Oncology Update: The 10 Most Talked About Breast Cancer Topics of 2013

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Minnesota Oncology

The Top 10

- 1. The Awareness Debate
- 2. The Angelina Jolie Effect
- 3. Extended Tamoxifen Use (Sometimes More is Better)
- 4. Breast Cancer Subtypes (Molecular Profiling)
- 5. Personalized Medicine (Genomic Assays)
- 6. New Options for Triple Negative Disease (Platinums and PARPs)
- 7. Extending Survival in ER+ Disease
- 8. New Options for Her2+ Disease
- 9. New Surveillance Guidelines (Sometimes Less is More)
- 10. Exercise

The Awareness Debate

Do Mammograms save lives?

Have we been Pink-washed?

Would our time and money be better spent elsewhere?

Annals of Internal Medicine

SCREENING FOR BREAST CANCER USING FILM MAMMOGRAPHY
CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

RSNA Position on Mammography Screening

1. Screening mammography has reduced the US breast cancer death rate by a highly significant 30% since 1990.
2. Screening mammography, as it is currently practiced in the US, reveals 1 invasive cancer for every 556 mammograms performed in women in their 40s.
3. Mammography performed every other year in women 50-74 would miss 19-33% of cancers detectable with annual screening.
4. Delaying screening mammography until age 50 would sacrifice 33 years of life per 1,000 women screened that could have been saved had screening started at age 40.
5. Only 2% of women who receive screening mammograms eventually require biopsy.

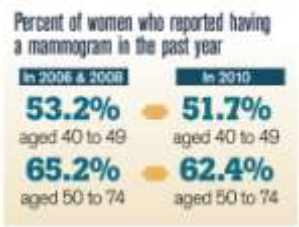
Relative Risk and Number Needed to be Screened to Prevent One Death for Breast Cancer by Age Group

Age (years)	Relative Risk	Number Needed to be Screened to Prevent One Death
39-49	0.85	1904
50-59	0.86	1339
60-69	0.68	377
70-74	1.12	Not available

-Mammography is now widely available in the US

-Breast cancer is no longer a taboo subject

-Ultimately it is a personal decision between a woman and her physician

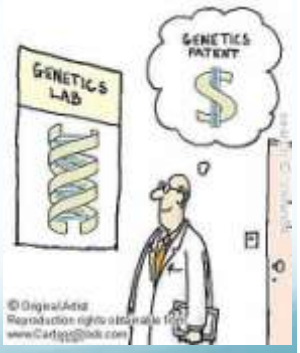


MYRIAD

-BRCA1/2 mutations effect ~8% of women with breast cancer

-Increased risk of breast, ovarian, prostate and pancreatic cancers

-Myriad Genetics has held the patent on BRCA1/2 mutation testing since 1994 ($400-$4000)



