Post Neoadjuvant Treatment Surgery Intervention: BCS vs Mactectomy

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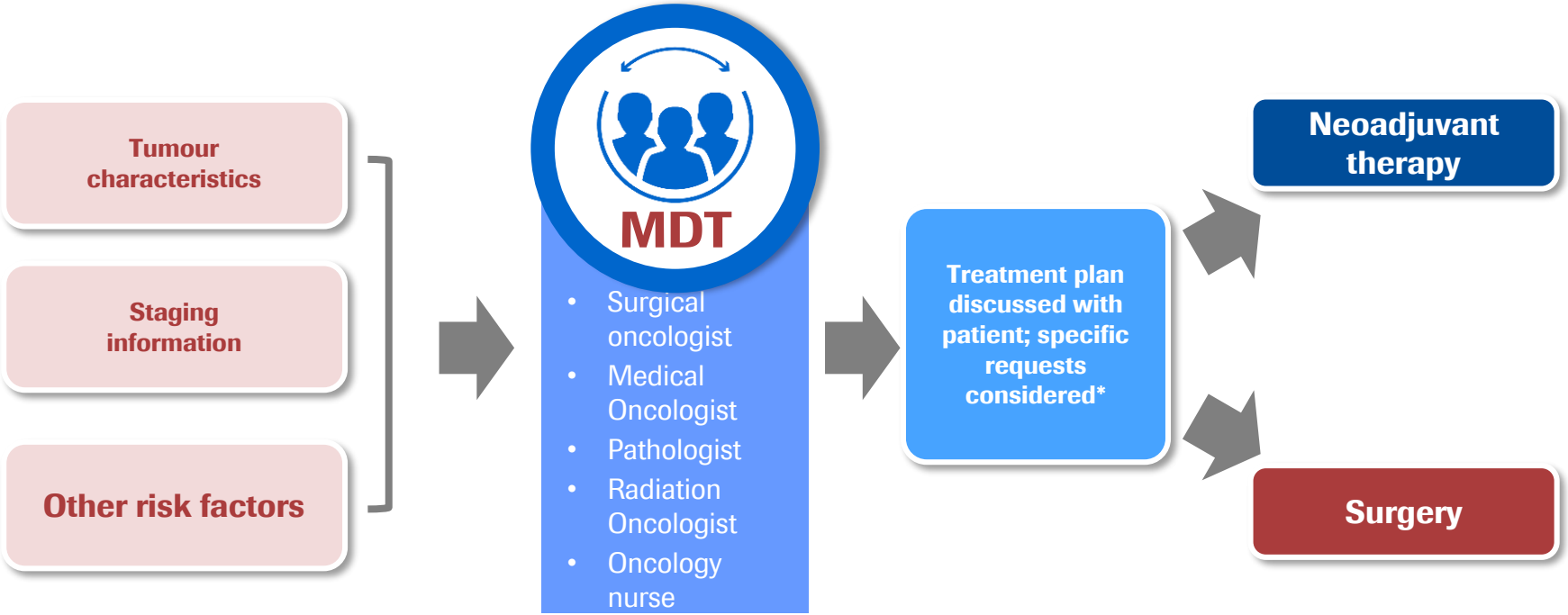
Agenda

- The importance of MDT in eBC Management
- Benefit Neoadjuvant Treatment for HER2 eBC patients
- BCS (Breast Conserving Surgery) or Mastectomy: Guideline Recommendation
- How BCS may benefit surgical candidates with eBC in Asian women?
- Response-directed adjuvant therapy and how it shapes our practice as surgeon

The importance of MDT in eBC management

MDTs are essential for optimal management of patients with HER2-positive eBC[1,2]

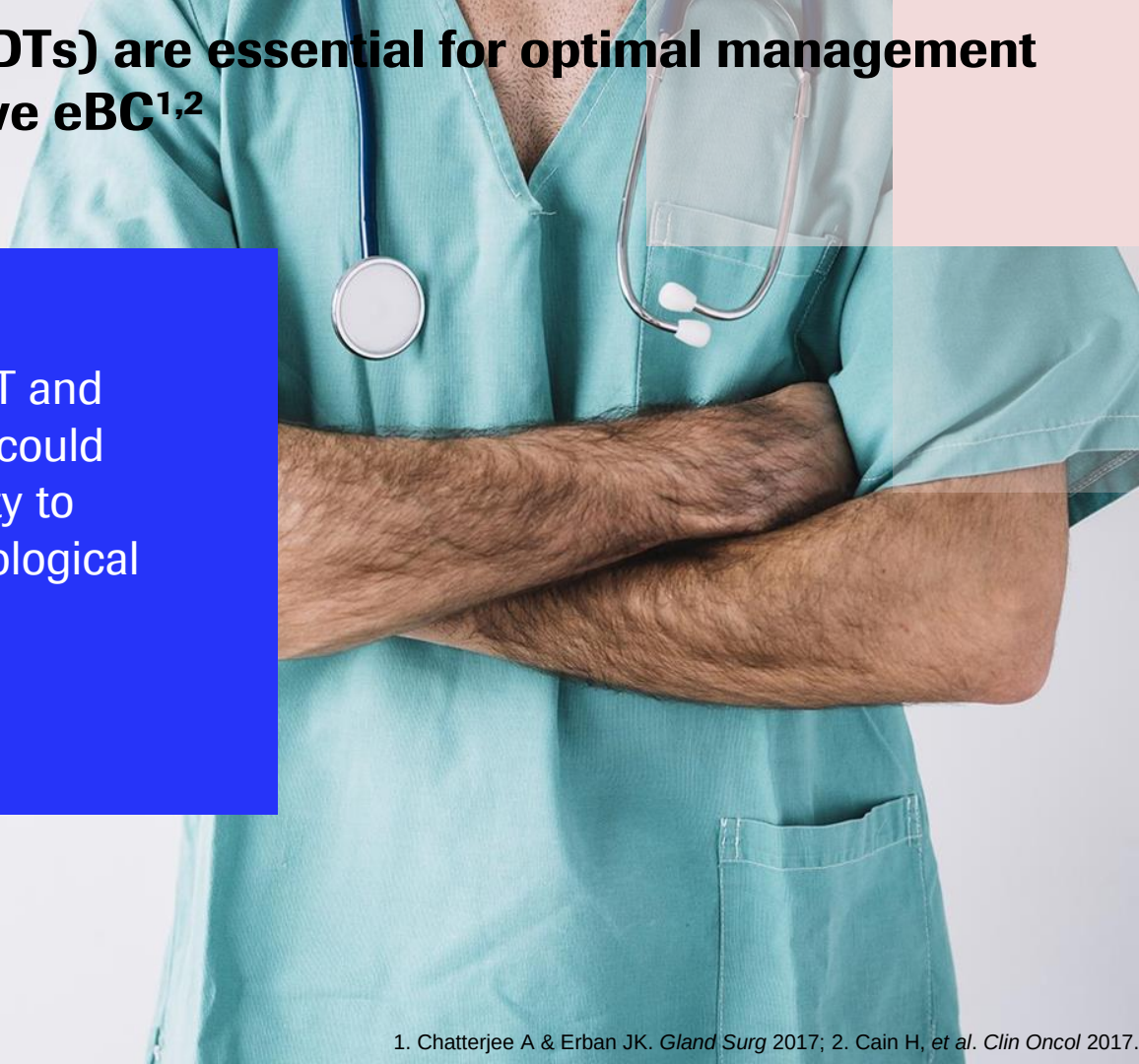


* Patient requests, e.g. desire for neoadjuvant therapy, breast-conserving surgery vs. mastectomy.
MDT, multidisciplinary team.

