When is Chemotherapy needed for Luminal B Advanced Breast Cancer?

Dr. Paul N Mainwaring
Brisbane, Australia
Disclosures; last 10 years

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• Astellas, AstraZeneca, BMS, Eisai, Genentech, GSK, Ipsen, Janssen/JnJ, Lilly, Medivation, Merck, Novartis, Pfizer, Roche, XING Technologies
Outline

• Definition of Luminal ABC
  • DNA, epigenetic, RNA, Protein

• Endocrine therapy
  • SERM, SERD, CDK4/6i, mTORi reviewed by Dr Yap

• Chemotherapy
  • When do I introduce ?
  • Which drugs ?
  • Which schedule and why ?
  • pK; Dose modification
  • pK: Dose interruption
  • pD; surrogate measures of efficacy (NLR, neuts, rash etc)
  • Can biology help guide treatment ?

• Immunotherapy
  • Immune checkpoint-therapy

• Other approaches
How do we define Luminal Breast Cancer?

Intrinsic Subtypes by Gene Expression Profiling

**HER2 +**
- ER and/or PR +
- Low/high grade
- Low/high proliferative index (Ki67)

**HER2 -**
- ER/PR+ (low expression)
  - OR
  - ER+/PR- OR ER-/PR+
- High grade/ High proliferative index (Ki67)

**LUMINAL A**
- ER+/PR+ (high expression)
  - Low grade
  - Low proliferative index (Ki67)

**LUMINAL B (Heterogeneous group)**
- ER/PR+ (low expression)
  - OR
  - ER+/PR- OR ER-/PR+
  - High grade/ High proliferative index (Ki67)

**HER2 +**
- ER and/or PR +
  - Low/high grade
  - Low/high proliferative index

**Chemotherapy**

**Endocrine therapy**

**Chemo-immunotherapy**

Derived from cDNA microarray now RNA-Seq (PAM50)

In reality, most pathology reports use protein immunohistochemistry

Perou Nature 2000
Sørlie PNAS 2001
<table>
<thead>
<tr>
<th>Subtype</th>
<th>Luminal A</th>
<th>Luminal B</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER+/HER2−, (%)</td>
<td>87</td>
<td>82</td>
</tr>
<tr>
<td>HER2+, (%)</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>TNBCs, (%)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>TP53 pathway</td>
<td>TP53 mut (12); gain of MDM2 (14)</td>
<td>TP53 mut (32); gain of MDM2 (31)</td>
</tr>
<tr>
<td>PIK3CA/PTEN pathway</td>
<td>PIK3CA mut (49); PTEN mut/loss (13); INPP4B loss (9)</td>
<td>PIK3CA mut (32); PTEN mut/loss (24); INPP4B loss (16)</td>
</tr>
<tr>
<td>RB1 pathway</td>
<td>Cyclin D1 amp (29); CDK4 gain (14); low expression of CDKN2C; high expression of RB1</td>
<td>Cyclin D1 amp (58); CDK4 gain (25)</td>
</tr>
<tr>
<td>mRNA expression</td>
<td>High ER cluster; low proliferation</td>
<td>Lower ER cluster; high proliferation</td>
</tr>
<tr>
<td>Copy number</td>
<td>Most diploid; many with quiet genomes; 1q, 8q, 8p11 gain; 8p, 16q loss; 11q13.3 amp (24)</td>
<td>Most aneuploid; many with focal amp; 1q, 8q, 8p11 gain; 8p, 16q loss; 11q13.3 amp (51)</td>
</tr>
<tr>
<td>DNA mutations</td>
<td>PIK3CA (49); TP53 (12); GATA3 (14); MAP3K1 (14)</td>
<td>TP53 (32); PIK3CA (32); MAP3K1 (5)</td>
</tr>
<tr>
<td>DNA methylation</td>
<td>—</td>
<td>Hypermethylated phenotype for subset</td>
</tr>
<tr>
<td>Protein expression</td>
<td>High estrogen signaling; high MYB; RPPA reactive subtypes</td>
<td>Less estrogen signaling; high FOXM1 and MYC; RPPA reactive subtypes</td>
</tr>
</tbody>
</table>

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CornejoAPLM 2014
Vasconcelos Breast 2016
Questions

1. What are the goals of treatment after endocrine therapy?
2. Is there a role for chemotherapy in general in this setting?
3. Is there a subset of patients who may benefit more?
   1. De-novo endocrine resistant disease
   2. Acquired endocrine resistant disease
   3. Visceral crisis

