THE BREAST
'Il Punto di Vista dell'Esperto'

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Disclosures

Scientific advisory board, meeting, congress:

Astra Zeneca
Celgene
Lilly
Novartis
Pfizer
Roche

…

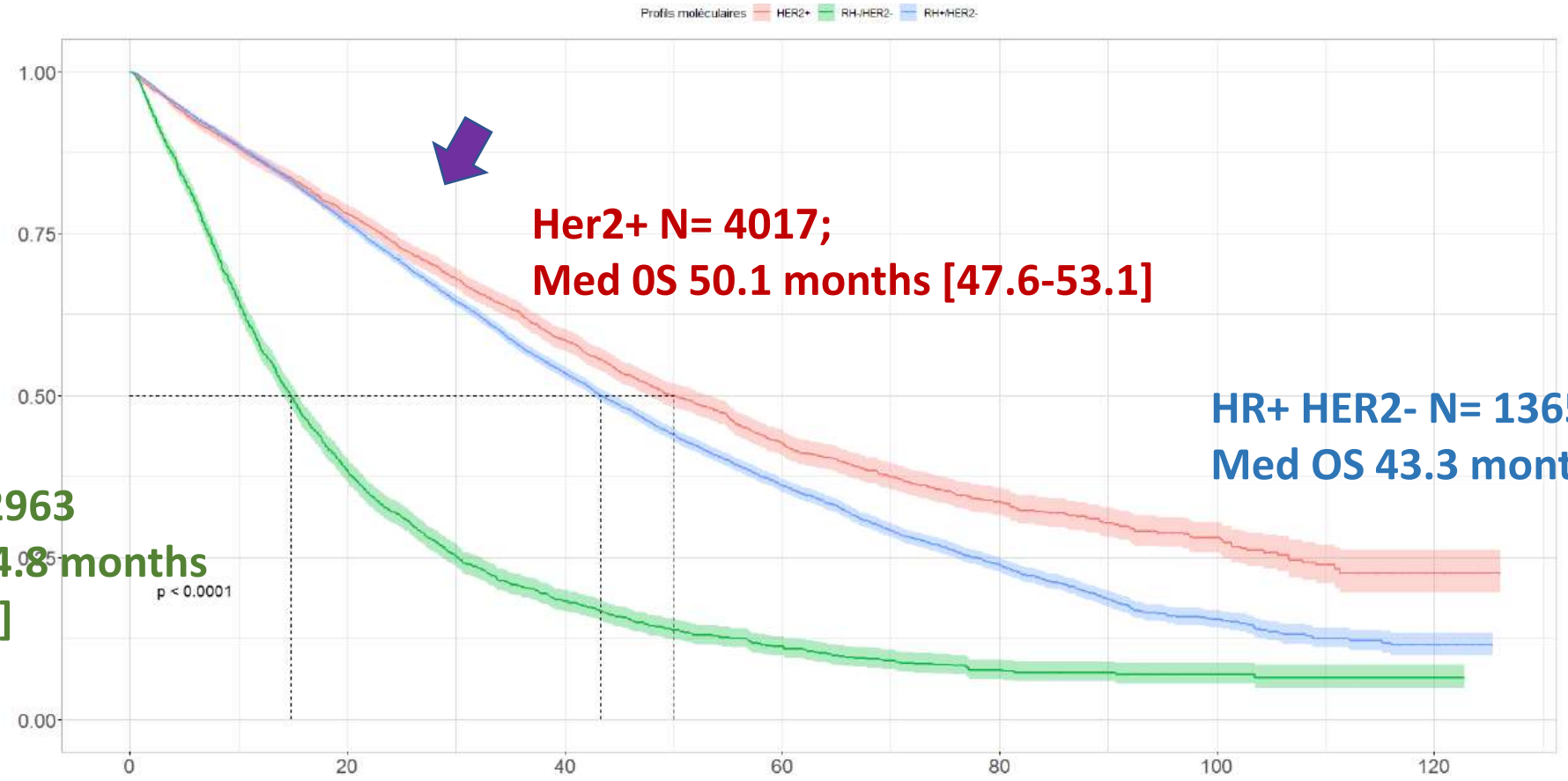
My Thoughts on 2 December 2019

- **TN: what to work on?**
  - What biomarker to chooce?
  - Can we improve outcome?

- **Luminal and Cyclins'….**
  - is the story over?
  - Biomarkers….the story begins

Metastatic TNBC: still a very poor outcome

French National multicenter ESME COHORT
N= 22000 included 2008-2016



Her2+ N= 4017;
Med 0S 50.1 months [47.6-53.1]

HR+ HER2- N= 13656;
Med OS 43.3 months [42.5-44.5]

TNBC N= 2963
Med OS 14.8 months
[14.1-15.5]

My Thoughts on 2 December 2019

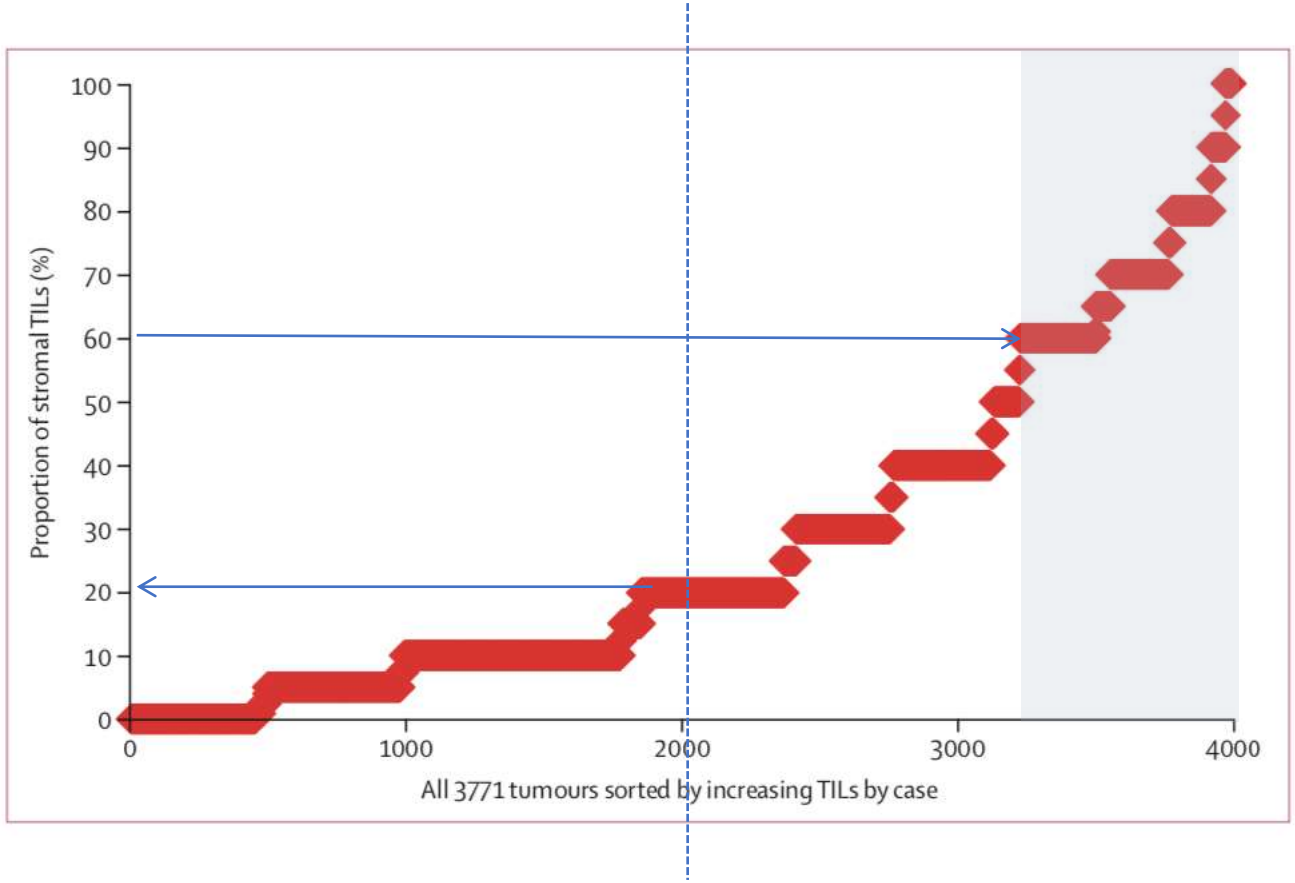
- **TN: what to work on?**
  - **What biomarker to chooce?** **TIL & PDL1**
  - Can we improve outcome?

- **Luminal and Cyclins'….**
  - is the story over?
  - Biomarkers….the story begins

Definition of TILs

Mononuclear immune cells that infiltrate tumor tissue

TILs as a continous measurement
(Denkert C et al, Lancet Oncology 2018)



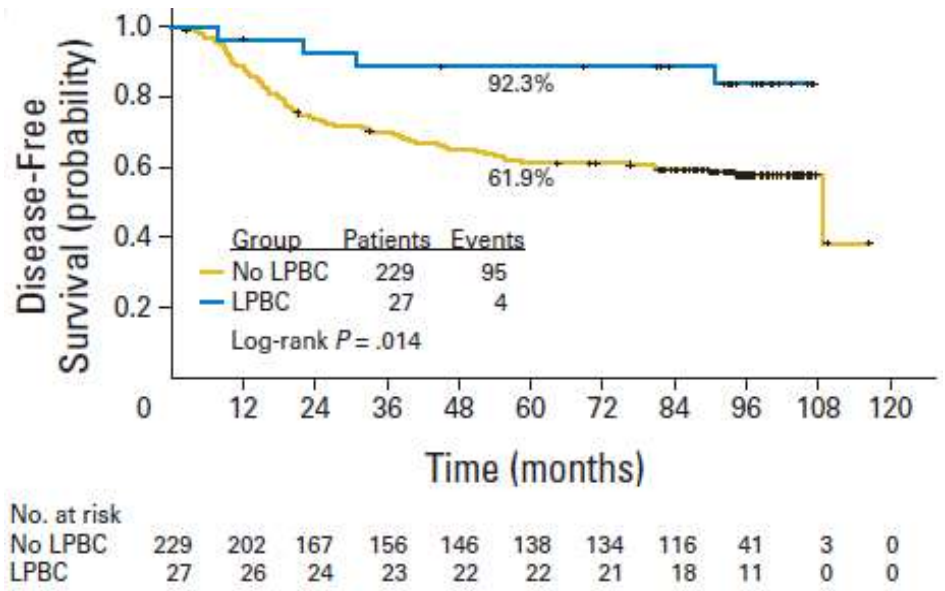
Proportion of inflammed/immunogenic breast cancers

Stanton SE et al, JAMA Oncol 2016; Nathan MR et al. The Breast 2017; Cimino-Mathews A et al, Hum Pathol 2016

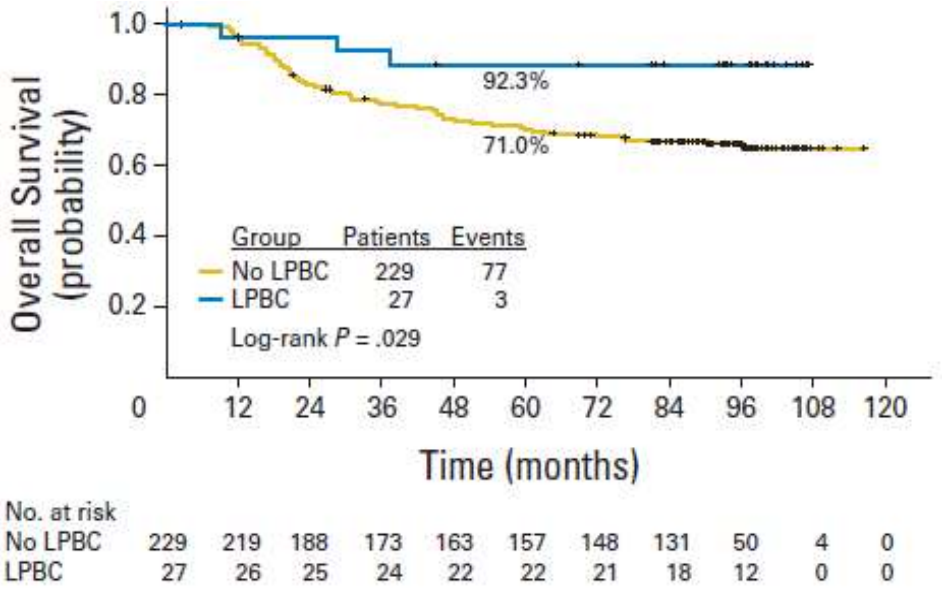
“Lymphocyte-predominant” ER-negative/ HER2-negative breast cancers have a significantly better outcome

Lymphocyte-predominant BC

DFS



OS



Loi et al. J Clin Oncol 2013

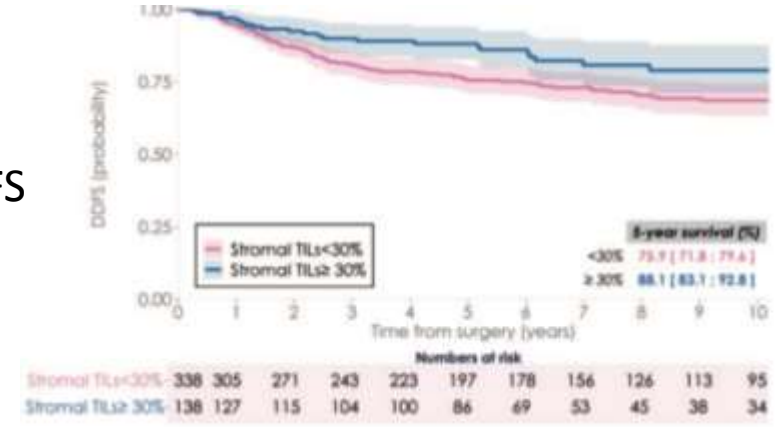
Prognostic value of tumor-infiltrating lymphocytes in patients with early-stage triple-negative breast cancers (TNBC) who did not receive adjuvant chemotherapy

