Immunotherapy for Breast Cancer

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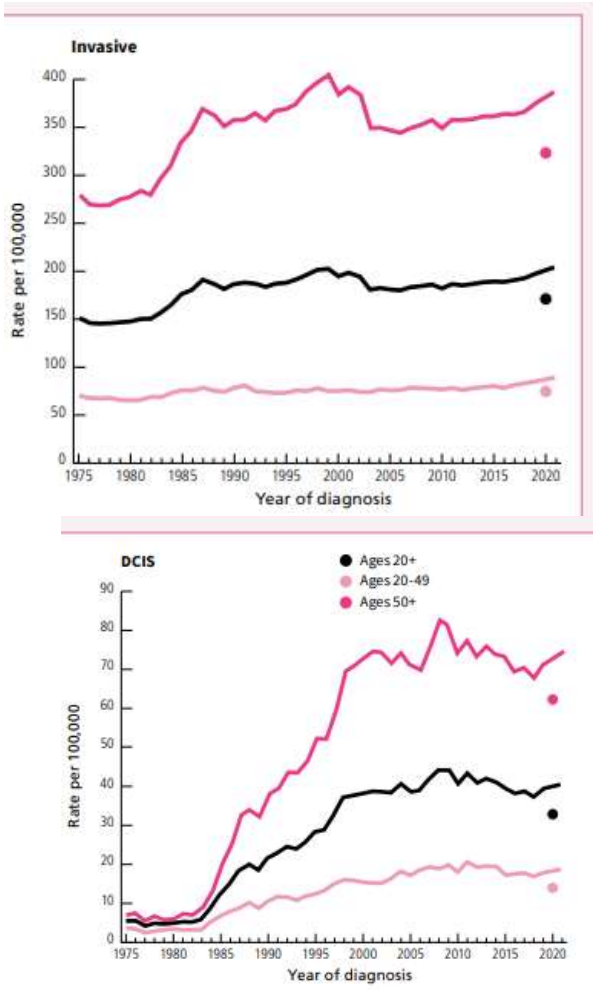
Disclosures

- None

Breast Cancer –Stats

- About 13.1% (1 in 8) women in the US will be diagnosed with invasive breast cancer.
- One in 43 women (2.3%) will die from breast cancer.
- About 310,720 new invasive cancers and 56,500 cases of ductal carcinoma in situ will be diagnosed in women in 2024.
  - About 2790 breast cancers will be diagnosed in men.
- Breast cancer incidence increased 1% annually overall over the past decade (2012-2021).
  - Incidence has increased by 1.4% per year in women under 40 years, and declined to 0.7% in 50 or older cohort



American Cancer Society, *Breast Cancer Facts and Figures 2024-2025. Atlanta: American Cancer Society;* 2024

Breast Cancer—Stats

- Mortality from breast cancer is declining since 1990.
- Relative survival from breast cancer is 91% at 5 years, 86% at 10 years, and 81% at 15 years.
- When cancer remains localized to the breast, 5 year relative survival is > 99%. When it has advanced to regional disease, it is 87%. Once breast cancer metastasizes, 5 year relative survival is 32%.
- Black, American Indian/Alaska Native women are more likely be diagnosed with more advanced disease, and in turn have a higher mortality.
  - For black women, this is partially due to less access to high quality care, but also a higher likelihood to present with triple negative breast cancer.

American Cancer Society, *Breast Cancer Facts and Figures 2024-2025. Atlanta: American Cancer Society;* 2024

Breast Cancer –Diagnosis

- Physical Exam
- Imaging:
  - Mammogram
  - Breast US
  - Breast MRI
- Biopsy
  - Subtype:
    - Invasive Ductal Carcinoma
    - Invasive Lobular Carcinoma
    - Less common subtypes: micropapillary, metaplastic, tubular, mucinous, cribiform, adenoid cystic
  - Receptor Status:
    - Hormone receptors
      - Estrogen Receptor (ER)
      - Progesterone Receptor (ER)
    - Human Epidermal growth factor receptor 2 (Her2) receptor status

Breast Cancer –Treatment

- Multimodal Treatment
  - Surgery
    - Breast: Mastectomy vs. Lumpectomy
    - Axilla: Sentinel lymph node biopsy vs. Axillary lymph node dissection
  - Systemic Therapy
    - Adjuvant vs. Neoadjuvant
      - Endocrine therapy
      - Chemotherapy
      - Targeted Therapy
      - Immunotherapy
  - Radiation (XRT)
    - Adjuvant Therapy (whole breast, partial breast, post mastectomy, radiation to the axilla)
    - Intra-operative radiation

