Review of the following abstracts from the 39th Annual Miami Breast Cancer Conference®, hosted by Physicians’ Education Resource®, LLC (PER®), was conducted by the program chairs and planning committee.

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In HER2+ MBC following 1L progression and beyond*

EMBRACE
SUPERIOR SURVIVAL
WITH PROVEN SAFETY

TUKYSA + trastuzumab + capecitabine vs placebo + trastuzumab + capecitabine
- Median PFS: 7.8 months (95% CI: 7.5-9.6) vs 5.6 months (95% CI: 4.2-7.1); HR = 0.54 (95% CI: 0.42-0.71); P < 0.00001 (primary endpoint)†

More than 2 years median overall survival at follow-up analysis‡
- Primary analysis‡: 21.9 months (95% CI: 18.3-31.0) vs 17.4 months (95% CI: 13.6-19.9); HR = 0.66 (95% CI: 0.50-0.87); P = 0.0048 (secondary endpoint)
- Follow-up analysis§: 24.7 months (95% CI: 21.6-28.9) vs 19.2 months (95% CI: 16.4-21.4); HR = 0.73 (95% CI: 0.59-0.90); median follow-up: 29.6 months²

Follow-up OS analysis: Results of this prespecified exploratory analysis are descriptive but not conclusive, are not controlled for type 1 error, and should be interpreted with caution.

Safe and well tolerated³
- The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, PPE, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash¹
- 6% of patients discontinued TUKYSA due to adverse reactions vs 3% with placebo³

Indication
TUKYSA is indicated in combination with trastuzumab and capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

Select Important Safety Information
- The Prescribing Information for TUKYSA contains warnings and precautions for diarrhea, hepatotoxicity, and embryo-fetal toxicity, some of which may be severe
- The most common serious adverse reactions in ≥2% of patients who received TUKYSA were diarrhea, vomiting, nausea, abdominal pain, and seizure

Study design: HER2CLIMB was a randomized (2:1) trial of TUKYSA or placebo each in combination with trastuzumab and capecitabine in 612 patients with HER2+ MBC, previously treated with trastuzumab, pertuzumab, and T-DM1. Primary endpoint was PFS per BICR in the first 480 patients enrolled. Secondary endpoints included OS. A prespecified exploratory analysis was included to evaluate OS at ~2 years. Please see additional study design on the following page.

See additional follow-up data inside >

The TUKYSA regimen is the #1 prescribed treatment for patients with brain metastases in 2L+ HER2+ MBC⁴

Please see full Important Safety Information on the following pages.

*≥1 anti-HER2-based regimen in the metastatic setting.¹
†Data from the first 480 patients.¹
‡Primary analysis (data cutoff: September 4, 2019).³
§Prespecified exploratory analysis (data cutoff: February 8, 2021).⁴
²Based on brand prescriptions from 10/20 to 05/21.⁵
1L = first-line; 2L = second-line; BICR = blinded independent central review; CI = confidence interval; HER = human epidermal growth factor receptor; HR = hazard ratio; MBC = metastatic breast cancer; OS = overall survival; PFS = progression-free survival; PPE = palmar-plantar erythrodysesthesia; T-DM1 = ado-trastuzumab emtansine.

TUKYSA tucatinib
50 mg | 150 mg tablets
In combination with trastuzumab + capecitabine

**TUKYSA ACHIEVED A MEDIAN OVERALL SURVIVAL OF MORE THAN 2 YEARS AT FOLLOW-UP ANALYSIS**

**OS in the total population (N = 612)**

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>TUKYSA arm</th>
<th>Control arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>3</td>
<td>387</td>
<td>387</td>
</tr>
<tr>
<td>6</td>
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<td>51</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>54</td>
<td>14</td>
<td>14</td>
</tr>
</tbody>
</table>

Results of this prespecified exploratory analysis are descriptive but not conclusive, are not controlled for type 1 error, and should be interpreted with caution. Data cutoff for follow-up analysis was February 8, 2021.

**Important Safety Information**

**Warnings and Precautions**

- **Diarrhea:** TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 81% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 and 0.5% with Grade 4. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. Median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to TUKYSA dose reductions in 6% of patients and TUKYSA discontinuation in 1% of patients. Prophylactic use of antidiarrheal treatment was not required on HER2CLIMB. If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

- **Hepatotoxicity:** TUKYSA can cause severe hepatotoxicity. In HER2CLIMB, 8% of patients who received TUKYSA had an ALT increase >5 × ULN, 6% had an AST increase >5 × ULN, and 1.5% had a bilirubin increase >3 × ULN (Grade ≥3). Hepatotoxicity led to TUKYSA dose reductions in 8% of patients and TUKYSA discontinuation in 1.5% of patients. Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

- **Embryo-Fetal Toxicity:** TUKYSA can cause fetal harm. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential, and male patients with female partners of reproductive potential, to use effective contraception during TUKYSA treatment and for at least 1 week after the last dose.

**Adverse Reactions**

Serious adverse reactions occurred in 26% of patients who received TUKYSA; those occurring in ≥2% of patients were diarrhea (4%), vomiting (2.5%), nausea (2%), abdominal pain (2%), and seizure (2%). Fatal adverse reactions occurred in 2% of patients who received TUKYSA including sudden death, sepsis, dehydration, and cardiogenic shock. Adverse reactions led to treatment discontinuation in 6% of patients who received TUKYSA; those occurring in ≥1% of patients were hepatotoxicity (1.5%) and diarrhea (1%). Adverse reactions led to dose reduction in 21% of patients who received TUKYSA: those occurring in ≥2% of patients were hepatotoxicity (8%) and diarrhea (6%).

The most common adverse reactions in patients who received TUKYSA were diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

**Lab Abnormalities**

In HER2CLIMB, Grade ≥3 laboratory abnormalities reported in ≥5% of patients who received TUKYSA were decreased phosphate, increased ALT, decreased potassium, and increased AST.
CONSISTENT SAFETY PROFILE AT FOLLOW-UP ANALYSIS²

At the 2-year follow-up analysis²

The most common adverse reactions (≥20%) were diarrhea, PPE, nausea, fatigue, vomiting, decreased appetite, stomatitis, headache, AST increased, anemia, ALT increased, and blood bilirubin increased.

<table>
<thead>
<tr>
<th>TEAEs Grade ≥3</th>
<th>TUKYSA vs PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>61% (245/404) in the TUKYSA arm vs 51% (101/197) in the control arm</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TEAEs leading to death</th>
<th>TUKYSA vs PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>2% (8/404) in the TUKYSA arm vs 3% (6/197) in the control arm</td>
<td></td>
</tr>
</tbody>
</table>

The rate of discontinuation due to adverse reactions for the TUKYSA arm remained consistent with the primary analysis²,³†

<table>
<thead>
<tr>
<th>PRIMARY ANALYSIS²</th>
<th>TUKYSA 6% vs PLACEBO 3%</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLLOW-UP ANALYSIS²</td>
<td>TUKYSA 6% vs PLACEBO 4%</td>
</tr>
</tbody>
</table>

*Study design: HER2CLIMB was a randomized (2:1), double-blind trial of TUKYSA or placebo each in combination with trastuzumab and capecitabine in 612 patients with HER2+ MBC, previously treated with trastuzumab, pertuzumab, and T-DM1. Primary endpoint was PFS per BICR in the first 480 patients enrolled. Secondary endpoints assessed in the full study population included OS, PFS in patients with brain metastases, confirmed ORR, and safety.

The protocol included a prespecified exploratory analysis to evaluate OS, PFS (by investigator assessment), and safety in the total study population (N = 612) at ~2 years from the last patient randomized. After the primary analysis, 12.9% of patients in the placebo arm (26/202) crossed over to receive TUKYSA in combination with trastuzumab and capecitabine, with the first patient crossover in February 2020. Median overall study follow-up: 29.6 months (data cutoff: February 8, 2021). Because formal testing of all alpha-controlled endpoints was considered final at the primary analysis, data from this prespecified updated analysis are for descriptive purposes only.²,³

†Follow-up safety analysis was done as part of a prespecified exploratory analysis. Results are presented as descriptive data that are not intended to provide conclusions about safety and should be interpreted with caution.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ORR = objective response rate; TEAE = treatment-emergent adverse event.

The mean increase in serum creatinine was 32% within the first 21 days of treatment with TUKYSA. The serum creatinine increases persisted throughout treatment and were reversible upon treatment completion. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

Drug Interactions

- **Strong CYP3A/Moderate CYP2C8 Inducers**: Concomitant use may decrease TUKYSA activity. Avoid concomitant use of TUKYSA.

- **Strong or Moderate CYP2C8 Inhibitors**: Concomitant use of TUKYSA with a strong CYP2C8 inhibitor may increase the risk of TUKYSA toxicity; avoid concomitant use. Increase monitoring for TUKYSA toxicity with moderate CYP2C8 inhibitors.

- **CYP3A Substrates**: Concomitant use may increase the toxicity associated with a CYP3A substrate. Avoid concomitant use of TUKYSA where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP3A substrate dosage.

- **P-gp Substrates**: Concomitant use may increase the toxicity associated with a P-gp substrate. Consider reducing the dosage of P-gp substrates where minimal concentration changes may lead to serious or life-threatening toxicity.

Use in Specific Populations

- **Lactation**: Advise women not to breastfeed while taking TUKYSA and for at least 1 week after the last dose.

- **Renal Impairment**: Use of TUKYSA in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment (CLcr < 30 mL/min), because capecitabine is contraindicated in patients with severe renal impairment.

- **Hepatic Impairment**: Reduce the dose of TUKYSA for patients with severe (Child-Pugh C) hepatic impairment.

Please see Brief Summary of Prescribing Information on adjacent pages.

References:
The recommended dosage of TUKYSA is 300 mg taken orally twice daily in combination with trastuzumab and capecitabine until disease progression or unacceptable toxicity. Advise patients to swallow TUKYSA tablets whole and not to chew, crush, or split prior to swallowing. Advise patients not to ingest tablet if it is broken, cracked, or not otherwise intact. Advise patients to take TUKYSA approximately 12 hours apart and at the same time each day with or without a meal. If the patient vomits or misses a dose of TUKYSA, instruct the patient to take the next dose at its usual scheduled time.

When given in combination with TUKYSA, the recommended dosage of capecitabine is 1000 mg/m² orally twice daily taken within 30 minutes after a meal. TUKYSA and capecitabine can be taken at the same time. Refer to the Full Prescribing Information for trastuzumab and capecitabine for additional information.

Dosage Modifications for Adverse Reactions

The recommended TUKYSA dose reductions and dosage modifications for adverse reactions are provided in Tables 1 and 2. Refer to the Full Prescribing Information for trastuzumab and capecitabine for information about dosage modifications for these drugs.

Table 1: Recommended TUKYSA Dose Reductions for Adverse Reactions

<table>
<thead>
<tr>
<th>Dose Reduction</th>
<th>Recommended TUKYSA Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>250 mg orally twice daily</td>
</tr>
<tr>
<td>Second</td>
<td>200 mg orally twice daily</td>
</tr>
<tr>
<td>Third</td>
<td>150 mg orally twice daily</td>
</tr>
</tbody>
</table>

Permanently discontinue TUKYSA in patients unable to tolerate 150 mg orally twice daily.

Table 2: Recommended TUKYSA Dosage Modifications for Adverse Reactions

<table>
<thead>
<tr>
<th>Severity</th>
<th>TUKYSA Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.</td>
</tr>
<tr>
<td>Grade 3 without anti-diarrheal treatment</td>
<td>Permanent discontinuation of TUKYSA.</td>
</tr>
<tr>
<td>Grade 3 with anti-diarrheal treatment</td>
<td>Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Permanent discontinuation of TUKYSA.</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td></td>
</tr>
<tr>
<td>Grade 2 bilirubin (&gt;1.5 to 3 × ULN)</td>
<td>Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.</td>
</tr>
<tr>
<td>Grade 3 ALT or AST (&gt;5 to 10 × ULN)</td>
<td>Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.</td>
</tr>
<tr>
<td>Grade 4 ALT or AST (&gt;20 × ULN) or Grade 4 bilirubin (&gt;10 × ULN)</td>
<td>Permanently discontinue TUKYSA.</td>
</tr>
<tr>
<td>ALT or AST &gt;3 × ULN AND Bilirubin &gt;2 × ULN</td>
<td>Permanently discontinue TUKYSA.</td>
</tr>
</tbody>
</table>

Other adverse reactions

| Grade 3                          | Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level. |
| Grade 4                          | Permanent discontinuation of TUKYSA. |

1. Grades based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.
2. Abbreviations: ULN = upper limit of normal; ALT = alanine aminotransferase; AST = aspartate aminotransferase

Dosage Modifications for Severe Hepatic Impairment: For patients with severe hepatic impairment (Child-Pugh C), reduce the recommended dosage to 200 mg orally twice daily.