J. H. Park[1,2†], S. F. Jonas[3,4†], G. Bataillon[5†], C. Criscitiello[6†], R. Salgado[7,8], S. Loi[8], G. Viale[9], H. J. Lee[10], M. V. Dieci[11,12], S.-B. Kim[1], A. Vincent-Salomon[5,13], G. Curigliano[6,14‡], F. André[15,16‡] & S. Michiels[3,4*,‡]

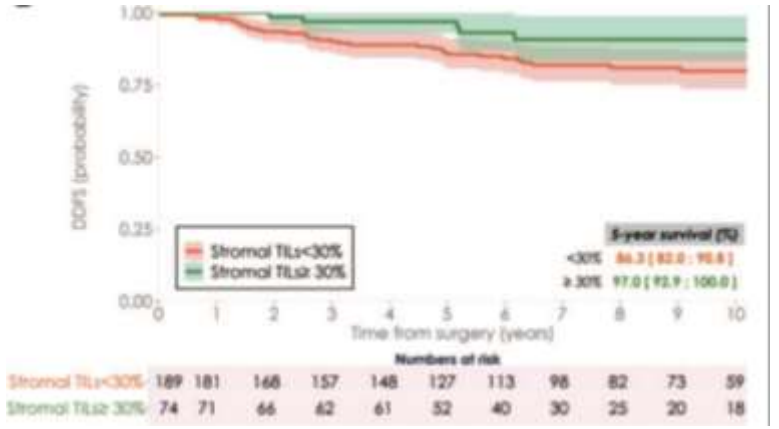
Annals of Oncology 0: 1–9, 2019

518 patients collected from four centers
83% of patients were node-negative
All underwent surgery+ 69% received RT

DFS



TILs≥30%
TILs<30%

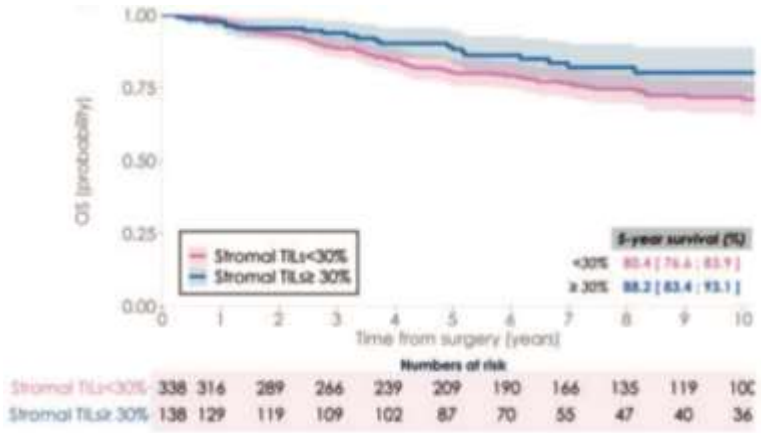


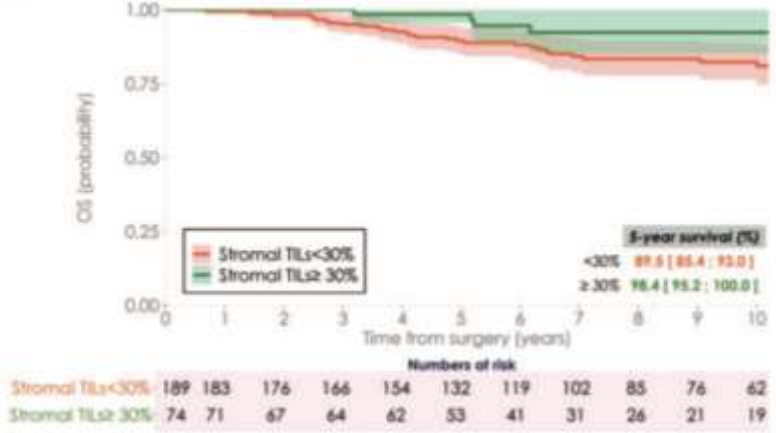
TILs≥30%
TILs<30%

Entire population

Stage I disease

OS





Clin Cancer Res; 2019

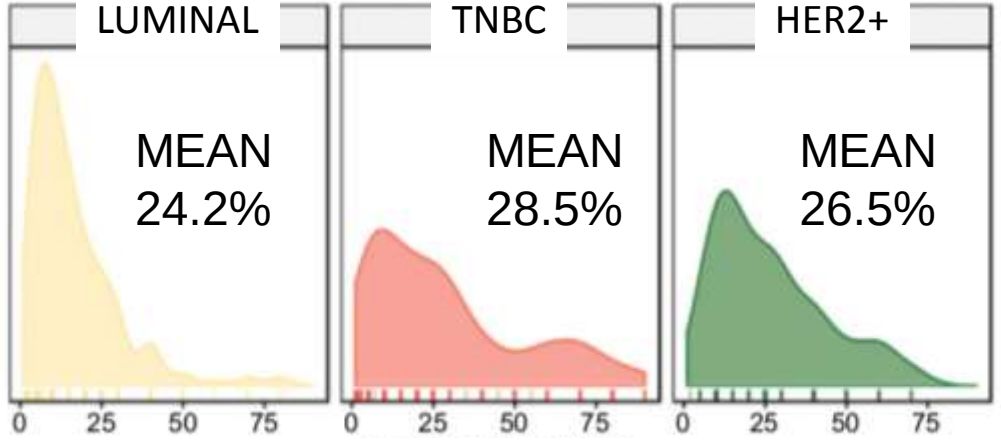
Interaction between Molecular Subtypes and Stromal Immune Infiltration before and after Treatment in Breast Cancer Patients Treated with Neoadjuvant Chemotherapy

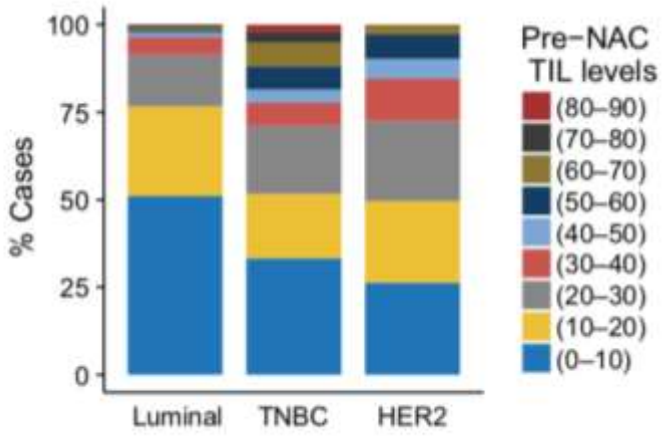
Anne-Sophie Hamy[1,2], Hélène Bonsang-Kitzis[1,3], Diane De Croze[4], Enora Laas[3], Lauren Darrigues[3], Lucian Topciu[5], Emmanuelle Menet[4], Anne Vincent-Salomon[5], Florence Lerebours[6], Jean-Yves Pierga[2,7], Etienne Brain[6], Jean-Guillaume Feron[3], Gabriel Benchimol[3], Giang-Thanh Lam[3,8], Marick Laé[5], and Fabien Reyal[1,3,7]

TILs levels across subtypes

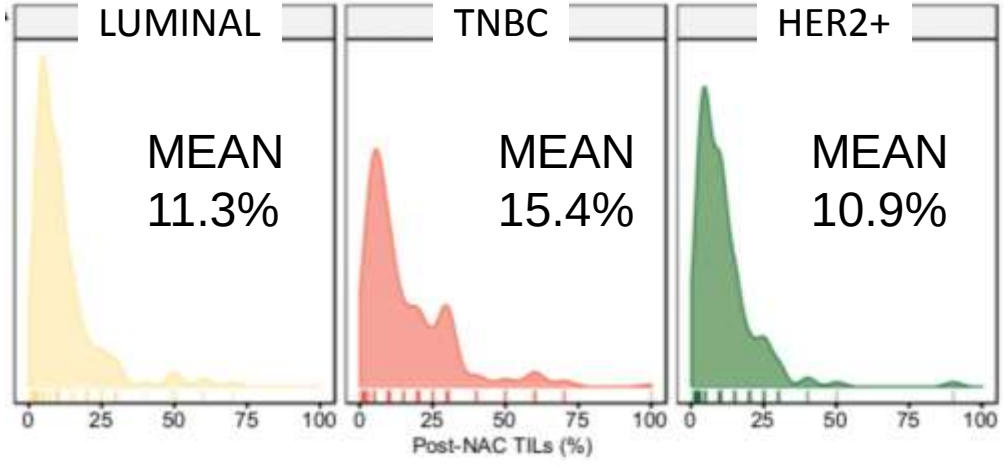
718 patients
luminal (n= 223), TNBC (n= 320), HER2+ (n= 175)

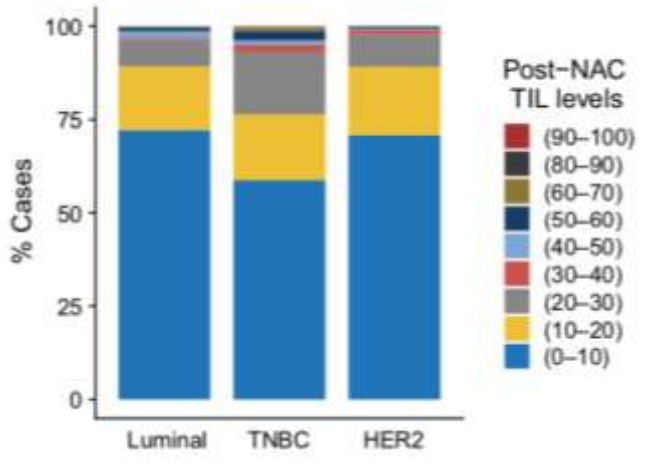
Pre-NACT →



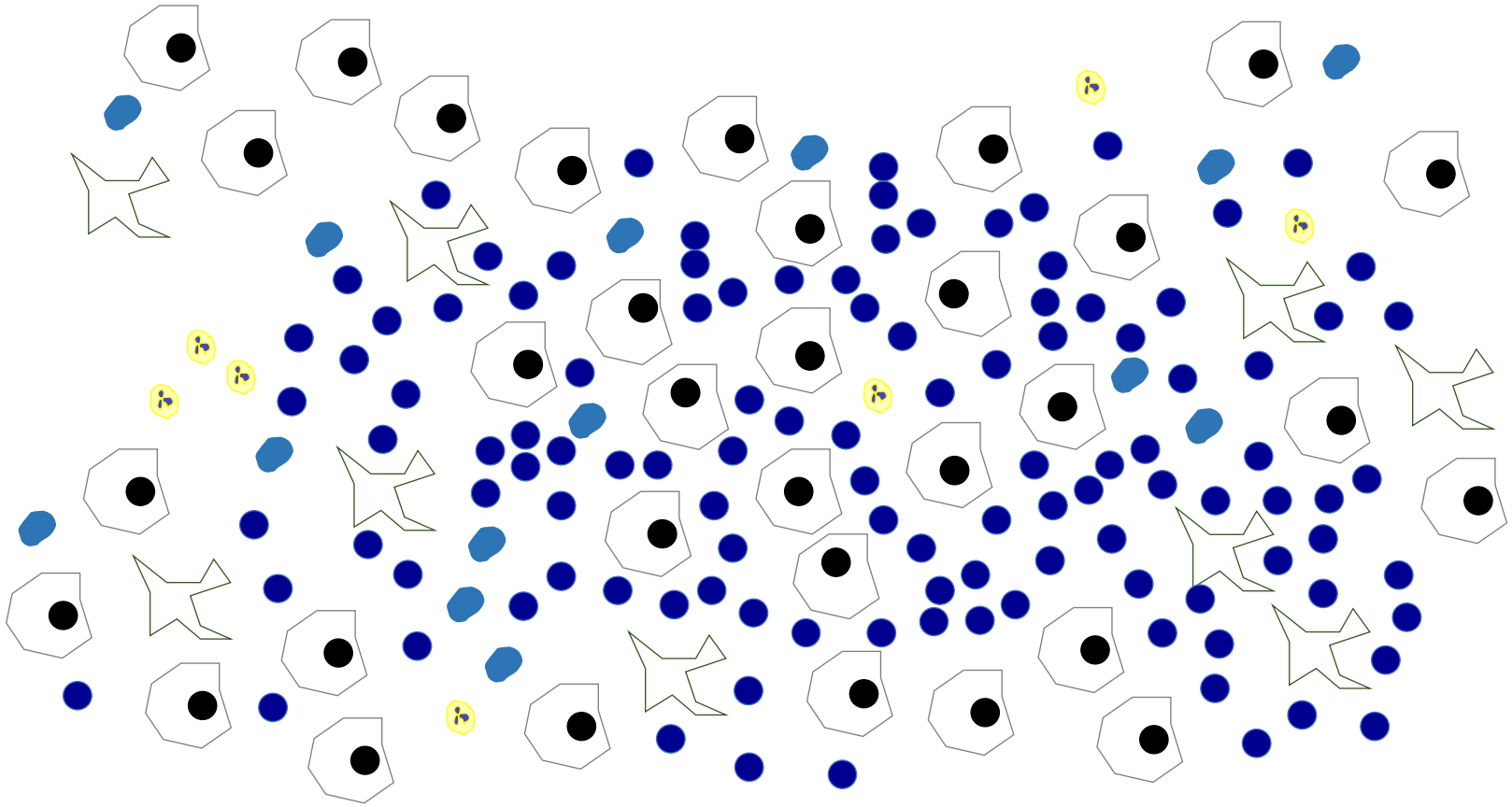


Post-NACT →





Beyond TILs?



