FONDAZIONE MICHELANGELO

RAGMA23

Madrid, 15-16 Junio 2023

Further meaning of complete response and residual disease in early breast cancer

Luca Gianni

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Neoadjuvant Systemic Therapy of Breast Cancer: four decades of accomplishements

- Control breast cancer locally (LABC and IBC)
- Increase rate of breast conserving surgery (BCS)
- Measure antitumor activity and rank therapies
- Study biomarkers
- Predict benefit and failure (pCR and RD)
- Tailor treatment to individual needs (pCR and RD)
- Register new drugs through accelerated approval (FDA and EMA)
- Substitute for adjuvant trials **(??)**
- Ideal for immunotherapy (**??)**

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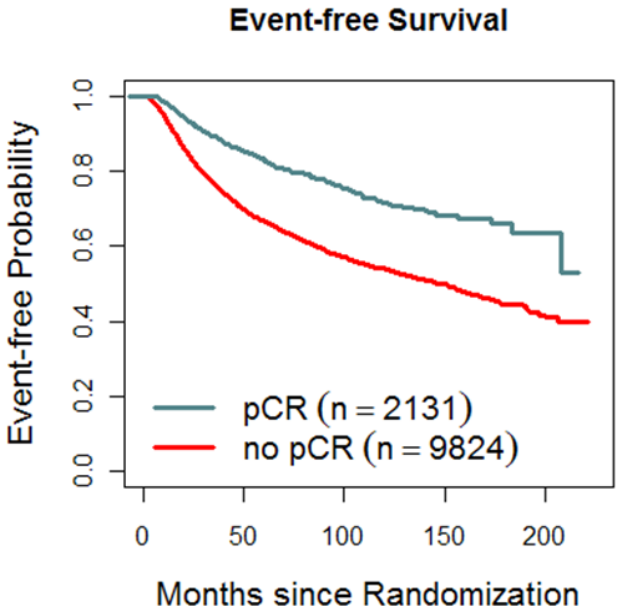
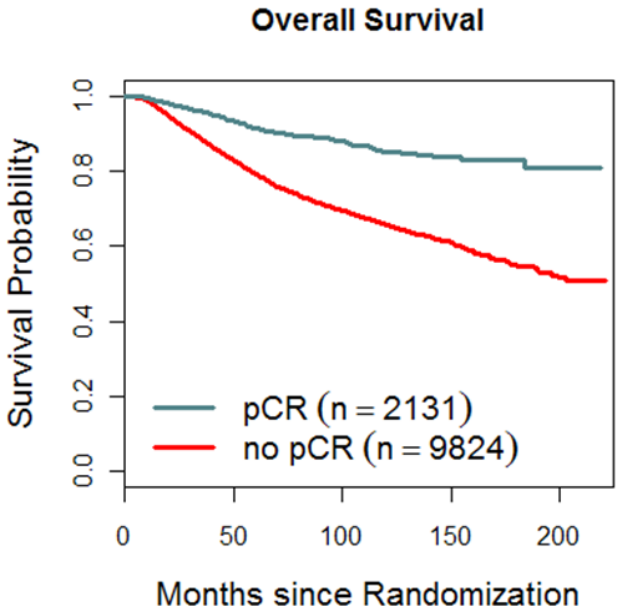
Better EFS and OS for patients achieving pCR





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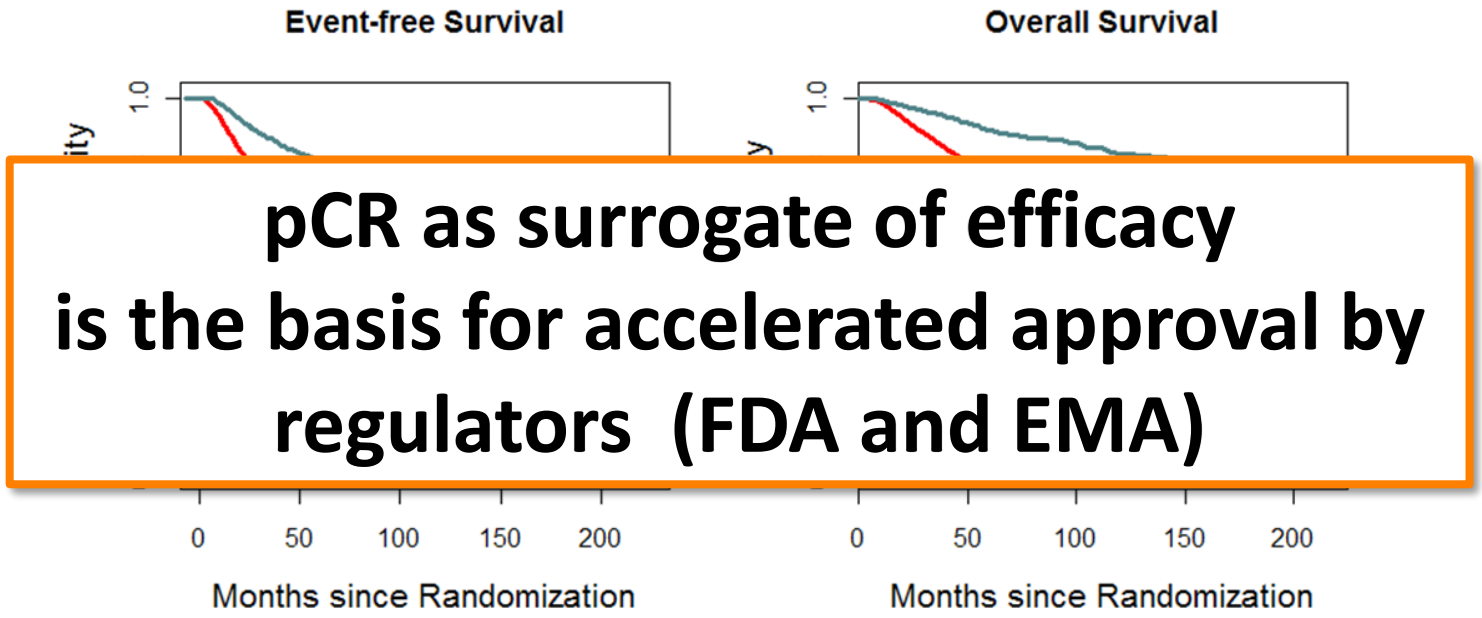

pCR as surrogate of efficacy is the basis for accelerated approval by regulators (FDA and EMA)

Adapted form Cortazar P. et al., The Lancet, 2014

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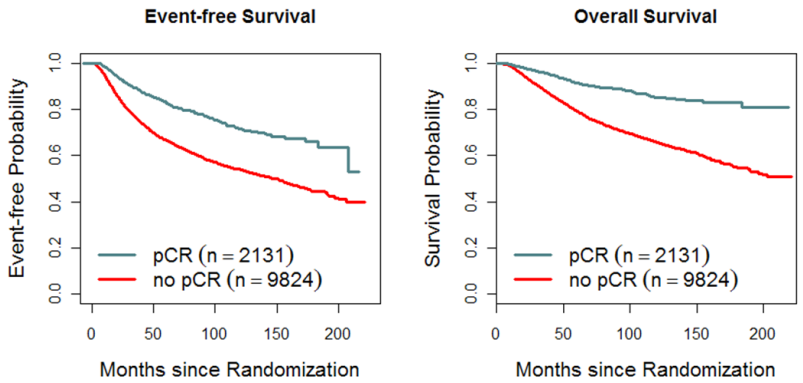
pCR/RD at individual v. trial level

Patient level (Responder)

Trial level (ITT)



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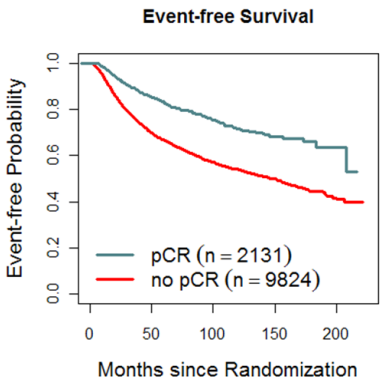

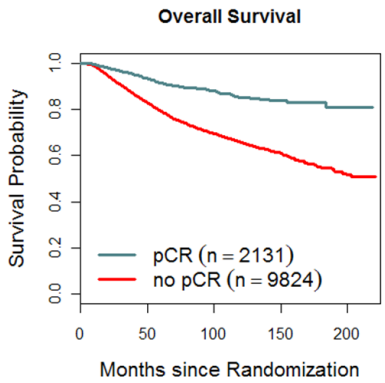

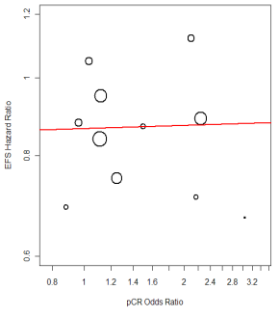

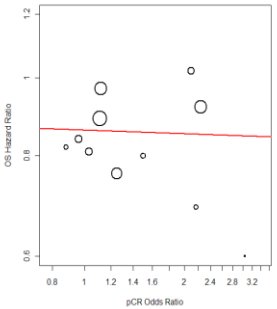

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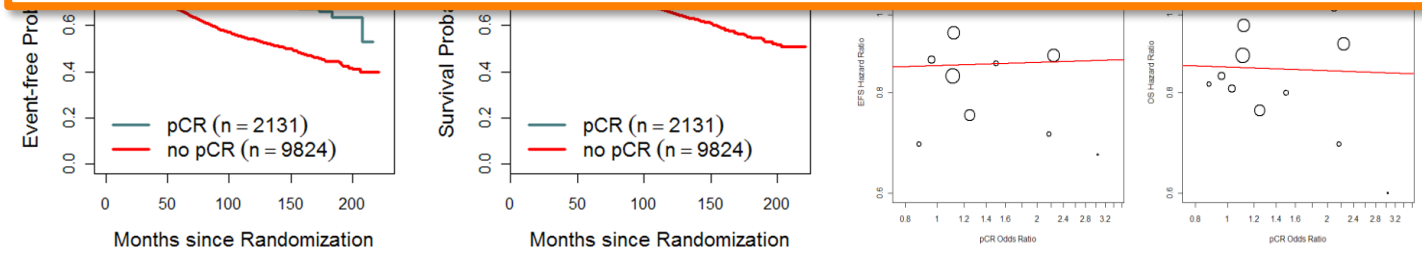
Patient level (Responder) **Trial level (ITT)**

pCR is prognostic at individual level, less so at trial level



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pCR/RD at individual v. trial level

Patient level (Responder) **Trial level (ITT)**

pCR is prognostic at individual level, less so at trial level

almost all studies in CTneo were with chemotherapy

Adapted form Cortazar P. et al., The Lancet, 2014

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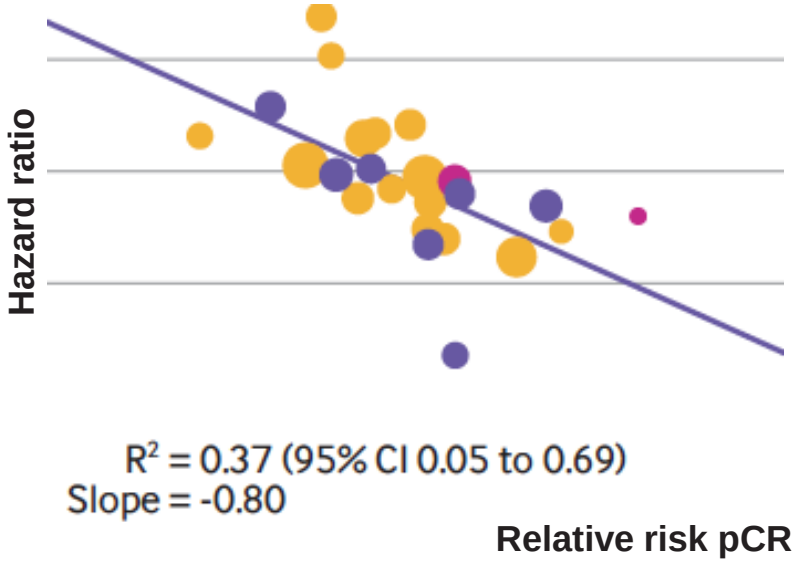
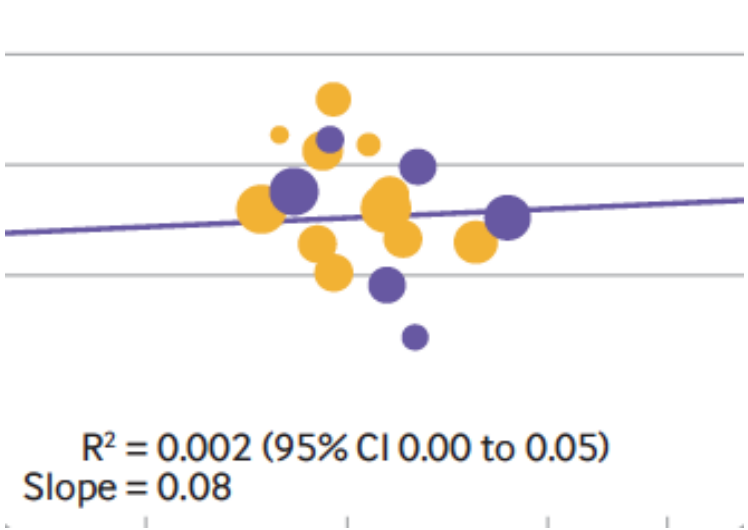
Weak association at trial level also for HER2+ EBC treated with HER2-targeted therapies

EFS



OS



Conforti F. et al *BMJ* 2021;375:e066381

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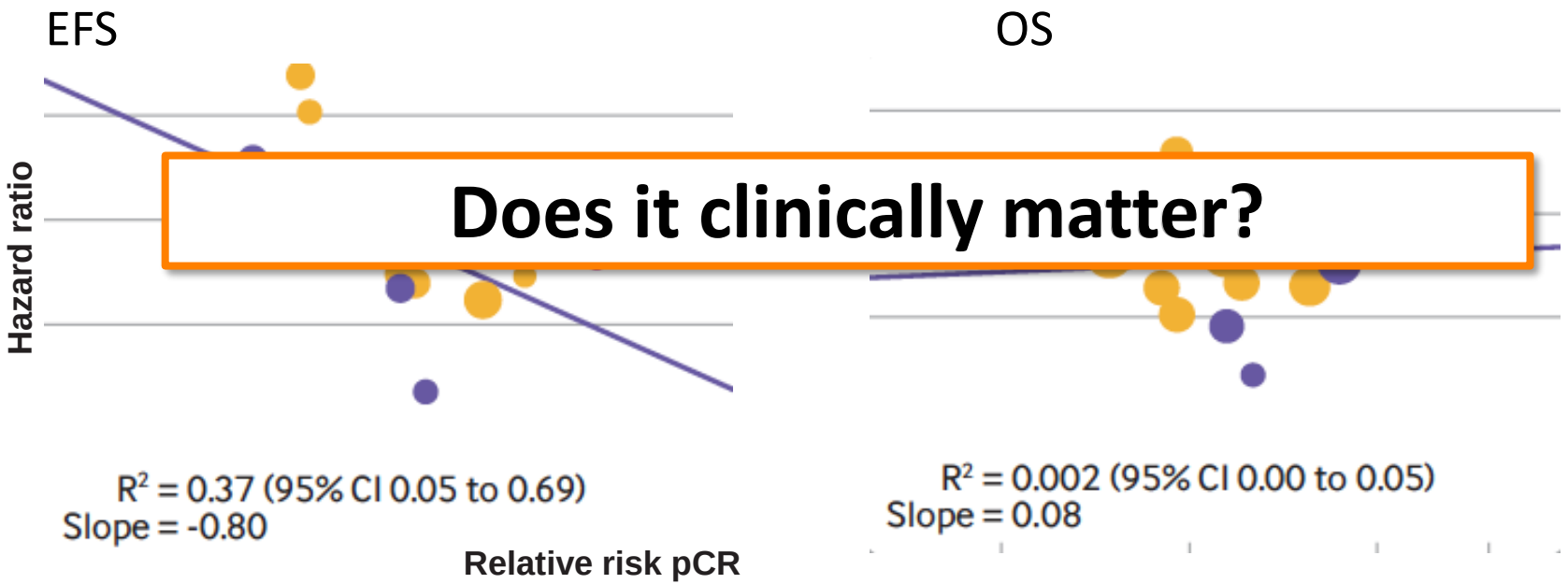

