Memorial
Cancer Institute

How do I treat Stage IV TNBC

Aurelio B. Castrellon

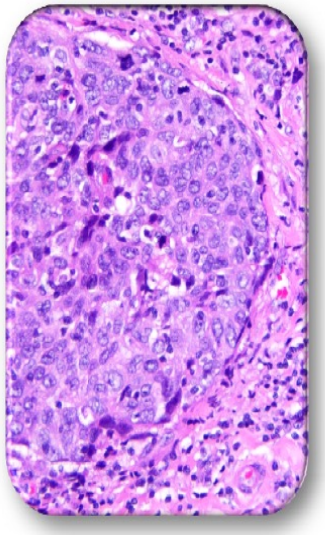
Medical Oncology

Memorial Healthcare

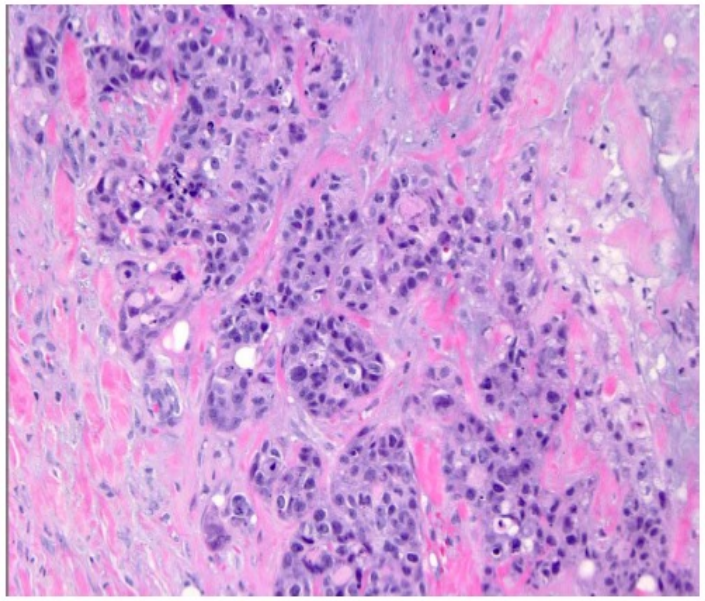
Histology

Triple Negative Breast Cancer

ER(-)
PR(-)
HER2(-)

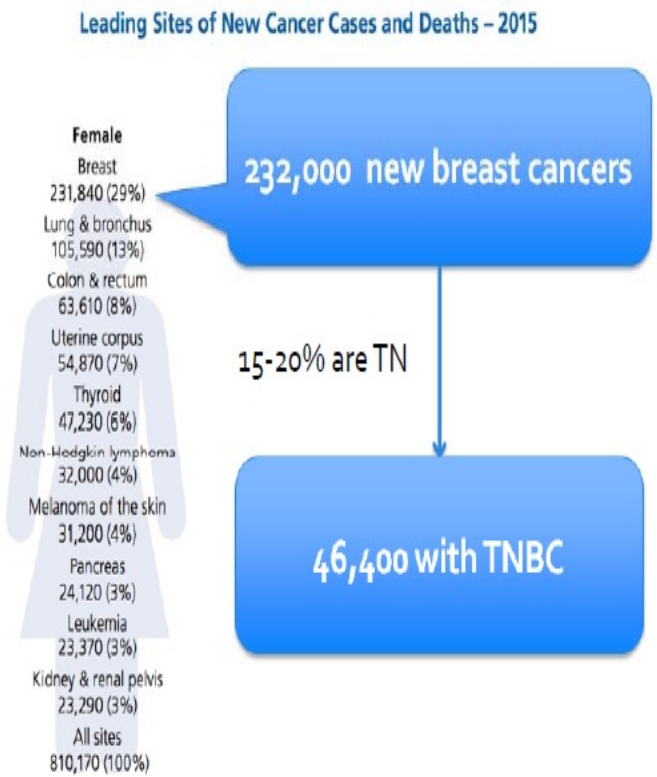


Clinicopathologic Features of TNBC



High grade
Solid architecture
"pushing" rounded borders
Intense lymphocytic infiltration
Many mitotic figures
High necrosis
EGFR expression
p53 mutations
BRCA1
CK 5/6
P-cadherin

Observations about TNBC



Who gets TNBC?

Younger women

African-American & Hispanic

Hereditary predisposition

BRCA1

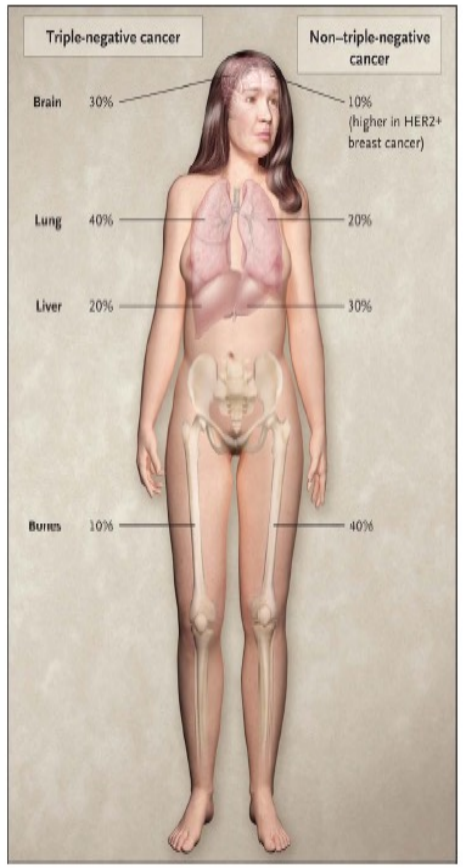
Parity ≥3

Menarche <13

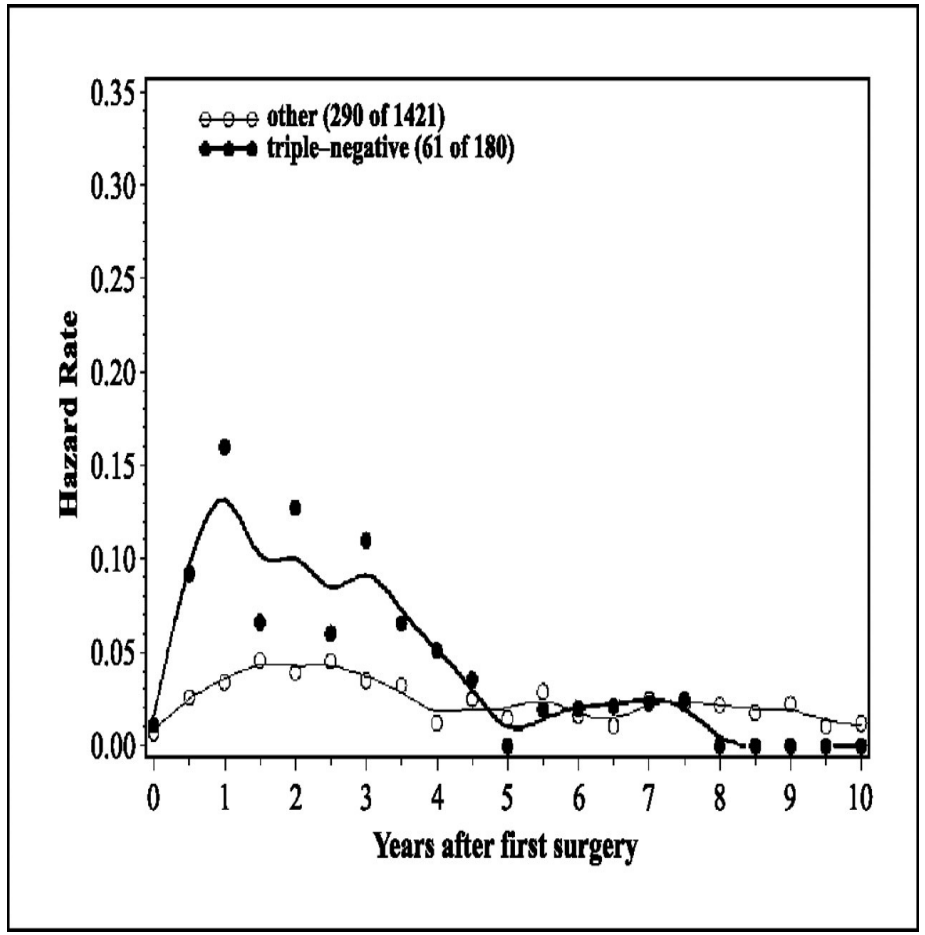
1st birth < 26yo

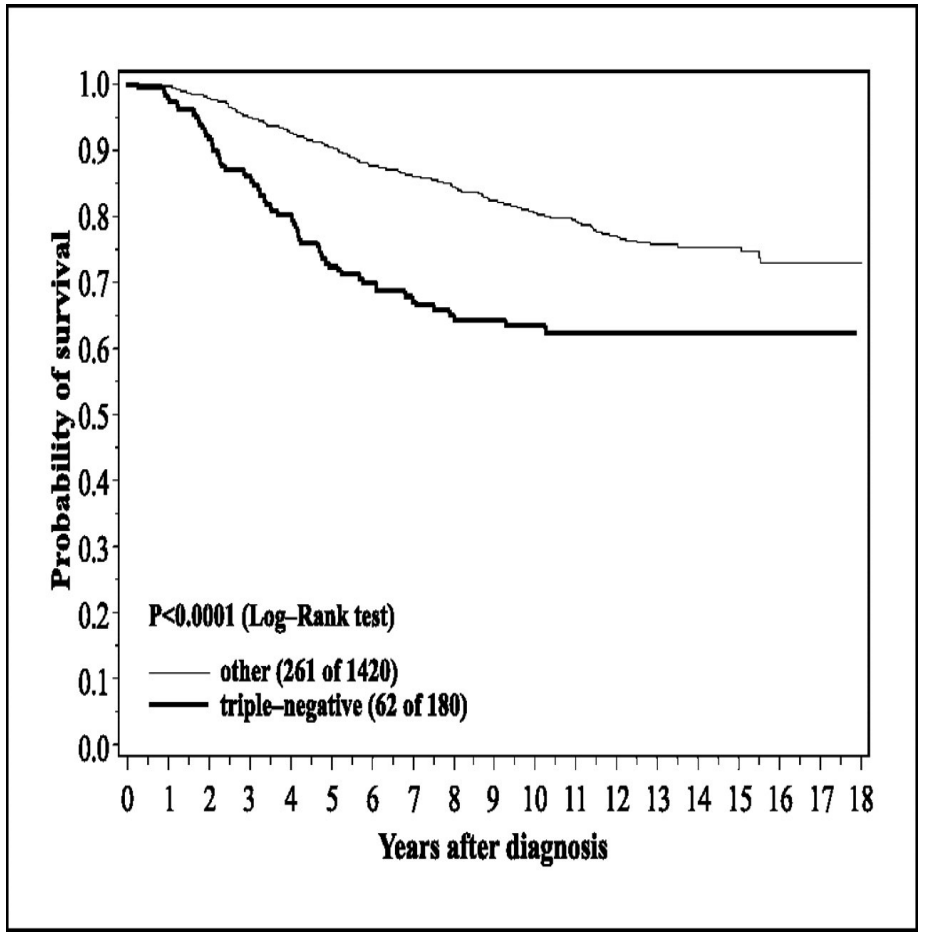
Observations about TNBC

- Higher risk of recurrence than ER+ breast cancer
- Most recurrences occur in first 2-3 years
- More likely to spread to visceral organs



