

Riunione Gruppo di Studio Sul Carcinoma
Della Mammella, Rete Oncologica del
Piemonte e della Valle D'Aosta

Neoadjuvant (chemo)-therapy

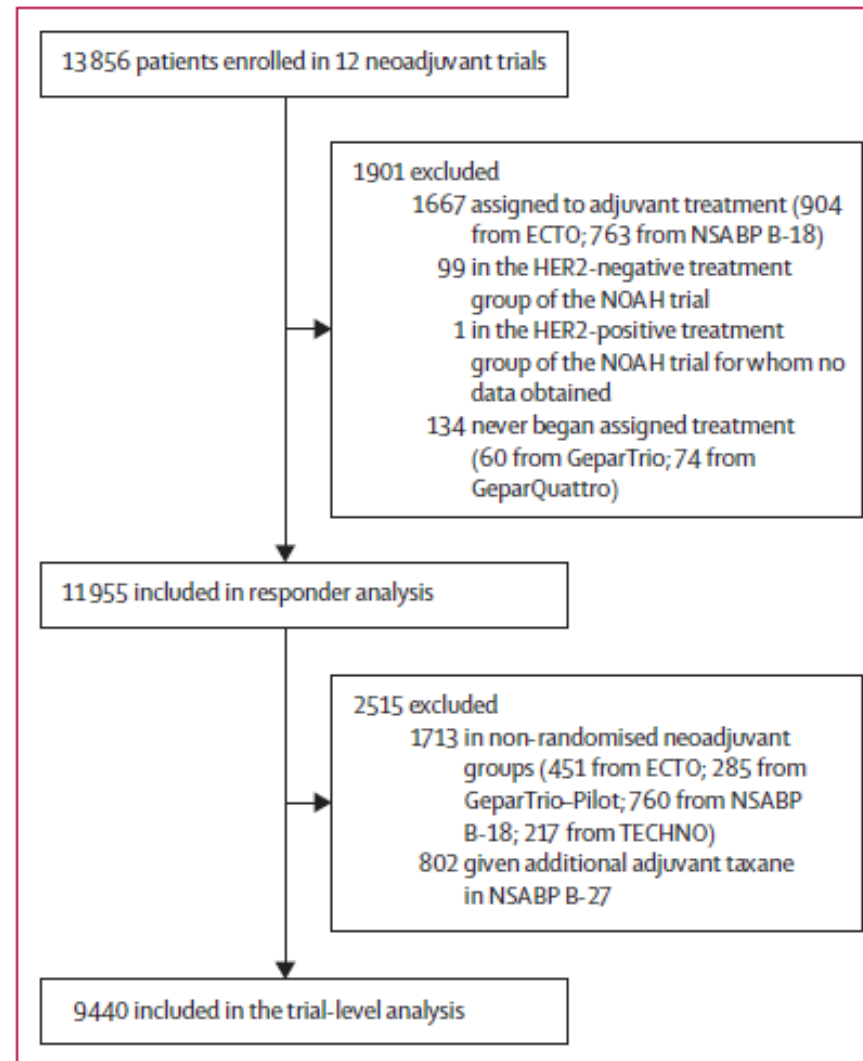
The FDA may grant accelerated approval on the basis of a surrogate end point that is “reasonably likely to predict clinical benefit.”

For neoadjuvant breast-cancer treatment, we propose that the rate of pathological complete response be used as this surrogate.

Prowell T, Pazdur R. N Engl J Med 366; 2438, 2012

Metanalysis of Randomized Clinical Trials (individual patient data)

- 12 neoadjuvant randomized controlled trials
- pCR clearly defined with all necessary data collected
- Long-term follow-up EFS and OS data collected



Cortazar et al, Lancet epub 2014

Question 1: does pCR predict better outcome compared with no-CR?

Responder analysis (11955 patients, 12 clinical trials)

