Triple negative breast cancer and novel agents
GASCO Review of SABCS 2017
January 6th 2018
Atlanta, GA

Ruth M. O'Regan, MD
Professor and Division Chief Hematology
and Medical Oncology,
Department of Medicine,
University of Wisconsin

Carbone Cancer Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

THE UNIVERSITY of WISCONSIN
MADISON

Topics to cover

- Adjuvant therapy:
  - Increasing chemotherapy dose intensity (#101)
  - Duration of adjuvant bisphosphonates (#306)
- Neo-adjuvant therapy:
  - Prognosis of PCR (#308, 305)
- Novel agents and metastatic disease
  - BRCA-mutated, HER2-negative (#607)
  - TNBC specific: Sacituzumab Govitecan (#107)
  - HER2-negative (#306)
  - HR-positive (#207, 407)

SAN ANTONIO BREAST CANCER SYMPOSIUM®

Increasing the dose intensity of adjuvant chemotherapy : an EBCTCG meta-analysis

Richard Gray, Rosie Bradley, Jeremy Braybrooke, Christina Davies, Hongchao Pan, Richard Peto, Judith Bliss, David Cameron, John Mackey, Lucia Del Mastro, Sandra Swain, Michael Untch, Jonas Bergh, Kathleen Pritchard, Larry Norton, for the

Early Breast Cancer Trialists' Collaborative Group

All authors declare no relevant conflict of interest

SAN ANTONIO BREAST CANCER SYMPOSIUM®

Background

- Adjuvant chemotherapy with anthracycline and taxane-based combinations for early breast cancer reduces the risk of breast cancer mortality by about one third*
- Cytokinetic modelling suggests that increasing the dose intensity of cytotoxic chemotherapy may enhance efficacy

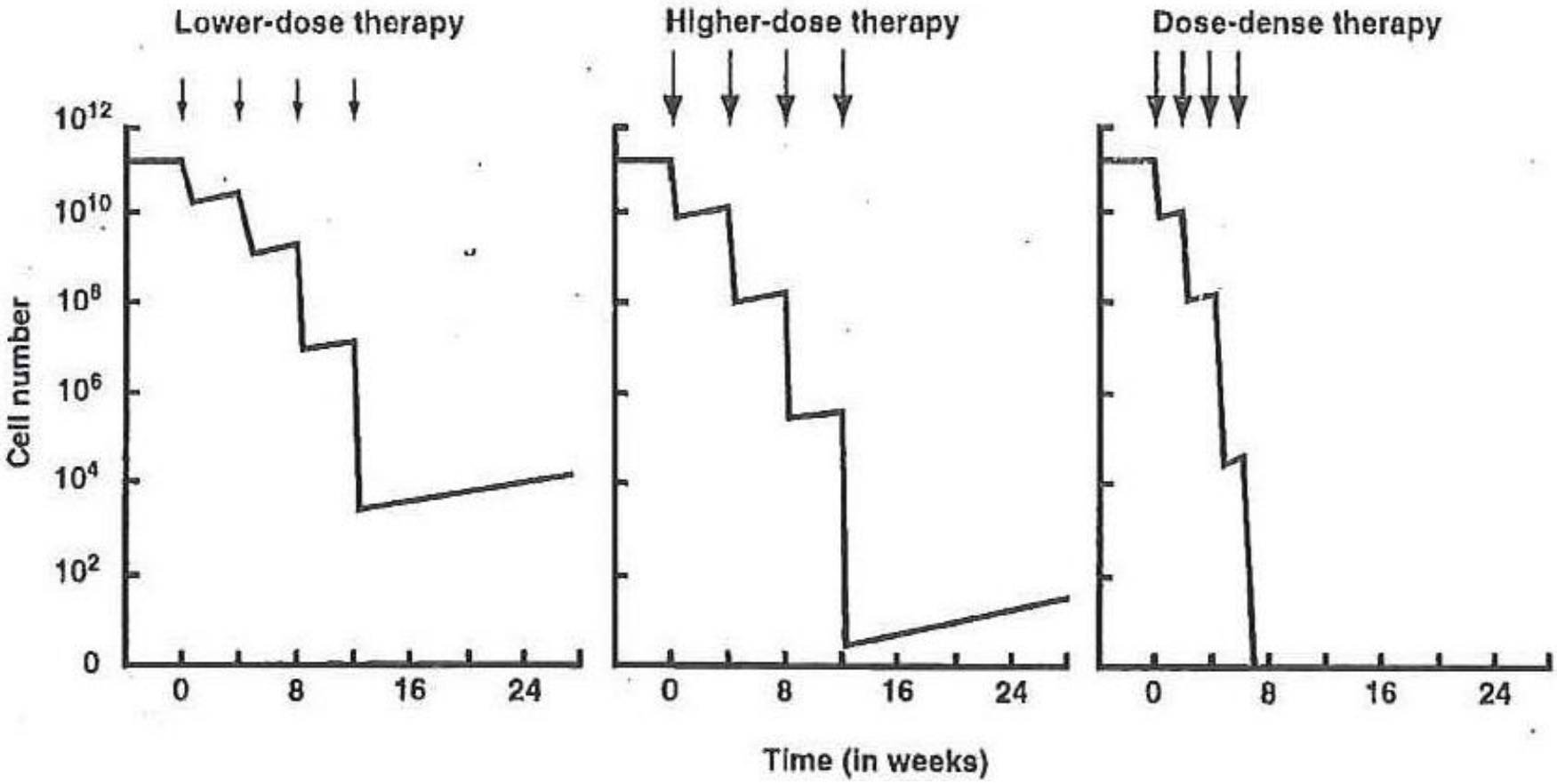
*EBCTCG, Lancet 2012

Three ways to increase dose intensity (ie, the drug dose in mg/m^2 per week)*

1. Use higher doses of drugs in each cycle
2. Reduce the interval between treatment cycles
3. Give drugs sequentially rather than concurrently

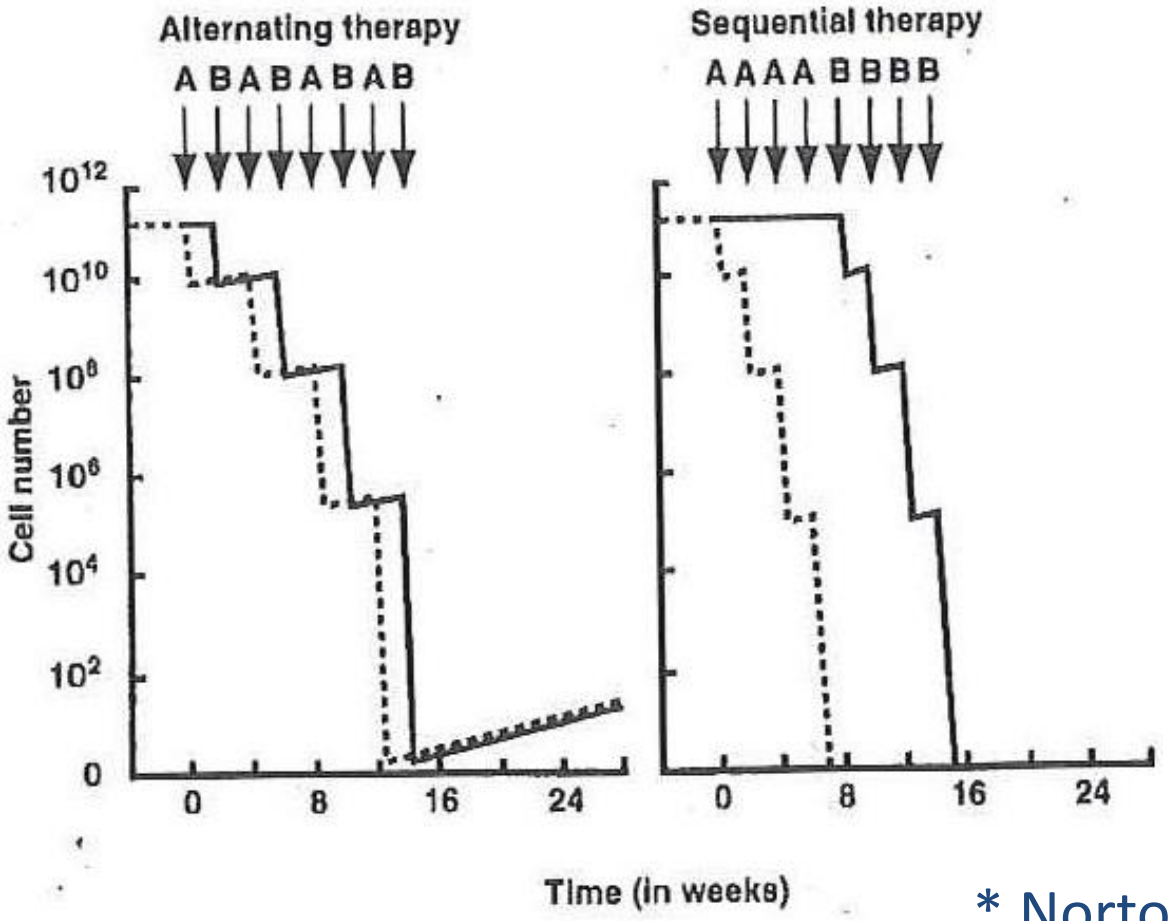
* Norton L. Sem Oncol 1997

Models of tumour cytoreduction and regrowth following conventional, dose-escalated and dose-dense chemotherapy*



* Norton L. Sem Oncol 1997

Models of tumour cytoreduction and regrowth following alternating and sequential dose-dense chemotherapy*



Broken lines indicate cells sensitive to treatment A; solid lines cells sensitive to treatment B

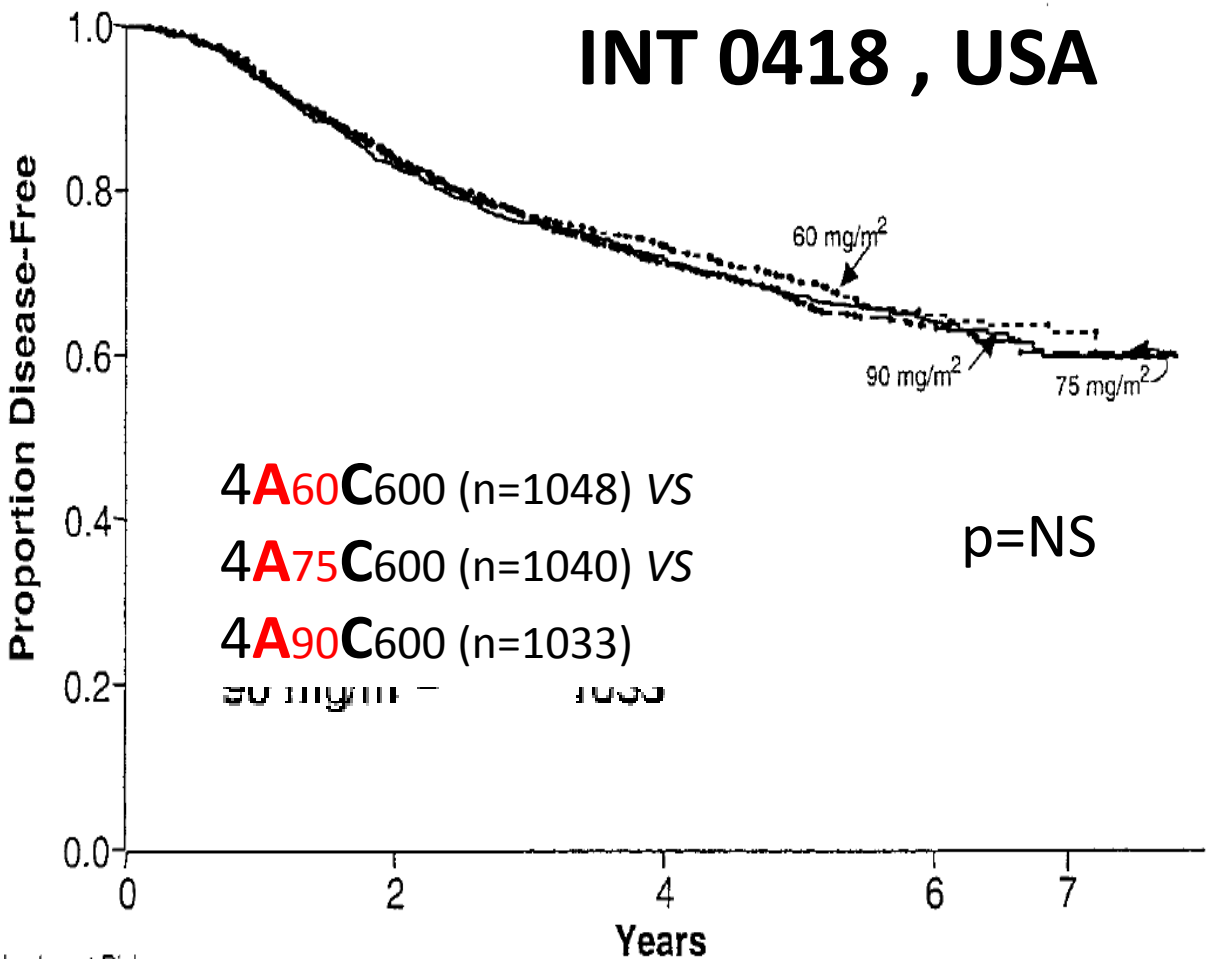
* Norton L. Sem Oncol 1997

Three ways to increase dose intensity (ie, the drug dose in mg/m^2 per week)*

1. **Use higher doses of drugs in each cycle**
2. Reduce the interval between treatment cycles
3. Give drugs sequentially rather than concurrently

* Norton L. Sem Oncol 1997

Anthracyclines : no apparent benefit from escalation beyond standard dose



Henderson IC, et al. *J Clin Oncol* 2003; 21:976-983

Three ways to increase dose intensity (ie, the drug dose in mg/m^2 per week)*

1. Use higher doses of drugs in each cycle
2. **Reduce the interval between treatment cycles ("dose-dense" chemotherapy)**
3. **Give drugs sequentially rather than concurrently**

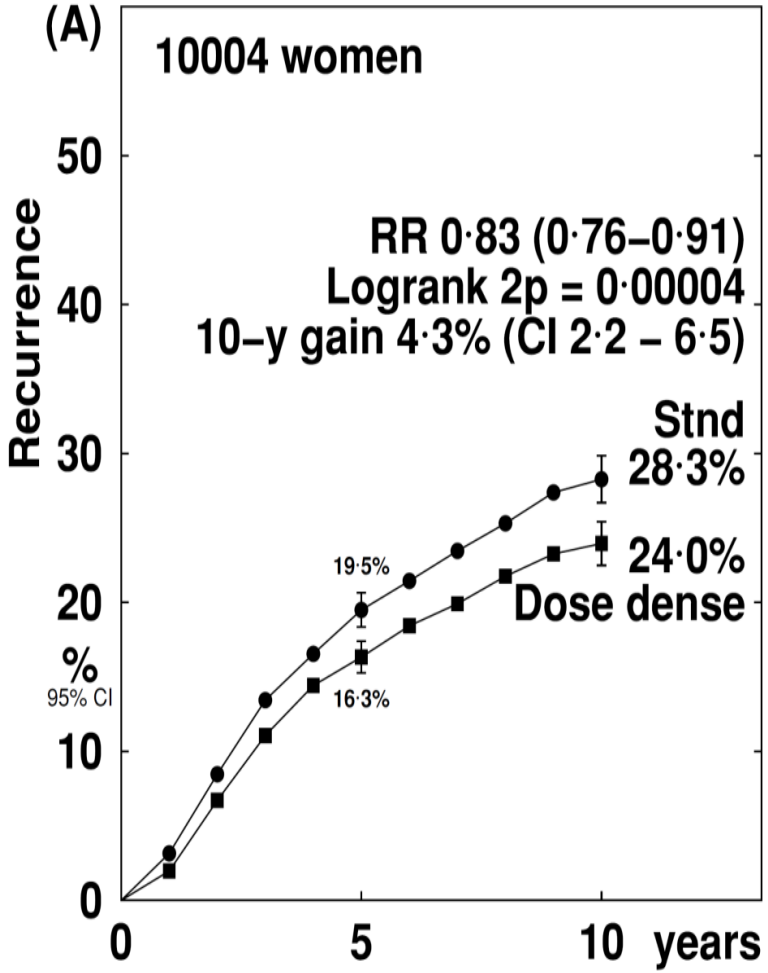
SAN ANTONIO BREAST CANCER SYMPOSIUM®

Dose intensity trials

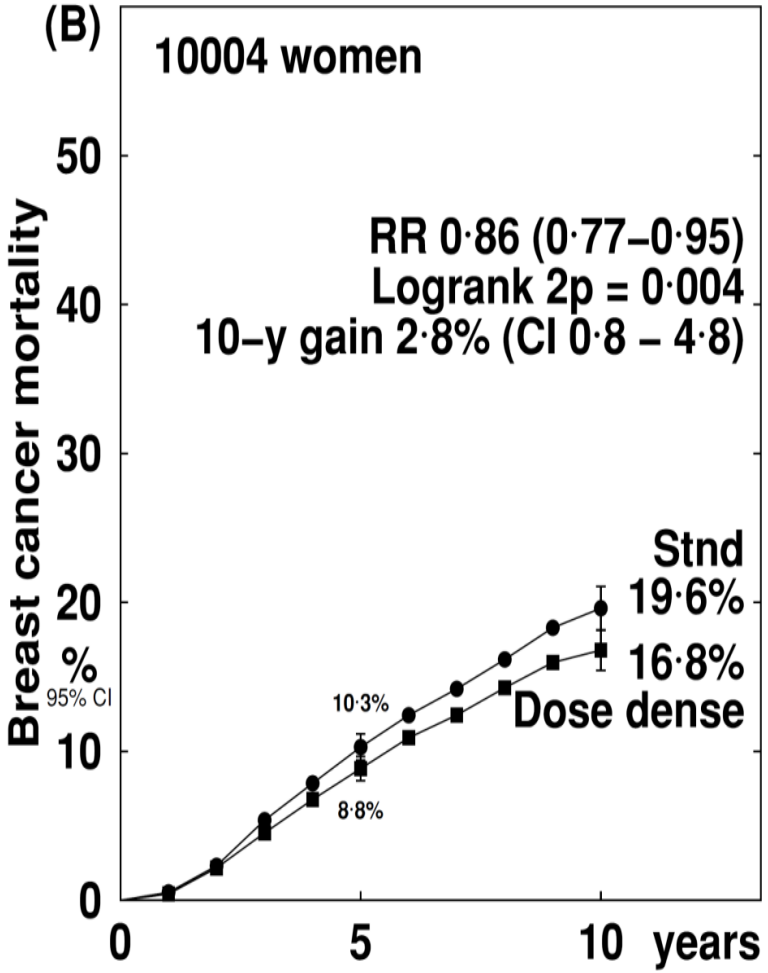
1. **Dose-dense (2-weekly) vs Standard (3-weekly)**
   a. **Same chemotherapy drugs and doses: 7 trials, n=10,004**
   b. **Some differences in chemotherapy: 5 trials, n=5,508**
2. **Sequential (3-weekly) vs Concurrent (3-weekly)**
   a. **Same drugs in each group: 5 trials, n=9,644**
   b. **Some differences in drugs used: 1 trial, n=1,384**
3. **Sequential (2-weekly) vs Concurrent (3-weekly)**
   a. **Some differences in drugs used: 6 trials, n=6,532**

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

Any Recurrence

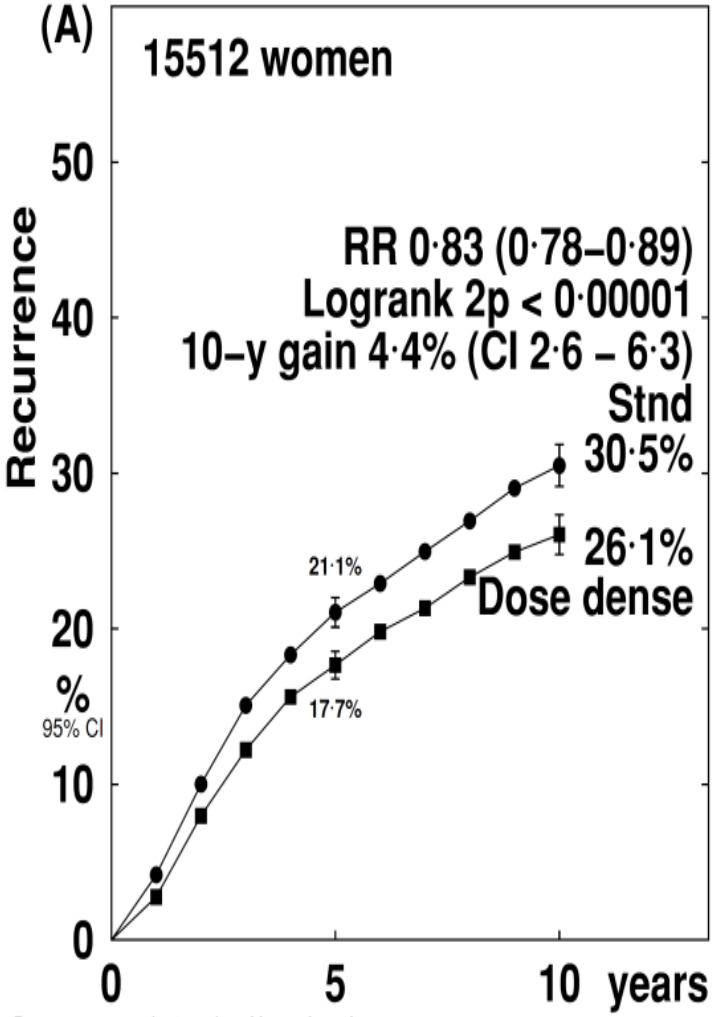


Breast Cancer Mortality

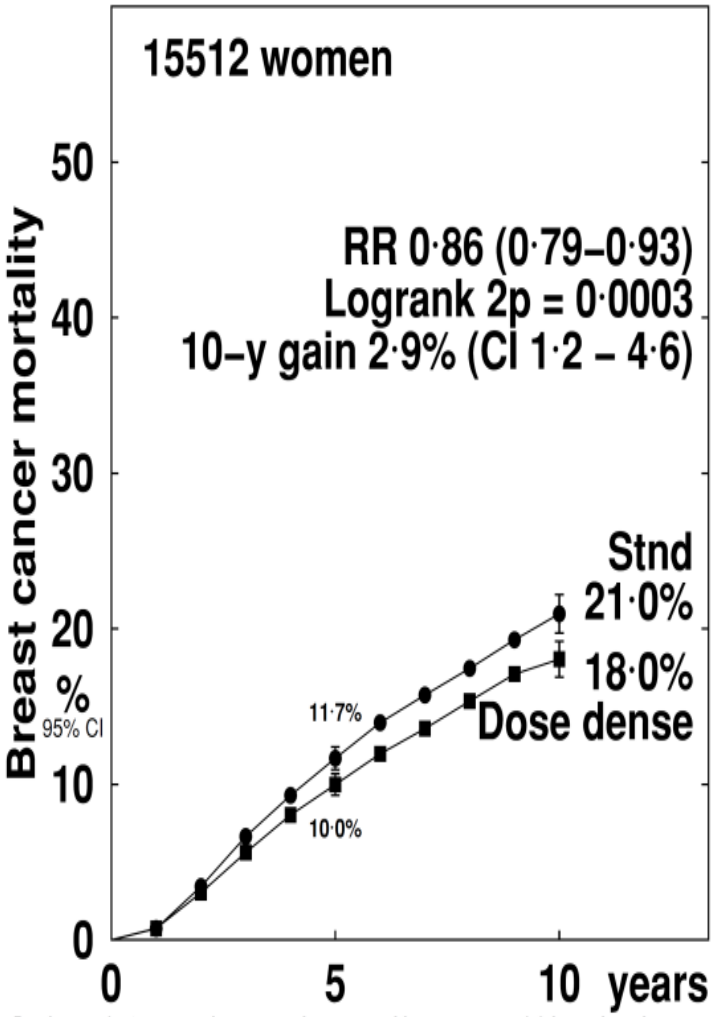


2-weekly vs 3-weekly chemotherapy: all trials
(including the 5 trials where chemotherapy differed between arms)

