Advances in Oncology: Breast Cancer Update 2018

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Advances in Oncology

September 29, 2018

Outline

- Adjuvant
  - Hormone positive, HER-2 negative
    - TAILORx
  - HER-2 positive
    - PERSEPHONE
- Metastatic
  - *BRCA1, 2* mutated
    - EMBRACA
  - TNBC
    - LOTUS

ADJUVANT HORMONE POSITIVE, HER-2 NEGATIVE

Standard of care

Genomic assay?

Oncotype DX

2003 – Prognostic

NSABP and Genomic Health- large prospective trial validate 21 gene assay to quantify likelihood of breast cancer recurrence-low (0-17), intermediate (18-30), high risk (31-100)

668 patient samples from NSABP B-14 (placebo vs tamoxifen 1982-1988)

2004 – Predictive

NSABP and Genomic Health- predicts magnitude of chemo benefit

651 patient samples from NSABP B-20 (CMF + T or T)- high RS- large benefit from chemo, low RS- low benefit from chemo

Chemo benefit in the intermediate risk group?

re: CT/endo vs endo)
RS > 31-high risk CT/endo

TAILORx

TAILORx: The Trial Assigning Individualized Options for Treatment

Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer

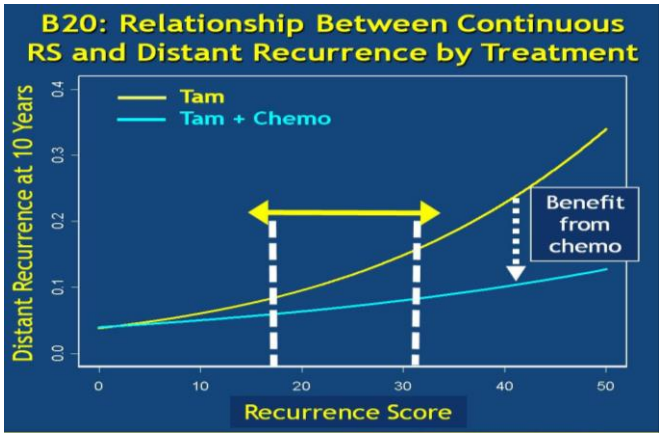
J.A. Sparano, R.J. Gray, D.F. Makower, K.I. Pritchard, K.S. Albain, D.F. Hayes, C.E. Geyer, Jr., E.C. Dees, M.P. Goetz, J.A. Olson, Jr., T. Lively, S.S. Badve, T.J. Saphner, L.I. Wagner, T.J. Whelan, M.J. Ellis, S. Paik, W.C. Wood, P.M. Ravdin, M.M. Keane, H.L. Gomez Moreno, P.S. Reddy, T.F. Goggins, I.A. Mayer, A.M. Brufsky, D.L. Toppmeyer, V.G. Kaklamani, J.L. Berenberg, J. Abrams, and G.W. Sledge, Jr.

TAILORx: Eligibility Criteria

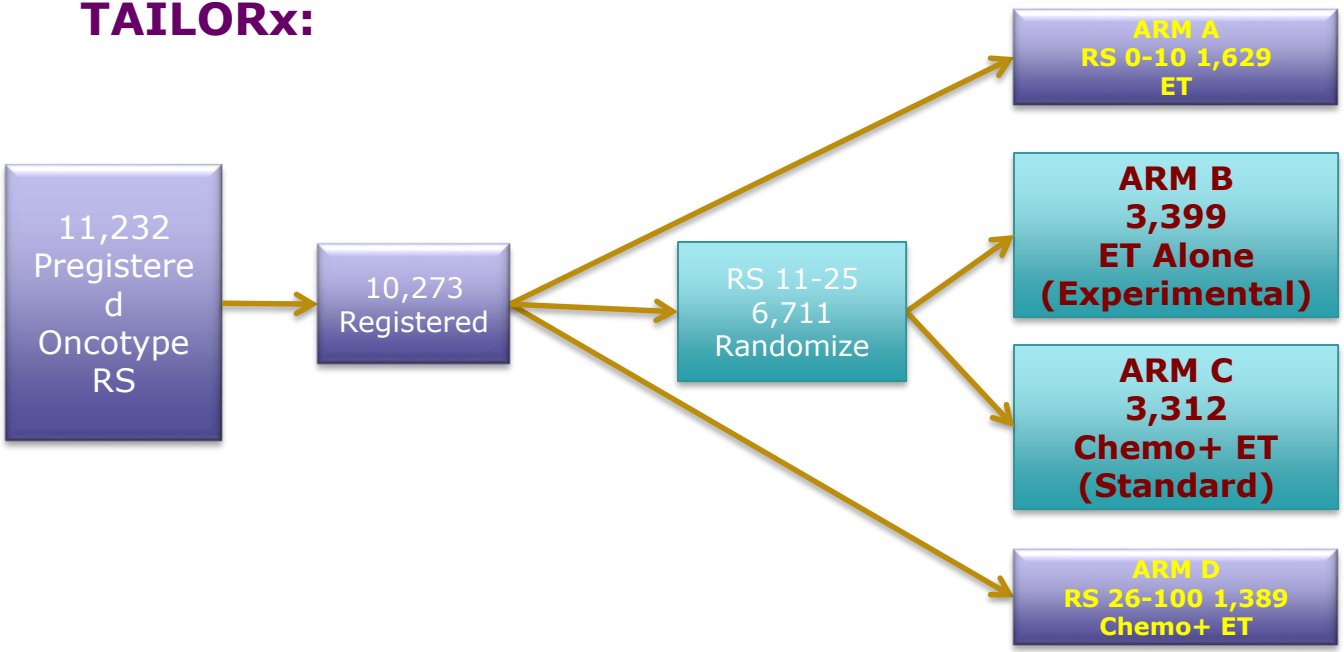
- Age 18-75 w/invasive mammary cancer
- Node negative
- ER and/or PR positive, HER-2 negative
- Tumor size:
  - 0.6- 1 cm if grade 2 or 3
  - 1.1- 5 cm
- Chemo candidate

Rationale for adjusting recurrence score range

- RS range adjusted for mid-range (B20)
  - Preserve prediction in high risk group
  - Minimize potential for undertreatment



TAILORx:


11,232 Pregistered Oncotype RS
10,273 Registered
RS 11-25 6,711 Randomize
ARM A RS 0-10 1,629 ET
ARM B 3,399 ET Alone (Experimental)
ARM C 3,312 Chemo+ ET (Standard)
ARM D RS 26-100 1,389 Chemo+ ET

TAILORx: Methods

- Phase III, randomized, non-inferiority
- Intention to treat for primary analysis, as treated analysis also planned
- Hazard ratio margin exceeding was 1.322 was selected as the non-inferiority margin for IDFS
- Endpoints
  - Primary endpoint
    - Invasive disease free survival (RS 11-25)
    - Distance recurrence free interval (RS 0-10)
  - Secondary endpoints
    - Relapse free interval
    - OS

TAILORx: Patient Characteristics

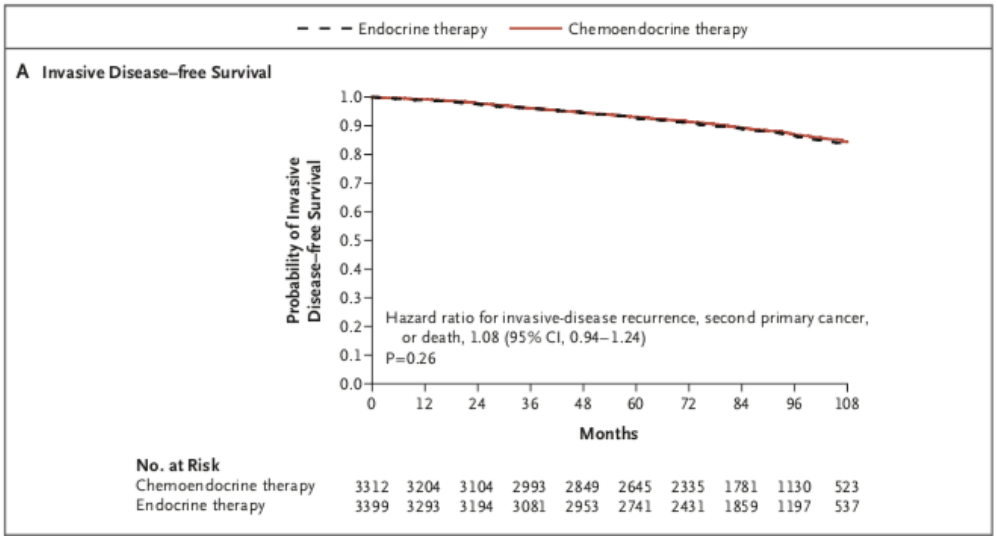
Table 1. Characteristics of the Patients in the Intention-to-Treat Population at Baseline.*

