19th Conference of the International Society of Geriatric Oncology

Integrative oncology – Leaving no one behind

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#SDGACTION26996
UN Partnerships for Sustainable Development Goals (SDGs)
INDICATION, TIMING AND TYPE OF CHEMOTHERAPY IN OLDER ADULTS WITH TRIPLE-NEGATIVE BREAST CANCER

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CURRENT ISSUES IN THE MANAGEMENT OF LOCALIZED HER2+ AND TRIPLE-NEGATIVE BREAST CANCER IN OLDER PATIENTS

15TH NOVEMBER 2019
Disclosures

• Travel grants: Genomic Health, Pfizer

• Speaker fees: Pfizer
Older adults are heterogeneous - TNBC is heterogeneous

Denkert C, Lancet, 2017; Chan JJ, J Oncol Pract, 2018; Lehmann BD, PLOS One, 2016
## Neoadjuvant versus adjuvant chemotherapy

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Neoadjuvant Rx</th>
<th>Adjuvant Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induce tumour response and <strong>reduce extent of surgery</strong> in breast/axilla</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Test the disease <strong>chemosensitivity in vivo</strong></td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Enable <strong>genetic testing</strong> ahead of surgery</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Improve <strong>cosmesis</strong></td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td><strong>Reduce the risk of disease recurrence</strong> (micrometastatic disease)</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Provide <strong>prognostic information</strong> (pCR)</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td><strong>Guide adjuvant Rx</strong> based on pathological response</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>

![Graph showing Event Free Survival with 5-year EFS pCR vs RD: 90% vs 57%](image)

Cortazar P, Lancet, 2014; Spring L, SABCS, 2018
High TILs (≥30%) are associated with excellent prognosis in patients with pN0 TNBC treated with adjuvant anthracycline- and taxane-based chemo (N=2,148).

In TNBC patients not treated with chemo, worse outcomes (as expected) (N=581).

In stage IA TNBC (T1N0) not treated with chemo, even better outcomes.

Can we possibly omit adjuvant chemotherapy here?

Loi S, JCO, 2019; Park JH, ESMO, 2019.
Different chemotherapy regimens?

Different taxanes?

GeparSepto trial (N=1,206): nab-P + EC vs P + EC
Patients aged 70+: n = 24 (4%) versus 27 (5%)

ETNA trial (N=695): nab-P + EC versus P + EC
Median age: 50 years (25-79) – no age-specific data

Platinum compounds?

CALGB 40603 trial (N=443)
Patients aged 60+: n = 74 (17%)

GeparSixto trial (N=695): nab-P + EC versus P + EC
Median age: 50 (25-79) – no age-specific data

New agents? Immunotherapy?

**BrighTness trial (N=634)**
Median age: 50 years - patients aged 50+: ≥46%

**KEYNOTE-522 trial (N=1174)**
Median age: 48-49 years (22-80) – no age-specific data

Loibl S, Lancet Oncol, 2018; Shmid P, ESMO, 2019
Should ALL older adults with TNBC receive NACT?

- Consider **aims** of systemic treatment
  - Is the patient already suitable for **breast conserving surgery**?
    - And be spared anthracyclines preoperatively and receive an “easier” regimen postop?

- Consider disease **biology** and **anatomic stage**
  - **Stage I** vs **stage II-III**
  - **Heterogeneity** of TNBC
  - What is the likelihood of breast conservation?
  - Role of TILs?

- Consider patient **fitness**
  - Would NACT impact on patient’s ability to undergo surgery?

- Consider patient **preferences**

---


In addition to these familiar biomarkers, the Panel recommended that tumor-infiltrating lymphocytes (TILs) be routinely characterized in triple-negative breast cancer (TNBC) because of their prognostic value. However, data are inadequate to recommend TILs as a test to guide neo/adjuvant treatment choices in TNBC, as treatments are largely governed by anatomic stage. Tumor PD-L1 or immune-cell PD-1 expression are recognized as markers that may predict benefit from immunotherapy treatment in advanced breast cancer. However, the Panel recommended against routine PD-L1 tumor or PD-1 immune cell testing in early-stage TNBC, as current treatment algorithms are not based on such testing.

Burstein H, Ann Oncol, 2019 (St Gallen consensus)
Pathological response driven approach?

