Terapia neo-adiuvante
MALATTIA TRIPLO NEGATIVA

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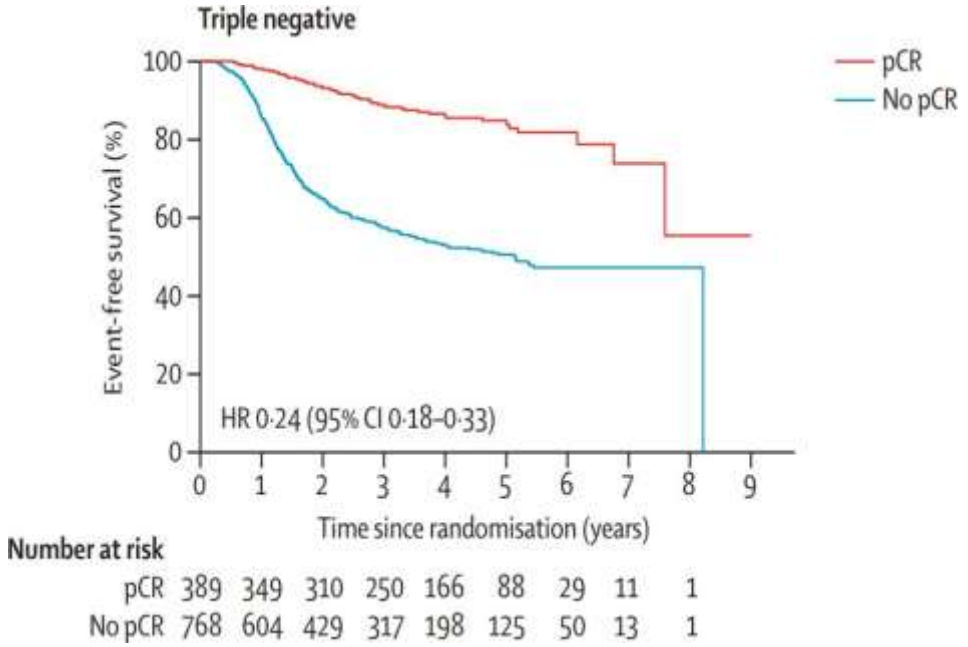
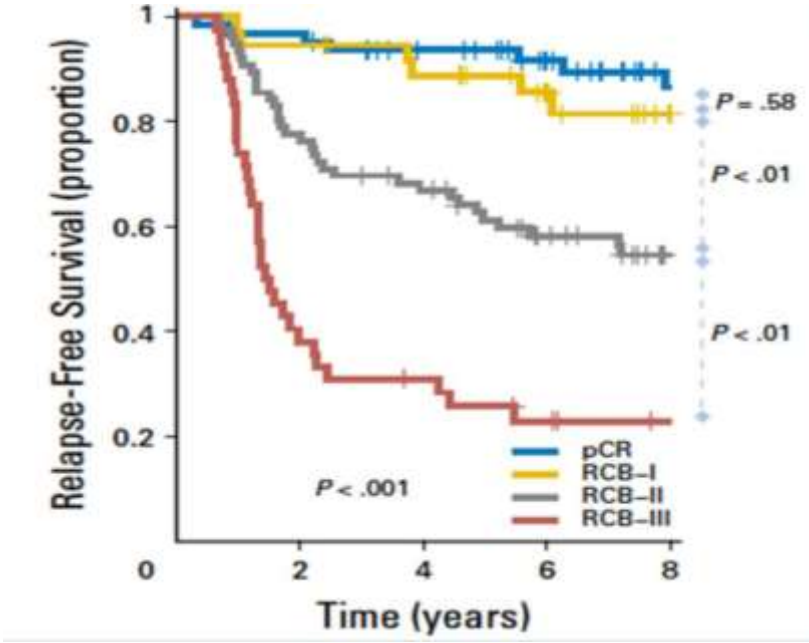
Neoadjuvant treatment for TNBC: what is the aim?

pCR
and long-term outcome in TNBC



Cortazar P, et al. Lancet Oncol 2014

Residual Cancer Burden
and long-term outcome in TNBC



TNBC N=219

RCB-0 (pCR)	35%
RCB-1	16%
RCB-2	33%
RCB-3	17%

Symmans et al. J Clin Oncol 2017

Neoadjuvant treatment for TNBC: what was new in 2017?

- Platinum salts
- PARPi
- Immune-checkpoints inhibitors
- Predictive markers

Neoadjuvant treatment for TNBC: what was new in ~~2017~~ 2018?

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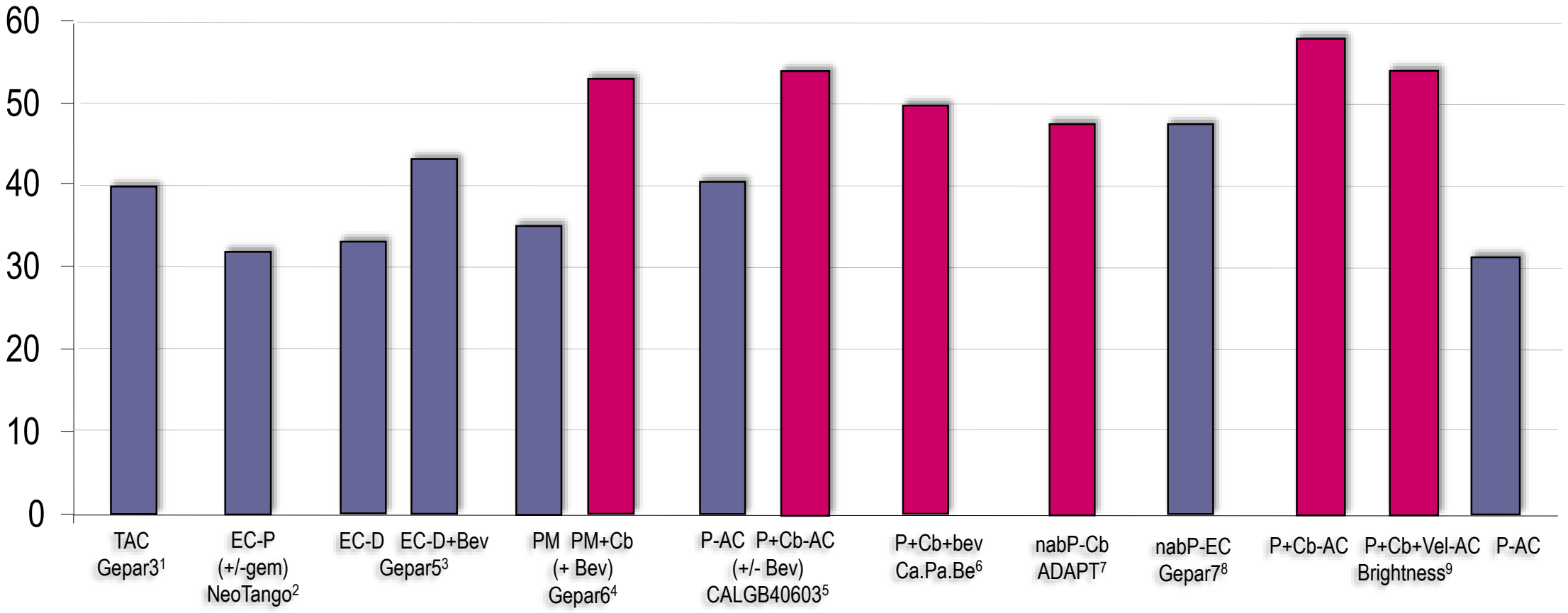
Neoadjuvant treatment for TNBC: what was new in ~~2017 2018~~ 2019?

- Platinum salts — The Old and Debated
- PARPi
- Immune-checkpoints inhibitors

} The New and Shiny

- Predictive markers — The Sacred Graal

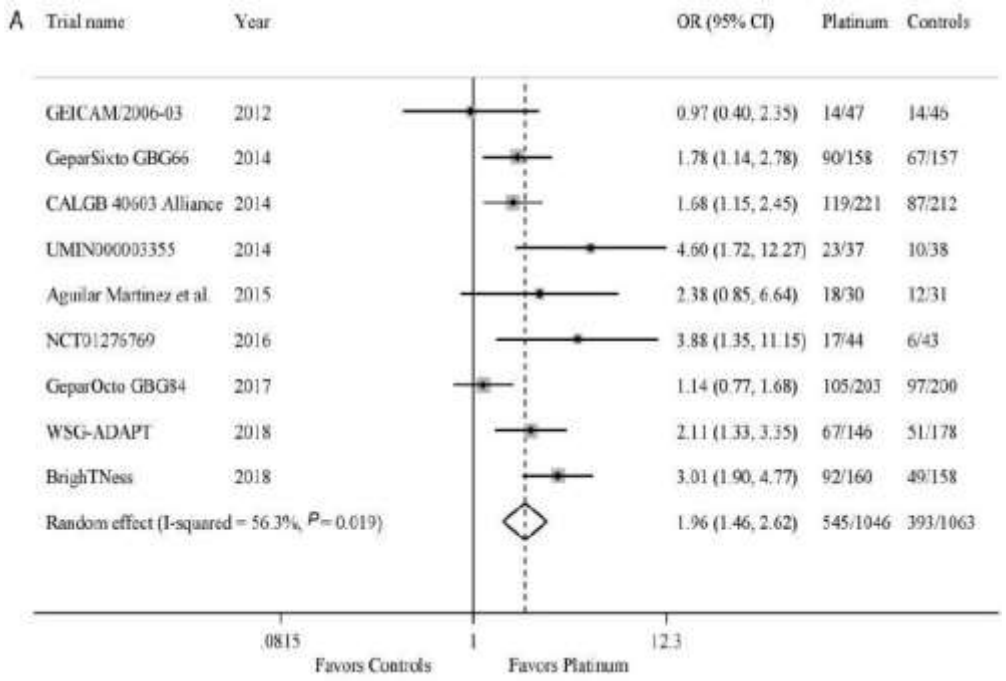
Evidence for Platinums in TNBC: pCR rates (breast/axilla)



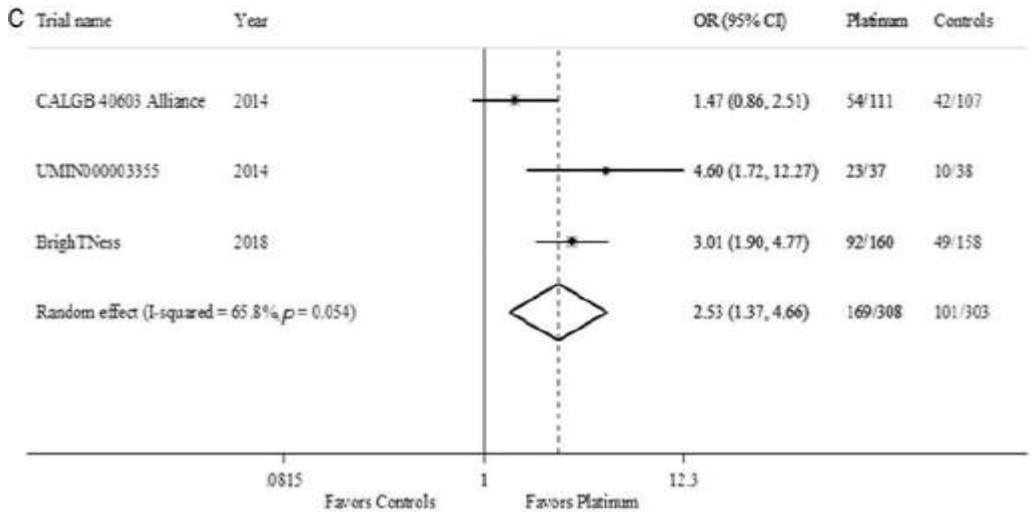
1. Huober J, BCRT 2010; 2. Earl HM, Lancet Oncol 2014; 3. von Minckwitz, NEJM 2012; 4. von Minckwitz, Lancet Oncol 2014; 5. Sikov, J Clin Oncol 2015; 6. Guarneri V, Ann Surg Oncol 2015; 7. Gluz O, SABCS 2015; 8. Untch M, Lancet Oncol 2016; 9. Loibl S, Lancet Oncol 2018

