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Neoadjuvant (Primary) Systemic Therapy

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Neoadjuvant Systemic Therapy

- **Versions 2002–2016:**
  Bauerfeind / Blohmer / Costa / Dall / Fersis / Friedrich / Göhring / Harbeck / Heinrich / Huober / Jackisch / Kaufmann / Liedtke / Loibl / Lux / von Minckwitz / Müller / Nitz / Schneeweiss / Schütz / Solomayer / Untch

- **Version 2017:**
  Loibl / Müller

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Subtype-specific General Systemic Strategies

	AGO
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 & escalated in case of high tumor burden	+
➢ Followed by endocrine therapy	++
HER2+	
➢ Trastuzumab (plus Pertuzumab neoadjuvant) plus	++
• Sequential A/T-based regimen with concurrent T + H	++
• Anthracycline-free, carboplatinum-containing regimen	+
• Anthracycline-free, taxane regimen for low tumor burden	+
• Dose dense & escalated in case of high tumor burden	+
TNBC	
➢ Conventionally dosed AT-based chemotherapy	++
➢ Dose dense & escalated	+
➢ Neoadjuvant platinum containing chemotherapy	+

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Neoadjuvant Systemic Chemotherapy Clinical Benefit

	Oxford / AGO LoE / GR		
➢ Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy (with same regimen and cycle number)	1a	A	
➢ Pathological complete response is associated with improved survival in particular subgroups (HR+/HER2neg/Grade3, HER2-pos and TNBC)	1b	A	
➢ Can achieve operability in primary inoperable tumors	1b	A	++
➢ Improved options for breast conserving surgery	1b	A	++
➢ Allows individualization of therapy according to mid-course treatment effect	1b	B	+*
➢ Allows individualization of post-neoadjuvant treatment	2b	B	+/-*

* Study participation recommended

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Neoadjuvant Systemic Chemotherapy Indications

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	Oxford / AGO LoE / GR		
➢ Inflammatory breast cancer	2b	B	++
➢ Inoperable breast cancer	1c	A	++
➢ Large operable breast cancer primarily requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation	1b	B	+
➢ If similar postoperative adjuvant chemotherapy is indicated	1b	A	+

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Neoadjuvant Systemic Chemotherapy Response Prediction I

Factor	CTS	LoE_{Ox2001}	GR	AGO
➢Young age	B	1a	A	+
➢cT1 / cT2 tumors o. N0 o. G3	B	1a	A	++
➢Negative ER and PgR status	B	1a	A	++
➢Triple negative breast cancer (TNBC)	B	1a	A	++
➢Positive HER2 status	B	1a	A	++
➢Non-lobular tumor type	B	1a	A	+
➢Early clinical response	B	1b	A	+

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Neoadjuvant Systemic Therapy Response Prediction II

Factor	LoE_{2009}	CTS	GR	AGO
➢Multigene signatures	III	C	B	+/-
➢Ki-67	I	B	A	+
➢Tumor infiltrating lymphocytes*	I	B	B	+
➢*PIK3CA* mutation	I	B	B	+/-
➢*gBRCA in TNBC*	II	B	B	+

**defined as dense lymphocytic infiltration of inner peritumoral stroma outside of the invasion front (>50% lymphocytes of stromal area).*

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Neoadjuvant Systemic Chemotherapy Recommended Regimens and Schedules

	Oxford / AGO LoE	GR	
➢ Standard protocols used in the adjuvant setting with a duration of at least 18 weeks	1a	A	++
➢ AC or EC → D q3w or P q1w	2b	A	++
➢ DAC	2b	B	++
➢ Taxane followed by anthracycline	1a	A	+
➢ Dose-dense regimen (e.g. E -P-CMF, E-P-C)	1b	B	+*
➢ Platinum in TNBC (irrespective of BRCA status)	2b	B	+
➢ Nab-Paclitaxel weekly instead of Paclitaxel weekly	1b	B	+/-

*Study participation recommended

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References

Potential Carboplatin Containing Regimens in the Neoadjuvant Setting

Author	Study	Regimen	pCR rate	3-yr EFS rates
Sikov WM, et al. JCO 2015 SABCS 2015	CALGB 40603 Phase II	Paclitaxel 80mg/m² qw x12 + Carboplatin AUC 6 q3w x4 – dd AC q2w x4	TNBC ± Cb: 54% vs 41% (ypT0/is ypN0)	TNBC ± Cb: 72% vs. 77% (HR 0.84 (95%CI 0.58-1.22)
von Minckwitz G, et al. Lancet Oncol 2014 SABCS 2015	Gepar Sixto Phase II	NPLD 20mg/m² qw x18 + Paclitaxel 80mg/m² qw x18 + Carboplatin AUC 1.5 qw x18 + Bev 15 mg/kg q3w x6	TNBC ± Cb: 53% vs. 37% (ypT0 ypN0)	TNBC ± Cb: 76% vs. 86% (HR 0.56 (95%CI 0.33-0.96))
Ando M, et al. BCRT 2014	Phase II	Paclitaxel 80mg/m² qw x12 + Carboplatin AUC 5 q3w x4 – FEC q3w x4	TNBC ± Cb: 61% vs. 26%	

Neoadjuvant Systemic Chemotherapy Recommended Methods of Monitoring of Response

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	Oxford / AGO LoE / GR		
➢ Breast ultrasound	2b	B	++
➢ Palpation	2b	B	++
➢ Mammography	2b	B	++
➢ MRI	2b	B	+
➢ PET(-CT)*	2b	B	+/-
➢ Clip tumor region	5	D	++
➢ Clip positive lymph node	3	C	+/-

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References

* Study participation recommended

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Neoadjuvant Targeted Therapy in HER2 Positive Tumors

	Oxford / AGO LoE	GR	
➢ Trastuzumab in combination with chemotherapy	1b	A	++
➢ Pertuzumab + Trastuzumab in combination with chemotherapy	2b	B	++
➢ Lapatinib in combination with chemotherapy	1a	B	-
➢ Lapatinib + Trastuzumab in combination with chemotherapy	1a	B	+/-
➢ Two anti-HER2 agents without chemotherapy	2b	B	+/-

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Neoadjuvant Targeted Therapy in HER2 Negative Tumors

Oxford / AGO
LoE / GR

Bevacizumab in combination with chemotherapy

➢ In hormone receptor positive BC	1b	B	-
➢ In TNBC	1b	B	+/-

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Neoadjuvant Systemic Therapy
Procedures in Case of Early Response

Oxford / AGO
LoE / GR

In case of early response following 6 to 12 weeks of neoadjuvant chemotherapy:

- **Complete all chemotherapy before surgery i.e. ≥ 18 weeks of treatment** — **1b A ++**
- **In case of response after 2 cycles of DAC in HR positive breast cancer consider 8 instead of 6 cycles of DAC** — **2b C +**

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Neoadjuvant Systemic Therapy
Procedures in Case of No Early Response

