Endocrine and “Targeted” Therapy in Metastatic Breast Cancer
Endocrine Therapy of Metastatic Breast Cancer

- **Version 2002:**
  Gerber / Friedrichs

- **Versions 2003–2013:**
  Albert / Bischoff / Dall / Fersis / Friedrich / Gerber / Huober / Janni / Jonat / Kaufmann / Loibl / Lück / von Minckwitz / Müller / Nitz / Schneeweiß / Stickeler

- **Version 2014:**
  Mundhenke / Schütz
Endocrine Therapy in Metastatic Breast Cancer

Indication

Endocrine therapy represents the first choice for metastatic breast cancer with positive (unknown) hormone receptor status.

- Exception: acute life threatening disease
- Cave: HR might change during the course of the disease. Histology of recurrent site should be obtained, whenever possible
## Comparison ER/PgR and HER2 Metastasis vs. Primary Tumor

<table>
<thead>
<tr>
<th>Publication</th>
<th>Number of patients</th>
<th>ER %</th>
<th>PgR%</th>
<th>HER2%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospektiv</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thompson</td>
<td>137</td>
<td>10</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>Amir</td>
<td>94</td>
<td>14</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>Retrospektiv</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lindström</td>
<td>459</td>
<td>33</td>
<td>40</td>
<td>14</td>
</tr>
<tr>
<td>Niikura</td>
<td>182</td>
<td>-</td>
<td>-</td>
<td>24</td>
</tr>
</tbody>
</table>

Changes from primary tumor to metastatic disease
## Endocrine Therapy in Premenopausal Patients with HER2 Negative Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>GnRHa + tamoxifen (vs. OFS or Tam)</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Ovarian function suppression (OFS)</td>
<td>2b B +</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>2b B +</td>
</tr>
<tr>
<td>GnRHa + AI (first or second line)</td>
<td>2b B +</td>
</tr>
<tr>
<td>GnRHa + Fulvestrant</td>
<td>4 C +/-</td>
</tr>
<tr>
<td>Aromatase inhibitors without OFS</td>
<td>3 D - -</td>
</tr>
</tbody>
</table>
Endocrine Therapy in Postmenopausal Patients with HER2 Negative Metastatic Breast Cancer

Treatment options for postmenopausal patients pretreated with adjuvant tamoxifen or without adjuvant endocrine therapy

- Aromatase inhibitors (3rd gen) (> non-AI*)
- Tamoxifen (vs. no therapy)
- Fulvestrant 500 mg
- Fulvestrant 250 mg (= AI)
- MPA/MA (< AI)
- Fulvestrant 250 mg + Anastrozol (vs. Ana)

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Option</th>
<th>Grade</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aromatase inhibitors (3rd gen) (&gt; non-AI*)</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Tamoxifen (vs. no therapy)</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Fulvestrant 500 mg</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Fulvestrant 250 mg (= AI)</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>MPA/MA (&lt; AI)</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Fulvestrant 250 mg + Anastrozol (vs. Ana)</td>
<td>1b</td>
<td>B</td>
</tr>
</tbody>
</table>

*There is no evidence for superiority of a single aromatase inhibitor. As everolimus + exemestane are indicated after AI treatment, a non-steroidal AI should be preferred in first line.
Endocrine Therapy in Postmenopausal HER2 Negative Metastatic Breast Cancer Patients after Adjuvant Tamoxifen or no Prior Endocrine Treatment

### Treatment sequence

<table>
<thead>
<tr>
<th>Line</th>
<th>Treatment Options</th>
</tr>
</thead>
</table>
| 1st line: | aromatase inhibitors (3rd gen)*  
fulvestrant 250 mg + anastrozole |
| 2nd line: | fulvestrant  
fulvestrant 500 mg  
fulvestrant 250 mg  
exemestane + everolimus |
|  | tamoxifen  
|  | aromatase inhibitor**  
tamoxifen + everolimus |
| Further Lines: | MPA/MA  
| | estradiol 6 mg daily  
| | repeat prior treatments |

**Oxford / AGO LoE / GR**

<table>
<thead>
<tr>
<th>Line</th>
<th>1a</th>
<th>A</th>
<th>++</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st line:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd line:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Further Lines:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Further</td>
<td>4</td>
<td>D</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td>3b</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>3b</td>
<td>C</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>B</td>
<td>+</td>
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<td></td>
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<td>+</td>
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<td></td>
<td>2b</td>
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<td>+/-</td>
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<td></td>
<td>1b</td>
<td>B</td>
<td>++</td>
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<td></td>
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<td>A</td>
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<td></td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>

* To date, there is no evidence for superiority of a single aromatase inhibitor.