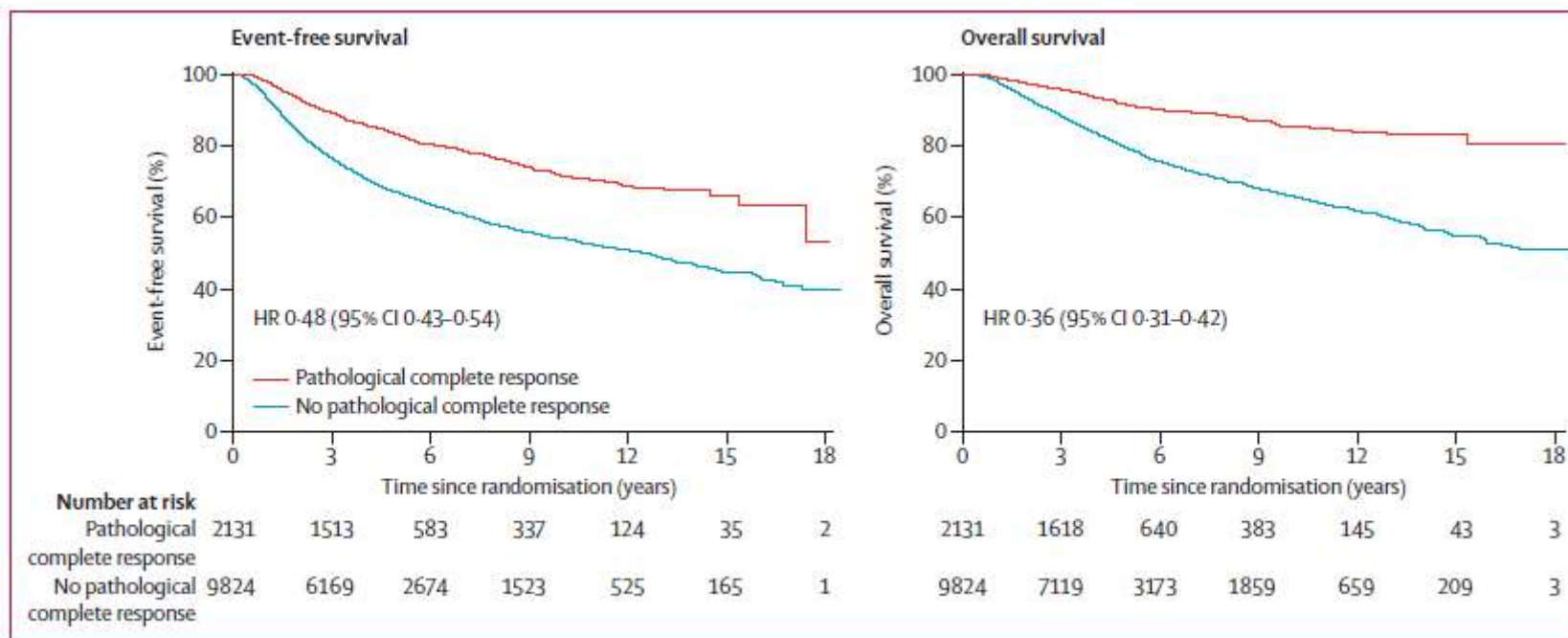


Figure 2: Associations between pathological complete response and event-free survival and overall survival

Cortazar et al, Lancet epub 2014

Question 2: which is the definition of pCR that best correlates with outcome?

Responder analysis (11955 patients, 12 clinical trials)

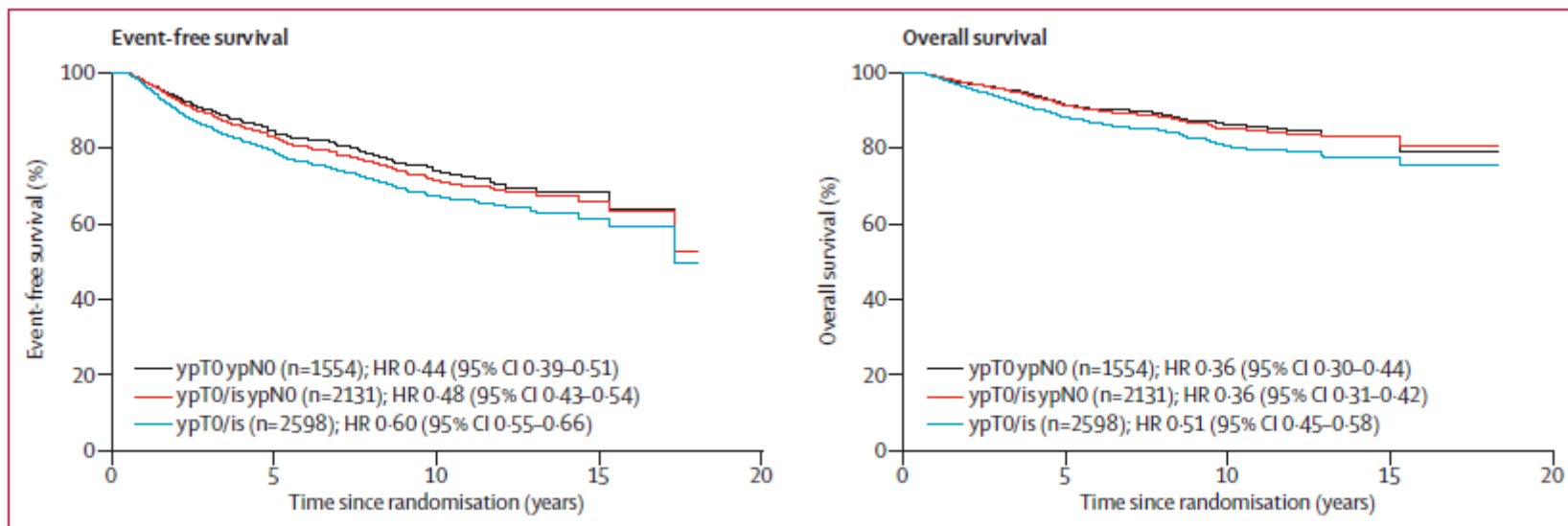


Figure 3: Associations between three definitions of pathological complete response and event-free survival and overall survival

Question 3: does pCR predict better outcome in different biologic subsets of breast cancer?

