Triple Negative Breast Cancer: Still Jurassic Park?

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WCS WINTER CANCER SYMPOSIUM

Agenda

1. Biology of TNBC
2. BRCA, PARP's and Platinum
3. Immunotherapy in TNBC
4. Other Targets: AR, PI3K, Antibody Drug Conjugates

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Triple Negative Breast Cancer

Relevant financial relationships in the past twelve months by presenter or spouse/partner.

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TRIPLE NEGATIVE BREAST CANCER: STILL JURASSIC PARK?

CHEMOTHERAPY REGIMENS FOR RECURRENT OR STAGE IV (M1) DISEASE[1]

HER2-Negative
Single agent[2]
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)[3]
  - Olaparib[3] (category 1)
  - Talazoparib[3] (category 1)

Other recommended regimens:
- Cyclophosphamide
- Carboplatin
- Docetaxel
- Albumin-bound paclitaxel
- Cisplatin
- Epirubicin
- Ixabepilone

HER2-Negative
Combination regimens[2]
Preferred regimens:
- None[2]

Useful in certain circumstances[2]:
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)
- Gemcitabine/carboplatin
- Paclitaxel/bevacizumab[4]

HER2-Positive
Preferred regimens:
- Pertuzumab + trastuzumab + docetaxel (category 1)[5]
- Pertuzumab + trastuzumab + paclitaxel[5]

Other recommended regimens:
- Ado-trastuzumab emtansine (T-DM1)
- Trastuzumab + paclitaxel[5] ± carboplatin
- Trastuzumab + docetaxel[5]
- Trastuzumab + vinorelbine[5]
- Trastuzumab + capecitabine
- Lapatinib + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents[5,6,7]

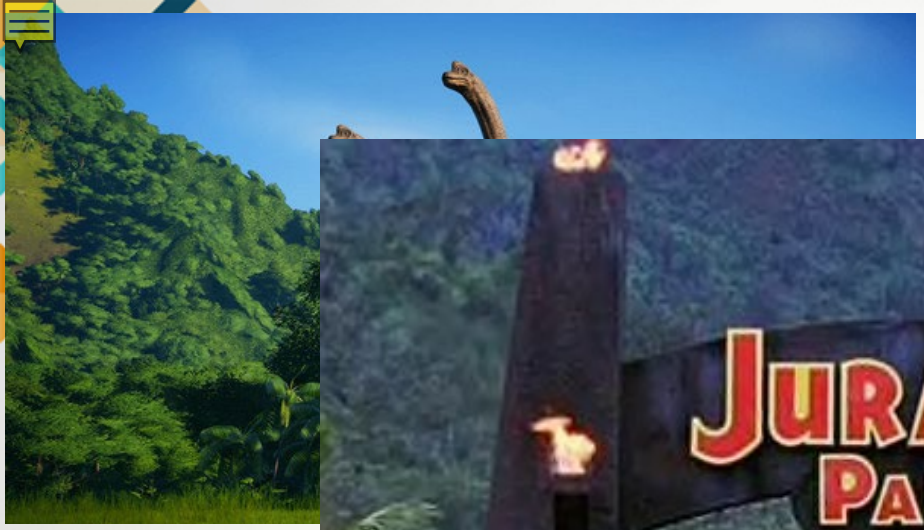
[1]Nab-paclitaxel may be substituted for paclitaxel or docetaxel due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of nab-paclitaxel should not exceed 125 mg/m^2.
[2]Sequential single agents are preferred, but chemotherapy combinations may be used in select patients with high tumor burden, rapidly progressing disease, and visceral crisis.
[3]Patients with HER2-negative disease eligible for single-agent therapy, strongly consider for germline *BRCA 1/2* testing.
[4]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.
[5]Patients previously treated with chemotherapy plus trastuzumab in the absence of pertuzumab in the metastatic setting may be considered for one line of therapy including both trastuzumab plus pertuzumab in combination with or without cytotoxic therapy (such as vinorelbine or taxane). Further research is needed to determine the ideal sequencing strategy for anti-HER2 therapy.
[6]Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.
[7]Trastuzumab may be safely combined with all non-anthracycline containing preferred and other single agents listed above for recurrent or metastatic breast cancer.

