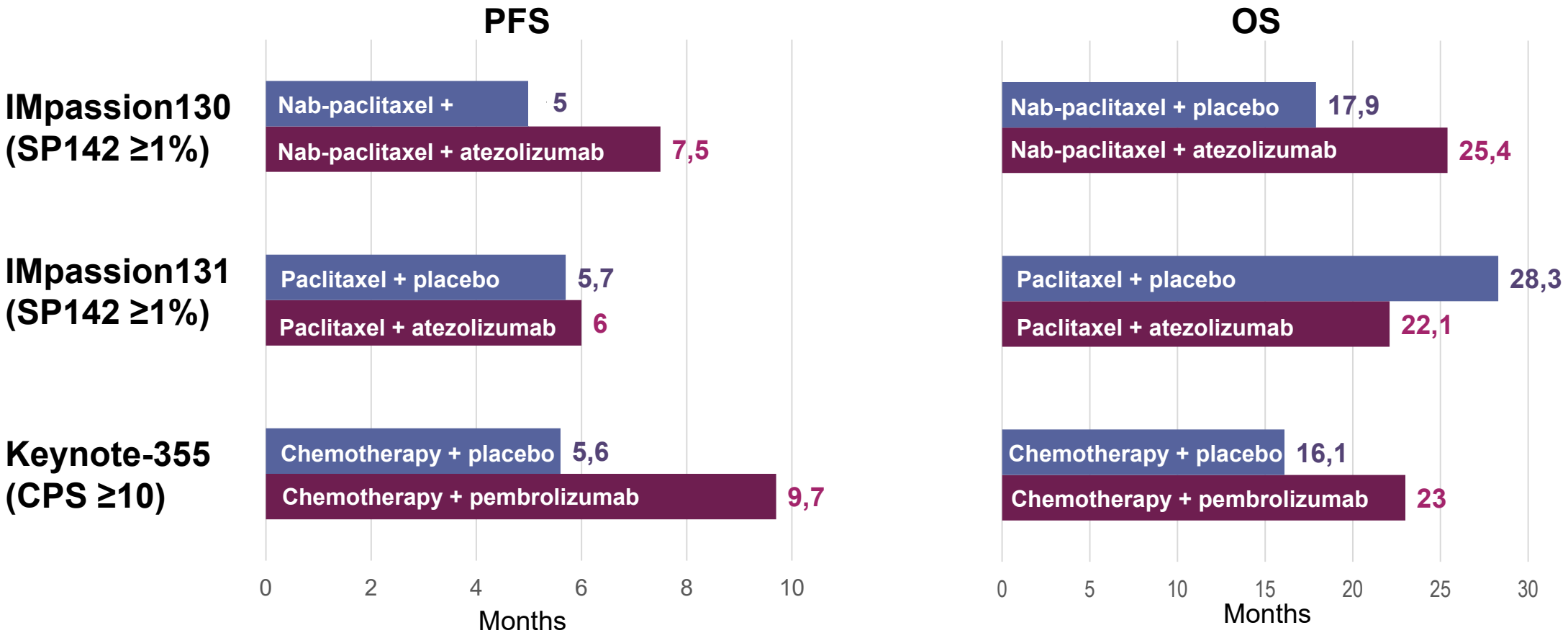
Introduzione al best paper Internazionale

Maria Vittoria Dieci

Disclosure slide

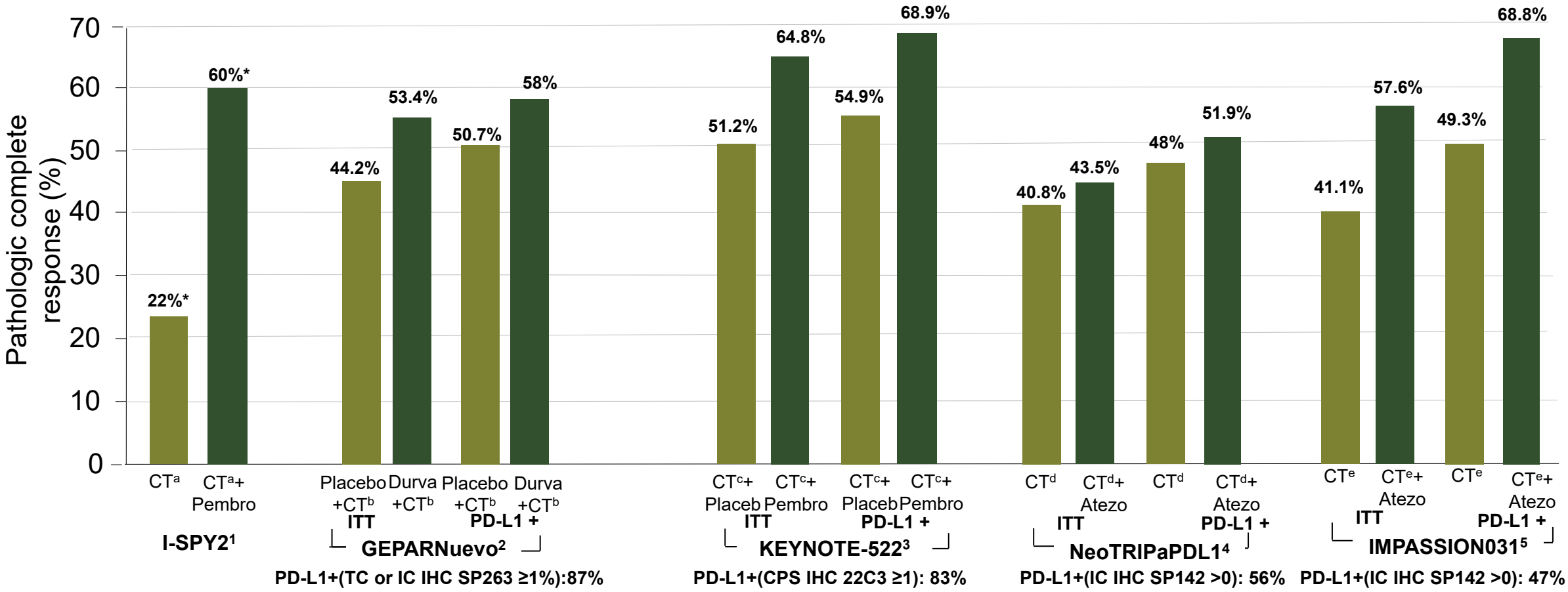
- Personal fees for advisory/consultancy role from:
- EliLilly
- Pfizer
- Novartis
- Roche
- Exact Sciences
- AstraZeneca
- MSD
- Daiichi Sankyo
- Gilead
- Seagen

Chemo-immunotherapy: standard 1st line in PD-L1+ mTNBC



Schmid P, *et al.* NEJM 2018; Emens LA, *et al.* Ann Oncol 2021; Miles D, *et al.* Ann Oncol 2021; Cortes J, *et al.* Lancet 2020; Rugo H, *et al.* ESMO 2021.

NEOADJUVANT IMMUNOTHERAPY + CT IN TNBC: RANDOMIZED TRIALS



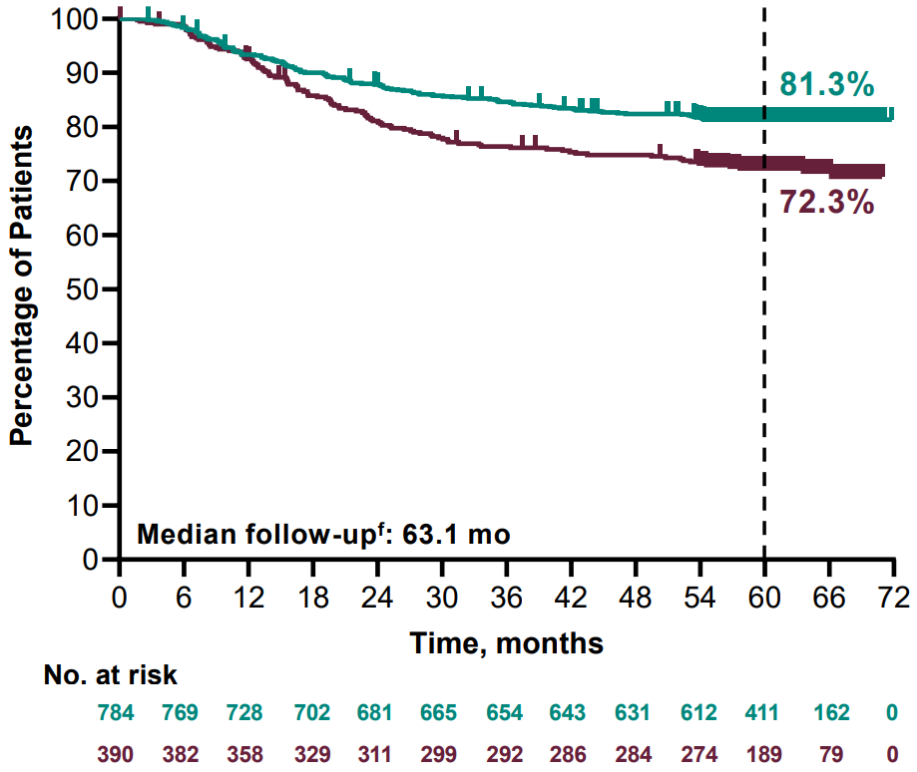
a. Pac →DC; b. Nab-Pac→ EC(dd); c. Carboplatin+Pac → EC/DC; d. Carboplatin+Nab-Pac (anthra given after surgery); e. Nab-Pac-> DC(dd)
*Estimated probabilities of pCR.

