HealthCare
MARKEY CANCER CENTER
Network

AN UPDATE ON THE MANAGEMENT OF TRIPLE NEGATIVE BREAST CANCER (TNBC):

June 14, 2023

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60-minute LIVE Webinar

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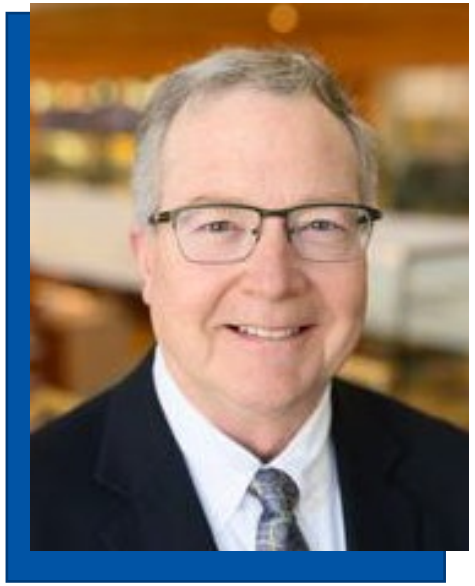
Wednesday, September 13th
12:00 PM EST

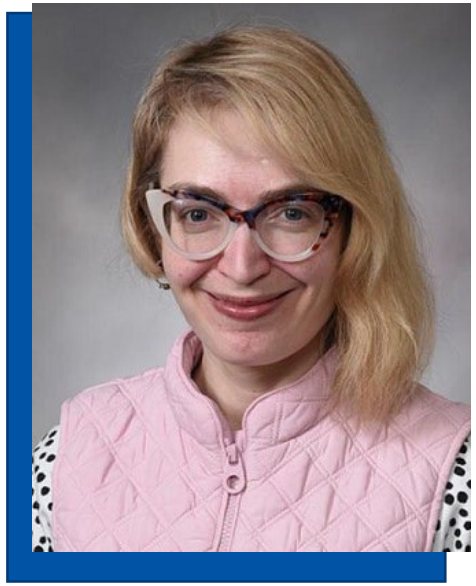
Tuesday, November 7th
12:00PM

WELCOME
Today's Moderator and Speaker



Timothy Mullett, MD, MBA, FACS

Professor
Division of Cardiothoracic Surgery and Medical Director, University of Kentucky, Markey Cancer Center Network Development



Ruta Arays, MD

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Objectives

- Overview of biology of TNBC
- Discuss current treatment options for early stage/locally advanced TNBC
- Discuss options for advanced or unresectable TNBC.

Question #1

- What percentage of patients will relapse within 5 years of their initial diagnosis of triple negative Breast Cancer?

A. 15-20%
B. 30-40%
C. 50-60%
D. 70-80%

Question #2

- What is the benefit of neoadjuvant chemotherapy compared with adjuvant chemotherapy?

A. Overall survival advantage with neoadjuvant chemotherapy has been definitively demonstrated.

B. Neoadjuvant therapy offers prognostic information in the form of tumor response to pre-operative therapy.

C. Neoadjuvant therapy results in fewer distant relapses.

D. Neoadjuvant therapy is always preferred in triple negative breast cancer to allow for better surgical outcomes.

Question #3

- What are the indications to perform genetic testing for ‘high penetrance breast cancer susceptibility genes (including BRCA1/2, PALB2, CDH1, PTEN and TP53)’?

A. Family history of breast cancer in any relative.
B. Age >50 yo
C. Greater than or equal to 3 diagnoses of breast cancer in patient and or a close blood relative.
D. Diagnosis of Triple negative breast cancer
E. C and D
F. All of the above

Question #4

- The addition of which of the following medications to standard chemotherapy has resulted in improved outcomes in triple negative breast cancer patients?

A. Durvalumab
B. Capecitabine
C. Olaparib
D. Pembrolizumab

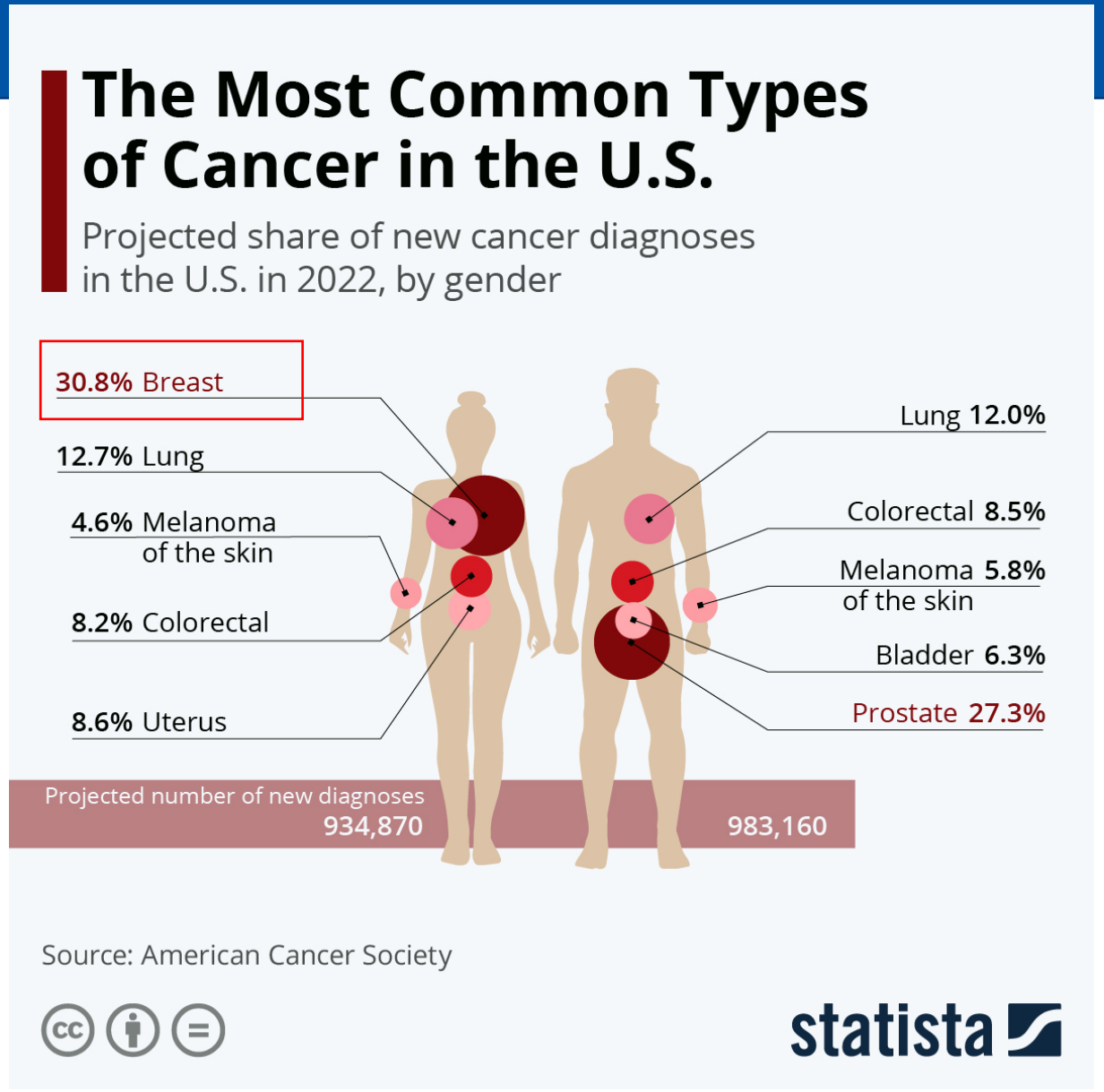
Question #5

- It is necessary to get PDL1 testing on all Stage II and Stage III TNBC patients being considered for neoadjuvant chemotherapy with KEYNOTE 522 regimen using pembrolizumab.