ER+,
HER2-

HER2
+

Triple
Negative

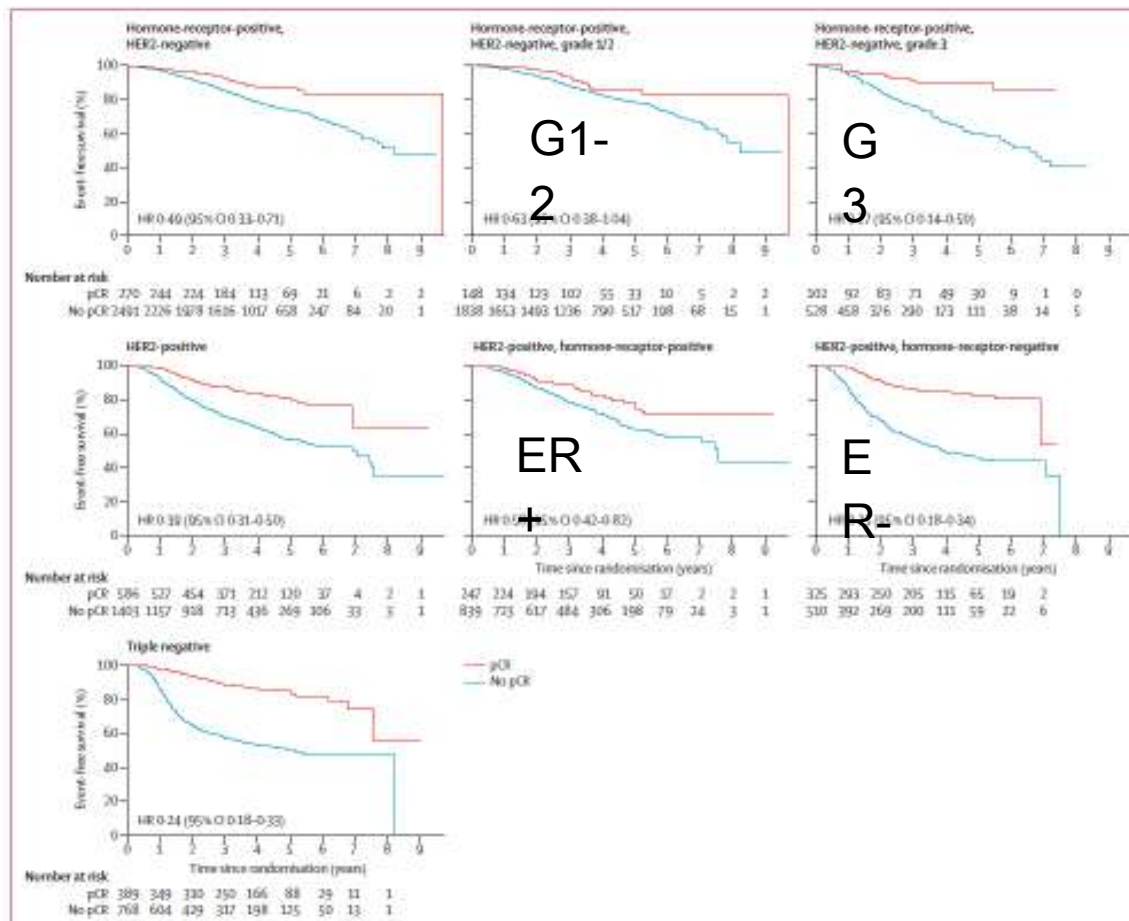


Figure 5: Association between pCR and event-free survival, by breast cancer subtype.

Cortazar e al, Lancet epub
2014

A simple summary

	HR+, G1/2 (Mostly Luminal A)	HR+/G3 (mostly Luminal B)	Luminal/HER 2+	Pure HER2+	TNBC
pCR probability	Low	Moderate	High	Highest	High
Prognosis if no pCR	Good	Less Good/Poor	Good	Poorest	Poor

Legend:

Low: 7%

Moderate: 16%

High: 30%

Highest: 50%

Legend:

Good: HR 1.59-1.70

Less good: HR 3.7

Poor: HR 4.2

Poorest: HR 6.6



Question 4: what is the minimum increase in pCR rate that results in a long term-outcome vantage?

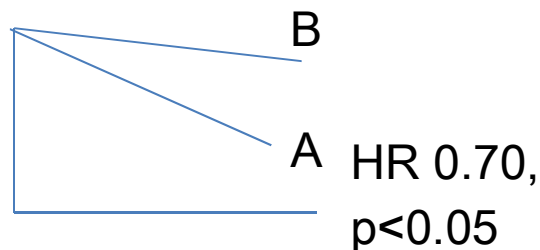
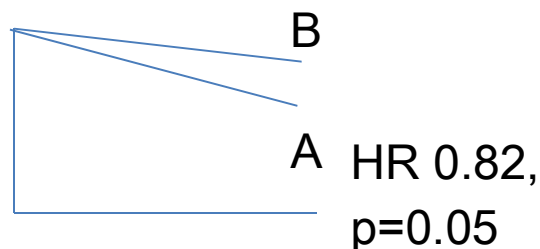
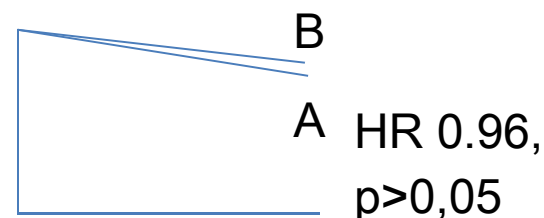
A= standard treatment

B = investigational treatment

1) $pCR (B1-A1) = \Delta 1pCR$
(OR 1.20)

2) $pCR (B2-A2) = \Delta 2pCR$
(OR 1.8)

3) $pCR (B3-A3) = \Delta 1pCR$
(OR 2.2)



Question number 4: does an increase in pCR frequency between treatment groups predict better outcome?