Immunotherapy—Mechanism

- Harnesses the body's own immune system to fight cancer by boosting its ability to recognize and attack cancer cells.
  - Cytokines
    - Interferon, IL-2
  - Immune checkpoint inhibitors (ICI)
    - Block the binding of receptors to their targets (Programmed Death Protein-1 (PD-1) to Programmed Death Ligand (PDL-1)) or CTLA-4.
    - This prevents inhibitory signals to be sent, and allows someone's own T cells to kill cancer cells.
  - Adoptive Cell Transfer
  - Cancer Vaccines

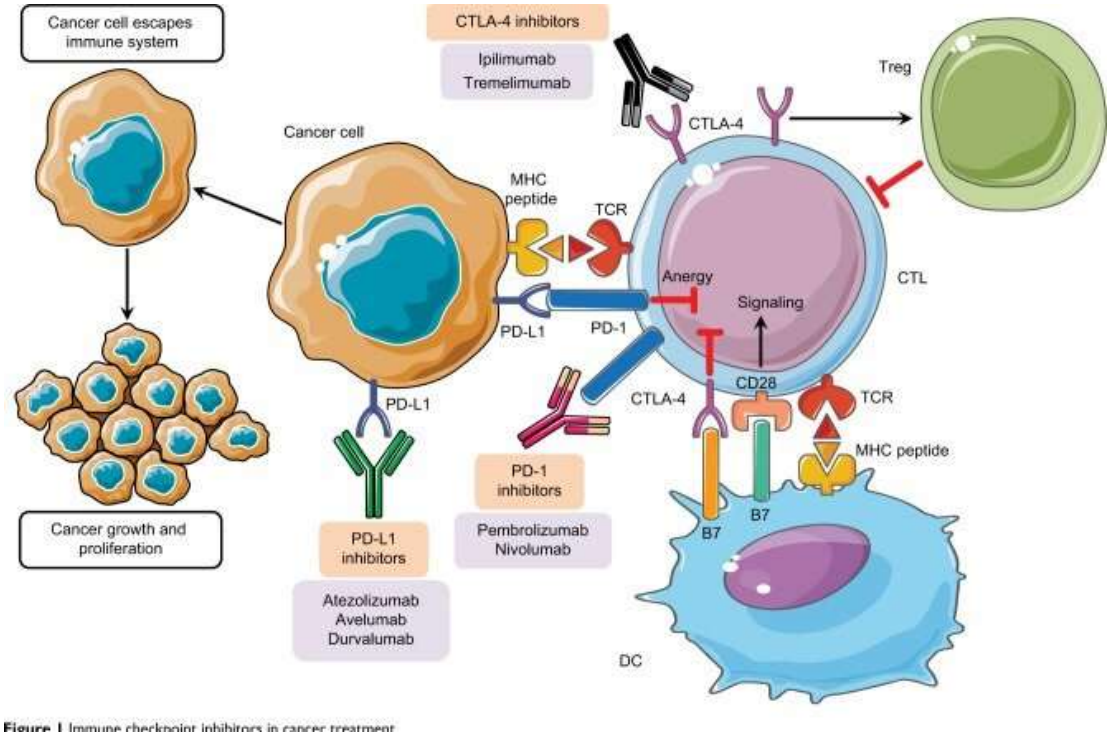


Figure 1 Immune checkpoint inhibitors in cancer treatment

Ribas, A. et al. *Science* 2018, 359, 1350–1355
Paucek, R.D. et al. *Trends Immunol.* 2019, 40, 292–309.
Ayoub, N. et al. *Breast Cancer: Targets and Therapy.* 2019, 11:53-69

Immunotherapy—History

- Initial studies in other disease types including melanoma
- First FDA approval of an immunotherapy was in 1986 with interferon-a2 for hairy cell leukemia and later expanded to melanoma in 1995.
- First ICI—ipilimumab approved in 2011 for metastatic melanoma.
- Since then it was been approved for over 20 different disease types.
  - Not all histologies were initially thought to be responsive to immunotherapy.
    - Including breast cancer which was felt to be poorly immunogenic