CREATE-X trial (N=910)
Median age: 48 years (25-74) – no age-specific data

CIBOMA-GEICAM trial (N=910)
Median age: 50 years (20-82) – no age-specific data
ECOG ACRIN EA1131 Phase III trial of adjuvant platinum in patients with basal-like residual TNBC following NACT

**Hypothesis:**
In patients that have the highest risk of recurrence - basal-like TNBC with <1cm residual disease post neoadjuvant chemo - the addition of adjuvant platinum-based chemo will improve DFS

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**Step 0:**
- **Screening**
- **Tissue Submission**
- **PAM50 Analysis**

**Stratification factors:**
1. Basal-like subtype (yes or no)
2. Clinical stage at diagnosis (I or II)
3. Residual cancer burden after NAC (1-3 cm or < 3 cm)
4. Planned platinum agent choice (capcitabine or carboplatin)
5. Anthracycline exposure (yes or no)
6. Administration of radiation therapy (yes or no)

**Accrual:** 750
1 cycle = 3 weeks

1. TNBC: ER/PR less than 10% positive staining with weak intensity score, or less than 1% positive staining with weak or intermediate intensity score; HER2 negative per ASCO guidelines.
2. Tumor s anthracycline based; platinum agents or capcitabine not allowed.
3. Choice of platinum agent will be per treating physician discretion.
4. Primary endpoint: DFS in patient with basal-like TNBC.
5. Secondary endpoints: DFS in patient with non-basal-like TNBC, OS and RFS.
6. Patient must have completed adjuvant radiotherapy (if applicable) prior to randomization.
7. Tumor tissue from the residual disease on the definitive surgical specimen must be submitted within 21 weeks post surgery for PAM50 analysis for determination of patient eligibility as outlined in Section 10.2. Patients cannot be randomized to treatment until institution receives confirmation of PAM50 analysis from the Molecular Diagnostics Laboratory performing the assessments.
8. Females of child-bearing potential must have a blood test or urine study within 2 weeks prior to treatment initiation to rule out pregnancy.

**Arm A:**
- Capcitabine 3000 mg/m²
  - 14 every 3 weeks x 6 cycles

**Arm B:**
- Carboplatin 75 mg/m²
  - Day 1 every 3 weeks x 6 cycles
  - OR
  - Carboplatin AUC 6
  - Day 1 Q3W x 6 cycles

**Follow-up:**
4, 5
Should this patient be offered adjuvant capecitabine?

- Depends on **pathological response** post NACT
- One size does not fit all TNBCs
- **No data about patients’ fitness** from CREATE-X and CIBOMA-GEICAM
- **Balance potential benefits and toxicities** on capecitabine
  - Consider renal function (check CrCl)

