Thanks for The Mammaries:

Exploring New Treatment Approaches in Triple Negative Breast Cancer

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November 28, 2022

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Objectives

1. Define triple negative breast cancer and identify pitfalls in treatment

2. Compare and contrast previous treatment strategies vs new treatment strategies in triple negative breast cancer

3. Analyze current literature supporting novel treatment methods and discuss future treatment strategies

Introduction

Breast cancer is the most common cancer in women

Cancer type	Estimated new cases (US 2022)
Breast	287,850
Lung and bronchus	123,400
Colon and rectum	70,300

Breast Cancer Death Rates
Overall decline of 43% from 1989-2020

CA CANCER J CLIN 2022;72:524–541.
American Cancer Society. Cancer Facts & Figures 2022.

Terminology

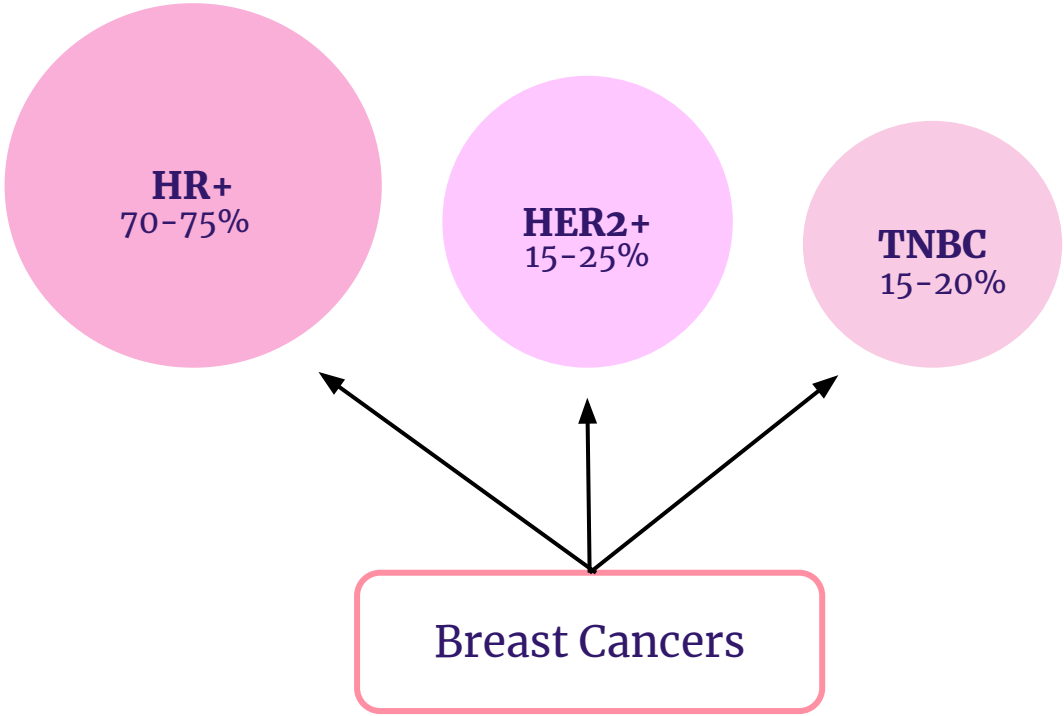
ER (-/+):
Estrogen Receptor

PR (-/+):
Progesterone Receptor

HER2 (-/+):
Human Epidermal Growth Factor Receptor 2

TNBC
Triple Negative Breast Cancer

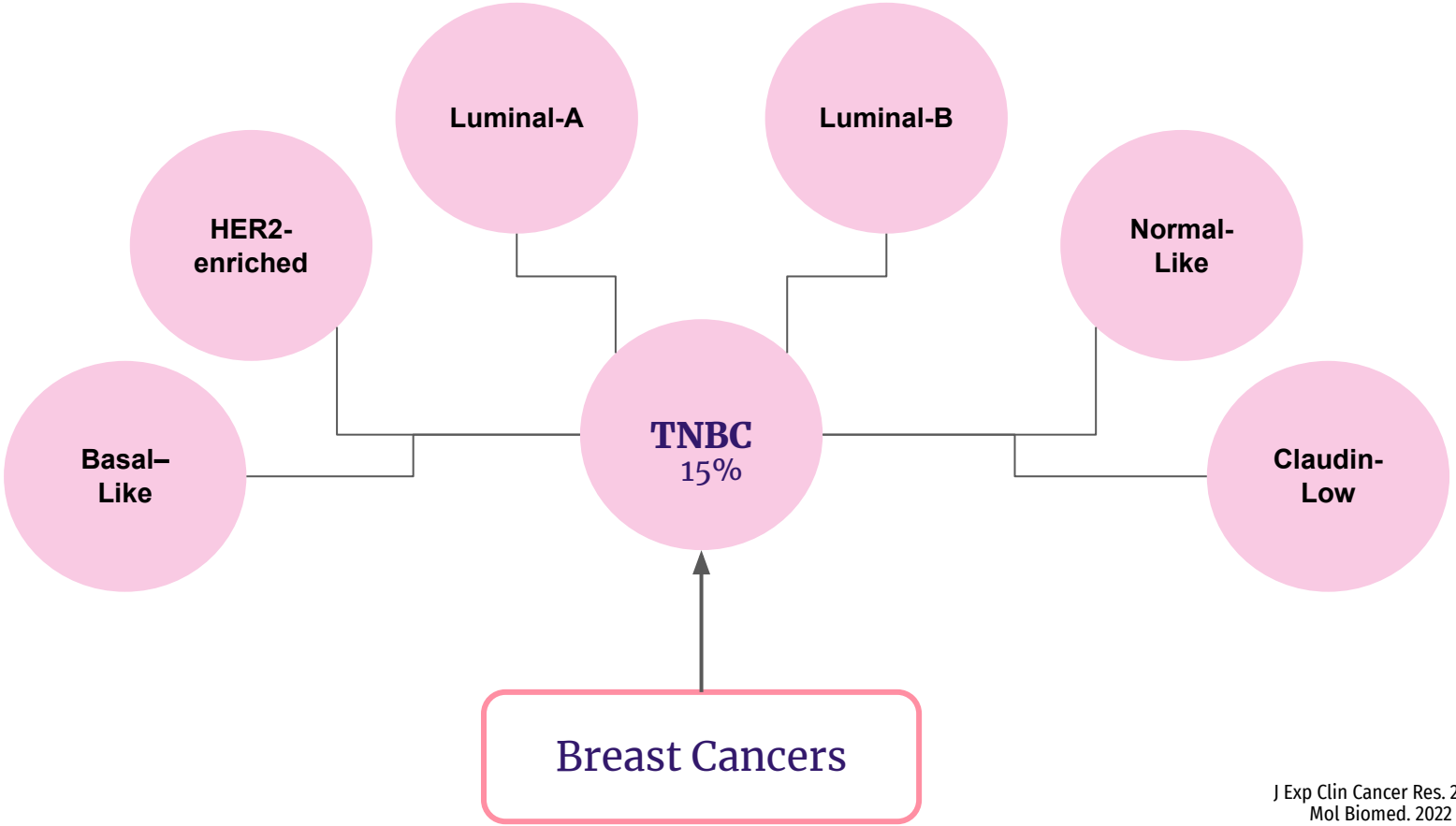
Breast Cancer Subtypes



HR: Hormone receptor

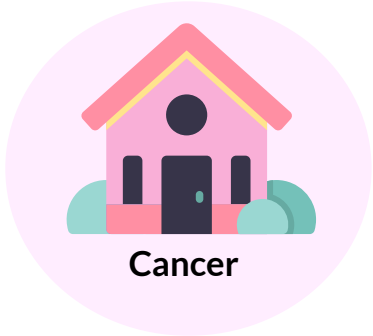
Biomed Rep. 2014 Jan;2(1):41-52.
NPJ Breast Cancer. 2022; 8: 95.

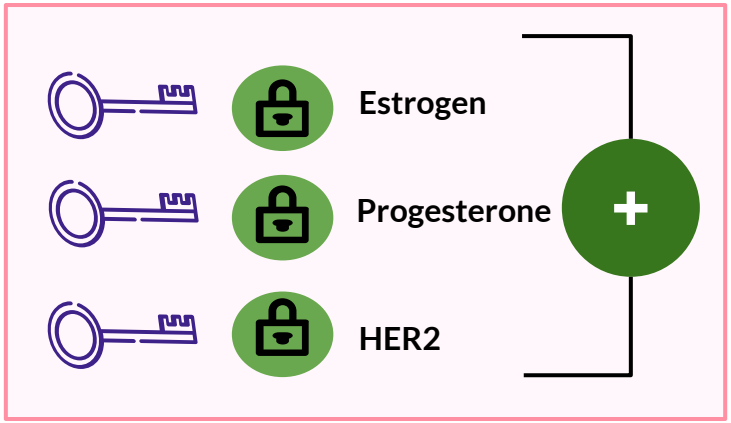
TNBC Subtypes

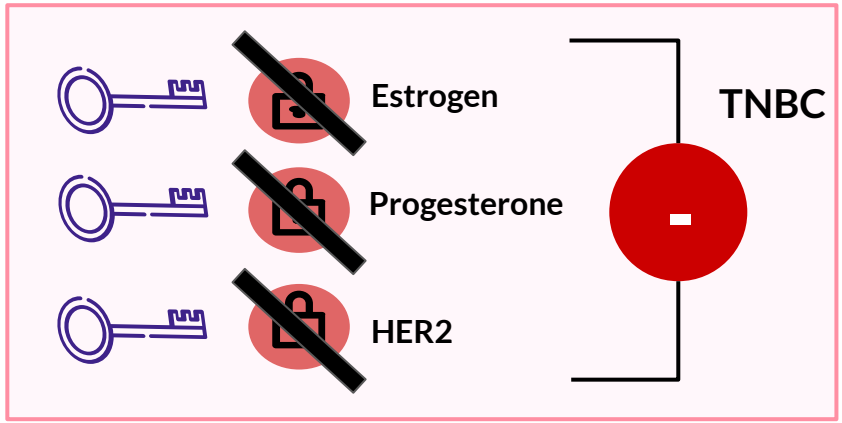


J Exp Clin Cancer Res. 2022; 41: 265.
Mol Biomed. 2022 Mar 4;3(1):8.

Triple Negative Breast Cancer







TNBC. Division of Cancer Prevention and Control 2022.

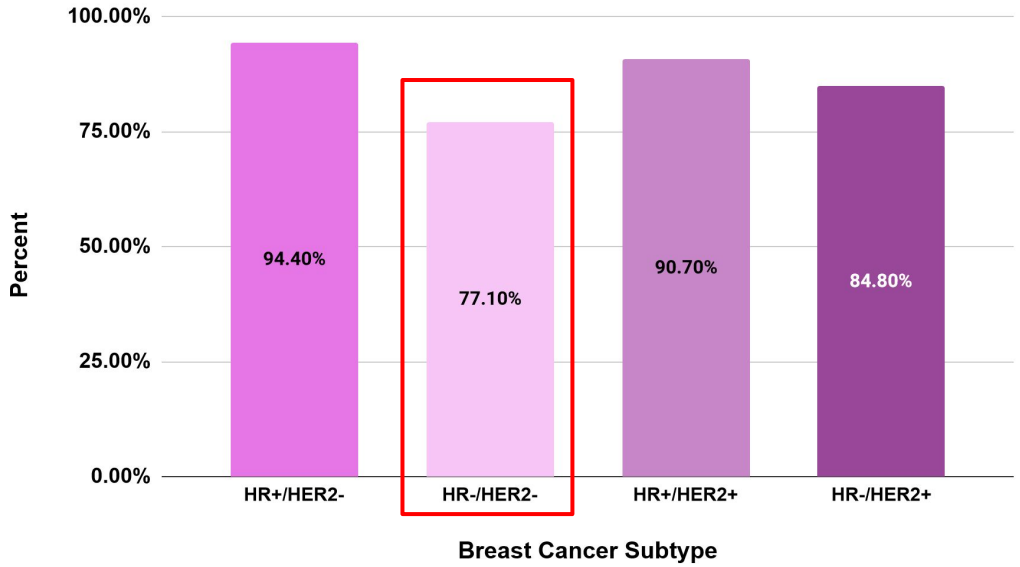
Triple Negative Breast Cancer

Characteristics	Epidemiology
Most malignant subtype	**Incidence** 200,000 cases each year worldwide
Limited treatment options	**Risk factors** Women ≤ 40 years old African american women Gene mutation (BRCA)
Poor prognosis	

BRCA: Breast cancer gene

5-Year Survival Rates

Breast Cancer Subtype



TNBC type

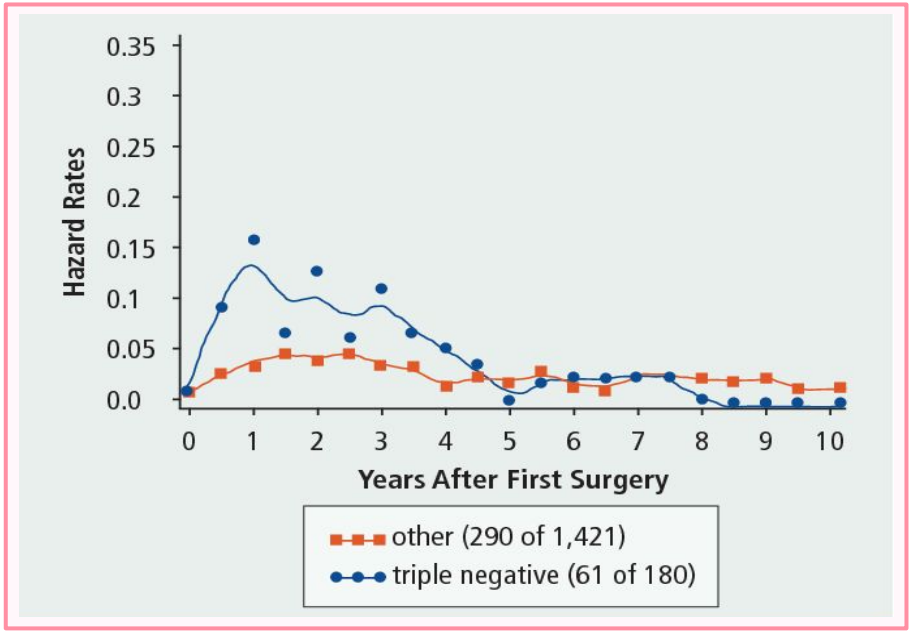
Localized	91%
Regional	65%
Distant	12%

Statistics from seer.cancer.gov. 2022.
Oncology (Williston Park). 2008 Oct; 22(11): 1233–1243.

