Best of ASCO 2018
Annual Meeting Tea symposium

The treatment continuity conundrum:

Navigating systemic therapy for patients with HER2+ early breast cancer at high risk of recurrence

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Meetoo

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137-968-042

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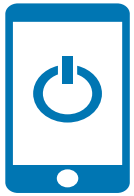
Housekeeping

Phones



Please keep mobile phones on silent mode

Questions

Please raise your hand and we will pass you a microphone

Evaluation form

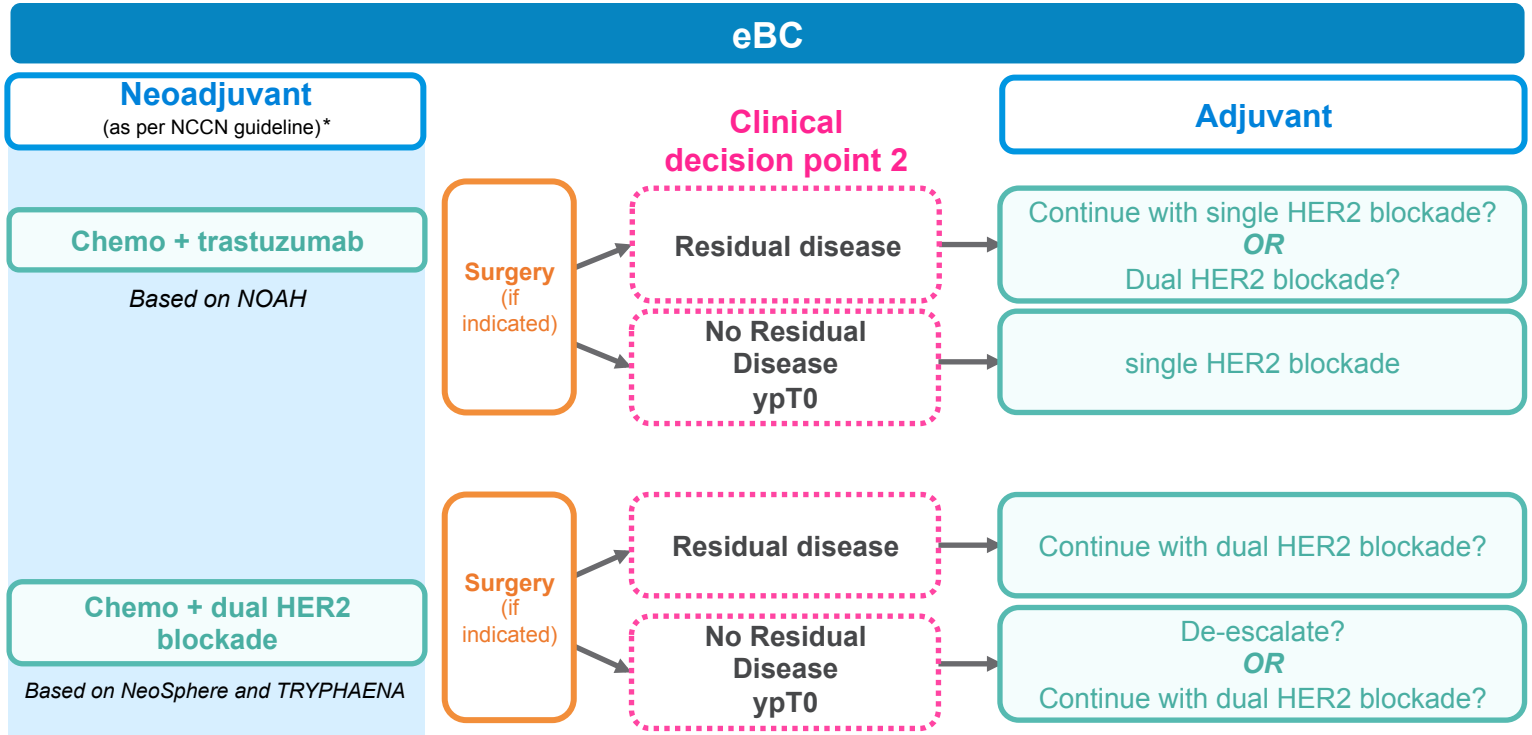
Please fill in the evaluation form before leaving

Please note, this meeting is being recorded for the purpose of developing a meeting report

Systemic treatment algorithm and clinical decision point for patients with HER2+/HR– early breast cancer at high risk of recurrence

Clinical decision point 1

High risk of recurrence patients



*National Comprehensive Cancer Network. Breast Cancer (version 1.2018)). https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed 20/06/2018.

Polling question 1

Take part in the polling on Meetoo:
137-968-042

For patients with high-risk of relapse, who achieve pathological complete response (pCR) following dual anti-HER2 in the neoadjuvant setting, would you continue with the same treatment regimen?

1. Yes
2. No, I will de-escalate
3. I do not give neoadjuvant treatment

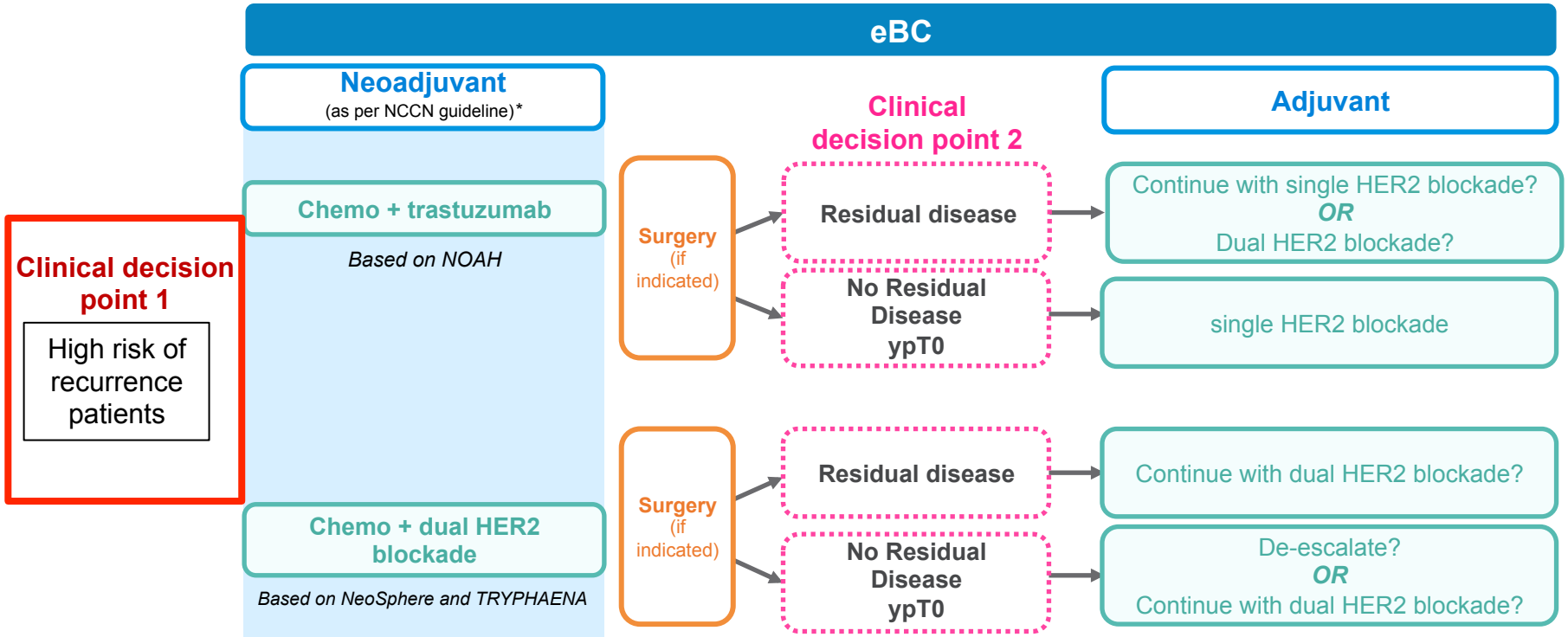
Navigating systemic therapy for patients with HER2+ eBC at high risk of recurrence

What can we learn from clinical practice and trial data?