1. Chatterjee A & Erban JK. *Gland Surg* 2017; 2. Cain H, *et al*. *Clin Oncol* 2017.

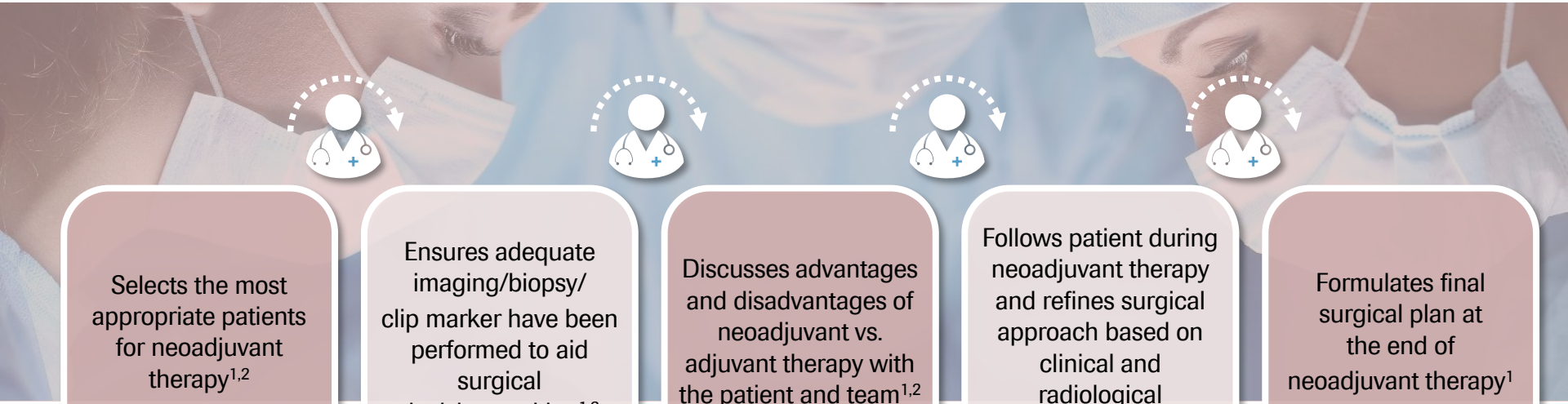
Multi-disciplinary teams (MDTs) are essential for optimal management of patients with HER2-positive eBC[1,2]

Lack of a functioning MDT and decision-making process could mean a missed opportunity to improve surgical and oncological outcomes



1. Chatterjee A & Erban JK. *Gland Surg* 2017; 2. Cain H, *et al*. *Clin Oncol* 2017.

As part of a multi-disciplinary team (MDT), surgeons play an important role in selecting the most effective treatment approach for patients

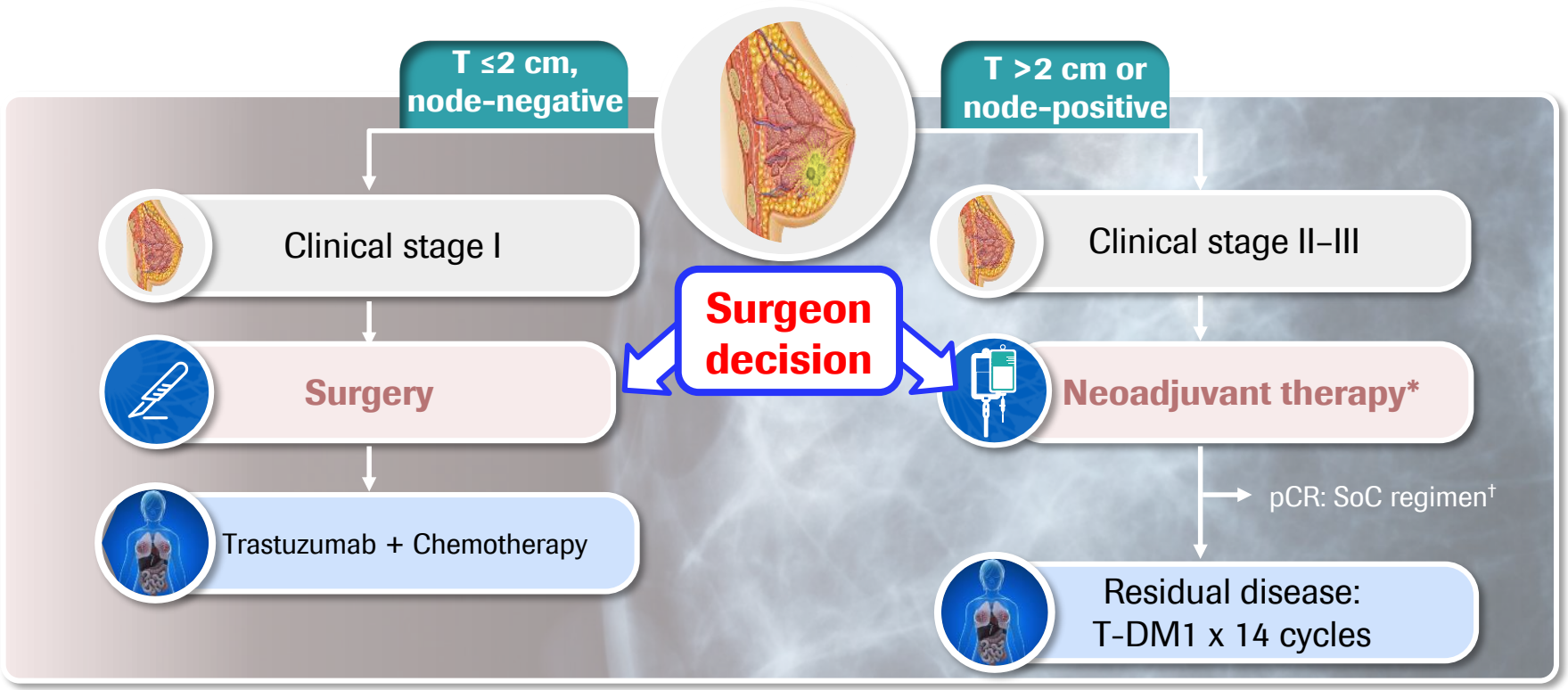


- Selects the most appropriate patients for neoadjuvant therapy[1,2]
- Ensures adequate imaging/biopsy/clip marker have been performed to aid surgical decision-making[1,2]
- Discusses advantages and disadvantages of neoadjuvant vs. adjuvant therapy with the patient and team[1,2]
- Follows patient during neoadjuvant therapy and refines surgical approach based on clinical and radiological response[1,2]
- Formulates final surgical plan at the end of neoadjuvant therapy[1]

MDTs are essential for the appropriate selection of patients eligible for neoadjuvant therapy

1. Association of Breast Surgery at Baso 2009. *Eur J Surg Oncol* 2009; 2. Chatterjee A & Erban JK. *Gland Surg* 2017.

Selection of patients with HER2-positive eBC for neoadjuvant therapy



pCR, pathological complete response; SNB, sentinel node biopsy; SoC, standard of care.
* Anthracyclines + taxanes or TCH ± P, minimum of 6 cycles of chemotherapy. †Based on HER2-positive eBC clinicopathologic characteristics.

1. Gianni L, et al. Lancet Oncol 2016; 2. AGO Breast Cancer Guidelines 2019; 3. NCCN Breast Cancer Guidelines – Version 6. 2020; 4. Cardoso F, et al. Ann Oncol 2019; 5. Burstein HJ, et al. Ann Oncol 2019;

Benefit Neoadjuvant Treatment for HER2 eBC patients

Improving surgical options is only one key benefit of neoadjuvant therapy

Impact on surgery

- Converts patients with inoperable tumours to surgical candidates[1]
- Downstages from mastectomy to BCS[1,2]
- Downstages axilla, avoiding axillary dissection[1,2]
- Improves cosmetic outcomes of BCS[1,2]
- Reduces surgical morbidity[2,3]
- Allows time for more complex reconstructive surgery options[1]

BCS, breast-conserving surgery.

