Temi aperti sui trattamenti adiuvanti: Malattia Her 2+

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Anti HER2 Adjuvant Therapy Challenges with Evidence

- De-escalation of anti HER2 therapy
  - non inferiority RCTs

- Combination vs Sequence
  - Trastuzumab + Lapatinib
  - Trastuzumab + Pertuzumab
  - Trastuzumab → Neratinib

- Biosimilars
  - Equivalence trials

Courtesy of PF Conte

9 weeks vs 1 year adjuvant trastuzumab in combination with chemotherapy: results of the phase III multicentric Italian Short-HER study

PF Conte, G. Bisagni, A. Frassoldati, A. Brandes, E. Anselmi, F. Giotta, M. Aieta, V. Gebbia, A. Musolino, O. Garrone, C. Taverniti, G. Cavazzini, A. Turletti, D. Rubino, A. Ferro, E. Picardo, F. Piacentini, S. Balduzzi, R. D'Amico, V. Guarneri

Medical Oncology 2, Istituto Oncologico Veneto IRCCS
DiSCOG-University of Padova, Italy
On behalf of the Short-HER Study Team

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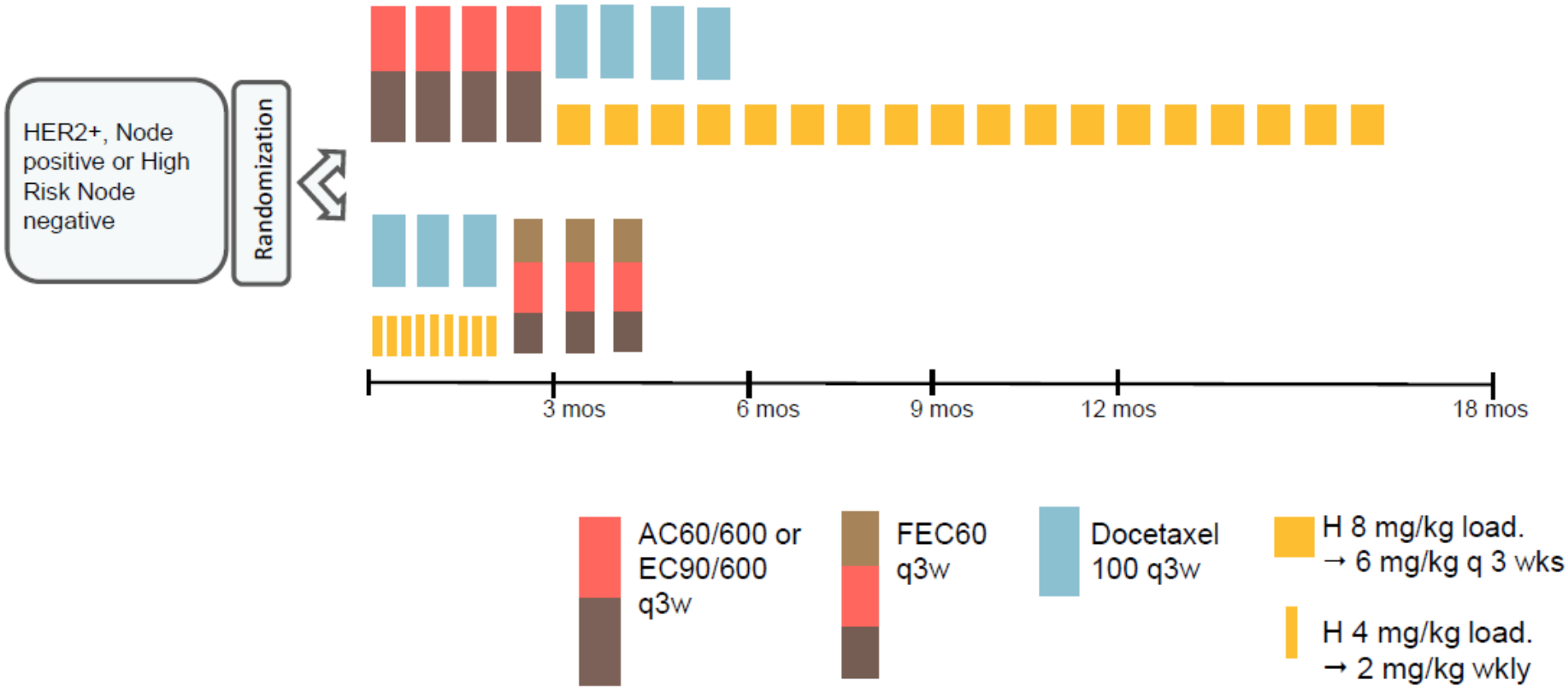
Short-HER: Study Design

