Systemic treatment of metastatic breast cancer ; palliative or curative?

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Loco-regional Recurrence
Risk Factors at first diagnosis

Increased risk for loco-regional recurrence	Oxford LoE
Clinical factors:	
▪ Young age	1a
▪ First diagnosis with clinical symptoms	2b
▪ Obesity (Body mass index)	1a
▪ Non-alcoholic fatty disease of the liver	2b
▪ Persistent lymphopenia after systemic therapy	4
Tumor related factors:	
▪ Inflammatory breast cancer	2b
▪ Multizentricity	3b
▪ Medial tumor localisation	4
▪ Axillary lymph node metastasis and number of involved lymph nodes	1a
▪ pT > 2 cm	1a
* node-negativ	1b*
▪ HER 2 +++ and tripel-negativ > Luminal B-like > Luminal A-like	1a
▪ Grade G3	1b*
▪ Elevated proliferation markers: e.g. Ki-67	2b
▪ pPR (residual disease) after NACT	2b
▪ Nipple sparing mastectomy and tumor distance to nipple <1cm	2b
Other factors (nomograms/risk-scores):	
▪ Increased risk according to nomogram (f.e. INFLUENCE)	1a
▪ CPS+EG Score	2c
▪ Adjuvant Radiotherapy Intensification Classifier (ARTIC)	2b

Loco-regional Recurrence Staging

	Oxford LoE	Oxford GR	AGO
Examinations before treatment			
▪ Tissue biopsy	5	D	++
▪ Re-assessment of ER, PgR, HER2	3b	B	++
▪ Complete re-staging	5	D	++
▪ „Liquid biopsy“	5	D	-
▪ ^{18}F-FDG PET-CT	2b	B	-

Loco-regional Recurrence
Prognostic / Predictive factors

Parameters of the locally recurrent tumor to define the risk for re-recurrence	Oxford LoE	Oxford GR	AGO
▪ Tumor size	2a	B	
▪ Multifocality	2a	B	
▪ Localisation	2b	B	
▪ Negative progesterone receptor	3b	B	
▪ High grade	3b	C	
▪ Omitted radiotherapy at first recurrence	3b	C	
▪ Omitted chemotherapy at first recurrence	3b	C	
Parameters of the locally recurrent tumor to define the risk for distant metastasis/survival			
▪ Early (< 2-3 yrs.) vs. late recurrence	2b	B	
▪ LVSI / Grade / ER-neg / positive margins (if ≥ 2 factors positive)	3b	B	
Predictive factors for treatment considerations			
▪ HER2	2b	B	++
▪ ER and PgR	2b	B	++

Ipsilateral Recurrence after BCT Surgery

	Oxford		
	LoE	GR	AGO
▪ Mastectomy (aim: R0)	3b	B	++
▪ Re-BCS with tumor-free margins (R0)	2b	B	+/-
▪ Axillary intervention after prior AxDiss if cN0	4	C	-
▪ SLNE after prior SLNE if cN0*	2a	B	-
▪ Palliative surgery in M1-situation (e.g. pain, ulceration, psychosocial indication)	5	D	+

* If no sentinel lymph node can be identified, axillary dissection is not recommended; no operation outside the ipsilateral axilla is recommended

Chest-Wall Recurrence after Mastectomy / Axillary Recurrence - Surgery

	Oxford LoE	GR	AGO
▪ **Curative situation: R0-resection (including deeper parts of the chest wall in selected cases: HR-positive, primary N-)**	2b	A	++
▪ **Palliative situation: Resection of deep parts of the chest wall**	5	D	+/-
▪ **Palliative surgery in M1-situation (e.g. pain, ulceration, psychosocial)**	5	D	+
▪ **SLNE after prior SLNE if cN0***	3b	B	-

* If no sentinel lymph node can be identified, axillary dissection is not recommended; no operation outside the ipsilateral axilla is recommended

Loco-regional Recurrence after R0-Resection Systemic Treatment

	Oxford LoE	GR	AGO
According to pathohistological re-evaluation of the recurrent tumor (ER, PgR, HER2)			
▪ Endocrine therapy in endocrine responsive tumors	2b	B	++
▪ Chemotherapy (consider preoperative)	2b	B	+
▪ In case of HER2-positive disease, chemotherapy + HER2-targeted therapy	5	D	+

Locoregional Recurrence in Case of R1-Resection/Inoperability – Systemic Treatment