TPE-VGH Breast Cancer Center

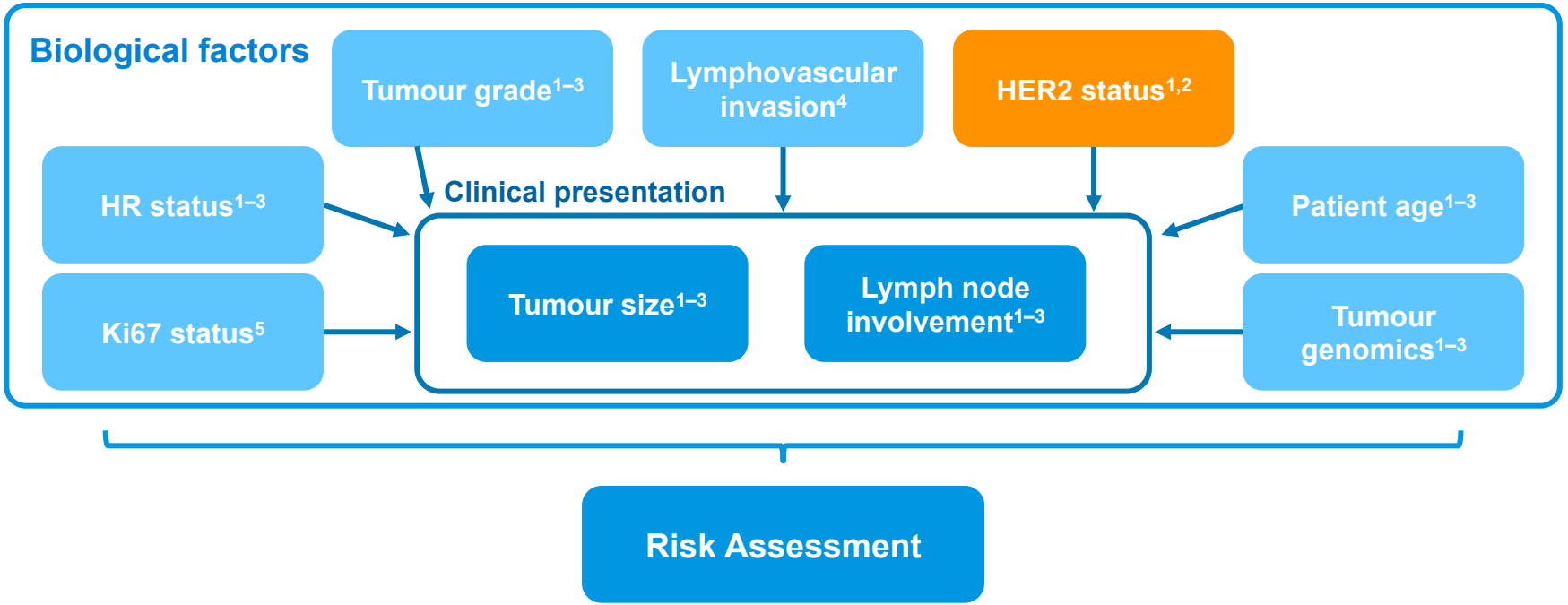
Ling-Ming Tseng, MD
Chief of Comprehensive Breast Health Center,
TPE-VGH Associate professor,
National Yang-Ming University, Taipei, Taiwan

Systemic treatment algorithm and clinical decision point for patients with HER2+/HR– early breast cancer at high risk of recurrence



*National Comprehensive Cancer Network. Breast Cancer (version 1.2018)). https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed 20/06/2018.

Various risk factors including tumour biology determine the prognosis of patients with HER2+ eBC who are treated with trastuzumab

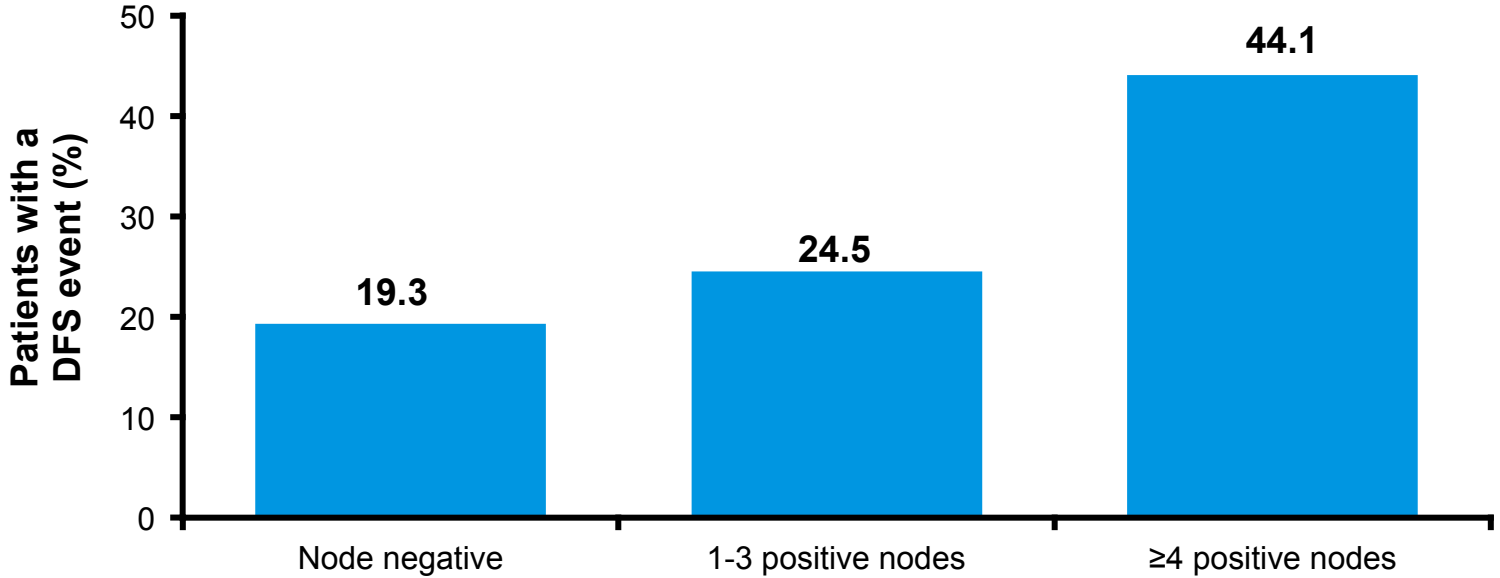


1. Martei YM & Matro JM. *Breast Cancer (Dove Med Press)* 2015; **7**:337–343;
2. Sparano JA, *et al. N Engl J Med* 2015; **373**:2005–2014; 3. Drukker CA, *et al. Int J Cancer* 2013; **133**:929–936;
4. Zhang S, *et al. BMC Cancer* 2017; **17**:335; 5. Inwald EC, *et al. Breast Cancer Res Treat* 2013; **139**:539–552.

Lymph node involvement

HERA: DFS event rate increases with increasing numbers of positive nodes

HERA 11-year FU: DFS events by nodal status with 1 year of adjuvant trastuzumab

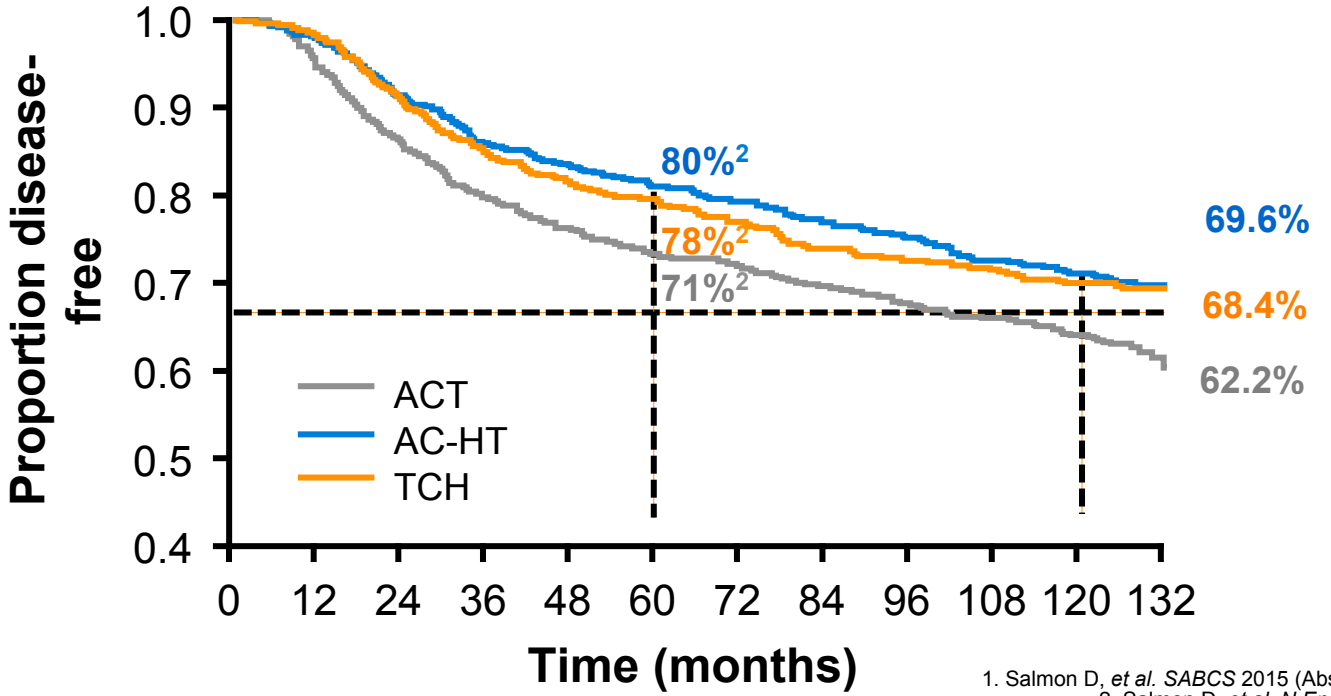


Cameron D, *et al. Lancet* 2017;389:1:1195–1205 (Supplementary information).

