Is Timing and Selection Everything in Localized Breast Cancer?

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DISCLOSURES (of presenter, last 36 months)

<table>
<thead>
<tr>
<th>Research Support:</th>
<th>Deciphera, Prescient Therapeutics</th>
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<tr>
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# Abstracts and Relevant Topics for Discussion

<table>
<thead>
<tr>
<th>Abstract</th>
<th>Presenting Author</th>
<th>Title</th>
<th>Topic for Discussion</th>
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<tr>
<td>GS-03: 1698</td>
<td>Spring</td>
<td>Pathological complete response after neoadjuvant chemotherapy and impact on breast cancer recurrence and survival, stratified by breast cancer subtypes and adjuvant chemotherapy usage. Patient-level meta-analysis of over 27,000 patients.</td>
<td>PCR as a pharmacodynamic biomarker</td>
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<tr>
<td>GS-05:1578</td>
<td>Morante Cruz</td>
<td>Impact of the delayed initiation of adjuvant chemotherapy in the outcomes of triple negative breast cancer.</td>
<td>Timing of adjuvant chemo in TNBC</td>
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## Abstract 1698: Pathologic complete response (pCR) as a pharmacodynamic (PD) biomarker

### What we knew before
- No difference in outcomes for NACT vs. ACT\(^1\)
- Advantages of NACT include less axillary surgery and more breast conservation\(^2\)
- pCR after NACT is a prognostic PD biomarker\(^3,4\)
  - Correlates with EFS and OS on patient level
  - Association strongest for high grade breast cancers - TN (HR 0.24), HER2+ (HR 0.39), and ER+ gr3 (HR 0.27)
- Conclusions derived from metaanalysis including 12,993 patients in 12 trials

### What we know now
- Metaanalysis confirmed what we knew before
  - Now including more nearly 2-fold more patients (27,895), but with most new data derived from retrospective cohort studies
  - Novel analytical method that simulates individual patient data analysis without requiring the actual data
- New information
  - No benefit from additional adjuvant chemotherapy if pCR to NACT
  - Model to project trial level EFS improvement associated with improved pCR rates
- Remaining challenges
  - Large improvements in pCR (> 20%) required to achieve detectable and clinically meaningful improvements in EFS at the trial level

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1. EBCTG. Lancet Oncol 2016 [PMID: 25242241]
2. Aronsson et al. JCO Monographs 2015 [PMID: 26063566]
4. Berry et al. JAMA Oncology 2016 [PMID: 26111319]
Abstract 864: Role of adjuvant capecitabine

What we knew before

- No benefit from adjuvant 5-FU added to a modern sequential EC-paclitaxel regimen\(^1\)
- Adjuvant capecitabine inferior to CMF/AC in older women\(^2\)
- Metaanalysis showed improved DFS (HR 0.72) and OS, but more toxicity with adjuvant capecitabine in TNBC, generally given concurrent with other agents
- Improved EFS and OS when given in TNBC if residual disease after NACT in the CREATE-X trial\(^4\)

What we know now

- Prospective clinical trial
  - Stage I-II TNBC (N=876)
  - Only about 20% received NACT, and 25% of those (5% of overall population) had pCR
  - Design tested concept of chemotherapy duration in addition to drug
- Results
  - Control arm did better than expected (5 year DFS 77% vs. 67% projected)
  - HR 0.79 \((P=0.082)\) similar to metaanalysis
  - Prespecified subset analysis showed benefit in 28% with non-basal subtype (EGFR & CK 5/6 neg)
- Conclusions
  - Primary trial endpoint not met
  - Biomarker subset analysis, while prespecified, requires further validation

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Why Differing Results for Capecitabine in CIBOMA & CREATE-X?

