Breast Cancer in Older Patients
What is new?

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Conflicts of interest

• Receipt of grants/research supports
  – TEVA (Cephalon), HalioDX (Qiagen/Ipsogen), Amgen

• Receipt of honoraria or consultation fees
  – AstraZeneca, BMS, Celgene, Clinigen, Hospira, Janssen, Mylan, OBI Pharma, Pfizer, Puma, Roche, Samsung
Highlights since 2017

• Numbers and factfulness!
• Targeted treatments
• Prediction
• Some thoughts
• Most common shortcut in statistics
  
  “1 in 8 women will develop BC in their lifetime”
  
  instead of
  
  “If everyone lived beyond the age of 70, 1 in 8 of those women would get or have had BC”
  
• Since BC risk increases with age, lifetime risk changes depending on age

  - Age 20-29  1 in 2,000
  - Age 30-39  1 in 229
  - Age 40-49  1 in 68
  - Age 50-59  1 in 37
  - Age 60-69  1 in 26
  - Ever  1 in 8
46% of cancer survivors are ≥ 70 yo
All adult oncologists are geriatric oncologists.

They just do not know it yet!
No simple dichotomy but 4 income levels
No country on level 4 has really short LE nor on level 1 has long LE
Most people in the middle, on levels 2 and 3 w/ huge ≠ in LE, depending on how income is used
Few older adults included in registration studies! Breast cancer as an example

<table>
<thead>
<tr>
<th>Agent Name</th>
<th>Approval</th>
<th>N</th>
<th>Age ≥ 65</th>
<th>N</th>
<th>Age ≥ 75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palbociclib</td>
<td>2/2015</td>
<td>37</td>
<td>44%</td>
<td>8</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>86</td>
<td>25%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>7/2012</td>
<td>290</td>
<td>40%</td>
<td>109</td>
<td>15%</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>6/2012</td>
<td>60</td>
<td>15%</td>
<td>5</td>
<td>1%</td>
</tr>
<tr>
<td>Eribulin mesylate</td>
<td>11/2010</td>
<td>121</td>
<td>15%</td>
<td>17</td>
<td>2%</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>1/2010</td>
<td>34</td>
<td>17%</td>
<td>2</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>282</td>
<td>44%</td>
<td>77</td>
<td>12%</td>
</tr>
<tr>
<td>Ixabepilone</td>
<td>10/2007</td>
<td>45</td>
<td>10%</td>
<td>3</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32</td>
<td>13%</td>
<td>6</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

*Package Insert, “Geriatric Usage” section*

Courtesy to Arti Hurria (adapted)
Cleopatra double-blinded phase III trial

- Pertuzumab: 840 mg loading dose → 420 mg
- Trastuzumab: 8 mg/kg loading dose → 6 mg/kg
- Docetaxel: 75 mg/m$^2$ → 100 mg/m$^2$ depending on tolerance
- Primary objective: PFS
- Secondary objectives: OS, ORR, tolerance
- Stratification: geography, (neo)adjuvant treatment

MBC L1 HER2+ (central review) $N = 808$

R

1:1

Pertuzumab + trastuzumab + docetaxel ($n = 402$)

Placebo + trastuzumab + docetaxel ($n = 406$)

Final OS Analysis
Median follow-up 50 months (range 0–70 months)

HR 0.68
95% CI = 0.56, 0.84
p = 0.0002

Time (months)

OS (%)

n at risk

Plz + T + D 402 371 318 268 226 104 28 1
Pla + T + D 406 350 289 230 179 91 23 0

ITT population. Stratified by geographic region and neo/adjuvant chemotherapy.
CI, confidence interval; D, docetaxel; HR, hazard ratio; OS, overall survival; Pla, placebo; Plz, pertuzumab; T, trastuzumab.