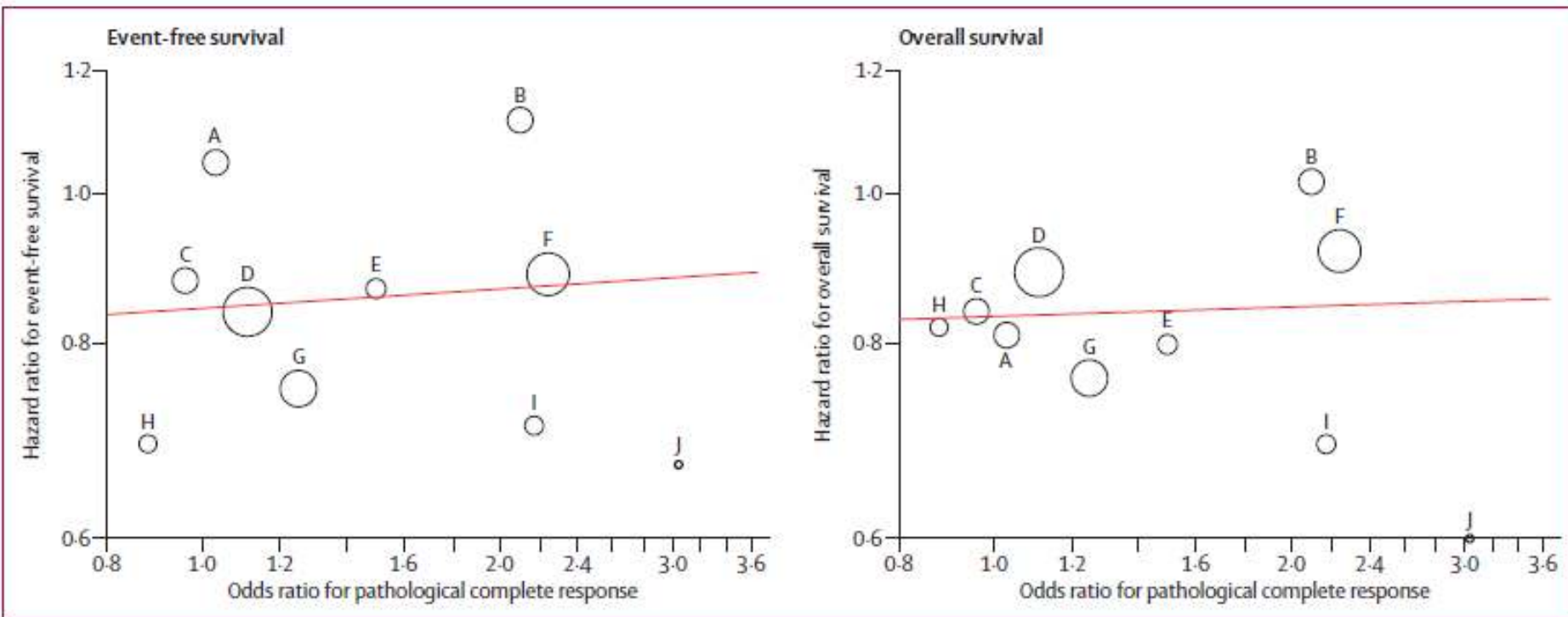
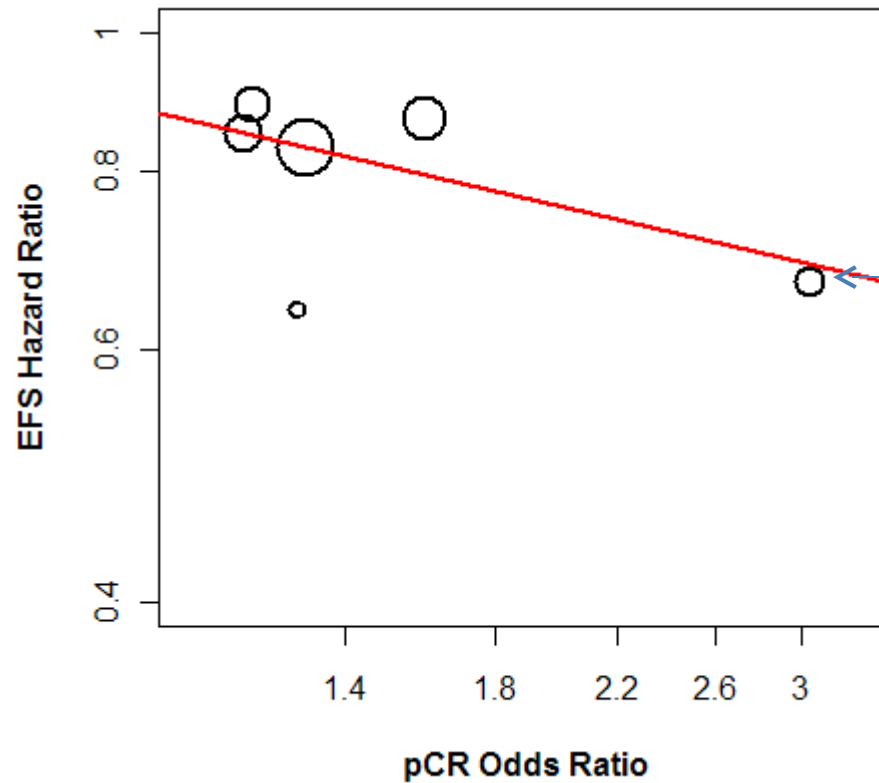


Figure 6: Trial-level correlation between treatment effect on pathological complete response and event-free survival or overall survival

