“Genes and signatures” associati a pCR: i dati derivanti dagli studi clinici

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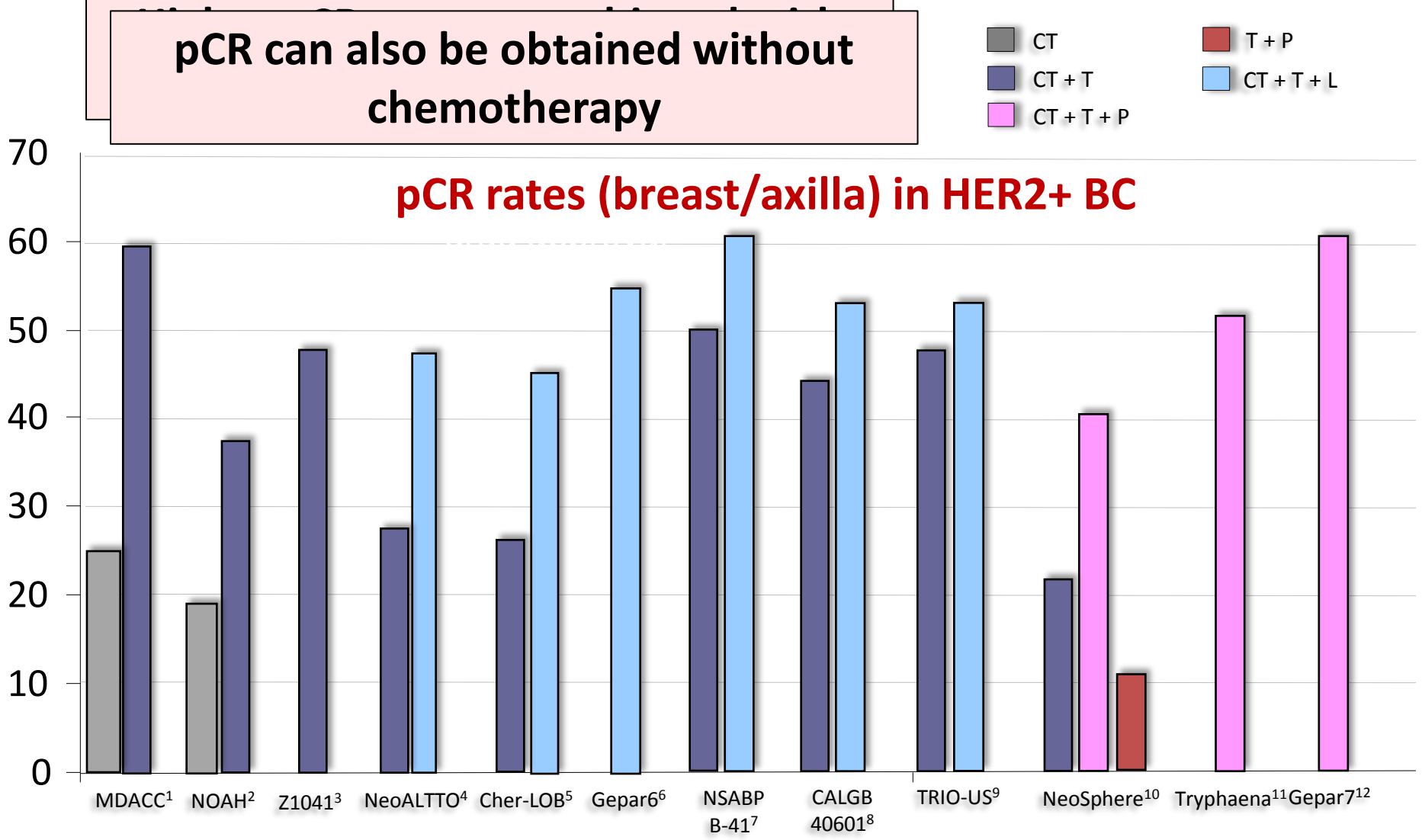
Optimizing patients selction

- **HER2+ BC:** predicting response to HER2-targeted agents
  - Gene-expression and intrinsic subtypes
  - PIK3CA mutational status
- **HR+ BC:** chemo vs endocrine neoadjuvant treatment
  - Gene-expression profiling

  can we predict sensitivity to additional agents?
  - PIK3CA mutational status
- **TNBC:** Taclking tumor heterogeneity

Neoadjuvant therapy in HER2+ BC

pCR can also be obtained without chemotherapy



1. Buzdar AU, J Clin Oncol 2005, CCR 2007; 2. Gianni L, Lancet 2010. 3. Buzdar AU, Lancet Oncol 2013. 4. Baselga J. Lancet 2012; 5. Guarneri V. J Clin Oncol 2012; 6. von Minckwitz. Lancet Oncol 2014; 7. Robidoux A. Lancet Oncol 2013; 8. Carey L .ASCO 2013; 9. Hurvitz S SABCS 2013 10. Gianni L . Lancet Oncol 2012; 11. Schneeweiss A . Ann Oncol 2013 ; 12 Untch M. SABCS 2014;

pCR rates are lower in HR+ HER2+ BC

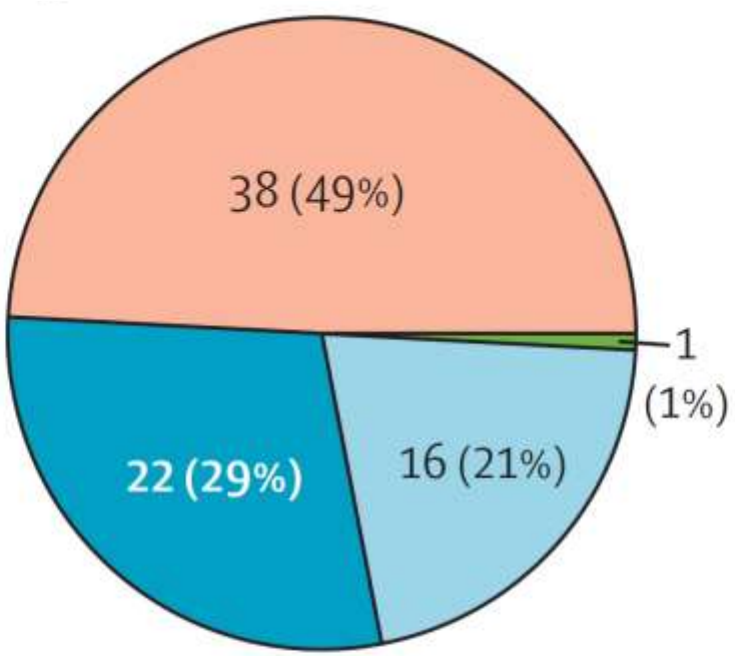
Trial	HER2 targeted agents	pCR in HR+	pCR in HR-
NeoSphere[1]	**Pertuzumab** + Trastuzumab	26%	63%
NeoALTTO[2]	**Lapatinib** + Trastuzumab	42%	61%
CALGB 40601[3]	**Lapatinib** + Trastuzumab	42%	77%
TRYPHAENA[4]	**Pertuzumab** + Trastuzumab	46-50%	65-84%
NeoSphere[1] (chemofree arm)	**Pertuzumab** + Trastuzumab	5.9%*	27.3%*
TBCRC-006[5]	**Lapatinib** + Trastuzumab (+ endocrine if HR+)	21%*	36%*
PAMELA[6]	**Lapatinib** + Trastuzumab (+ endocrine if HR+)	18.2%*	43.2%*
CherLOB[7]	**Lapatinib** + Trastuzumab	27%	44%

*pCR in breast only

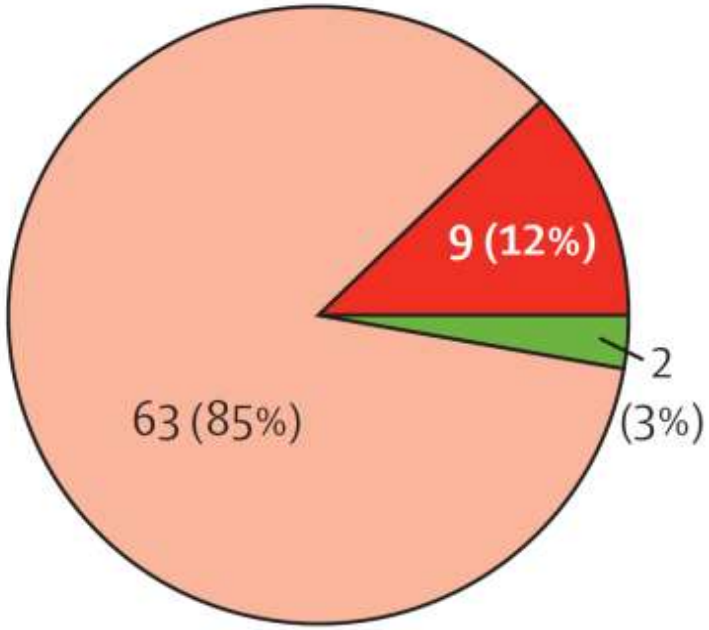
1. Gianni L, et al. Lancet Oncol 2012. 2. Baselga J, et al. Lancet 2012 and de Azambuja E, et al. Lancet Oncol 2014. 3. Carey LA, et al. J Clin Oncol 2016.4. Schneeweiss A, et al. Ann Oncol 2013. 5. Rimawi MF, et al. J Clin Oncol 2013. 6. Llombart-Cussac A, et al. Lancet Oncol 2017. 7. Dieci et al,The Oncologist 2015

