Triple Negative Breast Cancer / *BRCA* Mutated Breast Cancer: What's New?

CALIFORNIA CANCER™ CONSORTIUM CONFERENCE

Mili Arora, MD

UC Davis Comprehensive Cancer Center

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Disclosures

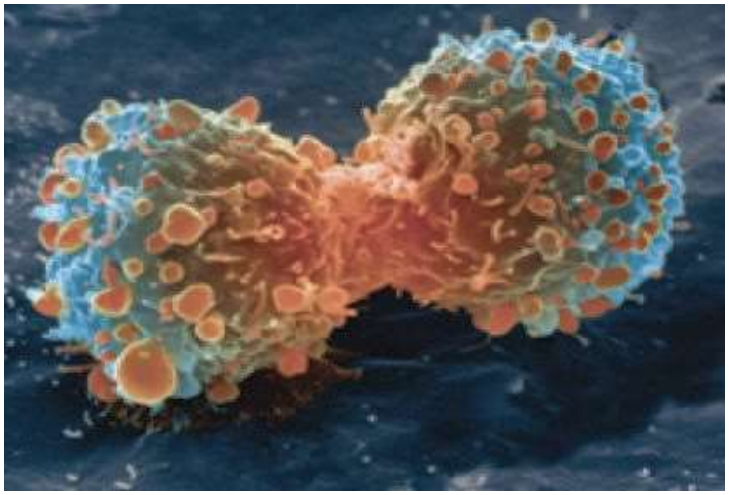
- No relevant financial disclosures to report

Outline

I. Immunotherapy
   A. IMpassion 130
II. PARP inhibitors
   A. TOPACIO/KEYNOTE 162
III. Sacituzumab govitecan-hziy
IV. Androgen receptor

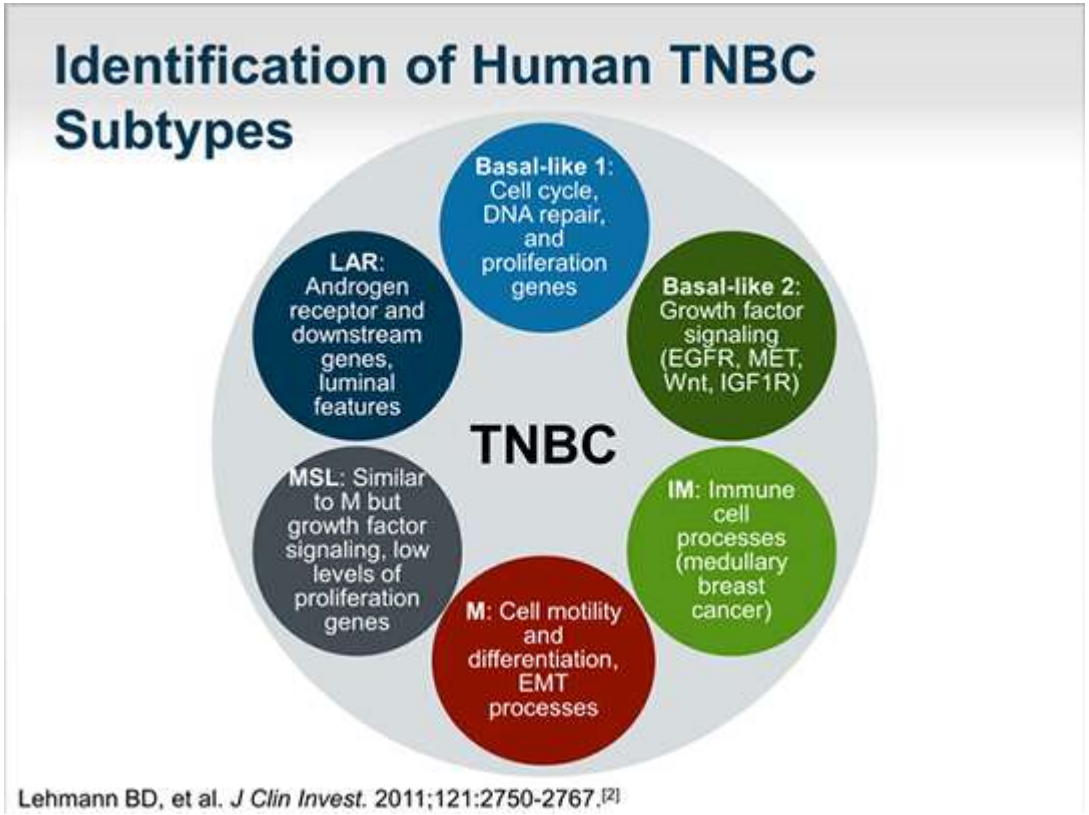
Triple Negative Breast Cancer (TNBC)

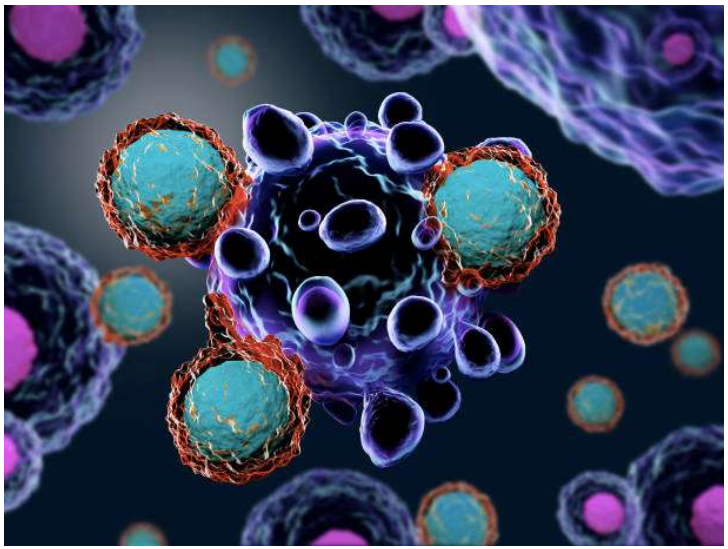
- Estrogen- and progesterone-receptor negative and HER2 non-amplified
- ~15% breast cancers
- Characterized by persistent tumor growth, treatment resistance, metastasis
- Disproportionate toll of breast cancer mortality
- Greatest unmet need in breast oncology
- ~20% BRCA mutant cancers



