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Discussion of Abstracts LBA11, LBA12, A3170

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Disclosures

- Advisor
  - Roche, Novartis, Celgene
- Honoraria
  - Roche, Novartis, Celgene, Eisai

Abstracts to discuss

- LBA11. An open label randomized phase III study comparing the incidence of CNS metastases in patients (pts) with HER2+ Metastatic Breast Cancer (MBC), treated with Lapatinib plus Capecitabine (LC) versus Trastuzumab plus Capecitabine (TC) **(CEREBEL)**

- LBA12. Updated Overall Survival Results From EMILIA, a Phase 3 Study of Trastuzumab Emtansine (T-DM1) vs Capecitabine and Lapatinib in HER2-Positive Locally Advanced or Metastatic Breast Cancer **(EMILIA)**

- A3170. First efficacy results from the TURANDOT phase III trial comparing two bevacizumab (BEV) - containing regimens as first-line therapy for HER2-negative metastatic breast cancer (MBC) **(TURANDOT)**

CEREBEL Trial (X Pivot, et al)

Phase III Planned N=650

Key eligibility:
- HER2+ MBC*
- Prior anthracyclines *or* taxanes
- Any line therapy
- No CNS metastases*
- Evaluable systemic dx

Stratification:
- **Prior trastuzumab**
  - **-yes vs no**
- Prior MBC tx
  - -0 vs ≥1

RANDOMISE

→ **Lapatinib 1250 mg/day + Capecitabine 2000 mg/m²**

→ **Trastuzumab 6 mg/kg q21 days + Capecitabine 2500 mg/m²**

***No CNS mets at baseline confirmed by independently reviewed MRI scan**

Study was a Specific Obligation measure required by CHMP in 2008

CEREBEL Trial (X Pivot, et al)

- **Primary Endpoint**
  - Incidence of CNS as site of first relapse

Trastuzumab-based: 20% → **Lapatinib-based: 12%**

- CNS metastasis incidence assumptions based on unscreened patient population

	Lapatinib + capecitabine (N=251)	Trastuzumab + capecitabine (N=250)	OR (95% CI)	p-value
CNS as first site of relapse, n (%)	8 (3)	12 (5)	0.65 (0.26, 1.63)	0.360
Incidence of CNS progression at any time, n (%)	17 (7)	15 (6)	1.14 (0.52, 2.51)	0.8646
Time to first CNS progression, median (range)	5.7 (2–17)	4.4 (2–27)	-	-

CEREBEL Trial (X Pivot, et al)

1. Is the primary endpoint appropriate?

YES

- HER2 overexpression is an independent prognostic factor for the development of brain metastases[1]

- The incidence of CNS metastases ranged from 21% to 34% in patients with trastuzumab-pretreated MBC[2]

- Trials comparing the incidence of CNS metastases in patients with MBC who received trastuzumab to those who did not, have shown conflicting results[2]

[1]Gabos et al. JCO 2006; [2]Leyland-Jones et al. JCO 2009

CEREBEL Trial (X Pivot, et al)

1. Is the primary endpoint appropriate?

YES

•Brain metastases as first site of progression was lower in patients who received capecitabine + lapatinib (2%) vs patients who received capecitabine alone (6%)[1]

Protective effect?

EMA requested a confirmatory study

[1]Cameron et al. BCRT 2008

CEREBEL Trial (X Pivot, et al)

2. Any conclusions?

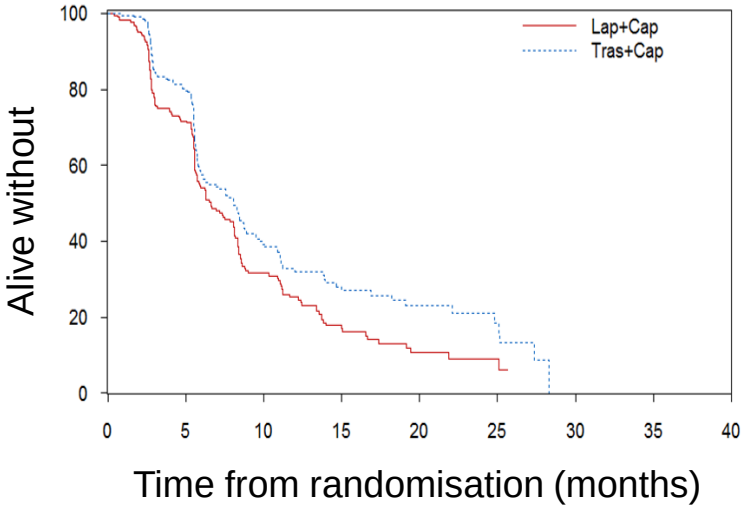
- Very small number of events in both arms
  - ~20% patients excluded for having brain metastases[1]
  - Longer follow-up? Will not change the primary endpoint!
  - Best strategy in patients with known brain metastases?
  - Brain metastases screening?
    - Impact in OS unknown
    - Importance of asymptomatic disease
      - Randomization?
- Secondary endpoints!!!

[1]Pivot X et al. SABCS 2011

CEREBEL Trial (X Pivot, et al)

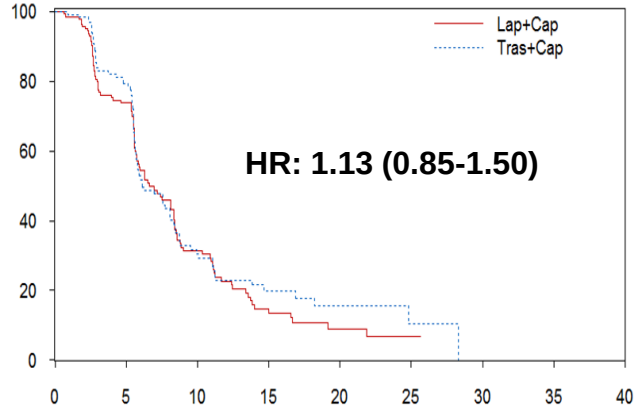
Secondary endpoints: Clinical relevance
Is lapatinib as good as trastuzumab?

ITT Population

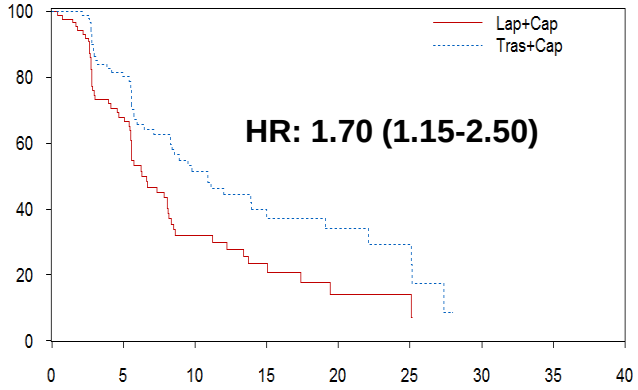


	Lap + Cap (N=271)	Tras + Cap (N=269)
Median PFS, months	6.6	8.0
Hazard ratio (95% CI)	1.30 (1.04, 1.64)	
Stratified log-rank p-value	0.021	

Trastuzumab-pretreated



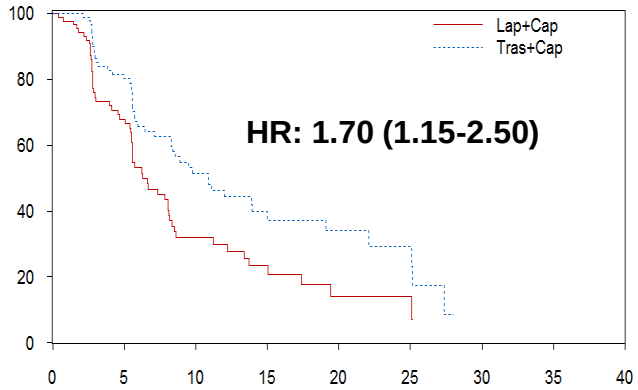
Trastuzumab-naive



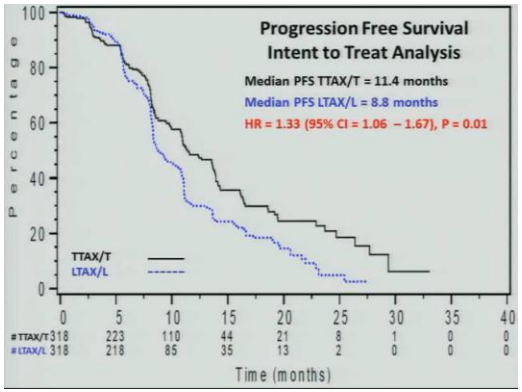
CEREBEL Trial (X Pivot, et al)