Intrinsic subtypes and heterogeneity in HER2+ BC

HR+/HER2+



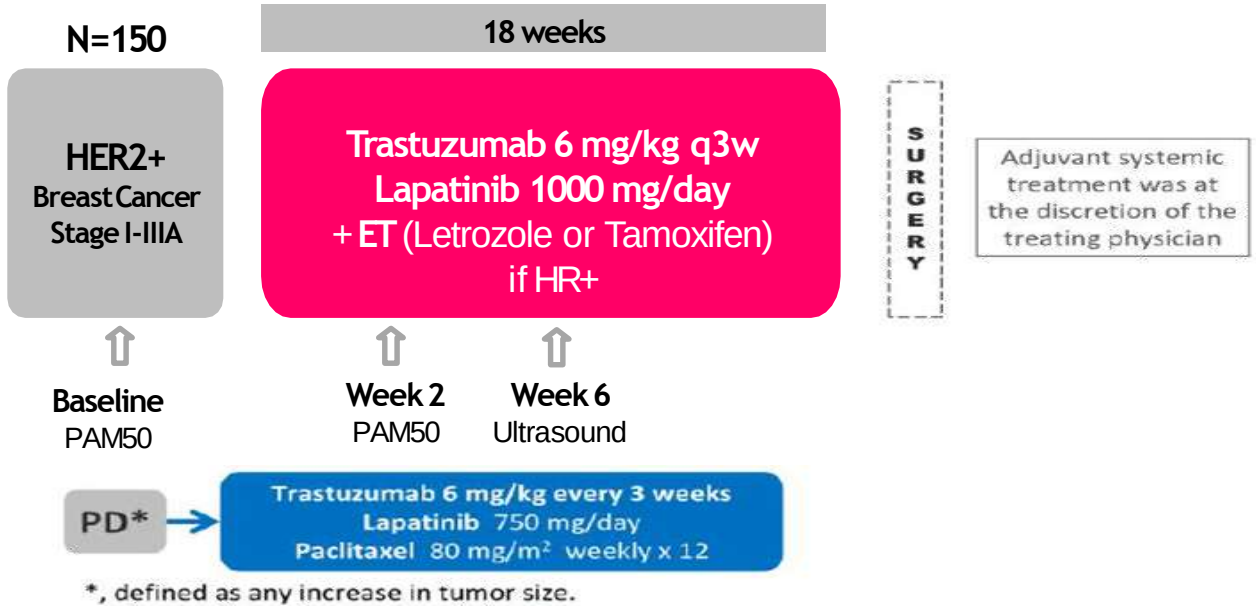
HR-/HER2+



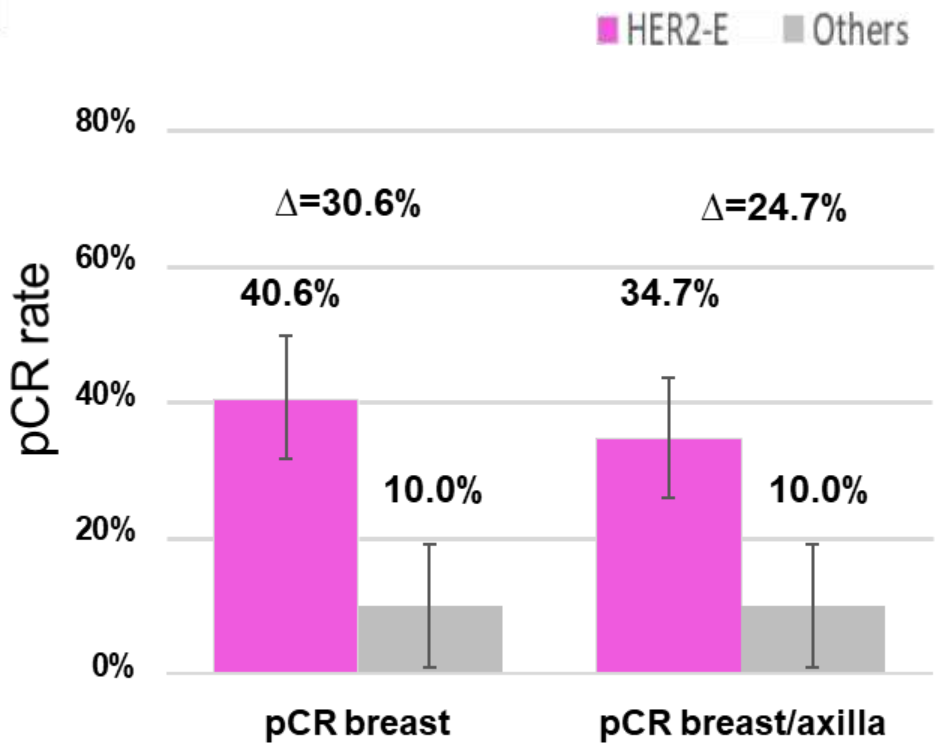
Luminal A
Luminal B
HER2-enriched
Basal-like
Normal-like

Llombart-Cussac et al. Lancet Oncology 2017

PAMELA: Intrinsic Subtype as a predictor of response to a neoadjuvant anti-HER2-based chemo-free regimen



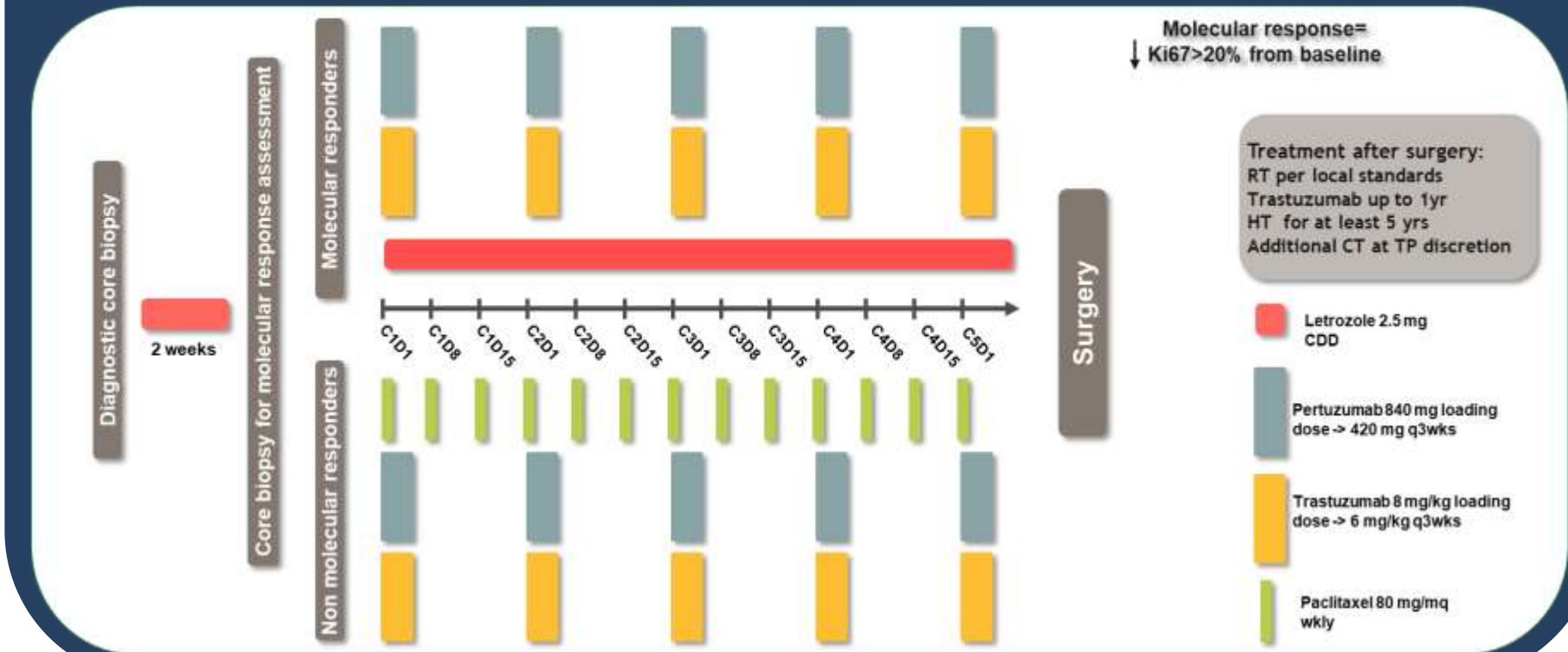
HER2-enriched tumors presented significantly **higher pCR rates**



Prat A, et al. SABCS 2016. Llombart-Cussac A, et al. Lancet Oncol 2017

PerElisa

Preoperative Study With Trastuzumab, Pertuzumab and Letrozole in Patients With Breast Cancer Sensitive to Hormonal Therapy



Main inclusion criteria:

- Stage II-IIIA breast cancer
- HR positivity (ER≥10%)
- HER2 positivity (IHC 3+ or ISH +)
- Postmenopausal status

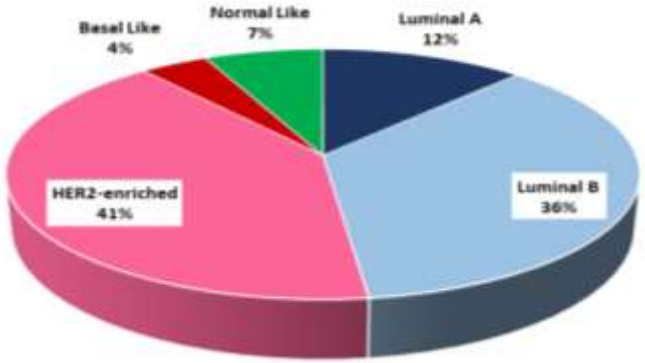
Primary endpoint:

- pathologic complete response (pCR) rate in breast and axilla (8pCR/43 responder pts)

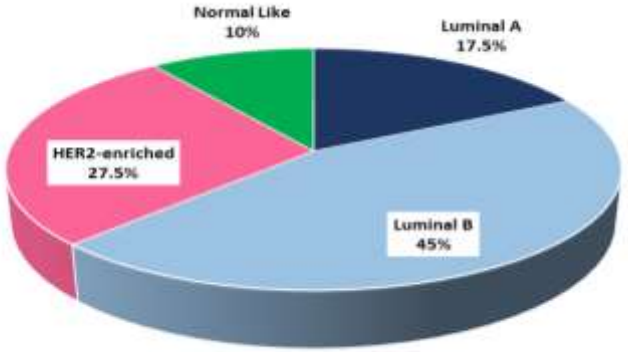
Investigator-driven, non profit study.
EUDRACT 2013-0022662-40

Guarneri V et al. Ann Oncol 2019

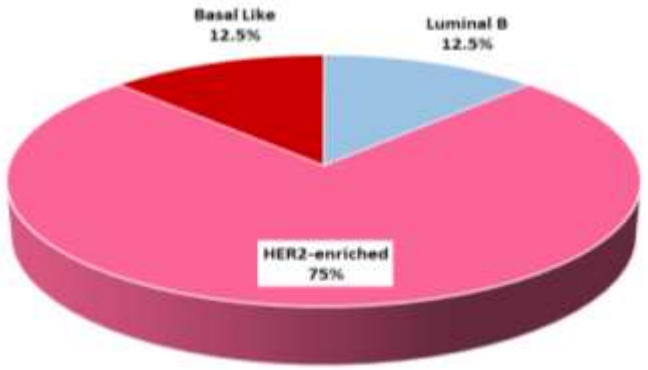
PAM50 subtype according to molecular response



