Current and Future Management of PD-L1-Negative Metastatic Triple Negative Breast Cancer

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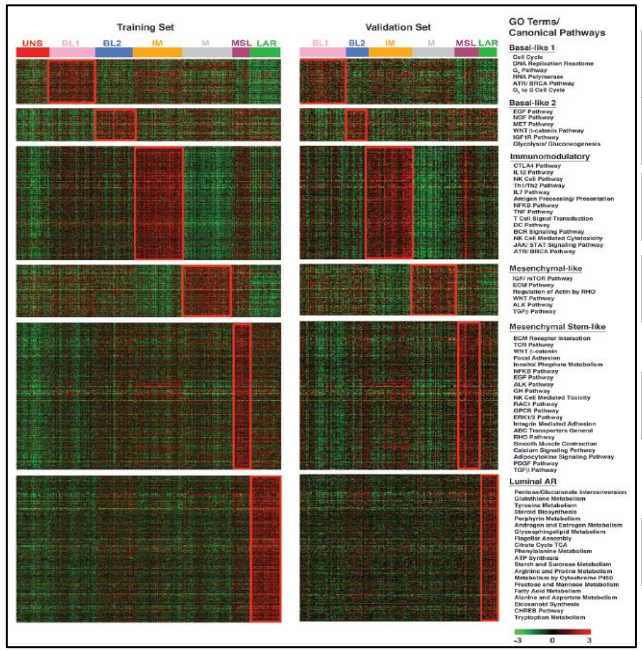
Heterogeneity of TNBC



BL1: Basal-like 1

BL2: Basal-like 2

IM: Immunomodulatory

M: Mesenchymal

MSL: Mesenchymal stem cell-like

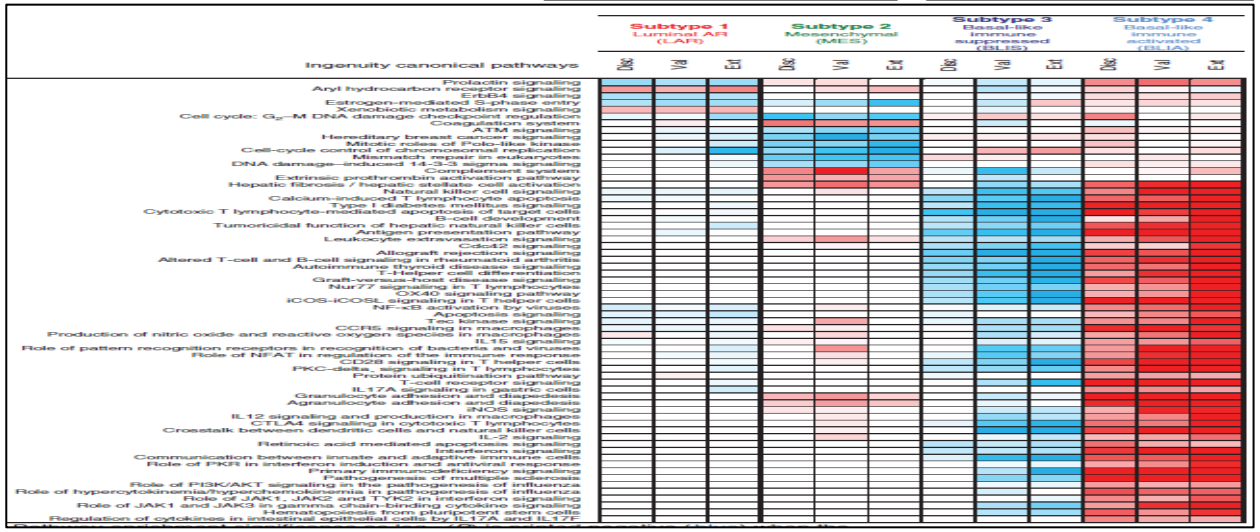
LAR: Luminal androgen receptor

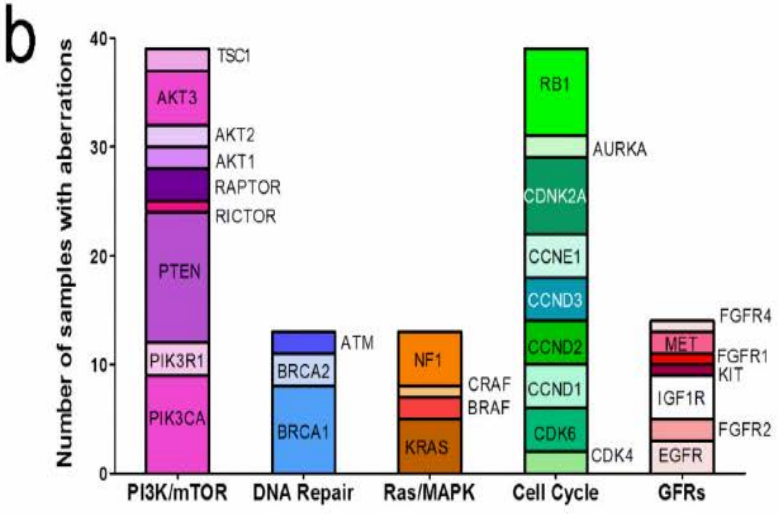
Luminal AR

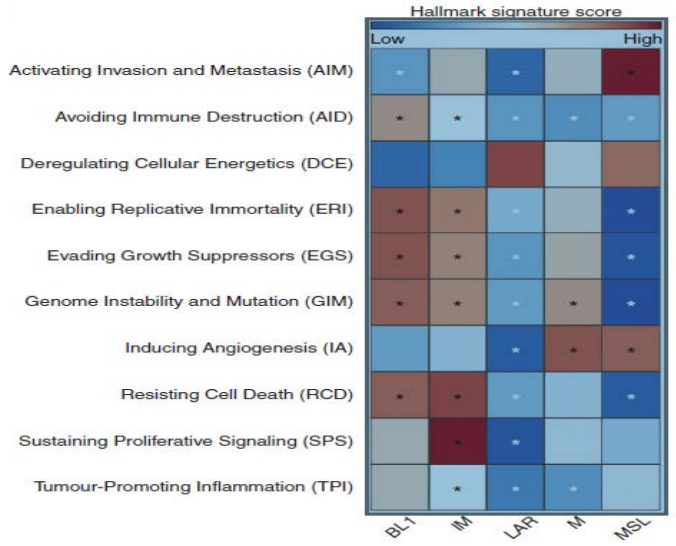
Mesenchymal

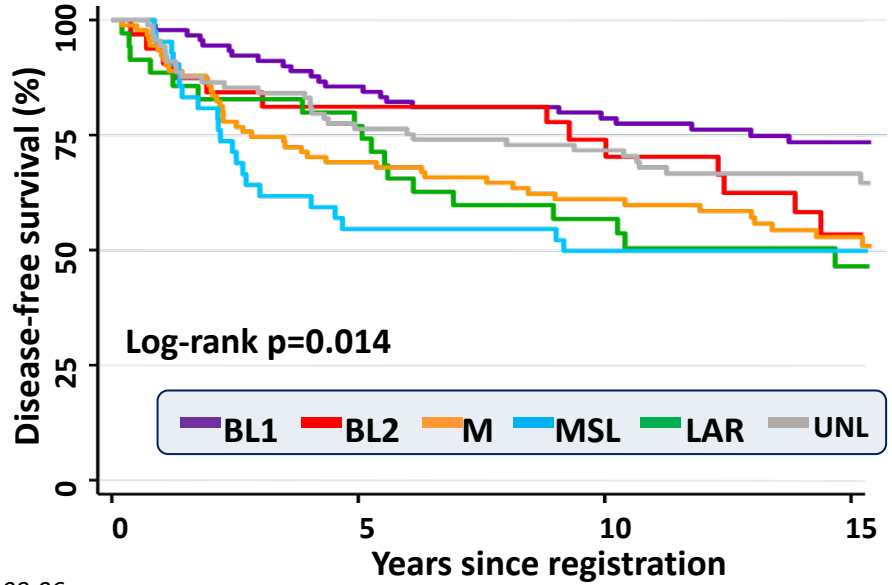
Basal-like
Immune-suppressed

Basal-like
Immune-activated









Courtesy of Joyce O'Shaughnessy, MD

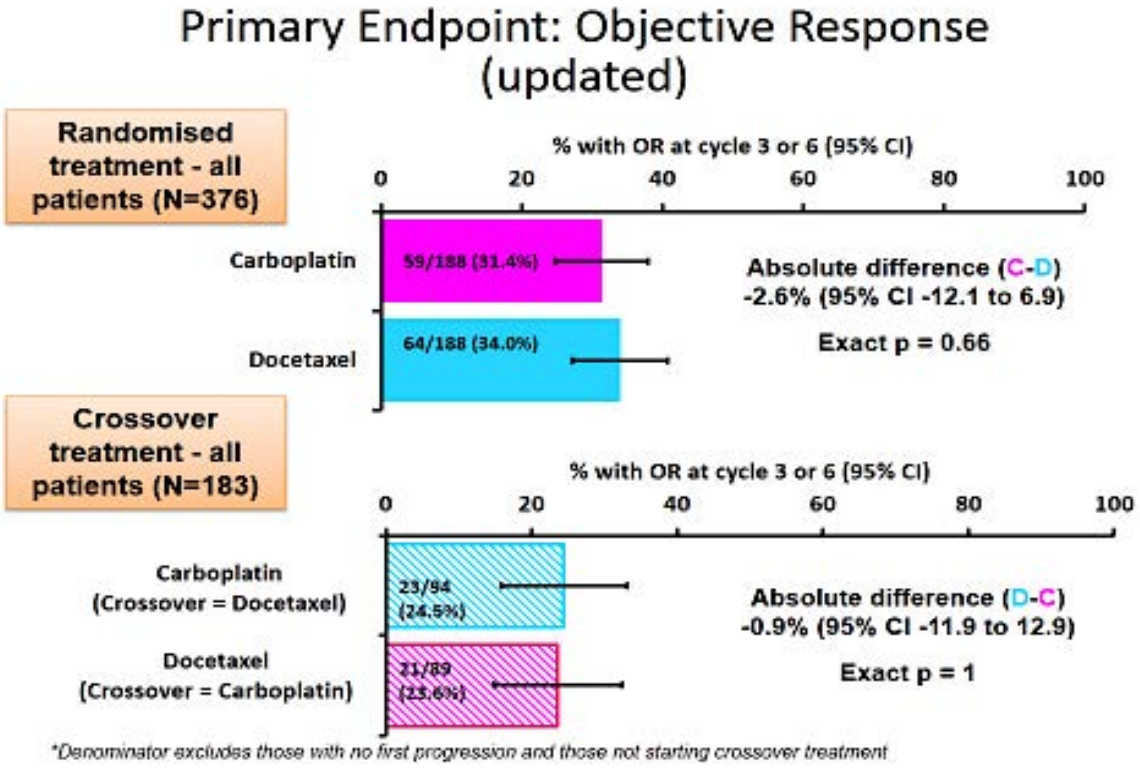
Lehmann J Clin Invest 2011, Lehmann PLoS One 2016, Balko et al 2014, Burstein Clin Cancer Res 2015, Bareche Ann Oncol 2018, Sharma SABCS 2018 P4-08-06

