ANCO's ASCO Highlights 2018 Breast Cancer Track

Joshua Gruber, M.D., Ph.D

Stanford University School of Medicine

Adjuvant Tx Early Stage Breast Cancer

Abstract	Presenter	Title
LBA1	Sparano	TAILORx: Phase III trial of chemoendocrine therapy versus endocrine therapy alone in hormone receptor-positive, HER2-negative, node-negative breast cancer and an intermediate prognosis 21-gene recurrence score.
503	Regan	Absolute improvements in freedom from distant recurrence with adjuvant endocrine therapies for premenopaual women with hormone receptor-positive (HR+) and HER2-negative breast cancer (BC): Results from TEXT and SOFT.
506	Earl	PERSEPHONE: 6 versus 12 months (m) of adjuvant trastuzumab in patients (pts) with HER2 positive (+) early breast cancer (EBC): Randomized phase 3 non-inferiority trial with definitive 4-year (yr) disease-free survival (DFS) results.

Role of chemotherapy for intermediate recurrence score on Oncotype Dx.

8 year update on the role of ovarian suppression + Tam/AI in ER+ BC.

Duration of therapy for adjuvant trastuzumab in HER2+ BC.

Metastatic Triple-Negative Breast Cancer

Abstract	Presenter	Title
1007	Schmid	AZD5363 plus Paclitaxel versus Placebo plus Paclitaxel as first-line therapy for metastatic triple-negative breast cancer (PAKT): A randomised, double-blind, placebo-controlled, phase II trial

Role of AKT inhibition in 1st line metastatic TNBC?

Trial Assigning IndividuaLized Options for TReatment (TAILORx):

Phase III trial of chemoendocrine therapy versus endocrine therapy alone in hormone receptor-positive, HER2-negative, node-negative breast cancer and an intermediate prognosis 21-gene recurrence score

Joseph A. Sparano, Robert J. Gray, William C. Wood, Della F. Makower, Tracy G. Lively, Thomas J. Saphner, Maccon M. Keane, Henry L. Gomez, Pavan Reddy, Timothy F. Goggins, Ingrid A. Mayer, Deborah Toppmeyer, Adam Brufsky, Matthew P. Goetz, Daniel F. Hayes, Elizabeth Claire Dees, Kathleen I. Pritchard, Charles E. Geyer, John A. Olson, & George W. Sledge

on behalf of the TAILORx Investigators

Canadian Cancer Trials Group | Alliance for Clinical Trials in Oncology | Federally Funded Research | ECOG-ACRIN cancer research group | Reshaping the future of patient care | National Cancer Institute | SWOG Leading cancer research. Together. | NRG Oncology

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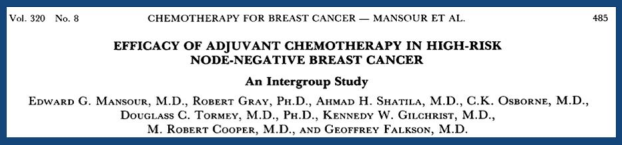
Background: Role of Adjuvant Chemotherapy in Early Breast Cancer

- Adjuvant chemotherapy reduces recurrence in ER+, node-neg BCA
- U.S. N.I.H consensus panel in 2000 concluded "…*adjuvant ..chemotherapy … should be recommended to the majority of women with localized breast cancer regardless of lymph node, menopausal, or … receptor status.*"



Vol. 320 No. 8 CHEMOTHERAPY FOR BREAST CANCER — MANSOUR ET AL. 485

EFFICACY OF ADJUVANT CHEMOTHERAPY IN HIGH-RISK NODE-NEGATIVE BREAST CANCER

An Intergroup Study

EDWARD G. MANSOUR, M.D., ROBERT GRAY, PH.D., AHMAD H. SHATILA, M.D., C.K. OSBORNE, M.D., DOUGLASS C. TORMEY, M.D., PH.D., KENNEDY W. GILCHRIST, M.D., M. ROBERT COOPER, M.D., AND GEOFFREY FALKSON, M.D.

Mansour et al. N Eng J Med 1989; 320:485-490

SPECIAL ARTICLE

National Institutes of Health Consensus Development Conference Statement: Adjuvant Therapy for Breast Cancer, November 1–3, 2000

*National Institutes of Health Consensus Development Panel***

JNCI 2001; 93: 979-989

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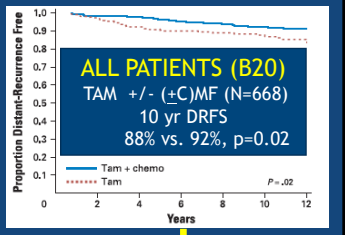
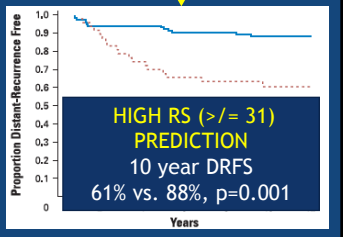
Background: Rationale for Design of TAILORx Precision Medicine Trial
Biomarker Directed Chemotherapy

- Target Population: HR+, HER2-neg, node-neg BCA
  - 50% of all breast cancers in U.S.
  - Adjuvant chemo recommended, but benefit small
  - Most are overtreated
- Assay Selected: 21-Gene Assay (Recurrence Score)
  - Two prospective validation studies in ER+, node-neg BCA
    - Prognostic (B14 study - tamoxifen): low recurrence with ET if RS low
    - Predictive (B20 study – tam +/- CMF): large chemo benefit if RS high
  - Uncertain chemo benefit for mid-range RS





Paik et al. N Eng J Med 2004;351:2817-26; Paik et al. J Clin Oncol 2006;24:3726-34; Sparano J, Paik S. J Clin Oncol 2008; 26: 721-728

TAILORx Methods: Treatment Assignment & Randomization

Accrued between April 2006 – October 2010

Preregister - Oncotype DX RS (N=11,232)

↓

Register (N=10,273)

ARM A: Low RS 0-10 (N=1629 evaluable) ASSIGN Endocrine Therapy (ET)	Mid-Range RS 11-25 (N=6711 evaluable) **RANDOMIZE** Stratification Factors: Menopausal Status, Planned Chemotherapy, Planned Radiation, and RS 11-15, 16-20, 21-25	ARM D: High RS 26-100 (N=1389 evaluable) ASSIGN ET + Chemo

ARM B: Experimental Arm (N=3399) ET Alone	ARM C: Standard Arm (N=3312) ET + Chemo