Immunotherapy for Breast Cancer

- Studies found that while they initially thought immunotherapy was not effective in breast cancer, there were certain subtypes for which a benefit was shown.
  - Triple negative breast cancer (TNBC)
  - Her2 positive (Her2+)

- Higher levels of PD-L1 expression
- Higher levels of tumor infiltrating lymphocytes (TILs) and tumor mutational burden (TMB)

Heater et al. Journal of Hematology & Oncology (2024) 17:131

Immunotherapy for Breast Cancer—Initial Studies for Metastatic Disease

- Studies looking at PD-1/PD-L1 ICI using monotherapy in metastatic patients who were heavily pretreated only showed response rates (RR) of 5-20% and were most effective in those who were PD-L1, TNBC, lower tumor burden, non-visceral disease.
  - However, if there actually was a response, this was long-lasting.

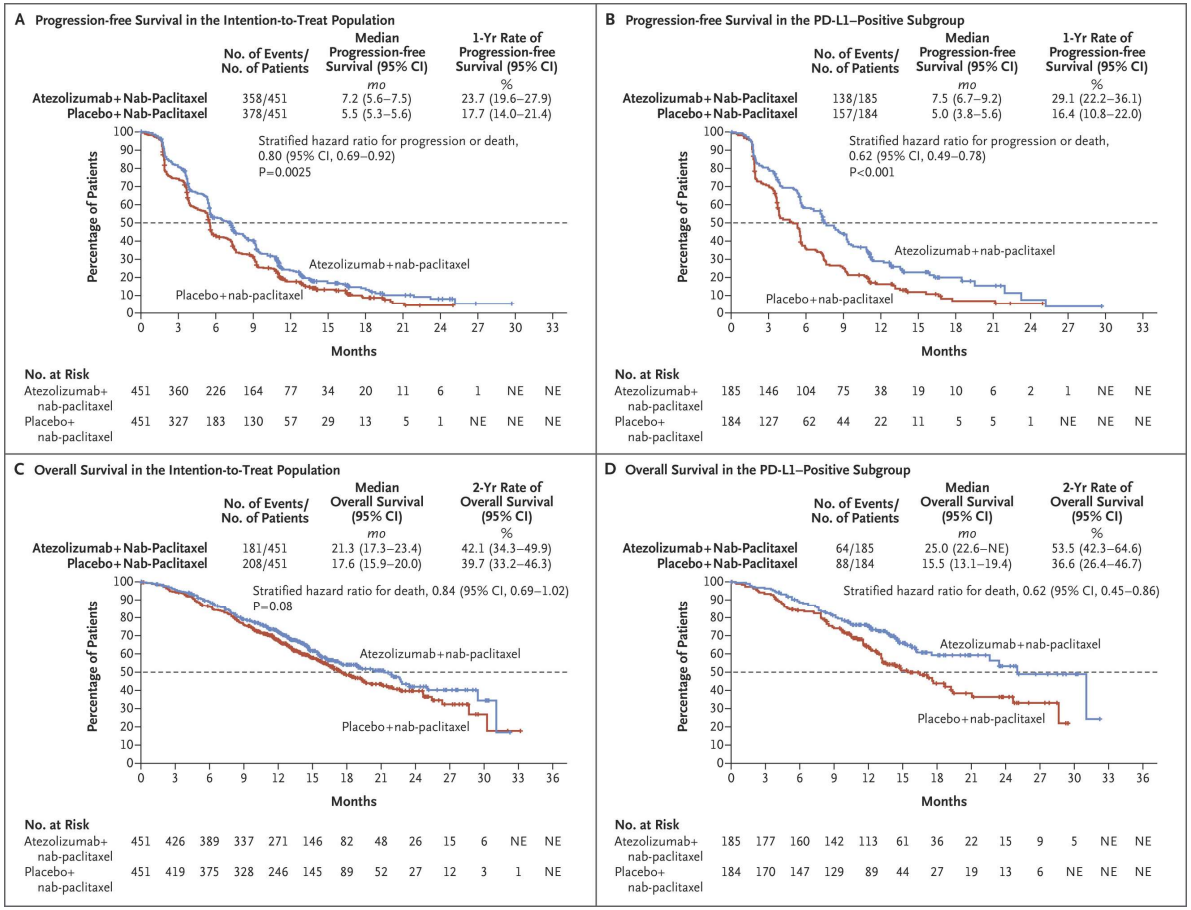
- Keynote 119—no survival benefit when pembrolizumab was compared to chemotherapy beyond the first line in metastatic TNBC

- Higher response rates were found with combined therapy when used as first line drug for patients with advanced TNBC.