The Best Evidence in TNBC: Platinum increases pCR

All trials



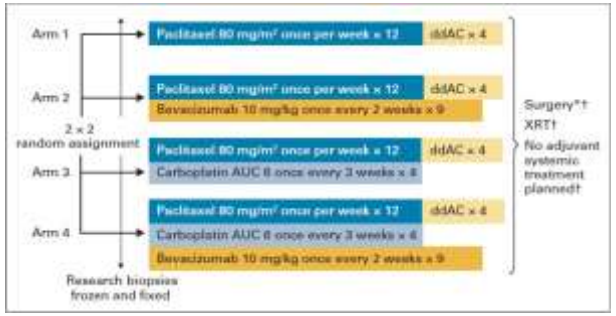
Only trials with the same chemo in both arms +/- platinum

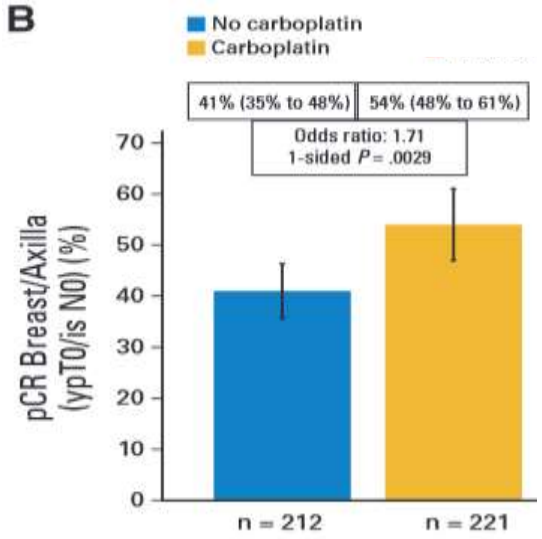


Poggio et al, Ann Oncol 2018

The Best Evidence in TNBC: Platinum increases pCR

CALGB 40603



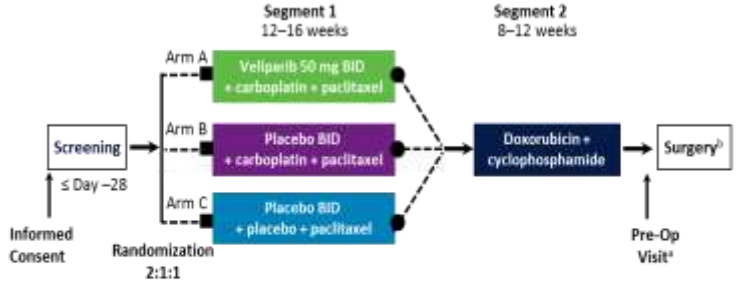


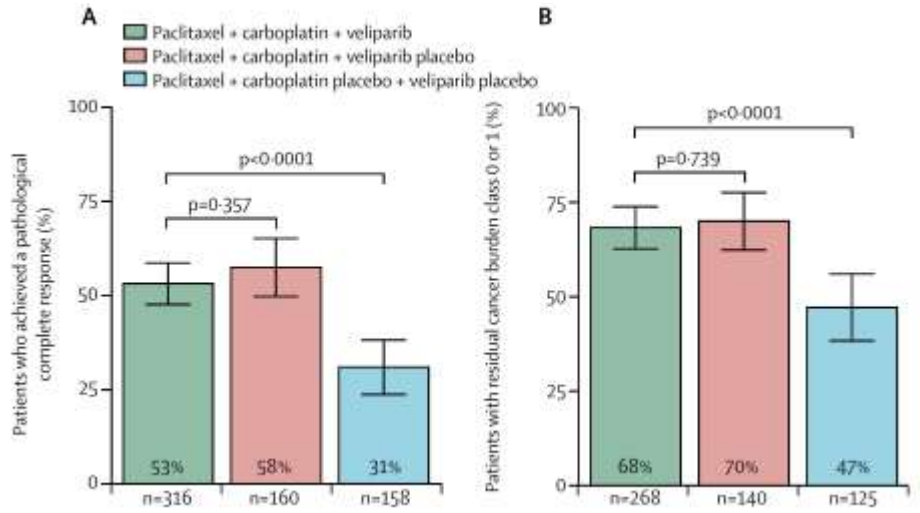
Standard arm +/-bevacizumab: **41%** pCR breast/axilla
Platinum arm +/-bevacizumab: **54%** pCR breast/axilla

Δ 13%

OR 1.71 p=0.0029

BRIGHTNESS





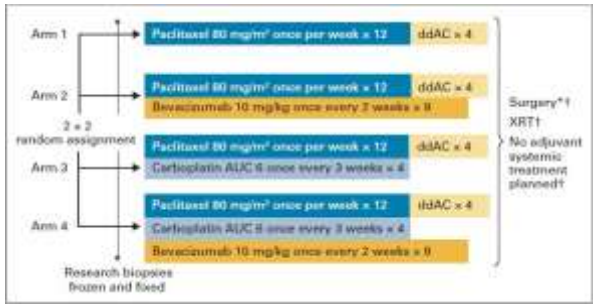
Standard arm: **31%** pCR breast/axilla
Platinum arm: **58%** pCR breast/axilla

Δ 27%

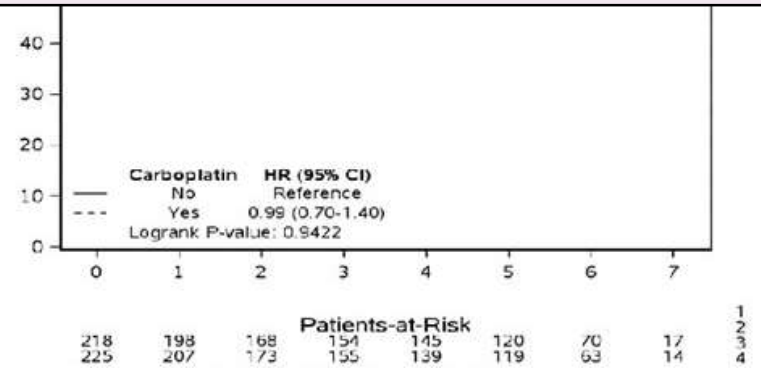
P<0.001

Evidence for Platinums in TNBC: Impact on Survival is uncertain

CALGB 40603

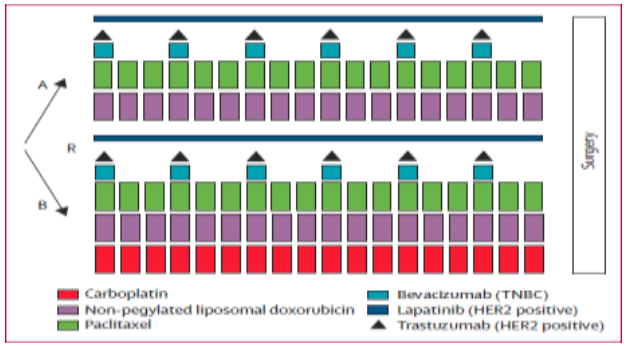


One study
Not powered to assess impact on EFS
Same standard chemo +/- carboplatin

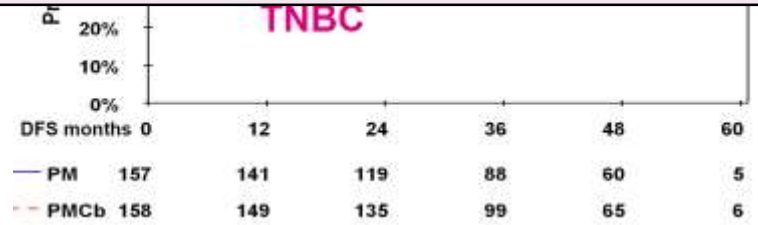


HR 0.99 (0.70-1.40) **p=0.942**

GEPARSIXTO



One study
Subgroup analysis (TNBC pts)
No cytoxan in standard arm

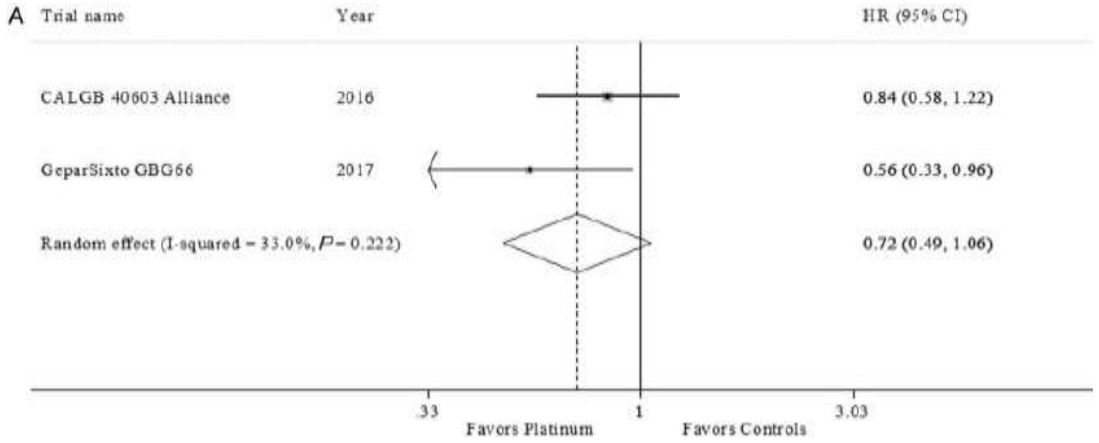


Standard arm : **76.1% 3-yr EFS**
Platinum arm : **85.8% 3-yr EFS**
Median follow-up 47 months
HR 0.56 (0.34-0.93) **p=0.022**

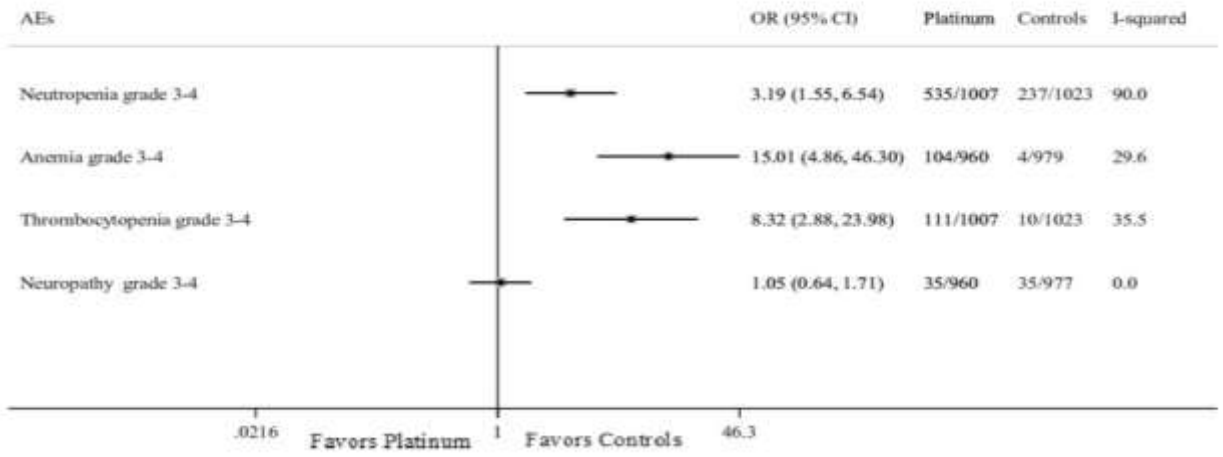
Sikov WM et al. ASCO 2019
Untch M et al. ESMO 2017; Ann Oncol 2018

Evidence for Platinums in TNBC: Impact on Survival is uncertain

Metanalysis are not going to solve this uncertainty, data from more trials will



Evidence for Platinums in TNBC: Impact on toxicity is certain



But schedule matters:

- Carboplatin AUC 5-6 q3w
- Carboplatin AUC 2 – 1,5 qw

Poggio et al, Ann Oncol 2018

Neoadjuvant platinum for TNBC: recommendations

Associazione Italiana di Oncologia Medica

QUESITO CLINICO N. 14 (RIFERIRSI AL quesito GRADE n. 5) (Figura n. 9)

Nelle donne con carcinoma mammario TRIPLO NEGATIVO (recettori ormonali negativi ed HER2-negativo) candidate a ricevere chemioterapia primaria/neoadiuvante, è raccomandabile l'aggiunta del platino ad uno schema standard con antracicline e taxani rispetto alla sola chemioterapia a base di antracicline e taxani?