Overall



Molecular responder



Molecular non responder

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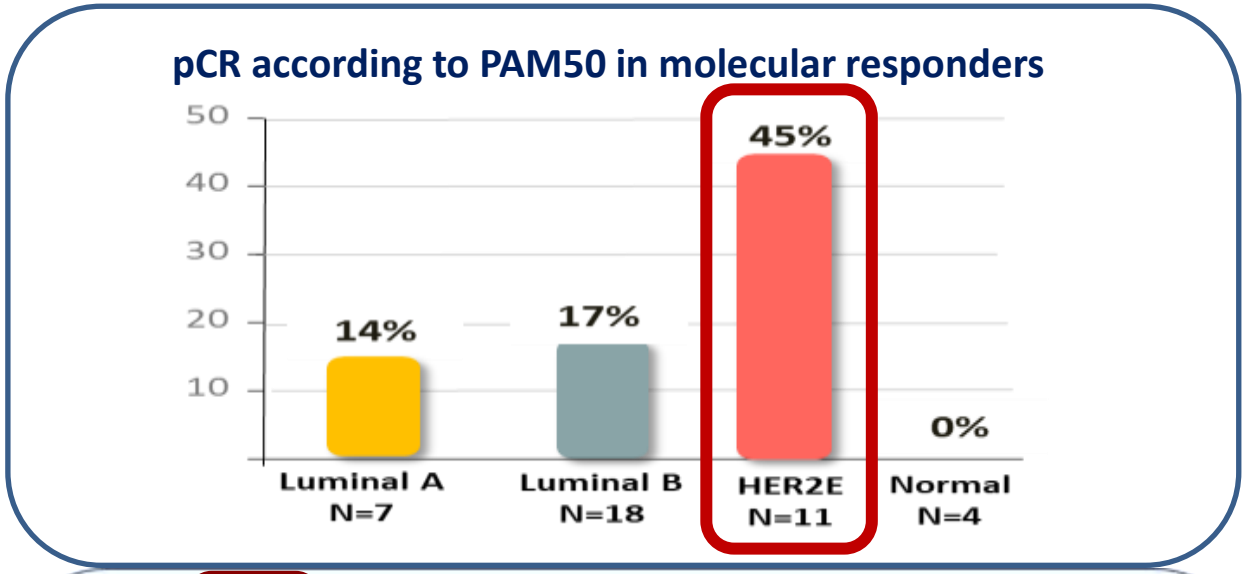
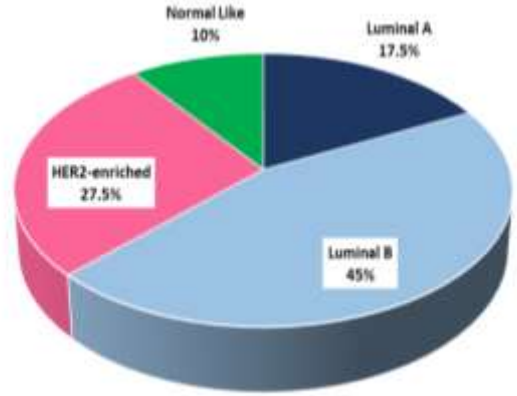
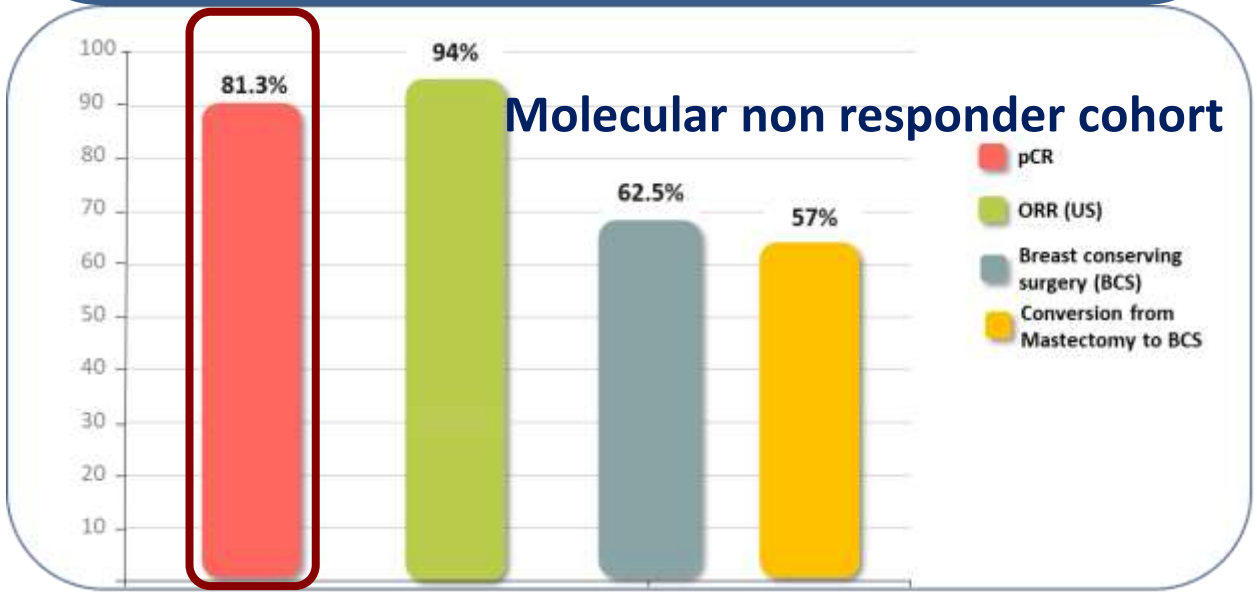
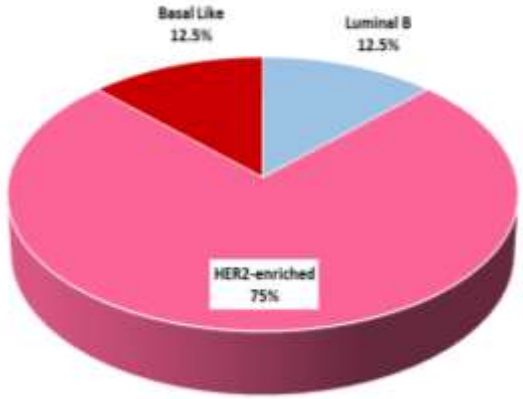
Efficacy outcomes









Guarneri V et al. Ann Oncol 2019

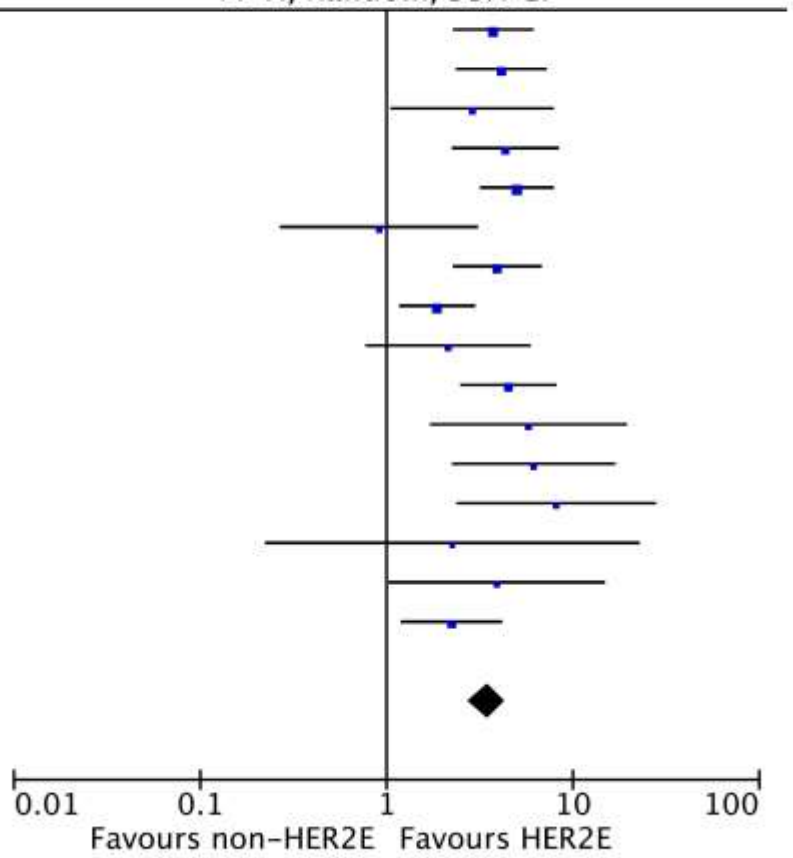
HER2-enriched subtype and pCR following anti-HER2-based neoadjuvant treatment

(16 studies – 2,703 patients)

Study or Subgroup	HER2E Events	HER2E Total	non-HER2E Events	non-HER2E Total	Weight	Odds Ratio M-H, Random, 95% CI
BERENICE	130	175	52	119	10.4%	3.72 [2.27, 6.11]
CALGB40601	57	82	64	180	9.2%	4.13 [2.36, 7.24]
Cher-LOB	11	22	16	62	4.1%	2.88 [1.05, 7.90]
ICO-CLINIC	63	102	19	70	7.5%	4.34 [2.24, 8.40]
KRISTINE	131	194	47	160	11.3%	5.00 [3.18, 7.87]
LPT109096	30	41	15	20	2.9%	0.91 [0.27, 3.10]
NeoALTTO	57	110	31	144	9.4%	3.92 [2.27, 6.77]
NEOSPHERE	53	135	52	202	11.0%	1.86 [1.17, 2.98]
NOAH	18	34	10	29	4.0%	2.14 [0.77, 5.93]
NSABP-B41	120	197	19	74	8.6%	4.51 [2.49, 8.18]
Opti-HER HEART	25	30	13	28	3.0%	5.77 [1.71, 19.42]
PAMELA	41	101	5	50	4.1%	6.15 [2.25, 16.81]
PerELISA	15	23	6	32	2.9%	8.13 [2.36, 27.93]
TBCRC006	6	22	1	7	0.9%	2.25 [0.22, 22.79]
TBCRC023	14	51	3	34	2.5%	3.91 [1.03, 14.86]
TRYPHAENA	57	82	46	91	8.1%	2.23 [1.19, 4.16]
Total (95% CI)		**1401**		**1302**	**100.0%**	**3.50 [2.79, 4.39]**
Total events	828		399			

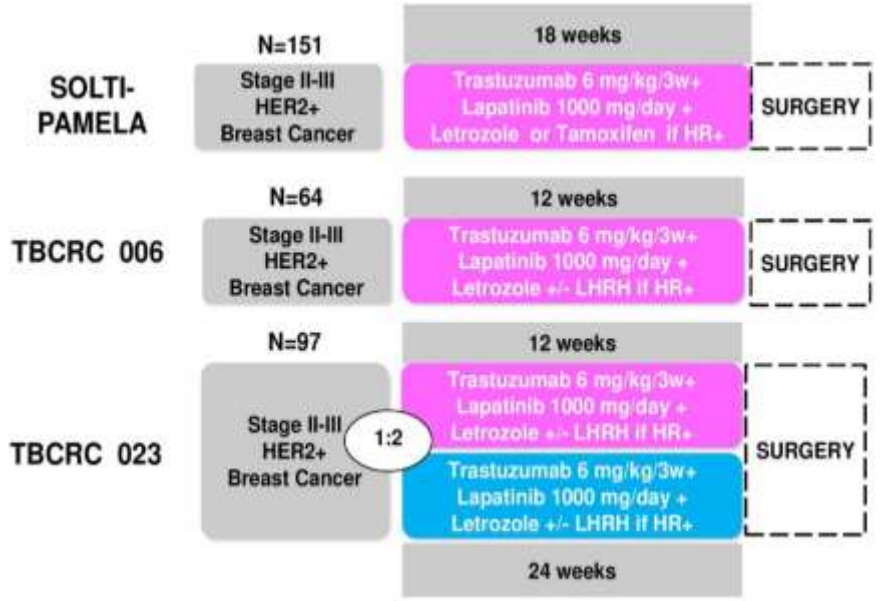
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 22.51$, df = 15 (P = 0.10); $I^2 = 33\%$

Test for overall effect: Z = 10.80 (P < 0.00001)



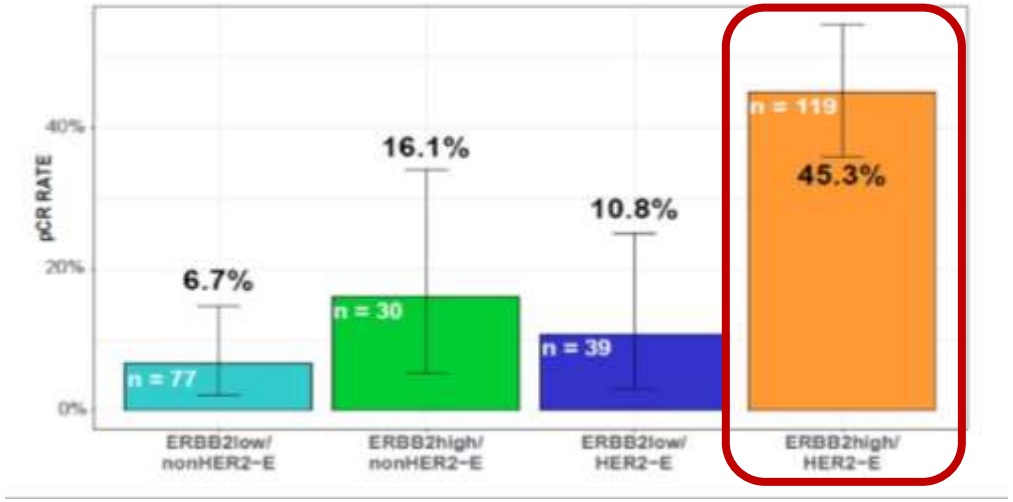
Schettini F, ESMO 2019

Refining biomarkers to predict pCR in early HER2+ BC treated with dual HER2-blockade (w/o chemo)



