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TNBC/BRCA MUTATED TUMORS: WHAT'S NEW?

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14th Annual California Cancer Consortium Meeting

COI

Grant/research support: Puma, Novartis, Merck, Genentech, Eisai
consultant: Puma
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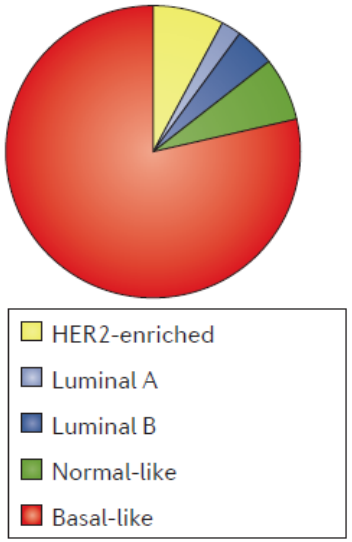
Outline

- Overview of TNBC Biology
- PI3K/AKT/MTOR Targeting:
  - LOTUS (ipatasertib)
  - PKAT (AZD5363, capivasertib)
- PARP inhibitor: Neoadjuvant Talazoparib
- PARP inhibitor + Immune Check Point Inhibitor:
  - TOPACIO (Niraparib + Pembrolizumab)
- Drug-Antibody Conjugates: IMMU-132

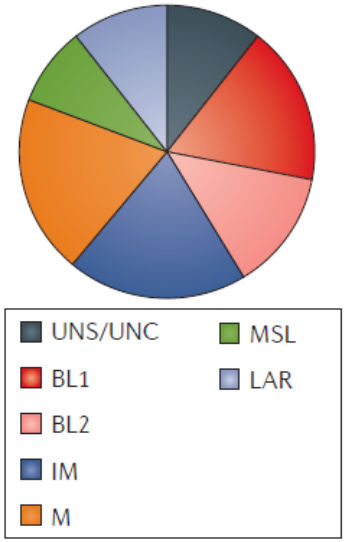
Overview of Triple Negative Breast Cancer (TNBC) and Molecular Heterogeneity

- Defined by lack of ER/PR/HER2 receptors
- 15 -20% of all invasive breast cancers
- Significantly more aggressive: visceral metastasis
- Lack of effective therapy
- Medium survival in mTNBC:
  - OS 13 month
  - PFS:
    - 1st line 12 weeks
    - 2nd line 9 weeks
    - 3rd line 4 weeks

Intrinsic PAM50 Subtypes

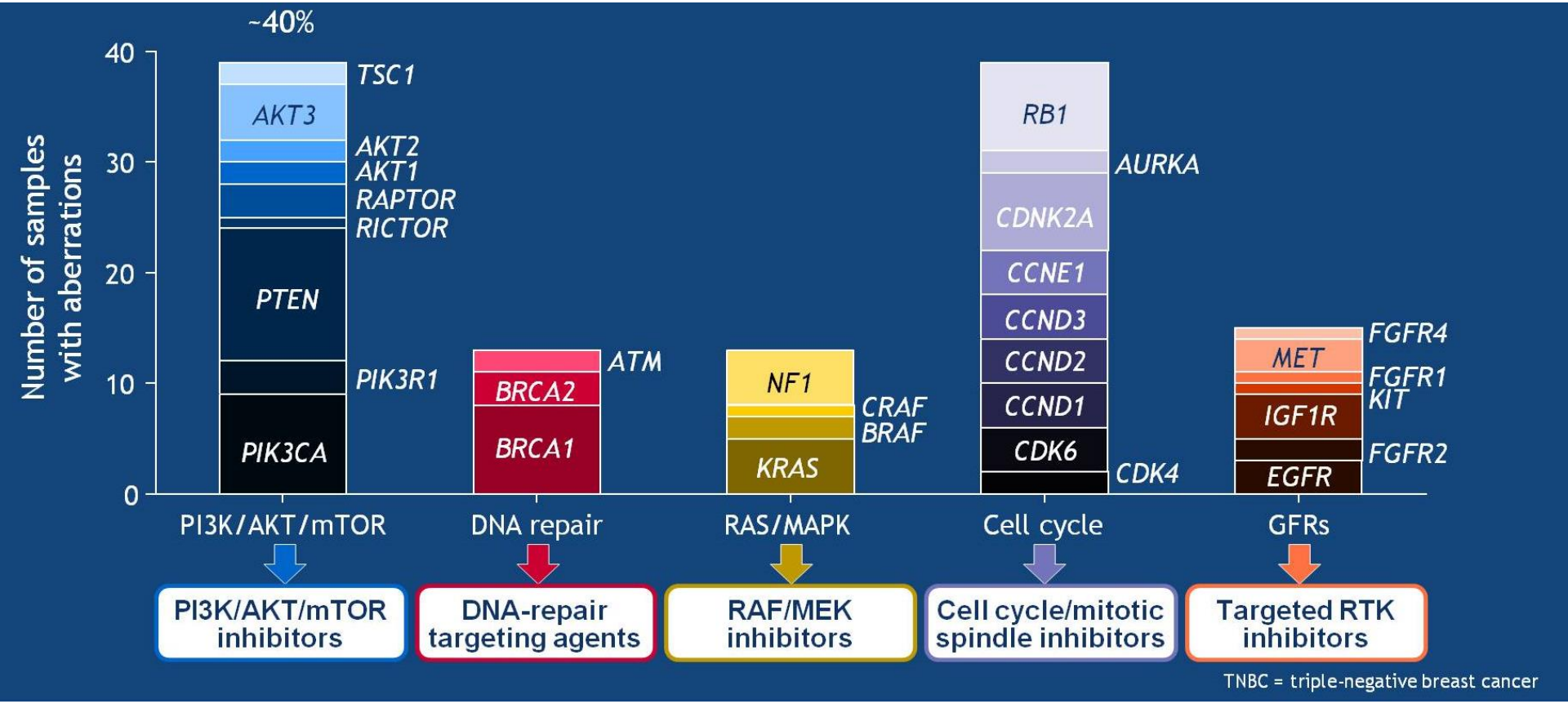


Lehmann et al Subtypes



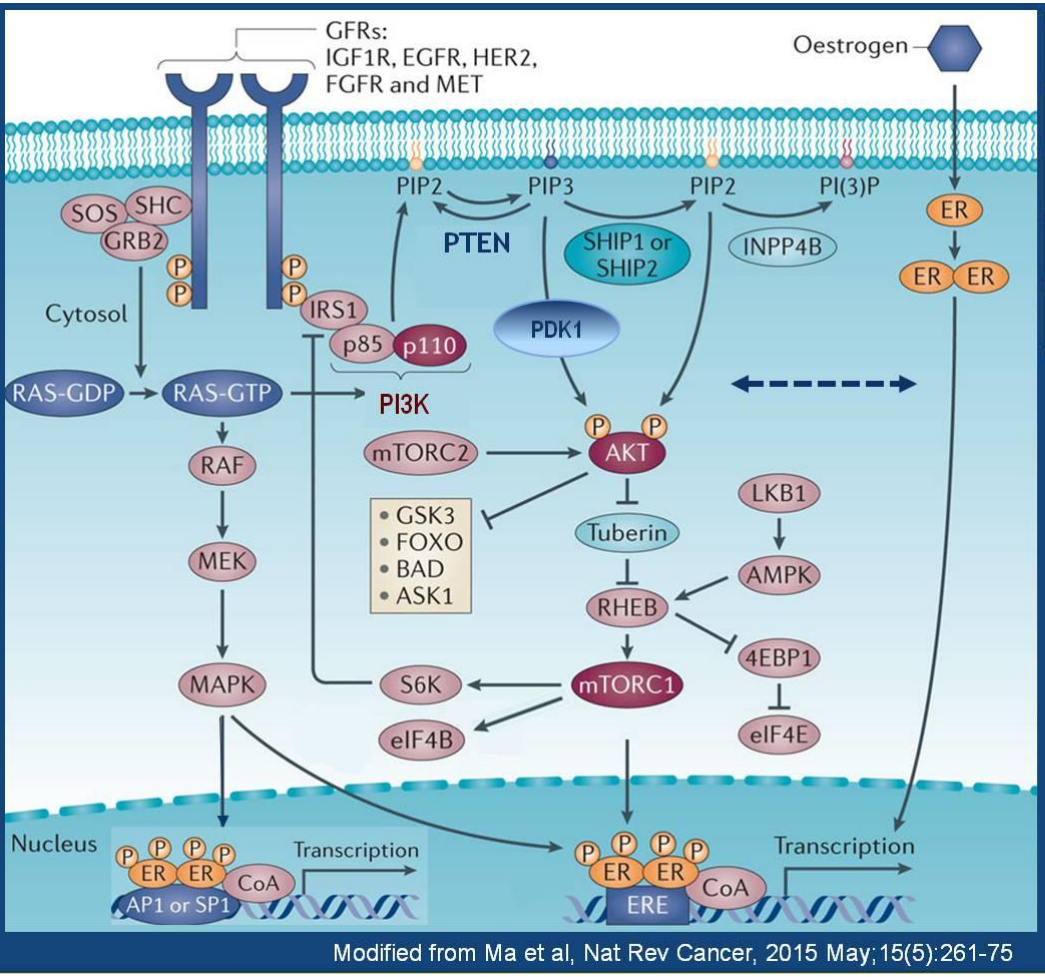
Hartman AR et al Cancer 2012
Dent R et al Clin Cancer Res 2007
Bianchini et al Nature Review 2016