	Oxford / AGO LoE / GR		
In case of no change:			
➢ Completion of NST, followed by surgery	2b	C	++
➢ Continuation of NST with non cross-resistant regimen	2b	B	+
➢ AC or EC x 4 → D x 4 or Pw x 12	2b	B	+
➢ DAC x 2 → NX x 4	1b	B	+
In case of progressive disease:			
➢ Stop of NST and surgery or radiotherapy	4	D	++*
➢ Additional adjuvant chemotherapy with non cross-resistant regimen	4	D	+/-*

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* Study participation recommended

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Local / Regional Procedure after Neoadjuvant Therapy

	Oxford / AGO LoE	GR	
➢ Mark previous tumor region	5	D	++
➢ Surgery	2b	C	++
➢ Microscopically clear margins	5	D	++
➢ Tumor resection according to imaging result	3b	C	+

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Axillary Intervention Before or After NACT

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				Oxford / AGO LoE / GR		
SLNB before or after NACT in cN0						
SLNB before NACT **SLNB after NACT**				**2b** **2b**	**B** **B**	**+/-** **+**
Further surgical procedures depending on SLNB status						
cN-Status (before NST)	**pN-Status (before NST)**	**cN-Status (after NST)**		**Surgical Procedure (after NST)**		
cN0	**pN0(sn)**	**-**		**nihil**	**1a**	**A**	**+**
cN0	**pN+(sn)** (analog ACOSOG Z0011)	**ycN0**		**nihil** **Re-SLNB alone** **ALND**	**3** **2b** **3**	**B** **B** **B**	**+** **-** **+/-**
cN0	**pN+(sn)** (not analog ACOSOG Z0011)	**ycN0**		**Re-SLNB alone** **ALND** **Axilla XRT**	**2b** **2b** **2b**	**B** **B** **B**	**-** **+** **+**
cN0	**not done**	**ycN0**	**ypN0 (sn)**	**SLNB alone** **ALND**	**2b** **2b**	**B** **B**	**+** **+/-**
			ypN+ (sn)	**ALND**	**2b**	**B**	**+**
cN+	**pN+ (CNB/FNA)**	**ycN0** **ycN+**		**SLNB alone*** **ALND** **ALND**	**2b** **2b** **2b**	**B** **B** **B**	**+/-** **+** **++**

Neoadjuvant Systemic Therapy
Indications for Mastectomy

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	Oxford / AGO LoE	GR	
➢ **Positive margins after repeated excisions**	3b	C	++
➢ **Radiotherapy not feasible**	5	D	++
➢ **In case of clinical complete response**			
➢ **Inflammatory breast cancer**	2b	C	+
➢ **In case of pCR**			+/-
➢ **Multicentric lesions**	2b	C	+/-
➢ **cT4a-c breast cancer**	2b	B	+/-

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References

Neoadjuvant Systemic Therapy
Timing of Surgery and Radiotherapy

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	Oxford / AGO LoE / GR
➢ **Surgery**	**4 C ++**
➢ **After the nadir of the leucocyte count (2 to 4 weeks after last course of chemotherapy)**	
➢ **Radiotherapy within 2–3 weeks after surgery BCS**	**2b B ++**

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Adjuvant Systemic Therapy after Neoadjuvant Systemic Treatment

	Oxford / AGO LoE	GR	
➢ **Endocrine treatment in endocrine responsive disease**	1a	A	++
➢ **Complete trastuzumab treatment for 1 year in HER2-positive disease**	2b	B	++
➢ **Complete pertuzumab treatment for 1 year in HER2-positive disease**	3	C	-
➢ **If insufficient response in case of non-pCR (invasive residual tumor in the breast and / or axillary nodes) after adequate NACT (antracyclines, taxanes, 18 weeks)**			
➢ **Capecitabine adjuvant in TNBC**	2b[a]	B	+/-
➢ **Further chemotherapy**	3	C	-
➢ **Experimental therapies in clinical trials**	5	D	+

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Neoadjuvant Endocrine Therapy
in Patients with Endocrine-responsive Breast Cancer

	Oxford / AGO LoE	GR	
Postmenopausal patients:			
Who are inoperable and can / will not receive chemotherapy	2a	B	+
Optimizes the option for breast conserving therapy	1b	A	+
Aromatase inhibitors (for > 3 months)	1a[a]	B	+
Aromatase inhibitor + lapatinib (HER2+ BC)	2b	B	+/-
Premenopausal patients			
Who are inoperable and can / will not receive chemotherapy	5	C	+
Tamoxifen	2b	C	+
Aromatase inhibitors + LHRH	1b	C	+/-
Concurrent chemo-endocrine therapy	1b	A	-
Prognostic factors during/after NST: quantitative ER-expression, level of Ki-67, N status, T status	1b	B	+

Optimal duration of neoadjuvant endocrine therapy is unknown

No long term results for neoadjuvant endocrine therapy (vs. adjuvant endocrine therapy)

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Further Information

References

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Neoadjuvant (Primary) Systemic Therapy (2/20 and 3/20)

Further information and references:

Systematic review of published evidence:
PUBMED 1999-2016
ASCO 1999-2016
SABCS 1999-2016
ECCO/ESMO 1999-2016

Neoadjuvant Systemic Chemotherapy - Clinical Benefit (4/20)

Further information and references:

Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy (with same regimen and cycle number)
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Fisher B, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998: 16; 2672
2. Van der Hage JA, et al. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol 2001: 19; 4224
3. Rastogi P, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol 2008: 26; 778
4. Gianni L et al. Phase III trial evaluating the addition of paclitaxel to doxorubicin followed by cyclophosphamide, methotrexate, and fluorouracil, as adjuvant or primary systemic therapy: European Cooperative Trial in Operable Breast Cancer. J Clin Oncol 2009: 27; 2474

Pathological complete response is associated with improved survival in particular subgroups (HR+/HER2neg/Grade3, HER2-pos and TNBC)
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Gianni L et al. Phase III trial evaluating the addition of paclitaxel to doxorubicin followed by cyclophosphamide, methotrexate, and fluorouracil, as adjuvant or primary systemic therapy: European Cooperative Trial in Operable Breast Cancer. J Clin Oncol 2009: 27; 2474
2. Untch M, et al. Pathologic complete response after neoadjuvant chemotherapy plus trastuzumab predicts favorable survival in human epidermal growth factor receptor 2-overexpressing breast cancer: results from the TECHNO trial of the AGO and GBG study groups. J Clin Oncol 2011: 29; 3351

3. Von Minckwitz G, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012: 30; 1796
4. Cortazar P, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014: 384; 164
5. Berruti A, et al. Pathologic complete response as a potential surrogate for the clinical outcome in patients with breast cancer after neoadjuvant therapy: a meta-regression of 29 randomized prospective studies. J Clin Oncol 2014: 32; 3883
6. Loibl S, et al. Response and prognosis after neoadjuvant chemotherapy in 1,051 patients with infiltrating lobular breast carcinoma. Breast Cancer Res Treat 2014: 144; 153

Can achieve operability in primary inoperable tumors
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Makhoul I, et al. Neoadjuvant systemic treatment of breast cancer. J Surg Oncol 2011: 103; 348
2. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

