Her2neu directed and Targeted Therapy in Breast Cancer

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HER2/Neu Oncogene Discovery

- 1984: *Neu* transforming gene identified in chemically induced rat neuro-glioblastoma[1]
- 1985: *HER2* amplification identified in human breast cancer[2]
- 1985: *HER2* and *c-erbB2* identified and found to be the same gene as *neu*[3]
- 1986: *Neu* oncogene had activating point mutation in transmembrane domain[4]
- 1987: *HER2/neu* amplification associated with worse prognosis in operable breast cancer[5]

[1]Schecter AL et al. *Nature* 1984;312:513-516

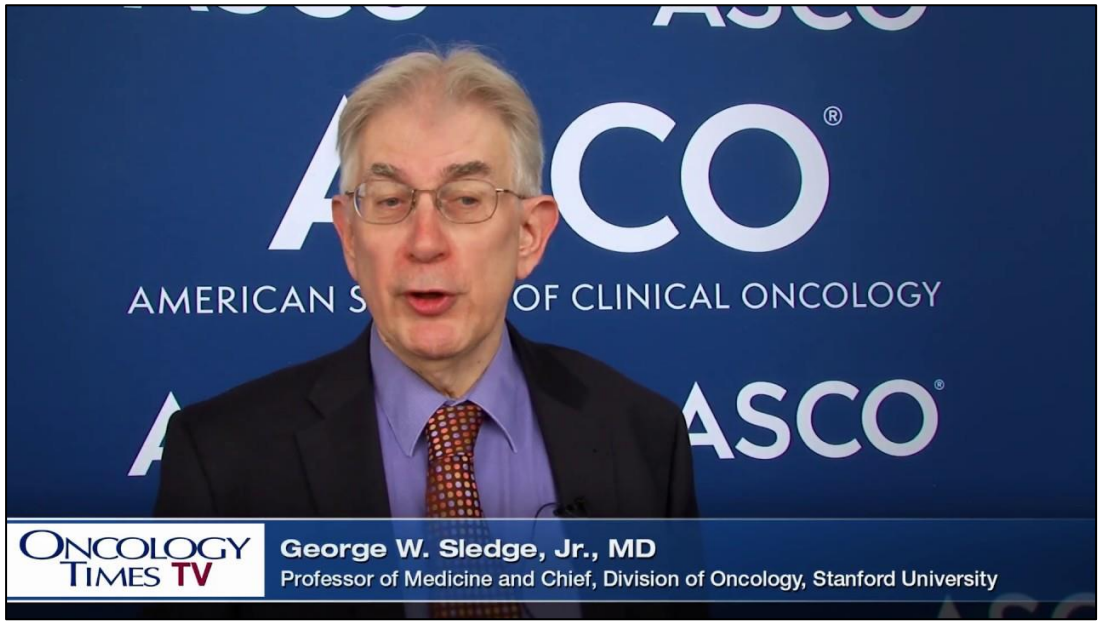
[2]King CR et al. *Science* 1985;229:974-976

[3]Coussens L et al. *Science* 1985; 230:1132-1139

[4]Bargmann CI et al. *Cell* 1986;45:649-657

[5]Slamon DJ et al. *Science* 1987; 237:177-182

May 2005: American Society of Clinical Oncology (ASCO) meeting in Orlando, Florida

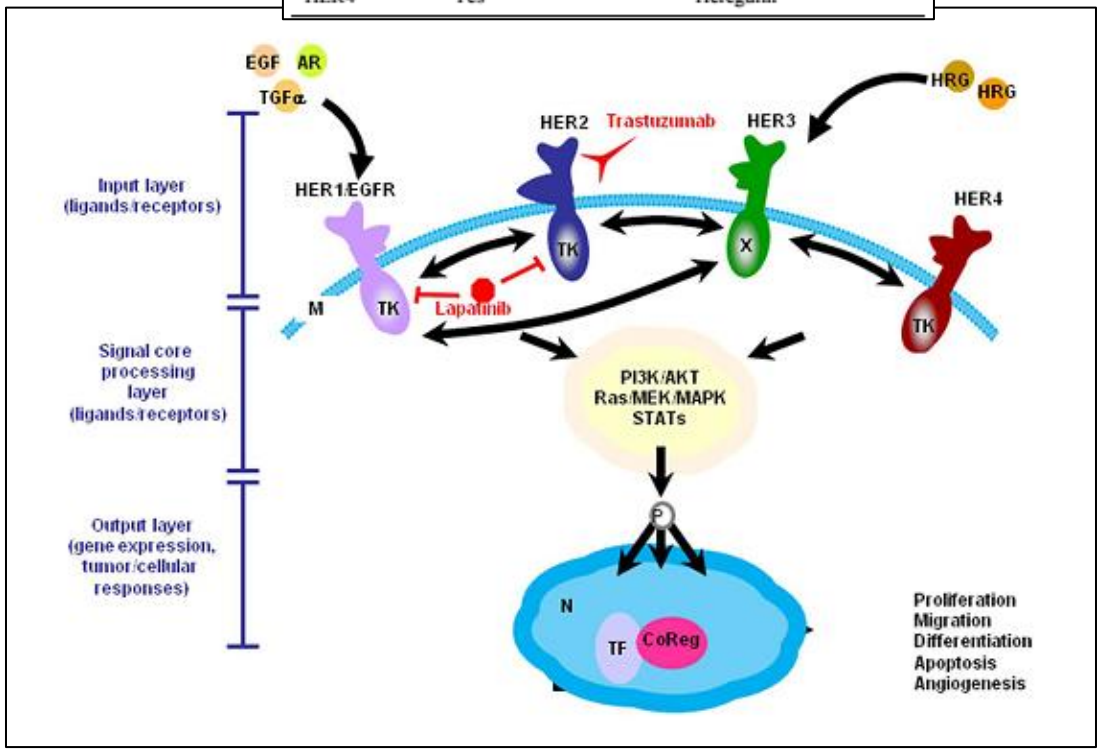


“Biology has spoken, and we should listen.”

Biological Significance of HER

- The HER pathway has been described in systems biology terms as a complex biological network comprised of three layers,
  - an input layer of membrane receptors and their ligands to trigger the signal coming from outside the cell,
  - a core system processing layer of protein kinases transmitting the signal to the nucleus,
  - an output layer of transcription factors regulating genes that affect various cellular functions

Receptor	Tyrosine Kinase Activity	Major Ligands
HER1 (EGFR)	Yes	EGF, amphiregulin, TGFα
HER2	Yes	None
HER3	No	Heregulin
HER4	Yes	Heregulin



Importance of HER2Neu

- Input layer is comprised of 4 membrane receptors/tyrosine kinases (TKs) (HER1–4) and their many ligands
- Upon ligand binding to their extracellular domains, HER proteins undergo dimerization and trans phosphorylation of their intracellular domains
- In breast cancer, HER2 is the dominant TK receptor, being amplified in 20% of cases
- HER2 does not have a ligand and relies on heterodimerization with another family member or homodimerization with itself when expressed at very high levels to be activated
- HER2 has the strongest catalytic kinase activity and HER2 containing heterodimers have the strongest signaling activity

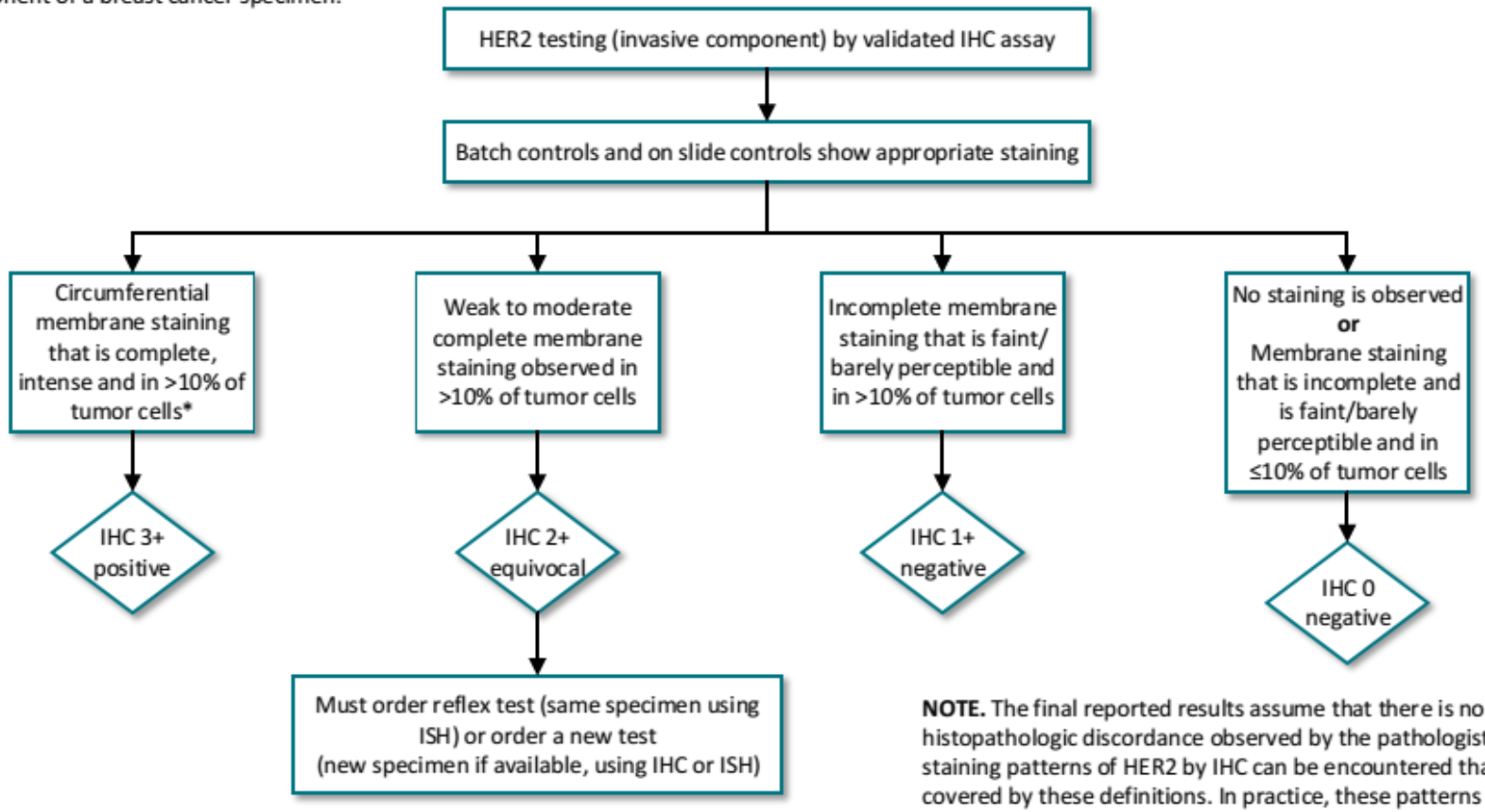
Characteristics of HER2-Amplified Breast Cancer

Increased proliferation rates
High histologic and nuclear grade
Low ER and PR levels
More aneuploidy
Propensity to metastasize to CNS and viscera
Relative resistance to endocrine therapy
Increased sensitivity to doxorubicin; Co-amplification of topoisomerase 2
Relative resistance to endocrine therapy
Response to HER2-targeted therapy

HER2 Detection in Breast Cancer

- In 2007 the American Society of Clinical Oncology and the College of American Pathologists developed recommendations for HER2 testing performance to reduce assay errors
- Historically assay error rates were as high as 20% when compared to centralized laboratories
- Tests are performed on tumour samples that are fixed in buffered formalin and embedded in paraffin
  - Immunohistochemistry (IHC),
  - Molecular testing with in situ hybridization: single and dual probe
    - fluorescence in situ hybridization (FISH),
    - chromogenic in situ hybridization (CISH)
    - silver enhanced in situ hybridization (SISH)

Figure 1. Algorithm for evaluation of human epidermal growth factor receptor 2 (HER2) protein expression by immunohistochemistry (IHC) assay of the invasive component of a breast cancer specimen.