1. Cain H, *et al. Clin Oncol* 2017; 2. Volders JH, *et al. Br Can Res Treat* 2018;
3. Franceschini G, *et al*. *Ann Ital Chir* 2018.

Neoadjuvant therapy has important benefits that go beyond making inoperable disease operable

Impact on surgery

- Converts patients with inoperable tumours to surgical candidates[1]
- Downstages from mastectomy to BCS[1,2]
- Downstages axilla, avoiding axillary dissection[1,2]
- Improves cosmetic outcomes of BCS[1,2]
- Reduces surgical morbidity[3]
- Allows time for more complex reconstructive surgery options[1]

Other key benefits

- Allows time for *BRCA*1/2 testing[1]
- Provides in vivo assessment of response[1]
- Patients are encouraged by early treatment responses[4]
- Allows early treatment of micrometastases
- Provides the opportunity to adjust adjuvant treatment depending on neoadjuvant treatment outcome[1,4]

BCS, breast-conserving surgery.

1. Cain H, *et al. Clin Oncol* 2017; 2. Volders JH, *et al. Br Can Res Treat* 2018;
3. Franceschini G, *et al*. *Ann Ital Chir* 2018; 4. Thill M, *et al. Geburtshilfe Frauenheilkd* 2016.

Neoadjuvant therapy offers several benefits for eBC management

Enables early response assessment[1]

- Provides ***in vivo*** **assessment of response**
- Provides an **opportunity to adjust adjuvant treatment** depending on the outcome of neoadjuvant treatment (pCR or residual disease)
- Prognostic factor: **pCR correlate with prolong OS (overall survival)**

Enhances surgical options[1,2]

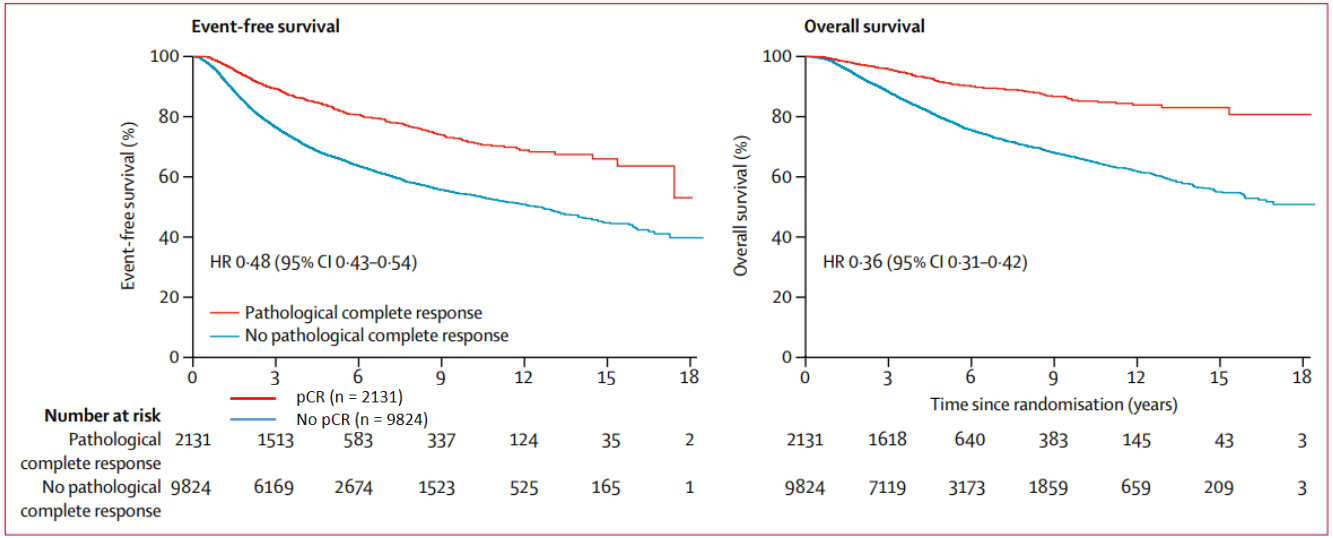
- **Downstages breast tumour**, leading to improved chances of conservative surgery
- **Downstages axilla**, avoiding axillary dissection
- Potentially **decreases surgical morbidity**
- Allows time for planning **reconstruction surgery**

Early systemic treatment[3]

- Allows **early treatment of micrometastases**

1. Cain H, *et al. Clin Oncol* 2017; 2. Volders JH, *et al. Breast Cancer Res Treat* 2018;
3. Pernaut C, *et al. Breast Care (Basel)* 2018.

Pathological complete response as surrogate endpoint for prediction of long-term clinical benefit (DFS, EFS, OS)



12 international neo-adjuvant trials:

• CBG/AGO: 7	6.377
• NSABP : 2	3.171
• EORTC/BIG: 1	1.856
• ITA : 2	1.589
• TOTAL # Pts.	12.993

Interpretation: Patients who attain pCR defined as ypT0 ypN0 or ypT0/is ypN0 have improved survival.
The prognostic value is greatest in aggressive tumour subtypes.
This pooled analysis could not validate pCR as a surrogate endpoint for improved EFS and OS

Cortazar P, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014; 384: 164–72

BCS (Breast Conserving Surgery) or Mastectomy: Guideline Recommendation

ESMO Asia: BCS is the preferred local treatment option for the majority if eBC patients

- Studies suggest **2 out of 3** Asian women with breast cancer may **still receive a mastectomy** (Mx) despite guidelines recommending BCS as the preferred surgical option for eligible patients[4-6]
- The decision is often based on the patient's[7] : - fear of cancer recurrence
  - perception that health outweighs breast retention
  - Possibility of second surgery for margin
- However, research shows, **1 in 5** women may regret their initial choice of Mx despite eligibility for BCS[7]

This reality exists despite the fact most local/international guidelines recommend BCS as the preferred surgical option for eligible patients[1-3]

NCCN GUIDELINES	A mastectomy is indicated for patients who are not candidates for BCS or those who choose to undergo this procedure over BCS.[1]
ESMO PAGA Pan-Asian Guidelines Adaptation	BCS is the preferred local treatment option for the majority of eBC patients, with the use of oncoplastic techniques, to maintain good cosmetic outcomes in technically challenging cases, when needed [A=100% and I, A][2]
SGBCC	Surgical resection to remove known malignancy and achieve 'no ink on tumour' margins is the standard, regardless of tumour histology or grade, or the patient's age.[3]

References: 1. National Comprehensive Cancer Network®: Breast Cancer. Version 4.2024. Retrieved from https://www.nccn.org/. Accessed Septt 2024. 2. Y.H. Park, E. Senkus-Konefka, S.A. Im, et al. Ann Oncol. 2020;31(4):451-469. 3. Burstein HJ, Curigliano G, Thürlimann B, et al. Ann Oncol. 2021;32(10):1216-1235. 5. Sinnadurai S, Kwong A, Hartman M, et al. BJS Open. 2018;3(1):48-55. 6. Huang S, Yang Q, Zheng X, et al. BMC Cancer.2023;23(1):23. 7. Sarkar P, Huffman KN, Williams T, et al. J Surg Oncol. 2024;129(5):953-964. 8. Lee WQ, Tan VKM, Choo HMC, et al. BJS Open. 2018;3(1):31-37.

Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

F. Cardoso[1], S. Kyriakides[2], S. Ohno[3], F. Penault-Llorca[4,5], P. Poortmans[6,7], I. T. Rubio[8], S. Zackrisson[9] & E. Senkus[10], on behalf of the ESMO Guidelines Committee*

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SPECIAL ARTICLE

Surgery in Early Breast Cancer

The major change in the surgical treatment of primary breast cancer has been **a shift towards Breast Conservation techniques, which started >30 years ago.**

Currently, in western Europe, 60%–80% of newly diagnosed cancers are amenable to breast conservation (wide local excision and RT), at diagnosis or after PST.
A neo-adjuvant approach should be preferred in subtypes highly sensitive to ChT, such as triple-negative and HER2-positive, in tumours >2 cm [II, A] and/or a positive axilla

In some patients, **Mastectomy is still carried out due to**:

- Tumour size (relative to breast size)
- Tumour multi-centricity
- Inability to achieve negative surgical margins after multiple resections
- Prior radiation to the chest wall/breast or other contraindications to RT
- Unsuitability for oncoplastic breast conservation
- Patient choice

Cardoso F, et al. Early Breast Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2019 Annals of Oncology 30: 1194-1220. DOI:10.1093/annonc/mdz173

How BCS may benefit surgical candidates with eBC in Asian women?

BCT+RT presents comparable OS with Mastectomy in Asian women[1-3]

	No. of women	5-year OS (%)	Crude HR	Adjusted HR
Overall cohort	3536			
Mastectomy	2245	92.9 (91.7, 94.1)	1.00 (reference)	1.00 (reference)
BCS	1291	94.9 (93.5, 96.3)	0.80 (0.64, 1.02)	0.81 (0.64, 1.03)*
Subgroups				
Age at diagnosis 20–39 years	911			
Mastectomy	566	90.0 (87.3, 92.7)	1.00 (reference)	1.00 (reference)
BCS	355	91.4 (87.9, 94.9)	0.80 (0.55, 1.17)	0.80 (0.52, 1.21)*
Age at diagnosis 40–49 years	2625			
Mastectomy	1699	93.8 (92.4, 95.2)	1.00 (reference)	1.00 (reference)
BCS	936	96.2 (94.8, 97.6)	0.79 (0.60, 1.03)	0.82 (0.61, 1.10)*

Cox regression analysis stratified by propensity score *20 quantiles and deciles estimated using various factors as described in the table.

- This is consistent with meta analysis including 22,598 patients (T1-2 N0-N+) aged ≤ 40 years from five population based studies and pooled study of two clinical trials comparing BCS with mastectomy[1]
- The study assessed trends in the surgical management of Asian women (n=3.536) with stage I-II breast cancer in 4 hospitals in Malaysia, Siangapore, Hong Kong between 1990 and 2012. [1]

1. Sinnadurai S, Kwong A, Hartman M, et al. BJS Open. 2018;3(1):48-55. 2. Vila J, Gandini S, Gentilini O. Breast. 2015;24:175-181. 3. De la Cruz Ku G, Karamchandani M, Chambergo-Michilot D, et al. Ann Surg Oncol. 2022;29(10):6163-6188.

Meta-analysis: BCS was associated with improved OS compared with Mastectomy

- With respect to similar OS outcomes for BCS+RT and Mx documented in several randomised trials, some studies have shown improved survival and fewer post-surgical complications with BCS
- In a meta-analysis of 30 studies (6 RCTs + 24 retrospective cohorts) studying 1,802,128 patients with a follow-up ranging from 4 to 20 years; 1,075,563 and 744,565 underwent BCS+RT and Mx, respectively

BCS was associated with improved OS compared with Mx

	BCS+RT	Mx			
Study	Total	Total	Risk ratio	RR	95% CI
Study type: Retrospective cohort Random effects model Heterogenity: I^2=100%, τ^2=0.1677, p=0	1,055,545	742,650		0.57	(0.49, 0.67)
Study type: RCT Random effects model Heterogenity: I^2=100%, τ^2=0.0008, p=0.34	2018	1915		1.03	(0.96, 1.10)
Overall study: Random effects model Heterogenity: I^2=100%, τ^2=0.1853	1,057,563	744,565		0.64	(0.55, 0.74)

De la Cruz Ku G, Karamchandani M, Chambergo-Michilot D, et al. Ann Surg Oncol. 2022;29(10):6163-6188.

Meta-Analysis

ANNALS OF SURGERY OPEN

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Breast-Conserving Surgery or Mastectomy?

Impact on Survival

Peer Christiansen, MD, DMSc,* Marco Mele, MD,† Anne Bodilsen, MD, PhD,‡ Nicola Rocco, MD, PhD,§ and Robert Zachariae, DMSc||

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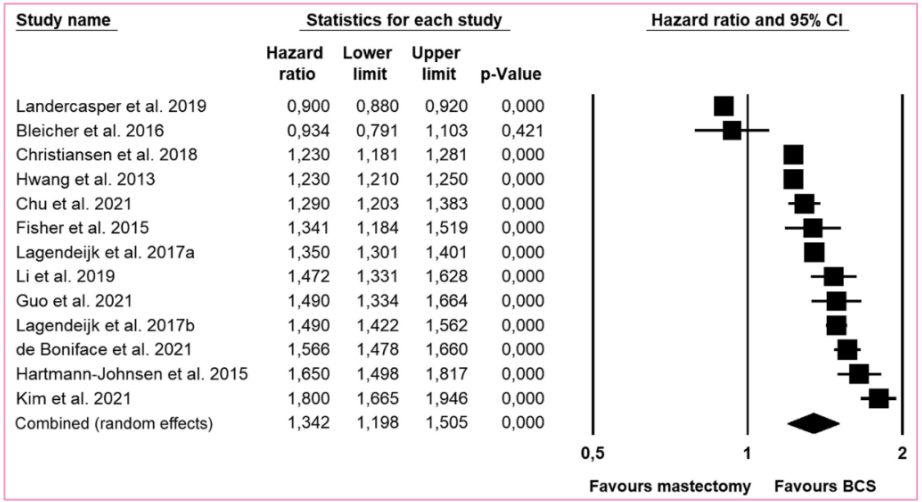
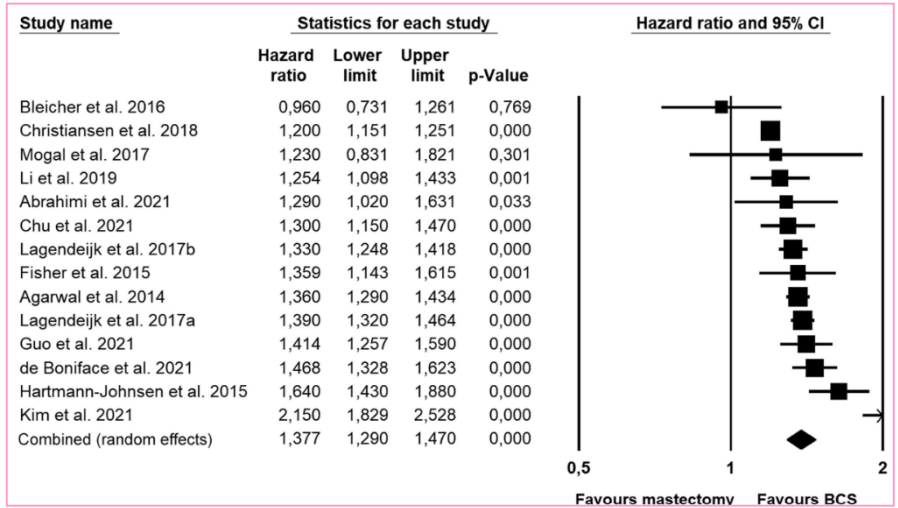
- Data demonstrating that patients with early-stage breast cancer who opt for **BCT might have an even better survival compared with those who have a mastectomy**
- Conclusion: The combined findings from **large population** based studies indicate that **BCS is associated with survival benefit compared with mastectomy**, **suggesting that BCS be the recommended treatment of early breast cancer** (T1-2N0M0) if radical lumpectomy can be performed

Meta-analysis of survival data in population-based independent cohorts of breast cancer patients.