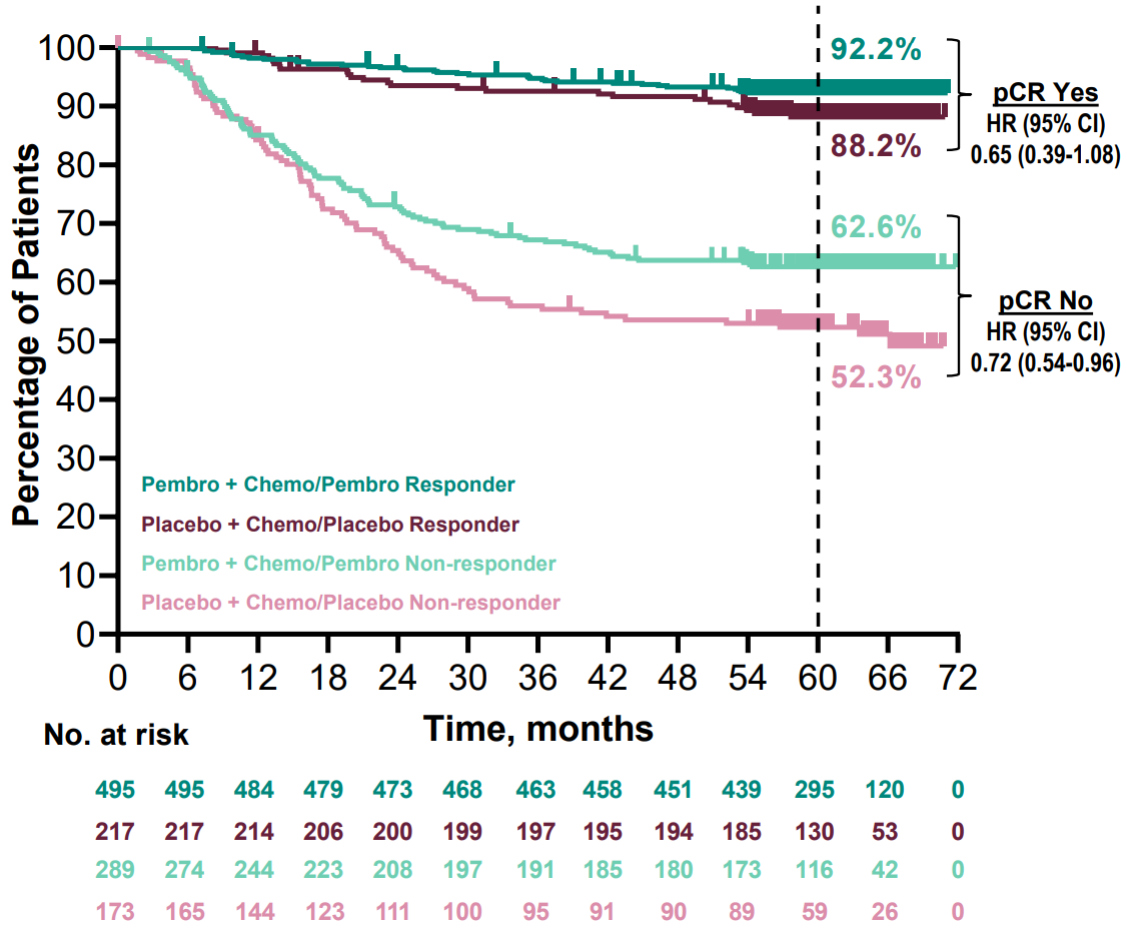
1. Nanda R, *et al.* JAMA Oncol 2020; 2. Loibl S, *et al.* Ann Oncol 2019; 3. Schmid P, *et al.* NEJM 2020; 4. Gianni L, *et al.* SABCS 2019; 5. Mittendorf EA, Lancet 2020.

NEOADJUVANT PEMBROLIZUMAB SIGNIFICANTLY PROLONGS EFS

UPDATED ANALYSIS OF THE KEYNOTE-522 TRIAL, mFU 63 MONTHS

IA6[b]	Events	HR (95% CI)
Pembro + Chemo/Pembro	18.5%	0.63[c] (0.49-0.81)
Placebo + Chemo/Placebo	27.7%	



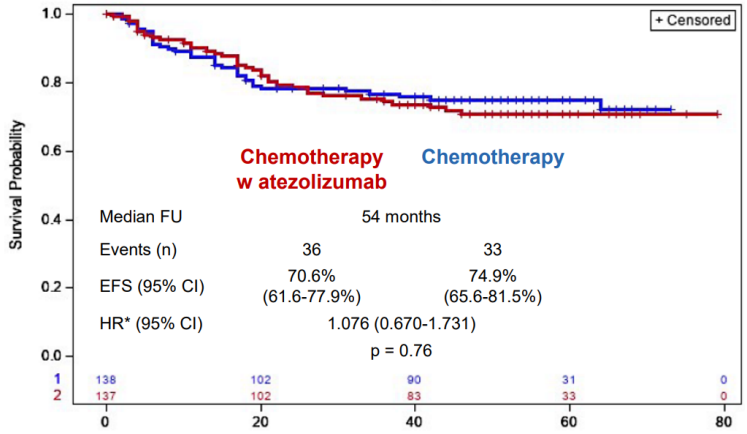


Schmid P. et al., ESMO 2023

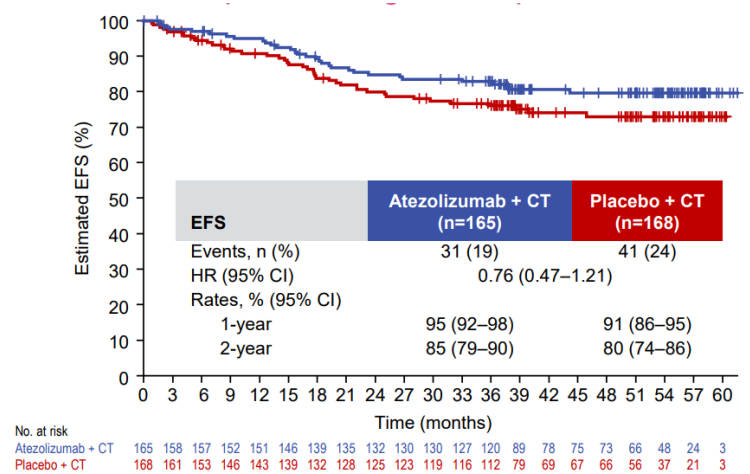
All that glitters is not (always) gold...

