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Immunotherapy in Operable Breast Cancer

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Outline

- Triple negative breast cancer
  - Current standards of care
  - Future directions
- ER+ breast cancer
- HER2+ breast cancer

Rationale for checkpoint inhibitors in TNBC

- Higher mutational burden than HER2+ or HR+ tumors
  - Can lead to a higher frequency of immunogenic mutations
  - Marker of improved survival following immunotherapy across multiple tumor types
- Higher mean quantities of tumor infiltrating lymphocytes (TILs) relative to other breast cancer subtypes
  - In early TNBC, higher TIL count correlates with improved survival, reduced recurrence risk, and better response to NACT
- Higher rate of PD-L1 expression relative to other breast cancer subtypes
  - Potential therapeutic target for anti-PD1 or –PDL1 antibodies

Lancet. 2017; 389 (10087): 2430-42. J Pathol Clin Res. 2015; 1(4): 225-38. Nat Genet. 2019; 51 (2): 202-6. Ann Oncol 2014; 25 (8): 1544-50. Cancer Immunol Res. 2014; 2 (4): 361-70.

Neoadjuvant checkpoint inhibition

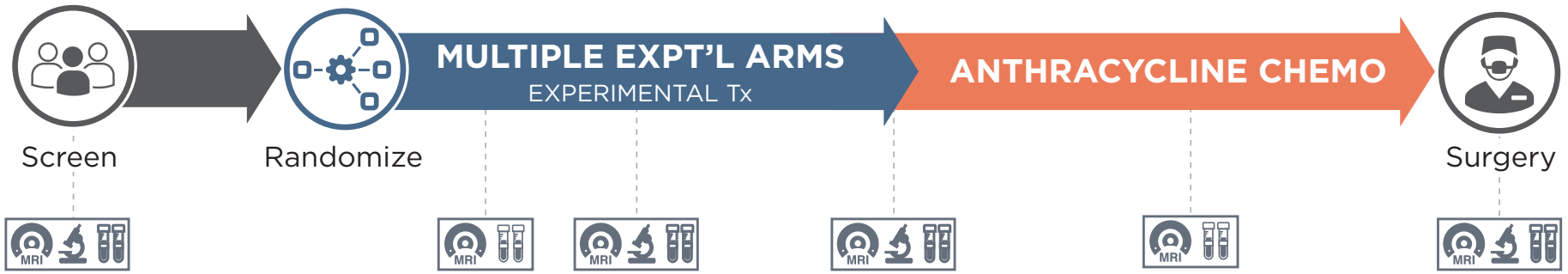
- Preclinical data shows that administering immunotherapy in the neoadjuvant setting before tumor resection results in **better survival**

- **Immune analyses** show that stronger and broade immune responses are stimulated when immunotherapy is administered with the primary tumor is still present

- Neoadjuvant chemo-immunotherapy may provide a unique opportunity to stimulate the immune system to **find and destroy micrometastases** while the tumor and its microenvironment are still intact

Am Soc Clin Oncol Educ Book
. 2022 Apr:42:1-15.