Lymph node involvement

BCIRG 006: Regardless of chemotherapy partner, after 1 year of adjuvant trastuzumab, ~30% of node-positive patients still relapse

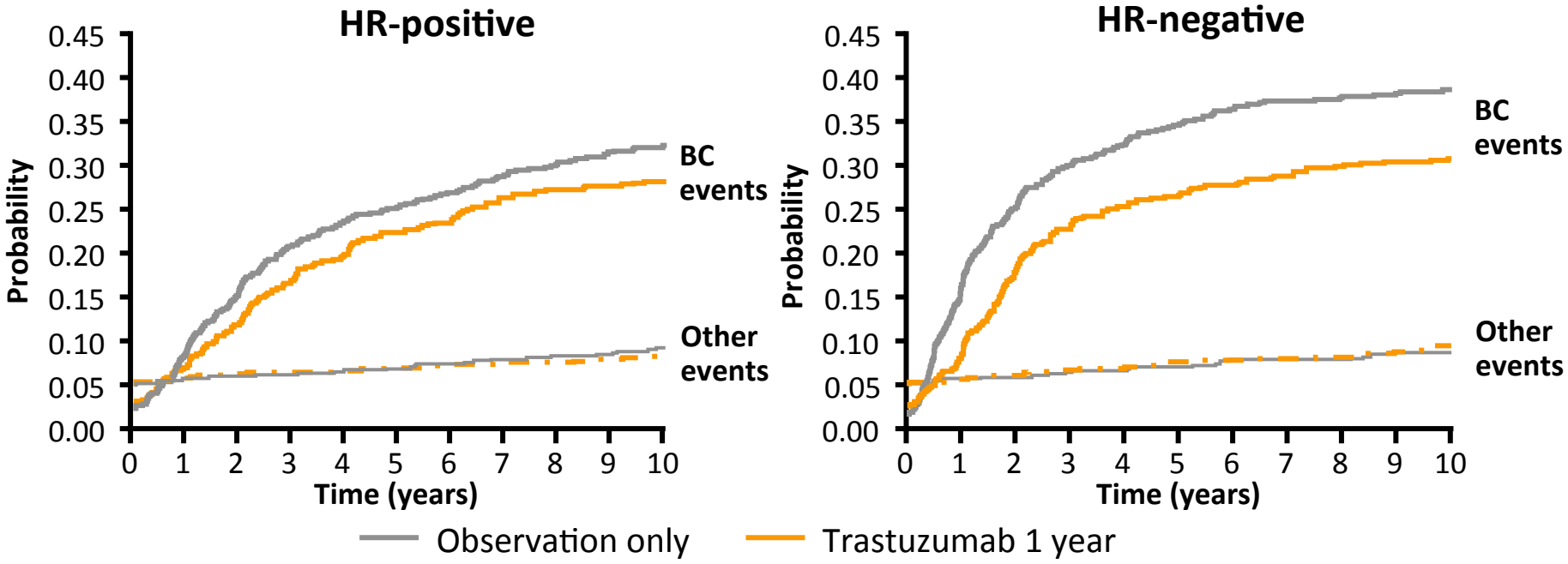
BCIRG 006: DFS in node-positive disease after 10 year follow-up[1]



1. Salmon D, *et al. SABCS* 2015 (Abstract S5-04; oral presentation);
2. Salmon D, *et al. N Engl J Med* 2011; **365**:1273–1283.

HERA: HR– status confers a higher risk of early relapse within a shorter timeframe

HERA 11-year FU: Cumulative incidence of type DFS event with 1 year of adjuvant trastuzumab

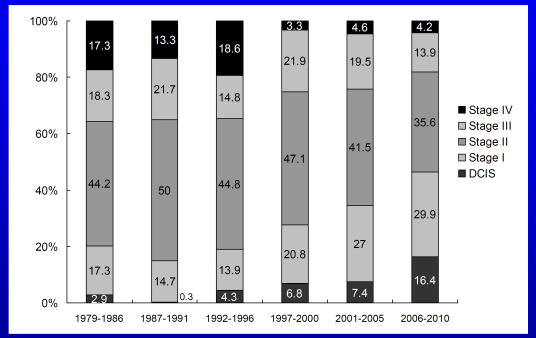


Cameron D, *et al. Lancet* 2017;389:1:1195–1205 (Supplementary information).

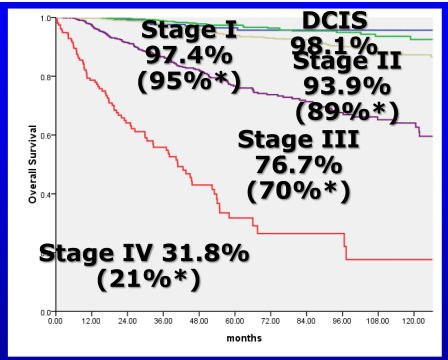
Age

Trend of age shift and decreasing mortality of breast cancer in Taiwanese women: a 30 years cohort observation

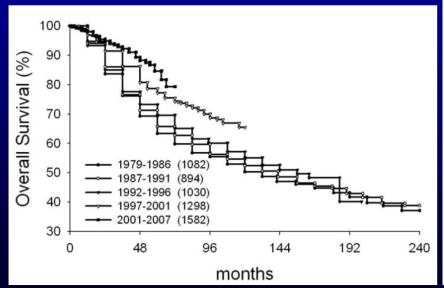
TPE-VGH 1979–2010 (N=7233)

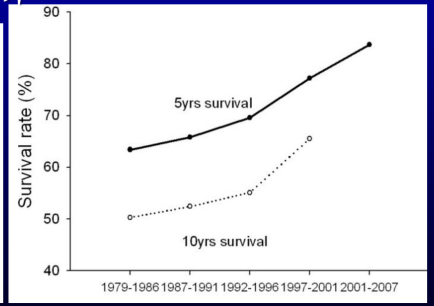


早期乳癌診斷率明顯提升

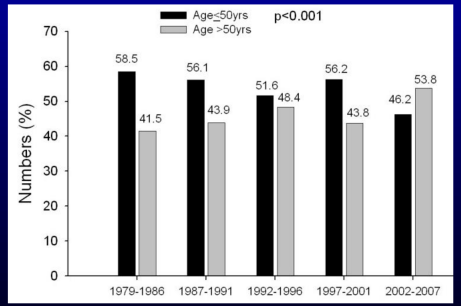


1997-2010 (N=3822) *癌登





存活率明顯改善



診斷年齡逐漸老化(in submission)

Subtype Multiple Cox Regression for breast cancer overall survival

TPE-VGH 2000–2016/08 (N=6922)

	Co-efficient	S.E.	p	HR	95% C.I. for HR	
Age ≤ 35yrs	ref	-	-	-	-	-
36 - 50yrs	-.332	.209	.113	.718	.476	1.081
51 - 65yrs	-.131	.207	.527	.877	.585	1.316
> 65yrs	.424	.209	.043	1.528	1.014	2.301
LN +/-	.603	.095	<0.0001	1.828	1.517	2.202
ER +/-	-.487	.123	<0.0001	.615	.483	.782
PR +/-	-.247	.118	.037	.781	.619	.985
HER2 +/-	-.357	.101	<0.0001	.700	.574	.853
T size < 2cm	ref	-	-	-	-	-
2 - 5cm	.487	.088	<0.0001	1.627	1.368	1.934
> 5cm	1.027	.146	<0.0001	2.792	2.097	3.717
LV Inva +/-	.423	.097	<0.0001	1.527	1.262	1.847

Data not published

Can multiple biomarkers predict treatment outcomes for patients with HER2+ expression?

