Triple Negative Breast Cancer Updates

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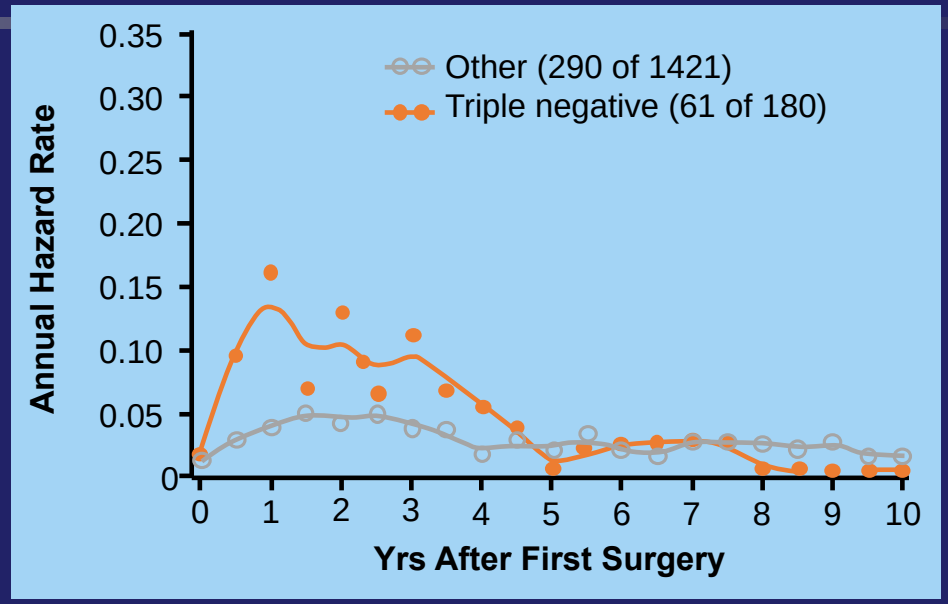
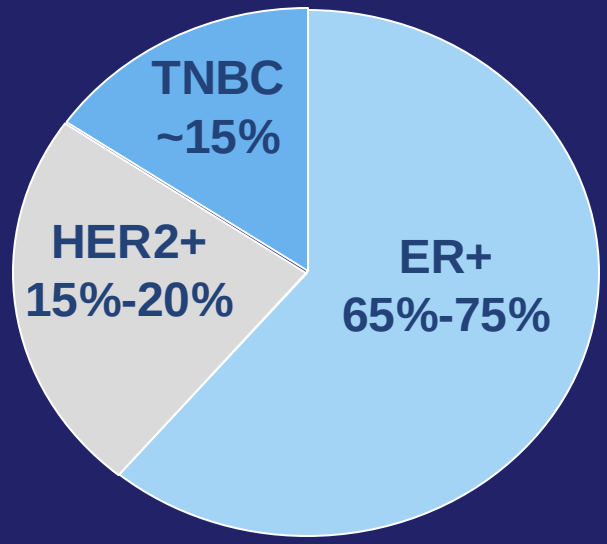
Triple Negative Breast Cancer

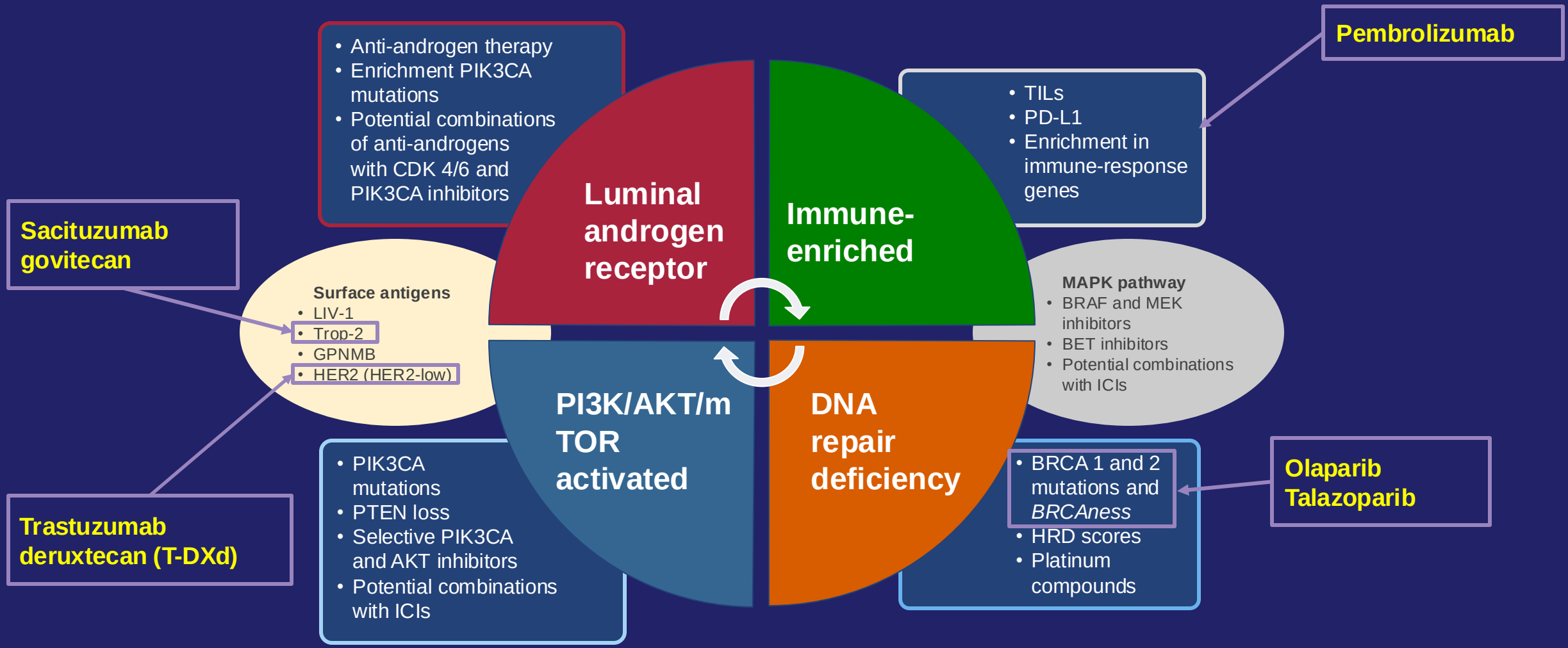
- 10-15% of all breast cancer, defined by what it is not
- Heterogeneous disease
  - Highly proliferative, usually chemotherapy responsive
  - Rapid development of resistance
- High risk of early recurrence, esp first 5 years
  - Visceral dominant disease, early/frequent brain metastases
  - Short median survival (<2yrs) after diagnosis of metastases
- Generally affects younger women; Black women have a higher proportion of TNBC than other races
- Rare indolent subtypes, generally in older women
- *P53* mutations common; may be associated with *BRCA1* mutations and/or *BRCA* pathway dysfunction





Lin NU, et al. *Cancer.* 2008;113:2638-2645; Liedtke C, et al. *J Clin Oncol*. 2008;26:1275-1281' Dent R, et al. *Clin Cancer Res*. 2007;13:4429-4434; Ahn SG et al. *J Breast Cancer*. 2016;19(3):223-30.

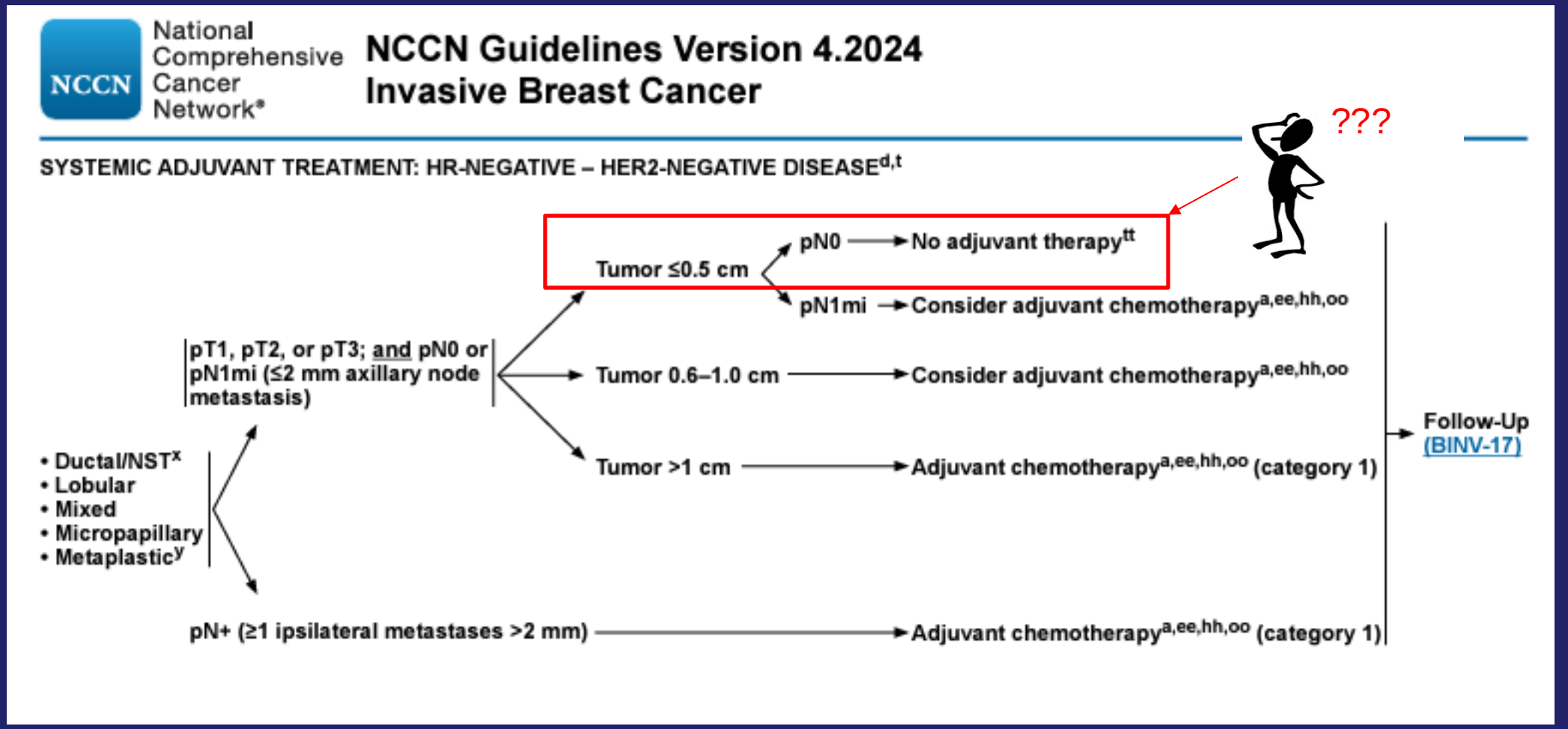
Biomarker-Driven Therapies Are Becoming a Reality



Marra A, et al. *NPJ Breast Cancer*. 2020;6:54.

Early Stage Disease

NCCN Guidelines for When to Use Chemotherapy for TNBC



Benefits of Neoadjuvant Therapy

- Increases chance breast conservation
- Treatment response provides prognostic information for TNBC, allows change in therapy if no response
- Allows time for genetic testing
- Allows time to plan reconstruction
- Allows time for delayed decision making regarding definitive surgery
- May allow SLNB alone if cN+ becomes cN0
- Excellent research platform; those with residual disease may be candidates for adjuvant clinical trial
- Consider for cT1c+, or node positive TNBC
- Do not use if extensive *in situ* disease limits ability to tell extent of invasive disease, poorly evaluable tumors

Standard Preoperative Neoadjuvant Therapy

- **Preoperative pembrolizumab + chemotherapy followed by adjuvant pembrolizumab[4]**
  - Preoperative:
    - ◊ Pembrolizumab 200 mg IV Day 1
    - ◊ Paclitaxel 80 mg/m^2 IV Days 1, 8, 15
    - ◊ Carboplatin AUC 5 IV Day 1

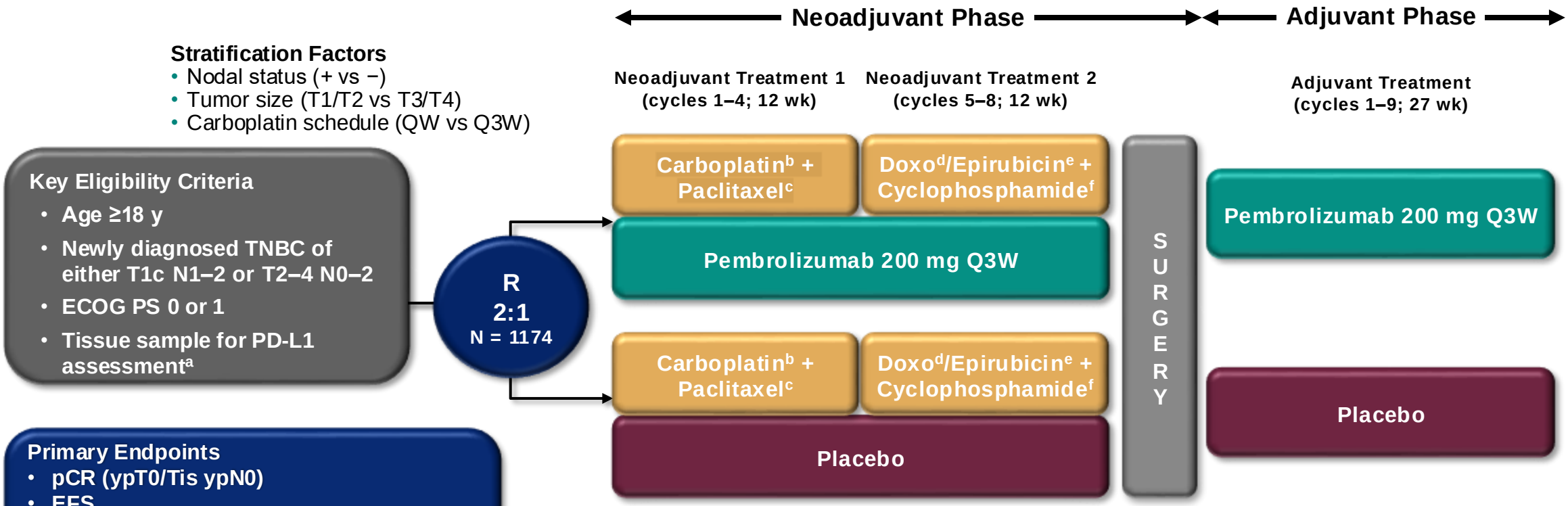
      Or
    - ◊ Carboplatin AUC 1.5 IV Days 1, 8, 15
      - – Cycled every 21 days x 4 cycles (cycles 1–4)

    Followed by:
    - ◊ Pembrolizumab 200 mg IV Day 1
    - ◊ Doxorubicin 60 mg/m^2 IV Day 1 or Epirubicin 90 mg/m^2 IV Day 1
    - ◊ Cyclophosphamide 600 mg/m^2 IV Day 1
      - – Cycled every 21 days x 4 cycles (cycles 5–8)

    Followed by:
  - Adjuvant pembrolizumab 200 mg IV Day 1
    - ◊ Cycled every 21 days x 9 cycles

- Based on KEYNOTE 522 Trial
- Regardless of PD-L1 status
- Consider for cT1, cN0 or higher TNBC
- Pembrolizumab continued to complete full year after surgery regardless of surgical outcome

KEYNOTE-522 Study Design (NCT03036488)

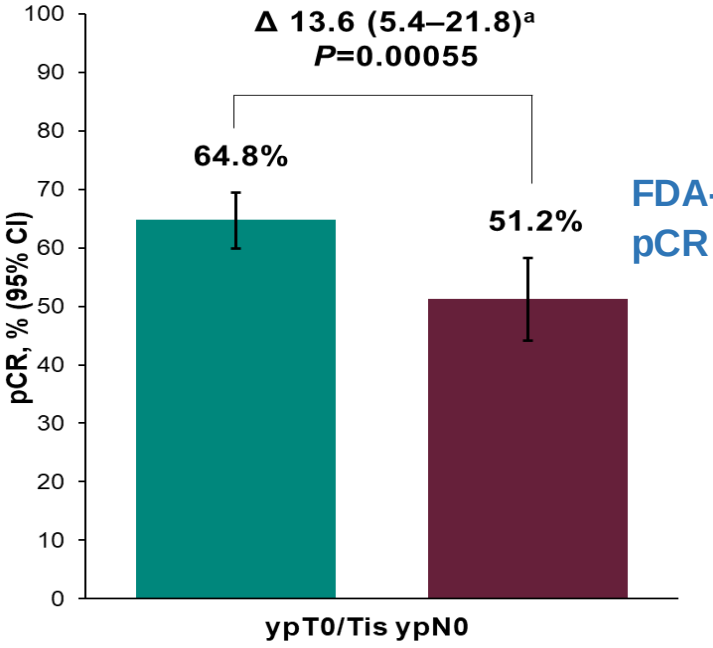


Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (posttreatment included)