Dosage Modifications for Concomitant Use with Strong CYP2C8 Inhibitors: Avoid concomitant use of strong CYP2C8 inhibitors with TUKYSA. If concomitant use with a strong CYP2C8 inhibitor cannot be avoided, reduce the recommended dosage to 100 mg orally twice daily. After discontinuation of the strong CYP2C8 inhibitor for 3 elimination half-lives, resume the TUKYSA dose that was taken prior to initiating the inhibitor.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Diarrhea: TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 81% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 diarrhea and 0.5% with Grade 4 diarrhea. Both patients who developed Grade 4 diarrhea subsequently died with diarrhea as a contributor to death. The median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to dose reductions of TUKYSA in 6% of patients and discontinuation of TUKYSA in 1% of patients. Prophylactic use of anti-diarrheal treatment was not required on HER2CLIMB. If diarrhea occurs, administer anti-diarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

Hepatotoxicity: TUKYSA can cause severe hepatotoxicity. In HER2CLIMB, 8% of patients who received TUKYSA had an ALT increase >5 × ULN, 6% had an AST increase >5 × ULN, and 1.5% had a bilirubin increase >3 × ULN (Grade ≥3). Hepatotoxicity led to dose reduction of TUKYSA in 8% of patients and discontinuation of TUKYSA in 1.5% of patients. Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

Embryo-Fetal Toxicity: Based on findings from animal studies and its mechanism of action, TUKYSA can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of tucatinib to pregnant rats and rabbits during organogenesis caused embryo-fetal mortality, reduced fetal weight and fetal abnormalities at maternal exposures ≥1.3 times the human exposure (AUC) at the recommended dose. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose. TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information for trastuzumab and capecitabine for pregnancy and contraception information.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. HER2-Positive Metastatic Breast Cancer (HER2CLIMB)

The safety of TUKYSA in combination with trastuzumab and capecitabine was evaluated in HER2CLIMB. Patients received either TUKYSA 300 mg twice daily plus trastuzumab and capecitabine (n=404) or placebo plus trastuzumab and capcitabine (n=197). The median duration of treatment was 5.6 months (range: 3 days, 2.9 years) for the TUKYSA arm. Serious adverse reactions occurred in 26% of patients who received TUKYSA. Serious adverse reactions in ≥2% of patients who received TUKYSA were diarrhea (4%), vomiting (2.5%), nausea (2%), abdominal pain (2%), and seizure (2%). Fatal adverse reactions occurred in 2% of patients who received TUKYSA including sudden death, sepsis, dehydration, and cardiogenic shock.

Adverse reactions leading to treatment discontinuation occurred in 6% of patients who received TUKYSA. Adverse reactions leading to treatment discontinuation of TUKYSA in ≥1% of patients were hepatotoxicity (1.5%) and diarrhea (1%). Adverse reactions leading to dose reduction occurred in 21% of patients who received TUKYSA. Adverse reactions leading to dose reduction of TUKYSA in ≥2% of patients were hepatotoxicity (8%) and diarrhea (6%). The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

Table 2: Adverse Reactions (≥10%) in Patients Who Received TUKYSA and with a Difference Between Arms of ≥5% Compared to Placebo in HER2CLIMB (All Grades)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TUKYSA + Trastuzumab + Capecitabine (N=404)</th>
<th>Placebo + Trastuzumab + Capcitabine (N=197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>55</td>
<td>49</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>12</td>
</tr>
</tbody>
</table>

| Gastrointestinal disorders                     |                                             |                                             |
|------------------------------------------------|                                             |                                             |
| Diarrhea                                       | 81                                          | 53                                          |
| Nausea                                         | 58                                          | 44                                          |
| Vomiting                                       | 36                                          | 25                                          |
| Stomatitis                                     | 32                                          | 21                                          |

| Skin and subcutaneous tissue disorders         |                                             |                                             |
|------------------------------------------------|                                             |                                             |
| Palmar-plantar erythrodysesthesia syndrome     | 63                                          | 53                                          |
| Rash                                           | 20                                          | 15                                          |

| Hepatic disorders                              |                                             |                                             |
|------------------------------------------------|                                             |                                             |
| Hepatotoxicity                                 | 42                                          | 24                                          |

| Metabolism and nutrition disorders             |                                             |                                             |
|------------------------------------------------|                                             |                                             |
| Decreased appetite                             | 25                                          | 0                                           |
with a CYP3A substrate. Avoid concomitant use of TUKYSA with CYP3A substrates, plasma concentrations of CYP3A substrate, which may increase the toxicity associated with a P-gp substrate, where minimal concentration changes may lead to serious or life-threatening toxicities.

Concomitant use of TUKYSA with a CYP3A substrate increased the plasma concentrations of CYP3A substrate, which may increase the toxicity associated with a P-gp substrate. Consider reducing the dosage of a P-gp substrates, where minimal concentration changes may lead to serious or life-threatening toxicities.

Effects of Other Drugs on TUKYSA

**CYP3A Substrates:** Concomitant use of TUKYSA with a CYP3A substrate increased the plasma concentrations of CYP3A substrate, which may increase the toxicity associated with a CYP3A substrate. Avoid concomitant use of TUKYSA with CYP3A substrates,

### Table 4: Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received TUKYSA and with a Difference of ≥5% Compared to Placebo in HER2CLIMB

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TUKYSA + Trastuzumab + Capecitabine (N = 404)</th>
<th>Placebo + Trastuzumab + Capecitabine (N = 197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades %</td>
<td>Grades ≥3 %</td>
<td>All Grades %</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>59.3</td>
<td>51.5</td>
</tr>
<tr>
<td>Increased phosphate</td>
<td>5.7</td>
<td>4.5</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>4.8</td>
<td>2.7</td>
</tr>
<tr>
<td>Increased AST</td>
<td>4.3</td>
<td>2.5</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>4.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Decreased potassium</td>
<td>3.6</td>
<td>3.1</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>3.3</td>
<td>6.0</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>2.8</td>
<td>2.3</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>2.6</td>
<td>17.0</td>
</tr>
</tbody>
</table>

1. The denominator used to calculate the rate varied from 351 to 400 in the TUKYSA arm and 173 to 197 in the control arm based on the number of patients with a baseline value and at least one post-treatment value. Grading was based on NCI-CTCAE v.4.03 for laboratory abnormalities; 1.0 for increased creatinine which only includes patients with a creatinine increase based on the upper limit of normal definition for grade 1 events (NCI CTCAE v5.0).
2. Laboratory criteria for Grade 1 is identical to laboratory criteria for Grade 2.
3. Due to inhibition of renal tubular transport of creatinine without affecting glomerular function.
4. There is no definition for Grade 2 in CTCAE v4.03.
5. Increased Creatinine: The mean increase in serum creatinine was 32% within the first 21 days of treatment with TUKYSA. The serum creatinine increases persisted throughout treatment and were reversible upon treatment completion. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

## Drug Interactions

### Effects of Other Drugs on TUKYSA

**Strong CYP3A Inducers or Moderate CYP2C8 Inducers:** Concomitant use of TUKYSA with a strong CYP3A or moderate CYP2C8 inducer decreased tucatinib plasma concentrations, which may reduce TUKYSA activity. Avoid concomitant use of TUKYSA with a strong CYP3A inducer or a moderate CYP2C8 inducer.

**Strong or Moderate CYP2C8 Inhibitors:** Concomitant use of TUKYSA with a strong CYP2C8 inhibitor increased tucatinib plasma concentrations, which may increase the risk of TUKYSA toxicity. Avoid concomitant use of TUKYSA with a strong CYP2C8 inhibitor.

**Effects of TUKYSA on Other Drugs**

**CYP3A Substrates:** Concomitant use of TUKYSA with a CYP3A substrate increased the plasma concentrations of CYP3A substrate, which may increase the toxicity associated with a CYP3A substrate.

Where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP3A substrate dosage in accordance with approved product labeling.

**P-glycoprotein (P-gp) Substrates:** Concomitant use of TUKYSA with a P-gp substrate increased the plasma concentrations of P-gp substrate, which may increase the toxicity associated with a P-gp substrate. Consider reducing the dosage of a P-gp substrates, where minimal concentration changes may lead to serious or life-threatening toxicities.

### USE IN SPECIFIC POPULATIONS

#### Pregnancy

**Risk Summary:** TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for pregnancy information. Based on findings in animals and its mechanism of action, TUKYSA can cause fetal harm when administered to a pregnant woman. There are no available human data on TUKYSA use in pregnant women to inform a drug-associated risk.

In animal reproduction studies, administration of tucatinib to pregnant rats and rabbits during organogenesis resulted in embryo-fetal mortality, reduced fetal weight and fetal abnormalities at maternal exposures ≥ 1.3 times the human exposure (AUC) at the recommended dose. Advise pregnant women and females of reproductive potential of the potential risk to the fetus.

**Lactation**

**Risk Summary:** TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for lactation information. There are no data on the presence of tucatinib or its metabolites in human or animal milk or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with TUKYSA and for at least 1 week after the last dose.

**Females and Males of Reproductive Potential**

TUKYSA can cause fetal harm when administered to a pregnant woman. TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for contraception and infertility information.

**Pregnancy Testing:** Verify the pregnancy status of females of reproductive potential prior to initiating treatment with TUKYSA.

**Contraception:**

Females: Advise females of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose.

Males: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose.

**Infertility:** Based on findings from animal studies, TUKYSA may impair male and female fertility.

**Pediatric Use:** The safety and effectiveness of TUKYSA in pediatric patients have not been established.

**Geriatric Use:** In HER2CLIMB, 82 patients who received TUKYSA were ≥ 65 years, of whom 8 patients were ≥ 75 years. The incidence of serious adverse reactions in those receiving TUKYSA was 34% in patients ≥ 65 years compared to 24% in patients < 65 years. The most frequent serious adverse reactions in patients who received TUKYSA and ≥ 65 years were diarrhea (9%), vomiting (6%), and nausea (5%). There were no observed overall differences in the effectiveness of TUKYSA in patients ≥ 65 years compared to younger patients. There were too few patients ≥ 75 years to assess differences in effectiveness or safety.

**Renal Impairment:** The use of TUKYSA in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment (Clcr < 30 mL/min estimated by Cockcroft-Gault Equation), because capecitabine is contraindicated in patients with severe renal impairment. Refer to the Full Prescribing Information of capecitabine for additional information in severe renal impairment. No dose adjustment is recommended for patients with mild or moderate renal impairment (creatinine clearance [ClCr] 30 to 89 mL/min).

**Hepatic Impairment:** Tucatinib exposure is increased in patients with severe hepatic impairment (Child-Pugh C). Reduce the dose of TUKYSA for patients with severe (Child-Pugh C) hepatic impairment. No dose adjustment for TUKYSA is required for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.
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6. Real-world Adherence and Persistence With Palbociclib Treatment Among Insured Patients With HR+/HER2– Metastatic Breast Cancer in the United States

7 TiP. Randomized, Multicenter, International Phase 3 ARTEST Study to Evaluate the Efficacy and Safety of Enobosarm Versus Active Control for the Treatment of AR+, ER+, HER2– Metastatic Breast Cancer in Patients Who Previously Received an Estrogen-Blocking Agent and CDK4/6 Inhibitor

8 TiP. Randomized, Multicenter, Phase 3 Study to Evaluate the Combination of Enobosarm and Abemaciclib Compared With Estrogen-Blocking Agent for the Second-Line Treatment of AR+, ER+, HER2– Metastatic Breast Cancer in Patients Who Have Previously Received Palbociclib and an Estrogen-Blocking Agent Combination Therapy

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48. A Comparison of Race and Ethnicity and Germline Results in ASBrS vs NCCN Guidelines

49. Racial/Ethnic Groups Have Different Clustering of Common Cancer Genes
Incidence, Clinical and Laboratory Predictors of Adverse Events (AEs) and Outcomes in Patients (Pts) With Breast Cancer Receiving Alpelisib in the Real World: A Single Institution Experience

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Background/Aim
The aim was to identify the incidence and predictors of alpelisib (Piqray)-related AEs in clinical practice. Although clinical trials provided data on AEs of alpelisib, there is a need to study AEs in the real world due to differences in patient characteristics and alpelisib use following multiple lines of therapy.

Methods
We reviewed charts of pts with metastatic, hormone receptor (HR)+, HER2-negative, PIK3CA-mutated breast cancer who were treated with alpelisib from 2019 to 2021. Laboratory and clinical variables including comorbidities, metastasis site, prior therapy, clinical responses, time from alpelisib initiation to progression, and last follow-up were collected. Association of these factors with AEs and clinical response were evaluated using a logistic regression model. SAS statistical software, version 9.4 (SAS Institute Inc) was used to perform statistical analysis at a significance level of 0.05.