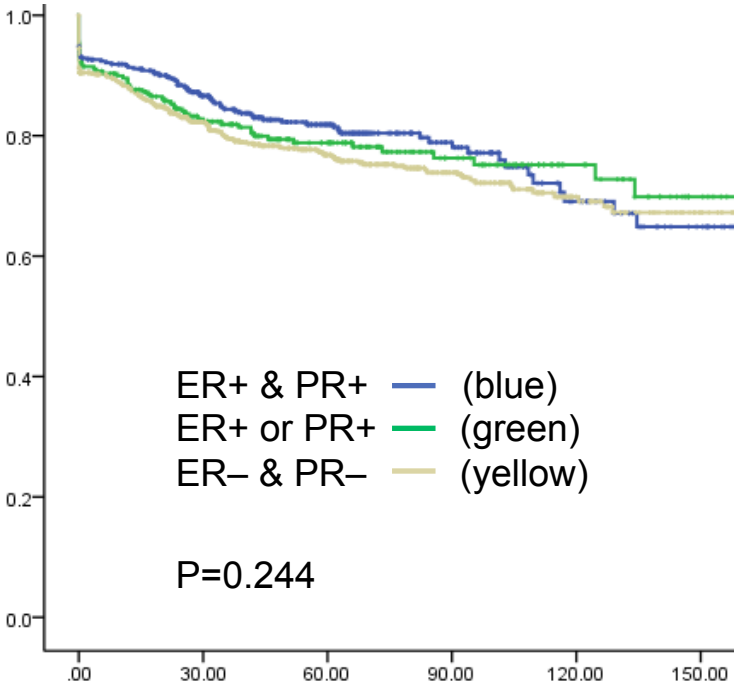
TPE-VGH breast cancer database 2010–2016/08 (N=1417)

HER2 (+)		Overall Survival		Disease-Free Survival	
		5y-Survival	p	5y-Survival	p
Age	≤ 35yrs	80.0		65.2	
	36-50	89.0		82.0	
N=1417	51-65	89.3		78.8	
	> 65yrs	84.4	0.005	73.5	0.012
LN	(-)	95.8		90.6	
N=1334	(+)	79.5	<0.001	65.2	<0.001
Size	T1	94.1		87.1	
N=1291	T2	86.3		79.1	
	T3、T4	68.8	<0.001	44.7	<0.001
Grade	1	100.0		93.0	
	2	89.0		79.2	
N=1285	3	86.6	0.043	77.9	0.080
LVI.	(-)	91.8		83.8	
N=1249	(+)	77.7	<0.001	65.9	<0.001
ER+ & PR+		91.7		81.9	
ER+ or PR+		87.1		78.8	
ER- & PR-	N=1416	86.4	0.046	76.8	0.244
ER	(-)	86.5		76.9	
N=1416	(+)	89.9	0.034	80.7	0.112
PR	(-)	86.6		77.3	
N=1416	(+)	91.6	0.027	81.8	0.115

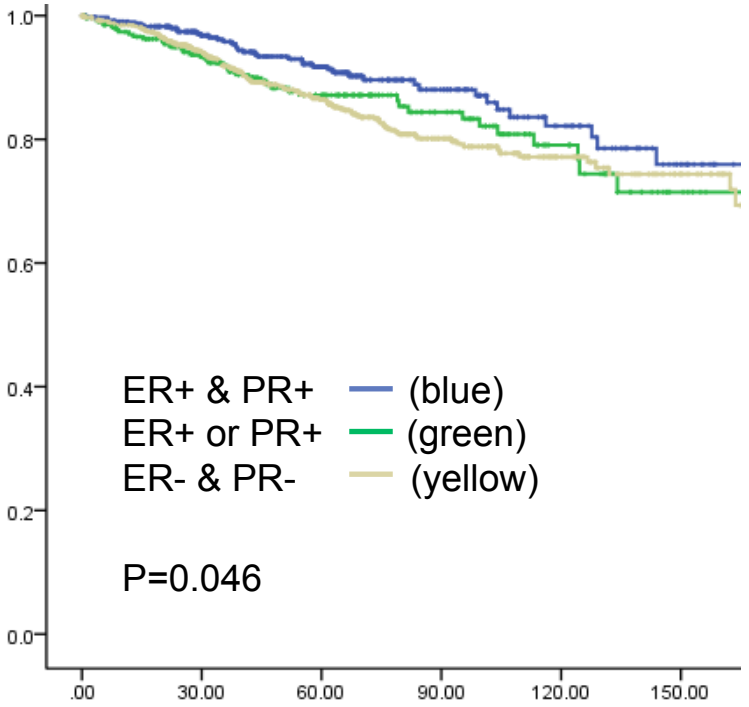
DFS and OS for HER2+/Neu3+ breast cancer patients according to HR status

TPE-VGH data 2000–2016/08

DFS



OS



Multiple cox regression for HER2+ Breast cancer overall survival

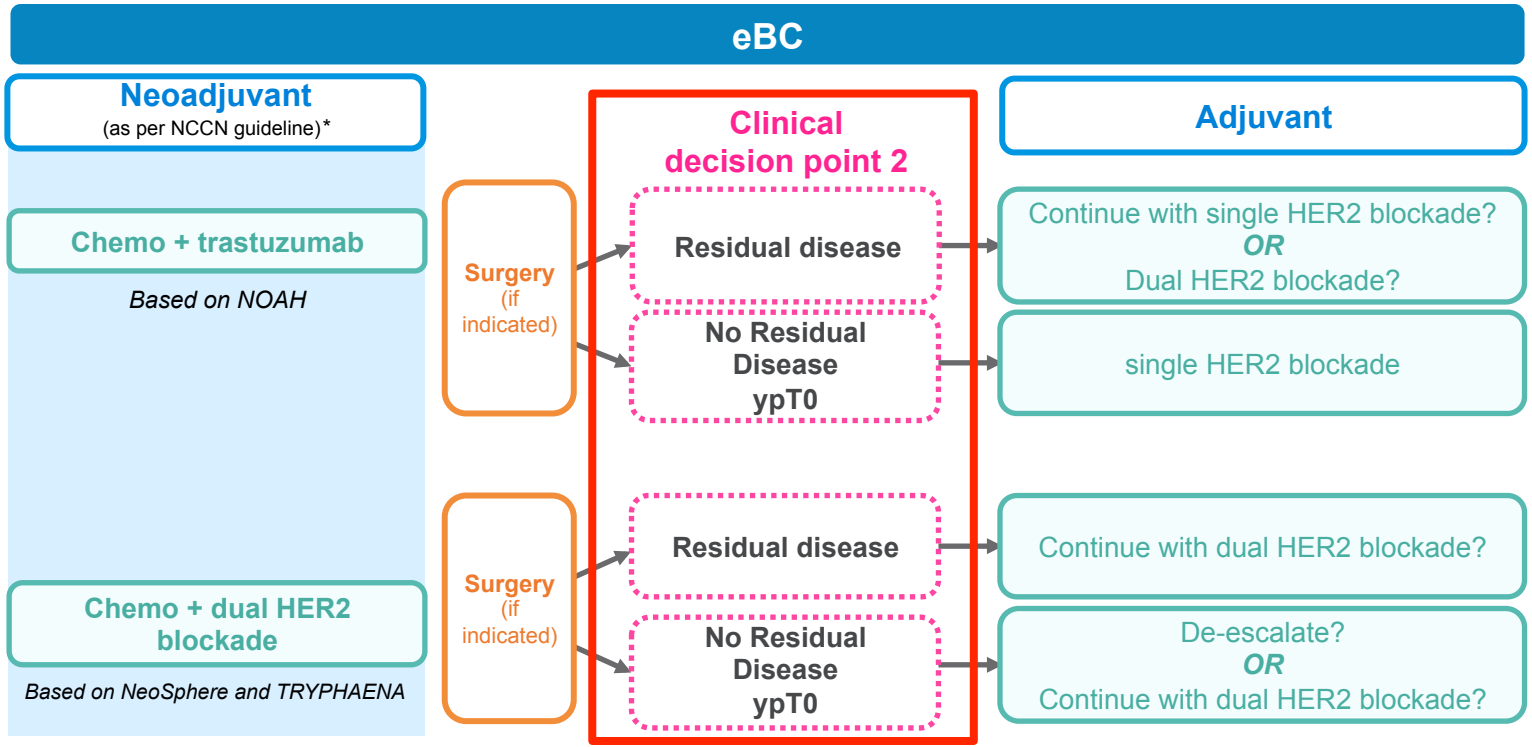
TPE-VGH 2000–2016/08 (N=1326)

	Coefficient	S.E.	p	HR	95% C.I. for HR	
LN +/-	1.717	.619	.005	5.570	1.657	18.724
Target therapy +/-	-1.264	.555	.023	.283	.095	.839

Put in covariance: Age, Surgery, Tumor Type, ER, PR, Ki67, Invasion Necrosis

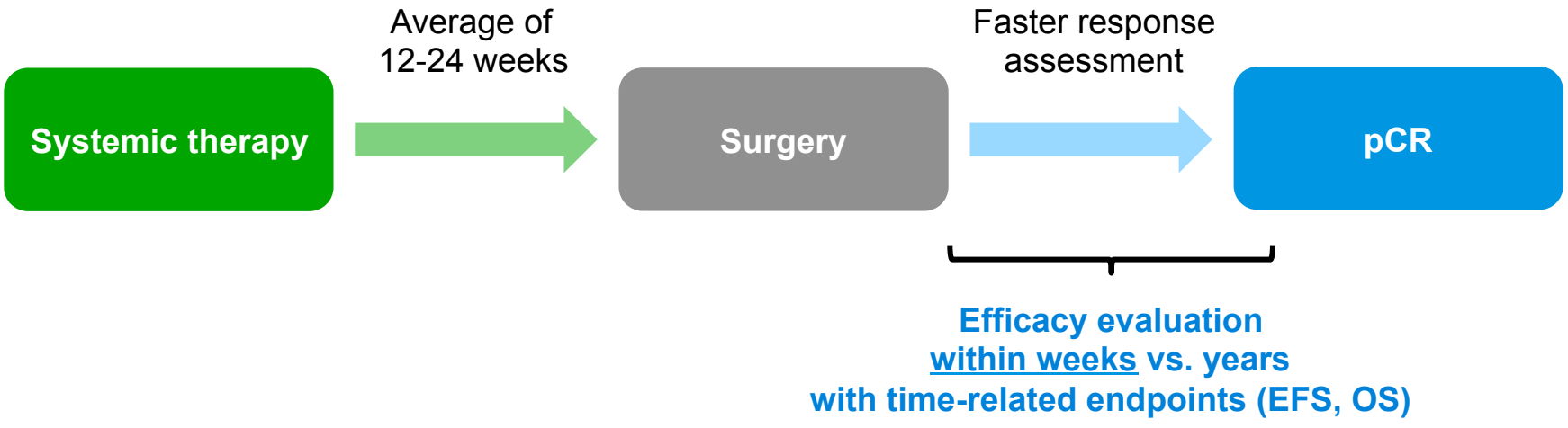
data not published

Systemic treatment algorithm and clinical decision point for patients with HER2+/HR– early breast cancer at high risk of recurrence



*National Comprehensive Cancer Network. Breast Cancer (version 1.2018)). https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed 20/06/2018.

