE study yet, so we don't know about abemaciclib. We recently saw some data from PALOMA-2, which did not show a significant benefit for survival for patients who received palbociclib plus ET compared with ET alone. For that reason, a lot of clinicians have switched to first-line management with ribociclib

combined with either a nonsteroidal aromatase inhibitor or fulvestrant, depending on what the patient has been treated with previously.

OncLive®: What role has biomarker testing played in HR+ BC, and how do patients with *ESR1* mutations differ in terms of treatment options?

GRAFF: Biomarkers for HR+ BC are here and ready for prime time when it comes to *PIK3CA* mutation testing. *PIK3CA* is clearly a driver mutation in BC. When a patient with a *PIK3CA* mutation is identified, we want to consider treatment with alpelisib or clinical trials investigating some of the emerging [agents] for that patient population. The other emerging biomarker is the *ESR1* mutation. We know that patients with *ESR1* mutations respond differently to hormonal blockade in the first-line and second-line [settings]. When someone is identified with an *ESR1* mutation, it may change the hormonal ET backbone that you choose. It may also be a reason to change their ET backbone while leaving their CDK4/6 inhibitor alone if it is paired with disease progression. However, doing serial studies to look for evidence of circulating tumor DNA (ctDNA) and the emergence of *ESR1* mutations, I still consider [that as] something that is done in a clinical trial. Increasingly, we're seeing elements like that embedded in our clinical trial design, but I don't consider that a part of our routine practice. We can still use our usual metrics of symptoms and scans to monitor for disease progression in our patients.

O'REGAN: We are finding that a lot of cancers harbor *ESR1* mutations, depending on how you assess mutations, and they appear to be associated with resistance to nonsteroidal aromatase inhibitors. It is not clear with selective ER degraders (SERDS), particularly fulvestrant, how effective that drug is in patients whose tumors have *ESR1* mutations. The oral SERDs appear to have activity in this setting. From the initial data we have, the CDK4/6 inhibitors appear to be equally effective in wild-type disease versus [tumors] that harbor *ESR1* mutations. The MAINTAIN study with ribociclib, in a small number of patients, did show that ribociclib was not beneficial in cancers that were *ESR1*-mutant versus those that were wild-type. So, these mutations do have therapeutic implications. For now, using a SERD, either fulvestrant or an oral SERD, would make sense. There are also data showing that everolimus appears to be effective in cancers that have *ESR1* mutations; however, it is only retrospective data at this time.

OncLive®: How could oral SERDs potentially fit in this space, and what's been seen with them in clinical trials thus far?

GRAFF: Oral SERDs are really exciting. For patients, advocates, and the professional community, it [has] been disappointing to see some of the earliest data presented; however, trials have been looking at SERDs, selective ER modulators (SERMs), and other next-generation estrogen blockers as single agents, which is not how we use those drugs. What matters is the efficacy of SERDs in combination with other agents. All of these emerging drugs are going to have little differences in their adverse effect profile and tolerance. For example, the EMERALD study showed a high rate of GI toxicity [with elacestrant]. We may not see that same rate of toxicity with other agents as [data] emerge. It is important that we continue to look across [the drug] class at which agents are going to be the most tolerable for patients and figure out if these oral agents are going to give patients more independence, satisfaction, and a better experience than an injectable like fulvestrant, [which is] currently where we sit in terms of the third-line non-oral [therapy] for patients on estrogen blockade.

O'REGAN: There are a lot of [oral SERDs] in development, and we have many early-phase trials and 1 randomized trial [that included] patients with HR+ pretreated mBC which showed an advantage for the SERD elacestrant over standard ET. It was a fairly modest difference; however, these agents do appear to have efficacy in the HR+ BC that have *ESR1* mutations, which are increasingly more common. We are waiting for data in earlier stage settings. These agents offer an advantage over fulvestrant regardless, because they are oral, and they do not have the same bioavailability problems that fulvestrant has. But we really have to wait for the data. [Oral SERDs] show efficacy in the first-line metastatic setting, and they could become the go-to drugs, particularly in patients who have had prior aromatase inhibitors. There are also adjuvant studies being planned with these agents, which is interesting, because we do not have much compelling data in this setting. The other thing to mention about them is that there is some GI toxicity with them, more than what we see with fulvestrant, so it remains to be seen how much of a problem that is going to be. [It is] a very interesting class of drugs, because we have struggled with fulvestrant in terms of dosing and the frequency [at which doses] are given. Because [these agents] are oral, [they] should be easier to manage with regard to [dosing and frequency of dosing]. In the early-phase setting, there is encouraging data with CDK4/6 inhibitors, [which is] a partner that could be used in the first-line setting if these trials are positive.

OncLive®: How has the treatment landscape evolved in recent years for adjuvant settings?