TIL

Dendritic Cell

Macrophage

Polymorphous neutrophilic granulocyte

IMpassion130, a phase 3 trial with a PD-L1 inhibitor

ORIGINAL ARTICLE

Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer

P. Schmid, S. Adams, H.S. Rugo, A. Schneeweiss, C.H. Barrios, H. Iwata, V. Diéras, R. Hegg, S.-A. Im, G. Shaw Wright, V. Henschel, L. Molinero, S.Y. Chui, R. Funke, A. Husain, E.P. Winer, S. Loi, and L.A. Emens, for the IMpassion130 Trial Investigators*

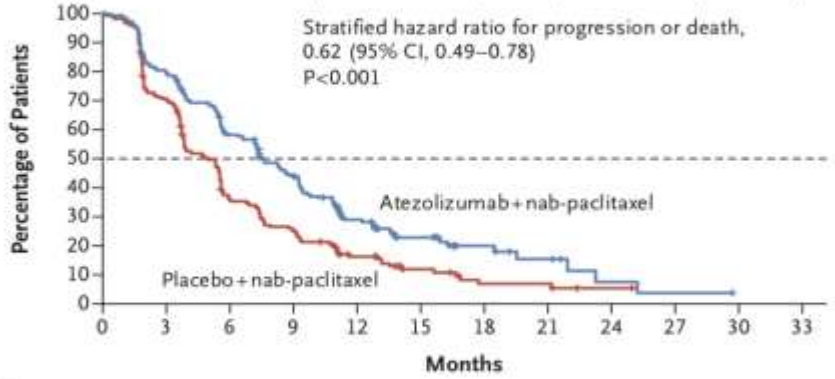
N ENGL J MED 379;22 NEJM.ORG NOVEMBER 29, 2018

Atezolizumab plus nab-paclitaxel prolonged PFS among patients with metastatic triple-negative breast cancer in both the intention-to-treat population and the PD-L1–positive subgroup

PD-L1 positivity: tumor-infiltrating **immune cells** ≥1% of the **tumor area**

B Progression-free Survival in the PD-L1–Positive Subgroup

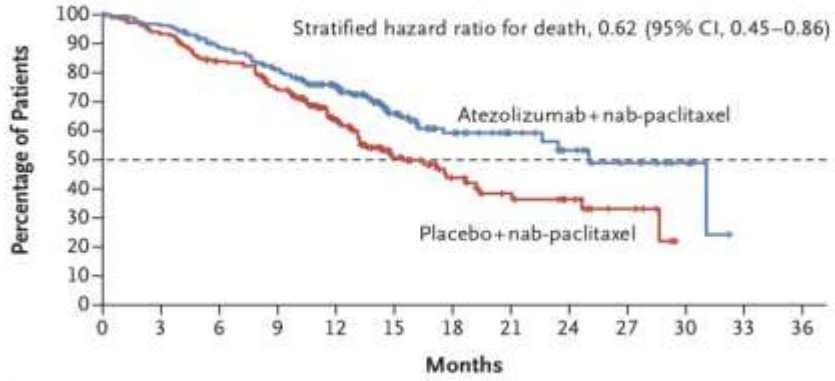
	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)	1-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	138/185	7.5 (6.7–9.2)	29.1 (22.2–36.1)
Placebo+Nab-Paclitaxel	157/184	5.0 (3.8–5.6)	16.4 (10.8–22.0)



No. at Risk												
Atezolizumab+nab-paclitaxel	185	146	104	75	38	19	10	6	2	1	NE	NE
Placebo+nab-paclitaxel	184	127	62	44	22	11	5	5	1	NE	NE	NE

D Overall Survival in the PD-L1–Positive Subgroup

	No. of Events/ No. of Patients	Median Overall Survival (95% CI)	2-Yr Rate of Overall Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	64/185	25.0 (22.6–NE)	53.5 (42.3–64.6)
Placebo+Nab-Paclitaxel	88/184	15.5 (13.1–19.4)	36.6 (26.4–46.7)



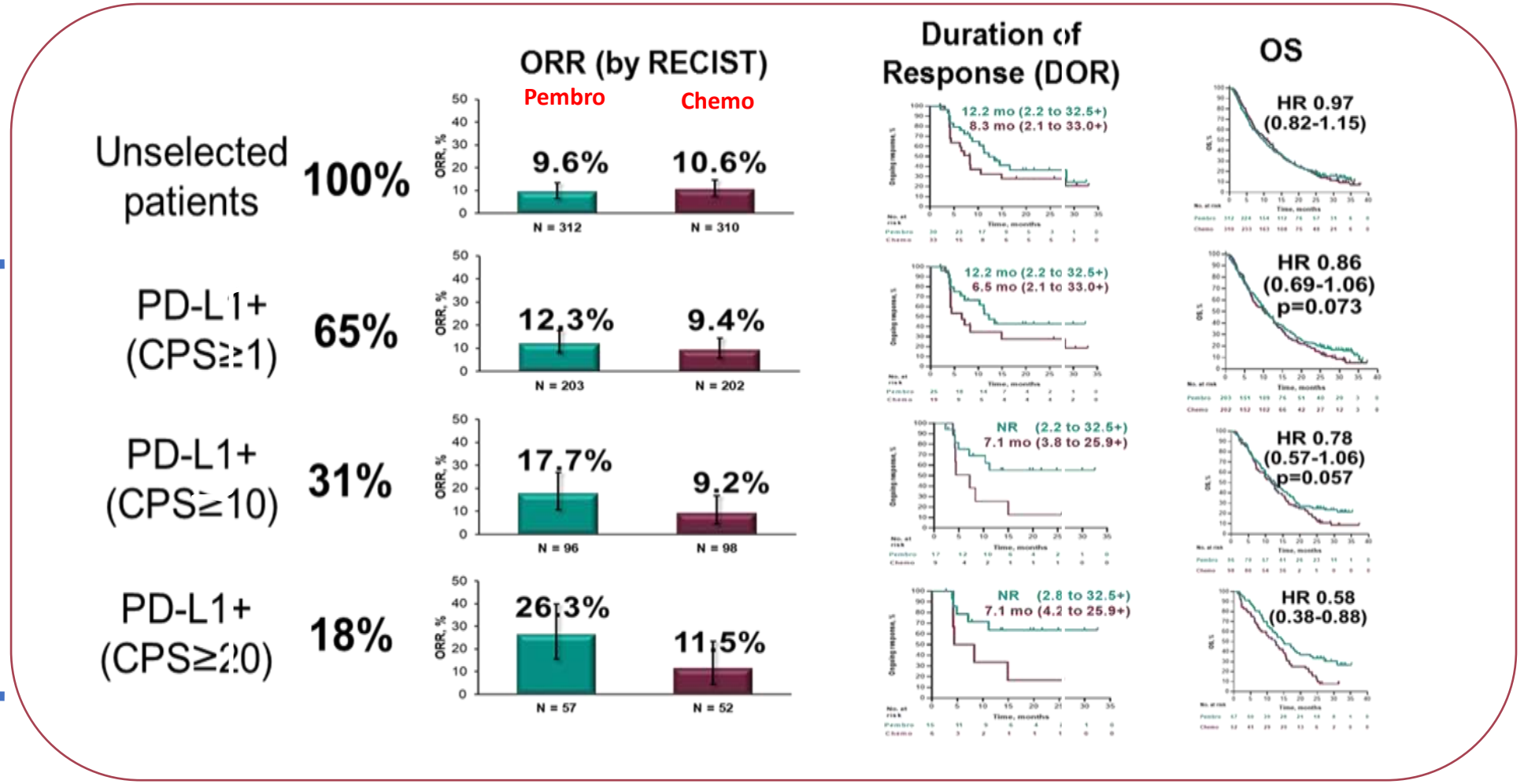
No. at Risk												
Atezolizumab+nab-paclitaxel	185	177	160	142	113	61	36	22	15	9	5	NE	NE
Placebo+nab-paclitaxel	184	170	147	129	89	44	27	19	13	6	NE	NE	NE

Why do we need to consider combination IO therapy?

We might further increase activity by:

Blocking other checkpoints

Activating stimulatory signals

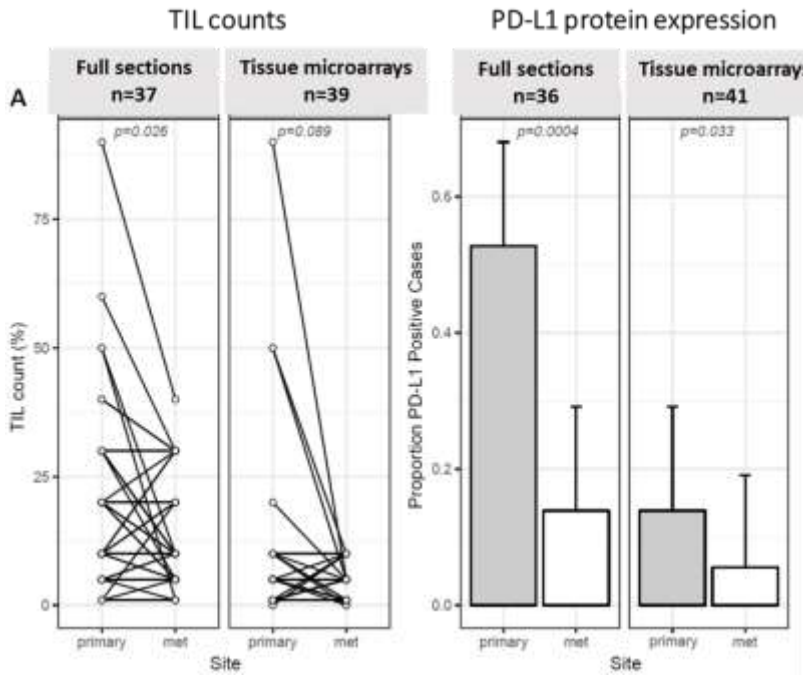


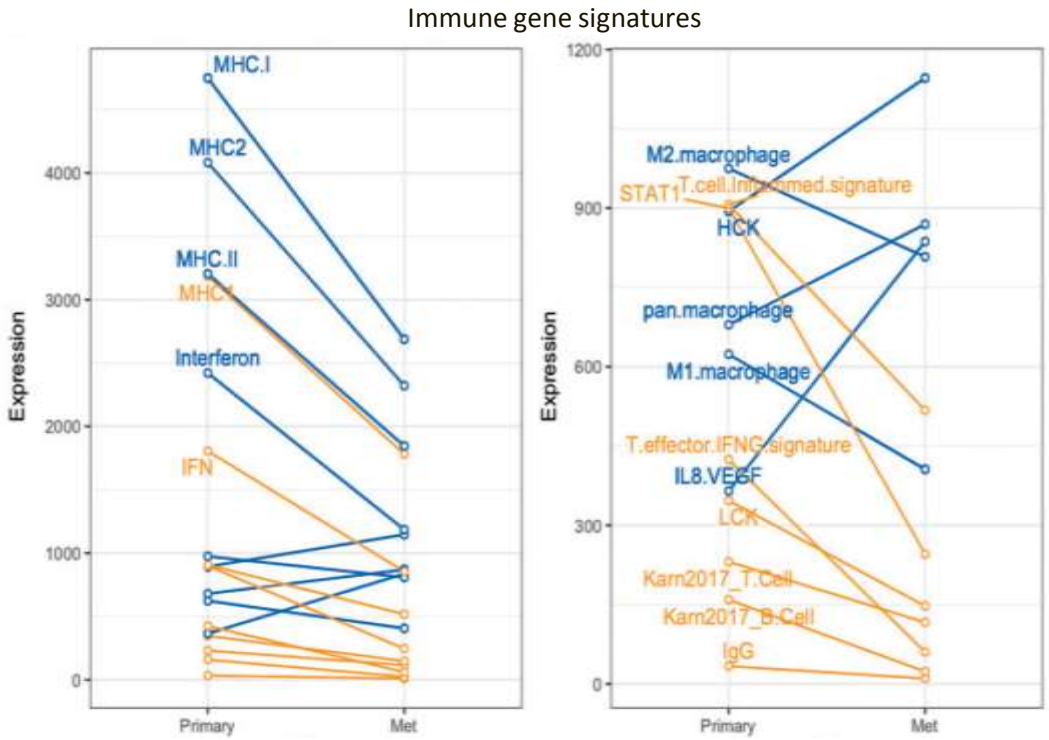
*Combined Positive **Score**(**CPS**), number of **PD-L1** staining cells (tumor cells, lymphocytes, macrophages) /total number of viable tumor cells x 100*

Cortes KN119 ESMO 2019

Immunological differences between primary and metastatic breast cancer

- Cohort 1: FFPE full sections from N=41 cases of paired primary and metastasis → - TIL count, PD-L1 IHC
  - → - Nanostring Immune Profiling (770 immune genes)
    - Immune cell type metagenes
    - Immune function metagenes
    - Gene level differences
- Cohort 2: TMAs of N=42 cases of paired primary and metastasis → - TIL count, PD-L1 IHC





Differentially expressed Immune Oncology targets between primary and metastatic breast cancers