Characteristic	Recurrence Score of ≤10	Recurrence Score of 11–25		Recurrence Score of ≥26
	Endocrine Therapy (N = 1619)	Endocrine Therapy (N = 3399)	Chemoendocrine Therapy (N = 3312)	Chemoendocrine Therapy (N = 1389)
Median age (range) — yr	58 (25–75)	55 (23–75)	55 (25–75)	56 (23–75)
Age ≤50 yr — no. (%)	429 (26)	1139 (34)	1077 (33)	409 (29)
Menopausal status — no. (%)†				
Premenopausal	478 (30)	1212 (36)	1203 (36)	407 (29)
Postmenopausal	1141 (70)	2187 (64)	2109 (64)	982 (71)
Tumor size in the largest dimension — cm‡				
Median (IQR)	1.5 (1.2–2.0)	1.5 (1.2–2.0)	1.5 (1.2–2.0)	1.7 (1.3–2.3)
Mean	1.74±0.76	1.71±0.81	1.71±0.77	1.88±0.99
Histologic grade of tumor — no./total no. (%)				
Low	530/1572 (34)	959/3282 (29)	934/3216 (29)	89/1363 (7)
Intermediate	931/1572 (59)	1884/3282 (57)	1837/3216 (57)	590/1363 (43)
High	111/1572 (7)	439/3282 (13)	445/3216 (14)	681/1363 (50)

TAILORx: Patient Characteristics

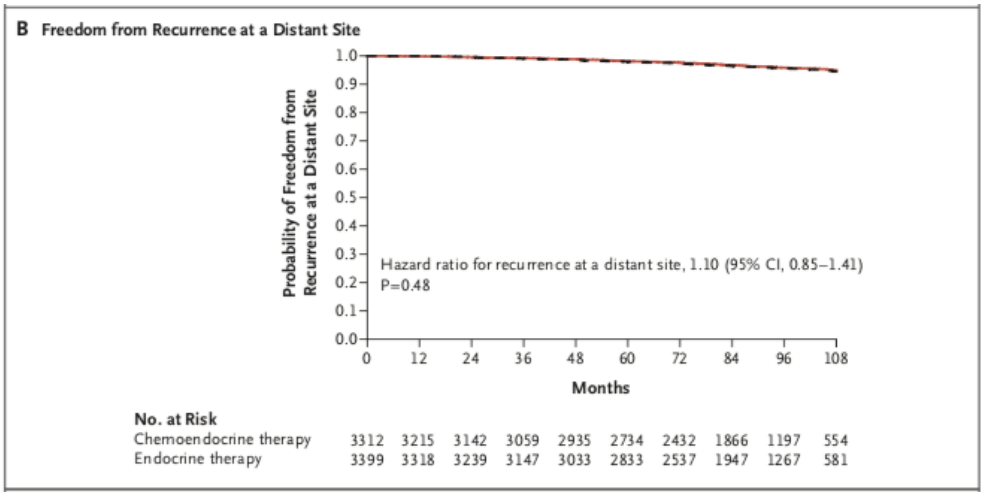
Estrogen-receptor expression — no. (%)				
Negative	5 (<1)	6 (<1)	3 (<1)	40 (3)
Positive	1614 (>99)	3393 (>99)	3309 (>99)	1349 (97)
Progesterone-receptor expression — no./total no. (%)				
Negative	28/1583 (2)	267/3339 (8)	251/3240 (8)	405/1353 (30)
Positive	1555/1583 (98)	3072/3339 (92)	2989/3240 (92)	948/1353 (70)
Clinical risk — no./total no. (%)§				
Low	1227/1572 (78)	2440/3282 (74)	2359/3214 (73)	589/1359 (43)
High	345/1572 (22)	842/3282 (26)	855/3214 (27)	770/1359 (57)
Primary surgery — no. (%)				
Mastectomy	516 (32)	935 (28)	917 (28)	368 (26)
Breast conservation	1103 (68)	2464 (72)	2395 (72)	1021 (74)
Adjuvant chemotherapy — no. (%)				
Yes	8 (0.5)	185 (5.4)	2704 (81.6)	1300 (93.6)
No	1611 (99.5)	3214 (94.6)	608 (18.4)	89 (6.4)

TAILORx: Results- invasive disease free survival (primary endpoint)



Median f/u time 7.5 years after 836 IDFS events

TAILORx: Results- distant relapse free interval (secondary endpoint)



TAILORx: Results- exploratory analysis

- Subgroups to evaluate if any group benefit from chemo
  - No significant interactions in tumor size, grade, menopausal status, or clinical risk status
  - Significant interaction with age and RS

TAILORx – subgroup analysis – 9 year event rates

- ≤50 RS 16-25 chemo benefit
  - 16-20 1.6% fewer distant recurrences
  - 21-25 6.5% fewer distant recurrences

TAILORx – Conclusions

- In women over 50 w/RS 11-25, ET was shown to be non-inferior to chemo and ET
- RS of 0-10 with very low distant recurrence rate (2-3%) at 9 yrs
- Chemo benefit in women ≤ age 50 with scores of 16-25
  - Some benefit RS 16-20
  - More benefit RS 21-25
  - Most benefit > 26

TAILORx – Practice Changing?

- >50 RS 0-25- no chemo benefit!
- ≤ 50 RS 11-15- no chemo benefit!
- ≤ 50 RS 16-25- risk/benefit convo

ADJUVANT HER-2 POSITIVE

Background

- Adjuvant early stage HER2 positive breast cancer 2007- chemo with 12 months trastuzumab
  - 2005- HERA, NSABP B-31, N9831 –
    - 12 months of trastuzumab on empirical basis
  - 2006- FinHer 9 weeks of trastuzumab better than none
  - HERA- 2 years study, no add'l improvement
  - PHARE- 6 mos vs 12 mos - 3.5 years follow up, 6 months was NOT non-inferior to 12 months of trastuzumab

De-escalation in HER-2+ breast cancer

- APT
  - Adjuvant paclitaxel and trastuzumab for node negative, HER2+ breast cancer
- RESPECT
  - Adjuvant trastuzumab monotherapy for HER2+ breast cancer in elderly patients
- ATEMPT
  - Adjuvant TDM-1 versus paclitaxel/trastuzumab for breast cancer
- ATOP
  - Adjuvant TDM-1 for older patients with HER2 + breast cancer
- PerELISA
  - Neoadjuvant trastuzumab/pertuzumab/letrozole for HR+/HER2 operable breast cancer with Ki67 response
- ADAPT
  - Neoadjuvant 12 weeks of trastuzumab/pertuzumab with or without paclitaxel in HER2+/HR- early breast cancer
- PAMELA
  - Neoadjuvant trastuzumab, lapatanib in early stage HER2+ breast cancer

PERSEPHONE

- 6 vs 12 months of adjuvant trastuzumab in patients with HER2 positive early breast cancer: Randomized phase III non-inferiority trial with definitive 4 year disease free survival results

PERSEPHONE – Hypothesis and Endpoints

- Six months of trastuzumab has similar efficacy as compared to 12 months, but less toxicity and cost
- Endpoints
  - Primary Endpoint
    - DFS
  - Secondary Endpoint
    - OS
    - Cost
    - Cardiac function