Clinically targetable pathways in TNBC



Balko et al Cancer Discov 2014
Dent 2018 ASCO

PI3K/AKT/mTOR Pathway in Breast Cancer



Modified from Ma et al, Nat Rev Cancer, 2015 May;15(5):261-75

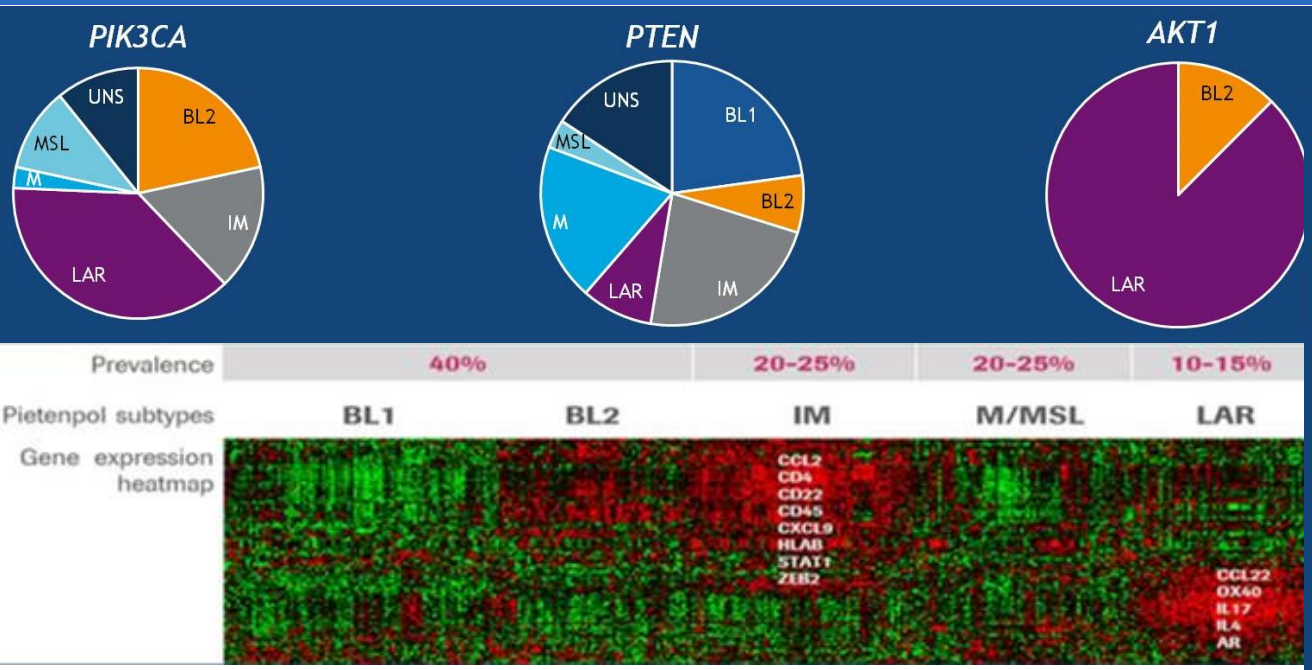
Subtype	HR+ HER2-	TNBC
PIK3CA mut	40%	7-9%
PTEN mut/loss	2-4%	30-40%
PIK3R1 mut	3%	1%
AKT1 mut	2-3%	Rare

AKT can be activated by:

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

Ma 2018 ASCO
Dent 2018 ASCO

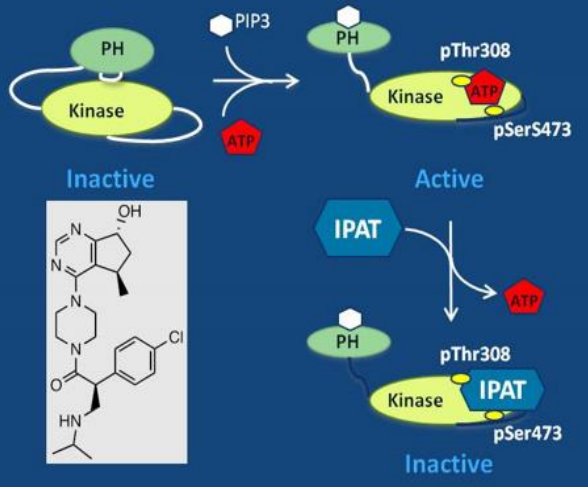
PIK3CA/PTEN/AKT Alterations Among TNBC Subtypes



IPAT enzymatic potency

Enzyme	IC_{50} (nM)
Akt1	5
Akt2	18
Akt3	8
PKA	3100 (620x)

IPAT targets only active AKT



Pereira Nat Commun 2016
Dent 2018 ASCO

LOTUS: A Randomized Phase II Trial of Paclitaxel + Ipatasertib

- Measurable locally advanced/metastatic TNBC not amenable to curative resection
- No prior systemic therapy for advanced/metastatic disease
- ECOG performance status 0/1
- Archival or newly obtained tumor tissue for central PTEN assessment
- Chemotherapy-free interval ≥6 months

(n=124)

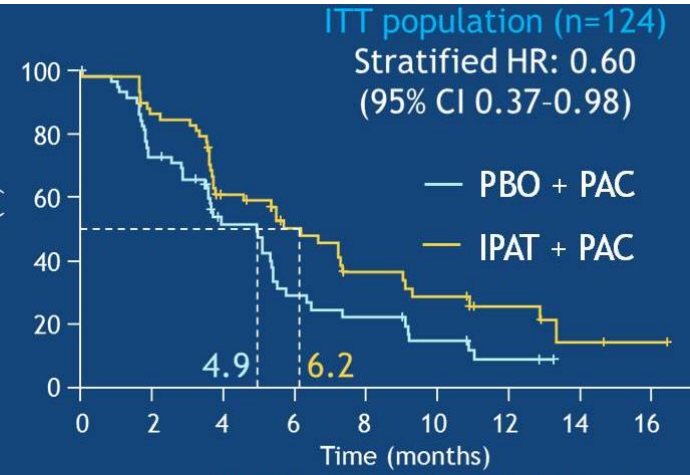
R 1:1

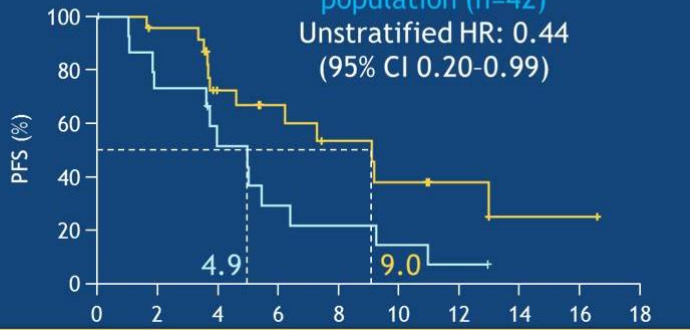
PAC 80 mg/m^2 days 1, 8, & 15 + IPAT 400 mg qd days 1-21 q28d

PAC 80 mg/m^2 days 1, 8, & 15 + PBO days 1-21 q28d

Treatment until disease progression, intolerable toxicity,[b] or withdrawal of consent

Endpoint	ITT population		PTEN-low population (by IHC)		*PIK3CA/AKT/PTEN*-altered tumor population (by NGS)	
	PBO + PAC (n=62)	IPAT + PAC (n=62)	PBO + PAC (n=23)	IPAT + PAC (n=25)	PBO + PAC (n=16)	IPAT + PAC (n=26)
ORR, % (95% CI)	32 (21-45)	40 (29-54)	26 (12-47)	48 (30-68)	44 (20-70)	50 (30-70)
Median DoR, months (95% CI)	7.4 (3.9-9.2)	7.9 (5.6-NE)	7.5 (7.3-NE)	6.5 (4.4-NE)	6.1 (3.8-7.6)	11.2 (5.6-NE)
Clinical benefit rate, % (95% CI)[a]	37 (25-50)	48 (36-61)	30 (13-53)	56 (35-76)	44 (20-70)	54 (33-72)





Kim et al, Lancet Oncol 2017
Dent R ASCO 2018
Presented by Cynthia Ma ASCO 2018

LOTUS: Overall survival

Population	N	PBO + PAC (mon.)	IPAT + PAC (mon.)	HR (95% CI)
ITT	124	18.4 (15.1-29.1)	23.1 (18.6-28.1)	0.62 (0.37, 1.05)
PIK3CA/AKT1/PTEN Alt.	42	NE (8.7-NE)	9.7 (18.6-28.6)	0.9 (0.38, 2.15)
PIK3CA/AKT1/PTEN WT	61	16.2 (13.8-22.2)	23.1 (17.7-NE)	0.58 (0.26, 1.31)
PTEN low*	48	16.1 (9.0-29.1)	21.8 (18.3-28.1)	0.86 (0.4, 1.83)
PTEN not low	53	18.6 (10.1-24.9)	28.5 (17.8-NE)	0.56 (0.26, 1.23)

