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- Antibody–Drug Conjugates for Ovarian Cancer
- Checkpoint Inhibitors & Non–Small-Cell Lung Cancer
- Palliative Care for Cancer Patients
- Interview with Dr. Jennifer Brown on the ALPINE Trial

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FROM the Editor

In Volume 1 of *Clinical Oncology Update*, some of the key advances over the last year in the areas of ovarian and lung cancers and palliative care are reviewed by invited experts, while NEJM Journal Watch editors present important developments from two major oncology meetings. Finally, an interview with Dr. Jennifer Brown, the lead author of the phase 3 ALPINE study, provides insight into the practice-changing findings of this trial in patients with relapsed/refractory chronic lymphocytic leukemia or small lymphocytic lymphoma.

The evolving role of antibody–drug conjugates in platinum-resistant advanced/recurrent epithelial cancers of the ovary, fallopian tube, or peritoneum is reviewed by Dr. Linda Duska. Her discussion focuses on targeting folate receptor α, which is expressed in approximately 80% of patients, making it an attractive target with several candidate agents in trials.

Drs. Ryan Gentzler and Richard Hall update the evolving role of immune checkpoint inhibitors in the neoadjuvant and adjuvant settings for patients with non–small-cell lung cancer. They highlight some of the promising results from phase 3 studies and discuss the challenges in making individual patient management decisions given the lack of comparative data with regards to adjuvant versus neoadjuvant approaches.

Dr. Mellar Davis provides an update in the evolving role of palliative medicine in oncology care. He focuses on the critical area of goals-of-care conversations, providing a framework for these discussions to be integrated into patient management and methods to ensure better communication within the broader care team.

Dr. William Gradishar and guest author Dr. Erika Hamilton review some of the key reports from the 2022 San Antonio Breast Cancer Symposium, including phase 3 data supporting the use of trastuzumab deruxtecan in patients with HER2-positive, metastatic breast cancer in the second-line setting.

Dr. David Ilson provides updates from the 2023 ASCO Gastrointestinal Cancers Symposium, including a study that may inform practice in advanced hepatocellular cancer, with provocative data suggesting that liver-directed stereotactic body radiotherapy may improve survival when added to sorafenib.

We hope the topics covered in this issue of *Clinical Oncology Update* will provide a useful and concise overview for the busy clinical oncologist.

Robert Dreicer, MD, MS, MACP, FASCO, Editor

Dr. Dreicer is Deputy Director of the University of Virginia Comprehensive Cancer Center and Professor of Medicine and Urology at the University of Virginia School of Medicine, Charlottesville. He also serves as Section Head of Medical Oncology and Co-Director of the Paul Mellon Urologic Institute. Dr. Dreicer reports consultant/advisory roles with Astellas, AstraZeneca, Aveo, Bayer, EMD Serono, Exelixis, Gilead, Hinova, Hengrui, Janssen, Merck, Myovant, Pfizer, Seagen, Sanofi Genzyme, and Tavanta; royalties from MSN Pharmaceuticals; and grant/research support from Exelixis, Arvinas, Seagen, and Gilead. He serves on the editorial boards of *Clinical Genitourinary Cancer* and *Current Urology Reports* and is a member of the Communications Committee for the American Society of Clinical Oncology.

Topic Update

The Evolving Role of Antibody–Drug Conjugates in Ovarian Cancer

Linda R. Duska, MD, MPH

Advanced and recurrent epithelial cancer of the ovary, fallopian tube, or peritoneum (EOC) remains a lethal disease, despite recent progress with the incorporation of poly(adenosine diphosphate [ADP]–ribose) polymerase (PARP) inhibitors and bevacizumab into treatment strategies. Most patients with advanced/recurrent EOC will develop platinum resistance; outcomes for patients with platinum-resistant EOC (PROC) are poor, with low response rates to traditional chemotherapy even when combined with bevacizumab (*J Clin Oncol* 2014; 32:1302). Novel therapies are needed that prolong life but also maintain quality by minimizing the overlapping toxicities of prior chemotherapy regimens.

The development of molecular targeted therapy for EOC has been challenging. High-grade serous ovarian cancer (HGSOC), the most common histologic subtype, has a low mutational burden and, except for the nearly universal mutation of *TP53*, has few common gene mutations (*Cancer Manag Res* 2020;12:10423). While underlying defects in homologous recombination in HGSOC are common and have led to the successful implementation of PARP inhibitors in several treatment settings, the effective use of immunotherapy and targeted agents has remained elusive.

In the context of these challenges, there has been significant interest in the use of antibody–drug conjugates (ADCs) in patients with EOC. This update summarizes recent advances in this area, particularly with regard to targeting ovarian cancer expressing folate receptor α.

Basics of ADCs

ADCs are composed of three elements: a monoclonal antibody that binds to an antigen on the tumor cell surface, a cytotoxic drug "payload," and a linker. High doses of cytotoxic agent are delivered by the antibody to a tumor-associated antigen, directly targeting the tumor without associated systemic toxicity. Thus, cytotoxic drugs can be used at concentrations that cannot be given systemically, with high doses of drug delivered directly to the tumor.

Folate Receptor α

Folate receptor (FR) α is a transmembrane glycoprotein that facilitates the unidirectional transport of folate into cells via receptor-mediated endocytosis. FRα is expressed by approximately 80% of EOCs, particularly HGSOC, and serous endometrial cancers. Additionally, FRα expression is retained in recurrent/metastatic tumors and is not significantly altered in response to chemotherapy. The expression of FRα is more restricted in normal adult tissues. Thus, this target is ideal for patients with EOC. Early approaches to targeting FRα evaluated the small molecule folate–cytotoxic agent conjugate vintafolide and a nonconjugated humanized antibody (farletuzumab), both with disappointing clinical activity.

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Disclosures: Dr. Duska reports an advisory board role with Regeneron Scientific; a data safety monitoring board role with Inovio; and external grant support from Harpoon Therapeutics, GlaxoSmithKline, Plexxikon, the GOG Foundation, Eisai, Clinipace, Ludwig Institute for Cancer Research, Seattle Genetics, Corcept Therapeutics, the Henry M. Jackson Foundation, Johns Hopkins University, NRG Oncology Foundation, ECOG-ACRIN Cancer Research Group, Parexel, University of Oklahoma, Arch Oncology, CE3, Duke University, Psi Pharma Support America, Merck Sharp & Dohme, K-Group Beta, OncoQuest, NRG, PharmaMar, Pfizer, Lycera, Aduro Biotech, Syndax, and Leap Therapeutics. Dr. Duska is an author for UpToDate, has produced educational content for Clinical Care Options, and is a scientific editor for the *British Journal of Obstetrics and Gynaecology*.

Mirvetuximab Soravtansine

In contrast, the early clinical experience with the ADC mirvetuximab soravtansine (MIRV) was encouraging. MIRV is composed of an FRα-binding antibody, a cleavable linker, and a potent tubulin-targeting agent. The cleavable linker design allows active cytotoxic metabolites to diffuse into neighboring cells, creating a "bystander" killing effect. In the phase 1 study of MIRV in 46 patients with PROC (NCT01609556), there was an objective response rate (ORR) of 26%, including 1 complete response and 11 partial responses; the ORR was 39% in patients who had received ≤3 prior lines of therapy (*J Clin Oncol* 2017; 35:1112). Equally important, the safety profile was manageable, with primarily mild adverse events (AEs) — most commonly diarrhea, blurred vision, nausea, and fatigue.

The subsequent randomized, phase 3 trial of MIRV versus physician's choice chemotherapy (FORWARD I; NCT02631876) did not meet its primary end point of progression-free survival (PFS), but there were some important lessons learned, most notably the need for appropriate biomarker eligibility (*Ann Oncol* 2021; 32:757). In the subgroup of patients with high FRα expression, antitumor activity was noted across all efficacy end points; due to study design, this finding was not statistically significant. Analysis of patient-reported outcomes supported MIRV over chemotherapy, showing improvements across multiple quality-of-life measures (*Ann Oncol* 2022; 33:S790).

Studying MIRV in Patients with High Biomarker Expression

Lessons learned from FORWARD I resulted in a phase 2 study evaluating efficacy and safety of MIRV in 105 patients with FRα-high PROC who had received ≤3 prior lines of therapy (SORAYA, NCT04296890; *J Clin Oncol* 2023 Jan 30; [e-pub]: DOI:10.1200/JCO.22.01900). In this trial, the ORR was 32.4% including 5 complete responses and 29 partial responses, with a median response duration of 6.9 months. Blurred vision, keratopathy, and nausea were the most common treatment-related AEs. Based on these results, in late 2022, the Food and Drug Administration (FDA) granted accelerated approval to MIRV for patients with high-FRα–positive PROC who have received 1 to 3 prior systemic regimens, with an approved companion test for FRα. The MIRASOL trial is a randomized, phase 3 trial of MIRV versus investigator's-choice chemotherapy in PROC with high FRα; the trial has completed accrual and results are pending (NCT04209855).

What's Next for ADCs in Ovarian Cancer

What is the future for ADCs in EOC? For MIRV, there are opportunities to consider combinations, as preclinical data suggest that MIRV potentiates the activity of conventional agents. In the multiple-arm, phase 1b/2 study FORWARD II, MIRV is being combined with bevacizumab, carboplatin, pegylated doxorubicin, pembrolizumab, and carboplatin plus bevacizumab (NCT02606305). Mature data of the combination with bevacizumab were reported at the International Gynecologic Cancer Society (IGCS) 2022 meeting and showed an ORR of 44% in a mixed population (platinum-resistant, 75%; prior bevacizumab, 52%; prior PARP, 27%; *Int J Gynecol Cancer* 2022; 32:A7–A8). There are also opportunities for considering MIRV at other times in the treatment spectrum, including a phase 2 trial evaluating the efficacy of MIRV plus carboplatin in first-line therapy (NCT04606914), and a randomized, phase 3 trial comparing the maintenance options of bevacizumab versus bevacizumab plus MIRV (NCT05445778).