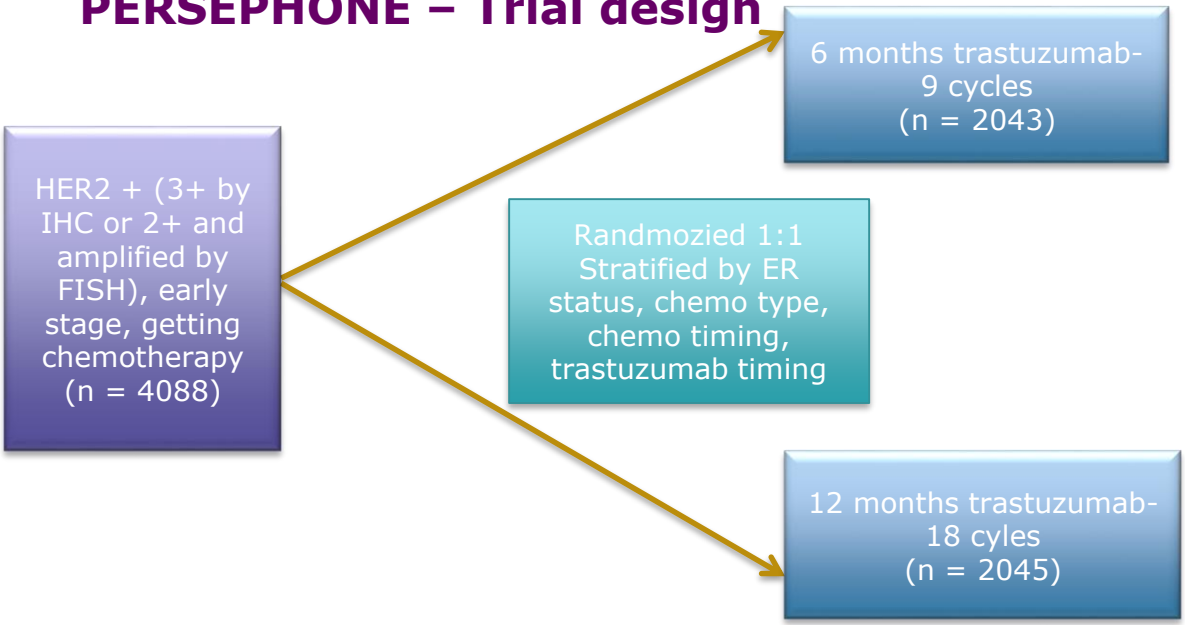
PERSEPHONE – Eligibility criteria

- HER2 positive- 3+ by IHC, or 2+ and FISH amplified
- Hormone positive or negative
- No metastatic disease
- Chemo eligible
- Neoadjuvant or adjuvant
- Concurrent or sequential trastuzumab

PERSEPHONE – Trial design

- Phase III, non-inferiority- "no worse than 3% below control arm"
- 3 interim futility analyses
- 152 sites in UK

PERSEPHONE – Trial design



PERSEPHONE – Patient Characteristics I

	N (%)	12 months (n=2045)	6 months (n=2043)	Overall (n=4088)
*ER Status	Negative	633 (31)	632 (31)	1265 (31)
	Positive	1412 (69)	1411 (69)	2823 (69)
*Chemotherapy type	Anthracycline based	854 (42)	846 (41)	1700 (42)
	Taxane based	200 (10)	203 (10)	403 (10)
	Anthracycline + Taxane based	989 (48)	991 (49)	1980 (48)
	Other (CMF)	2 (<1)	3 (<1)	5 (<1)
*Trastuzumab timing	Concurrent	951 (47)	952 (47)	1903 (47)
	Sequential	1094 (53)	1091 (53)	2185 (53)
Age	<=50 years old	657 (32)	677 (33)	1334 (33)
	>50 years old	1388 (68)	1366 (67)	2754 (67)
Doses received	0	898 (44)	888 (43)	1786 (44)
pre-randomisation	1 - 4	780 (38)	755 (37)	1535 (37)
	5 - 9	367 (18)	400 (20)	767 (19)

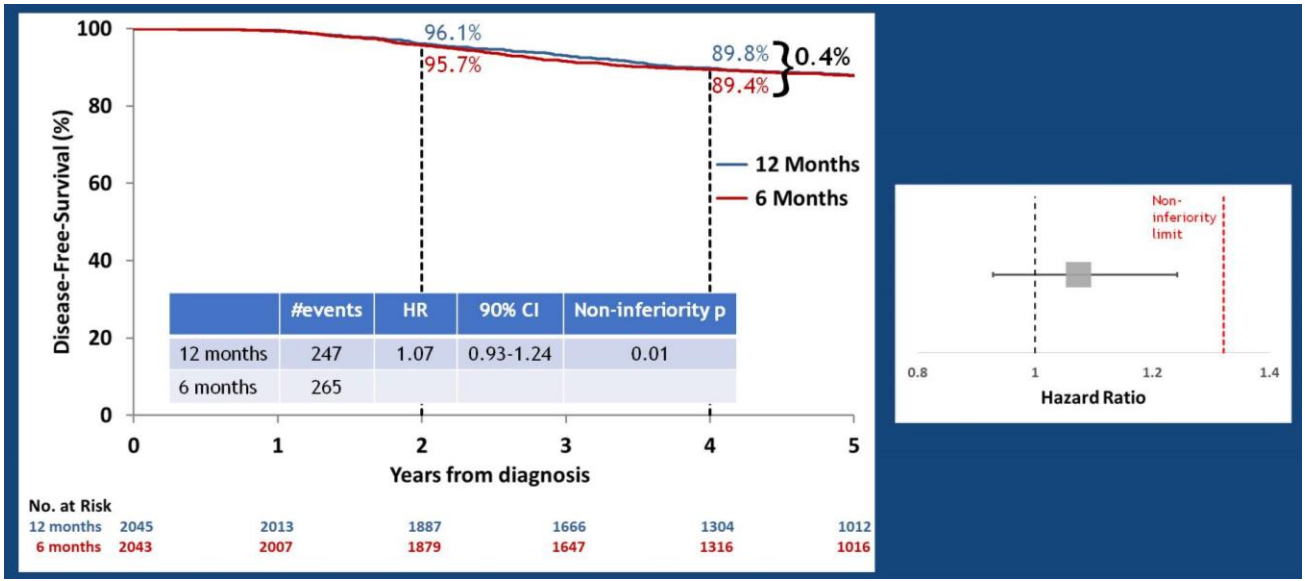
Source: Helena Earl, 2018 ASCO Annual Meeting.

PERSEPHONE – Patient Characteristics II

	N (%)	12 months (n=2045)	6 months (n=2043)	Overall (n=4088)
*CT timing	Neo-adjuvant	308 (15)	312 (15)	620 (15)
	Adjuvant	1737 (85)	1731 (85)	3468 (85)
For Adjuvant patients only				
Nodal involvement	Negative	1003 (58)	1019 (60)	2022 (59)
	1-3 nodes involved	479 (28)	486 (28)	965 (28)
	4+ nodes involved	244 (14)	211 (12)	455 (13)
Tumour size	<=2cm	824 (49)	807 (48)	1631 (48)
	>2 to 5cm	778 (46)	786 (47)	1564 (47)
	>5cm	87 (5)	83 (5)	170 (5)
Tumour Grade	I	28 (2)	34 (2)	62 (2)
	II	511 (30)	523 (31)	1034 (31)
	III	1153 (68)	1128 (67)	2281 (67)

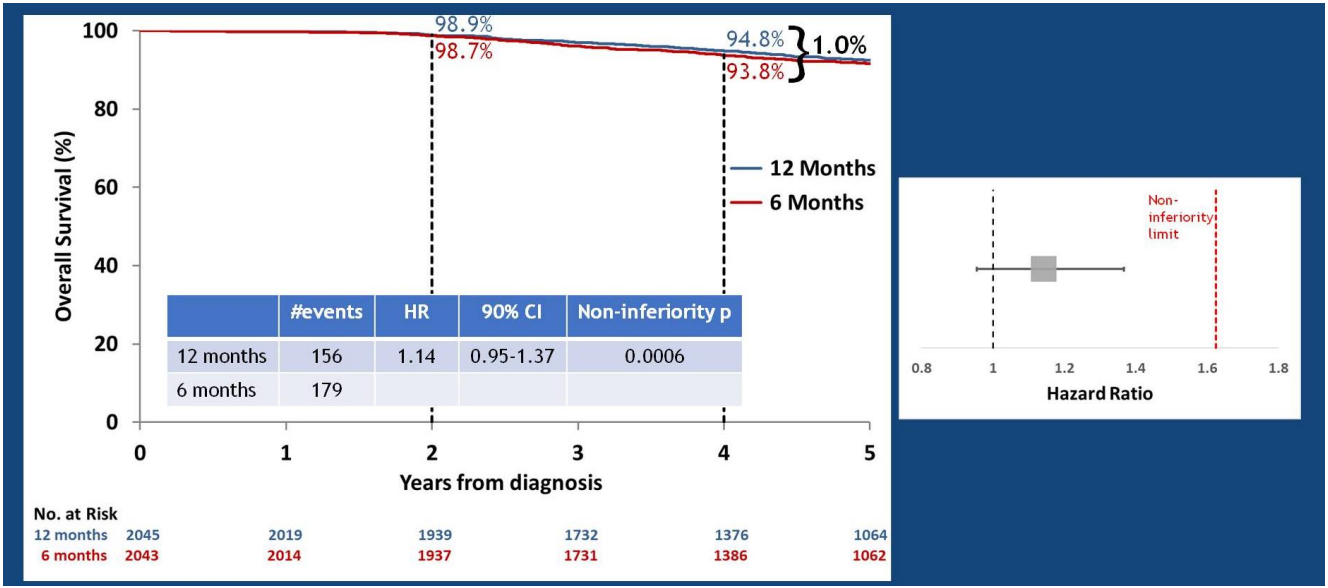
Source: Helena Earl, 2018 ASCO Annual Meeting.