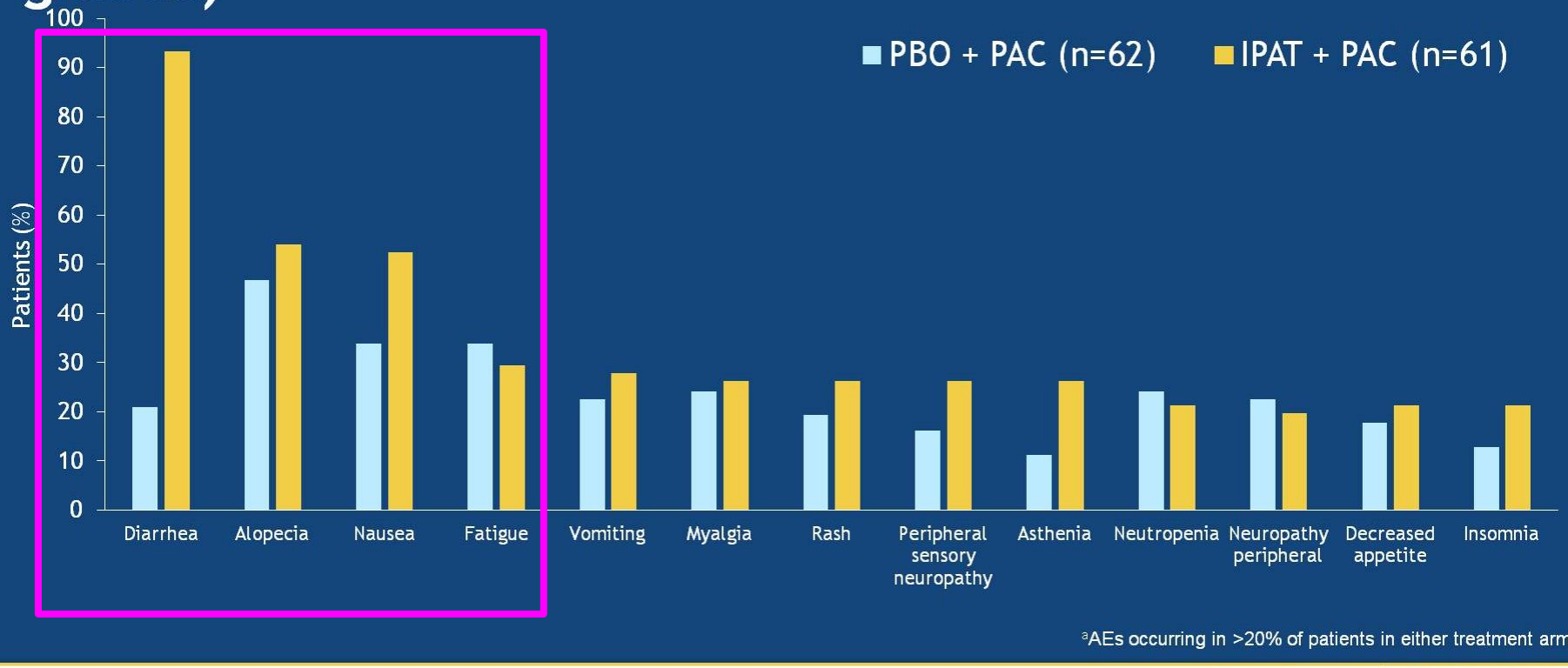
*PTEN low: IHC score 0 in at least 50% tumor cells by Ventana IHC assay.

5 mon OS benefit in IIT
Final OS in 2019

Dent R ASCO 2018

LOTUS: Safety

Updated safety: Most common[a] adverse events (all grades)

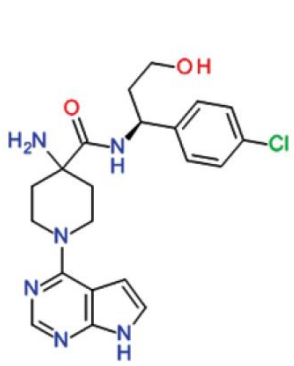


[a]AEs occurring in >20% of patients in either treatment arm

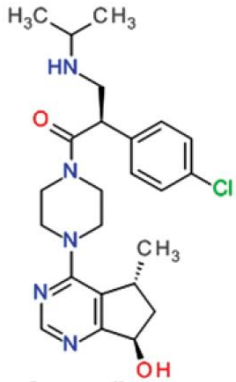
Dent R et al ASCO 2018

LOTUS: Conclusion

- In LOTUS, a placebo-controlled randomized trial, the previously observed PFS improvement with IPAT is followed by a trend toward improved OS (~5-month difference in the medians in the ITT population)
  - Type of subsequent anti-cancer therapy was similar in the two arms
  - Final OS results are expected in 2019
  - Diarrhea was the most clinically relevant additive toxicity
- Findings support further evaluation of first-line IPAT + PAC for metastatic TNBC
- The ongoing IPATunity130 (NCT03337724) randomized phase III trial is evaluating IPAT + PAC as first-line chemotherapy for *PIK3CA/AKT1/PTEN*-altered advanced TNBC or hormone receptor-positive HER2-negative breast cancer



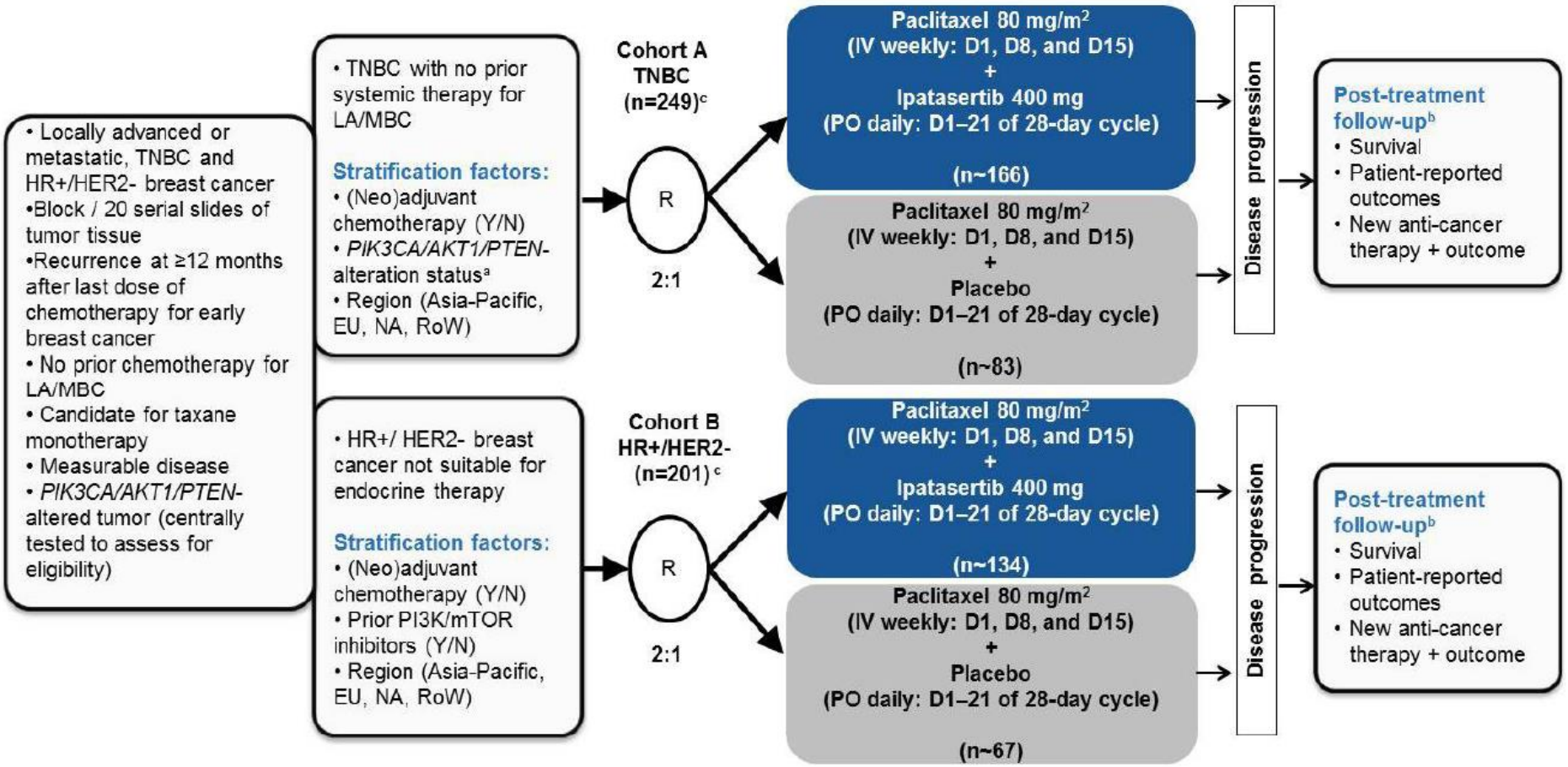
AZD5363



Ipatasertib

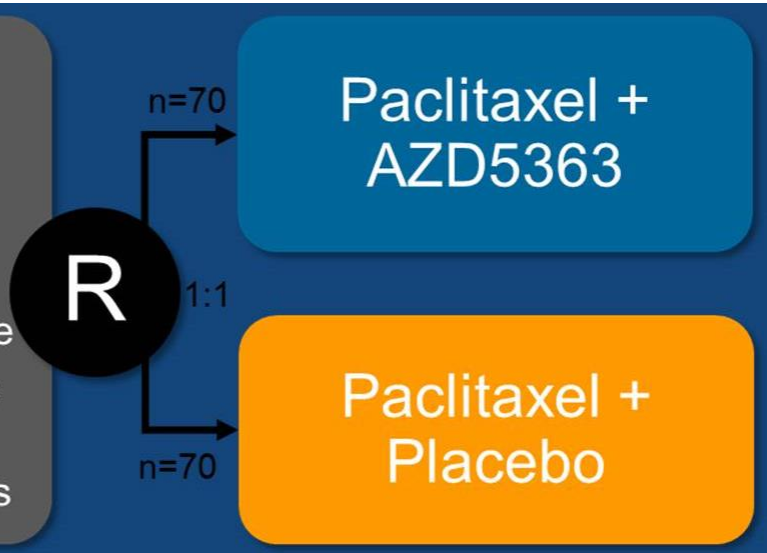
Dent R et al ASCO 2018

Phase III IPATunity 130 Trial



PAKT: phase II trials of Paclitaxel +/- AZD5363

- Metastatic breast cancer
- Triple-negative disease:
  - ER/PR <1%
  - HER2 IHC0-2 and/or ISH negative
- Measurable or evaluable disease
- No prior treatment for metastatic breast cancer
- No taxane treatment <12 months



Population	n	PFS	OS
ITT	138	4.2 vs 5.9 m. HR 0.74 (0.5,1.08) p=0.06	12.6 vs 19.1 m. HR: 0.61 (0.37, 0.99) p=0.02
PIK3CA/AKT1/PTEN Alt.	28	3.8 vs 9.3 m. HR 0.3 (0.11-0.79) p=0.01	10.4 vs NR. HR 0.37 (0.12-1.12) p=0.61
PIK3CA/AKT1/PTEN WT	84	4.4 vs 5.3 m. HR 1.13 (0.7,1.82) p=0.067	13.2 vs 16.6 m. HR 0.84 (0.48,1.49) p=0.56

