Ottimizzare il trattamento nella malattia triplo negativa: chemioterapia, immunoterapia, ADC, PARP-inibitori

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DECLARATION OF INTERESTS

- **Grant/Funding**: travel support by Novartis and Lilly

OUTLINE

- **Triple-negative breast cancer**

  - Early setting
    - Immunotherapy
    - Adjuvant immunotherapy
    - Anthracycline

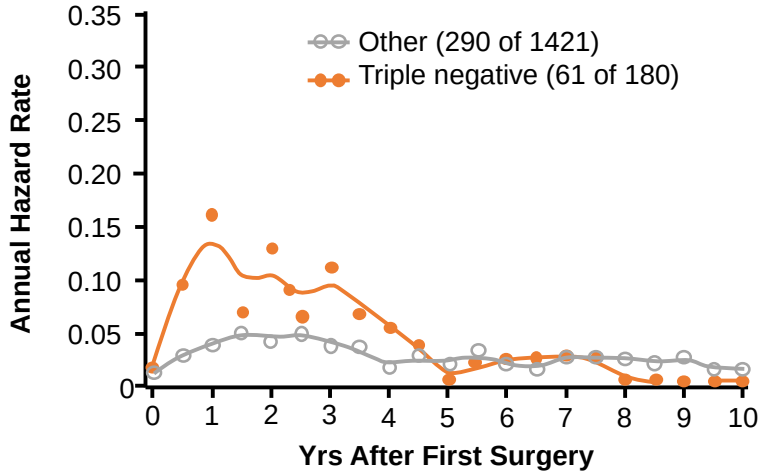
  - Advanced/metastatic setting
    - Immunotherapy
    - ADC
    - PARPi

Triple-negative breast cancer (TNBC)

Triple-negative breast cancer (TNBC) is pragmatically named, denoting the absence of treatment targets

- Heterogeneous disease
  - Highly proliferative, generally chemotherapy responsive
  - Rapid development of resistance
- High risk of early recurrence
  - Visceral dominant disease, early/frequent brain metastases
  - Short median survival (<2yrs) after diagnosis of metastases
- Rare indolent subtypes, generally in older women

TNBC defines an unmet need because of an aggressive biology, resulting in a worse prognosis both in early and metastatic setting



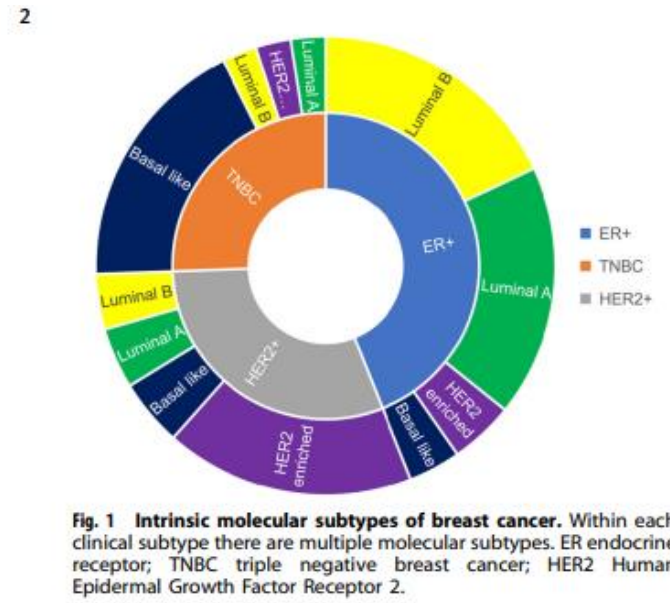
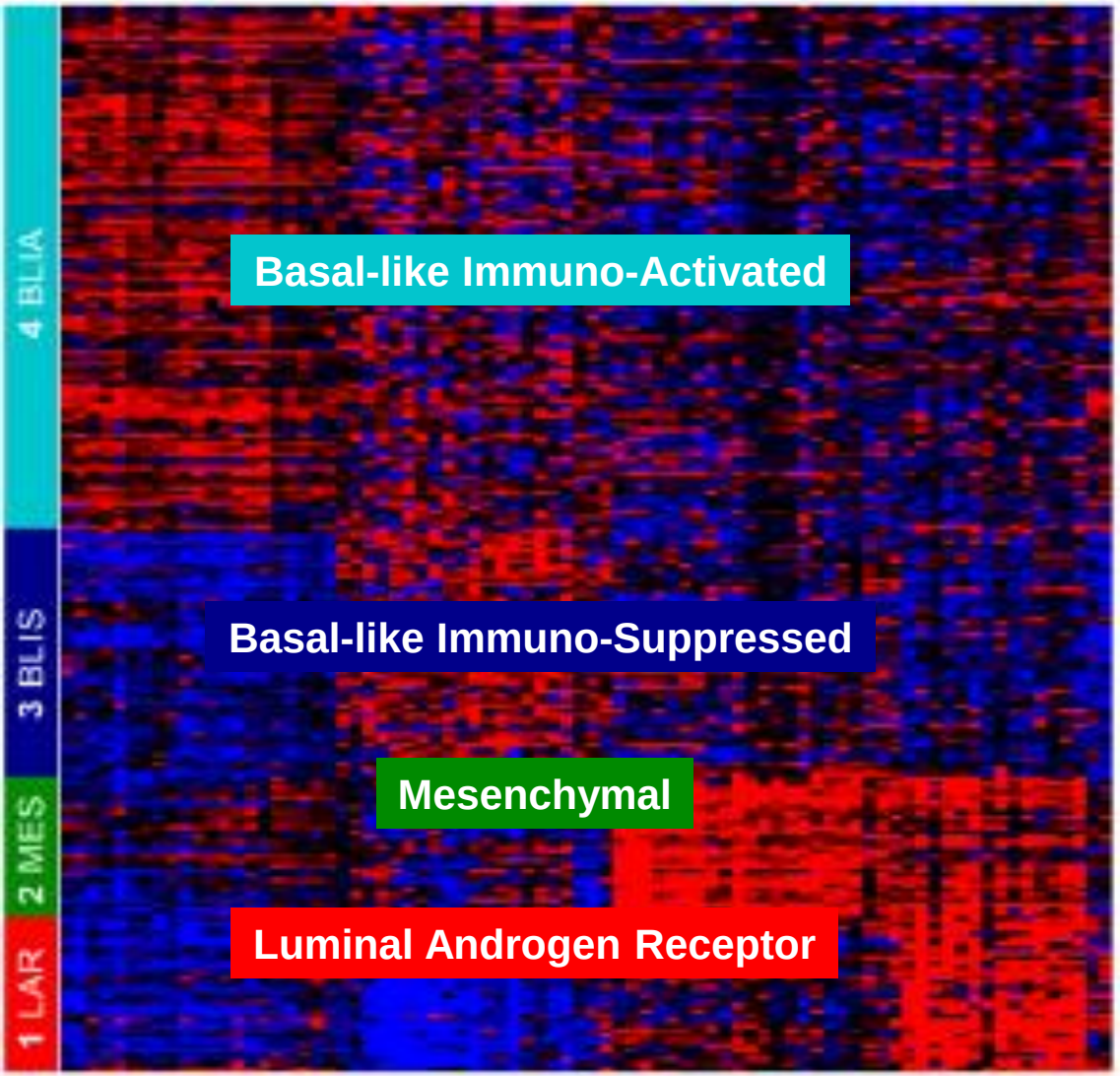


Fig. 1 Intrinsic molecular subtypes of breast cancer. Within each clinical subtype there are multiple molecular subtypes. ER endocrine receptor; TNBC triple negative breast cancer; HER2 Human Epidermal Growth Factor Receptor 2.

Zagami npj 2023, Lin NU, et al. Cancer. 2008; Liedtke C, et al. J Clin Oncol. 2008; Dent R, et al. Clin Cancer Res. 2007

Molecular subtyping of TNBC

Heterogeneity in intrinsic subtypes



- Complex genomic profiles
- *TP53* mutations in >90%
- Higher frequency of HRD
- Higher pCR rates
- Majority of TNBCs

- Complex genomic profiles
- *TP53* mutations in >90%
- Lower TILs and lower pCR rates

- Lower genomic complexity
- Activation of the PI3K pathway
- Intermediate pCR rates

- Lower genomic complexity
- *PIK3CA*, *AKT1*, *NF1*, *GATA3* and *CDH1* mutations
- Lower TILs
- Lower pCR rates

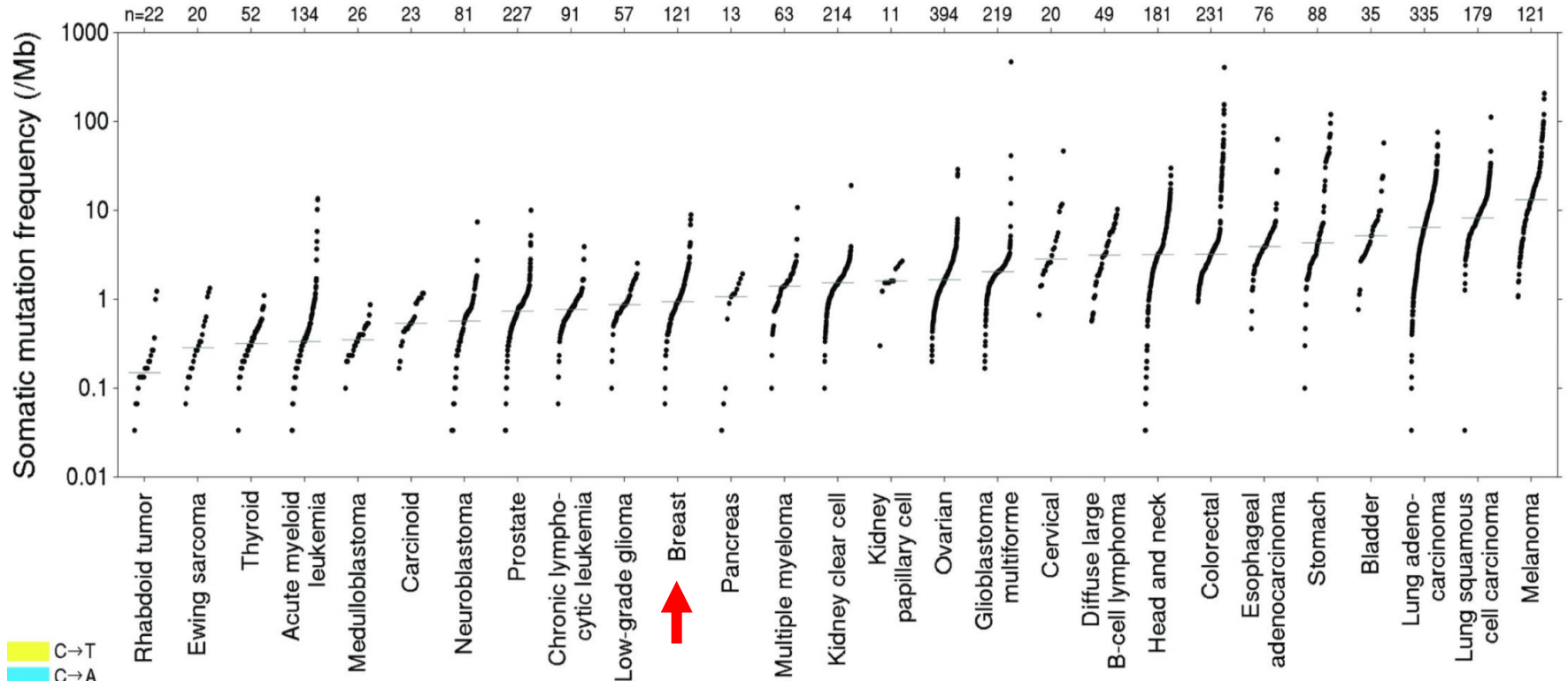
Therapeutic targets

Perou, Nature 2000
Lehmann, JCI 2011
Curtis, Nature 2012
Lehmann, PLoS ONE 2016
Burstein, CCR 2016
Jiang, Cancer Cell 2019

TNBC: heterogeneity

Immune microenvironment

Breast cancer is less immune activated than many other tumor types…

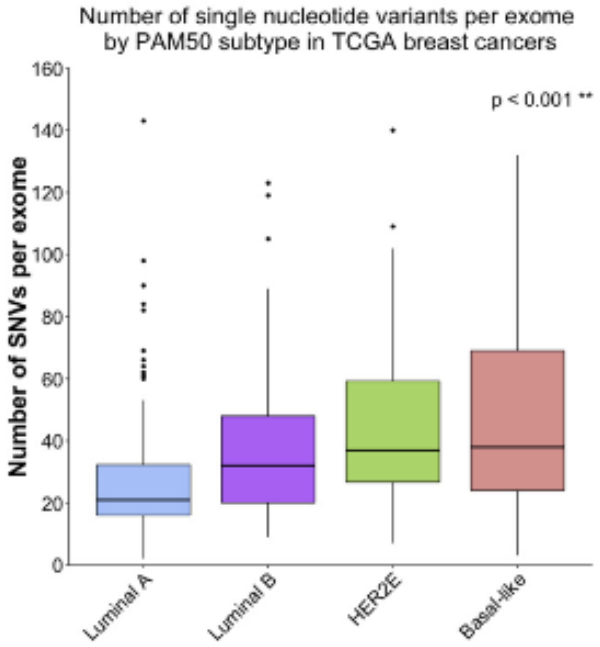


Lawrence et al, Nature 2013

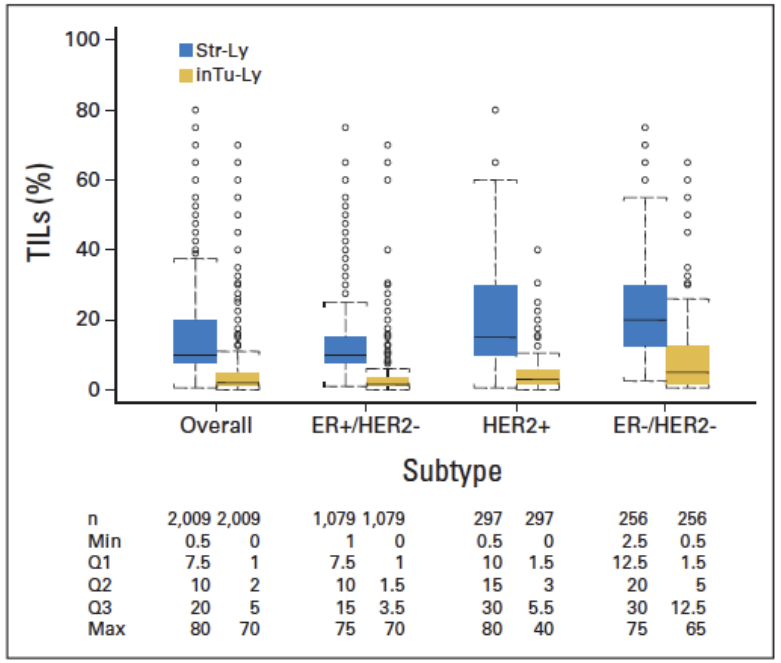
Why TNBC is a target for immunotherapy?

…but, compared to the other breast cancer subtypes, triple-negative BC is characterized by higher:

High mutation burden

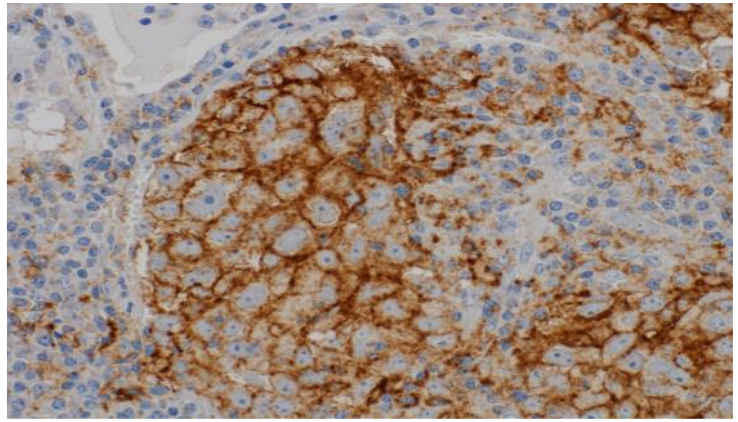


T-cell infiltration



n	2,009	2,009	1,079	1,079	297	297	256	256
Min	0.5	0	1	0	0.5	0	2.5	0.5
Q1	7.5	1	7.5	1	10	1.5	12.5	1.5
Q2	10	2	10	1.5	15	3	20	5
Q3	20	5	15	3.5	30	5.5	30	12.5
Max	80	70	75	70	80	40	75	65

PD-L1 expression



TCGA, Nature 2012
Luen, Breast 2016
Lehmann, J Clin Invest 2011
Cimino Matthews, Hum Pathol 2013
Loi, JCO 2013
Loi, Ann Oncol 2014
Chen and Mellman, Immunity 2013
Mittendorf, Cancer Immunol Res 2014

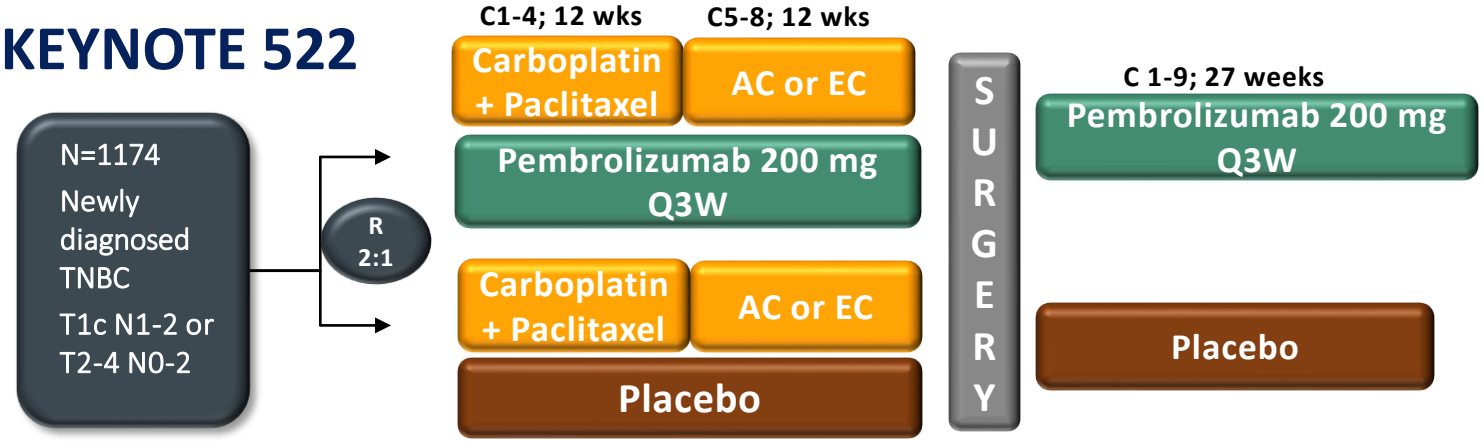
Immune checkpoint inhibitors in early TNBC

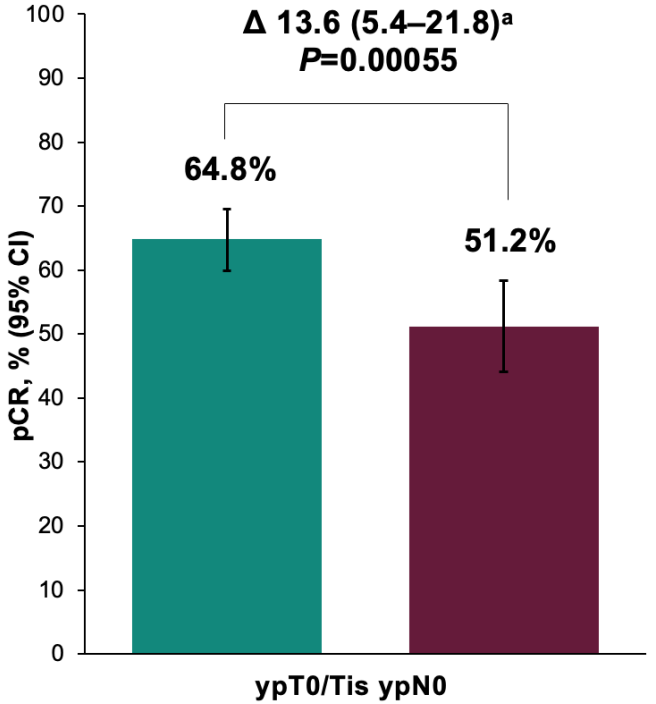
Variable	I-SPY	KEYNOTE-522	IMPASSION 031	NeoTRIP	GeparNUEVO
Total patients	69/180	**1174 (602)**	**333**	**280**	**174**
Type of CPi	PD1 **Pembro x 4**	**PD1** **Pembro x 1 year**	**PD-L1** **Atezo x 1 year**	**PD-L1** **Atezo x 8**	**PD-L1** **Durva x 8**
Stage	**Stage II/III**	**Stage II/III**	**Stage II/III**	**+ N3 disease**	**35% stage I**
Anthracycline pre-op	**yes**	**yes**	**yes**	**no***	**yes**
Included carboplatin	**no**	**yes**	**No (nab-pac)**	**Yes (nab-pac)** **2 wks on, 1 wk off x 8**	**no**
Improved pCR	**Yes**	**Yes** **51.2 v 64.8%** **P=0.00055**	**Yes** **41.1 v 57.6%** **P=0.0044**	**No** **(43.5 v 40.5%)**	**Numeric improvement** **(53 v 44%, p=0.18)**
Improved EFS	**NR:** **pCR>nonpCR**	**Yes**	**NR**	**NR**	**Yes** **EFS, DDFS and OS**

Nanda et al, JAMA Onc 2020; Schmid et al, NEJM 2020 and ESMO Plenary 2021; Mittendorf, Lancet 2020; Gianni et al, SABCS 2019; Loibl et al, Ann Oncol 2019 and ASCO 2021;
*Callari et al, PD10-09:, SABCS 2021

Key Phase III Neoadjuvant Immunotherapy Trials in TNBC

KEYNOTE 522

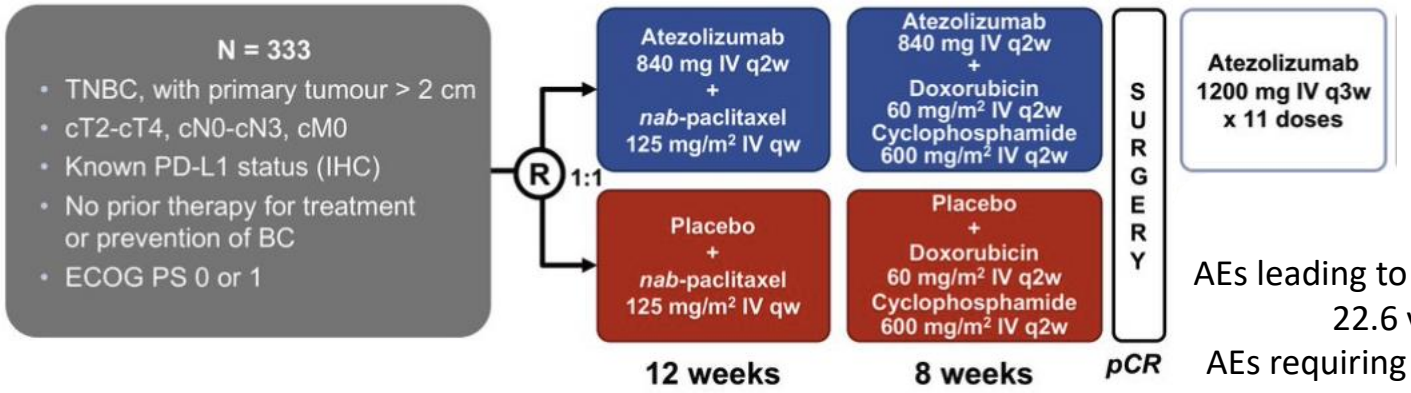




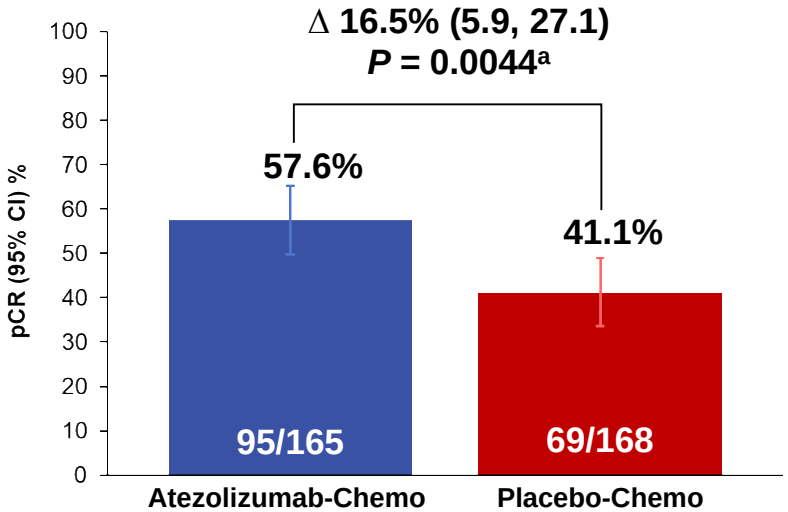
Patient population

- ~51% node positive
- 75% stage II/25% stage III
- ~56% premenopausal

IMpassion 031



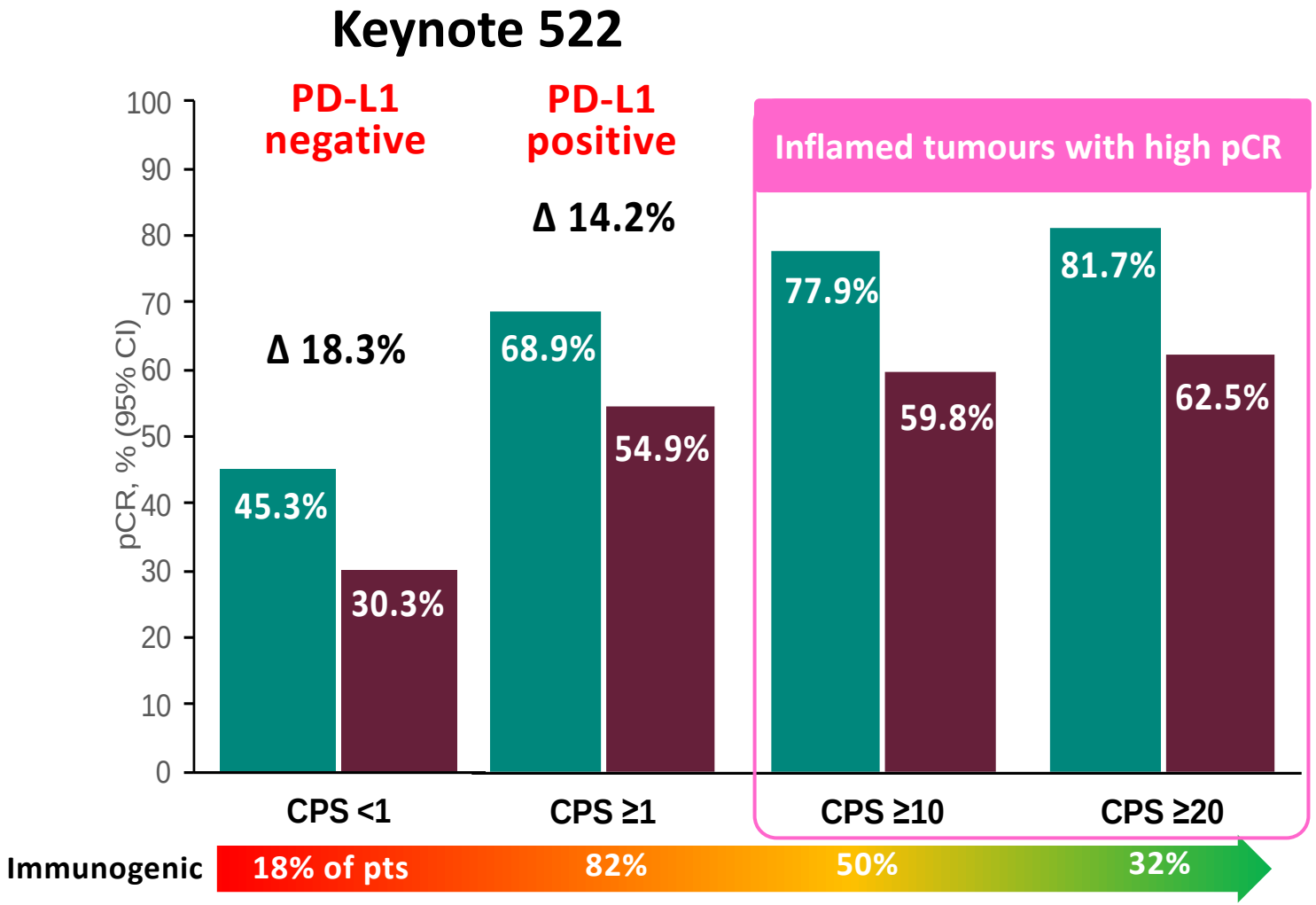
AEs leading to D/C of any drug:
22.6 v 19.8%
AEs requiring corticosteroids:
12.8 v 9.6%