NOTE. The final reported results assume that there is no apparent histopathologic discordance observed by the pathologist. Unusual staining patterns of HER2 by IHC can be encountered that are not covered by these definitions. In practice, these patterns are rare and if encountered should be considered IHC 2+ equivocal. As one example, some specific subtypes of breast cancers can show IHC staining that is moderate to intense but incomplete (basolateral or lateral) and can be found to be HER2 amplified. Another example is circumferential membrane IHC staining that is intense but within ≤10% of tumor cells (heterogeneous but very limited in extent). Such cases can be considered 2+ equivocal but additional samples may reveal different percentages of HER2 positive staining. (*)Readily appreciated using a low power objective and observed within a homogeneous and contiguous invasive cell population

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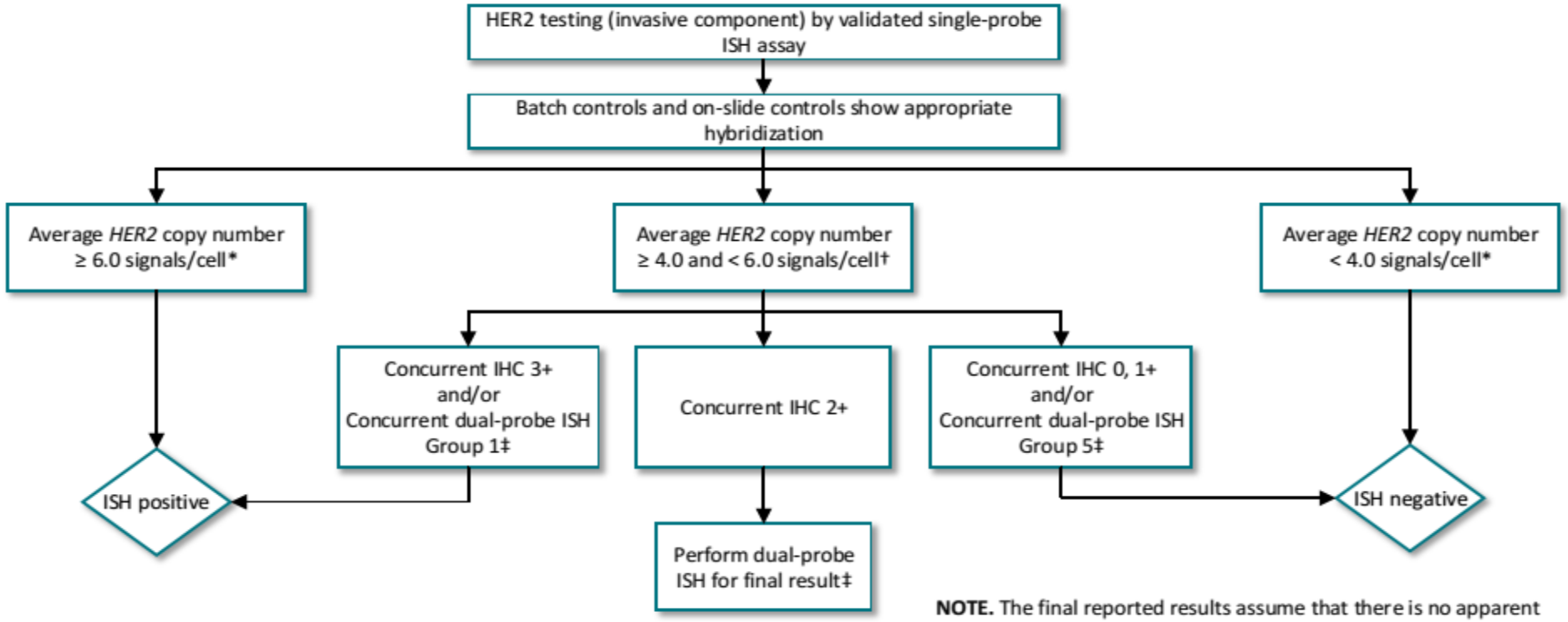
ASCO® Guidelines

This algorithm is derived from recommendations in Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. This is a tool based on an ASCO and CAP guideline and is not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients. This tool does not purport to suggest any particular course of medical treatment. Use of the guideline and this tool are voluntary.

IHC

Figure 2. Algorithm for evaluation of human epidermal growth factor receptor 2 (HER2) gene amplification by in situ hybridization (ISH) assay of the invasive component of a breast cancer specimen using a single-signal (HER2 gene) assay (single-probe ISH).



NOTE. The final reported results assume that there is no apparent histopathologic discordance observed by the pathologist

***It is recommended that concomitant IHC review should become part of the interpretation of single-probe ISH results. The Expert Panel also preferentially recommends the use of dual-probe instead of single-probe ISH assays.**

†Using sections from the same tissue samples used for single-probe ISH, perform IHC (if not already done) and/or dual-probe ISH. If IHC results are 2+ equivocal, it is recommended to also perform dual probe ISH.

‡If initial assessment of dual-probe ISH suggestive of Groups 2, 3, or 4, follow the algorithm described in Figure 3.

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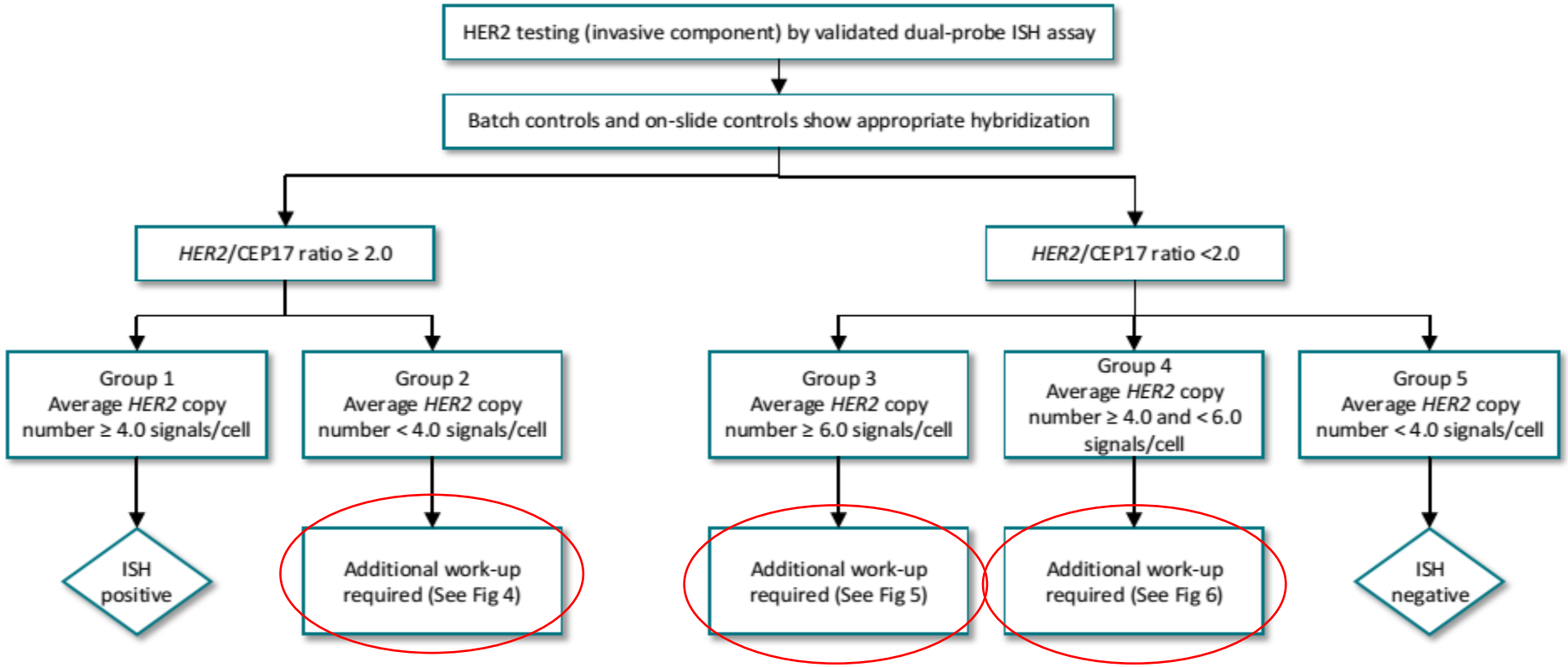
Single probe ISH

Figure 3. Algorithm for evaluation of human epidermal growth factor receptor 2 (HER2) gene amplification by in situ hybridization (ISH) assay of the invasive component of a breast cancer specimen using a dual-signal (HER2 gene) assay (dual-probe ISH).



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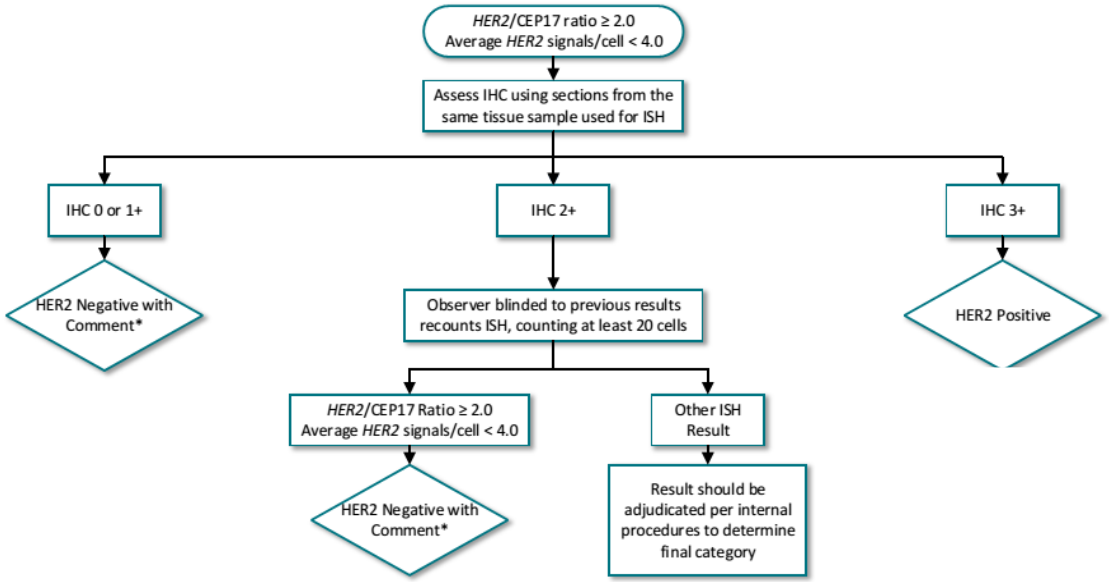
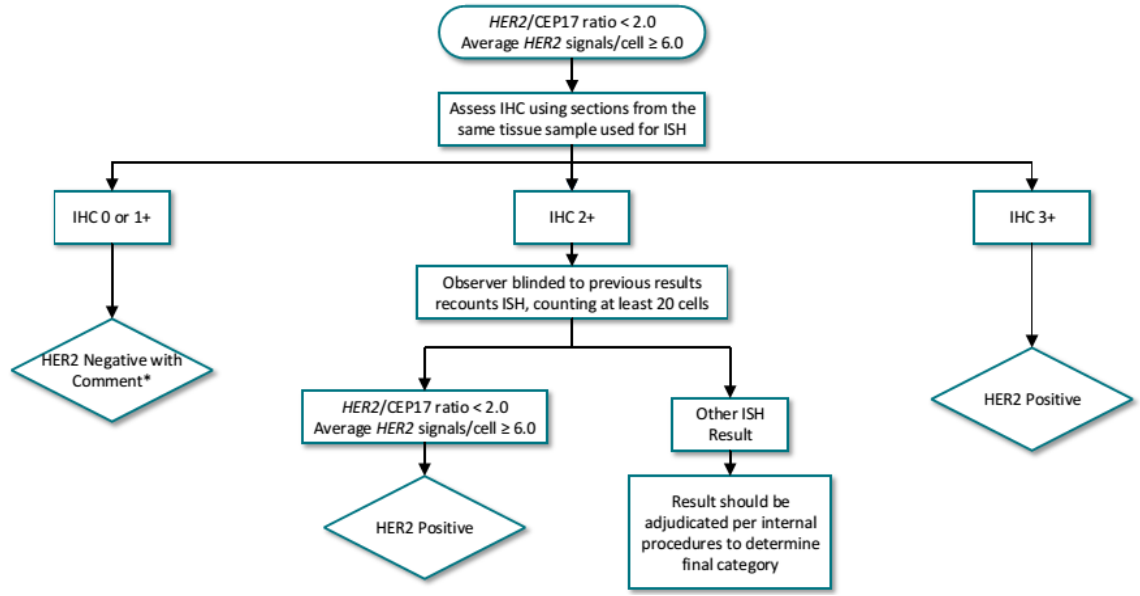
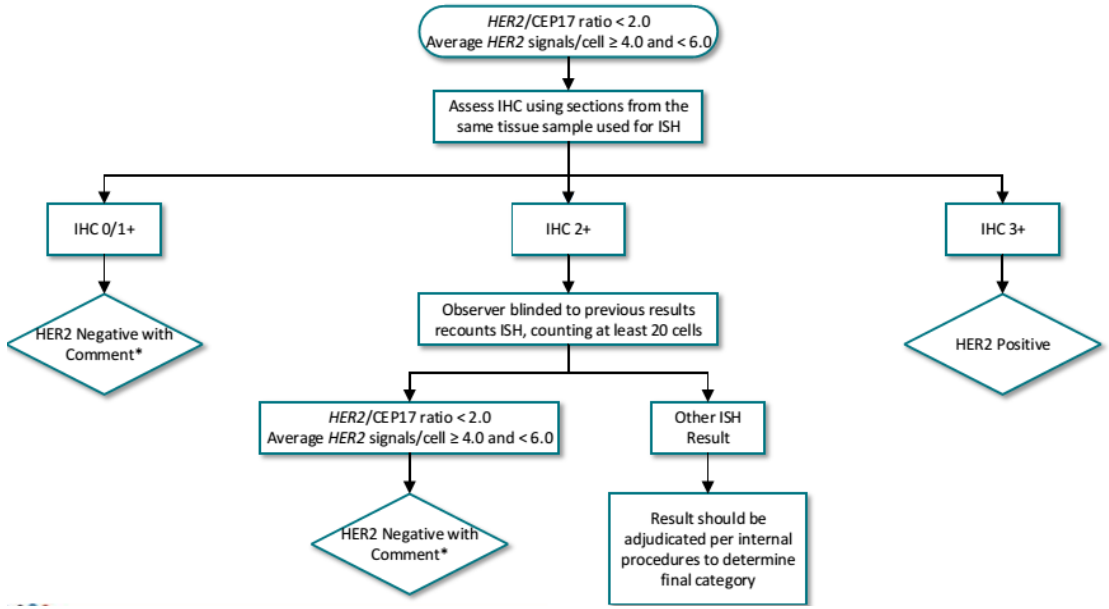
NOTE. The final reported results assume that there is no apparent histopathologic discordance observed by the pathologist. Regarding Groups 2, 3, and 4, If not already assessed by the institution/lab performing the ISH test, IHC testing for HER2 should be performed using sections from the same tissue sample used for ISH and the slides from both ISH and IHC be reviewed together to guide the selection of areas to score by ISH (local practice considerations will dictate the best procedure to accomplish this concomitant assessment).

This algorithm is derived from recommendations in Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. This is a tool based on an ASCO and CAP guideline and is not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients. This tool does not purport to suggest any particular course of medical treatment. Use of the guideline and this tool are voluntary.