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Discrepancy between individual patient's level and trial level

- pCR is a direct measure of treatment effect
- Efficacy measured as EFS and OS depends on:
  - Treatment effect
  - Tumor characteristics not captured by selection criteria (sTILs, HR expression) that influence timing and extent of treatment effect
  - Intrinsic prognosis of the patient

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Not all pCRs are equally "good"

Not all RDs are "bad"

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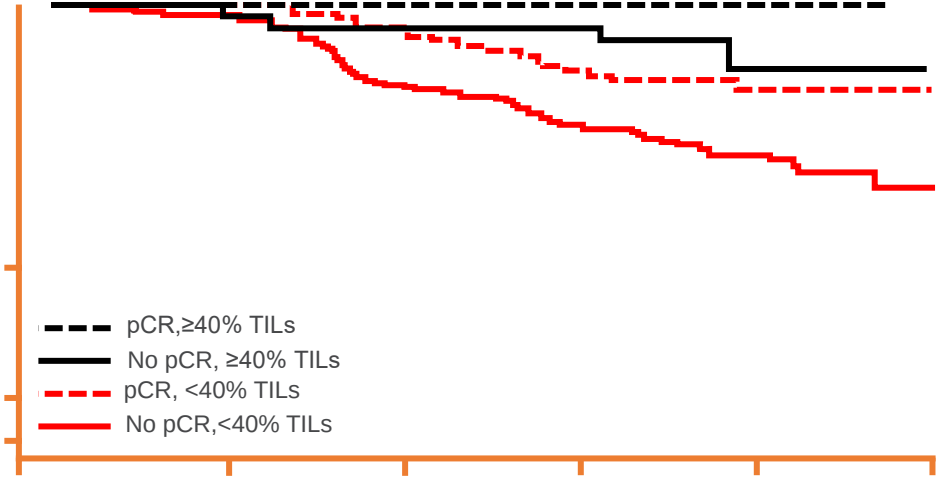
Baseline TILs in HER2+ eBC refine the risk of recurrence in patients with pCR



No. at risk						
pCR, ≥40% TILs	21	21	20	20	9	0
pCR, <40% TILs	98	97	89	75	33	3
No pCR, ≥40% TILs	39	36	33	33	13	0
No pCR, <40% TILs	218	188	155	134	69	1

Salgado R *JAMA Oncol* 2015

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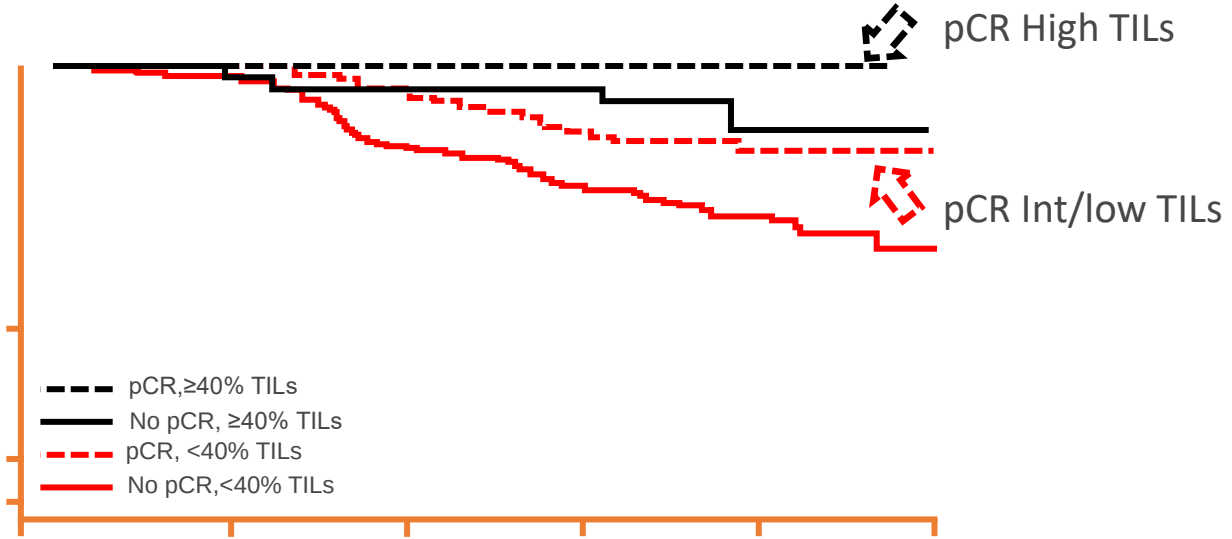

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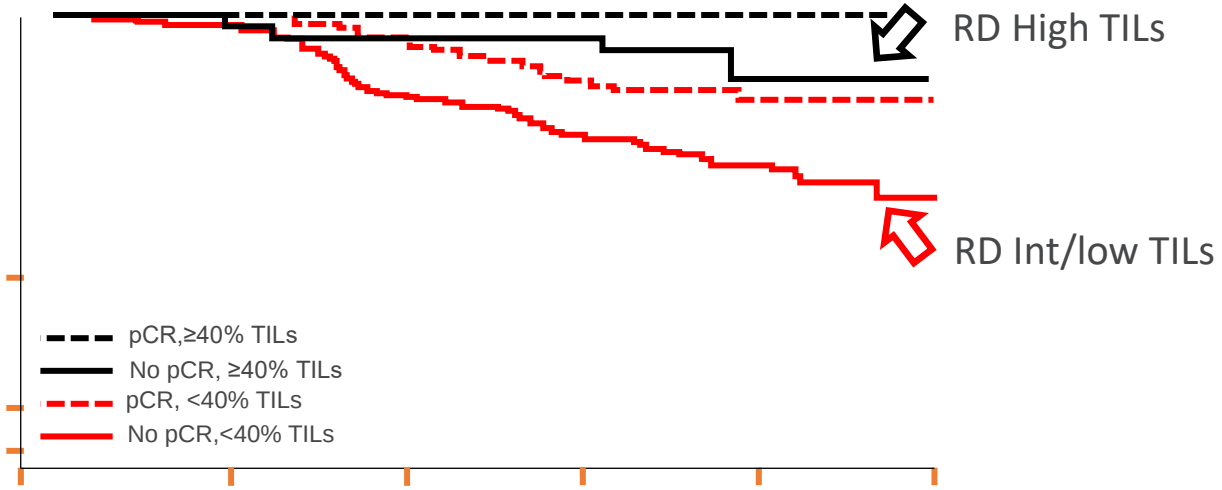
Baseline TILs in HER2+ eBC refine the risk of recurrence in patients with RD



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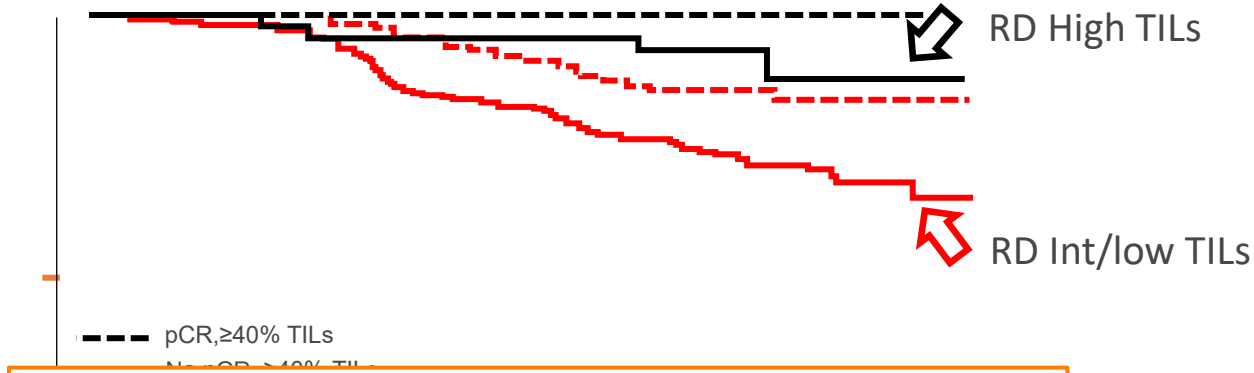

Patients received Trastuzumab

No. at risk						
pCR, ≥40% TILs						
pCR, <40% TILs						
No pCR, ≥40% TILs	39	36	33	33	13	0
No pCR, <40% TILs	218	188	155	134	69	1

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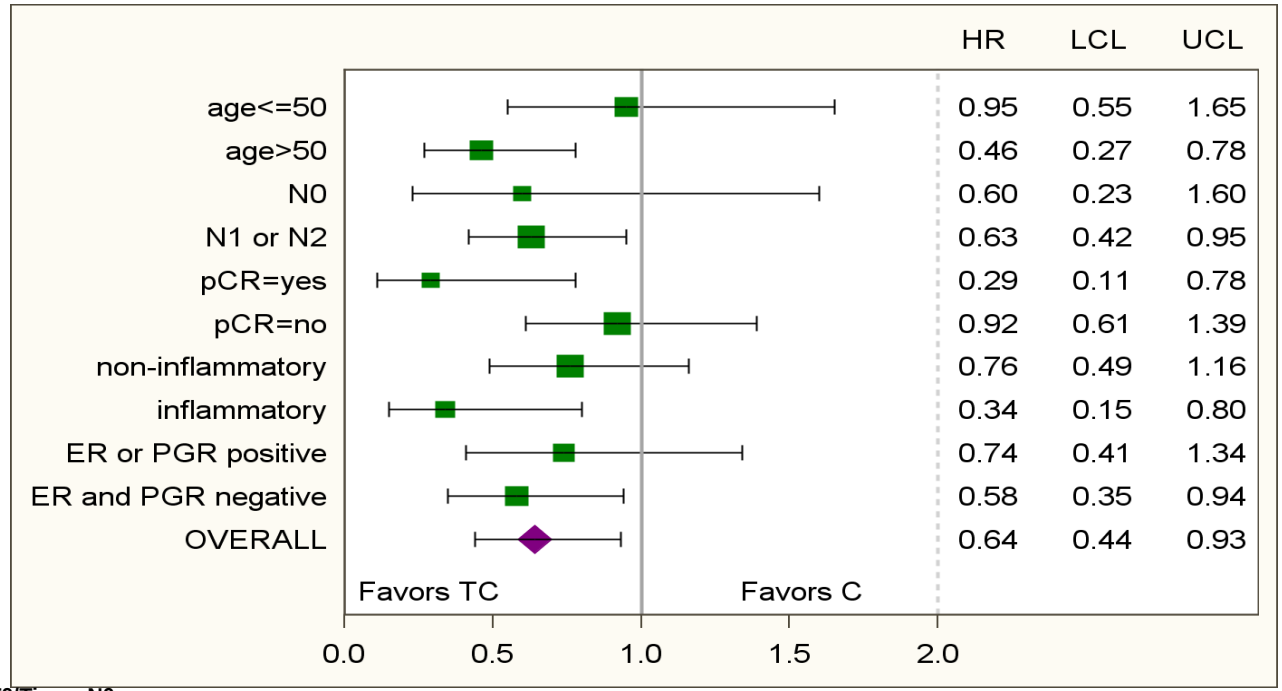
Trastuzumab/chemotherapy v. CT in the NOAH trial shows a «quality effect» for pCR



pCR: ypT0/Tis, ypN0

Gianni L et al, Lancet Oncol 2014

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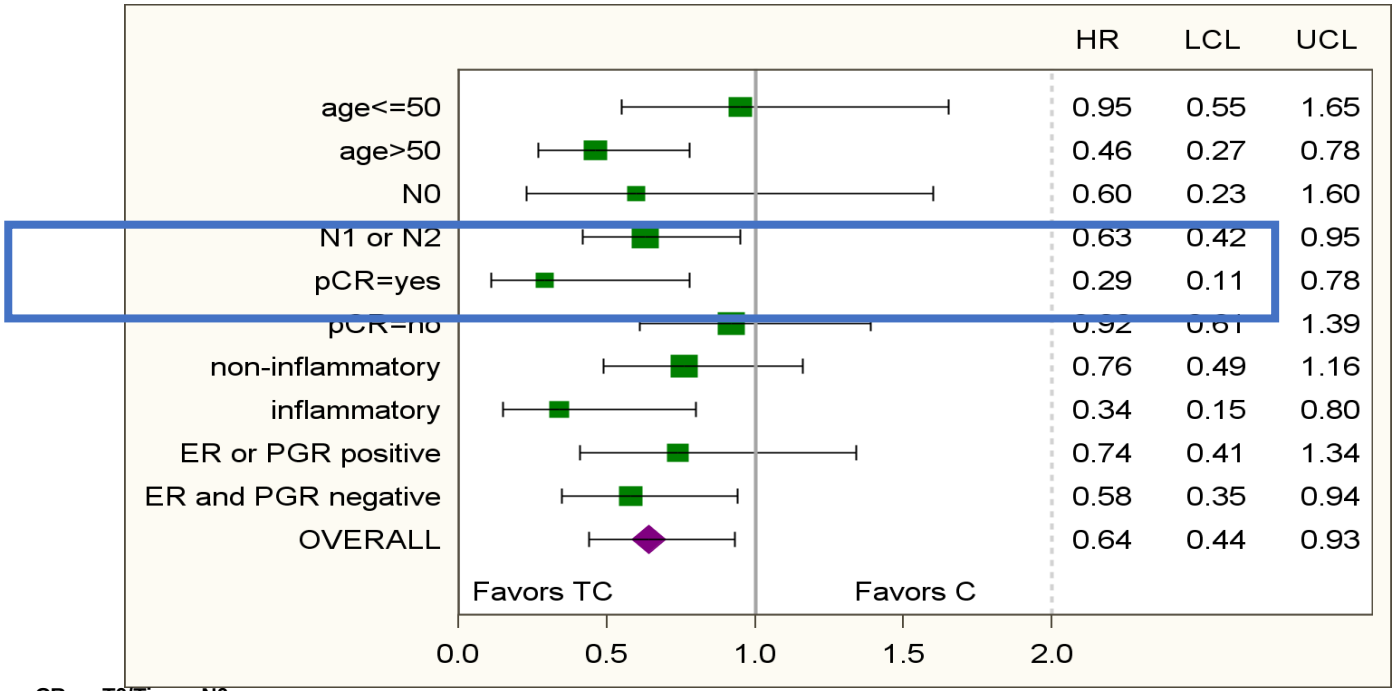