Results
Twenty pts were included. Median age was 67 years (48-77 years); 80% of pts (16/20) had received 2 or more lines of prior treatment, 36.8% (7/19) had no comorbidities, and 95% (19/20) had more than 1 site of visceral metastases. Eighty-five percent of pts (17/20) experienced AEs; the most common were hyperglycemia (76.5%), nausea (41.2%), diarrhea (35.3%), and fatigue (29.4%). The most common grade 3 (G3) AEs leading to alpelisib interruption/dose reduction/discontinuation were hyperglycemia (60%) and skin rash (30%). No significant difference in clinical characteristics between pts who did or did not experience an AE was observed. Median duration of alpelisib treatment was 2 months (IQR, 0.6-8.5) for pts who developed AEs and 5.5 months (IQR, 1.2-10.4) for pts without AEs (P = .5). As expected, 88.9% of pts (8/9) who experienced grade 3 or greater AEs had a dose reduction and 80% (8/10) interrupted/discontinued the treatment, while only 22.2% (2/9) who did not have grade 3 or greater AEs had a dose reduction and only 12.5% (1/8) discontinued/interrupted the treatment (P = .015 for both); 44.4% of pts (8/18) achieved a partial response (PR). Pts with a PR had a lower likelihood of visceral metastases (38%) compared with those having stable/progressive disease (90%; P = .043). Lower median absolute lymphocyte count (1.23 × 109/L) was associated with a higher likelihood of PR (P = .046).

Conclusion
In this single-institution study, we found a higher incidence of AEs than reported in prior trials with promising responses in a heavily pretreated population. This emphasizes the need for strategies to mitigate toxicities that would allow continuation of alpelisib, given the observed clinical benefit.

Real-world Adherence and Persistence With Palbociclib Treatment Among Insured Patients With HR+/HER2-Metastatic Breast Cancer in the United States

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1Optum, Inc
2Pfizer Inc

Background/Significance
Palbociclib (Ibrance), the first oral cyclin-dependent kinase inhibitor, is standard care for hormone receptor-positive (HR+), HER2-advanced or metastatic breast cancer (mBC). Palbociclib adherence and persistence are necessary to achieve optimal clinical outcomes in patients treated in real-world settings.

Materials and Methods
This was a retrospective cohort study of insured adults in the Optum Research Database, an administrative health care claims database capturing about 20% of commercial...
and Medicare Advantage Part D enrollees in the United States. Adults diagnosed with mBC between February 2015 and December 2019 who initiated palbociclib in the first-line (1L) setting were selected for analysis. The index date was the first fill date of palbociclib before or anytime after the mBC diagnosis. Continuous enrollment 12 or more months pre- and 1 or more months post index was required. Palbociclib treatment was evaluated over the variable follow-up period. Medication possession ratio (MPR) was calculated as palbociclib days’ supply between the first and last fill divided by the total time treated. MPR of 80% or more was considered adherent. Palbociclib discontinuation was defined by the occurrence of a 60- or 90-day gap in days’ supply, adjusted for inpatient stays during which time medication was assumed to be supplied by the facility. Persistence was calculated as the time to palbociclib discontinuation using Kaplan-Meier methods over variable follow-up.

**Results**

One thousand sixty-six patients initiated 1L palbociclib, with 811 patients receiving palbociclib with aromatase inhibitors (P+AI) and 255 patients receiving palbociclib with fulvestrant (P+F). Mean follow-up time was 17 (P+AI) and 16 months (P+F). Mean age was 67 years for P+F and 66 years for P+AI. Overall, 79.9% of patients were adherent; mean MPR was 0.88 (median, 0.94) within each group. During the variable follow-up period, 41.3% of patients receiving P+AI and 45.9% receiving P+F discontinued palbociclib. Among those who discontinued, 23.9% and 21.4% discontinued within the first 3 months, respectively. Median time to discontinuation was 19.9 months (P+AI) and 15.2 months (P+F). 59.1% receiving P+F and 68.7% receiving P+AI remained on palbociclib at 12 months post index (90-day gap).

**Conclusions**

This analysis suggests most patients are well adherent with 1L palbociclib and persist on therapy. Further research is needed to understand reasons for early discontinuation in real-world practice.

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**7TiP Randomized, Multicenter, International Phase 3 ARTEST Study to Evaluate the Efficacy and Safety of Enobosarm Versus Active Control for the Treatment of AR+, ER+, HER2– Metastatic Breast Cancer in Patients Who Previously Received an Estrogen-Blocking Agent and CDK4/6 Inhibitor**

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6Veru Inc, Miami, FL
7Dana Farber Cancer Institute, Boston, MA

**Background/Significance**

Targeting the androgen receptor (AR) may be the next important endocrine therapy for women with advanced breast cancer. AR, the most abundantly expressed steroid receptor in breast cancer, has been demonstrated to be a tumor suppressor when activated. Enobosarm is an oral, selective AR-targeting agonist that activates the AR in breast cancer. Enobosarm has an extensive clinical experience in 25 clinical trials and 1450 dosed subjects, including in 2 phase 2 studies conducted in women (158 subjects) who had AR-positive (AR+), estrogen receptor-positive (ER+), HER2-negative (HER2–) metastatic breast cancer (mBC). An open-label, parallel-design, phase 2 study was conducted in women with heavily pretreated ER+, HER2– mBC who were randomized to daily oral enobosarm at a dose of 9 mg or 18 mg. The evaluable group were patients who were AR+ (> 10% AR nuclear staining). The primary end point was clinical benefit rate (CBR) at 24 weeks. The CBRs at 24 weeks were 32% with the 9-mg dose and 29% with 18 mg. Median duration of clinical benefit was not reached in the 9-mg group (range, 8.2 months to not reached) and 14.1 months for the 18-mg group (range, 11-16.5 months). A post hoc AR expression subset analysis conducted in the intent-to-treat population who had measurable disease at baseline revealed that the best overall response rate (ORR) was significantly higher in patients with 40% or greater AR nuclear staining versus
those less than 40%, at 34% and 2.7%, respectively ($P = .0003$). CBR at 24 weeks was significantly higher for those with 40% or greater AR nuclear staining versus less than 40%, at 52% and 14%, respectively ($P < .0004$). Median radiographic progression-free survival (PFS) for 40% or greater AR was 5.47 months (95% CI, 2.83-11.13) versus 2.73 months for less than 40% AR (95% CI, 2.63-2.80; $P < .001$). Overall, treatment with enobosarm was well tolerated with significantly positive effects on quality-of-life measurements.

**Design and Methods**

The ARTEST trial (NCT04869943) is a phase 3, multicenter, international, randomized, open-label, 2 treatment-arm efficacy and safety study. Approximately 210 subjects with AR+, ER+, HER2- mBC and with AR nuclei staining of 40% or greater are being randomized 1:1 to either enobosarm 9-mg oral daily dose or an active comparator (either exemestane, everolimus [Afinitor], or a selective estrogen receptor modulator; physician's choice). Subjects are being treated until disease progression or an unacceptable adverse event is observed. The primary end point of the study is imaging-based progression-free survival as measured by RECIST 1.1. The secondary objectives/end points of this study include the objective response rate, duration of response, overall survival, change from baseline in Short Physical Performance Battery (SPPB), and change in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ).

**Status**

The study is currently ongoing, and it is anticipated that enrollment will be completed this year.

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**8TiP Randomized, Multicenter, Phase 3 Study to Evaluate the Combination of Enobosarm and Abemaciclib Compared With Estrogen-Blocking Agent for the Second-Line Treatment of AR+, ER+, HER2- Metastatic Breast Cancer in Patients Who Have Previously Received Palbociclib and an Estrogen-Blocking Agent Combination Therapy**

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2Magee-Womens Hospital, University of Pittsburgh Medical Center, Pittsburgh, PA
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**Background/Significance**

Targeting the androgen receptor (AR) may be the next important endocrine therapy for women with advanced breast cancer. AR, the most abundantly expressed steroid receptor in breast cancer, has been demonstrated to be a tumor suppressor when activated. Enobosarm is an oral selective AR-targeting agonist that activates the AR in breast cancer. Enobosarm has an extensive clinical experience in 25 clinical trials and 1450 dosed subjects including in 2 phase 2 studies conducted in women (158 subjects) who had AR+, estrogen receptor–positive (ER+), HER2-negative metastatic breast cancer (mBC). An open-label, parallel-design phase 2 study was conducted in women with heavily pretreated ER+, HER2- metastatic breast cancer who were randomized to oral daily enobosarm at a dose of 9 mg or 18 mg. The evaluable group (EE) were patients who were AR-positive (>10% AR nuclear staining). In the EE population with measurable disease at baseline, 10 patients had received prior endocrine therapy plus a CDK4/6 inhibitor. Subsequent treatment with enobosarm in this cohort resulted in a clinical benefit rate of 50%, and the best objective response rate (ORR) was 30% (2 complete responses and 1 partial response). Of the 10 patients, 7 had AR nuclear staining of 40% or greater, which included the 3 patients who achieved partial and complete disease responses to enobosarm. None of the 3 patients in this cohort with AR nuclear staining less than 40% responded to enobosarm. Although in a small subset of the entire study, it appears that enobosarm monotherapy had activity in patients who had 40% or greater AR staining and who had progressed on standard endocrine therapy with
a CDK4/6 inhibitor. Overall, treatment with enobosarm was well tolerated with significant positive effects on quality-of-life measurements.

**Design and Methods**

The phase 3 ENABLAR-2 trial is a multicenter, randomized, open-label, 2 treatment-arm efficacy and safety study. Patients are being randomized to 2 treatment arms in a 1:1 fashion. If first-line therapy for mBC was a nonsteroidal aromatase inhibitor (AI) plus palbociclib (Ibrance), then the patient is randomized to either enobosarm plus abemaciclib (Verzenio) or fulvestrant. If first-line therapy for metastatic breast cancer was fulvestrant plus palbociclib, then the patient is randomized to either enobosarm plus abemaciclib or an AI (steroidal or nonsteroidal). The key objectives are to determine the safety and efficacy of the enobosarm and abemaciclib combination versus an alternative estrogen blocking agent in the treatment of AR+, ER+, HER2-negative (AR% nuclei staining ≥ 40%) mBC with a primary end point of imaging progression-free survival. Secondary end points include objective response rate, duration of response, overall survival, change from baseline in Short Physical Performance Battery (SPPB), change in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ), and change in body composition as measured by dual-energy x-ray absorptiometry (DEXA).

**Status**

The study is currently ongoing, and it is anticipated that enrollment will be completed this year.
Assessing Intratumor Heterogeneity in Programmed Death-Ligand 1 (PD-L1) Protein Expression in Early-Stage Breast Cancer

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Background
Programmed death–ligand 1 (PD-L1) expression is required for benefit from immune checkpoint inhibitors in metastatic triple-negative breast cancer (TNBC), although in the neoadjuvant setting, patients benefited regardless of PD-L1 expression. We aimed to examine intratumor spatial heterogeneity of PD-L1 protein expression in multiple regions of primary breast cancers.

Materials and Methods
Biopsies were collected from 3 separate tumor regions of surgically resected primary tumors without prior neoadjuvant systemic therapy. E1L3N antibody was used to assess PD-L1 status. The combined positivity score (CPS) method was used for scoring (PD-L1 positive defined as CPS >10). Fleiss Multirater Kappa assessed heterogeneity of PD-L1 expression among the different samples of the same tumor. Optimal agreement is suggested by a kappa agreement coefficient of 0.6 or more. Association between PD-L1 status and tumor-infiltrating lymphocyte (TIL) counts was assessed using Mann-Whitney test.

Results
Of the 33 included patients, 9 (27%) had TNBC, 5 (15%) had HER2-positive disease, and 19 (58%) had hormone receptor-positive, HER2-negative disease. Four of 33 patients (12%) had 1 biopsy sample showing PD-L1 positive status with additional biopsies of different regions of the tumor showing negative results. Fleiss’ kappa analysis on patients with all 3 biopsy samples per tumor available and able to be stained for PD-L1 (29 of 33 [88%]) showed an overall agreement of –0.36 (95% CI, –0.246 to 0.174; P = .739) when using CPS as categorical variable (positive vs negative) and 0.410 (95% CI, 0.286-0.535; P <.01) when using CPS as continuous variable. PD-L1 status was associated with TIL counts, with a median TIL count of 5% for PD-L1 positive and 0% for PD-L1 negative (P = .2949).

Conclusions
Our study showed that in 12% of the cases, PD-L1 was found to be positive in one of the tumor areas and all remaining biopsy samples of the same tumor were found to be negative, suggesting intratumor spatial heterogeneity regarding PD-L1 expression in early-stage breast cancer. However, due to the overall low incidence of PD-L1 positivity, it seems unlikely that the benefit of immunotherapy in early-stage breast cancer would be simply explained by sampling error. Further studies are required to investigate effective predictive biomarkers of response to immunotherapy, as well as to standardize PD-L1 assessment in breast cancer.