PERSEPHONE – DFS (primary endpoint)



Source: Helena Earl, 2018 ASCO Annual Meeting.

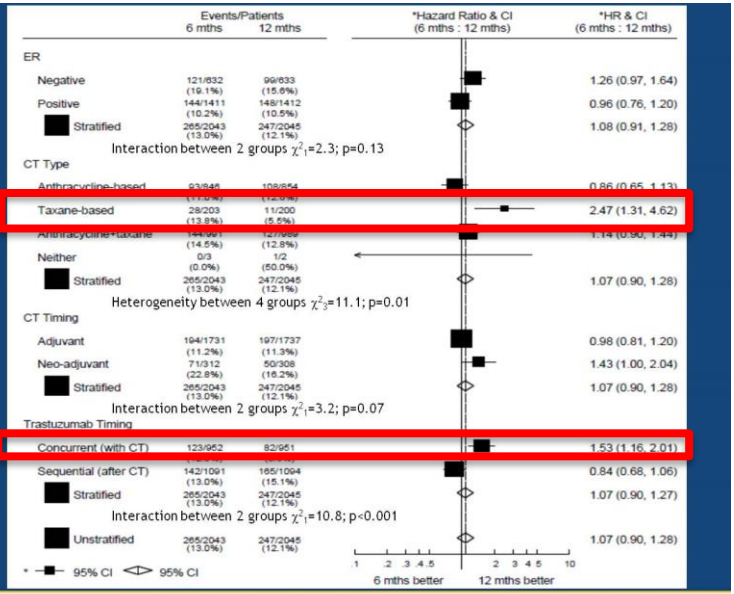
PERSEPHONE – OS (secondary endpoint)



Source: Helena Earl, 2018 ASCO Annual Meeting.

DFS:

Pre-defined subgroup analysis



Source: Helena Earl, 2018 ASCO Annual Meeting.

PERSEPHONE – Cardiotoxicity

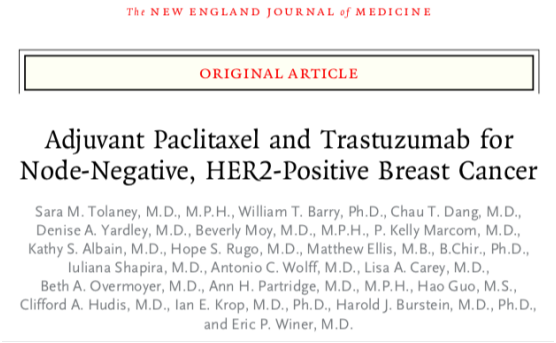
- 6 month trastuzumab
  - 4% patients had to stop the drug
- 12 month trastuzumab
  - 8% patients had to stop the drug
- Cardiac function recovered post trastuzumab
- Recovery faster in 6 month group

PERSEPHONE CONCLUSIONS

- 6 months of trastuzumab was non-inferior to 12 months
- 6 months less cardiotoxicity
- Reduce cost to patient and health care system
- Forest plot subgroup analysis, maybe favored 12 month trastuzumab for concurrent chemo w/trastuzumab and taxane based chemo (small numbers)

PRACTICE CHANGING?

- Are we asking the right question with de-escalation of trastuzumab?



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer

Sara M. Tolaney, M.D., M.P.H., William T. Barry, Ph.D., Chau T. Dang, M.D., Denise A. Yardley, M.D., Beverly Moy, M.D., M.P.H., P. Kelly Marcom, M.D., Kathy S. Albain, M.D., Hope S. Rugo, M.D., Matthew Ellis, M.B., B.Chir., Ph.D., Iuliana Shapira, M.D., Antonio C. Wolff, M.D., Lisa A. Carey, M.D., Beth A. Overmoyer, M.D., Ann H. Partridge, M.D., M.P.H., Hao Guo, M.S., Clifford A. Hudis, M.D., Ian E. Krop, M.D., Ph.D., Harold J. Burstein, M.D., Ph.D., and Eric P. Winer, M.D.

- Pre-pertuzumab era
- Is this relevant in 2018?

METASTATIC *BRCA* ASSOCIATED BREAST CANCER

Standard of care

- Sequence appropriate endocrine, HER-2 directed, or cytotoxic therapy
- Heterogeneous disease
- Clinical trial whenever possible!

EMBRACA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Talazoparib in Patients with Advanced Breast Cancer and a Germline *BRCA* Mutation

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

EMBRACA

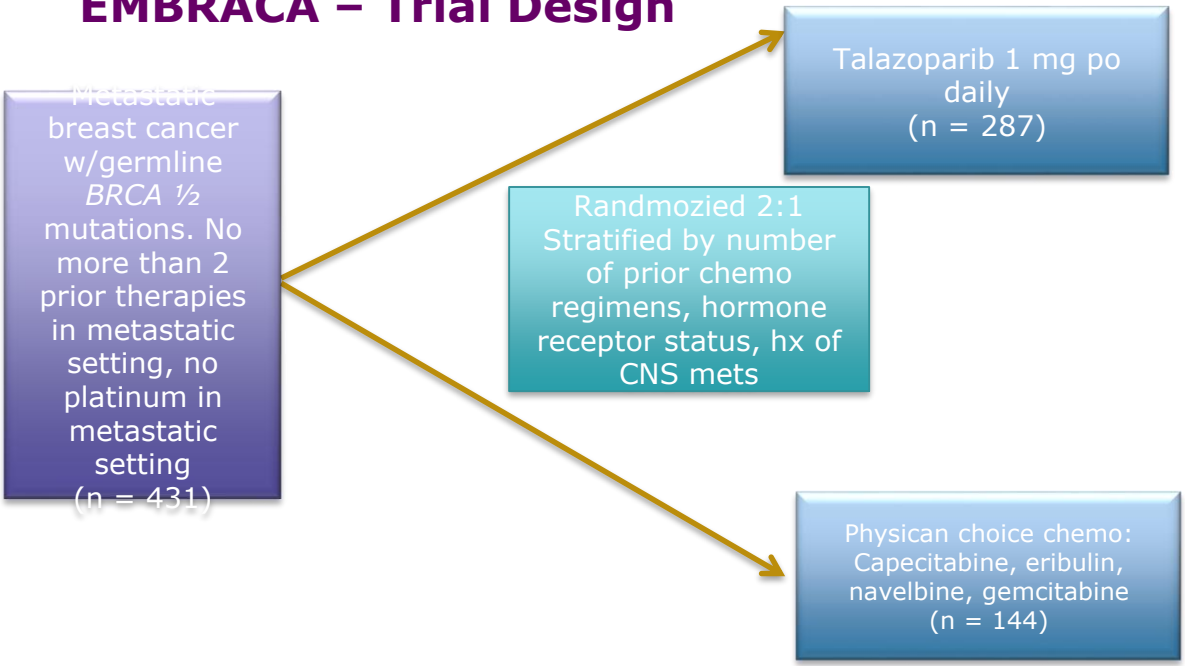
- Talozaparib more potent PARPi (dual mechanism PARPi)
- Appx 55% pts ECOG 0
- Prior platinum allowed if no progression on the agent
- Randomized 2:1
- Primary endpoint- PFS

vs

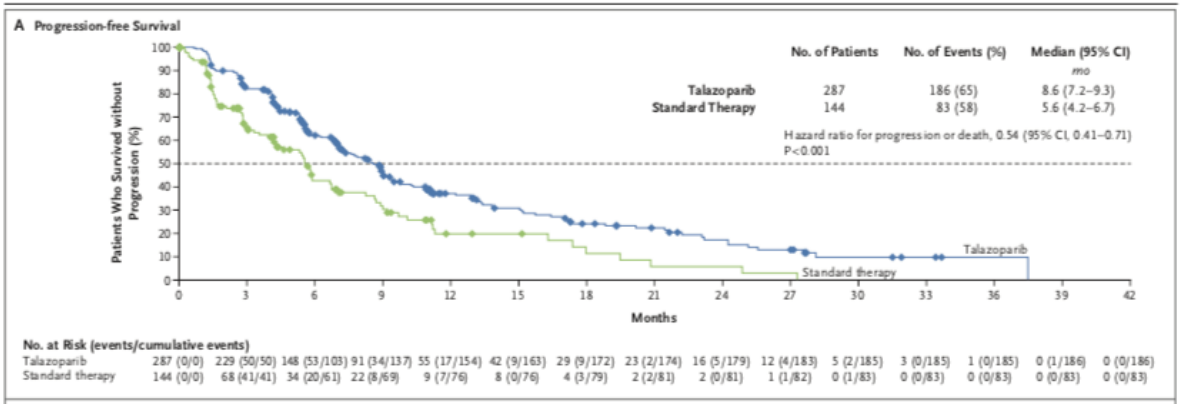
OlympiAD

- Olaparib
- Appx 72% pts ECOG 0
- No prior platinum allowed
- Randomized 2:1
- Primary endpoint- PFS