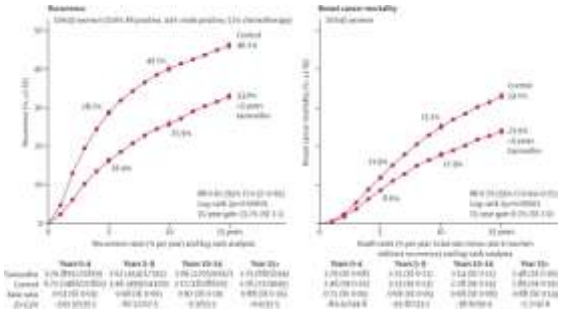
SUPREME COURT OF THE UNITED STATES

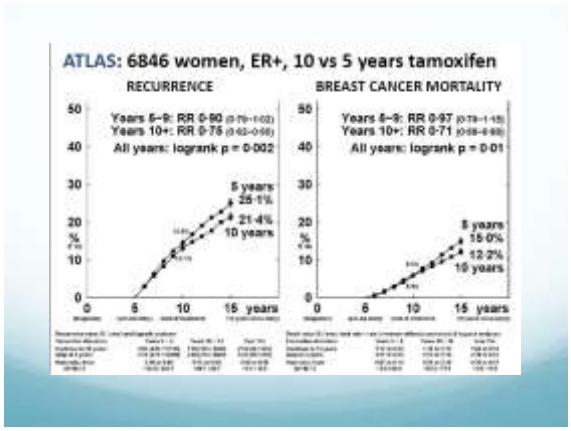
No. 12-398

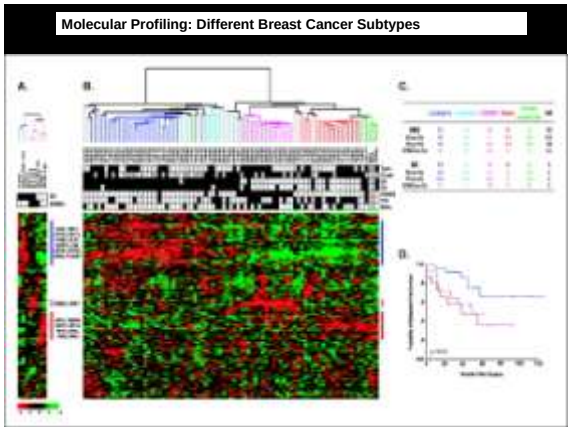
ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL., PETITIONERS8 v. MYRIAD GENETICS, INC., ET AL.

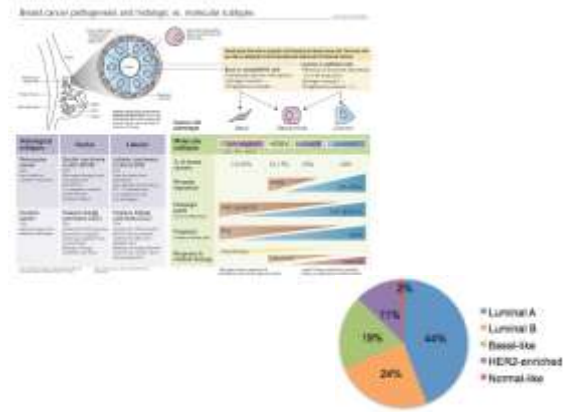
ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Extended Tamoxifen Use



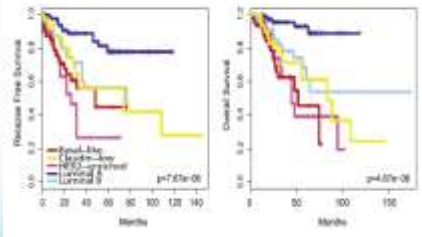

ATLAS: 6846 women, ER+, 10 vs 5 years tamoxifen
RECURRENCE
BREAST CANCER MORTALITY
Years 5–9: RR 0·90
Years 10+: RR 0·75
All years: logrank p = 0·002
5 years 25·1%
10 years 21·4%
Years 5–9: RR 0·97
Years 10+: RR 0·71
All years: logrank p = 0·01
5 years 15·0%
10 years 12·2%
0 5 10 15 years


Molecular Profiling: Different Breast Cancer Subtypes
A.
B.
C.
D.