Potential negative correlation HER2-positive BC



NOHA trial
pCR with trast
38%
pCR w/p
trast 19%

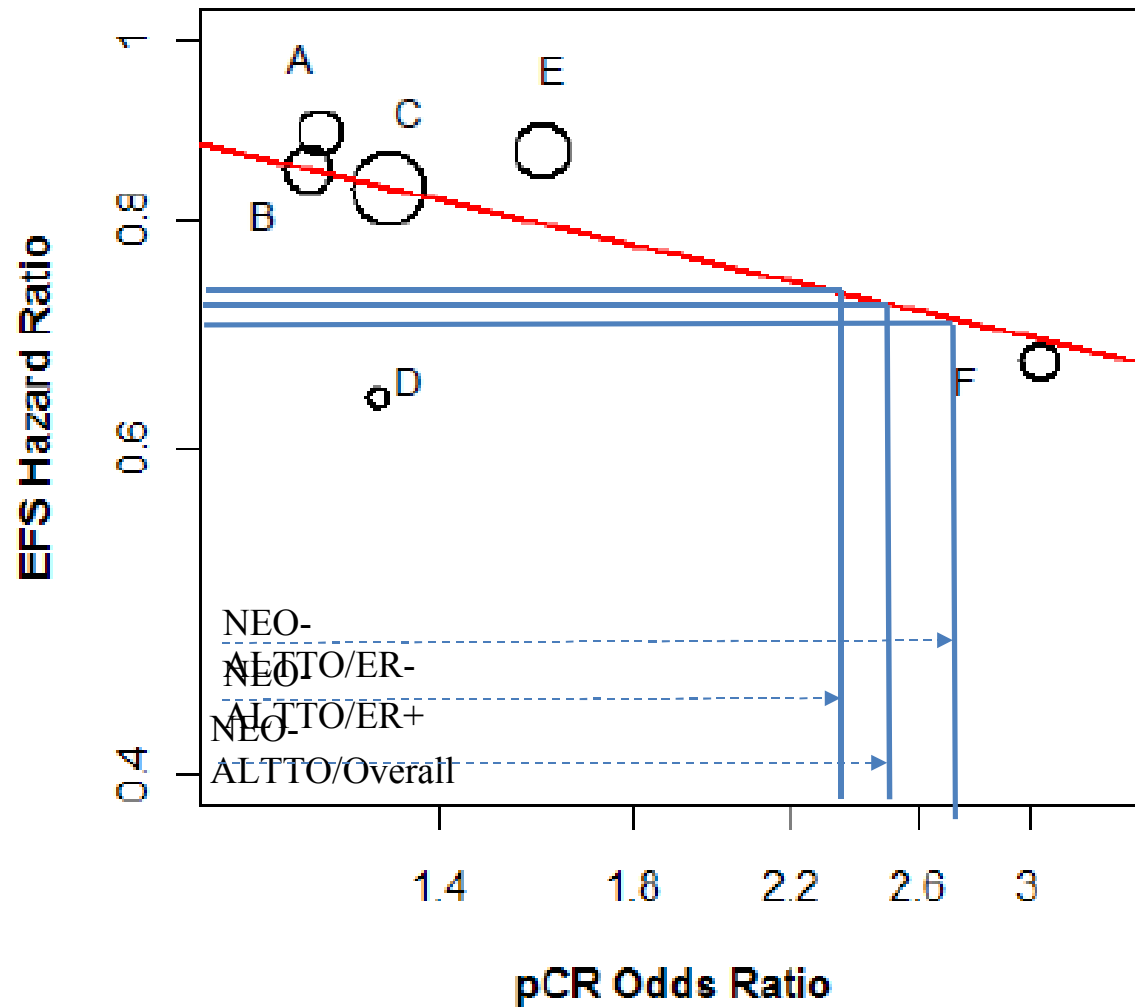
HR EFS
0.64
HR OS
0.66

Neoadjuvant trials with double HER2 targeting

Author	Treatment	Overall	ER-	ER+
Baselga NEO-ALTTO	T + Pacli	29.3	36.5	22.7
	T+L + Pacli	51.3	61.3	41.6
Odds Ratio favouring combo		2.52	2.76	2.43
Gianni NEO-Sphere	T + Doce	29.0	36.8	20.0
	T + P + Doce	45.8	63.2	26.0
Odds Ratio favouring combo		2.07	2.93	1.41

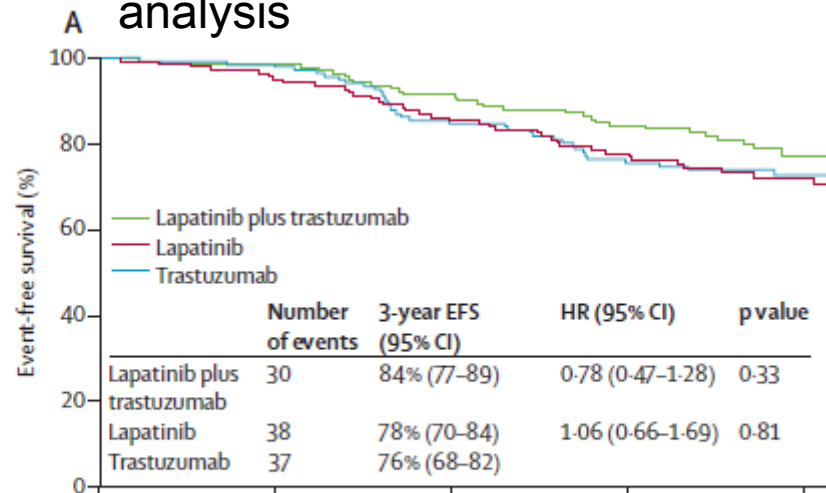
Baselga et al, Lancet 18;379, 2012
 Gianni et al, Lancet Oncol 13;25,
 2012