Pattern of recurrence / survival

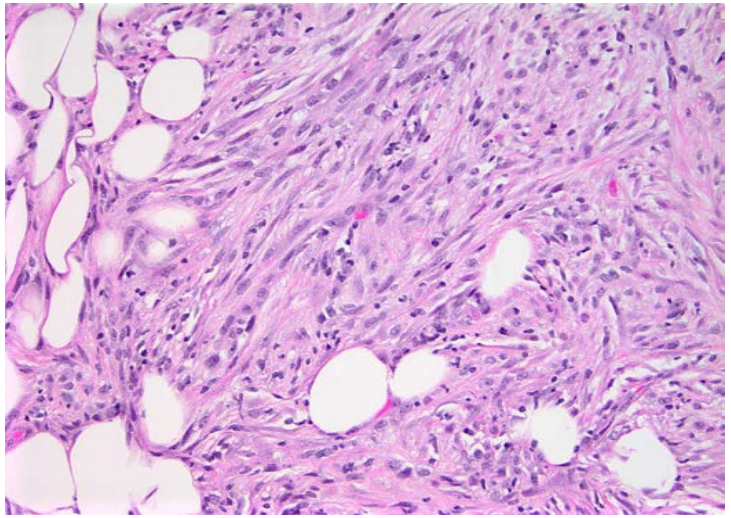




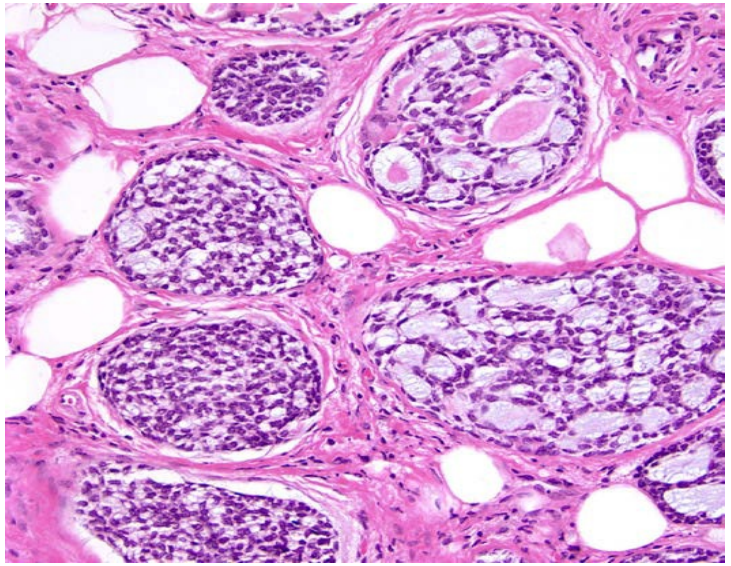
Dent et al, Clin Cancer Res 2007

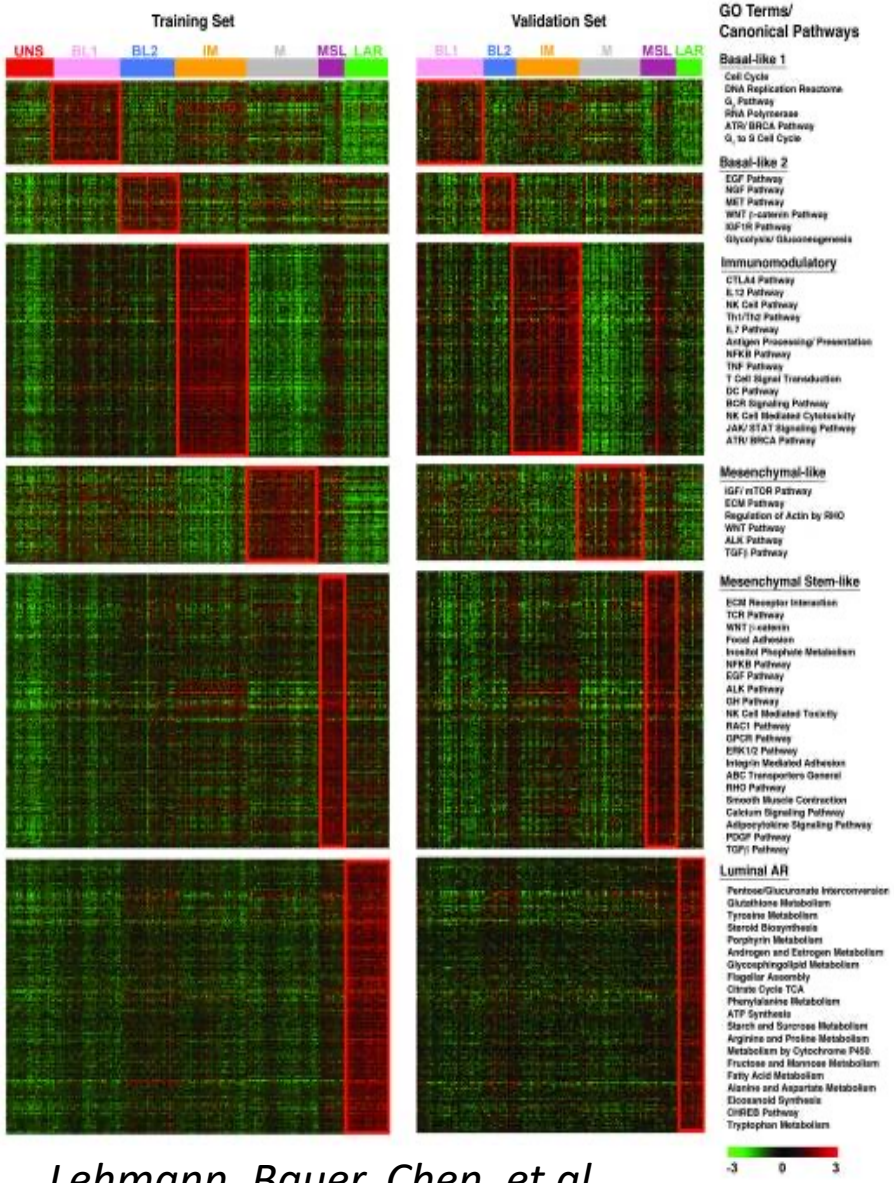
Histologic and Molecular heterogeneity of TNBC

Metaplastic



Adenoid cystic





Lehmann, Bauer, Chen, et al.,
J Clin Invest doi:10.1172/JCI45014

National Comprehensive Cancer Network®

SYSTEMIC THERAPY REGIMENS FOR RECURRENT OR STAGE IV (M1) DISEASE[a,b,c]

HER2-Negative

Preferred Regimens

- Anthracyclines
  - Doxorubicin
  - Liposomal doxorubicin
- Taxanes
  - Paclitaxel
- Anti-metabolites
  - Capecitabine
  - Gemcitabine
- Microtubule inhibitors
  - Vinorelbine
  - Eribulin
- For germline *BRCA1/2* mutations[d] see additional targeted therapy options (BINV-R)[e]
- Platinum (for TNBC and germline *BRCA1/2* mutation)[d]
  - Carboplatin
  - Cisplatin
- For PD-L1–positive TNBC see additional targeted therapy options (BINV-R)[e]

Other Recommended Regimens[f]

- Cyclophosphamide
- Docetaxel
- Albumin-bound paclitaxel
- Epirubicin
- Ixabepilone
- Sacituzumab govitecan-hziy (for TNBC)[g]

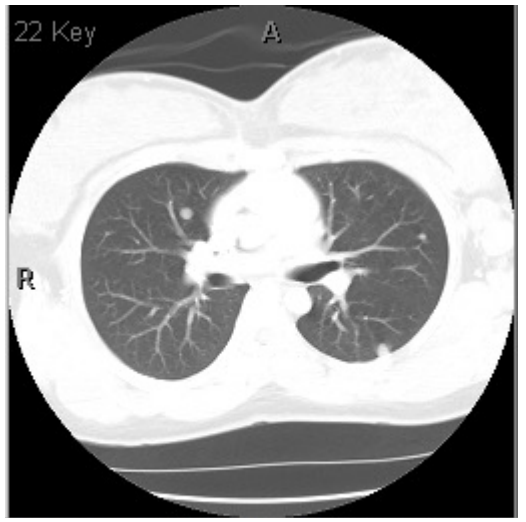
- **Olaparib[1] tablet[i]**
  - 300 mg PO twice daily
  - Cycled every 28 days
- **Talazoparib[2] tablet**
  - 1 mg PO daily
  - Cycled every 28 days

Useful in Certain Circumstances[f]

- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)
- Gemcitabine/carboplatin
- Paclitaxel/bevacizumab[h]
- Carboplatin + paclitaxel or albumin-bound paclitaxel

HR-negative/ HER2-negative[c]	PD-L1 expression • Threshold for positivity: ≥1% on tumor-infiltrating immune cells	IHC	Atezolizumab + albumin-bound paclitaxel[e]	Category 1	Preferred first-line therapy[h]
	PD-L1 expression • Threshold for positivity combined positive score ≥10		Pembrolizumab + chemotherapy (albumin-bound paclitaxel, paclitaxel, or gemcitabine and carboplatin)[e]	Category 1	