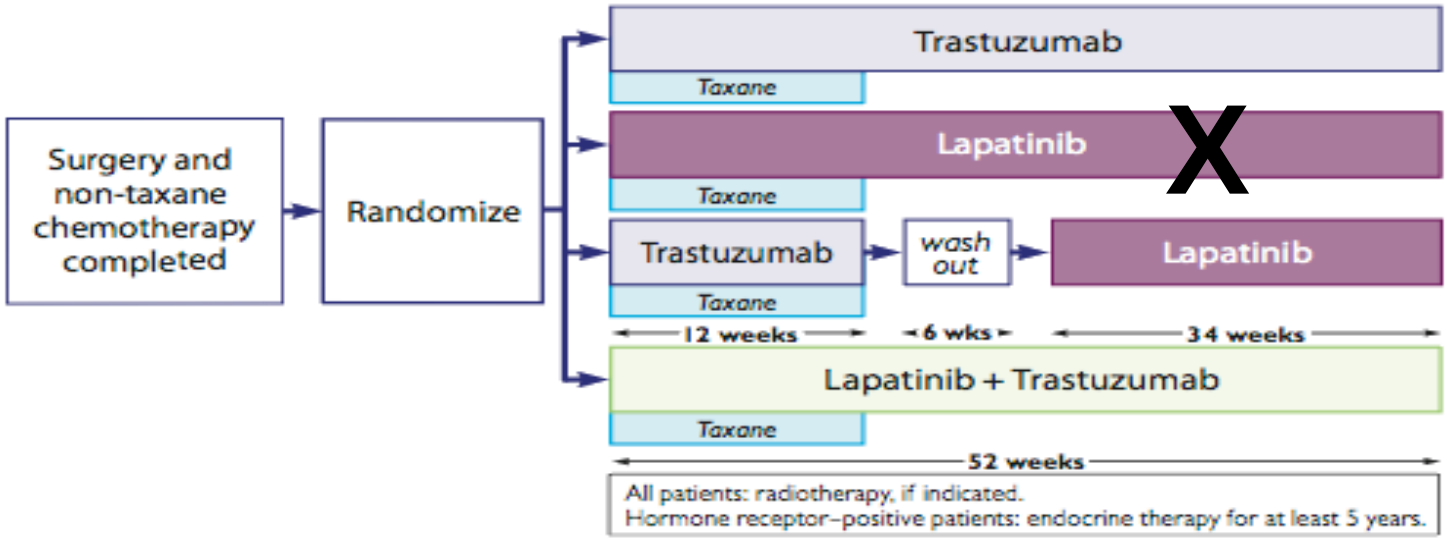
Secondary endpoints: Clinical relevance
Is lapatinib as good as trastuzumab?

Trastuzumab-naive



MA 31 Trial[1]





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[1]Gelmon et al. ASCO 2012

CEREBEL Trial (X Pivot, et al)

Secondary endpoints: Clinical relevance

Is lapatinib as good as trastuzumab?

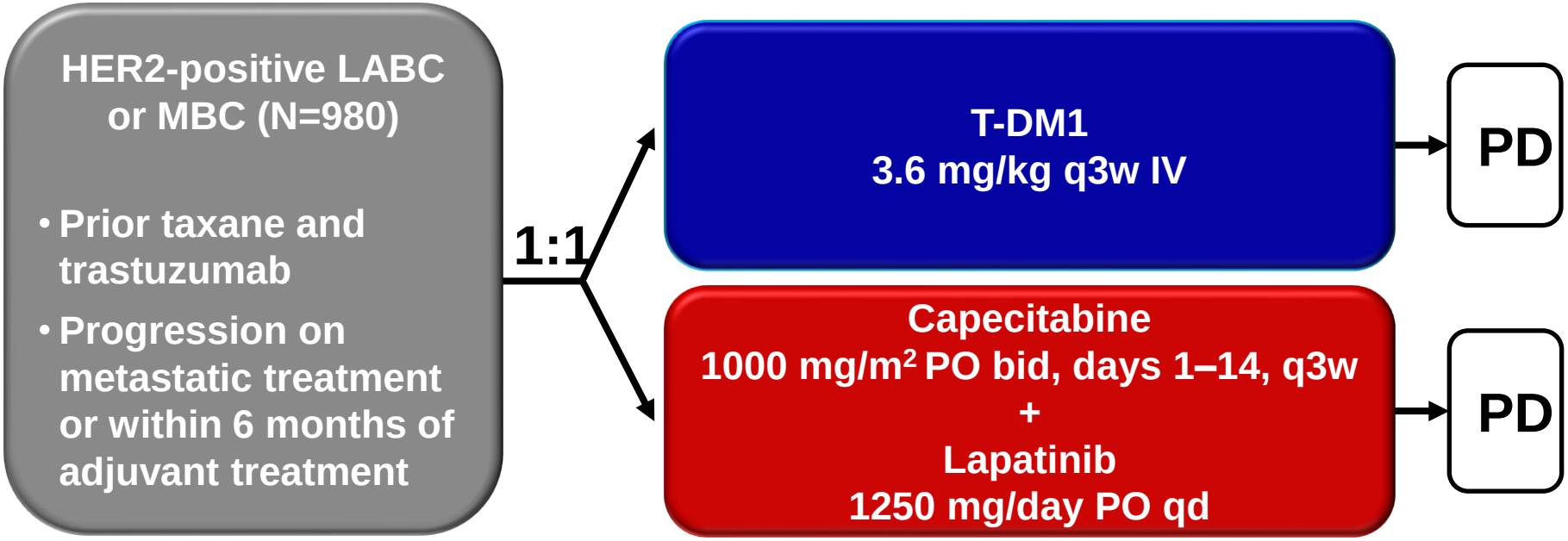
	NOAH[1]	GeparQuinto[2]		NeoAltto[3]			CHER-LOB[4]			NSABP B-41[5]		
Scheme	Ch + T	Ch + T	Ch + L	Ch + T	Ch + L	Ch + TL	Ch + T	Ch + L	Ch + TL	Ch + T	Ch + L	Ch + TL
Primary endpoint	**EFS**	**pCR breast & axilla***		**pCR breast**			**pCR breast & axilla**			**pCR breast**		
n	115	307	308	154	149	152	36	39	46	177	171	171
pCR (%) breast	43	50	35	29	25	51	NR	NR	NR	52	53	62
pCR (%) breast & axila	38	**31**	**22**	28	20	47	26	29	43	49	47	60

*pCR excludes ducatl in situ carcinoma

Ch, chemotherapy; EFS, event free-survival; L, lapatinib; n, sample; pCR, pathological complete response; T, trastuzumab

[1]Gianni et al. Lancet 2010; [2]Untch et al. Lancet Oncol 2012; [3]Baselga et al. Lancet 2012; [4]Guarneri et al. JCO 2012; [5]Robidoux et al. ASCO 2012

EMILIA Trial (S Verma, et al)



- **Primary endpoints:** PFS by independent review, OS, and safety
- **Key secondary endpoints:** PFS by investigator, ORR, DOR
- **Statistical considerations:** Hierarchical statistical analysis was performed in pre-specified sequential order: PFS by independent review → OS → secondary endpoints

EMILIA Trial (S Verma, et al)

2nd Interim OS Analy

Data cut-off July 31, 2012

Following health authority interactions

- 50% of targeted final number of events
- 80% power to detect HR=0.80; 2-sided alpha 5%

Median follow-up:

- Cap+Lap 18.6 mos; T-DM1 19.1 mos

	Median (months)	No. of events
Cap + Lap	25.1	182
T-DM1	30.9	149

Stratified HR=0.682 (95% CI, 0.548, 0.849)