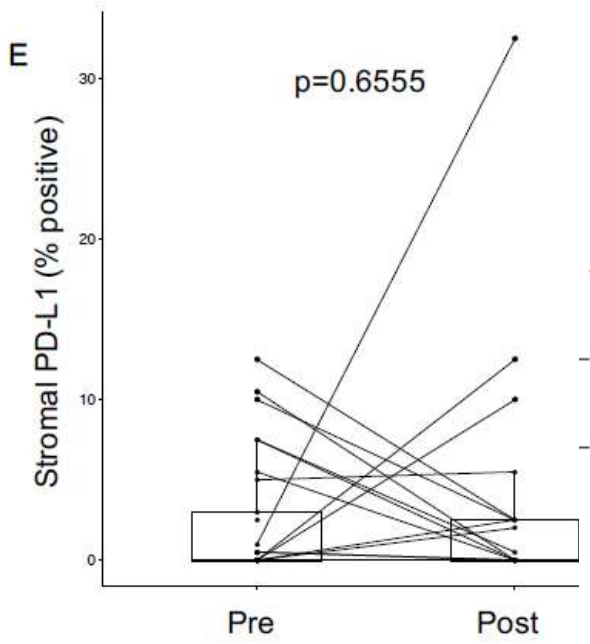
Gene Names	Median in Primary	Median in Metastasis	Fold-change of median	FDR adjusted p-value
IO targets decreased in metastatic lesions				
CD276 (B7H3)	2640	1780	0.67	0.047
JAK1	1596	1325	0.83	0.019
CD27	146	30	0.202	0.003
SLAMF7	132	39	0.294	0.007
CTLA4	130	17	0.133	0.003
TIGIT	100	26	0.258	0.003
KLRC1	78	41	0.53	0.003
CD274 (PD-L1)	67	38	0.564	0.033
TNFRSF4 (OX40)	66	29	0.435	0.053
ICOS	48	21	0.439	0.005
TNFRSF9 (CD137)	37	11	0.311	0.003
CCR4	30	12	0.396	0.008
PDCD1 (PD1)	24	11	0.44	0.004
IO targets preserved in metastatic lesions				
STAT3	**8612**	**6837**	**0.793**	**0.399**
CXCR4	**3384**	**1552**	**0.458**	**0.321**
CXCL12	**1378**	**851**	**0.617**	**0.377**
JAK2	**933**	**697**	**0.746**	**0.803**
TLR1	**502**	**459**	**0.914**	**0.961**
NT5E (CD73)	**373**	**367**	**0.985**	**0.786**
TLR2	**273**	**234**	**0.858**	**0.774**
TNFRSF18 (GITR)	**189**	**115**	**0.615**	**0.928**
CSF1	**185**	**169**	**0.914**	**0.991**
HAVCR2 (TIM3)	**161**	**137**	**0.854**	**0.904**
IL8	**154**	**128**	**0.825**	**0.539**
IDO1	**134**	**43**	**0.323**	**0.226**
CCR2	**88**	**42**	**0.479**	**0.336**
TLR7	**76**	**63**	**0.825**	**0.326**
LAG3	**73**	**56**	**0.774**	**0.165**
TLR8	**39**	**30**	**0.779**	**0.75**

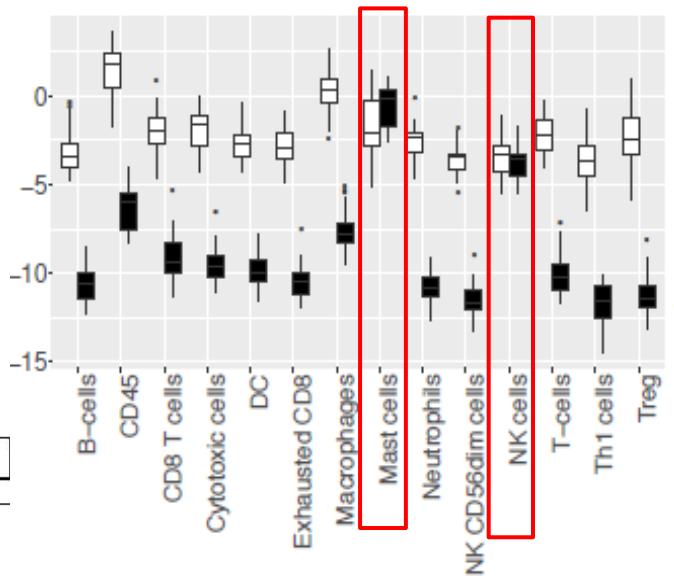
IO targets significantly decreased in metastatic breast cancer

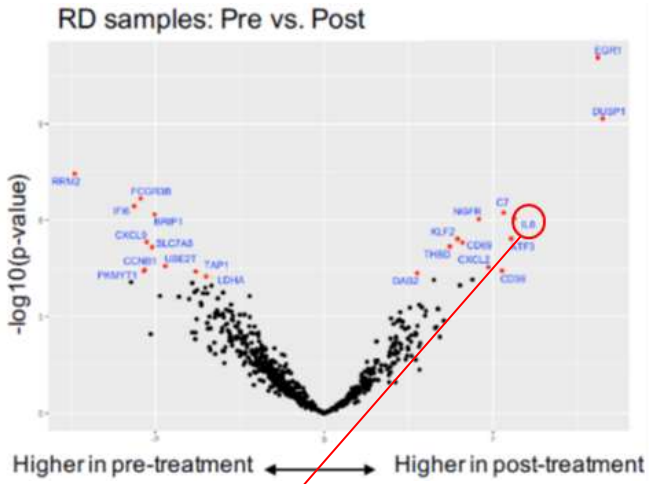
IO targets preserved in metastatic lesions and represent promising combination partners for immune checkpoint therapy.

B. Szekely et al. Ann Onc 29:2232-39, 2018

PDL1 and immune gene expression before and after neoadjuvant chemotherapy in patients with residual disease







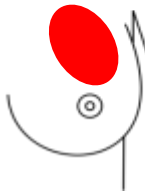
Stromal PDL1 expression remains high, or even increases in many residual disease samples

Most immune cell types decreased in residual cancer, except mast cells and NK cells

IL6 expression is increased in residual disease

Testable therapeutic hypotheses

Phase III Trials ongoing in TNBC early setting



Neoadjuvant

Adjuvant

High risk TNBC

SWOG/NCI

Post-neoadjuvant

R

- **Pembrolizumab**
- Placebo

A-BRAVE

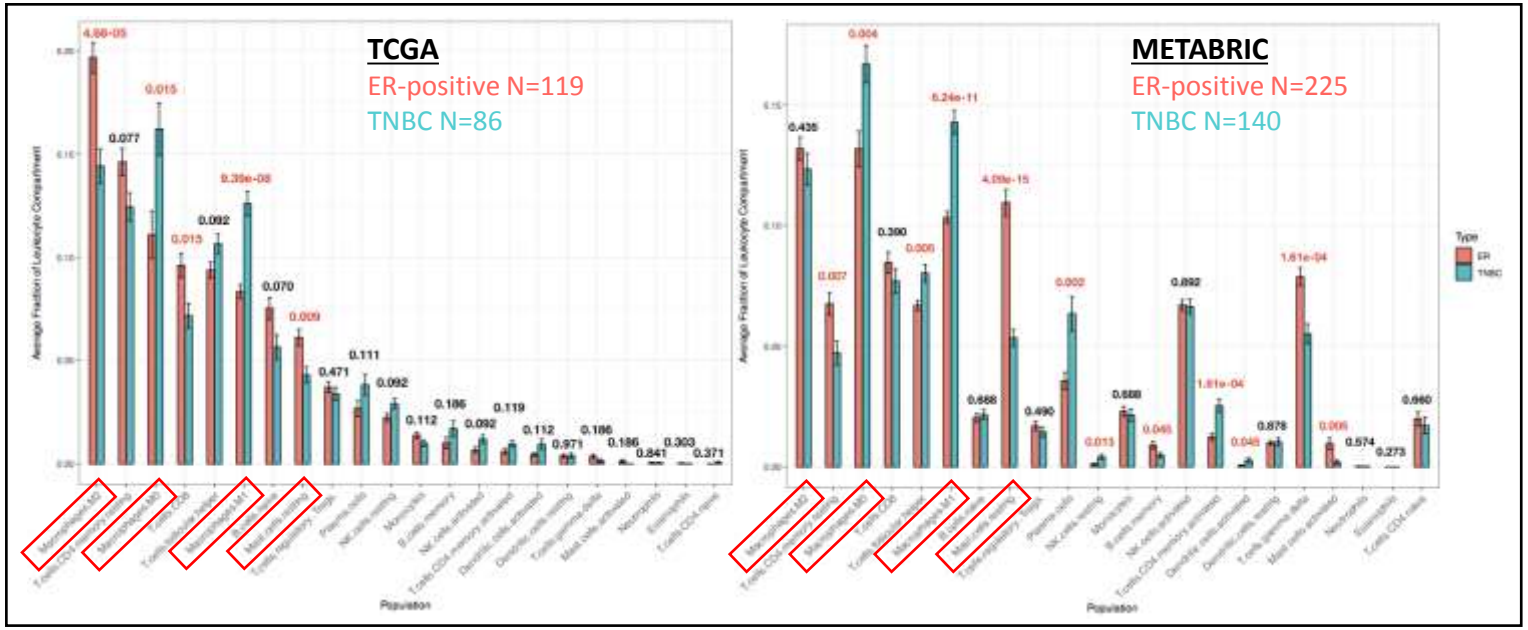
Post-neoadjuvant
or adjuvant
(≥ 4 nodes)

R

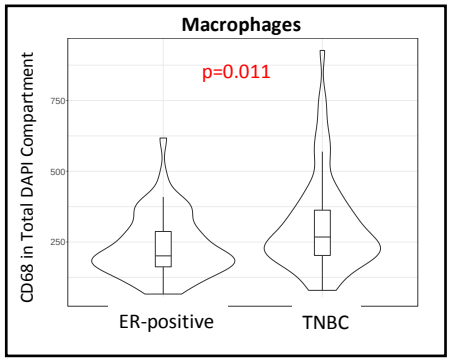
- **Avelumab**
- Placebo

Differences in immune cell populations in immune-rich TNBC and immune-rich ER + cancers

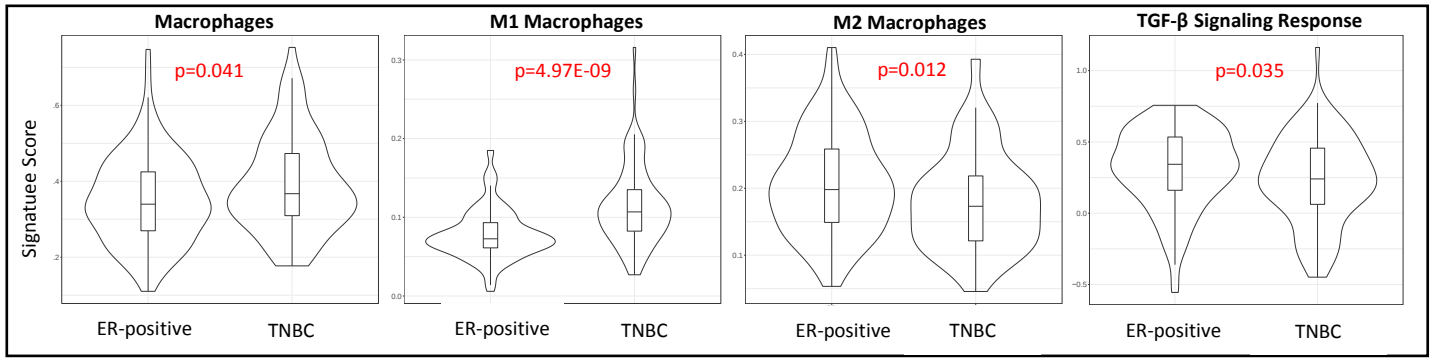
Leukocyte Compartment Deconvolution



Quantitative Immunofluorescence (Yale Cases)



Immune Metagene Scores (TCGA Cases)



Fractions of M2 macrophages, resting mast cells, and a TGF-β signature are higher in immune-rich ER-positive cancers.
Fractions of overall macrophages, M0 macrophages and M1 macrophages are higher in immune-rich TNBC.

Immuno-oncology drug targets overexpressed in immune-rich ER-positive cancer relative to immune-rich TNBC

	TCGA ER+ Mean Log2 Expression	TCGA TNBC Mean Log2 Expression	TCGA Log2 FC Expression	TCGA p-adj.	METABRIC ER+ Mean Log2 Expression	METABRIC TNBC Mean Log2 Expression	METABRIC Log2 FC Expression	METABRIC p-adj.
IL6ST	10.7	9.1	2.00	6.64E-17	9.53	8.33	1.20	9.38E-33
CX3CR1	7.7	6.7	1.13	2.22E-08	7.70	6.88	0.83	9.67E-11
TGFB3	10.5	9.3	1.12	3.48E-17	8.86	7.86	1.00	9.12E-28
RORC	9.3	7.8	0.92	2.46E-07	6.52	6.16	0.36	6.27E-09
CSF3R	8.9	8.2	0.87	4.68E-08	7.64	7.42	0.22	2.81E-02
ADORA2A	8.4	8.0	0.69	1.64E-04	7.11	6.85	0.26	6.98E-03
GARP/LRRC32	10.0	9.3	0.61	1.69E-05	8.29	7.87	0.43	2.23E-06
CXCL12	11.6	11.0	0.53	1.03E-03	9.77	9.24	0.54	2.36E-05
CLEC14A	8.9	8.3	0.50	4.21E-04	7.70	7.22	0.47	1.15E-11
TLR3	7.5	7.1	0.45	5.36E-03	6.03	5.89	0.14	1.74E-04
TGFBR2	11.5	11.1	0.37	1.03E-02	9.57	9.22	0.35	3.52E-04

T. O'Meara, et al. *Ann Oncol;* 2019

My Thoughts on 2 December 2019

- **TN: what to work on?**
  - What biomarker to chooce?
  - **Can we improve outcome**