While these opportunities are exciting, they are only relevant for the less than half of patients with EOC who have high-FRα–expressing disease. In SORAYA, only 36% of screened patients had tumors that were FRα-high. For the remaining patients, the search for novel therapies continues; in the case of ADCs, this means a need for more viable and ubiquitous surface molecules to target. Currently, there are several ADCs in early development that utilize alternative targets and cytotoxic payloads and may show promise, either as single agents or in combination (*Int J Gynecol Cancer* 2023; 33:420).

Until new targets are found, MIRV offers a well-tolerated, effective treatment for appropriate patients with EOC tumors that highly express FRα. *It is time for us to add this novel agent to our treatment armamentarium.* Given the enthusiasm for the development of ADCs across the spectrum of disease, we can anticipate more opportunities to improve the lives of our patients in the near future.

Topic Update

Checkpoint Inhibitors in Operable NSCLC: New Adjuvant and Neoadjuvant Approaches to Treatment Are Improving Outcomes

Ryan D. Gentzler, MD, MS, and Richard Hall, MD, MS

For over 15 years, platinum doublet chemotherapy provided modest benefits in survival for stages IB to IIIA non–small-cell lung cancer (NSCLC) following surgical resection (*J Clin Oncol* 2008; 26:3552). However, even after more than a decade of clear support for its postoperative use, only 57% of eligible patients received at least one dose of adjuvant chemotherapy, according to a 2022 analysis (*JAMA Oncol* 2022; 8:717). Adjuvant osimertinib, approved in 2020, was the first new adjuvant NSCLC therapy to become available in over a decade, but its use is restricted to patients whose tumors harbor common *EGFR*-activating mutations (*N Engl J Med* 2020; 383:1711). Thus, to improve survival outcomes in the majority of NSCLC patients, new approaches incorporating checkpoint inhibitors into adjuvant and neoadjuvant treatment paradigms will be crucial. This update details recent progress toward this goal.

Efficacy of Adjuvant Immunotherapy

Checkpoint inhibitors targeting programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1) expression, such as pembrolizumab and atezolizumab, respectively, have been widely employed in the treatment of advanced metastatic NSCLC, either alone or in combination with chemotherapy.

In October 2021, the FDA approved atezolizumab as the first adjuvant checkpoint inhibitor in stage II–IIIA NSCLC patients whose tumors had PD-L1 expression ≥1% and were negative for *EGFR* and *ALK* alterations. In the phase 3 IMpower010 trial, among patients with resected stage IB–IIIA NSCLC of any histology who received prior platinum-based adjuvant chemotherapy, atezolizumab improved median disease-free survival (DFS) over best supportive care (BSC) in stage II–IIIA patients with PD-L1 expression ≥1% (median DFS, not reached vs. 35.3 months, respectively; hazard ratio, 0.66; *Lancet* 2021; 398:1344). In a subset analysis, the DFS improvement was more striking in the patients with PD-L1 expression ≥50% (atezolizumab vs. BSC: not reached vs. 35.7 months; HR, 0.43).

Just over a year later, in January 2023, pembrolizumab received FDA approval for adjuvant therapy in stage IB–IIIA NSCLC patients regardless of PD-L1 expression. In the phase 3 PEARLS/KEYNOTE-091 study, among patients with resected stage IB–IIIA NSCLC of any histology and any PD-L1 expression who received prior platinum-based adjuvant chemotherapy, pembrolizumab significantly extended median DFS over placebo (53.6 months vs. 42.0 months; HR, 0.76; *Lancet Oncol* 2022; 23:1274). In the subgroup with PD-L1 ≥50%, statistical significance was not reached (HR, 0.82). For the secondary end points of DFS in PD-L1 ≥1% and overall survival (OS), follow-up is ongoing.

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Disclosures: Dr. Hall reports advisory board fees or compensation from Bristol Myers Squibb, Oncocyte, and Jazz Pharmaceuticals; and external grant support and research funding to his institution from the National Cancer Institute, Daiichi Sankyo, Genentech, Lilly, and Merck.

Both the IMpower010 and PEARLS/KEYNOTE-091 studies demonstrated improved DFS among NSCLC patients of any histology who underwent both surgical resection and adjuvant chemotherapy prior to receipt of a checkpoint inhibitor. Ultimately, these studies will need to be evaluated in the context of ongoing neoadjuvant studies that have shown promising results as well.

Neoadjuvant Combination Approaches

Advantages of neoadjuvant over adjuvant immunotherapy approaches to surgically resectable NSCLC include earlier systemic treatment, more feasible delivery of prescribed therapy, potential for downstaging, and opportunities to assess disease response, which has prognostic value.

Based on promising results of a phase 1 trial of three cycles of neoadjuvant single-agent nivolumab (*N Engl J Med* 2018; 378:1976), the randomized, phase 3 CheckMate 816 trial was conducted to evaluate neoadjuvant chemotherapy plus nivolumab for three cycles, followed by surgical resection for stage IB (≥4 cm)–IIIA NSCLC. This regimen was approved by the FDA in March 2022 based on results that demonstrated significantly improved pathologic complete response (pCR; 24.0% vs. 2.2%) and significantly longer event-free survival (EFS; median, 31.6 vs. 20.8 months) compared with chemotherapy alone (*N Engl J Med* 2022; 386:1973). At interim analysis, survival data remain immature (HR, 0.57; 99.67% CI, 0.30–1.07).

In a smaller phase 2 study, NADIM II, patients with NSCLC stage IIIA–B were randomized to three cycles of neoadjuvant treatment with carboplatin, paclitaxel, and nivolumab or chemotherapy alone. In this trial, patients with R0 resection received adjuvant nivolumab for 6 months. The primary end point of pCR was significantly improved with the nivolumab-containing neoadjuvant treatment (36.2% vs. 6.8%; *J Clin Oncol* 2022; 40:8501).

In both the CheckMate 816 and NADIM II trials, patients treated with both nivolumab and chemotherapy were more likely than those treated with chemotherapy alone to complete surgery and achieve an R0 resection.

Areas of Uncertainty

The end points achieved in these adjuvant and neoadjuvant checkpoint inhibitor trials reported to date have demonstrated clinical benefit and changed practice. However, there is ongoing debate about which subgroups benefit, particularly in those with low or negative PD-L1 expression in the adjuvant setting. Ultimately, we still await maturation of OS, the ultimate gold standard in the curative setting. Early looks at immature survival data are promising, and previous retrospective data have correlated major pathologic response (MPR) to neoadjuvant therapy with OS (*Lancet Oncol* 2014; 15:e42). It is unknown whether pCR, MPR, or lesser responses will predict OS differences that could have implications for different approaches to surveillance or treatment in the adjuvant setting. Also, because head-to-head comparisons of neoadjuvant and adjuvant immunotherapy approaches are lacking, it remains unclear which is preferable.

In light of these new immunotherapy approvals in the perioperative setting, another challenge is how and when to incorporate molecular testing for *EGFR* and other actionable mutations that may reduce the likelihood of benefit from immunotherapy and indicate use of osimertinib as an adjuvant treatment strategy. Until additional data are available, the best practice is for all surgically resectable NSCLC cases to be discussed prospectively at a multidisciplinary tumor board to develop individualized approaches based on patient and tumor characteristics, patient preferences, and expertise of a particular center.

Future Directions of Perioperative Therapy in NSCLC

After waiting over a decade to see improved outcomes among operable NSCLC patients, there are now multiple adjuvant and neoadjuvant treatment options. Currently, we await results of three additional studies that have completed accrual — the ALCHEMIST ANVIL substudy comparing adjuvant nivolumab with observation (NCT02595944) and two studies combining neoadjuvant chemotherapy plus a checkpoint inhibitor with surgery followed by additional checkpoint inhibitor therapy — KEYNOTE-671 (NCT03425643) and the AEGEAN study (NCT03800134). Understanding which patients to select for the variety of newly available adjuvant and neoadjuvant therapies will be a critical area of future investigation.

Topic Update

Conversations, Current Practices, and Challenges in Palliative Care

Mellar P. Davis, MD, FCCP, FAAHPM

The integration of palliative care into cancer treatment occurs through management of physical and psychological symptoms, spiritual support, and through the clarification of patients' values and understanding of their treatment goals. Recent advances in areas of goals-of-care conversations, cannabis use for symptom support, and pharmacological research centered on nausea and dyspnea are discussed in this update.

Goals-of-Care Conversations

The Alliance of Dedicated Cancer Centers has been undergoing a concerted effort to improve the goals-of-care conversation (GOCC), which aims to align treatment with patient values (*Oncologist* 2021; 26:533). These conversations may occur when there is a discrepancy between treatment goals and patient expectations, when sentinel events such as cancer relapse or cancer complications occur, or when transitioning from cancer treatment to symptom management alone. A GOCC should include the following elements: intent of current therapy, the physician's estimated prognosis, an inquiry regarding the patient's prognostic awareness, a prognostic disclosure, communication regarding the patient's values and personalized goals, and recommendations for a course of action. A patient's understanding of their prognosis is important to goals clarification and autonomy (*Bioethics* 2003; 17:142).