Source: Harvard Stem Cell Institute

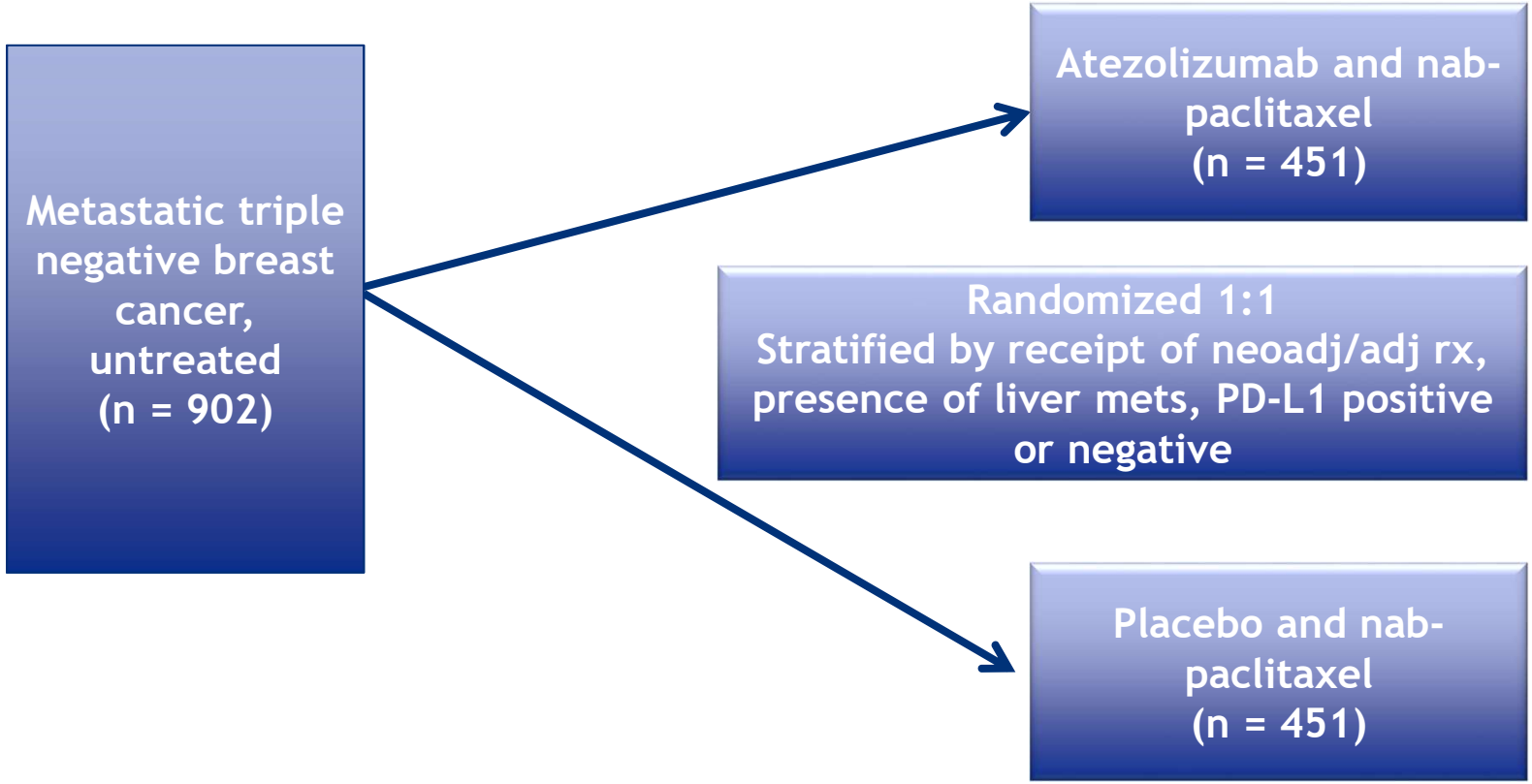
Heterogeneity of TNBC





Immunotherapy

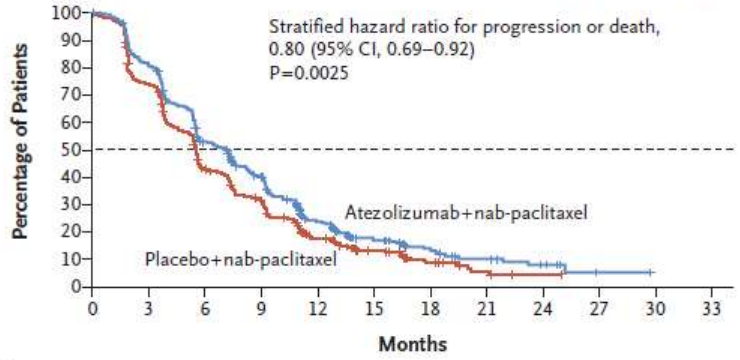
IMpassion130 – Trial Design



IMpassion 130: PFS

A Progression-free Survival in the Intention-to-Treat Population

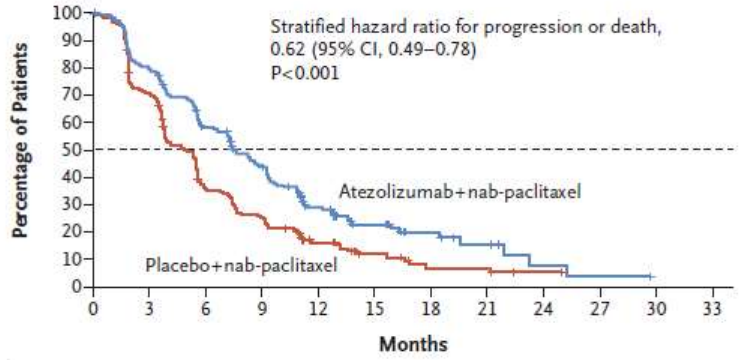
	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)	1-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	358/451	7.2 (5.6–7.5)	23.7 (19.6–27.9)
Placebo+Nab-Paclitaxel	378/451	5.5 (5.3–5.6)	17.7 (14.0–21.4)



No. at Risk												
Atezolizumab+ nab-paclitaxel	451	360	226	164	77	34	20	11	6	1	NE	NE
Placebo+ nab-paclitaxel	451	327	183	130	57	29	13	5	1	NE	NE	NE

B Progression-free Survival in the PD-L1–Positive Subgroup

	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)	1-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	138/185	7.5 (6.7–9.2)	29.1 (22.2–36.1)
Placebo+Nab-Paclitaxel	157/184	5.0 (3.8–5.6)	16.4 (10.8–22.0)



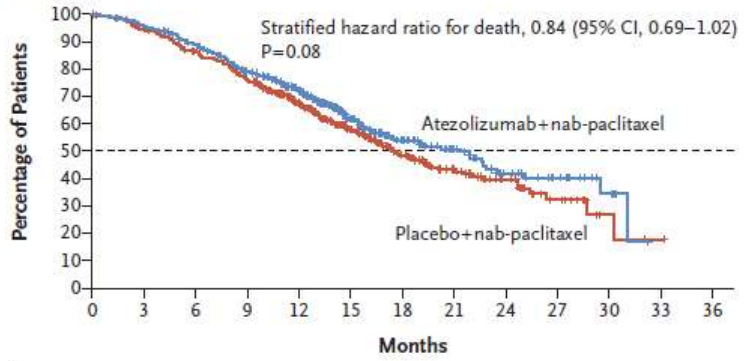
No. at Risk												
Atezolizumab+ nab-paclitaxel	185	146	104	75	38	19	10	6	2	1	NE	NE
Placebo+ nab-paclitaxel	184	127	62	44	22	11	5	5	1	NE	NE	NE

Source: Schmid, P., Adams, S., Rugo, H. S., Schneeweiss, A., Barrios, C. H., Iwata, H., … Emens, L. A. (2018). Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. New England Journal of Medicine, 379(22), 2108–2121.

IMpassion 130: OS

C Overall Survival in the Intention-to-Treat Population

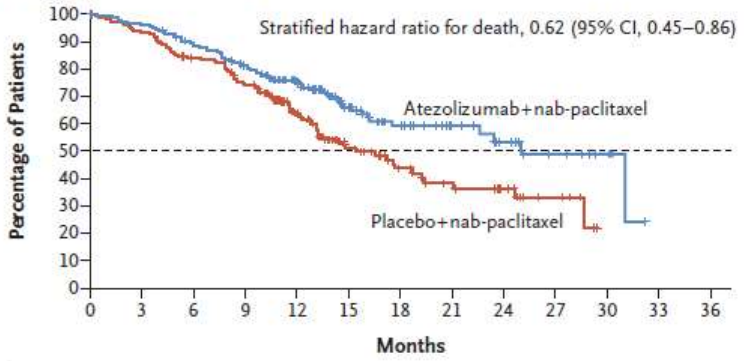
	No. of Events/ No. of Patients	Median Overall Survival (95% CI)	2-Yr Rate of Overall Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	181/451	21.3 (17.3–23.4)	42.1 (34.3–49.9)
Placebo+Nab-Paclitaxel	208/451	17.6 (15.9–20.0)	39.7 (33.2–46.3)



No. at Risk												
Atezolizumab+ nab-paclitaxel	451	426	389	337	271	146	82	48	26	15	6	NE	NE
Placebo+ nab-paclitaxel	451	419	375	328	246	145	89	52	27	12	3	1	NE

D Overall Survival in the PD-L1–Positive Subgroup

	No. of Events/ No. of Patients	Median Overall Survival (95% CI)	2-Yr Rate of Overall Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	64/185	25.0 (22.6–NE)	53.5 (42.3–64.6)
Placebo+Nab-Paclitaxel	88/184	15.5 (13.1–19.4)	36.6 (26.4–46.7)



No. at Risk												
Atezolizumab+ nab-paclitaxel	185	177	160	142	113	61	36	22	15	9	5	NE	NE
Placebo+ nab-paclitaxel	184	170	147	129	89	44	27	19	13	6	NE	NE	NE

Source: Schmid, P., Adams, S., Rugo, H. S., Schneeweiss, A., Barrios, C. H., Iwata, H., … Emens, L. A. (2018). Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. New England Journal of Medicine, 379(22), 2108–2121.