A cutoff for ERBB2 expression (high vs low) was determined on samples from the PAMELA trial

and was then applied on the combined three study cohort

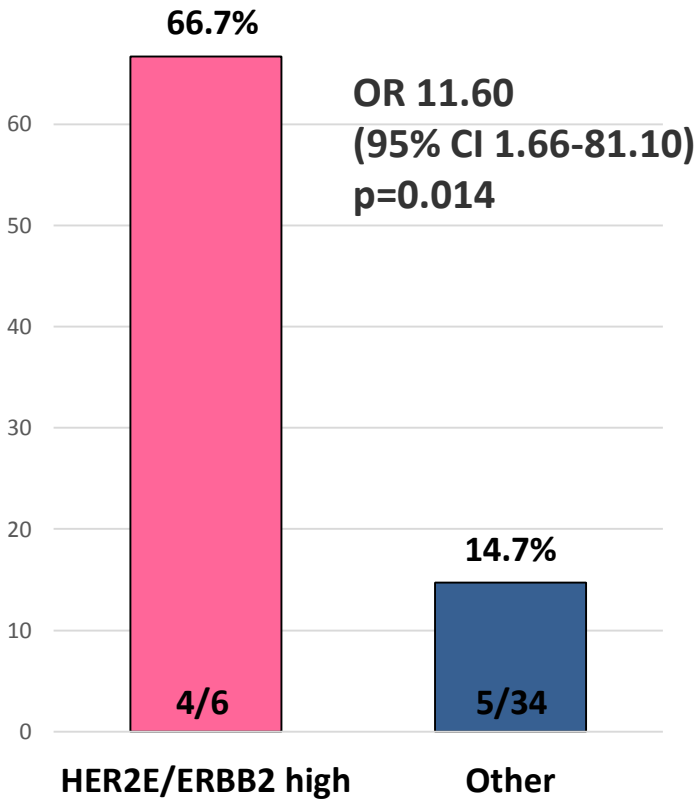


Combining HER2-E and ERBB2 mRNA levels better identifies anti-HER2 sensitivity than each variable alone

Prat A et al, ASCO 2018, JNCI 2019

Combined biomarker to predict pCR in early HER2+ BC treated with dual HER2-blockade (w/o chemo)

pCR rates according to combined biomarker in responder cohort



The combined biomarker (HER2E/ERBB2 high) confirmed its association with pCR in the molecular responder cohort of the PerElisa trial

Prat A et al, JNCI 2019

Refining biomarkers to predict pCR in early HER2+ BC: 41-gene classifier TRAR

Association of TRAR with pCR in the NeoALTTO trial (N=226)

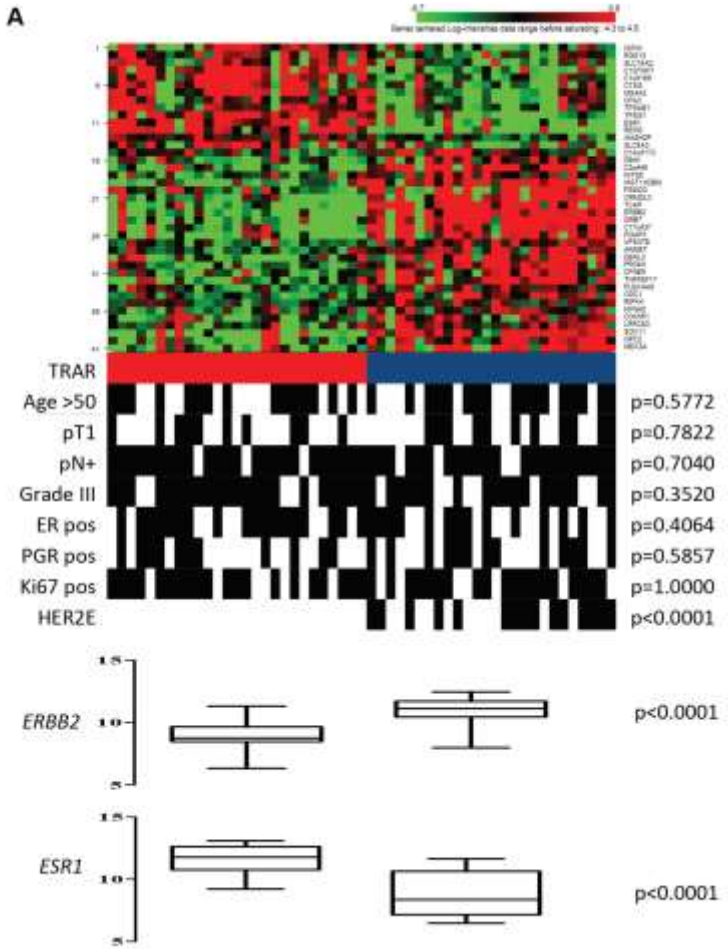
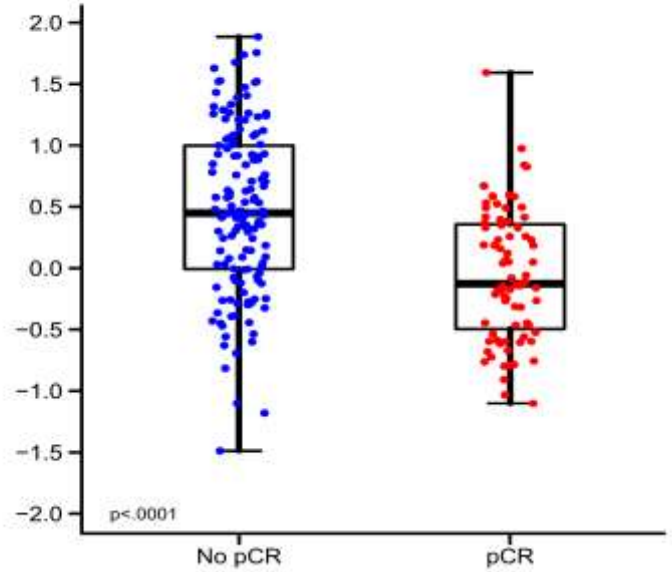


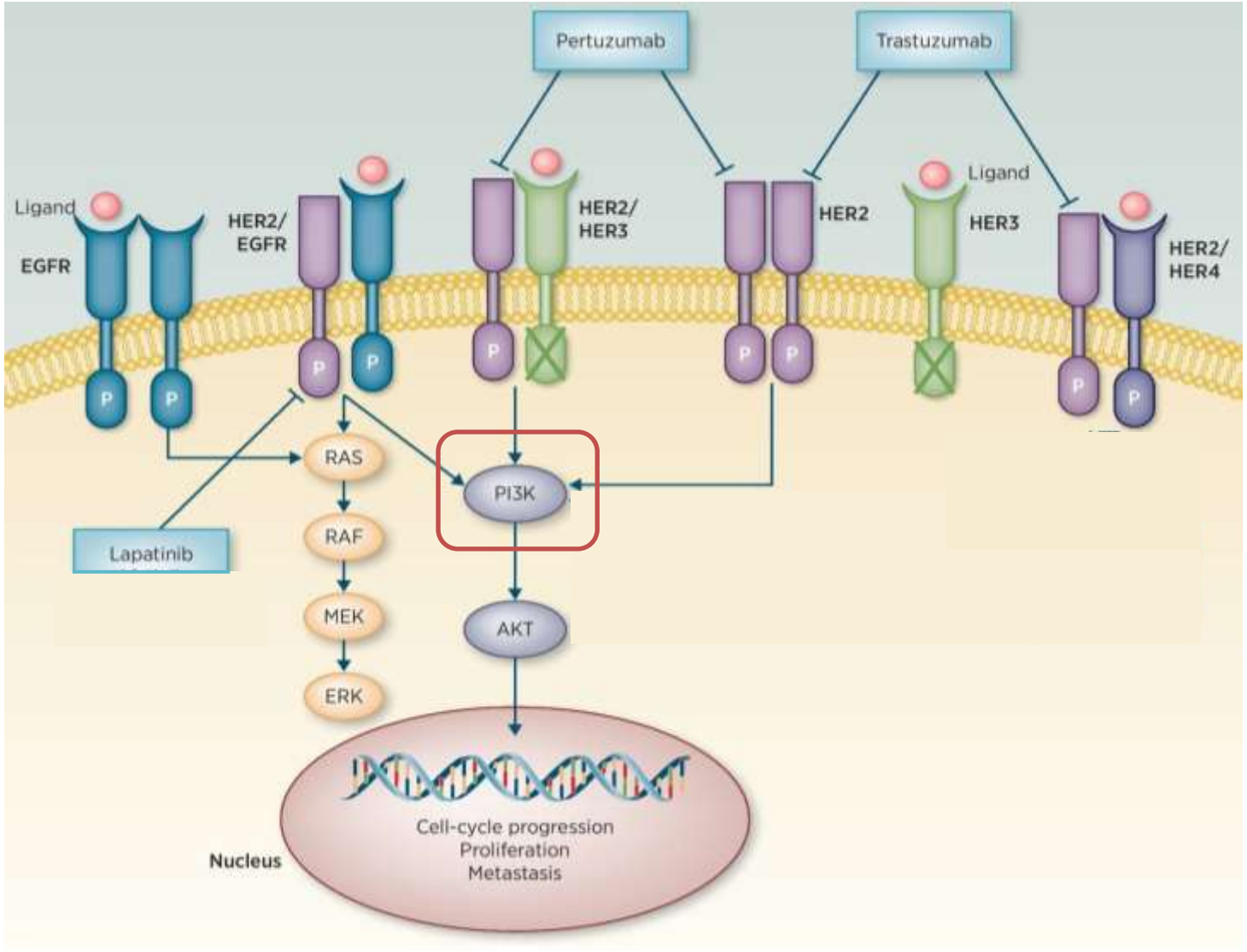
Table 1
Association of TRAR and clinicopathological variables with pathological complete response (pCR): Univariate and multivariate logistic regression model.