I-SPY 2



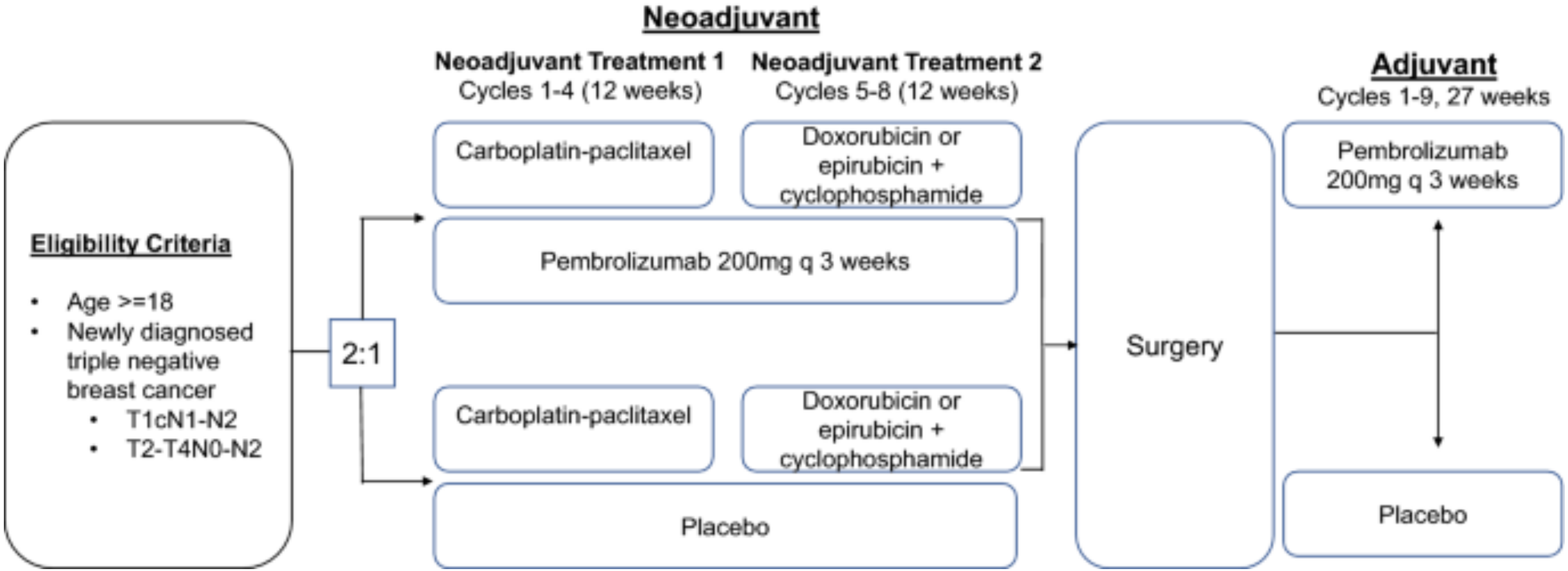
- Paclitaxel + pembrolizumab x 4 cycles → AC x 4 cycles→ surgery
- 69 women received this combination (40 HR+ patients, 29 TNBC patients)

Subgroup	pCR with pembrolizumab	pCR rate control
ERBB2-	44%	17%
HR+/ERBB2-	30%	13%
TNBC	60%	22%

- Patients with pCR following pembrolizumab plus chemotherapy had high event-free survival rates (93% at 3 years with 2.8 years' median follow-up).

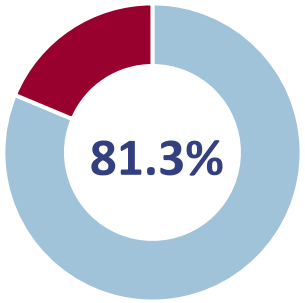
JAMA Oncol. 2020;6(5):676-684.