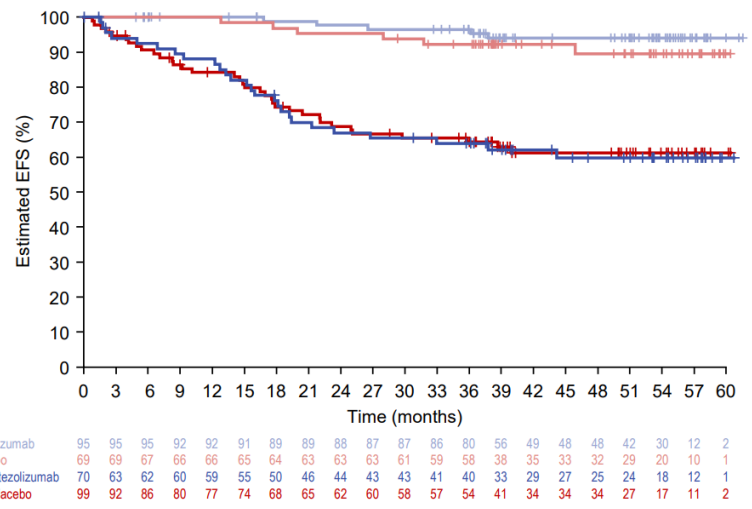
Inconsistent EFS results from other neoadjuvant trials

NeoTRIP (primary EP)

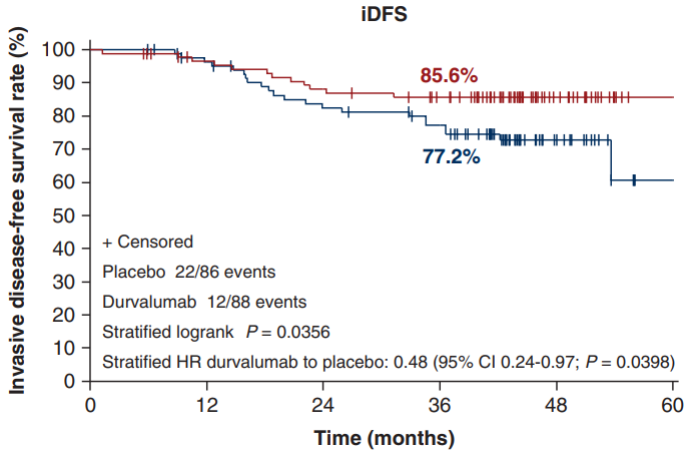


Impassion-031 (secondary EP)



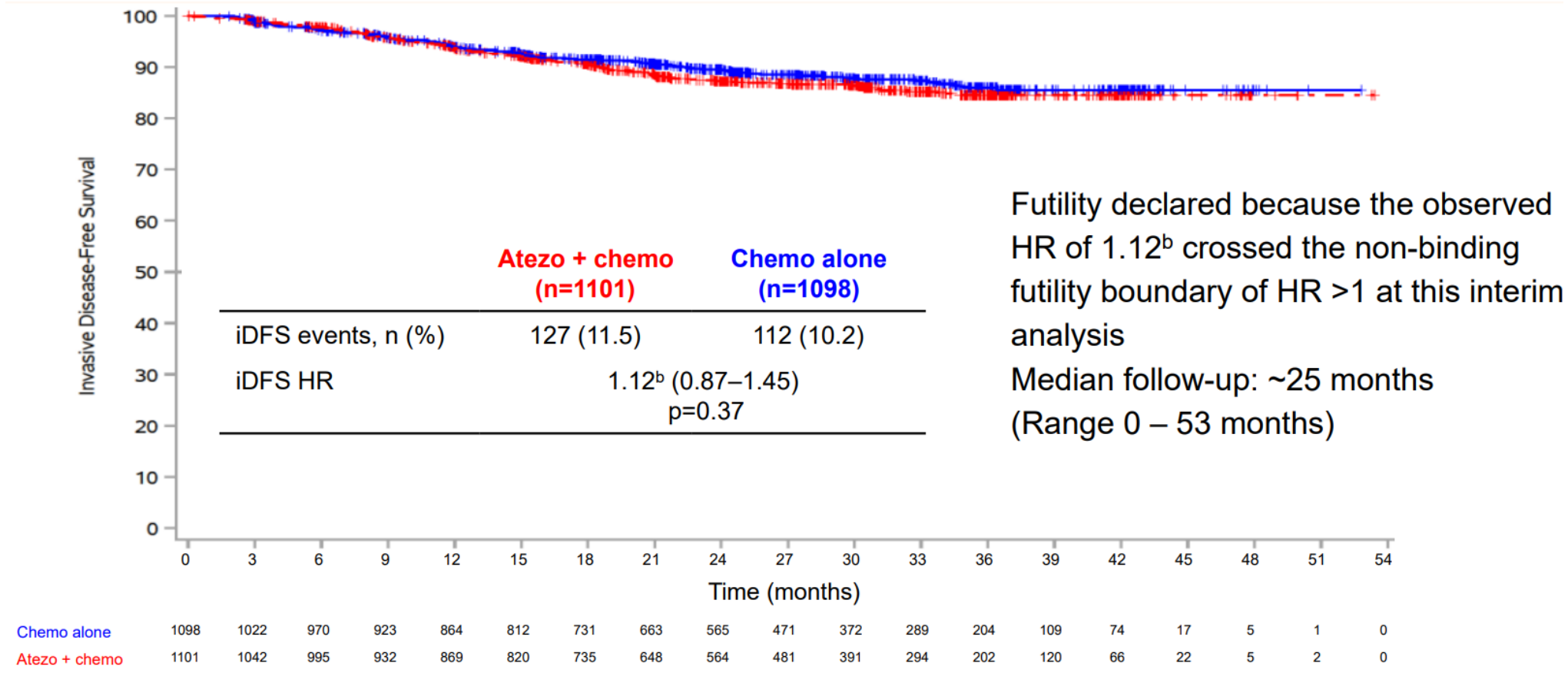


Geparnuevo (secondary EP, phase II)



Gianni L. et al., ESMO 2023; Loibl S. et al., Ann Oncol 2022; Barrios C. et al., Esmo Breast Cancer 2023

Disappointing results for pure adjuvant IMpassion-030 trial



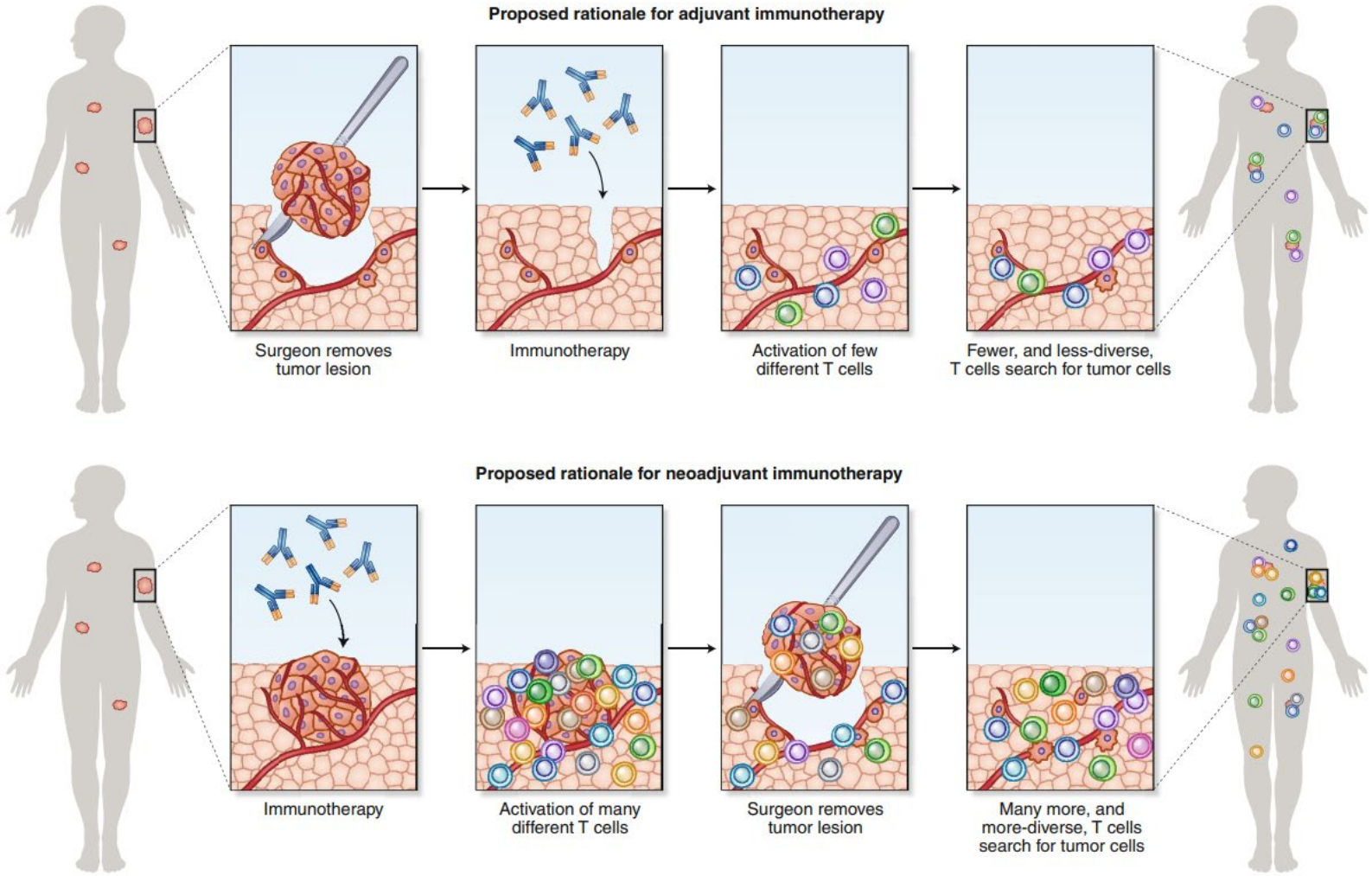
	Atezo + chemo (n=1101)	Chemo alone (n=1098)
iDFS events, n (%)	127 (11.5)	112 (10.2)
iDFS HR	1.12[b] (0.87–1.45) p=0.37	

