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Implementation Research Takes On an Increasingly Essential Role in Oncology

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Clinical trials play a central role in oncology. The existence of solid, evidence-based disease management would not be possible without well-designed and well-conducted studies.

However, the publication of the objectively meaningful outcomes of such efforts in high-impact peer-reviewed medical journals does not necessarily result in the observations being implemented into routine clinical care. Several reasons may explain the substantial delays noted between the publication of highly relevant data and uptake of the results into practice.

Reasons include the following:

- The results alter well-established, widely accepted approaches to disease treatment.
- Changes may lead to potentially complex, unproductive, and expensive training for clinicians and staff.
- Changes may add time to a routine clinical encounter without adding remuneration.

- There may be a lack of local resources or supportive personnel to implement a new practice.

- Implementation may negatively affect personal and practice finances.

Conversely, if essential training is provided by a source outside the practice on the evidence-based treatment approach, effectively marketed clinical trial results that suggest a new approach to disease management may lead to a greater willingness to carefully evaluate and subsequently employ the tactic. Further, if such implementation is associated with a favorable financial return, a practice will almost certainly show more interest.

If a new anticancer agent demonstrates meaningful activity for new clinical indications in initial registration trials or in subsequent studies leading to regulatory approval, a drug manufacturer may be willing to spend considerable time (and money) to inform oncologists of this development. This may include providing assistance in obtaining third-party insurance coverage for

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individual patients or any required training related to drug administration and safety.

However, the situation is likely to be quite different if the trial is not associated with a sponsor or any other form of support necessary to optimize meaningful implementation. In the opinion of this commentator, an increasing

number of critically relevant observations and important study results published in peer-reviewed medical and oncology literature stagnate because there is no implementation plan or subsequent effort at encouraging clinical uptake.

Investigators of such projects may win awards for the quality of their research, subsequently obtain precious peer-reviewed grant funding, achieve promotion at their institution or elsewhere, or be awarded membership in prestigious national organizations, but their research findings themselves sometimes go nowhere. To be clear, there is no suggestion that this was ever the investigator's intent, but it may be the result of the absence of an effective implementation plan.

There is a critical need in the oncology community for meaningful, focused efforts in implementation research. Consider the following: A recent study looked at adherence to established guidelines for venous thromboembolism prophylaxis following pancreatic surgery. The study's results revealed that among 888 patients deemed eligible to receive such therapy upon hospital discharge, only 3.8% (34 individuals) "filled a prescription for venous thrombotic prophylaxis within 5 days of hospital discharge."¹ This is rather concerning considering that data from both clinical guidelines and trials support the use of such prophylaxis after major surgery involving the abdominal cavity.^{2,3}

How might surgeons be encouraged to use and inform patients of a known effective and safe measure to reduce the risk of this serious surgery complication?

A second example within the realm of cancer surgery suggests the need to understand and positively affect findings from thoracic oncology studies. A specific example is a retrospective cohort analysis of individuals with stage IB to IIIA non-small cell lung cancer (NSCLC) in the ALCHEMIST Screening Trial (NCT02194738) who did not subsequently participate in an adjuvant therapy trial and who had a cancer measuring at least 4 cm in diameter, with or without positive lymph nodes.⁴

Among 2833 patients (53% women), 95% were underwent surgical resection, but only 53% were found to have had "adequate lymph node dissection."⁴ A similarly low percentage of individuals (57%) received any adjuvant therapy, with only 44% receiving a minimum of 4 cycles of platinum-based chemotherapy, despite solid evidence revealing the value of such treatment. Although the authors of this provocative and concerning analysis appropriately conclude that "efforts are needed to optimize the use of proven therapies for early-stage NSCLC"⁴ the question is how do we effectively implement efforts to change what for many oncologists appears to be current routine surgical practice?⁴

It is not difficult to find documented evidence outside the realm of surgical oncology that challenges the oncology community to focus research on strategies to more effectively improve outcomes or enhance patients' quality of life. Topics highlighted in recent publications include disparities in electronic screening for cancer-related psychosocial distress⁵ and inadequacies in

performance guideline–recommended geriatric assessments.⁶

In the opinion of this commentator, there must be a more prominent role in our community's investigative agenda for implementation research designed to discover and activate strategies to encourage widespread use of new, effective approaches to cancer management. ■

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CART-ddBCMA Generates Deep Responses in Relapsed/Refractory Multiple Myeloma

RYAN SCOTT

CART-ddBCMA elicited an overall response rate (ORR) of 100% in patients with previously treated relapsed/refractory multiple myeloma (n = 31), according to data from a phase 1 trial (NCT04155749) presented at the 2022 ASCO Annual Meeting.¹ Notably, patients achieved responses that were found to deepen over time, according to Matthew J. Frigault, MD.

