Advances in the Treatment of Triple-Negative Metastatic Breast Cancer

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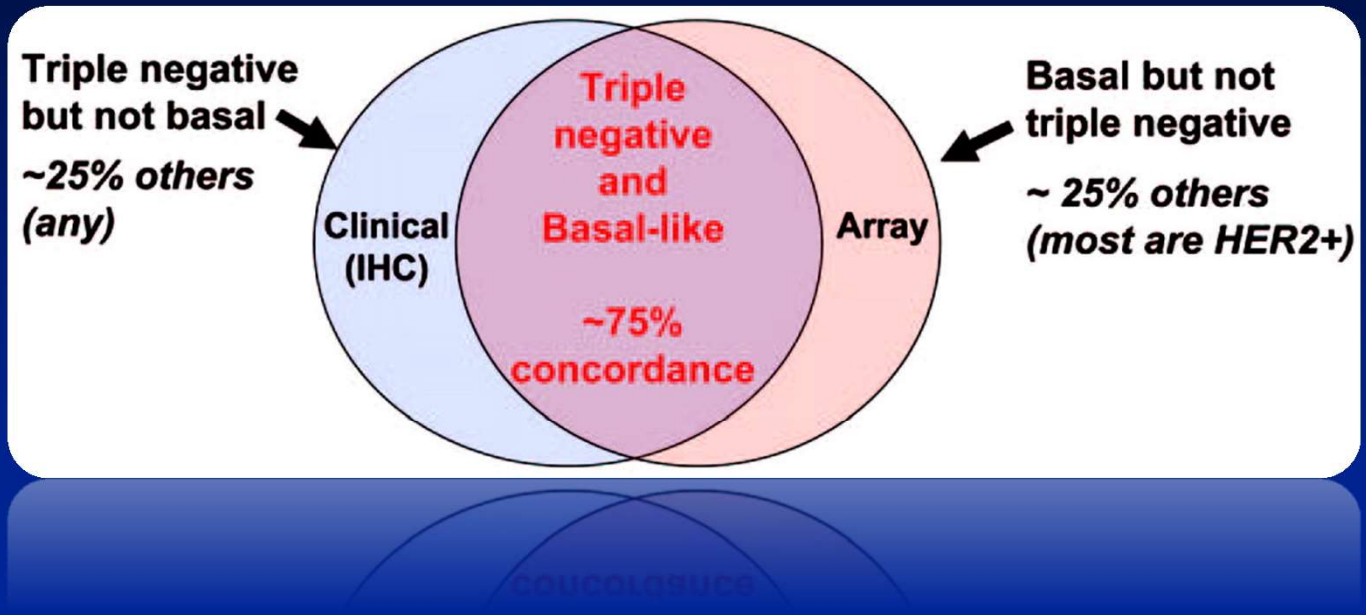
Who gets triple negative breast cancer?

- 15% of patients in the US
- Young women
- African American women
- BRCA1 positive

(Any woman can get any type of breast cancer)

Triple-negative phenotype and molecular sybtypes.



Carey L A The Oncologist 2010;15:49-56

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2019
Invasive Breast Cancer

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SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV (M1) DISEASE: ER AND/OR PR NEGATIVE; HER2 NEGATIVE[d]

Chemotherapy[ooo] until progression or unacceptable toxicity[nnn,ppp] → Another line of chemotherapy → Most patients will be candidates for multiple lines of systemic therapy to palliate advanced breast cancer. At each reassessment clinicians should assess value of ongoing treatment, the risks and benefits of an additional line of chemotherapy, patient performance status, and patient preferences through a shared decision-making process. → Consider no further cytotoxic therapy[rrr] and continue supportive care See NCCN Guidelines for Palliative Care and NCCN Guidelines for Supportive Care

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Discussion

CHEMOTHERAPY REGIMENS FOR RECURRENT OR STAGE IV (M1) DISEASE[a,b]

HER2-Negative

Preferred regimens

- Anthracyclines
  - Doxorubicin
  - Liposomal doxorubicin
- Taxanes
  - Paclitaxel
- Anti-metabolites
  - Capecitabine
  - Gemcitabine
- Microtubule inhibitors
  - Vinorelbine
  - Eribulin
- PARP inhibitors (options for patients with HER2-negative tumors and germline *BRCA1/2* mutation)[d]
  - Olaparib[d] (category 1)
  - Talazoparib[d] (category 1)
- Platinum (option for patients with triple-negative tumors and germline *BRCA1/2* mutation)[d]
  - Carboplatin
  - Cisplatin
- Atezolizumab + albumin-bound paclitaxel (option for patients with PD-L1-positive TNBC)[e]

Other recommended regimens[c]

- Cyclophosphamide
- Docetaxel
- Albumin-bound paclitaxel
- Epirubicin
- Ixabepilone

Useful in certain circumstances[c]

- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)
- Gemcitabine/carboplatin
- Paclitaxel/bevacizumab[f]

HER2-Positive[g]

Preferred regimens

- Pertuzumab + trastuzumab + docetaxel (category 1)[h]
- Pertuzumab + trastuzumab + paclitaxel[g]

Other recommended regimens:

- Ado-trastuzumab emtansine (T-DM1)
- Trastuzumab + paclitaxel[h] ± carboplatin
- Trastuzumab + docetaxel[h]
- Trastuzumab + vinorelbine[h]
- Trastuzumab + capecitabine
- Lapatinib + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents[h,i,j]

[f] Randomized clinical trials in metastatic breast cancer document that the addition of bevacizumab to some first- or second-line chemotherapy agents modestly improves time to progression and response rates but does not improve overall survival. The time-to-progression impact may vary among cytotoxic agents and appears greatest with bevacizumab in combination with weekly paclitaxel.

[g] Trastuzumab and hyaluronidase-oysk injection for subcutaneous use may be substituted for trastuzumab. It has different dosage and administration instructions compared to intravenous trastuzumab. Do not substitute trastuzumab and hyaluronidase-oysk for or with ado-trastuzumab emtansine.

Drugs

Approved Drugs

Hematology/Oncology (Cancer) Approvals & Safety Notifications

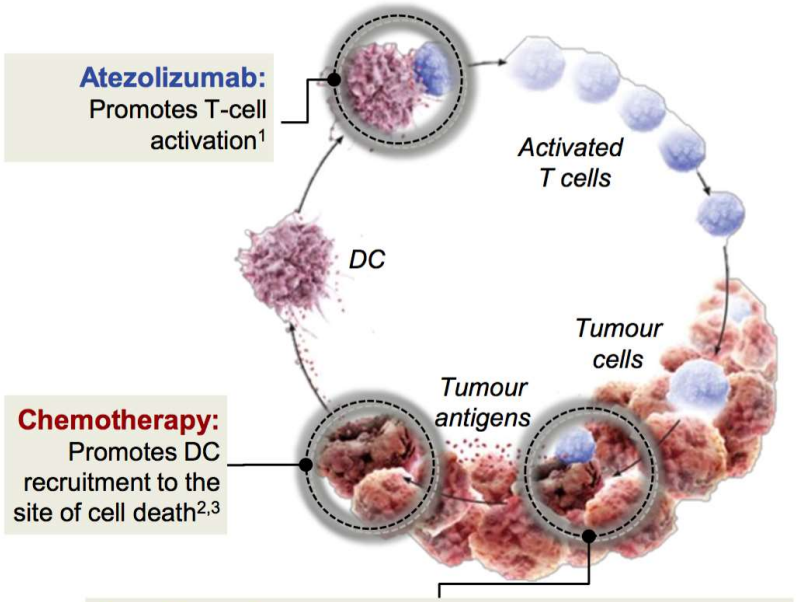
Drug Information Soundcast in Clinical Oncology (D.I.S.C.O.)

Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)

FDA approves atezolizumab for PD-L1 positive unresectable locally advanced or metastatic triple-negative breast cancer

On March 8, 2019, the Food and Drug Administration granted accelerated approval to atezolizumab (TECENTRIQ, Genentech Inc.) in combination with paclitaxel protein-bound for adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] of any intensity covering ≥ 1% of the tumor area), as determined by an FDA-approved test.

Atezolizumab and chemotherapy



- Atezolizumab (anti–PD-L1) monotherapy is approved in the United States, Europe and elsewhere for certain types of metastatic urothelial carcinoma and lung cancer[4]
- In a Phase I study, atezolizumab monotherapy was active in multiple cancers, including TNBC,[5,6] with greater activity in patients whose tumours had PD-L1 IC ≥ 1%[6]
- The addition of chemotherapy can enhance atezolizumab's anti-tumour activity[7,8]
  - In a Phase Ib study in mTNBC, concurrent administration of *nab*-paclitaxel did not inhibit atezolizumab-mediated immunodynamic effects[8]

DC, dendritic cell.
1. Chen *Immunity* 2013. 2. Zitvogel *Immunity* 2013. 3. Emens *CIR* 2015. 4. TECENTRIQ US PI/SmPC 2018. 5. Herbst *Nature* 2014.
6. Emens *JAMA Oncol* 2018. 7. Jotte ASCO 2018. 8. Pohlmann AACR 2018.