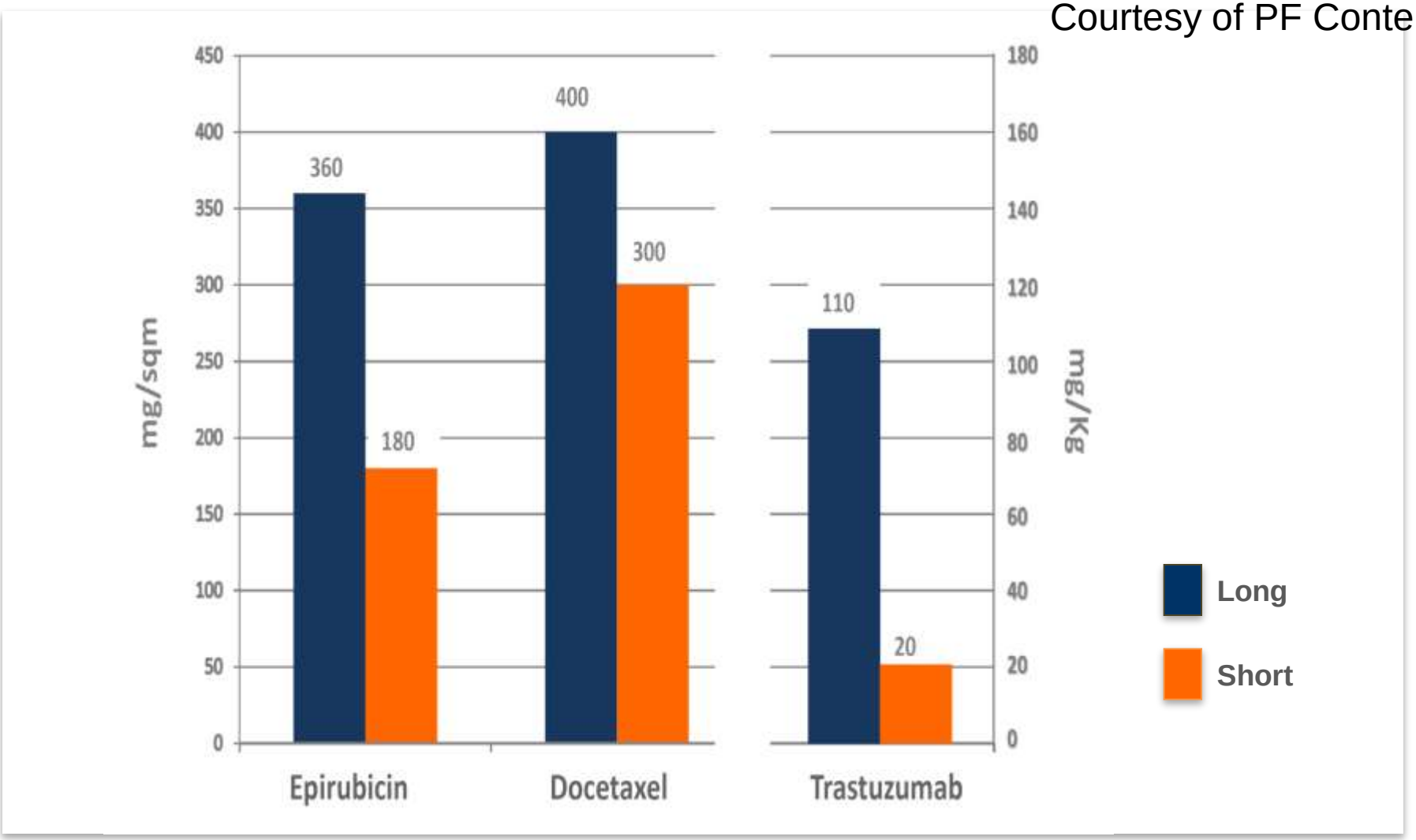
Courtesy of PF Conte



Stratification factors: HR status, Nodal status

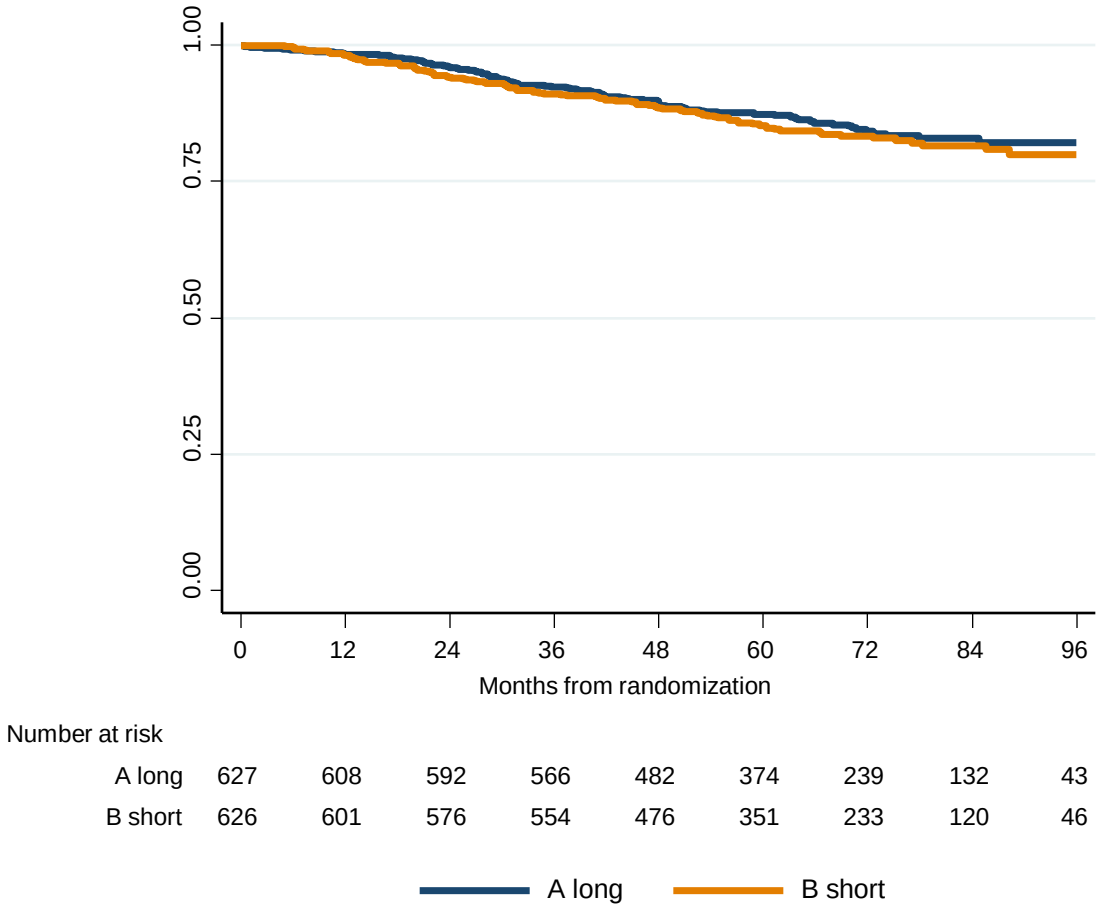
Total planned amount of chemotherapy and trastuzumab in the two treatment arms

Courtesy of PF Conte



Presented by: PierFranco Conte, ASCO 2017

Short-HER: Disease Free Survival



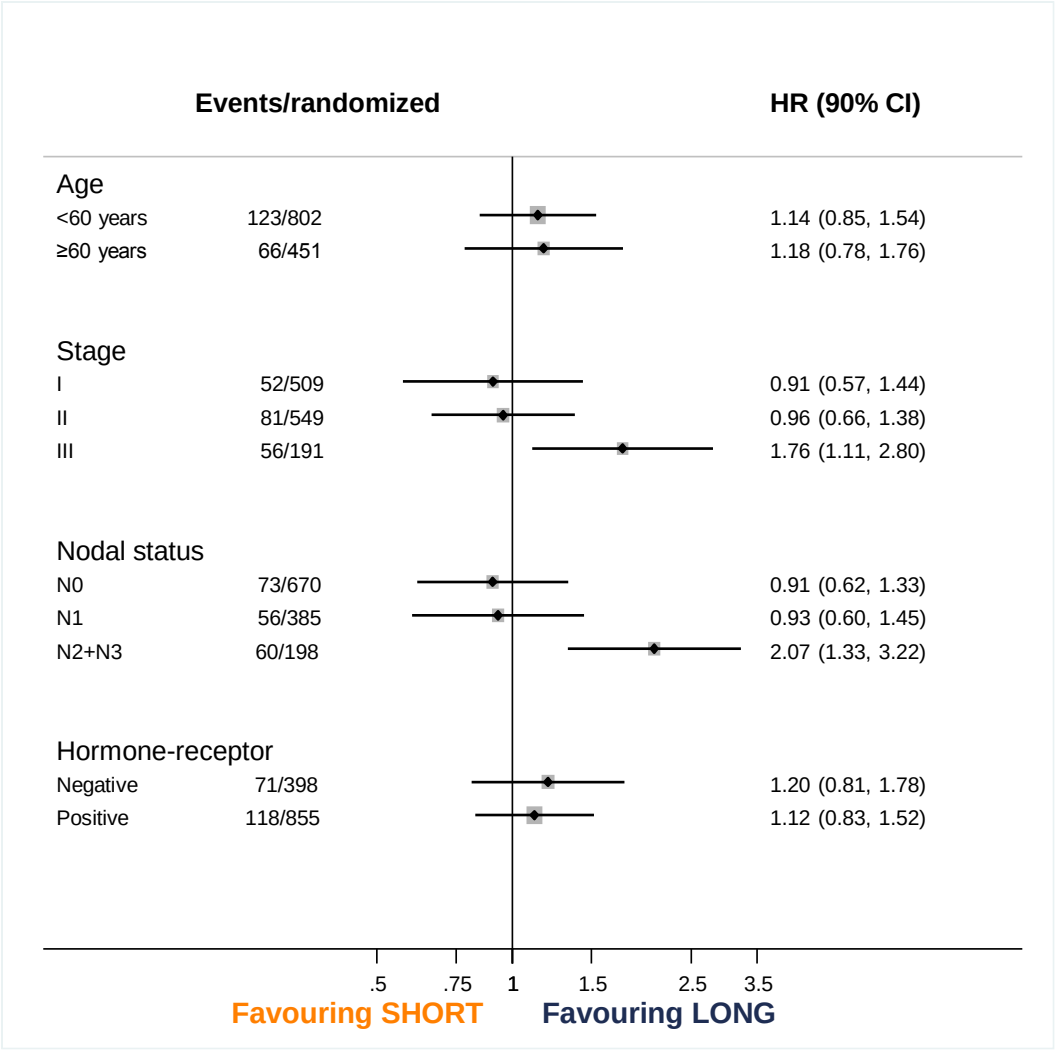
Courtesy of PF Conte

	Long (N=627)	Short (N=626)
DFS events #	89	100
5y DFS %	87.5	85.4
HR (90% CI)	1.15 (0.91-1.46)	