IMpassion 130: Adverse Events

Table 3. Key Adverse Events.*

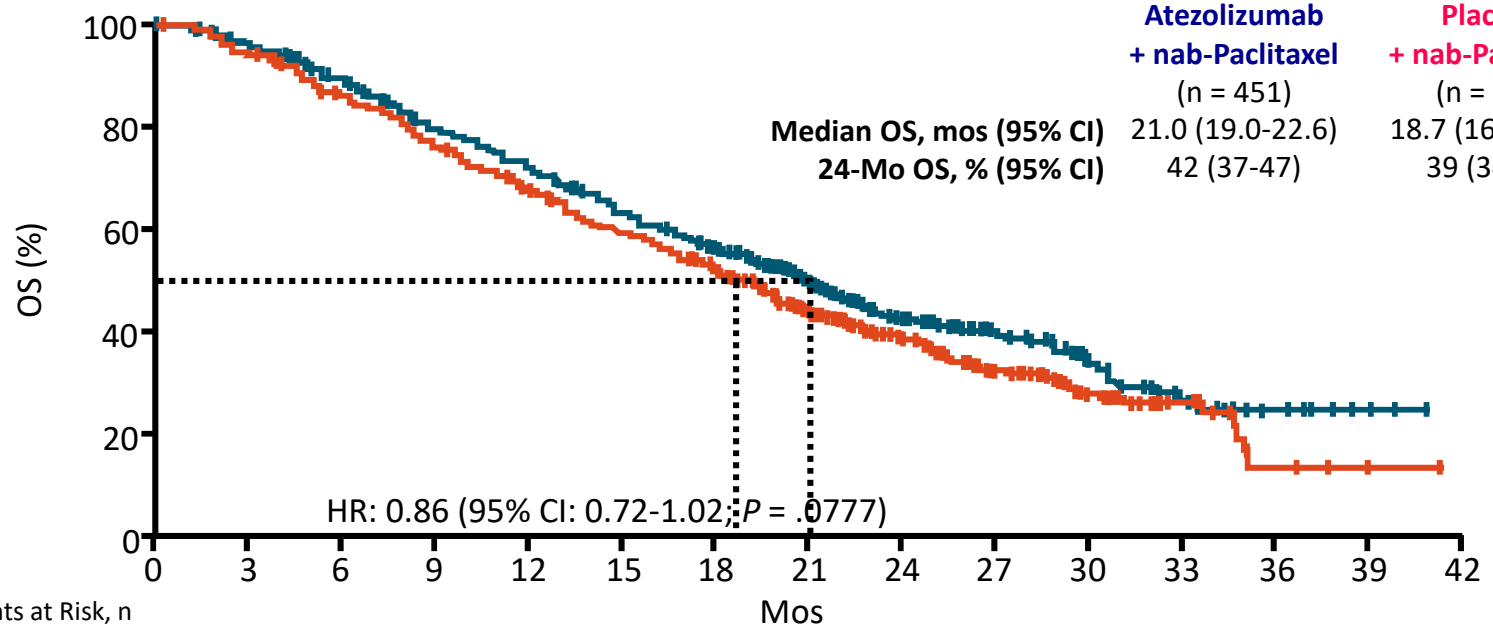
Event	Atezolizumab + Nab-Paclitaxel (N=452)		Placebo + Nab-Paclitaxel (N=438)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with event (percent)			
Alopecia	255 (56.4)	3 (0.7)	252 (57.5)	1 (0.2)
[redacted]				
Cough	112 (24.8)	0	83 (18.9)	0
Peripheral neuropathy	98 (21.7)	25 (5.5)	97 (22.1)	12 (2.7)
[redacted]				
Pyrexia	85 (18.8)	3 (0.7)	47 (10.7)	0
Hypothyroidism	62 (13.7)	0	15 (3.4)	0

Source: Schmid, P., Adams, S., Rugo, H. S., Schneeweiss, A., Barrios, C. H., Iwata, H., … Emens, L. A. (2018). Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. New England Journal of Medicine, 379(22), 2108–2121.

IMpassion130

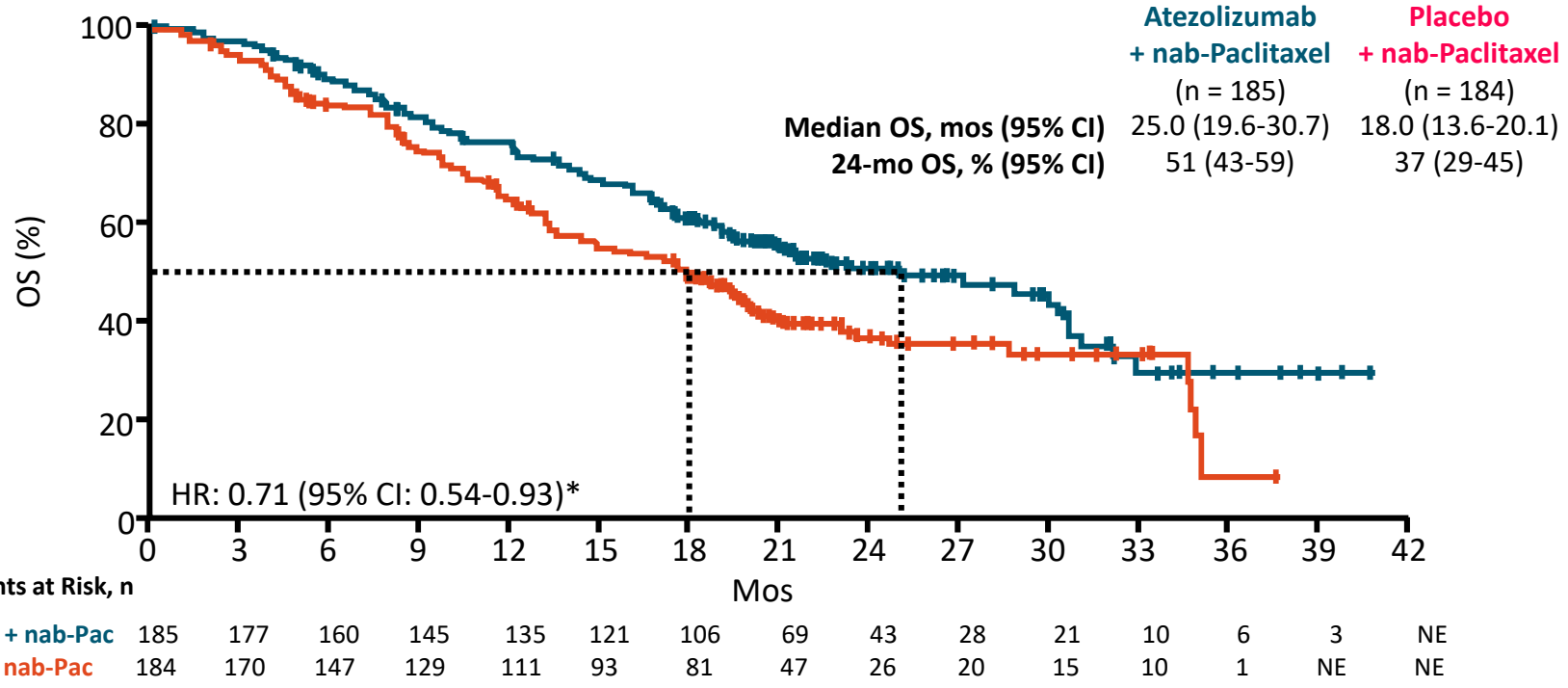
- FDA approved atezolizumab with nab-paclitaxel, along with Ventana Medical Systems' SP142 PD-L1 IHC assay as companion diagnostic test to identify PD-L1 IC ≥ 1% in March 2019
- ASCO 2019 Updated OS Analysis
  - Second interim OS: median f/u time 18 months

