Guidelines Breast
Version 2017.1

Adjuvant Cytotoxic and Targeted Therapy

Adjuvant Cytotoxic and Targeted Therapy

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Version 2017.1

- **Version 2002:**
  Möbus / Nitz
- **Versions 2003–2016:**
  Harbeck / Jackisch / Janni / Loibl / Lux / von Minckwitz / Möbus / Müller / Nitz / Schneeweiss / Simon / Schütz / Solomeyer / Stickeler / Thomssen / Untch
- **Version 2017:**
  Dall / Stickeler

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Further Information

References

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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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Adjuvant Chemotherapy without Trastuzumab: Overview

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	Oxford LoE	AGO GR	
➢ **Anthracycline / taxane based chemotherapy**	1a	A	++
➢ **If anthracyclines cannot be given**			
➢ **Docetaxel plus cyclophosphamide**	1b	B	+
➢ **Paclitaxel mono weekly**	1b	B	+/-
➢ **CMF**	1a	A	+/-
➢ **Dose-dense in case of high tumor burden**	1a	A	++
➢ **Low dose maintenance chemo**	1b	B	-

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Further Information

References

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

Recommended Regimens for Adjuvant Chemotherapy

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Further Information

References

		Oxford / AGO LoE	GR	
Anthracycline / taxane based regimen				
➢ *EC → P_w	$E_{90}C$ q3w x 4 → P_{80} qw1 x 12	1b	B	++
➢ AC → P_w	$A_{60}C$ q3w x 4 → P_{80} qw1 x 12	1b	A	++
➢ AC → D	$A_{60}C$ q3w x 4 → D_{100} qw3 x 4	1b	A	++
➢ *EC → D	$E_{90}C$ q3w x 4 → D_{100} qw3 x 4	1b	B	++
➢ DAC	$D_{75}A_{50}C$ q3w x 6	1b	A	++
Anthracycline-free regimen				
➢ DC	D_{75} C_{600} x4	1b	B	+
➢ Pac mono	P_{80} q1w x 12	1b	B	+/-
➢ CMF		1a	A	+/-

*** Extrapolated from doxorubicin trials**

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Dose-dense and / or Dose-escalated Adjuvant Chemotherapy in Case of High Tumor Burden

	Oxford LoE	/ GR	AGO
Dose-dense regimen			
➢ *EC q3w x 4 → Pac q1w x 12	1b	B	++
➢ AC q3w x 4 → Pac q1w x 12	1b	A	++
➢ AC q2w x 4 → Pac q2w x 4	1b	B	+
➢ EC q2w x 4 → Pac q2w x 4	1b	A	+
➢ EC q2w x 4 → Pac q1w x 12	1b	B	+
Dose-dense and dose-escalated regimen (N ≥ 4+)			
➢ E-Pac-C q2w	1b	A	++

* Extrapolated from doxorubicin trials

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Adjuvant Chemotherapy
Other Drugs

	Oxford LoE	/	AGO GR	
➢ Capecitabine containing regimen in TNBC	1a		B	+/-
➢ Platinum containing regimen in TNBC	5		D	+/-
➢ 5- Fluorouracile added to EC/AC	1b		A	- -

Adjuvant Treatment with Trastuzumab I

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	Oxford LoE	/	AGO GR	
➢ **Node-positive disease**	1a		A	++
➢ **Node-negative disease (whenever chemotherapy is considered as adequate)**				
➢ **> 10 mm**	1a		A	++
➢ **> 5–10 mm**	2b		B	+
➢ **≤ 5 mm**	2b		B	+/-

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References

Adjuvant Treatment with Trastuzumab II

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	Oxford LoE	/ AGO GR	
Start of treatment			
➢ Simultaneously with taxanes	1a	A	++
➢ Sequentially up to 3 months after chemotherapy	1b	B	+
Duration			
➢ For 1 year	1b	A	++
➢ For 2 years	1b	A	-
➢ For 0.5 years	1b	A	+/-

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References

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Adjuvant Trastuzumab
Cardiac Monitoring for CHF

Oxford LoE: 5 **GR: D** **AGO: ++**

Before start of trastuzumab

- History, physical examination (edema, hepatomegaly)
- Echocardiography (alternative to MUGA)

} Assessment of LVEF

During trastuzumab

Regular assessment of

- Heart rate increase > 15% above individual base level
- Body weight increase ≥ 2 kg/week
- Cardiac signs and symptoms

3 monthly assessment of LVEF

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Adjuvant Treatment with Trastuzumab: Schedules

	Oxford LoE	/ AGO GR	
Simultaneously			
➢ With paclitaxel / docetaxel after AC / EC	1b	A	++
➢ With P q1w 12 x without A in pT < 3 cm, pN0	2b	B	+
➢ With docetaxel and carboplatin	1b	A	+
➢ With anthracyclines	2b	B	+/-
➢ With taxanes dose-dense	2b	B	+ *
Radiotherapy concurrent with Trastuzumab	2b	B	+

