Breast Cancer Year in Review 2017: The Evolving Story of Chemotherapy

Heather McArthur, MD, MPH
Medical Director, Breast Oncology
Cedars-Sinai Medical Center
Los Angeles, CA

Disclosures

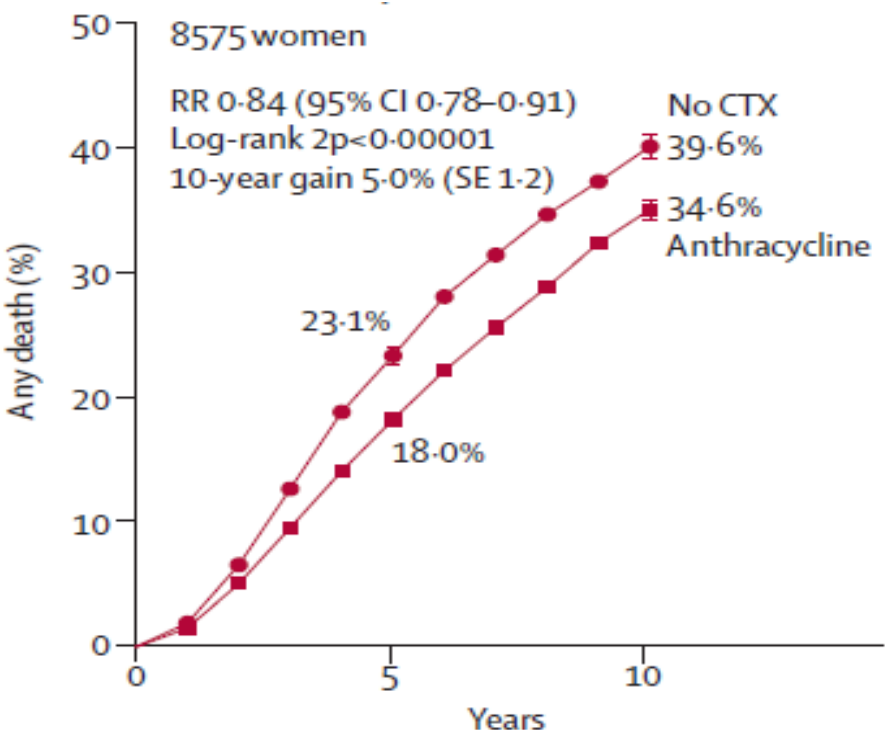
Consultant/Advisory boards:

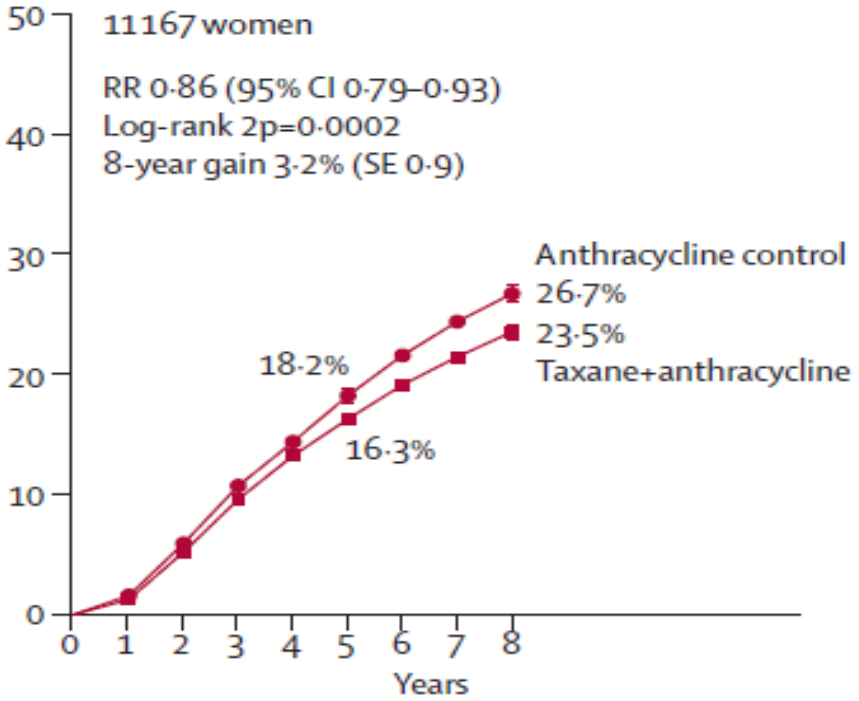
- Amgen
- Merck
- OBI
- Spectrum Pharmaceuticals
- Syndax Pharmaceuticals
- Roche
- Peregrine
- Calithera
- Eli Lilly
- TapImmune

IIT research currently supported by:

- Bristol-Myers Squibb
- MedImmune, LLC/AstraZenica
- Merck

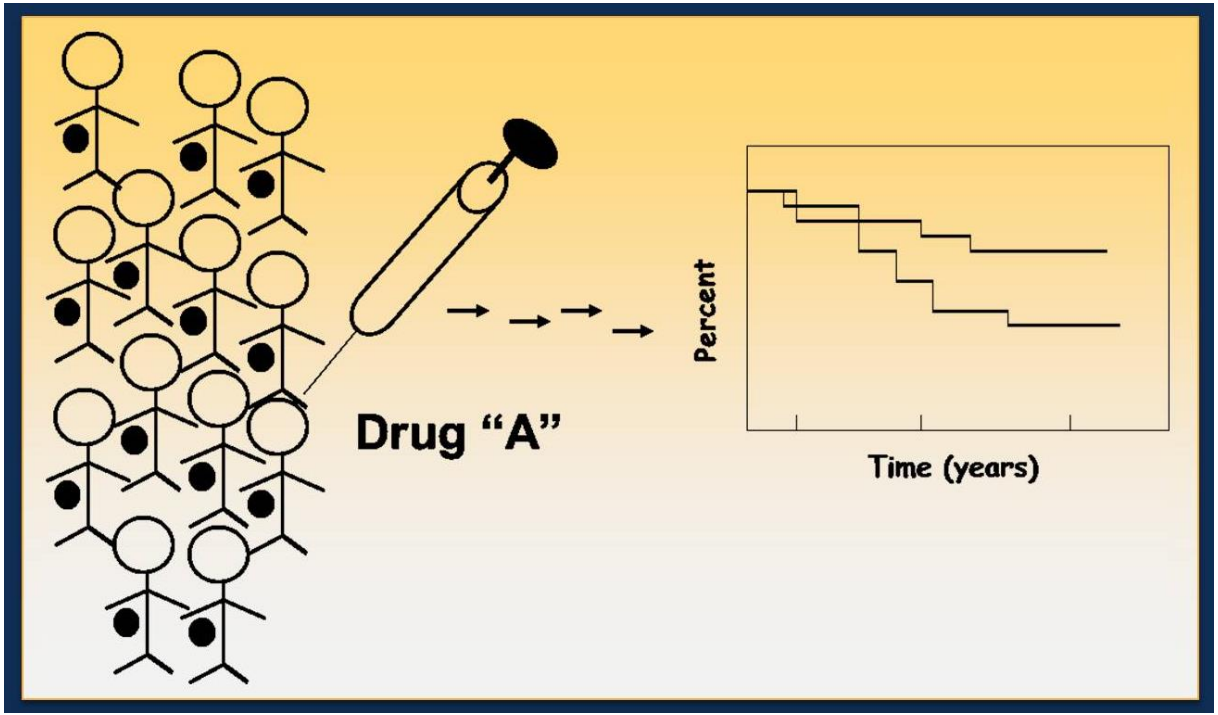
Curative Intent Chemotherapy Saves Lives





EBCTCG. *Lancet.* 2012;379:432-444.

Patient and tumor heterogeneity precludes "one size fits all" treatment strategies



Henry ASCO 2017

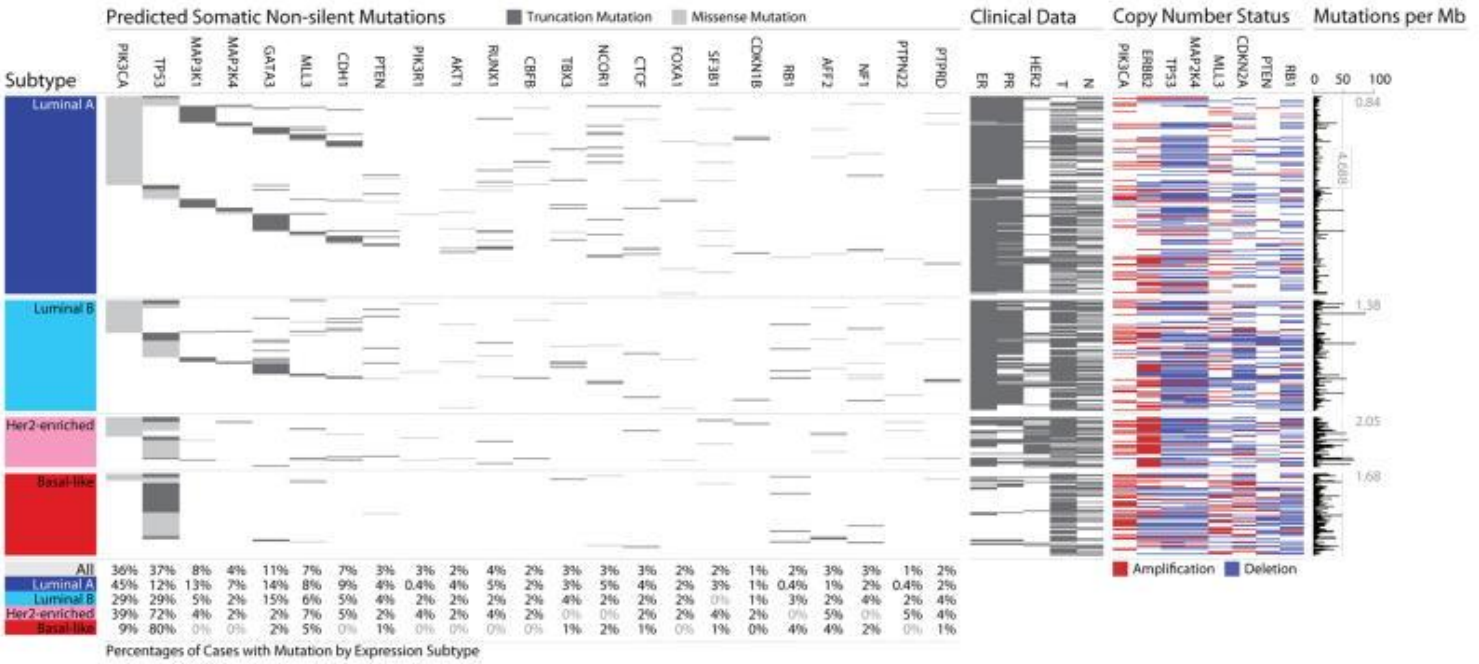
The Dilemma

--RNA expression categorizes breast cancers

--RNA expression is linked to DNA mutations

--The mutations are linked to functions

--The functions are targetable



TCGA Network, Nature: 2012

A sharpshooter can help you here

Courtesy Larry Norton

A sharpshooter can help you here

…but not here!

Courtesy Larry Norton

Courtesy Larry Norton

Biggest Stories of 2017

- OLYMPIAD, EMBRACA – PARP inhibitors
- APHINITY – dual HER2-directed therapy
- Antibody Drug Conjugates
- MONALEESA 7 and others – CDK4/6 inhibitors
- SOFT/TEXT – targeted hormone therapies

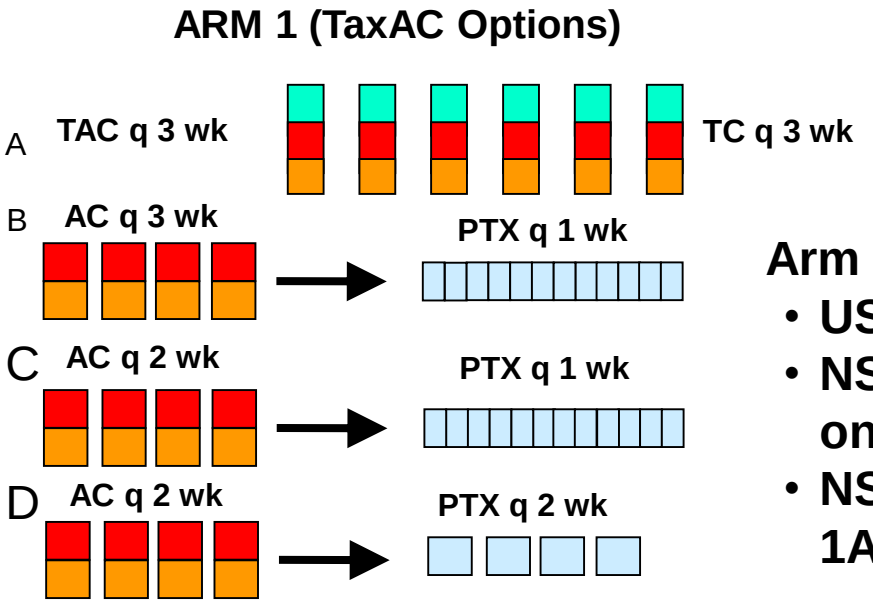
If chemotherapy still has a key role to play can we administer it more “precisely”

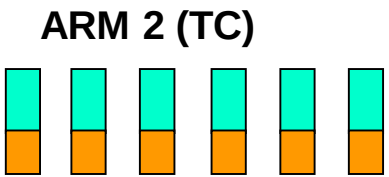
- Escalate cytotoxics for those who need it
- De-escalate cytotoxics for those who don’t
- Better scheduling and sequence
- Better combinations
- Better targets and/or delivery methods

If chemotherapy still has a key role to play can we administer it more “precisely”

- Escalate cytotoxics for those who need it
- De-escalate cytotoxics for those who don’t
- Better scheduling and sequence
- Better combinations
- Better targets and/or delivery methods

ABC Trial Schema





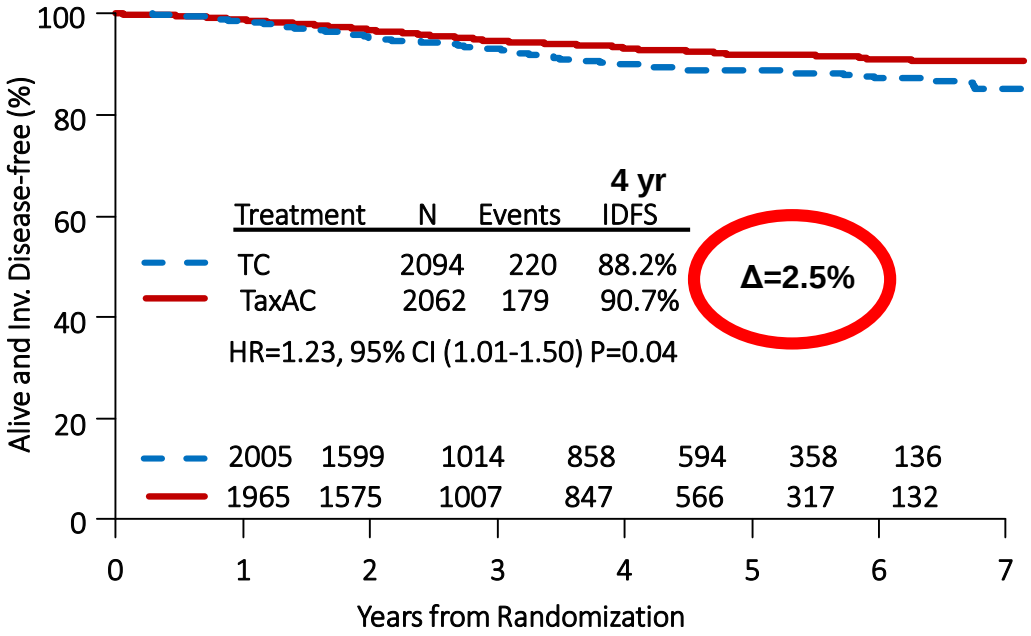
Arm 1 Options Per Study

- **USOR 06-090 - 1A only**
- **NSABP B-46I/USOR 07132 - 1A only**
- **NSABP B-49 - investigator choice 1A-1D**

Endocrine therapy for ER+ or PgR+ patients for minimum of 5 years

Blum J, et al. *J Clin Oncol*. 2017;35:2647-2655.

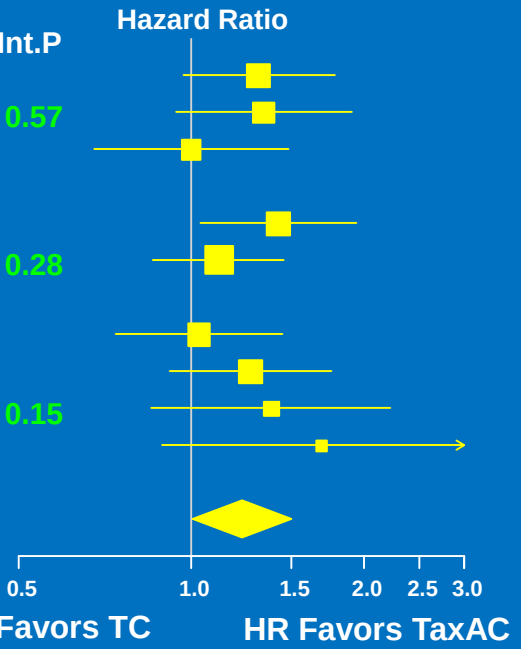
ABC Trials: Invasive Disease-Free Survival



Blum J, et al. *J Clin Oncol*. 2017;35:2647-2655.