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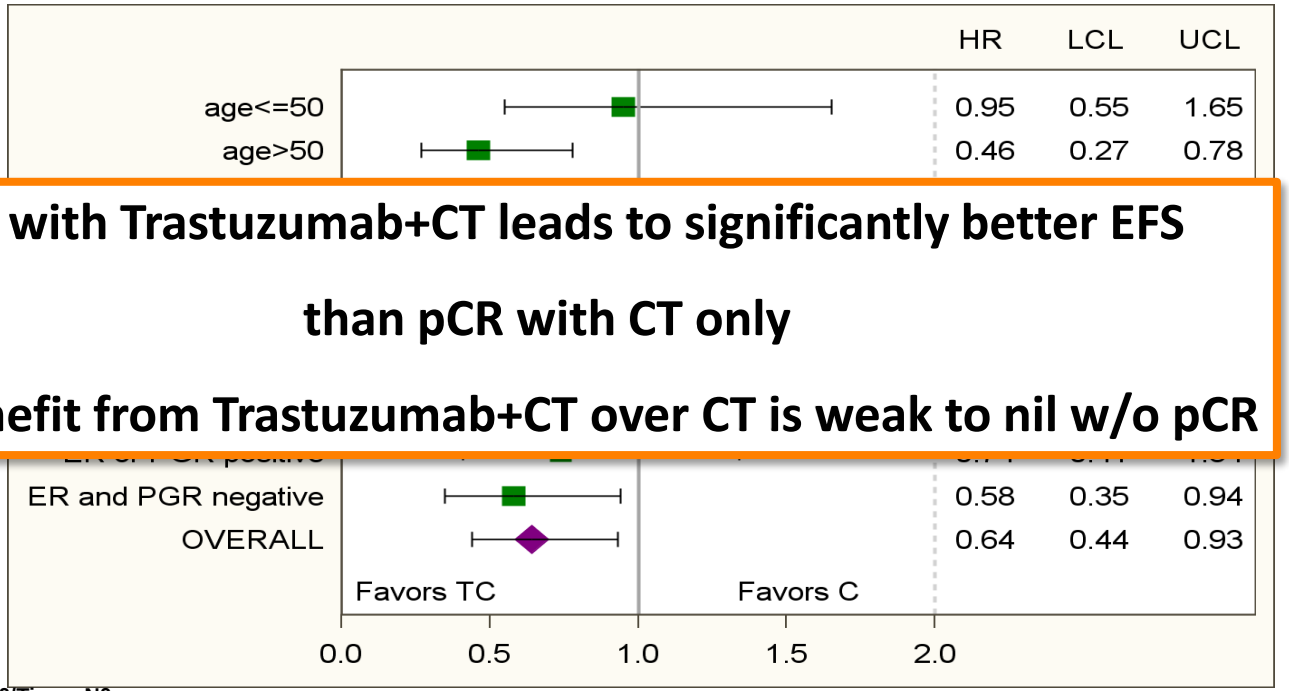

pCR with Trastuzumab+CT leads to significantly better EFS

than pCR with CT only

EFS benefit from Trastuzumab+CT over CT is weak to nil w/o pCR

pCR: ypT0/Tis, ypN0

Gianni L et al, Lancet Oncol 2014

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Lessons learned from the pCR/RD dichotomy

- pCR is a powerful predictor of long-term benefit in women with HER2+ or TNBC (examples in HR+ are also available)
  - Improving the chances of pCR is a legitimate goal to be pursued with new drugs and new studies
- Different drugs/regimens have different effects that provide different quality to the dichotomous opposition of pCR and RD
- RD is not equivalent to failure

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We treat individual patients and seek their individual benefit

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We treat individual patients and seek their individual benefit

Neoadjuvant therapy provides key information

to individually tailor treatments

KATHERINE Study Design

- cT1–4/N0–3/M0 at presentation (cT1a–b/N0 excluded)
- HER2-positive eBC*
- Neoadjuvant therapy†
  - Minimum 6 cycles chemo
    - Minimum 9 weeks taxane
    - Anthracyclines and alkylating agents allowed
    - All chemo prior to surgery
  - Minimum 9 weeks H
    - Second HER2-targeted agent allowed
- Residual invasive tumour in the breast or axillary nodes

→ SURGERY → Residual invasive tumour (breast/node) N = 1486 → R 1:1

H
6 mg/kg IV q3w

14 cycles
± ET
± RT‡

T-DM1
3.6 mg/kg IV q3w

Stratification factors:
- Clinical stage at presentation: inoperable vs. operable
- HR status: ER- or PR-positive vs. ER- and PR-negative
- Neoadjuvant HER2-directed therapy: H vs. dual HER2 targeting
- Pathological nodal status evaluated after neoadjuvant therapy

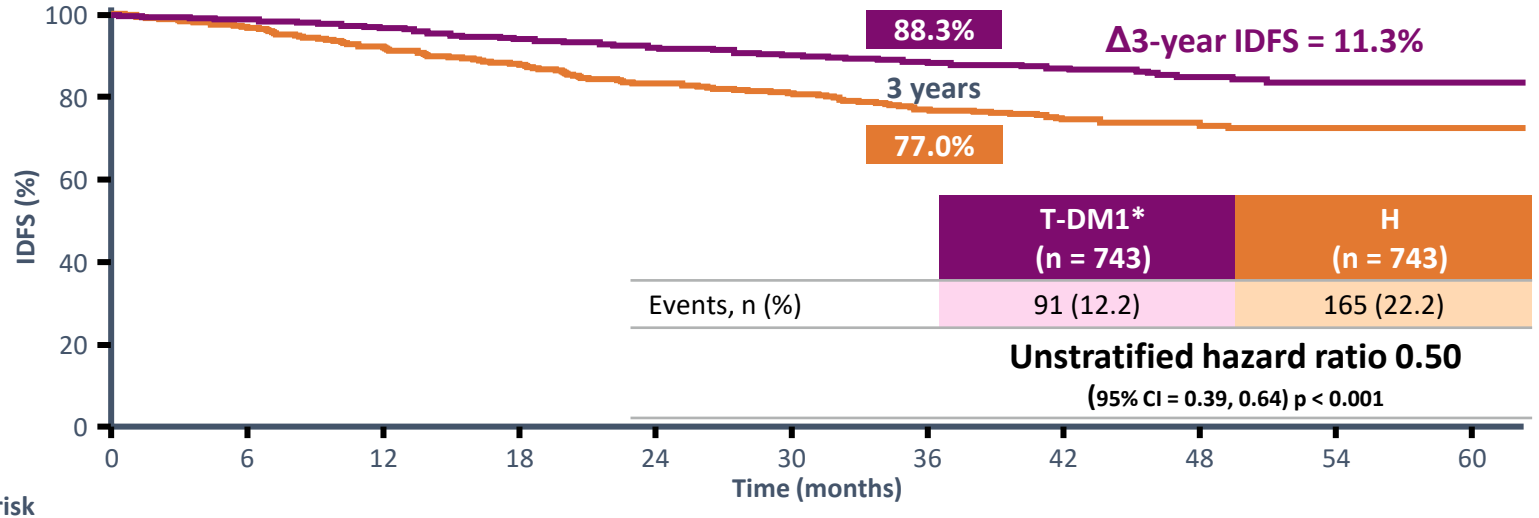
Primary endpoint: IDFS

Key secondary endpoints: IDFS (second primary non-breast cancers included), DFS, OS, DRFI, safety

* Centrally confirmed HER2-positive BC.
† Neoadjuvant systemic treatment was given for at least 6 cycles, with a total duration of at least 16 weeks, including at least 9 weeks of anti-HER2 therapy and at least 9 weeks of taxane-based chemotherapy (or, if receiving dose-dense chemotherapy regimens, at least 8 weeks of taxane-based therapy and at least 8 weeks of anti-HER2 therapy).
‡ ET and RT given per the protocol and local guidelines.
DRFI, distant recurrence-free interval; ET, endocrine therapy; PR, progesterone receptor; RT, radiotherapy.

1. Roche. Data on File. Protocol BO27938 (KATHERINE) – version 6;
2. von Minckwitz G, *et al. N Engl J Med* 2019.

KATHERINE Results: a game changer for high risk HER2+ eBC



No. at risk											
T-DM1	743	707	681	658	633	561	409	255	142	44	4
H	743	676	635	594	555	501	342	220	119	38	4

T-DM1 increased the 3-year IDFS rate from 77.0% to 88.3%

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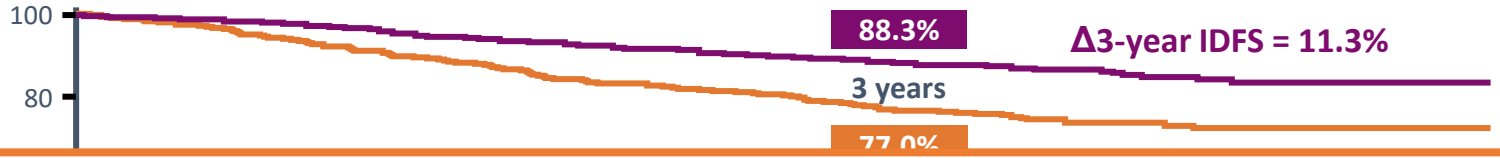

After KATHERINE the application of an adjuvant strategy to patients with high risk HER2+ eBC is suboptimal and in many of them detrimental

Time (months)

No. at risk											
T-DM1	743	707	681	658	633	561	409	255	142	44	4
H	743	676	635	594	555	501	342	220	119	38	4

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Neoadjuvant Systemic Therapy of Breast Cancer: four decades of accomplishements

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for adjuvant trials **(??)**

or immunotherapy (**??**)

Neoadjuvant Systemic Therapy of Breast Cancer: four decades of accomplishements

dual needs (pCR and RD)

ed approval (FDA and EMA)

(??)

Neoadjuvant Systemic Therapy of Breast Cancer: four decades of accomplishements

dual needs (pCR and RD)

ed approv

(??)

Going beyond the stereotype of “one size fits all”

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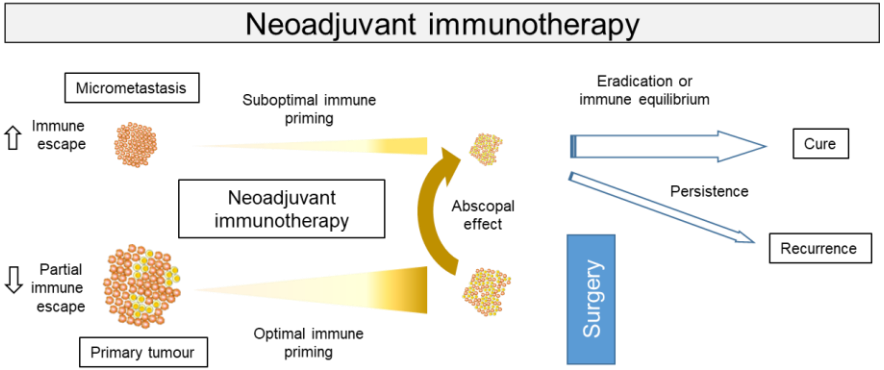
Possible mechanism of improved efficacy of neoadjuvant “immunotherapy”



Bianchini G, De Angelis C, Licata L, Gianni L. Nat Rev Clin Oncol 2022

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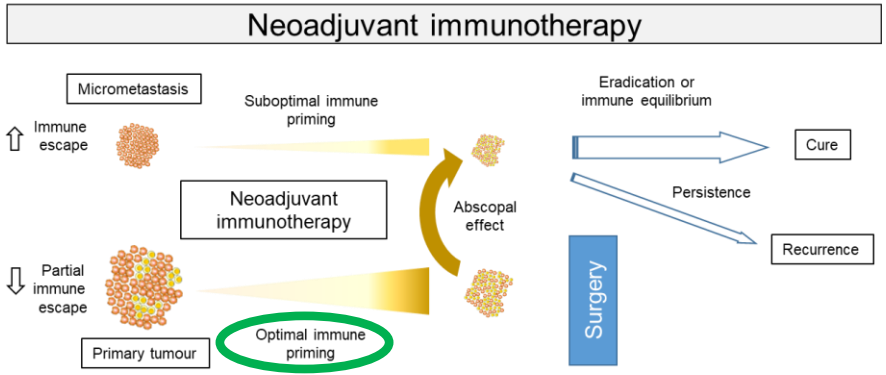

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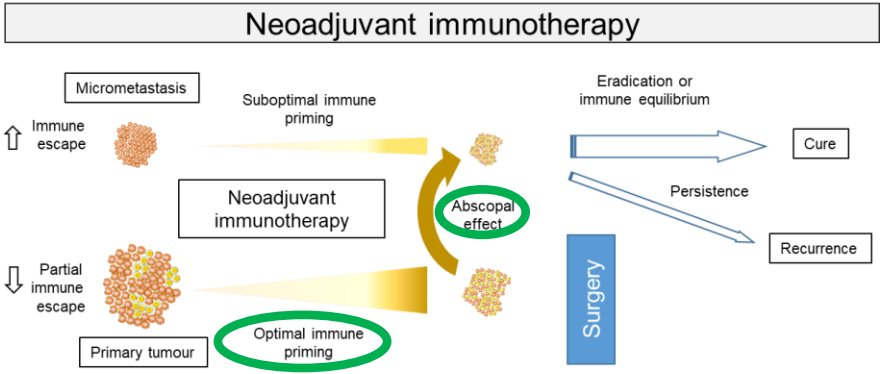

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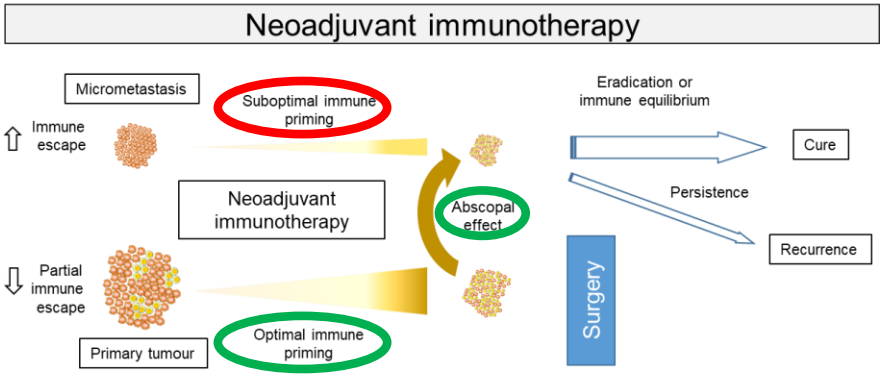

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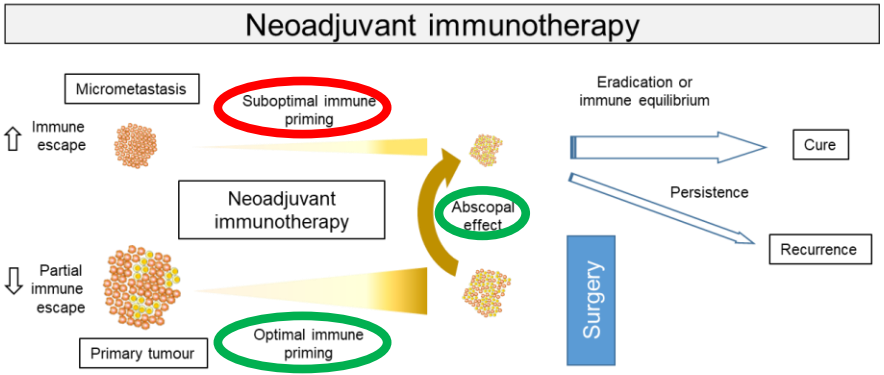