KEYNOTE 522 study design



KEYNOTE 522: pCR and EFS rates with neoadjuvant pembrolizumab

Pembrolizumab + chemotherapy
N=784



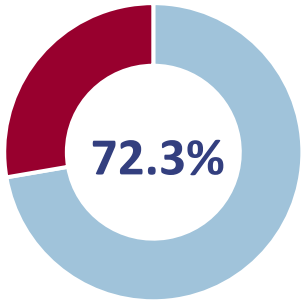
5-Year Event-Free Survival

64.8%

pCR rate

EFS HR: 0.63
95% CI: 0.49-0.81

Placebo + chemotherapy
N=390



5-Year Event-Free Survival

51.2%

pCR rate

P < 0.001

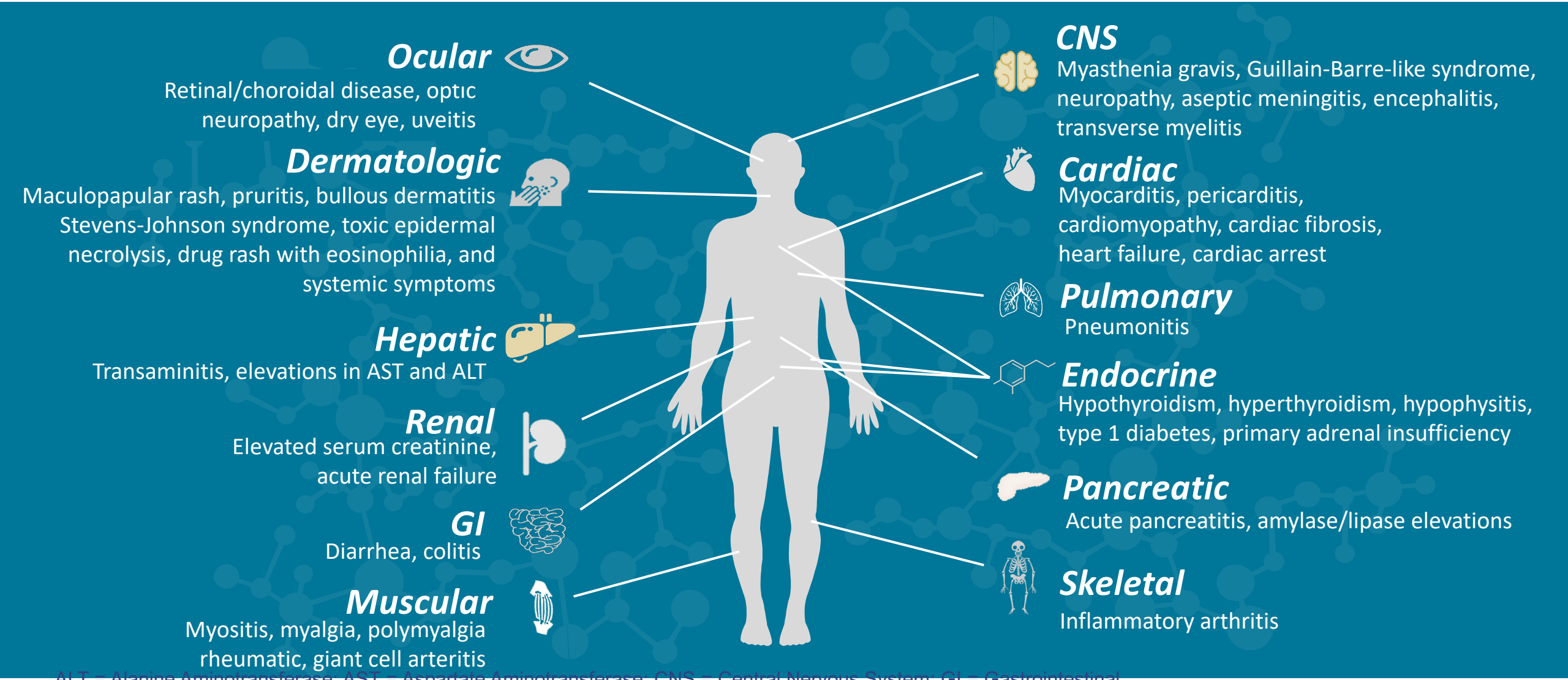
Effects seen regardless of PD-L1 status
Benefit seen even in patients with RCB-0, RCB-1, and RCB-2*

*Exploratory analysis

TNBC = Triple-negative Breast Cancer; pCR = pathologic Complete Response; EFS = Event-Free Survival; PD-L1 = Programmed Death-Ligand 1

Schmid P, et al. *N Engl J Med.* 2022;386:556-567; Schmid P, et al. *Ann Oncol*. 2023;34(suppl_2):S1257; Puszti L, et al. *Ann Oncol*. 2024;35(5):429-436.

Immunotherapy-Related Toxicities



ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; CNS = Central Nervous System; GI = Gastrointestinal

NCCN. Clinical Practice Guidelines: Management of Immunotherapy-Related Toxicities. Version 1.2024. www.nccn.org. Accessed 4/22/2024.

Tolerability of Neoadjuvant Pembrolizumab

KEYNOTE-522 Adverse Events of Special Interest		
	Pembrolizumab+CT	**PBO+CT**
Infusion Reactions, any / G3+	16.9 / 2.6	11.1 / 1
Hypothyroidism	13.7 / 0.4	3.3 / 0
Hyperthyroidism	4.6 / 0.3	1 / 0
Severe Skin Reaction	4.4 / 3.8	1 / 0.3
Adrenal Insufficiency	2.3 / 1.3	0 / 0

- **Treatment-related adverse effects more common during neoadjuvant portion of treatment**
- **AEs led to discontinuation of any drug in 23.3% of the patients in the pembrolizumab–chemotherapy group and 12.3% of the patients in the placebo–chemotherapy group**

Schmid P, et al. *N Engl J Med.* 2022;386:556-567.

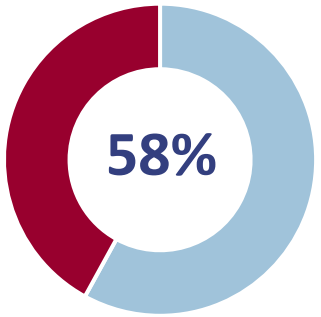
Could less be more in some situations?

