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Stage I Triple Negative Breast Cancer: Neoadjuvant Therapy? Yes or No

Winship Cancer Institute Annual Cancer Conference: 2022 Debates and Didactics in Hematology and Oncology

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Disclosures

- Merck
- Daiichi Sankyo

Outline

- Case presentation
- Decision making re: neoadjuvant chemotherapy
- Addition of Immunotherapy?
  - Benefits
  - Risks
  - In practice
- Conclusions:
  - T1a/bN0 TNBC: Recommend surgery first, followed by consideration of adjuvant chemotherapy based on final pathology
  - T1cN0 TNBC: Consider neoadjuvant chemotherapy, followed by surgery and adjuvant chemotherapy based on residual disease
  - Lack of data to support the addition of immunotherapy to chemotherapy for stage I TNBC

Case Description: History

- **CASE 1 Patient:** 60-year-old female presents with a right breast mass on screening MMG
- **PMH:** Osteoarthritis
- **PSH:** Cholecystectomy
- **Family history:**
  - ❖ Breast ca in paternal aunt (age 58)
  - ❖ Uterine ca in paternal GM (age 67)
- **Physical exam:** Right breast with **no palpable abnormalities**, no overlying skin changes, no palpable cervical, supra/infraclavicular or axillary lymphadenopathy
- **Germline testing:** Negative for pathogenic mutations with multi-gene testing

- **CASE 2 Patient:** 60-year-old female presents with a palpable right breast abnormality
- **PMH:** Osteoarthritis
- **PSH:** Cholecystectomy
- **Family history:**
  - ❖ Breast ca in paternal aunt (age 58)
  - ❖ Uterine ca in paternal GM (age 67)
- **Physical exam:** Right breast with ~**1.5cm** palpable hardened breast mass, mildly tender on palpation, no overlying skin changes, no palpable cervical, supra/infraclavicular or axillary lymphadenopathy
- **Germline testing:** Negative for pathogenic mutations with multi-gene testing

Case Description: Imaging

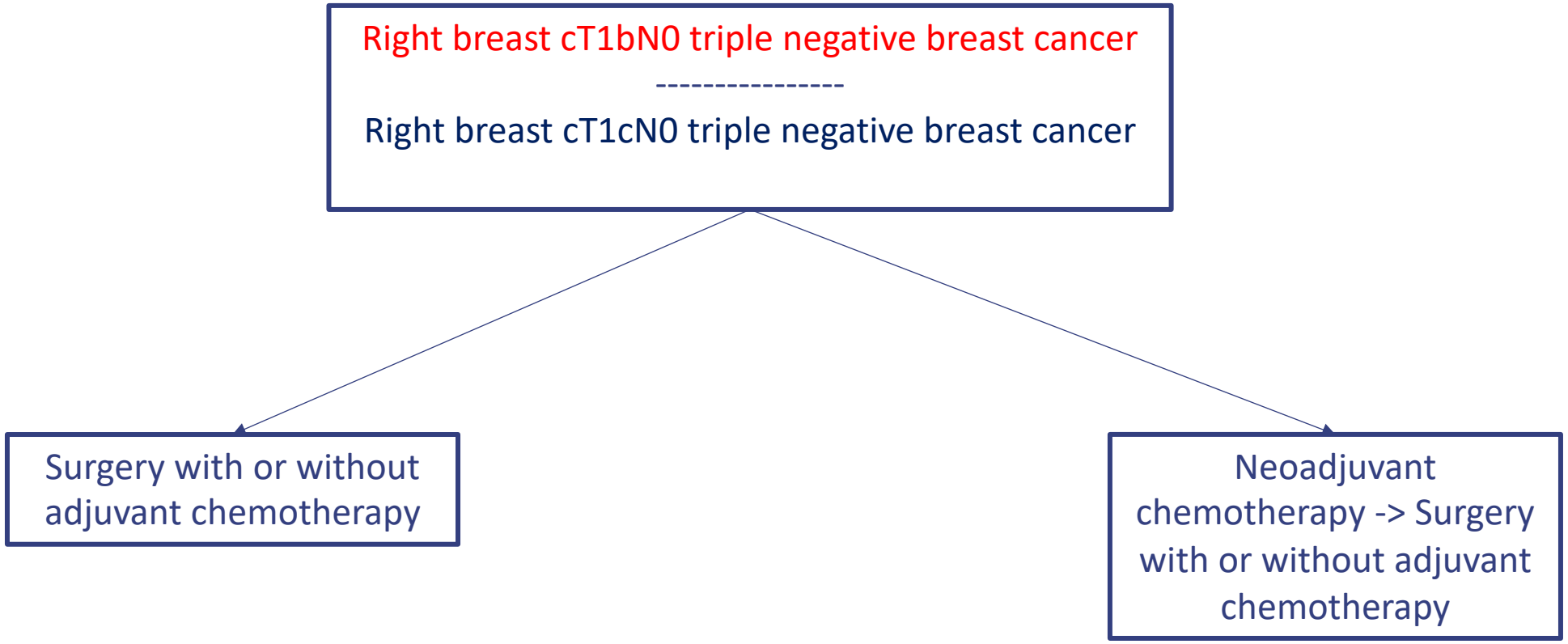
- **CASE 1 BL MMG and US:**
  - ❖R breast spiculated mass UOQ periareolar aspect
  - ❖US R breast 9:00 axis 1 CFN irregular hypoechoic mass measuring 8x6x9mm
  - ❖BL axilla neg
- **CASE 2 BL MMG and US:**
  - ❖R breast spiculated mass UOQ periareolar aspect
  - ❖US R breast 9:00 axis 1 CFN irregular hypoechoic mass measuring 1.6 x 1.2 x 1.4 cm
  - ❖BL axilla neg