** steroidal or non-steroidal depending on previous AI
Therapy Algorithm After Adjuvant Tamoxifien

Non-steroidal AI 3rd generation

Exemestane + everolimus

Fulvestrant 500mg

Tamoxifien

Fulvestrant 500mg

Exemestane + everolimus

Tamoxifien
# Endocrine Therapy in Postmenopausal HER2 Negative Metastatic Breast Cancer Patients after Adjuvant AI

## Treatment sequence

<table>
<thead>
<tr>
<th>1\textsuperscript{st} line:</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>tamoxifen</td>
<td>2b B ++</td>
</tr>
<tr>
<td>fulvestrant 500 mg</td>
<td>1b B ++</td>
</tr>
<tr>
<td>exemestane + everolimus* (relapse within 12 mths)</td>
<td>1b A ++</td>
</tr>
<tr>
<td>steroidal after non-steroidal AI</td>
<td>2b B +</td>
</tr>
<tr>
<td>non-steroidal after steroidal AI</td>
<td>2b B +</td>
</tr>
<tr>
<td>tamoxifen + everolimus</td>
<td>2b B +</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2\textsuperscript{nd} line:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>fulvestrant 500 mg</td>
<td>1b B ++</td>
</tr>
<tr>
<td>exemestane + everolimus*</td>
<td>1b A ++</td>
</tr>
<tr>
<td>tamoxifen (if previously not given)</td>
<td>5 D +</td>
</tr>
<tr>
<td>tamoxifen + everolimus</td>
<td>2b B +</td>
</tr>
</tbody>
</table>

## Further lines:

- MPA/MA: 4 C +/-
- repeat prior treatments: 5 D +/-

\*After pretreatment with at least a non-steroidal AI in the metastatic and/or adjuvant setting

\**trial participation
Therapy Algorithm After Adjuvant AI

**Short treatment free interval ≤12 months**
- Exemestane + everolimus
  - Fulvestrant 500 mg
  - Tamoxifen

**Long treatment free interval >12 months**
- Fulvestrant 500 mg
- Tamoxifen
  - Exemestane + everolimus
  - Tamoxifen
  - Fulvestrant 500 mg
HER2 Positive and HR-Positive Metastatic Breast Cancer
Endocrine Therapy in Postmenopausal HER2 Positive Metastatic Breast Cancer Patients

- Anastrozole and trastuzumab
- Letrozole and trastuzumab
- Letrozole and lapatinib
- Fulvestrant and lapatinib

Poor efficacy of endocrine therapy alone. Consider chemotherapy + anti-HER2-therapy!
Combination of Endocrine Treatment with Anti-HER2-Treatment

<table>
<thead>
<tr>
<th>Treatment (no. of pats)</th>
<th>PFS (mo)</th>
<th>Response (CBR)</th>
<th>OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab + anastrozole vs. anastrozole (n=207)</td>
<td>4.8 vs. 2.4 (5.6 vs. 3.8 with central confirmed receptor status)</td>
<td>42.7% vs. 27.9%</td>
<td>28.5 vs. 23.9 mo; n.s.</td>
</tr>
<tr>
<td>Trastuzumab + letrozole vs. letrozole (n=57)</td>
<td>14 vs. 3.3</td>
<td>27% vs. 13%</td>
<td>n.r.</td>
</tr>
<tr>
<td>Lapatinib + letrozole vs. letrozole (n=219/1286)</td>
<td>8.2 vs. 3.0</td>
<td>48% vs 29%</td>
<td>33.3 vs. 32.3 mo</td>
</tr>
<tr>
<td>Lapatinib + fulvestrant vs. fulvestrant (n=267/324)</td>
<td>5.2 vs. 4.0 (all) 5.9 vs. 2.8 (HER2+)</td>
<td></td>
<td>22.3 vs. 21.9 (all)</td>
</tr>
</tbody>
</table>
Concomitant or Sequential Endocrine-Cytostatic Treatment