Real-world Patient Characteristics, Treatment Patterns, and Clinical Outcomes Among Talazoparib-Treated Patients With HER2-Negative, Locally Advanced or Metastatic Breast Cancer and Germline BRCA Mutations

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Background
Germline BRCA (gBRCA) mutations are detected in less than 5% of unselected patients with metastatic breast cancer (mBC). Talazoparib (Talzenna) is a PARP inhibitor approved by the FDA on October 16, 2018, for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), HER2-negative locally advanced or metastatic breast cancer (LA/mBC). The objective of this retrospective chart review study is to describe the demographic and clinical characteristics, treatment patterns, and clinical outcomes among adult patients with
gBRCAm, HER2-negative LA/mBC treated with talazoparib in the real-world setting in the United States.

**Methods**
A subset of physicians from the Cardinal Health Oncology Provider Extended Network abstracted data from the medical records of US adult patients with gBRCAm, HER2-negative LA/mBC who initiated talazoparib monotherapy on or after October 16, 2018. Demographic and clinical characteristics, treatment patterns, and clinical outcomes were reported using descriptive statistics. The Kaplan-Meier method was used to describe time-to-event outcomes.

**Results**
Eighty-four patients treated by 9 community practice physicians met eligibility criteria and were included in this study. Among eligible patients, 98% were female, median age at initiation of talazoparib was 62 years, and 71% were White. Hormone receptor–positive status was reported for 36% of patients, while triple-negative breast cancer classification was reported for 64% of patients. At the time of talazoparib initiation, all patients had stage IV disease, 30% had an ECOG performance status ≥2, 19% had brain metastases, and 96% had visceral metastases. A gBRCA1 mutation was detected among 64% of patients, while a mutation in gBRCA2 was detected among 36%. Talazoparib was given as first-line therapy for LA/mBC in 14% of patients, as second-line in 41%, and as third- or fourth-line in 45%. Patients had a median of 8.2 months duration of follow-up from initiation of talazoparib. Median time to talazoparib treatment discontinuation for any reason was 8.6 months (95% CI, 8.0-9.7). Median progression-free survival for talazoparib was 8.7 months (95% CI, 8.0-9.9). The overall tumor response rate during talazoparib treatment was 63%.

**Conclusion**
Findings from this study show the clinical benefits of talazoparib treatment in gBRCAm, HER2-negative LA/mBC in real-world practice in the United States. Clinical outcomes in this real-world population were consistent with those reported in the phase 3 EMBRACA randomized clinical trial (NCT01945775).

Funding: Pfizer, Inc

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**24 Real-world Use of Neratinib Post-Pertuzumab (P) and Ado- Trastuzumab Emtansine (T-DM1)**
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**Background**
Neratinib’s (Nerlynx) pivotal study was performed before pertuzumab (Perjeta) and trastuzumab emtansine (Kadcyla; T-DM1) adjuvant approvals. There is interest in neratinib’s treatment patterns after pertuzumab and T-DM1 use. Neat-HER was a United States virtual registry pilot of patients with early HER2-positive breast cancer (EBC) receiving neratinib as extended adjuvant therapy in clinical practice.

**Methods**
Eligibility included age 18 years and older and no clinical trial participation. Patients were recruited mainly through social media, patient advocacy group and the Puma patient texting program. Electronic health records (EHRs) for EBC treatment were collected 7 years pre- to 1 year post enrollment. We evaluated personal/tumor characteristics for those who did and did not receive neoadjuvant therapy and treatment received. Treatment information came from EHR via machine learning with physician review. Neratinib status and start/stop dates were abstracted from the physician narrative, and duration of neratinib treatment was the difference between the start and stop dates, inclusive of dose holds.

**Results**
Forty-six patients with EBC who received neratinib as extended adjuvant treatment enrolled in the registry in December 2018. The majority, 76% (n = 35), had neoadjuvant therapy with adjuvant treatment and 24% (n = 11) had only adjuvant treatment. Median age (50 vs 48 years) and race (91% White) were similar for neoadjuvant and adjuvant-only patients. Treatment settings were mostly in the South (52% overall), followed by the Midwest (22% overall). Among neoadjuvant therapy patients, 80% had hormone receptor
(ER/PR)-positive and 74% had lymph node–positive EBC. In adjuvant-only patients, 91% had hormone receptor–positive and 46% had lymph node–positive EBC. Fifty-four percent of neoadjuvant therapy (vs 82% adjuvant only patients) had high-grade EBC. The most common neoadjuvant therapy agents used were in order: taxanes, trastuzumab, pertuzumab, and platinum. For adjuvant treatment, pertuzumab use was less frequent (34% vs 64% of patients) and T-DM1 use more frequent (14% vs 0%) among neoadjuvant therapy patients vs those with only adjuvant treatment. Median duration of neratinib treatment in patients who had received neoadjuvant therapy was 12 months (mean, 11 months) with 94% of these patients completing or having ongoing treatment. In patients who received adjuvant treatment, only 55% of patients either completed or had ongoing neratinib treatment at the time of this analysis.

**Conclusions**

Neat-HER provided useful information on neoadjuvant therapy/adjuvant treatment patterns in patients receiving extended adjuvant neratinib. It was the first known examination of real-world treatment patterns of neratinib post pertuzumab and T-DM1. The high proportion of neoadjuvant therapy use and long duration of neratinib suggest the selective nature of these patients. Results need to be reproduced in larger patient cohorts.

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32 Impact of Comorbid HIV Infection on Breast Cancer Time to Treatment and Chemotherapy Relative Dose Intensity

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**Background/Significance**

Patients with breast cancer (BC) living with comorbid HIV (BCLWH) have poorer survival than patients with BC without HIV. Delayed time of treatment initiation (TTI) after BC diagnosis and reduced adjuvant chemotherapy relative dose intensity (RDI) both increase BC mortality. We aim to understand whether patients with BC with and without comorbid HIV experience differences in receipt of timely and complete BC treatment, which could contribute to survival disparities.

**Materials and Methods**

We used diagnostic codes from 2 centers to identify a cohort of women with stage I to III BC diagnosed between January 1, 2000, and December 31, 2018, and concurrent HIV infection. Tumor registry data were then used to identify a control cohort of patients with BC without HIV, with 2 controls matched by institution, BC stage, and year of diagnosis for each patient with BC living with HIV. Our primary end point was TTI after BC diagnosis. For patients who received neoadjuvant or adjuvant chemotherapy, we also measured RDI. We used a Cox proportional hazards model to compare TTI and a linear regression model to compare RDI.

**Results**

We identified 38 patients with BCLWH and matched 76 women with BC alone. They differed by race/ethnicity, relationship status, and estrogen receptor (ER) status, but had similar stage, HER2 status, and BC grade. Median TTI was 50 days (interquartile range IQR, 35-68) for patients with BCLWH and 44.5 days (IQR, 36-59.5) for control patients (HR adjusted for ER, race, and relationship status, 0.85; 95% CI, 0.58-1.56). Median chemotherapy RDI was 0.92 (IQR, 0.86-0.96) in 22 patients with BCLWH and 0.98 (IQR, 0.92-1.00) in 43 control patients (adjusted \( P = .008 \)).

**Conclusions**

RDI was lower in patients with BCLWH; TTI was not significantly different. RDI differences do not entirely explain survival disparities in patient with BC living with HIV but may point to further differences in treatment quality. Future work will explore whether patients with BCLWH experience increased chemotherapy toxicity or if social determinants limit chemotherapy access.
Tissue and Liquid Biopsy–Based Comprehensive Genomic Profiling Reveal Mechanisms of Therapy Resistance and Rare Targetable Alterations in Breast Cancer

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Background
Pathological and genomic profiling aid in the selection of targeted treatments for patients with breast cancer. However, tumors often evolve and evade therapeutic interventions. Here we examine patients profiled with tissue and liquid biopsy, to characterize the genomic landscape and identify potential vulnerabilities in the relapsed setting.

Patients and Methods
Comprehensive genomic profiling (CGP) was carried out on 29,704 patients with breast cancer profiled with tissue biopsy, 3339 with liquid biopsy (targeting up to 70 genes), and 712 patients profiled on both platforms during routine clinical care. Additionally, CGP profiles from 1430 patients tested on the most recent liquid biopsy assay (FoundationOne Liquid CDx) targeting 324 genes were also examined.

Results
Potentially actionable driver alterations were observed in both cohorts, including PIK3CA (34.0% tissue biopsy vs 33.3% liquid biopsy) and BRCA1/2 (7.1% vs 7.4%). In an analysis limited to the recent liquid biopsy assay, similar results were seen (PIK3CA 30.2% vs BRCA1/2 7.9%). Among 712 patients with paired tissue/liquid biopsies, presumably tumor-initiating truncal alterations were frequently shared. When sufficient circulating tumor DNA was present (≥10% tumor fraction), positive percent agreement was high, especially for PIK3CA (93.4%), BRCA (95.0%), and TP53 (92.8%). Acquired liquid biopsy alterations were detected in a majority of patients, with the highest frequency in estrogen receptor-positive disease (60%) and in patients with longer biopsy intervals (71% for biopsies taken >3 years apart). In addition to well-characterized resistance mutations (ESR1, NF1, RB1, and ERBB2), a diversity of potentially actionable alterations were identified in follow-up liquid biopsies, including activating mutations in PIK3CA, HRAS, NRAS, KRAS, FGFR1/2/3, and BRAF. Rare, acquired fusions included FGFR1/2 fusions in multiple patients with estrogen receptor-positive/HER2-negative disease, an ERBB2 fusion in a patient with HER2-positive disease, and an acquired RET fusion. Acquired mutations were primarily identified at a low clonal fraction and were often polyclonal, suggesting convergent evolutionary mechanisms to evade therapeutic pressure.

Conclusions
Liquid biopsy profiling provides evidence for therapeutic and selection-driven evolution, with a high frequency of shared driver alterations and a diverse set of in-pathway subclonal acquired alterations. Potentially actionable baseline and acquired alterations identified in liquid biopsies may provide insights into additional treatment options, potentially through combinatorial strategies.
16 Magseed Versus Wire Localisation: A Comparison of Breast Margin Re-excision Rates at One UK Centre

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Background
The localization of impalpable breast lesions has historically been wire-guided. However, this is associated with such challenges as patient discomfort, wire migration, and restrictive scheduling. Magseed, which provides scheduling flexibility and improves patient comfort, has recently been adopted in our unit. Our study compares the efficacy of Magseed with the wire, with a particular focus on reexcision rates.

Methods
Data were collected retrospectively from 1 United Kingdom (UK) breast unit from consecutive cases over a 10-month period in 2021, from the start of Magseed adoption, comparing reexcision rates for Magseed-guided to wire-guided wide local excisions (WLE). Baseline data on body mass index (BMI), ethnicity, age, and previous breast procedures were recorded. The other outcomes were breast quadrant, localization technique, largest tumor size on all imaging modalities, histology size, core biopsy, and final histology. Locally, American Society of Clinical Oncology margin guidelines are followed: no ink on tumor for invasive disease, 2-mm clearance for ductal carcinoma in situ.

Results
We identified 62 patients (63 breasts) in the Magseed group and 50 patients (52 breasts) in the wire group. The median age in the Magseed group was 59 years (range, 28-89) and the median BMI was 28.23 (range, 19.10-59.40), vs median age of 61 years (range, 37-92) and median BMI 27.85 (range, 18.50-43.50) for the wire group.

The median size on imaging for the Magseed group was 17 mm (range, 0-54), vs 12.5 mm (range, 0-67) for the wire group. On final histology, the median size in Magseed cases was 21 mm (range, 0-82) vs 17 mm (range, 0-68.8) for wire cases. There was a significant difference between largest size on imaging and final histology size in both groups (Magseed, \( P = .034 \); wire, \( P = .028 \)). The median histology size in reexcision cases in the Magseed group was 40 mm (range, 17-82) vs 26.75 mm (range, 17-58) in the wire group.

The overall reexcision rate in the Magseed group was 14.5% (9/63), compared with 15.4% (8/52) in the wire group.

Conclusions
Our data show similar reexcision rates when comparing Magseed with the traditional wire-guided localization. The significant difference between size on imaging and histology has implications for reexcision rates and therefore additional work is required to improve the preoperative estimation of cancer size and address this discrepancy. A reduction in reexcision rates may also be improved over time as operators move up the learning curve and become more experienced with Magseed. Our data reflect “snapshot” early results, and we therefore aim to report further with a larger cohort in future analysis.

17 Comparing Outcomes of Sequential vs Concurrent Breast and Gynecologic Risk Reduction Surgery

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Background/Significance
Women who are diagnosed with breast cancer and/or inherited cancer gene mutations may be presented with ovariectomy as part of their breast cancer treatment plan, either for risk reduction or for ovarian suppression as an adjunct to endocrine therapy in premenopausal women with high-risk features. Many hospitals have begun to offer concurrent breast and gynecologic surgery in order to minimize the number of surgeries, operative time, and length of stay. We examined the outcomes of women undergoing breast and gynecologic operations in order to determine the safety of concurrent operations.
Materials and Methods
We conducted a retrospective chart review of patients undergoing breast and gynecologic surgery, either sequentially or concurrently, for a newly diagnosed breast cancer and/or inherited cancer gene mutation at a single institution from 2015 to 2020.