Case Description: Pathology

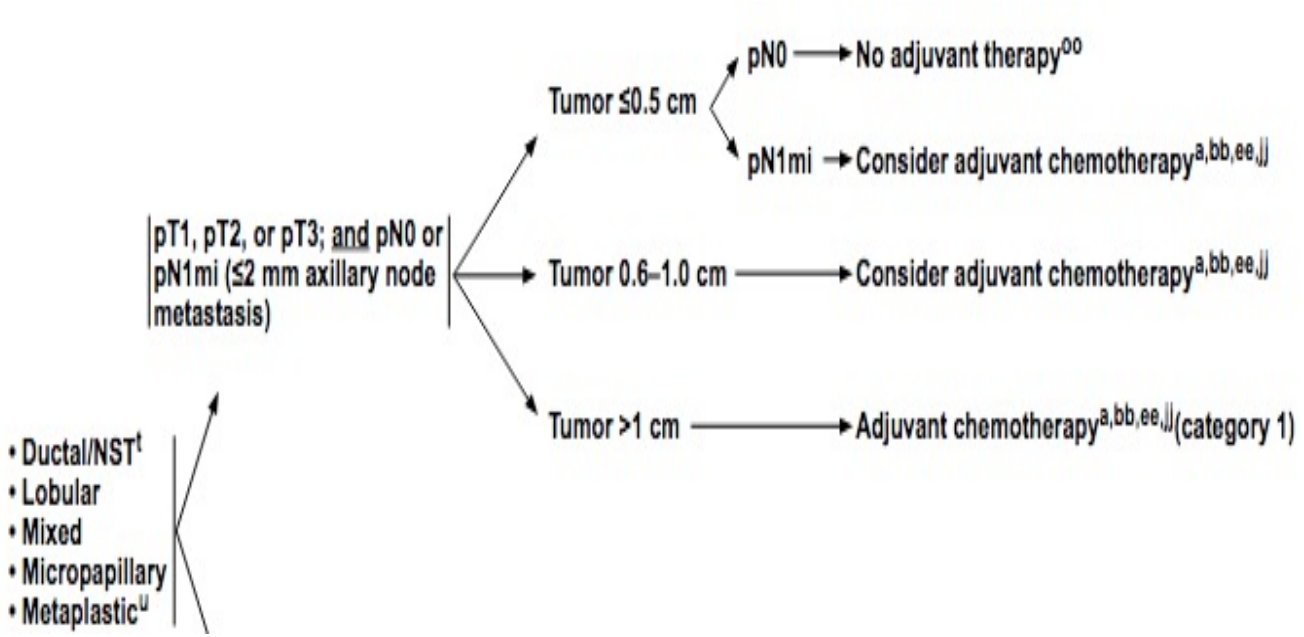
- **CASE 1 and CASE 2 US-guided core biopsy:**
  - ❖IDC, grade III
  - ❖ER 0% PR 0% HER2 1+ IHC
  - ❖Ki-67 68%