Improved options for breast conserving surgery
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

Allows individualization of therapy according to mid-course treatment effect
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Von Minckwitz G, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012: 30; 1796

Allows individualization of post-neoadjuvant treatment
Abstimmungsergebnis der AGO-Empfehlungen: 2/7/20/1/0 (2016)

1. Symmans WF, et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. J Clin Oncol 2007: 25; 4414
2. Mittendorf EA, et al. Validation of a novel staging system for disease-specific survival in patients with breast cancer treated with neoadjuvant chemotherapy. J Clin Oncol 2011: 29; 1956
3. Von Minckwitz G, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012: 30; 1796
4. Leone JP, et al. Sixteen years follow-up results of a randomized phase II trial of neoadjuvant fluorouracil, doxorubicin, and cyclophosphamide (FAC) compared with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) in stage III breast cancer: GOCS experience.Breast Cancer Res Treat 2014: 143; 313
5. Berruti A, et al. Pathologic complete response as a potential surrogate for the clinical outcome in patients with breast cancer after neoadjuvant therapy: a meta-regression of 29 randomized prospective studies. J Clin Oncol 2014: 32, 3883
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Neoadjuvant Systemic Chemotherapy Indications (5/20)

Further information and references:

Inflammatory breast cancer
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol 2007: 18; 1927
2. Dawood S, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol 2011: 22; 515

Inoperable breast cancer
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol 2007: 18; 1927
2. Dawood S, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol 2011: 22; 515

Large operable breast cancer primarily requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol 2007: 18; 1927
2. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

If similar postoperative adjuvant chemotherapy is indicated
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Untch M, et al. Neoadjuvant chemotherapy: early response as a guide for further treatment: clinical, radiological, and biological. J Natl Cancer Inst Monogr 2011: 43; 138
2. Loibl S, et al. Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol 2012: 13 ; 887

Neoadjuvant Systemic Chemotherapy Response Prediction I (6/20)

Further information and references:

Young age
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Von Minckwitz G, et al. Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. Breast Cancer Res Treat 2011: 125; 145
2. Huober J, et al. Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. Breast Cancer Res Treat 2010: 124; 133
3. Loibl S, et al. Outcome after neoadjuvant chemotherapy in young breast cancer patients: a pooled analysis of individual patient data from eight prospectively randomized controlled trials.Breast Cancer Res Treat. 2015;152(2):377-87.

cT1 / cT2 tumors o. N0 o. G3
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Von Minckwitz G, et al. Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. Breast Cancer Res Treat 2011: 125; 145
2. Huober J, et al. Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. Breast Cancer Res Treat 2010: 124; 133
3. Loibl S, et al. Response and prognosis after neoadjuvant chemotherapy in 1,051 patients with infiltrating lobular breast carcinoma. Breast Cancer Res Treat 2014: 144; 153

Negative ER and PgR status
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Von Minckwitz G, et al. Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. Breast Cancer Res Treat 2011: 125; 145
2. Huober J, et al. Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. Breast Cancer Res Treat 2010: 124; 133
3. Loibl S, et al. Response and prognosis after neoadjuvant chemotherapy in 1,051 patients with infiltrating lobular breast carcinoma. Breast Cancer Res Treat 2014: 144; 153

Triple negative breast cancer (TNBC)
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Von Minckwitz G, et al. Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. Breast Cancer Res Treat 2011: 125; 145
2. Huober J, et al. Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. Breast Cancer Res Treat 2010: 124; 133
3. Loibl S, et al. Response and prognosis after neoadjuvant chemotherapy in 1,051 patients with infiltrating lobular breast carcinoma. Breast Cancer Res Treat 2014: 144; 153

Positive HER2 status
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Von Minckwitz G, et al. Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. Breast Cancer Res Treat 2011: 125; 145
2. Huober J, et al. Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. Breast Cancer Res Treat 2010: 124; 133
3. Loibl S, et al. Response and prognosis after neoadjuvant chemotherapy in 1,051 patients with infiltrating lobular breast carcinoma. Breast Cancer Res Treat 2014: 144; 153

Non-lobular tumor type
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Von Minckwitz G, et al. Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. Breast Cancer Res Treat 2011: 125; 145
2. Huober J, et al. Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. Breast Cancer Res Treat 2010: 124; 133
3. Loibl S, et al. Response and prognosis after neoadjuvant chemotherapy in 1,051 patients with infiltrating lobular breast carcinoma. Breast Cancer Res Treat 2014: 144; 153

Early clinical response

1. Von Minckwitz G, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012: 30; 1796

Neoadjuvant Systemic chemotherapy - Response Predictiong II (7/20)

Further information and references:

Multigene signature
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Denkert C, et al. Ki67 levels as predictive and prognostic parameters in pretherapeutic breast cancer core biopsies: a translational investigation in the neoadjuvant GeparTrio trial. Ann Oncol 2013: 24; 2786, JCOm 32:
2. Masuda H, et al. Differential response to neoadjuvant chemotherapy among 7 triple-negative breast cancer molecular subtypes. Clin Cancer Res 2013: 19; 5533-40
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4. Ali HR, Chlon L, Pharoah PD, Markowetz F, Caldas C Patterns of Immune Infiltration in Breast Cancer and Their Clinical Implications: A Gene-Expression-Based Retrospective Study. PLoS Med. 2016 Dec 13;13(12):e1002194. doi: 10.1371/journal.pmed.1002194

Ki-67
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Du Y, et al. The role of topoisomerase IIα in predicting sensitivity to anthracyclines in breast cancer patients: a meta-analysis of published literatures. Breast Cancer Res Treat 2011: 129; 839
2. Denkert C, et al. Ki67 levels as predictive and prognostic parameters in pretherapeutic breast cancer core biopsies: a translational investigation in the neoadjuvant GeparTrio trial. Ann Oncol 2013: 24; 2786
3. Klauschen F, et al. Standardized Ki67 diagnostics using automated scoring - clinical validation in the GeparTrio breast cancer study. Clin Cancer Res 2014

4. Ellis MJ, et al. Ki67 Proliferation Index as a Tool for Chemotherapy Decisions During and After Neoadjuvant Aromatase Inhibitor Treatment of Breast Cancer: Results From the American College of Surgeons Oncology Group Z1031 Trial (Alliance). J Clin Oncol. 2017 Jan 3:JCO2016694406. [Epub ahead of print]
5. Diaz-Botero S, et al. Different Prognostic Implications of Residual Disease After Neoadjuvant Treatment: Impact of Ki 67 and Site of Response. Ann Surg Oncol. 2016 Nov;23(12):3831-3837

Tumour infiltrating lymphocytes

Abstimmungsergebnis der AGO-Empfehlungen: 0/15/10/0/0 (2016)

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3. Miyshita M, et al. Tumor-infiltrating CD8+ and FOXP3+ lymphocytes in triple-negative breast cancer: its correlation with pathological complete response to neoadjuvant chemotherapy. Breast Cancer Res Treat 2014: 148; 525
4. Denkert C, et al . Tumor-Infiltrating Lymphocytes and Response to Neoadjuvant Chemotherapy With or Without Carboplatin in Human Epidermal Growth Factor Receptor 2–Positive and Triple-Negative Primary Breast Cancers. JCO; 32: 2014
5. Ingold Heppner B, et al. Tumor-Infiltrating Lymphocytes: A Predictive and Prognostic Biomarker in Neoadjuvant-Treated HER2-Positive Breast Cancer. Clin Cancer Res. 2016 Dec 1;22(23):5747-5754.