Schmid P, et al. IMpassion13
ESMO 2018 (LBA1_PR
http://bit.ly/2DMhay

IMpassion130 study design

Key IMpassion130 eligibility criteria[a]:

- Metastatic or inoperable locally advanced TNBC
  - Histologically documented[b]
- No prior therapy for advanced TNBC
  - Prior chemo in the curative setting, including taxanes, allowed if TFI ≥ 12 mo
- ECOG PS 0-1

Stratification factors:

- Prior taxane use (yes vs no)
- Liver metastases (yes vs no)
- PD-L1 status on IC (positive [≥ 1%] vs negative [< 1%])[c]

R 1:1

Atezo + nab-P arm:

Atezolizumab 840 mg IV
- On days 1 and 15 of 28-day cycle

+ *nab*-paclitaxel 100 mg/m^2 IV
- On days 1, 8 and 15 of 28-day cycle

Double blind; no crossover permitted

Plac + nab-P arm:

Placebo IV
- On days 1 and 15 of 28-day cycle

+ *nab*-paclitaxel 100 mg/m^2 IV
- On days 1, 8 and 15 of 28-day cycle

RECIST v1.1
PD or toxicity

- Co-primary endpoints were PFS and OS in the ITT and PD-L1+ populations[d]
  - Key secondary efficacy endpoints (ORR and DOR) and safety were also evaluated

IC, tumour-infiltrating immune cell; TFI, treatment-free interval. [a] ClinicalTrials.gov: NCT02425891. [b] Locally evaluated per ASCO–College of American Pathologists (CAP) guidelines. [c] Centrally evaluated per VENTANA SP142 IHC assay (double blinded for PD-L1 status). [d] Radiological endpoints were investigator assessed (per RECIST v1.1).

Schmid P, et al. IMpassion130 ESMO 2018 (LBA1_PR) http://bit.ly/2DMhayg

IMpassion130 baseline characteristics

Characteristic	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
Median age (range), y	55 (20-82)	56 (26-86)
Female, n (%)	448 (99%)	450 (100%)
Race, n (%)[a]		
White	308 (68%)	301 (67%)
Asian	85 (19%)	76 (17%)
Black/African American	26 (6%)	33 (7%)
Other/multiple	20 (4%)	26 (6%)
ECOG PS, n (%)[b,c]		
0	256 (57%)	270 (60%)
1	193 (43%)	179 (40%)
Prior (neo)adjuvant treatment, n (%)	284 (63%)	286 (63%)
Prior taxane	231 (51%)	230 (51%)
Prior anthracycline	243 (54%)	242 (54%)

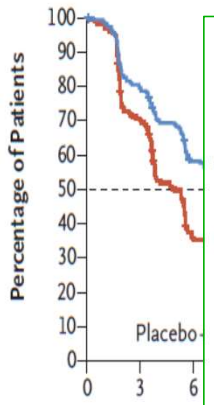
Characteristic	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
Metastatic disease, n (%)	404 (90%)	408 (91%)
No. of sites, n (%)[d]		
0-3	332 (74%)	341 (76%)
≥ 4	118 (26%)	108 (24%)
Site of metastatic disease, n (%)		
Lung	226 (50%)	242 (54%)
Bone	145 (32%)	141 (31%)
Liver	126 (28%)	118 (26%)
Brain	30 (7%)	31 (7%)
Lymph node only[d]	33 (7%)	23 (5%)
PD-L1+ (IC), n (%)	185 (41%)	184 (41%)

Data cutoff: 17 April 2018. [a] Race was unknown in 12 patients in the Atezo + nab-P arm and 15 in the Plac + nab-P arm. [b] Of n = 450 in each arm. [c] ECOG PS before start of treatment was 2 in 1 patient per arm. [d] Of n = 450 in the Atezo + nab-P arm and n = 449 in the Plac + nab-P arm arm.

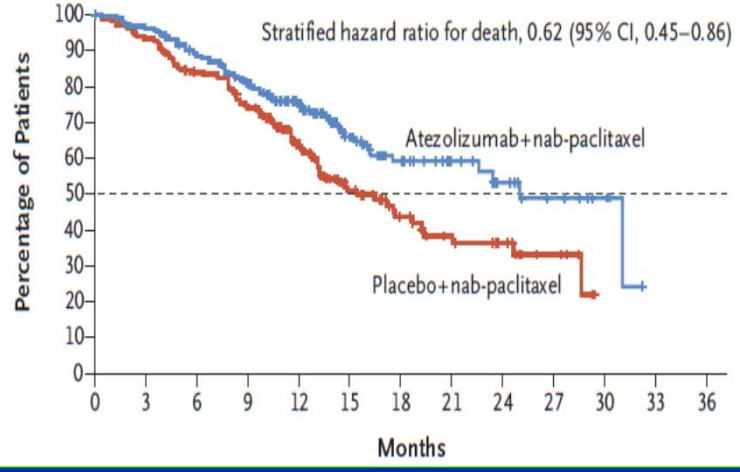
Schmid P, et al. IMpassion130 ESMO 2018 (LBA1_PR) http://bit.ly/2DMhayg

IMPASSION130: PDL1+ COHORT

	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. of Events/ No. of Patients	Median Overall Survival (95% CI)	2-Yr Rate of Progression-free 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)



Schmid P et al. NEJM 2018

IMpassion 130: Overall Survival Update

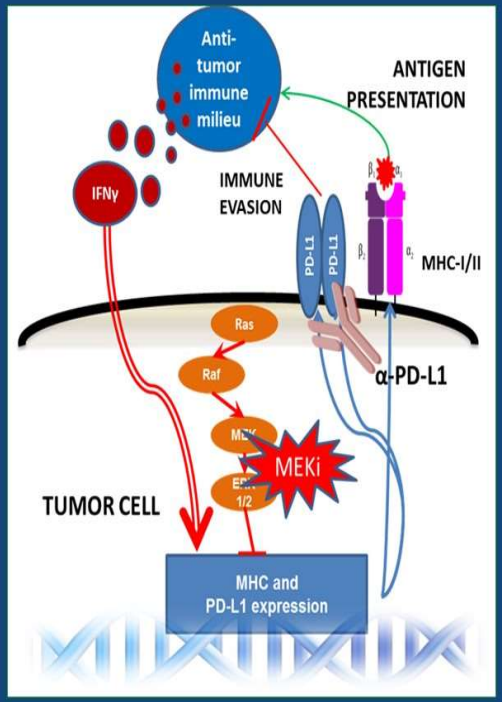
- Second interim OS analysis with median followup 18 mos with 60% of OS events
- Median OS ITT: 21 mos nP/atezo vs 18.7 mos nP/placebo
  - HR 0.86 (0.72, 1.02) p= 0.078
- PD-L1+ Median OS: 25 mos nP/atezo vs 18 mos nP/placebo
  - HR 0.71 (0.54, 0.93) 2-year OS 51% nP/atezo vs 37% nP/placebo
- Safety nP/atezo/nP/placebo: Steroid use 14%/6%; hypothyroid 18%/5%; hyperthyroid 5%/1%; pneumonitis 4%/<1%

- Clinically meaningful improvement in OS in PD-L1+ population with atezolizumab and no new safety signals/concerns

Schmid P et al. ASCO 2019 Abst 1003
Schneeweiss A et al. ASCO 2019 Abst 1068

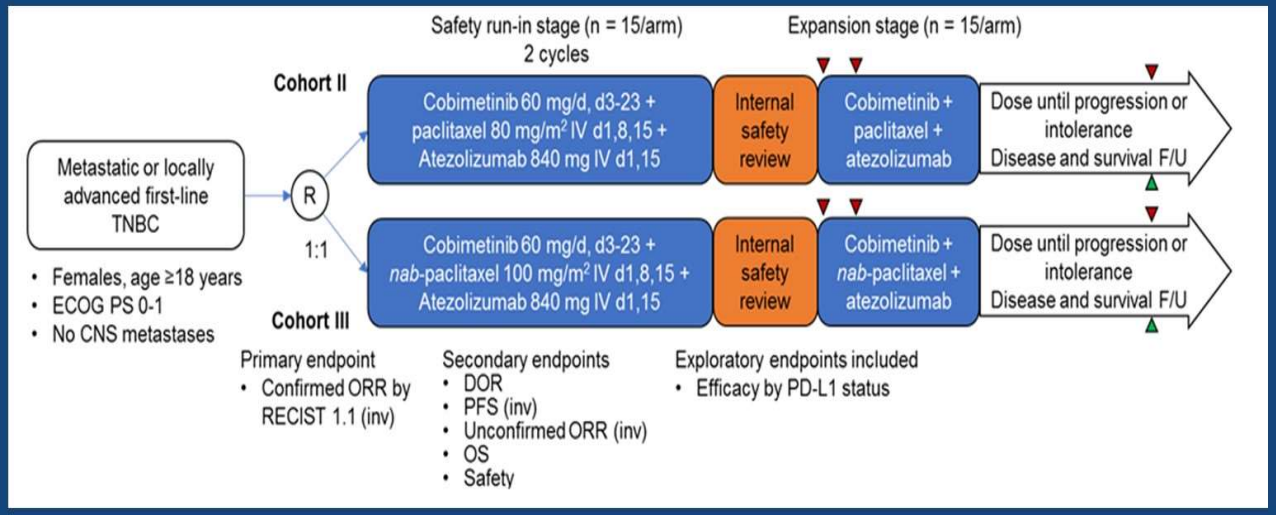
Can targeted agents improve response?