Among those who responded to treatment, 94% experienced a very good partial response or better rate of 94%, and 71% experienced a complete response (CR)/stringent CR (CR/sCR). Of the 24 patients who had a minimum follow-up of 6 months and a median follow-up of 13.3 months, 92% still responded to treatment at 6 months. Of the 16 patients who had a minimum follow-up of 12 months and a median follow-up of 17.7 months, 94% had an ongoing response at 6 months and 69% were still responding at 12 months.

“CART-ddBCMA appears to be a highly effective, durable CAR T-cell therapy for highly refractory patients with high-risk features,” said Frigault, who is the administrative director of Cellular Therapy Service at Massachusetts General Hospital and an assistant professor of Medicine at Harvard Medical School. “It was [well] tolerated, and the pivotal phase 2 study [NCT05396885] should hopefully recapitulate the findings [we observed] from [the] phase 1.”

In an interview with *OncLive*®, Frigault discussed the findings from a phase 1 trial investigating the safety and efficacy of CART-ddBCMA in patients with multiple myeloma in

whom all previous lines of treatment had failed and shared additional research opportunities for the CAR T-cell therapy.

***OncLive*®: What was the design of the phase 1 trial evaluating CART-ddBCMA in patients with relapsed/refractory multiple myeloma?**

Frigault: [At the 2022 ASCO Annual Meeting,] we presented data from the phase 1 trial of CART-ddBCMA; [this was] a first-in-human, dose-escalation study, where we examined how CART-ddBCMA would work in relapsed/refractory multiple myeloma.

This was [done in] a patient population that had to have been exposed to all 3 major classes of multiple myeloma therapy: [a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 antibody]. They had to have [received] at least 3 prior lines of therapy or be triple refractory, and they needed [to have] measurable disease at the time of treatment.

We [examined the therapy at] 2 dose levels: 100 x 10⁶ CAR-positive cells and 300 x 10⁶ CAR-positive cells. The most impressive component of all this was that we saw an 100% ORR [with the therapy] across both dose levels. These were exciting data, and we look forward to expanding this into a pivotal [phase 2] study.

What else should be known about the population examined in the trial?

This was a heavily pretreated group of patients. They had [received] a

median of 5 prior lines of therapy, and they had multiple high-risk features, including high disease burden. In particular, something that we know [correlates with] a poor prognosis for durability of responses, is extramedullary disease; 39% of patients had extramedullary disease at the time of treatment. [Furthermore], 68% of patients were penta-refractory, meaning that they were refractory to all 3 major drug classes, including 2 drugs from 2 of those classes.

Could you expand on the efficacy data reported during the meeting?

We saw impressive findings. [I mentioned that the therapy elicited] an ORR of 100%, [which included] a 71% CR/sCR rate. The interesting thing [to note] is that these responses continued to deepen over time.

Although we had a median follow-up of 12.1 months for the total patient population, if you looked at patients who [had] beyond 12 months [of follow-up], the 16 patients with a median follow-up of 17.7 months, half of those patients had extramedullary disease, which is a higher-risk prognostic factor. Despite that, [69% of those] patients were still in an ongoing response.

We are still waiting for the data to mature, but [this] is promising for these patients.

What were the safety data reported with CART-ddBCMA?

Something that was encouraging was the fact that [CART-ddBCMA] was very well tolerated. Only 1 grade

3 event of immune effector cell-associated neurotoxicity syndrome [(ICANS) occurred in someone who received the therapy at 100 x 10⁶ CAR-positive cells], which is our recommended phase 2 dose. All [cases of] cytokine release syndrome [CRS] was grade 1 or 2 [at 100 x 10⁶ CAR+ cells]. CRS [cases] were all managed with tocilizumab [Actemra] and steroids.

Importantly, we did not see any atypical neurotoxicity, [like] the Parkinson-like syndrome that we are seeing with some other BCMA-directed therapies. It is reassuring

that this treatment was very tolerated and appeared to be safe.