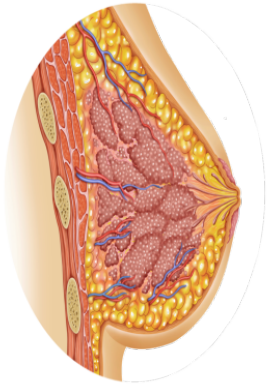
pCR allows early assessment of tumor response



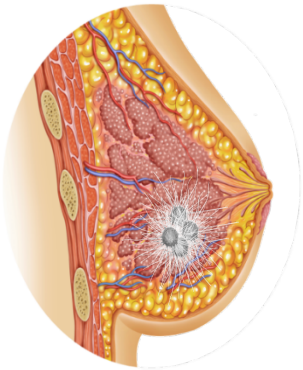
Cortazar P, Zhang L, Untch M et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014; 384:164–172.
EFS: event free survival; OS: overall survival.

What does a “no pCR” tell us?

Roche



Therapy



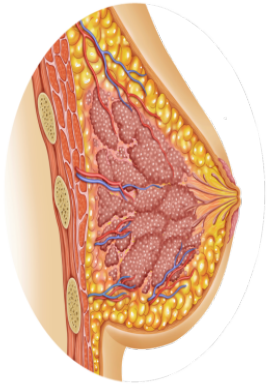
Therapy

Neoadjuvant treatment effect

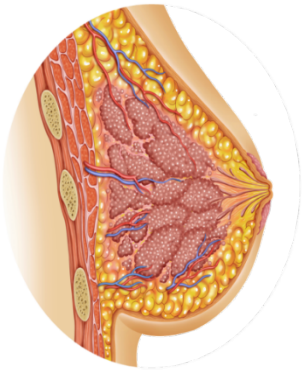
Pathological evidence of residual invasive carcinoma in the breast or axillary lymph nodes

Residual invasive carcinoma in the breast or axillary lymph nodes does not give us a complete picture of the quality of the response to the neoadjuvant treatment

What does a pCR tell us?



Therapy



Therapy

Neoadjuvant treatment effect

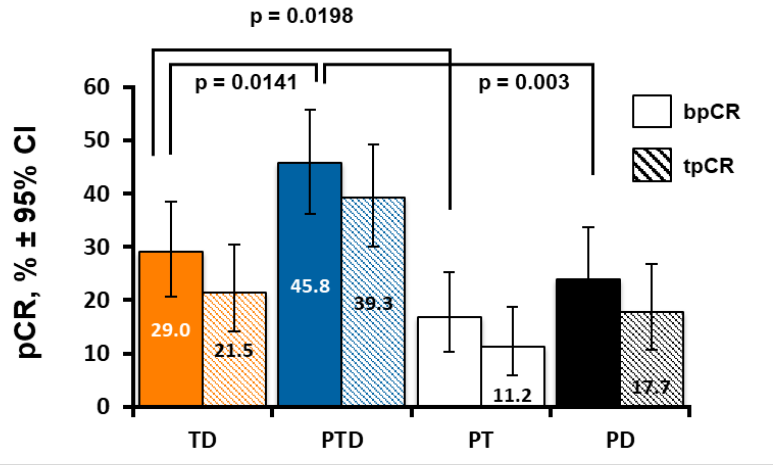
Breast and nodes are free of disease[1]

Presence of micro-metastatic systemic disease is unknown[1]

Sensitivity of systemic disease to therapy is unknown[1]

[1] Rose BS, et al. J Clin Oncol 2016; 34:3959–3962

NeoSphere
Phase II Neoadjuvant HER2+ study



Patients with operable or locally advanced/ inflammatory HER2+ BC

Chemo-naive & primary tumors >2 cm (N=417)

TD (n=107) trastuzumab (8→6 mg/kg) docetaxel (75→100 mg/m^2)	SURGERY	**FEC** q3w x 3 **trastuzumab** q3w cycles 5–17
PTD (n=107) pertuzumab (840→420 mg) trastuzumab (8→6 mg/kg) docetaxel (75→100 mg/m^2)		**FEC** q3w x 3 **trastuzumab** q3w cycles 5–17
PT (n=107) pertuzumab (840→420 mg) trastuzumab (8→6 mg/kg)		**docetaxel** q3w x 4→**FEC** q3w x 3 **trastuzumab** q3w cycles 5–17
PD (n=96) pertuzumab (840→420 mg) docetaxel (75→100 mg/m^2)		**FEC** q3w x 3 **trastuzumab** q3w cycles 5–21

Study dosing: q3w x 4

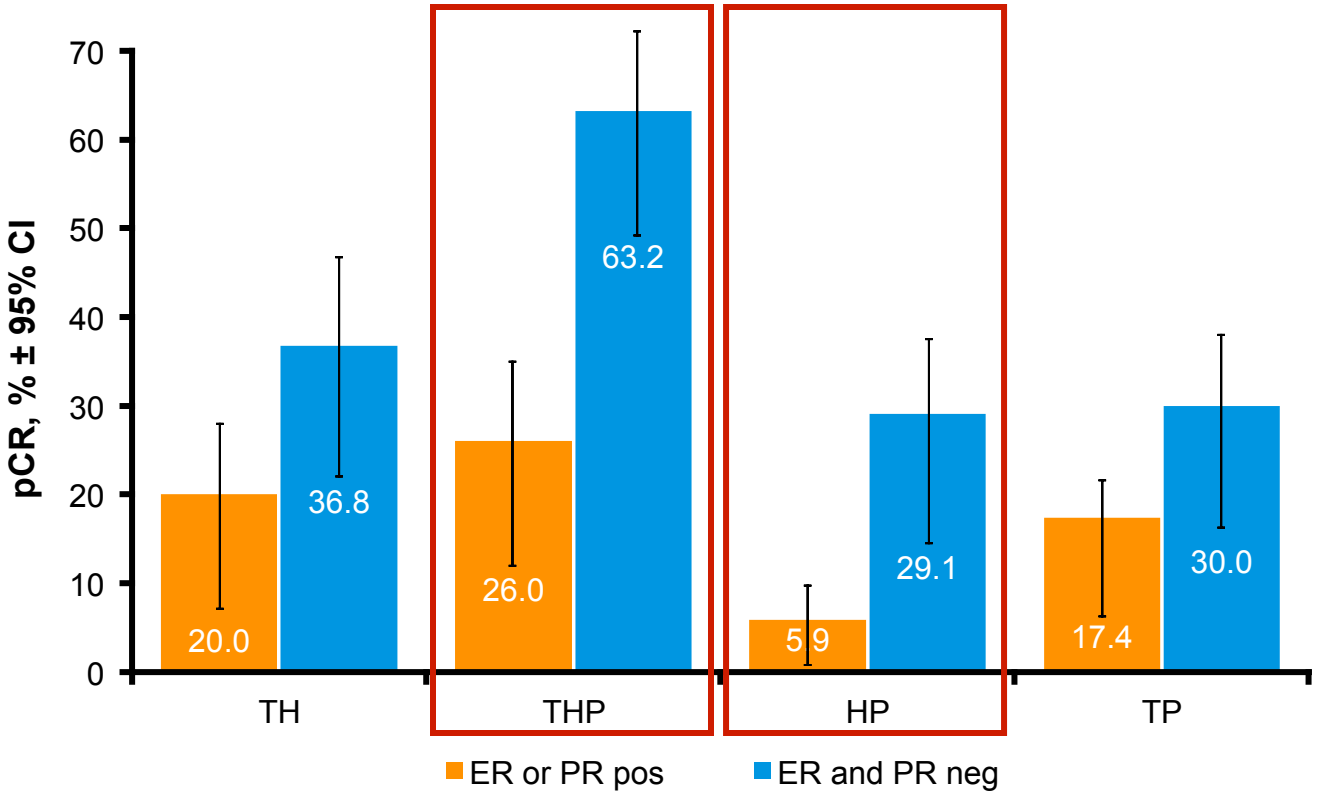
Primary endpoint:
- **comparison of bpCR rates**
  - **TD vs PTD**
  - **TD vs PT**
  - **PTD vs PD**

Secondary endpoints:
- **PFS**
- **DFS**
- **Safety**

Exploratory analyses:
- **PFS by hormone receptor status**
- **PFS–tpCR association**

Gianni L, *et al. Lancet Oncol* 2012; 13:25–32.
FEC, 5-fluorouracil, epirubicin, and cyclophosphamide.