- Can we go back to endocrine therapy after chemotherapy?
  - “Maintenance therapy”
Treatment Algorithm Luminal ABC

- **Luminal A**
  - HER2 neg
  - CDK4/6i Endocrine Tx
  - No visceral crisis
- **Luminal B**
  - HER2 neg
  - CDK4/6i Endocrine Tx
  - No visceral crisis
- **Triple positive**
  - Taxane/Pert/Trast
  - AI/Trastuzumab
  - No visceral crisis
- **PFS1**
  - Everolimus Exemestane
- **PFS2**
  - Everolimus Exemestane
  - SERD
  - Chemo therapy
- **PFS3**
  - Lap/Cape
  - Chemo/trast
  - Overall Survival
- **PFS4**
- **PFS5**

Overall Survival

- T-DM1
- Taxane/Pert/Trast
- AI/Trastuzumab
- Lap/Cape
- Chemo/trast
Chemotherapy doesn’t make the list
Chemotherapy doesn’t make the list

ASCO

Rugo JCO 2018
Questions

1. What are the goals of treatment after endocrine therapy?
2. Is there a role for chemotherapy in general in this setting?
3. Is there a subset of patients who may benefit more?
   1. De-novo endocrine resistant disease
   2. Acquired endocrine resistant disease
   3. Visceral crisis

• Can we go back to endocrine therapy after chemotherapy?
  • “Maintenance therapy”
RR Chemotherapy vs Endocrine Therapy ABC
OS Chemotherapy vs Endocrine Therapy ABC

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>endocrine therapy n/N</th>
<th>chemotherapy n/N</th>
<th>Hazard Ratio Exp((O-E)/V), Fixed,95% CI</th>
<th>Weight</th>
<th>Hazard Ratio Exp((O-E)/V), Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dixon 1992</td>
<td>18/30</td>
<td>14/30</td>
<td></td>
<td>4.2 %</td>
<td>0.76 [0.34, 1.66]</td>
</tr>
<tr>
<td>Tashiro 1990</td>
<td>23/30</td>
<td>24/26</td>
<td></td>
<td>8.7 %</td>
<td>0.76 [0.42, 1.36]</td>
</tr>
<tr>
<td>ANZBCTG 1986</td>
<td>95/113</td>
<td>100/113</td>
<td></td>
<td>39.1 %</td>
<td>0.85 [0.65, 1.12]</td>
</tr>
<tr>
<td>Taylor 1986</td>
<td>68/99</td>
<td>69/95</td>
<td></td>
<td>29.0 %</td>
<td>0.84 [0.61, 1.16]</td>
</tr>
<tr>
<td>Clavel 1982</td>
<td>17/34</td>
<td>16/30</td>
<td></td>
<td>3.6 %</td>
<td>1.61 [0.65, 4.00]</td>
</tr>
<tr>
<td>Priestman 1978</td>
<td>40/47</td>
<td>33/45</td>
<td></td>
<td>14.9 %</td>
<td>1.65 [1.06, 2.57]</td>
</tr>
</tbody>
</table>

Total (95% CI)

Heterogeneity: Ch² = 9.22, df = 5 (P = 0.10); I² = 46%
Test for overall effect: Z = 0.66 (P = 0.51)
Test for subgroup differences: Not applicable

Cochrane Database Syst Rev 2003
Subsequent therapy; reduction in Rx

<table>
<thead>
<tr>
<th>Study</th>
<th>2nd Line</th>
<th>3rd Line</th>
<th>4th Line</th>
<th>5th Line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dufresne et al. (2008)</td>
<td>100%</td>
<td>56%</td>
<td>25%</td>
<td>11%</td>
</tr>
<tr>
<td>Tacca et al. (2009)</td>
<td>100%</td>
<td>68%</td>
<td>43%</td>
<td>23%</td>
</tr>
<tr>
<td>Bernardo et al. (2010)</td>
<td>100%</td>
<td>82%</td>
<td>36%</td>
<td>11%</td>
</tr>
<tr>
<td>Planchat et al. (2011)</td>
<td>100%</td>
<td>76%</td>
<td>56%</td>
<td>37%</td>
</tr>
<tr>
<td>Current Jackisch (2014)</td>
<td>100%</td>
<td>70%</td>
<td>46%</td>
<td>27%</td>
</tr>
</tbody>
</table>
# Clinical Efficacy of Chemotherapeutic Agents in Each Line of Therapy