Both Longer Duration of ACT, but Response-Adapted Paradigm Only in CREATE-X

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Abstract 1578: Timing of adjuvant chemotherapy (ACT) in TNBC

What we knew before

- Interval of < 120 days between diagnosis and ACT quality metric for stage II-III ER/PR-neg BC in women < 70 years (National Quality Forum, ASCO, NCCN)

- Population-based studies have shown > 90 day interval between surgery and ACT associated with inferior BCSS in TNBC

- Systematic review and metaanalysis
  - 78,462 patients in 12 reports
  - Compared interval < 30 days vs. 31-60 days
  - Inferior OS in TNBC (HR 1.26, 95% CI 1.08-1.48)
  - No impact on OS in HER2+ or ER+ BC
  - Not adjusted for comorbidities or type of surgery

What we know now

- Retrospective analysis
  - Stage I-III TNBC (N=608)
  - 90% stage II-III & 63% had mastectomy
  - Multivariate model adjusted for age, stage, surgery, time period, and type of ACT

- Results
  - Worse DRFS if TTC > 30 days
    - 31-60 days: HR for distant recurrence 1.9
    - 61-90 days: HR 2.47
    - > 90 days: HR 2.79
  - Similar trends for OS

- Conclusions & Implications
  - Consistent with metaanalysis, but strengthened by adjustment for other covariates

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Is Timing and Selection Everything in Early Breast Cancer?

Step 1

- Surgery

Step 2

- Standard Rx +/- Investigational Regimen

Step 3

- Systemic Endocrine and/or anti-HER2 Therapy Depending on Subtype

Standard Adjuvant Paradigm
- Timing of ACT matters in TNBC
- < 30 days optimal

Step 1

- Standard Rx +/- Investigational Regimen

Step 2

- Systemic Endocrine and/or anti-HER2 Therapy Depending on Subtype

Standard Neoadjuvant Paradigm
- Reduce extent of surgery
- No impact on recurrence

Step 1

- “Early” PD Biomarker (eg KI-67, FDG-PET)

Step 2

- Therapy adapted to “early” to PD biomarker

Late Response-Adapted Paradigm
- Reduced extent of surgery
- Reduce recurrence & mortality

Step 3

- Surgery

Early Response-Adapted Paradigm
- Reduced extent of surgery
- Reduce recurrence & mortality
- Reduce toxicity of therapy

Step 4

- Surgery

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Is Timing and Selection Everything in Early Breast Cancer?

Success in Response-Adapted Paradigm after Failure in Standard Neoadjuvant Paradigm

Primary End Point: PCR (ypT0/N0, ypN0)

Standard Neoadjuvant Paradigm – KRISTINE
TDM-1+P pCR rate not better than TCH+P

Response-Adapted Paradigm – KATHERINE
TDM-1 improves IDFS compared with T

Can an Early Response-Adapted Paradigm Find a Role for TDM-1 Upfront?

T-DM1 +/- P X 1 Cycle

PD Biomarker (FDG-PET)

Response
No Response

T-DM1 +/- P x 5
TCH+P x 5

Surgery

Is Timing and Selection Everything in Early Breast Cancer?
Clinical Trials Using the Response-Adapted Paradigm

**Triple Negative**

**EA1131**
(NCT 02445391)
N=652 basal (750 total)
Capecitabine
Platinum
Residual tumor 2 cm after NACT
Results expected May 2024

**S1418**
(NRG BR-006
(NCT 029548746)
N=1000
Pembrolizumab
No therapy
Residual tumor after NACT
Results expected May 2026

*Source of Information: ClinicalTrials.gov

ALTERNATE: EARLY RESPONSE-ADAPTED PARADIGM
Treatment adapted based on Ki67 response after 4 week course of endocrine therapy.
## Implications for clinical practice in TN and HER2+ BC
- Response to neoadjuvant therapy is a **dynamic** PD biomarker that captures information not otherwise captured by **static** biomarkers.
- Lack of or pCR after NACT is **prognostic** for higher recurrence and **predictive** of benefit from ACT
  - HER+ BC: T-DM1 in KATHERINE
  - TNBC: Capecitabine in TNBC in CREATE-X
- Provides rationale for “lowering the bar” for NACT to less advanced disease in order to leverage the response adapted paradigm and tailor therapy based on PD response.