EVOLUTION OF GOCCs DURING A PATIENT'S CARE

Early in the patient's care, GOCCs between the oncologist and patient focus on treatment and setting expectations. In this setting, the oncologist's and patient's goals are usually congruent. During the intermediate phase of the disease trajectory — i.e., at the time of relapse, incurability, or a sentinel event — the conversation should focus on the patient's expectations, understanding of prognosis, values, risks, and the benefits of additional therapy. The final discussions center on advanced directives — when disease-modifying therapy is no longer appropriate or desired by patients.

DOCUMENTING GOCCs

With the advent of the electronic medical record (EMR), GOCCs and advance directives may now be included in a separate section of the EMR rather than within the history and physical or clinical notes sections, thus providing easier access for review. One cancer center found that implementing such a GOCC documentation system was associated with favorable end-of-life care quality measures, such as fewer inpatient days, fewer intensive care unit days, more hospice referrals, and less chemotherapy in the last 2 weeks of life (*Cancer* 2022; 128:3400).

CHALLENGES

There are currently several barriers to achieving best practices in this area. First, GOCCs are sometimes not understood to be different from discussions regarding advance directives, health-care agency, and code status. Though advance directives are necessary and may change with the course of cancer, they are limited to end-of-life decisions. In a recent systematic review, GOCC practices were often confused as prognostic communication or conversations about the end of life (*Patient Educ Couns* 2022; 105:1138). Although the GOCC aims to align treatment with patient values, the outcomes are usually described in terms of completed advance directives, hospice referrals, and reduced health-care utilization, which are physician- and health-care

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system–centered outcomes. At the present time, there is little evidence of GOCCs leading to higher-value cancer care in randomized trials (*Patient Educ Couns* 2022; 105:1138).

Another challenge is the timing of conversations. Both GOCCs and advance directive discussions may be delayed by oncologists claiming uncertainty about prognosis, while patients often prefer to avoid GOCCs and advance directives until all treatment options have been played out. This avoidance on the part of both physician and patient delays discussions, which may lead to aggressive cancer treatment at the end of life (*Patient Educ Couns* 2022; 105:1138; *J Clin Oncol* 2012; 30:4387).

Resource limitation can also be an issue within care centers. For hospitalized cancer patients requiring goal clarification, use of interdisciplinary rapid response teams for GOCC before palliative care consultations was shown to be feasible during the Covid-19 pandemic (*J Pain Symptom Manage* 2022; S0885-3924). In this study, patients had poor prognoses, had not previously established goals of care, and were critically ill; therefore, the focus was mainly on improving end-of-life care, and unfortunately, most patients died during the index hospitalization. However, descriptive data showed that goal-concordant care limitation occurred in a majority of patients.

Antiemetics in Advanced Cancer

Physicians often use antiemetics recommended for chemotherapy prophylaxis to treat nausea and vomiting in advanced cancer. Ondansetron, a 5-HT3 receptor antagonist, is frequently prescribed. A recent guideline update from the Multinational Association of Supportive Care in Cancer recommends three lines of therapy based on an updated systematic review of randomized trials (*Support Care Cancer* 2021; 29:8097). Metoclopramide or haloperidol are first-line antiemetics. Second-line antiemetics are methotrimeprazine (not available in the United States) or olanzapine. Third-line antiemetics are tropisetron or levosulpiride (not available in the United States). Empirical use of single antiemetics is as effective as guideline-driven therapy (*BMC Cancer* 2018; 18:510).

Cannabis

Cannabis use is prevalent among cancer survivors and patients with active cancer. Oncologists are often unaware of a patient's cannabis consumption and the type or amount used, which may adversely influence cancer treatment. It is estimated that 20% to 40% of patients with cancer are taking some form of cannabis (*Cancer* 2017; 123:4488; and 2019; 125:2242). A recent review of the placebo arms in 20 randomized trials of cannabis for pain management (including non–cancer-related pain) found a moderate-to-large placebo effect, which was associated with high-impact social media attention on cannabis trials (*JAMA Netw Open* 2022; 5:e2243848). In a recent randomized, double-blind, placebo-controlled trial comparing cannabidiol oil with placebo for symptom control, cannabidiol did no better than placebo. Studies of tetrahydrocannabinol dominant cannabis are ongoing. Notably, three of four nonrandomized studies have found that cannabis, due to immunosuppression, blocks checkpoint inhibitor responses and reduces progression-free intervals and survival (*Cancers [Basel]* 2020; 12:2447).

Dexamethasone and Dyspnea

Dexamethasone is frequently used at the end of life for multiple symptoms, including anorexia and fatigue. Does dexamethasone improve dyspnea? A recent randomized, double-blind study comparing dexamethasone with a placebo in 128 patients was stopped early for futility (*Lancet Oncol* 2022; 23:1321). Serious adverse effects were more prevalent with dexamethasone (28%) than with placebo (7%), possibly due in part to dexamethasone's effect of accelerating sarcopenia. Interestingly, dyspnea did not correlate with radiographic findings. Dyspnea in advanced cancer is more likely related to diaphragmatic weakness resulting from qualitative or quantitative changes in muscle associated with cachexia and sarcopenia (*Respir Med* 2012; 106:294).

Conclusion

I am encouraged by the multiple ways that palliative care is incorporated into cancer care and the creative pathways of cancer management that have included palliative care early in the treatment trajectory. Only a few groups have completed randomized trials regarding symptom management. A concerted financial investment in developing such trials within cooperative groups would be a step forward in improving the quality of cancer care.

NEJM Research Summary

Rucaparib or Physician's Choice in Metastatic Prostate Cancer

Fizazi K et al. DOI: 10.1056/NEJMoa2214676

CLINICAL PROBLEM

The poly(ADP–ribose) polymerase (PARP) inhibitor rucaparib has shown high antitumor activity in metastatic, castration-resistant prostate cancer associated with deleterious *BRCA* alterations in patients previously treated with a second-generation androgen-receptor pathway inhibitor (ARPI) and taxane-based chemotherapy. The efficacy of rucaparib in patients who have not received previous chemotherapy for metastatic disease is unknown.

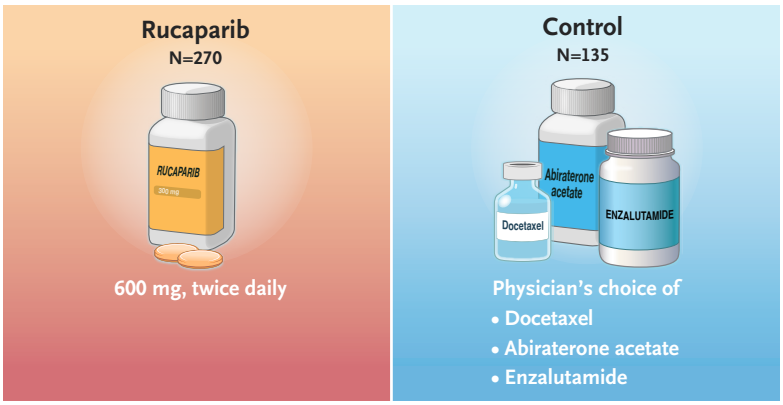
CLINICAL TRIAL

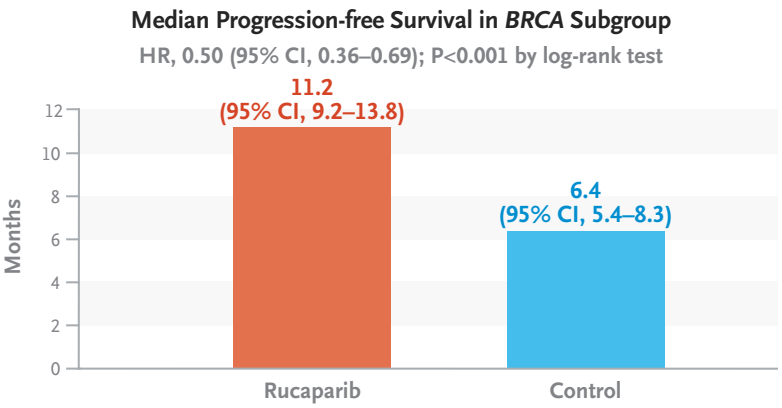
Design: A phase 3, multicenter, randomized, open-label trial assessed the efficacy and safety of rucaparib, as compared with physician's choice of treatment, in men with metastatic, castration-resistant prostate cancer and deleterious *BRCA* alterations who had received no previous chemotherapy for metastatic disease.

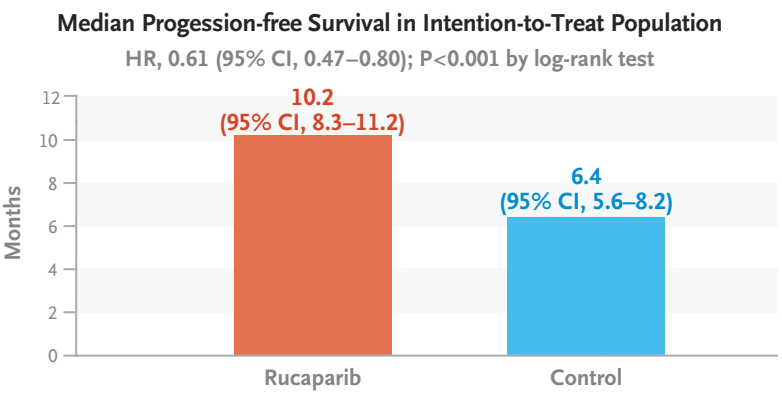
Intervention: 405 patients with disease progression after one second-generation ARPI were assigned in a 2:1 ratio to receive oral rucaparib (600 mg twice daily) or physician's choice of docetaxel, abiraterone acetate, or enzalutamide; approximately 75% of participants had deleterious *BRCA* alterations. The primary efficacy end point was imaging-based progression-free survival as assessed by independent imaging review.

