RECENT ADVANCES IN TRIPLE-NEGATIVE BREAST CANCER

Dr. Caroline A. Rivera Olmo
Hematology-Oncology
Clínica Mi Alicia

TRIPLE NEGATIVE BREAST CANCER

- Cancers that lack expression of:
  - Estrogen and progesterone receptors (<1%)
  - Human epidermal growth factor receptor 2 (her 2)
    - 0 to 1+ by IHC or IHC 2+ with negative FISH
- 15% of all breast cancer
- More common in younger women (<40 y/o), Hispanics and African American
- May be associated with BRCA 1 and 2 mutations
  - Up to 20% (particularly in BRCA1)
  - Do genetic testing in early BC if < 60 y/o or in all patients, if metastatic
- Aggressive tumor with higher recurrence rate

EARLY STAGE TNBC

- Chemotherapy is recommended for TNBC >0.5 cm or node-positive
  - Neoadjuvant chemotherapy AND immunotherapy (if no contraindication) is the preferable approach in locally advanced TNBC
    - Achievement of pathologic complete response in the breast and axilla (ypT0/is ypN0) correlates with improved survival (risk of death was reduced by 84%)
  - Consider NACT in patients that are not candidates for breast conservation surgery or are unlikely to have a good cosmetic outcome
    - High tumor-to-breast ratio
    - Consider NACT in smaller tumor (T1c) and negative axillary nodes
      - Premenopausal
      - Candidates for additional treatment
      - Only chemo: usually anthracycline based

ADJUVANT CAPECITABINE

- The CREATE-X trial (2017): 900 patients with HER2-negative breast cancer (approximately one-third of whom had TNBC) and residual disease after neoadjuvant anthracycline and/or taxane therapy
  - Capecitabine 1,000-1,250 mg/m2 PO BID x 14 days q 21 days x 8 cycles after meals
  - higher rates of five-year disease-free survival (DFS; 74 versus 68 percent)
  - Higher rates of overall survival (OS; 89 versus 84 percent
  - improved outcomes among patients with TNBC (70 versus 56 percent)
  - Toxicities: neutropenia, and hand-foot syndrome.