Qualità Globale delle evidenze GRADE	Raccomandazione clinica	Forza della raccomandazione clinica
Moderata	Nelle donne con carcinoma mammario triplo negativo (recettori ormonali negativi ed HER2 negativo) candidate a ricevere chemioterapia primaria/neoadiuvante, l'aggiunta del platino ad uno schema standard con antracicline e taxani può essere preso in considerazione.	**Positiva debole**

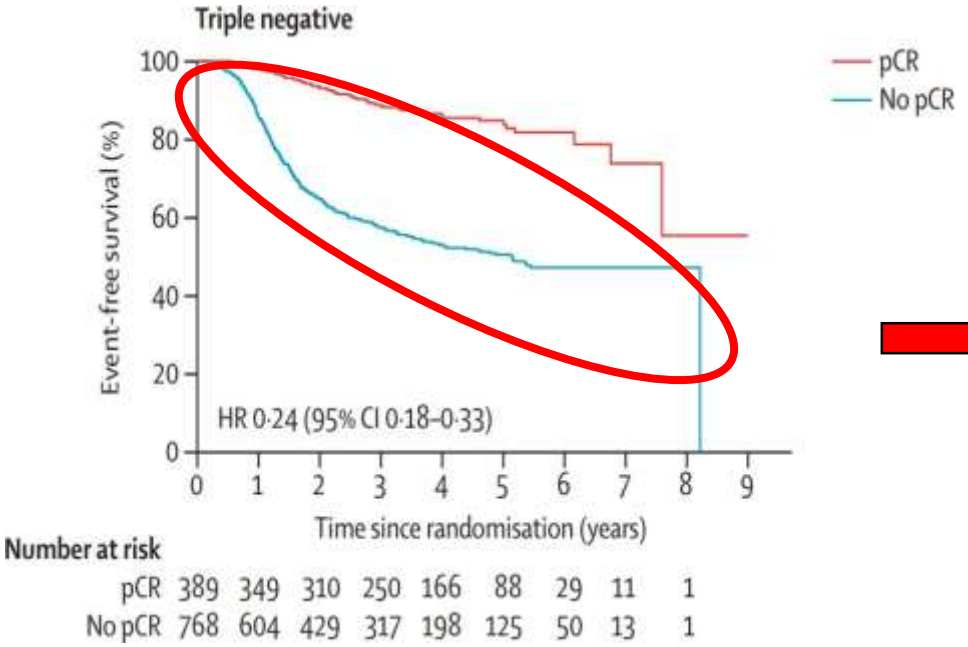
Leggere capitolo 14- Raccomandazioni prodotte secondo metodologia GRADE

The Panel voted against the routine inclusion of platinum-based chemotherapy in women already slated to receive alkylator-, taxane- , and anthracycline-based regimens.

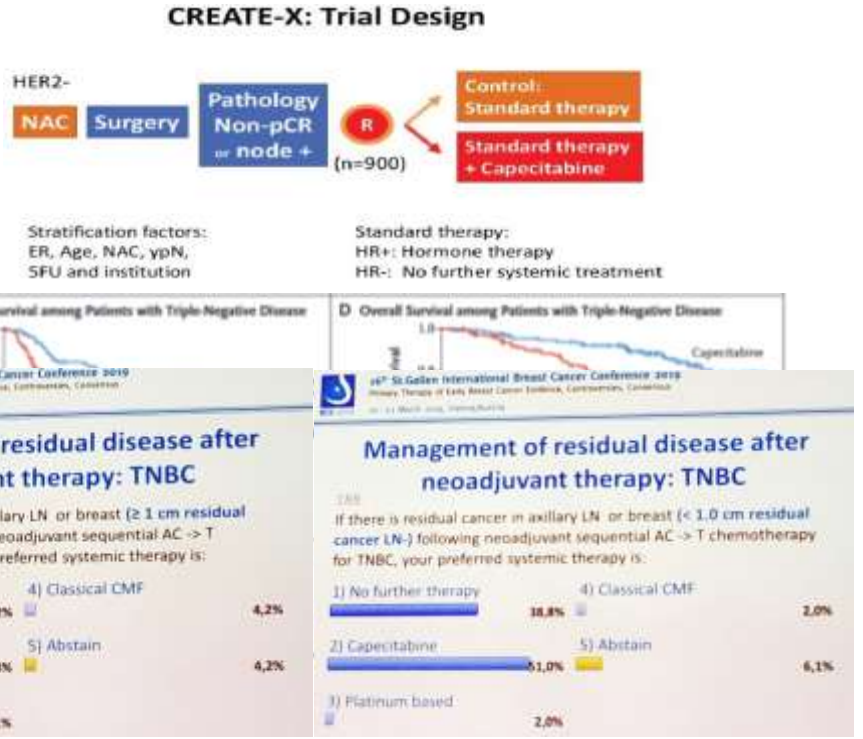
Linee guida AIOM 2018; Early Breast Cancer: St Gallen International Consensus Guidelines for the Primary Therapy of Early Breast Cancer 2019

What are we not taking into account?
What comes after neoadjuvant treatment

pCR
and long-term outcome in TNBC



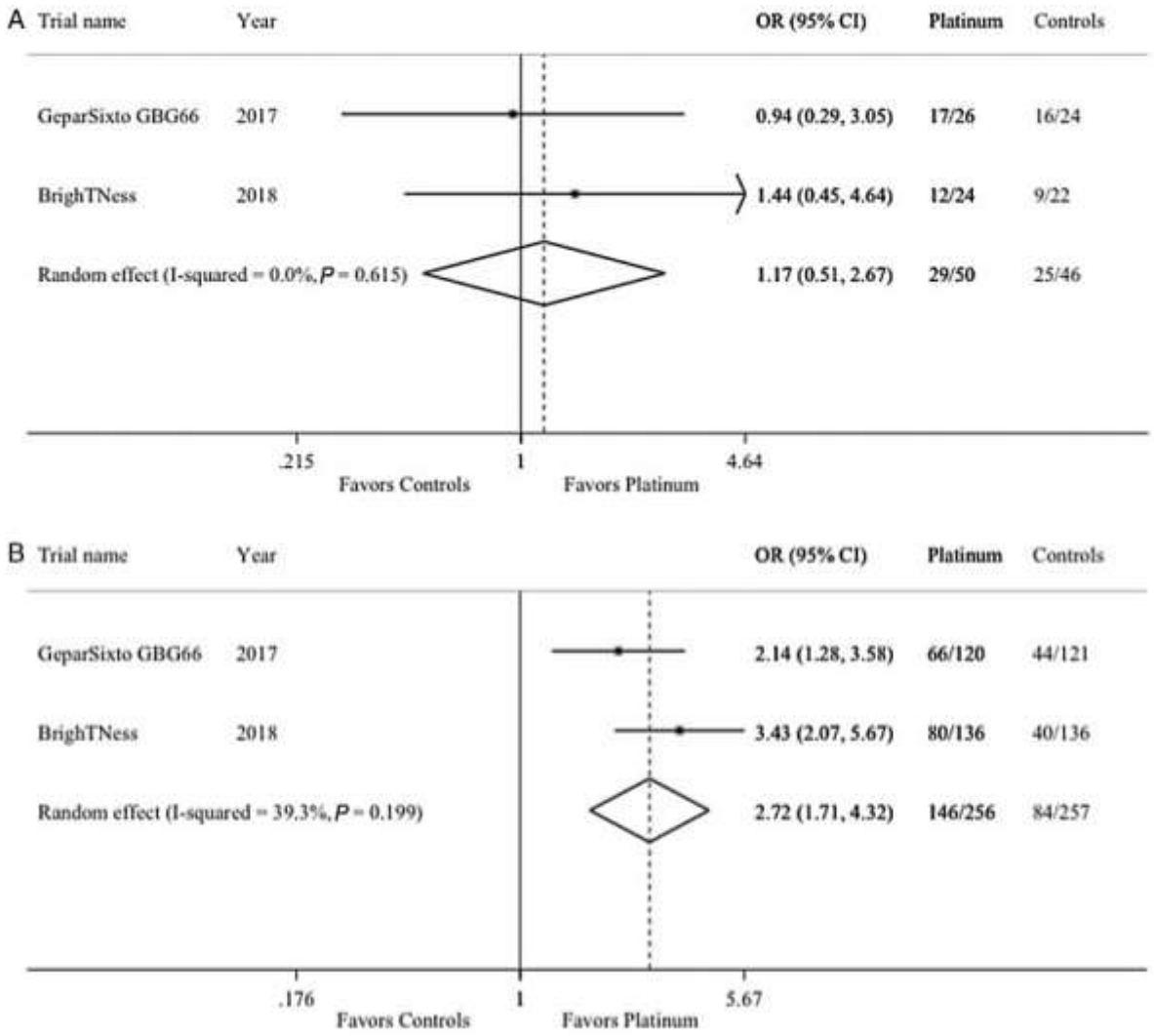
Cortazar P, et al. Lancet Oncol 2014



Variable	Number of studies	OR	95% CI	p
Treatment-related death	6	1.45	0.65–3.27	0.37
Treatment discontinuation	3	3.80	2.98–4.85	<0.001
Grade 3/4 diarrhoea	7	2.30	1.56–3.40	<0.001
Grade 3/4 hand-foot syndrome	8	13.23	6.05–28.92	<0.001

Still debated, but definitely out there

Evidence for Platinums in TNBC: benefit is not limited to BRCA mut



BRCA mutated BC patients

BC patients without BRCA mutation

Poggio F. et al. Ann Oncol 2018

Neoadjuvant treatment for TNBC: what was new in ~~2017 2018~~ 2019?