NeoSphere: pCR and hormone receptors status



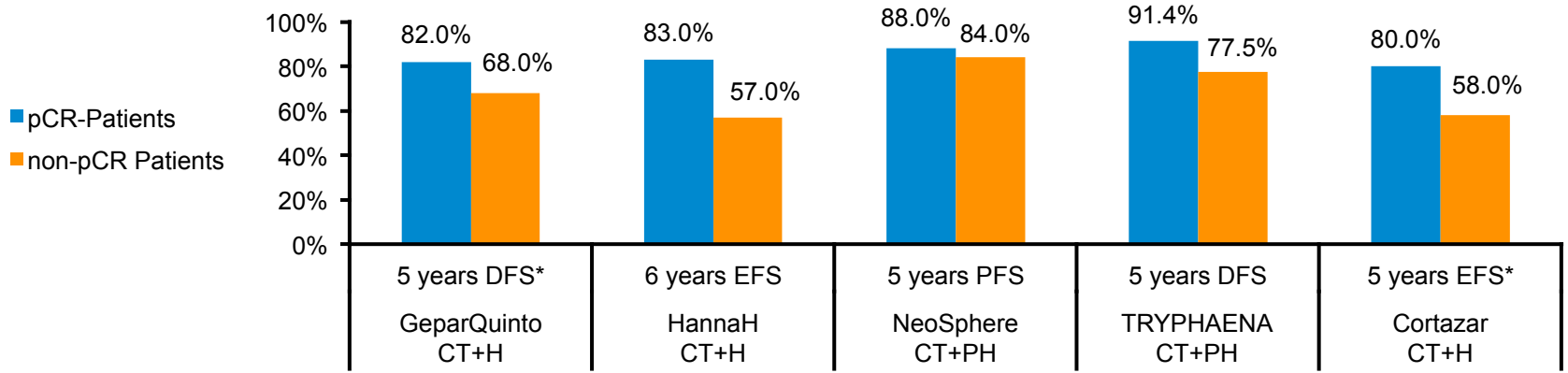
H, trastuzumab; P, pertuzumab; T, docetaxel

Disease and event free survival according to pCR status

pCR is a prognostic information for the individual patient

10-15% of the patients achieving a pCR relapse within 5 years

	GeparQuinto 5 years DFS	HannaH 6 years EFS	NeoSphere 5 years PFS	TRYPHAENA 5 years DFS	Cortazar 5 years EFS*
DFS/EFS after pCR	ca. 82 %	83%	88%	91,4%	ca. 80%
DFS/EFS after non-pCR	ca. 68 %	57%	84%	77,5%	ca. 58%

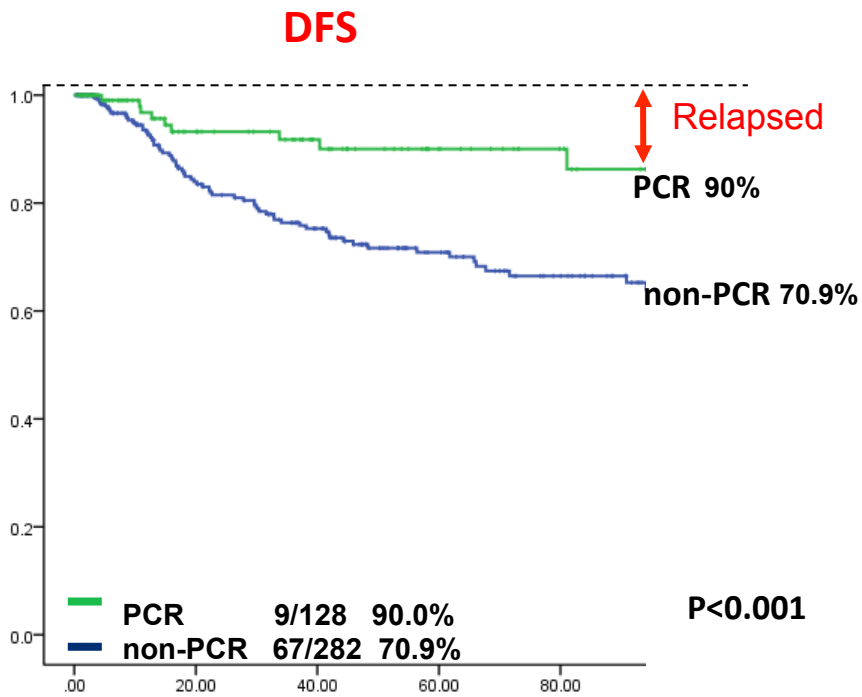


Gianni L, *et al. Lancet Oncol* 2016; **6**:791-800 incl. appendix.; Cortazar *et al*., Lancet 2014; Roche data on file; Jackisch C SABCS 2017 abstr. PD3-11.

* From Kaplan-Meier-Curve.

DFS rate for eBC patients that achieved pCR following neoadjuvant therapy

TPE-VGH database 2007–2018/02 (N=410)



DFS /OS Mean ： 48.99/53.48 (2.53~117.8) months，FU to 201803

CAUTION!

pCR predicts better outcome, but not absolute event free status.

A surrogate, but not the final endpoint.

Question: Current treatment is good enough for Her2+ EBC ? What's the recurrence rate who receive current standard chemo and one year herceptin treatment ?

URL: web.meetoo.io | Meeting ID:137-968-042

Polling question 2

Take part in the polling on Meetoo:
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Based on your knowledge, what is the **10-year relapse rate** of HER2+ eBC patients following one year of Herceptin therapy?

1. ≤10%
2. 11% – 20%
3. 21% – 30%
4. 31% – 40%
5. >40%

Polling question 3

Take part in the polling on Meetoo:
137-968-042

What is the basis for your answer to the previous question (Q2) based on?

1. Country Registry data
2. Hospital data
3. Publication data
4. Personal experience and observation

Polling question 4

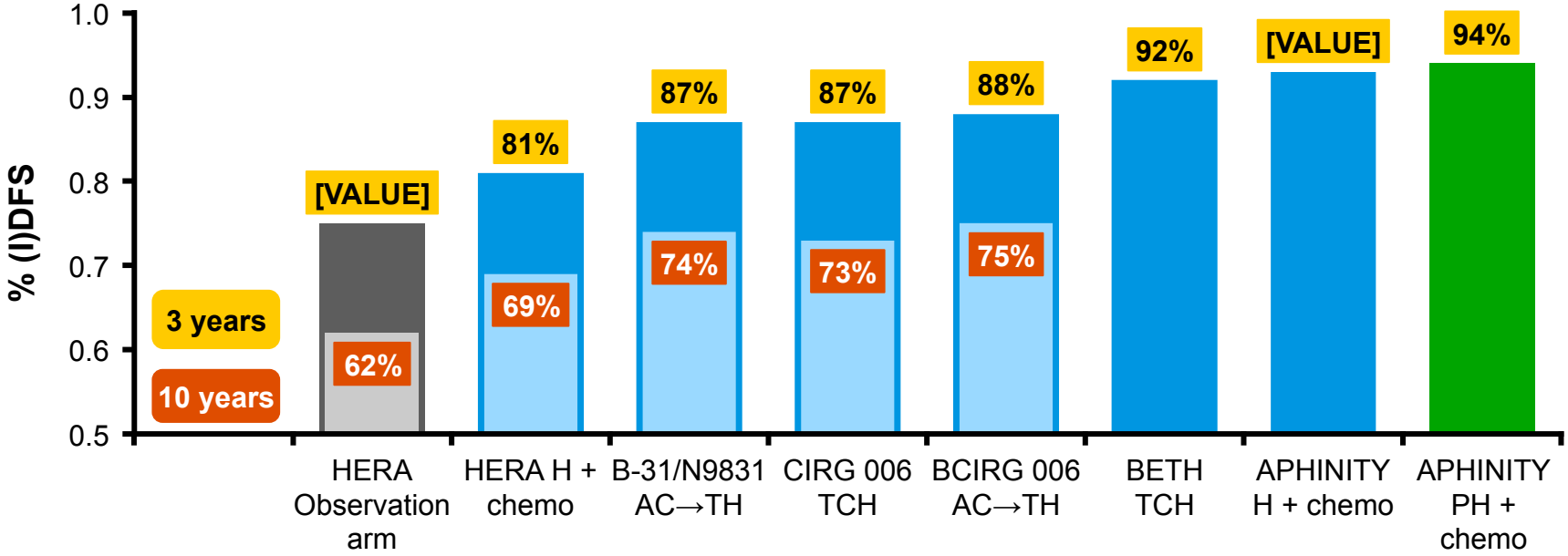
Take part in the polling on Meetoo:
137-968-042

How many years of clinical experience do you have in managing early breast cancer (eBC)?

