De-Escalation in Early Stage Breast Cancer: When Can Less Be More?

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The big picture

- De-escalation is a hot topic, but we have to be careful when we discuss it with our patients
  - I sometimes prefer “personalization of therapy”
- The importance of clinical trials to help us de-escalate treatment safely cannot be overestimated
- We have opened a number of these types of trials at Winship in recent years, and enrollment has been notably robust: patients vote with their feet
- In the next 15 minutes, we will discuss the current standards of care and ongoing trials looking at de-escalation of therapy in HR+, HER2+, and triple negative breast cancer; and talk about a future where ctDNA may play a role in personalizing care for patients with early-stage disease

Ductal Carcinoma In Situ (DCIS)

- **TAM-01**: 500 women (20% ADH, 11% LCIS, 69% DCIS) randomized to 5mg tamoxifen x 3y vs placebo
  - 10-year follow-up data revealed a 50% risk reduction in the DCIS group (HR 0.40 (0.28-0.91), p=0.02))

- As a results, 3y of low-dose tamoxifen has become a viable option for many women

  - On the horizon: the **BabyTEARS** trial (NCT06364267) is studying low-dose tamoxifen (10mg qod) vs low-dose exemestane (25mg qod) x 1 year in patients with ER+ DCIS, recent history of high-risk lesion (ADH, ALH, LCIS), or women with a sufficiently high lifetime risk of breast cancer

- Based on this, the question has come up of whether women with lower-risk early-stage breast cancer can safely take lower doses of endocrine therapy for shorter durations

- The **Lo-TAM** trial (NCT06671912) is studying low-dose tamoxifen (10mg qod) x 5 years versus standard ET (AI or tamoxifen 20mg daily) x 5 years in postmenopausal women with T2N0 (T must be <3cm) ER+ breast cancer and low-risk genomic scores (Oncotype <25, Prosigna <40, Mammaprint low-risk)

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ER+ Breast Cancer

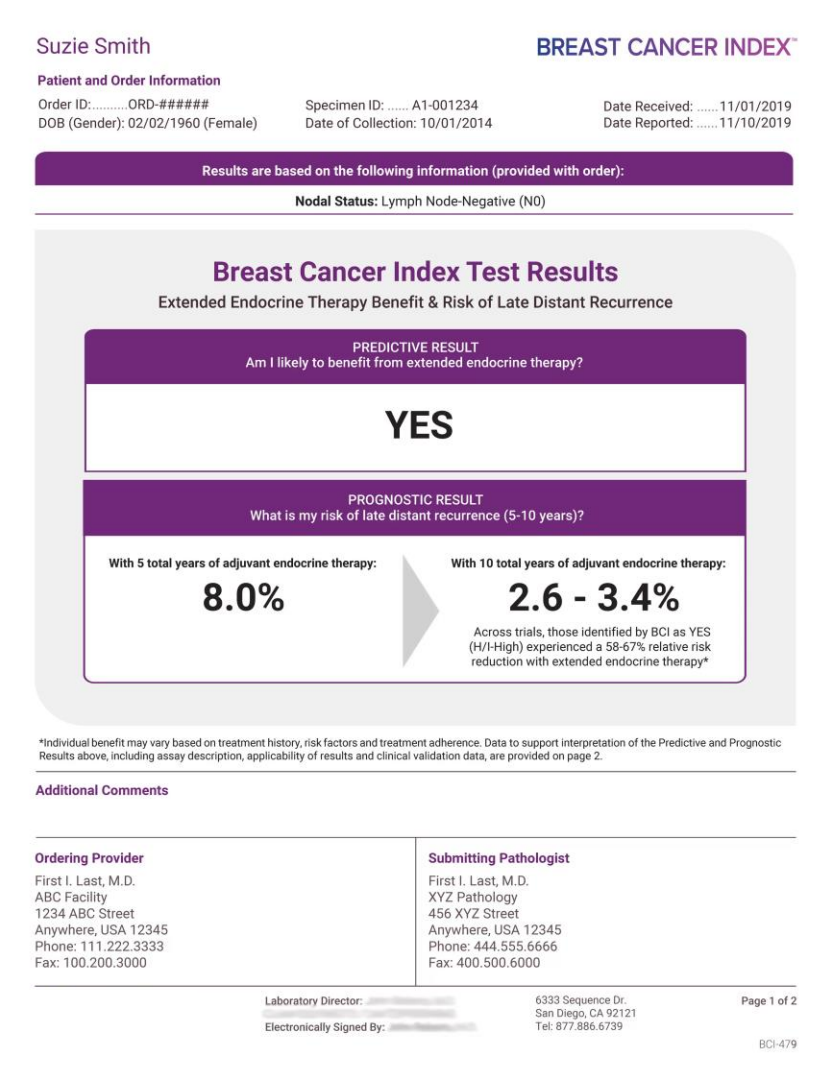
- There has been a long history of de-escalation trials in ER+ breast cancer
- In fact, genomic assays were designed with the intent to personalize therapy and in many cases, de-escalate – we give far less chemotherapy in ER+ disease than we used to since Oncotype, Prosigna, and Mammaprint became standard of care
- But, important questions remain:
  - Now, with the advent of adjuvant CDK 4/6i, which node-positive patients really require this additional therapy and which do not?
  - What about the duration of endocrine therapy?
  - For premenopausal patients who are node-positive with low genomic risk scores, is chemotherapy the important part of their treatment or just the ovarian suppression that chemotherapy can cause?