Presented by: PierFranco Conte, ASCO 2017

DFS – Subgroup analysis

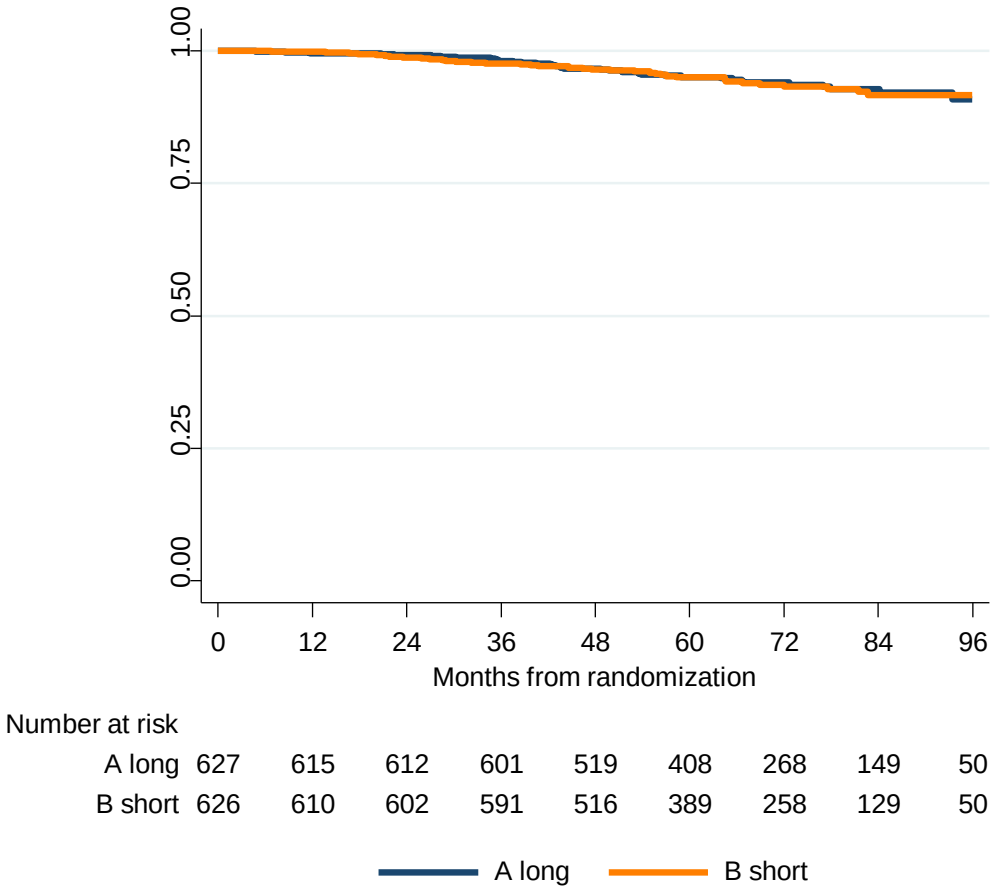
Courtesy of PF Conte



	Ratio of HRs (90%CI)	p-value
Stage III vs I+II	**2.30** (1.35, 3.94)	**< 0.001**
Nodal status N2+N3 vs N0+N1	**2.25** (1.33, 3.83)	**< 0.001**

Short-HER: Overall Survival

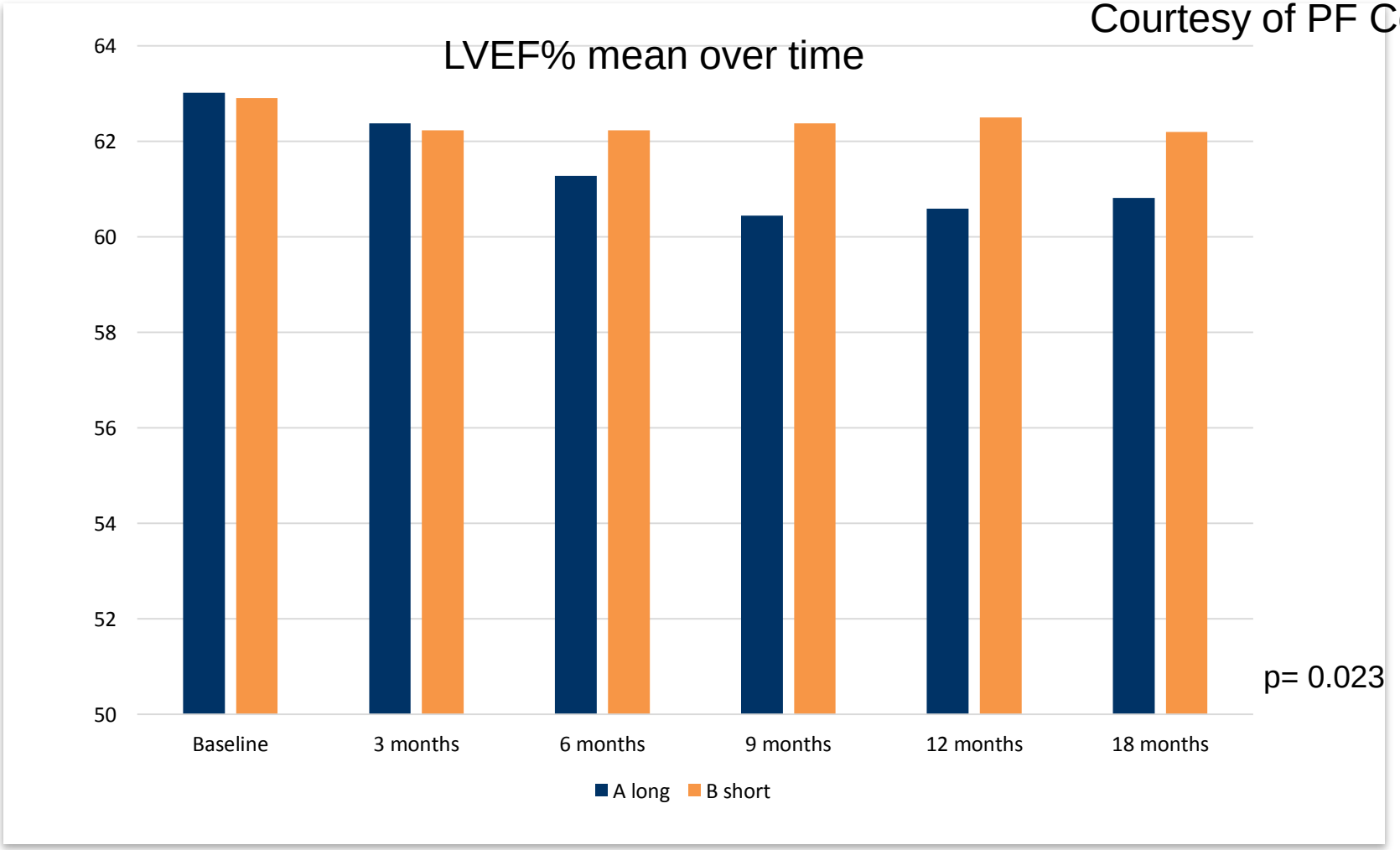
Courtesy of PF Conte



	Long (N=627)	Short (N=626)
OS events #	37	38
5y OS %	95.1	95.0
HR (90% CI)	1.06 (0.73-1.55)	

LVEF change from baseline

Courtesy of PF Conte



p= 0.023

Conclusions

Courtesy of PF Conte

- At a median FUp of 5.2 years:

  5y DFS Long Arm 87.5%, Short Arm 85.4%

  HR= 1.15 (90% CI 0.91-1.46)
- Non inferiority cannot be claimed on the basis of the frequentist approach
- According to the pre-planned Bayesian analysis, probability that the short treatment is not inferior is 0.78
- Significant lower cardiac toxicity for the short treatment (HR 0.32, 95% CI 0.21-0.50; $p < 0.0001$)

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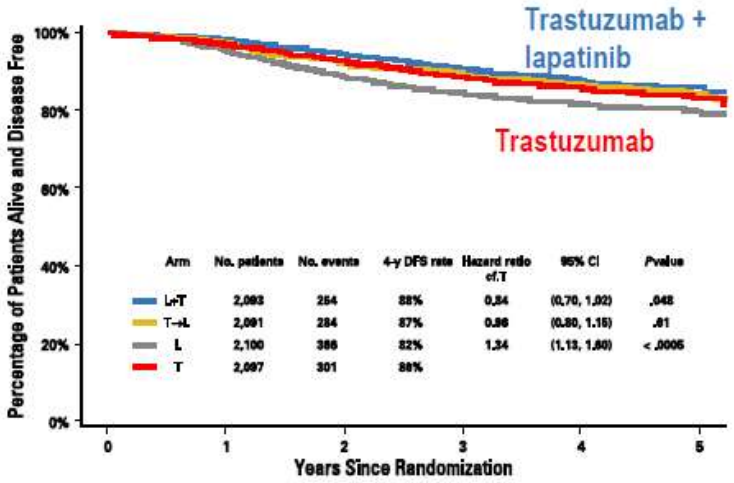
HER2 POSITIVE EARLY STAGE BREAST CANCER

- After adjuvant chemotherapy plus 1 year of trastuzumab, 15% to 20% of patients recur with invasive breast cancer at a median FU of 10 years