---

**Table 2**: Adverse Events Assessed with 6 Months after Randomization.

<table>
<thead>
<tr>
<th>Event</th>
<th>Capcitabine Group (N=443)</th>
<th>Control Group (N=439)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic adverse event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Grade 1: 84, Grade 2: 81, Grade 3: 26, Grade 4: 2</td>
<td>Grade 1: 28, Grade 2: 15, Grade 3: 0, Grade 4: 0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>Grade 1: 130, Grade 2: 143, Grade 3: 6, Grade 4: 1</td>
<td>Grade 1: 67, Grade 2: 19, Grade 3: 1, Grade 4: 0.2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Grade 1: 203, Grade 2: 37, Grade 3: 3, Grade 4: 0</td>
<td>Grade 1: 32, Grade 2: 2, Grade 3: 0, Grade 4: 0</td>
</tr>
<tr>
<td>Anemia</td>
<td>Grade 1: 365, Grade 2: 10, Grade 3: 0, Grade 4: 0</td>
<td>Grade 1: 46, Grade 2: 7, Grade 3: 0, Grade 4: 0</td>
</tr>
<tr>
<td>Nonhematologic adverse event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Grade 1: 67, Grade 2: 17, Grade 3: 3, Grade 4: 2</td>
<td>Grade 1: 1, Grade 2: 0, Grade 3: 0, Grade 4: 0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Grade 1: 88, Grade 2: 20, Grade 3: 5, Grade 4: 0</td>
<td>Grade 1: 8, Grade 2: 1, Grade 3: 0, Grade 4: 0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>Grade 1: 61, Grade 2: 12, Grade 3: 3, Grade 4: 0</td>
<td>Grade 1: 5, Grade 2: 1, Grade 3: 1, Grade 4: 0.2</td>
</tr>
<tr>
<td>Bilirubin level increased</td>
<td>Grade 1: 99, Grade 2: 41, Grade 3: 2, Grade 4: 0.3</td>
<td>Grade 1: 6, Grade 2: 2, Grade 3: 0, Grade 4: 0.2</td>
</tr>
<tr>
<td>Aspartate aminotransferase level increased</td>
<td>Grade 1: 220, Grade 2: 6, Grade 3: 3, Grade 4: 0.2</td>
<td>Grade 1: 27, Grade 2: 1, Grade 3: 2, Grade 4: 0.4</td>
</tr>
<tr>
<td>Mucositis or stomatitis</td>
<td>Grade 1: 80, Grade 2: 13, Grade 3: 1, Grade 4: 0.2</td>
<td>Grade 1: 2, Grade 2: 0, Grade 3: 0, Grade 4: 0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Grade 1: 23, Grade 2: 6, Grade 3: 3, Grade 4: 0.2</td>
<td>Grade 1: 2, Grade 2: 0, Grade 3: 1, Grade 4: 0.2</td>
</tr>
<tr>
<td>Nausea</td>
<td>Grade 1: 92, Grade 2: 6, Grade 3: 0</td>
<td>Grade 1: 1, Grade 2: 2, Grade 3: 0</td>
</tr>
<tr>
<td>Alkaline phosphatase level increased</td>
<td>Grade 1: 143, Grade 2: 15, Grade 3: 0</td>
<td>Grade 1: 37, Grade 2: 4, Grade 3: 2, Grade 4: 0.4</td>
</tr>
<tr>
<td>Lactic dehydrogenase level increased</td>
<td>Grade 1: 310, Grade 2: 3, Grade 3: 0</td>
<td>Grade 1: 65, Grade 2: 2, Grade 3: 1, Grade 4: 0.2</td>
</tr>
<tr>
<td>Creatinine level increased</td>
<td>Grade 1: 141, Grade 2: —, Grade 3: —</td>
<td>Grade 1: 36, Grade 2: —, Grade 3: —</td>
</tr>
<tr>
<td>Hand-foot syndrome*</td>
<td>Grade 1: 360, Grade 2: 111, Grade 3: 49</td>
<td>Grade 1: —, Grade 2: —, Grade 3: 13.3</td>
</tr>
</tbody>
</table>

Masuda N, NEJM, 2017
Efficacy

- **N = 1,711 aged 66+** with HR- nonmet BC (1992-1999)
- **Greatest OS benefit in pN+ and pN0 most likely to receive chemo**
- **N = 41,390 aged 65+** with stage I-III BC (1991-1999)
- **No OS benefit in pN0 or pN+ ER+**
- **OS benefit in pN+ ER-**

Retrospective evidence (SEER) (Elkin E, JCO, 2006; Giordano SH, JCO, 2006; Barcenas CH, JCO, 2014; Rosenstock AS, Breast Cancer Res Treat, 2016; Pinder MC, JCO, 2007)

Safety

- **N = 3,567 patients aged 65+** diagnosed with EBC in 2003-2007
- **Hospitalization rates significantly higher with TAC, AC+T, AC or AC+ weekly P (23.0%) versus TC (12.7%)**
- **N = 43,338 women aged 66-80** diagnosed with stage I-III BC in 1992-2002

CHF rates in patients aged 66-70 at 5 and 10 years:

- After anthracyclines: 19% and 38%
- Without an anthracycline: 18% and 33%
- Without chemotherapy: 15% and 29%
- No association with chemo type in women aged 71-80
- Age, ethnicity, trastuzumab, hypertension, diabetes and CAD were significant predictors

Table 4. Cox Proportional Hazards Model for Association Between Baseline Characteristics and Subsequent CHF, Adjusted for Charlson Comorbidity Index

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 66-70 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant therapy received</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonanthracycline</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>Anthracycline</td>
<td>1.26</td>
<td>1.12 to 1.42</td>
</tr>
<tr>
<td>None</td>
<td>0.90</td>
<td>0.86 to 0.99</td>
</tr>
<tr>
<td>Age 71-80 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant therapy received</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonanthracycline</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>Anthracycline</td>
<td>1.01</td>
<td>0.90 to 1.13</td>
</tr>
<tr>
<td>None</td>
<td>0.92</td>
<td>0.86 to 0.99</td>
</tr>
</tbody>
</table>
Combined analysis of CALGB 7581, 8082, 8541 and 9344