Dual probe ISH


HER2/CEP17 ratio ≥ 2.0
Average *HER2* signals/cell < 4.0
Assess IHC using sections from the same tissue sample used for ISH
IHC 0 or 1+
IHC 2+
IHC 3+
HER2 Negative with Comment*
Observer blinded to previous results recounts ISH, counting at least 20 cells
HER2 Positive
HER2/CEP17 Ratio ≥ 2.0
Average *HER2* signals/cell < 4.0
Other ISH Result
HER2 Negative with Comment*
Result should be adjudicated per internal procedures to determine final category


HER2/CEP17 ratio < 2.0
Average *HER2* signals/cell ≥ 6.0
Assess IHC using sections from the same tissue sample used for ISH
IHC 0 or 1+
IHC 2+
IHC 3+
HER2 Negative with Comment*
Observer blinded to previous results recounts ISH, counting at least 20 cells
HER2 Positive
HER2/CEP17 ratio < 2.0
Average *HER2* signals/cell ≥ 6.0
Other ISH Result
HER2 Positive
Result should be adjudicated per internal procedures to determine final category


HER2/CEP17 ratio < 2.0
Average *HER2* signals/cell ≥ 4.0 and < 6.0
Assess IHC using sections from the same tissue sample used for ISH
IHC 0/1+
IHC 2+
IHC 3+
HER2 Negative with Comment*
Observer blinded to previous results recounts ISH, counting at least 20 cells
HER2 Positive
HER2/CEP17 ratio < 2.0
Average *HER2* signals/cell ≥ 4.0 and < 6.0
Other ISH Result
HER2 Negative with Comment*
Result should be adjudicated per internal procedures to determine final category

Clinical decision making
Anti her2neu therapy

Indications

- Curative intent
  - Adjuvant
    - Sequential
    - Concurrent
  - Neoadjuvant
- Palliative intent

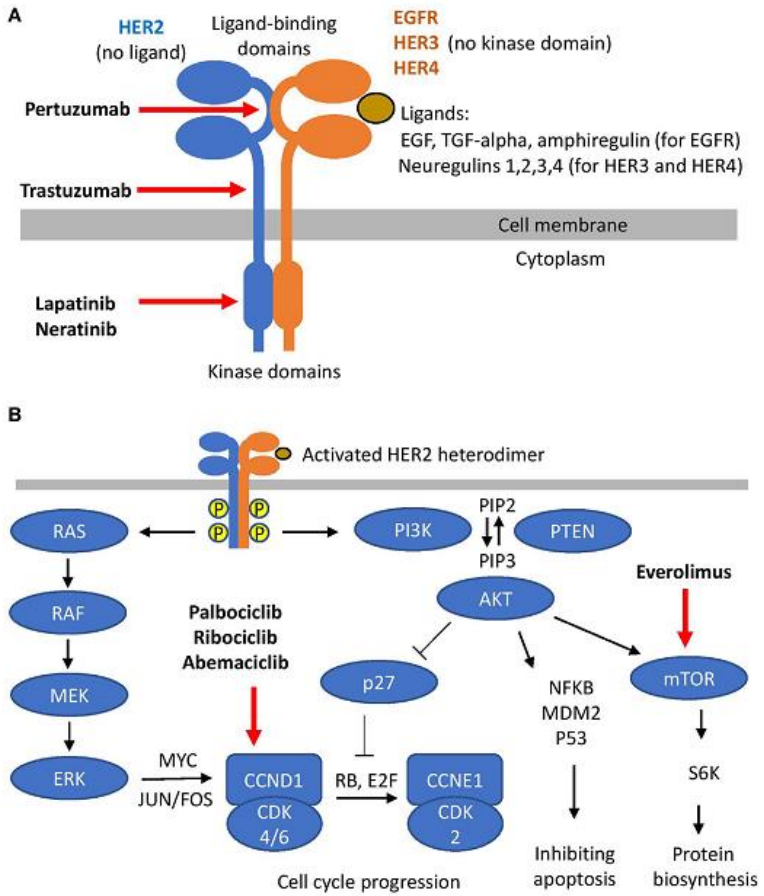
Monoclonal Antibodies

- Trastuzumab
- Pertuzumab
- “Ado-Trastuzumab”

Tyrosine Kinase Inhibitors

- Lapatinib
- *Neratinib*
- *Tucatinib*

The molecules



Anti-HER2 agent	Indication	Year of approval by the US FDA
Trastuzumab	Trastuzumab (Herceptin™) combined with paclitaxel in patients with mBC whose tumors overexpress HER2 protein and who have not received chemotherapy for their metastatic disease	1998
Lapatinib	Lapatinib (Tykerb®) for use in combination with capecitabine for treatment of patients with advanced breast cancer or mBC whose tumors overexpress HER2 (ErbB2), and who have received prior therapy including anthracycline, taxane, and trastuzumab	2007
Pertuzumab	Pertuzumab (Perjeta™) for use in combination with trastuzumab and docetaxel for the treatment of HER2-positive mBC who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease	2012
T-DM1	Trastuzumab emtansine (Kadcyla™) for use as a single agent for the treatment of patients with HER2-positive mBC, who had previously received treatment with trastuzumab and taxane, either separately or in combination	2013

Curative setting: Adjuvant

- Trastuzumab combined with Chemotherapy in patients with HER2 overexpression/amplification approximately halves the recurrence and mortality risk, compared with ChT alone, translating into a 10% absolute improvement in long-term DFS and 9% increase in 10-year OS
- Trastuzumab is approved in patients with node-positive disease and in N0 patients with tumours > 1 cm
- In patients with N0 tumours >5mm and < 1 cm, it should also be considered in this patient group, particularly in ER negative disease

Evidence

24 mos

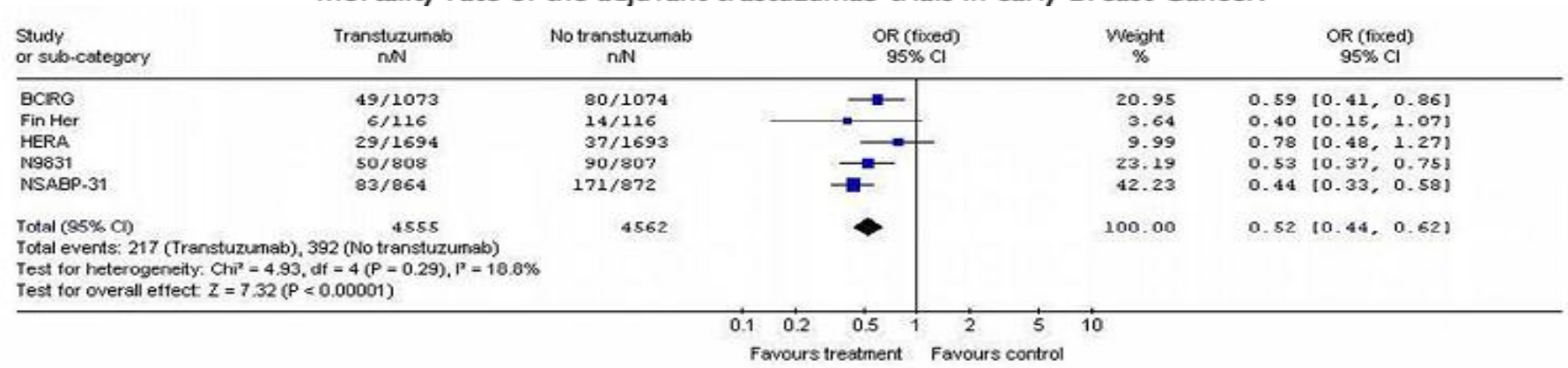
9 weeks

Table 1. Characteristics of eligible trials in this analysis

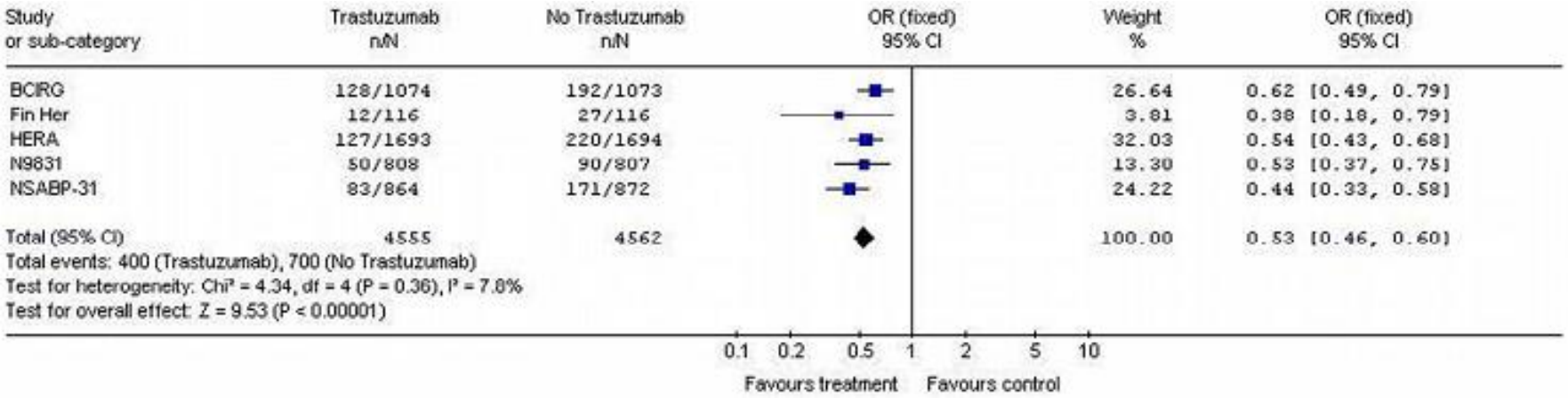
Study	Median follow-up (years)[a]	Tumor characteristics	Treatment regimens per arm	*n* of patients	Node positive (%)	HR positive (%)
HERA[b]	2	Early-stage invasive breast cancer, node positive or high-risk node negative (tumor >1 cm)	Arm A CT ± RT → observation Arm B CT ± RT → H ×12 mos Arm C CT ± RT → H ×24 mos	1,698 1,703 1,689	964 (56.8) 965 (56.7) NR	855 (50.4) 860 (50.5) NR
NCCTG N9831[c]	2.9	Early-stage invasive breast cancer, node positive or high-risk node negative (tumor >1 cm if HR negative or >2 cm if HR positive)	Arm A AC → P Arm B AC → P+H Arm C AC → P → H	807 808 981	701 (86.9) 719 (89) NR	426[g] (52.8) 414[g] (51.2) NR
NSABP B-31[d]	2.9	Early-stage, node-positive invasive breast cancer	Arm A AC → P Arm B AC → P+H	872 864	872 (100) 864 (100)	460[g] (52.8) 448[g] (51.9)
BCIRG 006[e]	3	Node positive or high-risk node negative	Arm A AC → D Arm B AC → D+H → H Arm C D + Carbo + H	1,073 1,074 1,075	762 (71) 763 (71) 774 (72)	579 (54) 580 (54) 581 (54)
FinHER[f]	3	Early-stage, node-positive or node-negative breast cancer (>2 cm and PgR negative)	Arm A D or V → CEF Arm B D or V + H → CEF	116 116	91 (78.4) 104 (89.7)	51[g] (44) 58[g] (50)

→ Sequential versus concurrent

mortality rate of the adjuvant trastuzumab trials in early Breast Cancer.



Recurrence rate of the adjuvant trastuzumab trials in early Breast Cancer.



Duration

Authors/Study	Period	N	Study Design	Treatment	MF	Survival HR (95% CI)	Cardiac events (shorter vs 1y)
Conte et al. Short-HER	2007.12–2013.10	1253	multicenter, phase III RCT, non-inferiority (HR < 1.29)	D + H → FEC AC/EC → T/D + H 9w vs 1y	6 y	DFS:1.13 (0.89–1.42) OS: 1.07 (0.74–1.56)	8/626 vs 18/627
Earl et al. PERSEPHONE	2007.10–2015.7	4088	multicenter, phase III RCT, open-label non-inferiority (HR < 1.29)	Anthracycline/ Taxane +H (concurrent/sequential) 6 m vs 1y	64.8m	DFS: 1.07 (0.90–1.28) OS: 1.14 (0.92–1.42)	82/2043 vs 164/2045
Joensuu et al. SOLD	2008.1–2014.12	2174	multicenter, phase III RCT, open-label superiority → non-inferiority (HR < 1.3)	D + H → FEC ± H 9w vs 1y	62.4m	DFS: 1.39 (1.08–1.79) OS: 1.36 (0.92–2.01)	22/1085 vs 42/1089
Mavroudis et al. HORG	2004.6–2012.5	481	multicenter, phase III RCT, non-inferiority (HR < 1.53)	FEC → D + H 6 m vs 1y	51m	DFS: 1.57 (0.86–2.10) OS: 1.45 (0.57–3.67)	-
Pivot et al. PHARE	2006.5–2010.7	3380	multicenter, phase III RCT, open-label non-inferiority (HR < 1.15)	Anthracycline/ Taxane +H (concurrent/sequential) 6 m vs 1y	7.5y	DFS: 1.08 (0.93–1.25) OS: 1.13 (0.92–1.39)	67/1690 vs 111/1690
Schneider et al. E2198	1999.8–2000.10	120*	phase II RCT	T + H → AC ± H 12w vs 1y	77m	DFS: 0.85 (0.41–1.77) OS: 1.21 (0.46–3.13)	-