* Study participation recommended

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References

Adjuvant Therapy with Other Targeted Agents

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	Oxford LoE	/ AGO GR	
➢ **Lapatinib**	1b[a]	B	-
➢ **(delayed adjuvant treatment)**	1b	B	-
➢ **Lapatinib + Trastuzumab**	1b[a]	B	-
➢ **Pertuzumab**	5	D	-
➢ **Bevacizumab**	1b	B	--

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Further Information

References

Adjuvant Cytotoxic and Targeted Therapy (2/13)

No further information

No references

Subtype-specific General Systemic Strategies (3/13)

No further information:

References:

1. Schmidt M. Chemotherapy in early breast cancer: when, how and which one? Breast Care (Basel). 2014 Jul;9(3):154-60.
2. Goldhirsch A, Winer EP, Coates AS et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol 2013; 24:2206–2223.

Adjuvant Chemotherapy without Trastuzumab: Overview (4/13)

Further information and references:

Statement: Anthracycline/ taxane based chemotherapy (1a A ++)
Vote result of the AGO recommendation: 100%

1. Budd GT, Barlow WE, Moore HC, Hobday TJ, Stewart JA, Isaacs C, Salim M, Cho JK, Rinn KJ, Albain KS, Chew HK, Burton GV, Moore TD, Srkalovic G, McGregor BA, Flaherty LE, Livingston RB, Lew DL, Gralow JR, Hortobagyi GN. SWOG S0221: A Phase III Trial Comparing Chemotherapy Schedules in High-Risk Early-Stage Breast Cancer. J Clin Oncol. 2015 Jan 1;33(1):58-64.
2. Nitz U, Gluz O, Huober J, Kreipe HH, Kates RE, Hartmann A, Erber R, Scholz M, Lisboa B, Mohrmann S, Möbus V, Augustin D, Hoffmann G, Weiss E, Böhmer S, Kreienberg R, Du Bois A, Sattler D, Thomssen C, Kiechle M, Jänicke F, Wallwiener D, Harbeck N, Kuhn W. Final analysis of the prospective WSG-AGO EC-Doc versus FEC phase III trial in intermediate-risk (pN1) early breast cancer: efficacy and predictive value of Ki67 expression. Ann Oncol. 2014 Aug;25(8):1551-7.

Statement: If anthracyclines cannot be given - Docetaxel plus cyclophosphamide (1b B +)
Vote result of the AGO recommendation: 100%

1. Jones S, Holmes FA, O'Shaughnessy J, Blum JL, Vukelja SJ, McIntyre KJ, Pippen JE, Bordelon JH, Kirby RL, Sandbach J, Hyman WJ, Richards DA, Mennel RG, Boehm KA, Meyer WG, Asmar L, Mackey D, Riedel S, Muss H, Savin MA. Docetaxel With Cyclophosphamide Is Associated With an Overall Survival Benefit Compared With Doxorubicin and Cyclophosphamide: 7-Year Follow-Up of US Oncology Research Trial 9735. Clin Oncol. 2009 Mar 10;27(8):1177-83.

Statement: If anthracyclines cannot be given - Paclitaxel mono weekly (1b B +/-)
Vote result of the AGO recommendation: 100%

1. Amoroso V, Pedersini R, Sharratt P, Vassalli L, Ferrari L, Sigala S, Simoncini E, Berruti A. Should adjuvant weekly Paclitaxel be considered less efficacious than anthracyclines plus cyclophosphamide for lower-risk patients with early-stage breast cancer? J Clin Oncol. 2015 Jan 20;33(3):290.
2. Shulman LN, Berry DA, Cirrincione CT, Becker HP, Perez EA, O'Regan R, Martino S, Shapiro CL, Schneider CJ, Kimmick G, Burstein HJ, Norton L, Muss H, Hudis CA, Winer EP. Comparison of doxorubicin and cyclophosphamide versus single-agent paclitaxel as adjuvant therapy for breast cancer in women with 0 to 3 positive axillary nodes: CALGB 40101 (Alliance). J Clin Oncol. 2014 Aug 1;32(22):2311-7.
3. Sparano JA, Wang M, Martino S, Jones V, Perez EA, Saphner T, Wolff AC, Sledge GW Jr, Wood WC, Davidson NE. N Engl J Med. 2008 Apr 17;358(16):1663-71

Statement: If anthracyclines cannot be given - CMF (1a A +/-)
Vote result of the AGO recommendation: 100%