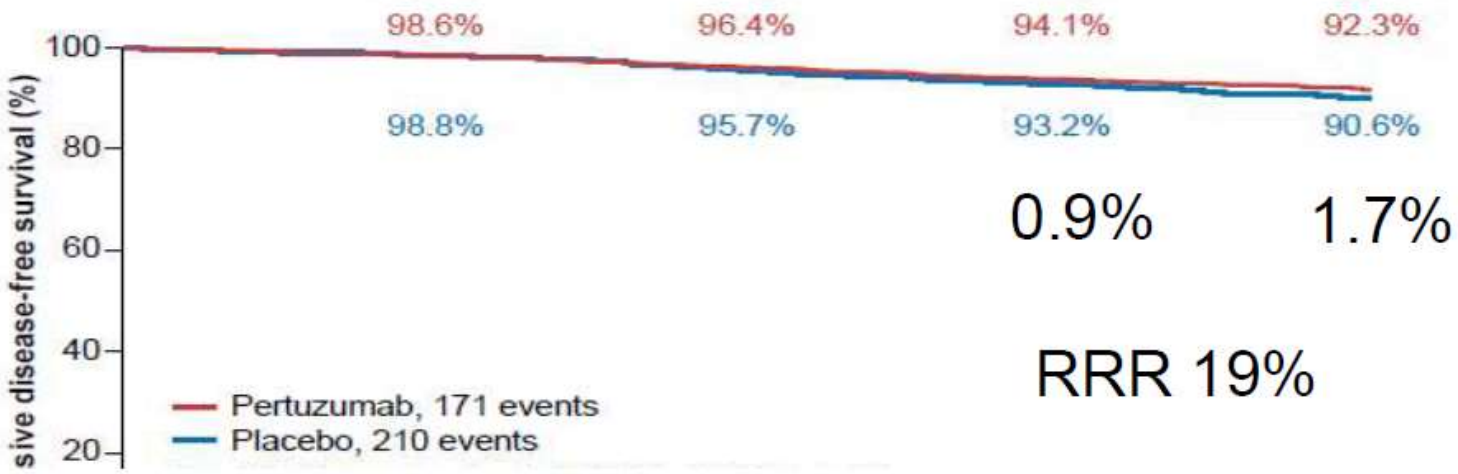
Regimen	5-year DFS rate, %			
	ITT	Node-negative	Node-positive	≥ 4 positive nodes
AC→TH	84	93	80	73
TCH	81	90	78	72

- Metastatic breast cancer remains incurable
- ALTTO: adding lapatinib to trastuzumab did not improve DFS
- In HER2 positive disease, biology differs based on expression of hormone receptors



Perez E, et al. *J Clin Oncol*. 2014; Goldhirsch A, et al. *Lancet*. 2013; Piccart-Gebhart M, et al. *J Clin Oncol*. 2016, Slamon et al, NEJM 2011

Aphinity – ITT – iDFS Analysis (md FU 3.8y)



0.9% 1.7%

RRR 19%

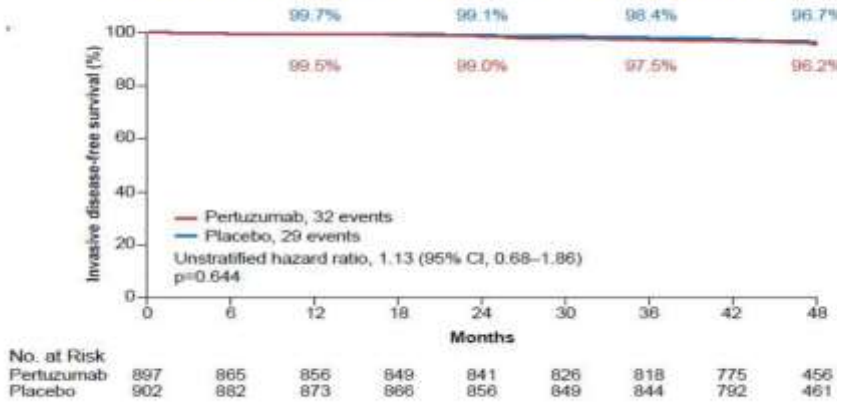
HR=0.81 (95% CI: 0.66-1.00)

p=0.045

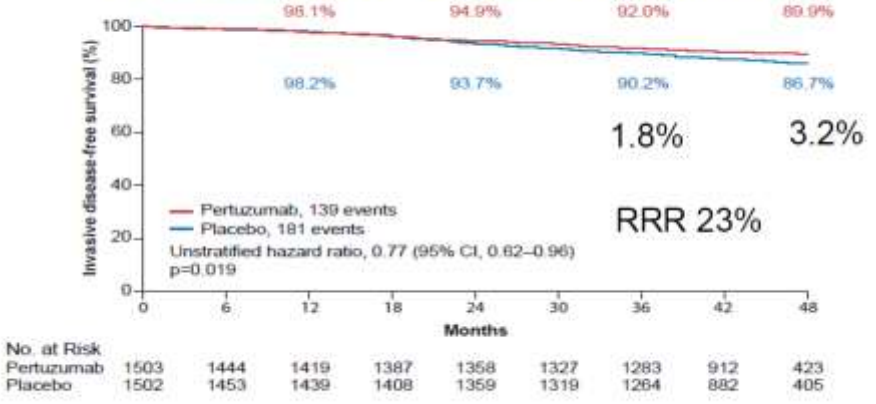
Criticism 1. "Aphinity is a positive trial (stat. significant) <u>BUT</u> the magnitude of the benefit is too small (not clinically significant)"

Pertuzumab by Nodal Status

Aphinity: Node-negative Subgroup

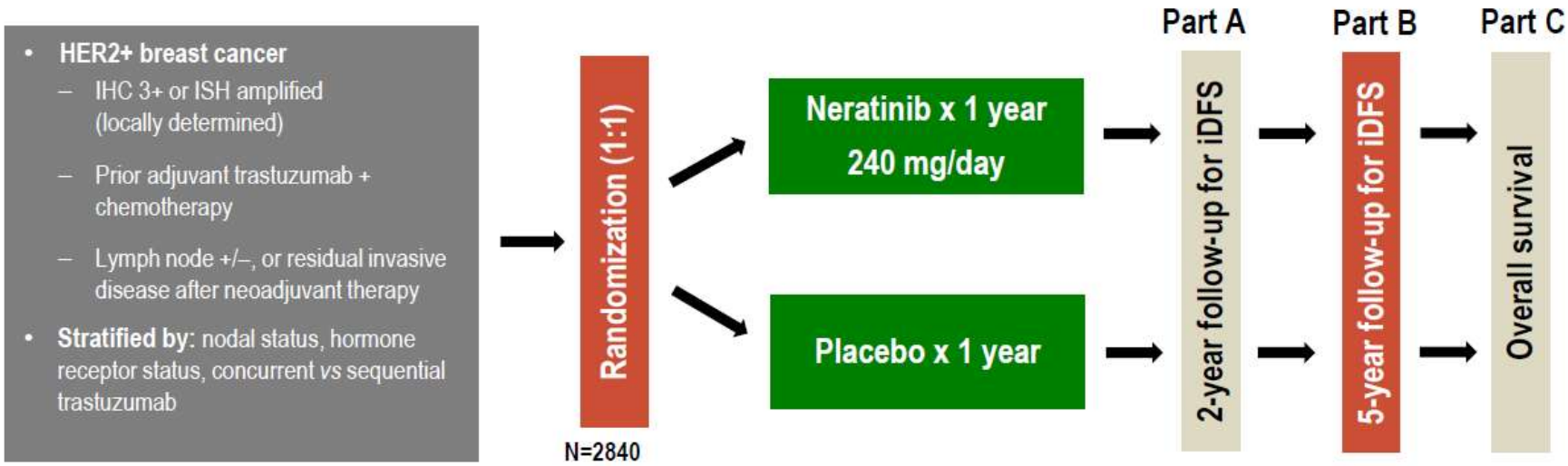


Aphinity: Node-positive Subgroup



Magnitude of benefit will be HIGH in “high-risk” patients

ExteNET: study design



Primary endpoint: invasive disease-free survival (iDFS)