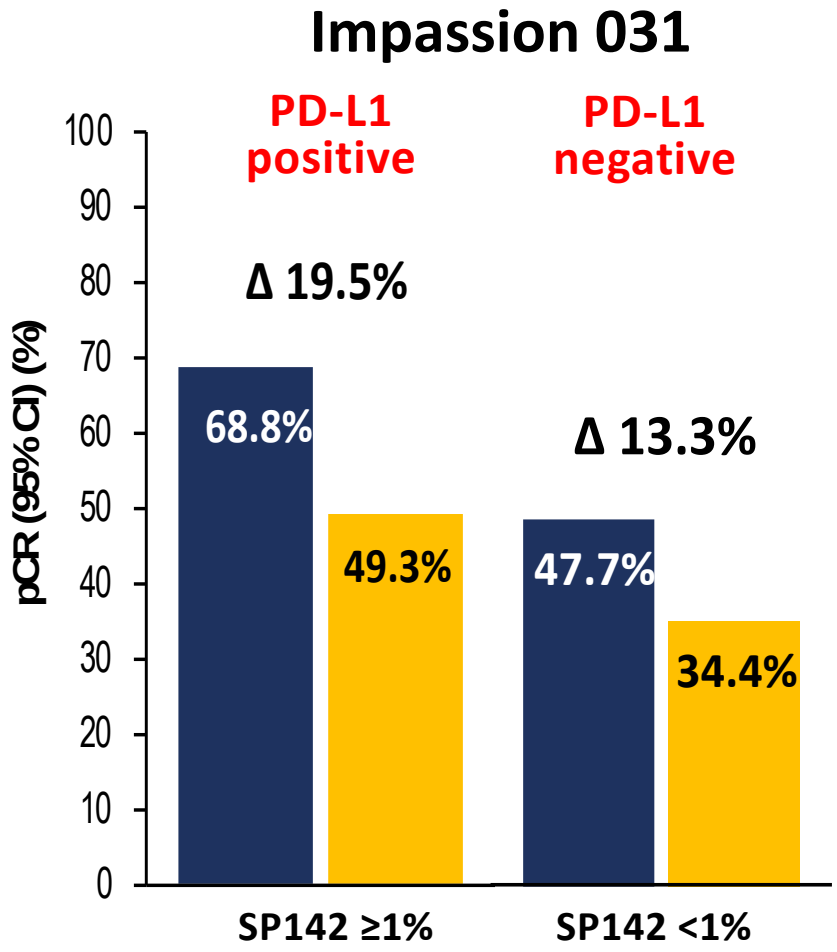


Schmidt et al, SABCS 2019, Mittendorf, Lancet 2020

Neoadjuvant ICI in TNBC: pCR rates by PD-L1 expression

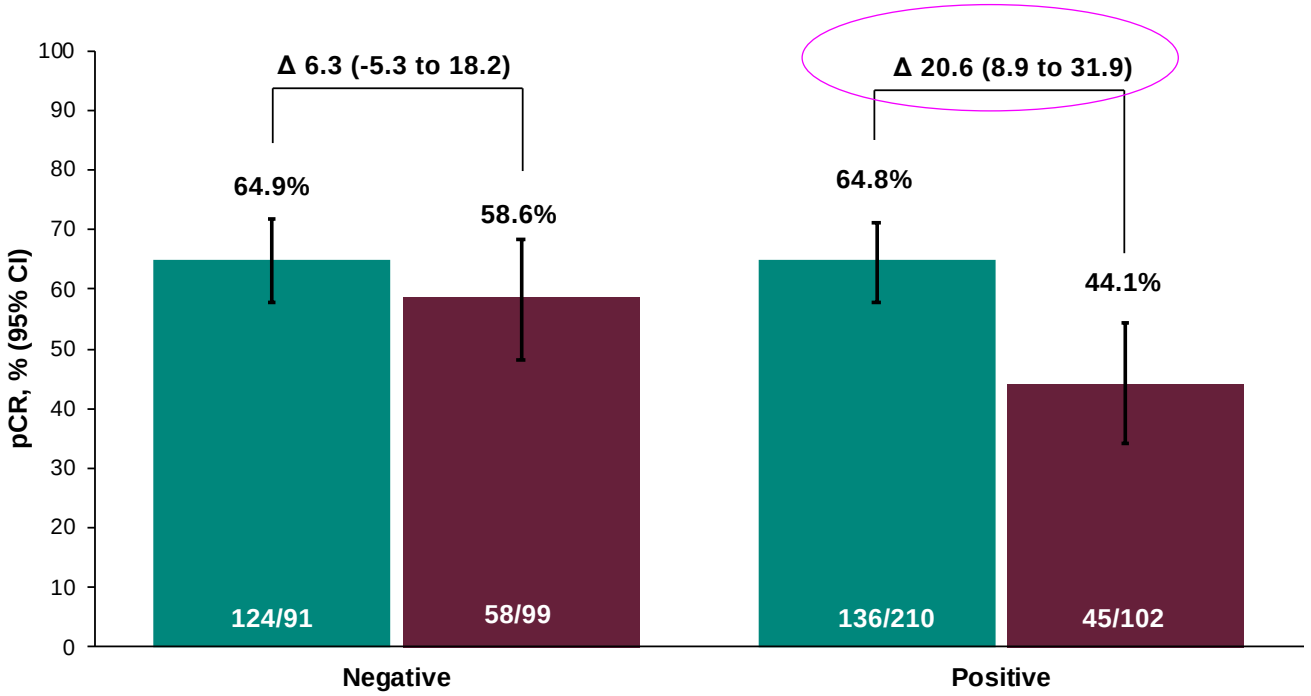
PDL1-positive and PDL1-negative patients benefit from CIT





Schmid P, et al. ESMO 2019, Schmid, et al NEJM 2020, Mittendorf et al, Lancet. 2020

pCR: Greater Benefit in Node Positive Disease Inflamed Tumors or Greater Tumor Burden?

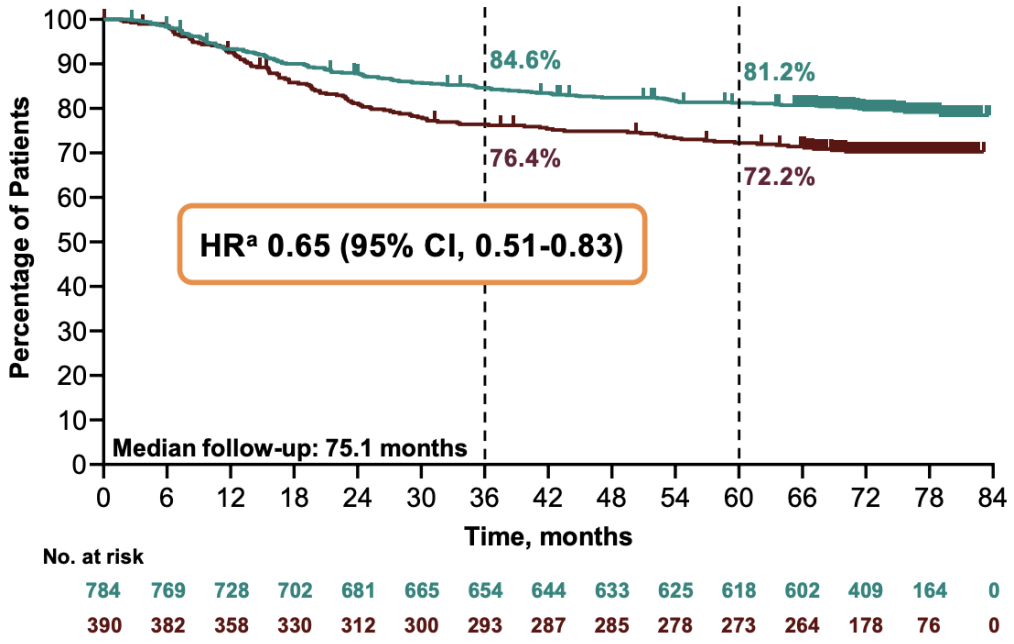


Subgroup	Atezolizumab-Chemo		Placebo-Chemo		Difference in pCR (95% CI)		
	pCR (%)	n/n	pCR (%)	n/n		Δ (%)	95% CI
Overall	57.6	95/165	41.1	69/168		16.5	5.9, 27.1
Regional lymph node							
LN-negative	57.8	63/109	49	47/96		8.8	−4.8, 22.5
LN-positive	57.1	32/56	30.6	22/72		26.6	9.8, 43.4

Schmidt et al, SABCS 2019, Mittendorf et al, Lancet 2020

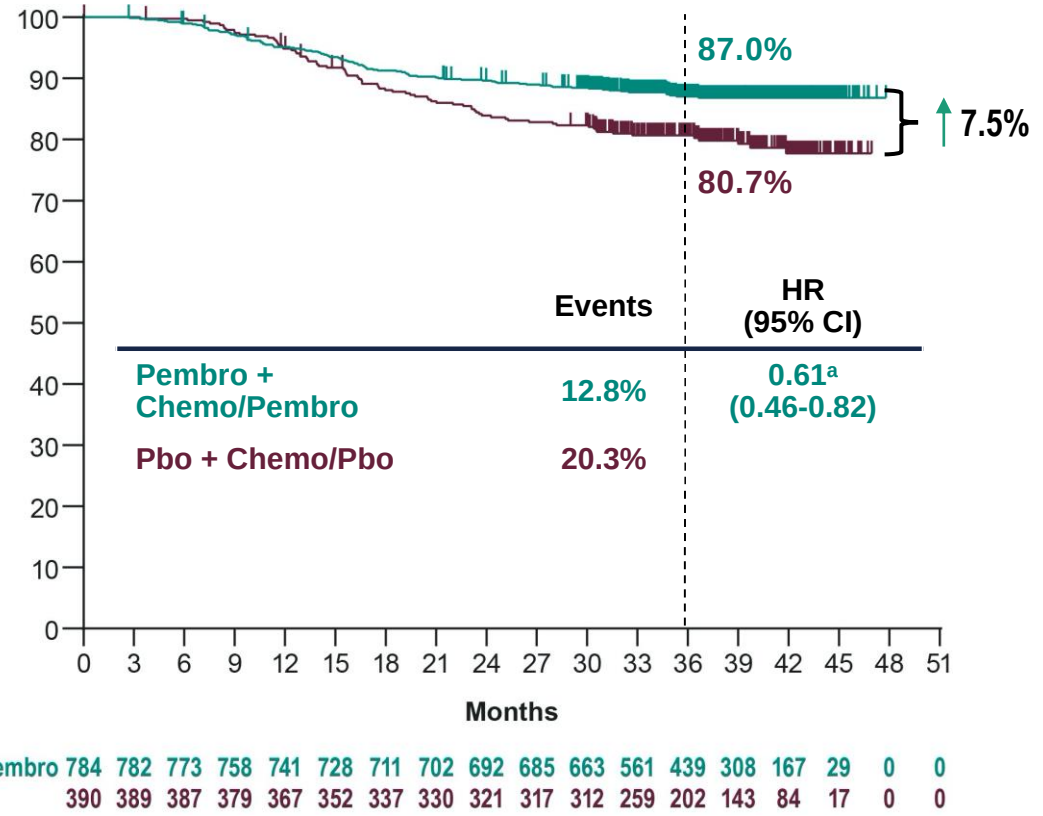
KEYNOTE 522 : EFS and DRFS

EFS



	Pts w/ Event
Pembro + Chemo/Pembro	20.3%
Placebo + Chemo/Placebo	29.2%

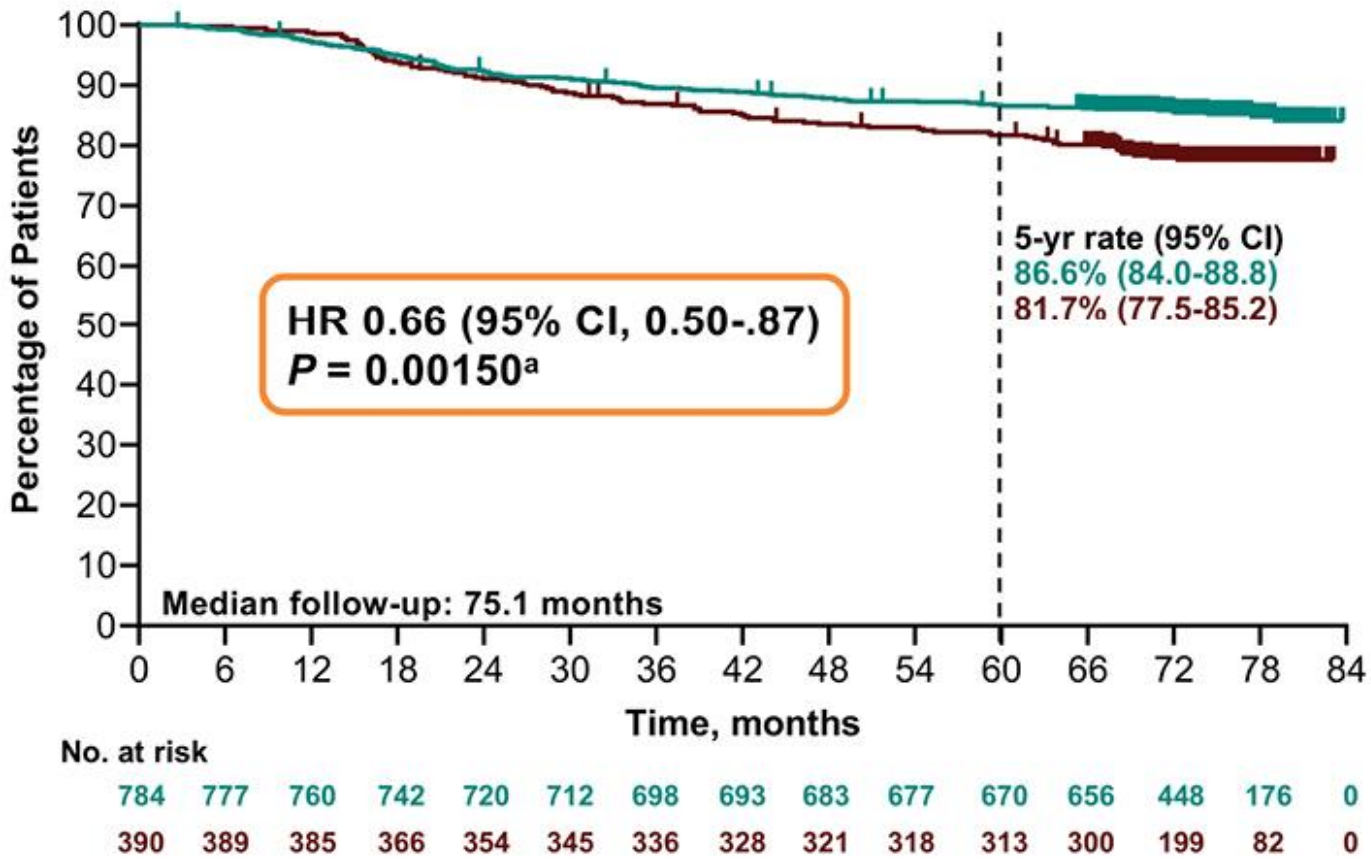
DRFS



Schmid, ESMO 24

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [c]Defined as the time from randomization to the data cutoff date of March 23, 2021.

KEYNOTE 522: Overall survival



	Pts w/ Event
Pembro + Chemo/Pembro	14.7%
Placebo + Chemo/Placebo	21.8%

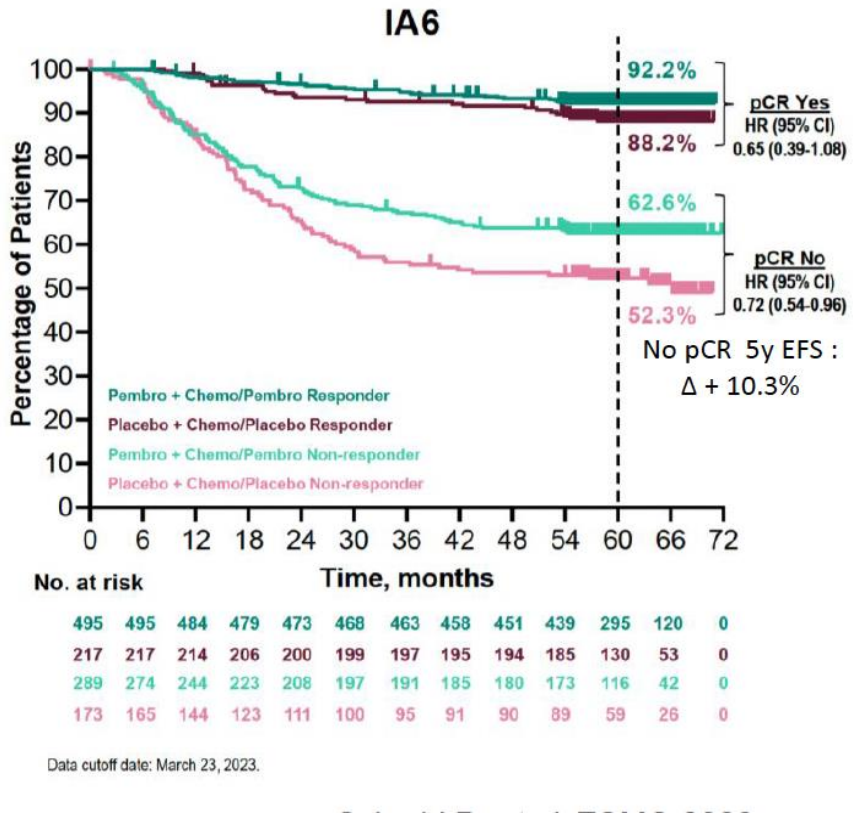
67.3% information fraction[a]

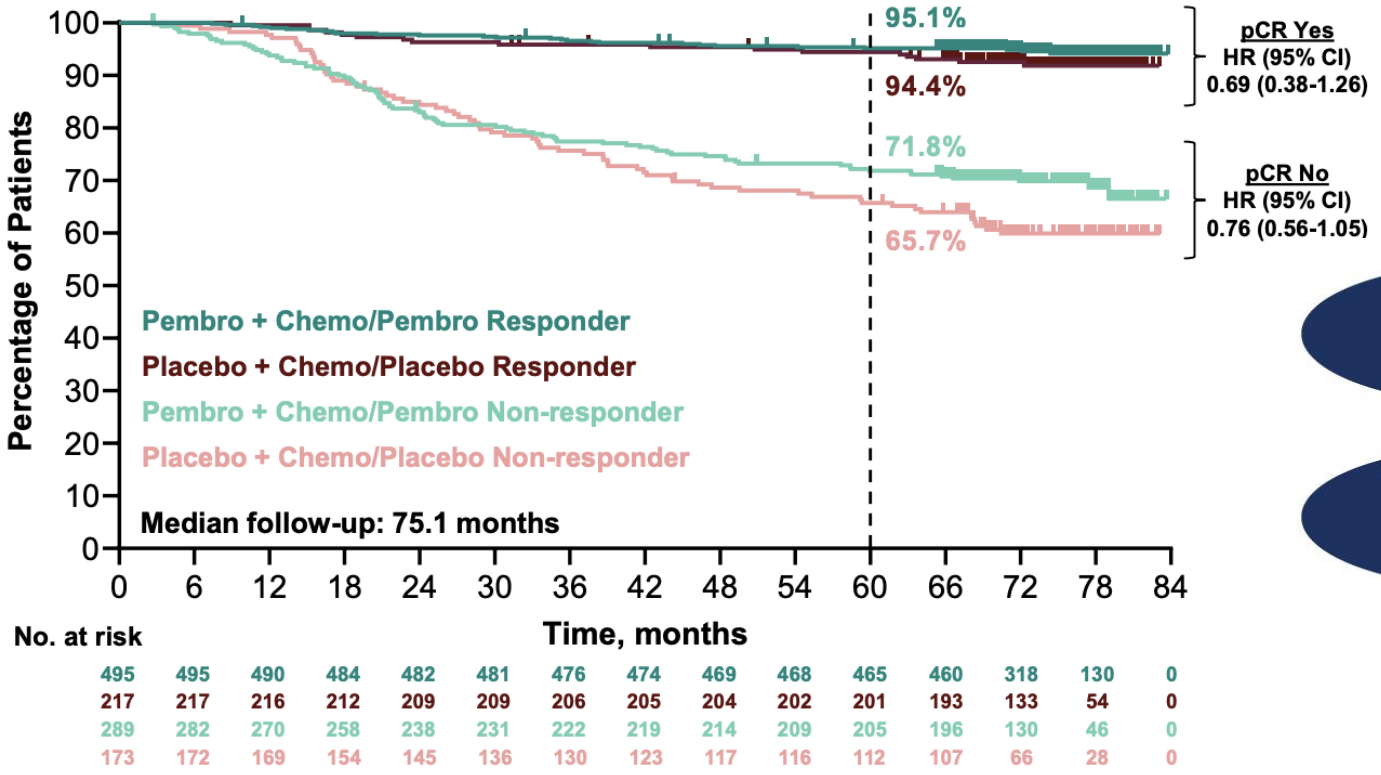
aWith 200 events (67.3% information fraction), the observed P-value crossed the prespecified nominal boundary of 0.00503 (1-sided) at this interim analysis. Overall, 86/115 (74.8%) deaths in the pembro group and 62/85 (72.9%) deaths in the placebo group were due to disease progression or recurrence. The unstratified piecewise HR was 0.87 before the 2-year follow-up and 0.51 afterwards. The weighted average HR with weights of number of events before and after 2-year follow-up was 0.66. Data cutoff date: March 22, 2024.

Schmid et al, ESMO plenary 2024

[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.

EFS by pCR (ypT0/Tis ypN0)





Patients with pCR have a good outcome

if no pCR, there is a higher benefit of adding pembrolizumab

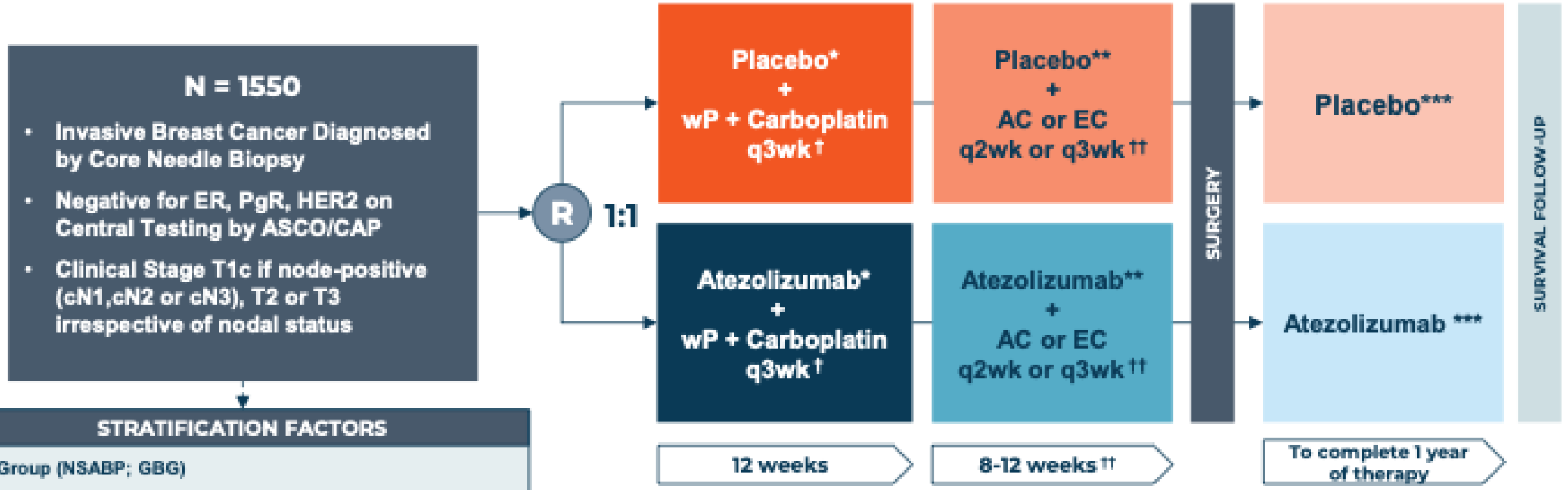
GS3-05 NSABP B-59/GBG-96-GeparDouze

A randomized double-blind phase III clinical trial of neoadjuvant chemotherapy with atezolizumab or placebo followed by adjuvant atezolizumab or placebo in patients with Stage II and III triple-negative breast cancer

Charles E. Geyer, Jr, MD
NSABP Foundation, Inc.
UPMC Hillman Cancer Center, Pittsburgh, PA, USA

Charles E. Geyer, Jr., Gong Tang, Valentina Nekljudova, Priya Rastogi, Mattea Reinisch, Joshua Acosta, Andreas Schneeweiss, Christie Hilton, Sabine Seiler, Carsten Denkert, Rohit Bhargava, Patricia Cortazar, Fernando Moreno, Jay Andersen, Stephani Christensen, Peter Klare, Sujatha Murali, Serafín Morales, Jens Huober, Jean-François Boileau, Christian Jackisch, Álvaro Rodríguez-Lescure, Dominique Boudreau, Dirk-Michael Zahm, Claus A. Hanusch, Peter J. Polewski, Kerstin Lüdtke-Heckenkamp, Saima Hassan, João Mouta, Eleftherios P. Mamounas, Norman Wolmark, and Sibylle Loibl

Study Design



STRATIFICATION FACTORS

- Group (NSABP; GBG)
- Clinical Size of Primary Tumor (1.1-3.0 cm; >3.0 cm)
- Clinical Nodal Status Documented by Imaging, FNA or Core Biopsy (negative; positive)
- PD-L1 status by VENTANA SP142 assay (positive ≥1% IC [proportion of tumor area occupied by PDL-1+ immune cells]; negative; indeterminate; not available#)
- AC/EC Schedule (q2wk; q3wk)

\# PD-L1 status was not available at randomization for 374 patients enrolled prior to amendments in July 2019.