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

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

KEYNOTE-522

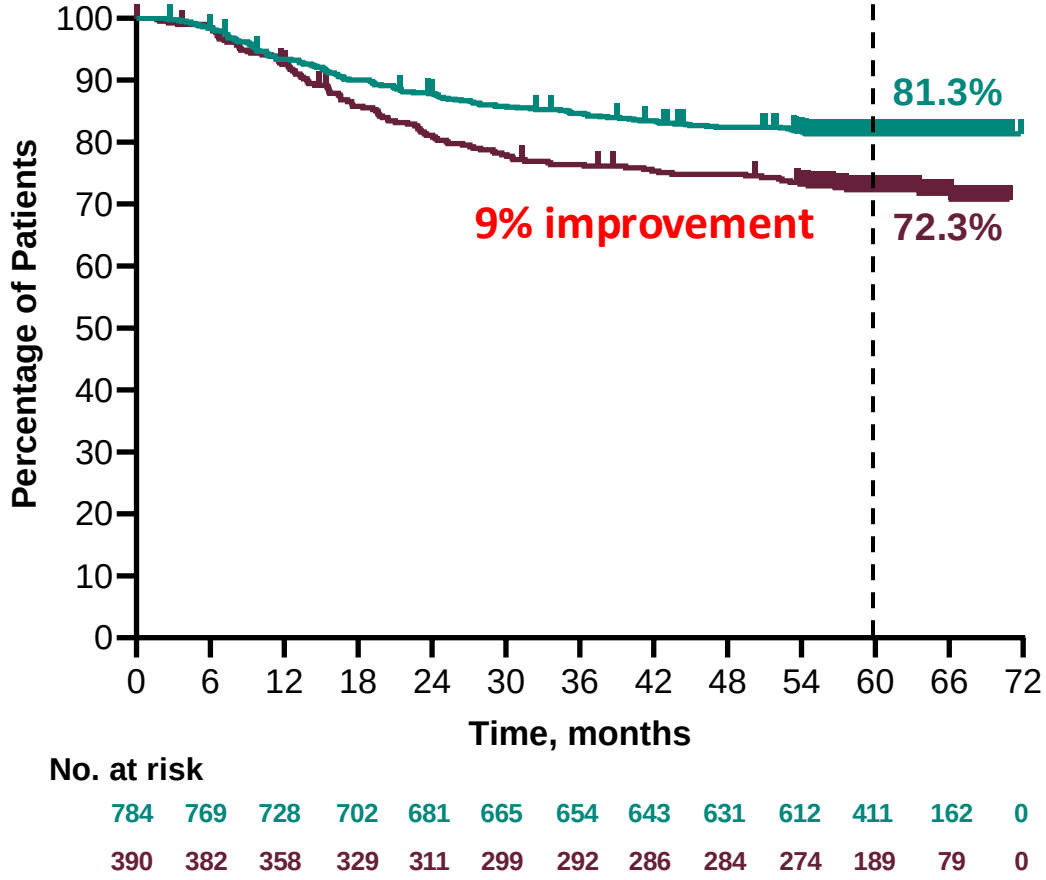


FDA-report
pCR △7.5

Keynote-522:
PDL1 Status does NOT predict Benefit from Pembro

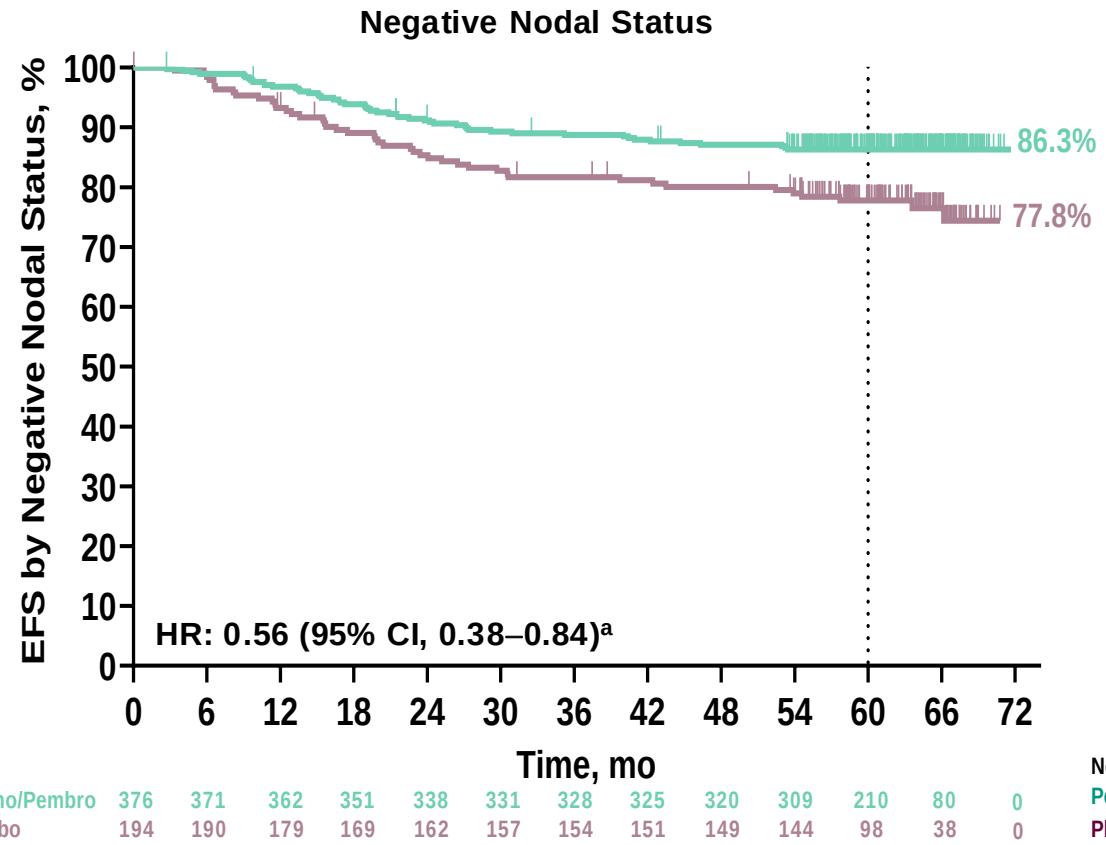
Schmid et al NEJM 2020 ,Schmid et al NEJM 2022, Schmid SABCS 2023

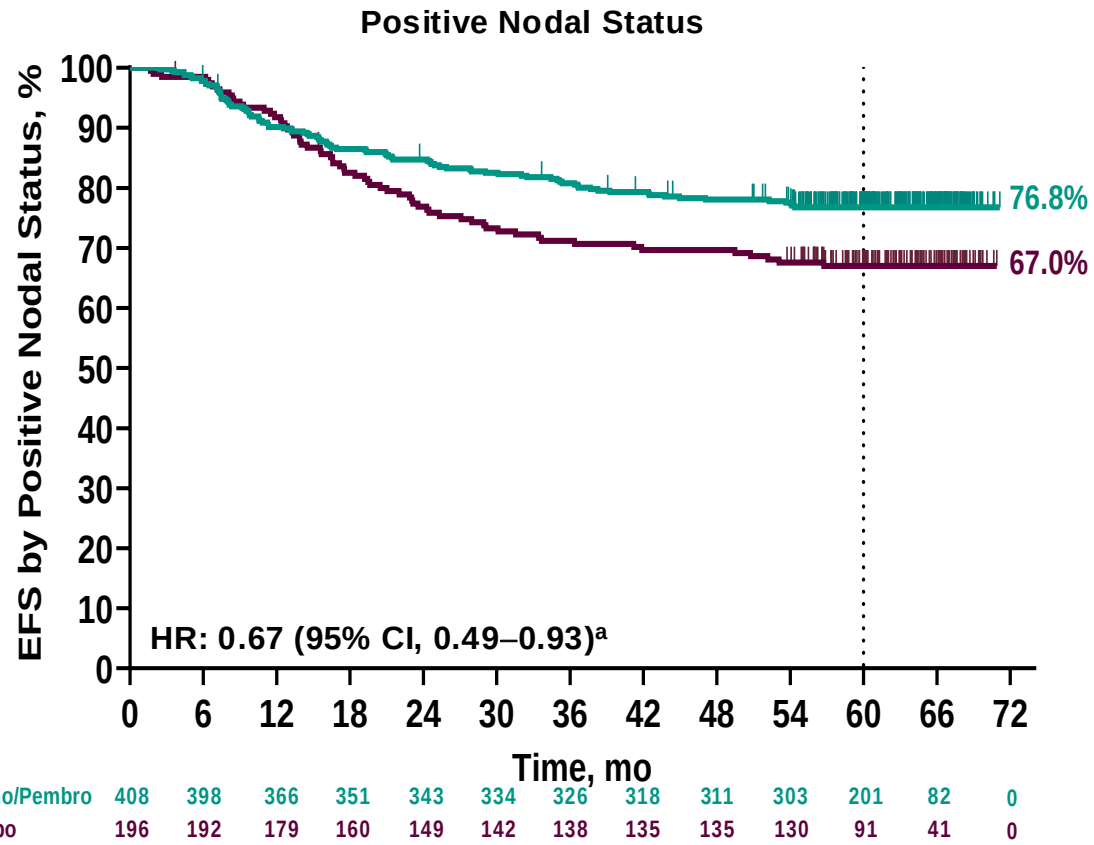
IA6[b]	Events	HR (95% CI)
Pembro + Chemo/Pembro	18.5%	0.63[c] (0.49–0.81)
Placebo + Chemo/Placebo	27.7%	



7/2021, the FDA granted approval to pembrolizumab in combination with chemotherapy for neoadjuvant treatment and then continued as a single agent for adjuvant treatment for patients with high-risk, early-stage TNBC

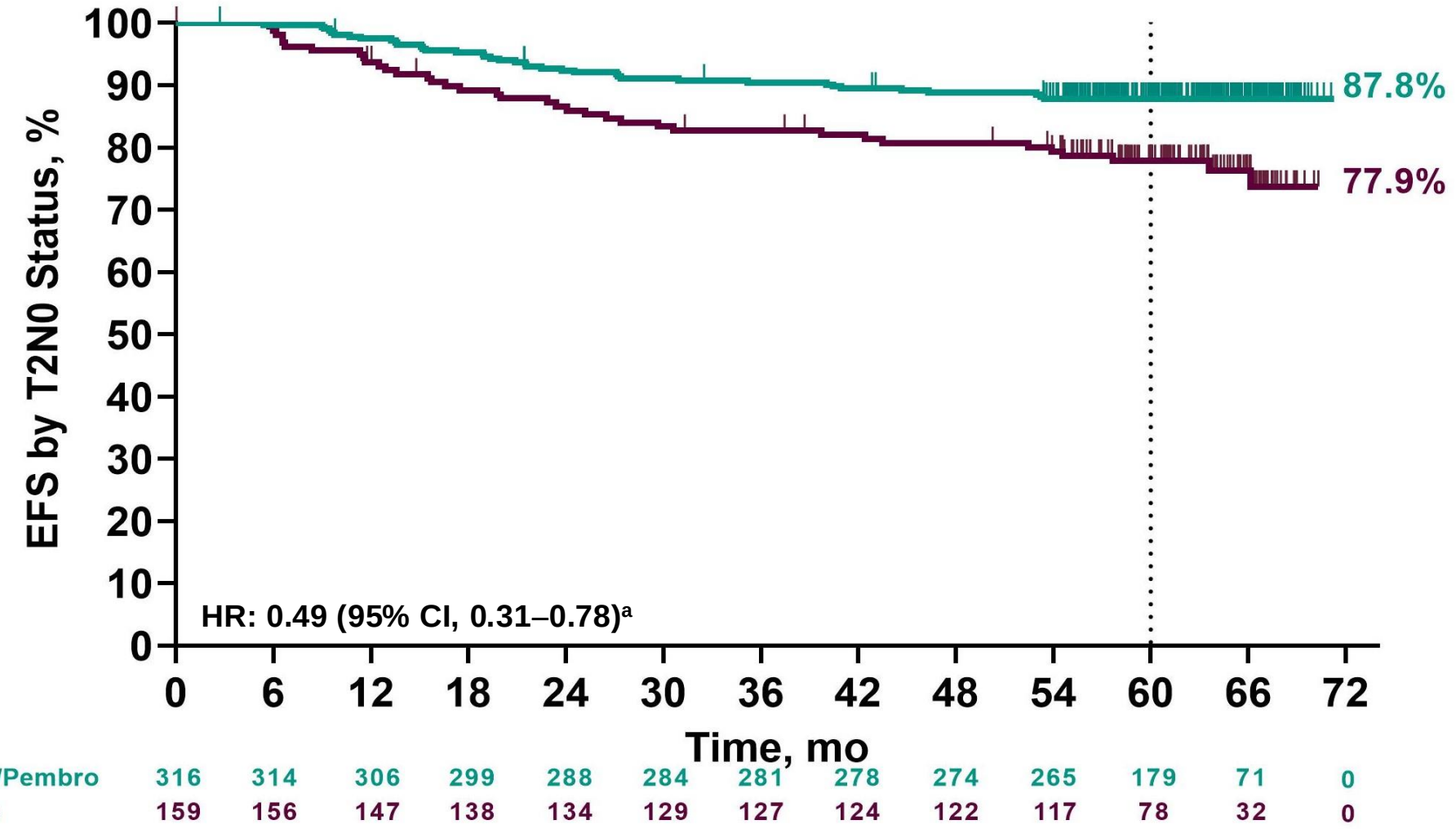
EFS at IA6 by Baseline Clinical Nodal Status





[a]Hazard ratio (95% CI) analyzed based on the unstratified Cox model.
Data cutoff date of March 23, 2023.

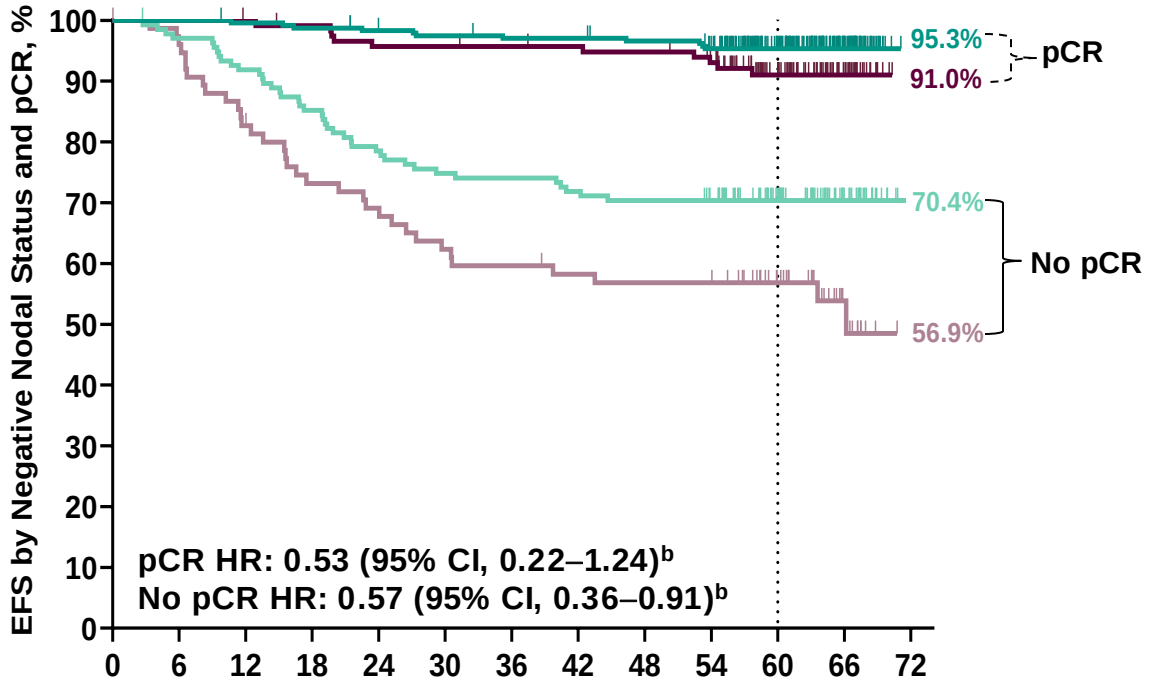
EFS at IA6 in Patients With Baseline T2N0



[a]Hazard ratio (95% CI) analyzed based on the unstratified Cox model.
Data cutoff date of March 23, 2023.

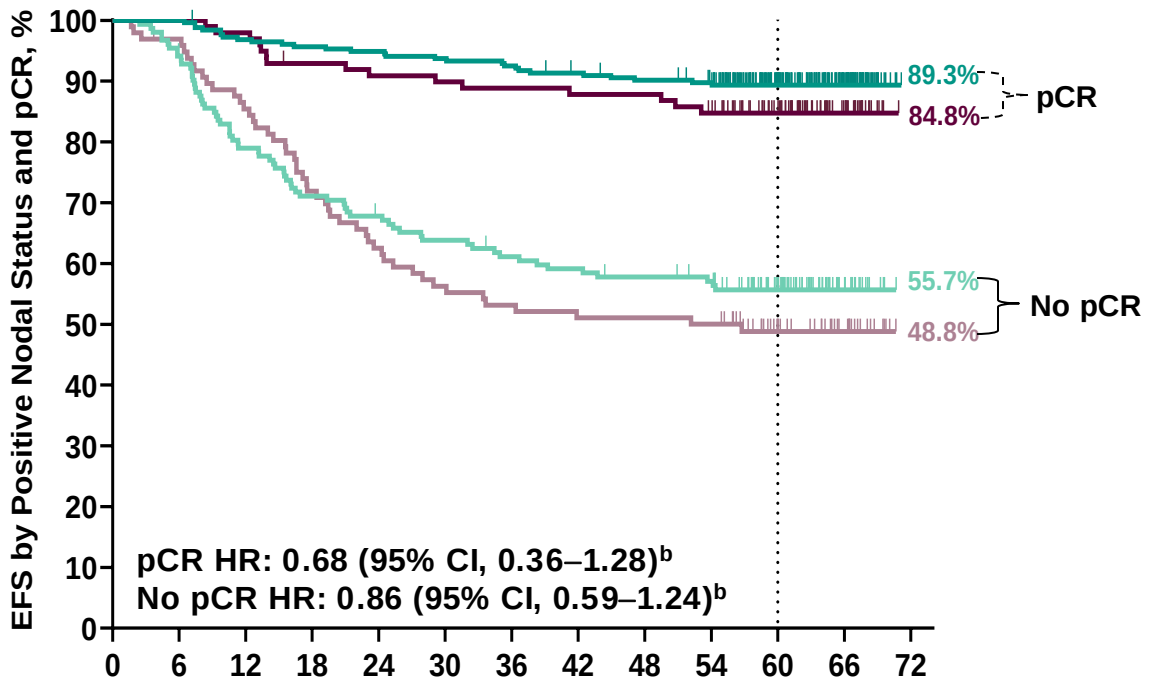
EFS at IA6 by Baseline Clinical Nodal Status in Patients With and Without pCR

Negative Nodal Status by pCR Status[a]



No. at risk													
Pembro + Chemo/Pembro pCR	240	240	238	236	232	230	228	228	225	218	149	55	0
Pbo + Chemo/Pbo pCR	118	118	117	115	111	111	110	109	108	103	70	28	0
Pembro + Chemo/Pembro no pCR	136	131	124	115	106	101	100	97	95	91	61	25	0
Pbo + Chemo/Pbo no pCR	76	72	62	54	51	46	44	42	41	41	28	10	0

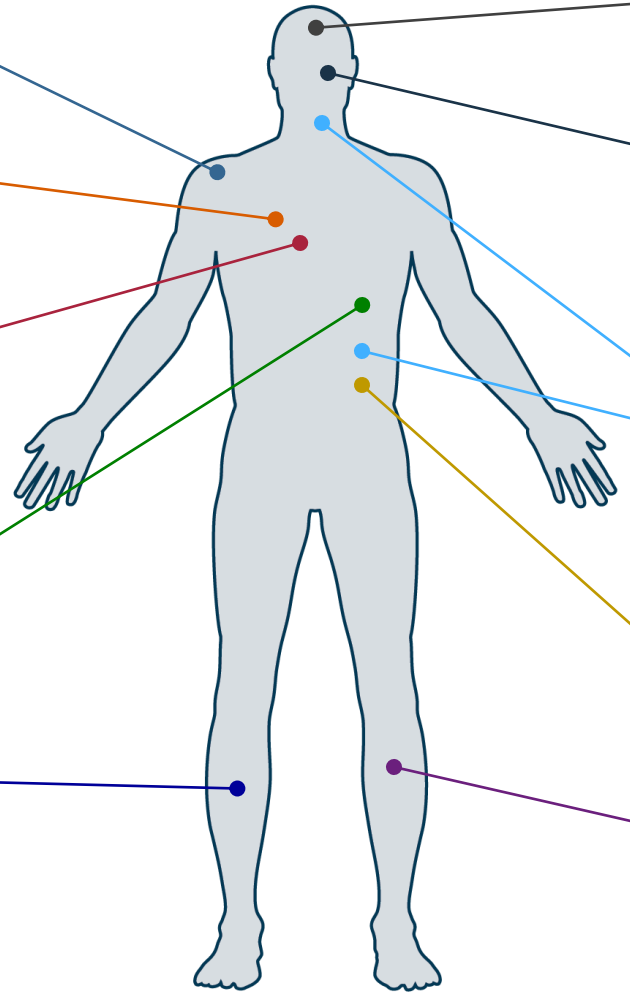
Positive Nodal Status by pCR Status[a]



No. at risk													
Pembro + Chemo/Pembro pCR	255	255	246	243	241	238	235	230	226	221	146	65	0
Pbo + Chemo/Pbo pCR	99	99	97	91	89	88	87	86	86	82	60	25	0
Pembro + Chemo/Pembro no pCR	153	143	120	108	102	96	91	88	85	82	55	17	0
Pbo + Chemo/Pbo no pCR	97	93	82	69	60	54	51	49	49	48	31	16	0

[a]Post-hoc exploratory analyses, non-randomized comparison. [b]Hazard ratio (95% CI) analyzed based on the unstratified Cox model.
Data cutoff date of March 23, 2023.