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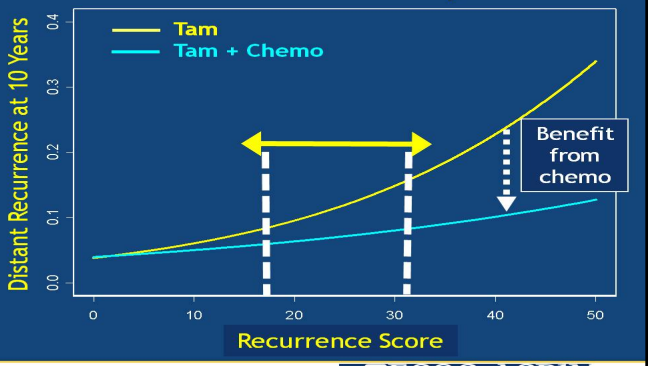
Background: Rationale for Adjusting RS Ranges in TAILORx

- **TAILORx population excluded HER2+**
  - 21-gene assay includes HER2 module (*HER2*, *GRB7*) - higher recurrence
  - Most HER2+ tumors have high RS
  - Different RS distribution
- **RS assay used selectively in practice - therapeutic equipoise**
  - Typically int. grade tumors, 1-2 cm in size
  - More tumors in mid-range group
- **RS range adjusted for mid-range (B20)**
  - Preserve prediction in high risk group
  - Minimize potential for undertreatment

B20: Relationship Between Continuous RS and Distant Recurrence by Treatment



1 Sparano J, Paik S. J Clin Oncol 2008; 26: 721-728

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TAILORx Methods: Endpoints

- Primary endpoints:
  - RS 11-25: IDFS
  - RS 0-10: DRFI

	Distant Recurrence	Local-Regional Recurrence	Contralateral Breast Cancer	Other Second Primary Cancer	Death
Invasive disease-free survival (IDFS)	X	X	X	X	X
Distant recurrence-free interval (DRFI)	X				
Relapse-free interval (RFI)	X	X			
Overall survival (OS)					X

Hudis et al. J Clin Oncol 2007; 25(15):2127-32

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TAILORx Methods: Statistical Analysis Plan for RS 11-25

- Non-inferiority design for randomized arms
- Intention-to-treat for primary analysis, as-treated analysis also planned
- Hazard ratio margin 1.322 for IDFS (5 year IDFS rate 90% vs. 87%)
  - Null hypothesis of no difference, type I error rate 10% (1-sided), type II 5%
  - *P* values shown are stratified log-rank test, and hazard ratios shown are from stratified proportional hazards models
  - Sample size adjusted for non-adherence rate (12%) - Lachin-Foulkes correction
  - Full information - 835 IDFS events
- Exploratory interaction tests for subgroups that may derive chemo benefit (ITT)

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TAILORx Results – ITT Population: Demographics & Treatment in RS 11-25 Arms (N=6,711)

- **Patient characteristics**
  - Median age 55 years, and 33% were 50 or younger
  - 63% had tumor size 1-2 cm and 57% had intermediate grade histology (57%)
  - Clinical risk criteria: 74% low risk, 26% high risk
- **Systemic Treatment**
  - Endocrine therapy
    - Comparable adherence and duration in both arms
    - Postmenopausal – included AI in 90%
    - Premenopausal – included OS in 15%
  - Chemotherapy
    - Most common regimens were TC (56%) and anthracycline-containing (36%)

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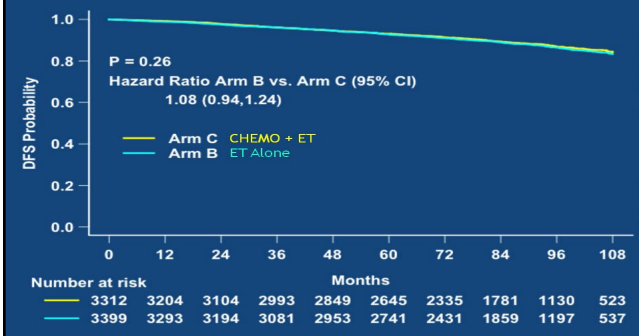
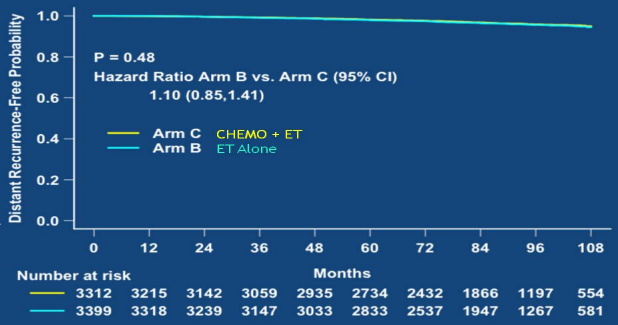
TAILORx Results - ITT Population: RS 11-25 (Arms B & C)

836 IDFS events (after median of 7.5 years), including 338 (40.3%) with recurrence as fist event, of which 199 (23.8%) were distant

Primary Endpoint
Invasive Disease-Free Survival



Secondary Endpoint
Distant Relapse-Free Interval



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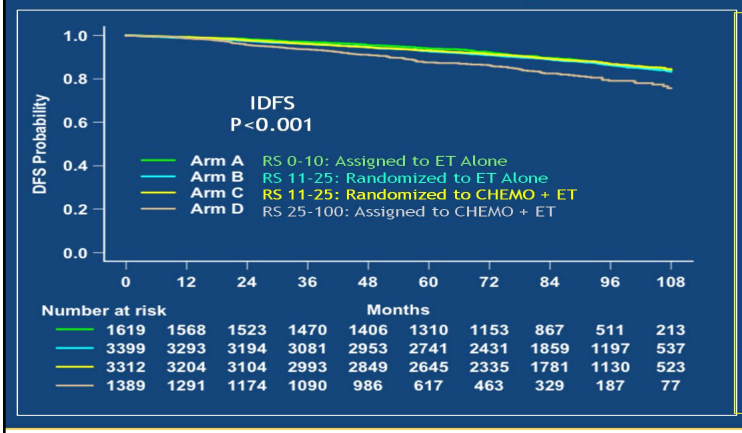
TAILORx Results - ITT Population: All Arms (A,B,C & D)



9-Year Event Rates

- **RS 0-10 (Arm A)**
  - 3% distant recurrence with ET alone
- **RS 11-25 (Arms B & C)**
  - 5% distant recurrence rate overall
  - ≤ 1% difference for all endpoints
    - IDFS (83.3 vs. 84.3%)
    - DRFI (94.5 vs. 95.0%)
    - RFI (92.2 vs. 92.9%)
    - OS (93.9 vs. 93.8%)
- **RS 26-100 (Arm D)**
  - 13% distant recurrence despite chemo + ET

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TAILORx Results – ITT Population: Exploratory Analysis of Chemotherapy Treatment Interactions in RS 11-25 Arms

No statistically significant chemo treatment interactions

- RS
  - 11-15 vs. 16-20 vs. 21-25
  - 11-17 vs. 18-25
- Tumor size (≤ 2 cm vs. > 2 cm)
- Grade (low vs. int. vs. high)
- Menopausal status (pre vs. post)
- Clinical risk category (high vs. low)