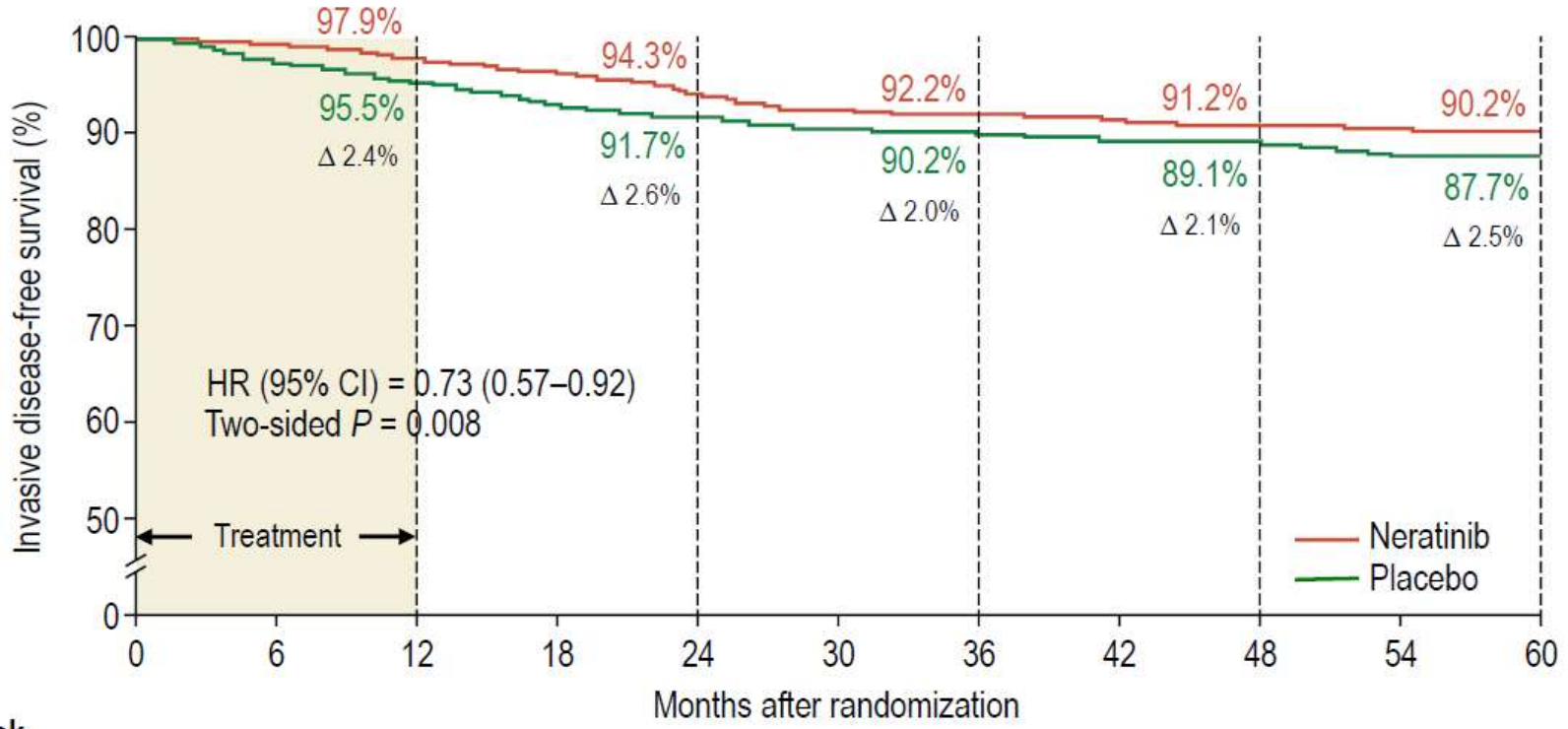
Secondary endpoints: DFS-DCIS, time to distant recurrence, distant DFS, CNS recurrences, OS, safety

Other analyses: biomarkers, health outcome assessments (FACT-B, EQ-5D)

Endocrine adjuvant therapy given to patients with HR-positive tumors according to local practice

MADRID 2017 ESMO congress

5-year analysis: iDFS



No. at risk

Neratinib	1420	1316	1272	1225	1106	978	965	949	938	920	885
Placebo	1420	1354	1298	1248	1142	1029	1011	991	978	958	927

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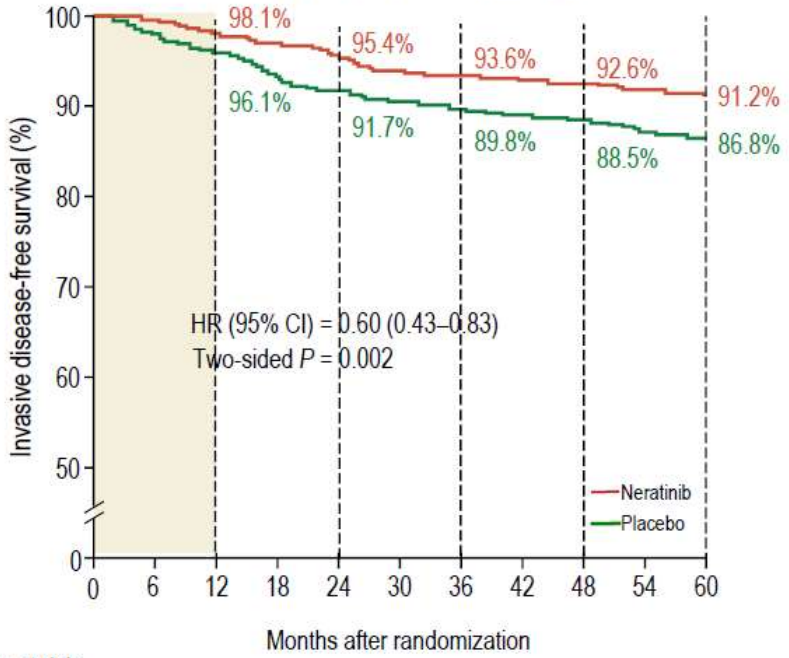
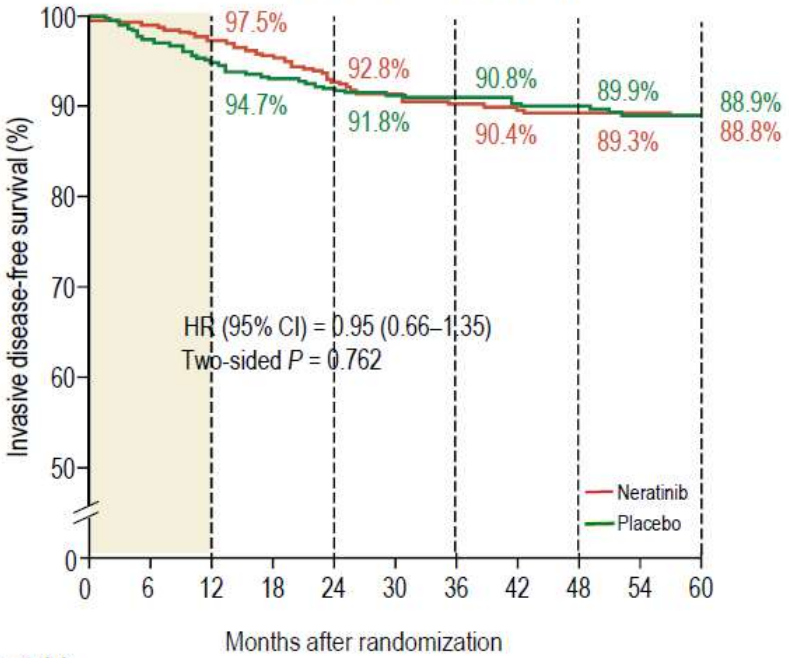
iDFS by hormone receptor status

HR-positive subgroup



No. at risk											
Neratinib	816	757	731	705	642	571	565	558	554	544	523
Placebo	815	779	750	719	647	581	567	556	551	542	525

HR-negative subgroup



No. at risk											
Neratinib	604	559	541	520	464	407	400	391	384	376	362
Placebo	605	575	548	529	495	448	444	435	427	416	402