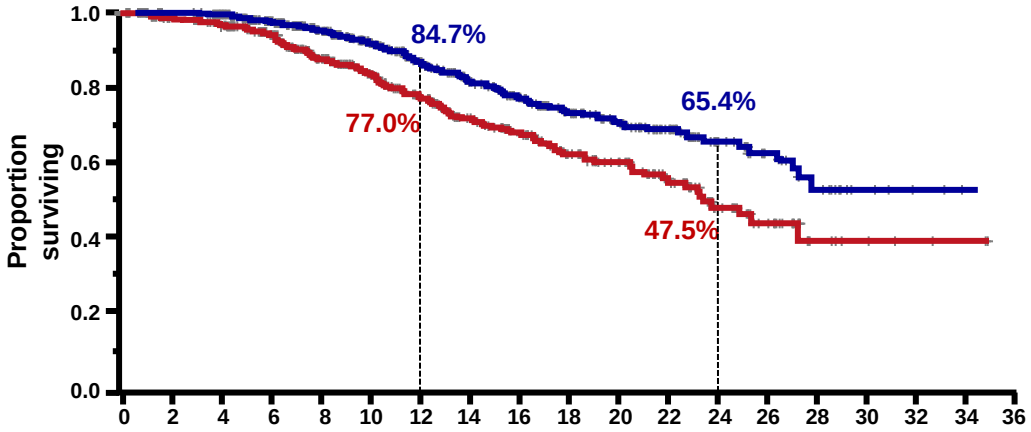
***P*=0.0006**

Efficacy stopping boundary P=0.0037 or HR=0.727

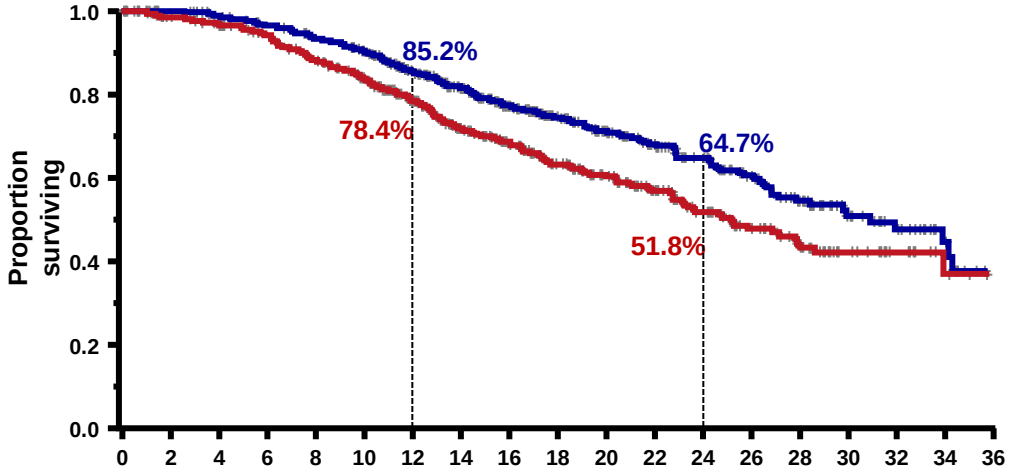
EMILIA Trial (S Verma, et al)

After previous ASCO data, are these new data clinically relevant?

OS:
First Interim Analysis[1]



OS:
Second Interim Analysis[2]



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[1]Blackwell et al. ASCO 2012; [2]Verma et al. ESMO 2012

EMILIA Trial (S Verma, et al)

After previous ASCO data, are these new data clinically relevant?

OS IMPROVEMENT ???

	Median (months)	No. of events
Cap + Lap	23.3	129
T-DM1	NR	94

Stratified HR=0.621 (95% CI, 0.475, 0.813)

***P*=0.0005**

Efficacy stopping boundary P=0.0003 or HR=0.617

OS IMPROVEMENT

	Median (months)	No. of events
Cap + Lap	25.1	182
T-DM1	30.9	149

Stratified HR=0.682 (95% CI, 0.548, 0.849)

***P*=0.0006**

Efficacy stopping boundary P=0.0037 or HR=0.727

[1]Blackwell et al. ASCO 2012; [2]Verma et al. ESMO 2012

EMILIA Trial (S Verma, et al)

After previous ASCO data, are these new data clinically relevant?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer

Sunil Verma, M.D., David Miles, M.D., Luca Gianni, M.D., Ian E. Krop, M.D., Ph.D., Manfred Welslau, M.D., José Baselga, M.D., Ph.D., Mark Pegram, M.D., Do-Youn Oh, M.D., Ph.D., Véronique Diéras, M.D., Ellie Guardino, M.D., Ph.D., Liang Fang, Ph.D., Michael W. Lu, Pharm.D., Steven Olsen, M.D., Ph.D., and Kim Blackwell, M.D., for the EMILIA Study Group

EMILIA Trial (S Verma, et al)

After previous ASCO data, are these new data clinically relevant?

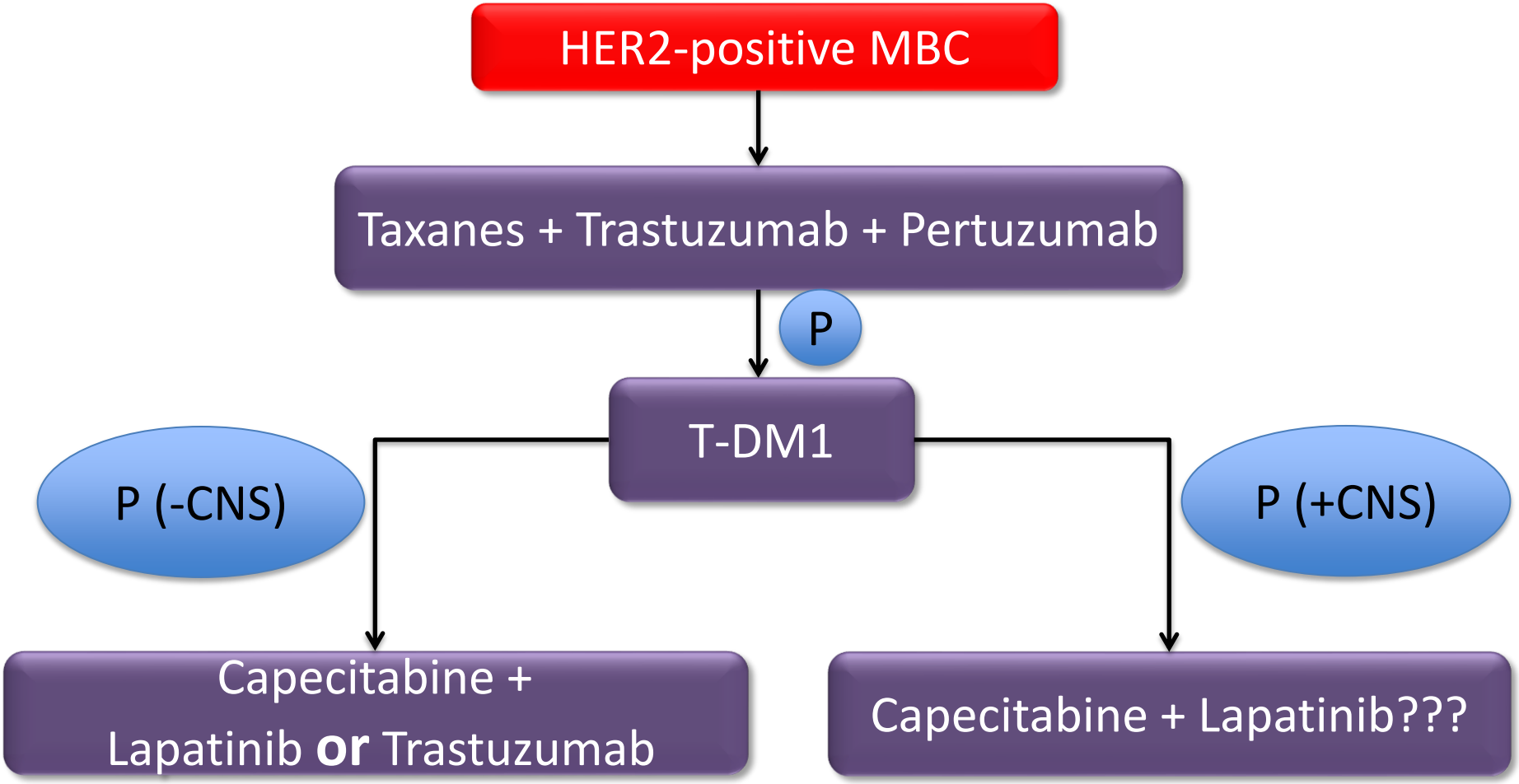
Cardiotoxicity

	Cap + Lap	T-DM1
Cardiac dysfunction AEs,[a] n (%)	(n=488)	(n=490)
All grades	15 (3.1)	9 (1.8)
Grade 3	**2 (0.4)**	**1 (0.2)**