Statistically significant chemo treatment interactions

- Age (≤ 50, 51-65, > 65) and chemo benefit
  - IDFS (p=0.003)
  - RFI (p=0.02)
- Age (or menopause), RS (11-15, 16-20, 21-25), and chemo benefit
  - IDFS - Age-RS (p=0.004)
  - IDFS - Menopause-RS (p=0.02)

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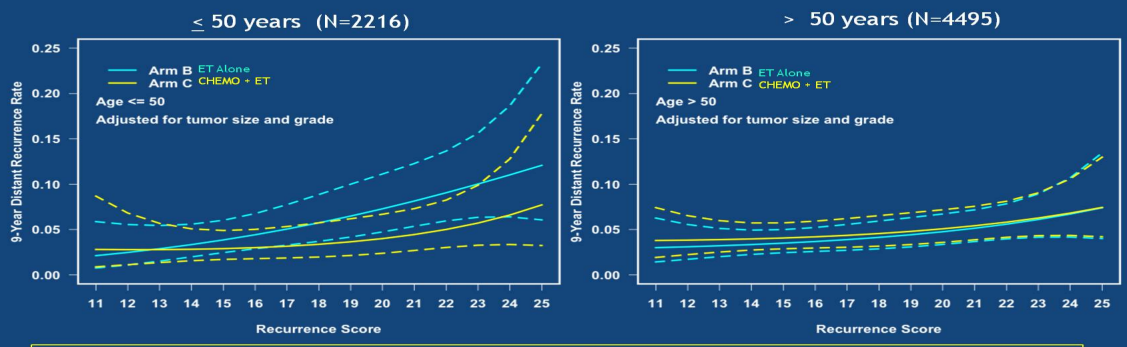
TAILORx Results: Association between Continuous RS 11-25 and 9-Year Distant Recurrence Rate by Treatment Arms Stratified by Age (</=50 vs. >50 Years)



RS modeled with a natural spline with 2 degrees of freedom, adjusted for tumor size and grade

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TAILORx Results: Summary

- **Primary conclusions**
  - **RS 11-25:** ET was non-inferior to chemotherapy + ET (primary endpoint - ITT)
  - **RS 0-10:** Distant recurrence rates very low (2-3%) with ET alone at 9 years
  - **RS 25-100:** Significantly higher event rates, driven by more recurrences despite adjuvant chemo plus ET
- **Other observations**
  - **Age – RS – Chemo treatment interaction:**
    - Some chemo benefit in women 50 or younger with a RS 15-25
    - Greatest impact on distant recurrence with RS 21-25

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TAILORx Take-Home points

- There are a large group of women for whom chemotherapy does not provide meaningful benefit:
  - age > 50, ER+, LN-, Recurrence Score <26
- Women < 50 may benefit from therapy beyond tamoxifen
  - TAILORx provides evidence for chemotherapy benefit for RS > 15
  - Ovarian suppression +/- AI ???
  - Most benefit for RS 21-25
- Chemotherapy should be considered for RS >25 across all groups
  - This is an expansion from the old "high-risk" RS > 31

Absolute Improvements in Freedom from Distant Recurrence with Adjuvant Endocrine Therapies for Premenopausal Women with HR+ HER2-negative Breast Cancer: Results from TEXT and SOFT

Meredith M. Regan, Prudence A. Francis, Olivia Pagani, Gini F. Fleming, Barbara A. Walley, Giuseppe Viale, Marco Colleoni, István Láng, Henry L. Gómez, Carlo Tondini, Graziella Pinotti, Angelo Di Leo, Alan S. Coates, Aron Goldhirsch, Richard D. Gelber, for the SOFT and TEXT Investigators and International Breast Cancer Study Group

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Premenopausal Adjuvant Endocrine Therapy

- SOFT and TEXT investigate adjuvant endocrine therapy for premenopausal women with hormone receptor-positive (HR+) early breast cancer
- Primary results in 2014 expanded adjuvant endocrine therapy options and changed treatment guidelines
  - *ASCO, BCY, ESMO, St. Gallen*
- Addition of ovarian function suppression (OFS) to tamoxifen, or use of aromatase inhibitor with OFS, for those women at *higher risk of recurrence*

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SOFT and TEXT Designs

Enrolled: Nov03 - Apr11

- Premenopausal HR+
- ≤12 wks after surgery
- Planned OFS
- No planned chemo (40%)
  OR planned chemo (60%)

RANDOMIZE

TEXT (n=2672)

→ **Tamoxifen+OFS x 5y**

→ **Exemestane+OFS x 5y**

Current Follow-up

Median follow-up 9 years

- Premenopausal HR+
- ≤12 wks after surgery
- No chemo (47%)
  OR
- Remain premenopausal
  ≤ 8 mos after chemo (53%)

RANDOMIZE

SOFT (n=3066)

→ **Tamoxifen x 5y**

→ **Tamoxifen+OFS x 5y**

→ **Exemestane+OFS x 5y**

Median follow-up 8 years

OFS=ovarian function suppression

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SOFT and TEXT Updates

- Updated results with longer follow-up published today:
  - Adding OFS to tamoxifen significantly improved disease-free and overall survival
  - Exemestane+OFS further reduced recurrence, including distant recurrence, and particularly in women with HER2-negative cancers
- Further characterize the magnitude of **absolute improvement** in freedom from distant recurrence, to guide treatment selection

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Analysis Approach

- 4891 (86%) of 5707 SOFT and TEXT patients with HER2-negative cancers
  - excluded HER2+ by local or central lab, and/or absent HRs by central lab
- Endpoint: distant recurrence-free interval (DRFI)
  - From randomization until distant recurrence (censored at last follow-up or death without recurrence)
  - 8-yr freedom from distant recurrence, by Kaplan-Meier estimate
- Assessed magnitude of absolute improvement across a continuum of *risk of recurrence*
- Examined 4 cohorts of patients, defined by trial and chemotherapy use

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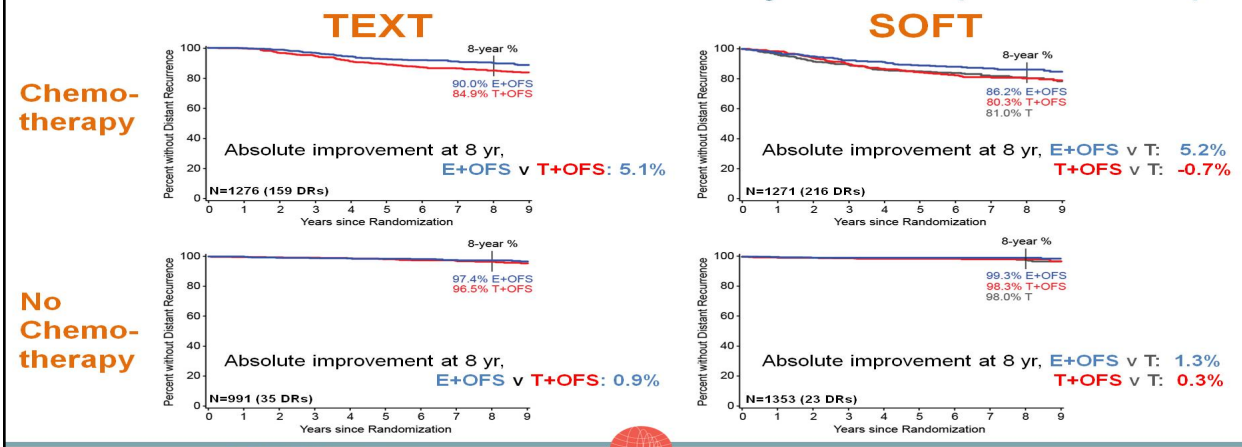
Distant Recurrence-free Interval by Cohort (HR+/HER2-)