- N = 6,487 with pN+ BC
  - 542 (8%) aged 65+; 159 (2%) aged 70+
  - 172 (32%) ER-; 159 (29%) PgR-

- Smaller pT, lower pN, >chemo and tamoxifen use associated with longer DFS and OS

- No association between age and DFS

- OS worse for patients aged 65+ due to other causes

- 33 deaths (0.5%) attributed to treatment
  - 1.3-1.5% of older patients receiving died during the chemotherapy administration

- Higher treatment-related mortality in older patients

- Similar reductions in BC-mortality and recurrence from regimens containing >chemo in older and younger patients

### Table 4. Disease-Free and Overall Survival in Multivariate Proportional Hazards Model

<table>
<thead>
<tr>
<th>Comparison, Lower vs Higher Risk</th>
<th>Degrees of Freedom</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More vs less chemotherapy</td>
<td>1</td>
<td>0.76 (0.72-0.85)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age × chemotherapy interaction</td>
<td>2</td>
<td></td>
<td>.16</td>
</tr>
<tr>
<td>&lt;65 vs ≥65</td>
<td>2</td>
<td>0.97 (0.96-1.00)</td>
<td>.001</td>
</tr>
<tr>
<td>Age × chemotherapy interaction</td>
<td>2</td>
<td></td>
<td>.03</td>
</tr>
<tr>
<td>1 vs 10 positive lymph nodes</td>
<td>1</td>
<td>0.43 (0.40-0.46)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Tumor size, &lt;2 cm vs ≥2 cm</td>
<td>1</td>
<td>0.65 (0.70-0.97)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Estrogen receptor positive vs negative</td>
<td>1</td>
<td>0.90 (0.81-0.99)</td>
<td>.03</td>
</tr>
<tr>
<td>Tamoxifen use vs no use</td>
<td>1</td>
<td>0.49 (0.52-0.67)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

US Oncology Trial 9735

- N = 1,016 with operable stage I-III BC
  - 16% aged 65+ with median age 69 (65-77)
  - 27% ER-/PgR-

- Median 7 years of follow-up

- Longer DFS and OS with TC versus AC in the overall population and in older women

- In patients aged 65+, different toxicity profile with AC versus TC

### Table 1. Grade 3-4 Toxicities by Age Group

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>TC</th>
<th>AC</th>
<th>TC</th>
<th>AC</th>
<th>TC</th>
<th>AC</th>
</tr>
</thead>
<tbody>
<tr>
<td>% by Age Group</td>
<td>65</td>
<td>65</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Muss H, JAMA, 2005; Jones S, JCO, 2009
FASG-08 study

- N = 338 patients aged 65-85 with pN+ operable BC randomized to tamoxifen versus epirubicin 30mg/m² d1,8,15 q28 + tamoxifen
  - ER-/PgR-: 16% in TAM arm, 21% in EPI-TAM arm
  - 70+: 42.7% in TAM arm, 40.8% in EPI-TAM arm
- 6-year DFS 69.3% with TAM versus 72.6% with EPI-TAM
- 6-year OS 79.1% versus 79.8%
- Good compliance: 96.9% received 6 cycles
- Mild acute toxicity
- 1 death due to dysrhythmia related to carcinomatous lymphangitis

Fargeot P, JCO, 2004
Prospective evidence: different regimens?

**ICE study**
- **N** = 1,358 patients aged 65+ with pN+ or pN-/pT≥2cm/G2-3/HR- BC
  - >24% aged 75+
  - >13% TNBC

**CALGB 49907 study**
- **N** = 600 patients aged 65+ with pT1-4/any N, any HR BC
  - 65% aged 70+
  - >32% ER-/PgR-; >75% HER2-
  - Randomized to **CMF x6 vs AC x4 vs capecitabine x6**