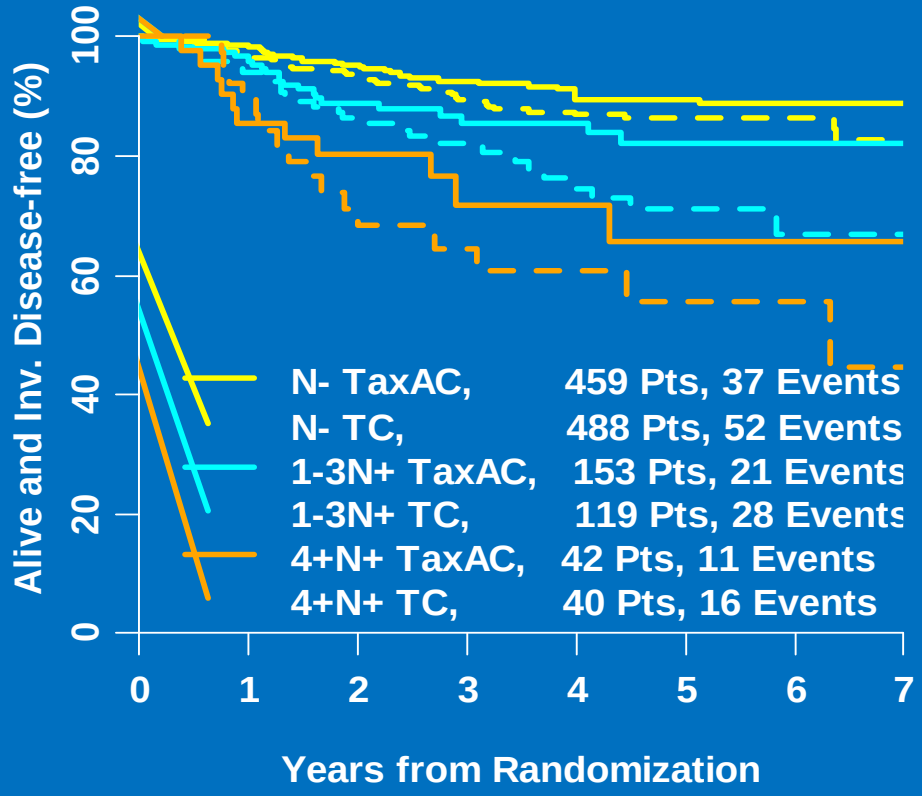
Forest Plot of IDFS By Stratification Variables

	No. of Events				
Protocol	**TC**	**TaxAC**	**HR**	**95% CI**	**Int.P**
USOR06-090	98	72	1.31	0.97-1.78	
B-46/07132	71	54	1.34	0.94-1.91	**0.57**
B-49	51	53	1.00	0.68-1.48	
Hormone					
Negative	96	69	1.42	1.04-1.94	
Positive	124	110	1.12	0.86-1.45	**0.28**
No. Nodes					
0	74	66	1.03	0.74-1.44	
1-3	81	67	1.27	0.92-1.76	
4-9	40	29	1.38	0.85-2.22	**0.15**
≥10	25	17	1.69	0.89-3.19	
Overall	**220**	**179**	**1.23**	**1.01-1.50**	

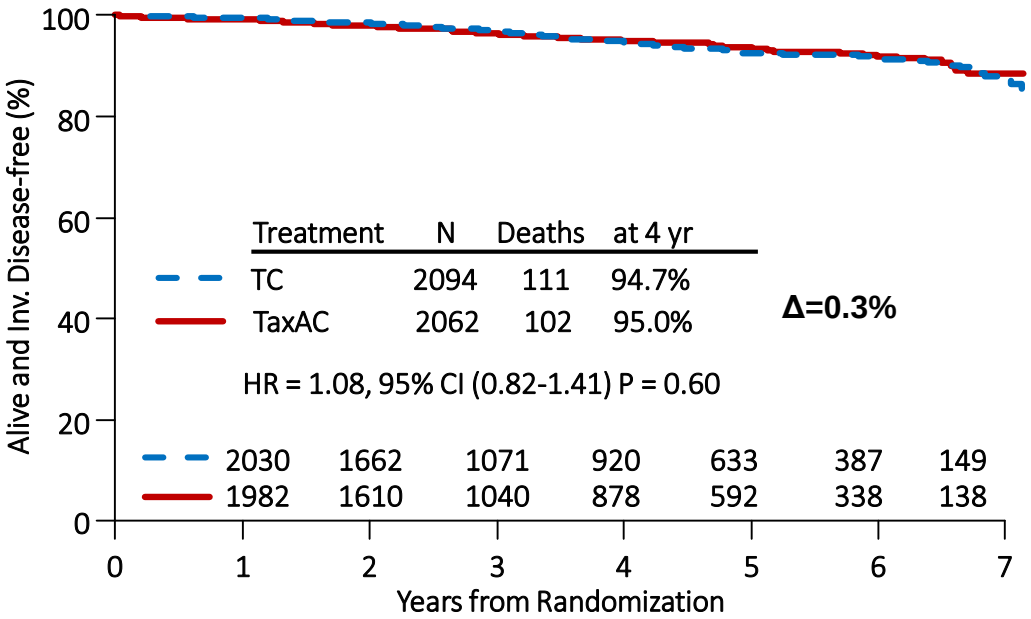


HR = Hazard Ratio

ABC Trials: IDFS by Nodal Status in TNBC



ABC Trials: Overall Survival



Blum J, et al. *J Clin Oncol*. 2017;35:2647-2655.

PlanB: Design
HER2-negative early breast cancer

WSG
WOMEN'S HEALTHCARE STUDY GROUP

- **Age≤75 years**
- **cM0**
- free margins
- **pN+**
- **pN0 high risk**

- pT≥2
- G2-3
- uPA/PAI-1↑
- HR-
- age ≤35 years

HR-

HR+

RECURRENCE SCORE

0-3 LN and RS>11 or >/= 4 LN

0-3 LN and RS≤11

Recurrence Score: after early amendment

RANDOMIZATION

$Doc_{75}C_{600}$ x 6*

$E_{90}C_{600}$x4 →Doc_{100} x4*

Endocrine therapy*

*** Endocrine Therapy and RT according to national guidelines**
E: Epirubcin; Doc: Docetaxel;
C: Cyclophosphamide

PlanB: Design
HER2-negative early breast cancer

WSG
WOMEN'S HEALTHCARE STUDY GROUP

- **Age≤75 years**
- **cM0**
- free margins
- **pN+**
- **pN0 high risk**

- pT≥2
- G2-3
- uPA/PAI-1↑
- HR-
- age ≤35 years

HR- →

HR+

RECURRENCE SCORE

0-3 LN and RS>11 or >/= 4 LN

0-3 LN and RS≤11

Recurrence Score: after early amendment

RANDOMIZATION

→ **$Doc_{75}C_{600}$ x 6***

→ **$E_{90}C_{600}$x4 →Doc_{100} x4***

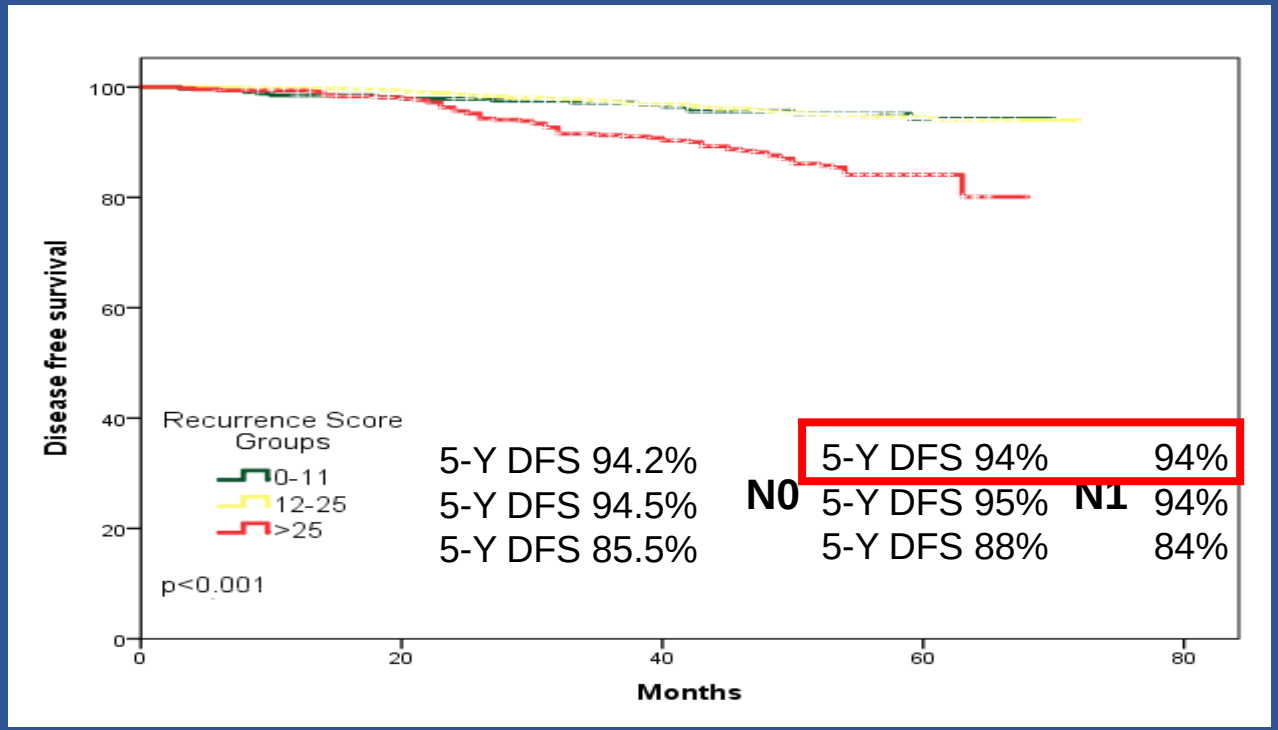
→ **Endocrine therapy***

*** Endocrine Therapy and RT according to national guidelines**
E: Epirubcin; Doc: Docetaxel;
C: Cyclophosphamide

PlanB: Translational subprotocol

5-year DFS in per-protocol population
(no chemotherapy in pN0-1 and Recurrence Score 0-11)

WSG
WOMEN'S HEALTHCARE STUDY GROUP

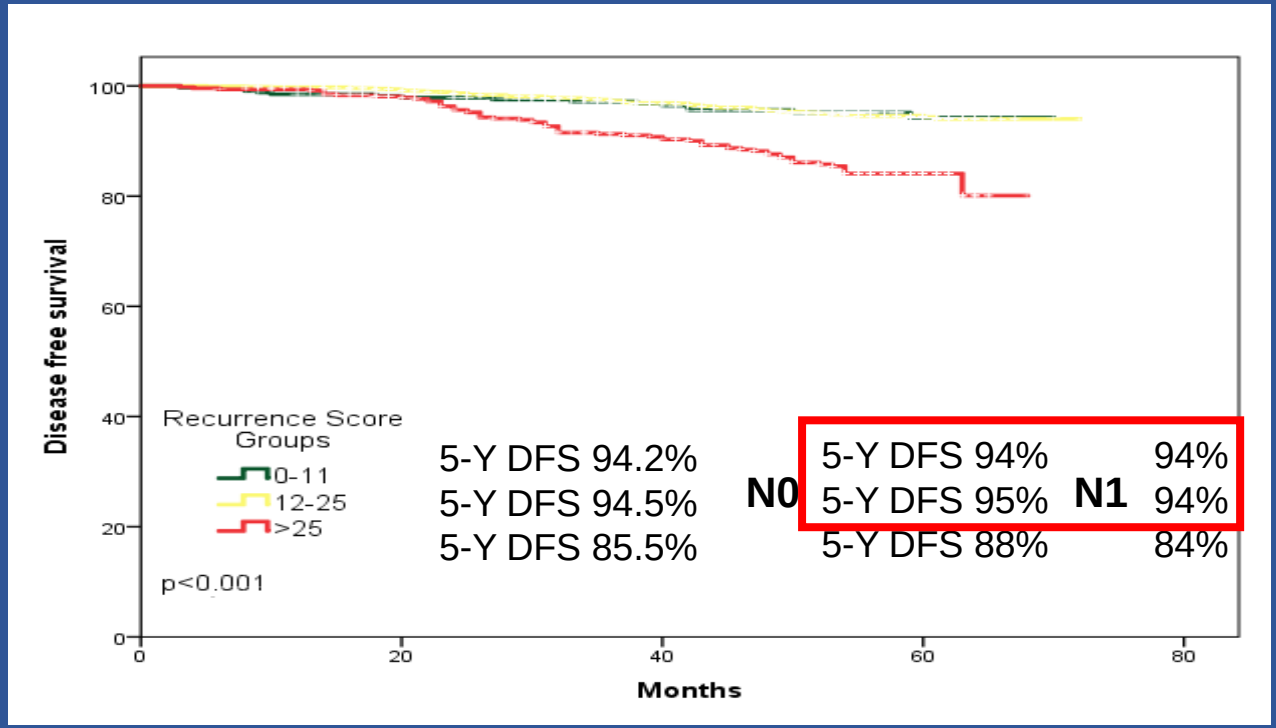


Gluz et al, EBCC 2016, plenary lecture

PlanB: Translational subprotocol

5-year DFS in per-protocol population
(no chemotherapy in pN0-1 and Recurrence Score 0-11)

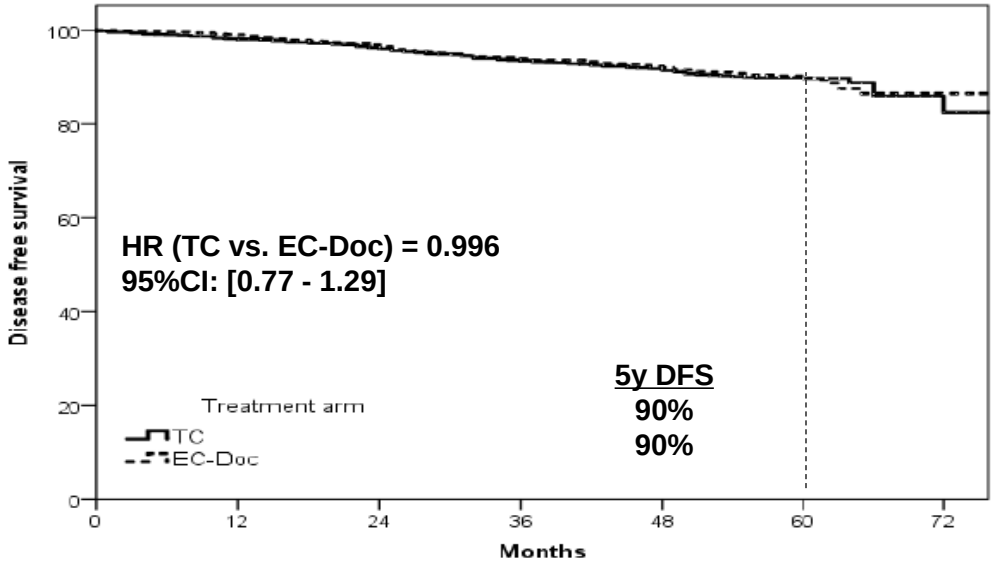
WSG
WOMEN'S HEALTHCARE STUDY GROUP



Gluz et al, EBCC 2016, plenary lecture

PlanB: Disease-free survival (DFS) by chemotherapy arm (ITT population)

