SAN ANTONIO BREAST CANCER SYMPOSIUM®

sion: Abstracts GS2-03 (#1698), 04 (#864), and 05 (#1578)

Is Timing and Selection Everything in Localized Breast Cancer?

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DISCLOSURES (of presenter, last 36 months)

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Abstracts and Relevant Topics for Discussion

Abstract	Presenting Author	Title	Topic for Discussion
GS-03: 1698	Spring	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-analyses of over 27,000 patients	**pCR as a pharmacodynamic biomarker**
GS-04: 864	Martin	Efficacy results from GEICAM/2003-11_CIBOMA/2004-01 study: a randomized phase III trial assessing adjuvant capecitabine after standard chemotherapy for patients with early triple negative breast cancer	**Role of adjuvant capecitabine**
GS-05:1578	Morante Cruz	Impact of the delayed initiation of adjuvant chemotherapy in the outcomes of triple negative breast cancer	**Timing of adjuvant chemo in TNBC**

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

1. EBCTG. Lancet Oncol 2018 (PMID: 29242041)
2. Amoroso et al. JNCI Monographs 2015 (PMID: 26063896
3. Cortazar et al. Lancet 2014 (PMID: 24529560)
4. Berry et al. JAMA Oncology 2016 (PMID: 26181139)

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 concurrently 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

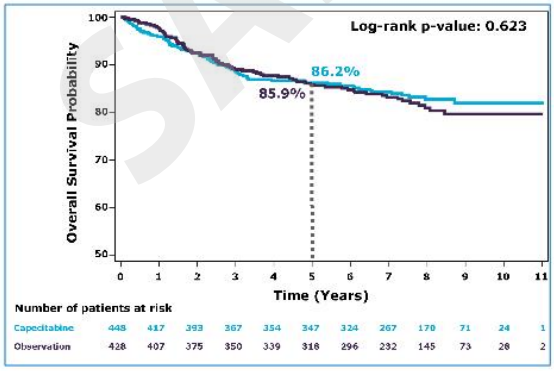
- **Prospective clinical trial**
  - Stage I-III TNBC (N=876)
  - Only about 20% received NACT, and 25% of those (5% of overall population) had pCR
  - Design tested concept of chemotherapy duration in addition to drug
- **Results**
  - Control arm did better than expected (5 year DFS 77% vs. 67% projected)
  - 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

1. Del Mastro et al. Lancet 2015 (PMID: 25740286)
2. Wolff et al. NEJM 2009 (PMID: 19439741)
3. Natori et al. Eur J Oncol 2017 (PMID: 28355581)
4. Masuda et. NEJM 2015 2016 (PMID: 28564564)

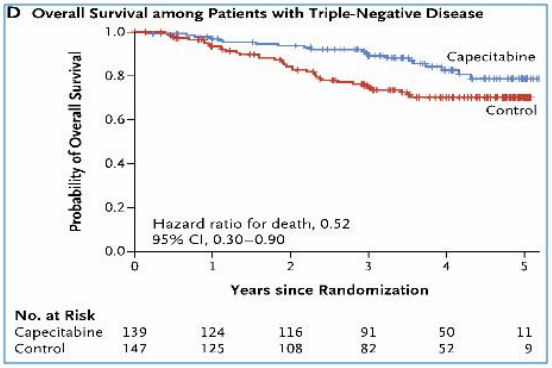
Why Differing Results for Capecitabine in CIBOMA & CREATE-X?