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Composite Risk and STEPP Analysis

- Combined standard clinico-pathologic features into a single value for each patient – a continuous, composite measure of recurrence risk "composite risk" *(Regan et al, JCO 2016)*
  - age (5-yr groups), nodal status (0, 1-3, ≥4), T size (≤2, >2 cm),
  - ER (<50%, ≥50%), PgR (<20%, 20-49%, ≥50%), tumor grade, Ki-67 (<14%, 14-19%, 20-25%, ≥26%) *[centrally-assessed]*
- Determined "composite risk" from a Cox model for DRFI
  - stratified by 4 cohorts and treatment assignment
- Analyzed by Subpopulation Treatment Effect Pattern Plot (STEPP)

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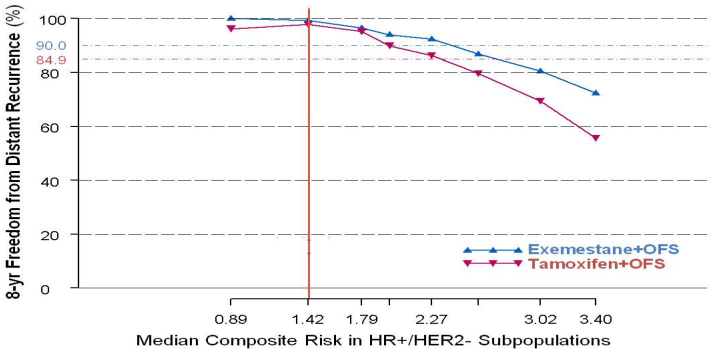
STEPP of 8-yr Freedom from Distant Recurrence: TEXT Chemotherapy



In the cohort, 8-yr %:
90.0% E+OFS
84.9% T+OFS

5.1% E+OFS vs T+OFS, avg. improvement

Improvement increases with increasing composite risk, to **15%** at highest composite risks

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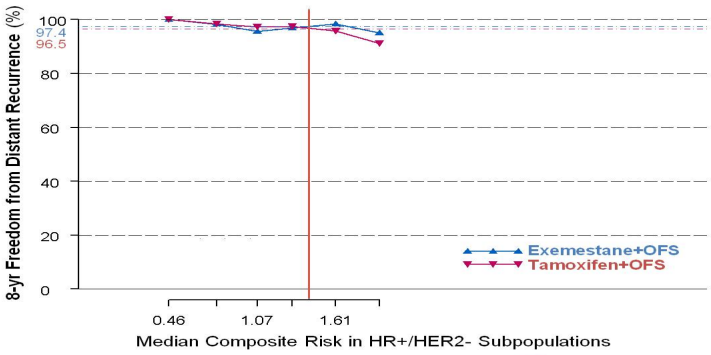
STEPP of 8-yr Freedom from Distant Recurrence: TEXT No Chemotherapy



In the cohort, 8-yr %:
97.4% E+OFS
96.5% T+OFS

<1% E+OFS vs T+OFS, avg. improvement

Improvement ranged **2.5%** to **4%** at higher composite risks above overall median

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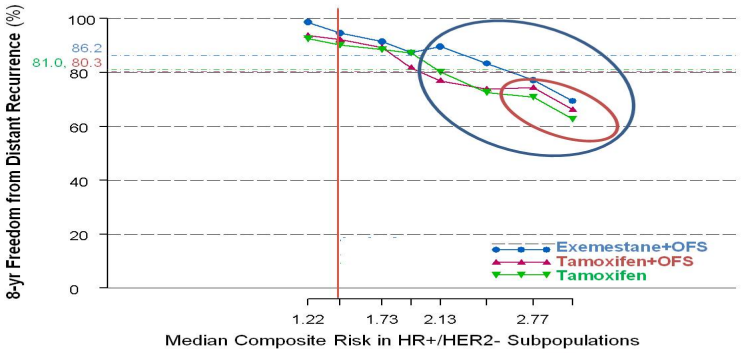
STEPP of 8-yr Freedom from Distant Recurrence: SOFT Prior Chemotherapy



In the cohort, 8-yr %:
86.2% E+OFS
80.3% T+OFS
81.0% T

5.2% E+OFS vs T, avg. improvement; max **10%** for higher composite risks

T+OFS vs T, max **3.5%** at highest composite risks

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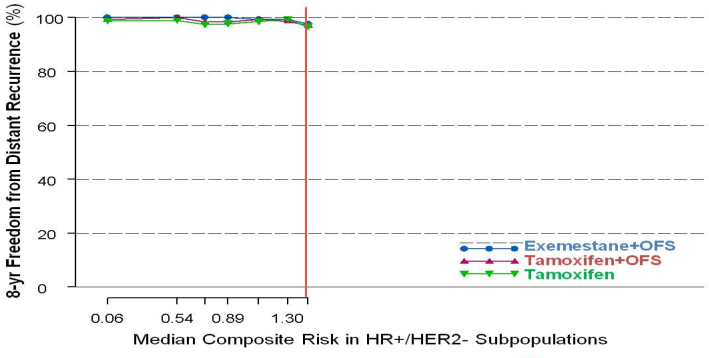
STEPP of 8-yr Freedom from Distant Recurrence: SOFT No Chemotherapy



In the cohort, 8-yr %:
99.3% E+OFS
98.3% T+OFS
98.0% T

1.3% E+OFS vs T, avg. improvement ranged **1** to **2.5%**

<1% avg. improvement T+OFS vs T

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Conclusions

Among premenopausal women in SOFT & TEXT with HR+/HER2- cancers, magnitude of absolute improvement in 8-yr freedom from distant recurrence varied widely according to *risk of recurrence*:

- Those at higher risk may experience 10-15% improvement with E+OFS vs T+OFS or T alone
- Improvement with E+OFS may be 4-5% for patients at intermediate risk, most of whom also received chemotherapy
- For those at low risk, potential benefit of escalating endocrine therapy from T-alone may be minimal, as >97% of these women were without distant recurrence at 8 years