Solinas, C. et al. *ESMO Open 2*, e000255 (2017).

Immunotherapy for Breast Cancer—Initial Studies

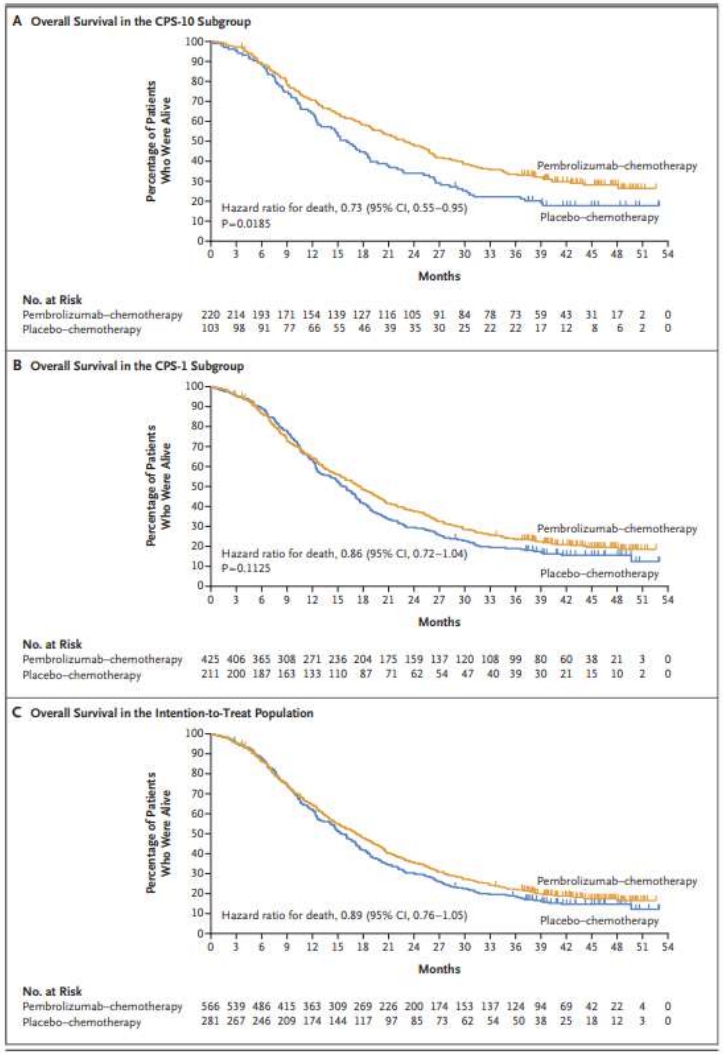
- IMpassion 130
  - Phase 3
  - Atezolizumab plus nab-paclitaxel
  - Improved progression free survival (PFS) of 2.5 months in patients with tumors who are PD-L1 ≥1%
  - Lead to its FDA approval in March 2019
- IMpassion 131
  - Atezolizumab plus paclitaxel failed to demonstrate an improved outcome (neither PFS nor OS) even in the PD-L1-positive subgroup
  - Possibly due to steroids needed for premedication for paclitaxel
  - FDA subsequently withdrew its approval as a result of these findings
- IMpassion 132
  - Atezolizumab plus carboplatin and gemcitabine or capecitabine for early relapse TNBC patients
  - No difference in median disease-free interval or OS



Schmid, P. et al. *N. Engl. J. Med*. 379, 2108–2121 (2018).
Emens, L. A. et al. *Ann. Oncol*. 32, 983–993 (2021)
Milles, D. et al.. *Ann. Oncol*. 32, 994–1004 (2021).

Immunotherapy for Breast Cancer—Subsequent Studies

- KEYNOTE-355
  - Phase 3 trial
  - Pembrolizumab with paclitaxel, nab-paclitaxel, or gemcitabine plus carboplatin in first-line therapy for patients with mTNBC.
  - Patients with PD-L1-positive (CPS > 10) TNBC in first-line setting:
    - mOS: 23 months vs. 16 months; HR: 0.73, 95% CI: 0.55–0.95, p = 0.0185
    - mPFS: 9.7 months vs. 5.6 months; HR: 0.66; 95% CI, 0.50 to 0.88.
  - FDA approval in November 2020



Cortes, J. et al. *Lancet* 396, 1817–1828 (2020).
Cortes J. et al. *N Engl J Med* 2022;387:217-26.