Schmid P et al ASCO 2018

PAKT: Toxicities

PAKT

AEs ≥5% (All grade)

	Paclitaxel + Placebo (n = 70)	Paclitaxel + AZD5363 (n = 68)
Number of patients with at least one AE	91.4%	97.1%
Diarrhoea	27.1%	72.1%
Fatigue	25.7%	44.1%
Nausea	32.9%	35.3%
Rash	15.7%	41.2%
Neuropathy	18.6%	25.0%
Stomatitis	14.3%	26.5%
Infection	14.3%	22.1%
Decreased appetite	11.4%	20.6%
Alopecia	12.9%	16.2%
Vomiting	8.6%	19.1%
Constipation	14.3%	7.4%
Abdominal pain	10.0%	10.3%
Dry skin	2.9%	14.7%
Dyspnoea	7.1%	8.8%
Headache	4.3%	11.8%
Oedema	5.7%	8.8%
Dysgeusia	4.3%	10.3%
Anaemia	5.7%	7.4%
Dyspepsia	5.7%	7.4%
Joint pain	8.6%	2.9%
Musculoskeletal pain	7.1%	4.4%
Asthenia	4.3%	7.4%
Neutropenia	2.9%	8.8%
Cough	8.6%	1.5%
Hyperglycaemia	1.4%	8.8%

Grade 3 and 4 AEs

	Paclitaxel + Placebo (n = 70)	Paclitaxel + AZD5363 (n = 68)
Diarrhoea	1.4%	13.2%
Infection	1.4%	4.4%
Neutropenia	2.9%	2.9%
Fatigue	0.0%	4.4%
Rash	0.0%	4.4%
Vomiting	1.4%	1.5%
ALT increased	0.0%	1.5%
Anaemia	1.4%	0.0%
AST increased	0.0%	1.5%
Asthenia	0.0%	1.5%
Decreased appetite	0.0%	1.5%
Headache	0.0%	1.5%
Hyperglycaemia	0.0%	1.5%
Hypophosphatemia	0.0%	1.5%
Infusion related reaction	0.0%	1.5%
Musculoskeletal pain	0.0%	1.5%
Nausea	0.0%	1.5%
Neuropathy	0.0%	1.5%
Rash acneiform	0.0%	1.5%
Retinal detachment	0.0%	1.5%
Stomatitis	0.0%	1.5%

Dent R et al ASCO 2018

Outline

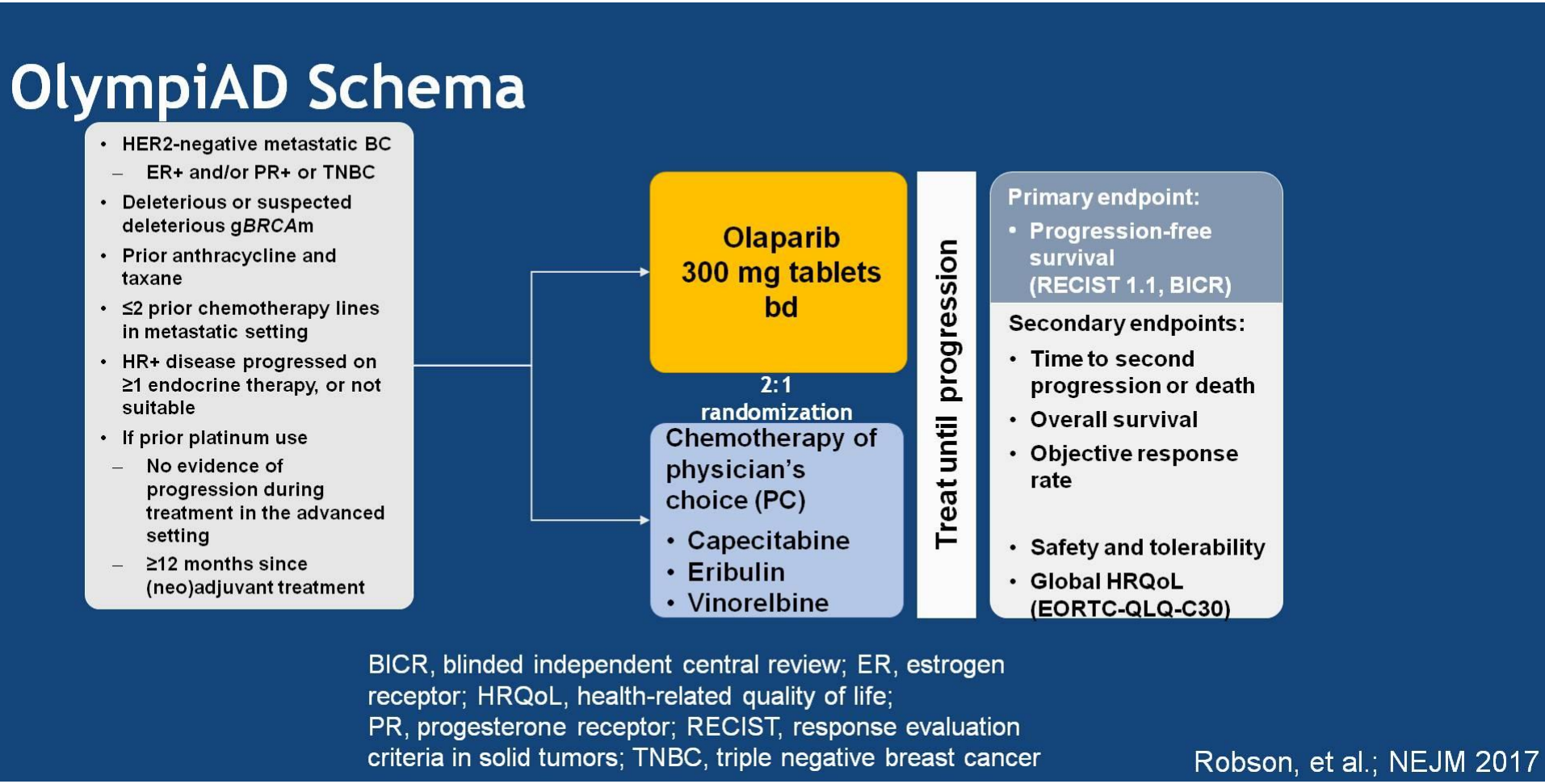
- Overview of TNBC Biology
- PI3K/AKT/MTOR Targeting:
  - LOTUS (ipatasertib)
  - PKAT (AZD5363, capivasertib)

- PARP inhibitor: Neoadjuvant Talazoparib

- PARP inhibitor + Immune Check Point Inhibitor:
  - TOPACIO (Niraparib + Pembrolizumab)

- Drug-Antibody Conjugates: IMMU-132

First FDA Approved PARP inhibitor in Breast Cancer: Phase III OlympiAD Trial in MBC with Germline BRCA Mutations



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

Robson, et al.; NEJM 2017

First FDA Approved PARP inhibitor in Breast Cancer: Phase III OlympiAD Trial in MBC with Germline BRCA Mutations