* Atezolizumab (atezo) 1200 mg or placebo IV Day 1 every 3 wks for

† Paclitaxel 80 mg/m2 IV weekly x 12 doses (WP) + Carboplatin AU

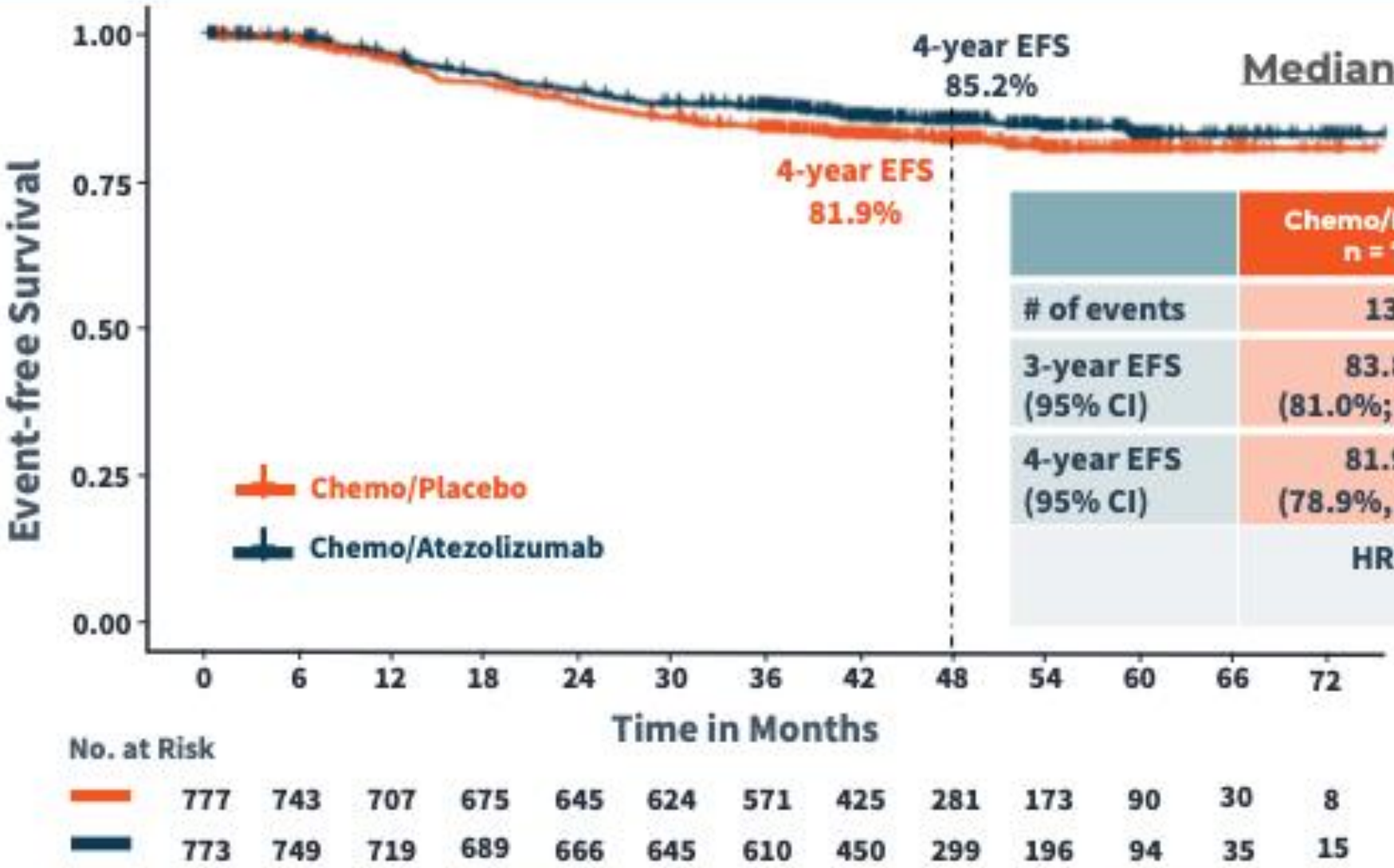
** Atezo 1200 mg or placebo IV Day 1 every 3 wks for 3 to 4 doses

†† Doxorubicin (A) 60 mg/m2 IV + cyclophosphamide (C) 600 mg/m2
OR Epirubicin (E) 90 mg/m2 IV + cyclophosphamide (C) 600 mg/m

*** Atezo 1200 mg or placebo IV Day 1 every 3 wks after surgery until 1 yr after the first dose. Adjuvant capecitabine was allowed for non-pCR as of February 2020 and olaparib as of December 2021.

Primary Endpoint:
EFS

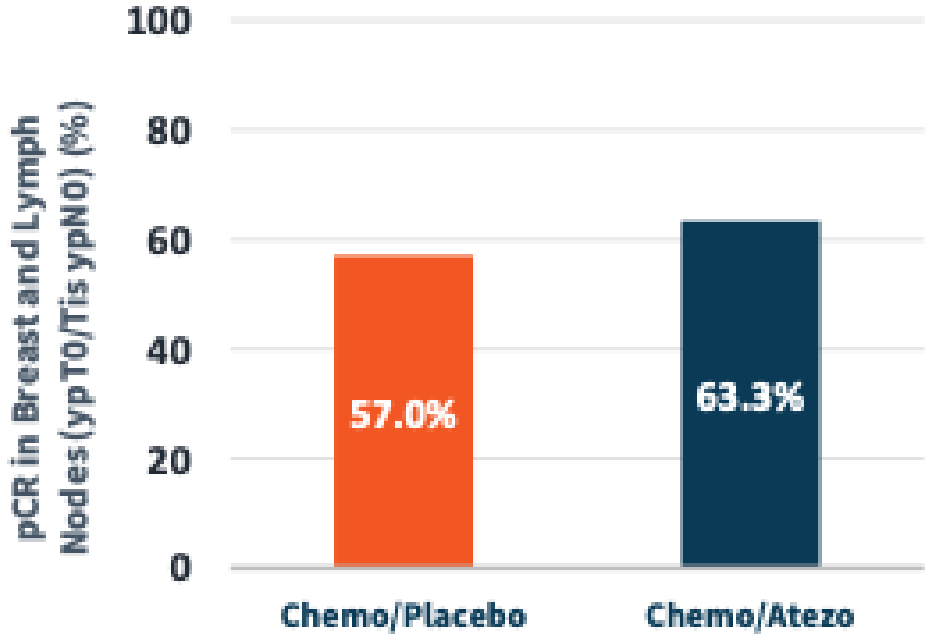
Event-free Survival



Median follow-up 46.9 months

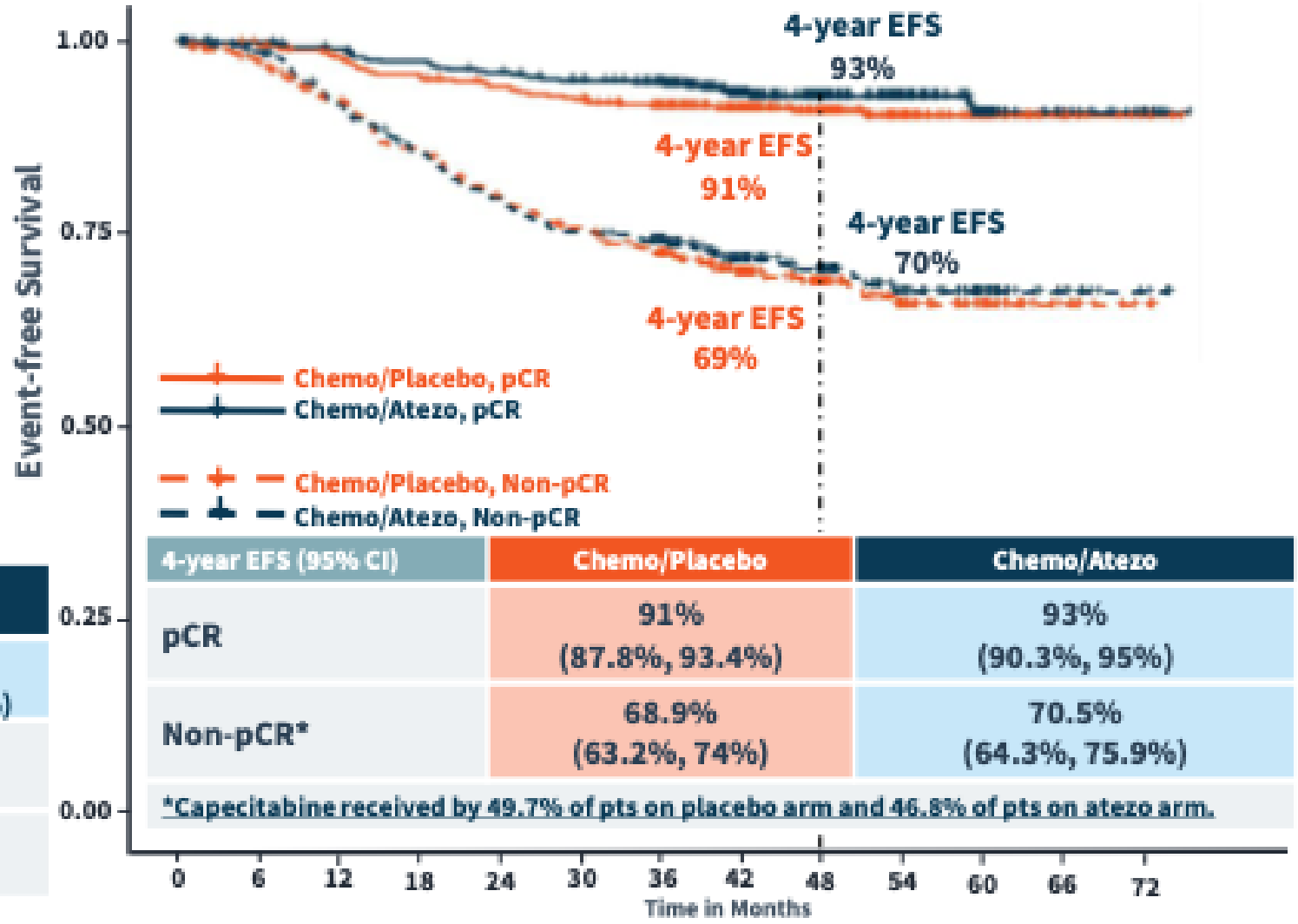
	Chemo/Placebo n = 777	Chemo/Atezolizumab n = 773
# of events	133	110
3-year EFS (95% CI)	83.8% (81.0%; 86.3%)	87.7% (85.1%; 89.9%)
4-year EFS (95% CI)	81.9% (78.9%, 84.6%)	85.2% (82.4%, 87.7%)
	HR = 0.8 (95% CI = 0.62, 1.03) Log rank p = 0.08	

pCR by Arm and EFS by pCR Status



	Chemo/Placebo n = 777	Chemo/Atezo n = 773
% pCR [a] (95% CI)	57.0% (53.5%, 60.5%)	63.3% (59.9%, 66.7%)
Difference in % pCR (95% CI)	6.3% (1.4%, 11.1%) ($p_{adj} = 0.0091$) [b]	

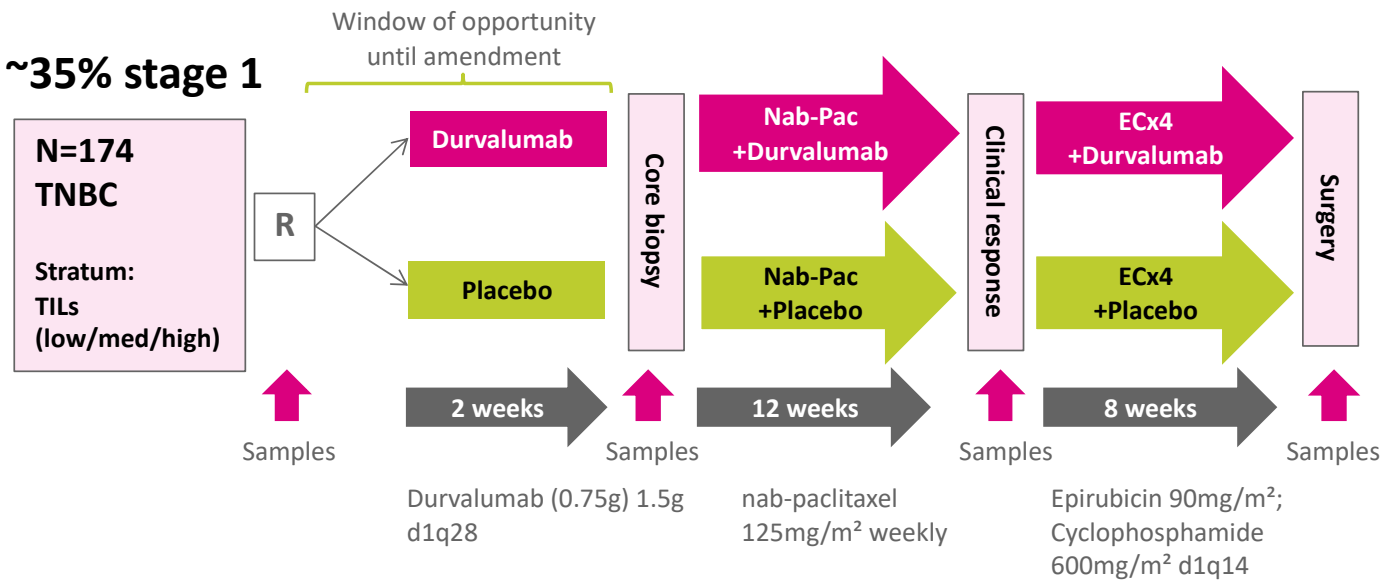
[a] Those with missing pCR status are considered as non-responders.
[b] 2-sided CMH test adjusted by stratification factors collapse of PD-L1 status.



4-year EFS (95% CI)	Chemo/Placebo	Chemo/Atezo
pCR	91% (87.8%, 93.4%)	93% (90.3%, 95%)
Non-pCR*	68.9% (63.2%, 74%)	70.5% (64.3%, 75.9%)

*Capecitabine received by 49.7% of pts on placebo arm and 46.8% of pts on atezo arm.

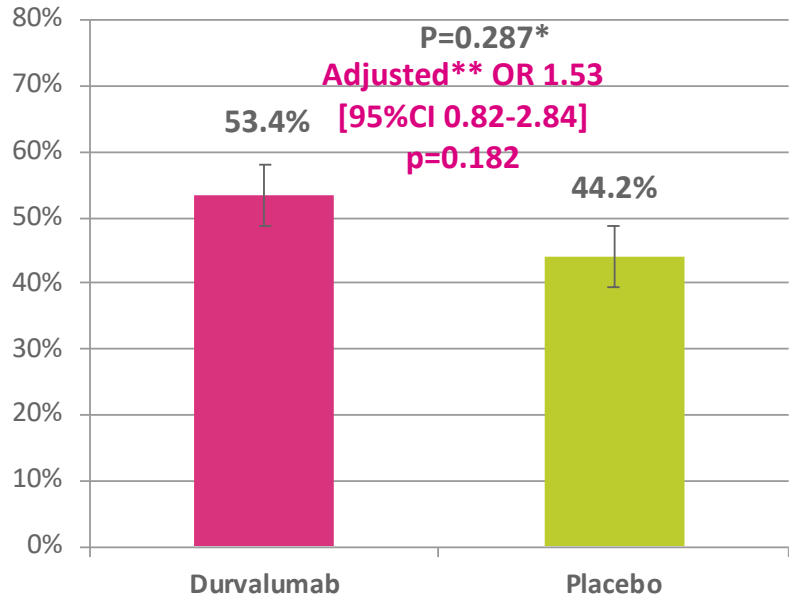
GeparNUEVO: Phase II Durvalumab Neoadjuvant Trial

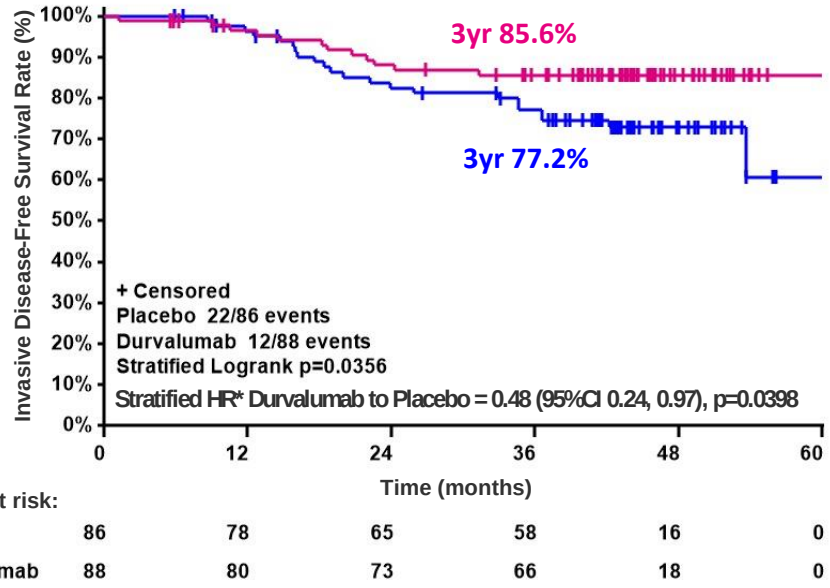


Primary endpoint: pCR (ypT0, ypN0)

Main secondary endpoints: iDFS, DDFS, OS

Primary endpoint: pCR – ypT0, ypN0





iDFS between arms

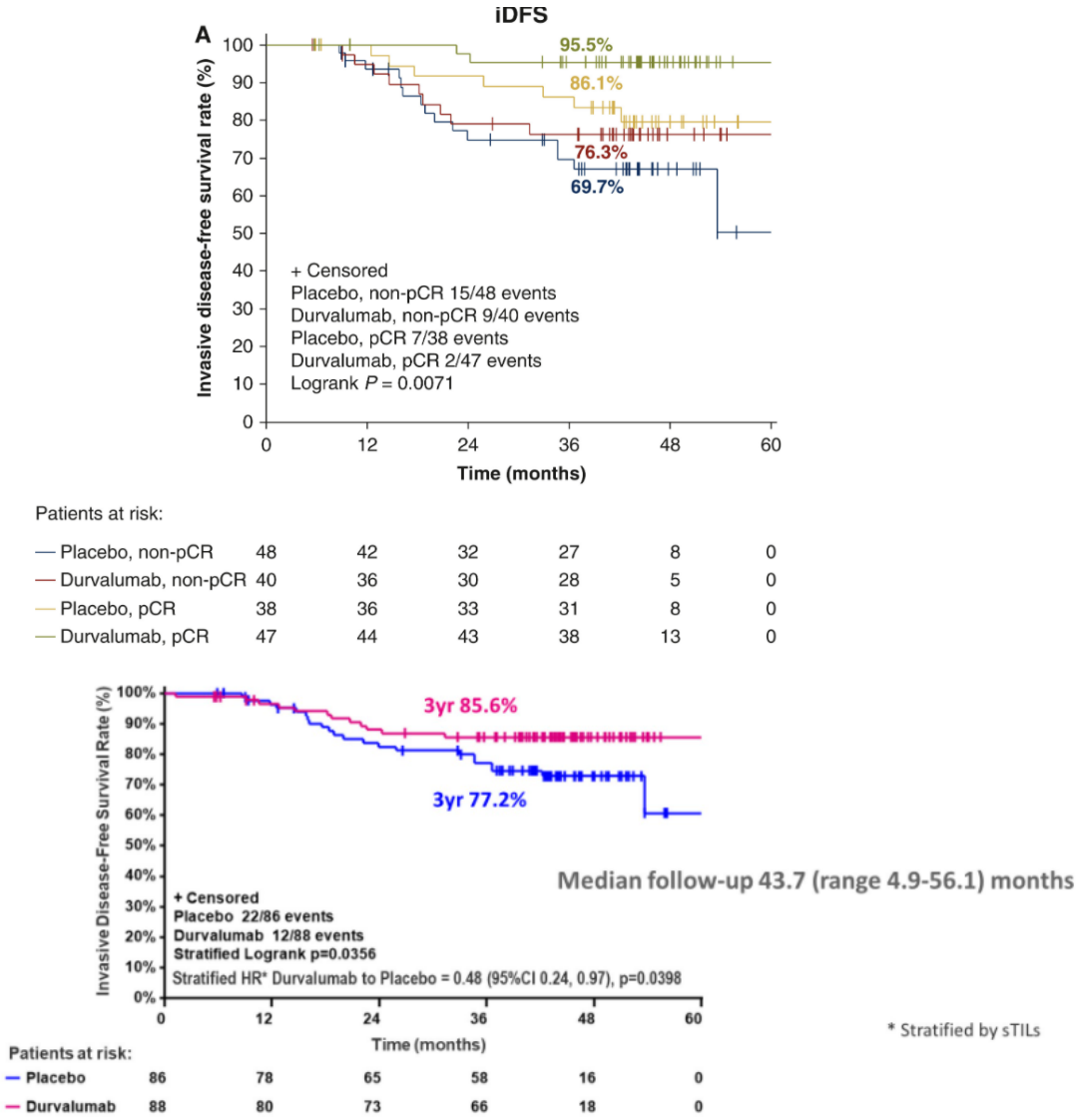
Median FU 43.7 months

* Stratified by sTILs

Loibl S, et al. Ann Oncol 2019; Loibl et al, ASCO 2021

Adjuvant phase → IO needed?

DFS benefit observed in Gepar Nuevo with durvalumab administered only in the neoadjuvant phase

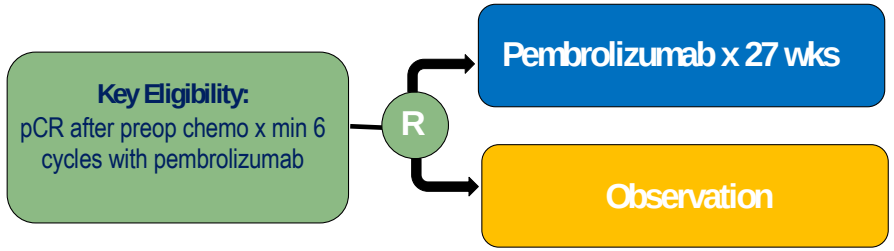


Gepar Nuevo not powered for survival outcomes

Additional trials required to clarify if adjuvant phase is needed and in whom

The HR for CIT vs no CIT is similar for pCR and no pCR patients

OptimICE-pCR



Stratification Factors:

- Baseline nodal status
- Receipt of anthracycline chemotherapy: yes vs. no

Loibl, J Clin Oncol 2021

Alexandra-IMpassion030:ADJUVANT CHEMO+ ATEZOLIZUMAB

Eligibility

- **Adequately excised primary invasive TNBC (stage II/III)** 50:50 node negative/positive–enriched population

Stratification

- Axillary nodal status (0 vs 1-3 vs ≥4 positive lymph nodes)
- Surgery (breast conserving vs mastectomy)
- PD-L1 IC0 vs IC1/2/3

N = 2,300

R 1:1

1 year

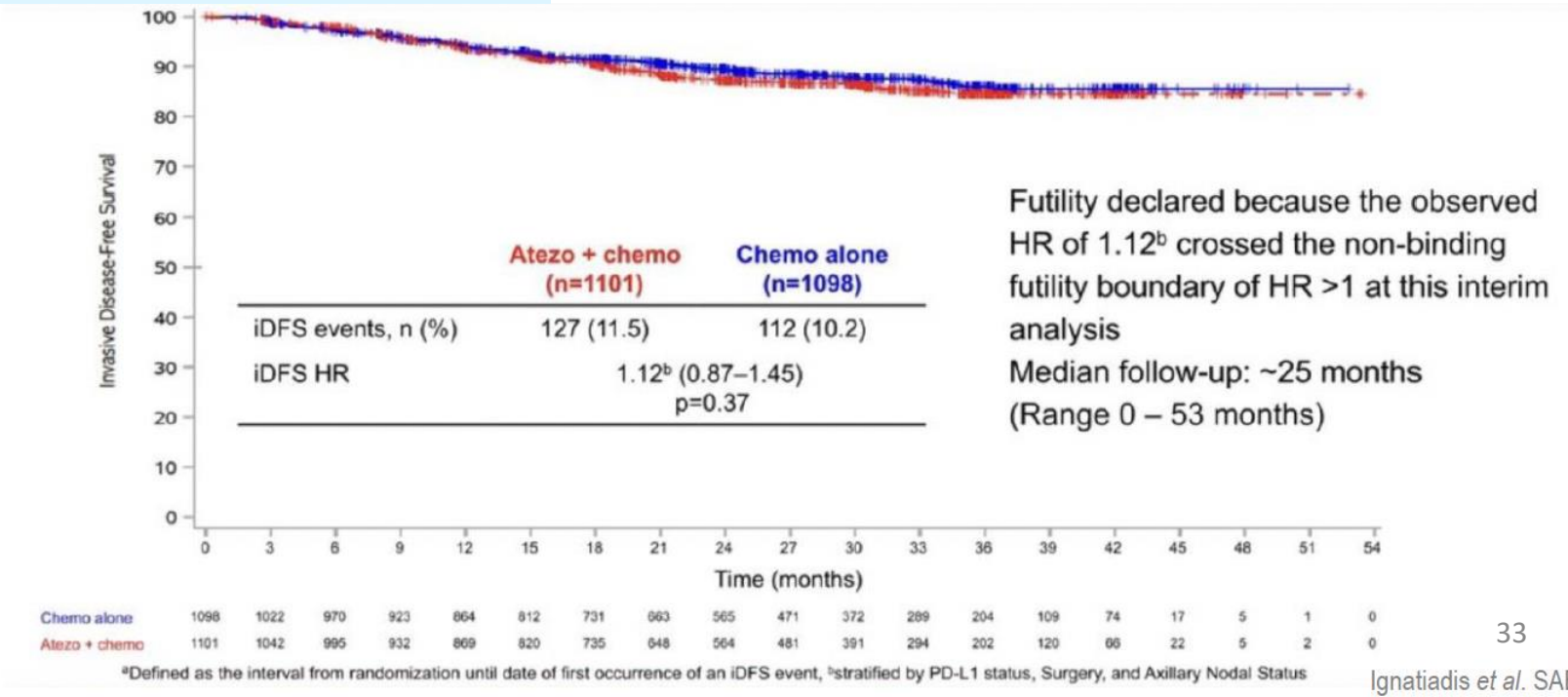
Paclitaxel weekly for 12 weeks → **Doxorubicin + cyclophosphamide** every 2 weeks for 4 cycles → Atezolizumab

Atezolizumab

Post-chemo XRT per SOC

Paclitaxel weekly for 12 weeks → **Doxorubicin + cyclophosphamide** every 2 weeks for 4 cycles

- **Primary endpoint:** iDFS in ITT
- **Secondary endpoints:** iDFS PD-L1 IC1/2/3, OS, RFI, distant RFI, safety, and health-related QoL



	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)

[a]Defined as the interval from randomization until date of first occurrence of an iDFS event, [b]stratified by PD-L1 status, Surgery, and Axillary Nodal Status

Ignatiadis *et al*. SABCS 2023

A-BRAVE trial: Avelumab in eTNBC with RD after NACT: No improvement in DFS

KEY ELIGIBILITY CRITERIA

- ECOG PS 0-1
- TNBC (ER & PR <10%, HER2 IHC 0-1+ or 2+/ISH–)[a]
- Anthracycline and taxane (neo)-adjuvant ChemoRx (no preop IO)
- Randomization <10 weeks from last chemo or surgery

RANDOMIZED

1:1

Avelumab
10 mg/kg, iv, q2w for 52 wks (n=238)

Control
Observation (n=239)

N=477

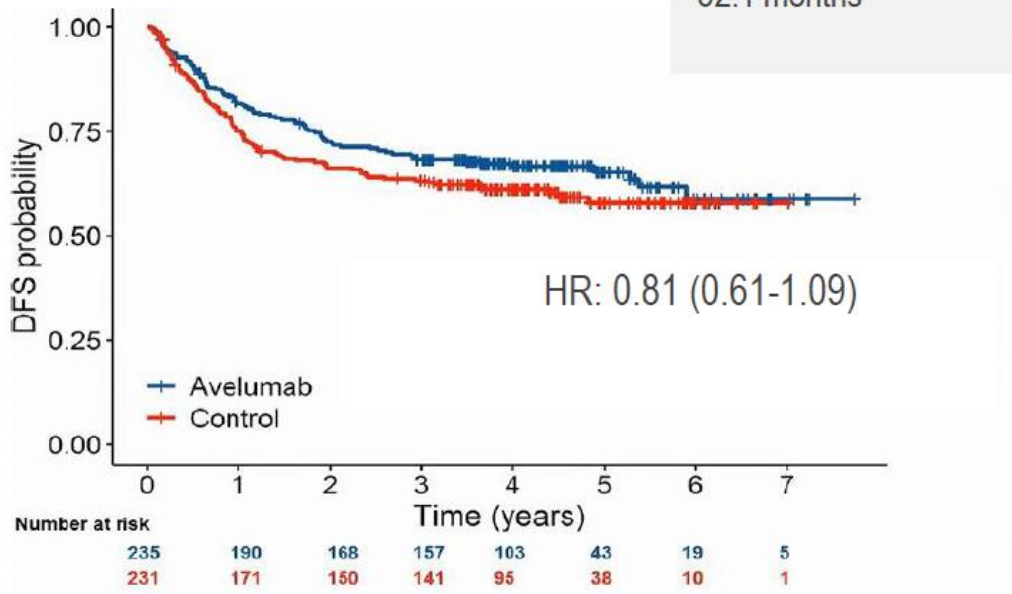
Stratum A (Adjuvant): pT2N1, pT3-4 N0-3, pN2-3 anyT (18%)

Stratum B (Post-neoadjuvant): residual invasive carcinoma in the breast and/or axillary lymph nodes (82%)