Any Recurrence

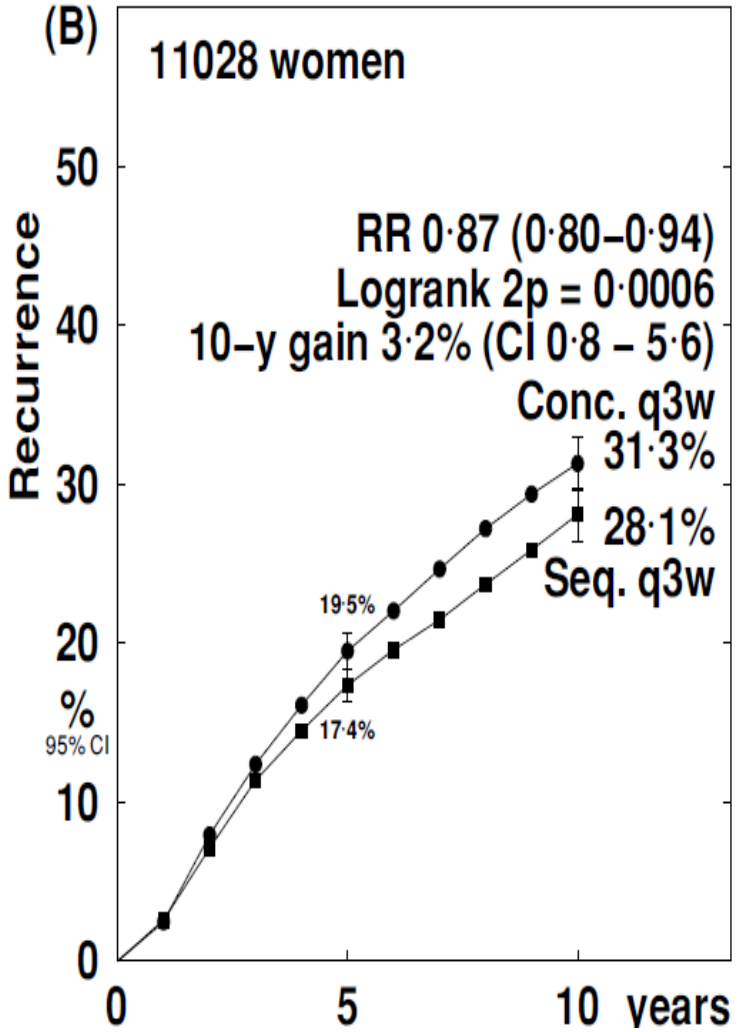


Breast Cancer Mortality

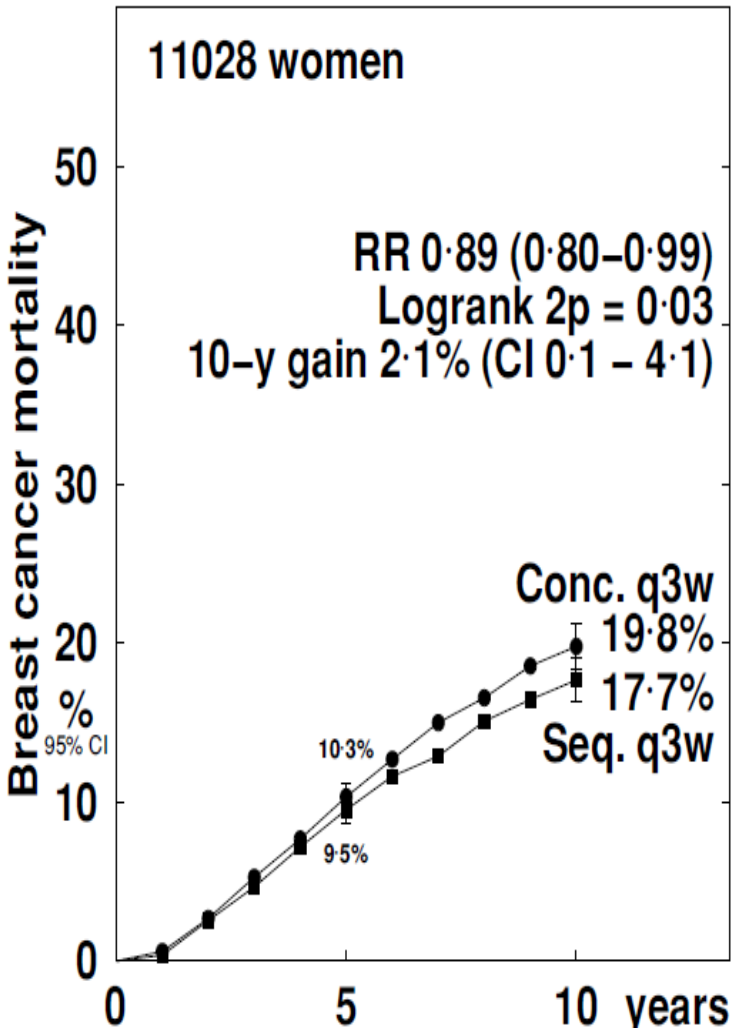


Sequential (3-weekly) vs Concurrent (3-weekly) chemotherapy

Any Recurrence

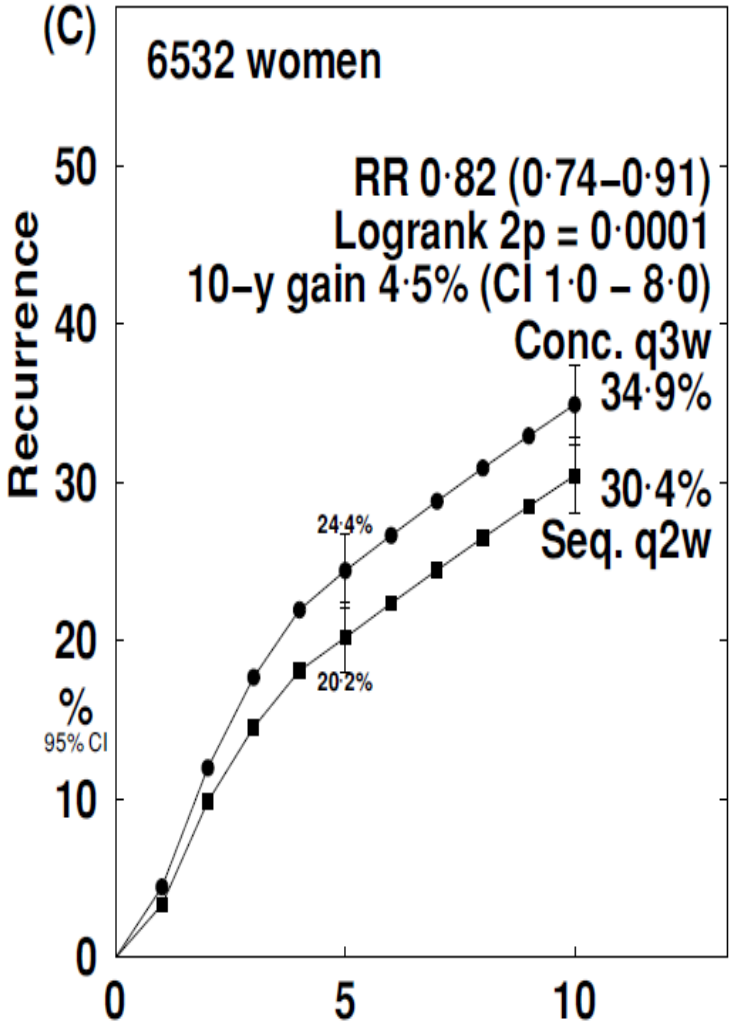


Breast Cancer Mortality

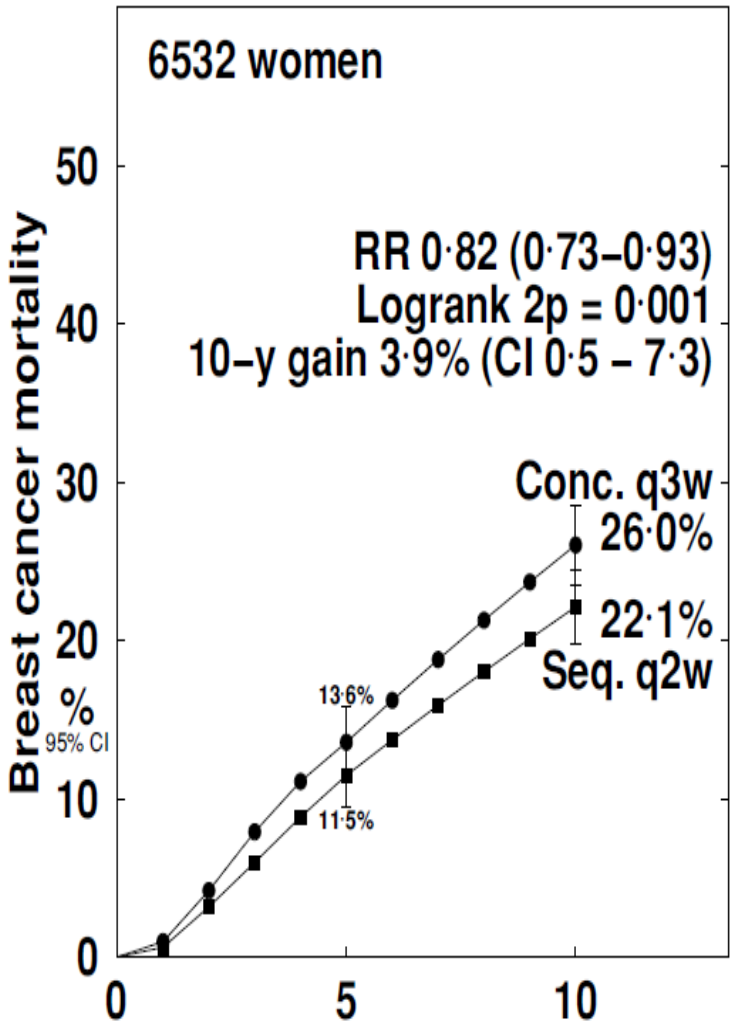


Sequential (2-weekly) vs Concurrent (3-weekly) chemotherapy

Any Recurrence

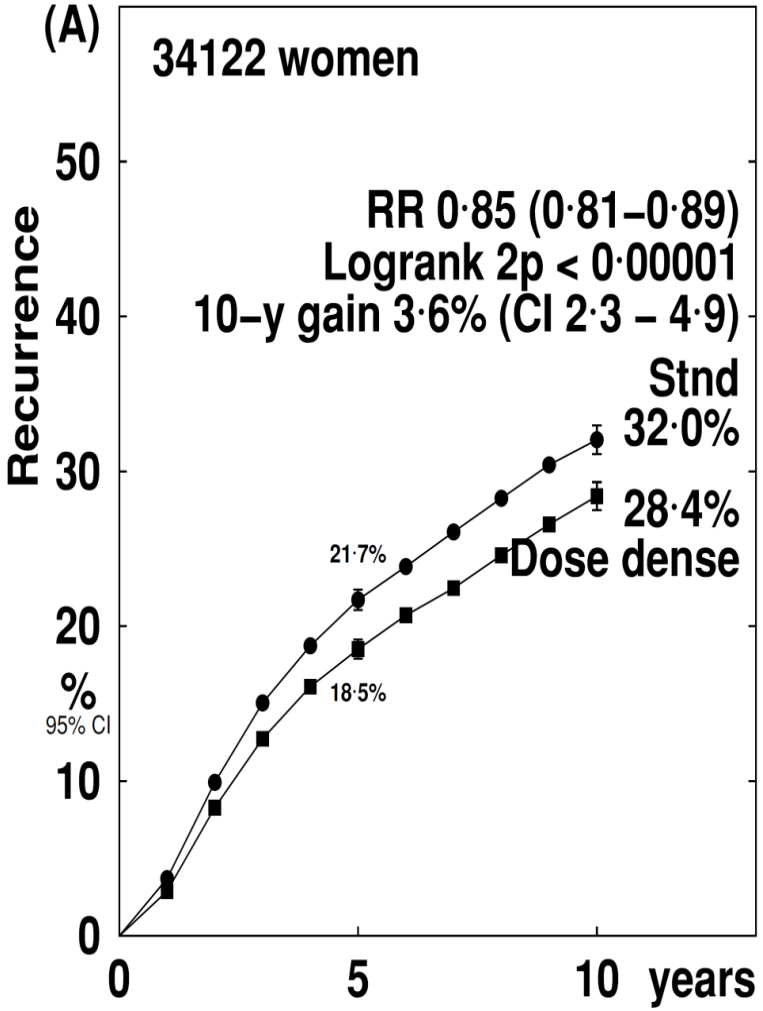


Breast Cancer Mortality

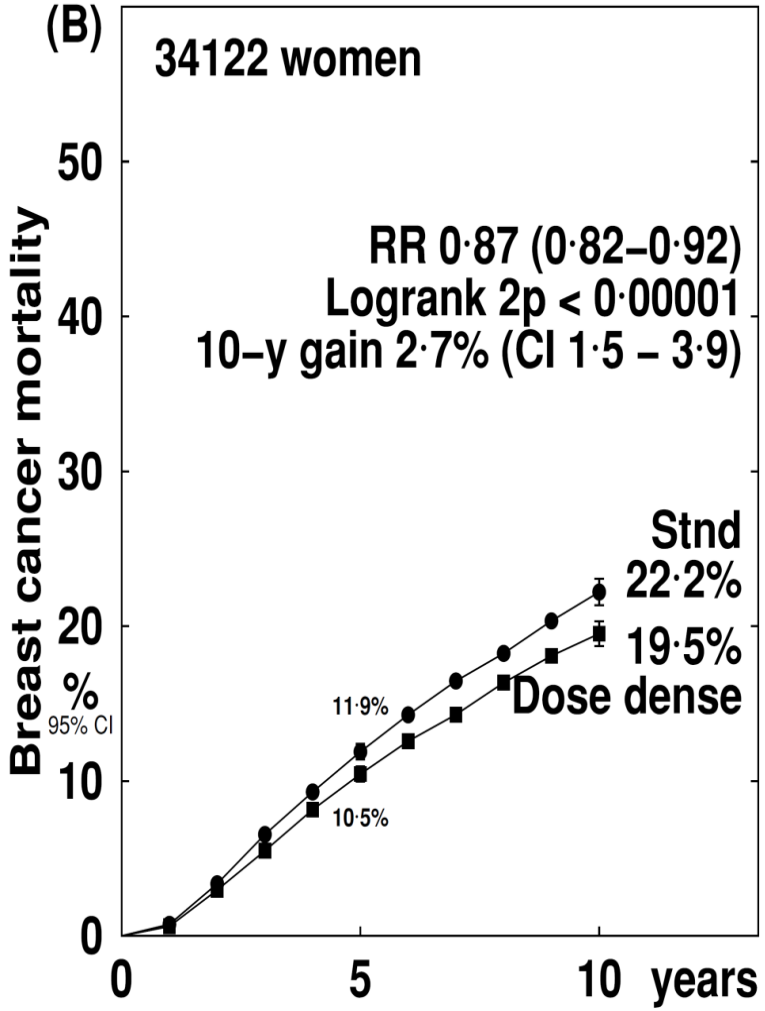


Pooled analysis of all 25 dose-dense and sequential trials

Recurrence

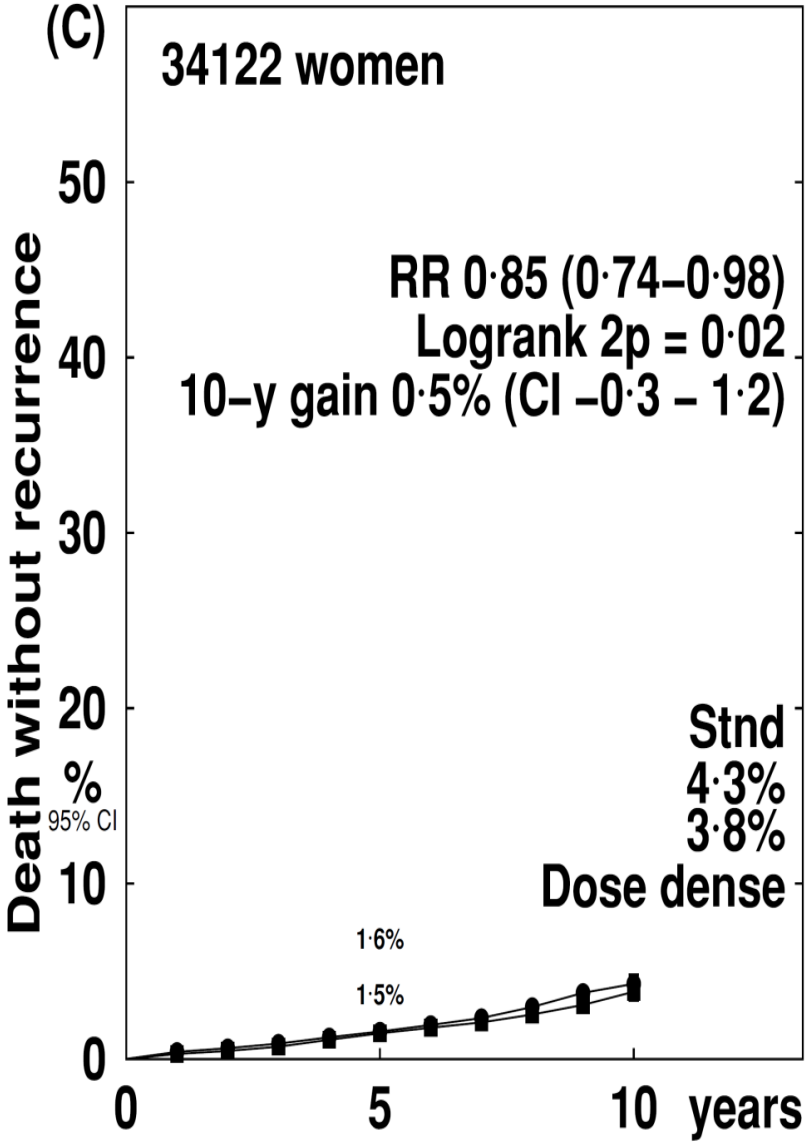


Breast Cancer Mortality

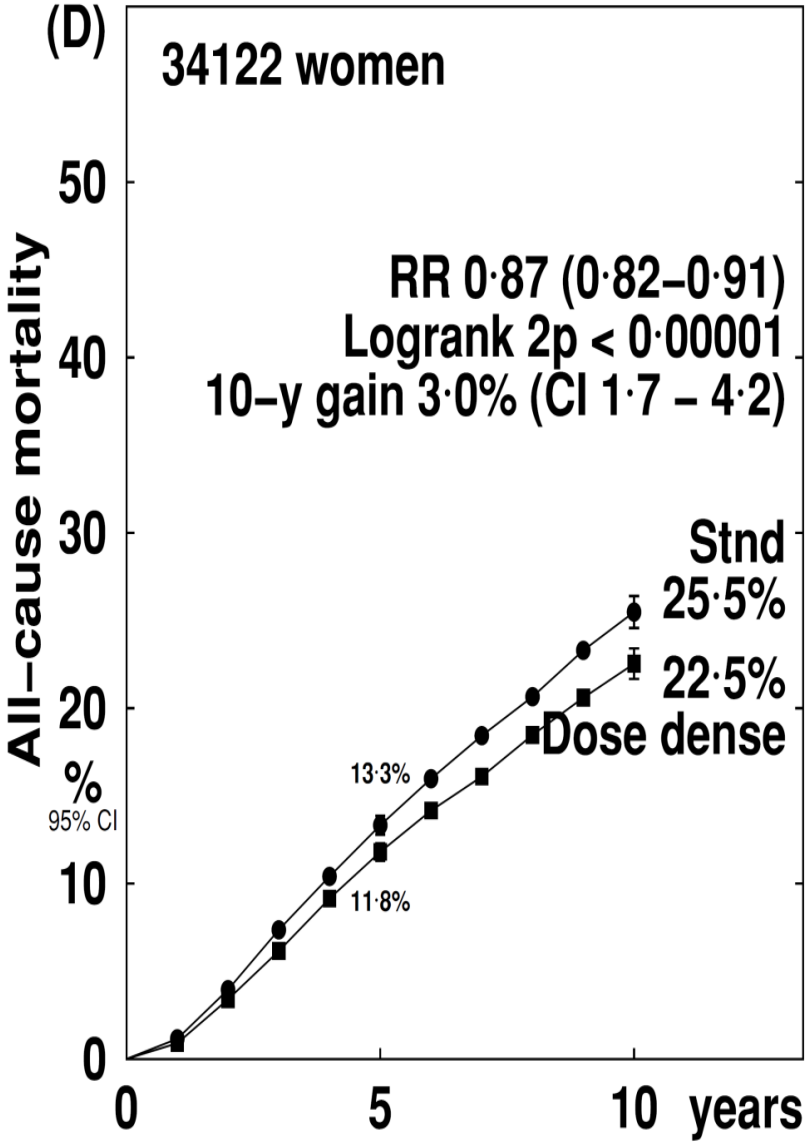


Pooled Analysis

Death without recurrence

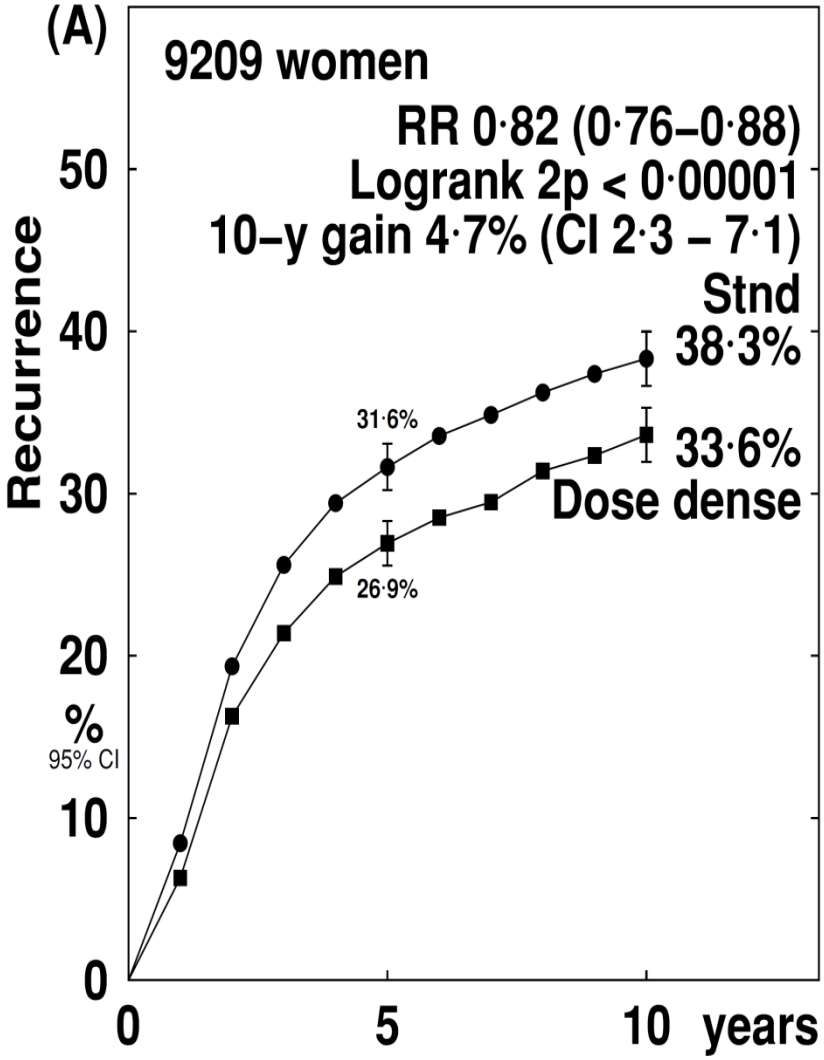


All cause mortality

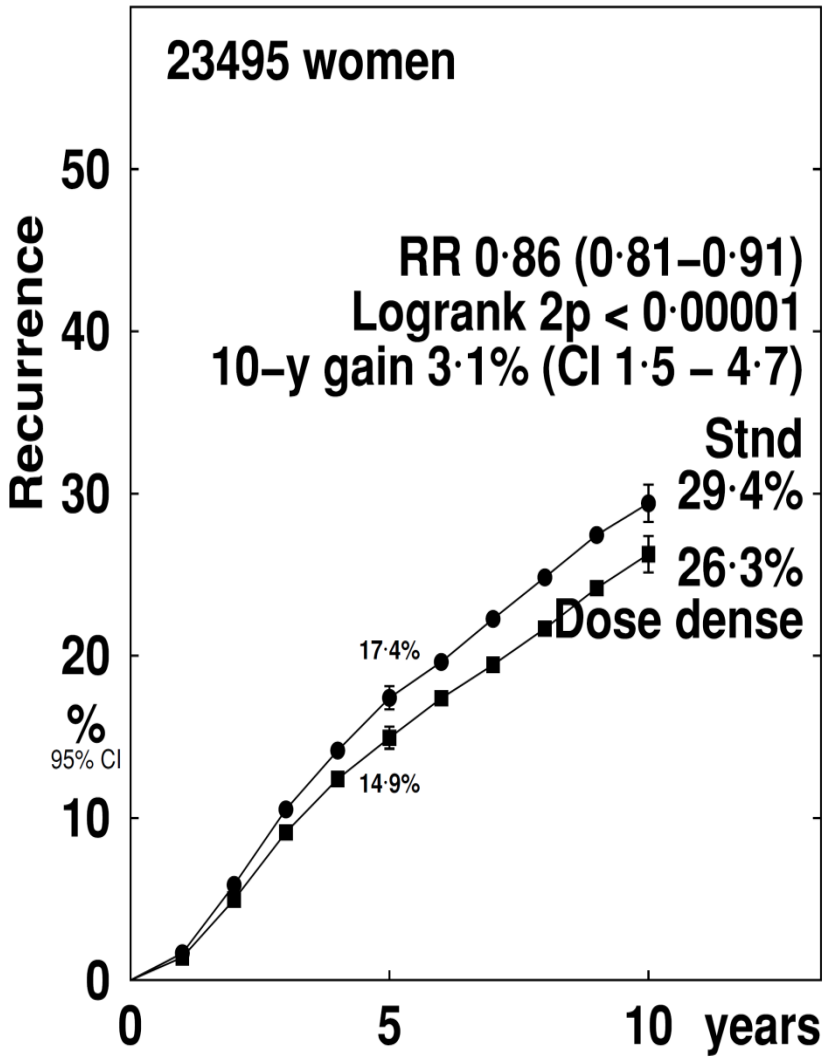


Pooled Analysis: recurrence by ER status

ER- Negative



ER - Positive



SAN ANTONIO BREAST CANCER SYMPOSIUM®

Conclusions

- Shortening the interval between cycles and sequential administration of anthracycline and taxane chemotherapy reduces recurrence and death from breast cancer
- Reductions in recurrence of about 15% were similar in ER-positive and ER-negative disease and did not differ significantly by any other tumour or patient characteristic
- No increase seen in death without recurrence (overall or during chemotherapy)

Extended adjuvant bisphosphonate treatment over five years in early breast cancer does not improve disease-free and overall survival compared to two years of treatment: Phase III data from the SUCCESS A study

Wolfgang Janni, Thomas WP Friedl, Tanja Fehm, Volkmar Mueller, Werner Lichtenegger, Jens Blohmer, Ralf Lorenz, Helmut Forstbauer, Emanuel Bauer, Visnja Fink, Inga Bekes, Jens Huober, Julia Jückstock, Andreas Schneeweiss, Hans Tesch, Sven Mahner, Sara Y Brucker, Georg Heinrich, Lothar Häberle, Peter A. Fasching, Matthias W Beckmann, Robert Coleman, Brigitte Rack

SUCCESS
BIG-Member

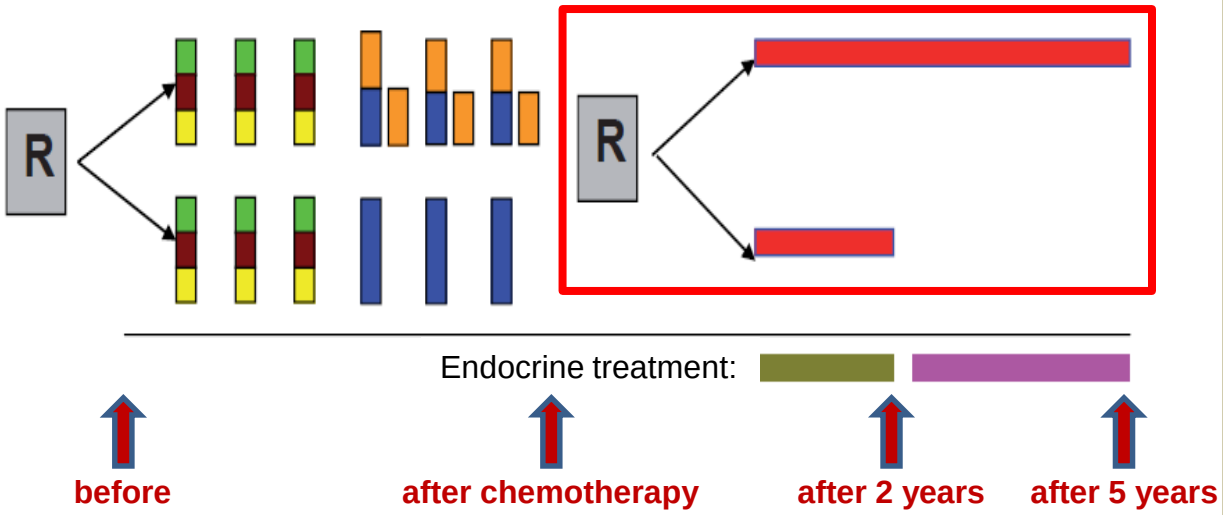
Background: Bisphosphonates

- Bisphosphonates prevent the loss of bone density and have been shown to reduce skeletal-related events in cancer patients
- Adjuvant bisphosphonate treatment in early breast cancer patients leads to improved breast cancer survival and reduced rate of breast cancer recurrences in the bone, especially in postmenopausal patients[1]
- Based on the AGO guidelines, adjuvant bisphosphonates should be offered to postmenopausal women as part of their adjuvant systemic treatment
- However, optimal treatment duration is unclear

[1] *Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Lancet Oncol. 2015; 386:1353-61.*

SUCCESS A – study design

(open-label, multicenter, 2x2 factorial design, randomized controlled Phase III study)



Blood sampling for CTC assessment

5- FU 500 mg/m², Epirubicin 100 mg/m², Cyclophosphamide 500 mg/m² q3w

Docetaxel 100 mg/m² q3w

Docetaxel 75 mg/m², Gemcitabine 1.000 mg/m² d1,8 q3w

Tamoxifen 20 mg qid p.o. x 2a
(plus Goserelin 3.6 mg depot

Anastrozole 1 mg qid p.o. x 3a in postmenopausal pts
(Tam in premenopausal pts)

First randomization:
3 cycles FEC100 followed by 3 cycles docetaxel vs. 3 cycles FEC100 followed by 3 cycles docetaxel plus gemcitabine

Second randomization:
5 years vs. 2 years of zoledronate
(4 mg i.v. every 3 months for 2 years, followed by 4 mg i.v. every 6 months for 3 years vs. 4 mg i.v. every 3 months for 2 years)

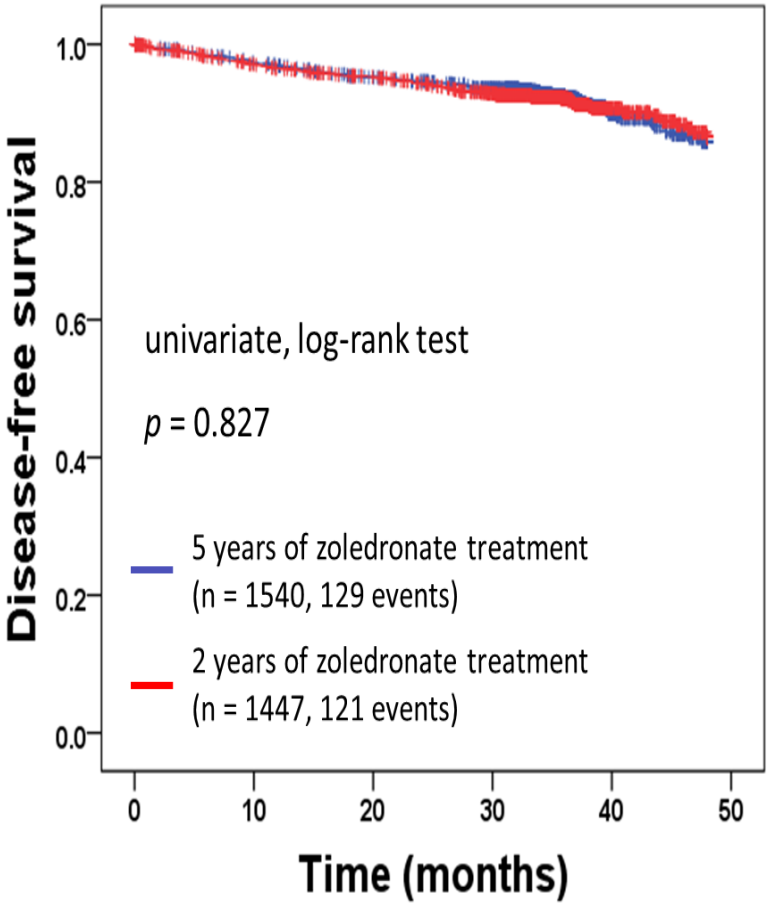
Patient characteristics (n = 2987)

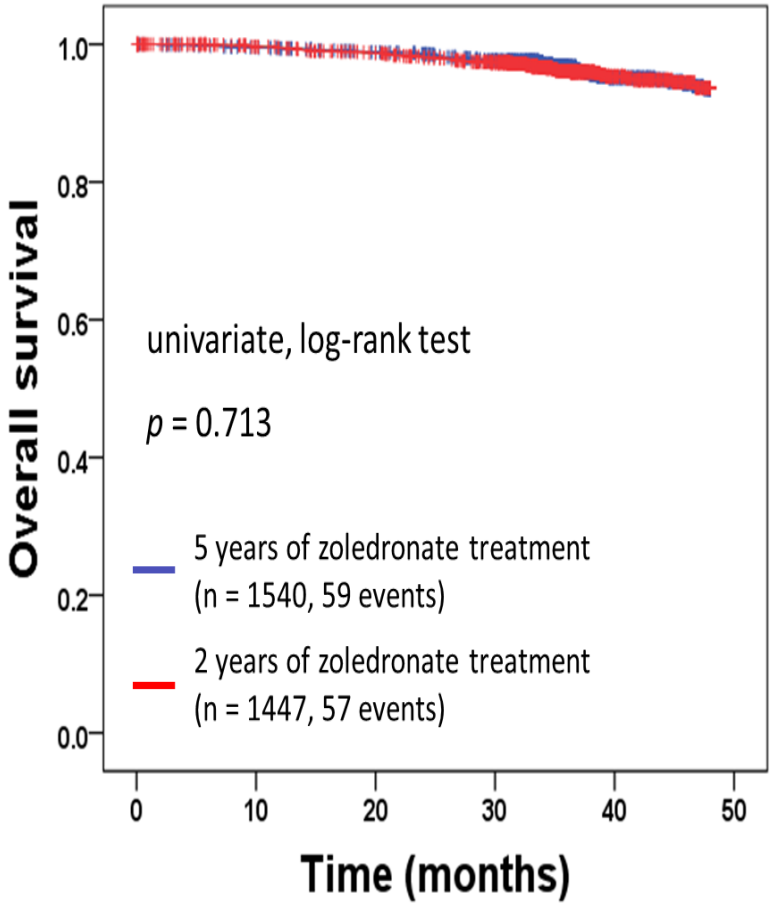
Patient and tumor characteristics*		5 years of zoledronate		2 years of zoledronate	
		n	%	n	%
Tumor size	*pT1/pT2*	1451	94.2	1351	93.4
	pT3/pT4	86	5.6	95	6.6
Nodal stage	*pN0*	516	33.5	520	35.9
	pN+	1018	66.1	924	63.9
Histological grading	*G1*	82	5.3	68	4.7
	G2	752	48.8	707	48.9
	G3	705	45.8	672	46.4
Histological type	*ductal*	1280	83.1	1181	81.6
	other	258	16.8	266	18.4
Hormone receptor status	*negative*	406	26.4	422	29.2
	positive	1132	73.5	1024	70.8
HER2 status	*negative*	1151	74.7	1083	74.8
	positive	357	23.2	341	23.6
Menopausal status	*premenopausal*	649	42.1	614	42.4
	postmenopausal	891	57.9	833	57.6
Type of surgery	*breast conserving*	1090	70.8	1054	72.8
	mastectomy	449	29.2	393	27.2
Adjuvant chemotherapy	*FEC-DocG*	744	48.3	732	50.6
	FEC-Doc	796	51.7	715	49.4

Patients in the two randomization arms well balanced with regard to clinicopathological characteristics (all $p > 0.05$)

* missing data in some categories

Adapted disease-free survival (DFS) and overall survival (OS) by zoledronate treatment arm

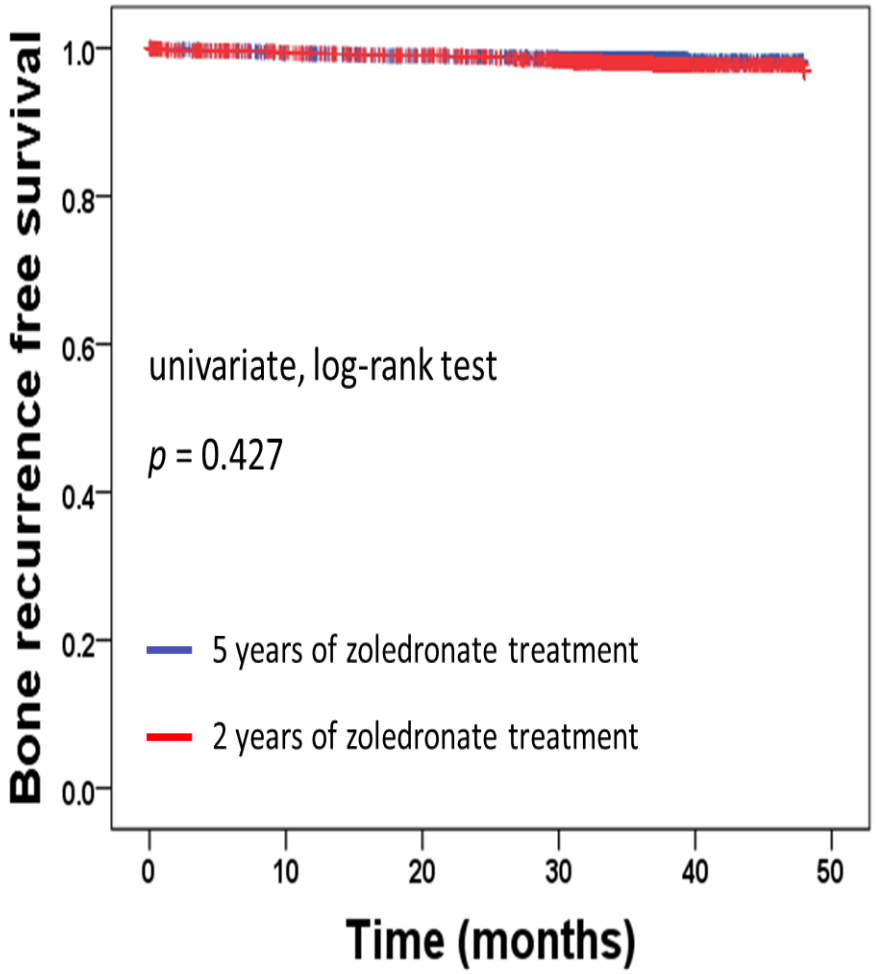




Bone recurrences by zoledronate treatment arm
(as of 2 years after the start of zoledronate treatment)