RESULTS

Efficacy: Progression-free survival was significantly longer with rucaparib than with physician's choice,







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both in the subgroup with *BRCA* alterations and in the overall intention-to-treat population.

Safety: The most common adverse events with rucaparib were fatigue, nausea, and anemia or decreased hemoglobin. The most common adverse events with physician's choice were fatigue, diarrhea, and neuropathy.

LIMITATIONS AND REMAINING QUESTIONS

- Fewer patients with *BRCA1* alterations than with *BRCA2* alterations were enrolled, and the treatment benefit was inconclusive for those with *BRCA1* alterations.
- Data regarding overall survival from the trial were not mature.

CONCLUSIONS

In men with metastatic, castration-resistant prostate cancer with BRCA *alterations, treatment with oral rucaparib resulted in longer progression-free survival than physician's choice of docetaxel, abiraterone acetate, or enzalutamide.*

Interview

Zanubrutinib for Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

During the American Society of Hematology (ASH) meeting in December 2022, NEJM Group's Christine Sadlowski talked with Jennifer R. Brown, MD, PhD, about results of the phase 3 ALPINE study, which favored the second-generation Bruton's tyrosine kinase inhibitor zanubrutinib over ibrutinib for relapsed or refractory chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL). Brown is the lead author of the ALPINE study and the director of the Chronic Lymphocytic Leukemia Center at the Dana-Farber Cancer Institute in Boston.

Jennifer R. Brown, MD, PhD

In January, after the interview was conducted, the FDA approved zanubrutinib for chronic lymphocytic leukemia and small lymphocytic lymphoma.

What follows is an edited, condensed version of their conversation.

Sadlowski: First I'd like to ask you, why were you comparing zanubrutinib with ibrutinib in this study? I know that ibrutinib is part of the standard of care right now.

Brown: Right, so both zanubrutinib and ibrutinib are inhibitors of Bruton tyrosine kinase, or BTK, which is a molecule that is chronically active and a driver of CLL survival and proliferation. So inhibitors of BTK have really transformed the landscape of CLL therapy. Ibrutinib is the first-in-class BTK inhibitor that was approved and has become a standard of care in either frontline or relapsed CLL. Zanubrutinib is a next-generation BTK inhibitor. It was designed to be more specific in its inhibition of BTK so that there are fewer off-target effects.

It was also designed to have continuous drug levels throughout the dosing interval maintained. Ibrutinib and zanubrutinib are both covalent inhibitors. So they'll inhibit BTK initially, and ibrutinib, for example, doesn't maintain drug levels throughout the dosing interval, but inhibition is still maintained in many patients because of the initial covalent binding. Zanubrutinib has the initial covalent binding but then also maintains drug levels throughout the dosing interval so that, for example, if new BTK is made, zanubrutinib could still inhibit it. So these are the rationales for why zanubrutinib would be thought to be potentially more efficacious and safer than ibrutinib. In order to test that, we performed this randomized trial comparing zanubrutinib to ibrutinib in relapsed CLL patients.

Sadlowski: What you're reporting now at ASH is final results of your phase 3 study, correct?

Brown: That's right. The primary end point was actually overall response rate, initially noninferiority and then superiority. That has been reported in an interim and final analysis previously. This is the final progression-free survival analysis, which was a key secondary end point and was event-triggered. So when we reached a number of events, the analysis was performed,

and we were able to present the data at this meeting.

Sadlowski: You haven't reached the time point where you can really speak about overall survival conclusively yet?

Brown: Right. There were few events in either arm.

Sadlowski: Tell me about progression-free survival and what you found in this analysis.

Brown: The median follow-up is about 30 months, so about 2.5 years. We found that at a landmark of 2 years, 79% of the patients are progression free on zanubrutinib, and that's a 12% improvement compared with ibrutinib — so a pretty substantial difference. Another pretty notable finding is we have a specific subgroup of CLL that's higher risk — the patients who carry deletion of 17p or mutation of the *TP53* gene. So this was a planned analysis and also a stratification factor during the randomization. In that subgroup in 2 years, there was actually 22% improvement in progression-free survival with zanubrutinib compared with ibrutinib. So a pretty striking finding.

"We found that at a landmark of 2 years, 79% of the patients are progression free on zanubrutinib, and that's a 12% improvement compared with ibrutinib — so a pretty substantial difference."
— Dr. Jennifer Brown

Sadlowski: Yes, those are patients who are particularly difficult to treat, correct?

Brown: That's right.

Sadlowski: What were your safety findings?

Brown: The safety findings were also a key point in evaluation. We found that fewer patients discontinued zanubrutinib for adverse events compared with ibrutinib. There were also fewer patients who required dose reductions, dose interruptions, or as I mentioned, drug discontinuation. A key safety point is around cardiac events because it's become clear that ibrutinib is associated with significant rates of atrial fibrillation, as well as hypertension, which is increasing over time. It's also associated with sudden death in ventricular arrhythmias. So we saw fewer cardiac serious adverse events, fewer cardiac discontinuations (only 1 with zanubrutinib versus 14 with ibrutinib), and there were also no cardiac deaths in the zanubrutinib arm, but there were six in the ibrutinib arm. Then the rates of atrial fibrillation were about 5% on zanubrutinib and 12% with ibrutinib. So all of these cardiac findings were substantially better with zanubrutinib.

Sadlowski: And it doesn't matter whether patients had preexisting cardiovascular disease or not?

Brown: No. We did see some cardiac events in patients who had preexisting disease but also some in those who didn't.

Sadlowski: What is this going to mean in clinical practice?

Brown: I think this means that zanubrutinib is a preferred choice of BTK inhibitor for most CLL patients. The NCCN [National Comprehensive Cancer Network] guidelines have indicated that it is a preferred option for both frontline and relapsed disease prior to these data. These data will also obviously confirm that. I think the improvement in progression-free survival as well as improvement in efficacy is really a very strong set of data indicating that this is the BTK inhibitor of choice.

Sadlowski: What are you going to do next in this research?

Brown: I think longer-term toxicities follow-up, particularly with the cardiac toxicities, is certainly of interest, as well as how long people are able to stay on drug. These drugs are planned to be given continuously, and we know they control disease best if patients are able to stay on drugs.

So that's something that we definitely want to see in longer-term follow-up. Another aspect of CLL research in general is that we're doing combination therapies and are interested in time-limited therapies. So, for example, we're often combining BTK inhibitors with BCL2 inhibitors. So I think studies combining zanubrutinib with venetoclax will be of interest.

Sadlowski: Is there anything else you think clinicians in particular should know?

Brown: The one point I would make is that I think clinicians are sometimes afraid to use BTK inhibitors in patients with significant cardiac comorbidities because of experience with ibrutinib. I can say that it really is different with the next-generation BTK inhibitors like zanubrutinib. I've used them in patients with quite significant cardiac comorbidities successfully and so that is actually a very big help as we consider the treatment landscape for our CLL patients.

Sadlowski: Is there anyone you would not consider zanubrutinib for, for cardiac reasons?

Brown: No. I would say not.

Sadlowski: Well, that's really good news. Thank you very much. Good luck with your research and presentation, and I hope you enjoyed the meeting.

Brown: Thank you.

Meeting Report

The 2022 San Antonio Breast Cancer Symposium

Highlights of the latest research presented at the meeting

Presenters at the 2022 San Antonio Breast Cancer Symposium (SABCS; December 6–10) reported the latest findings in breast cancer research. NEJM Group was on hand to cover the meeting. Here, *NEJM Journal Watch Oncology and Hematology* reports on some of the key studies, with clinical perspective provided by Editor-in-Chief Dr. William J. Gradishar and guest author Dr. Erika Hamilton. Dr. Hamilton is Director of Breast Cancer Research for Sarah Cannon Research Institute at Tennessee Oncology, Nashville.

Abstracts are available at www.sabcs.org; account registration is required to access all abstracts.

DESTINY-Breast03: Longer Overall Survival with Trastuzumab Deruxtecan Than with Trastuzumab Emtansine

In second-line treatment of patients with human epidermal growth factor receptor 2 (HER2)–positive metastatic breast cancer, overall survival (OS) was longer with trastuzumab deruxtecan (T-DXd) than with trastuzumab emtansine (T-DM1), updated findings from the industry-supported, phase 3, randomized DESTINY-Breast03 trial show.

Among 524 patients, OS was significantly higher with T-DXd than with T-DM1 at 12 months (94% vs. 86%, respectively) and at 24 months (77% vs. 70%, respectively). Neither group reached median OS. Median progression-free survival was 28.8 months with T-DXd versus 6.8 months with T-DM1. Objective response rates were 79% with T-DXd versus 35% with T-DM1; complete response rates were 21% versus 10%, respectively.

Grade 3 or higher treatment-related adverse events were similar between the groups (56% and 52%). Mild-to-moderate drug-related interstitial lung disease (ILD)/pneumonitis occurred in 15% and 3%, respectively.