PRIMARY OBJECTIVES: DFS, DFS in Stratum B
SECONDARY OBJECTIVES: OS, safety

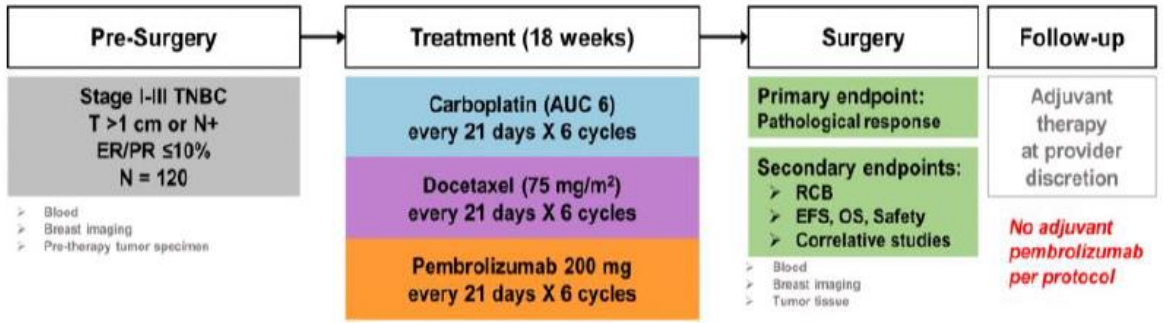
DFS in ITT

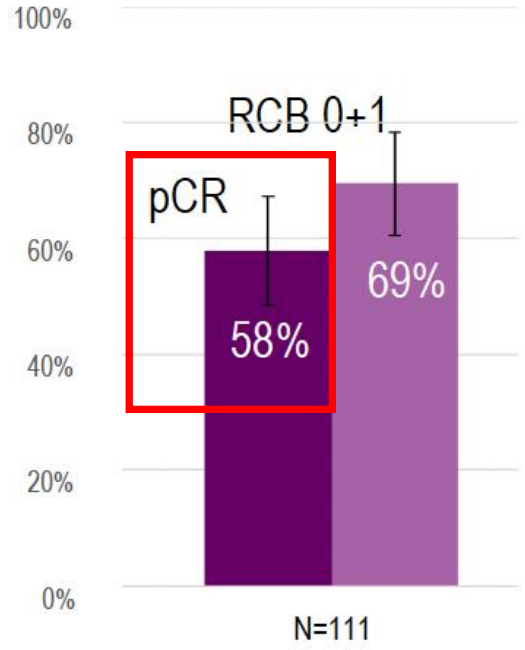
Median follow up:
52.1 months

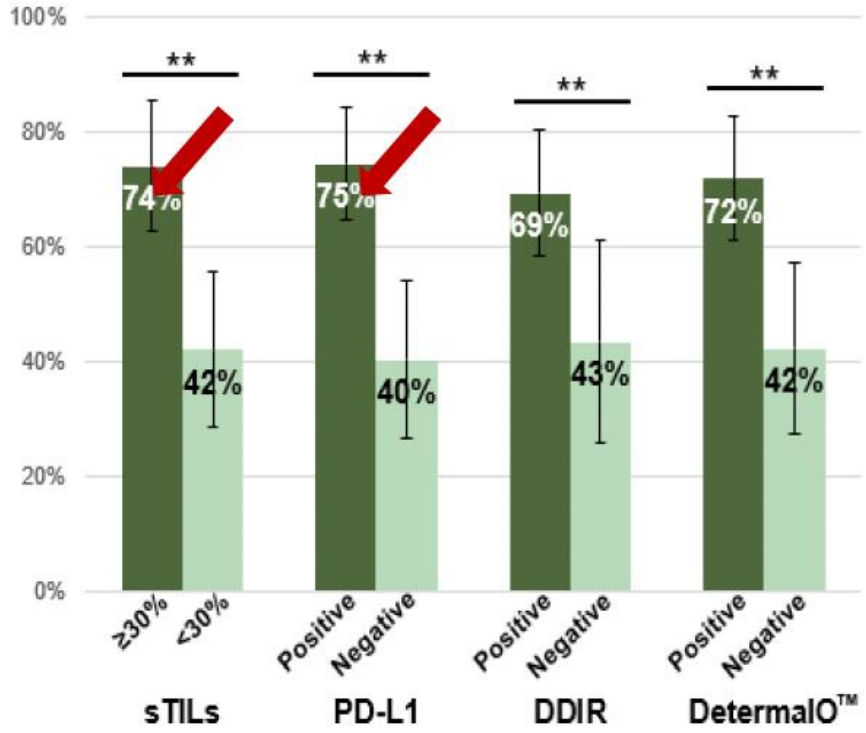


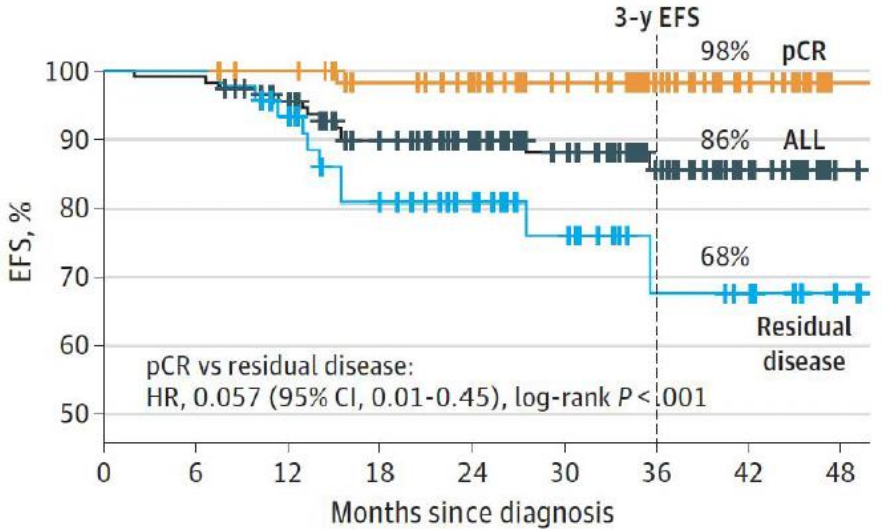
DFS		Avelumab	Control	Δ	HR (95%, CI)	P value
OS, ITT	Events, n	46	62			
	3-year OS (95%, CI), %	84.8 (79.5-88.8)	76.3 (70.1-81.3)	8.5%	0.66 (0.45-0.97)	0.035
DDFS, ITT	Events, n	66	85			
	3-year DDFS (95%, CI), %	75.4 (69.3-80.4)	67.9 (61.4-73.5)	7.5%	0.70 (0.50-0.96)	0.0277

NeoPACT: can we eliminate anthracycline?





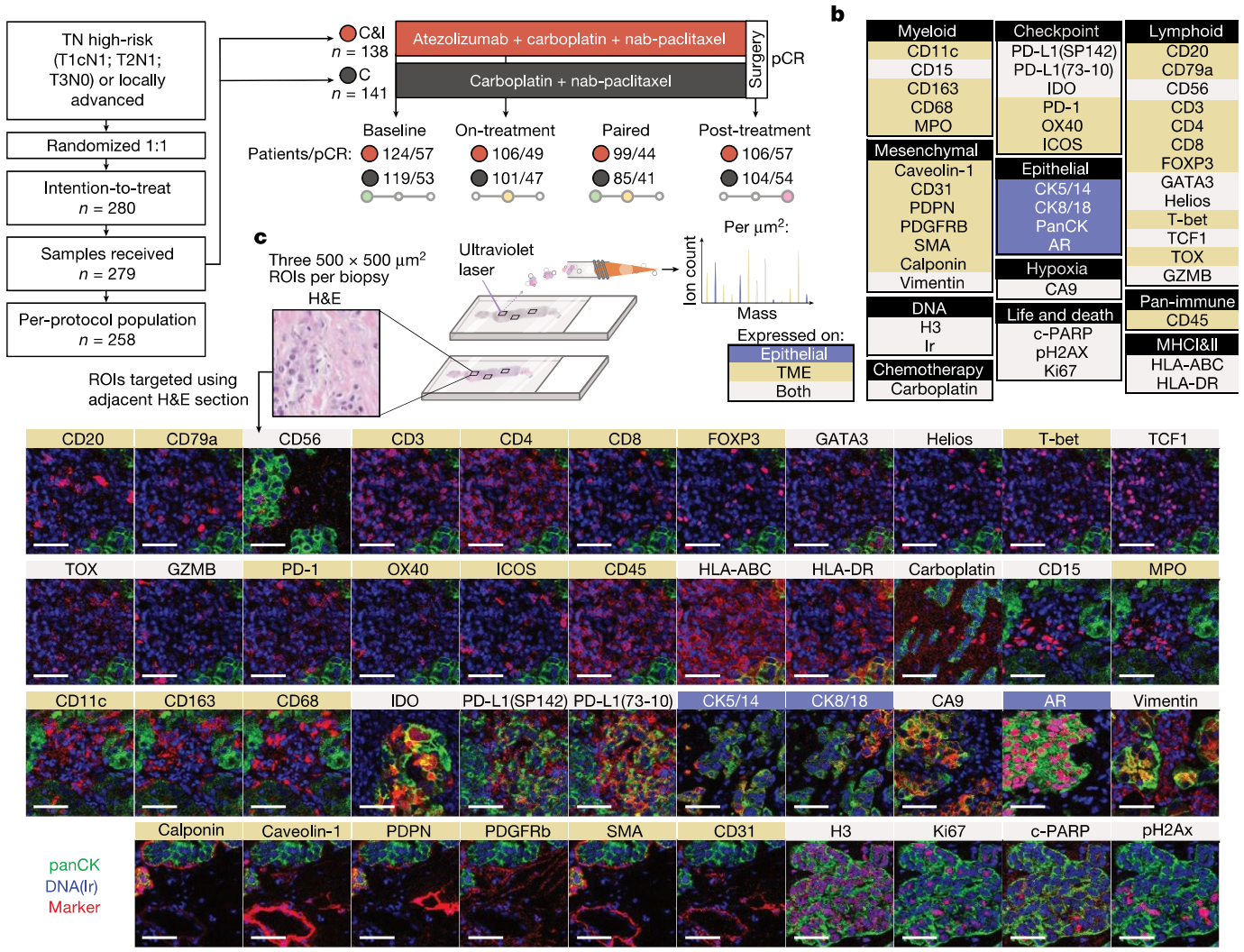




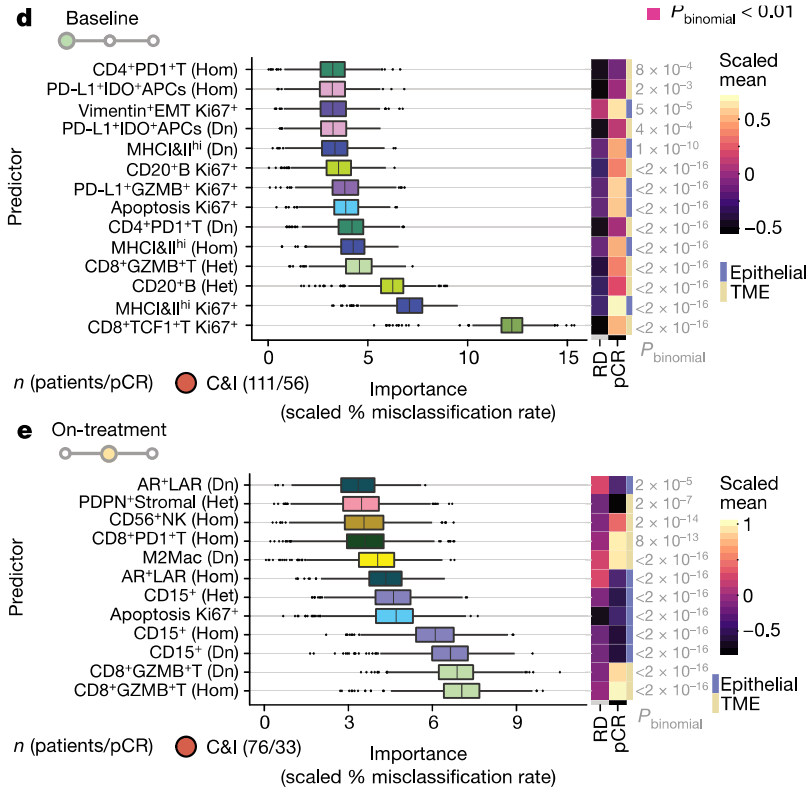
No. at risk									
ALL	115	114	103	87	71	53	32	17	1
pCR	64	64	62	55	46	37	24	11	0
Residual disease	47	47	40	31	25	16	8	6	1

- Immune enrichment assessed by sTILs, PD-L1 or DetermaIO™ signature was noted in almost 50% of patients and was associated with high pCR rates exceeding 70%.
- pCR delta: 30-35% in immune high vs immune low

Spatial predictors of immunotherapy response in TNBC and ctDNA



CD8+TCF1+T cells and **MHCII+ cancer cells** are dominant predictors of response to ICI



Wang et al, Nature 2023

OlympiA: Trial schema

- Local genetic testing or on-study central screening (Myriad Genetics Inc.)
- Germline pathogenic or likely pathogenic *BRCA1/2* mutation
- HER2–negative (ER and/or PgR positive or TNBC)
- Stage II-III Breast Cancer or lack of PathCR to NACT

Neoadjuvant Group
- *TNBC:* non-pCR
- *ER and/or PgR positive:* non-pCR and CPS+EG score ≥ 3

Neoadjuvant Chemotherapy (≥ 6 cycles) → **Surgery** → **+/- Radiotherapy**

Adjuvant Group
- *TNBC:* ≥ pT2 or ≥ pN1
- *ER and/or PgR positive:* ≥ 4 positive lymph nodes

Surgery → **Adjuvant Chemotherapy** (≥ 6 cycles) → **+/- Radiotherapy**

1:1 Randomization N=1836

Olaparib 300 mg twice daily for 1 year

Placebo twice daily for 1 year

Primary End Point
- Invasive disease-free survival (IDFS) by STEEP system[1]

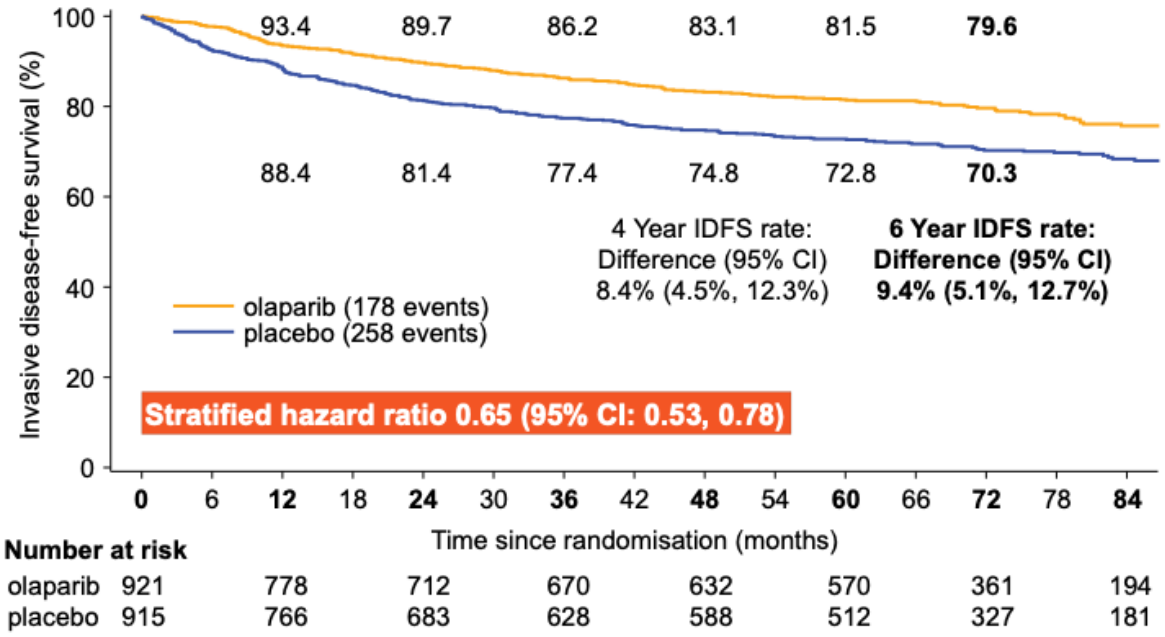
Secondary End Points
- Distant disease-free survival[1] (DDFS)
- Overall survival[1] (OS)
- BRCA1/2 associated cancers
- Symptom / Health related QoL
- Safety

Stratification Factors
- ER and/or PgR positive vs. TNBC
- Neoadjuvant vs. adjuvant
- Prior platinum-based chemotherapy (yes vs. no)

Concurrent Adjuvant Therapy
- Endocrine therapy
- Bisphosphonates
- No 2nd Adjuvant Chemotherapy

ER and/or PgR positive defined as IHC staining ≥1%.
Triple Negative defined as ER and PgR negative (IHC staining < 1%)
[1]Hudis CA, *J Clin Oncol* 2007

Analysis of IDFS (ITT)

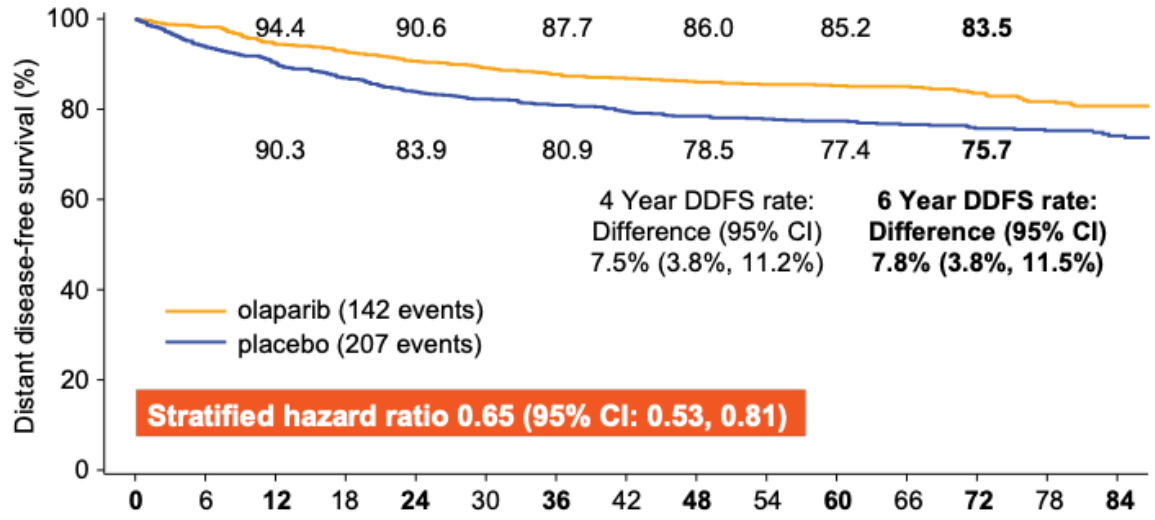


Number at risk

olaparib	921	778	712	670	632	570	361	194
placebo	915	766	683	628	588	512	327	181

Judy

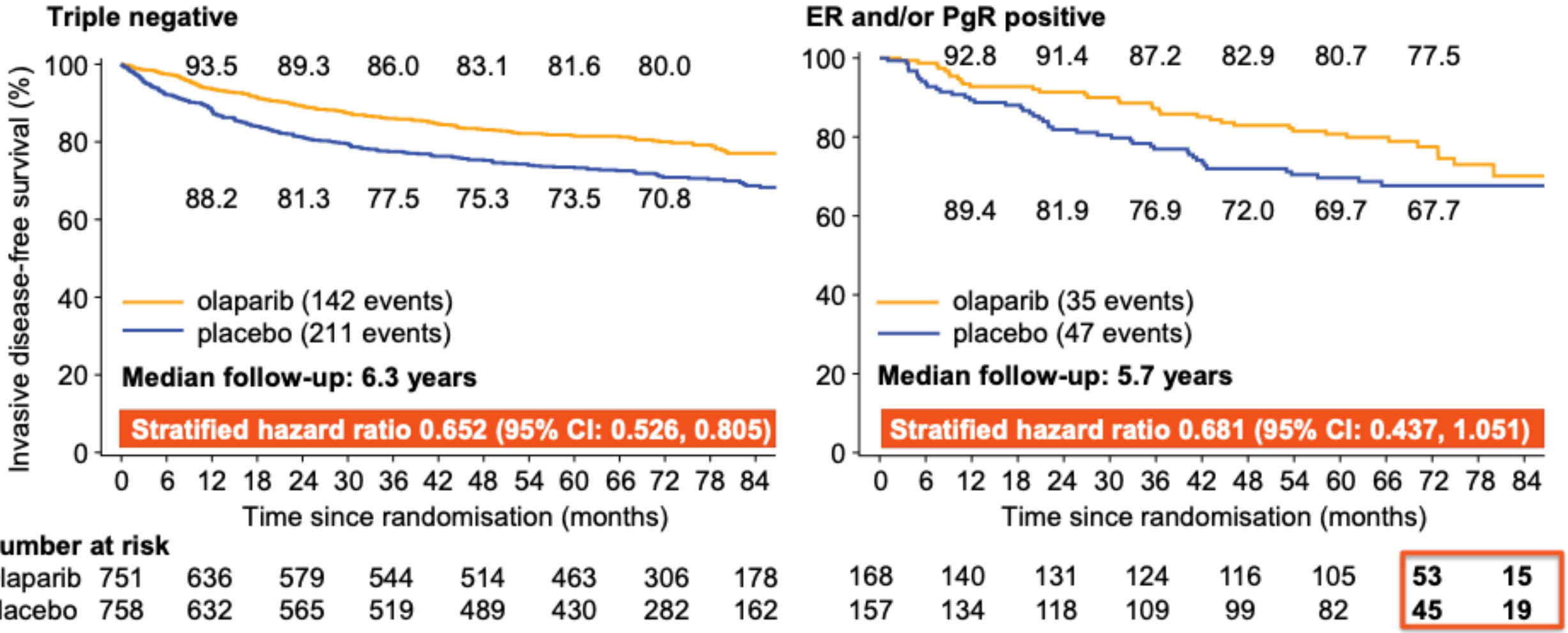
Analysis of DDFS (ITT)



Number at risk

olaparib	921	785	718	679	649	588	373	200
placebo	915	778	698	649	604	534	340	189

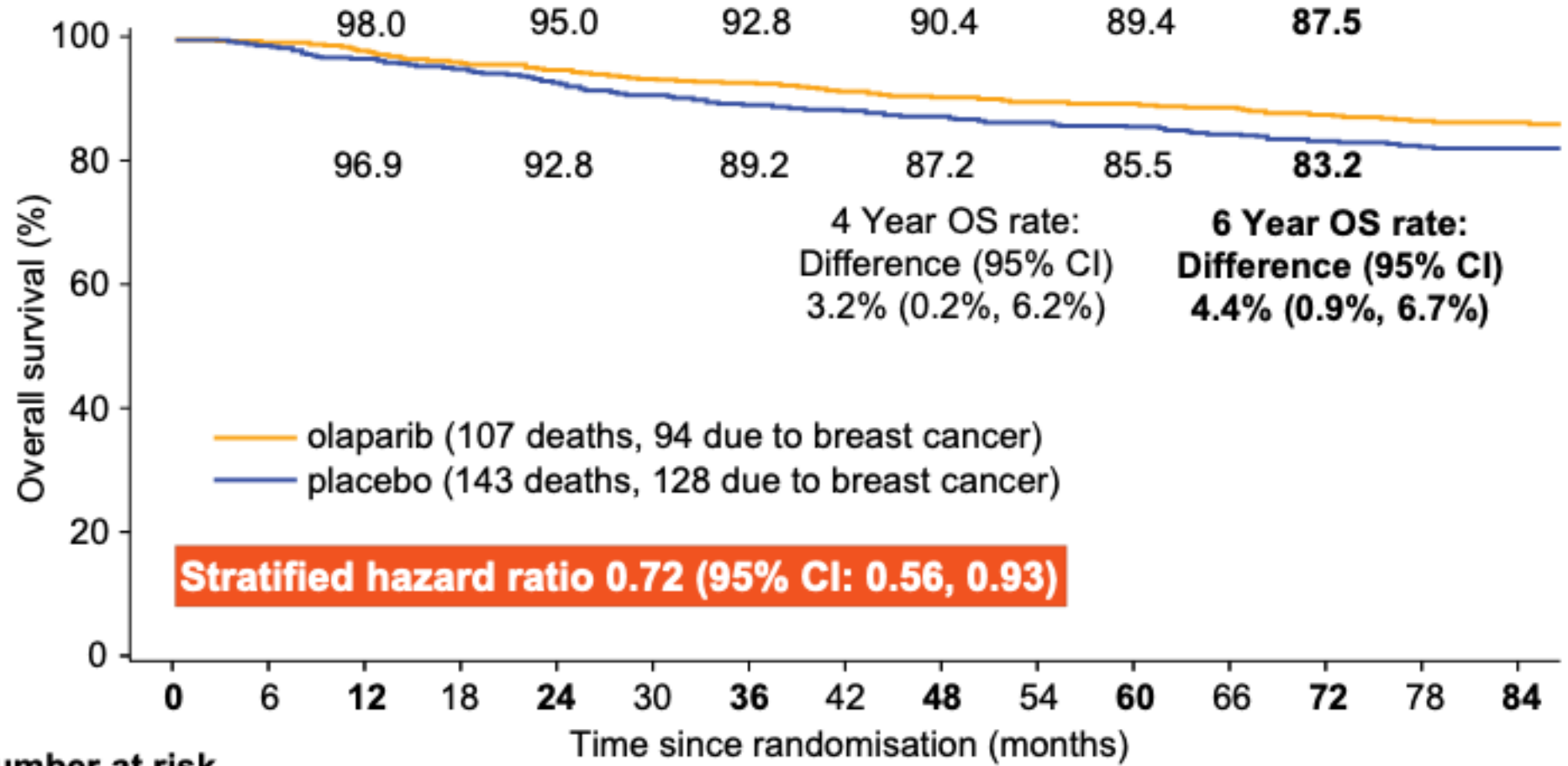
Analysis of IDFS by HR status



Number at risk

Olaparib	751	636	579	544	514	463	306	178	168	140	131	124	116	105	**53**	**15**
Placebo	758	632	565	519	489	430	282	162	157	134	118	109	99	82	**45**	**19**

Analysis of OS (ITT)



Number at risk

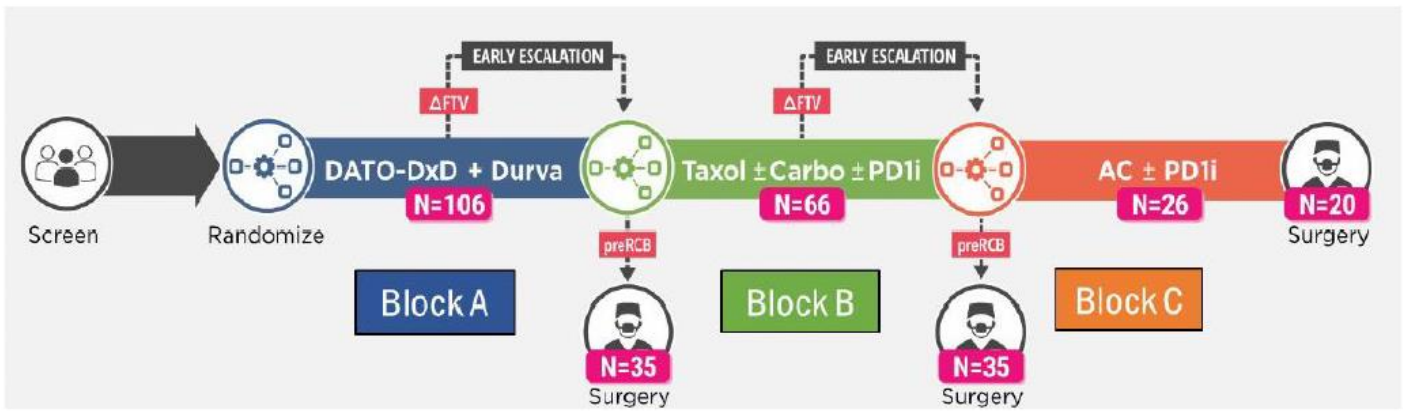
olaparib	921	846	795	765	728	660	420	224
placebo	915	843	788	739	698	616	390	221