Immunotherapy for Breast Cancer – Metastatic Disease

- Atract1B trial
  - Phase II trial
  - Paclitaxel, atezolizumab and bevacizumab (a VEGF-inhibitor) in the first line for advanced TNBC
  - 97% of patients having PD-L1 negative disease.
  - Median PFS was 11.0 months, with an ORR of 63%, including thirteen complete responses and 50 partial responses

Gion M et al. *Cancer Res*. 2024;84(9_ Supplement):PS16-02-PS16-02

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

HR-Negative and HER2-Negative (Triple-Negative Breast Cancer; TNBC)		
See BINV-Q (1) for Considerations for systemic therapy.		
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)[i] (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[j] (category 1, preferred)
		Systemic chemotherapy BINV-Q (5) or targeted agents BINV-Q (6) and BINV-Q (7)
	No germline *BRCA1/2* mutation[b] and HER2 IHC 0+, 1+, or 2+/ISH negative[d]	Fam-trastuzumab deruxtecan-nxki[k] (category 1, preferred)
Third Line and beyond	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	Targeted agents and emerging biomarker options BINV-Q (7) and BINV-Q (8)
	Any	Systemic chemotherapy BINV-Q (5)

Immunotherapy for Breast Cancer—Other Subtypes

- Initial attempts for single agent or combination of ICI and chemotherapy with modest results or were unsuccessful.
  - Phase Ib trial KEYNOTE-028, pembrolizumab was tested as a single agent in 25 patients with heavily pretreated HR+/HER2– metastatic breast cancer with PD-L1 CPS ≥ 1. ORR of 12.0% (95% CI, 2.5 to 31.2) with a median duration of response of 12 months.
  - Initial trials, phase 2 study evaluating eribulin with or without pembrolizumab in metastatic luminal BC showing no improved outcomes.

Tolaney, S. M. et al. *JAMA Oncol*. 6, 1598–1605 (2020).

Immunotherapy for Breast Cancer—Neoadjuvant Approach

- Given the success of immunotherapy in the metastatic setting, trials were attempted in the earlier stages.
  - Rationale for neoadjuvant approach:
    - Smaller burden of disease
    - More homogenous biology
    - Less immunosuppressive environment since the patient's immune systems had not been suppressed yet by chemotherapy
    - Primary tumor could act as a neoantigen to further stimulate the immune system to act.
  - Use of pathologic response as indicator of success, as a pathologic complete response is associated with improved DFS and OS.

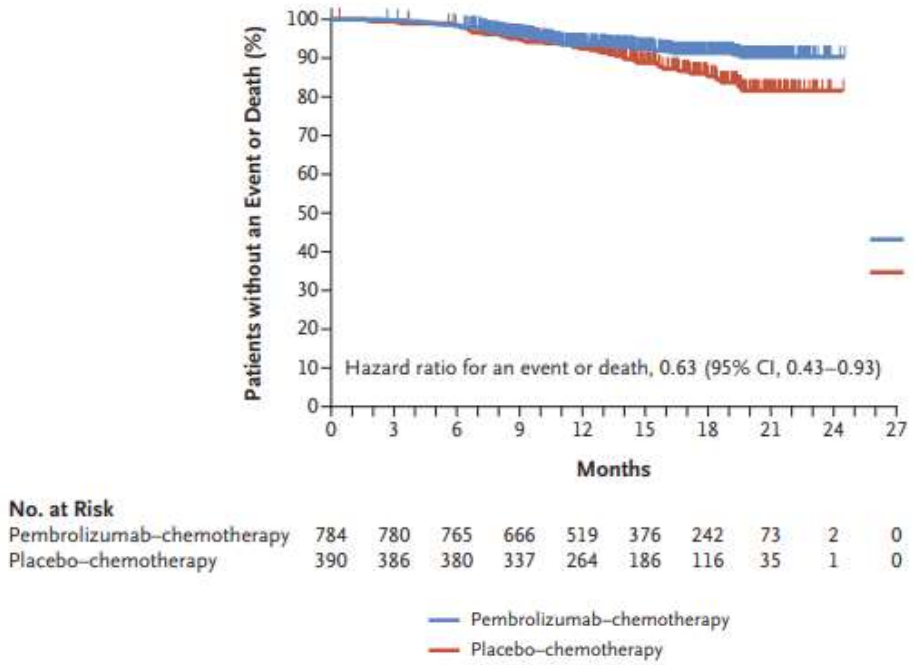
Immunotherapy for Breast Cancer—Neoadjuvant Approach