WSG
WOMEN'S HEALTHCARE STUDY GROUP

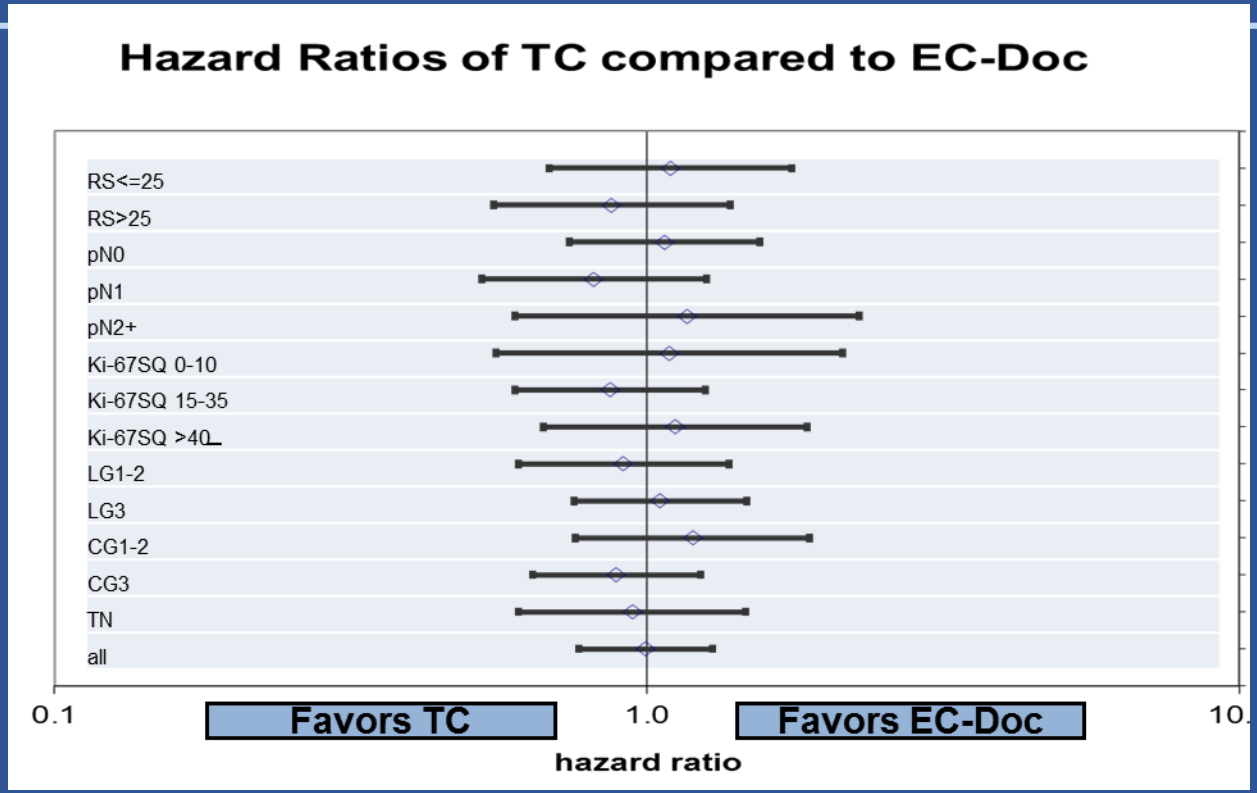


Numbers at risk

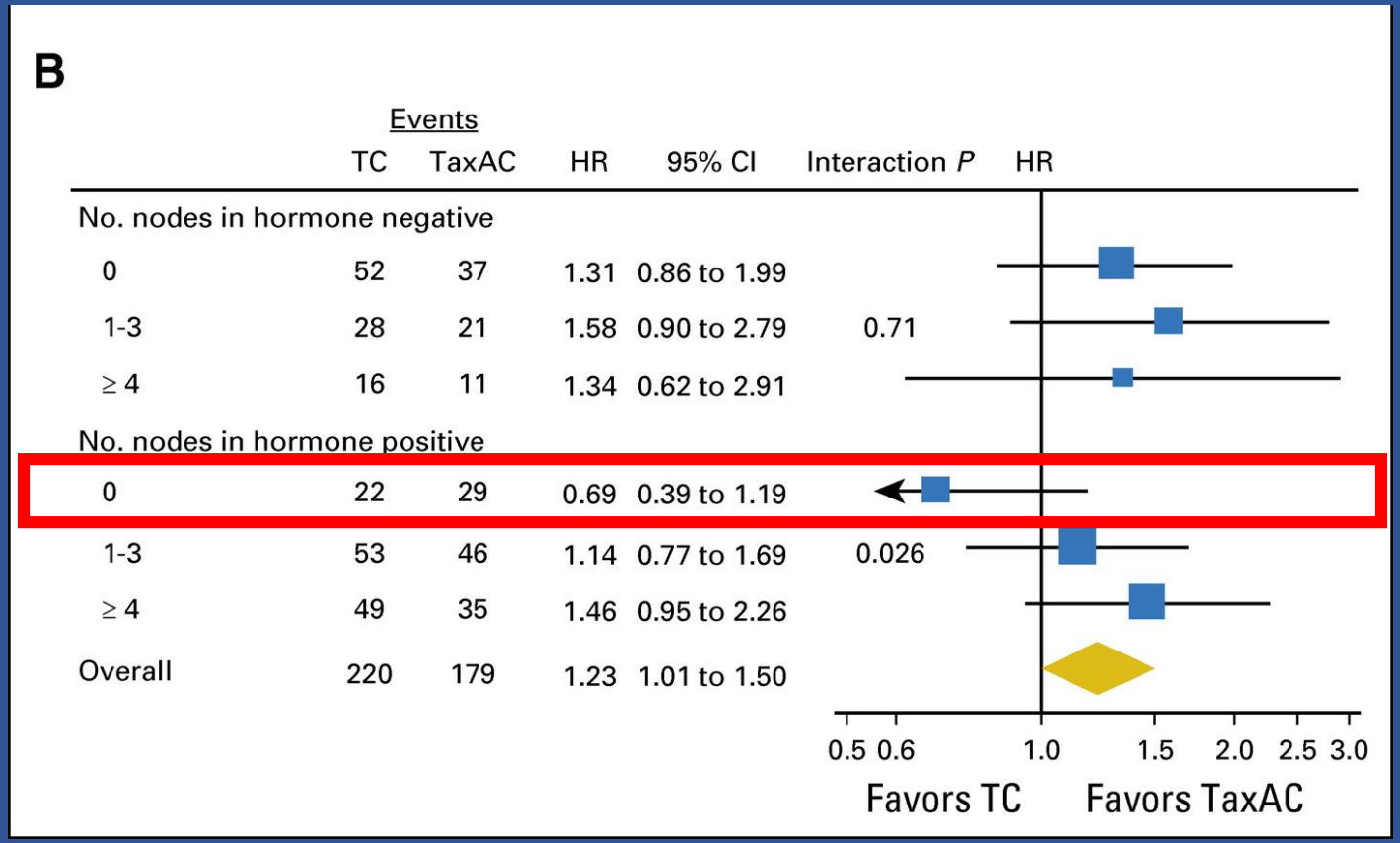
TC	1153	1126	1065	1003	952	736	25
EC-Doc	1128	1105	1051	993	936	729	32

PlanB: DFS in subgroups (ITT population)

WSG
WOMEN'S HEALTHCARE STUDY GROUP



ABC Trials: Contradicting Results



Comparison of Populations

	ABC Trials (%)	PlanB (%)
Triple negative	**31**	**19**
No. of positive nodes		
0	**41**	**59**
1-3	**44**	**35**
4-9	**12**	**5**
>=10	**4**	**2**
Histologic grade		
Low-intermediate	**47**	**64**
High	**51**	**36**

Comparison of Populations

	ABC Trials (%)	PlanB (%)
Triple negative	**31**	**19**
No. of positive nodes		
0	**41**	**59**
1-3	**44**	**35**
4-9	**12**	**5**
>=10	**4**	**2**
Histologic grade		
Low-intermediate	**47**	**64**
High	**51**	**36**

Comparison of Populations

	ABC Trials (%)	PlanB (%)
Triple negative	**31**	**19**
No. of positive nodes		
0	**41**	**59**
1-3	**44**	**35**
4-9	**12**	**5**
>=10	**4**	**2**
Histologic grade		
Low-intermediate	**47**	**64**
High	**51**	**36**

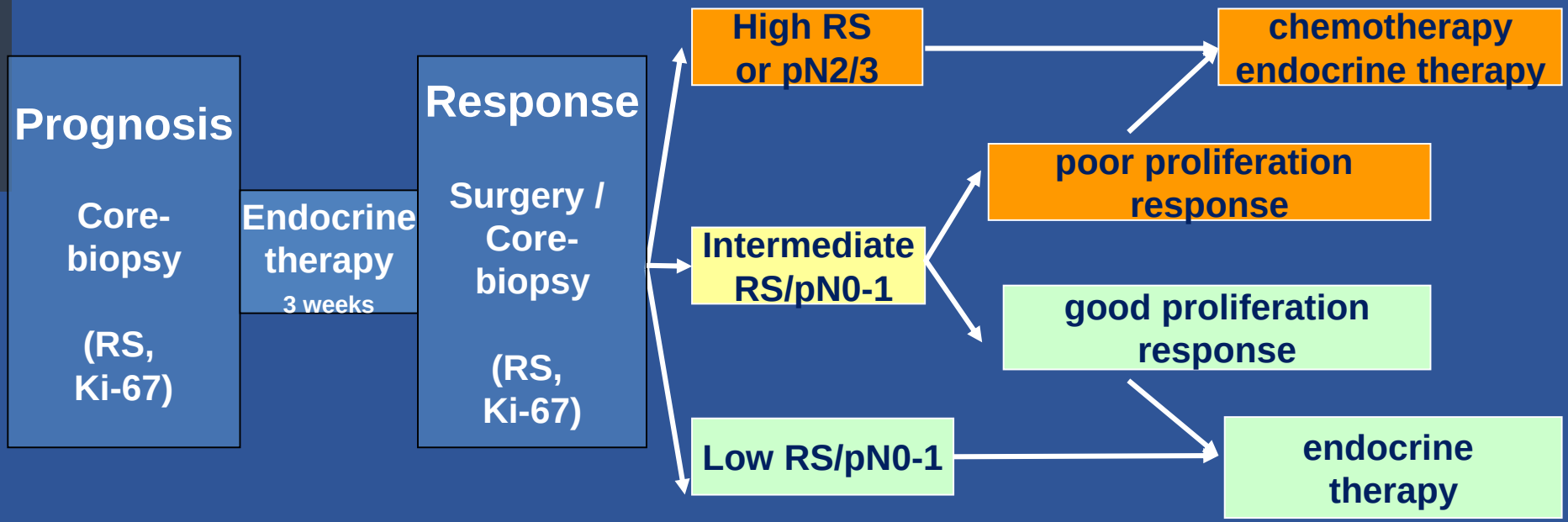
Conclusions

Risk	Features	
Low	HR+, pT1/2, pN0-1, RS 0-11	Endocrine therapy (94% 5y DFS) [1]
Intermediate	HR+, pT1/2, pN0-1, RS 12-25 HR+ N2	TC x4 (86% 5y DFS) [2] or TC x6 (90% 5y DFS, 94-95% in RS **≤25**)[1]
High	TNBC or HR+ pT3/4 or pN3/4 or RS >25	Dose dense anthracycline-taxane

- **Additional data coming from TailoRx and S1007 (RxPonder) and other trials on degree of chemotherapy benefit as a function of Recurrence Score**
- **More studies using biomarker and clinical selection so that fewer low risk ER positive patients are treated with chemotherapy**

[1]Harbeck ASCO 2017, [2]Jones JCO 2006

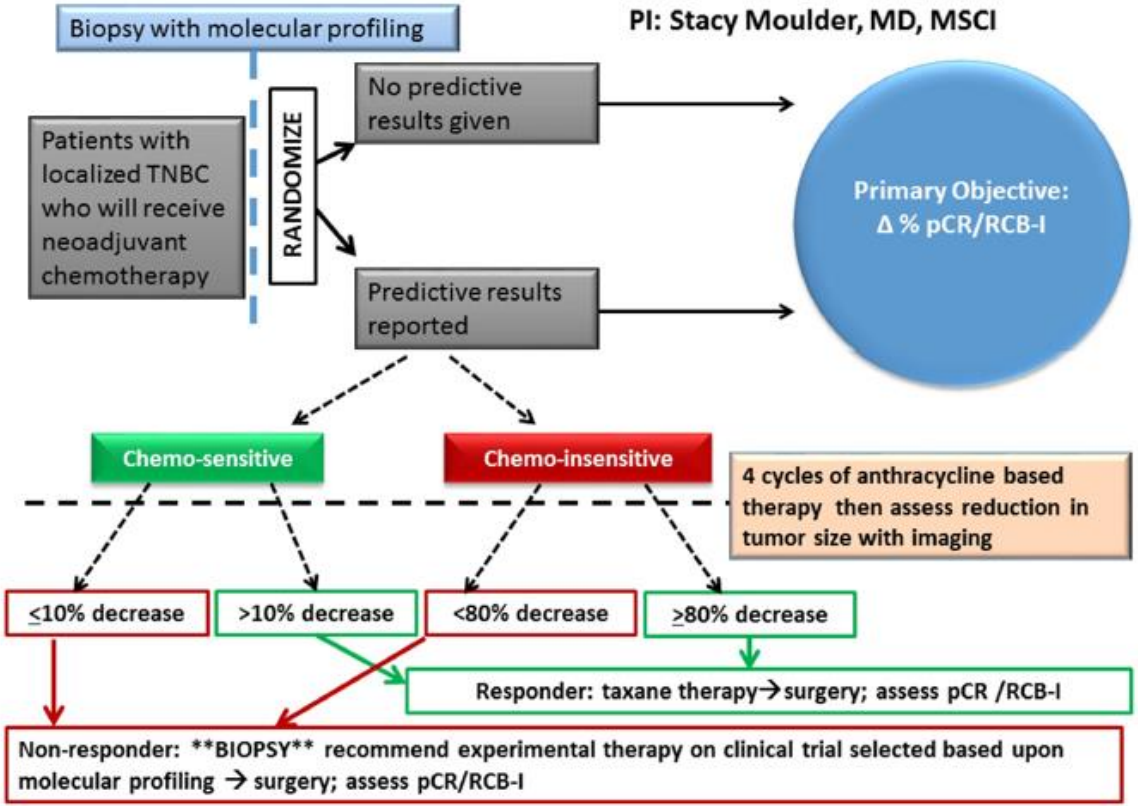
WSG-ADAPT Trial:
HR+/HER2- Subprotocol (n~4500)



Principal investigators: N. Harbeck (LKP), Munich; U. Nitz, Mönchengladbach

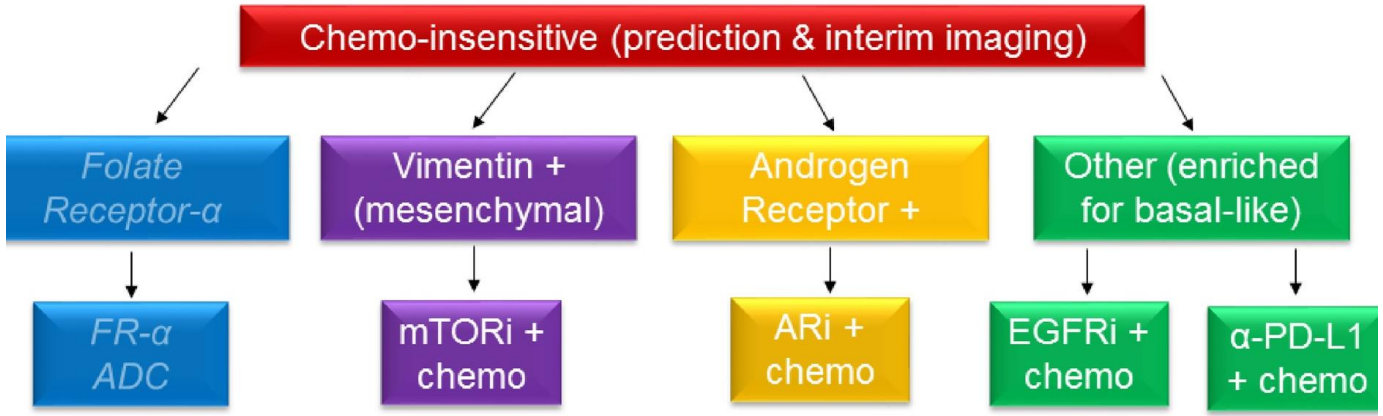
ARTEMIS

Gene expression profiling and chemosensitivity testing in localized TNBC



Moulder ASCO 2017

Phase II Trial Portfolio



*comparison to historical controls

Improved rate of pCR/RCB-I?

Single arm phase II trials
pCR improvement: 5%→20%
N=37
Two stage design; close if pCR/RCB-I not seen in ≥ 1 of 14 patients

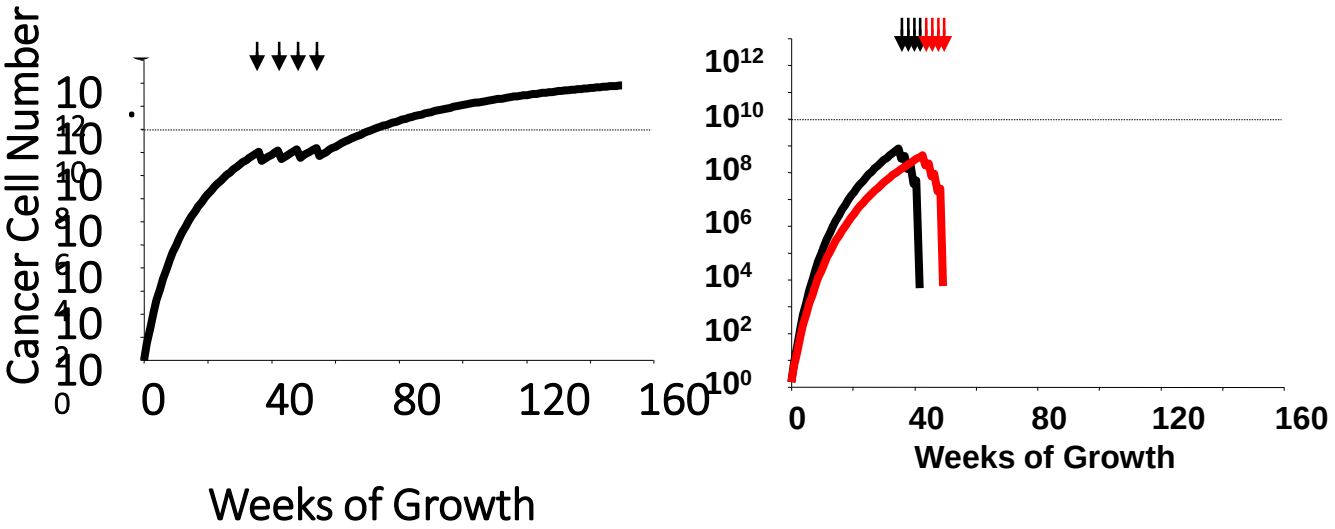
Trial	Agent
α-PD-L1	Atezolizumab
EGFRi	Panitumumab
ARi	Enzalutamide
mTORi	Everolimus
FR-α ADC	Mirvetuximab soravtansine

Moulder ASCO 2017

If chemotherapy still has a key role to play can we administer it more “precisely”

- Escalate cytotoxics for those who need it
- De-escalate cytotoxics for those who don’t
- Better scheduling and sequence
- Better combinations
- Better targets and/or delivery methods

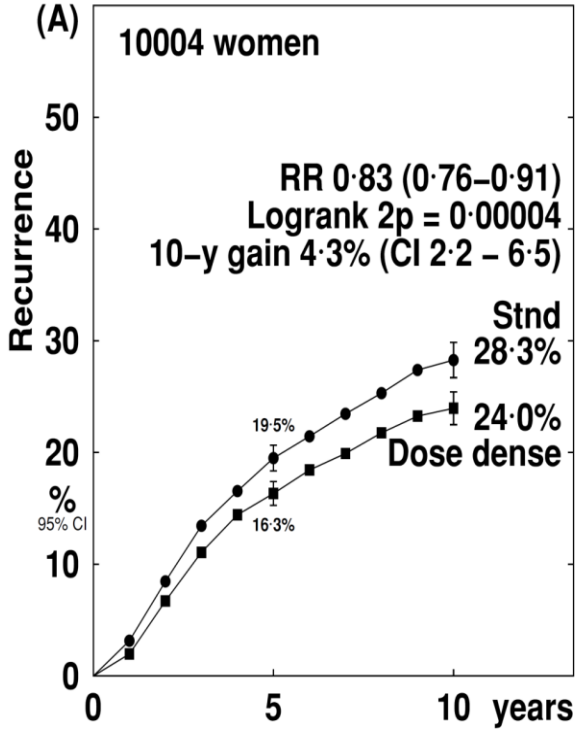
Dose-dense sequential therapy should maximize the curative impact of cytotoxic chemotherapy



