Therapy algorithms

Preamble:
Therapy options shown in the algorithms are based on the current AGO recommendations, but cannot represent all evidence-based treatment options, since prior therapies, performance status, comorbidities, patient preference, etc. must be taken into account for the actual treatment choice. In individual cases, other evidence-based treatment options (not listed here) may also be appropriate and justified.
Regardless of approval status, the algorithms only take into account drugs that were available in Germany at the time the algorithm was last updated.
Therapy Algorithms

- **Version 2021:**
  Schneeweiss / Bauerfeind / Fehm / Müller / Thomssen / Witzel / Wöckel / Janni

- **Format legend:**
  - Text Definitions, features, parameters
  - Text Therapy with grade of recommendation AGO+ or AGO++
  - Text Therapy with grade of recommendation AGO+/- (case by case decision)
  - Text Recommended path with grade of recommendation AGO+ oder AGO++
  - Text Path of case by case decision (grade of recommendation AGO+/-)
  - Text Arrow points to the next therapy option at progression
  - AGO++ AGO grade of recommendation of this path
Content

- **eBC**
  - (Neo)adjuvant therapy of HER2-positive breast cancer
  - Axillary surgery and neoadjuvant chemotherapy (NACT)
  - Adjuvant endocrine therapy in premenopausal patients
  - Adjuvant endocrine therapy in postmenopausal patients

- **mBC**
  - HR-positive/HER2-negative metastatic breast cancer: strategies
  - HR-positive/HER2-negative metastatic breast cancer: endocrine-based first line treatment
  - HER2-positive metastatic breast cancer: 1st-3rd-line
  - Triple-negative metastatic breast cancer
(Neo)adjuvant Therapy of HER2-positive Breast Cancer

- **cT1 and cN0**
  - Surgery
  - **pT1 and pN0**
    - **pN0**
    - **pT ≥ 2 or pN+**
      - **pN+**
      - **pCR and cN0**
        - **pCR and pN_CNB+**
          - Surgery
          - **non-pCR**
            - **14 x T-DM1 q3w**

- **cT ≥ 2 or pN_CNB+**
  - **PzTz-based regimen (6-8 cycles)**
  - **Tz + paclitaxel (Tz for 1y)**
  - **Tz-based regimen (Tz for 1y)**
  - **PzTz-based regimen (PzTz for 1y)**
  - **PzTz to complete 1y**
  - **Tz to complete 1y**

**CNB**, core needle biopsy; **HR**, hormone receptor; **Nx**, Neratinib; **pCR**, pathological complete response; **Pz**, Pertuzumab; **q3w**, every 3 weeks; **T-DM1**, Trastuzumab emtansine; **Tz**, Trastuzumab; **y**, year
Adjuvant Endocrine Therapy in Premenopausal Patients

- **Pre- or perimenopausal**
  - Higher risk for recurrence*
    - No: Tam for 5y\(^1\)
    - Yes:
      - Tam plus OFS** for 2-5y\(^3\)
      - Al plus OFS for 5y\(^{3,4}\)
      - Continue Tam for 5y\(^2\)

*Administration of chemotherapy was a surrogate marker for higher risk of recurrence in clinical trials
**OFS also in case of remaining or recurring ovarian function within 24 months after chemotherapy induced amenorrhea

Al, aromatase inhibitor; OFS, ovarian function suppression; Tam, tamoxifen; y, years
Adjuvant Endocrine Therapy in Postmenopausal Patients

Postmenopausal before the start of adjuvant therapy

- **AGO+**
  - **Tam for 5y**
    - (very old, very low risk of recurrence or if contraindications for AI are present)
  - **Discuss EAT**

- **AGO++**
  - **Tam for 2-3y followed by AI (complete 5y)**
  - **AI for 2-3y followed by Tam (complete 5y)**
  - **AI for 5y**
  - **Non-steroidal AI for 5y**
    - (invasive-lobular histology)

- **AGO+**
  - **Recommend EAT with AI for 2- (5)y**

High risk of recurrence

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AI, aromatase inhibitor; EAT, extended adjuvant therapy; Tam, tamoxifen; y, years;

* decision criteria may include: condition after neo(adjuvant) chemotherapy (indicating high risk), positive lymph node status, T2/T3 tumors, elevated risk of recurrence based on immuno-histochemical criteria or based on multi-gene expression assays, high CTS5-Score; *b* up to date no impact on overall survival.
HR-positive/HER2-negative Metastatic Breast Cancer: Strategies

**Imminent organ failure**
- CTx combination<sup>1-4</sup>
- Single agent CTx
- CTx + bevacizumab<sup>b</sup>

**Standard therapy**
- CDK4/6<sup>i</sup> + AI or CDK4/6<sup>i</sup> + fulvestrant<sup>5,6</sup>

**Endocrine resistant** (progression ≤ 6 months)
- PARP inhibitor<sup>7-13</sup>
- Single agent CTx<sup>14</sup>
- CTx + bevacizumab<sup>b</sup>