Futility declared because the observed HR of 1.12[b] crossed the non-binding futility boundary of HR >1 at this interim analysis

Median follow-up: ~25 months (Range 0 – 53 months)

Ignatiadis M. et al., SABCS 2023

Neoadjuvant/perioperative vs «pure» adjuvant



Versluis J. Et al., Nat Med 2020

A-BRAVE-TRIAL

Sponsor: University of Padova
PI: Valentina Guarneri

HIGH RISK PRIMARY TNBC PTS WHO COMPLETED TREATMENT WITH CURATIVE INTENT INCLUDING SURGERY AND CHEMOTHERAPY

Stratum A: Adjuvant (high stage)

Stratum B: Post-neoadjuvant (non-pCR)

R

Avelumab for 1 year

Observation

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

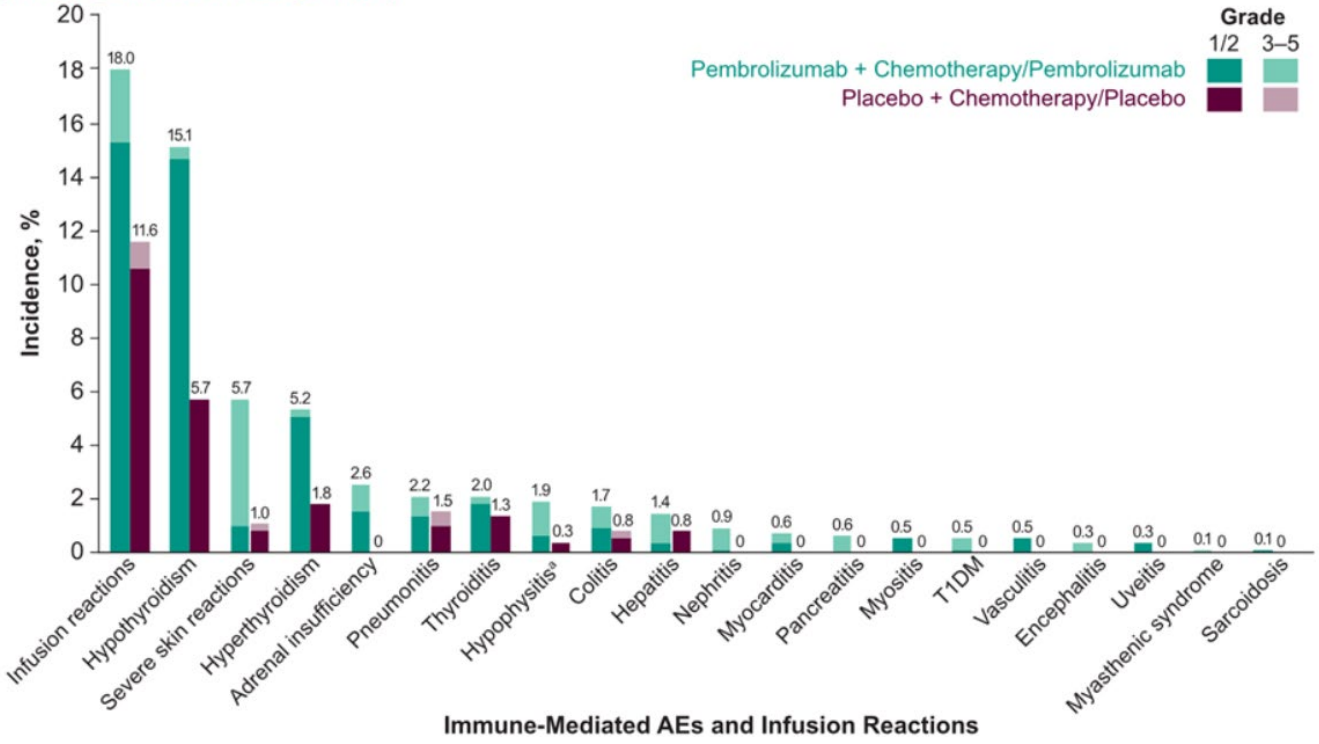
Co-primary endpoints: 1. DFS in all-comers; 2. DFS in Stratum B post-neoadjuvant
Secondary endpoints: OS, DFS in PD-L1+, Safety, Biomarkers
n=474

2024 ASCO® ANNUAL MEETING

SUMMARY OF SAFETY DATA FROM KN-522 (IA4)

- **Serious treatment-related adverse events:**
  34.1% pembro vs of 20.1%
- **Discontinuation:**
  27.7% pembro vs 14.1% placebo
- **G5 events:**
  4 pembro vs 1 placebo
- **Immune-mediated adverse events:**
  33.5% pembro vs 11.3% placebo
- **Immune-mediated adverse events G3+:**
  12.9% pembro vs 1.0% placebo.
- **Immune-mediated adverse events G5:**
  2 pembro vs 0 placebo

Figure 2. Immune-mediated AEs and infusion reactions by grade in combined phases (neoadjuvant and adjuvant)



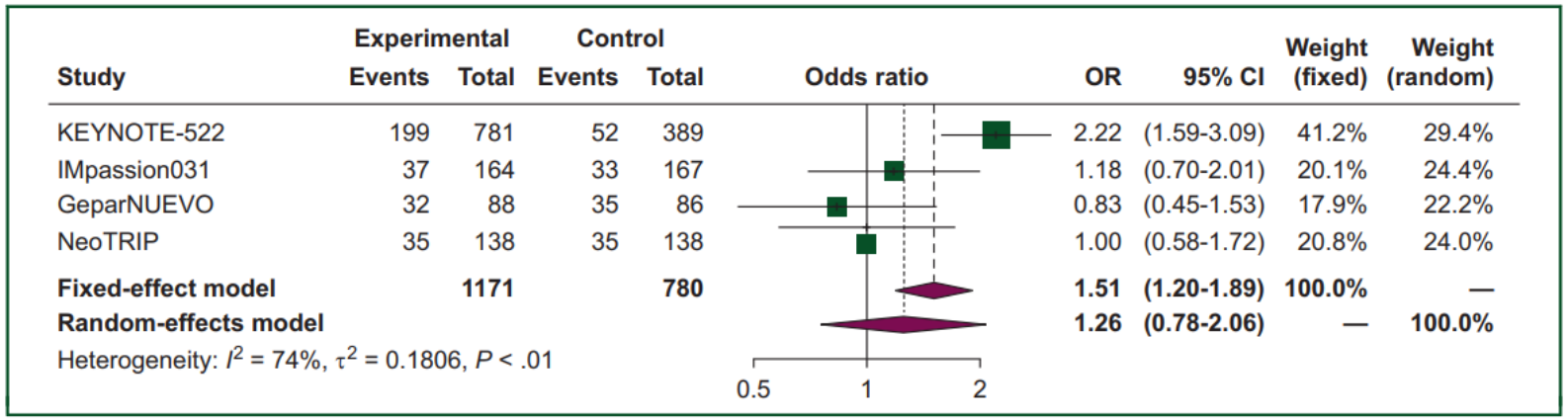
Schmid P. et al., NEJM 2022; Cortes J. Et al., SABCS 2023

Discontinuation rate and serious adverse events of chemoimmunotherapy as neoadjuvant treatment for triple-negative breast cancer: a systematic review and meta-analysis