1 year still standard despite higher incidence of cardiac dysfunction

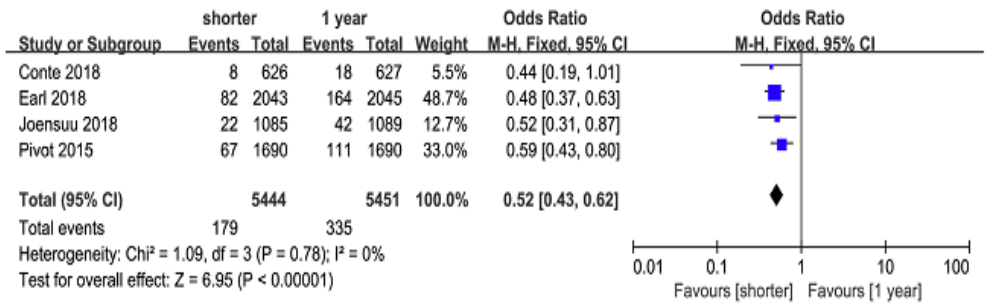
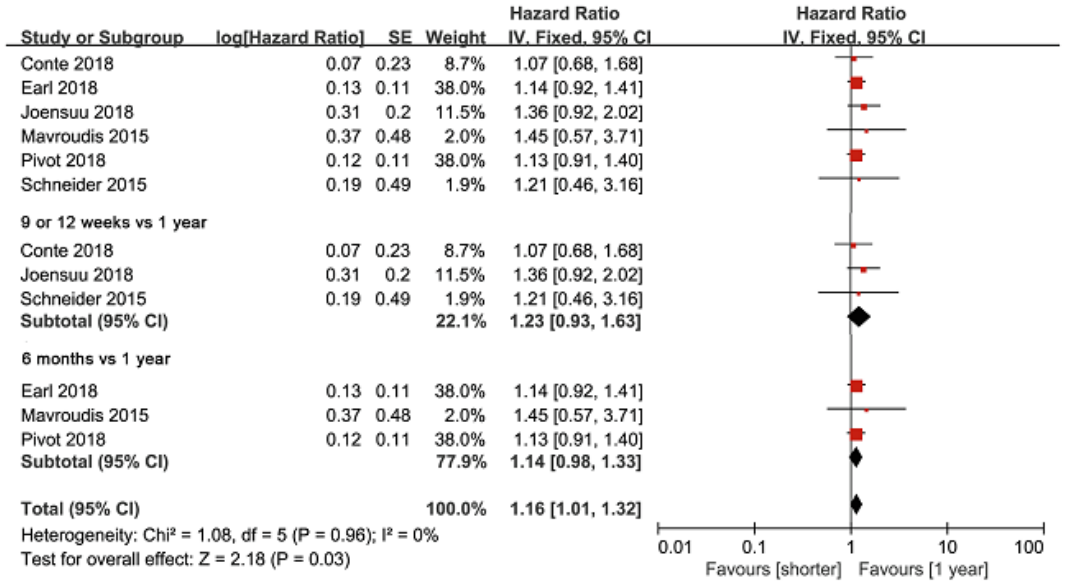
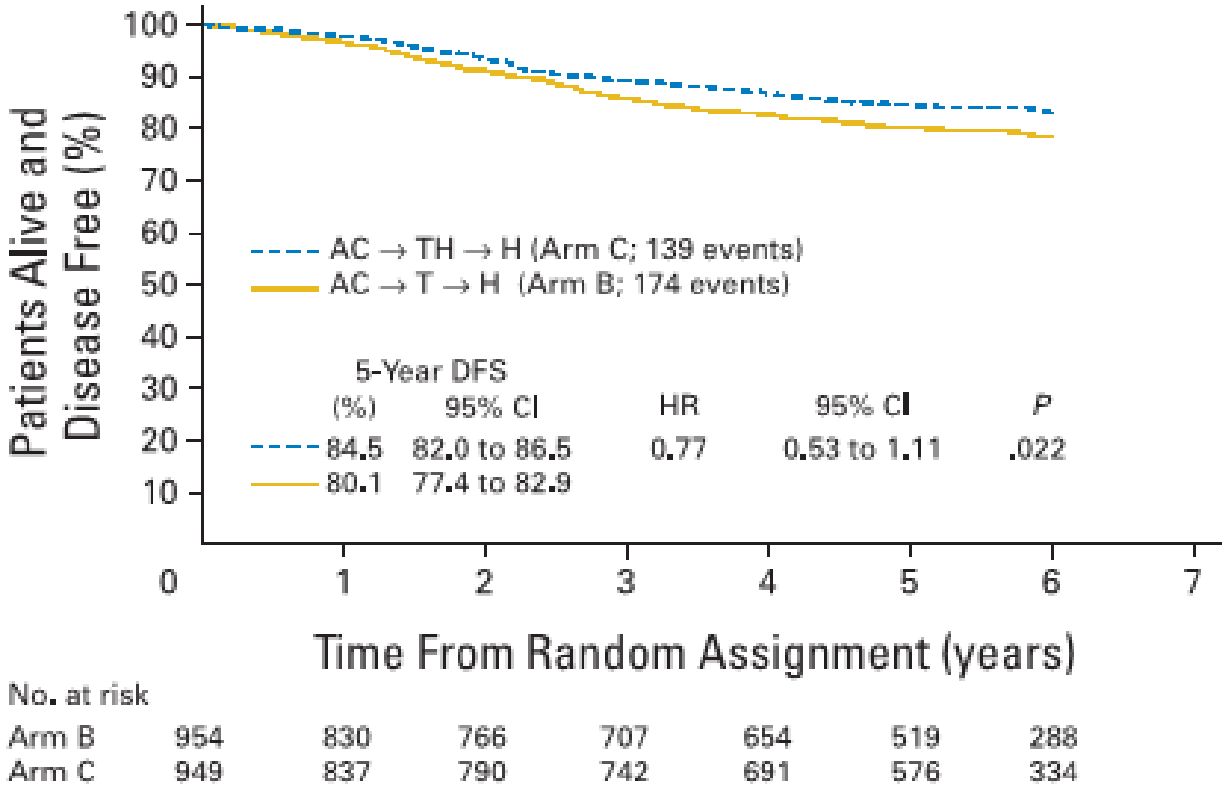


Fig. 5. Forest plot of odds ratios comparing cardiac events of patients treated with shorter-duration versus 1-year trastuzumab.



Sequential versus concurrent : NCCTG (North Central Cancer Treatment Group) N9831

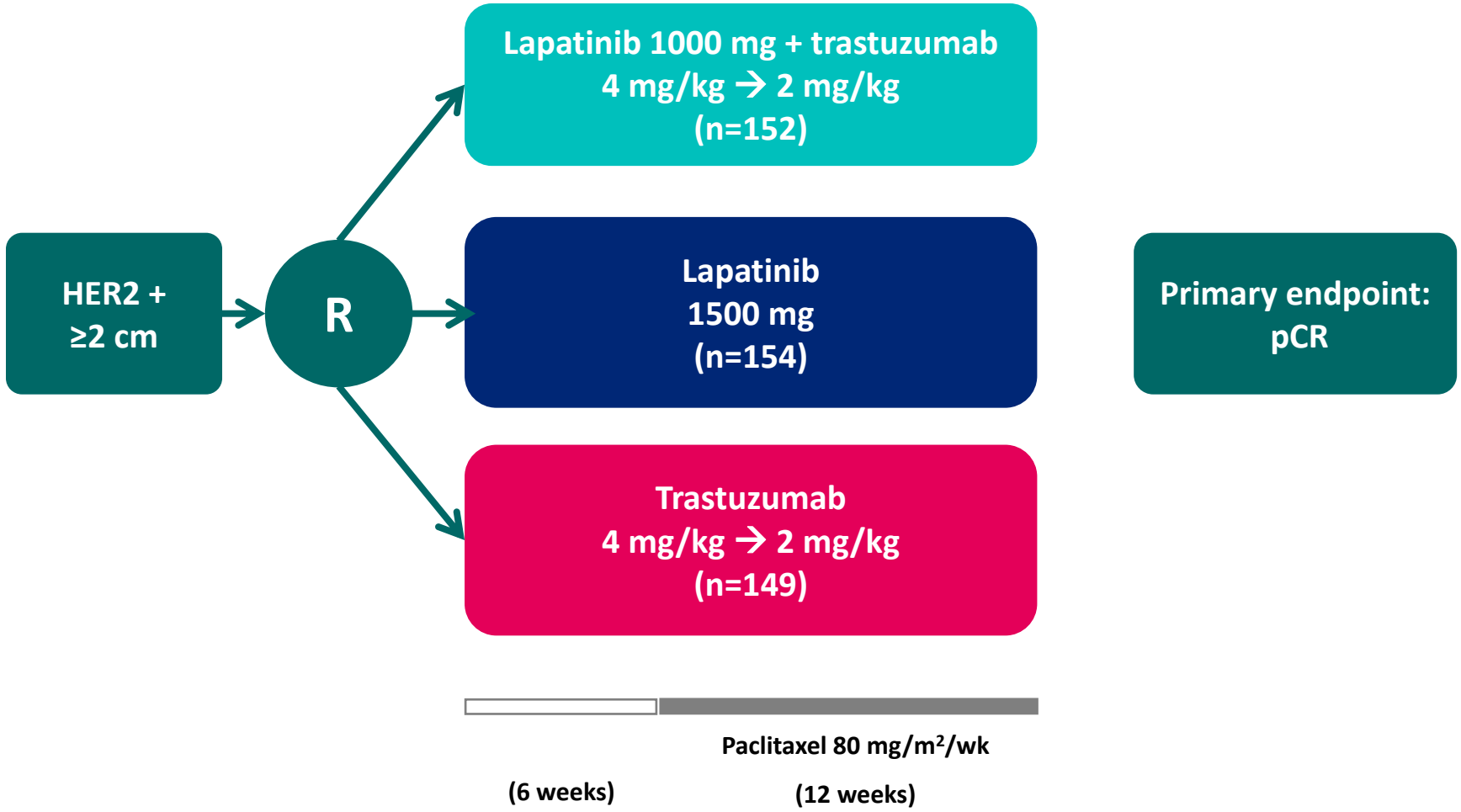


Increase in DFS with concurrent trastuzumab and paclitaxel relative to sequential administration

Neoadjuvant therapy

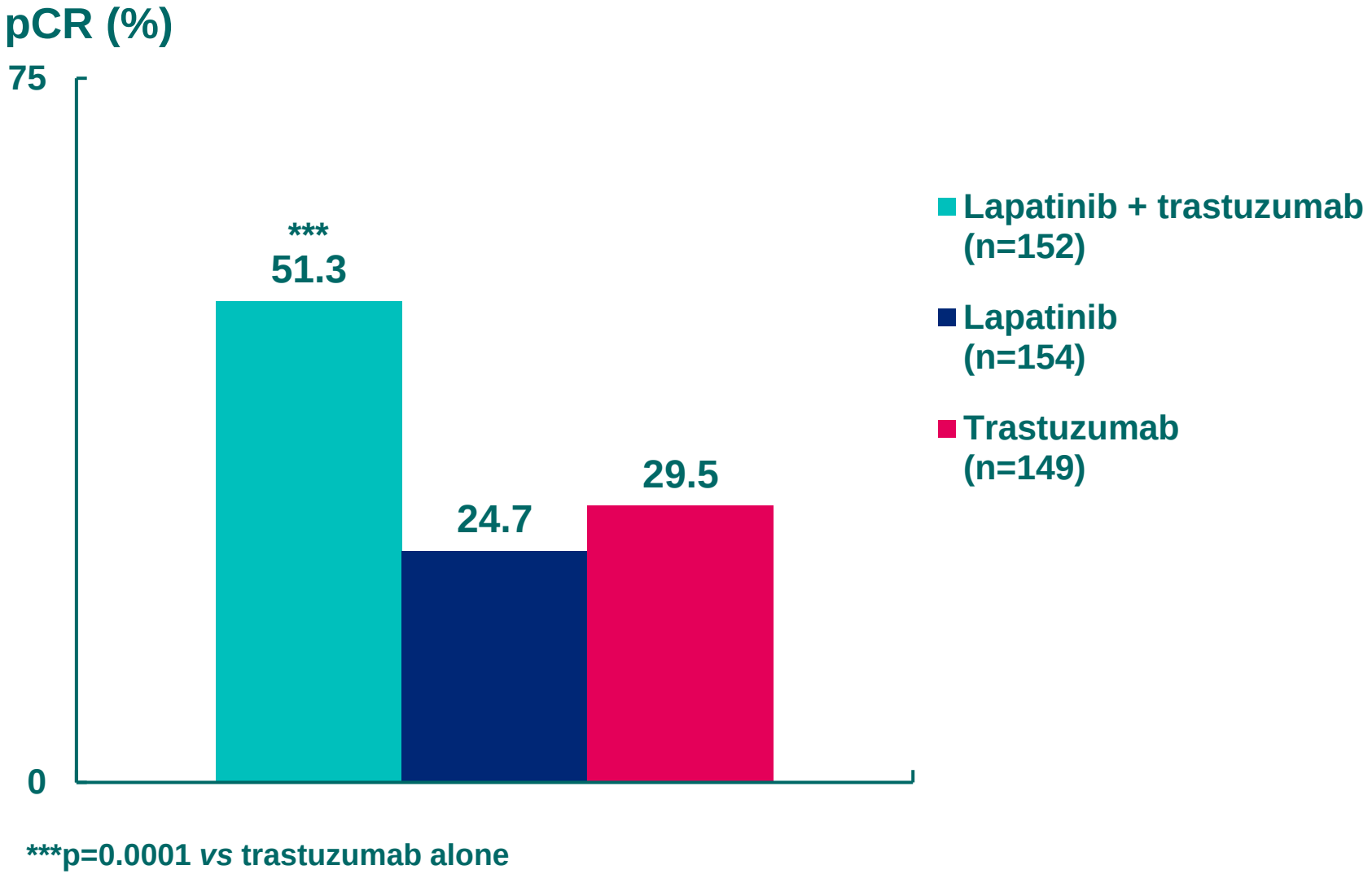
- Pathological CR is the primary objective
- Introduction of anti her2 therapy in neoadjuvant setting promising
- Effective alternative of combination targeted therapy available

NeoALLTO – Effect of dual HER2 blockade: Lapatinib and trastuzumab



Baselga et al, Lancet. 2012;379:633-40.