Doxorubicin

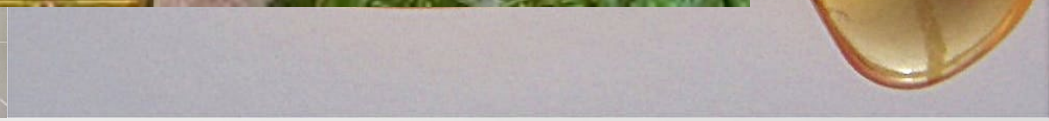
Paclitaxel

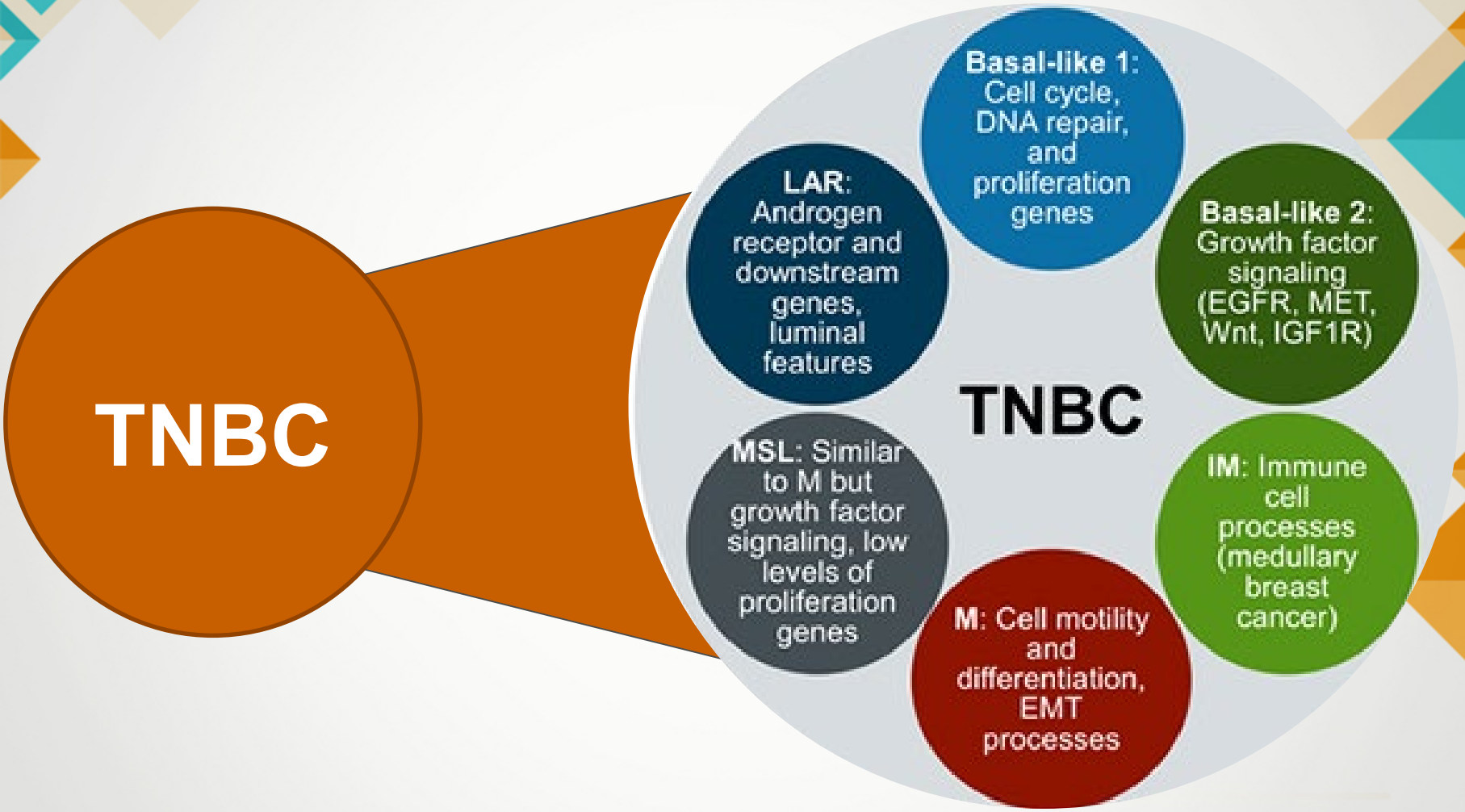
Cyclophosphamide

CMF



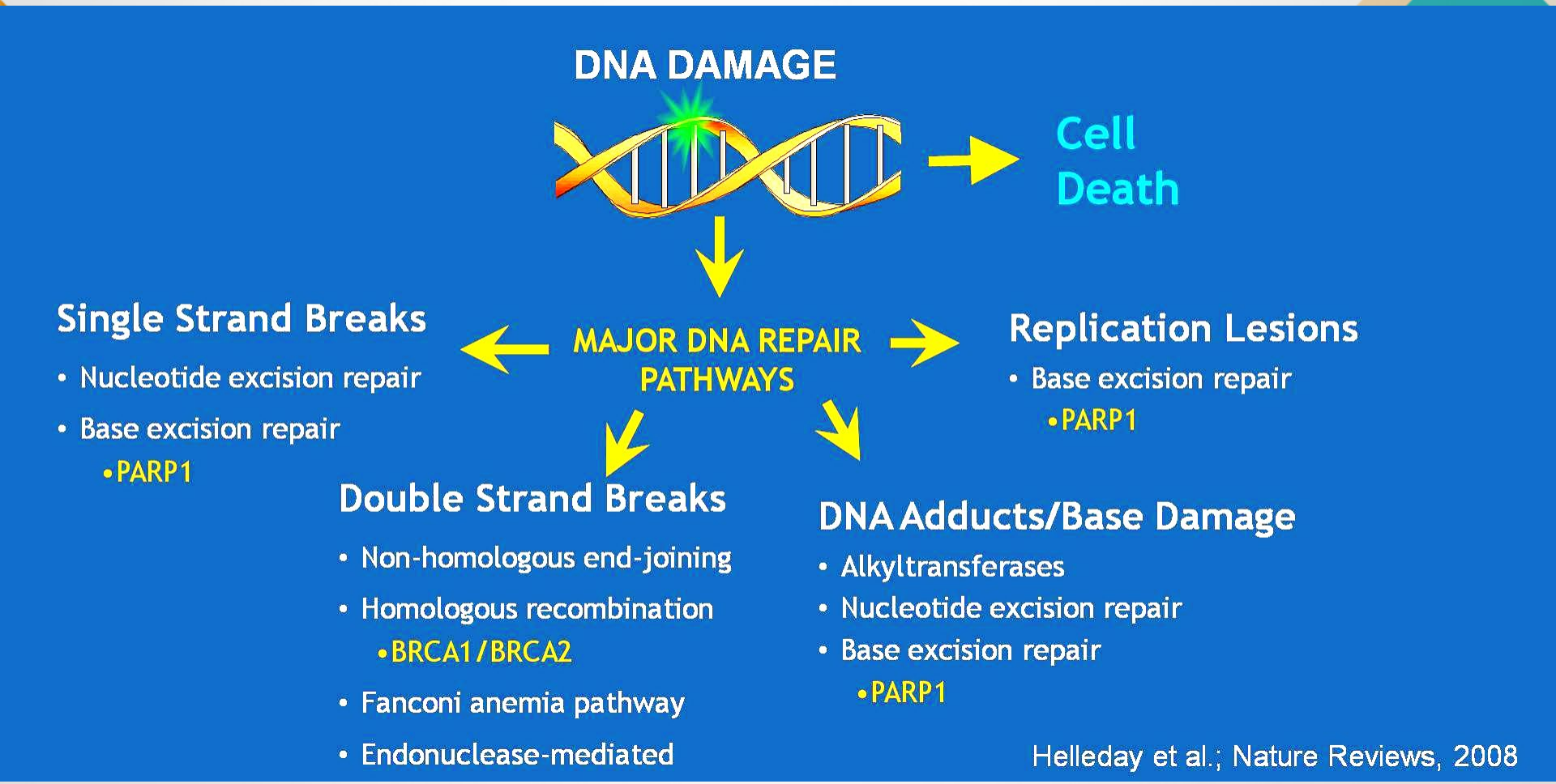
JURASSIC
PARK



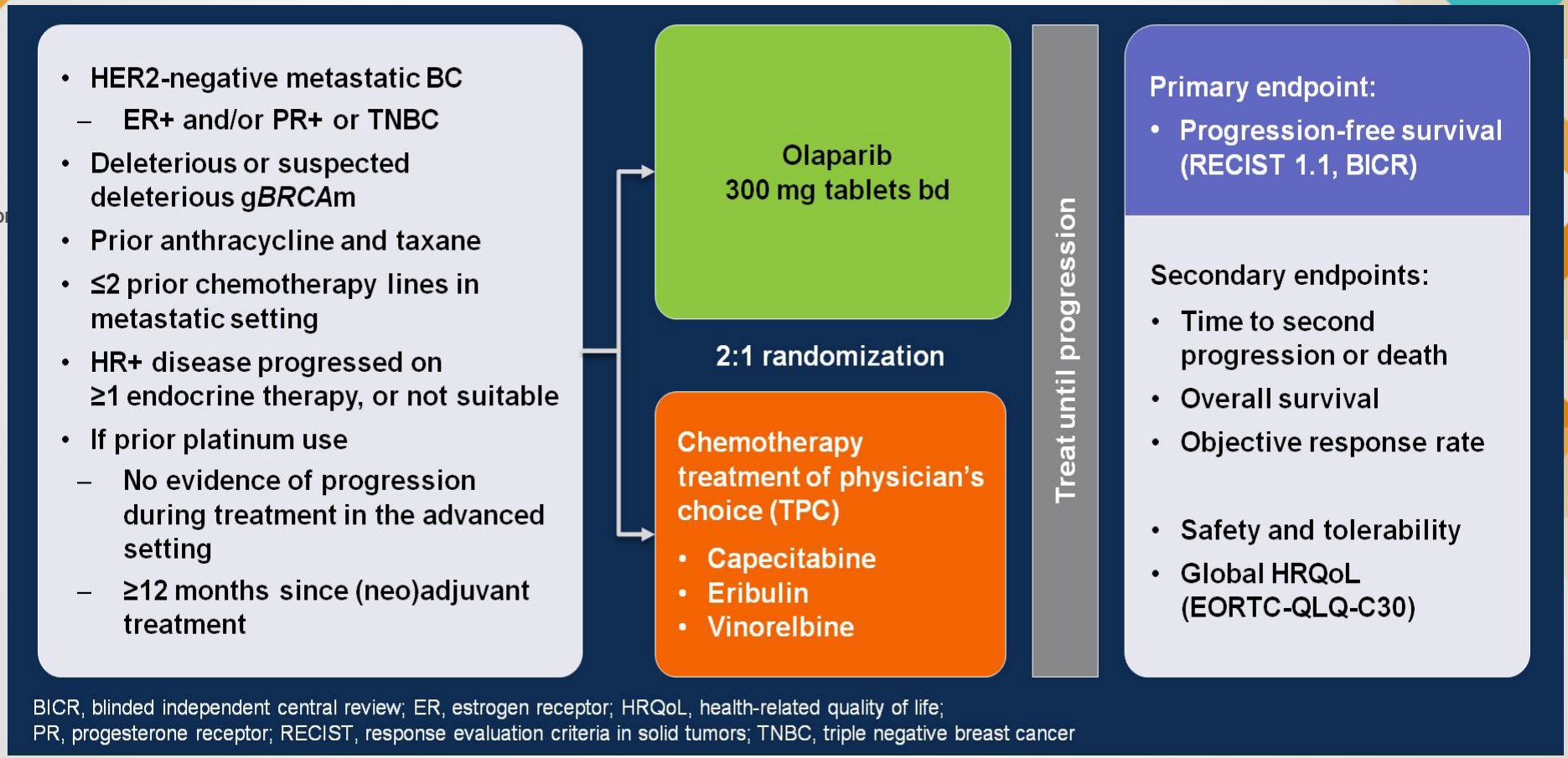


Lehmann BD, et al. *J Clin Invest.* 2011;121:2750-2767.[2]