Variables	Univariate OR (95% CI)	Multivariate OR (95% CI)
TRAR score	**0.25 (0.15–0.42)**	**0.26 (0.14–0.47)**
Treatment		
L versus T	0.95 (0.46–1.97)	0.95 (0.43–2.09)
L+T versus T	**2.77 (1.39–5.52)**	**3.08 (1.45–6.58)**
ER status		
Neg versus Pos	**2.62 (1.46–4.69)**	1.25 (0.61–2.57)
Age	0.99 (0.96–1.01)	
Tumour size		
≤5 versus > 5	0.91 (0.52–1.59)	
Nodal status		
N0/1 versus ≥ N2	0.62 (0.31–1.26)	



Triulzi T et al, OncoTarget 2015, Di Cosimo S et al, Eur J Cancer 2019

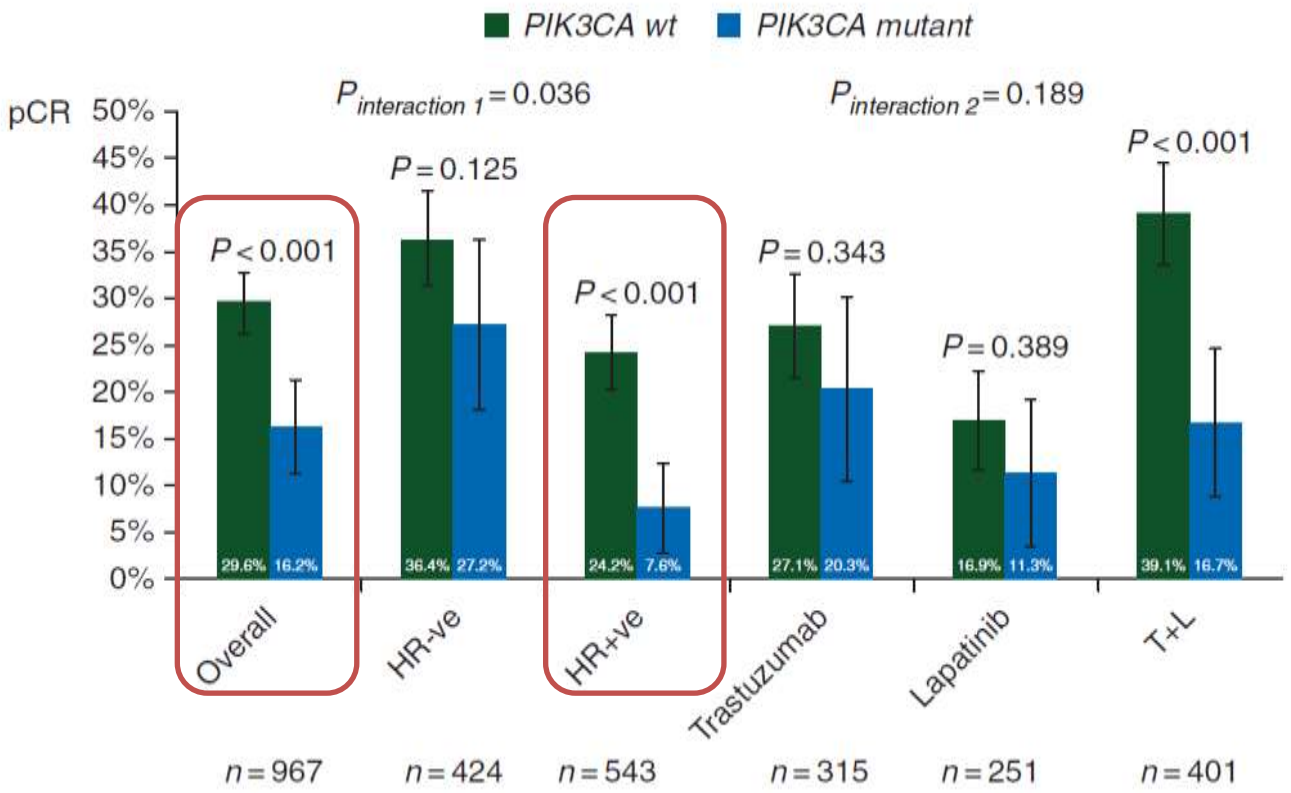
HER2 Signaling and PI3K pathway



Netanya I. Pollock, and Jennifer R. Grandis Clin Cancer Res 2015

PIK3CA mutations are associated with reduced pathological complete response rates in primary HER2-positive breast cancer: pooled analysis of 967 patients from five prospective trials investigating lapatinib and trastuzumab†

S. Loibl[1*], I. Majewski[2], V. Guarneri[3], V. Nekljudova[1], E. Holmes[4], E. Bria[5], C. Denkert[6], C. Schem[7], C. Sotiriou[8], S. Loi[9], M. Untch[10], P. Conte[3], R. Bernards[2], M. Piccart[8], G. von Minckwitz[1] & J. Baselga[11]



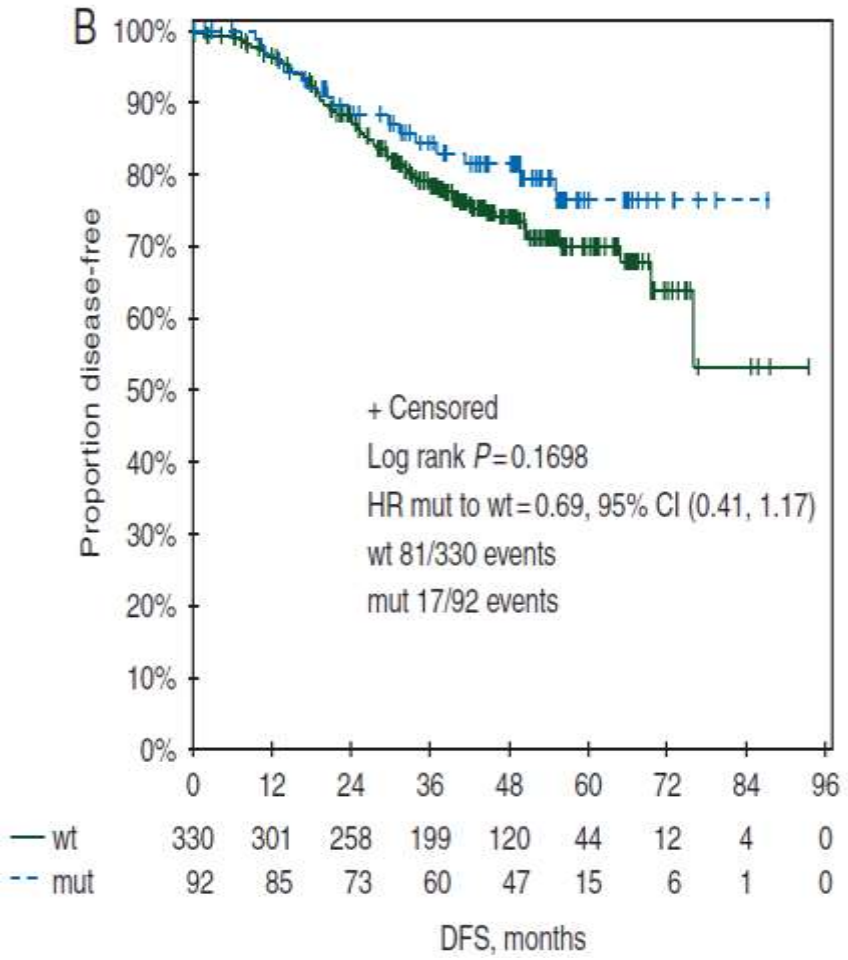
- N=967 (GeparQuattro, GeparQuinto, GeparSixto, NeoALTTO, CHERLOB)
  Chemotherapy + antiHER2 (single vs. dual)
- **pCR rate was lower for PIK3CA mut** compared with wt (16.2% vs 29.6%; P<0.001)
- In **HR+HER2+ BC**, **PIK3CA mut** had a pCR rate of only 7.6% (vs 24.2% of wt; p<0.001)

Loibl S, et al. Ann Oncol 2016

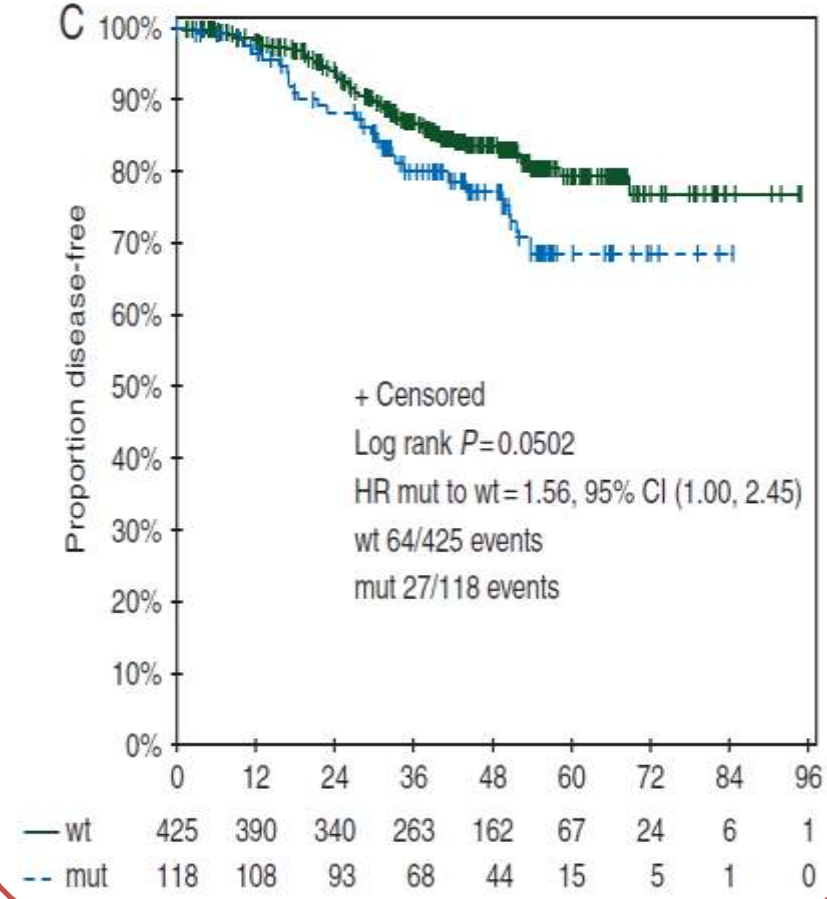
PIK3CA mut tumors have worse survival in HER2+/HR+ BC

N=967 (GeparQuattro, GeparQuinto, GeparSixto, NeoALTTO, CHERLOB)
Chemotherapy + antiHER2 (single vs. dual)