  - ❖Diagnosis:
  - ❖CASE 1: Right breast cT1bN0 triple negative breast cancer
  - ❖CASE 2: Right breast cT1cN0 triple negative breast cancer

Case Description: Treatment Decision-Making



NCCN Guidelines



Candidates for Preoperative Systemic Therapy

- Patients with inoperable breast cancer:
  - IBC
  - Bulky or matted cN2 axillary nodes
  - cN3 nodal disease
  - cT4 tumors
- In select patients with operable breast cancer
  - Preoperative systemic therapy is preferred for:
    - ◊ HER2-positive disease and TNBC, if ≥cT2 or ≥cN1
    - ◊ Large primary tumor relative to breast size in a patient who desires breast conservation
    - ◊ cN+ disease likely to become cN0 with preoperative systemic therapy
  - Preoperative systemic therapy can be considered for cT1c, cN0 HER2-positive disease and TNBC
- Patients in whom definitive surgery may be delayed.

Non-candidates for Preoperative Systemic Therapy

- Patients with extensive in situ disease when extent of invasive carcinoma is not well-defined
- Patients with a poorly delineated extent of tumor
- Patients whose tumors are not palpable or clinically assessable

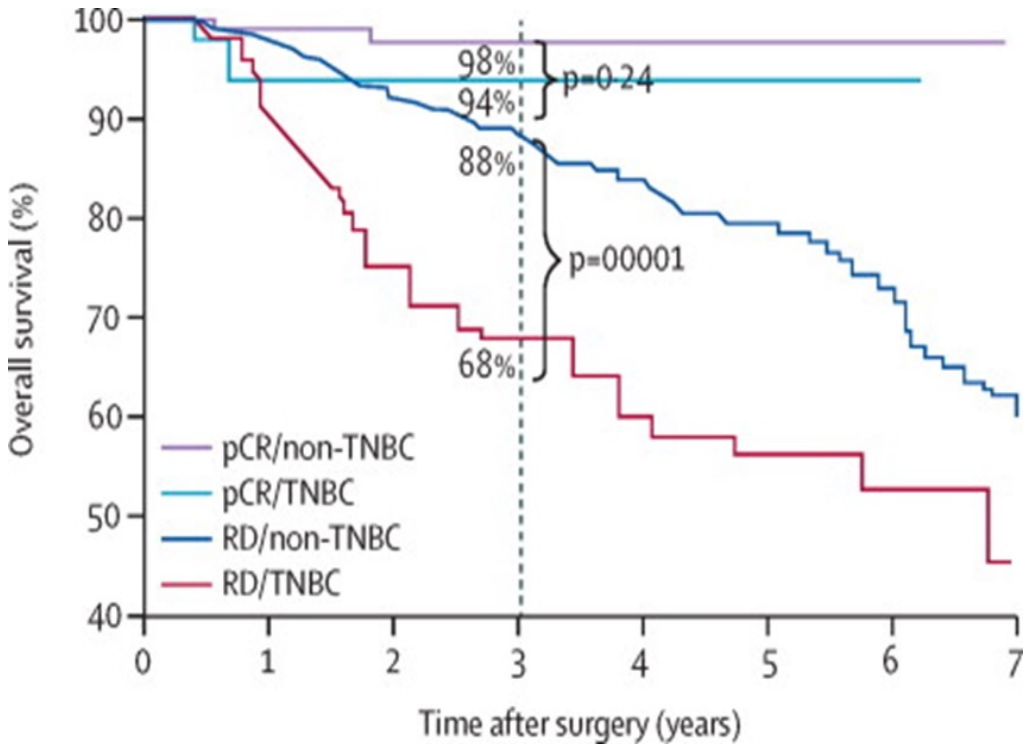
Stage T1aN0 TNBC: Surgery only

Stage T1bN0 TNBC: Surgery with consideration of adjuvant chemotherapy

Stage T1cN0 TNBC: Consider preoperative chemotherapy, followed by surgery and adjuvant chemotherapy based on residual disease

Early-Stage TNBC Survival

- 91% 5-year survival rate for patients with stage I TNBC
  - Higher in those with T1a or T1b N0 TNBC
  - Risks of chemotherapy outweigh the benefit
- Can make the argument that those with moderately high risk TNBC (cT1cN0) disease should receive neoadjuvant chemotherapy
  - Allows for use of adjuvant systemic chemotherapy (capecitabine) if residual disease seen