RATES OF pCR AFTER NEOADJUVANT DATO-DXD + DURVALUMAB FROM THE I-SPY2.2 TRIAL: STUDY DESIGN AND PATIENTS

KEY ELIGIBILITY CRITERIA
- Stage II/III BC
- HER2–
- Mammaprint high-risk

PRIMARY ENDPOINT: pCR

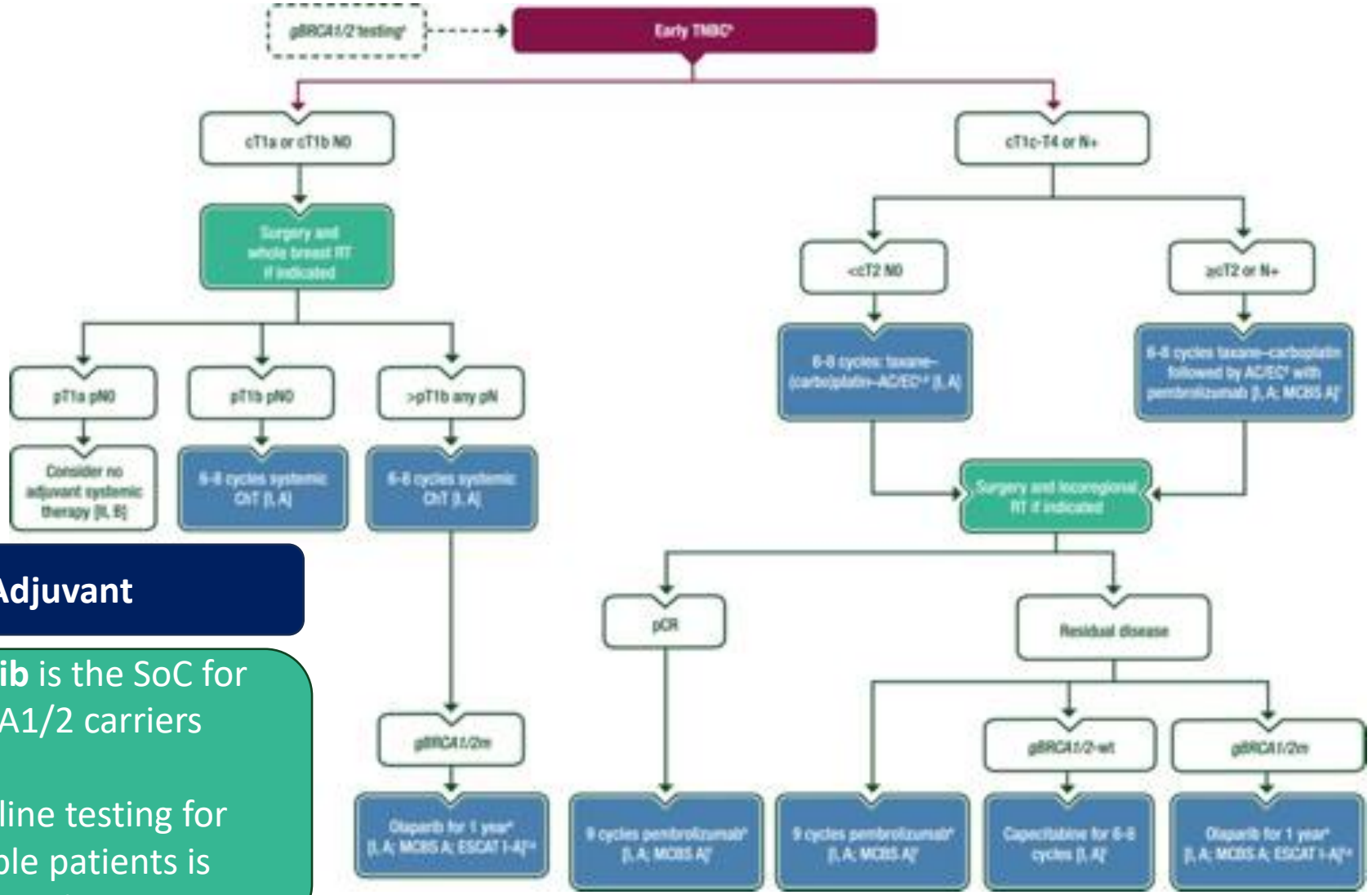
Block A	Block B	Block C	Surgery
4 cycles()Dato-DXd (6 mg/kg Q3W) + Durvalumab (1120 mg Q3W)	• Optimal regimens based on RPS and SOC • Investigational agents to improve response	• Adriamycin/ Cytoxan • Adriamycin/ Cytoxan + IO per SOC	• pCR and RCB endpoints



pCR for Dato-DXd+ Durvalumab

RPS	n	pCR, n	Non-pCR,[a] n	Modeled Rate (95% CI)
HR+/Immune–/DRD–	25	0	23	3% (0-7%)
HR–/Immune–/DRD–	23	2	14	13% (3-23%)
Immune+	47	20	11	65% (47-83%)
Immune–/DRD+	11	3	6	24% (4-44%)
Receptor Subtypes	**n**	**pCR, n**	**Non-pCR,[a] n**	**Modeled Rate (95% CI)**
HR+/HER2–	42	4	29	18% (6-30%)
HR–/HER2–	64	21	25	44% (32-56%)

Triple-negative Early Breast Cancer



Adjuvant

Olaparib is the SoC for BRCA1/2 carriers

Germline testing for eligible patients is mandatory

Loibl, Ann Oncol 2024 (ESMO Guidelines)

Neoadjuvant

Pembrolizumab + CT is the SoC for patients with cT1c-T4 or N4

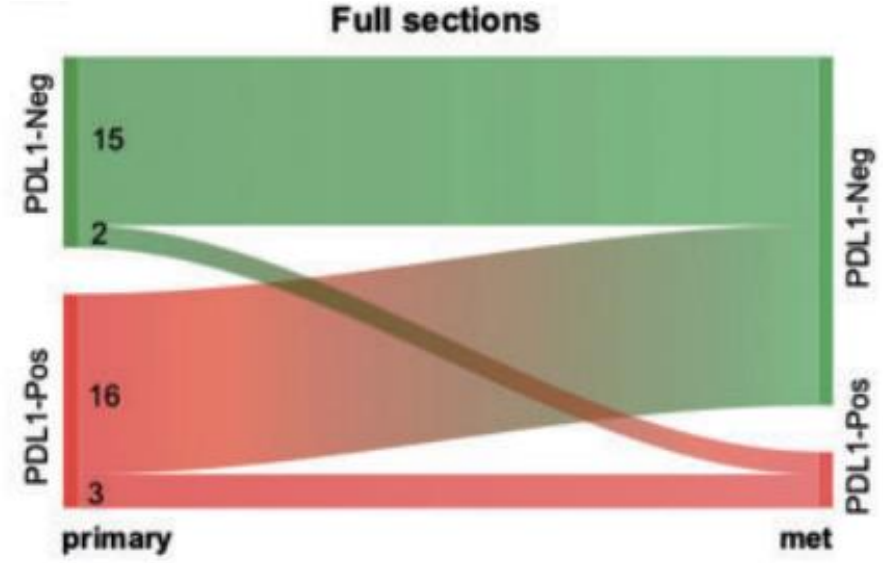
- Questions remains on the use of pembrolizumab in patients with pCR (trials ongoing)
- In patients with residual disease, trials are testing escalation strategies with ADC +/- IO

OUTLINE

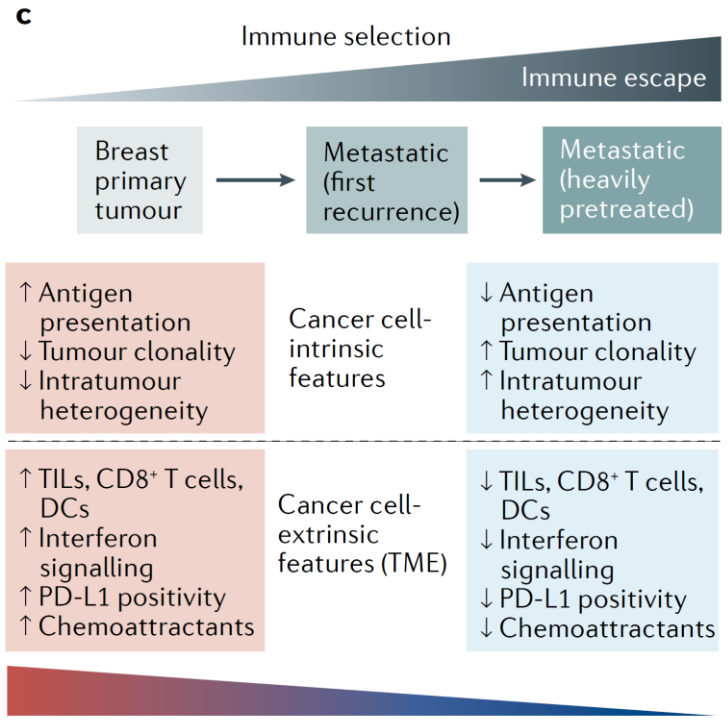
- **Triple-negative breast cancer**
  - Early setting
    - Immunotherapy
    - Adjuvant immunotherapy
    - Anthracycline
  - Advanced/metastatic setting
    - Immunotherapy
    - ADC
    - PARPi

TNBC: heterogeneity

Immune activation decreases in metastatic disease compared to early disease

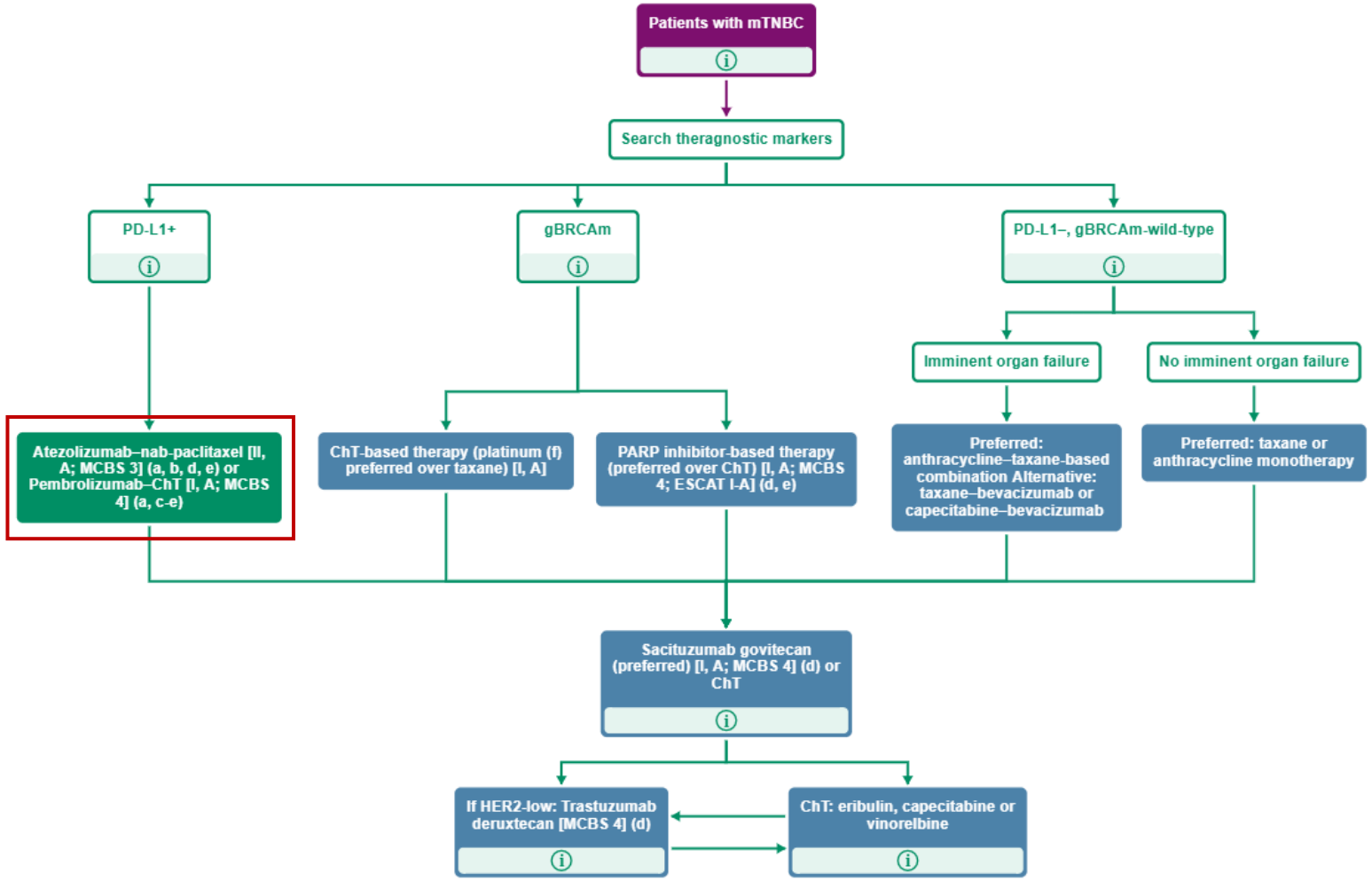


Szekely, Ann Oncol 2019



Bianchini G Nat Rev Clin Oncol 2022

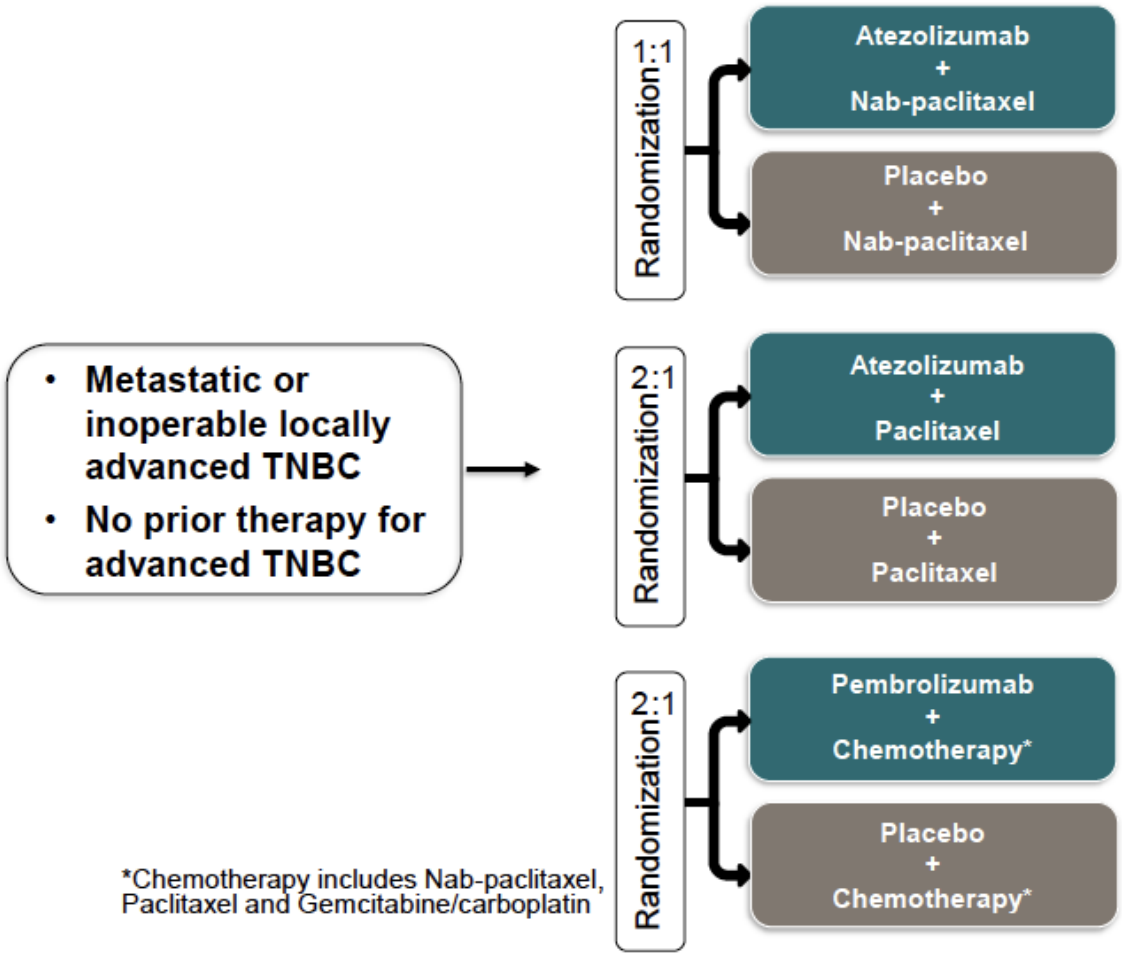
Immunotherapy in metastatic triple-negative breast cancer



Curigliano, ESMO Living Guidelines 2023

Immunotherapy in metastatic triple-negative breast cancer

Phase 3 trials assessing immune-checkpoint inhibitors in first-line setting **(TFI>6 months)**



IMpassion 130[1]
N=902
TFI ≥12 months
VENTANA SP142 assay

Co-Primary endpoints:
PFS & OS
(ITT → Others)

Positive

IMpassion 131[2]
N=943

Primary endpoint:
PFS
(PDL1+ 1% → Others)

Negative

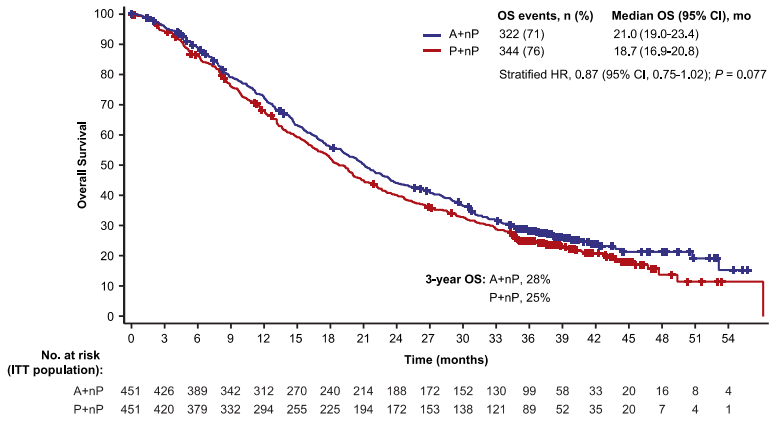
Keynote 355[3]
N=847
TFI ≥6 months
Dako 223C assay

Co-Primary endpoints:
PFS & OS
(PDL1+ CPS≥10 → Others)

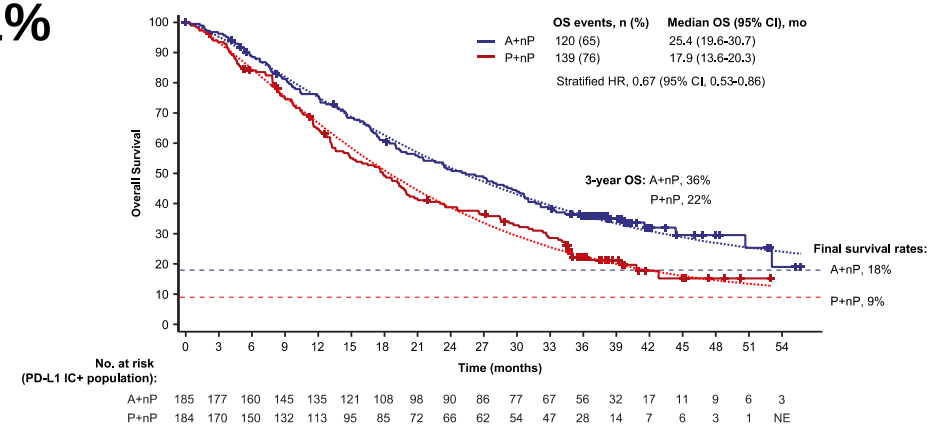
Positive

IMpassion130: Final overall survival

ITT

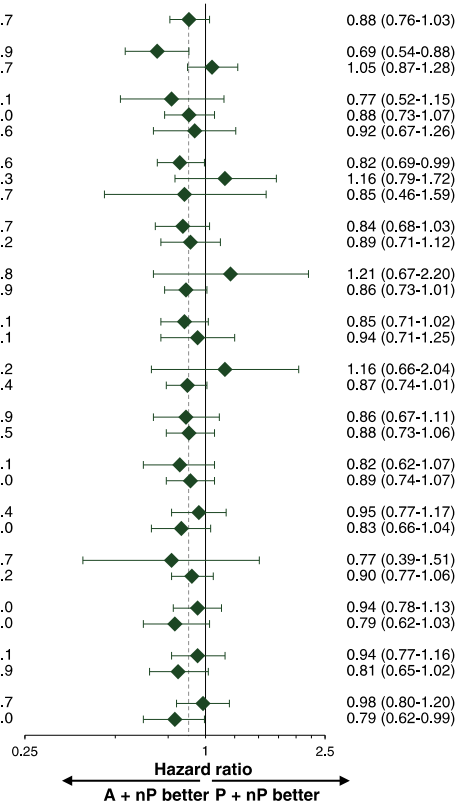


PD-L1 >1%



ITT

Baseline characteristic	A + nP Patients, *n*	A + nP Median OS, months	P + nP Patients, *n*	P + nP Median OS, months	HR (95% CI)
All	451	21.0	451	18.7	0.88 (0.76-1.03)
PD-L1 status					
Positive	185	25.4	184	17.9	0.69 (0.54-0.88)
Negative	266	19.7	267	19.7	1.05 (0.87-1.28)
Age, years					
18-40	63	16.8	51	13.1	0.77 (0.52-1.15)
41-64	284	21.1	285	20.0	0.88 (0.73-1.07)
≥65	104	22.6	115	19.6	0.92 (0.67-1.26)
Race[a]					
White	308	21.0	301	17.6	0.82 (0.69-0.99)
Asian	85	27.9	76	29.3	1.16 (0.79-1.72)
Black/African American	26	18.5	32	15.7	0.85 (0.46-1.59)
ECOG PS[a]					
0	256	25.0	270	22.7	0.84 (0.68-1.03)
1	193	16.3	179	13.2	0.89 (0.71-1.12)
Baseline disease status[a]					
Locally advanced	46	29.6	42	38.8	1.21 (0.67-2.20)
Metastatic	404	20.4	408	17.9	0.86 (0.73-1.01)
Number of metastatic sites[a]					
0-3	332	24.1	341	21.1	0.85 (0.71-1.02)
>3	118	12.7	108	12.1	0.94 (0.71-1.25)
Brain metastases					
Yes	30	14.3	31	16.2	1.16 (0.66-2.04)
No	421	21.6	420	19.4	0.87 (0.74-1.01)
Bone metastases					
Yes	145	17.1	141	14.9	0.86 (0.67-1.11)
No	306	22.6	310	20.5	0.88 (0.73-1.06)
Liver metastases					
Yes	126	14.0	118	12.1	0.82 (0.62-1.07)
No	325	23.7	333	22.0	0.89 (0.74-1.07)
Lung metastases					
Yes	227	17.8	242	17.4	0.95 (0.77-1.17)
No	224	23.7	209	20.0	0.83 (0.66-1.04)
Lymph node-only disease[a]					
Yes	33	34.4	23	34.7	0.77 (0.39-1.51)
No	417	20.3	426	18.2	0.90 (0.77-1.06)
Prior (neo) adjuvant chemotherapy					
Yes	284	21.4	286	20.0	0.94 (0.78-1.13)
No	167	20.8	165	16.0	0.79 (0.62-1.03)
Prior taxane treatment					
Yes	231	20.5	230	20.1	0.94 (0.77-1.16)
No	220	21.1	221	17.9	0.81 (0.65-1.02)
Prior anthracycline treatment					
Yes	243	20.2	242	19.7	0.98 (0.80-1.20)
No	208	22.0	209	18.0	0.79 (0.62-0.99)

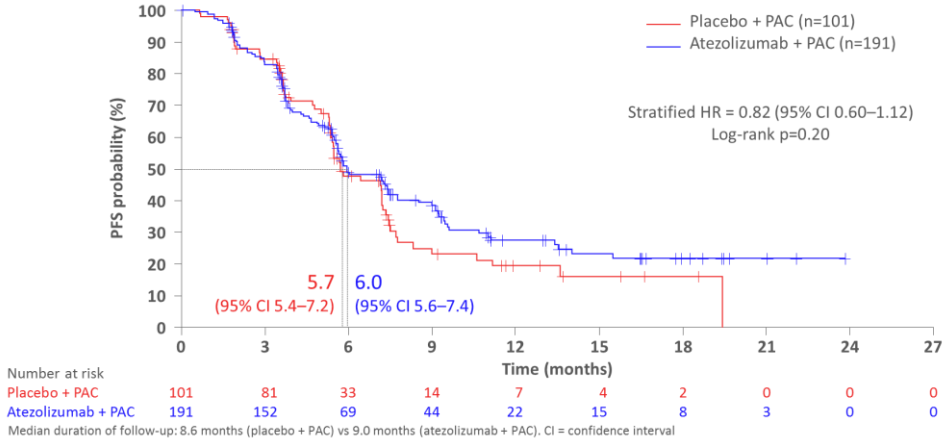


Emens, Ann Oncol 2021

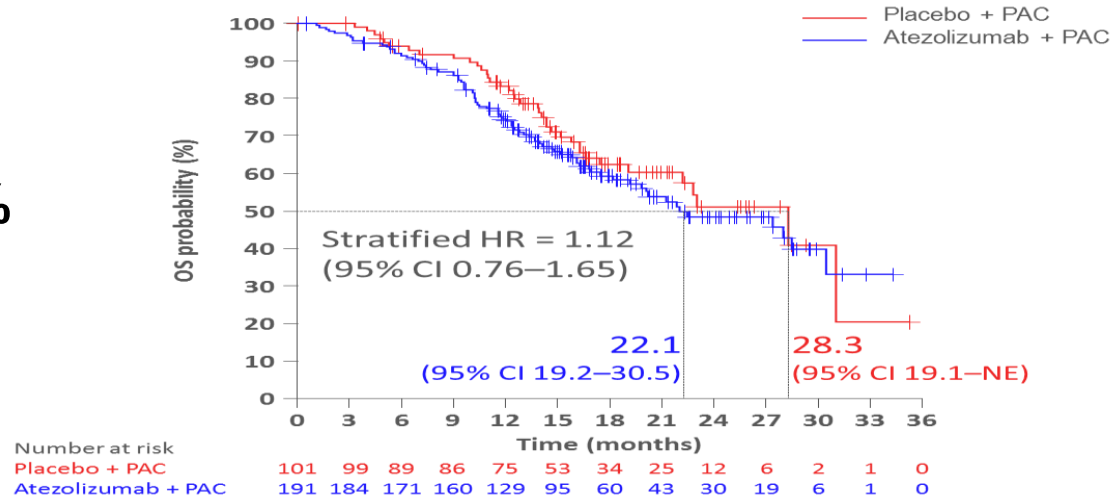
Immunotherapy in metastatic triple-negative breast cancer

IMpassion 131: no PFS and OS benefit in PD-L1+ subgroup

PFS - PD-L1 ≥ 1%



OS - PD-L1 ≥ 1%

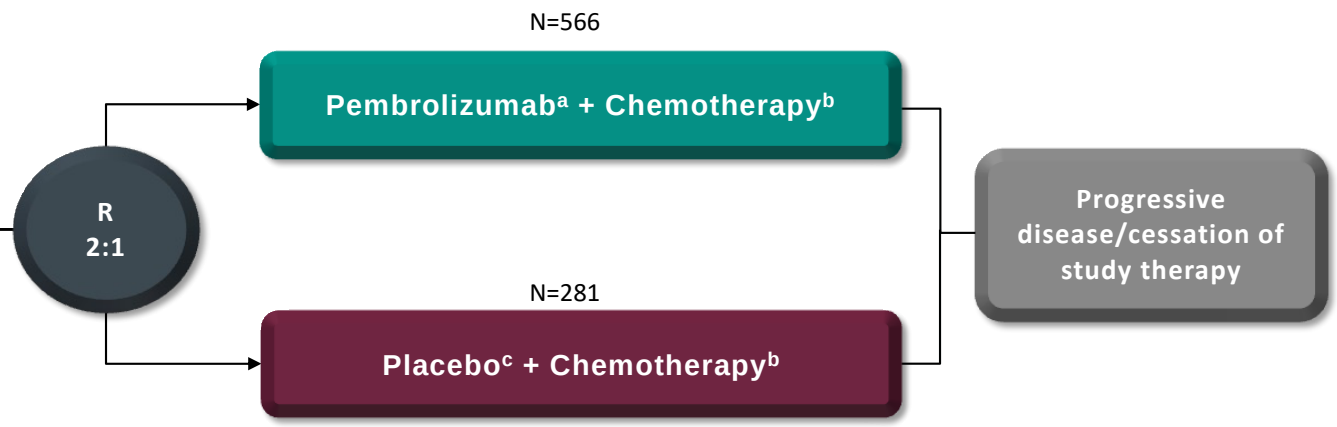


- Good performance of paclitaxel alone arm in IMpassion131
- Different chemotherapy backbone compared to Impassion 130:
  - Paclitaxel requiring steroids premedication
  - Different immune effects of paclitaxel vs. nab-paclitaxel