1. Perrone F, Nuzzo F, Di Rella F, Gravina A, Iodice G, Labonia V, Landi G, Pacilio C, Rossi E, De Laurentiis M, D'Aiuto M, Botti G, Forestieri V, Lauria R, De Placido S, Tinessa V, Daniele B, Gori S, Colantuoni G, Barni S, Riccardi F, De Maio E, Montanino A, Morabito A, Daniele G, Di Maio M, Piccirillo MC, Signoriello S, Gallo C, de Matteis A. Weekly docetaxel versus CMF as adjuvant chemotherapy for older women with early breast cancer: final results of the randomized phase III ELDA trial. Ann Oncol. 2014 Dec 8. pii: mdu564. [Epub ahead of print]

Statement: Dose-dense in case of high tumor burden (1a A ++)
Vote result of the AGO recommendation: 100%

1. Moylan EJ, Connell LC, O'Reilly S. Are dose-dense and triplet chemotherapy regimens optimal adjuvant therapy in the majority of women with node-positive early breast cancer? J Clin Oncol. 2014 Feb 20;32(6):605-6.
2. Lemos Duarte I, da Silveira Nogueira Lima JP, Passos Lima CS, Deeke Sasse A. Dose-dense chemotherapy versus conventional chemotherapy for early breast cancer: a systematic review with meta-analysis. Breast. 2012 Jun;21(3):343-9.

3. Moebus V, Jackisch C, Lueck HJ, du Bois A, Thomssen C, Kurbacher C, Kuhn W, Nitz U, Schneeweiss A, Huober J, Harbeck N, von Minckwitz G, Runnebaum IB, Hinke A, Kreienberg R, Konecny GE, Untch M. Intense dose-dense sequential chemotherapy with epirubicin, paclitaxel, and cyclophosphamide compared with conventionally scheduled chemotherapy in high-risk primary breast cancer: mature results of an AGO phase III study. J Clin Oncol. 2010 Jun 10;28(17):2874-80.

Statement: Low dose maintenance Chemotherapy (1b B -)
Vote result of the AGO recommendation:

1. Colleoni et al., Low-dose oral cyclophosphamide and methotrexate maintenance for hormone receptor-negative early nreast cancer: International Breast Cancer Study Group trial 22-00. J Clin Oncol 2016, 34:3400-8 Epub

Collenoni et al. (5/13)

No further information

No references

Recommended Regimens for Adjuvant Chemotherapy (6/13)

Further information and references:

Statement: Anthracycline/ taxane based regimen
*EC → Pw E90C q3w x 4 → P80 qw1 x 12 (1b B ++)
Vote result of the AGO recommendation: 100%

1. Budd GT, Barlow WE, Moore HCF, et al: S0221: Comparison of two schedules of paclitaxel as adjuvant therapy for breast cancer. J Clin Oncol 31:51s, 2013 (suppl; abstr CRA1008)
2. Sparano JA, Zhao F, Martino S, et al. Long-Term Follow-Up of the E1199 Phase III Trial Evaluating the Role of Taxane and Schedule in Operable Breast Cancer. J Clin Oncol 33:2353-60. 2015

Statement: Anthracycline/ taxane based regimen
AC → Pw A60Cq3w x 4 → P80qw1 x 12 (1b A ++)
Vote result of the AGO recommendation: 100%

1. Eleftherios P. Mamounas, John Bryant, Barry Lembersky, Louis Fehrenbacher, Scot M. Sedlacek, Bernard Fisher, D. Lawrence Wickerham, Greg Yothers, Atilla Soran, and Norman Wolmark.Paclitaxel After Doxorubicin Plus Cyclophosphamide As Adjuvant Chemotherapy for Node-Positive Breast Cancer: Results From NSABP B-28 J Clin Oncol 2005. 23:3686-3696.

Statement: Anthracycline/ taxane based regimen
AC → D A60C q3w x 4 → D100 qw3 x 4 (1b A ++)
EC → D E90C q3w x 4 → D100 qw3 x 4 (1b B ++)

Statement: Anthracycline/ taxane based regimen
DAC D75A50C q3w x 6 (1b A ++)
Vote result of the AGO recommendation: 21 ++/ 13 + / 2 +/-

1. Swain SM, Tang G, Geyer CE Jr, Rastogi P, Atkins JN, Donnellan PP, Fehrenbacher L, Azar CA, Robidoux A, Polikoff JA, Brufsky AM, Biggs DD, Levine EA, Zapas JL, Provencher L, Northfelt DW, Paik S, Costantino JP, Mamounas EP, Wolmark N. Definitive results of a phase III adjuvant trial comparing three chemotherapy regimens in women with operable, node-positive breast cancer: the NSABP B-38 trial. J Clin Oncol. 2013 Sep 10;31(26):3197-204..