BRCA and PAPR inhibition

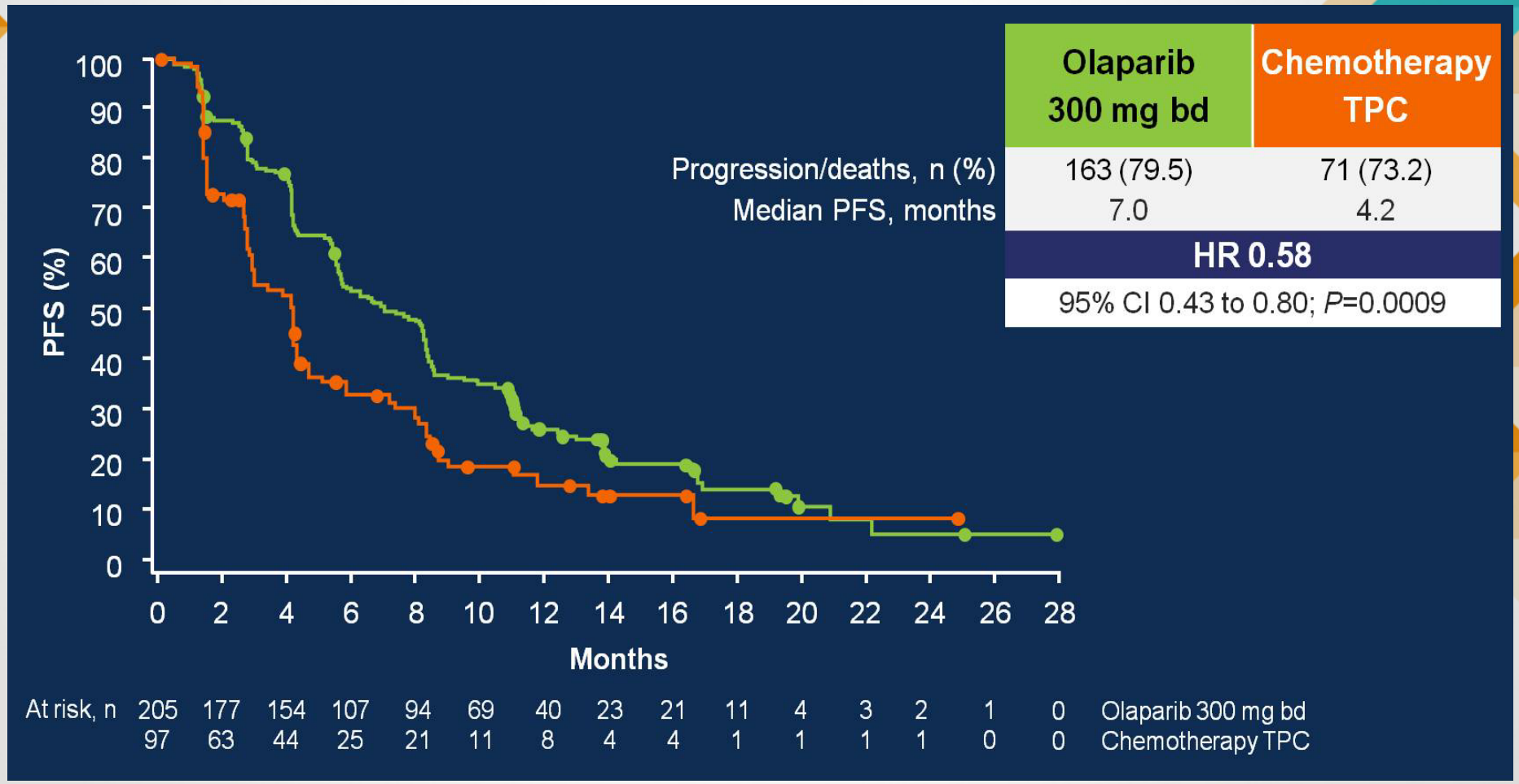


OlympiAD: BRCA TNBC or HR+



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

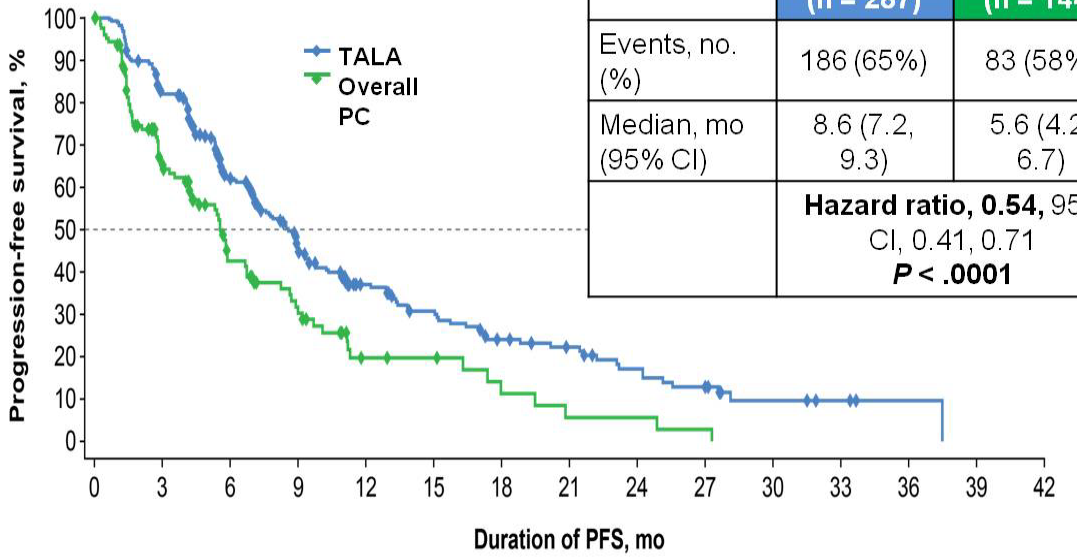
OlympiAD: Primary Endpoint PFS



	Olaparib 300 mg bd	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		

Talazoparib

EMBRACA: Talazoparib PFS



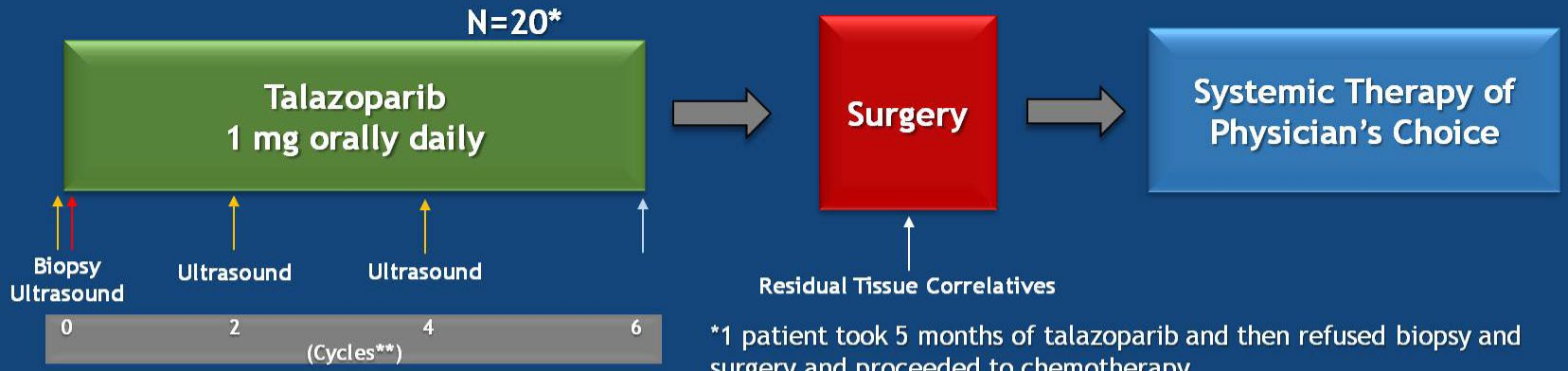
	TALA (n = 287)	Chemo PC (n = 144)
Events, no. (%)	186 (65%)	83 (58%)
Median, mo (95% CI)	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
	Hazard ratio, 0.54, 95% CI, 0.41, 0.71 ***P* < .0001**	

No. at risk (events/cumulative events)

TALA	287 (0/0)	229 (50/50)	148 (53/103)	91 (34/137)	55 (17/154)	42 (9/163)	29 (9/172)	23 (2/174)	16 (5/179)	12 (4/183)	5 (2/185)	3 (0/185)	1 (0/185)	0 (1/186)	0 (0/186)
PCT	144 (0/0)	68 (41/41)	34 (20/61)	22 (8/69)	9 (7/76)	8 (0/76)	4 (3/79)	2 (2/81)	2 (0/81)	1 (1/82)	0 (1/83)	0 (0/83)	0 (0/83)	0 (0/83)	0 (0/83)

Litton et al.; SABCS 2017

Talazoparib in the Neoadjuvant Setting



*1 patient took 5 months of talazoparib and then refused biopsy and surgery and proceeded to chemotherapy
** 1 cycle=28 days

Eligibility

- Tumors > 1 cm
- Clinical Stage I-III
- Germline BRCA mutation
- No previous therapy for invasive breast cancer

Exclusion

- HER2 positive

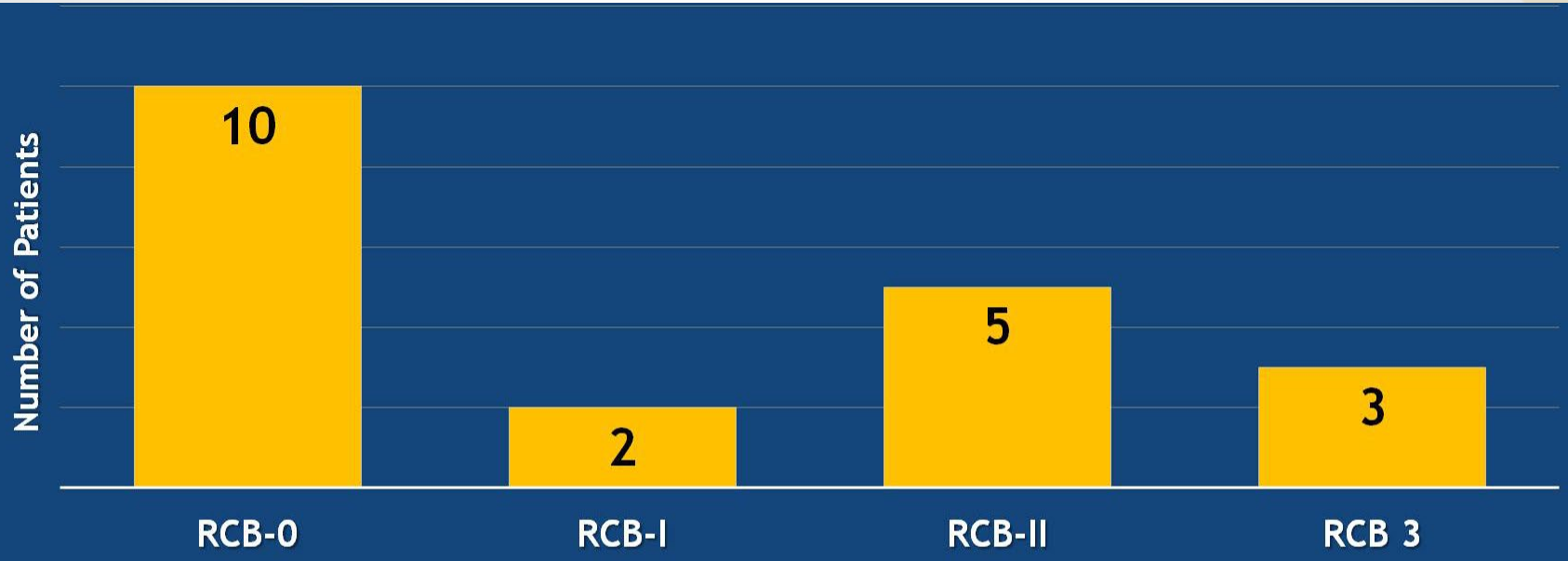
Primary Objectives

- pCR (ypT0/is ypN0)
- RCB-0 + RCB-I

Secondary Objective

- Evaluate toxicity

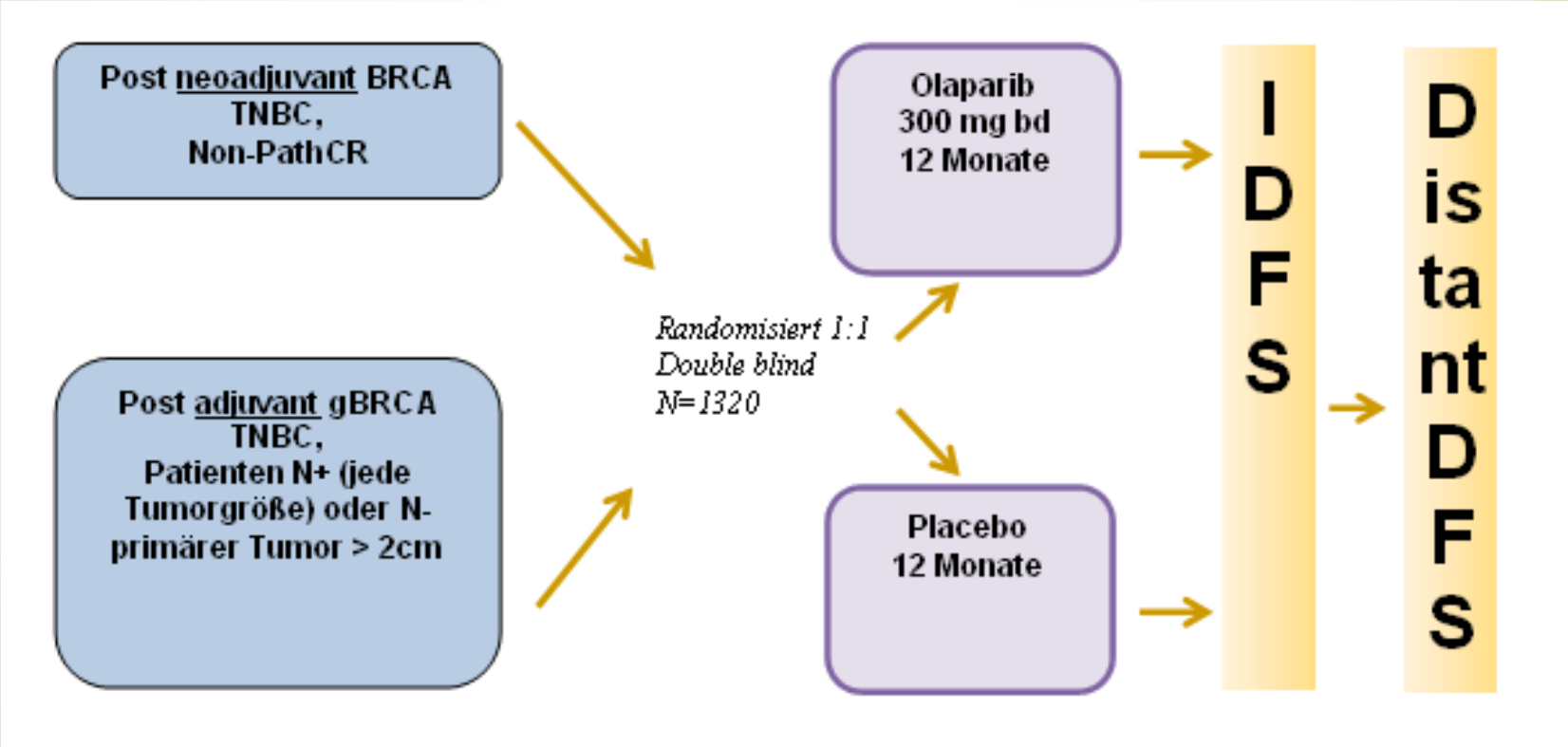
Pathologic Results: RCB



pCR (RCB-0): 10/19 = 53%, 95% CI = 32%, 73%

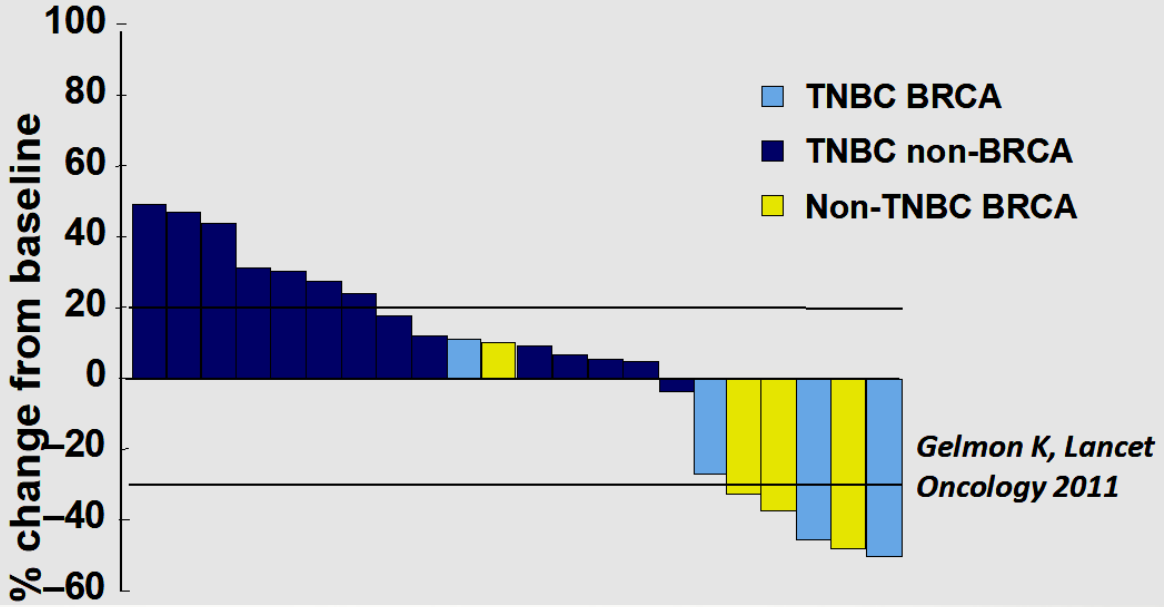
RCB-0+I: 12/19 = 63%, 95% CI = 41%, 81%

Adjuvant PARPi in BRCA+ TNBC: Olympia



Parp inhibition in BRCA1+ and Sporadic

Randomized phase II olaparib in sporadic TNBC and known BRCA mutation carriers:



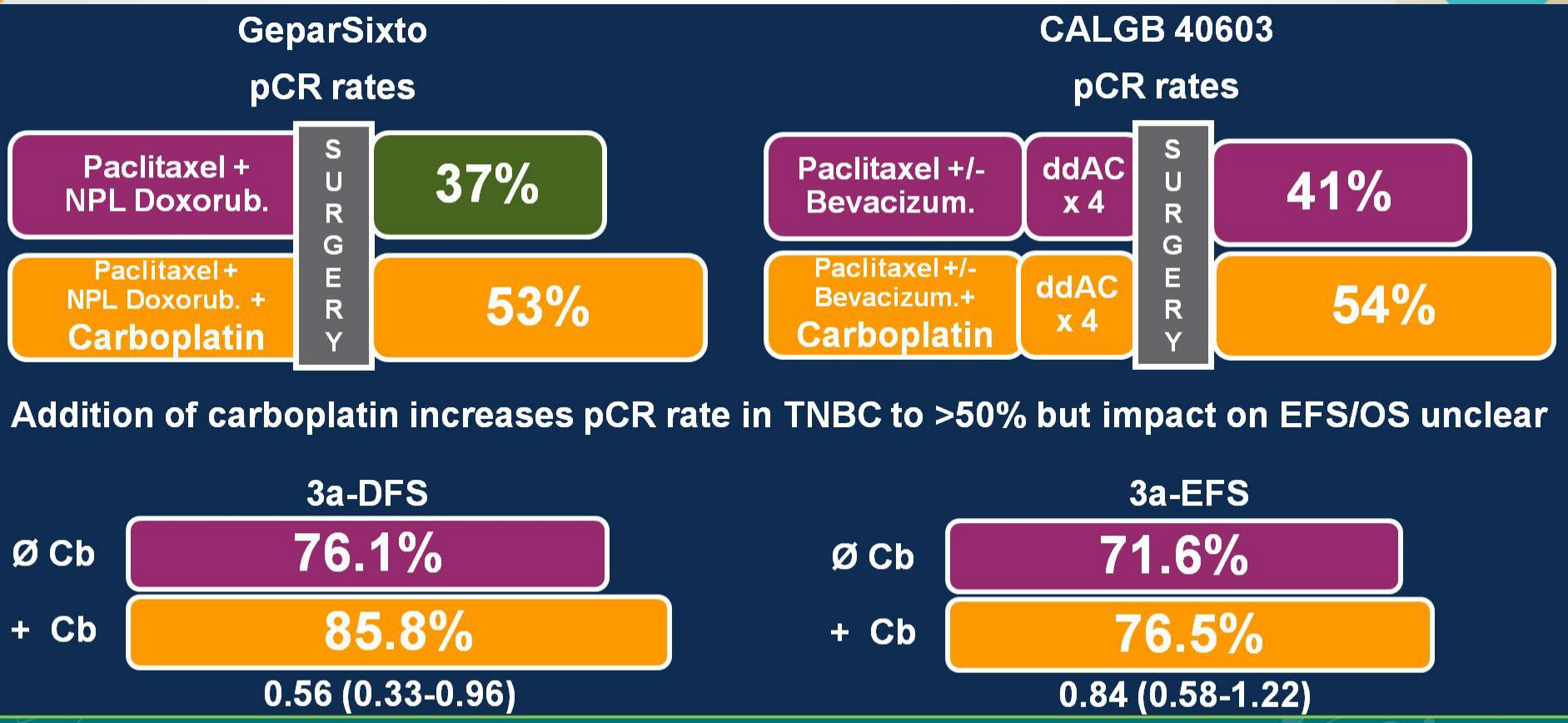
Clinical data to date: BRCA not encouraging in sporadic TNBC

Platinum in TNBC: What we know

- ✓ Cisplatin had 47% response rate in first line metastatic breast cancer reported by Segal et al (JCO 1988)
- ✓ Use was replaced by taxanes, mostly due to concerns with toxicities
- ✓ Regain interest, especially in TNBC due to DNA crosslinking mechanism of action
- ✓ Great responses in TNBC in the neoajuvant setting and in BRCA carriers

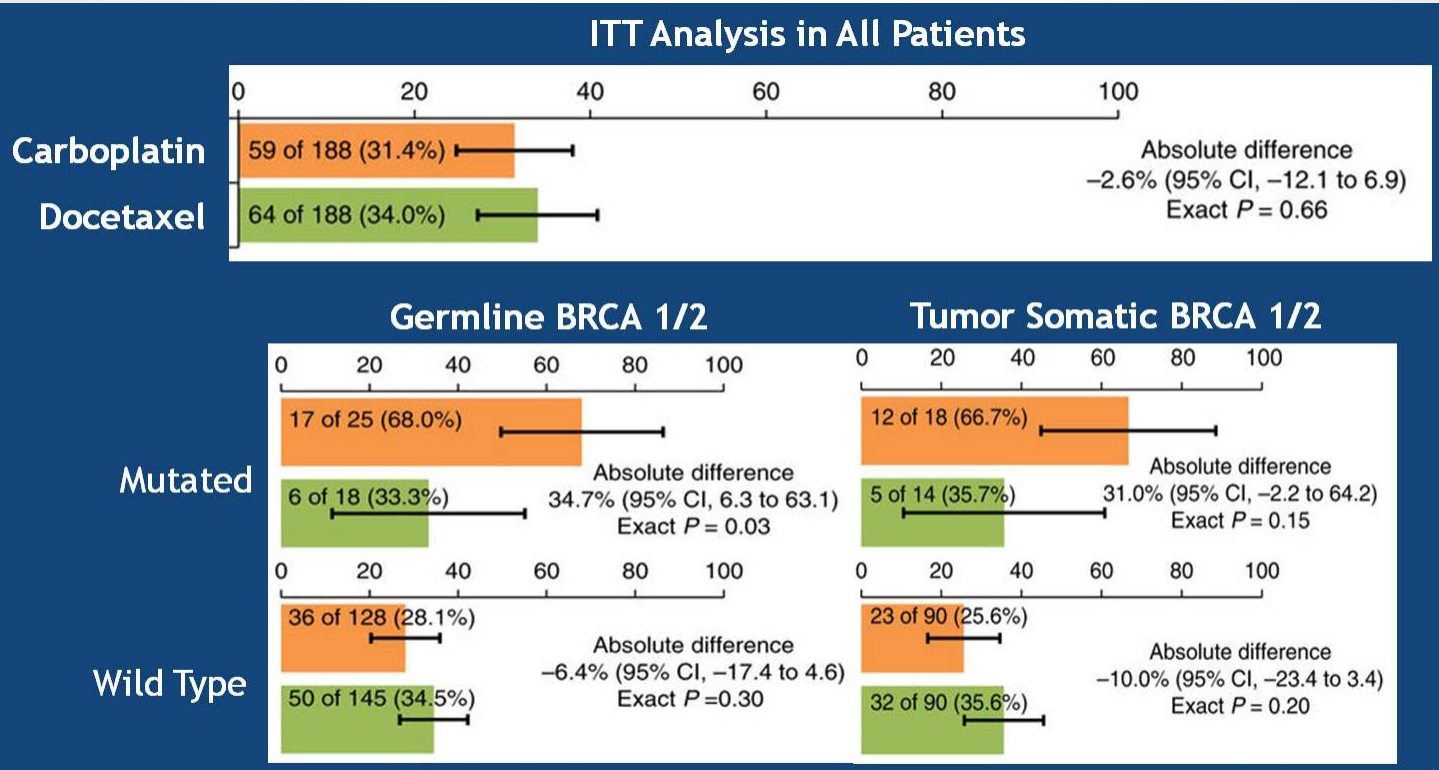
Sledge et al, JCO 2008; Silver et al JCO 2010; Gronwold et al, ASCO 2009

Carboplatin in unselected TNBC, Neoadjuvant



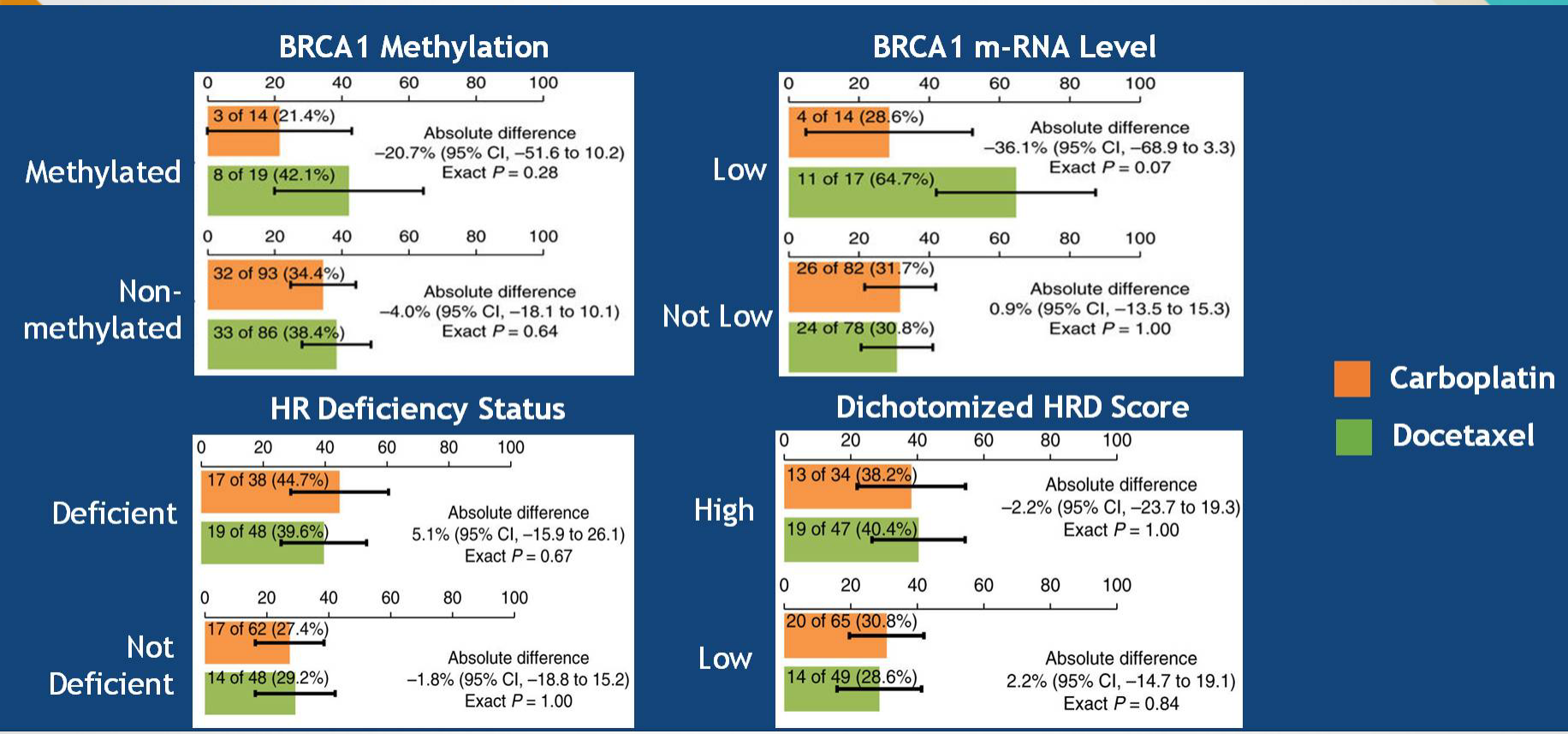
von Minckwitz G Lancet Oncol 2014; Sikov W JCO 2015