Recurrence Rates

TNBC

- High rates of early recurrence
- Metastatic recurrence higher
- Death from recurrence greater in TNBC versus other subtypes

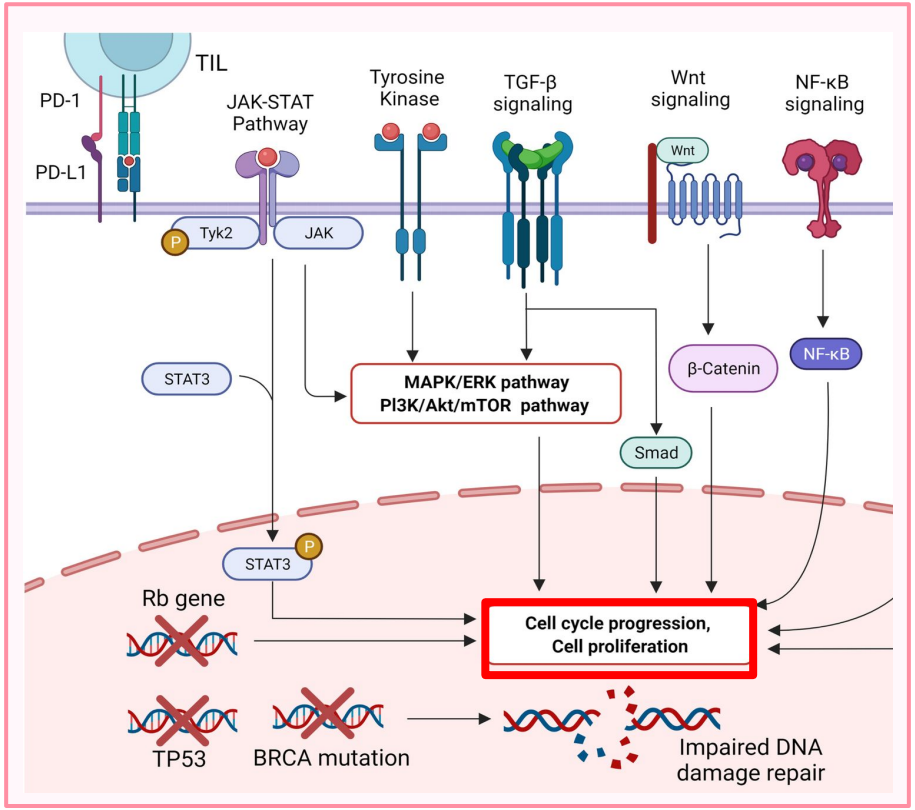


Clin Cancer Res. 2007 Aug 1;13(15 Pt 1):4429-34.

Pathogenesis

TNBC

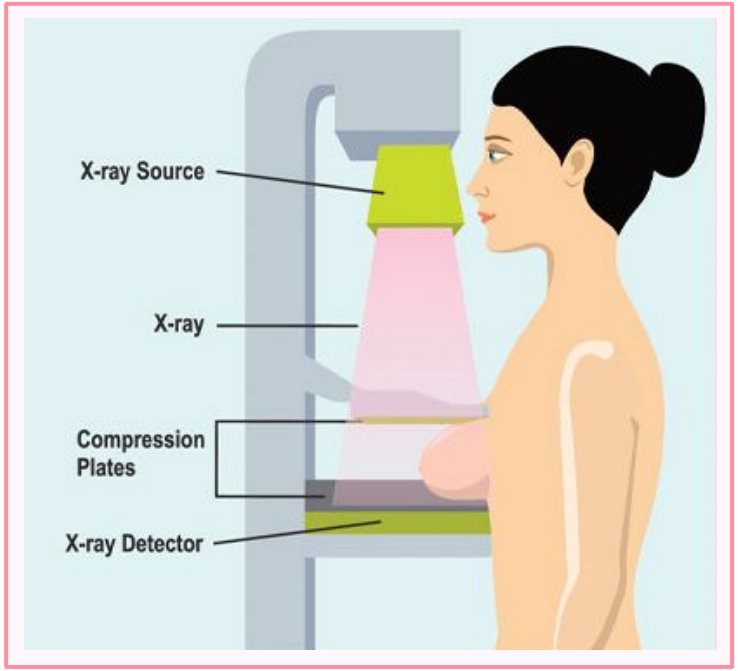
- Genetic mutations
  - TP53
  - BRCA1/2
  - RB1



TP53: Tumor protein 53
BRCA1/2: Breast cancer gene 1/2
RB1: Retinoblastoma protein

Pathogenesis and Therapies. BioNanoSci. (2022).

Diagnosis and Testing



TNBC

- **Tests**
  - Breast exam, mammogram, MRI
  - Genetic counseling and testing
  - Biopsy and tumor status

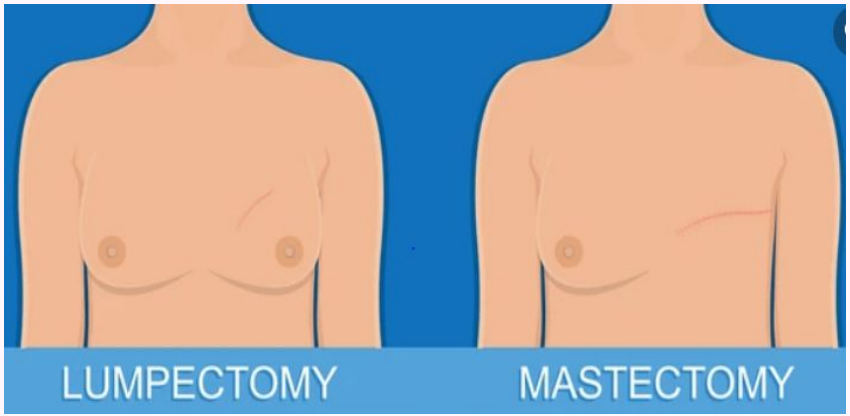
MRI: Magnetic resonance imaging

Mammography. Stock Vector ID: 1183123222.
PET Clin. 2018 Jul;13(3):301-323.

Non-Pharmacologic Treatments

TNBC

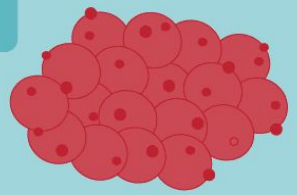
- **Surgery**
  - Lumpectomy
  - Mastectomy
- **Radiation**
  - External beam



Lumpectomy vs. Mastectomy. Stock Vector ID: 1484214197.
NCCN guideline. Invasive Breast Cancer. Version 2022.

TNM Staging System

T



Tumor size

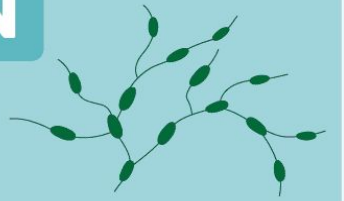
T-1: 0-2 centimeters

T-2: 2-5 centimeters

T-3: >5 centimeters

T-4: Tumor has broken through skin or attached to chest wall

N



Lymph Node Status

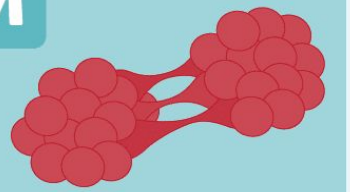
N-0: Surgeon can't feel any nodes

N-1: Surgeon can feel swollen nodes

N-2: Nodes feel swollen and lumpy

N-3: Swollen nodes located near collarbone

M



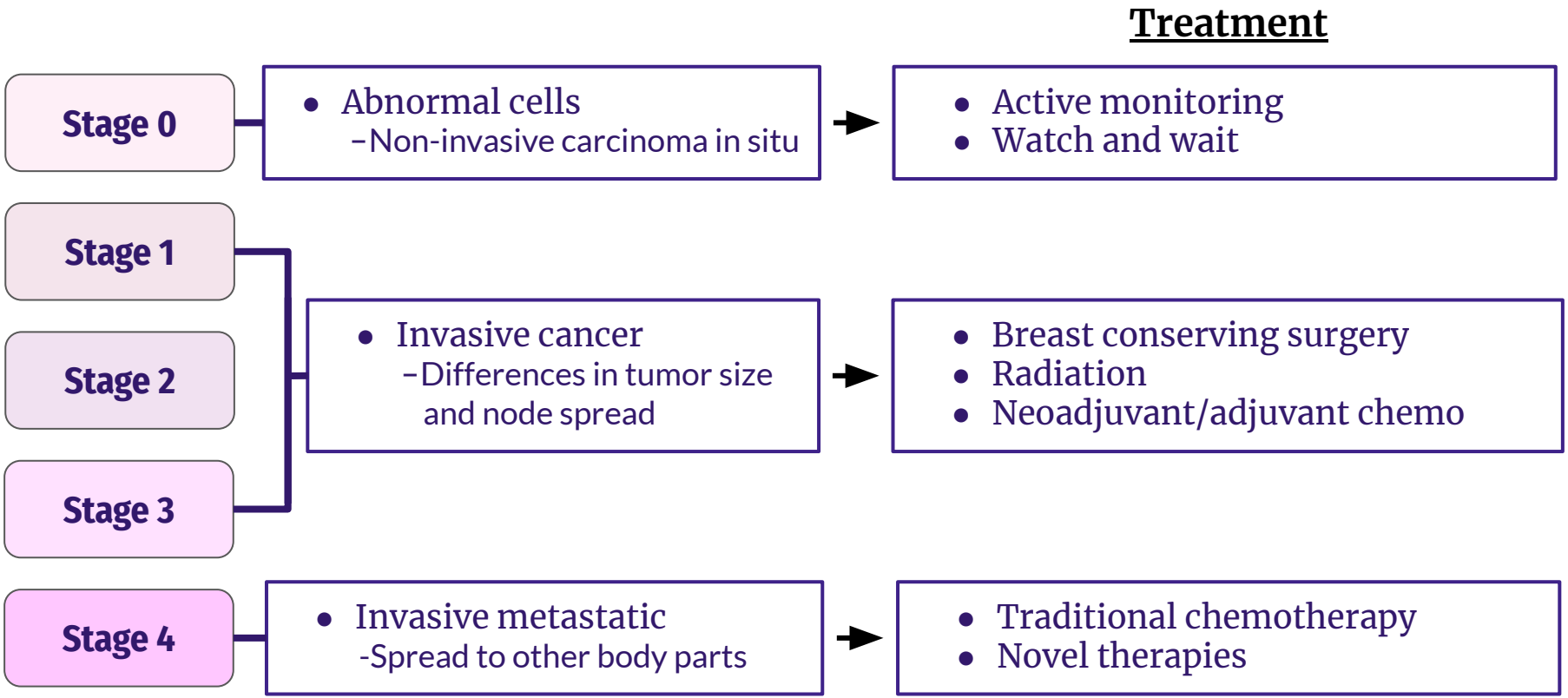
Metastasis

M-0: Tested nodes are cancer-free

M-1: Tested nodes show cancer cells or micrometastasis

Gary Ferster. TNM Staging. 4114640.
NCCN guideline. Invasive Breast Cancer. Version 2022.

TNBC Stages



NCCN guideline. Invasive Breast Cancer. Version 2022.

Pitfalls in TNBC

Lack of therapeutic targets

TNBC heterogeneity not well understood

Reliable biomarkers not well identified

Mol Biomed. 2022 Mar 4;3(1):8.
npj Breast Cancer volume 8, Article number: 95 (2022).

Summary

TNBC lacks ER, PR and HER2. It accounts for 15-20% of breast cancer worldwide and is associated with greater recurrence and mortality rates

Diagnosis and management are similar to other breast cancers. However, complexity of TNBC leads to limited treatment and poor outcomes

Assessment Question 1

Triple negative breast cancer is an aggressive type of breast cancer compared to other subtypes. What characteristics of triple negative breast cancer is associated with difficulty in treatment and poor prognosis?

a. Lack of receptors present (ER,PR,HER2)
b. Complex pathogenesis
c. Heterogeneity
d. All of the above

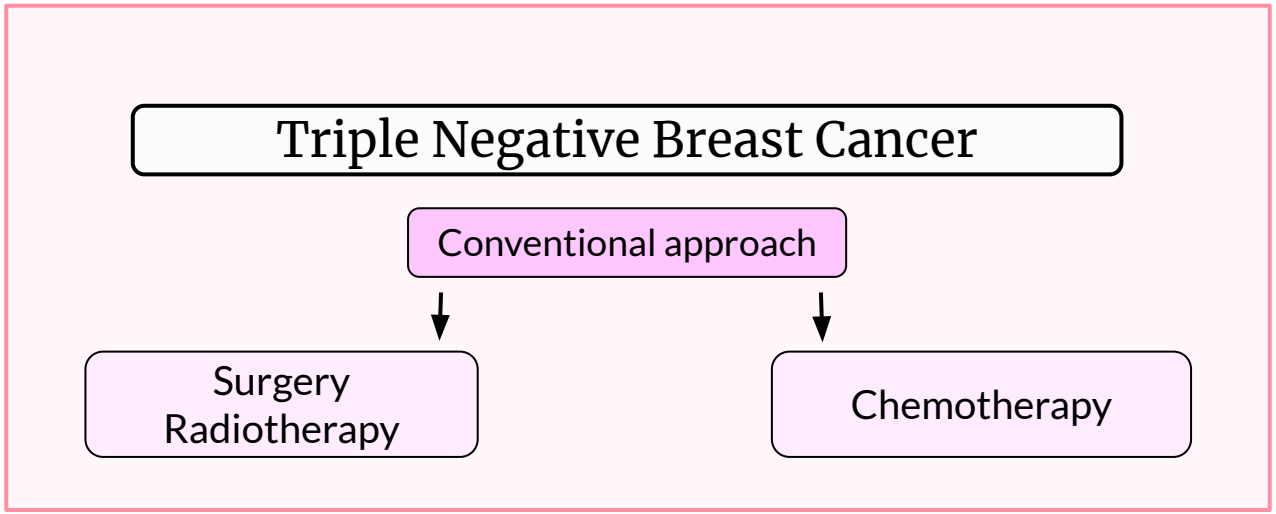
Assessment Question 1

Triple negative breast cancer is an aggressive type of breast cancer compared to other subtypes. What characteristics of triple negative breast cancer is associated with difficulty in treatment and poor prognosis?

a. Lack of receptors present (ER,PR,HER2)
b. Complex pathogenesis
c. Heterogeneity
d. All of the above

Treatment Approaches for Triple Negative Breast Cancer

TNBC Treatment Strategies



NCCN guideline. Invasive Breast Cancer. Version 2022.