Results
A total of 104 patients with a mean age of 50 years (range, 26-72) were identified. Seventy patients (69%) had breast and/or reconstructive surgery followed by gynecologic surgery and 32 patients (31%) had concurrent operations. Most patients had an invasive cancer diagnosis or ductal carcinoma in situ (94%) and 40 patients had a high-risk mutation (39%). Minimally invasive bilateral salpingectomies were the most common gynecologic procedure performed (98%). Of the concurrent operations, 3 were performed with breast surgery, 12 were performed with breast surgery and immediate reconstruction, 15 were performed with later-stage reconstruction and 2 were performed with surgery on the axilla. Thirty-one patients (30%) experienced a total of 35 surgical complication (Clavian grade I-III) during their breast cancer treatment. Most of the complications were minor and did not require hospitalization or reoperation. On univariate analysis, there was no difference between the complication rates for patients who opted for concurrent surgeries vs sequential surgeries (25.0% vs 32.9%; P = .57). In a multivariate regression, patients who had concurrent surgery were not more likely than patients who had sequential operations to experience complications, controlling for race, medical comorbidities, smoking history, and if the patient had reconstruction (odds ratio, 0.81; 95% CI, 0.26-2.54).

Conclusions
We observed no increase in complication rates in patients who underwent combination breast and gynecologic surgery. Based on these results, we can continue to increase coordination among specialties in order to reduce the burden of multiple operations placed on patients with breast cancer.

21TiP Pivotal Phase 3, Randomized Controlled Trial Evaluating the Safety and Efficacy of Aminolevulinic Acid for the Real-time Visualization of Cancer Through Fluorescent Imaging During Breast-Conserving Surgery
Eleftherios P. Mamounas,1 Rachel E. Eisenberg,1 Danielle Henry,1 Michael P. Kahky,1 Marisa P. Cooke1, Jennifer Durant,1 Michael T. Roberts,1 Janice M. Porter,1 Amy Nester,1 Nayana Thalanki,2 Kathryn Ottolino-Perry,1 Ralph. S. DaCosta2

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2SBI ALA Pharma Canada Inc. Toronto, ON

Background
Breast-conserving surgery (BCS) aims to adequately resect the primary breast tumor while conserving as much healthy tissue as possible. Despite best efforts, positive margins are common after BCS, resulting in repeated surgical procedures. Based on results from a phase 2 study (Ottolino-Perry K et al, Breast Cancer Research, 2021), this phase 3 randomized controlled trial (NCT04815083) evaluates the safety and efficacy of the optical imaging agent aminolevulinic acid hydrochloride (ALA HCl; PD G 506 A). ALA HCl collects in cancer cells as the fluorescent molecule protoporphyrin IX (PpIX), which can be visualized intraoperatively using the Eagle V1.2 Imaging System. The study’s objectives are to (1) evaluate the safety and efficacy of PD G 506 A and (2) characterize the diagnostic performance of ALA HCl to identify malignant breast tissue using the Eagle V1.2 Imaging System.

Design & Method
Eligibility includes: female patients 18 years or older, histologically confirmed primary breast cancer, normal organ and bone marrow function, and planned BCS for primary breast cancer. Patients will be randomized to receive PD G 506 A or placebo orally 3 hours prior to anesthesia. All patients will undergo standard-of-care (SOC) BCS. Intraoperative fluorescence imaging will be performed using the Eagle V1.2 Imaging System to
Surgical Oncology

An Institution Wide Surgeon and Radiologist Survey of Savi Scout Versus Other Localization Procedure Preferences in Breast Conservation Surgery
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2Sidney Kimmel Medical College, Philadelphia, PA
3Asplundh Cancer Pavilion, Abington Hospital-Jefferson Health, Willow Grove, PA

Background
Savi Scout is a newer technique used to localize nonpalpable breast cancer. It has recently been adopted by some physicians at our multilocation hospital network for breast conservation surgery (BCS). Numerous studies have found it to be a feasible alternative to wire localization. Physician preference plays a role in selection of localization techniques. Despite this, only 1 study has explored provider attitudes regarding Savi Scout implementation, but those physicians found it to improve workflow in and out of the operating room.

Materials & Methods
An electronic survey of radiologists and surgeons from a single institution who practice with Savi Scout, wire localization, or both was conducted. Data were collected from October to December 2021 using Qualtrics, a Health Insurance Portability and Accountability Act–compliant survey software. Physicians’ demographics were collected along with survey responses assessing clinician attitudes and beliefs.

Results
A total of 26 survey responses from 15 radiologists and 11 surgeons were recorded, 7 of which were incomplete. The average physician age was 45 years (n = 19), 9 physicians self-identified as male, 14 as female, and 1 preferred not to say (n = 24). The average number of years of use with Savi Scout ranged from less than 1 to 4 years (n = 15) while use of wire localization ranged from 2 to 33 years (n = 19).

The reported reasons for not using Savi Scout included lack of knowledge (n = 2), lack of training (n = 2), lack of access (n = 2), and other reasons (n = 13). Reasons for selecting one localization or another included physician preference (n = 14), availability (n = 7), cost (n = 6), patient preference (n = 5), and other reasons (n = 5). Physicians reported similar perceptions of overall patient satisfaction and patient cosmetic satisfaction between wire localization and Savi Scout. Open-ended responses showed multiple common themes.

Conclusions
Our research has demonstrated that there may be insufficient and conflicting data on physician opinions about the use of Savi Scout or wire localization for BCS throughout the institution. Given our limited sample size, a follow-up survey open to practitioners in multiple institutions, generating a greater number of responses, may elucidate a more conclusive understanding of reasons for or against the use of Savi Scout. Follow-up surveys could also include patient preferences and chart reviews data of long-term surgical outcomes.
The Effect of Personality Type on Satisfaction With Information Exchange in Breast Cancer Patients

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2Rutgers University, The State University of New Jersey, New Brunswick, NJ
3Breast Surgery, Miller School of Medicine, University of Miami, Miami, FL
4Department of Clinical Research, Maimonides Cancer Center, Brooklyn, NY
5Department of Biostatistics, Research Administration, Maimonides Medical Center, Brooklyn, NY

Background

Type D (distressed) personality is a concept that was coined in the field of medical psychology and is defined as a tendency toward negative affectivity and social inhibition. Previous studies have demonstrated that when compared with other personality types, patients with cancer who have personality Type D experience lower quality of life and mental health status. One theory to explain this difference is that patient dissatisfaction with perceived receipt of information negatively impacts overall well-being. To further evaluate this hypothesis, this study aimed to identify differences in satisfaction with perceived receipt of information among 2 patient populations with a new cancer diagnosis: those with Type D personality and those with non-Type D personality.

Materials and Methods

A prospective survey study included patients diagnosed with breast cancer at a single institution between January 2019 and December 2021. Participants completed a global assessment survey instrument to determine their personality type prior to speaking to their physician. Immediately following their visit, patients then completed the European Organisation for Research and Treatment of Cancer – Quality of Life information module (INFO 25). INFO25 is a validated questionnaire composed of 25 questions based on a 4-point Likert scale used to assess patients’ perceived understanding of their diagnosis and treatment. All analyses were conducted using SPSS v27.

Results

Ninety-eight patients with a diagnosis of breast cancer were enrolled in the study. Presentation, stage, and treatment receipt were similar between both personality groups. Among the 98 patients in the study cohort, 23 (23.5%) patients were Type D. Compared with the non-Type D patients, those with Type D were less satisfied with the provision of information by their physician (1.6 vs 1.8; P < .05). Following their consultation, patients in the Type D arm felt less confident than those in the non-Type D arm, with respect to their level of understanding of “disease diagnosis,” “medical tests,” and “treatment options.”

Conclusions

In this study cohort from a nationally accredited urban cancer center, patients with breast cancer with Type D personality had lower perceived satisfaction with the information provided by their physician. Further studies should investigate methods to optimize information transfer and improve shared decision-making for breast cancer patients with Type D personality.

Turn page for Table >>
### TABLE CONTINUED FROM PREVIOUS PAGE

**Study Cohort Demographics, Clinical Data, and INFO25 Score**

<table>
<thead>
<tr>
<th></th>
<th>Type D, n = 23 (%)</th>
<th>Non-Type D, N = 75 (%)</th>
<th>P value</th>
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<td><strong>Age</strong></td>
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<tr>
<td></td>
<td>65 (58 - 75)</td>
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<td>Yes</td>
<td>9 (39)</td>
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<td>38 (51)</td>
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<td>Abnormal imaging</td>
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<td>Palpable mass</td>
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<td><strong>Clinical T stage</strong></td>
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<td>.72</td>
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<td>cTis</td>
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<td>cT1a</td>
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<td>18 (24)</td>
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<tr>
<td>cT1b</td>
<td>3 (13)</td>
<td>12 (16)</td>
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<tr>
<td>cT1c</td>
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<td>cT2</td>
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<td>6 (8)</td>
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<td>Primary endocrine therapy</td>
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<td>Observation</td>
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<td>Adjuvant chemotherapy</td>
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<td>5 (6.5)</td>
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<td>Radiation</td>
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<td>1 (1)</td>
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<tr>
<td>Adjuvant chemotherapy with radiation</td>
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<td>4 (6)</td>
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<td><strong>INFO25 Scores: higher score corresponds to more information received by patient from their physician</strong></td>
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<td>Diagnosis of disease</td>
<td>3.54 (304)</td>
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<td>4 (3.33-4)</td>
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<td>Treatment for disease</td>
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<td>4 (3.33-4)</td>
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<td>Satisfaction</td>
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<td>1.8 (1.6-2)</td>
<td>.027</td>
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</table>

*aValues indicate median score on the INFO25 4-point Likert scale (1-Not at all, 2-A little, 3-Quite a bit, 4-Very much).

*bValues in parentheses indicate 25th to 75th percentile.
36 Are Positive Margins in DCIS a True Indication of Inadequate Surgery?
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Background/Significance
According to the American Society of Breast Surgeons’ 2017 “Consensus Guideline on Breast Cancer Lumpectomy Margins,” margin status serves as a surrogate marker of residual disease in the breast and has an impact on a patient’s risk of in-breast tumor recurrence. Margins for pure ductal carcinoma in situ (DCIS) treated with lumpectomy and radiation should be 2 mm or more. Close margins (<1 mm) at the chest wall or skin do not necessarily mandate reexcision. The use of margin status and lumpectomy reexcision rates as a measure of quality is controversial and may not reflect tumor biology.

Materials and Methods
To explore this in our academic community hospital, we identified 213 women diagnosed with DCIS who underwent lumpectomy and had margins assessed for a 2-mm standard from 2015 to 2020 in a retrospective study.

Results
Of 213 DCIS patients, 38 (17.8%) underwent breast conservation treatment and had positive margins on their initial pathology. Of these, 23 (60.5%) underwent a reexcision of margins in which the margins were able to be cleared: 20 of the 23 patients (87%) were found to have no residual disease in their second specimen and 3 (13%) required at least 2 additional surgical excisions of margins to be cleared after their initial surgeries. Ten of the 38 patients (26.3%) with positive margins following lumpectomy elected to proceed directly to mastectomy. All 10 were found to have residual disease. Five (13.2%) patients with positive margins had residual disease that was unable to be cleared despite surgical attempts. Negative margins were achieved in 23 (82.1%) of the 28 patients who elected to conserve their breasts.

Conclusions
While there is a consensus that 2-mm margins in DCIS are ideal, the technique to evaluate those margins is not uniform and the decisions for assessing and excising margins are still unclear. Almost half of patients with “positive margins” had no residual disease on reexcision, and in 13.2% of patients, we were unable to obtain satisfactory margins. Clearly, we need to improve our pathological assessment of margins as we learn more about the biology of DCIS.

41 A Single-Centre Report on the Upgrade Rate of Complex Sclerosing Lesions of the Breast
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1David Geffen School of Medicine at UCLA, Los Angeles, CA
2Department of Surgical Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA
3Department of Pathology, David Geffen School of Medicine at UCLA, Los Angeles, CA

Introduction
Radial scar or complex sclerosing lesion (CSL) of the breast is a benign and uncommon breast lesion characterized by stellate configuration of a fibroelastic core with entrapped ducts and lobules. The incidence of radial scar ranges from 0.6% to 3.7%. Despite benign pathology, the radiographic appearance of CSL can overlap or be indistinguishable from invasive or in situ carcinoma. The upgrade rate to malignancy at excision varies between 2% and 26%, with most studies reporting around 10%. Radial scar can coexist with other proliferative high-risk lesions, thereby contributing to the overall upgrade rate. The greatest risk factor for upgrade is the presence of atypia on core needle biopsy (CNB), with upgrade rates consistently around 25% when atypia is present. The objective of this study was to evaluate factors associated with the upgrade rate of CSL and subsequent impact on treatment.