- **Concomitant endocrine-cytotoxic treatment**
  - Increases response rates without prolongation of progression free interval or overall survival
  - Increases toxicity

- **Maintenance endocrine therapy after chemotherapy induced response**
  - Increases progression free interval
Endocrine Therapy of Metastatic Breast Cancer (2/14)

Further information:

Search:
Medline, PubMed Central 12/2012-01/2013

References


zurück
Endocrine Therapy in Metastatic Breast Cancer – Indication (3/14)

Further information:

Endocrine therapy as the first choice in hormone receptor positive breast cancer
Endocrine therapy remains the most important approach to the treatment of hormone-sensitive non-life-threatening metastatic breast cancer. This systemic therapy has the advantage of combining efficacy, minimal toxicity, and good quality of life. Endocrine therapy use in clinical practice is based on a positive estrogen receptor (ER) and/or progesterone receptor status of the primary tumour or, if at all possible, of an easily accessible metastasis. This type of therapy is usually the first choice when the risk of rapid disease progression is low, i.e. if there is no life-threatening disease. The selection of the most appropriate endocrine therapy takes into account the receptor status of the metastasis, menopausal status of the patient, the type of adjuvant endocrine therapy received, and past medical history of thrombolic disease.

A Cochrane Data Base Meta-Analysis was performed in 2003 whether chemotherapy alone versus endocrine therapy alone for metastatic breast cancer is more favorable. The primary analysis of overall effect using hazard ratios derived from published survival curves involved six trials (692 women). There was no significant difference seen (HR=0.94, 95%CI 0.79-1.12, p=0.5). A test for heterogeneity was p=0.1. A pooled estimate of reported response rates in eight trials involving 817 women shows a significant advantage for chemotherapy over endocrine therapy with RR=1.25 (1.01-1.54, p=0.04). However the two largest trials showed trends in opposite directions, and a test for heterogeneity was p=0.0018.

There was little information available on toxicity and quality of life. Six of the seven fully published trials commented on increased toxicity with chemotherapy, mentioning nausea, vomiting and alopecia. Three of the seven mentioned aspects of quality of life, with differing results. Only one trial formally measured quality of life, concluding that it was better with chemotherapy.

The Reviewers concluded that in women with metastatic breast cancer and where hormone receptors are present, a policy of treating first with endocrine therapy rather than chemotherapy is recommended except in the presence of rapidly progressive disease (Cochrane 2011).
Responserate to endocrine treatment (De Laurentiis M, et al. 2005):

<table>
<thead>
<tr>
<th>ER</th>
<th>PR</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>negative</td>
<td>&lt; 10%</td>
</tr>
<tr>
<td>Positive</td>
<td>negative</td>
<td>20 – 30%</td>
</tr>
<tr>
<td>Negative</td>
<td>positive</td>
<td>30 – 50%</td>
</tr>
<tr>
<td>Positive</td>
<td>positive</td>
<td>50 – 75%</td>
</tr>
</tbody>
</table>

References


Comparison ER/PgR and HER2 Metastasis vs. Primary Tumor (4/14)

Further information:

Changes in receptor profiles

Changes in receptor profiles are an important issue, since the molecular phenotype of the primary tumor is often used for treatment decisions in the metastatic setting.

Several retrospective studies have evaluated this biological phenomenon.

There is evidence for a prognostic impact of receptor profile changes in metastatic breast cancer: In a retrospective analysis, patients with tumors that changed from ER positive primary to negative metastasis experienced a significantly shorter median survival than patients with unchanged receptor profiles, while changes in PR status were not associated with a change in survival. Therefore, optimal metastatic treatment cannot be determined solely on primary ER and PR analyses (Lower et al. 2005).

A published retrospective study (Broom et al. 2009). evaluated data from 100 patients for whom tissue from primary and metastatic sites was available. Estrogen receptor (ER), progesterone receptor (PR) and Her-2/neu status in the primary and metastasis were compared. The discordance rate for ER was 17.7% (2-sided p=0.0039) with 9.7% of tumors changing from ER-positive to ER-negative and 8.0% changing from ER-negative to ER-positive. The discordance rate for PR was 37.3% (2-sided p<0.0001), with all of these tumors changing from PR-positive to PR-negative. No significant discordance for Her-2/neu was found. This study suggested that significant discordance exists for hormone receptor status between primary and metastatic breast cancer samples. Loss of PR was particularly frequent.