IMpassion130 Update: OS in ITT Population



Source: clinicaloptions.com

IMpassion130 Update: OS in PD-L1+ Subgroup

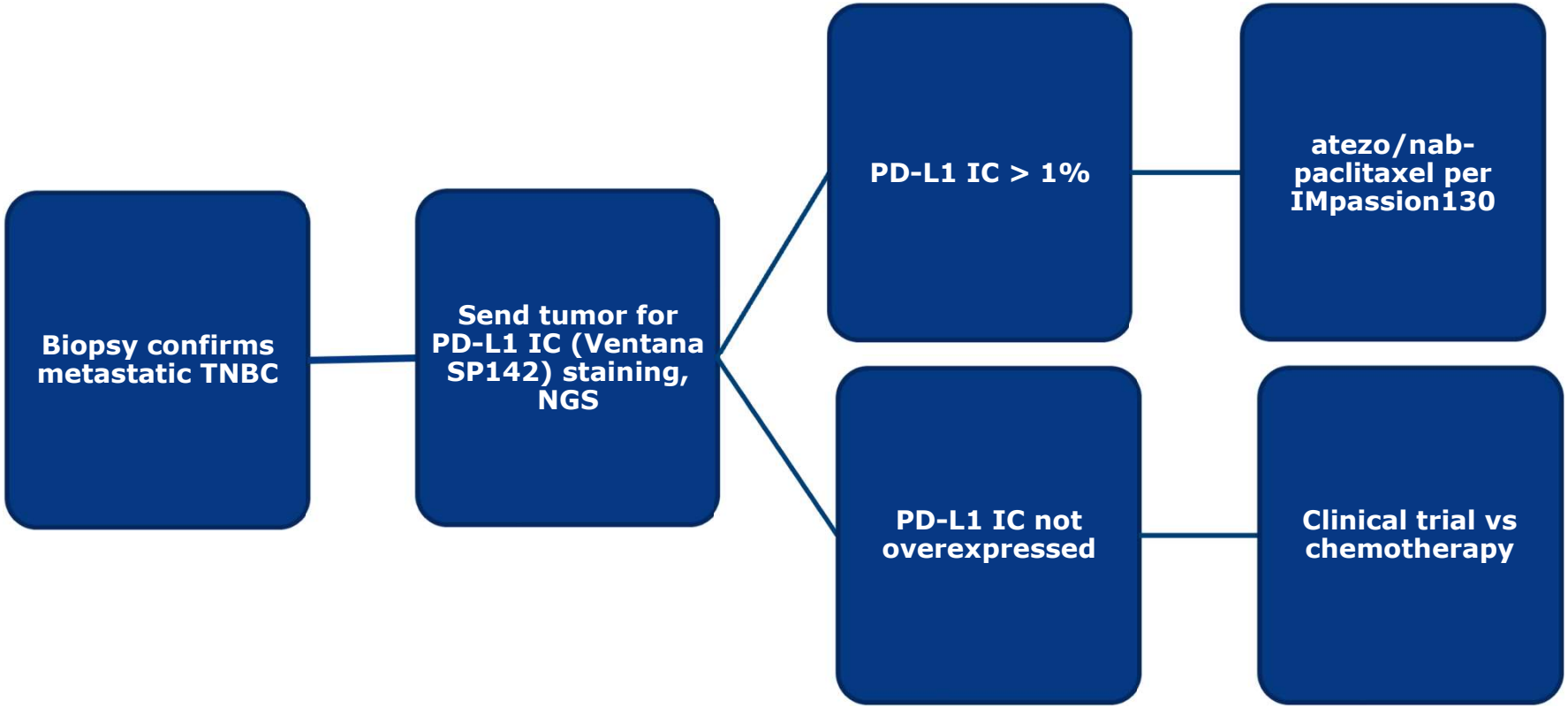


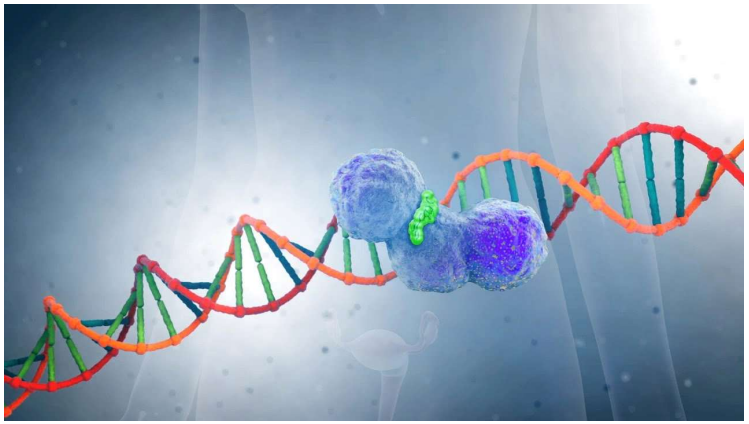
Source: clinicaloptions.com

IMpassion 130: Biomarker Analysis

- 15% patients *BRCA* mutated
  - PD-L1 IC negative group: no association between treatment and survival noted
  - PD-L1 IC positive group: significant benefit of PFS and OS
  - Small numbers
- PD-L1 IC
  - PD-L1 IC most predictive of atezolizumab/nab-paclitaxel efficacy on PFS and OS with expression > 1%

Therapeutic Algorithm in TNBC



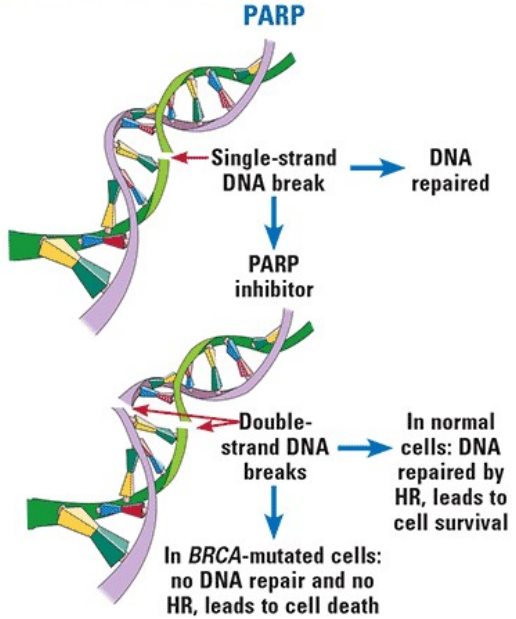


PARP inhibitors

PARP inhibitors (PARPi) MOA

- PARP enzymes detect and repair DNA damage
- PARPi
  - Cancer cells synthetic lethality in homologous recombination deficient (HRD) cells → cell death
  - Normal cells homologous recombination repairs cell → cell survival

Figure 1 Schematic mechanism of PARP inhibitors



SSBs in DNA recruit PARP. With a PARP inhibitor, more DSBs occur. In normal cells, SSBs and DSBs can be repaired. In BRCA-mutated cells, DSBs are not repaired effectively. DSB: double-strand break; HR: homologous recombination; PARP: Poly (ADP-ribose) polymerase; SSB: single-strand break. Source: References 1, 2.