	Oxford LoE	GR	AGO
According to pathohistological re-evaluation of the recurrent tumor (ER, PgR, HER2)			
▪ Endocrine based therapy in endocrine responsive tumors corresponding to metastatic disease	2b	B	++
▪ Chemotherapy and targeted therapy (pre- or postoperative) corresponding to metastatic disease	2b	B	++

Osteo-oncology and Bone Health

	Oxford		
	LoE	GR	AGO
▪ Hypercalcemia	1a	A	++
▪ Reduction of skeletal events (complications)	1a	A	++
▪ Reduction of bone pain	1a	A	++
▪ Increasing bone pain-free survival	1a	A	++
▪ Treatment beyond osseous progression	5	D	++
▪ Use of bone resorption marker for therapy monitoring	5	D	-
▪ Bisphosphonates used alone for pain control	5	D	-

Specific Sites of Metastases

- Liver and lung metastases
- Malignant pleural and pericardial effusions
- Ascites
- Bone marrow involvement
- Soft tissue metastases
- Any other organs

General Treatment Aspects of Metastases

	Oxford		
	LoE	GR	AGO
▪ Histological / cytological verification	3	B	+
▪ Systemic therapy preferred	2a	B	++*
▪ Consider surgery only in case of good response to palliative treatment	2b	C	+
▪ Radiation for patients in good physical condition with late onset of oligometastases	3a	B	+
▪ Local treatment in the case of pain, exulceration, persistence after systemic treatment, bowel obstruction, hydrocephalus occlusus, spinal cord compression	5	D	+/-
▪ Systemic treatment after surgery	5	D	++

* See chapters with systemic treatment recommendations

Local Therapy in Primary Metastatic Disease

	Oxford LoE	Oxford GR	Oxford AGO
Surgery (R0) of the primary tumor			
In case of bone metastases only	2b[a]	B	+/-
In case of visceral metastases	2b[a]	B	-
Axillary surgery for cN1	5	D	+/-
Sentinel if cN0	5	D	-
Radiotherapy of the primary tumor			
Alone (without surgery)	3a	C	+/-
After local surgical treatment with BCS or mastectomy (according to adjuvant indication)	3a	C	+

Liver Metastases
Local Therapy

	Oxford LoE	GR	AGO
▪ **Resection of liver metastases (R0)** **HR-positive: chemotherapy-sensitive, long disease-free interval, absence of extrahepatic disease, ≤ 3 metastases** **HER2-positive: age ≤ 50y, metastasis < 5 cm, no further metastasis**	3a	B	+/-
▪ **Regional chemotherapy**	3b	C	+/-
▪ **Regional radiotherapy** **[SIRT, stereotactic body radiosurgery with volumetric intensity modulated arc therapy (SRS-VMAT), radiochemo-embolization, other modalities]**	3b	C	+/-
▪ **Thermoablation** **(RFA, LITT, cryotherapy)**	3b	C	+/-

Malignant Pleural Effusion (MPE)
Local Therapy

	Oxford LoE	GR	AGO
▪ If short life expectancy, less invasive procedures should be considered	4	C	++
▪ VATS and Talcum-pleurodesis*	1b	B	++
▪ Chemical pleurodesis*			
▪ Talcum powder	1a	B	+
▪ Bleomycin, Doxycycline, Mitoxantrone	2b	C	+/-
▪ Povidone-iodine (20 ml of 10% solution)	1b	B	+
▪ Continous pleural drainage	2a	B	++
▪ Systemic treatment after pleurodesis	3b	C	+/-
▪ Serial thoracocentesis	4	C	+/-

* Adequate pain-relief

VATS: video-assisted thoracoscopic surgery

Soft Tissue Metastasis
Local Therapy

	Oxford LoE	GR	AGO
▪ **Surgery of limited locoregional metastasis (skin, muscular, nodal) with complete resection (R0) after exclusion of further metastasis**	4	C	+
▪ **Radiotherapy (after surgery or, if immediate surgery is not indicated):**			
▪ Soft tissue metastasis	3b	C	+
▪ Paresis, spinal cord compression	2b	C	++
▪ Plexus infiltration	3b	C	++

Metastatic Breast Cancer Disease-Free and Overall Survival

In MBC, an increase in survival over time has been shown in some retrospective analyses 2a

- Multiple lines of sequential therapy are beneficial (at least same efficacy, less toxicity)
- Targeted drugs in combination with chemotherapy can induce substantial survival benefits

Metastatic Breast Cancer Endocrine Resistance

Primary endocrine resistance:

- Relapse within 2 years of adjuvant endocrine treatment (ET)
- Progressive disease within first 6 months of first-line ET for MBC

Secondary endocrine resistance:

- Relapse while on adjuvant ET but after the first 2 years or a relapse within12 months after completing adjuvant ET
- PD ≥ 6 months after initiation of ET for MBC

Endocrine Therapy in Metastatic Breast Cancer

Indication

Oxford LoE: 1a **GR: A** **AGO: ++**

Endocrine-based therapy is first line treatment in patients with metastatic breast cancer and positive (or unknown) hormone receptor (HR) status.