Further evidence was shown by a retrospective analysis of 97 consecutive relapsed patients (Nishimura et al 2011). Changes in the positive/negative evaluation were seen at the rate of 10.3% and 25.8% for ER and PgR. Ki-67 index increased significantly from a mean of 29.1% at primary tumor to 36.6% at relapse. The rates of change in HER2 and p53 positivity were 14.4% and 12.4%. The change of subtypes were seen in 25%, however the lowest rate of change was seen
in the triplenegative cases. A multivariat analysis revealed that the status of distant metastasis and PgR level at relapse, and Ki-67 levels at primary tumor were all significant factors.

One prospective study, BRITS (Breast Recurrence In Tissue Study), investigated 137 matched primary and recurrent breast cancer tissue samples. The recurrent biopsy was excisional tissue in 100 (73%) and core biopsy in 37 (27%). Central laboratory analysis of the original primary was ER positive in 109 (79.6%), PR positive in 85 (62.0%) and HER2 positive in 14 (10.2%); the recurrent disease was ER positive in 101 (73.7%), PR positive in 75 (54.7%) and HER2 positive in 16 (11.7%). A switch in receptor status, in either direction, was identified for ER in 14 patients (10.2%; p=0.983 Wilcoxon sign rank test), PR in 34 (24.8%; p=0.003 Wilcoxon sign rank test) and HER2 in 4 (2.9%; p=0.074 Wilcoxon sign rank test). There was no difference between locoregional or distant recurrence in the proportion who switched. In the judgement of the investigators the switch led to a change in the subsequent treatment in 24 patients (17.5%).

This study demonstrated that the management of locally recurrent or metastatic breast cancer should include tissue sampling, since switches of ER, PR or HER2 status in the breast cancer recurrence may change the planned treatment for one in six patients (Thompson 2010).

However if treatment guided by the new ER, PR or HER2 status of the metastasis is superior when findings are different to the primary tumor has not been investigated so far.

References:


Further information and references:

GnRHa + tamoxifen
The combination of GnRH + tamoxifen represents the first choice as endocrine first line therapy of hormone receptor positive premenopausal breast cancer.

Due to the results of one randomized trial and a metaanalysis of additional 4 trials in a three-arm, randomized, prospective trial a total of 161 premenopausal patients with advanced breast cancer were randomly assigned to treatment with buserelin, tamoxifen, or both. The median follow-up was 7.3 years. Combined treatment with buserelin and tamoxifen was superior to treatment with buserelin or tamoxifen alone by objective response rate (48%, 34%, and 28% respectively; P = .11 [chi(2) test]), median progression-free survival (9.7 months, 6.3 months, and 5.6 months; P = .03), and overall survival (3.7 years, 2.5 years, and 2.9 years; P = .01). Actuarial 5-year survival percentages were 34.2%, 14.9%, and 18.4%, respectively. No differences in antitumor effects were observed between single-agent treatment groups (Klijn et al. 2000). For patients with solitary bone metastasis a prospective multicenter study on 318 patients revealed even a survival benefit besides a significant improvement of pregression free survival (Jonat et al 1995).

The metaanalysis (Klijn et al. 2001) confirmed the above findings in four clinical trials randomizing a total of 506 premenopausal women with advanced breast cancer to LHRH agonist alone or to the combined treatment of LHRH agonist plus tamoxifen. With a median follow-up of 6.8 years, there was a significant survival benefit (P = .02; hazards ratio [HR] = 0.78) and progression-free survival benefit (P = .0003; HR = 0.70) in favor of the combined treatment. The overall response rate was significantly higher on combined endocrine treatment (P = .03; odds ratio = 0.67).
**References:**


**Ovarian function suppression, tamoxifen**

A further option in the treatment of metastasized premenopausal hormone receptor positive breast cancer is ovarian ablation. Oophorectomy and GnRHa have been demonstrated to be equally efficacious in the metastatic setting. Taylor et al. evaluated these two methods for premenopausal patients with ER-positive, PR-positive, and unknown hormone status metastatic breast cancer. 136 patients were randomly assigned to either bilateral oophorectomy (n = 67) or goserelin (n = 69). The overall response rate was 31% for those in the goserelin group versus 27% in the oophorectomy group. The complete response (CR) rate for the two arms was 14 and 10%, respectively. The response rates between the two arms were not statistically significant.
An additional randomized, nonblinded trial compared oophorectomy and radiation ablation for metastatic breast cancer, 97 patients were treated with oophorectomy, and 61 had ovarian ablation by radiation. In the oophorectomy arm, 30% had a response (CR + partial response), and 18% had stable disease. In the radiation arm, 21% had a response (CR + partial response), and 15% had stable disease. These differences were not statistically significant (Lees et al. 1980).