<table>
<thead>
<tr>
<th>Regimen</th>
<th>First Line (n=240)</th>
<th>Second Line (n=209)</th>
<th>Third Line (n=166)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mPFS1 7.6 [95% CI, 6.7–8.5] mo</td>
<td>mPFS2 5.1 [95% CI, 4.3–5.9] mo</td>
<td>mPFS3 3.6 [95% CI, 2.8–4.4] mo</td>
</tr>
<tr>
<td></td>
<td>PFS1, mo</td>
<td>ORR1, %</td>
<td>PFS2, mo</td>
</tr>
<tr>
<td>Anthracyline based</td>
<td>8.6 (4.9–12.3)</td>
<td>26 (60.5)</td>
<td>5.2 (4.4–6.0)</td>
</tr>
<tr>
<td>Taxane based</td>
<td>7.7 (6.8–8.6)</td>
<td>91 (54.8)</td>
<td>6.3 (3.3–9.3)</td>
</tr>
<tr>
<td>Capecitabine based</td>
<td>5.7 (2.3–9.1)</td>
<td>10 (35.7)</td>
<td>5.8 (3.4–8.2)</td>
</tr>
<tr>
<td>Gemcitabine/vinorelbine based</td>
<td>NA</td>
<td>NA</td>
<td>4.0 (2.8–5.2)</td>
</tr>
<tr>
<td>P value</td>
<td>0.788</td>
<td>0.105</td>
<td>0.015</td>
</tr>
<tr>
<td>Eribulin</td>
<td>9.2</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

CDK 4/6i + ETx 27.6 mo + OS control arm PALOMA-3 28 = 56 mo

Turner NEJM 2018

Basaran Ca Treat Rev 2017
A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS)

N. I. Chemy\textsuperscript{1*}, R. Sullivan\textsuperscript{2}, U. Dafni\textsuperscript{3}, J. M. Kerst\textsuperscript{4}, A. Sobrero\textsuperscript{5}, C. Zielinski\textsuperscript{6}, E. G. E. de Vries\textsuperscript{7} & M. J. Piccart\textsuperscript{8,9}

<table>
<thead>
<tr>
<th>Living longer</th>
<th>Improved OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Improved surrogate of OS</td>
</tr>
<tr>
<td></td>
<td>DFS (when OS data are immature in adjuvant setting)</td>
</tr>
<tr>
<td></td>
<td>Improved PFS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Living better</th>
<th>Improved quality of life</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Improved surrogate of quality of life</td>
</tr>
<tr>
<td></td>
<td>Improved PFS</td>
</tr>
<tr>
<td></td>
<td>Reduced toxicity</td>
</tr>
</tbody>
</table>

**Table 1. Potential benefits of a new treatment**

**ESMO MCBS evaluation**

Curative:
- A: 5
- B: 4
- C: 3

Non-curative:
- 3
- 2
- 1
Old data but still relevant concepts

Pre-HER2/TNBC era

Progression-Free Survival

Overall Survival

Gennari JCO 2011
Chemotherapy choices I

• Thoughts not Guideline
• Proliferation is driver
  • Taxanes: Prior exposure, Disease-free interval
  • Anthracyclines: Prior exposure, Disease-free interval
  • Capecitabine p.o. outpatient
  • Vinorelbine IV p.o.
• DNA repair deficiency; Chromosomal instability
  • Platinum/doublet first-line ?
  • CMF, irinotecan, etoposide
• Wnt pathway/EMT
  • Eribulin
PEARL; GEICAM/2013-02

Study Design and Treatment

- Phase 3, international, multicenter, open-label, controlled, randomized study.

Cohort 1 (fully enrolled)
- Exemestane 25 mg daily + Palbociclib 120 mg 3 weeks on, followed by 1 week off, in 28-day cycles
- Capcitabine 1250 mg/m² (1000 mg/m² in patients aged >70 years) twice daily for 2 weeks followed by 1 week off, in 21-day cycles

Cohort 2 (open for enrollment)
- Fulvestrant 500 mg on days 1 & 15 of cycle 1 and day 1 of each 28-day cycle + Palbociclib 120 mg 3 weeks on, followed by 1 week off, in 28-day cycles
- Capcitabine 1250 mg/m² (1000 mg/m² in patients aged >70 years) twice daily for 2 weeks followed by 1 week off, in 21-day cycles

Stratification: visceral vs non visceral metastases, prior sensitivity to hormonal treatment: (yes vs no), prior chemotherapy for MBC: (yes vs no), country.

Treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death or withdrawal of consent, whichever occurs first.
Questions

1. What are the goals of treatment after endocrine therapy?
2. Is there a role for chemotherapy in general in this setting?
3. Is there a subset of patients who may benefit more?
   1. De-novo endocrine resistant disease
   2. Acquired endocrine resistant disease
   3. Visceral crisis

• Can we go back to endocrine therapy after chemotherapy?
  • “Maintenance therapy”
### Guideline statement

<table>
<thead>
<tr>
<th>Biologic factor</th>
<th>LoE/GoR</th>
<th>Consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visceral crisis</strong> is defined as severe organ dysfunction as assessed by signs and symptoms, laboratory studies and rapid progression of disease. Visceral crisis is not the mere presence of visceral metastases but implies important visceral compromise leading to a clinical indication for a more rapidly efficacious therapy, particularly since another treatment option at progression will probably not be possible.</td>
<td>Expert opinion/ n/a</td>
<td>95%</td>
</tr>
<tr>
<td><strong>Primary endocrine resistance</strong> is defined as relapse while on the first 2 years of adjuvant ET, or PD within first 6 months of first-line ET for ABC, while on ET.</td>
<td>Expert opinion/ n/a</td>
<td>67%</td>
</tr>
<tr>
<td><strong>Secondary endocrine resistance</strong> is defined as relapse while on adjuvant ET but after the first 2 years, or relapse within 12 months of completing adjuvant ET, or PD ≥ 6 months after initiating ET for ABC, while on ET.</td>
<td>Expert opinion/ n/a</td>
<td>67%</td>
</tr>
<tr>
<td><strong>Oligometastatic disease</strong> is defined as low volume metastatic disease with limited number and size of metastatic lesions (up to 5 and not necessarily in</td>
<td>Expert opinion/ n/a</td>
<td>78%</td>
</tr>
</tbody>
</table>

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**Biological Factors**
- Low ER
- Low PR
- High proliferation
- Loss PR

*Cardoso Annals 2018*
Landscape ER-resistant disease

DeNovo resistance
~15-30 %

Acquired resistance
Should Every Metastatic Breast Cancer Patient Undergo Next-Generation Sequencing?

Yap et al. Nature PJ: Breast Cancer 2018
Elucidating therapeutic molecular targets in premenopausal Asian women with recurrent breast cancers
Potential mechanisms resistance CDK4/6i
I would argue continue to biopsy Tissue or Liquid @ progression For clinical trial inclusion
Questions

1. What are the goals of treatment after endocrine therapy?
2. Is there a role for chemotherapy in general in this setting?
3. Is there a subset of patients who may benefit more?
   1. De-novo endocrine resistant disease
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   3. Visceral crisis

• Can we go back to endocrine therapy after chemotherapy?
  • “Maintenance therapy”
ABC follow-up and supportive care

Supportive care

Diagnosis and treatment
- Access to personalised supportive and psychological care and symptom-related intervention from time of diagnosis, allowing for safer/more tolerable delivery of treatment, taking into account patient preferences, values and needs

Survivorship issues

End-of-life care
- Discussed with patients early in course of metastatic disease
- Facilitate return/continue to work

Suspicion of locoregional progression
- Breast imaging

Open communication between patients and care team

Educating patients on treatment and supportive care

Encouraging patients to be proactive in their care and share decision making with cancer care teams

Empowering patients to improve their own QoL

Systematic monitoring of patients to permit early intervention of supportive care to enhance QoL

Do no harm
Management of symptoms

Assess using PROMs

- Pain
  - Early information on pain relief and supportive care
  - Access to pain relief including early access to morphine

- Cancer-related fatigue
  - Multidimensional approach

- CDK inhibitor-induced neutropenia
  - Continue at current dose to complete cycle or interrupt the drug until recovery to grade < 3
  - Repeat complete blood count on Day 21
  - Consider dose reduction in cases of prolonged (> 1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia in subsequent cycles

- Non-infectious pneumonia
  - Patient education critical for early symptom reporting

- Mucositis/stomatitis
  - Prevention from start with steroid mouthwash

- Dyspnoea
  - Patient support essential as well as treatment of causes (e.g. if pleural effusion, pleuritis)

- Nausea and vomiting
  - Refer to ESMO/MASC guidelines

- Endocrine toxicities of mTOR inhibition
  - Regular monitoring

Pharmacological interventions

- Pain
  - Non-pharmacological interventions (e.g. exercise)
  - Treatment interruption/dose reduction
  - Systemic steroids treatment discontinuation

- Grade 2
  - Lower dose of targeted agent/delay treatment

- Grade 2
  - Oral antidiabetics and basal insulin

- Grade 1/2 hyperglycaemia
  - Treatment discontinuation

- Grade 3/4 hyperglycaemia
  - Statins, fibrates
  - Treatment interruption
  - Dose reduction