Study name	Hazard ratio	Lower limit	Upper limit	p-Value
Landercasper et al. 2019	0,900	0,880	0,920	0,000
Bleicher et al. 2016	0,934	0,791	1,103	0,421
Christiansen et al. 2018	1,230	1,181	1,281	0,000
Hwang et al. 2013	1,230	1,210	1,250	0,000
Chu et al. 2021	1,290	1,203	1,383	0,000
Fisher et al. 2015	1,341	1,184	1,519	0,000
Lagendeijk et al. 2017a	1,350	1,301	1,401	0,000
Li et al. 2019	1,472	1,331	1,628	0,000
Guo et al. 2021	1,490	1,334	1,664	0,000
Lagendeijk et al. 2017b	1,490	1,422	1,562	0,000
de Boniface et al. 2021	1,566	1,478	1,660	0,000
Hartmann-Johnsen et al. 2015	1,650	1,498	1,817	0,000
Kim et al. 2021	1,800	1,665	1,946	0,000
Combined (random effects)	1,342	1,198	1,505	0,000



Study name	Hazard ratio	Lower limit	Upper limit	p-Value
Bleicher et al. 2016	0,960	0,731	1,261	0,769
Christiansen et al. 2018	1,200	1,151	1,251	0,000
Mogal et al. 2017	1,230	0,831	1,821	0,301
Li et al. 2019	1,254	1,098	1,433	0,001
Abrahimi et al. 2021	1,290	1,020	1,631	0,033
Chu et al. 2021	1,300	1,150	1,470	0,000
Lagendeijk et al. 2017b	1,330	1,248	1,418	0,000
Fisher et al. 2015	1,359	1,143	1,615	0,001
Agarwal et al. 2014	1,360	1,290	1,434	0,000
Lagendeijk et al. 2017a	1,390	1,320	1,464	0,000
Guo et al. 2021	1,414	1,257	1,590	0,000
de Boniface et al. 2021	1,468	1,328	1,623	0,000
Hartmann-Johnsen et al. 2015	1,640	1,430	1,880	0,000
Kim et al. 2021	2,150	1,829	2,528	0,000
Combined (random effects)	1,377	1,290	1,470	0,000

"In this meta-analysis of large, population-based studies, BCS + RT was found to be associated with survival benefit compared with mastectomy

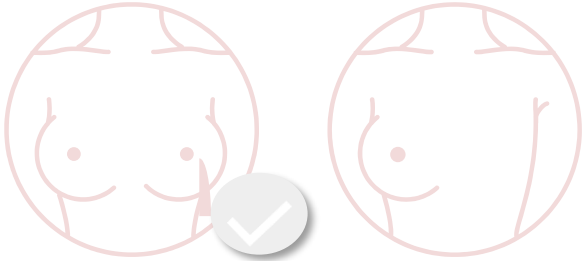
(A) Overall survival. The 13 studies included 1,311,600 patients. (B) Breast cancer-specific survival. Fourteen studies with 494,267 patients.

Christiansen P et al. Breast Conserving Surgery or Mastectomy? Annals of Surgery Open. 2022

Is tumour downstaging safe?

BCS is comparable to mastectomy for all tumour and patient variables

- Long-term LRR rates with tumour downstaging and BCS are similar to those for traditional mastectomy with adjuvant therapy[1,2]
- LRR rates are 10.3% for BCS plus XRT compared with 12.6% for mastectomy without XRT, after 10 years of follow-up[3]



No increase in complications even with immediate reconstructions[4]

BCS, breast-conserving surgery; LRR, locoregional recurrence; OS, overall survival; XRT, radiotherapy.

1. Chatterjee A & Erban JK. *Gland Surg* 2017; 2. Cain H, *et al*. *Clin Oncol* 2017; 3. Mamounas EP, *et al*. *J Clin Oncol* 2012; 4. Decker MR, *et al*. *Surgery* 2012

Who is BCS for?[1-5]

The right candidate for BCS[1-3]

Patients eligible for BCS are those who:

Have a tumour **<5 cm**, that is also small relative to the size of the breast

Are able and willing to have **radiation therapy**

Do not have active **connective tissue diseases** such as scleroderma or lupus

Have persistently **positive pathologic margin**

Have no known or suspected **genetic predisposition** (i.e., *BRCA1, BRCA2* mutations)

The benefits of BCS [4]

BCS leads to better outcomes and higher QoL compared with Mx.

As seen in a meta-analysis including 920 Asian patients.[12]

- Body image
  - ▶ SMD=1.742 (95% CI, 0.579–2.905; p=0.003)
- Future perspectives
  - ▶ SMD=0.606 (95% CI, 0.075–1.138; p=0.025)
- Lowering systemic side effects
  - ▶ SMD = –0.641 (95% CI, -1.181 to -0.101; p=0.020)

Multiple studies show advanced BCS techniques delivering good cosmetic outcomes in patients and lower rates of post-operative complications.[5]

1. National Comprehensive Cancer Network®: Breast Cancer. Version 4.2024 Retrieved from https://www.nccn.org/. Accessed Sept 2024. 2. Burstein HJ, Curigliano G, Thürlimann B, et al. Ann Oncol. 3. Jordan RM, Oxenberg J. Breast Cancer Conservation Therapy. [Updated 2022 Sep 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK547708/.2021;32(10):1216-1235. 4. Ng ET, Ang RZ, TranBX, et al. Int J Environ ResPublic Health. 2019;16(24):4970. 5. Campbell EJ, Romics L. Breast Cancer. 2017;9:521-530.

Does neoadjuvant therapy increase BCS rates?

Two measures to consider:

1 Increase in BCS rate

- Most neoadjuvant trials show a modest increase in BCS rate vs. adjuvant trials
- Increase in pCR rates in neoadjuvant trials (e.g NeoALTTO, GeparSixto) has not translated into increased BCS rates[4,5]

Trial	BCS rate (adjuvant)	BCS rate (neoadjuvant)
NSABP B18[1]	60%	68%
Institute Curie[2]	77%	82%
CALGB 40603[3]	54%*	68%

2 Conversion rate from mastectomy to BCS

- Rates of conversion from mastectomy to BCS less widely published (but are estimated to be 40–50%)[6–8]

* 54% of patients in CALGB 40603 were eligible for BCS before receiving neoadjuvant therapy.
BCS, breast-conserving surgery.

1. Rastogi R, *et al. J Clin Oncol* 2008;;
2. Scholl SM, *et al Eur J Cancer* 1994; 3. Golshan, M, *et al. Ann Surg*. 2015;
4. Criscitiello C, *et al. Ann Oncol* 2013; 5. von Minckwitz G, *et al. Lancet Oncol* 2014; 6. Chang YK, *et al. Breast Cancer* 2020; 7. Kaufmann P, *et al. Am Surg* 2006;
8 Petruolo O, *et al Ann Surg Oncol* 2020.