C Liedtke, C Mazouni, KR Hess, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol, 26 (2008), pp. 1275–1281

Pros & Cons of Neoadjuvant Therapy for TNBC

PROS

- Provides important prognostic information at an individual patient level
- Identifies patients with residual disease at higher risk for relapse to allow for supplemental adjuvant systemic therapy
- Facilitates breast conservation; allows time for genetic testing and finalizing surgical plan with breast reconstruction if needed

cT1cN0 PROS > CONS

CONS

- Overtreatment, particularly for smaller, node negative TNBC
  - Risks outweigh the benefit of neoadjuvant systemic therapy
- Possibility of disease progression during preoperative systemic therapy
- Non-palpable tumors or clinical in-assessable tumors should NOT be treated with neoadjuvant therapy

cT1a-bN0 tumors CONS >> PROS

Case Description: Treatment

- **Case 1:** Recommend surgery, followed by adjuvant chemotherapy based on final surgical pathology

- **Case 2:** Recommend neoadjuvant chemotherapy, followed by surgery and adjuvant chemotherapy based on residual disease

Addition of Immunotherapy???

- Should we add immunotherapy to neoadjuvant chemotherapy for stage I TNBC??

FDA Approval for Pembrolizumab in Early-Stage TNBC

On July 26, 2021, the FDA approved pembrolizumab for high-risk, early-stage, triple-negative breast cancer in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

High-Risk, Early-Stage TNBC defined as stage II or III TNBC:

- **T1c, N1–2**
- **T2–4, N0–2**

NOT approved for patients with T1a-T1c N0 Disease

Trial name	Phase	Primary endpoint	Population enrolled	Regimen	pCR outcome (95% CI), %	Survival outcomes
KEYNOTE-522	3	pCR and EFS in ITT	Untreated stage II–III TNBC patients ($n = 1174$)	Neoadjuvant TCb -> AC ± pembro, followed by pembro (or placebo) for 1 year after surgery	64.8% vs 51.2%; delta 13.6% (5.4–21.8), $p <$ 0.001	3-year EFS 84.5% vs 76.8% (HR 0.63, 95% CI 0.48–0.82, $p = 0.0003$) 3-year DDFS 87% vs 80.7% (HR 0.61, 95% CI 0.46-0.82) 3-year OS 89.7% vs 86.9% (HR 0.72, 95% CI 0.51–1.02, $p = 0.032$)
Impassion031	3	pCR in ITT and in PD-L1 + patients	Untreated stage II–III TNBC patients ($n = 333$)	Neoadjuvant nabT -> AC ± atezo, followed by atezo (or placebo) for 1 year after surgery (capecitabine also allowed)	58% vs 41%; delta 17% (6–27), $p = 0.0044$	EFS HR 0.76 (95% CI 0.40–1.40) DFS HR 0.74 (95% CI 0.32–1.70) OS HR 0.69 (95% CI 0.25–1.87)
NeoTRIPaPDL1	3	EFS	Untreated stage II–III TNBC patients ($n = 280$)	Neoadjuvant nabTCb ± atezo followed by adjuvant anthracyclines after surgery	43.5% vs 40.8%; OR, 1.11 (0.69–1.79), $p =$ 0.66	Pending
GeparNuevo	2	pCR in ITT	Untreated stage I–III TNBC patients ($n = 174$)	Neoadjuvant nabT -> AC ± durva followed by physician's choice of adjuvant treatment after surgery	53.4% vs 44.2%; OR, 1.45 (0.80–2.63), $p =$ 0.287	3-year iDFS 84.9% vs 76.9% (HR 0.54, 95% CI 0.27–1.09, $p = 0.0559$) 3-year DDFS 91.4% vs 79.5% (HR 0.37, 95% CI 0.15–0.87, $p = 0.0148$) 3-year OS 95.1% vs 83.1% (HR 0.26, 95% CI 0.09–0.79, $p = 0.0076$)
I-SPY2	2	pCR in ITT	Untreated stage II–III TNBC and HR+/HER2- BC patients ($n = 107$)	Neoadjuvant T - > AC ± pembro followed by physician's choice of adjuvant treatment after surgery	60% (44–75) vs 22% (13–20) (TNBC patients)	EFS HR 0.60 (TNBC patients)