Methods
A single-center retrospective study was performed with females over 18 with radiographic- and pathology-concordant diagnosis of radial scar between 2015 and 2020. We excluded patients with biopsy-proven invasive or in situ disease within 3 months prior to and after biopsy-proven radial scar. The clinicodemographic information collected about our population included menopausal status, personal and family history of
malignancy, radiographic method of lesion detection, associated high-risk lesions, and adjuvant endocrine treatment. Primary outcome of upgrade rate was determined based on evidence of in situ or invasive disease on final pathology.

Results
In our institutional series, 82 patients were included, of whom 58 (70%) received surgery. After surgical excision, 1 case upgraded to ductal carcinoma in situ. Calcifications were seen in more than half of all lesions on CNB (53%).

Conclusion
Upgrade rates of radial scar remain low regardless of the presence of atypia or associated high-risk lesions. Omission of routine excision of complex sclerosing lesions can be safely considered.

45 The Informed Consent Experience for Breast Cancer Surgery and Its Association With Patient Satisfaction

Marisa C. Weiss, Adam Leitenberger, Frank J. Della Croce, Melissa Bollmann Jenkins, Donna-Marie Manasseh

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2Editorial director, Breastcancer.org
3Founding partner, Center for Restorative Breast Surgery, New Orleans, LA
4Community director, Breastcancer.org
5Chief of breast surgery, Maimonides Breast Cancer Center, Brooklyn, NY

Background
Informed consent is a fundamental ethical and legal requirement to ensure that patients are aware of the risks and benefits of surgical interventions. An effective informed consent process provides adequate information, prioritizes patient comprehension, and facilitates shared decision-making with the goal of optimal patient outcomes and satisfaction.

Objective
We sought to characterize the informed consent process for patients undergoing breast cancer surgery and investigate the extent to which certain elements of the process are associated with patient satisfaction.

Methods
Breastcancer.org visitors and registered online community members in the United States were invited to complete an online survey between August 5 and October 2, 2021. The survey included multiple-choice and rank-order questions about their informed consent and breast cancer surgery experience. All data were deidentified and analyzed in aggregate.

Results
The survey was completed by 2009 adult women diagnosed with breast cancer (mean age, 58 years; 85% White) who had surgery within the past 5 years (mean time since surgery, 17 months). Overall, 42% reported that they were alone when they signed the informed consent form, which was more common during vs before the pandemic (47% vs 34%; P < .05). Patients who were not alone were more likely to report being very/extremely satisfied with their surgical outcomes (61% vs 39%; P < .05). Patients reported being most comfortable when their surgeon was the health care provider who spoke with them before they signed the consent form (91%), as compared with a nurse (79%) or other health care provider (64%). Patients were also more satisfied with surgical outcomes when they felt their surgeons effectively informed them about their surgical options, adequately answered their questions, provided written educational materials, or referred them to reputable online sources. Of patients who were very/extremely satisfied with their surgical outcomes, 92% felt very/extremely well informed at the end of their surgical consultation process.

Conclusions
Patients with breast cancer reported higher satisfaction with surgical decisions when they had a positive informed consent experience that prioritized patient education, comfort, and engagement with the surgeon. This survey highlights the importance of investing in the informed consent process to facilitate shared decision-making for better patient satisfaction with surgical outcomes.
5 Feasibility of WF-OCT as an Adjunct to Intraoperative Specimen X-ray for Breast Conservation Surgical Specimens

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Background/Significance
Margin status after breast-conserving surgery (BCS) is a critical prognostic factor in breast cancer. Adjunct, intraoperative analysis of excised tumor margins reduces the risk of reexcision surgery by allowing the surgeon to take additional tissue if an involved margin is detected. While intraoperative specimen radiography (SXR) is commonly used as such an adjunct, wide-field optical coherence tomography (WF-OCT) imaging has also demonstrated performance for this purpose. WF-OCT uses near-infrared interferometry to produce high-resolution images of tissue microarchitecture at a depth up to 2 mm and may detect residual malignant tissue not apparent on SXR.

Materials and Methods
This retrospective case series compared SXR with WF-OCT images, collected, and analyzed prospectively. Adult women undergoing BCS for biopsy-proven invasive ductal carcinoma (IDC) or ductal carcinoma in situ (DCIS) at 2 centers were included. Primary excised tumor specimens were imaged intraoperatively with SXR and WF-OCT (Perimeter Medical Imaging AI). Additional shaves were taken based on SXR results. WF-OCT images were blinded and reviewed, and not used for clinical decision-making. After closing, all tissue was sent for permanent histopathology, which was designated as ground truth. Histopathology-positive margins in patients without additional cavity shaves were designated as SXR false negatives (SXR-FNs). The WF-OCT results and images from FN patients were compared with the corresponding SXR and final histopathology images.

Results
Eighty-nine consecutive patients undergoing BCS were imaged with SXR and WF-OCT prior to permanent histopathology. Average sensitivity and specificity of SXR were 76.5% and 69.6%, respectively. Six cases, comprising 4 DCIS, 1 IDC, and 1 DCIS with IDC, were designated SXR-FN (additional shaves not taken intraoperatively; positive margin present on final histopathology). In the 5 SXR-FN DCIS cases, suspicious tissue changes were present on WF-OCT; the 1 SXR-FN case not detected by WF-OCT was IDC. Side-by-side comparison of SXR-FN, WF-OCT, and ground-truth histology shows the correlating lesion features.

Conclusions
This case series demonstrates that, consistent with ground-truth permanent histology, WF-OCT is able to detect margin positivity in excised tissue that was not apparent on SXR, particularly with respect to DCIS. Although a small case series, these results are encouraging. Additional studies should be tested in a randomized controlled trial.

20 Evaluating Number, Age, and Radiographic BI-RADS of Patients Visiting Mammography Unit in Baghdad, Iraq, in 2019, 2020, and 2021: A Retrospective Study

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Background
Breast cancer is the most commonly registered cancer in Iraq, and 67.9% of patients present with stage III or IV disease, with 45% of patients presenting before the age of 50 years. Breast mammography represents the best screening tool in patients aged above 35 to 40 years of age. The objectives of this study are to find the number of patients having mammography and evaluate their age and radiography based on the Breast Imaging Reporting and Data System (BI-RADS) 0 to 6 score to provide baseline data for future screening programs and to direct appropriate resources.
**Materials and Methods**

This study was conducted retrospectively in an oncology teaching hospital from the period September 2019 to January 2022. The data were collected from the radiology unit. The records included data from patients who visited the unit for mammography. Patients were either on regular follow-up due to previous breast issues or had breast complaints for which a clinician referred them for mammography. The data were collected and administered using Excel and analyzed with Python programming language version 3.1. Data were analyzed using a 95% confidence interval and the study was approved by the ethical committee.

**Results**

The number of patients who had a diagnostic or follow-up mammography was 4838. The mean age was 50.93 ± 9.5 years (range, 14-95), with 75% of patients being younger than 57 years. In total, 35.96% of patients had BIRADS 1 status and 16% had BIRADS 4 or 5 status. Of the 35.79% who were on regular follow-up mammography, 75% had BIRADS 1 or 2 and 10% had BIRADS 3. The most crowded days were Sunday and Wednesday, which accounted for 49.5% of the total patient appointments weekly.

**Conclusion**

During the 2 years and 3 months of the study, the center received 4838 patients for mammography, 75% of whom were younger than 57 years. This volume of participants creates a burden on the mammography unit and increases the need for human and financial resources, especially if a screening program is implemented.

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**28 Case Series: Imaging Appearance of Non-Breast Cancer Solid Masses in the Male Breast**

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**Background**

Benign-appearing masses in male patients should be approached thoughtfully, given the overlapping morphologic features of benign and malignant tumors. In addition to gynecomastia, other benign male breast tumors include lipoma, pseudoangiomatous stromal hyperplasia, granular cell tumor, fibromatosis, myofibroblastoma, schwannoma, and hemangioma. Diseases in the male breast can affect any component of the normal breast anatomy, including the skin, subcutaneous fat, stroma, glands, neurovascular structures, and lymphatic vessels. Typically, fat makes up most of the breast volume in men, with few residual ducts and stroma due to involution and atrophy from androgenic antagonistic effects.

**Learning Objectives**

Present cases of male patients presenting with solid breast masses as well as the radiologic and clinical management.

**Abstract Content**

This is a case series of 12 solid breast masses identified in male patients who did not receive a breast cancer diagnosis. We will discuss the patient presentation, imaging findings, and histopathological appearance. Surgical or clinical management recommendations, when available, will also be presented.

**Conclusion**

Solid breast masses in male patients should be evaluated thoroughly to exclude malignancy, given the overlapping features of benign and malignant tumors. This could include clinical evaluation and thorough history, imaging and/or tissue sampling, and possible surgical consultation and/or excision.

**References**


Clinicopathological Risk Factors, Poorly Stratified Baseline Risk, and RT Benefit Compared to DCISionRT in Patients With Ductal Carcinoma in Situ

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Objective
Over- and undertreatment of ductal carcinoma in situ (DCIS) has been a persistent clinical problem with traditional clinicopathologic features unable to stratify patients appropriately. DCISionRT reports a decision score (DS) validated in multiple cohorts, including the randomized SweDCIS Trial, which is prognostic for 10-year ipsilateral breast recurrence (IBR) risk after breast-conserving surgery (BCS) and predictive for radiotherapy (RT) benefit. Here, stratification of IBR risk and RT benefit by clinicopathology was assessed with DCISionRT.

Methods
DCISionRT and its integrated residual risk subtype (RRt) was evaluated in 493 patients from 3 cohorts at a Clinical Laboratory Improvement Amendments (CLIA) lab (PreludeDx, Laguna Hills, CA) who were treated with BCS or BCS plus RT. Clinicopathology features were analyzed in a multivariable analysis with DCISionRT and its integrated RRt-classified risk groups for 10-year IBR.

Results
The biosignature classified patients into low (DS ≤ 2.8, n = 173), elevated (DS > 2.8 without RRt, n = 209), and residual (DS > 2.8 with RRt, n = 111) risk groups. Patients had increased 10-year rates of IBR risk in the elevated (21.4%, P < .001) and residual (43.4%, P < .001) risk groups without RT, and benefited from RT (elevated: HR, 0.15, P = .002; residual: HR, 0.27, P = .004) versus the low-risk group (5.5%; HR, 1.28; P = .7). The residual versus elevated risk group had an increased 10-year IBR risk rate after RT (20.5% vs 3.2%, P = .008).

Clinicopathologic features (age, grade, size, palpability, and necrosis) were not associated with the 10-year IBR risk rate in multivariable analysis including DCISionRT and treatment. The distribution of clinicopathologic features varied between biosignature risk groups; the residual risk group had a higher proportion of patients with nuclear grade 3 (71% vs 31%, P < .001), necrosis (89% vs 56%, P < .001), and size greater than 1 cm (54% vs 35%, P < .001) when compared with low- and elevated- risk groups, but no significant change was noted in the distribution between DCISionRT risk groups for age.

Conclusions
DCISionRT classified patients into 3 groups with distinct risk and RT benefit profiles, where the residual risk group had the highest 10-year IBR risk rate without RT and significantly elevated IBR risk after RT. The distribution of clinicopathological features varied between biosignature risk groups but were not significantly associated with the 10-year IBR risk rate, accounting for DCISionRT risk groups and treatment.

The PREDICT Registry: A Prospective Registry Study to Evaluate the Effect of a Predictive Assay on Treatment Decisions in Patients with DCIS Following Breast Conserving Therapy

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Background/Significance
The benefits of adjuvant radiation therapy (RT) in patients with ductal carcinoma in situ (DCIS) treated with breast-conserving surgery (BCS) remains controversial. Although there is level 1 evidence supporting the role of RT in reducing the risk of local recurrence, the absolute benefit is variable. Current guidelines generally recommend RT for all patients having BCS, but it is important to develop prognostic and predictive tools to better assess risk and understand the impact such a tool would have on treatment decisions. The DCISionRT Test (PreludeDx, Laguna Hills, CA) is a biologic signature that provides a validated score for assessing 10-year risk of recurrence and RT benefit using individual tumor biology as assessed by clinical and pathologic biomarkers.
**Design and Methods**

This is a prospective cohort study for patients diagnosed with DCIS of the breast. Treating physicians complete a treatment recommendation survey before and after receiving DCISionRT test results. Test results, treatment recommendations, patient preferences, and clinicopathologic features are stored in a deidentified registry for participating institutions from a variety of geographic regions across the United States. The study will also collect 5- and 10-year recurrence and survival data. The study includes women over 25 years of age who are candidates for BCS and eligible for RT and/or systemic treatment with sufficient tissue to generate test results. Subjects must not have been previously treated for DCIS or have previous or current invasive or microinvasive breast cancer. The primary end points are changes in treatment recommendations for surgical, radiation, and hormonal therapy. Secondary end points are identification of key drivers for treatment recommendations, including age, size, grade, necrosis, hormone receptor status, and other clinicopathologic factors. Changes in treatment recommendations will be assessed using McNemar’s test with an α level of 0.05. Differences in recurrence-free and overall survival will be evaluated by Kaplan-Meier survival analysis using the log-rank test and/or the Cox proportional hazards model.