Common Chemo Regimen

Regimen:	Dose Dense Doxorubicin + Cyclophosphamide followed by Paclitaxel
(dd)AC → T	

Agent	DD Dosing* (Every 2 weeks)	Cycles	Adverse Events
(dd) Doxorubicin +	60 mg/m^2 IV	4	Cardiotoxicity
Cyclophosphamide	600 mg/m^2 IV	4	Hemorrhagic Cystitis

**Non dose dense (every 3 weeks)*

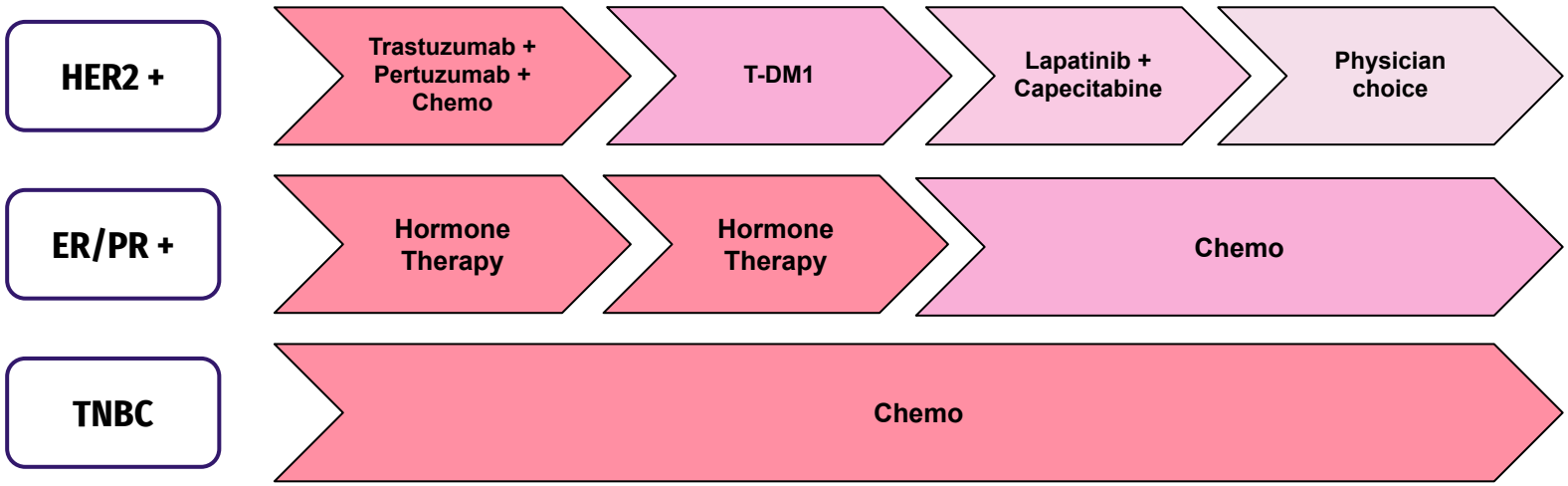
Agent	Dosing (Every 1 week x 12 doses)	Cycles	Adverse Events
Paclitaxel	175 mg/m^2 IV	4	Hypersensitivity reactions

DD: Dose Dense
A: Adriamycin® (Doxorubicin)
C: Cytoxan ® (Cyclophosphamide)
T: Taxotere ® (Docetaxel)

NCCN guideline. Invasive Breast Cancer. Version 2022.

Treatments for Metastatic Breast Cancer

Stage 4
- Traditional chemotherapy
- Novel therapies



***Potential treatment algorithm. Treatment varies between each patient**

T-DM1: Trastuzumab emtansine

Int J Environ Res Public Health. 2020 Mar; 17(6): 2078.

Traditional Chemotherapy Agents for mTNBC

mTNBC

- Individualized
- Mono or combination therapy
- Selection factors
  - Prior treatment
  - Tumor burden
  - Side effect profile

Taxanes

- Paclitaxel
- Docetaxel

Anthracyclines

- Doxorubicin
- Epirubicin

Antimetabolites

- Capecitabine
- Gemcitabine

Platinums

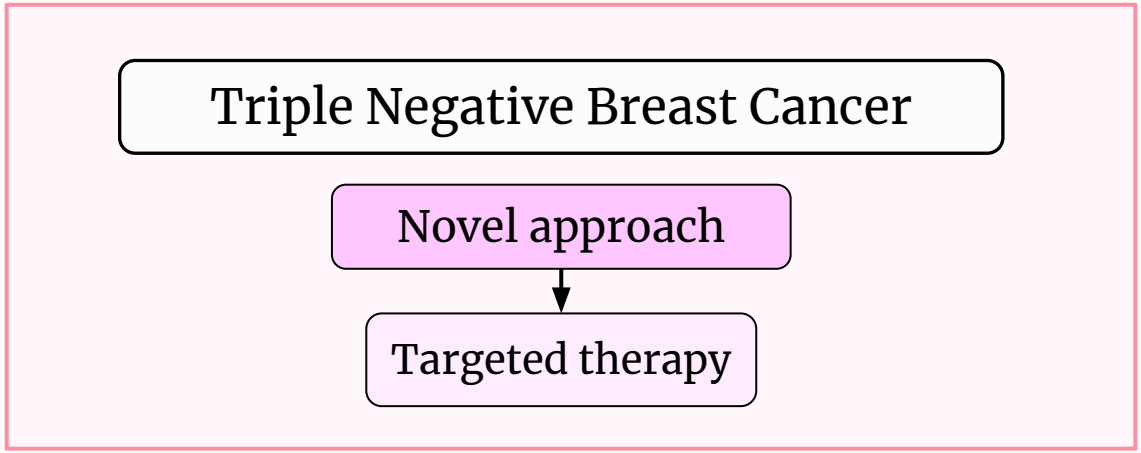
- Cisplatin
- Carboplatin

Antimicrotubules

- Vinorelbine
- Eribulin

Int J Environ Res Public Health. 2020 Mar; 17(6): 2078.

Novel Treatment Approaches in TNBC



Antibody Drug Conjugate (ADCs)

Immunotherapy: Anti-PD-L1/PD-1

Poly-ADP Ribose Polymerase Inhibitors (PARP)

PD-1: Programmed cell death protein 1
PD-L1: Programmed death-ligand 1

NCCN guideline. Invasive Breast Cancer. Version 2022.

Olaparib

Indication*	Early, high-risk, or metastatic HER2 negative breast cancer with germline BRCA-mutation in the adjuvant setting
Dosing	Tablet: 300 mg BID until disease progression or unacceptable toxicity
Adverse Effects	Common: Nausea, anemia, fatigue, vomiting, neutropenia
Monitoring	Laboratory: Hemoglobin, platelets, absolute neutrophil count

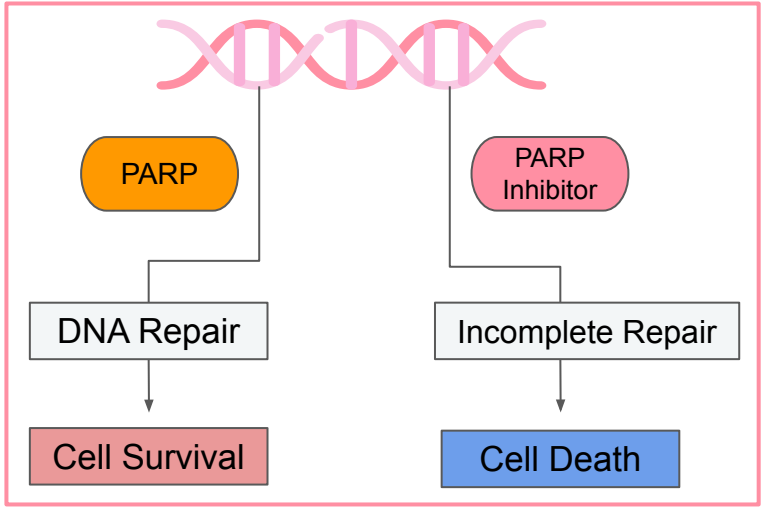
*Other types of cancer indication not listed

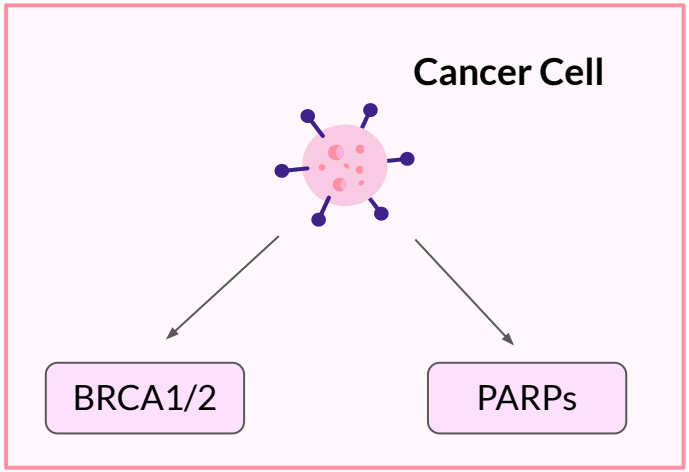
J Adv Pract Oncol. 2019 Mar; 10(2): 167–174.

PARP Inhibitors

Poly-ADP Ribose Polymerase

- **BRCA proteins** (BRCA1/2)
  - Abnormal BRCA
    - Lose repairing mechanism
    - Increase chance of cancer





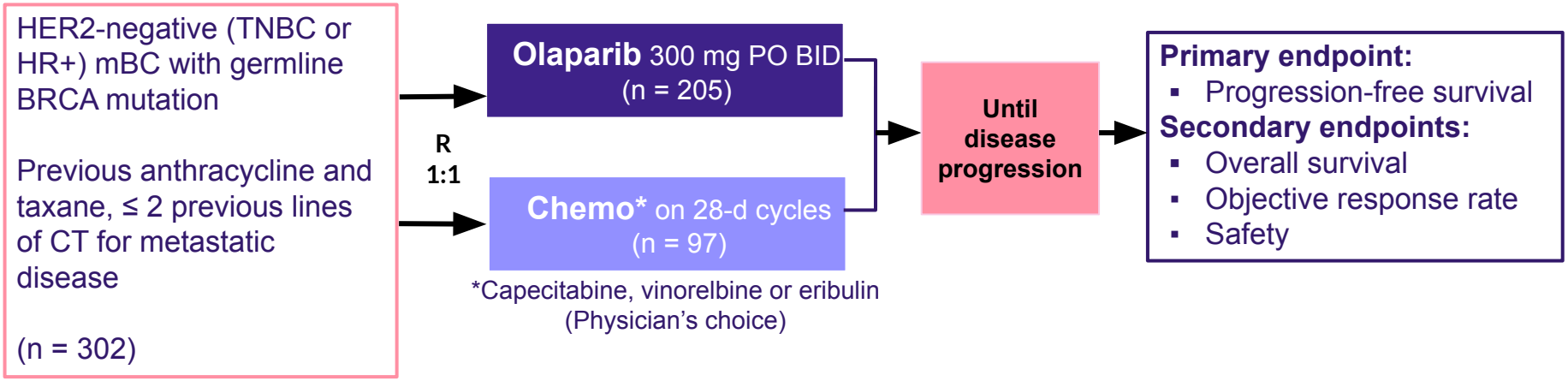
Cancer J. 2021 Jan-Feb;27(1):67-75.

OlympiAD: Olaparib vs Chemotherapy

Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation	
Design	International, multicenter, randomized, controlled, phase 3 trial
Objective	Compared the efficacy of olaparib vs chemotherapy for metastatic breast cancer in patients with a germline BRCA mutation
Primary Outcome	Progression-free survival
Secondary Outcomes	Overall survival, objective response rate, and safety outcomes

N Engl J Med 2017; 377:523-533.