-True
-False

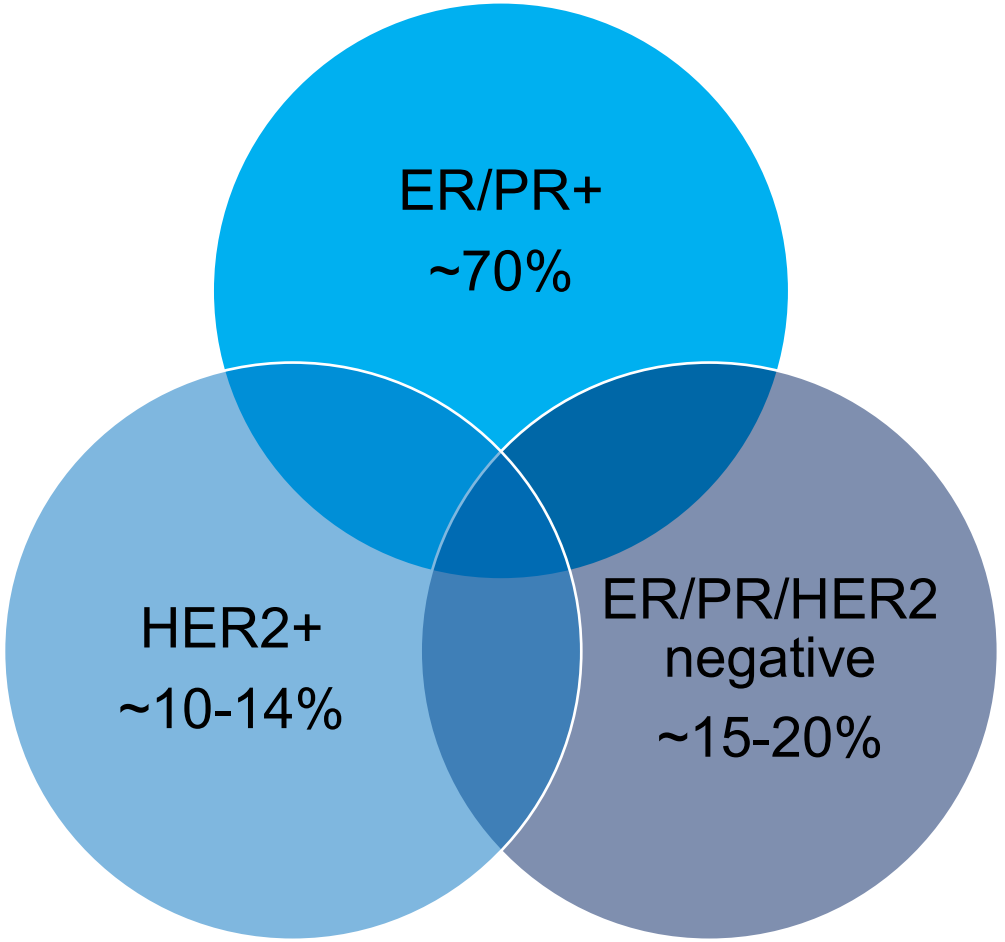
Patient Case

- A 50 year-old female presents to her primary care physician with complaints of a palpable nodule in her left breast. Diagnostic mammogram shows a 2.5 cm mass at the 3 o'clock position. Left breast ultrasound confirms findings of a mass and shows one axillary lymph node with prominent cortical thickening. Biopsy of the breast mass indicates an invasive ductal carcinoma. ER negative, PR negative and HER2 negative (0). Left axillary biopsy shows metastatic adenocarcinoma consistent with breast primary.



Buchholz, K. (February 4, 2022). The Most Common Types of Cancer in the U.S. [Digital image]. Retrieved September 15, 2022, from https://www.statista.com/chart/20692/most-common-types-of-cancer-us/

Breast Cancer by type



Cancer Stat Facts: Female Breast Cancer Subtypes, NIH

Background: TNBC

- TNBC is an aggressive form of breast cancer that tends to occur more frequently in younger women as well as women of color compared to the other breast cancer subtypes.
- It accounts for about 15-20% of all breast cancers and, by definition lacks estrogen, progesterone and HER2 expression
  - ER/PR <1% by Immunohistochemistry (IHC) is considered negative (ASCO/CAP guideline update 2020)
  - HER2 0-1+ by IHC or 2+ with negative FISH has traditionally been considered negative*

*ASCO Expert panel recently updated guidelines considering data from DESTINY-Breast-04 incorporating trastuzumab deruxtecan (T-DXd) for patients with HER2 ‘low’ expression who have received at lest 1 prior line of therapy.

Bagegni NA, Davis AA, Clifton KK, Ademuyiwa FO. Targeted Treatment for High-Risk Early-Stage Triple-Negative Breast Cancer: Spotlight on Pembrolizumab. Breast Cancer (Dove Med Press). 2022 Apr 29;14:113-123. doi: 10.2147/BCTT.S293597. PMID: 35515356; PMCID: PMC9064451.

Background: TNBC

- Treatments for early stage TNBC have typically included anthracyclines and taxanes in the neoadjuvant setting. While a portion of patients is cured with conventional chemotherapy, approximately 30-40% experience recurrence by 5 years.

- Interest remains high in finding optimal regimens and sequencing of treatments in order to reduce recurrence rates and improve outcomes.

Bagegni NA, Davis AA, Clifton KK, Ademuyiwa FO. Targeted Treatment for High-Risk Early-Stage Triple-Negative Breast Cancer: Spotlight on Pembrolizumab. Breast Cancer (Dove Med Press). 2022 Apr 29;14:113-123. doi: 10.2147/BCTT.S293597. PMID: 35515356; PMCID: PMC9064451.

Multidisciplinary Approach

- Overall management typically includes:
  - Surgery: Mastectomy versus Lumpectomy
  - **Systemic therapy: Neoadjuvant versus Adjuvant**
  - Radiation: Post-operative

- Other Considerations:
  - Genetic testing/counseling
    - May affect type of surgery and on occasion systemic treatment.

NCCN Guidelines Version 3.2023
Hereditary Cancer Testing Criteria

NCCN Guidelines Index
Table of Contents
Discussion

TESTING CRITERIA FOR HIGH-PENETRANCE BREAST CANCER SUSCEPTIBILITY GENES
(Specifically *BRCA1, BRCA2, CDH1, PALB2, PTEN,* and *TP53*. See GENE-A)[a,e,f,g]

Testing is clinically indicated in the following scenarios:

- See General Testing Criteria on CRIT-1.
- Personal history of breast cancer with specific features:
  - ≤50 y
  - Any age:
    - Treatment indications
      - To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting[h,i] (See NCCN Guidelines for Breast Cancer)
      - To aid in adjuvant treatment decisions with olaparib for high-risk,[j] HER2-negative breast cancer[h]
    - Pathology/histology
      - Triple-negative breast cancer
      - Multiple primary breast cancers (synchronous or metachronous)[k]
      - Lobular breast cancer with personal or family history of diffuse gastric cancer See NCCN Guidelines for Gastric Cancer
    - Male breast cancer
    - Ancestry: Ashkenazi Jewish ancestry
  - Any age (continued):
    - Family history[l]
      - ≥1 close blood relative[m] with ANY:
        - breast cancer at age ≤50
        - male breast cancer
        - ovarian cancer
        - pancreatic cancer
        - prostate cancer with metastatic,[n] or high- or very-high-risk group (Initial Risk Stratification and Staging Workup in NCCN Guidelines for Prostate Cancer)
      - ≥3 total diagnoses of breast cancer in patient and/or close blood relatives[m]
      - ≥2 close blood relatives[m] with either breast or prostate cancer (any grade)
- Family history of cancer only
  - An affected individual (not meeting testing criteria listed above) or unaffected individual with a first- or second-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making).[o]
    - If the affected relative has pancreatic cancer or prostate cancer only first-degree relatives should be offered testing unless indicated based on additional family history.
  - An affected or unaffected individual who otherwise does not meet the criteria above but has a probability >5% of a *BRCA1/2* pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk)[p]