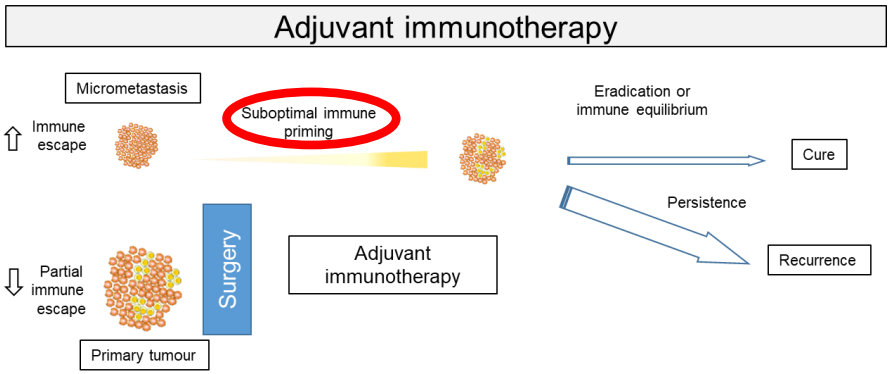

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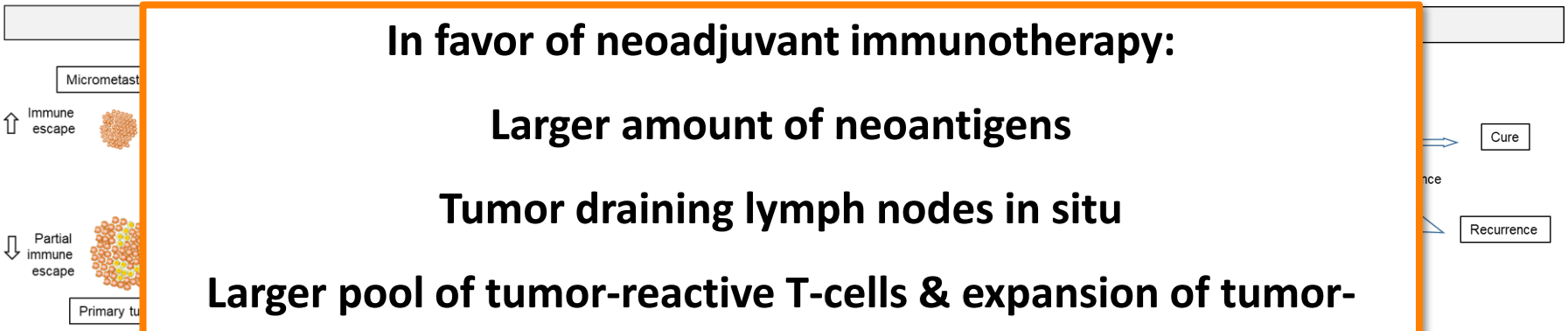


In favor of neoadjuvant immunotherapy:

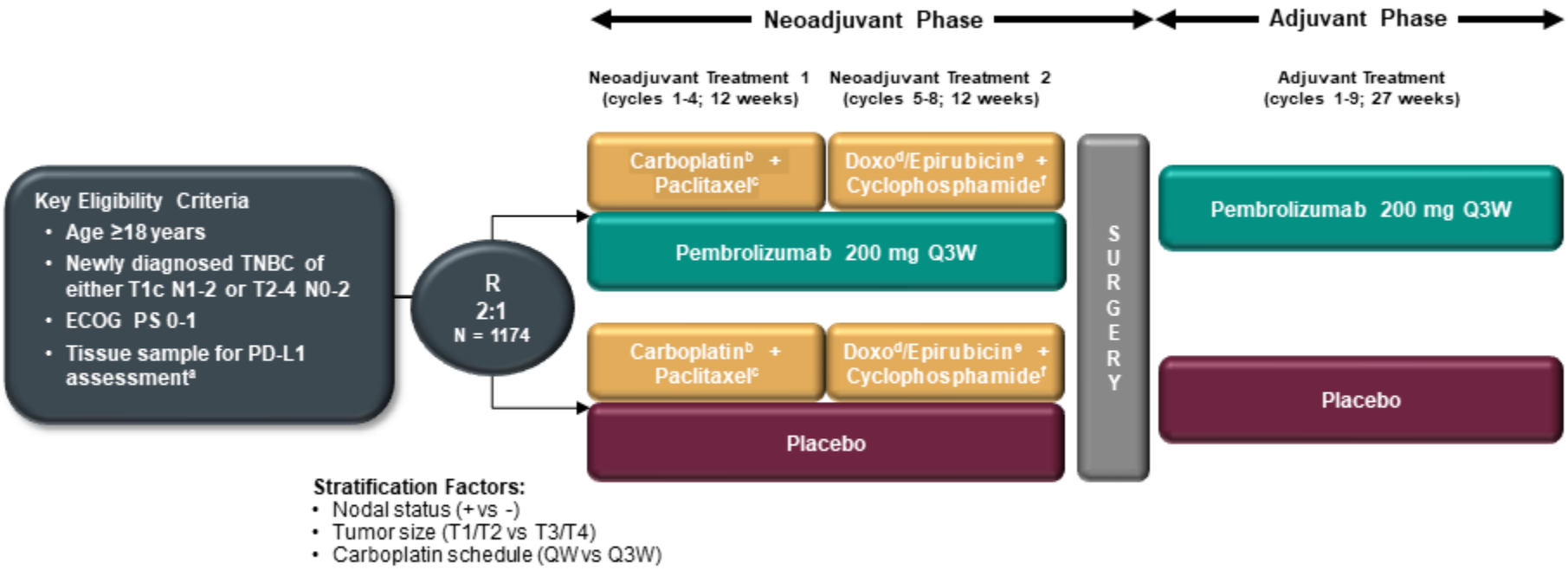
Larger amount of neoantigens

Tumor draining lymph nodes in situ

Larger pool of tumor-reactive T-cells & expansion of tumor-resident T-cell clones

Bianchini G, De Angelis C, Licata L, Gianni L. Nat Rev Clin Oncol 2022

KEYNOTE-522 Study Design (NCT03036488)



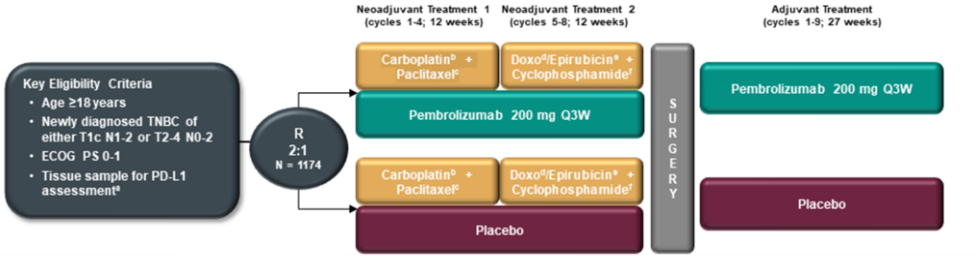
Stratification Factors:
- Nodal status (+ vs -)
- Tumor size (T1/T2 vs T3/T4)
- Carboplatin schedule (QW vs Q3W)

Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

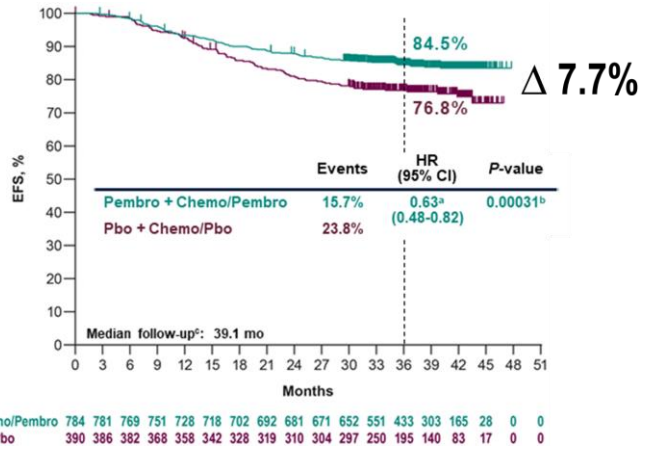
Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

[a]Must consist of at least 2 separate tumor cores from the primary tumor.
[b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW.
[c]Paclitaxel dose was 80 mg/m² QW.
[d]Doxorubicin dose was 60 mg/m² Q3W.
[e]Epirubicin dose was 90 mg/m² Q3W.
[f]Cyclophosphamide dose was 600 mg/m² Q3W.

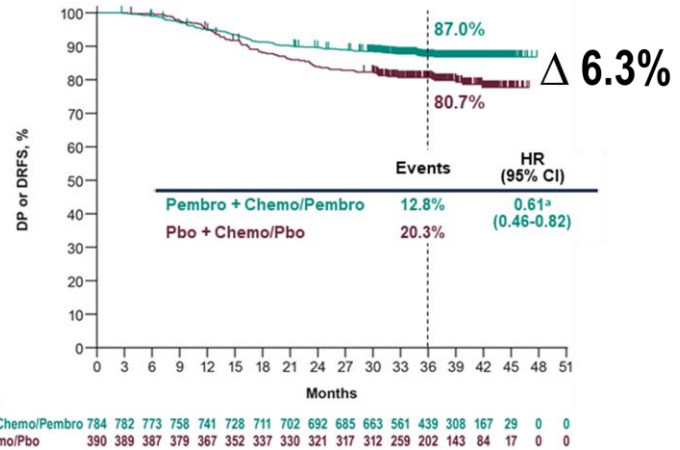
KEYNOTE 522: the new standard in high-risk eTNBC



EFS

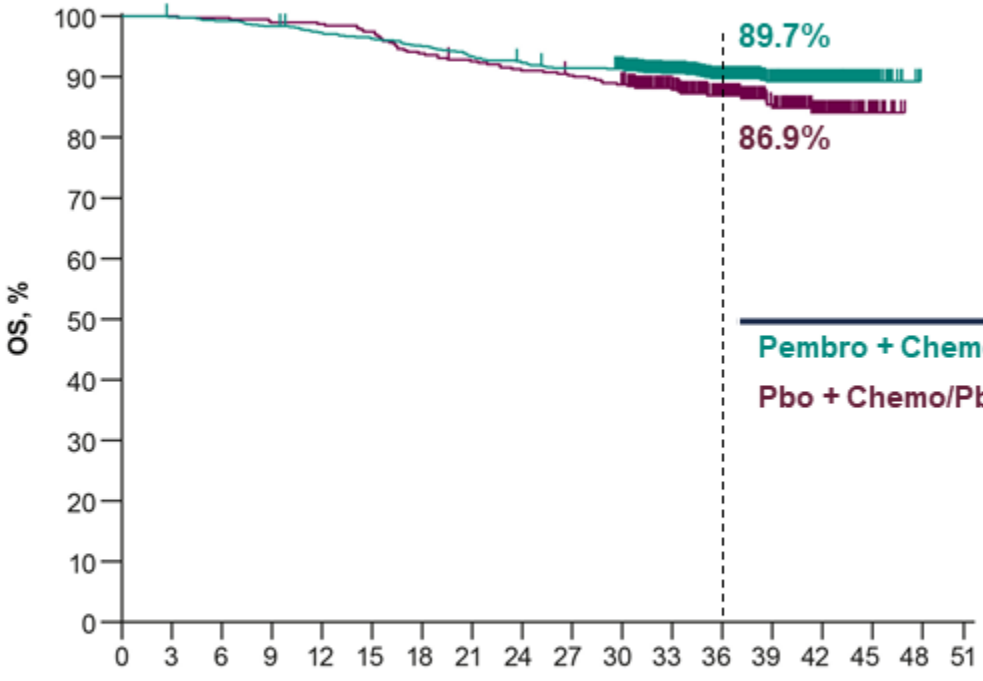


DDFS



Schmid P ESMO Virtual Plenary 2021; Schmid P NEJM 2022

Overall Survival



	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	10.2%	0.72[a] (0.51-1.02)	0.03214[b]
Pbo + Chemo/Pbo	14.1%		

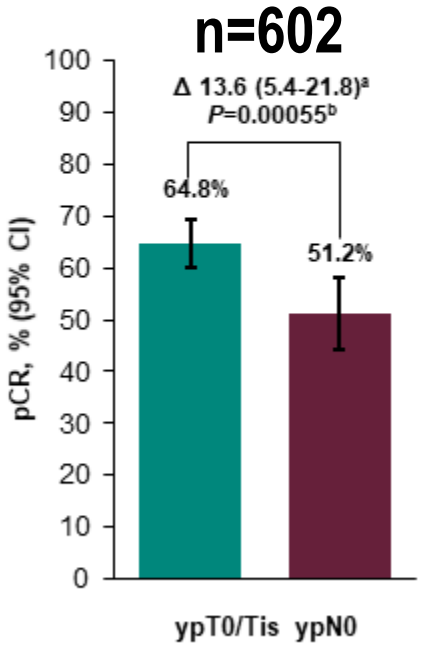
No. at Risk																		
Pembro + Chemo/Pembro	784	782	777	770	759	752	742	729	720	712	701	586	461	323	178	30	0	0
Pbo + Chemo/Pbo	390	390	389	386	385	380	366	360	354	350	343	286	223	157	89	17	0	0

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [b]Prespecified *P*-value boundary of 0.00086 not reached at this analysis.
Data cutoff date: March 23, 2021.

Prior Analyses of KEYNOTE-522

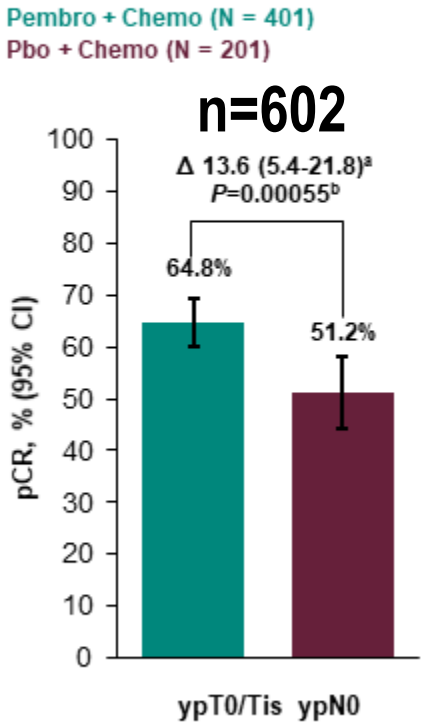
Primary pCR Endpoint at IA1[1]

Pembro + Chemo (N = 401)
Pbo + Chemo (N = 201)



Prior Analyses of KEYNOTE-522

Primary pCR Endpoint at IA1[1]



ODAC (ITT population, IA3, n=1174)