Immune-Related Adverse Events



Dermatologic
Rash
Pruritis
Mucositis
Xerostomia
Vitiligo*
Bullous pemphigoid
Drug reaction with eosinophilia and systemic symptoms
Steven-Johnson syndrome
Acute generalized exanthematous pustulosis
Dermatomyositis

Pulmonary
Pneumonitis
Sarcoidosis
Pleural effusion
Reactive airway disease

Cardiovascular
Myocarditis
Pericarditis
Arrhythmia
Heart failure
Accelerated atherosclerosis

Gastrointestinal
Diarrhea
Colitis
Hepatitis
Gastritis
Enteritis
Pancreatitis

Marrow
Thrombocytopenia
Hemolytic anemia
Neutropenia
Aplastic anemia
Pure red cell aplasia
Hemophagocytic lymphohistiocytosis

Neurotoxicity
Encephalitis
Aseptic meningitis
Posterior reversible Encephalopathy syndrome
Demyelinating diseases
Cranial nerve syndromes
Polyneuropathies
Sensory/ small fiber/ autonomic neuropathies
Guillain-Barre syndrome
Not otherwise specified (ataxia, movement disorders)

Ocular
Uveitis
Scleritis
Retinitis
Conjunctivitis
Keratoconjunctivitis sicca
Blepharitis

Endocrine
Hypothyroidism
Hyperthyroidism
Hypophysitis
Hypoparathyroidism
Type 1 diabetes
Adrenal insufficiency

Renal
Nephritis

Musculoskeletal
Arthralgias
Myalgias
Arthritis
Myositis
Vasculitis

- **≥ 10% incidence**
- ≥ 1 and < 10% incidence
- < 1% incidence
- * ≥ 10% in melanoma

ICIs
- Ipilimumab
- Pembrolizumab
- Nivolumab
- Atezolizumab
- Avelumab
- Durvalumab
- Cemiplimab
- Dostarlimab

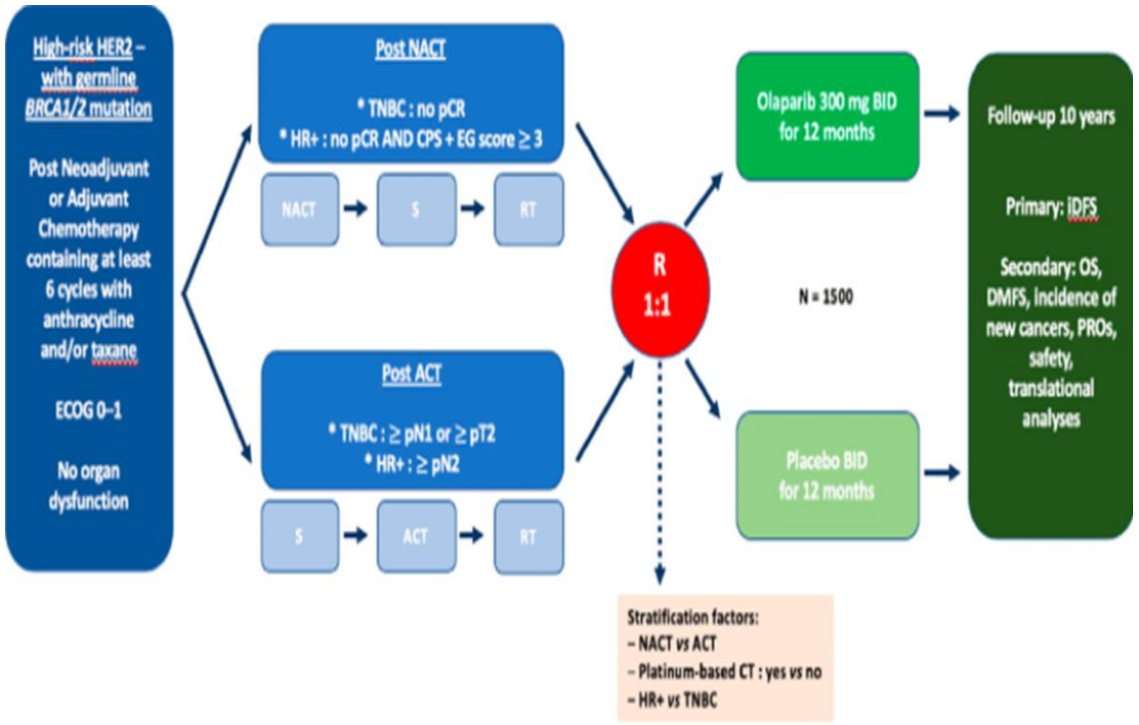
irAE, immune-related adverse event.

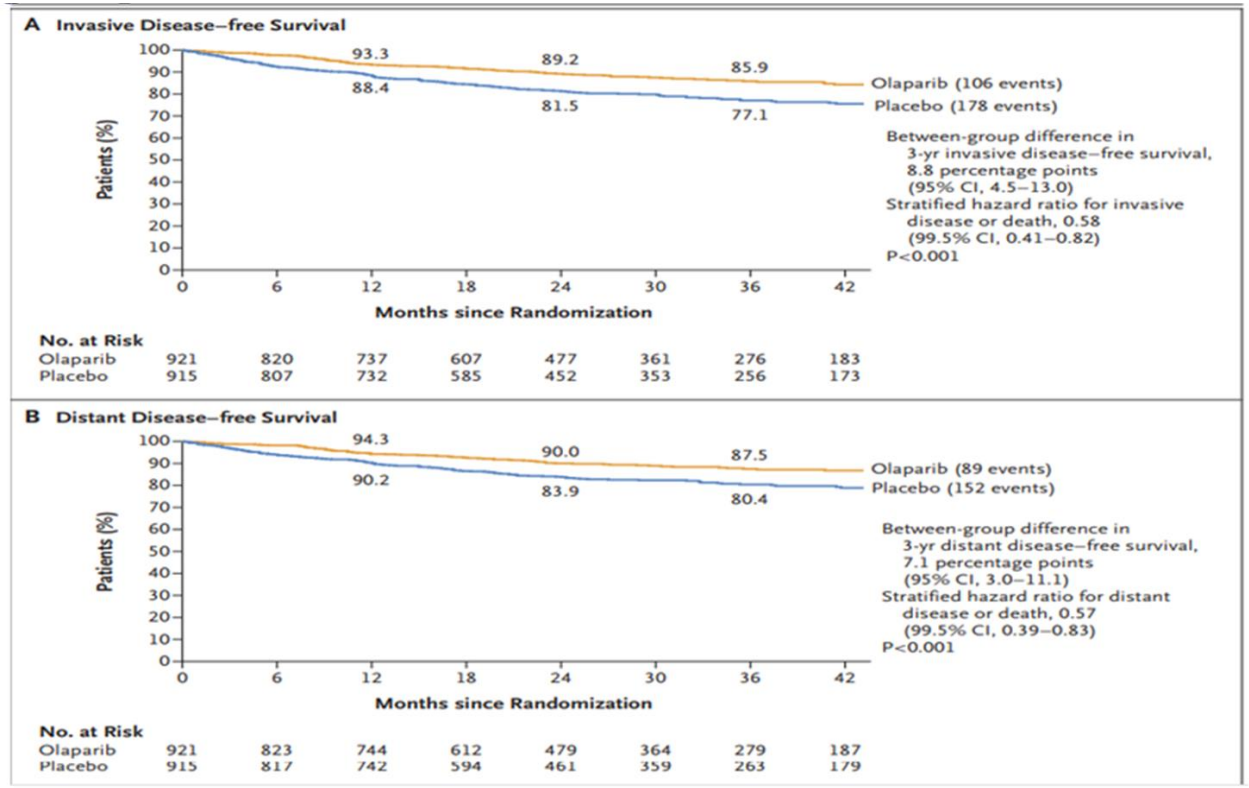
Darnell EP, et al. *Curr Oncol Rep*. 2020;22:3.9.

Adjuvant PARPi in Germline *BRCA1/2* mutated TNBC

OLYMPIA

PARPi in gBRCA: OLYMPIA



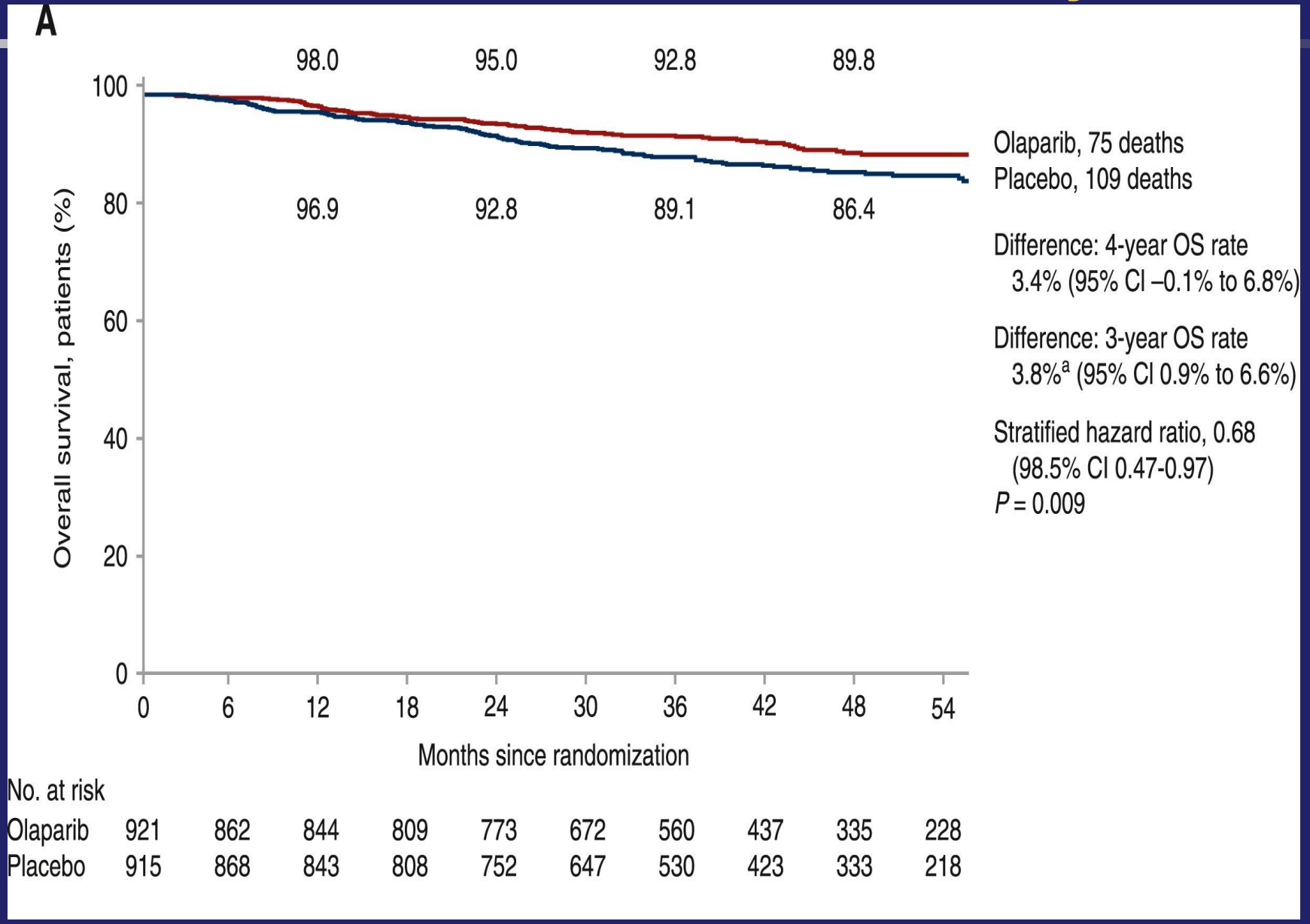


Δ 8.8%

Δ7.1%

Tutt et al, NEJM 2021; Tutt et al ESMO plenary 2022.
Geyer CE, et al. *Ann Oncol*. 2022;33:1250-1268.

OLYMPIA: Overall Survival with Adjuvant Olaparib



Unanswered question:

Should we give olaparib plus pembrolizumab in one who has residual disease following neoadjuvant KN522 regimen?

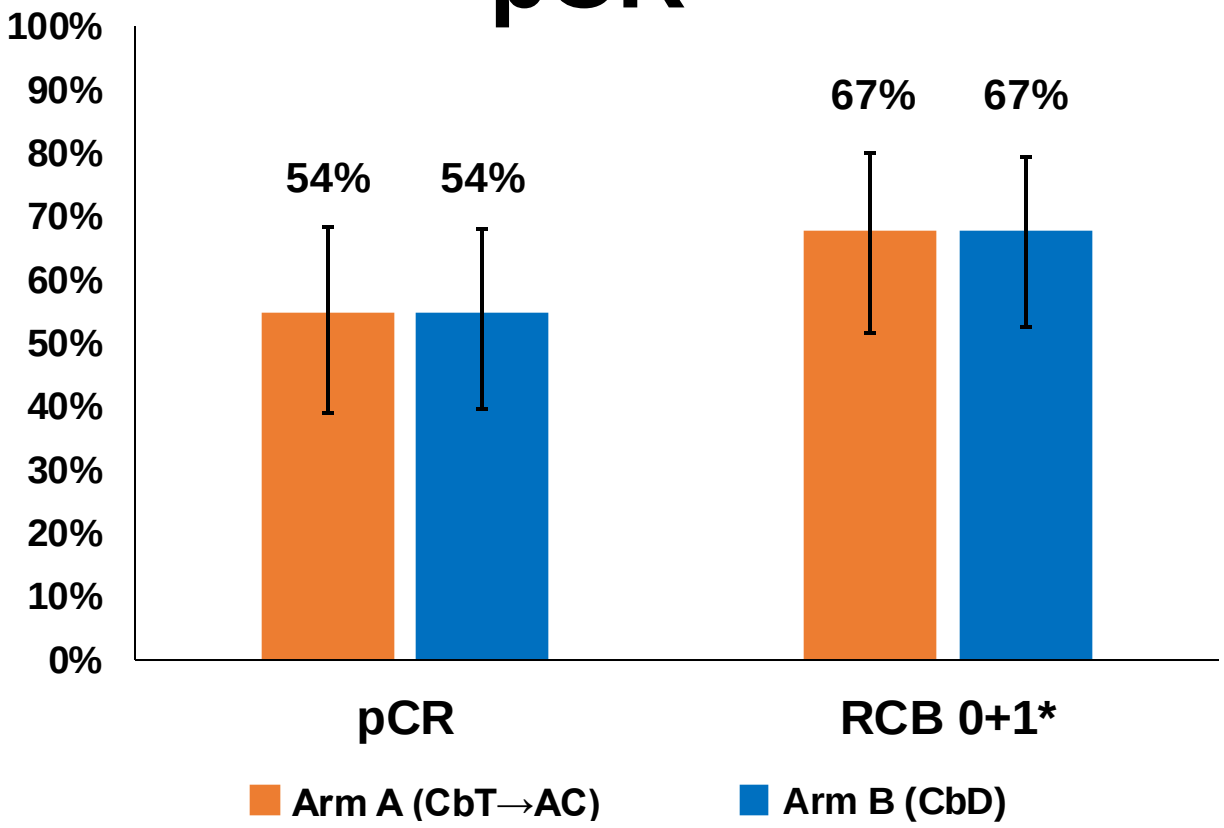
Geyer CE, et al. *Ann Oncol*. 2022;33:1250-1268.

Unanswered Question

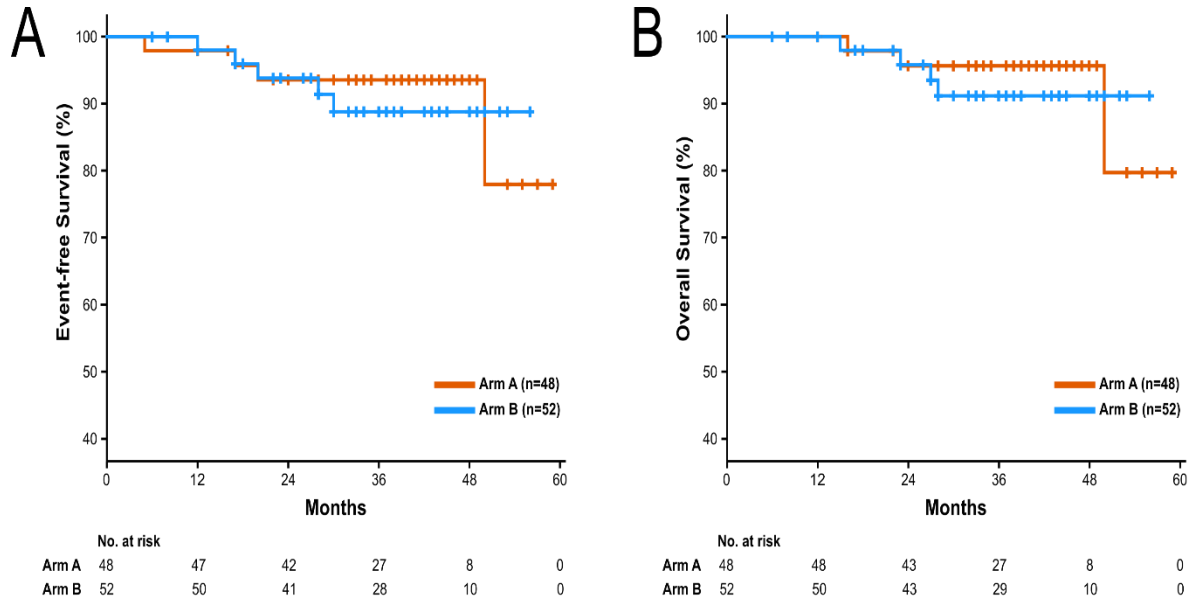
Do we need to use the anthracycline?

NeoSTOP:
pCR similar with 6 cycles of Cb+Tax and CbTax→AC

pCR



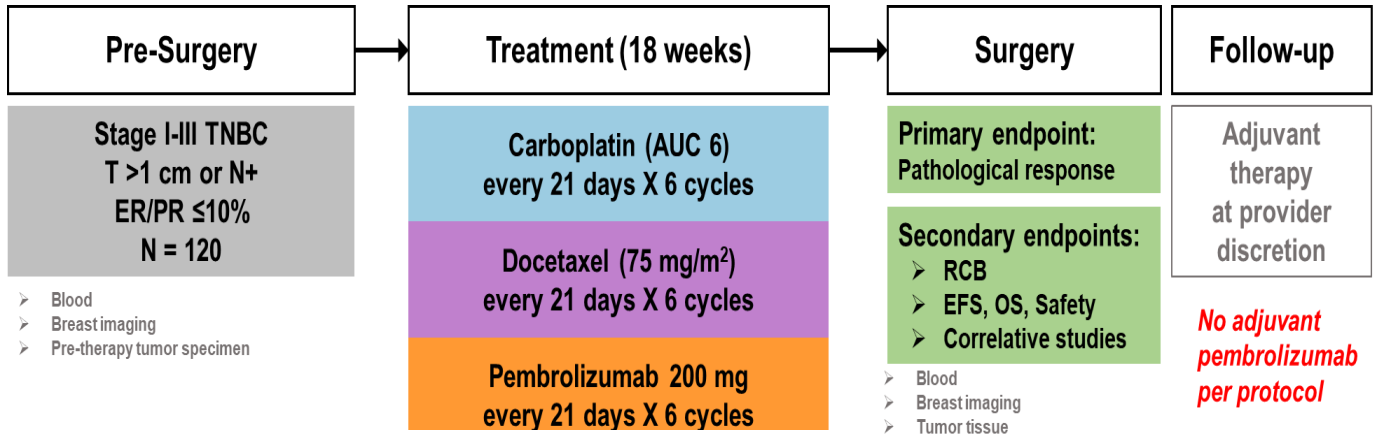
EFS and OS

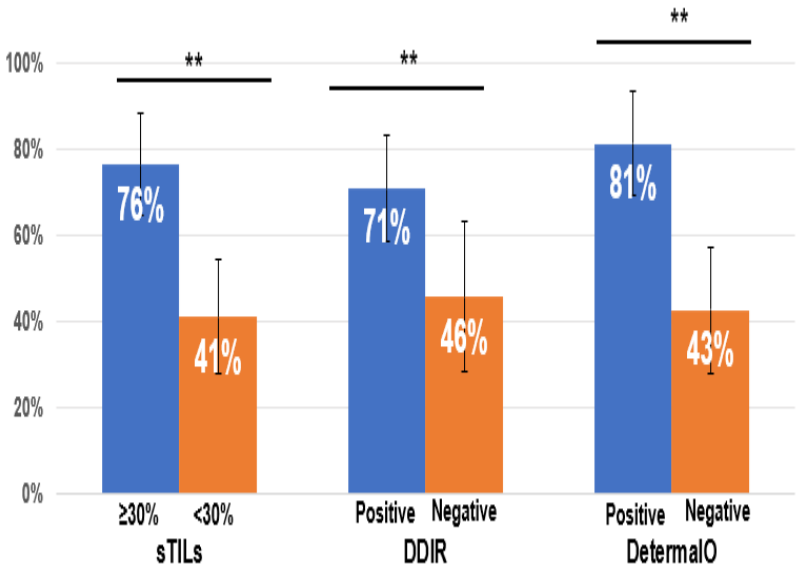


Compared to 4 drug CbP→AC regimen, the two-drug CbD regimen was associated with more favorable toxicity profile and lower treatment associated cost.