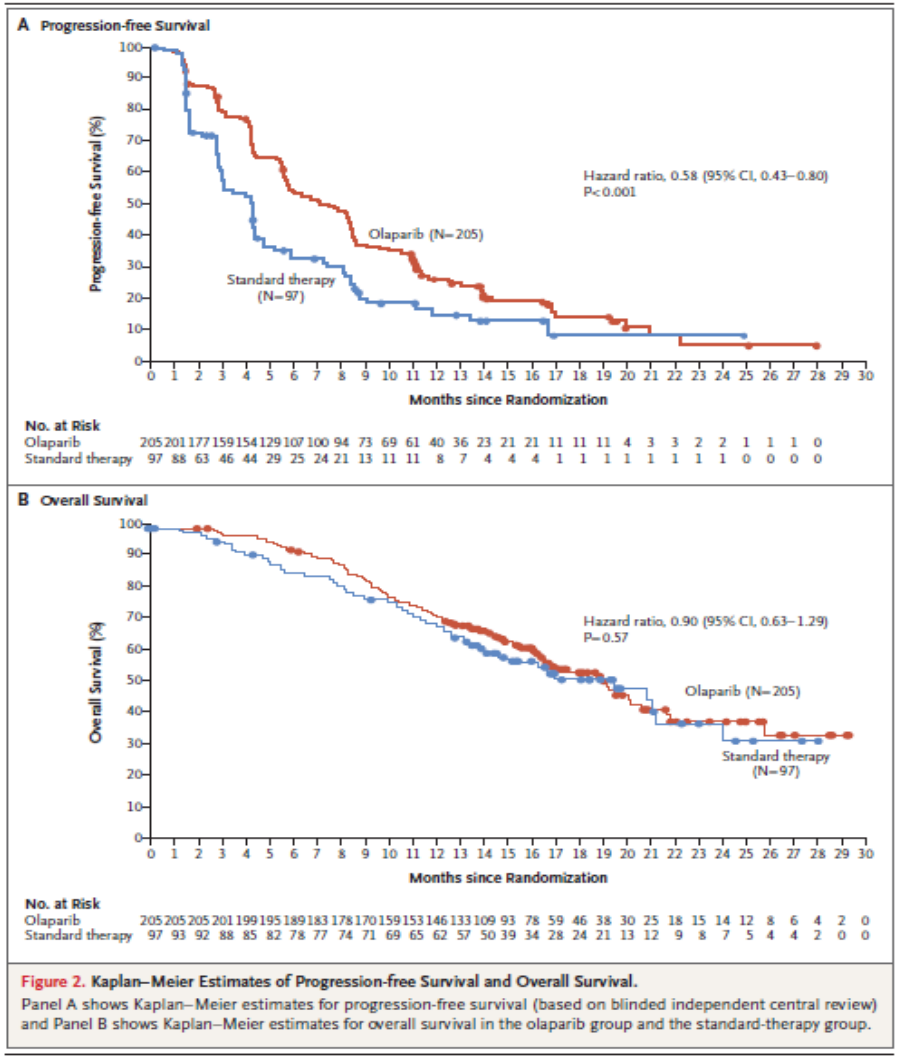


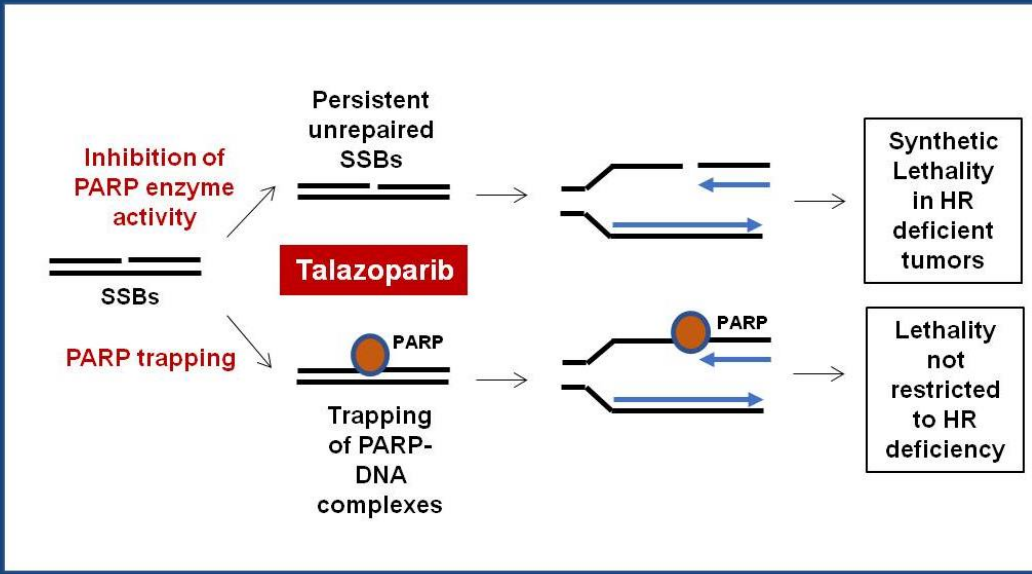
Figure 2. Kaplan–Meier Estimates of Progression-free Survival and Overall Survival.
Panel A shows Kaplan–Meier estimates for progression-free survival (based on blinded independent central review) and Panel B shows Kaplan–Meier estimates for overall survival in the olaparib group and the standard-therapy group.

- Median PFS for Olaparib vs SOC (7.0 months vs. 4.2 months; hazard ratio for disease progression or death, 0.58; 95% confidence interval, 0.43 to 0.80; P<0.001).
- RR was 59.9% in the olaparib group and 28.8% in the SOC group

Robson NEJM 2018

Neoadjuvant Talazoparib for Early Stage Breast Cancer Patients with a BRCA Mutation

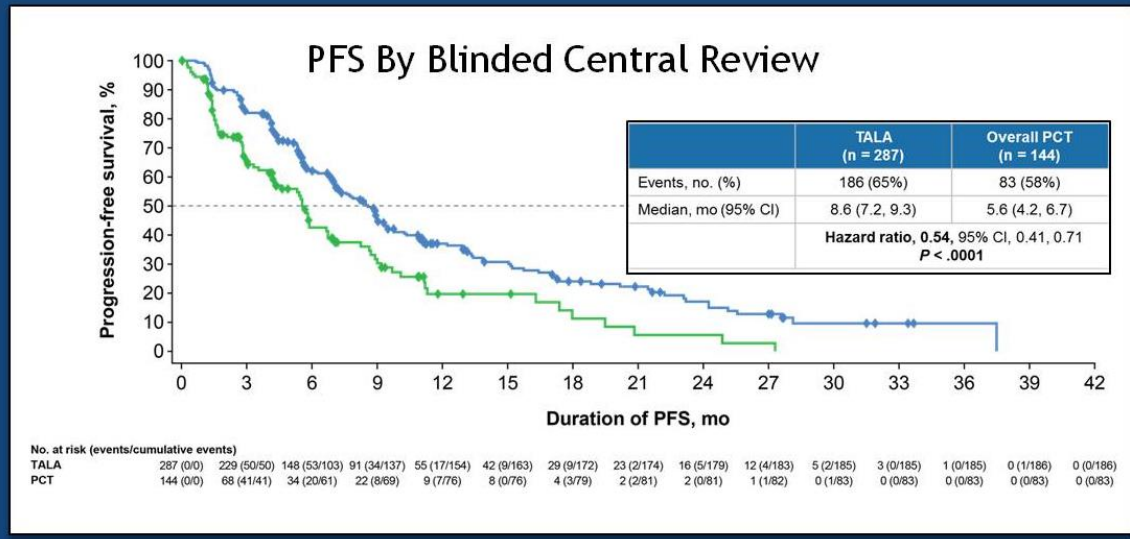
- Talazoparib is a highly potent, dual-mechanism PARP inhibitor[1-4]
  - Inhibits PARP enzymes
  - Traps PARP on single-stranded DNA breaks
  - Prevents repair of DNA damage, resulting in cell death



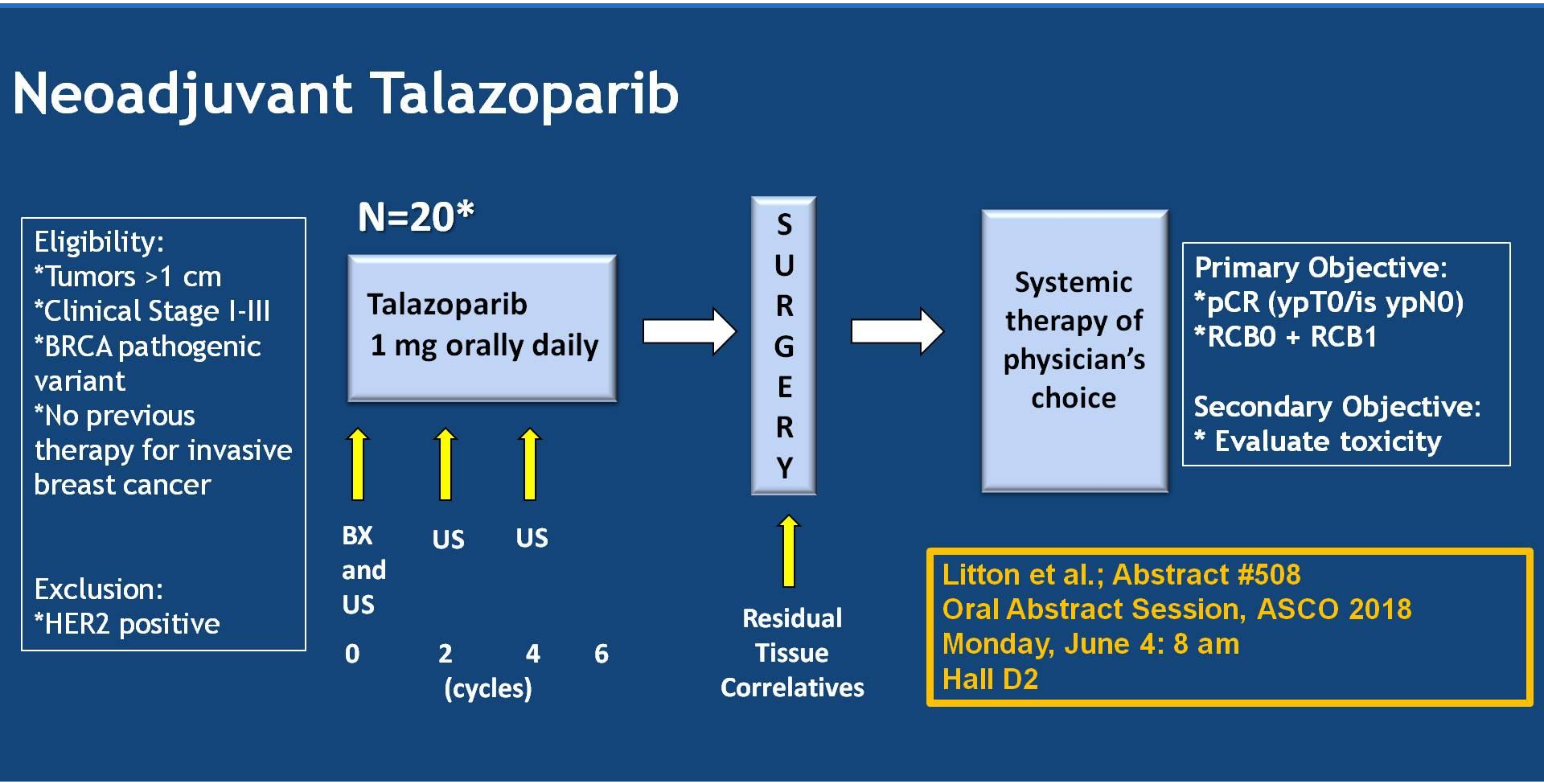
Ashworth JCO 2008
Ashworth Science 2017
Murai Cancer Res 2012
Helleday Mol Oncol 2011
Litton J. 2018 ASCO