Neo-ALTTO: prediction based on the metanalysis

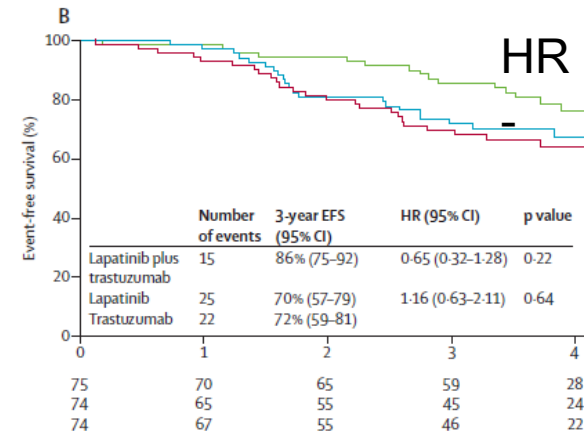


NEO-ALTTO: Event-free survival

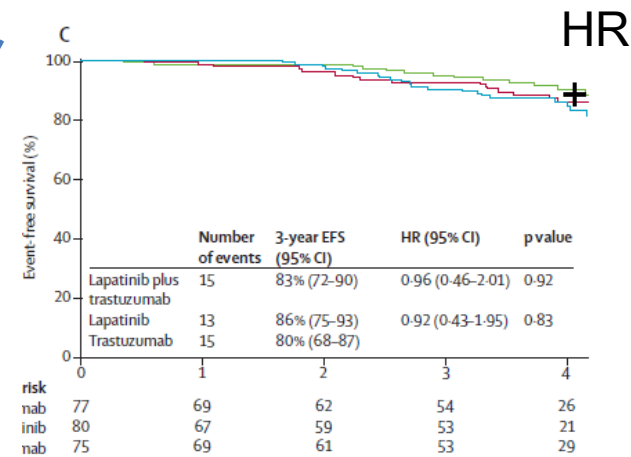
Event-free survival, ITT analysis



Number at risk	0	1	2	3	4
Lapatinib plus trastuzumab	152	139	127	113	54
Lapatinib	154	132	114	98	45
Trastuzumab	149	136	116	99	51



risk	0	1	2	3	4
nab	75	70	65	59	28
inib	74	65	55	45	24
nab	74	67	55	46	22

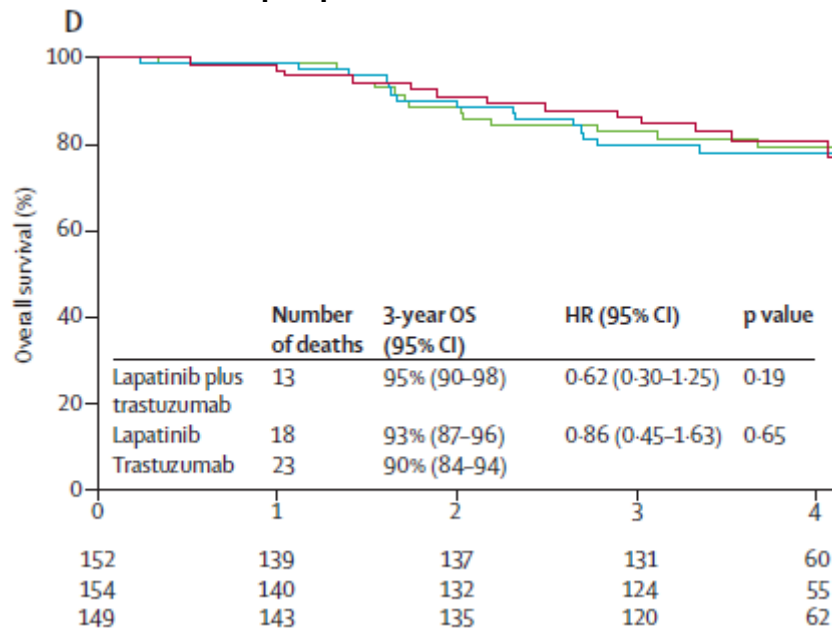


risk	0	1	2	3	4
nab	77	69	62	54	26
inib	80	67	59	53	21
nab	75	69	61	53	29

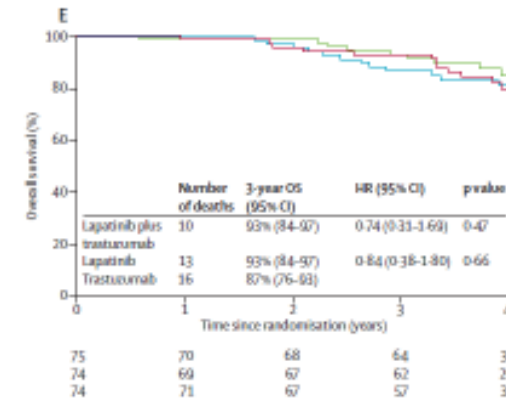
De Azambuja et al, Lancet Oncol 15;1137, 2014