→ Δ pCR 7.5%

Prior Analyses of KEYNOTE-522

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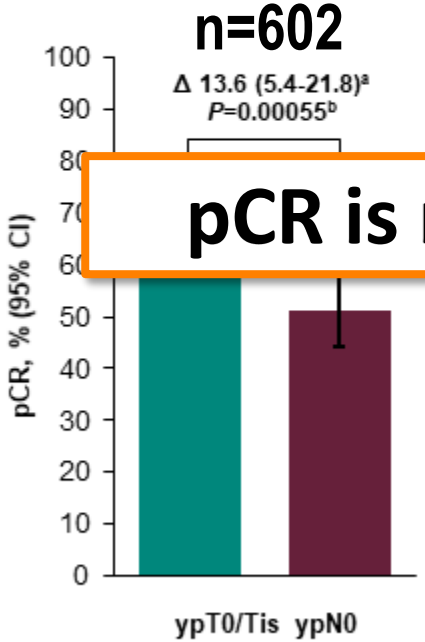
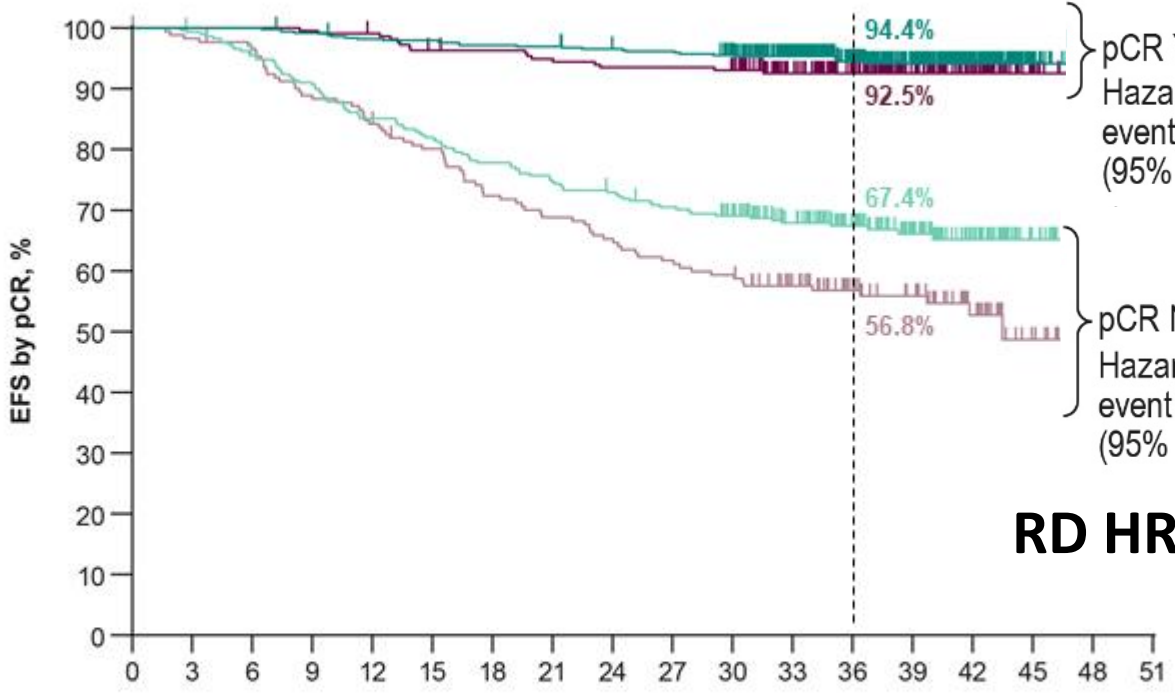
Pbo + Chemo (N = 201)



pCR is not the only driver of benefit

→ Δ pCR 7.5%

EFS by pCR (ypT0/Tis ypN0)

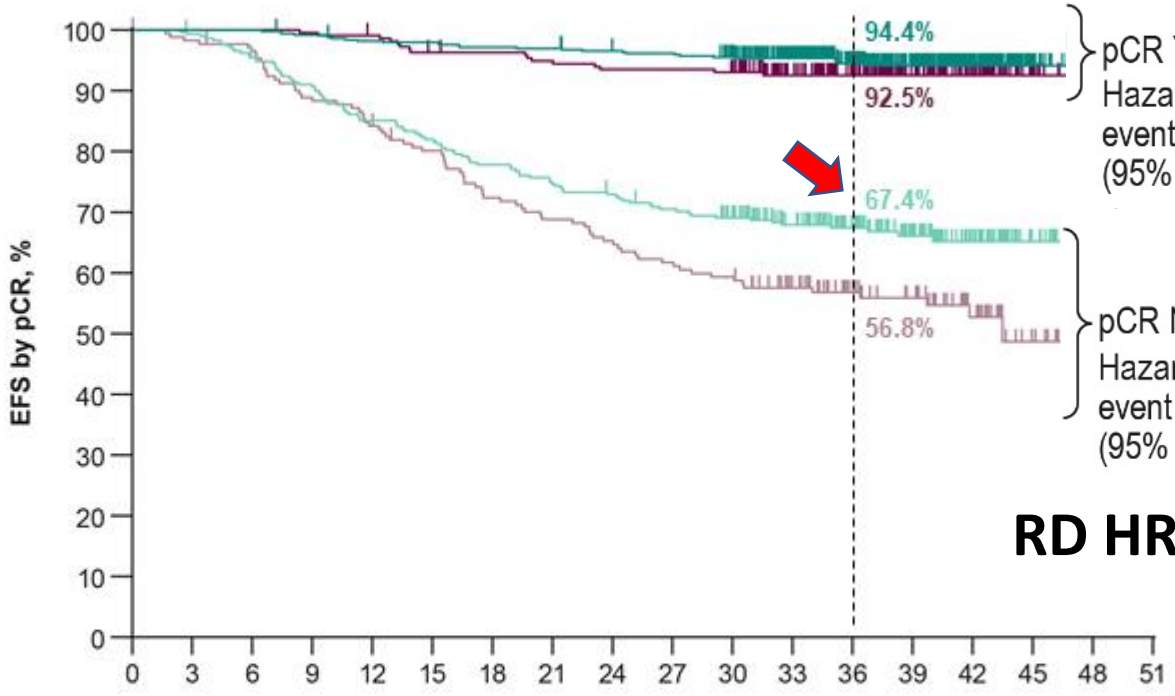


RD HR 0.70

No. at Risk																		
Pembro + Chemo/Pembro Responder	494	494	494	489	483	482	478	477	472	470	460	387	307	220	122	18	0	0
Pbo + Chemo/Pbo Responder	217	217	217	216	214	207	206	203	200	200	197	165	130	87	56	9	0	0
Pembro + Chemo/Pembro Non-Responder	290	287	275	262	245	236	224	215	209	201	192	164	126	83	43	10	0	0
Pbo + Chemo/Pbo Non-Responder	173	169	165	152	144	135	122	116	110	104	100	85	65	53	27	8	0	0

Data cutoff date: March 23, 2021.

EFS by pCR (ypT0/Tis ypN0)



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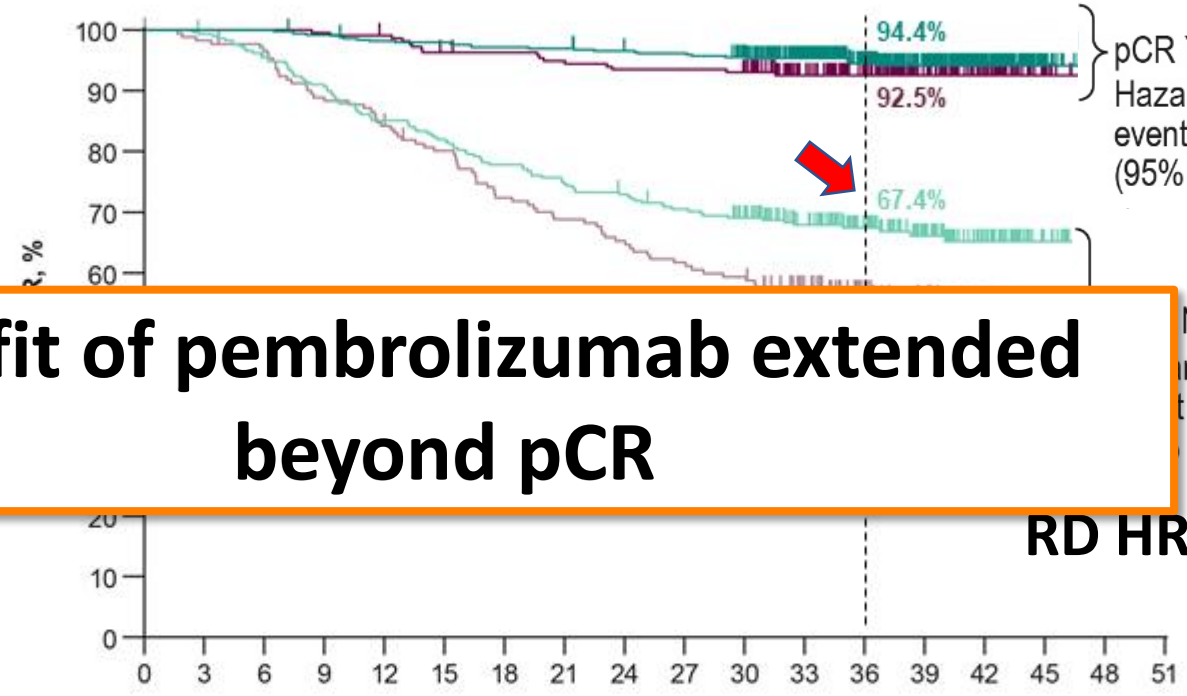

Benefit of pembrolizumab extended beyond pCR

RD HR 0.70

No. at Risk																		
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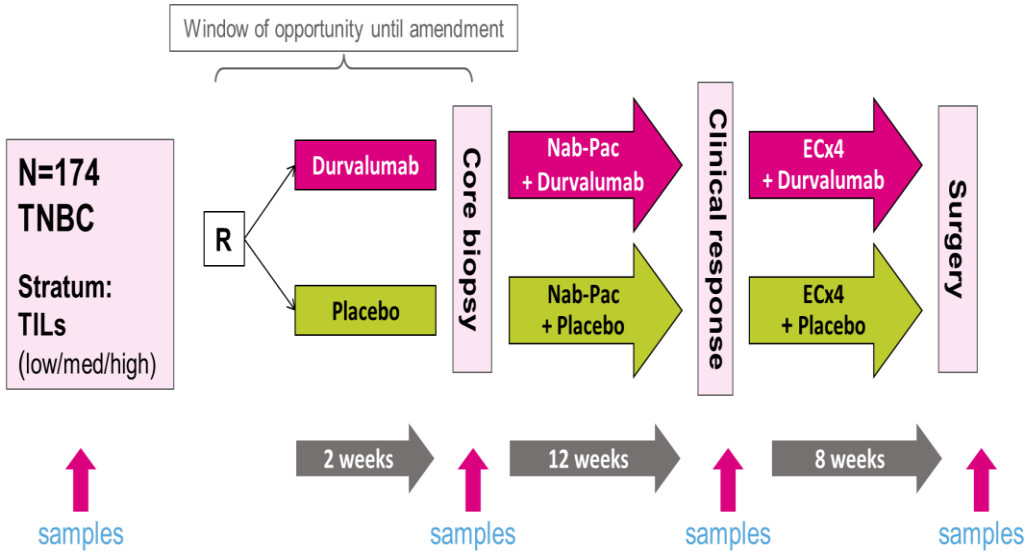
GeparNuevo: addition of Durvalumab to a taxane-anthracycline containing chemotherapy in early TNBC

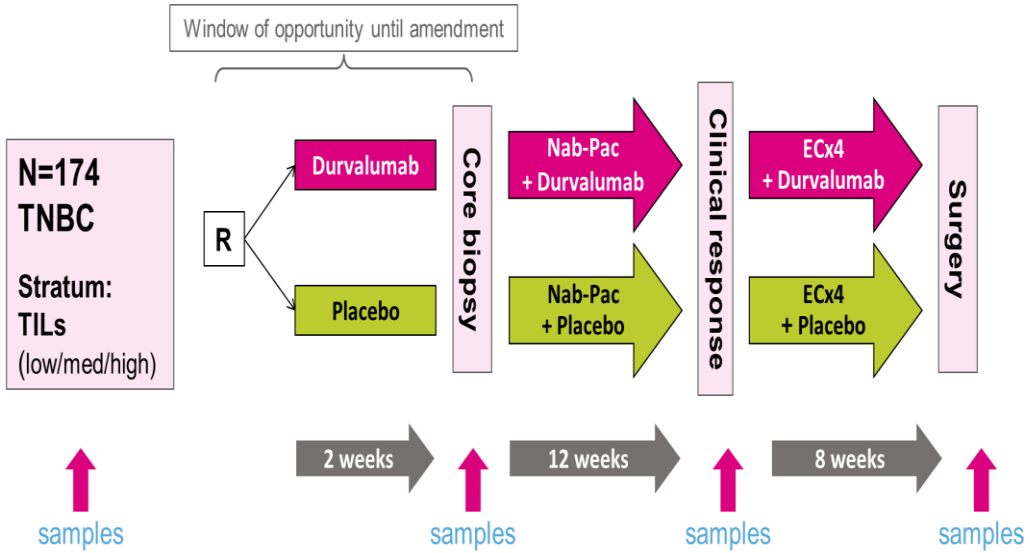


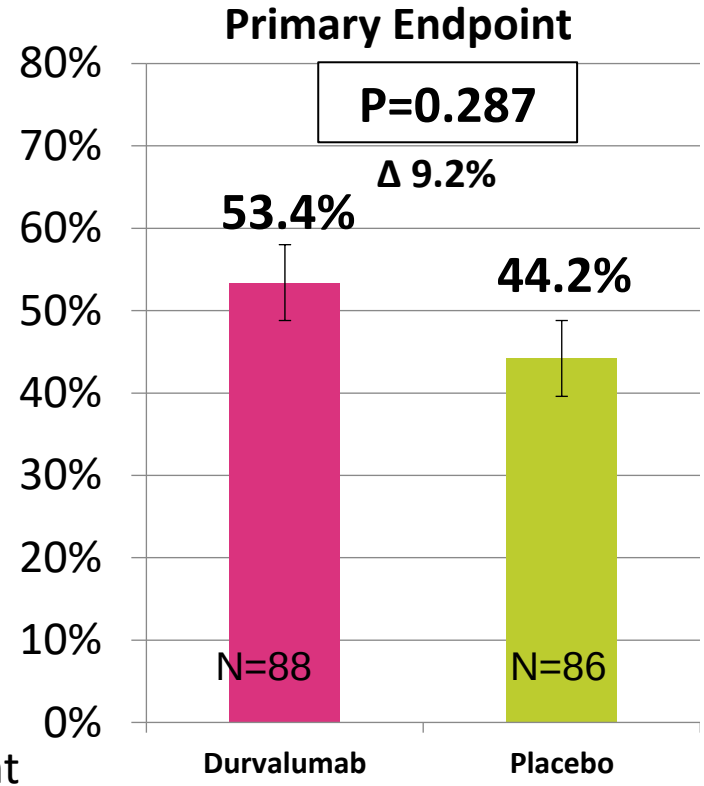
No adjuvnat ICB

(patients were allowed to receive a post-neoadjuvant treatment according to the treating physician)

Loibl S Annals of Oncology 2019

GeparNuevo: addition of Durvalumab to a taxane-anthracycline containing chemotherapy in early TNBC





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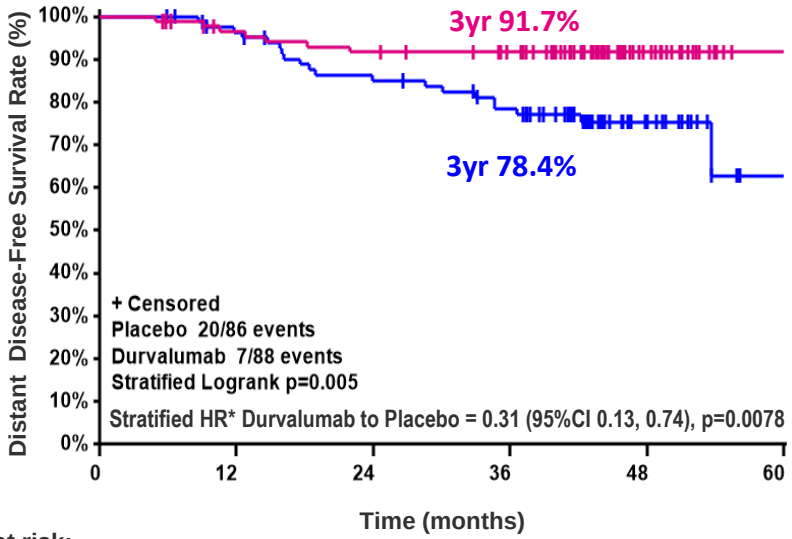
Loibl S Annals of Oncology 2019

GeparNuevo: DDFS and OS (exploratory)