HER2+/HR-

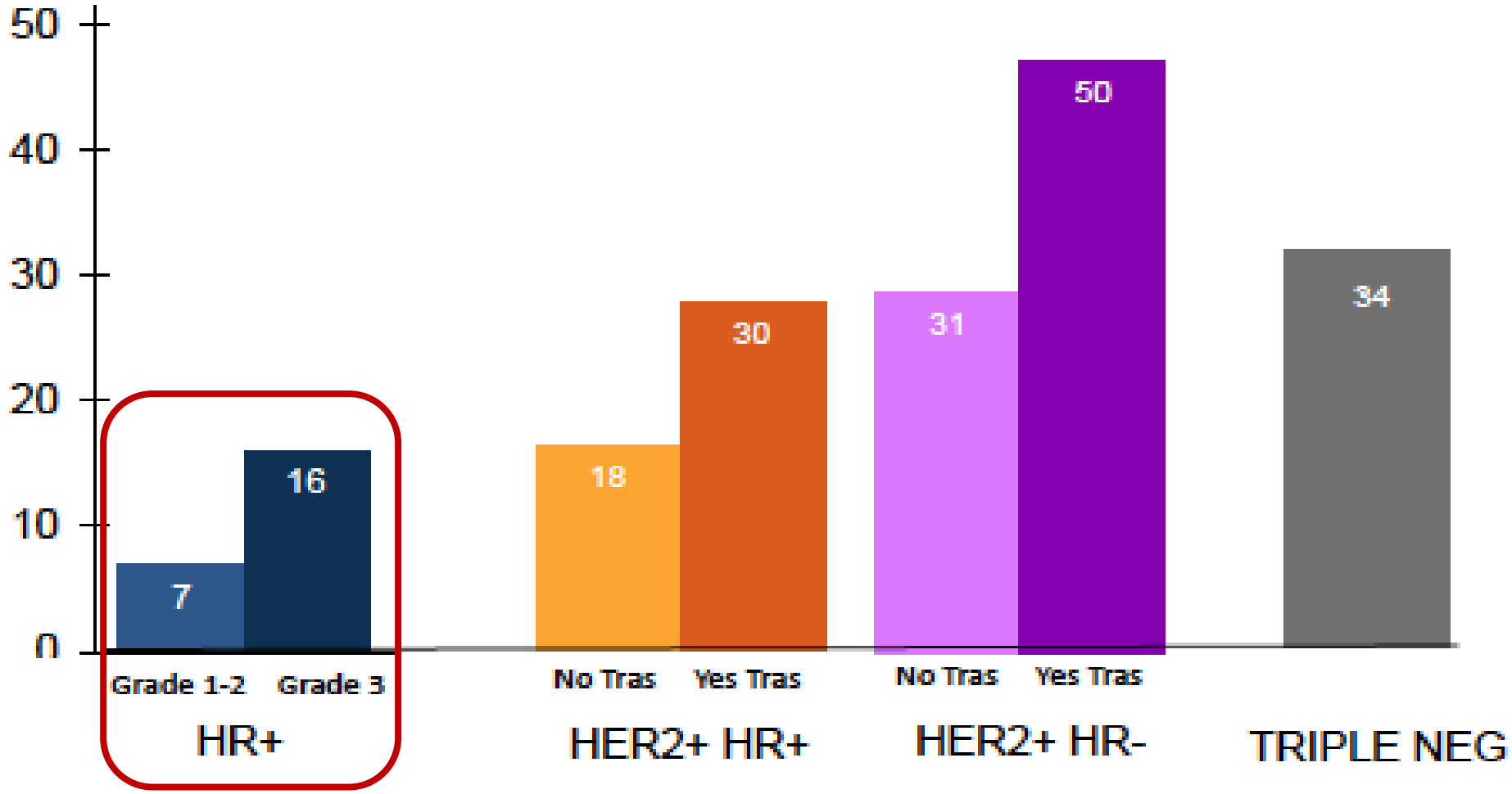


HER2+/HR+



Loibl S, et al. Ann Oncol 2016

pCR rates by tumor subtypes



Cortazar P et al; Lancet, 2014

Strategies in the neoadjuvant therapy of HR+ BC

- Tumor biology, rather than stage, is the driver of treatment selection
- Many patients with HR+/HER2- disease can be offered adjuvant hormonal therapy alone, even in case of N+ disease
- Aromatase inhibitors have opened the possibility of using HT as neoadj treatment

	NET	N	Duration	Clinical Response
Thomas (2007)	Letrozole	103	3 months	89% vs 85%
Semiglazov (2007)	Anastrazole or Exemestane	239	3 months	65% vs 64%
Generali (2011)	Letrozole	114	6 months	73% vs 88%
Alba (2011)	Exemestane +/- goserelin	95	6 months	48% vs 66%
Palmieri (2014)	Letrozole	44	18-23 weeks	59% vs 55%

Patient selection remains a problem

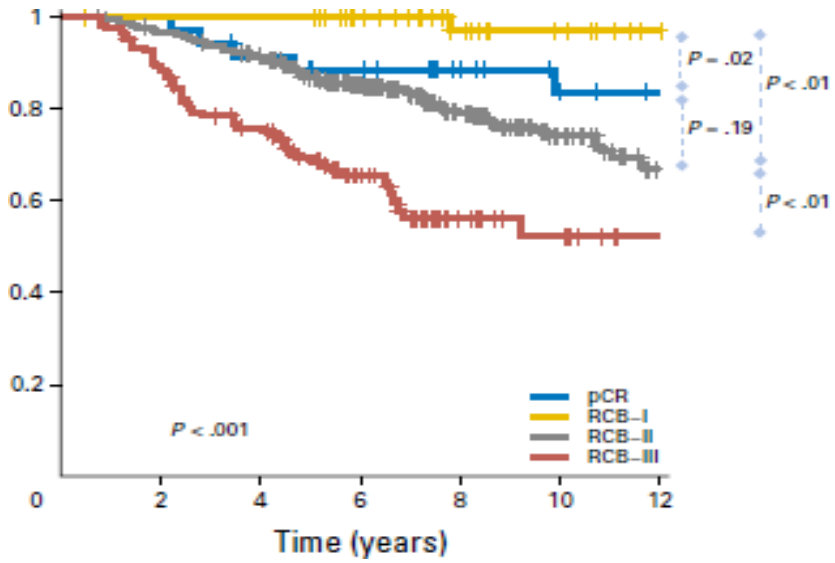
Charehbili et al. Can Treat Rev 2014

Goals of neoadjuvant therapy in HR+ BC

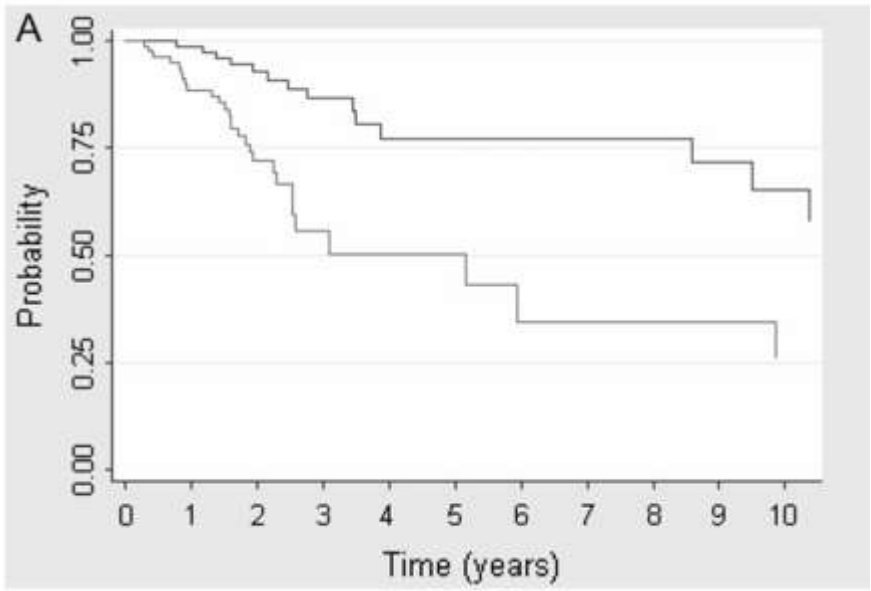
- Improve surgical options and reduce the extent of surgery (ORR and BCS)
- Refine prognosis based on response to neoadjuvant treatment

Which response predicts for long term prognosis?

Residual Cancer Burden (RCB)[1]
standardized method to assess pathological response after NACT



Biological Response[2]
DFS according to post-treatment Ki67≥15% vs < 15%

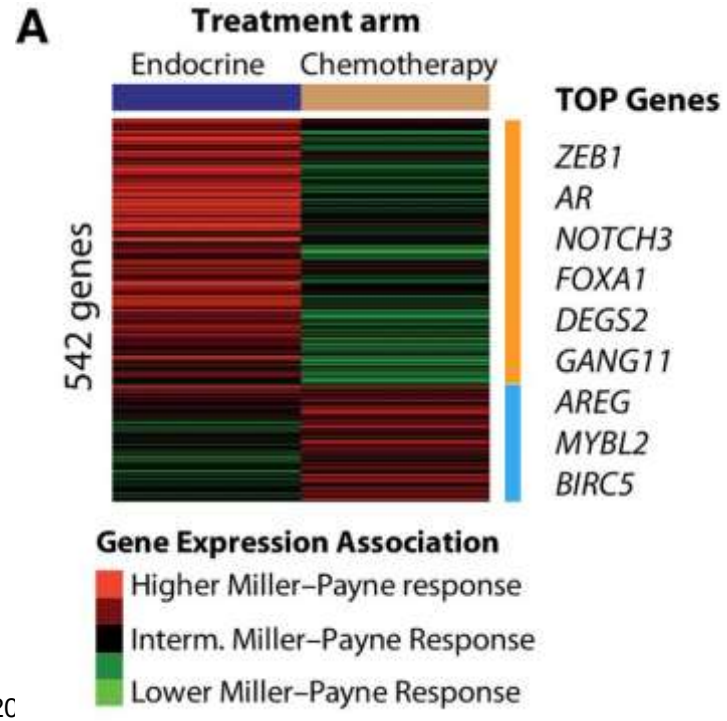


[1]Symmans et al, JCO 2017; [2] Guarneri V et al, Ann Oncol 2009

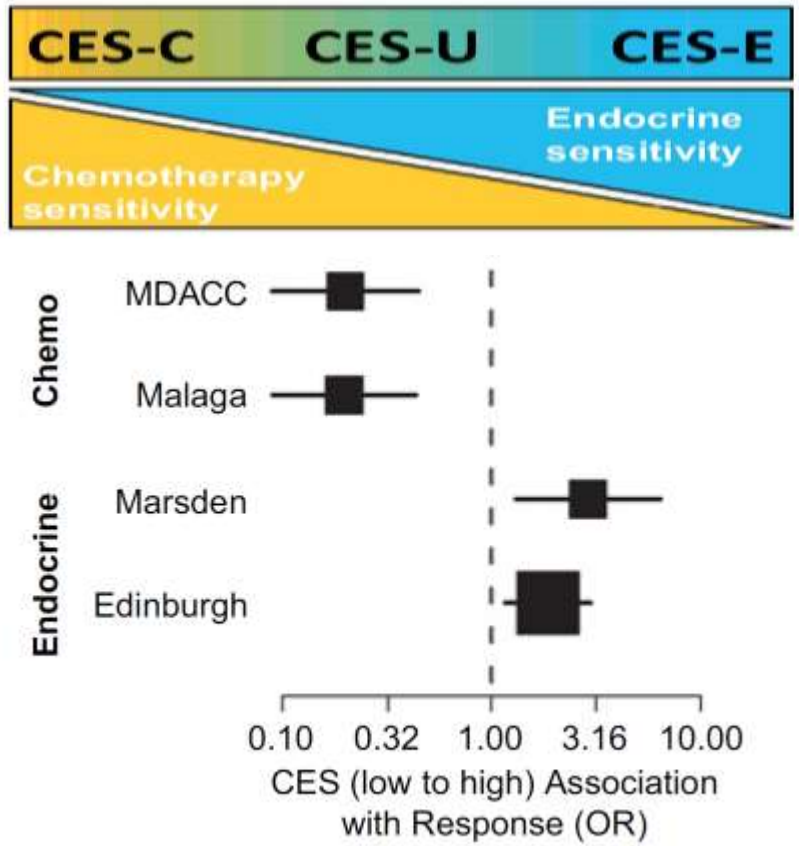
Endocrine sensitivity vs Chemosensitivity

In BC endocrine sensitivity and sensitivity to chemotherapy are biologically opposite phenomena

Genes whose expression is associated with endocrine sensitivity are usually associated, at the same time, with chemotherapy resistance, and vice versa.