Intention-to-treat population. Cut-off date: March 1, 2017

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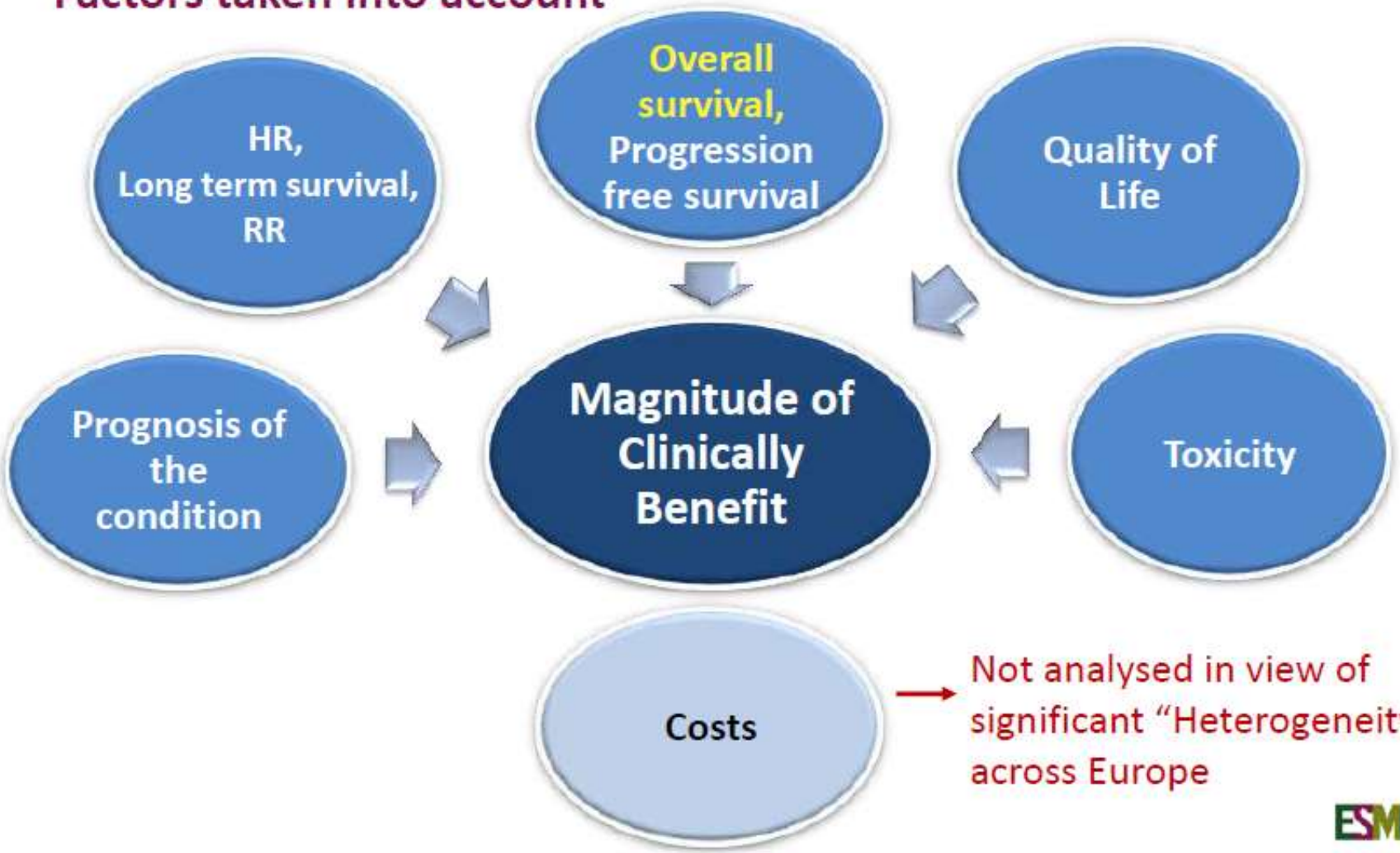
ExteNET: conclusions

- The 5-year analysis of the ExteNET trial confirms sustained benefit with extended adjuvant neratinib:
  - 2.5% absolute benefit in intent-to-treat population (HR=0.73; *P*=0.008)
  - 4.4% absolute benefit in HR-positive cohort (HR=0.60; *P*=0.002)
  - 3.2% absolute benefit in patients starting neratinib within 1 year of completing trastuzumab (HR=0.70; *P*=0.006)
- No evidence of long-term toxicity (i.e. no increased symptomatic cardiac toxicity or second primary malignancies) with neratinib versus placebo or late-term consequences from neratinib-associated diarrhea
- Overall survival data expected to mature in 2019

ESMO
GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE
European Society for Medical Oncology

ESMO Magnitude of Clinical Benefit Scale

Factors taken into account



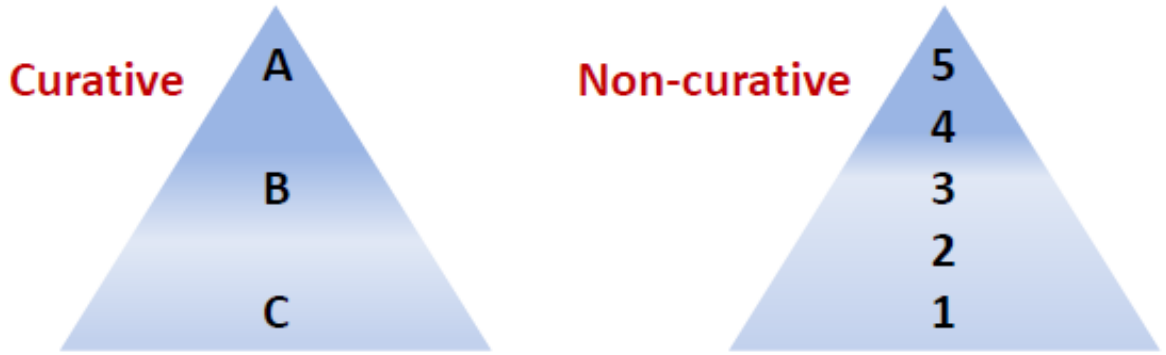
→ Not analysed in view of significant "Heterogeneity" across Europe

ESMO

ESMO-MCBS

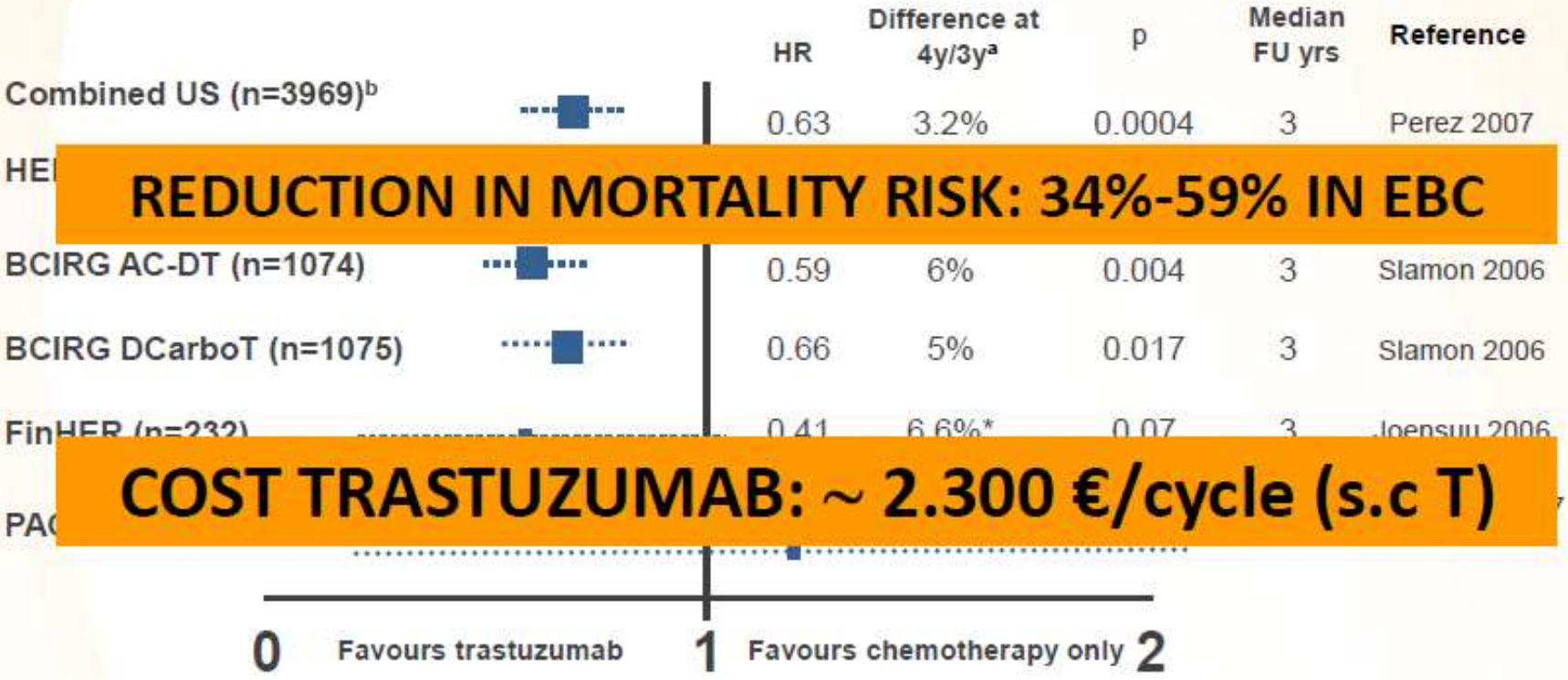
Scoring

When a new anticancer medicine is EMA approved, its benefit is «scaled» by the Guidelines Committee and reviewed by the ESMO-MCBS Working Group



1. All new anticancer EMA approved medicines will be highlighted in the ESMO Guidelines where relevant or as an eUpdate
2. **Medicines which obtain the highest scores (A&B or 5&4), represent the highest priority for rapid endorsement by national bodies across Europe**

Adjuvant chemotherapy ± trastuzumab trials: overall survival



REDUCTION IN MORTALITY RISK: 34%-59% IN EBC

COST TRASTUZUMAB: ~ 2.300 €/cycle (s.c T)