NEOPACT

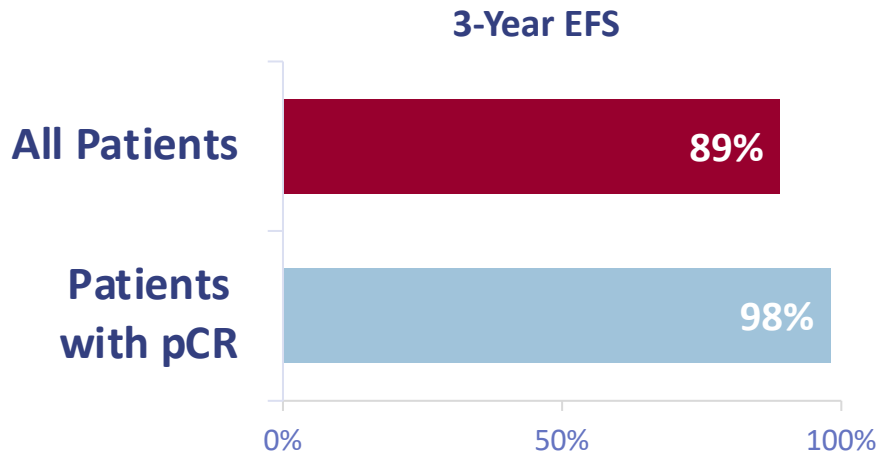
*Single-arm, phase 2 trial

*115 women with stage I-III TNBC
-39% node positive

*All patients received six cycles of:
-carboplatin AUC 6
-docetaxel 75mg/m2
-pembrolizumab 200mg



pCR rate



Addition of neoadjuvant pembrolizumab yields meaningful pCR rates and encouraging EFS, and offers an alternative to SOC

SCARLET: KN 522 vs NeoPACT (will use EFS as primary endpoint)

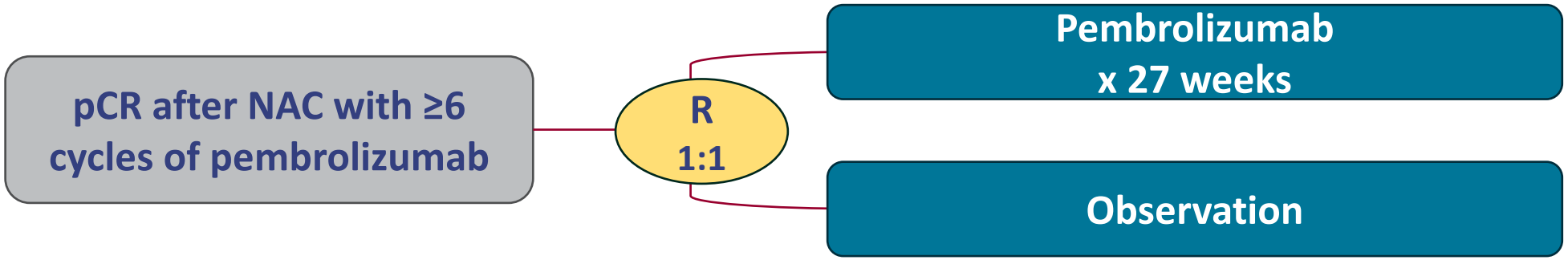
JAMA Oncol. 2024; 10 (2): 227-235.

Clinical Scenarios

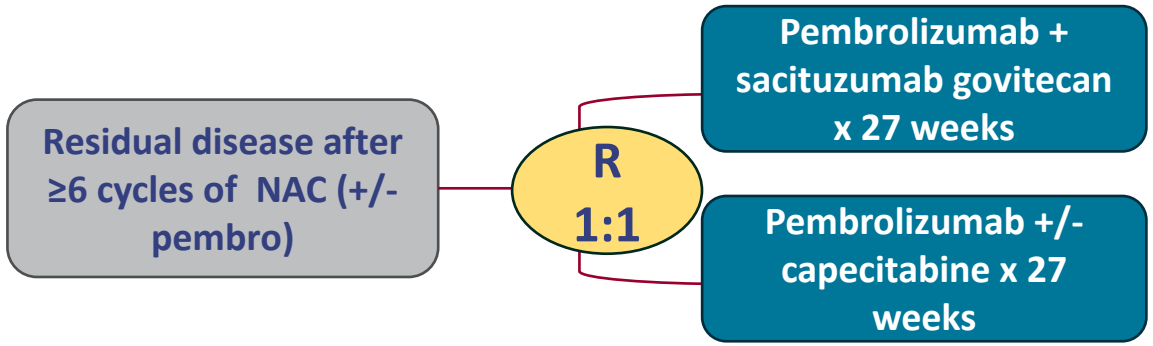
- 55F with a new diagnosis of TNBC of the left breast, cT2N1
- History of TNBC of the right breast 15 years ago; at that time received dose-dense AC-paclitaxel
- 42F with a new diagnosis of node-positive TNBC of the right breast
- Found to carry a BRCA1 mutation
- Does well with four cycles of carbo/taxol/pembro with excellent tumor shrinkage
- Has first cycle of AC-pembro and has debilitating nausea, bone pain and fatigue