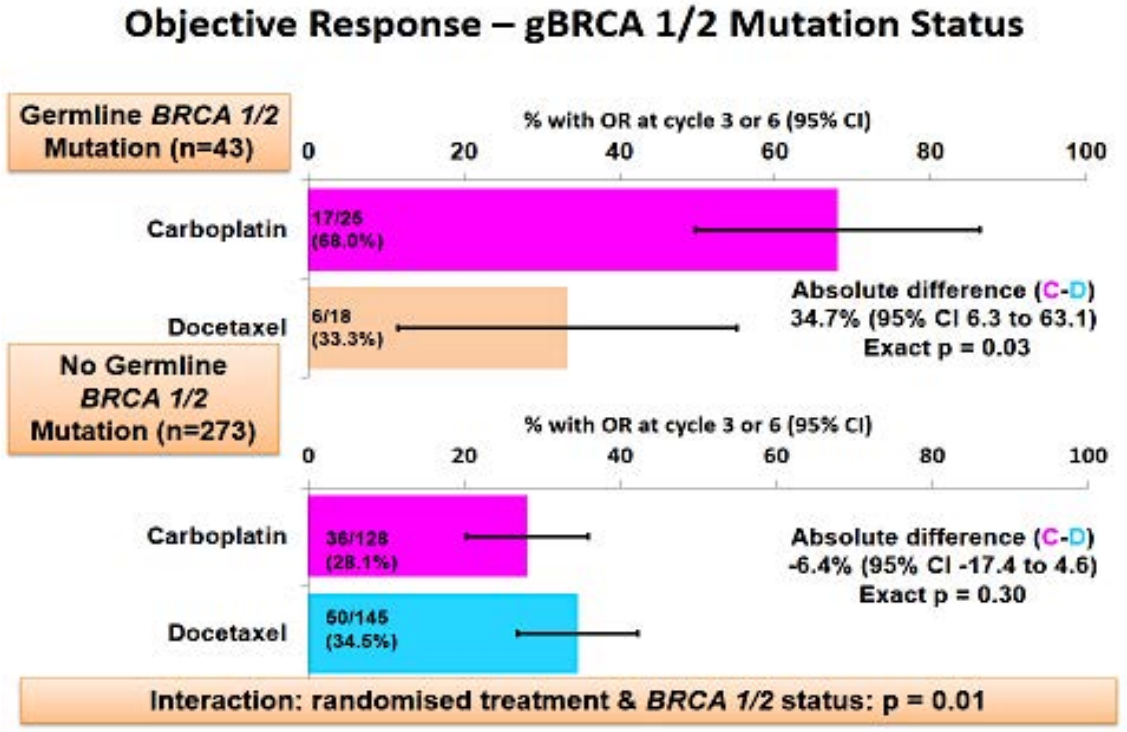
NCCN Guidelines 2020: Preferred Regimens for HER2-Negative Recurrent or Stage IV (M1) Disease

Drug Class	Recommended Agents
Anthracycline	Doxorubicin Liposomal doxorubicin
Taxane	Paclitaxel
Antimetabolite	Capecitabine Gemcitabine
Microtubule Inhibitor	Vinorelbine Eribulin
PARP Inhibitors (for TNBC and g*BRCA*m)	Olaparib Talazoparib
Platinum Agent	Carboplatin Cisplatin
Immunotherapy (for PD-L1+ TNBC)	Atezolizumab + *nab*-paclitaxel

Courtesy of Joyce O'Shaughnessy, MD

TNT: Carboplatin vs Docetaxel First-Line Metastatic TNBC





PFS by BRCA mutation status

	BRCA 1/2 mutated	BRCA 1/2 not mutated
D	4.4 mo (1.9-7.0)	4.6 mo (4.2-5.5)
C	6.8 mo (4.6-8.5)	2.9 mo (2.3-4.2)

Tutt, A. Nature Med 2018

Courtesy of Joyce O'Shaughnessy, MD

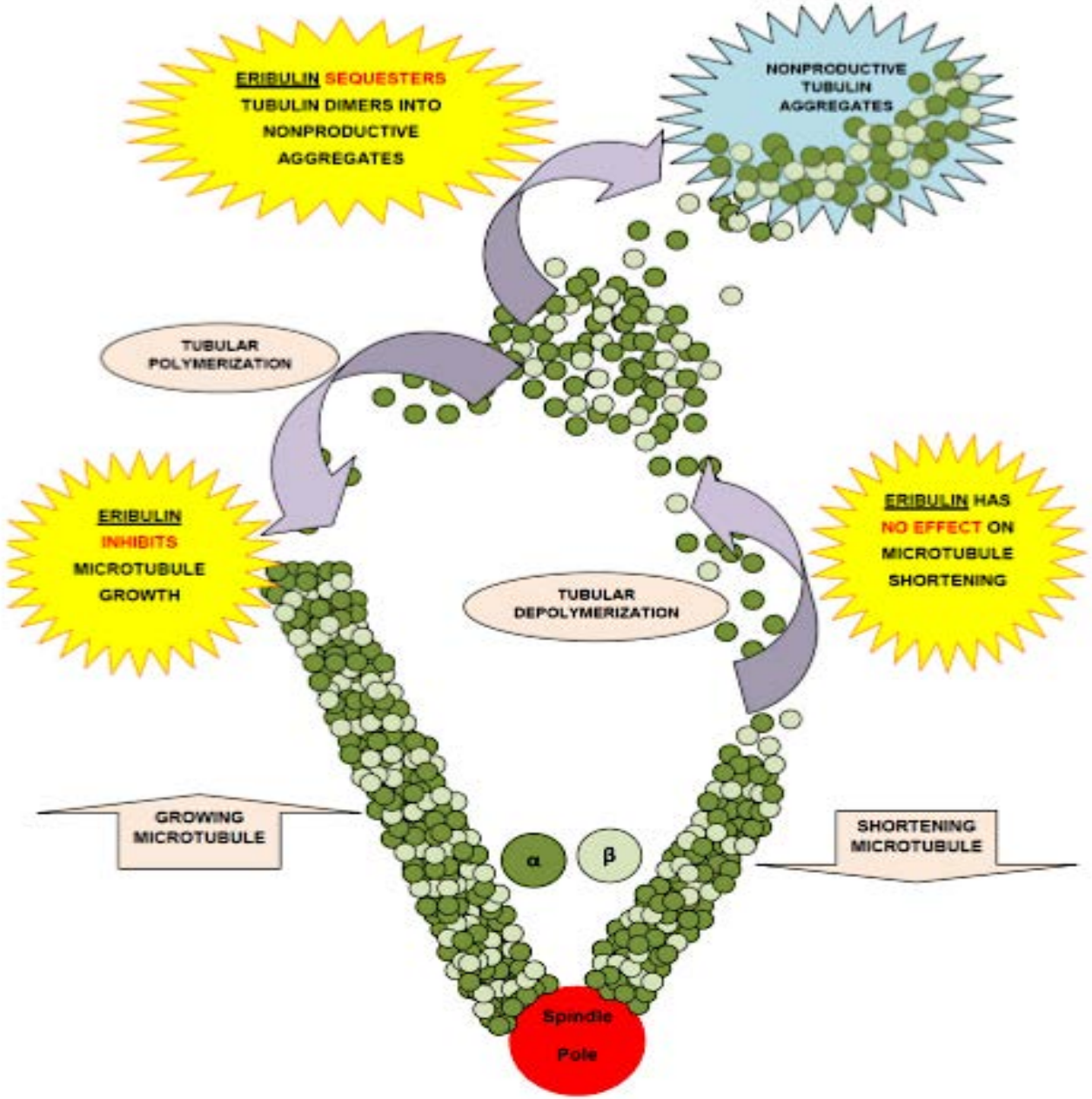
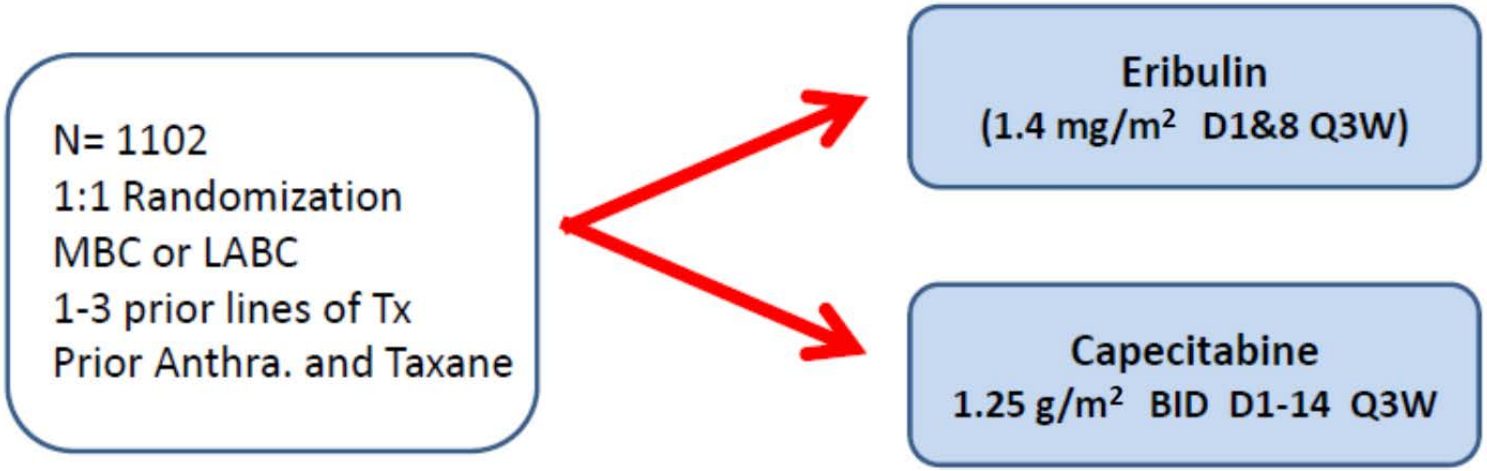


Figure 2. Mechanism of action of eribulin mesylate.