Clinical case

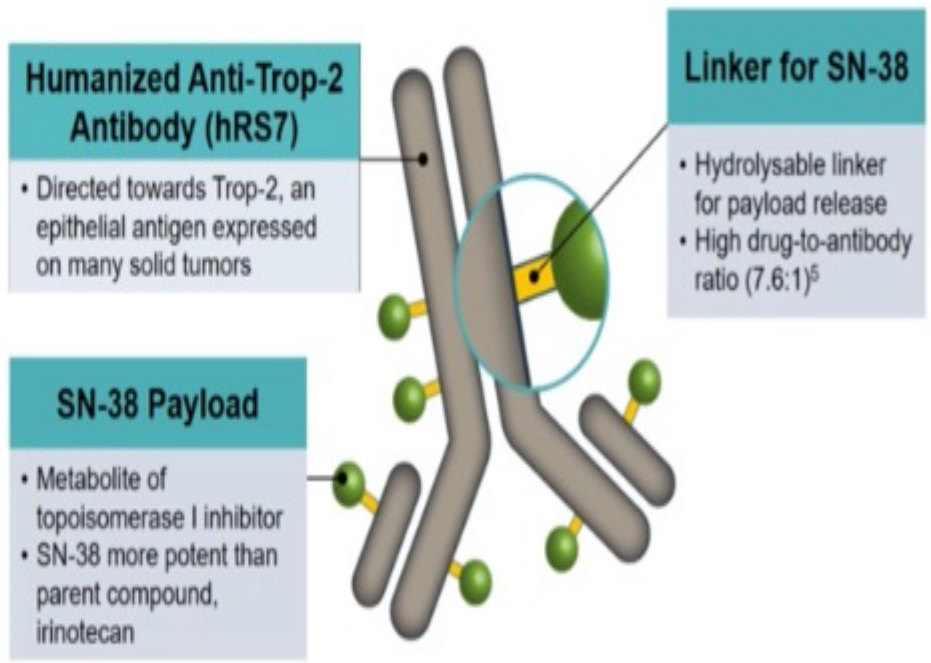


- This is a 35 y.o. female with breast cancer history as follows :
- Patient presented with rapidly enlarging left breast mass and swelling , she was s/p partum about 3 months and was lactating. The mass initially believed to be a clogged milk duct, patient was given oral antibiotics without improvement.
- She visited the ER based on worsening of symptoms, proceeded to be admitted with the presumptive diagnoses of inflammatory breast cancer.
- Biopsy 11/12/19 left breast and axillary lymph node invasive ductal carcinoma ER negative PR negative HER 2 neu negative
- CT scan of C/A/P Several scattered non calcified bilateral pulmonary nodules of varying sizes, ranging in size from a few millimeters to the largest measuring approximately 9 mm in the posterior left lower lobe.

- Based on the urgent need for local therapy (inflammatory breast cancer) patient was given inpatient the first cycle of AC on 11/16/19. Completed neoadjuvant ddAC outpatient 12/30/19 followed by weekly paclitaxel 1/13/20-4/9/20.
- Molecular profiling results: negative for BRCA 1 or 2, negative for PDL1 expression.
- Started Gemcitabine + carboplatin 6/2020 due to delay in surgery and subsequent regrowth of tumor until 8/2020.
- Palliative breast radiation completed 10/19/2020.
- Sacituzumab-govitecan started 11/16/20 - 9/13/2021
- Mastectomy palliative on 4/9/2021 with residual multifocal invasive ductal carcinoma largest focus 1.2 cm, invasive carcinoma focally involves skeletal muscle, posterior margin 7 mm, ypT1c.
- Capecitabine started on October 2021

Sacituzumab Govitecan (SG) Is a Trop-2–Directed Antibody-Drug Conjugate (ADC)

- Trop-2 is an epithelial cell surface antigen highly expressed in UC[1]
- SG is distinct from other ADCs[2-6]:
  - High drug-to-antibody ratio[5]
  - Linker hydrolysis releases SN-38 intracellularly and in the tumor microenvironment[6a]
- SG has shown significant activity across tumor types[3,7-10]
  - Breakthrough therapy designation for mTNBC; accelerated approval submission pending
  - Phase 3 trials ongoing in breast cancer



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

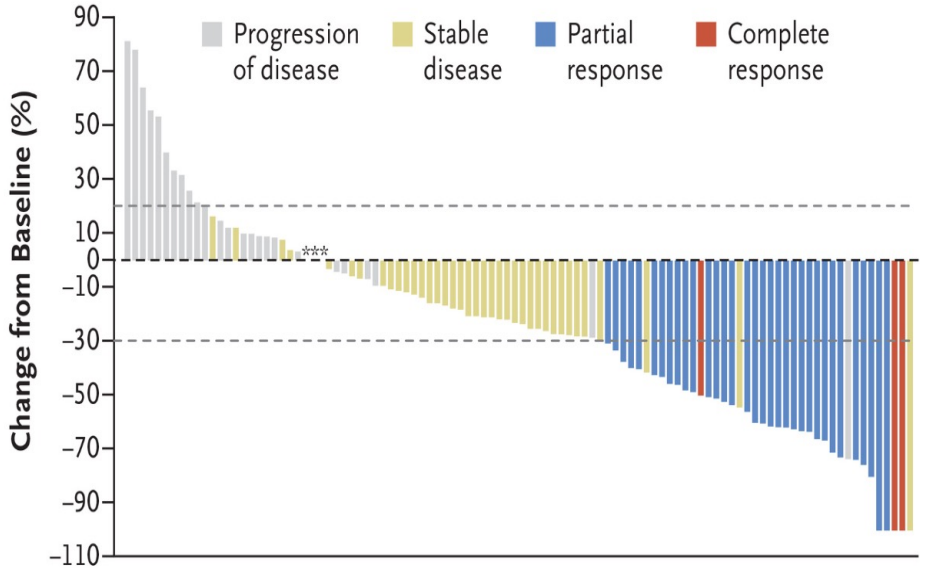
Sacituzumab Govitecan-hziy in Refractory Metastatic Triple-Negative Breast Cancer

Aditya Bardia, M.D., Ingrid A. Mayer, M.D., Linda T. Vahdat, M.D., M.B.A., Sara M. Tolaney, M.D., M.P.H., Steven J. Isakoff, M.D., Ph.D., Jennifer R. Diamond, M.D., Joyce O'Shaughnessy, M.D., Rebecca L. Moroose, M.D., Alessandro D. Santin, M.D., Vandana G. Abramson, M.D., Nikita C. Shah, M.D., Hope S. Rugo, M.D., et al.

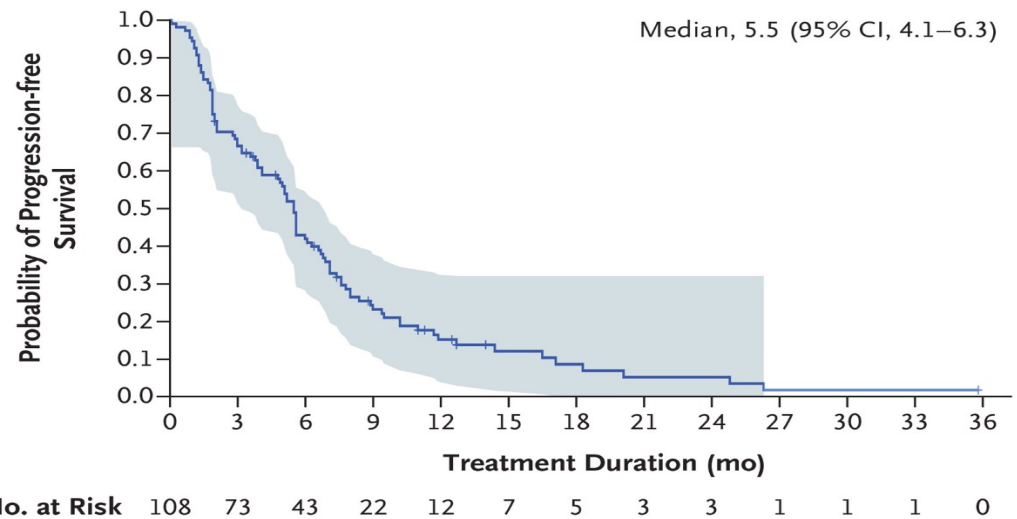
Previous anticancer regimens — median no. (range)	3 (2–10)
Previous use of taxanes or anthracyclines for metastatic or nonmetastatic disease — no. (%)	
Taxanes	106 (98.1)
Anthracyclines	93 (86.1)
Previous use of chemotherapy drugs for metastatic disease — no. (%)	
Cyclophosphamide	20 (18.5)
Platinum agents	74 (68.5)
Gemcitabine	59 (54.6)
Fluoropyrimidine agents	56 (51.9)
Eribulin	49 (45.4)
Vinorelbine	17 (15.7)
Previous use of checkpoint inhibitors — no. (%)	18 (16.7)
Most common sites of disease — no. (%)	
Visceral organ§	83 (76.9)
Lung or pleura	61 (56.5)
Liver	45 (41.7)
Other visceral organ: adrenal glands, pancreas, and kidneys	7 (6.5)
Nonvisceral site	25 (23.1)

Adverse Event	Patients (N=108)		
	Any Grade	Grade 3	Grade 4
	number of patients with event (percent)		
Any adverse event	108 (100)	71 (66)	21 (19)
Gastrointestinal disorders	102 (94)	21 (19)	0
Nausea	72 (67)	7 (6)	0
Diarrhea	67 (62)	9 (8)	0
Vomiting	53 (49)	7 (6)	0
Constipation	37 (34)	1 (1)	0
Abdominal pain†	27 (25)	1 (1)	0
Mucositis‡	15 (14)	0	0