Primary Systemic Therapy (PST) for HER2+ Operable BC Increases the number of BCS from 5.3% to 41.4%

Patients characteristic:

- N = 152
- Stage I and II HER2/neu-positive BC
- ≥ 18 yo, median age 47 (37 – 67)
- T2: 44.1%, T3: 55.9%
- N0: 68.4%, N1: 28.9%, N2: 2.6%
- 95.7% has nonspecific type of BC
- 67% ER/PR negative
- 75.5% grade III
- 100% Ki67>20%
- 90% HER2/neu-positive through IHC
- 100% HER2/neu-positive through FISH or DISH
- 7% had indication for mastectomy

PST Regimen:

- Docetaxel 75mg/m^2 every 3 weeks
- FEC (5-fluorouracil 600mg/m^2 , Epirubicin 75mg/m^2 , Cyclophosphamide 600mg/m^2), every 3 weeks at 4 cycles
- Trastuzumab 8 mg/kg IV loading dose, followed by 6 mg/kg IV, every 3 weeks in a year including in the neoadjuvant and adjuvant setting

Following PST, pCR was achieved in **44.7%** evaluable patients

Breast Conserving Surgery was performed in **41.4%** patients

Table 3 Type of surgery pre and post primary systemic therapy (PST)

Type Surgery	Pre-PST	Post-PST
BCS	8 (5.3%) →	63 (41.4%)
Mastectomy	144 (94.7%) →	83 (58.6%)

Yohana Azhar et al. Primary Systemic Therapy for HER2/Neu-Positive Operable Breast Cancer Increases the Number of Breast-Conserving Surgery and Disease-Free Survival: Retrospective Cohort Analysis at Single Institution. Asian Journal of Oncology 2021; 07(02): 089-095. DOI https://doi.org/ 10.1055/s-0041-1729481

How to approach BCS in HER2+ or TNBC patients[1,2]

Utilising neoadjuvant therapy (NAT) to facilitate BCS outcomes[1,2]

NAT aids in optimising BCS outcomes, including in:

Downstaging the tumour to potentially reduce excision volumes in patients with large tumours.

De-escalating surgical treatment of the axilla and reduction in surgical morbidity.

Delaying surgery to afford time for genetic testing and thorough surgical planning, enabling the tailoring of surgery and facilitating informed decision-making.

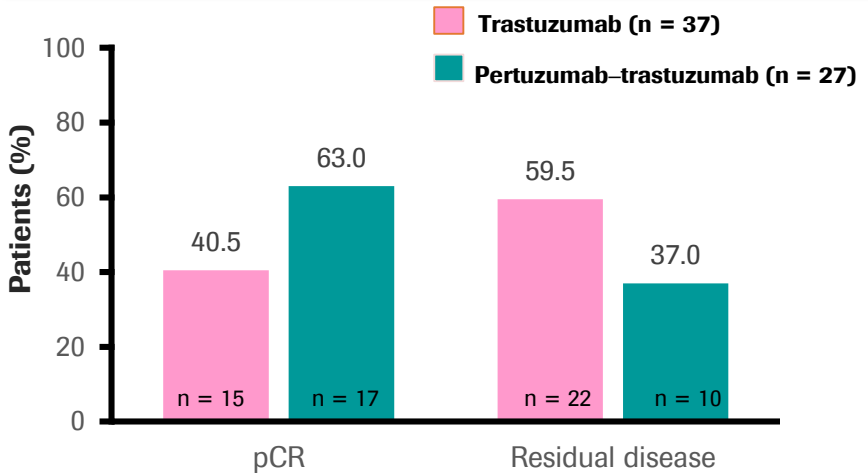
Recommendations for NAT initiation in eBC[3,4]

- NAT should be used to reduce the extent of surgery in locally advanced and large operable cancers, in particular when mastectomy is required due to tumour size [A=100% and I, A]. It should also be considered in all patients with tumours >2 cm for which chemotherapy is deemed necessary, in particular with HER2+ and TNBC subtypes [A=100% and I, B][3]
- In HER2+ patients with clinical stage II-III disease, the preferred option is initial NAT followed by local therapy. Dual blockade combined with chemotherapy achieves higher pathological complete response rates and is recommended for NAT [I, A; ESMO-MCBS v1.1 score].[4]

1. Cain H et al. Clin Oncol. 2017;29:642-652 **2.** Chatterjee A, Erban J. Gland Surg. 2017;6:119-124 3.Y.H. Park, E. Senkus-Konefka, S.A. Im, et al. Ann Oncol. 2020;31(4):451-469. 4. Loibl S, André F, Bachelot T, et al. Ann Oncol. 2024;35(2):159-182.

What can be achieved with surgical de-escalation in real clinical practice?

pCR and residual disease in patients treated with single or dual anti-HER2 therapy*



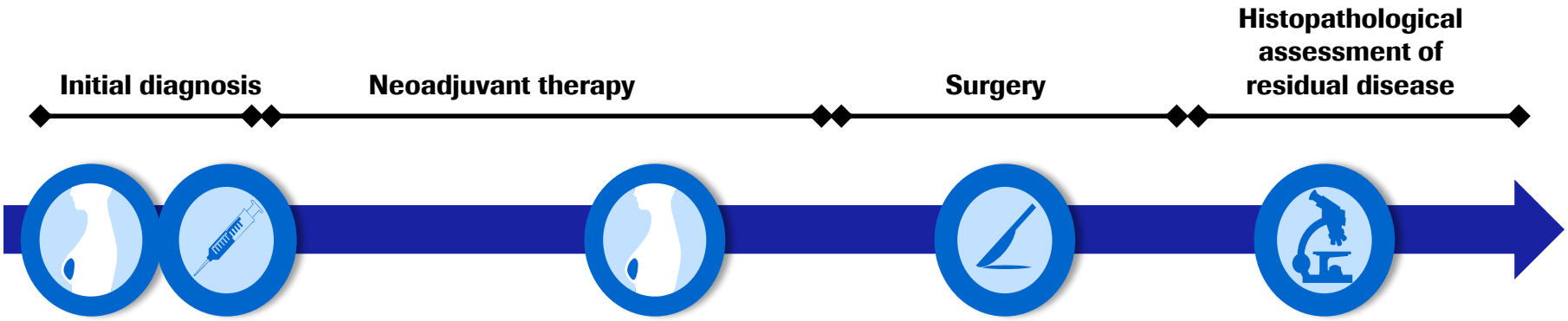
- **Downstaging** was attempted in 51 patients requiring mastectomy and was achieved in 38 **(75%) who received neoadjuvant treatment with trastuzumab or pertuzumab–trastuzumab**
- Eighteen patients **(86%) who received pertuzumab–trastuzumab achieved successful downstaging to BCS** (single vs. dual therapy, p = 0.56)

pCR and successful BCS were higher in patients receiving pertuzumab–trastuzumab vs. trastuzumab

* Retrospective analysis data from a large screening institution (Royal Victoria Infirmary) of all patients undergoing neoadjuvant treatment with single or dual anti-HER2 therapy from May 2014–November 2017.
McLean R, *et al*. *Eur J Surg Oncol* 2019 (Abstract P086).

Response-directed adjuvant therapy and how it shapes our practice as surgeon

Assessment of residual disease is done both clinically and histopathologically



Clinical assessment of residual disease

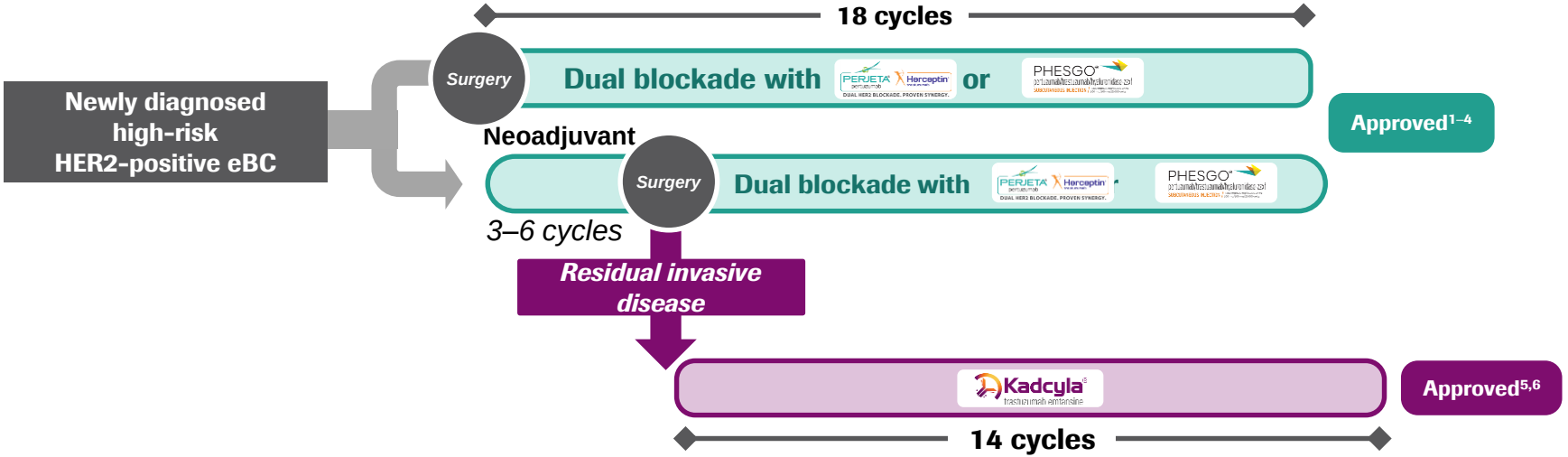
Assessment may involve palpation, ultrasound or MRI