Criteria met → See GENE-1

If testing criteria not met, consider testing criteria for other hereditary syndromes → If criteria for other hereditary syndromes not met, then cancer screening as per NCCN Screening Guidelines

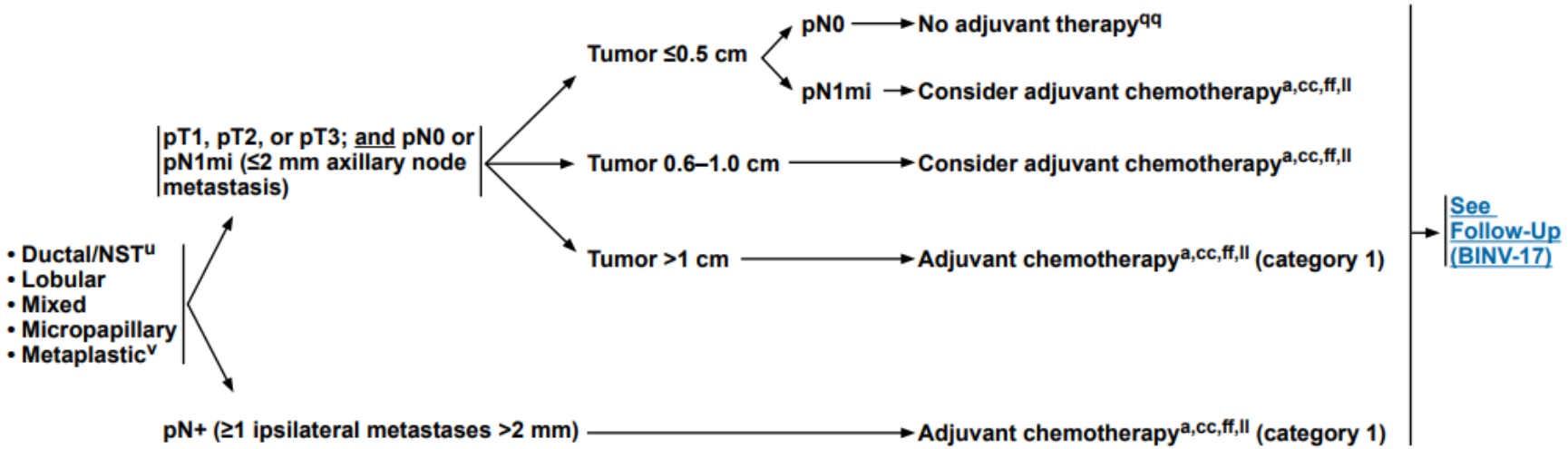
NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. In this guideline, the terms male and female refer to sex assigned at birth.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued on CRIT-3

Footnotes on CRIT-2A

SYSTEMIC ADJUVANT TREATMENT: HR-NEGATIVE - HER2-NEGATIVE DISEASE[d,r,z]



[a] For tools to aid optimal assessment and management of older adults, see NCCN Guidelines for Older Adult Oncology.
[d] See Principles of Biomarker Testing (BINV-A).
[r] See Special Considerations for Breast Cancer in Males (Sex Assigned at Birth) (BINV-J).
[u] According to WHO, carcinoma of NST encompasses multiple patterns including medullary pattern, cancers with neuroendocrine expression, and other rare patterns.
[v] There are rare subtypes of metaplastic carcinoma (eg, low-grade adenosquamous and low-grade fibromatosis-like carcinoma) that are considered to have a favorable prognosis without adjuvant systemic therapies.
[z] Although patients with cancers with 1%–100% ER IHC staining are considered ER-positive and eligible for endocrine therapies, there are more limited data on the subgroup of cancers with ER-low–positive (1%–10%) results. The ER-low–positive group is heterogeneous with reported biologic behavior often similar to ER-negative cancers; thus, individualized consideration of risks versus benefits of endocrine therapy and additional adjuvant therapies should be incorporated into decision-making. See Principles of Biomarker Testing (BINV-A).

[cc] See Preoperative/Adjuvant Therapy Regimens (BINV-L).
[ff] Consider adjuvant bisphosphonate therapy for risk reduction of distant metastasis for 3–5 years in postmenopausal patients (natural or induced) with high-risk node-negative or node-positive tumors.
[ll] Addition of 1 year of adjuvant olaparib is an option for select patients with germline *BRCA1/2* mutation after completion of adjuvant chemotherapy. See BINV-L.
[qq] In select patients with high-risk features (eg, young patients with high-grade histology), adjuvant chemotherapy may be considered (category 2B). See BINV-L.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Adjuvant versus Neoadjuvant Approach

- Neoadjuvant chemotherapy (NACT) is considered in locally advanced disease (Stage II or Stage III).
  - Associated with increased rate of breast conserving surgery according to some trials (65% vs 49%). There does not appear to be a significant impact on risk of distant recurrence and breast cancer mortality with adjuvant versus neoadjuvant approach[1].
  - Benefit is prognostic information to see if patients can achieve a pathologic Complete Response which typically correlates with improved overall survival[2].
  - In clinical practice neoadjuvant therapy is considered for tumors at least 2 cm in size or those with positive lymph nodes.

1) Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomized trials. Lancet Oncol. 2018; 19:27-39
2) Xia, LY., Hu, QL., Zhang, J. *et al.* Survival outcomes of neoadjuvant versus adjuvant chemotherapy in triple-negative breast cancer: a meta-analysis of 36,480 cases. *World J Surg Onc* **18**, 129 (2020). https://doi.org/10.1186/s12957-020-01907-7

PREOPERATIVE/ADJUVANT THERAPY REGIMENS[a]

HER2-Negative[b]	
Preferred Regimens: • Dose-dense AC (doxorubicin/cyclophosphamide) followed or preceded by paclitaxel every 2 weeks[c] • Dose-dense AC (doxorubicin/cyclophosphamide) followed or preceded by weekly paclitaxel[c] • TC (docetaxel and cyclophosphamide) • Olaparib, if germline *BRCA1/2* mutations[d,e] • High-risk[f] TNBC: Preoperative pembrolizumab + carboplatin + paclitaxel, followed by preoperative pembrolizumab + cyclophosphamide + doxorubicin or epirubicin, followed by adjuvant pembrolizumab • TNBC and residual disease after preoperative therapy with taxane-, alkylator-, and anthracycline-based chemotherapy:[e] Capecitabine	
Useful in Certain Circumstances: • Dose-dense AC (doxorubicin/cyclophosphamide) • AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B) • CMF (cyclophosphamide/methotrexate/fluorouracil) • AC followed by weekly paclitaxel[c] • Capecitabine (maintenance therapy for TNBC after adjuvant chemotherapy)	**Other Recommended Regimens:** • AC followed by docetaxel every 3 weeks[c] • EC (epirubicin/cyclophosphamide) • TAC (docetaxel/doxorubicin/cyclophosphamide) • Select patients with TNBC:[g,1] ▸ Paclitaxel + carboplatin (various schedules) ▸ Docetaxel + carboplatin[g,1] (preoperative setting only)

See Additional Considerations for Those Receiving Preoperative/Adjuvant Therapy (BINV-L, 3)

[a] Alternative taxanes (ie, docetaxel, paclitaxel, albumin-bound paclitaxel) may be substituted for select patients due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of albumin-bound paclitaxel should not exceed 125 mg/m^2.