Carboplatin in Metastatic Setting: TNT Trial



Tutt, et al.; Nature Med., 2018

TNT Trial



Presented By Stacy Moulder at 2018 ASCO Annual Meeting

Immunomodulatory PD-1

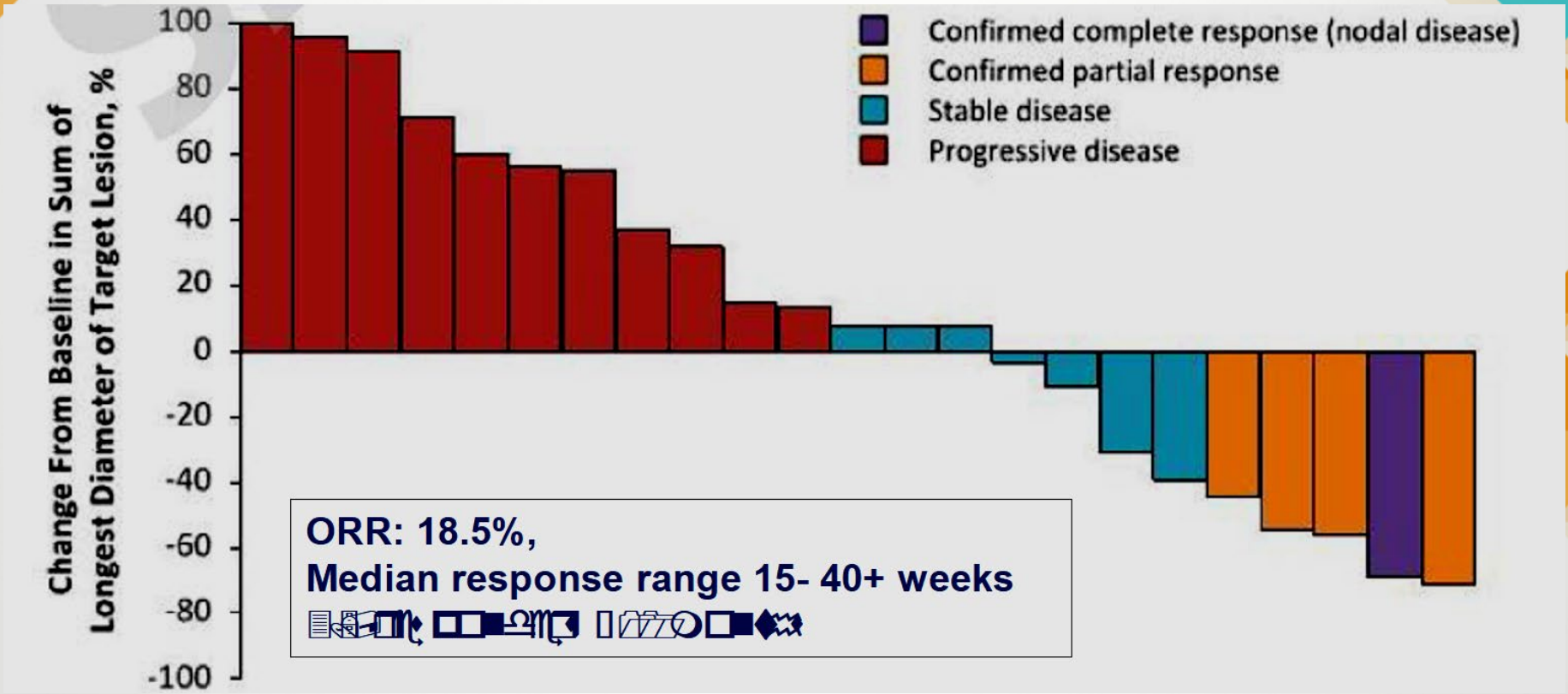
- ✓ Higher PD-L1 expression in TNBC than non TNBC
- ✓ Robust presence of tumor infiltrating lymphocytes (TILs) in the immunomodulatory subtype
  - High TILs are an independent predictor for pCR/ response to chemotherapy
  - High TILs are associated with increased PD-1expression inTNBC – May suggest sensitivity to immune directed therapies
- ✓ TNBC might have a higher mutational load than other breast cancer subtypes that can produce neoantigents

Ibrahim E et al, Br Ca Res Treat, 2014; Denkert C et al, JCO, 2010, 2014, 2015

PD-1 and PD-L1

	n	Median # prior lines therapy (range)	Agent(s)	ORR (95% CI)	Median duration response
KEYNOTE-012 (NCT01848834)	32	2 (0-9)	Pembro	18.5%	NR
KEYNOTE-086 (NCT02447003)	A (>1 prior therapy)= 170	NR	Pembro	5%	6.3 mths
	B (1st line, PD-L1+)= 52	0		23%	8.4 mths
Javelin	58	2 (1-6)	Avelu	5.2%	5.9 mths
Phase I	54 (evaluable=21)	NR	Atezo	19%	NR

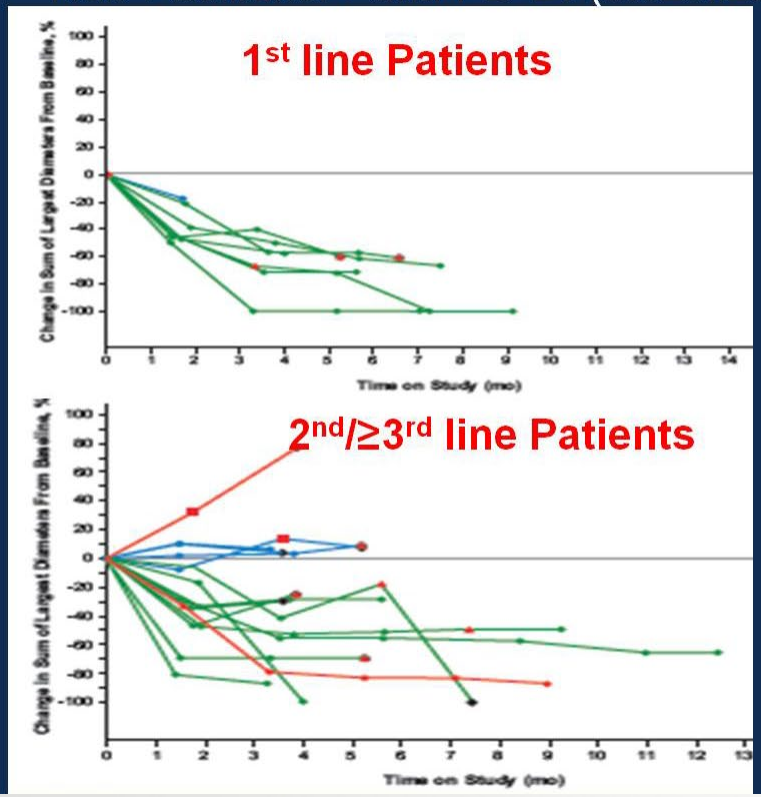
Keynote 012:
Pembrolizumab in the TNBC group



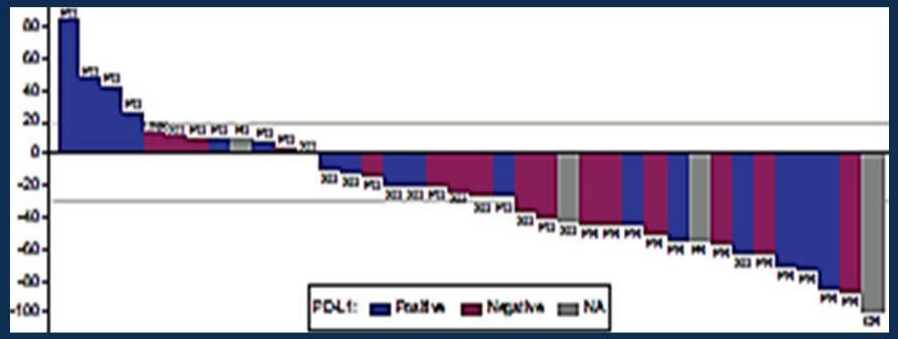
Nanda, SABCS 2014, JCO 2016

Combination Immune and Chemotherapy in TNBC

Nab-Paclitaxel + anti-PD-L1 (atezolizumab)



Eribulin + anti-PD-1 (pembrolizumab)



	All	1st line (n=17)	2nd/3rd L (n=18)
ORR	34.4%	41.2%	27.3%
CBR	40.6%	47.1%	36.4%

Atezolizumab + nab-Paclitaxel

Best Overall Response	1L (n = 9)	2L (n = 8)	3L+ (n = 7)	All Patients N = 24 % (95% CI)
Confirmed ORR (95% CI)[a]	66.7% (29.9, 92.5)	25% (3.2, 65.1)	28.6% (3.7, 71.0)	41.7% (22.1, 63.4)
ORR (95% CI)[b]	88.9% (51.7, 99.7)	75.0% (34.9, 96.8)	42.9% (9.9, 81.6)	70.8 % (48.9, 87.4)
CR	11.1%	0	0	4.2%
PR	77.8%	75.0%	42.9%	66.7%
SD	11.1%	25.0%	28.6%	20.8%
PD	0	0	28.6%	8.3%

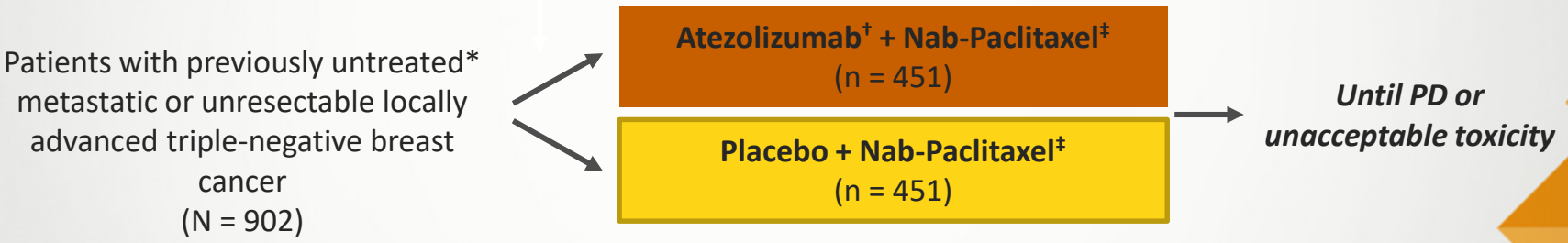
*Nab-paclitaxel 53% |--------22%--------|

Adams et al, ASCO 2016
*Forrero-Torres, Clinical Cancer Res, 2015

IMpassion130: Biomarker Analysis in TNBC Patients Receiving Frontline Atezolizumab + Nab-Paclitaxel

✓ International, randomized, double-blind phase III study[1,2]

Stratified by prior taxane use, liver metastases, and PD-L1 expression on IC



*Prior chemo in curative setting permitted if tx-free for ≥ 12 mos. †840 mg IV Q2W. ‡100 mg/m^2 IV on D1, 8, and 15 of 28-day cycle.