Phase III EMBRACA Trial

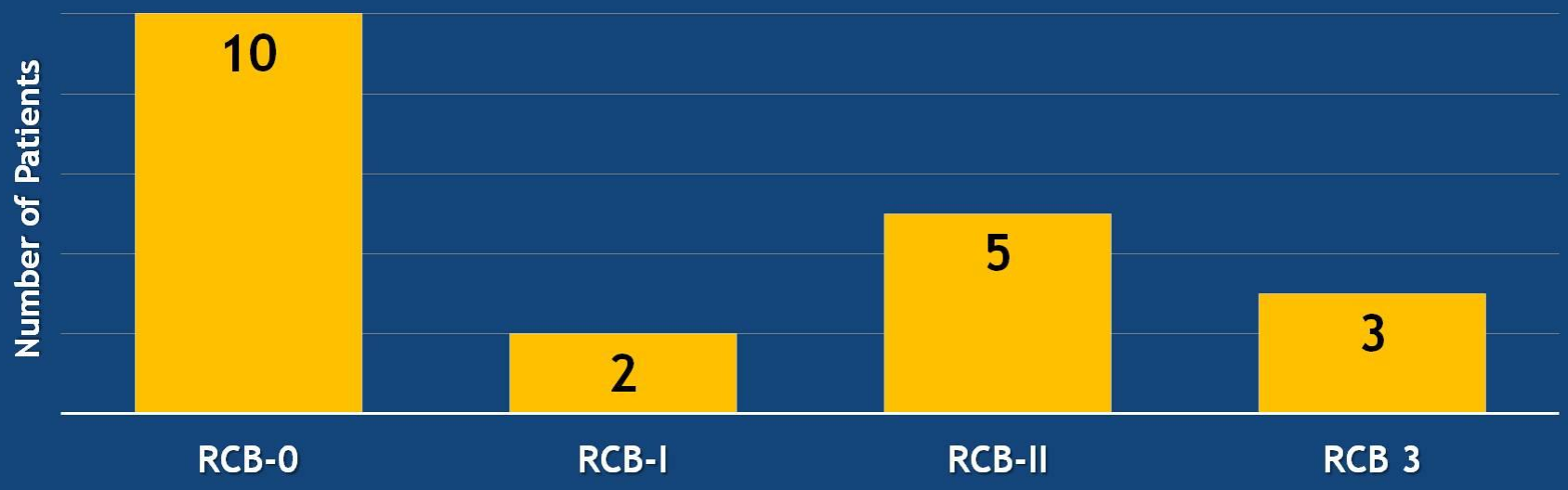
- Phase 3 EMBRACA trial
  - 1 mg orally daily vs. physician's choice of chemotherapy
  - Improvement in PFS (HR 0.54, 95% CI: 0.41-0.71)
  - OS was immature with 51% events (HR 0.76, 95% CI: 0.54-1.06)



Neoadjuvant Talazoparib Study Design



Pathology Response



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

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

Hematological Toxicities & RBC Transfusions

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	4	3	8	-
WBC Decreased	8	4	-	-
Thrombocytopenia	-	-	-	1
Neutropenia	-	4	3	-

Total Number of Transfusions During Study	Number of Patients
1 Transfusion	3
2 Transfusions	3
3 Transfusions	2
Total Units PRBCs	29 (1-2 PRBCs per transfusions)

Non-hematological Toxicities

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	14	1	-	-
Fatigue	14	-	-	-
Alopecia	11	-		
Dizziness	6	-	-	-
Dyspnea	5	-	-	-
Hyperglycemia	5	-	-	-
Pain (in breast and other)	8	1	-	-
Increased transaminases	4	-	-	-
Mucositis	4	-	-	-
Vomiting	2	1	-	-
UTI		2	1	-
Hypomagnesemia	3	-	-	-

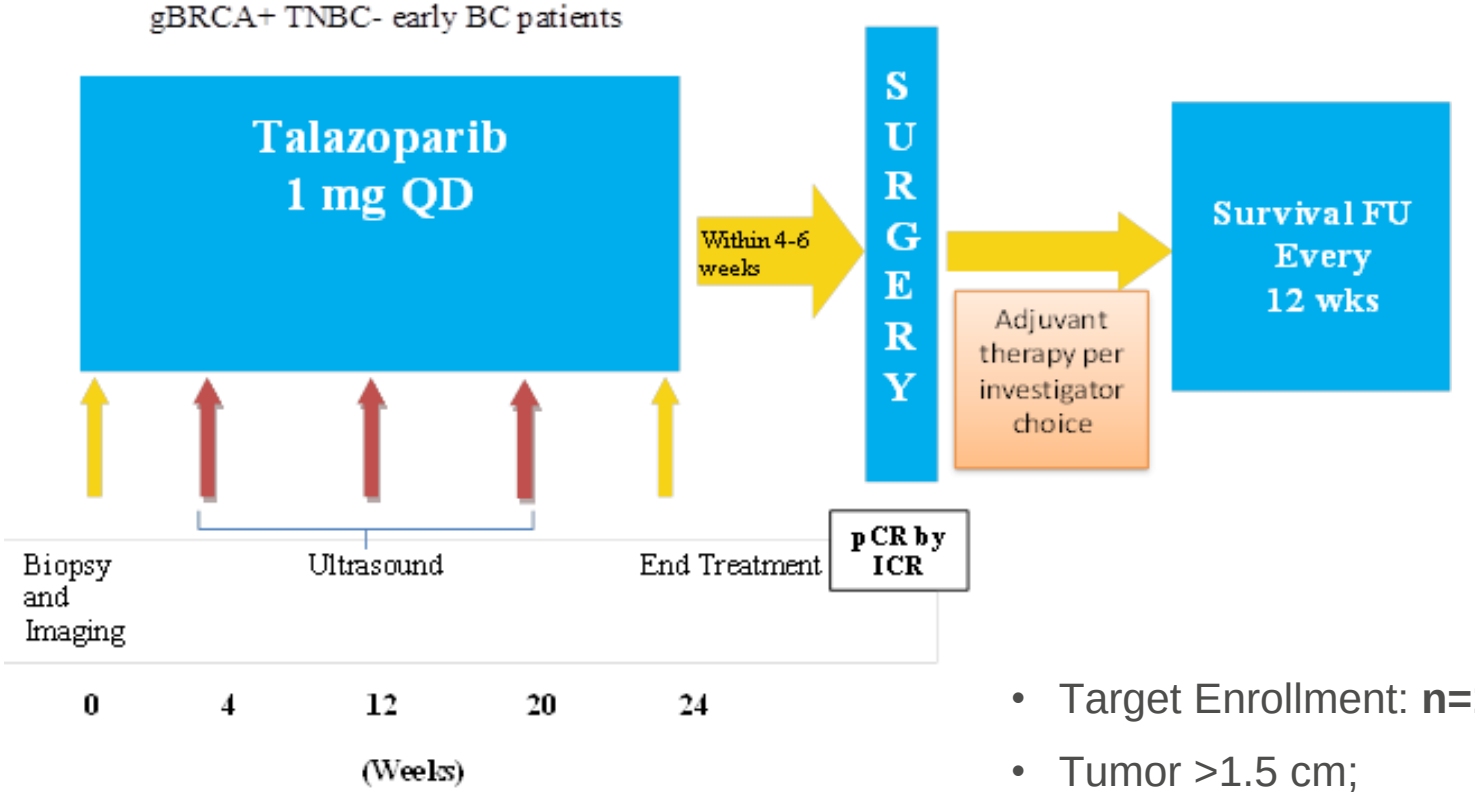
Litton 2018 ASCO

Conclusion

- Pathologic responses to single agent talazoparib
  - pCR: 10/19 = 53%, 95% CI = 32%, 73%
  - RCB-0+I: 12/19 = 63%, 95% CI = 41%, 81%
- First study of a single targeted therapy to achieve pCR in BRCA+ patients, including TNBC
- Talazoparib was well tolerated with acceptable adherence
- Common toxicities were predominately hematologic and managed by dose delays, reductions and transfusions
- This study warrants the larger confirmatory trial (NCT02282345)

Litton 2018 ASCO

C3441020 Study Schema



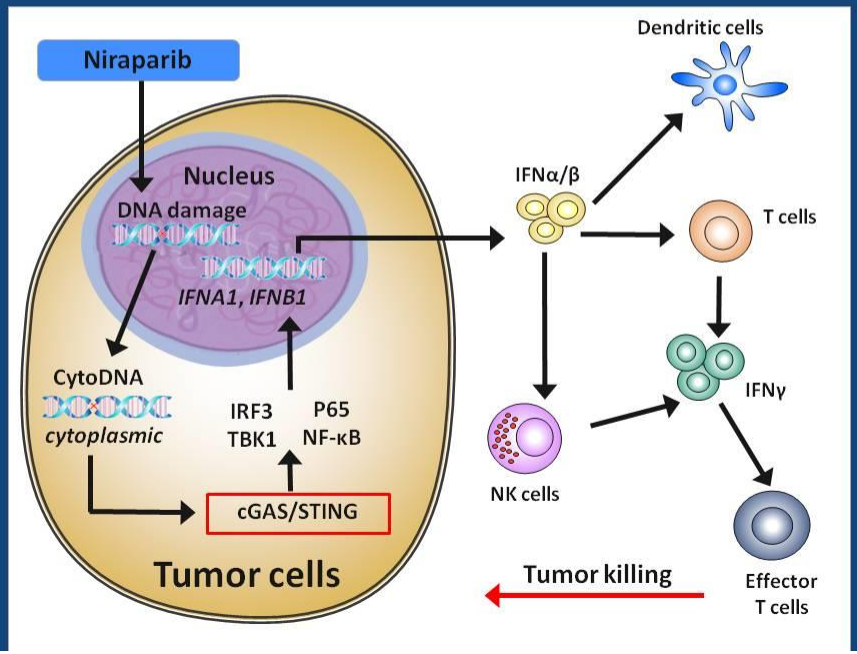
- Target Enrollment: **n=122**
- Tumor >1.5 cm;
- No evidence of distant metastasis;
- Triple negative breast cancer (TNBC);
- gBRCA mutation-positive;

PARP inhibitor + Immune check point inhibitor
TOPACIO/Keynote-162: Ph II Niraparib + Pembro in mTNBC