Luminal A
Luminal B
Basal-like
HER2-enriched
Normal-like

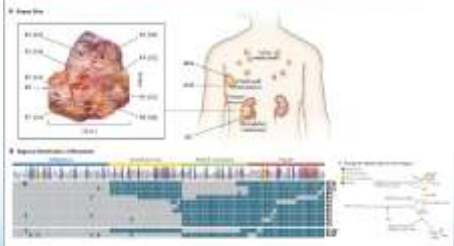
Prognostic Molecular Classification

RFS and OS



Prat and Perou, 2011

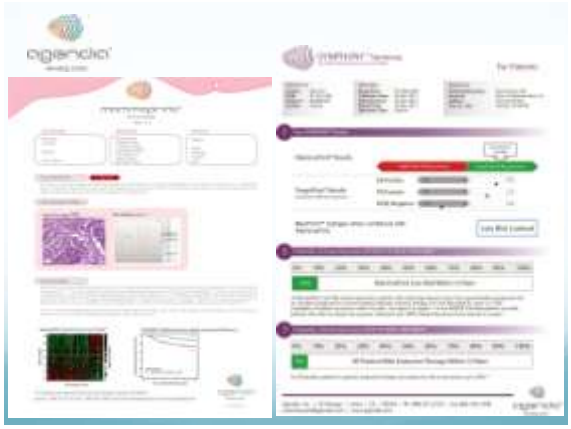
Intratumoral Mutational Heterogeneity



Gerlinger et al. NEJM 366:883, 2012

Personalized Cancer Therapy


Do I really need chemotherapy?
oncotype DX
Breast Cancer Assay
Oncotype DX Clinical Validation:
Recurrence Score as Continuous Predictor
My RS is 26. What is the chance of recurrence within 10 years?
95% CI
Recurrence Score


cgiancer


FOUNDATIONONE
CURRENT GENE LIST
ABL1 BTK CTNNB1 FGF23 IL7R MLH1 PDGFRA SMO
AKT1 CARD11 DAXX FGF3 INHBA MLL PDGFRB SOCS1
AKT2 CBFB DDR2 FGF4 IRF4 MLL2 PDK1 SOX10
AKT3 CBL DNMT3A FGF6 IRS2 MPL PIK3CA SOX2
ALK CCND1 DOT1L FGFR1 JAK1 MRE11A PIK3CG SPEN
APC CCND2 EGFR FGFR2 JAK2 MSH2 PIK3R1 SPOP
AR CCND3 EMSY (C11orf30) FGFR3 JAK3 MSH6 PIK3R2 SRC
ARAF CCNE1 EP300 FGFR4 JUN MTOR PPP2R1A STAG2
ARFRP1 CD79A EPHA3 FLT1 KAT6A (MYST3) MUTYH PRDM1 STAT4
ARID1A CD79B EPHA5 FLT3 KDM5A MYC PRKAR1A STK11
ARID2 CDC73 EPHB1 FLT4 KDM5C MYCL1 PRKDC SUFU
ASXL1 CDH1 ERBB2 FOXL2 KDM6A MYCN PTCH1 TET2
ATM CDK12 ERBB3 GATA1 KDR MYD88 PTEN TGFBR2
ATR CDK4 ERBB4 GATA2 KEAP1 NF1 PTPN11 TNFAIP3
ATRX CDK6 ERG GATA3 KIT NF2 RAD50 TNFRSF14
AURKA CDK8 ESR1 GID4 (C17orf39) KLHL6 NFE2L2 RAD51 TOP1
AURKB CDKN1B EZH2 GNA11 KRAS NFKBIA RAF1 TP53
AXL CDKN2A FAM123B (WTX) GNA13 LRP1B NKX2-1 RARA TSC1
BAP1 CDKN2B FAM46C GNAQ MAP2K1 NOTCH1 RB1 TSC2
BARD1 CDKN2C FANCA GNAS MAP2K2 NOTCH2 RET TSHR
BCL2 CEBPA FANCC GPR124 MAP2K4 NPM1 RICTOR VHL
BCL2L2 CHEK1 FANCD2 GRIN2A MAP3K1 NRAS RNF43 WISP3
BCL6 CHEK2 FANCE GSK3B MCL1 NTRK1 RPTOR WT1
BCOR CIC FANCF HGF MDM2 NTRK2 RUNX1 XPO1
BCORL1 CREBBP FANCG HRAS MDM4 NTRK3 SETD2 ZNF217
BLM CRKL FANCL IDH1 MED12 NUP93 SF3B1 ZNF703
BRAF CRLF2 FBXW7 IDH2 MEF2B PAK3 SMAD2
BRCA1 CSF1R FGF10 IGF1R MEN1 PALB2 SMAD4
BRCA2 CTCF FGF14 IKBKE MET PAX5 SMARCA4
BRIP1 CTNNA1 FGF19 IK2F1 MITF PBRM1 SMARCB1
SELECT REARRANGEMENTS
ALK BCR BCL2 BRAF EGFR ETV1 ETV4 ETV5
ETV6 EWSR1 MLL MYC NTRK1 PDGFRA RAF1 RARA