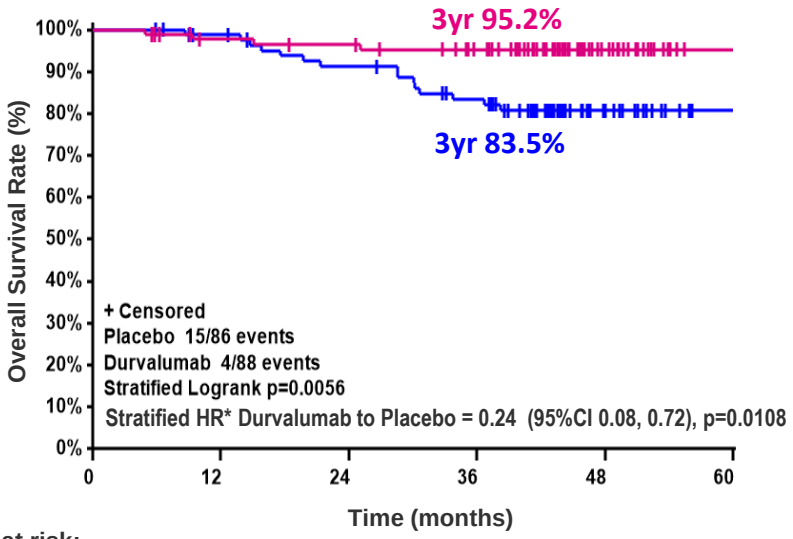
DDFS



Patients at risk:

Placebo	86	78	67	59	16	0
Durvalumab	88	80	76	70	20	0

OS



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* Stratified by sTILs

Loibl S Annals of Oncology 2022

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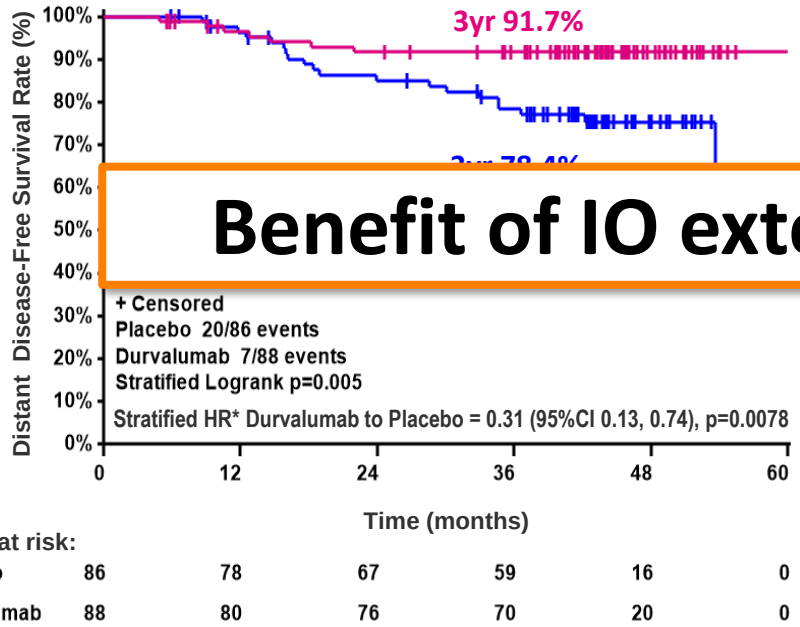
DDFS



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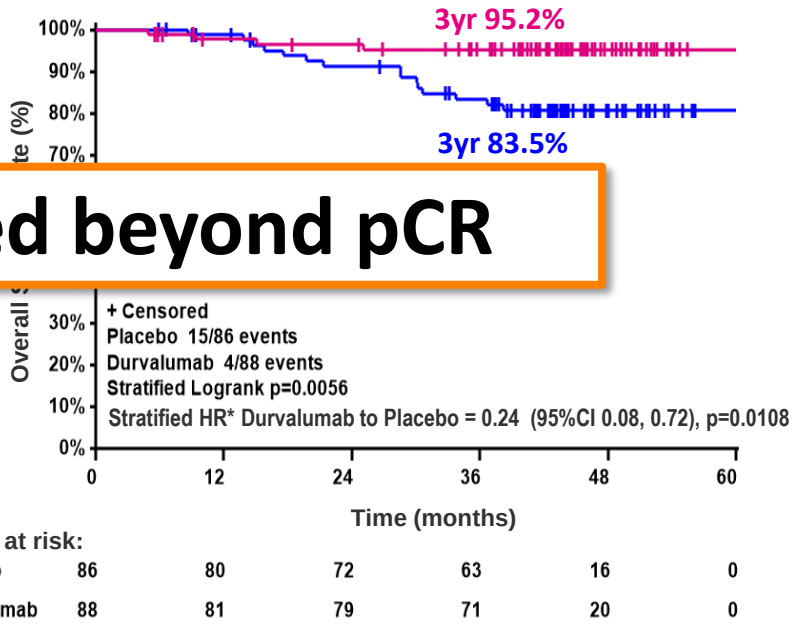

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Benefit of IO extended beyond pCR

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Loibl S Annals of Oncology 2022

NeoTRIP trial: addition of atezolizumab has minor impact on pCR

TN high-risk **(T1cN1; T2N1; T3N0)** or locally advanced

n=280

R

Carboplatin+*nab*-paclitaxel

Carboplatin + *nab*-paclitaxel + Atezolizumab

Surgery

Not evaluable patients
Arm CT (11 pts)
- 5 pts (Consent withdrawal)
- 3 pts (Screening failure post-randomization)
- 3 pts (No surgery without PD)

Arm CT/Atezo (11 pts)
- 2 pts (Consent withdrawal)
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- 1 pts (Lost during treatment)
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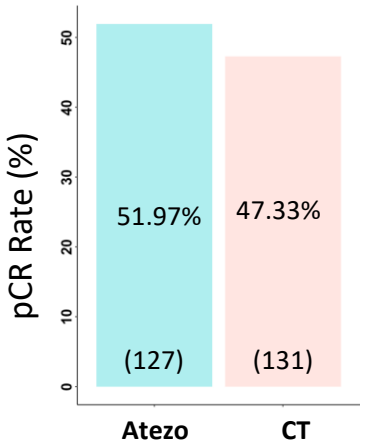
280 patients
(Intention-to-treat)

258 patients
(Per-protocol-population)

p = 0.53
$\Delta = \mathbf{4.64}\%$



Carboplatin (AUC2) + *nab*-paclitaxel (125 mg/m^2) weekly for 2 wks every 3; 8 cy; Atezolizumab (1200 mg) day 1 every 3 wks for 8 cycles
Gianni L SABCS 2019 (Abstract G3-02); Gianni L Ann Oncol 2022; Bianchini G ESMO 2020

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FONDAZIONE MICHELANGELO

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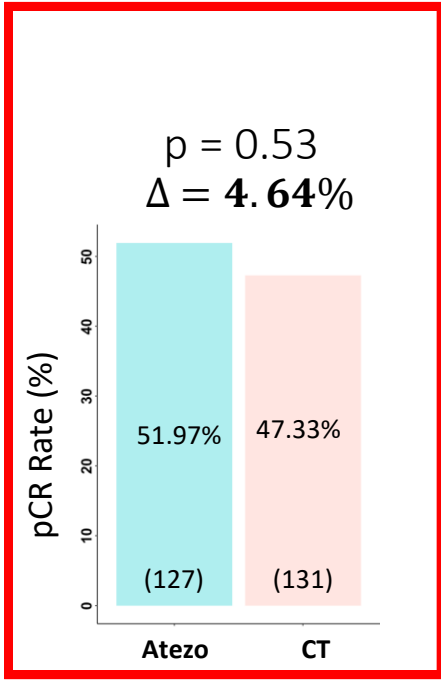

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FONDAZIONE MICHELANGELO

Summary on neoadjuvant IO in EBC TN

- IO has higher chances of efficacy as addition to neoadjuvant chemotherapy in TN EBC
- Neoadjuvant pembrolizumab (Keynote-522), durvalumab (Geparnuevo) and atezolizumab (neoTRIP) added to chemotherapy lead to minor improvement of pCR rates over chemotherapy alone
- A significant EFS and OS benefit from neoadjuvant/adjuvantIO (Keynote-522) can be measured irrespective of pCR also in RD cases, and is consistent with exploratory findings in Geparnuevo (neoadjuvant IO only)

Summary on neoadjuvant IO in EBC TN

- IO has higher chances of efficacy as addition to neoadjuvant chemotherapy in TN EBC
- Neoadjuvant pembrolizumab (Keynote-522), durvalumab

Immunotherapy is toxic and expensive

We need predictor(s) of individual benefit

(Keynote-522) can be measured irrespective of pCR also in RD cases, and is consistent with exploratory findings in Geparnuevo (neoadjuvant IO only)

GeparNuevo – Correlative Studies

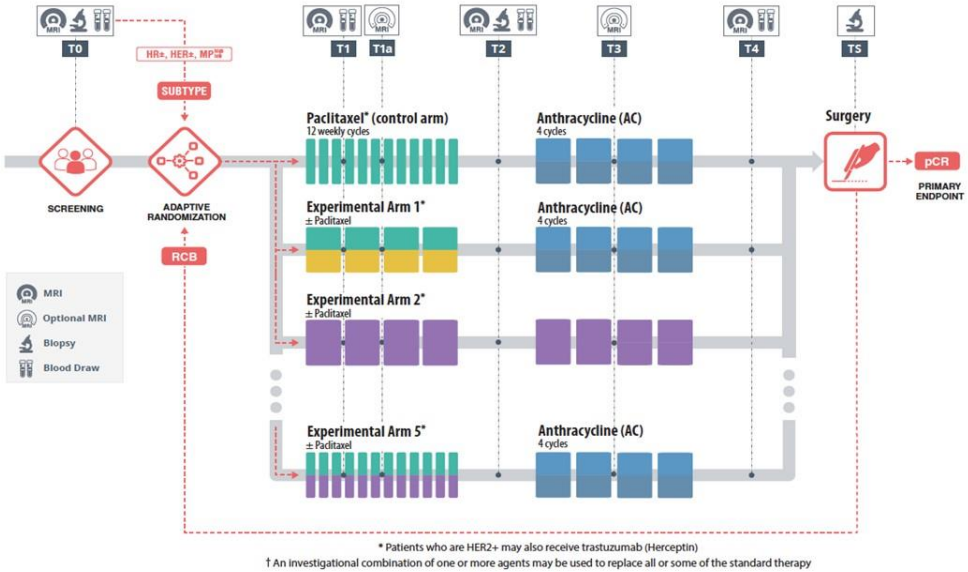
- PD-L1 expression
- TIL
- TMB
- Gene expression signatures

Predicted response to neoadjuvant therapy but not to the addition of immunotherapy

Loibl S, et al. *Ann Oncol* 2019;30:1279-1288
Karn T, et al. *Ann Oncol* 2020;31:1216-1222
Sinn BV, et al. *Clin Cancer Res* 2021;27:2584-2591

The I-SPY 2 TRIAL Standing Platform for High Risk Early Stage Breast Cancer (I-SPY 2.0)

- Phase II, adaptively-randomized neoadjuvant trial
- Shared control arm
  - Standard neoadjuvant chemotherapy
  - HER2+ also gets standard of care for targeted agents
- Simultaneous experimental arms
  - Up to four
- Primary endpoint: pathologic complete response (pCR)
  - Defined as **no residual invasive cancer in the breast or lymph nodes**
- Match therapies with most responsive subtypes
  - Defined by **HR, HER2**, MammaPrint High1/(ultra) High 2 (**MP1/2**) status



- Agents/combinations **"graduate"** for efficacy = reaching >85% predictive probability of success in a subsequent phase III trial in the most responsive patient subset (HR/HER2/MP)

Denise Wolf et al. , ASCO 2023

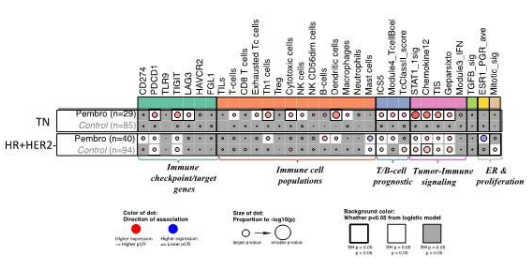
Immune modulatory agents in the I-SPY 2 TRIAL

- I-SPY2 has tested 22 agents in ~2500 patients, including >8 IO arms

- We focus on 5 anti-PD1/PDL1 IO arms (plus taxane and anthracycline)
  - IO1: anti-PD1
  - IO2: anti-PDL1/PARPi combination
  - IO3: anti-PD1/TLR9 dual-IO combination
  - IO4: anti-PD1
  - IO5: anti-PD1/LAG3 dual-IO combination

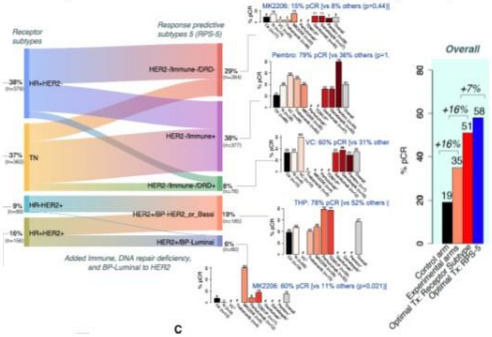
All *graduated for efficacy in TN and/or HR+HER2-*

Denise Wolf et al. , ASCO 2023



Analysis of continuous immune biomarkers

Response Predictive Subtypes (RPS)



Research grade Immune+/- response predictor

Wolf, Yau, van 't Veer et al; 2022 Cancer Cell 40, p1-15

ImPrint → FDA → IDE

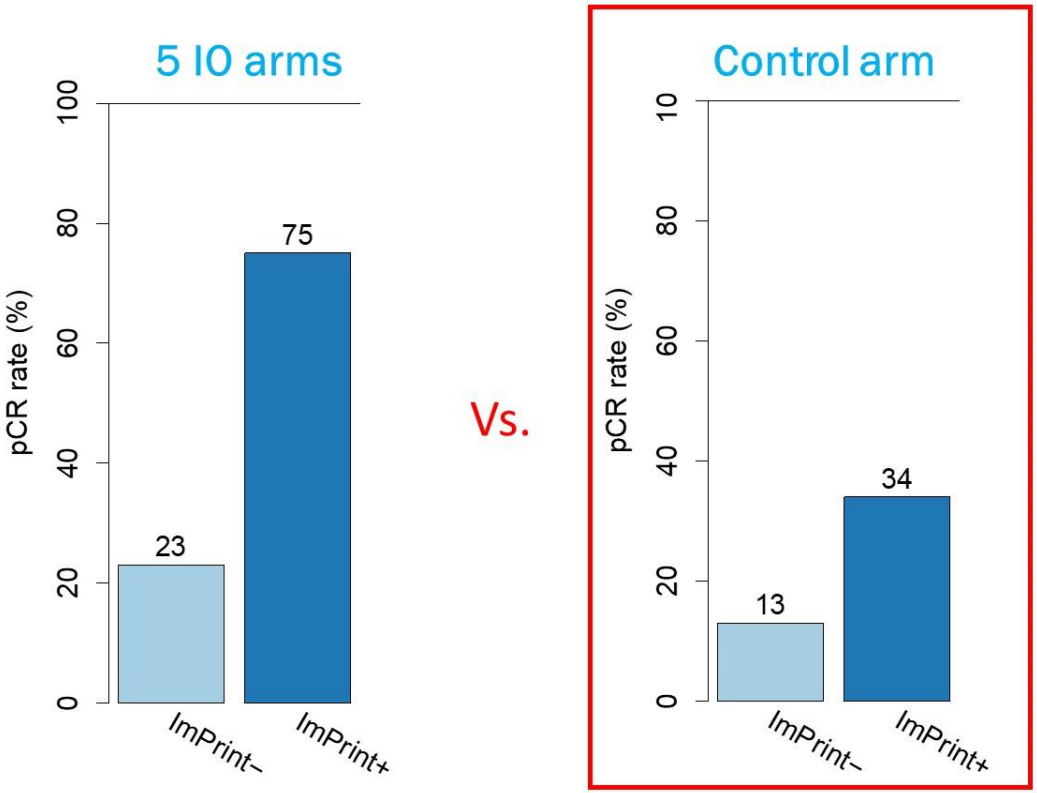
- *Stability*
- *performance*

Clinical-grade Immune+/- response classifier (w/Agendia)