What are the next steps for CART-ddBCMA?

I am hoping that the pivotal [phase 2] study can begin enrollment by the end of 2022. We have a lot of patients who need highly effective BCMA-directed therapies. Currently, there are not sufficient slots for manufacturing, and there are many patients who would substantially benefit from CART-ddBCMA and other BCMA-directed CAR T-cell therapies.

This product can significantly impact access and could improve outcomes for patients, many of which are passing away prior to getting their slot allocation. I am optimistic to be able to enroll [patients to this] pivotal study and potentially see a new product on the block that can benefit patients. ■

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Retrospective Analysis Highlights Disparities in Germline Testing in Prostate Cancer

MEGAN HOLLASCH

Widening disparities in genetically informed cancer care prompted investigators to conduct a study of germline testing (GT) rates among racially diverse groups of men with prostate cancer, which highlighted the importance of GT in prostate cancer treatment.

A retrospective analysis of patients used the 14-gene prostate cancer panel to evaluate 427 men: African American (n = 237; 56%) and White (n = 190; 44%). The overall pathogenic/likely pathogenic (P/LP) variant rate was 8.2%.

Lower P/PL variant rates were reported among African American men (5.91%) vs White men (11.05%; $P = .05$). Further, rates of variants of uncertain significance (VUS) were 25.32% vs 16.32%,

respectively ($P = .02$). Multiple VUSs were reported among 5.1% and 0.53% individuals, respectively ($P = .008$).¹

“The idea is to not shy away from identifying the disparities. I think in the past there has been a stigma, but we can’t solve the problem by not looking at it” said Carrie Horton, MS, CGC. “It’s been exciting to see Ambry [Genetics] rally behind a lot of health disparity research and I hope it can motivate other groups to do the same thing.”

In an interview with *OncologyLive*®, Horton, a senior clinical research specialist who designs and conducts studies at Ambry Genetics, discussed how the findings of the retrospective analysis of genetic testing in prostate cancer care will guide future research and influence the steps community oncologists can take to increase testing rates.

What was the catalyst for this investigation?

This specific study came about when the lead principal investigator Veda Giri, MD, a medical oncologist at Thomas Jefferson University Hospital, approached [Ambry Genetics]. She had seen a paper that we had done previously looking at the genetic testing results in individuals with prostate cancer, but it wasn’t selected for any one race or ethnicity. Since African Americans are more likely to develop and die of prostate cancer, there’s a real area of opportunity for targeted therapeutics in that group. Therefore the need for accurate genetic testing is even more important.

[Giri] came to us and wanted to see if we could use our existing data set and design a protocol with the intent to evaluate disparities between African American males with prostate cancer and White males. In doing that,

we enriched our cohort for African Americans so that our sample was about equal. In most of the past studies looking at genetic testing in prostate cancer, identifying these disparities was a byproduct and not the whole focus of the study; there were a lot of inconsistencies [such as] the genes tested, not every [individual] had prostate cancer, or only 10% of the population was African American and 90% were other ethnicities. This study was specifically to evaluate the differences we're seeing in genetic testing results in African Americans compared with White males.

We were excited to be able to help Giri with this because we have such a huge data set which is one of the benefits of working with Ambry [Genetics]; we can leverage that volume to find meaningful results.

What methods were used throughout the study?

We had our existing data set results of genetic testing in White males with prostate cancer from 2016 to 2017 and [all individuals] had the same multigene panel test—a 14-gene panel targeted for hereditary prostate cancer. We had the population needed for White individuals but wanted to make sure that we enriched for African Americans as well, so we expanded our timeline and our recruitment for African Americans through 2020.

We also looked at personal history and reviewed the clinic notes that were provided, [such as] pathology [reports] to see if there were any differences in when [individuals] were being sent for testing. [For example,] we wanted to see if African Americans were being sent only when they were extremely high risk but didn't find a huge difference in who was being sent for testing in terms of the severity of the presentation. However, we saw a

stark difference in the positive and VUS rates, where White individuals were almost twice as likely to have a positive result compared with African Americans. The VUS rate was half in White individuals compared with African Americans.

Was there anything particularly surprising in the findings?