Rationale for Niraparib (PARPi) + anti-PD-1 Combination

Preclinical studies demonstrated synergistic activity of PARPi + anti-PD-1, regardless of *BRCA* mutational status or PD-1 sensitivity

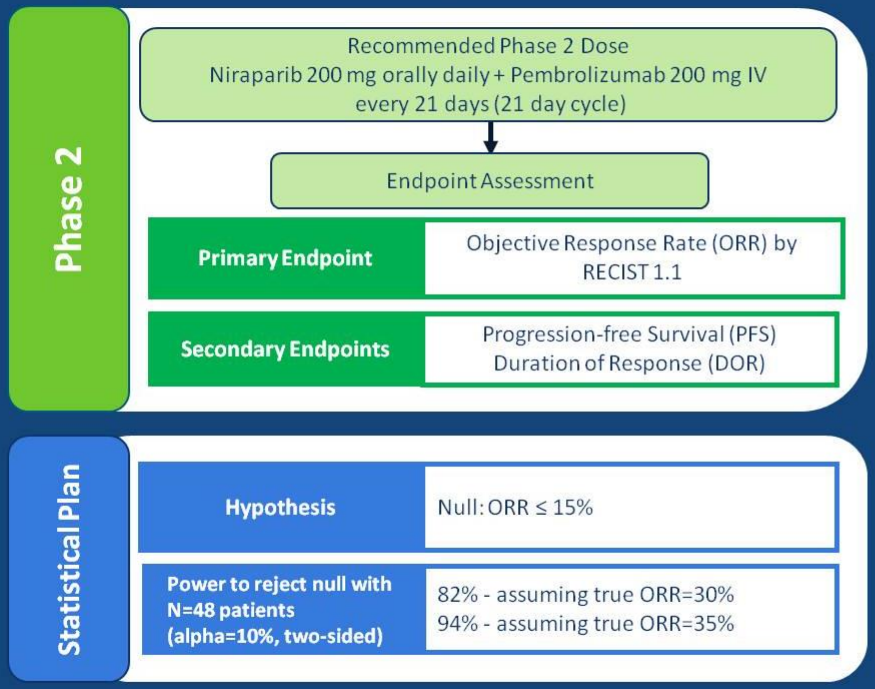
- Potential Mechanism of Action
  - Unrepaired DNA damage resulting from niraparib treatment leads to the abnormal presence of DNA in the cytoplasm, activating Stimulator of Interferon Genes (STING) pathway
  - Activation of the STING pathway leads to increased expression and release of type 1 interferons, subsequent induction of γ-interferon, and intratumoral infiltration of effector T-cells



Huang Biochem Biophys Res Commun 2015
Sato Nat Commun 2017
Jiao CCR 2017
Vinayak 2018 ASCO

TOPACIO: Study Design

Objective: Evaluate niraparib and anti-PD-1 combination therapy in metastatic TNBC patients



*ER and PR < 1% per ASCO/CAP guidelines
#Prior amendment allowed up to 3 prior lines of cytotoxic therapy for advanced disease
**Prior amendment had no restriction on platinum for inclusion or exclusion criteria

Key Inclusion Criteria

- TNBC (ER-negative, PR-negative, and HER-2 negative)*
- Disease recurrence or progression following neoadjuvant/adjuvant therapy
- ≤2 prior lines of cytotoxic treatment for advanced disease (not including neoadjuvant/adjuvant therapies or targeted small molecules)#
- Prior platinum allowed in metastatic setting if no progression documented while on or within 8 weeks of last platinum**

Key Exclusion Criteria

- Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or PARP inhibitor

Response Assessments

- Scans every 9 weeks

TOPACIO: Study Demographics & Baseline Characteristics

Characteristics	N=55
Median Age (years)	54
ECOG performance status	
0	30 (55%)
1	25 (45%)
Prior lines of therapies in advanced/metastatic setting, median (range)*	1 (0 – 3)
0	19 (35%)
1	21 (38%)
2	14 (25%)
3	1 (2%)
Previous neoadjuvant or adjuvant therapy	43 (78%)
Previous chemotherapy in advanced/metastatic setting	
Platinum	21 (38%)
Gemcitabine	14 (26%)
Taxane	14 (26%)
Capecitabine	12 (22%)
Eribulin	7 (13%)
Anthracycline	4 (7%)
Cyclophosphamide	3 (6%)
Ixabepilone	1 (2%)

ECOG = Eastern Cooperative Oncology Group.
*Small molecules and investigational agents were not counted towards lines of therapy.

- 27% with ≥ 2 prior lines of therapies
- 78% with prior neoadjuvant or adjuvant therapy
- 38% with prior platinum (Median time from prior platinum therapy to first treatment on TOPACIO: 8.7 months (range: 0.7 - 30.6))

TOPACIO: ORR

Response	Response Rate, n (%) Efficacy Evaluable (N=46)*
Complete Response (CR)	3 (7%)
Partial Response (PR)**	10 (22%)
Stable Disease (SD)	10 (22%)
Progressive Disease (PD)	23 (50%)
ORR (CR+PR)	13 (28%)
DCR (CR+PR+SD)	23 (50%)

9 Patients still on treatment
- 2 CR
- 6 PR
- 1 SD

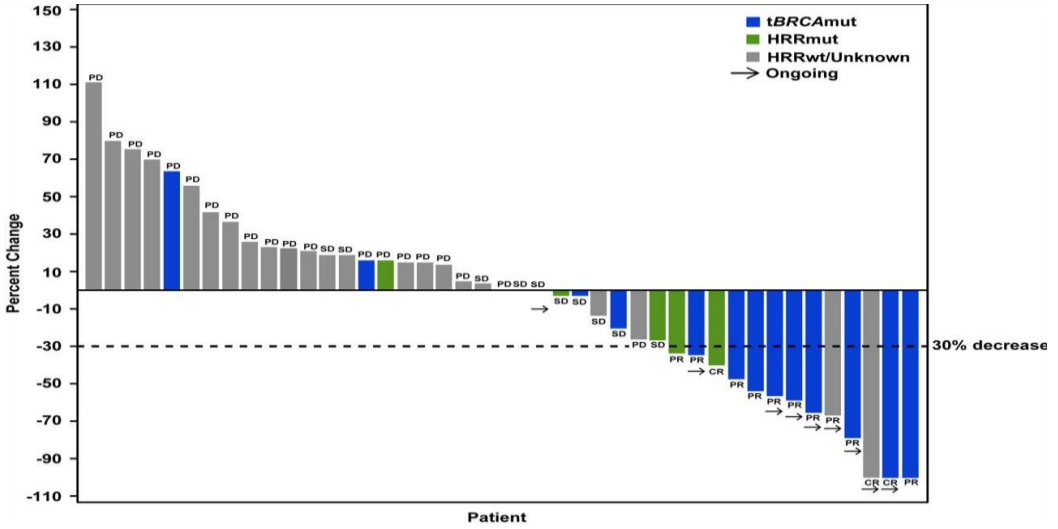
*9 pts did not have evaluable post-baseline tumor assessments and were not included in the evaluable population (6 pts discontinued due to AE; 1 due to clinical progression and 2 for other reasons).

**Responses include both confirmed and unconfirmed; DCR: Disease Control Rate; Data as of April 02, 2018

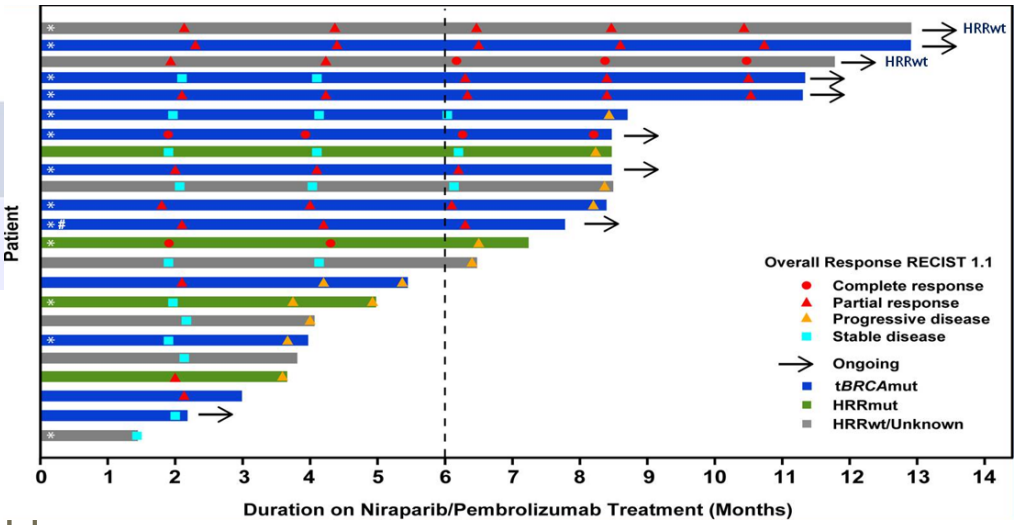
TOPACIO: Response in Biomarker Selected Patients

Efficacy Evaluable Patients	ORR (CR+PR)	DCR (CR+PR+SD)
t*BRCA*mut patients (n=15)	9 (60%)	12 (80%)
HRRmut + t*BRCA*mut (n=20)	11 (55%)	16 (80%)
PD-L1 positive patients (n=25)	9 (36%)	13 (52%)

• Overall Response Rate in all evaluable (biomarker-unselected) patients (N=46): ORR 28%, DCR=50%



Biomarker	mPFS (months)
t*BRCA*mut patients (n=15)	8.3
HRRmut + t*BRCA*mut (n=20)	6.4



Vinayak 2018 ASCO

TOPACIO: Safety

Event	Any Grade (N=55)	Grade ≥3 (N=55)
Nausea	30 (55%)	0
Fatigue	23 (42%)	4 (7%)
Anemia	17 (31%)	8 (15%)
Thrombocytopenia	13 (24%)	7 (13%)
Constipation	11 (20%)	0
Diarrhea	10 (18%)	0
Decreased appetite	9 (16%)	0
Vomiting	7 (13%)	0