OlympiAD: Olaparib vs Chemotherapy



CT: Chemotherapy
R: Randomization
mBC: Metastatic breast cancer

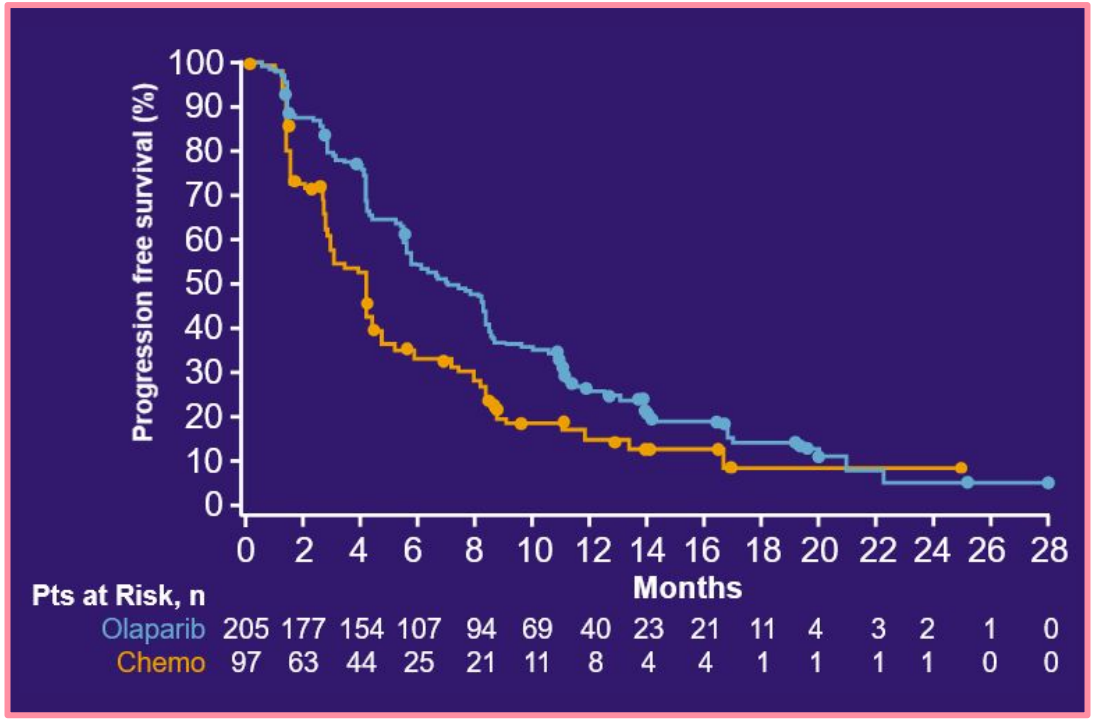
N Engl J Med 2017; 377:523-533.

OlympiAD: Results

Primary Outcome

	Olaparib	Chemo
Progression, n(%)	**163 (79.5)**	**71 (73.2)**
Median PFS, months	**7.0**	**4.2**

Hazard ratio: 0.58
95% CI: 0.43-0.80
p<0.001



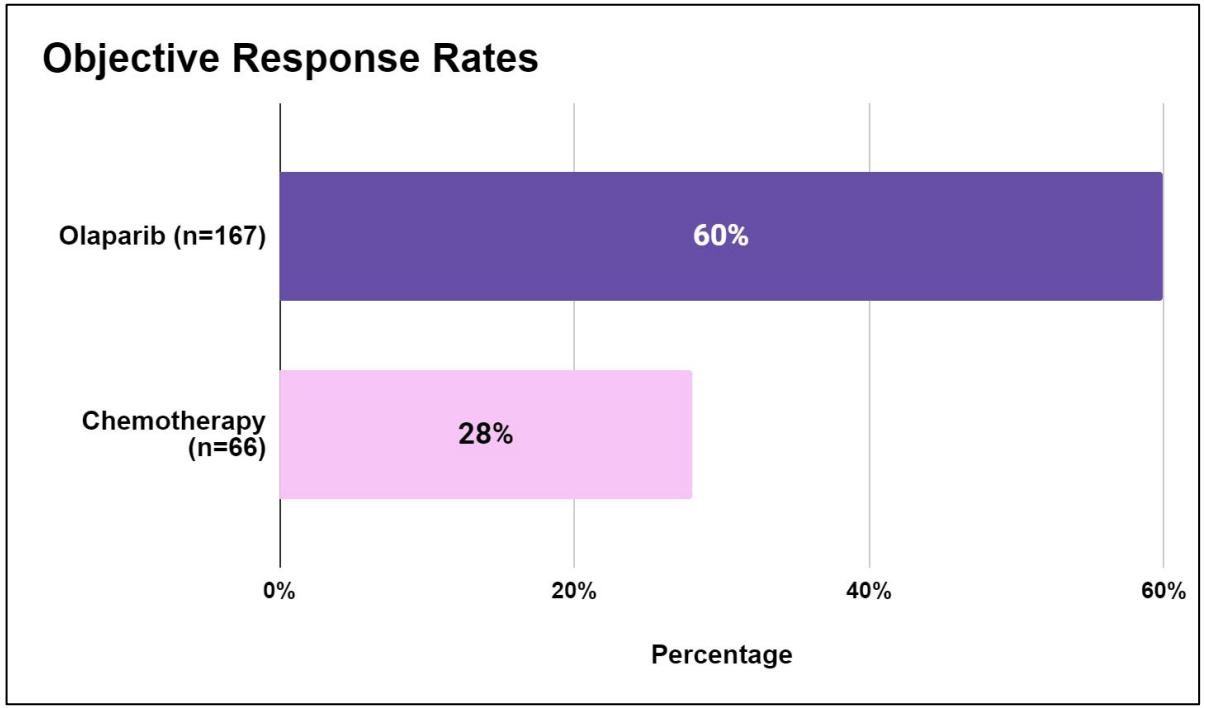
PFS: Progression free survival

N Engl J Med 2017; 377:523-533.

OlympiAD: Results

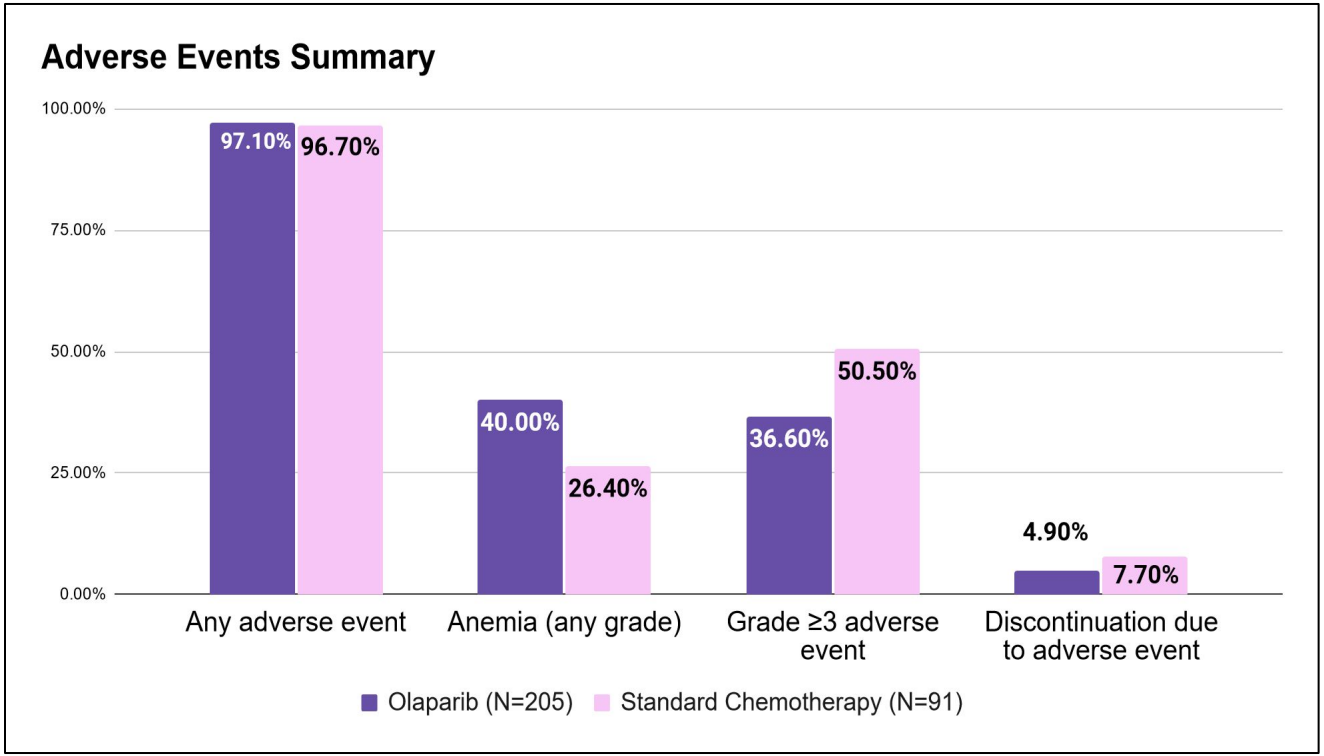
Greater tumor shrinkage with olaparib

Effective in patients with BRCA1 and BRCA2 mutations



N Engl J Med 2017; 377:523-533.

OlympiAD: Results



CTCAE

Grade 1- Mild
Grade 2 - Moderate
Grade 3 - Severe (not life threatening)
Grade 4 - Life threatening
Grade 5 - Death

CTCAE: Common terminology criteria for adverse events

N Engl J Med 2017; 377:523-533.

OlympiAD: Olaparib vs Chemotherapy

CONCLUSION

Olaparib monotherapy showed significant benefit over standard chemotherapy for patients with metastatic TNBC with a germline BRCA mutation

N Engl J Med 2017; 377:523-533.

Summary

Chemotherapy remains the backbone of treatment in TNBC regardless of poor outcomes

New treatment strategies in mTNBC have shown to improve prognosis compared to standard chemotherapy

Assessment Question 2

According to the OlympiAD trial, olaparib showed an increase in progression-free survival and resulted in fewer grade 3 or higher side effects than standard chemotherapy. What is a common side effect often seen in patients taking olaparib?

a. Anemia
b. Dysphagia
c. Hives
d. None of the above

Assessment Question 2

According to the OlympiAD trial, olaparib showed an increase in progression-free survival and resulted in fewer grade 3 or higher side effects than standard chemotherapy. What is a common side effect often seen in patients taking olaparib?

a. **Anemia**
b. Dysphagia
c. Hives
d. None of the above

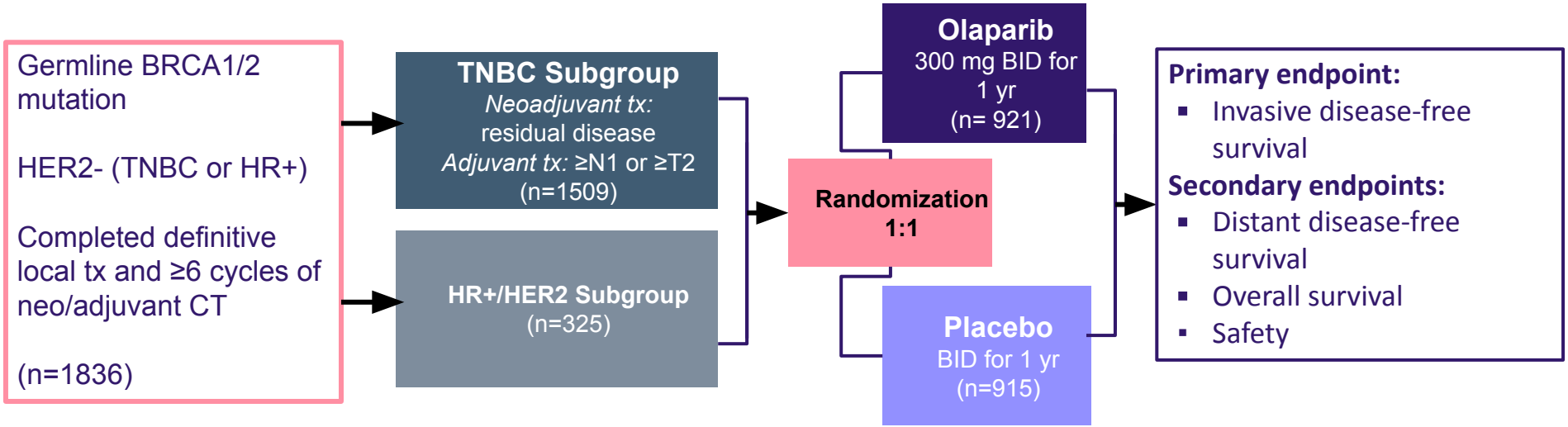
Novel Therapies for Triple Negative Breast Cancer

OlympiA: Adjuvant Olaparib

Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer	
Design	Multicenter, randomized, placebo controlled, phase 3 clinical trial
Objective	Assess the efficacy of olaparib as adjuvant therapy for patients with BRCA mutations in breast cancer
Primary Outcome	Invasive disease-free survival
Secondary Outcomes	Distant disease-free survival, overall survival and safety outcomes

N Engl J Med 2021; 384:2394-2405.