A Change in Tumor Size

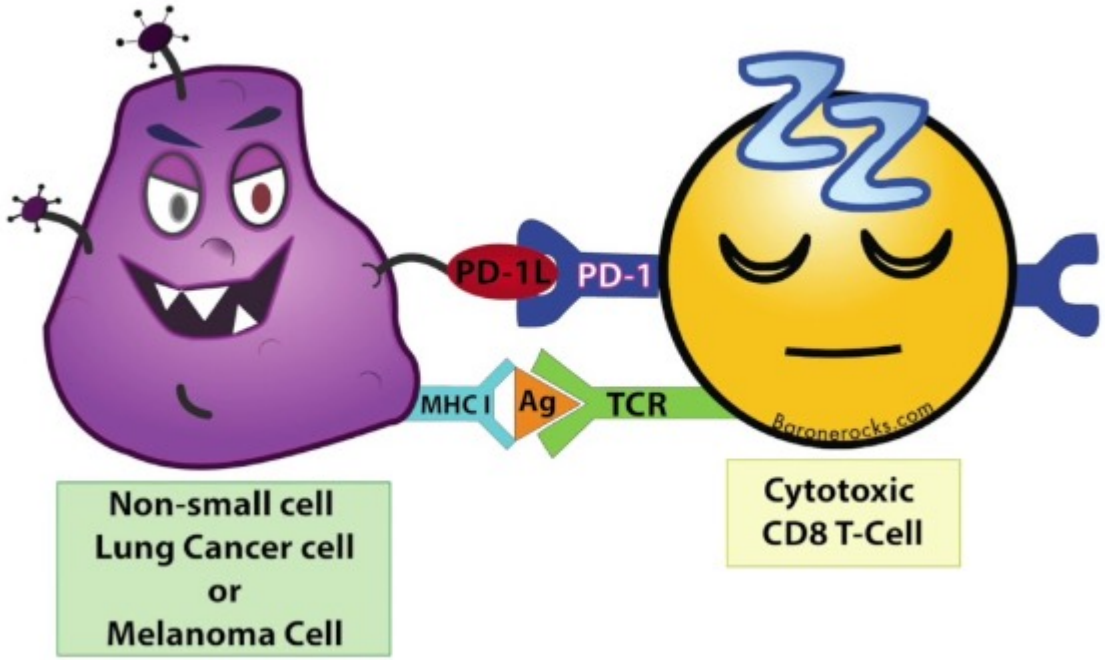


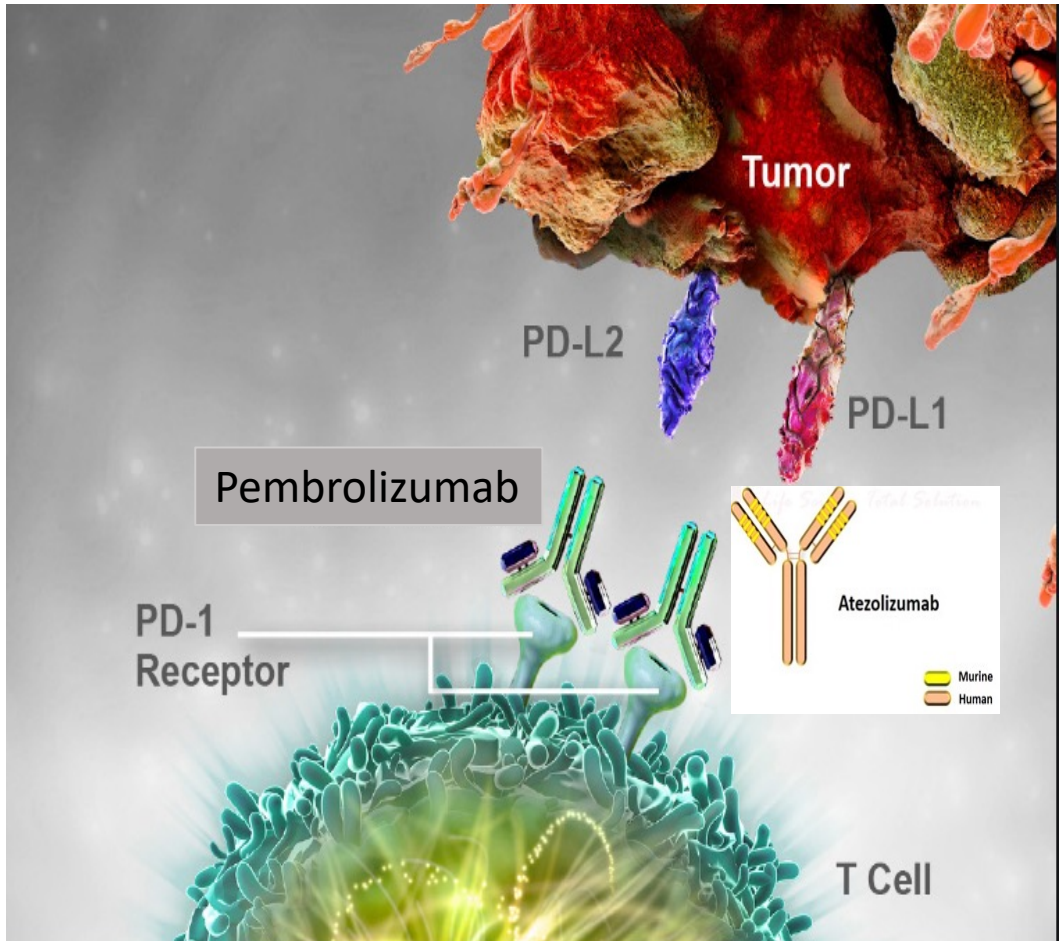
C Progression-free Survival



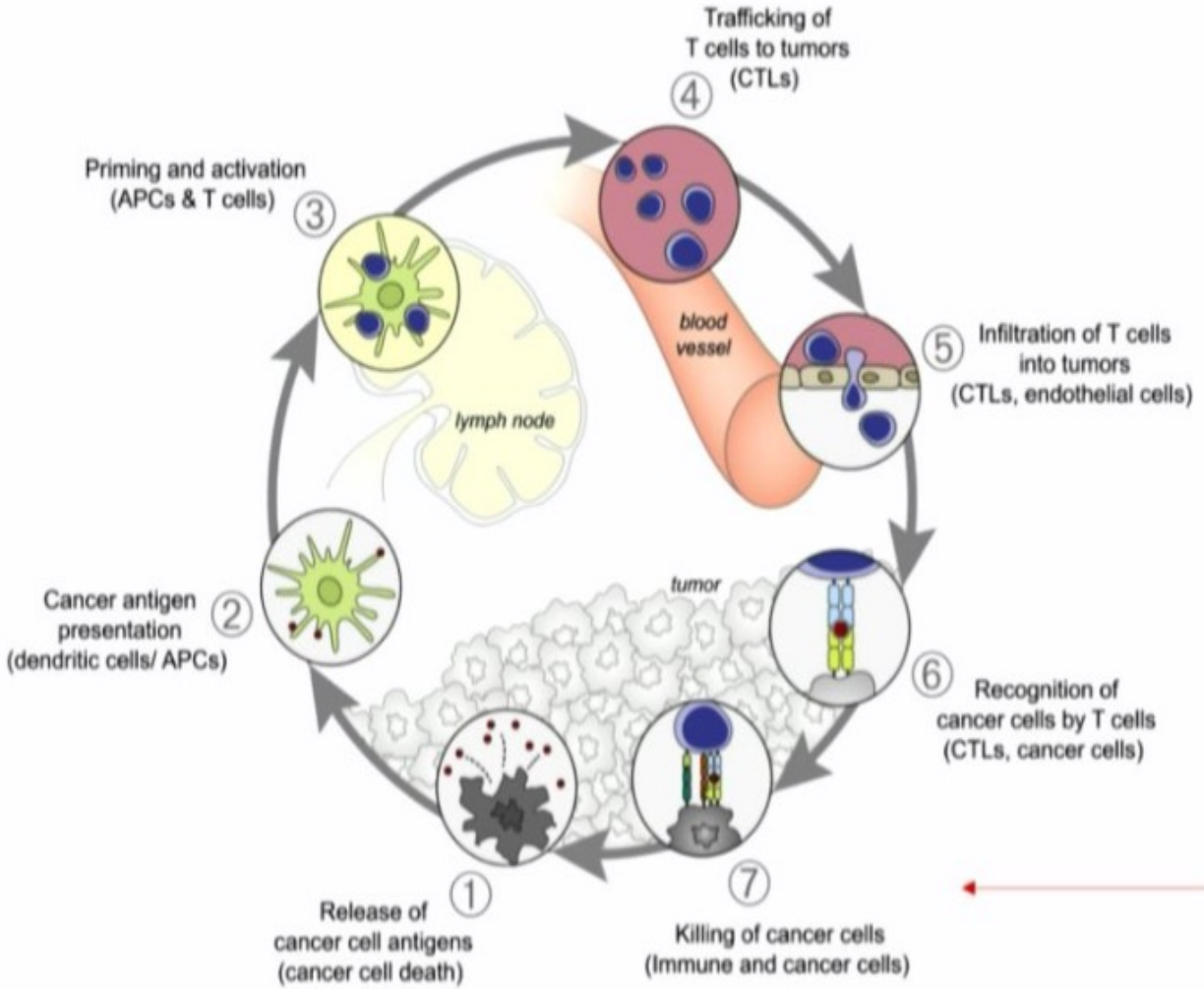
Summary of Treatment Efficacy, According to Local Assessment.

Variable	Patients (N=108)
Complete response — no. of patients (%)	3 (2.8)
Partial response — no. of patients (%)	33 (30.6)
Stable disease — no. of patients (%)	40 (37.0)
Progressive disease — no. of patients (%)	28 (25.9)
Not evaluated — no. of patients (%)*	4 (3.7)
Objective response rate†	
No. of patients	36
% of patients (95% CI)	33.3 (24.6–43.1)
Clinical benefit rate‡	
No. of patients	49
% of patients (95% CI)	45.4 (35.8–55.2)
Median duration of response (95% CI) — mo	7.7 (4.9–10.8)


PD-1L
PD-1
MHC I
Ag
TCR
Baronerocks.com
Non-small cell
Lung Cancer cell
or
Melanoma Cell
Cytotoxic
CD8 T-Cell