Statement: Anthracycline-free regimen
DC D75 C600 x4 (1b B +)
Vote result of the AGO recommendation: 100%

1. Jones S, Holmes FA, O'Shaughnessy J, Blum JL, Vukelja SJ, McIntyre KJ, Pippen JE, Bordelon JH, Kirby RL, Sandbach J, Hyman WJ, Richards DA, Mennel RG, Boehm KA, Meyer WG, Asmar L, Mackey D, Riedel S, Muss H, Savin MA. Docetaxel With Cyclophosphamide Is Associated With an Overall Survival Benefit Compared With Doxorubicin and Cyclophosphamide: 7-Year Follow-Up of US Oncology Research Trial 9735. Clin Oncol. 2009 Mar 10;27(8):1177-83.

Statement: Anthracycline-free regimen
Pac mono 80 mg q1w x 4-6 (1b B +/-)
Vote result of the AGO recommendation: 100%

1. Shulman LN, Berry DA, Cirrincione CT, Becker HP, Perez EA, O'Regan R, Martino S, Shapiro CL, Schneider CJ, Kimmick G, Burstein HJ, Norton L, Muss H, Hudis CA, Winer EP. Comparison of doxorubicin and cyclophosphamide versus single-agent paclitaxel as adjuvant therapy for breast cancer in women with 0 to 3 positive axillary nodes: CALGB 40101 (Alliance). J Clin Oncol. 2014 32:2311-7.

Statement: Anthracycline-free regimen
CMF 600/40/600 mg q3w x 6 (1a A +/-)
Vote result of the AGO recommendation: 100%

1. Perrone F, Nuzzo F, Di Rella F, Gravina A, Iodice G, Labonia V, Landi G, Pacilio C, Rossi E, De Laurentiis M, D'Aiuto M, Botti G, Forestieri V, Lauria R, De Placido S, Tinessa V, Daniele B, Gori S, Colantuoni G, Barni S, Riccardi F, De Maio E, Montanino A, Morabito A, Daniele G, Di Maio M, Piccirillo MC, Signoriello S, Gallo C, de Matteis A. Weekly docetaxel versus CMF as adjuvant chemotherapy for older women with early breast cancer: final results of the randomized phase III ELDA trial. Ann Oncol. 26:675-82, 2014

Dose-dense and/ or Dose-escalated Adjuvant Chemotherapy in Case of High Tumor Burden (7/13)

Further information and references:

Statement: Dose-dense regimen
*EC q3w Pac q1w x 12 (1b B ++)
AC q3w / Pac q1w x 12 (1b A++)
Vote result of the AGO recommendation: 100%

1. Burnell M, Levine MN, Chapman JA, Bramwell V, Gelmon K, Walley B, et al. Cyclophosphamide, epirubicin, and fluorouracil versus dose-dense epirubicin and cyclophosphamide followed by paclitaxel versus doxorubicin and cyclophosphamide followed by paclitaxel in node-positive or high-risk nodenegative breast cancer. J Clin Oncol 28:77-82, 2010.

Statement: Dose-dense regimen
ACPac / AC-Pac q2w (1b B +)
Vote result of the AGO recommendation: 9 ++ / 15 +/ 1 +/-/ 0 -/ 1 --

1. Citron ML, Berry DA, Cirrincione C, Hudis C, Winer EP, Gradishar WJ, et al.Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 2003;21:1431-9.

Statement: Dose-dense regimen
EC q3w / Pac q2w (1b A +)
EC q2w / Pac q1w (1b B +)
Vote result of the AGO recommendation: 100%

1. Jones RL, Walsh G, Ashley S, Chua S, Agarwal R, O'Brien M, et al. A randomized pilot phase II study of doxorubicin and cyclophosphamide (AC) or epirubicin and cyclophosphamide (EC) given 2 weekly with pegfilgrastim (accelerated) vs 3 weekly (standard) for women with early breast cancer. Br J Cancer 2009;100:305-10.

Statement: Dose-dense and dose-escalated regimen (N ≥ 4+)
E-Pac-C q2w (1b A ++)
Vote result of the AGO recommendation: 100%

1. Moebus V, Jackisch C, Lueck HJ, du Bois A, Thomssen C, Kurbacher C, Kuhn W, Nitz U, Schneeweiss A, Huober J, Harbeck N, von Minckwitz G, Runnebaum IB, Hinke A, Kreienberg R, Konecny GE, Untch M. Intense dose-dense sequential chemotherapy with epirubicin, paclitaxel, and cyclophosphamide compared with conventionally scheduled chemotherapy in high-risk primary breast cancer: mature results of an AGO phase III study. J Clin Oncol. 2010 Jun 10;28(17):2874-80.