- Grade 2/3 hypercholesterolaemia
  - Treatment discontinuation

- Grade 4 hypercholesterolaemia

ABC, advanced breast cancer; CDK, cyclin-dependent kinase; ESMO, European Society for Medical Oncology; MASCC, Multinational Association of Supportive Care in Cancer; mTOR, mechanistic target of rapamycin; PROM, patient-reported outcome measure
Triple Positive

No trials comparing anti-HER2 agent + chemotherapy Vs. anti-HER2 agent + endocrine therapy
Triple Positive: Anti-HER2 only adds modestly to Endocrine Therapy
Improved PFS but not OS

**HER2+, HR+ MBC (TAnDEM)**
No prior chemo; prior hormonal therapy allowed

- **Anastrozole**
  - Trastuzumab + Anastrozole
  - 4.8 vs 2.4 months
  - P=0.0016
  - OS 28.5 vs 23.9 months, p=0.325

- **Letrozole**
  - Lapatinib + Letrozole
  - 8.2 vs 3.0 months
  - P=0.019
  - OS 33.3 vs 32.3 months, p=0.113

PERTAIN; Triple positive
ALTERNATIVE: Study Design

- Global study conducted across 112 sites, 29 countries; Data cutoff: March 11, 2016
- N=355
- Postmenopausal women with confirmed ER+ and/or PgR+, HER2+ MBC

Stratification factors:
- Prior TRAS in neo/adjuvant or metastatic setting
- Investigator’s choice of AI (steroidal/nonsteroidal)

Therapy until disease progression, unacceptable toxicity or death, withdrawal of consent or investigator discretion

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>LAP + TRAS + AI n = 120</th>
<th>TRAS + AI n = 117</th>
<th>LAP + AI n = 118</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, No. (%)</td>
<td>62 (52)</td>
<td>75 (64)</td>
<td>74 (63)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>11</td>
<td>5.7</td>
<td>8.3</td>
</tr>
<tr>
<td>95% CI</td>
<td>8.3 to 13.8</td>
<td>5.5 to 8.4</td>
<td>5.8 to 11.2</td>
</tr>
<tr>
<td>HR (95% CI) versus TRAS + AI</td>
<td>0.62 (0.45 to 0.88)</td>
<td>-</td>
<td>0.71 (0.51 to 0.98)</td>
</tr>
<tr>
<td>P value</td>
<td>.0064</td>
<td>-</td>
<td>.0361</td>
</tr>
</tbody>
</table>

Proportion of Patients Alive and Free of Disease Progression

Time Since Random Assignment (months)
PATINA – maintenance therapy

HER2+HR+ Metastatic Breast Cancer (N=496)

- No prior treatment in the advanced setting beyond induction treatment
- Induction treatment: Anti-HER2 based chemotherapy given prior to study randomization
- Screening procedures (before during or after induction treatment):
  - Screening consent
  - Biopsy of metastatic disease strongly recommended (not mandatory)
  - Baseline clinico-pathologic characteristics

**Randomization**

**ARM A**
- Palbociclib 125mg PO daily (D1 to D21 followed by 7 days off) + Anti-HER2 Therapy * (every 3 weeks) + Endocrine Therapy ** until disease progression ***

**ARM B**
- Anti-HER2 Therapy * (every 3 weeks) + Endocrine Therapy ** until disease progression ***

**Clinical Follow-up** (for pts who discontinue treat prior to disease progression): q12 weeks until tumor progression

**Survival Follow-up:** Every 6 months until 5 years from randomization
Treatment Algorithm Luminal ABC

Overall Survival

Luminal A
HER2 neg
Start Chemotherapy
CDK4/6i Endocrine Tx
Endocrine Tx
CDK4/6i Endocrine Tx
Everolimus Exemestane
SERD Chemo

Luminal B
HER2 neg
Start Chemotherapy
CDK4/6i Endocrine Tx
Endocrine Tx
CDK4/6i Endocrine Tx
Everolimus Exemestane
SERD Chemo

Triple positive
Start Chemotherapy
Taxane/Pert/Trast
Al/Trastuzumab
Start Chemotherapy
T-DM1
Lap/Cape Chemo/trast

Resistant
No visceral crisis
Visceral crisis

Taxane/Pert/Trast
Al/Trastuzumab
Start Chemotherapy
T-DM1
Lap/Cape Chemo/trast

Biology
ER, PR, HER2 Proliferation "Omics"