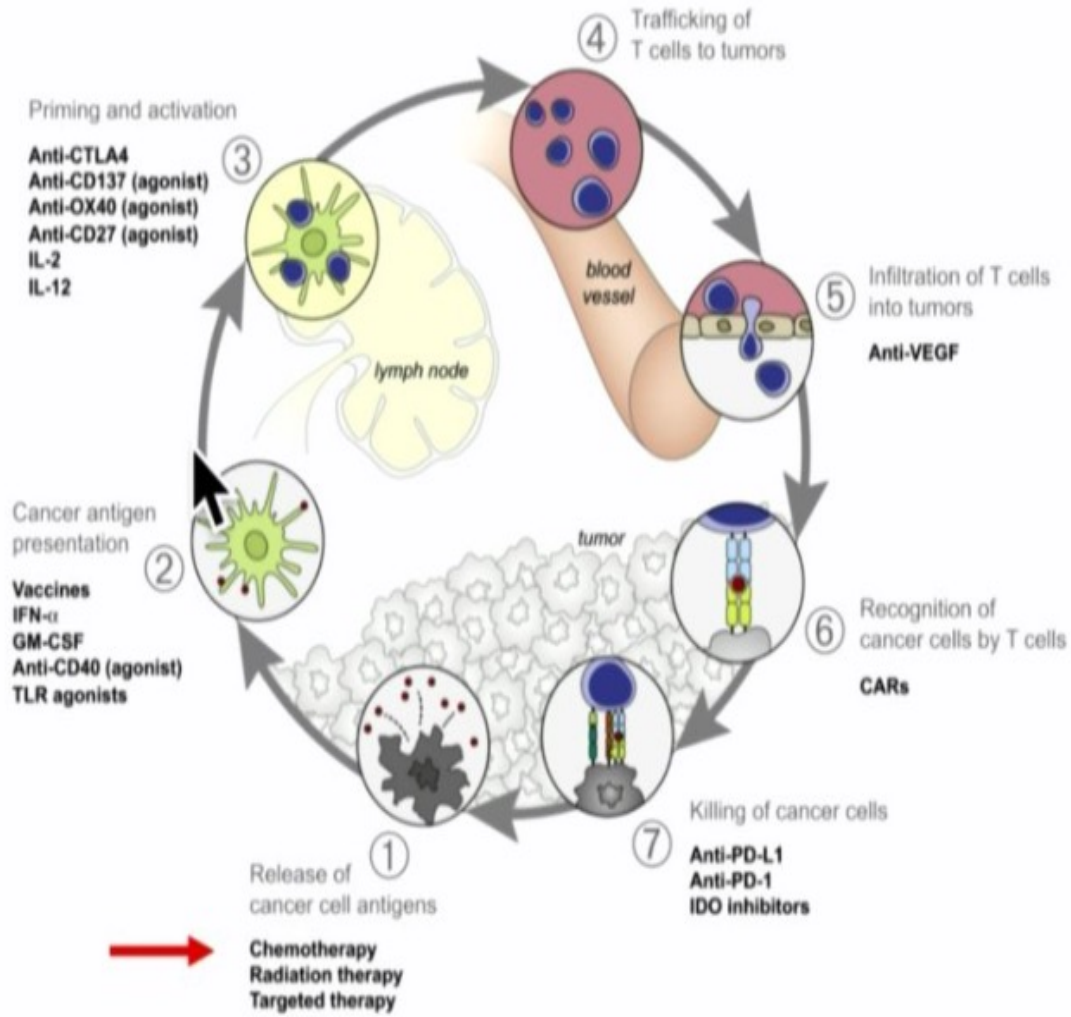

Tumor
PD-L2
PD-L1
Pembrolizumab
PD-1
Receptor
Atezolizumab
Murine
Human
T Cell

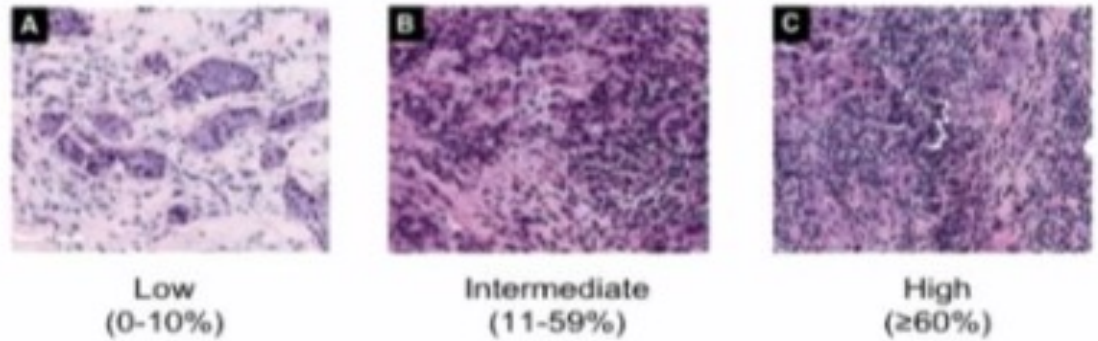
Cancer Immunity Cycle

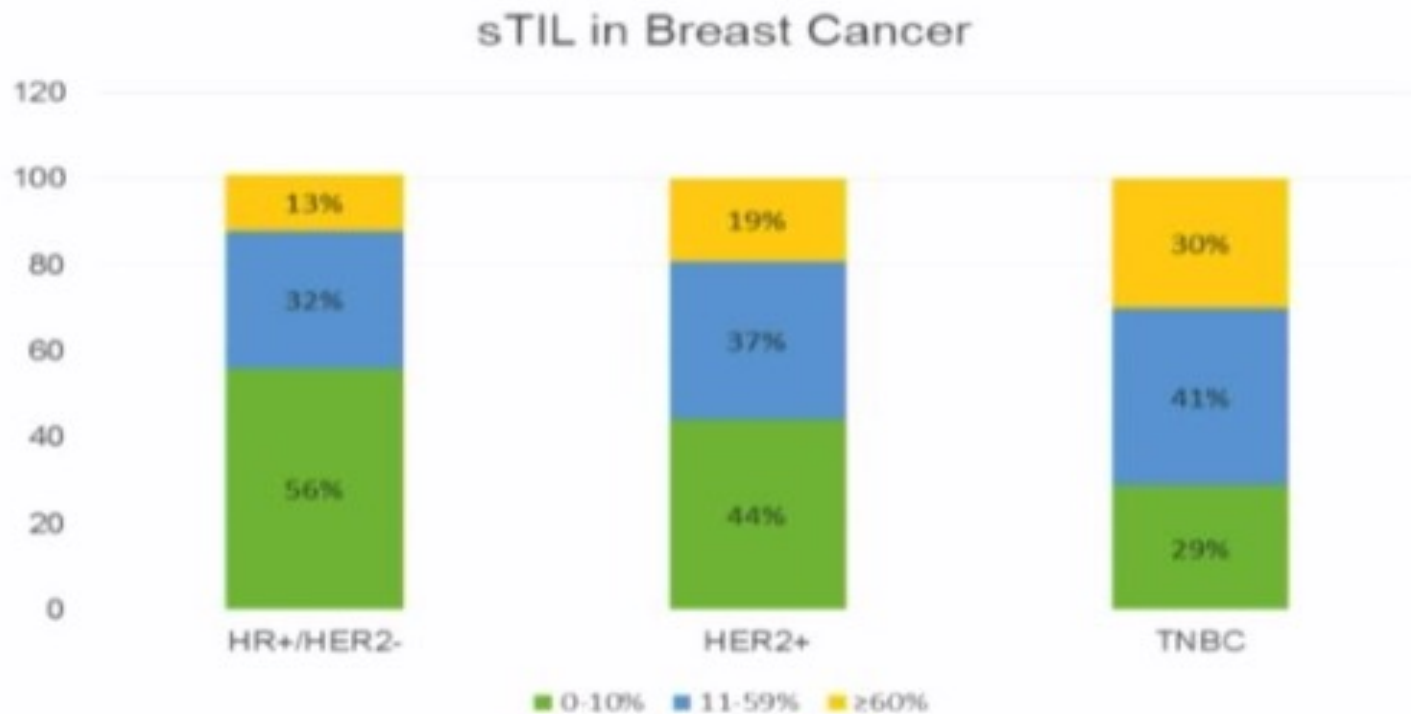


PD-L1 inhibits T cell killing of cancer cells

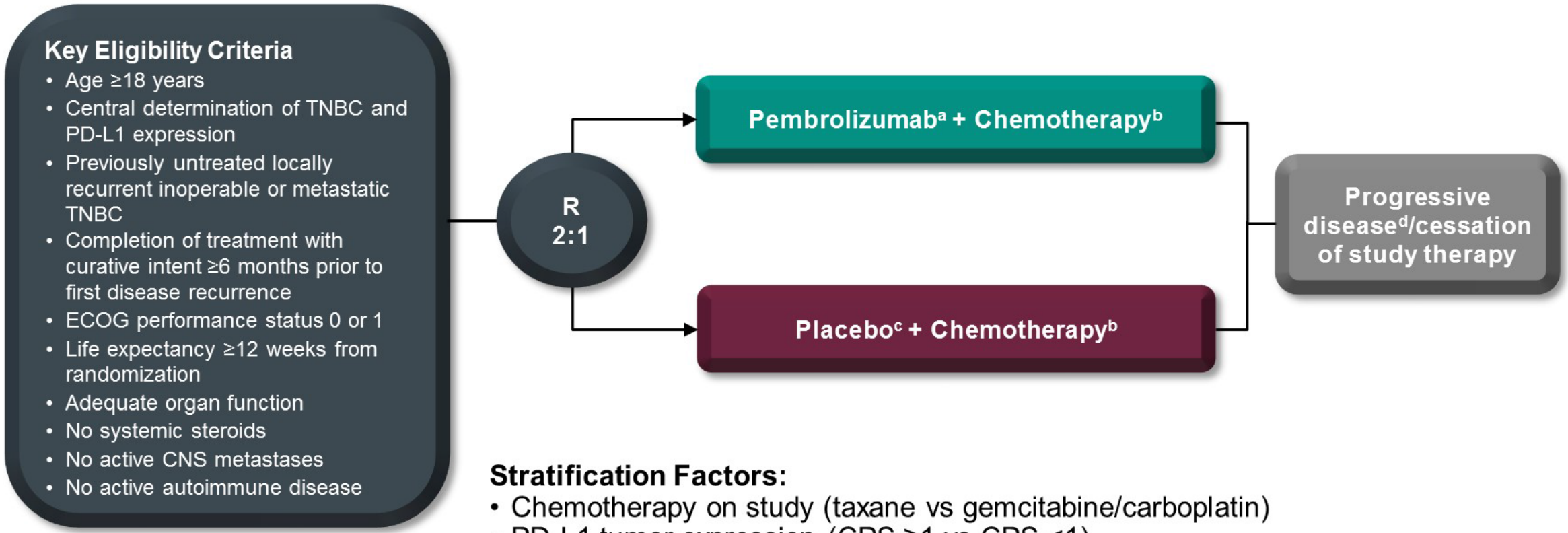
Augmenting Response to Checkpoint Blockade




A
B
C
Low
(0-10%)
Intermediate
(11-59%)
High
(≥60%)


sTIL in Breast Cancer
120
100
80
60
40
20
0
13%
32%
56%
19%
37%
44%
30%
41%
29%
HR+/HER2-
HER2+
TNBC
0-10%
11-59%
≥60%

KEYNOTE-355 Study Design (NCT02819518)