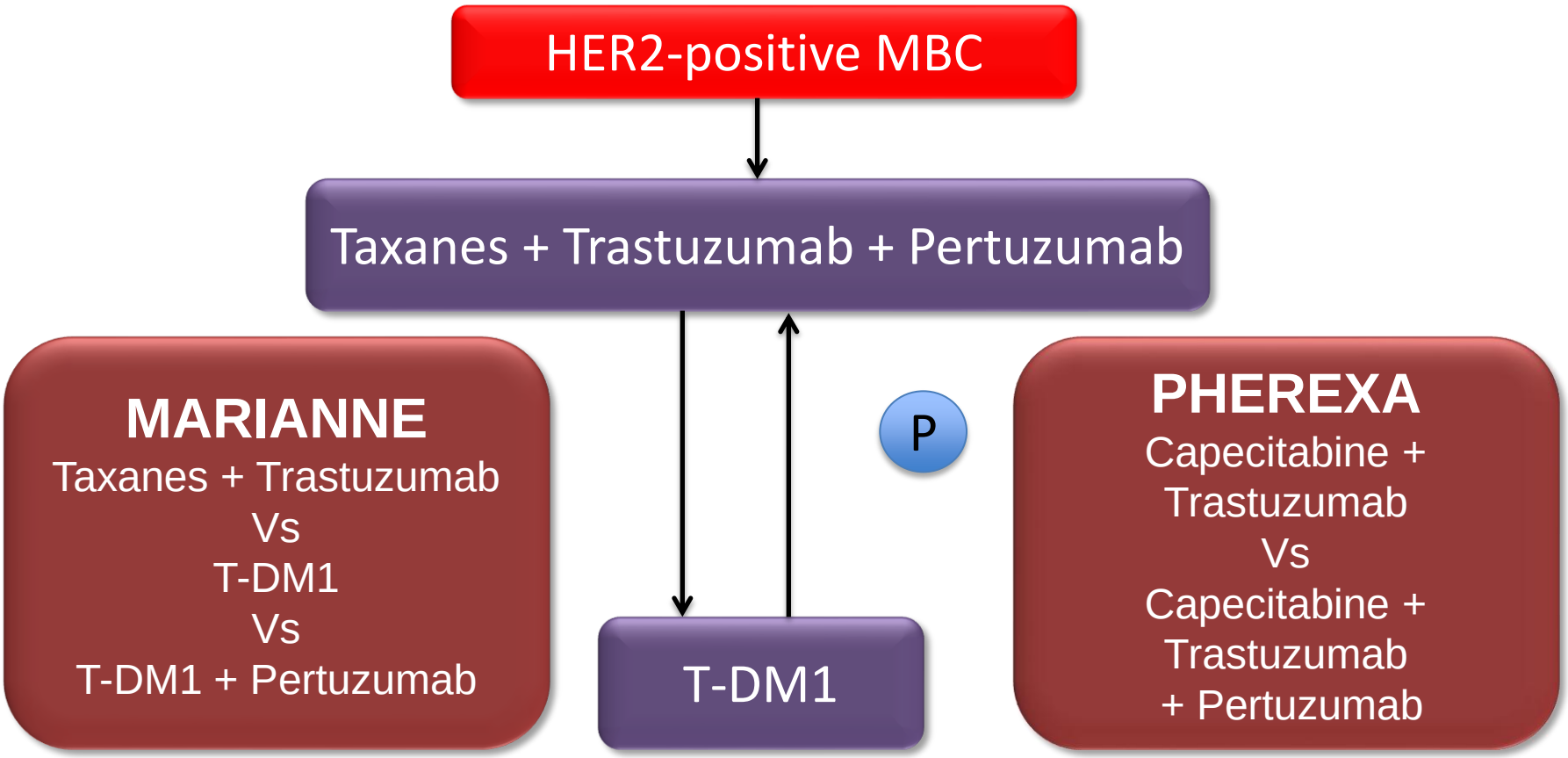
These data justify to explore T-DM1 in patients with heart disease-related contraindications to receive trastuzumab

EMILIA & CEREBEL trials

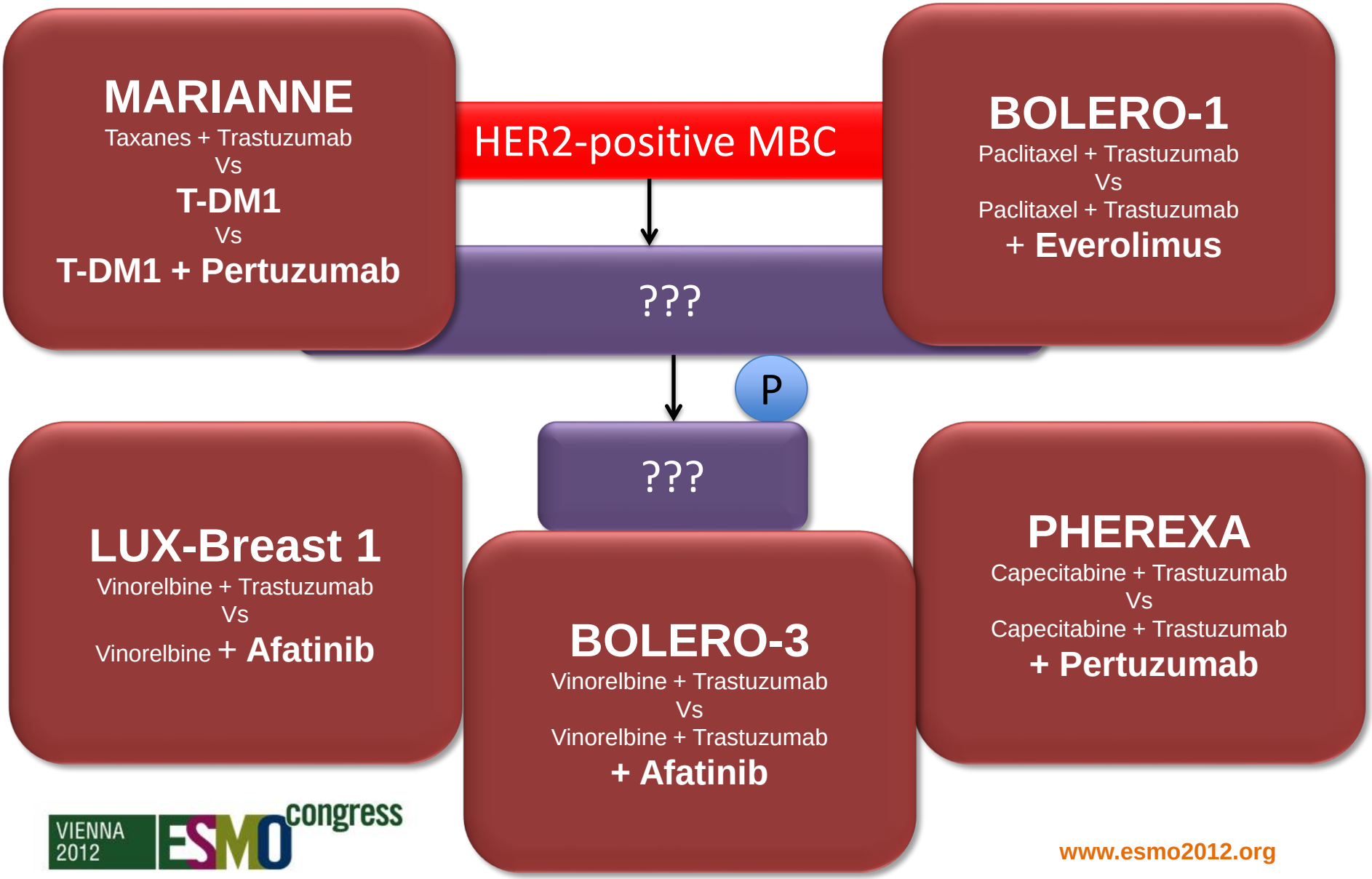
Do they have an impact in the current "clinical" SOC?