Negative Trial

1. Swain SM, Tang G, Geyer CE Jr, Rastogi P, Atkins JN, Donnellan PP, Fehrenbacher L, Azar CA, Robidoux A, Polikoff JA, Brufsky AM, Biggs DD, Levine EA, Zapas JL, Provencher L, Northfelt DW, Paik S, Costantino JP, Mamounas EP, Wolmark N. Definitive results of a phase III adjuvant trial comparing three chemotherapy regimens in women with operable, node-positive breast cancer: the NSABP B-38 trial. J Clin Oncol. 2013 Sep 10;31(26):3197-204.

Adjuvant Chemotherapy Other Drugs (8/13)

Further information and references:

Statement: Capecitabine containing regimen in TNBC (1a B +/-)
Vote result of the AGO recommendation: 100%

1. O'Shaughnessy J, Koeppen H, Xiao Y, et al. Patients with Slowly Proliferative Early Breast Cancer Have Low Five-Year Recurrence Rates in a Phase III Adjuvant Trial of Capecitabine. Clin Cancer Res. 2015, 21:4305-11
2. Jiang Y, Yin W, Zhou L, Yan L, Zhou Q, Du Y, Shen Z, Shao Z, Lu J. First efficacy results of capecitabine with anthracycline-and taxane-based adjuvant therapy in high-risk early breast cancer: a meta-analysis. PLoS ONE 2012 7(3): e32474.

Statement: Platinum containing regimen in TNBC (5 D +/-)
Vote result of the AGO recommendation: 100%

No references available.

Statement: 5- Fluorouracile added to EC/AC (1b A - -)
Vote result of the AGO recommendation: 100%

1. Del Mastro L, De Placido S, Bruzzi P,et al. Fluorouracil and dose-dense chemotherapy in adjuvant treatment of patients with early-stage breast cancer: an open-label, 2 × 2 factorial, randomised phase 3 trial. Lancet. 2015;385(9980):1863-72

Adjuvant Treatment with Trastuzumab I (9/13)

Further information and references:

Statements: Node-positive and node-negative disease (1a A ++)
Vote result of the AGO recommendation: 100%

1. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, Gianni L, Baselga J, Bell R, Jackisch C, Cameron D, Dowsett M, Barrios CH, Steger G, Huang CS, Andersson M, Inbar M, Lichinitser M, Láng I, Nitz U, Iwata H, Thomssen C, Lohrisch C, Suter TM, Rüschoff J, Suto T, Greatorex V, Ward C, Straehle C, McFadden E, Dolci MS, Gelber RD; Herceptin Adjuvant (HERA) Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005 Oct 20;353(16):1659-72.
2. Smith I, Procter M, Gelber RD, Guillaume S, Feyereislova A, Dowsett M, Goldhirsch A, Untch M, Mariani G, Baselga J, Kaufmann M, Cameron D, Bell R, Bergh J, Coleman R, Wardley A, Harbeck N, Lopez RI, Mallmann P, Gelmon K, Wilcken N, Wist E, Sánchez Rovira P, Piccart-Gebhart MJ; HERA study team.2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Lancet. 2007 Jan 6;369(9555):29-36.
3. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, de Azambuja E, Procter M, Suter TM, Jackisch C, Cameron D, Weber HA, Heinzmann D, Dal Lago L, McFadden E, Dowsett M, Untch M, Gianni L, Bell R, Köhne CH, Vindevoghel A, Andersson M, Brunt AM, Otero-Reyes D, Song S, Smith I, Leyland-Jones B, Baselga J; Herceptin Adjuvant (HERA) Trial Study Team. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. Lancet. 2013 Sep 21;382(9897):1021-8.
4. Jackisch C, Kim SB, Semiglazov V, Melichar B, Pivot X, Hillenbach C, Stroyakovskiy D, Lum BL, Elliott R, Weber HA, Ismael G. Subcutaneous versus intravenous formulation of trastuzumab for HER2-positive early breast cancer: updated results from the phase III HannaH study. Ann Oncol. 2014 Nov 17. pii: mdu524. [Epub ahead of print]
5. Denduluri N, Somerfield MR, Eisen A, Holloway JN, Hurria A, King TA, Lyman GH, Partridge AH, Telli ML, Trudeau ME, Wolff AC Selection of optimal adjuvant chemotherapy regimens for human epidermal growth factor receptor (Her2)- negative and adjuvant targeted therapy for Her2-positive breast cancers: an American Society of

Clinical Oncology Guideline adaptation of the Cancer Care Ontario Clinical Practice Guideline. J Clin Oncol 2016 Jul 10;34(20):2416-27. Doi10.1200/JCO2016.67.0182

Statements: >10 mm/> 5-10 mm/ <= 5mm (1a A ++ / 2b B + / 2b B +/-)