Swami U et al Marine Drugs 13:5016, 2017

Courtesy of Joyce O'Shaughnessy, MD



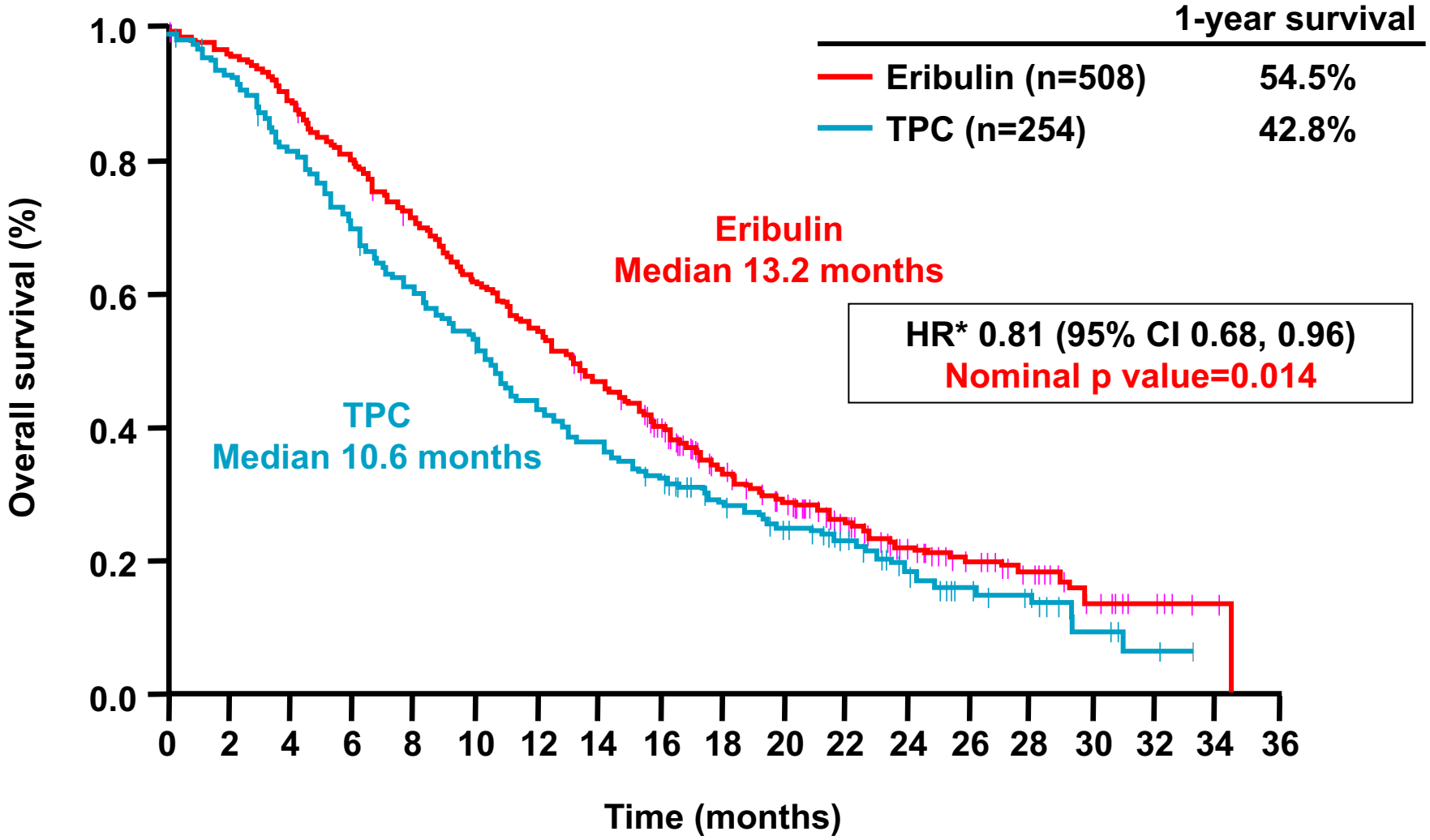
Study 301: eribulin vs capecitabine 2L MBC

Median OS	Eribulin	Cape	Hazard ratio
HER2 status			
Positive	14.3 mo	17.1 mo	0.965
Negative	15.9 mo	13.5 mo	0.838
ER status			
Positive	18.2 mo	16.8 mo	0.897
Negative	14.4 mo	10.5 mo	0.779
Triple-negative BC (TNBC)			
Yes	14.4 mo	9.4 mo	0.702
No	17.5 mo	16.6 mo	0.927
Overall	**15.9 mo**	**14.5 mo**	**0.879**

Courtesy of Joyce O'Shaughnessy, MD

Kaufman PA et al. J Clin Oncol 2015

EMBRACE: OS (ITT Population)
Eribulin vs Treatment of Physician's Choice



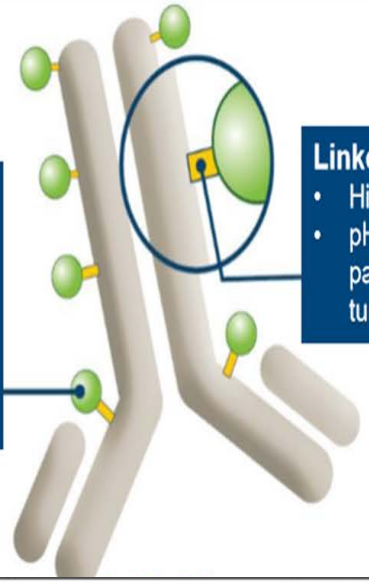
Courtesy of Joyce O'Shaughnessy, MD

Cortes J, et al. Lancet 2011;377:914-923.

Phase II Trial Sacituzumab Govitecan

Sacituzumab Antibody-Drug Conjugate (ADC)

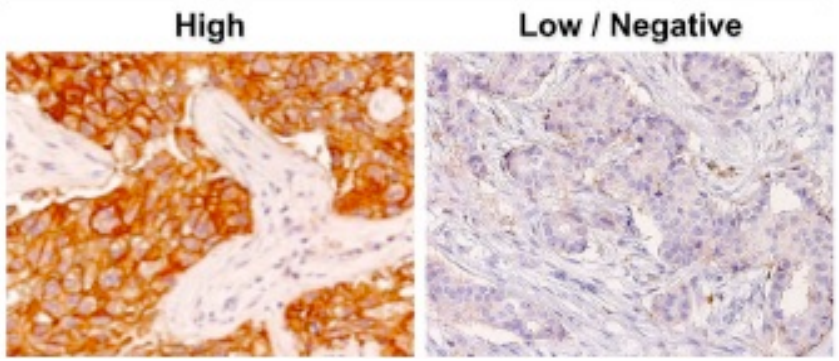
Humanized RS7 antibody
- Targets Trop-2, an epithelial antigen expressed on many solid cancers, including mTNBC



SN-38 payload
- Targets 136-fold more SN-38 than the parent compound, irinotecan (topoisomerase I inhibitor)
- ADCs unique chemistry avoids low solubility and selectively delivers SN-38 to the tumor

Linker for SN-38
- High drug-to-antibody ratio (7.6:1)
- pH-sensitive linker for rapid payload release at or inside the tumor

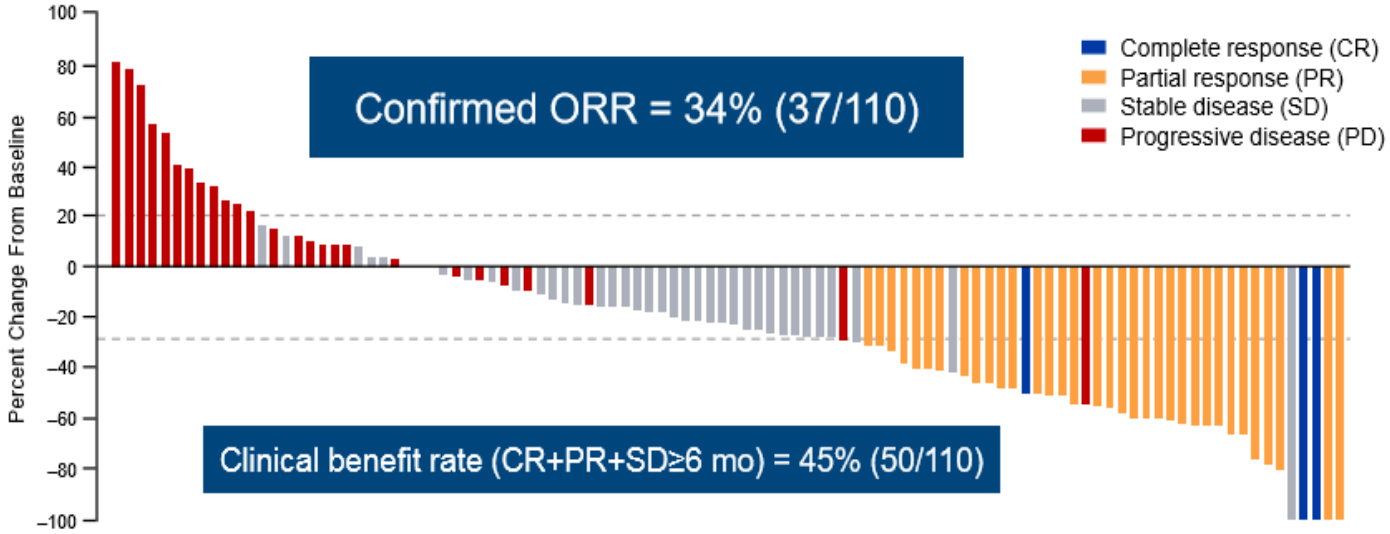
5



> 90% TNBCs express Trop-2

Met TNBC 3/4/5th-line Phase II

Tumor Response to Treatment



- 74% (75/102) of patients with at least one CT response assessment had reduction of target lesions (sum of diameters)
- 102 patients had ≥1 scheduled CT response assessment
- 8 patients withdrew prior to assessment (4 PD, 4 MRI brain mets)