Summary by Christine Sadlowski, Staff Writer

GRADISHAR COMMENT

The results of DESTINY-Breast03 reaffirm that T-DXd should be the preferred option for most patients with HER2-positive metastatic breast cancer in the second-line setting. Every clinical end point is improved with T-DXd compared with T-DM1, while cases of ILD with T-DXd were relatively infrequent and not high grade.

(Editors' note: Dr. Erika Hamilton is a coauthor on this abstract but did not contribute to our coverage of it.)

Abemaciclib's Benefits Sustained 2 Years After Treatment Ends

The benefits of adding abemaciclib to endocrine therapy for hormone receptor (HR)–positive, HER2-negative, node-positive, high-risk early breast cancer persists — and increases — 2 years after stopping abemaciclib, according to an interim analysis from the monarchE trial.

In the industry-funded trial, 5637 patients were randomized to standard adjuvant endocrine therapy for up to 10 years with or without abemaciclib for 2 years. In previously reported analyses at 2 and 3 years, invasive disease-free survival (IDFS) and distant relapse-free survival

(DRFS) were significantly improved in the abemaciclib group.

Now, at 4 years, with all patients having finished abemaciclib therapy, the absolute IDFS benefit with versus without abemaciclib increased to 6.4%, compared with 4.8% at 3 years and 2.8% at 2 years. The benefit was observed in all subgroups. Similarly, at 4 years the absolute DRFS benefit with abemaciclib increased to 5.9%, compared with 4.1% at 3 years and 2.5% at 2 years. The IDFS and DRFS benefits were observed regardless of Ki-67 index. Mortality was lower in the abemaciclib group at 4 years (5.6% vs. 6.1%), although overall survival data remained immature.

There were no new safety signals.

Summary by Cara Adler, Staff Writer

GRADISHAR COMMENT

The longer follow-up now available in the monarchE dataset offers reassurance that the IDFS curves continue to separate rather than come together. Additionally, the vast majority of patients were able to complete 2 years of treatment while maintaining good quality of life.

HAMILTON COMMENT

With longer follow-up in monarchE, we see that for patients with high-risk estrogen receptor–positive breast cancer, cure rates continue to increase over time with the addition of abemaciclib to endocrine therapy.

Sacituzumab Govitecan Improves Survival in Pretreated, Endocrine-Resistant HR+/HER2– Metastatic Breast Cancer, Regardless of Trop-2 Expression

In patients with heavily pretreated, HR-positive, HER-negative metastatic breast cancer, sacituzumab govitecan — a Trop-2–directed antibody–drug conjugate (ADC) — appears to confer a survival benefit regardless of patients' level of Trop-2 expression, according to a subgroup analysis of the industry-supported TROPiCS-02 study.

Roughly 550 patients with inoperable or metastatic breast cancer who had received at least one prior taxane, a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor, endocrine therapy, and two to four chemotherapy regimens were randomized to receive sacituzumab govitecan (10 mg/kg IV on day 1 and 8, every 21 days) or treatment of physician's choice (eribulin, gemcitabine, capecitabine, or vinorelbine).

Previously, sacituzumab govitecan showed improved PFS and OS. Now, researchers examined efficacy by Trop-2 expression on archival tumor tissue based on histochemical scores (H-score, with higher scores indicating more Trop-2 expression).

Median PFS and OS were generally improved in the sacituzumab govitecan group, regardless of H-score. For instance, for those with an H-score below 100, median PFS was 5.3 months with sacituzumab govitecan and 4.0 months with treatment of choice, although the difference wasn't statistically significant. For those with an H-score of 100 or more, median PFS was significantly longer with sacituzumab govitecan (6.4 vs. 4.1 months).

Summary by Kelly Young, Staff Writer

HAMILTON COMMENT

This is another ADC where we see that high expression of the target is not required for good activity. With trastuzumab deruxtecan's approval in HER2-low breast cancer and sacituzumab showing benefit across Trop-2 levels, ADCs are stealing the show and are here to stay.

GRADISHAR COMMENT

Like in the ASCENT trial in triple-negative breast cancer, sacituzumab govitecan outperformed standard chemotherapy options and did so regardless of Trop-2 expression. These data support the use of this compound in endocrine refractory patients, where until recently, the only option was standard chemotherapy.

Adding Palbociclib to Fulvestrant Doesn't Boost PFS in HR+/HER2– Metastatic Disease After Prior Progression

Adding palbociclib to the selective estrogen receptor degrader fulvestrant doesn't seem to improve PFS in patients with HR-positive, HER2-negative metastatic breast cancer with prior progression on a CDK4/6 inhibitor, according to results of the phase 2, industry-supported PACE trial.

Some 220 patients whose breast cancer had progressed after an aromatase inhibitor and a CDK4/6 inhibitor (91% received palbociclib) were randomized to receive one of the following regimens:

- Fulvestrant alone
- Fulvestrant plus palbociclib
- Fulvestrant, palbociclib, and the programmed death ligand 1 (PD-L1) inhibitor avelumab

At a median 24 months' follow-up, median PFS was not significantly improved with fulvestrant plus palbociclib compared with fulvestrant alone (4.6 and 4.8 months, respectively). Median PFS was somewhat higher with fulvestrant, palbociclib, and avelumab (8.1 months) than with fulvestrant alone, but the difference was not statistically significant.

Summary by Kelly Young, Staff Writer

HAMILTON COMMENT

This is our first look at the benefits of continuing the same CDK4/6 inhibitor after progression on a CDK4/6 inhibitor. It appears that continuation does not confer additional benefit. This is in contrast to the exploratory trial MAINTAIN, where switching CDK4/6 inhibitors from palbociclib to ribociclib with endocrine therapy at progression showed more benefit than endocrine therapy alone. It appears that novel endocrine therapies are the most promising therapies in the second line.

GRADISHAR COMMENT

The benefit of a different CDK4/6 inhibitor following disease progression while receiving another CDK4/6 inhibitor remains controversial. The PACE trial had a different design than MAINTAIN and is not comparable, but collectively these results do not support this strategy as a standard of care.

Trastuzumab Deruxtecan Improves Survival in Patients Previously Treated with Trastuzumab Emtansine

In patients with HER2-positive unresectable or metastatic breast cancer who've previously received trastuzumab emtansine (T-DM1), treatment with trastuzumab deruxtecan (T-DXd) in the third-line setting improves PFS and OS, as compared with treatment of physician's choice. The findings come from the industry-supported, phase 3 DESTINY-Breast02 trial.

In the multicenter, open-label trial, roughly 600 patients were randomized to T-DXd or treatment of physician's choice (trastuzumab + capecitabine or lapatinib + capecitabine). The primary outcome was PFS.

During a median follow-up of roughly 20 months, patients in the T-DXd group were 64% less likely than those in the physician's choice group to experience disease progression. Median PFS was 17.8 months versus 6.9 months, respectively. OS also favored T-DXd, with a median duration of 39.2 months versus 26.5 months.

Grade 3 or higher adverse events occurred in 53% of T-DXd recipients and 44% of physician's choice recipients. Adjudicated drug-related interstitial lung disease (usually low grade) occurred in 10.4% and 0.5% of patients, respectively.

Summary by Amy Herman, Staff Writer

GRADISHAR COMMENT

The antibody–drug conjugate T-DXd has dramatically improved outcomes in multiple settings: in the second-line setting as treatment for HER2-positive breast cancer, for those developing

disease progression following treatment with T-DM1, and in those with HER2-low disease. With greater experience by clinicians using T-DXd, the concerns regarding T-DXd–associated interstitial lung disease, particularly high-grade, have diminished. We await the results of other trials exploring the use of T-DXd as a first-line therapy as well as combination strategies.

HAMILTON COMMENT

It is extremely reassuring to see how well T-DXd outperformed standard chemotherapy in DESTINY-Breast02 in terms of PFS and OS. However, these data are really only practice-confirming at this point, and in fact, most patients are likely to receive T-DXd in the second-line setting with the results of DESTINY-Breast03 instead of third-line.

Racial Disparities in Breast Cancer Survival, Worse Cognitive Outcomes with Chemoendocrine Therapy: New Findings from RxPONDER

A new analysis from the RxPONDER trial finds worse breast cancer survival in Black compared with white women despite similar recurrence scores (RS), and a second new analysis finds greater cancer-related cognitive impairment (CRCI) with chemoendocrine therapy (CET) compared with endocrine therapy (ET) alone.

In RxPONDER, which received some industry support, roughly 5000 women with HR-positive, HER2-negative breast cancer with 1 to 3 positive axillary lymph nodes and 21-gene RS ≤25 were randomized to chemotherapy followed by ET or ET alone.

The analysis of racial/ethnic disparities involved some 4000 participants; 70% were non-Hispanic (NH) white, 6% NH Black, 15% Hispanic, and 8% Asian. The 21-gene RS was similar across groups, as was tumor size and number of positive nodes. High-grade tumors were more common among NH Black and Hispanic patients. Five-year invasive disease-free survival was significantly lower in NH Black than in NH white patients overall (87% vs. 92%) and in premenopausal and postmenopausal subgroups.

The analysis of CRCI involved cognitive function questionnaires completed by roughly 100 premenopausal and 400 postmenopausal participants at baseline through 36 months. Scores were similar in the CET and ET groups at baseline and decreased (indicating worse cognitive function) in both groups at 6 and 12 months, with greater decreases in the CET group. At 36 months, impairment scores had returned to baseline with ET but not CET. Results were similar in premenopausal and postmenopausal women.