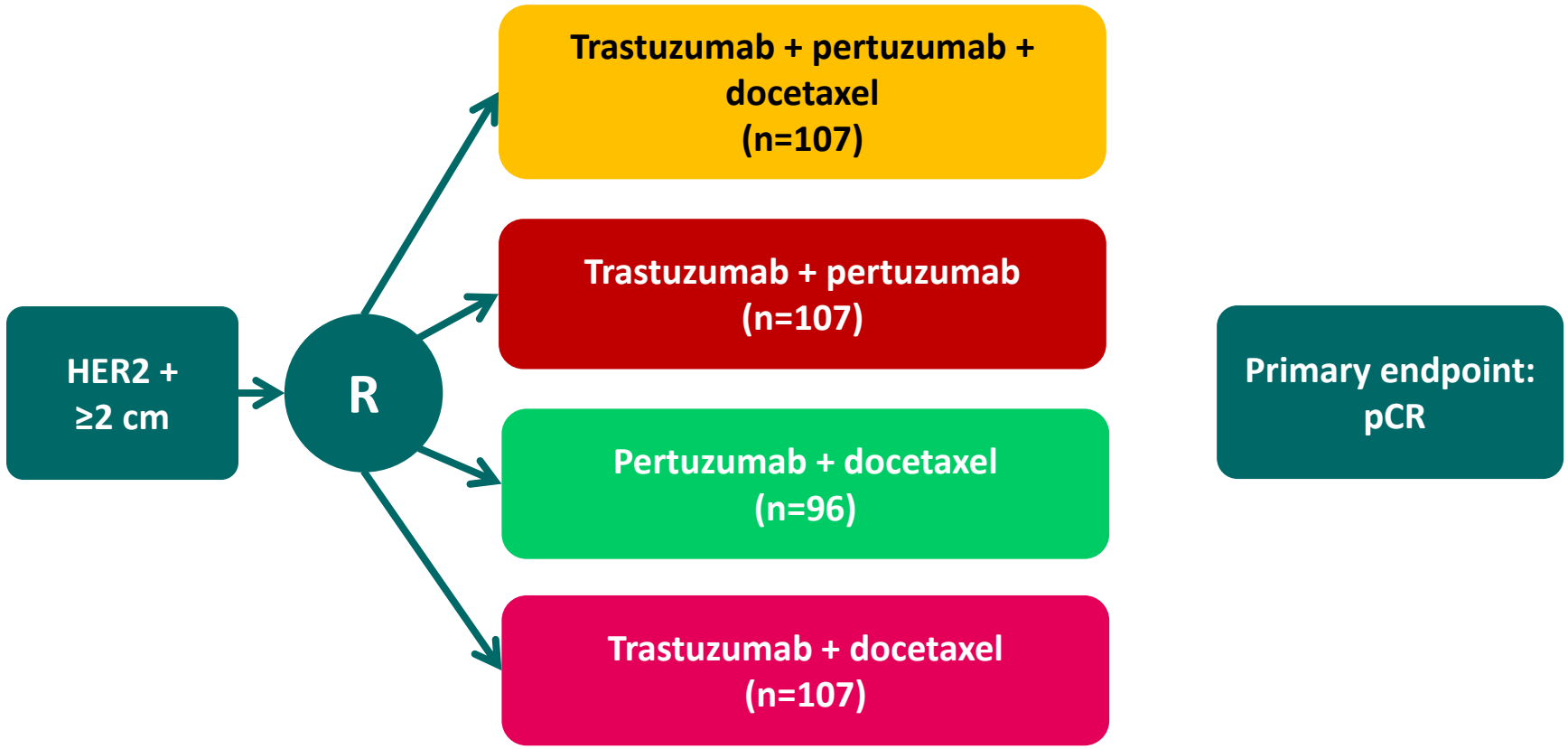
NeoALLTO – Effect of dual HER2 blockade: Pathologic CR



***p=0.0001 *vs* trastuzumab alone

Baselga et al, Lancet. 2012;379:633-40.

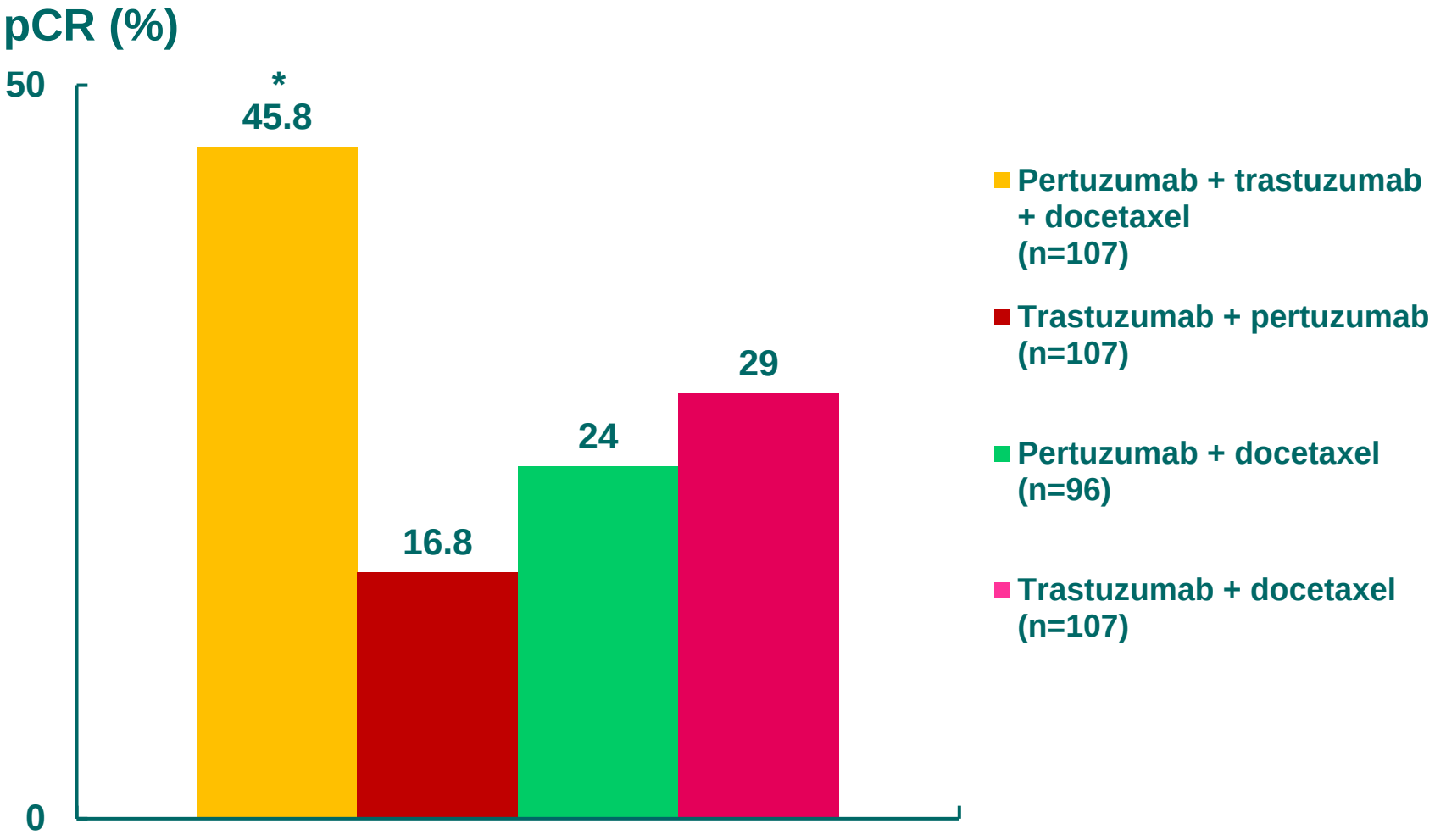
NeoSphere – Neoadjuvant pertuzumab + trastuzumab: Study design



Docetaxel 75 mg/m² q3w
Trastuzumab 8 mg/kg → 6 mg/kg
Pertuzumab 840 mg/kg → 420 mg/kg
(4 cycles)

Gianni et al, Lancet Oncol. 2012;13:25-32.

NeoSphere – Neoadjuvant pertuzumab + trastuzumab: Pathologic CR

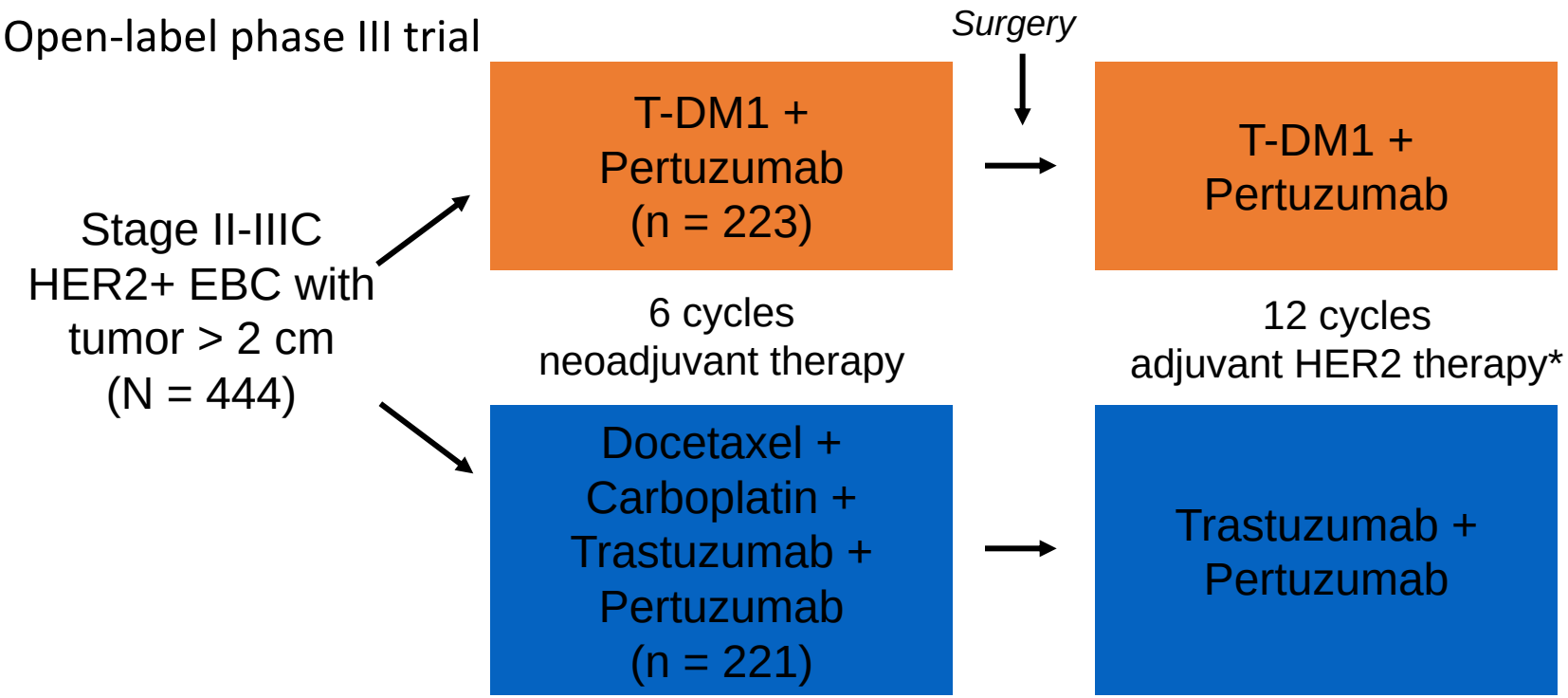


*p=0.0141 *vs* trastuzumab + docetaxel

Gianni et al, Lancet Oncol. 2012;13:25-32.

Neoadjuvant therapy: KRISTINE Study Design

- Open-label phase III trial



*Adjuvant therapy recommended for pts in T-DM1/pertuzumab group with residual disease in lymph nodes or breast (> 1 cm).

- Primary endpoint: pCR by local assessment in breast, lymph nodes (ypT0/is, ypN0)
- Secondary endpoints: safety, BCS rate, PROs, EFS, iDFS, OS
- Stratified by: local hormone receptor status, geographic location, stage

Hurvitz SA, et al. ASCO 2016. Abstract 500.

KRISTINE: Clinical Response

Outcome	TCHP (n = 221)	T-DM1 + P (n = 223)
pCR (ypT0/is, ypN0), %	56	44
	Difference: -11.3 (95% CI: -20.5 to -2.0; *P* = .0155)	
pCR by receptor status, %		
▪ ER- and PR-	73	54
▪ ER+ and/or PR+	44	35
BCS rate, %		
▪ Actual	53	42
▪ Conversion*	70	66

*Pts originally needing mastectomy who became eligible for BCS after neoadjuvant therapy.

- Longer maintenance of health-related QoL (HR: 0.60) and physical function (HR: 0.47) with T-DM1 + P vs TCHP

Hurvitz SA, et al. ASCO 2016. Abstract 500.

KRISTINE: Safety (Neoadjuvant Phase)

Outcome, %	TCHP (n = 219)	T-DM1 + P (n = 223)
Any AE	98.6	88.3
Serious AE	28.8	4.9
Grade ≥ 3 AE (> 5%)		
▪ Any	64.4	13.0
▪ Neutropenia	25.1	0.4
▪ Febrile neutropenia	15.1	0
▪ Diarrhea	15.1	0.9
▪ Anemia	9.6	0.9
▪ Decreased neutrophil count	9.1	0
AE leading to discontinuation of any treatment component	8.7	3.1
LVEF < 50% and ≥ 10% points decrease from baseline	0.5	0.4

Hurvitz SA, et al. ASCO 2016. Abstract 500.