Bone recurrences as first distant recurrence*

- 5 years of zoledronate: 25 events
- 2 years of zoledronate: 28 events

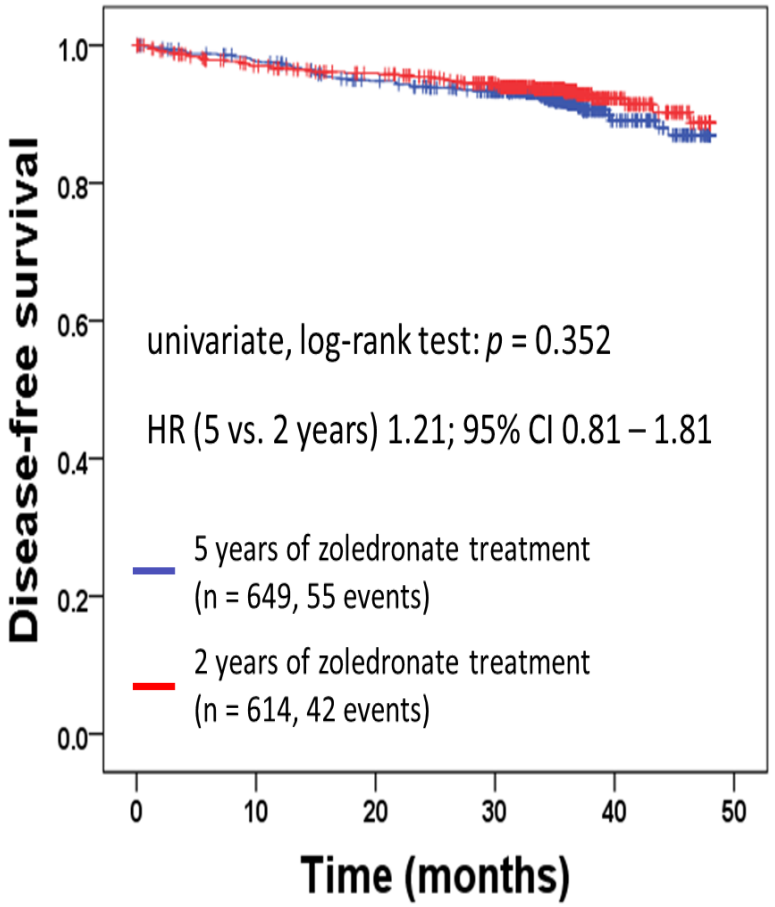


* with or without concurrent other recurrence

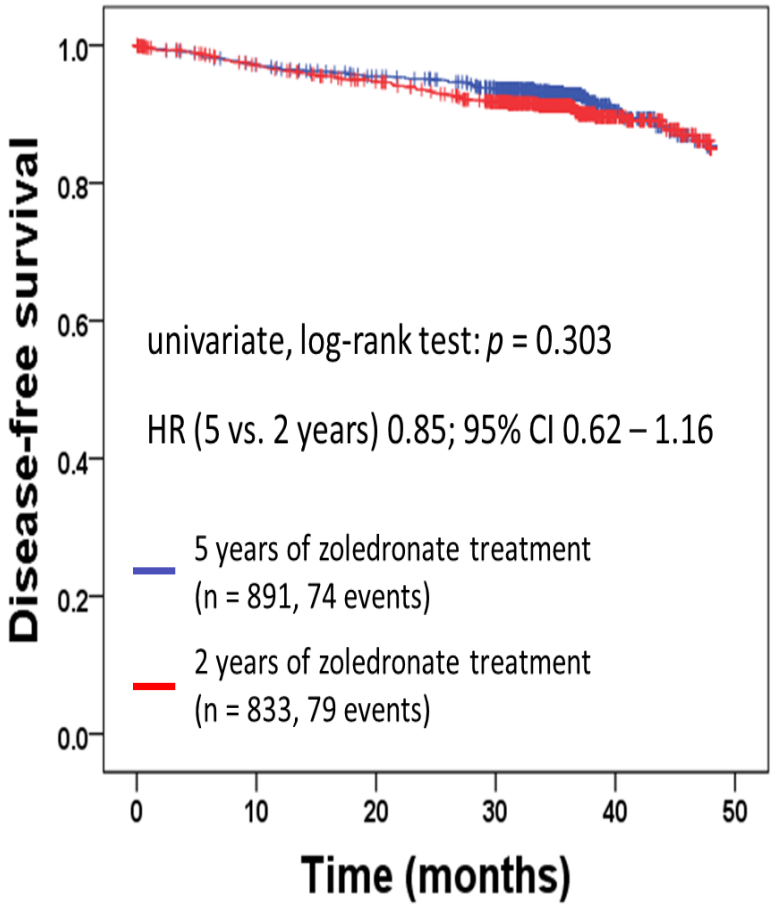
Subgroups – adapted DFS by menopausal status

SUCCESS
BIG-Member

premenopausal



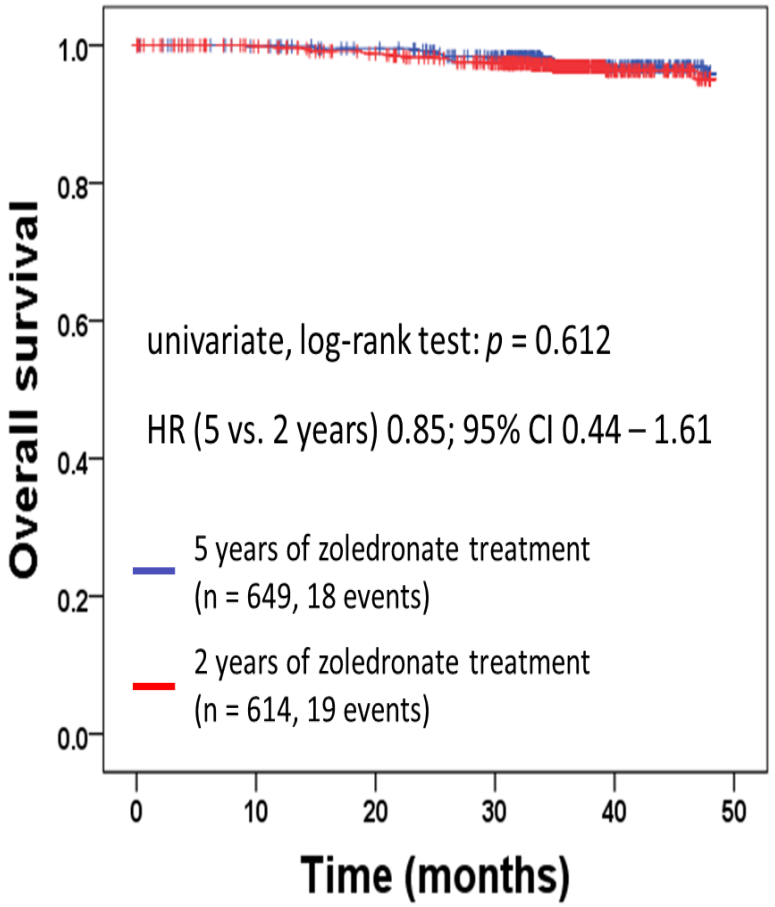
postmenopausal



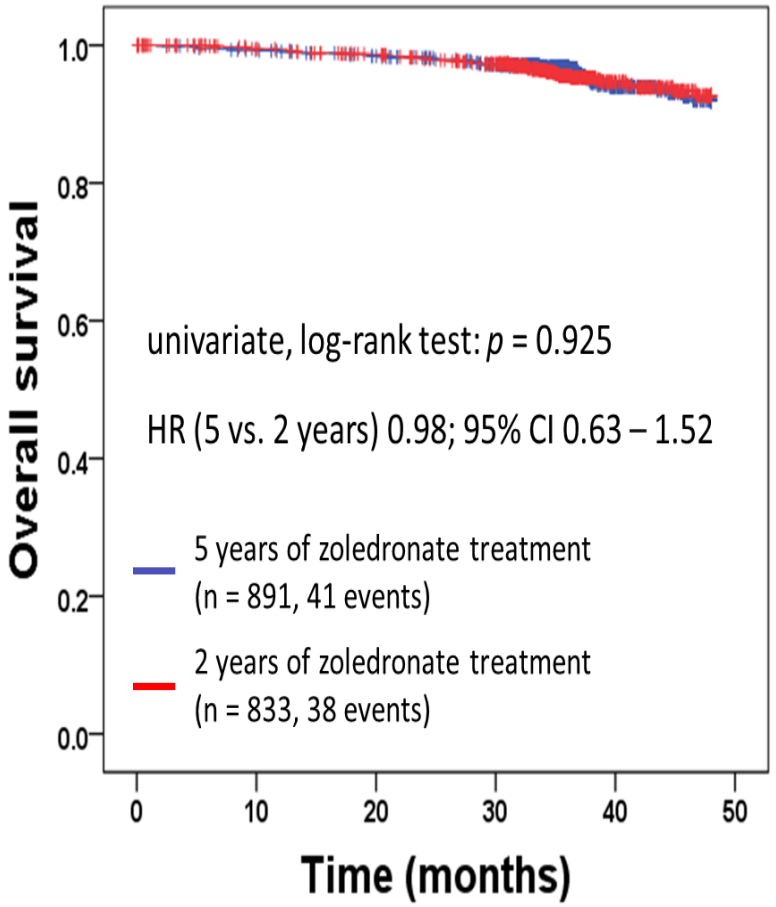
Subgroups – adapted OS by menopausal status

SUCCESS
BIG-Member

premenopausal



postmenopausal

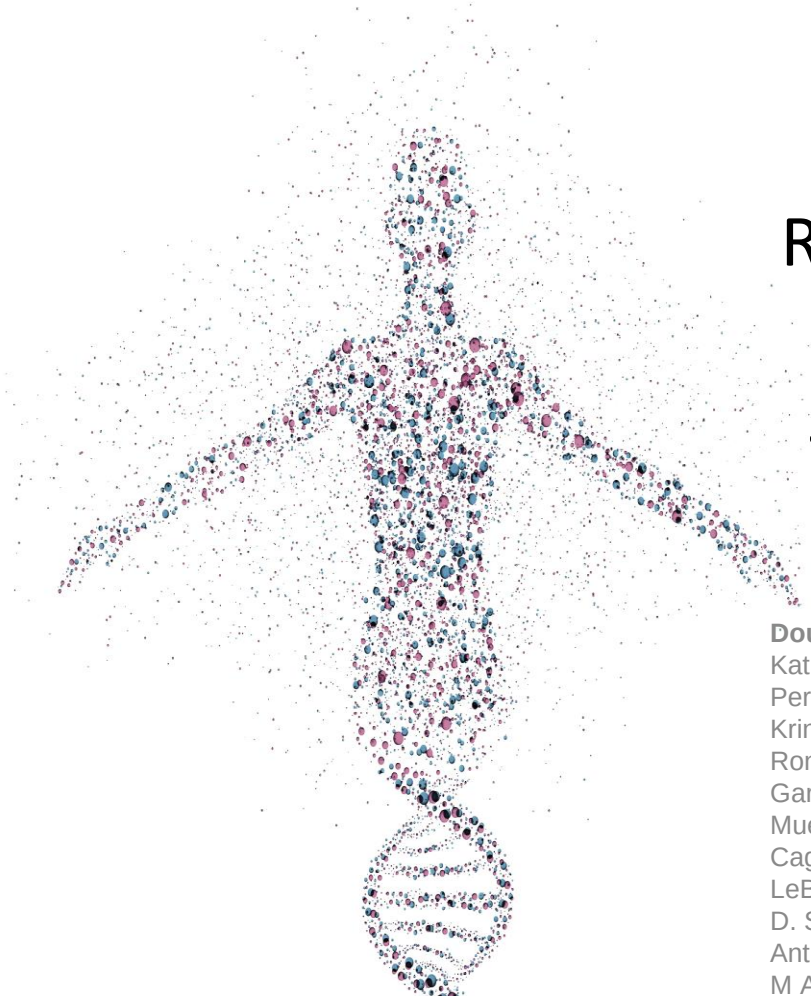


Conclusion

- At this early time point, our study showed no difference in DFS or OS between 5-years and 2-years of adjuvant zoledronate treatment following adjuvant chemotherapy in high-risk early breast cancer patients, irrespectively of menopausal status

- 5 years of adjuvant zoledronate treatment should not be considered currently in these patients in the absence of decreased bone density

San Antonio Breast Cancer Symposium, December 5 -9, 2017

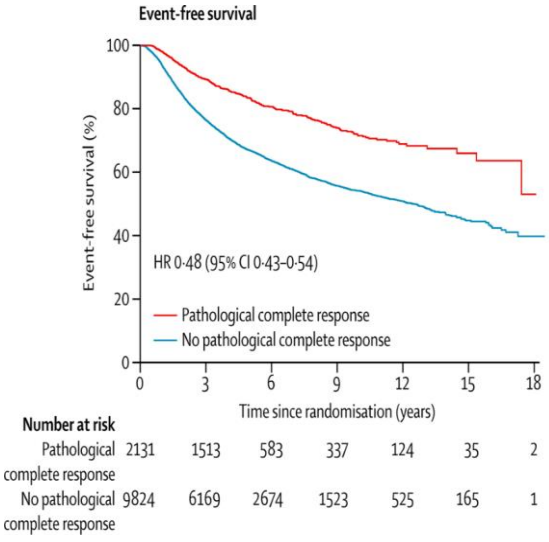


Pathological Complete Response Predicts Event-Free and Distant Disease Free Survival in the I-SPY 2 TRIAL

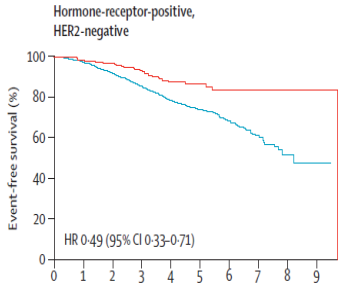
Doug Yee, Angela DeMichele, Claudine Isaacs, Fraser Symmans, Christina Yau, Kathy S Albain, Nola M Hylton, Andres Forero-Torres, Laura J van't Veer, Jane Perlmutter, Hope S Rugo, Michele Melisko, Yunn-Yi Chen, Ron Balassanian, Gregor Krings, Brian Datnow, Farnaz Hasteh, Anne Tipps, Noel Weidner, Hong (Amy) Zhang, Ronald Tickman, Sean Thornton, Jon Ritter, Khalid Amin, Molly Klein, Beiyun Chen, Gary Keeney, Tolgay Ocal, Mike Feldman, Nancy Klipfel, Husain Sattar, Jeffery Mueller, Katja Gwin, Gabrielle Baker, Bhaskar Kallakury, Jay Zeck, Xiuzhen Duan, Cagatay Ersahin, Roberto Gamez, Megan Troxell, Atiya Mansoor, Lauren Grasso LeBeau, Sharon Sams, Josh Wisell, Shi Wei, Shuko Harada, Tuyethoa Vinh, Michael D. Stamatakos, Ossama Tawfik, Fang Fan, Amy Adams, Mara Rendi, Susan Minton, Anthony Magliocco, Sunati Sahoo, Yisheng Fang, Gillian Hirst, Ruby Singhrao, Smita M Asare, Anne M Wallace, A.J. Chien, Erin D. Ellis, Heather S Han, Amy S Clark, Judy C Boughey, Anthony D Elias, Rita Nanda, Larissa Korde, Rashmi Murthy, Julie Lang, Donald Northfelt, Qamar Khan, Kirsten K Edmiston, Rebecca Viscusi, Barbara Haley, Kathleen Kemmer, Amelia Zelnak, Donald A Berry, Laura J Esserman

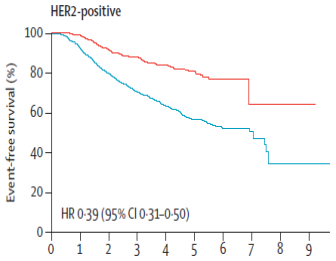
Background

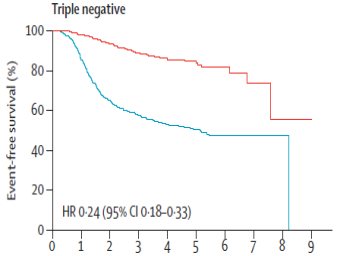
- FDA Meta Analysis (Cortazar et al, Lancet 2014)
- >11K patients from 12 neoadjuvant trials
- Median follow-up for EFS: 5.4 years



pathological complete response defined as ypT0/is ypN0



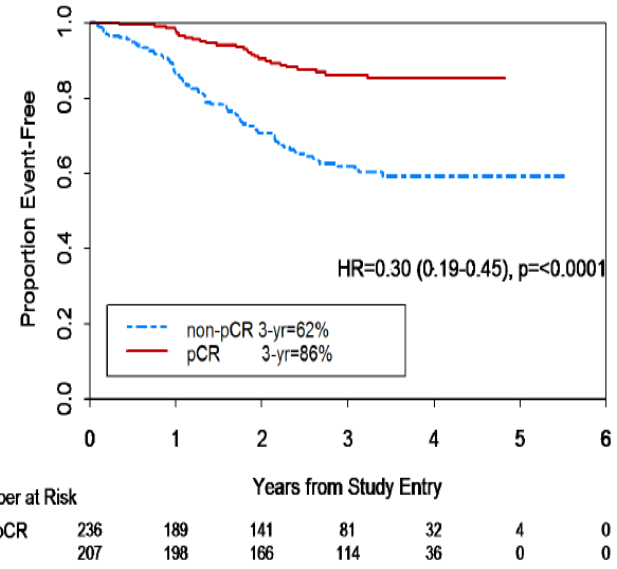




Cooperative Group Data: Better coordination

San Antonio Breast Cancer Symposium, December 8-12, 2015

CALGB 40603 – EFS by pCR Breast/Axilla



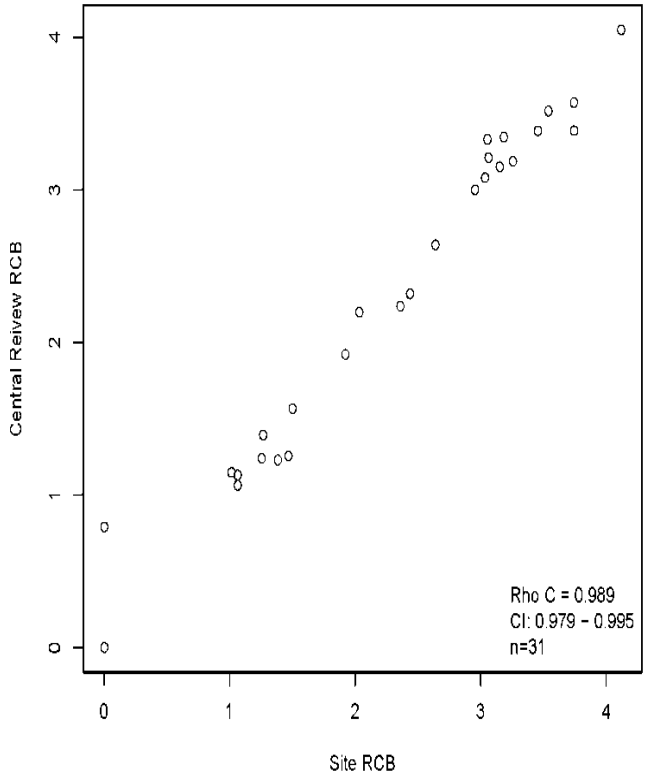
Number at Risk

non-pCR	236	189	141	81	32	4	0
pCR	207	198	166	114	36	0	0

I-SPY2 Analysis

- **Primary Endpoint:**
  - Pathological complete response (pCR)
  - Defined as no residual invasive cancer in breast or lymph nodes
  - Assessed using the Residual Cancer Burden (RCB) method
  - Highly reproducible between local and central pathologist review
- **Intent-to-treat:**
  - Patients who received therapy, but later withdrew, leave the institution, went to non-protocol therapy, or progressed are considered non-pCR
- **Secondary endpoints:**
  - RCB
  - EFS

Scatterplot of RCB index entered by Site vs. Central Review

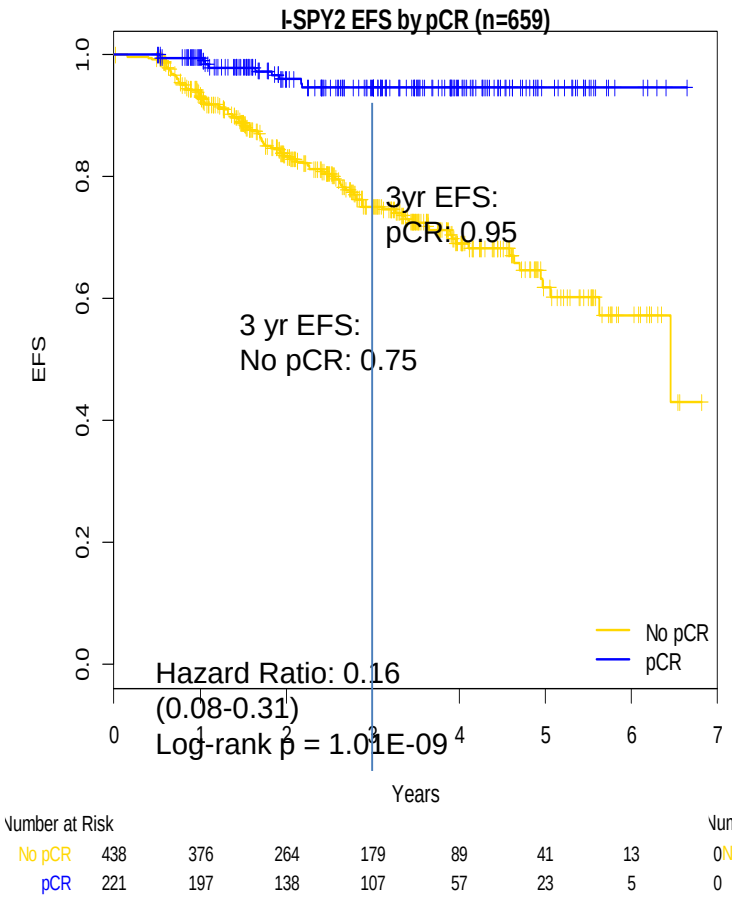


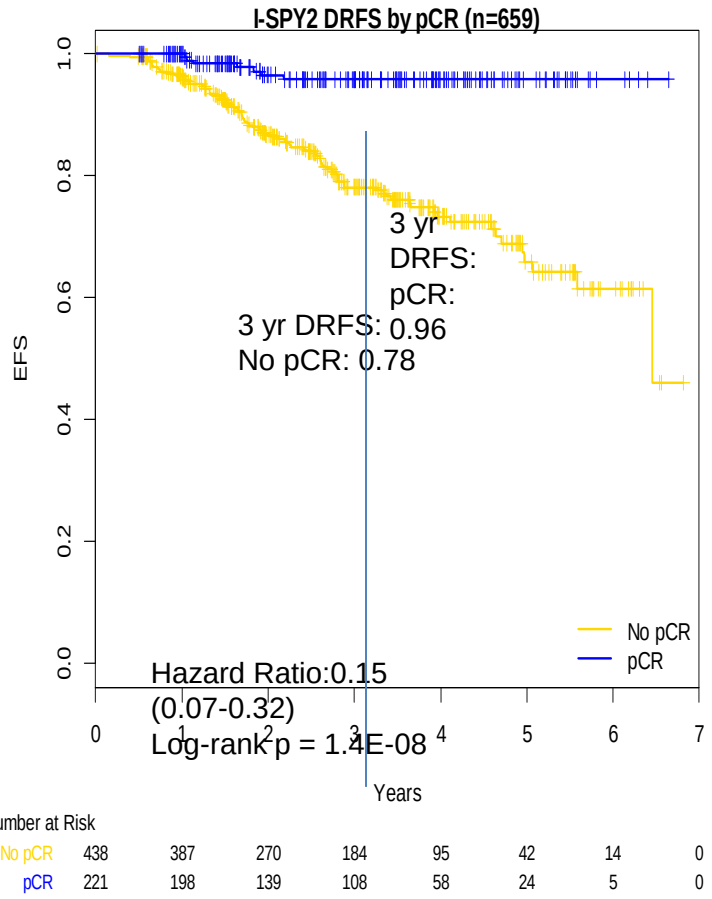
I-SPY 2 To Date

>1000 patients completed surgery

12 investigational agents/combinations

pCR is a very significant predictor of EFS and DRFS





Multivariate Cox Model:
EFS ~ pCR + HR + HER2 + Tx

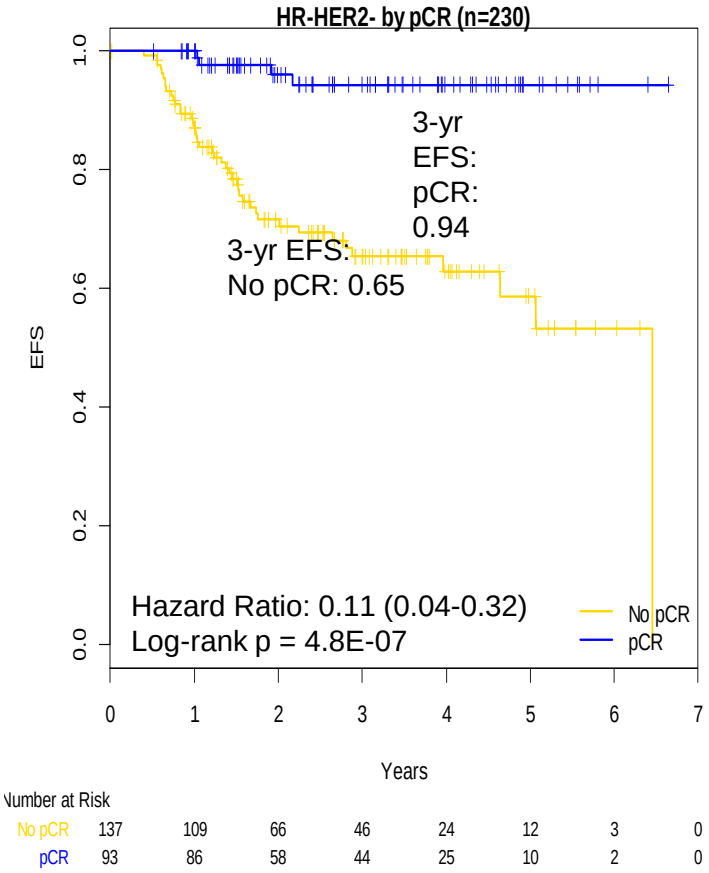
Hazard Ratio for pCR term : 0.13 (0.06-0.26)
Wald p: 1.62E-08

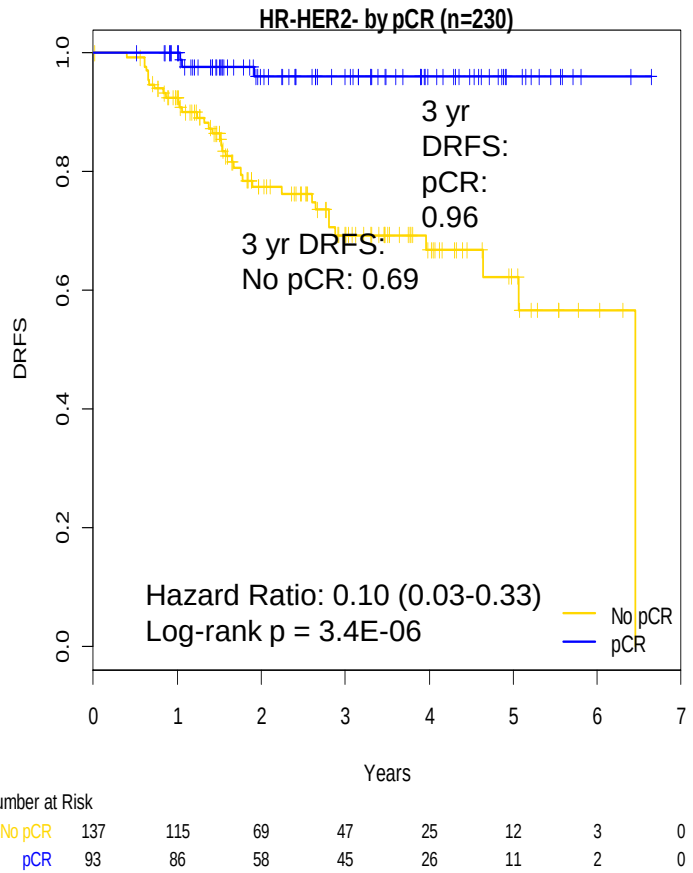
Multivariate Cox Model:
DRFS ~ pCR + HR + HER2 + Tx