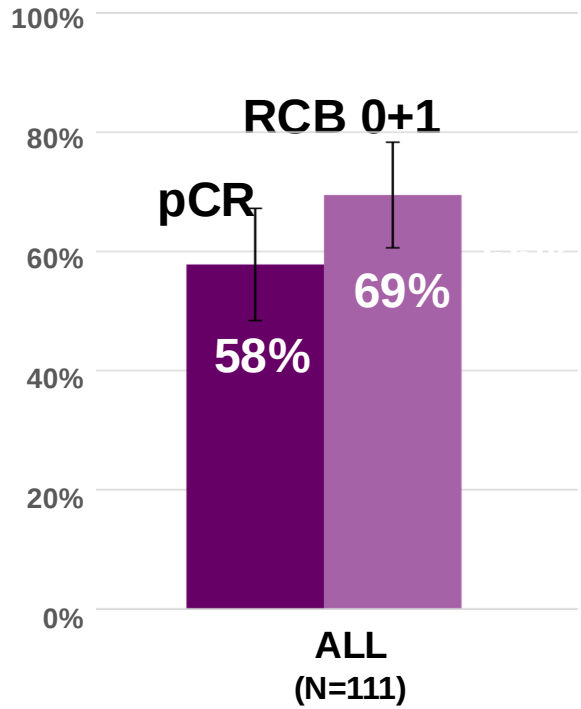
Sharma P et al CCR, Feb 2021

NeoPACT: Neoadjuvant phase II study of pembrolizumab and carboplatin plus docetaxel in TNBC





Immune enrichment assessed by sTILs was noted in almost 50% of patients and was associated with high pCR rates exceeding 75%.

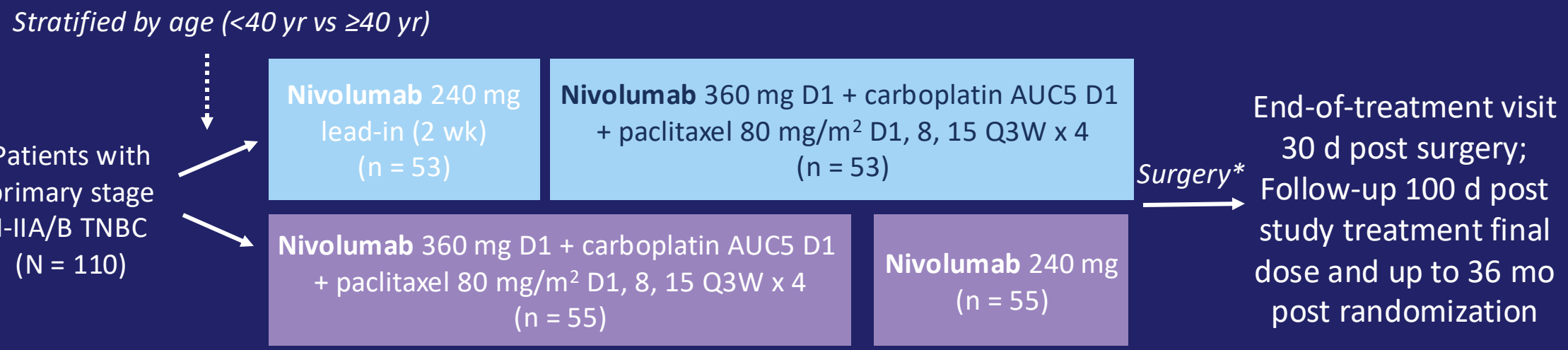


- No patients had disease progression during neoadjuvant treatment.
- **pCR in TNM stage I, II, and III disease was 69%, 59%, and 43%, respectively.**

Sharma et al ASCO 2022

BCT1902/IBCSG 61-20 Neo-N: Study Design

- Multicenter, randomized, noncomparative phase II trial



- Primary endpoint: pCR (ypT0/is ypN0)
- Secondary endpoints: EFS, RCB, pCR by PD-L1 expression and TIL status, safety

Loi. SABCS 2023. Abstr LBA01-03.

BCT1902/IBCSG 61-20 Neo-N: pCR

pCR, %	Lead-in With Nivolumab (n = 53)	Concurrent Nivolumab (n = 55)	Total (n = 108)
Overall PCR (90% CI)	51 (39-63)	54 (43-66)	53 (44-61)
PCR based on Tumor stage: ▪ I ▪ II	 NR NR	 NR NR	 49 55
TILs: ▪ High ▪ Low	 72 NR	 61 NR	 67 46
PD-L1: ▪ ≥1% ▪ <1%	 70 NR	 71 NR	 71 33
RCB 0-1	64	73	69

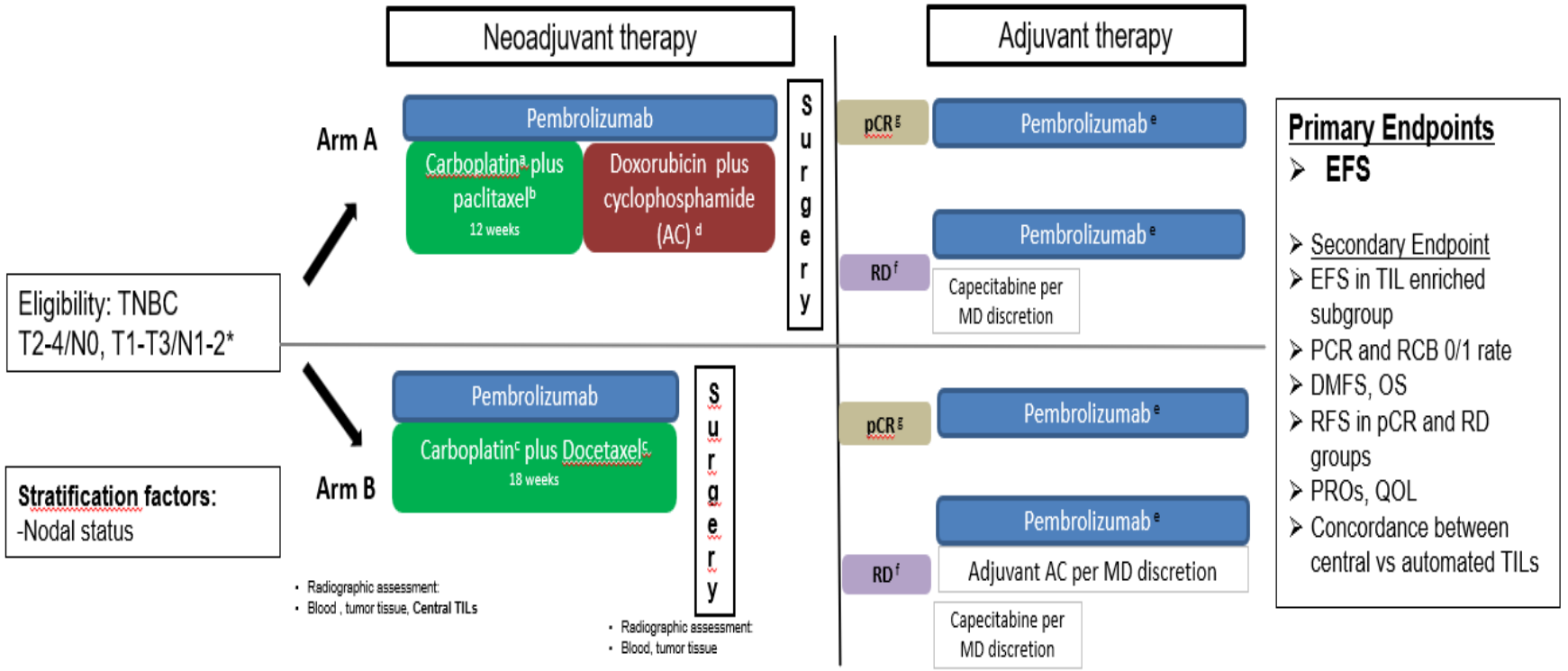
- High TILs only predictor of pCR in multivariable logistic regression model (OR: 2.47)

Loi. SABCS 2023. Abstr LBA01-03.

Ongoing SWOG 2212: Shorter anthracycline-free Chemoimmunotherapy Adapted to pathological Response in Early TNBC (SCARLET)

Randomized non-inferiority trial

Hypothesis: In patients with early stage TNBC, carboplatin-taxane chemoimmunotherapy is non-inferior to taxane-platinum-anthracycline-based chemoimmunotherapy



*T4/N+ , any N3 and inflammatory breast cancer excluded

[a]Carboplatin QW or Q 3W, [b] Paclitaxel QW.

[c] Carboplatin Q3W, Docetaxel Q 3W, [d] AC every 2 or 3 weeks

[e] Total duration of neo plus adjuvant pembrolizumab = 51 weeks

[f] Olaparib per MD discretion in gBRCA allowed

[g] No Further Adjuvant chemotherapy.

PI: P. Sharma and Z. Mitri

SWOG CANCER RESEARCH NETWORK

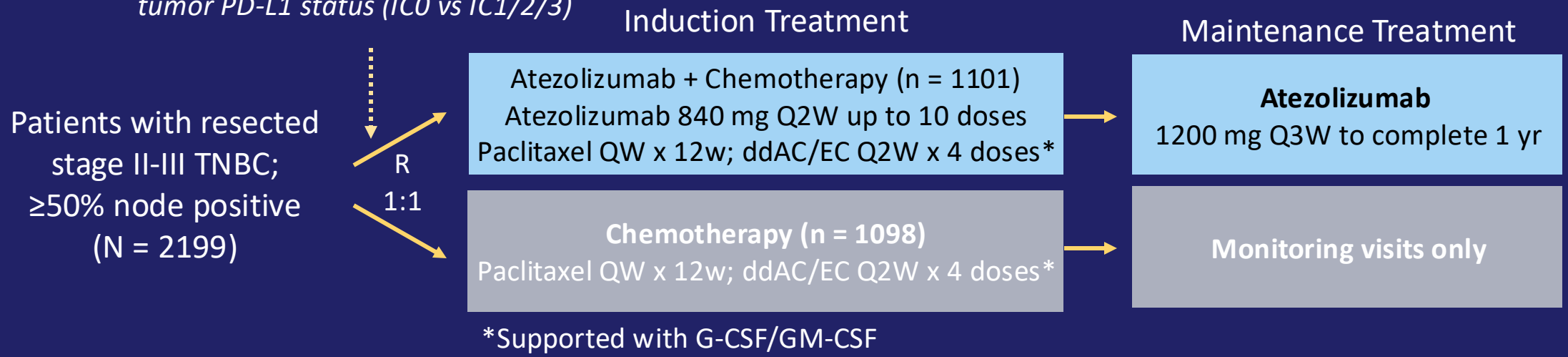
Unanswered Question

Does giving immune therapy in the adjuvant setting benefit patients if not given in the neoadjuvant setting

ALEXANDRA/IMpassion030: Study Design

- Randomized, open-label phase III trial

Stratified by axillary nodal status (0 vs 1-3 vs ≥4 positive LN), surgery (breast conserving vs mastectomy), and tumor PD-L1 status (IC0 vs IC1/2/3)



*Supported with G-CSF/GM-CSF

- **Primary endpoint:** iDFS in ITT population
- **Secondary endpoints:** iDFS in PD-L1–positive and node-positive subpopulations, iDFS including second primary nonbreast invasive cancer, OS, RFI, DRFI, DFS

Ignatiadis. SABCS 2023. Abstr GS01-03.

ALEXANDRA/IMpassion030: Baseline Factors

Characteristic	Atezo + CT (n = 1101)	CT (n = 1098)
Primary tumor stage, n (%)		
▪ pT1-pT2	1024 (93.0)	1045 (95.2)
▪ pT3	71 (6.4)	51 (4.6)
▪ Other*	6 (0.5)	2 (0.2)
Axillary nodal status, n (%)		
▪ 0	577 (52.4)	573 (52.2)
▪ 1-3	390 (35.4)	390 (35.5)
▪ ≥4	134 (12.2)	135 (12.3)
AJCC stage at surgery, n (%)		
▪ II	935 (84.9)	940 (85.6)
▪ III	161 (14.6)	157 (14.3)
▪ Other†	5 (0.5)	1 (<0.1)
Breast-conserving surgery/ mastectomy, %	47.6/52.4	47.6/52.4
PD-L1: IC 0/IC 1, 2, or 3, %	28.7/71.3	28.8/71.2

Ignatiadis. SABCS 2023. Abstr GS01-03.

ALEXANDRA/IMpassion030: Efficacy

Parameter	Atezo + Chemotherapy (n = 1101)	Chemotherapy (n = 1098)	HR (95% CI)	P Value
iDFS events, ITT, n (%)	127 (11.5)	112 (10.2)	1.12 (0.87-1.45)	.37
iDFS events, PD-L1+, n/N (%)	77/785 (9.8)	73/782 (9.3)	1.03 (0.75-1.42)	NR
OS events, ITT, n (%)	61 (5.5)	49 (4.5)	1.20 (0.82-1.75)	NR

- After median follow-up of ~25 mo (range: 0-53), futility was declared for the primary endpoint of iDFS in the ITT population
  - Similar outcomes were observed across subgroups

Ignatiadis. SABCS 2023. Abstr GS01-03.

A-BRAVE: Adjuvant Avelumab vs Observation in High-Risk Early TNBC Post (Neo)adjuvant CT

- Open-label, randomized phase III trial (median f/u: 52.1 mo)

Stratified by adjuvant therapy (pN2-3 any T, pT2N1, pT3-4 N0-3) or postneoadjuvant patients (residual invasive disease in breast and/or axillary lymph nodes)

Adults with high-risk TNBC; previous locoregional and systemic therapy with curative intent; prior (neo)adjuvant anthracycline and taxane CT; tissue for PD-L1 expression; ECOG PS ≤1
(N = 477)

Avelumab 10 mg/kg IV Q2W x 52 wk
(n = 238)

Observation
(n = 239)

Follow-up assessment 3 times during first yr of therapy, every 4 mo during second yr, then every 6 mo thereafter

Adjuvant ET allowed for ER 1%-9% at treating physician's discretion; radiotherapy allowed where indicated.

- Coprimary endpoints: DFS, DFS in postneoadjuvant population
- Key secondary endpoints: OS, DFS in PD-L1–positive patients, safety
- Exploratory objectives: biomarker analysis

NCT02926196. Conte. ASCO 2024. Abstr LBA500.

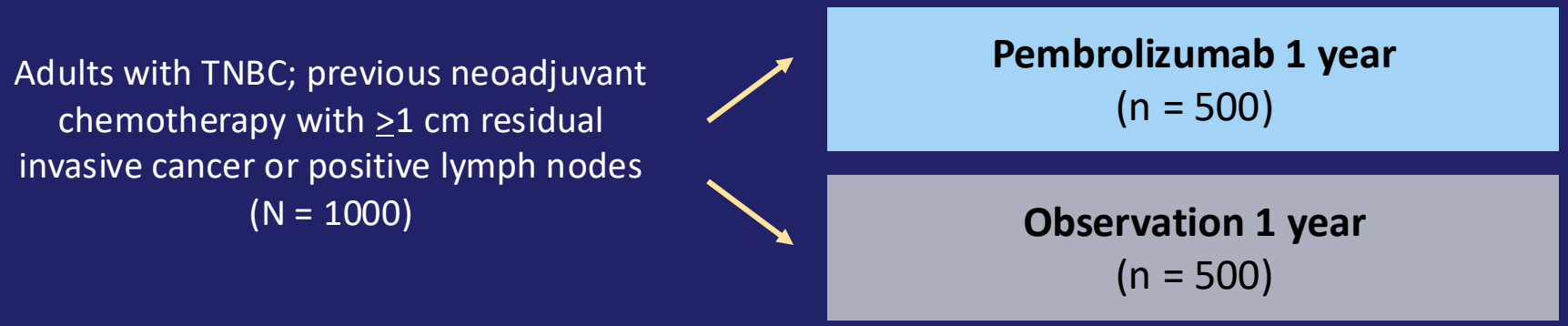
A-BRAVE: DFS and OS

Outcome in ITT, %	Avelumab (n = 235)	Observation (n = 231)	Difference	HR (95% CI)	*P* Value
3-yr DFS	68.3	63.2	5.1	0.81 (0.61-1.09)	.172
3-yr OS	84.8	76.3	8.5	0.66 (0.45-0.97)	.035
3-yr DDFS	75.4	67.9	7.5	0.70 (0.50-0.96)	.0277

Outcome in Postneoadjuvant Population, %	Avelumab (n = 195)	Observation (n = 188)	Difference	HR (95% CI)	*P* Value
3-yr DFS	66.9	60.7	6.2	0.80 (0.58-1.10)	.170

Conte. ASCO 2024. Abstr LBA500.

Ongoing SWOG S1418/NRG BR006
Phase III (closed to accrual 2021, 5 year f/u underway)



Primary endpoint: iDFS

Key secondary endpoints: OS, DRFS in PD-L1+ and all patients

Toxicity, tolerability with/without RT, Biomarkers, PROs

NCT02926196. Conte. ASCO 2024. Abstr LBA500.