Tamoxifen is well established as an alternative to ovarian suppression as first-line treatment for hormone receptor-positive breast cancer in the metastatic setting, especially in case of contraindications against a combination therapy with GnRHa (Oborne 1998). Several studies were reported over the last decade (Ingle et al. 1986, Buchanan et al. 1986, Sawka et al. 1997).

A meta-analysis of randomized trials comparing tamoxifen to ovarian ablation carried out either by surgery or irradiation as first-line hormonal therapy for pre-menopausal women with metastatic breast cancer enrolled 220 patients in four trials. There was no difference in overall response rate between tamoxifen and oophorectomy across the four trials (p = 0.94, Mantel-Haenszel test). The odds reduction for progression was 14% +/- 12% and for mortality 6% +/- 13% in favour of tamoxifen, which was not statistically significant (p = 0.32 and 0.72, respectively). Although the design of all four studies included a cross-over to the other therapy, only 54/111 patients receiving ovarian ablation and 34/109 patients receiving tamoxifen as primary therapy actually crossed over to the other arm at the time of disease progression. The efficacy of tamoxifen appears to be similar to that of ovarian ablation by surgery or irradiation as first-line therapy for premenopausal, ER positive metastatic breast cancer (Crump et al. 1997).

References


**GnRH-A + AI**

Even if the evidence is rather limited, aromatase inhibitors can be an option in the treatment of metastatic premenopausal breast cancer.

Based on a Phase II trial (Forward et al. BR J Cancer 2004) the combination of GNRHa plus aromatase inhibitors is a second line option after GNRHa + tamoxifen treatment failure.

A total of 16 premenopausal women with metastatic breast cancer (N=13) or locally advanced primary breast cancer (N=3) were treated with a combination of a gonadotropin-releasing hormone agonist goserelin, and a selective aromatase inhibitor anastrozole. All had previously been treated with goserelin and tamoxifen. In all, 12 patients (75%) achieved objective response or durable stable disease at 6 months, with a median duration of remission of 17+ months (range 6-47 months). Four patients still have clinical benefit. Introduction of goserelin and tamoxifen resulted in an 89% reduction in
mean oestradiol levels (pretreatment vs 6 months=224 vs 24 pmol l(-1)) (P<0.0001). Substitution of tamoxifen by anastrozole on progression resulted in a further 76% fall (to 6 pmol l(-1) at 3 months) (P<0.0001) (Forward et al. 2004).

Additionally there is evidence for GnRHa+ aromatase inhibitors as first line treatment in premenopausal patients. Besides a case study of 3 patients (El-Saghir et al. 2006), a small randomized trial compared GnRHa + anastrozol vs. GnRHa+ tamoxifen in 119 peri/premenopausal women with hormone dependent metastatic breast cancer (Milla-Santos et al.2002). In comparison to GnRHa+tamoxifen the study combination showed higher response rates (80% vs. 53%, P=0.023), improved clinical benefit rates (P=0.05) as well as prolonged overall survival (18.9 vs. 14.3 months).

A phase II trial (Carlson RW et al JCO 2010) with a cohort of 32 patients with metatastic disease were treated with GnRHa+anastrozol: One participant (3.1%) experienced a complete response, 11 (34.4%) experienced partial response, and 11 (34.4%) experienced stable disease for 6 months or longer for a clinical benefit rate of 71.9%. Median time to progression was 8.3 months (range, 2.1 to 63+) and median survival was not been reached (range, 11.1 to 63+).

References:


Further information:

In women with advanced (metastatic) breast cancer, aromatase inhibitors including those in current clinical use show a survival benefit when compared to other endocrine therapy. 3rd Generation aromatase agents should be the first endocrine treatment choice in patients with distant metastases of hormone responsive breast cancer and no adjuvant aromatase inhibitor treatment. This is demonstrated in numerous clinical trials and confirmed in a meta-analysis updated in 2009 (see references).