TOPACIO: Conclusion

- Niraparib in combination with a PD-1 inhibitor has shown promising durable anti-tumor activity in patients with advanced TNBC
- Clinical activity was observed in both t*BRCA*wt and t*BRCA*mut patients
  - HRR mutations may enrich activity in t*BRCA*wt
- Median DOR has not been reached; 8/13 (62%) responders are still on treatment
  - Five patients with long-term ongoing clinical benefit for ~1 year
- Combination is well-tolerated
  - Substantially reduced thrombocytopenia with 200 mg starting dose of niraparib
  - No augmentation of immune-mediated AEs with the addition of a PD-1 inhibitor

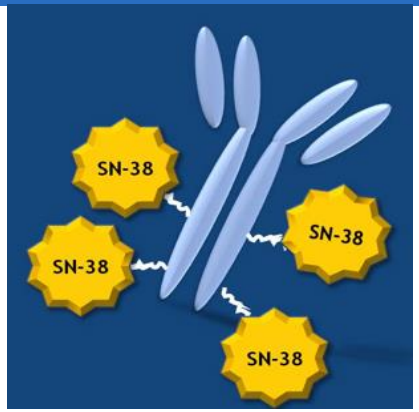
Outline

- Overview of TNBC Biology
- PI3K/AKT/MTOR Targeting:
  - LOTUS (ipatasertib)
  - PKAT (AZD5363, capivasertib)
- PARP inhibitor: Neoadjuvant Talazoparib
- PARP inhibitor + Immune Check Point Inhibitor:
  - TOPACIO (Niraparib + Pembrolizumab)

- Drug-Antibody Conjugates: IMMU-132

IMMU 132: anti-Trop-2-SN-38 antibody-drug conjugate, as ≥ 3rd line therapy in refractory mTNBC

Anti-Trop-2 Antibody
Trop-2: up to 80% TNBCs
SN-38: active metabolite of irinotecan



Metastatic TNBC (ASCO/CAP guidelines) → **N = 110** → **Sacituzumab govitecan 10 mg/kg Days 1 and 8, every 21 days** Scanned every 8 weeks → **Until progression or unacceptable toxicity**

Key Eligibility Criteria

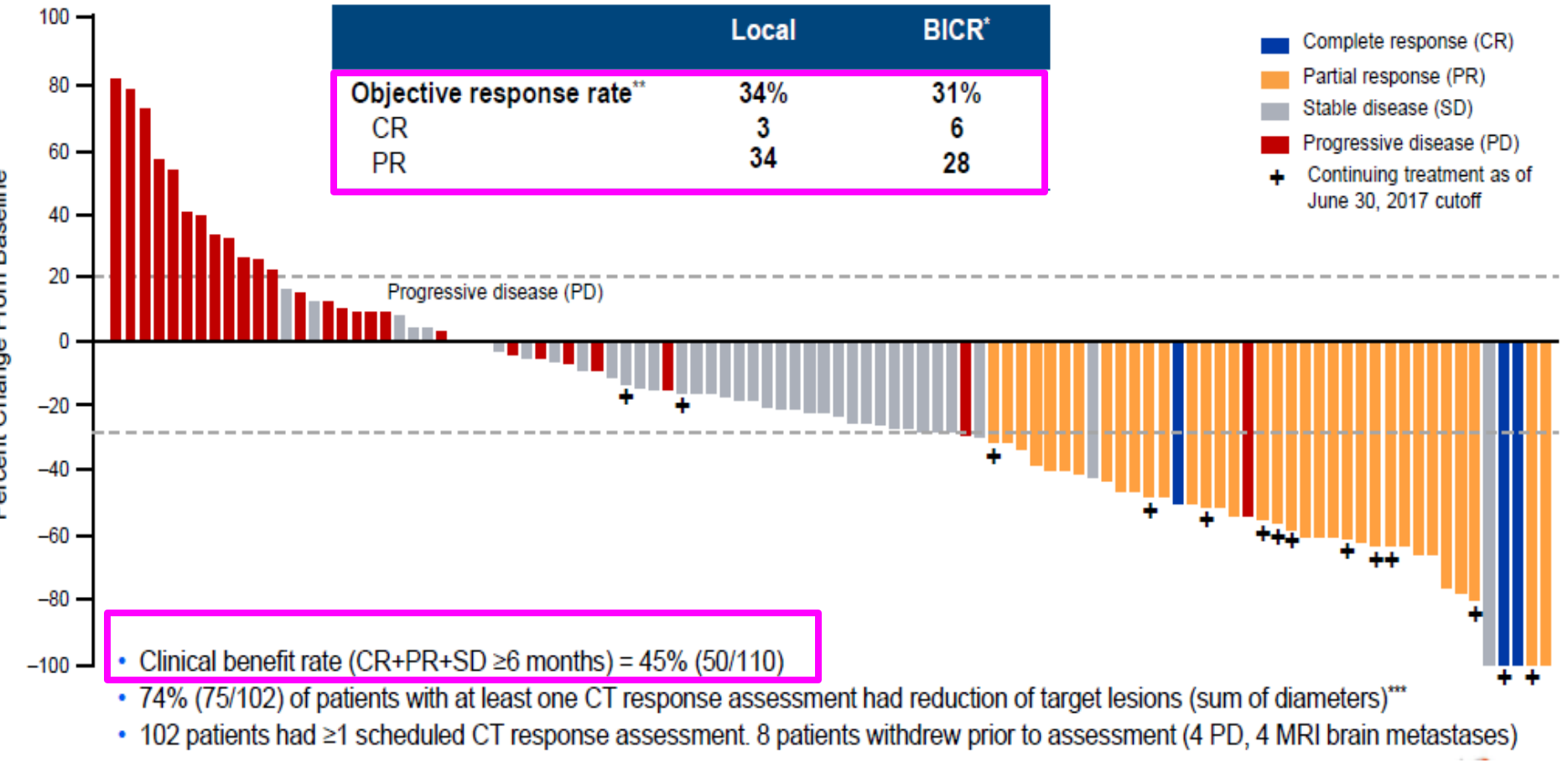
- Adults, ≥18 years of age
- ECOG 0-1
- ≥2 prior therapies in metastatic setting or >1 therapy if progressed within 12 months of (neo)adjuvant therapy
- Prior taxane therapy
- Measurable disease

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 SABCS 2017

Response to treatment



PFS: 5.5 mon, OS 12.7 mon, estimated median DOR 7.6 mon
G3 Tox: 39% neutropenia, 13% diarrhea, 7% febrile neutropenia

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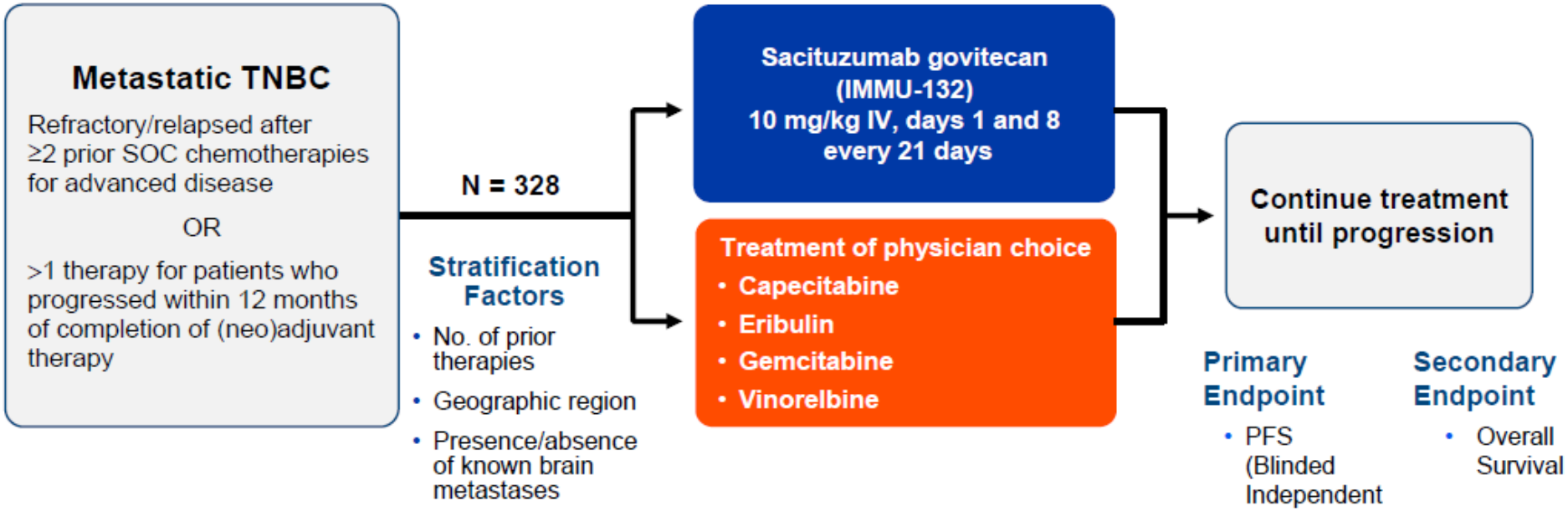
Phase III ASCENT Trial



- Clinical trials number: NCT02574455

Bardia et al SABCS 2017

Take Home Messages

- Promising activities of AKT inhibitors + paclitaxel as 1st line therapy with more pronounced effects in PI3K/AKT/PTEN altered met TNBC
- Neoadjuvant PARP inhibitor is promising in BRCA1/2 mutation
- Combination of PARP inhibitor + IO warrant further investigation
- Anti-Trop-2 Drug-Antibody conjugate shows promises

We are a step-closer to precision medicine in TNBC !