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

CIBOMA



CREATE-X



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

What we knew before

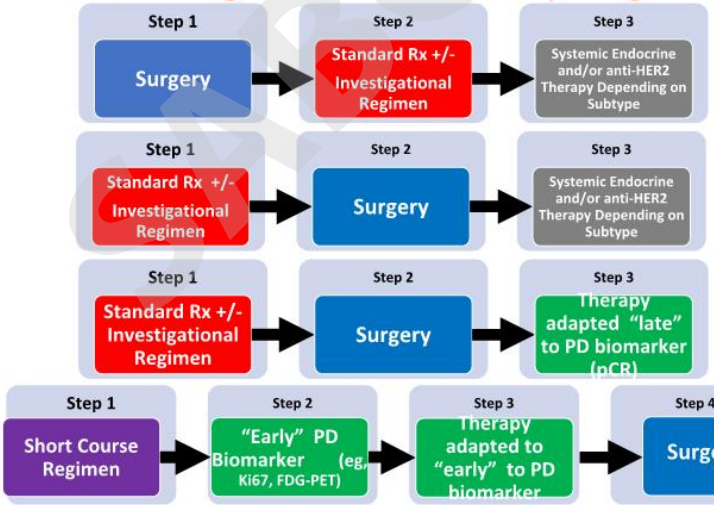
- Interval of < 120 days between diagnosis and ACT quality metric for stage II-III ER/PR-neg BC in women < 70 years (National Quality Forum, ASCO, NCCN)[1]
- Population-based studies have shown > 90 day interval between surgery and ACT associated with inferior BCSS in TNBC[2]
- Systematic review and metaanalysis[3]
  - 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

1. Desch et al. J Clin Oncol 2018 (PMID:18640941)
2. Chavez-MacGregor et al. JAMA Oncol 2016 (PMID: 26659132)
3. Zhan et al. Oncotarget 2017 (PMID: 29416807)

Is Timing and Selection Everything in Early Breast Cancer?



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

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

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

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

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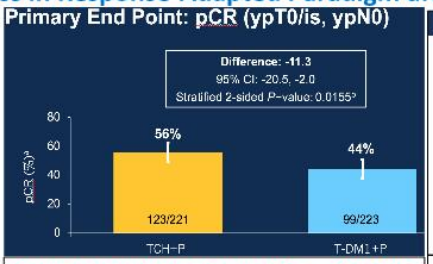
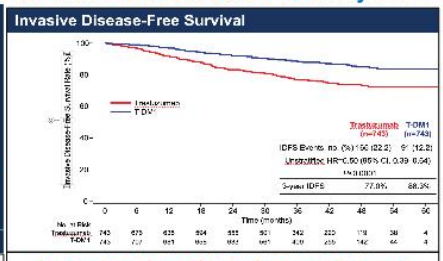
Success in Response-Adapted Paradigm after Failure in Standard Neoadjuvant Paradigm



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 ?

San Antonio Breast Cancer Symposium®, December 4-8, 2018

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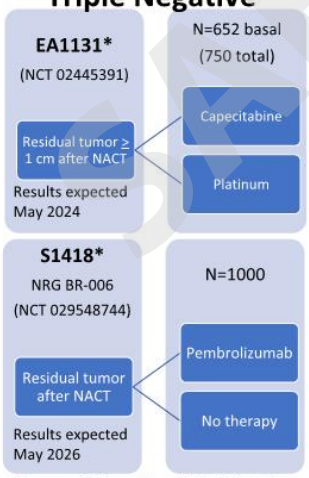
Clinical Trials Using the Response-Adapted Paradigm

Triple Negative



*Source of information: ClinicalTrials.Gov

ALTERNATE: EARLY RESPONSE-ADAPTED PARADIGM

Treatment adapted based on Ki67 response after 4 week course of endocrine therapy

Is Timing and Selection Everything in Early Breast Cancer?

Conclusions and Potential Future Directions

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 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 TAILORx 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