PIK3CA mutation

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Loibl S, et al. PIK3CA mutations are associated with lower rates of pathologic complete response to anti-human epidermal growth factor receptor 2 (her2) therapy in primary HER2-overexpressing breast cancer. J Clin Oncol 2014: 32; 3212
2. Sueta A, et al. An Integrative Analysis of PIK3CA Mutation, PTEN, and INPP4B Expression in Terms of Trastuzumab Efficacy in HER2-Positive Breast Cancer. PloS One 2014: 9; e116054

3. Loibl S, Integrated Analysis of PTEN and p4EBP1 Protein Expression as Predictors for pCR in HER2-Positive Breast Cancer. Clin Cancer Res. 2016 1;22(11):2675-83.
4. Loibl S, PIK3CA mutations are associated with reduced pathological complete response rates in primary HER2-positive breast cancer: pooled analysis of 967 patients from five prospective trials investigating lapatinib and trastuzumab. Ann Oncol. 2016;27(8):1519-25.

gBRCA mutation

Abstimmungsergebnis der AGO-Empfehlungen:

1. Spugnesi L, et al. Germline mutations in DNA repair genes may predict neoadjuvant therapy response in triple negative breast patients. Genes Chromosomes Cancer. 2016 Dec;55(12):915-924.

Neoadjuvant Systemic Chemotherapy Recommended Regimens and Schedules (8/20 and 9/20)

Further information and references:

Standard regimens used in the adjuvant setting with a duration of at least 18 weeks
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

AC or EC → D q3w or P q1w
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Rastogi P, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol 2008: 26; 778
2. von Minckwitz G, et al. Doxorubicin with cyclophosphamide followed by docetaxel every 21 days compared with doxorubicin and docetaxel every 14 days as preoperative treatment in operable breast cancer: the GEPARDUO study of the German Breast Group. J Clin Oncol 2005: 23; 2676

DAC
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Von Minckwitz G, et al. Neoadjuvant vinorelbine-capecitabine versus docetaxel-doxorubicin-cyclophosphamide in early nonresponsive breast cancer: phase III randomized GeparTrio trial. J Natl Cancer Inst 2008: 100; 542
2. Von Minckwitz G, et al. Intensified neoadjuvant chemotherapy in early-responding breast cancer: phase III randomized GeparTrio study. J Natl Cancer Inst 2008: 100; 552

Taxane followed by anthracycline sequence
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Bines J, et al. Anthracyclines and taxanes in the neo/adjuvant treatment of breast cancer: does the sequence matter? Ann Oncol 2014: 25; 1079
2. Earl HM, et al. Effects of the addition of gemcitabine, and paclitaxel-first sequencing, in neoadjuvant sequential epirubicin, cyclophosphamide, and paclitaxel for women with high-risk early breast cancer (Neo-tAnGo): an open-label, 2×2 factorial randomised phase 3 trial. Lancet Oncol 2014: 15; 201

Dose-dense regimen (e.g. E -P-CMF, E-P-C)
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Untch M. et al. Intensive dose-dense compared with conventionally scheduled preoperative chemotherapy for high-risk primary breast cancer. J Clin Oncol 2009: 27; 2938
2. Untch M, et al. PREPARE trial: a randomized phase III trial comparing preoperative, dose-dense, dose-intensified chemotherapy with epirubicin, paclitaxel and CMF versus a standard-dosed epirubicin/cyclophosphamide followed by paclitaxel ± darbepoetin alfa in primary breast cancer--results at the time of surgery. Ann Oncol 2011: 22; 1988
3. Untch M, et al. PREPARE trial: a randomized phase III trial comparing preoperative, dose-dense, dose-intensified chemotherapy with epirubicin, paclitaxel, and CMF versus a standard-dosed epirubicin-cyclophosphamide followed by paclitaxel with or without darbepoetin alfa in primary breast cancer--outcome on prognosis. Ann Oncol 2011: 22; 1999

Platinum in TNBC (irrespective of BRCA status)
Abstimmungsergebnis der AGO-Empfehlungen: XXX

1. Alba E, et al. A randomized phase II trial of platinum salts in basal-like breast cancer patients in the neoadjuvant setting. Results from the GEICAM/2006-03, multicenter study. Breast Cancer Res Treat 2012: 136; 487
2. Von Minckwitz G , et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. Lancet Oncol 2014: 15; 747

3. Ando M, et al. Randomized phase II study of weekly paclitaxel with and without carboplatin followed by cyclophosphamide/epirubicin/5-fluorouracil as neoadjuvant chemotherapy for stage II/IIIA breast cancer without HER2 overexpression. Breast Cancer Res Treat 2014: 145; 401
4. Petrelli F, et al. The value of platinum agents as neoadjuvant chemotherapy in triple-negative breast cancers: a systematic review and meta-analysis. Breast Cancer Res Treat 2014: 144; 223
5. Sikov WM, et al. Impact of the Addition of Carboplatin and/or Bevacizumab to Neoadjuvant Once-per-Week Paclitaxel Followed by Dose-Dense Doxorubicin and Cyclophosphamide on Pathologic Complete Response Rates in Stage II to III Triple-Negative Breast Cancer: CALGB 40603 (Alliance). J Clin Oncol 2015: 33; 13
6. Byrski T, et al. Pathologic complete response to neoadjuvant cisplatin in BRCA1-positive breast cancer patients. Breast Cancer Res Treat 2014: 147; 401
7. Von Minckwitz et al. ASCO 2014 (abs 1005)
8. Von Minckwitz G, et al "Early survival analysis of the randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple-negative and HER2-positive early breast cancer (GeparSixto)" SABCS 2015; Abstract S2-04.
9. Sikov WM, Berry DA, Perou CM, et al: Impact of the Addition of Carboplatin and/or Bevacizumab to Neoadjuvant Once-per-Week Paclitaxel Followed by Dose-Dense Doxorubicin and Cyclophosphamide on Pathologic Complete Response Rates in Stage II to III Triple-Negative Breast Cancer: CALGB 40603 (Alliance). J Clin Oncol, 2014

<u>Nab-Paclitaxel weekly instead of Paclitaxel weekly</u>
Abstimmungsergebnis der AGO-Empfehlungen

1. M Untch et al. Nab-paclitaxel versus solvent-based paclitaxel in neoadjuvant chemotherapy for early breast cancer (GeparSepto—GBG 69): a randomised, phase 3 trial. *Lancet Oncol* 2016, Published Online, February 8, 2016. http://dx.doi.org/10.1016/ S1470-2045(15)00542-2
2. Gianni L, et al. ETNA ASCO 2016
3. Futamura M, et al.Preoperative neoadjuvant chemotherapy using nanoparticle albumin-bound paclitaxel followed by epirubicin and cyclophosphamide for operable breast cancer: a multicenter phase II trial.Breast Cancer. 2017 Jan 3. doi:
4. Zong Y, Wu J, Shen K Nanoparticle albumin-bound paclitaxel as neoadjuvant chemotherapy of breast cancer: a systematic review and meta-analysis. Oncotarget. 2017 Jan 3.