GeparNUEVO: Study Design

- Randomized, double-blind phase II trial
  - Current analysis of long-term outcomes after median follow-up of 43.7 mo (range: 4.9-56.1)

Stratified by stromal TILs (low vs med vs high)

Patients with previously untreated uni-/bilateral primary, nonmetastatic, invasive TNBC; tumor size ≥2 cm (cT1c-cT4a-d); no autoimmune disease; ECOG PS 0/1 (N = 174)

Durvalumab 0.75 g IV x 1 (n = 88)	**Durvalumab** 1.5 g IV Q28D + nab-Pac 125 mg/m^2 QW	Durvalumab 1.5 g IV Q28D + EC† D1Q14 for 4 cycles	SURGERY
Placebo (n = 86)	Placebo Q28D + nab-Pac 125 mg/m^2 QW	Placebo Q28D + EC† D1Q14 for 4 cycles	

*Window of opportunity closed after n = 117 enrolled due to IDMC concerns about delay in patients starting CT in placebo arm. †Epirubicin 90 mg/m^2 + cyclophosphamide 600 mg/m^2.

Primary endpoint:
pCR (ypT0, ypN0) at surgery

Secondary endpoints:
invasive DFS, distant DFS, OS

GeparNUEVO: Survival Analysis

- The addition of durvalumab to neoadjuvant CT modestly improve pCR, though this was NOT statistically significant
  - 53.4% versus placebo 44.2% (OR 1.45, 95% CI 0.80–2.63, p = 0.224)

- However, it significantly prolonged iDFS, distant DFS, and OS vs placebo + neoadjuvant CT in patients with early TNBC
  - 3-yr rates:
    - iDFS, 85.6% vs 77.2% (HR: 0.48; *P* = .0398)
    - Distant DFS, 91.7% vs 78.4% (HR: 0.31; *P* = .0078)
    - OS, 95.2% vs 83.5% (HR: 0.24; *P* = .0108)

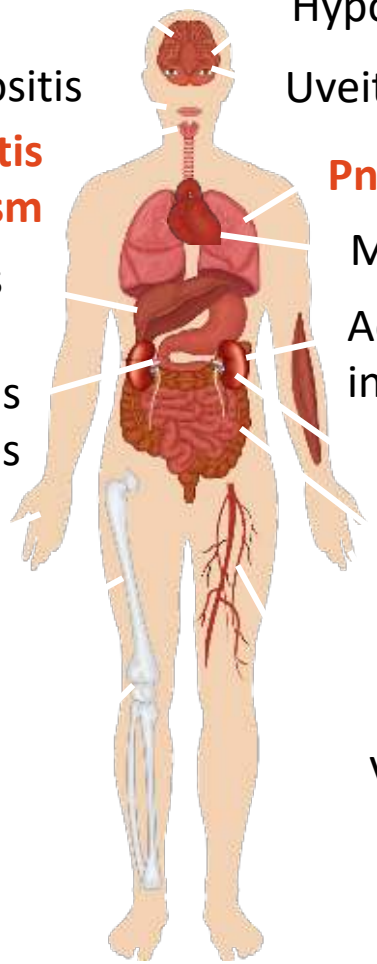
GeparNUEVO Survival Analysis: Baseline Characteristics, Patient Disposition

Characteristic, n (%)	Durvalumab (n = 88)	Placebo (n = 86)
Median age, yr (range)	49.5 (25.0-74.0)	49.5 (23.0-76.0)
Tumor stage cT3/4	7 (8.0)	3 (3.5)
Nodal stage cN+	27 (30.7)	27 (31.4)
Stage IIA and higher	56 (63.6)	57 (66.3)
Grade 3	74 (84.1)	71 (82.6)
TILs		
▪ Low (0% to 10%)	34 (38.6)	32 (37.2)
▪ Intermediate (11% to 59%)	42 (47.7)	41 (47.7)
▪ High (≥60%)	12 (13.6)	13 (15.1)
Received durvalumab or placebo alone in window before CT	59 (67.0)	58 (67.4)

Disposition, n	Durvalumab (n = 88)	Placebo (n = 86)
Discontinued any tx	32	35
Completed all tx regularly	56	51
Received surgery	88	85*
With recent f/u (up to 1 yr)	62	67
▪ Events	12	22
▪ Deaths	4	15