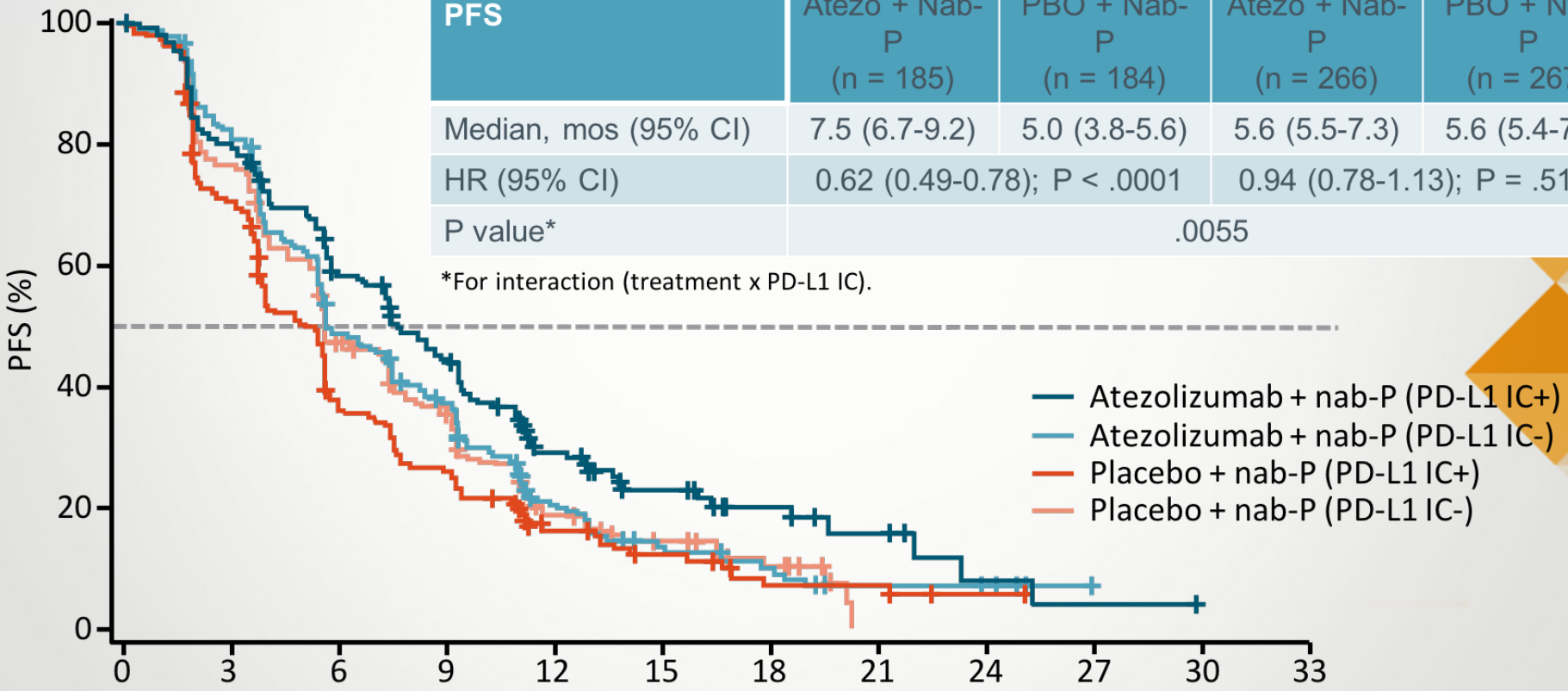
- Coprimary endpoints: PFS, OS in ITT population and PD-L1+ subgroup (≥ 1% on tumor infiltrating IC)[1]
- Exploratory analysis: efficacy by PD-L1 expression on TC, intratumoral CD8+ T-cells, sTILs, *BRCA1/2* status[2]

1. Schmid. NEJM. 2018;379:2108. 2. Emens. SABCS 2018. Abstr GS1-04.

IMpassion130: PFS by PD-L1 Expression

PFS	PD-L1 IC Positive		PD-L1 IC Negative	
	Atezo + Nab-P (n = 185)	PBO + Nab-P (n = 184)	Atezo + Nab-P (n = 266)	PBO + Nab-P (n = 267)
Median, mos (95% CI)	7.5 (6.7-9.2)	5.0 (3.8-5.6)	5.6 (5.5-7.3)	5.6 (5.4-7.2)
HR (95% CI)	0.62 (0.49-0.78); P < .0001		0.94 (0.78-1.13); P = .5152	
P value*	.0055			

*For interaction (treatment x PD-L1 IC).

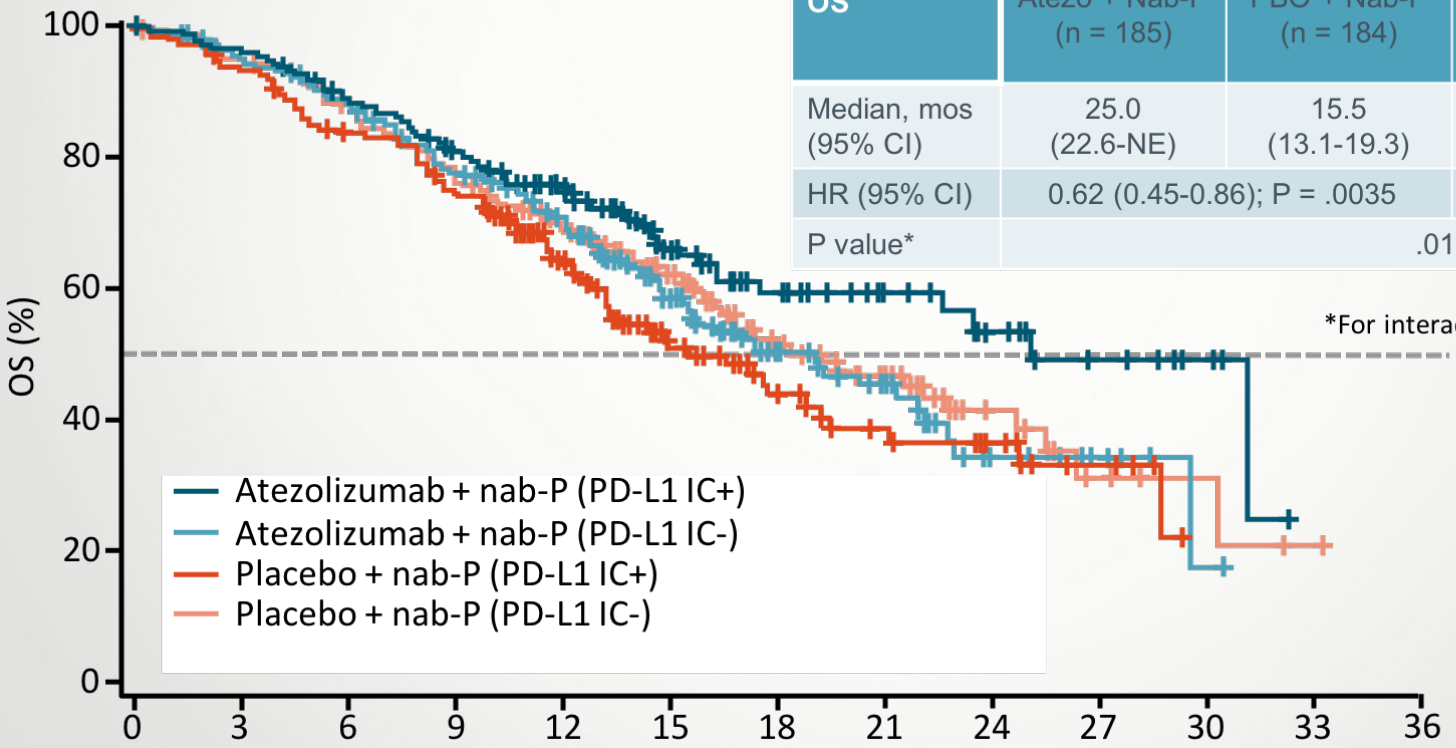


Emens. SABCS 2018. Abstr GS1-04.

IMpassion130:OSby PD-L1 Expression

OS	PD-L1 IC Positive		PD-L1 IC Negative	
	Atezo + Nab-P (n = 185)	PBO + Nab-P (n = 184)	Atezo + Nab-P (n = 266)	PBO + Nab-P (n = 267)
Median, mos (95% CI)	25.0 (22.6-NE)	15.5 (13.1-19.3)	18.9 (15.5-22.0)	18.4 (16.4-24.7)
HR (95% CI)	0.62 (0.45-0.86); P = .0035		1.02 (0.79-1.31); P = .9068	
P value*	.0178			

*For interaction (treatment x PD-L1 IC).



Emens. SABCS 2018. Abstr GS1-04.