There's been precedent that we see a higher VUS rate in underrepresented populations across most genetic testing indications. However, one thing that was fairly novel [in this study] was that we found approximately half the positive findings in genes exclusive to White individuals. We need to improve our interpretation of the existing variants, and the fact that half the genes were exclusive to White individuals signals to me that perhaps there's some room to improve our gene discovery.

We may not have found all the predisposition risk genes for prostate cancer in African Americans yet; there's 2 genes where the positive rate is driven by a single mutation in White individuals. So, maybe there is a gene that has a mutation in an underrepresented group, and we just haven't been able to find it because that's not who has historically been presented for testing.

What effect can these data have for the testing moving forward? What action steps would you like to relay to your colleagues to take to help address these disparities?

There's a shift now into focusing on identifying disparities and when we set out to shine a spotlight on the inequities, it allows us to figure out what's really going on and provides

an opportunity to improve and mitigate those disparities. I'm hoping this helps motivate [individuals] to revisit the idea of gene discovery in diverse populations and to come up with new ways for varying interpretation that are agnostic of race and ethnicity, that don't rely on volume in order to accurately interpret variants. The more accurate we can get a test, especially in the hereditary prostate cancer space, the more opportunities there are for targeted medicine for PARP inhibitors such as olaparib [Lynparza].

It's a multi-level [issue]. At the base level, we must] try to come up with better ways to engage underrepresented communities in genetic testing. We've seen studies that showed that underrepresented groups are preferred for genetic testing and adopt genetic testing at lower rates. [Solutions may include] looking more at genetic testing recruitment through nontraditional settings, such as health fairs or community gatherings. We first need to get [individuals] in the door to even get their result.

A more diverse population improves the accuracy that we can interpret the results with both in reference population databases, but also in the clinical and research cohorts. For laboratorians, I would encourage them to look at health disparities and what to do to circumvent existing gaps in evidence. For example, there are newer ways to derive functional evidence that does not rely on the accumulation of observing a variant multiple times.■

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Pembrolizumab Plus Chemoradiation Misses EFS End Point in Head and Neck Squamous Cell Carcinoma

CAROLINE SEYMOUR

Pembrolizumab (Keytruda) plus concurrent chemoradiation followed by pembrolizumab maintenance did not lead to a statistically significant improvement in event-free survival (EFS) vs concurrent chemoradiation alone in patients with unresected locally advanced head and neck squamous cell carcinoma (HNSCC), missing the primary end point of the phase 3 KEYNOTE-412 trial (NCT03040999).¹

At the final analysis of the study, there was a numerical improvement in EFS in patients who received the addition of pembrolizumab, but the results did not meet statistical significance according to the prespecified statistical plan.

Full results from the study will be presented at an upcoming medical meeting.

“There have been limited advances for patients with locally advanced HNSCC and unfortunately, these results suggest that this disease remains very challenging to treat,” Eliav Barr, MD, senior vice president, head of global clinical development and chief medical officer, Merck Research Laboratories, said in a news release. “We are proud of the significant role pembrolizumab plays in the treatment of certain later stages of HNSCC, and we are committed to investigating

pembrolizumab-based regimens for this debilitating type of cancer in earlier stages of disease. We are grateful to the patients and investigators for their participation in this study.”

KEYNOTE-412 is a randomized, double-blind, phase 3 trial evaluating pembrolizumab with concurrent chemoradiation, followed by pembrolizumab as maintenance therapy for the treatment of patients with unresected locally advanced HNSCC.² The trial enrolled approximately 780 patients with newly diagnosed oropharyngeal or larynx/hypopharynx/oral cavity squamous cell carcinoma. Eligibility criteria stipulated patients be eligible for definitive chemoradiation, provide tissue for PD-L1 biomarker analysis, and have evaluable tumor burden and an ECOG performance status of 0 or 1.

Patients were excluded if they were currently participating or had participated in a study with an investigational agent or had used an investigational device within 4 weeks of the first dose of study therapy, had received prior therapy with a PD-1, PD-L1, or PD-L2 inhibitor or with an agent directed to another co-inhibitory T-cell receptor; had received a live vaccine within 30 days prior to the first dose of study therapy, and had prior systemic therapy, targeted therapy, radiotherapy

treatment, or radical surgery for head and neck cancer.

The primary end point of the study was EFS, and key secondary end points included overall survival and safety.