OlympiA: Olaparib



CT: Chemotherapy

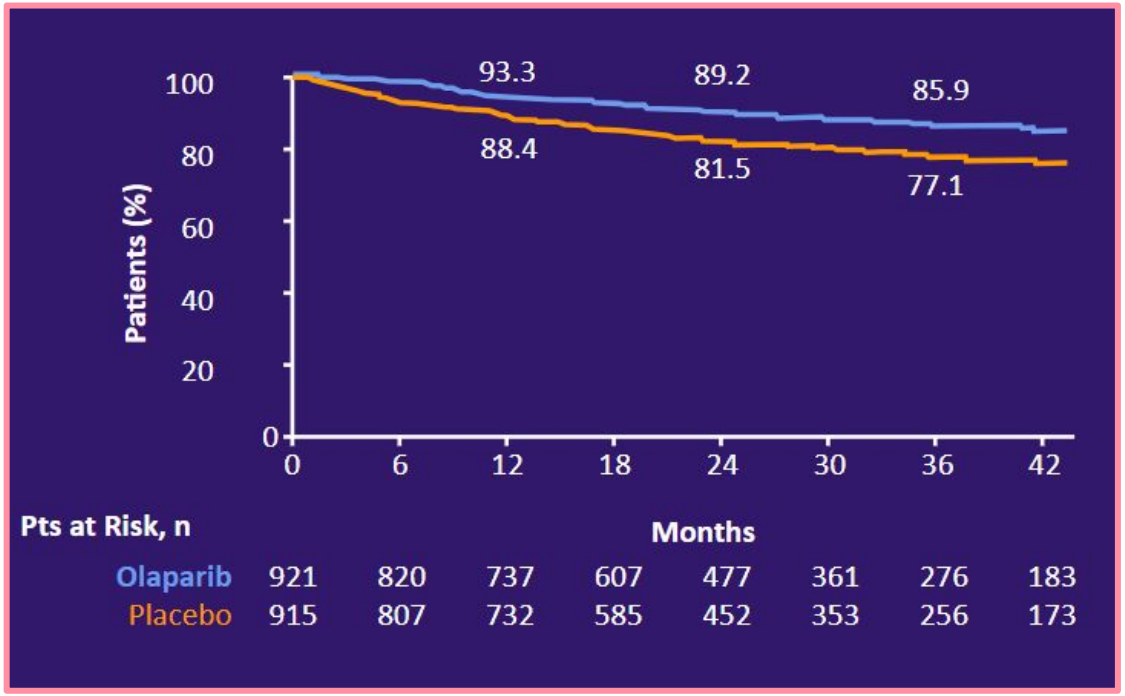
N Engl J Med 2021; 384:2394-2405.

OlympiA: Results

Primary Outcome

	Olaparib	Placebo
Events, n	**106**	**178**
3-Yr IDFS, %	**85.9**	**77.1**
Difference, %	**8.8**	

Hazard ratio: 0.58
95% CI: 0.41-0.82
p<0.001



IDFS: Invasive disease free survival

N Engl J Med 2021; 384:2394-2405.

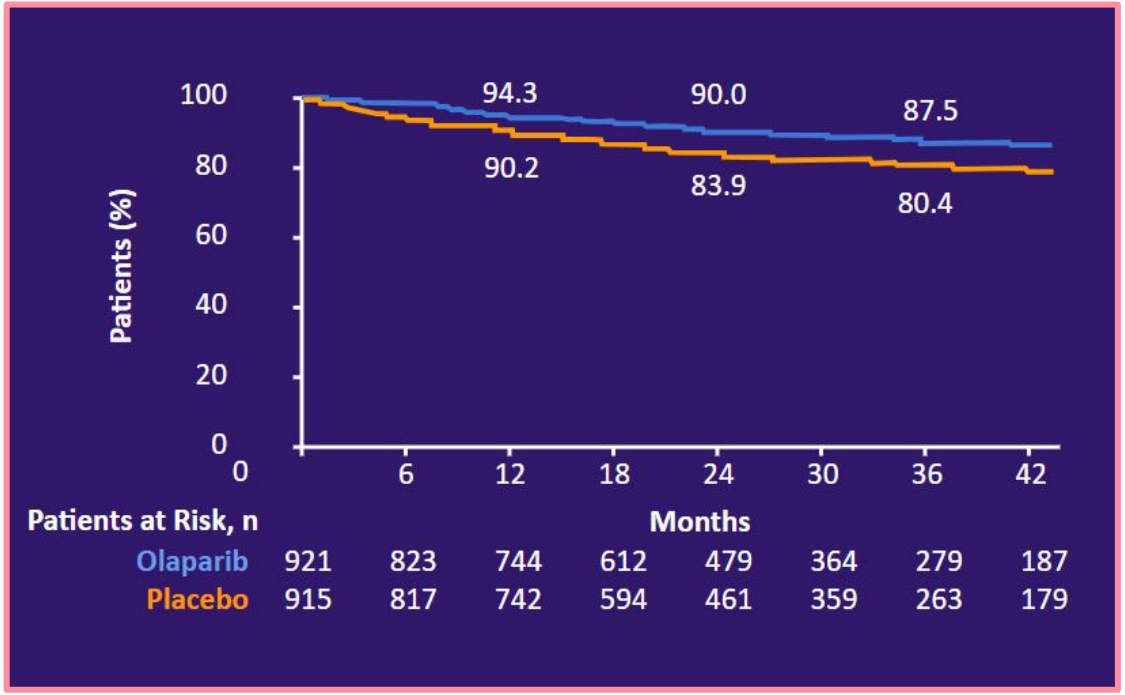
OlympiA: Results

Secondary Outcome

	Olaparib	Placebo
Events, n	89	152
3-Yr DDFS, %	87.5	80.4
Difference, %	7.1	

Hazard ratio: 0.57
99.5% CI: 0.39-0.83
p<0.001

Adjuvant olaparib significantly improved distant disease-free survival vs placebo



DDFS: Distant disease free survival

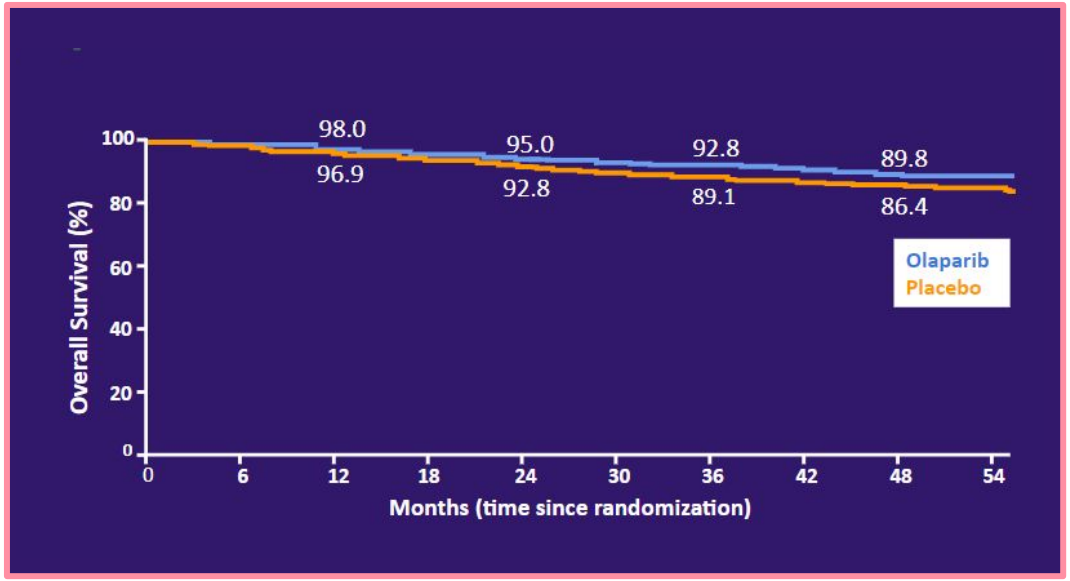
N Engl J Med 2021; 384:2394-2405.

OlympiA: Results

Secondary Outcome

	Olaparib	Placebo
3-yr OS rate, %	**92.0**	**89.1**
Median follow up	**3.5 years**	
Difference, %	**7.1**	

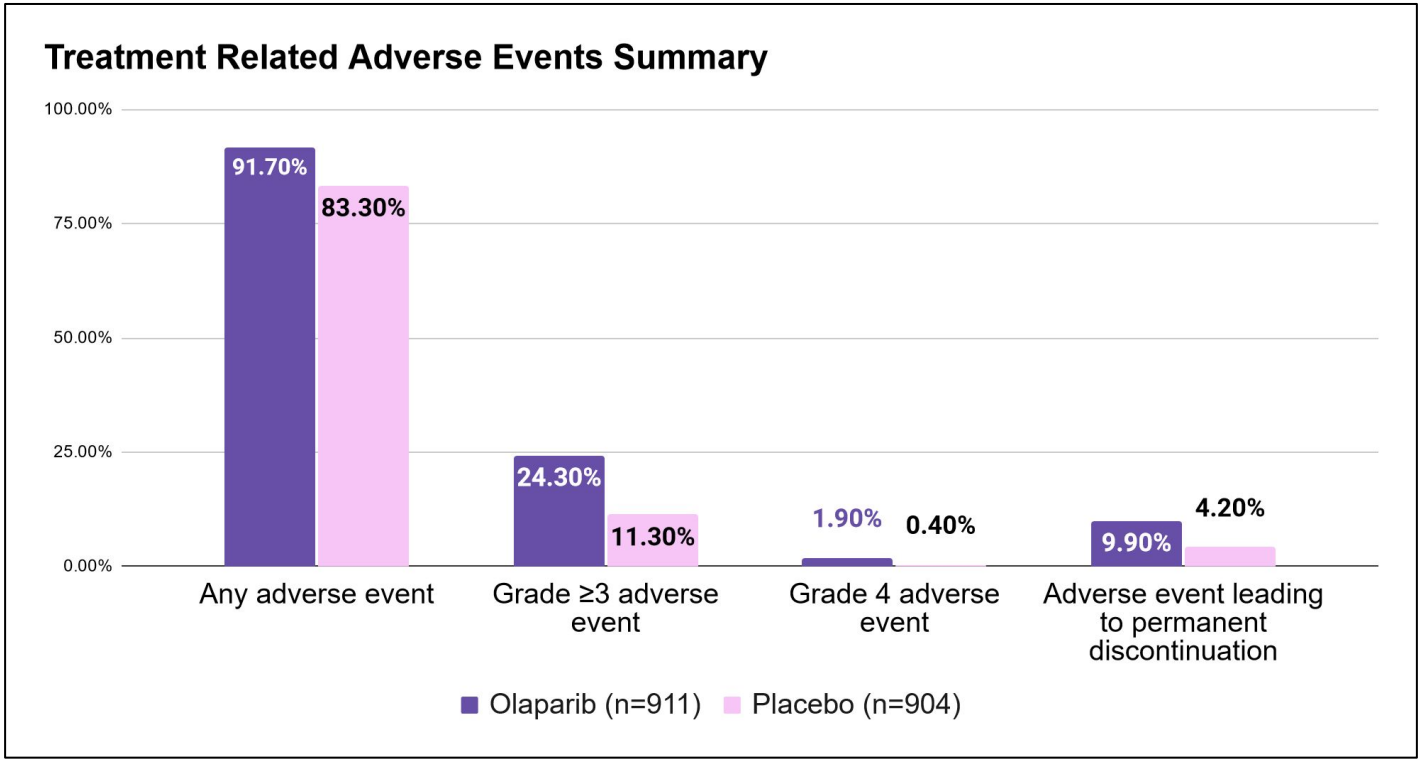
Hazard ratio: 0.68
98.5% CI: 0.47-0.97
p<0.009



OS: Overall survival

N Engl J Med 2021; 384:2394-2405.

OlympiA: Results



N Engl J Med 2021; 384:2394-2405.

OlympiA: Olaparib

CONCLUSION

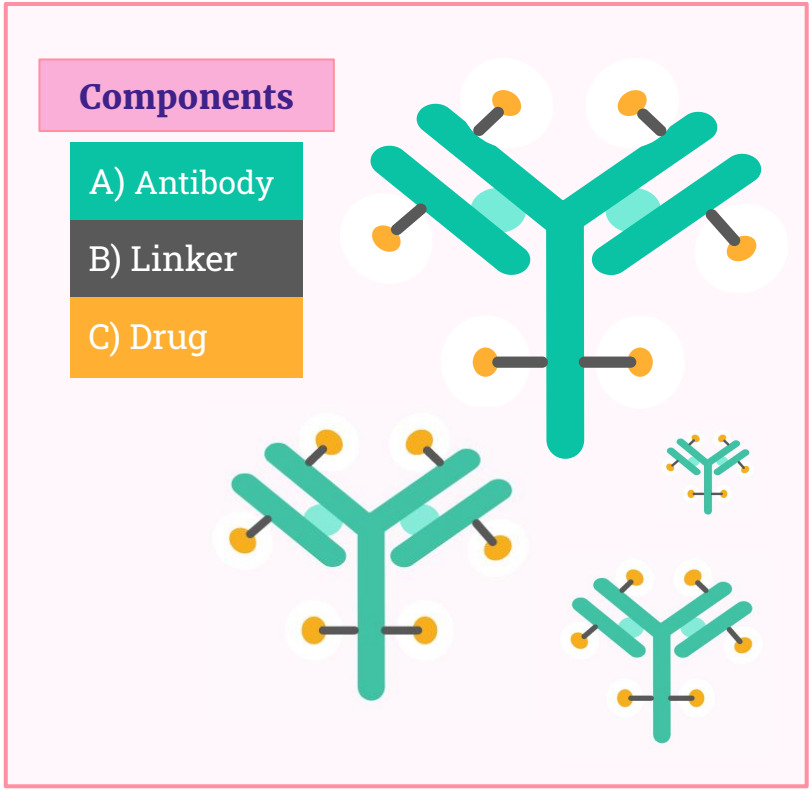
In patients with TNBC, adjuvant olaparib after treatment with chemotherapy showed significantly longer survival free of invasive or distant disease than placebo in patients with germline BRCA mutations

N Engl J Med 2021; 384:2394-2405.

Antibody–Drug Conjugates (ADCs)

ADCs

- **Anticancer targeted therapy**
  - Activity against solid tumors
    - Cytotoxic payload
  - Four ADCs currently approved for solid tumors



J Hematol Oncol 14, 20 (2021).
Ther Adv Med Oncol. 2020; 12: 1758835920915980.

Sacituzumab Govitecan

Indication*	Locally advanced or metastatic, relapsed or refractory TNBC
Dosing	IV: 10 mg/kg on days 1 and 8 of a 21-day treatment cycle; continue until disease progression or unacceptable toxicity
Adverse Effects	Common: Fatigue, neutropenia, diarrhea, nausea, alopecia
Monitoring	Laboratory: Neutropenia, electrolytes

*Other types of cancer indication not listed

Future Oncol. 2021 Oct 1;17(30):3911-3924.