TNBC AR luminal type

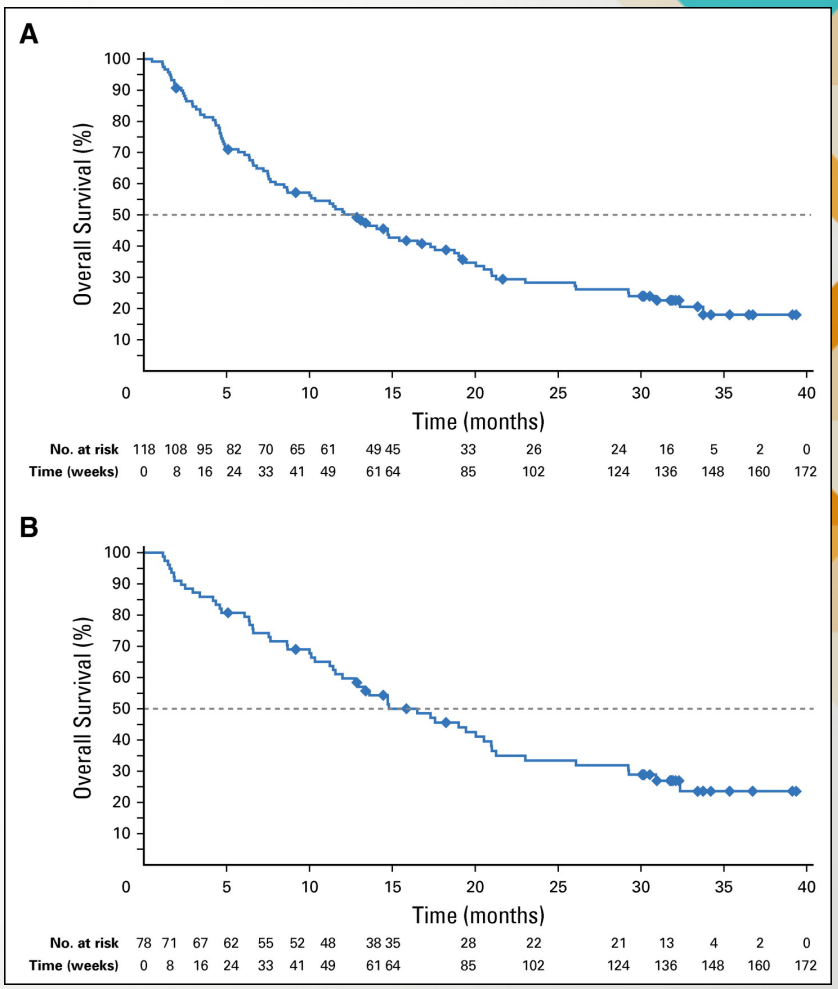
- ✓ Seems to be hormonally regulated, clustering closer to estrogen receptor (ER)–positive/progesterone receptor (PgR)–positive disease, despite lacking expression of these receptors
- ✓ Growth of this subtype is thought to be driven by signaling through the androgen receptor (AR)
- ✓ AR-expressing TNBC cell lines and in vivo models have demonstrated growth activation by AR stimulation and decreased growth by AR antagonists

Enzalutamide for the Treatment of Androgen Receptor–Expressing Triple-Negative Breast Cancer

Table 2. Clinical Benefit

Benefit	Evaluable Subgroup (n = 78)	ITT Population (N = 118)
CBR16		
No.	26	29
% (95% CI)	33 (23 to 45)	25 (17 to 33)
CBR24		
No.	22	24
% (95% CI)	28 (19 to 39)	20 (14 to 29)
CR or PR		
No.	6	7
%	8	6

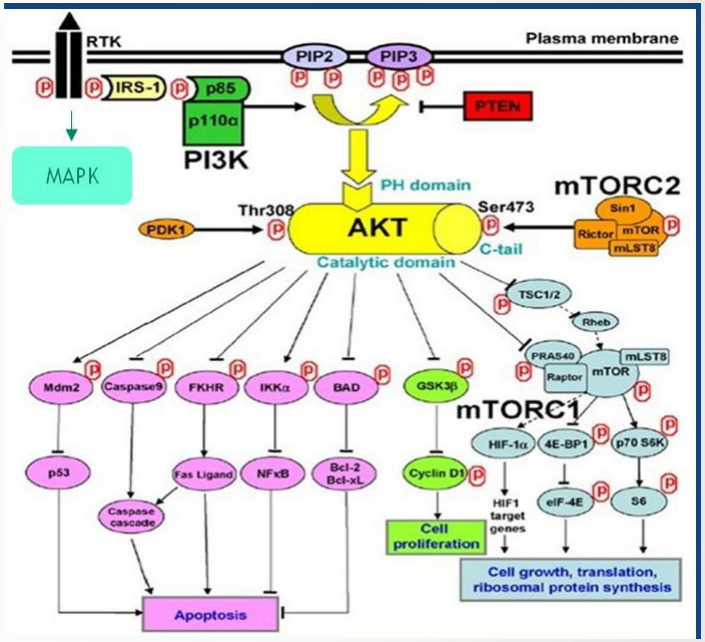
Abbreviations: CBR16, clinical benefit rate at 16 weeks; CBR24, clinical benefit rate at 24 weeks; CR, complete response; ITT, intent-to-treat; PR, partial response.



Traina T et al JCO, 2018

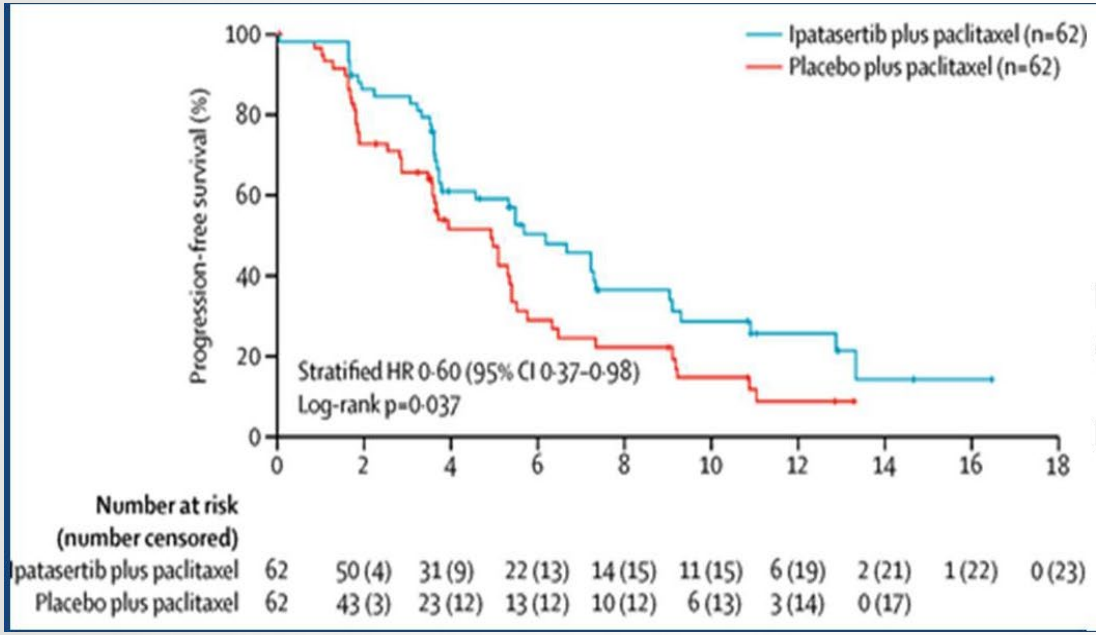
PI3K/AKT pathway

- ✓ One of the most frequently altered pathways in breast cancer and is key for survival and growth of tumors
- ✓ AKT can be activated by
  - Loss of function of negative regulators (ie PTEN)
  - Gain of function of positive regulators (PI3K, AKT, HER2)



Toker A. Cell 2017

Lotus: Ipatasertib with paclitaxel



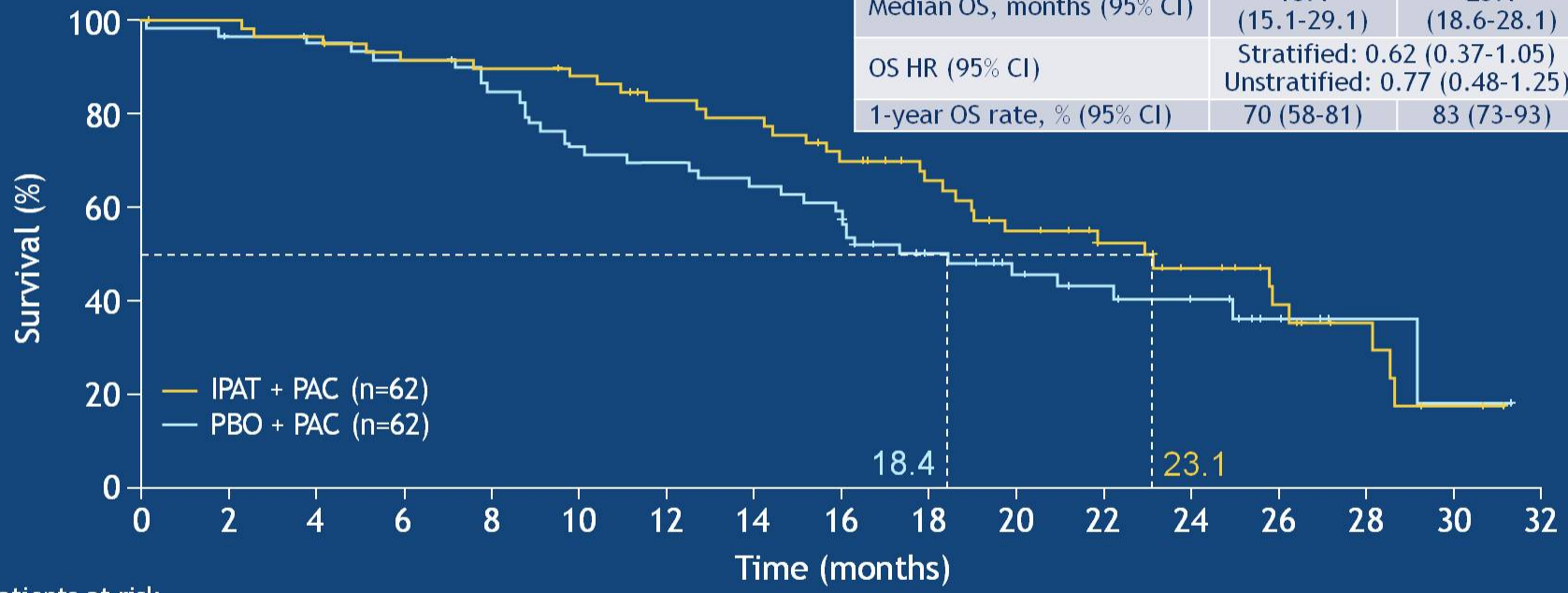
	Ipatasertib 400 mg daily + paclitaxel (n=62)	Placebo + paclitaxel (n=62)
Progression/deaths, n (%)	39 (62.9)	45 (72.6)
Median PFS, months	6.2	4.9
	HR 0.60 95% CI 0.37 to 0.98; *P*=0.037	

Kim et al Lancet Oncol, 2017

OS Update on Lotus Trial

OS in the ITT population

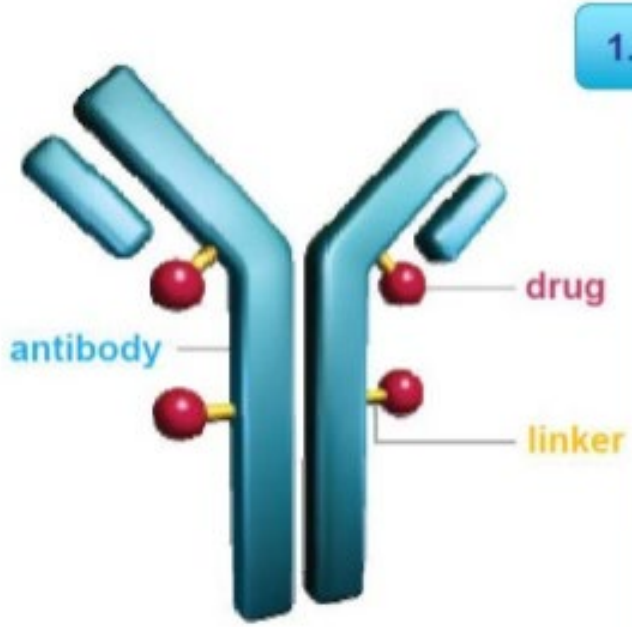
	PBO + PAC (n=62)	IPAT + PAC (n=62)
OS events, n (%)	35 (56)	33 (53)
Median OS, months (95% CI)	18.4 (15.1-29.1)	23.1 (18.6-28.1)
OS HR (95% CI)	Stratified: 0.62 (0.37-1.05) Unstratified: 0.77 (0.48-1.25)	
1-year OS rate, % (95% CI)	70 (58-81)	83 (73-93)