Near Future…

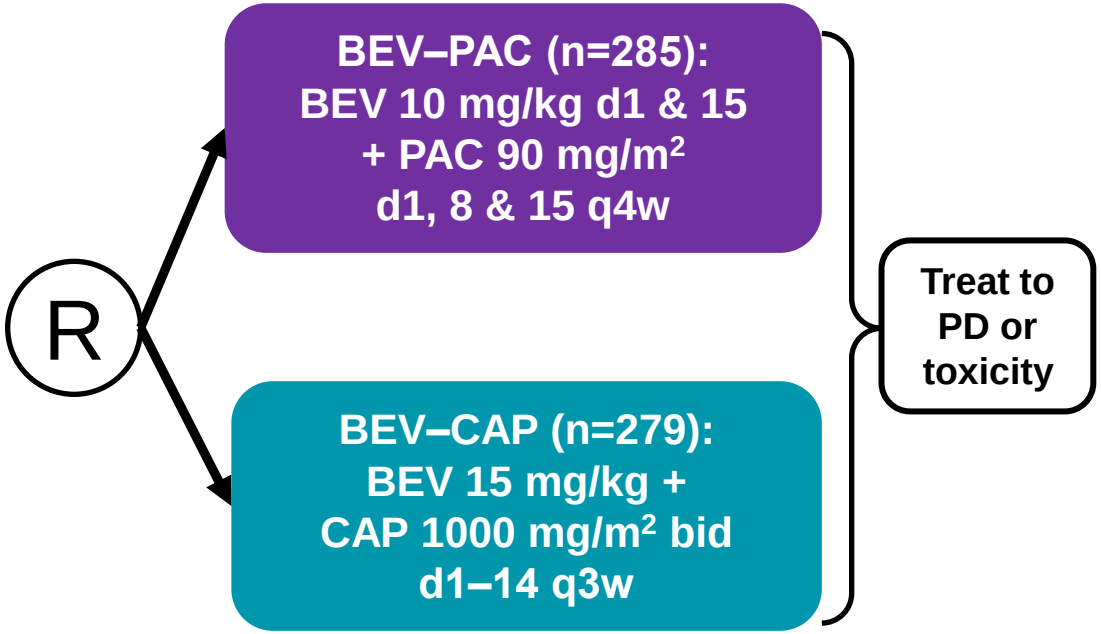

HER2-positive MBC
Taxanes + Trastuzumab + Pertuzumab
MARIANNE
Taxanes + Trastuzumab
Vs
T-DM1
Vs
T-DM1 + Pertuzumab
P
T-DM1
PHEREXA
Capecitabine +
Trastuzumab
Vs
Capecitabine +
Trastuzumab
+ Pertuzumab

Near Future…


MARIANNE
Taxanes + Trastuzumab
Vs
T-DM1
Vs
T-DM1 + Pertuzumab
HER2-positive MBC
???
BOLERO-1
Paclitaxel + Trastuzumab
Vs
Paclitaxel + Trastuzumab
+ Everolimus
P
???
LUX-Breast 1
Vinorelbine + Trastuzumab
Vs
Vinorelbine + Afatinib
BOLERO-3
Vinorelbine + Trastuzumab
Vs
Vinorelbine + Trastuzumab
+ Afatinib
PHEREXA
Capecitabine + Trastuzumab
Vs
Capecitabine + Trastuzumab
+ Pertuzumab

TURANDOT Trial (C Zielinski, et al)

- HER2-negative measurable/non-measurable LR/mBC
- ECOG PS 0–2
- No prior chemotherapy for LR/mBC
- Prior (neo)adjuvant chemotherapy and/or radiotherapy permitted only if completed ≥6 months before randomisation[a]



- **Primary objective: Non-inferior OS** with BEV–CAP vs BEV–PAC
  - Power: 80% . Null hypothesis of inferiority (**HR ≥1.33**) **(0.752)**
- Secondary objectives: ORR, PFS, Safety, QoL

TURANDOT Trial (C Zielinski, et al)

- **OS:**

  In the planned interim efficacy analysis, the criterion for non-inferiority has not yet been met

	BEV–PAC (n=268)	BEV–CAP (n=265)
Events, n (%)	89 (33)	92 (35)
Median, months (95% CI)	30.5 (26.2–NR)	26.0 (22.2–NR)
HR, stratified (97.5% repeated CI)	1.042 (–∞ to 1.686)	
p-value[b]	0.0593	

- **PFS:**

  Significantly better with BEV–PAC

	BEV–PAC (n=285)	BEV–CAP (n=279)
Events, n (%)	177 (62)	214 (77)
Median, months (95% CI)	11.0 (10.4–12.9)	8.1 (7.1–9.2)
HR, stratified (95% CI)	1.36 (1.09–1.68)	
p-value[a]	0.0052	

TURANDOT Trial (C Zielinski, et al)

1. Is the primary endpoint appropriate?

			RIBBON-1[3]	
	E2100[1]	**AVADO[2]**	**Cap**	**Taxane/ anthracycline**
Chemotherapy	Weekly paclitaxel	3-weekly docetaxel	Cap	3-weekly docetaxel/nab-paclitaxel or AC/FAC/EC/FEC
Primary endpoint	PFS (inv)	PFS (inv)	PFS (inv)	
HR	0.48 p<0.0001	0.67 p=0.0002[d]	0.69 p=0.0002	0.64 p<0.0001
OS (HR)	0.87 p=0.14	1.03 p=0.85	0.85 p=0.27	1.03 p=0.83

Cap; Capecitabine

[1]Miller et al. NEJM 2007; [2]Miles et al. JCO 2010; [3]Robert et al. JCO 2011

TURANDOT Trial (C Zielinski, et al)

1. Is the primary endpoint appropriate[1]?

Advantages of PFS as the primary Endpoint in MBC Clinical Trials (First-Line)

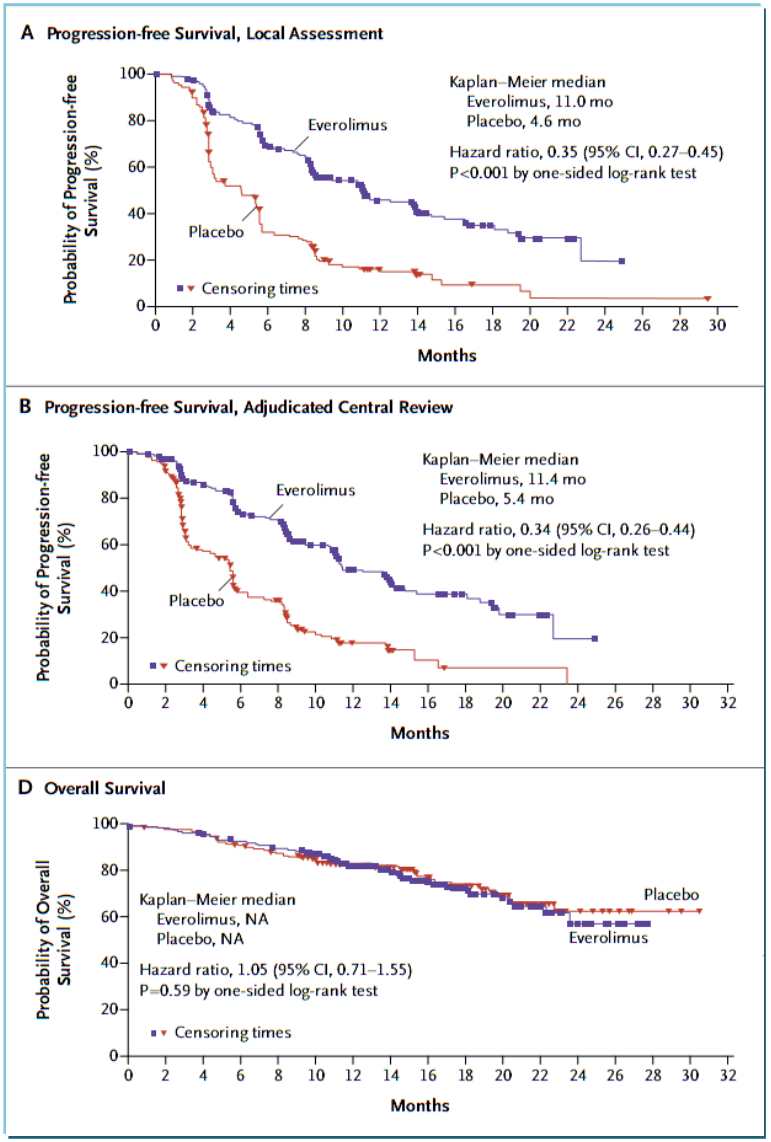
- Increase number of agents available for use in MBC
- Imbalance in subsequent therapies might impact OS
- It is very difficult to randomize for subsequent therapies