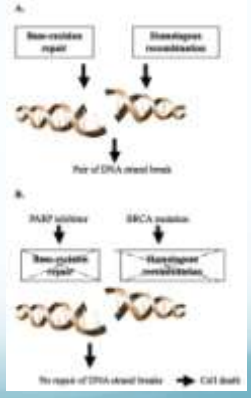
Triple Negative Disease

TRIPLE NEGATIVE BREAST CANCER FOUNDATION

-Triple negative tumors and BRCA mutated tumors have greater susceptibility to DNA damaging chemotherapy agents

-PARP inhibitors impair base-excision repair. BRCA mutated tumors have Impaired homologous recombination. This combination makes such tumors more susceptible to this type of treatment

-New interest in the role of platinum chemotherapy for triple negative and BRCA mutated tumors



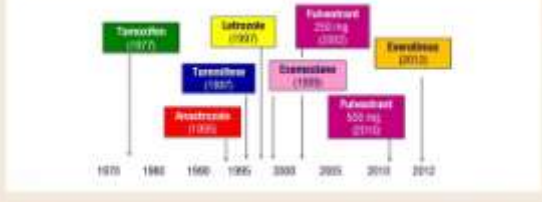
Triple Negative Disease

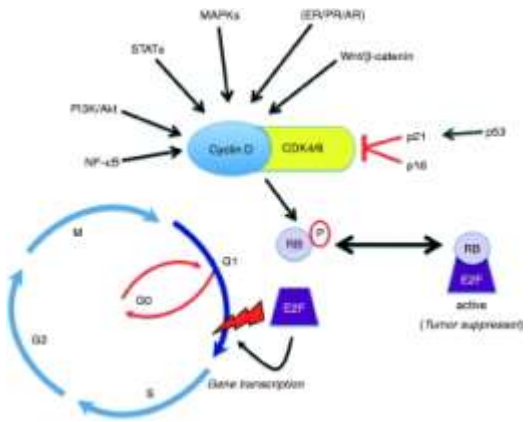
- Polish neo-adjuvant trial with 25 BRCA positive, 80% triple negative, patients treated with 4 cycles of Cisplatin showed a pCR of 72% (compared to historic controls with AC-T pCR of 37%)
- GeparSixto study from ASCO 2013 evaluated the addition of carboplatin to standard neo-adjuvant chemotherapy in TN and Her2+ patients. pCR rate of 46.7% with carbo vs 37% standard. Among TN patients pCR 58.7% vs 37.9%
- PrECOG 0105 phase 2 single arm study with TN and BRCA mutations patients treated with Carbo, Gemzar, Iniparib show CR 36% overall, 47% BRCA mutation, 56% TN and BRCA mutation

Advances in Triple Negative Disease

- Androgen Receptor – On going clinical trials looking at Enzalutamide treatment for triple negative, AR+ disease
- New homologous recombination deficiency assay from Myraid suggests high degrees of homologous recombination deficiency may predict response to DNA repair targeting strategies
- Molecular profiling assays (Foundation One and others) looking to identify specific molecular targets in individuals tumors to guide therapy (PI3K, MEK, etc.)