The clinical benefit of tamoxifen for treatment of metastatic breast cancer is shown in numerous trials and tamoxifen remains a mayor treatment option in the metastatic setting despite the superiority of aromatase inhibitors for first line treatment.

Fulvestrant in the dose of 250mg every four weeks is not superior to aromatase inhibitors or tamoxifen as first line or second line treatment of MBC. In the recently approved dose of 500mg four weeks it is superior to aromatase inhibitors as second line treatment of MBC.

MPA/MA are options as sequential therapies after other endocrine therapies have been used. However, they seem to be inferior to AI.

Trials comparing aromatase inhibitors for their efficacy have not delivered conclusive results, although one study stated that response with anastrozole was higher compared with letrozole. However, this was not the primary end point of this trial (see references “comparison of different AI”)

Endocrine Therapy in Postmenopausal Patients with HER2 Negative Metastatic Breast Cancer (6/14)
References:

„Aromatase inhibitors (3rd gen) (> non-AI*)“


4. Thuerlimann, B, Robertson, JFR, Nabholtz, JM, Buzdar, A, Bonneterre, J, Efficacy of tamoxifen following anastrozole (‘Arimidex’) compared with anastrozole following tamoxifen as first-line treatment for advanced breast cancer in postmenopausal women European Journal of Cancer 2003 39

5. Bonneterre, J, Buzdar, A, Nabholtz, JA, Robertson, JFR, Thuerlimann, B, von Euler, M, Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma Cancer 2001 92


„Fulvestrant is equivalent to AI (or tamoxifen) in the first line endocrine treatment of metastatic breast cancer.“


2. Howell, A, Robertson, JFR, Quaresma Albano, J, Ascgermannova, A, Mauriac, L, Kleeberg, UR, Fulvestrant, formerly ICI 182, 780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment Journal of Clinical Oncology 2002 20

3. Mauriac, L, Pippen, JE, Quaresma Albano, J, Gertler, SZ, Osborne, CK, Fulvestrant (Faslodex) versus anastrozole for the second-line treatment of advanced breast cancer in subgroups of postmenopausal women with visceral and non-visceral metastases: combined results from two multicentre trials European Journal of Cancer 2003 39

4. Osborne, CK, Pippen, J, Jones, SE, Parker, LM, Ellis, M, Come, S, Double-blind, randomized trial comparing the efficacy and tolerability of the fulvestrant versus anastrozole in postmenopausal women with advanced breast
cancer progressing on prior endocrine therapy: results of a North American Trial Journal of Clinical Oncology 2002 20


“MPA/MA inferior to AI”


5. Goss, PE, Winer, EP, Tannock, IF, Schwarz, LH, Randomized phase III trial comparing the new potent and selective third generation aromatase inhibitor vorozole with megestrol acetate in postmenopausal advanced breast cancer patients Journal of Clinical Oncology 1999 17


**Fulvestrant + Anastrozole**


Comparison of different AI


Endocrine Therapy in Postmenopausal HER2 Negative Metastatic Breast Cancer Patients after Adjuvant Tamoxifen or no prior Endocrine Treatment (7/14)

Further information and references:

AI (3rd gen), bevacizumab

Additional aspects not discussed on the previous slide:
- Evidence suggests that switching therapy from non-steroidal to a steroidal AI is as effective as fulvestrant in its approved dose of 250mg/q4 weeks (study “EFFECT”). It seems likely that also the switch from steroidal to non steroidal AI is effective and is therefore a therapeutic option.

References:


**Fulvestrant 500 mg > AI**

The “FIRST” trial using the higher dose of 500mg/q4w stated first-line fulvestrant HD was at least as effective as anastrozole for CBR (the primary end point) and ORR, but was associated with significantly longer TTP (a secondary end point) in patients pre-treated with endocrine treatment. A follow up analysis showed an even stronger superiority with a median TTP of 23.4 months for fulvestrant HD and 13.1 months for anastrozole (p=0.01).