ER+ Breast Cancer

- **CDK 4/6 inhibitors**
  - Studies at ASCO 2026 showed that all patients benefited from adjuvant CDK 4/6i regardless of biomarker profile
  - Therefore, adjuvant CDK remains a discussion between doctors and patients

- **Duration of endocrine therapy**
  - **Breast Cancer Index** (for T1/T2 and N0/N1 disease) is both **predictive** (of benefit of extended ET) and **prognostic** (able to determine risk of distant recurrence with or without extended ET)

  - **Caris MI Clarity,** launched more recently, evaluates digitized pathology images to predict the likelihood of early (0–5 years) and late (5–15 years) distant recurrence for postmenopausal patients with HR+/HER2−, node-negative breast cancer without requiring genomic sequencing



Suzie Smith

BREAST CANCER INDEX™

Patient and Order Information

Order ID:.....ORD-######
DOB (Gender): 02/02/1960 (Female)
Specimen ID: A1-001234
Date of Collection: 10/01/2014
Date Received: 11/01/2019
Date Reported: 11/10/2019

Results are based on the following information (provided with order):

Nodal Status: Lymph Node-Negative (N0)

Breast Cancer Index Test Results

Extended Endocrine Therapy Benefit & Risk of Late Distant Recurrence

PREDICTIVE RESULT
Am I likely to benefit from extended endocrine therapy?

YES

PROGNOSTIC RESULT
What is my risk of late distant recurrence (5-10 years)?

With 5 total years of adjuvant endocrine therapy:
8.0%

With 10 total years of adjuvant endocrine therapy:
2.6 - 3.4%

Across trials, those identified by BCI as YES (H/I-High) experienced a 58-67% relative risk reduction with extended endocrine therapy*

*Individual benefit may vary based on treatment history, risk factors and treatment adherence. Data to support interpretation of the Predictive and Prognostic Results above, including assay description, applicability of results and clinical validation data, are provided on page 2.