1. ≈5 years
2. ≈10 years
3. ≈5 years
4. ≈20 years
5. >20 years

Short versus long term recurrence

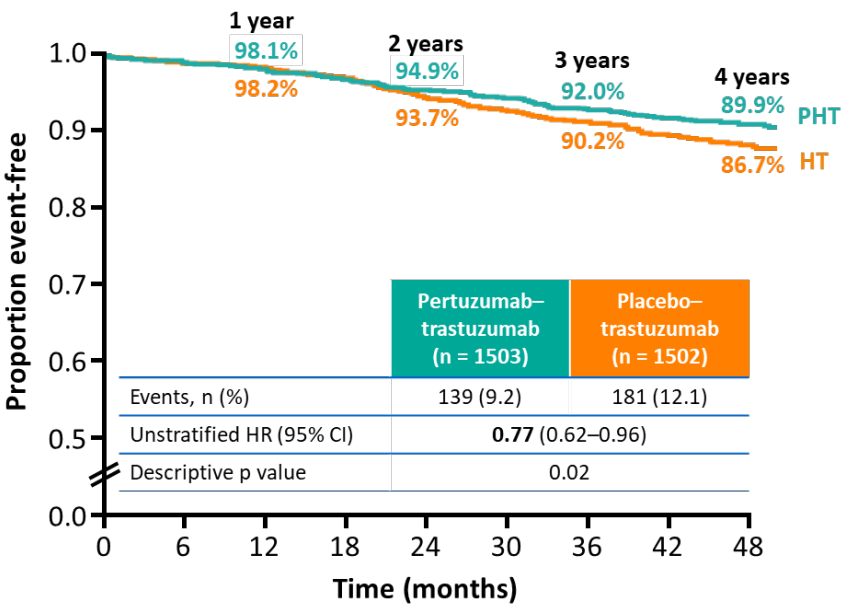
3 years versus 10 years iDFS in HER2+ eBC patients who received Herceptin and Chemo in adjuvant setting



Slamon dj, 2013. Cancer Res 73(24 Suppl): Abstract nr S1-03;
Cameron D, 2017, *Lancet* 389:1195-205;
Perez EA, 2014, *J Clin Oncol* 32:3744-3752;
Slamon D, 2011, *N Engl J Med* 365:1273-83;
Slamon D, 2015, SABCS, Abstract S5-04;
Von Minckwitz, 2017, *N Engl J Med* DOI: 10.1056/NEJMoa1703643.

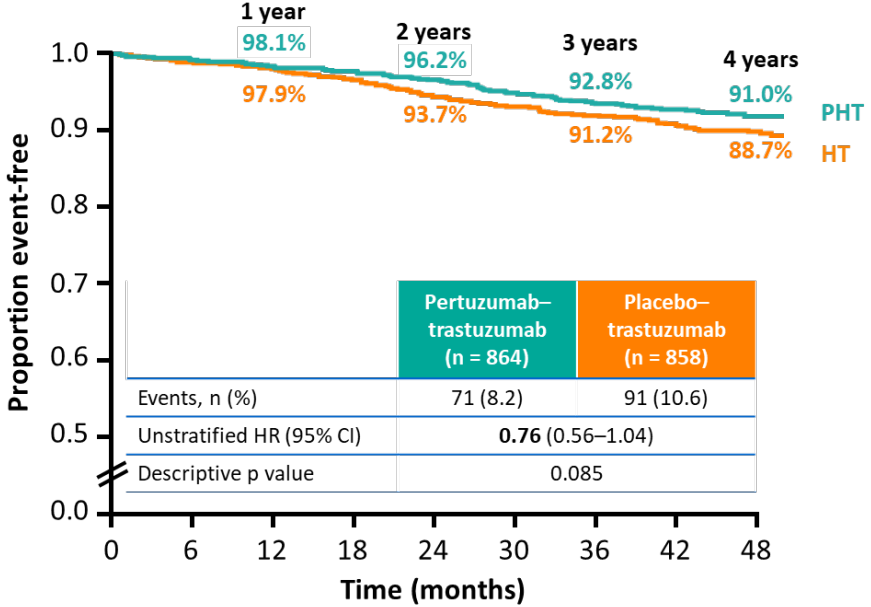
APHINITY: the positive outcome of the study was driven by results in patients with disease at high risk of recurrence

Lymph node-positive subgroup (n=3005)



	Pertuzumab–trastuzumab (n = 1503)	Placebo–trastuzumab (n = 1502)
Events, n (%)	139 (9.2)	181 (12.1)
Unstratified HR (95% CI)	**0.77** (0.62–0.96)	
Descriptive p value	0.02	

PFS by HR status



	Pertuzumab–trastuzumab (n = 864)	Placebo–trastuzumab (n = 858)
Events, n (%)	71 (8.2)	91 (10.6)
Unstratified HR (95% CI)	**0.76** (0.56–1.04)	
Descriptive p value	0.085	

Hazard ratios were estimated by Cox regression. Pertuzumab is only approved in the adjuvant setting in Russia, the USA, Bangladesh, El Salvador, Peru, Brazil, Nicaragua and Guatemala; it is not currently approved in Spain or the European Union.

von Minckwitz G, et al . N Engl J Med 2017; 377:122–131.

The benefit observed with APHINITY is within a range observed in the past for a change to SoC involving a treatment improvement

		INTRODUCTION of a new treatment modality	IMPROVEMENT of a treatment modality
Chemotherapy		CMF vs. no chemo	Anth + taxane vs. anth
	Relative risk*[1]	0.70	0.84
Endocrine therapy		Tam 5 years vs. no tam	AI 5 years vs. tam 5 years
	Relative risk*[2]	0.50	0.80
Anti-HER2 therapy		Trastuzumab vs. observation	APHINITY
	Relative risk*[3]	0.52	**0.81**
		9.9 – 12% improvement in recurrence rate for new modalities[1,3,4]	0.5 – 3.6% improvement in recurrence rate for improving a modality[1,5]

* Analysis conducted at different time points;
AI, aromatase inhibitor; anth, anthracycline; tam, tamoxifen.

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Lancet* 2012; 2. EBCTCG. *Lancet* 2005;
3. Perez EA, *et al. J Clin Oncol* 2011; 4. EBCTCG. Cochrane Database Syst Rev 2001; 5. EBCTCG. *Lancet* 2015.

Patient-reported function and symptoms in APHINITY: A randomized comparison of chemotherapy (C) + trastuzumab (H) + placebo (Pla) versus C + H + pertuzumab (P) as adjuvant therapy in patients with HER2+ early breast cancer (eBC)

Baselga J, et al. ASCO 2018 Abstract 521

Overview

- APHINITY demonstrated an almost 25% reduction in the risk of recurrence or death for patients at high risk of recurrence[a]
- Patient-reported outcomes was a secondary endpoint of APHINITY, assessed by EORTC QLQ-C30 and QLQ-BR23 questionnaires

Results

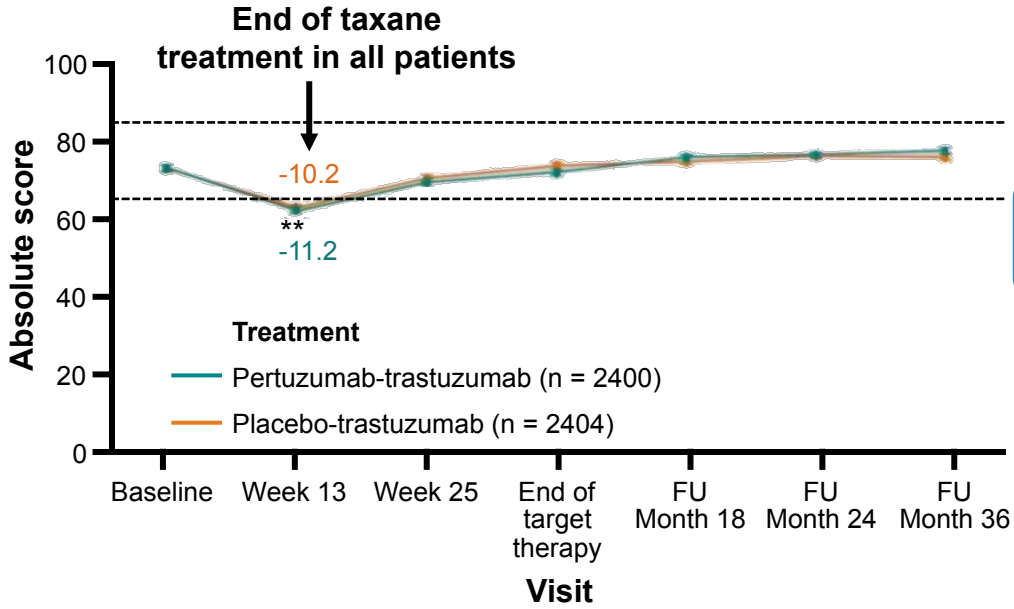
- Questionnaire completion rates were >87%
- Regardless of the HRQoL measures used, results were broadly similar in both arms

[a]In the curative setting with 18 cycles of PERJETA–Herceptin compared with 1 year of Herceptin plus chemo[1]

1. von Minckwitz G, *et al. N Engl J Med* 2017;
2. Osoba D, *et al. J Clin Oncol* 1998.