EMBRACA – Trial Design



EBRACA: PFS


A Progression-free Survival
Patients Who Survived without Progression (%)
100
90
80
70
60
50
40
30
20
10
0
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42
Months
No. of Patients
No. of Events (%)
Median (95% CI)
mo
Talazoparib 287 186 (65) 8.6 (7.2–9.3)
Standard Therapy 144 83 (58) 5.6 (4.2–6.7)
Hazard ratio for progression or death, 0.54 (95% CI, 0.41–0.71)
P<0.001
Talazoparib
Standard therapy
No. at Risk (events/cumulative events)
Talazoparib 287 (0/0) 229 (50/50) 148 (53/103) 91 (34/137) 55 (17/154) 42 (9/163) 29 (9/172) 23 (2/174) 16 (5/179) 12 (4/183) 5 (2/185) 3 (0/185) 1 (0/185) 0 (1/186) 0 (0/186)
Standard therapy 144 (0/0) 68 (41/41) 34 (20/61) 22 (8/69) 9 (7/76) 8 (0/76) 4 (3/79) 2 (2/81) 2 (0/81) 1 (1/82) 0 (1/83) 0 (0/83) 0 (0/83) 0 (0/83) 0 (0/83)

EMBRACA: OS

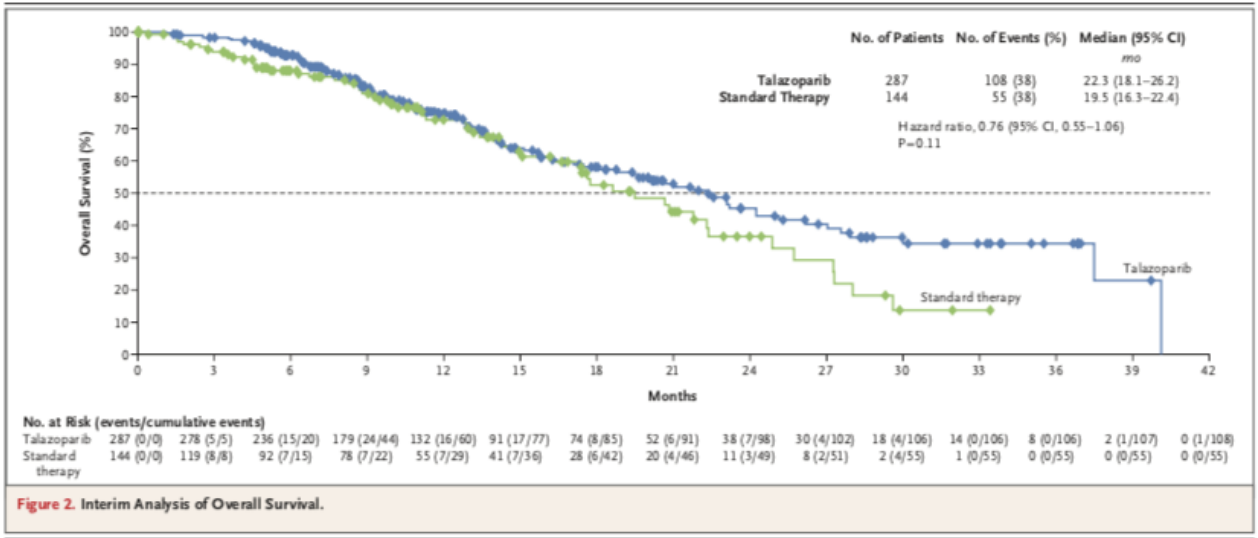


Figure 2. Interim Analysis of Overall Survival.

ASCO 2018 Annual Meeting | June 1–5, 2018 Chicago, IL

Poster 1069

EMBRACA: Efficacy Outcomes in Clinically Relevant Subgroups Comparing Talazoparib (TALA), an Oral Poly (ADP-ribose) Polymerase (PARP) Inhibitor, to Physician's Choice of Therapy (PCT) in Patients With Advanced Breast Cancer and a Germline *BRCA* Mutation

Hope S. Rugo, MD,[1] Johannes Ettl, MD,[2] Natasha E. Woodward,[3] Sara A. Hurvitz, MD,[4] Anthony Gonçalves, MD, PhD,[5] Kyung-Hun Lee, MD, PhD,[6] Louis Fehrenbacher, MD,[7] Rinat Yerushalmi, MD,[8] Lida A. Mina, MD,[9] Miguel Martin, MD, PhD,[10] Henri Hubert Roché, MD, PhD,[11] Young-Hyuck Im, MD, PhD,[12] Denka Markova, PhD,[13] Iulia Cristina Tudor, PhD,[13] Wolfgang Eiermann, MD,[14] Joanne L. Blum, MD, PhD, FACP,[15] Alison L. Hannah, MD,[13] Jennifer Keating Litton, MD[16]

[1]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [2]Department of Obstetrics and Gynecology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany; [3]Mater Cancer Care Centre – Mater Health Services, South Brisbane, Australia; [4]University of California, Los Angeles, Los Angeles, CA, USA; [5]Institut Paoli-Calmettes, Marseille, France; [6]Seoul National University Hospital, Seoul, South Korea; [7]Kaiser Permanente, Northern California, Vallejo, CA, USA; [8]Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel; [9]Banner Health, Phoenix, AZ, USA; [10]Instituto de Investigación Sanitaria Gregorio Marañón, CIBERONC, GEICAM, Universidad Complutense, Madrid, Spain; [11]Institut Claudius Regaud, Institut Universitaire du Cancer Toulouse, Toulouse, France; [12]Samsung Medical Center, Seoul, South Korea; [13]Pfizer Inc., San Francisco, CA, USA; [14]Interdisziplinäres Onkologisches Zentrum München, München, Germany; [15]Baylor Sammons Cancer Center, Texas Oncology, US Oncology, Dallas, TX, USA; [16]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

BACKGROUND

- Talazoparib inhibits the PARP enzyme and traps PARP on DNA, preventing DNA damage repair, causing cell death in breast cancer susceptibility genes 1 or 2 (*BRCA1/2*)-mutated cells.[1,2]
- The phase 3 EMBRACA trial (NCT01945775) is an open-label, randomized, 2-arm study comparing efficacy and safety of talazoparib (1 mg/day) with standard single-agent physician's choice of therapy (PCT) (capecitabine, eribulin, gemcitabine, or vinorelbine) in patients with advanced breast cancer and germline *BRCA1/2* mutations (g*BRCA*m).[3]
  - Progression-free survival (PFS) was prolonged for talazoparib vs PCT (8.6 mos vs 5.6 mos, respectively; hazard ratio, 0.54; 95% CI, 0.41, 0.71; $P < .0001$).
  - Secondary efficacy endpoints were improved in those receiving talazoparib (eg, ORR; 62.6% for talazoparib; 27.2% for PCT).
  - Talazoparib showed a very tolerable safety profile.
- In this subgroup analysis, PFS by blinded independent central review (BICR) and ORR by investigator were investigated in clinically important subgroups.

METHODS

Inclusion Criteria

- Includes locally advanced or metastatic human epidermal growth factor receptor 2 (HER2)-negative breast cancer and g*BRCA*m; no more than 3 prior cytotoxic chemotherapy regimens for locally advanced or metastatic disease; prior treatment with a taxane and/or anthracycline unless medically contraindicated. PCT was determined before randomization.