KRISTINE: Conclusions

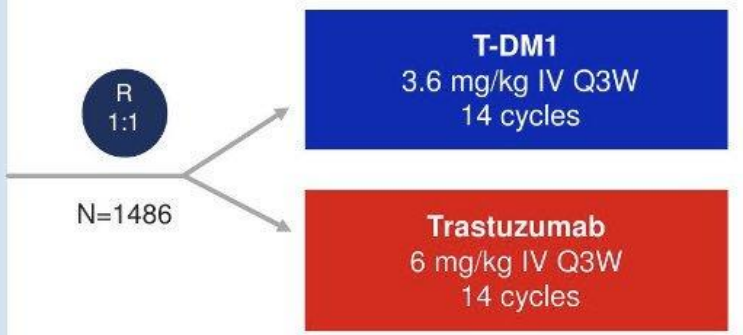
- Superior pCR rate with neoadjuvant TCHP compared with T-DM1 + P in early breast cancer
  - Same effect in hormone receptor status subgroup analysis
- Rate BCS lower in T-DM1 + P arm
- Favorable safety profile of T-DM1 + P with lower incidence of serious and grade ≥ 3 AEs
- Longer health-related QoL and physical functioning with T-DM1 + P compared with TCHP
- Investigators suggest chemotherapy with trastuzumab + pertuzumab remain neoadjuvant standard of care for HER2+ breast cancer

Hurvitz SA, et al. ASCO 2016. Abstract 500.

The KATHERINE study

KATHERINE Study Design

- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Centrally confirmed HER2-positive breast cancer
- Neoadjuvant therapy must have consisted of
  - Minimum of 6 cycles of chemotherapy
    - Minimum of 9 weeks of taxane
    - Anthracyclines and alkylating agents allowed
    - All chemotherapy prior to surgery
  - Minimum of 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery

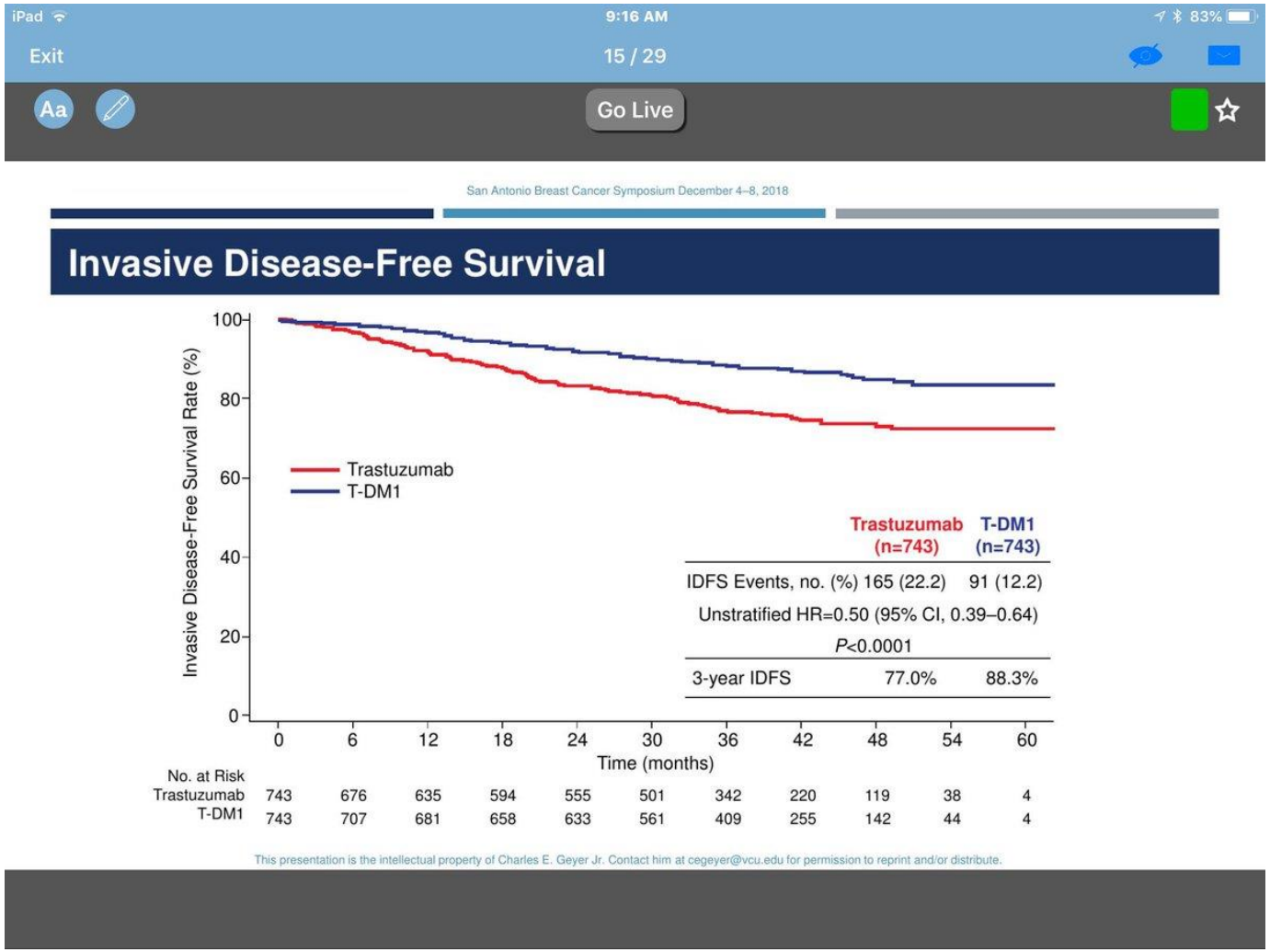


Radiation and endocrine therapy per protocol and local guidelines

Stratification factors:

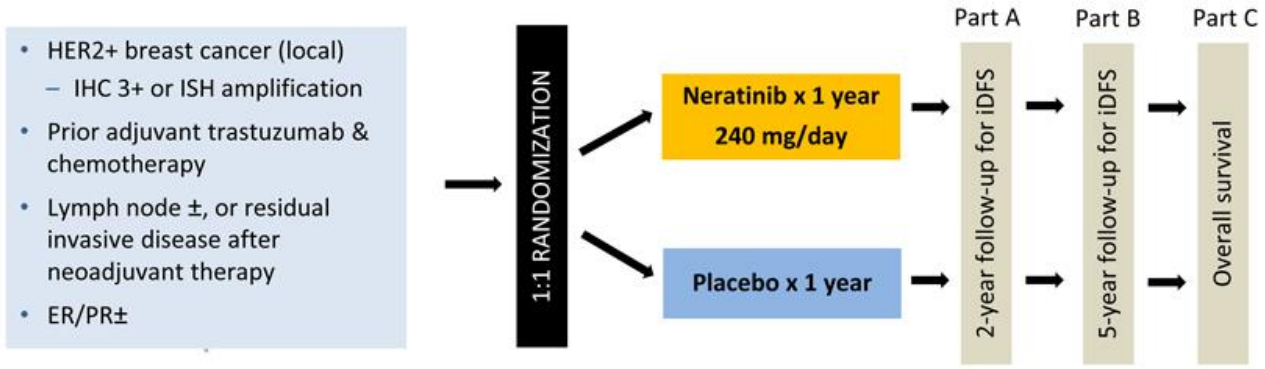
- Clinical presentation: Inoperable (stage cT4 or cN2–3) vs operable (stages cT1-3N0-1)
- Hormone receptor: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: Trastuzumab vs trastuzumab plus other HER2-targeted therapy
- Pathological nodal status after neoadjuvant therapy: Positive vs negative/not done

TDM1 scores over trastuzumab for adjuvant therapy with post neoadjuvant residual



ExteNET: extended Anti her2 adjuvant therapy with NERATINIB

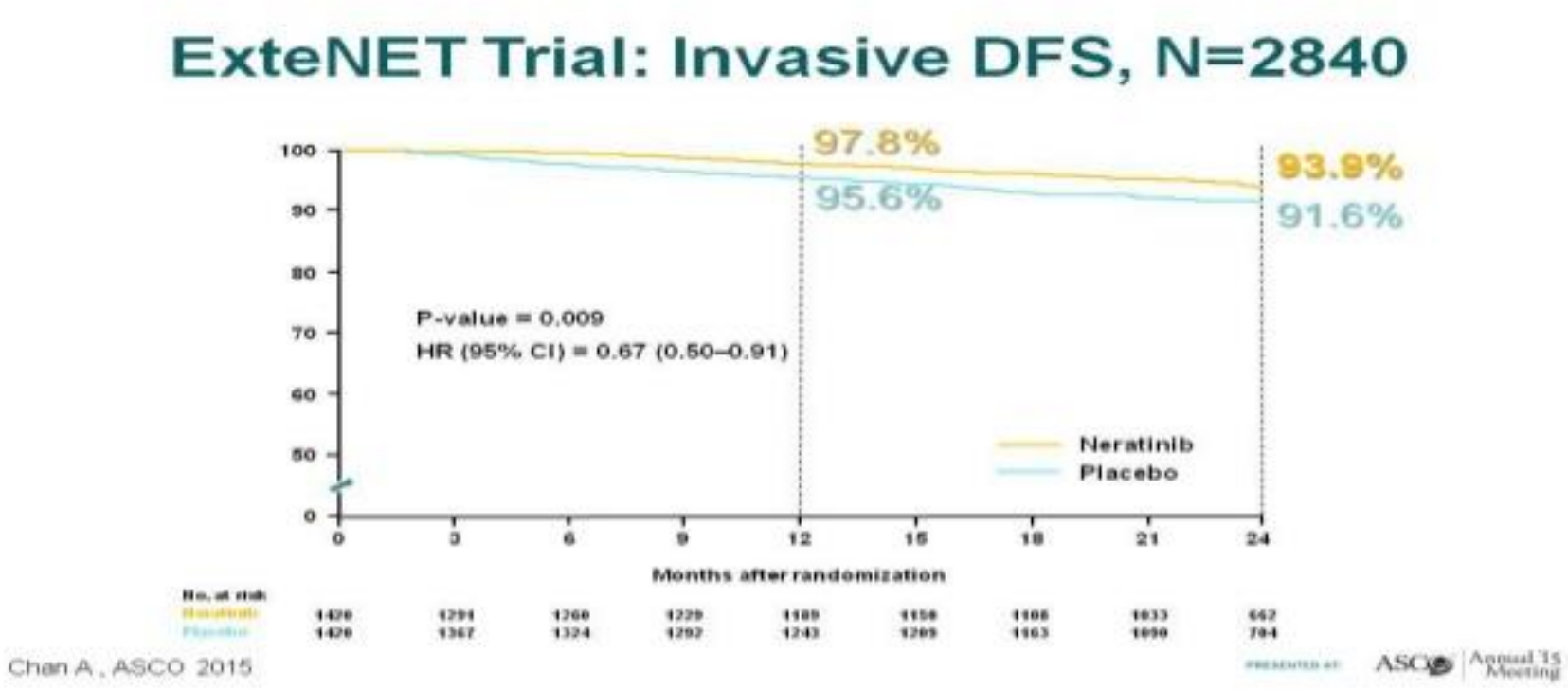
ExteNET: study design



- **Primary endpoint:** invasive disease-free survival (iDFS)
- **Secondary endpoints:** DFS-DCIS, time to distant recurrence, distant DFS, CNS metastases, overall survival, safety
- **Other analyses:** biomarkers, health outcome assessment (FACT-B, EQ-5D)
- **Stratified by:** nodes 0, 1–3 vs 4+, ER/PR status, concurrent *vs* sequential trastuzumab