Performance of ImPrint classifier characterized in the 5 IO arms

Denise Wolf et al. , ASCO 2023

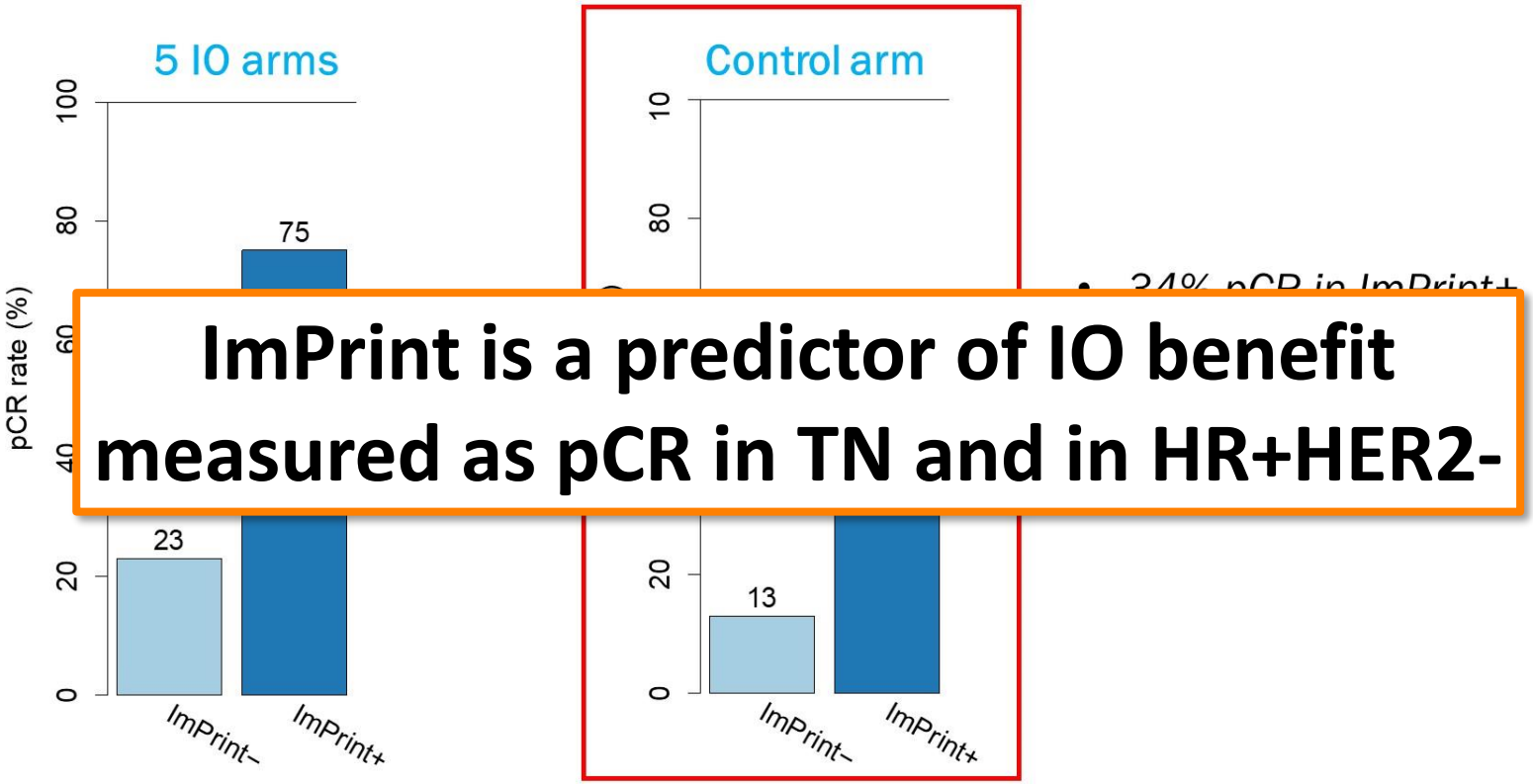
vs. pCR rates in Control arm (n=343)



- *34% pCR in ImPrint+*
  - (HR+:33%; TN: 34%)
- *13% pCR in ImPrint-*
  - (HR+:8%; TN: 21%)

Denise Wolf et al. , ASCO 2023

vs. pCR rates in Control arm (n=343)



ImPrint is a predictor of IO benefit measured as pCR in TN and in HR+HER2-

Denise Wolf et al. , ASCO 2023

NeoTRIP trial: tissue sample collection

TN high-risk **(T1cN1; T2N1; T3N0)** or locally advanced

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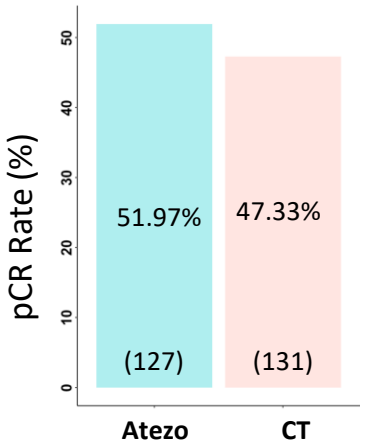

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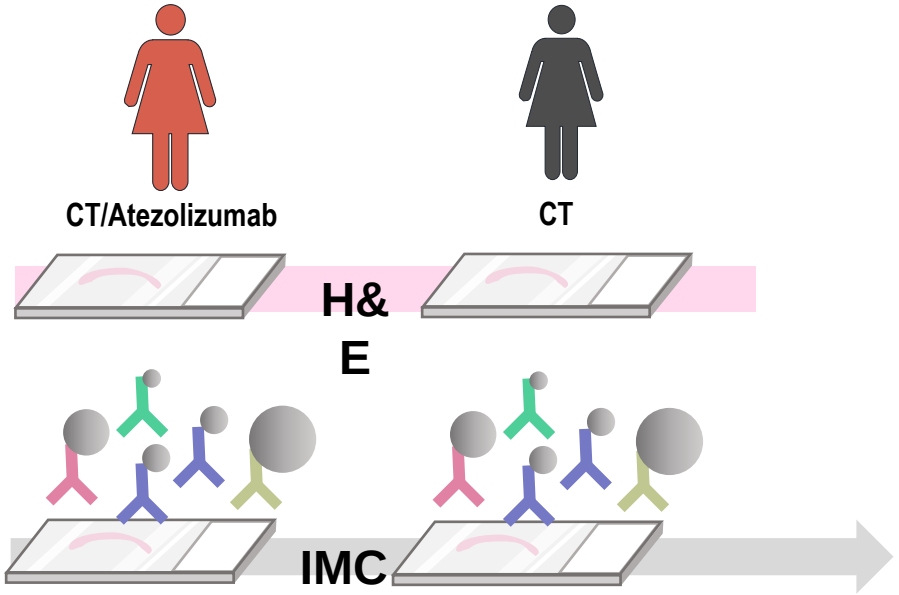
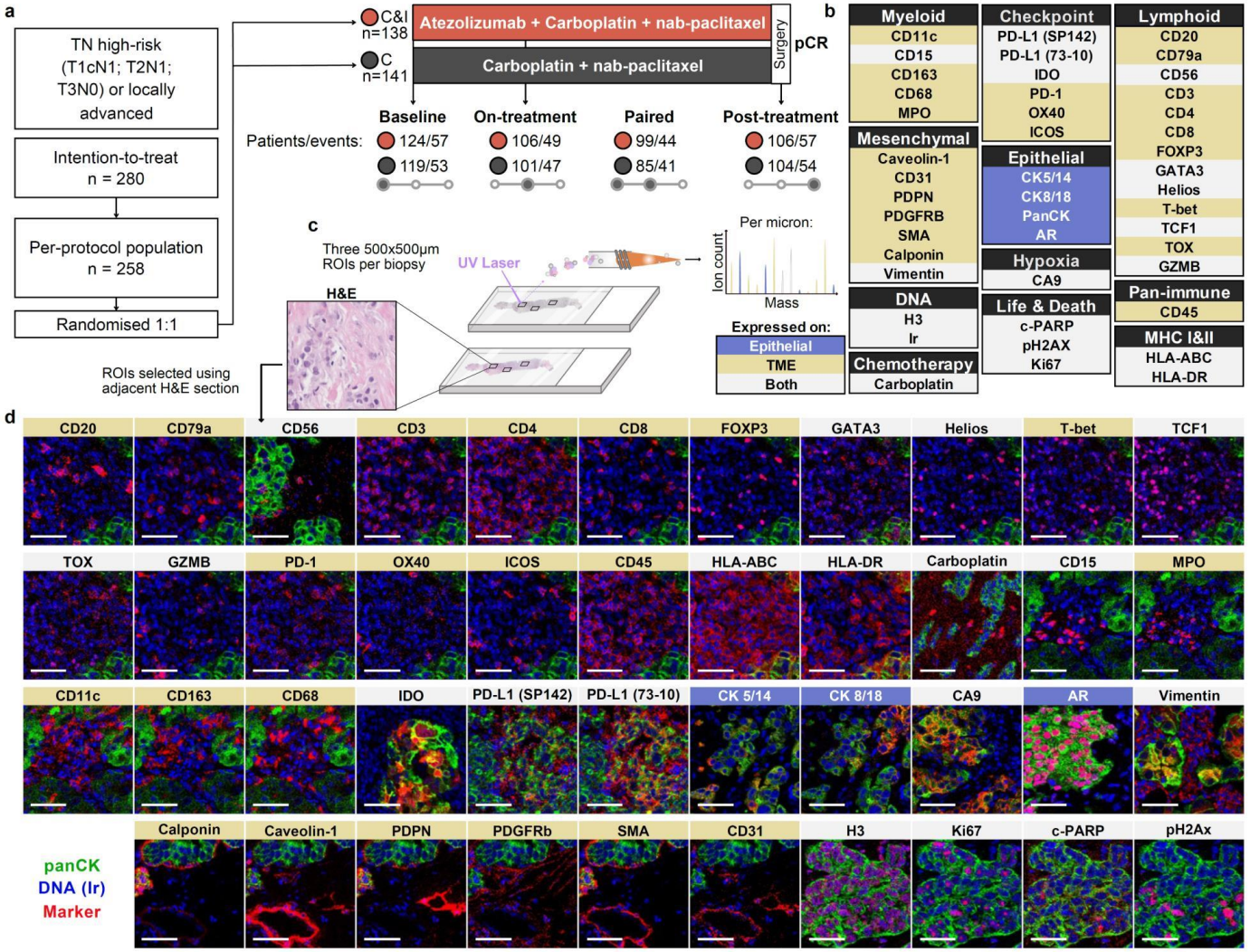
FONDAZIONE MICHELANGELO

Imaging Mass Cytometry panel

- Forty-three proteins spanning cancer cells and the tumor microenvironment (TME) were assessed on pre-treatment FFPE biopsies using imaging mass cytometry (IMC). A second biopsy section was stained with H&E.

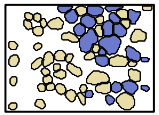


Checkpoint	Lymphoid	Epithelial	Life & Death
PD-L1 (SP142)	CD56	CK5/14	c-PARP
PD-L1 (73-10)	CD20	CK8/18	pH2AX
IDO	CD79a	PanCK	Ki67
PD-1	CD3	**Heterogeneity**	**DNA**
OX40	CD4	AR	H3
ICOS	CD8	GATA3	Ir
Myeloid	FOXP3	CD15	
CD11c	GATA3	**Mesenchymal**	
CD15	Helios	Caveolin-1	
CD163	T-bet	CD31	
CD68	TCF	PDPN	
MPO	TOX	PDGFRB	
MHC I&II	GZMB	SMA	
HLA-ABC	**Pan-immune**	Vimentin	
HLA-DR	CD45	Calponin	


a
TN high-risk (T1cN1; T2N1; T3N0) or locally advanced
Intention-to-treat n = 280
Per-protocol population n = 258
Randomised 1:1
C&I n=138
Atezolizumab + Carboplatin + nab-paclitaxel
C n=141
Carboplatin + nab-paclitaxel
Surgery
pCR
Baseline
On-treatment
Paired
Post-treatment
Patients/events:
124/57
119/53
106/49
101/47
99/44
85/41
106/57
104/54
b
Myeloid
CD11c
CD15
CD163
CD68
MPO
Mesenchymal
Caveolin-1
CD31
PDPN
PDGFRB
SMA
Calponin
Vimentin
DNA
H3
Ir
Chemotherapy
Carboplatin
Checkpoint
PD-L1 (SP142)
PD-L1 (73-10)
IDO
PD-1
OX40
ICOS
Epithelial
CK5/14
CK8/18
PanCK
AR
Hypoxia
CA9
Life & Death
c-PARP
pH2AX
Ki67
Lymphoid
CD20
CD79a
CD56
CD3
CD4
CD8
FOXP3
GATA3
Helios
T-bet
TCF1
TOX
GZMB
Pan-immune
CD45
MHC I&II
HLA-ABC
HLA-DR
c
Three 500x500µm ROIs per biopsy
H&E
UV Laser
Per micron:
Ion count
Mass
Expressed on:
Epithelial
TME
Both
ROIs selected using adjacent H&E section
d
CD20
CD79a
CD56
CD3
CD4
CD8
FOXP3
GATA3
Helios
T-bet
TCF1
TOX
GZMB
PD-1
OX40
ICOS
CD45
HLA-ABC
HLA-DR
Carboplatin
CD15
MPO
CD11c
CD163
CD68
IDO
PD-L1 (SP142)
PD-L1 (73-10)
CK 5/14
CK 8/18
CA9
AR
Vimentin
Calponin
Caveolin-1
PDPN
PDGFRb
SMA
CD31
H3
Ki67
c-PARP
pH2Ax
panCK
DNA (Ir)
Marker

Spatial connectivity between Epithelial and TME

- Heterotypic spatial connectivity between epithelial and TME cells w assessed

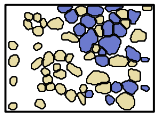


Epithelial cells

TME cells

Spatial connectivity between Epithelial and TME

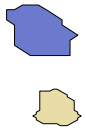
- Heterotypic spatial connectivity between epithelial and TME cells w assessed
- Only tight contacts between epithelial and TME cells were considered interactions



Epithelial cells

TME cells

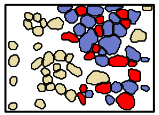
Interaction



NO interaction

Spatial connectivity between Epithelial and TME

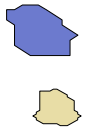
- Heterotypic spatial connectivity between epithelial and TME cells w assessed
- Only tight contacts between epithelial and TME cells were considered interactions