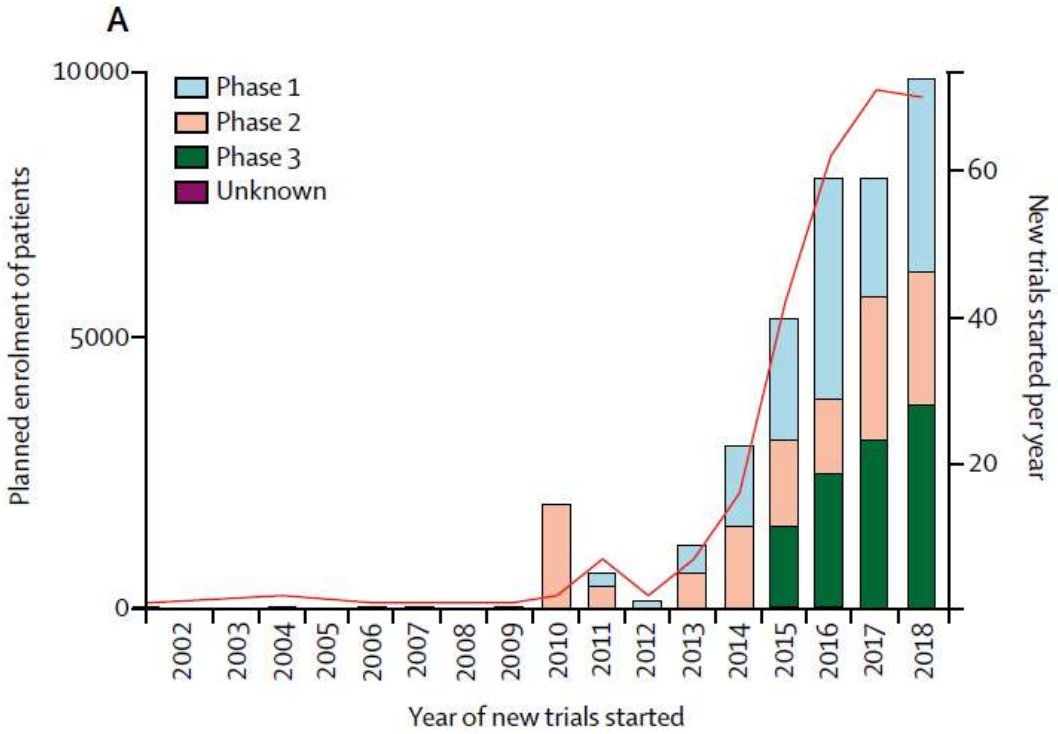
- **Luminal and Cyclins'….**
  - is the story over?
  - Biomarkers….the story begins

Immunotherapy and targeted therapy combinations in metastatic breast cancer

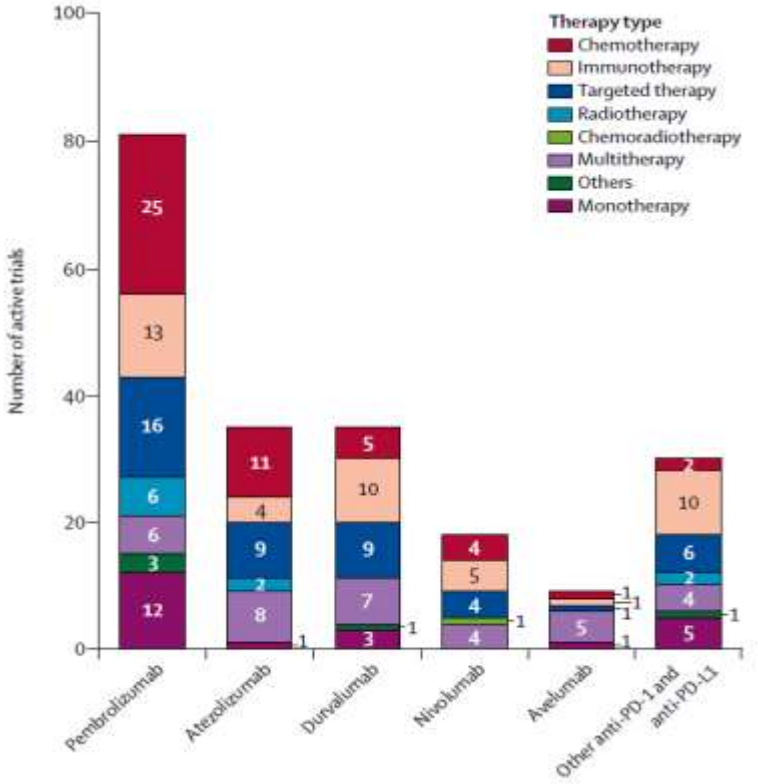
Francisco J Esteva, Vanessa M Hubbard-Lucey, Jun Tang, Lajos Pusztai

Lancet Oncol 2019; 20: e175–86

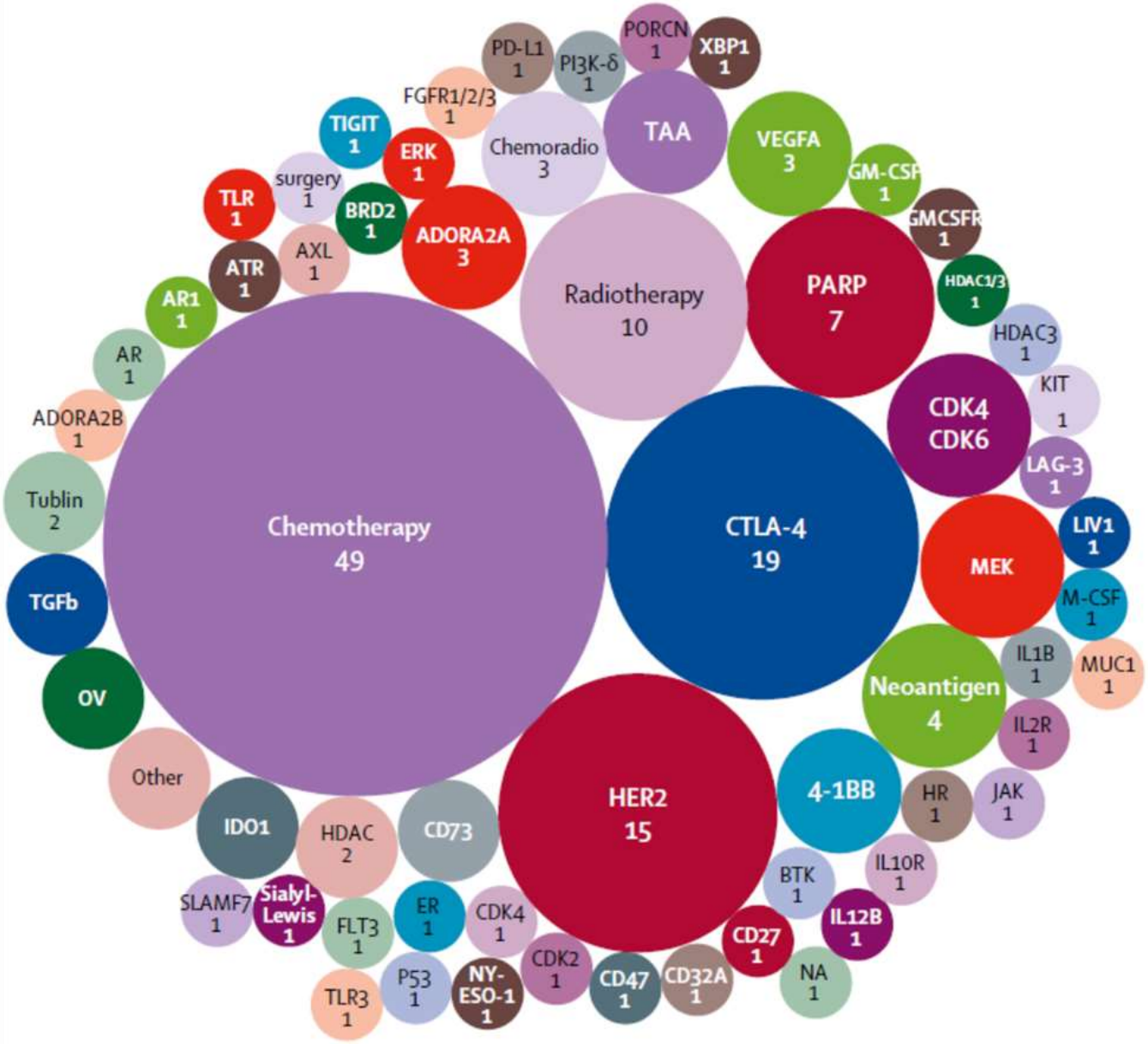
285 IO trials aim to accrue 38,424 breast cancer patients



Trials by type of checkpoint inhibitor



Immuno-oncology combination trial landscape of breast cancer (1stQ 2019)



75% of these trials are Phase I and II.

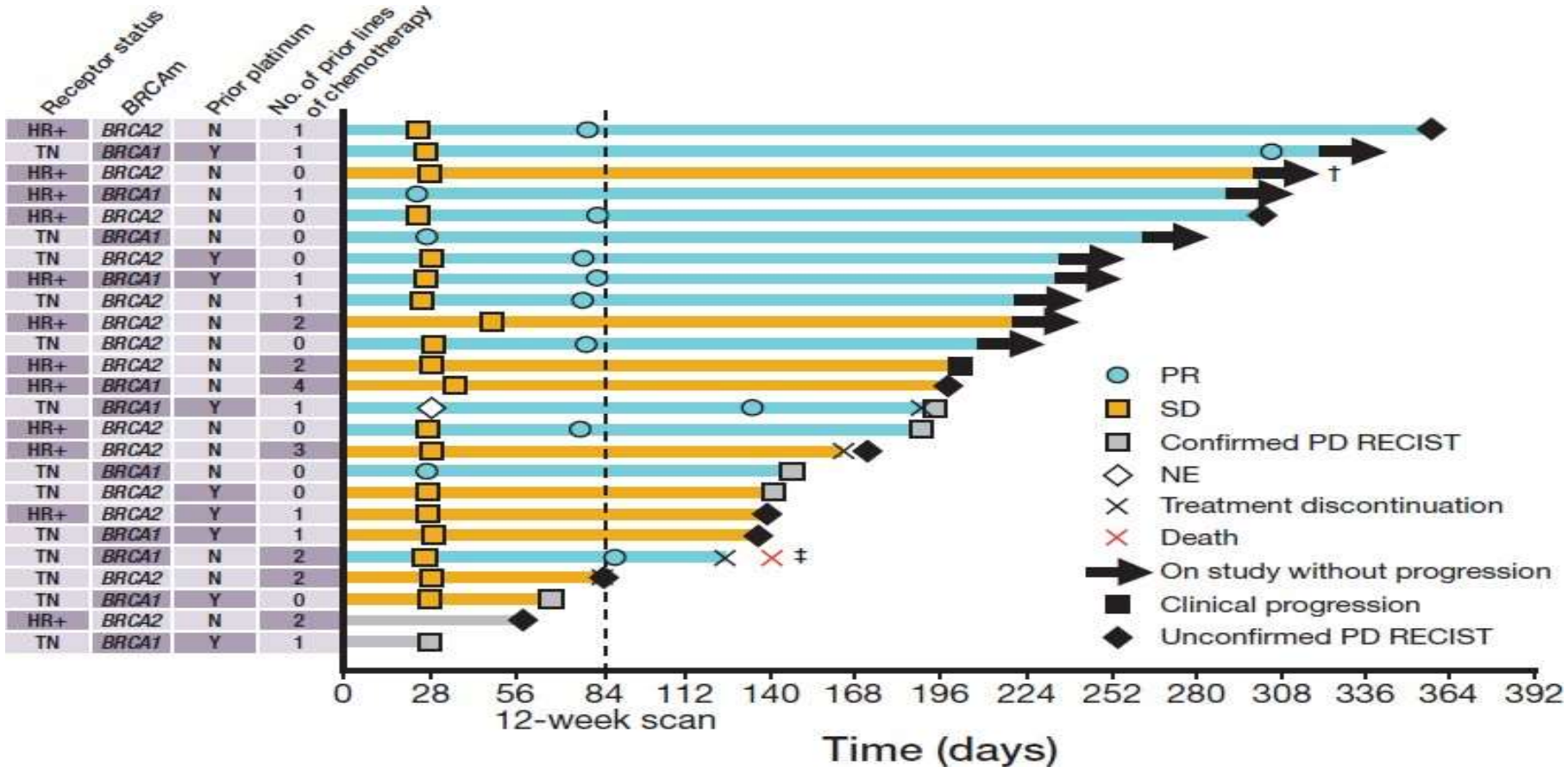
Very few reported final results.

Many will likely not proceed further.

How to design the next generation of combination trials?

Combining PARP inhibition and IO?