Exception: imminent organ failure

Caveat: HR may change during the course of disease.
Histology of recurrent site should be obtained whenever possible

Metastatic Breast Cancer
Predictive Factors

Therapy	Factor	Oxford LoE	Oxford GR	Oxford AGO
Endocrine therapy	ER / PR (primary tumor, metastasis)	1a	A	++
	prior response	2b	B	++
Chemotherapy	prior response	1b	A	++
Anti-HER2-drugs	HER2 (primary tumor, better in metastasis)	1a	A	++
Checkpoint-inhibitors (Atezolizumab)	PD-L1 IC# positive in TNBC	1b	B	+
PARP inhibitors	gBRCA 1/2 mutation	1a	A	++
Bone modifying drugs	bone metastasis	1a	A	++
Any therapy	CTC monitoring	1b	A	+*

* Within clinical trials

(for additional potential biological factors see chapter„Predictive factors“)

(# ≥ 1% on immune cells (IC) (for more information see chapter “ pathology”)

Comparison ER/PR and HER2 Metastasis vs. Primary Tumor (N=5.521)

Meta-analysis based on 39 (mostly retrospective) analyses, exclusively comparing primary tumor and metastasis (no lymph nodes):

Pooled discordance proportions were:

- 19,3% (95% CI 1⁄4 15.8% to 23.4%) for ER
- 30,9% (95% CI1⁄4 26.6% to 35.6%) for PR
- 10,3% (95% CI 1⁄4 7.8% to 13.6%) for HER2

Pooled proportions of tumors shifting from positive to negative

- 22.5% (95% CI = 16.4% to 30.0%) for ER
- 49.4% (95% CI = 40.5% to 58.2%) for PR
- 21.3% (95% CI = 14.3% to 30.5%)) for HER2

Pooled proportions of tumors shifting from negative to positive

- 21.5% (95% CI = 18.1% to 25.5%) for ER
- 15.9% (95% CI = 11.3% to 22.0%) for PR
- 9.5% (95% CI = 7.4% to 12.1%) for HER2

Endocrine Therapy in Premenopausal Patients with HER2-Negative Metastatic Breast Cancer

	Oxford		
	LoE	GR	AGO
▪ GnRH-A + Fulvestrant + Palbociclib	2b	B	++
▪ GnRH-A + AI + Palbociclib*	3b[a]	C	++
▪ GnRH-A + AI + Ribociclib	1b	B	++
▪ GnRH-A + Fulvestrant + Abemaciclib	2b	B	++
▪ GnRH-A + Tamoxifen (vs. OFS or Tam)	1a	A	++
▪ Ovarial function suppression (OFS)	2b	B	+
▪ Tamoxifen	2b	B	+
▪ GnRH-A + AI (first + second line)	2b	B	+
▪ GnRH-A + Fulvestrant	1b	B	+
▪ Aromatase inhibitors without OFS	3	D	--

* Extrapolated from data of postmenopausal patients (with AI)

Endocrine Mono-Therapy in Postmenopausal Patients with HER2-Negative Metastatic Breast Cancer

	Oxford		
	LoE	GR	AGO
▪ Fulvestrant 500 mg	1b	B	+
▪ Aromatase inhibitor*	1a	A	+
▪ Tamoxifen	1a	A	+
▪ Fulvestrant 250 mg + Anastrozole	1b	B	+/-
▪ Repeat prior treatments	5	D	+/-

* There is no evidence for superiority of a single aromatase inhibitor. As everolimus plus exemestane is indicated after AI treatment, a non-steroidal AI should be used in first line.