Summary Early Stage TNBC

- Consider use of neoadjuvant pembrolizumab-based chemo (KN522) if cT1c or node positive
  - Evaluate axilla preop, do genetic testing
  - Consider non-anthracycline backbone if patient unable to tolerate anthracycline
  - No need to test for PD-L1 status
  - Follow thyroid function, cortisol on patients during and after pembrolizumab therapy!
- No data to support use of immune therapy in patient who did not receive preoperatively
- If *BRCA1/2* carrier, consider 1 year adjuvant olaparib if residual disease or high risk and did not receive neoadjuvant therapy
  - Probably ok to give adjuvant pembro + olaparib but not studied this way
  - Would not give adjuvant capecitabine with olaparib

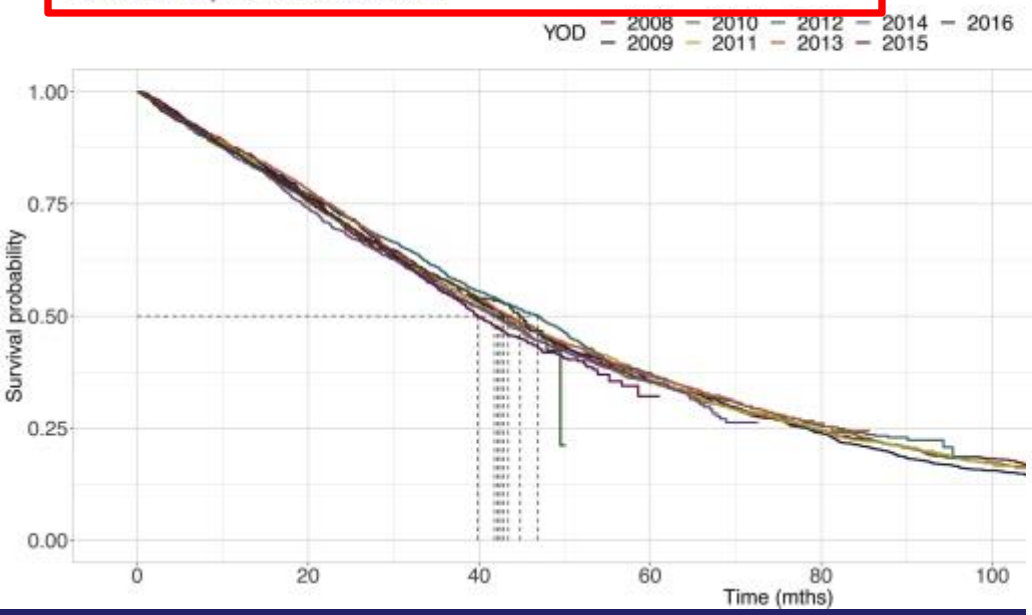
Metastatic Disease

Overall Survival by Year of Diagnosis for HR+ or HER2+

B

Overall survival in the HR+/HER2−subcohort according to the YOD

Based on Kaplan–Meier estimates

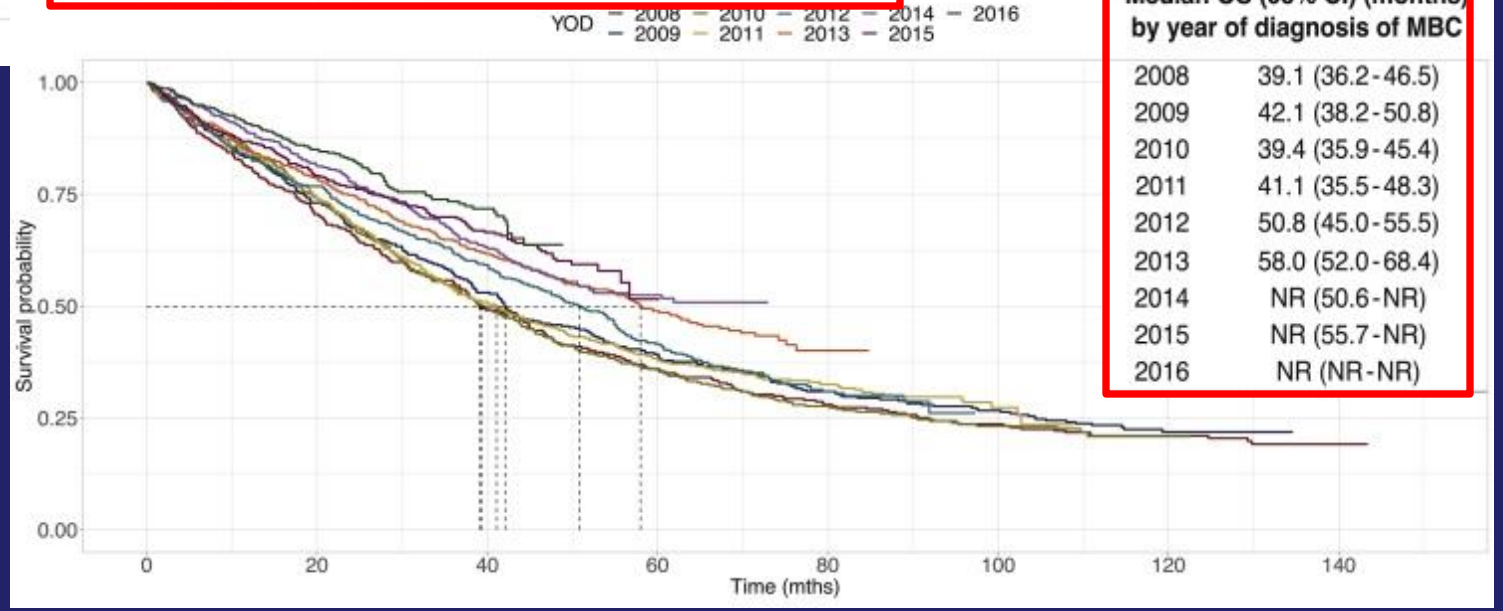


Median OS (95% CI) (months) by year of diagnosis of MBC	
2008	43.4 (40.9-46.5)
2009	42.8 (40.5-45.7)
2010	41.8 (38.9-44.1)
2011	42.5 (40.0-45.9)
2012	46.9 (43.4-49.3)
2013	43.4 (41.4-46.4)
2014	42.2 (39.3-44.5)
2015	39.8 (38.0-42.6)
2016	44.8 (42.5-NR)

C

Overall survival in the HER2+ subcohort according to the YOD

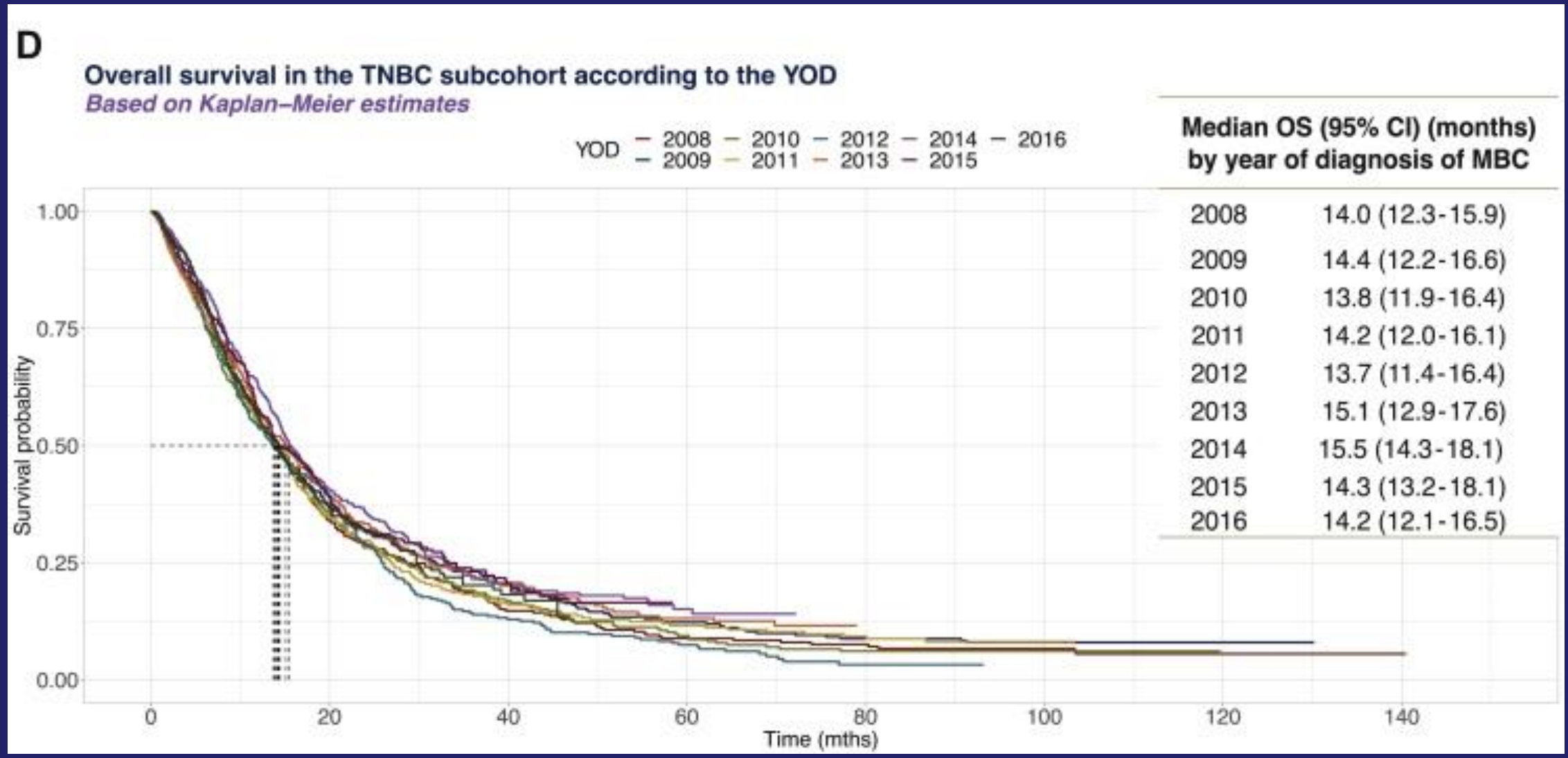
Based on Kaplan–Meier estimates



Median OS (95% CI) (months) by year of diagnosis of MBC	
2008	39.1 (36.2-46.5)
2009	42.1 (38.2-50.8)
2010	39.4 (35.9-45.4)
2011	41.1 (35.5-48.3)
2012	50.8 (45.0-55.5)
2013	58.0 (52.0-68.4)
2014	NR (50.6-NR)
2015	NR (55.7-NR)
2016	NR (NR-NR)

Grinda T et al. ESMO Open 2021;6:100114

Overall Survival Triple Negative Breast Cancer Has Not Changed 2008-2016



Grinda T et al. ESMO Open 2021;6:100114

NCCN Testing Recommendations for Advanced TNBC

Biomarkers Associated with FDA-Approved Therapies					
Subtype	**Biomarker**	**Detection**	**FDA-Approved Agents**	**NCCN Category of Evidence**	**NCCN Category of Preference**
Any	*BRCA1* Mutation *BRCA2* mutation	Germline sequencing	Olaparib Talazoparib	Category 1 Category 1	Preferred
TNBC	PD-L1 ≥10 by CPS	IHC (using 22C3 antibody)	Pembrolizumab + chemo (nab-paclitaxel, paclitaxel, or gem/carbo	Category 1	Preferred first-line therapy
Any	*NTRK* fusion	FISH, NGS, PCR (tumor tissue or blood)	Larotrectinib Entrectinib Repotrectinib	Category 2A	Useful in certain circumstances
Any	MSI-H/dMMR	IHC, NGS, PCR (tumor tissue)	Pembrolizumab Dostarlimab-gxly	Category 2A	
Any	TMB-H (≥10 mut/mb)	NGS (tumor tissue or blood)	Pembrolizumab	Category 2A	
Any	*RET*-fusion	NGS (tumor tissue or blood)	Selpercatinib	Category 2A	
Any	Somatic *BRCA1/2* mutation	NGS	Olaparib	Category 2B	
Any	Germline *PALB2*	Germline sequencing	Olaparib	Category 2B	
TNBC	HER2 activating mutations	NGS	Neratinib	Category 2B	

CPS=combined positive score; IHC = immunohistochemistry; MSI-H=microsatellite instability high; NGS = next-generation sequencing

NCCN Guidelines®. Breast Cancer. Version 4.2024. BINV-Q www.nccn.org.

Pembrolizumab + Chemotherapy for Previously Untreated Advanced TNBC

Phase 3 KEYNOTE-355: Study Design

N=847

- Adult patients with previously untreated locally recurrent inoperable or metastatic TNBC
- De novo metastasis or completed curative intent Tx ≥ 6 mos before first recurrence
- PD-L1 expression
- ECOG 0,1
- Adequate organ function
- No active CNS mets

Stratified by:

- *Chemotherapy (taxane vs gem/carbo)*
- *PD-L1 tumor expression (CPS > 1 vs < 1)*
- *Previous Tx with same class of chemotherapy for EBC (Y vs N)*

R
2:1

Pembrolizumab 200 mg IV Q3W
+ **chemotherapy***
(n = 566)

Placebo + **chemotherapy***
(n = 281)

Until progression, toxicity, or completion of 35 cycles of pembrolizumab

Primary Endpoint

PFS and OS
(PD-L1 CPS ≥ 10, PD-L1 CPS ≥ 1, and ITT)

Secondary Endpoints

ORR, DoR, DCR, safety

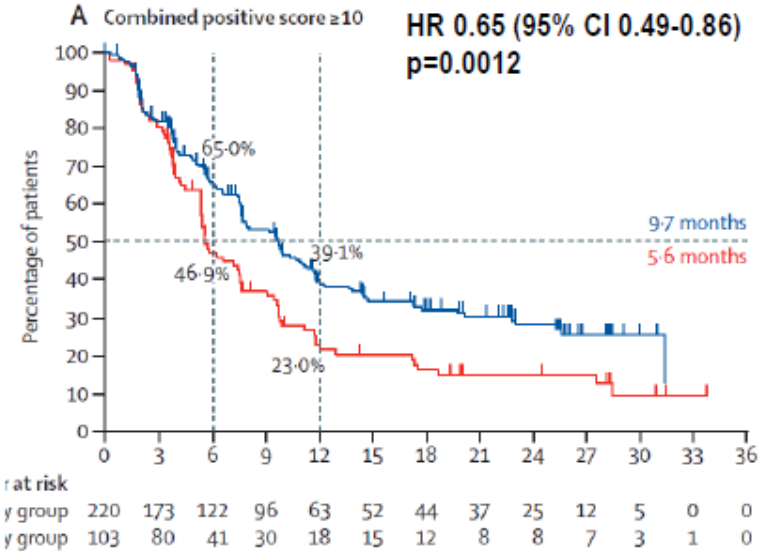
*Investigator's choice of chemotherapy was permitted:

- Nab-paclitaxel 100 mg/m^2 IV on Days 1, 8, 15 of 28-day cycle
- Paclitaxel 90 mg/m^2 IV on Days 1, 8, 15 of 28-day cycle
- Gem 1000 mg/m^2 + carbo AUC 2 on Days 1, 8 of 21-day cycle

Cortes J, et al. *Lancet.* 2020;396:1817-1828.

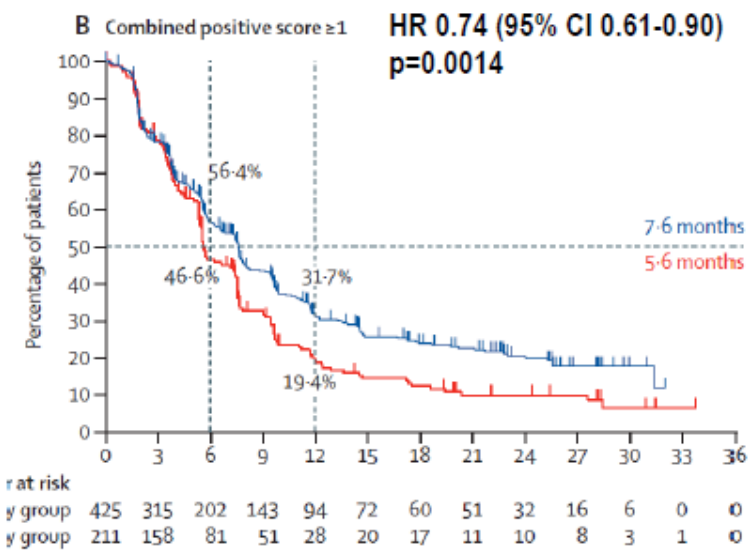
KEYNOTE 355: Progression-free survival

CPS score ≥10 (38% of patients)



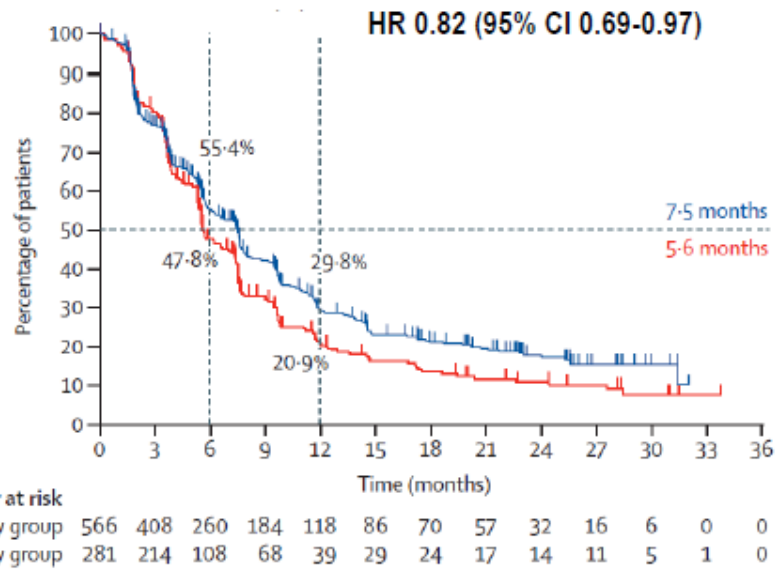
PFS superiority CPS ≥10 boundary α=0.00411

CPS score ≥1 (75% of patients)



PFS superiority CPS ≥1 boundary α=0.00111 not met

ITT population



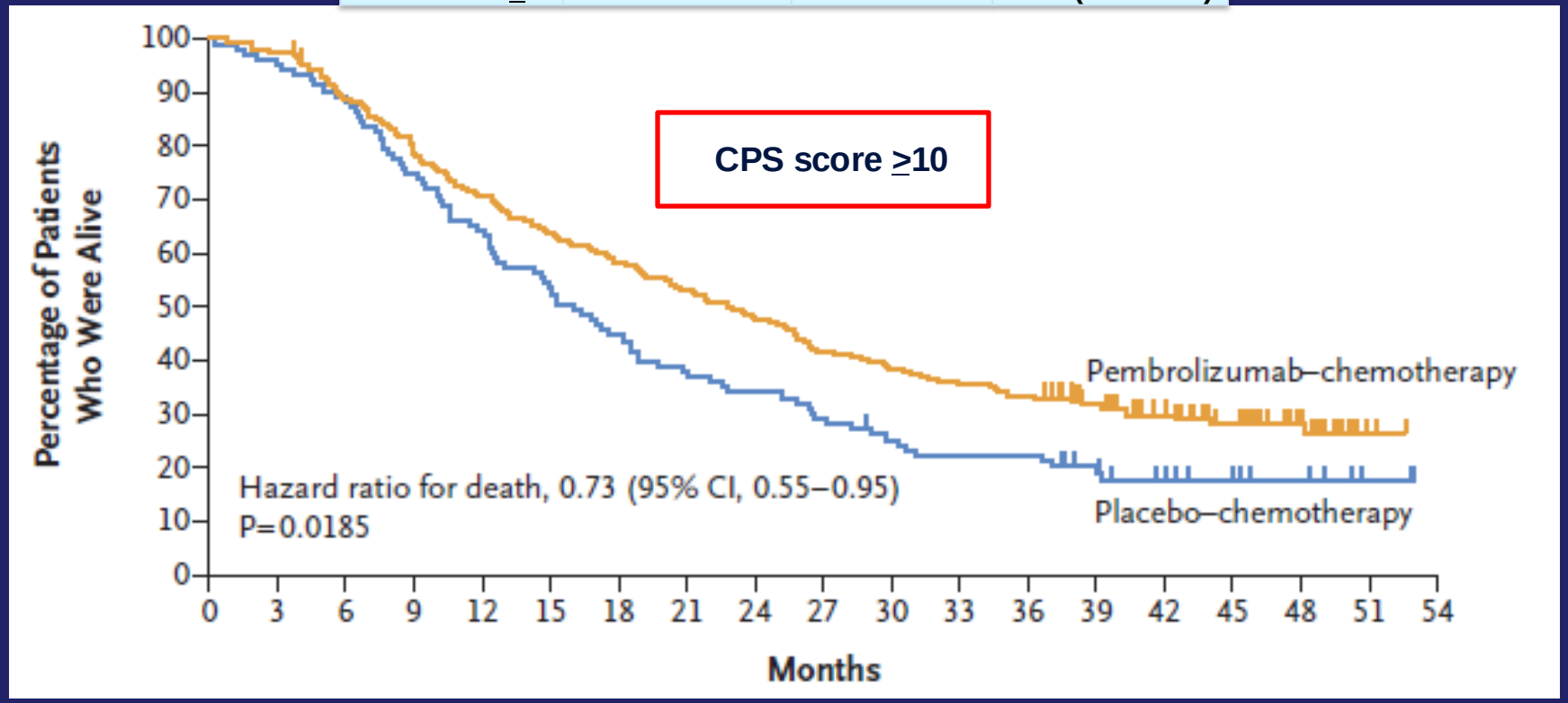
Significance not tested according to hierarchical statistical design

Based on PFS results, pembro + chemo was FDA approved for tx of pts with metastatic TNBC whose tumors express PD-L1 (CPS ≥10)