Summary by Cara Adler, Staff Writer

GRADISHAR COMMENT

Although the subset of Black patients in RxPONDER was quite small compared with white patients, who account for the majority of patients in the study, the results suggest that the molecular tools we utilize (RS) do not necessarily "level the playing field." Even when the biology of the disease is evaluated at a molecular level, beyond clinical features alone, disparities between white and Black patients exist both in terms of outcome and toxicity.

HAMILTON COMMENT

Black and Hispanic patients did worse than white patients in terms of cancer recurrence in RxPONDER even when tumor size, number of positive nodes, and recurrence scores were similar. This really underscores disparities across racial/ethnic groups and makes it even more important to have higher representation of underserved populations in the clinical trials that determine standards of care.

Adding Capivasertib to Fulvestrant Improves Outcomes in HR+/HER2– Disease Resistant to Aromatase Inhibitors

Adding capivasertib to fulvestrant improves PFS in patients with HR-positive, HER2-negative advanced breast

cancer that has become resistant to aromatase inhibitor therapy, according to findings from the CAPItello-291 trial. Capivasertib is an investigational AKT inhibitor.

In the industry-supported, phase 3 trial, roughly 700 patients were randomized to receive fulvestrant with either capivasertib (400 mg twice daily; 4 days on, 3 days off) or placebo. Some 41% of participants had AKT-pathway–altered tumors. Among patients' prior treatments for advanced disease: 87% had received at least one prior line of treatment, 69% had received a CDK4/6 inhibitor, and 18% had received chemotherapy.

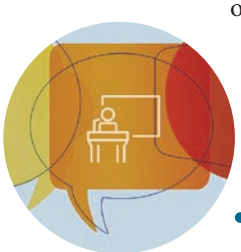
Overall, median PFS was twice as long with fulvestrant plus capivasertib compared with fulvestrant plus placebo (7.2 vs. 3.6 months), representing a 40% reduction in risk of disease progression with capivasertib. Findings were similar in the subgroup with AKT-pathway–altered tumors (7.3 vs. 3.1 months; hazard ratio for progression, 0.50).

The most frequent adverse events with fulvestrant plus capivasertib were diarrhea, rash, and nausea; these occurred much more often with capivasertib than with placebo. Roughly 13% of the capivasertib group and 2% of the placebo group discontinued treatment owing to adverse events.

Summary by Amy Herman, Staff Writer

HAMILTON COMMENT

Novel endocrine strategies after endocrine therapy or CDK4/6 inhibitors are a huge unmet clinical need, with standard endocrine agents showing poor activity. Here we see data for fulvestrant plus an AKT inhibitor showing a doubling in PFS from 3.6 to 7.2 months, at a cost of moderately more toxicity in terms of nausea, diarrhea, and rash. Endocrine therapy with AKT blockade may be one strategy to overcome endocrine resistance.



GRADISHAR COMMENT

Partnering endocrine therapy with targeted therapy improved clinical outcomes for patients with metastatic, ER+/HER2-negative breast cancer. Typically following disease progression on a CDK4/6 inhibitor, clinicians will determine if a *PIK3CA* mutation is present, allowing for the use of alpelisib. The results from CAPItello may offer yet another targeted option for patients with pathway-altered mutations, or not, extending the time until chemotherapy is required.

Interrupting Endocrine Therapy for Pregnancy Not Tied to Worse Breast Cancer Recurrence Rates

Pausing endocrine therapy to attempt pregnancy is not associated with worse breast cancer outcomes, suggest results from the POSITIVE study.

Researchers enrolled over 500 premenopausal women aged 42 or under who hoped to become pregnant and who'd had 18–30 months of adjuvant endocrine therapy for stage I–III HR-positive breast cancer. Women stopped endocrine therapy for up to 2 years to attempt pregnancy, delivery, and breastfeeding. Patients were strongly encouraged to resume endocrine therapy after pregnancy to complete 5–10 years' therapy.

At 3 years, the rate of local, regional, or distant recurrence or new invasive contralateral breast cancer, the primary end point, was 8.9% in the POSITIVE cohort, compared with 9.2% in a historical cohort of 1500 patients whose endocrine therapy was not interrupted. Nearly three quarters of women in POSITIVE had at least one pregnancy, and 86% of these had at least one live birth. The rate of birth defects was low, around 2%.

Summary by Kelly Young, Staff Writer

HAMILTON COMMENT

This is a really reassuring study regarding those patients who wish to stop adjuvant endocrine therapy to have children. It appears that after at least 1.5 years of therapy, temporary cessation of endocrine therapy was not associated with any clinically significant detriment in terms of relapse.

GRADISHAR COMMENT

These data address a critically troubling issue to both patients and their physicians, that is, whether interruption of adjuvant endocrine therapy in young women to get pregnant will raise the risk of recurrence. POSITIVE reassures all that it is safe to allow interested women to pursue pregnancy without compromising breast cancer outcomes, with the caveat that resumption of endocrine therapy is a necessity to complete a full course. Longer follow-up of this trial will continue.

Novel Estrogen Receptor Degraders Show Promise in HR+/HER2– Advanced Disease

Two new trials offer promising results for novel estrogen receptor degraders in patients with HR-positive, HER2-negative advanced breast cancer.

First, in the industry-supported, phase 2 SERENA-2 trial, 240 postmenopausal patients with disease progression or recurrence after no more than one endocrine therapy or chemotherapy regimen in the advanced setting were randomized either to camizestrant, an investigational next-generation oral selective estrogen receptor degrader (SERD), or to fulvestrant, an FDA-approved injectable SERD. During a median 17 months' follow-up, the proportion of patients with disease progression was significantly lower with 75- or 150-mg camizestrant (68%–70%) than with fulvestrant (80%). Median PFS was twice as long with camizestrant (roughly 7.5 months) as with fulvestrant (3.7 months).

Next, VERITAC, a phase 2, industry-supported trial, enrolled 71 patients with locally advanced or metastatic disease who had received at least one prior endocrine therapy, at least one CDK4/6 inhibitor, and no more than one chemotherapy regimen. Patients received oral ARV-471, an investigational proteolysis targeting chimera (PROTAC) estrogen receptor degrader, at either 200 mg or 500 mg daily. The clinical benefit rate — combining rates of confirmed complete response, partial response, and stable disease at 24 weeks — was 37%–39% with the two doses. In both trials, drug discontinuations due to adverse events were rare.

Summary by Amy Herman, Staff Writer

GRADISHAR COMMENT

The new oral estrogen receptor degraders offer the promise of greater convenience (oral versus intramuscular injection) as well as greater efficacy compared to fulvestrant. Additionally, these drugs may be superior to fulvestrant in certain tumors where molecular markers of resistance have developed. Though not all oral estrogen receptor degrader candidates have been successful, camizestrant and ARV-471 appear promising.

(Editors' note: Dr. Erika Hamilton is a coauthor on both of these trials but did not contribute to our coverage of them.)

Recurrence Rate Low with Breast-Conserving Surgery in Multiple Ipsilateral Breast Cancer

For patients with multiple ipsilateral breast cancer, lumpectomy followed by radiotherapy has a low rate of recurrence, suggests the ACOSOG (Alliance) Z11102 trial.

In this phase 2, single-arm, prospective trial, researchers studied nearly 200 patients with 2 or 3 foci of biopsy-proven breast cancer, with each site less than 5 cm and at least one invasive site. Sites were separated by more than 2–3 cm of normal breast tissue, and disease was limited to two breast quadrants. Patients underwent lumpectomy followed by whole breast radiation with boosts to the lumpectomy beds.

At 5 years, the estimated cumulative incidence of local recurrence was 3.2%, which is in line with the historical rate among patients with a single breast tumor who undergo lumpectomy. Of note, patients who did not undergo a presurgery breast MRI had a higher rate of recurrence (23% vs. 2% for those with MRI).

Summary by Kelly Young, Staff Writer

HAMILTON COMMENT

This abstract suggests that even patients with multifocal cancer may be able to be managed with breast-conserving surgery. This has previously been considered a high-risk factor that could possibly necessitate more radical surgery techniques. This finding comes on the heels of an increasing body of data suggesting that some patients may need less to have good outcomes.

GRADISHAR COMMENT

Mastectomy was frequently recommended for patients with more than one primary tumor in the breast. This study should reassure patients, and surgeons, that with appropriate preoperative evaluation (MRI), patients meeting the criteria of this study do not have a higher rate of recurrence with lumpectomy than those with a single breast tumor. The issue of cosmetic outcome may be the primary driver when considering removal of more than one tumor.

Genetic Profile May Identify Patients Who Can Skip Adjuvant Radiotherapy

An investigational 16-gene molecular signature identifies patients with breast cancer who might safely forego local radiotherapy after breast-conserving surgery, according to a validation study.

The molecular signature, called Profile for the Omission of Local Adjuvant Radiotherapy (POLAR), includes genes involved in cellular proliferation and immune response that are expressed differently in patients with and without locoregional recurrence (LRR) after breast-conserving surgery.

The meta-analysis included 623 patients with ER-positive, HER2-negative, node-negative breast cancer who were enrolled in three randomized, controlled trials evaluating breast-conserving surgery with or without local radiotherapy. Using tumor samples from each patient, investigators assigned a POLAR score and used modeling to examine the effects of radiotherapy in patients with high versus low scores.

Among patients with low scores, rates of LRR were similar with and without radiotherapy (10-year cumulative incidence of LRR, 7% and 5%, respectively). Among patients with high scores, the LRR rate was reduced by 63% with radiotherapy compared to without radiotherapy (10-year cumulative incidence, 7% vs. 20%, respectively).