Swain ESMO 2014; Swain NEJM 2015
Pertuzumab

CLEOPATRA
808 patients

→ 127 (16%) 65+
→ 19 (2%) 75+

More frequent in elderly patients

- **Any grade**: diarrhea, asthenia, fatigue, anorexia, vomiting and dysgeusia
- **Grade 3**: diarrhea, peripheral neuropathy
- **Dose intensity**: 12% dose escalation, 31% dose reduction, 20-30% G-CSF
EORTC 75111-10114
(Co-PI Hans Wildiers & Etienne Brain)

80 pts HER2+ MBC ≥ 70 Years
(≥65/≥60y with co-morbidity)

Primary endpoint
PFS at 6 months of PH or PHM

Secondary endpoints
OS, BCSS, toxicity, RR (RECIST v1.1),
HRQoL, evolution of GA during treatment

Pertuzumab + Trastuzumab

Pertuzumab + Trastuzumab + metronomic CT

Stratification: ER/PgR, previous HER2 treatment, G8

Pertuzumab
840 mg loading dose, further 420 mg q3w iv

Trastuzumab
8 mg/kg loading dose, further 6 mg/kg q3w iv

Chemotherapy
Metronomic chemotherapy: cyclophosphamide 50 mg/d po continuously

On progression
Option to have T-DM1 (3.6 mg/kg iv q3w) till progression

→ PD → T-DM1

Wildiers Lancet Oncol 2018
Pertuzumab and trastuzumab with or without metronomic chemotherapy for older patients with HER2-positive metastatic breast cancer (EORTC 75111-10114): an open-label, randomised, phase 2 trial from the Elderly Task Force/Breast Cancer Group

Hans Wildiers, Konstantinos Tryfonidis, Lisandra Dal Lago, Peter Vuylsteke, Giuseppe Curigliano, Simon Waters, Barbara Brouwers, Sevilay Altintas, Nathan Touati, Fatima Cardoso, Etienne Brain

Elderly/frail HER2+ MBC population

TP + metronomic CT > TP
(7-month longer median PFS: 12.7 vs 5.6)

Acceptable safety profile

T-DM1 at progression active
Competing risks for mortality

Dutch & Belgian postmenopausal pts w/ EBC ER+ in the TEAM trial (2001-2006) exemestane vs sequential tamoxifen → exemestane 5 yr

3,159 pts (70% <70 yr); median FU 10 yr; cumulative incidence of BC mortality
Competing risks for mortality

≥70 yr & no comorbidity (33%)
→ higher BC mortality

22.2%, 95% CI, 17.5–26.9 vs 15.6%, 95% CI, 13.6–17.7

sHR 1.49, 95% CI, 1.12–1.97, p = .005
5-year BCSM by Age and RS Group

- RS predicts BCSM in both age groups (p<0.001)
- Low 5-y BCSM was observed with RS <18 in both age groups
- Higher 5-y BCSM was observed with RS 18-30 and RS ≥31 in older patients
### Reported Chemotherapy (CT) Use

<table>
<thead>
<tr>
<th>Age &lt;70 years</th>
<th>Age ≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tested (N=43,693)</td>
<td>Not Tested (N=100,519)</td>
</tr>
<tr>
<td>Tested</td>
<td>Not Tested</td>
</tr>
</tbody>
</table>

- CT use was lower in patients ≥70 years, in both RS-tested and untested cohorts

- CT use reported as ‘yes’
- CT use reported as ‘no/unknown’

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*Chemotherapy use is known to be under-reported to SEER*
5-year Other-Cause Mortality by Age and RS Group

As expected, RS group does not predict other-cause mortality (p=NS)
As expected, higher other-cause mortality was observed in older patients
ASTER 70s (EUDRACT N° 2011-004744-22, PHRC national 2011, NCT01564056)
Adjuvant chemotherapy for ER+ HER2- BC in 70+ patients

Complete curative surgery

Group I* High GG
- Arm A = HT
- Arm B = CT + HT
- Chemo tolerance
- Standard Lab
- 1 blood + serum
- MMSE, IADL, QLQ C30 & ELQ15
- Socioeconomic

Group II Low GG
- NO CHEMOTHERAPY IS RECOMMENDED - Follow-up
- CCI
- Polymedications
- Events

Chemo = 4 TC or 4 AC or 4 MC

Hypothesis B > A Δ±7.5% (A 80% vs B 87.5%) HR 0.60 ± 5% ± 10%
4-yr OS

screened 1,989
randomized 1,089

April 2012
April 2016
1. 58% grade ≥ 3 toxicity
2. Risk increased w/ increasing risk score
3. AUC/ROC 0.65 (95%CI 0.58-0.71) ~ development cohort 0.72 (95%CI 0.68-0.77) (P = .09)
4. No association between PS and chemo toxicity (P = .25)
CARG-BC

473 pts evaluable/501
- 283 development
- 190 validation

Median age 70 (65-85)
Stage I/II/III 39%/41%/20%
TNBC/ER+/HER2+ER+/HER2+ER- 24%/48%/10%/17%
Grade 3-5 AEs 46% (Heme 25%/Non-Heme 36%

<table>
<thead>
<tr>
<th>Risk factors for Gr. 3-5 Toxicity</th>
<th>OR (95% CI)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARG Score: Medium Risk</td>
<td>2.47 (1.35-4.51)</td>
<td>3</td>
</tr>
<tr>
<td>High Risk</td>
<td>2.26 (0.70-7.35)</td>
<td></td>
</tr>
<tr>
<td>Anthracycline</td>
<td>1.37 (0.65-2.85)</td>
<td>1</td>
</tr>
<tr>
<td>Stage II/III</td>
<td>1.79 (1.00-3.23)</td>
<td>2</td>
</tr>
<tr>
<td>Duration of tx &gt; 3 months</td>
<td>2.98 (1.46-6.09)</td>
<td>4</td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>2.21 (0.90-5.47)</td>
<td>3</td>
</tr>
<tr>
<td>Limited in walking a mile</td>
<td>2.22 (1.21-4.05)</td>
<td>3</td>
</tr>
<tr>
<td>Lack of someone to provide advice</td>
<td>2.34 (0.99-5.58)</td>
<td>3</td>
</tr>
</tbody>
</table>
CARG-BC score \(\rightarrow\) prediction of grade 3-5 toxicity better than CARG or KPS

But also: dose reduction, delay, reduced RDI, hospitalization
Adjuvant palbociclib as an alternative to chemotherapy for older patients with high risk luminal early breast cancer

EORTC–ETF-BCG Study 1745 (APPALACHES)

Hans Wildiers & Etienne Brain
Non-comparative randomized (2:1) phase II study

70+, surgery for stage II-III EBC ER pos, HER2 neg
adjuvant chemotherapy required according to treating physician and patient

Stratification for clinical frailty (G8 >14 vs ≤ 14) and stage

Adjuvant chemo choice:
- 4 TC + G-CSF
- 4 EC or AC + G-CSF
- 12 taxol weekly

Primary endpoint
3y DRFI (distant metastases or death from breast cancer) for Al+Palbo arm
- 3-year DRFI of <88% is unacceptable.
- 3-year DRFI of ≥93% is success

Pros:
- Easy endpoint, clinically relevant
- Feasible numbers
- Similar endpoint in 1 arm was used in Mindact and Tolaney study (both NEJM)
- If study is + (88% not included in CI), the conclusion and consequences can be similar as for Mindact and Tolaney study: new standard
- QoL and OS/BCSS can be compared to chemo as secondary

Cons:
- No formal comparison w/ chemo group for primary endpoint
- Less data on QoL/OS/BCSS versus chemo

1
Adjuvant chemo -> Al

2
Al + Palbo 1y

366 patients required (244:122)
Accrual 2y
80 centres required
Tumour extent
TNM

Tumour biology
Luminal A/B
HER2 & TNBC
Gene expression profile

General health status
Geriatric assessment
Life expectancy
Treatment toxicity

Patient preference & acceptability
Past Presidents: Etienne Brain, Arti Hurrria, Riccardo Audisio, Martine Extermann, Jean-Pierre Droz, Harvey Cohen, Silvio Monfardini

Key persons: Matti Aapro, Lodovico Balducci

Stuart Lichthman
Immediate Past President
MSKCC, USA

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University Hospitals Leuven, Belgium

Ravindran Kanesvaran
President Elect
NCCS, Singapore

Najia Musolino
CEO
SIOG HO, Geneva, Switzerland
Optimising treatment in older cancer patients is precision medicine too!