Additional Comments

Ordering Provider
First I. Last, M.D.
ABC Facility
1234 ABC Street
Anywhere, USA 12345
Phone: 111.222.3333
Fax: 100.200.3000

Submitting Pathologist
First I. Last, M.D.
XYZ Pathology
456 XYZ Street
Anywhere, USA 12345
Phone: 444.555.6666
Fax: 400.500.6000

Laboratory Director:
Electronically Signed By:

6333 Sequence Dr.
San Diego, CA 92121
Tel: 877.886.6739

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BCI-479

ER+ Breast Cancer

- **OPTIMA trial**: presented at ASCO in June
  - 4400 patients age ≥ 40 with HR+HER2- breast cancer, T1-T2 disease (or T > 30mm if node negative)
  - Prosigna ROR scores were calculated on each patient, with scores ≤ 60 classified as low risk
  - For low-risk patients, **5y IDFS was 93.7% with ET** (with OFS if premenopausal) **vs 94.9% for chemo + ET** (with OFS if premenopausal), HR 1.06 [90% CI 0.78- 1.46] NI p = 0.0051
    - Patient characteristics: 37% premenopausal, 73% had pN1 and 19% pN2 tumors
  - There was no significant outcome heterogeneity between subgroups including for menopausal and nodal status.

- Questions
  - What does this mean for the OFSET trial (chemo + OFS + ET vs OFS + ET for node-positive premenopausal patients with Oncotype <25, or node-negative patients with Oncotype 16-25)?

  - Will we continue to use Oncotype or switch to Prosigna?

Applying OPTIMA

- We should keep **Oncotype as our test of choice for postmenopausal N1 patients and for all N0 patients**
  - RxPonder and TailoRx were dedicated trials in these areas
- We will likely use **Prosigna for premenopausal N1 patients ages 40 and over** (because of the definitive results in this population showing equivalence of OFS + ET to chemo/OFS/ET in this population)
- We will also use **Prosigna for postmenopausal N2 patients** (if an assay feels appropriate, to try to omit chemo in this population)
- This will make enrollment to OFSET even more challenging, but does offer premenopausal node-positive patients an option right now

J Clin Oncol **44**, 500(2026) Volume 44, Number 16_suppl

HER2+ Breast Cancer: Personalized NACT

- We have moved away from anthracyclines in this population
  - **Neoadjuvant TCHP x 6** has become the established norm for most patients with T2+ or N1+ disease **Adjuvant TH x 12 weeks** for stage 1 disease

- COMPASS HER2 and NeoCARHP showed that for many patients with HER2 3+ disease, carboplatin may be the least critical part of the TCHP combination (4 cycles of NACT with THP (COMPASS) and 6 cycles of NACT with THP (NeoCARHP) were the de-escalation strategies)

- Now, neoadjuvant T-DXd (T-DXd x 4→ THP x 4, DESTINY-Breast 11) is approved as another SOC option

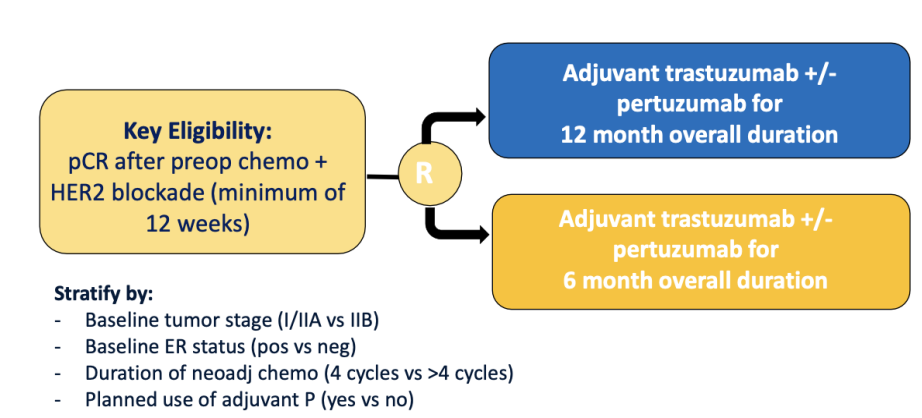
A 56yo Caucasian female presents with a 2.6cm left breast mass that is biopsied and found to be grade 3, ER 65% PR 35% HER2 3+ invasive ductal carcinoma. Two abnormal left axillary nodes are seen on imaging, and one is biopsied and is found to be involved with carcinoma.

What do you recommend?