Cortes J et al. Lancet 2020

KEYNOTE 355: Overall survival

	Overall survival (months)		
	Pembrolizumab + chemo	Placebo + chemo	HR (95% CI)
Intent to treat	17.2	15.5	0.89 (0.76-1.05)
PD-L1 CPS ≥1	17.6	16	0.86 (0.72-1.04)
PD-L1 CPS ≥10	23	16.1	0.71 (0.54-0.93)



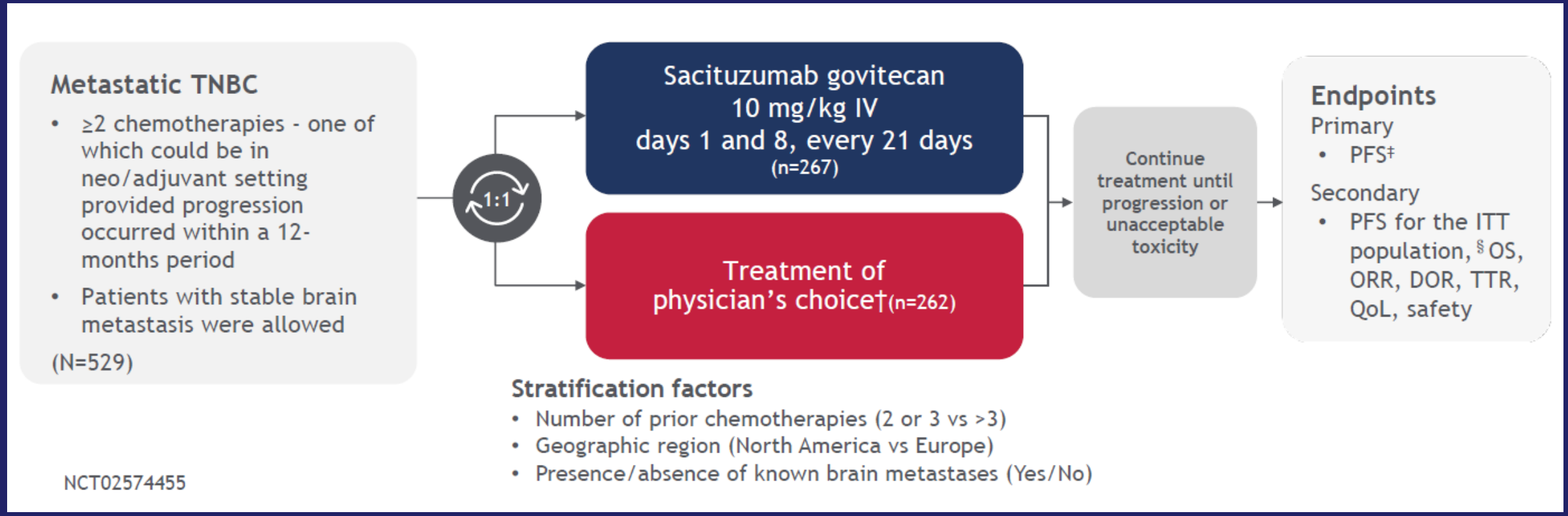
Cortes J et al. NEJM 2022

Second Line: Antibody Drug Conjugates

Sacituzumab Govitecan

Trastuzumab Deruxtecan

ASCENT : Phase 3 Trial

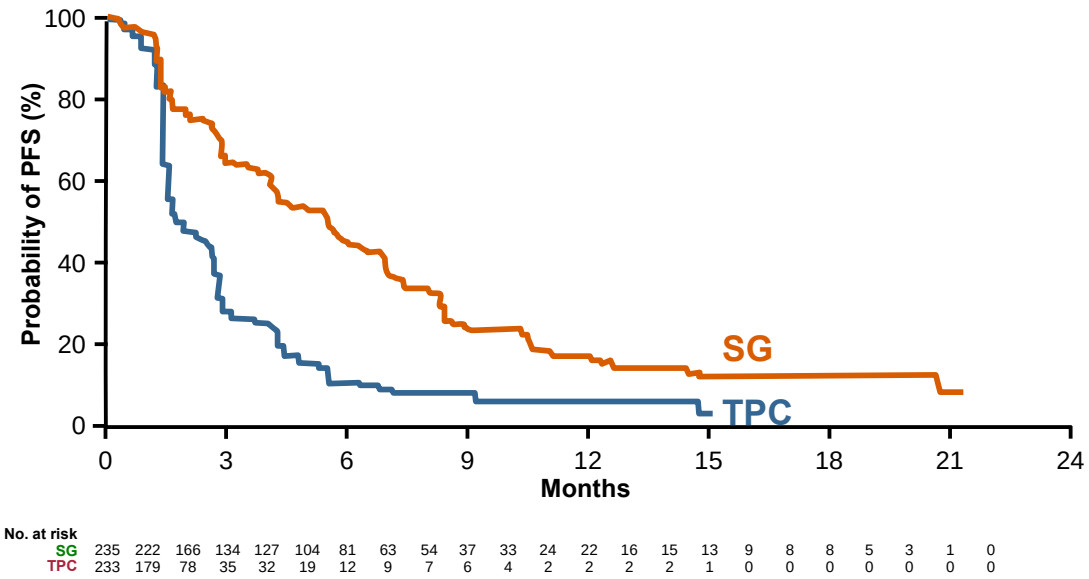


Bardia A et al. ESMO 2021; NEJM 2021

Phase 3 ASCENT: Efficacy

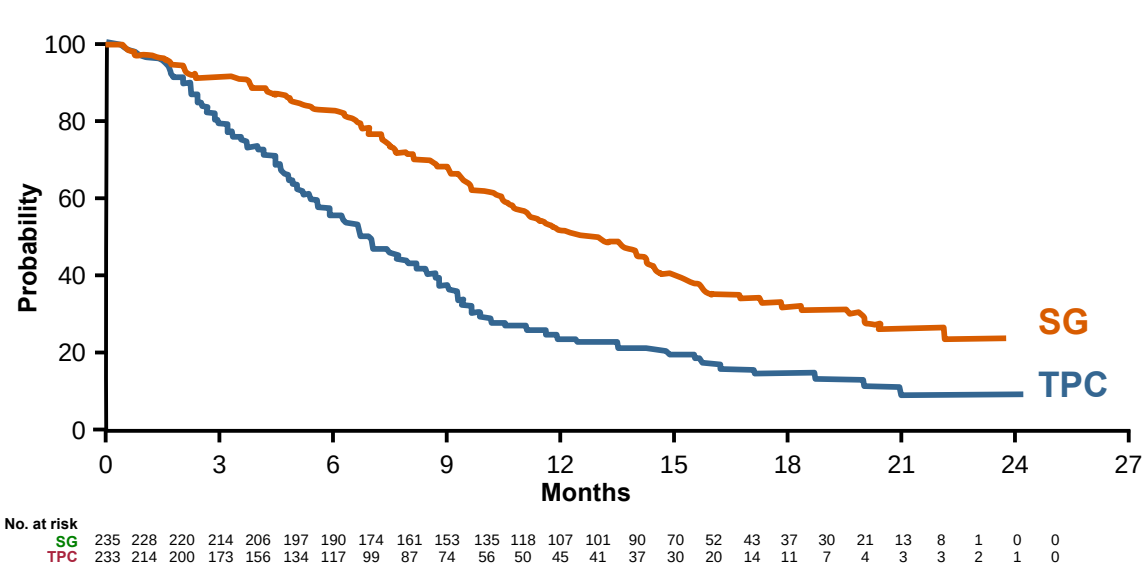
Progression-free survival

BICR Analysis	SG (n=235)	TPC (n=233)
No. of events	166	150
Median PFS, mo (95% CI)	**5.6** (4.3-6.3)	**1.7** (1.5-2.6)
HR (95% CI), P-value	**0.41** (0.32-0.52), **P < 0.0001**	



Overall survival

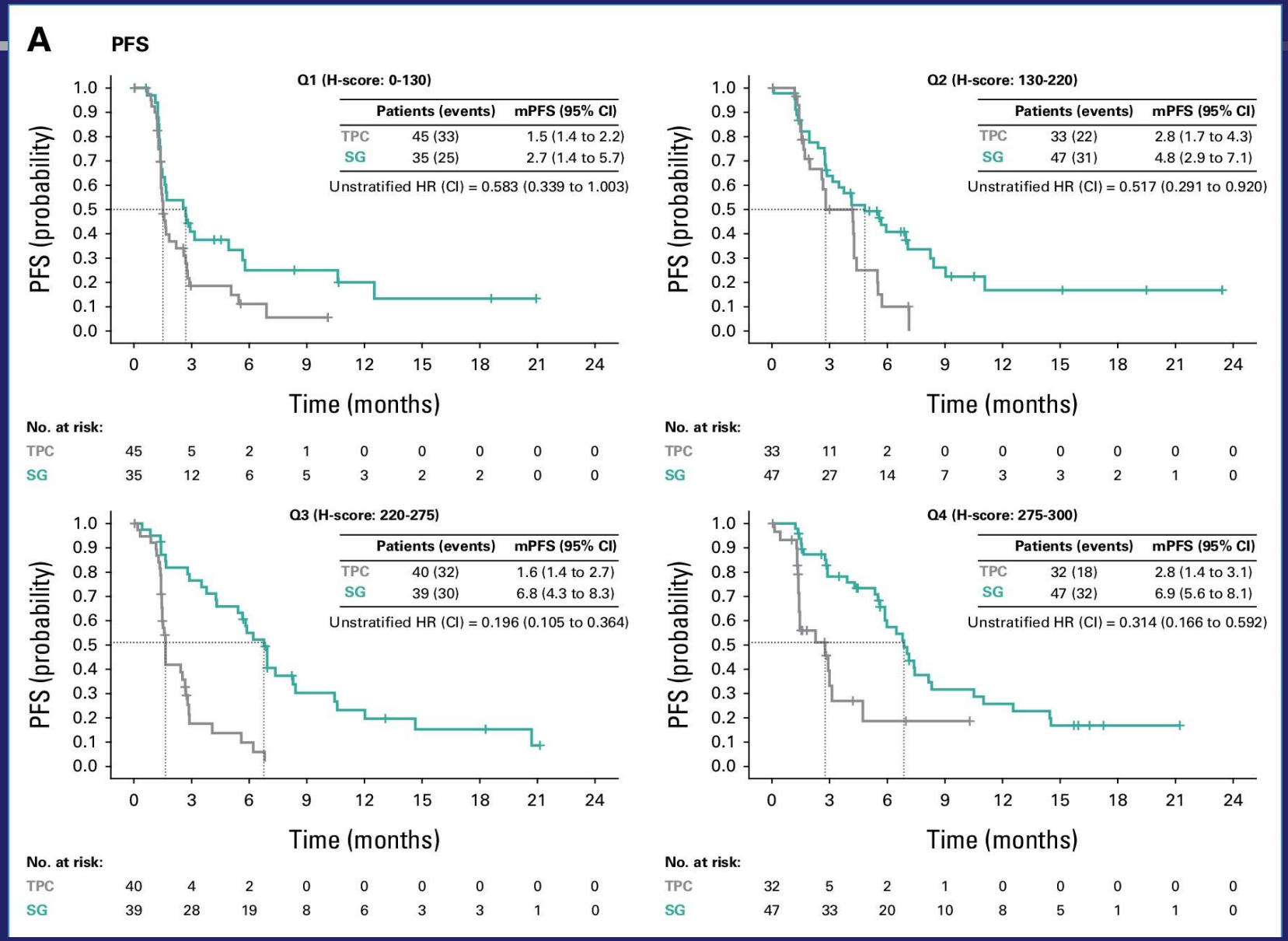
	SG (n=235)	TPC (n=233)
No. of events	155	185
Median OS, mo (95% CI)	**12.1** (10.7-14.0)	**6.7** (5.8-7.7)
HR (95% CI), P-value	**0.48** (0.38-0.59), **P < 0.0001**	



SG, sacituzumab govitecan; TPC, treatment of physician's choice.
Bardia A, et al. *N Engl J Med*. 2021; 384:1529-1541.

SG, sacituzumab govitecan; TPC, treatment of physician's choice.
Bardia A, et al. *N Engl J Med*. 2021; 384:1529-1541.

ASCENT : Clinical benefit irrespective of Trop-2 expression



Bardia A…Hurvitz S; *Journal of Clinical Oncology* 2024 DOI: 10.1200/JCO.23.01409

Phase 3 ASCENT: Safety

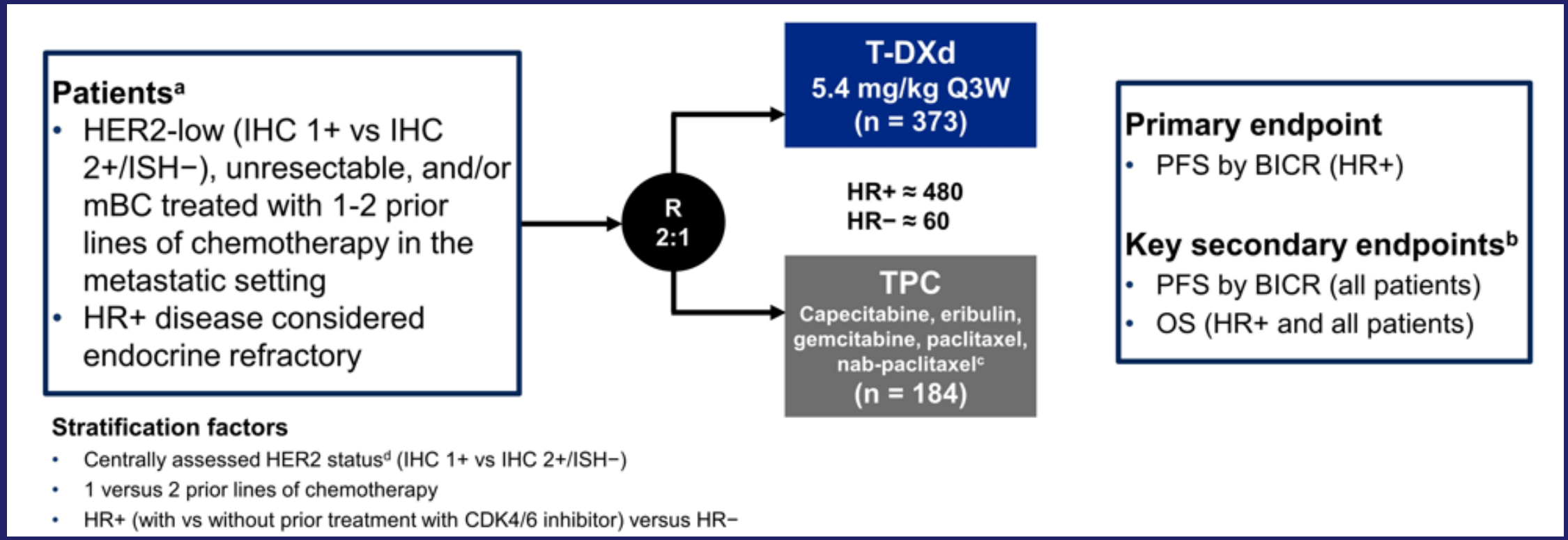
		SG (n=258)			TPC (n=224)		
	TRAE	**All grade, %**	**Grade 3, %**	**Grade 4, %**	**All Grade, %**	**Grade 3, %**	**Grade 4, %**
Hematologic	**Neutropenia**	63	**34**	17	43	**20**	13
	Anemia	34	**8**	0	24	**5**	0
	Leukopenia	16	**9**	1	11	**4**	1
	Febrile neutropenia	6	**5**	1	2	**2**	<1
Gastrointestinal	**Diarrhea**	59	**10**	0	12	**<1**	0
	Nausea	57	2	<1	26	<1	0
	Vomiting	29	1	<1	10	<1	0
Other	Fatigue	45	3	0	30	5	0
	Alopecia	46	0	0	16	0	0

Key grade 3 TRAEs (SG vs TPC): neutropenia (34% vs 20%), diarrhea (10% vs < 1%), leukopenia (9% vs 4%), anemia (8% vs 5%), and febrile neutropenia (5% vs 2%)

SG, sacituzumab govitecan; TPC, treatment of physician's choice.

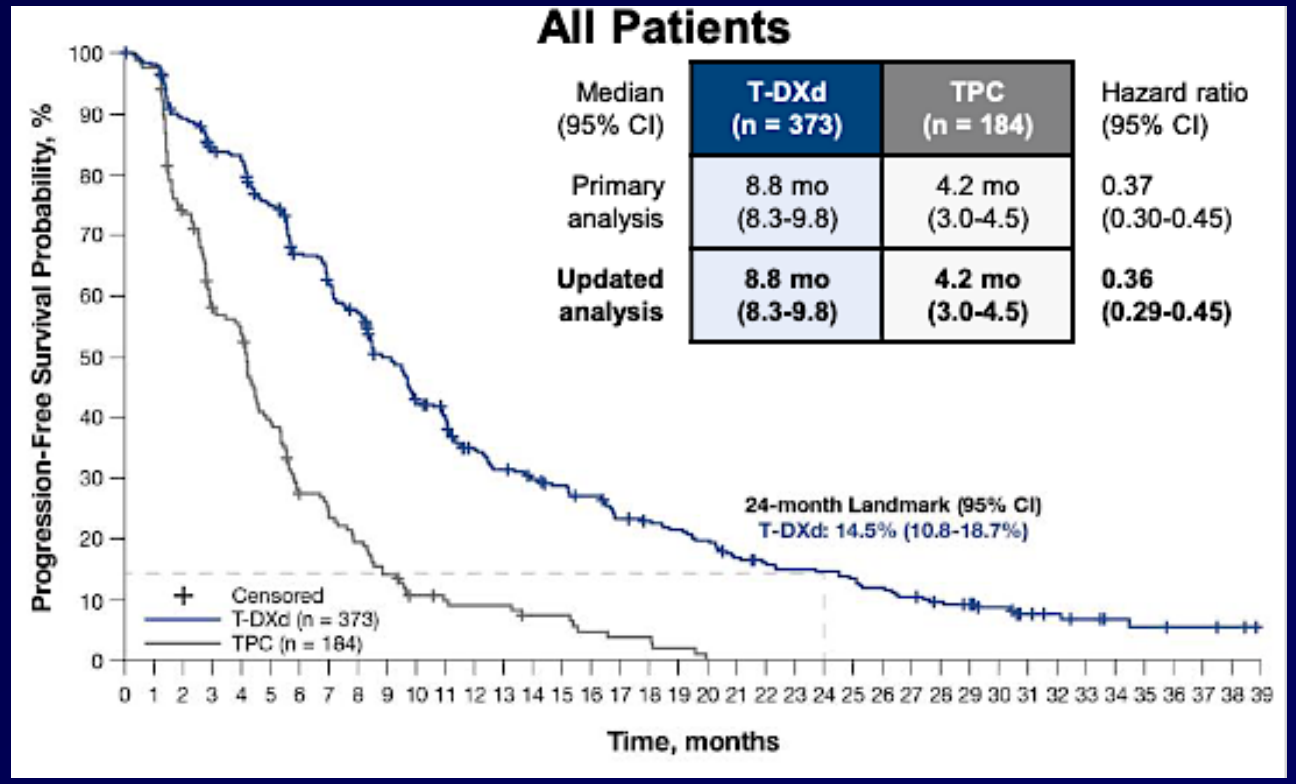
Bardia A, et al. *N Engl J Med*. 2021; 384:1529-1541.