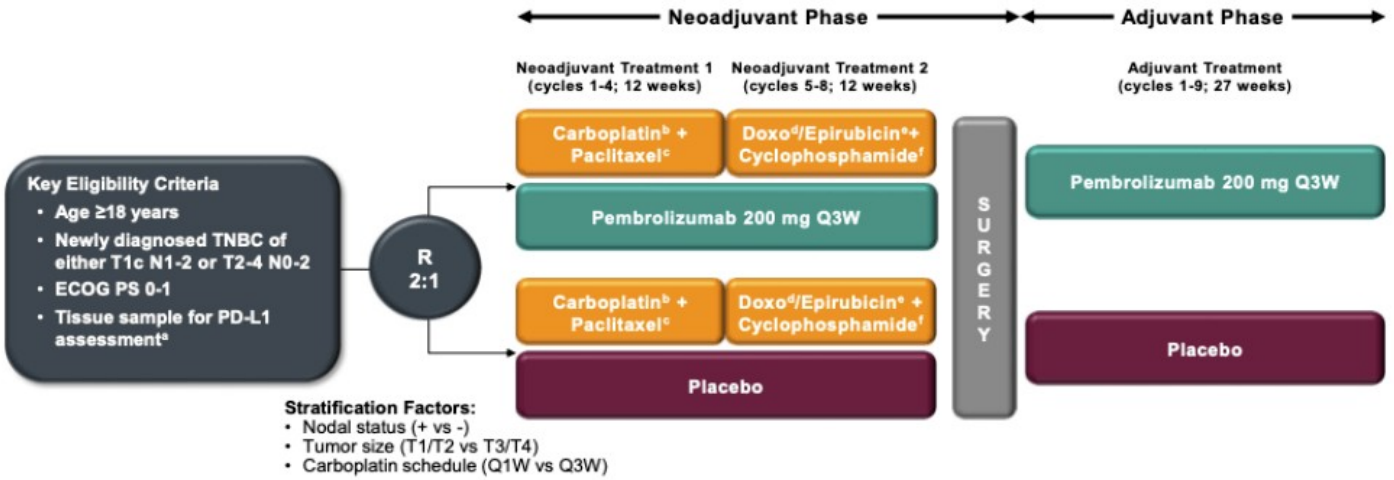
ADJUVANT OLAPARIB IN TNBC

- The Olympia trial (2021): 1836 patients
  - Improvement in three-year DFS (86 versus 77 percent).
  - Four-year overall survival was 90 versus 86 percent.
- Olaparib (PARP inhibitor) 300 mg orally BID x 1 year
  - On breast cancer susceptibility genes (BRCA) carriers (germline pathogenic or likely pathogenic mutatations)
  - If residual disease after NACT
  - If upfront surgery and final pathology with tumor of 2 or more cm and/or positive nodes

CHEMOTHERAPY AND PEMBRO (FDA 7/2021)

San Antonio Breast Cancer Symposium®, December 10-14, 2019

KEYNOTE-522 Study Design (NCT03036488)



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

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

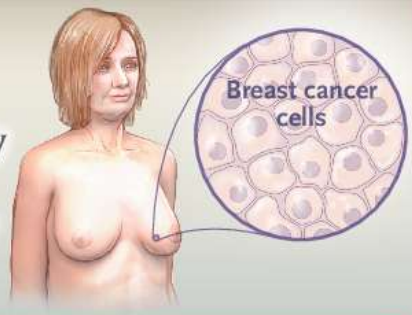
[a]Must consist of at least 2 separate tumor cores from the primary tumor.
[b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 Q1W.
[c]Paclitaxel dose was 80 mg/m² Q1W.
[d]Doxorubicin dose was 60 mg/m² Q3W.
[e]Epirubicin dose was 90 mg/m² Q3W.
[f]Cyclophosphamide dose was 600 mg/m² Q3W.

The NEW ENGLAND JOURNAL of MEDICINE

Pembrolizumab for Triple-Negative Breast Cancer

RANDOMIZED, DOUBLE-BLIND, PHASE 3 TRIAL

1174 Patients with previously untreated triple-negative breast cancer



	Neoadjuvant Pembrolizumab + chemotherapy, followed by surgery and adjuvant pembrolizumab (N=784)	Neoadjuvant Placebo + chemotherapy, followed by surgery and adjuvant placebo (N=390)
Pathological complete response at time of surgery	64.8%	51.2%
	Difference, 13.6 percentage points; 95% CI, 5.4–21.8; P<0.001	
Event-free survival	91.3% (95% CI, 88.8–93.3)	85.3% (95% CI, 80.3–89.1)
	HR for an event or death, 0.63; 95% CI, 0.43–0.93	
Grade ≥3 adverse events	76.8%	72.2%

P. Schmid et al. 10.1056/NEJMoa1910549

ON TREATMENT EVALUATION

- Clinical breast exam every 2-4 weeks
- Imaging studies if suspected progression (Breast US or MRI)
- Labs before therapy

- 9/2024 → longer follow up of Pembrolizumab and chemotherapy for stage II and III TNBC showed an improvement in 5 year OS over placebo + chemo (87 v 82%)