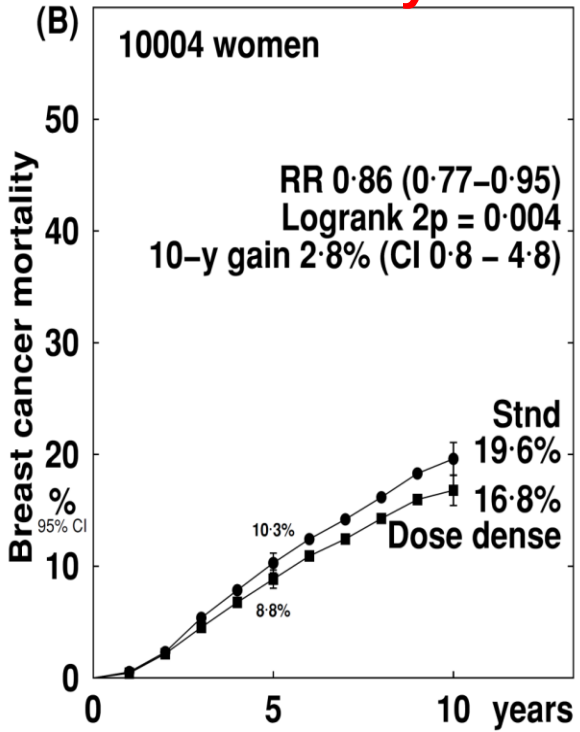
Norton L *et al.*, Cancer Medicine 2009

2-weekly (dose dense) *vs* the same chemotherapy given 3-weekly

Any Recurrence



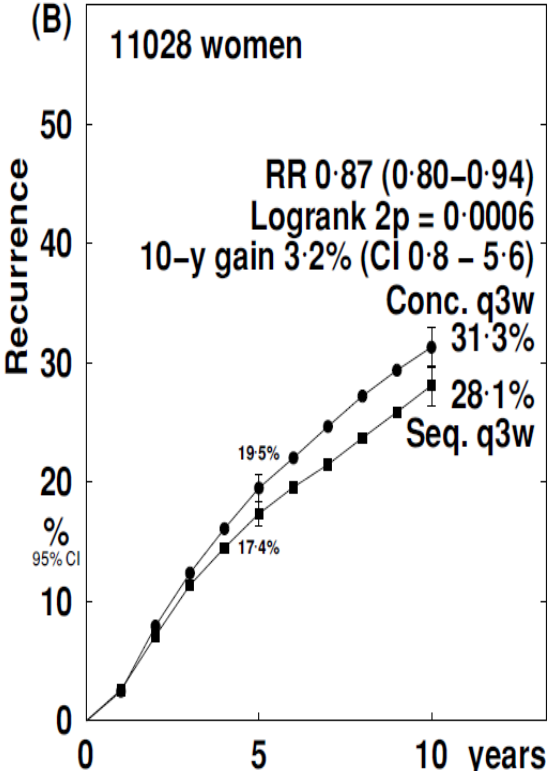
Breast Cancer Mortality



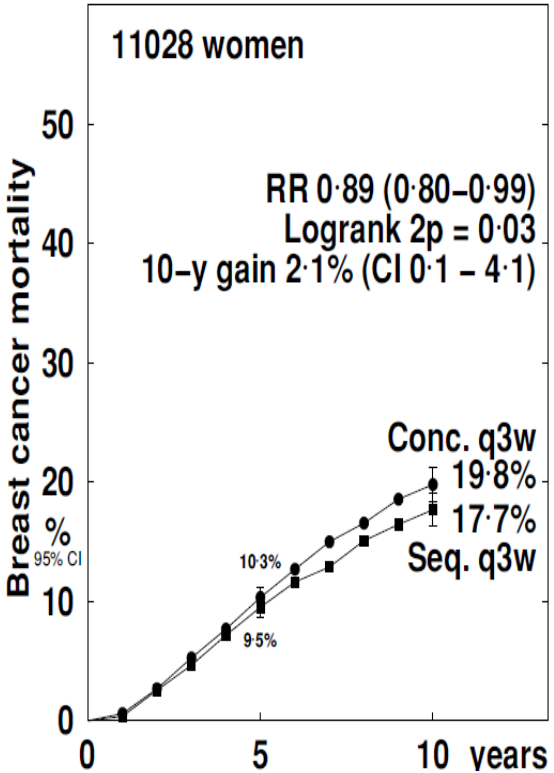
Gray R, EBCTCG
SABCS 2017

Sequential (3-weekly) vs Concurrent (3-weekly) chemotherapy

Any Recurrence



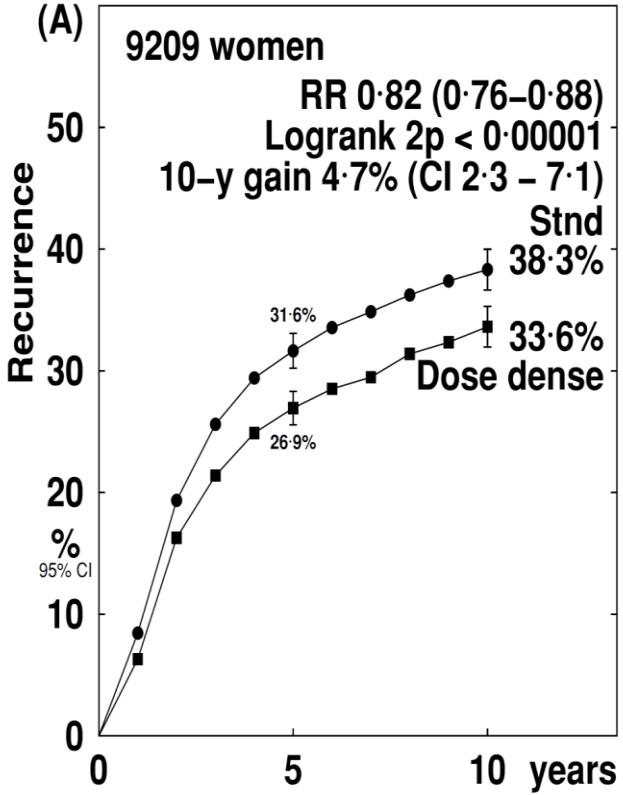
Breast Cancer Mortality



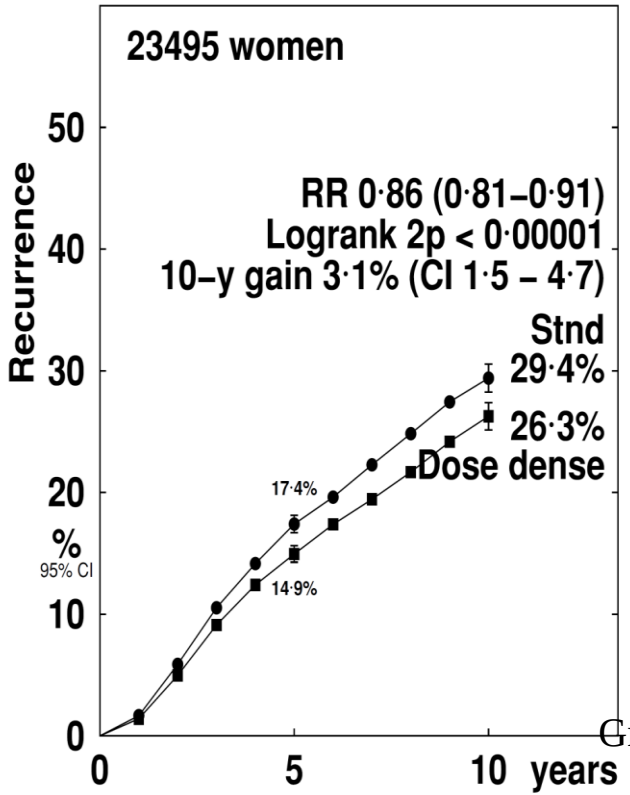
Gray R, EBCTCG
SABCS 2017

Pooled Analysis: Recurrence by ER status

ER-Negative



ER-Positive

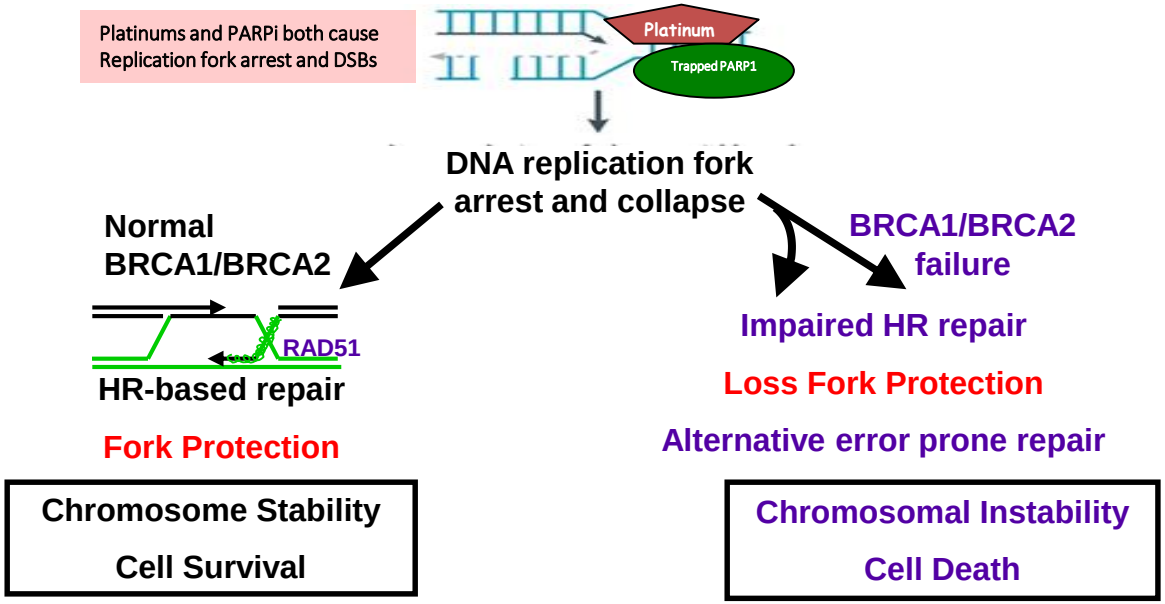


Gray R, EBCTCG
SABCS 2017

If chemotherapy still has a key role to play can we administer it more “precisely”

- Escalate cytotoxics for those who need it
- De-escalate cytotoxics for those who don’t
- Better scheduling and sequence
- Better combinations
- Better targets and/or delivery methods

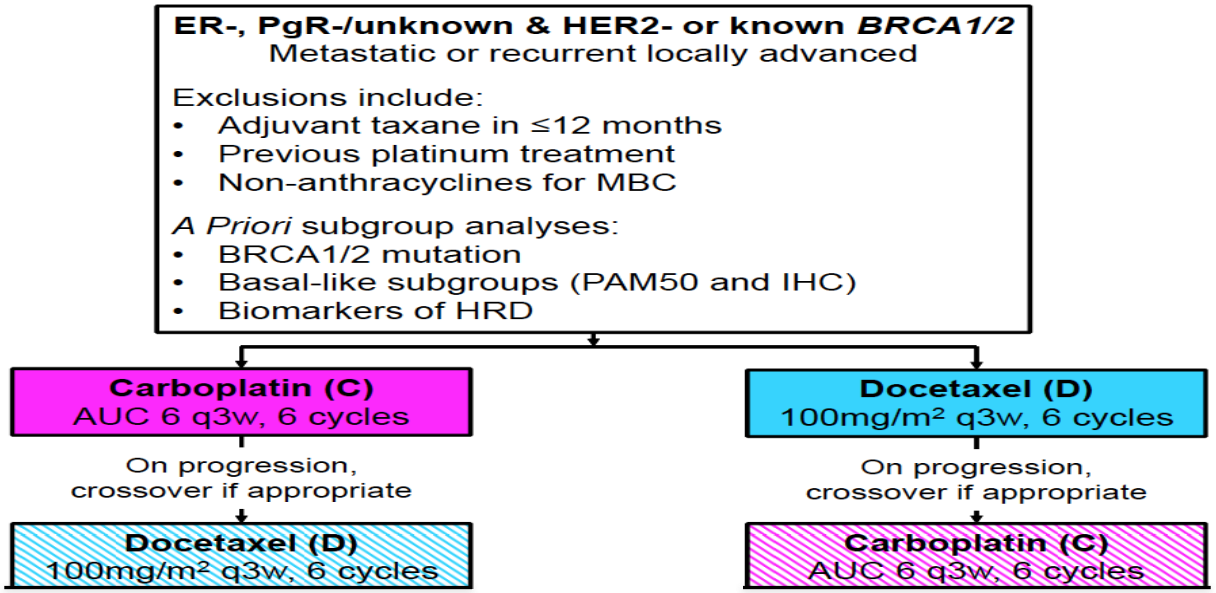
Platinums form adducts that arrest DNA replication forks and require BRCA1/2 for repair