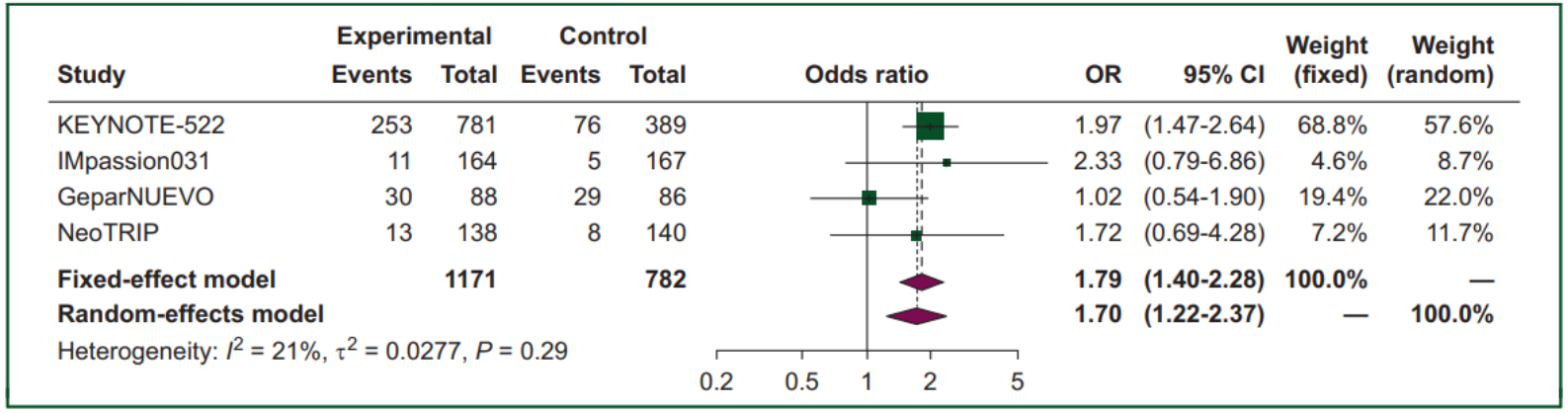
A. Rizzo[1†], F. M. Schipilliti[2†], F. Di Costanzo[3], S. Acquafredda[1], G. Arpino[3], F. Puglisi[4,5], L. Del Mastro[6,7], F. Montemurro[8], M. De Laurentiis[9] & M. Giuliano[3*]

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

Discontinuation



Serious AEs



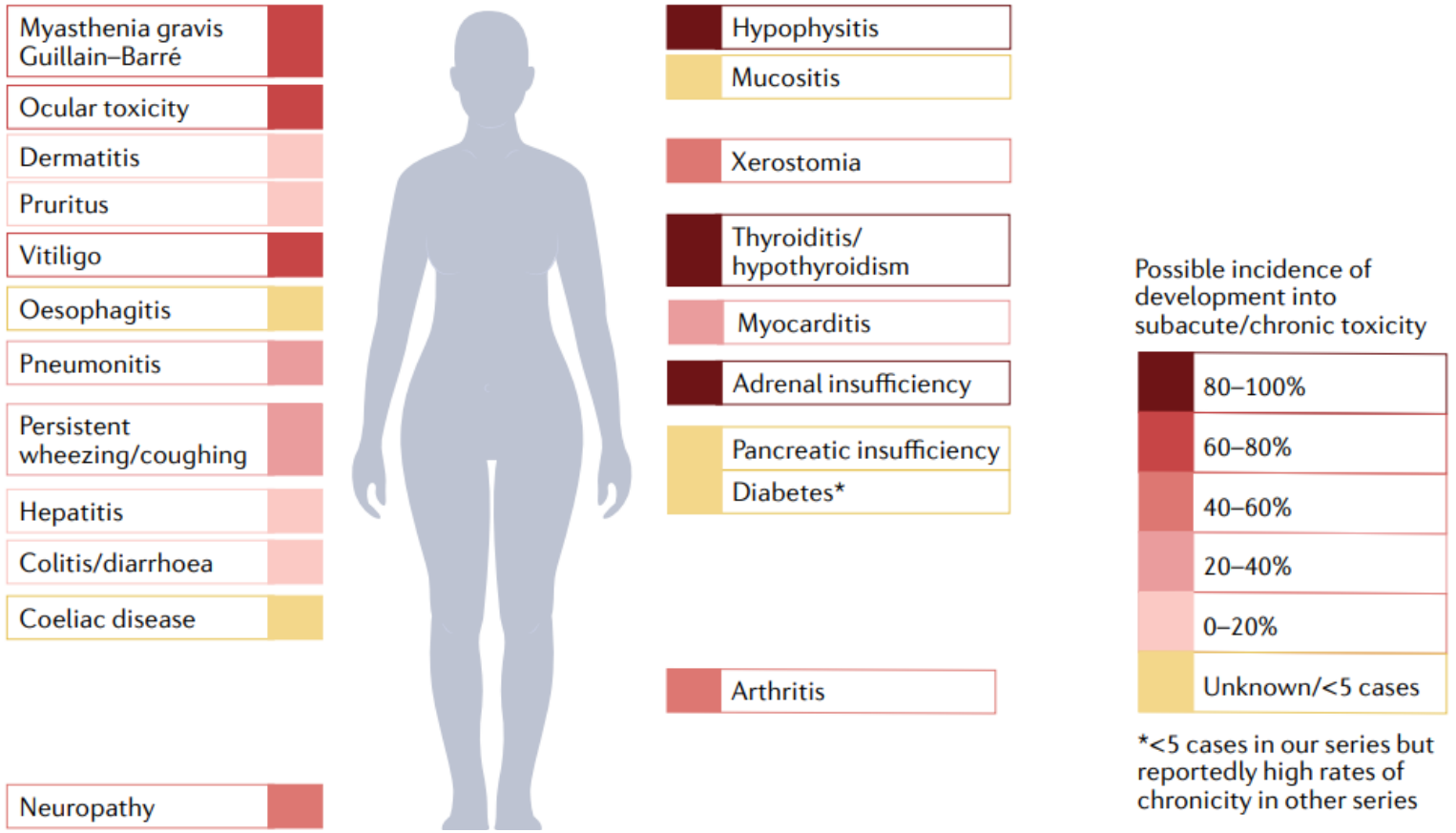
REAL WORLD SAFETY OF KN522-LIKE REGIMEN

Safety	Any Grade (n=577)	Grade 3+	KN522, Any Grade (n= 783)	KN522 Grade 3+
Adverse Drug Event (ADE) Causing Dose Reductions	217 (37.6%)		No equivalent reported	
ADE Causing Early Discontinuation	228 (39.5%)		216 (27.7%)	
Patients who experienced an immune-related adverse effect (irAE)?	412 (71.4%)	184 (31.9%)	262 (33.5%)	101 (12.9%)

Hofherr M. et al., SABCS 2023

Consequences of irAEs

- Treatment discontinuation
- Fatal toxicity
- Chronic toxicity



Johnson et al, Nature Review Clin Oncol, 2022

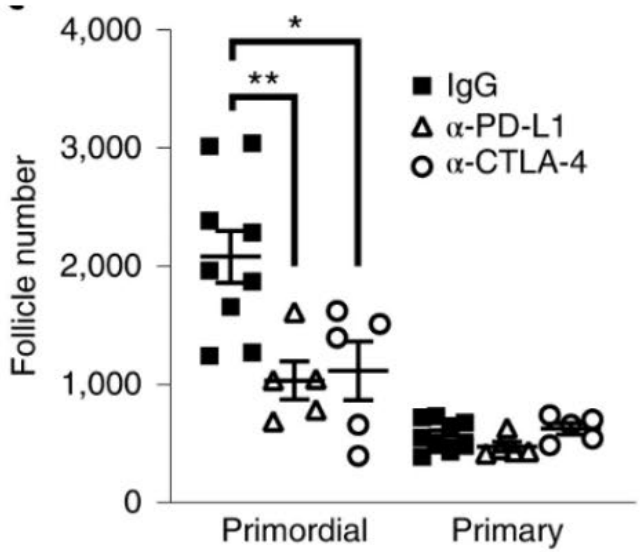
Could ICI *even* affect fertility?