Neoadjuvant Systemic Chemotherapy Recommended Methods of Monitoring of Response (10/20)

Further information and references:

1. Rauch GM, et al. Multimodality Imaging for Evaluating Response to Neoadjuvant Chemotherapy in Breast Cancer. AJR Am J Roentgenol. 2016 Nov 3:1-10

Breast ultrasound
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508
2. Von Minckwitz G, et al. Neoadjuvant vinorelbine-capecitabine versus docetaxel-doxorubicin-cyclophosphamide in early nonresponsive breast cancer: phase III randomized GeparTrio trial. J Natl Cancer Inst 2008: 100; 542
3. Von Minckwitz G, et al. Intensified neoadjuvant chemotherapy in early-responding breast cancer: phase III randomized GeparTrio study. J Natl Cancer Inst 2008: 100; 552
4. Schwentner L,et al. Using ultrasound and palpation for predicting axillary lymph node status following neoadjuvant chemotherapy - Results from the multi-center SENTINA trial. Breast. 2017 Feb;31:202-207.

Palpation
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

Mammography
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

MRI

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Javid S, et al. Can breast MRI predict axillary lymph node metastasis in women undergoing neoadjuvant chemotherapy. Ann Surg Oncol 2010: 17; 1841
2. Morrow M, et al. MRI for breast cancer screening, diagnosis, and treatment. Lancet 2011: 378; 1804
3. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508
4. Bolan PJ, et al. MR spectroscopy of breast cancer for assessing early treatment response: Results from the ACRIN 6657 MRS trial. J Magn Reson Imaging. 2016 Dec 16. doi: 10.1002/jmri.25560. [Epub ahead of print]

PET(-CT)

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Dose-Schwarz J, et al. Assessment of residual tumour by FDG-PET: conventional imaging and clinical examination following primary chemotherapy of large and locally advanced breast cancer. Br J Cancer 2010: 102; 35
2. Coudert B, et al. Use of [(18)F]-FDG PET to predict response to neoadjuvant trastuzumab and docetaxel in patients with HER2-positive breast cancer, and addition of bevacizumab to neoadjuvant trastuzumab and docetaxel in [(18)F]-FDG PET-predicted non-responders (AVATAXHER): an open-label, randomised phase 2 trial. Lancet Oncol 2014: 15; 1493
3. Groheux D,et al. ¹⁸FDG-PET/CT for predicting the outcome in ER+/HER2- breast cancer patients: comparison of clinicopathological parameters and PET image-derived indices including tumor texture analysis. Breast Cancer Res. 2017 Jan 5;19(1):3

Clip tumour region

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Caudle AS, Yang WT, Krishnamurthy S, Mittendorf EA, Black DM, Gilcrease MZ, Bedrosian I, Hobbs BP, DeSnyder SM, Hwang RF, Adrada BE, Shaitelman SF, Chavez-MacGregor M, Smith BD, Candelaria RP, Babiera GV, Dogan BE, Santiago L, Hunt KK, Kuerer HM.Improved Axillary Evaluation Following Neoadjuvant Therapy for Patients With Node-Positive Breast Cancer Using Selective Evaluation of Clipped Nodes: Implementation of Targeted Axillary Dissection. J Clin Oncol. 2016;34(10):1072-8.

Neoadjuvant Targeted Therapy in HER2 Positive Tumors (11/20)

Further information and references:

Trastuzumab in combination with chemotherapy
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Buzdar AU, et al. Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: an update of the initial randomized study population and data of additional patients treated with the same regimen. Clin Cancer Res 2007: 13; 228
2. Gianni L, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet 2010: 375; 377
3. Untch M, et al. Neoadjuvant treatment with trastuzumab in HER2-positive breast cancer: results from the GeparQuattro study. J Clin Oncol 2010: 28; 2024
4. Pierga JY, et al. A multicenter randomized phase II study of sequential epirubicin/cyclophosphamide followed by docetaxel with or without celecoxib or trastuzumab according to HER2 status, as primary chemotherapy for localized invasive breast cancer patients. Breast Cancer Res Treat 2010: 122; 429-437
5. Untch M, et al. Pathologic complete response after neoadjuvant chemotherapy plus trastuzumab predicts favorable survival in human epidermal growth factor receptor 2-overexpressing breast cancer: results from the TECHNO trial of the AGO and GBG study groups. J Clin Oncol 2011: 29; 3351
6. Von Minckwitz G, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012: 30; 1796
7. Cortazar P, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014: 384; 164
8. Gianni L, et al. Neoadjuvant and adjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer (NOAH): follow-up of a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet Oncol 2014: 15; 640

9. De Azambuja E, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): survival outcomes of a randomised, open-label, multicentre, phase 3 trial and their association with pathological complete response. Lancet Oncol 2014: 15; 1137
10. Jackisch C, Hegg R, Stroyakovskiy D, Ahn JS, Melichar B, Chen SC, Kim SB, Lichinitser M, Starosławska E, Kunz G, Falcon S, Chen ST, Crepelle-Fléchais A, Heinzmann D, Shing M, Pivot X.HannahHannaH phase III randomised study: Association of total pathological complete response with event-free survival in HER2-positive early breast cancer treated with neoadjuvant-adjuvant trastuzumab after 2 years of treatment-free follow-up. Eur J Cancer. 2016 Jul;62:62-

Lapatinib in combination with chemotherapy
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Untch M et al. Lapatinib versus trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy (GeparQuinto, GBG 44): a randomised phase 3 trial. Lancet Oncol 2012: 13; 135 - 144
2. Robidoux A, et al. Lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer (NSABP protocol B-41): an open-label, randomised phase 3 trial. Lancet Oncol 2013: 14; 1183-1192
3. Alba E, et al. Trastuzumab or lapatinib with standard chemotherapy for HER2-positive breast cancer: results from the GEICAM/2006-14 trial. Br J Cancer 2014: 110; 1139
4. Bonnefoi H, et al. Neoadjuvant treatment with docetaxel plus lapatinib, trastuzumab, or both followed by an anthracycline-based chemotherapy in HER2-positive breast cancer: results of the randomised phase II EORTC 10054 study. Ann Oncol 2014 [Epub ahead of print]
5. Nagayama A, et al. Comparative effectiveness of neoadjuvant therapy for HER2-positive breast cancer: a network meta-analysis. J Natl Cancer Inst 2014; 106(9): [EpuB ahead of print]