Mediola trial: Olaparib + durvalumab (ph I)



Domcheck et al SABCS2017

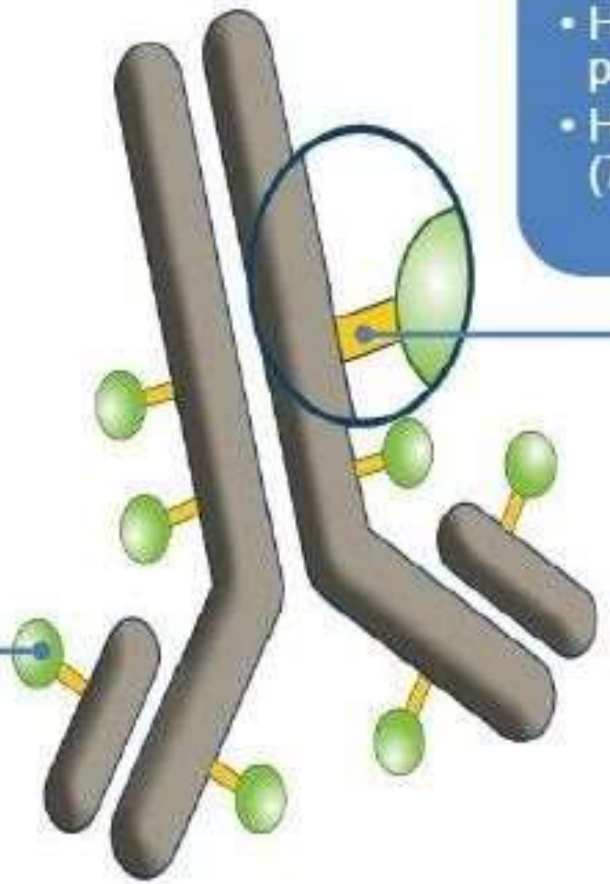
ADCs: E.g. Sacituzumab Govitecan (IMMU-132)

Humanized anti-Trop-2 antibody

- Targets Trop-2, an epithelial antigen expressed on many solid cancers, including mTNBC

Linker for SN-38

- Hydrolysable linker for payload release
- High drug-to-antibody ratio (7.5:1)

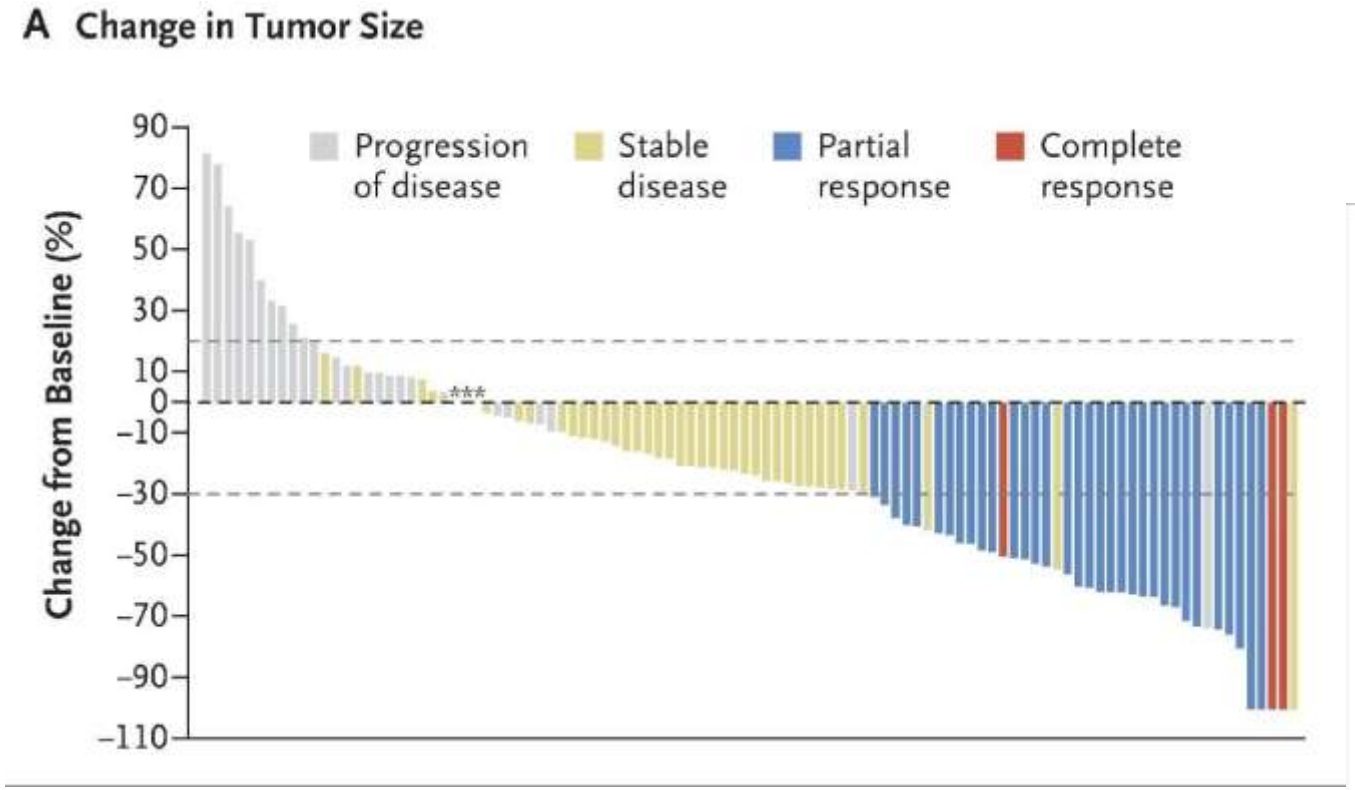


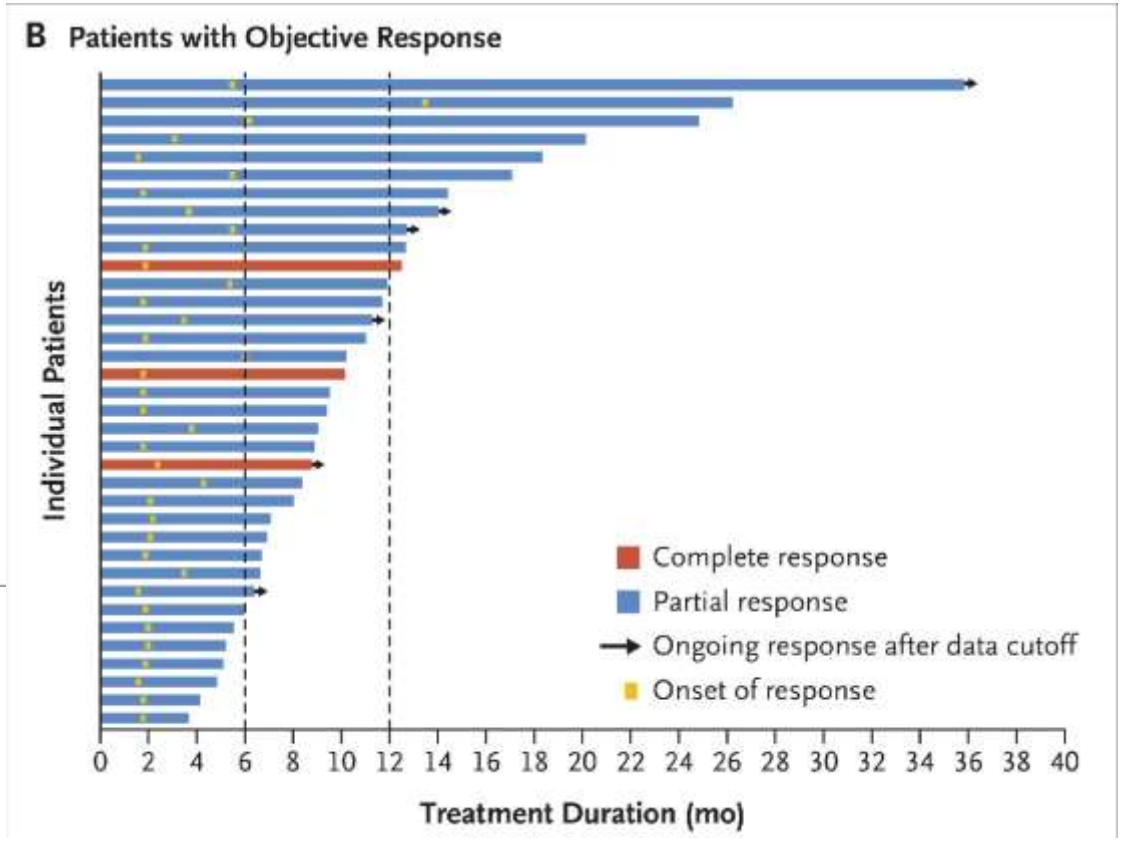
SN-38 payload

- SN-38 more potent than parent compound, irinotecan
- ADC delivers up to 136-fold more SN-38 than irinotecan *in vivo*

ADCs: Sacituzumab Govitecan (IMMU-132)

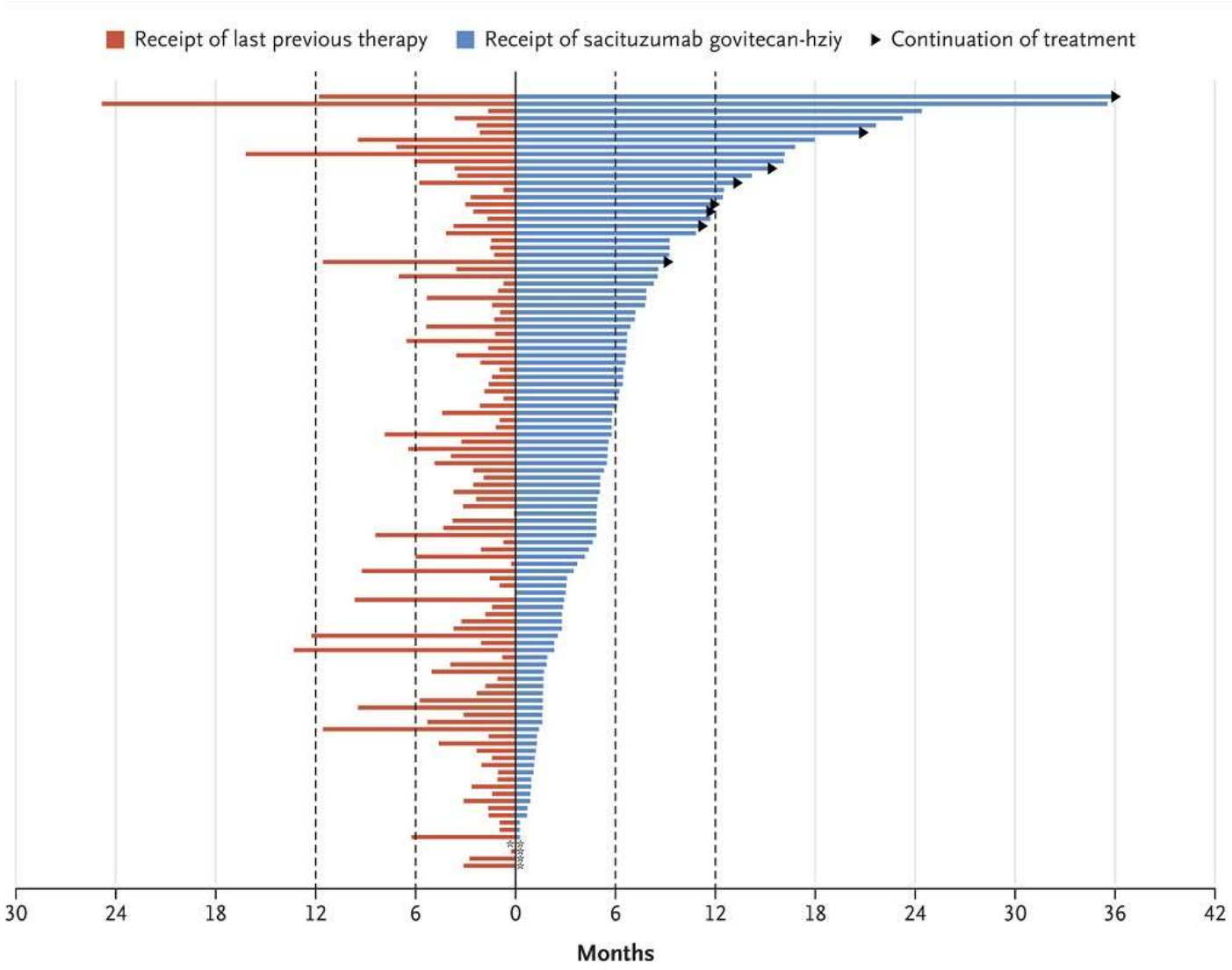
Single Arm Phase II study
N= 108 TNBC





Bardia A et al, N Engl J Med 2019

ADCs: Sacituzumab Govitecan (IMMU-132)



Single Arm Phase II study
N= 108 TNBC

Bardia A et al, N Engl J Med 2019

Sacituzumab Govitecan: ASCENT Phase III Trial(NCT02574455)

Patients (n=328)

- mTNBC
- Refractory or relapsed to ≥2 prior SOC chemotherapies for advanced disease
- OR >1 therapy for patients who progressed within 12 months of completion of (neo)adjuvant therapy
- Prior taxane in the advanced setting required
- ECOG 0-1

R 1:1

Stratification factors

- *Number of prior therapies*
- *Geographic region*
- *Presence/absence of known brain metastases*

Sacituzumab govitecan

IV 10 mg/kg

Days 1 and 8, q3w

Scanned every 8 weeks

Treatment of physician's choice

Capecitabine

Eribulin

Vinorelbine

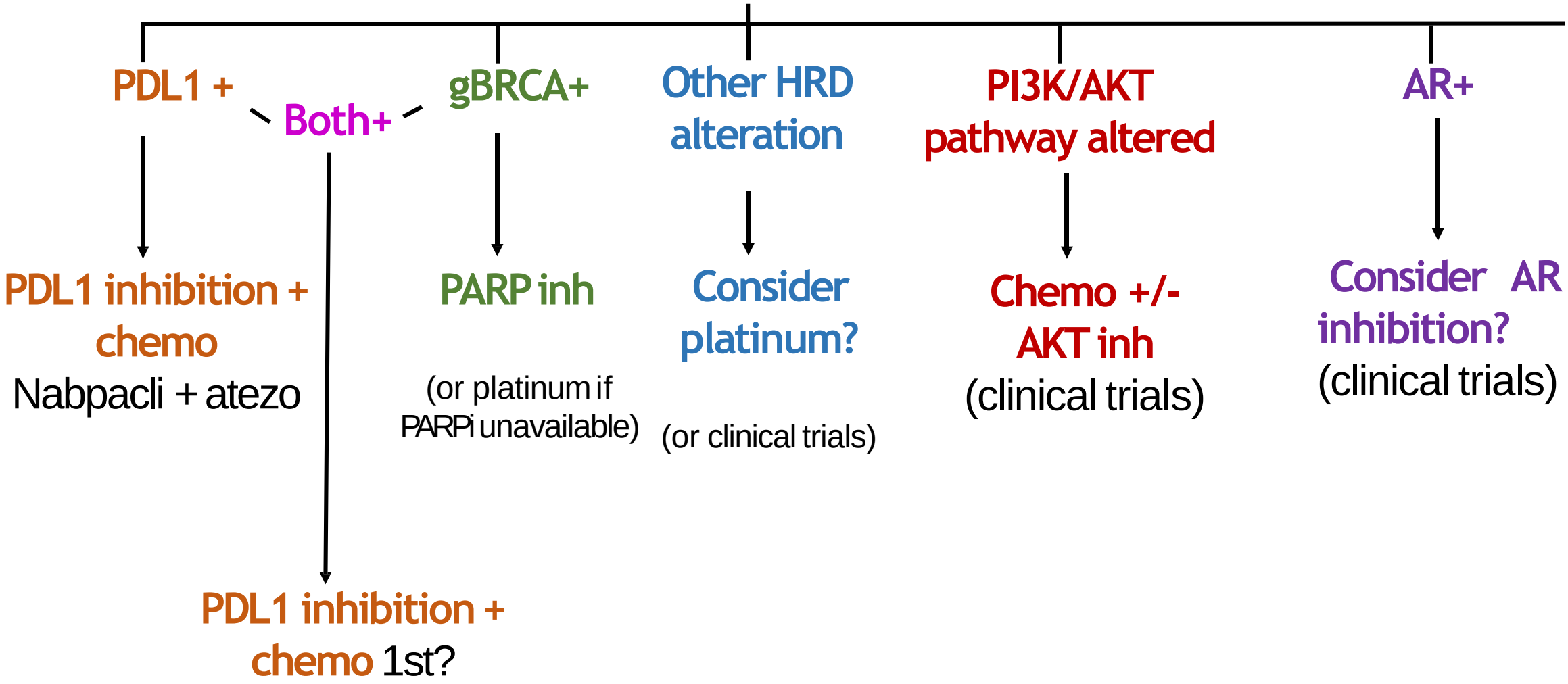
Gemcitabine

Endpoints

Primary: PFS (BICR)

Secondary: OS

Decision tree?