Noting that further validation is needed, the authors conclude, "To our knowledge, POLAR is the first genomic classifier that is not only prognostic for LRR but also predictive."

Summary by Cara Adler, Staff Writer

HAMILTON COMMENT

This goes along with the theme of "right sizing" therapy for the individual patient and discusses a POLAR score that can help make the decision whether patients need radiation to improve outcomes — or whether they have a good enough prognosis that radiation therapy is excessive and they can be spared this intervention.

GRADISHAR COMMENT

The POLAR study suggests that clinicians may be able to identify patients, based on a molecular signature, who can safely avoid radiation therapy. These data were generated from a meta-analysis of three separate trials. It will be important to determine how well clinical features suggesting a good or poor outcome track with the results of the molecular signature.

Potential Contributor to Racial Disparity in Breast Cancer Prognosis Identified

Prometastatic changes to the tumor microenvironment in response to neoadjuvant chemotherapy may contribute to the worse breast cancer prognosis in Black patients compared with white patients with HR-positive, HER2-negative disease, according to a multicenter, retrospective study. Prior research suggests that neoadjuvant chemotherapy can induce prometastatic changes in some patients.

Roughly 200 patients who had residual disease after neoadjuvant chemotherapy underwent residual tumor tissue analysis. Tumor microenvironment of metastasis (TMEM) doorways — portals for tumor cell dissemination to distant sites — were visualized by triple immunohistochemistry for macrophages, tumor cells, and endothelial cells.

Overall, Black patients were more likely than white patients to develop a distant recurrence (50% vs. 34%). Black patients' tumors had more macrophages and higher TMEM scores in the entire study population and also in the HR-positive, HER2-negative subgroup — but not in the triple-negative subgroup. After multivariable adjustment, high TMEM score was a significant predictor of worse distant recurrence-free survival in the overall cohort and showed a trend toward significance in the HR-positive, HER2-negative subset — but not in the triple-negative subset.

The study's senior author notes, "Our study provides a potential explanation for the persistent racial disparities in ER-positive/HER2-negative breast cancer outcomes that are not fully explained by disparities in social determinants of health."

Summary by Amy Herman, Staff Writer

GRADISHAR COMMENT

Though seemingly counterintuitive, the effects of preoperative therapy may create an environment that actually promotes the development of metastatic disease. The differences in outcome between white and Black patients with similar clinical disease characteristics as well as treatment speak to a more complex interplay between cellular players in the microenvironment that differ between populations.

HAMILTON COMMENT

The disparities that exist in breast cancer care across racial/ethnic groups present a huge unmet clinical challenge, with Black patients being 41% more likely to die from breast cancer than their white counterparts.

Beyond social differences and treatment disparities, this study identifies biologic possibilities to account for some of the disparity in breast cancer outcomes. Identifying differences in biology is the first step in potentially developing a strategy to overcome any related outcome disparities.

Dr. Gradishar is Professor of Medicine in the Feinberg School of Medicine at Northwestern University and a member of the Robert H. Lurie Comprehensive Cancer Center. He serves as Director of Maggie Daley Center for Women's Cancer Care at Northwestern University and Northwestern Memorial Hospital. **Disclosures:** He reports consultant or advisory board roles with Roche–Genentech, AstraZeneca, Macrogenics, Seagen, and Merck. He reports receiving grant or research support from the Breast Cancer Research Foundation. He serves on the editorial boards of *Clinical Breast Cancer, Oncology, Annals of Surgery,* and *Breast Cancer Research and Treatment.* He has held leadership positions in the following professional societies: National Comprehensive Cancer Network (Chair, Breast Cancer Panel) and American Board of Internal Medicine (Medical Oncology Board).

Dr. Hamilton is Director of Breast Cancer Research for Sarah Cannon Research Institute at Tennessee Oncology, Nashville. **Disclosures:** She reports research funding (all payments made to her institution) from: AbbVie, Acerta Pharma, Accutar Biotechnology, ADC Therapeutics, AKESOBIO Australia, Amgen, Aravive, ArQule, Artios, Arvinas, AstraZeneca, AtlasMedx, Black Diamond, Bliss BioPharmaceuticals, Boehringer Ingelheim, Cascadian Therapeutics, Clovis, Compugen, Cullen-Florentine, CytomX, Daiichi Sankyo, Dana-Farber Cancer Institute, Dantari, Deciphera, Duality Biologics, eFFECTOR Therapeutics, Ellipses Pharma, Elucida Oncology, EMD Serono, Fochon, FujiFilm, G1 Therapeutics, H3 Biomedicine, Harpoon, Hutchinson MediPharma, Immunogen, Immunomedics, Incyte, Infinity Pharmaceuticals, InvestisBio, Jacobio, Karyopharm, Leap Therapeutics, Lilly, Lycera, Mabspace Biosciences, Macrogenics, MedImmune, Merck, Mersana, Merus, Millennium, Molecular Templates, Myraid Genetic Laboratories, Novartis, Nucana, Olema, OncoMed, Onconova Therapeutics, ORIC Pharmaceuticals, Orinove, Pfizer, PharmaMar, Pieris Pharmaceuticals, Pionyr Immunotherapeutics, Plexxikon, Radius Health, Regeneron, Relay Therapeutics, Repertoire Immune Medicine, Rgenix, Roche/Genentech, Seagen, Sermonix Pharmaceuticals, Shattuck Labs, Silverback, StemCentRx, Sutro, Syndax, Syros, Taiho, TapImmune, Tesaro, Tolmar, Torque Therapeutics, Treadwell Therapeutics, Verastem, Vincerx Pharma, Zenith Epigenetics, and Zymeworks; and consulting advisory roles (all payments made to her institution) with: Arcus, Arvinas, AstraZeneca, Black Diamond, Boehringer Ingelheim, CytomX, Daiichi Sankyo, Dantari, Deciphera Pharmaceuticals, Eisai, Greenwich LifeSciences, H3 Biomedicine, iTeos, Janssen, Lilly, Loxo, Merck, Mersana, Novartis, Orum Therapeutics, Pfizer, Propella Therapeutics, Puma Biotechnology, Relay Therapeutics, Roche/Genentech, Seagen, and Silverback Therapeutics.

Meeting Report

ASCO Gastrointestinal Cancers Symposium 2023

Highlights of the latest research in hepatocellular, pancreatic, biliary, colon, and gastroesophageal cancer

Celebrating a 20-year milestone, the 2023 ASCO Gastrointestinal Cancers Symposium, held January 19–21 in San Francisco, was a key venue for important and awaited trial results across the spectrum of gastrointestinal malignancies. *NEJM Journal Watch Oncology and Hematology* Associate Editor David H. Ilson, MD, PhD, reports on some of the most clinically impactful presentations. Abstracts can be viewed in the symposium's meeting library.

Sorafenib plus Stereotactic Body Radiotherapy in Advanced Hepatocellular Cancer

In the phase 3 NRG/RTOG trial 1112, researchers compared sorafenib alone versus sorafenib plus stereotactic body radiotherapy (SBRT) in advanced hepatocellular cancer (HCC; abstract 489). Patients with HCC not amenable to surgery, ablation, or transarterial chemoembolization (TACE), with lesion sum ≤20 cm and limited distant metastatic disease were randomized to either sorafenib 400 mg twice daily or SBRT (27.5–50 Gy in 5 fractions) followed by sorafenib 200 mg twice daily for 28 days then increased to 400 mg twice daily. Of 193 patients, 41% had hepatitis C and 19% had hepatitis B or B and C, 74% had macrovascular invasion, and 4% had distant metastases.

The primary end point of overall survival (OS) was improved from a median of 12.3 months with sorafenib alone to 15.8 months with the addition of SBRT (hazard ratio, 0.77; one sided P=0.0554). Progression-free survival (PFS) was also improved with the addition of SBRT, from 5.5 to 9.2 months (HR 0.55; 2-sided P=0.0001). Incidence of treatment-related adverse events did not differ with and without SBRT.

These provocative results indicate that liver-directed SBRT may improve survival when added to systemic therapy in patients with HCC largely confined to the liver. Further evaluation of SBRT with more active contemporary systemic therapies in HCC is needed.

Gemcitabine/Nab-Paclitaxel vs. NALIRIFOX in Advanced Pancreatic Cancer

The industry-sponsored, open-label, randomized, phase 3 NAPOLI-3 trial compared standard two-drug chemotherapy with gemcitabine/nab-paclitaxel versus three-drug therapy with infusional 5-FU, oxaliplatin, and nanoliposome-encapsulated irinotecan (NALIRIFOX) in 770 patients with advance pancreatic cancer (abstract LBA661).

At a median follow up of 16.1 months, OS — the primary outcome — was improved with NALIRIFOX compared to gemcitabine/nab-paclitaxel (median, 11.1 vs. 9.2 months; HR, 0.84; P=0.04). PFS was also improved with NALIRIFOX (median, 7.4 vs. 5.6 months; HR, 0.70; P=0.0001). Grade 3/4 treatment-related adverse events that were more frequent with NALIRIFOX than with gemcitabine/nab-paclitaxel included diarrhea (20.3% vs. 4.5%) and nausea (11.9% vs. 2.6%); those that were more frequent with gemcitabine/nab-paclitaxel than with NALIRIFOX included anemia (17.4% vs. 10.5%) and neutropenia (24.5% vs. 14.1%).

This first head-to-head comparison of two-drug versus three-drug therapy in advanced pancreatic cancer supports both use of NALIRIFOX and FOLFIRINOX as the preferred first-line regimens in patients who are considered candidates for three-drug therapy.