Endpoints

- Subgroups included: age <50 years; Eastern Cooperative Oncology Group (ECOG) performance status >0; *BRCA1*; *BRCA2*; triple-negative breast cancer (TNBC), hormone receptor positive (HR+); history of central nervous system (CNS) metastases; visceral disease; prior platinum; disease-free interval (DFI) <12 months.
  - ***Primary endpoint*: radiographic PFS** by BICR using Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1.
    - PFS was defined as time from randomization to the date of first documented radiographic progression per RECIST or the date of death from any cause, whichever occurred first.
  - Patients underwent imaging (computerized tomography, magnetic resonance imaging, nuclear medicine bone scans) at baseline, every 6 weeks until week 30, and then every 9 weeks; with head imaging repeated as clinically indicated and bone scans every 12 weeks.
  - All imaging was centrally reviewed by 2 radiologists, with an adjudication assessment in case of disagreement.
  - A stratified log-rank 2-sided test was used to compare treatment groups. Median PFS (95% CI) for each arm was estimated using the Kaplan-Meier method. Subgroup analyses were prespecified.
- ***Secondary endpoint*: ORR by investigator** (percentage of patients with a partial response [PR] or complete response [CR] as defined by RECIST v.1.1 with modifications).
  - Assessment of unconfirmed + confirmed ORR was performed in the intent-to-treat (ITT) population with measurable disease. Comparison between arms was performed using the stratified Cochran-Mantel-Haenszel test.
- ***Other endpoints*: clinical benefit (CR or PR or stable disease) rate (CBR) ≥24 weeks (CBR24).**
  - CBR24 was analyzed using the ITT population. Comparison between arms was performed using the stratified Cochran-Mantel-Haenszel test.

RESULTS

- 431 patients were randomized, 287 to talazoparib and 144 to PCT. Baseline characteristics were generally balanced, although more patients were <50 years of age or had a DFI <12 months in the talazoparib arm (**Table 1**).
- Median PFS was consistently higher for each subgroup with talazoparib versus PCT (**Figure 1**).
- A reduction in the risk of progression with talazoparib versus PCT was observed in all subgroups (**Figure 1**).
- Patients with a history of CNS metastases had improved PFS with talazoparib (HR 0.322, 95% CI: 0.154, 0.675, $P = .0016$).
- ORR was greater for all subgroups with talazoparib vs overall PCT or individual chemotherapy (**Table 2**).
- CBR at 24 weeks was superior in all subgroups with talazoparib vs PCT (**Figure 2**).
- Common adverse events among all subgroups included anemia, fatigue, and nausea with talazoparib and nausea, fatigue, and neutropenia for PCT.

Table 1. Baseline Characteristics

	Talazoparib (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)
Female, %	98.6	97.9
ECOG PS 0 / 1 / 2, %	53.3 / 44.3 / 2.1	58.3 / 39.6 / 1.4
Stage of breast cancer		
Locally advanced, No. (%)	15 (5.2)	9 (6.3)
Metastatic, No. (%)	271 (94.4)	135 (93.8)
Measurable disease by investigator, No. (%)	219 (76.3)	114 (79.2)
History of CNS metastases, No. (%)	43 (15.0)	20 (13.9)
Visceral disease, No. (%)	200 (69.7)	103 (71.5)
Hormone receptor status, No. (%)		
HR+	157 (54.7)	84 (58.3)
TNBC	130 (45.3)	60 (41.7)
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, No. (%)	108 (37.6)	42 (29.2)
Prior adjuvant/neoadjuvant therapy, No. (%)	238 (82.9)	121 (84.0)
De novo BC (stage IV)	53 (18.5)	22 (15.3)
No. of prior hormonal therapy–based regimens in any setting (for patients with HR+ BC), median (range)	2.0 (0-6) (patients with HR+ BC: n = 157)	2.0 (0-6) (patients with HR+ BC: n = 84)
Prior platinum therapy, No. (%)	46 (16.0)	30 (20.8)
Prior cytotoxic regimens for ABC, No. (%)		
0	111 (38.7)	54 (37.5)
1	107 (37.3)	54 (37.5)
2	57 (19.9)	28 (19.4)
≥3	12 (4.2)	8 (5.6)

Figure 1. PFS (Primary Endpoint) Based on BICR for Specific Subgroups

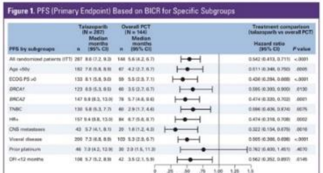
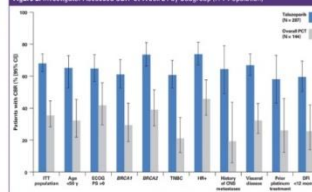


Table 2. Investigator-Assessed Unconfirmed + Confirmed ORR by Subgroup for PCT (ITT With Measurable Disease)

	Talazoparib (N = 219)	Overall PCT (N = 114)	Capecitabine (N = 44)	Eribulin (N = 48)	Gemcitabine (N = 13)	Vinorelbine (N = 9)
ORR, No. (%)	137 (62.6)	31 (27.2)	12 (27.3)	11 (22.9)	4 (30.8)	4 (44.4)
95% CI	(55.78, 68.99)	(19.28, 36.33)	(14.96, 42.79)	(12.03, 37.31)	(9.09, 61.43)	(13.70, 78.80)
Odds ratio (95% CI)	4.99 (2.93, 8.83); $P < .0001$					
Age <50 y	142	49	19	19	5	6
ORR, No. (%)	88 (62.0)	11 (22.4)	2 (10.5)	7 (36.8)	0 (0.0)	2 (33.3)
95% CI	(53.45, 69.98)	(11.77, 36.62)	(1.30, 33.14)	(16.29, 61.64)	(47.82, 100.00)	(4.33, 77.72)
Odds ratio (95% CI)	5.77 (2.54, 13.67); $P < .0001$					
ECOG PS score >0	98	49	19	21	5	4
ORR, No. (%)	60 (61.2)	17 (34.7)	7 (36.8)	5 (23.8)	2 (40.0)	3 (75.0)
95% CI	(50.85, 70.90)	(21.67, 49.64)	(16.29, 61.64)	(8.22, 47.17)	(5.27, 85.34)	(19.41, 99.37)
Odds ratio (95% CI)	3.32 (1.47, 7.37); $P = .0014$					
BRCA status = *BRCA 1*	92	50	18	21	7	4
ORR, No. (%)	59 (64.1)	11 (22.0)	3 (16.7)	6 (28.6)	1 (14.3)	1 (25.0)
95% CI	(53.46, 73.87)	(11.53, 35.96)	(3.58, 41.42)	11.28, 52.18)	(0.36, 57.87)	(0.63, 80.59)
Odds ratio (95% CI)	7.01 (2.99, 19.54); $P < .0001$					
BRCA status = *BRCA 2*	114	60	24	25	6	5
ORR, No. (%)	71 (62.3)	18 (30.0)	8 (33.3)	4 (16.0)	3 (50.0)	3 (60.0)
95% CI	(52.72, 71.19)	(18.85, 43.21)	(15.63, 55.32)	(4.54, 36.08)	(11.81, 88.19)	(14.66, 94.73)
Odds ratio (95% CI)	4.15 (1.90, 8.52); $P < .0001$					
Triple-negative status based on most recent biopsy = yes	102	48	19	19	6	4
ORR, No. (%)	63 (61.8)	6 (12.5)	1 (5.3)	4 (21.1)	0 (0.0)	1 (25.0)
95% CI	(51.61, 71.21)	(4.73, 25.25)	(0.13, 26.03)	(6.05, 45.57)	(54.07, 100.00)	(0.63, 80.59)
Odds ratio (95% CI)	11.89 (4.54, 41.37); $P < .0001$					
HR+ = yes	117	66	25	29	7	5
ORR, No. (%)	74 (63.2)	25 (37.9)	11 (44.0)	7 (24.1)	4 (57.1)	3 (60.0)
95% CI	(53.84, 71.97)	(26.22, 50.66)	(24.40, 65.07)	(10.30, 43.54)	(18.41, 90.10)	(14.66, 94.73)
Odds ratio (95% CI)	2.89 (1.43, 5.83); $P = .0012$					
History of CNS metastasis = yes	38	19	6	9	3	1
ORR, No. (%)	24 (63.2)	3 (15.8)	1 (16.7)	1 (11.1)	1 (33.3)	0 (0.0)
95% CI	(45.99, 78.19)	(3.38, 39.58)	(0.42, 64.12)	(0.28, 48.25)	(0.84, 90.57)	(2.50, 100.00)
Odds ratio (95% CI)	8.95 (1.86, 52.26); $P = .0013$					
Visceral disease = yes	180	98	37	42	12	7
ORR, No. (%)	112 (62.2)	25 (25.5)	10 (27.0)	9 (21.4)	4 (33.3)	2 (28.6)
95% CI	(54.71, 69.33)	(17.24, 35.31)	(13.79, 44.12)	(10.30, 36.81)	(9.92, 65.11)	(3.67, 70.96)
Odds ratio (95% CI)	5.27 (2.87, 9.74); $P < .0001$					
Prior platinum treatment = yes	38	25	9	10	3	3
ORR, No. (%)	19 (50.0)	6 (24.0)	0 (0.0)	4 (40.0)	1 (33.3)	1 (33.3)
95% CI	(33.38, 66.62)	(9.36, 45.13)	(66.37, 100.00)	(12.16, 73.76)	(0.84, 90.57)	(0.84, 90.57)
Odds ratio (95% CI)	3.16 (0.88, 15.67); $P = .0456$					
Time from initial diagnosis of breast cancer to initial diagnosis of ABC <12 months	90	32	12	15	2	3
ORR, No. (%)	45 (50.0)	6 (18.8)	2 (16.7)	2 (13.3)	0 (0.0)	2 (66.7)
95% CI	(39.27, 60.73)	(7.21, 36.44)	(2.09, 48.41)	(1.66, 40.46)	(15.81, 100.00)	(9.43, 99.16)
Odds ratio (95% CI)	4.86 (1.85, 19.71); $P = .0006$					