Endocrine-Based Treatment Options for Postmenopausal Patients with HER2-Negative Metastatic Breast Cancer

	Oxford		
	LoE	GR	AGO
▪ **CDK4/6-Inhibitor (Abemaciclib, Palbociclib, Ribociclib)**			
▪ + non-steroidal AI	1b	B	++
▪ + Fulvestrant	1b	B	++
▪ **Abemaciclib Monotherapie**	3	C	+/-
▪ **Alpelisib + Fulvestrant (PIK3CA mutated)**	1b	B	+
▪ **Everolimus**			
▪ + Exemestane	1b	A	+
▪ + Tamoxifen	2b	B	+
▪ + Letrozole	2b	B	+/-
▪ + Fulvestrant	2b[a]	B	+
▪ **CDK4/6i beyond progression**	5	D	-
▪ **CDK4/6i switch based on toxicity**	5	D	+/-

HER2-Positive and HR-Positive Metastatic Breast Cancer

Endocrine Therapy in Postmenopausal HER2-Positive Metastatic Breast Cancer Patients

	Oxford LoE	Oxford GR	Oxford AGO
▪ Anastrozole plus trastuzumab	1b	B	+/-
▪ Letrozole plus trastuzumab	2b	B	+/-
▪ Letrozole plus lapatinib	1b	B	+/-
▪ Fulvestrant plus lapatinib	1b	B	+/-
▪ Abemaciclib plus fulvestrant plus trastuzumab (after T-DM1)	2b[a]	B	+/-
▪ Aromatase inhibitors plus trastuzumab / pertuzumab*	2b	B	+/-

Poor efficacy of endocrine therapy alone.
Consider induction chemotherapy + anti-HER2-therapy (followed by endocrine + anti-HER2-therapy as maintenance therapy)!

* Study participation recommended

Concomitant or Sequential Endocrine-Cytostatic Treatment

	Oxford LoE	GR	AGO
▪ **Concomitant endocrine-cytotoxic treatment** ▪ May increase response rate and progression free interval but not overall survival ▪ May increase toxicity	1b	A	-
▪ **Endocrine maintenance therapy after chemotherapy +/- anti-HER2 therapy-induced response +/- anti HER2 therapy** ▪ Increases progression free interval	2b	B	+

Chemotherapy With or Without Targeted Drugs* in Metastatic Breast Cancer

Metastatic Breast Cancer
Disease-Free and Overall Survival

	Oxford LoE
▪ In MBC, an increase in survival over time has been shown in some retrospective analyses	2a
▪ Multiple lines of sequential therapy are beneficial (at least same efficacy, less toxicity)	1b
▪ Targeted drugs in combination with chemotherapy can induce substantial survival benefits	1b

Metastatic Breast Cancer
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Metastatic Breast Cancer
Treatment Rationale

Oxford LoE: 1b **GR: A** **AGO: ++**

- **Mono-Chemotherapy:**
  - **Favorable therapeutic index**
  - **Indicated in case of**
    - **Slow, not life-threatening progression**
    - **Insensitivity to or progression during endocrine therapy**

- **Poly-Chemotherapy:**
  - **Unfavorable therapeutic index**
  - **Indicated to achieve rapid remission in the case of**
    - **Extensive symptoms**
    - **Visceral crisis (ABC-4 definition)**
  - **Survival benefit in comparison to sequential single-agent therapies with the same compounds not proven**

Therapeutic index evaluates overall efficacy, toxicity, and impact on quality of life

MBC HER2-negative/HR-positive: Cytotoxic Therapy after adjuvant Taxane and Anthracycline Treatment

	Oxford LoE	GR	AGO
▪ Capecitabine	2b	B	++
▪ Eribulin	1b	B	++
▪ Vinorelbine	2b	B	++
▪ (Peg)-liposomal Doxorubicin	2b	B	+
▪ Taxane re-challenge*	2b	B	+
▪ Anthracycline re-challenge*	3b	C	+
▪ Metronomic therapy (e.g. cyclophos. + MTX)	2b	B	+
▪ Gemcitabine + Cisplatin / Carboplatin	2b	B	+/-
▪ Gemcitabine + Capecitabine	2b	B	+/-
▪ Gemcitabine + Vinorelbine	1b	B	-

* At least one year disese-free after adjuvant treatment

MBC HER2-negative/HR-pos: Cytotoxic Therapy after Anthracycline Treatment*

	Oxford LoE	GR	AGO
▪ Paclitaxel q1w	1a	A	++
▪ Docetaxel q3w	1a	A	++
▪ Capecitabine	2b	B	++
▪ Nab-paclitaxel	2b	B	++
▪ Peg-liposomal doxorubicin	2b	B	+
▪ Eribulin	1b	B	+
▪ Vinorelbine	2b	B	+
▪ Docetaxel + Peg-liposomal doxorubicin	1b	B	+/-

* Independent whether anthracyclines were used in adjuvant or 1st line metastatic situation