[b] The regimens listed in the table for HER2-negative disease are all category 1 (except where indicated) when used in the adjuvant setting.

[c] It is acceptable to change the administration sequence to taxane (with or without HER2-targeted therapy) followed by AC.

[d] Consider addition of adjuvant olaparib for 1 y for those with germline *BRCA1/2* mutations and:
- TNBC, if 1) ≥pT2 or ≥pN1 disease after adjuvant chemotherapy, or 2) residual disease after preoperative chemotherapy
- HR-positive, HER2-negative tumors, if 1) ≥4 positive lymph nodes after adjuvant chemotherapy (category 2A), or 2) residual disease after preoperative therapy and a clinical stage, pathologic stage, ER status, and tumor grade (CPS+EG) score ≥3 (category 2A).

Adjuvant olaparib can be used concurrently with endocrine therapy.

[e] Patients in the OlympiA trial did not receive capecitabine; thus, there are no data on sequencing or to guide selection of one agent over the other.

[f] High-risk criteria include stage II–III TNBC. The use of adjuvant pembrolizumab (category 2A) may be individualized.

[g] The inclusion of platinum agents as neoadjuvant chemotherapy for TNBC remains controversial. Several studies have shown improved pCR rates with incorporation of platinum. However, long-term outcomes remain unknown. The routine use of platinum agents as part of neoadjuvant therapy for TNBC is not recommended for most patients (including *BRCA* mutation carriers), but it may be considered in select patients (such as those for whom achieving better local control is necessary). The use of platinum agents in the adjuvant setting is not recommended. If platinum agents are included in an anthracycline-based regimen, the optimal sequence of chemotherapy and choice of taxane agent is not established. Carboplatin may be used as part of the pembrolizumab regimen.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Immunotherapy in Early stage TNBC

- Early-stage TNBC patients tend to achieve higher responses to neoadjuvant treatment, however they are still at risk for early disease recurrence.

- Prognosis is worse for those who have residual disease after neoadjuvant treatment. Therefore, studies have been focused on optimal regimens in this setting to achieve pathologic Complete Response (pCR).

Bagegni NA, Davis AA, Clifton KK, Ademuyiwa FO. Targeted Treatment for High-Risk Early-Stage Triple-Negative Breast Cancer: Spotlight on Pembrolizumab. Breast Cancer (Dove Med Press). 2022 Apr 29;14:113-123. doi: 10.2147/BCTT.S293597. PMID: 35515356; PMCID: PMC9064451.

pCR as a surrogate marker for long-term outcomes

- Previous data raised the questions whether pCR ultimately correlated with long-term outcomes such as OS.
- Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC):
  - Meta-analysis of 11,955 patients in 12 randomized clinical trials looked at relationship between pCR, Event Free Survival (EFS) and OS.
  - Long-term benefit found for patients achieving a pCR (EFS Hazard ratio was 0.48 for pCR versus non-PCR and was observed in all breast cancer subtypes).

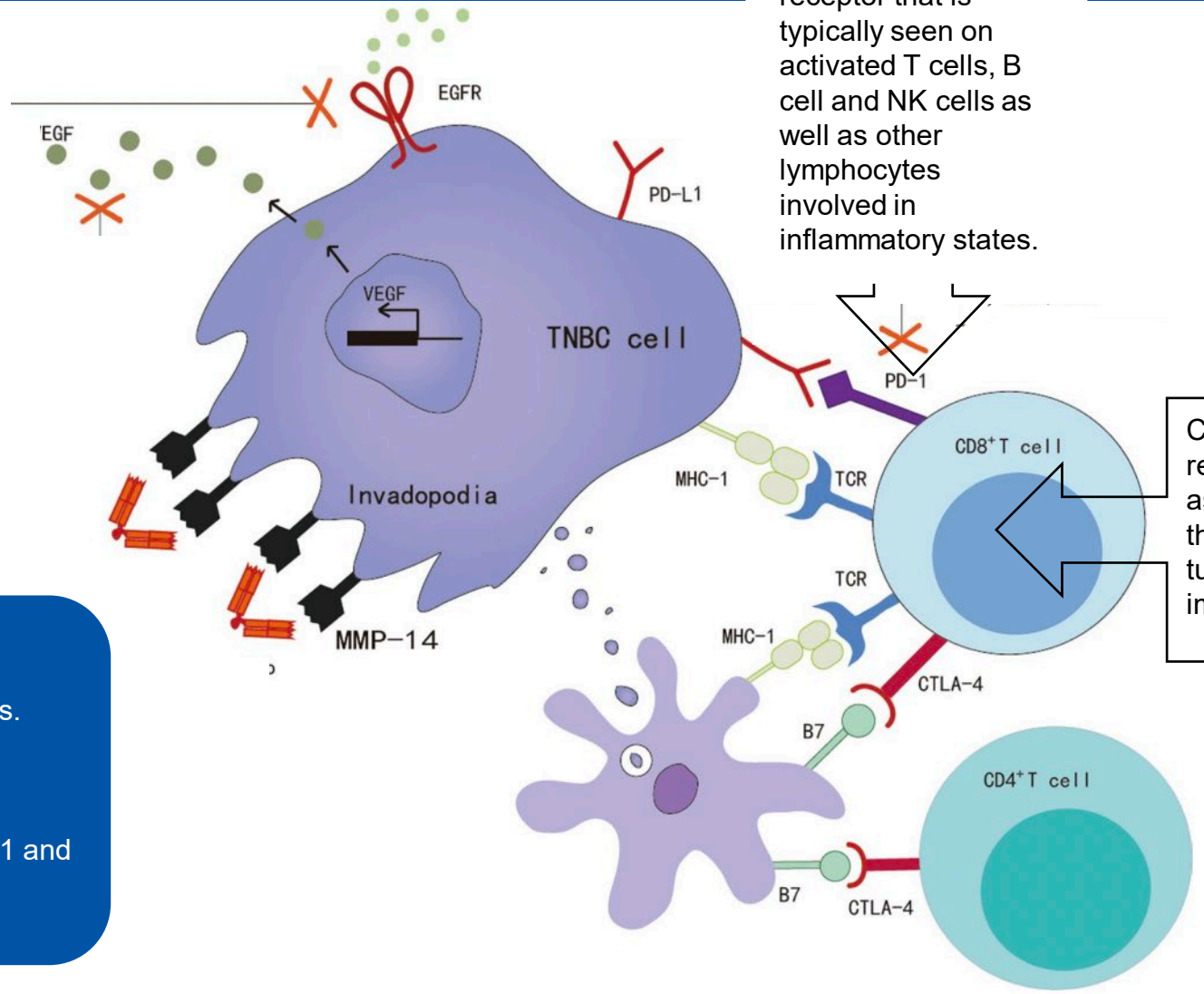
Wang H, Yee D. I-SPY 2: a Neoadjuvant Adaptive Clinical Trial Designed to Improve Outcomes in High-Risk Breast Cancer. Curr Breast Cancer Rep. 2019 Dec;11(4):303-310. doi: 10.1007/s12609-019-00334-2. Epub 2019 Nov 20. PMID: 33312344; PMCID: PMC7731787.

Role of Immunotherapy

- Immunotherapy has revolutionized treatment of several solid tumor types including lung cancer and melanoma.
- Agents include antibodies to cytotoxic T-lymphocyte antigen 4 (CTLA-4) as well as antibodies against PD-1 and PD-L1. These act to increase the immune response against tumors by blocking downregulatory proteins.
- TNBC appears to possess certain characteristics that would suggest susceptibility to checkpoint inhibition.