- Platinum salts — The Old and Debated
- PARPi
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} The New and Shiny

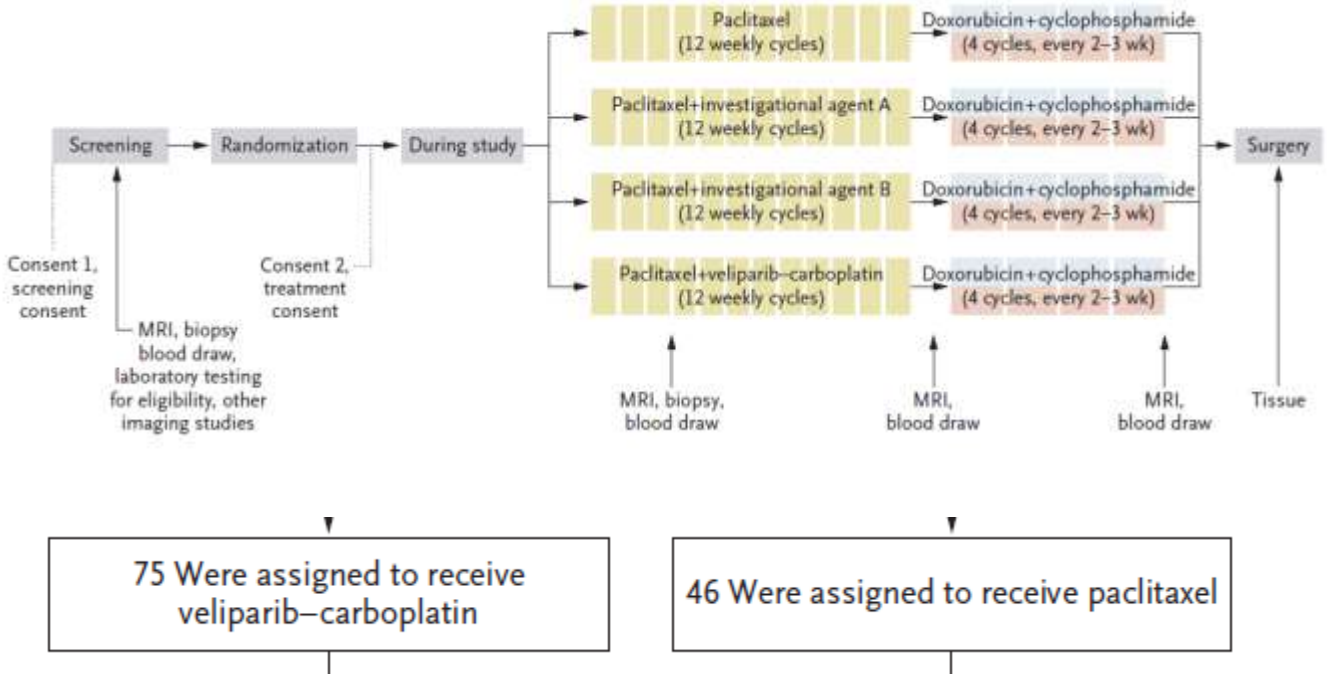
- Predictive markers — The Sacred Graal

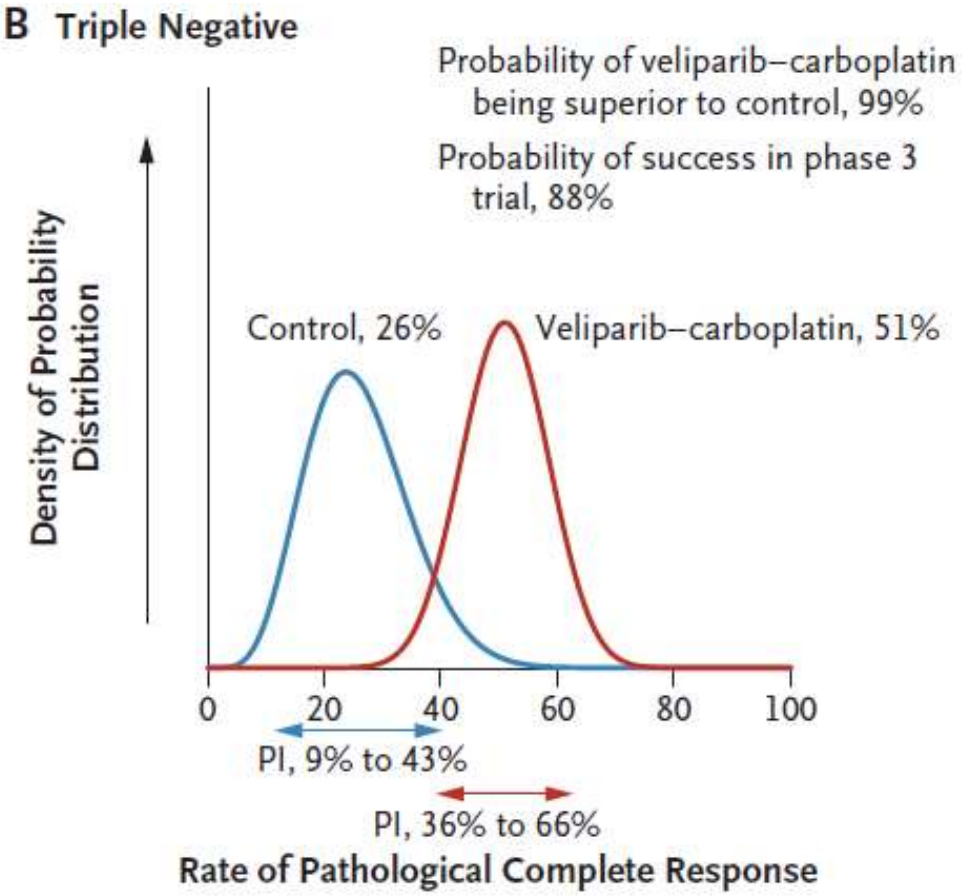
PARPi for neoadjuvant treatment of TNBC: I-SPY2

The NEW ENGLAND JOURNAL of MEDICINE

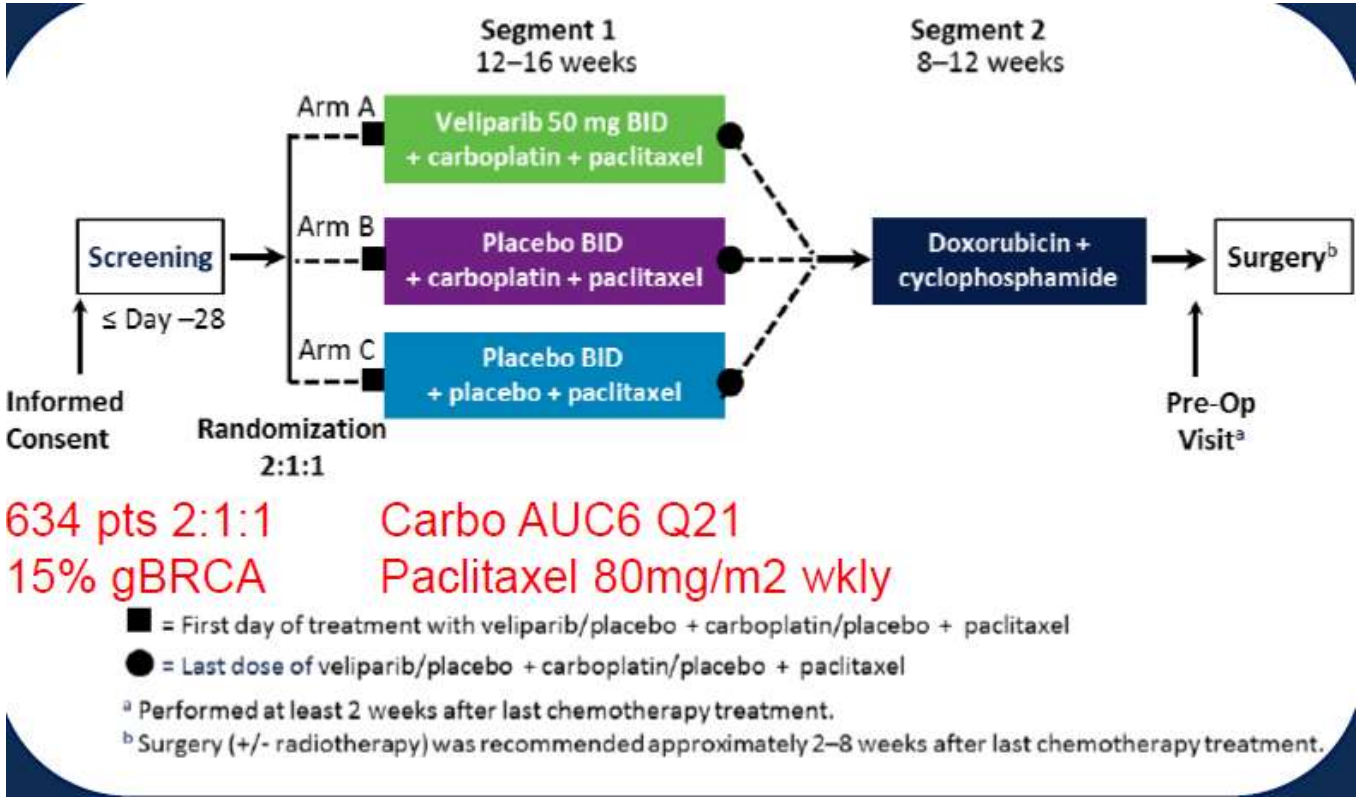
ORIGINAL ARTICLE

Adaptive Randomization of Veliparib–Carboplatin Treatment in Breast Cancer





BRIGHTNESS Trial



634 pts 2:1:1 Carbo AUC6 Q21

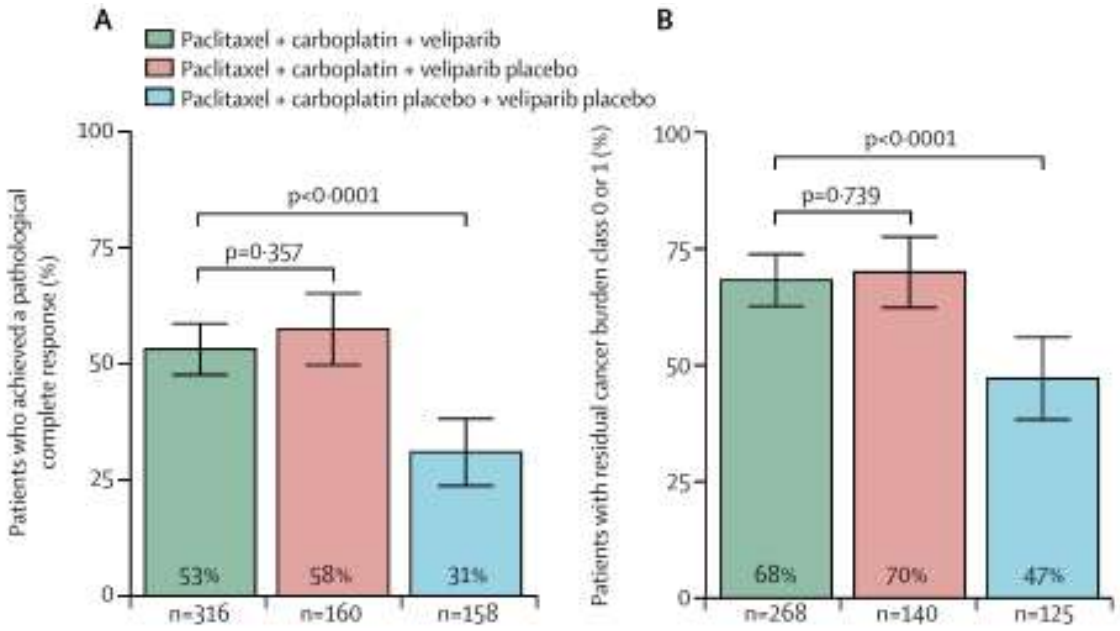
15% gBRCA Paclitaxel 80mg/m2 wkly

■ = First day of treatment with veliparib/placebo + carboplatin/placebo + paclitaxel

● = Last dose of veliparib/placebo + carboplatin/placebo + paclitaxel

[a] Performed at least 2 weeks after last chemotherapy treatment.

[b] Surgery (+/- radiotherapy) was recommended approximately 2–8 weeks after last chemotherapy treatment.