NEO-ALTTO: Event-free survival

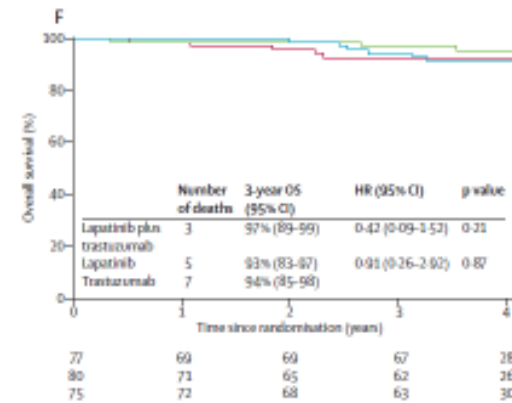
Overall survival, ITT



HR



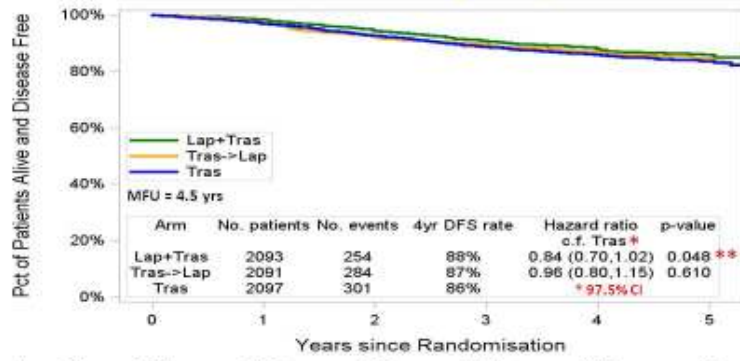
HR +



De Azambuja et al, *Lancet Oncol* 15;1137, 2014

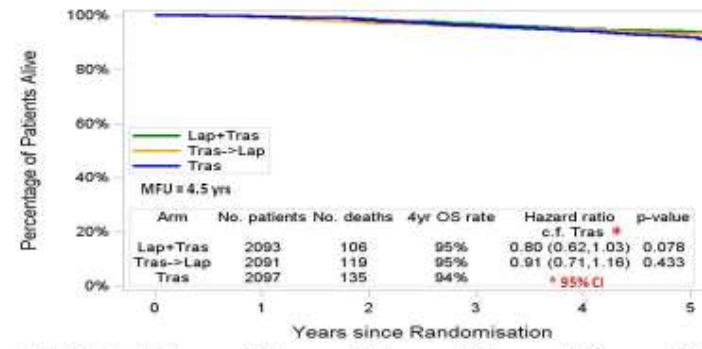
Adjuvant ALTTO trial

DISEASE-FREE SURVIVAL (DFS) ANALYSIS



Arm	No. patients	No. events	4yr DFS rate	Hazard ratio c.f. Tras*	p-value	
Lap+Tras	2093	1938	1832	1672	1256	474
Tras->Lap	2091	1957	1822	1684	1281	476
Tras	2097	1959	1838	1658	1246	448

OVERALL SURVIVAL (OS) ANALYSIS



Arm	No. patients	No. deaths	4yr OS rate	Hazard ratio c.f. Tras*	p-value	
Lap+Tras	2093	1979	1830	1785	1362	533
Tras->Lap	2091	2005	1833	1805	1368	521
Tras	2097	2023	1949	1804	1373	508

**p-value ≤ 0.025 required for statistical significance

OR for pCR tends to be smaller in studies with regimens delivering the whole chemotherapy treatment before surgery

Trial	pCR Trastuzumab	pCR Trastuzumab+ Lapatinib	OR
NSABP-B41	49.4%	60.2%	1.57
CALGB 40601	43%	52%	1.41
CHER-LOB	25%	46.7%	1.81*
TRIO-US B07	47%	52%	1.21

*Statistically significant

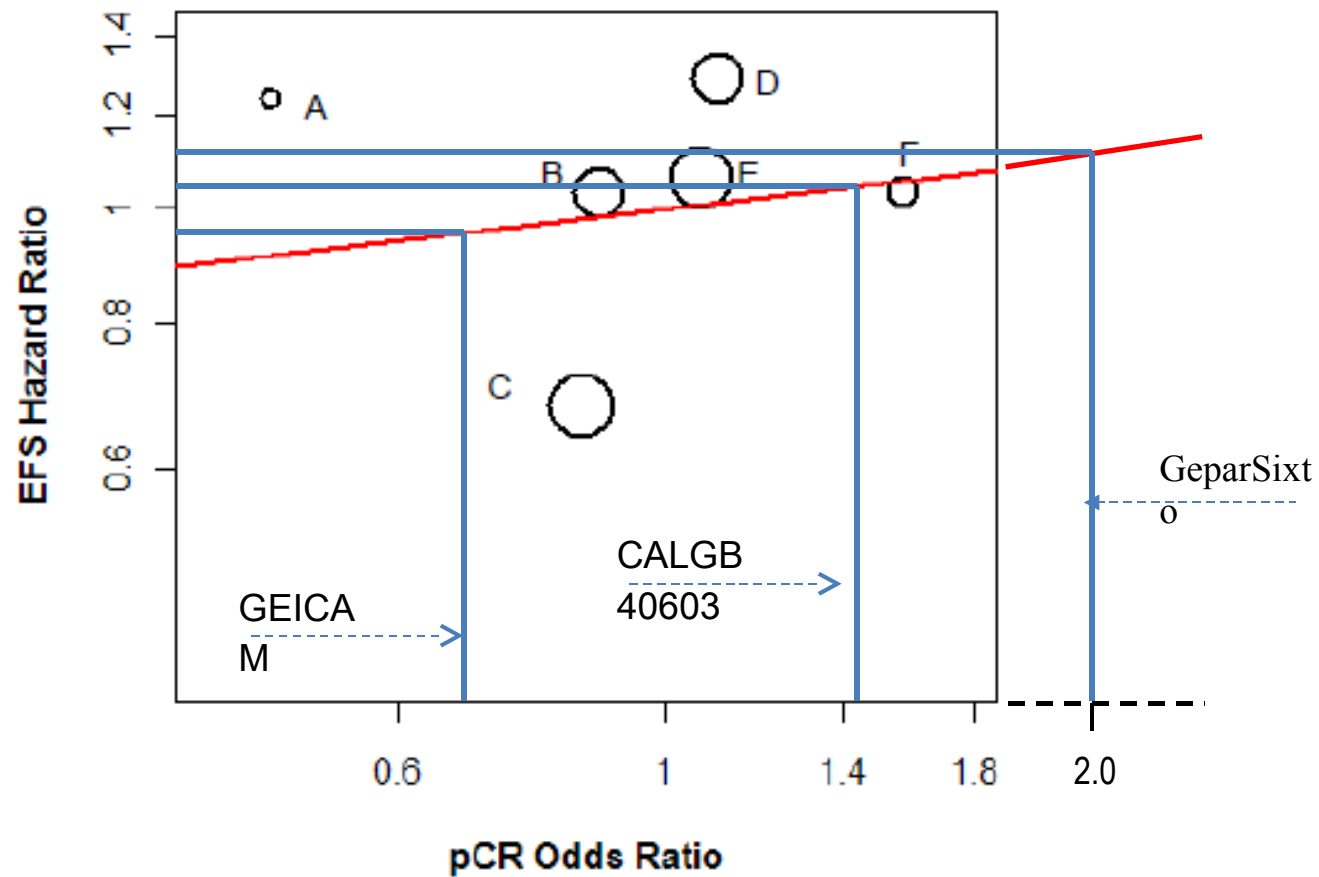
Robidoux et al, Lancet Oncol 14;1183, 2013
Carey et al, ASCO 2013, abstr 500
Guarneri et al, J Clin Oncol 30;1989, 2012