Slide courtesy of J O'Shaughnessy

Is there a subset of TNBC that benefits from platinums? TNT mTNBC study

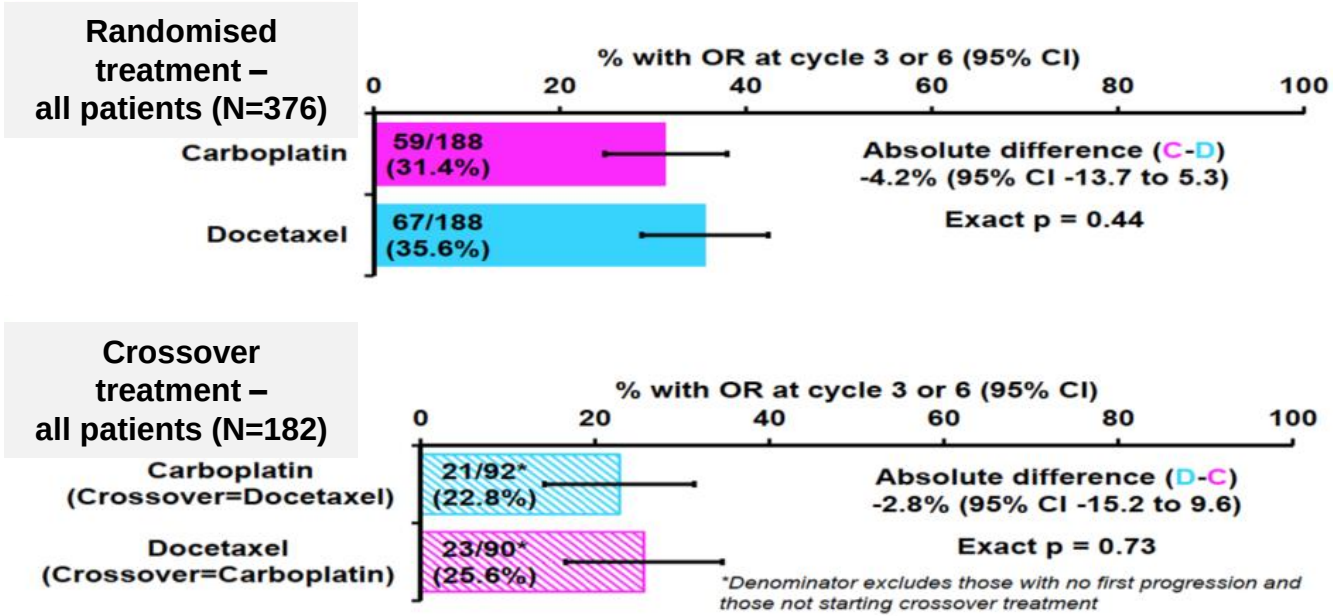
Trial design



Tutt A SABCS 2016

Overall No Difference with Platinum

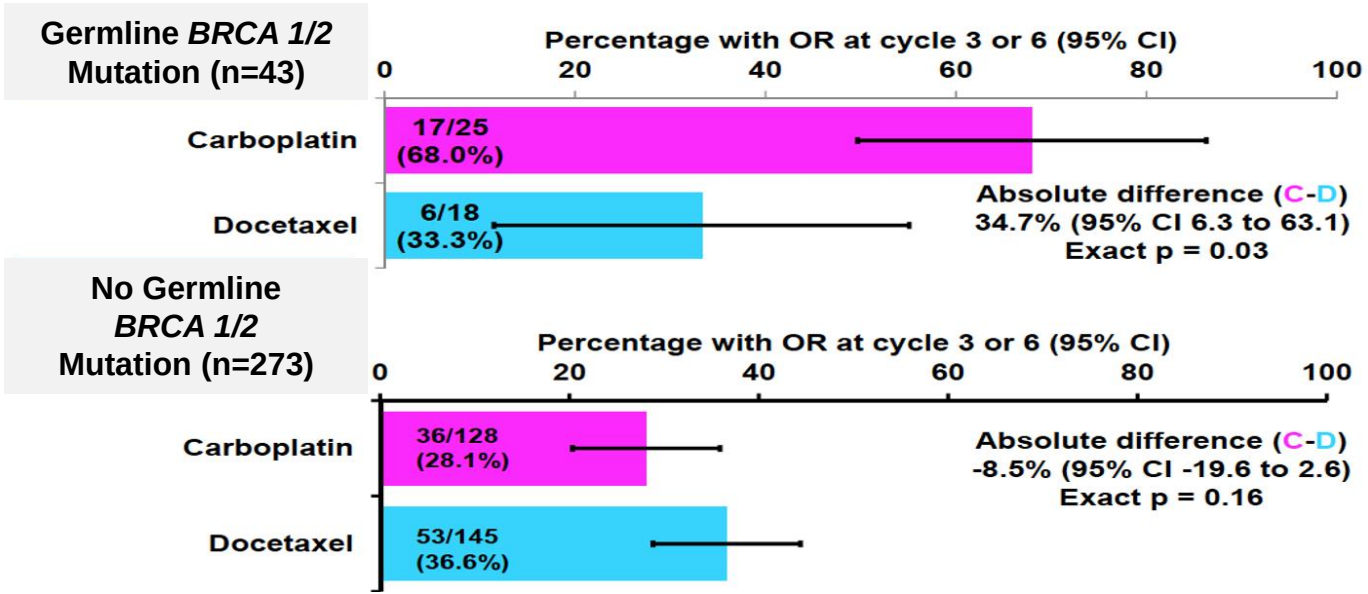
Objective Response



Tutt A, et al. SABCS 2016

In gBRCA Carboplatin Superior to Docetaxel

Objective response- BRCA 1/2 status



Interaction: randomized treatment & BRCA 1/2 status: *P* = 0.01

Tutt A, et al. SABCS 2016

GeparSixto

N = 595

TNBC
or
HER2+

R

Paclitaxel
80 mg/m² q1w

Non-pegylated liposomal
doxorubicin 20mg/m²q1w

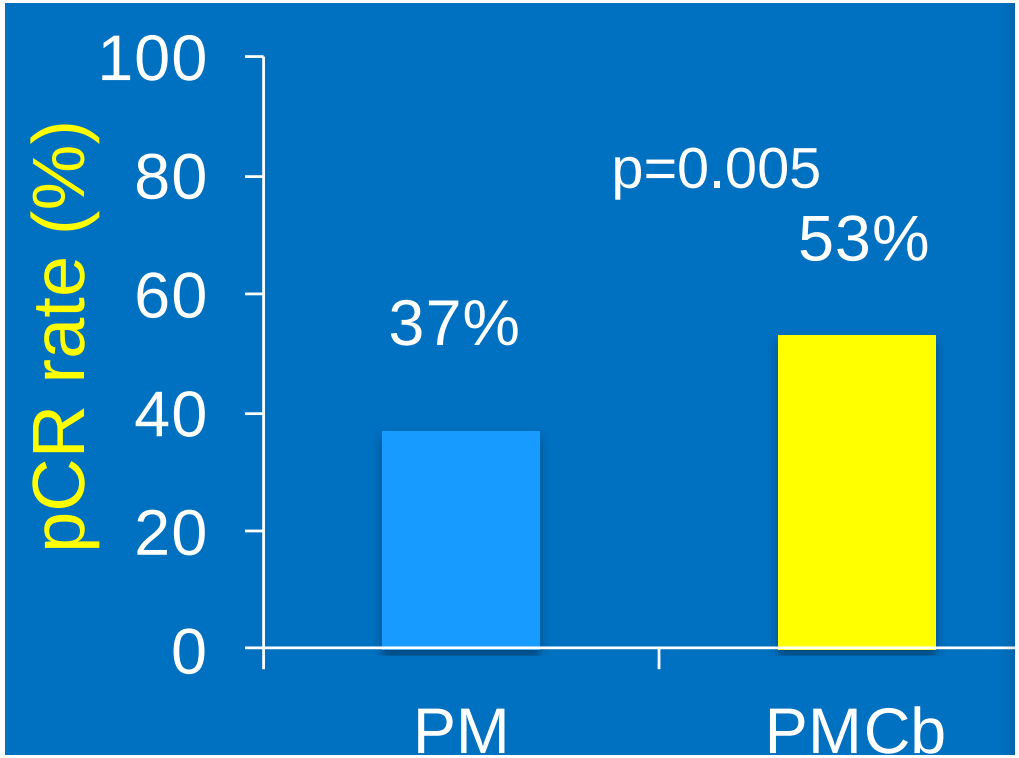
Carboplatin AUC 1.5* q1w
*reduced from AUC 2 at amendment 1 after enrollment of 330 patients

Her2-pos: Trastuzumab 6(8) mg/kg q3w (for 1 year)
+
Lapatinib 750 mg/d 18 wks

TNBC: Bevacizumab
15 mg/kg q3w

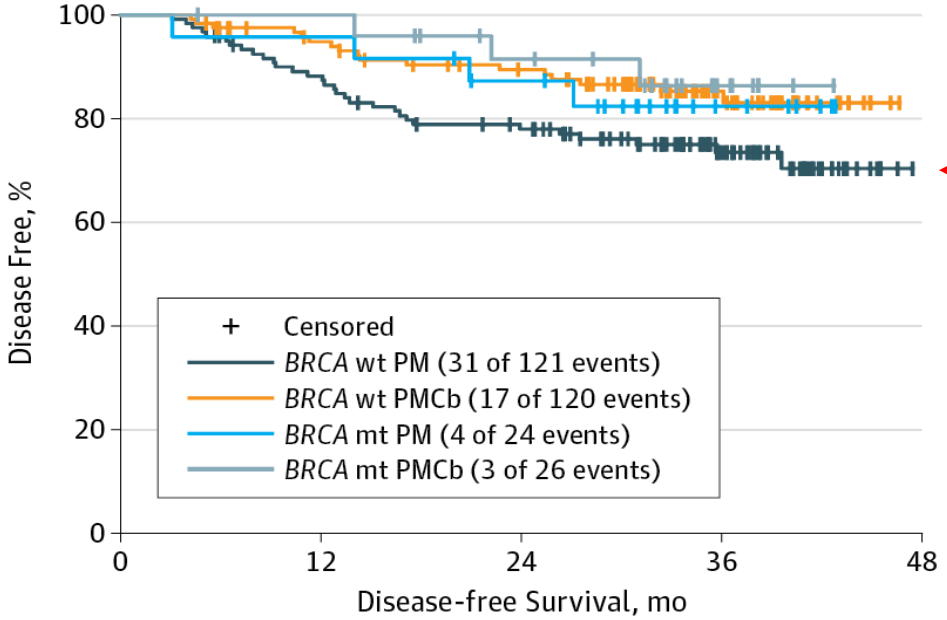
Slide Courtesy of C. Denkert. US National Library of Medicine. Clinicaltrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT01426880. Accessed December 13, 2017.

Carboplatin Improved pCR Overall



von Minckwitz G, et al. ASCO 2013.
Von Minckwitz G, et al. *Lancet Oncol*. 2014;15:747-756.
Denkert C, et al. SABCS 2013 (GeparSixto)

GeparSixto:



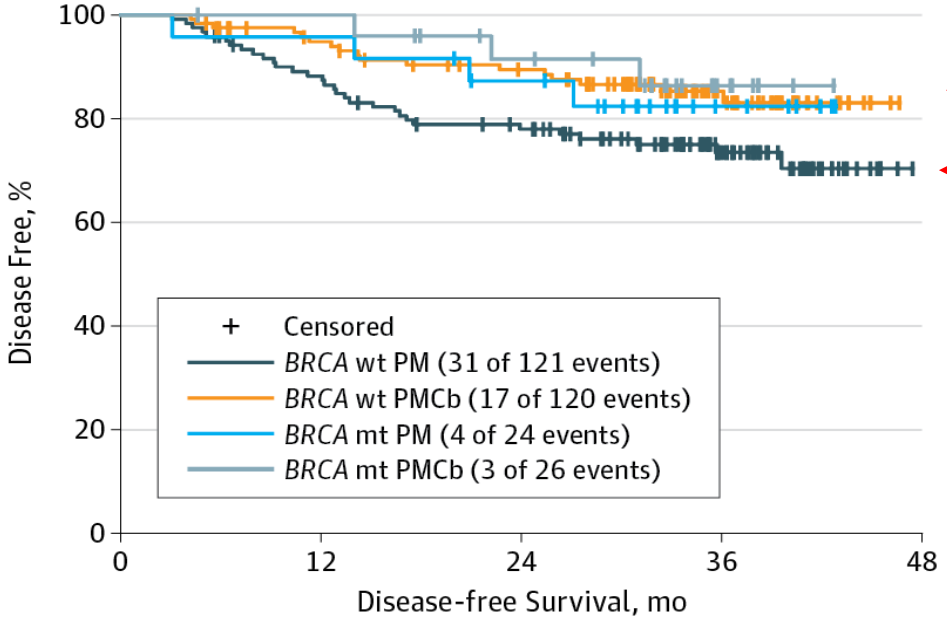
BRCA wt
No Carbo

No. at risk

BRCA wt PM	121	104	88	43	0
BRCA wt PMCb	120	107	95	40	0
BRCA mt PM	24	23	19	6	0
BRCA mt PMCb	26	25	20	7	0

Hahnen E, et al. *JAMA Oncol*. 2017;3:1378-1385.

GeparSixto: BRCA wt Benefitted from Carboplatin



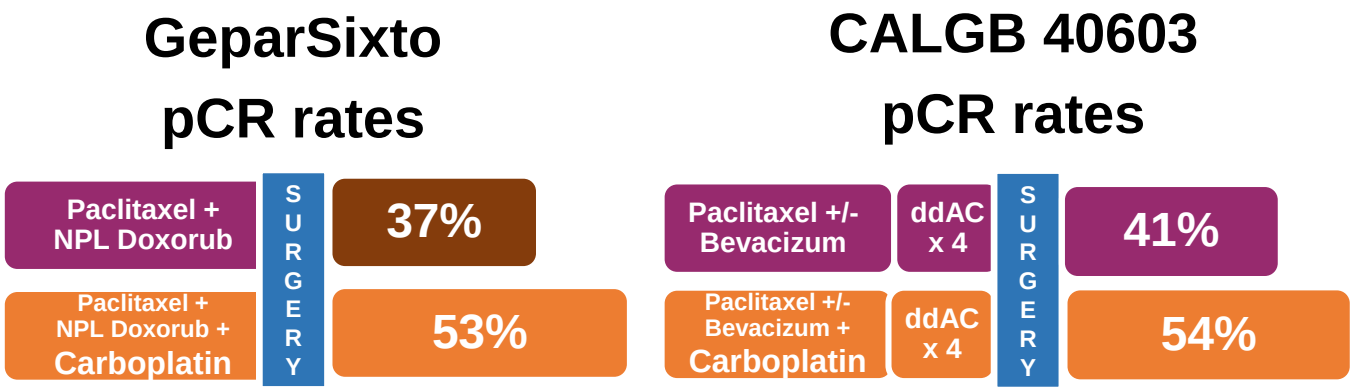
Everybody Else

BRCA wt No Carbo

No. at risk					
BRCA wt PM	121	104	88	43	0
BRCA wt PMCb	120	107	95	40	0
BRCA mt PM	24	23	19	6	0
BRCA mt PMCb	26	25	20	7	0

Hahnen E, et al. *JAMA Oncol*. 2017;3:1378-1385.

Role of Carboplatin in Unselected TNBC?

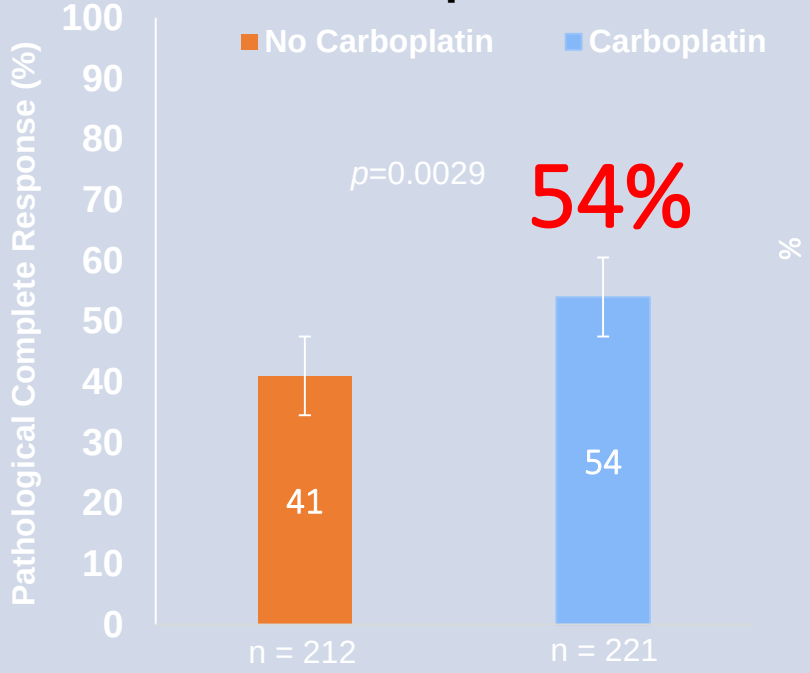


Addition of carboplatin increases pCR rate
in TNBC to >50%, but impact on EFS/OS unclear

Von Minckwitz G, et al. *Lancet Oncol*. 2014;15:747-756.
Sikov WM, et al. *J Clin Oncol.* 2015;33:13-21.
Slide courtesy of Rebecca Dent, MD

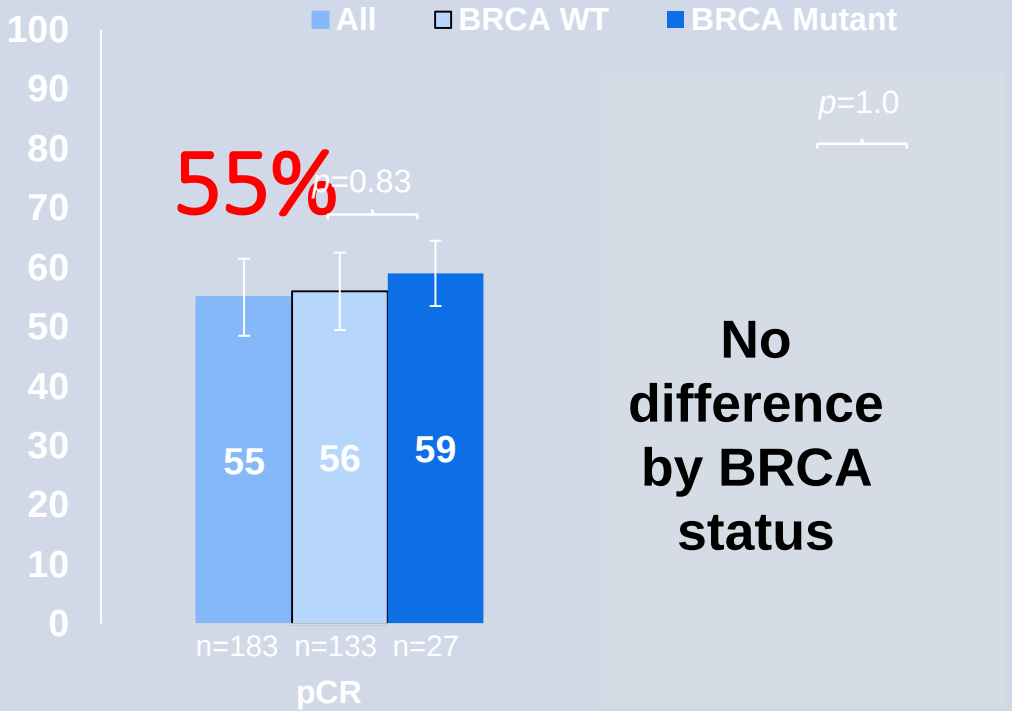
Neoadjuvant platinum in TNBC

CALGB 40603
T +/- Carboplatin → AC



Sikov W JCO, 2015

Carboplatin plus Docetaxel x 6 cycles



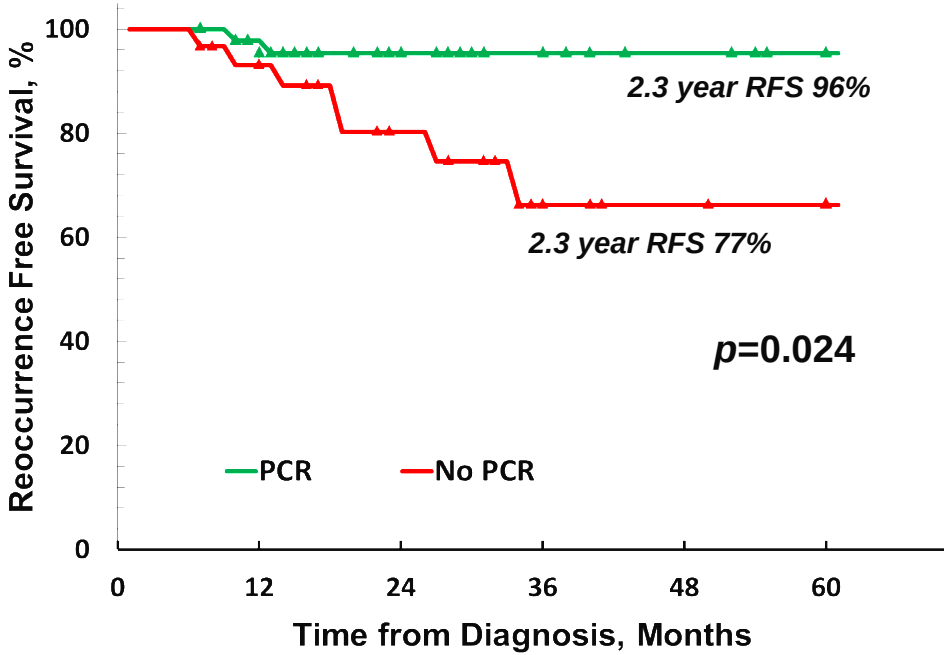
No difference by BRCA status

Sharma P. CCR , 2016

What is Prognosis of TNBC with pCR and no Anthracycline?