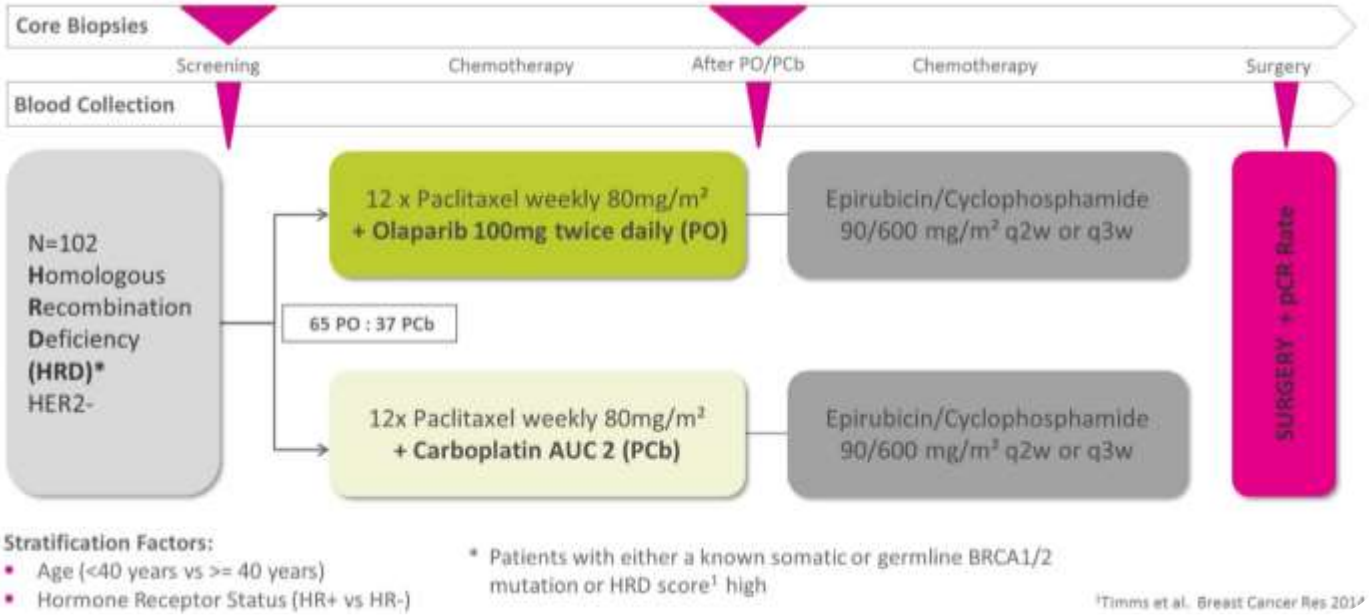


Platinum arm: **58%** pCR breast/axilla

Platinum+veliparib arm: **53%** pCR breast/axilla

P=0.357

GeparOLA trial

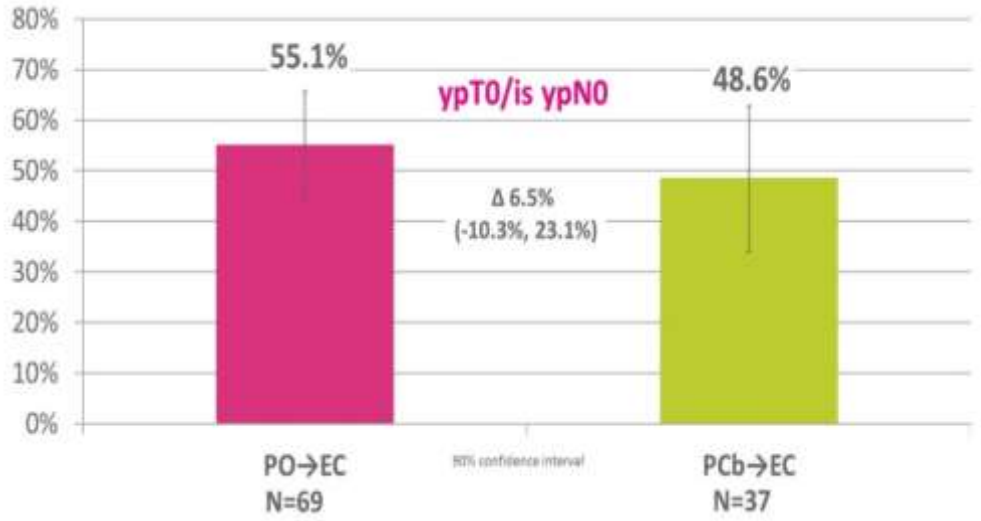


g/t BRCA 1/2 mutation: **60.4%**

PRIMARY ENDPOINT

- Assess pCR rate of neoadjuvant paclitaxel-olaparib (PO) → EC in HRD pts
- A rate in the PO arm of 55% or lower should be excluded with α=0.1 to support a subsequent phase III trial
- No formal comparison between arms

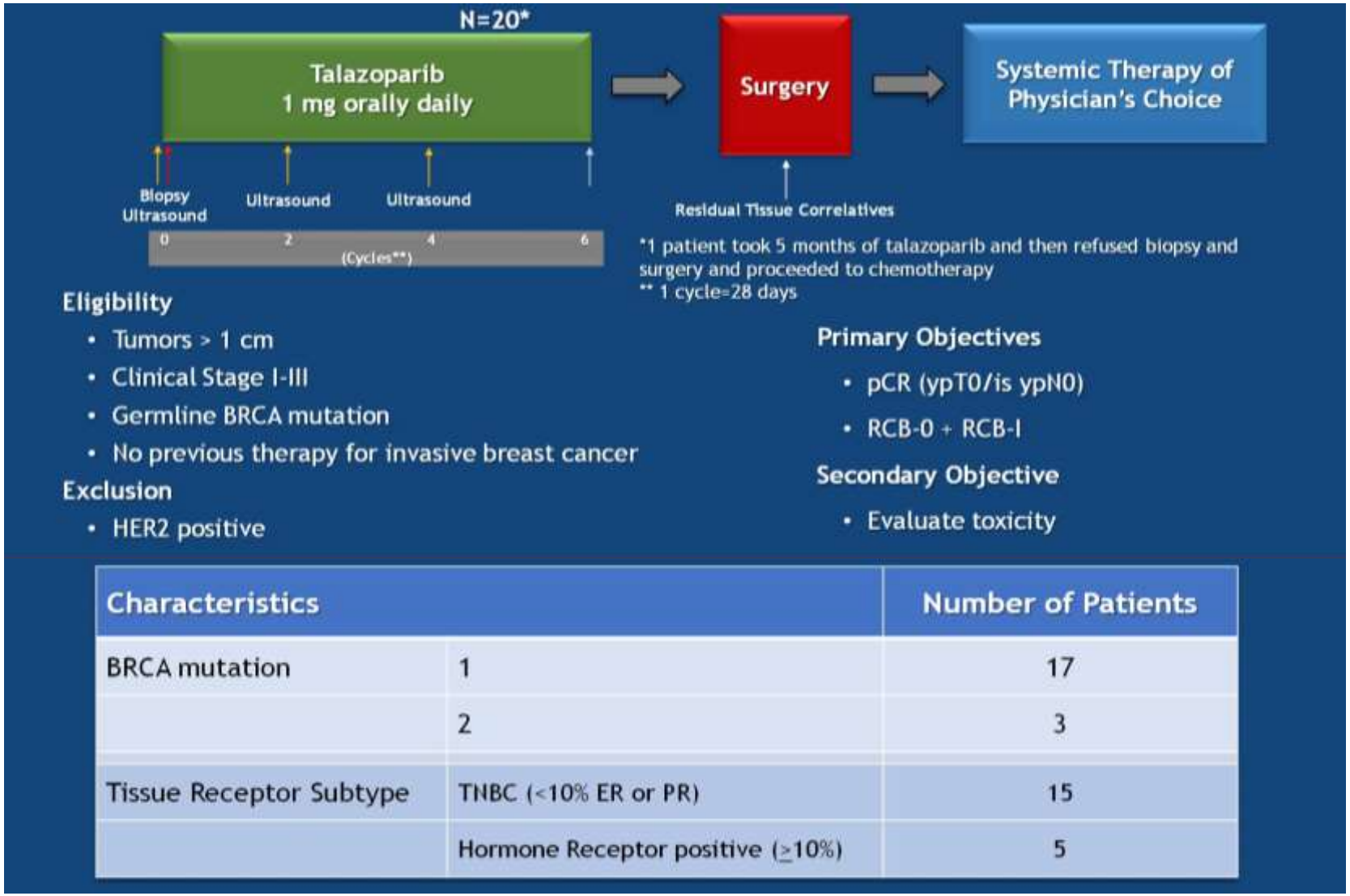
Primary endpoint - pCR



N+ population: 24.5% in PO vs 45.7% in PCb

	Olaparib-Paclitaxel pCR Rate (95% CI)	Carboplatin-Paclitaxel pCR Rate (95% CI)
HR+ (n=29)	52.6% (32.0-72.6)	20.0% (3.7-50.7)
HR- (n=77)	56.0% (43.4-68.0)	59.3% (41.7-75.2)
Age <40	76.2% (56.3-90.1)	45.5% (20.0-72.9)
Age ≥40	45.8% (33.4-58.6)	50.0% (32.7-67.3)

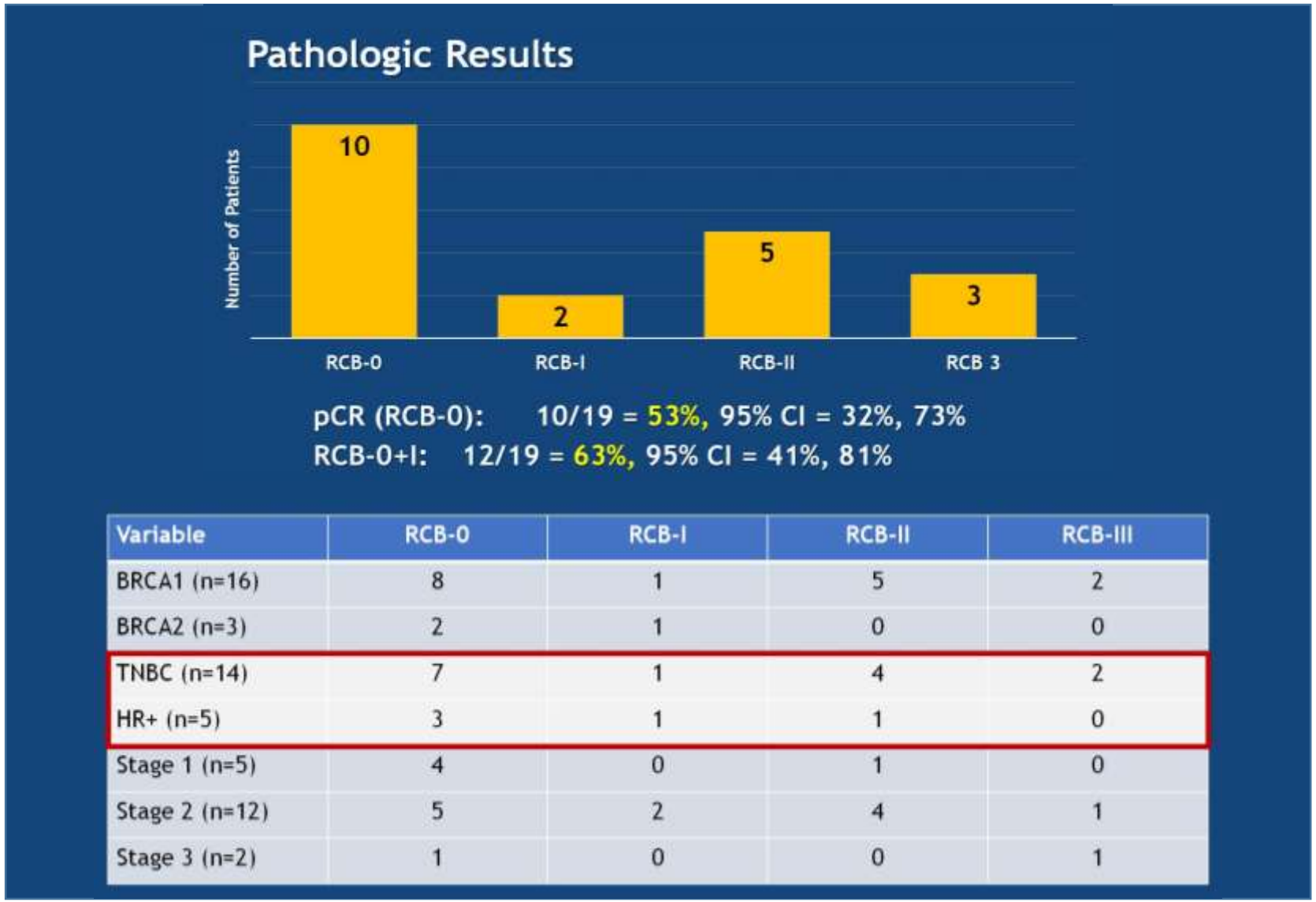
Neoadjuvant Talazoparib for BRCA mut TNBC



Characteristics		Number of Patients
BRCA mutation	1	17
	2	3
Tissue Receptor Subtype	TNBC (<10% ER or PR)	15
	Hormone Receptor positive (≥10%)	5

Litton et al, JCO 2019

Neoadjuvant Talazoparib for BRCA mut TNBC



Variable	RCB-0	RCB-I	RCB-II	RCB-III
BRCA1 (n=16)	8	1	5	2
BRCA2 (n=3)	2	1	0	0
TNBC (n=14)	7	1	4	2
HR+ (n=5)	3	1	1	0
Stage 1 (n=5)	4	0	1	0
Stage 2 (n=12)	5	2	4	1
Stage 3 (n=2)	1	0	0	1

Litton et al, JCO 2019

Neoadjuvant treatment for TNBC: what was new in ~~2017 2018~~ 2019?