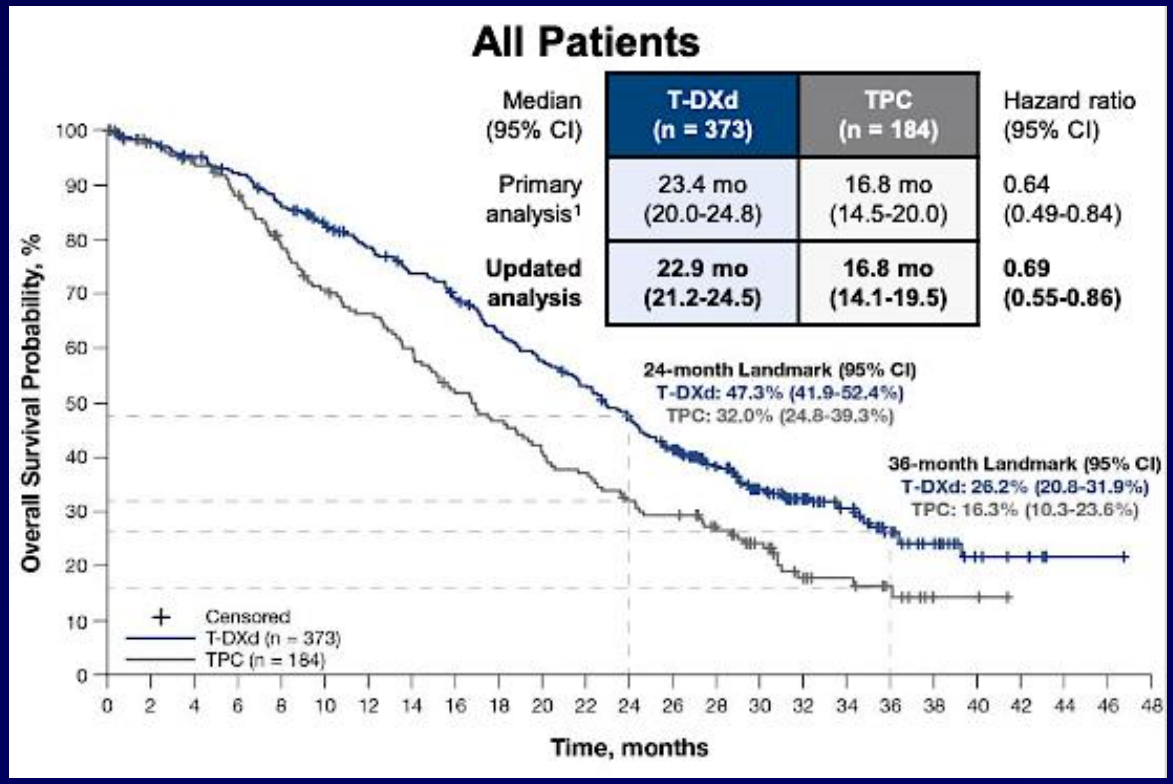
DESTINY Breast04: T-DXd in HER2-low MBC



Modi S et al. Plenary session ASCO 2022

DESTINY-Breast04 Updated Survival Results: T-DXd in HER2-Low BC





Modi S et al. ESMO 2023;Abstract 376O.

DESTINY Breast04: T-DXd in HER2-low MBC

Table 2. Overall Efficacy in All Cohorts.*

Variable	Hormone Receptor–Positive Cohort		All Patients		Hormone Receptor–Negative Cohort	
	Trastuzumab Deruxtecan	Physician's Choice of Chemotherapy	Trastuzumab Deruxtecan	Physician's Choice of Chemotherapy	Trastuzumab Deruxtecan	Physician's Choice of Chemotherapy
Progression-free and overall survival						
No. of patients evaluated	331	163	373	184	40	18
Median progression-free survival (95% CI) — mo	10.1 (9.5–11.5)	5.4 (4.4–7.1)	9.9 (9.0–11.3)	5.1 (4.2–6.8)	8.5 (4.3–11.7)	2.9 (1.4–5.1)
Hazard ratio for disease progression or death (95% CI)	0.51 (0.40–0.64)		0.50 (0.40–0.63)		0.46 (0.24–0.89)	
P value	<0.001		<0.001		—	
Median overall survival (95% CI) — mo	23.9 (20.8–24.8)	17.5 (15.2–22.4)	23.4 (20.0–24.8)	16.8 (14.5–20.0)	18.2 (13.6–NE)	8.3 (5.6–20.6)
Hazard ratio for death (95% CI)	0.64 (0.48–0.86)		0.64 (0.49–0.84)		0.48 (0.24–0.95)	
P value	0.003		0.001		—	
Response to treatment						
No. of patients evaluated	333	166	373	184	40	18
Confirmed overall response						
No. with response	175	27	195	30	20	3
Percent (95% CI)	52.6 (47.0–58.0)	16.3 (11.0–22.8)	52.3 (47.1–57.4)	16.3 (11.3–22.5)	50.0 (33.8–66.2)	16.7 (3.6–41.4)
Best overall response — no. (%)						
Complete response	12 (3.6)	1 (0.6)	13 (3.5)	2 (1.1)	1 (2.5)	1 (5.6)
Partial response	164 (49.2)	26 (15.7)	183 (49.1)	28 (15.2)	19 (47.5)	2 (11.1)
Stable disease	117 (35.1)	83 (50.0)	129 (34.6)	91 (49.5)	12 (30.0)	8 (44.4)
Progressive disease	26 (7.8)	35 (21.1)	31 (8.3)	41 (22.3)	5 (12.5)	6 (33.3)
Not evaluable	14 (4.2)	21 (12.7)	17 (4.6)	22 (12.0)	3 (7.5)	1 (5.6)
Disease control — no. (%)†	293 (88.0)	110 (66.3)	325 (87.1)	121 (65.8)	32 (80.0)	11 (61.1)
Clinical benefit — no. (%)‡	237 (71.2)	57 (34.3)	262 (70.2)	62 (33.7)	25 (62.5)	5 (27.8)
Median duration of response — mo	10.7	6.8	10.7	6.8	8.6	4.9
Median time to response — mo	2.76	2.73	2.73	2.22	1.51	1.41

Modi S et al. NEJM 2022;387:9-20.

DESTINY Breast04: Adverse events

Table 3. Most Common Drug-Related Adverse Events (in ≥20% of Patients) in the Safety Analysis Set.*

Event	Trastuzumab Deruxtecan (N=371)		Physician's Choice of Chemotherapy (N=172)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Blood and lymphatic system disorders				
Neutropenia†	123 (33.2)	51 (13.7)	88 (51.2)	70 (40.7)
Anemia‡	123 (33.2)	30 (8.1)	39 (22.7)	8 (4.7)
Thrombocytopenia§	88 (23.7)	19 (5.1)	16 (9.3)	1 (0.6)
Leukopenia¶	86 (23.2)	24 (6.5)	54 (31.4)	33 (19.2)
Gastrointestinal disorders				
Nausea	271 (73.0)	17 (4.6)	41 (23.8)	0
Vomiting	126 (34.0)	5 (1.3)	17 (9.9)	0
Diarrhea	83 (22.4)	4 (1.1)	31 (18.0)	3 (1.7)
Constipation	79 (21.3)	0	22 (12.8)	0
Investigations: increased aminotransferase levels‖	87 (23.5)	12 (3.2)	39 (22.7)	14 (8.1)
General disorders: fatigue**	177 (47.7)	28 (7.5)	73 (42.4)	8 (4.7)
Metabolism and nutrition disorders: decreased appetite	106 (28.6)	9 (2.4)	28 (16.3)	2 (1.2)
Skin and subcutaneous tissue disorders: alopecia	140 (37.7)	0	56 (32.6)	0

Interstitial lung disease: (12.1%):
Grade 1: 13 (3.5%)
Grade 2: 24 (6.5%)
Grade 3: 5 (1.3%)
Grade 5: 3 (0.8%)

Modi S et al. NEJM 2022;387:9-20.

PARP inhibition

Phase III Trials PARPi: OLYMPIAD and EMBRACA

OlympiAD trial – Olaparib

- HER2-negative metastatic BC
  - ER+ and/or PR+ or TNBC
- Deleterious or suspected deleterious gBRCAm
- Prior anthracycline and taxane
- ≤2 prior chemotherapy lines in metastatic setting
- HR+ disease progressed on ≥1 endocrine therapy, or not suitable
- If prior platinum use
  - No evidence of progression during treatment in the advanced setting
  - ≥12 months since (neo)adjuvant treatment

R 2:1

Olaparib
300 mg tablets bd

Chemotherapy treatment of physician's choice (TPC)
- **Capecitabine**
- **Eribulin**
- **Vinorelbine**

EMBRACA trial – Talazoparib

Patients with locally advanced or metastatic HER2 negative BC and a germline BRCA1/2 mutation

Stratification factors
- Number of prior CT regimens (0 or ≥1)
- TNBC or HR+
- History of CNS mets or no CNS mets

R 2:1

Talazoparib
1 mg PO daily

Treatment (21-day cycles) continues until progression or unacceptable toxicity

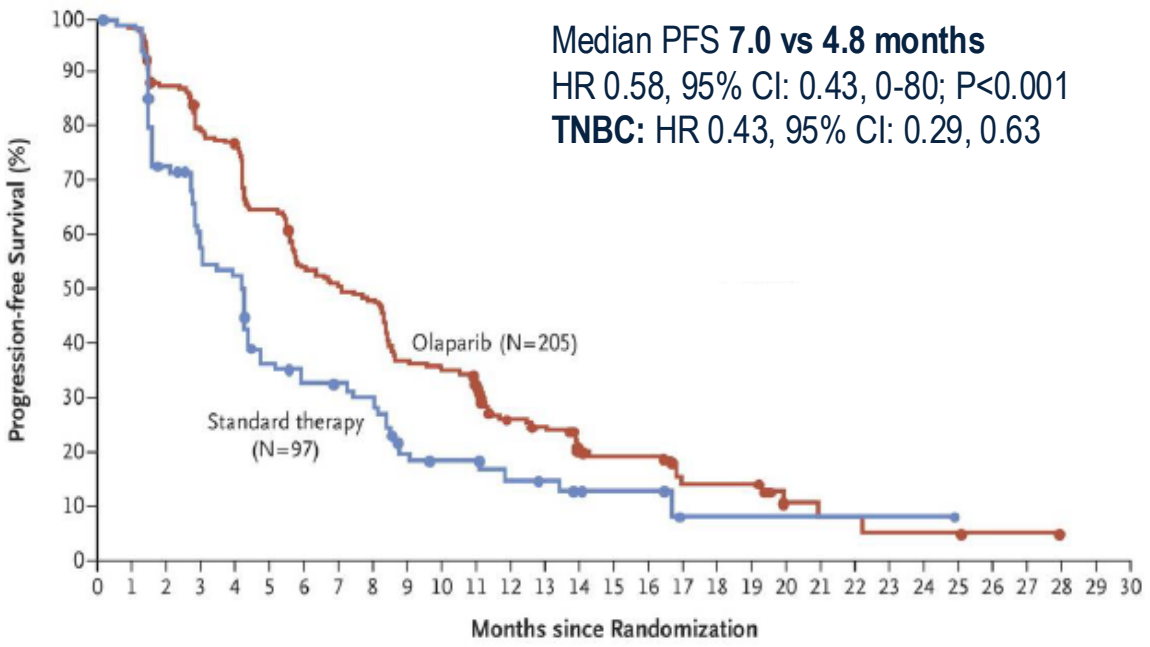
Physicians choice of therapy (PCT): capecitabine, eribulin, gemcitabine or vinorelbine

Robson M et al. NEJM 2017; Litton JK et al. NEJM 2018

OLYMPIAD and EMBRACA: Progression-free survival

OLYMPIAD

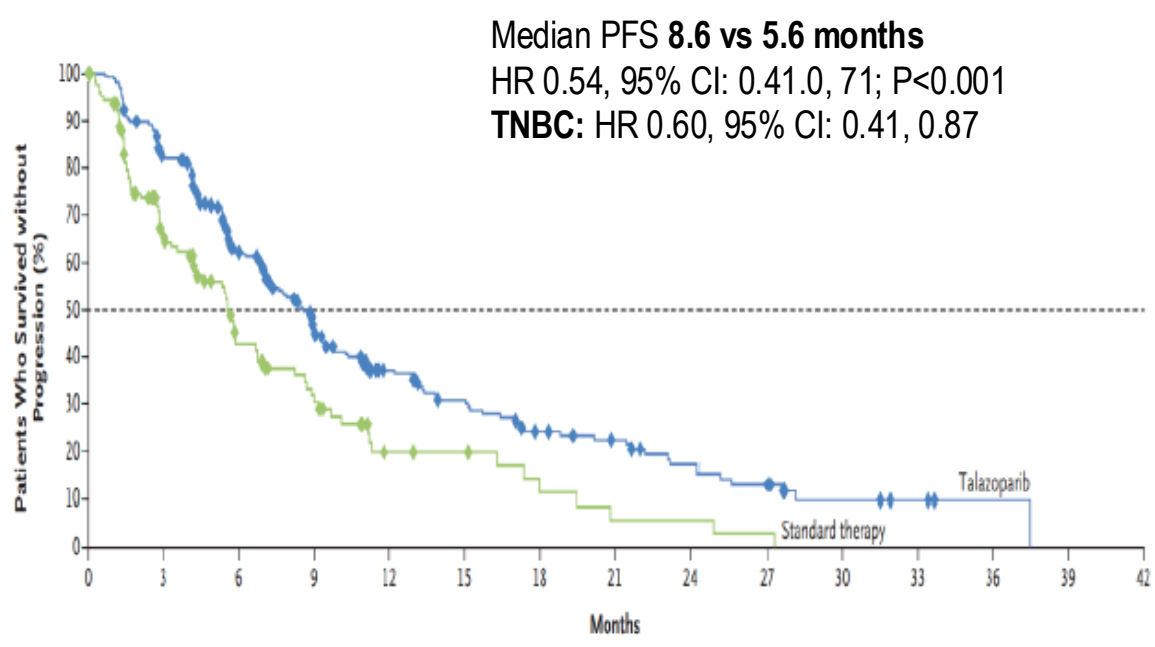
50% TN; A/T pretreated; 71% prior CT for MBC;
TN: non-platinum resistant



Median PFS **7.0 vs 4.8 months**
HR 0.58, 95% CI: 0.43, 0-80; P<0.001
TNBC: HR 0.43, 95% CI: 0.29, 0.63

EMBRACA

44% TN; A/T pretreated; 62% prior CT for MBC;
TN: non-platinum resistant



Median PFS **8.6 vs 5.6 months**
HR 0.54, 95% CI: 0.41.0, 71; P<0.001
TNBC: HR 0.60, 95% CI: 0.41, 0.87

- Olaparib received regular FDA approval in Jan 2018 for tx of pts with deleterious or suspected deleterious gBRCA mutated HER2- MBC
- Talazoparib was FDA approved in Oct 2018 for tx of pts with deleterious or suspected deleterious gBRCA mutated HER2- MBC
- No improvement in overall survival for either

Robson M et al. NEJM 2017; Litton JK et al. NEJM 2018

NCCN Treatment Recommendations for Advanced TNBC

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2024
Invasive Breast Cancer

NCCN Guidelines Index
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Discussion

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

HR-Negative and HER2-Negative (Triple-Negative Breast Cancer; TNBC)		
Setting	**Subtype/Biomarker**	**Regimen**
First Line	PD-L1 CPS ≥10[g] regardless of germline *BRCA* mutation status[b]	Pembrolizumab + chemotherapy (albumin-bound paclitaxel, paclitaxel, or gemcitabine and carboplatin)[h] (Category 1, preferred)
	PD-L1 CPS <10[g] and no germline *BRCA1/2* mutation[b]	Systemic chemotherapy BINV-Q (5)
	PD-L1 CPS <10[g] and germline *BRCA1/2* mutation[b]	• PARPi (olaparib, talazoparib) (Category 1, preferred) • Platinum (cisplatin or carboplatin) (Category 1, preferred)
Second Line	Germline *BRCA1/2* mutation[b]	PARPi (olaparib, talazoparib) (Category 1, preferred)
	Any	Sacituzumab govitecan[i] (Category 1, preferred)
		Systemic chemotherapy BINV-Q (5)
	No germline *BRCA1/2* mutation[b] and HER2 IHC 1+ or 2+/ISH negative[d]	Fam-trastuzumab deruxtecan-nxki[e] (Category 1, preferred)
Third Line and beyond	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	Targeted agents BINV-Q (6)
	Any	Systemic chemotherapy BINV-Q (5)

Unanswered questions

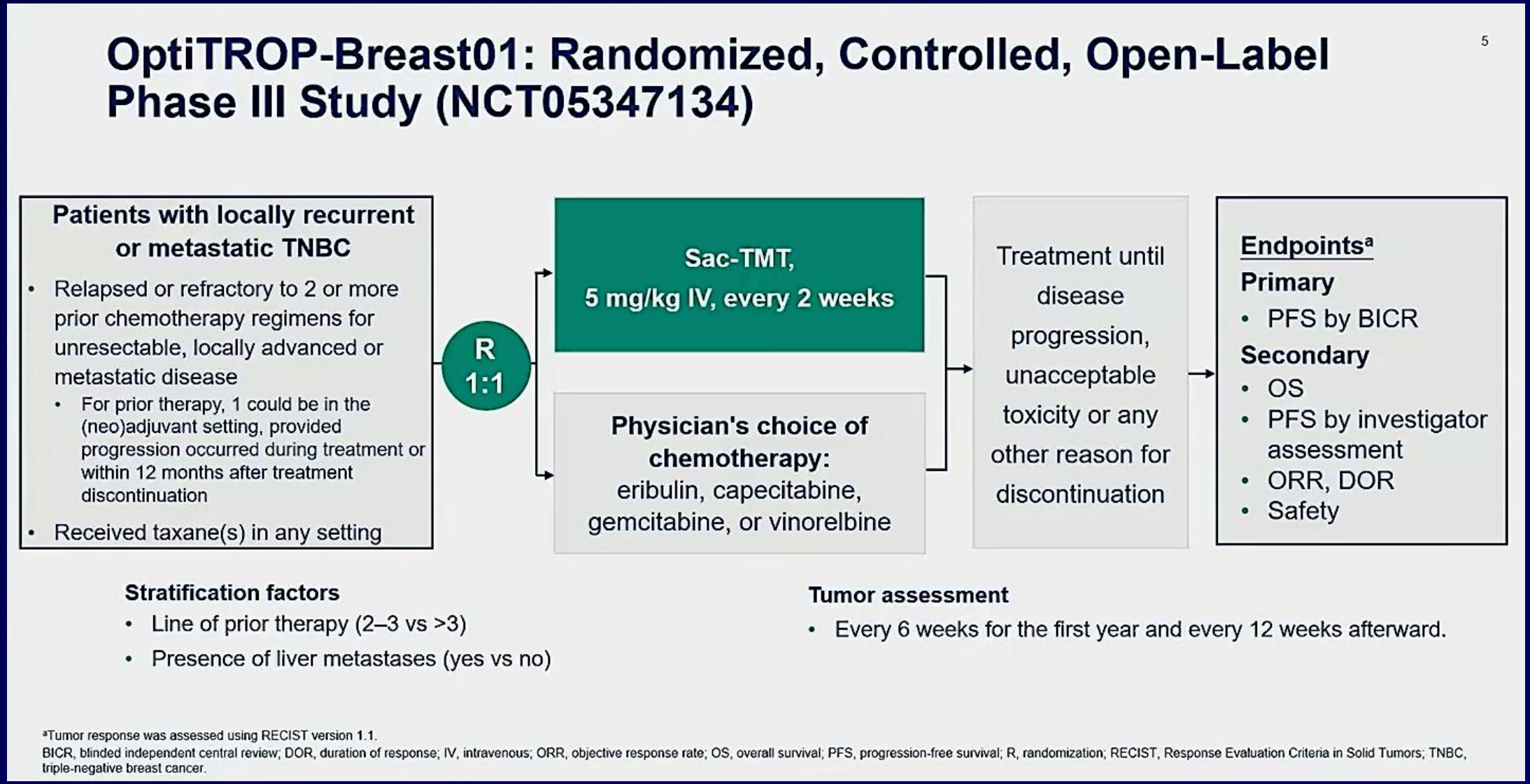
- How will phase III data for Dato-DXd turn out (TROPION-Breast02)
- Will patritumab deruxtecan be beneficial in TNBC
- How do Sacituzumab, T-DXd, dato-DXd, and others compare to one another?
- Mechanisms of resistance
- Is sequencing ADCs effective
  - Does target matter
  - Does payload matter
- Can PARPi be effective in non-germline BRCA1/2 mutated cancers

Thank you!!