**Status**

On January 4, 2022, the study met its phase 1 accrual goal of 2500 patients from 67 institutions. Additional research objectives are being planned, and accrual is scheduled to reopen around midyear 2022.

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**44 Implementation of a Novel Radiopaque Filament Marker at a Single Breast Cancer Surgery Center**

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**Background**

Marking of lumpectomy sites for adjuvant radiation therapy (XRT) in breast-conserving surgery historically uses metal clips, with reports of suboptimal tumor bed delineation. A novel radiopaque filament marker (FM) has been adopted at our breast center to map tumor beds. The aim of our project is to understand the clinical characteristics of the population in which the FM is placed and optimize device utilization through collaboration with radiation oncologists.

**Methods**

Patients undergoing breast surgery receiving the radiopaque FM at our breast cancer center from 2019 to 2021 were retrospectively queried. Patient demographics, tumor characteristics, and surgical and radiation treatment data were recorded. An anonymous REDCap survey was sent to local breast radiation oncologists evaluating their impressions on the use of the FM. Continuous and categorical variables were analyzed by independent t-test and chi-square test, respectively. Survey responses were compiled.

**Results**

The radiopaque FM was placed in 104 patients, with 50 patients having complete follow-up data. The average age of this all-female cohort was 62 years (standard deviation, ± 11.2). Invasive ductal carcinoma was the most common pathology (39.2%), followed by ductal carcinoma in situ (31.4%). Over half were stage IA on clinical (50%) and pathologic (52.9%) staging. The surgical treatment was lumpectomy (98.1%), with 58.8% having a sentinel lymph node biopsy and all patients undergoing some level of oncoplastic reconstruction. XRT was given in 82.4% of cases. The survey was completed by 5 local breast radiation oncologists, with 100% agreeing that the use of the FM simplified radiation planning and 80% agreeing that its use enhanced target coverage and reduced normal tissue exposure. Free text suggestions included the strategic use of FM in deeper lumpectomy beds to distinguish between surgery tract and cavity as well as the containment of filament tails within the lumpectomy defect.

**Conclusion**

Our study found that radiopaque FM is mainly used in patients undergoing breast-conserving surgery with anticipated adjuvant XRT and that it can be used with oncoplastic reconstruction. In addition, our survey proposes actionable technical changes and raises salient questions regarding the permanent nature of the device and how it may affect patients’ longitudinal care. Ultimately, multidisciplinary investigations are needed to determine how to best integrate new FM technologies into surgical and radiation oncology practices.
3 Frequency of Germline Variants in Breast Cancer Predisposing Genes: Genetic Background of Brazilian Women With Breast Cancer

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Background

Five percent to 10% of breast cancer cases present strong hereditary components; to date, several genes have been associated with breast cancer predisposition. The population background has to be considered, combined with other criteria, to assign pathogenicity to germline variants following the American College of Medical Genetics (ACMG) guidelines. However, there is a bias in large databases against underrepresented admixed populations, such as Brazilians, which makes it difficult to accurately interpret the clinical relevance of germline variants. To contribute to the characterization of the genetic background of breast cancer predisposition in the Brazilian population, we evaluate the frequency and spectrum of germline variants of breast cancer susceptibility genes in a cohort of Brazilian patients with breast cancer.

Material and Methods

Two hundred and five unrelated women with breast cancer were tested for germline variants in breast cancer predisposition genes between 2014 and 2021 in 2 Brazilian centers: the Human Genome and Stem Cell Research Center (n = 150) and the Institute of Fetal Medicine and Human Genetics of São Paulo (n = 55). Of the 205 women, 108 (52.7%) were diagnosed at 45 years or younger; 44.91% had a positive family history, defined as 1 or more first- or second-degree relatives diagnosed with breast or ovarian cancer. Genetic testing was performed using custom panels containing up to 37 breast cancer-predisposing genes. We selected only variants with frequency less than 0.5% in an international (Genome Aggregation Database) and a Brazilian population database (Online Archive of Brazilian Mutations). Filtered variants were classified as pathogenic (P), likely pathogenic (LP), or variant of uncertain significance (VUS) using the ACMG 2015 guidelines.

Results

Thirty-seven patients were found to carry P/LP variants (18.1%), and a VUS was detected in 33 (16.1%). Twenty of the P/LP variants affected the \( \text{BRCA1} \) and \( \text{BRCA2} \) genes, and the remaining 17 patients carry variants mapped to \( \text{ATM}, \text{BRIP1}, \text{CHEK2}, \text{FANCD2}, \text{MUTYH}, \text{RAD51C}, \text{RAD51D}, \text{PALB2}, \text{and TP53} \) genes. The \( \text{BRCA1} \) c.5074+2T>C pathogenic variant was identified in 3 patients, which represents 8.1% of the total molecular diagnosis (P/LP). It is interesting to note that this variant is absent from consulted population databases.

Conclusions

Our findings contribute to the characterization of the genetic background of breast cancer predisposition in the highly admixture Brazilian population as a useful resource to discriminate among deleterious variants.

Funding: This work was funded by FAPESP-CEPID (2013/08028-1) and CNPq Grants: CNPq (307611/2018-3), INCT-CETGEN (573633/2008-8).

15 COVID-19 Disease Course in Immunocompetent and Immunocompromised Patients in a Breast Cancer Registry

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The demographics, comorbidities, menopausal status, endocrine therapy, breast cancer morphology, and treatment history of 45 patients with non–stage IV breast cancer and COVID-19 were analyzed. Immune status at COVID-19 diagnosis, COVID-19 disease severity and treatment, complete blood count (CBC) with differentials at and within 2 weeks of COVID-19 diagnosis, hospital/intensive care unit admission, and mortality were explored in relation to the influence of SARS-CoV-2 on the mononuclear phagocyte system (via M1/M2 macrophages) and the multimodal influences of menopause, estrogen, immunomodulatory drugs, and endocrine therapy on the immune system as well as gene expression of \( \text{ACE2}, \text{NRIP1}, \) and \( \text{TMPRSS2} \). Within each ethnicity group, percentages by number of comorbidities and body mass index ranges were correlated with disease severity and mortality. In the second analysis, COVID-19 outcomes were then examined, taking note of menopausal status, endocrine therapy, and receptor positivity.
Hispanic individuals had a similar percentage of obese patients as African Americans, the highest percentage of class III obesity (16.67%), and the highest percentage of severe COVID-19 disease (10.57%). Recent studies report reliable laboratory markers such as neutrophil-to-lymphocyte ratio in a COVID-19 hematocytometric index for severity and mortality. No appreciable changes in CBC differentials were noted due to limited serial CBCs. All immunocompetent patients with breast cancer hospitalized for hypoxia or acute hypoxic respiratory failure had a mild COVID-19 disease course and the vast majority displayed eosinopenia; aromatase inhibitors were the known form of endocrine therapy in usage. There was a significantly greater number of postmenopausal patients infected irrespective of immune status. Recording of periodic CBC differentials, immunomodulatory drugs, endocrine therapy, and menopausal status can determine priority groups of care for non-stage IV breast cancer during the COVID-19 pandemic. Further investigation of the protective roles of selective estrogen receptor modulators and other forms of endocrine therapy against SARS-CoV-2 is warranted.

18 Psychosocial Wellbeing and Health Care Resource Utilization Among Patients With Breast Cancer During COVID-19
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Background
Global efforts are underway to assess the impact of COVID-19 on patients with cancer; data on outcomes from the perspective of patients with breast cancer (BC) are limited. This study described psychosocial well-being and health care resource utilization (HCRU) among patients with BC during the pandemic.

Materials and Methods
From March 30 to July 6, 2021, 669 patients with BC 18 years or older from Citizen, a patient-mediated health records and real-world evidence platform, and patient advocacy groups participated in an online survey. Sociodemographic and health characteristics, HCRU in the past 3 months, and psychosocial well-being were assessed via descriptive analysis.

Results
Of 669 patients, median age was 52 years (range, 28-82), 83.9% were White, and 51.4% had metastatic BC. More than half (58.7%) were currently being treated with hormone therapy. A total of 62 (9.3%; 95% CI, 7.3%-11.7%) reported ever being diagnosed with COVID-19. Patients had a median of 9 (interquartile range [IQR], 5-15) health care provider (HCP) visits in the past 3 months, of which a median of 6 (IQR, 3-12) were BC related. Of the 12.9% with ≥1 emergency department visits in the past 3 months, a median of 1 (IQR, 0-1) was BC related; of the 9.1% with ≥1 hospitalizations in the past 3 months, a median of 2 (IQR, 1-3) were BC related. The prevalence of depressive symptoms in the past 2 weeks was 31.1% (95% CI, 27.7%-34.7%). The lowest Functional Assessment of Cancer Therapy subscale scores were observed for emotional and functional well-being; of those Psychological Impact of Cancer subscales that measure negative coping responses, scores were highest on emotional distress (Table).

Conclusions
The prevalence of COVID-19 diagnosis among patients with BC was high. HCRU in the past 3 months was primarily driven by HCP visits, both all-cause and due to BC. Results also suggest impairments to psychosocial well-being, particularly aspects of mental health and emotional functioning. These findings underscore the unique vulnerability, burden, and unmet needs among patients with BC during the COVID-19 pandemic.

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<td>Cognitive distress</td>
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<td>Cognitive avoidance</td>
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<td>Emotional distress</td>
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<td>Fighting spirit</td>
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<td><strong>FACT</strong></td>
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<td>BC subscale</td>
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BC, breast cancer; FACT, Functional Assessment of Cancer Therapy; PIC, Psychological Impact of Cancer.
The Routine Use of Bioimpedance Spectroscopy Measurements in the Clinic as a Surrogate for Bone Mineral Content in Oncology Patients: Practical Application of the SOZO Device

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Background
Many patients with cancer, particularly those with breast or prostate cancer, receive hormonal manipulation therapies that can significantly impact their bone mineral content (BMC), potentially leading to life-threatening fractures, especially given the often advanced age of patients with these malignancies. Bioimpedance spectroscopy (BIS) is a noninvasive tool that measures fluid and body composition values including skeletal muscle mass (SMM) and fat-free mass (FFM). ImpediMed’s SOZO BIS device can be used easily and quickly at point-of-care as the patient stands on the device, placing their hands and feet on metal electrodes. Multiple studies have shown a strong correlation between SMM and bone, suggesting that a SOZO reading can provide a reproducible, simple, and quick estimate of BMC. To that end, we present initial findings correlating SOZO BIS readings with dual x-ray absorptiometry (DXA) to determine if BIS readings can be applied as an accurate surrogate measure of BMC.

Materials and Methods
Concurrent BIS measures and DXA scans were performed in 75 healthy patients and in 76 with cancer (during and after cancer treatment), including: Group 1 (75 healthy cases [32 male, 43 female]; mean age, 27.4 years [range, 18-66]); Group 2 (35 patients undergoing cancer treatment [8 male, 27 female]; 13 breast, 5 lung, 4 endometrial, 4 colorectal, 3 prostate, 6 other cancers; mean age, 60.4 years [range, 39-79]); and Group 3 (41 patients participating in a 12-week exercise program after cancer treatment [11 males, 30 females]; 20 breast, 5 prostate, 3 colorectal, 3 endometrial, 10 other cancers; mean age, 58.4 years [range, 20-79]).

Results
The Pearson correlation coefficient (R) for DXA BMC and SOZO SMM were strong for all 3 groups (R = 0.92, 0.86, and 0.78 for groups 1, 2, and 3, respectively). Stepwise multiple linear regression for BMC was performed. For group 1, age, FFM, and height resulted in a multiple correlation coefficient of 0.94 (P <.001); for groups 2 and 3 combined, BMC was dependent on height (P = .03) and SMM (P <.0001) for a multiple correlation coefficient of 0.815 (P <.001).

Conclusions
Concurrent measures of SOZO SMM correlated strongly with DXA BMC, demonstrating that SOZO SMM may be a useful surrogate in the clinic to provide a quick, easy, and reproducible indicator of change in BMC, particularly for those patients undergoing treatments that may affect BMC. Tracking SMM during or after cancer treatment with SOZO may provide an estimate of changes in BMC, allowing clinicians to obtain additional diagnostic testing and/or consider treatment modifications.

Early Detection of Breast Cancer-Related Lymphedema: Accuracy of Indocyanine Green Lymphography Compared With Bioimpedance Spectroscopy and Symptoms

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Background
The incidence of breast cancer-related lymphedema (BCRL) is highly variable within an average of 25% to 40% occurrence among different studies. Although the extent and modality of breast cancer therapies, the timeliness of referrals for evaluation, and the duration of follow-up all have major impacts on BCRL incidence, high variability among studies is also a result of the different diagnostic techniques used and the lack of a standardized definition. The objective superiority of indocyanine green lymphography (ICG-L) for detection of BCRL is in its ability to provide not only an accurate diagnosis but also a chance to intervene and prevent progression. In this study, we aimed to compare...
sensitivity and specificity of ICG-L with lymphedema (LE) symptoms and bioimpedance spectroscopy (BIS) to detect LE in patients with no clinically detectable swelling.