Both treatment arms experienced a clinically meaningful decline in HRQoL at the end of taxane therapy (week 13) only

Mean EORTC QLQ-C30 global health status scores by treatment regimen in the ITT population[1]



HRQoL/GHS scale of the EORTC QLQ-C30 (2 items)[1,2]

How would you rate your overall health during the past week?

How would you rate your overall quality of life during the past week?

* Indicates time points where there was a clinically meaningful change in absolute score.
FU, follow-up; GHS, global health status; HRQoL, health-related quality of life; ITT, intention-to-treat.

1. Baselga J, *et al.* ASCO 2018 (Abstract 521);
2. Aaronson NK, *et al. J Natl Cancer Inst* 1993; **85**:365–376.

International guidelines recommend the APHINITY regimen in patients with tumours at high risk of recurrence

Recommendations in the adjuvant setting:
Dual blockade with pertuzumab-trastuzumab for HER2+ patients at high risk of relapse

St. Gallen Expert Consensus[1]
High risk due to lymph node involvement or HR-negativity

NCCN Breast Cancer Guidelines[2]
If node-positive (HR-positive and HR-negative disease)

ASCO Guidelines[3]
High-risk, such as node-positive disease

AGO Guidelines[4]
Node-positive or HR-negative disease

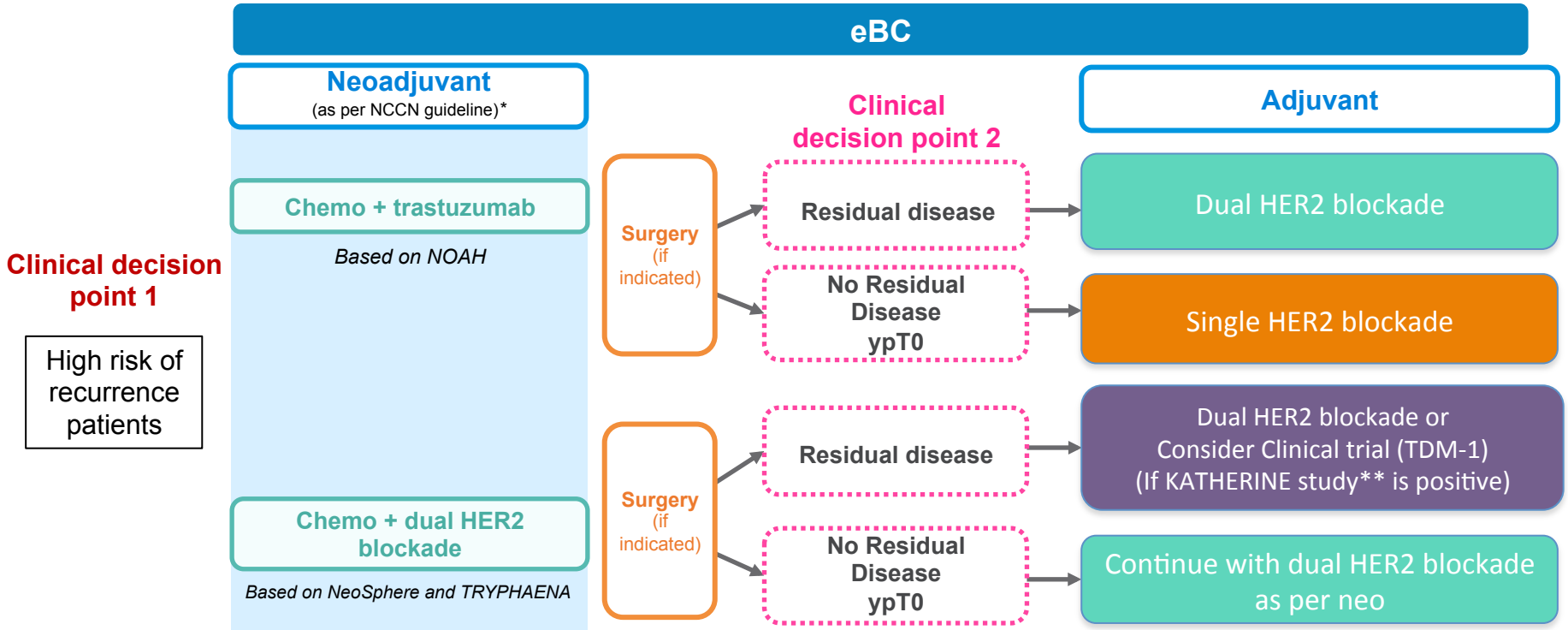
AGO, Arbeitsgemeinschaft Gynäkologische Onkologie E.V.;
ASCO, American Society of Clinical Oncology;
HR, hormone receptor; NCCN, National Comprehensive Cancer Network.

1. Curigliano G, *et al. Ann Oncol* 2017; **28**: 1700–1712;
2. NCCN Breast Cancer Guidelines. Version 4, 2017 – February 7, 2018;
3. Denduluri N, *et al. J Clin Oncol* 2018; doi: 10.1200/JCO.2018.78.8604 (ePub ahead of print);
4. https://www.ago-online.de/en/guidelines-mamma/march-2018 (Accessed May 2018).

Taiwan consensus for neoadjuvant therapy
Recommendation of neoadjuvant systemic treatment regimens

- The regimens recommended in adjuvant setting can be considered in the neoadjuvant setting.
- Similar to that in adjuvant setting, the determination of regimens should be balanced in anti-tumor activity and toxicity to avoid under or over treatment.
- **To avoid over-treatment for HER2+ disease, patients who fit the main characteristics (not eligibility) of adjuvant trial of weekly paclitaxel/trastuzumab[1]or docetaxel/cyclophosphamide/ trastuzumab[2] (tumor ≤ 2 cm, LN–, HR+) may prefer surgery first followed by standard adjuvant treatment.**
- **To avoid under-treatment for HER2+ disease, patients should considered completion of standard adjuvant regimens even the patients achieved pathological complete response.**
- **For advanced disease, with lymph node involvement, neoadjuvant dual blockade plus chemotherapy is the preferred regimen.**
- Generally, the sample size of neoadjuvant trials is small, so most of them could not provide sufficient statistical power to demonstrate the survival difference. This weakness resulted in several controversial issues. For controversial issues, we need to evaluate the evidence from both of adjuvant and neoadjuvant setting.

Potential future treatment algorithm for high risk of recurrence HER2+/HR– eBC patients



*National Comprehensive Cancer Network. Breast Cancer (version 1.2018)). https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed 20/06/2018; **KATHERINE Study NTC01772472

Conclusion

- Neoadjuvant therapy is a good choice for eBC, especially for HER2+ breast cancer
  - Makes clinical decision points clearer
  - Be cautious of under- or over-treatment

- pCR predicts better outcome, but does not mean an absolute event free status
  - A surrogate, but not the final endpoint
  - Regardless of anti-HER2 therapy response in the neoadjuvant setting, it is important to continue treatment following surgery

- Following the positive APHINITY study, patients at high risk of recurrence should receive 18 cycles of pertuzumab–trastuzumab entirely in the adjuvant setting or split across the neoadjuvant and adjuvant settings

Summary of experience from TPE-VGH:

- LN+, larger tumor size, ER/PR– and LVI are poor prognostic factors for HER+ BC survival
- ER– and T3 & 4 are poor prognostic factors for HER2+/N– BC (data not shown)
- HR–/HER2+ & HR+/HER2+ are different entities
- LN metastasis and the absence of targeted therapy are two independent prognostic factors for HER2+ BC survival.


TPE-VGH Breast Cancer Center
THANK YOU

Panel discussion and Q&A session

Panelists:

Dr Elaine Lim

National Cancer Centre, Singapore

Dr Wong Nan Soon

OncoCare Cancer Centre, Singapore

Polling question 5

Take part in the polling on Meetoo:
137-968-042

For patients at high-risk of relapse, who achieve pathological complete response (pCR) following **dual anti-HER2** in the neoadjuvant setting, would you continue with the same treatment regimen?

1. Yes
2. No, I will de-escalate
3. I do not give neoadjuvant treatment

Q&A

Polling question 6

Take part in the polling on Meetoo:
137-968-042

Patient Case

- 35-year-old female, previously well
- Right breast 4cm clinical, grade 2, ER- and PR-negative, HER2-positive, right axilla lymph node positive on core biopsy
- Treated with AC-THP
- Patient had compete clinical response
- Went for wide local excision and pathology showed pCR without residual invasive disease in breast and axilla

What would you do?

1. Complete adjuvant pertuzumab/trastuzumab for total 1 year
2. Continue adjuvant trastuzumab (H) only for total 1 year
3. No further systemic treatment

Thank you for your participation

Evaluation form

Please remember to fill in the evaluation form.

You can also complete the form online on Meetoo:

URL: web.Meetoo.io

Meeting code: 137-968-042

Your feedback is greatly appreciated.

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