**Endocrine sensitive** (progression > 6 months)
- ETx + everolimus<sup>15</sup>

**sPIK3CA mutation**
- ETx + alpelisib<sup>16</sup>

**Single agent CTx / ETx / CDK4/6i**

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AI, aromatase inhibitor; CDK4/6i, CDK4/6 inhibitor; CTx, chemotherapy; ETx, endocrine therapy; gBRCA1/2, germ line BRCA1/2 mutation; HR, hormone receptor; mBC, metastatic breast cancer; sPIK3CA, somatic PIK3CA mutation; <sup>a</sup> premenopausal add OFS; <sup>b</sup> bevacizumab + paclitaxel or + capecitabine; <sup>c</sup> after approval
HR-positive/HER2-negative Metastatic Breast Cancer: Endocrine-based First Line Treatment

**Premenopausal standard therapy**

**Postmenopausal standard therapy (adjuvant tamoxifen)**

**Postmenopausal standard therapy (adjuvant AI)**

**HR+ / HER2- mBC**

- **AGO++**
  - GnRHa + fulvestrant + CDK4/6i
  - GnRHa + Al + ribociclib
  - GnRHa + Al + palbociclib or abemaciclib
  - GnRHa + tamoxifen
  - GnRHa + Al or GnRHa + fulvestrant
  - Tamoxifen

- **AGO+**
  - CDK4/6i + Al
  - Al

- **AGO+/-**
  - CDK4/6i + fulvestrant

- **AGO+**
  - Fulvestrant
  - Tamoxifen

- **AGO-**
  - Tamoxifen

**Guidelines Breast Version 2021.1E**

**Abbreviations:**

- AI, aromatase inhibitor
- CDK4/6i, CDK4/6 inhibitor
- GnRHa, GnRH agonist
- HR, hormone receptor
- mBC, metastatic breast cancer
HER2-positive Metastatic Breast Cancer: 1st-3rd-line

De novo metastatic or TFI > 6 mths after (neo-)adjuvant anti-HER2 regimen

Unsuitable for CTx / patient's preference

ETx + anti-HER2-regimen

Taxane + Tz + Pz

Vinorelbine + Tz + Pz

After (neo)adjuvant Tz +/- Pz

Secondary metastatic and TFI ≤ 6 mths after (neo-)adjuvant anti-HER2 regimen

T-DM1

After (neo)adjuvant Tz +/- Pz followed by adjuvant T-DM1

Tuc + Tz + Cap

Cap + Lap

Cap + Ner

Tz-Deruxtecan

CTx + Tz (TBP)

Al + Tz + Pz

Tz + Lap

Experimental anti-HER2-regimen

Al, aromatase inhibitor; Cap, capecitabine; CTx, chemotherapy; ETx, endocrine treatment; Lap, lapatinib; mths, months; Ner, neratinib; Pz, pertuzumab; TBP, treatment beyond progression; T-DM1, trastuzumab emtansine; TFI, treatment-free interval; Tuc, tucatinib; Tz, trastuzumab;
a no OS benefit, consider induction chemotherapy + anti-HER2-therapy (followed by ETx + anti-HER2-therapy as maintenance therapy); b docetaxel (++), paclitaxel (+++) or nab-paclitaxel (+); c only HR positive; d only for HR negative
Triple-negative Metastatic Breast Cancer

Determination of PD-L1 IHC and gBRCA

- PD-L1 neg\(^a\) and gBRCA\(^{wt}\)
  - No previous therapy with A/T
  - AGO+
- PD-L1 neg\(^a\) and gBRCA\(^{mut}\)
  - Previous therapy with A/T
  - AGO+/
  - AGO++
- PD-L1 pos\(^a\) and gBRCA\(^{wt}\)
  - AGO+
- PD-L1 pos\(^a\) and gBRCA\(^{mut}\)
  - AGO+/--
  - AGO++/
  - AGO++/-

Chemotherapy

- Paclitaxel or capecitabine + bevacizumab, cisplatinum + gemcitabine, carboplatin ± nab-paclitaxel\(^{1,3,5,9,11,13,14}\)
  - AGO++
- Chemotherapy ± bevacizumab\(^{1,3,5,9,11,13,14}\)
  - AGO++/
  - AGO+
  - AGO+/

PARP-inhibitor\(^{4,8,9}\)

- Carboplatin\(^{11}\)
- PARP-inhibitor\(^{4,6}\)

Alternative CTx\(^b\), 1-3,12-14

- Pac or Cap + bevacizumab, carboplatin ± nab-paclitaxel etc.\(^{1,3,5,9,11,13,14}\)
- Carboplatin, Capecitabine etc.\(^{1-3,12-14}\)

PARP inhibitor\(^{4,8,9}\)

- Atezo + nPac\(^{10}\) (TFI≥12 mths)
- Pembro + CTx\(^{c,11}\) (TFI≥26 mths)
- PARP inhibitor\(^{4,8,9}\)
- Atezo + nPac\(^{10}\) (TFI≥12 mths)
- Pembro + CTx\(^{c,11}\) (TFI≥26 mths)
- PARP inhibitor\(^{4,8,9}\)
- Carboplatin\(^{12}\)

A, anthracycline; Atezo, atezolizumab; Cap, capecitabine; gBRCA, germ line BRCA mutation; IHC, immunohistochemistry; mths, months; mut, mutated; neg, negative; nPac, nab-paclitaxel; Pac, paclitaxel; PD-L1, programmed cell death ligand 1; Pembro, pembrolizumab; pos, positive; T, taxane; TFI, treatment-free interval; wt, wild type; \(^*\) IC<1\% (neg) or ≥1\% (pos); \(^*\) use of not previously used compounds or regimen; \(^*\) nPac, Pac oder Carboplatin+Gemcitabine