Can we use pCR for further optimization?

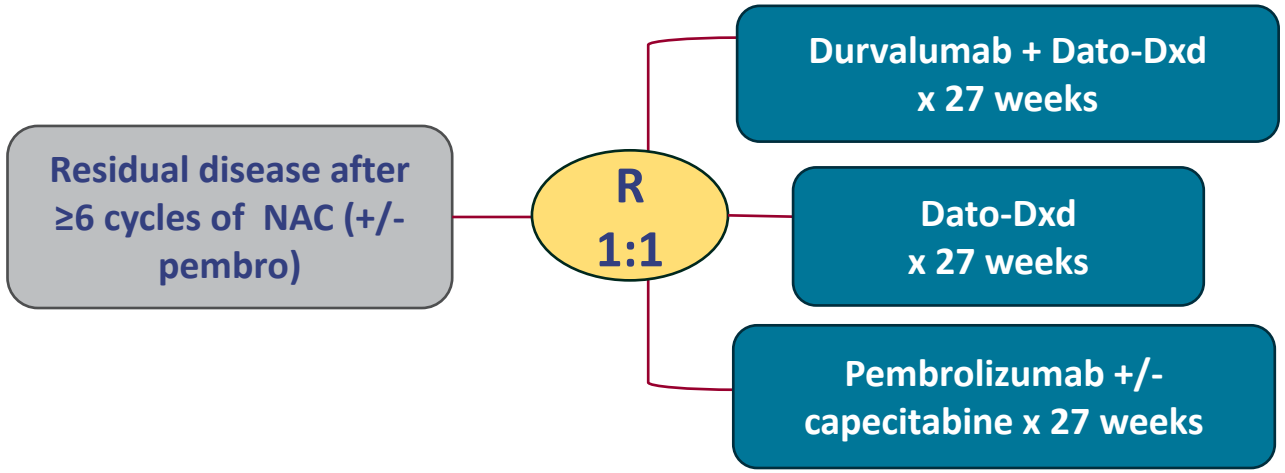
- **OPTIMICE-pCR** (NCT05812807)



- **OptimICE-RD** (NCT05633654)



- **TROPION-Breast 03** (NCT05629585)



Other novel neoadjuvant immunotherapy combinations

- **ISPY 2 (and ISPY 2.2)**
  - Durvalumab + olaparib + paclitaxel→AC
  - Intratumoral SD-101 + pembrolizumab
  - Durvalumab + Dato-Dxd→ taxane-based chemotherapy →AC
- **TROPION-Breast 04**
  - Phase 3 RCT of neoadjuvant Dato-DXd + durvalumab followed by adjuvant durvalumab versus SOC (KN 522 regimen)

Cancer Cell 2021 Jul 12;39(7):989-998.e5., J Clin Oncol 29 (15), May 2021.

High risk HR+ early breast cancer

- There is limited evidence demonstrating the benefit of endocrine therapy in patients with HR-low cancers
  - Defined as tumors where 1–10% of cells stain positive for ER and/or PR
  - These account for 2–3% of HR+ breast cancers.
- Several studies have shown that the prognosis for patients with HR-low/HER2– cancers and the biology of their tumors are comparable to TNBC
  - Probably a continuum of how we define this group of patients
- Perhaps these patients could benefit from immunotherapy as well