Carbo AUC 6 plus docetaxel 75 mg/m2 q 3 weeks x 4-6 cycles

77 patients, 21% BRCA mutations

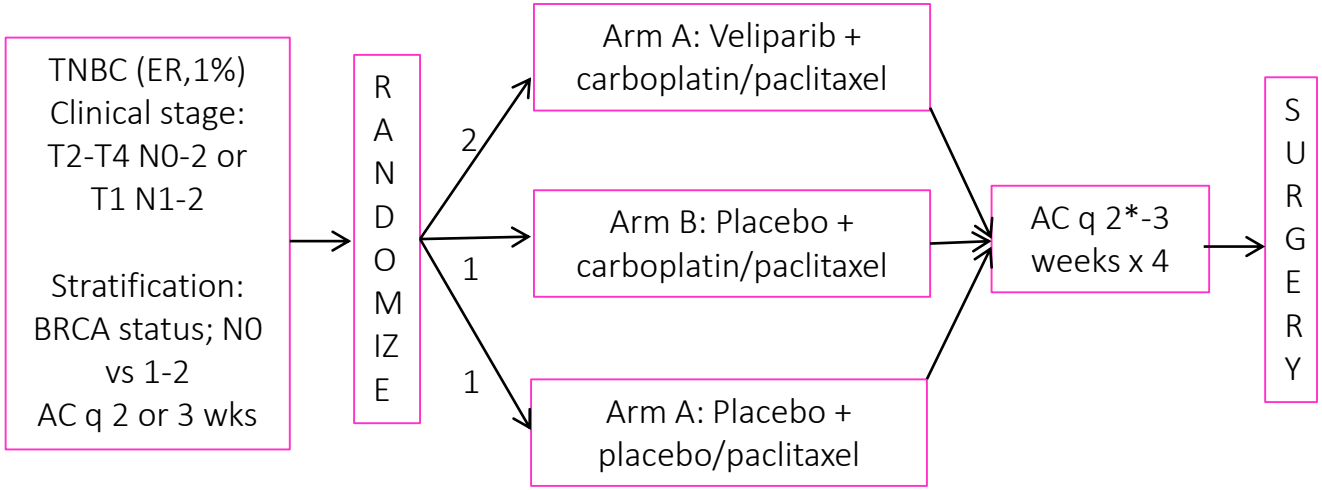


* pCR ypT0/is ypN0

Sharma et al, Clin Ca Res 2016

BrighTNess: A Randomized Phase III Neoadjuvant Trial in TNBC

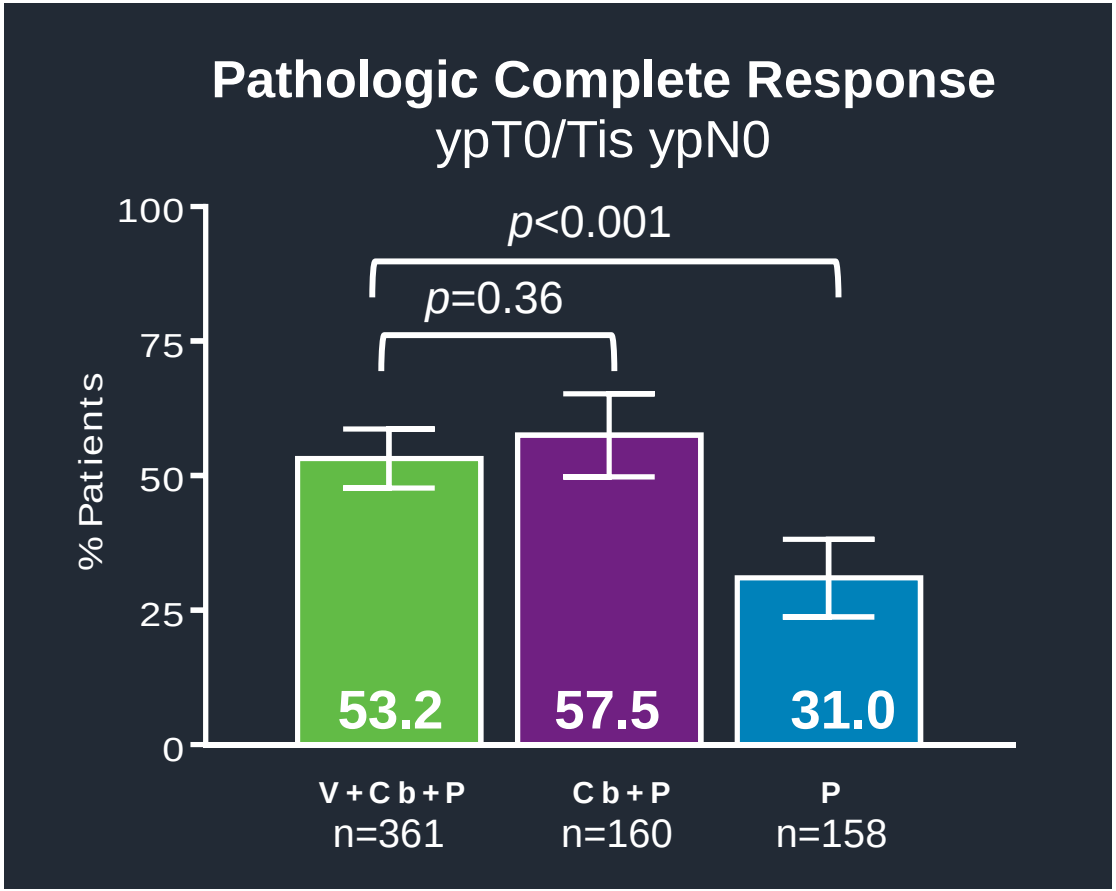
N=624; primary endpoint pCR breast/axilla



Veliparib: 50 mg PO BID x 12 weeks; carboplatin: AUC 6 IV q 3 weeks x 4; paclitaxel 80 mg/m^2 IV weekly x 12, AC: doxorubicin 60 mg/m^2/cyclosphosphamide 600 mg/m^2

*with G-CSF support

Geyer et al, ASCO 2017



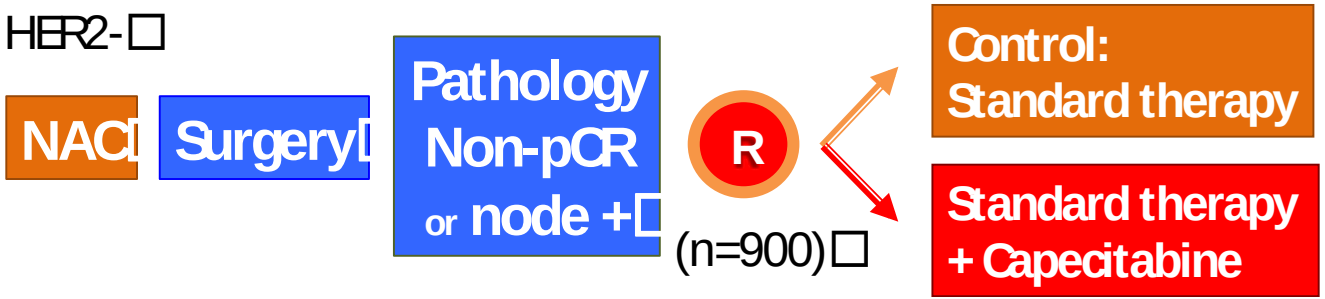
EFS events at primary analysis: **8.5% V+Cb+P vs 8.1% Cb+ P vs 13.9% P**

Take away

- Patient selection for platinums in unselected TNBC is unclear
- The addition of platinums to taxanes may mitigate the need for anthracyclines, particular when a pCR is achieved
- The addition of PARPi to taxane/platinum regimens does not appear to confer benefit

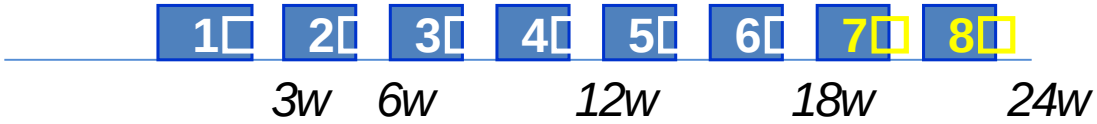
Can we Decrease Risk of Recurrence in Patients without a pCR?

- CREATE-X: primary endpoint DFS



Capecitabine (X): 2,500 mg/m^2/day, po, day 1-14

Repeat every 3 weeks for 8 cycles



Toi et al, NEJM 2017

Patients & Tumor Characteristics

		Capecitabine (N=443)	Control (N=444)
Age	Median (range)	48 (25-74)	48 (25-74)
Menopausal status	Pre (%)	262 (59.1)	248 (55.9)
	Post (%)	181 (40.9)	196 (44.1)
Stage	I/IIA/IIB	259 (58.9)	276 (62.0)
	IIIA/IIIB	178 (40.5)	167 (37.5)
ER & PgR	ER (+) or PgR (+)	304 (68.6)	297 (66.9)
	ER (-) & PgR (-)	139 (31.4)	147 (33.1)
Nodal metastases	0	176 (39.7)	171 (38.5)
	1-3	165 (37.2)	174 (39.2)
	4+	102 (23.0)	99 (22.3)
Histological effect grading by NAC*	0/1a/1b	251 (57.9)	233 (53.6)
	2/3	183 (42.2)	202 (46.4)

Masuda N, et al. *NEJM*. 2017;376:2147-2159.

*General Rules for Clinical and Pathological Recording of Breast Cancer, from The Japanese Breast Cancer Society

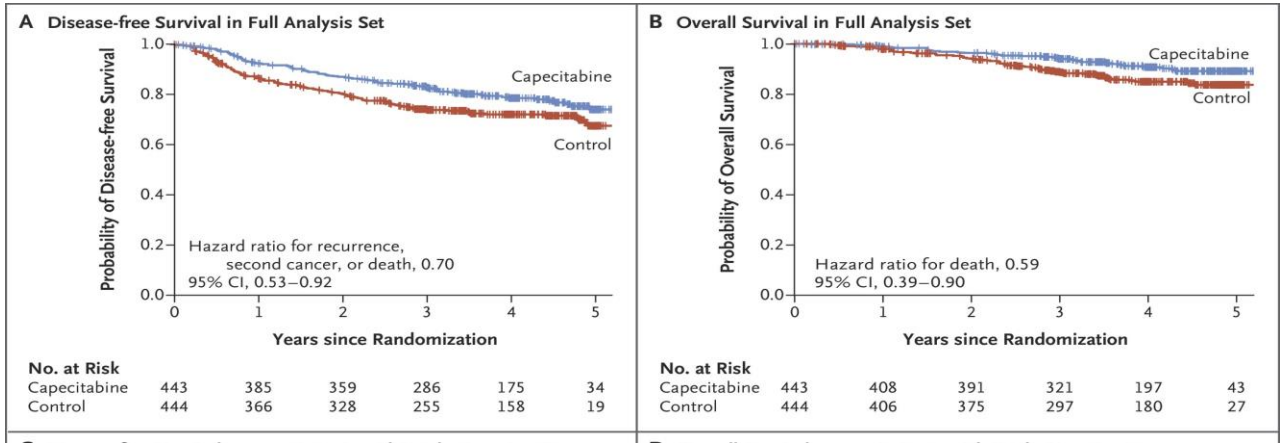
Patients & Tumor Characteristics (2)

		Capecitabine (n=443)	Control (n=444)
Neoadjuvant chemotherapy	A containing* A-T (sequential)* AT (concurrent)* TC*	23 (5.2) 357 (80.6) 63 (14.2) 5 (1.1)	19 (4.3) 372 (83.8) 53 (11.9) 3 (0.7)
5FU containing regimen	Yes No	262 (59.1) 181 (40.9)	271 (61.0) 173 (39.0)
Adjuvant endocrine therapy	Yes for premenopausal Yes for postmenopausal No	187 (42.5) 108 (24.5) 145 (32.7)	178 (40.0) 127 (28.5) 140 (31.5)
Radiation therapy	Yes No	321 (72.5) 122 (27.5)	326 (73.4) 118 (26.6)

*A: Anthracydine containing, T: Taxane (docetaxel or Paclitaxel), TC: Docetaxel+Cyclophosphamide

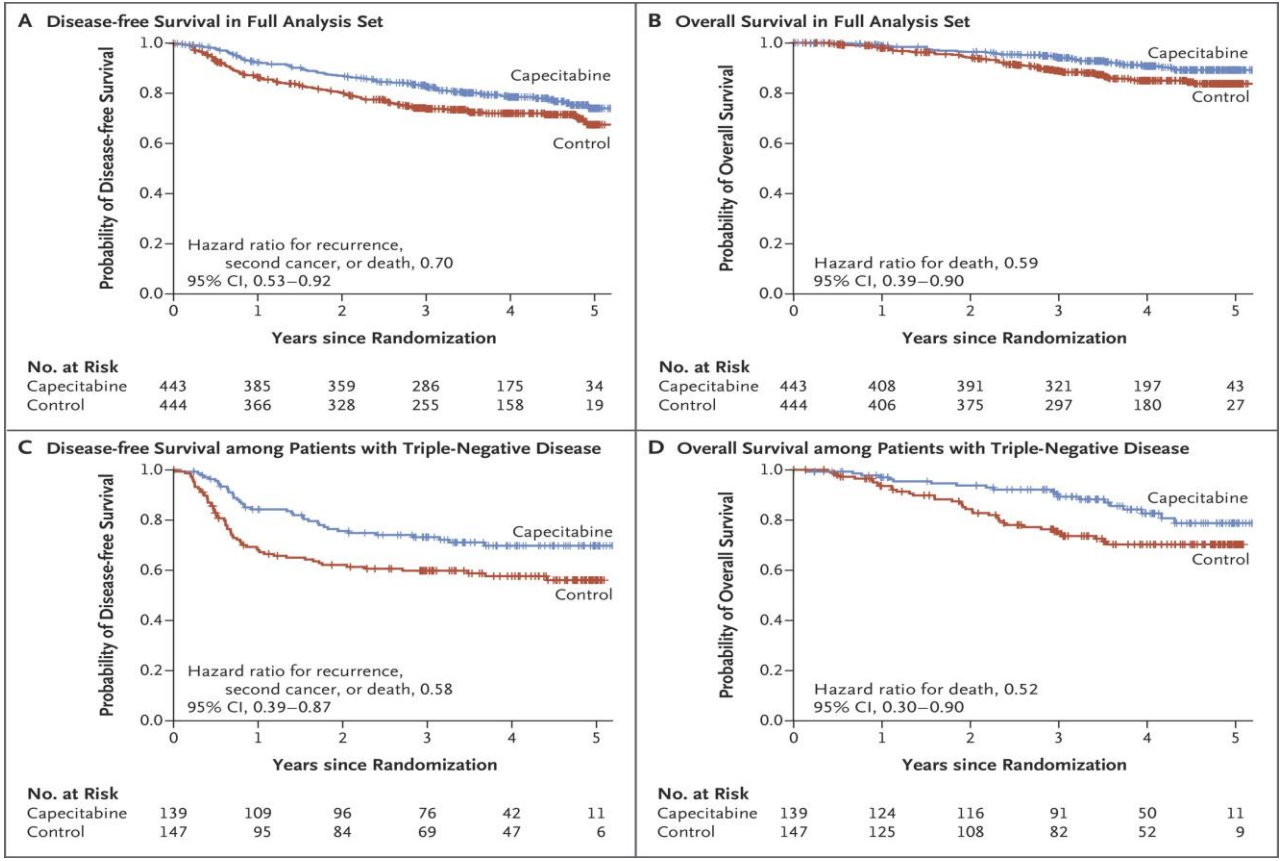
Masuda N, et al. *NEJM*. 2017;376:2147-2159.

Disease-Free Survival and Overall Survival



Masuda N, et al. *NEJM*. 2017;376:2147-2159.

Disease-Free Survival and Overall Survival



Masuda N, et al. *NEJM*. 2017;376:2147-2159.

Unanswered Questions…

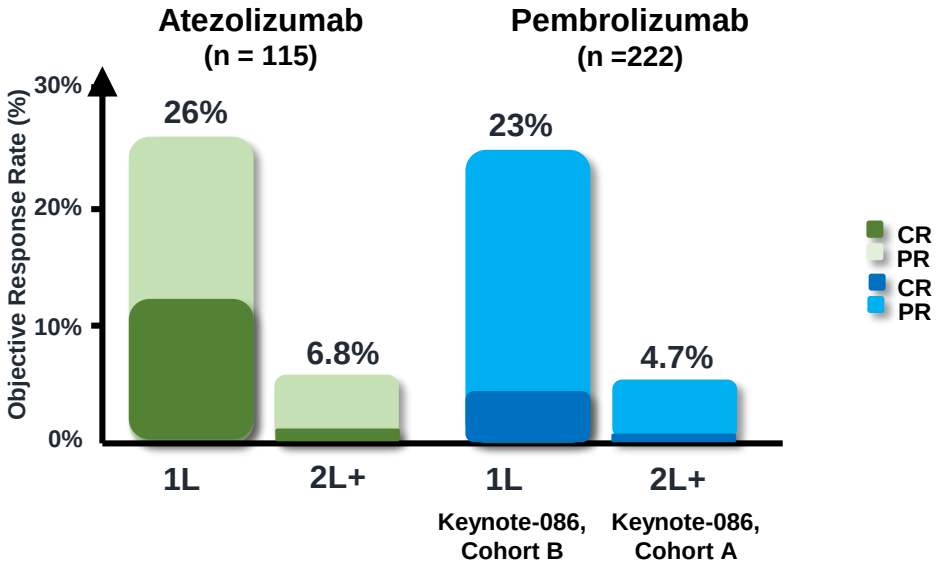
- No DFS/RFS benefit when capecitabine was added to standard sequential adjuvant anthracycline-taxane backbone (US Oncology 01062, FinXX)[1-2]
- In CREATE-X, 81.1% had sequential anthracycline-taxane, so why would capecitabine lead to DFS/OS benefit in adjuvant setting after standard Rx?
- Over 60% pts had neoadjuvant 5FU, so why would more 5FU in an adjuvant setting be helpful?
- Tolerability of the studied dose/schedule?