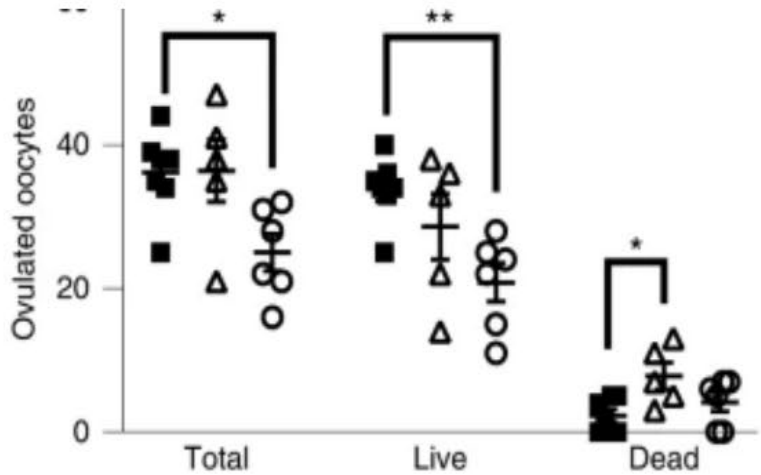
Article | Published: 25 August 2022

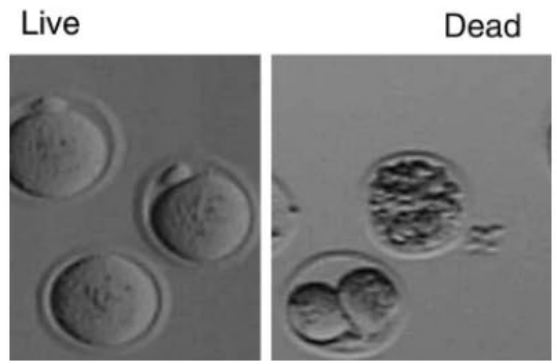
Checkpoint inhibitor immunotherapy diminishes oocyte number and quality in mice

Amy L. Winship, Lauren R. Alesi, Sneha Sant, Jessica M. Stringer, Aldana Cantavenera, Teharn Hegarty, Carolina Lliberos Requesens, Seng H. Liew, Urooza Sarma, Meaghan J. Griffiths, Nadeen Zerafa, Stephen B. Fox, Emmaline Brown, Franco Caramia, Pirooz Zareie, Nicole L. La Gruta, Kelly-Anne Phillips, Andreas Strasser, Sherene Loi & Karla J. Hutt

Nature Cancer **3**, 1–13 (2022) | Cite this article







In mice, treatment with ICI decreases the ovarian reserve and disrupts ovulation

Winship et al., *Nature Cancer 2022*

5 «rights» of safe medication use

The PD-L1 story

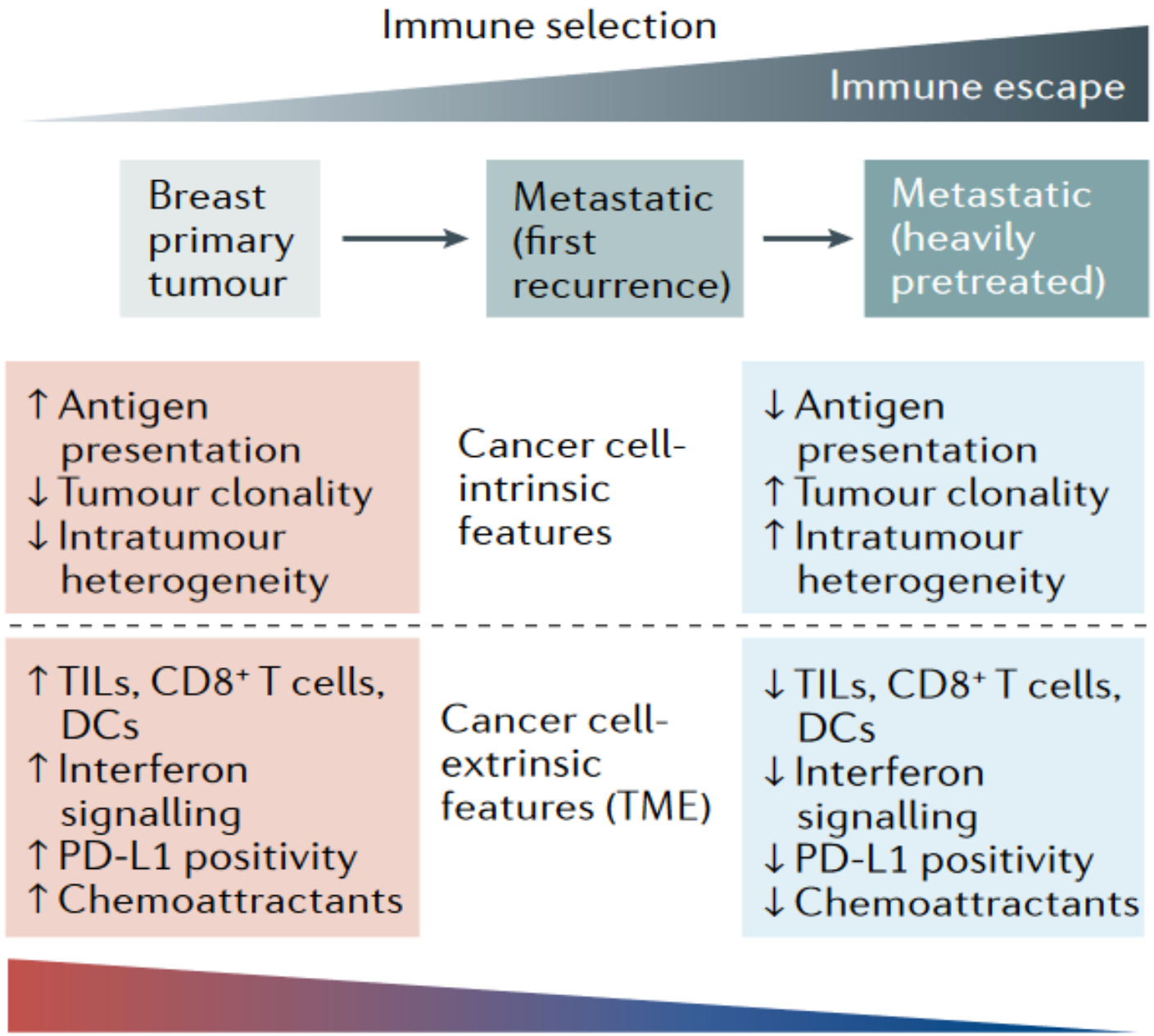
PEMBROLIZUMAB IN eTNBC

Subgroup	Pembrolizumab–Chemotherapy	Placebo–Chemotherapy	Hazard Ratio for Event or Death (95% CI)
	no. of patients with event/total no. (%)		
Overall	123/784 (15.7)	93/390 (23.8)	0.63 (0.48–0.82)
PD-L1 status			
Positive	98/656 (14.9)	68/317 (21.5)	0.67 (0.49–0.92)
Negative	25/128 (19.5)	25/69 (36)	0.48 (0.28–0.85)

PEMBROLIZUMAB IN mTNBC

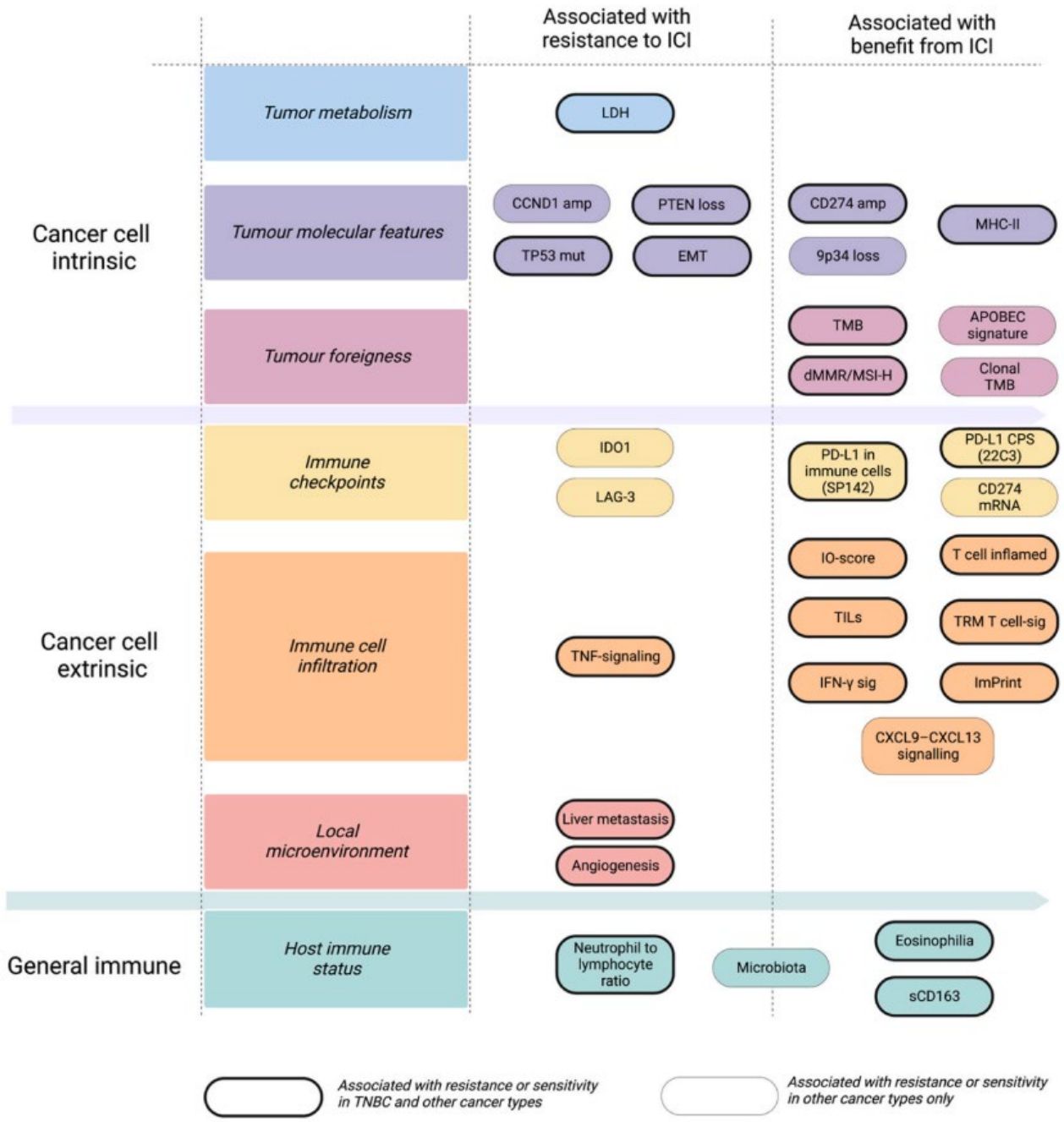
Subgroup	No. of Patients	Median Overall Survival		Hazard Ratio for Death (95% CI)
		Pembrolizumab–chemotherapy	Placebo–chemotherapy	
		mo		
Overall	847	17.2	15.5	0.89 (0.76–1.05)
PD-L1 CPS cutoff of 10				
CPS ≥10	323	23.0	16.1	0.71 (0.54–0.93)
CPS <10	524	14.7	15.2	1.04 (0.85–1.26)