1. Denduluri N, Somerfield MR, Eisen A, Holloway JN, Hurria A, King TA, Lyman GH, Partridge AH, Telli ML, Trudeau ME, Wolff AC Selection of optimal adjuvant chemotherapy regimens for human epidermal growth factor receptor (Her2)- negative and adjuvant targeted therapy for Her2-positive breast cancers: an American Society of Clinical Oncology Guideline adaptation of the Cancer Care Ontario Clinical Practice Guideline. J Clin Oncol 2016 Jul 10;34(20):2416-27. Doi10.1200/JCO2016.67.0182
2. O'Sullivan CC, Bradbury I, Campbell C, Spielmann M, Perez EA, Joensuu H, Costantino JP, Delaloge S, Rastogi P, Zardavas D, Ballman KV, Holmes E, de Azambuja E, Piccart-Gebhart M, Zujewski JA, Gelber RD. Efficacy of Adjuvant Trastuzumab for Patients With Human Epidermal Growth Factor Receptor 2-Positive Early Breast Cancer and Tumors ≤ 2 cm: A Meta-Analysis of the Randomized Trastuzumab. J Clin Oncol. 2015 Aug 20;33(24):2600-8. doi: 10.1200/JCO.2015.60.8620. Epub 2015 Jun 22.

Adjuvant Treatment with Trastuzumab II (10/13)

Further information and references:

Statement: Start of treatment simultaneously with taxanes (1 A ++)
Vote result of the AGO recommendation: 100%

1. Smith I, Procter M, Gelber RD, Guillaume S, Feyereislova A, Dowsett M, Goldhirsch A, Untch M, Mariani G, Baselga J, Kaufmann M, Cameron D, Bell R, Bergh J, Coleman R, Wardley A, Harbeck N, Lopez RI, Mallmann P, Gelmon K, Wilcken N, Wist E, Sánchez Rovira P, Piccart-Gebhart MJ; HERA study team.2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Lancet. 2007 Jan 6;369(9555):29-36.
2. E. A. Perez, E. H. Romond, V. J. Suman, J. Jeong, N. E. Davidson, C. E. Geyer, S. Martino, E. P. Mamounas, P. A. Kauffman, N. Wolmark, NCCTG/NSABP. Updated results of the combined analysis of NCCTG N9831 and NSABP B-31 adjuvant chemotherapy with/without trastuzumab in patients with HER2-positive breast cancer. Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 512
3. Joensuu H, Bono P, Kataja V, Alanko T, Kokko R, Asola R, Utriainen T, Turpeenniemi-Hujanen T, Jyrkkiö S, Möykkynen K, Helle L, Ingalsuo S, Pajunen M, Huusko M, Salminen T, Auvinen P, Leinonen H, Leinonen M, Isola J, Kellokumpu-Lehtinen PL. Fluorouracil, epirubicin, and cyclophosphamide with either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatments of breast cancer: final results of the FinHer Trial. J Clin Oncol. 2009 Dec 1;27(34):5685-92. Epub 2009 Nov 2.
4. Yin W, Jiang Y, Shen Z, Shao Z, Lu J. Trastuzumab in the adjuvant treatment of HER2-positive early breast cancer patients: a meta-analysis of published randomized controlled trials. PLoS One. 2011;6(6):e21030. Epub 2011 Jun 9.
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7. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, de Azambuja E, Procter M, Suter TM, Jackisch C, Cameron D, Weber HA, Heinzmann D, Dal Lago L, McFadden E, Dowsett M, Untch M, Gianni L, Bell R, Köhne CH, Vindevoghel A, Andersson M, Brunt AM, Otero-Reyes D, Song S, Smith I, Leyland-Jones B, Baselga J; Herceptin Adjuvant (HERA) Trial Study Team. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. Lancet. 2013 Sep 21;382(9897):1021-8. doi: 10.1016/S0140-6736(13)61094-6. Epub 2013 Jul 18.

Statement: Duration

Duration Trastuzumab 1 year (1b A ++)
Vote result of the AGO recommendation: 100%

Duration Trastuzumab 2 year (1b A -)
Vote result of the AGO recommendation: 100%

Duration Trastuzumab 0.5 years (1b A +/-)
Vote result of the AGO recommendation: 1 +/ 23 +/-/ 6 -/ 1 --

1. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, de Azambuja E, Procter M, Suter TM, Jackisch C, Cameron D, Weber HA, Heinzmann D, Dal Lago L, McFadden E, Dowsett M, Untch M, Gianni L, Bell R, Köhne CH, Vindevoghel A, Andersson M, Brunt AM, Otero-Reyes D, Song S, Smith I, Leyland-Jones B, Baselga J; Herceptin Adjuvant (HERA) Trial Study Team. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. Lancet. 2013 Sep 21;382(9897):1021-8.
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Pauporté I, Kramar A; PHARE trial investigators. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. Lancet Oncol. 2013 Jul;14(8):741-8.