Source: Iqbal, S & Rattu, Mohammad & Shah, N. (2018). Role of PARP inhibitors in BRCA-related malignancies. U.S. Pharmacist. 43. HS-10.

OlympiAD

- Olaparib
- Germline *BRCA* 1/2 mutated patients
- Appx 72% pts ECOG 0
- No prior platinum allowed
- Randomized 2:1
- Primary endpoint- PFS
- ORR 55%
- PFS 7.0 vs 4.2 months
- FDA approved Jan 2018

EMBRACA

- Talozaparib
- Germline *BRCA* 1/2 mutated patients
- Appx 55% pts ECOG 0
- Prior platinum allowed if no progression on the agent
- Randomized 2:1
- Primary endpoint- PFS
- ORR 62%
- PFS 8.6 vs 5.6 months
- FDA approved Oct 2018

PARP Inhibitors

- Optimal sequence?
- Other HRD?
- Overcome resistance by inhibiting other repair pathways?
- Monotherapy
  - Platinum combination?
    - SWOG 1416
  - Immunotherapy w/PARPi?
    - TOPACIO/KEYNOTE-162

TOPACIO/KEYNOTE-162

- Niraparib in Combination with Pembrolizumab in Patients with Ovarian Cancer and Triple Negative Breast Cancer
- Hypothesis
  - Combination of Niraparib and Pembrolizumab would be safe and effective for advanced or metastatic TNBC
- Preclinical data: synergistic activity of PARPi and PD-L1 antibodies in cells **irrespective of *BRCA* mutation status or PD-L1 expression**
- Phase II trial with phase I lead in portion reported previously

Advanced/metastatic triple negative breast cancer, up to 3 prior lines (n = 55)

→

Niraparib 200 mg daily Pembrolizumab 200 mg IV q 21 days (n =47)

Endpoints:
Primary- ORR (objective response rate)
Secondary- safety, DOR, DCR, PFS, OS

Results

Best Overall Response	Study Population	
	Full Analysis (N = 55)	Efficacy Evaluable (n = 47)
[redacted]		
Stable disease, No. (%)	13 (24)	13 (28)
Progressive disease, No. (%)	24 (44)	24 (51)
Not performed or not evaluable, No. (%)	8 (15)	NA
[redacted]		

Abbreviations: DCR, disease control rate; NA, not applicable; ORR, objective response rate.

[a] Includes complete and partial responses.

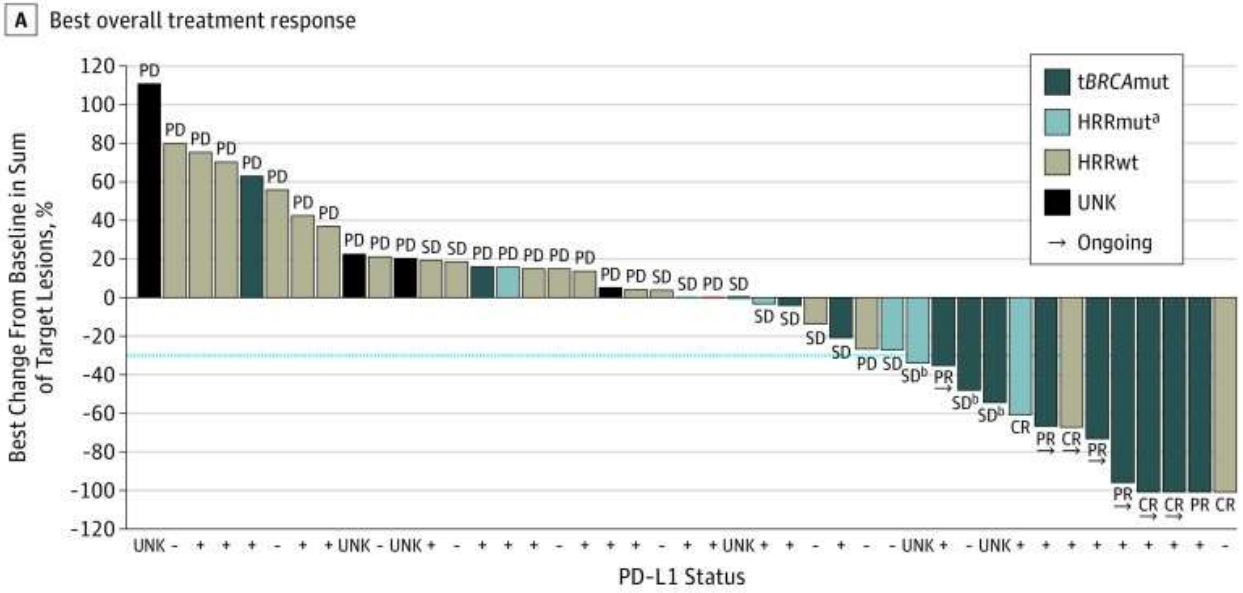
[b] Includes complete and partial responses and stable disease.

Source: Vinayak, Shaveta, et al. "Open-Label Clinical Trial of Niraparib Combined With Pembrolizumab for Treatment of Advanced or Metastatic Triple-Negative Breast Cancer." JAMA Oncology, American Medical Association, 13 June 2019, www.ncbi.nlm.nih.gov/pmc/articles/PMC6567845/figure/coi190028f2/.

Results

- 15/47 patients with tumor *BRCA* mutation
  - 47% ORR
  - 80% DCR
  - mPFS 8.3 months
- 27/47 patients with tumor *BRCA* wild type
  - 11% ORR
  - 33% DCR
  - mPFS 2.1 months
- 5/47 patients with unknown tumor *BRCA* status

Results



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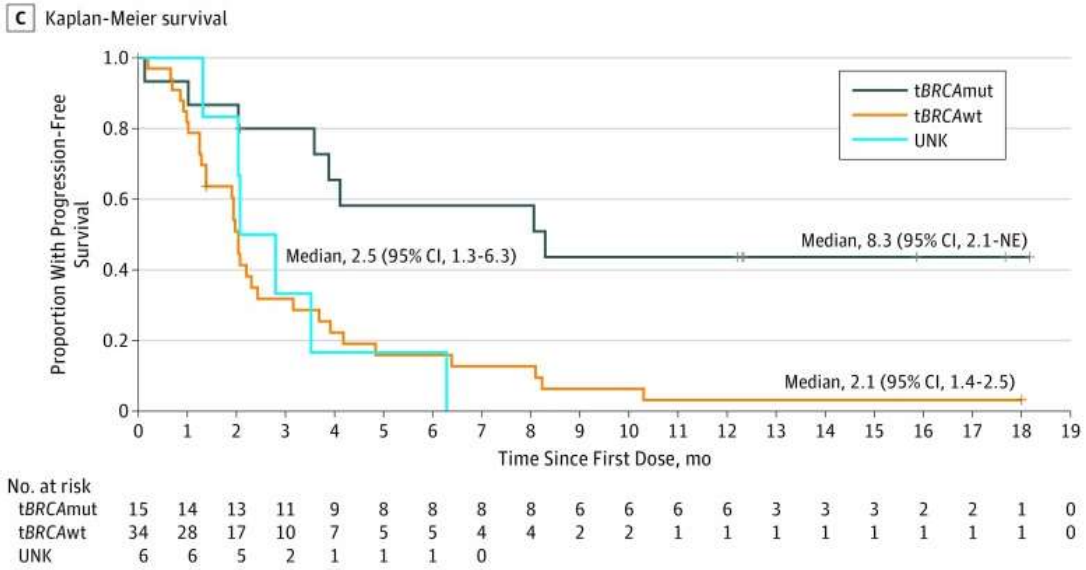
PFS



Source: Vinayak, Shaveta, et al. "Open-Label Clinical Trial of Niraparib Combined With Pembrolizumab for Treatment of Advanced or Metastatic Triple-Negative Breast Cancer." JAMA Oncology, American Medical Association, 13 June 2019, www.ncbi.nlm.nih.gov/pmc/articles/PMC6567845/figure/coi190028f2/.