Induction Chemotherapy followed by PARPi

- PARPi may upregulate PD-L1 expression and be synergistic with immune therapy in BRCA wild-type and mutated breast cancer
- Phase I data indicate PARPi are safe with PD-(L)1 blockade
- Olaparib is used in ovarian cancer regardless of BRCA status

OptiTROP-Breast01 Phase III Trial Schema of Sacituzumab Tirumotecan in TNBC



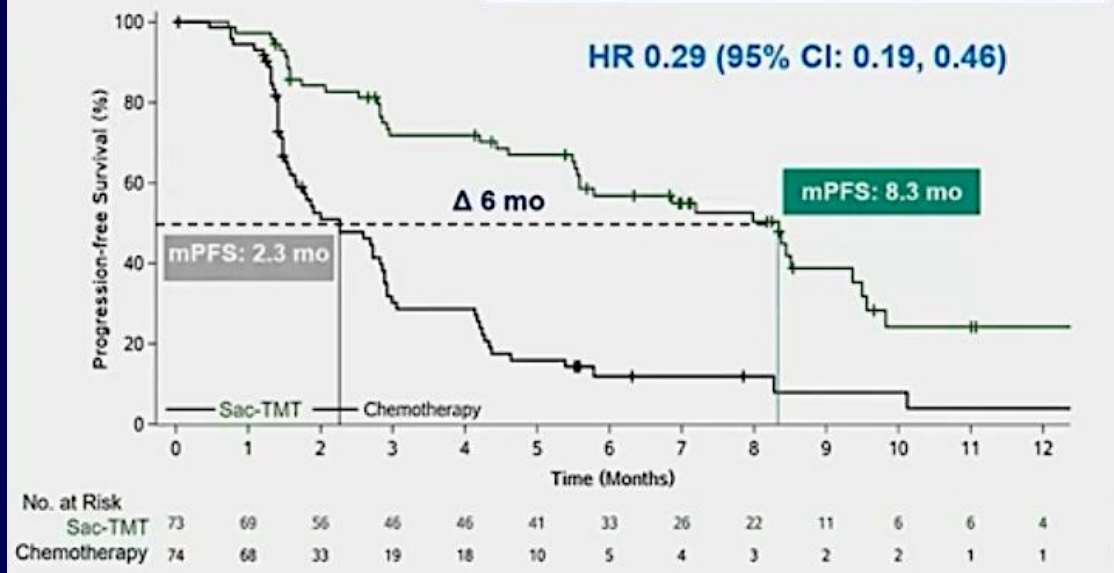
Xu B et al. ASCO 2024;Abstract 104.

OptiTROP-Breast01: Sacitzumab Tirumotecan in Locally Recurrent or Metastatic TNBC

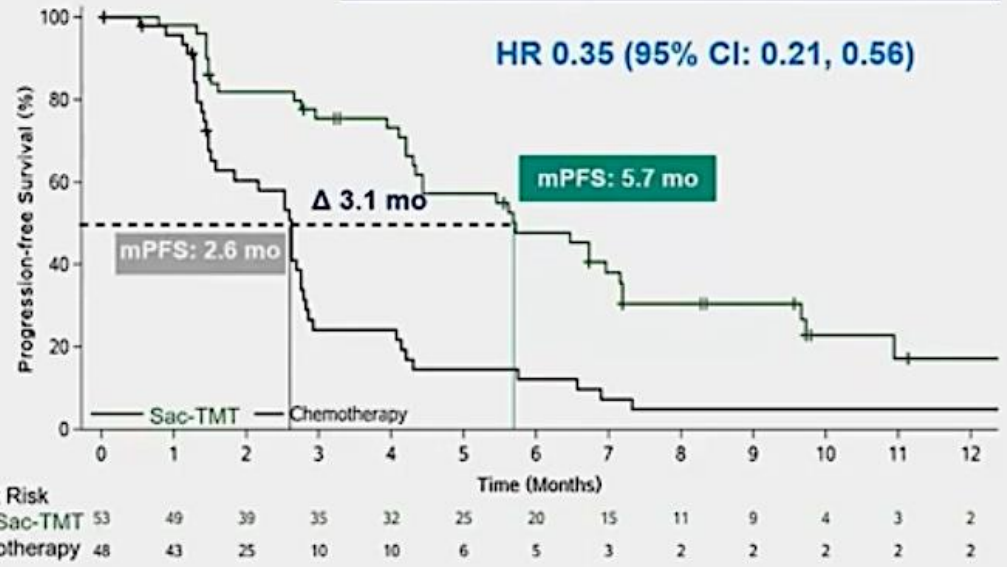
Progression-Free Survival (per BICR) by TROP2 Expression

PFS benefit was observed with sac-TMT over chemotherapy regardless of TROP2 expression.

High TROP2 expression (H-Score >200)	Sac-TMT (n = 73)	Chemotherapy (n = 74)
PFS events, n (%)	41 (56.2)	59 (79.7)
Median PFS (95% CI), mo	8.3 (5.6, 9.4)	2.3 (1.6, 2.9)



Low/medium TROP2 expression (H-Score ≤200)	Sac-TMT (n = 53)	Chemotherapy (n = 48)
PFS events, n (%)	34 (64.2)	40 (83.3)
Median PFS (95% CI), mo	5.7 (4.3, 7.2)	2.6 (1.5, 2.8)

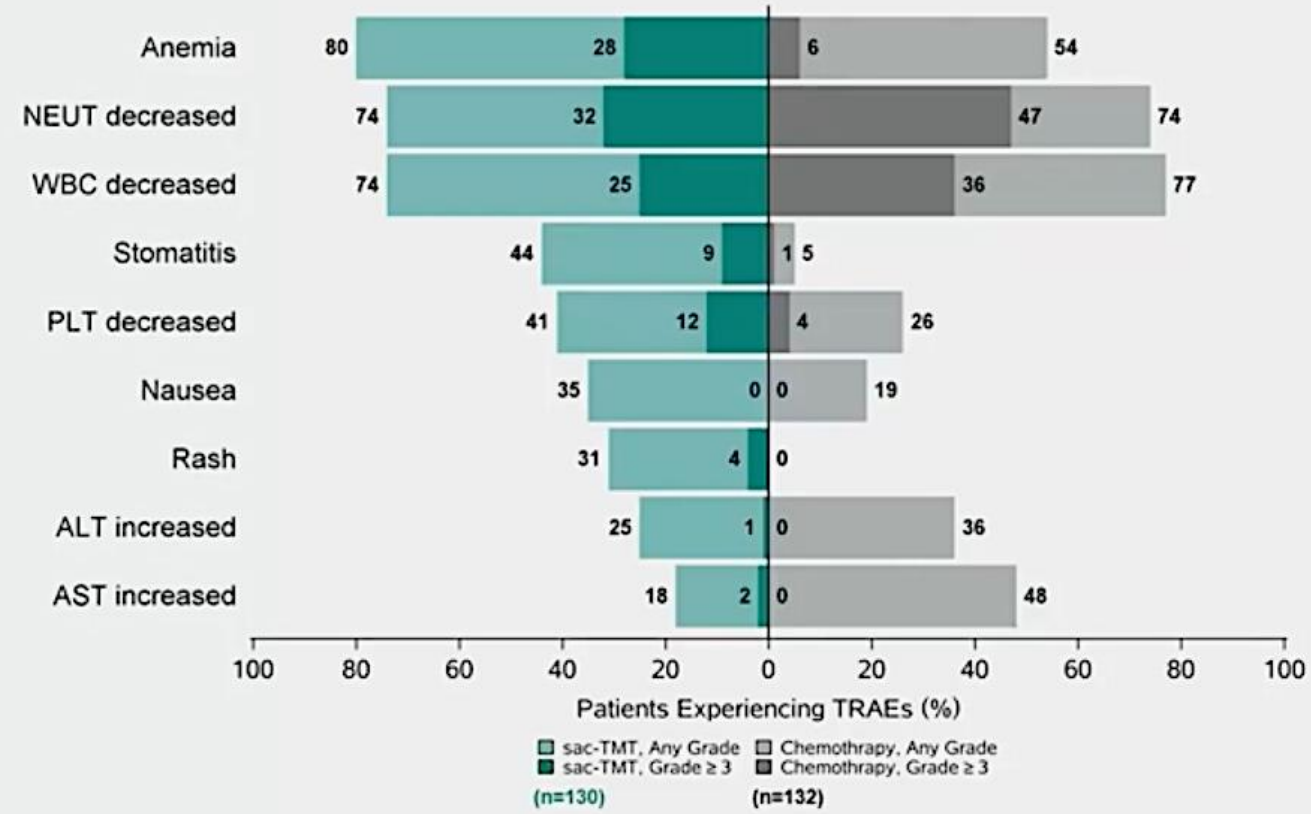


Data cutoff: Nov 30, 2023; the protocol-specified final analysis of PFS.
BICR, blinded independent central review; Chemo, chemotherapy; CI, confidential interval; HR, hazard ratio; mPFS, median progression-free survival; TROP2, trophoblast cell surface antigen 2.

Xu B et al. ASCO 2024;Abstract 104.

OptiTROP-Breast01: Treatment-Related Adverse Events with Sacitzumab Tirumotecan in Locally Recurrent or Metastatic TNBC

TRAEs in ≥ 30% of Patients

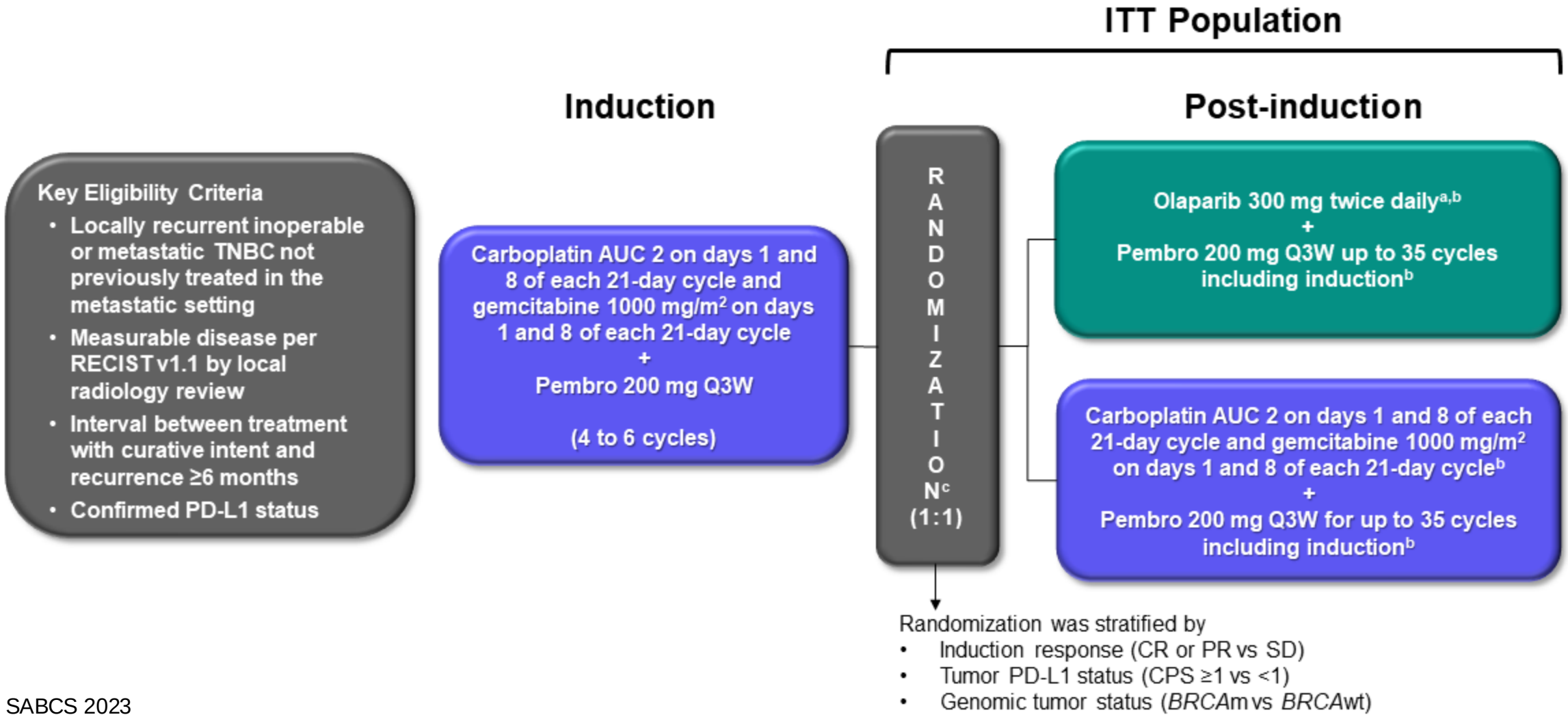


- The most common TRAEs for both sac-TMT and chemotherapy were hematologic toxicities.
- Two patients (1.5%) reported peripheral neuropathy (all were grade 1) and one patient (0.8%) reported grade 2 interstitial lung disease (recovered) with sac-TMT.
- Xerophthalmia (grade 2) and blurred vision (grade 1) occurred in one patient each (0.8%) with sac-TMT.

Data cutoff: Jun 21, 2023.
AEs were classified according to the MedDRA system of preferred terms and system organ class and according to severity by NCI CTCAE v5.0.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, common terminology criteria for adverse events; MedDRA, Medical Dictionary for Regulatory Activities; NCI, National Cancer Institute; NEUT, neutrophil count; PLT, platelet; TRAE, treatment-related adverse event; WBC, white blood cell.

Xu B et al. ASCO 2024;Abstract 104.

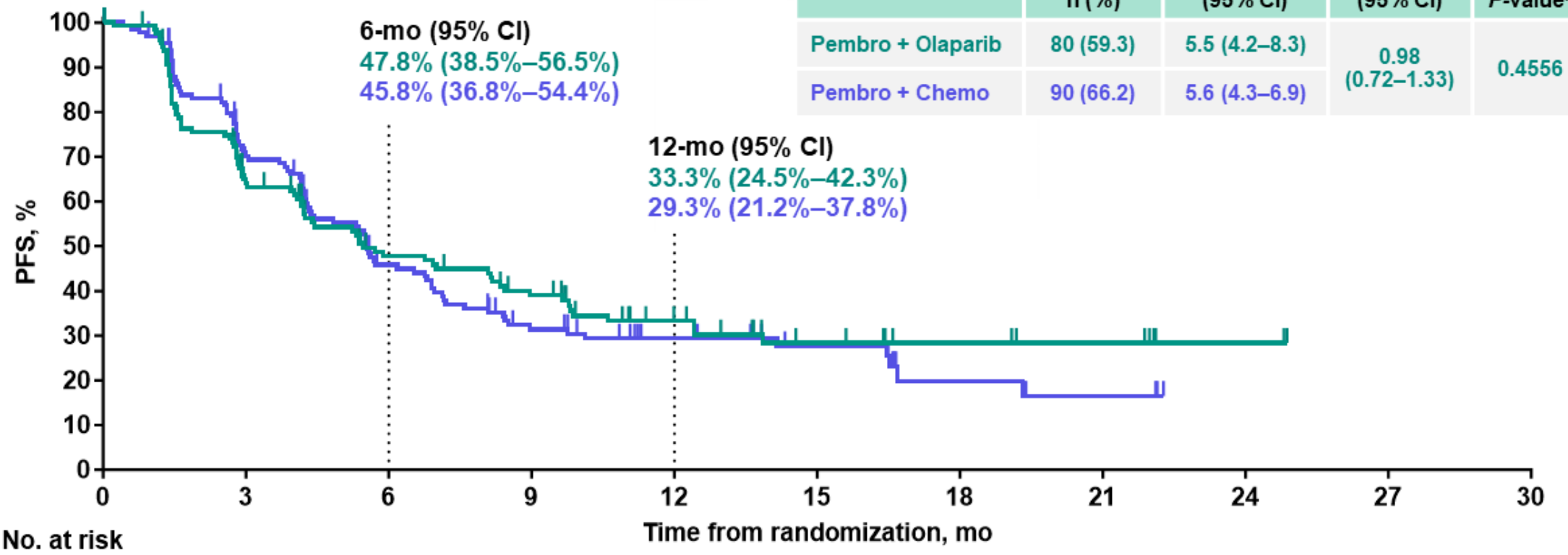
KEYLYNK-009 Design



Rugo H SABCS 2023

KEYLYNK-009: PFS by BICR ITT pop

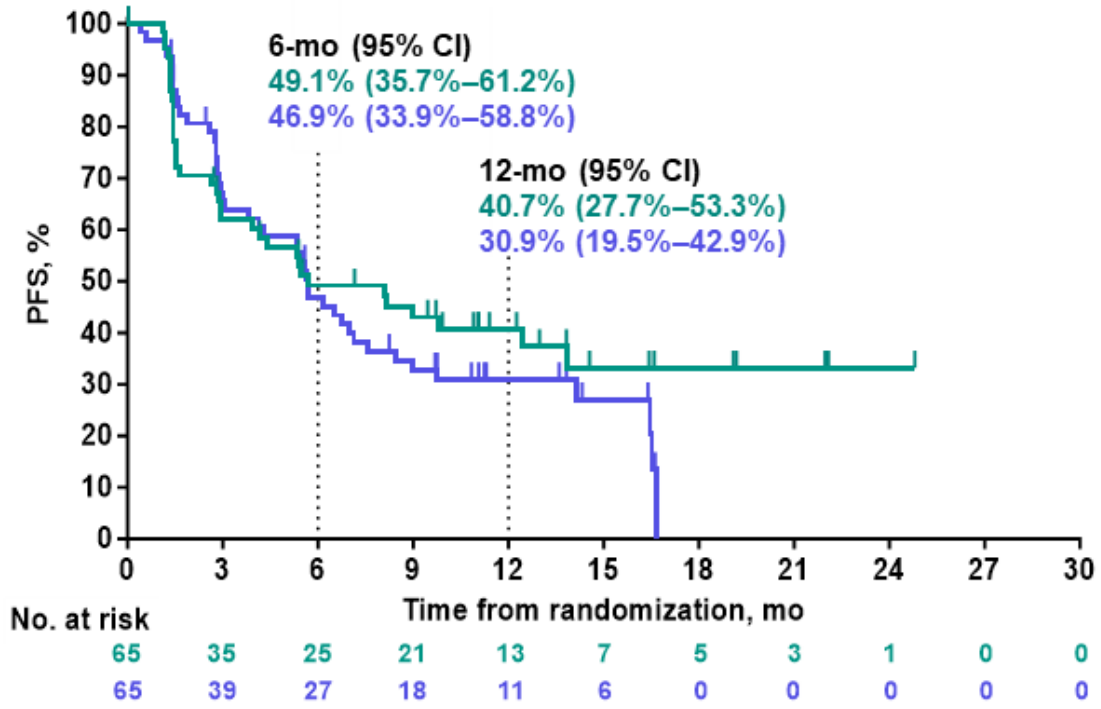
	Events, n (%)	Median, mo (95% CI)	HR[a] (95% CI)	*P*-value[b]
Pembro + Olaparib	80 (59.3)	5.5 (4.2–8.3)	0.98 (0.72–1.33)	0.4556
Pembro + Chemo	90 (66.2)	5.6 (4.3–6.9)		



KEYLYNK-009: PFS for PD-L1 CPS ≥10 and t*BRCA*m

Tumor PD-L1 CPS ≥10 Population

	Events, n (%)	Median, mo (95% CI)	HR[a] (95% CI)
Pembro + Olaparib	36 (55.4)	5.7 (2.9–13.9)	0.92 (0.59–1.43)
Pembro + Chemo	45 (69.2)	5.7 (3.8–7.6)	



t*BRCA*m Population

	Events, n (%)	Median, mo (95% CI)	HR[b] (95% CI)
Pembro + Olaparib	12 (41.4)	12.4 (8.3–NR)	0.70 (0.33–1.48)
Pembro + Chemo	17 (56.7)	8.4 (5.4–NR)