- The MEK pathway is active in TNBC
- Activation suppresses inflammatory responses to T cells, leading to reduced antigen presentation and PD-L1 expression
- Combining MEK inhibitors with anti-PD-L1 inhibitors may improve antigen presentation while blocking PD-L1-mediated suppression



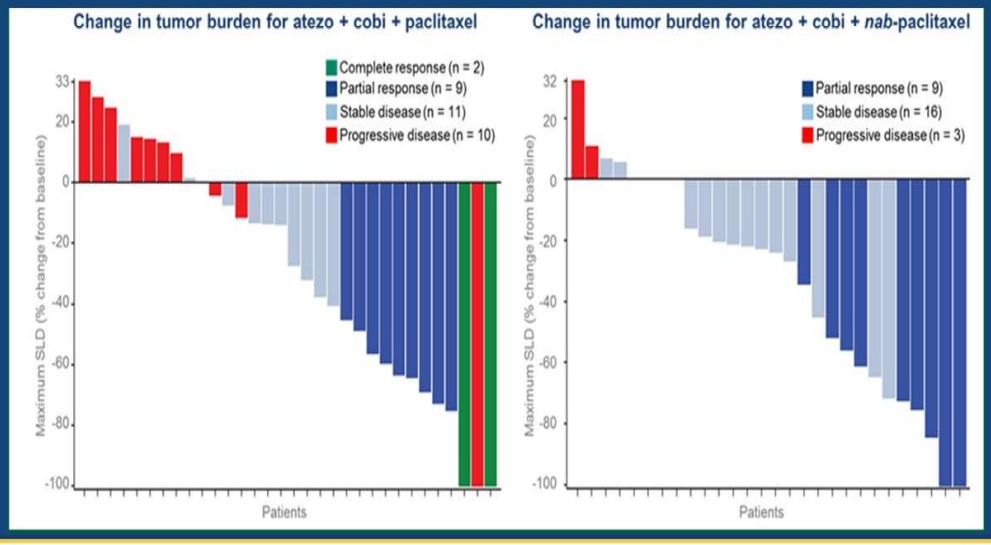
Can targeted agents improve response?

- Phase II COLET Study: Atezolizumab + Cobimetinib + Paclitaxel/*nab*-paclitaxel as First-line Treatment for Patients with Locally Advanced or Metastatic Triple-negative breast Cancer (Brufsky et al)



Phase II COLET Study: Atezolizumab + Cobimetinib + Paclitaxel/nab-paclitaxel

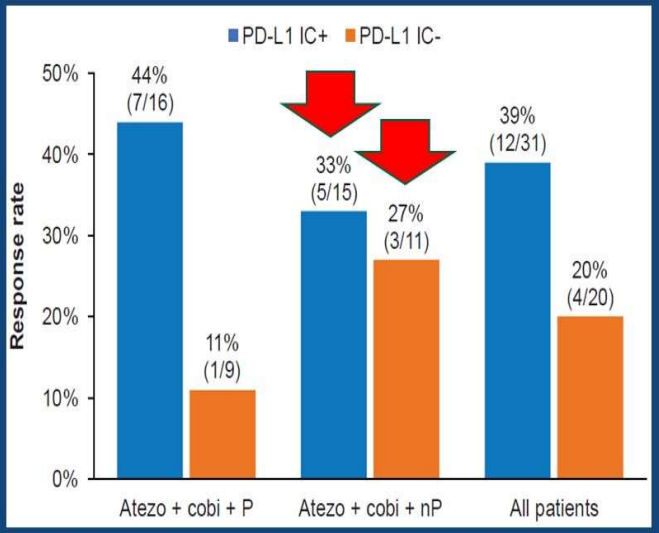
- Safety
  - 2 grade 5 events in P arm
  - Diarrhea and rash obvious changes from A + nP (i130)
- Outcomes - positive
- Comparison to IM130?



PD-L1 IC status in COLET

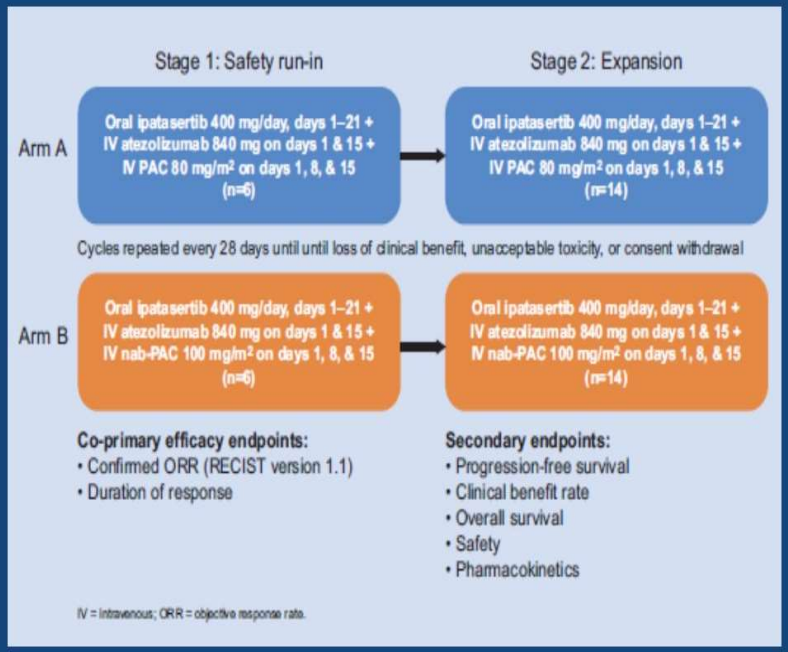
N=63

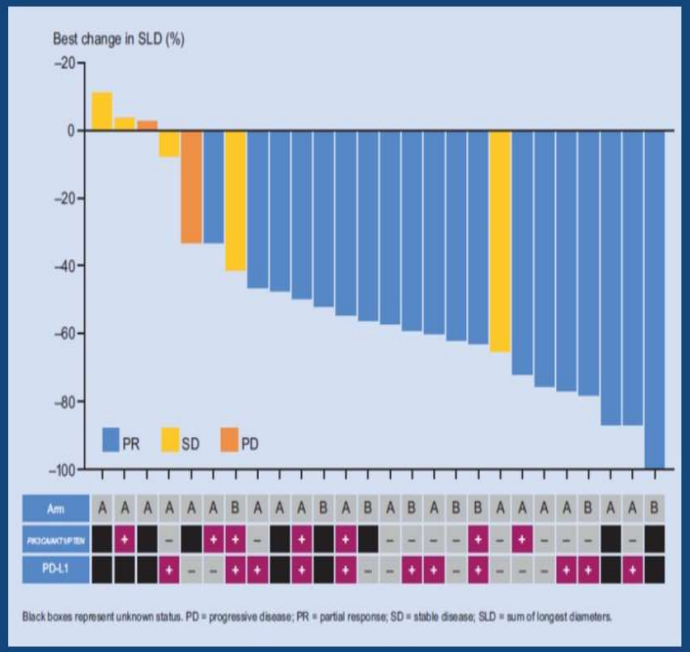
- Generally higher response rates in PD-L1 IC+ tumors
- Does MEKi enhance activity in PD-L1 IC- tumors? What about PD-L1-IC+?
- Biomarkers
  - On-therapy biopsies do not appear to have been collected
  - Open question as to whether MEKi is 'working'



6 months PFS 55% vs 20% in PDL1+ vs PDL-1-
(65% had received neo/adjuvant therapy)

MEKi versus AKTi: Phase Ib of ipatasertib, atezo and P/nab-P





Results being confirmed in IPATunity130

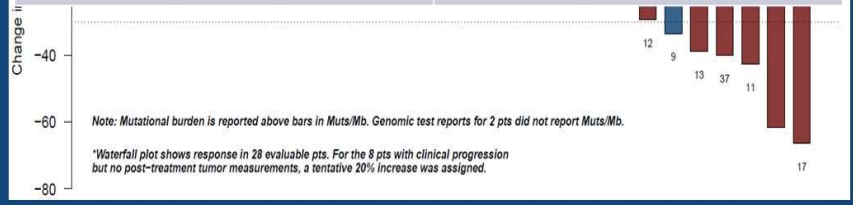
Are high TMB patients better responders to ICI?

- Pembrolizumab in Patients with Metastatic Breast Cancer with reported High TMB (TAPUR) (Alva et al)
  - Advanced MBC without standard treatment options.
  - Single-arm study (pembro).
  - High TMB – platform dependent
  - Primary endpoint is objective response (OR) or stable disease (SD) at 16+ wks.
  - Secondary endpoints are progression-free survival (PFS), overall survival (OS) and toxicity per CTCAE.

Pembrolizumab in Patients with Metastatic Breast Cancer with reported High TMB (TAPUR)

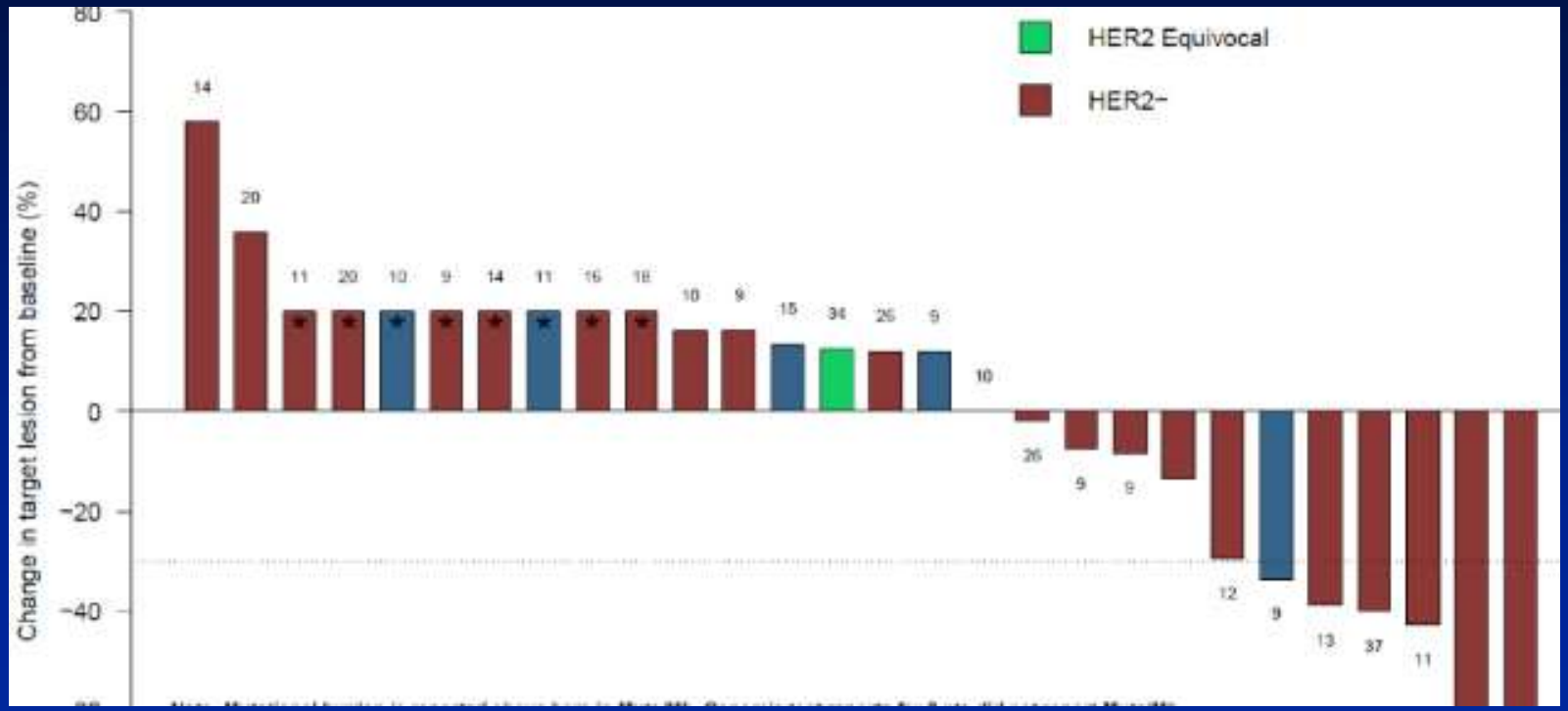
- ~10% of highest TMB mBC patients
- HR status currently unknown
- Activity, particularly in HER2- patients
- No study-internal association with TMB
- Difficult to identify a 'control'