Histopathological evidence of residual disease is assessed using resected tumour samples, supported by specimen radiography

Role: Surgical Oncologist, PA

MRI, magnetic resonance imaging.
Bossuyt V, *et al. Ann Oncol* 2015.

Treatment algorithm for HER2-positive eBC in adjuvant setting

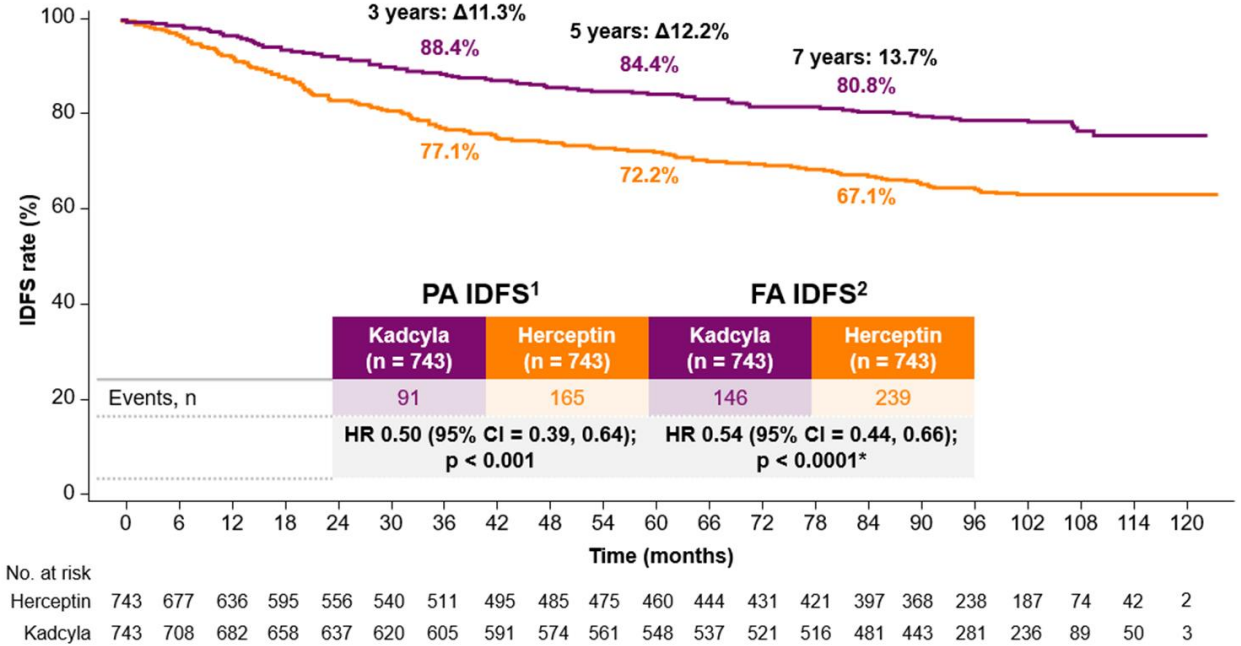


SoC for patients with HER2-positive eBC at high risk of recurrence is 18 cycles of PH/PHESGO, irrespective of the time of surgery, except in the presence of any residual invasive disease after neoadjuvant treatment, when therapy should be changed to Kadcyla for 14 cycles post-surgery[1-5]

BC, breast cancer; eBC, early breast cancer; PH, PERJETA–Herceptin; PHESGO, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous use; SoC, standard of care.

1. BPOM. Product Information Perjeta 2023; 2. BPOM. Product Information PHESGO 2023;; 3. BPOM Product Information Kadcyla June 2022; 4. NCCN Breast Cancer Guidelines – Version 4. 2024; 5. Cardoso F, *et al. Ann Oncol* 2019; **30:**1194–1220.

KATHERINE Final Analysis demonstrates the benefit of adapting treatment in patients with residual invasive disease after neoadjuvant therapy



Δ7-year IDFS = 13.7%

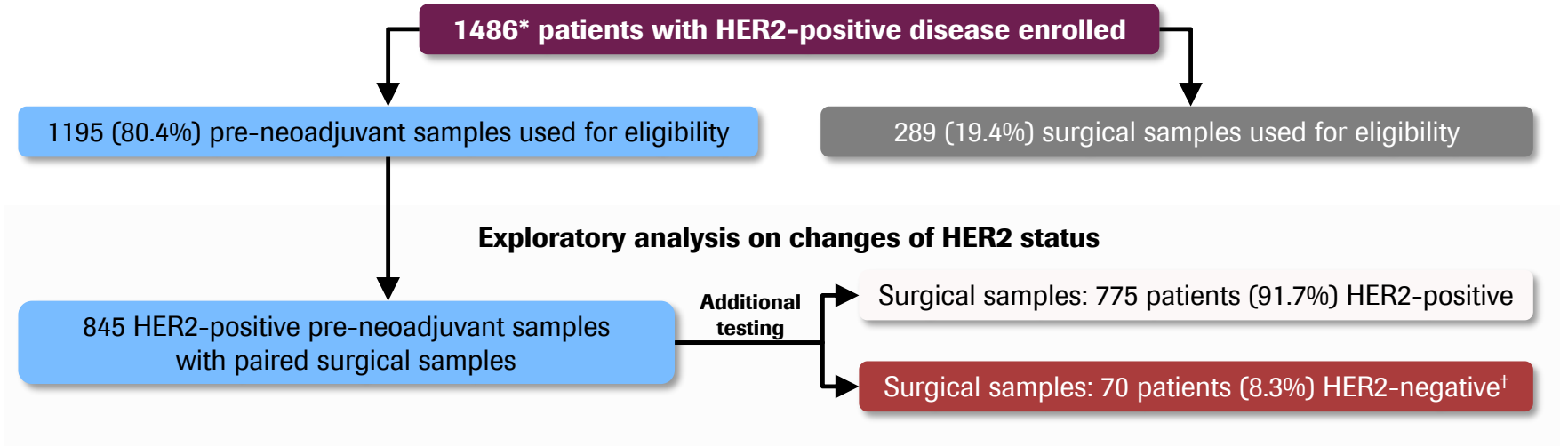
With this results of KATHERINE, the recommendation and rationale to do neoadjuvant treatment prior to surgery for HER2-positive patients become stronger than ever.

IDFS benefit of Kadcyla was sustained with longer median follow-up (101 mo), with a 46% reduction in risk of recurrence of invasive disease or death vs. Herceptin

* Median follow-up of 41.4 months.

Reference: 1. Von Minckwitz G, *et al. N Engl J Med* 2019. 2. Loibl S, *et al.* SABCS 2023 (Abstract GS03-12; oral presentation).