In clinical trials with a PFS benefit, the lack of statistical difference in OS, does not mean a lack of improvement in OS, particularly for disease with long median SPPs[2]

[1]Cortes et al. JCO 2012; [2]Broglio and Berry. JNCI 2009

TURANDOT Trial (C Zielinski, et al)

Pancreatic NETs



Everolimus vs. Placebo

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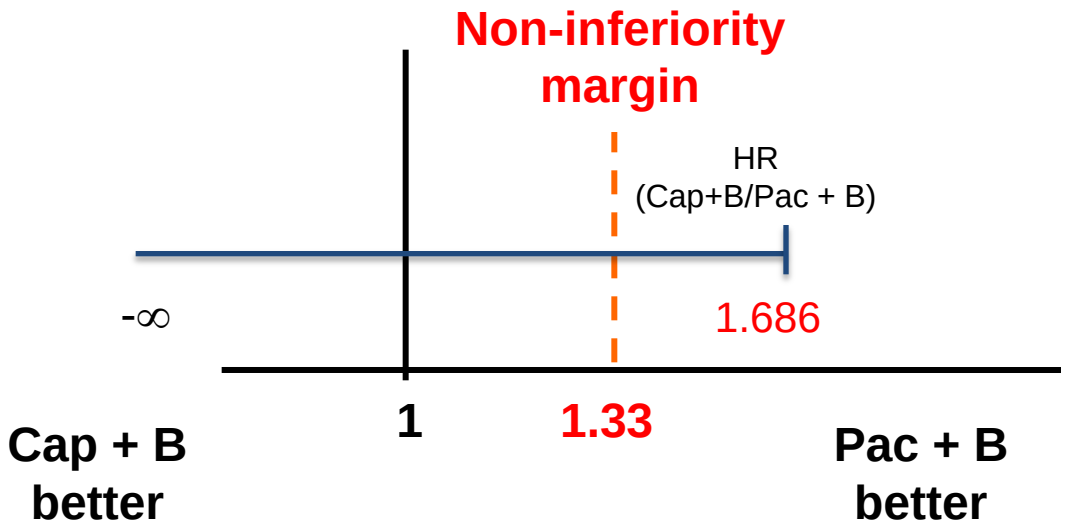
Yao et al. NEJM 2011

TURANDOT Trial (C Zielinski, et al)

2. How much is good enough?

Null hypothesis of inferiority (HR ≥1.33) (0.752)

It means that if the “true HR” for OS is 1.33 (0.752), the trial would be considered positive



TURANDOT Trial (C Zielinski, et al)

2. How much is good enough?

Null hypothesis of inferiority (HR ≥1.33) (0.752)

Which is the smallest improvement in HR (PFS and OS) to consider new data clinically relevant?

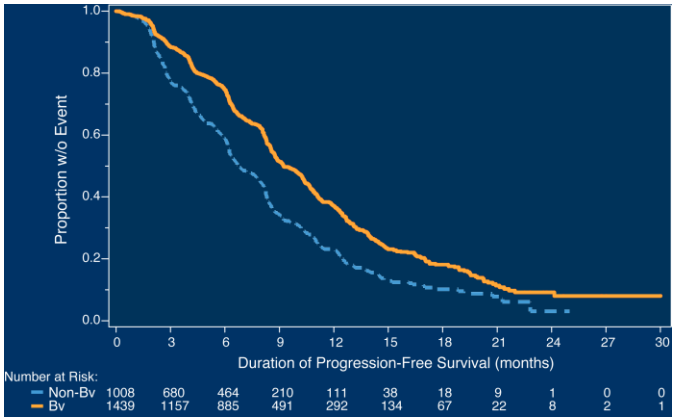
What is the highest difference for non-inferiority clinical trials we can accept?

- Is HR=1.33 acceptable for non-inferiority?
- EMBRACE Trial (Eribulin vs TPC): HR=0.81

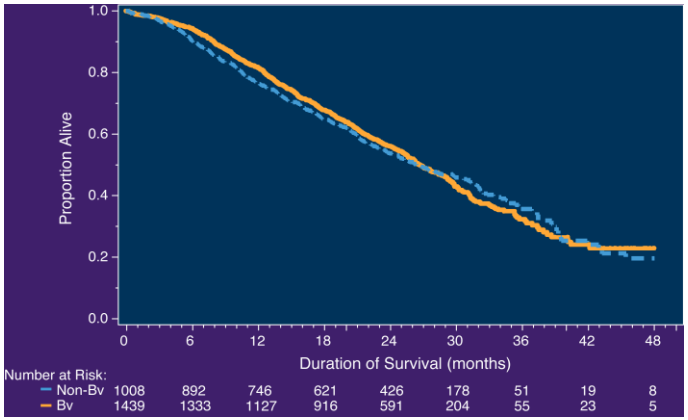
TURANDOT Trial (C Zielinski, et al)

3. Lessons learnt from secondary endpoints

META-ANALYSIS: PFS and OS



	Non-BV (n=1008)	BV (n=1439)
Median, mo	6.7	9.2
HR (95% CI)	0.64 (0.57–0.71)	



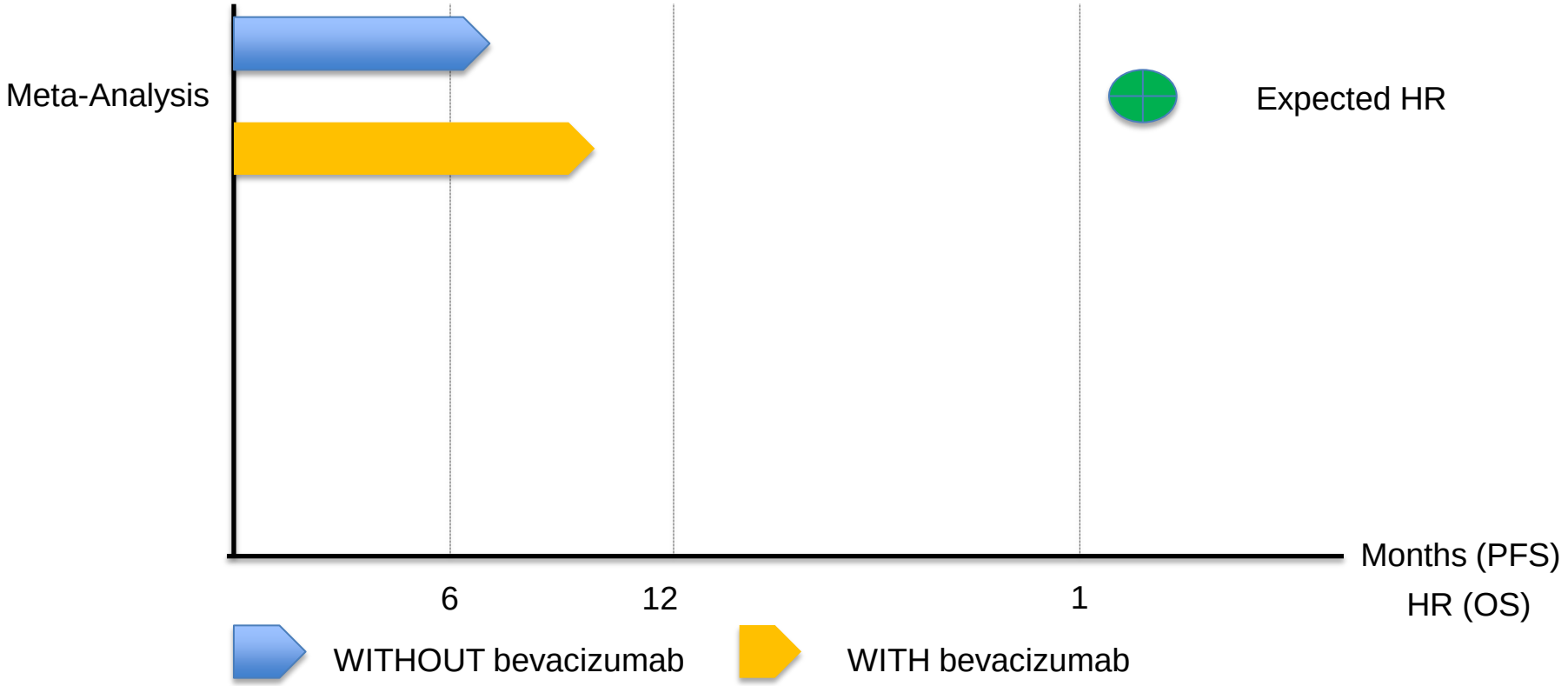
	Non-BV (n=1008)	BV (n=1439)
Median, mo	26.4	26.7
HR (95% CI)	0.97 (0.78–01.01)	

Hypothesis: Tumor re-growth?