- Evaluable for long-term outcomes: n = 129

Toxicities Associated With Immune Checkpoint Inhibitors

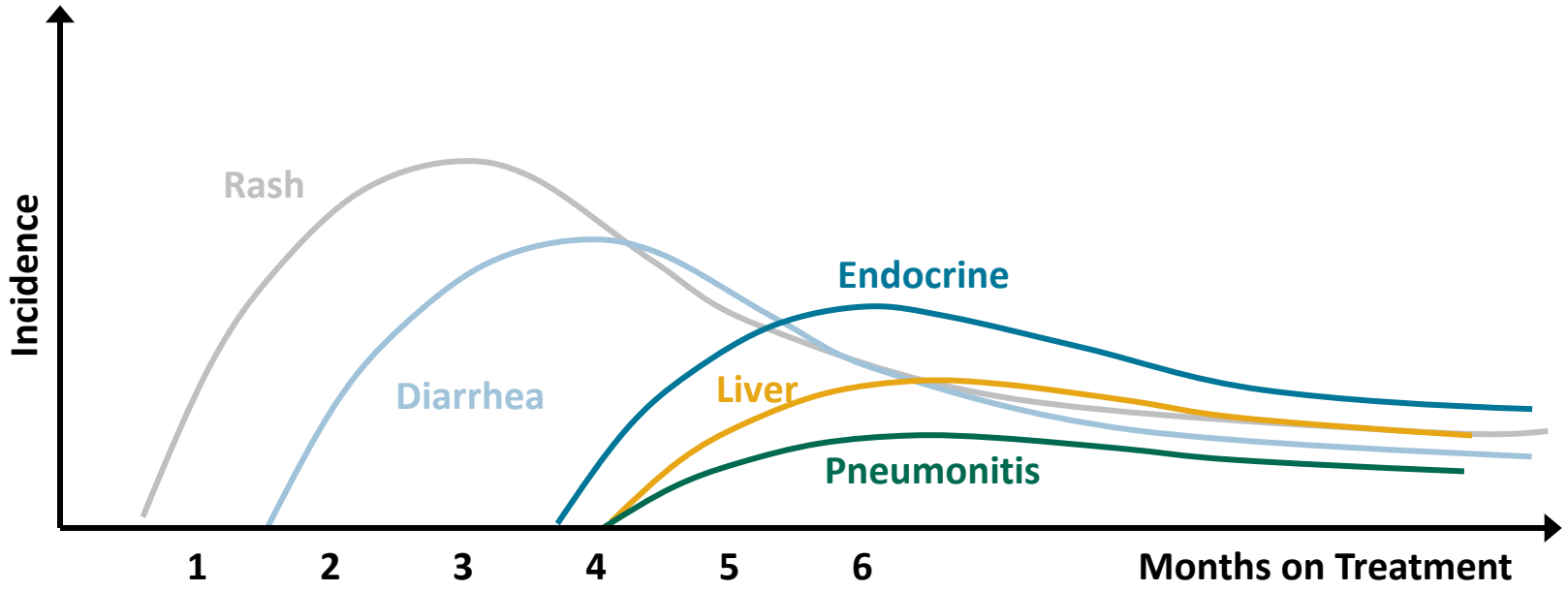


- Majority of irAEs are mild to moderate
- Severity can be asymptomatic to life-threatening; prompt recognition is crucial
- Onset is variable; can occur after cessation of therapy
- Most reversible with steroids; some require discontinuation of therapy
- Important to educate care team, patient, and caregivers on signs and symptoms of irAEs

Brahmer. 2018;36:1714. Postow. NEJM. 2018;378:158. Puzanov. JIC. 2017;5:95. Michot. EJC. 2016;54:139.