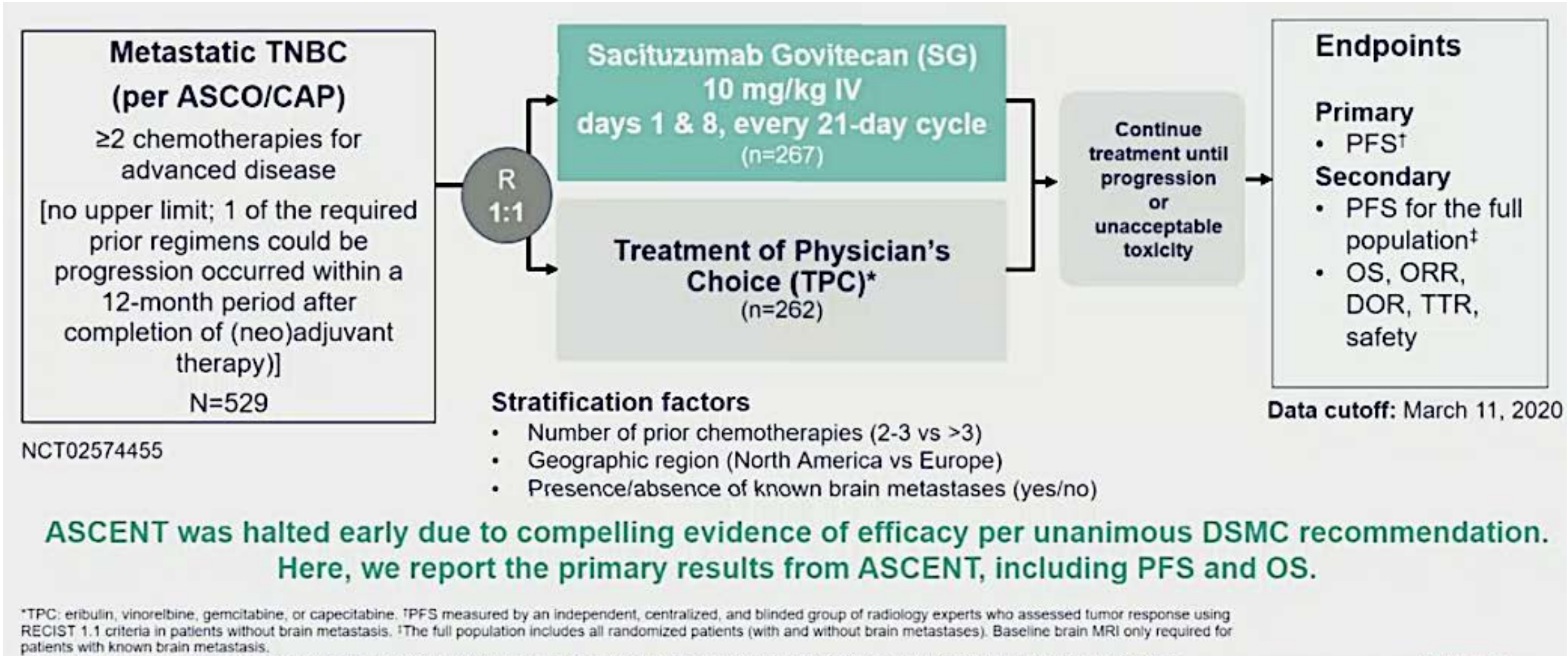
11

Median DoR 7.6 mos
Med PFS 5.5 mos

Bardia A et al. SABCS 2017

Courtesy of Joyce O'Shaughnessy, MD

ASCENT (Phase III): Sacituzumab Govitecan (SG) vs Treatment of Physician´s Choice (TPC) in pretreated mTNBC (N=529) – *Study Design*

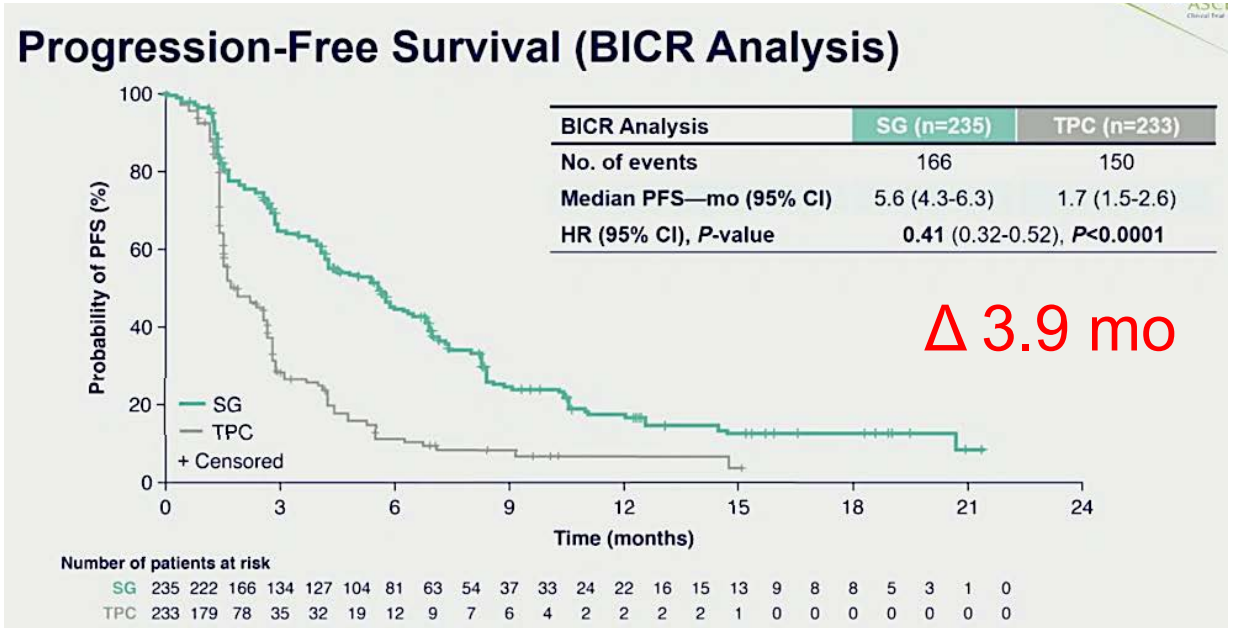


Bardia A, et al. ESMO 2020 (LBA17)

Courtesy of Joyce O'Shaughnessy, MD

ASCENT (Phase III): Sacituzumab Govitecan (SG) vs Treatment of Physician´s Choice (TPC) in pretreated mTNBC (N=529) – PFS and OS in BM-Neg Patients

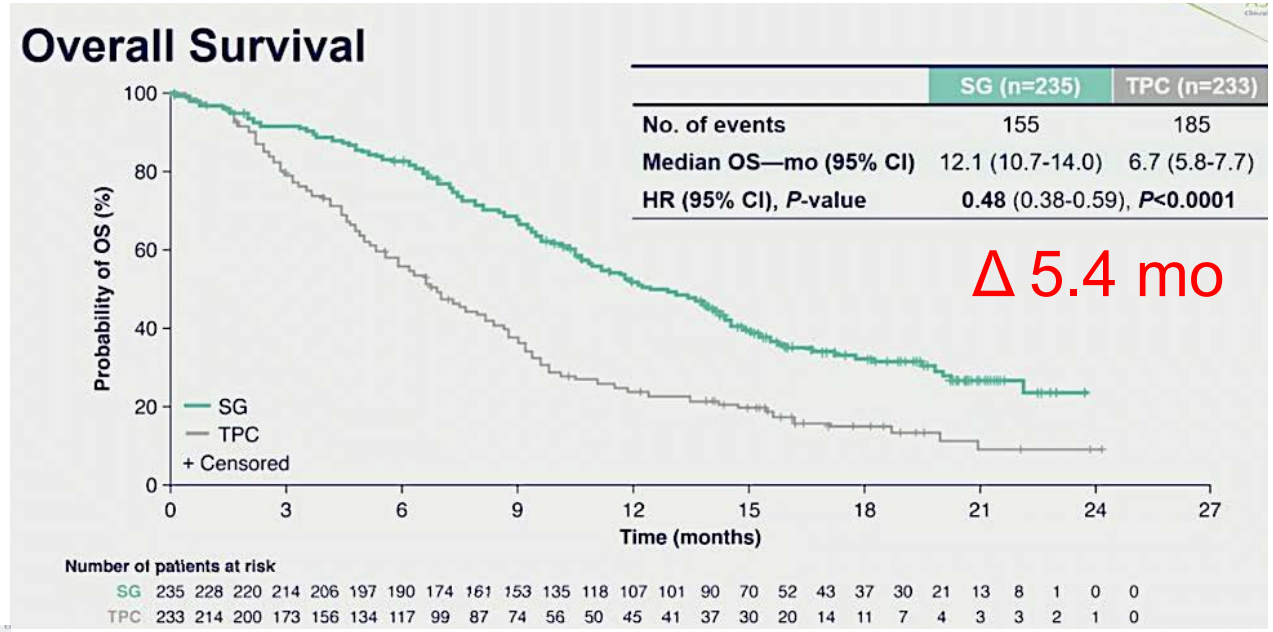
Progression-Free Survival (BICR Analysis)



BICR Analysis	SG (n=235)	TPC (n=233)
No. of events	166	150
Median PFS—mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P*-value	**0.41** (0.32-0.52), ***P*<0.0001**	

Δ 3.9 mo

Overall Survival



	SG (n=235)	TPC (n=233)
No. of events	155	185
Median OS—mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P*-value	**0.48** (0.38-0.59), ***P*<0.0001**	

Δ 5.4 mo

TRAEs (All Grade, >20%; Grade 3/4, >5% of Patients)

		SG (n=258)			TPC (n=224)		
	TRAE*	All grade %	Grade 3, %	Grade 4, %	All grade, %	Grade 3, %	Grade 4, %
Hematologic	**Neutropenia†**	**63**	**46**	**17**	**43**	**27**	**13**
	Anemia‡	**34**	**8**	**0**	**24**	**5**	**0**
	Leukopenia§	16	10	1	11	5	1
	Febrile neutropenia	6	5	1	2	2	<1
Gastrointestinal	**Diarrhea**	**59**	**10**	**0**	12	<1	0
	Nausea	**57**	**2**	**<1**	**26**	**<1**	**0**
	Vomiting	29	1	<1	10	<1	0
Other	**Fatigue**	**45**	**3**	**0**	**30**	**5**	**0**
	Alopecia	**46**	**0**	**0**	**16**	**0**	**0**