By Suzette Delaloge ……from ESMO 2019

My Thoughts on 2 December 2019

- **TN: what to work on?**
  - What biomarker to chooce?
  - **Can we improve outcome**

- **Luminal and Cyclins'….**
  - **is the story over?**
  - Biomarkers….the story begins

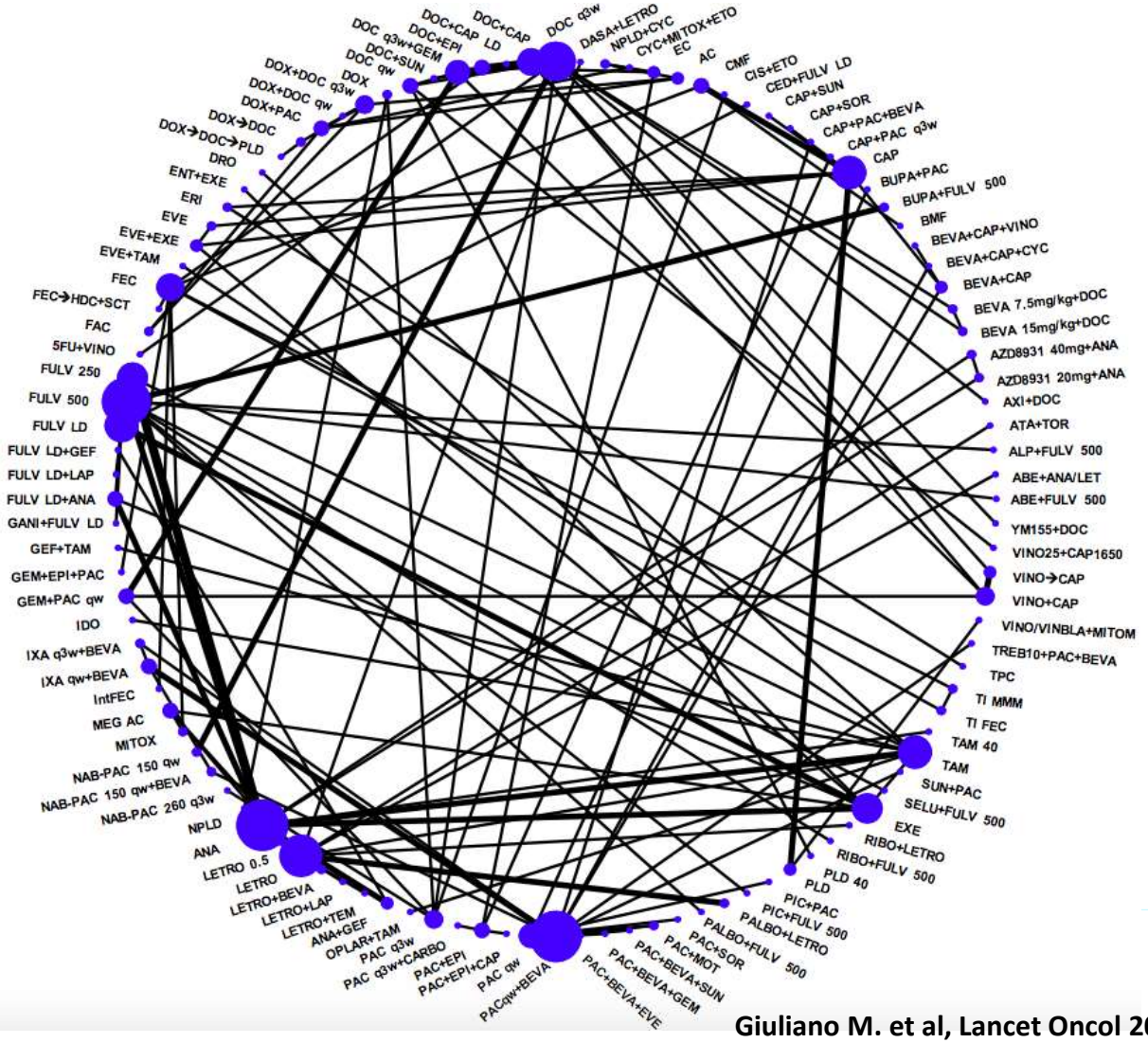
Endocrine treatment versus chemotherapy in postmenopausal women with hormone receptor-positive, HER2-negative, metastatic breast cancer: a systematic review and network meta-analysis

Network meta-analysis eligibility criteria and source strategy/results:

- Phase II/III randomized clinical trials
- 1st and 2nd line MBC
- Trials 2689 record screened
- 140 trials included
- >50,000 pts

Results:

No chemotherapy ± targeted therapy was superior to ET+CDK4/6i as 1st or 2nd line treatment for HR+/HER2- MBC



Giuliano M. et al, Lancet Oncol 2019

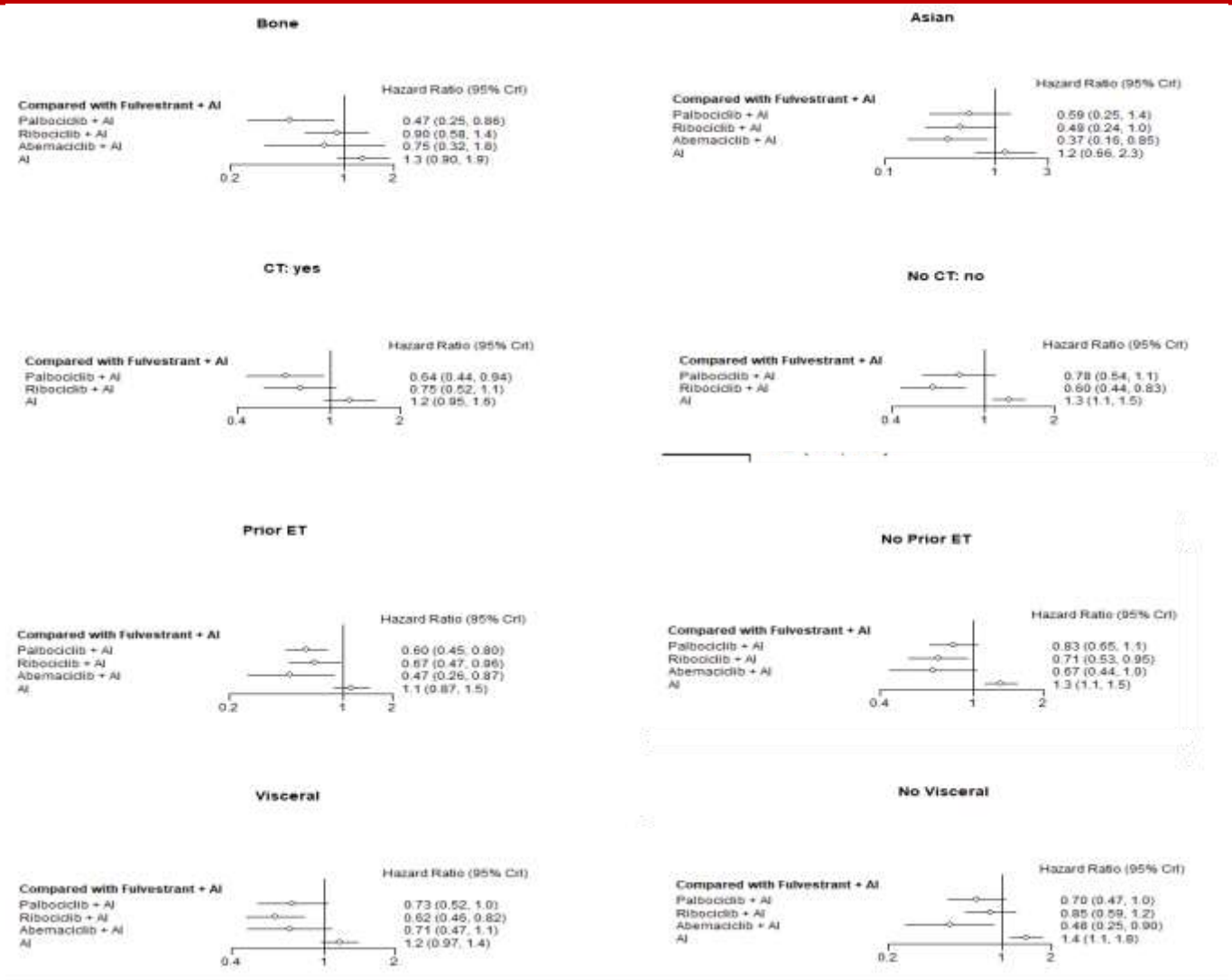
Should all patients with HR-positive HER2-negative metastatic breast cancer receive CDK 4/6 inhibitor as first-line based therapy? A network meta-analysis of data from the PALOMA 2, MONALEESA 2, MONALEESA 7, MONARCH 3, FALCON, SWOG and FACT trials

Network meta-analysis eligibility criteria and source strategy/results:

- Phase III randomized clinical trials
- 1st line MBC
- 7 trials included
- > 4500 pts

Results:

ET+CDK4/6i was superior to FLV (or FLV+AI) as 1st HR+/HER2- MBC



Rossi V et al, Cancers 2019

My Thoughts on 2 December 2019

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76 y/o F with ER+/PR+/HER2- MBC with PD on AI/CDK4/6 therapy

Summary of Somatic Alterations & Associated Treatment Options

KEY ✓ Approved in indication ◎ Approved in other indication ⊗ Lack of response

Alteration	% cfDNA or Amplification	Associated FDA-approved therapies	Clinical trial availability (see page 3)
ESR1 D538G	2.3%	✓ Fulvestrant ⊗ Anastrozole, Exemestane, Letrozole	Yes
ESR1 L536P	0.6%	✓ Fulvestrant ⊗ Anastrozole, Exemestane, Letrozole	Yes
ESR1 L536R	0.2%	✓ Fulvestrant ⊗ Anastrozole, Exemestane, Letrozole	Yes
ESR1 E380Q	0.1%	✓ Fulvestrant ⊗ Anastrozole, Exemestane, Letrozole	Yes
PIK3CA E542K	6.0%	✓ Alpelisib ◎ Copanlisib	Yes
CCND1 Amplification	Medium (++)	✓ Abemaciclib, Palbociclib, Ribociclib	Yes

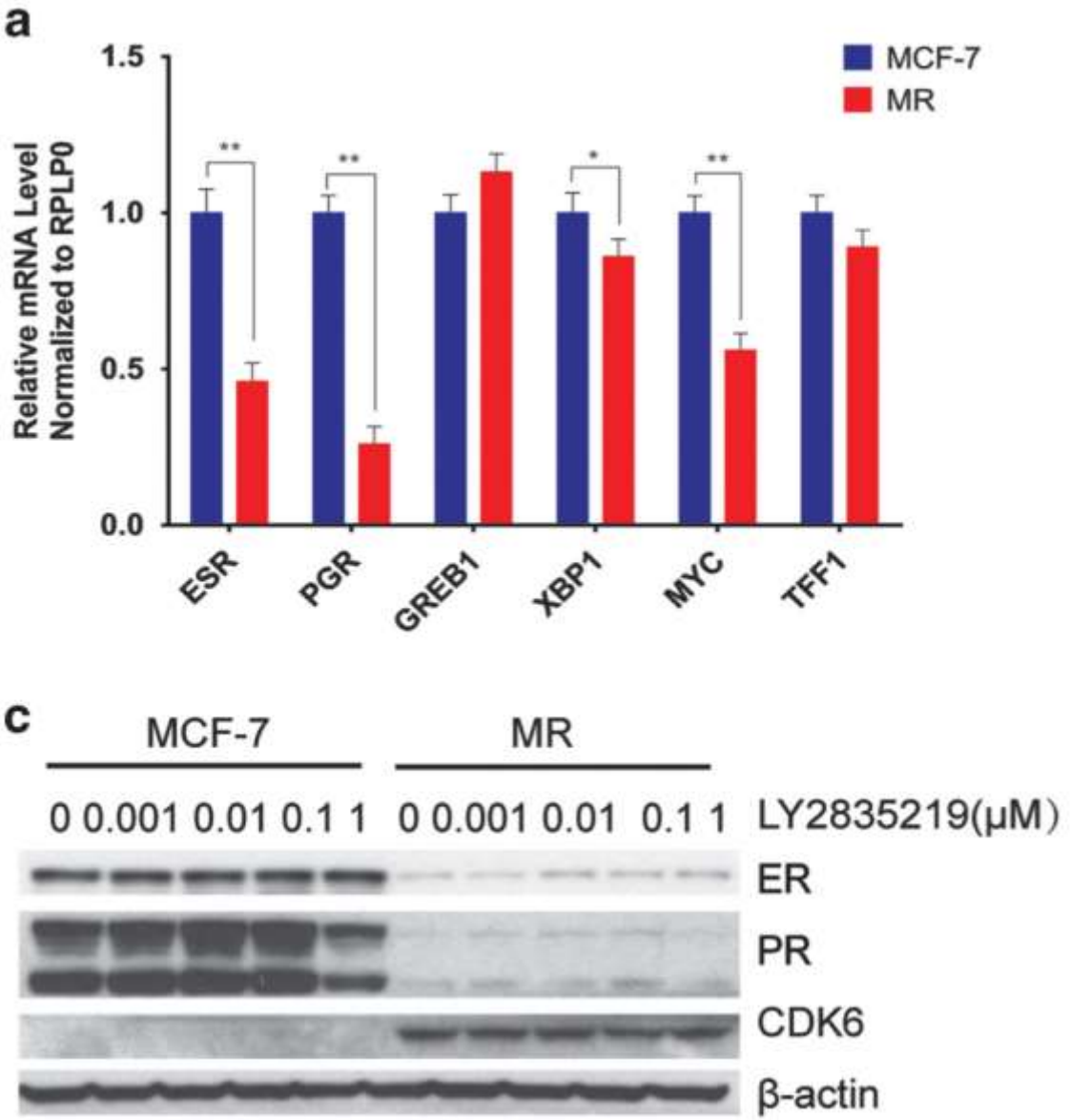
Quindi?