Advances in Endocrine Therapy

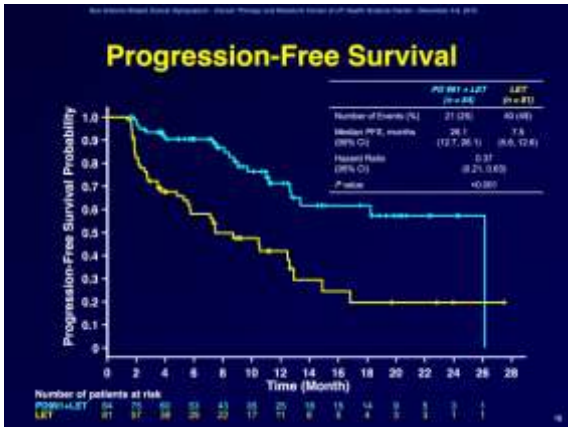




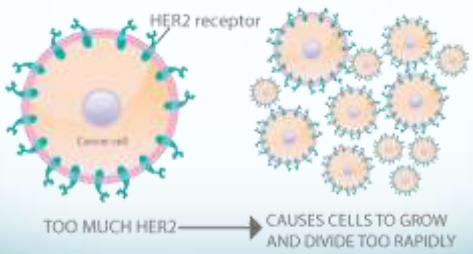
PD 0332991/Letrozole in Estrogen Receptor Positive Advanced Breast Cancer

- PD 0332991 is an oral selective inhibitor of cyclin-dependent kinase 4/6 (prevents cellular DNA synthesis)
- Phase 2 study including women with ER+/Her2- advanced breast cancer randomized 1:1 PD/letrozole vs letrozole alone
- Median progression-free survival was 26.1 months in the combination arm vs 7.5 months for letrozole alone (p = .006), representing a 63% improvement in risk of progression
- Neutropenia, leukopenia, anemia and fatigue were the most common adverse events with combination therapy

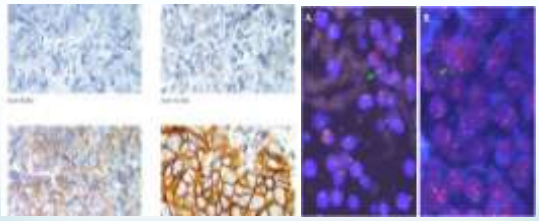
Finn RS, et al. 2012 SABCS. Abstract S1-6.

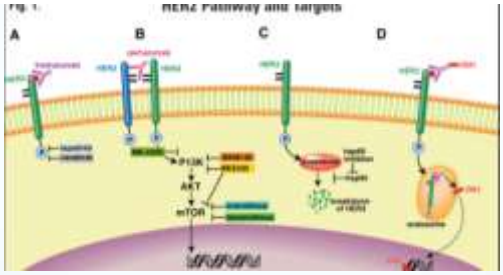


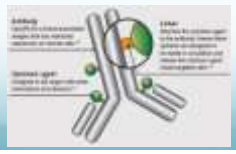
Advances in Her2 positive Disease



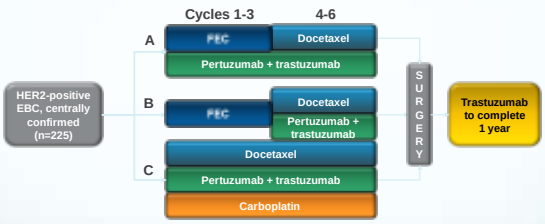
Advances in Her2 positive Disease







TRYPHAENA* Phase II Neoadjuvant Trastuzumab and Pertuzumab in HER2-Positive EBC: Study Design



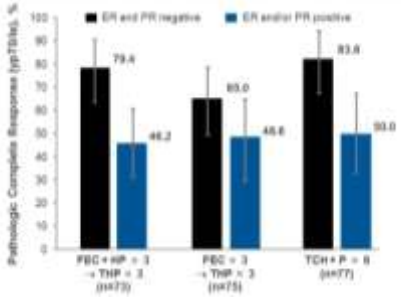
- All 3 arms were experimental
- Study dosing q3w:
  - FEC: 500 mg/m², 100 mg/m², 600 mg/m²
  - Carboplatin: AUC 6
  - Trastuzumab: 8 mg/kg loading dose, 6 mg/kg maintenance
  - Pertuzumab: 840 mg loading dose, 420 mg maintenance
  - Docetaxel: 75 mg/m² (escalating to 100 mg/m² if tolerated, in Arms A and B only)
- Stratification:
  - Operable, locally advanced, and inflammatory breast cancer
  - Hormone receptor positivity

EBC=early-stage breast cancer; FEC=5-fluorouracil, epirubicin, cyclophosphamide

Schneeweiss A, et al. Ann Oncol. 2013 May 22 [Epub ahead of print].