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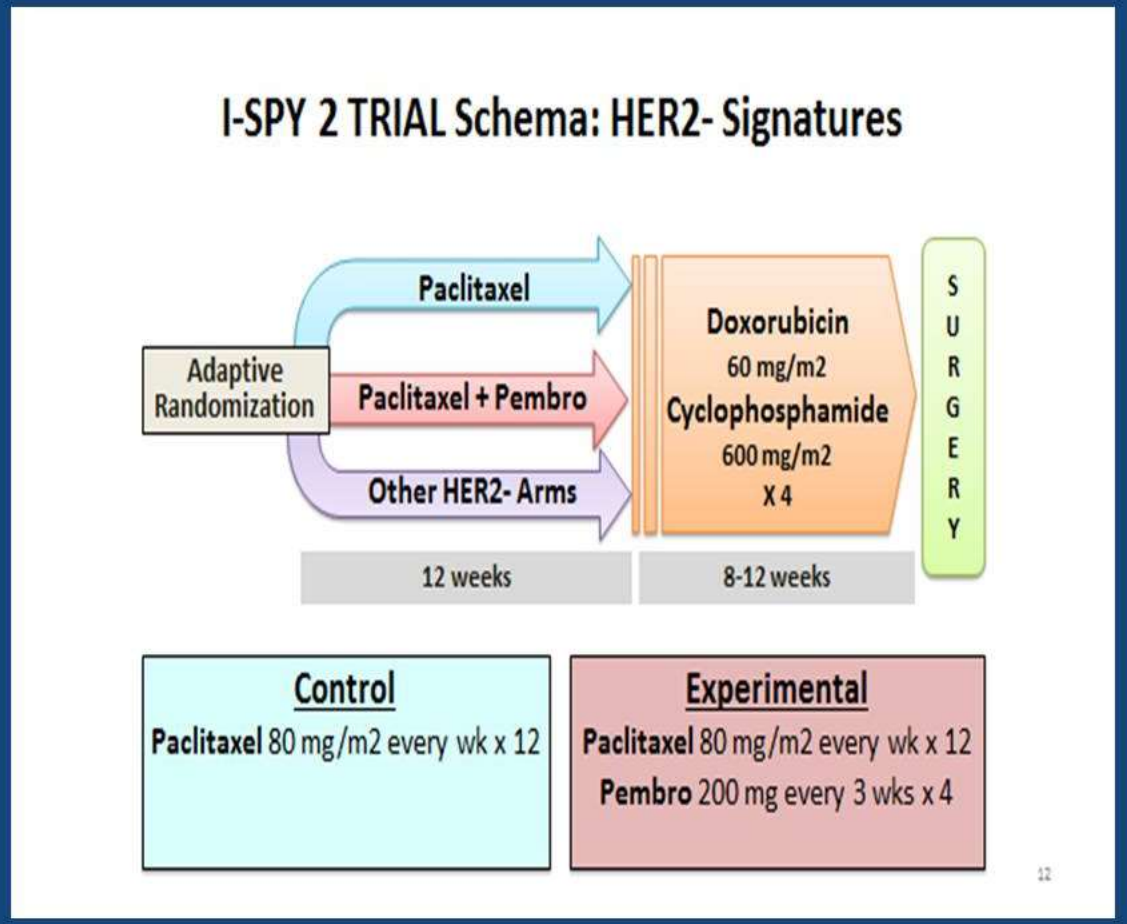
- PARPi
- Immune-checkpoints inhibitors

} The New and Shiny

- Predictive markers — The Sacred Graal

Immuno for neoadjuvant treatment of TNBC: I-SPY2

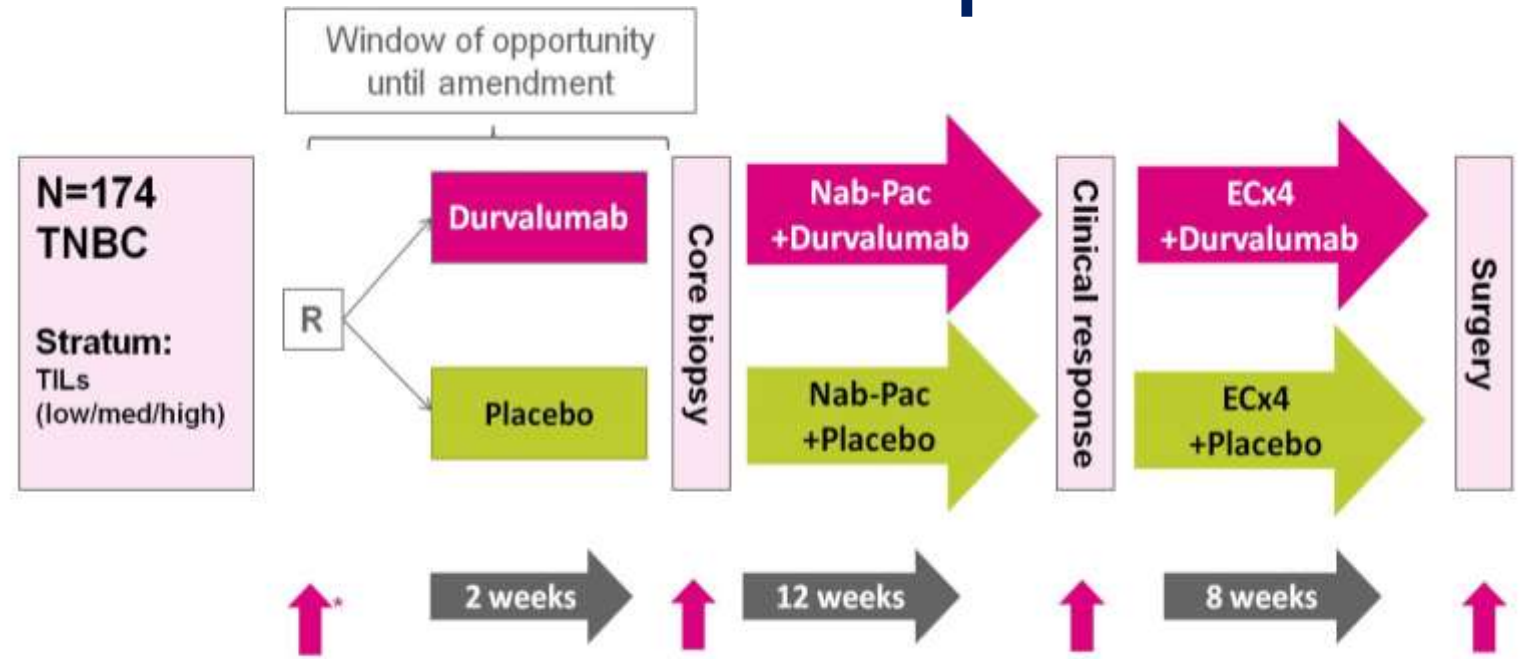


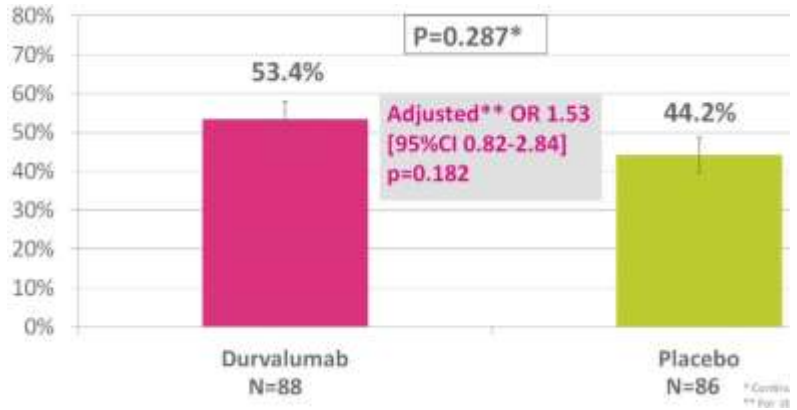
Pembrolizumab graduated in all HER2- signatures: Both HR+/HER2- and TN

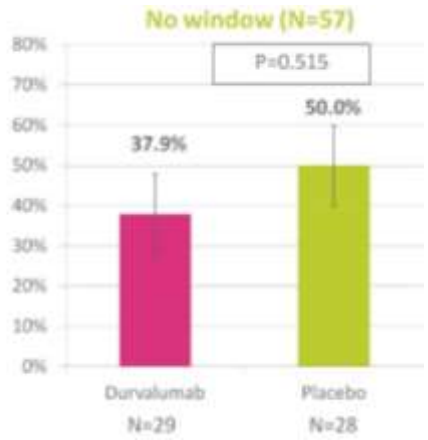
Signature	Estimated pCR rate (95% probabilty interval)		Probability pembro is superior to control	Predictive probability of success in phase 3
	Pembro	Control		
All HER2-	**0.46** (0.34 – 0.58)	**0.16** (0.06 – 0.27)	> 99%	99%
TNBC	**0.60** (0.43 – 0.78)	**0.20** (0.06 – 0.33)	>99%	>99%
HR+/HER2-	**0.34** (0.19 – 0.48)	**0.13** (0.03 – 0.24)	>99%	88%