Clinical Outcomes	
DC (OR or SD 16+wks) N (%), [90% CI]	10 (37%), [24%, 46%]
OR (CR or PR) N (%), [95% CI]	6 (21%), [8%, 41%]
mPFS, wks, (95% CI)	10.6 (7.7, 21.1)
mOS, wks, (95% CI)	31.6 (11.9, inf)



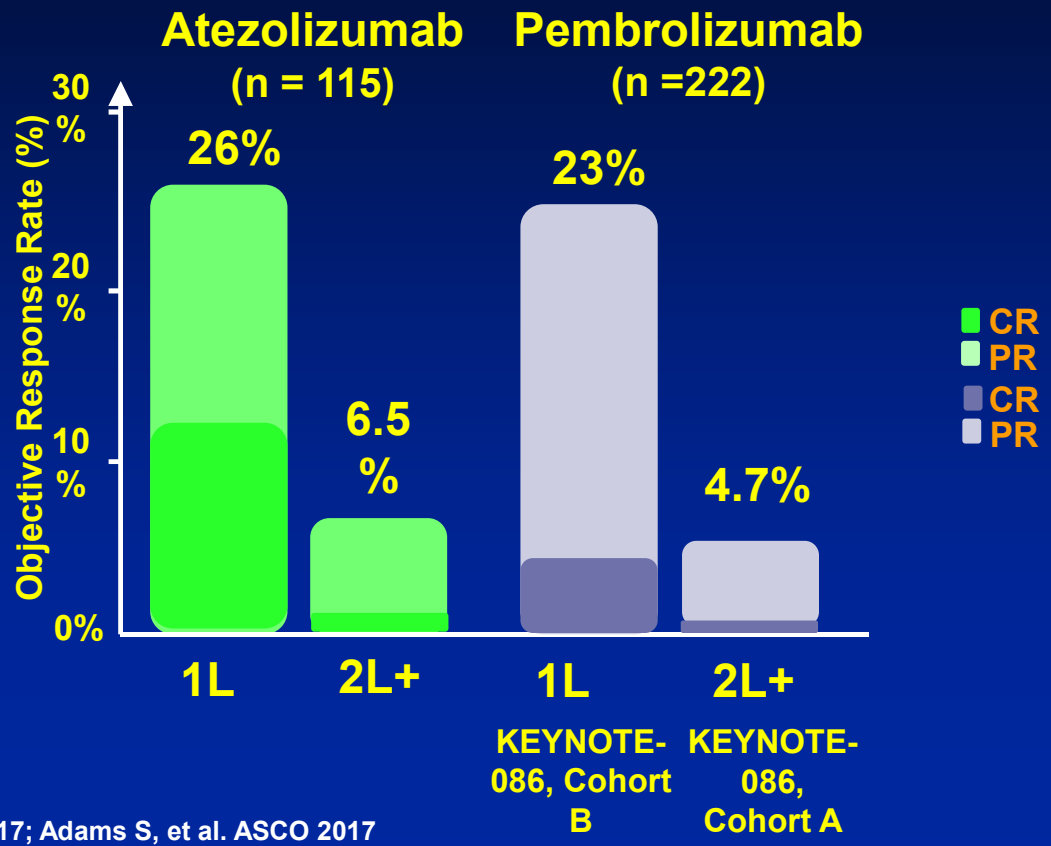
TAPUR: Percent Change in Size from Baseline

N=28



Response to single agent anti-PD-L1/PD-1

Anti-PD-L1/PD-1 single agent in mTNBC ≥1L, PD-L1+/-



Schmid P, et al. AACR 2017; Adams S, et al. ASCO 2017

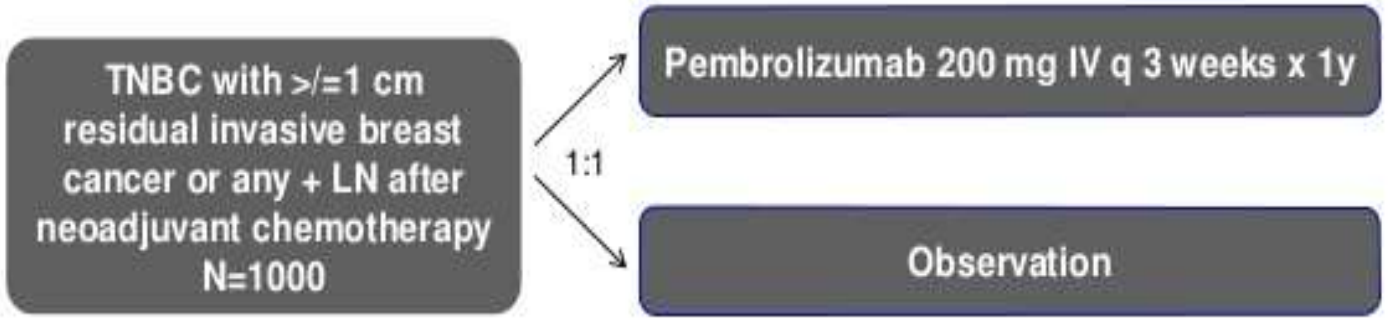
Small group of TNBC with transformative benefit but unable to define subgroup

Strategies going forward concentrating on combinations

Synergistic effect of chemotherapy and anti-PD-L1 treatment in vivo

1. Reduce T-regulatory cell activity
2. Enhance cross-presentation of tumour antigens
3. Chemo to increase tumour PD-L1 expression/infiltration of CD8+ T cells

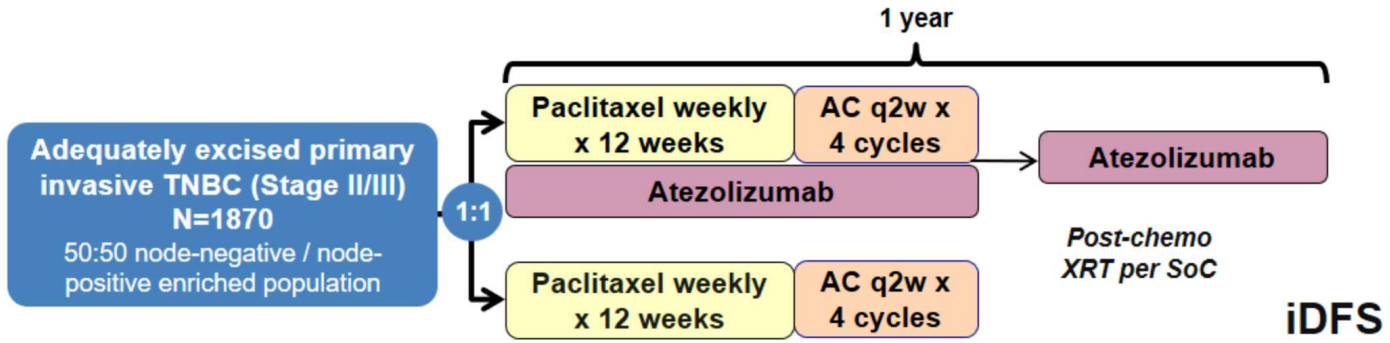
Post NAC residual disease: SWOG 1418



- **Registration:**
  - Central PD-L1 testing
- **Stratification:**
  - Nodal stage ypNo vs ypN+
  - Residual tumor ≥2 vs < 2cm
  - PD-L1 pos vs neg
  - Prior adjuvant chemo yes vs no

- **Hypothesis:**
  - Pembrolizumab reduces IDFS by 33% c/w observation alone
- **Primary Endpoint:**
  - Invasive DFS in PD-L1-positive and overall cohort
- **Secondary Endpoints:**
  - Toxicity
  - OS
  - DRFS
  - QOL (PROMIS, PRO-CTCAE forms, inflammatory markers)
  - Tissue banking

IMpassion030: Phase III randomized, open label adjuvant TNBC trial (Alliance/BIG)



Stratification factors:

- Axillary nodal status (0 vs. 1-3 vs. ≥4 positive lymph nodes)
- Surgery (breast conserving vs mastectomy)
- PD-L1 IC0 vs IC1/2/3

Primary endpoint:

- iDFS in ITT

Assumptions:

- iDFS HR=0.75
- 3-yr iDFS +4.4% *(81% ➔ 85.4%)*
- 80% power, alpha =5% (two sided)

Secondary endpoints:

- iDFS PD-L1 IC1/2/3
- OS
- Recurrence-free interval (RFI)
- Distant RFI
- Safety
- Health-related QoL

Candidate Biomarkers for Immunotherapy

Tumor antigens

- Biomarkers indicative of hypermutation & neoantigens may predict response to immuno-oncology therapies

Examples:

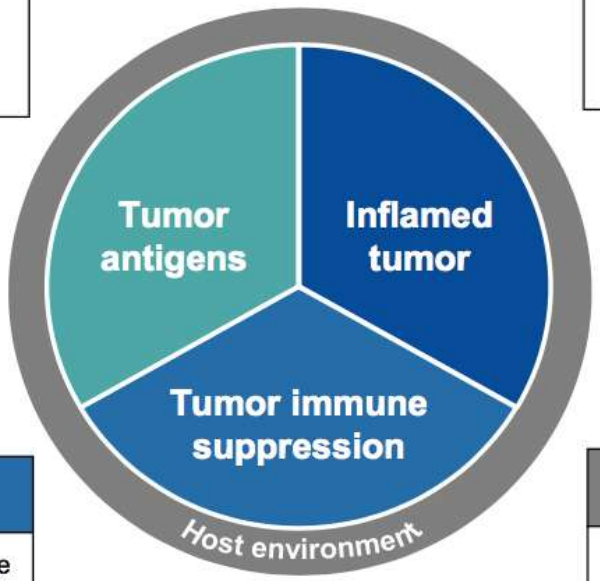
– ***TMB, MSI-high, neoantigens***

Inflamed tumor microenvironment

- Biomarkers (intra- or peri-tumoral) indicative of an inflamed phenotype may predict response to immuno-oncology therapies

Examples:

– ***PD-L1, inflammatory signatures***



Tumor immune suppression/evasion

- Biomarkers that identify tumor immune system evasion beyond PD-1/CTLA-4 to inform new immuno-oncology targets and rational combinations

Examples:

– ***Tregs, MDSCs, IDO, LAG-3***

Host environment

- Biomarkers that characterize the host environment, beyond tumor microenvironment, may predict response to immuno-oncology therapies

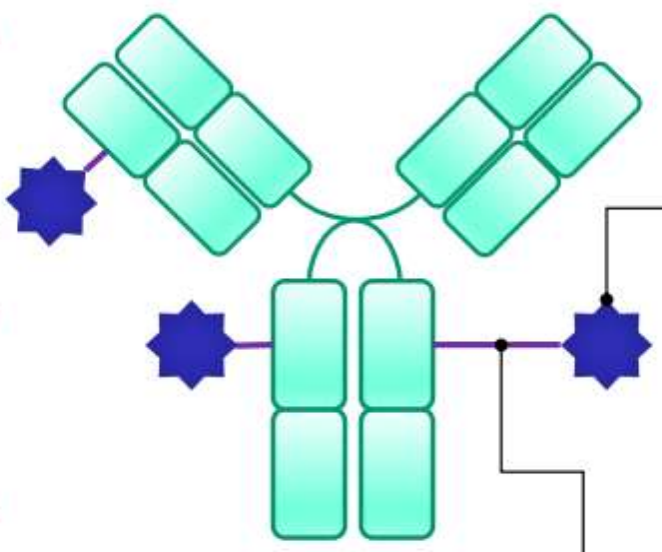
Examples:

– ***Microbiome, germline genetics***

Adapted from Blank CU, et al. Science 2016;352:658-660; Presented by Peters S. et al. AACR 2017

Antibody-Drug Conjugates (ADCs)

Components of ADC



Antibody

- High affinity and specificity to tumor antigen
- Efficient internalization
- Reduced immunogenicity

Payload

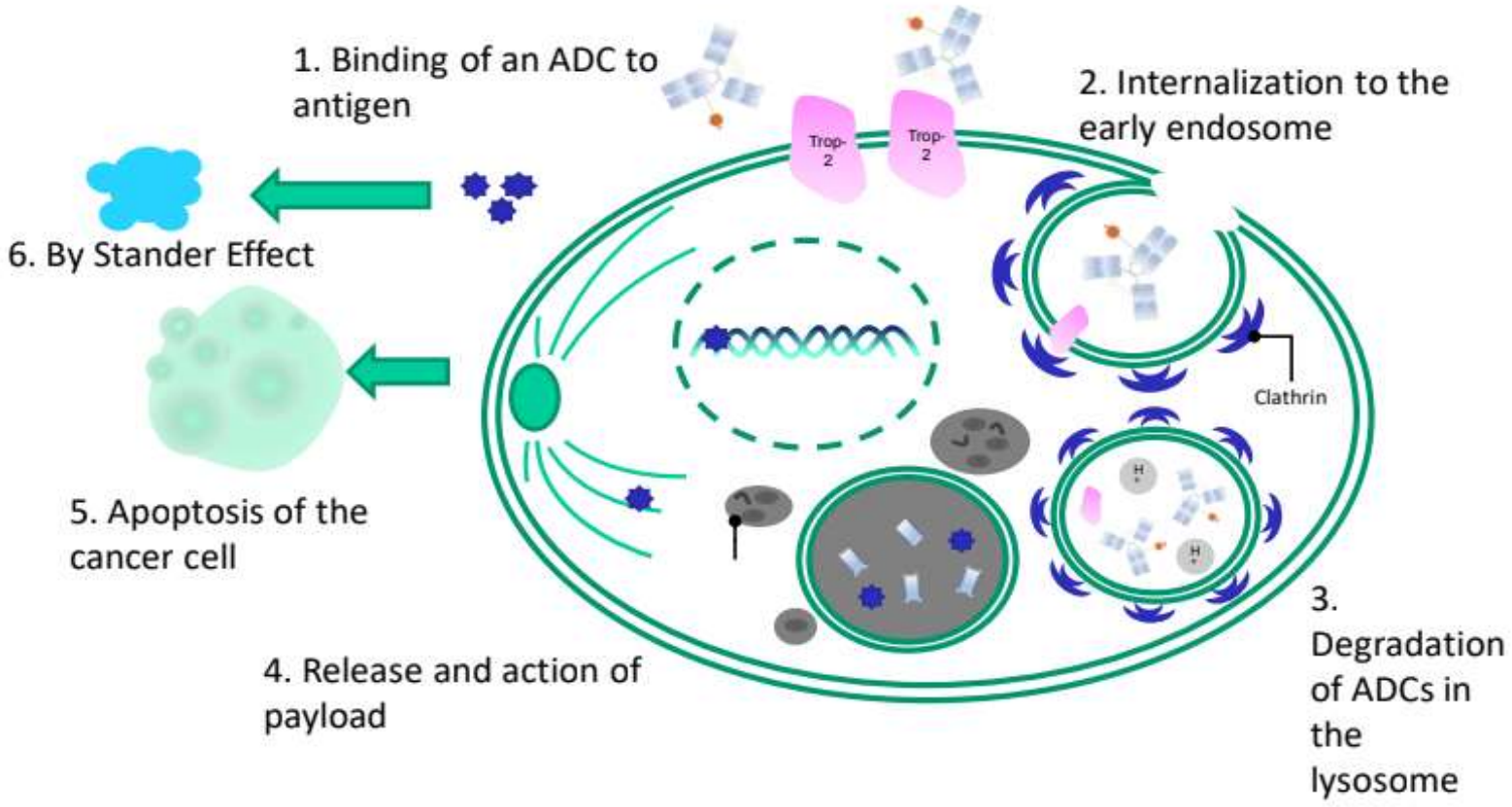
- Highly potent
- Microtubule inhibitors
  - Auristatins
  - Maytansines
- DNA damaging agents
  - Calicheamicin
  - Duocarmycins
  - SN-38

Linker

- Stable in the blood stream
- Capable of releasing payload once internalized
- Cleavable linker
- Non-cleavable linker

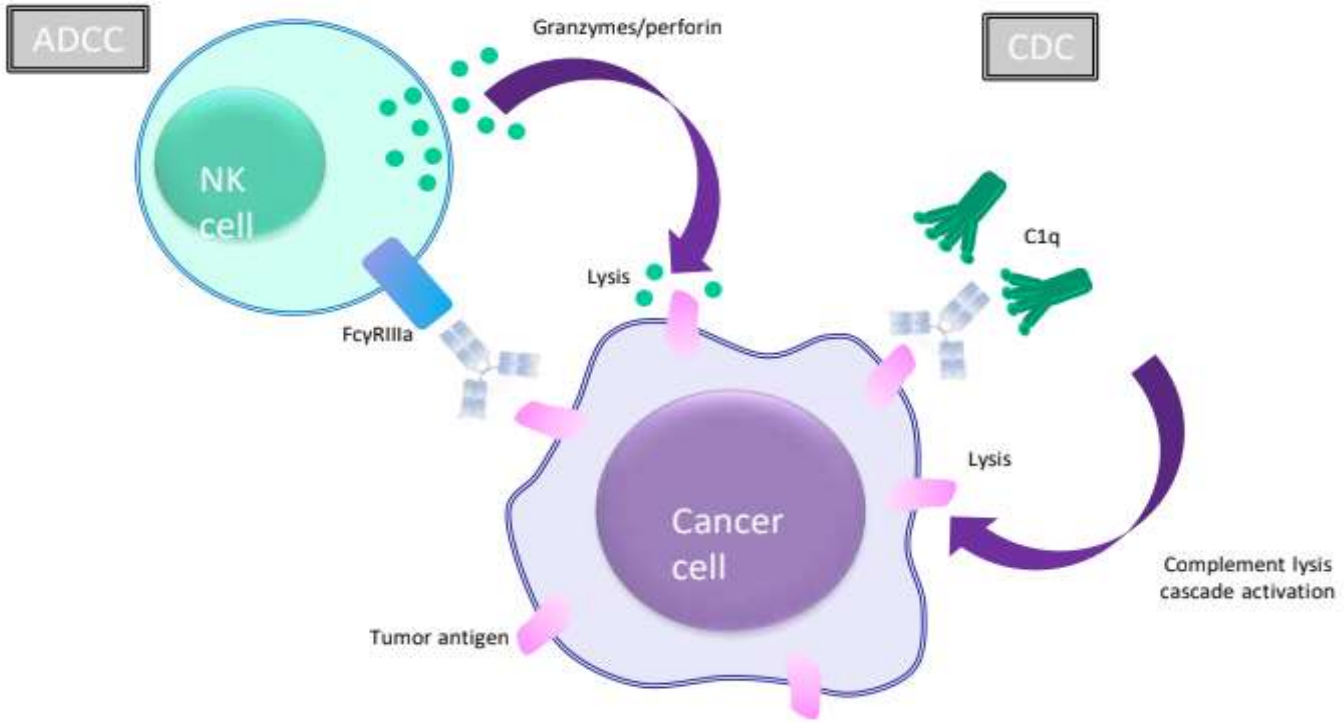
Nagayama, A, Ellisen L, Chabner B, Bardia A. Target Oncol. 2017