Adjuvant Trastuzumab – Cardiac Monitoring for CHF (11/13)

Further information and references:

Statement: Cardiac Monitoring (5 D ++)
Vote result of the AGO recommendation: 100%

1. Perez EA, Suman VJ, Davidson NE, Sledge GW, Kaufman PA, Hudis CA, Martino S, Gralow JR, Dakhil SR, Ingle JN, Winer EP, Gelmon KA, Gersh BJ, Jaffe AS, Rodeheffer RJ. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. J Clin Oncol. 2008 Mar 10;26(8):1231-8. Epub 2008 Feb 4.
2. Mackey JR, Clemons M, Côté MA, Delgado D, Dent S, Paterson A, Provencher L, Sawyer MB, Verma S. Cardiac management during adjuvant trastuzumab therapy: recommendations of the Canadian Trastuzumab Working Group.
3. Curr Oncol. 2008 Feb;15(1):24-35.

Adjuvant Treatment with Trastuzumab: Schedules (12/13)

Further information and references:

Statement: with paclitaxel/docetaxel after AC/EC (1b A ++)
Vote result of the AGO recommendation: 100%

1. Edith A. Perez, Vera J. Suman, Nancy E. Davidson, Julie R. Gralow, Peter A. Kaufman, Daniel W. Visscher, Beiyun Chen, James N. Ingle, Shaker R. Dakhil, JoAnne Zujewski, Alvaro Moreno-Aspitia, Thomas M. Pisansky, and Robert B. Jenkins. Sequential Versus Concurrent Trastuzumab in Adjuvant Chemotherapy for Breast Cancer. J Clin Oncol 29:4491-4497. 2011
2. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, de Azambuja E, Procter M, Suter TM, Jackisch C, Cameron D, Weber HA, Heinzmann D, Dal Lago L, McFadden E, Dowsett M, Untch M, Gianni L, Bell R, Köhne CH, Vindevoghel A, Andersson M, Brunt AM, Otero-Reyes D, Song S, Smith I, Leyland-Jones B, Baselga J; Herceptin Adjuvant (HERA) Trial Study Team. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. Lancet. 2013 Sep 21;382(9897):1021-8.

Statement: P q1w12 without A in pT < 3 cm pN0 (2b B +)
Vote result of the AGO recommendation: 100%

1. Tolaney SM, Barry WT, Dang CT, Yardley DA, Moy B, Marcom PK, Albain KS, Rugo HS, Ellis M, Shapira I, Wolff AC, Carey LA, Overmoyer BA, Partridge AH, Guo H, Hudis CA, Krop IE, Burstein HJ, Winer EP. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. N Engl J Med. 2015 Jan 8;372(2):134-41.

Statement: with docetaxel and carboplatin (1b A +)
Vote result of the AGO recommendation: 100%

1. Valero V, Forbes J, Pegram MD, Pienkowski T, Eiermann W, von Minckwitz G, Roche H, Martin M, Crown J, Mackey JR, Fumoleau P, Rolski J, Mrsic-Krmpotic Z, Jagiello-Gruszfeld A, Riva A, Buyse M, Taupin H, Sauter G, Press MF, Slamon DJ. Multicenter phase III randomized trial comparing docetaxel and trastuzumab with docetaxel, carboplatin, and trastuzumab as first-line chemotherapy for patients with HER2-gene-amplified metastatic breast cancer (BCIRG 007 study): two highly active therapeutic regimens. J Clin Oncol. 2011 Jan 10;29(2):149-56.
2. Harold J. Burstein, Martine J. Piccart-Gebhart, Edith A. Perez, Gabriel N. Hortobagyi, Norman Wolmark, Kathy S. Albain, Larry Norton, Eric P. Winer, Clifford A. Hudis. Choosing the Best Trastuzumab-Based Adjuvant Chemotherapy Regimen: Should We Abandon Anthracyclines? Journal of Clinical Oncology, Vol 30, No 18 (June 20), 2012: pp 2179-2182

Statement: with anthracyclines (2b B+/-)
Vote result of the AGO recommendation: 100%

See references slide 7.

Statement: with taxanes dose-dense (2b B+)
Vote result of the AGO recommendation: 100%

See references slide 7.