Lapatinib + Trastuzumab in combination with chemotherapy
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Robidoux A, et al. Lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer (NSABP protocol B-41): an open-label, randomised phase 3 trial. Lancet Oncol 2013: 14; 1183-1192

2. De Azambuja E, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): survival outcomes of a randomised, open-label, multicentre, phase 3 trial and their association with pathological complete response. Lancet Oncol 2014: 15; 1137
3. Bonnefoi H, et al. Neoadjuvant treatment with docetaxel plus lapatinib, trastuzumab, or both followed by an anthracycline-based chemotherapy in HER2-positive breast cancer: results of the randomised phase II EORTC 10054 study. Ann Oncol 2014 [Epub ahead of print]
4. Nagayama A, et al. Comparative effectiveness of neoadjuvant therapy for HER2-positive breast cancer: a network meta-analysis. J Natl Cancer Inst 2014; 106(9): [EpuB ahead of print]

Pertuzumab + Trastuzumab in combination with chemotherapy
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Gianni L, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 2012: 13; 25-32
2. Schneeweiss A, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Annals Oncol 2013: 24; 2278-84
3. Nagayama A, et al. Comparative effectiveness of neoadjuvant therapy for HER2-positive breast cancer: a network meta-analysis. J Natl Cancer Inst 2014; 106(9): in print
4. Gianni L et al. Five-year analysis of the phase II NeoSphere trial evaluating four cycles of neoadjuvant docetaxel (D) and/or trastuzumab (T) and/or pertuzumab (P). J Clin Oncol 33, 2015 (suppl; abstr 505)
5. Loibl S, et al. Dual HER2-blockade with pertuzumab and trastuzumab in HER2-positive early breast cancer: a subanalysis of data from the randomized phase III GeparSepto trial. Ann Oncol. 2016 Nov 9. pii: mdw610. [Epub ahead of print]

Two anti-HER2 agents without chemotherapy
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Gianni L, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 2012: 13; 25-32
2. Rimawi M, et al. Multicenter phase II study of neoadjuvant lapatinib and trastuzumab with hormonal therapy and without chemotherapy in patients with human epidermal growth factor receptor 2-overexpressing breast cancer: TBCRC 006. J Clin Oncol 2013: 31; 1726
3. Ismael G, et al. Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I-III breast cancer (HannaH study): a phase 3, open-label, multicentre, randomised trial. Lancet Oncol 2012: 13; 869

Anti-HER2 agent in combination with endocrine treatment
Abstimmungsergebnis der AGO-Empfehlungen: 3+, 16+/-, 6-

1. Rimawi MF, et al. SABCS 2014 (S6-02)
2. Guarneri V, et al. Double-blind, placebo-controlled, multicenter, randomized, phase IIb neoadjuvant study of letrozole-lapatinib in postmenopausal hormone receptor-positive, human epidermal growth factor receptor 2-negative, operable breast cancer. J Clin Oncol 2014: 32; 1050

Neoadjuvant Targeted Therapy in HER2 Negative Tumors (12/20)

Further information and references:

Bevacizumab in combination with chemotherapy in hormone receptor positive
Abstimmungsergebnis der AGO-Empfehlungen: 13+/-, 17-

1. Von Minckwitz G, et al. Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. N Engl J Med 2012: 366; 299
2. Bear HD, et al. Bevacizumab added to neoadjuvant chemotherapy for breast cancer. N Engl J Med 2012: 366; 310
3. Von Minckwitz G, et al. Survival after neoadjuvant chemotherapy with or without bevacizumab or everolimus for HER2-negative primary breast cancer (GBG 44-GeparQuinto)†. Ann Oncol 2014: 25; 2363
4. Smith JW, 2nd, Buyse ME, Rastogi P, Geyer CE, Jr., Jacobs SA, Patocskai EJ, et al. Epirubicin With Cyclophosphamide Followed by Docetaxel With Trastuzumab and Bevacizumab as Neoadjuvant Therapy for HER2-Positive Locally Advanced Breast Cancer or as Adjuvant Therapy for HER2-Positive Pathologic Stage III Breast Cancer: A Phase II Trial of the NSABP Foundation Research Group, FB-5. Clin Breast Cancer 2016.

Bevacizumab in combination with chemotherapy in TNBC
Abstimmungsergebnis der AGO-Empfehlungen: 2+/-, 13+/-, 9-

1. Von Minckwitz G, et al. Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. N Engl J Med 2012: 366; 299
2. Bear HD, et al. Bevacizumab added to neoadjuvant chemotherapy for breast cancer. N Engl J Med 2012: 366; 310
3. Gerber B, et al. Neoadjuvant bevacizumab and anthracycline-taxane-based chemotherapy in 678 triple-negative primary breast cancers; results from the geparquinto study (GBG 44). Annals Oncol 2013: 24; 2978
4. Von Minckwitz G, et al. Survival after neoadjuvant chemotherapy with or without bevacizumab or everolimus for HER2-negative primary breast cancer (GBG 44-GeparQuinto)†. Ann Oncol 2014: 25; 2363

5. Sikov WM, et al. Impact of the Addition of Carboplatin and/or Bevacizumab to Neoadjuvant Once-per-Week Paclitaxel Followed by Dose-Dense Doxorubicin and Cyclophosphamide on Pathologic Complete Response Rates in Stage II to III Triple-Negative Breast Cancer: CALGB 40603 (Alliance). J Clin Oncol 2015: 33; 13
6. Ma X, et al. Bevacizumab Addition in Neoadjuvant Treatment Increases the Pathological Complete Response Rates in Patients with HER-2 Negative Breast Cancer Especially Triple Negative Breast Cancer: A Meta-Analysis. PLoS
7. Nahleh ZA, Barlow WE, Hayes DF, Schott AF, Gralow JR, Sikov WM, et al. SWOG S0800 (NCI CDR0000636131): addition of bevacizumab to neoadjuvant nab-paclitaxel with dose-dense doxorubicin and cyclophosphamide improves pathologic complete response (pCR) rates in inflammatory or locally advanced breast cancer. Breast Cancer Res Treat 2016;158(3):485-95.One 2016;11(8):e0160148.
8. Bertucci F, Fekih M, Autret A, Petit T, Dalenc F, Levy C, et al. Bevacizumab plus neoadjuvant chemotherapy in patients with HER2-negative inflammatory breast cancer (BEVERLY-1): a multicentre, single-arm, phase 2 study. Lancet Oncol 2016;17(5):600-11.