- KEYNOTE-173
  - Phase 1b trial demonstrated safety and preliminary efficacy of pembrolizumab in the first line with neoadjuvant chemotherapy for early-stage, high-risk TNBC, with higher PD-L1 CPS and TILs significantly associated with higher rates of pCR
- I-SPY2
  - Phase II trial established the benefit of pembrolizumab added to standard neoadjuvant chemotherapy. Twenty nine patients with TNBC>2.5 cm and any nodal status were included.
  - Patients in the experimental arm were treated with pembrolizumab with weekly paclitaxel followed by dose-dense doxorubicin and cyclophosphamide (AC), with estimated pCR rates of 60% vs. 22% for patients treated with paclitaxel followed by AC.
  - Another I-SPY2 regimen evaluated paclitaxel with pembrolizumab in an anthracycline-free regimen, but did not reach target pCR rates

Schmid P,et al. *Ann Oncol.* 2020;31(5):569–81. 64.
Nanda R et al. *JAMA Oncol*. 2020;6(5):676. 65.
Liu MC et al. *Can Res*. 2020;80(4_Supplement):P3-09- 02-P3-09-02

Immunotherapy for Breast Cancer—Neoadjuvant Trials

- KEYNOTE-522
  - Phase 3 trial
  - Stage II-III TNBC patients
  - Neoadjuvant regimen:
    - Four cycles pembrolizumab or placebo plus paclitaxel and carboplatin, then additional four cycles of pembrolizumab or placebo, then anthracycline and cyclophosphamide.
  - Followed by surgery, then adjuvant pembrolizumab or placebo
  - Improved pathological complete response (pCR) rates in the immunotherapy arm (64.8 vs. 51.2%)
  - Overall pCR benefit was more significant for patients with node-positive disease (Δ pCR rate of 20.6 vs. 6.3%).
  - Improved event-free survival (EFS) rate at 36 months in the pembrolizumab-chemotherapy combination (HR = 0.63, 95% CI 0.48–0.82, absolute gain 7.7%)
  - FDA-approved regimen for early TNBC as of July 2021



Schmid, P. et al. N. Engl. J. Med. 386, 556–567 (2022).

Immunotherapy for Breast Cancer—Neoadjuvant Trials

- IMpassion031—nab-paclitaxel ± atezolizumab, followed by dose dense anthracycline based chemo
  - Improved pCR : 41 vs. 58%, (Δ pCR rate 17%, 95% CI 6–27, one-side p = 0.0044)
- GeparNUEVO—nab-paclitaxel ± durvalumab
  - No improved pCR
- NeoTRIPaPDL1—nab-paclitaxel with carboplatin without anthracyclines ± atezolizumab
  - No improved pCR

Durvalumab did show improved disease free survival (DFS) and OS. Is pCR a good surrogate endpoint in the neoadjuvant setting?

Interestingly PD-L1 IHC expression was not predictive of pCR, while TIL levels and dynamic TILs increase were associated with a better response

Mittendorf, E. A. et al. *Lancet* 396, 1090–1100 (2020). 36.
Loibl, S. et al. *Ann. Oncol.* 30, 1279–1288 (2019).
Gianni, L. et al. *Ann. Oncol.* S0923-7534, 00113–2 (2022)
Loibl, S. et al. *JCO* 39, 506–506 (2021).

For T2 and/or cN+ preoperative systemic therapy should be considered

PREOPERATIVE/ADJUVANT THERAPY[a,b]

The regimens listed in the table are all category 1 (except where indicated) when used in the adjuvant setting. See BINV-M, 1 for Considerations for Those Receiving Preoperative/Adjuvant Systemic Therapy.