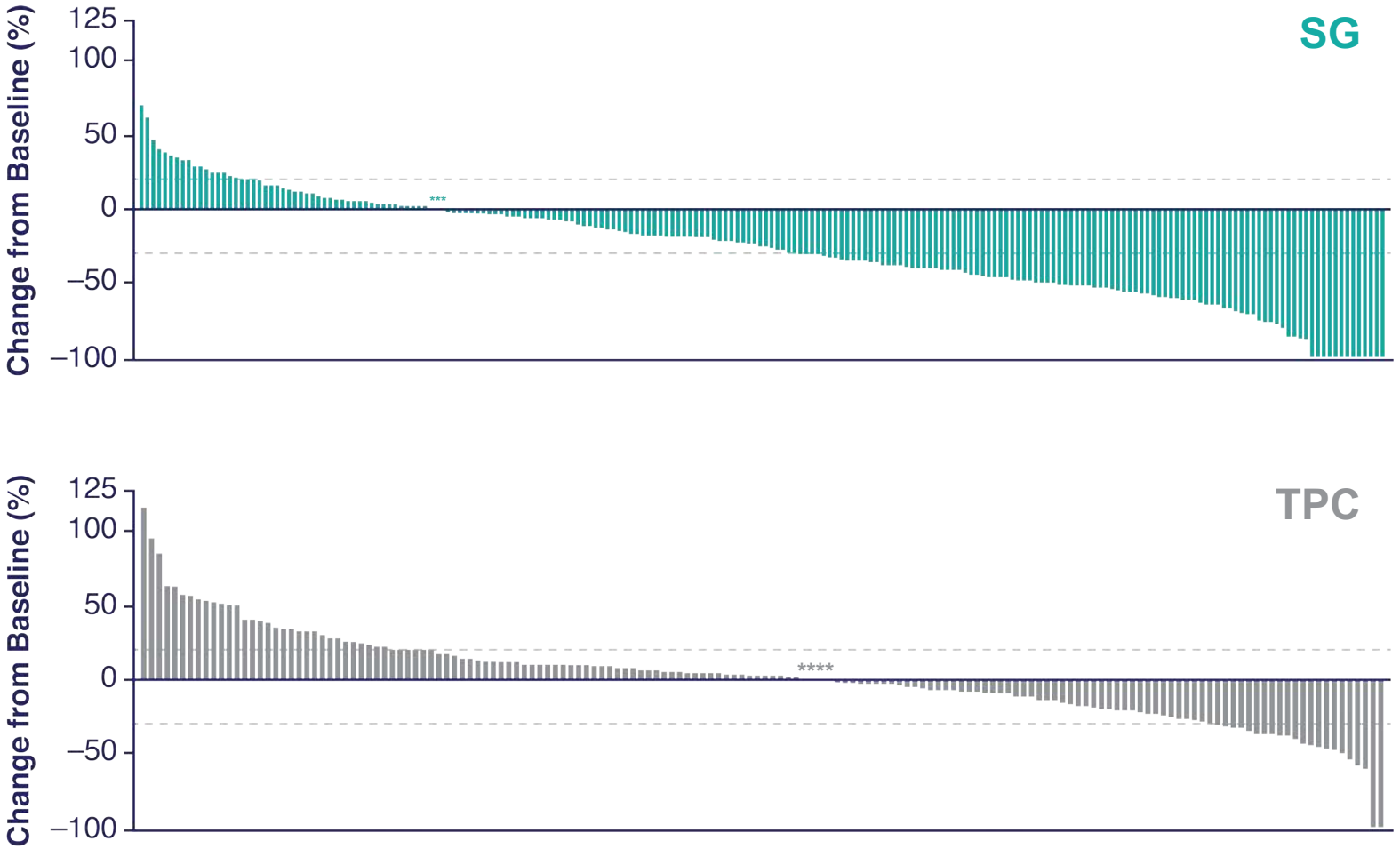
SG was well tolerated with manageable safety profile

- AE leading to treatment discontinuation 4.7%
- No severe cardiotoxicity
- No grade >2 neuropathy
- No grade >3 interstitial lung disease

Courtesy of Joyce O'Shaughnessy, MD

Bardia A, et al. ESMO 2020 (LBA17)

Overall Response and Best Percent Change From Baseline in Tumor Size

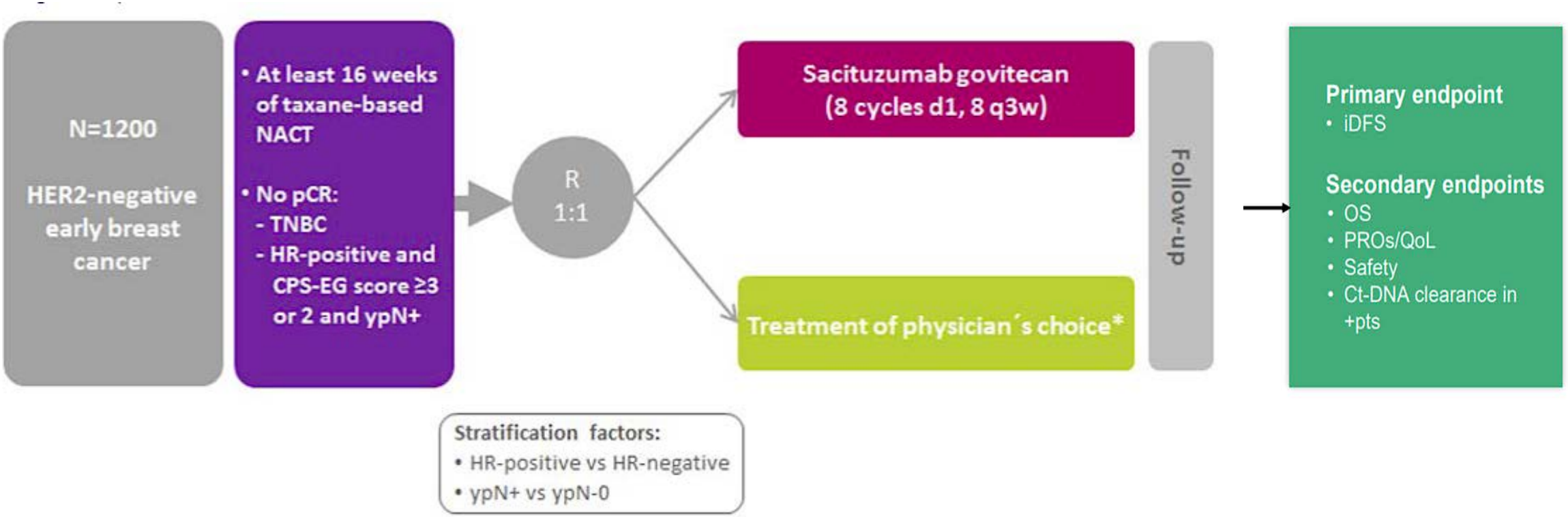


	SG (n=235)	TPC (n=233)
ORR—no. (%)	**82 (35)**	**11 (5)**
***P*-value**	**<0.0001**	
CR	10 (4)	2 (1)
PR	72 (31)	9 (4)
CBR—no. (%)	**105 (45)**	**20 (9)**
***P*-value**	**<0.0001**	
Median DOR —mo (95%CI)	**6.3 (5.5–9.0)**	**3.6 (2.8–NE)**
***P*-value**	**0.057**	

Assessed by independent central review in brain metastases-negative population.
*Denotes patients who had a 0% change from baseline in tumor size.
BICR, blind independent central review; CBR, clinical benefit rate (CR + PR + SD ≥6 mo); CR, complete response; DOR, duration of response; ORR, objective response rate; PR, partial response; SG, sacituzumab govitecan; TPC, treatment of physician's choice; TTR, time to response.

Courtesy of Joyce O'Shaughnessy, MD

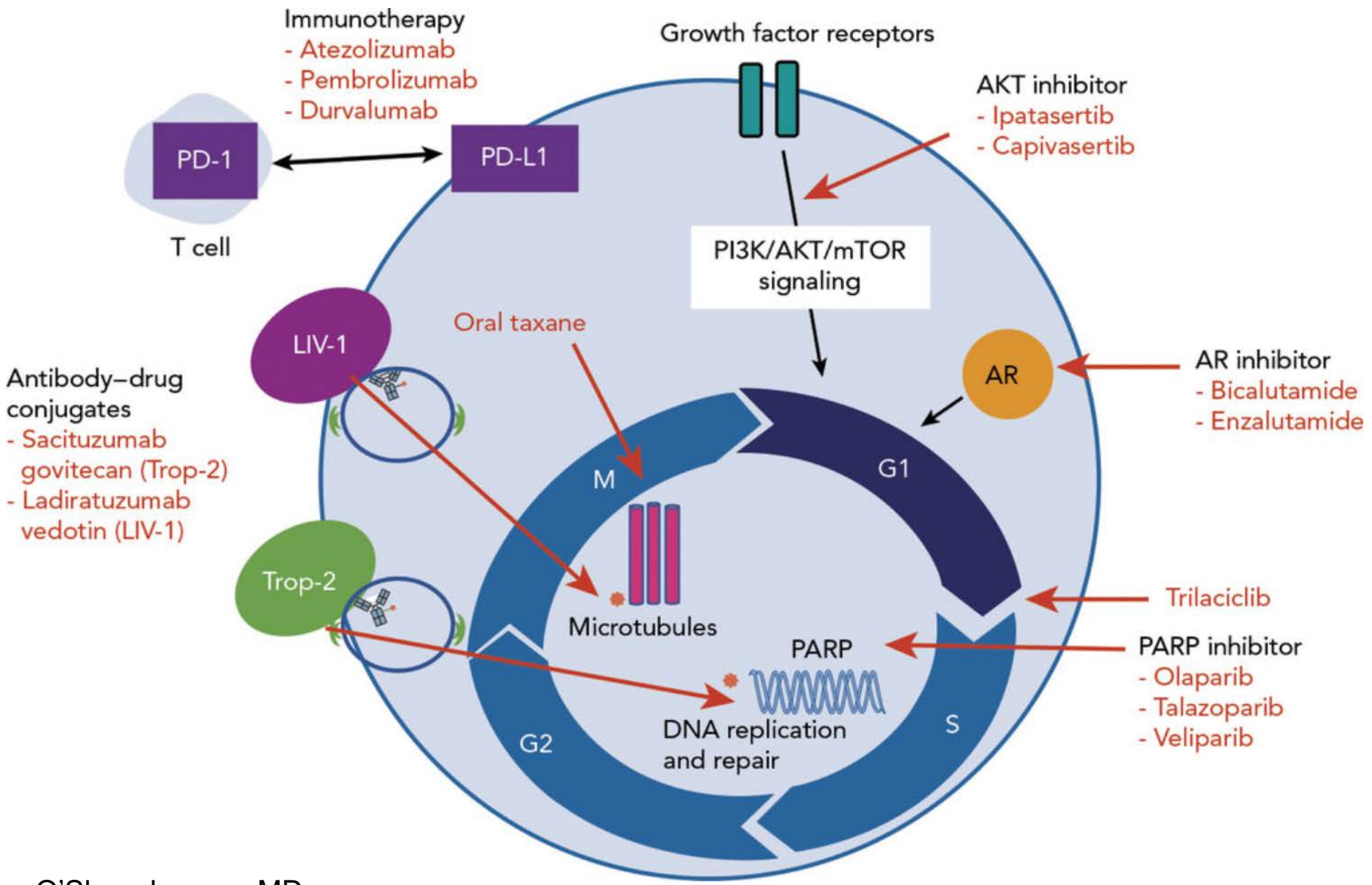
SASCIA trial schema



*Capecitabine (8 cycles) or platinum-based chemotherapy (8 cycles) or observation.
Background therapy: in patients with HR-positive breast cancer, endocrine-based therapy will be administered according to local guidelines.