Carey K. Anders, Vandana Abramson, Tira Tan, and Rebecca Dent. The Evolution of Triple-Negative Breast Cancer: From Biology to Novel Therapeutics.. American Society of Clinical Oncology Educational Book 2016 :36, 34-42

PD-1 is an inhibitory immune checkpoint receptor that is typically seen on activated T cells, B cell and NK cells as well as other lymphocytes involved in inflammatory states.



CD8+ T-cells typically recognize tumor-associated antigens that are presented by tumor cells resulting in immune system attack.

- PD-L1/PD-1 inhibits T-cell proliferation, cytokine production and cytolytic activity.
- Leads to inactivation/exhaustion of T cells.
- Tumor can evade the anti-tumor immune response.

*Disruption of the interaction between PDL-1 and PD1 should limit the ability of tumor cells to evade the anti-tumor immune response.

Fig. 1 Current and potential future immune-related drug targets in TNBC, including immune checkpoint inhibitors, cytokines, and their antibodies

Carey K. Anders, Vandana Abramson, Tira Tan, and Rebecca Dent. The Evolution of Triple-Negative Breast Cancer: From Biology to Novel Therapeutics.. American Society of Clinical Oncology Educational Book 2016 :36, 34-42

Immunotherapeutic interventions of Triple Negative Breast Cancer Zehuan Li1,2, Yiran Qiu1,2, Weiqi Lu1,2, Ying Jiang1,2* and Jin Wang. Li et al. J Transl Med (2018) 16:147

Role of the Immune System in TNBC

- The tumor microenvironment (includes tumor cells, stromal cells and lymphocytes) seems to influence breast cancer outcomes.
- There is a connection between greater tumor infiltrative lymphocytes (TILs) and better prognosis in breast cancer.
- TNBC appears to have significant infiltration with TILs
  - Associated with ER negativity, higher proliferation rate, higher grade and positive lymph nodes.
  - Despite high-risk features, a higher TIL expression appears associated with improved DFS and OS which may highlight the role of the immune system in a subtype of TNBC.

1) The Evolution of Triple-Negative Breast Cancer: From Biology to Novel Therapeutics. Carey K. Anders, Vandana Abramson, Tira Tan, and Rebecca Dent. American Society of Clinical Oncology Educational Book 2016 :36, 34-42
20 Ono M, Tsuda H, Shimizu C, et al. Tumor-infiltrating lymphocytes are correlated with response to neoadjuvant chemotherapy in triple-negative breast cancer. Breast Cancer Res Treat. 2012;132:793-805.

TNBC and Role of Immunotherapy

- Higher proportion of TILs is associated with better response to Immune Checkpoint Inhibitors (ICIs) in other solid tumor types.
- TNBC has higher expression of PD-L1 on both tumor and immune cells which has shown correlation with response to anti-PD1 therapies.
- Greater number of mutations in TNBC gives rise to tumor-specific neo-antigens that activate neoantigen-specific T cells for an anti-tumor response, and this in turn can be amplified by ICIs.

Keenan TE, Tolaney SM. Role of Immunotherapy in Triple-Negative Breast Cancer. J Natl Compr Canc Netw. 2020 Apr;18(4):479-489. doi: 10.6004/jnccn.2020.7554. PMID: 32259782.

TNBC and single agent immunotherapy

- Response to immunotherapy appears higher in TNBC compared to hormone positive or HER2 positive. However, single agent efficacy is on the order of approx. 5% in unselected patients and about 23% in PDL1 positive patients who have not had prior treatment.

- KEYNOTE-086 (phase II trial) and KEYNOTE 119 (phase III trial) showed trend toward better overall response rate (ORR) in PDL1 positive patients but otherwise no significant benefit from single agent pembrolizumab.

Keenan TE, Tolaney SM. Role of Immunotherapy in Triple-Negative Breast Cancer. J Natl Compr Canc Netw. 2020 Apr;18(4):479-489. doi: 10.6004/jnccn.2020.7554. PMID: 32259782.

Role of Immunotherapy in Metastatic TNBC

- NCT01375842: Phase IB trial of Atezolizumab and nab-paclitaxel
  - ORR of 39.4% in 33 patients who had 0-2 previous lines of therapy.
- IMpassion 130:
  - Phase III trial
  - Treatment naïve mTNBC patients received atezolizumab/nab-paclitaxel, clinically meaningful Overall Survival (OS) improvement of 7 months seen in PDL-1+ group but not entire cohort.
- IMpassion 131:
  - Phase III trial
  - First Line Atezolizumab/paclitaxel in mTNBC patients.
  - Primary endpoint was Progression free survival (PFS) tested in PDL1+ and then Intention to treat population. No statistically significant difference in OS or PFS in either population.
- KEYNOTE 355: Chemotherapy with Pembrolizuamb showed improved PFS in patients who were PDL1+ (defined as Combined Positive score [CPS] of >/= 10 using 22C3 antibody for PDL1 testing).

Keenan TE, Tolaney SM. Role of Immunotherapy in Triple-Negative Breast Cancer. J Natl Compr Canc Netw. 2020 Apr;18(4):479-489. doi: 10.6004/jnccn.2020.7554. PMID: 32259782.

Keynote 522: Pembrolizumab for Early Triple-Negative Breast Cancer

- Phase 3 trial of patient with previously untreated Stage II or Stage III triple negative breast CA.
  - Patients received 4 cycles of Pembrolizumab (200mg) every 3 weeks with paclitaxel and carboplatin or placebo every 3 weeks with paclitaxel and carboplatin (784 patients and 390 patients in each group respectively).
  - Additional four cycles of Pembrolizumab or Placebo with doxorubicin-cyclophosphamide were given.
  - After definitive surgery patients received adjuvant pembrolizumab or placebo every 3 weeks for up to 9 cycles.

Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, Denkert C, Park YH, Hui R, Harbeck N, Takahashi M, Foukakis T, Fasching PA, Cardoso F, Untch M, Jia L, Karantza V, Zhao J, Aktan G, Dent R, O'Shaughnessy J; KEYNOTE-522 Investigators. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med. 2020 Feb 27;382(9):810-821. doi: 10.1056/NEJMoa1910549. PMID: 32101663.

Keynote 522: Pembrolizumab for Early Triple-Negative Breast Cancer

- Primary end points:
  - pCR response at time of definitive surgery
  - Event Free Survival (EFS)

Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, Denkert C, Park YH, Hui R, Harbeck N, Takahashi M, Foukakis T, Fasching PA, Cardoso F, Untch M, Jia L, Karantza V, Zhao J, Aktan G, Dent R, O'Shaughnessy J; KEYNOTE-522 Investigators. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med. 2020 Feb 27;382(9):810-821. doi: 10.1056/NEJMoa1910549. PMID: 32101663.