Chan et al. Lancet Oncol 2016
Clinicaltrials.gov identifier: NCT00878709

First evidence of benefit of anti-her 2 therapy beyond 1 year



Presented By Shanu Modi at 2015 ASCO Annual Meeting

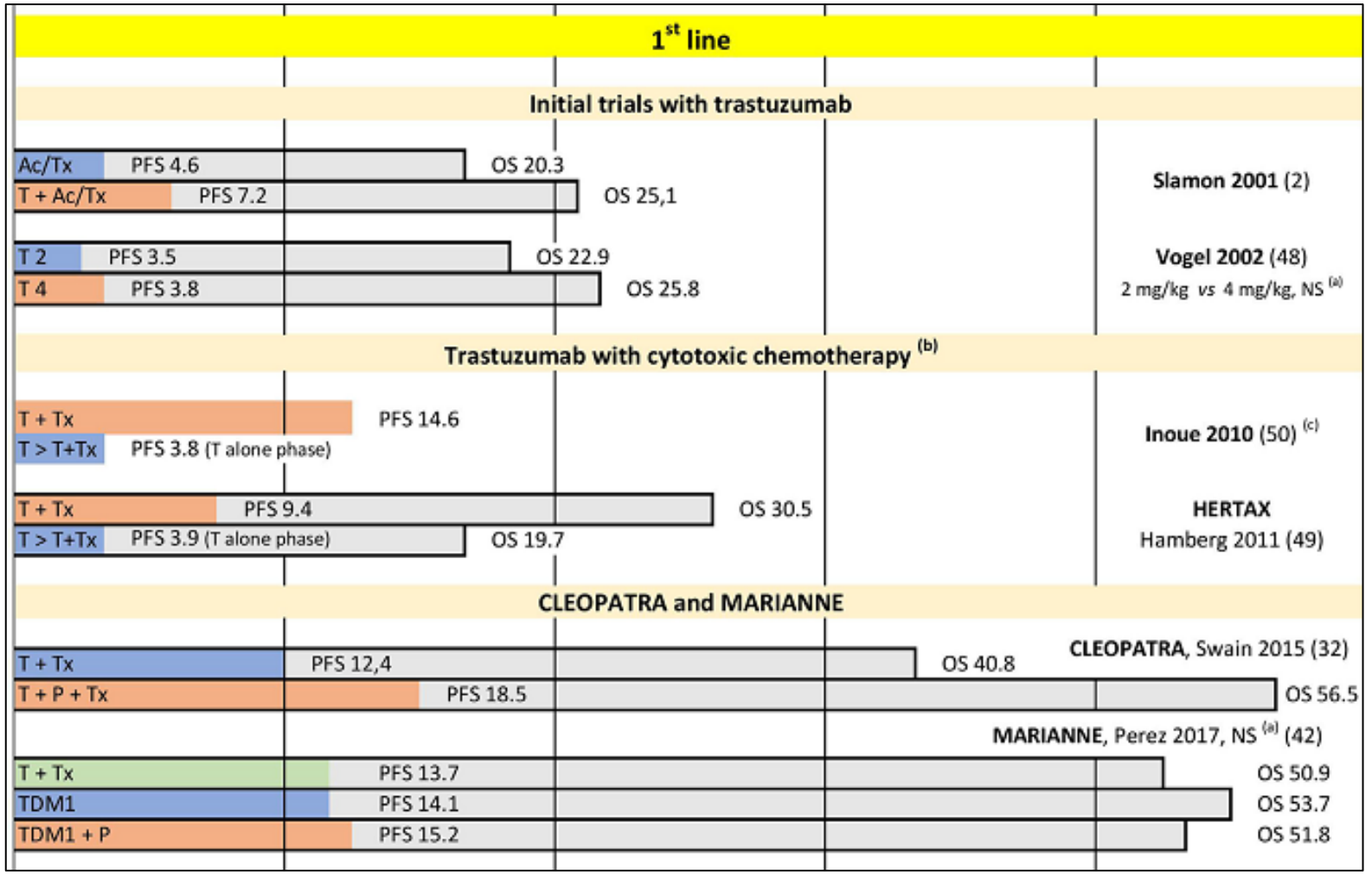
Summary

- Adjuvant trastuzumab is highly effective and should be given to all HER2-positive early breast cancer patients who do not have contraindications for its use, with the possible exception of selected cases with very low risk, such as T1aN0 tumours
- One year of (neo)adjuvant trastuzumab remains a standard for the vast majority of HER2- positive patients: however, in highly selected, low-risk patients who receive anthracycline/taxane-based ChT, shortening trastuzumab duration to 6 months may be discussed
- Trastuzumab should usually not be given concomitantly with anthracycline-based ChT and it can be safely combined with non-anthracycline-based ChT (i.e. taxanes) and its concomitant use is more effective than sequential treatment [I
- Regular cardiac monitoring is mandatory before starting and during trastuzumab treatment
- Dual blockade with trastuzumab/pertuzumab can be considered in high-risk patients, defined as N-positive or ER-negative, for the duration of 1 year, starting before or after
- In cases of residual invasive disease after completion of neoadjuvant ChT combined with anti-HER2 therapy, adjuvant trastuzumab should be replaced by adjuvant T-DM1, once approved and where available
- Extended anti-HER2 therapy with neratinib may be considered in selected high-risk patients, not previously treated with dual blockade, and with appropriate diarrhoea prophylaxis and management

Anti Her2 Neu therapy in metastatic carcinoma breast

First line	• Trastuzumab + Pertuzumab + Taxanes (vinorelbine may be considered instead of taxanes) • Trastuzumab-emtansine (T-DM1) may be considered if patient is not suitable for the above or in case of a fast progression on/ after adjuvant Trastuzumab
Second line	• Trastuzumab-emtansine (T-DM1) • Trastuzumab + pertuzumab + cytotoxic chemotherapy (taxanes, vinorelbine, or capecitabine) may be considered if not exposed to pertuzumab previously
Third line	• Regimens currently recommended for first or second line should be considered for the later lines, if not used previously • Trastuzumab or lapatinib + cytotoxic chemotherapy (including vinorelbine, capecitabine, gemcitabine, eribulin, and others, if not used previously) • Trastuzumab + lapatinib if not suitable for cytotoxic chemotherapy

KEY TRIALS SUPPORTING CURRENT CLINICAL PRACTICE



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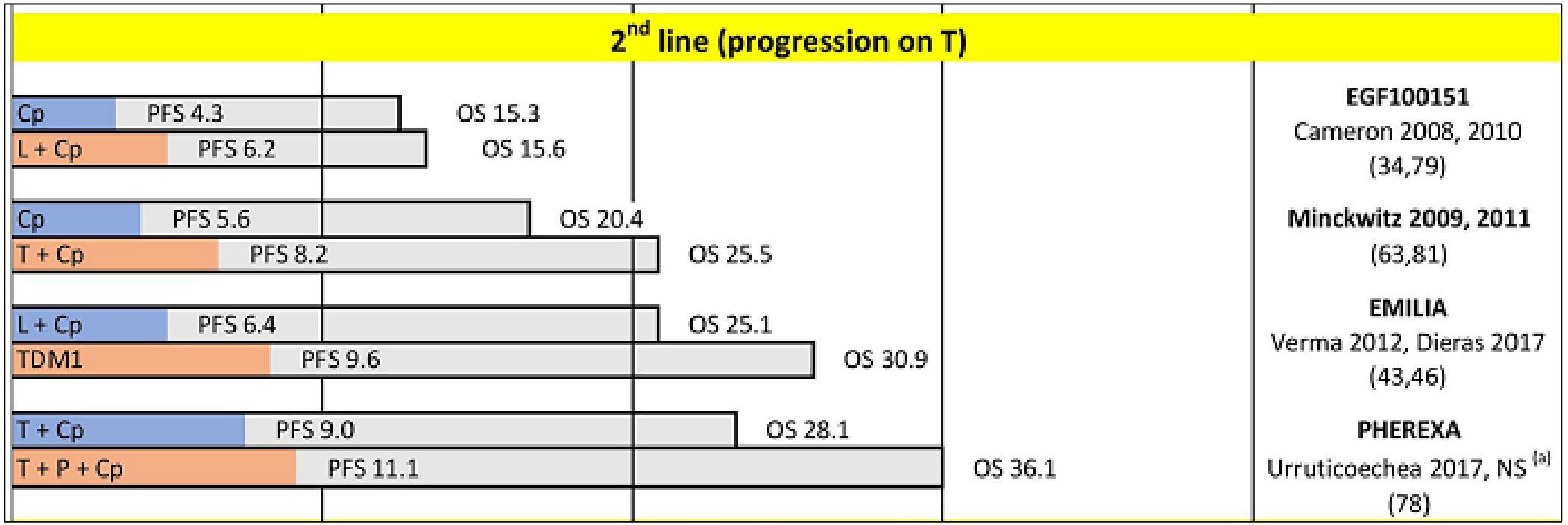
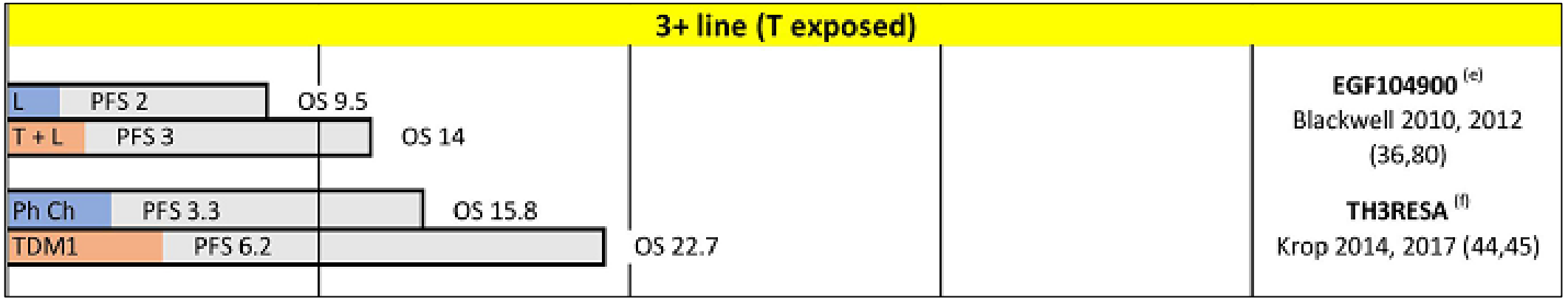


KEY TRIALS SUPPORTING CURRENT CLINICAL PRACTICE



Central Nervous System Metastases in HER 2-Positive Breast Cancer

Trials	Treatment arms	Treatment-specific criteria	Results
HER2-positive mBC without CNS metastasis at baseline			
CEREBEL[37]	Capecitabine + lapatinib (n=271) versus capecitabine + trastuzumab (n=269)	HER2-positive mBC without CNS metastasis at baseline	Capecitabine + lapatinib versus capecitabine + trastuzumab Incidence of CNS metastasis as first site of relapse: 3% versus 5% (HR: 0.65; P=0.36) Median PFS: 6.6 months versus 8.1 months; (HR: 1.30; P=0.021) Median OS: 22.7 months versus 27.3 months; (HR: 1.34; P=0.095)
CLEOPATRA@[38]	Trastuzumab + docetaxel + pertuzumab (n=55) versus trastuzumab + docetaxel + placebo (n=51)	Patients without CNS metastasis at baseline	Pertuzumab arm versus placebo arm Median TTP in CNS: 15 months versus 11.9 months (HR: 0.59; P=0.0049) Median OS in patients with CNS progression 34.4 months versus 26.3 months (HR: 0.66; P=0.1139)
HER2-positive mBC with CNS metastasis at baseline			
LANDSCAPE[39]	Lapatinib + capecitabine (n=45)	HER2-positive mBC: At least one measurable CNS lesion of ≥10 mm in diameter on MRI	Objective CNS response§: 65.9%
EMILIA*[40]	T-DM1 (N=45) versus lapatinib + capecitabine (n=50)	HER2-positive mBC patients who had stable CNS disease at baseline#	T-DM1 versus lapatinib+capecitabine Median PFS: 5.9 months versus 5.7 months (HR: 1; P=1.000) Median OS: 26.8 m vs. 12.9 m (HR: 0.38; P=0.0081)
LUX breast-3[41]	Vinorelbine + afatinib (n=38) versus Afatinib (n=40) versus investigator's choice	HER2-positive breast cancer with documented CNS recurrence/ progression (on imaging) during or after trastuzumab and/or lapatinib-based therapy	Patient benefit at 12 weeks (absence of CNS or extra-CNS disease progression, no tumor-related worsening of neurological signs or symptoms, and no increase in corticosteroid dose) Vinorelbine + afatinib, 34·2% Afatinib, 30·0% Investigator's choice: 41·9%
KAMILLA[42]	T-DM1 (n=399)	Subgroup of HER2-positive breast cancer received prior HER2-targeted therapy and chemotherapy with CNS metastasis at baseline	Partial response: 44% Clinical benefit rate: 59% Median PFS: 6.1 months

Initial locoregional treatment of CNS metastasis, followed by T-DM1 as a preferred option in this scenario, although trastuzumab- or lapatinib-based combination therapy could also be considered.

Other targeted therapy strategies

- Hormone receptor positive cases
- Adjuncts to hormone therapy
- Triple negative breast cancer

Subtyping of Triple-Negative Breast Cancer: Implications for Therapy

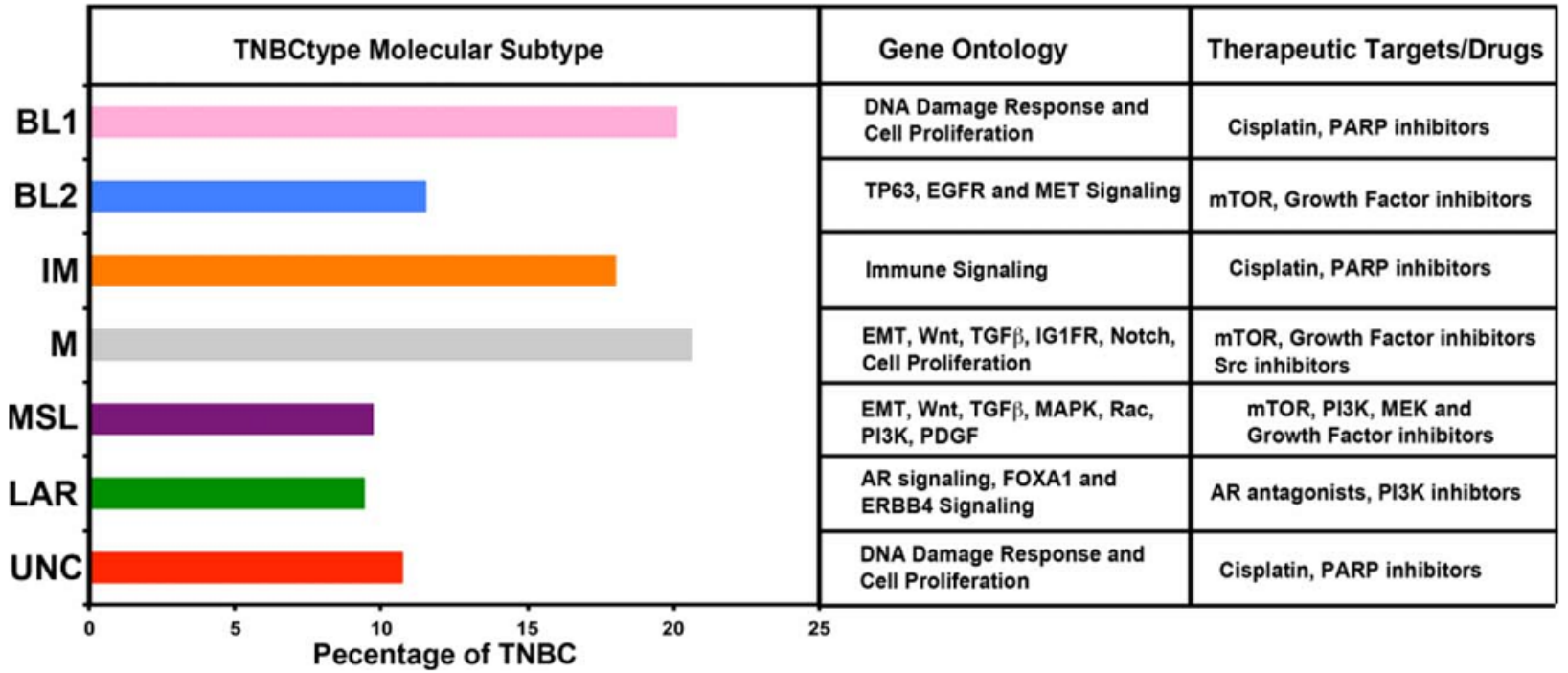


Figure 1. The distribution of triple-negative breast cancer (TNBC) subtypes from The Cancer Genome Atlas is illustrated with enriched gene ontology and potential therapeutic targets. Bar graphs display the subtype percentage relative to TNBC. BL1 indicates basal-like subtype 1; BL2, basal-like subtype 2; IM, immunomodulatory subtype; M, mesenchymal subtype; MSL, mesenchymal stem cell-like subtype; LAR, luminal subtype expressing androgen receptor; PARP, poly-AD-ribose polymerase; TP63, tumor protein 63; EGFR, epidermal growth factor receptor; MET, MET proto-oncogene receptor tyrosine kinase; mTOR, mammalian target of rapamycin; EMT, epithelial-mesenchymal transition; Wnt, Wnt proto-oncogene; TFGβ, transforming growth factor β; IG1FR, insulin-like growth factor 1 receptor; MAPK, mitogen-activated protein kinase; Rac, ras-related family of proteins; PI3K, phosphatidylinositol 3-kinase; PDGF, platelet-derived growth factor; MEK, mitogen-activated protein kinase kinase; FOXA1, forkhead box protein A1; ERBB4, v-erb-a erythroblastic viral oncogene homolog 4; AR, androgen receptor; UNC, unclassified.