No. of patients at risk

IPAT + PAC	62	60	58	54	53	51	46	44	37	31	25	20	15	10	6	2
PBO + PAC	62	59	57	55	50	43	41	38	32	24	19	16	13	6	2	1

Antibody drug conjugates



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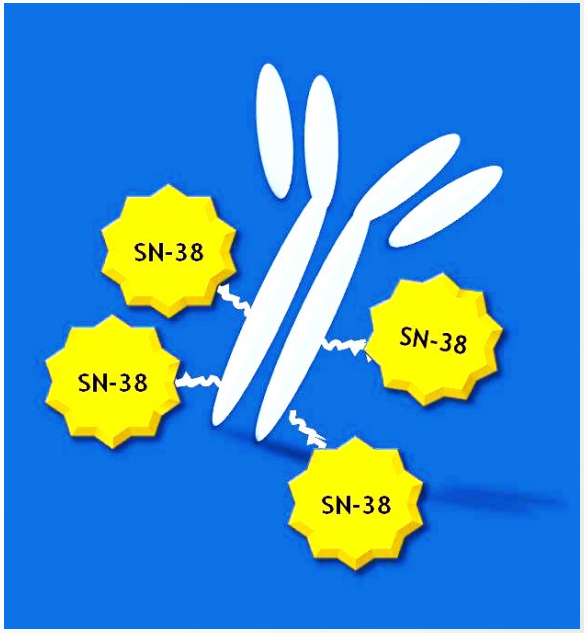
1. Antibody | 2. Linker | 3. Drug

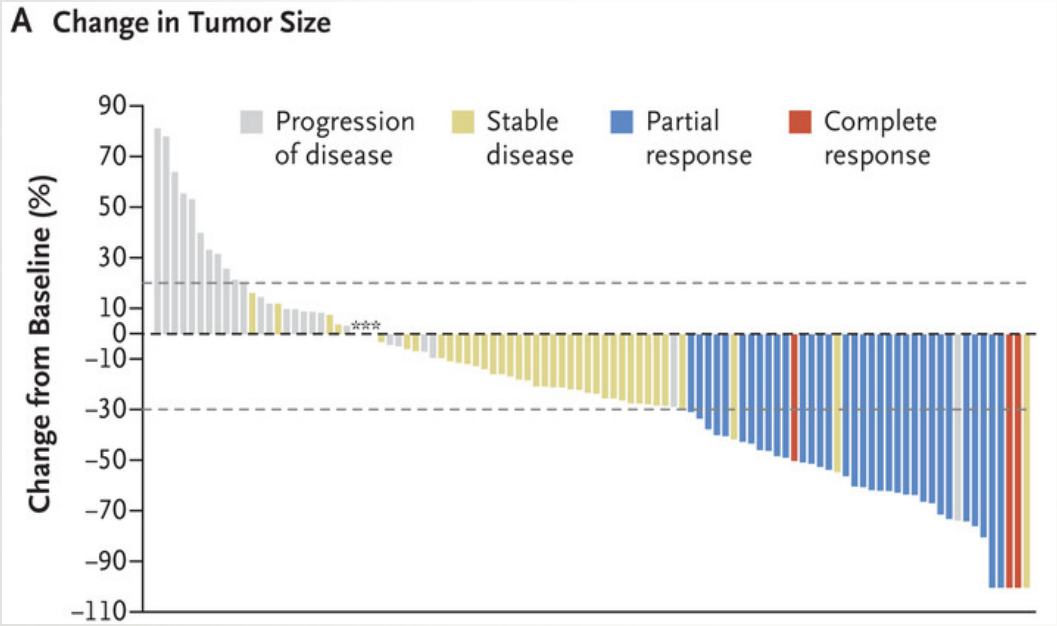
1. Monoclonal antibody specific for a tumor antigen with little/no expression on normal cells
2. Linker that is stable in circulation but releases the cytotoxic agent in target cells
3. Potent cytotoxic agent designed to induce target cell death when internalized and released

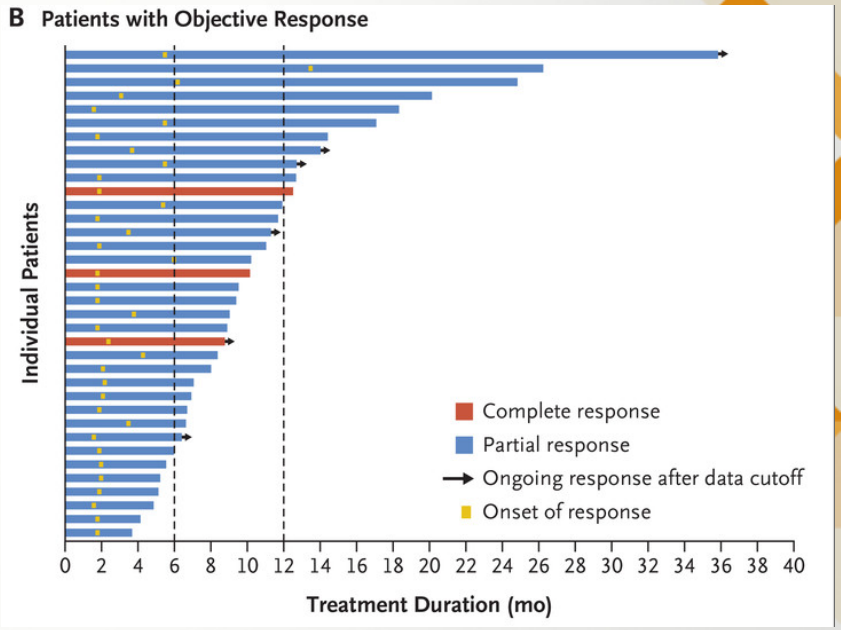
Sacituzumab Govitecan

- ✓ Anti Trop-2 antibody
- ✓ Trop-2 expressed in up to 80% of TNBC
- ✓ Linked to SN-38 (active metabolite of irinotecan



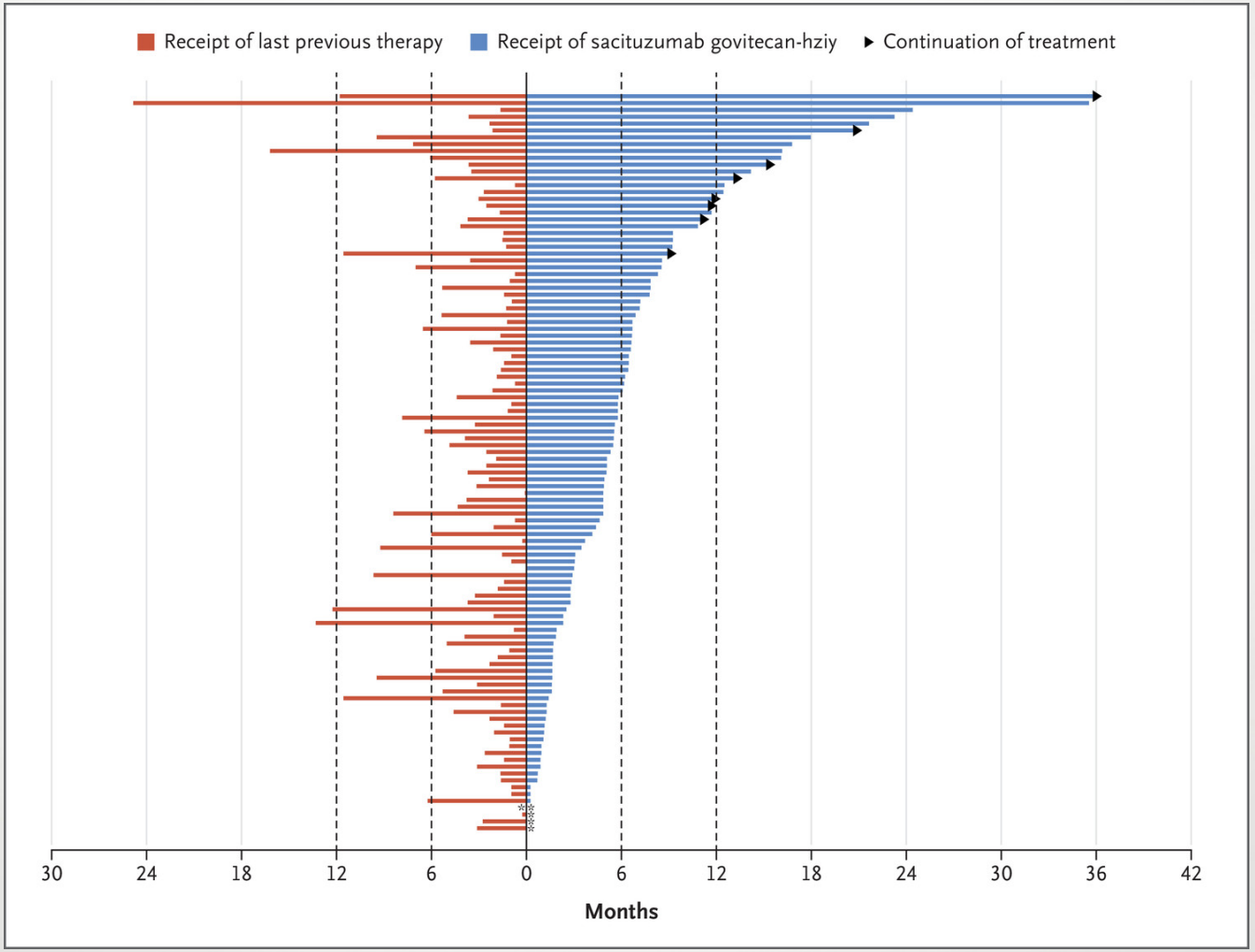
Response and Survival among 108 Patients with Metastatic Triple-Negative Breast Cancer.





A Bardia et al. N Engl J Med 2019;380:741-751.

Duration of Treatment with Sacituzumab Govitecan-hziy and with the Last Previous Therapy in the 108 Patients with Metastatic Triple-Negative Breast Cancer.



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Conclusions

- TNBC is a very heterogenous disease: no single target
- Platinum chemotherapy may have a role for some mTNBC, but not all
- PAPR inhibition is a therapeutic option in BRCA carriers in the metastatic setting
- New promising approaches including immunotherapy, TKI, and antibody drug conjugates
- Need for better biomarkers to be used at the clinic for better selection of patients and treatment options.

Triple Negative Breast Cancer: Still Jurassic Park?