Cortes J. et al., NEJM 2022; Schmid P. et al., NEJM 2022



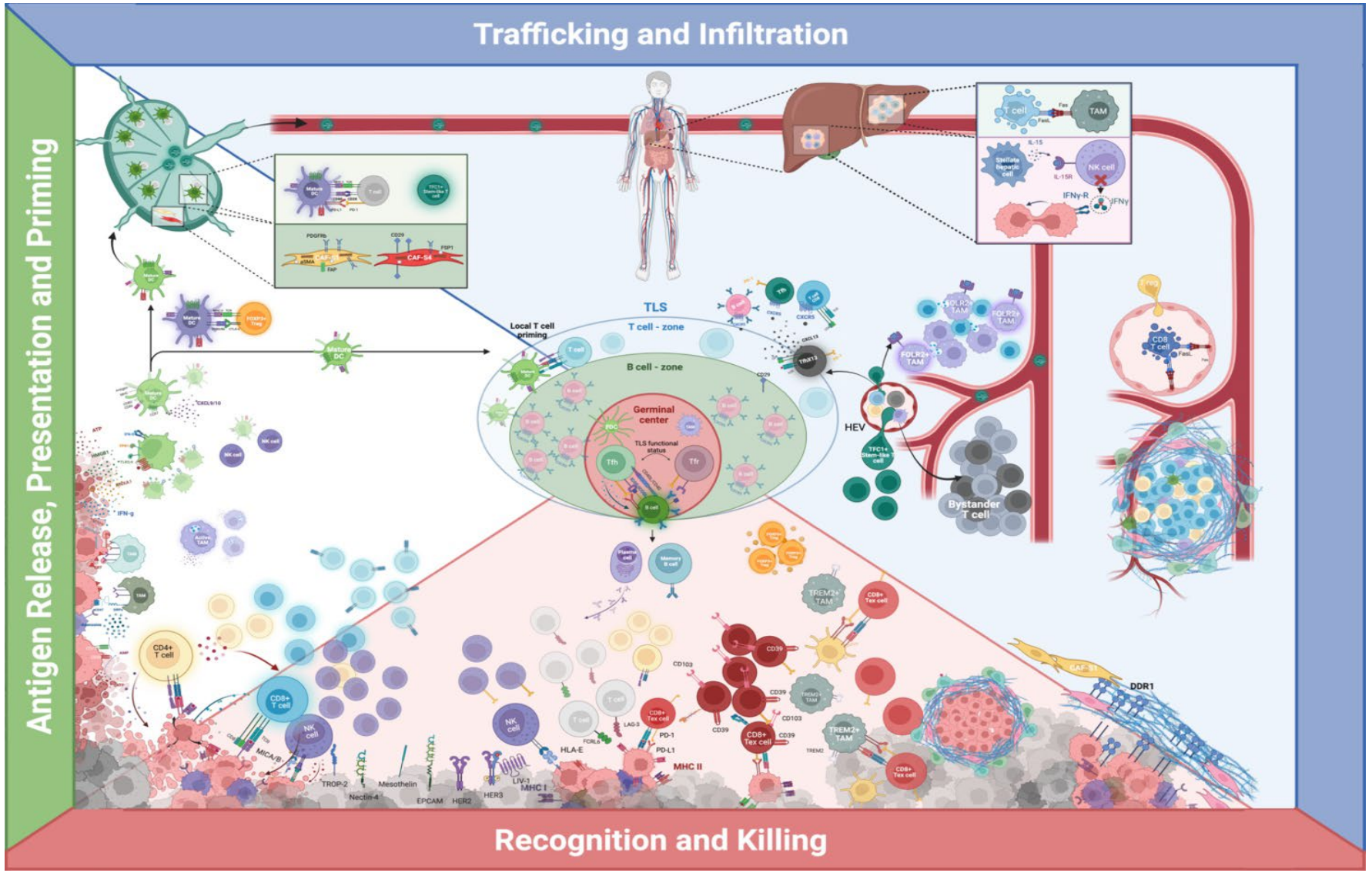
- Predictive factors in mTNBC may not work in the early setting
- We need curative setting-specific biomarkers
- Accounting for dynamic changes during treatment may be relevant

Bianchini G et al., Nat Rev Clin Oncol 2022



Licata L. et al.,
The Breast 2023

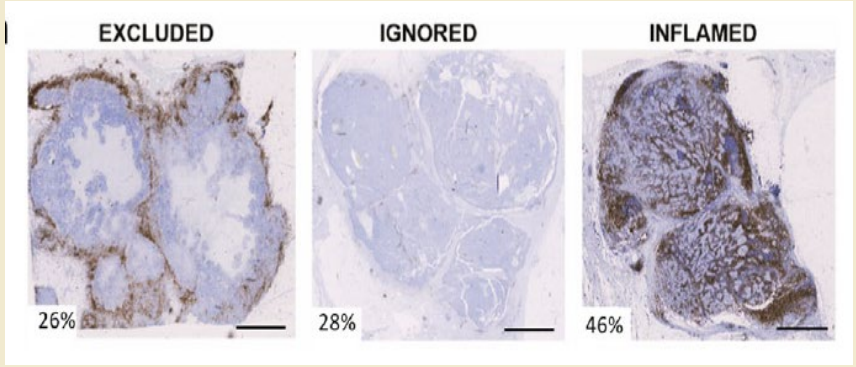
Complexity of the TIME: how close should we look at it?



Massa D. et al., Cancers 2022

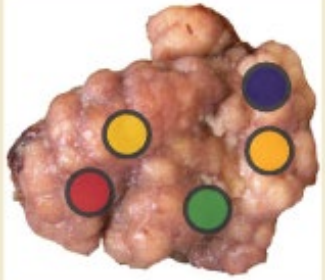
What is spatial profiling and what can it add

Breast Cancer Spatial Phenotyping



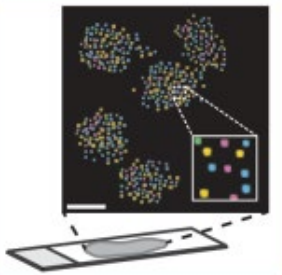
IHC

Multiregion DNA sequencing

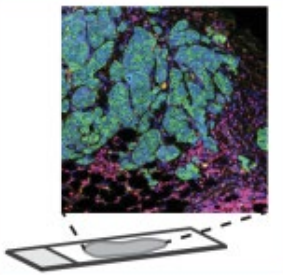


Multiregion sampling

In situ transcriptomics



Multiplexed imaging proteomics



In situ profiling

Modified from Caswell-Jin JL et al, Ann Rev Cancer Biol 2021

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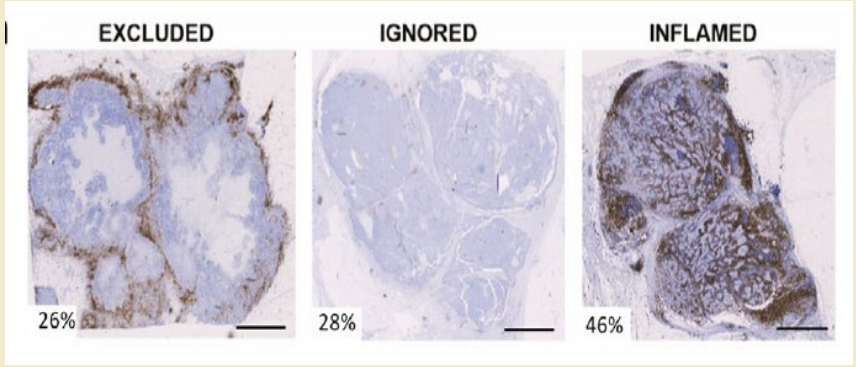