Hazard Ratio for pCR term : 0.14 (0.07-0.32)
Wald p: 1.53E-06

pCR is similarly predictive of EFS and DRFS within each HR/HER2 subtype

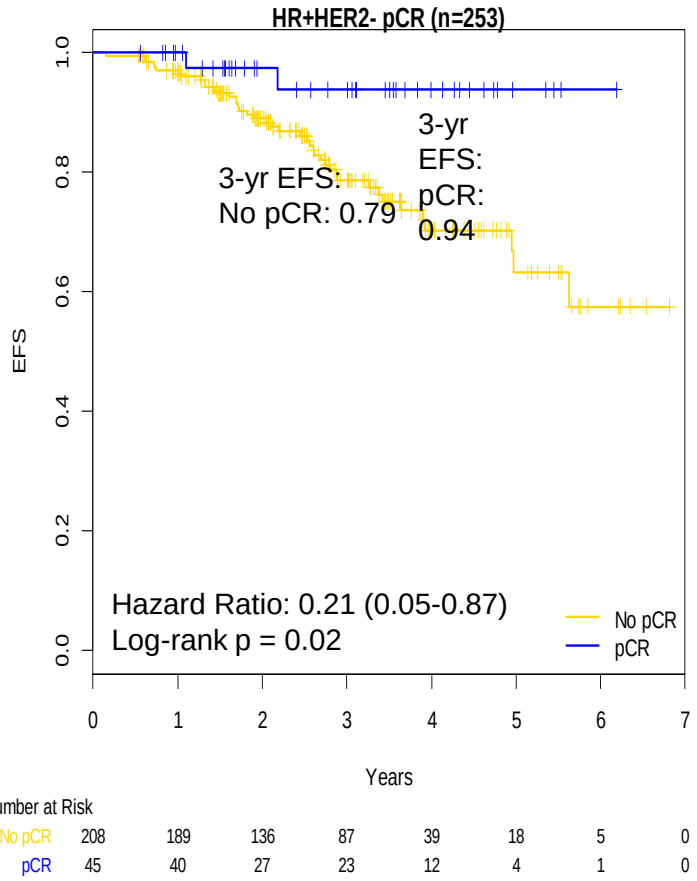
HR-HER2-

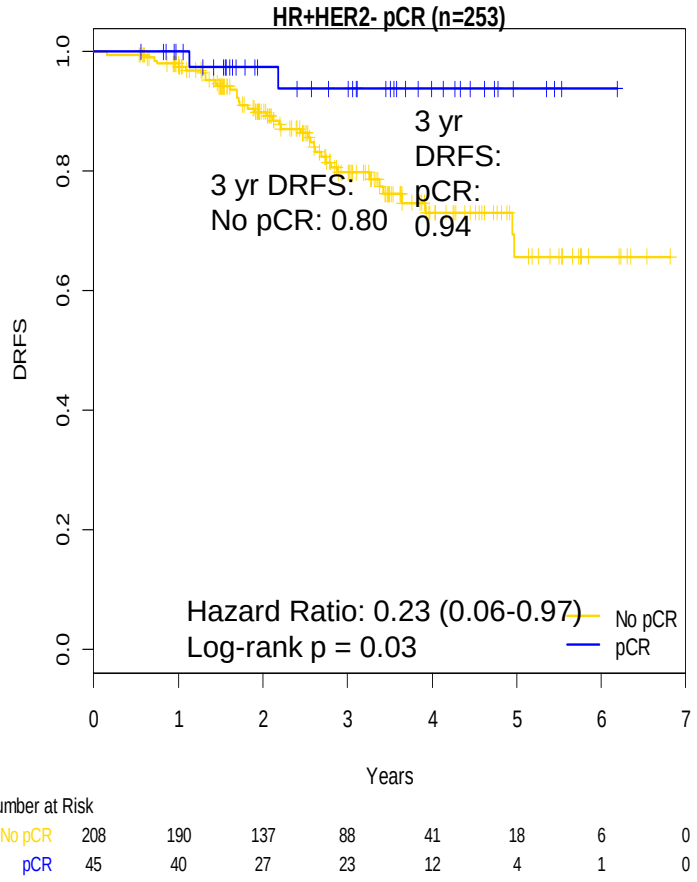




pCR is similarly predictive of EFS and DRFS within each HR/HER2 subtype

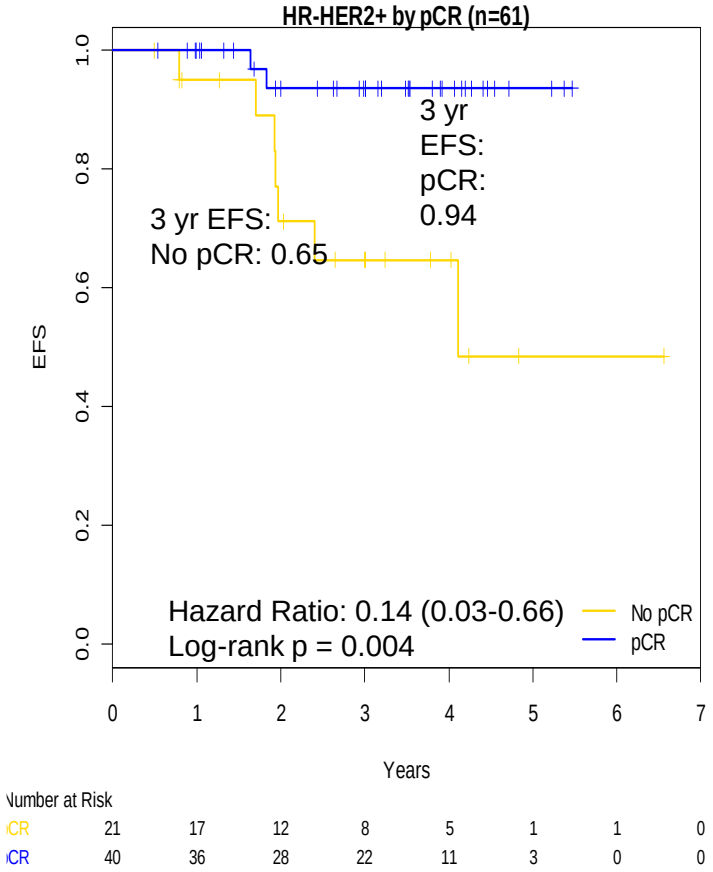
HR+HER2-

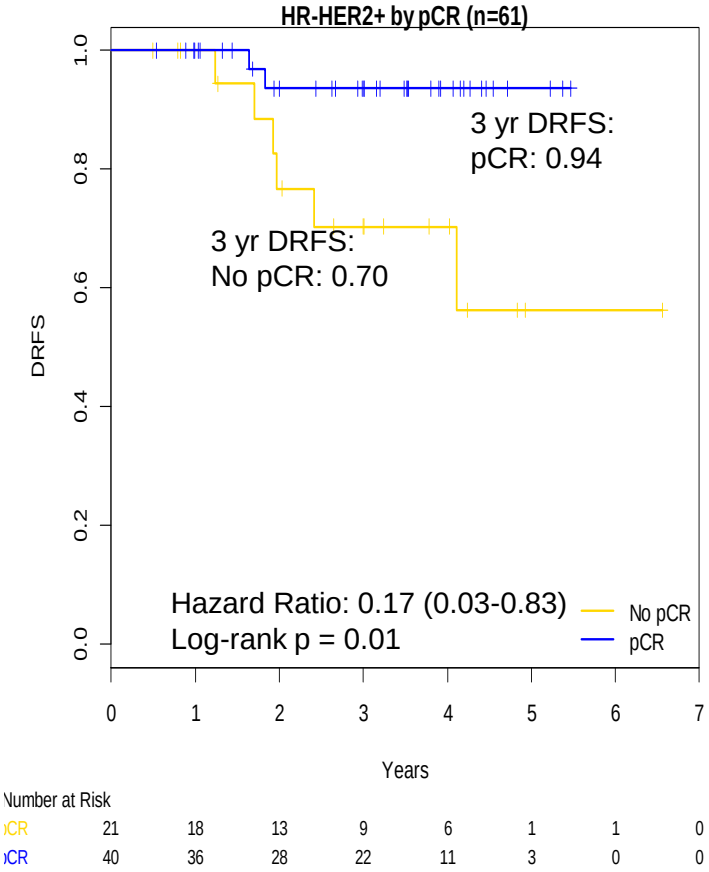




pCR is similarly predictive of EFS and DRFS within each HR/HER2 subtype

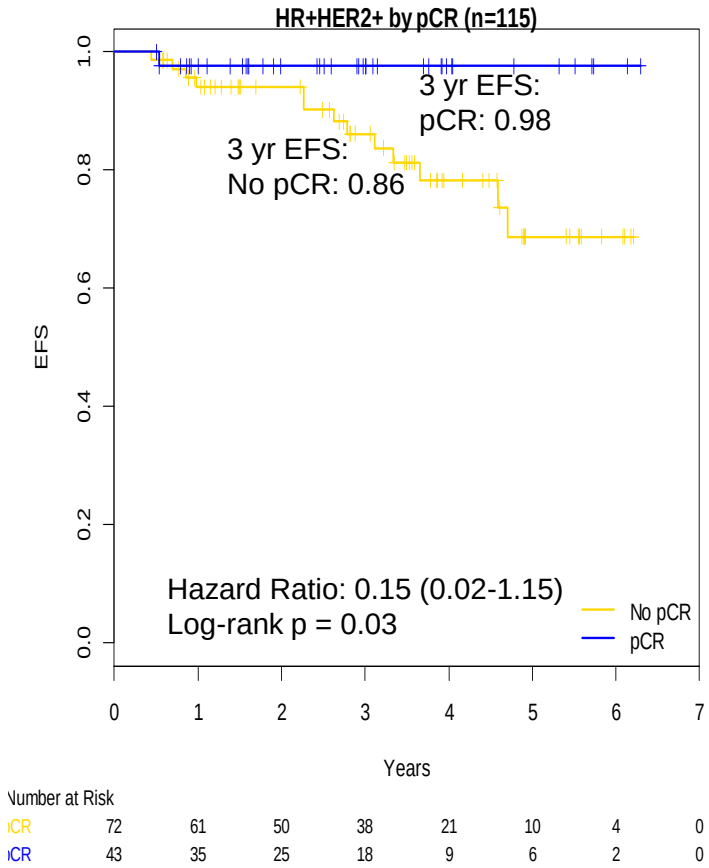
HR-HER2+

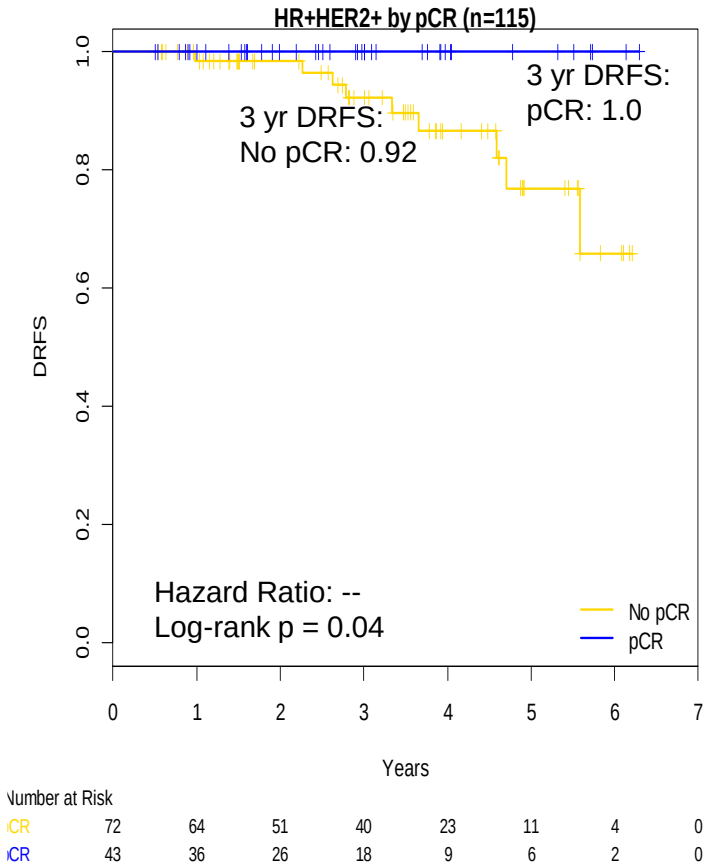




pCR is similarly predictive of EFS and DRFS within each HR/HER2 subtype

HR+HER2+





I SPY Data: pCR predicts EFS and DRFS with HR 0.08

	Hazard Ratio	**P Value**
Cortazar Meta-analysis	0.48 (0.43-0.54)	<0.01
Cooperative Group CALGB 40603	0.30 (0.19-0.45)	<0.0001
Platform Trial: I-SPY 2	0.16	<0.000000001

Key Lessons Learned

- pCR is a great early endpoint in the setting of a well run platform trial set up as a **learning system** with:
  - Standards for eligibility (high risk for early recurrence)
  - Long term follow-up of all patients over time (correlation of early , intermediate and late endpoints)
- pCR is equally predictive across all tumor subsets
- pCR as an endpoint enables rapid evaluation of novel therapy combinations and can accelerate the identification of effective regimens
- Achieving pCR after the first regiment may be sufficient
  - And can serve to test de-escalation of therapy, decrease in toxicity
  - Randomization to AC v. not after pCR with Taxane combination is being tested in I-SPY 2+

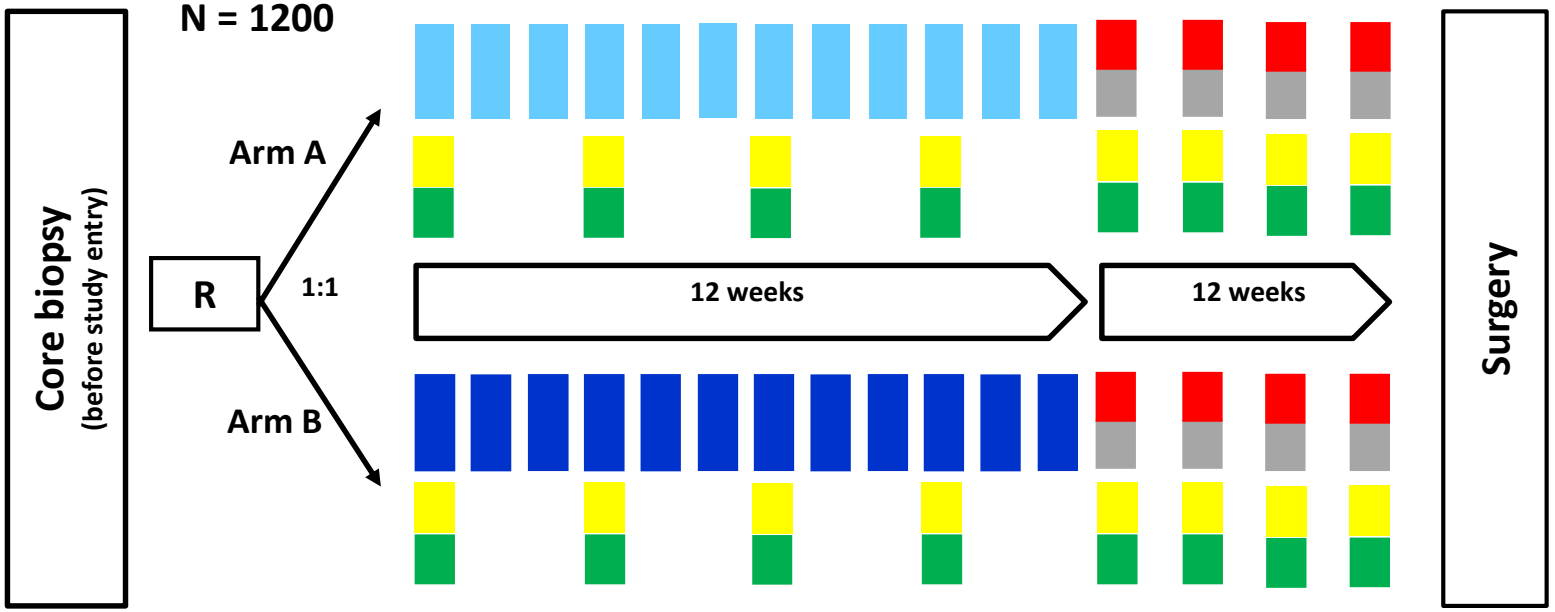
San Antonio Breast Cancer Symposium, December 5-9, 2017

Survival analysis of the prospectively randomized phase III GeparSepto trial comparing neoadjuvant chemotherapy with weekly nab-paclitaxel with solvent-based paclitaxel followed by anthracycline/cyclophosphamide for patients with early breast cancer – GBG69

Andreas Schneeweiss, Christian Jackisch, Sabine Schmatloch, Bahriye Aktas, Carsten Denkert, Christian Schem, Hermann Wiebringhaus, Sherko Kümmel, Kerstin Rhiem, Mathias Warm, Peter A. Fasching, Marianne Just, Claus Hanusch, John Hackmann, Jens Uwe Blohmer, Bernd Gerber, Jenny Furlanetto, Gunter von Minckwitz, Valentina Nekljudova, Sibylle Loibl, Michael Untch

- A joint study of the AGO Breast and the German Breast Group -

Study Design



STRATIFICATION FACTORS:

- HER2+/HR- vs. HER2+/HR+ vs. HER2-/HR- vs. HER2-/HR+
- Ki67 (≤20% vs. >20%)
- SPARC (positive vs. negative)

Paclitaxel
80 mg/m² weekly

Nab-paclitaxel 150 mg/m² weekly
The dose was reduced to 125 mg/m² after recruitment of 464 patients

Epirubicin 90 mg/m²
Cyclophosphamide 600 mg/m²

HER2 positive patients:

Trastuzumab 8 mg/kg (loading dose) → 6 mg/kg
Pertuzumab 840 mg (loading dose) → 420 mg

Untch et al. Lancet Oncol 2016

Main Eligibility Criteria

- Unilateral or bilateral primary breast cancer
- Stages
  - cT2 - cT4a-d
  - cT1c and additional high risk
    - cN+ *or*
    - pN_{SLN+} *or*
    - ER-neg and PR-neg *or*
    - Ki67 > 20% *or*
    - HER2-positive
- Central testing for HER2, HR, Ki67, and SPARC[1]

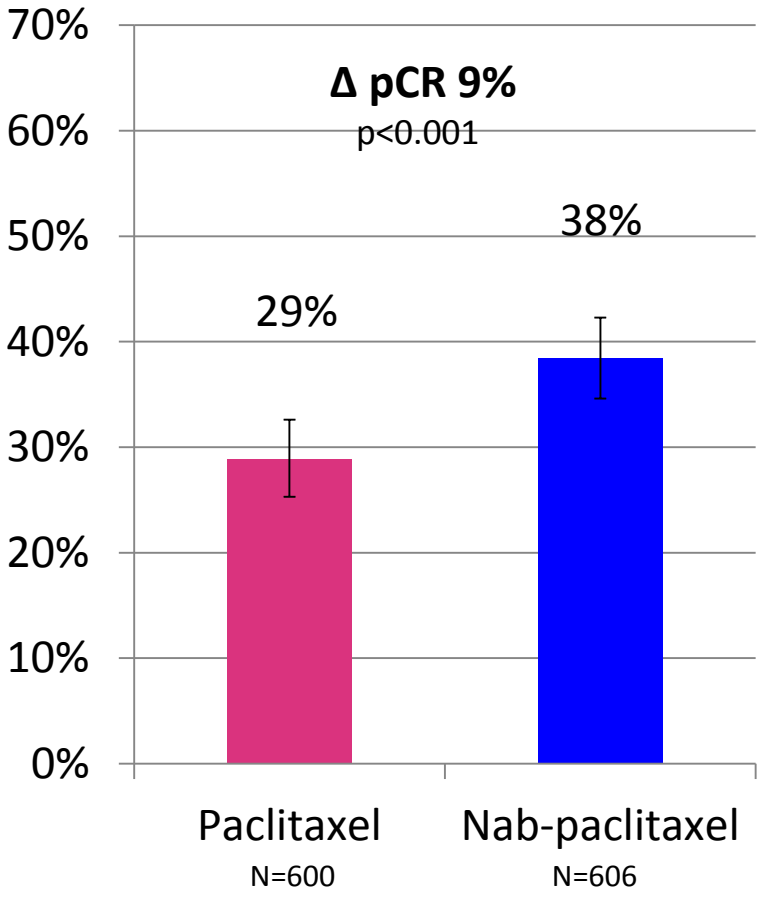
[1]**Lindner J et al. Ann Oncol 2015**

Patient and tumor characteristics (baseline)

	Paclitaxel N=600 (%)	Nab-paclitaxel N=606 (%)	Overall N=1204 (%)
Age (median, yrs)	48 (22 - 76)	49 (21 - 75)	49 (21 - 76)
Palpable tumor size (median, mm)	30 (5 - 150)	30 (4 -150)	30 (4 - 150)
cT3 / 4 (palpation)	86 (16.5)	81 (15.8)	167 (16.2)
cN+	265 (45.1)	275 (46.3)	540 (45.7)
Ki67 >20%	415 (69.2)	418 (69.0)	833 (69.1)
SPARC positive (IRS 6-12)	94 (15.7)	97 (16.0)	191 (15.9)
Grade 3	338 (56.3)	319 (52.6)	657 (54.5)
Breast cancer subtype			
TNBC	137 (22.8)	139 (22.9)	276 (22.9)
HER2-negative / HR-positive	266 (44.3)	268 (44.2)	534 (44.3)
HER2-positive / HR-positive	149 (24.8)	140 (23.1)	289 (24.0)
HER2-positive / HR-negative	48 (8.0)	59 (9.7)	107 (8.9)

Untch et al. Lancet Oncol 2016

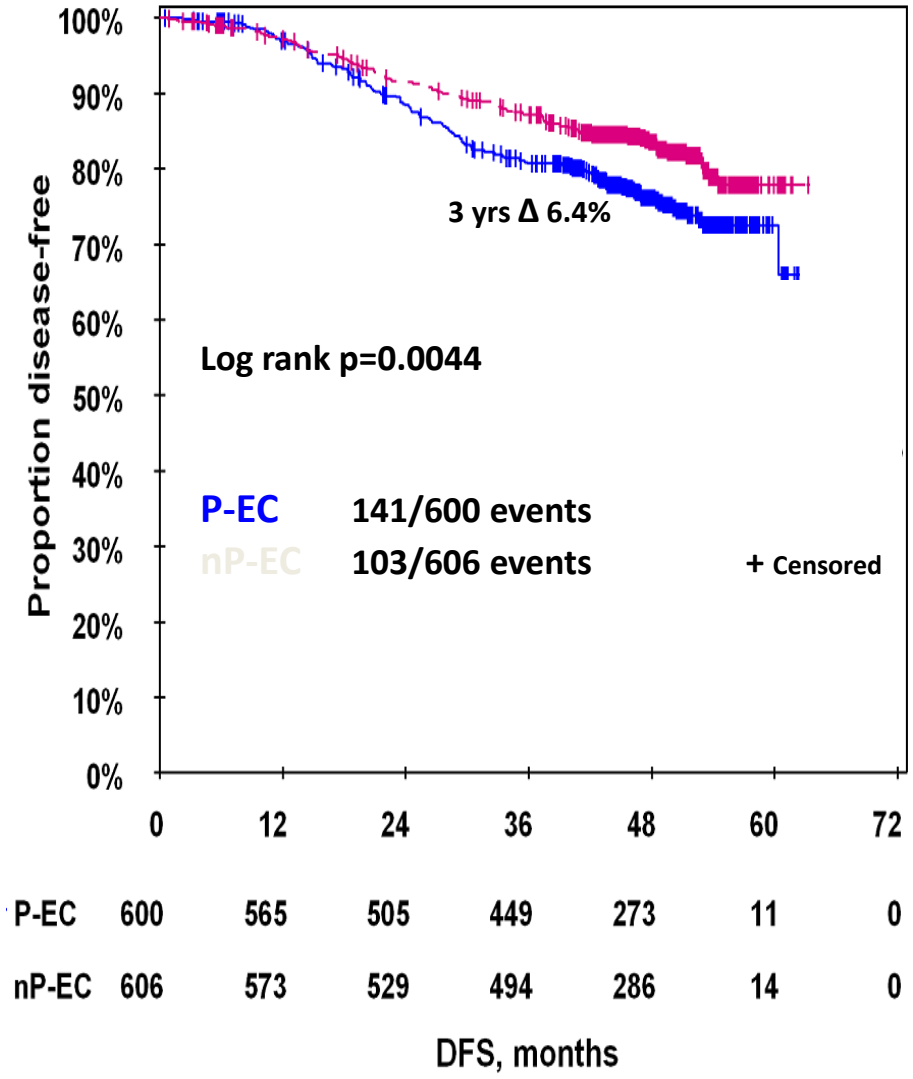
Primary Endpoint: pCR (ypT0 ypN0)



- The substitution of solvent-based paclitaxel (P) with nab-paclitaxel (nP) as neoadjuvant chemotherapy significantly increased the pathological complete response rate (pCR; ypT0 ypN0) overall from 29% to 38% (p<0.001).
- The largest pCR improvement of absolute 22% (from 26% to 48%; p<0.001) was achieved in patients with TNBC.
- It has not yet been shown whether this will translate into an improved survival.

Untch et al. Lancet Oncol 2016

Disease-Free Survival



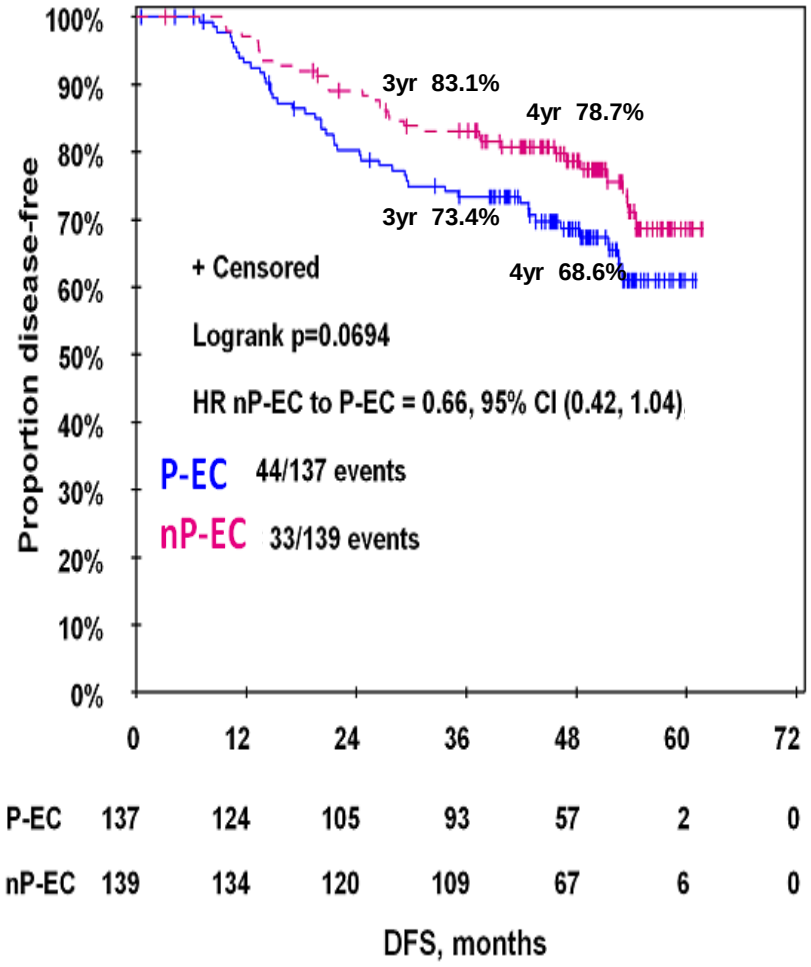
- **Median follow-up of 49 months (IQR 44.6 - 52.9)**
- **HR (nP-EC vs. P-EC) = 0.69 (95% CI 0.54-0.89)**
- **Number needed to treat (NNT; 3yrs) = 16 pts**

DFS rates (estimated):

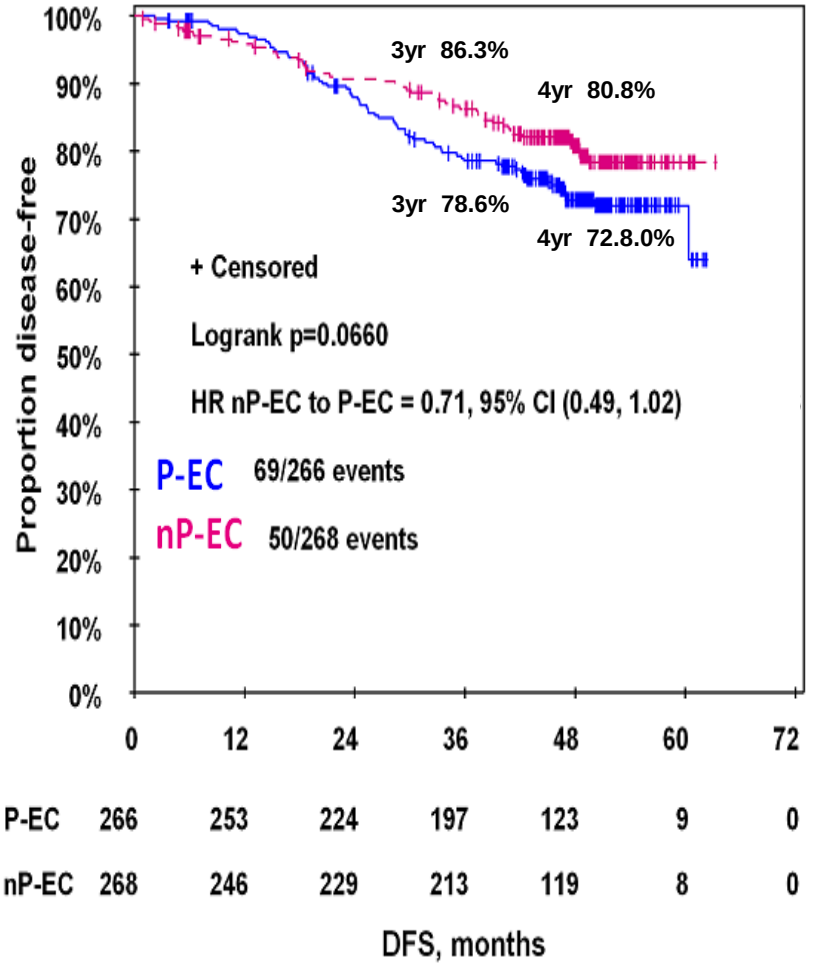
Time	P-EC	95% CI, P-EC	nP-EC	95% CI, nP-EC
3 yrs	**80.7%**	(77.2-83.7)	**87.1%**	(84.1-89.6)
4 yrs	**76.2%**	(72.3-79.5)	**83.5%**	(80.2-86.4)

Disease-Free Survival per Subtype

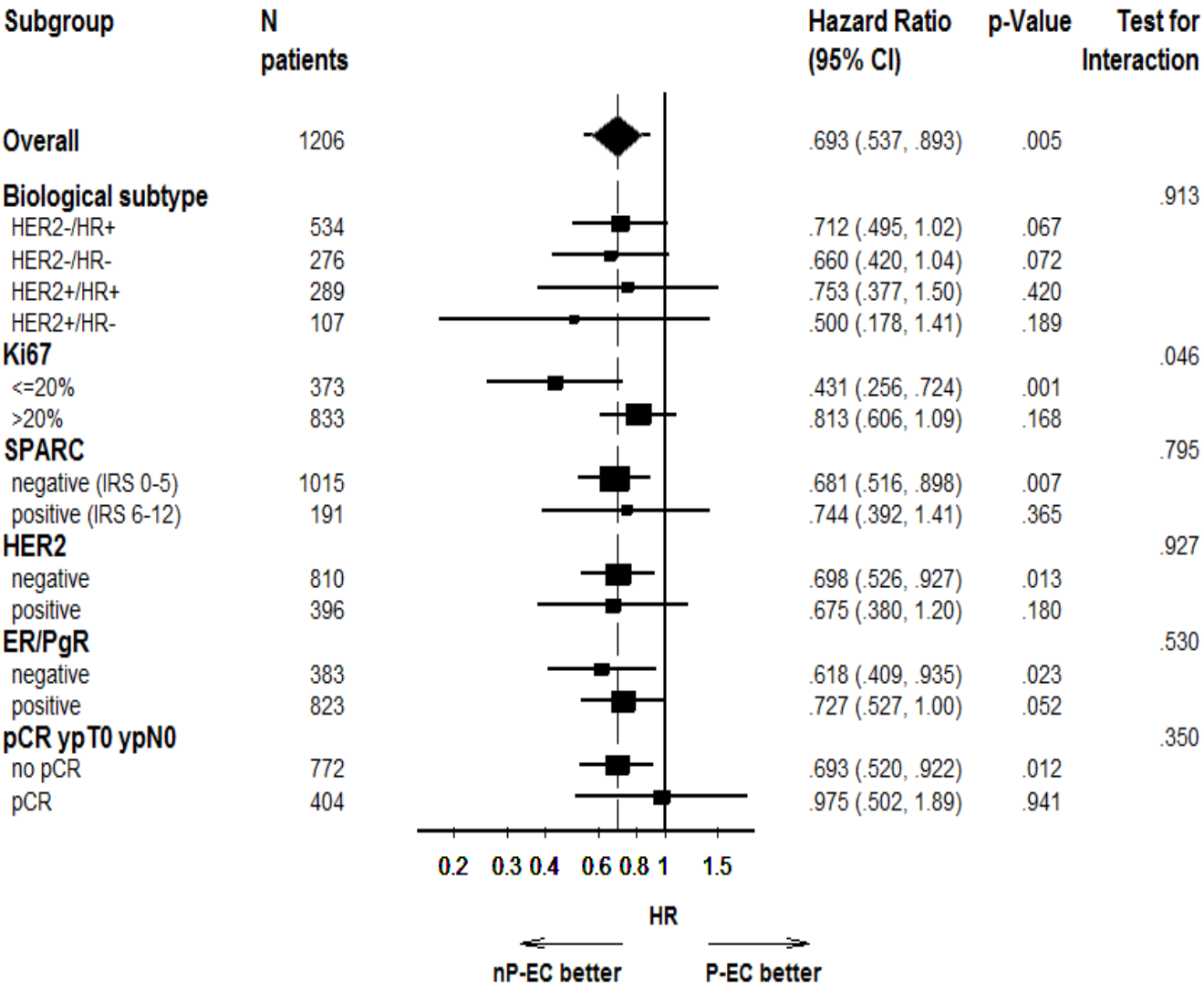
TNBC



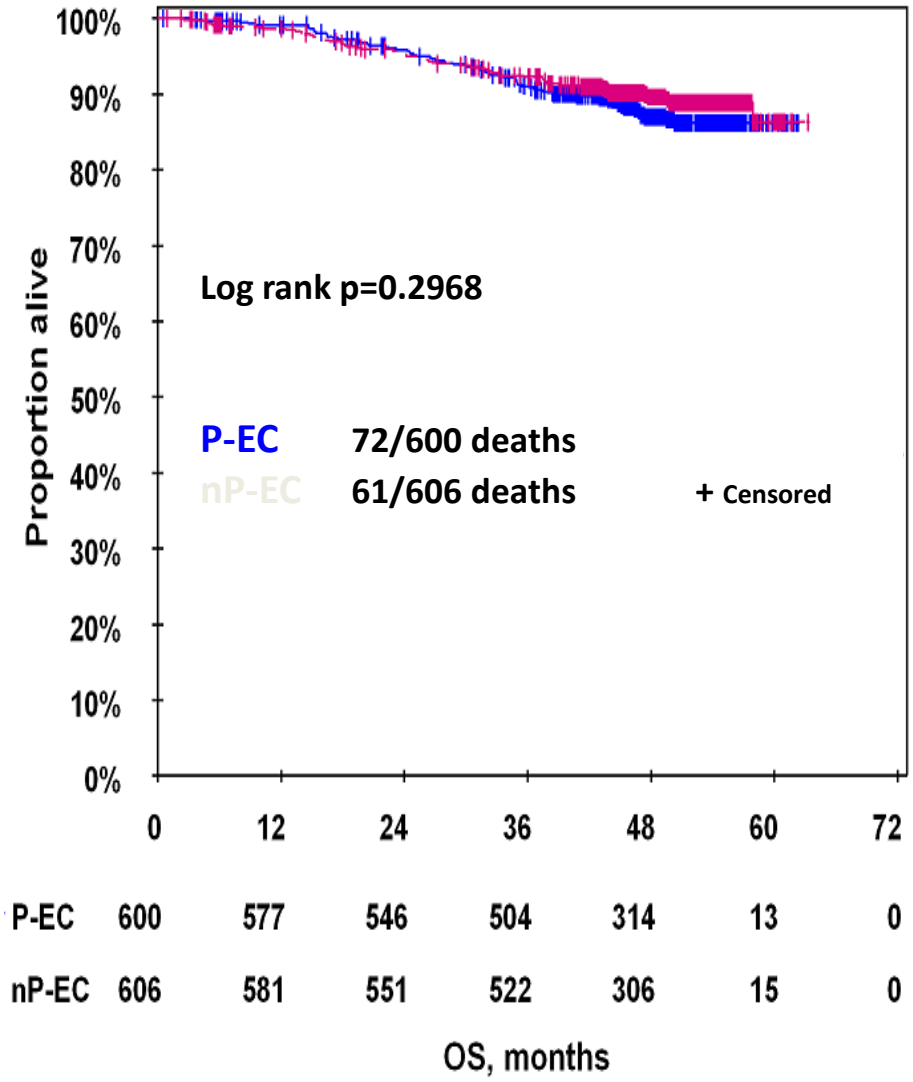
HR+HER2-



Forest Plot: Disease-Free Survival



Overall Survival: Overall



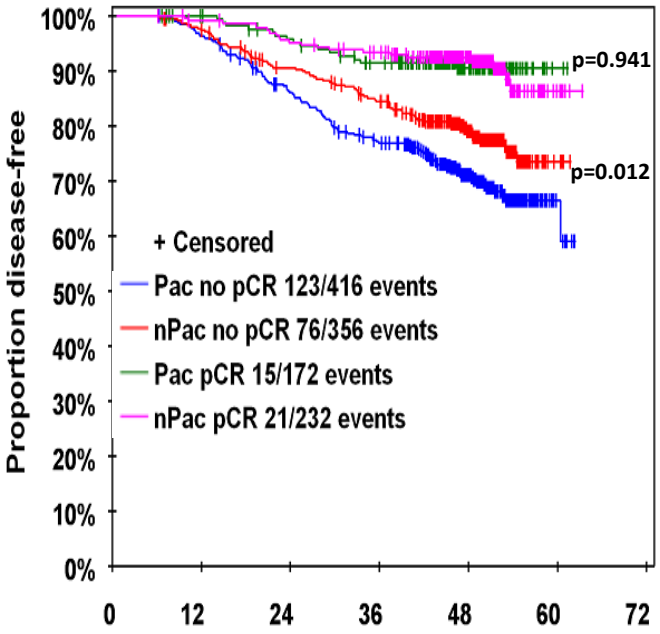
- **HR (nP-EC vs. P-EC) = 0.83 (95% CI 0.59-1.17)**