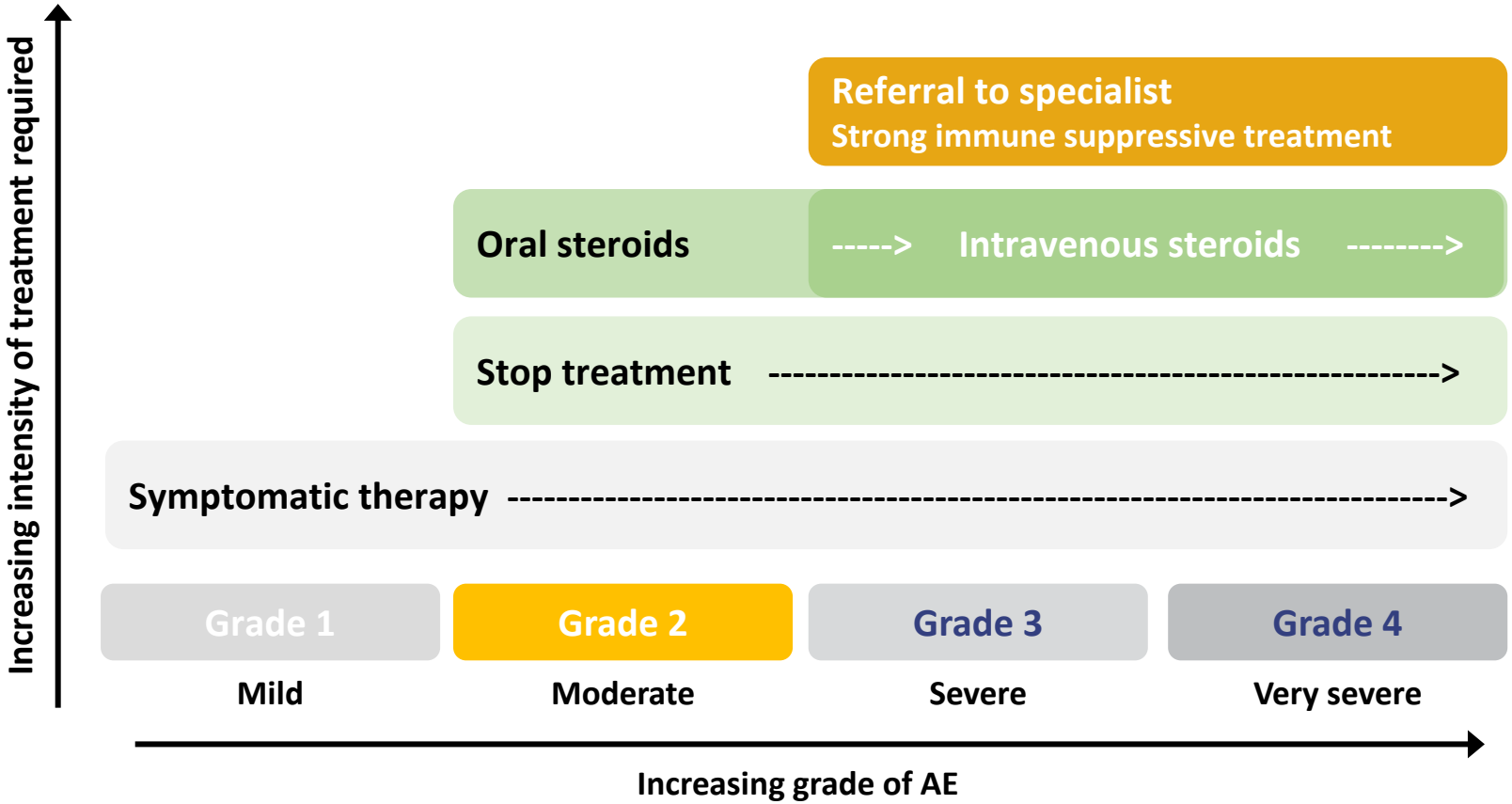
Toxicities Associated With Immune Checkpoint Inhibitors

- Timing can be highly variable
- irAE can occur months and even a year after the end of treatment
- Time course might be even more variable with novel combinations



Martins. Nat Rev Clin Oncol. 2019;16:563.