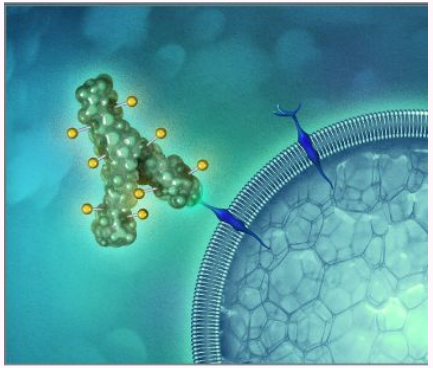
Sacituzumab Govitecan

ADCs

- FDA approved April 2020
- Antibody
  - Humanized anti-trop-2
- Linker
  - High drug to antibody ratio
- Cytotoxic payload
  - Antineoplastic SN-38

Mechanism

1. Attach
2. Penetrate
3. Destroy



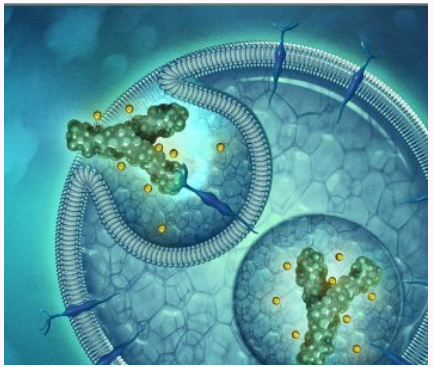


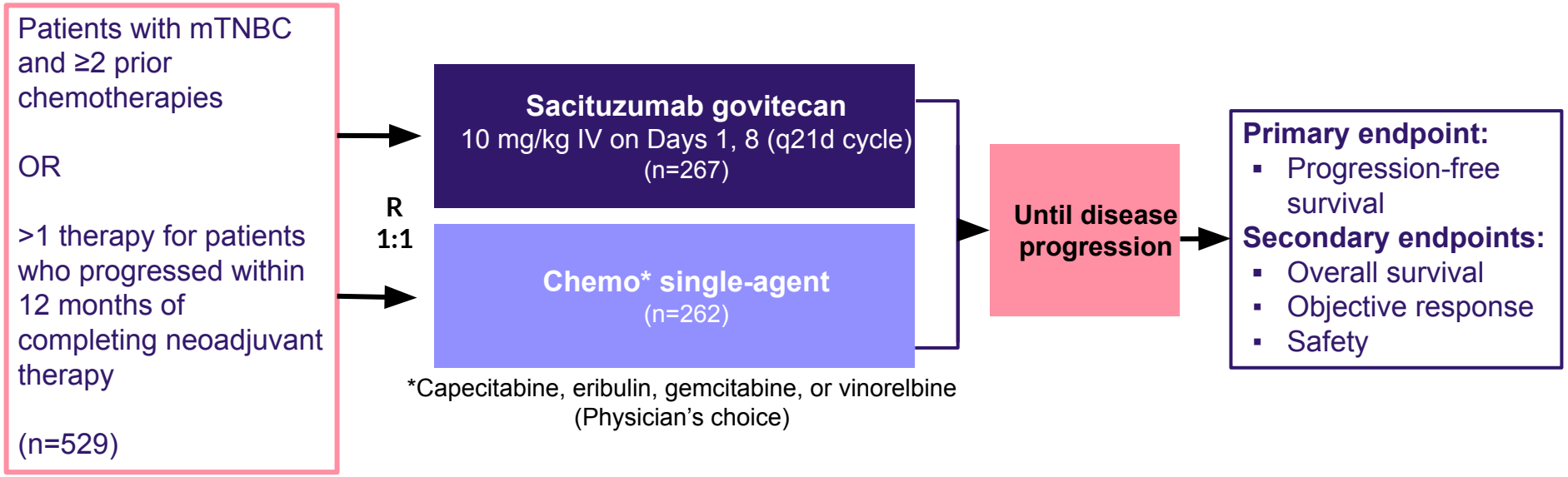
Image from trodelvy.com. 2020.
J Hematol Oncol 14, 20 (2021).

ASCENT Study: Sacituzumab Govitecan

Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer	
Design	Global, open-label, randomized, phase 3 trial
Objective	Evaluate the efficacy of sacituzumab govitecan compared to single agent chemotherapy in patients with relapsed or refractory mTNBC
Primary Outcome	Progression-free survival among patients without brain metastases
Secondary Outcomes	Overall survival, objective response, and safety outcomes

N Engl J Med 2021; 384:1529-1541.

ASCENT Study: Sacituzumab Govitecan



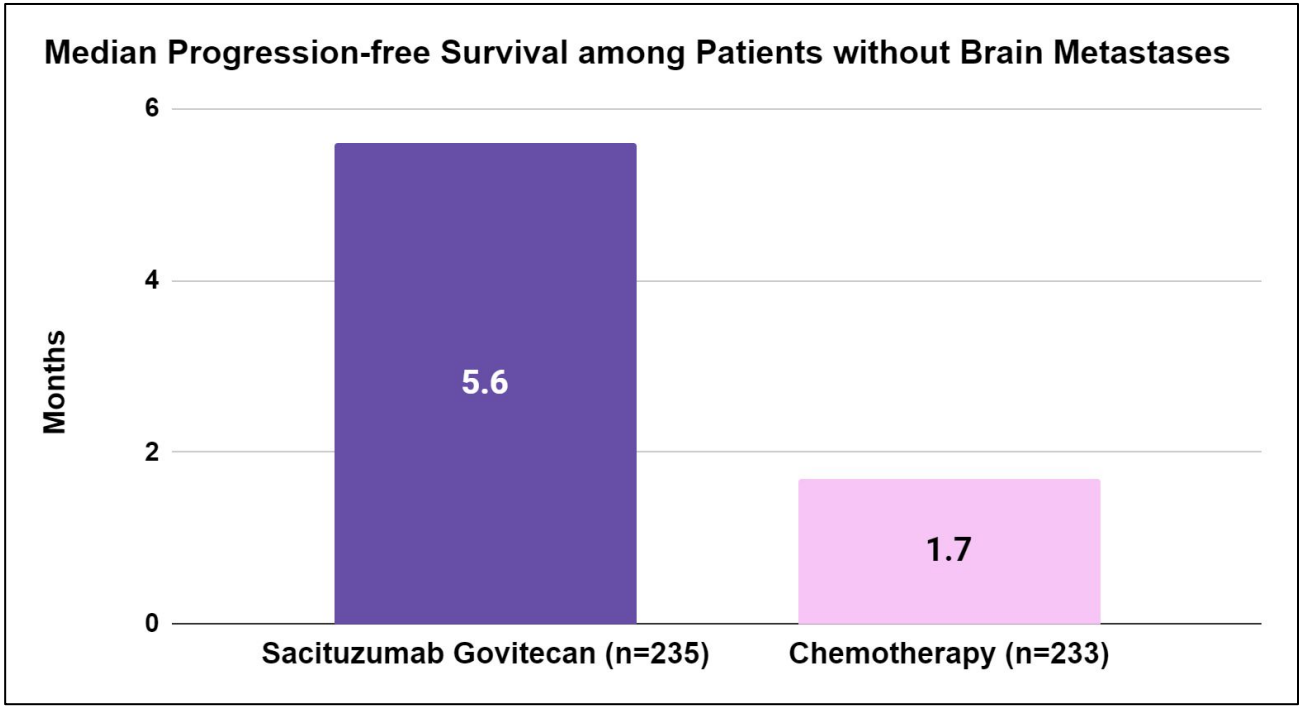
R: Randomization

N Engl J Med 2021; 384:1529-1541.

ASCENT Study: Results

Primary Outcome

Hazard ratio: 0.41
(95% CI: 0.32-0.52)
p<0.001

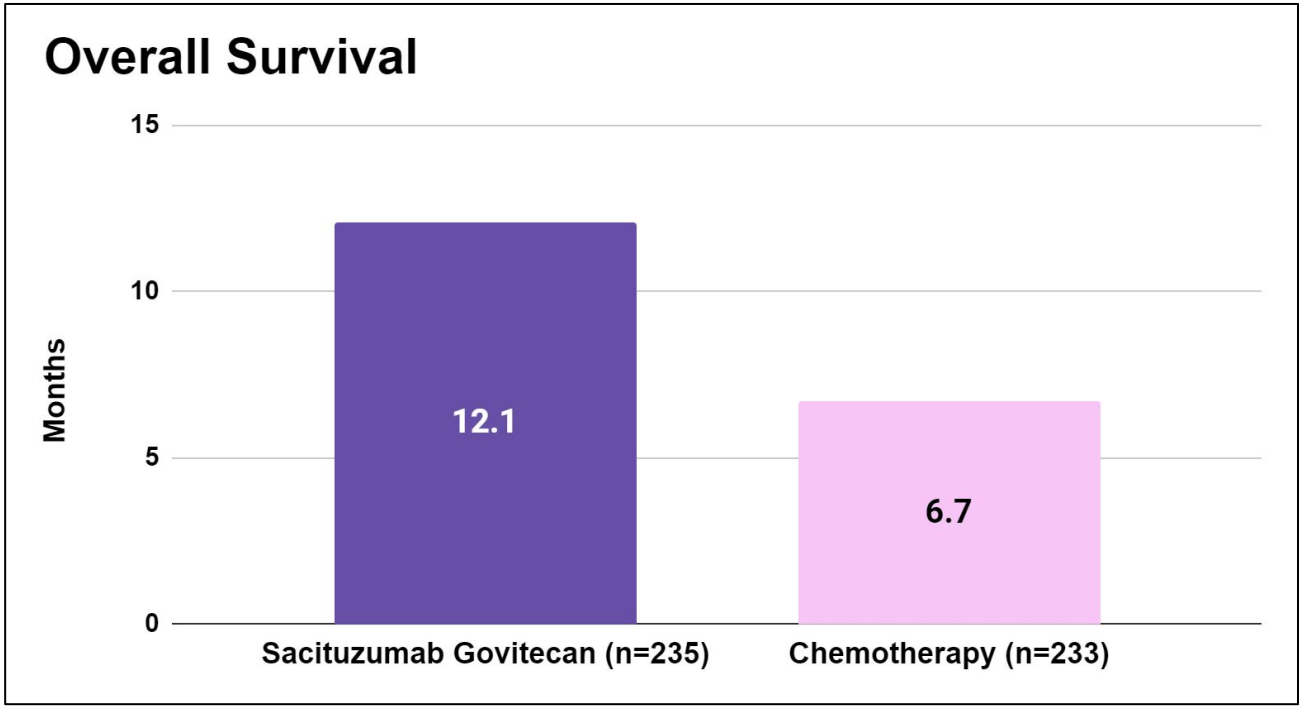


N Engl J Med 2021; 384:1529-1541.

ASCENT Study: Results

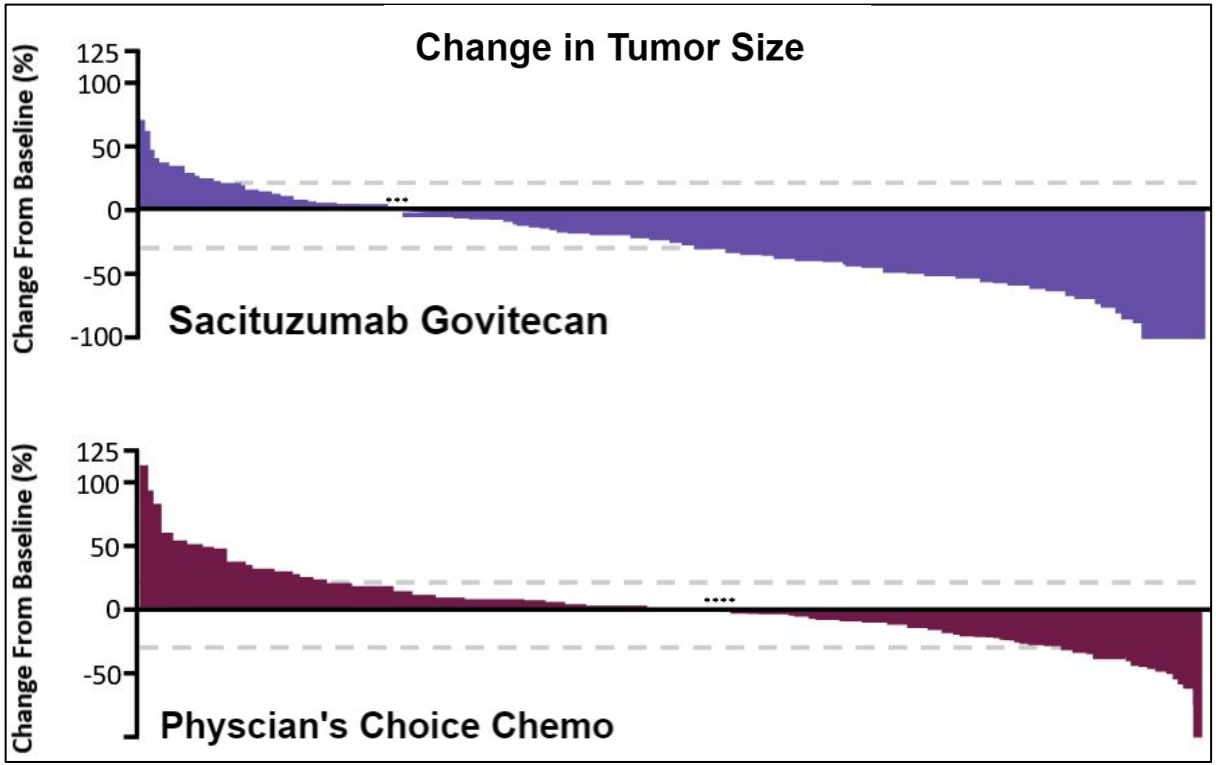
Secondary Outcome

Hazard ratio: 0.48
(95% CI: 0.38-0.59)
p<0.001



N Engl J Med 2021; 384:1529-1541.