Selective Delivery of Toxic Payload



Nagayama, A, Ellisen L, Chabner B, Bardia A. Target Oncol. 2017

Another Mechanism of Action: Activation of ADCC?



Nagayama, A, Ellisen L, Chabner B, Bardia A. Target Oncol. 2017

Sacituzumab Govitecan (IMMU132): ADC Targeting *trop-2* in TNBC

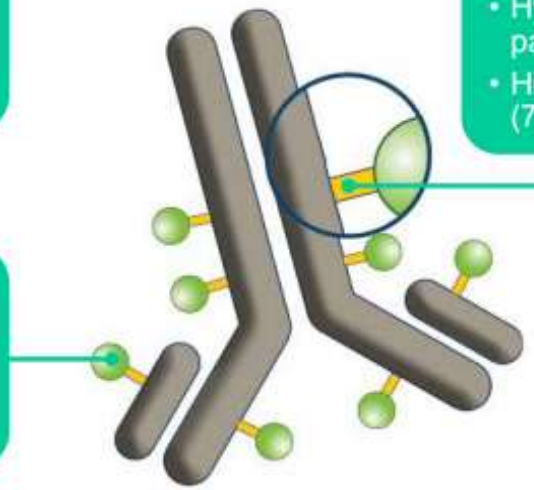
Sacituzumab Govitecan: ADC

Humanized anti-Trop-2 antibody

- Targets Trop-2, an epithelial antigen expressed on many solid cancers, including mTNBC

Linker for SN-38

- Hydrolysable linker for payload release
- High drug-to-antibody ratio (7.5:1)



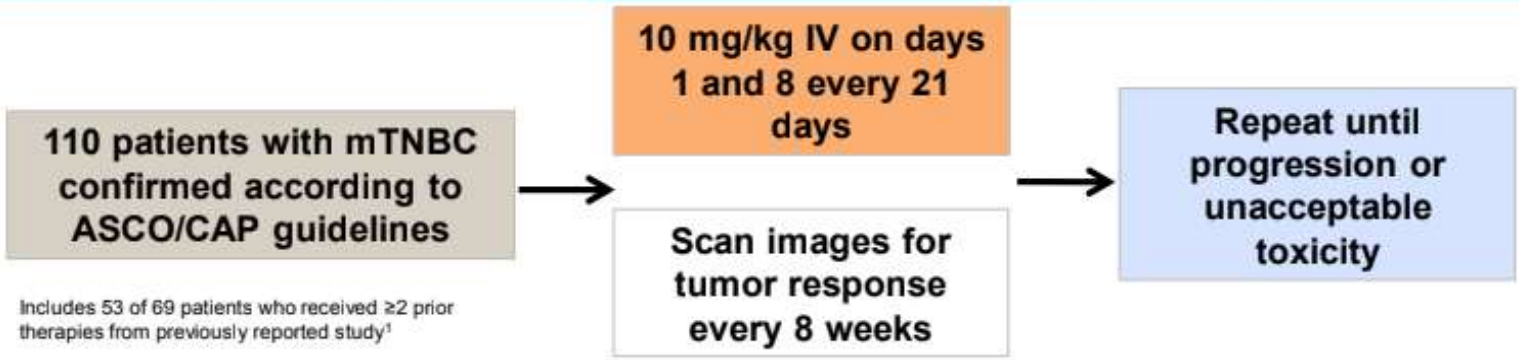
SN-38 payload

- SN-38 more potent than parent compound, irinotecan
- ADC delivers up to 136-fold more SN-38 than irinotecan *in vivo*

Bardia et al. 2017 SABCS. Abstract GS1-07.

Clinical Results in mTNBC

Single-Arm, Open-Label Study Design



Jul 2013 and Feb 2017. Data cutoff date of June 30, 2017.

Key eligibility criteria

- Female or male, ≥18 years of age, ECOG PS 0-1
- ≥2 prior therapies or >1 therapy for patients who progressed within 12 months of adjuvant therapy
- Prior taxane therapy
- Measurable disease

Evaluations

- Response evaluation by investigators
- Blinded independent central review of all CRs, PRs and ≥20% tumor reductions
- Other evaluations: safety, immunogenicity, Trop-2 expression

Bardia et al. *J Clin Oncol.* 2017.

Sacituzumab Govitecan: Demographics and Patient Characteristics

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)
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)

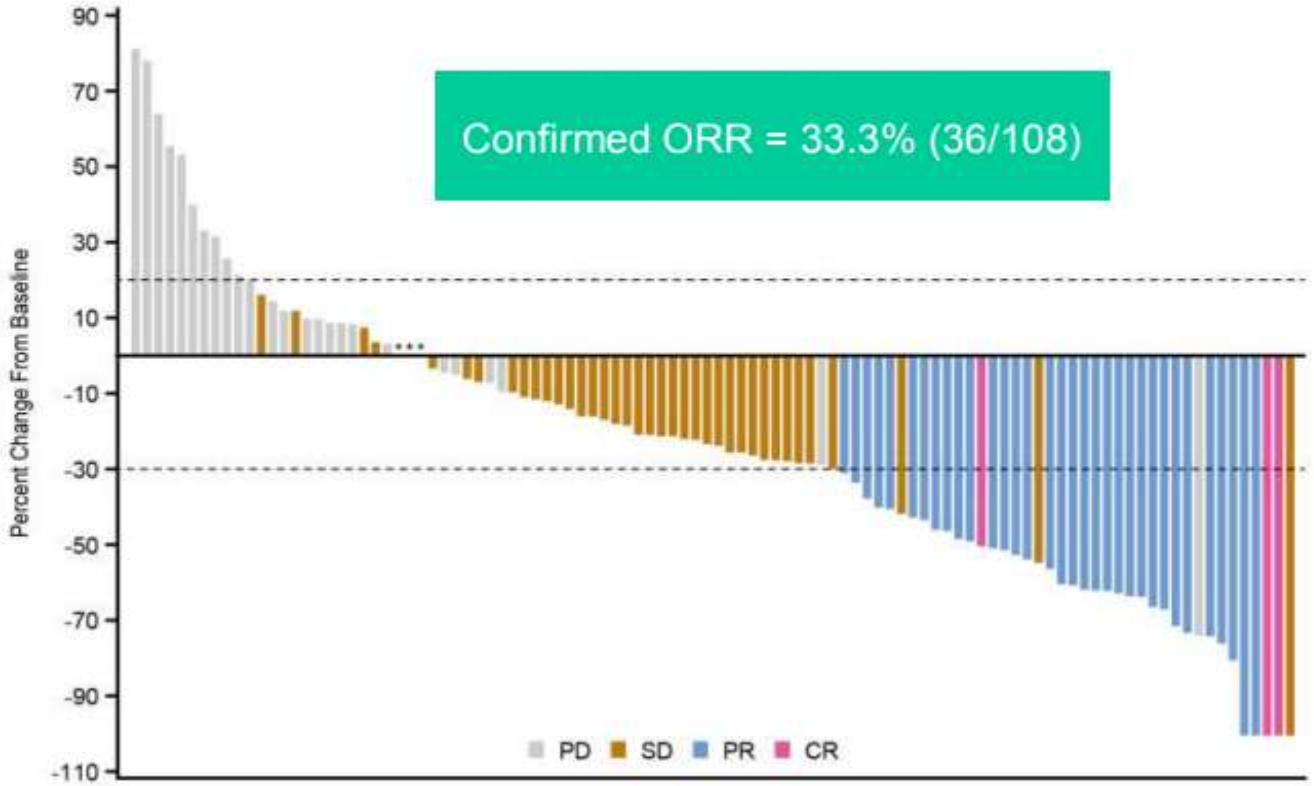
Bardia et al. *NEJM*. 2019.

Sacituzumab Govitecan: AEs in ≥10% of Patients by Worst CTCAE Grade

Adverse Event	mTNBC Population (N=108) All Grades no. (%)	Grade 3 no. (%)	Grade 4 no. (%)
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
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)
Neutropenia‡	**69 (64)**	**28 (26)**	**17 (16)**
Anemia	**54 (50)**	**12 (11)**	**0**

Bardia et al. *NEJM*. 2019.