San Antonio Breast Cancer Symposium®, December 4-8, 2018

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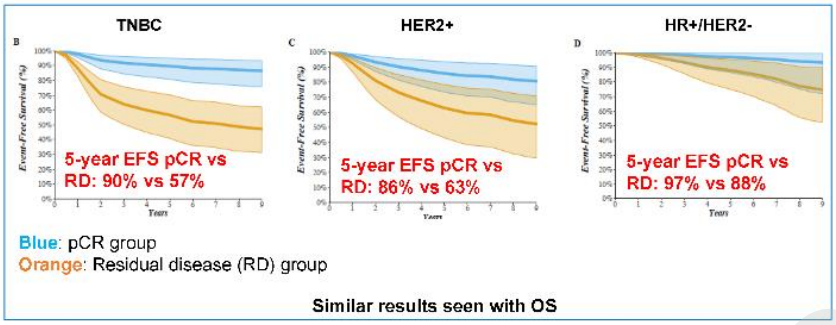
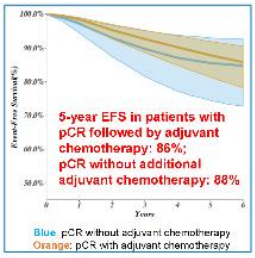
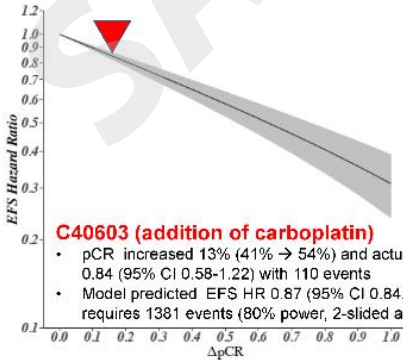
Abstract 1698: Pathologic complete response (pCR) as a pharmacodynamic (PD) biomarker





Abstract 1698: Pathologic complete response (pCR) as a pharmacodynamic (PD) biomarker

Results: ΔEFS vs. ΔpCR



Change in (Δ) pCR	Corresponding HR	95% PI
0	1	N/A
0.1	0.90	0.88-0.92
0.2	0.81	0.78-0.84
0.3	0.72	0.68-0.77
0.4	0.65	0.60-0.70
0.5	0.58	0.52-0.64
0.6	0.52	0.46-0.58
0.7	0.46	0.39-0.53
0.8	0.40	0.34-0.48
0.9	0.36	0.28-0.43
1	0.31	0.24-0.39

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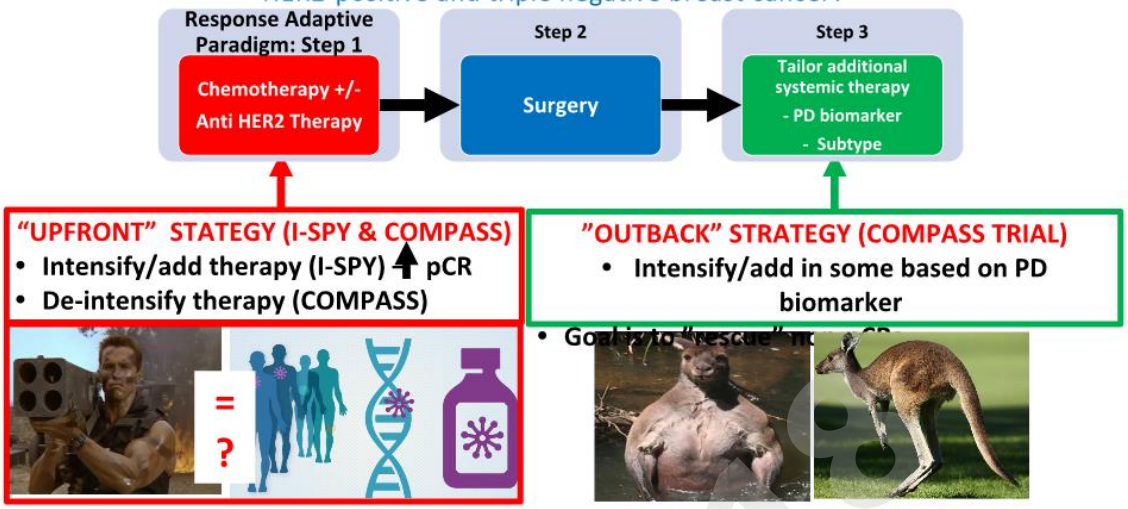
Can broader application of response adaptive paradigm reduce morbidity and mortality in HER2-positive and triple negative breast cancer?



Is Timing and Selection Everything in Early Breast Cancer?

Is the Early Response Adaptive Paradigm Ideal for ER+, HER2- Breast Cancer?