Investigators randomly assigned to 200 mg of pembrolizumab every 3 weeks in combination with cisplatin and radiation, followed by pembrolizumab as maintenance therapy for approximately 1 year or placebo plus cisplatin and chemoradiation, followed by placebo.

Investigators will continue exploring pembrolizumab alone and in combination with other agents, including in the phase 3 KEYNOTE-689 trial (NCT03765918). Investigators in that trial evaluating the agent for neoadjuvant and adjuvant treatment in patients with resectable locally advanced HNSCC. ■

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CDK4/6 Inhibitors Could Fill Treatment Void for Patients with HR+/HER2- Early Breast Cancer

KYLE DOHERTY

CDK4/6 inhibitors have the potential to fill an unmet need in the treatment of patients

with early-stage breast cancer, especially for those who develop primary resistance to endocrine therapy, according to a presentation by Joyce O’Shaughnessy, MD, at the 21st

Annual International Congress on the Future of Breast Cancer® East.¹

“We still have a lot of work to do in hormone receptor [HR]-positive/HER2-negative breast cancer,”

O'Shaughnessy, the Celebrating Women Chair in breast cancer research, Baylor University Medical Center, Texas Oncology, US Oncology, said during the presentation. "We have the issue of primary endocrine therapy resistance. Some of those patients are chemotherapy sensitive, but some of them are [also] cross-resistant to chemotherapy. In the first couple years of being diagnosed with HR-positive/HER2-negative breast cancer, patients start recurring in spite of optimal single-agent endocrine therapy. In the first 2-3 years after a diagnosis of HR-positive/HER2-negative breast cancer, [there] are the highest annual odds of recurrence. Those are the patients with primary endocrine therapy-resistant disease that we do not have good tools for."

The CDK4/6 inhibitors palbociclib (Ibrance) and abemaciclib (Verzenio) have previously displayed striking data in the metastatic setting, O'Shaughnessy explained. Thus, investigators made it a priority to evaluate the agents in the adjuvant setting. The agents are similar, though abemaciclib inhibits significantly more kinases compared with palbociclib and can also be given continuously because it is not as myelosuppressive, she noted.

Palbociclib Not the Answer for HR+/HER2- Early Breast Cancer

The phase 3 PALLAS trial (NCT02513394) compared the efficacy of palbociclib plus adjuvant endocrine treatment with that of endocrine treatment alone among patients with stage II-III HR-positive/HER2-negative breast cancer. Eligible patients underwent prior surgery, with or without chemotherapy or radiotherapy, were within 12 months of their diagnosis, and were within 6 months of starting adjuvant endocrine treatment. Palbociclib was administered at

a dose of 125 mg daily for 3 weeks on and 1 week off, plus standard endocrine therapy. Patients in the control group received standard endocrine therapy alone. The primary end point was invasive disease-free survival (iDFS).²

At a median follow-up of 31 months, no significant difference was observed in terms of 4-year iDFS. The 4-year iDFS was 84.2% and 84.5% in the combination and monotherapy arms, respectively (HR, 0.96; 95% CI, 0.81-1.14; $P = .65$).

In the phase 3 PENELOPE-B trial (NCT01864746) patients with HR-positive/HER2-negative breast cancer with residual disease received palbociclib plus endocrine therapy or placebo plus endocrine therapy following neoadjuvant chemotherapy and surgery. Similar to PALLAS, at a median follow-up of 42.8 months, no significant difference in iDFS was reported between the 2 arms (HR, 0.93; 95% CI, 0.74-1.17; $P = .525$).³

"The curves have come together at 4 years," O'Shaughnessy said. "There was this intriguing split in the curve early on, but it came back together. This raises the question, in a high-risk population, of whether a longer duration of therapy might have benefited these patients."

Abemaciclib Shows Greater Promise

In the phase 3 monarchE trial (NCT03155997), patients with high-risk HR-positive/HER2-negative early breast cancer were randomly assigned 1:1 to received either abemaciclib plus standard of care endocrine therapy or endocrine therapy alone. Patients were divided into cohorts based on high-risk clinical pathological features (cohort 1) or high-risk Ki-67 scores (cohort 2). Patients in the investigational arm were treated with abemaciclib 150 mg twice daily continuously without a break.⁴

At a median follow-up of 27 months, patients in the intent-to-treat

population who received abemaciclib experienced a 30.4% reduction in the risk of experiencing an iDFS event compared with those who received endocrine therapy alone (HR, 0.696; HR, 95% CI, 0.588-0.823; $P = .0001$). There was also an absolute difference in the 3-year iDFS rates of 5.4% that favored the abemaciclib arm. The distant recurrence-free survival risk was reduced by 31.3% in abemaciclib arm (HR, 0.687; 95% CI, 0.571-0.826; $P < .0001$) with an absolute difference of 4.2% between the 3-year rates.