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PERSEPHONE: 6 versus 12 months of adjuvant trastuzumab in patients with HER2 positive early breast cancer: Randomised phase 3 non-inferiority trial with definitive 4-year disease-free survival results

Helena Earl, Louise Hiller, Anne-Laure Vallier, Shrushma Loi, Donna Howe, Helen Higgins, Karen McAdam, Luke Hughes-Davies, Adrian Harnett, Mei-Lin Ah-See, Richard Simcock, Daniel Rea, Janine Mansi, Jean Abraham, Carlos Caldas, Claire Hulme, David Miles, Andrew Wardley, David Cameron, Janet Dunn, on behalf of the PERSEPHONE Trial Investigators

Cambridge University Hospitals NHS Foundation Trust

WARWICK CLINICAL TRIALS UNIT

UNIVERSITY OF CAMBRIDGE

NHS National Institute for Health Research

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PRESENTED BY: Prof Helena Earl MD PhD

https://warwick.ac.uk/fac/med/research/ctu/trials/cancer/persephone

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Persephone

NHS National Institute for Health Research

- **Hypothesis** - Six months adjuvant trastuzumab has similar efficacy to standard twelve months but reduced toxicity and cost
- **PERSEPHONE Trial** – Randomised phase 3 multicentre UK trial of 6 versus 12 months trastuzumab – non-inferiority design (n=4000)
- **Funding acknowledgement**
  NIHR HTA programme (project number 06/303/98)

Department of Health and Social Care disclaimer
The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

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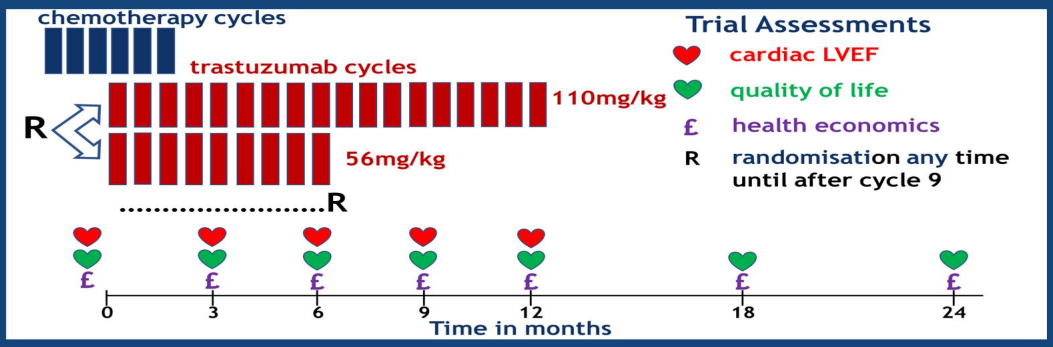
Persephone Study Design



1° : DFS [Diagnosis to 1st relapse (local or distant) or death]
2° :OS ; Cost effectiveness ; Cardiac function

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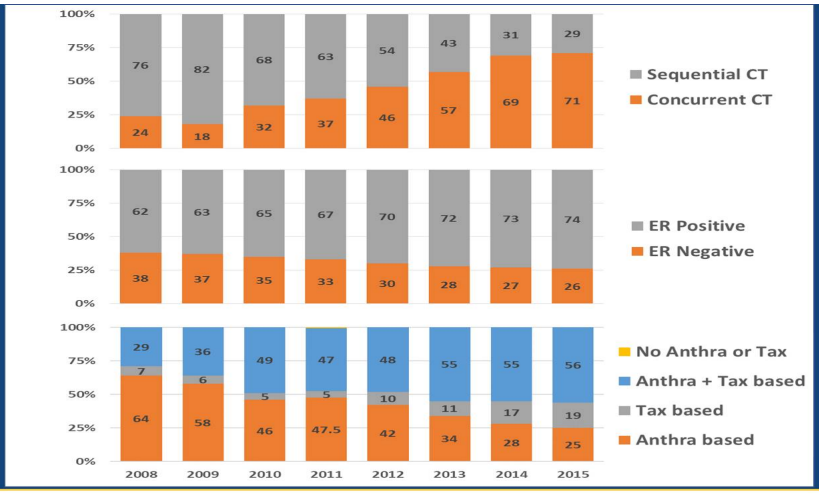
Stratification variables over time



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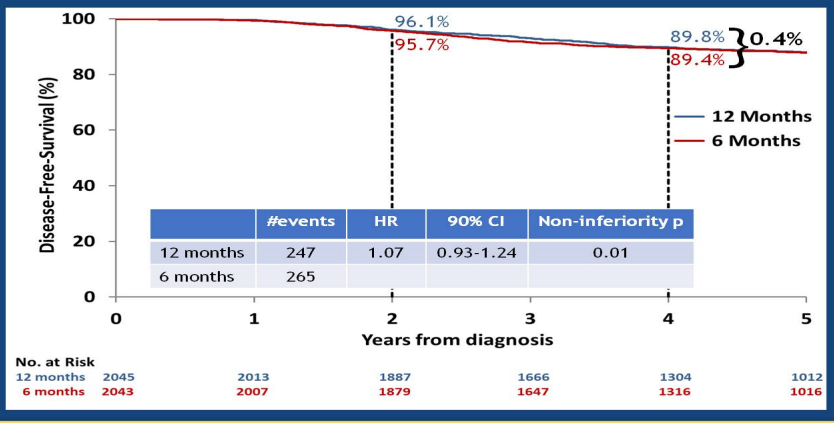
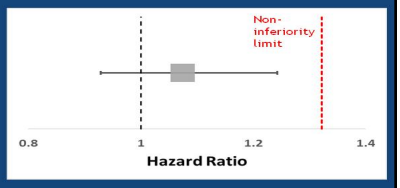
Disease-free survival



	#events	HR	90% CI	Non-inferiority p
12 months	247	1.07	0.93-1.24	0.01
6 months	265			



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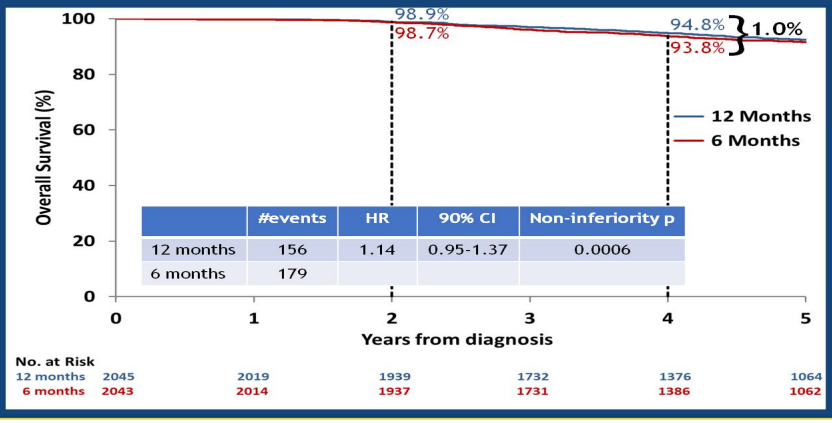
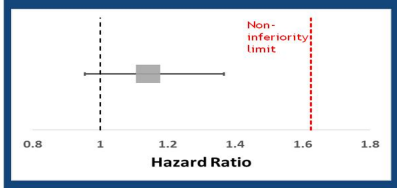
Overall survival