Results

- 28 patients with PD-L1 positive disease
  - 32% ORR
  - 50% DCR
- 13 patients with PD-L1 negative disease
  - 8% ORR
  - 46% DCR

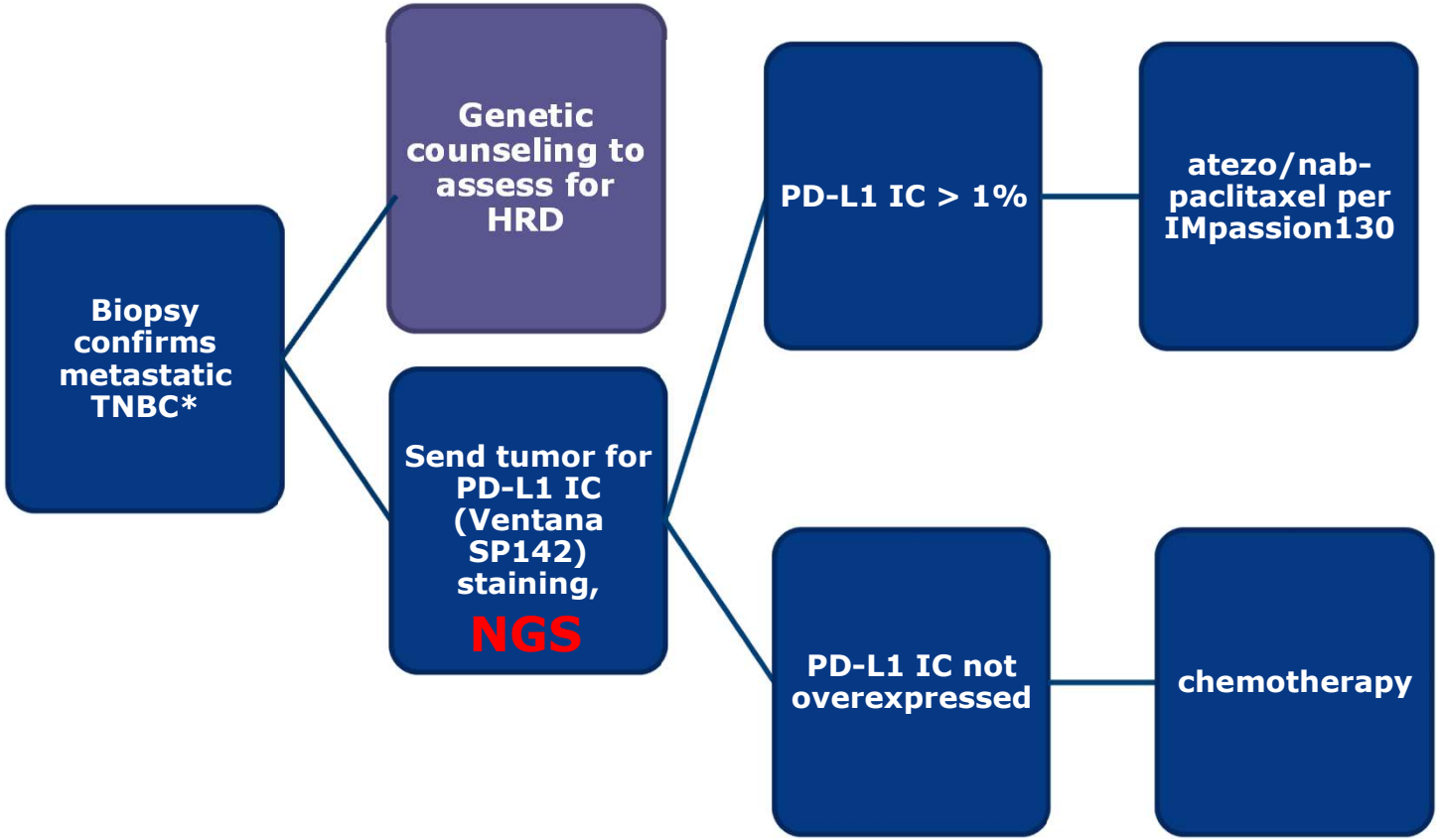
TOPACIO: Adverse Events

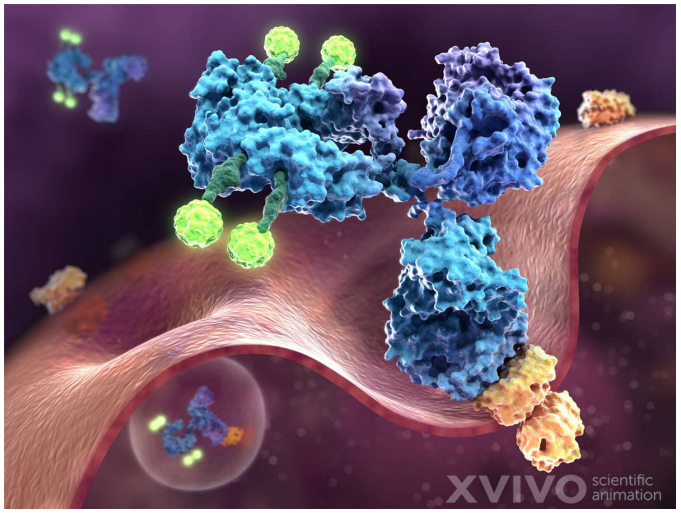
- Adverse Events ≥ grade 3
  - Anemia 18%
  - Thrombocytopenia 15%
  - Fatigue 7%
- Immune related side effects 15%
  - Hypothyroidism 7%
  - Grade 3 events in 2 patients
    - Adrenal insufficiency
    - PMR

TOPACIO Summary

- First trial to report on safety and efficacy of PARPi and immunotherapy
- Niraparib and pembrolizumab promising antitumor activity in metastatic TNBC cohort
- Better response in BRCA mutated tumors
- Tolerable safety profile
- Data warrants further investigation

Therapeutic Algorithm in TNBC





Antibody-drug conjugate

Sacituzumab govitecan-hziy

- Antibody drug conjugate: human trophoblast cell-surface antigen 2 (Trop-2) with SN-38 (topoisomerase-I inhibitor)
  - Trop-2 overexpressed in many epithelial cells including up to 85% of TNBC
  - SN-38 released intracellularly and in tumor microenvironment
- IMMU-132-01
  - Phase I/II open label, multi-center, basket design, single group trial
  - Prelim data reported on 69 pts TNBC who rec'd at least 1 prior line of therapy (J Clin Oncol 2017; 35: 2141-8)
  - Breakthrough therapy designation by FDA for TNBC patients in Feb 2016 who had rec'd at least 2 prior lines of therapy
  - NEJM Feb 2019 reporting on patients rec'd as third line or beyond in metastatic TNBC

Metastatic triple negative breast cancer, at least 2 prior lines (n = 108) → **Sacituzumab govitecan-hziy 10 mg/kg IV on days 1, 8 of 21 day cycle (n= 108)**

Endpoints:
Primary- ORR (objective response rate)
Secondary- TTR, DOR, CBR, PFS, OS

Baseline Characteristics

Table 1. Characteristics of the Patients at Baseline.

Characteristic	Patients (N=108)
Sex — no. (%)	
Female	107 (99.1)
Male	1 (0.9)
Median age (range) — yr	55 (31–80)
Race or ethnic group — no. (%)*	
White	82 (75.9)
Black	8 (7.4)
Asian	3 (2.8)
Other or not specified†	15 (13.9)
ECOG performance-status score — no. (%)‡	
0	31 (28.7)
1	77 (71.3)
[redacted]	
Previous use of taxanes or anthracyclines for metastatic or nonmetastatic disease — no. (%)	
[redacted]	
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)
[redacted]	

Source: Bardia, A., Mayer, I. A., Vahdat, L. T., Tolaney, S. M., Isakoff, S. J., Diamond, J. R., … Kalinsky, K. (2019). Sacituzumab Govitecan-hziy in Refractory Metastatic Triple-Negative Breast Cancer. New England Journal of Medicine, 380(8), 741–751.