Characteristics of the Patients at Baseline.*

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Pembrolizumab–Chemotherapy (N = 784)	Placebo–Chemotherapy (N = 390)
Age		
Median (range) — yr	49 (22–80)	48 (24–79)
<65 yr — no. (%)	701 (89.4)	342 (87.7)
Menopausal status — no. (%)		
Premenopausal	438 (55.9)	221 (56.7)
Postmenopausal	345 (44.0)	169 (43.3)
PD-L1 status — no. (%)†		
Positive	656 (83.7)	317 (81.3)
Negative	127 (16.2)	69 (17.7)
ECOG performance-status score — no. (%)‡		
0	678 (86.5)	341 (87.4)
1	106 (13.5)	49 (12.6)
Lactase dehydrogenase level — no. (%)		
≤ULN	631 (80.5)	309 (79.2)
>ULN	149 (19.0)	80 (20.5)
Administration of carboplatin — no. (%)		
Every 3 wk	335 (42.7)	167 (42.8)
Weekly	449 (57.3)	223 (57.2)
Primary tumor classification — no. (%)		
T1 to T2	580 (74.0)	290 (74.4)
T3 to T4	204 (26.0)	100 (25.6)
Nodal involvement — no. (%)		
Positive	405 (51.7)	200 (51.3)
Negative	379 (48.3)	190 (48.7)
Overall disease stage — no. (%)		
Stage II	590 (75.3)	291 (74.6)
Stage III	194 (24.7)	98 (25.1)
HER2 status score — no. (%)§		
0–1	595 (75.9)	286 (73.3)
2+	188 (24.0)	104 (26.7)

* Data shown are for the intention-to-treat population. Percentages may not total 100 because of rounding and missing data. ULN denotes upper limit of normal range.
† Programmed death ligand 1 (PD-L1) positivity was defined as a combined positive score of 1 or greater. The PD-L1 combined positive score was defined as the number of PD-L1–positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells multiplied by 100.
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating greater disability.
§ Tumors with human epidermal growth factor receptor 2 (HER2) expression of 0 or 1 according to immunohistochemical analysis were negative. All tumors with HER2 expression of 2+ according to immunohistochemical analysis were negative for HER2 amplification on in situ hybridization.

P Schmid et al. N Engl J Med 2020;382:810-821.

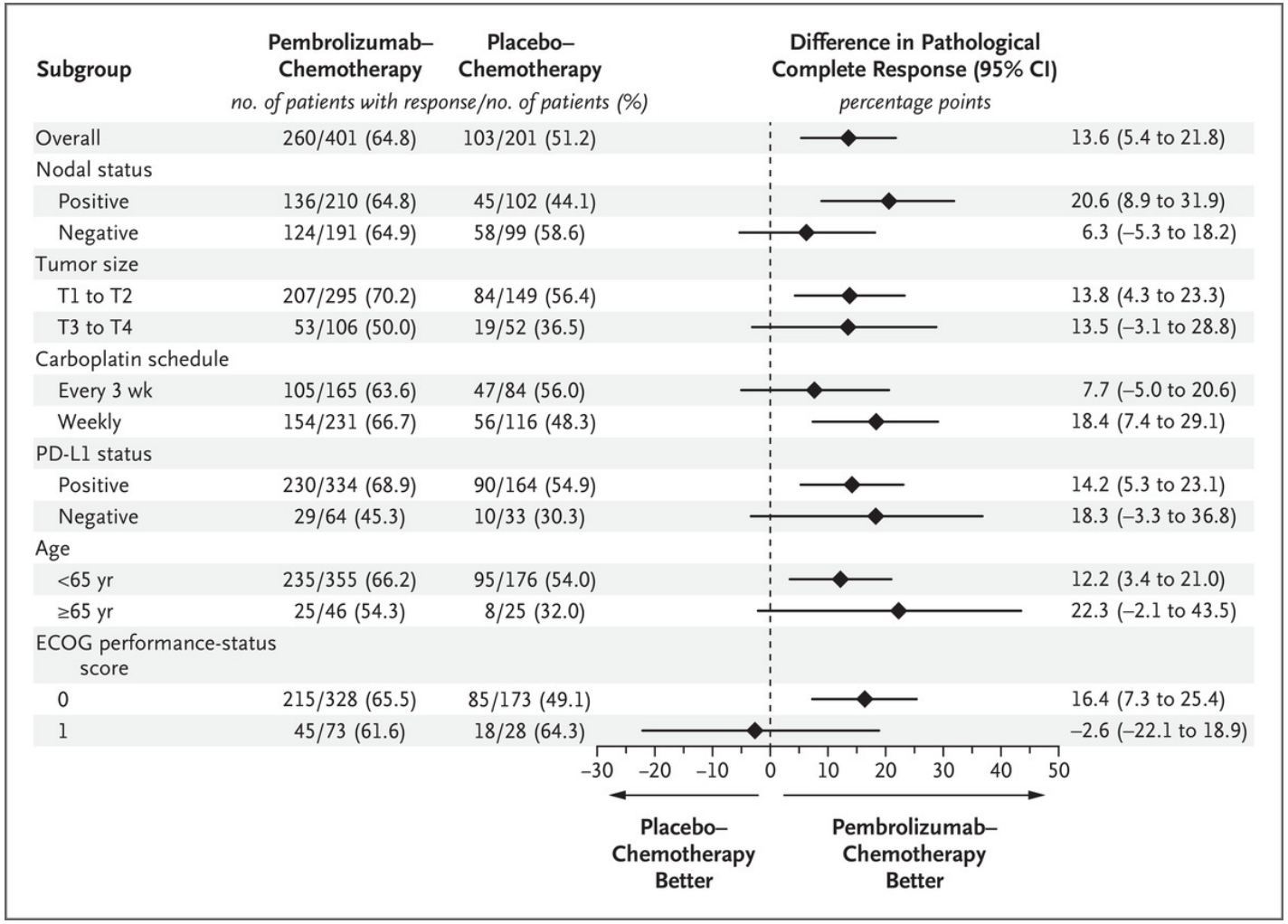
Keynote 522: Pembrolizumab for Early Triple-Negative Breast Cancer

- A total of 1174 patients were randomly assigned to the Pembro group between March 2017 and September 2018 compared with 784 patients in the placebo group (2:1 randomization).

- Interim analysis among first 602 patients showed that 64.8% of the Pembro group patients had pCR compared with 51.2% of patients in the placebo group (an estimated difference of 13.6 percentage points [95% CI, 5.4-21.8]; P <0.001).
  - This result was regardless of PDL1 expression.

Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, Denkert C, Park YH, Hui R, Harbeck N, Takahashi M, Foukakis T, Fasching PA, Cardoso F, Untch M, Jia L, Karantza V, Zhao J, Aktan G, Dent R, O'Shaughnessy J; KEYNOTE-522 Investigators. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med. 2020 Feb 27;382(9):810-821. doi: 10.1056/NEJMoa1910549. PMID: 32101663.

Subgroup Analysis of Difference in Percentages of Patients with a Pathological Complete Response (Stage ypT0/Tis ypN0).



P Schmid et al. N Engl J Med 2020;382:810-821.

Patient Case

- A 50-year-old female presents to her primary care physician with complaints of a palpable nodule in her left breast. Diagnostic mammogram shows a 2.5 cm mass at the 3 o'clock position. Left breast ultrasound confirms findings of a mass and shows one axillary lymph node with prominent hilar thickening. Biopsy of the mass indicates an invasive ductal carcinoma. ER negative, PR negative and HER2 negative (0). Left axillary biopsy shows metastatic adenocarcinoma consistent with breast primary. Genetic testing is negative for mutations.

Patient Case

- The patient is started on KEYNOTE 522 regimen with Carboplatin/Paclitaxel/Pembrolizumab followed by Doxorubicin/Cyclophosphamide/Pembrolizumab. Mid-treatment Breast ultrasound shows response to therapy and patient proceeds with Lumpectomy and Sentinel lymph node biopsy.
- Pathology shows a small focus of remaining triple negative breast cancer measuring 5 mm with three sentinel lymph nodes negative for malignancy and evidence of treatment response. Margins are negative. The patient is referred for post-operative radiation and returns to her Oncologist for discussion of next steps in treatment.

Questions Remaining after Keynote 522: Adjuvant Pembrolizumab after pCR?

- Currently, patients receive up to 9 cycles of adjuvant Pembrolizumab after surgery although the questions arises if this is beneficial in the setting of pCR.
- 3-year EFS in patients with pCR was 94.4% in pembrolizumab group and 92.5% in placebo group (HR 0.73, 95% CI 0.39-1.36).
- Can de-escalation be considered?