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Table 1. Results of Multivariate Analysis of Relapse-free and Overall Survival among 622 Patients.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relapse-free survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment (capecitabine vs. standard therapy)</td>
<td>2.09 (1.38–3.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tumor size (5 cm vs. 2 cm)</td>
<td>1.47 (1.00–2.13)</td>
<td>0.05</td>
</tr>
<tr>
<td>No. of positive lymph nodes (4 vs. 1)</td>
<td>1.35 (1.10–1.67)</td>
<td>0.004</td>
</tr>
<tr>
<td>Hormone receptor status (negative vs. positive)</td>
<td>3.02 (2.02–4.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment (capecitabine vs. standard chemotherapy)</td>
<td>1.85 (1.11–3.08)</td>
<td>0.02</td>
</tr>
<tr>
<td>Tumor size (5 cm vs. 2 cm)</td>
<td>1.75 (1.11–2.76)</td>
<td>0.02</td>
</tr>
<tr>
<td>No. of positive lymph nodes (4 vs. 1)</td>
<td>1.22 (0.94–1.57)</td>
<td>0.13</td>
</tr>
<tr>
<td>Hormone-receptor status (negative vs. positive)</td>
<td>2.62 (1.58–4.35)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

von Minckwitz G, SABCS, 2014; Muss H, NEJM, 2009; Muss H, JCO, 2019
Prospective evidence: different regimens?

ELDA study

- **N = 302 patients aged 65-79** operated for average/high risk BC
  - 74 (25%) ER- and PgR-; 239 (80%) HER2-
  - 69 (23%) aged 75+

- **HR of DFS for weekly docetaxel versus CMF: 1.21**

- No interaction between treatment arms and geriatric scales measuring ability and comorbidity

- **Side effects:**
  - Myelosuppression, mucositis and nausea worse with CMF
  - Allergy, fatigue, alopecia, onychopathy, dysgeusia, diarrhea, abdo pain, neuropathy, cardiac and skin tox worse with docetaxel

- **QOL worse with docetaxel** for NV, appetite loss, diarrhea, body image, future perspective, treatment side effects and alopecia
California Cancer Registry data

- N = 24,843 patients with stage I-III BC diagnosed in 2005-2010 and treated with adjuvant chemotherapy
- Median age 53 years – 7,363 patients aged 60+
- Age associated with longer time to chemo
- Longer time to chemo (>91 days) caused TNBC patients to have worse OS (HR, 1.53; 95%CI, 1.17-2.00) and worse BC-specific survival (HR, 1.53; 95%CI 1.17-2.07)
Should this patient receive adjuvant chemotherapy? Which regimen?

- Consider **life expectancy**
  - **ePrognosis**: 10-year all-cause mortality (w/out cancer): 52%

- Consider **risk of toxicity**
  - Higher risk of toxicity on anthracyclines
  - **CARG**: grade 3-5 30%
  - **CRASH**: low risk

- Consider **expected benefit**
  - **PREDICT**: +4% OS benefit at 5 years
    - *Overestimated* in patients aged ≥85 years, after mastectomy and with comorbidities

- **Lack of data** in nonagenarians

---

Should this patient be offered genetic testing?

- Yes

- Therapeutic implications only for advanced disease (EMBRACA and OlympiAD)

- Important information for patient and family
  - Surgical implications
  - Surveillance
  - Screening relatives

GeparOcto study (N=393 with TNBC)
17.6% gBRCA mutations

Ellsworth D, J Oncol, 2019; Pohl–Rescigno E, ASCO, 2019
Conclusions

- For fit, older patients with high-risk breast cancer (e.g., pN+, large tumors): **sequential anthracycline-based and taxanes-based chemotherapy regimens**, but
  - Consider that benefit of anthracyclines was **tested in younger and selected fit older patients**
  - Balance **higher risk of toxicity** on anthracyclines (hematological, cardiac, leukemia/MDS)
- For lower-risk tumors (e.g., pN0 HR+ or pN0 TN <1cm) or if concerns on anthracyclines: **docetaxel/cyclophosphamide (TC)**
  - Primary G-CSF prophylaxis remains mandatory
  - Impact on QOL reversible
- If concerns about safety of multiagent chemo regimens: **weekly paclitaxel**
- If patient not fit for chemo, consider **surgery upfront** and/or **radiotherapy**

Geriatric assessment is key for decision-making in the context of life expectancy, predicted chemotherapy benefits and toxicities and patient’s preferences
THANK YOU!

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#gerionc
#gerihem

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