Adverse Events

Table 2. Summary of Adverse Events in Patients Receiving Sacituzumab Govitecan-hziy.*

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
[redacted]			
Vomiting	53 (49)	7 (6)	0
Constipation	37 (34)	1 (1)	0
Abdominal pain†	27 (25)	1 (1)	0
Mucositis‡	15 (14)	0	0
General disorders and administration-site conditions	82 (76)	10 (9)	0
Fatigue and asthenia	59 (55)	9 (8)	0
Peripheral edema	17 (16)	0	0
Pyrexia	13 (12)	0	0
Blood and lymphatic system disorders	80 (74)	25 (23)	15 (14)
[redacted]			

Source: Bardia, A., Mayer, I. A., Vahdat, L. T., Tolaney, S. M., Isakoff, S. J., Diamond, J. R., … Kalinsky, K. (2019). Sacituzumab Govitecan-hziy in Refractory Metastatic Triple-Negative Breast Cancer. New England Journal of Medicine, 380(8), 741–751.

Results

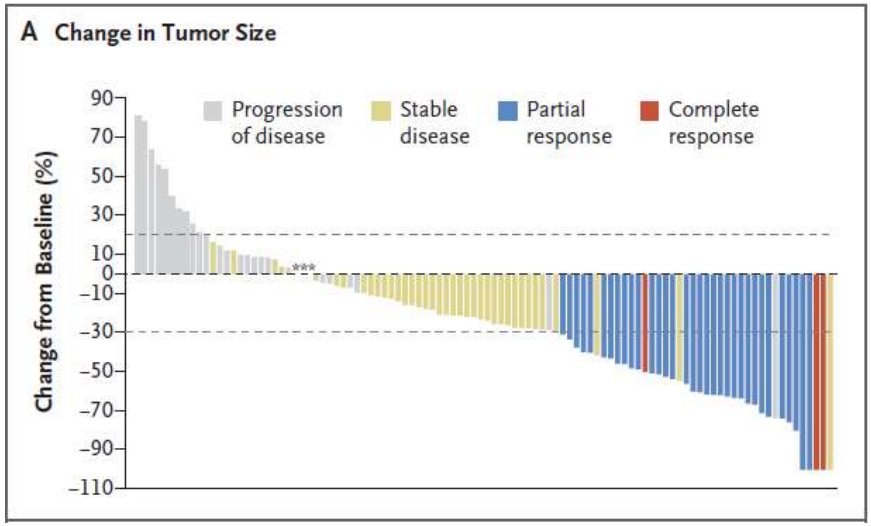
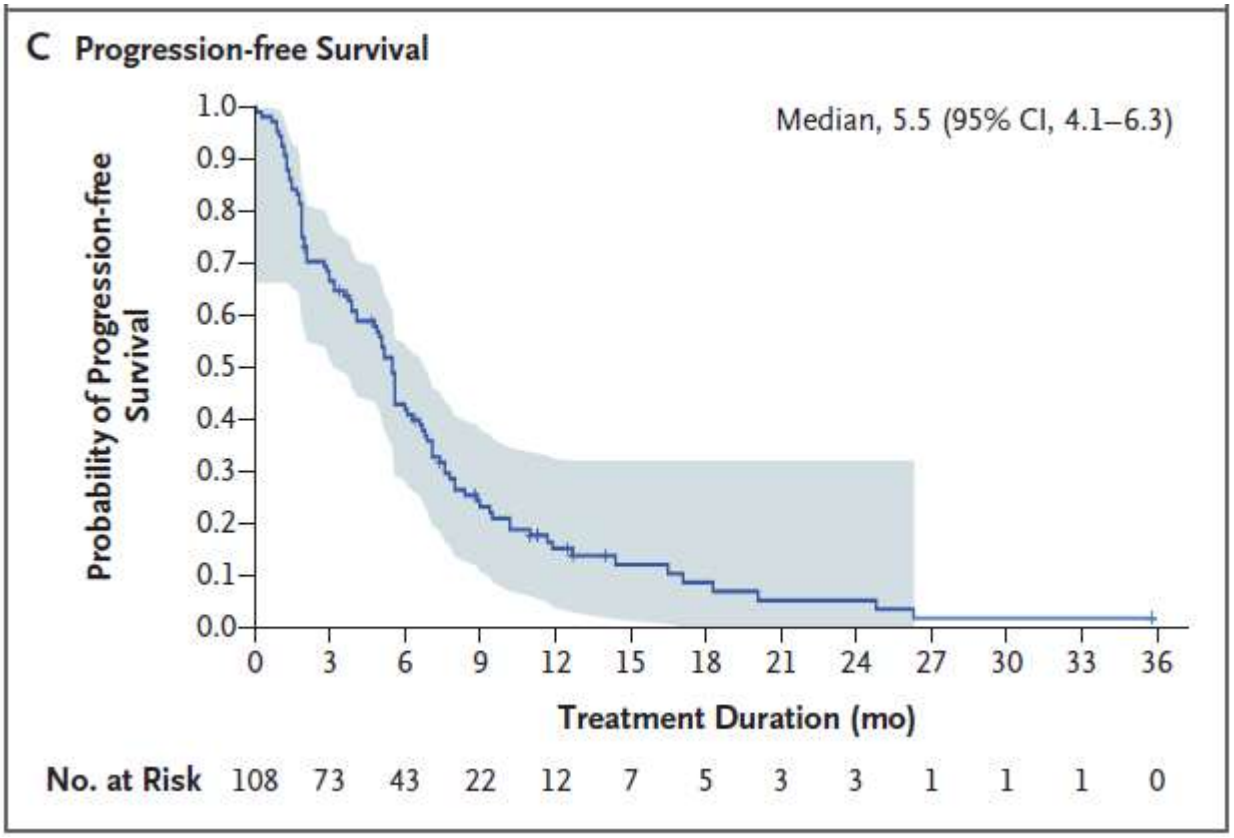


Table 3. Summary of Treatment Efficacy, According to Local Assessment.

Variable	Patients (N=108)
[redacted]	
Stable disease — no. of patients (%)	40 (37.0)
Progressive disease — no. of patients (%)	28 (25.9)
Not evaluated — no. of patients (%)*	4 (3.7)
[redacted]	

Source: Bardia, A., Mayer, I. A., Vahdat, L. T., Tolaney, S. M., Isakoff, S. J., Diamond, J. R., … Kalinsky, K. (2019). Sacituzumab Govitecan-hziy in Refractory Metastatic Triple-Negative Breast Cancer. New England Journal of Medicine, 380(8), 741–751.