OS rates (estimated):

Time	P-EC	95% CI, P-EC	nP-EC	95% CI, nP-EC
3 yrs	**91.1%**	(88.4-93.1)	**92.3%**	(89.8-94.2)
4 yrs	**87.0%**	(83.8-89.6)	**89.6%**	(86.8-91.9)

Surrogate Value of pCR (exploratory analysis)

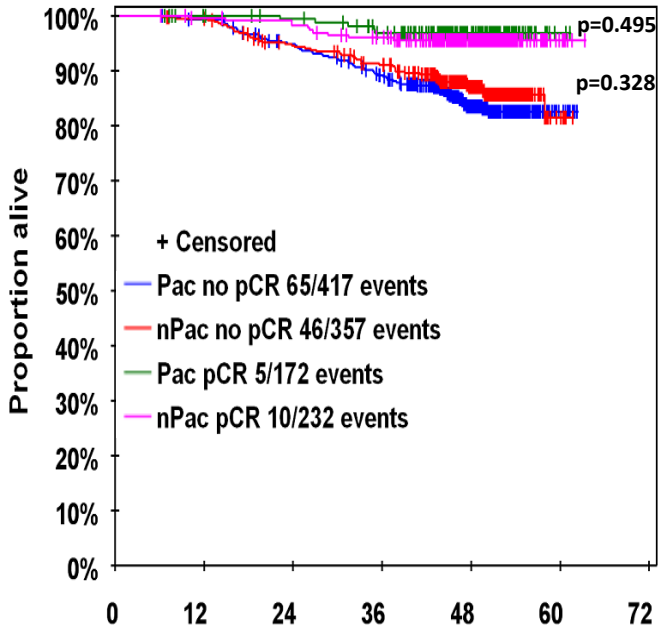
Disease-Free Survival



Pac no pCR	416	398	348	305	194	9	0
nPac no pCR	356	346	312	286	163	7	0
Pac pCR	172	167	157	144	79	2	0
nPac pCR	232	227	217	208	123	7	0

DFS, months

Overall Survival



Pac no pCR	417	410	383	352	229	11	0
nPac no pCR	357	353	327	308	180	8	0
Pac pCR	172	167	163	152	85	2	0
nPac pCR	232	228	224	214	126	7	0

OS, months

Summary

- GeparSepto demonstrates a significantly improved DFS when patients received nab-paclitaxel instead of paclitaxel (HR=0.69, 95% CI [0.54-0.89; log rank p=0.0044).
- A similar treatment effect was observed for patients with TNBC and HR+/HER2- tumors.
- The interaction with Ki67 suggests that nab-paclitaxel generates a long term benefit in particular in tumors with lower proliferation.
- Irrespective of the treatment group, patients achieving a pCR had a significantly better DFS.
- Patients without pCR have a significantly better DFS with nab-paclitaxel than paclitaxel.

San Antonio Breast Cancer Symposium, December 5-9, 2017

EMBRACA

A phase 3 trial comparing talazoparib, an oral PARP inhibitor, to physician's choice of therapy in patients with advanced breast cancer and a germline *BRCA*-mutation

Jennifer K. Litton, Hope S. Rugo, Johannes Ettl, Sara Hurvitz, Anthony Gonçalves, Kyung-Hun Lee, Louis Fehrenbacher, Rinat Yerushalmi, Lida A. Mina, Miguel Martin, Henri Roché, Young-Hyuck Im, Ruben G. W. Quek, Iulia Cristina Tudor, Alison L. Hannah, Wolfgang Eiermann, Joanne L. Blum

Background

- Talazoparib (TALA) is a highly potent dual-mechanism PARP inhibitor[1-3]
  - Inhibits the PARP enzyme
  - Traps PARP on single-stranded DNA breaks[4]
  - Prevents repair of DNA damage, resulting in cell death
- Phase 1 trial established a tolerable dose of 1 mg/day for continuous dosing (fed or fasting)[5]
  - Single-agent activity in other tumor types (prostate, ovarian, SCLC)
- The phase 2 ABRAZO trial showed encouraging efficacy and safety in patients with germline *BRCA1/2* mutations and prior platinum therapy or at least 3 prior cytotoxic regimens[6]

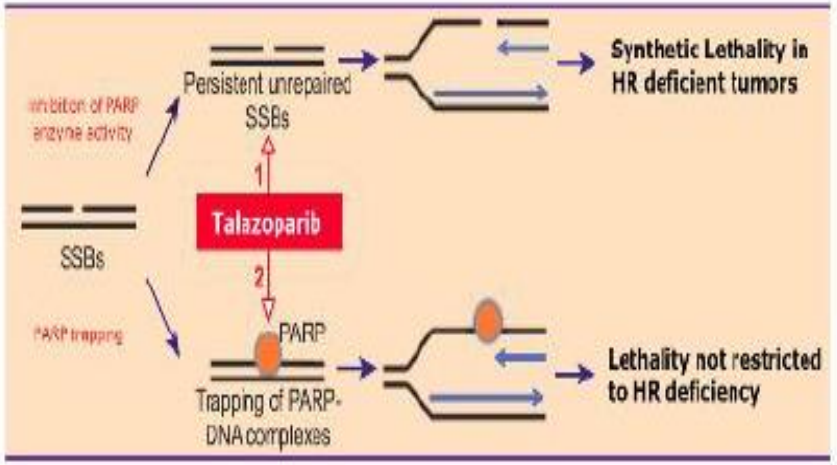


Figure adapted from Murai J et al *Cancer Res* 2012;72:5588-5599, with permission from AACR.

		ABRAZO	
	Phase 1 (n = 14)[a]	Prior Platinum (n = 48)	≥ 3 Lines, No Platinum (n = 35)
Confirmed ORR, % (95% CI)	50%	21% (10, 35)	37% (22, 55)
PFS, mo (95% CI)	7.5	4.0 (2.8, 5.4)	5.6 (5.5, 7.8)
CBR24, % (95% CI)	86%	38% (24, 53)	66% (48, 81)

[a]Data shown for the phase 1 study is only in breast cancer patients.

Abbreviations: CI, confidence interval; CBR24, clinical benefit rate at 24 weeks; HR, homologous recombination; PARP, poly(ADP-ribose) polymerase; ORR, objective response rate; PFS, progression-free survival; SCLC, small cell lung cancer; SSB, single-strand break.

1. Ashworth A. *J Clin Oncol*. 2008;26:3785-3790. 2. Jalve M, Curtin NJ. *Ther Adv Med Oncol*. 20113:257-267. 3. Helleday T. *Mol Oncol*. 2011;5:387-393. 4. Lord CJ, Ashworth A. *Science*. 2017;355:1152-1158. 5. de Bono J et al. *Cancer Discov*. 2017;7:620-629. 6. Turner NC et al. Presented at ASCO; June 3, 2017; Chicago, IL. Abstract 1007.

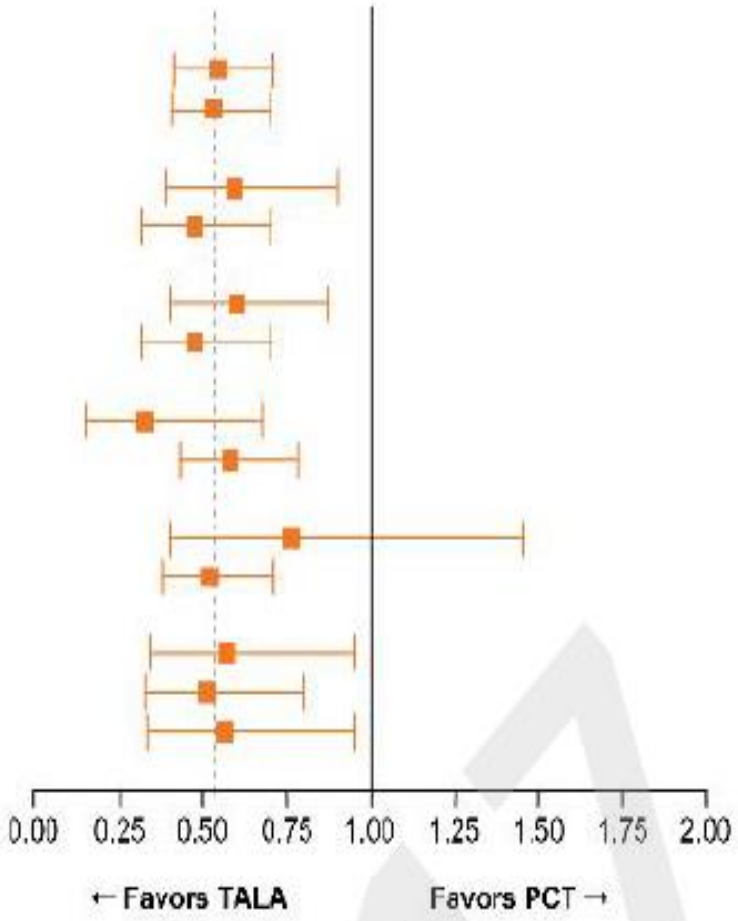
Baseline Characteristics (ITT Population)

	TALA (n = 287)	Overall PCT (n = 144)
Age, median (range), y	45 (27.0-84.0)	50 (24.0-88.0)
<50 y, no. %	182 (63.4%)	67 (46.5%)
Gender, % female	98.6%	97.9%
ECOG = 0 / 1 / 2, %	53.0% / 44.0% / 2.0%	58.0% / 40.0% / 1.0%
Measurable disease by investigator, no. (%)	219 (76.3%)	114 (79.2%)
History of CNS metastasis, no. (%)	43 (15.0%)	20 (13.9%)
Visceral disease, no. (%)	200 (69.7%)	103 (71.5%)
Hormone receptor status, no. (%)		
TNBC	130 (45.3%)	60 (41.7%)
HR+	157 (54.7%)	84 (58.3%)
BRCA status, no. (%)		
BRCA1+	133 (46.3%)	63 (43.8%)
BRCA2+	154 (53.7%)	81 (56.3%)
Disease free interval (initial diagnosis to aBC) <12 months	108 (37.6%)	42 (29.2%)

Abbreviations: aBC, advanced breast cancer; ITT, intent to treat.

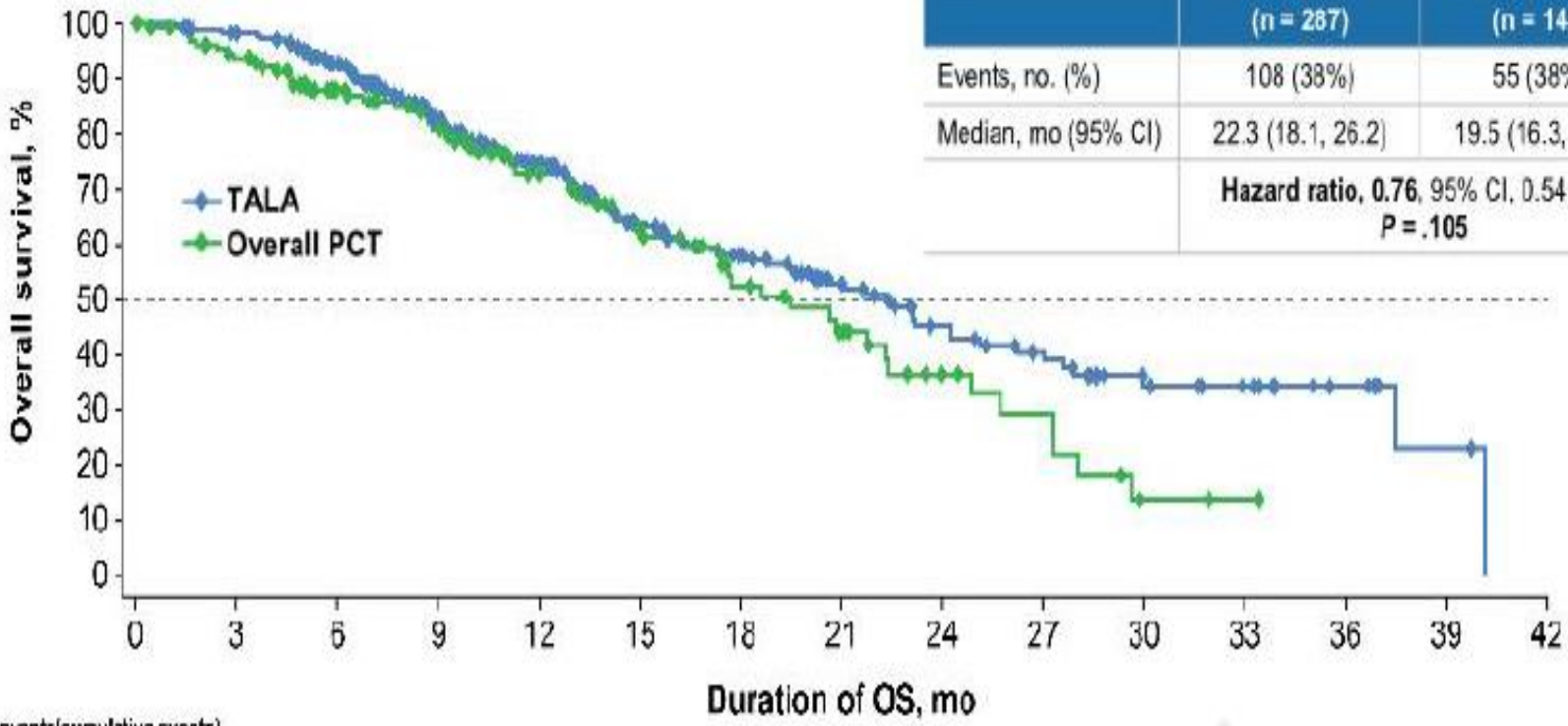
PFS: Subgroup Analysis

Subgroup	Patients, no. (%)	Hazard ratio (95% CI)
All randomized patients (ITT)	431 (100)	0.54 (0.41-0.71)
Patients with central testing available	408 (94.7)	0.53 (0.40-0.70)
BRCA status by central testing		
BRCA1	183 (42.5)	0.59 (0.39-0.90)
BRCA2	225 (52.2)	0.47 (0.32-0.70)
Hormone receptor status		
TNBC based on most recent biopsy	190 (44.1)	0.60 (0.41-0.87)
HR+ based on most recent biopsy	241 (55.9)	0.47 (0.32-0.71)
History of CNS metastasis		
Yes	63 (14.6)	0.32 (0.15-0.68)
No	368 (85.4)	0.58 (0.43-0.78)
Prior platinum treatment		
Yes	76 (17.6)	0.76 (0.40-1.45)
No	355 (82.4)	0.52 (0.39-0.71)
Prior regimens of cytotoxic chemo for aBC		
0	165 (38.3)	0.57 (0.34-0.95)
1	161 (37.4)	0.51 (0.33-0.80)
≥ 2	105 (24.4)	0.56 (0.34-0.95)



Interim OS Analysis: Secondary Endpoint

	TALA (n = 287)	Overall PCT (n = 144)
Events, no. (%)	108 (38%)	55 (38%)
Median, mo (95% CI)	22.3 (18.1, 26.2)	19.5 (16.3, 22.4)
	Hazard ratio, 0.76, 95% CI, 0.54, 1.06 *P* = .105	

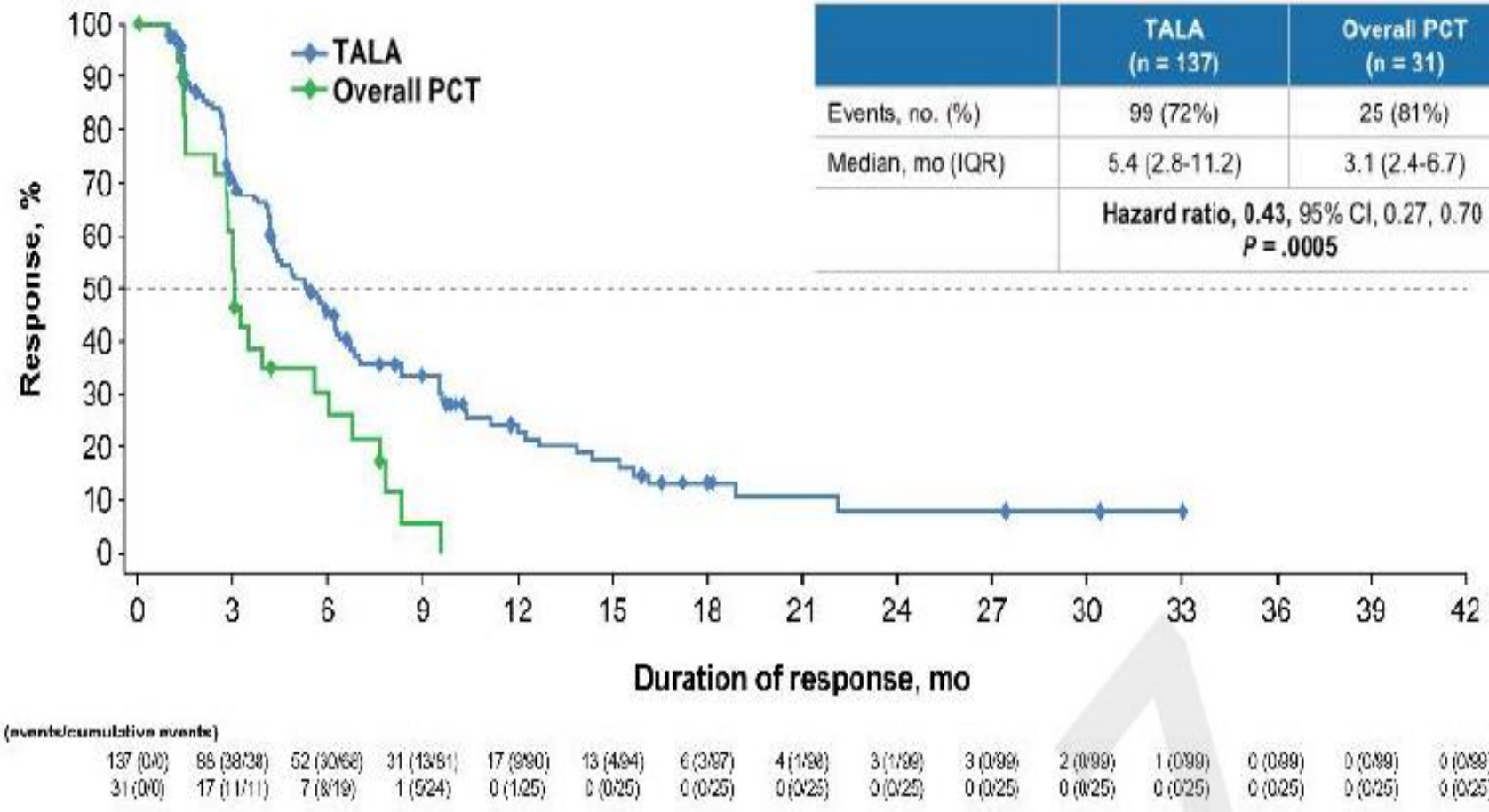


No. at risk (events/cumulative events)

TALA	287 (0/0)	279 (5/5)	236 (15/20)	179 (24/44)	132 (16/60)	91 (17/77)	71 (8/85)	52 (6/91)	38 (7/98)	30 (1/102)	18 (1/106)	11 (0/106)	8 (0/106)	2 (1/107)	0 (1/108)
PCT	141 (0/0)	119 (5/5)	92 (7/15)	78 (7/22)	55 (7/29)	41 (7/36)	28 (6/42)	20 (4/46)	11 (3/49)	8 (2/51)	2 (1/55)	1 (0/55)	0 (0/55)	0 (0/55)	0 (0/55)

Survival Probability at:	TALA (n = 287)	Overall PCT (n = 144)
Month 24, % (95% CI)	45% (36.7-53.5)	37% (24.1-49.1)
Month 36, % (95% CI)	34% (25.3-43.7)	0%

DOR by Investigator Assessment



	TALA (n = 137)	Overall PCT (n = 31)
Events, no. (%)	99 (72%)	25 (81%)
Median, mo (IQR)	5.4 (2.8-11.2)	3.1 (2.4-6.7)
	Hazard ratio, 0.43, 95% CI, 0.27, 0.70 ***P* = .0005**	

No. at risk (events/cumulative events)

TALA	137 (0/0)	88 (38/38)	52 (30/68)	31 (13/81)	17 (9/90)	13 (4/94)	6 (3/97)	4 (1/98)	3 (1/99)	3 (0/99)	2 (0/99)	1 (0/99)	0 (0/99)	0 (0/99)	0 (0/99)
PCT	31 (0/0)	17 (11/11)	7 (8/19)	1 (5/24)	0 (1/25)	0 (0/25)	0 (0/25)	0 (0/25)	0 (0/25)	0 (0/25)	0 (0/25)	0 (0/25)	0 (0/25)	0 (0/25)	0 (0/25)

1-year probability of sustained response is 23% vs 0% with TALA and PCT, respectively

Adverse Events: Hematologic

	TALA (n = 286)			Overall PCT (n = 126)		
	All Grade	Grade 3	Grade 4	All Grade	Grade 3	Grade 4
No. of patients with ≥ 1 AE, no. (%)	194 (67.8%)	140 (49.0%)	17 (5.9%)	63 (50.0%)	29 (23.0%)	19 (15.1%)
Anemia	151 (52.8%)	110 (38.5%)	2 (0.7%)	23 (18.3%)	5 (4.0%)	1 (0.8%)
Neutropenia	99 (34.6%)	51 (17.8%)	9 (3.1%)	54 (42.9%)	25 (19.8%)	19 (15.1%)
Thrombocytopenia	77 (26.9%)	32 (11.2%)	10 (3.5%)	9 (7.1%)	2 (1.6%)	0
Lymphopenia	21 (7.3%)	9 (3.1%)	0	4 (3.2%)	0	1 (0.8%)
Febrile neutropenia	1 (0.3%)	0	1 (0.3%)	1 (0.8%)	0	1 (0.8%)

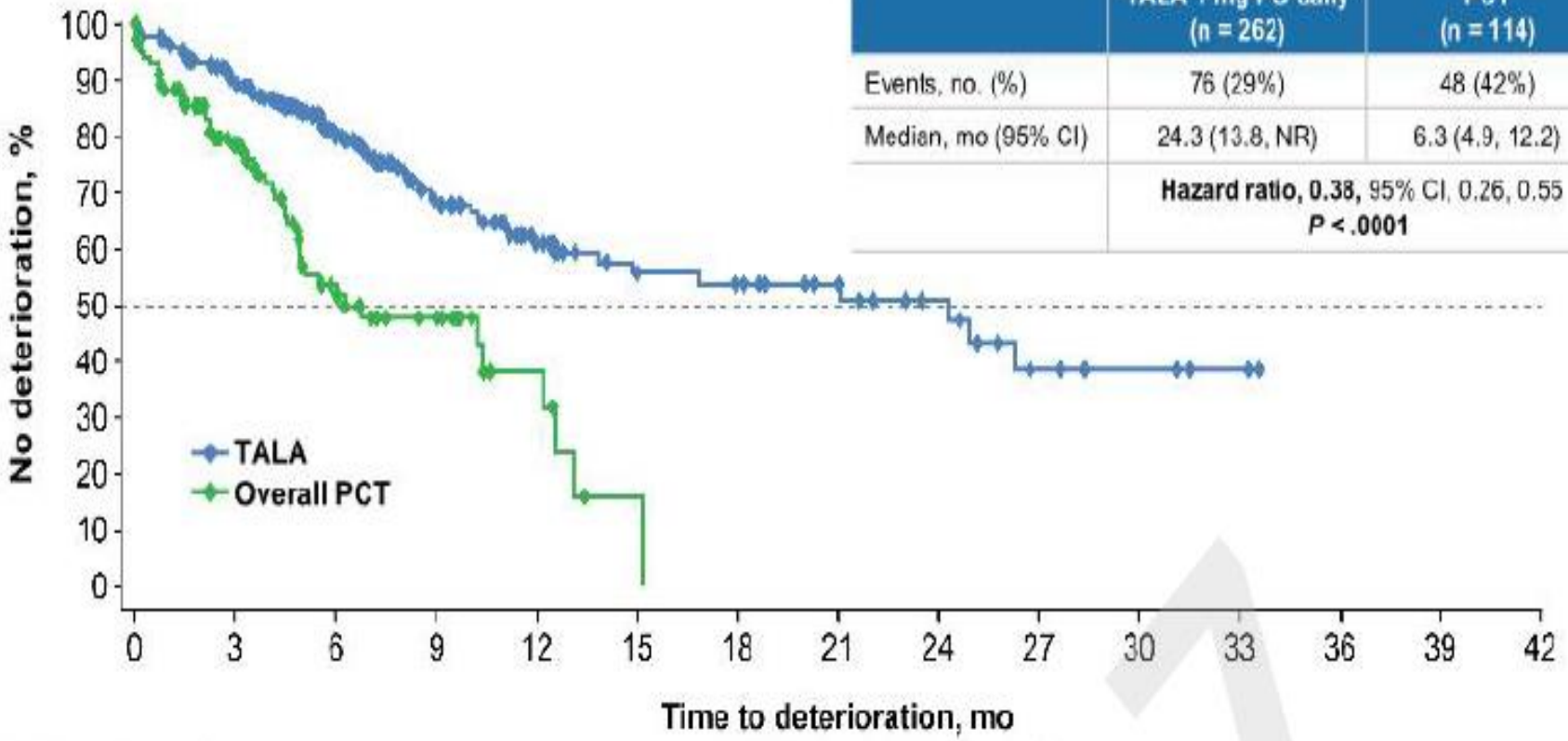
MDS / AML: none reported in the TALA arm; 1 patient on capecitabine

Abbreviations: AML, acute myeloid leukemia; MDS, myelodysplastic syndrome

Time to Deterioration in EORTC QLQ-C30: GHS/QoL

Statistically significant delay in the time to clinically meaningful deterioration* in GHS/QoL favoring TALA

	TALA 1 mg PO daily (n = 262)	PCT (n = 114)
Events, no. (%)	76 (29%)	48 (42%)
Median, mo (95% CI)	24.3 (13.8, NR)	6.3 (4.9, 12.2)
	Hazard ratio, 0.38, 95% CI, 0.26, 0.55 ***P* < .0001**	



No. at risk (events/cumulative events)

TALA	262 (0/0)	212 (26/26)	138 (18/44)	78 (17/61)	44 (7/68)	25 (3/71)	25 (1/72)	20 (0/72)	14 (1/73)	7 (0/73)	4 (0/73)	2 (0/73)	0 (0/73)	0 (0/73)	0 (0/73)
PCT	111 (0/0)	64 (22/22)	30 (17/39)	17 (3/42)	6 (2/44)	1 (3/47)	0 (1/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)

Abbreviation: NR, not reached. *≥ 10-point decrease and no subsequent observation with a < 10-point decrease from baseline.

Conclusions

- Talazoparib significantly improved PFS compared to PCT
- Benefit of talazoparib was significant in both HR-positive and TNBC
- Overall survival favors talazoparib
- Grade ≥ 3 hematologic adverse events were more common with talazoparib
- Time to deterioration of QOL was significantly prolonged with talazoparib compared to PCT

Sacituzumab Govitecan (IMMU-132), an Anti-Trop-2-SN-38 Antibody-Drug Conjugate, as ≥3rd-line Therapeutic Option for Patients With Relapsed/Refractory Metastatic Triple-Negative Breast Cancer (mTNBC): Efficacy Results

Aditya Bardia,[1] Linda T. Vahdat,[2,†] Jennifer R. Diamond,[3] Kevin Kalinsky,[4] Joyce O'Shaughnessy,[5] Rebecca L. Moroose,[6] Steven J. Isakoff,[1] Sara M. Tolaney,[7] Alessandro D. Santin,[8] Vandana Abramson,[9] Nikita C. Shah,[6] Serengulam V. Govindan,[10] Pius Maliakal,[10] Robert M. Sharkey,[10] William A. Wegener,[10] David M. Goldenberg,[10] Ingrid A. Mayer[9]

[1]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; [2]Weill Cornell Medicine, New York, NY; [3]University of Colorado Cancer Center, Aurora, CO; [4]Columbia University-Herbert Irving Comprehensive Cancer Center, New York, NY; [5]Texas Oncology, Baylor University Medical Center, US Oncology, Dallas, TX; [6]UF Health Cancer Center, Orlando, FL; [7]The Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; [8]Yale University School of Medicine, New Haven, CT; [9]Vanderbilt-Ingram Cancer Center, Nashville, TN; [10]Immunomedics, Inc., Morris Plains, NJ; [†]Current affiliation: Memorial Sloan Kettering Cancer Center, New York, NY.