*Benefit at 3y

[a]Absolute difference in percentage of patients with OS at 4 or 3 years

[b]Combined US: Joint analysis of NSABP B-31 and NCCTG N9831

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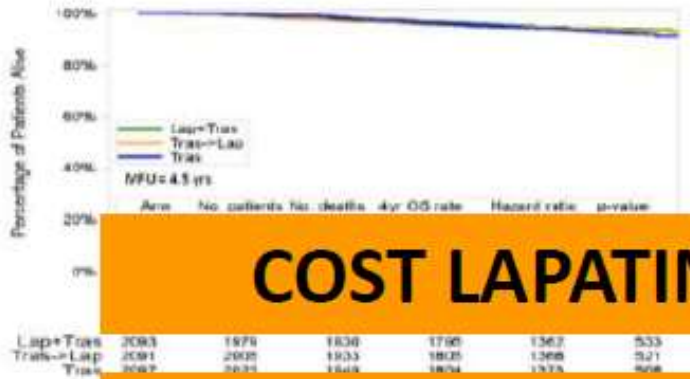
MCBS: A

oncology academy

EFFICACY RESULTS: OS

- N = 6281 → excluding patients in the lapatinib-alone arm, stopped for futility



- No significa

Lap: lapatinib; Tras: trastuzumab

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ALTTO trial

COST LAPATINIB: ~ 3.500 €/cycle

DUAL BLOCKADE COST: ~ 5.800 €/cycle

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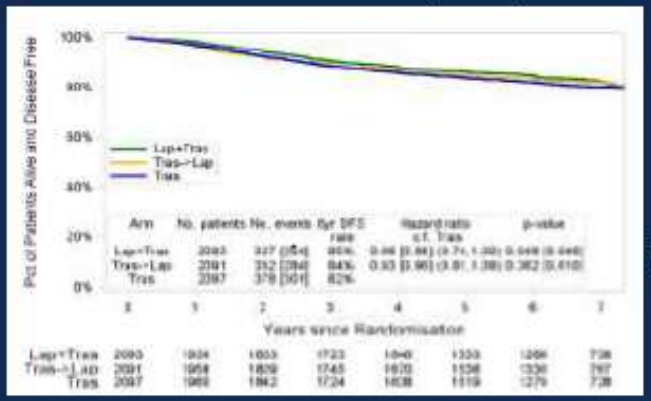
European Society for Medical Oncology

MCBS:
No Evaluable Benefit

DISEASE-FREE SURVIVAL (DFS) ANALYSIS

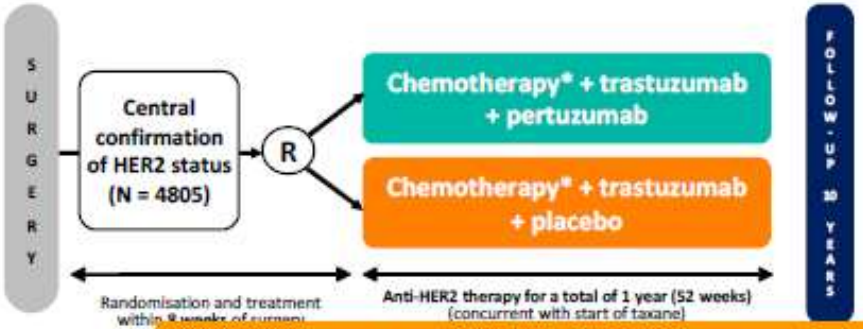


*Simulated data in all KM curves represent results of the Primary Analysis – ASCO 2014

ALTTO Investigators

ASCO ANNUAL MEETING 17 #ASCO17 Presented by: A. Moreno-Aspitia et al. ASCO 2017

APHINITY: Trial Design



APHINITY trial

COST PERTUZUMAB: ~ 4.100 €/cycle

G. von Minckwitz et al, ASCO 2017

ASCO ANNUAL MEETING '17

DUAL BLOCKADE COST: ~ 6.400 €/cycle

APHINITY: Intent-to-Treat Primary Endpoint Analysis
Invasive Disease-free Survival

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Provisional
MCBS: B

ASCO ANNUAL MEETING '17 #ASCO17
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G. von Minckwitz et al, ASCO 2017, NEJM 2017

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Anti HER2 Adjuvant Therapy Challenges with Evidence

- De-escalation of anti HER2 therapy
  - non inferiority RCTs

- Combination and Sequence
  - Trastuzumab + Lapatinib
  - Trastuzumab + Pertuzumab
  - Trastuzumab → Neratinib

- Biosimilars
  - Equivalence trials

Double-blind RCTs comparing biosimilars to trastuzumab as neoadjuvant (and adjuvant) therapy for HER2+ breast cancer

Presenter	N	Neoadjuvant cycles (chemo)	Biosimilar	Endpoints
Von Minckwitz	725	4 (paclitaxel) after 4 x AC	ABP 980	pCR
Esteva	549	8 (4Doc→4FEC)	CT-P6	pCR
Pivot	875	8 (4Doc→4FEC)	SB3	pCR & EFS (12mos)
Lammers	226	6 (Doc/carbo)	PF-05280014	pK (cycle 5 trough) & pCR

Each RCT found similar (i) rate of pCR & (ii) safety of the biosimilar and trastuzumab

Presenter	N	Biosimilar	pCR (%)	
			Biosimilar	Trastuzumab
Von Minckwitz	725	ABP 980	48%	41%
Esteva	549	CT-P6	49%	52%
Pivot	875	SB3	52%	42%
Lammers	226	PF-05280014	51%	47%

No significant difference between arms in any endpoint

EMA Guideline: Requirements and Study Design for Biosimilar and Innovator Clinical Trials

	Biosimilar	Innovator
Patient Population	Sensitive and homogeneous patient population	Any
Clinical Design	Comparative vs innovator (equivalence studies)	Superiority vs standard of care
Study Endpoints	Sensitive ORR, pCR	Efficacy data (OS, PFS)
Safety	Similar safety profile to innovator	Acceptable risk/benefit profile vs standard of care
Immunogenicity	Similar immunogenicity profile to innovator	Acceptable risk/benefit profile vs standard of care
Extrapolation	Possible	Not allowed

EMA GUIDELINE
Extrapolations of Indication

"Extrapolation of clinical efficacy and safety data to other indications of the reference mAb, not specifically studied during the clinical development of the biosimilar mAb, is possible based on the overall evidence of comparability provided from the comparability exercise and with adequate justification."

Why do we need biosimilars?

Importance Treatment with the anti-ERBB2 humanized monoclonal antibody trastuzumab and chemotherapy significantly improves outcome in patients with ERBB2 (HER2)–positive metastatic breast cancer; a clinically effective biosimilar may help increase access to this therapy.

Hope S. Rugo, MD[1]; Abhijit Barve, MD, PhD, MBA[2,3]; Cornelius F. Waller, MD[4]; et al *JAMA*. 2017;317(1):37-47.

Physicians worldwide often encounter barriers to prescribing trastuzumab, leading to suboptimal treatment of patients with HER2+ breast cancer.[5,6]

- The availability of biosimilars may address patient and physician needs by providing additional safe and efficacious treatment options that improve access to biologic therapies, such as trastuzumab.

Lammers' poster

ESMO European Consortium Study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in Europe *Annals of Oncology* 27: 1423–1443, 2016

N. Cherny[1*], R. Sullivan[2], J. Torode[3], M. Saar[4] & A. Eniu[5]

Limited access to trastuzumab – even in Europe

Country	Formulary and cost	Actual Availability	Country	Formulary and cost	Actual Availability
Cyprus	Free	Usually	Czech Rep	Free	Usually
Greece	Free	Usually	Georgia	Full cost	Usually
Sweden	Free	Usually	Kyrgyzstan	Full cost	50%
Switzerland	<25% cost	Always	Romania	Free	Usually
			Russia	50-100%	Occasionally
Albania	Free	50%	Turkmenistan	N/A	Occasionally
Armenia	Full cost	50%	Uzbekistan	Full cost	50%