Neoadjuvant Systemic Therapy Procedures in Case of Early Response (13/20)

Further information and references:

In case of early response following 6 to 12 weeks of neoadjuvant chemotherapy:

Complete all chemotherapy before surgery i.e. ≥ 18 weeks of treatment
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Von Minckwitz G, et al. Dose-dense doxorubicin, docetaxel, and granulocyte colony-stimulating factor support with or without tamoxifen as preoperative therapy in patients with operable carcinoma of the breast: a randomized, controlled, open phase IIb study. J Clin Oncol 2001: 19; 3506
2. Von Minckwitz G, et al. Neoadjuvant vinorelbine-capecitabine versus docetaxel-doxorubicin-cyclophosphamide in early nonresponsive breast cancer: phase III randomized GeparTrio trial. J Natl Cancer Inst 2008: 100; 542
3. Von Minckwitz G, et al. Intensified neoadjuvant chemotherapy in early-responding breast cancer: phase III randomized GeparTrio study. J Natl Cancer Inst 2008: 100; 552
4. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

In case of response after 2 cycles of DAC in HR positive breast cancer consider 8 instead of 6 cycles of DAC
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Von Minckwitz G, et al. Response-guided neoadjuvant chemotherapy for breast cancer. J Clin Oncol. 2013: 31; 3623-30

Neoadjuvant Systemic Therapy Procedures in Case of No Early Response (14/20)

Further information and references:

In case of no change:
Completion of NST, followed by surgery
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508
2. Smith IC, et al. Neoadjuvant chemotherapy in breast cancer: significantly enhanced response with docetaxel. J Clin Oncol 2002: 20; 1456
3. Von Minckwitz G, et al. Neoadjuvant vinorelbine-capecitabine versus docetaxel-doxorubicin-cyclophosphamide in early nonresponsive breast cancer: phase III randomized GeparTrio trial. J Natl Cancer Inst 2008: 100; 542
4. Von Minckwitz G, et al. Response-guided neoadjuvant chemotherapy for breast cancer. J Clin Oncol. 2013: 31; 3623-30

Continuation of NST with non-cross-resistant regimen
AC or EC x 4 → D x 4 or Pw x 12
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Bear HD, et al. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 2003: 21; 4165
2. Bear HD, et al. Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer:National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 2006: 24; 2019

DAC x 2 → NX x 4
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Von Minckwitz G, et al. Response-guided neoadjuvant chemotherapy for breast cancer. J Clin Oncol. 2013: 31; 3623-30

In case of progressive disease:
Stop of NST and immediate surgery or radiotherapy
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

Additional adjuvant chemotherapy with non-cross-resistant regimen
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Mittendorf EA, et al. Validation of a novel staging system for disease-specific survival in patients with breast cancer treated with neoadjuvant chemotherapy. J Clin Oncol 29, 1956, 2011
2. Lee S-J et al. A phase III trial of adjuvant capecitabine in breast cancer patients with HER2-negative pathologic residual invasive disease after neoadjuvant chemotherapy (CREATE-X/JBCRG-04). San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, TX. Abstract: S1-07
3. Colleoni M, Gray KP, Gelber S, Lang I, Thurlimann B, Gianni L, et al. Low-Dose Oral Cyclophosphamide and Methotrexate Maintenance for Hormone Receptor-Negative Early Breast Cancer: International Breast Cancer Study Group Trial 22-00. J Clin Oncol 2016;34(28):3400-8.

Local/Regional Procedure after Neoadjuvant Systemic Therapy - Surgical Procedures (15/20 and 16/20)

Further information and references:

Mark previous tumor region
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol 2007: 18; 1927
2. Kaufmann M, et al. Locoregional treatment of primary breast cancer: consensus recommendations from an International Expert Panel. Cancer 2010: 116; 1184
3. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

Surgery
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol 2007: 18; 1927
2. Kaufmann M, et al. Locoregional treatment of primary breast cancer: consensus recommendations from an International Expert Panel. Cancer 2010: 116; 1184
3. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

Microscopically clear margins
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol 2007: 18; 1927

2. Kaufmann M, et al. Locoregional treatment of primary breast cancer: consensus recommendations from an International Expert Panel. Cancer 2010: 116; 1184
3. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

Tumor resection according to imaging result
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol 2007: 18; 1927
2. Kaufmann M, et al. Locoregional treatment of primary breast cancer: consensus recommendations from an International Expert Panel. Cancer 2010: 116; 1184
3. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer.. Ann Surg Oncol 2012: 19; 1508

Sentinel node biopsy (see chapter "Surgery")
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kühn T, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol 2013
2. Boughey JC et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. JAMA 2013: 310; 1455-1461
3. Classe JM, Bordes V, Campion L, Mignotte H, Dravet F, Leveque J, Sagan C, Dupre PF, Body G, Giard S. Sentinel lymph node biopsy after neoadjuvant chemotherapy for advanced breast cancer: results of Ganglion. J Clin Oncol. 2009 Feb 10;27(5):726-32
4. El Hage Chehade H, Headon H, El Tokhy O, Heeney J, Kasem A, Mokbel K.Is sentinel lymph node biopsy a viable alternative to complete axillary dissection following neoadjuvant chemotherapy in women with node-positive breast cancer at diagnosis? An updated meta-analysis involving 3,398 patients. Am J Surg. 2016 Nov;212(5):969-981.

5. Mamtani A, et al. How Often Does Neoadjuvant Chemotherapy Avoid Axillary Dissection in Patients With Histologically Confirmed Nodal Metastases? Results of a Prospective Study. Ann Surg Oncol. 2016 Oct;23(11):3467-74.

Neoadjuvant Systemic Therapy - Indications for Mastectomy (17/20)

Further information and references:

Positive margins after repeated excisions
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508
2. Dawood S, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol 2011: 22; 515

Radiotherapy not feasible
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

In case of clinical complete response:
Inflammatory breast cancer in case of pCR
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Dawood S, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol 2011: 22; 515
2. Brzezinska M, Williams LJ, Thomas J, Michael Dixon J. Outcomes of patients with inflammatory breast cancer treated by breast-conserving surgery. Breast Cancer Res Treat 2016;160(3):387-91.

Multicentric lesions
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Ataseven B, et al. Impact of Multifocal or Multicentric Disease on Surgery and Locoregional, Distant and Overall Survival of 6,134 Breast Cancer Patients Treated With Neoadjuvant Chemotherapy. Ann Surg Oncol 2014 [Epub ahead of print]

cT4a-c breast cancer
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Ataseven B, et al. Impact of Multifocal or Multicentric Disease on Surgery and Locoregional, Distant and Overall Survival of 6,134 Breast Cancer Patients Treated With Neoadjuvant Chemotherapy. Ann Surg Oncol 2014

Neoadjuvant Systemic - Therapy Timing of Surgery and Radiotherapy (18/20)

Further information and references:

Surgery after the nadir of the leucocyte count (2 to 4 weeks after last course of chemotherapy)
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Ring A, et al. Is surgery necessary after complete clinical remission following neoadjuvant chemotherapy for early breast cancer? J Clin Oncol 2003: 21; 4540
2. Omarini C, Guaitoli G, Noventa S, Andreotti A, Gambini A, Palma E, et al. Impact of time to surgery after neoadjuvant chemotherapy in operable breast cancer patients. Eur J Surg Oncol 2016.
3. Sanford RA, Lei X, Barcenas CH, Mittendorf EA, Caudle AS, Valero V, et al. Impact of Time from Completion of Neoadjuvant Chemotherapy to Surgery on Survival Outcomes in Breast Cancer Patients. Ann Surg Oncol 2016;23(5):1515-21.