O´Shaughnessy et al. ASCO 2010

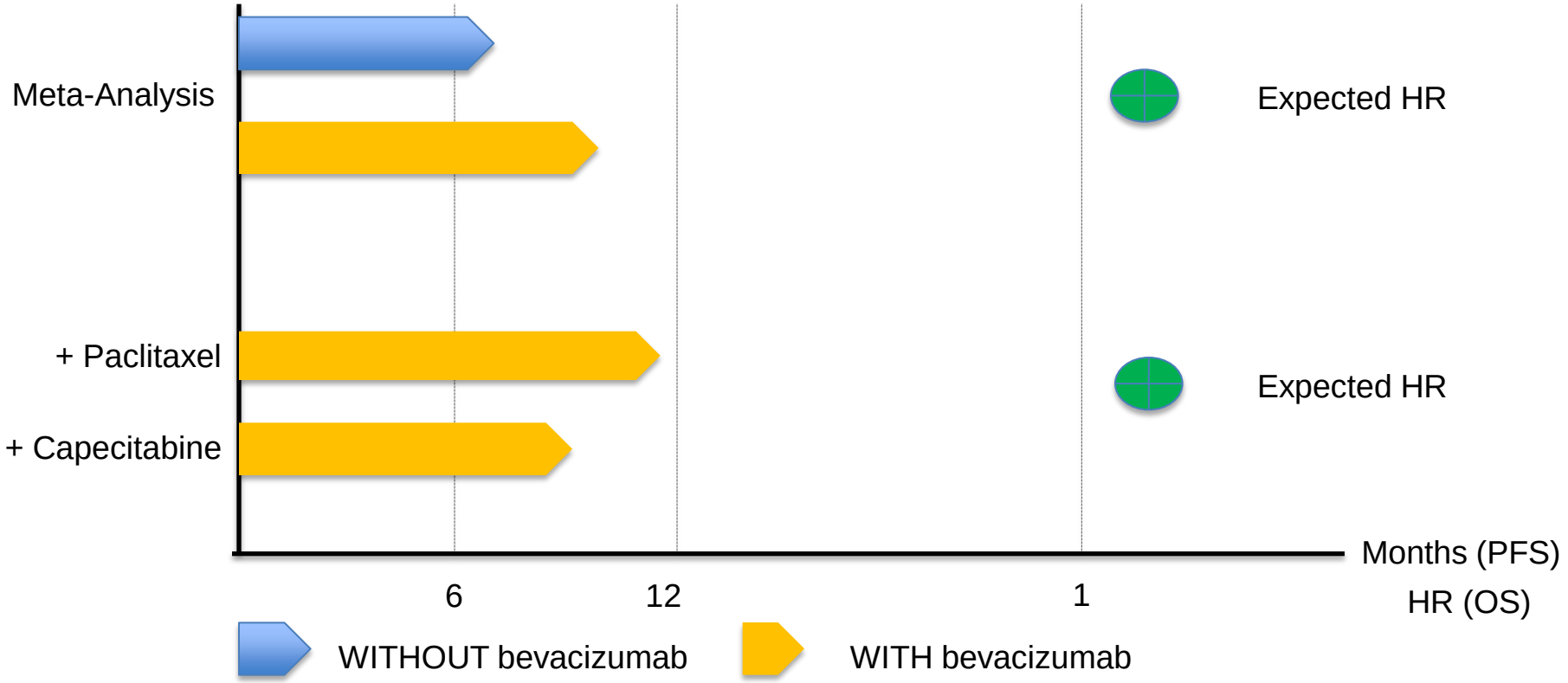
TURANDOT Trial (C Zielinski, et al)

3. Lessons learnt from secondary endpoints



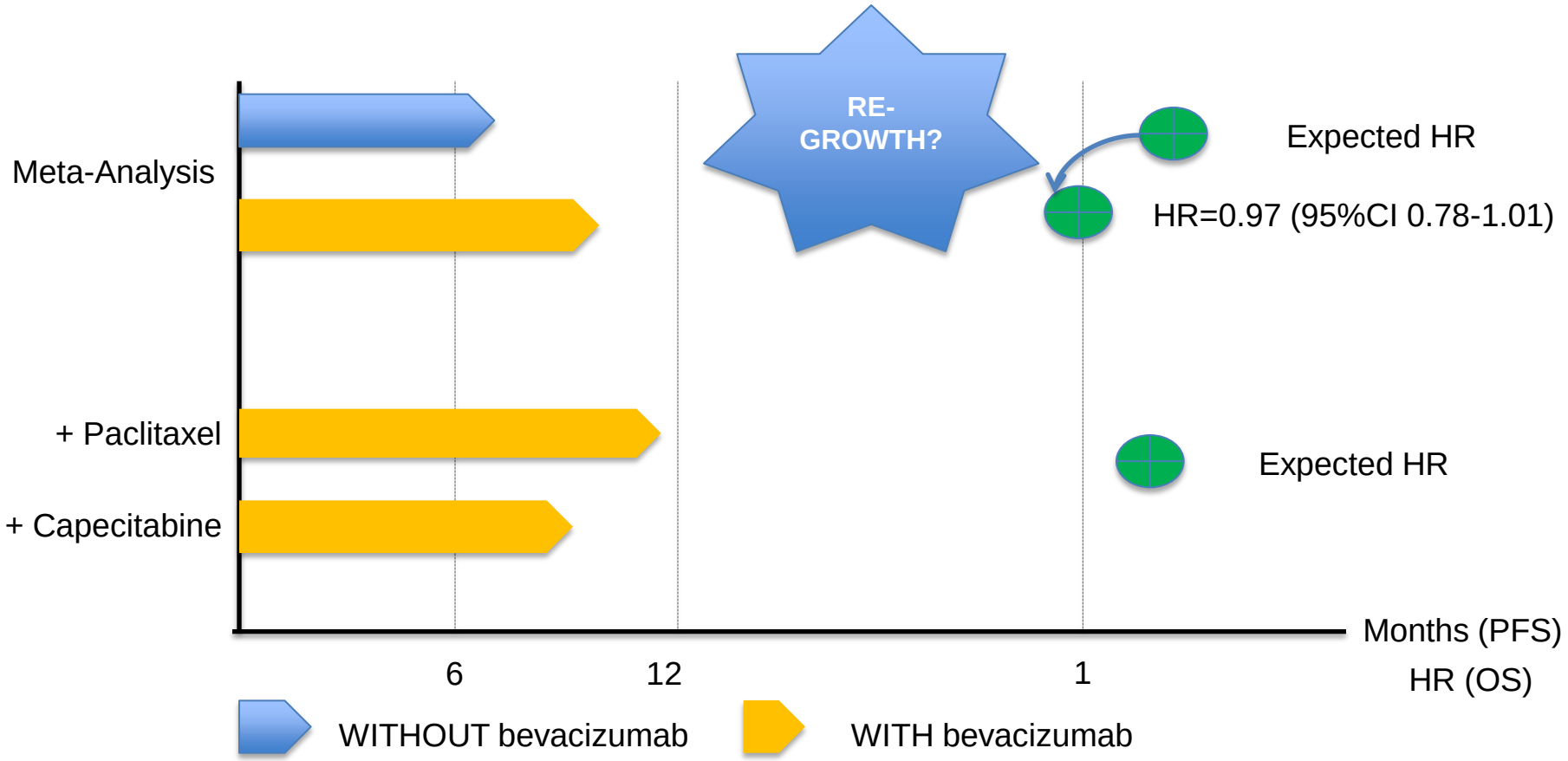
TURANDOT Trial (C Zielinski, et al)