Sacituzumab Govitecan: Tumor Response to Treatment

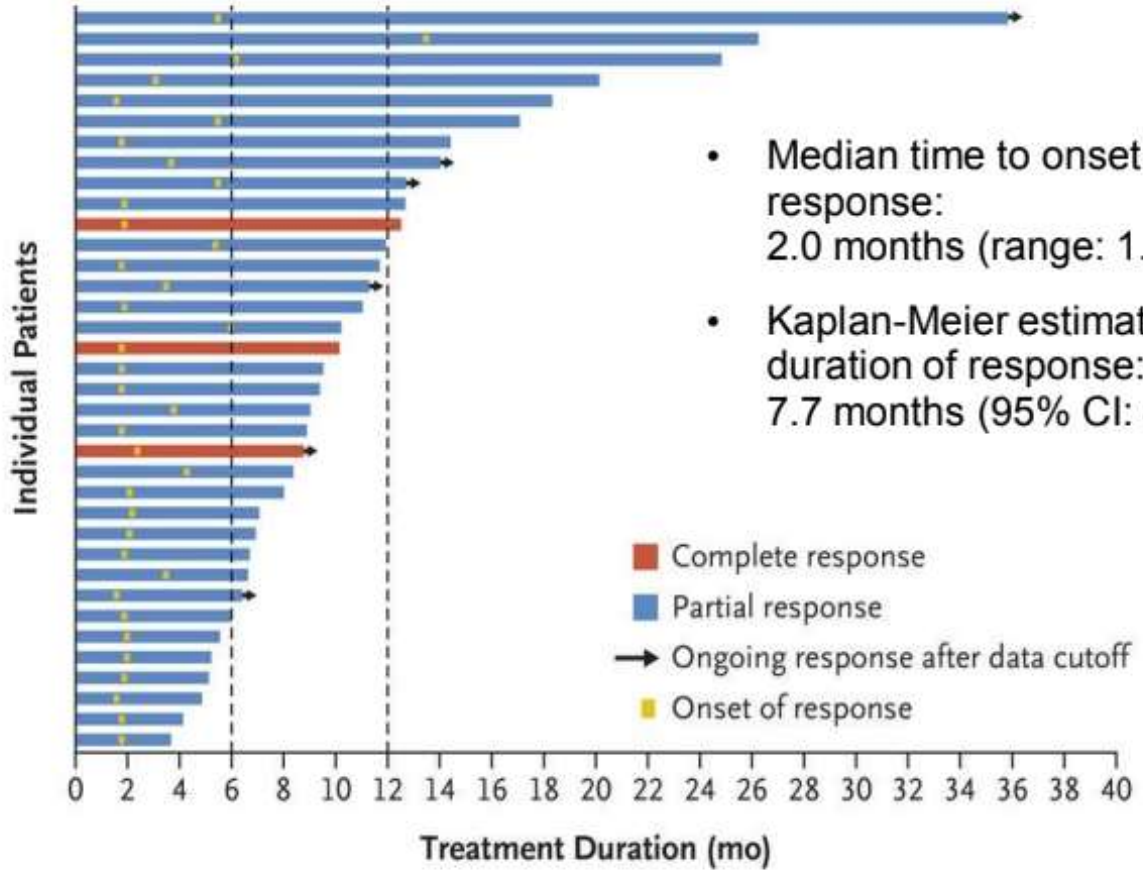


Confirmed ORR = 33.3% (36/108)

Clinical benefit rate (CR+PR+SD≥6 mo) = 45.4% (49/108)

Bardia et al. *NEJM*. 2019.

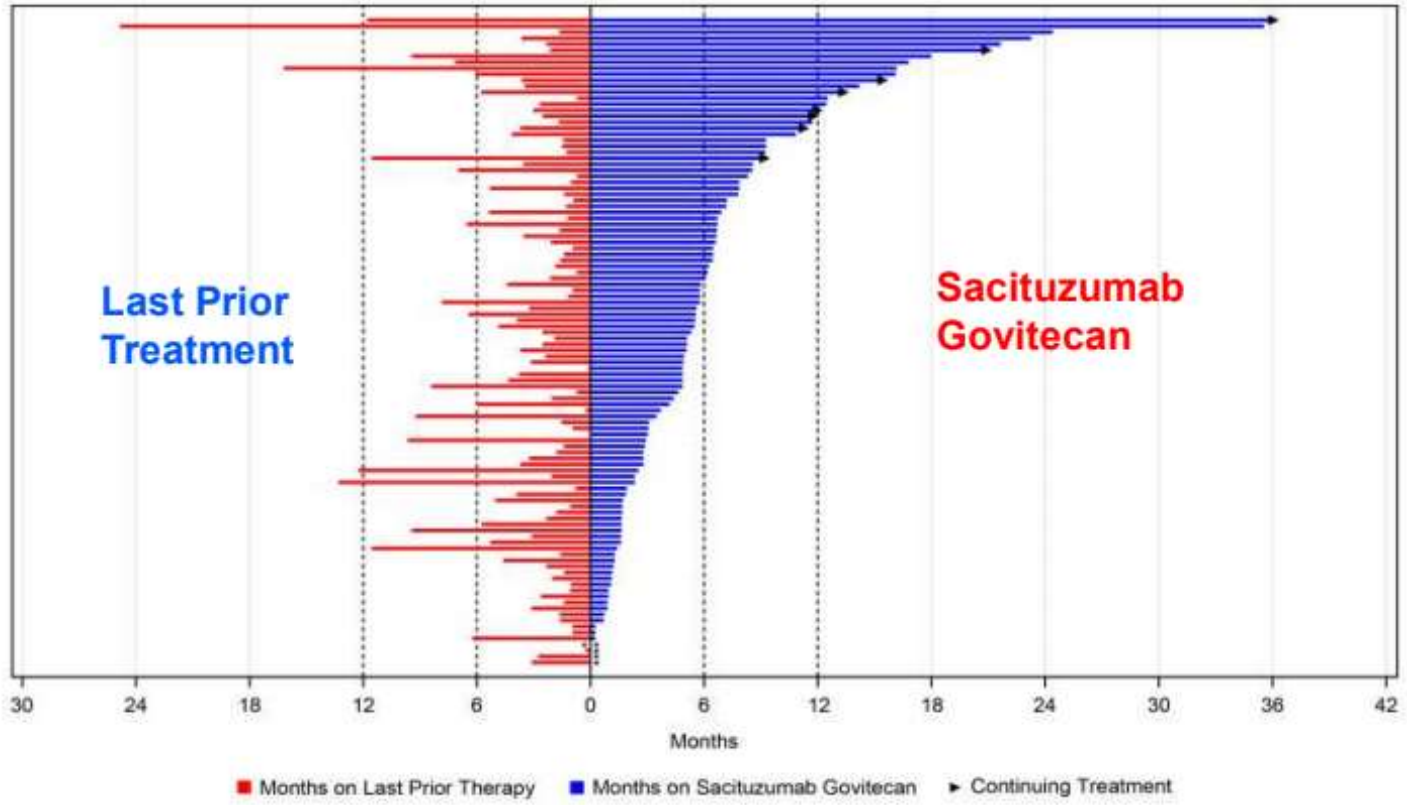
Sacituzumab Govitecan: Response Onset and Durability (n = 36)



- Median time to onset of response:
  2.0 months (range: 1.6-13.5)
- Kaplan-Meier estimated median duration of response:
  7.7 months (95% CI: 4.9, 10.8)

Bardia et al. *NEJM*. 2019.

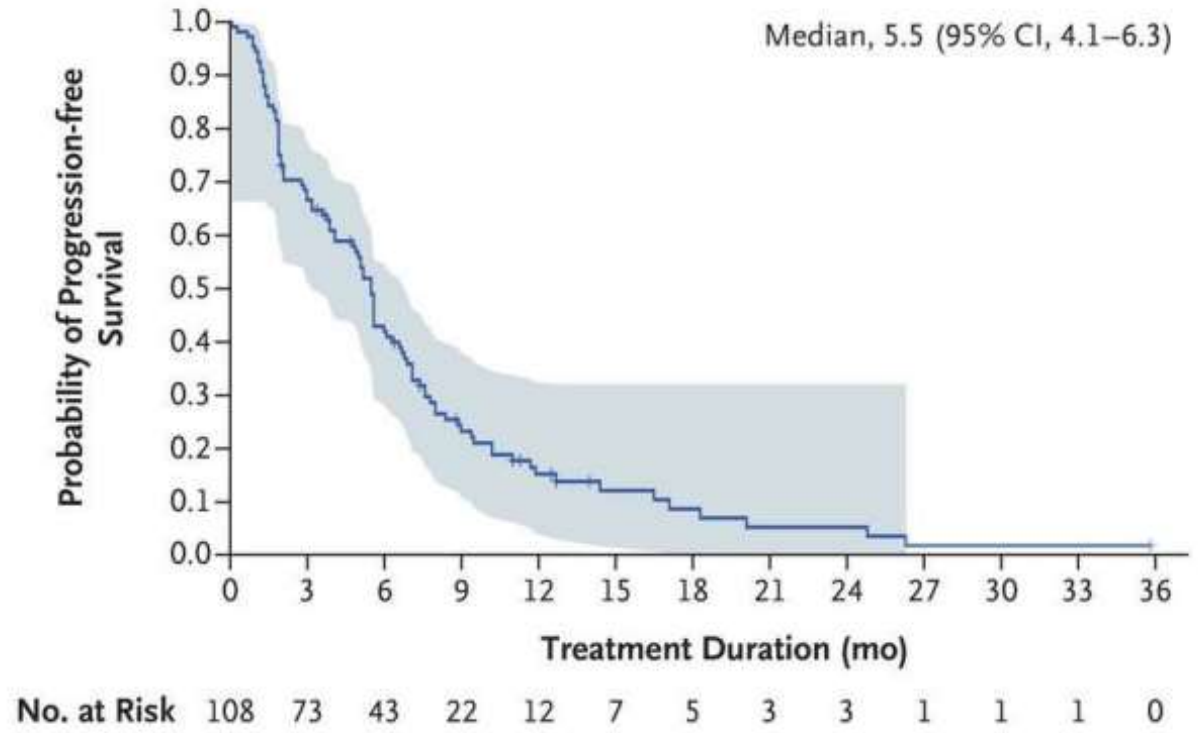
Sacituzumab Govitecan: Time on Treatment for All Patients (N = 110)