Miles. Ann Onc 2021

KEYNOTE-355:
Pembrolizumab + chemotherapy as first-line in mTNBC

Key Eligibility Criteria
- Age ≥18 years
- Central determination of TNBC and PD-L1 expression
- Previously untreated locally recurrent inoperable or metastatic TNBC
- Completion of treatment with curative intent ≥6 months prior to first disease recurrence
- ECOG performance status 0 or 1
- Life expectancy ≥12 weeks from randomization
- Adequate organ function
- No systemic steroids
- No active CNS metastases
- No active autoimmune disease



Stratification Factors:
- Chemotherapy on study (taxane vs gemcitabine/carboplatin)
- PD-L1 tumor expression (CPS ≥1 vs CPS <1)
- Prior treatment with same class chemotherapy in the neoadjuvant or adjuvant setting (yes vs no)

Endpoints:
- Primary: **PFS and OS in patients with PD-L1+ tumors (CPS ≥10 and CPS ≥1) and in the ITT population**
- Secondary: ORR, DOR, DCR, Safety in all treated patients

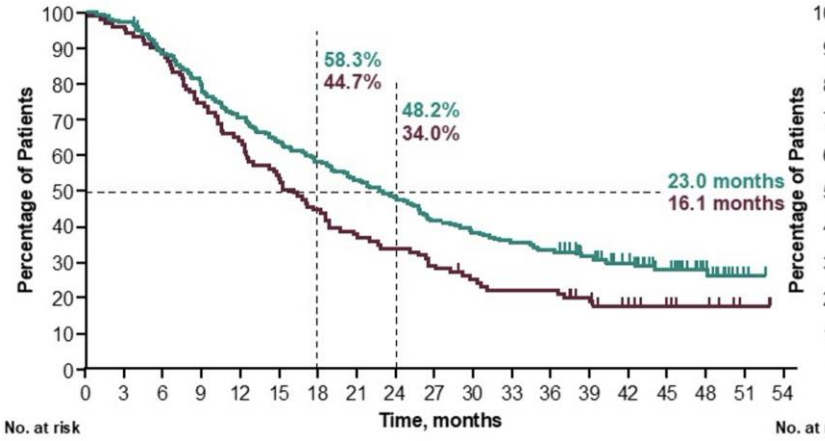
[a] Chemotherapy dosing regimens are as follows:
Nab-paclitaxel 100 mg/m^2 IV on days 1, 8, and 15 every 28 days
Paclitaxel 90 mg/m^2 IV on days 1, 8, and 15 every 28 days
Gemcitabine 1000 mg/m^2/carboplatin AUC 2 on days 1 and 8 every 21 days

Cortes, ASCO 2020; Cortes, Lancet 2020

Keynote-355: Overall Survival

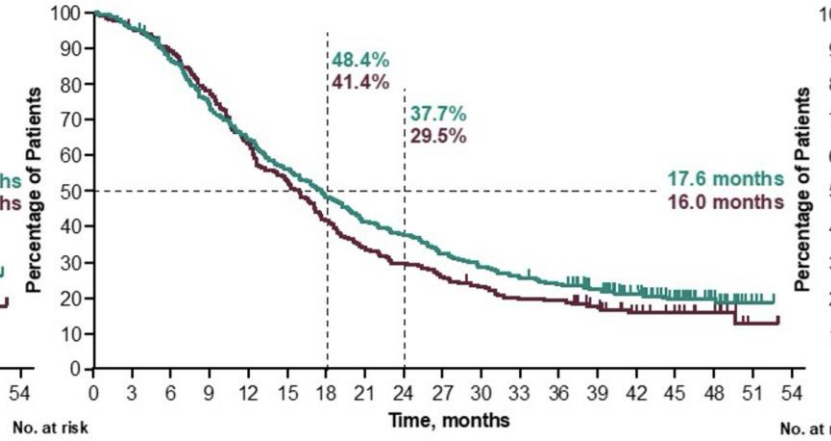
CPS ≥10

	n/N	Events	HR (95% CI)	P-value (one-sided)
Pembro + Chemo	155/220	70.5%	0.73 (0.55-0.95)	0.0093[a]
Placebo + Chemo	84/103	81.6%		



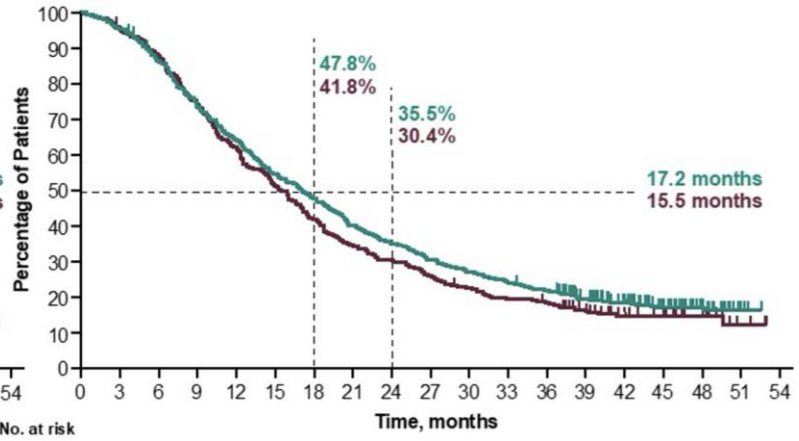
CPS ≥1

	n/N	Events	HR (95% CI)	P-value (one-sided)
Pembro + Chemo	336/425	79.1%	0.86 (0.72-1.04)	0.0563[a]
Placebo + Chemo	177/211	83.9%		



ITT

	n/N	Events	HR (95% CI)
Pembro + Chemo	460/566	81.3%	0.89 (0.76-1.05)
Placebo + Chemo	238/281	84.7%	

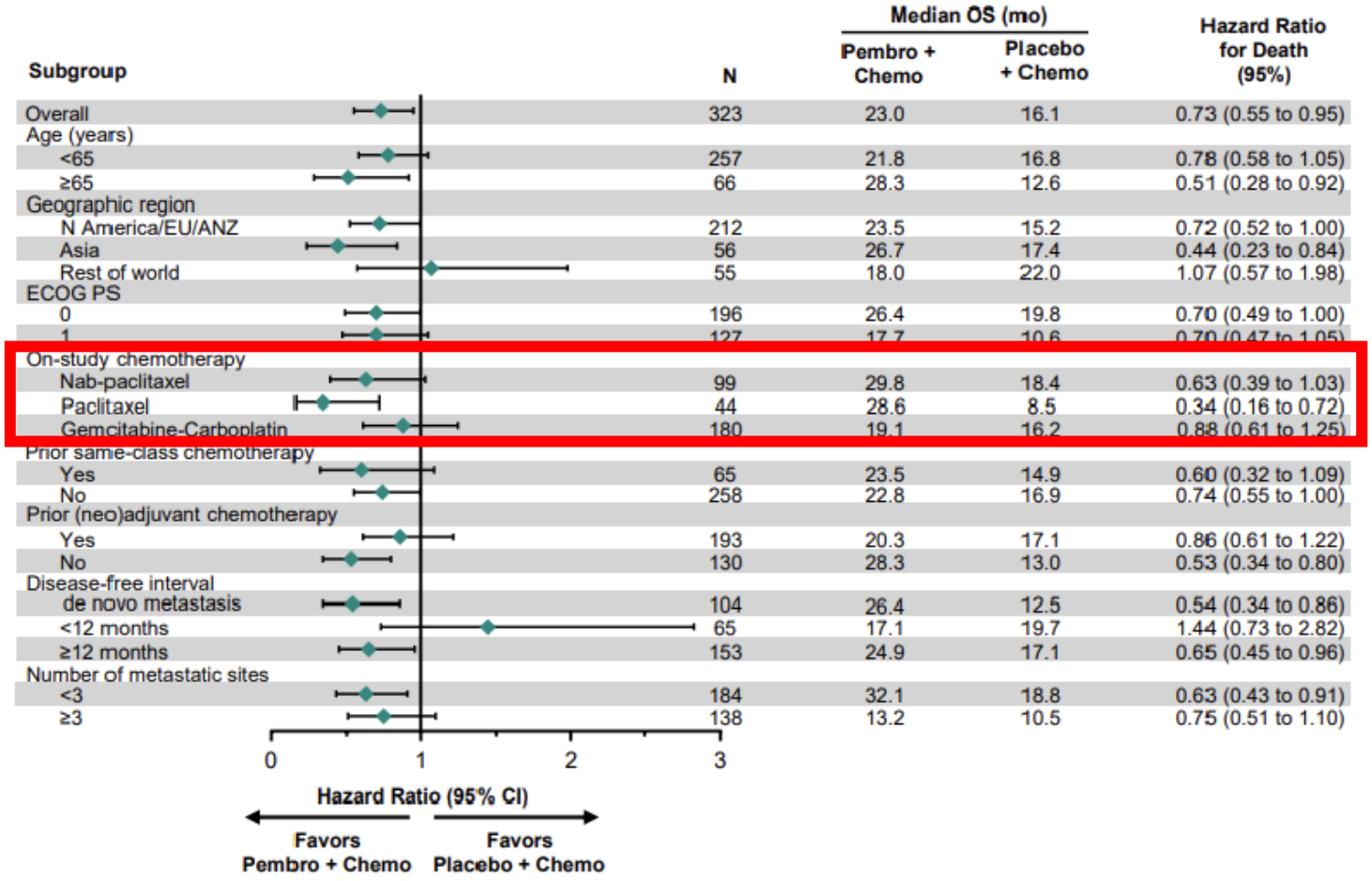


No significant difference in CPS ≥1 and ITT

For pembrolizumab + chemotherapy in mTNBC, CPS ≥10 is the best cut-off to define those expected to benefit

Cortes, NEJM 2022

KEYNOTE-355: Overall survival in subgroups CPS ≥10



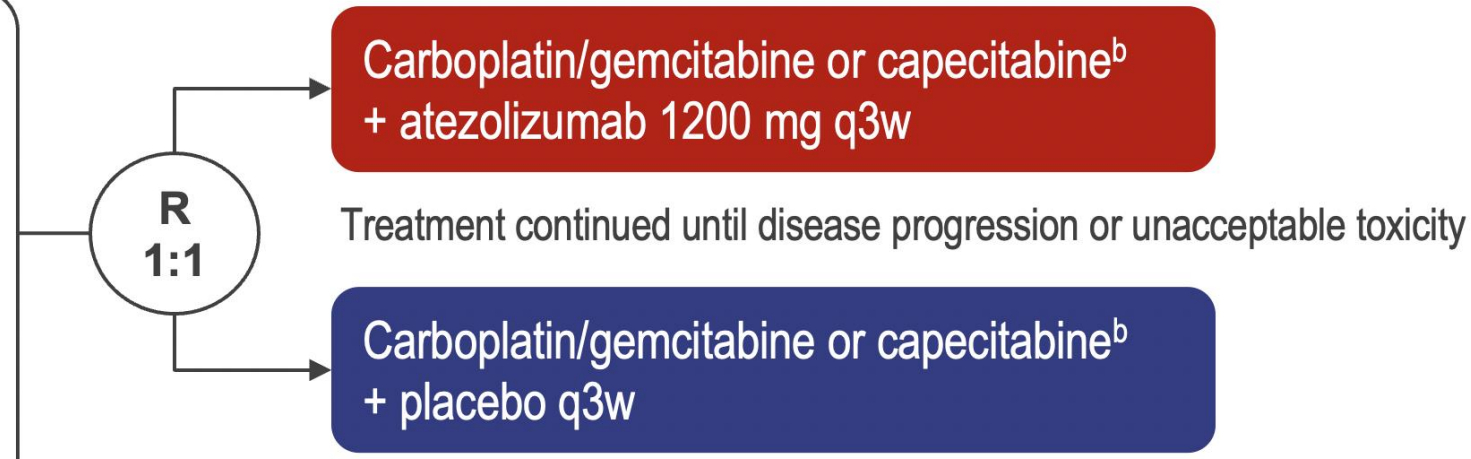
Subgroup	N	Median OS (mo) Pembro + Chemo	Median OS (mo) Placebo + Chemo	Hazard Ratio for Death (95%)
Overall	323	23.0	16.1	0.73 (0.55 to 0.95)
Age (years)				
<65	257	21.8	16.8	0.78 (0.58 to 1.05)
≥65	66	28.3	12.6	0.51 (0.28 to 0.92)
Geographic region				
N America/EU/ANZ	212	23.5	15.2	0.72 (0.52 to 1.00)
Asia	56	26.7	17.4	0.44 (0.23 to 0.84)
Rest of world	55	18.0	22.0	1.07 (0.57 to 1.98)
ECOG PS				
0	196	26.4	19.8	0.70 (0.49 to 1.00)
1	127	17.7	10.6	0.70 (0.47 to 1.05)
On-study chemotherapy				
Nab-paclitaxel	99	29.8	18.4	0.63 (0.39 to 1.03)
Paclitaxel	44	28.6	8.5	0.34 (0.16 to 0.72)
Gemcitabine-Carboplatin	180	19.1	16.2	0.88 (0.61 to 1.25)
Prior same-class chemotherapy				
Yes	65	23.5	14.9	0.60 (0.32 to 1.09)
No	258	22.8	16.9	0.74 (0.55 to 1.00)
Prior (neo)adjuvant chemotherapy				
Yes	193	20.3	17.1	0.86 (0.61 to 1.22)
No	130	28.3	13.0	0.53 (0.34 to 0.80)
Disease-free interval				
de novo metastasis	104	26.4	12.5	0.54 (0.34 to 0.86)
<12 months	65	17.1	19.7	1.44 (0.73 to 2.82)
≥12 months	153	24.9	17.1	0.65 (0.45 to 0.96)
Number of metastatic sites				
<3	184	32.1	18.8	0.63 (0.43 to 0.91)
≥3	138	13.2	10.5	0.75 (0.51 to 1.10)

Rugo, ESMO 2021; Cortes, NEJM 2022

Impassion 132: Study design

Double-blind placebo-controlled randomised phase 3 trial

- **Unresectable locally advanced/ metastatic TNBC**
- **Prior anthracycline and taxane for early TNBC**
- **Disease progression <12 months after last treatment with curative intent for early TNBC[a]**
- **No prior CT for advanced TNBC**
- **Known PD-L1 status (SP142)**



Treatment continued until disease progression or unacceptable toxicity

Stratification factors:

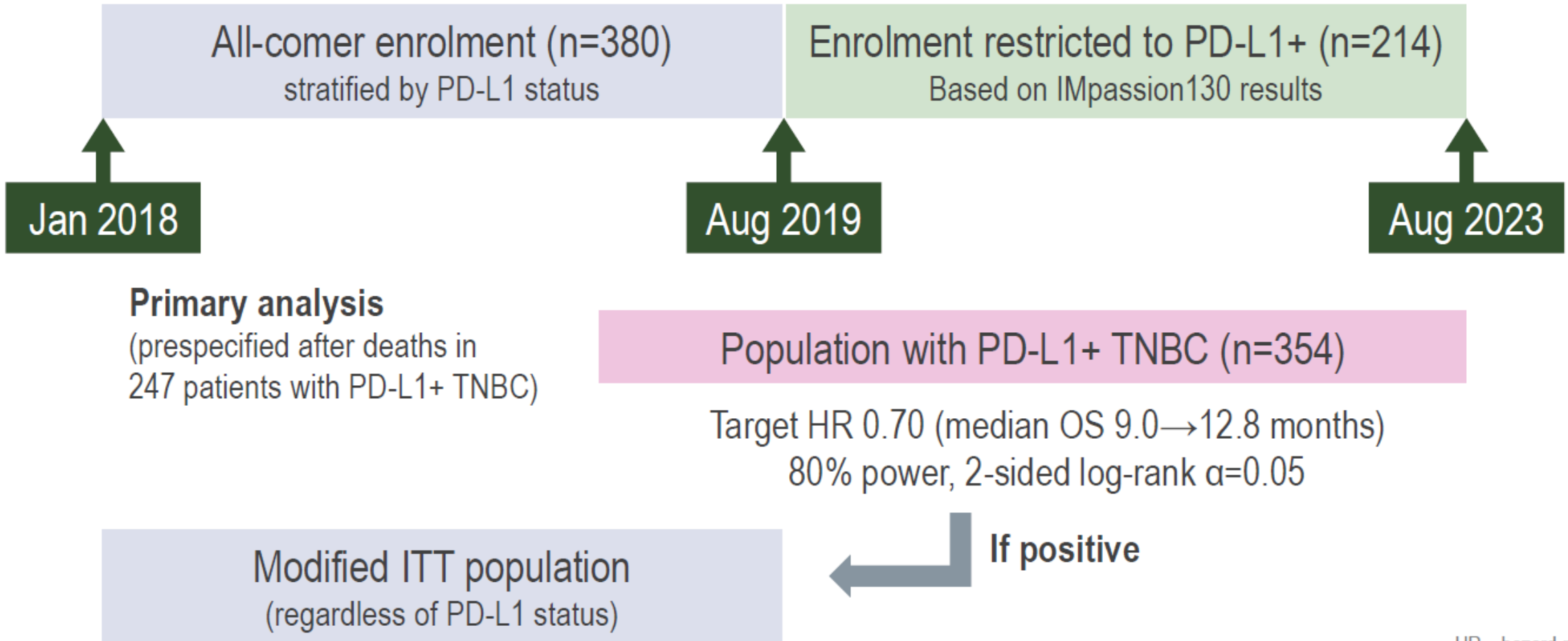
- Visceral (lung and/or liver) metastases
- CT backbone
- PD-L1 status (during all-comer enrolment)

Primary endpoint:

- OS (hierarchical testing: PD-L1+ TNBC[c] then, if positive, modified ITT population[d])

Dent, Ann Onc 2024

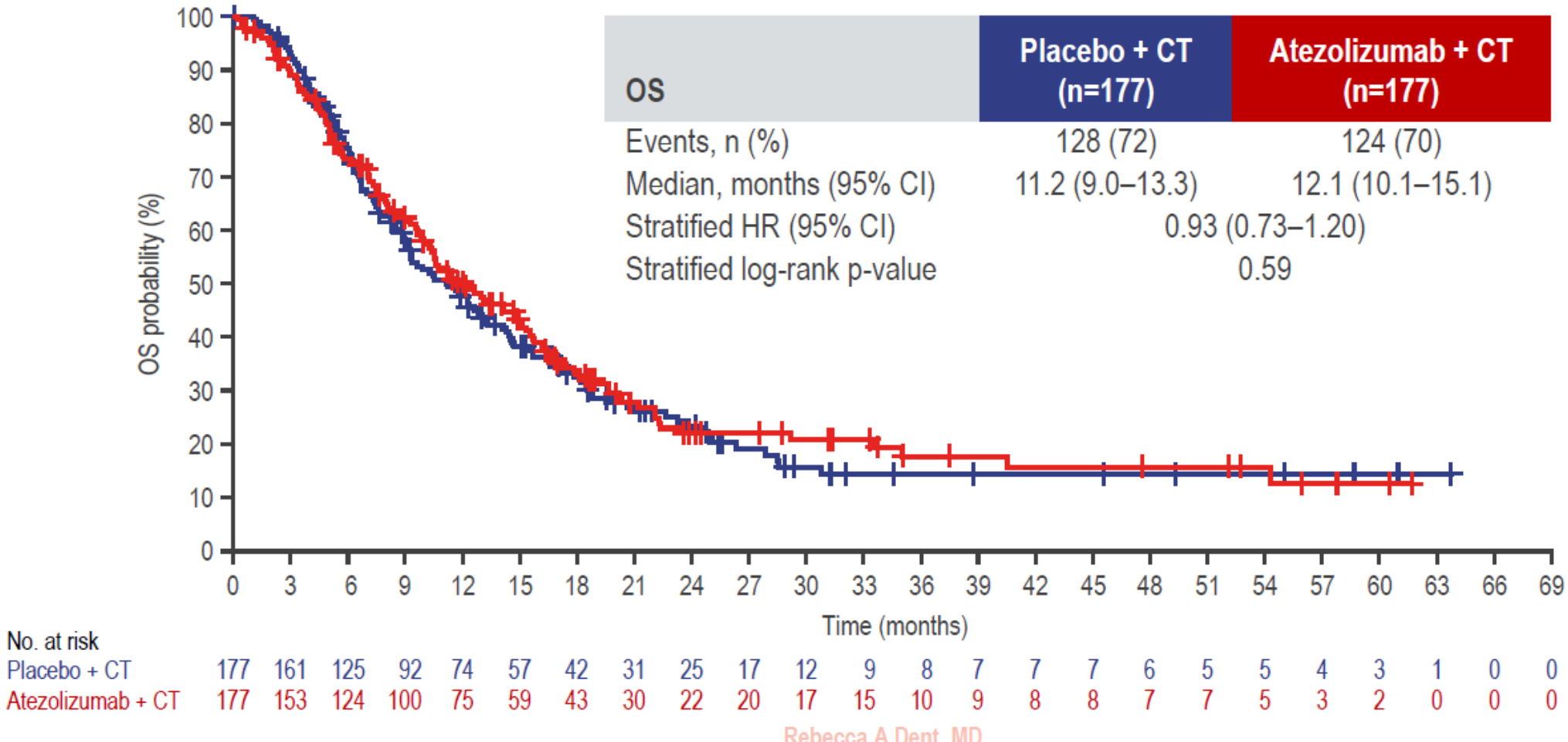
PATIENT POPULATIONS AND STATISTICAL DESIGN



HR = hazard ratio

PRIMARY ENDPOINT: OS (PATIENTS WITH PD-L1+ TNBC)

No significant improvement in OS with atezolizumab (median follow-up: 9.8 months)



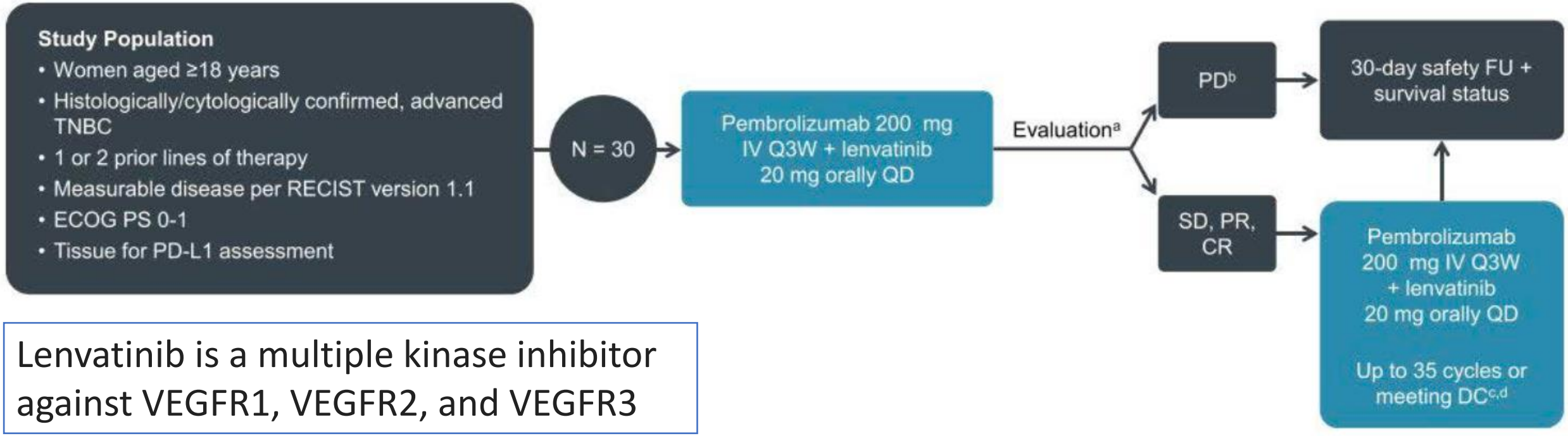
OS	Placebo + CT (n=177)	Atezolizumab + CT (n=177)
Events, n (%)	128 (72)	124 (70)
Median, months (95% CI)	11.2 (9.0–13.3)	12.1 (10.1–15.1)
Stratified HR (95% CI)	0.93 (0.73–1.20)	
Stratified log-rank p-value	0.59	

No. at risk																								
Placebo + CT	177	161	125	92	74	57	42	31	25	17	12	9	8	7	7	7	6	5	5	4	3	1	0	0
Atezolizumab + CT	177	153	124	100	75	59	43	30	22	20	17	15	10	9	8	8	7	7	5	3	2	0	0	0

Immunotherapy in metastatic triple-negative breast cancer

Immunotherapy and VEGF inhibition

Figure 1. LEAP-005 Study Design

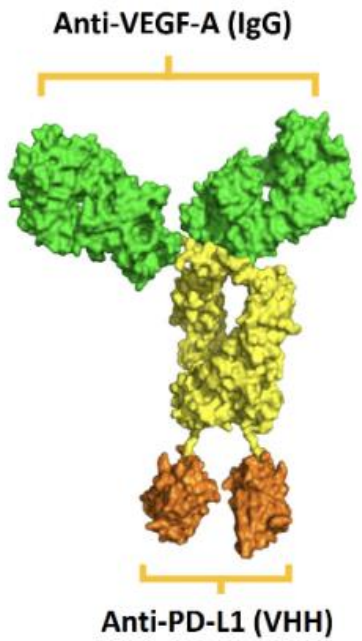


Lenvatinib is a multiple kinase inhibitor against VEGFR1, VEGFR2, and VEGFR3

Immunotherapy in metastatic triple-negative breast cancer

Immunotherapy and VEGF inhibition: **bispecific antibodies**

PM8002



Key Eligibility Criteria

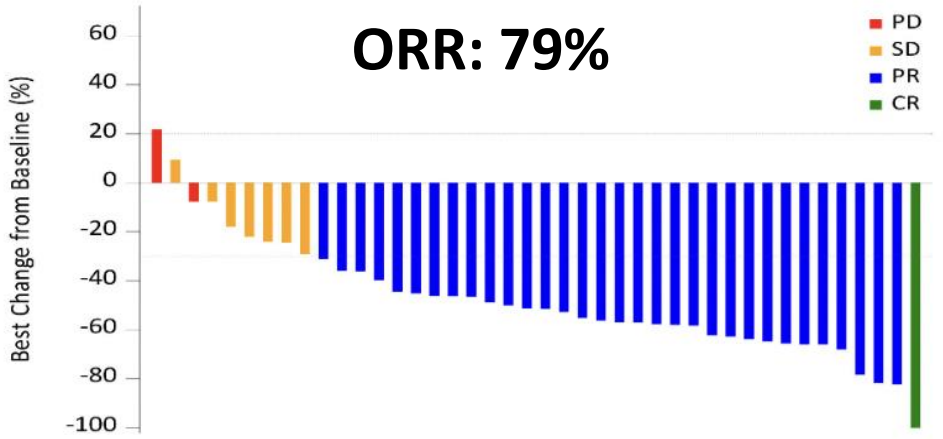
- Patients with locally advanced or metastatic TNBC who have not received prior systemic treatment for TNBC;
- Age ≥ 18 years;
- ECOG score 0-1;
- Adequate organ function.

Open label, Single arm study
PM8002+Nab-paclitaxel
PM8002 20mg/kg
- On days 1 and 15 of 28-day cycle
Nab-paclitaxel 100 mg/m²
- On days 1, 8 and 15 of 28-day cycle

Disease progression/ unacceptable toxicity

Primary endpoint: Objective Response Rate (ORR) assessed by investigators per RECIST1.1, the incidence and severity of Treatment-Related Adverse Events (TRAEs) graded according to NCI-CTCAE v5.0.
Secondary endpoint: Progression Free Survival(PFS), Disease Control Rate (DCR).