1. O'Shaughnessy J. *Clin Cancer Res*. 2015;21:4305-4311.
2. Joensuu H, et al. *J Clin Oncol*. 2012;30:11-18.

If chemotherapy still has a key role to play can we administer it more “precisely”

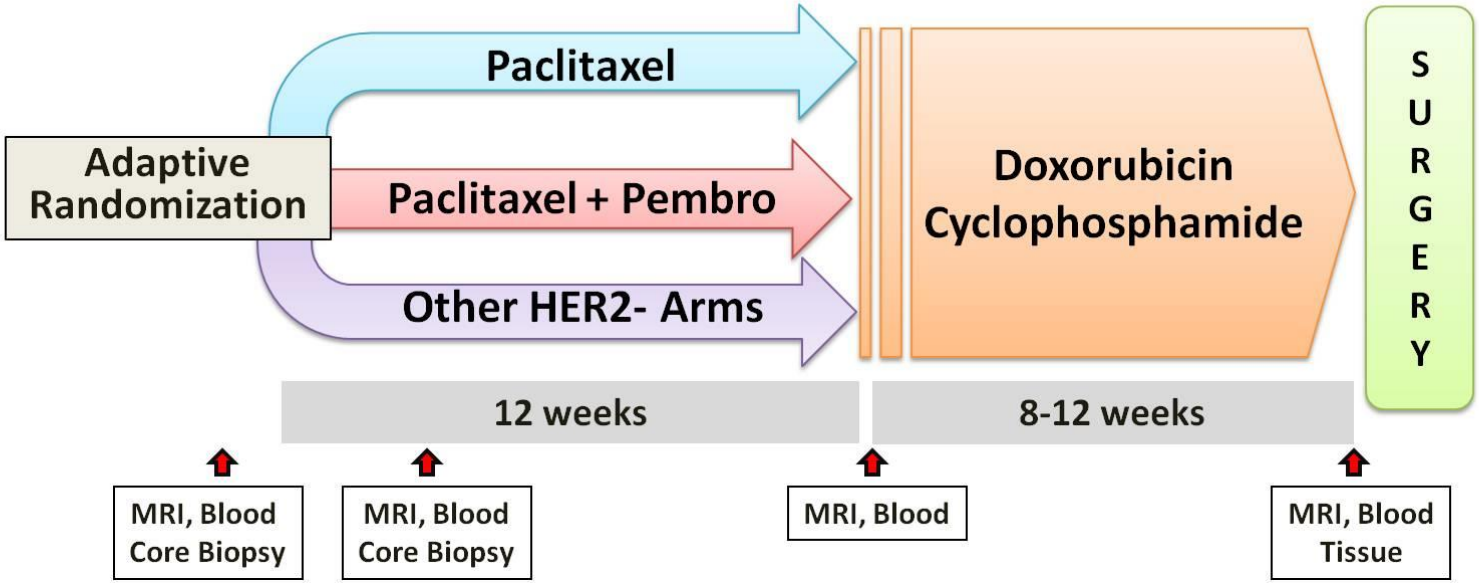
- Escalate cytotoxics for those who need it
- De-escalate cytotoxics for those who don’t
- Better scheduling and sequence
- Better combinations
- Better targets and/or delivery methods

Moving Immune Therapy into the Curative Intent Setting

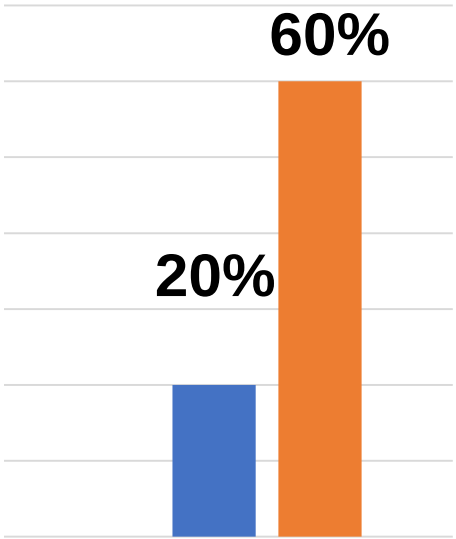


Schmid P, et al. AACR 2017; Adams S, et al ASCO 2017
Modified from Schmid ESMO 2017

I-SPY 2 TRIAL Schema: HER2- Signatures



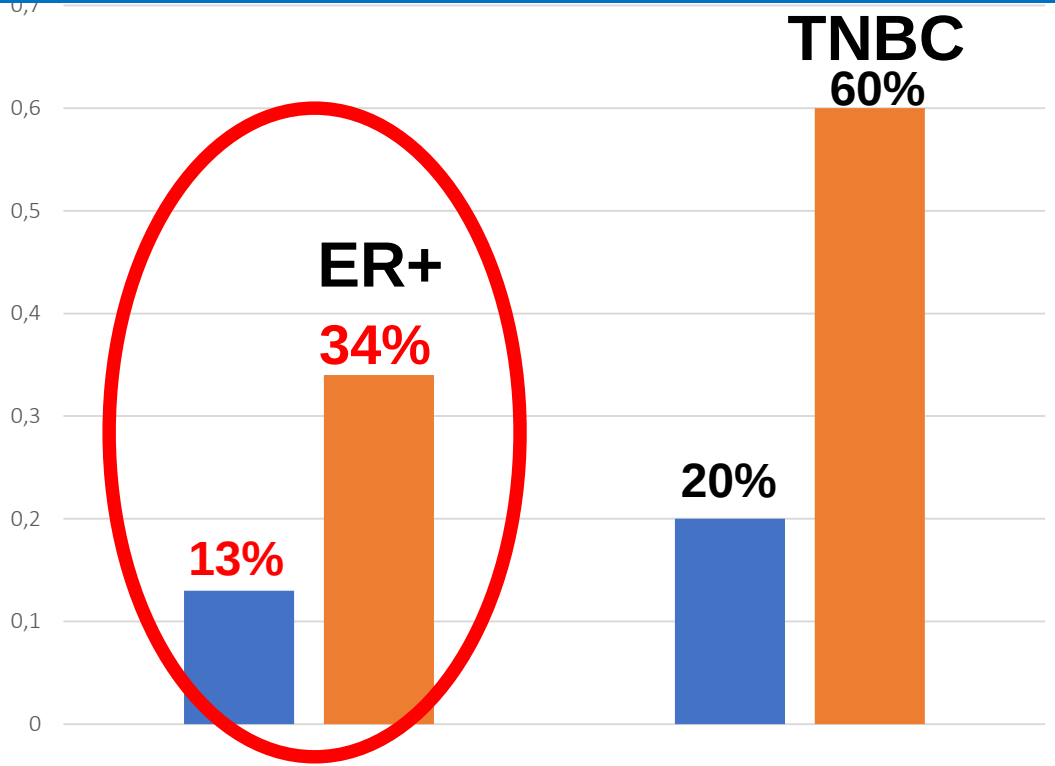
Estimated pCR Rates in TNBC



Probability of phase III success: >99%

Nanda ASCO 2017

Estimated pCR Rates in TNBC and ER+

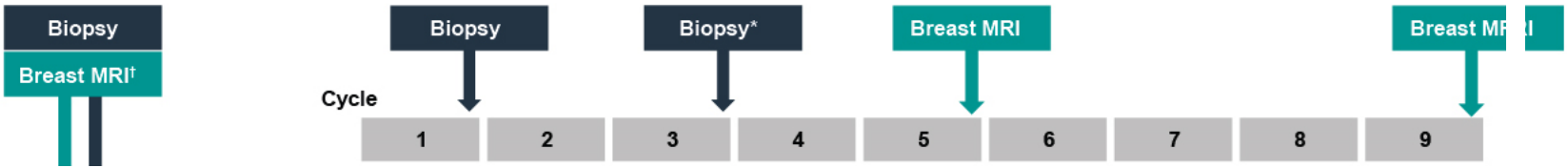


Pembro graduates in all signatures
Including ER+

Nanda ASCO 2017

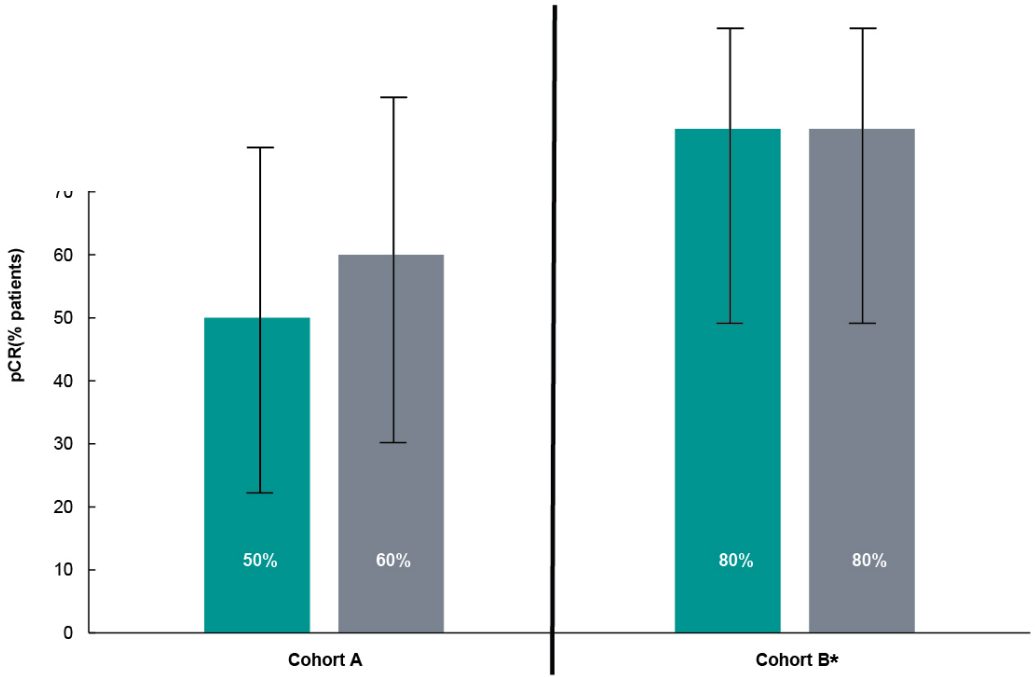
	Pembrolizumab (n=69) % (n)		Control (n=180) % (n)	
	All grades	Grade 3-5	All grades	Grade 3-5
Hypothyroidism	8.7 (6)*	1.4 (1)	0.6 (1)*	0 (0)
Hyperthyroidism	4.3 (3)*	0 (0)	0 (0)*	0 (0)
Adrenal Insufficiency	8.7 (6)	7.2 (5)*	0 (0)*	0 (0)
Hepatitis	2.9 (2)	2.9 (2)	0 (0)	0 (0)
Pneumonitis	2.9 (2)	0 (0)	1.1 (2)	0.6 (1)
Colitis	1.4 (1)	1.4 (1)	0.6 (1)	0.6 (1)
Pruritis	24.6 (17)*	0 (0)	11.1 (20)*	0.6 (1)
TOTAL	**54%**	**13%**		

KEYNOTE-173: Phase Ib Trial of Pembrolizumab + Chemotherapy in Neoadjuvant TNBC



*An optional biopsy was performed between Days 15 and 21 of Cycle 3
†MRI, magnetic resonance imaging; pCR, pathologic complete response; Q3W, every 3 weeks.

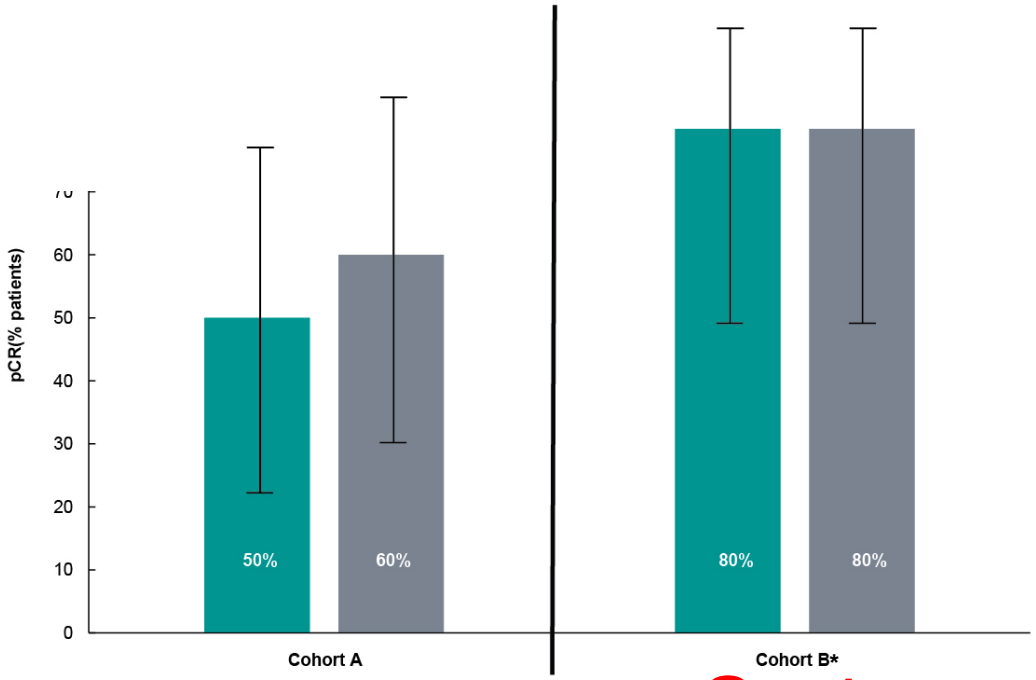
Pathologic Complete Response



No Carbo
50%

Carbo
80%

Pathologic Complete Response

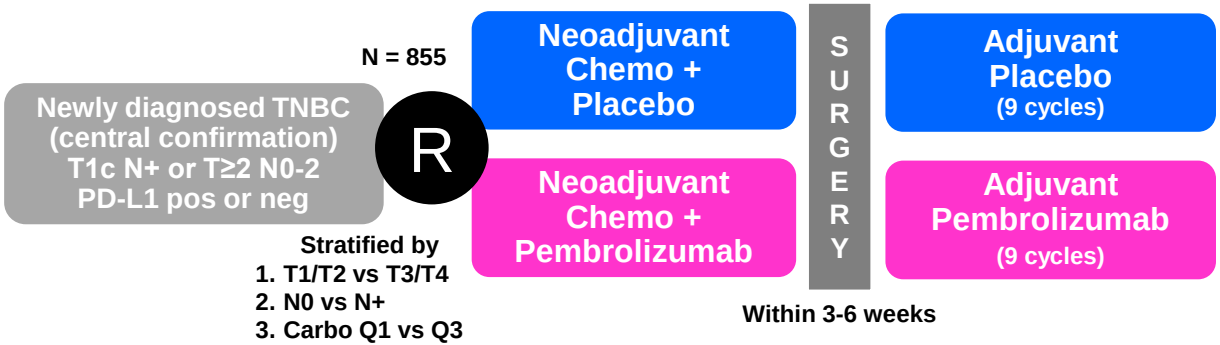


Cost:

100% neutropenia

80% grade 3/4

Neoadjuvant Studies – KEYNOTE 522

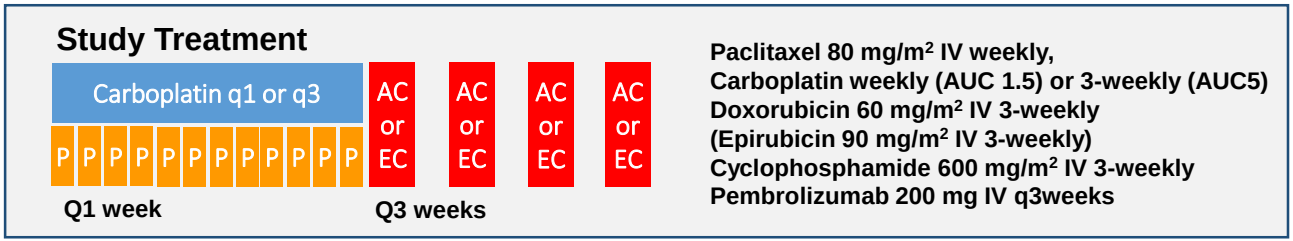


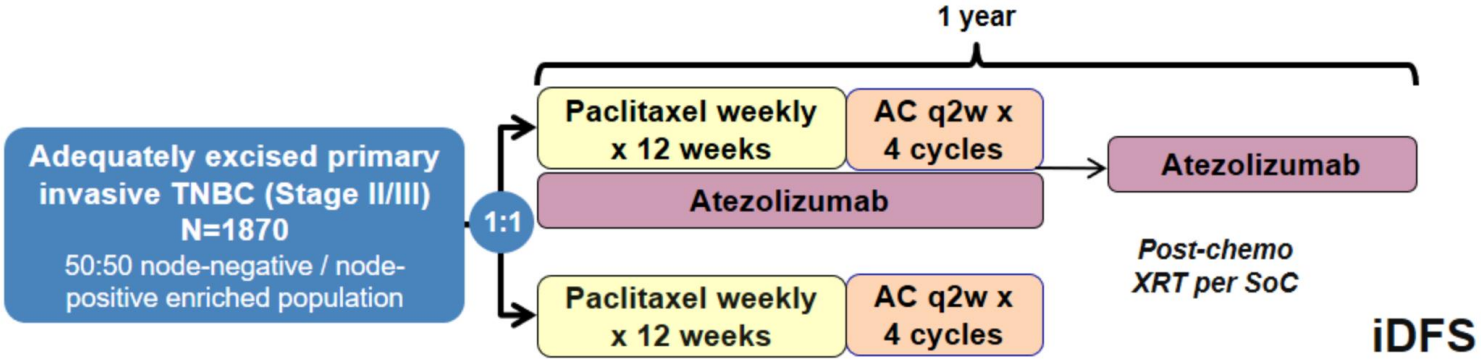
Primary Endpoints:

- pCR rate (ypT0/Tis ypN0)
- EFS

Secondary Endpoints:

- Alternative pCR rate (ypT0 ypN0)
- pCR rate in PD-L1+
- EFS in PD-L1+
- OS





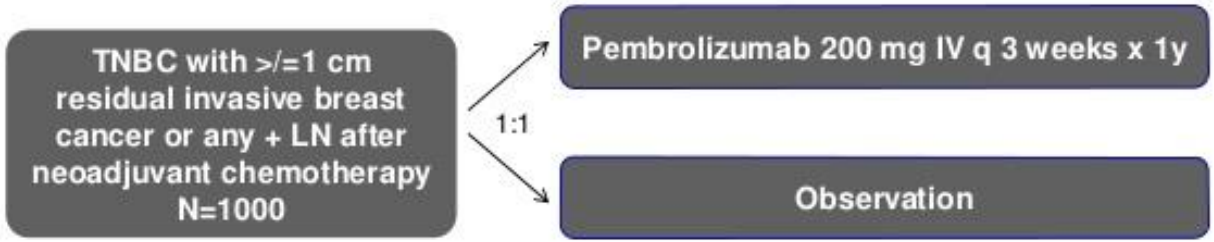
Stratification factors:

- 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

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

ISPY2: Toxicity

	Pembrolizumab (n=69) % (n)		Control (n=180) % (n)	
	All grades	Grade 3-5	All grades	Grade 3-5
Hypothyroidism	8.7 (6)*	1.4 (1)	0.6 (1)*	0 (0)
Hyperthyroidism	4.3 (3)*	0 (0)	0 (0)*	0 (0)
Adrenal Insufficiency^	8.7 (6)*	7.2 (5)*	0 (0)*	0 (0)
Hepatitis	2.9 (2)	2.9 (2)	0 (0)	0 (0)
Pneumonitis	2.9 (2)	0 (0)	1.1 (2)	0.6 (1)
Colitis	1.4 (1)	1.4 (1)	0.6 (1)	0.6 (1)
Pruritis	24.6 (17)*	0 (0)	11.1 (20)*	0.6 (1)
	53.6%(37)	**12.9% (9)**		

If chemotherapy still has a key role to play can we administer it more “precisely”

- Escalate cytotoxics for those who need it
- De-escalate cytotoxics for those who don’t
- Better scheduling and sequence
- Better combinations
- Better targets and/or delivery methods

Antibody Drug Conjugates In Development In TNBC

	Glembatumumab vedotin	Ladiratuzumab vedotin	Sacituzumab govitecan
Target	gpNMB (40%)	LIV-1 (71%)	Trop-2 (88%)
Cytotoxic	MMAE	MMAE	SN-38
Single Agent Activity	ORR = 28%	ORR=37%	ORR= 30%
Development Status	METRIC (1-3 lines prior therapy)		ASCENT (≥ 3 lines)

Yardley et al., J Clin Oncol, 2015; Ferero et al., SABCS 2016; Bardia, SABCS, 2017

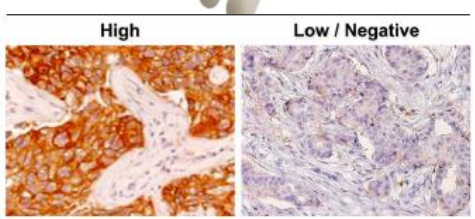
Phase II Trial Sacituzumab Govitecan

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

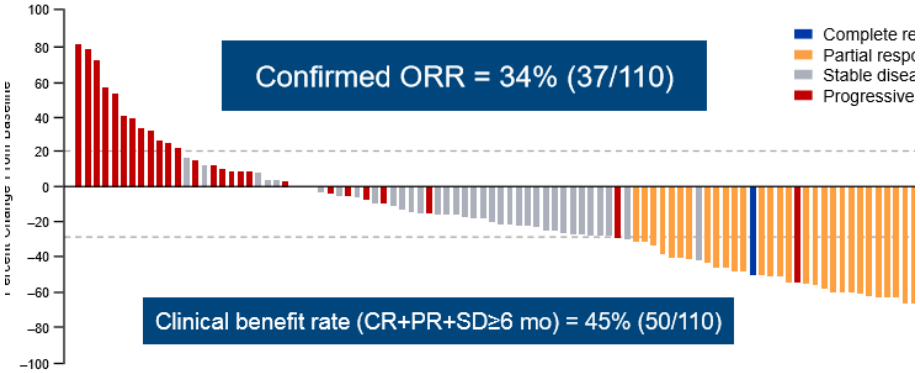
Linker for SN-38
- High drug-to-antibody ratio (7.6:1)
- pH-sensitive linker for rapid payload release at or inside the tumor



> 90% TNBCs express Trop-2

mTNBC 3/4/5th-line Phase II

Tumor Response to Treatment

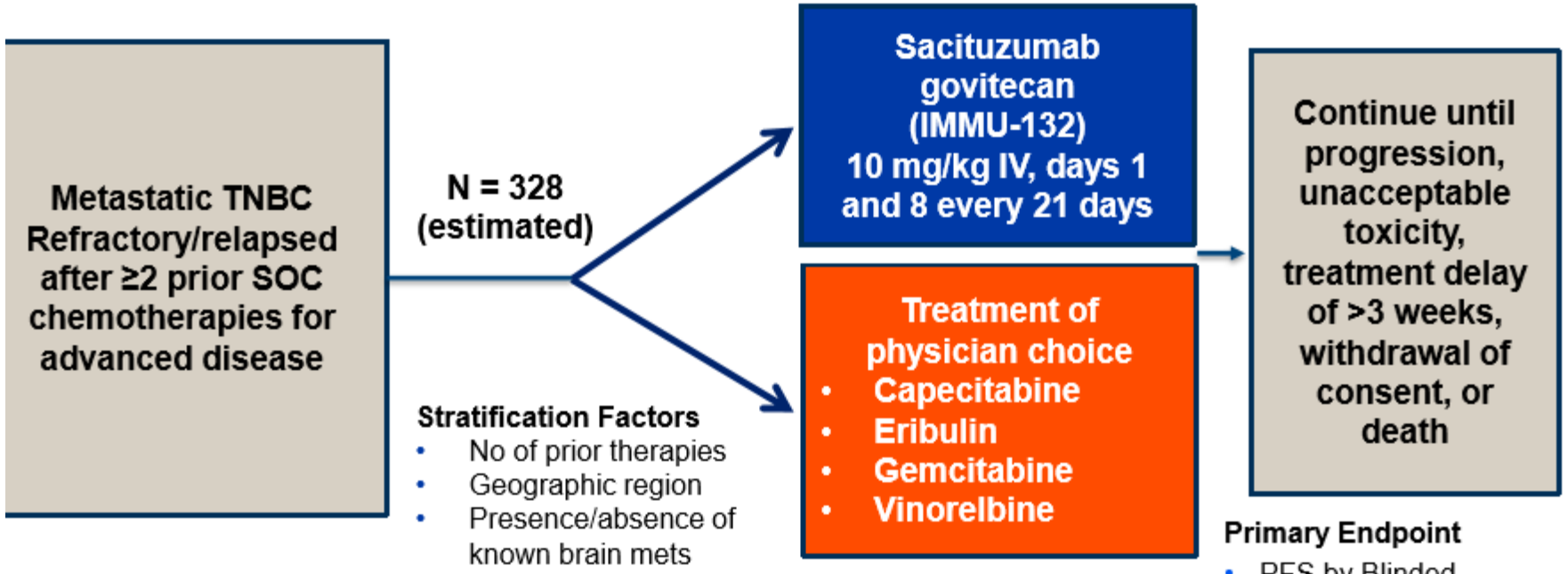


- 74% (75/102) of patients with at least one CT response assessmer reduction of target lesions (sum of diameters)
- 102 patients had ≥1 scheduled CT response assessment
- 8 patients withdrew prior to assessment (4 PD, 4 MRI brain mets)

Median DoR 7.6 mos
Med PFS 5.5 mos

Bardia A et al. SABCS 2017

ASCENT Phase III Study Overview



Primary Endpoint

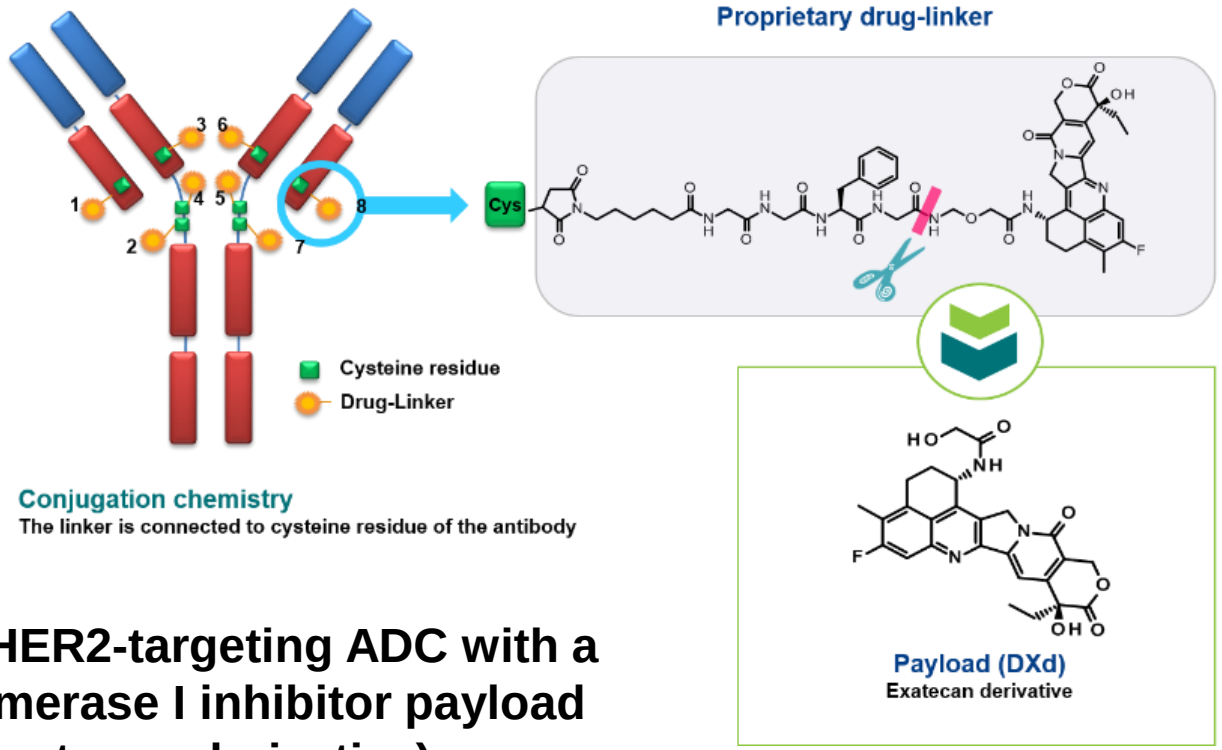
- PFS by Blinded Independent Central Read

Secondary Endpoint

- Overall Survival

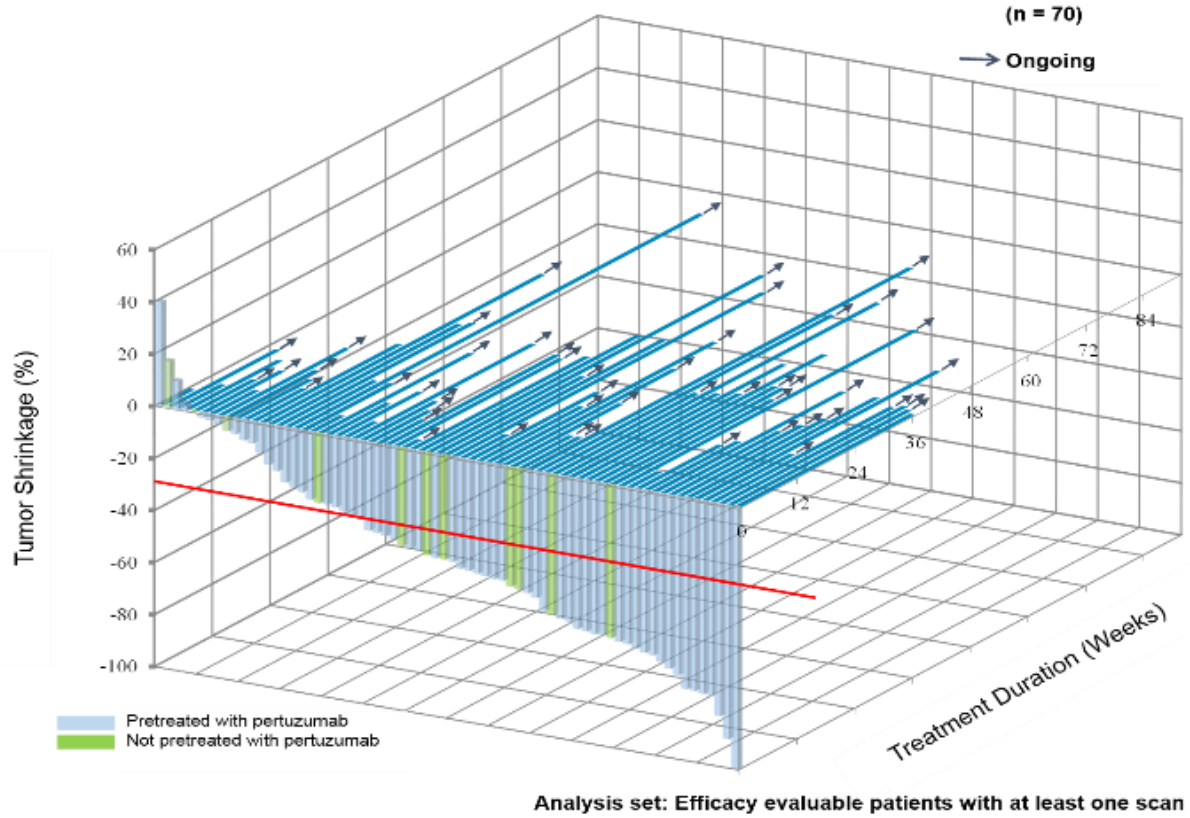
- Clinical trials number: NCT02574455
- Presented at: New Agents and Strategies; December 7, 2017; 5:00-7:00 PM, Hall 1 (abstract# 733)

Trastuzumab Deruxtecan



a novel HER2-targeting ADC with a topoisomerase I inhibitor payload (exatecan derivative),

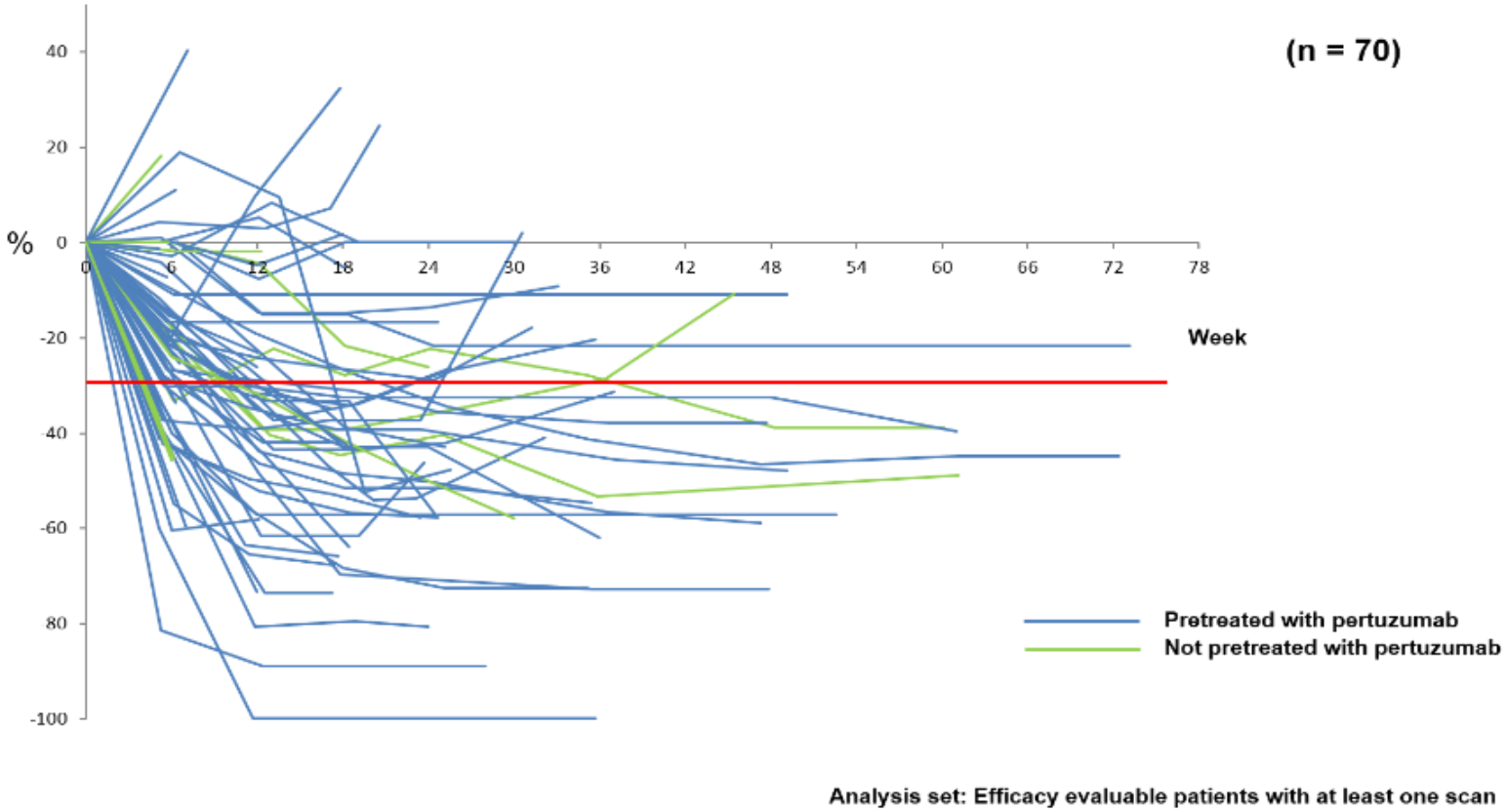
Phase 1 in HER2+ MBC: Response and Treatment Duration



HER2, human epidermal growth factor receptor 2.

Modi SABCS 2017

Tumor size: % Change from Baseline



Analysis set: Efficacy evaluable patients with at least one scan

Chemotherapy still has a key role to play and we strive to administer it more “precisely”

- Escalate cytotoxics for those who need it (ABC)
- De-escalate cytotoxics for those who don’t (PlanB)
- Better scheduling (dose density) and sequence (Oxford overview)
- Better combinations
  - Platinums in TNBC (forgo anthracyclines?)
  - No clear role for PARPi (BrighTNess)
  - Immune therapy in TNBC and ER+? (ISPY2)
- Better delivery methods
  - ADC

Thank You!