*Genentech/Roche Sponsored Study

TRYPHAENA* Phase II Neoadjuvant Trastuzumab and Pertuzumab in HER2-Positive EBC: **Pathologic Complete Response by Hormone Receptor**



C=carboplatin; EBC=early-stage breast cancer; ER=estrogen receptor; FEC=5-fluorouracil, epirubicin, cyclophosphamide; H=trastuzumab; P=pertuzumab; PR=progesterone receptor; T=docetaxel

Schneeweiss A, et al. Ann Oncol. 2013 May 22 [Epub ahead of print].

MO.P.BC.Early.Ow.72

*Genentech/Roche Sponsored Study

TRYPHAENA* Phase II Neoadjuvant Trastuzumab and Pertuzumab in HER2-Positive EBC: **Clinical Response Rate**

	FEC + HP × 3 → THP × 3 n (%) (n=73)	FEC × 3 → THP × 3 n (%) (n=75)	TCH + P × 6 n (%) (n=77)
Objective response rate CR rate Partial response rate	67 (91.8) 37 (50.7) 30 (41.1)	71 (94.7) 21 (28.0) 50 (66.7)	69 (89.6) 31 (40.3) 38 (49.4)
Stable disease	3 (4.1)	1 (1.3)	5 (6.5)
Progressive disease	0 (0.0)	1 (1.3)	0 (0.0)
No assessment	3 (4.1)	2 (2.7)	3 (3.9)

C=carboplatin; EBC=early-stage breast cancer; FEC=5-fluorouracil, epirubicin, cyclophosphamide; H=trastuzumab; P=pertuzumab; T=docetaxel

Schneeweiss A, et al. Ann Oncol. 2013 May 22 [Epub ahead of print].

MO.P.BC.Early.Ow.73

*Genentech/Roche Sponsored Study

TRYPHAENA* Phase II Neoadjuvant Trastuzumab and Pertuzumab in HER2-Positive EBC: **Authors' Summary and Conclusions**

- Results from TRYPHAENA indicate a low incidence of symptomatic and asymptomatic LVSD across all arms
  - Concurrent administration of pertuzumab + trastuzumab with epirubicin resulted in similar cardiac tolerability compared with sequential administration or the anthracycline-free regimen
- Neutropenia, febrile neutropenia, leukopenia, and diarrhea were the most frequently reported AEs (grade ≥3) across all arms
- Regardless of chemotherapy chosen, the combination of pertuzumab with trastuzumab in the neoadjuvant setting resulted in high pCR rates (57%-66%)
- TRYPHAENA supports the ongoing APHINITY study, a phase III trial to evaluate pertuzumab and trastuzumab + standard chemotherapy in the adjuvant setting (NCT01358877)

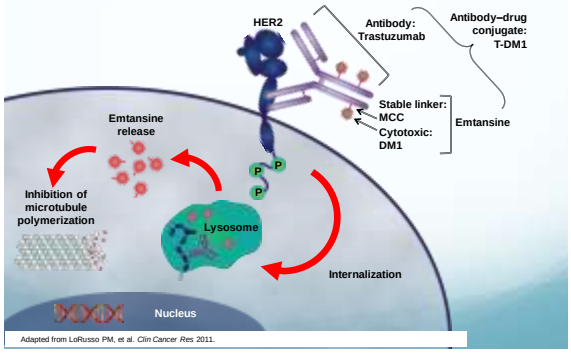
EBC=early-stage breast cancer; LVSD=left ventricular systolic dysfunction; pCR=pathologic complete response

Schneeweiss A, et al. Ann Oncol. 2013 May 22 [Epub ahead of print]. Schneeweiss A, et al. Presented at SABC. 2011 (abstr S5-6).