Zhao, F., et al. (2025). *JCO*, 43(16_suppl), 501-501. Gao, P., et al. (2026). *JCO*, [DOI: 10.1200/JCO-25-02176. Harbeck, N., et al. (2026). *Annals of Oncology*, 37(2), 166-179

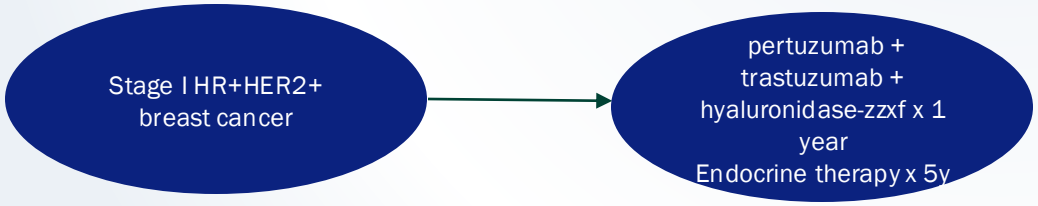
De-escalation in the adjuvant setting

- SHORT-STOP-HER2



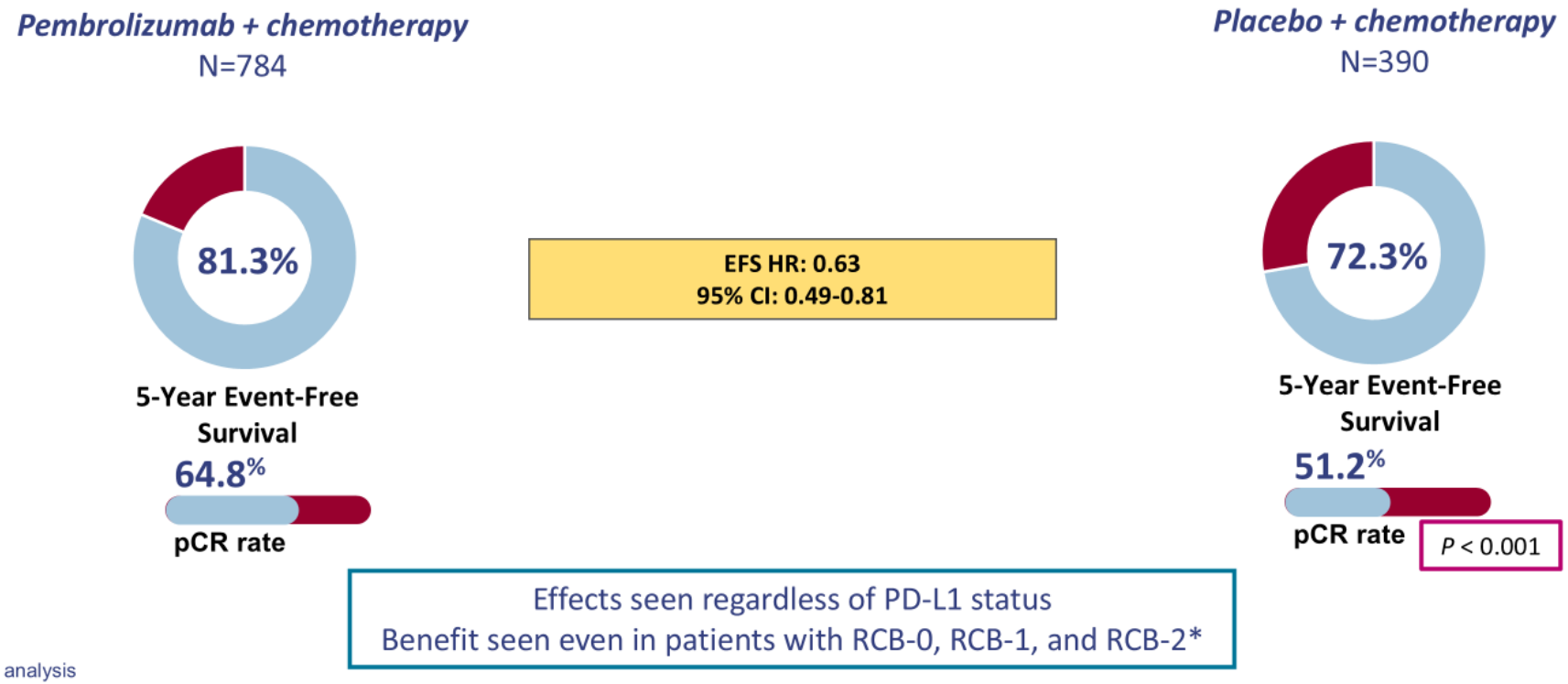
Goal: to see if 6 months of HP is as effective as 12 months of HP for those with pCR to NACT