Poly (adenosine diphosphate-ribose) polymerase inhibitors

- Play a key role in these pathways by mediating the repair of single-strand DNA breaks via base-excision repair
- Loss of PARP activity results in the accumulation of single-strand breaks, which are normally repaired by double-strand homologous recombination pathways that include the important tumor-suppressor proteins BRCA1 and BRCA2

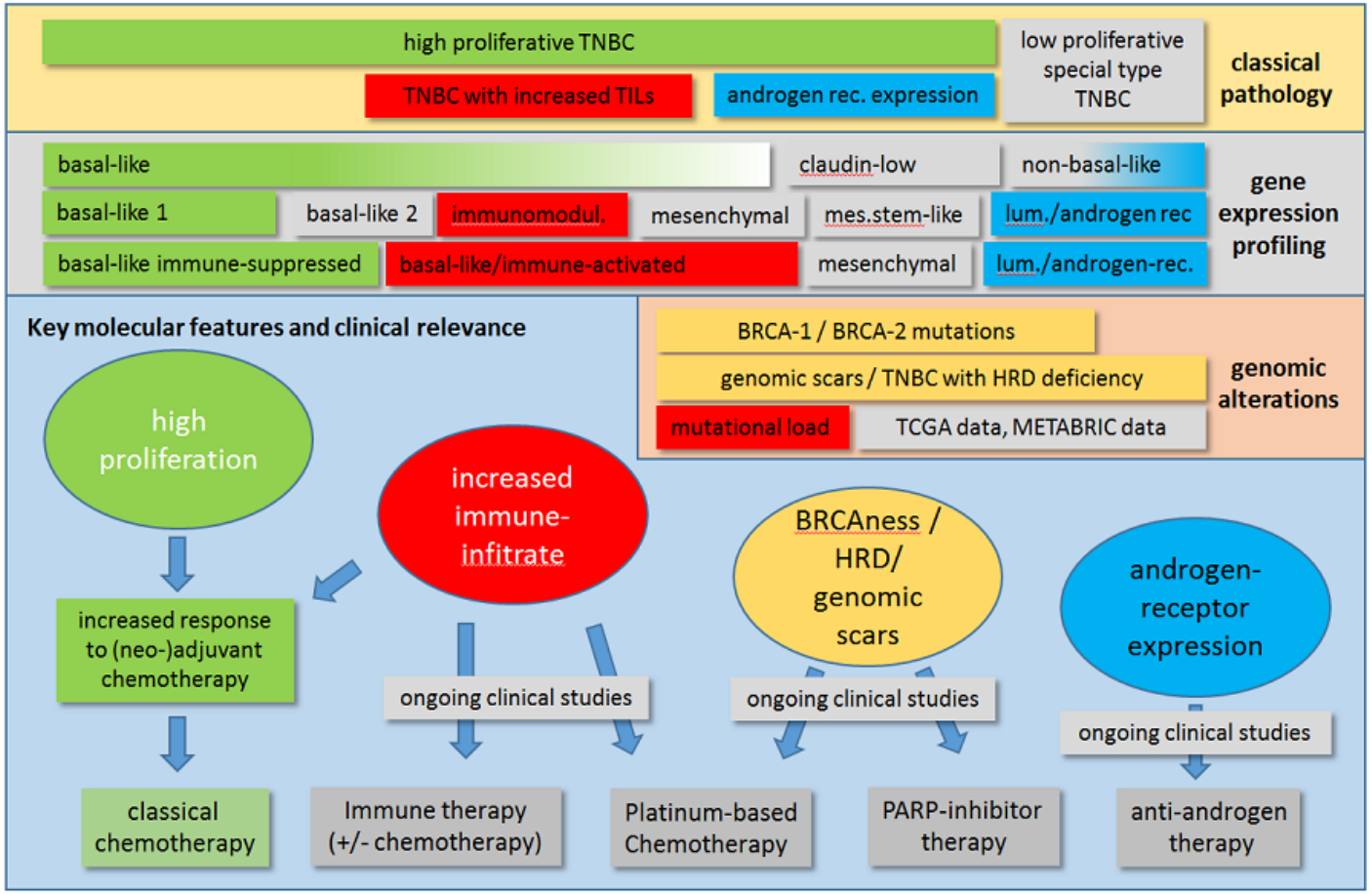
Trial	Line of treatment	Schedule	Patients, n	Median age, years	ORR (%)	Median PFS (months), HR	Median OS (months), HR
PARP inhibitors							
O'Shaughnessy et al,[76]	First-line +	Gem, carbo, ini	61	56	52 (*P*=0.02)	5.9; 0.59 (*P*=0.01)	12.3; 0.57 (*P*=0.01)
Phase II	(0–3 prior regimens)	Gem, carbo	62	53	32	3.6	7.7
O'Shaughnessy et al,[77]	First-line +	Gem, carbo, ini	261	53	34	5.1; 0.79 (*P*=0.027)	11.8; 0.88 (*P*=0.28)
Phase III	(0–2 prior regimens)	Gem, carbo	258	54	30	4.1	11.1

Anti VEGF studies

Trial	Line of treatment	Schedule	Patients, n	Median age, years	ORR (%)	Median PFS (months), HR	Median OS (months), HR
Anti-VEGF/VEGFR monoclonal antibody							
Miller et al,[99]	First-line	Pacli + beva	NR	NR	NR	10.6; 0.49	NR
E2100 – Phase III, subgroup		Pacli				5.3	
Miles et al,[100]	First-line	Doce, beva (15 mg/kg)	53	NR	NR	8.2; 0.53	NR
AVADO – Phase III		Doce, beva (7.5 mg/kg)	52			6.2; 0.69	
		Doce, placebo	96			5.4	
Robert et al,[101]	(Tax/Anthra) first-line	Tax- or anthra-based + beva	46	NR	NR	6.5; 0.78	NR
RIBBON-1 – Phase III		Tax- or anthra-based + placebo	87			6.2	
	(Cape) first-line	Cape-based + beva	50	NR	NR	6.1; 0.72	NR
		Cape-based + placebo				4.2	
Brufsky et al,[102] RIBBON-2,	Second-line	Cape-, tax-, gem-, vino-based + beva	112	55	41 (0.0078)	6.0; 0.494 (*P*=0.0006)	17.9 (*P*=0.0534)
Phase III – subgroup		Cape-, tax-, gem-, vino-based + placebo	47	49	18	27	12.6
Cameron et al,[106]	Adjuvant	Anthra – tax-based + beva	1,301	NR			
Phase III – BEATRICE		Anthra – tax-based	1,290				

Trial	Line of treatment	Schedule	Patients, n	Median age, years	ORR (%)	Median PFS (months), HR	Median OS (months), HR
Anti-VEGFR tyrosine kinase inhibitors							
Curigliano et al,[109]	Second-line +	Sun 37.5 mg, continuous daily dosing	113	52	9	2.0	9.4
Phase II	(≥1 prior regimen)	Standard of care	104	52	12 (*P*=0.814)	2.7; 1.16 (*P*=0.847)	10.5; 1.22 (*P*=0.892)
Bergh et al,[110]	First-line	Doce, sun	58	NR	55 (*P*=0.001)	8.6; 0.92 (*P*=0.265)	24.8 (*P*=0.904)
Phase III		Doce	69		42	8.3	25.5
Baselga et al,[112]	First- or second-line	Cape, sora	20	NR	NR	4.3; 0.596 (0.3–1.1)	17.5; 0.98 (0.50–1.89)
SOLTI-0701,	(0–1 prior regimens)	Cape, placebo	33			2.5	16.1
Phase II – subgroup							
Gradishar et al,[114]	First-line	Pacli, sora	48	NR	NR	5.6; 0.856	NR
Phase II		Pacli	46			5.5	
Schwartzberg et al,[115]	First- or second-line	Sora, gem, or cape	23	NR	NR	3.1; 0.57	NR
Phase II – subgroup	(0–1 prior regimen)	Placebo, gem, or cape	27			2.6	

Approach to targeted therapy in TNBC



Important studies: chemotherapy platinum

TNT trial Randomized phase 3 trial NCT00532727	Recurrent locally advanced or metastatic TNBC, n=376 Carboplatin vs. docetaxel	No difference in response rates to therapy arms in the complete cohort; Increased response rate to carboplatin (68% vs. 33% with docetaxel) in the subgroup of BRCA1/2 mutated tumors: HRD-assay: increased score linked to increased response in both therapy arms; PAM50 assay, non-basal subtype: higher response to docetaxel compared to carboplatin

Important studies: Immunotherapy

Immune checkpoint inhibitors		
KEYNOTE-012 nonrandomized, multicohort, phase Ib study NCT01848834	Metastatic PD-L1-positive TNBC (all therapy lines) the PD-L1 inhibitor pembrolizumab given intravenously at 10 mg/kg every 2 weeks 32 patients with TNBC enrolled, 28 pts. wiith evaluable response	Efficacy: overall response rate: 18.5% median time to response: 17.9 weeks Safety: 15.6% incidence of grade 3 to 5 treatment-related AEs
NCT01375842 multicenter Phase Ia study	pts with pretreated metatatic PD-L1 positive TNBC enrolled (n=27) received the PD-L1 inhibitor atezolizumab (MPDL3280A) at 15 mg/kg, 20 mg/kg or 1200 mg flat dose IV q3w.	Efficacy: unconfirmed RECIST ORR 24%; Safety: Grade 3-5 related AE in 11% of pts
GP28328 Phase Ib multicenter NCT01633970	metastatic TNBC treated with ≤ 3 prior lines of therapy (n=32) atezolizumab (MPDL3280A; 800 mg q2w (d1,15)) in combination with nab-paclitaxel (125 mg/m2 q1w (d1,8,15) q3 of 4 weeks)	Data from ongoing study presented at SABCS 2015: Efficacy: overall response rates were 1st line: 67% 2nd line 25% 3rd line 29% all patients: 42% Safety: 56% Grade 3-4 AEs

Important studies: AR positive

Androgen receptor inhibitors		
UCBG 12-1 Single arm open label multicenter Phase II NCT01842321	metastatic or locally advanced, triple negative and AR-positive BC (n=30) abiraterone acetate (AA, 1000 mg) once a day + prednisone (5 mg) twice a day	Clinical benefit rate (CBR) 20.0% [95%CI 7.7%-38.6%] ORR 6.7% (0.8%-22.1%) median PFS 2.8 months (1.7%-5.4%). Safety: 14.7% grade 3 AEs
MDV3100-11 phase 2 study NCT01889238	evaluating single agent enzalutamide in advanced AR+ TNBC (n=118 treaten, n=75 evaluated for response) evaluation of AR signature as possible biomarker	Clinical benefit rate (16 wks): 35% (all pts) 39% (AR signature +) Safety: 5% AE >= grade 3

Important studies: PARP inhibitor

PARP inhibitor therapy		
NCT00494234 Phase 2 multicenter trial	Recurrent advanced breast cancer with BRCA1/2 mutations Subcohort 1 (n=27): olaparib (AZD2281) 400mg twice daily, 50% TNBC Subcohort 2 (n=27): olaparib 100mg twice daily, 64% TNBC	Objective response rates: 41% (subcohort 1) 22% (subcohort 2) Safety: grade 3-4 SAEs in 24% of pts.
I-SPY 2 multicenter neoadjuvant, adaptively randomized phase 2 study NCT01042379	Stage 2-3 breast cancer, paclitaxel, doxorubicin, cyclophosphamide with or without veliparib (ABT888)-carboplatin (n=116, all TNBC)	Estimated pCR rates (Bayesian predicted probability) higher for veliparib–carboplatin Tx (51% vs. 26%); Probability of success in phase 3 trial: 88% in TNBC ; Higher rate of toxic effects in veliparib-carboplatin group
Brightness Phase 3 randomized multicenter study NCT02032277	Planned N=624, T2-T4 TNBC Standard NACT vs. NACT+carboplatin vs. NACT+carboplatin+veliparib	Study under follow-up
OlympiA Phase 3 randomized multicenter trial NCT02032823	adjuvant olaparib in high –risk TNBC and ER+/HER2-ve BC with germline BRCA1/2 mutation; planned n=1500	Recruitment ongoing