MO.P.BC.Early.Ow.75

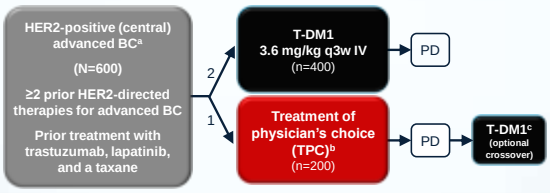
*Genentech/Roche Sponsored Study

T-DM1 Mechanism of Action



Adapted from LoRusso PM, et al. *Clin Cancer Res* 2011.

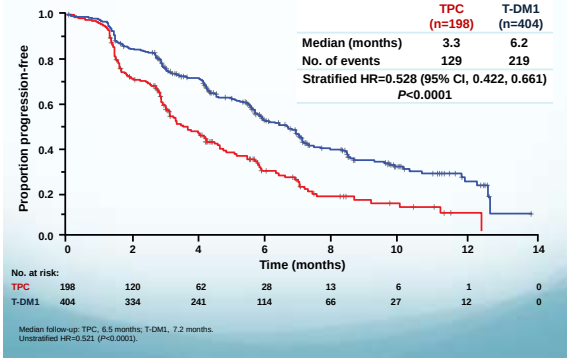
TH3RESA Study Schema



- **Stratification factors:** World region, number of prior regimens for advanced BC,[d] presence of visceral disease
- **Co-primary endpoints:** PFS by investigator and OS
- **Key secondary endpoints:** ORR by investigator and safety

[a] Advanced BC includes MBC and unresectable locally advanced/recurrent BC.
[b] TPC could have been single-agent chemotherapy, hormonal therapy, or HER2-directed therapy, or a combination of a HER2-directed therapy with a chemotherapy, hormonal therapy, or other HER2-directed therapy.
[c] First patient in: Sep 2011. Study amended Sep 2012 (following EMILIA 2nd interim OS results) to allow patients in the TPC arm to receive T-DM1 after documented PD.
[d] Excluding single-agent hormonal therapy.
BC, breast cancer; IV, intravenous; ORR, objective response rate; PD, progressive disease; q3w, every 3 weeks.

PFS by Investigator Assessment

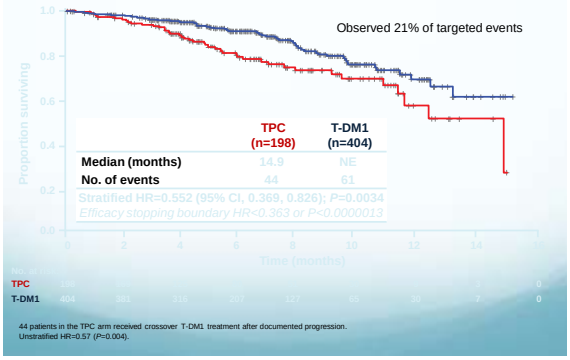


	TPC (n=198)	T-DM1 (n=404)
Median (months)	3.3	6.2
No. of events	129	219

Stratified HR=0.528 (95% CI, 0.422, 0.661)
P<0.0001

Median follow-up: TPC, 6.5 months; T-DM1, 7.2 months.
Unstratified HR=0.521 (*P*<0.0001).

First Interim OS Analysis



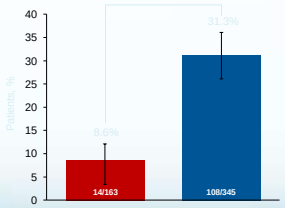
	TPC (n=198)	T-DM1 (n=404)
Median (months)	14.9	NE
No. of events	44	61

Stratified HR=0.552 (95% CI, 0.369, 0.826); *P*=0.0034
Efficacy stopping boundary HR<0.363 or P<0.0000013

44 patients in the TPC arm received crossover T-DM1 treatment after documented progression.
Unstratified HR=0.57 (*P*=0.004).