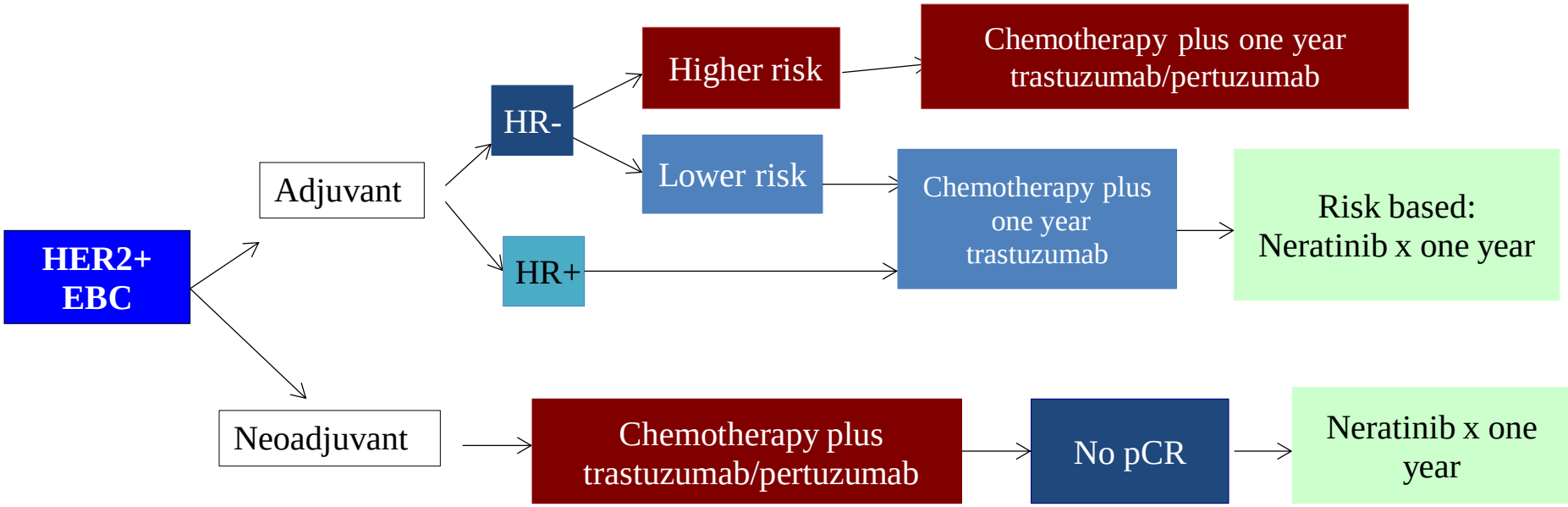
Will more patients will access treatment?

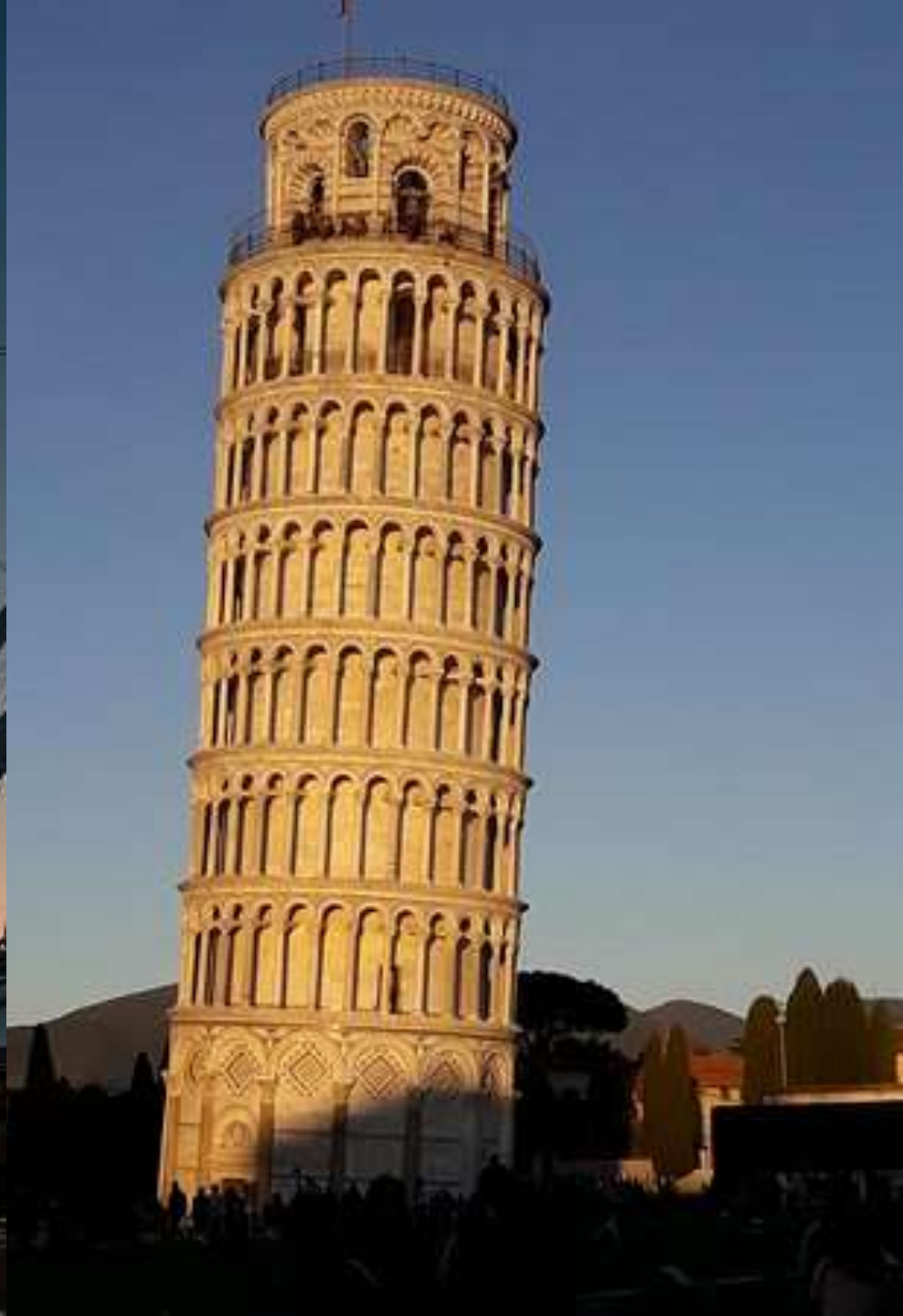
Probably yes – savings may help pay for other new drugs

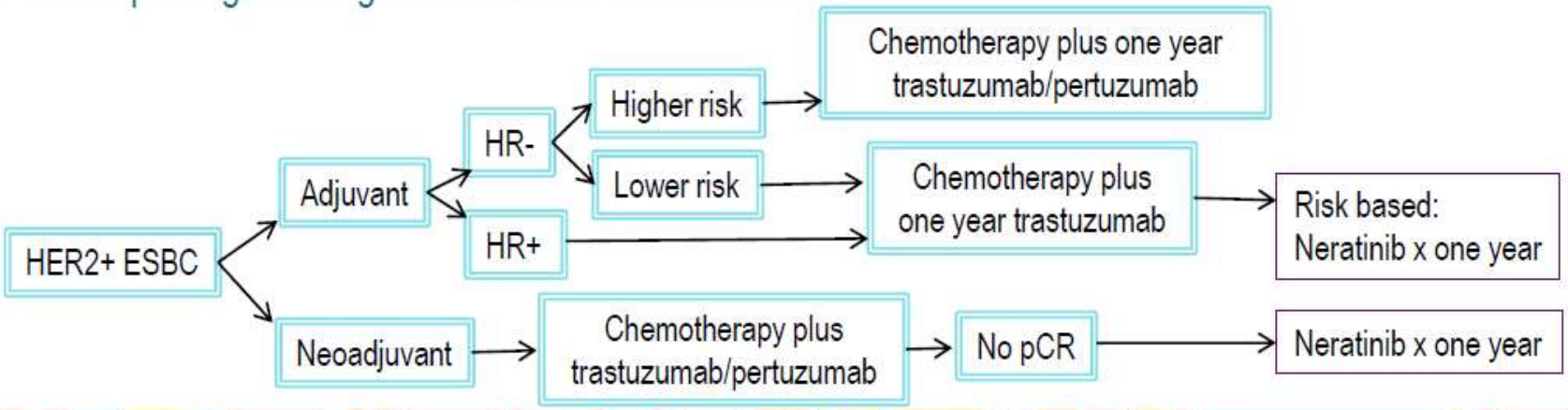
But there are already ways to increase access:

- Give 6 months of adjuvant trastuzumab instead of 1 year (differences in efficacy were small in pivotal trials)
- Give 9 weeks of trastuzumab as per FINHER study

Implications for the clinic
New treatment algorithm





IMPLICATIONS FOR THE CLINIC

- For ESBC, disease outcome can be modified by treatment decisions based on tumor biology
- Extenet
  - Continued demonstration of clinically significant benefit, particularly in higher risk, HR+ disease despite limitations due to change in sponsor and initial plan for short FU
  - Diarrhea a limiting factor, reduced significantly with prophylaxis (mandatory component of treatment)
  - Survival data pending; reduction in distant events encouraging
  - Extended therapy for HER2+ disease with neratinib FDA approved in the US; metastatic trial data to follow
  - A new paradigm? Along with endocrine rx as indicated: