Optimal Early Breast Cancer Diagnosis & Management: A Collaborative Approach

DR dr Denni Joko Purwanto, SpB.Subs.Onk(K)

M-ID-00001567-10-2024

Disclaimer

- These educational sessions are conducted for scientific educational purpose, they may contain information relating to products not yet approved by BPOM, or contain information that is not within the current product label
- This slide contains patients case owned by this speaker and are not influenced by the sponsoring company or the event owner
- These materials are intended only for healthcare professionals

Pregnancy disclaimers

- If a patient becomes pregnant while receiving Phesgo, Perjeta, or Herceptin or within 7 months following the last dose of the product, please immediately report pregnancy to the Roche Patient Safety via email indonesia.safety@roche.com
- 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 Product Information

Timeline of oncologic breast surgery.

J. Heil et al., Annal of Oncology 2020

1894 – William S Halsted
Radical mastectomy

1948 – Patey and Dyson
Modified radical mastectomy

1991 – Toth and Lappert
Skin-sparing mastectomy

2019 – Future vision (next decade)
Clinical trials testing oncologic safety of omitting surgery for patients with pCR

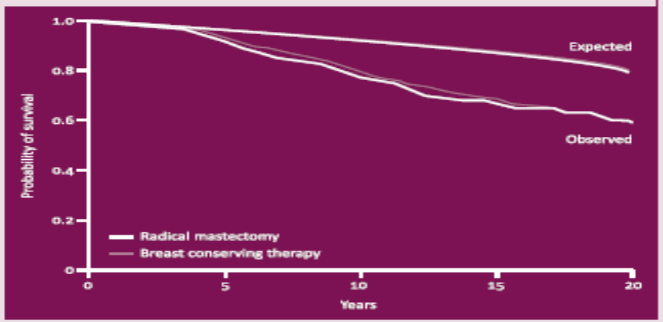
1937 – Geoffrey Keynes
Radical mastectomy – radiation therapy

1973 – EBCTG
First adjuvant systemic treatment: tamoxifen improves overall survival

2001 – Crowe
Nipple-sparing mastectomy

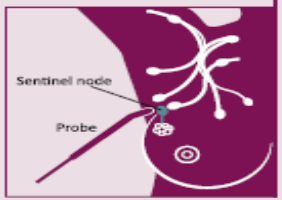
1894 → 1937 → 1948 → 1973 → 1981 → 1985 → 1991 → 1994 → 2001 → 2016 → 2019

Surgical invasiveness



1981 – Milan trials

1985 – NSAPB B-04 trial
Lumpectomy – modified radical mastectomy



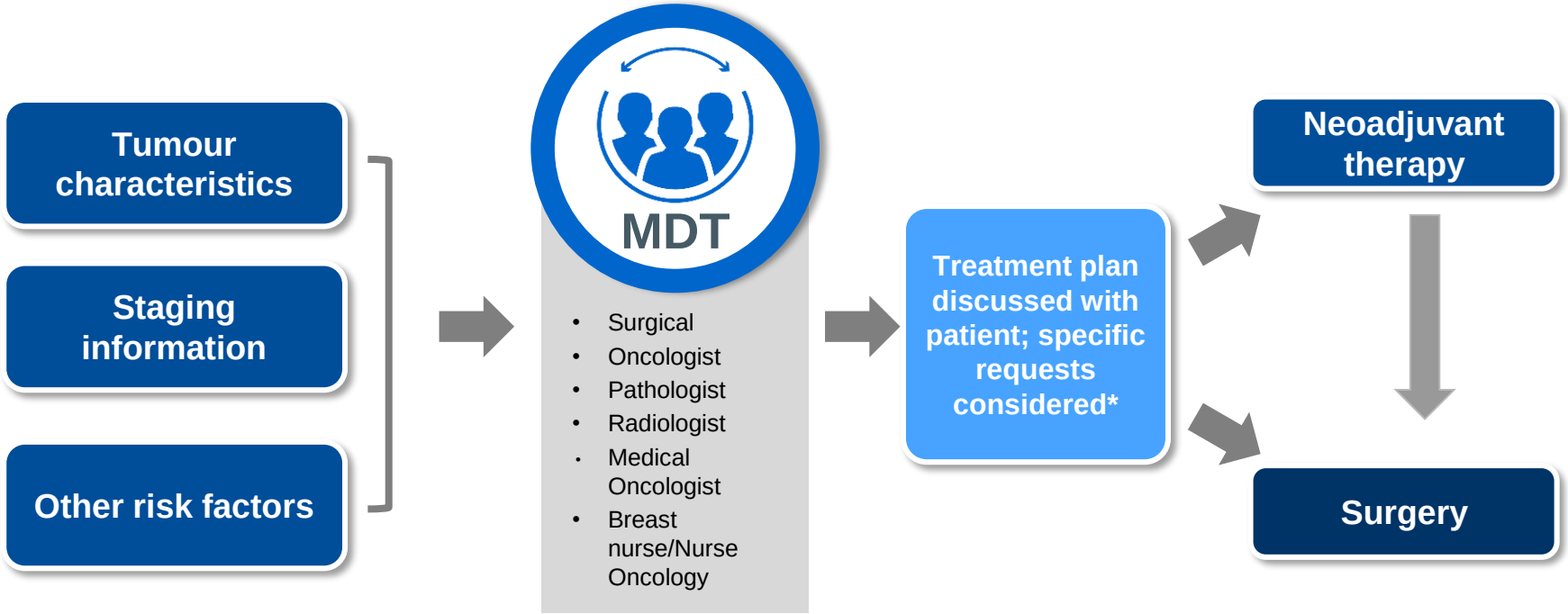
1994 – Giuliano et al
Sentinel lymph node biopsy by blue dye mapping

2016 – ACOSOG Z0011 trial
SLND – ALND (in patients with 1–2 lymph nodes containing metastasis)

Caudle
Targeted axillary dissection by clipmarking

2019 – Ongoing trials
Dignosing pCR by minimal-invasive biopsy instead of surgery after neo-adjuvant treatment

MDTs are essential for optimal management of patients with Early Breast Cancer[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.

Article

The Improved Effects of A Multidisciplinary Team on the Survival of Breast Cancer Patients: Experiences from China

Jianlong Lu [1,2], Yan Jiang [2], Mengcen Qian [1], Lilang Lv [2] and Xiaohua Ying [1,*]

1 NHC Key Laboratory of Health Technology Assessment (Fudan University), School of Public Health, Fudan University, Dongan Road 130, Shanghai 200032, China; 17111020025@fudan.edu.cn (J.L.); qianmengcen@fudan.edu.cn (M.Q.)

2 Shanghai Cancer Center, Fudan University, Dongan Road 270, Shanghai 200032, China; sandyjy@126.com (Y.J.); lvlanglang@hotmail.com (L.L.)

* Correspondence: xhying@fudan.edu.cn

Received: 2 December 2019; Accepted: 25 December 2019; Published: 31 December 2019

A total of **16.354 patients undergoing breast cancer surgery** during the **period 2006–2016 at the Fudan University Shanghai Cancer Center** were retrospectively extracted. Patients treated by MDT were divided into **A well-organized group and A disorganized group based on their organized MDT**, professional attendance, style of data and information delivery, and the length of discussion time for each patient. Other patients, who were not treated by MDT, were placed in A non-MDT group as A comparator group. Each MDT patient was matched with A non-MDT patient, using propensity score matching to reduce selection bias

Multidisciplinary teams (MDTs) are composed of healthcare professionals **(including surgeons, oncologists, radiologists, pathologists, and specialist nurses), and aim to reach A consensus on the diagnosis and treatment of patients, based on scientific and experiential evidence.** A coordinator is responsible for organizing the MDT meetings . MDTs make decisions regarding diagnosis and treatment programs through MDT meetings

Table 1. The main organizational differences of MDT before and after 2011.

Determinants	Before 2011 (Disorganized MDT)	After 2011 (Well-Organized MDT)
Organization	Chairman	Secretary
Attendance	Surgeons, physicians, Imaging doctors	Surgeons, physicians, Imaging doctors, Pathology doctor
Information delivery	At the meeting	Before the meeting
Number of patients	Unlimited	About four patients
Discussion time per patient	5–10 min	20–30 min
Patient data	Photographic, paper	Electronic

MDT: Multidisciplinary teams.

Int. J. Environ. Res. Public Health 2020, 17, 277; doi:10.3390/ijerph17010277 w

Table 4. The effects of MDT group and N-MDT group after PSM (patients from 2006 to 2016, $n = 436$).

Groups	1-Year Survival Rate (%)	3-Year Survival Rate (%)	5-Year Survival Rate (%)	Median Survival Time (Day)
MDT (2006–2016)	98.5	81.6	65.6	1131
N-MDT (2006–2016)	97.6	77.4	72.8	946
p value $^{\alpha}$	0.475	0.285	0.097	0.126
Panel A				
MDT (2006–2010)	99.0	79.5	58.8	1785
N-MDT (2006–2010)	99.0	82.2	78.7	2358
p value $^{\beta}$	0.983	0.643	0.004	0.001
Panel B				
MDT (2011–2016)	98.1	84.1	78.8	790
N-MDT (2011–2016)	95.4	67.9	63.2	647
p value $^{\gamma}$	0.250	0.004	0.007	0.043

MDT: Multidisciplinary teams; N-MDT: without multidisciplinary teams' treatment; PSM: propensity score matching; Panel A: patients who were treated during 2006–2010 after PSM; Panel B: patients who were treated during 2011–2016 after PSM; p value $^{\alpha}$: the probability of the hypothesis that the difference between MDT (2006–2016) and N-MDT (2006–2016) was caused by sampling error; p value $^{\beta}$: the probability of the hypothesis that the difference between MDT (2006–2010) and N-MDT (2006–2010) was caused by sampling error; p value $^{\gamma}$: the probability of the hypothesis that the difference between MDT (2011–2016) and N-MDT (2011–2016) was caused by sampling error; the p value comes from chi-square.

The Improved Effects of A Multidisciplinary Team on the Survival of Breast Cancer Patients Experiences from China : Well Organized MDT give the best survival outcome

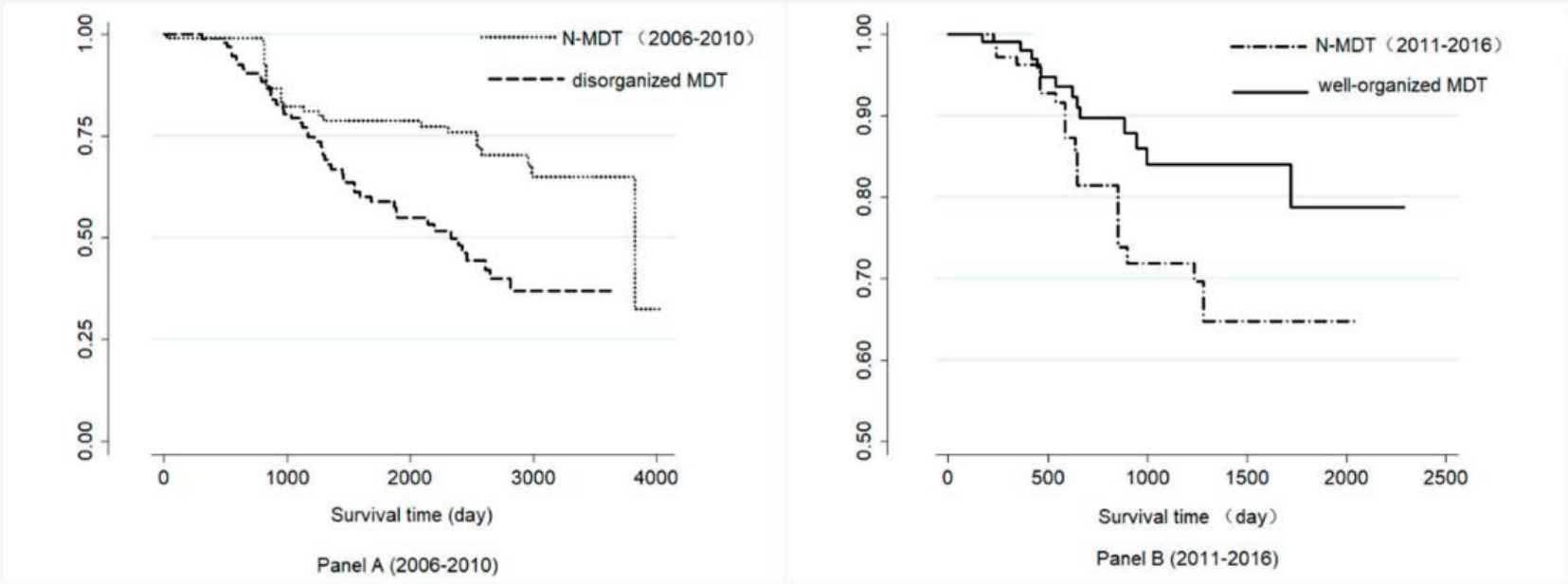


Figure 3. Survival curves of the different groups in Panel A and Panel B. MDT: Multidisciplinary teams, N-MDT: without multidisciplinary teams' treatment; Panel A: patients who were treated during 2006–2010 after PSM; Panel B: patients who were treated during 2011–2016 after PSM.

Int. J. Environ. Res. Public Health 2020, 17, 277; doi:10.3390/ijerph17010277 w

Several imaging techniques are used for radiological work-up of eBC

Ultrasound or mammogram

Accurate staging (cT)

MRI[1,2]

- Better concordance with pCR in HER2-positive BC and TNBC
- Superior with regards to operative planning

PET-CT[2]

- Role for response assessment is unclear
- Suggested higher specificity but lower sensitivity than MRI for prediction of pCR

MRI, magnetic resonance imaging; pCR, pathological complete response; PET-CT, positron emission tomography - computed tomography.

1. Lobbes MB, *et al, Insights Imaging* 2013; 2. Li H, *et al. Breast* 2018.

Pre-therapeutic Assessment of Breast

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ Clinical examination	5	D	++
▪ Mammography (completion of the imaging)	2b	B	++
▪ + Tomosynthesis (DBT)***	2b	B	+
▪ Contrast-enhanced mammography (alone) adjusted with regards of radiation sensitivity of patient and availability*	2a	B	+
▪ Sonography (breast)	2b	B	++
▪ MRI*	1b	A	+
▪ Minimally invasive biopsy**	1b	A	++
▪ Breast-CT	4	D	-
▪ Axillary PET (PET-CT, PET-MR)	2b	B	-

* MRI- or CEM guided vacuum biopsy is mandatory in case of MRI- or CEM detected additional lesions (in house or with cooperations). Individual decision for patients at high familiar risk, with dense breast (density C / D), lobular invasive tumors, suspicion of multilocular disease.

** Histopathology of additional lesions if relevant for treatment

*** Replacement of additional FFDM with SM

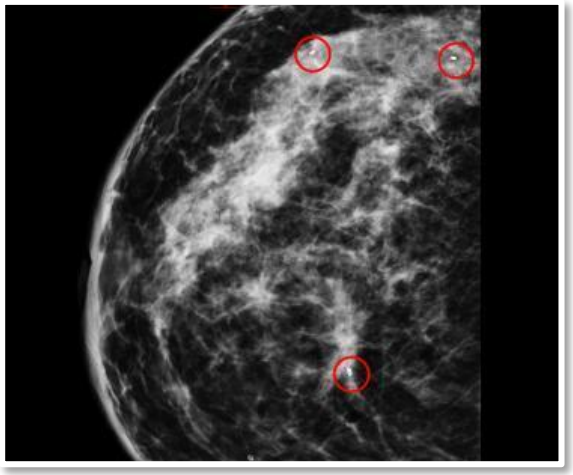
Pre-treatment marking is essential if breast and axillary surgery are to be altered following treatment

- Many patients will have a complete radiological response (CRR) so pre-treatment marking is essential
- Axillary clips improve the false-negative rate of post-neoadjuvant axillary staging
- Even if mastectomy is mandated or planned, marking the original disease facilitates pathological assessment after surgery

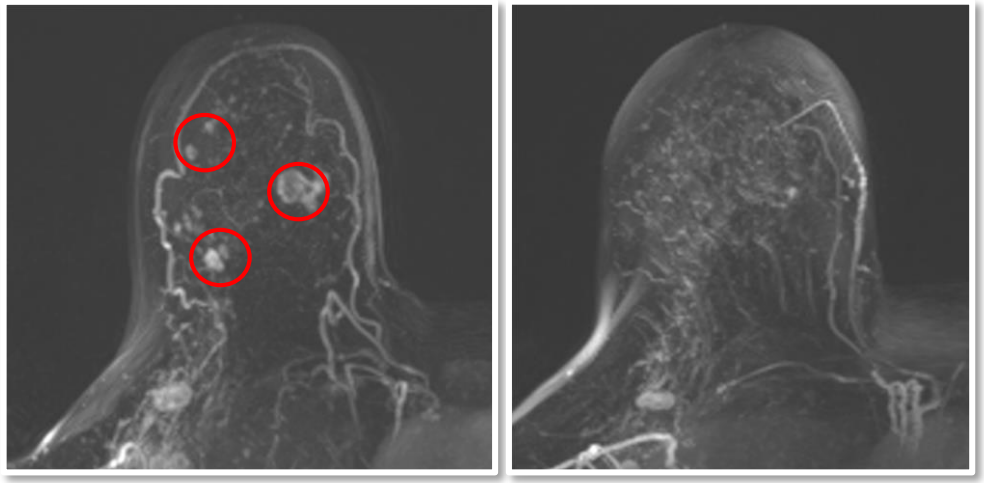
Caudle AS, *et al. J Clin Oncol* 2016.

Radiological clips are especially useful in multifocal HER2+, TNBC. HR+/HER2- disease (recommended Neoadjuvant)

Pre-treatment clips



Pre- and post-treatment MRI



MRI, magnetic resonance imaging.

Images courtesy of Mr Henry Cain.

Pathological workup is critical for ensuring the correct treatment plan for each patient

Establishes tumour type (e.g. lobular, ductal) to give an indication of predicted response to neoadjuvant treatment

Establishes tumour biology (e.g. HER2+, HR+) to select patients for neoadjuvant therapy

Axillary assessment: FNA or core biopsy

FNA, fine needle aspiration; HR, hormone receptor.

Viale G, *The Breast* 2011.

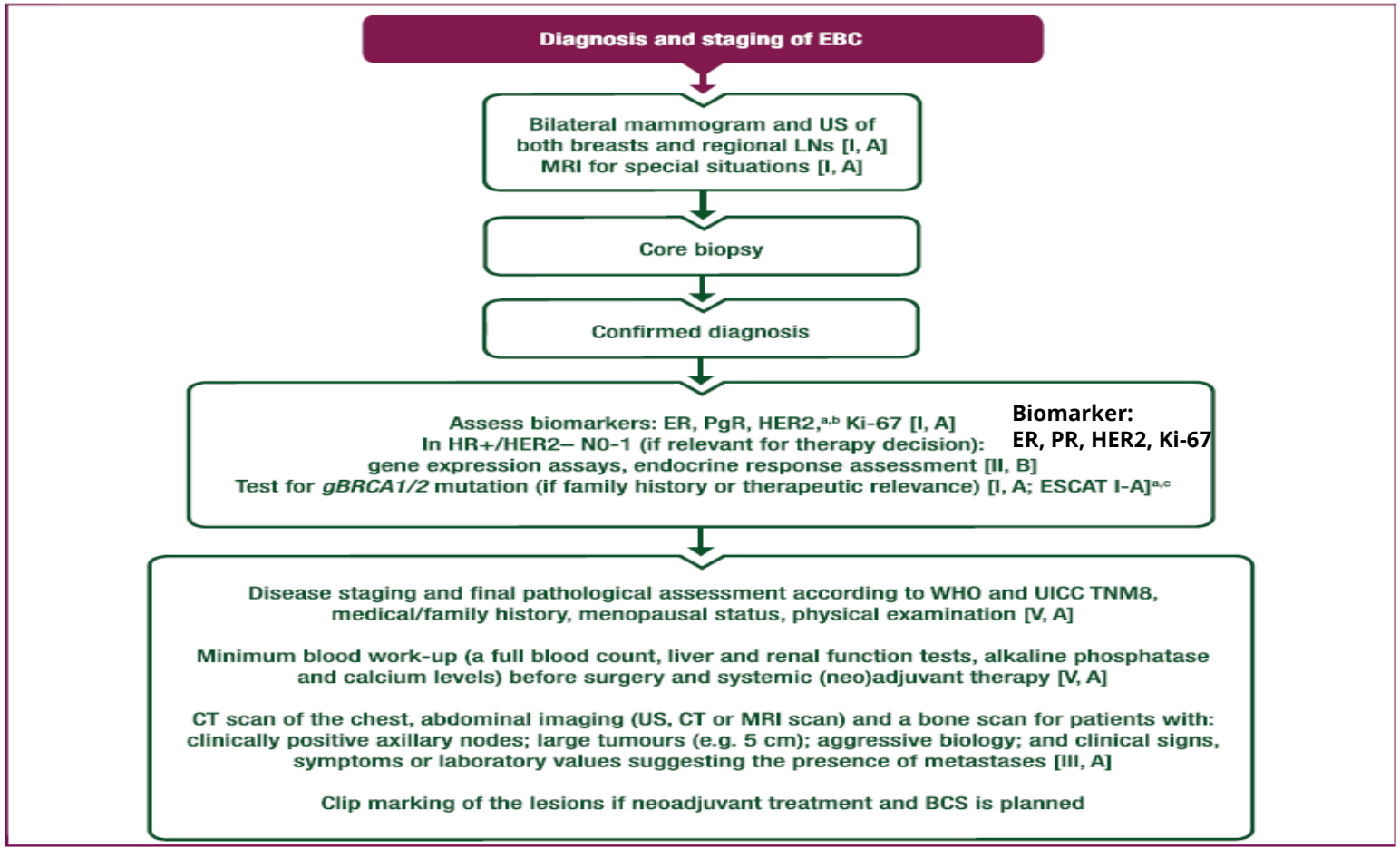
Guidelines Breast
Version 2024.1E

Preanalytics: Fixation

	Oxford		
	LoE	GR	AGO
▪ Minimize time to fixation (cold ischemia time)	5	D	++
★ ▪ Minimal fixation time of 6 hours for optimal antigen preservation	5	D	++
★ ▪ Optimal fixation time 6 - 72 h for core biopsies	5	D	++
★ ▪ Optimal fixation time for resection specimens: 12 - 72 h	5	D	++
★ ▪ Use of neutral buffered formalin	5	D	++

ESMO EBC 2024 Guideline

S. Loibl et al., Annal Oncology, 2024, Vol.35 Issue 2



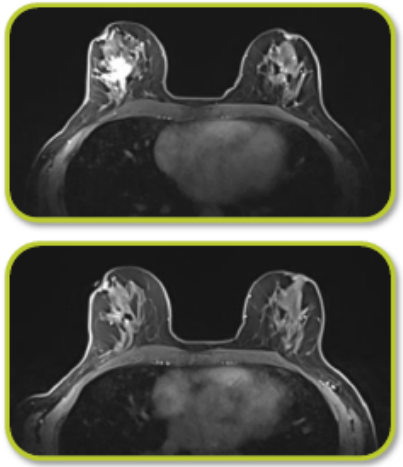
The primary aim of neoadjuvant therapy

St. Gallen Expert Consensus

HER2-positive patients in stage II with lymph node involvement (N+) or those in stage III should preferably receive neoadjuvant combination therapy

Impact on surgery[1,2]

- Downstages from mastectomy to BCS
- Downstages axilla, avoiding axillary dissection
- Improves cosmetic outcomes of BCS



Other key advantages[1–3]

- Allows time for *BRCA1/2* testing
- Allows time for more complex reconstructive surgery option
- Provides an opportunity to adjust adjuvant treatment depending on NAT outcome
- Patients are encouraged by early treatment responses

Disadvantages ?

- Risk of cancer progressing and becoming inoperable[1]
- Less optimal for fertility preservation[1]

BCS, breast conserving surgery; NAT, neoadjuvant therapy.

1. Cain H, et al . Clin Oncol 2017; 2. Volders JH, et al . Breast Cancer Res Treat 2018; 3. KH Park, et al., Pan ESMO Asia 2024.

PRINCIPLES OF PREOPERATIVE SYSTEMIC THERAPY

Known Benefits of Preoperative Systemic Therapy
- Facilitates breast conservation
- Can render inoperable tumors operable
- Treatment response provides important prognostic information at an individual patient level, particularly in patients with TNBC or HER2-positive breast cancer
- Identifies patients with residual disease at higher risk for relapse to allow for the addition of supplemental adjuvant regimens, particularly in patients with TNBC or HER2-positive breast cancer.
- Allows time for genetic testing
- Allows time to plan breast reconstruction in patients electing mastectomy
- Allows time for delayed decision-making for definitive surgery

Opportunities
- May allow SLNB alone if initial cN+ becomes cN0 after preoperative therapy
- May provide an opportunity to modify systemic treatment if no preoperative therapy response or progression of disease
- May allow for more limited radiation fields in patients with cN+ who become cN0/pN0 after preoperative therapy
- Provides excellent research platform to test novel therapies and predictive biomarkers

Cautions
- Possible overtreatment with systemic therapy if clinical stage is overestimated
- Possible undertreatment locoregionally with radiotherapy if clinical stage is underestimated
- Possibility of disease progression during preoperative systemic therapy

Candidates for Preoperative Systemic Therapy
- Patients with inoperable breast cancer:
  - IBC
  - Bulky or matted cN2 axillary nodes
  - cN3 nodal disease
  - cT4 tumors
- In select patients with operable breast cancer
  - Preoperative systemic therapy is preferred for:
    - HER2-positive disease and TNBC, if ≥cT2 or ≥cN1
    - Large primary tumor relative to breast size in a patient who desires breast conservation
    - cN+ disease likely to become cN0 with preoperative systemic therapy
  - Preoperative systemic therapy can be considered for cT1c, cN0 HER2-positive disease and TNBC
- Patients in whom definitive surgery may be delayed.

Non-candidates for Preoperative Systemic Therapy
- Patients with extensive in situ disease when extent of invasive carcinoma is not well-defined
- Patients with a poorly delineated extent of tumor
- Patients whose tumors are not palpable or clinically assessable

Pan ESMO Asia EBC 2024 Guideline

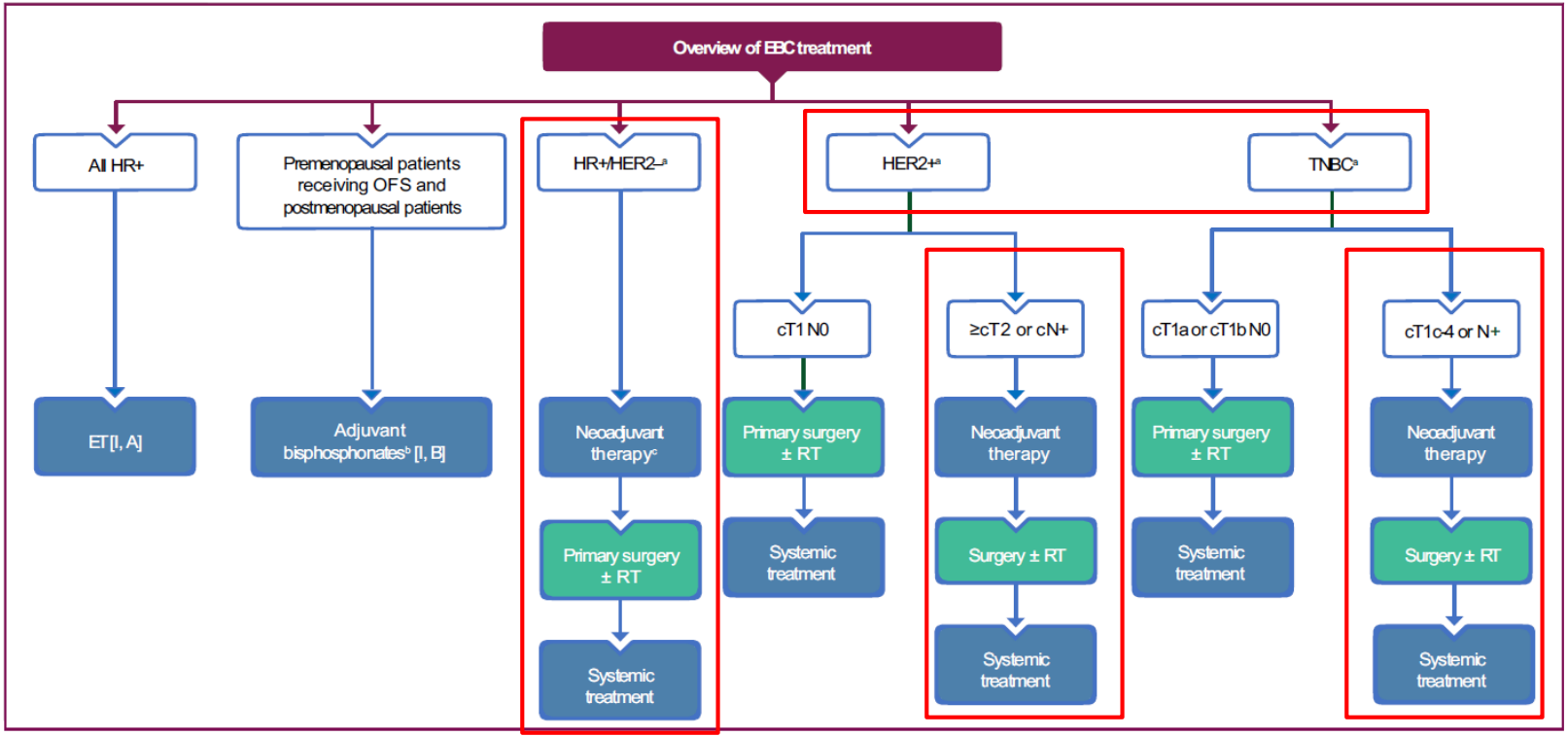


Figure 1. EBC treatment overview. Burgundy box: general categories or stratification; blue boxes: systemic anticancer therapy; turquoise boxes: combination of treatments or other systemic treatments; white boxes: other aspects of management.
ALN, axillary lymph node; c, clinical; ChT, chemotherapy; CPG, Clinical Practice Guideline; DCIS, ductal carcinoma *in situ*; EBC, early breast cancer; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; N, node; OFS, ovarian function suppression; RT, radiotherapy; T, tumour; TNBC, triple-negative breast cancer.

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, April 2024. https://doi.org/10.1016/j.esmoop.2024.102974

St Gallen International Consensus Conference for the Primary Therapy of Individuals with Early Breast Cancer 2023

Table 2. Systemic therapy for HER2-positive or TNBCs

Stage		Tumor subtype	
		HER2 positive	TNBC
Stage I Typically as adjuvant therapy	T1a	TH—case by case (with ET therapy if HR positive)	Chemo—case by case
	T1b	TH	TC or AC/EC chemo
	T1c	TH	AC/T or TC chemo
Stage II Neoadjuvant therapy preferred		AC/TH or TCH, with addition of P if neoadjuvant and/or node-positive	AC/T chemo[a] (For cT2 cN0, consider addition of pembrolizumab[b])
Stage III Neoadjuvant therapy preferred		AC/THP or TCHP[c]	AC/T chemo[a] and pembrolizumab[d]
Residual invasive cancer after neoadjuvant therapy		Trastuzumab emtansine (T-DM1) for 14 cycles	Capecitabine every 3 weeks for six or eight cycles if gBRCA1/2-wt Olaparib for 1 year if gBRCA1/2-mut Pembrolizumab for nine courses (if given in the neoadjuvant setting)

A, anthracycline such as doxorubicin or epirubicin; C, cyclophosphamide; ET, Endocrine therapy; H, trastuzumab; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; P, pertuzumab; T, taxane; TC, Docetaxel and cyclophsphamide; TNBC, triple-negative breast cancer.

[a]Some panelists favor inclusion of carboplatin in neoadjuvant therapy for TNBC, particularly if used in node-positive cancers and in conjunction with pembrolizumab-based treatment.

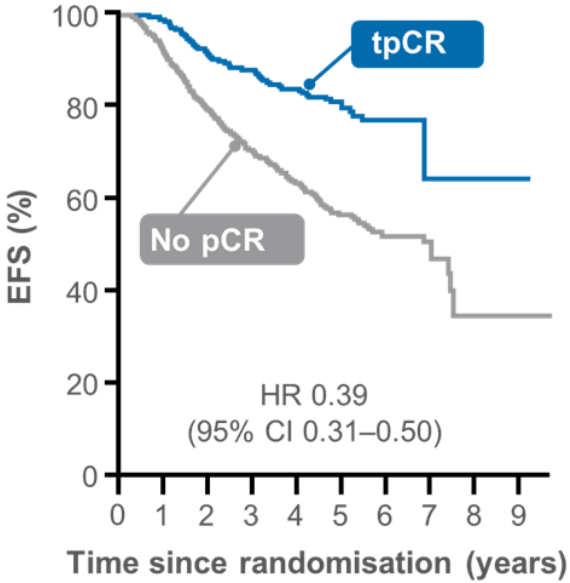
[b]In KEYNOTE-522, patients cT2 cN0 were eligible to pembrolizumab.

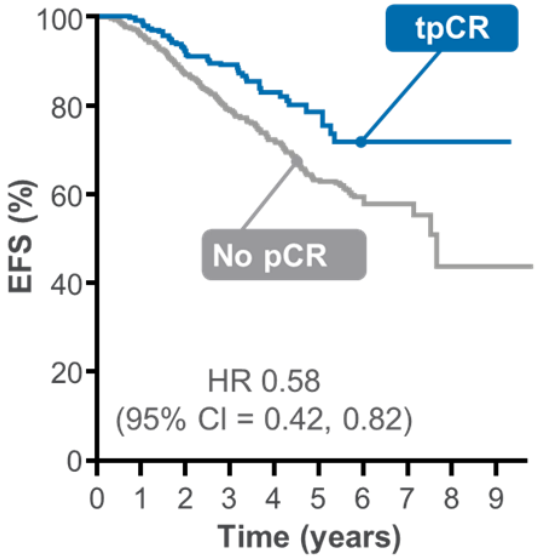
[c]Consider addition of adjuvant neratinib after trastuzumab if tumor is ER-positive and four or more positive LN; however, the panel noted there are no data for use in patients also receiving pertuzumab or trastuzumab emtansine as is often standard for such patients.

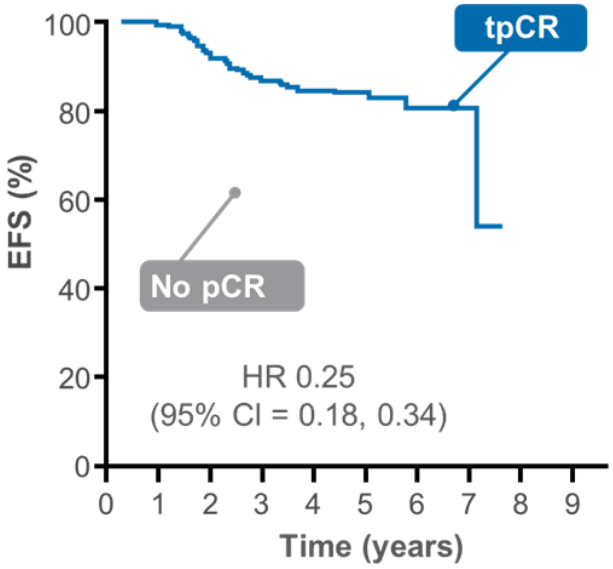
[d]Consider adjuvant pembrolizumab regardless of extent of response.

G. Curigliano et al. St Gallen Consensus EBC 2023, Annals Oncology 2023

CTNeoBC meta-analysis: EFS benefit after pCR was more pronounced in HER2-positive, HR-negative tumours







* Meta-analysis included patients treated with chemotherapy only and with HER2-targeted therapy plus chemotherapy.
CI, confidence interval; HR, hazard ratio.

Cortazar P, *et al*. *Lancet* 2014; **384**:164–172.

pCR Following Neoadjuvant Chemotherapy plus anti HER2 as Prognosis Factor for Better Survival Outcome

CONSORT Diagram of Patients in 11 NAT trials for HER2+ eBC

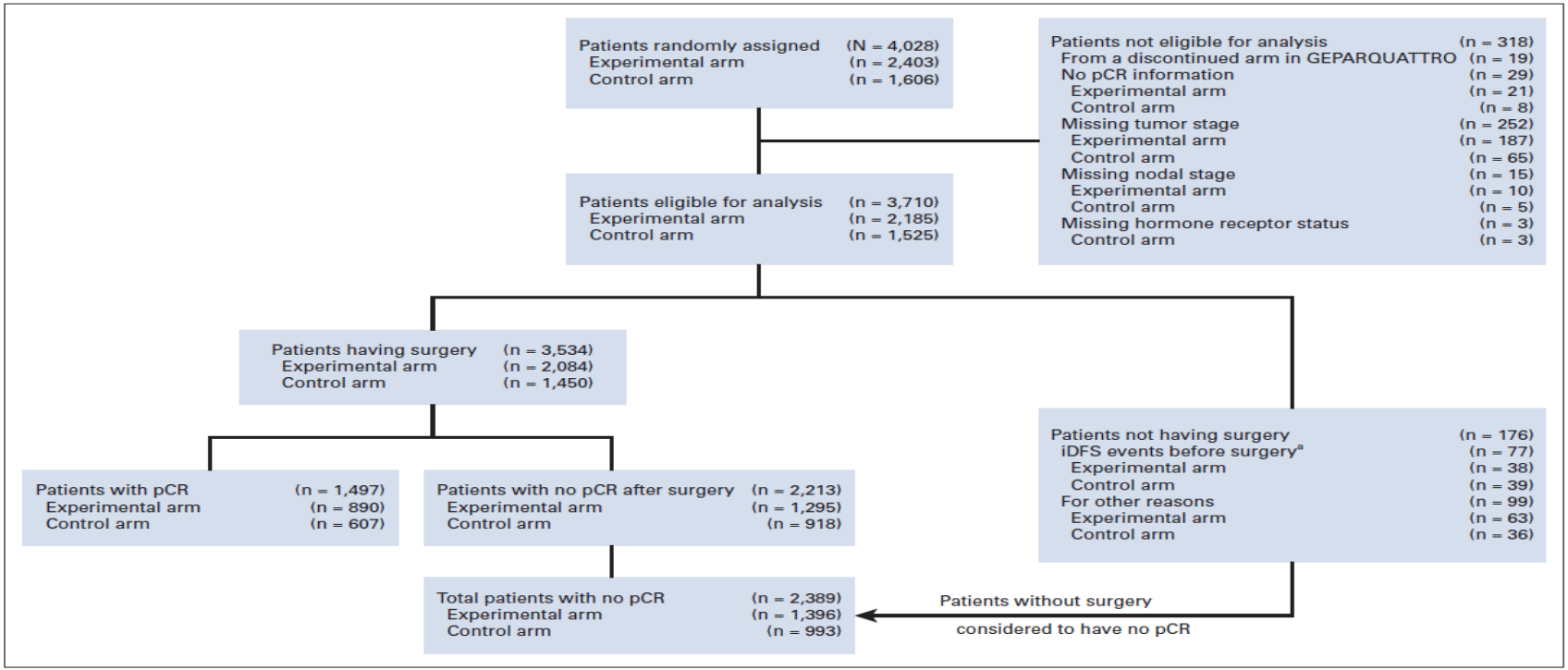


FIG 1. CONSORT diagram. [a]Events before surgery not necessarily within the planned neoadjuvant therapy period. iDFS, invasive disease-free survival; pCR, pathologic complete response.

Mackelenbergh M et al. pCR and Prognosis in HER2-Positive Early Breast Cancer, J Clin Oncol 2023

pCR Following Neoadjuvant Chemotherapy plus anti HER2 as Prognosis Factor for Better Survival Outcome

Results and Conclusion

RESULTS The median follow-up overall was 61.2 months. In pCR+ patients, cT and cN were significant independent prognostic factors for EFS, whereas only cT was a significant predictor for OS. In pCR− patients, cT, cN, and hormone receptor status were significant independent predictors for both EFS and OS. Regardless of hormone receptor status, cT, and cN, the 5-year EFS/OS rates were higher in pCR+ patients than in pCR− patients. In most subsets with regards to hormone receptor and pCR status, cT and cN were independent prognostic factors for both EFS and OS, including pCR+ patients.

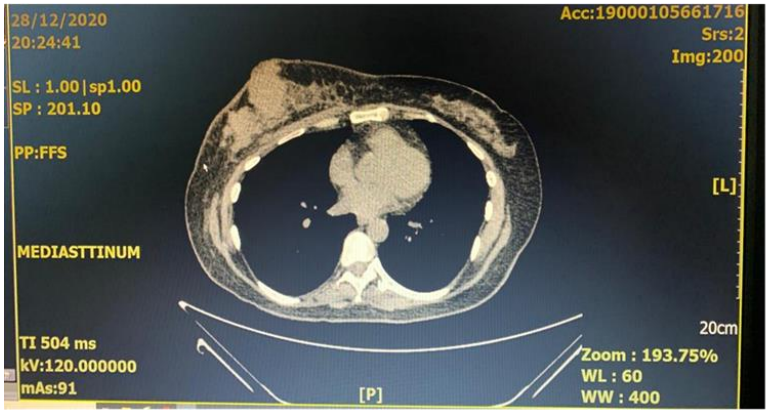
CONCLUSION These results confirm that patients achieving pCR have far better survival outcomes than patients who do not. The traditional poor prognostic features, namely tumor size and nodal status, remain important even after a pCR.

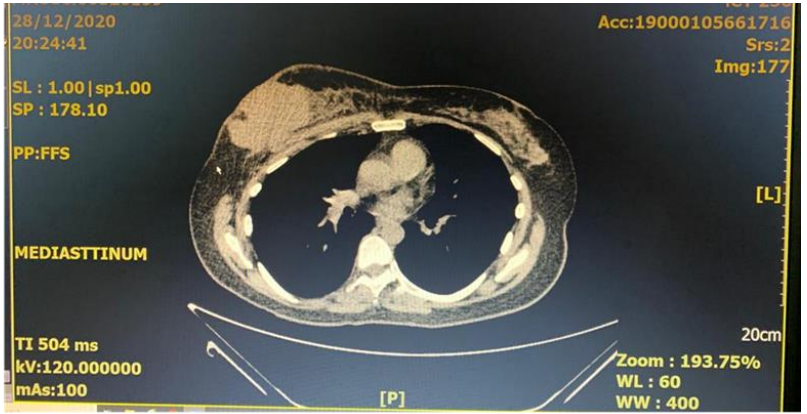
J Clin Oncol 41:2998-3008. © 2023 by American Society of Clinical Oncology

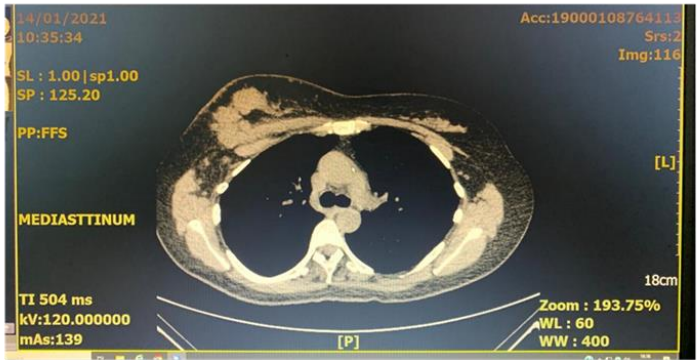
Mackelenbergh M et al. pCR and Prognosis in HER2-Positive Early Breast Cancer, J Clin Oncol 2023

Case Study

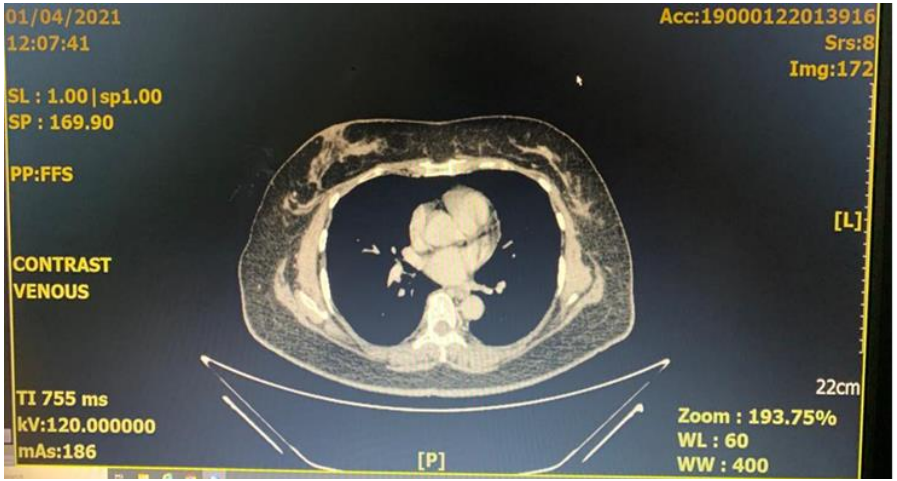
Case Neoadjuvant HER2+ eBC with Pertuzumab Trastuzumab

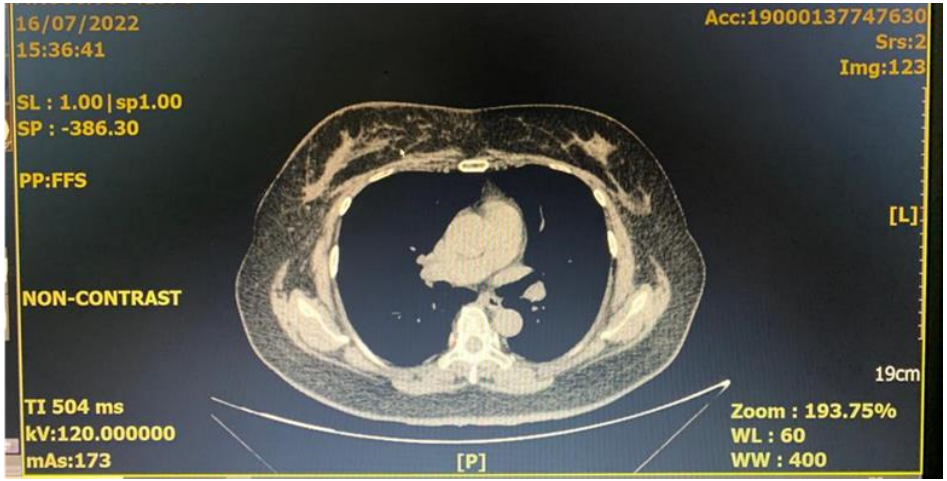






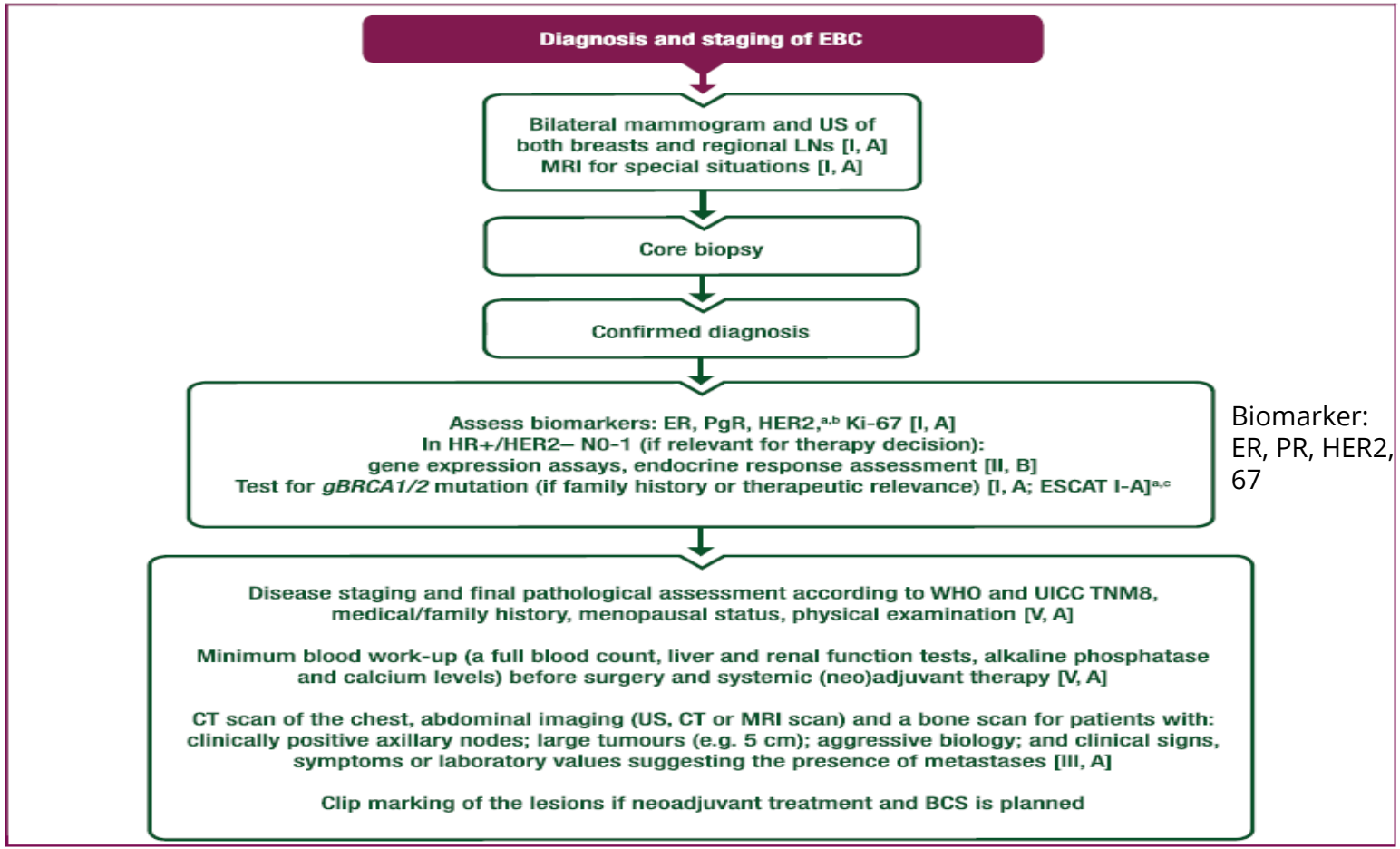
Case Neoadjuvant HER2+ eBC with Pertuzumab Trastuzumab





Summary 1:

S. Loibl et al., Annal Oncology, 2024, Vol.35 Issue 2



Biomarker:
ER, PR, HER2, Ki-67

Summary 2 :

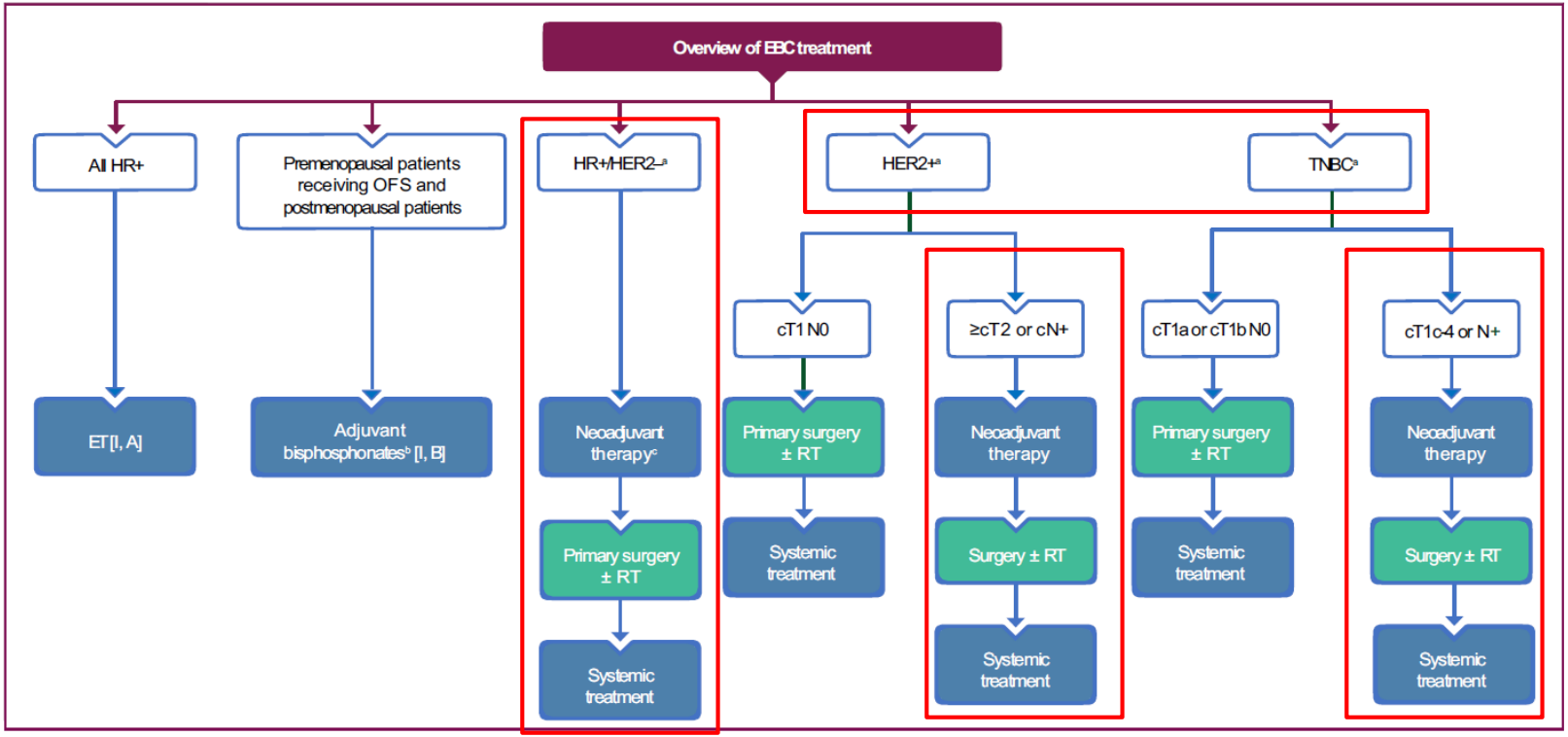
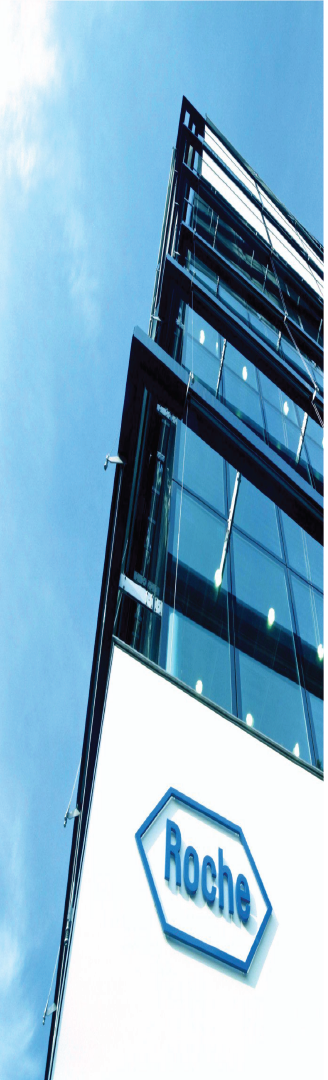


Figure 1. EBC treatment overview. Burgundy box: general categories or stratification; blue boxes: systemic anticancer therapy; turquoise boxes: combination of treatments or other systemic treatments; white boxes: other aspects of management.
ALN, axillary lymph node; c, clinical; ChT, chemotherapy; CPG, Clinical Practice Guideline; DCIS, ductal carcinoma *in situ*; EBC, early breast cancer; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; N, node; OFS, ovarian function suppression; RT, radiotherapy; T, tumour; TNBC, triple-negative breast cancer.

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, April 2024. https://doi.org/10.1016/j.esmoop.2024.102974



ADVERSE EVENT REPORTING

Roche is committed to the collection and management of safety information relating to our products and we highly encourage healthcare professionals to report adverse events pertaining to Roche products.

Adverse Event (AE)

Any **untoward medical occurrence** in a patient or clinical investigation subject administered a pharmaceutical drug and **which does not necessarily have a causal relationship with this treatment.**

REPORTING ADVERSE EVENT IS MANDATORY ACCORDING TO BPOM REGULATION No. 15 Year 2022 on PHARMACOVIGILANCE IMPLEMENTATION

If you are aware of any AE pertaining to Roche products, please report to:

Patient Safety
PT Roche Indonesia

indonesia.safety@roche.com

https://go.roche.com/medinfoID

Your data will be processed with greatest care and diligence in accordance with specific GVP (pharmacovigilance) legislation, as described in the Privacy Policy related to pharmacovigilance. Your data will not be used for any other purpose. For more information, please visit Roche Privacy Notice for Pharmacovigilance and Medical Information.

Your data will be processed with greatest care and diligence in accordance with specific GVP (pharmacovigilance) legislation, as described in the Privacy Policy related to pharmacovigilance. Your data will not be used for any other purpose. For more information, please visit Roche Privacy Notice for Pharmacovigilance and Medical Information.

Do you have questions on Roche products or their associated therapeutic areas ?

Roche Indonesia
Medical Information (MI) Service

E-mail: jakarta.medical_information@roche.com

Local MI Site: https://go.roche.com/medinfoID


Thank
You