Nanda et al, ASCO 2017

GeparNUEVO trial

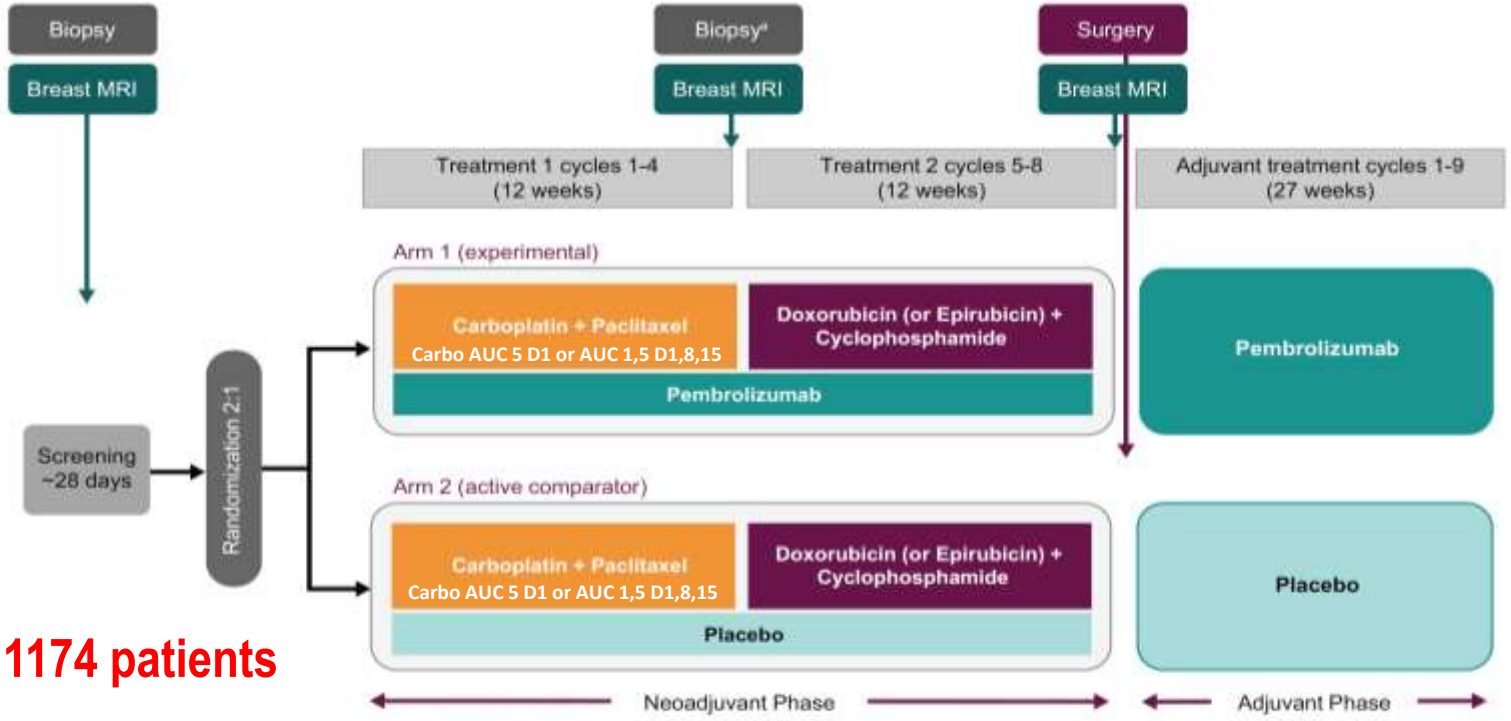






Loibl S, ASCO 2018, Ann Oncol 2019

KEYNOTE-522: phase III trial



MRI, magnetic resonance imaging.
[a]If they agree to participate, patients with adequate tumor volume at the end of treatment 1 cycle 4 will undergo an optional core needle biopsy.

Dual-primary endpoints:

- **pCR**
- **EFS**

Merck's KEYTRUDA® (pembrolizumab) in Combination with Chemotherapy Met Primary Endpoint of Pathological Complete Response (pCR) in Pivotal Phase 3 KEYNOTE-522 Trial in Patients with Triple-Negative Breast Cancer (TNBC)

Release Date:
Monday, July 29, 2019 6:55 am EDT

A-BRAVE-TRIAL

HIGH RISK PRIMARY TNBC PTS WHO COMPLETED TREATMENT WITH CURATIVE INTENT INCLUDING SURGERY, CHEMOTHERAPY AND RADIOTHERAPY (if indicated)

Stratum A: Adjuvant
Stratum B: Post-neoadjuvant

R

Avelumab for 1 year

Observation

Randomization 1:1 balanced for adjuvant and post-neoadjuvant patients.

Co-primary endpoints: 1. DFS in all-comers; 2. DFS in PD-L1+ patients
Secondary endpoints: OS, Safety, Biomarkers

n=335 (for the 1st co-primary endpoint)

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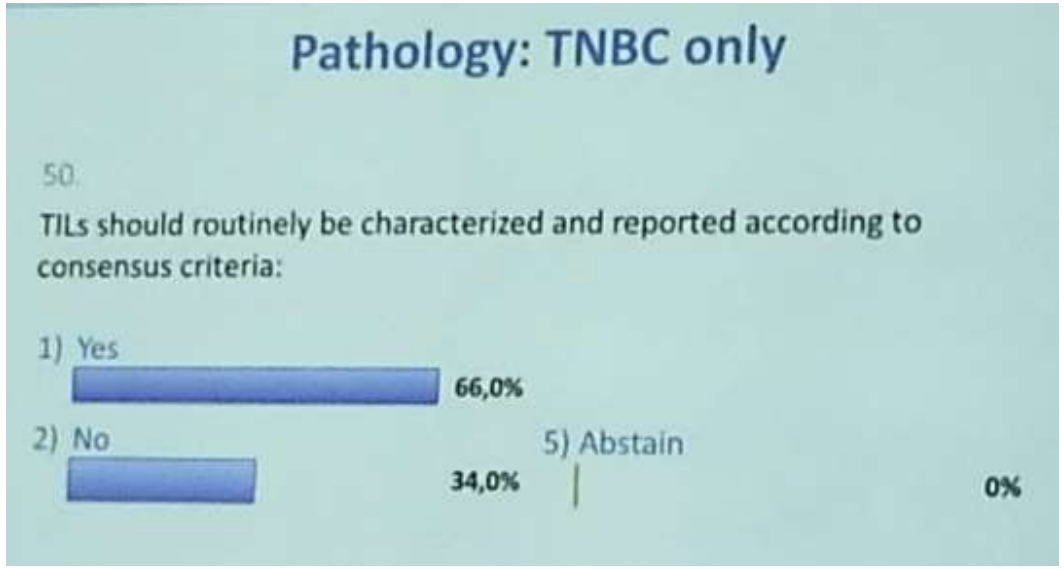
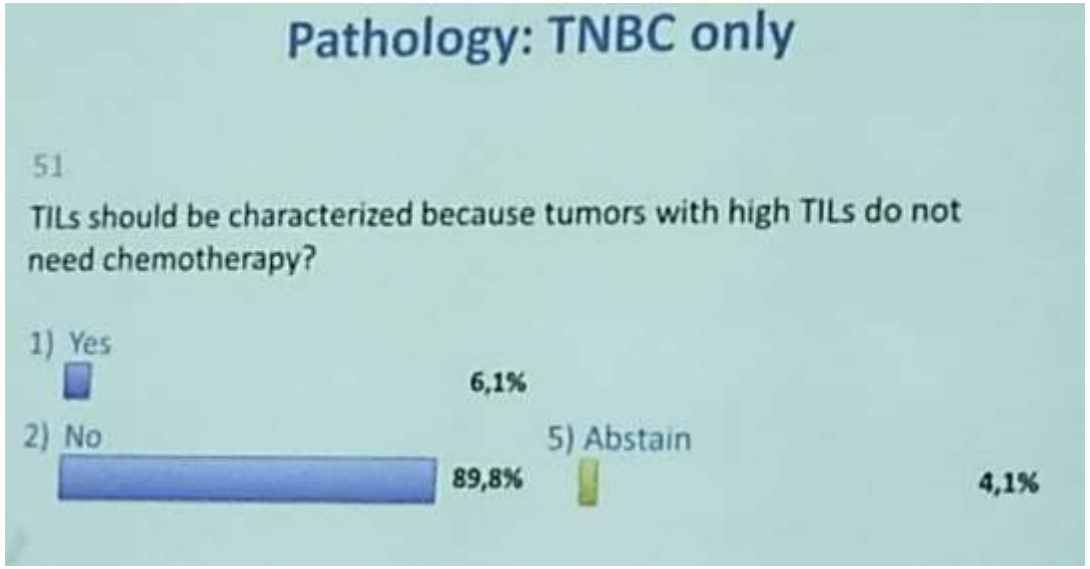
TILs in TNBC at St.Gallen 2019

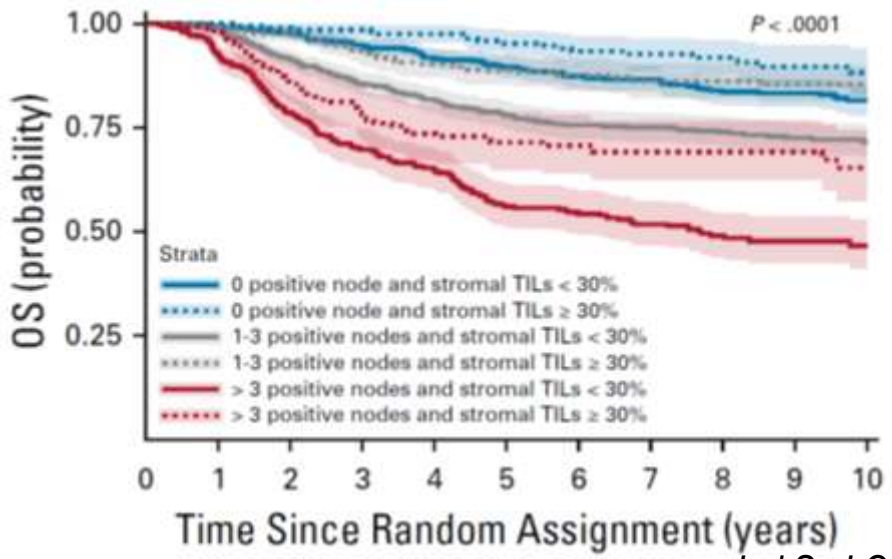




- Clinical utility still to be demonstrated

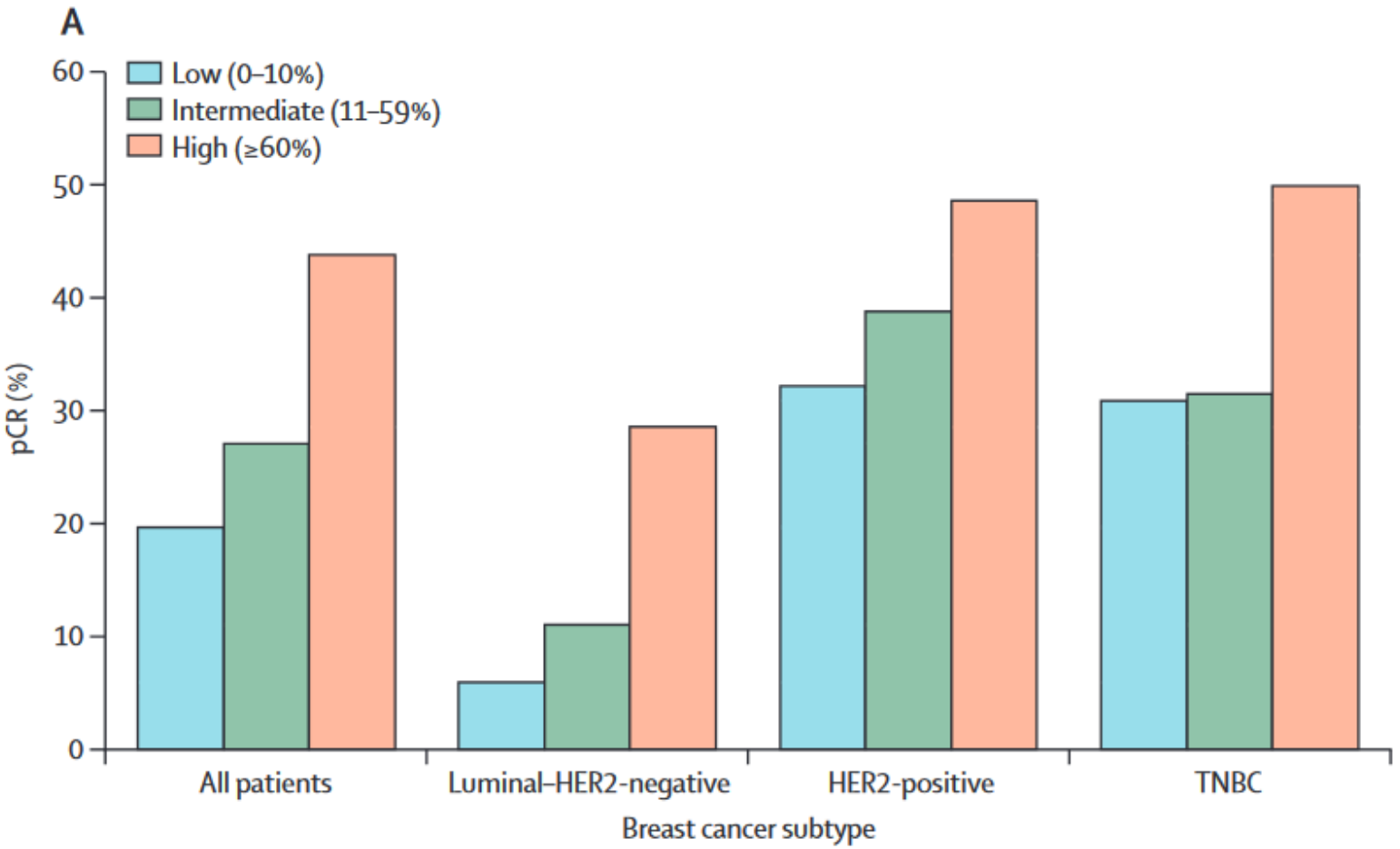
However:

- Reproducible and standardized
- LoE1B clinical validity
- Provide additional prognostic info for discussion with patient
- Cheap, quick



Loi S, J Clin Oncol 2019

High TILs are associated with increased pCR rates and with EFS beyond pCR

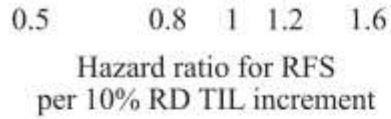


Denkert C, Lancet Oncol 2018

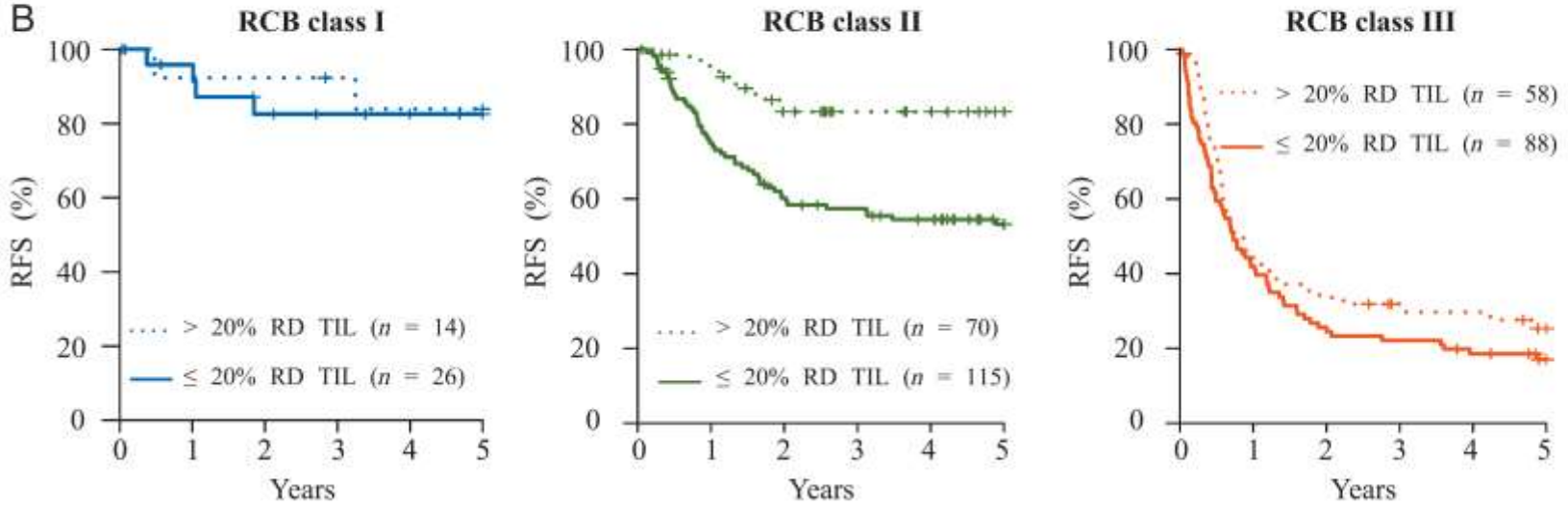
High TILs in residual disease are associated with better EFS and OS

A

RCB class	Number	Events	HR (95% CI)	*P* interaction
I	40	6	1.05 (0.67 – 1.63)	0.003
II	185	69	0.69 (0.58 – 0.82)	
III	146	114	0.94 (0.84 – 1.04)	

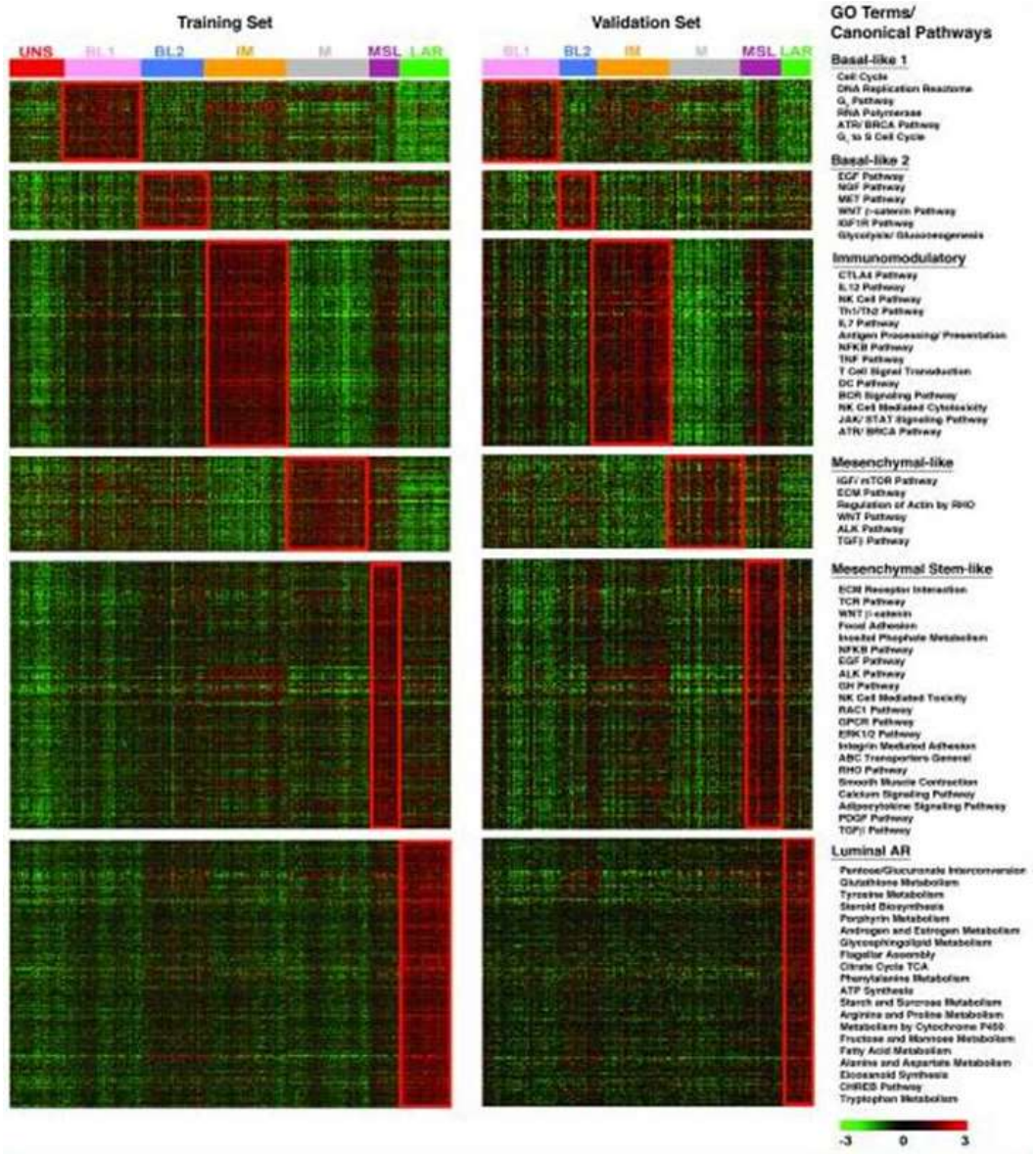


B



Luen SJ et al, Ann Oncol 2019

Heterogeneity in TNBC to identify targets



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

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

Immunomodulatory: Immune signalling

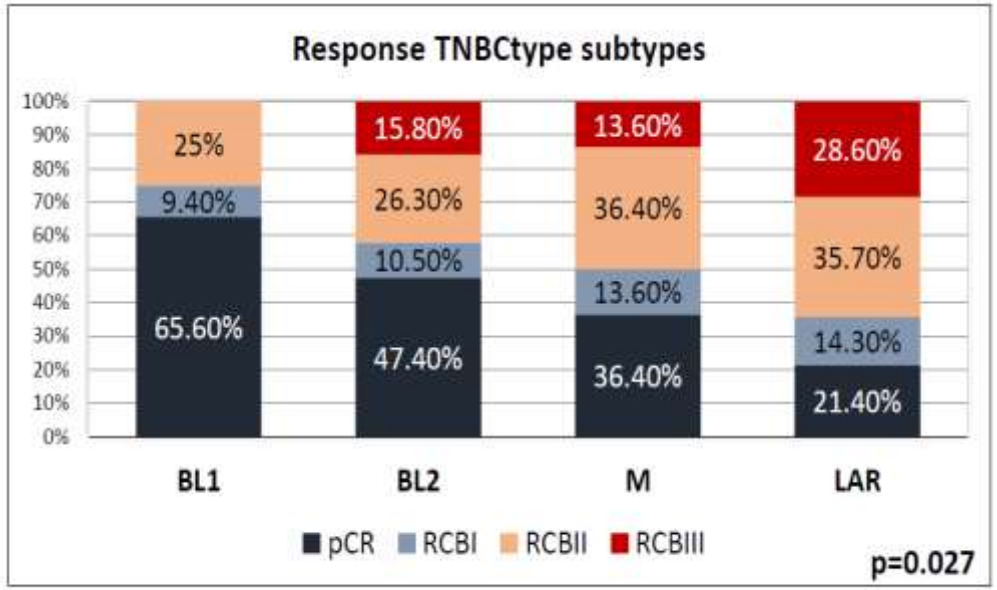
Mesenchymal-like and **Mesenchymal stem-like**: EMT, motility and growth-factor pathways

Luminal AR: Androgen receptor signaling

Lehmann et al, JCI 2011

TNBC subtypes predict for response to CT

	pCR	Non-pCR	pCR rate	95% CI	*P* value
BL1	11	10	0.52	0.31–0.73	
BL2	0	8	0.00	0.00–0.00	
M	8	18	0.31	0.13–0.48	
IM	8	19	0.30	0.12–0.46	*P*=0.043
MSL	3	10	0.23	0.0001–0.45	
LAR	2	18	0.10	0.03–0.23	
UNS	5	10	0.33	0.09–0.57	



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

TNBCtype-4 shows a significant predictive value of response in a TNBC cohort homogeneously treated with TCb, with BL1 and LAR displaying the best and worse responses to NACT respectively.

Masuda et al, CCR 2013; Echavarria Diaz-Guardamino et al, ASCO2018

GRAZIE DELLA VOSTRA ATTENZIONE