What about TNBC and carboplatin?

Trial	N randomized	pCR Chemo alone	pCR Chemo+Carboplatin	OR
CALGB 40603	218	39%	49%	1.42
GeparSixto	315	37.9%	58.7%	2.31
GEICAM 2006-03	94	35%	30%	0.77

Sikow et al, SABCS 2013, abstr S5-01
Von Minckwitz et al, ASCO 2013, abstr 1004
Alba et al, Breast Cancer Res Treat 136;487, 2012

Prediction based on the metanalysis



What are the main aims of
neoadjuvant chemotherapy?

16/09/2014 Dibattito



CHIRURGI

ONCOLOGI

ANATOMOPATOLOGI

RADIOTERAPISTI

Radiologi

Domanda 1

Domanda 1

Domanda 1

Domanda 1

Domanda 1

Domanda 2

Domanda 2

Domanda 2

Caso clinico 1

Domanda 2

Domanda 3

Domanda 3

Domanda 3

Caso Clinico 2

Domanda 3

Chirurghi domanda 1

- ❑ Quali sono gli elementi che prendi in considerazione quando ritieni che una paziente sia eleggibile per un trattamento chemioterapico neoadiuvante?

Chirurghi domanda 2

- Uno studio di chemioterapia neoadiuvante con doppio blocco di HER2 ha fatto discutere per un eccesso di mastectomie rispetto a quanto atteso (Es. studio NEO-ALTTO, Criscitiello et al, Ann Oncol 24;1980, 2013). Quali possono essere le spiegazioni ed i suggerimenti per la pratica clinica dal punto di vista chirurgico?

Dibattito

Chirurghi domanda 3

- Esiste uno strumento che permetta “misurare” l’impatto della terapia neoadiuvante sulle conversioni da mastectomia ad intervento conservativo? E’ adottabile nelle breast units?



Dibattito

Oncologi domanda 1

- ❑ Quali sono i messaggi che trasferisci alla paziente discutendo un trattamento chemioterapico neoadiuvante?



Dibattito

Oncologi domanda 2

- Utilizzi schemi chemioterapici differenti a seconda del setting neoadiuvante o adiuvante post-chirurgico?

Dibattito

Oncologi domanda 3

- Cosa comunichi ad una paziente che ha ottenuto una pCR dopo chemioterapia neoadiuvante e ad una che non l'ha ottenuta

Great, you had pCR, thus you'll do just fine!

Well, ehm, your tumor shrank...but, just a little bit, buth..ehm, no pCR and, ... well, I will see, maybe with more chemotherapy you'll do fine!



Dibattito

Anatomo Patologi domanda 1

- Una singola core biopsy è sufficiente per fornire all'oncologo medico gli elementi necessari per decidere che tipo di trattamento neoadiuvante effettuare?



Dibattito

Anatomo Patologi domanda 2

- ❑ Quanto sono fattibili (ed utili) nella pratica clinica le core biopsy multiple?



Dibattito

Anatomo Patologi domanda 3

- ❑ Che cosa preoccupa il patologo quando nel campione di un intervento conservativo non si trovano più cellule tumorali dopo neoadiuvante?



Horror Vacui #10, Londo, Uk
2011



Dibattito

Radioterapisti domanda 1

- ❑ Quali sono gli elementi che prendi in considerazione al momento dell'inquadramento terapeutico iniziale in una paziente candidata al trattamento neoadiuvante?

Radioterapisti domanda 2

- Caso clinico; paziente con tumore localmente avanzato, stadio IIIc per interessamento linfonodale sovraclavicolare in remissione completa patologica dopo chemioterapia neoadiuvante. Che ruolo ha la radioterapia?

Radioterapisti domanda 3

- Caso clinico; paziente con tumore mammario T2 di 21 mm, multiple adenopatie ascellari all'esame ecotomografico, di cui 2 biopsiate e positive. Dopo trattamento, mastectomia e dissezione ascellare con remissione completa patologica. Cosa indichi?

Dibattito

Radiologi domanda 1

- Quale impatto pensi possa avere l'uso della RMN dell'inquadramento diagnostico iniziale in una paziente candidabile a trattamento chemioterapico neoadiuvante.

Radiologi domanda 2

- Sarebbe sempre ottimale il reperimento in una paziente candidata a chemioterapia neoadiuvante?

Radiologi domanda 3

- Qual è la tecnica più promettente per prevedere precocemente la remissione completa patologica durante trattamento neoadiuvante?