*References:*


**Fulvestrant 500 mg > 250 mg**

In addition to the approved dose of 250 mg by intramuscular injection, highdose (HD) regimen of fulvestrant (500 mg once a month plus 500 mg on day 14 of month 1) is associated with a significantly longer progression-free survival (PFS) and can be recommended for patients who had progressed on prior endocrine therapy (Effect Trial, Confirm Trial, Finder I and II Trial).
References:


Estradiol

In women with advanced breast cancer and acquired resistance to aromatase inhibitors, a daily dose of 6 mg of estradiol provided a similar clinical benefit rate of 28% as 30 mg, with fewer serious adverse events.

References:

Therapy Algorithm After Adjuvant Tamoxifen (8/14)

No further information

No references
For patients with progression or relapse after the adjuvant use of an AI Fulvestrant plays an important role for second line treatment.

In the Bolero-2 study a phase 3, randomized trial, everolimus (10mg/die) and exemestane versus exemestane and placebo (randomly assigned in a 2:1 ratio) was compared in 724 patients with hormone-receptor-positive advanced breast cancer who had recurrence or progression while receiving previous therapy with a nonsteroidal aromatase inhibitor in the adjuvant setting or to treat advanced disease (or both). The primary end point was progression-free survival. Secondary end points included survival, response rate, and safety. A preplanned interim analysis was performed by an independent data and safety monitoring committee after 359 progression-free survival events were observed. The median age was 62 years, 56% had visceral involvement. Previous therapy included letrozole or anastrozole (100%), tamoxifen (48%), fulvestrant (16%) and prior chemotherapy for metastatic disease (25%). The number of previous therapies was at least 3 regimens in 54% of the patients. Overall response (0.4 vs 9.5%, p< 0.0001) and clinical benefit rate (18 vs 33.4%, p< 0.0001) was significantly higher in the combination group versus exemestane alone. Further at interim analysis median PFS was significantly increased with the combination of exemestane and everolimus both by local (2.8 vs 6.9 months, HR 0.43, 59% CI 0.35-0.54, p< 0.001) and central assessment (4.1 vs 10.6 months, HR 0.36, 95% CI 0.27-0.47, p<0.001). The most common grade 3/4 adverse events were stomatitis (8 vs 1%), anemia (4 vs <1%), dyspnea (4 vs 1%), and pneumonitis (3 vs 0%) and more frequently seen with the combination of exemestane and everolimus.

The potential of everolimus to benefit patient survival is not yet known.

In a small randomized phase 2 study 111 patients with hormone receptor positive metastatic disease and prior aromatase inhibitor therapy were randomized to tamoxifen (n=57) or tamoxifen and everolimus (n=54; 10mg/die). The clinical benefit rate (42.1 vs 61.1%, p=0.045) time to progression (4.5 vs 8.6 months, HR 0.53, 95% CI 0.35-0.81, p=0.0026 exploratory log rank) and overall survival (HR 0.32 95% CI 0.15-0.68, p=0.0019) were significantly superior in the combination treatment compared to tamoxifen alone.
References:


Therapy Algorithm After Adjuvant AI (10/14)

No further information

No references
Endocrine Therapy in Postmenopausal HER2 Positive Metastatic Breast Cancer Patients (12/14)

Further information:

Several lines of evidence support the hypothesis that HER2-positive breast cancer is associated with endocrine resistance. The addition of trastuzumab or lapatinib to aromatase inhibitor treatment is able to enhance the efficacy over endocrine treatment alone. However, given the relative short progression free interval in the phase III trials compared to those observed in trials with chemotherapy, we recommend to consider chemotherapy in HER2-positive patients.

One phase III trial comparing fulvestrant + placebo vs. Fulvestrant + lapatinib could not demonstrate an improved PFS or OS in 324 patients pretreated with an AI.
For further information on trials combining enocrine treatment with anti-HER2 therapy, see following slide.

References:


Combination of Endocrine Treatment with Anti-HER2-Treatment (13/14)

No further information

References:


**Concomitant or Sequential Endocrine-Cytostatic Treatment (14/14)**

**Further information:**

Concomitant endocrine cytostatic therapy can not be recommended because it induces an increase in toxicity and does not induce a prolongation of disease free interval or overall survival despite the increase of response rates. Thus, endocrine – cytostatic therapy should be performed as sequential treatment modality.

Endocrine mainenance therapy after chemotherapy induced response might be considered, even if the evidence is quite small and not homogeneous, since only relatively little side effects are observed with this sequential treatment option.

**References:**

