Adjuvant Cytotoxic and Targeted Therapy
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- **Versions 2002–2017:**
  Harbeck / Jackisch / Janni / Loibl / Lux/
  von Minckwitz / Möbus / Müller / Nitz /
  Schneeweiss / Simon / Schütz / Solomeyer /
  Stickeler / Thomssen / Untch

- **Version 2018:**
  Thill / Untch
Subtype-specific Strategies for Systemic Treatment

- If chemotherapy is indicated due to tumor biology consider systemic treatment before surgery (neoadjuvant)
  - ++
  - HR+/HER2- and „low risk”
    - Endocrine therapy without chemotherapy
      - ++
  - HR+/HER2- and „high risk”
    - Conventionally dosed AT-based chemotherapy
      - ++
    - Dose dense chemotherapy
      - ++
    - Followed by endocrine therapy
      - ++
  - HER2+
    - Trastuzumab (plus Pertuzumab neoadjuvant at high risk)
      - ++
        - Sequential A/T-based regimen with concurrent T + H
          - ++
        - Anthracycline-free, platinum-containing regimen
          - +
        - Anthracycline-free, taxane-containing regimen
          - +
  - Triple-negativ (TNBC)
    - Conventionally dosed AT-based chemotherapy
      - ++
    - Dose dense chemotherapy
      - ++
    - Neoadjuvant platinum-containing chemotherapy
      - +

Systematic review of published evidence
PUBMED 1999-2016
ASCO 1999-2016
SABCS 1999-2016
ECCO/ESMO 1999-2016
## Adjuvant Chemotherapy without Trastuzumab: Overview

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
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<tbody>
<tr>
<td>Anthracycline / taxane based chemotherapy</td>
<td>1a</td>
<td>A</td>
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### If anthracyclines cannot be given
- Docetaxel plus cyclophosphamide
- Paclitaxel mono weekly
- CMF

### Dose-dense therapy
- Low dose maintenance chemo

### Statement: Anthracycline/ taxane based chemotherapy

### Statement: If anthracyclines cannot be given - Docetaxel plus cyclophosphamide

### Statement: If anthracyclines cannot be given - Paclitaxel mono weekly
Statement: If anthracyclines cannot be given - CMF


Statement: Dose-dense in case of high tumor burden


4. Gray R et al. Increasing the dose density of adjuvant chemotherapy by shortening intervals between courses or by sequential drug administration significantly reduces both disease recurrence and breast cancer mortality: An EBCTCG meta-analysis of 21,000 women in 16 randomised trials. SABCS 2017, abstr. GS1-01

Statement: Low dose maintenance Chemotherapy

Colleoni et al., J Clin Oncol 2016, 34: 3400-8

rand. phase 3-study of IBCSG: trial 22-00

n = 1086 pat., HR neg.,

DFS as primary endpoint

**OP -> adj. CT -> R ->** Cyclophos. 50 mg p.o. cont. plus
 Mtx 2.5 mg 2 x tgl. p.o. d 1 + 2, q1w
 versus
 control (nil)

**Results:**
FU 6.9 yrs.,
n.s. DFS difference,
more side effects (14% WHO3/4) in the CM-arm

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Statement: Anthracycline/ taxane based regimen
*EC → Pw  E90C q3w x 4 → P80 qw1 x 12


Statement: Anthracycline/ taxane based regimen
AC → Pw  A60Cq3w x 4 → P80qw1 x 12


Statement: Anthracycline/ taxane based regimen
AC → D  A60C q3w x 4 → D100 qw3 x 4
EC → D  E90C q3w x 4 → D100 qw3 x 4

Statement: Anthracycline/ taxane based regimen

* Extrapolated from doxorubicin trials
DAC D75A50C q3w x 6


Statement: Anthracycline-free regimen

DC $\rightarrow$ D75 C600 x4 corresponds to EC $\rightarrow$ D

1. Harbeck N et al. No age-related outcome disparities according to 21-gene recurrence score groups in early breast cancer patients treated by adjuvant chemotherapy in the prospective WSG PlanB trial. SABCS 2017, abstr.P1-06-06

Statement: Anthracycline-free regimen

DC $\gg$ 4 x AC


Statement: Anthracycline-free regimen

Pac mono 80 mg q1w x 4-6


Statement: Anthracycline-free regimen

CMF 600/40/600 mg q3w x 6

**Recommended Dose-dense and / or Dose-escalated, Sequential Adjuvant Chemotherapy**

<table>
<thead>
<tr>
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<tr>
<td>E90-Pac175-C600 q2w</td>
<td>1b</td>
<td>A</td>
<td>++</td>
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<tr>
<td>AC q2w x4 → Pac q2w x 4</td>
<td>1b</td>
<td>B</td>
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<tr>
<td>EC q2w x4 → Pac q2w x 4</td>
<td>1b</td>
<td>A</td>
<td>++</td>
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<tr>
<td>EC q2w x4 → Pac q1w x 12</td>
<td>1b</td>
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Dose-dense and dose-escalated regimen (N ≥ 4+)