- ADEPT



Goal: to see if HP + ET is as effective as chemo + HP for stage 1 HR+HER2+ breast cancer

KEYNOTE 522: pCR and EFS rates with neoadjuvant pembrolizumab



*Exploratory analysis

TNBC = Triple-negative Breast Cancer; pCR = pathologic Complete Response; EFS = Event-Free Survival; PD-L1 = Programmed Death-Ligand 1

Schmid P, et al. *N Engl J Med.* 2022;386:556-567; Schmid P, et al. *Ann Oncol.* 2023;34(suppl_2):S1257; Puszti L, et al. *Ann Oncol.* 2024;35(5):429-436.

Triple Negative Breast Cancer

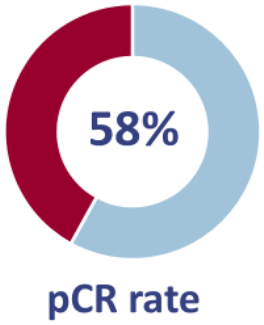
Could less be more in some situations?

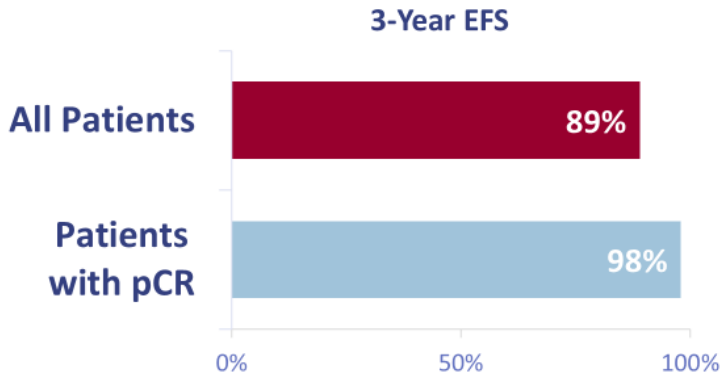
NEOPACT

*Single-arm, phase 2 trial

*115 women with stage I-III TNBC
-39% node positive

*All patients received six cycles of:
-carboplatin AUC 6
-docetaxel 75mg/m2
-pembrolizumab 200mg





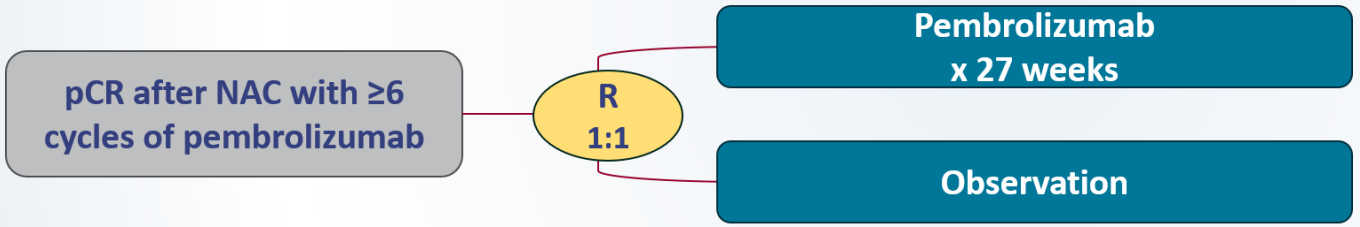
Addition of neoadjuvant pembrolizumab yields meaningful pCR rates and encouraging EFS, and offers an alternative to SOC

JAMA Oncol. 2024; 10 (2): 227-235.