ORR: 79%



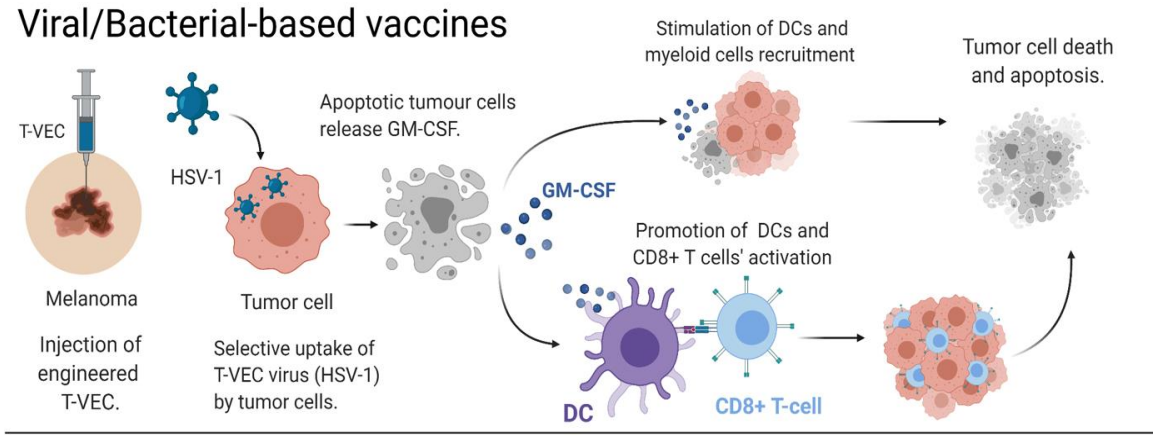
Conclusions

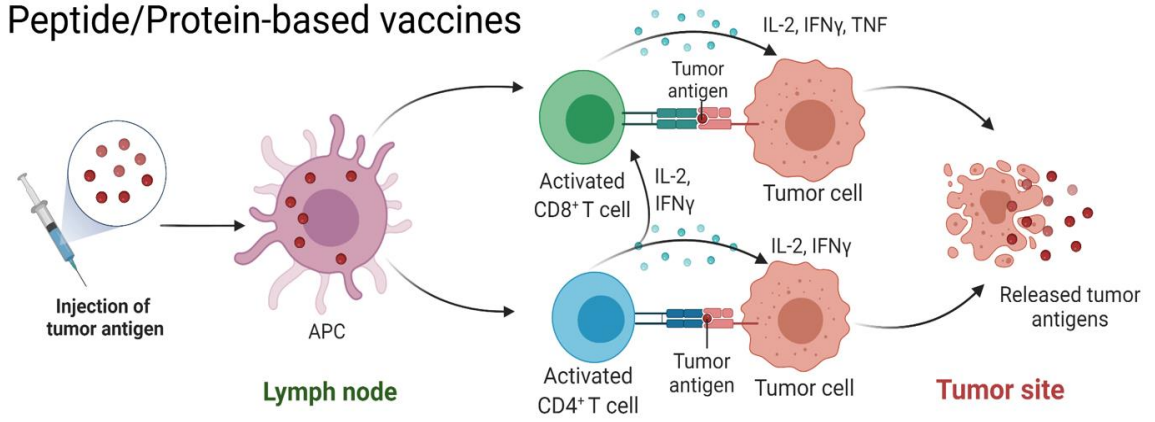
PM8002 combined with nab-paclitaxel showed encouraging antitumor activity regardless of PD-L1 status and good safety profile as a first-line therapy for TNBC patients.
This phase II study is still ongoing with near-term plans to enter phase III trials.

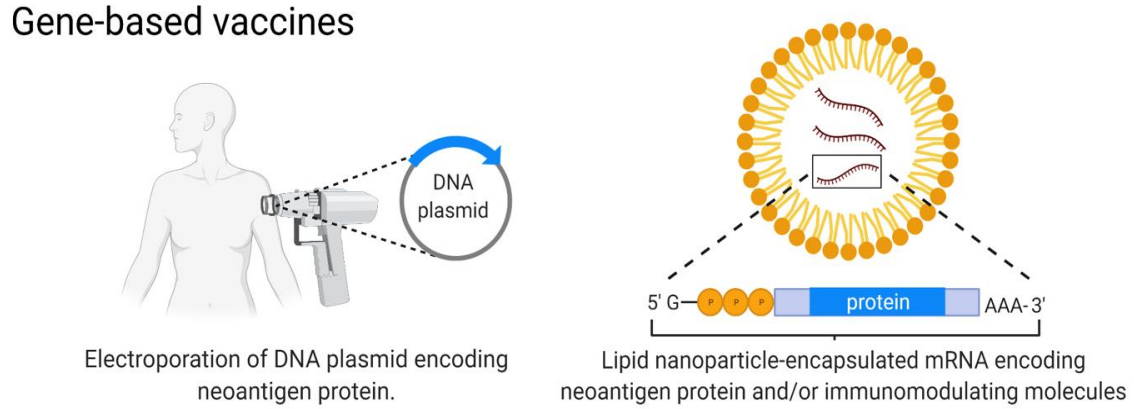
Wu, SABCS 2023

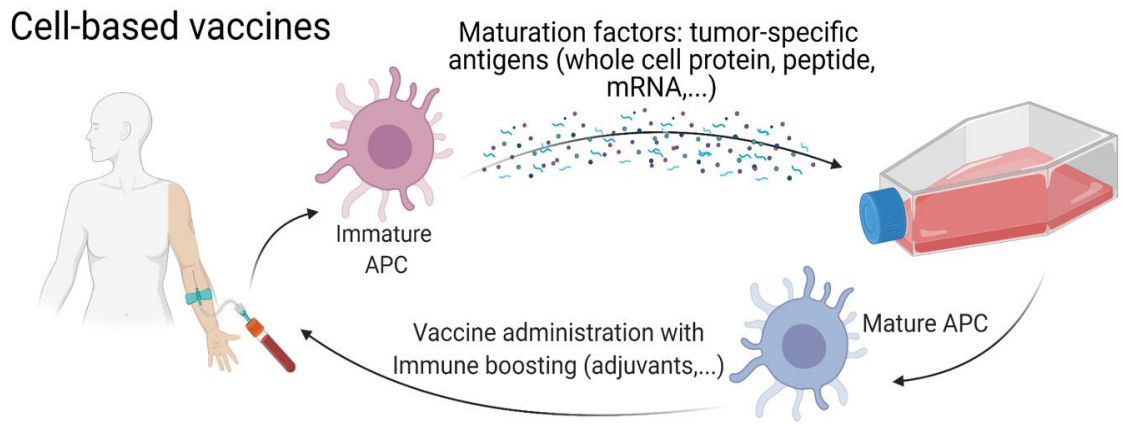
Immunotherapy in metastatic triple-negative breast cancer

… and future perspectives









Corti, EJC 2022; Antonarelli, Ann Onc 2021

SYNERGY TRIAL

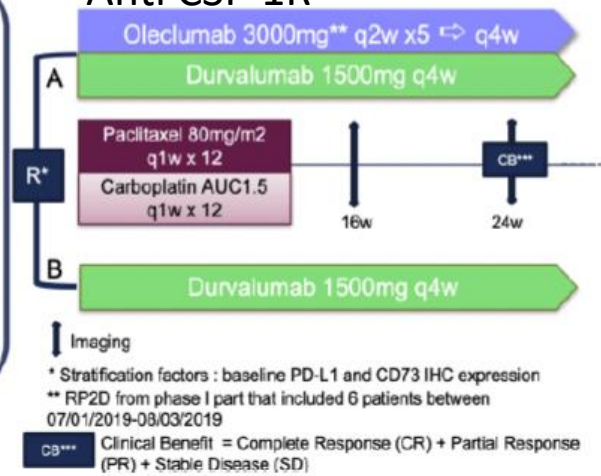
First-line treatment in advanced TNBC

Phase II : study design

Multicenter, open-label, randomized (1:1 ratio)

Anti CSF-1R

Key eligibility criteria:
- Female, ≥18yo
- Locally advanced or metastatic TNBC
- 1st Line
- ≥ 6mo since end of adjuvant treatment
- ECOG 0-1
- Adequate organ function
- Measurable disease per RECIST v1.1
- No prior treatment with checkpoint inhibitor
- No major auto-immune disease



* Stratification factors : baseline PD-L1 and CD73 IHC expression

** RP2D from phase I part that included 6 patients between 07/01/2019-08/03/2019

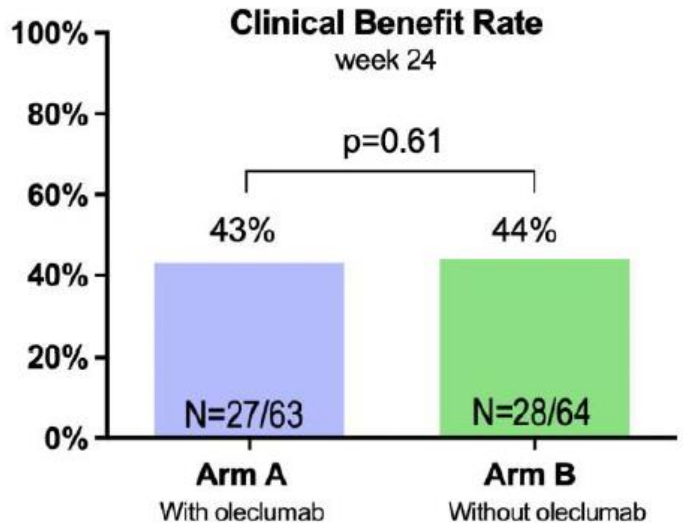
CB*** Clinical Benefit = Complete Response (CR) + Partial Response (PR) + Stable Disease (SD)

Primary endpoint:
- Clinical Benefit (CB) at week 24

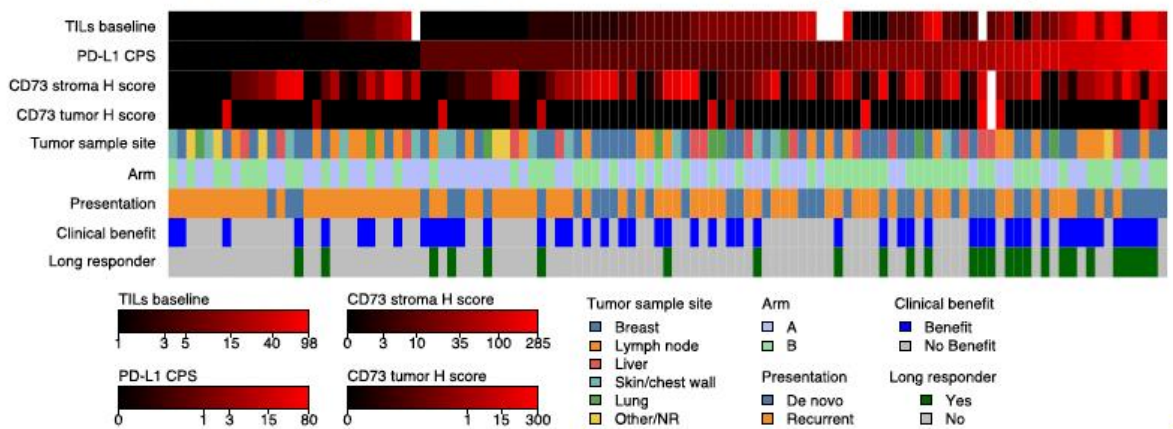
Secondary endpoints:
- OR
- DOR
- PFS
- OS
- CBR according to PD-L1 and CD73

Exploratory endpoints:
- Response RECIST v1.1 vs iRESIST v1.1
- PFS RECIST v1.1 vs iRESIST v1.1

OR: objective response; DOR: duration of response; PFS: progression free survival; OS: overall survival



Heterogenous disease → heterogenous responses

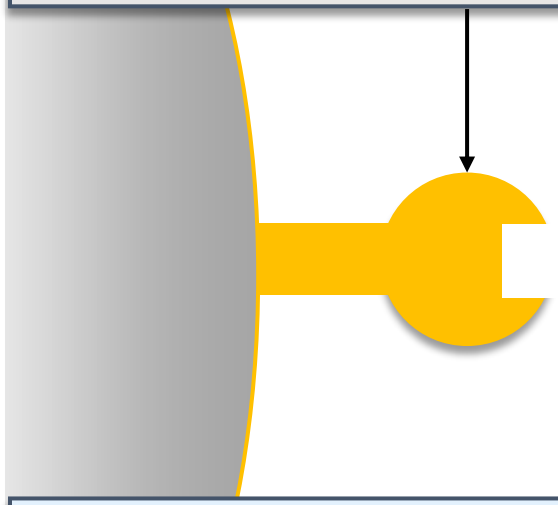


URGENT need for effective biomarkers

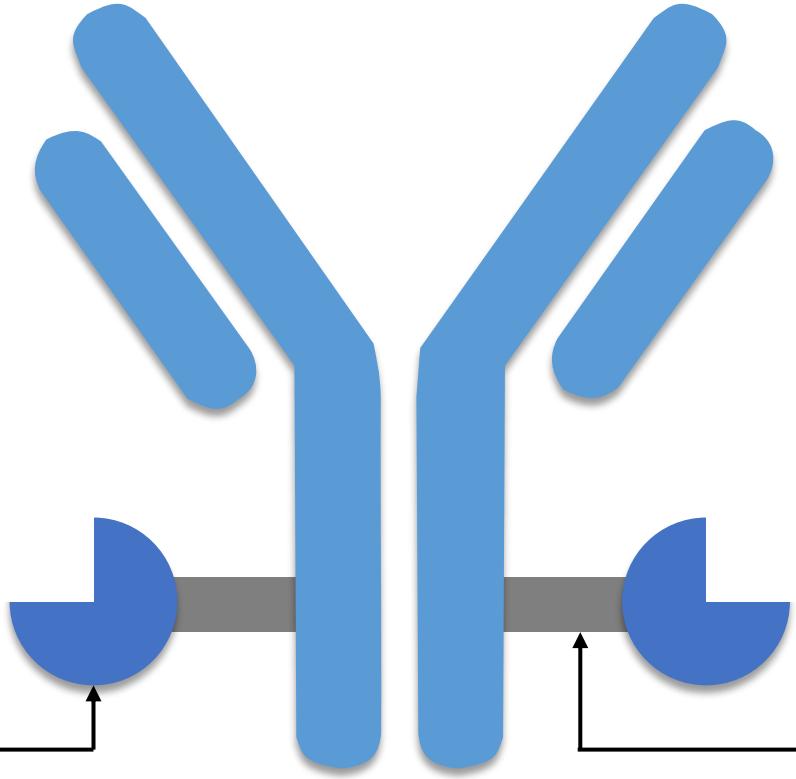
Buisseret *et al*. Nature Com 2023

ADC in metastatic triple-negative breast cancer

Antigen target/receptor
- High homogeneous expression in tumor
- Limited/absent expression in normal tissue
- Limited heterogeneity
- Efficient internalization following ADC binding



Drug/payload
- Highly potent (eg, microtubule inhibitor, DNA-damaging agents)
- Amenable to linker attachment
- Maximized drug-to-antibody ratio (DAR)

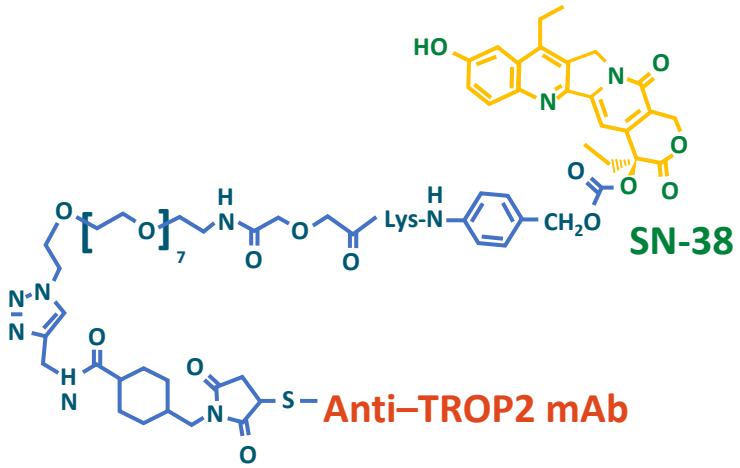


Antibody
- High affinity and avidity for target antigen
- Long half-life
- Conjugation sites with minimal impact on ADC stability, internalization, and pharmacokinetics (eg, cysteine, lysine)
- Chimeric or humanized (decreasing immunogenicity)

Antibodies	IgG1	IgG2	IgG3	IgG4
Serum half-life	21 days	21 days	7–21 days	21 days
C1q binding	Yes	Yes	Yes	No
Fcγ avidity	High	Low	High	Moderate

Linker
- Controlled release of payload:
  - Noncleavable (eg, lysosomal degradation of mAb)
  - Cleavable (eg, acid/redox/lysosomal/protease sensitive, cathepsin)

Sacituzumab Govitecan

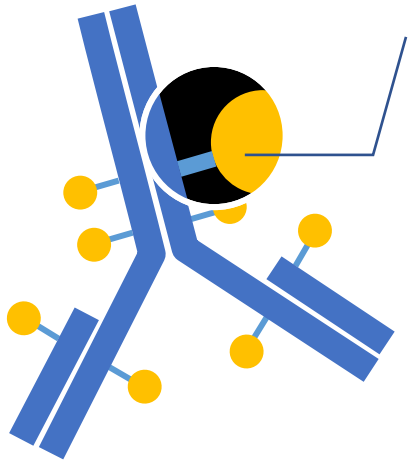


Humanized Anti-TROP2 Antibody

- Targets TROP2, an antigen expressed in many epithelial cancers
- Antibody type: hRS7 IgG1κ

SN-38 Payload Payload (Topoisomerase I Inhibitor)

- Delivers up to 136-fold more SN-38 to tumors than parent compound irinotecan
- Unique chemistry improves solubility, selectively delivers SN-38 to tumor



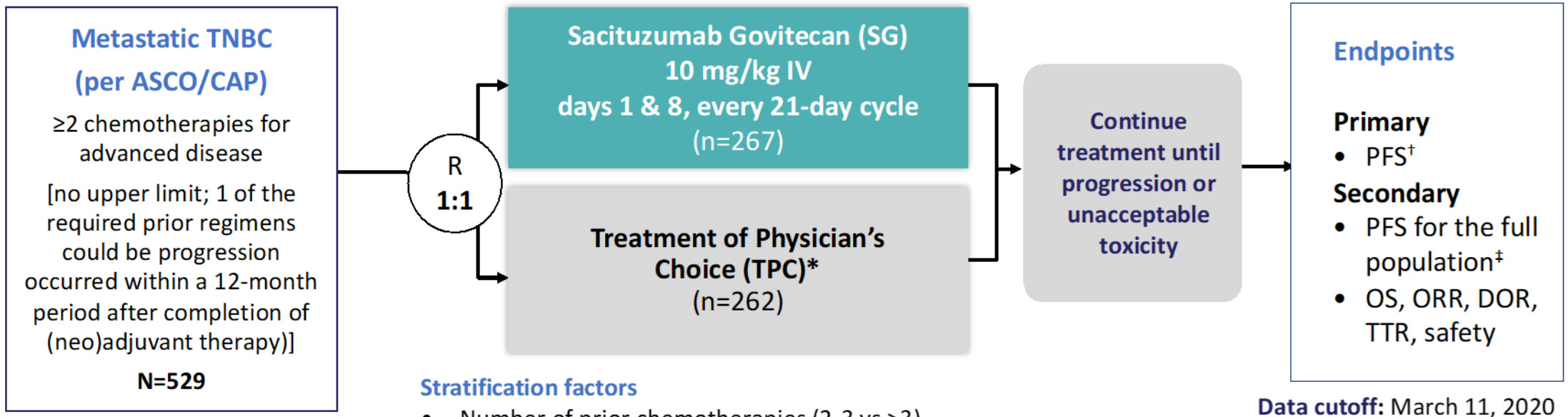
Linker for SN-38

- High drug-to-antibody ratio (7.6:1)
- pH-sensitive linker for rapid release of payload at or inside tumor

Bystander effect: In acidic tumor microenvironment, SN-38 is released from anti-TROP2 antibody, diffuses into neighboring cells

Goldenberg. Oncotarget. 2015;6:22496. Khoury. ASCO 2019. Abstr e14651. Ambrogi. PLoS One. 2014;9:e96993. Vidula. ASCO 2017. Abstr 1075. Sacituzumab govitecan PI. Tagawa. ASCO 2019. Abstr TPS3153. Bardia. JCO. 2017;35:2141. Goldenberg. MAbs. 2019;11:987. Sharkey. Clin Cancer Res. 2015;21:5131.

Phase III ASCENT: Sacituzumab Govitecan vs CT in Relapsed/Refractory Metastatic TNBC



Stratification factors

- Number of prior chemotherapies (2-3 vs >3)
- Geographic region (North America vs Europe)
- Presence/absence of known brain metastases (yes/no)

Data cutoff: March 11, 2020

NCT02574455

Demographics:

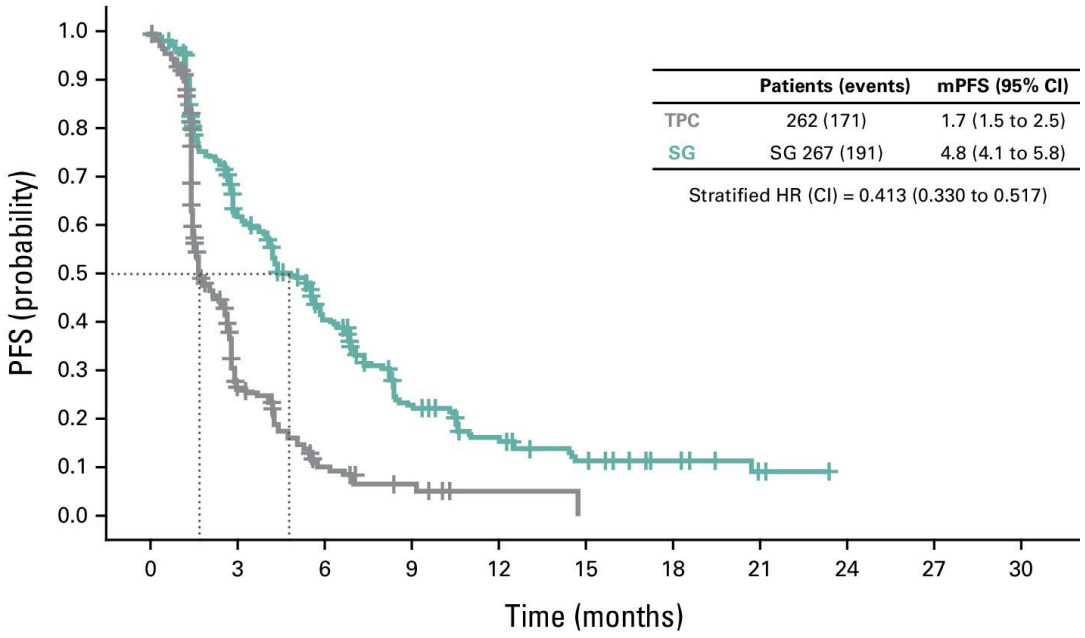
TPC: 53% eribulin, 20% vinorelbine, 15% gemcitabine, 13% capecitabine; 70% TN at initial diagnosis

Median prior regimens 4 (2-17); ~88% with visceral disease

ASCENT was halted early due to compelling evidence of efficacy per unanimous DSMC recommendation.

ASCENT:
PFS and OS Among Patients w/o Brain Metastases (Final Analysis)

PFS

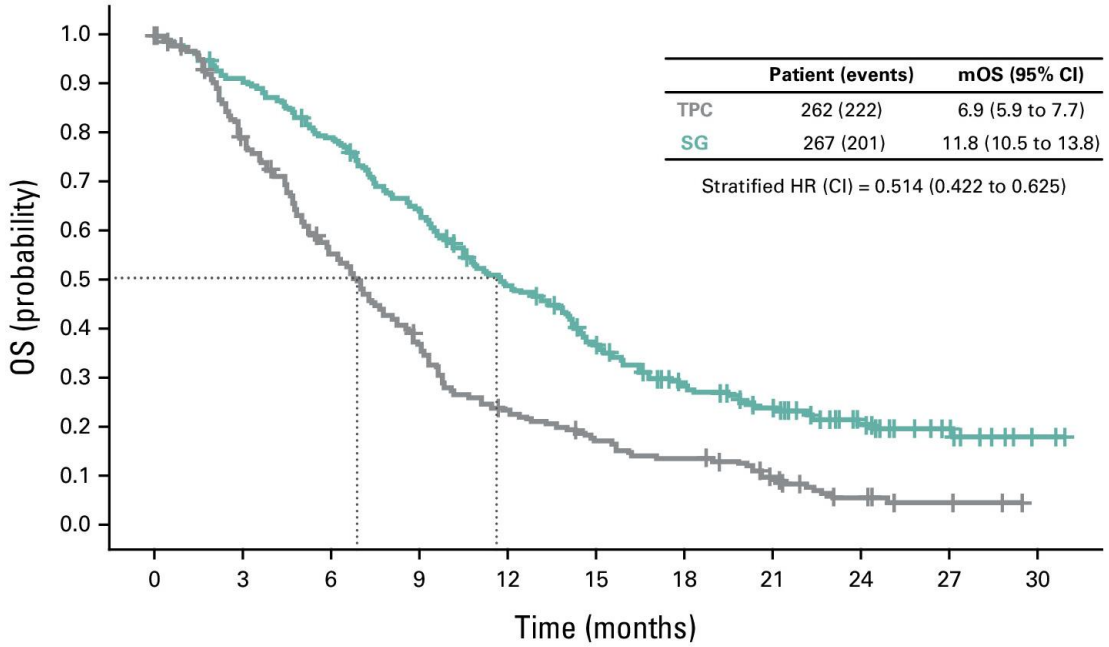


	Patients (events)	mPFS (95% CI)
TPC	262 (171)	1.7 (1.5 to 2.5)
SG	SG 267 (191)	4.8 (4.1 to 5.8)

Stratified HR (CI) = 0.413 (0.330 to 0.517)

No. at risk:									
TPC	262	40	12	5	1	0	0	0	0
SG	267	145	82	38	23	14	8	3	0

OS



	Patient (events)	mOS (95% CI)
TPC	262 (222)	6.9 (5.9 to 7.7)
SG	267 (201)	11.8 (10.5 to 13.8)

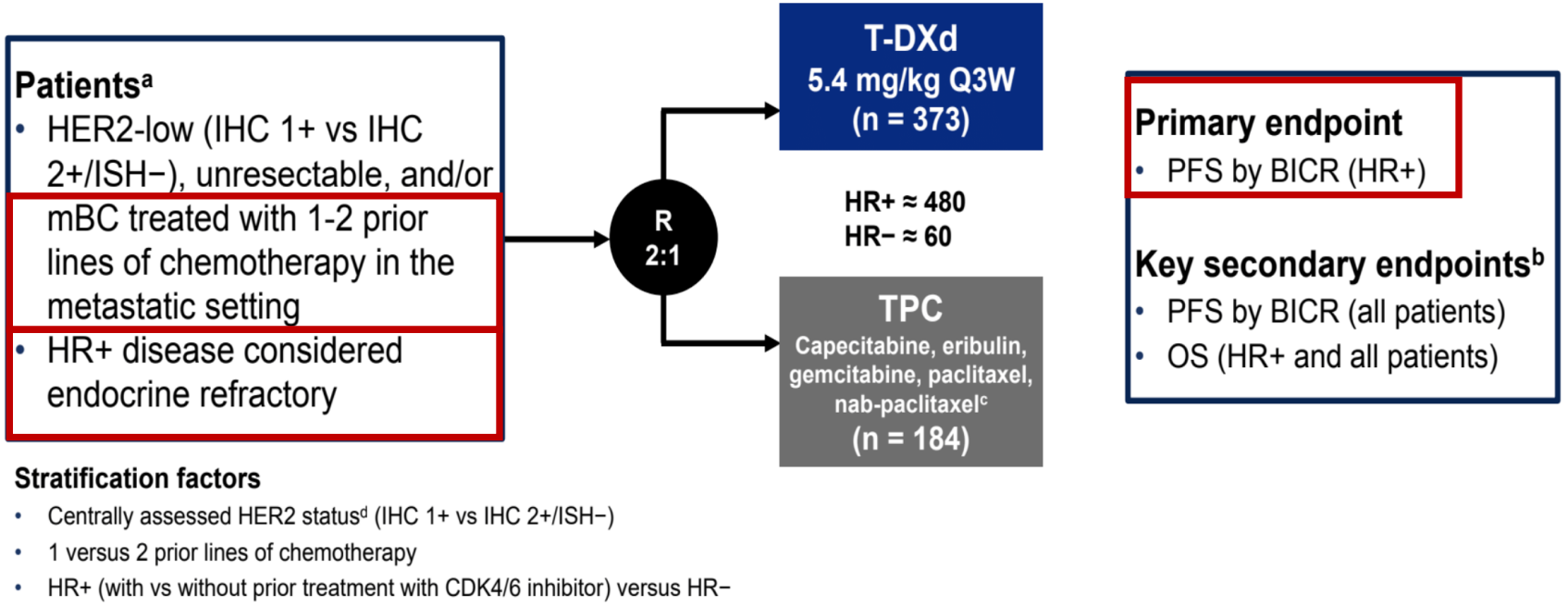
Stratified HR (CI) = 0.514 (0.422 to 0.625)