Figure 2. Investigator Assessed CBR at Week 24 by Subgroup (ITT Population)



Subgroup	Odds Ratio (95% CI)	P value
ITT population with measurable disease	[illegible]	[illegible]
Age <50 y	[illegible]	[illegible]
ECOG PS score >0	[illegible]	[illegible]
BRCA1	[illegible]	[illegible]
BRCA2	[illegible]	[illegible]
TNBC	[illegible]	[illegible]
HR+	3.27 (1.77, 6.07)	<.0001
History of CNS metastasis	7.18 (1.70, 31.91)	.0018
Visceral disease by investigator	[illegible]	<.0001
Prior platinum treatment	4.21 (1.26, 16.11)	.0087
Disease-free interval <12 months	5.36 (2.19, 14.11)	<.0001

CONCLUSIONS

- In patients with advanced g*BRCA*m breast cancer, talazoparib consistently demonstrated a statistically significant improvement in PFS, ORR, and CBR24 in clinically relevant subgroups compared with PCT.
  - Including subgroups such as patients with a history of CNS metastases, poor performance status, younger age, and visceral disease.
  - Improvement was seen with talazoparib irrespective of hormone receptor expression or *BRCA1/2* status.
- This subgroup analysis is supportive of the overall population conclusion that talazoparib provides a significant clinical benefit compared with PCT.

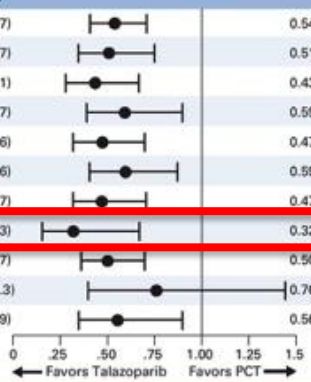
REFERENCES

ACKNOWLEDGMENTS

PLAIN LANGUAGE SUMMARY

Figure 1. PFS (Primary Endpoint) Based on BICR for Specific Subgroups

PFS by subgroups	Talazoparib (N = 287) n	Talazoparib (N = 287) Median months (95% CI)	Overall PCT (N = 144) n	Overall PCT (N = 144) Median months (95% CI)	Treatment comparison (talazoparib vs overall PCT) Hazard ratio (95% CI)	*P* value
All randomized patients (ITT)	287	8.6 (7.2, 9.3)	144	5.6 (4.2, 6.7)	0.542 (0.413, 0.711)	<.0001
Age <50y	182	7.6 (5.8, 8.9)	67	4.2 (2.7, 6.7)	0.511 (0.348, 0.750)	.0005
ECOG PS >0	133	8.1 (5.8, 9.0)	59	5.5 (2.9, 7.1)	0.436 (0.284, 0.668)	<.0001
BRCA1	123	6.9 (5.3, 8.5)	60	3.5 (2.7, 6.7)	0.595 (0.393, 0.900)	.0130
BRCA2	147	9.8 (8.3, 13.0)	78	5.7 (4.6, 8.6)	0.474 (0.320, 0.702)	.0001
TNBC	130	5.8 (5.3, 7.7)	60	2.9 (1.7, 4.6)	0.596 (0.406, 0.874)	.0075
HR+	157	9.4 (8.8, 13.0)	84	6.7 (5.6, 8.7)	0.474 (0.318, 0.708)	.0002
CNS metastases	43	5.7 (4.1, 8.1)	20	1.6 (1.2, 4.3)	0.322 (0.154, 0.675)	.0016
Visceral disease	200	7.3 (6.8, 8.9)	103	5.3 (2.9, 6.7)	0.505 (0.366, 0.698)	<.0001
Prior platinum	46	7.0 (4.2, 12.9)	30	2.9 (1.5, 11.3)	0.762 (0.400, 1.451)	.4070
DFI <12 months	108	5.7 (5.2, 8.9)	42	3.5 (2.1, 5.9)	0.562 (0.352, 0.897)	.0145



Abbreviations: *BRCA1*/*BRCA2*, breast cancer susceptibility gene 1 or 2; CI, confidence interval; CNS, central nervous system; DFI, disease-free interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR+, hormone receptor positive; ITT, intent to treat; PCT, physician's choice of therapy; PFS, progression-free survival; TNBC, triple-negative breast cancer; y, years.

Summary

- Talazoparib is the most potent PARPi yet
- Talazoparib improves PFS as compared to physician's choice chemo
- Benefit in certain subgroups such as CNS mets
- Safety- well tolerated
  - Most common toxicities- myelosuppression, fatigue, nausea

EMBRACA: Practice changing?

- Not yet FDA approved
- Option for single agent in HRD patients
- Combination with chemo?
- Clinical trials

METASTATIC TNBC

Standard of care

- Sequence cytotoxic therapy
- Heterogeneous disease
- Clinical trial whenever possible!

LOTUS

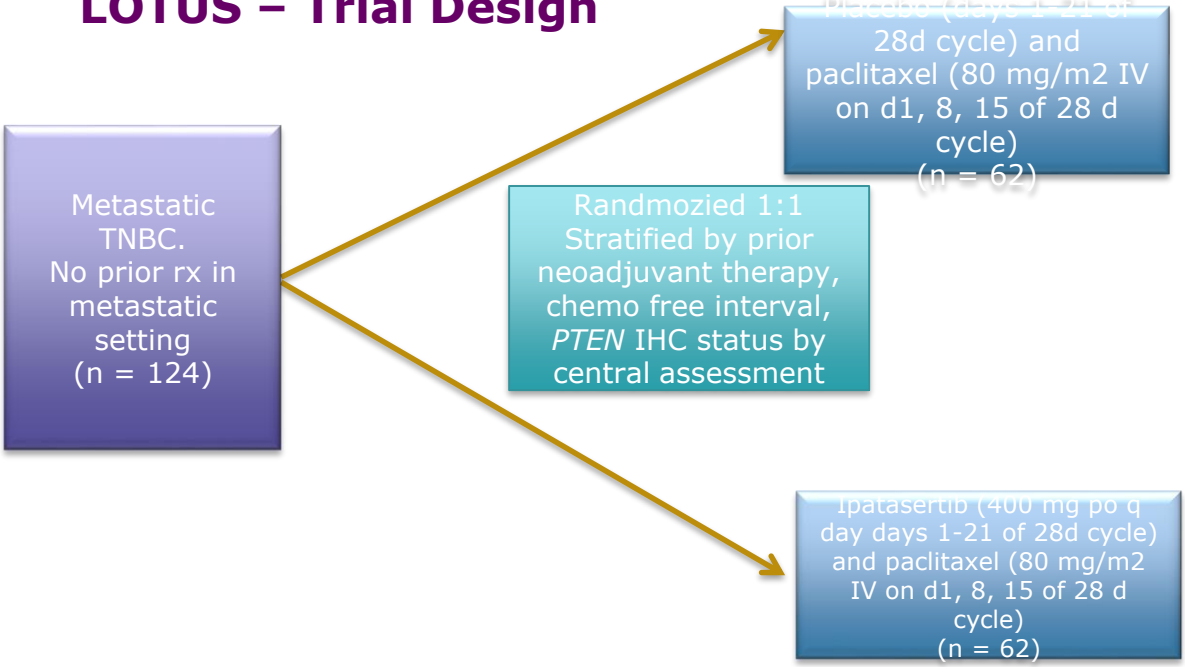
Ipatasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (LOTUS): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial

Sung-Bae Kim, Rebecca Dent*, Seock-Ah Im, Marc Espié, Sibel Blau, Antoinette R Tan, Steven J Isakoff, Mafalda Oliveira, Cristina Saura, Matthew J Wongchenko, Amy V Kapp, Wai Y Chan, Stina M Singel, Daniel J Maslyar, José Baselga, on behalf of the LOTUS investigators†*

LOTUS

- Phase II, randomized, placebo controlled, double blind, international
- Phase I trial showed promise in *AKT* inhibitor, Ipatasertib in triple negative tumors, particularly those with *PTEN/AKT/PIK3CA* alterations
  - Marked synergy with taxane combination

LOTUS – Trial Design

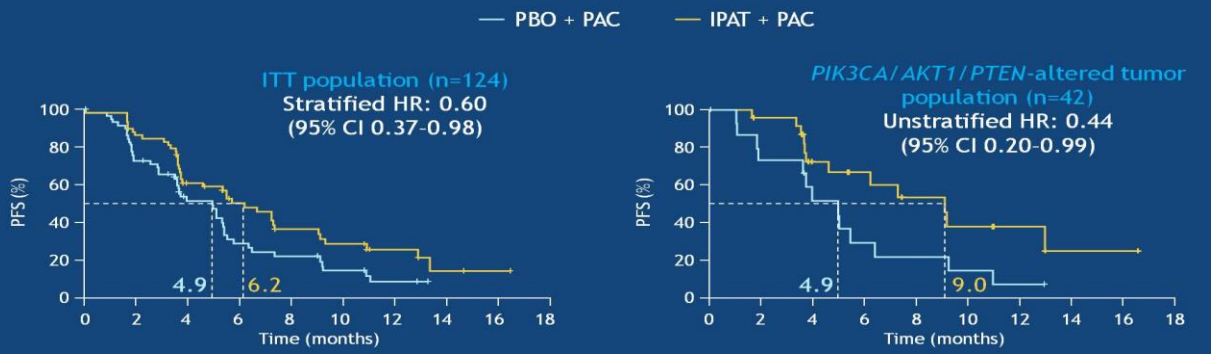


LOTUS – Endpoints

- Primary endpoint
  - PFS in ITT and low *PTEN* group
- Secondary endpoint
  - ORR
  - OS
  - Duration of response
  - Safety

LOTUS – PFS

Primary analysis: IPAT effect on PFS enhanced in *PIK3CA/AKT1/PTEN*-altered subgroup (Foundation Medicine[a])



[a]FoundationOne
CI = confidence interval; HR = hazard ratio

Kim et al. Lancet Oncol 2017

LOTUS – Summary of Endpoints

Primary analysis: Summary of additional efficacy endpoints

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

[a]Defined as either an objective response, or a best overall response of complete or partial response or stable disease together with PFS of ≥24 weeks
NE = not estimable; NGS = next-generation sequencing

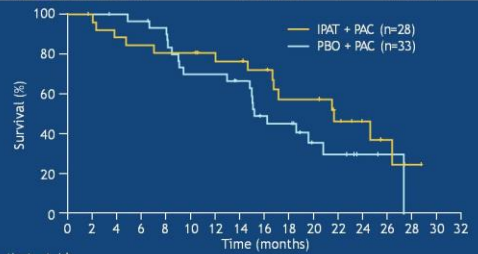
Kim et al. Lancet Oncol 2017. Roche data on file 2018

LOTUS OS in ITT and *PTEN/AKT/PIK3CA* altered group

OS according to *PIK3CA/AKT1/PTEN* status by NGS

Non-altered

	PBO + PAC (n=33)	IPAT + PAC (n=28)
OS events, n (%)	20 (61)	14 (50)
Median OS, months (95% CI)	16.2 (13.8-22.2)	23.1 (17.7-NE)
Unstratified OS HR (95% CI)	0.65 (0.32-1.30)	
1-year OS rate, % (95% CI)	70 (54-86)	81 (66-96)

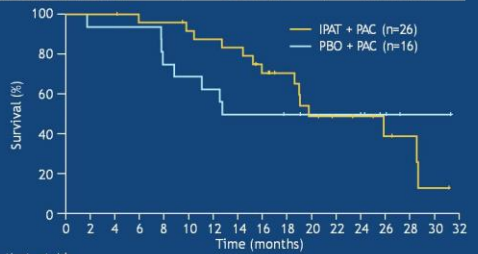


No. of patients at risk

IPAT + PAC	28	26	24	22	21	21	19	18	16	13	12	11	7	5	3	1
PBO + PAC	33	32	31	30	28	22	21	20	17	12	9	6	5	2	1	

Altered

	PBO + PAC (n=16)	IPAT + PAC (n=26)
OS events, n (%)	8 (50)	14 (54)
Median OS, months (95% CI)	NE (8.7-NE)	19.7 (18.6-28.6)
Unstratified OS HR (95% CI)	0.90 (0.38-2.15)	
1-year OS rate, % (95% CI)	63 (39-86)	88 (75-100)



No. of patients at risk

IPAT + PAC	26	26	26	24	24	22	21	20	16	13	9	7	6	4	3	1
PBO + PAC	16	15	15	15	12	11	10	8	8	7	6	6	5	3	1	1

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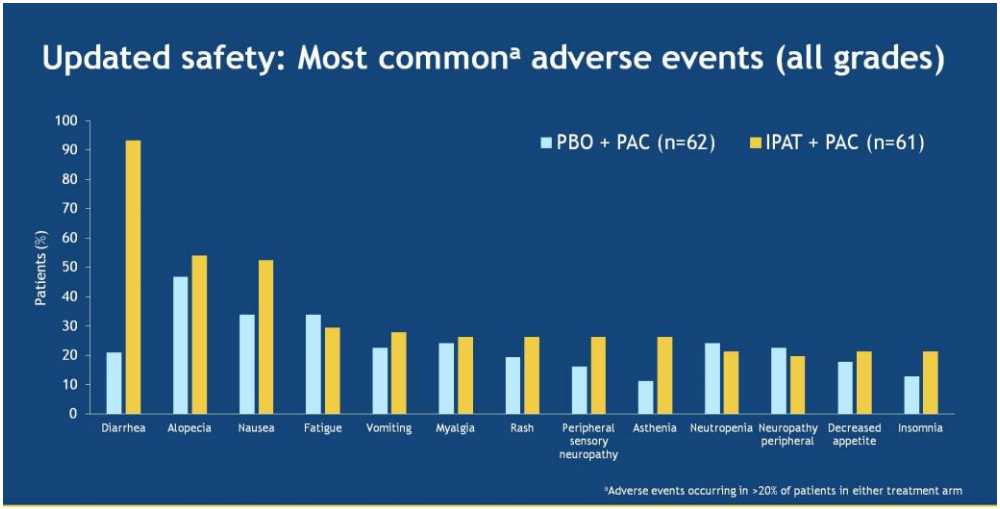
PRESENTED BY: Rebecca A Dent

LOTUS – Safety



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PRESENTED BY: Rebecca A Dent

LOTUS- Conclusion

- PFS benefit of Ipatasertib- pronounced in *PIK3CA/AKT/PTEN* altered tumors
- OS trend noted in update presented at ASCO 2018, final results in 2019
- Diarrhea most common AE

LOTUS – Practice changing?

- Ongoing phase III- open at UCD!
  - IPATunity130- randomized phase III evaluating Ipatasertib and paclitaxel as first line chemo in *PTEN/AKT/PIK3CA* altered TNBC, or in hormone positive, HER-2 negative breast cancer after progression on endocrine therapy

Summary

- Adjuvant- de-escalate when you can!
  - TAILORx
    - Chemo can be avoided in more patients!
    - Women over 50 with an Oncotype recurrence score 0-25, measured conversation in women under 50 with scores of 16-25
  - PERSEPHONE
    - 6 months of trastuzumab is non-inferior to 12 months in appropriate population- how relevant is this today?
- Metastatic
  - Clinical trial whenever possible!