Courtesy of Joyce O'Shaughnessy, MD

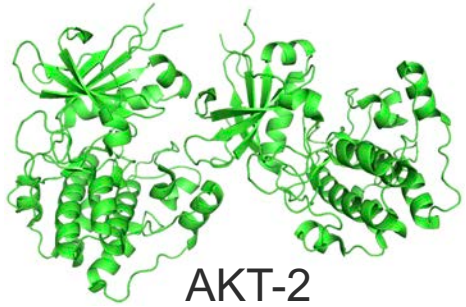
Novel Targets in Triple Negative Breast Cancer

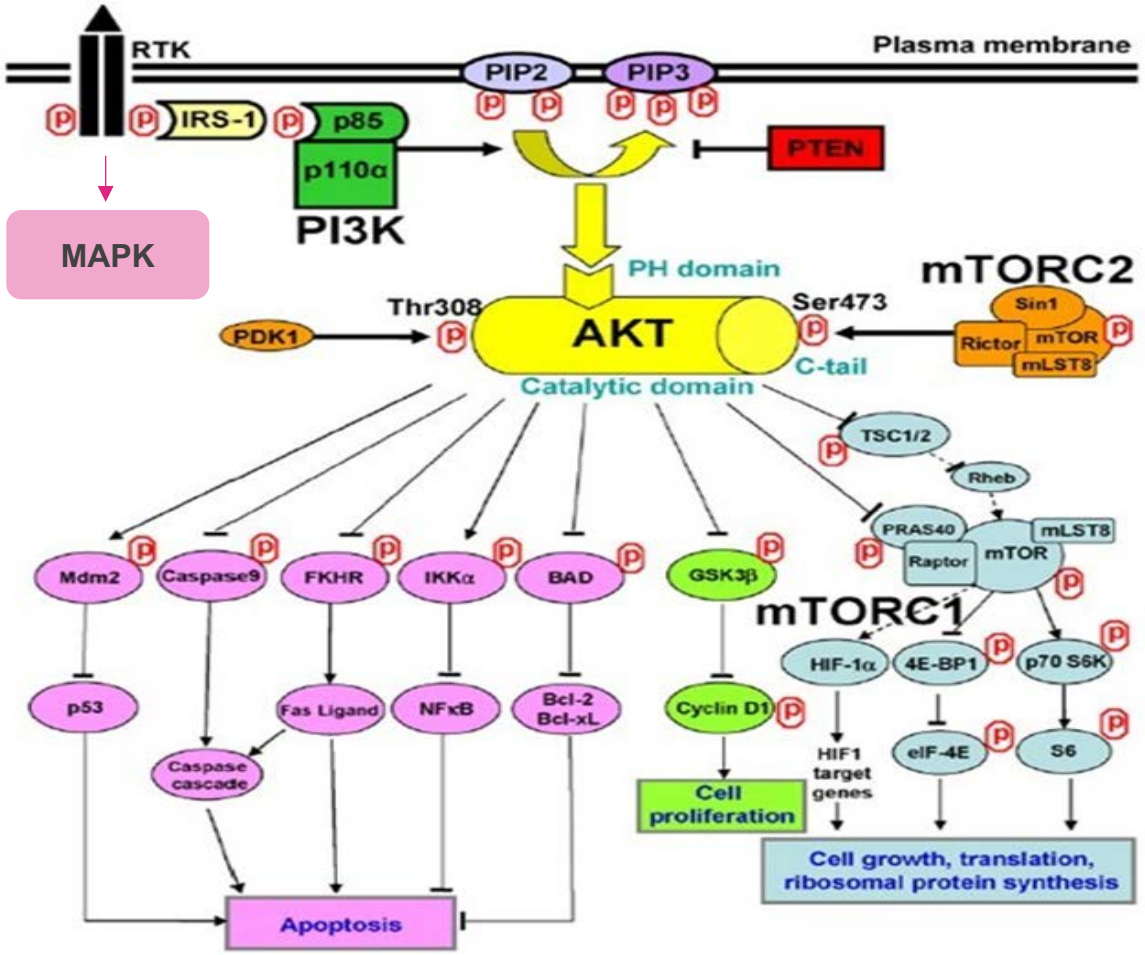


Courtesy of Joyce O'Shaughnessy, MD

Breast cancer and PI3K/AKT pathway

The PI3K/AKT pathway is one of the most frequently altered pathways in breast cancer and is key for survival and growth of tumors





Courtesy of Joyce O'Shaughnessy, MD

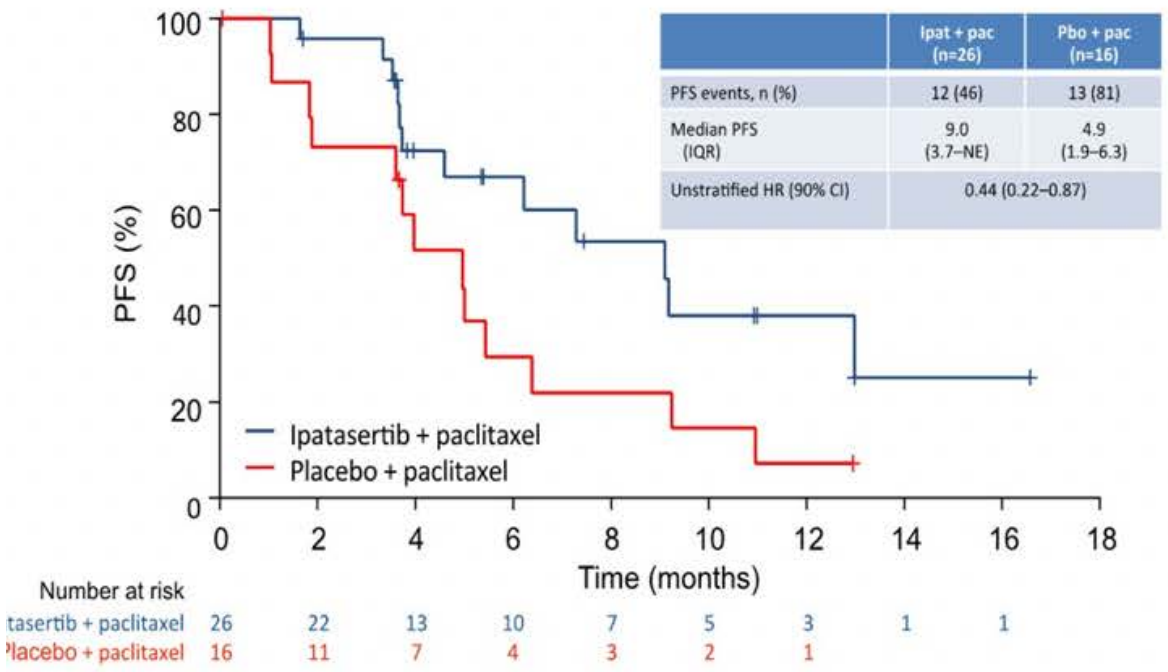
AKT can be activated by:

- Gain of function of positive regulators
  - PI3K
  - AKT
  - Receptor tyrosine kinases (HER2)
- Loss of function of negative regulators
  - PTEN
  - INPP4B
  - PHLPP
  - PP2A
- Therapy-induced survival response
  - Chemotherapy
  - Hormone therapy

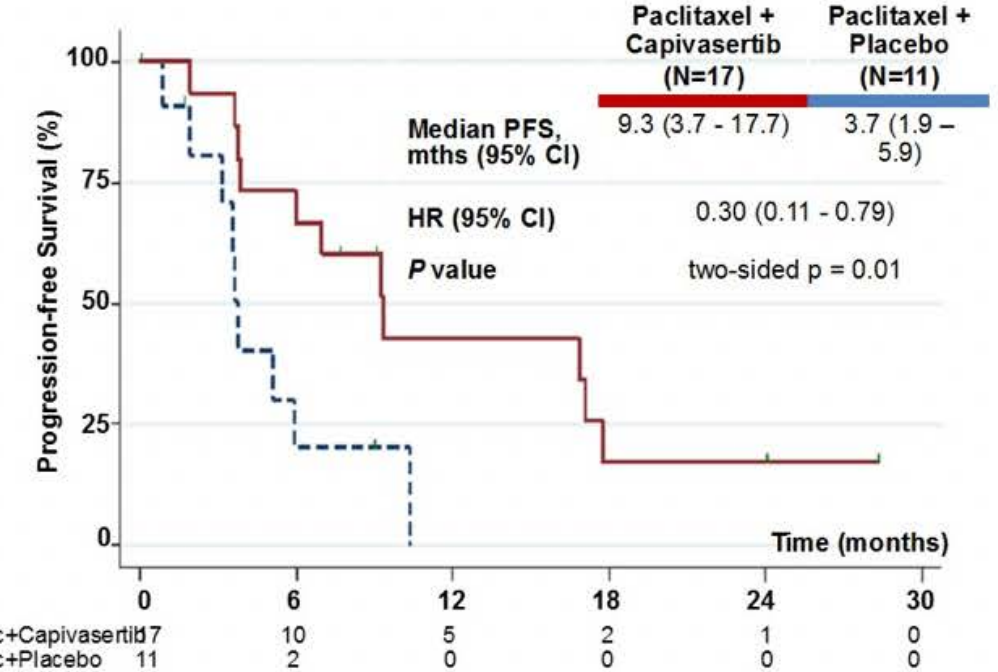
AKT Inhibitors Ipatasertib and Capivasertib for Metastatic TNBC