Last prior treatment time calculated as last dose date – first dose date. Sacituzumab govitecan time on treatment calculated as (date off study or data cut off date) – first dose date. If more than 1 agent is given in the regimen, the time of the regimen treatment is taken as the longest time for any one of the agents used

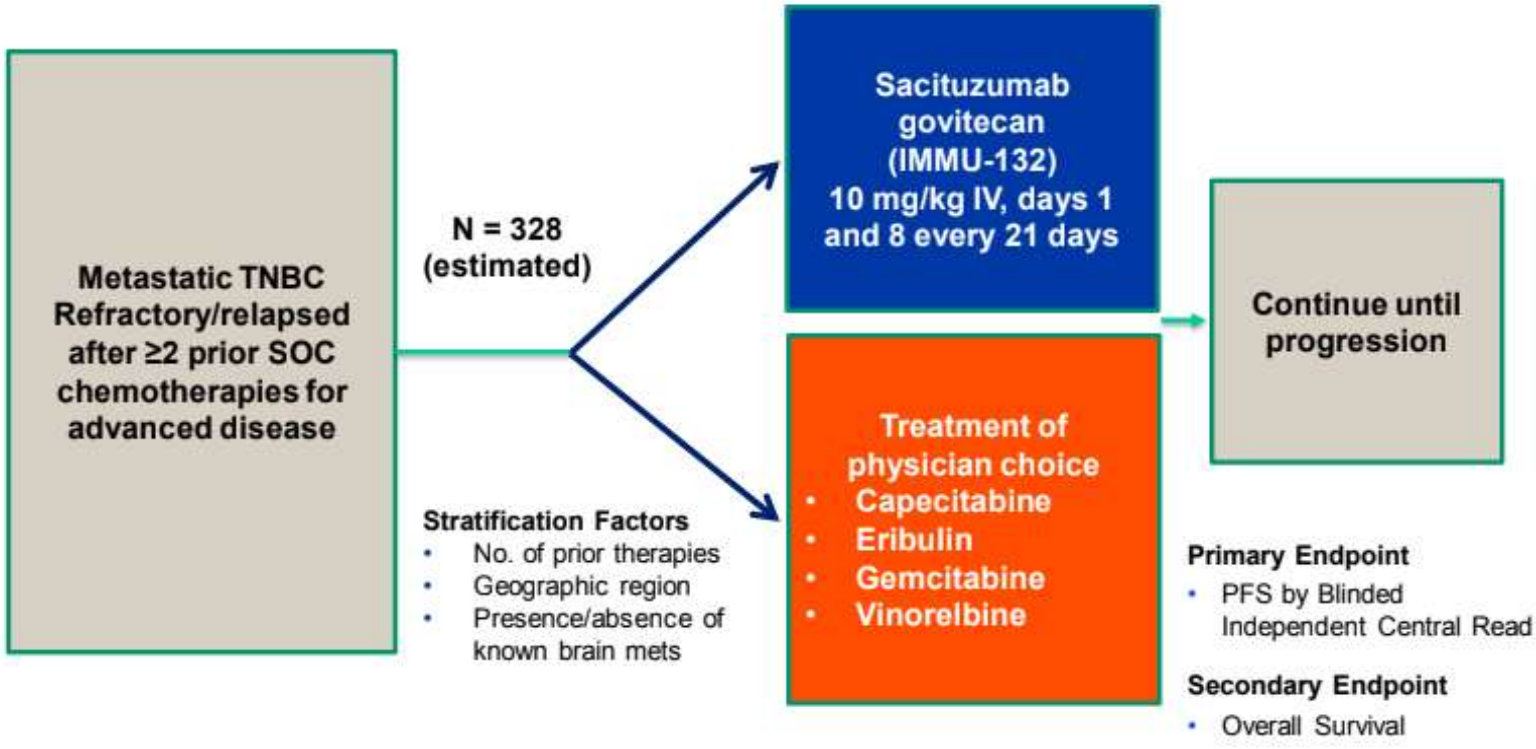
Bardia et al. *NEJM*. 2019.

Sacituzumab Govitecan: Progression-Free Survival



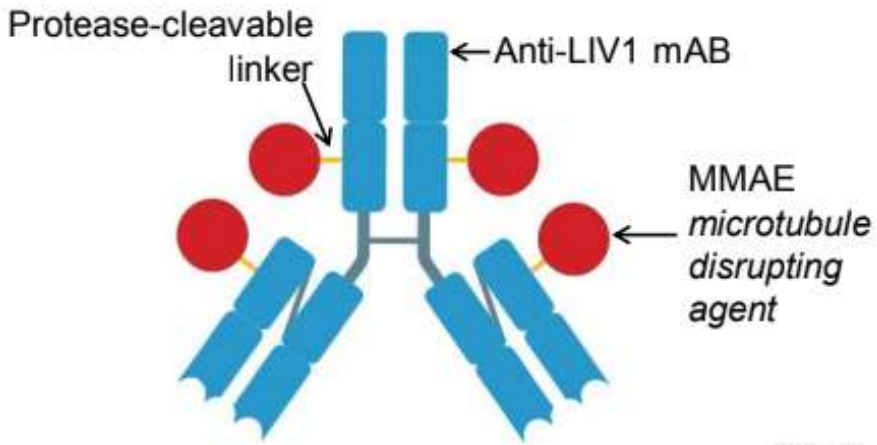
Bardia et al. *NEJM*. 2019.

ASCENT Phase III Study of Sacituzumab Govitecan: Overview



- Clinical trials number: NCT02574455
- Presented at: New Agents and Strategies; December 7, 2017(abstract# 733)

Ladiratuzumab Vedotin: ADC Targeting LIV1



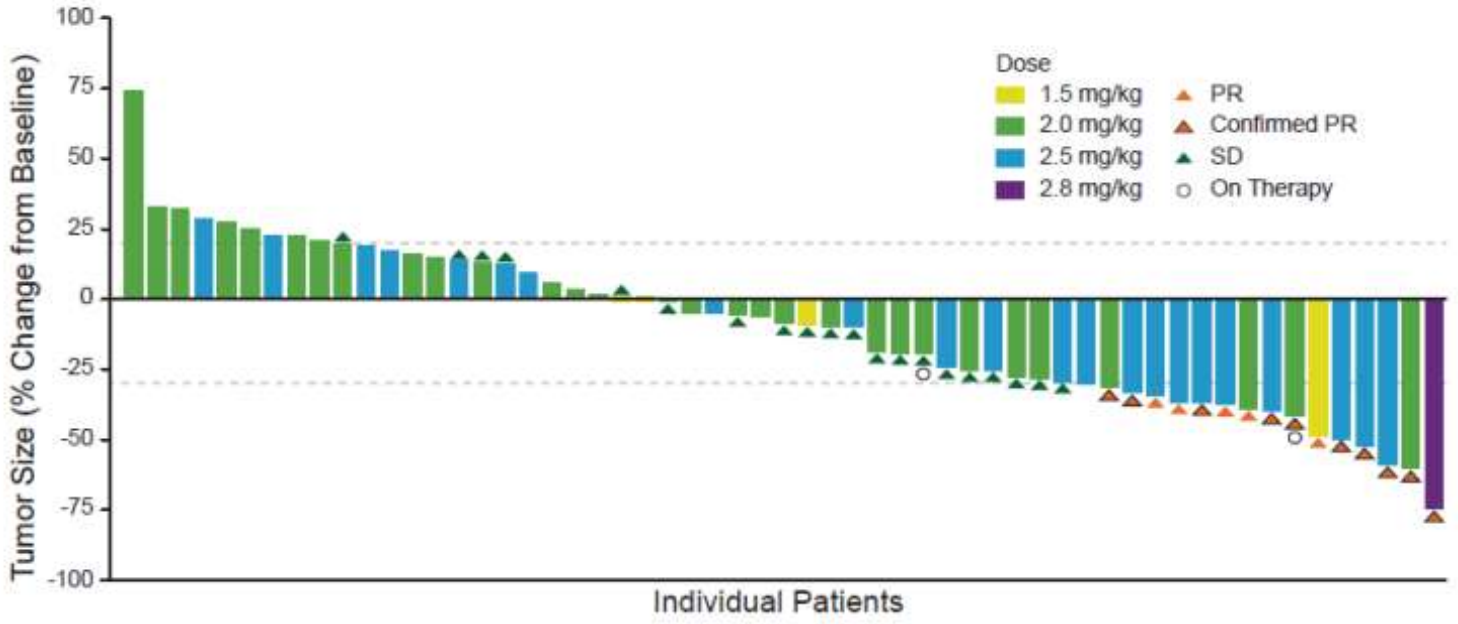
LIV1 is a transmembrane cell adhesion molecule highly expressed in metastatic breast cancer

Mech. of Action:

1. Binds to antigen
2. Complex internalized and trafficked to lysosome
3. Release of MMAE payload
4. Microtubule disruption
5. Cell cycle arrest/disruption

Ladiratuzumab Vedotin: ADC Targeting LIV1

Confirmed ORR = 25% (15/60)



Shanu et al. *SABCS*. 2017

SUMMARY

- Treatment of triple-negative MBC is finally becoming individualized with atezolezomab gaining approval
- PDL-1 testing should become part of the workup for such patients
- ADCs have shown promise and may be the next approval
- It is becoming increasingly clear that PDL-1 is an imperfect biomarker and there are other markers to select patients; perhaps a combination of biomarkers will emerge to better define optimal candidates
- Incorporation in curative settings is eagerly awaited