	#events	HR	90% CI	Non-inferiority p
12 months	156	1.14	0.95-1.37	0.0006
6 months	179			



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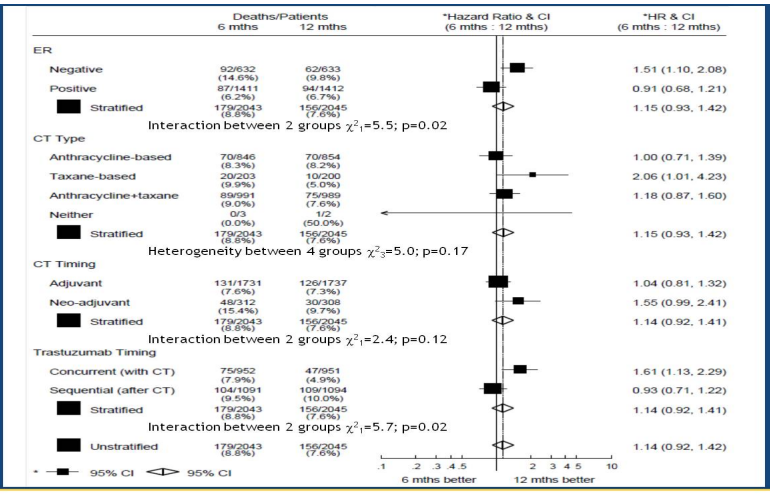
OS:

Pre-defined subgroup analysis



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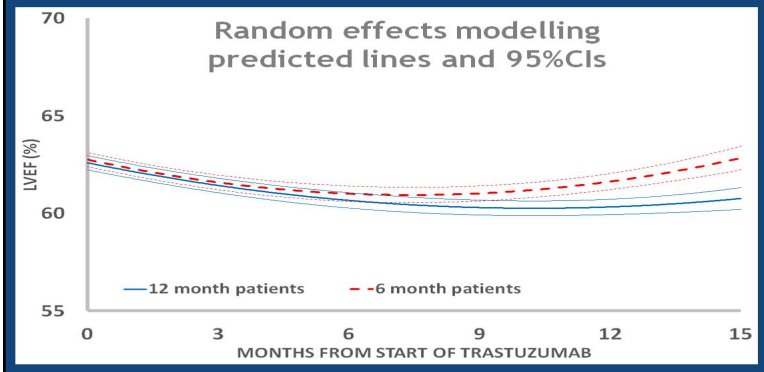
Cardiotoxicity



Stopped trastuzumab because of cardiotoxicity
- in **8%** of 12-month patients
- in **4%** of 6-month patients
(p<0.0001)

- Cardiac function recovers post-trastuzumab (p<0.0001)
- 6-month patients had a more rapid recovery (p=0.02)

Ref: Earl et al. British Journal of Cancer (2016) 115, 1462–1470

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Conclusions

- The PERSEPHONE Trial demonstrates that 6m adjuvant trastuzumab is non-inferior to 12m (6m arm 89.4% 4-yr DFS: 12m arm 89.8% 4-yr DFS; HR = 1.07 [90% CI 0.93,1.24] p=0.01)
- 6m compared with 12m treatment reduces cardiac and other toxicities, and costs both to patients and healthcare systems
- Ongoing - QoL, Patient Reported Experiences, and Health Economics
- Future - translational research (blood and tumour samples on these patients)
- These exciting results mark the first steps to the reduction of treatment duration for many women with HER2 positive breast cancer

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Persephone thoughts

- potentially practice changing
- enthusiasm tempered by
  - relatively short follow-up
  - small number of events recorded
  - restricted patient population (UK only)
  - large number of cases receiving sequential chemo + herceptin
- further work needed to identify who benefits from 6 versus 12 months

AZD5363 plus Paclitaxel versus Placebo plus Paclitaxel as first-line therapy for metastatic triple-negative breast cancer (PAKT): A randomised, double-blind, placebo-controlled, phase II trial.

Peter Schmid[1], Jacinta Abraham[2], Stephen Chan[3], Duncan Wheatley[4], Adrian Murray Brunt[5], Gia Nemsadze[6], Richard Baird[7], Yeon Hee Park[8], Peter Hall[9], Timothy Perren[10], Rob Stein[11], Mangel László[12], Jean-Marc Ferrero[13], Melissa Phillips[14], John Conibear[14], Javier Cortes[15], Shah-Jalal Sarker[1], Aaron Prendergast[1], Hayley Cartwright[1], Kelly Mousa[1], Nick Turner[16]

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Queen Mary University of London · ECMC · CANCER RESEARCH UK · NCRN · Barts Health NHS NHS Trust

Background

- The PI3K/AKT signalling pathway is frequently activated in TNBC through activating mutations in *PIK3CA* or *AKT1* and alterations in *PTEN*[1-3]
- In addition, deficient expression of PTEN is a common finding in TNBC and has been associated with a higher degree of AKT pathway activation[4]
- Capivasertib (AZD5363) is a highly-selective, oral, small molecule AKT inhibitor.
- Capivasertib has shown preclinical activity in TNBC models with and without alterations of *PIK3CA, AKT1* and *PTEN,* but sensitivity was associated with activation of *PI3K* or *AKT* and/or deletions of *PTEN*.

1. Cancer Genome Atlas Network, Nature 2012; 490: 61–70.; 2. Curtis C, et al.. Nature 2012; 486: 346–52.; 3. Pereira B, et al. Nat Commun 2016; 7: 11479.; 4Millis SZ, et al. Clin Breast Cancer 2015; 15: 473–81.