CHEMO AND PEMBRO

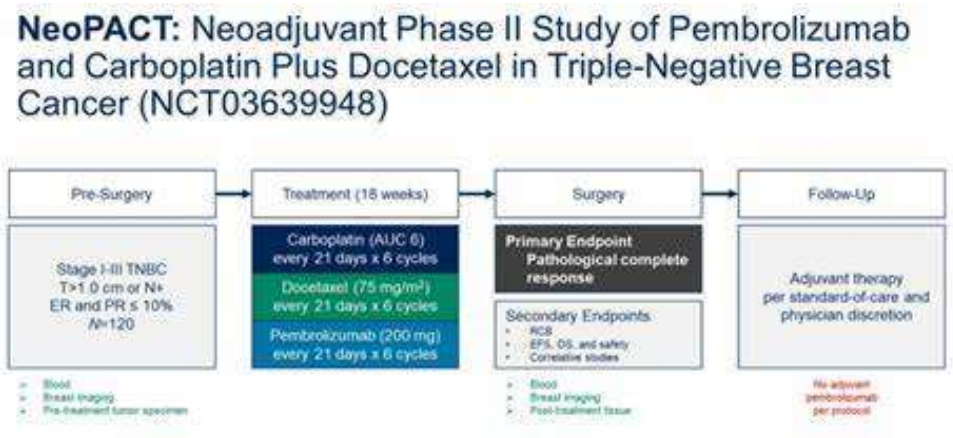
- Chemotherapy-related toxicities were similar in the 2 arms
  - Neutropenia
  - Nausea/vomiting
  - Diarrhea
  - Peripheral neuropathy
- Pembro arm were more likely to develop an immune-related adverse event (34 vs 11)
  - Hypo- and hyperthyroidism
  - Severe skin reactions
  - Adrenal insufficiency
  - Pneumonitis

ADJUVANT THERAPY

- If no residual disease: Adjuvant Pembrolizumab x 9 cycles
- If residual disease: Adjuvant Pembrolizumab x 9 cycles + Xeloda or Olaparib (BRCA mutation)
  - No data informing use but small studies and clinical experience suggest safety with this combinations

NEOPACT PHASE II

- 115 Patients with TNBC
  - 6 cycles of docetaxel + carboplatin + pembrolizumab every 3 weeks
  - pCR of 58% (better for node-negative and PDL1 positive but little difference if weakly ER 1-10% vs ER negative)



ADJUVANT CARBOPLATIN

- Pearly trial (6/2024)
  - Stage II and III TNBC treated with surgery first
  - The addition of carboplatin to standard anthracycline follow by taxane therapy significantly improved the event free survival (82% vs 74%).
  - Overall survival data were immature

METASTATIC TNBC

- REPEAT BIOPSY
  - ER/PR/HER2 by IHC
- Molecular testing
  - PDL-1
  - MSI/MMR
  - TMB
  - NTRK
  - RET
- Genetic testing (germline and somatic)
  - BRCA

IMMUNOTHERAPY

- Keynote 355
  - Pembrolizumab in combination with chemotherapy (nabpaclitaxel, paclitaxel, or gemzar/carboplatin)
  - PDL-1 CPS of 10 or more
    - Improved PFS by 4 mo
    - Improved OS 23 vs 16.1 mo

PARP INHIBITORS

- Germline BRCA mutation (but also on somatic BRCA 1 and 2 and Germline Palb2)
  - For most patients with TNBC who have previously been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic disease setting, since the data suggest improved efficacy and fewer side effects
  - Olympiad trial → olaparib (Lynparza)
  - Embraca trial → talazoparib (Talzenna)

ANTIBODY DRUG CONJUGATES

- Sacituzumab govitecan (Trodelvy)
  - targets Trop-2 for the selective delivery of SN-38, the active metabolite of irinotecan.
  - It is approved by the FDA for the treatment of adult patients with unresectable locally advanced or metastatic TNBC who have received at least two prior therapies, at least one of them for metastatic disease
    - OS: 12.1 vs 6.7
    - PFS: 5.6 VS 1.7
    - Objective response rate: 35 vs 5
    - Toxicity: severe neutropenia and diarrhea

ANTIBODY DRUG CONJUGATES

- Fam-trastuzumab deruxtecan (Enhertu)
  - ER/PR negative but her 2 low (1+ or 2+ with negative fish)
  - Indicated after at least one line of chemotherapy (on the adjuvant or metastatic setting)
  - T-DxD is an antibody-drug conjugate consisting of a trastuzumab targeting molecule conjugated to deruxtecan, a topoisomerase-1 inhibitor.

MSI/MMR/TMB

- Pembrolizumab (Keytruda)
  - Based on solid tumors trials
  - In MSI high, deficient MMR or TMB high
  - In later lines, when no other satisfactory alternative treatment is available