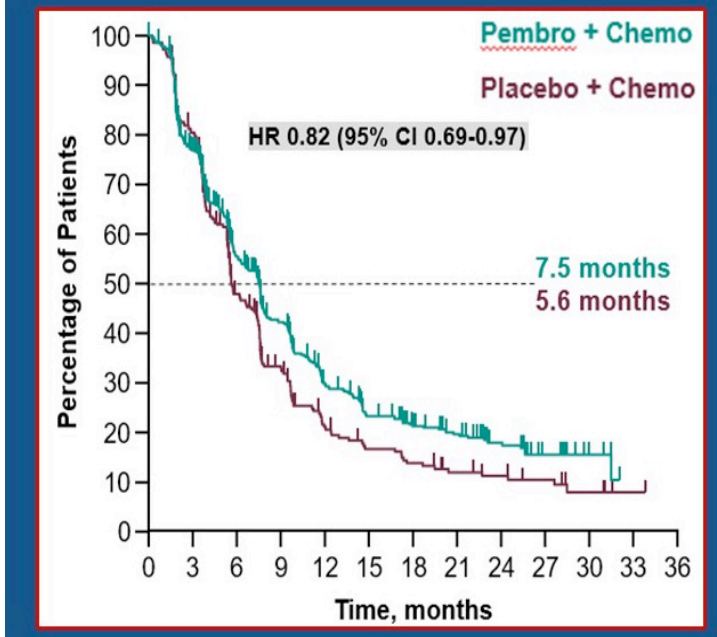
Stratification Factors:
- Chemotherapy on study (taxane vs gemcitabine/carboplatin)
- PD-L1 tumor expression (CPS ≥1 vs CPS <1)
- Prior treatment with same class chemotherapy in the neoadjuvant or adjuvant setting (yes vs no)

[a]Pembrolizumab 200 mg intravenous (IV) every 3 weeks (Q3W)
[b]Chemotherapy dosing regimens are as follows:
Nab-paclitaxel 100 mg/m^2 IV on days 1, 8, and 15 every 28 days
Paclitaxel 90 mg/m^2 IV on days 1, 8, and 15 every 28 days
Gemcitabine 1000 mg/m^2/carboplatin AUC 2 on days 1 and 8 every 21 days

[c]Normal saline
[d]Treatment may be continued until confirmation of progressive disease
CNS=central nervous system; ECOG=Eastern Cooperative Oncology Group; PD-L1=programmed death ligand 1; R=randomized; TNBC=triple-negative breast cancer

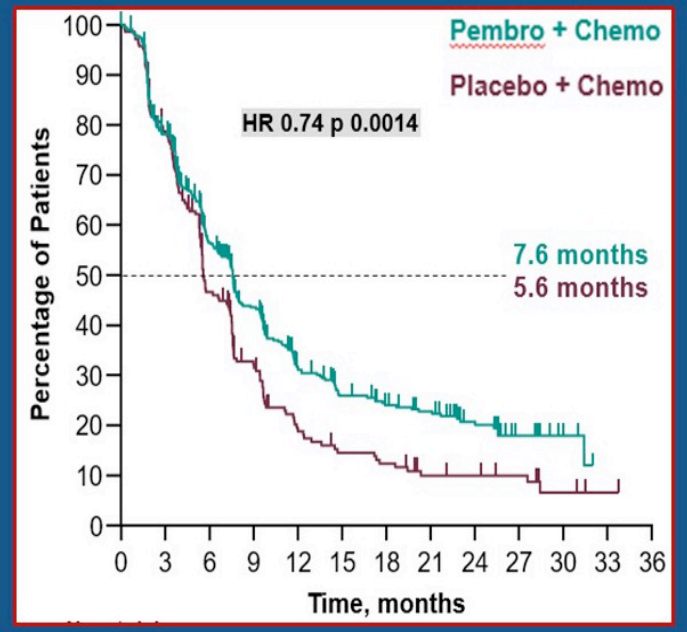
KEYNOTE 355: Progression-free survival

ITT



Statistical significance was not tested due to the prespecified hierarchical testing strategy

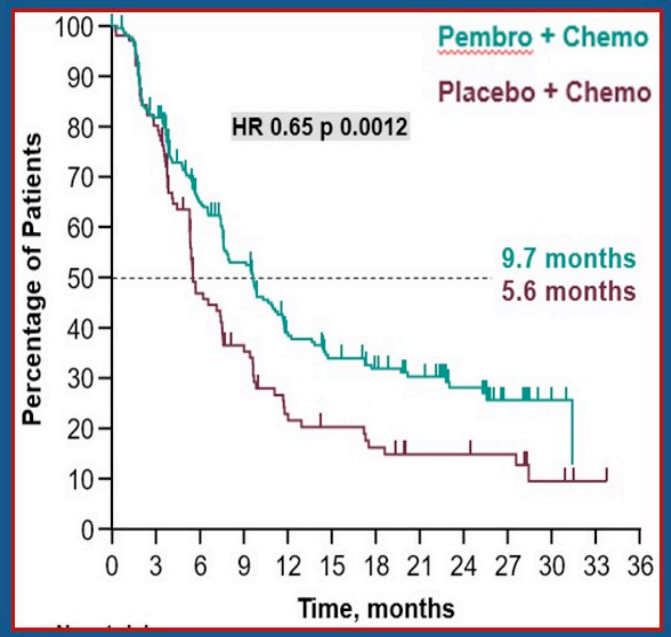
PD-L1 CPS ≥1



Prespecified *P* value boundary of 0.00111 not met

75% of pts

PD-L1 CPS ≥10



Prespecified *P* value boundary of 0.00411 met

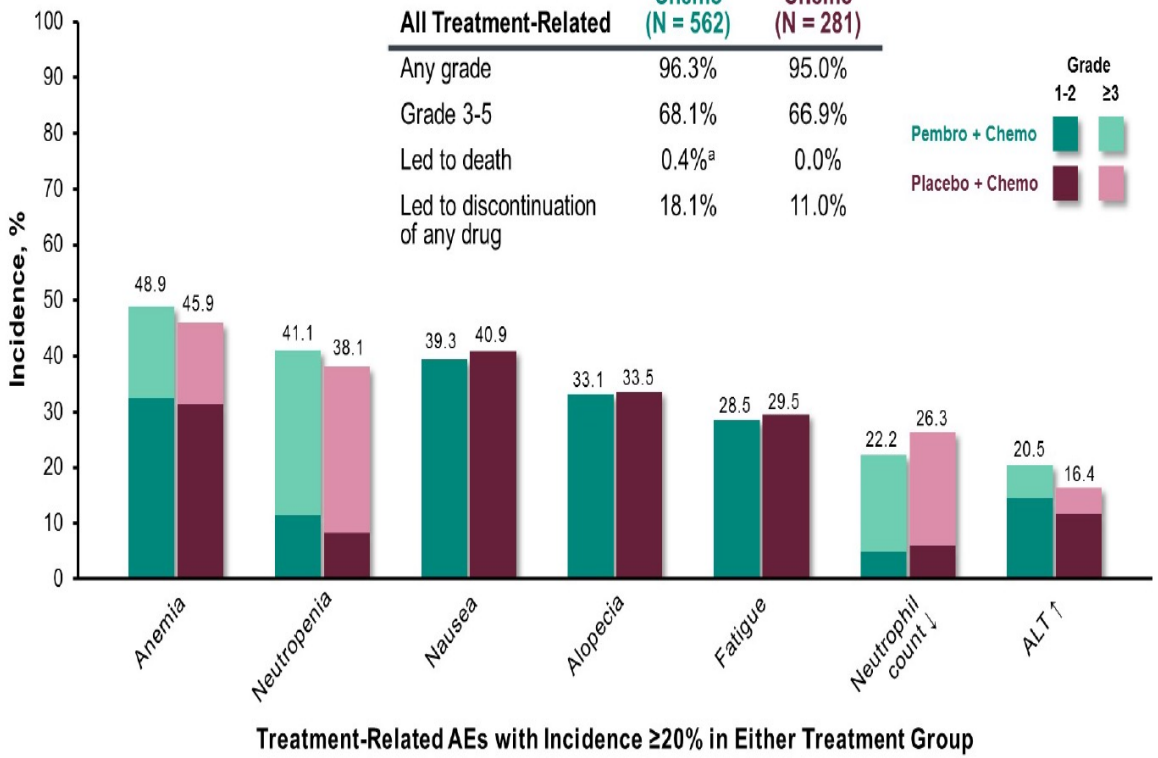
38% of pts

Immune-Mediated AEs

Keynote-355

Treatment-Related AEs

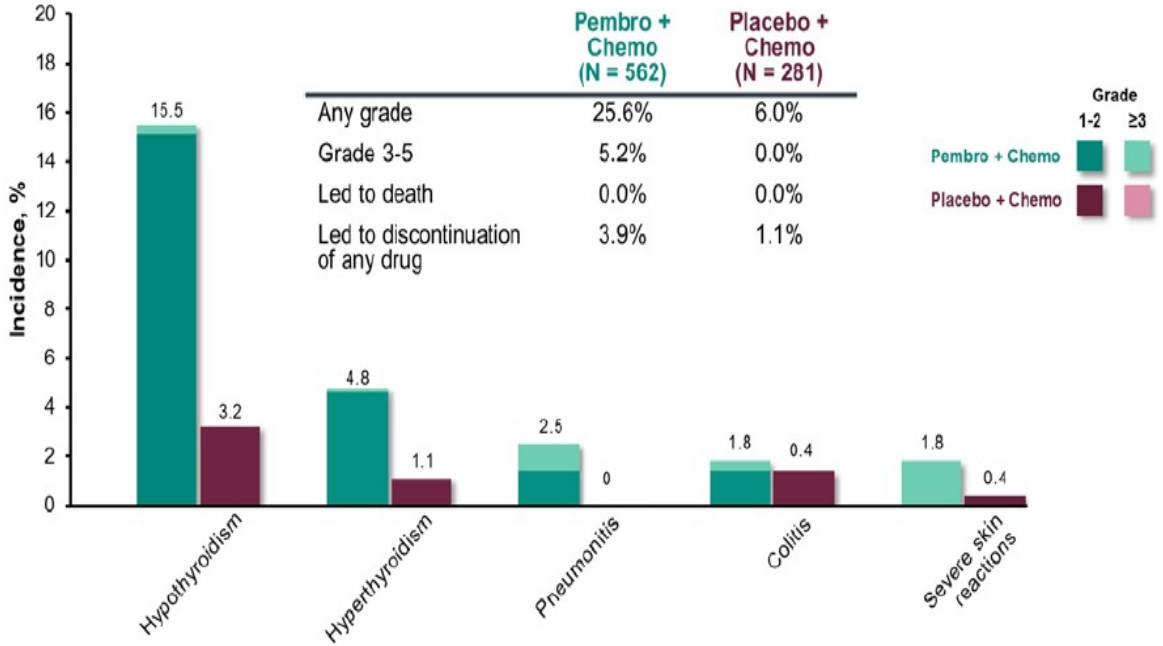
All Treatment-Related	Pembro + Chemo (N = 562)	Placebo + Chemo (N = 281)
Any grade	96.3%	95.0%
Grade 3-5	68.1%	66.9%
Led to death	0.4%[a]	0.0%
Led to discontinuation of any drug	18.1%	11.0%