No. at risk:											
TPC	262	192	132	87	54	39	31	16	7	3	0
SG	267	242	209	169	125	92	62	42	25	11	2

Bardia A., et al. NEJM 2021; J Clin Oncol 2024

T-DXd (DESTINY Breast 04)

DESTINY-Breast04
Phase 3 trial initiated to confirm the benefit of targeting HER2-low expression in mBC



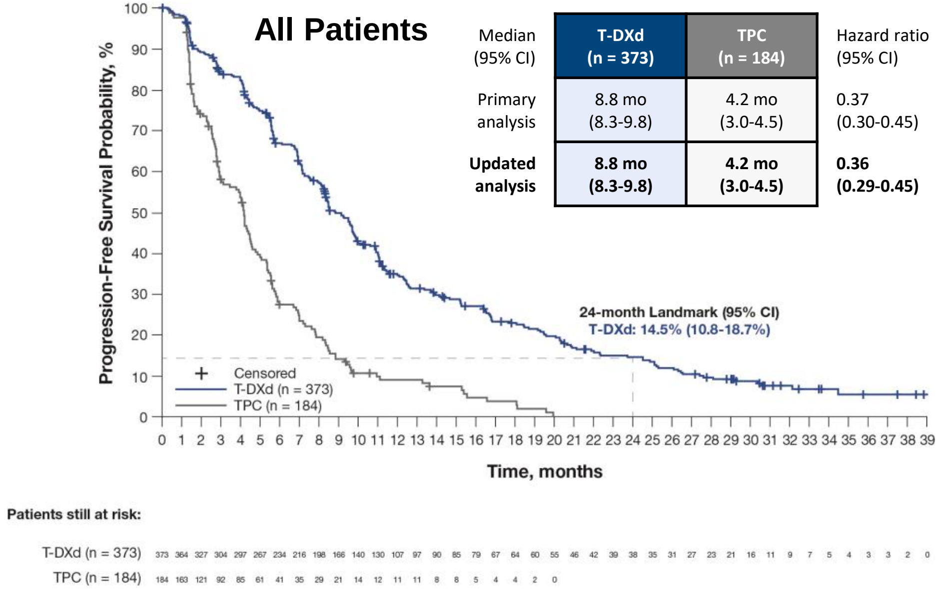
Modi S., et al. ASCO 2022; NEJM 2022

DESTINY Breast 04 – PFS and OS

Progression-Free Survival

All Patients

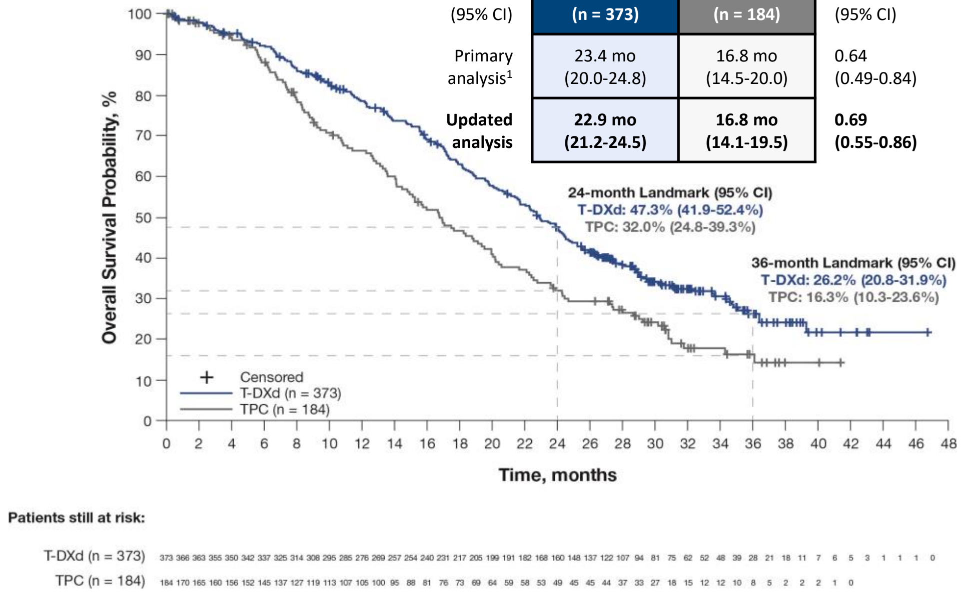
Median (95% CI)	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis	8.8 mo (8.3-9.8)	4.2 mo (3.0-4.5)	0.37 (0.30-0.45)
Updated analysis	**8.8 mo (8.3-9.8)**	**4.2 mo (3.0-4.5)**	**0.36 (0.29-0.45)**



Overall Survival

All Patients

Median (95% CI)	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis[1]	23.4 mo (20.0-24.8)	16.8 mo (14.5-20.0)	0.64 (0.49-0.84)
Updated analysis	**22.9 mo (21.2-24.5)**	**16.8 mo (14.1-19.5)**	**0.69 (0.55-0.86)**

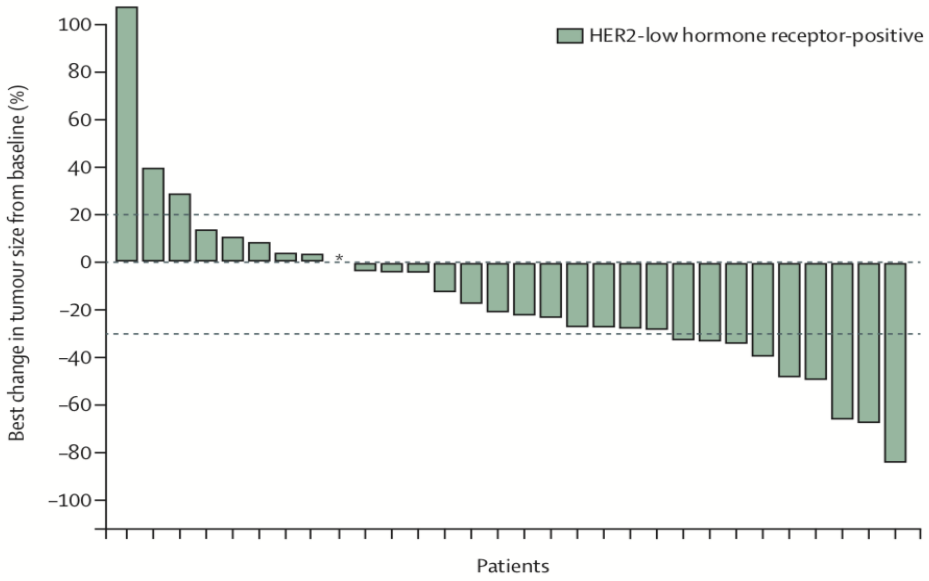


Results from the 32-month median follow-up for DESTINY-Breast04 confirm the sustained clinically meaningful improvement for T-DXd vs TPC previously demonstrated in HER2-low (IHC 1+, IHC 2+/ISH−) mBC, regardless of HR status

Modi S., et al. ASCO 2022; NEJM 2022; ESMO 2023

Other active ADCs in HER2-low

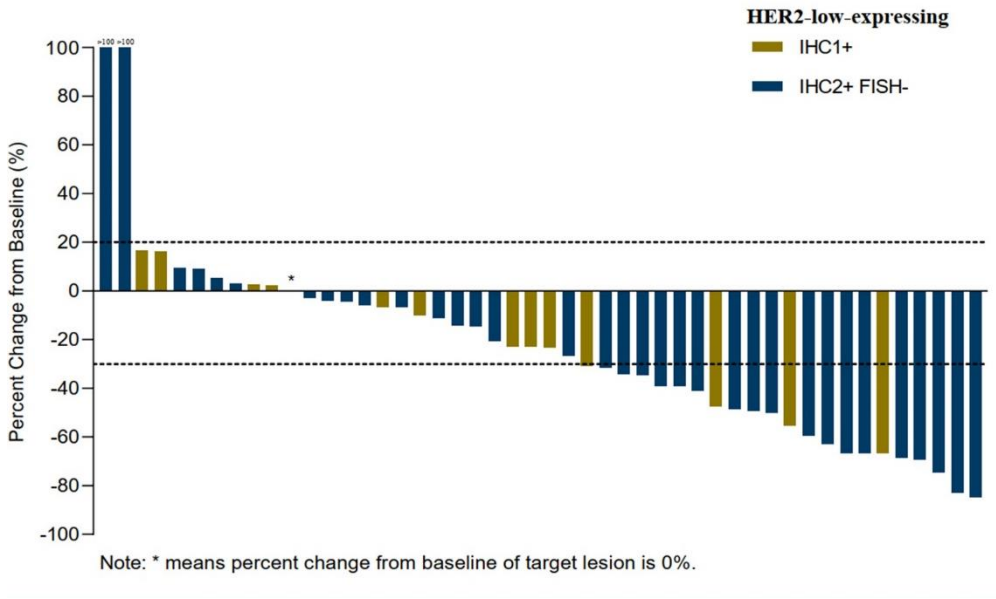
Trastuzumab duocarmazine (SYD985)[1]



49 HER2-low mBC patients: ORR 32%, mPFS 4 mo

Grade 1–4 TRAEs were fatigue (33%), conjunctivitis (31%), and dry eye (31%). Most patients (71%) had at least one ocular AE, with Grade 3 events reported in 7% of patients

Disitamab Vedotin (RC48-ADC)[2]



48 HER2-low mBC patients: ORR 40%, mPFS 5.7 mo

Grade ≥3 TRAEs occurred in 45.8% of patients.
The most common Grade ≥3 TRAEs were neutrophil count decrease (16.9%) and γ-GT increase (12.7%)

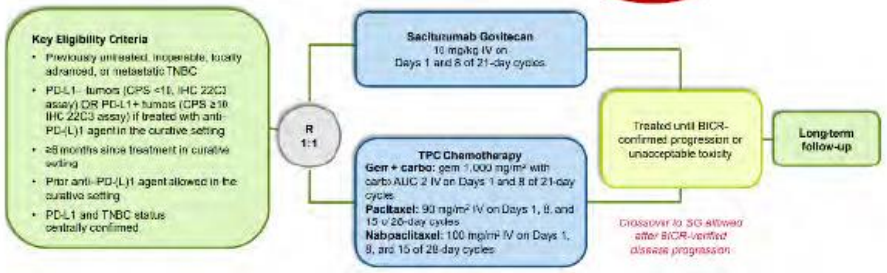
1. Banerji U, et al. Lancet Oncol. 2019; 2. Wang J, et al. ASCO 2021

ADCs in earlier treatment strategies

Sacituzumab Govitecan

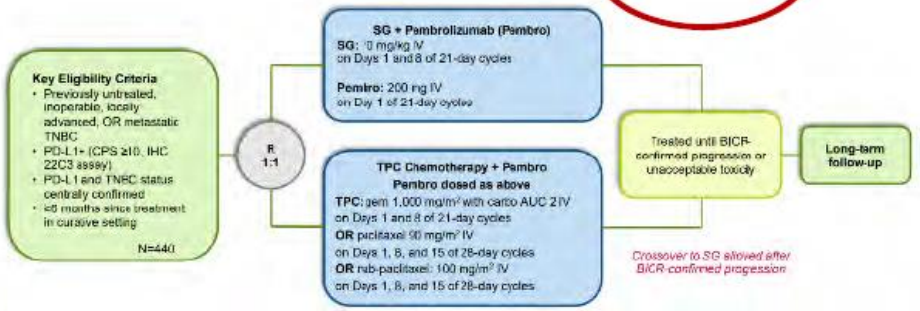
ASCENT-03 (NCT05382299)

Sacituzumab Govitecan vs TPC for 1L PDL1-



ASCENT-04 (NCT05382286)

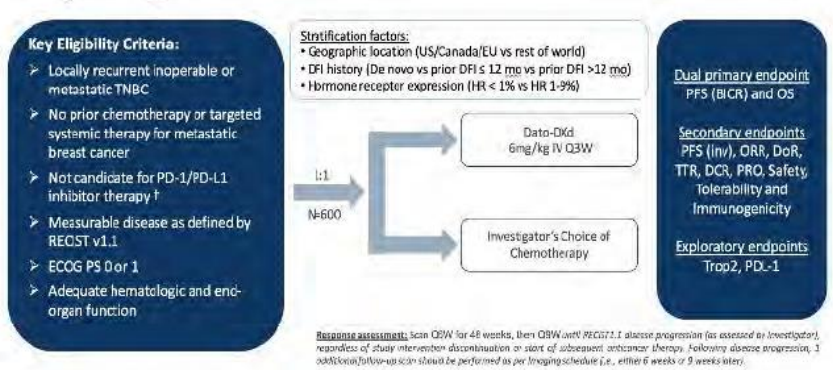
SG + Pembro vs Pembro + CT for 1L PDL1+



1st line Datopotamab Deruxtecan

TROPION-Breast02 (NCT05374512)

Dato-DXd vs TPC 1L mTNBC not candidate for anti-PD-(L)1 therapy
Including subset of early relapsers and CNS mets



TIP Dent R et al. SABCS 2022

TROPION-BREAST 05

Key Eligibility Criteria
- Previously untreated locally recurrent inoperable or metastatic TNBC
- ECOG PS 0 or 1
- Measurable disease as defined by RECIST 1.1
- Adequate haematologic and end-organ function
- PD-L1 centrally confirmed
- PD-L1 positive by 22C3 assay CPS ≥ 10 IHC
- No systemic steroids
- No active autoimmune diseases
- No active brain metastases
- DFI ≥ 6 months since treatment in curative setting
- Prior PD-1/PD-L1 treatment for early stage TNBC allowed

Stratification Factors
- DFI history (de novo versus prior DFI 6 to 12 months[a] versus prior DFI > 12 months)
- Geographic location (US/Canada/Europe versus Dato-DXd Monotherapy Enrolling Countries versus Rest of World)
- Prior PD-1/PD-L1 treatment for early stage TNBC (yes versus no)

N=625

1:1:1[c]

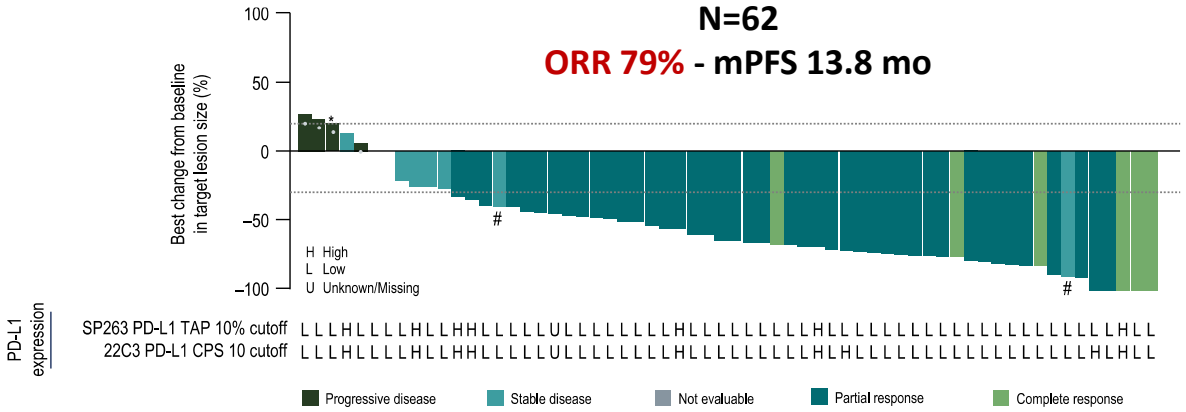
Arm 1
Dato-DXd
6.0 mg/kg IV Q3W
+
Durvalumab
1120 mg IV Q3W
(n=275)

Arm 2
Investigator's Choice Chemotherapy[b]
+
Pembrolizumab
200 mg IV Q3W
(n=275)

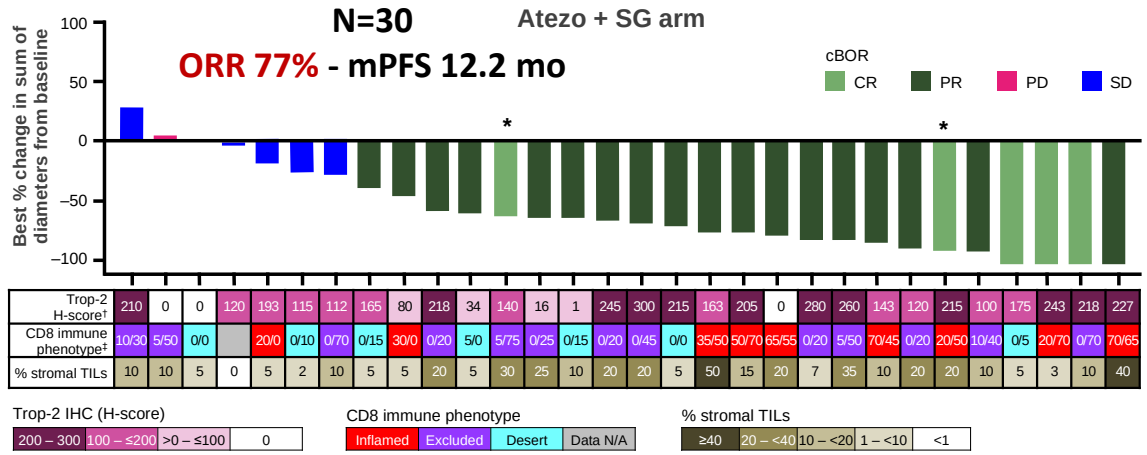
Arm 3
Dato-DXd
6.0 mg/kg IV Q3W
(n=75)[d]

Combining ADCs and immune-checkpoint inhibitors

BEGONIA Trial
Dato-DXd + Durvalumab
in 1st line mTNBC



Morpheus-PAN BC Trial
Sacituzumab Govitecan + Atezolizumab
in PD-L1+ 1st line mTNBC



Antitumour responses were observed **regardless of PD-L1 expression** level as assessed by 2 separate PD-L1 assays and scoring methods

Schmid et al, ESMO 2023

Schmid et al, ESMO Breast 2024

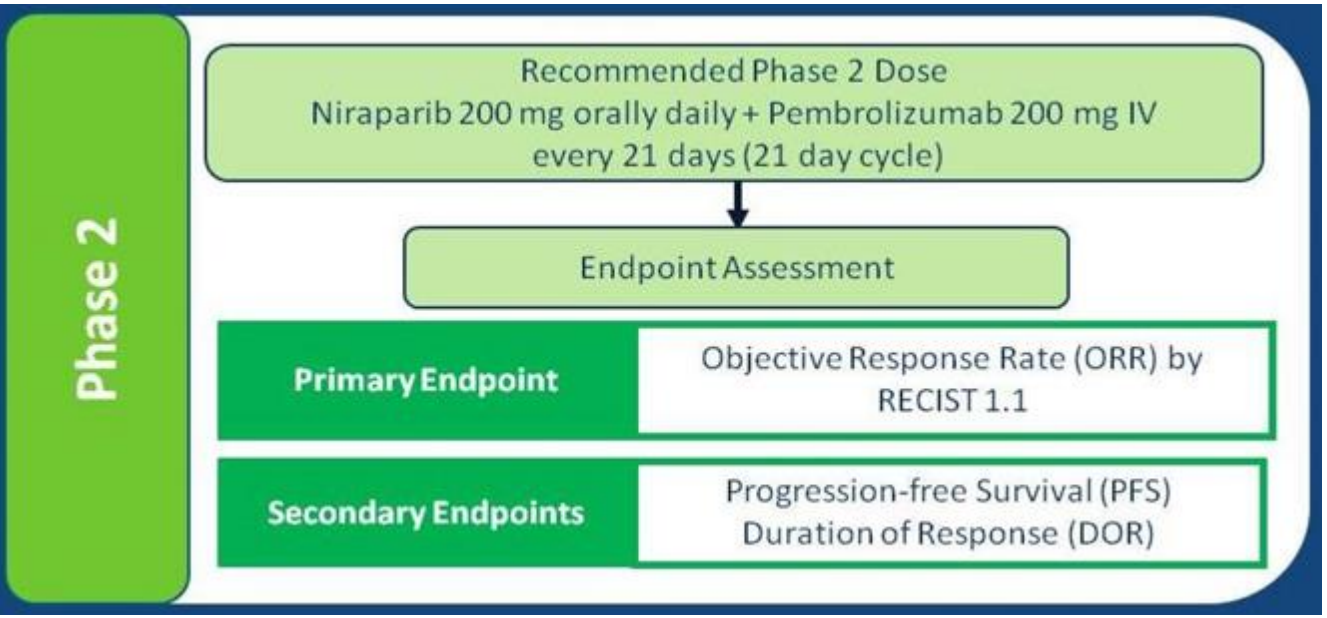
MEDIOLA & TOPACIO trials

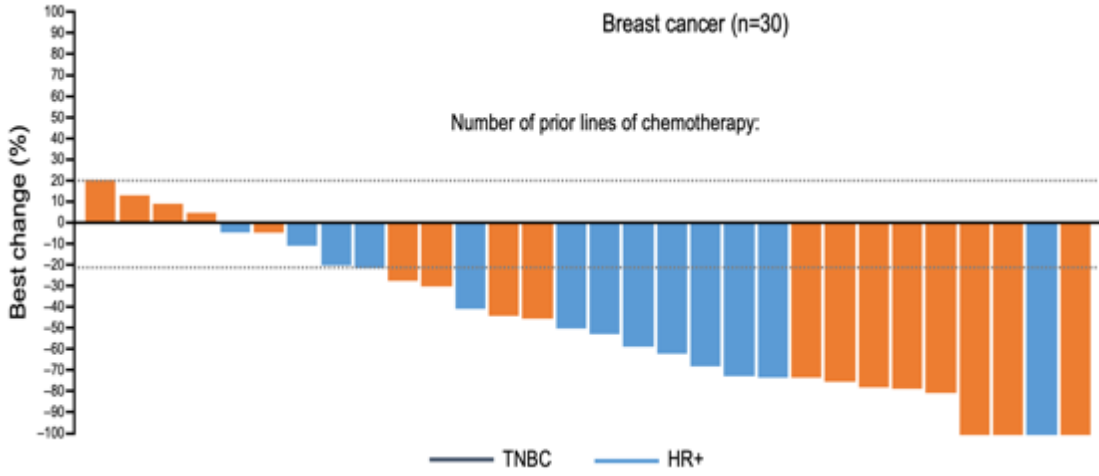
HER2– MBC
gBRCAm
≤2 prior lines of chemotherapy
PARPi and IO naïve

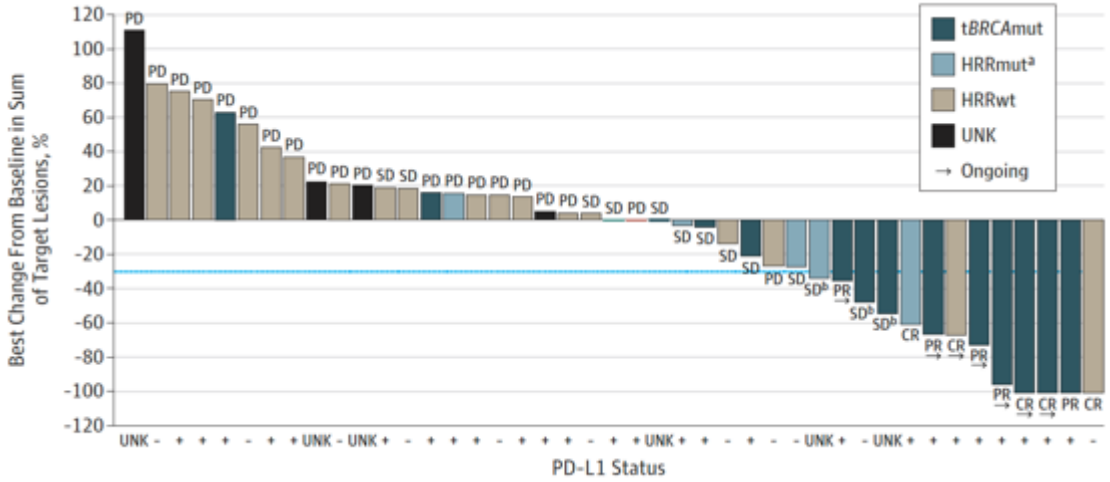
Olaparib 300 mg po bid

4w run in

Durvalumab 1.5 g IV q4w



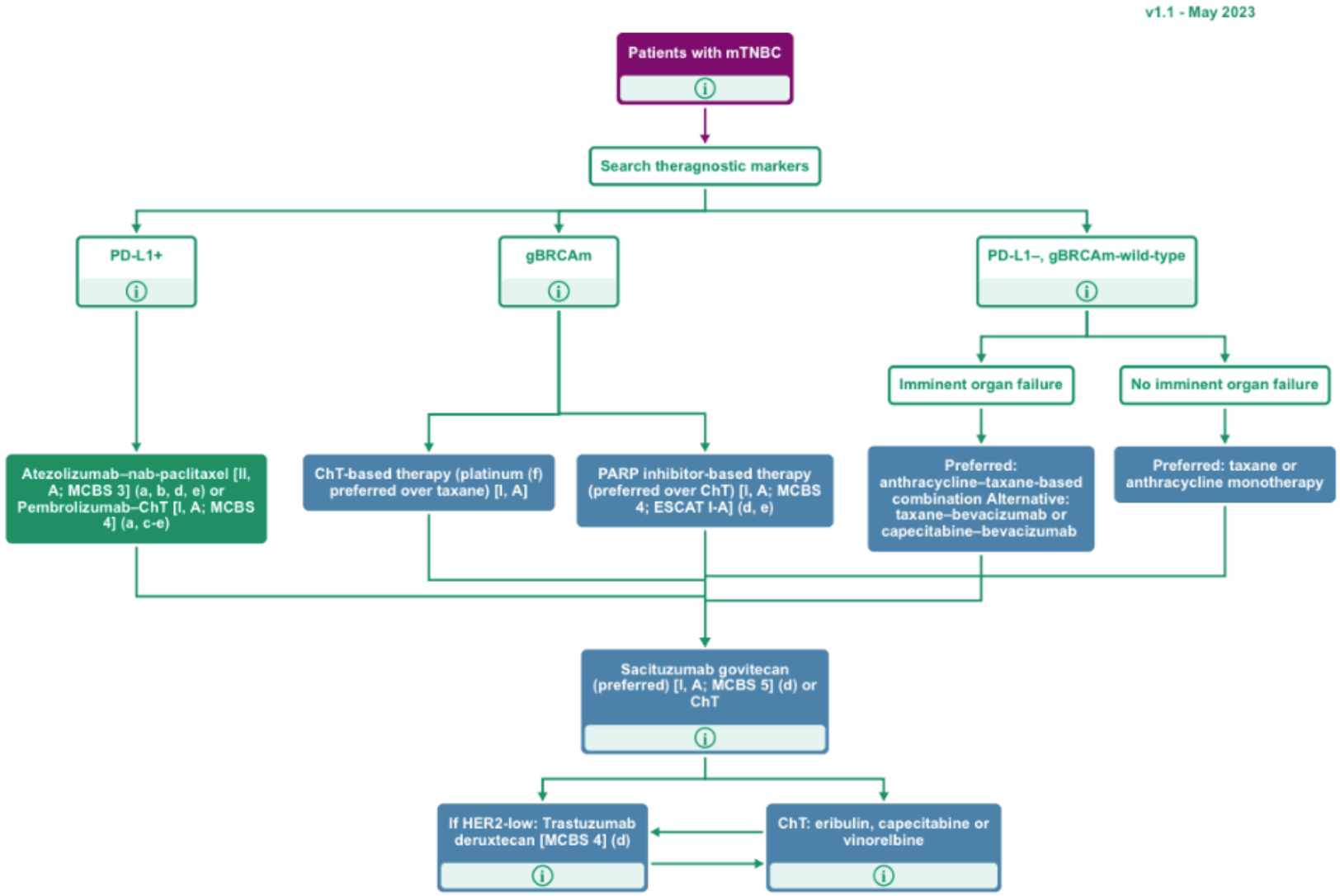




However, MOR to PARPi well described e.g. reversion mutations, restoration fork stability, upstream alternate repair MOA

Domchek S. et al. Lancet Oncology 2020; Vinayak et al JAMA Onc 2019; Dias NRCO 2021

Triple-negative Metastatic Breast Cancer



Studies testing frontline ADC +/- IO are ongoing and might change this algorithm in the near future

Patients who relapse after (neo)adjuvant CT + IO represent a relevant clinical unmet need

ESMO Living Guidelines. Accessed Feb 2025

Thank you

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