Managing AEs From Immune Checkpoint Inhibitors

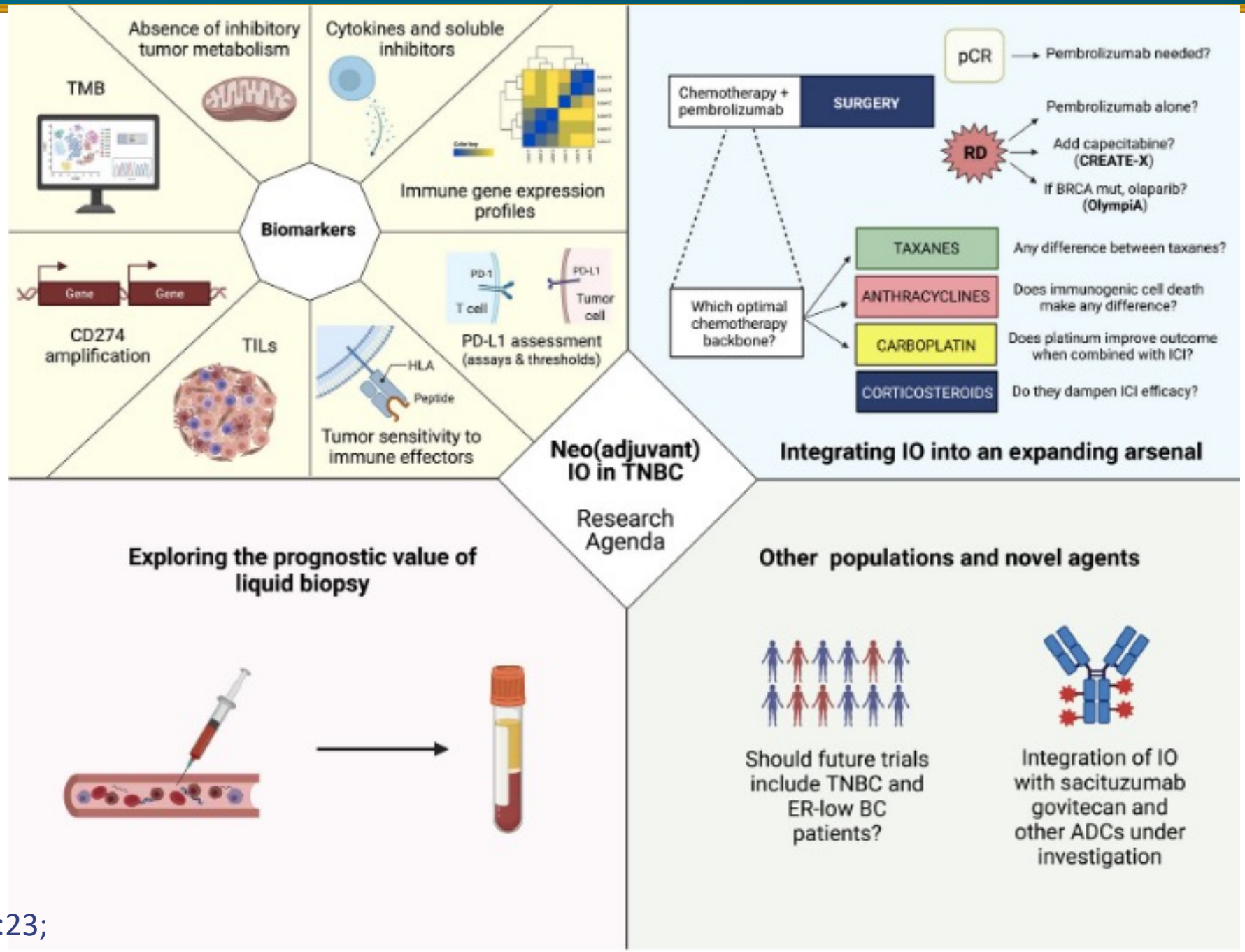


- Steroids (PO/IV): 1-2 mg/kg/day prednisone or equivalent, slow taper over 4-6 wk/52 days
- For some AEs, treatment can be restarted after resolution (eg, rash)
- For endocrinopathies:
  - ICI usually continued
  - Generally managed with hormone replacement, no steroids

Adapted from Champiat. ESMO Patient Guide Series. 2017.

Economic Challenge

Future Directions for Neoadjuvant Immuno-Chemotherapy for Early Stage TNBC



Tarantino et al. npjBreastCancer 8:23; https://doi.org/10.1038/s41523-022-00386-1. 2022.

Should we add neoadjuvant immunotherapy to chemotherapy for stage I TNBC?

My conclusions for now…

- Do NOT recommend neoadjuvant chemotherapy in cT1a/bN0 TNBC
- Consider neoadjuvant chemotherapy in cT1cN0 TNBC
- Do NOT recommend neoadjuvant immunotherapy in stage I TNBC until we fully understand clinical benefit (and long-term risks) and identify biomarkers of response (pCR) to IO in early-stage TNBC

THANK YOU!

- Questions?