CDK4/6 inhibitor resistance promotes diminished ER expression and activity

Table 1. ER/PR levels by IHC staining from patients treated with CDK4/6 inhibitors

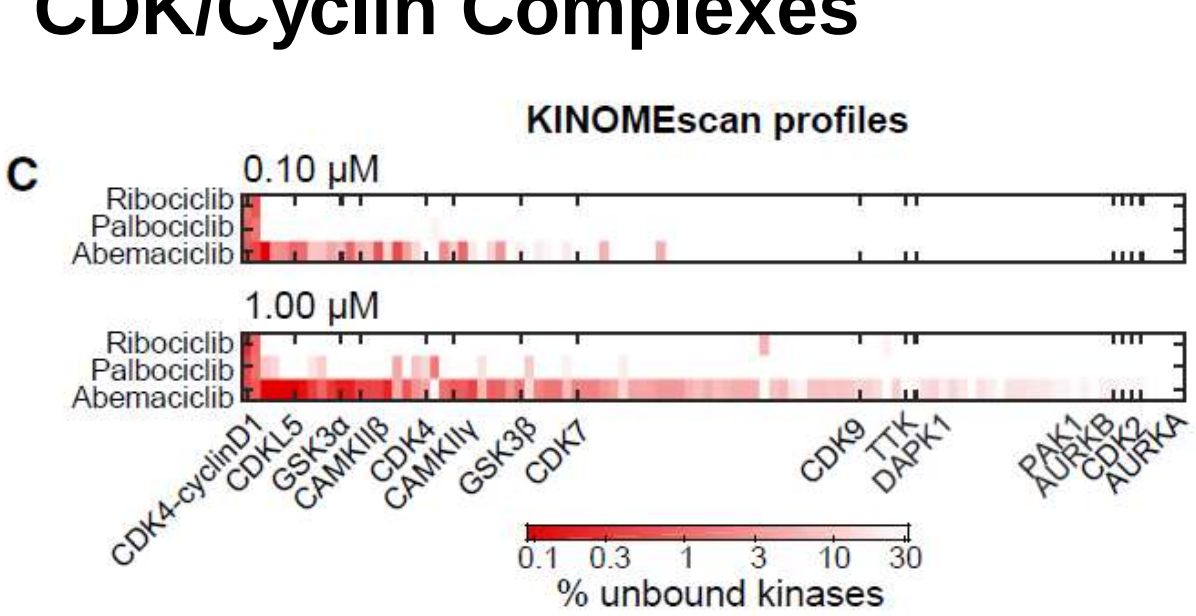
Patient number	*Drug*	*Duration (months)*	*Pretreatment*		*Post-treatment*	
			ER	*PR*	*ER*	*PR*
1	LEE011	13	99	90	85	< 1
2	LEE011	4	25	0	0	0
3	LY2835219	11	90	0	0	0
4	LEE011	9	98	0	2	0
5	LEE011	5	99	0	95	0
6	LEE011	8	'++' external	'0'	60	0
7	LY2835219	6	+	–	70	30

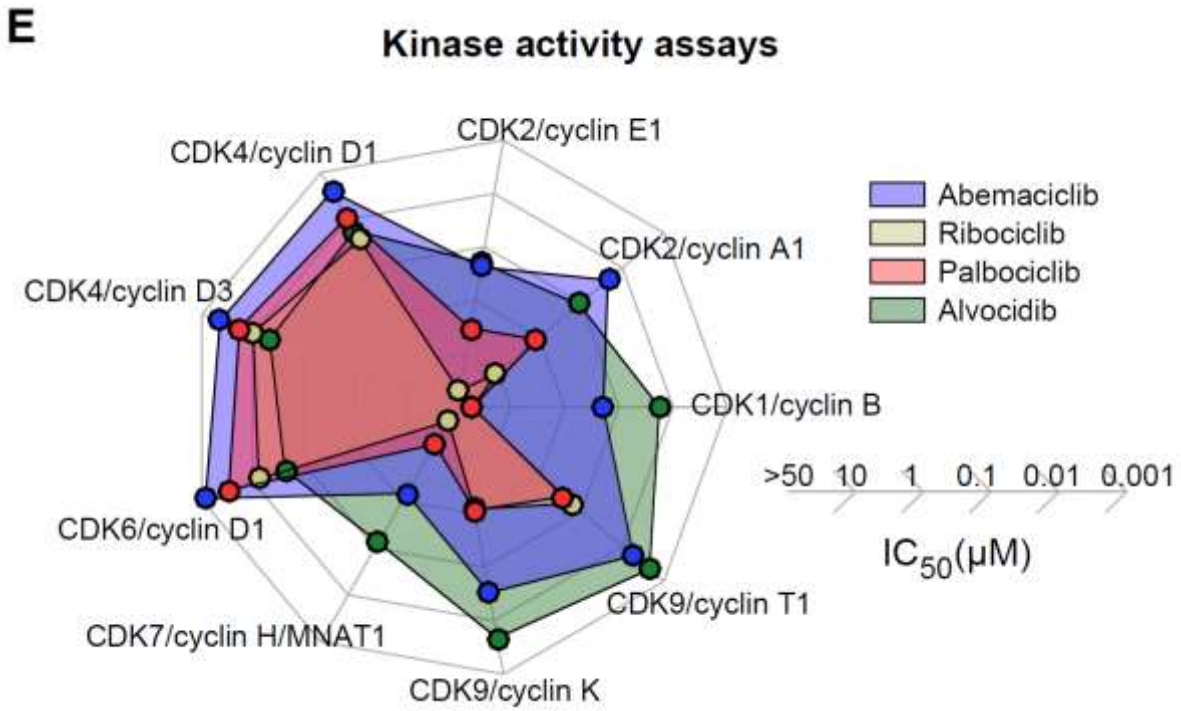
Abbreviations: CLIA, ChemiLuminescent Immuno Assay; ER, estrogen receptor; IHC, immunohistochemistry; PR, progesterone receptor. Immunohistochemical analysis of ER and PR in tumor biopsies from patients treated either with LEE011 or LY2835219 for metastatic breast cancer. Reported is the % staining using standard CLIA assays for ER and PR levels.

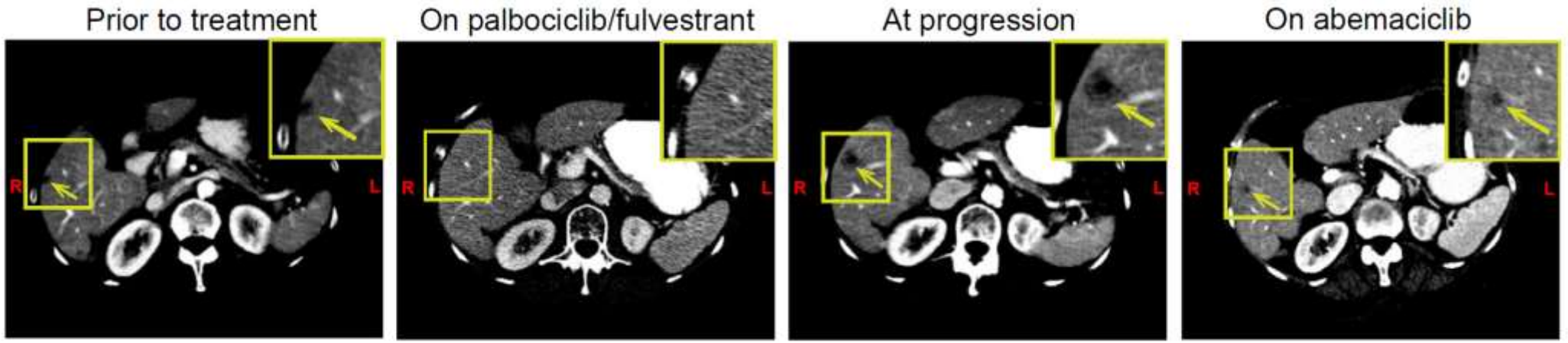


Yang et al., Oncogene, 2016

Differential Effects of CDK4/6 Inhibitors on the Activity of CDK/Cyclin Complexes



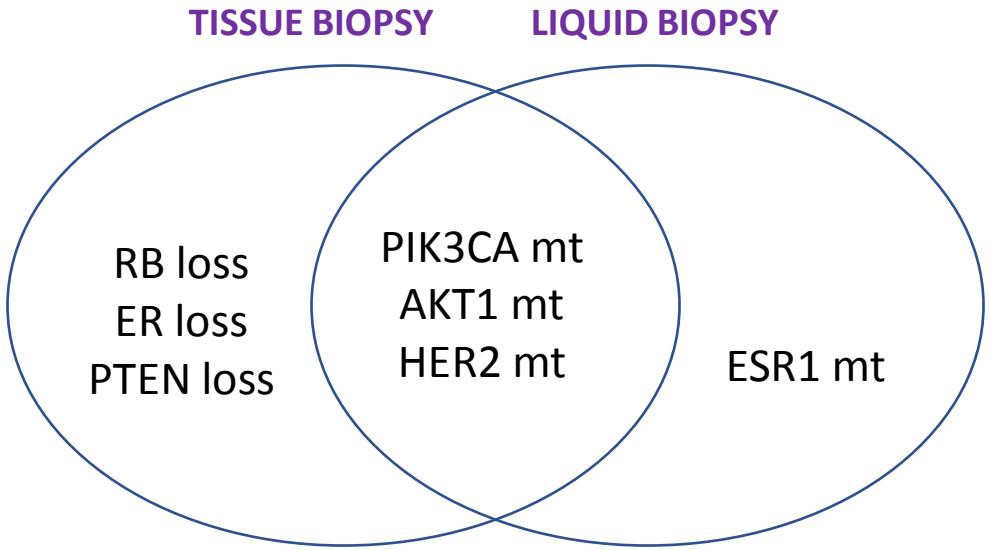




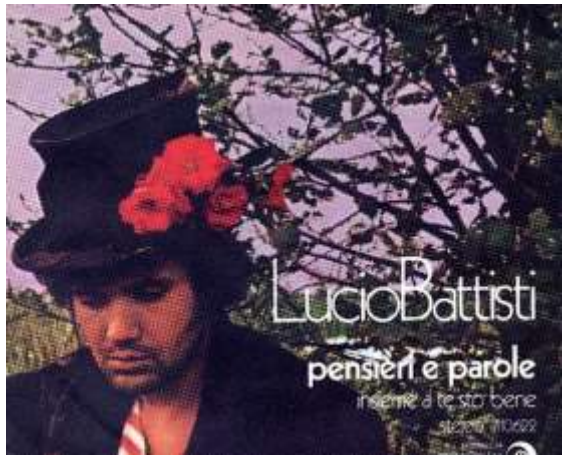
Hatner et al. Cell Chem Biol, 2019

Tissue vs. Liquid Biopsy….

- Tissue biopsies and liquid biopsies are complementary tests for interrogation of biomarkers of response and resistance in MBC
- SOLAR-1 demonstrated prolongation of PFS with alpelisib/fulvestrant vs placebo/fulvestrant in both tissue-based and ctDNA-based analyses, demonstrating clinical utility of **both tests** in selecting patients with a **PIK3CA** mutation
- Compared to **PIK3CA mutations, ESR1 mutations** are more often subclonal and/or polyclonal events more suitable for **ctDNA-detection**
- **Rb loss, ER loss and PTEN loss** are mediators of resistance to **CDK4/6 and/or PI3K-alpha inhibition** and can be accurately determined only by protein level assays such as IHC analysis **of tissue biopsies**
- **HER2 mutations and AKT1 mutations** can be detected by **both** **tissue and liquid biopsies**



Thoughts and Words



★ TIL and the “right” PDL1 are very strond prognostic & predictive factors

★ There are immunological differences between primary versus metastatic lesions

★ Immune microenvironment before and after neoadjuvant chemotherapy +/- IO therapy is different

★No doubt to exclude CDK4/6i in I-line. After failure we accept the challenges!

★ Tomorrow's job will be to find the target: Tissue or LB?

Post ESMO:
to Barcelona to Real World

Thanks