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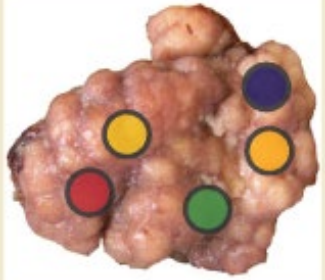

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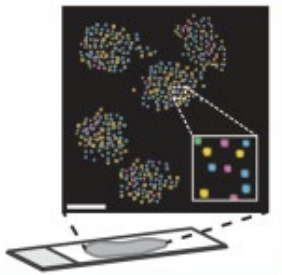

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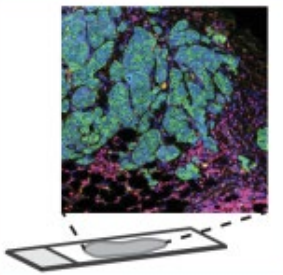

In situ profiling

- **GeoMx DSP, CosMx**
- **10X Visium**
- **Slide-RNA-seq**

- **Multiplex IHC/IF**
- **Imaging mass cytometry**
- **MIBI**
- **CODEX**
- **GeoMx DSP**

Modified from Caswell-Jin JL et al, Ann Rev Cancer Biol 2021

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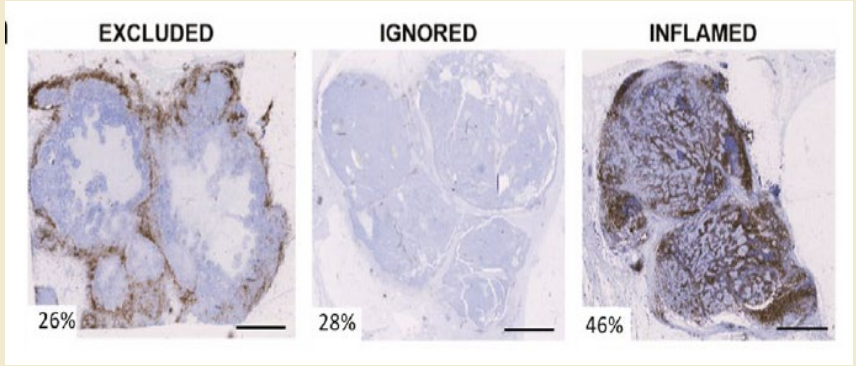
Breast Cancer Spatial Phenotyping



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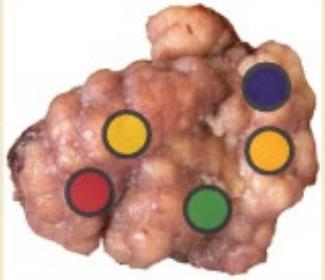

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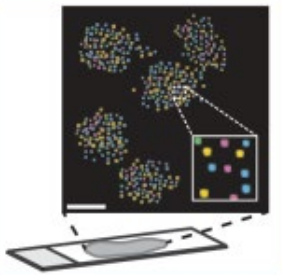

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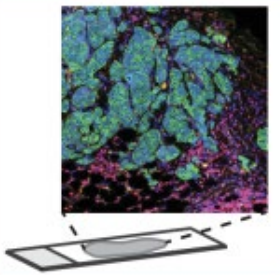
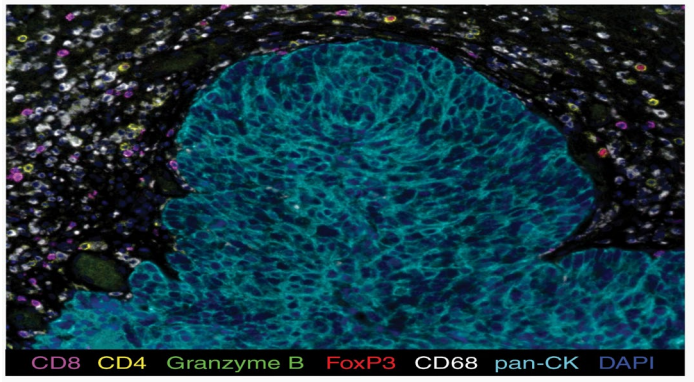


In situ profiling

Identification of key cell subpopulations



Modified from Caswell-Jin JL et al, Ann Rev Cancer Biol 2021

Griguolo G et al, NeuroOncology 2022

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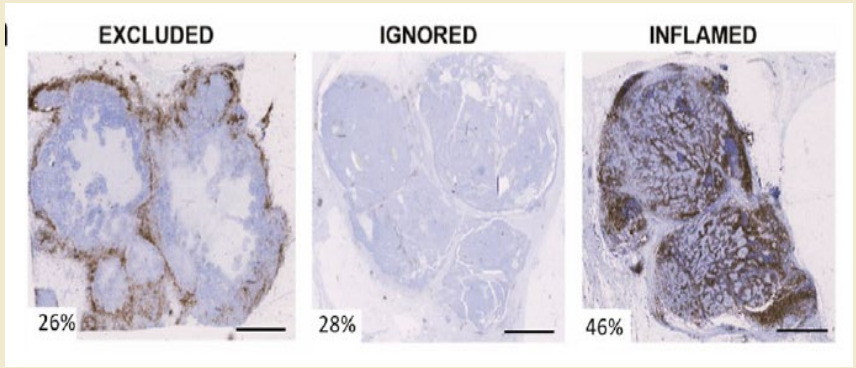

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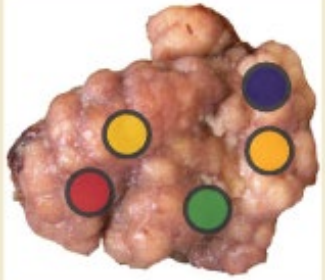

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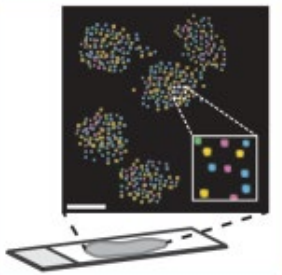

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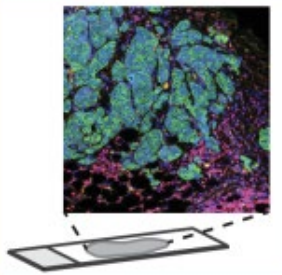
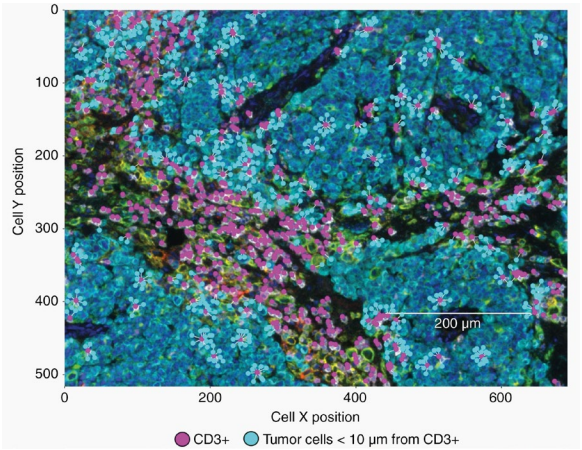
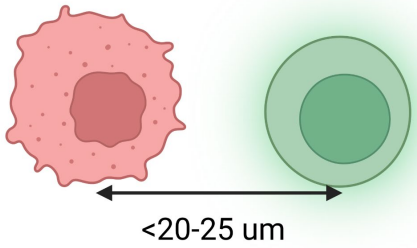


In situ profiling

Which cells are close to each other



To exert cell-cell interactions cells need to be spatially near



Modified from Caswell-Jin JL et al, Ann Rev Cancer Biol 2021

Griguolo G et al, NeuroOncology 2022

FINDING THE RIGHT DISTANCE

«If you stand too close to a painting – all you see are patches of color, if you stand too far back, you can't see any of the details»

Mandy Patinkin