Immunomedics

40 YEAR ANNIVERSARY SAN ANTONIO BREAST CANCER SYMPOSIUM®

Low Response Rates in Pretreated mTNBC

Drug	Phase	N	Population	ORR, %	PFS, months	OS, months	Source
1st-line treatment							
Carboplatin	III	188	1st line	31	3.1	12.4	Tutt A, SABCS 2014
Docetaxel	III	188	1st line	36	4.5	12.3	Tutt A, SABCS 2014
Cisplatin/ Carboplatin	II	86	1st line (80.2%)	26	2.9	11.0	Isakoff SJ, J Clin Oncol, 2015
≥1st-line treatment							
Ixabepilone	II (pooled analysis)	60	Resist to AC-T or just to T	6-17	1.6-2.7	--	Perez EA, Breast Cancer Res Treat 2010
Capecitabine	III (pooled analysis)	208	Prior A, T or resist to A, T	15	1.7	--	Perez EA, Breast Cancer Res Treat 2010
Eribulin	III (pooled analysis)	199	≥1 prior chemo	11	2.8	12.4	Pivot X, Ann Oncol 2016

Includes breast cancer drugs with data from Phase II/III trials with minimum mTNBC sample size ≥60; ORR and PFS data

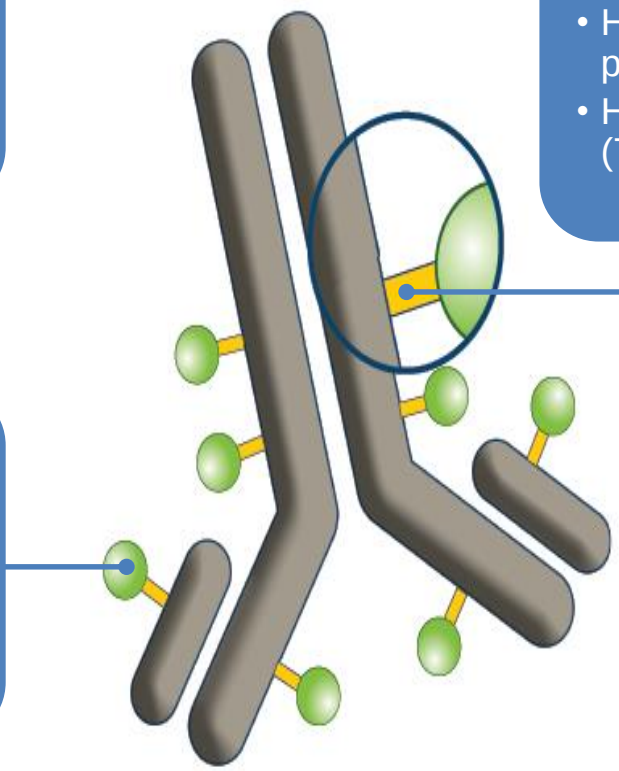
Sacituzumab Govitecan Antibody-Drug Conjugate (ADC)

Humanized anti-Trop-2 antibody

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

Linker for SN-38

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



SN-38 payload

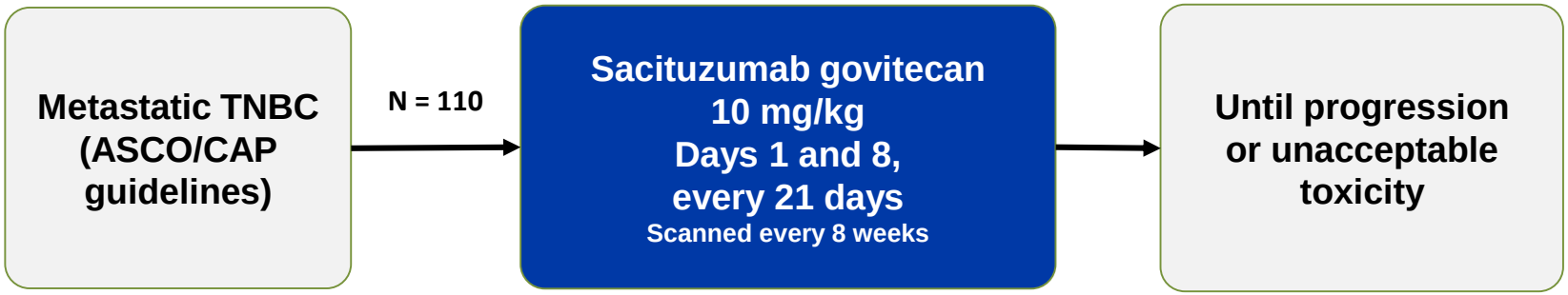
- SN-38 more potent than parent compound, irinotecan
- ADC delivers up to 136-fold more SN-38 than irinotecan *in vivo*

Clinical Trial Experience

- Preliminary results in 69 patients with mTNBC showed an objective response rate of 30%, which was published earlier this year in the *Journal of Clinical Oncology*[1]
- In 2016, sacituzumab govitecan was awarded breakthrough therapy designation by the FDA, and enrollment was resumed in a more defined population in ≥3rd-line setting
- 110 mTNBC patients were treated with sacituzumab govitecan 10 mg/kg on days 1 and 8 every 21 days until progression or unacceptable toxicity
  - Includes 53 of 69 patients who received ≥2 prior therapies from previously reported study

1. Bardia et al. *J Clin Oncol.* 2017;35:2141-2148.

Single-Arm, Open-Label Study Design



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

Demographics and Patient Characteristics

	N = 110
Female/male, n	109/1
Median age, years (range)	55 (31-81)
Race	
White	75%
Black	7%
Asian	4%
Other	4%
Not specified	10%
ECOG performance status	
0	30%
1	70%
Median time from metastatic disease to study entry, years (range)	1.5 (0.2-9.8)
≥3rd line for metastatic disease	100%
3rd line*	41%
≥4th line	59%

	N = 110
Prior chemotherapy drugs**	
Taxanes	98%
Anthracyclines	86%
Cyclophosphamide	85%
Platinum agents	75%
Gemcitabine	57%
Fluoropyrimidine agents	51%
Eribulin	45%
Vinorelbine	15%
Prior checkpoint inhibitors	17%
Sites of metastatic disease at study entry***	
Lung/mediastinum	58%
Liver	46%
Bone	45%
Chest wall	24%

*2 patients who progressed within 12 months of (neo)adjuvant therapy only received one line in the metastatic setting;
**Used in >10% patients; ***Metastatic sites reported in >20% patients

Adverse Events (Regardless of Causality)

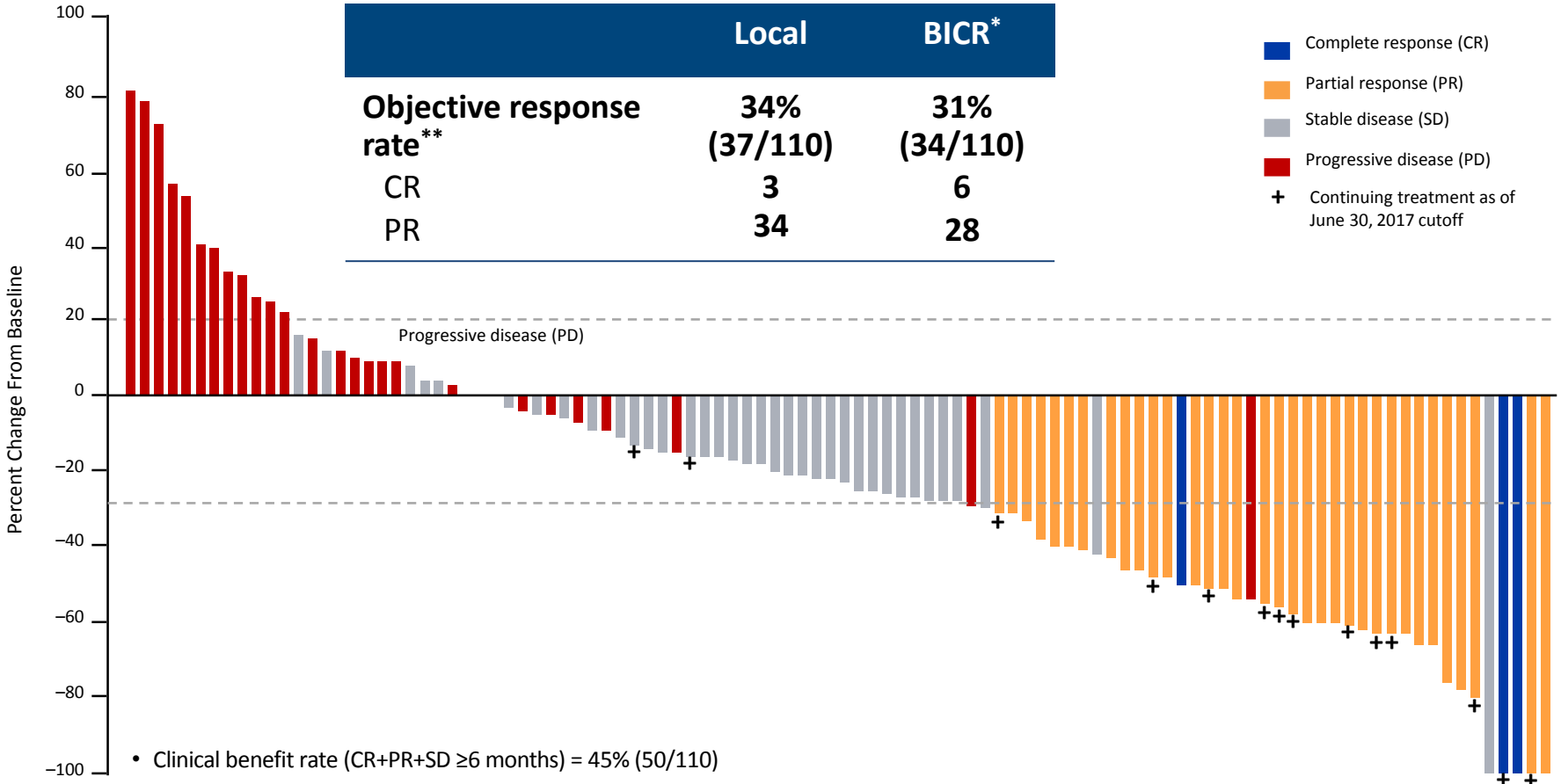
- AEs were managed with supportive medication or dose modifications
  - 25% of patients had dose modifications, predominantly to 7.5 mg/kg
- Two patients (1.8%) discontinued due to AEs (grade 3 transient infusion reaction/ grade 2 fatigue)
- There were no treatment-related deaths

Body system	Adverse event (AE)	All grades	Grade 3 or 4
Hematologic	Neutropenia	63%	41%
	Febrile neutropenia	8%	7%
	Anemia	52%	10%
	Leukopenia	24%	14%
Gastrointestinal	Nausea	63%	5%
	Diarrhea	56%	8%
	Vomiting	46%	5%
	Constipation	32%	1%
Other	Fatigue	50%	7%
	Alopecia	36%	NA
	Decreased appetite	30%	0%
	Hyperglycemia	23%	4%
	Hypomagnesemia	21%	1%
	Hypophosphatemia	15%	8%

Includes all events >20% (all grades) or >5% (grade 3 or 4); NA = not applicable.

Tumor Response to Treatment

	Local	BICR*
Objective response rate**	**34% (37/110)**	**31% (34/110)**
CR	**3**	**6**
PR	**34**	**28**



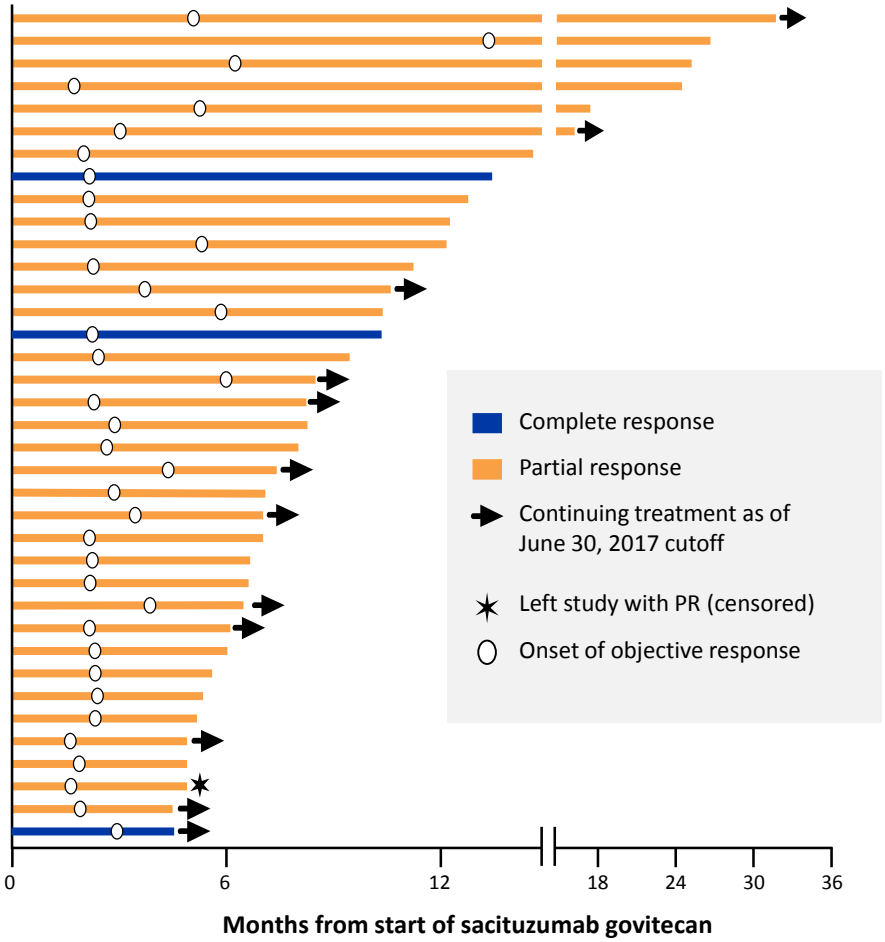
- Clinical benefit rate (CR+PR+SD ≥6 months) = 45% (50/110)
- 74% (75/102) of patients with at least one CT response assessment had reduction of target lesions (sum of diameters)***
- 102 patients had ≥1 scheduled CT response assessment. 8 patients withdrew prior to assessment (4 PD, 4 MRI brain metastases)

*Patients with at least 20% tumor reduction (n = 56) were reviewed; **Confirmed objective response rate per RECIST; ***Waterfall is based on local assessment; BICR = Blinded Independent Adjudicated Central Review.

Response Onset and Durability (n = 37)

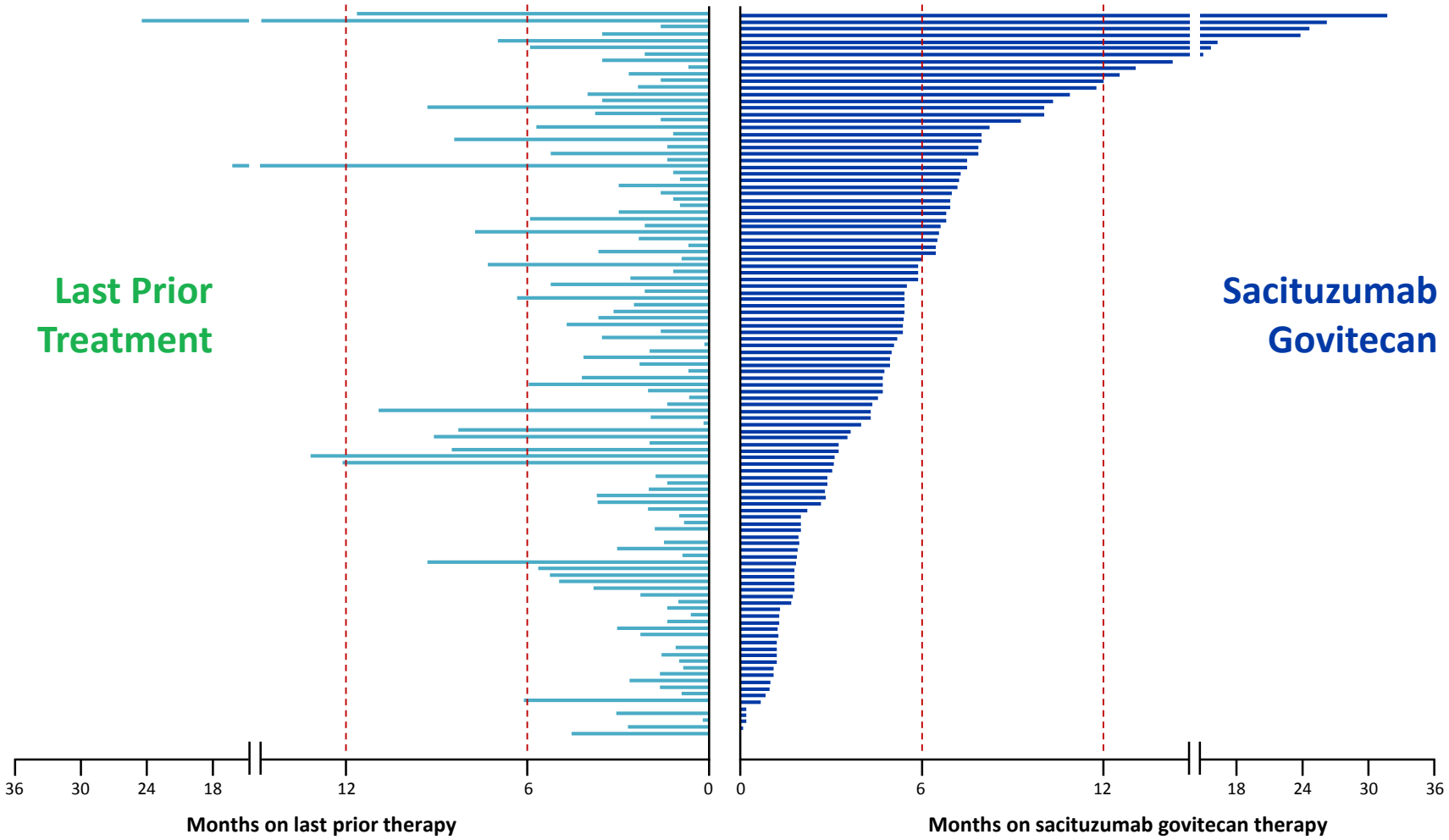
	Local	BICR*
Median duration of response, months (95% CI)	**7.6** (4.8, 11.3)	**9.1** (4.1, 14.3)

- Median time to onset of response: 2.0 months (range: 1.5-13.4)
- 9 long-term responders were progression free for >1 year from start of treatment (4 responders >2 years)
- 12 responders were still receiving sacituzumab govitecan at time of data cutoff, June 30, 2017



*Patients with at least 20% tumor reduction (n = 56) were reviewed; BICR = Blinded Independent Adjudicated Central Review. 1 patient left study with PR due to clinical progression.

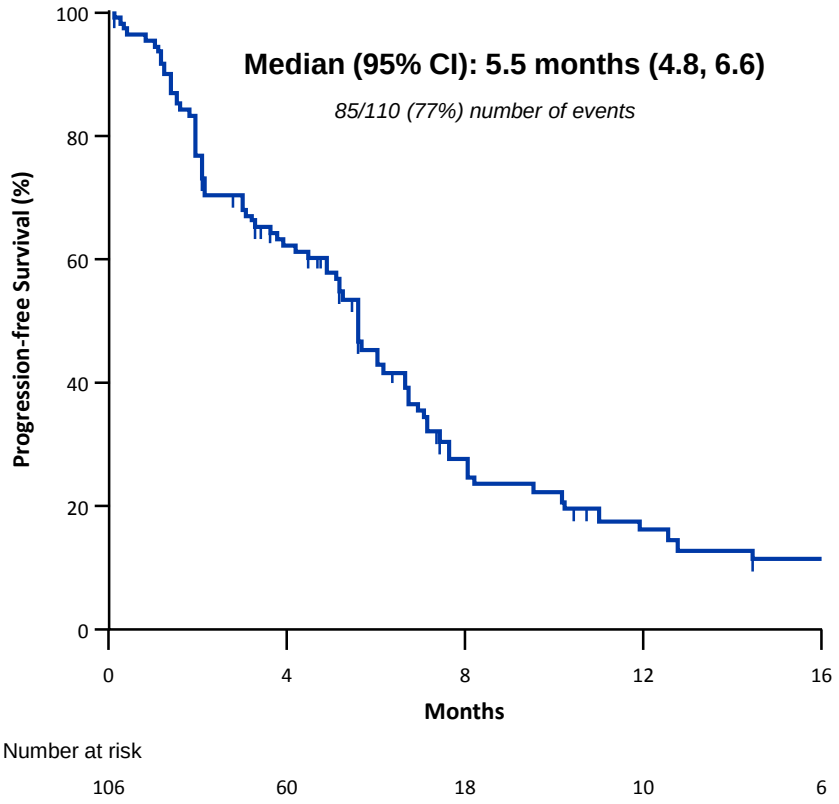
Time on Treatment for All Patients (N = 110)



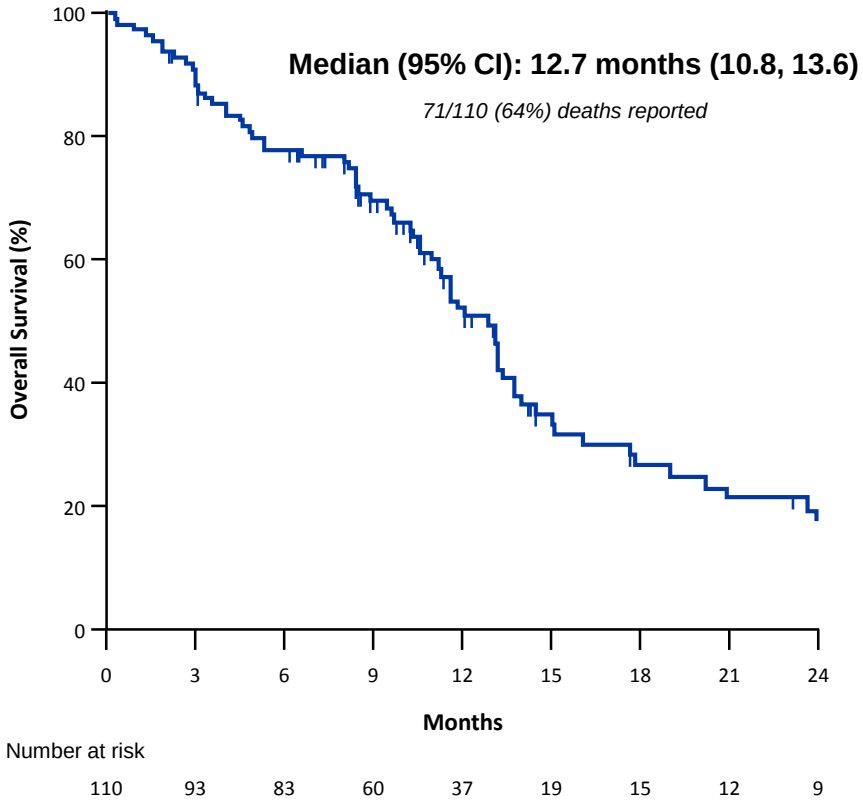
Last prior time on treatment calculated as last dose date – first dose date. Sacituzumab govitecan time on treatment calculated as (date off study or data cut off date) – first dose date. If more than 1 agent is given in the last prior regimen, the time of treatment is taken as the longest time for any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

Progression-Free and Overall Survival

Progression-free survival



Overall survival



Based on local assessment

Response to Sacituzumab Govitecan in Subgroups

	ORR, % (n/N)
Overall	34% (37/110)
Age	
<55	37% (20/54)
≥55	30% (17/56)
Onset of metastatic disease	
<1.5 years	29% (16/55)
≥1.5 years	38% (21/55)
Prior regimens for metastatic disease	
3rd line	36% (16/45)
≥4th line	32% (21/65)
Visceral involvement at study entry	
Yes	30% (26/88)
No	50% (11/22)
Trop-2 IHC (n = 62)	
0-1 (weak, absent)	0% (0/5)
2-3 (moderate, strong)	40% (23/57)
No Trop-2 IHC	29% (14/48)
Prior checkpoint inhibitors	47% (9/19)

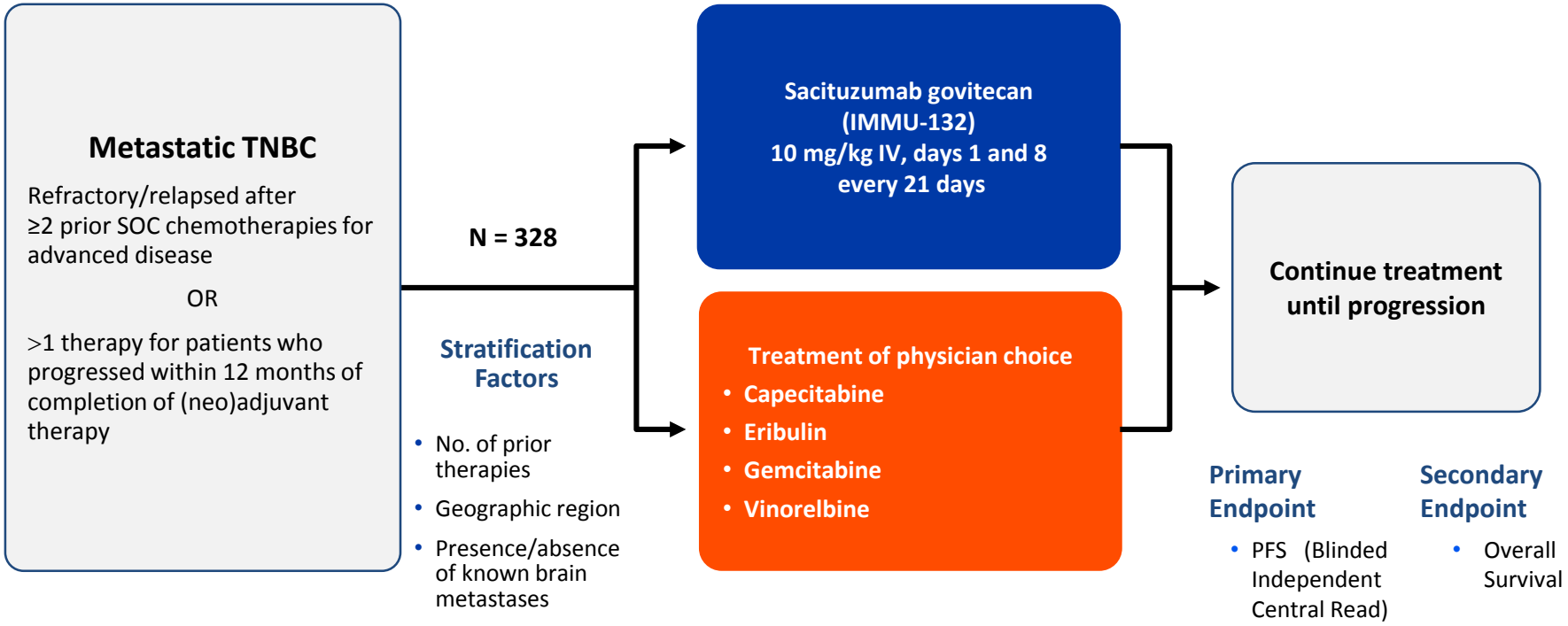
Based on local assessment

Conclusions

- Sacituzumab govitecan as a single agent demonstrated significant clinical activity as ≥3rd-line therapy in patients with relapsed/refractory mTNBC
  - Confirmed ORR*: 34%
  - Clinical benefit rate (6 months)*: 45%
  - The responses were durable (estimated median duration of response was 7.6 months based on local assessment)
  - All data consistent with central review
- Results suggest that sacituzumab govitecan has a predictable and manageable safety profile
- Additional studies including rational combinations are currently being evaluated for mTNBC and other breast cancer subsets

*Based on local assessment

ASCENT Phase III Trial is Recruiting



- Now enrolling in the US; European enrollment to begin in first half of 2018
- Clinical trials number: NCT02574455
- Presented at: New Agents and Strategies; December 7, 2017; 5:00-7:00 PM, Hall 1 (abstract# 733), SABCS

Long-term Follow-up of CALGB 40502/NCCTG N063H (Alliance): A Randomized Phase III Trial of Weekly Paclitaxel Compared to Weekly Nanoparticle Albumin Bound Nab-Paclitaxel or Ixabepilone +/- Bevacizumab as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer

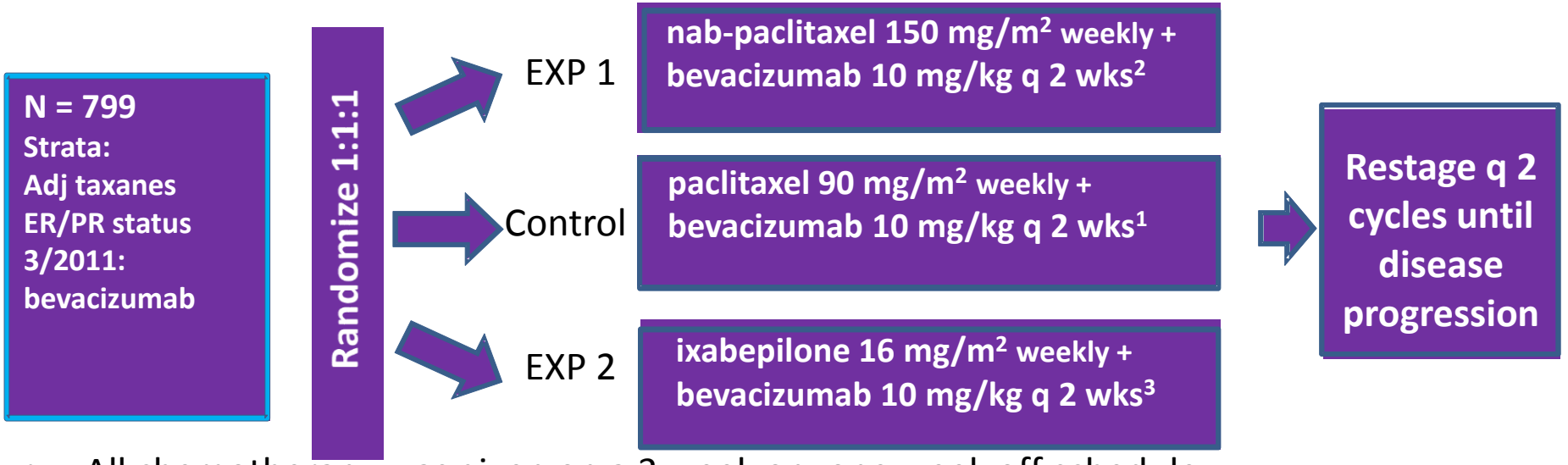
HS Rugo. WT Barry, A Moreno-Aspitia, A Lyss, L Huebner, EL Mayer, M Naughton, RM Layman, LA Carey, RA Somer, D Toppmeyer, M Velasco, EA Perez, CA Hudis, E Winer

Support: U10CA180820, U10CA180821, U10CA180882, U10CA180888
ClinicalTrials.gov Identifier: NCT00785291

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

CALGB 40502 - NCCTG N063H - CTSU 40502

An Open Label Phase III Trial of First-line Therapy for Locally Recurrent or Metastatic Breast Cancer

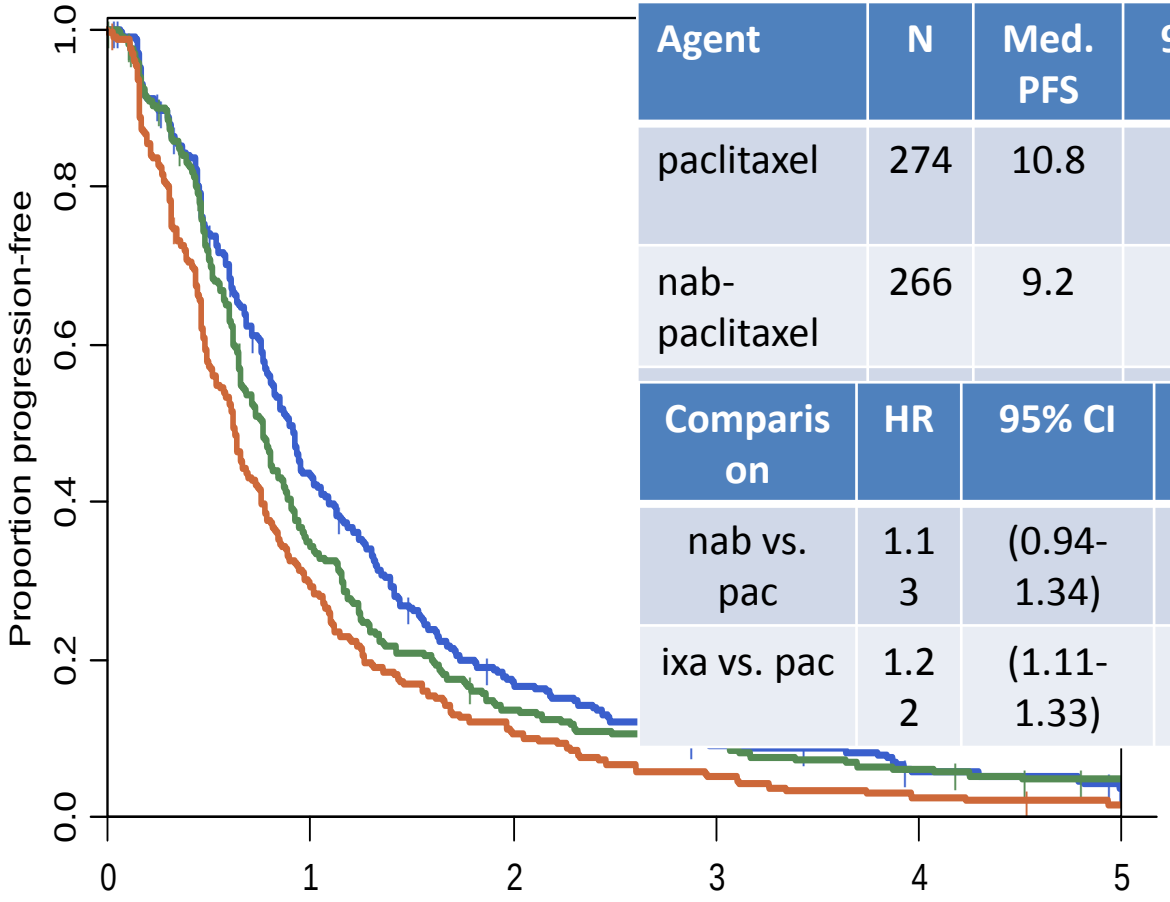


- All chemotherapy was given on a 3 week on, one week off schedule
- Patients could discontinue chemotherapy and continue bevacizumab alone after 6 cycles if stable or responding disease
  - 98% of patients received bevacizumab
- Primary objective: to compare PFS between EXP 1 or EXP 2 and paclitaxel
- 98% of patients received bevacizumab