Treatment-Related AEs with Incidence ≥20% in Either Treatment Group

Immune-Mediated AEs

	Pembro + Chemo (N = 562)	Placebo + Chemo (N = 281)
Any grade	25.6%	6.0%
Grade 3-5	5.2%	0.0%
Led to death	0.0%	0.0%
Led to discontinuation of any drug	3.9%	1.1%



Immune-Mediated AEs with Incidence ≥10 Patients in Either Treatment Group[a]

Phase II Study of Eribulin ± Pembrolizumab for Metastatic HR+ Breast Cancer

Key eligibility criteria

- Metastatic breast cancer
- HR + (ER and/or PR >1%, HER2-negative)
- Measurable or evaluable disease
- At least 2 prior lines of hormonal therapy (adjuvant plus metastatic setting) or appropriate candidates for chemotherapy
- 0-2 prior lines of chemotherapy for advanced disease
- No prior eribulin or PD-1/PD-L1 inhibitor therapy
- Archival tumor tissue required (or biopsy)*
- ECOG PS 0-2

N=88

R 1:1

Eribulin + Pembrolizumab
Pembrolizumab 200 mg IV
– On day 1 of 21-day cycle
+ Eribulin 1.4 mg/m^2 IV
– On days 1, 8 of 21-day cycle

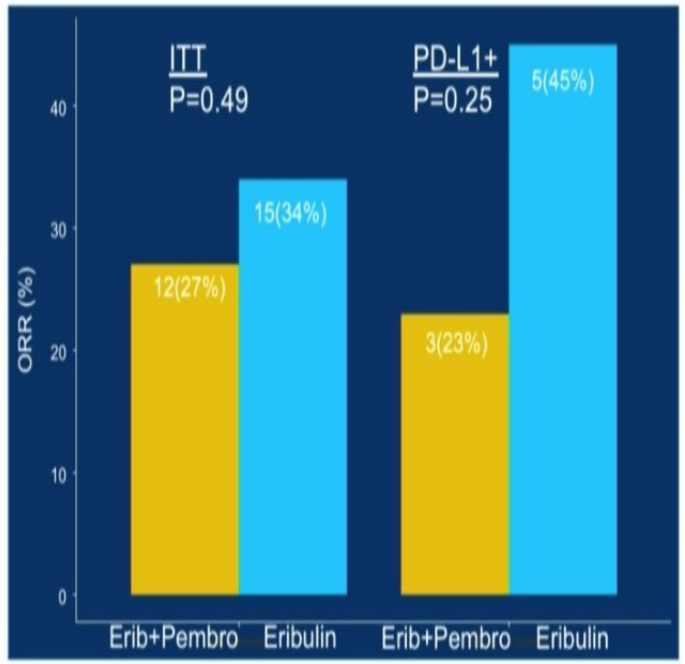
Eribulin:
Eribulin 1.4 mg/m^2 IV
– On days 1, 8 of 21-day cycle

Pembrolizumab:
Pembrolizumab 200 mg IV
– On day 1 of 21-day cycle

Restaging scans obtained every 9 weeks

Biopsy at time of progression

ORR



Response (RECIST 1.1)	Eribulin + Pembrolizumab	Eribulin
ITT population		
PR	27%	34%
SD	43%	36%
SD>24 wks	20%	16%
CBR (PR +SD>24wks)	48%	50%
DOR, median (range)	1.5 (0-13.6)	2.1 (0.2-4.6)
PD-L1+ patients		
PR	23%	45%
SD	46%	45%
SD>24 wks	15%	18%
CBR (PR +SD>24wks)	39%	63%
DOR, median (range)	0.6 (0-1)	2.1 (1-4.6)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

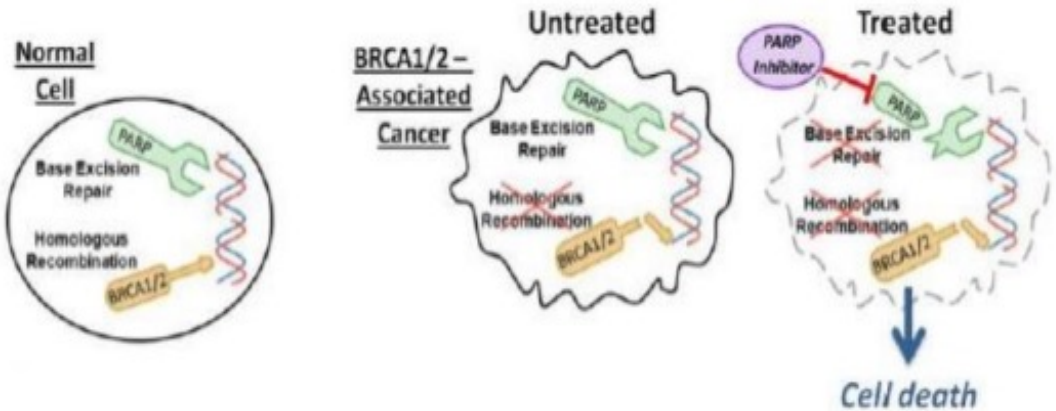
Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer

Peter Schmid, M.D., Ph.D., Sylvia Adams, M.D., Hope S. Rugo, M.D., Andreas Schneeweiss, M.D., Carlos H. Barrios, M.D., Hiroji Iwata, M.D., Ph.D., Véronique Diéras, M.D., Roberto Hegg, M.D., Seock-Ah Im, M.D., Ph.D., Gail Shaw Wright, M.D., Volkmar Henschel, Ph.D., Luciana Molinero, Ph.D., et al., for the IMpassion130 Trial Investigators*

CONCLUSIONS

Atezolizumab plus nab-paclitaxel prolonged progression-free survival among patients with metastatic triple-negative breast cancer in both the intention-to-treat population and the PD-L1–positive subgroup. Adverse events were consistent with the known safety profiles of each agent. (Funded by F. Hoffmann–La Roche/Genentech; IMpassion130 ClinicalTrials.gov number, NCT02425891.)