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PAKT Study Design

Trial Sponsor: Queen Mary University of London

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

R 1:1

n=70 → Paclitaxel + Capivasertib

n=70 → Paclitaxel + Placebo

Stratification factors:
- Number of metastatic sites (<3, ≥3)
- DFI (end of (neo)adjuvant chemotherapy ≤12 months ago, end of (neo)adjuvant) chemotherapy >12 months or no prior chemotherapy)

Treatment:
- **Paclitaxel, 90 mg/m^2, IV, days 1, 8, & 15, q4 weeks**
- **Capivasertib/Placebo, 400mg orally BD, days 2-5, 9-12, 16-19**
- Paclitaxel for ≥6 cycles, Capivasertib/Placebo until PD
- If paclitaxel stopped prior to PD, Capivasertib/Placebo to be continued until PD
- Tumour assessments every 8 weeks

Primary endpoint:
- Investigator-assessed PFS (ITT)

Secondary endpoints:
- PFS in patients with/without *PIK3CA/AKT1/PTEN* alterations
- Overall Survival
- Response rates (ORR)
- Clinical benefit rate (CBR)
- Duration of response
- Safety
- Health-related quality of life

ER = Estrogen Receptor; PR = Progesterone Receptor; IHC = Immunohistochemistry; ISH = In situ Hybridisation; PFS = Progression-free survival

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Patient and Disease Characteristics

		Paclitaxel + Capivasertib (N=68)	Paclitaxel + Placebo (N=70)
Age (years), median (IQR)		55.2 (48.2 - 61.4)	51.9 (40.8 - 60.7)
ECOG performance status, n (%)	0 1 2	43 (63.2) 24 (35.3) 1 (1.5)	48 (68.6) 22 (31.4) 0 (0.0)
Number of metastatic sites, n (%)	<3 ≥3	36 (52.9) 32 (47.1)	38 (54.3) 32 (45.7)
Visceral disease, n (%)	Yes No	41 (60.3) 27 (39.7)	54 (77.1) 16 (22.9)
Metastatic sites, n (%)	Liver Lung Bone Lymph node/soft tissue	17 (25.0) 34 (50.0) 28 (41.2) 48 (70.6)	21 (30.0) 45 (64.3) 28 (40.0) 51 (72.9)
Prior taxanes, n (%)	Yes No	39 (57.4) 29 (42.6)	40 (57.1) 30 (42.9)
(Neo)adjuvant chemotherapy, n (%)	End ≤12 months End >12 months No prior chemotherapy	4 (5.9) 48 (70.6) 16 (23.5)	4 (5.7) 50 (71.4) 16 (22.9)

ECOG = eastern cooperative oncology group; IQR = interquartile range

Safety: Reported Adverse Events

	Paclitaxel + Capivasertib (N=68)				Paclitaxel + Placebo (N=70)			
	All Grades		Grade 3/4		All Grades		Grade 3/4	
Number of patients with at least one AE	66	97.1%	-	-	64	91.4%	-	-
Diarrhoea	49	72.1%	9	13.2%	19	27.1%	1	1.4%
Fatigue	30	44.1%	3	4.4%	18	25.7%	0	-
Nausea	24	35.3%	1	1.5%	23	32.9%	0	-
Rash	28	41.2%	3	4.4%	11	15.7%	0	-
Neuropathy	17	25.0%	1	1.5%	13	18.6%	0	-
Stomatitis	18	26.5%	1	1.5%	10	14.3%	0	-
Infection	15	22.1%	3	4.4%	10	14.3%	1	1.4%
Decreased appetite	14	20.6%	0	-	8	11.4%	0	-
Alopecia	11	16.2%	0	-	9	12.9%	0	-
Vomiting	13	19.1%	1	1.5%	6	8.6%	1	1.4%
Constipation	5	7.4%	0	-	10	14.3%	0	-
Abdominal pain	7	10.3%	0	-	7	10.0%	0	-
Dry skin	10	14.7%	0	-	2	2.9%	0	-
Dyspnoea	6	8.8%	0	-	5	7.1%	0	-
Headache	8	11.8%	0	-	3	4.3%	0	-
Oedema	6	8.8%	0	-	4	5.7%	0	-
Dysgeusia	7	10.3%	0	-	3	4.3%	0	-
Joint pain	2	2.9%	0	-	6	8.6%	0	-
Neutropenia	6	8.8%	2	2.9%	2	2.9%	2	2.9%
Cough	1	1.5%	0	-	6	8.6%	0	-
Hyperglycaemia	6	8.8%	1	1.5%	1	1.4%	0	-

AEs occurring in ≥8% in at at least one of the treatment groups

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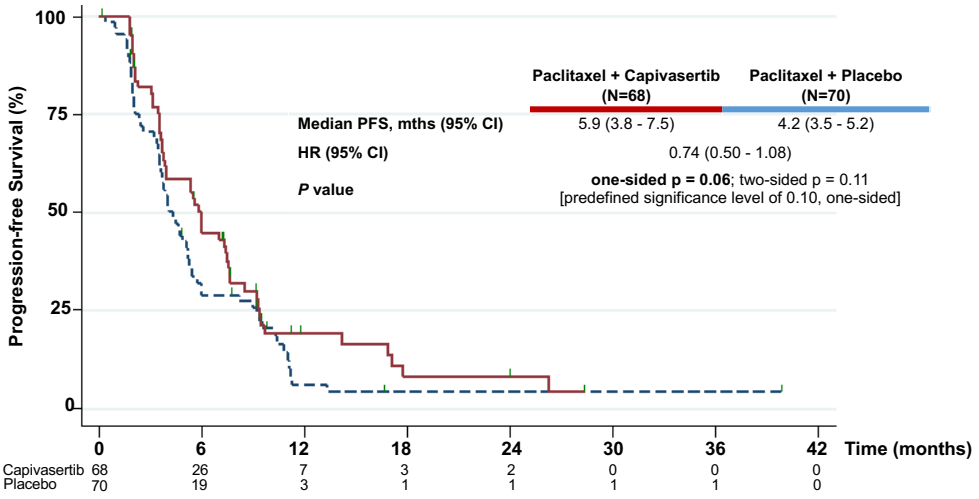
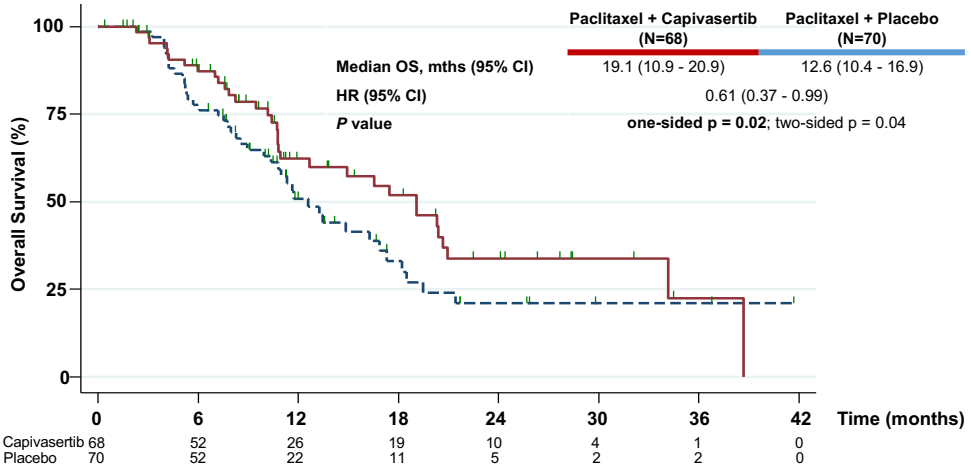
PFS by investigator assessment (ITT)



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

Overall Survival (ITT Population)