ASCENT Study: Results

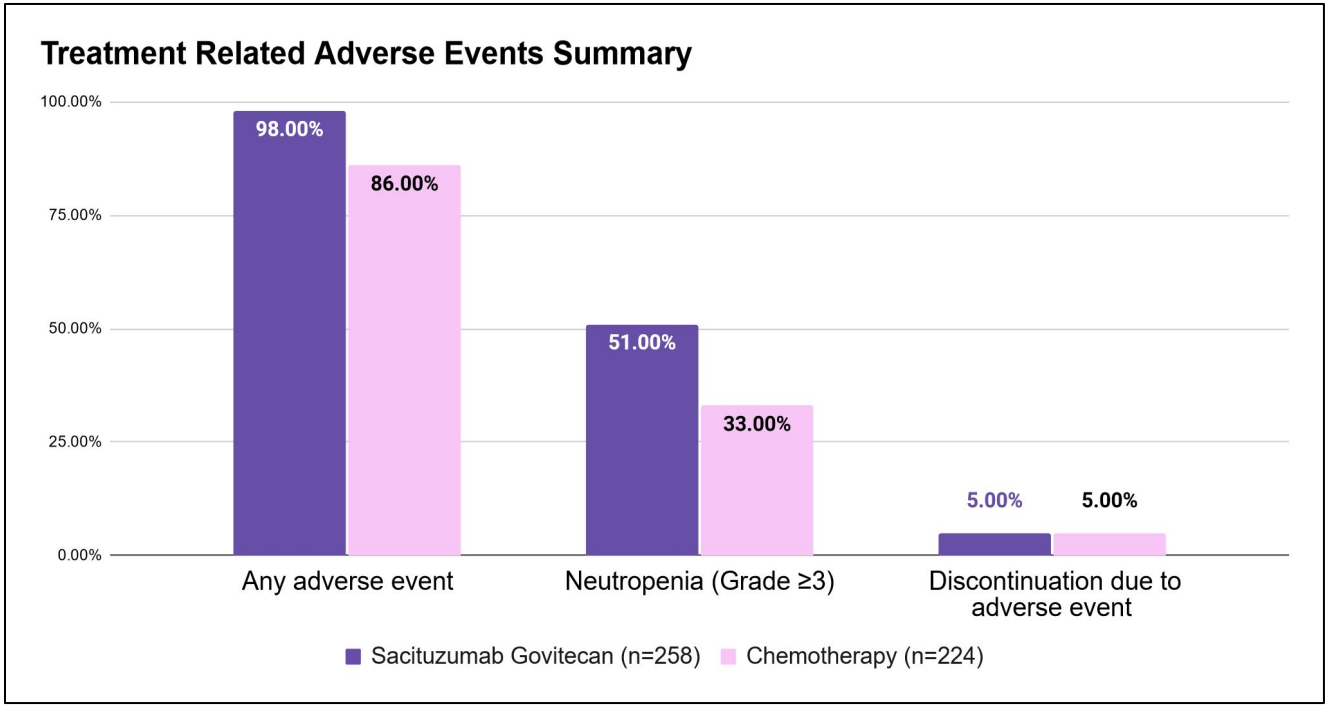


Greater tumor shrinkage in sacituzumab group

Decreased disease progression and increased complete or partial response

N Engl J Med 2019; 380:741-751.
N Engl J Med 2021; 384:1529-1541.

ASCENT Study: Results



Low discontinuation rates related to treatment adverse effects

No treatment related death in sacituzumab group

N Engl J Med 2021; 384:1529-1541.

ASCENT Study: Sacituzumab Govitecan

CONCLUSION

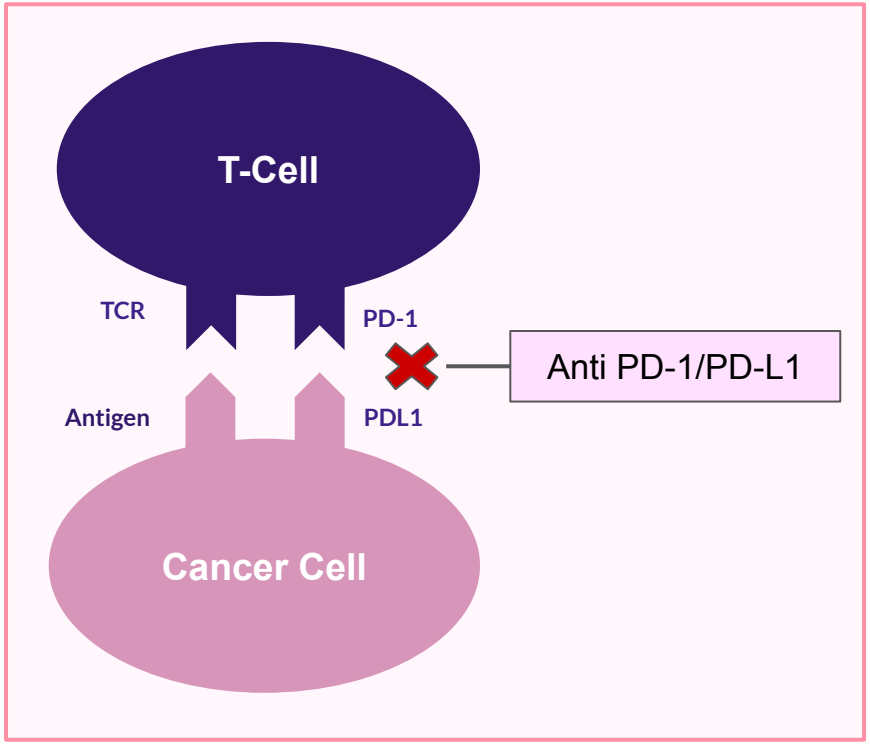
Patients with mTNBC who received sacituzumab govitecan had significantly longer progression-free and overall survival compared to single-agent chemotherapy, especially in patients who previously failed with chemotherapy

N Engl J Med 2021; 384:1529-1541.

Immune Checkpoint Inhibitor

Anti PD-1/PD-L1

- Humanized monoclonal antibody
  - Target checkpoint proteins
  - Activate T lymphocytes
    - Detect and attack tumor cells



TCR: T cell receptor

Front Oncol. 2021 May 19;11:648139.

Pembrolizumab

Indication*	Locally recurrent, unresectable or metastatic triple negative breast cancer
Dosing	IV: 200 mg once every 3 weeks or 400 mg once every 6 weeks until disease progression given with chemotherapy
Adverse Effects	Common: Fatigue, myalgia, rash, shortness of breath, hypothyroidism
Monitoring	Laboratory: AST/ALT, SCr, TSH/T4, glucose levels

*Other types of cancer indication not listed

Eur J Cancer. 2020 May;131:68-75.

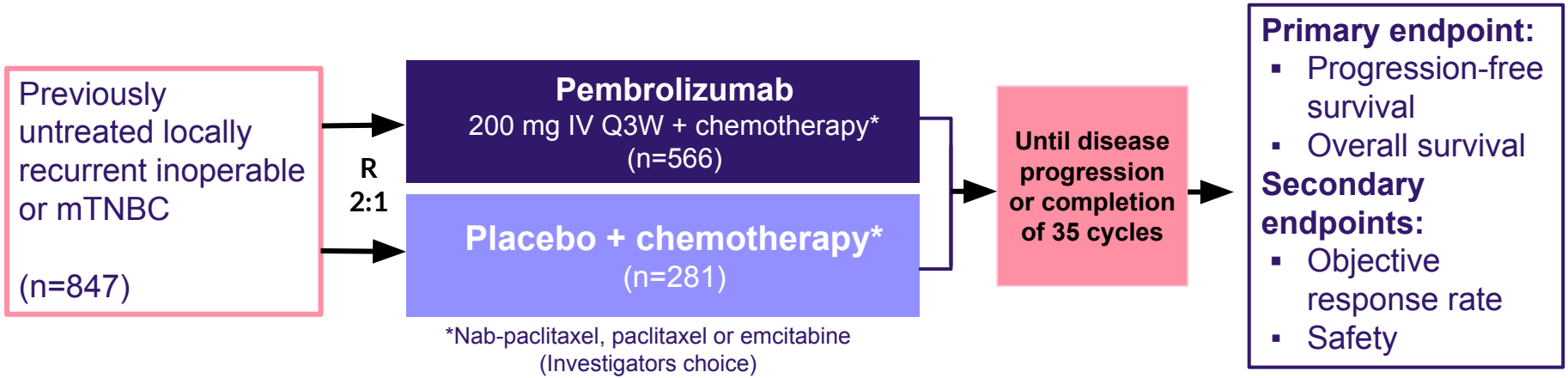
KEYNOTE-355: Pembrolizumab

Pembrolizumab plus Chemotherapy in Advanced Triple-Negative Breast Cancer	
Design	Randomized, double-blind, international, phase 3 trial
Objective	Evaluate the efficacy of the addition of pembrolizumab plus chemotherapy in patients with previously untreated locally recurrent inoperable or mTNBC
Primary Outcome	Progression-free survival and overall survival among patients whose tumors expressed PD-L1 with a CPS ≥ 10 and CPS < 1
Secondary Outcomes	Objective response, and safety outcomes

CPS: Combined positive score

N Engl J Med 2022; 387:217-226.

KEYNOTE-355: Pembrolizumab



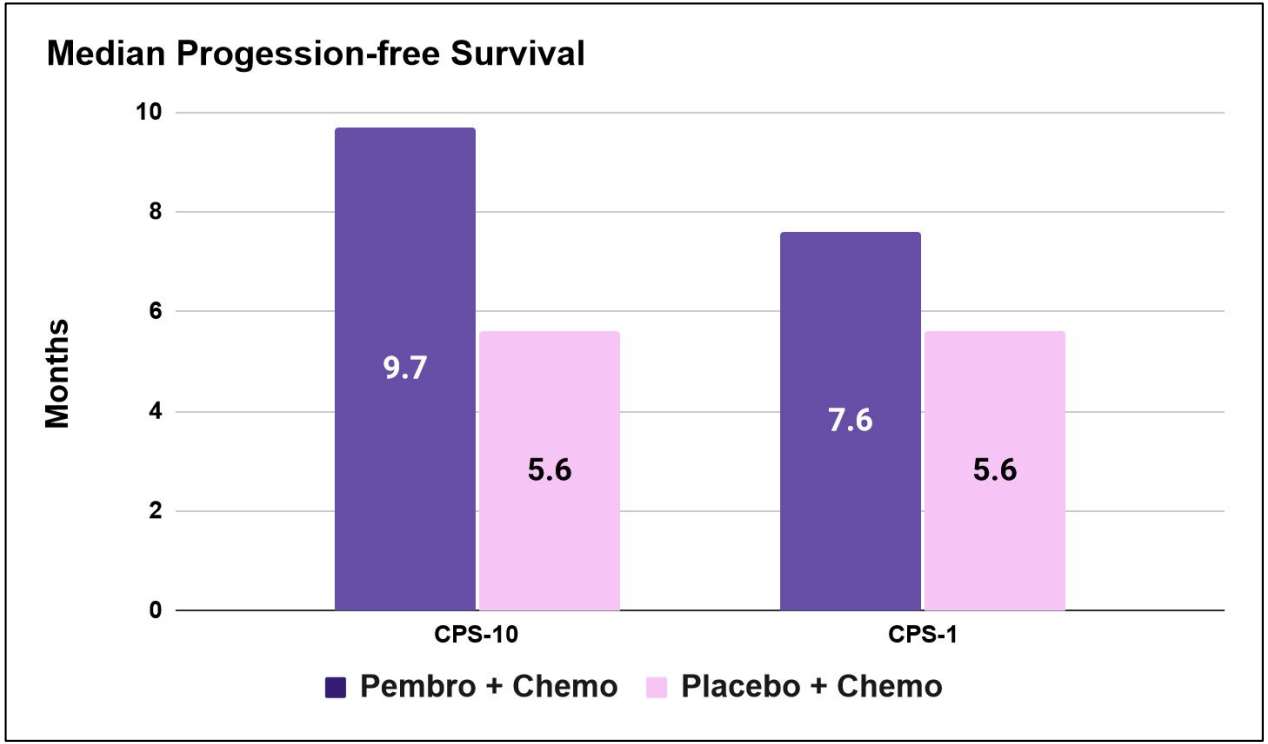
N Engl J Med 2022; 387:217-226.