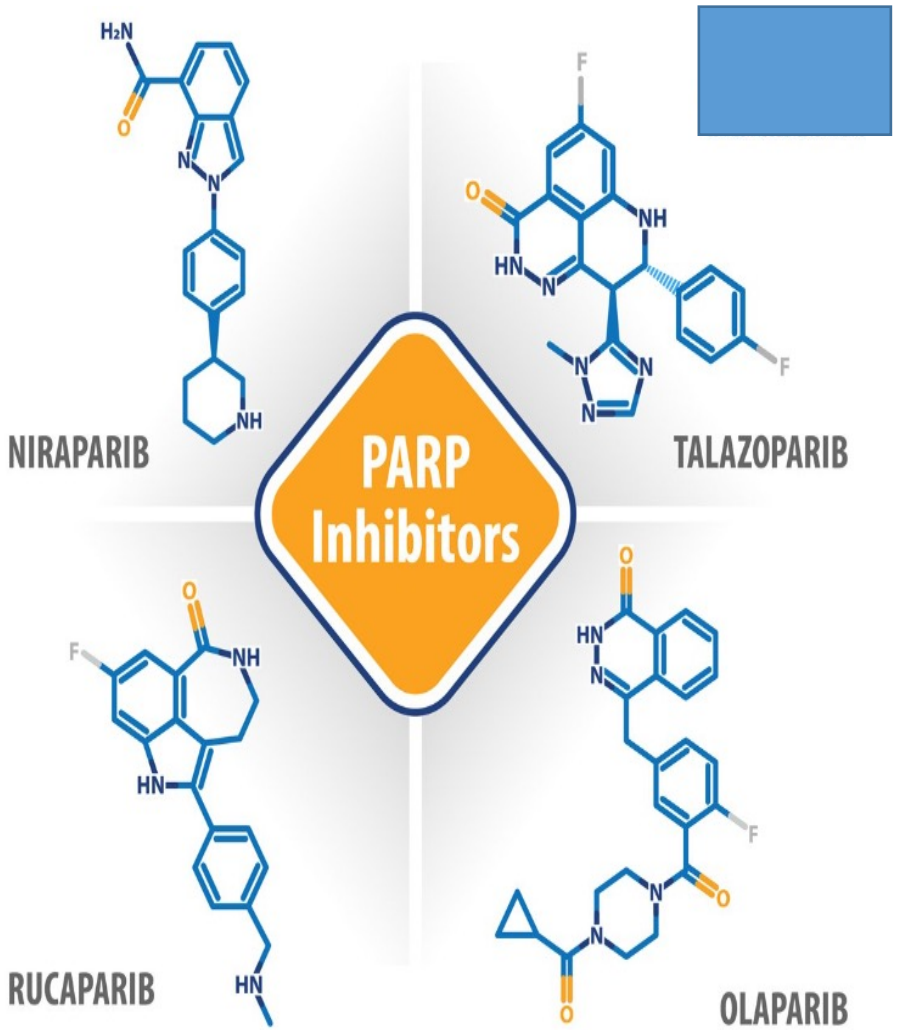
PARP Inhibitors: Mechanism



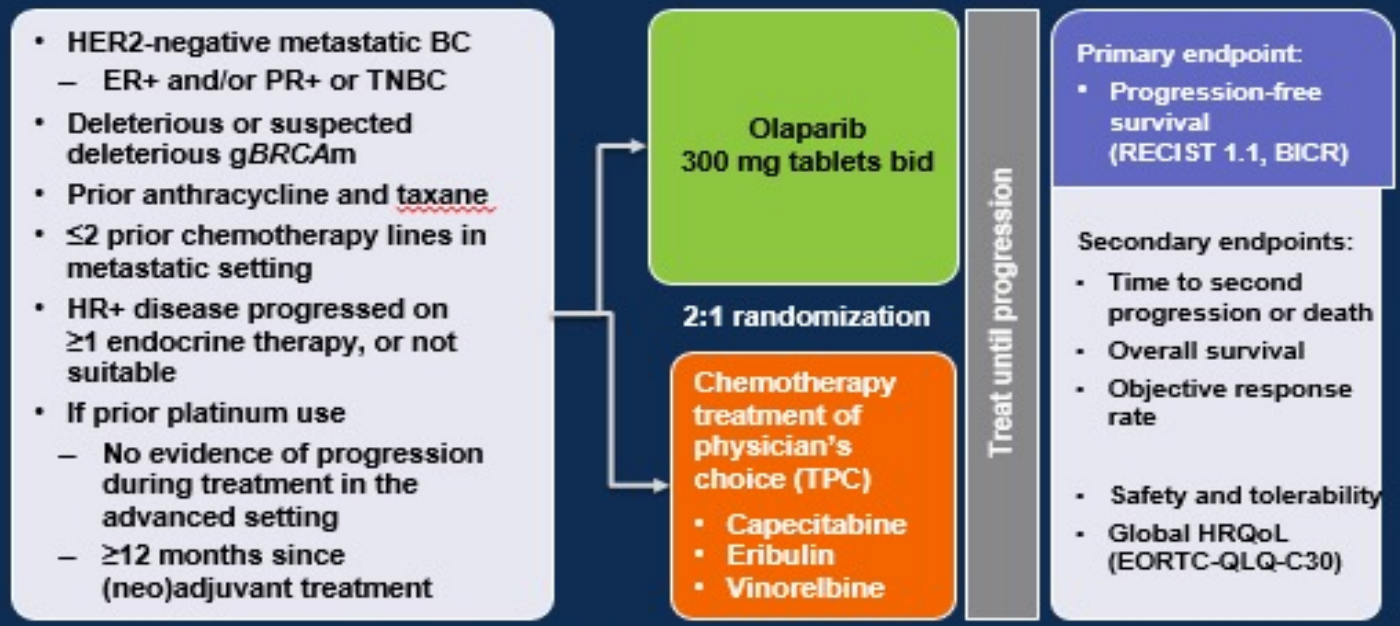
- PARP and BRCA1/2 normally function to repair daily DNA damage
- Allows cells to grow in a healthy way
- Too much DNA damage-> cell death

- If BRCA1/2 is damaged or not working, the cell is dependent on PARP for all DNA repair
- PARP inhibitors prevent DNA repair in cancer cells
  - May increase cancer cell death
  - May help chemo and radiation work better

Ellisen, Cancer Cell 2011; Tutt et al, Lancet 2010



OlympiAD study design

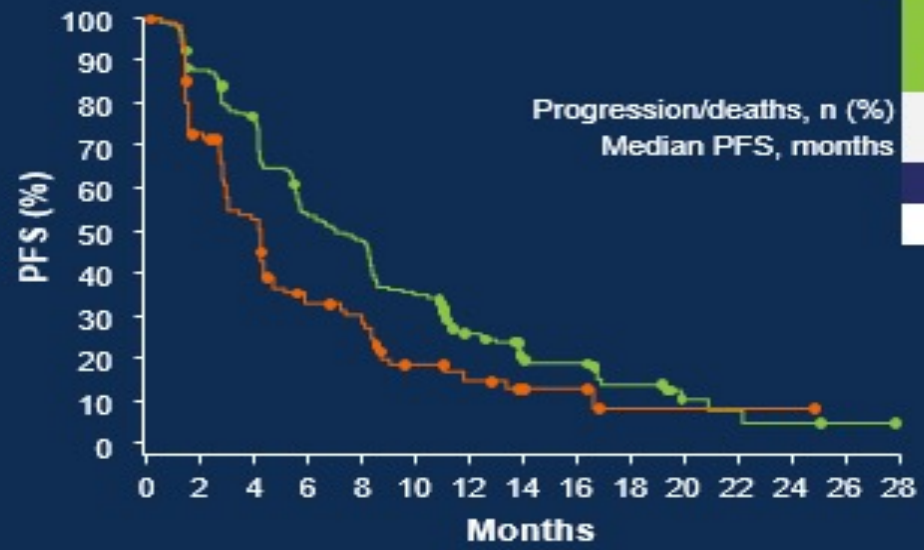


BICR, blinded independent central review; ER, estrogen receptor; HRQoL, health-related quality of life;
PR, progesterone receptor; RECIST, response evaluation criteria in solid tumors; TNBC, triple negative breast cancer

Patient characteristics

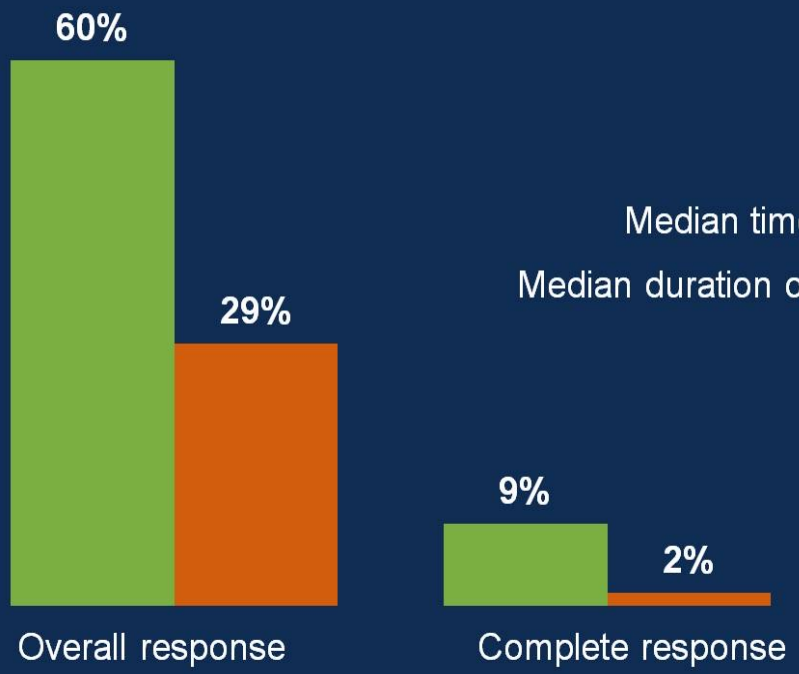
	Olaparib 300 mg bid (N=205)	Chemotherapy TPC (N=97)
Age, years (median, range)	44 (22–76)	45 (24–68)
Male, n (%)	5 (2)	2 (2)
White race, n (%)	134 (65)	63 (65)
***BRCA* mutation status, n (%)**		
BRCA1	117 (57)	51 (53)
BRCA2	84 (41)	46 (47)
Both	4 (2)	0
Hormonal receptor status, n (%)		
ER+ and/or PR+	103 (50)	49 (51)
TNBC	102 (50)	48 (49)
Prior chemotherapy for metastasis, n (%)	146 (71)	69 (71)
Prior platinum treatment, n (%)	60 (29)	26 (27)

Primary endpoint: progression-free survival by BICR



	Olaparib 300 mg bid	Chemotherapy TPC
Progression/deaths, n (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2
HR 0.58		
95% CI 0.43 to 0.80; *P*=0.0009		

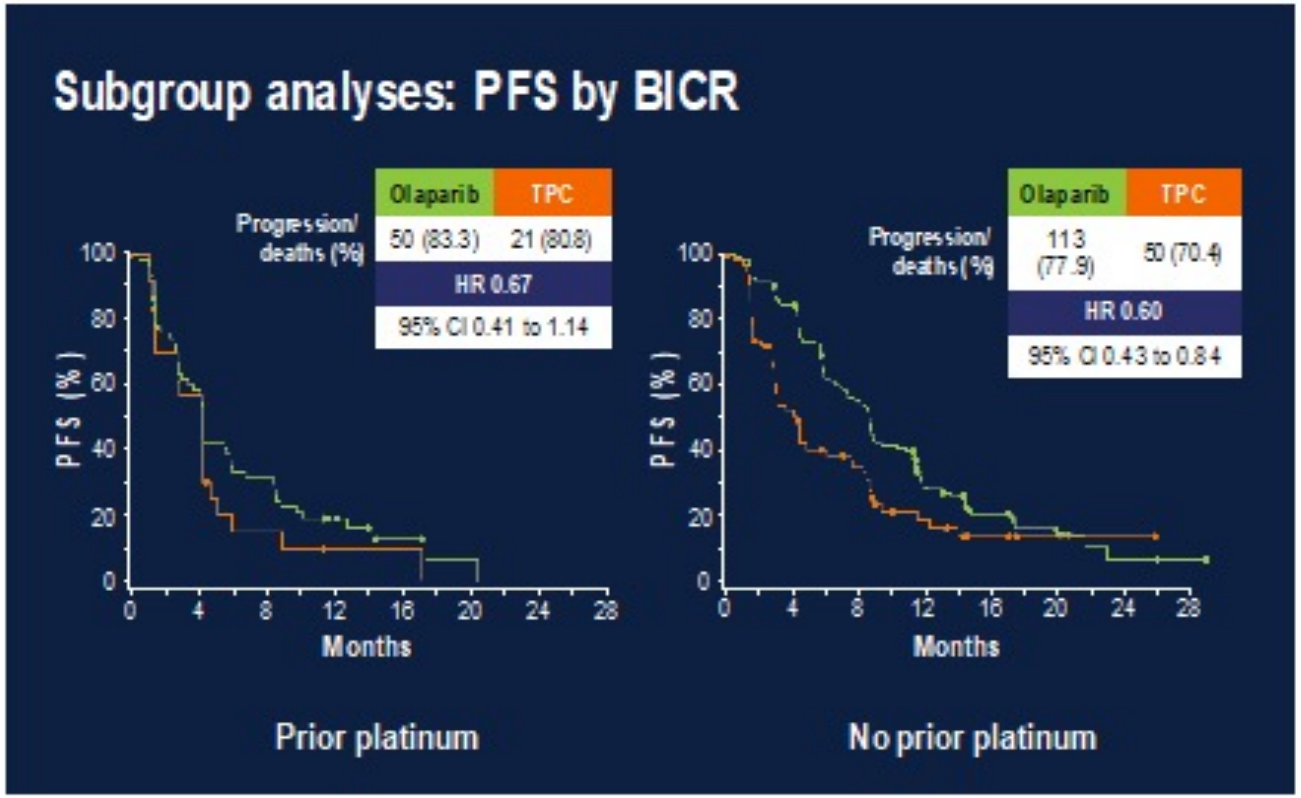
Objective response by BICR



	Olaparib 300 mg bd	Chemotherapy TPC
n	167	66
Median time to response, days	47	45
Median duration of response, months	6.2 (4.6–7.2)	7.1 (2.8–12.2)

Subset Analysis: Role of ER and Prior Platinum

Results driven by TN and platinum naïve?



Thanks for your kind attention