Bonadio et al. Management of patients with early stage triple negative breast cancer following pembrolizumab-based neoadjuvant therapy: What are the evidences. Cancer Treatment Reviews, 2022-11-01. Volume 110. Article 102459

GeparNUEVO

- This Phase II trial investigated addition of durvalumab to standard neoadjuvant chemotherapy in patient with early TNBC.
- Patients randomized to received Durvalumab versus placebo plus nab paclitaxel x 12 weeks and then Durvalumab/placebo plus epirubicin/cyclophosphamide Q2 weeks for 4 cycles.
- The patients then proceeded to surgery.
- No adjuvant phase

Loibl S, Untch M, Burchardi N, Huober J, Sinn BV, Blohmer JU, Grischke EM, Furlanetto J, Tesch H, Hanusch C, Engels K, Rezai M, Jackisch C, Schmitt WD, von Minckwitz G, Thomalla J, Kümmel S, Rautenberg B, Fasching PA, Weber K, Rhiem K, Denkert C, Schneeweiss A. A randomised phase II study investigating durvalumab in addition to an anthracycline taxane-based neoadjuvant therapy in early triple-negative breast cancer: clinical results and biomarker analysis of GeparNuevo study. Ann Oncol. 2019 Aug 1;30(8):1279-1288. doi: 10.1093/annonc/mdz158. Erratum in: Ann Oncol. 2022 Jul;33(7):743-744. PMID: 31095287.

GeparNUEVO

- Primary objective of the study was pCR and secondary endpoints included invasive disease-free survival (iDFS), distant disease-free survival (DDFS) and OS.

- 174 patients were enrolled between June 2016-Sept 2017. The pCR rate with Durvalumab was 53.4% versus 44.2% with placebo.

Loibl S, Untch M, Burchardi N, Huober J, Sinn BV, Blohmer JU, Grischke EM, Furlanetto J, Tesch H, Hanusch C, Engels K, Rezai M, Jackisch C, Schmitt WD, von Minckwitz G, Thomalla J, Kümmel S, Rautenberg B, Fasching PA, Weber K, Rhiem K, Denkert C, Schneeweiss A. A randomised phase II study investigating durvalumab in addition to an anthracycline taxane-based neoadjuvant therapy in early triple-negative breast cancer: clinical results and biomarker analysis of GeparNuevo study. Ann Oncol. 2019 Aug 1;30(8):1279-1288. doi: 10.1093/annonc/mdz158. Erratum in: Ann Oncol. 2022 Jul;33(7):743-744. PMID: 31095287.

GeparNUEVO

- Long term outcomes including pCR appeared improved with addition of Durvalumab. As this trial did not have continuation of Durvalumab post-operatively the study authors suggest further investigation into whether adjuvant immunotherapy is a necessary part of the current paradigm after pCR.

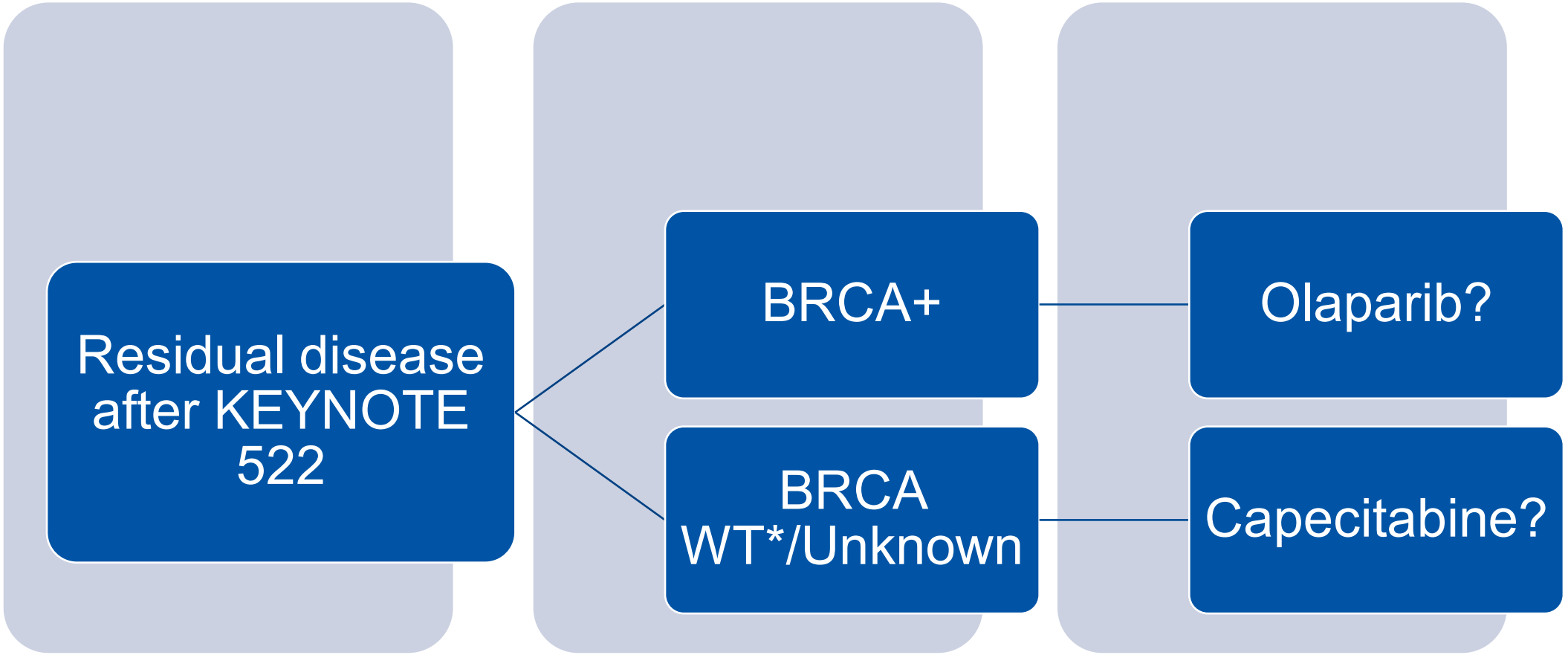
Loibl S, Untch M, Burchardi N, Huober J, Sinn BV, Blohmer JU, Grischke EM, Furlanetto J, Tesch H, Hanusch C, Engels K, Rezai M, Jackisch C, Schmitt WD, von Minckwitz G, Thomalla J, Kümmel S, Rautenberg B, Fasching PA, Weber K, Rhiem K, Denkert C, Schneeweiss A. A randomised phase II study investigating durvalumab in addition to an anthracycline taxane-based neoadjuvant therapy in early triple-negative breast cancer: clinical results and biomarker analysis of GeparNuevo study. Ann Oncol. 2019 Aug 1;30(8):1279-1288. doi: 10.1093/annonc/mdz158. Erratum in: Ann Oncol. 2022 Jul;33(7):743-744. PMID: 31095287.

Patients with residual disease

3-year EFS for Pembrolizumab arm with residual disease was only 67.4%.

Exploratory Analysis from KEYNOTE 522 focusing on Residual Cancer Burden (RCB) found patients with highest RCB (3) had 3-year EFS of 34.6% in Placebo group and 26.2% in Pembrolizumab group

Patients with Residual disease



*WT: Wild Type

Questions Remaining after Keynote 522: Adjuvant Olaparib

- PARP inhibitors olaparib and talazoparib approved in patients with BRCA 1/2 mutations.
  - OLYMPIA: Phase III trial using adjuvant olaparib in high-risk triple negative or hormone + breast CA patients resulted in 8.8% improvement in 3-year invasive disease-free survival in olaparib arm.
  - TOPACIO: Phase II trial of niraparib with pembrolizumab. ORR was 47% in patients with BRCA mutation and 11% in BRCA WT.
  - MELODIA Trial: Phase 1/2 Trial of Durvalumab and Olaparib in solid tumors.
    - Germline BRCA mutated metastatic breast CA, germline BRCA mutated metastatic ovarian cancer, metastatic gastric cancer and relapsed small cell lung cancer.
    - Breast cohort included patients who received 300mg Olaparib twice daily for 4 weeks and afterward received a combination of Olaparib 300mg twice daily and durvalumab 1.5 g infusion every 4 weeks.
    - Results indicated similar efficacy and safety to what was observed with Olaparib and Durvalumab monotherapy.