## Implications for research strategies in ER+ BC
- Findings from TAILRx support use of molecular markers to select ER+ BC unlikely to benefit from NACT or ACT – up to 85% don’t benefit
- More investigation of neoadjuvant endocrine therapy (NET) as a therapeutic and research strategy, especially in postmenopausal women, using novel endpoints (PEPI score) and agents added to NET
- Leverage new technologies that provide additional information, especially non-pCR
  - Prognostic: ctDNA, CTC
  - Predictive: ctDNA (ESR1 mutations)
  - Mechanistic: metastasis biomarkers

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- Jesus Anampa, MD – Albert Einstein/Montefiore
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Abstract 1698: Pathologic complete response (pCR) as a pharmacodynamic (PD) biomarker

Results: \( \Delta \text{EFS vs. } \Delta \text{pCR} \)

<table>
<thead>
<tr>
<th>Change in (( \Delta ))</th>
<th>Corresponding HR</th>
<th>95% PI</th>
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<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>N/A</td>
</tr>
<tr>
<td>0.1</td>
<td>0.90</td>
<td>0.88-0.92</td>
</tr>
<tr>
<td>0.2</td>
<td>0.81</td>
<td>0.78-0.84</td>
</tr>
<tr>
<td>0.3</td>
<td>0.72</td>
<td>0.68-0.77</td>
</tr>
<tr>
<td>0.4</td>
<td>0.66</td>
<td>0.60-0.70</td>
</tr>
<tr>
<td>0.5</td>
<td>0.56</td>
<td>0.52-0.64</td>
</tr>
<tr>
<td>0.6</td>
<td>0.52</td>
<td>0.48-0.58</td>
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<tr>
<td>0.7</td>
<td>0.46</td>
<td>0.39-0.53</td>
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<tr>
<td>0.8</td>
<td>0.40</td>
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<tr>
<td>0.9</td>
<td>0.36</td>
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<tr>
<td>1</td>
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C40503 (addition of carboplatin)
- pCR increased 13% (44% \( \rightarrow \) 57%) and actual EFS HR 0.94 (95% CI 0.86-1.02) with 110 events
- Model predicted EFS HR 0.87 (95% CI 0.84-0.90) - requires 1318 events (80% power, 2-sided alpha 0.05)
Is Timing and Selection Everything in Early Breast Cancer?
Can broader application of response adaptive paradigm reduce morbidity and mortality in HER2-positive and triple negative breast cancer?

**Response Adaptive Paradigm: Step 1**
- Chemotherapy +/- Anti HER2 Therapy

**Step 2**
- Surgery

**Step 3**
- Tailor additional systemic therapy
  - PD biomarker
  - Subtype

**“UPFRONT” STRATEGY (I-SPY & COMPASS)**
- Intensify/add therapy (I-SPY) \( \uparrow \) pCR
- De-intensify therapy (COMPASS)

**“OUTBACK” STRATEGY (COMPASS TRIAL)**
- Intensify/add in some based on PD biomarker

Is Timing and Selection Everything in Early Breast Cancer?
Is the Early Response Adaptive Paradigm Ideal for ER+, HER2- Breast Cancer?

**Step 1**
- Short Course Targeted Therapy

**Step 2**
- “Early” PD biomarker (eg Ki67)

**Step 3**
- Intensify adapted to “early” PD biomarker

**Step 4**
- Surgery

**“UPFRONT” STRATEGY (ALTERNATE TRIAL)**
- Test standard or novel therapies

**“OUTBACK” STRATEGY - ADAPT AND TREAT**
- Adapt based on early PD biomarker
- Goal is to rescue “non-responders”

**CANDIDATE PD BIOMARKERS**
- Change in Ki67
- Circulating markers (CTC, ctDNA)
- Metastasis markers (TMEM)