KEYNOTE-355: Results

Primary Outcome

CPS-10
HR 0.66 (95% CI: 0.50-0.88)

CPS-1
HR 0.75 (95% CI: 0.62-0.91)



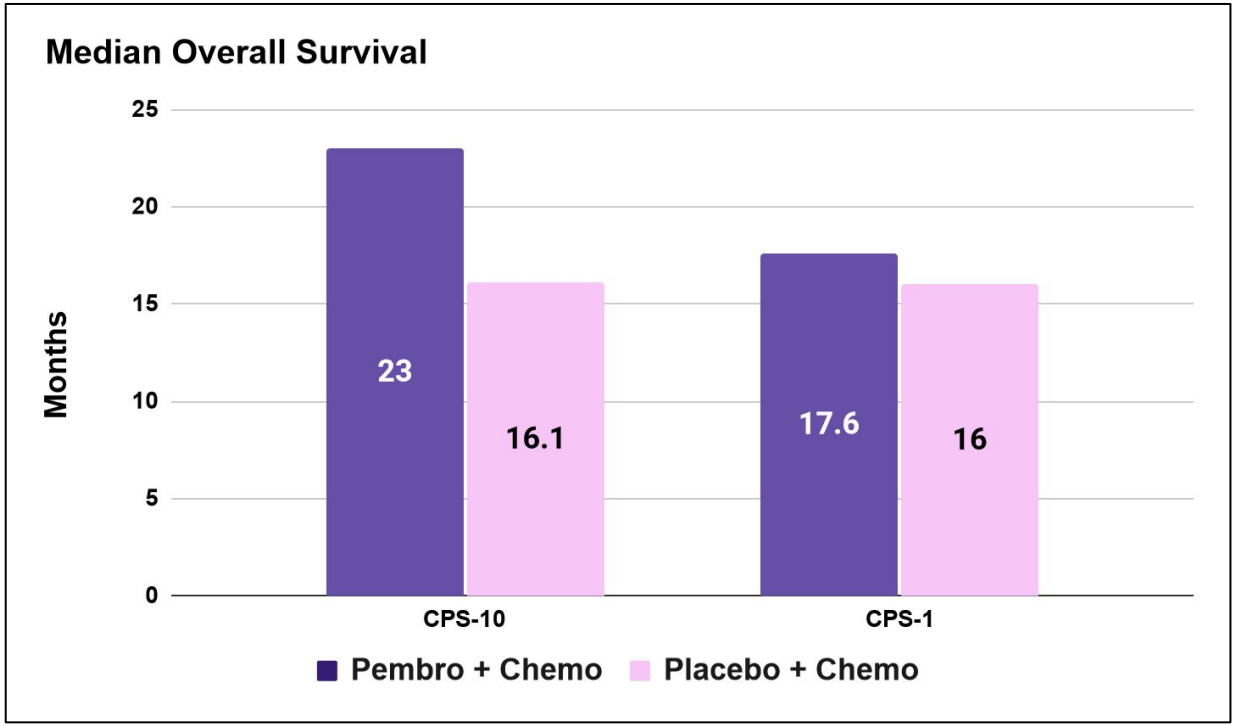
N Engl J Med 2022; 387:217-226.

KEYNOTE-355: Results

Primary Outcome

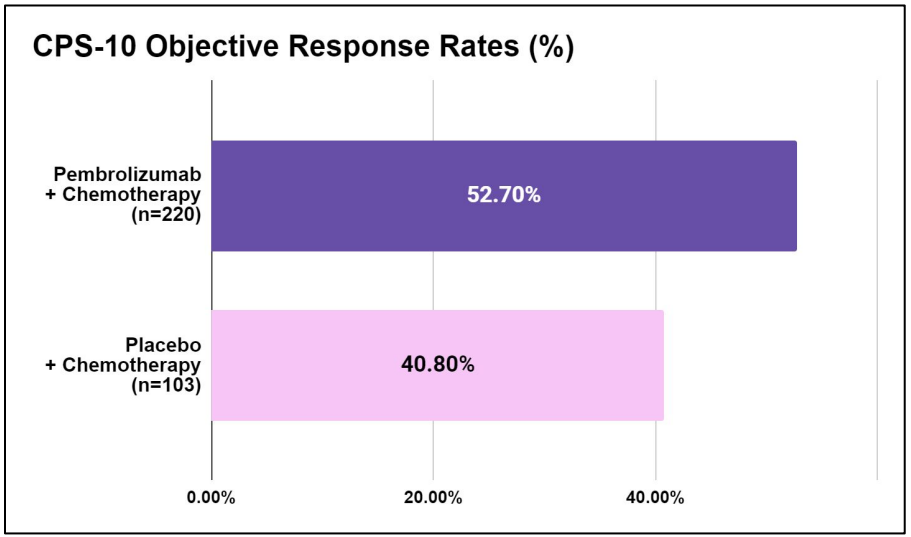
CPS-10
HR 0.73 (95% CI: 0.55-0.95)

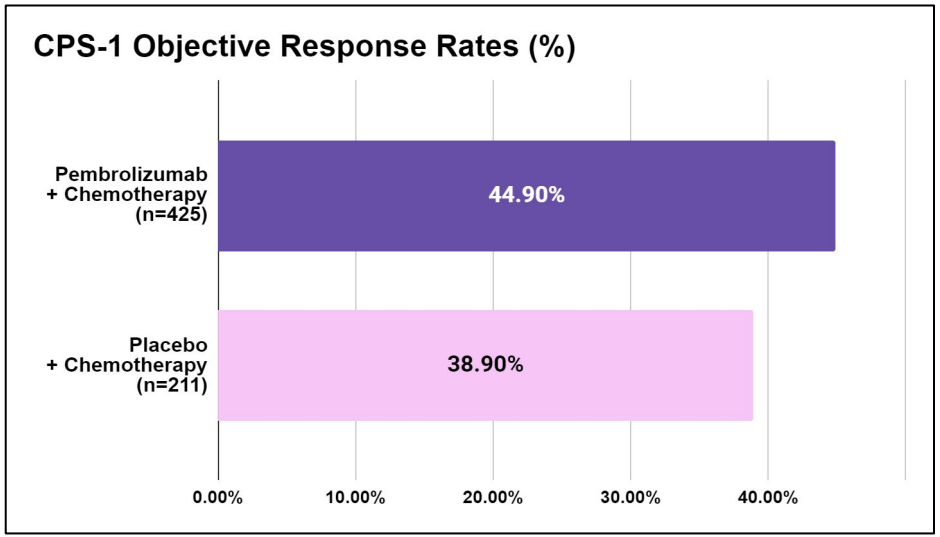
CPS-1
HR 0.86 (95% CI: 0.72-1.04)



N Engl J Med 2022; 387:217-226.

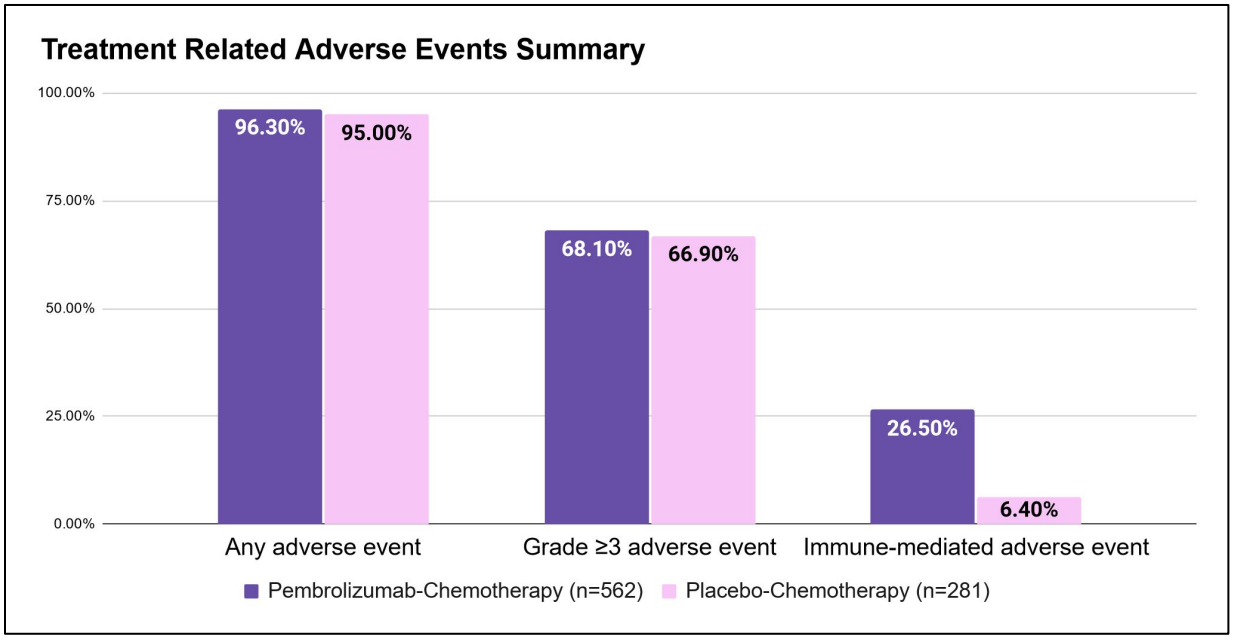
KEYNOTE-355: Results





N Engl J Med 2022; 387:217-226.

KEYNOTE-355: Results



Discontinuation due to immune-mediated adverse events

- 2.8% in Pembro + CT
- 0% in Placebo +CT

N Engl J Med 2022; 387:217-226.

KEYNOTE-355: Pembrolizumab

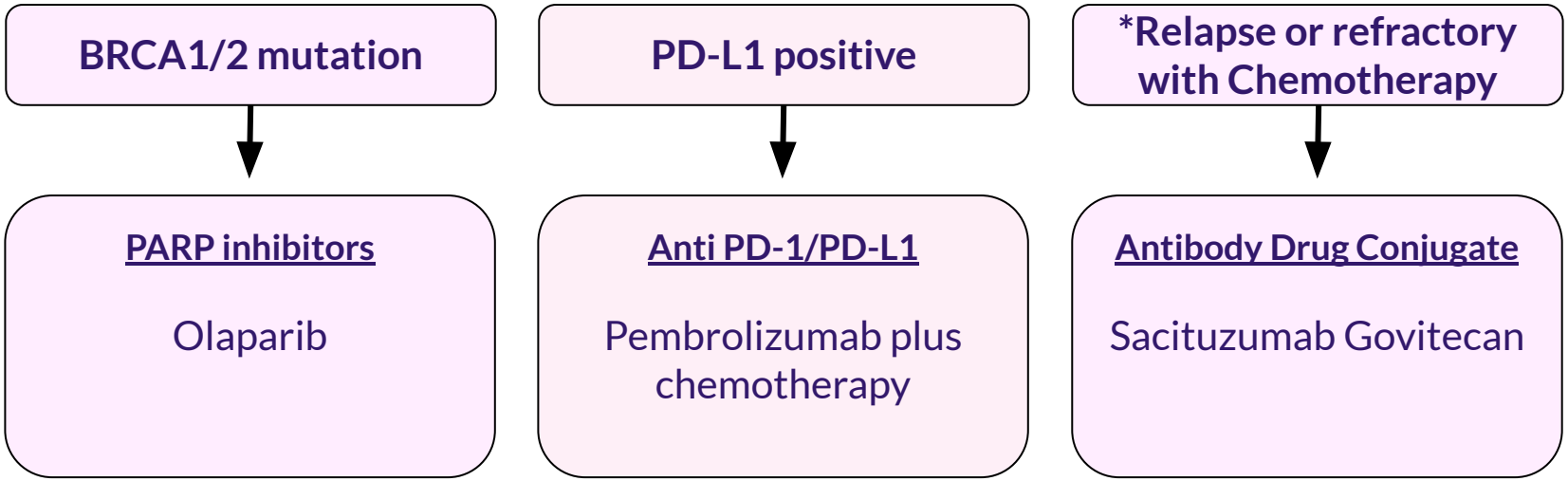
CONCLUSION

Pembrolizumab in combination with chemotherapy showed significantly longer overall survival compared to chemotherapy alone in patients with advanced TNBC whose tumors expressed PD-L1 with a CPS ≥ 10

N Engl J Med 2022; 387:217-226.

Novel Therapies Summary

First line treatment for mTNBC



*received 2 or more prior systemic therapies, at least 1 for metastatic disease

Am J Manag Care. 2021;27(suppl 5):S87-S96.

Future Treatment Strategies

Saci-IO TNBC

Randomized Phase II Study of Sacituzumab Govitecan With or Without Pembrolizumab in PD-L1-negative Metastatic Triple Negative Breast Cancer (TNBC)

ADC + PARP Inhibitor

Phase I/II Study to Evaluate Antibody-Drug Conjugate Sacituzumab Govitecan in Combination With PARP Inhibitor Talazoparib in Patients With Metastatic Breast Cancer

Summary

Olaparib has shown benefits among patients with HER2-negative metastatic breast cancer with a germline BRCA mutation

Sacituzumab govitecan is used as the standard of care in pretreated mTNBC with early relapse who may be chemotherapy resistant

Pembrolizumab + chemo is the new standard of care for patients with unresectable or mTNBC whose tumors express PD-L1 (CPS ≥10)

Assessment Question 3

BC has metastatic TNBC. She is not a candidate for resection and has failed two systemic chemotherapy agents to date. She has no BRCA mutation and her PD-L1 tumor expression is <1. According to the ASCENT trial, which therapy is the most appropriate treatment for BC's breast cancer, given her relapse with chemotherapy?

a. Sacituzumab Govitecan
b. Olaparib + Chemotherapy
c. Pembrolizumab + Chemotherapy
d. Consider a third attempt with chemotherapy

Assessment Question 3

BC has metastatic TNBC. She is not a candidate for resection and has failed two systemic chemotherapy agents to date. She has no BRCA mutation and her PD-L1 tumor expression is <1. According to the ASCENT trial, which therapy is the most appropriate treatment for BC's breast cancer, given her relapse with chemotherapy?

a. **Sacituzumab Govitecan**
b. Olaparib + Chemotherapy
c. Pembrolizumab + Chemotherapy
d. Consider a third attempt with chemotherapy

Takeaways

Triple-negative breast cancer carries the worst prognosis of the 3 major subtypes

Novel approaches in TNBC have shown to improve prognosis compared to conventional therapy

Advancement in treatment has improved survival in TNBC and new clinical trials are underway

Thanks for The Mammaries:

Exploring New Treatment Approaches in Triple Negative Breast Cancer

Christopher Sta.Ana, PharmD
PGY1 Acute Care Pharmacy Resident
Ascension St. Vincent's Riverside
November 28, 2022

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Logging into the mobile app: After downloading the CloudCME® mobile app,open the application on your mobile device and use the organization code Ascension-CE-CME. When prompted, login using your Ascension Single Sign On (SSO) or the email address used to
create your account in the Ascension Interprofessional Continuing Education (IPCE) site.