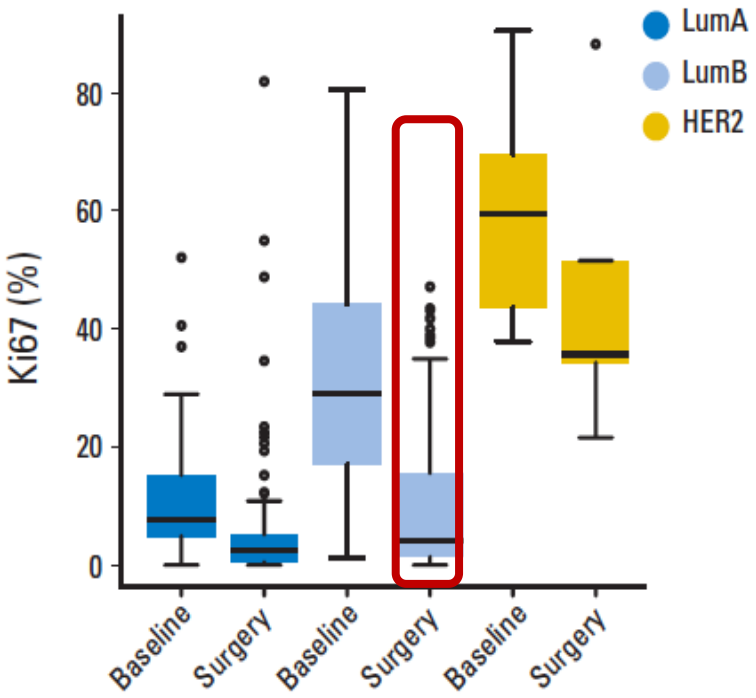
CES = CC to Luminal A –CC to Basal-like



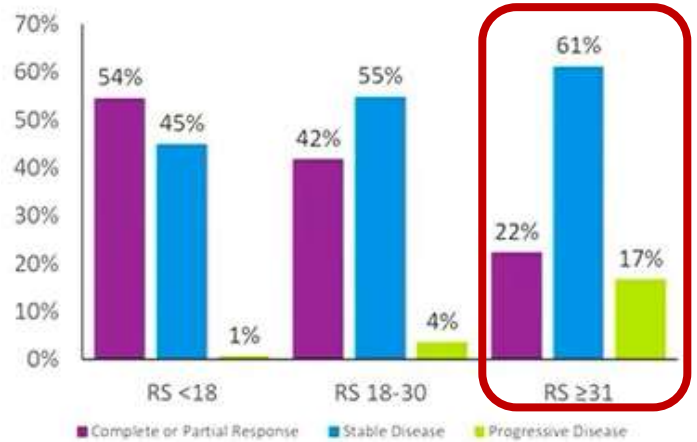
Prat A et al. Clin Cancer Res 20

Biology predicts response to neoadjuvant HT

Ki67 suppression by PAM50 subtype in patients receiving neoadjuvant AIs



Clinical response by OncotypeDX RS in patients receiving neoadjuvant AIs



Clinical response, n	RS <18	RS 18-30	RS ≥31	Total
CR + PR	85	35	12	132
SD	70	46	33	149
PD	1	3	9	13
Total	156	84	54	294

But none of these methods are validated for use in clinical practice as tests to decide if a patient should receive neoadjuvant CT or HT

Ellis M et al, J Clin Oncol 2011

Iwata et al, SABCS 2017

Biology predicts response to neoadjuvant HT

989 patients identified from the National Cancer Database:

- available RS
- underwent neoadjuvant CT

TABLE 1 Study cohort characteristics according to pCR subgroup

Characteristic	No pCR $n = 947$ (95.8%) %	PCR $n = 42$ (4.3%) %	p value
Age (years)			
Mean (SD)	54.6 (11.0)	51.4 (12.3)	
Ethnicity			
Non-hispanic white	97.0	3.0	< 0.001
Other	91.6	8.4	
Clinical T stage			
T1	98.6	1.4	< 0.001
T2/T3	93.6	6.5	
Node status			
Negative	95.2	4.8	0.152
Positive	97.4	2.6	
Tumor grade			
1	99.2	0.8	< 0.001
2	97.3	2.7	
3	92.3	7.7	
Oncotype score			
Low	97.8	2.2	< 0.001
Intermediate	98.4	1.6	
High	90.4	9.6	

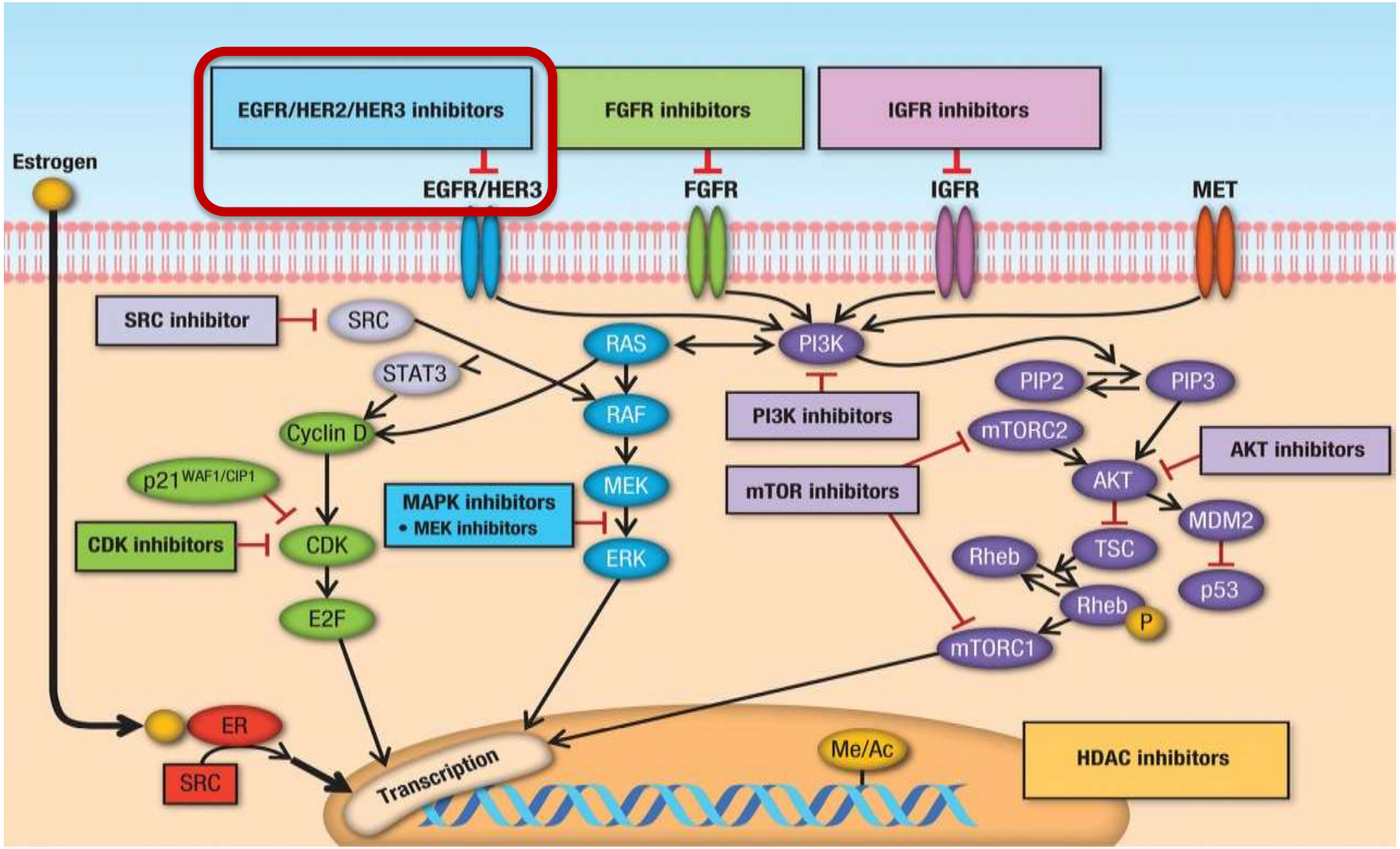
<18
18-30
>30

High RS was positively associated with **pCR** (compared to intermediate RS): **OR 6.73; 95% CI 2.92–15.54**

Multivariable logistic regression analysis confirmed association between **pCR and high RS: OR 4.87; 95% CI 2.01–11.82**

Pease MA et al, Ann Surg Oncol 2018

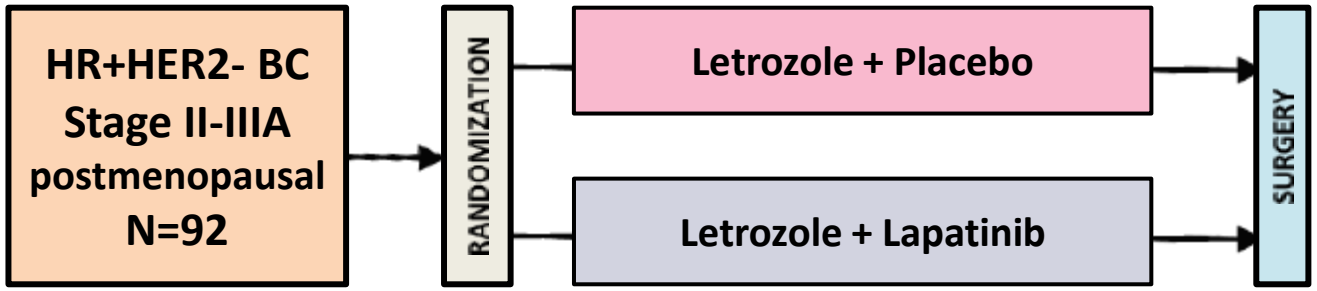
Can novel agents address resistance to HT in a biologically driven way?



Johnston S. et al JNCI 2015

LET-LOB trial: preoperative letrozole +/- lapatinib for HR+HER2- operable BC

6 months

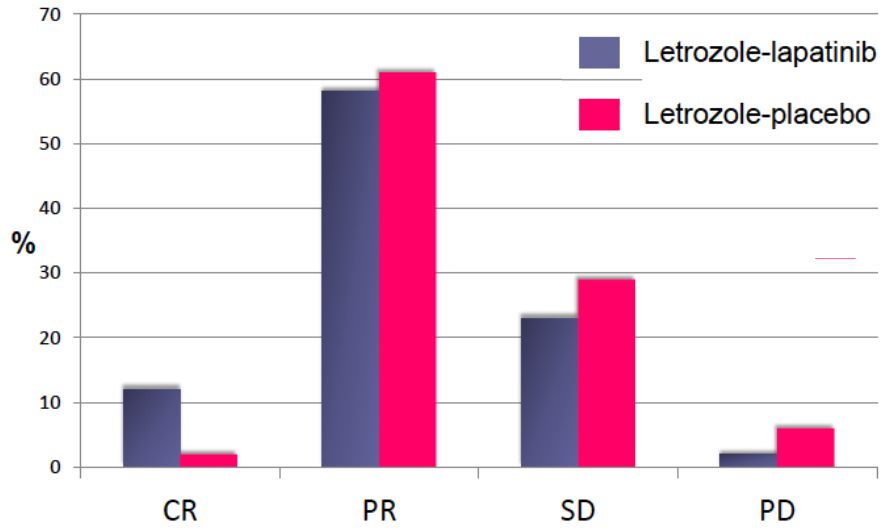


Endpoint

clinical response assessed by US

clinical objective response

Response rate per treatment arm



Numerically similar clinical response rates (CR+PR) were observed:

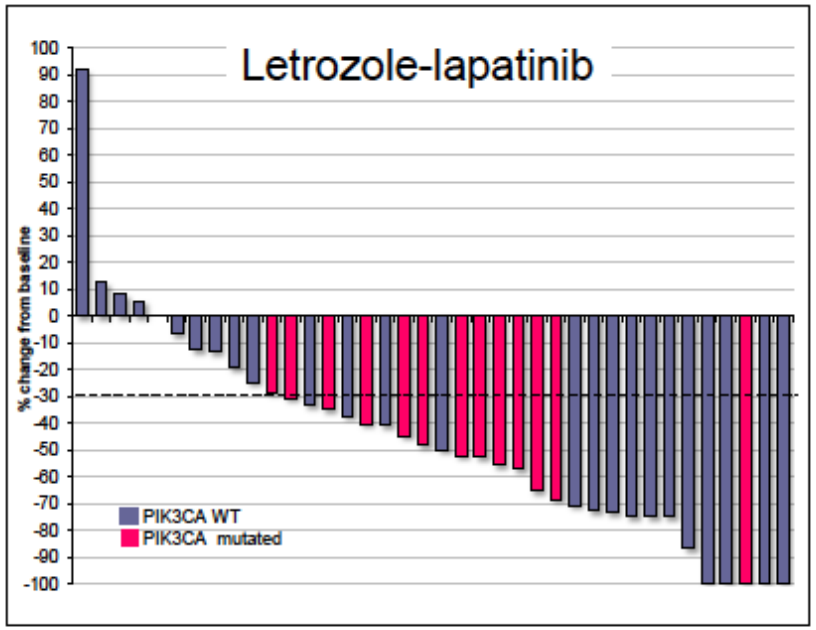
- 70% for letrozole-lapatinib
- 63% for letrozole-placebo

Guarneri V, et al JCO 2014

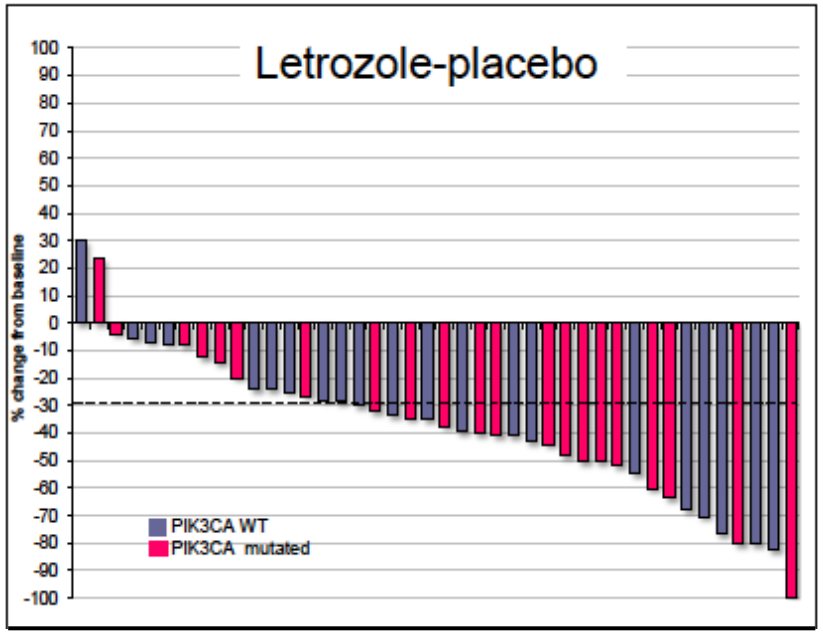
LET-LOB trial: preoperative letrozole +/- lapatinib for HR+HER2- operable BC

Responses (ORR) according to PIK3CA status

63% in WT tumors
vs 93% in PIK3CA mutated tumors
p=0.037

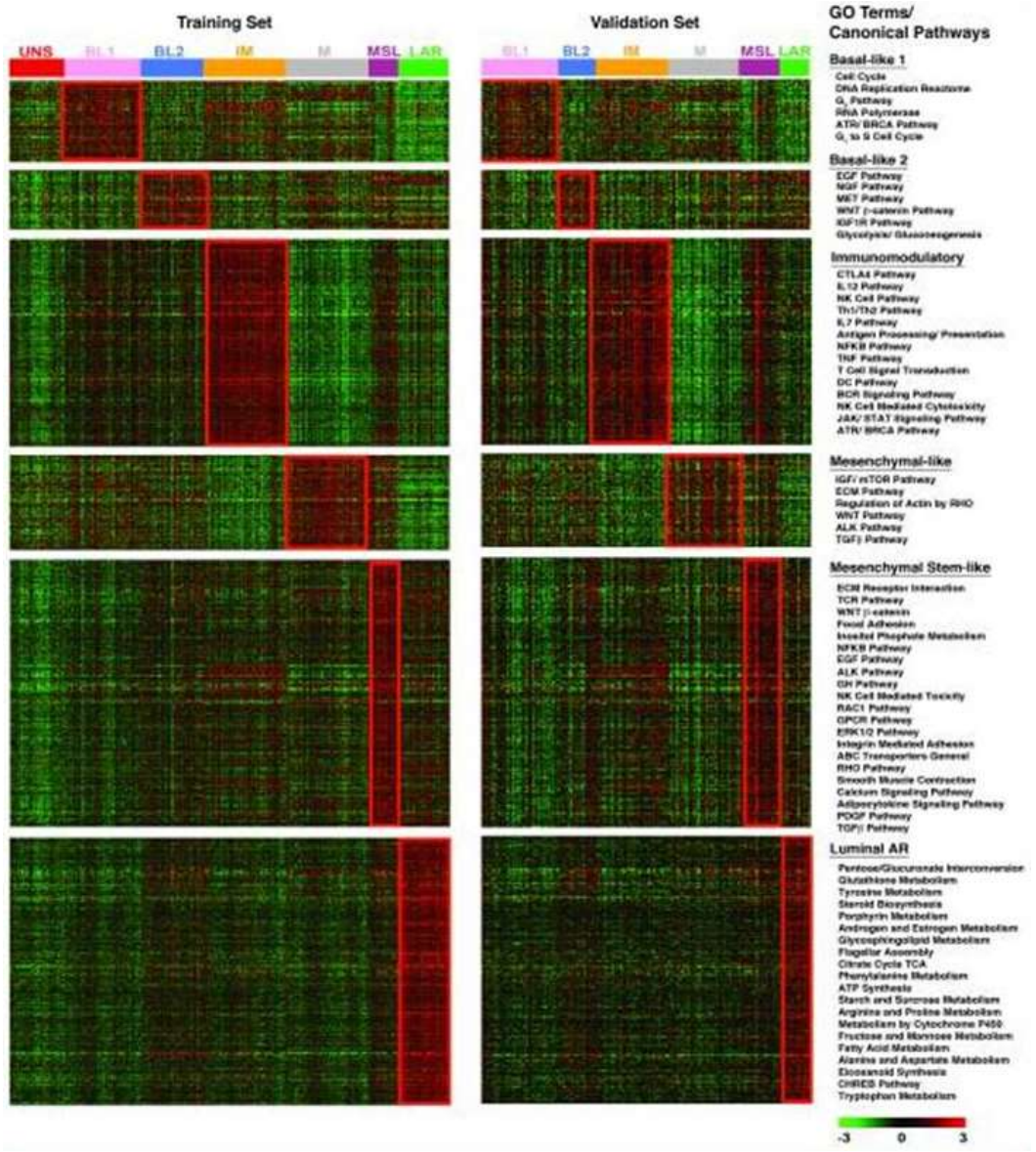


66% in WT tumors
vs 63% in PIK3CA mutated tumors
p=0.79



Guarneri V, et al JCO 2014

Tackling TNBC heterogeneity



Basal-like 1: cell cycle, DNA repair and proliferation genes

Basal-like 2: growth factors (EGFR, MET, Wnt, IGF1R)

Immunomodulatory: Immune signalling

Mesenchymal-like and **Mesenchymal stem-like**: EMT, motility and growth-factor pathways

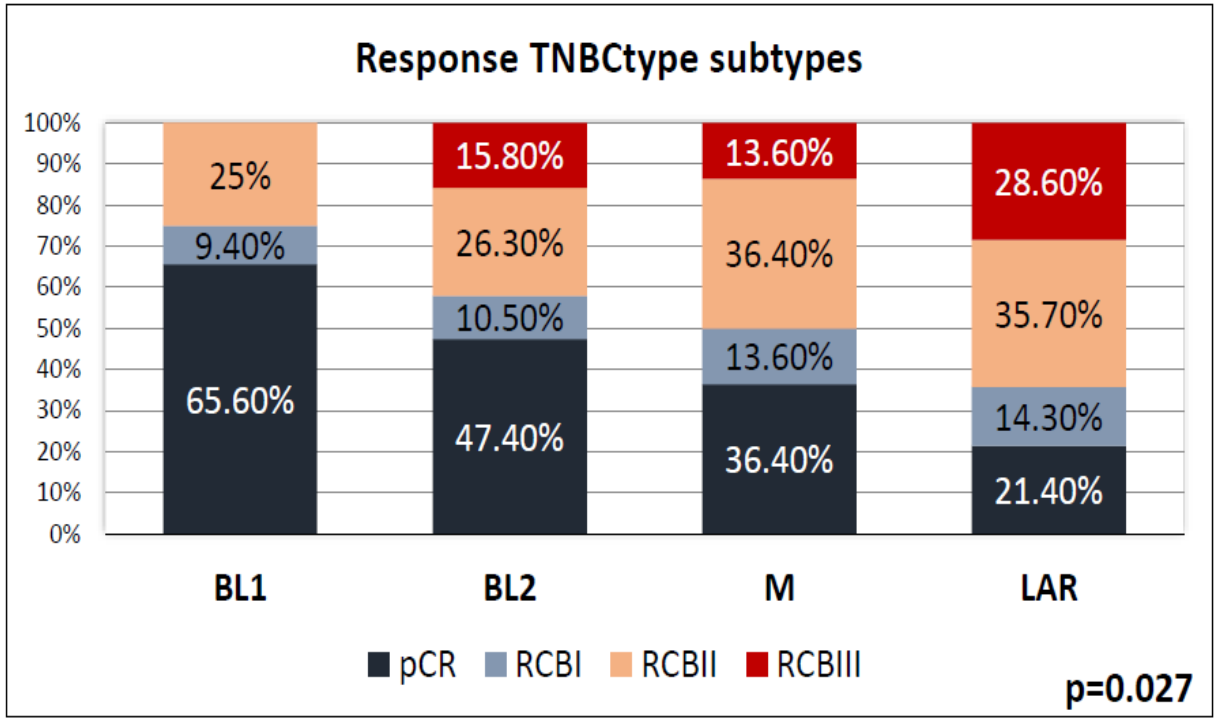
Luminal AR: Androgen receptor signaling

Lehmann et al, JCI 2011

TNBC subtypes predict for response to CT

	BL1	BL2	M	LAR	P
N	32	19	22	14	
Age median	41	51	50.5	67.5	<0.001
T size (median)	48	40	40	58.5	0.40
N + (%)	78.1%	52.6%	63.6%	85.7%	0.13
Median Ki67	80%	60%	70%	40%	<0.001
G3 (%)	84.4%	63.2%	72.7%	64.3%	0.17

- BL1 was associated with a significant younger age at diagnosis and higher ki67 values.



Echavarria Diaz-Guardamino et al, CCR 2018

Conclusions

- Neoadjuvant treatment gives the opportunity to **test tumor biology** and **refine prediction of prognosis** based on response
- Evaluation of gene expression profiling and mutational status can help predict response to neoadjuvant treatment, but are **not** currently **validated in the clinic**
- More and more trials are selecting patients based on GEP and mutational status, so this will probably change in the near future