NPJ Breast Cancer. 2021;7(1):101. Ann Oncol. 2021;32(11):1410-1424

IO and HR+: What we know so far

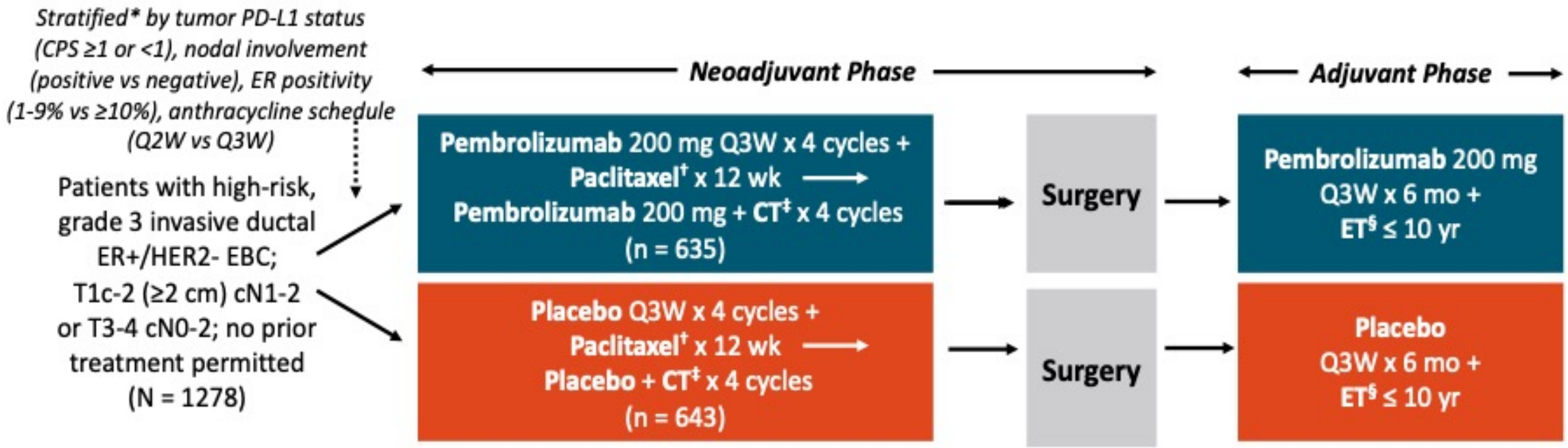
- **I-SPY trial**
  - Pembrolizumab + paclitaxel→AC: pCR= 34.2% in MammaPrint high risk HR+/HER2- patients
  - Durvalumab, olaparib and weekly paclitaxel→AC: pCR=28% in MammaPrint high-risk HR+HER2– patients

- **CheckMate 7FL**
  - Nivolumab + neoadjuvant chemotherapy: pCR= 24.5% in nivolumab arm vs 13.8% in NAC alone
    - Stage 3: pCR 30.7% vs 8.1%

Journal of Clinical Oncology **35**, 506–506 (2017). *Cancer Cell* **39**, 989-998.e5 (2021). *Annals of Oncology* **34**, S1259–S1260 (2023).

KEYNOTE 756: Study schema

- International, randomized, open-label phase III trial



*Patients in Eastern Europe stratified by PD-L1 status only; no stratification in China; all other countries stratified by all factors. †80 mg/m² QW. ‡Doxorubicin 60 mg/m² Q3W, epirubicin 100 mg/m² Q3W, cyclophosphamide 600 mg/m² Q3W or Q2W. §ET according to institution. Radiotherapy permitted in adjuvant phase.

- Primary endpoints: pCR (ypT0/Tis ypN0) at time of surgery; EFS
- Secondary endpoints: OS; pCR (ypT0 ypN0); pCR (ypT0/Tis); efficacy in PD-L1 CPS ≥1 group; safety

Annals of Oncology. 34 (2), S1260, Oct 2023. Presented with permission from Dr. Aditya Bardia.