1. Miller et al, NEJM, 2007 2. Gradishar et al, JCO, 20093. 3. Dickson et al, Proc ASCO 2006.

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Updated Progression Free Survival



Agent	N	Med. PFS	95% CI
paclitaxel	274	10.8	(9.6-12.0)
nab-paclitaxel	266	9.2	(7.9-10.1)

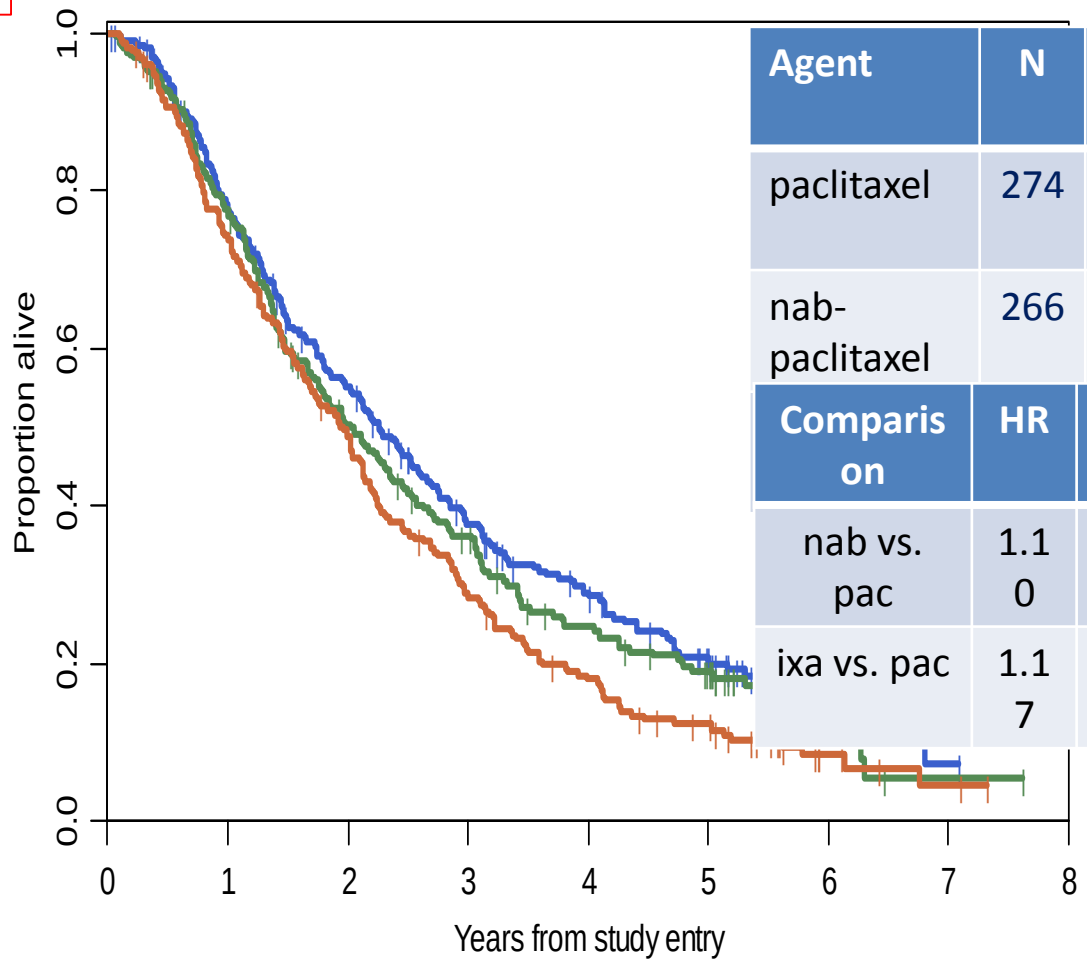
Comparison	HR	95% CI	P-value
nab vs. pac	1.13	(0.94-1.34)	0.16
ixa vs. pac	1.22	(1.11-1.33)	<0.0001

Number at risk

Paclitaxel	274	114	43	22	12	6
Nab-paclitaxel	266	88	34	24	15	9
Ixabepilone	241	70	25	12	6	3

Updated Overall Survival

* Median follow-up is 5.5 years



Agent	N	Med. OS	95% CI
paclitaxel	274	27.1	(23.5-31.8)
nab-paclitaxel	266	24.2	(21.0-28.3)

Comparison	HR	95% CI	P-value
nab vs. pac	1.10	(0.91-1.33)	0.33
ixa vs. pac	1.17	(1.06-1.29)	0.0024

Number at risk

Paclitaxel	274	206	141	90	63	37	7	1	0
Nab-paclitaxel	266	198	123	86	55	39	5	1	0
Ixabepilone	241	176	113	65	39	24	6	2	0

Multivariate Model for PFS

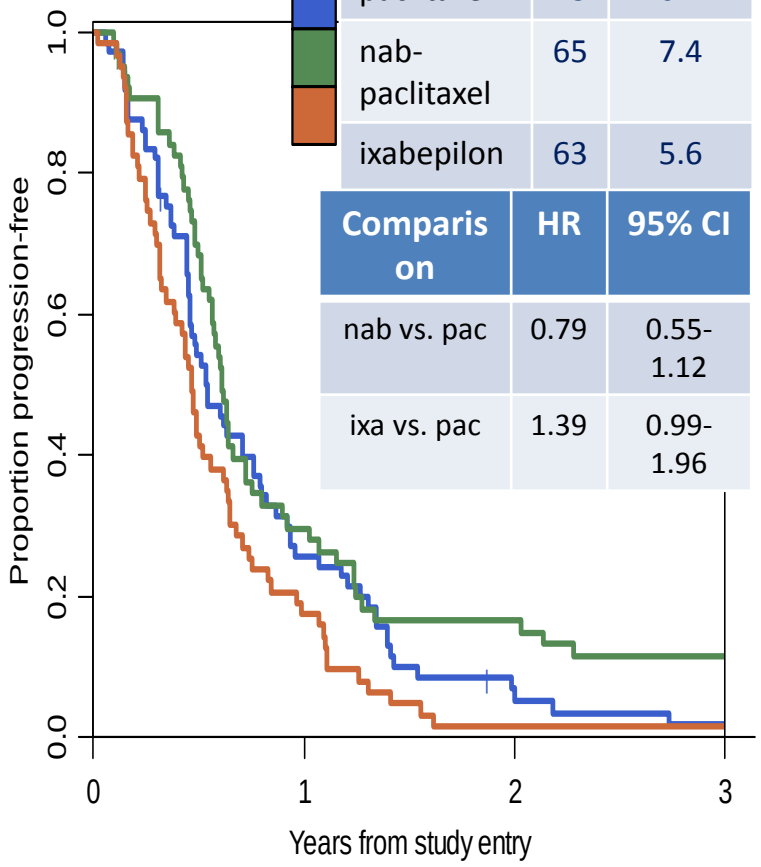
	Comparison of nab-paclitaxel to paclitaxel			Comparison of ixabepilone to paclitaxel		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Univariate model						
Treatment Arm (Exp : Ctrl)	1.13	0.94-1.34	0.16	1.22	1.11-1.33	<0.0001
Multivariate model [1, 2]						
Treatment Arm in HR+ (Exp : Ctrl)	1.35	1.09-1.66	0.0047	1.22	1.10-1.36	0.0003
Treatment Arm in HR- (Exp : Ctrl)	0.71	0.51-1.00	0.052	1.22	1.02-1.45	0.030
Prior taxane (No : Yes)	0.64	0.51-0.79	<0.0001	0.71	0.57-0.88	0.012
Disease-free interval (>2yr : ≤2yr)	0.97	0.88 – 1.06	0.46	0.97	0.88-1.07	0.49
Visceral metastases (Any : None)	1.46	1.17-1.82	0.0010	1.21	0.95-1.54	0.12

Progression Free Survival: TN and HR+

Triple Negative (n=201)

Agent	N	PFS
paclitaxel	73	6.4
nab-paclitaxel	65	7.4
ixabepilon	63	5.6

Comparison	HR	95% CI
nab vs. pac	0.79	0.55-1.12
ixa vs. pac	1.39	0.99-1.96



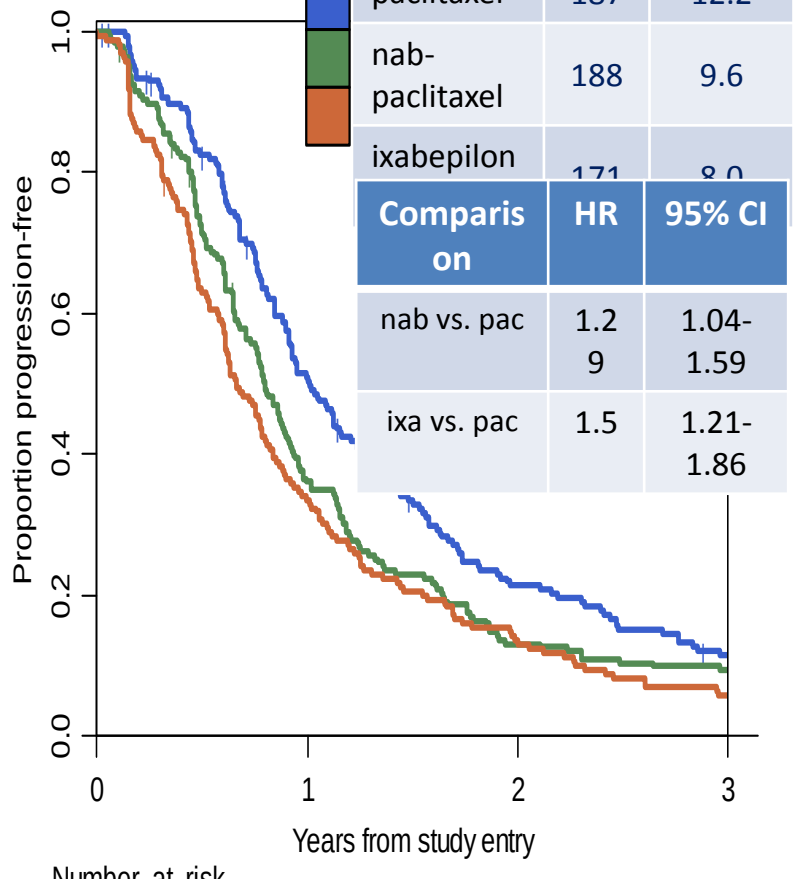
Number at risk

73	18	4	1
65	18	10	7
63	11	1	1

HR positive / HER2- (n=546)

Agent	N	PFS
paclitaxel	187	12.2
nab-paclitaxel	188	9.6
ixabepilon	171	8.0

Comparison	HR	95% CI
nab vs. pac	1.29	1.04-1.59
ixa vs. pac	1.5	1.21-1.86



Number at risk

187	91	37	19
188	66	24	17
171	57	22	10

Multivariate Model for Overall Survival

	Comparison of nab-paclitaxel to paclitaxel			Comparison of ixabepilone to paclitaxel		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Univariate model						
Treatment Arm (Exp : Ctrl)	1.10	0.91-1.33	0.33	1.17	1.06-1.29	0.0024
Multivariate model [1, 2]						
Treatment Arm in HR+ (Exp : Ctrl)	1.30	1.03-1.63	0.027	1.16	1.03-1.30	0.016
Treatment Arm in HR- (Exp : Ctrl)	0.73	0.51-1.04	0.078	1.15	0.95-1.37	0.14
Prior taxane (No : Yes)	0.68	0.54-0.85	0.0009	0.73	0.58-0.92	0.0067
Disease-free interval (>2yr : ≤2yr)	0.95	0.86 – 1.05	0.32	0.96	0.87-1.07	0.47
Visceral metastases (Any : None)	1.71	1.33-2.20	<0.0001	1.61	1.23-2.11	0.0006

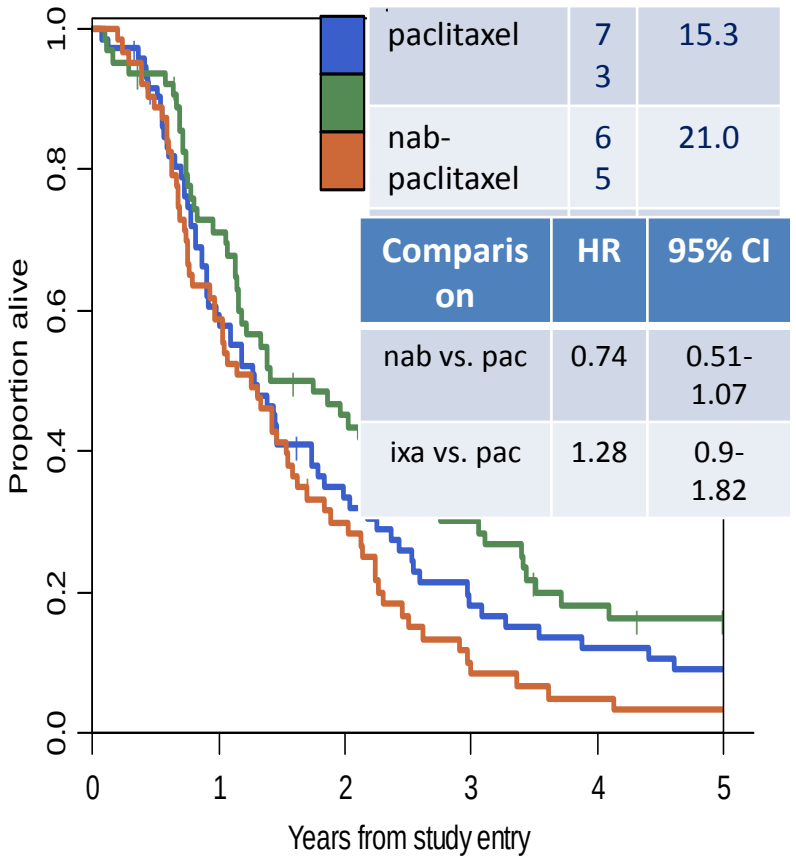
- p-
- Test of interaction with ixabepilone was not significant (p = 0.92)

Overall Survival: TN and HR+

Triple Negative (n=201)

Agent	N	PFS
paclitaxel	73	15.3
nab-paclitaxel	65	21.0

Comparison	HR	95% CI
nab vs. pac	0.74	0.51-1.07
ixa vs. pac	1.28	0.9-1.82



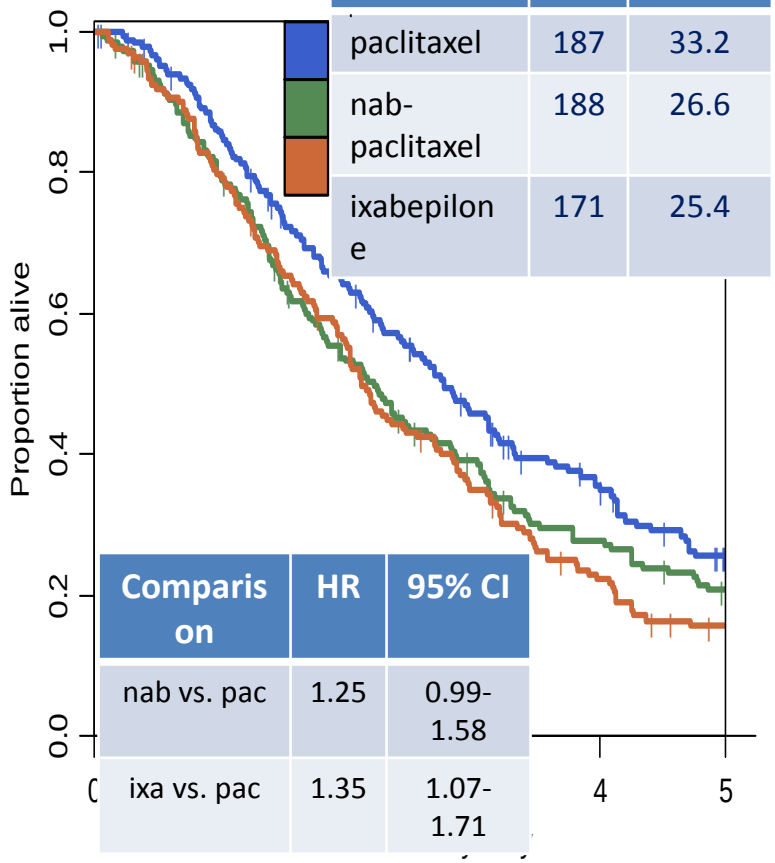
Number at risk

73	41	22	12	8	6
65	44	27	18	10	7
63	37	18	5	3	2

HR Positive (n=546)

Agent	N	PFS
paclitaxel	187	33.2
nab-paclitaxel	188	26.6
ixabepilone	171	25.4

Comparison	HR	95% CI
nab vs. pac	1.25	0.99-1.58
ixa vs. pac	1.35	1.07-1.71



Number at risk

187	154	112	75	52	29
188	145	92	65	45	32
171	134	91	57	34	21

Conclusions

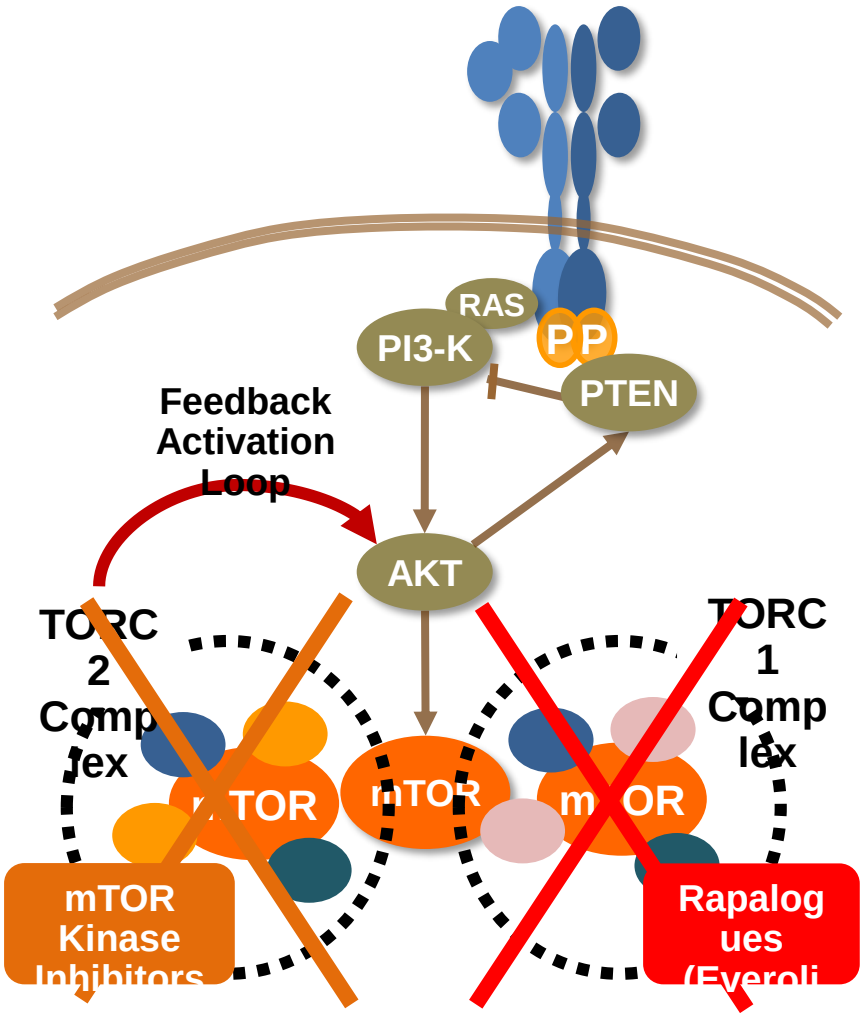
- In this updated analysis in patients with chemotherapy-naive MBC, ixabepilone continued to be inferior to paclitaxel for PFS
  - Now also inferior for OS
- In this *post-hoc* subset analysis, a significant interaction was found between nab-paclitaxel ad paclitaxel with receptor status for PFS
  - In patients with HR+ disease, ixabepilone and nab-paclitaxel were inferior to paclitaxel
  - In patients with TNBC, suggestion of improved PFS and OS with nab-paclitaxel

MANTA – A randomized phase II Study of Fulvestrant in combination with the dual mTOR inhibitor AZD2014 or Everolimus or Fulvestrant alone in ER-positive advanced or metastatic breast cancer.

Peter Schmid[1], Matthias Zaiss[2], Catherine Harper-Wynne[3], Marta Ferreira[4], Sidharth Dubey[5], Stephen Chan[6], Andreas Makris[7], Gia Nemsadze[8], Adrian M. Brunt[9], Sherko Kuemmel[10], Isabel Ruiz[11], Antonia Perelló[12], Anne Kendall[13], Janet Brown[14], Hartmut Kristeleit[15], John Conibear[1], Cristina Saura[16], Julien Grenier[17], Károly Máhr[18], Michael Schenker[19], Sohn Joo Hyuk[20], Lee Keun Seok[21], Shah-Jalal Sarker[1], Aaron Prendergast[1], Carike Coetzee[1], Kelly Mousa[1], Javier Cortes[22]

Background

- Randomised trials have shown a substantial benefit of adding everolimus to ET
- mTORC1 inhibition alone (e.g. with everolimus) can set off a negative feedback mechanism via AKT signaling leading to resistance
- Vistusertib (AZD2014) is a dual inhibitor of both mTORC1 (rapamycin-sensitive) and mTORC2 (rapamycin insensitive)
- Vistusertib has demonstrated a broad range of activity in preclinical ER+ models, showing superior activity to Everolimus in hormone-sensitive and -resistant models



ET = endocrine therapy; ER+ = Estrogen receptor positive

MANTA Study Design

Trial Sponsor: Queen Mary University of London

- ER+, HER2- ABC
- Postmenopausal
- Measurable or evaluable disease
- Disease refractory to AI
  - relapsed on or ≤12 months from adjuvant AI, or
  - progressed on AI in the advanced setting
- Max. 1 line of chemotherapy

R

n=90 → Fulvestrant + Vistusertib (Continuous daily schedule)

n=90 → Fulvestrant + Vistusertib (intermittent schedule; 2d on 5d off)

n=60 → Fulvestrant + Everolimus

n=60 → Fulvestrant

Primary endpoint:

- Investigator-assessed PFS

Secondary endpoints:

- Response rates (ORR)
- Clinical benefit rate (CBR)
- Duration of response
- OS
- Safety

Stratification factors:

- Measurable Disease (vs non-measurable)
- Sensitivity to prior ER (sensitive vs resistant)

- **Fulvestrant: 500 mg i.m. injection on day 1, 15 & 29, and then q28 days**
- **Everolimus: 10 mg orally, once daily, continuous schedule**
- **Vistusertib (continuous): 50 mg orally, twice daily, continuous schedule**
- **Vistusertib (intermittent): 125 mg orally, twice daily, day 1&2 every week**

Sensitivity to prior ET is defined as

- **≥24 months of adjuvant ET before recurrence or**
- **CR or PR or SD for ≥24 weeks with ≥1 ET for MBC**

ET = endocrine therapy; ER = Estrogen Receptor, ABC = advanced breast cancer, AI = Aromatase inhibitor; PR/CR = Partial/Complete response, SD = stable disease, d = days; PFS = Progression-free survival

Patient and Disease Characteristics

		F + V_{cont}	F + V_{int}	F	F + E
N		100	96	66	64
Sensitivity to prior ET, n (%)	Sensitive Resistant	84 (84) 15 (15)	81 (84) 14 (15)	55 (83) 11 (17)	58 (91) 6 (9)
Prior lines of therapy for ABC, n (%)	None 1 ≥2	38 (38) 30 (30) 33 (33)	41 (43) 29 (31) 25 (26)	24 (36) 25 (38) 17 (26)	24 (38) 20 (31) 20 (31)
Number of prior ET for ABC	None 1 ≥2	44 (44) 45 (45) 12 (12)	45 (47) 36 (38) 14 (15)	29 (44) 27 (41) 10 (15)	27 (42) 25 (39) 12 (19)
Prior (neo)adjuvant chemotherapy, n (%)	Yes No	63 (62) 38 (38)	56 (59) 39 (41)	47 (71) 19 (29)	38 (59) 26 (41)
Prior metastatic chemotherapy, n (%)	Yes No	24 (24) 77 (76)	24 (25) 71 (75)	13 (20) 53 (80)	14 (22) 50 (78)

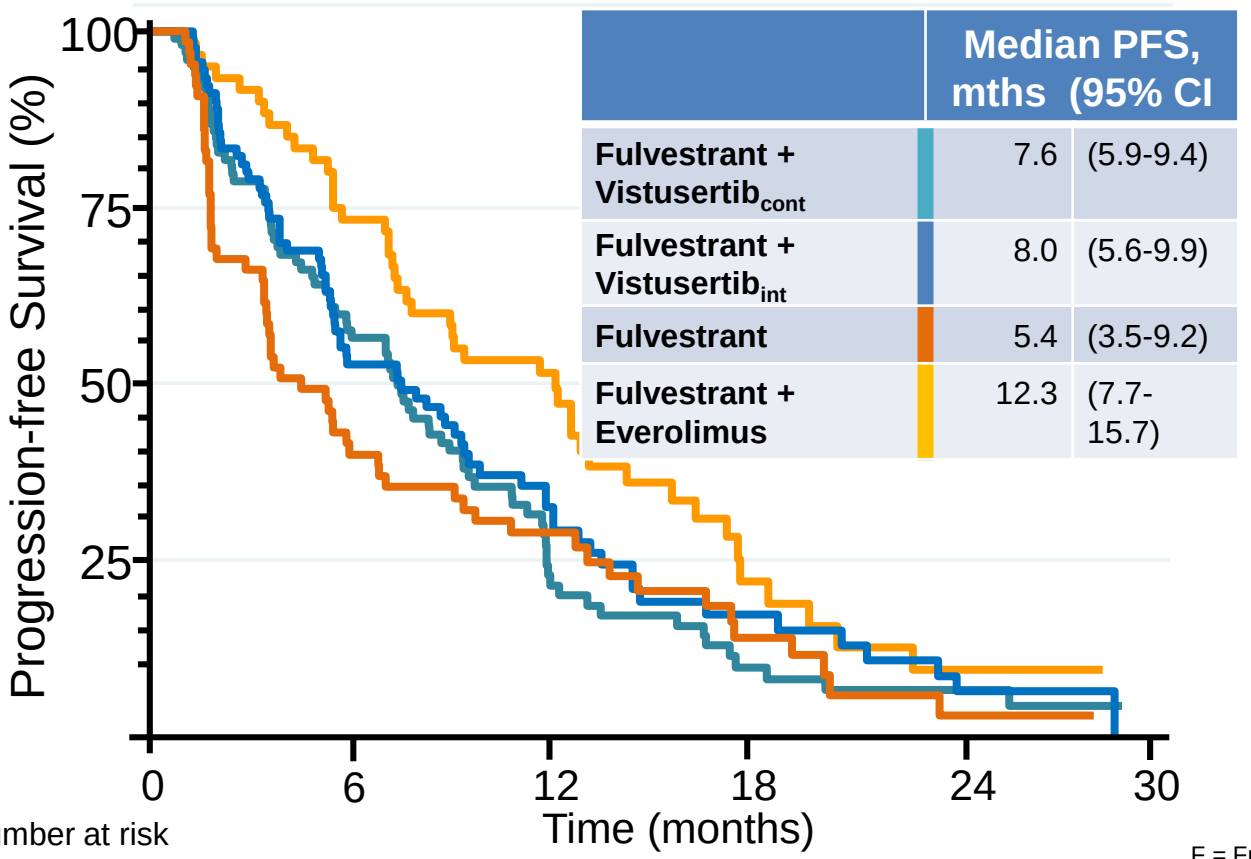
F = Fulvestrant; F+E = Everolimus; F+V(cont) = Vistusertib, continuous daily schedule; F+V(int) = Vistusertib, intermittent schedule (2 days on, 5 days off);
ABC = advanced breast cancer; ET = endocrine therapy; ITT = intent-to-treat
* The denominator for percentages in this row is the number of patients with ≥1 prior lines of therapy for ABC

Safety

	F + V_{cont}		F + V_{int}		F		F + E	
	All grades	G3/4	All grades	G3/4	All grades	G3/4	All grades	G3/4
Asthenia (%)	34.8	2.2	45.7	5.4	16.1	0	53.3	3.3
Nausea (%)	31.5	0	68.5	3.3	12.5	0	26.7	0
Rash (%)	54.3	20.7	22.8	4.3	0	0	50.0	5.0
Stomatitis (%)	40.2	13.0	29.3	4.3	0	0	60.0	11.7
Diarrhoea (%)	25.0	2.2	35.9	5.4	5.4	0	31.7	1.7
Decreased appetite (%)	16.3	0	32.6	0	5.4	0	30.0	1.7
Vomiting (%)	12.0	1.1	40.2	5.4	0	0	11.7	0
Headache (%)	9.8	1.1	22.8	2.2	12.5	0	18.3	0
Pruritus (%)	23.9	2.2	12.0	3.3	1.8	0	16.7	0
Musculoskeletal pain (%)	9.8	1.1	16.3	2.2	10.7	0	13.3	0
Dry mouth (%)	13.0	0	12.0	0	3.6	0	20.0	0
Skin injury (%)	14.1	1.1	9.8	0	0	0	25.0	0
Infection (%)	15.2	5.4	10.9	1.1	3.6	0	16.7	6.7
Administration site reaction (%)	12.0	1.1	10.9	0	8.9	0	15.0	0
Oral pain (%)	10.9	3.3	12.0	0	0	0	21.7	0
Dysgeusia (%)	5.4	0	16.3	0	3.6	0	18.3	0

Events occurring in >10% of patients

Primary Endpoint: PFS (ITT Population)