PIK3CA-AKT1-PTEN mutations

Ipatasertib



Capivasertib



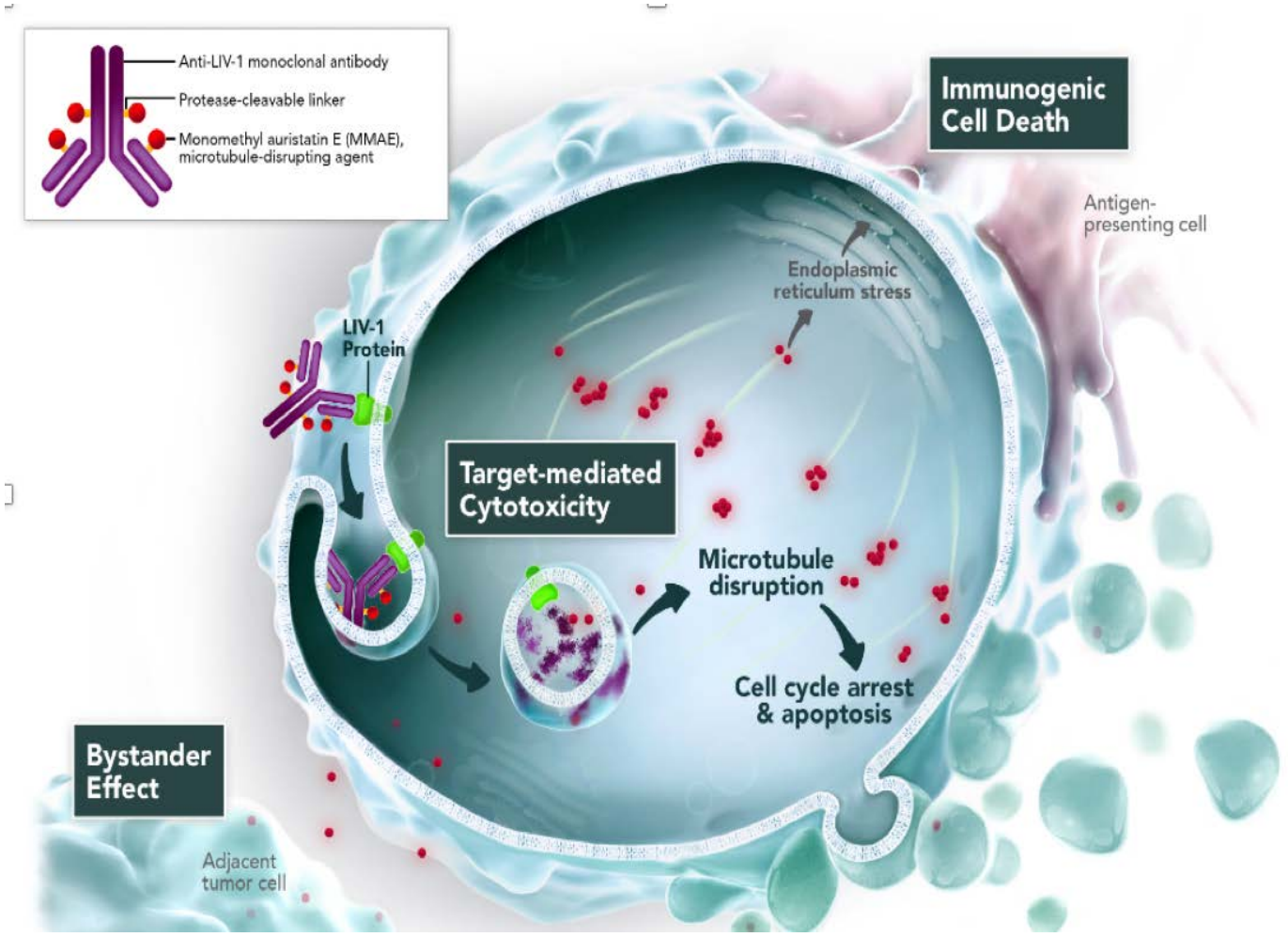
Phase III trials IPATunity and CAPItello-290 : Paclitaxel +/- AKT inhibitor in metastatic TNBC

Courtesy of Joyce O'Shaughnessy, MD

Schmid P et al. J Clin Oncol 2020; Kim SB et al. Lancet Oncol 2017

Ladiratuzumab Vedotin (LV) Novel Antibody Drug Conjugate

- LV
  - Humanized IgG1 ADC
  - Selectively binds to cells expressing LIV-1 (90%+ MBCs)
    - Conjugated to monomethyl auristatin E (MMAE)
- LV-mediated delivery of MMAE drives antitumor activity through
  - Cytotoxic cell killing
  - Inducing Immunogenic Cell Death



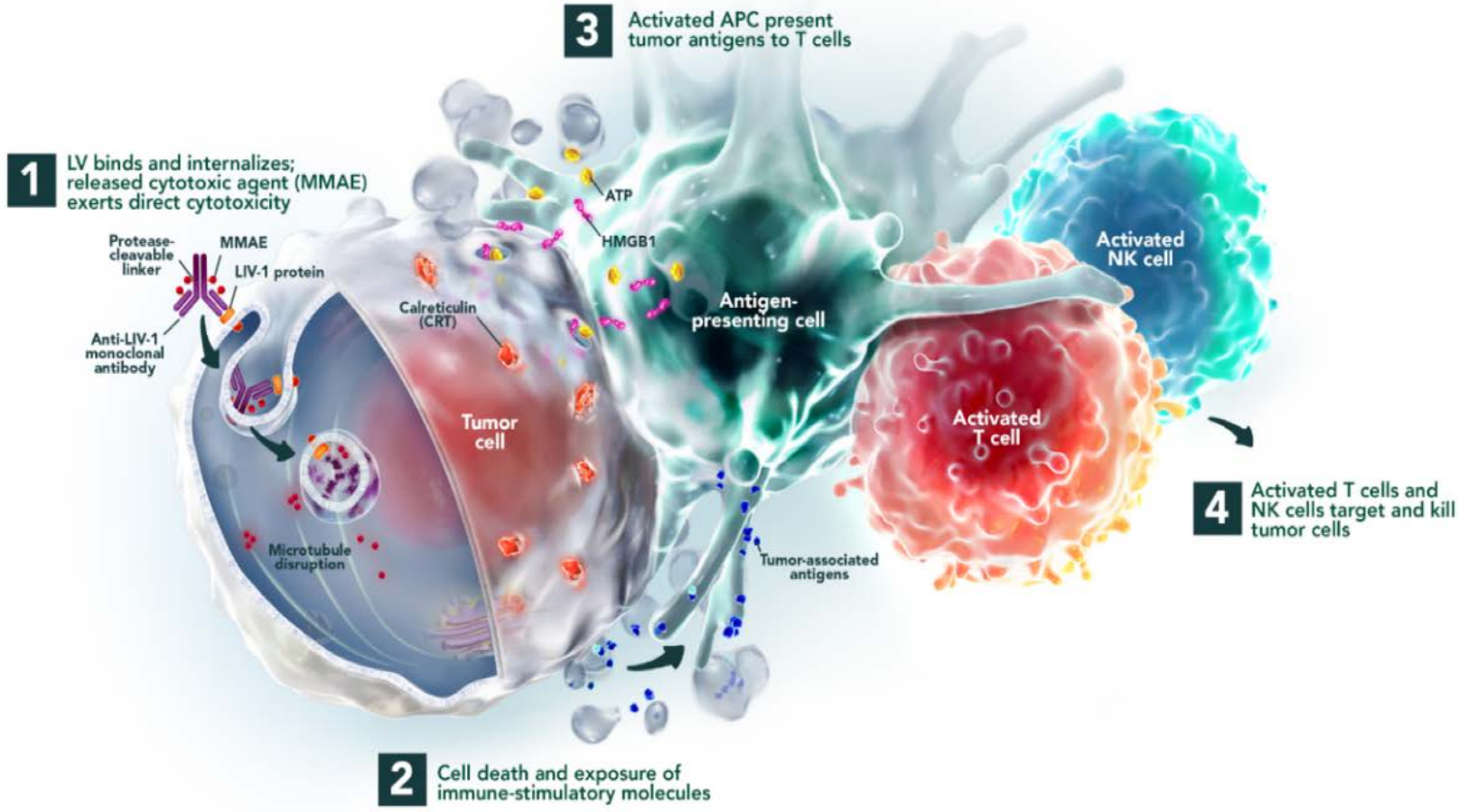
Courtesy of Joyce O'Shaughnessy, MD

Rationale for Combining LV with Pembrolizumab

- LV and pembrolizumab act through distinct and complementary mechanisms

- LV-induced ICD elicits an inflammatory response
  - Increases tumor immune cell infiltration[14]

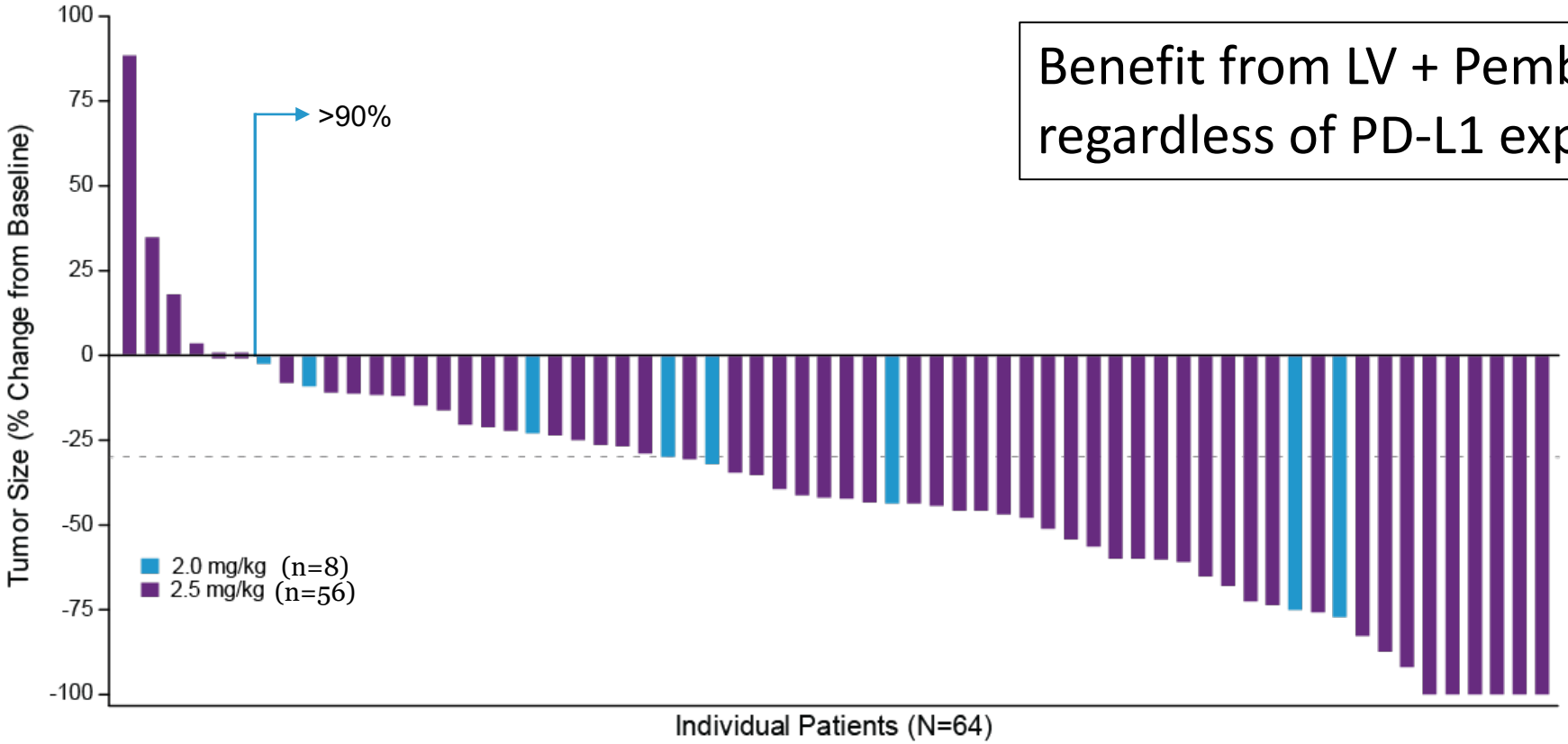
- LV-induced ICD creates a microenvironment favorable for enhanced pembrolizumab activity