KEYNOTE 756: pCR by Subgroup

Patients With pCR at First Interim Analysis by Subgroup, % (n/N)	Pembrolizumab	Placebo	Estimated Treatment Difference, % (95% CI)
Overall disease stage			
▪ II	25.8 (103/399)	16.7 (68/408)	9.1 (3.5-14.8)
▪ III	21.6 (51/236)	13.6 (32/235)	8.0 (1.1-14.9)
Clinical nodal involvement			
▪ Positive	25.1 (143/570)	15.8 (92/582)	9.3 (4.6-13.9)
▪ Negative	16.9 (11/65)	13.1 (8/61)	3.8 (-9.2-16.7)
Region			
▪ China	12.5 (11/88)	9.9 (9/91)	2.6 (-7.0-12.5)
▪ Eastern Europe	29.5 (41/139)	16.2 (21/130)	13.3 (3.3-23.2)
▪ Other countries	25.0 (102/408)	16.6 (70/422)	8.4 (2.9-13.9)
PD-L1 expression			
▪ CPS <1	7.2 (11/153)	2.6 (4/154)	4.5 (-0.4-10.1)
▪ CPS 1-9	15.7 (36/229)	9.1 (21/230)	6.4 (0.4-12.7)
▪ CPS ≥1	29.7 (143/482)	19.6 (96/489)	9.8 (4.4-15.2)
▪ CPS ≥10	42.3 (107/253)	29.0 (75/259)	13.2 (4.9-21.4)
▪ CPS ≥20	53.6 (67/125)	36.4 (47/129)	17.4 (5.1-29.1)

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KEYNOTE 756: pCR by Subgroup

Patients With pCR at First Interim Analysis, % (n/N)	Pembrolizumab	Placebo	Estimated Treatment Difference, % (95% CI)
PD-L1 CPS ≥1			
▪ ER+ <10%	57.6 (19/33)	33.3 (13/39)	24.2 (1. to -45.1)
▪ ER+ ≥10%	27.6 (124/449)	18.4 (83/450)	9.2 (3.7 to 14.6)
PD-L1 CPS <1			
▪ ER+ ≥10%	7.2 (11/152)	2.7 (4/150)	4.6 (-0.4 to 10.2)
CT exposure			
▪ Full exposure*	26.2 (142/543)	16.9 (95/563)	9.3 (4.5 to 14.1)
▪ < Full exposure	13.2 (12/91)	6.4 (5/78)	6.8 (-2.6 to 16.2)

*Paclitaxel 10-12 doses, doxorubicin or epirubicin 4 doses, and cyclophosphamide 4 doses.

**Degree of PDL1 positivity, low ER status, and full exposure to chemotherapy were all indicative of significant benefit from neoadjuvant immunotherapy

**Event-free survival still immature: not officially approved

Annals of Oncology. 34 (2), S1260, Oct 2023. Presented with permission from Dr. Aditya Bardia.

What about HER2+ breast cancer?

- **KEYRICHED-1**: a prospective single arm phase II trial
- The trial enrolled 48 women with stage I-III HER2+ early breast cancer who ALSO were HER2-enriched by PAM-50 subtype
- Patients received four cycles of pembrolizumab, pertuzumab and trastuzumab prior to surgery
  - 65% had tumors >2cm, 30% positive node

- **Results:** pCR-rate was 52% (95%CI 0.37-0.67) in all evaluable patients
  - Despite HER2-E subtype, no pCR was observed in the four patients with IHC 2+/FISH positive status in contrast to 20/39 (51.2%) pCR in IHC HER2 3+ tumors.
  - pCR-rate in HR+/HER2+ tumors was 38.5% compared to 58.5% in HR-/HER2+ tumors

Kuemmel S et al. *Cancer Res* (2022) 82 (4_Supplement): PD10-11

What about HER2+ breast cancer?

- **neoHIP**: adding pembrolizumab in the curative-intent, treatment-naive setting may:
  - allow for de-escalation of cytotoxics
  - confer life-long, tumor-specific immunity/improve cure rates
  - Investigators also hypothesize that synergy of pembrolizumab/trastuzumab with paclitaxel may overcome the need for dual HER2-blockade

- NeoHIP is a randomized phase II trial with three arms: **THP** vs **THP-pembrolizumab** vs **TH-pembrolizumab**

J Clin Oncol 41 (16), May 2023

Conclusions

- Immunotherapy (mostly in the form of pembrolizumab) has become a standard of care in stage 2-3 TNBC, in combination with chemotherapy
- Additional studies will allow us to further refine and individualize our approaches in this patient population
    - pCR as a biomarker
    - Tumor-infiltrating lymphocytes
- Patients with ER+ breast cancer (especially those with low ER expression) may soon have the opportunity to benefit from chemo-immunotherapy
- Studies of immunotherapy + anti-HER2-therapy in HER2+ breast cancer are ongoing
- Awareness of the toxicities of immunotherapy is critical, now that the use of these therapies is more widespread

Thank you!