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<tr>
<td>E150-Pac225-C2500 q2w</td>
<td>1b</td>
<td>A</td>
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* G-CSF obligatory

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**Statement: Dose-dense regimen**

AC q2w x 4 Pac q2w x 4


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**Statement: Dose-dense regimen**

E90-Pac175-c600 q2w / ACPac / AC-Pac q2w


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**Statement: Dose-dense regimen**

EC q3w / Pac q2w

EC q2w / Pac q1w

EBCTCG Metaanalyse

Gray R et al. Increasing the dose density of adjuvant chemotherapy by shortening intervals between courses or by sequential drug administration significantly reduces both disease recurrence and breast cancer mortality: An EBCTCG meta-analysis of 21,000 women in 16 randomised trials. SABCS 2017, abstr. GS1-01

Statement: Dose-dense and dose-escalated regimen (N ≥ 4+)
E-Pac-C q2w


Negative Trial


Statement: Capecitabine containing regimen in TNBC

Statement: Platinum containing regimen in TNBC

Statement: 5-Fluorouracil added to EC/AC
Statement Trastuzumab + Pertuzumab (N+ and/or HR- / N- and HR+)

Statements: Trastuzumab in node-negative disease (if chemotherapy is indicated)

7. Jackisch C et al. Efficacy and safety of subcutaneous or intravenous trastuzumab in patients with HER2-positive early breast cancer after 5 years' treatment-free follow-up: Final analysis from the phase III, open-label, randomized HannaH study. SABCS 2017, abstr. PD3-11


**Statements: >10 mm/ > 5-10 mm/ <= 5mm**


**Adjuvante Therapie mit Trastuzumab**

**Start of treatment**
- Simultaneously with taxanes
- Sequentially up to 3 months after chemotherapy
- S.c. = i.v.

**Duration**
- For 1 year
- For 2 years
- For 0.5 years

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**Statement: Start of treatment simultaneously with taxanes**


6. Perez E et al. Sequential Versus Concurrent Trastuzumab in Adjuvant Chemotherapy for...


Statement s.c.


Statement: Duration

Duration Trastuzumab 1 year

Duration Trastuzumab 2 year

Duration Trastuzumab 0.5 years


4. Joensuu H et al. A randomized phase III study of an adjuvant trastuzumab for a duration of 9 weeks versus 1 year, combined with adjuvant taxane-anthracycline chemotherapy, for early HER2-positive breast cancer (the SOLD study). SABCS 2017, abstr. GS3-04
**Statement: Cardiac Monitoring**


**Statement Cardiac monitoring trastuzumab/pertuzumab**

**Statement: with paclitaxel/docetaxel after AC/EC**


**Statement: P q1w12 without A in pT < 2 cm pN0**


2. Tolaney SM et al. Seven-year (yr) follow-up of adjuvant paclitaxel (T) and trastuzumab (H) (APT trial) for node-negative, HER2-positive breast cancer (BC). Journal of Clinical Oncology 2017;35:15 suppl: 511-511

**Statement: with docetaxel and carboplatin**


2. Burstein HJ et al. Choosing the Best Trastuzumab-Based Adjuvant Chemotherapy Regimen: Should We Abandon Anthracyclines? Journal of Clinical Oncology
Statement: Trastuzumab + Pertuzumab simultaneously with anthracyclines

Statement: Trastuzumab + Pertuzumab simultaneously with taxanes dose-dense

Statement: radiotherapy concurrent with trastuzumab
Adjuvant Therapy with Other Targeted Agents

- **Lapatinib**
  - (delayed adjuvant treatment)
- **Lapatinib + Trastuzumab**
- **Neratinib after 1 year of Trastuzumab**
  - HR+
  - HR-
- **Bevacizumab**

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**Statement: with Lapatinib**

**Delayed adjuvant treatment**


3. Perez EA et al. Disease-free survival (DFS) in the lapatinib alone arm and expanded results of the phase III ALTTO trial (BIG 2-06; NCCTG [Alliance] N063D) in the adjuvant treatment of HER2-positive early breast cancer (EBC) ESMO 2014

**Statement: with Lapatinib + Trastuzumab**


**Statement: Bevacizumab**

2013;14(10):933-42.


**Statement:** Neratinib after adjuvant trastuzumab

Biosimilars
General Considerations

Biosimilars, used for treatment (i.e. Trastuzumab) and supportive care of breast cancer (i.e growth factors) must be approved after passing the stringent development and validation processes required by EMA, FDA or other similarly strict authority, before used in daily practise.*