3. Lessons learnt from secondary endpoints



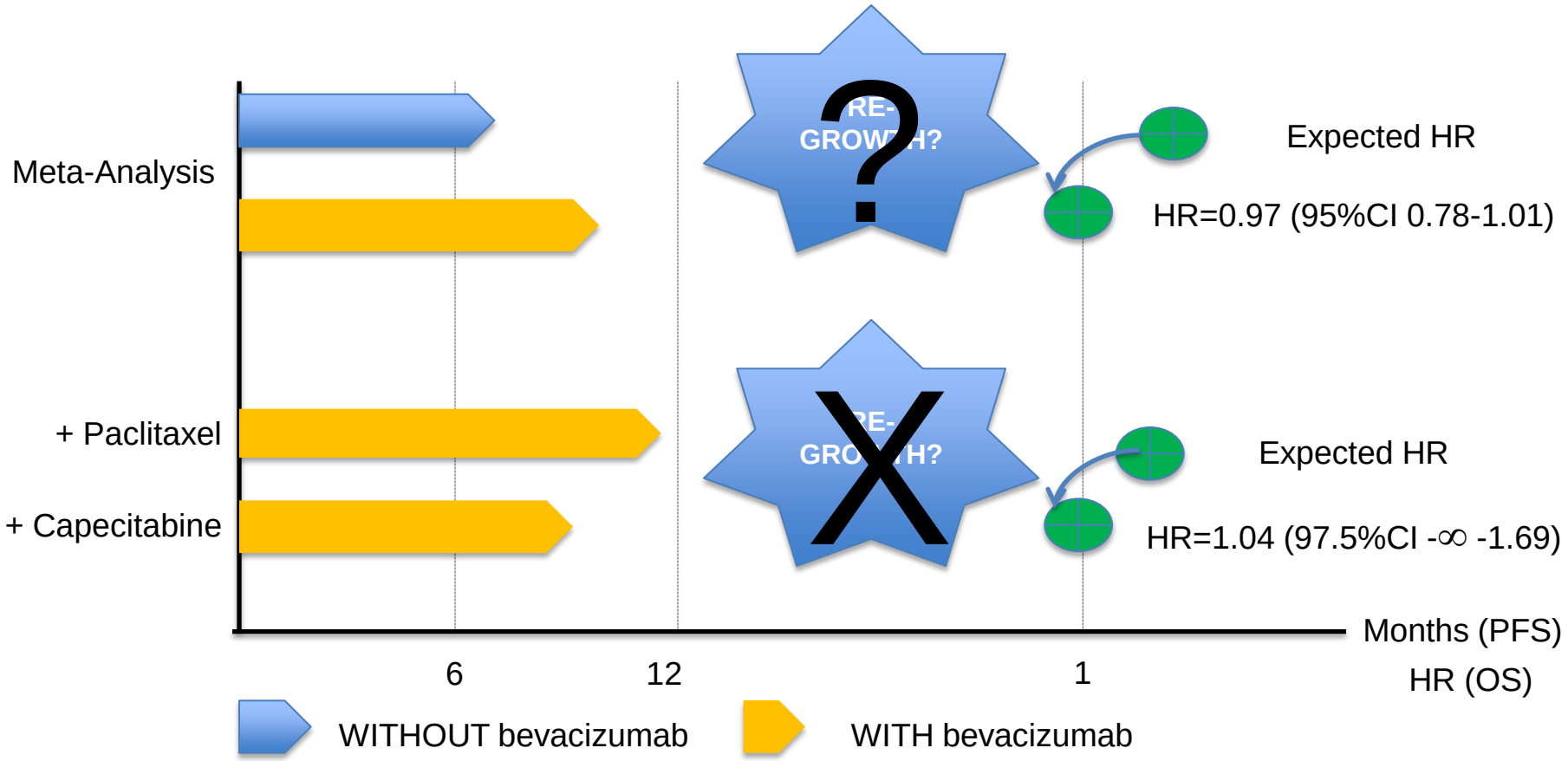
TURANDOT Trial (C Zielinski, et al)

3. Lessons learnt from secondary endpoints



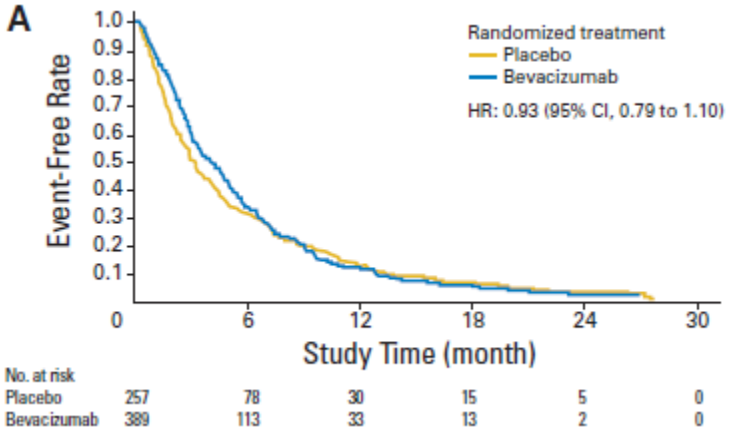
TURANDOT Trial (C Zielinski, et al)

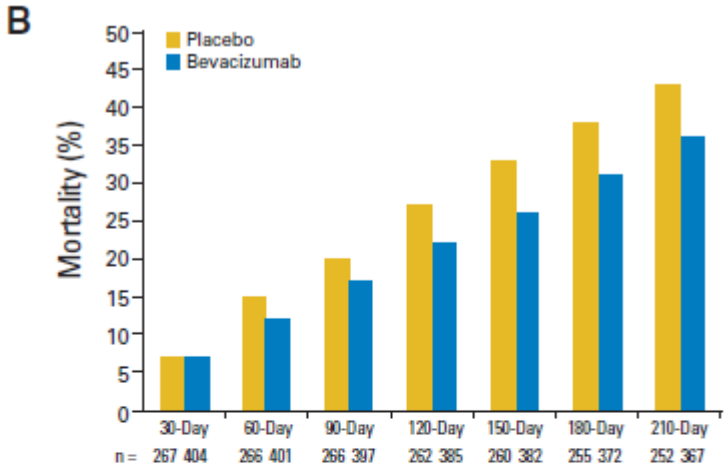
3. Lessons learnt from secondary endpoints

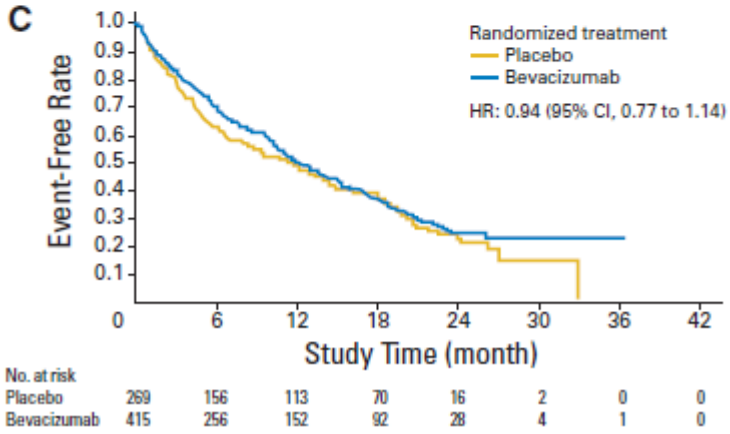


TURANDOT Trial (C Zielinski, et al)

3. Lessons learnt from secondary endpoints







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Miles et al. JCO 2011

TURANDOT Trial (C Zielinski, et al)

Some thoughts…

Bevacizumab-based therapy is a good treatment option for patients with HER2-negative MBC (first line)

Paclitaxel with bevacizumab might be a better option than capecitabine plus bevacizumab

Differences in OS between paclitaxel and capecitabine (when combined with bevacizumab) are unlikely to be found, but it does not mean that both schedules are the same

Conclusion

- From the discussant's perspective..
  - T-DM1 is a new standard of care in trastuzumab-progressing patients.
  - Capecitabine and lapatinib/trastuzumab are good options, probably after T-DM1.
  - If bevacizumab is used, paclitaxel might be more active than capecitabine.
- Biomarker studies will help to optimize the best strategy for patients, not only in HER2-negative disease, but also in HER2-positive