THE NEOADJUVANT APPROACH TO PERSONALISE BREAST CANCER CARE

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INTRODUCTION

Neoadjuvant therapy represents the use of systemic therapy as the first modality of treatment for a primary malignant tumour.

This strategy was first introduced into clinical practice in the’70s for inoperable locally advanced breast cancer and inflammatory breast cancer.

The primary aim was to achieve operability for large, bulky tumours, often accompanied by matted involved axillary nodes.

In subsequent years, this strategy has been progressively used in patients candidates for mastectomy to increase the chance for breast conserving surgery.
NEOADJUVANT THERAPY: A PLATFORM FOR PERSONALISED CARE

Increases surgical options
- Operability of LABC
- BCS for mastectomy candidates
- SNB for N+ converted to N−

Affords similar survival outcomes compared with adjuvant systemic therapy

Allows for in vivo evaluation of treatment sensitivity

LABC: Locally Advanced Breast Cancer; BCS: Breast Conserving Surgery; SNB: Sentinel Node Biopsy
The higher rate of local recurrence is largely driven by trials allowing to avoid surgery in case of complete response.
Neoadjuvant therapy is standard of care for the MAJORITY of stage IIB and stage III.

Complete diagnostic workout, including cytology of suspicious axillary nodes and marker placement in primary tumour should be performed before starting therapy, for proper surgical and radiotherapy planning.

Anthracycline-taxane sequential chemotherapy for 6–8 courses is the standard backbone.

Response is generally monitored with clinical examination, and breast imaging at the completion of the systemic treatment plan.

A multidisciplinary management is crucial.
NEOADJUVANT THERAPY: 
THE PROGNOSTIC VALUE OF pCR
NEOADJUVANT THERAPY: THE PROGNOSTIC VALUE OF PCR

pCR: pathologic complete response. RD: residual disease
pCR AND LONG-TERM OUTCOME: THE CTNeoBC POOLED ANALYSIS

RESULTS FROM NEOADJUVANT TRIALS TO ACCELERATE DRUG APPROVAL

Pathological Complete Response and Accelerated Drug Approval in Early Breast Cancer

Guidance for Industry
Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval

NEOADJUVANT STUDIES IN THE DIFFERENT BC SUBTYPES

The HER2 positive subtype: a history of success
Triple negative breast cancer: opening a new era?
Luminal BC: reshaping the model
NEOADJUVANT STUDIES IN THE DIFFERENT BC SUBTYPES

The HER2 positive subtype: a history of success

Triple negative breast cancer: opening a new era?

Luminal BC: reshaping the model
TARGETING HER2

The availability of anti-HER2 treatments has dramatically changed the prognosis of HER2+ breast cancer, in both early and advanced disease setting.

The role of trastuzumab in the adjuvant setting has been established by Phase 3 randomised trials.

Early neoadjuvant trials reported substantial impact on pCR rate.
ESCALATING STRATEGY IN HER2+ BC: ADDING TRASTUZUMAB

The MDACC trial

Early termination of the study due to the strong advantage for trastuzumab-based combination

<table>
<thead>
<tr>
<th></th>
<th>P-FEC (n=19)</th>
<th>P-FEC + T (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR</td>
<td>26.3%</td>
<td>65.2%</td>
</tr>
<tr>
<td>pCR ER+</td>
<td>27%</td>
<td>61%</td>
</tr>
<tr>
<td>pCR ER−</td>
<td>25%</td>
<td>70%</td>
</tr>
<tr>
<td>pN0</td>
<td>78.9%</td>
<td>86.9%</td>
</tr>
</tbody>
</table>

ESCALATING STRATEGY IN HER2+ BC: ADDING TRASTUZUMAB
The NOAH trial

bpCR, breast pathologic complete response; tpCR, total pathologic complete response (breast + axilla); OR, odds ratio.

Reprinted from The Lancet, 375(9712), Gianni L, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort, 377–84, Copyright 2010, with permission from Elsevier.
ESCALATING STRATEGY IN HER2 + BC: DUAL HER2 BLOCKADE

DUAL HER2 BLOCKADE: CT + TRASTUZUMAB-LAPATINIB (NeoALTTO)

DUAL HER2 BLOCKADE: CT + TRASTUZUMAB-LAPATINIB (Cher-LOB)

DUAL HER2 BLOCKADE: TRASTUZUMAB + PERTUZUMAB (NeoSphere)

Patients with operable or locally advanced / inflammatory* HER2-positive BC
Chemo-naïve and primary tumours >2 cm (N=417)

SURGERY

- TH (n=107)  Docetaxel + trastuzumab
- THP (n=107)  Docetaxel + trastuzumab + pertuzumab
- HP (n=107)  Trastuzumab + pertuzumab
- TP (n=107)  Docetaxel + pertuzumab

Study dosing: q3w x4

- FEC q3w x3
  - Trastuzumab q3w cycles 5–17
- Docetaxel q3w x 4 → FEC q3w x 3
  - Trastuzumab q3w cycles 5–17
- FEC q3w x3
  - Trastuzumab q3w cycles 5–21

`pCR, % ± 95% CI`

ER or PR positive
ER and PR negative
DUAL HER2 BLOCKADE: TRASTUZUMAB + PERTUZUMAB
(NeoSphere)

Reprinted from The Lancet Oncol, 17(6), Gianni L. et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial, 791–800, copyright 2016, with permission from Elsevier.
75% of the patients with operable breast cancer
72% HR+
18% neoadjuvant pertuzumab+trastuzumab
78% neoadjuvant anthracyclines

ESCALATING STRATEGY: T-DM1 IN PATIENTS WITH RESIDUAL DISEASE (KATHERINE)

- N=1486
- Centrally confirmed HER2-positive breast cancer
- Residual invasive tumour in breast or axillary nodes after PCT including:
  - Minimum of 6 cycles of CT
  - Minimum of 9 weeks of T

RANDOMISE 1:1

T-DM1 3.6 mg/kg IV q3w, 14 cycles

Trastuzumab 6 mg/kg IV q3w, 14 cycles
ESCALATING STRATEGY: T-DM1 IN PATIENTS WITH RESIDUAL DISEASE (KATHERINE)

iDFS: ipsilateral invasive BC, locoregional relapse, contralateral invasive BC, distant relapse, death

DE-ESCALATING STRATEGY

TRAIN2: no anthracycline

NeoSPHERE arm C: trastuzumab + pertuzumab, no chemo

Kristine

**DE-ESCALATING STRATEGY: ROLE OF PATIENT SELECTION**

**PAMELA trial:**
HER2-enriched subtype as a predictor of pCR following trastuzumab and lapatinib without chemotherapy\(^1\)

**PerELISA trial:**
trastuzumab+pertuzumab + letrozole in patients with HER2+/HR+ disease selected on the basis of Ki67 response after 2 weeks of letrozole\(^2,3\)

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**Distribution of intrinsic molecular subtypes at baseline**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>57%</td>
</tr>
<tr>
<td>Luminal B</td>
<td>25%</td>
</tr>
<tr>
<td>HER2-enriched</td>
<td>16%</td>
</tr>
<tr>
<td>Basal-like</td>
<td>2%</td>
</tr>
<tr>
<td>Normal-like</td>
<td>2%</td>
</tr>
</tbody>
</table>

**pCR rate in molecular responders according to PAM50**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>N</th>
<th>pCR Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>7</td>
<td>14%</td>
</tr>
<tr>
<td>Luminal B</td>
<td>18</td>
<td>17%</td>
</tr>
<tr>
<td>HER2E N=11</td>
<td>11</td>
<td>45%</td>
</tr>
<tr>
<td>Normal N=4</td>
<td>4</td>
<td>0%</td>
</tr>
</tbody>
</table>

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2. Guarneri V, et al. Presented at ASCO 2018; abstract 507. Figure provided courtesy of Prof V Guarneri;

Dual HER2 blockade significantly increases the chance of achieving a pCR, and is standard for high-risk patients (reimbursement issues in EU)

KATHERINE trial demonstrates a clinically meaningful advantage of T-DM1 in patients with residual disease after trastuzumab based neoadjuvant therapy

Effect of T-DM1 is consistent in pertuzumab-trastuzumab pretreated patients

De-escalating strategy (giving less initial treatment, with “rescue” postoperative treatment to suboptimal responders) is attractive, aiming for personalised therapy
NEOADJUVANT STUDIES IN THE DIFFERENT BC SUBTYPES

The HER2 positive subtype: a history of success

Triple negative breast cancer: opening a new era?

Luminal BC: reshaping the model
TRIPLE NEGATIVE BREAST CANCER

Triple negative breast cancer (TNBC) is the most lethal form of breast cancer
TNBC is more frequently diagnosed in younger women
Higher risk of earlier relapse
High risk for visceral involvement (CNS and lung)
Median survival from time of metastases rarely exceeds 18 months
Highly chemosensitive, with patients achieving pCR having similar outcome compared with the other BC subtypes
AIMING AT IMPROVING THE pCR RATE: INTRODUCING PLATINUM SALTS AND BEVACIZUMAB

<table>
<thead>
<tr>
<th>Study/Regimen</th>
<th>Pathologic complete response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAC Gepar3</td>
<td>40</td>
</tr>
<tr>
<td>EC-P (+/− gem) NeoTango</td>
<td>35</td>
</tr>
<tr>
<td>EC-D</td>
<td>45</td>
</tr>
<tr>
<td>EC-D +Bev</td>
<td>50</td>
</tr>
<tr>
<td>PM</td>
<td>40</td>
</tr>
<tr>
<td>PM+Cb (+ Bev) Gepar6</td>
<td>55</td>
</tr>
<tr>
<td>P-AC</td>
<td>50</td>
</tr>
<tr>
<td>P+Cb-AC (+/− Bev) CALGB40603</td>
<td>55</td>
</tr>
<tr>
<td>P+Cb+bev Ca.Pa.Be</td>
<td>60</td>
</tr>
<tr>
<td>nabP-Cb ADAPT</td>
<td>60</td>
</tr>
<tr>
<td>nabP-EC Gepar7</td>
<td>60</td>
</tr>
<tr>
<td>P+Cb -AC</td>
<td>50</td>
</tr>
<tr>
<td>P+Cb +Vel-AC Brightness</td>
<td>60</td>
</tr>
<tr>
<td>P-AC</td>
<td>40</td>
</tr>
</tbody>
</table>

PLATINUM-BASED NEOADJUVANT CHEMOTHERAPY IN TNBC
(Systematic review and meta-analysis)

Effect of platinum on pCR irrespective of BRCA status

No impact on event-free survival, but BrighTNess data pending

Increased G3/4 haematological AEs

ROLE FOR BEVACIZUMAB IN EARLY TNBC?

Despite interesting preclinical background, no convincing evidence for a clinical impact of adding bevacizumab to current chemotherapy standards.

In the CALGB 40603 neoadjuvant trial, bevacizumab was associated with a non-significant pCR increase over CT alone.

In the GEPAR5 trial, bevacizumab produced a significant pCR increase in HER2– BC, with the effect mainly driven by the TN cohort. No impact on survival reported.

In the NSABP B-40 trial, a non-significant pCR increase was observed in HER2– disease, with the effect driven by the HR+ cohort.

The BEATRICE adjuvant trial reported no impact on DFS for bevacizumab plus standard chemotherapy over standard chemotherapy alone.

AIMING AT IMPROVING THE pCR RATE: IMMUNE-CHECKPOINT INHIBITORS

*Estimated probabilities of pCR. a. Pac → DC; b. Nab-Pac → EC(dd); c. Carboplatin+Pac → EC/DC; d. Carboplatin+Nab-Pac (anthra given after surgery); e. Nab-Pac → DC(dd)

CHEMOTHERAPY +/- PEMBROLIZUMAB: KEYNOTE 522

Key eligibility criteria
Age ≥18 years
Newly diagnosed TNBC of either T1c N1-2 or T2-4 N0-2
ECOG PS 0-1
Tissue sample for PD-L1 assessment

Stratification factors:
Nodal status (+ vs –)
Tumour size (T1/T2 vs T3/T4)
Carboplatin schedule (qw vs q3w)

RANDOMISE 2:1

Neoadjuvant phase
Neoadjuvant Treatment 1 (cycles 1–4; 12 weeks)
Neoadjuvant Treatment 2 (cycles 5–8; 12 weeks)

Carboplatin⁸ + paclitaxel¹⁰
Doxo⁶/epirubicin⁴ + cyclophosphamide⁸

Pembrolizumab 200 mg q3w

Carboplatin⁸ + paclitaxel¹⁰
Doxo⁶/epirubicin⁴ + cyclophosphamide⁸

Placebo

SURGERY

Pembrolizumab 200 mg q3w

Placebo

Adjuvant phase
Adjuvant Treatment (cycles 1–9; 27 weeks)

KEYNOTE 522:
BASELINE CHARACTERISTICS AND pCR
IA1-Interim Analysis 1

IA1: Primary pCR analysis to test primary hypothesis of pCR based on prespecified first 602 subjects (pre-calculated P-value boundary for significance of 0.003)

IA2: If pCR hypothesis successful at IA1 (thus definitive), pCR will not be formally tested at IA2

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All subjects, N=602</th>
<th>Pembro + Chemo n=401</th>
<th>Placebo + Chemo n=201</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), yrs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>49 (22–80)</td>
<td>48 (24–79)</td>
<td></td>
</tr>
<tr>
<td>ECOG PS 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>73 (18.2)</td>
<td>28 (13.9)</td>
<td></td>
</tr>
<tr>
<td>PD-L1-positive(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>334 (83.3)</td>
<td>164 (81.6)</td>
<td></td>
</tr>
<tr>
<td>Carboplatin schedule</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>q1w</td>
<td>167 (41.6)</td>
<td>83 (41.3)</td>
<td></td>
</tr>
<tr>
<td>q3w</td>
<td>234 (58.4)</td>
<td>118 (58.7)</td>
<td></td>
</tr>
<tr>
<td>Tumour size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1/T2</td>
<td>296 (73.8)</td>
<td>148 (73.6)</td>
<td></td>
</tr>
<tr>
<td>T3/T4</td>
<td>105 (26.2)</td>
<td>53 (26.4)</td>
<td></td>
</tr>
<tr>
<td>Nodal involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>208 (51.9)</td>
<td>104 (51.7)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>193 (48.1)</td>
<td>97 (48.3)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) PD-L1 combined positive score defined as number of PD-L1–positive cells (tumour cells, lymphocytes, and macrophages) divided by total number of tumour cells x 100. PD-L1 positivity was defined as CPS ≥1.

KEYNOTE 522: PCR BY PD-L1 STATUS

By PD-L1 status: ypT0/Tis ypN0

KEYNOTE 522:
EVENT-FREE SURVIVAL
IA2-Interim Analysis 2

1174 patients randomised 2:1 from Mar 17 to Sep 18

- EFS at IA2 (first interim of EFS): precalculated P-value boundary for significance of 0.000051 (HR <0.4)
- Prespecified analysis plan allows alpha passing from successful endpoint(s) to other(s)

**Primary end point:** pCR

**Secondary:** pCR in PD-1 selected subgroups, EFS, OS, safety, PROs

**Patients with previously untreated Stage II/III TNBC**

N=204

**Stratification:**

Stage II vs III at diagnosis

PD-L1 lo vs IC1/2/3
IMPASSION031: CO-PRIMARY ENDPOINT pCR (ITT)

Atezolizumab-chemo: 57.6% (95/165) vs Placebo-chemo: 41.1% (69/168)

Δ16.5% (5.9, 27.1)
P=0.0044

a. One-sided significance boundary P=0.0184 (accounting for the adaptive enrichment design). P=0.0085 for the intersection hypothesis of pCR in the ITT and PD-L1–positive population.

IMPASSION031: CO-PRIMARY ENDPOINT pCR IN PD-L1 POSITIVE TUMOURS

**pCR (95% CI), ypT0/is ypN0 (PD-L1–positive)**

- **Atezolizumab-chemo**: 68.8% (53/77)
- **Placebo-chemo**: 49.3% (37/75)

Δ 19.5% (4.2, 34.8) \( P = 0.021 \)

- Did not cross significance boundary of 0.0184

**pCR (95% CI), ypT0/is ypN0 (PD-L1–negative)**

- **Atezolizumab-chemo**: 47.7% (42/88)
- **Placebo-chemo**: 34.4% (32/93)

Δ 13.3% (–0.9, 27.5)

---

aPD-L1+, PD-L1 IC ≥1%; PD-L1–, PD-L1 IC <1%. bOne-sided significance boundary \( P = 0.0184 \) (accounting for the adaptive enrichment design). \( P = 0.0085 \) for the intersection hypothesis of pCR in the ITT and PD-L1–positive population.

ADJUVANT CAPECITABINE IN PATIENTS WITH RESIDUAL DISEASE AFTER NEOADJUVANT CHEMOTHERAPY

CREATE-X trial

Possible pharmacogenomic effect of fluoropirimidine in Asian population?
Capecitabine use in adjuvant setting is off-label
A-BRAVE TRIAL

High-risk primary TNBC patients who completed treatment with curative intent including surgery, chemotherapy and radiotherapy (if indicated)

Stratum A: Adjuvant
Stratum B: Post-neoadjuvant

RANDOMISE 1:1
Balanced for adjuvant and post-neoadjuvant patients

Avelumab for 1 year

Observation

Co-primary endpoints:
1. DFS in all-comers;
2. DFS post-neoadjuvant stratum

Secondary endpoints:
OS, Safety, Biomarkers

Sequential anthra-taxanes remains standard for the majority of the patients.

Adding carboplatin to A-T as neoadjuvant therapy increases the rate of pCR independently of BRCA status. Because of higher risk of haematologic toxicity and lack of OS advantage, the addition of platinum salts remains an option

For patients with residual disease after neoadjuvant chemotherapy: consider capecitabine (CREATE-X) and or clinical trials

Immunotherapy improves pCR rate (and EFS in Keynote522), but additive side effects (early and late)
NEOADJUVANT STUDIES IN THE DIFFERENT BC SUBTYPES

The HER2 positive subtype: a history of success
Triple-negative breast cancer: opening a new era?
Luminal BC: reshaping the model
The pCR rate after neoadjuvant chemotherapy is consistently lower in patients with HR+ disease.

Tumour biology is the driver of treatment selection, and most patients with HR+/HER2– disease are offered adjuvant hormonal therapy alone, even in case of node-positive disease.

For several years, neoadjuvant hormonal therapy has been traditionally limited to elderly, unfit patients with large, inoperable disease.

New scenario with AIs, alone or as a backbone to targeted agents.
RANDOMISED TRIALS OF CHEMOTHERAPY VS. ENDOCRINE THERAPY

Neoadjuvant hormone therapy vs. neoadjuvant cytotoxic chemotherapy

**Clinical response**

<table>
<thead>
<tr>
<th>Source</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alba, et al. 2012</td>
<td>2.11 (0.92, 4.82)</td>
</tr>
<tr>
<td>Palmieri, et al. 2014</td>
<td>0.34 (0.06, 1.98)</td>
</tr>
<tr>
<td>Semiglazov, et al. 2007</td>
<td>0.93 (0.55, 1.57)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1.08 (0.50, 2.35)</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: $X^2=4.47$ (P=0.11), $I^2=55$
Test for overall effect: $z=0.19$ (P=0.85)

**Breast-Conserving Surgery**

<table>
<thead>
<tr>
<th>Source</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alba, et al. 2012</td>
<td>0.68 (0.30, 1.54)</td>
</tr>
<tr>
<td>Semiglazov, et al. 2007</td>
<td>0.63 (0.36, 1.11)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>0.65 (0.41, 1.03)</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: $X^2=0.03$ (P=0.87), $I^2=0$
Test for overall effect: $z=1.83$ (P=0.07)

**pCR**

<table>
<thead>
<tr>
<th>Source</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alba, et al. 2012</td>
<td>3.13 (0.12, 78.77)</td>
</tr>
<tr>
<td>Palmieri, et al. 2014</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Semiglazov, et al. 2007</td>
<td>1.84 (0.53, 6.47)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1.99 (0.62, 6.39)</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: $X^2=0.09$ (P=0.76), $I^2=0$
Test for overall effect: $z=1.16$ (P=0.25)
Prognostic value of pCR after primary chemotherapy in relation to hormone receptor status and other factors

<table>
<thead>
<tr>
<th></th>
<th>5-year OS</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR</td>
<td>79.7%</td>
<td>91.1%</td>
</tr>
<tr>
<td>No pCR</td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>ER-, pCR</td>
<td>67.4%</td>
<td>83.9%</td>
</tr>
<tr>
<td>ER-, no pCR</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ER+, pCR</td>
<td>84.5%</td>
<td>96.4%</td>
</tr>
<tr>
<td>ER-, no PCR</td>
<td></td>
<td>0.04</td>
</tr>
</tbody>
</table>

- Prognostic value of pCR appears weaker in HR+/HER2– BC than HER2+ and TN BC
- Need for alternative markers

Patients with low Ki67 after 2 weeks of pre-operative endocrine therapy experienced superior event-free survival.
PREOPERATIVE ENDOCRINE PROGNOSTIC INDEX

PEPI score

Validated algorithm, PEPI score combines anatomical and biological data at surgery after preoperative endocrine therapy

<table>
<thead>
<tr>
<th>RFS</th>
<th>BCSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathologic T1/2</td>
<td>HR: 0</td>
</tr>
<tr>
<td>Pathologic T3/4</td>
<td>2.8</td>
</tr>
<tr>
<td>Node Negative</td>
<td>-</td>
</tr>
<tr>
<td>Node Positive</td>
<td>3.2</td>
</tr>
<tr>
<td>Ki 67 0%-2.7% (0-1)</td>
<td>-</td>
</tr>
<tr>
<td>Ki 67 &gt;2.7%-7.3% (1-2)</td>
<td>1.3</td>
</tr>
<tr>
<td>Ki 67 &gt;7.3%-19.7% (2-3)</td>
<td>1.7</td>
</tr>
<tr>
<td>Ki 67 &gt;19.7%-53.1% (3-4)</td>
<td>2.2</td>
</tr>
<tr>
<td>Ki 67 &gt;53.1% (&gt;4)</td>
<td>2.9</td>
</tr>
<tr>
<td>ER Allred 0-2</td>
<td>2.8</td>
</tr>
<tr>
<td>ER Allred 3-8</td>
<td>-</td>
</tr>
</tbody>
</table>

Group 1: score 0; group 2: score 1-3; group 3: score >3

RFS and BCSS by PEPI groups

**Clinical response (WHO criteria)**

<table>
<thead>
<tr>
<th></th>
<th>E</th>
<th>L</th>
<th>A</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR (ITT)</strong></td>
<td>62.9%</td>
<td>74.8%</td>
<td>69.1%</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>21.8%</td>
<td>21.3%</td>
<td>17.9%</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>41.1%</td>
<td>53.5%</td>
<td>51.2%</td>
</tr>
<tr>
<td><strong>No change</strong></td>
<td>22.6%</td>
<td>15.7%</td>
<td>16.3%</td>
</tr>
<tr>
<td><strong>Disease progression</strong></td>
<td>6.5%</td>
<td>4.7%</td>
<td>7.3%</td>
</tr>
</tbody>
</table>

**Surgical procedures performed after neoadjuvant AI by baseline surgical feasibility**

<table>
<thead>
<tr>
<th>Surgical indication before neoadjuvant therapy</th>
<th>Surgery performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marginal for BCS (n=189)</td>
<td>BCS 83%</td>
</tr>
<tr>
<td></td>
<td>Mastectomy 17%</td>
</tr>
<tr>
<td>Mastectomy (n=159)</td>
<td>BCS 51%</td>
</tr>
<tr>
<td></td>
<td>Mastectomy 49%</td>
</tr>
<tr>
<td>Inoperable (n=4)</td>
<td>BCS 75%</td>
</tr>
<tr>
<td></td>
<td>Mastectomy 25%</td>
</tr>
</tbody>
</table>

ORR: Objective Response Rate; CR: Complete Response; PR: Partial Response; BCS: Breast Conserving Surgery

PHASE 2 NEOADJUVANT COMPARISON BETWEEN LETROZOLE, ANASTROZOLE AND EXEMESTANE
ACOSOG Z1031

Luminal A

Luminal B

Paradoxical Ki67 increase

PEPI 0
ypT1/2N0
Ki67 ≤2.7%
ER Allred 3–8

Adjuvant chemotherapy was administered in 18 (15.1%) of 119 PEPI 0 cases and 162 (47.5%) of 341 PEPI non-0 cases.
Eligible patients
Postmenopausal cT2-T4c, anyN, M0
ER pos (Allred 6-8) HER2– BC

Ki67 >10%
Week 4 or 12

Neoadjuvant chemo group

RANDOMISE

Eligible patients
Postmenopausal cT2-T4c, anyN, M0
ER pos (Allred 6-8) HER2– BC

Ki67 >10%
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Week 4 or 12

Neoadjuvant chemo group

RANDOMISE
**ALTERNATE PRIMARY ENDPOINT RESULT**

Endocrine-sensitive disease rate (ESRD) = mPEPI0+pCR

<table>
<thead>
<tr>
<th></th>
<th>ANA  n=434</th>
<th>FULV n=431</th>
<th>ANA + FULV n=434</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPEPI = 0, n (%)</td>
<td>77 (17.7)</td>
<td>94 (21.8)</td>
<td>87 (20.0)</td>
</tr>
<tr>
<td>pCR, n (%)</td>
<td>4 (0.9)</td>
<td>4 (0.9)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>ESDR, n (%)</td>
<td>81 (18.6)</td>
<td>98 (22.7)</td>
<td>89 (20.5)</td>
</tr>
<tr>
<td>(97.5% CI)</td>
<td>(14.6, 23.2)</td>
<td>(18.4, 27.6)</td>
<td>(16.3, 25.2)</td>
</tr>
<tr>
<td>Fisher’s Exact Test P-value compared to ANA arm</td>
<td>0.15</td>
<td>0.55</td>
<td></td>
</tr>
</tbody>
</table>

Degree of Ki67 suppression similar among treatments

Fewer than 2% of the patients progressed while on endocrine therapy, maybe because of the Ki67 triage strategy

Survival data awaited

<table>
<thead>
<tr>
<th>Trials</th>
<th>Arms</th>
<th>Patients, n</th>
<th>Main outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NeoPalAna</td>
<td>Pal+Ana (+/-LHRh)</td>
<td>50</td>
<td>87% complete cell cycle arrest</td>
</tr>
<tr>
<td>NeoMONARCH</td>
<td>Abema+Ana Abema Ana</td>
<td>223</td>
<td>Higher Ki 67 decrease for combo</td>
</tr>
<tr>
<td>PALLET</td>
<td>Let Palbo+Let</td>
<td>307</td>
<td>Higher Ki 67 decrease for combo</td>
</tr>
<tr>
<td>FELINE</td>
<td>Let-ribo (intermittent)</td>
<td>120</td>
<td>No difference in PEPI score 0, clinical and pathological response, higher Ki67 decrease for combo at D14 not maintained at surgery</td>
</tr>
<tr>
<td>NeoPAL</td>
<td>Let + Palbo Chemotherapy</td>
<td>53 53</td>
<td>Similar RCB, High Ki67 reduction for let-palbo</td>
</tr>
<tr>
<td>CORALLEEN</td>
<td>Let + Ribociclib Chemotherapy</td>
<td>49 52</td>
<td>Similar rates of ROR-low disease at surgery pCR 5.8% with CT vs 0 with let-R, PEPI score 0 17 % with Ct and 22% with Let-R</td>
</tr>
</tbody>
</table>
Endocrine therapy is a valuable option to allow for breast conservative surgery in HR+/HER2– patients

Primary endocrine therapy does not jeopardise local disease control

Endocrine therapy needs prolonged treatment to exert its maximum therapeutic benefit; however, early markers of benefit are available (Ki67, PEPI score) and might allow for a more personalised treatment

Neoadjuvant endocrine therapy is the ideal backbone to test new agents

Needs for additional data to confirm Ki67 as an early marker of benefit after endocrine therapy + CDK4/6i
OPTIMISING THE MODEL

Let’s dig a little deeper: pCR vs. no pCR may be too simplistic

“less-than-pCR” doesn’t necessarily mean poor outcome

pCR doesn’t guarantee cure
HETEROGENEITY OF “LESS THAN pCR”

Residual cancer burden validation

HETEROGENEITY OF “LESS THAN pCR”

Combined Nodal status and post neoadjuvant chemotherapy Ki67


Tumour Infiltrating ILymphocites (TILs) in TNBC with residual disease post neoadjuvant chemotherapy

Group | Patients | Events
--- | --- | ---
High-TIL | 27 | 3
Low-TIL | 251 | 122

p= 0.0017
HETEROGENEITY OF "LESS THAN pCR": HER2 LOSS

Loss of HER2 amplification after trastuzumab-based neoadjuvant therapy

Rate of HER2 loss according to neoadjuvant trastuzumab exposure and outcome


OPTIMISING THE MODEL: PLATFORM TO RANK
STRATEGIES TO BE TESTED IN THE ADJUVANT SETTING

Lesson learned from NeoSphere and NeoALLTO

OPTIMISING THE MODEL
Trial-level correlation between treatment effect on pCR and EFS/OS

Event-free survival

Overall survival

Consider the dilution effect of post-surgery treatments

CONCLUSIONS

Neoadjuvant therapy has a clear role in the management of BC
pCR at single patient level has an established prognostic value
Triage of new agents is faster and cheaper
To better identify pCR patients eligible for de-escalated systemic treatment, future research should be more focused on factors associated with distant events and on predictors of both pCR and EFS
Post-neoadjuvant studies allow for a rational clinical positioning of new agents
Post-neoadjuvant strategy taking into account the biology of residual disease might further improve the cure rate
THANK YOU!