KATHERINE: HER2-negative status at surgery did not impact on the efficacy of T-DM1



In the 70 patients with HER2-negative disease after re-testing of surgical samples:

- **No IDFS events in patients randomised to the T-DM1 arm (n = 28)**
- **11 IDFS events in patients randomised to the trastuzumab arm (n = 42)**

Note: These data should be interpreted with caution due to the small sample size

* Two patients (both in the trastuzumab arm) were not included in this analysis: One did not have centrally confirmed HER2-positive disease and one was inadvertently randomised twice.
† Fifty-three HER2-negative and 17 HER2-unknown by IHC 0-1+/ISH unknown.
IDFS, invasive disease-free survival.

Loibl S, *et al.* ESMO Breast Cancer 2020 (Abstract 96O and oral presentation).

T-DM1 is recommended by most international guidelines for patients with residual disease

NCCN Breast Cancer Guidelines V4. 2024 [1]

Category 1 listing*

If residual invasive disease after preoperative therapy:

Trastuzumab emtansine alone for 14 cycles

ESMO Guidelines for eBC (2019) [4]

Grade [I, A] recommendation

If residual invasive disease:

Trastuzumab emtansine recommended

AGO Guidelines 2022 [2]

If pathological complete response not achieved (non-PCR) :

Trastuzumab emtansine recommended to complete 1 year of anti-HER2 therapy (LoE 1b)†

St. Gallen Guidelines (2021) [5]

If residual invasive disease:

Trastuzumab emtansine recommended for patients with residual HER2 positive breast cancer following standard neoadjuvant regimens, including node-negative and residual cancers < 5mm

ASCO Guidelines 2021 [3]

If pathologic invasive residual disease after preoperative therapy

14 cycles of adjuvant trastuzumab emtansine is recommended, unless there is disease recurrence or unmanageable toxicity

Pan Asian Adapted ESMO Guidelines 2024 [6]

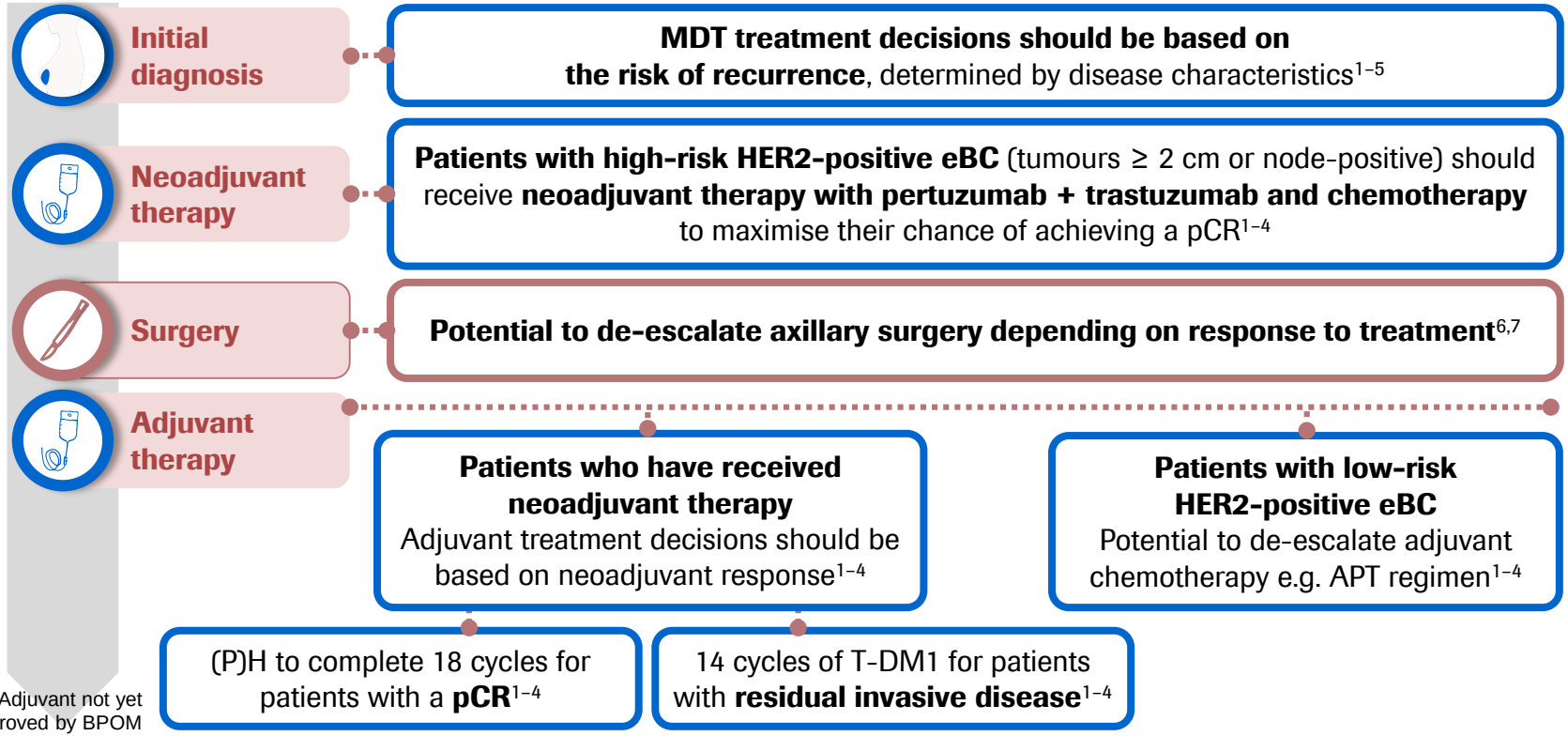
In cases of residual invasive disease after neoadjuvant therapy :

Adjuvant trastuzumab should be replaced by adjuvant T-DM1, once approved and where available

* Category 1 listings are based on high-level evidence with uniform NCCN consensus that the intervention is appropriate;
† Based on evidence of individual randomised controlled trials; ‡ Grade A recommendation based on strong evidence for efficacy with a substantial clinical benefit; strongly recommended.

1. NCCN Clinical Practice Guidelines: Breast Cancer. v4 2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf (accessed 11 July 2024)
2. Ditsch N, et al. AGO Recommendations for the Diagnosis and Treatment of Patients with Early Breast Cancer: Update 2022. Breast Care. 2022;17(4):403-420. doi: https://doi.org/10.1159/000524879.
3. Denduluri N, et al. Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer: ASCO Guideline Update. Journal of Clinical Oncology. 2021;39(6):685-693. doi: https://doi.org/10.1200/jco.20.02510
4. Cardoso F, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Annals of Oncology. 2019;30(8):1194-1220. doi: https://doi.org/10.1093/annonc/mdz173
5. Burstein HJ, Curigliano G, Thürlimann B, et al. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021. Ann Oncol.2021;32(10):1216-1235. doi:10.1016/j.annonc.2021.06.023
6. K.H Park., et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with early breast cancer. Volume 9, Issue 5, May 2024, https://doi.org/10.1016/j.esmoop.2024.102974

Summary



(P) Adjuvant not yet approved by BPOM

BCS, breast-conserving surgery; eBC, early breast cancer; MDT, multidisciplinary team; pCR, pathological complete response.

1. NCCN Breast Cancer Guidelines. Version 4, 2024; 2. AGO Breast Cancer Guidelines. 2023;
3. Cardoso F, *et al*. *Ann Oncol* 2019; 4. Burstein HJ, *et al*. *Ann Oncol* 2019;
5. Cain H, *et al*. *Clin Oncol* 2017; 6. Galimberti V, *et al. EJSO* 2016;
7. van der Noordaa MEM, *et al. Ann Surg Oncol* 2018.

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- Additional information will be requested during a product-exposed pregnancy and the first year of the infant's life. This will enable Roche to better understand the safety of the product and to provide appropriate information to health authorities, healthcare providers, and patients.
- For additional information, please refer to the Product Information.

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