HR-Negative, HER2-Negative	
Preferred Regimens: **Stage 1** **Preoperative or adjuvant setting:** • Dose-dense AC (doxorubicin/cyclophosphamide) followed or preceded by paclitaxel every 2 weeks[c,e] • Dose-dense AC (doxorubicin/cyclophosphamide) followed or preceded by weekly paclitaxel[c,e] • TC (docetaxel and cyclophosphamide)[e]	
Stage II–III **Preoperative followed by adjuvant:** • Preoperative pembrolizumab + carboplatin + paclitaxel, followed by preoperative pembrolizumab + cyclophosphamide + doxorubicin or epirubicin, followed by adjuvant pembrolizumab (category 1)	
Stages I–III **Adjuvant setting only:** • If residual disease after preoperative therapy with taxane-, alkylator-, and anthracycline-based chemotherapy[d,e]: Capecitabine • Germline *BRCA1/2* mutations[d]: Olaparib	
Useful in Certain Circumstances: **Preoperative only:** • Docetaxel/carboplatin/pembrolizumab **Preoperative or adjuvant:** • Dose-dense AC (doxorubicin/cyclophosphamide) • AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B) • CMF (cyclophosphamide/methotrexate/fluorouracil) • AC followed by weekly paclitaxel[c] • AC (doxorubicin/cyclophosphamide) followed or preceded by carboplatin + docetaxel[c] **Maintenance therapy after adjuvant chemotherapy:** • Capecitabine	**Other Recommended Regimens:** **Preoperative or adjuvant setting:** • AC followed by docetaxel every 3 weeks[c] • EC (epirubicin/cyclophosphamide) • TAC (docetaxel/doxorubicin/cyclophosphamide) • Paclitaxel + carboplatin (various schedules) (category 2A) • Docetaxel + carboplatin[f] (category 2A) • Regimens listed as "Preferred" for stage I, may be considered for patients with Stage II–III disease who are not eligible for pembrolizumab.

[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] Principles of Preoperative Systemic Therapy (BINV-L).
[c] It is acceptable to change the administration sequence to taxane followed by AC.
[d] 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. In patients eligible for both adjuvant olaparib and abemaciclib, the optimal sequence is not known. See BINV-K, 2.
[e] For patients with stage II–III disease who are not eligible for pembrolizumab, the regimens listed as "preferred" for stage 1 could be considered as other recommended options.

Immunotherapy for Breast Cancer—Neoadjuvant Approach in Other Subtypes

- IMpassion050
  - HER2-positive breast cancer
  - Addition of atezolizumab to NACT and dual anti-HER2 blockade
  - No significant increase in pCR rate in ITT nor PD-L1 positive population
  - Median EFS, a secondary endpoint, was not reached in both arms

Huober, J. et al. *JCO* 40, 2946–2956 (2022)

Immunotherapy for Breast Cancer—Side Effects

- Immune-related adverse events (irAE) –caused by disruptions in self-tolerance, or a nonspecifc autoinflammatory reaction
  - Cutaneous (maculopapular rash, pruritus, or lichenoid dermatitis)
  - Gastrointestinal (diarrhea and colitis)
  - Endocrine (hypothyroidism, hypophysitis or adrenal insufficiency)
  - Pneumonitis
  - Myocarditis
  - Hepatitis
  - Enteritis
- Management of irAE—high-dose corticosteroids, with immunosuppressive therapies in severe cases.
  - Permanent discontinuation of immunotherapy for grade 4 irAEs except endocrinopathies that can be controlled with hormone replacement

Yin Q et al. *Front Immunol*. 2023. https://doi.org/10.3389/fmmu.2023.1167975.
Schneider BJ et al. *J Clin Oncol.* 2021;39(36):4073–126.

Immunotherapy for Breast Cancer—Vaccines

- Attempts made to target HER2 tumors given the success with trastuzumab as the first monoclonal antibody for cancer treatment.
  - Mixed results in patients, including those with low HER2 expressing tumors
- Other targets:
  - Non-HER2 tumor associated antigens (TAAs)
    - Cancer testis antigens (NY-ESO-1, Wilms' tumor protein (WT1), MAGE-12, folate receptor alpha, T-box transcription factor brachyury)
    - Mucin 1 (MUC1)
    - PVX-410
    - Multiple peptides of CD105 (Endoglin), Y-box binding protein 1 (Yb-1), SRY-box 2 (SOX2), cadherin 3 (CDH3), and murine double minute 2 (MDM2) proteins.
    - Vaccine-based immunotherapy regimen-2 (VBIR-2)
    - Prostate-specific membrane antigen (PSMA) and PRAME
  - Non-HER2 Tumor-associated carbohydrate (TAC) antigens
    - P10s-PADRE
    - Globo H glycosphingolipid
  - Tumor Neoantigens