Courtesy of Joyce O'Shaughnessy, MD

LV + Pembrolizumab Maximum Change in Tumor Burden in 1L metTNBC

- >90% of subjects achieved tumor reduction



Benefit from LV + Pembrolizumab regardless of PD-L1 expression

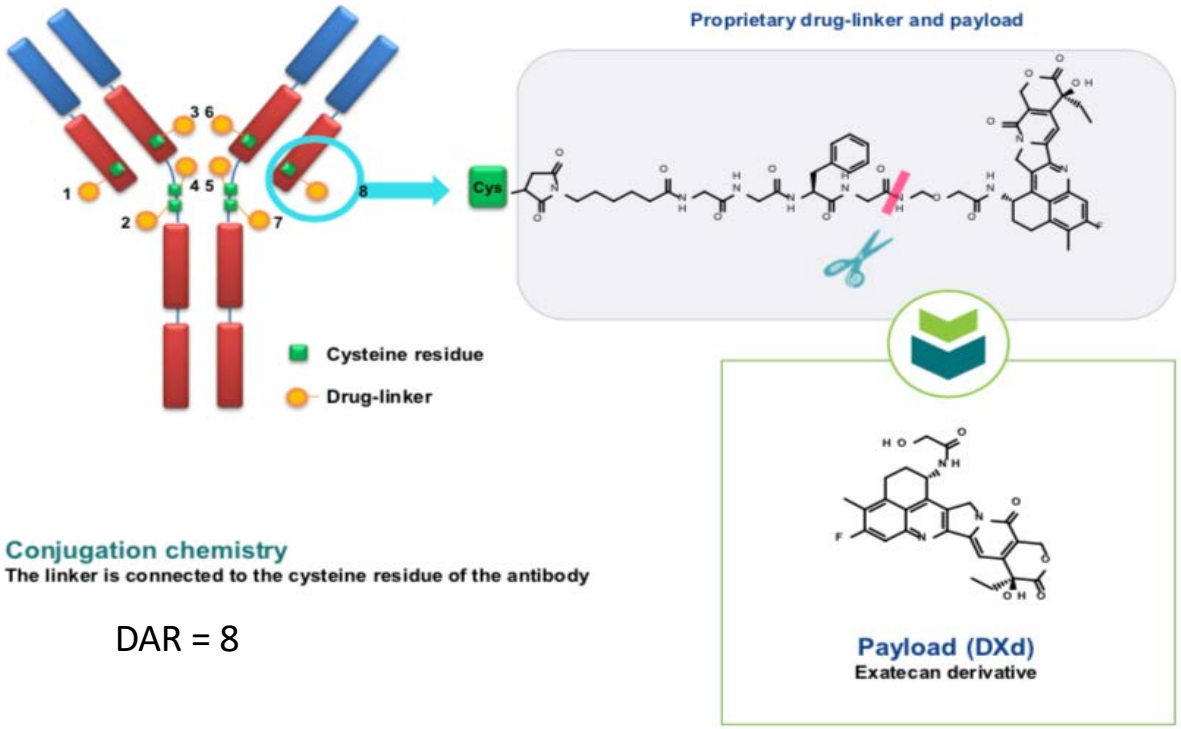
- The efficacy evaluable population includes all treated subjects with at least one evaluable post-baseline assessment according to RECIST v1.1 or who had discontinued from the study (N=69).
- Of the efficacy evaluable population, 5 subjects did not have evaluable response assessments before study discontinuation.

SABCS 2019, San Antonio, TX, Dec 10-14, 2019, Abstract No. 151

Courtesy of Joyce O'Shaughnessy, MD

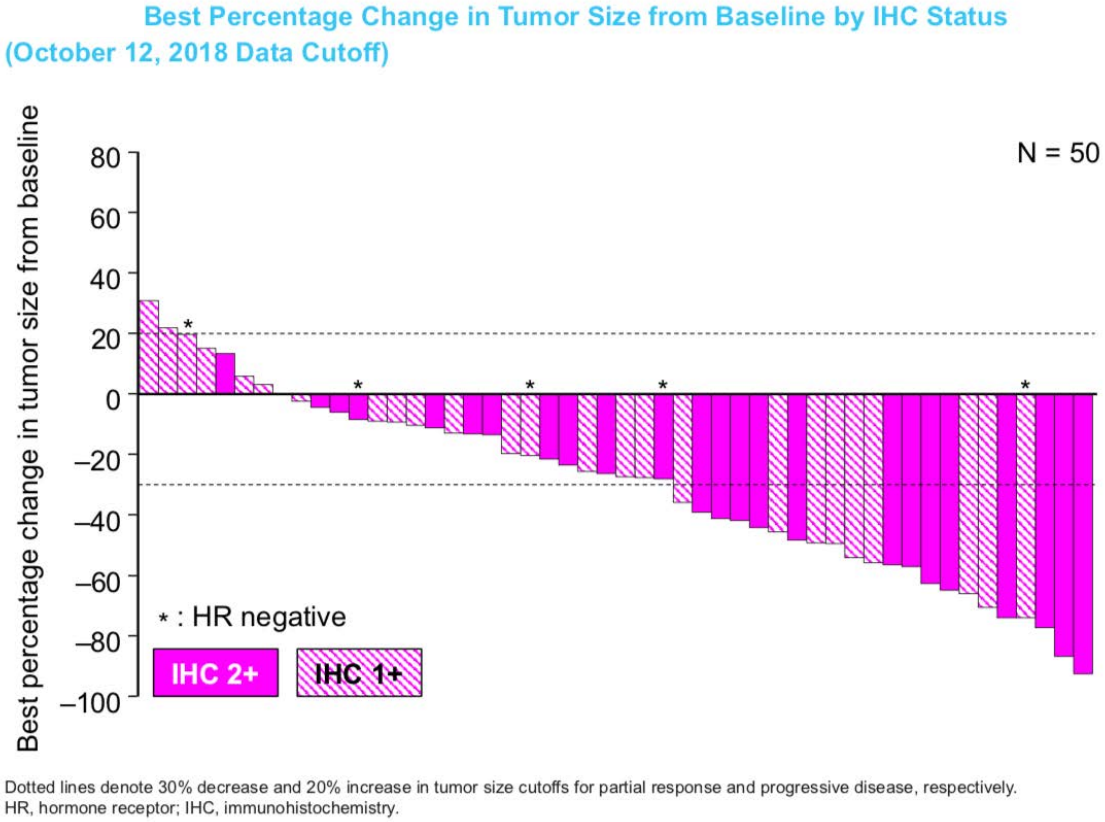
Other ADCs in TNBC…
trastuzumab deruxtecan

Trastuzumab deruxtecan
DS-8201a



DAR = 8

HER2 "low"



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Courtesy of Joyce O'Shaughnessy, MD

Conclusions: Therapeutics for PD-L1 Negative metTNBC

- Cytotoxic therapy is the mainstay of treatment for PD-L1-Negative metastatic TNBC
- Median OS is about 18 mos
- Eribulin improves OS in pretreated metastatic TNBC with neutropenia and neuropathy as treatment-limiting toxicities
- Sacituzumab govitecan improves OS in pretreated metastatic TNBC with neutropenia and diarrhea as treatment-limiting toxicities
- Other ADCs ladiratuzumab vedotin and trastuzumab deruxtecan have promising activity in metastatic TNBC patients
- Trials targeting AKT, DNA damage repair, AR, AURKA, FGFR1/2, CDK4/6, STAT3 in metastatic TNBC are underway

Courtesy of Joyce O'Shaughnessy, MD

Case 1: Triple Negative Brain Metastases

- A 40 year old woman with no family history of breast cancer presented with a grade 3, ki-67 90% T4N1M0 TNBC, had preoperative dose dense AC/T followed by mastectomy, and had a pCR followed by PMRT

- 18 mos later she presented with numerous brain metastases and a biopsy proven humerus metastasis that was triple negative. BRCA1/2 testing was negative

Courtesy of Joyce O'Shaughnessy, MD

Triple Negative Brain Metastases

- She underwent resection of two brain metastases for unremitting headache, followed by WBRT
- She was treated with 4 cycles of cisplatin + etoposide
- 2 years after the WBRT she underwent SRS as therapy for a questionable solitary CNS recurrence
- 8 years later, brain MRI detected a growing mass at the site of the prior SRS and a GBM was found at resection. She died from the GBM 1 year later

Courtesy of Joyce O'Shaughnessy, MD

Case 2: First-Line Metastatic TNBC

- A 30 yo G1P1 Latina woman presented with a T3N0 TNBC and was treated with preoperative AC then paclitaxel carboplatin. BRCA1/2 testing was negative
- At mastectomy there was 3cm residual disease with sarcomatous metaplastic features, node negative
- 9 mos later she presented to ER with abdominal pain and had a 7 cm liver metastasis and questionable second small lesion; biopsy showed TNBC

Courtesy of Joyce O'Shaughnessy, MD

First-Line Metastatic TNBC

- She was treated with eribulin 1.4 mg/m^2 days 1, 8 plus capecitabine 1650 mg/m^2 d1-14 q 21 d and had no toxicity including no alopecia, no disruption of menses, no neuropathy and no HFS
- The liver metastasis responded nearly completely and resection of residual disease showed 3-4 mm of TNBC. NSG showed multiple activating alterations in the AKT pathway

Courtesy of Joyce O'Shaughnessy, MD

First-Line Metastatic TNBC

- She remained on combined eribulin plus capecitabine for 4 additional years without toxicity
- She stopped therapy 2 years ago to have a second child, successfully, and she has remained NED

Courtesy of Joyce O'Shaughnessy, MD

Case 3: Pretreated Metastatic TNBC

- A 39 year old AA woman presented with a right T3N2 triple negative breast cancer and underwent preoperative dose dense AC followed by weekly paclitaxel/carboplatin
- Panel germline testing showed no deleterious mutation
- At mastectomy she had 3 cm residual disease in her breast and 6+ LNs and was treated with PMRT, with and followed by capecitabine
- 18 mos later during reconstructive surgery she was found to have recurrent right chest wall and axillary disease which was PD-L1 negative, as was the primary cancer

Courtesy of Joyce O'Shaughnessy, MD

Pretreated Metastatic TNBC

- Staging showed brachial plexus, axillary and lung metastases
- She was treated with eribulin with 5 mos of stable disease and then had no response to gemcitabine/carboplatin
- By then she had developed severe right upper extremity swelling and neuropathic pain due to axillary and brachial plexus disease
- She was treated with sacituzumab with partial response and marked decrease in arm pain and swelling and improved RUE mobility
- Her response to sacituzumab continues currently 7+ mos on therapy

Courtesy of Joyce O'Shaughnessy, MD