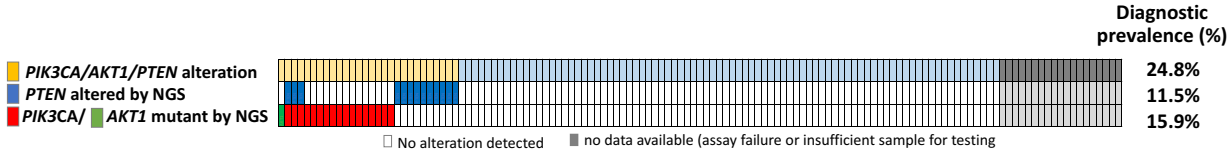


CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; mths = months; OS = overall survival

PIK3CA/AKT1/PTEN alterations

***PIK3CA/AKT1/PTEN*-altered tumours defined as the presence of at least one of the following changes:**

- *PIK3CA* activating mutations: Arg88Gln, Asn345Lys, Cys420Arg, Glu542X, Glu545X, Gln546X, Met1043Ile, His1047X, or Gly1049Arg (X represents any change in amino acid residue).
- *AKT1* Glu17Lys mutations
- *PTEN* deleterious mutations



Analysis of tumour *PIK3CA/AKT1/PTEN*-alterations:

- Central assessment using 600 gene next-generation sequencing (NGS) assay
- Sample availability: 127 FFPE samples (92%); NGS success rate: 121 FFPE (95%; 6 samples failed DNA QC)

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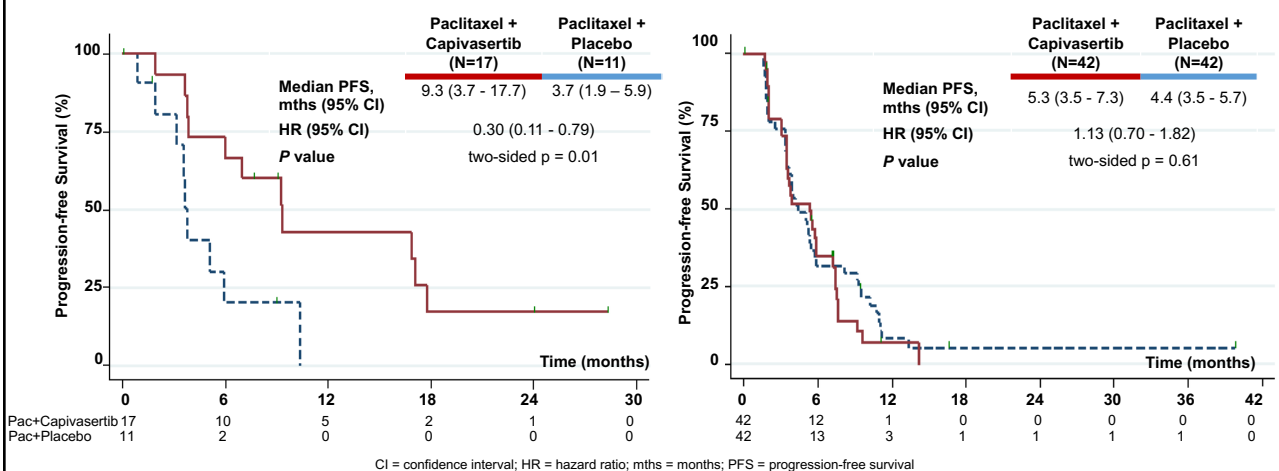
PFS by tumour *PIK3CA/AKT1/PTEN* status



CI = confidence interval; HR = hazard ratio; mths = months; PFS = progression-free survival

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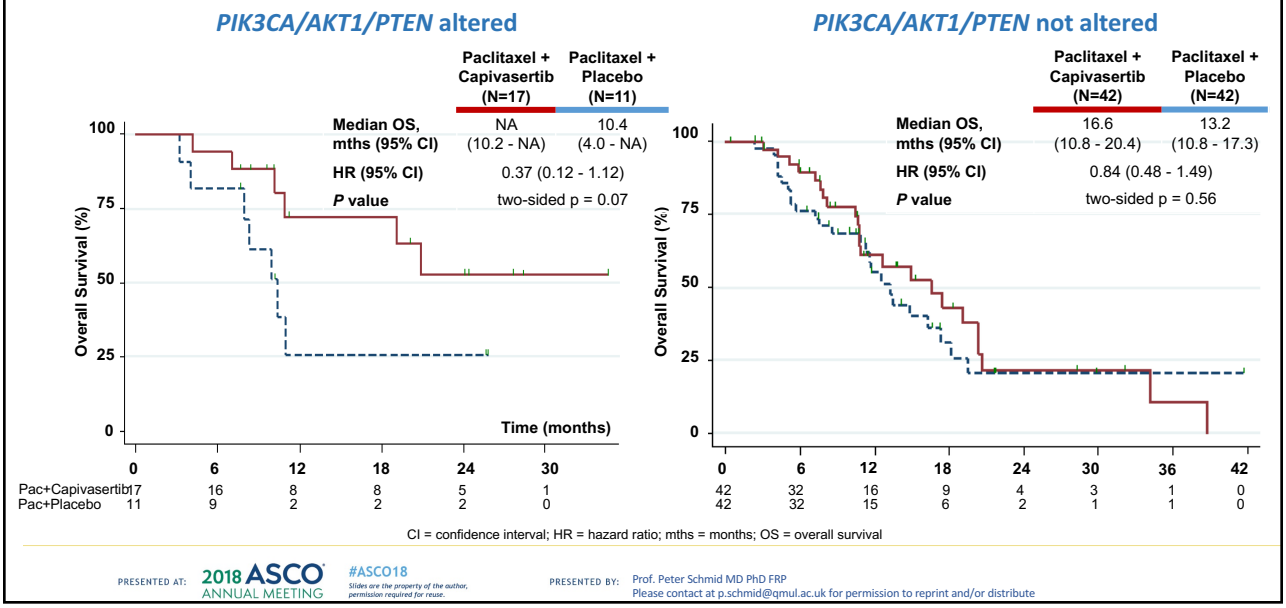
Overall Survival by *PIK3CA/AKT1/PTEN* status



CI = confidence interval; HR = hazard ratio; mths = months; OS = overall survival

Take Home Message

- **PAKT trial showed that the addition of the AKT inhibitor capivasertib to 1st line paclitaxel in mTNBC prolonged PFS**
  - Median PFS 5.9 vs 4.2 months in all patients; HR 0.74
  - Median PFS 9.3 vs 3.7 months in PIK3CA/AKT1/PTEN altered; HR 0.30
    - Alterations present in ~25% of study population
- **Overall survival also improved**
  - Median OS 19.1 vs 12.6 months in all patients; HR 0.61
  - Median OS NR vs 10.4 months in PIK3CA/AKT1/PTEN altered; HR 0.37
- **Most common grade 3 or higher AEs were diarrhea, infection, neutropenia, rash and fatigue**

Thank you