Radiotherapy after surgery 2–3 weeks after surgery BCS
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Ring A, et al. Is surgery necessary after complete clinical remission following neoadjuvant chemotherapy for early breast cancer? J Clin Oncol 2003: 21; 4540
2. Daveau C, et al. Is radiotherapy an option for early breast cancers with complete clinical response after neoadjuvant chemotherapy? Int J Radiat Oncol Biol Phys 2011: 79; 1452-145

Adjuvant Systemic Therapy after Neoadjuvant Systemic Treatment (19/20)

Further information:

Endocrine treatment in endocrine responsive disease
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

Complete trastuzumab treatment for 1 year in HER2-positive disease
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

Complete pertuzumab treatment for 1 year in HER2-positive disease
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

If insufficient response in case of non pcr (invasive residual tumor in the breast and / or axillary nodes) after adequate nact (antracyclines, taxanes, 18 weeks)

1. von Minckwitz G, Rezai M, Tesch H, Huober J, Gerber B, Zahm DM, Hilfrich J, Costa SD, Dubsky P, Blohmer JU, Denkert C, Hanusch C, Jackisch C, Kümmel S, Fasching PA, Schneeweiss A, Paepke S, Untch M, Burchardi N, Mehta K, Loibl S; German Breast Group and Austrian Breast and Colon Cancer Study Group Investigators.Zoledronate for patients with invasive residual disease after anthracyclines-taxane-based chemotherapy for early breast cancer - The Phase III NeoAdjuvant Trial Add-oN (NaTaN) study (GBG 36/ABCSG 29). Eur J Cancer. 2016 ;64:12-21.

Capecitabine adjuvant
Abstimmungsergebnis der AGO-Empfehlungen: 0/2/27/4/0 (2016)

1. Lee S-J et al. A phase III trial of adjuvant capecitabine in breast cancer patients with HER2-negative pathologic residual invasive disease after neoadjuvant chemotherapy (CREATE-X/JBCRG-04). San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, TX. Abstract: S1-07

Further chemotherapy

1. Colleoni M, Gray KP, Gelber S, Lang I, Thurlimann B, Gianni L, et al. Low-Dose Oral Cyclophosphamide and Methotrexate Maintenance for Hormone Receptor-Negative Early Breast Cancer: International Breast Cancer Study Group Trial 22-00. J Clin Oncol 2016;34(28):3400-8.
2. Tanaka S, et al. A Phase II Study of Adjuvant Chemotherapy of Tegafur-Uracil for Patients with Breast Cancer with HER2-negative Pathologic Residual Invasive Disease After Neoadjuvant Chemotherapy. Anticancer Res. 2016 Dec;36(12):6505-6509

Experimental therapies in clinical trials

Otherwise no references

Neoadjuvant Endocrine Therapy (20/20)

Further information and references:

Postmenopausal patients:
Who are inoperable and can / will not receive chemotherapy
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Semiglazov VF, et al. Phase 2 randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor-positive breast cancer. Cancer 2007: 110; 244

Optimizes the option for breast conserving therapy
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Eiermann W, et al. Preoperative treatment of postmenopausal breast cancer patients with letrozole: A randomized double-blind multicenter study. Ann Oncol 2001: 12; 1527
2. Smith I, et al. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. J Clin Oncol 2005: 23; 5108
3. Semiglazov VF, et al. Phase 2 randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor-positive breast cancer. Cancer 2007: 110; 244
4. Mathew J, et al. Neoadjuvant endocrine treatment in primary breast cancer - review of literature. Breast 2009: 18; 339
5. Ellis MJ, et al. Randomized phase II neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal women with estrogen receptor-rich stage 2 to 3 breast cancer: clinical and biomarker outcomes and predictive value of the baseline PAM50-based intrinsic subtype--ACOSOG Z1031. J Clin Oncol 2011: 29; 2342

Aromatase inhibitors (for > 3 months)
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Eiermann W, et al. Preoperative treatment of postmenopausal breast cancer patients with letrozole: A randomized double-blind multicenter study. Ann Oncol 2001: 12; 1527
2. Smith I, et al. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. J Clin Oncol 2005: 23; 5108
3. Mathew J, et al. Neoadjuvant endocrine treatment in primary breast cancer - review of literature. Breast 2009: 18; 339
4. Ellis MJ, et al. Randomized phase II neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal women with estrogen receptor-rich stage 2 to 3 breast cancer: clinical and biomarker outcomes and predictive value of the baseline PAM50-based intrinsic subtype--ACOSOG Z1031. J Clin Oncol 2011: 29; 2342
5. Spring LM, Gupta A, Reynolds KL, Gadd MA, Ellisen LW, Isakoff SJ, et al. Neoadjuvant Endocrine Therapy for Estrogen Receptor-Positive Breast Cancer: A Systematic Review and Meta-analysis. JAMA oncology 2016;2(11):1477-86.

AI and fulvestrant

1. Lerebours F, et al. Randomized phase 2 neoadjuvant trial evaluating anastrozole and fulvestrant efficacy for postmenopausal, estrogen receptor-positive, human epidermal growth factor receptor 2-negative breast cancer patients: Results of the UNICANCER CARMINA 02 French trial (UCBG 0609). Cancer. 2016 Oct;122(19):3032-40.

Aromatase inhibitor + lapatinib (HER2+ BC)
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

Premenopausal patients:
Who are inoperable and can / will not receive chemotherapy
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

Tamoxifen
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

Aromatase inhibitors + LHRH
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

Concurrent chemo-endocrine therapy
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Mathew J, et al. Neoadjuvant endocrine treatment in primary breast cancer - review of literature. Breast 2009: 18; 339Von Minckwitz G, et al. Dose-dense doxorubicin, docetaxel, and granulocyte colony-stimulating factor support with or without tamoxifen as preoperative therapy in patients with operable carcinoma of the breast: a randomized, controlled, open phase IIb study. J Clin Oncol 2001: 15; 3506
2. Fontein DB, et al. Efficacy of six month neoadjuvant endocrine therapy in postmenopausal, hormone receptor-positive breast cancer patients--a phase II trial. Eur J Cancer 2014: 50; 2190
3. Rimawi M, al. e. A phase III trial evaluating pCR in patients with HR+, HER2-positive breast cancer treated with neoadjuvant docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) +/- estrogen deprivation: NRG oncology/NSABP B-52. San Antonio Breast Cancer Symposium 2016:Abstract S3-06.
4. Spring LM, et al. Neoadjuvant Endocrine Therapy for Estrogen Receptor-Positive Breast Cancer: A Systematic Review and Meta-analysis. JAMA Oncol. 2016 Nov 1;2(11):1477-1486.

Prognostic factors during/after NST: quantitative ER-expression, level of Ki-67, N status, T status
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Ellis MJ, et al. Outcome prediction for estrogen receptor-positive breast cancer based on postneoadjuvant endocrine therapy tumor characteristics. J Natl Cancer Inst 2008: 100; 1380