GRAFF: [Clinical trial data in] the adjuvant setting for HR+ BC have been exciting. Trials such as RxPONDER and TAILORx have given us a lot more confidence in using genomic-derived assays and deciding who gets chemotherapy and who can safely omit chemotherapy in both lymph node–positive and lymph node–negative disease. Importantly, [this has] introduced some caveats into decision-making in pre-

menopausal [patients]. It has also given us a lot of additional insight and maybe just as many questions about the role of ovarian function suppression for premenopausal patients, [which] really broadens the landscape on how we treat those patients. Beyond that, trials like OlympiA and monarchE [are] expanding options for adjuvant therapy in patients with the highest-risk, HR+ breast cancer, beyond just hormonal blockade with agents such as abemaciclib in the case of the CDK4/6 inhibitors. [We also have] PARP inhibitors, including olaparib, for patients who have HR+ [disease and] *BRCA1/2* pathogenic variants and [for patients] with triple-negative [disease], as well.

O'REGAN: In the adjuvant setting, there are a number of trials, several of which have investigated CDK4/6 inhibitors in combination with ET. The monarchE study, which looked at abemaciclib [plus ET] in patients with really high-risk early-stage HR+ BC, had positive results. With longer follow-up, abemaciclib [plus ET] continues to show a significant benefit, particularly in patients with higher risk cancer. Based on somewhat immature survival data, the FDA did approve the use of abemaciclib in patients who had high-risk disease and a Ki-67 [level] of 20% or greater. It remains to be seen how important Ki-67 is, and many [clinicians] would consider using [abemaciclib] in patients who had high-risk disease, even if the Ki-67 [level] was less than 20%. The interesting thing is, there are 2 trials that reported [outcomes with] palbociclib. The PALLAS study, [which] was similar in design to the monarchE study but [included patients with] slightly less high-risk cancers, did not show any benefit for palbociclib [plus ET in the adjuvant setting]. The PENELOPE-B trial had an interesting design, because it [included] patients with HR+ BC who had received preoperative chemotherapy and randomly assigned [them] to palbociclib [or placebo] for a year. [The trial] initially showed a benefit for palbociclib at 2 and 3 years of follow-up. However, at 4 years [of follow-up], the curves had completely come together. So, it will be important to continue to follow the monarchE study, [in which] the curves continue [to] separate, which is encouraging. The [ongoing] NATALEE study is [investigating] 3 years [of treatment with] ribociclib [plus ET]. It will be interesting to see whether [the data from this] trial are positive or not. In addition to that, we have a SWOG study that is looking at everolimus in the early-stage setting, [but the data] have not [been] reported yet. We also have several trials in the pipeline looking at the oral SERDs, so [there are] a lot of very exciting trials coming down the pipeline.

OncLive®: What treatment considerations can be made regarding the use of CDK4/6 inhibitors?

GRAFF: After [treatment with] a CDK4/6 inhibitor in the metastatic setting, our standard of care is to consider things like disease, symptom burden, tolerance to therapy, and length of time on therapy and decide whether you're going to continue hormonal blockade with fulvestrant [or] alpelisib if [the tumor has] a *PIK3CA* mutation, [or] with everolimus if [the tumor] does not have a mutation. A clinical trial is [also an] option for patients in this space. We will see how the SERDs [and other investigational agents] fall into line. We've now seen data [from trials] of extended [treatment with] CDK4/6 inhibitors, which may not be ready for prime time, [but] they are commercially available. That is a discussion point, and [there is] a large phase 3 post-monarchE trial hoping to answer the question [of extended treatment with CDK4/6 inhibitors] accruing now. Sometimes, we use chemotherapy in patients whose disease] progresses rapidly [or in those] with heavy visceral disease burden.

O'REGAN: Most [clinicians] are doing either next-generation sequencing on tumor tissue or ctDNA analysis to see if a patient's cancer has a *PIK3CA* mutation. [Testing] can be done in the first-line setting or at the time of progression, because [the mutation] is not typically an acquired mutation. In patients whose tumors have a *PIK3CA* mutation, the general go-to drug is alpelisib, although it is a tough drug to give because of its toxicity, particularly the hyperglycemia that it causes. In the absence of a *PIK3CA* mutation, a lot of clinicians would consider everolimus or capecitabine, which is an oral chemotherapy. It is easy for patients to transition from ET to oral chemotherapy. The other big question out there is, does it make sense to continue a CDK4/6 inhibitor? We just saw the results of the first randomized trial, [namely], the MAINTAIN study. Investigators randomly assigned patients who had previously received a CDK4/6 inhibitor—in about 90% of cases, it was palbociclib in the first-line setting and at disease progression—to ET with or without ribociclib. The ET initially was fulvestrant, but they amended the trial to allow exemestane because of accrual difficulties. [The study] showed a significant advantage in terms of progression-free survival in patients who received ribociclib, with a difference of 2.5 months [among patients receiving placebo] to 5 months [in patients receiving ribociclib], which was statistically significant. It is the first study showing that continuing CDK4/6 inhibition actually makes sense. However, it was a randomized, phase 2 study, so [it included only] a small number of patients. The data were also analyzed based on whether the tumors had *ESR1* mutations or not. About 40% [of tumors] had *ESR1* mutations. The benefit of the ribociclib appeared to be restricted to patients whose tumors were wild-type for *ESR1*, [while] the patients with mutant *ESR1* did not benefit from ribociclib. There is still a lot of work to be done in this setting. There is also very interesting data with the AKT inhibitor capivasertib [combined with fulvestrant] from the FAKTION study, which continues to show a benefit in progression-free and overall survival. Clinical trials are a good option for patients, but we certainly have a number of [treatments available] in that setting. ■

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