Bonadio et al. Management of patients with early stage triple negative breast cancer following pembrolizumab-based neoadjuvant therapy: What are the evidences. Cancer Treatment Reviews, 2022-11-01. Volume 110. Article 102459

Questions Remaining after Keynote 522: Adjuvant Capecitabine

- CREATE-X trial showed improved DFS and OS in TNBC patients who had residual disease after neoadjuvant treatment and subsequently received 6 months of adjuvant capecitabine.
- Patients in KEYNOTE 522 were not allowed to receive adjuvant capecitabine.
  - ECOG-ACRIN EA 1131: Adjuvant platinum versus capecitabine for residual disease after treatment with neoadjuvant chemo (including investigational agents). Stopped early due to futility.
  - Cytotoxic treatments can disrupt tumor immune evasion and potentially increase antigen exposure leading to synergistic activity between immunotherapy and chemotherapy which may lead some to consider the addition of capecitabine to pembrolizumab in these patients.

Bonadio et al. Management of patients with early stage triple negative breast cancer following pembrolizumab-based neoadjuvant therapy: What are the evidences. Cancer Treatment Reviews, 2022-11-01. Volume 110. Article 102459

Summary: options after KEYNOTE 522

- pCR: More data suggesting that not all patients with pCR may need adjuvant immunotherapy after pCR. In selected patients, discontinuation may be considered.
- Residual Disease:
  - BRCA+: Data suggests that adding Olaparib to immunotherapy has similar safety and efficacy to single agent PARP inhibitor.
  - BRCA WT: Limited data to support use of agents such as capecitabine in this setting although in high-risk patients (high residual cancer burden) can consider this option.

Patient Case

- A 50-year-old female presents to her primary care physician with complaints of a palpable nodule in her left breast. Diagnostic mammogram shows a 2.5 cm mass at the 3 o'clock position. Left breast ultrasound confirms findings of a mass and shows one axillary lymph node with prominent hilar thickening. Biopsy of the mass indicates an invasive ductal carcinoma. ER negative, PR negative and HER2 negative (0). Left axillary biopsy shows metastatic adenocarcinoma consistent with breast primary.
  - The patient is s/p neoadjuvant treatment and surgery. She has had radiation to her left breast and axilla and has completed 9 adjuvant cycles of pembrolizumab.

- Two years after her initial diagnosis she develops abdominal pain. Liver ultrasound shows several lesions in the liver which are confirmed by abdominal MRI. Biopsy of one of the liver lesions shows adenocarcinoma consistent with breast primary, ER negative, PR negative, HER2 of 1+.
  - Caris molecular profiling is sent on her liver biopsy and does not find any actionable mutations. PDL1 is 0%

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 see 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 see 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 see BINV-Q (6)
	Any	Systemic chemotherapy see BINV-Q (5)

[a] For treatment of brain metastases, see NCCN Guidelines for Central Nervous System Cancers.
[b] Assess for germline *BRCA1/2* mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy
[d] See Principles of HER2 Testing (BINV-A).
[e] Fam-trastuzumab deruxtecan maybe considered in a later line for HER2 IHC 1+ or 2+/ISH negative, if not used in second–line. Fam-trastuzumab deruxtecan-nxki is associated with interstitial lung disease (ILD)/pneumonitis. Regular monitoring for this serious side effect is recommended. For patients with a history of ILD/ pneumonitis, there are no data on managing safety or toxicity of this drug in a trial.
[g] PD-L1 expression is assessed using 22C3 antibody. Threshold for positivity combined positive score ≥10.
[h] While available data are in the first-line setting, this regimen can be used for second and subsequent lines of therapy if PD-1/PD-L1 inhibitor therapy has not been previously used. If there is disease progression while on a PD-1/PD-L1 inhibitor, there are no data to support an additional line of therapy with another PD-1/PD-L1 inhibitor.
[i] Sacituzumab govitecan-hziy may be used for adult patients with metastatic TNBC who have received at least 2 prior therapies, at least one of which was for metastatic disease. It may be considered for later line if not used as second line therapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

DESTINY-Breast-04

- Phase 3 trial of patients with HER2 low metastatic breast cancer who had previously had at least one or two lines of therapy.
  - HER2 low defined as a score of 1+ on IHC or 2+ on IHC with negative FISH.
- Patients were randomly assigned in a 2:1 fashion to receive trastuzumab deruxtecan or physician's choice of treatment.
- Primary end point was progression free survival

Modi et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast cancer. N Engl J Med 2022; 387: 9-20.

DESTINY-Breast-04

- 557 patients enrolled, majority (88.7%) were hormone receptor positive but 11.3% were hormone receptor negative.
  - Progression free survival was 9.9 months in Trastuzumab deruxtecan group and 5.1 months in physician choice group.
  - OS was 23.4 mo in Trastuzumab deruxtecan group and 16.8 months in physician choice group.
  - NCCN has updated recommendations to reflect these findings and consider Trastuzumab deruxtecan in second line after progression on first line, in HER2 low patients.

Modi et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast cancer. N Engl J Med 2022; 387: 9-20.

Conclusions

- TNBC is an aggressive form of breast cancer with a high recurrence rate in the first 5 years after diagnosis.
- Immunotherapy, specifically pembrolizumab, has been shown to improve outcomes in this patient population.
- Studies are currently focusing on optimizing adjuvant portion of systemic treatment, specifically for those with residual disease.

Question #1

- What percentage of patients will relapse within 5 years of their initial diagnosis of triple negative Breast Cancer?

A. 15-20%
B. **30-40%**
C. 50-60%
D. 70-80%

Question #2

- What is the benefit of neoadjuvant chemotherapy compared with adjuvant chemotherapy?

A. Overall survival advantage with neoadjuvant chemotherapy has been definitively demonstrated.

B. Neoadjuvant therapy offers prognostic information in the form of tumor response to pre-operative therapy.

C. Neoadjuvant therapy results in fewer distant relapses.

D. Neoadjuvant therapy is always preferred in triple negative breast cancer to allow for better surgical outcomes.

Question #3

- What are the indications to perform genetic testing for ‘high penetrance breast cancer susceptibility genes (including BRCA1/2, PALB2, CDH1, PTEN and TP53)’?

A. Family history of breast cancer in any relative.
B. Age >50 yo
C. Greater than or equal to 3 diagnoses of breast cancer in patient and or a close blood relative.
D. Diagnosis of Triple negative breast cancer
E. **C and D**
F. All of the above

Question #4

- The addition of which of the following medications to standard chemotherapy has resulted in improved outcomes in triple negative breast cancer patients?

A. Durvalumab
B. Capecitabine
C. Olaparib
D. Pembrolizumab

Question #5

- It is necessary to get PDL1 testing on all Stage II and Stage III TNBC patients being considered for neoadjuvant chemotherapy with KEYNOTE 522 regimen using pembrolizumab.

-True

-**False**


Audience
Q&A Session

Thank you for Attending!

Join us for the next session: Wednesday, September 13th at 12 PM EST

"Lung Cancer Screening and Identification of Lung Cancer Patients at all Stages"

Dr. Timothy Mullett, MD, MBA, FACS

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