Statement: radiotherapy concurrent with trastuzumab (2b B +)
Vote result of the AGO recommendation: 100%

1. M. Y. Halyard, T. M. Pisansky, L. J. Solin, L. B. Marks, L. J. Pierce, A. Dueck, E. A. Perez. Trastuzumab can be administered concurrent to adjuvant radiotherapy of the breast or thoracic wall. Adjuvant radiotherapy (RT) and trastuzumab in stage I-IIA breast cancer: Toxicity data from North Central Cancer Treatment Group Phase III trial N9831 J Clin Oncol. 2009 27(16):2638-44

Adjuvant Therapy with Other Agents (13/13)

Further information and references:

Statement: with Lapatinib (1b[a] B -)
Delayed adjvuvant treatment (1b B -)
Vote result of the AGO recommendation: 100%

1. Moreno-Aspitia A1, Dueck AC, Ghanem-Cañete I, Patel T, Dakhil S, Johnson D, Franco S, Kahanic S, Colon-Otero G, Tenner KS, Rodeheffer R, McCullough AE, Jenkins RB, Palmieri FM, Northfelt D, Perez EA. RC0639: phase II study of paclitaxel, trastuzumab, and lapatinib as adjuvant therapy for early stage HER2-positive breast cancer. Breast Cancer Res Treat. 2013 Apr;138(2):427-35.
2. Goss PE1, Smith IE, O'Shaughnessy J, Ejlertsen B, Kaufmann M, Boyle F, Buzdar AU, Fumoleau P, Gradishar W, Martin M, Moy B, Piccart-Gebhart M, Pritchard KI, Lindquist D, Chavarri-Guerra Y, Aktan G, Rappold E, Williams LS, Finkelstein DM; TEACH investigators. Adjuvant lapatinib for women with early-stage HER2-positive breast cancer: a randomised, controlled, phase 3 trial. Lancet Oncol. 2013 Jan;14(1):88-96.
3. Edith A. Perez, Eileen Holmes, Evandro de Azambuja, Amylou Dueck, José Baselga, Giuseppe Viale, Jo Anne Zujewski, Aron Goldhirsch, Rocco Crescenzo, Kathleen I. Pritchard, Antonio C. Wolff, Christian Jackisch, Istvan Lang, Michael Untch, Ian Smith, Frances Boyle, Binghe Xu, Henry Gomez, Richard D. Gelber, Martine Piccart-Gebhart. 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 (1b[a] B -)
Vote result of the AGO recommendation: 100%

1. Piccart-Gebhart M, Holmes AP, Baselga J, de Azambuja E, Dueck A, Viale G, Zujewski JA, Goldhirsch A, Santillana S, Pritchard K, Wolff A, Jackisch C, Lang I, Untch M, Smith I, Boyle F, Xu B, Gomez H, Gelber RD, Perez EA. First results from the phase III ALTTO trial (BIG 02-06; NCCTG 063D) comparing one year of anti-

HER2 therapy with lapatinib alone (L), trastuzumab alone (T), their sequence (T→L) or their combination (L + T) in the adjuvant treatment of HER2-positive early breast cancer (EBC). ASCO, 2014

Statement: Pertuzumab (5 D -)
Vote result of the AGO recommendation: 100%

Trials are ongoing. No final results available.

Statement: Bevacizumab (1b B --)
Vote result of the AGO recommendation: 100%

1. Cameron D, Brown J, Dent R, Jackisch C, Mackey J, Pivot X, Steger GG, Suter TM, Toi M, Parmar M, Laeufle R, Im YH, Romieu G, Harvey V, Lipatov O, Pienkowski T, Cottu P, Chan A, Im SA, Hall PS, Bubuteishvili-Pacaud L, Henschel V, Deurloo RJ, Pallaud C, Bell R. Adjuvant bevacizumab-containing therapy in triple-negative breast cancer (BEATRICE): primary results of a randomised, phase 3 trial. Lancet Oncol. 2013 Sep;14(10):933-42.
2. D.Slamon, S.Swain, M.Buyse, M.Martin, C.Geyer, Y-H.Im, T.Pienkowski, S-B.Kim, N.Robert, G.Steger, J.Crown, S.Verma, W.Eiermann, J.Costantino, SA.Im, E.Mamounas, L.Schwartzberg, A.Paterson, J.Mackey, L.Provencher, M.Press, M.Thirlwell, V.Bee-Munteanu, V.Henschel, A.Crepelle-Flechais, N.Wolmark. BETH: A Randomized Phase III Study Evaluating Adjuvant Bevacizumab Added to Trastuzumab/Chemotherapy for Treatment of HER2+ Early Breast Cancer. SABCS 2013

Statement: Neratinib after adjuvant trastuzumab (1b[a] B +/-)
Vote result of the AGO recommendation:

1. Chan A, Delaloge S, Holmes FA, Moy B, Iwata H, Harvey VJ, Robert NJ, Silovski T, Gokmen E, von Minckwitz G, Ejlertsen B, Chia SK, Mansi J, Barrios CH, Gnant M, Buyse M, Gore I, Smith J 2nd, Harker G, Masuda N, Petrakova K, Zotano AG, Iannotti N, Rodriguez G, Tassone P, Wong A, Bryce R, Ye Y, Yao B, Martin M; ExteNET Study Group..

Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2016 Mar;17(3):367-77. doi: 10.1016/S1470-2045(15)00551-3. PMID: 26874901