Adding Nab-Paclitaxel to Gemcitabine/Cisplatin Therapy in Advanced Biliary Cancer

The randomized, open-label, phase 3 SWOG 1815 trial compared standard two-drug gemcitabine/cisplatin therapy with a three-drug regimen adding nab-paclitaxel in patients with advanced biliary cancers (abstract LBA490). Of 441 patients, 67% had intrahepatic primary tumors, 16% had gallbladder primary tumors, and 17% had extrahepatic primary tumors; 73% had distant metastatic disease.

There was no significant difference in OS — the primary end point — with three-drug versus two-drug therapy (median, 14.0 and 12.7 months; HR, 0.93; P=0.58). The response rate was numerically but not statistically significantly higher with three-drug versus two-drug therapy (34% and 25%; P=0.11) and there was no significant difference in PFS (median, 8.2 and 6.4 months; HR, 0.92; P=0.47). An exploratory analysis indicated potential survival benefits in patients with locally advanced versus metastatic disease and in the small subset of patients with gallbladder primary tumors. The rate of grade 3/4 hematologic toxicity was higher with three-drug versus two-drug therapy (60% vs. 45%) as was the rate of therapy discontinuation for toxicity (24% vs. 19%).

This important trial indicates that three-drug therapy does not offer benefit over two-drug therapy for patients with metastatic biliary cancers, with the potential exception of those with locally advanced disease or gallbladder primary tumors.

Adding Bevacizumab to Trifluridine/Tipiracil Therapy in Chemotherapy-Refractory Colon Cancer

The SUNLIGHT study, an international industry-sponsored, open-label, randomized, phase 3 trial, compared late-line treatment with trifluridine/tipiracil with or without bevacizumab in patients with chemotherapy-refractory colon cancer (abstract 4).

Among the 492 patients treated, the primary end point of OS was significantly improved with the addition of bevacizumab (median, 10.8 vs. 7.5 months without bevacizumab; HR, 0.61; P<0.001). PFS was also improved (median, 5.6 vs. 2.4 months; HR, 0.44; P<0.001). There was no significant increase in treatment-related grade 3/4 serious adverse events with the addition of bevacizumab.

Combining bevacizumab with trifluridine/tipiracil represents a new standard of care for colorectal cancer and this trial supports continuation of bevacizumab into serial lines of chemotherapy.

Regorafenib vs. Placebo in Chemotherapy-Refractory Gastroesophageal Adenocarcinoma

The industry-sponsored, double-blind, phase 3 INTEGRATE IIa trial compared treatment with regorafenib versus placebo in 251 patients with gastroesophageal adenocarcinoma who had received at least two or more prior chemotherapy regimens (abstract LBA294).

The primary end point of OS was improved with regorafenib compared to placebo (median 4.5 vs. 4.0 months; HR, 0.70; P=0.011), as was 12-month survival (19% vs. 6%). PFS was also improved with regorafenib (median, 1.8 vs. 1.6 months; HR, 0.52; P<0.001). No new safety signals were observed.

Regorafenib may emerge as a new late-line therapy option for refractory gastroesophageal adenocarcinoma.

Adding Zolbetuximab to FOLFOX6 in Gastric and Gastroesophageal Junction Adenocarcinoma

The SPOTLIGHT trial evaluated the addition of zolbetuximab to first-line chemotherapy with modified FOLFOX6 in patients with advanced gastric and esophageal adenocarcinoma overexpressing claudin-18.2 (abstract LBA292). In this international, industry-sponsored, phase 3 trial, 565 patients were randomized to the addition of zolbetuximab or placebo.

The primary end point of PFS was improved with the addition of zolbetuximab compared with placebo (median, 10.61 vs. 8.67 months; HR, 0.751; *P*=0.0066). OS was also improved with zolbetuximab (median, 18.23 vs. 15.54 months; HR, 0.750; *P*=0.0053). Anti-tumor response rates were similar in the two groups. Although rates of nausea, vomiting, and anorexia were higher with zolbetuximab, rates of serious treatment-related adverse events were similar in the two treatment arms (43.5% and 44.8%).

Zolbetuximab added to first-line chemotherapy in gastroesophageal cancers overexpressing claudin-18.2 will likely become a new care standard.

Adding Tislelizumab to First-Line Chemotherapy in Gastric and Gastroesophageal Junction Adenocarcinoma

The industry-sponsored, international, placebo-controlled, phase 3 Rationale 305 trial evaluated the addition of the anti–programmed death 1 (PD-1) antibody tislelizumab to first-line chemotherapy with capecitabine/oxaliplatin or infusional 5-FU/cisplatin in 546 patients with gastric or gastroesophageal junction adenocarcinoma testing positive for PDL-1 ≥5% based on a tumor-associated score (abstract 286).

At a median follow-up of 11.8 months, OS was superior with tislelizumab compared with placebo (median, 17.2 vs. 12.6 months; HR, 0.74; *P*=0.0056). Also improved with tislelizumab over placebo were PFS (7.2 vs. 5.9 months, HR 0.67), rate of response (50.4% vs. 43.0%), and response duration (9.0 vs. 7.1 months). No new safety signals were observed.

Tislelizumab is another anti–PD-1 antibody shown to improve treatment outcomes when added to first-line chemotherapy for patients with programmed death ligand 1 (PD-L1)–positive gastroesophageal cancer.

Immune Checkpoint Inhibitor Therapy in MSI-High Gastric and Gastroesophageal Junction Adenocarcinoma

The industry-sponsored, multicenter, phase 2 INFINITY trial evaluated the combination of tremelimumab and durvalumab as preoperative treatment over 12 weeks in patients with resectable microsatellite-instability (MSI)–high gastric or gastroesophageal junction adenocarcinoma (abstract 358).

Of 15 evaluable patients (14 underwent surgery), 9 (60%) had a pathologic complete response and another 3 (20%) had near pathologic complete response. An additional two patients with clinical complete response declined surgery. Grade 3 or higher immune treatment-related serious adverse events occurred in three patients and were treated with high-dose steroids.

This patient series adds to the accumulating evidence of high rates of pathologic complete response to immune checkpoint inhibitor therapy in MSI-high gastrointestinal cancers and continues the debate about potential nonoperative management in patients achieving a clinical complete response.

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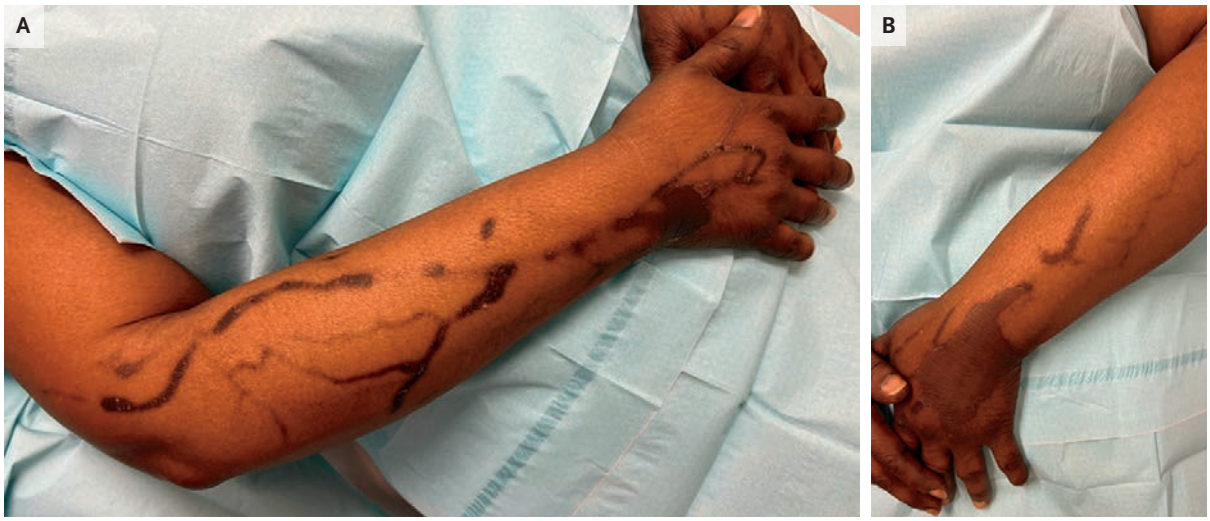
Images in Clinical Medicine

Serpentine Supravenous Hyperpigmentation



A 58-year-old woman with a history of metastatic uterine leiomyosarcoma presented to the dermatology clinic with a 1-month history of a nonpruritic rash on her arms. Six weeks before presentation, she had started palliative chemotherapy with gemcitabine and docetaxel, which had been administered through peripheral intravenous catheters. On examination, hyperpigmented plaques were observed on the dorsa of both hands at the sites of previous intravenous access. The darkened skin extended up the arms in a linear pattern along the network of superficial veins (Panels A and B). The skin lesions were slightly palpable but were not tender. A diagnosis of docetaxel-associated serpentine supravenous hyperpigmentation was made. Serpentine supravenous hyperpigmentation is a cutaneous side effect of several intravenous chemotherapy agents, including docetaxel, vinorelbine, and — most commonly — fluorouracil. The mechanism of skin hyperpigmentation remains unclear, but the reaction is benign; the underlying veins remain patent. The reaction can be avoided with the use of a central venous catheter for drug infusion. In this patient, a central venous catheter was placed for subsequent administration of chemotherapy. At a follow-up visit 2 months later, the rash had abated.

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