ONGOING TRIALS

- **SCARLET** (Shorter Anthracycline-Free Chemo Immunotherapy Adapted to Pathological Response in Early Triple Negative Breast Cancer)
  - NeoPACT vs KEYNOTE-522

- **OPTIMICE-pCR** (NCT05812807)



- **De-escalation based on TILs**
  - ETNA (NCT06078384): weekly paclitaxel/pembrolizumab or surveillance in stage 1 TNBC with high TILs
    - Age and % sTILs dictate which regimen a patient receives on study
  - DespaTIL (NCT07074106): carboplatin/taxane x 4 cycles followed by MRI to dictate surgery vs AC as next step, in patients with stage 1 TNBC or stage II with >50% sTILs

What about ctDNA as a de-escalation strategy?

- Common sense (and biology) tells us that cancer spreads through the bloodstream – so if there are no cancer cells in the bloodstream, it might be possible to stop, or limit, systemic therapy

- Retrospective research is starting to emerge that validates this thinking

- Prospective trials are on the horizon

Predicting nodal burden after neoadjuvant chemotherapy (NAC) with circulating tumor (ct)DNA for surgical planning: Results from the I-SPY2 trial

- Background:
  - ISPY-2 is a prospective trial for patients with high-risk stage II-III breast cancer
  - Patients are randomized to novel NAC agents, and pCR is the primary endpoint
  - ctDNA is assessed at baseline, 3 weeks, 12 weeks, and post-NAC

- Goal of this study: to determine whether ctDNA status post-NAC, or *change* in ctDNA from baseline, is associated with nodal burden at the time of surgery

RESULTS

ctDNA baseline/post-NAC	ypN0 (n=317)	ypN1 (n=116)	ypN2 (n=60)
ctDNA -/- (n=105)	72.4%	19.1%	8.6%
ctDNA -/+ (n=1)	0.0%	100%	0.0%
ctDNA +/+ (n=44)	34.1%	29.6%	36.4%
ctDNA +/- (n=343)	65.9%	23.9%	10.2%

- The study demonstrated a significant association between ctDNA dynamics and ypN category, with significantly more ypN2 patients among those who did not clear ctDNA, and more ypN0 patients who started out ctDNA- or were rendered ctDNA- by NAC

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TBCRC 040: PREDICT-DNA

- Invasive disease- free survival by breast cancer subtype, according to ctDNA after NACT and RD vs pCR

TNBC (total n= 64)	3y IDFS (n=40)	4y IDFS (n=32)	5y IDFS (n=18)
ctDNA- and pCR (n=20)	94.1%	94.1%	94.1%
ctDNA- and RD (n=25)	89.8%	89.8%	89.8%
ctDNA+ and RD (n=19)	48.9%	48.9%	48.9%

HER2+ (total n= 58)	3y IDFS (n=41)	4y IDFS (n=31)	5y IDFS (n=17)
ctDNA- and pCR (n=20)	94.1%	94.1%	94.1%
ctDNA- and RD (n=25)	92.6%	87.5%	87.5%
ctDNA+ and RD (n=19)	60.0%	60.0%	60.0%

- Lack of ctDNA after NACT did not reliably predict pCR
- However, ctDNA negative patients before surgery have excellent prognosis regardless of pCR, especially in the TNBC cohort
- ctDNA may be a better biomarker for long-term clinical outcomes than pCR, and could eventually be used to aid in clinical trial design and optimization of adjuvant therapy
    - For example, Safe-De trial in the UK (NCT05058183)

Conclusions

- Personalizing treatment further for all breast cancer patients is a goal, and that goal looks increasingly achievable
- Biomarkers (TILs, ctDNA, genomic tests) to understand how best to optimize treatment will be a critical part of this effort
- Because the field is moving fast, it will be critical to educate providers and patients about advances as they occur so that all populations can take full advantage of the science we have at our fingertips
- Clinical trials in diverse populations are badly needed

Q&A