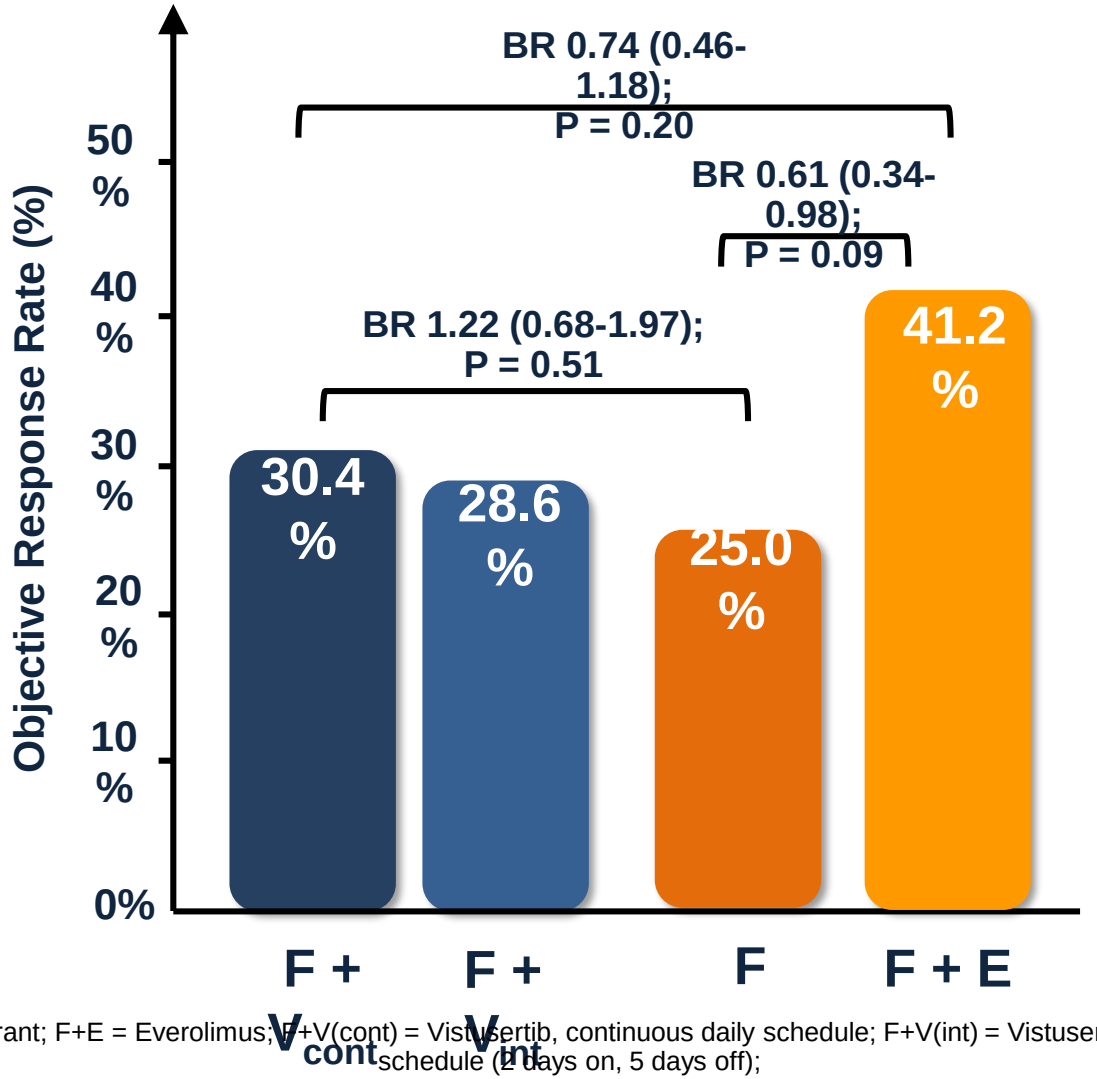


	Median PFS, mths (95% CI	
Fulvestrant + Vistusertib$_{cont}$	7.6	(5.9-9.4)
Fulvestrant + Vistusertib$_{int}$	8.0	(5.6-9.9)
Fulvestrant	5.4	(3.5-9.2)
Fulvestrant + Everolimus	12.3	(7.7-15.7)

CI = confidence interval;
ITT = intent-to-treat; mths = months;
PFS = progression-free survival

F = Fulvestrant; F+E = Everolimus;
F+V(cont) = Vistusertib, continuous schedule;
F+V(int) = Vistusertib, intermittent schedule (2 days on, 5 days off);

Objective Response Rates



F = Fulvestrant; F+E = Everolimus; F+V(cont) = Vistusertib, continuous daily schedule; F+V(int) = Vistusertib, intermittent schedule (2 days on, 5 days off);
BR = benefit ratio; P=2-sided p-value; PP = per-protocol

Summary and Conclusions

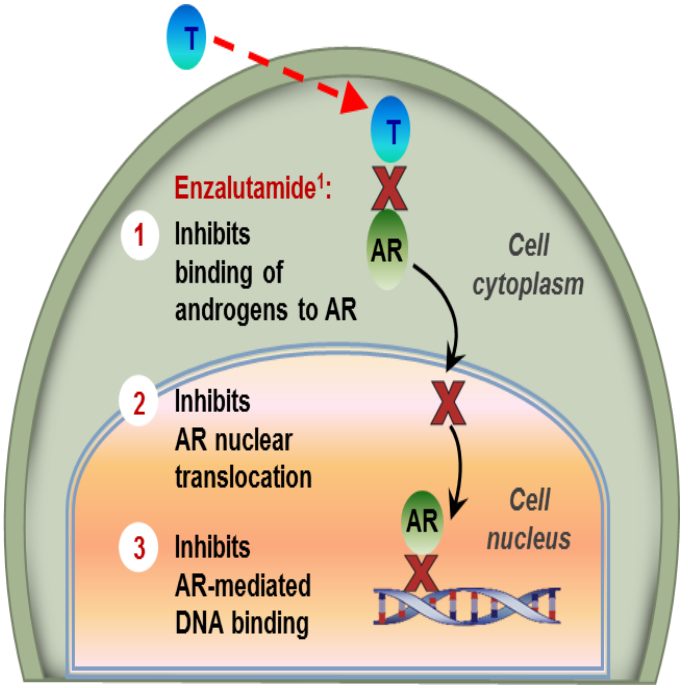
- The combination of Everolimus + Fulvestrant demonstrated improved PFS compared to Vistusertib + Fulvestrant (median PFS 12.3 vs 7.6 mths, HR 0.63) and to Fulvestrant (median PFS 12.3 vs 5.4 mths, HR 0.63)
- In the ITT population, the addition of Vistusertib to Fulvestrant failed to show a significant PFS improvement (median PFS 7.6 vs 5.4 mths, HR 0.88)
- Continuous daily and intermittent high-dose scheduling of Vistusertib resulted in similar anti-tumour activity

Results From a Randomized Placebo-controlled Phase 2 Trial Evaluating Exemestane ± Enzalutamide in Patients With Hormone Receptor–positive Breast Cancer

Ian Krop, Vandana Abramson, Marco Colleoni, Tiffany Traina, Frankie Holmes, Laura Estevez, Lowell Hart, Ahmad Awada, Claudio Zamagni, Patrick Morris, Lee Schwartzberg, Stephen Chan, Duncan Wheatley, Ayca Gucalp, Laura Biganzoli, Joyce Steinberg, Luca Gianni, Maureen Trudeau, Iulia Cristina Tudor, Denka Markova, Elly Barry, Jamal Tarazi, Eric Winer, Denise A. Yardley

Background

- Enzalutamide (ENZA) is a potent inhibitor of androgen receptor (AR) signaling approved to treat men with metastatic castration-resistant prostate cancer[1,2]
- ENZA demonstrated clinical activity and was well tolerated in patients with advanced AR-positive triple-negative breast cancer[3]
- In breast cancer, the AR is expressed in >75% of hormone receptor–positive (HR+) tumors[4,5]
- AR signaling has been associated with resistance to endocrine therapy (ET)[6]
- Aromatase inhibitors (AIs) divert estrogen precursors to androgens[7,8]

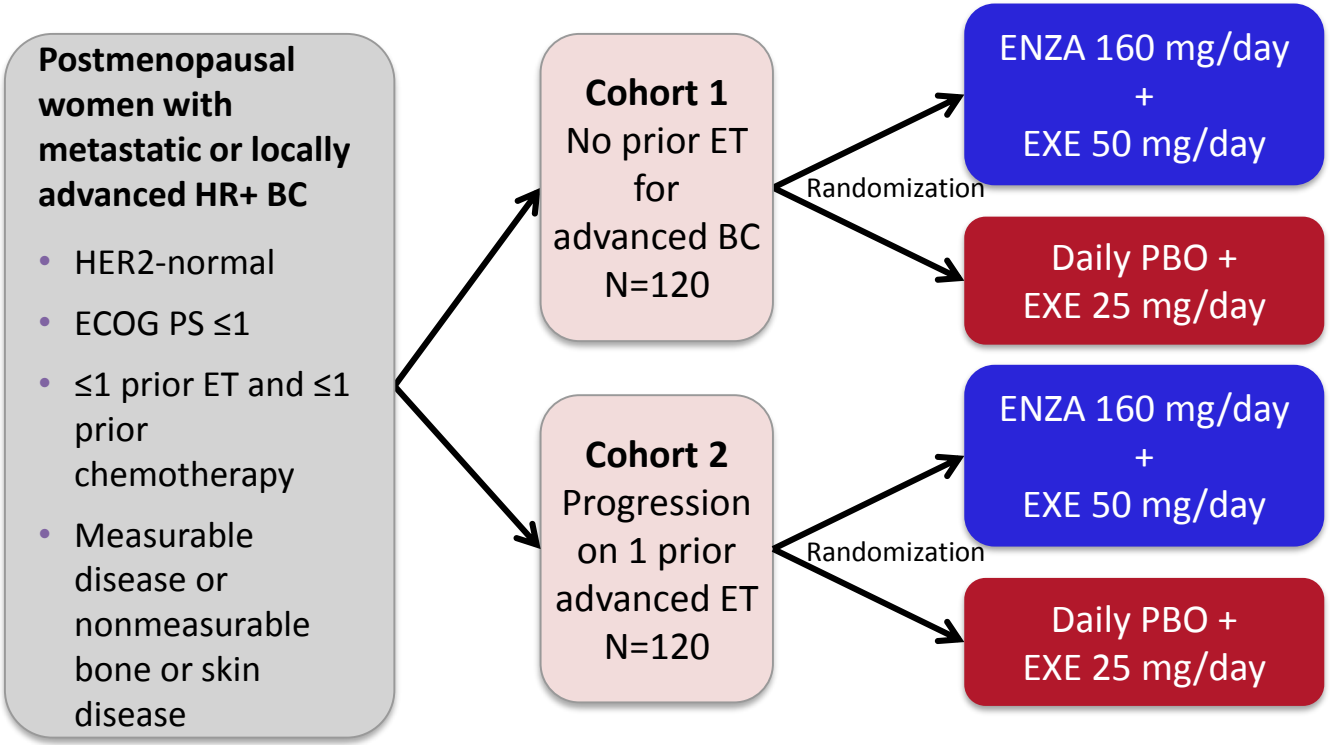


- In preclinical models, ENZA blocked both estrogen- and androgen-mediated growth of HR+ cells[9]
- In a phase 1 drug-drug interaction study of ET + ENZA in breast cancer, doubling the dose of exemestane (EXE) to 50 mg was necessary to restore exposure observed with 25 mg[7]

1. Scher HI et al. *N Engl J Med*. 2012;367:1187-1197; 2. Beer TM et al. *N Engl J Med*. 2014;371:424-433; 3. Traina TA et al. *J Clin Oncol*. In Press; 4. Collins LC et al. *Mod Pathol*. 2011;24:924-931; 5. Loibl S et al. *Breast Cancer Res Treat*. 2011;130:477-487; 6. Cochrane D et al. *Breast Cancer Res*. 2014;16:R7; 7. Gallicchio L et al. *Breast Cancer Res Treat*. 2011;130:569-577; 8. Campagnoli C et al. *Breast Cancer Res Treat*. 2013;139:1-11; 9. Schwartzberg LS et al. *Clin Cancer Res*. 2017;23:4046-4054.

Abbreviation: T, testosterone.

Study Design



Primary Endpoints

- PFS in ITT of cohort 1 and cohort 2
- PFS in Bmkr+ subset of cohort 1 and cohort 2

Key Secondary Endpoints

- Safety and tolerability
- Clinical benefit rate (CR, PR, or SD for >24 weeks)
- Objective response rate

- Stratification:
  - For cohort 1: based on prior ET for early disease; if yes, prior AI, and hormone resistance
  - For cohort 2: based on prior AI for advanced disease, hormone resistance
- Patients in the PBO arm progressing on EXE alone had the option to receive open-label treatment with ENZA + EXE

Abbreviations: BC, breast cancer; Bmkr+, biomarker positive; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intent-to-treat; HER2, human epidermal growth factor receptor 2; PBO, placebo; PFS, progression-free survival; PR, partial response; SD, stable disease. www.clinicaltrials.gov (NCT02007512).

Baseline Patient and Disease Characteristics

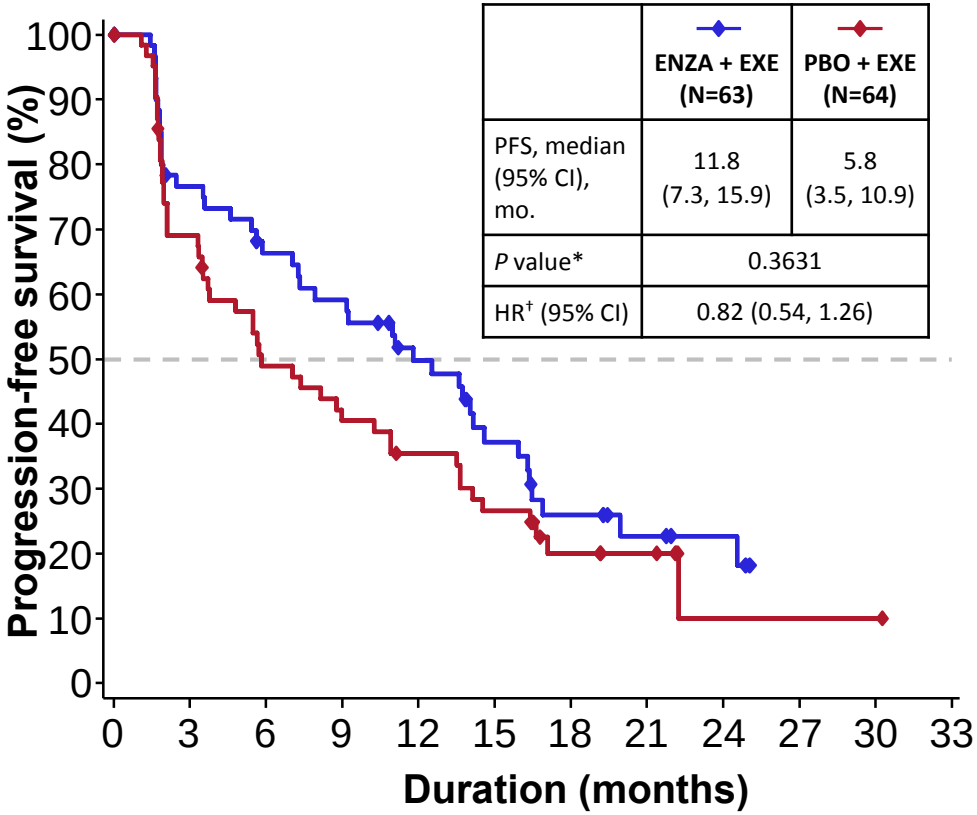
	Cohort 1: No prior ET for aBC		Cohort 2: 1 prior aET	
	ENZA + EXE (N=63)	PBO + EXE (N=64)	ENZA + EXE (N=60)	PBO + EXE (N=60)
Hormone receptor status at initial diagnosis, No. (%)				
ER+ and PgR+	49 (77.8)	45 (70.3)	42 (70.0)	48 (80.0)
ER+ and PgR–	7 (11.1)	10 (15.6)	8 (13.3)	4 (6.7)
ER or PgR unknown	7 (11.1)	7 (10.9)	10 (16.7)	8 (13.3)
Prior therapies for BC, No. (%)				
Neoadjuvant/adjuvant hormonal therapy	41 (65.1)	43 (67.2)	30 (50.0)	38 (63.3)
AI in adjuvant setting	25 (39.7)	31 (48.4)	13 (21.7)	20 (33.3)
Hormone resistant in adjuvant setting*	6 (9.5)	9 (14.1)	7 (11.7)	7 (11.7)
Neoadjuvant/adjuvant chemotherapy	34 (54.0)	38 (59.4)	21 (35.0)	36 (60.0)
Chemotherapy in advanced setting	10 (15.9)	9 (14.1)	14 (23.3)	19 (31.7)
Hormonal therapy in advanced setting	NA	NA	60 (100)	60 (100)
AI in advanced setting	NA	NA	41 (68.3)	40 (66.7)
Hormone resistant in advanced setting†	NA	NA	15 (25.0)	16 (26.7)

*Hormone resistance in adjuvant setting is defined as disease recurrence within 24 months after initiating adjuvant hormone. †Hormone resistance in advanced setting is defined as disease progression within 24 weeks after initiating advanced hormone treatment.

Abbreviations: ER+, estrogen receptor positive; NA, not applicable; PgR+, progesterone receptor positive; PgR–, progesterone receptor negative.

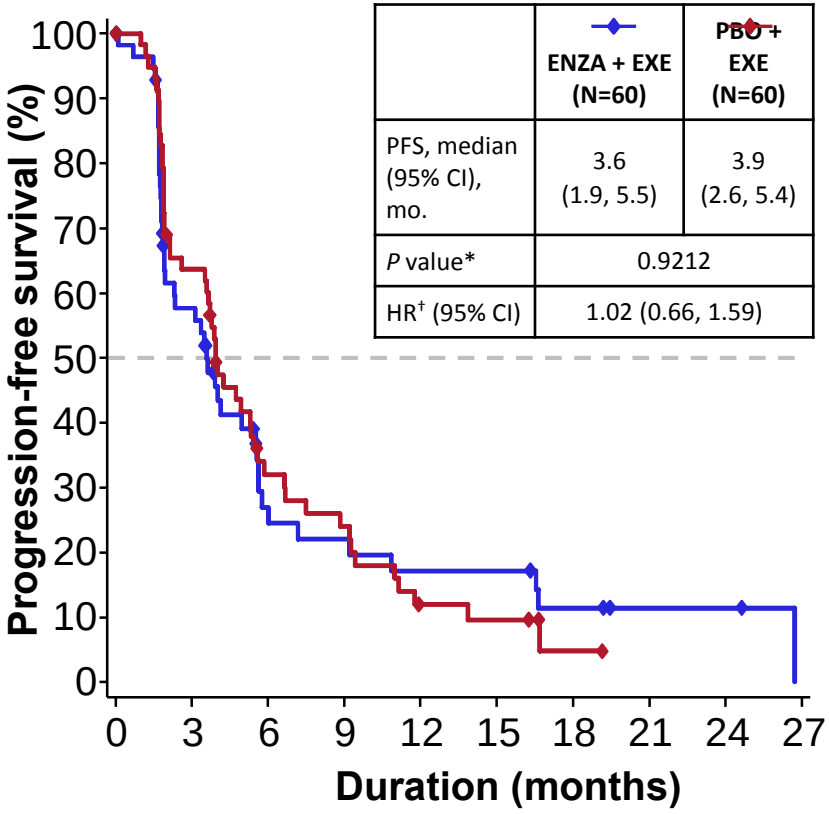
PFS: ITT Population

Cohort 1: No prior ET for aBC



	ENZA + EXE (N=63)	PBO + EXE (N=64)
PFS, median (95% CI), mo.	11.8 (7.3, 15.9)	5.8 (3.5, 10.9)
P value*	0.3631	
HR† (95% CI)	0.82 (0.54, 1.26)	

Cohort 2: 1 prior aET



	ENZA + EXE (N=60)	PBO + EXE (N=60)
PFS, median (95% CI), mo.	3.6 (1.9, 5.5)	3.9 (2.6, 5.4)
P value*	0.9212	
HR† (95% CI)	1.02 (0.66, 1.59)	

*Two-sided stratified log rank test. †Based on stratified Cox regression model relative to placebo with <1 favoring ENZA.
Abbreviations: CI, confidence interval; HR, hazard ratio.

Generation of Potential Predictive Gene Signature

- AR expression by immunohistochemistry (IHC) was examined to predict response to enzalutamide; however, in the first 112 patients enrolled the subset of patients with positive nuclear AR staining was similar to the ITT population and further IHC testing was halted
- A gene signature–based biomarker indicating AR signaling potentially predictive of response to ENZA was previously identified in patients with triple-negative BC[1]
- In a prespecified analysis, using tumor samples from patients enrolled in this study, a gene signature–based biomarker indicating AR signaling predictive of response to ENZA was developed in patients with HR+ BC
  - A training set of RNAseq data from 2/3 of randomized patients was used to develop the biomarker
  - Data from the remaining 1/3 of patients was used to validate the biomarker
  - Patients with Bmkr+ HR+ BC had longer PFS when treated with ENZA in both the training and validation sets (hazard ratios of 0.35 and 0.48 in the training and validation sets, respectively*)

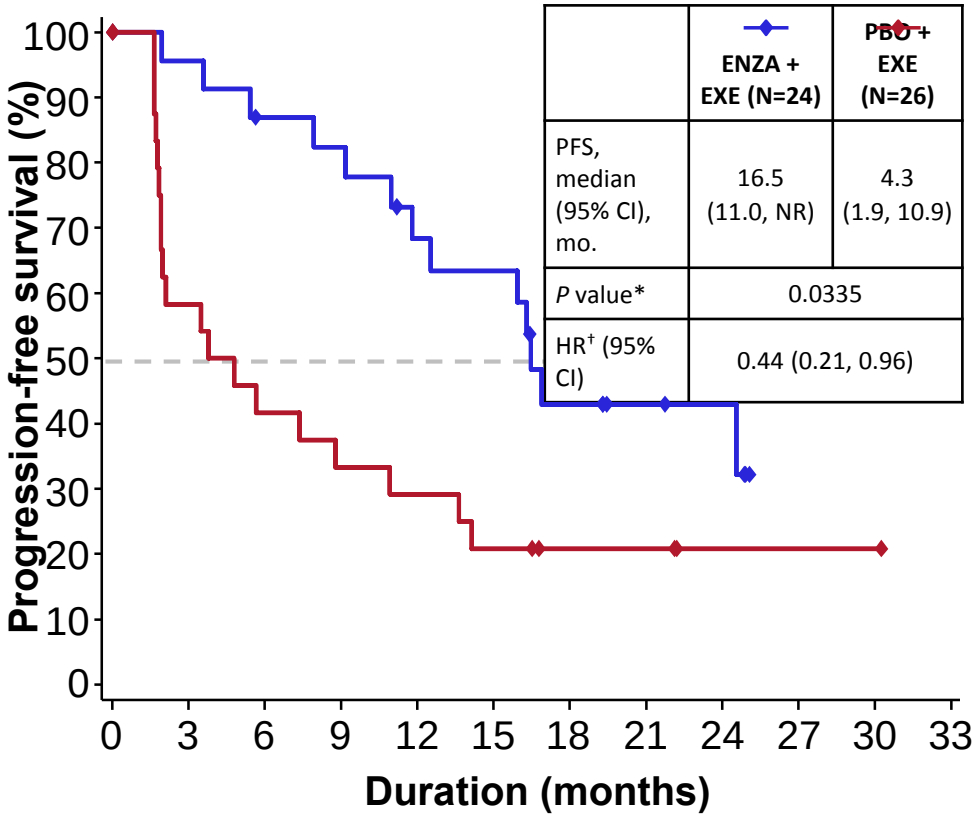
	Cohort 1: No prior ET for aBC		Cohort 2: 1 prior aET	
	ENZA + EXE (N=63†)	PBO + EXE (N=64†)	ENZA + EXE (N=60†)	PBO + EXE (N=60†)
Bmkr+, No. (%)	24 (38.1)	26 (40.6)	15 (25.0)	20 (33.3)
Bmkr–, No. (%)	35 (55.6)	30 (46.9)	35 (58.3)	28 (46.7)

*Cohorts 1 and 2 combined for analysis due to sample size. †12 patients in cohort 1 and 22 patients in cohort 2 were excluded due to lack of evaluable tissue.

1. Traina TA et al. *J Clin Oncol*.

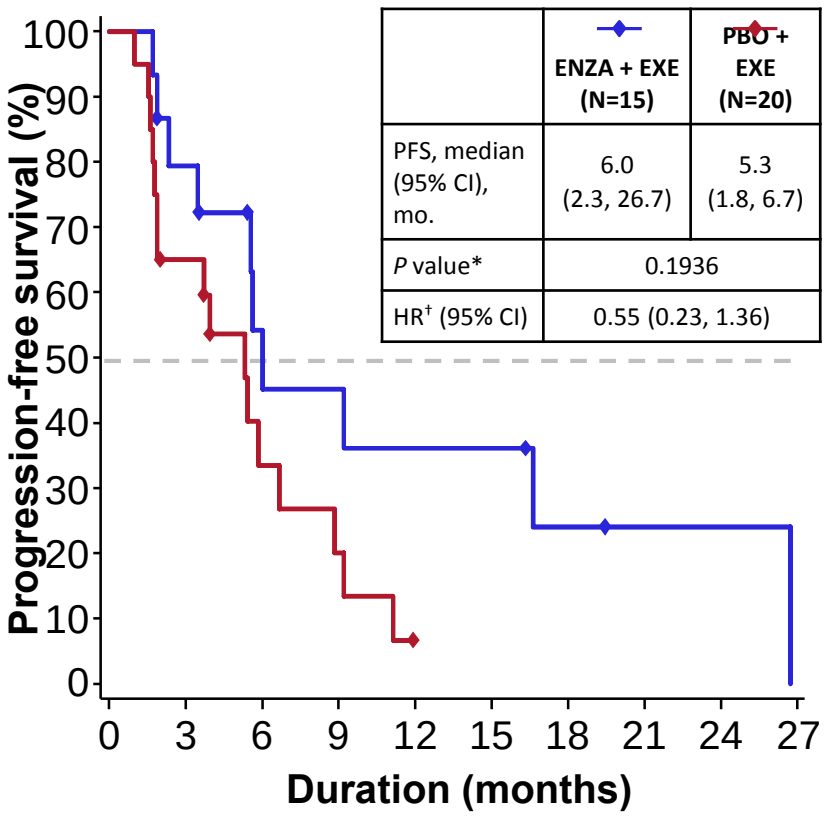
PFS: Bmkr+ Population from the ITT Population

Cohort 1: No prior ET for aBC



	ENZA + EXE (N=24)	PBO + EXE (N=26)
PFS, median (95% CI), mo.	16.5 (11.0, NR)	4.3 (1.9, 10.9)
P value*	0.0335	
HR† (95% CI)	0.44 (0.21, 0.96)	

Cohort 2: 1 prior aET

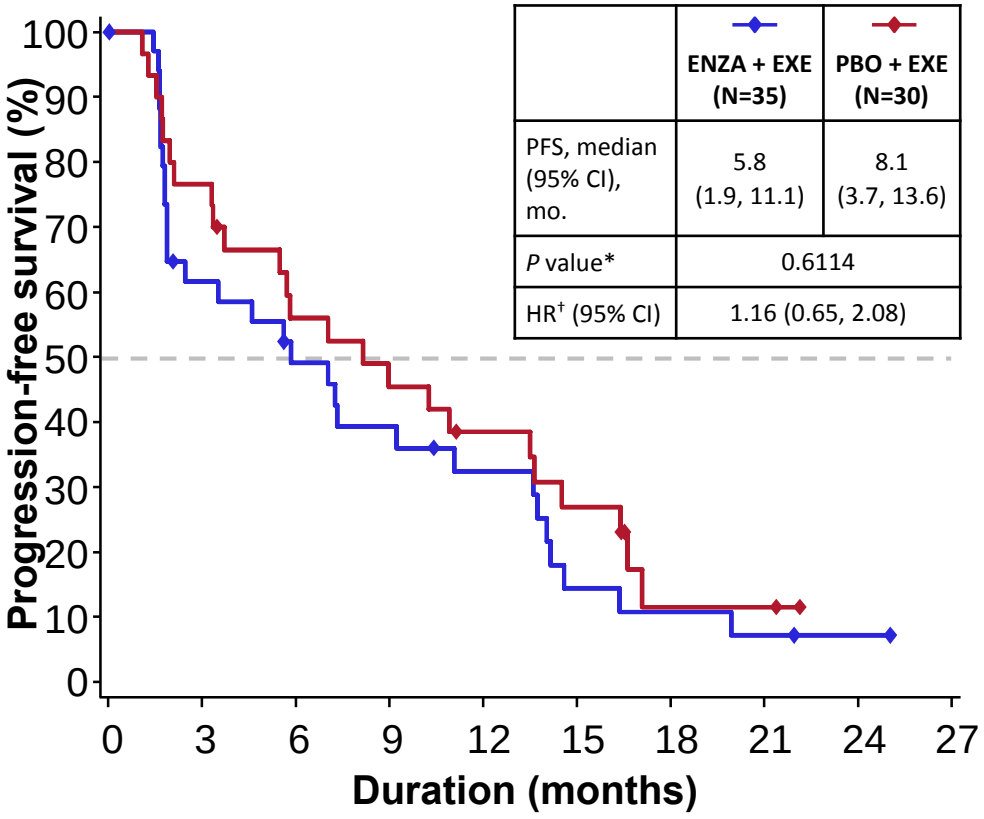


	ENZA + EXE (N=15)	PBO + EXE (N=20)
PFS, median (95% CI), mo.	6.0 (2.3, 26.7)	5.3 (1.8, 6.7)
P value*	0.1936	
HR† (95% CI)	0.55 (0.23, 1.36)	

*Two-sided stratified log rank test. †Based on stratified Cox regression model relative to placebo with <1 favoring ENZA.
Abbreviation: NR, not reached.

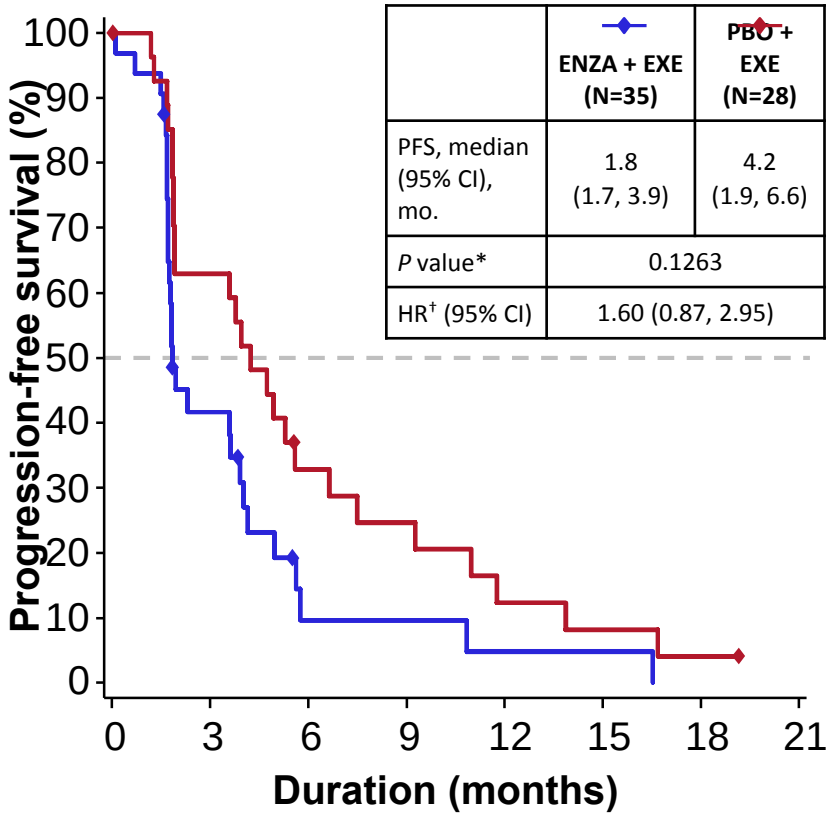
PFS: Bmkr– Population from the ITT Population

Cohort 1: No prior ET for aBC



	ENZA + EXE (N=35)	PBO + EXE (N=30)
PFS, median (95% CI), mo.	5.8 (1.9, 11.1)	8.1 (3.7, 13.6)
P value*	0.6114	
HR† (95% CI)	1.16 (0.65, 2.08)	

Cohort 2: 1 prior aET



	ENZA + EXE (N=35)	PBO + EXE (N=28)
PFS, median (95% CI), mo.	1.8 (1.7, 3.9)	4.2 (1.9, 6.6)
P value*	0.1263	
HR† (95% CI)	1.60 (0.87, 2.95)	

*Two-sided stratified log rank test. † Based on stratified Cox regression model relative to placebo with <1 favoring ENZA.

Conclusions

- This small phase 2 study is the first reported randomized trial of ENZA in HR+ BC
- The study met its primary endpoint in improving PFS in ENZA + EXE–treated patients with Bmkr+ HR+ BC and no prior ET for aBC, compared with EXE alone
- There was no statistically significant benefit in PFS in either cohort of the ITT population
- AEs were consistent with those reported in men with metastatic castration-resistant prostate cancer and in women with TNBC
- The role of the AR in HR+ BC and the predictive value of the identified biomarker are still unclear and will require further studies

Practice changing?

- Likely:
  - PARP inhibition in BRCA-mutated metastatic disease
  - Sacituzumab Govitecan (IMMU-132) in TNBC (await ASCENT)
- Confirmatory:
  - Dose-dense, sequential chemo approach
  - Prognostic ability of PCR
- Needs confirmation:
  - Use/duration of bisphosphonates
  - Superiority of nab-paclitaxel over paclitaxel
- Disappointing:
  - Dual mTORC inhibition, AR inhibition in HR-positive MBC