**Methods**

Patients who underwent axillary lymph node dissection (ALND) or had greater than 5 sentinel lymph nodes (sLNB) removed, regardless of their LE symptoms, were included in a prospectively maintained registry. All patients had bilateral arm circumferential tape measurements immediately after surgery and were monitored every 3 to 6 months. All patients had no detectable signs of clinical LE. Clinical LE was defined as having any girth difference of 2.0 cm or more in the involved limb as compared with the uninvolved limb. LE symptoms were defined as heaviness, fullness, and/or swelling. The L-Dex U400 or SOZO (ImpediMed limited and Impedi Med Inc) was used for BIS measurements. Subclinical LE was defined as either L-Dex values that lie outside the normal range (between -7 and +7 units) or a 7-unit change between 2 measurements. ICG-L was performed once anytime postoperatively. The near infrared camera system (PDE; Hamamatsu Photonics K.K.) was used for this study. ICG injection USP (25 mg; Patheon Italia S.p.A) was mixed with 10 mL of saline. ICG injections were in the distal aspect of the upper limb on the affected side including the first and fourth web spaces, and if necessary, additional wrist or elbow regions. If there were detectable changes in the lymphatic system after the ICG-L, patients were treated accordingly and are now being followed up for the development of clinical signs of LE.

**Results**

We enrolled 123 patients, which accounted for 133 arm ICG-L and BIS measurements. The mean age was 54 ± 12 years. Surgical procedures included 46 segmental mastectomies (34.6%), 86 total mastectomies (64.7%), and 1 other surgery in 1 patient (0.8%). SLNB was performed in 57 cases (42.9%) and ALND in 74 cases (55.5%). Based on BIS measurements, 43 arms (32.3%) had values outside the normal range. ICG-L detected lymphatic flow disruption in 63 (47.4%) arms. When compared with ICG-L, BIS had 51% positive predictive value (PPV), 54% negative predictive value (NPV), and 53% accuracy (R = .053; P = .545; AUC = 0.54). When comparing LE symptoms with ICG-L, the PPV of symptoms was 58%, NPV was 66%, and accuracy was 60% (R = .0231; P = .01; AUC = 0.62). Both L-Dex (BIS) and LE symptoms have less than 0.70 AUC-ROC curve; this shows that L-Dex and LE symptoms are not good tools for distinguishing between positive and negative LE in patients who had not presented with swelling.

**Conclusions**

Minimally invasive ICG-L appears to be the most reliable diagnostic tool available for identifying subclinical LE. ICG-L was able to accurately detect lymphatic flow disruption in patients following axillary surgery, even before clinical signs were present. Adapting ICG-L to the subclinical LE diagnosis protocol provides a great opportunity for earlier identification of problematic areas in lymphatic flow, which can lead to a more personalized plan of care and implementation of appropriate treatment accordingly.

**46 Racial/Ethnic Groups Have Different Clustering of Variants of Uncertain Significance**

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**Background**

Racial/ethnic disparities in access to genetic testing have been well established. This lack of testing not only leads to missing potentially lifesaving identification of pathogenic variants but may lead to more variants of unknown significance due to lack of broad population-based adjudication of these variants.

**Methods**

Patient data were obtained from the Informed Genetics Annotated Patient (iGAP) Registry, an institutional review board–approved, multicenter, longitudinal, observational study designed to capture genetic and genomic test results and their utilization and impact on treatment practices and outcomes. Patients self-declare race/ethnicity for the iGAP Registry. Choice of multigene panel testing lab is physician directed. Variant classification is determined by the performing genetic testing lab and reported as negative, variant of uncertain significance (VUS), or pathogenic/likely pathogenic. Descriptive statistics were used to assess and compare data of these populations and germline genetic testing results indicating variant of uncertain significance.
Results
Number of VUS/total tests were as follows: White, 886/1406 (63.1%); Hispanic, 117/156 (75.0%); Black, 116/124 (93.5%); Asian, 95/106 (89.6%). Average number of VUS per patient were as follows: White, 6.3; Hispanic, 7.5; Black, 9.4; Asian, 9.0. Examples of VUS rates (VUS/total tested) in BRCA1/2 were as follows: White, 2.1%; Hispanic, 2.6%; Black, 3.2%; Asian, 7.6%. VUS rates in ATM were as follows: White, 3.0%; Hispanic, 5.8%; Black, 8.1%; Asian, 4.7%.

Conclusions
Hispanic, Black, and Asian patients had a higher proportion of subjects with a VUS and had a greater number of VUS genes per subject compared with White patients for all cancer genes examined. Variant adjudication has disproportionately sorted out more uncertain results in White patients than in Hispanic, Black, and Asian patients. This leads to greater uncertainty in posttest counseling for these groups as well as attenuated overall benefit from appropriate testing. Variant adjudication in minority groups should be a focus for lab testing companies going forward.

Breast Cancer Categorized as Having High Risk of Recurrence and/or Basal-Type or Luminal B Molecular Subtype by MammaPrint and BluePrint, Respectively, Should Universally Undergo Germline Genetic Testing
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Background
With the rise of somatic testing, more clinicians are using panels to understand the genetic profile of breast cancer to help aid in clinical management. However, little is known about the relationship between the results of somatic tests and the likelihood of identifying an underlying germline variant.

Methods
Data were obtained from the Informed Genetics Annotated Patient (iGAP) Registry, an institutional review board–approved, multicenter, longitudinal registry designed to capture biomarker test results and their impact on treatment practices and outcomes. Two somatic tests were studied: MammaPrint and BluePrint. Of the 2765 subjects currently enrolled in the registry, 1526 have been diagnosed with breast cancer (55.19%). All subjects underwent germline genetic testing, with 403 and 226 individuals undergoing tumor profiling through MammaPrint and BluePrint, respectively; 222 individuals underwent both MammaPrint and BluePrint.

Results
Results indicate that of the individuals who were tested through MammaPrint (n = 403) and/or BluePrint (n = 226) panels and underwent germline genetic testing, 176 (43.67%) were classified as being at high risk for recurrence on MammaPrint, 218 (54.09%) were identified as being at low risk for recurrence, and 9 were identified as having ultralow risk of recurrence (2.23%). Individuals with a high risk of recurrence had a 17.61% positive germline variant rate compared with a positive rate of 11.01% in the low-risk group (ultralow, 11.11%; not significant [NS]). Of the 127 individuals categorized through the BluePrint panel, 22 were classified as basal type, 7 as HER2-type, 124 as luminal A type, and 73 as luminal B type. Basal and luminal B types had the highest positive germline rates of 18.18% and 17.81%, respectively, compared with HER2-type (14.29%) and luminal A (10.48%) types (all NS).

Conclusions
The iGAP real-world evidence revealed that individuals categorized as having a high risk of breast cancer recurrence through MammaPrint somatic testing were identified to harbor a pathogenic or likely pathogenic germline variant 17.61% of the time. A similarly high likelihood (18.18% and 17.81%) was seen in BluePrint-tested individuals with basal and luminal B unspecified molecular subtypes, respectively, with comparatively lower likelihood in HER2-positive (14.29%) and especially lower in luminal A (10.48%) types. These data argue that germline genetic testing should be offered to every individual, regardless of age, identified as having a high risk of breast cancer recurrence and/or basal or luminal B molecular subtype on MammaPrint and BluePrint tests.
A Comparison of Race and Ethnicity and Germline Results in ASBrS vs NCCN Guidelines

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Background
National and society guidelines play a critical role in qualifying patients for germline genetic testing. These guidelines’ purpose is to identify individuals who are at risk for carrying germline genetic variants responsible for cancer predisposition and to enable health care providers to intervene.

Methods
Data were obtained from the Informed Genetics Annotated Patient (iGAP) Registry, an institutional review board-approved, patient-consented, multicenter prospective registry that includes patients with cancer who are undergoing genetic testing as well as unaffected patients with pathogenic mutations. In total, 1815 subjects were assessed with the National Comprehensive Cancer Network High Risk Assessment for Breast, Ovarian, and Pancreatic Hereditary Genetic Testing Guidelines (NCCN BOP) and the American Society of Breast Surgeons (ASBrS) Guidelines for Genetic Testing (version up to date at time of screening, from 2019-2022).

Results
In total, 1815 subjects were risk assessed and completed a germline genetic test. Of these subjects, 849 met NCCN BOP criteria (46.78%) and 1491 (82.15%) met ASBrS Guidelines for Genetic Testing. Of the subjects who met NCCN BOP vs ASBrS Guidelines, the average age was 55.87 vs 60.47 years, respectively. Subjects with personal history of cancer accounted for 80.92% (687/849) vs 91.15% (1359/1491), respectively; those with a family history of cancer accounted for 85.04% (722/849) vs 42.59% (1017/1491). Proportionally more subjects who met the NCCN BOP criteria had a positive variant, with 23.67% (201/849), compared with 18.71% (279/1491) who met ASBrS criteria. Racial/ethnic categories were also examined in the 2 different guideline groups, with 36.25% more White patients (1096 vs 611) meeting ASBrS guidelines over NCCN; 25.20% (111 vs 79) more Hispanic patients; 53.77% (94 vs 37) more Asian patients; 33.33% (84 vs 52) more African/Black patients; and 3.57% (25 vs 26) fewer Ashkenazi patients (Table).

Conclusions
Germline genetic testing impacts patient care. Current national guidelines may miss a significant number of patients with germline mutations and variants of unknown significance. More studies are needed to evaluate the current underutilization of germline genetic testing.

<table>
<thead>
<tr>
<th>RE by guideline (%)</th>
<th>White</th>
<th>Hispanic</th>
<th>Asian</th>
<th>African/Black</th>
<th>Ashkenazi</th>
<th>Multiple</th>
<th>Other</th>
<th>Unknown</th>
</tr>
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<tbody>
<tr>
<td>Meets NCCN</td>
<td>45.67%</td>
<td>62.20%</td>
<td>34.91%</td>
<td>54.17%</td>
<td>92.86%</td>
<td>33.33%</td>
<td>40.00%</td>
<td>35.63%</td>
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<tr>
<td>Meets ASBrS</td>
<td>81.91%</td>
<td>87.40%</td>
<td>88.68%</td>
<td>87.50%</td>
<td>89.29%</td>
<td>100.00%</td>
<td>83.33%</td>
<td>35.63%</td>
</tr>
<tr>
<td>Total subjects (n)</td>
<td>1338</td>
<td>111</td>
<td>106</td>
<td>96</td>
<td>28</td>
<td>3</td>
<td>30</td>
<td>87</td>
</tr>
<tr>
<td>Meets ASBrS, not NCCN</td>
<td>36.25%</td>
<td>25.20%</td>
<td>53.77%</td>
<td>33.33%</td>
<td>-3.57%</td>
<td>66.67%</td>
<td>43.33%</td>
<td>0.00%</td>
</tr>
</tbody>
</table>

ASBrS, American Society of Breast Surgeons; NCCN, National Comprehensive Cancer Network; RE, race/ethnicity.
Racial/Ethnic Groups Have Different Clustering of Common Cancer Genes

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Background
Racial/ethnic disparities have been well documented in terms of access to cancer screening and treatment, as well as treatment outcomes. Less is known regarding the proportion of higher- and lower-penetrance genetic pathogenic variants in these populations.

Methods
Patient data were obtained from the Informed Genetics Annotated Patient (iGAP) Registry, an institutional review board-approved, multicenter, longitudinal, observational study designed to capture genetic and genomic test results and their utilization and impact on treatment practices and outcomes. Patients self-declare race/ethnicity for iGAP. Choice of multigene panel testing lab is physician directed. Variant classification is determined by the lab that performs the genetic testing, and the variants are reported as negative, variant of uncertain significance, or pathogenic/likely pathogenic. Descriptive statistics were used to assess and compare data from these populations, and the results of germline genetic testing included higher- and lower-penetrance pathogenic variants.

Results
BRCA1/2 pathogenic variant/total number of subjects tested rates were as follows: White, 16/1406 (1.14%); Hispanic, 20/156 (12.82%); Black, 8/124 (6.45%). Pathogenic variants of non-BRCA genes/total number of pathogenic variants rates were as follows: White, 289/305 (95%); Hispanic, 27/47 (57%); Black, 8/16 (50%). The Hispanic group has a considerably higher percentage of BRCA1/2 pathogenic variants compared with Black and White patients. However, White patients have considerably more pathogenic variants in lower-penetrance genes than other racial/ethnic groups.

Conclusions
Racial/ethnic groups varied by proportion of both BRCA1/2 and lower-penetrance pathogenic variants. The higher percentage of BRCA1/2 pathogenic variants in our Hispanic group could be due to the greater representation of Hispanics from New Mexico in the iGAP Registry, who may harbor Ashkenazi ethnicity. Further studies are needed to understand whether these differences are a result of disparate access to testing, true population differences, or other factors.