Debien et al. Breast Cancer (2023) 9:7

Immunotherapy for Breast Cancer—Adoptive Cell Transfer (ACT)

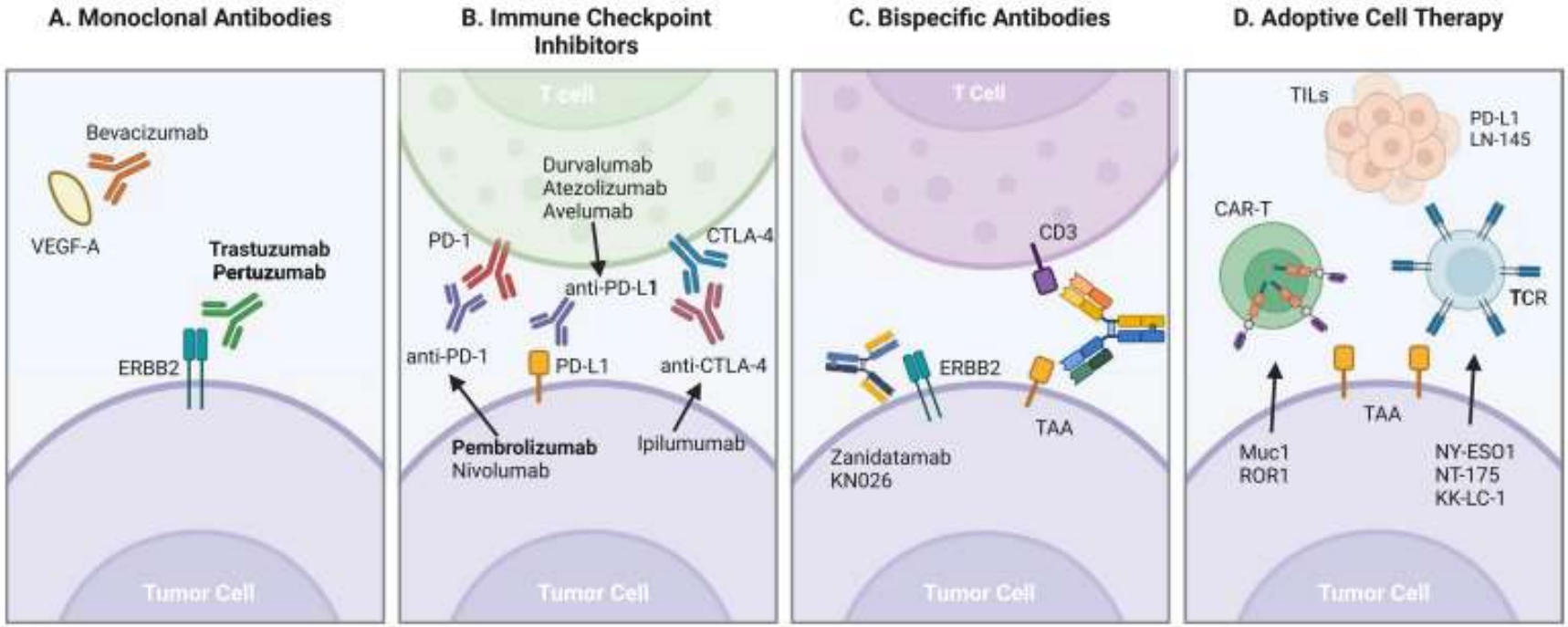
- Expanding peripheral blood or tumor-resident T cells ex-vivo to target the neoantigens in the tumor. These are then delivered to patients following lymphodepletion.
  - Include TIL based therapies, T cell receptors gene therapy, and CAR-T cells
- Many initial trials in this space were not effective
- Selective cases have shown promise

Rosenberg, S. A. et al *N. Engl. J. Med*. 316, 889–897 (1987)

Conclusions

- While initially thought to not be very sensitive to immunotherapy, select populations of breast cancer patients have shown significant benefit to it’s use.
- Ongoing studies are trying to enhance the response further, and understand how to harness its power in other populations.

Immunotherapy of Breast Cancer



TAA = tumor associated antigen

Heater et al. Journal of Hematology & Oncology (2024) 17:131