Additionally, among patients in the intent-to-treat population who received neoadjuvant chemotherapy, the 2-year iDFS rate also favored the abemaciclib arm compared with the endocrine therapy arm at 87.2% and 80.6%, respectively (HR, 0.61; 95% CI, 0.47-0.80; log-rank $P < .001$). The 2-year distant disease-free survival rates were 89.5% and 82.8%, respectively (HR, 0.61; 95% CI, 0.46-0.81; log-rank $P < .001$).

Similarly, patients in the intent-to-treat population with high Ki-67 ($\geq 20\%$) experienced a 33.7% reduction in the risk of developing an iDFS event when they were treated with abemaciclib (HR, 0.663; 95% CI, 0.524-0.839; $P = .0006$). The absolute difference in 3-year iDFS rates between the arms was 6.0%.

Notably, patients treated with abemaciclib in cohort 1 who also had high Ki-67 experienced a 37.4% reduction in the risk of developing an iDFS event (HR, 0.626; 95% CI, 0.488-0.803; $P = .0002$). The absolute difference in 3-year iDFS rates between the arms was 7.1%.

"The FDA wanted to take a look at the highest-risk population," O'Shaughnessy said. "The cohort 2 patients were a protocol amendment and started enrolling a bit after cohort 1, so the follow-up was not as great. The [cohort 1 patients

enrolled from the beginning] were a very high anatomic risk group, and the FDA wanted to look at those that were highly proliferative in addition. Basically, [we found] that the higher the risk, the higher the impact of abemaciclib. This is the group that led to the FDA [approval] for adjuvant abemaciclib.”

High Ki-67 is prognostic of a worse outcome, but it is not predictive of abemaciclib benefit, O’Shaughnessy stressed. Patients derived a benefit from treatment with abemaciclib regardless of Ki-67 score.

In October 2021, the FDA approved abemaciclib for the adjuvant treatment of adult patients with HR-positive/HER2-negative, node-positive early breast cancer at a risk of recurrence and a Ki-67 score of at least 20%.⁵

The Future of CDK4/6 inhibitors in HR+/HER2- Early Breast Cancer

CDK4/6 inhibitors are currently under investigation in patients with HR-positive/HER2-negative early breast cancer in multiple ongoing clinical trials. The phase 3 ADAPTLate trial (NCT04565054) is evaluating delayed extended abemaciclib in patients with high-risk disease. Adjuvant abemaciclib is also being examined in high-risk patients in the phase 3 POETIC-A trial (NCT04584853) Finally, the phase 2 CARABELA trial (NCT04293393) is

investigating neoadjuvant abemaciclib plus endocrine therapy among patients with intermediate or high-risk disease.¹

Neoadjuvant treatment with CDK4/6 inhibitors such as abemaciclib has the potential for clinical utility, O’Shaughnessy noted. In the phase 2 neoMONARCH trial (NCT02441946), 66.1% of patients who received abemaciclib plus anastrozole experienced complete cell cycle arrest (Ki-67 < 2.7%) at 2 weeks compared with 58.8% and 14.8% among patients who received abemaciclib monotherapy and anastrozole monotherapy, respectively.⁶ Similarly, in the phase 2 PALLET trial (NCT02296801), 90% of patients who received palbociclib plus letrozole achieved complete cell cycle arrest at week 14 compared with 59% who received letrozole monotherapy ($P < .001$).⁷

“If you have a patient who you know is going to be a good candidate [for the monarchE regimen], but they are not surgical candidates at that moment, and they are either not chemotherapy candidates or the biology of [their] disease is such that you do not feel they will benefit from chemotherapy, I have been starting the monarchE treatment with an aromatase inhibitor plus abemaciclib preoperatively to down size, get them to surgery, and then continue the adjuvant therapy,” O’Shaughnessy said. ■

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