ORR in Patients With Measurable Disease

Difference: 22.7% (95% CI, 16.2, 29.2)
P<0.0001



Survivor Surveillance Guidelines

VIRGINIA PIPER CANCER INSTITUTE

Can exercise reduce the risk of cancer?

Karen K. Swenson, RN, PhD
Manager/Scientific Advisor, VPCI Research
Annual BCAA Education Conference - October 12, 2013

Link between physical activity and primary cancer prevention

Kruk J, Czerniak U. Physical activity and its relation to cancer risk. *Asian Pac J Cancer Prev*. 2013; 14(7): 3993-4003.

- Moderate to high intensity exercise is protective.
- Risk reduction is 20-30%.
  - Colon cancer (greatest benefit)
  - Post-menopausal breast and uterine cancer (moderate benefit)
  - Premenopausal breast, lung, ovary, gastric and pancreatic cancer (benefit)

Plank by Nathan

Physical activity and secondary cancer prevention

Lemanne D, Cassileth B, Gubili J. The role of physical activity in cancer prevention, treatment, recovery, and survivorship. *Oncology (Williston Park)*. 2013 Jun;27(6):580-5.

- Observational studies show a decrease in cancer-specific mortality with post-diagnosis exercise.
- 3 – 6 hours of walking/week
- Benefits are for patients with breast, colon and prostate cancer.

Pancreatic Cancer Action Network PurpleRide – Sept 2013

Why does exercise work?

Potential mechanisms:

- Decrease in sex and metabolic hormones
- Changes in insulin resistance
- Improvement of immune function
- Reduction of inflammation

Kruk J, Czerniak U. Physical activity and its relation to cancer risk. *Asian Pac J Cancer Prev.* 2013;14(7):3993-4003.

Arcidiacono B, Iiritano S, Nocera A, et al. Insulin resistance and cancer risk: An overview of the pathogenic mechanisms. 2012; *Experimental Diabetes Research*, Article ID 78174.

Fitness vs. Cancer Rehabilitation

- **Special needs of oncology patients requiring cancer rehabilitation:**
  - Bone metastasis
  - Severe deconditioning and weakness
  - Lymphedema
  - Neuropathy
  - Education regarding safe exercise participation during and after cancer treatments.

Nancy A. Hutchison, Medical Director for Cancer Rehabilitation and Survivorship, Courage Kenny Rehabilitation Institute and Virginia Piper Cancer Institute

Allina Health Cancer Rehabilitation Program (STAR Program®)

- Allina Health STAR (Survivorship Training and Rehabilitation) Program® addresses unique needs of cancer survivors:
  - Fatigue
  - Musculoskeletal pain and stiffness
  - Weakness/fitness
  - Cognitive problems
  - Balance problems
  - Lymphedema
  - Difficulty with swallowing or eating after treatment.

Allina Health Cancer Rehabilitation Fitness Team Program Components

- Referral from health care provider
- Initial consultation with Physical Therapist
  - Assess status
  - Set goals
  - Assign to small group or individual sessions
- Program length based on patient need
- Transition to maintenance at community-based facility.

Formal evaluation of a 6 – 8 week cancer rehab conditioning and strengthening program found:

- Improved conditioning level
  - Increased distance on 6 Min Walk Test
  - Increased MET Level
- Improved functional status
  - Increased physical health score on SF-36
- Improved Quality of Life
  - Increased mental health score on SF-36
  - Reduced depression on MDASI
- Improved Symptoms
  - Decreased symptom severity
  - Less interference with daily life
  - Reduced fatigue

Swenson KK, Nissen MJ, Krippenberg K, Sistermans A, Spilde P, Bell EM, Nissen J, Chen C, Tsai ML. Cancer rehabilitation: Outcome evaluation of a strengthening and conditioning program. *Cancer Nurs*. 2013 Mar 20. [Epub ahead of print].

Thank you for your attention!