Epithelial cells

TME cells

Interaction



NO interaction

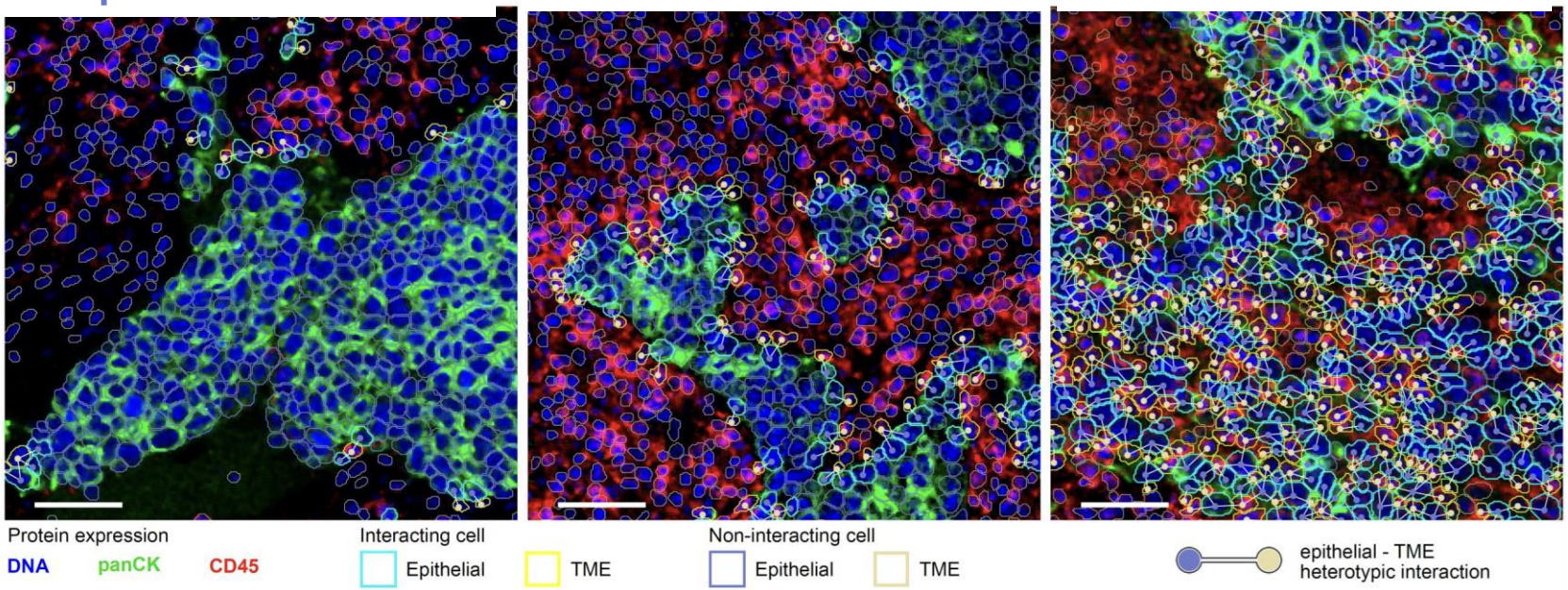
Spatial connectivity between Epithelial and TME

Low degree of interaction between Epithelial and TME

Medium degree of interaction between Epithelial and TME

High degree of interaction between Epithelial and TME

a



C. Wang, L. Gianni, G. Bianchini, R. Ali, accepted, *Nature* 2023

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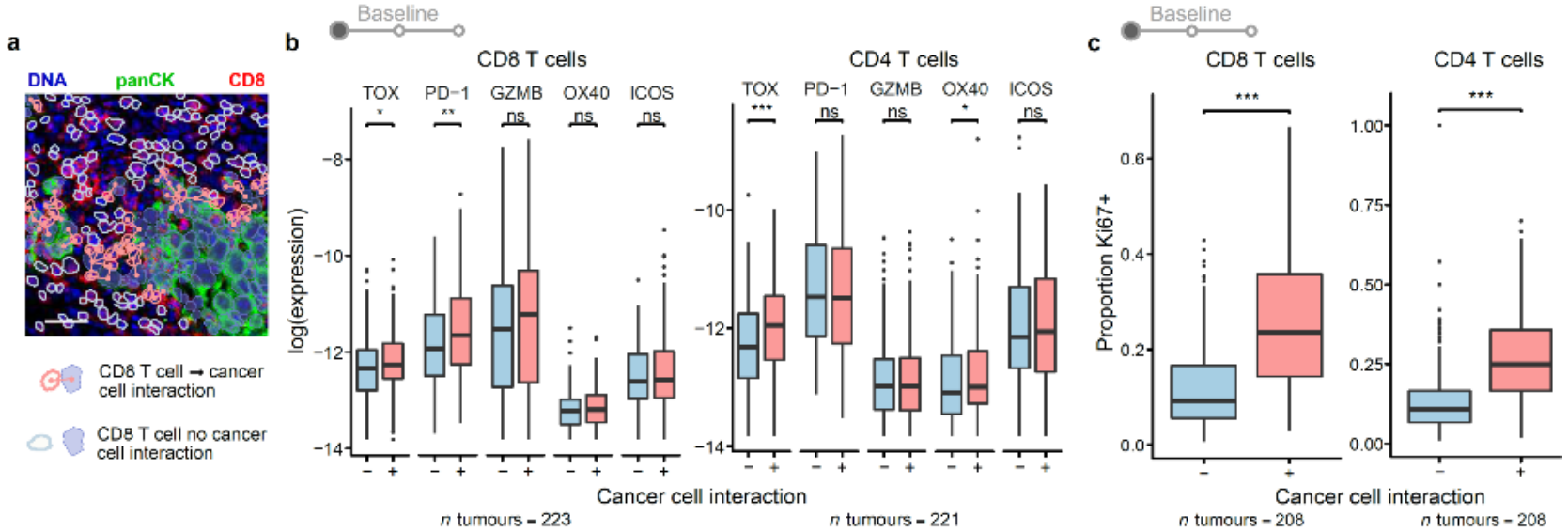
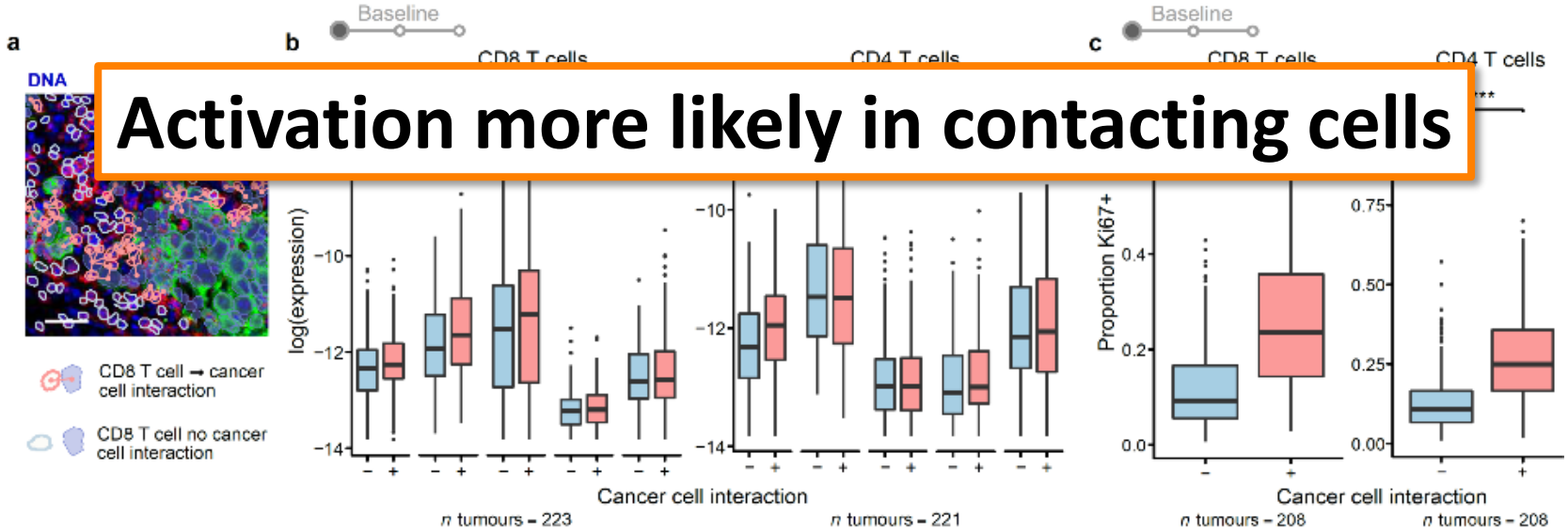
Differential activation of T cells in contact with cancer cells



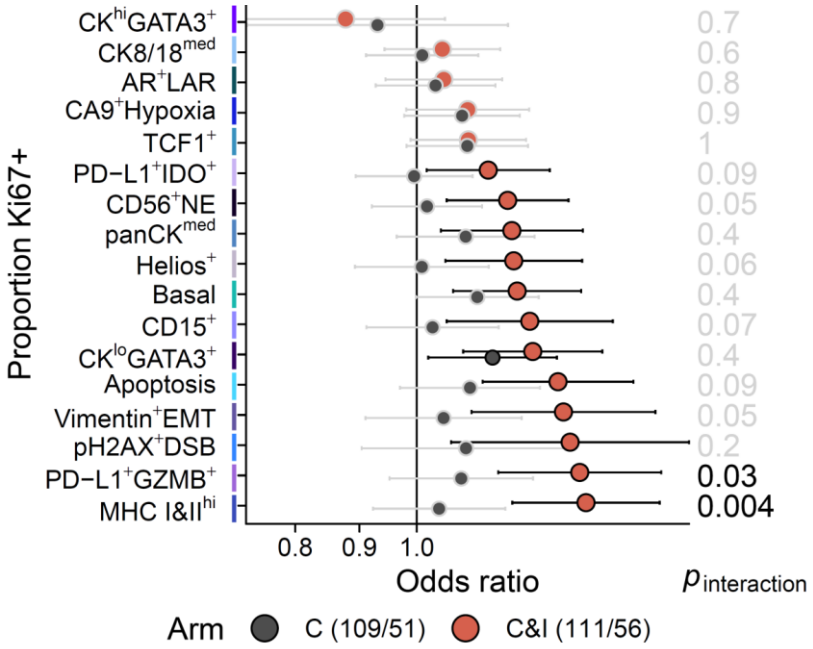
Differential activation of T cells in contact with cancer cells

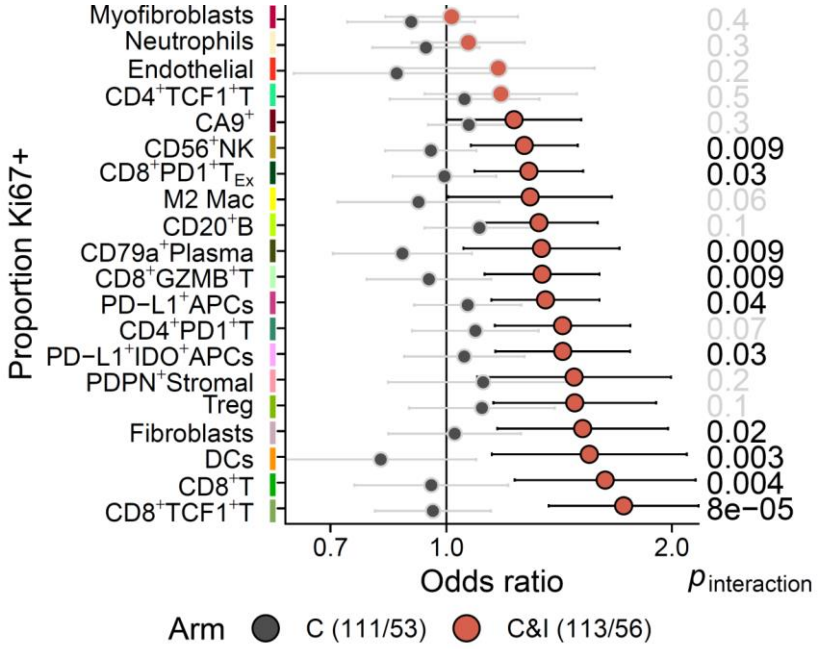


Activation more likely in contacting cells

C. Wang, L. Gianni, G. Bianchini, R. Ali, accepted, *Nature* 2023

Proliferative fraction and IO response





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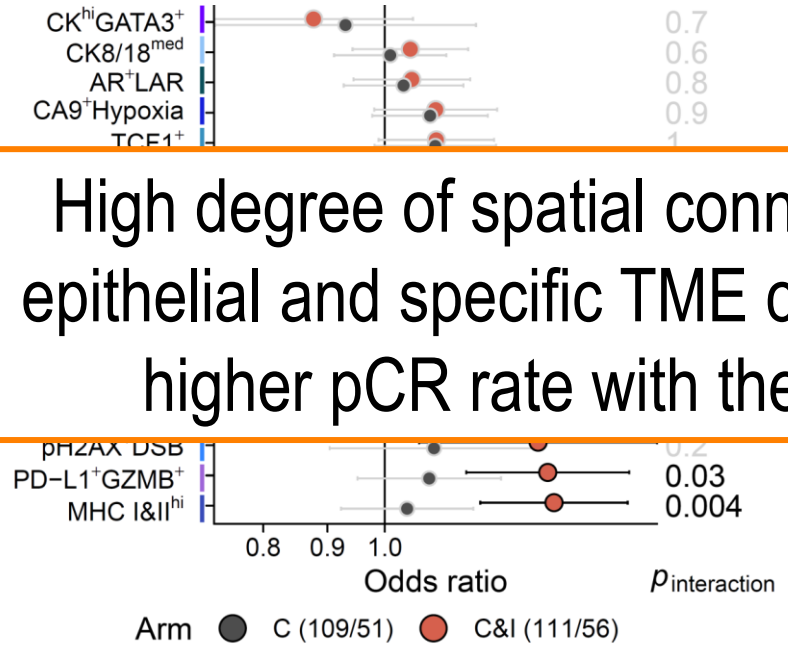
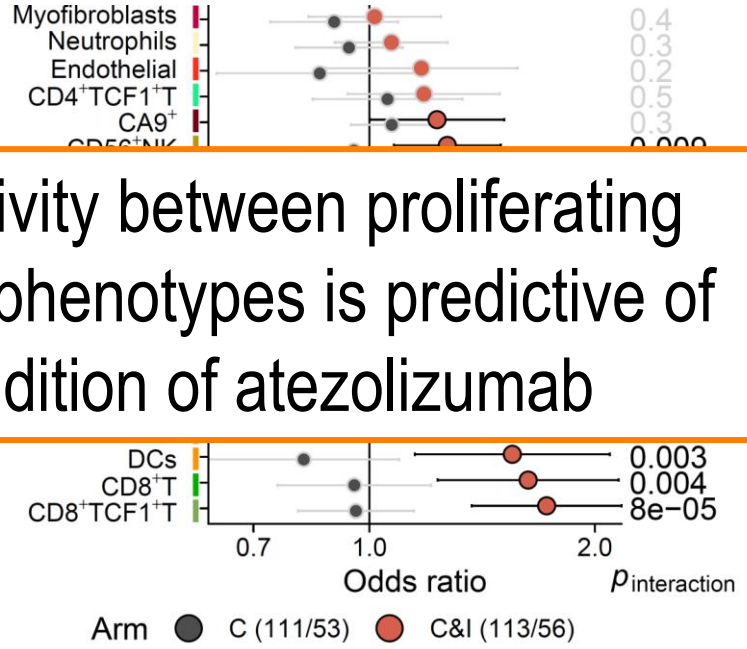
Proliferative fraction and IO response





High degree of spatial connectivity between proliferating epithelial and specific TME cell phenotypes is predictive of higher pCR rate with the addition of atezolizumab

C. Wang, L. Gianni, G. Bianchini, R. Ali, accepted, *Nature* 2023

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Summary

- Neoadjuvant therapy provides an outstanding opportunity to individually tailor treatment(s) around the probability of individual success
- Translational sciences are offering outstanding investigational tools that are paving the way to make individual treatments real and toxic/costly over-treatment less and less likely
- The challenge now is to transfer translational findings (ImPrint, IMC) from the complexity of omics analysis to simple tools for everyday practice: not impossible and ongoing

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Concluding remark

- Treatment tailored to invidual needs is the goal and the challenge
- The neoadjuvant approach is the tool to meet the challenge

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