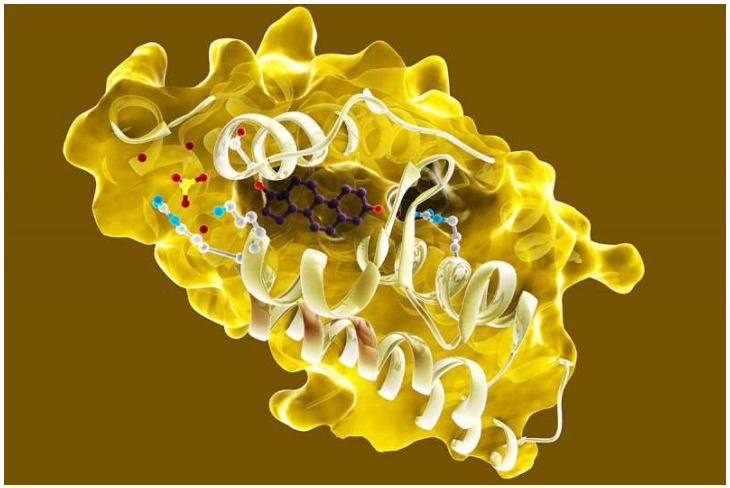

C Progression-free Survival
Median, 5.5 (95% CI, 4.1–6.3)
Probability of Progression-free Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 3 6 9 12 15 18 21 24 27 30 33 36
Treatment Duration (mo)
No. at Risk 108 73 43 22 12 7 5 3 3 1 1 1 0

Summary

- Sacituzumab govitecan-hziy – novel MOA with efficacy in heavily pretreated TNBC
  - ORR 33.3%
  - Median PFS 5.5 months
- Adverse events- myelotoxic, GI

Sacituzumab govitecan-hziy

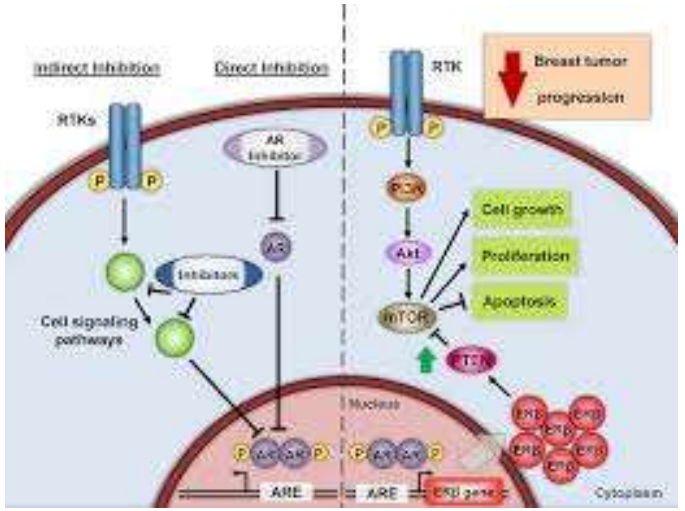
- FDA rejected in Jan 2019
  - Manufacturing facility issues
  - Immunomedics management change
- Ongoing phase III trial
  - FDA to wait on these results?



Androgen Receptor

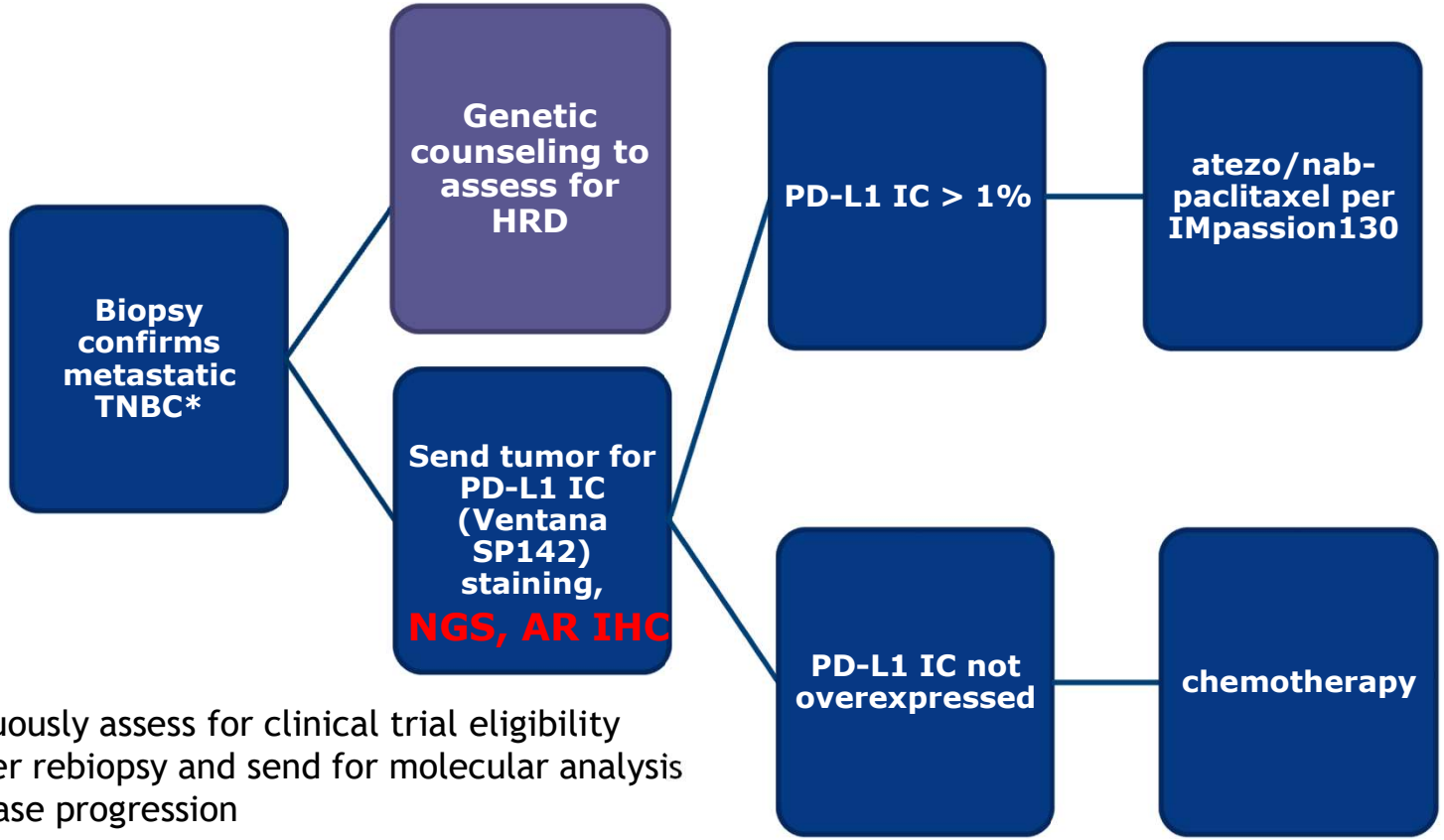
Androgen Receptor (AR) in Breast Cancer

- Steroid hormone
  - Expression can be ID'd by immunohistochemistry (IHC)
- Up regulated in 30% of TNBC- higher expression correlates to higher response?
- Multiple phase I and II trials
  - 20% responded to anti-androgen therapy
    - Durable responses (up to years)
  - Bicalutamide/Enzalutamide
- Combination therapy
  - GTx-024 (enobosarm) and pembrolizumab in AR+ TNBC
    - clinical activity to warrant ongoing investigation



Source: Is androgen receptor targeting an emerging treatment strategy for triple negative breast cancer? Anestis, Aristomenis et al. Cancer Treatment Reviews, Volume 41, Issue 6, 547 – 553.
Source: A phase II clinical trial of pembrolizumab and selective androgen receptor modulator GTx-024 in patients with advanced androgen receptor-positive triple-negative breast cancer. Jin Sun Lee-Bitar, Paul Henry Frankel, Susan Elaine Yost, Timothy W. Synold, Norma Martinez, Aileen Tang, Dan Schmolze, Sophia Apple, Arti Hurria, James Ross Waisman, George Somlo, Niki Tank Patel, Mina S. Sedrak, Joanne E. Mortimer, and Yuan Yuan Journal of Clinical Oncology 2019 37:15_suppl, 1069-1069.

Therapeutic Algorithm in TNBC



- ✓ Continuously assess for clinical trial eligibility
- ✓ Consider rebiopsy and send for molecular analysis at disease progression

Summary

- Highly heterogeneous disease
- PD-L1 IC staining up front in metastatic setting as well as NGS
- Genetic testing for HRD
- Clinical trial whenever possible

Questions?